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TI-6AL-4V β PHASE SELECTIVE DISSOLUTION: *IN VITRO* MECHANISM AND PREDICTION

A Dissertation Presented to the Graduate School of Clemson University

In Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy Bioengineering

> by Michael Anthony Kurtz December 2023

Received by: Dr. Jeremy L. Gilbert, Committee Chair Dr. Martine LaBerge Dr. John D. DesJardins Dr. Brian C. Dean

Abstract

Retrieval studies document Ti-6Al-4V β phase dissolution within total hip replacement systems. A gap persists in our mechanistic understanding and existing standards fail to reproduce this damage. This thesis aims to (1) elucidate the Ti-6Al-4V selective dissolution mechanism as functions of solution chemistry, electrode potential and temperature; (2) investigate the effects of adverse electrochemical conditions on additively manufactured (AM) titanium alloys and (3) apply machine learning to predict the Ti-6Al-4V dissolution state. We hypothesized that (1) cathodic activation and inflammatory species (H₂O₂) would degrade the Ti-6Al-4V oxide, promoting dissolution; (2) AM Ti-6Al-4V selective dissolution would occur and (3) near field electrochemical impedance spectra (nEIS) would distinguish between dissolved and polished Ti-6Al-4V, allowing for deep neural network prediction. First, we show a combinatorial effect of cathodic activation and inflammatory species, degrading the oxide film's polarization resistance (R_p) by a factor of $10^5 \Omega cm^2$ (p = 0.000) and inducing selective dissolution. Next, we establish a potential range (-0.3 V to -1 V) where inflammatory species, cathodic activation and increasing solution temperatures (24 °C to 55 °C) synergistically affect the oxide film. Then, we evaluate the effect of solution temperature on the dissolution rate, documenting a logarithmic dependence. In our second aim, we show decreased AM Ti-6Al-4V Rp when compared with AM Ti-29Nb-21Zr in H₂O₂. AM Ti-6Al-4V oxide degradation preceded pit nucleation in the β phase. Finally, in our third aim, we identified gaps in the application of artificial intelligence to metallic biomaterial corrosion. With an input of nEIS spectra, a deep neural network predicted the surface dissolution state with 96% accuracy. In total, these results support the inclusion of inflammatory species and cathodic activation in pre-clinical titanium devices and biomaterial testing.

Dedication

This thesis would not exist without the help of countless excellent teachers, fellow students, and friends throughout my academic career. First, I would like to thank Cindy Rogers for teaching me the fundamentals of writing and later advocating on my behalf when few still believed in me. At Camden Catholic, Nicholas Turner treated me like a brother and Dennis Quinn reminded me that any achievement requires, time, patience, and dedication. Indeed, neither Rome nor this thesis were built in a day. Finally, I thank Calvin Peck for wisdom I cannot repeat here, and Robert Pacana for helping me learn the importance of working through the noise.

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Chapter 1

Introduction

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1.1 Purpose

Permanently implanted devices are the standard of care for many medical procedures. Within orthopedics, total joint replacement surgeries rely on these devices to restore native tissue function. To restore structure, tissue engineers have created various biomaterials, constructs and 3D printed scaffolds to regenerate cartilage and bone [1-5]. However, the clinical impact of this work remains limited, and metals, polymers, and ceramics continue to dominate *in vivo* orthopedic material selection [6-10].

Metals are used as bearing surfaces and in cyclic loading applications due to their wear and fatigue resistance, respectively [7]. Stainless steel, cobalt chrome molybdenum, and titanium and its alloys comprise most metallic orthopedic implants. These metals generally have excellent biocompatibility, mechanical properties, and corrosion resistance. Additionally, all three metals are protected by a passive 1-10 nm thick oxide film, preventing active corrosion at the device-biology interface [11-13].

In vivo, the oxide film may be disrupted during tribological processes, promoting corrosion [14-20]. Corrosion of cobalt chrome has been linked to adverse local tissue reactions (ALTR) and aseptic lymphocyte-dominant vasculitis-associated lesions (ALVAL) [21-24]. While the use of cobalt chrome is decreasing, titanium devices continue to be implanted at increasing rates.

Though titanium was once thought of as an ideal biomaterial, it too corrodes *in vivo*. Retrieval studies in the 21st century document severe corrosion within the modular taper junctions of titanium alloy total hip replacement devices [25, 26]. These corrosion damage modes, including pitting, hydrogen embrittlement, and selective dissolution, are not solely caused by wear and remain poorly understood [25, 26].

It is important to note here that total hip arthroplasties are a successful clinical procedure with revision rates in the single percentages [27]. Documented cases of titanium alloy corrosion are rare, and it is unclear what impact they have on clinical failure [28]. However, many orthopedic problems remain unsolved. Patient satisfaction lags behind clinical and radiographical success for total knee replacement devices [29]. Few joint replacement surgeries replicate the success of the total hip. In many of the devices implanted, including in the upper extremities, ankle, and spine, titanium is used. Additive manufacturing adds additional complexity. Alloy microstructure, structurally related to the metal's corrosion properties, is fundamentally different [30-35]. Understanding the circumstances in which titanium alloy devices fail may inform preclinical device testing and improve future device design.

In this introduction, I present concepts that are critical to understanding Ti-6Al-4V β phase selective dissolution. My goal is to explain these concepts in an order that makes sense and at a level such that a first-year graduate student can understand. Selective dissolution, and more broadly, corrosion in the human body, is at the intersection of multiple disciplines including material science, electrochemistry, and biology. Predicting selective dissolution adds computer science, machine learning, and artificial intelligence. The breadth of concepts is extensive. Here, I have selected the most relevant.

1.2 Titanium Alloys in the Human Body

Titanium biomaterials address several challenges *in vivo*. First, titanium is biocompatible and corrosion resistant. While the human body may surround titanium devices with a fibrotic capsule, and a low level of chronic inflammation persists for the lifespan of the device, titanium avoids the acute inflammatory and allergic responses associated with CoCrMo corrosion. Second, titanium alloys exhibit excellent fatigue resistance. Originally engineered to safely

operate in the aerospace industry, Ti-6Al-4V may be cyclically loaded millions of times prior to fatigue crack initiation. Indeed, within the literature, Ti-6Al-4V stems rarely fracture. When they do, failure analysis reveals electrocautery and corrosion as underlying causes [36-38].

Finally, titanium alloy corrosion products generally do not harm the surrounding tissue at the interface. Prior to 1980, *In vitro* studies identified the β stabilizer vanadium as cytotoxic [39, 40]. To address these concerns, Smith and Nephew developed the alternative near- β alloy Ti-13Nb-13Zr in the 1990s. In the cold annealed state, the alloy shows improved corrosion resistance and decreased wear resistance compared to Ti-6Al-4V [41-48]. To increase the Ti-13Nb-13Zr wear resistance, oxygen diffusion generates a protective ceramic coating on the surface [49]. Despite cytotoxicity concerns, vanadium does not ionize *in vivo*. Decades of clinical evidence and safe use support the continued usage of Ti-6Al-4V. To date, Ti-6Al-4V remains the dominant titanium alloy used in medical devices.

Though once considered an ideal biomaterial, Ti-6Al-4V has several limitations. The Ti-6Al-4V modulus greatly exceeds that of the surrounding tissue and bone. Here, the gap between biomaterial structure and function becomes a concern. Titanium total hip and total knee devices replace the function of the failed joint. They do not, however, reproduce the structure of the cartilage, bone, and tissue removed during the primary surgery. While this statement may seem obvious (titanium ≠ bone is a safe assumption), the differences in properties between native tissue and the artificial device have clinical consequences. When confronted with the Ti-6Al-4V interface, stress shielding occurs [50-54]. The bone remodels, decreasing in volume. Periprosthetic fracture may occur, and should the device fail, revision surgery complications are more likely. Next, titanium and its alloys make poor bearing surfaces. Retrievals of monobloc titanium total hip replacements show wear on the femoral heads [55]. Last, scanning electron

micrographs of modular head-neck and neck-stem titanium junctions shows various chemically induced corrosion damage modes [25, 26]. To mitigate these issues, surface coatings and additively manufacturing reduce the Ti-6A1-4V modulus at the interface. Modular device design enables mixed component usage, replacing Ti-6A1-4V femoral heads with CoCrMo and ceramics. However, while metals are used in modular taper junctions, corrosion remains a concern.

Clinical adoption of new, orthopedic, titanium alloys has been limited within the United States. In 2002, Stryker introduced Ti-12Mo-6Zr-2Fe (TMZF) as an alloy to replace Ti-6Al-4V in hip stems [56]. With a lower modulus, more in line with the cortical bone interface, the goal of this alloy was to reduce stress shielding while replacing the native bone function. However, retrieval studies in the past decade show gross trunnion failure, including fracture and a "bird-beaking effect" where tribocorrosion between the femoral head and trunnion systematically files the trunnion into a point [57, 58]. Clinical failure may be related to both the lower modulus of the alloy, decreasing the trunnion rigidity and poor device design [59]. To address these failures, Stryker voluntarily recalled various CoCrMo head diameter sizes as well as certain offsets in 2016. The successor product, the Accolade II hip stem, replaced TMZF as the substrate alloy with Ti-6Al-4V. The legacy of TMZF is complicated. While retrieval studies highlight cases of severe corrosion and catastrophic failure, reported revision rates are in the single percentages (< 3%) [60]. Since TMZF, few new titanium alloys have reached widespread clinical use. Manufacturers instead have looked to additive manufacturing to alter the structure and decrease the modulus at the in vivo device interface.

1.3 Additive Manufacturing of Titanium Alloys

Additive Manufacturing (AM) is increasingly used to generate orthopedic devices [61, 62]. Examples from total knee and hip replacement systems include Ti-6Al-4V tibial trays and acetabular cups, respectively. AM is favored over traditional manufacturing due to its ability to produce customizable geometries at micron resolutions. At the interface of acetabular cups, AM surface structure replicates cancellous bone, promoting osseointegration [63]. Additionally, the structure decreases the modulus of the bone-titanium interface, reducing the effects of stress shielding. For revision or cancer patients suffering from substantial bone loss, AM fills a gap, creating customizable devices for patients on case-by-case basis. Beyond total joint replacements, AM Ti-6Al-4V is used for craniofacial repairs and dentistry [64, 65].

AM relies on computer aided design (CAD) files which are vertically sliced into layers the height of material deposition. A heat element traces layers of metal feedstock, fusing them to form a final 3D printed part or component. Feedstocks are generally limited to conventionally manufactured materials like aluminum, steel, CoCrMo and titanium alloys [34]. Current AM processes for metals include directed energy deposition, sheet lamination, material jetting and powder bed fusion [66]. Of these processes, directed energy deposition and powder bed fusion are the most common.

During powder bed fusion, a piston drives metal powder upwards from a well. Next, a roller brushes the powder onto the fabrication working area. A laser (selective laser melting) or electron beam (electron beam melting) melts the powder, forming one layer of an AM part [67]. A fabrication piston subsequently lowers the entire working area by the height of one layer, the roller removes and saves excess powder and the process repeats until the part is fully formed. Selective laser melted parts are particularly susceptible to residual stresses due to the rapid

melting and resolidification. While this cycle generates a fine grain structure responsible for improved material hardness and strength, it can also reduce fatigue strength and result in overmelting, increased defects, welding particles onto the layer surface, and void generation [68-70]. Comprised of the same elements in equal weight percentages, AM Ti-6Al-4V differs from the conventional alloy. First, the microstructure of as-built AM Ti-6Al-4V appears martensitic (Figure 1.1A). Fine needles are interspersed with α lathes. In contrast, conventionally manufactured Ti-6Al-4V microstructure is equiaxed. The α phase appears globular in micrographs, while the β phase is vein-like (Figure 1.1B). Additionally, under backscattered electron imaging, the two phases are easily distinguishable. The β phase appears bright in contrast to the darker α .



Figure 1.1. SEM Micrographs of (A) AM Ti-6Al-4V and (B) conventionally manufactured Ti-

6Al-4V. Note the differing microstructures. Image magnifications are 1.5k and 5k respectively.

Post-printing heat treatments alter the as-built AM microstructure. Microstructural changes directly affect the AM alloy's oxide, mechanical properties, and corrosion resistance [34]. Additionally, alloy properties are anisotropic, or directionally dependent, with the Z-direction being the weakest. Fatigue resistance of as built samples remains a challenge, as increased porosity and defects within the alloy may serve as sites for fatigue crack initiation [34]. Post

processing techniques including hot isostatic pressing may improve these properties in line with the conventionally manufactured alloy. While early revision returns suggest clinical success, the long-term *in vivo* behavior of AM Ti-6Al-4V remains unknown [71].

1.4 Modularity in Total Joint Replacement Systems

Many permanently implanted orthopedic implants comprise of multiple dependent, modular components. In total hip replacement systems, modularity provides several benefits [72]. First, the interchangeability of stem, head, and acetabular components decreases the needed device inventory [73]. Hospitals and clinics no longer store full femoral prosthesis of various sizes, and manufacturers reduce costs by generating the same number of permutations with fewer components. Next, surgeons can assemble components to fit a patient's specific biology [74]. During revision, most patients experience bone loss, ranging from negligible to unsalvageable [75-77]. Modularity allows the surgeon to select the most applicable device for a patient depending on their condition [78]. Additionally, revision of an osseointegrated device is nontrivial and may lead to patient complications [79]. Modular femoral heads and acetabular components enable partial revisions, where a new head and acetabular component are placed onto the pre-existing well-fixed stem. Finally, modularity allows for device systems of multiple materials including polymers, ceramics and metals [6]. It is common for total hip replacement devices to consist of a Ti-6Al-4V stem, ceramic biolox delta head, polyethylene liner, and Ti-6Al-4V acetabular cup [29]. Multiple materials are desired for the different functions they aim to reproduce *in vivo*. Titanium and its alloys, while excellent for fatigue resistance, make poor bearing surfaces [55]. Ceramic femoral heads mitigate ALTR and ALVAL, while enabling articulation. Thus, modularity provides important benefits to the various stakeholders in orthopedics.

While associated with improved clinical outcomes, modularity creates a crevice geometry *in vivo* where two interfaces are in proximity to one another [80]. In these small volume crevices, electrolyte solution is present. When patients cyclically load their device (i.e., walking), asperities at metal interfaces abrade the passive oxide film. Once interrupted, active corrosion occurs. Retrieval studies document corrosion in crevices at head-neck, neck-stem, and acetabular junctions [19, 81-85]. *In vivo*, Mechanically assisted crevice corrosion (MACC) is hypothesized to promote this damage, initiating an auto-catalytic cascade where initial corrosion creates favorable corrosion conditions [86].

1.5 Selective Dissolution In Vivo and In Vitro

Retrieval studies in the past two decades document chemically induced corrosion damage modes within the modular taper junctions of total hip replacement systems [20, 25, 26]. Damage modes include pitting, hydrogen embrittlement, the formation of thick oxides, and selective dissolution. MACC promotes this damage *in vivo* [84, 86]. Except for selective dissolution, to date, Ti-6Al-4V chemical corrosion damage modes remain unreplaceable within the lab under physiologically relevant conditions and poorly understood.

Micrographs of Ti-6Al-4V modular components (Figure 1.2A) and cross sectional analysis of Ti-6Al-4V pits at the device interface (Figure 1.2B) reveal preferential dissolution of the β phase [26]. Following β dissolution, the α phase also corrodes. Researchers reproduce characteristics of this damage in the lab using inflammatory simulating solutions and negative (cathodic) potential excursions [87-95]. Three methods exist within the literature. First, Ti-6Al-4V samples are held at -1 V, followed by potentiodynamic polarization to an anodic potential, where the surface is again statically held [96, 97]. Second, the Ti-6Al-4V surface is cathodically activated for a transient amount of time (~600 s) and allowed to freely recover [91]. In the final method, the Ti6A1-4V surface is continuously held at a negative potential for the duration of the experiment [88]. In all three methods, an inflammatory simulating solution (typically H₂O₂-phosphate buffered saline) is used. While free corrosion in hydrogen peroxide or HCl containing solutions degrade the β phase, cathodic activation decreases the experimental time needed to induce dissolution.



Figure 1.2. Micrographs of retrieved Ti-6Al-4V devices show selective dissolution of the β phase (A-B). Note the corrosion of the α phase following β dissolution (B). The micrographs in (A) and (B) were reproduced with permission from Kurtz et al., Orthop. Clin. North Am. 2023, and Gilbert et al., JBMR-B, 2012.

In vitro cathodic activation and inflammatory species represent adverse (but not uncommon) electrochemical events that occur at the Ti-6Al-4V interface *in vivo*. Following implantation, the inflammatory cascade initiates. Macrophages at the Ti-6Al-4V interface attempt to phagocytose foreign objects. Upon failure (The size of a femoral stem is much greater than a single macrophage), macrophages form foreign body giant cells (FBGCs), adhering to the surface, and secreting reactive oxygen species (ROS). H₂O₂ represents an intermediate ROS species, and may further react to produce hydroxyl radicals, hydroperoxyl radicals and hypochlorous acid [98, 99]. Should Fe²⁺ be present, Fenton reactions occur, oxidizing iron (II) to iron (III) (Fe³⁺). The second

critical component, cathodic activation, reproduces the negative potential excursions at the Ti-6Al-4V interface during tribology [100]. Abrasion of the Ti-6Al-4V surface interrupts the oxide film and decreases the potential to as low as -1 V. Additionally, sustained cathodic activation of CoCrMo surfaces generates ROS directly at the interface [101]. Thus, in the absence of biology, tribology alone may provide the necessary components to induce Ti-6Al-4V β dissolution.

Several gaps persist in our fundamental knowledge of Ti-6Al-4V selective dissolution. First, though we know the oxide film's polarization resistance decreases during the dissolution process, the evolution of the film, and its transition from the onset of dissolution to fully corroded remains unclear. Similarly, micrographs within the literature neatly capture the polished Ti-6Al-4V microstructure, initial corrosion, and complete dissolution. Understanding the in-between, or the path the Ti-6Al-4V surface undergoes to reach full dissolution is critical to understanding the corrosion mechanism. Mechanistic understanding not only informs pre-clinical corrosion testing but may act as a platform to reproduce other chemically induced corrosion damage modes *in vitro*. Finally, what is the relationship between the oxide, and the underlying substrate? The structure-property relationship between the Ti-6Al-4V surface and the protective oxide film remains unexplored during active selective dissolution.

1.6 Impedance Primer

In vivo, Ti-6Al-4V is protected by a passive oxide film, preventing active corrosion. Structurally, the oxide is comprised of three different layers of varying chemical composition. A thin TiO₂ layer forms the outermost surface of the oxide film [102]. Beneath it, a thick, intermediate, TiO_x layer exists [103]. Last, a TiO layer directly contacts the substrate alloy. When Ti-6Al-4V contacts oxygen, the oxide film rapidly and spontaneously forms, governed by the following oxidation half-cell reaction:

$Ti + 2H_2O \rightarrow TiO_2 + 4H^+ + 4e^-$

Film growth is hypothesized to be promoted by a point defect mechanism. Digby Macdonald developed various generations of this model, building off the work of Cabrera and Mott [104]. In the point defect model, oxide growth is facilitated by the transport of anion, cation and interstitial vacancies at the metal-oxide and oxide-solution-interfaces [105]. A high electric field is critical for film growth. First, electrons quantum-mechanic tunnel from within the alloy to the interface. Next, oxygen atoms at the interface may be trapped by tunnelling electrons, absorbing to the surface as O⁻. This generates a high electric field, driving the transport of cations from the metal substrate to the oxide-solution interface and anions from the solution to the metal. The combination of these two processes grows the oxide film. For TiO₂, film growth is directly dependent with electrode potential at the interface (approximately 1.8 to 2 nm/V). Additionally, increased anion vacancies in the TiO₂ film promote n-type semiconductor behavior.

Documenting structural and property changes to the oxide film *in vitro* presents a challenge. Under normal polished conditions, the oxide film is not visible, and the spatial scale (2-10 nm) requires advanced imaging techniques like atomic force microscopy or cross sectional transmission electron microscopy [106]. The oxide film dynamically remodels under mechanical abrasion and applied potentials. Additionally, the surrounding solution chemistry may impact the oxide film structure (e.g., thickness and chemistry), the number of vacancies present, and the film's ability to prevent corrosion. These changes likely occur on a timescale of seconds or less. While X-ray photoelectron spectroscopy (XPS) represents a useful technique for measuring alterations to the oxide film chemistry post-experiment, samples must be prepared in a vacuum and without solution [11, 107, 108]. In the absence of direct transfer from the electrochemical cell to the XPS under argon, changes to the oxide film chemistry and structure, as well as the surface's accumulated electrochemical history, are lost. Electrochemical impedance spectroscopy (EIS) circumvents this issue allowing for rapid monitoring of the oxide film properties *in-situ* [13, 109]. Changes in EIS properties are directly related to both the structure of the oxide film and the underlying metal substrate. Thus, EIS is a powerful technique for real-time monitoring of the oxide film during electrochemical experiments.

In the lab, impedance is measured by applying a 10 mV oscillating potential across the interface. A current response wave is generated and captured [110]. Resulting impedance responses acquired from the interface may be modeled using a combination of circuit elements. Common models in the literature include the Randles constant phase element circuit (CPE) and various coated models [13, 88, 91, 111, 112]. The Randles CPE circuit uses (1) a resistor, R_s , to model the solution resistance; (2) a second resistor, R_p , to model the oxide polarization resistance, and (3) a CPE, Q and α , to functionally represent the oxide's capacitive behavior (Figure 1.3). The elements R_p and Q are in parallel, and the $R_p ||Q$ elements are in series with R_s .



Figure 1.3. Model of The Ti-6Al-4V solution-oxide-metal interface. Under normal and simulated inflammatory conditions, a Randles CPE circuit approximates the impedance response. Severely corroded surfaces (e.g., following electrocautery) may elicit coated model responses.

Here, we define the impedance of a CPE as

$$Z_{CPE} = 1/(j\omega)^{\alpha}Q$$
 (Eq. 1)

where $j = \sqrt{-1}$, ω is the frequency in rad/s, α is the CPE exponent (unitless) and Q is the CPE parameter (Scm⁻²(s)^{α}). When α is close to one, Q is capacitive like. When α is near 0, the CPE behaves like a resistor. In most physiological systems, $\alpha > 0.7$ (e.g., 0.8, 0.9). The circuit parameters Q and α are intrinsically linked and may be related to capacitance using a modified version of the Brug equations [113, 114]:

$$C = Q^{\frac{1}{\alpha}} * (Rs^{-1} + Rp^{-1})^{(1-\frac{1}{\alpha})}$$
(Eq. 2)

Here, C is the capacitance, Q is the CPE parameter Q, α is the CPE exponent, R_s is the solution resistance and R_p is the oxide polarization resistance. Additionally, Q is hypothesized to be inversely proportional to the polarization resistance R_p.

Symmetry based EIS (sbEIS), which is a new method for analysis of CPE-Randles circuits that can determine the low frequency impedance response from the upper half of the response, allows for the rapid capture and analysis of multiple EIS spectra [115]. Because EIS data are acquired on a log-based frequency scale (Rad/s or Hz), recording the low frequency impedance response (< 1 Hz) exponentially increases the experimental time needed. While acquiring EIS from 10^4 Hz to 10^{-1} hz takes three minutes, extending the low frequency range to 10^{-2} increases acquisition time to thirty minutes. Though this may seem trivial for one spectra, real-time monitoring of impedance may require 10^3 spectra (50 vs. 500 hours). Thus, accurately predicting the low frequency data from the high frequency response increases flexibility in experimental design. sbEIS for Randles-like impedance data operates on the following mathematically observation: the derivative of the phase angle, Θ , with log ω is symmetric about $d\Theta/d\omega = 0$. Here, we define $d\Theta/d\omega = 0$ as the crossover frequency, or ω_x . Next, the maximum recorded value of $d\Theta/d\log\omega$ occurs at ω_1 (i.e., at $\omega = \omega_1$). The general idea behind sbEIS is that the global d $\Theta/d\omega$ minimum (at ω_2) is symmetric about the log of the crossover frequency. Both log ω_1 and log ω_2 are equidistant from $\log \omega_x$. In practice, sbEIS circuit fitting can either be done by hand, manually altering the values of ω_1 , ω_x , and α , or fitting using solver within Excel, minimizing the error between the predicted and experimental $d\Theta/d\omega$ or tan(θ) data.

Generally, EIS is acquired across the entire working electrode surface area. Post test, the real and imaginary components of the impedance, Z' and Z'', as well as the impedance magnitude, |Z|, must be area normalized. While practical for *in vitro* testing, retrieved CoCrMo and Ti-6Al-4V surface states vary. One retrieved component may exhibit multiple corrosion, wear, and biologically induced damage modes. In these cases, the nuances of the local impedance with respect to each of these areas are lost when the entire surface is used as the working electrode.

Nearfield EIS (nEIS) reduces the working electrode surface area, characterizing the localized impedance. Previous studies show nEIS "signatures" for different corrosion damage modes on retrieved CoCrMo components [116, 117]. nEIS is compatible with sbEIS, allowing for rapid acquisition of partial spectra as the working electrode setup is spatially moved across metal surface. This approach of scanning impedance imaging has not been described previously in the literature and some basic analysis of this approach is described in this dissertation.

1.7 Gaps in pre-clinical testing

Several gaps exist in pre-clinical testing, preventing accurate screening of device designs and titanium biomaterials. First, many standardized electrochemical tests for medical devices recommend stable electrolyte solutions. While PBS, Hanks' and NaCl electrolytes approximate the isotonic properties of the physiological environment, they do not adequately represent the array of oxidizers, acids, proteins, and cells that exist at device interfaces [87, 92]. Next, a lack of mechanistic understanding prevents accurate crevice corrosion tests. Most severe corrosion of total joint replacement devices is hypothesized to be caused by MACC. However, few *in vitro* models in the literature reproduce crevice corrosion damage modes (to date, selective dissolution is the exception for Ti-6Al-4V) [118]. Finally, a paradigm of testing to non-failure persists. The goal of pre-clinical testing is to avoid generating corrosion at modular junction interfaces. Thus, device designs and material combinations that corrode *in vivo* under adverse electrochemical conditions may inadvertently end up in patients [119, 120].

A clear need persists for representative, accelerated tests specifically designed for titanium alloys. Current FDA recognized standards like ASTM F2129 *Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices* and ASTM F746 *Standard Test Method for Pitting or Crevice Corrosion for* Metallic Surgical Implant Materials help evaluate device designs and materials for corrosion. However, both tests recommend scanning in the positive, or more noble direction. In contrast, in vivo, titanium alloy damage is hypothesized to occur because of cathodic activation, brought on by decreases to the working electrode potential induced from tribology, or challenged macrophages [100, 121]. Additionally, the TiO_2 oxide film remains passive at anodic potentials above the open circuit potential. Rather than degrade the film, positively applied potentials anodize the surface, increasing the film's thickness. Thus, little corrosion is likely to occur for Ti-6Al-4V devices under anodic conditions within the passive potential range. Additionally, ASTM F746 recommends a static crevice assembly. This contradicts the *in vivo* mechanics. Once implanted, the modular taper junctions of total hip replacement devices experience constant cyclic load and micromotion. No consensus tests exist to evaluate fretting or tribocorrosion [122]. Last, ASTM F2129 calls for cyclic polarization under deaerated solution. While this method may generate reproduceable polarization plots, oxygen is present *in vivo*, and is necessary for oxide formation and growth. Titanium alloy corrosion is rare and difficult to reproduce in the lab. However, incorporating the elements known to reproduce aspects of this damage would improve pre-clinical device testing.

Previous *in vitro* studies reproduce Ti-6Al-4V β dissolution using high concentrations of inflammatory simulating solutions and cathodic potential excursions. Several limitations exist within these models. While negative potential drops occur at the interface, they are likely cyclic rather than continuous. Additionally, ROS and inflammatory solution concentrations used to corrode Ti-6Al-4V in the lab exceed the maximum documented levels *in vivo* by several orders of magnitude [123]. However, the crevice solution volume, at the interface of modular taper junctions where most severe corrosion takes place, is much smaller than the bulk. Changes to the

solution chemistry within the crevice may have greater effects. Next, macrophages and foreign body giant cells adhere to the device surface, releasing ROS. Differences in the local solution produced during the post-implantation inflammatory cascade may be a second source of highly concentrated oxidizers at the device interface.

Severe corrosion, including β dissolution on Ti-6Al-4V components, has been documented on a time scale of 1 month to six years [25, 26]. Though we do not know whether the corrosion directly caused clinical failure, or when the corrosion occurred in relation to the revision surgery, titanium corrosion can clearly occur over a clinically short period of time. Within the lab, one month of experimental time is resource intensive, and, except for free corrosion, does not fit within the existing pre-clinical testing paradigm. In this context, accelerated corrosion testing is a useful tool. Non-physiological ROS concentrations and solution temperatures may be related to biological conditions using the Arrhenius equation. Establishing such a relationship would allow for rapid testing of (1) new titanium biomaterials; (2) new device designs and (3) help elucidate physiologically relevant titanium corrosion mechanisms.

1.8 Goals

We laid out the following goals for this thesis: (1) We wanted to elucidate the factors that induce Ti-6Al-4V crevice corrosion and translate them into more representative pre-clinical tests; (2) Because the field is increasingly moving towards additive manufacturing (AM), we wanted to apply these tests towards new AM titanium biomaterials; (3) We wanted to relate the structural changes occurring during selective dissolution to the oxide impedance, building a predictive, machine learning-based model. (4) Recent electrochemical research identifies new, powerful techniques to analyze corrosion including phase angle symmetry and near field-based impedance. Here, we wanted to combine these techniques to demonstrate their potential for

biomaterials research and corrosion detection. (5) We sought to develop new impedance methods, focusing on decreasing the acquisition time.

These research goals can be translated into three broad research questions. First, what mechanism drives selective dissolution of Ti-6Al-4V? Second, will additively manufactured titanium alloys, including Ti-6Al-4V, be susceptible to selective dissolution under similar conditions? Third, using impedance, can a deep neural network predict the surface dissolution state? To address these questions, we used a systematic approach, breaking the overarching questions into smaller pieces. Then, we constructed hypotheses, predicting outcomes using fundamental electrochemical, biology, and material science principles. Finally, we designed experiments to evaluate our hypotheses.

Much of this thesis comprises basic science research, far removed from the clinic. We isolated testing variables, and simplified the complex, dynamic interplay between the biology, physiological solution and Ti-6Al-4V interface. Indeed, polished titanium in saline solutions requires quite a few assumptions before it approximates porous titanium in cancellous bone. However, the testing conditions we selected relate directly to the hypothesized *in vivo* mechanism. Additionally, the conditions used supersede current standards for pre-clinical testing, more accurately reproducing negative electrochemical events that occur at the titanium interface. Finally, the work in this thesis may inform future clinical research directions, relating patient data and outcomes to corrosion damage.

Chapter 2

Aims & Hypotheses

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2.1A: Determine the critical conditions needed to induce Ti-6Al-4V selective dissolution.

Rationale: Preliminary experiments combining hydrogen peroxide (simulating *in vivo* inflammation) and cathodic activation (simulating negative potential drops during fretting) show the ability to preferentially dissolve the Ti-6Al-4V β phase. We <u>hypothesize</u> that the synergistic effect of H₂O₂ and cathodic activation degrades the oxide film, altering both its structure and properties such that the Ti-6Al-4V β phase is selectively dissolved.

2.1B: Systematically evaluate the effects of cathodic potential, solution concentration, and temperature on the Ti-6Al-4V oxide film structure and properties. *Rationale*: During fretting, the working electrode potential decreases as the oxide film repassivates. While the tribological mechanisms of fretting are well documented in the scientific literature, a gap persists in our knowledge of the oxide film's remodeling following cathodic activation. To address this aim, we propose a stepwise impedance methodology, acquiring impedance spectra in 100 mV intervals as the oxide film recovers from -1 V. We *hypothesize* that increases in temperature and H₂O₂ solution concentration will degrade the oxide film's polarization resistance in a potential-dependent manner.

2.1C: Investigate the effect of temperature on the selective dissolution mechanism.

Rationale: Our preliminary results show an effect of solution and temperature on the selective dissolution reaction rate kinetics. In this aim, we will test the <u>hypothesis</u> that the β phase dissolution rate is governed by the Arrhenius equation, investigating whether increases in temperature increase the rate of corrosion. Understanding the Ti-6Al-4V dissolution behavior in accelerated temperatures and solution concentrations may provide insight into how Ti-6Al-4V behaves under physiological conditions.
2.2A: Compare the fundamental corrosion properties of new, additively manufactured titanium biomaterials with Ti-6Al-4V. *Rationale*: Additively manufacturing is increasingly used to produce Ti-6Al-4V orthopedic implants, including acetabular cups and tibial trays. The rapid melting and solidification of powder beads during the AM process generates a martensitic microstructure, differing from the equiaxed $\alpha + \beta$ microstructure of conventionally manufactured Ti-6Al-4V. It is unclear how AM Ti-6Al-4V will perform in inflammatory simulating solutions. Additionally, new AM alloys and admixtures including Ti-29Nb-21Zr, and Ti-6Al-4V with added nano zirconia particles may not otherwise be reproduced using traditional manufacturing methods. We *hypothesize* that H₂O₂ containing solutions will degrade the AM Ti-6Al-4V oxide film's polarization resistance in a mechanism similar to conventional Ti-6Al-4V. In contrast, we expect the Ti-29Nb-21Zr biomaterial to have improved corrosion resistance, consistent with Ti-xNb-xZr alloys in the literature.

2.2B: Assess the dissolution mechanism of AM Ti-6Al-4V. *Rationale*: If inflammatory species degrade the AM Ti-6Al-4V film (2.2A), it is likely that the alloy is subject to selective dissolution. Additionally, AM Ti-6Al-4V may experience fretting, cathodic activation, and other adverse electrochemical events *in vivo*. Despite the martensitic microstructure, AM Ti-6Al-4V remains a two phase, $\alpha+\beta$ alloy. Additionally, the oxide film properties, chemical composition (TiO₂) and structure may be related to conventional Ti-6Al-4V, leaving the AM alloy susceptible to β dissolution under similar conditions (cathodic activation and inflammatory solutions). We *hypothesize* a dissolution mechanism where the oxide R_p degrades prior to pit nucleation in the β phase.

2.3A: Systematically review the corrosion-artificial intelligence (AI) literature. *Rationale*: Prior to engaging in or own application of AI, we wanted to survey the corrosion literature

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outside of biomaterials to identify common machine learning models. Additionally, AI models implemented within oil and gas, aerospace and marine corrosion may be translatable to the study of metallic biomaterials. We <u>hypothesized</u> that supervised machine learning, including neural networks, would dominate model selection.

2.3B: Predict selective dissolution using a deep neural network and near field impedance

spectroscopy. <u>*Rationale*</u>: Previous research identifies characteristic corrosion "signatures" using near field electrochemical impedance spectroscopy (nEIS) on both CoCrMo retrieved devices and *in vitro* damaged surfaces. These signatures may distinguish the local impedance of a corroded surface from a control surface. Here, we combine nEIS, phase angle symmetry-based EIS (sbEIS) and a deep neural network approach to predict the surface dissolution state using bode phase spectra as inputs. We <u>hypothesize</u> that the structural changes to the Ti-6Al-4V oxide and the underlying substrate alloy will manifest as changes to the constant phase element parameter, Q. While we propose a binary classification model here, future work involving multiple corrosion damage modes and severities may use our trained model as a platform.

In this thesis, we systematically investigated each of these seven aims. The next seven chapters may be divided into three broad topic areas associated with past, present, and future challenges within titanium biomaterial corrosion. First, we investigate the mechanism of Ti-6Al-4V selective dissolution, reproducing elements documented on *in vivo* retrievals. Chapters 3-5 detail the elements of the *in vitro* mechanism, and the effects of solution concentration, temperature dependence and cathodic activation. Second, we translate our tests developed on conventionally manufactured Ti-6Al-4V to AM titanium alloys. In Chapters 6-7, we investigate the fundamental corrosion properties of AM Ti-6Al-4V and elucidate its dissolution behavior. We compare AM Ti-6Al-4V to new AM Titanium alloys including Ti-29Nb-21Zr. Third, the development of

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artificial intelligence (AI) models allows for new techniques for the rapid detection and

classification of corrosion damage modes. In Chapter 8, we review prevailing AI techniques in

the corrosion literature. Then, in Chapter 9, we apply a deep neural network to classify Ti-6Al-

4V selective dissolution.

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Chapter 3

Cathodic Activation and Inflammatory Species Are Critical to Simulating In Vivo

Ti-6Al-4V Selective Dissolution

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Abstract: In vivo retrievals of metallic orthopedic implants have shown selective dissolution of Ti-6Al-4V, where the vanadium-rich β phase preferentially corrodes from the surface. This damage, typically observed in crevices, is not directly caused by wear mechanics and the underlying electrochemical mechanism remains poorly understood. Previous studies show that fretting corrosion can cause negative potential drops, resulting in a decrease in surface oxide passivation resistance and the electrochemical generation of reactive oxygen species (ROS) at metallic surfaces. In this study, we combine cathodic activation and hydrogen peroxide to induce selective dissolution in vitro. After a 600 s -1 V hold and 4 h recovery in 20 °C 1 M H₂O₂ solution, the Ti-6Al-4V β phase was preferentially dissolved. An initial activation threshold of -0.5 V induced a significant increase in β dissolution (p=0.000). Above this threshold, little selective dissolution occurred. In an Arrhenius-like fashion, decreasing solution concentration to 0.1 M required 72 h to generate β dissolution instead of 4 h at 1 M. Heating 0.1 M solution to body temperature (37°C) resulted in a decrease in the time needed to replicate a similar level of β dissolution (>90%). Electrochemical impedance shows that both cathodic activation and inflammatory species are necessary to induce selective dissolution, where the combinatorial effect causes a significant drop in oxide passivation resistance from 10^6 to 10^2 (p=0.000).



Keywords: Ti-6Al-4V; Selective dissolution; *In vitro* model; Metallic biomaterials; Cathodically activated corrosion

3.1 Introduction

Titanium, stainless steel, and cobalt chrome alloys make up the majority of permanently implanted metallic biomaterials due to their mechanical properties and proven biocompatibility. Titanium alloys, particularly commercially pure titanium and Ti-6Al-4V, are favored due to their superior corrosion resistance, the product of a nanometers thick TiO₂ oxide film that spontaneously forms on the metal surface, protecting it from corrosion attacks [1-3]. Conventionally-manufactured Ti-6Al-4V is typically utilized in a thermo-mechanically processed and mill-annealed state. It contains a near-alpha equiaxed two-phase microstructure with a globular aluminum-rich, hexagonally close packed α phase (with grains typically 2 to 5 mm in diameter) and a blocky body centered cubic vanadium-rich β phase [4].

Previous studies document *in vivo* corrosion of titanium and its alloys within modular junctions of total hip replacements at head-neck, neck-stem, and acetabular interfaces [5-15]. Modular junction geometry consists of a tapered cone and bore. When assembled, these tapers form a small volume crevice where solution is present in close proximity to the opposing surface [16]. These crevices promote a micro-environment within the implant where the physiological solution is more susceptible to alterations and adverse electrochemical events. Within these crevices *in vivo*, the most severe corrosion of Ti-6Al-4V occurs during mechanically assisted crevice corrosion (MACC) [17-19]. MACC initiates when fretting disrupts the surface oxide film, promoting both metal oxidation reactions and redox reactions within the crevice. Within this small volume microenvironment, redox reactions may consume oxygen within the solution until depletion. The resulting burst oxide repassivation currents leave behind electrons in the metal, which drive the potential of the metal-solution interface to become negative (cathodic). Metal ions accumulate within the relatively small volume of the crevice solution, and the resultant charge imbalance

draws in chloride ions. The interaction of chloride and metal ions generates metal hydroxides and hydrochloric acid, decreasing the solution pH. Local drops in potential and pH, cathodic activation of the surface and deaeration of the crevice may all further exacerbate corrosion. Thus, MACC promotes a positive feedback loop where initial corrosion reactions create conditions that promote further corrosion (i.e., auto-catalytic behavior) [17, 19-21]. While the mechanical component (i.e., fretting corrosion) of MACC is relatively well understood, the crevice corrosion mechanisms remain unclear.

Retrieval studies in the past two decades document non-mechanically assisted damage modes of Ti-6Al-4V within modular taper junctions, including the formation of hundreds of microns thick oxide films (Fig. 3.1A), hydrogen embrittlement, deep pitting (Fig. 3.1B) and selective dissolution (Fig. 3.1C) [11, 13, 14]. While the concept of Ti-6Al-4V β phase selective dissolution is established [22-25], this approach has not been considered as a potential degradation mechanism in modular taper fretting crevice corrosion. The specific conditions simulating such non-mechanical taper crevice degradation remain unelucidated. Indeed, the concept of cathodically activated corrosion (CAC), where transient negative potentials arising from tribocorrosion processes may result in degradation of adjacent (non-tribologically degraded) passive oxide films and induce accelerated corrosion, has not been well explored in biomedical alloys. When reactive oxygen species are introduced into such conditions, additional degradation of the passive oxide films on titanium alloys may result in accelerated degradation and selective dissolution.

Scanning electron micrographs of revised Ti-6Al-4V orthopedic hip implants document selective dissolution of the β phase within the crevice region of modular taper interfaces [14, 26]. Hundreds of microns wide pits (Fig. 3.1B), observed in vivo, penetrate the alloy surface. When cross sectioned, these pits reveal an initial preferential attack on the β phase followed by a conversion

of remaining α crystals to oxide via surface oxidation reactions (Fig. 3.1C). The β phase preferentially dissolves during these reactions and direct conversion of both α and β to oxide may take place at the metal surface. The leading edge of the corrosion attack in these cases exhibits selective dissolution of the β phase as the initiating step.



Figure 3.1. SEM Micrographs of retrieved modular neck-stem junctions show severe corrosion damage modes including, A) the formation of hundreds of microns thick oxide films (note the direct conversion of β phase to oxide in the top left corner); B) large scale pitting that when cross sectioned, reveal C) selective dissolution of Ti-6Al-4V β phase. These crevice corrosion damage modes are not induced solely by wear and their mechanisms remain poorly understood. Reproduced from Gilbert et al. with permission from Wiley & Sons [14].

Such severe corrosion mechanisms, observed in retrievals, have not been duplicated in any *in vitro* test method to date. Developing testing methods and solution conditions that recapitulate the modes and severity of corrosion *in vivo* would be an important step in assessing the safety and efficacy of implant alloys and device designs using Ti-6Al-4V. In this context, accelerated test conditions, with higher than physiological levels of oxidizing species, would be appropriate if one were able to link the test parameters, including solution concentration, temperature and time of the test, to the physiological conditions.

Cathodically activated corrosion arises *in vivo* when free electrons generate in the metal during metal oxidation reactions, decreasing the surface electrode potential. Ti-6Al-4V can drop as low as -1 V during oxide abrasion and passivation processes [21]. These potential excursions are dependent on the magnitude of the fretting corrosion currents and the impedance of the electrode. Additionally, they are limited by the onset potential for oxide film formation [27, 28]. The effects of cathodic potential on Ti-6Al-4V oxide film properties have been previously studied, where it was shown that oxide film resistance could drop up to three orders of magnitude with cathodic excursions [29]. These potential drops modify the film, resulting in a loss of its passive character and increasing its susceptibility to corrosion attack.

Another consequence of cathodic activation is increased reduction reactions directly at the metal solution-surface interface, generating reactive oxygen intermediates such as hydrogen peroxide and hydroxide radicals [30]. These highly oxidizing molecules may provide additional impetus to damage and degrade the surface oxide film properties.

The surrounding biology represents a second potential source of reactive oxygen species *in vivo*. During the post implantation inflammatory cascade, macrophages and foreign body giant cells may generate hydrogen peroxide (H₂O₂) in close proximity to the metal-oxide interface. Previous studies show that activated macrophages cultured on implant alloy surfaces measurably increase ion release and lower corrosion resistance, measured by the polarization resistance of the alloy [31, 32]. Thus, ROS generation, whether by biological processes or electrochemical ones, may be present at the alloy surface and may contribute to the corrosion attack of the alloy.

We hypothesize that the combined effect of H_2O_2 and cathodic activation modifies the oxide structure and function in Ti-6Al-4V inducing preferential dissolution of the β phase. In this study,

we assessed the effects of cathodic voltage, time in solution, solution concentration, and temperature on β phase dissolution. We sought to answer the following research questions: first, can the Ti-6Al-4V β phase be selectively dissolved *in vitro* under conditions consistent with modular tapers (cathodic activation and high ROS chemistry), generating corrosion damage similar to orthopedic retrievals? What are the necessary *in vitro* conditions to induce selective dissolution? Finally, what are the effects of H₂O₂ concentration and cathodic activation on the time-temperature characteristics of selective dissolution, as well as oxide structure and impedance characteristics?

3.2. Materials and Methods

Several different β phase selective dissolution experiments were performed in this study. These include tests of H₂O₂ concentration (1 M and 0.1 M), starting cathodic activation potential vs. Ag/AgCl (-1 V, -0.75 V, -0.5 V, -0.25 V), time post cathodic activation and temperature (22 °C and 37 °C). Additionally, it is known, that mechanical abrasion of oxide films on titanium and other passive alloys can result in large sustained cathodic potentials as low as -1 V [21]. While the length of time for such excursions is highly variable within patients, we chose a consistent 600 s interval to provide sufficient time to alter the oxide structure and induce selective dissolution. The details of each experiment are described in the sections below. Throughout these experiments, supra-physiological concentrations of H₂O₂ were used. The intent here was to use higher concentrations to induce the selective dissolution process in a reasonable amount of experimental time, and study the mechanism and the time-temperature-concentration effects. Clearly, 1 M and 0.1 M are not physiological levels of H₂O₂; rather, these are concentrations that represent accelerated conditions. Additionally, cathodic activation may generate ROS in excess of what is produced during the body's inflammatory response [30]. For all tests and test conditions, a

minimum of 3 samples were evaluated to provide for statistical analysis of the results. The primary analysis method utilized quantitative image analysis protocols (ImageJ) based on digital optical micrographs and backscattered scanning electron micrographs. The details of these methods are also described below.

3.2.1 Metallographic Preparation

Ti-6Al-4V ELI (ASTM F-136) samples were cut into cylinders (35 mm) and fixed in epoxy resin to isolate a single surface for electrochemical testing. The electrical connection was maintained by fixing insulated wires to the back of samples with copper tape prior to epoxying. Ti-6Al-4V surfaces were mechanically ground with progressively finer grit alumina paper (240, 320, 400 and 600 grit) before being polished with 1 μ m and 0.3 μ m alumina suspensions in water for a mirror finish and rinsed with deionized (DI) water.

3.2.2 Inducing Selective Dissolution in 3M H₂O₂

Control solutions were prepared by mixing 7.4 pH phosphate-buffered saline (PBS) pouches in 1 L of DI water. H₂O₂ solutions were prepared by diluting 30% H₂O₂ in water with PBS. Our electrochemical cell setup consisted of a carbon rod counter, Ag-AgCl reference, and Ti-6Al-4V working electrodes. Prior to treatment, samples (n = 3 for all tests and conditions) were imaged using an SEM at 2k, 3k, and 5k magnifications in both secondary (SE) and backscattered electron (BSE) modes. Selective dissolution was initially induced following the protocol described by Gilbert et al. [22, 23, 25]. Samples were cathodically held at -1 V for 600 s, followed by a potentiodynamic sweep at 1 mV/s to +0.1 V and a +0.1 V hold for 10³ s all in the presence of 3 M H₂O₂. The potentiodynamic sweep systematically exposes samples to the potential recovery they may undergo following fretting. This element was removed in the recovery method. H₂O₂ solution

concentration was increased above physiological levels to accelerate the time needed to induce selective dissolution.

3.2.3 Selective Dissolution Recovery Method

To simulate *in vivo* representative conditions, the potentiodynamic sweep and anodic hold were replaced with a 600 s cathodic potentiostatic hold, followed by a 4-hour recovery period (the so-called "recovery method"). In the recovery method, cathodic hold potentials were selected based on fretting potential drops recorded on Ti-6Al-4V surfaces [20]. Samples (n = 3 for all tests and conditions) were first held at various increasingly positive cathodic potentials (from -1 V to -0.25 V) and allowed to recover for 4 h in 1 M H₂O₂ PBS solution at room temperature (20 °C). Cathodic potentiostatic holds (VersaSTAT4, AMETEK, Berwyn, PA) were applied for 600 s and before the potential was allowed to recover. The open circuit potential (OCP) was continuously acquired during this process.

3.2.4 Evaluating the Effect of Cathodic Activation

The effect of initial cathodic potential magnitude was evaluated by statically holding samples (n = 3 for all tests and conditions) at increasingly electropositive potentials before allowing them to recover in 1 M H₂O₂ for 4 h. Samples were held at -1 V, -0.75 V, -0.50 V, -0.25 V, and 0.08 V respectively. After the 600 s hold and recovery, samples were imaged using digital optical microscopy (DOM, Keyence VHX-6000, Keyence Corp., Mahwah, NJ) and scanning electron microscopy (SEM, Hitachi S-3700N, Hitachi Inc., Tokyo). Both backscattered electron (BSE) and secondary electron (SE) modalities were used.

3.2.5 Contrast Thresholding SEM Analysis

SEM images were analyzed for β phase dissolution using ImageJ, a public domain image analysis tool developed by the NIH. A reference micrograph (Fig. 3.2A) shows Ti-6Al-4V's two phase

microstructure: globular α appears distinctly darker in comparison to the interspersed blocky β phase. An SEM micrograph showing the partial but not complete dissolution of the β phase was chosen for demonstration purposes. β has been preferentially dissolved at narrow interphase regions but remains visible where the initial β surface area was largest (Fig. 3.2B). The micrograph's contrast was adjusted twice, first to identify remaining β pixels (Fig. 3.2C) and then identify dissolved β pixels (Fig. 3.2D). Binary black and white maps were generated for both remaining β (Fig. 3.2E) and dissolved β (Fig. 3.2F). The white pixel count from the remaining β map (Fig. 3.2E) and the black pixel count from the dissolved β map (Fig. 3.2F) were combined to calculate a representative pixel count for total β . The percent dissolved β phase was calculated by dividing dissolved β by the total β . Samples were initially imaged using a DOM for evidence of selective dissolution prior to ImageJ contrast thresholding.



Figure 3.2. A) A reference micrograph of untreated Ti-6Al-4V shows both α (gray regions) and β phases (white interspersed regions); B) A Ti-6Al-4V surface shows partial β dissolution where

some β remains; C) The previous micrograph's (Fig. 3.2B) contrast threshold was adjusted until all remaining β pixels were highlighted; D) The contrast threshold was adjusted a second time to identify dissolved β pixels; E) Black and white maps of both remaining β and, F) dissolved β were generated respectively. 5k magnification.

3.2.6 Assessing the Effect of Time in Solution

For the recovery method experiments, surfaces were recorded continuously over time using the DOM, capturing a single 300x magnification image every three minutes for 12 h. These images were strung together to generate video animations of the dissolution process. Based on contrast changes associated with β dissolution, time points indicative of the various stages of selective dissolution were chosen for further evaluation under the SEM.

After 1, 2, 3, and 4 h in solution, samples were cleaned before being imaged. SEM micrographs were analyzed for dissolved β using contrast thresholding and ImageJ analysis (described above) and resultant dissolved β vs. time plots were fit with a Weibull cumulative distribution function (CDF) (Eq. 1) by minimizing the mean squared error (MSE) (Eq. 2).

$$f(t) = (1 - \exp(-kt^{\gamma})) * 100$$
 (Eq. 1)

$$\bar{\varepsilon}^2 = \frac{1}{n} \sum_{i=1}^n (x_i - f(t)_i)^2$$
(Eq. 2)

In these formulae, f(t) is the predicted Weibull CDF, x_i is percent β dissolved, t is time in h, k is the scale parameter and γ is the shape parameter. Residuals were minimized using a generalized reduced gradient algorithm for nonlinear optimization [33]. Characteristic times for 1%, 50%, and 99% dissolution were predicted by rearranging Eq.1 and solving for t where f(t) = 1, 50, and 99 respectively (Eq. 3).

$$t = \left(-\frac{\ln\left(1 - \frac{f(t)}{100}\right)}{k}\right)^{\gamma}$$
(Eq. 3)

3.2.7 Assessing Solution Chemistry and Temperature

0.1 M H₂O₂/PBS solutions were created by combining 5.1 mL of 30% H₂O₂ in water with 494.9 mL of PBS in DI water. In the 0.1 M solution, samples were held at -1.0 V for 600 s and then allowed to recover for 24, 48, and 72 h, respectively. Experiments were repeated in 37 °C solution at shorter time points. 0.1 M solution was heated to 37 °C in a water bath and samples recovered in solution post 600 s, -1 V hold for 6, 12, and 24 h. Solution temperature during experiments was maintained using a hot plate and measured post-test using a digital thermometer. Post-experiment analysis of β phase dissolution was similar to the 1 M recovery method experiments assessing the effect of time in solution. After SEM micrographs were analyzed for dissolved β using contrast thresholding, resultant dissolved β vs. time plots were fit with a Weibull distribution (Eq. 1) by minimizing MSE (Eq. 2).

3.2.8 Measuring Oxide Impedance

To evaluate the metal-oxide-solution impedance as a function of electrode potential and solution, electrochemical impedance spectroscopy (EIS) was performed (VersaSTAT4, AMETEK, Berwyn, PA). Data were captured over a range of frequencies (10⁵ Hz to 1 Hz) every 30 s during a 600 s -1 V cathodic hold. Full frequency impedance response was determined from these truncated impedance spectra, and the circuit elements were extracted using a novel phase-angle symmetry impedance analysis method [34]. This technique predicts the low frequency response of both Randles and coated circuit models based on their high frequency behavior and the symmetry properties of their impedance functions. This method additionally allows for rapid sampling of the

whole impedance response, requiring only a few seconds to obtain a measurement under cathodic activation and inflammatory conditions.

The resulting impedance data were fit with either a constant phase element (CPE) Randles circuit or a coated model to determine polarization resistance (R_p), solution resistance (R_s), CPE impedance (Q) and the CPE exponent (α). The coated model (see Fig. 3.8A) circuit elements R₂ and CPE2, corresponding with the dominating inner layer resistance response, were compared against Randles circuit elements R_p and CPE. Equivalent circuit model selection was determined by the number of local maxima in the Nyquist plots of each individual spectra. Plots with one local maximum were fitted with a Randles circuit, while those with two local maxima were fitted with the coated model. R_p , R_s and Q were made area independent by either multiplying (for R) or dividing (for Q) by the electrode area to give Ωcm^2 for R's and $\text{Scm}^{-2}(s)^a$ for Q. Final calculated values for R_p, R_s and Q were compared for the following four treatment groups: 1) 600 s hold at -1 V in PBS; 2) OCP in PBS; 3) 600 s hold at -1 V in 1 M H₂O₂ and 4) OCP in 1 M H₂O₂. Due to increased acquisition time for each spectrum, data for OCP in PBS were captured following a 600 s -1 V hold from 10⁵ Hz to 10⁻¹ Hz. Bode plots were constructed from the acquired data, showing the average (n=3) |Z| (Ω cm²) vs. frequency (log(ω)) and phase angle (θ) vs. frequency (log(ω)) respectively, for all four potential-solution combinations.

3.2.9 Statistical Methods

Apart from the DOM images (Fig. 3.5, n=1), all experiments were run in triplicate (n=3). Statistically significant differences in mean β dissolution and impedance values were determined using a one-way analysis of variance (ANOVA) with a post hoc Tukey's least significant difference test ($\alpha < 0.05$). Statistically significant differences in Weibull shape parameters (γ) were calculated by linearizing Weibull CDFs and testing the equality of slopes with a t-test. Error bars

plotted on figure graphs show sample standard deviation. The effects of cathodic potential, solution concentration, temperature and time were all assessed.

3.3. Results

3.3.1 Replicating Selective Dissolution In Vitro

The combination of cathodic hold, potentiodynamic sweep and anodic hold in the presence of 3 M H_2O_2 selectively dissolved β phase from the Ti-6Al-4V surface. SEM images of samples (Fig. 3.3A) show anodic dissolution of β , leaving the α microstructure etched proudly on the surface. Select areas of α -phase corroded at comparatively slower rates, resulting in an uneven topography. Replacing the potentiodynamic sweep with a 4-hour dwell time, the β phase was selectively dissolved in 1 M H₂O₂ PBS/solution. Micrographs of the resultant surface (Fig. 3.3B) show regions of attacked α phase and complete dissolution of β , though the resultant surface roughness is comparatively less than the 3 M H₂O₂/PBS solution protocol. Potentials after the 600 s, -1 V hold recovered to -0.50 V within seconds (Fig. 3.3C) and steadily increased before plateauing at +0.094 V after 4 h in 1 M H₂O₂/PBS solution (Fig. 3.3D).



Figure 3.3. A) BSE SEM of Ti-6Al-4V shows that β phase was selectively dissolved using the method of cathodic activation (-1 V vs. Ag/AgCl) followed by anodic activation (+0.1 V) in the presence of 3 M H₂O₂ at 20 °C. Note the complete loss of β phase and the irregular α phase topography. B) BSE SEM of Ti-6Al-4V after the recovery method (i.e., 600 s -1 V cathodic activation followed by a 4 h recovery) in 1 M H₂O₂ shows preferentially dissolved β ; C) OCP versus time for recovery method test; D) A longer time-frame view of the recovery method OCP variation with time out to 14,000 s. The potential recovered to +0.094 V after 4 h in solution. 5k magnification, (n=3).

3.3.2 Influence of Cathodic Hold Potential

To assess the role of the initial 600 s cathodic potential on the selective dissolution processes, samples were held at more positive cathodic potentials than -1 V, followed by a 4 h recovery in 1 M H₂O₂/PBS solution. The results show decreasing rates of selective dissolution with more positive starting potentials. An initial cathodic hold of -1 V (Fig. 3.4A) preferentially dissolved the β phase from the surface concurrent with α phase pitting. An initial hold at -0.75 V (Fig. 3.4B)

for 600 s followed by a 4 h recovery resulted in most of the β phase dissolving. Pits forming in the β phase begin to connect but a small amount of β remains undissolved at the edges of the phase. The corrosion attack of the α phase is surface-level since polishing scratches are still present. After initial cathodic holds of -0.50 V (Fig. 3.4C), -0.25 V (Fig. 3.4D) and +0.08 V (Fig. 3.4E), pits are observed in diminishing concentration with more positive potential within the β phase (compare Fig. 3.4C with Fig. 3.4E) and located primarily at the α - β phase boundaries at the more positive hold potentials (e.g., see Fig. 3.4D). Untreated samples (Fig. 3.4F) show no pitting in either the α or β phase. Image analysis of SEM micrographs was used to find the fraction of β dissolved for each potential condition (and fixed solution concentration, time and temperature) (Fig. 3.4G). These data show an increase in β phase dissolution (p < 0.05) as the cathodic hold potential became more negative. At potentials of -0.75 V and -1 V, selective dissolution significantly increased (p = 0.000). Though we observed small pits at potentials above -0.50 V, resulting in 10-18% dissolved β , there were no significant differences at these potentials.



Figure 3.4. To assess the role of initial cathodic potential on selective dissolution, samples (n=3) were potentiostatically held at potentials more positive than -1 V for 600 s before recovering in 20 $^{\circ}$ C 1 M H₂O₂/PBS solution for 4 h. A) -1 V; B) -0.75 V; C) -0.50 V; D) -0.25 V; E) 0.08 V; F)

Reference sample; G) Image analysis of SEM micrographs shows a potential-dissolution relationship where increasingly negative cathodic hold potentials resulted in increased β dissolution. 5k magnification, (n = 3).

3.3.3 Influence of Solution Dwell Time

Samples were held at -1 V for 600 s in 1M H₂O₂/PBS solution. In the subsequent dwell period, 300x DOM images, taken every 3 m for 12 h, show increased β dissolution over time (Fig. 3.5). Initially, the polished surface appears light gray and is undamaged besides a large scratch mark in the top left corner used to autofocus the DOM. During hour one (Fig. 3.5A) and after the initial 600 s -1 V hold, the surface remains relatively unchanged. From h 1-4, surface contrast increases as β dissolves, and the surface color becomes a light brown (Fig. 3.5B). After 8 h, darkening crevices on the surface are distinguishable as interphase regions where β was originally present and the remaining surface features are identifiable as globular α (Fig. 3.5C). Surface color remains relatively unchanged from h 8 to 12 but surface contrast continues to increase (Fig. 3.5D).



Figure 3.5. DOM images captured every 3 m for 12 h show increased β dissolution over time (-1 V hold for 600 s in 1 M H₂O₂ at 20 °C). Shown here are representative images from A) 1 h; B) 4 h; C) 8 h; and D) 12 h. During the initial 600 s -1 V cathodic hold, the surface remained relatively unchanged. As the surface potential increased anodically, surface contrast increased, indicating β dissolution. Contrast continued to increase for the duration of the experiment. Magnification = 300x.

SEM micrographs of samples held in 1 M H₂O₂/PBS solution show that increased dwell time resulted in increased β phase dissolution. Samples (Fig. 3.6A) show small (>2 microns) pits forming in α while β remains uncorroded after 1 h. After 2 h in solution (Fig. 3.6B), pits begin to form in the β phase along phase boundaries. Dissolution continues after 3 h (Fig. 3.6C) when β pits begin to interconnect, and the α phase experiences an increased attack resulting in increased surface roughness. After 4 h, the β phase is selectively dissolved from the surface (Fig. 3.6D) leaving behind crevices approximately 1 micron deep and ranging between 3-10 microns in length. Dissolved β in micrographs captured after 4 h is significantly higher than those acquired after 1, 2 or 3 h (p=0.002). After 4 h in solution, A Weibull CDF was fit to the dissolved β data (Fig. 3.6E), (MSE = 55.4, k = 3.83E-02, γ = 2.8). The predicted times needed to dissolve 1%, 50%, and 99% of β were 0.6, 2.9 and 5.7 h, respectively.



Figure 3.6. Samples (n=3) held in 20 °C 1 M solution post 600 s -1 V hold show increased dissolution of β phase over time A)1 h, B) 2 h, C) 3 h, D) 4 h. E) Contrast thresholded micrographs show a significant increase in dissolved β after 4 h. Predicted times for 1%, 50%, and 99% β dissolution were 0.6, 2.9, and 5.7 h respectively. 5k magnification.

3.3.4 Influence of Solution Concentration and Temperature

Reducing the solution concentration of the H₂O₂ to lower concentrations (0.1 M) increased the dwell time needed to induce selective dissolution. However, selective dissolution of the β phase at 20 °C still occurred within 48 h. Samples immersed in 0.1 M solution for 24 h (Fig. 3.7A) show small pits (<1 micron) in both α and β phases. Pits in the β phase propagated at the phase boundaries. After 48 h (Fig. 3.7B) in 0.1 M solution at 20 °C, the β phase was selectively dissolved from the surface. Near-complete dissolution of β was evident at 72 h (Fig. 3.7C), while the α phase appears relatively uncorroded. The percent of dissolved β (Fig. 3.7G) after 48 h (65.3%) and 72 h (92.6%) was significantly increased from dissolved β after 24 h (19.6%), (p=0.006). A Weibull CDF was fit with 43.1 MSE. The predicted times for 1%, 50%, and 99% dissolution were 5.3 h, 40.2 h and 99.5 h, respectively.

Increasing temperature from room temperature (20 °C) to 37 °C reduced the time in solution needed to selectively dissolve the β phase. Corrosion of the surface is minimal after 6 h (Fig. 3.7D). At 12 h at 37 °C, the β phase is clearly being selectively attacked with pitting and dissolution evident (Fig. 3.7E). After 24 h (Fig. 3.7F) in 37°C solution, the β phase appears fully selectively dissolved from the surface, with some of the α phase also showing signs of corrosion. Dissolved β (Fig. 3.7G) after 24 h (91.3%) was significantly higher than at both 6 h (5.5%) and 12 h (18.5%), (p=0.000). MSE after fitting data with a Weibull CDF was 25.7. Predicted characteristic times for 1%, 50% and 99% dissolution were 5.0 h, 16.8 h and 28.9 h, respectively. The shape parameter, γ , of the 37 °C Weibull CDF was significantly steeper than the 20 °C Weibull CDF shape parameter (p = 0.02).



Figure 3.7. Increasing 0.1 M solution temperature from 20 °C to 37 °C accelerated the rate of selective dissolution over time after a 600 s – 1 V hold. Images of surfaces after immersion in 20 °C solutions at A) 24 h, B) 48 h, and C) 72 h. D) Increasing temperature of 0.1 M solution from 20 °C to 37 °C decreased dwell time needed to induce β phase dissolution D) 6 h, E) 12 h, F) 24 h.

G) Image analysis results showing percent dissolved β vs time for both 20 °C and 37 °C 0.1 M solutions. The slope of the 37 °C Weibull CDF was significantly steeper than the 20 °C Weibull function (p = 0.02). 5k magnification, (n = 3).

3.3.5 Effect of Cathodic Activation and H2O2 on Surface Oxide Function

Representative bode plots for both PBS and H₂O₂ solutions at OCP and -1 V vs Ag/AgCl (Fig. 3.8B and 3.8C) show predominantly Randles-CPE behavior (Fig. 3.8A). The highest polarization resistance is shown for PBS at OCP (about 1.1 x $10^6 \ \Omega cm^2$, see Table 3.1), while either -1 V vs Ag/AgCl or 1 M H₂O₂ decreased the polarization resistance relative to PBS at OCP (1.1 x $10^4 \ \Omega cm^2$, p = 0.000, See Fig. 3.8D). When both -1 V and 1 M H₂O₂ are combined, the polarization resistance drops (26.1 Ωcm^2 , p < 0.000, see Table 3.1). Other calculated values from the impedance analysis are reported in Table 3.1 for each potential-solution combination, including Mean Q, R_s and α (n = 3 for each condition). The phase angle vs. Log ω plots demonstrate this shift to lower frequencies for the -1 V vs. Ag/AgCl conditions compared to OCP and the effects of both H₂O₂ and -1 V in the phase response.



Figure 3.8. A) Randles-CPE and coated circuit models used to fit EIS data. Representative Bode plots for B) Log|Z| vs Log(w) and C) the phase angle, θ , vs Log ω for different solution-potential combinations. D) Mean R_p versus solution-potential condition for PBS at OCP, 1 M H₂O₂ at OCP, PBS at -1 V, and 1 M H₂O₂ at -1 V. R_p significantly decreased by a factor of 10² upon the addition of either 1 M H₂O₂ or a 600 s -1 V hold (p=0.000). The combinatorial effect of both further significantly decreased R_p by a factor of 10³ (p=0.000). (n = 3).

Solution	Potential V	$\begin{array}{c} Q \\ \operatorname{Scm}^{-2}(s)^{\alpha} \end{array}$	<i>Std Dev</i> Scm ⁻² (s) ^α	R_p $\Omega \mathrm{cm}^2$	$\frac{Std \ Dev}{\Omega cm^2}$	R_s Ωcm^2	$\frac{Std \ Dev}{\Omega cm^2}$	α	Std Dev
PBS	OCP	2.02E-05	2.23E-05	1.10E+ 06	2.22E+05	7.73E+01	1.18E+01	8.57E-01	5.77E-03
1 M H ₂ O ₂	ОСР	3.28E-05	5.19E-06	1.12E+	2.43E+03	9.32E+00	2.68E+00	8.81E-01	1.65E-02
				04					
PBS	-1	2.18E-04	5.82E-05	1.14E+	2.24E+03	1.38E+01	1.06E+00	8.37E-01	1.15E-02
				04					
1 M H ₂ O ₂	-1	1.38E-04	1.07E-05	2.61E+ 01	4.26E+00	1.72E+01	1.92E+00	7.87E-01	1.53E-02

Table 3.1. Mean Q (Scm⁻²(s)^{α}), R_p (Ω cm²), R_s (Ω cm²) and α values calculated using phase angle symmetry. Standard deviations are listed to the right of each circuit element.

3.4. Discussion:

This study shows that a transient application of cathodic voltage combined with the exposure of the surface to H₂O₂/PBS solution can trigger β dissolution. The damage observed from our *in vitro* test closely resembles micrographically etched regions within modular taper junctions of orthopedic implants. On these retrieved devices, the β phase is dissolved from the surface, leaving the α phase at a higher relative elevation [14, 26]. After treatment in 1 M H₂O₂/PBS solution for 4 h, Ti-6Al-4V surfaces showed β phase dissolution, increased roughness and varying α crystal heights. Though large-scale Ti-6Al-4V pitting phenomenology, as documented *in vitro*, our test method successfully replicates the initial selective attack on the β phase, where β is initially completely dissolved with minimal corrosion of the α phase.

Cathodic activation potential, time in solution, solution concentration and temperature all affected selective dissolution kinetics. An arbitrarily chosen initial transient application of a 600 s cathodic potential below -0.5 V was used to initiate selective dissolution, but once initiated, it

progressed over time until complete dissolution was observed. If the initial activation potential was above -0.5 V, then little selective dissolution occurred. Both digital optical and SEM images show that β phase selective dissolution can be induced with such initial voltage treatments even if total dissolution requires 48 to 72 h. While longer initial cathodic activation times and potentials more negative than -1 V were not investigated in this study, other studies show that a sustained cathodic hold will similarly induce selective dissolution [24].

Lowering H₂O₂ concentrations from 1 M to 0.1 M induced selective dissolution with longer recovery times. The β phase was dissolved from the surface after 48 h in 0.1 M H₂O₂, while a dissolution time of 4 h was needed for 1 M. Additionally, elevating 0.1 M solution temperature from 20 °C to 37 °C decreased the recovery time needed to completely dissolve β from 48 h to 24 h. This temperature dependence, where the time needed to induce selective dissolution decreased as temperature increased, is supported by previous studies. Indeed, the relationship between temperature and steady state current density during preferential dissolution of the Ti-6Al-4V α phase has been documented in supra-physiological concentrations of hydrochloric acid [35].

Using EIS, we demonstrated that the combined effect of H_2O_2 and cathodic activation resulted in an almost 10^5 drop in surface polarization resistance, implying that the Ti-6Al-4V oxide film surface was significantly compromised. Besides decreasing passivation resistance, the addition of hydrogen peroxide may increase the porosity of the 3-9 nm thick oxide film, making it more defective. Cathodic activation likely introduces and promotes the number of point defects (e.g., vacancies), facilitating charge transport. Such alterations in the oxide structure are again evidenced by a decrease in R_p by a factor of 10^2 when either adverse electrochemical event is introduced. Simultaneously introducing H_2O_2 and cathodic bias synergistically affected the oxide
film's properties, lowering Rp to as low as 20 Ω cm². Our results support similar studies that show a significant decrease in oxide passivation resistance from H₂O₂ alone [36-40].

Though the combination of H_2O_2 and cathodic activation decreased polarization resistance across the entire surface of both α and β and attacked both phases, it is likely that β is preferentially dissolved due to the crystallographic relationship between the β phase and its protective oxide layer. β phase is BCC with a lower packing factor than the α phase. Thus, oxide film growth on β would not have the same metal-to-oxide crystallographic interaction, likely resulting in a more defective oxide than on α . Cathodic potentials may also induce the partial reduction of the oxide film to lower valence oxides (e.g., Ti₂O₃ and TiO) which may also alter the habit relationship with the substrate alloys (HCP and BCC). Additionally, Chemical differences may exist between the oxide film over α (aluminum-rich) and the oxide film over β (vanadium-rich) due to their different crystal structures and elemental compositions. In totality, these experiments support our initial hypothesis that the combined effect of H₂O₂ and cathodic activation modifies the oxide structure and function in Ti-6Al-4V, such that the β phase can be preferentially dissolved.

Since temperature played an important role in this work, we hypothesize that the reaction rates driving selective dissolution of the β phase behave according to an Arrhenius equation.

$$\frac{1}{\tau_{50}} = Ae^{-\frac{Q}{RT}}$$

In this equation, t_{50} is the time to dissolve 50% of the β phase, A is the pre-exponential frequency term, Q is the activation energy for the rate limiting step, R is the ideal gas constant (8.314 J/mol/K) and T is the temperature (K). The pre-exponential term (A) also contains any influence

of the solution concentration on the time for dissolution. More temperatures and concentrations are needed to confirm this behavior.

Concern over metal implant corrosion prompted an extensive white paper by the FDA in 2019 in which they identified three gaps that directly relate to this work [41]. First, there is a lack of accepted crevice corrosion tests and standards prior to clinical approval. Second, existing crevice corrosion standards are intended for biomaterial screening, leaving a significant gap in assessing implant design. Finally, most implant manufacturers gather pre-clinical corrosion data in ideal in vitro conditions. While achieving acceptance criteria in ideal conditions may expedite device commercialization, these conditions are not representative of the adverse (but not uncommon) electrochemical events that occur in vivo. In this paradigm of testing to "not-failure", implant design elements that may promote in vivo corrosion are difficult to identify in vitro. To address these gaps, an accelerated testing model using supra-physiological conditions is preferred. An Arrhenius relationship between the rate of selective dissolution, solution concentration, and temperature would allow for expedited screening of device designs and materials, with the ability to gain additional insight into their performance under physiologically representative conditions. While the corrosion behavior of Ti-6Al-4V in the presence of H₂O₂ is well established, this is the first study to systematically evaluate and quantify the combinatorial effect of H₂O₂ and cathodic activation on selective dissolution [42-44]. Other researchers have observed preferential dissolution of the β phase *in vitro*, both in simulated oral conditions and by combining cathodic potentials and hydrogen peroxide [24, 39, 45-47]. Prestat et al. show that the Ti-6Al-4V β phase dissolves after freely corroding for 5 days in 0.1 M H₂O₂/PBS solution [24]. Our results support this finding: we observe a pitting attack on β after just 4 h in 1 M solution at OCP (Fig. 3.4E). After 1 day under a -0.4 V sustained cathodic activation, they show that the time needed to

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induce β dissolution decreased to 1 day. Our results confirm that the combinatorial effect of hydrogen peroxide and cathodic activation accelerates β dissolution. Our study builds off this existing body of literature by systematically evaluating cathodic potentials that may occur within modular taper junctions of total hip replacement systems, where this damage mode is observed clinically *in vivo*. Though this is not the first study to show that cathodic potential and hydrogen peroxide induce β dissolution, we establish a relationship between temperature, solution concentration and reaction kinetics.

We also show that transient negative potentials below an approximate threshold of -0.5V accelerate selective dissolution. As a proxy for *in vivo* fretting corrosion, *in vitro* studies show that cathodic potentials (ranging from -0.60 V to -1 V) reduce material biocompatibility, generate ROS directly at the metal-solution interface and decrease both cell viability and surface oxide resistance [21, 29, 30, 48, 49]. Our results support these findings, furthering our understanding of cathodic activation and its role in inducing *in vivo* corrosion. Finally, our work supports the hypothesis of electrochemical history, where electrochemical events within the trunnion permanently alter the oxide film, making it more susceptible to future corrosion.

From this work, we do not know how long an initial cathodic activation potential is required to induce the subsequent selective dissolution process as the 600 s time was arbitrarily selected. Initial results indicate that when the cathodic activation is sustained for longer periods (24 h), a more rapid preferential attack occurs. This work is ongoing. Additionally, we have yet to investigate shorter cathodic activation times or potentials more negative than -1 V. It is likely that as the cathodic activation goes below -1 V, selective dissolution will occur more rapidly. However, there is likely a lower limit below which titanium is cathodically protected and hydrogen embrittlement becomes a dominant electrochemical reaction mode.

This study experienced several limitations. First, we use H₂O₂ as a proxy for all ROS at the biology-surface interface in much higher molarities than are prevalent within the human body. *In vivo*, devices are exposed to a biological milieu including terminal ROS species (hypochlorous and hypothiocyanous acids), extreme oxidizers like hydroxyl radicals and leukocytic enzymes (collagenase and gelatinase) [50]. The combinatorial effect of this solution likely has a greater oxidizing effect than the micromolar range of H₂O₂ reported in the human body [51]. Additionally, H₂O₂ is a well-accepted analogous solution for the cellular respiratory burst that metallic surfaces experience post implantation [24, 43, 50]. H₂O₂ itself is an intermediate species of biologically-induced reduction reactions at the metal surface including:

$$HO_2 + H_2O \rightarrow H_2O_2 + OH$$
(1)

$$H_2O_2 + 2e^- \rightarrow 2OH^-$$

$$H_2O_2 + e^- \to OH^- + OH^-$$
(3)

Recent work from our lab shows that biology may not be the sole source of ROS at the implantsolution interface. Wiegand et al. show that cathodic activation of cobalt chrome surfaces at -1V generates ROS directly at the metal surface [30]. In the context of a small volume, This second source of ROS may contribute to localized levels of ROS within the crevice that exceed the concentrations present in the bulk physiological solution.

In this study, we introduce contrast thresholding as a method to quantitatively assess dissolved β from an SEM micrograph (see Fig. 3.2). Our analysis assumes that the brightest pixels in a micrograph represent the β phase and the darkest pixels represent the dissolved β phase. This assumption, of course, does not always hold. In some micrographs, we observe small pits in the α phase that may be mislabeled as dissolved β . Surface imperfections resulting from sample

preparation like scratch marks may similarly count towards dissolved β pixel counts. To validate this method, we re-measured the dissolved β for both SEM micrographs in Figure 3.7A and 3.7B with the scratch marks removed and recalculated the percent dissolved β (dissolved β /total β). We calculated a 3.07% difference in percent dissolved β for Figure 3.7A and less than 1% (0.16%) difference in percent dissolved β for Figure 3.7B. The inclusion of such scratches did not result in large changes in the calculations. Thus, while this method is not perfect, our assumptions are valid.

Our test methods are limited to equiaxed Ti-6Al-4V. It is unknown if β phase dissolution occurs under similar conditions for lamellar or bimodal microstructures that may arise from heat treatments above the β transus temperature or from additive manufacturing processes. We additionally do not believe that the combinatorial effect of ROS and cathodic activation will elicit selective dissolution in either cobalt chrome or stainless steel alloys, but these studies are ongoing. *In vivo* retrieval studies instead suggest that crevice corrosion conditions within cobalt chrome head tapers are associated with columnar damage, a preferential attack resulting in column-like troughs and ion release into the surrounding tissue [32].

This study represents an important first step in understanding the mechanisms of crevice corrosion within Ti-6Al-4V modular taper junctions. Though we evaluate several critical factors (solution concentration, temperature, cathodic potential, time), the impact of crevice geometry, fretting potential drops in the absence of transient applied potential and continuous exposure to cathodic potential remains unexplored. Future studies will explore our hypothesis of selective dissolution's Arrhenius like behavior and translating our results into a more representative *in vitro* model to assess implant design. While we expect Ti-6Al-4V to continue to be used *in-vivo*, an accelerated crevice corrosion model would help screen new device geometries and metallic

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biomaterials. By furthering our understanding of selective dissolution's mechanism, we aim to elucidate other crevice corrosion damage modes documented within Ti-6Al-4V modular tapers.

3.5. Conclusion:

In this study, we found that the combinatorial effect of H₂O₂, cathodic activation, and dwell time in solution preferentially dissolved Ti-6Al-4V β phase *in vitro*. Both H₂O₂ as a proxy for ROS and cathodic potential are necessary components. H₂O₂ alone caused pitting at the α/β phase boundary, but when combined with cathodic activation, the β phase was dissolved from the surface. Initial cathodic hold potential, solution dwell time, concentration and temperature all affected the rate of selective dissolution. A minimum 600 s transient potential of -0.75 V was needed to dissolve the β phase from the surface. Increased dwell time in solution after initial cathodic activation increased β dissolution. Decreasing solution concentration resulted in a subsequent increase in necessary dwell time. Increasing solution temperature resulted in a decrease in time needed. Finally, both H₂O₂ and cathodic activation altered the surface oxide's impedance properties, decreasing oxide resistance by a factor of 10⁵.

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Chapter 4

Electrode Potential, Inflammatory Solution Chemistry and Temperature Alter Ti-6Al-4V Oxide Film Properties

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Graphical Abstract. *In vivo*, the Ti-6Al-4V oxide film is subject to destructive conditions including inflammation and tribocorrosion. In this study, we investigated the dynamic remodeling of the oxide film, using H₂O₂ as a proxy for inflammatory species and cathodic activation to simulate negative potential drops at the interface. We identify a synergistic effect of cathodic potential and H₂O₂ on oxide polarization resistance.

Abstract:

Post implantation, a thin TiO₂ film protects Ti-6Al-4V in vivo. Mechanically and chemically destructive conditions may disrupt this oxide film and promote corrosion at the device interface. While tribocorrosion has been explored in vitro, pre-clinical tests fail to fully reproduce the damage documented on retrievals. A gap persists in our fundamental knowledge of the oxide film and its response to adverse electrochemical events. In this study, we first characterized the TiO₂ oxide film structure after inducing β phase selective dissolution. Next, we used electrochemical impedance spectroscopy and Mott-Schottky analysis to investigate the oxide film on freshly prepared surfaces following negative potential excursions. We systematically increased electrode potential from -1 V vs. Ag/AgCl in 0.1 V steps to +0.5 V. Various H_2O_2 concentrations (0.1 M to 0.001 M) in phosphate buffered saline and temperatures ranging from 24 °C to 55 °C were investigated. Atomic force microscopy showed morphological changes to oxide domes over the α phase following β phase selective dissolution. Below the Ti-6Al-4V open circuit potential (ca. -0.3 V), we identified systematic variations in polarization resistance (R_p) and capacitance (C) with potential, solution chemistry, and temperature. The combined effect of cathodic activation and H₂O₂ solution concentration synergistically and systematically decreased R_p by orders of magnitude (p = 0.000). Increased solution temperatures decreased R_p (p = 0.000). At high concentrations of ROS (0.1 M), we documented changes in constant phase element capacitance, from n-type to p-type. Finally, we developed empirically obtained equations to predict R_p for a given concentration, temperature, and potential. In totality, these experiments help to further understand the complex interactions at the oxide-biology interface in vivo and provide guidance for in vitro testing methods development.

4.1. Introduction

Cobalt-chromium-molybdenum, stainless steel, and titanium alloys make up the majority of metallic biomaterials used in orthopedic implants due to their superior biocompatibility, corrosion resistance, and mechanical properties [1-3]. Titanium alloys, including Ti-6Al-4V, are particularly favored due to their high corrosion resistance, high fatigue resistance, and lower elastic modulus [4, 5]. Ti-6Al-4V is the most widely used titanium alloy and is a two-phase, near- α , α + β alloy. The Ti-6Al-4V α phase is hexagonally close-packed and stabilized by aluminum, while the β phase is body-centered cubic and vanadium rich [6]. *In vivo* applications of Ti-6Al-4V include dental implants, bone plates, cardiac valves, fracture fixation screws, and total knee and hip replacement devices [5]. Corrosion performance of Ti-6Al-4V *in vivo* is generally excellent, and revision rates of Ti-6Al-4V devices for corrosion/tribocorrosion-related degradation remain low [7, 8]. However, in the context of crevices inherent to modular implant device design, severe corrosion can occur [9]

Ti-6Al-4V's corrosion resistance results from a thin oxide film that passivates on its surface [10]. This oxide film is amorphous, approximately 3-9 nm thick, and predominantly composed of TiO₂ [11, 12]. Aluminum within the alloy may additionally precipitate Al₂O₃ oxide within the TiO₂ matrix [13, 14]. *In vivo*, the oxide acts as a barrier to metal ion release, preventing corrosion [15]. When disrupted, the oxide film spontaneously reforms and continuously repassivates under most physiological conditions [16, 17]. However, there are circumstances where such repassivation is slowed or prevented, and severe corrosion results [8].

The metal-oxide-solution interface impedance response can be modeled as a Randles circuit containing a resistor, R_p , in parallel with a capacitor C (or a constant phase element, *CPE*), all in series with a solution resistor, R_s . Indeed, various studies use this circuit model to

analyze the oxide film *in vitro* [18-22]. The polarization resistance, R_p , has a functional relationship with the oxide film's ability to prevent corrosion, and a structural relationship with the oxide film's thickness and defect density [23]. A higher magnitude of R_p indicates greater corrosion resistance (slower rate of corrosion), as structural changes to the oxide film (e.g., thickness, defect density, oxidation state, chemistry) resist the flow of corrosion currents [24]. In the Randles circuit model, the oxide additionally functions as a semiconducting capacitor, and the electrolyte solution provides resistance to ion transfer. Capacitance in this circuit model is hypothesized to be inversely proportional to oxide film thickness, and R_p is thought to be proportional to thickness and inversely related to capacitance [23].

In Mott-Schottky analysis (plots of C^2 vs. potential), the passive TiO₂ film behaves like an n-type semiconductor, characterized by two linear regions, one with a more positive slope [25, 26]. These linear sections show that as the potential increases, the C^2 also increases, with the slope representing the concentration of charge carriers in the film [25-27]. As the slope increases, charge carrier defects within the oxide film decrease [26, 27]. Transport of these defects (e.g., anion vacancies and donor electrons) is promoted by an electric field-driven migration process across the solution-oxide-metal interface [28]. At the metal-oxide interface, a high field is created by electrons quantum mechanically tunneling from the surface of the metal to the solution, trapping oxygen [28]. Once generated, the high field causes the oxide to grow through the interaction of cations and anions. Additionally, it is a primary driving force for ion migration, transporting cations from the metal toward the electrolyte and anions from the electrolyte to the metal [25].

In vivo, the Ti-6Al-4V oxide film is dynamic, responding to potential and solution changes. The film may experience partial dissolution, increased vacancies in localized areas, and

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constant remodeling as the properties of the surrounding environment shift. In addition, TiO₂ may experience cathodic excursions *in vivo* due to tribocorrosion processes [15, 29]. Such cathodic excursions may result in activation (i.e., cathodic activation) or electrochemical reactions that would not otherwise arise. Cathodic activation in this context is the concept that sustained bias in the negative voltage direction increases the oxide film's susceptibility to corrosion attack. While the oxide film is stable under normal biological conditions, adverse electrochemical and mechanical events, including wear, fretting, and reactive oxygen species (ROS), may temporarily alter the oxide [30-32].

Though Ti-6Al-4V devices are generally successful in orthopedic applications, retrieval studies in the past two decades show severe corrosion within modular taper interfaces of total hip replacement devices [33-35]. Observed damage modes include the formation of micron thick oxide layers (from direct oxidation of alloy to oxide), pitting, hydrogen embrittlement, and selective dissolution of the alloy's β phase [9, 36]. *In vitro*, selective dissolution can be reproduced from a combination of cathodic activation and inflammatory species [19, 20]. When subjected to sustained cathodic activation, oxide R_p drops by a factor of 10^2 or more. Once combined with 1 M H₂O₂, a synergistic decrease of 10^5 occurs, indicating a highly defective oxide film [20].

Understanding how the Ti-6Al-4V oxide film reacts to cathodic excursions and inflammatory species is essential to our understanding of *in vivo* selective dissolution, may help elucidate other electrochemically induced Ti-6Al-4V corrosion mechanisms, and has the potential to inform pre-clinical corrosion tests and standards. In this study, we first investigated the structure of the oxide film following *in vitro* selective dissolution. Next, we performed a step polarization electrochemical impedance spectroscopy (EIS) methodology to characterize the

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oxide properties, including resistance to corrosion (R_p) and Mott-Schottky behavior (C^2 vs. V). We aimed to answer the following research questions: (1) What structural changes arise at the oxide-metal interface following sustained cathodic activation? (2) How do H₂O₂ solution concentration and temperature affect the oxide film's polarization resistance following negative potential excursions? (3) How do H₂O₂ and temperature modify the oxide's Mott-Schottky-based semiconducting properties? We hypothesize that increases in solution concentration and temperature will decrease the oxide's R_p in a potential-dependent manner. Following the benchwork in this study, we empirically derived equations modeling the systematic variations in oxide properties. Given a potential, solution concentration, and temperature, R_p can be calculated. Understanding the oxide's response to these variables may provide insight into the mechanisms of clinical failure and assist in developing accelerated corrosion test methods.

4.2. Materials and Methods

In this study, we investigated the effects of solution concentration (0.1, 0.01, and 0.001 M concentrations) of H₂O₂ in phosphate-buffered saline (PBS, Sigma Aldrich P3818), temperature (24, 37, 45, and 55 °C), and electrode potential (-1.0 V to 0.5 V) on the structure and properties of the Ti-6Al-4V oxide film. Structural changes were induced by selectively dissolving the Ti-6Al-4V β phase and characterizing the resulting modifications using Atomic Force Microscopy (AFM). Property changes were systematically measured through a stepwise electrode potential EIS method. The maximum cathodic potential used in this study was -1 V, as fretting corrosion (mechanical abrasion of a portion of the oxide) is known to produce such potential drops for the entire electrode *in vitro* [37].

Previous work from our group used a transient 600 s application of -1 V to cathodically activate the working electrode, inducing β phase dissolution. Here, we used sustained and

continuous cathodic activation at -0.4 V vs. Ag/AgCl to decrease total experimental time. Similarly, when inducing selective dissolution *in vitro*, we used solutions with supraphysiological concentrations of H₂O₂. Except for potentiodyanmic polarization, all electrochemical experiments were performed in triplicate (n = 3).

4.2.1 Metallographic Preparation

Ti-6Al-4V ELI (ASTM F-136) samples were polished with increasing abrasive grits of emery paper, including 240, 320, and 400 grit, before finishing with 600 grit. A final mirror finish was obtained with 1 and 0.3 µm alumina suspensions. Polishing was finished once the sample surface was smooth and had no visible wear tracks, confirmed using digital optical microscopy (DOM, Keyence VHX-6000, Keyence Corp., Mahwah, NJ).

4.2.2 Solution Preparation

The PBS solution was prepared by dissolving 7.4 pH PBS powder (Sigma Aldrich, St. Louis, MO) in 1 L of deionized water. Next, the PBS/deionized water mixture was stirred for 2 minutes at 200 rpm. Stock 0.1 M H₂O₂ solution was made by mixing 989.8 mL PBS and 10.2 mL of 30% H₂O₂ in water. Both 0.01 M and 0.001 M H₂O₂ solutions were made by serially diluting the stock solution (e.g., 1 L of 0.01 M H₂O₂ solution was obtained by combining 100 mL of 0.1 M H₂O₂ with 900 mL of PBS).

4.2.3 Electrochemical Cell

The surface of polished Ti-6Al-4V samples was covered with non-conductive tape, isolating a small rectangular section for electrochemical testing. Next, the area of the exposed region was measured and recorded using the DOM. An insulated wire was secured to the opposite side of the Ti-6Al-4V sample with copper tape, and an ohm meter was used to check the resistance

across the wire and sample to ensure low resistance between the electrical connection. Then, non-conductive tape was placed around the circumference of the sample to protect the sample sides, top, and the wire-tape-sample electrical connection from unintentional contact with the electrolyte solution.

Insulated wires on the samples were supported using a laboratory stand and connected to a VersaSTAT 4 (AMETEK, Berwyn, PA) or bipotentiostat (Custom made, Northwestern University Electronics Shop, 1988) with alligator clips. Samples were submerged in approximately 50 mL of solution, ensuring that the isolated area of the Ti-6Al-4V working electrode was exposed to the solution but the top of the sample and the electrical connection remained dry. Ag-Ag/Cl wires and sintered Ag-Ag/Cl were used as reference electrodes, and carbon rods were used as counter electrodes in the setup.

4.2.4 Inducing Selective Dissolution

Polished Ti-6Al-4V samples were held at -0.4 V for 9 h in 0.1 M H₂O₂/PBS solution. Post-test, samples were sonicated for 15 minutes in 70% ethanol, 30% deionized water solution. Next, sonicated samples were air-dried and imaged using scanning electron microscopy (SEM, 5700N, Hitachi Inc., Tokyo, Japan). Both backscatter electron (BSE) and secondary electron (SE) micrographs were captured at 5k magnifications. Finally, the oxide surface was characterized using AFM (Dimension ICON AFM, Bruker, US). Images were captured over 5 and 1 μ m² surface areas in the contact imaging mode using both height and deflection images. Though the surface area of selectively dissolved samples likely increased, experimental time points for potentiodynamic polarization and stepwise impedance tests were chosen such that the working electrode surfaces remained uncorroded, allowing for post-test area normalization.

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4.2.5 Capturing Potentiodyanmic Polarization and Stepwise Impedance

EIS data for all experiments were acquired using a VersaSTAT 4. To provide additional insight, potentiodyanmic polarization plots were captured from -1 V to 0.5 V vs. Ag/AgCl in the following solutions: PBS; 0.001 M H₂O₂; 0.01 M H₂O₂ and 0.1 M H₂O₂. The scan rate was 0.1667 mV/s. One representative potentiodyanmic polarization scan was completed for each solution type (n = 1).

The potential-dependent impedance for samples in a fixed solution and temperature were obtained as follows: First, the surface was potentiostatically held at -1 V for 120 s. After this hold, impedance was captured from 10⁴ Hz to 10⁻¹ Hz for 0.1 M and 0.01 M H₂O₂ solution concentrations and from 10⁴ Hz to 10⁻² Hz for 0.001 M H₂O₂ and PBS solutions. Next, the sample hold was increased by 0.1 V to -0.9 V, held for 120 s, and impedance was again captured. This stepwise increase in hold potential, followed by impedance acquisition, was repeated until a 0.5 V hold was reached. Partial impedance spectra were fit using symmetry-based EIS (sbEIS, Figure 4.1A) and a constant phase element Randles (CPE-Randles) circuit. Resulting circuit elements (R_s , solution resistance, R_p , polarization resistance, and Q, CPE magnitude) were normalized with respect to the area of the working electrode [38]. sbEIS provided fast capture of the top half of the frequency range and allowed for determination of the associated lowfrequency domain response, shortening the time required to capture spectra to a few minutes. In this approach, the symmetry of the phase angle derivative about the crossover frequency (ω_x , $d\Theta/d\log \omega = 0$, equidistant between the time constants T₁ and T₂) allowed for the prediction of the low frequency data from partial EIS spectra (Figure 4.1B).

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Figure 4.1. sbEIS demonstration. (A) Symmetry about $d\Theta/dlog\omega = 0$ (ω_x) allowed for low frequency prediction (B) from partial EIS spectra acquired at higher frequencies. Note the overlay of the sbEIS fits with both complete and partial EIS spectra. Data are representative (n = 1) and the impedance magnitude, |Z|, is not area normalized.

The effect of solution temperature on oxide impedance was assessed by heating 0.001 M H_2O_2/PBS solution from room temperature (24 °C) to 37 °C, 45 °C, and 55 °C on a hot plate (± 3 °C). When the H_2O_2/PBS solution reached the desired temperature, samples were submerged, and beakers were covered with parafilm to prevent solution evaporation and heat loss. Stepwise impedance was captured from -1 V to 0.5 V, and final solution temperature was checked with a liquid-in-glass thermometer. EIS spectra were captured from 10^4 to 10^{-2} Hz for 24 °C and 37 °C solutions. This frequency range was reduced to 10^4 to 10^{-1} Hz for 45 °C and 55 °C. At these higher temperatures, less data were required to capture EIS spectra suitable for circuit fitting.

After circuit values were extracted from the EIS spectra, an Arrhenius analysis of temperature effects was performed where $1/R_p$ was log_{10} adjusted and plotted vs. 1/T in Kelvin for eleven potentials ranging from -1 V to 0 V [39]. Curves were linearly regressed, and activation energy G (J/mol) was calculated by multiplying the slope (-G/R) of the regressed line in equation (1) with the universal gas constant R (8.314 J/Mol*K).

(1)
$$\ln 1/R_p = \ln A - \frac{G}{R}T^{-1}$$

calculated activation energies (*G*) were plotted versus potential. It was assumed that $1/R_p$ is proportional to the rate of corrosion. In this analysis, $1/R_p$ was substituted for the rate constant in the simple Arrhenius equation [40].

4.2.6 Mott-Schottky Analysis.

Constant phase element impedance is similar to capacitance and looks like

$$(2) Z_{CPE} = \frac{1}{(j\omega)^{\alpha} Q}$$

where *j* is the imaginary number, ω is the frequency, α is the *CPE* exponent, and *Q* is the value for the *CPE* [41]. The values for *Q* were converted to *C* using equation (3) [42-45].

(3)
$$C = Q^{\frac{1}{\alpha}} * (Rs^{-1} + Rp^{-1})^{(1-\frac{1}{\alpha})}$$

in this equation, C (Scm⁻²s) is capacitance, Q (Scm⁻²(s)^{α}) is the magnitude of the constant phase element in the Randles circuit, α (unitless) is the *CPE* exponent, R_p is the oxide polarization resistance (Ω cm²) and R_s (Ω cm²) is the solution resistance [42-45]. Once a plot of C^2 was obtained, a straight line was regressed to the linearly increasing region of C^2 with respect to the potential. In the data reported in Figure 4.7A-C, this occurred between -0.1 V and 0.5 V. Mott-Schottky analysis was performed on the average C^{-2} for each solution concentration. The flat band potential, V_{FB} , was calculated by finding the x-intercept of the regressed line in the Mott-Schottky analysis by rearranging the following formula:

(4) $C^{-2} = mV + b$

where C^{-2} represents the inverse square of the capacitance, *m* is the slope of the regressed line, *V* is the potential, and *b* is the y-intercept. By setting C^{-2} equal to zero, V_{FB} was calculated using equation (5) [46].

(5)
$$V_{FB} = \frac{-b}{m}$$

the number of oxide defects (N_D) was calculated by rearranging equation (6) and solving for N_D .

(6)
$$C^{-2} = (2/\varepsilon\varepsilon_o eN_D)(V-V_{FB} - kT/e)$$

here, ε (50) is the dielectric constant of the TiO₂ oxide film, ε_o is the permittivity of free space, and *e* is the elementary charge of an electron [46-48]. *V* is the applied potential, *V_{FB}* is the flat band potential, *k* is Boltzmann's constant, and *T* is the temperature in Kelvin.

4.2.7 Empirical Equation Development

Acquired EIS data were combined to generate an equation that may predict $LogR_p$ for any combination of potential (*V*), chemistry [*C*], and temperature (*T*). Using empirically derived equations for [*C*] and *V* and the Arrhenius equation for *T*, families of $LogR_p$ curves as functions of these variables were obtained based on the behavior of the data and combined to provide an overall equation of $LogR_p([C], V, T)$.

4.2.8 Statistics

Statistically significant differences in oxide R_p values were determined using a two-way analysis of variance (ANOVA) with an alpha rejection region of 0.05. Differences between individual groups were assessed using a post hoc Tukey's multiple comparison test. R_p values were log₁₀adjusted prior to statistical analysis. All statistics were run in MATLAB 2019-2020b.

4.3. Results

4.3.1 Effect of sustained cathodic activation and inflammatory species on oxide structure

SEM/BSE micrographs of untreated Ti-6Al-4V samples (Figure 4.2A) show a two-phase, equiaxed microstructure. The α phase (darker and globular) occupies more surface area within the 5000x micrograph. The β phase appears vein-like, brighter, and interspersed throughout. AFM height images (Figure 4.2B) of the surface reveal a homogenous oxide film with closely packed oxide domes. Lines crisscrossing the surface are artifacts from polishing. AFM deflection images (Figure 4.2C) show a "side-lighted" 3D representation of the oxide domes with fine topographic features.



Figure 4.2. (A) 5000x BSE SEM micrograph of untreated and mirror-polished Ti-6Al-4V sample. Note the two-phase, equiaxed microstructure. (B) 1 μ m x 1 μ m AFM height and (C) deflection images show an oxide film approximately 11 nm in height with domes of similar heights.

SEM SE (Figure 4.3A) and BSE (Figure 4.3B) micrographs captured following 9 h at -0.4 V vs. Ag/Ag-Cl in 0.1 M H₂O₂/phosphate-buffered saline (PBS) solution show selective dissolution of the Ti-6Al-4V β phase. Dark crevices appear on the surface where β used to be, and several small pits less than one μ m in diameter appear in the α . Polishing scratches over α reveal comparatively less corrosion. Though the micrograph shows a small surface area, preferential β dissolution was relatively uniform across the approximately 0.20 cm² working electrode. AFM height (Figure 4.3C) and deflection (Figure 4.3D) images of a 5 μ m x 5 μ m area show an approximately 160 nm difference in surface height between the uncorroded α and the base of the dissolved β . Note the fuzzy appearance of the oxide overtop α in Figure 4.3C and the raised domes overtop α in Figure 4.3D. The rounded edges of α in Figure 4.3A and Figure 4.3D at the former α - β phase boundary indicate that once β is dissolved from the surface, α may begin to corrode. The 1 μ m² AFM height (Figure 4.3E) and deflection (Figure 4.3F) images show the oxide morphology over α on a nanoscale following selective dissolution. Oxide dome height appears visually larger than the untreated sample dome height in air (Figure 4.2C), evidenced by the increase in measured height difference (low of -6 nm and high of 5.4 nm for the untreated surface versus a low of -16.2 nm and high of 15.3 nm for the selectively dissolved surface).



Figure 4.3. (A) 5000 x SE and (B) corresponding BSE SEM micrographs show selective dissolution of the Ti-6Al-4V β phase following sustained cathodic activation at -0.4 V for 9 h (n = 3); (C) 25 μ m² AFM height and (D) deflection images show a difference in height between remaining α and dissolved β , as well as modifications to the oxide over α . When AFM height (E) and deflection images (F) are captured over a 1 μ m² region overtop α , they reveal more

pronounced oxide domes with increased height when compared to the oxide domes covering untreated samples (Figure 4.2B-C)

4.3.2 Effect of Solution Chemistry on Potentiodynamic Polarization and Oxide Impedance

Potentiodyanmic polarization plots acquired from -1 V to 0.5 V vs. Ag/AgCl reveal a systematic shift in the zero current potential as H_2O_2 solution concentration increases (Figure 4.4). Both cathodic and anodic arms of the polarization plot captured in 0.1 M H_2O_2 /PBS occur at higher current magnitudes compared to the reduced H_2O_2 solution concentrations (e.g., PBS, 0.01 M, 0.001 M). Polarization plot data are representative (n = 1).



Figure 4.4. Potentiodynamic polarization plots acquired from -1 V to 0.5 V for the following solutions: PBS; 0.001 M H₂O₂/PBS; 0.01 M H₂O₂/PBS; 0.1 M H₂O₂/PBS. Zero current potential increases as H₂O₂ solution increases.

EIS spectra acquired at -0.3 V conform to a Randles-Constant Phase Element (Randles-*CPE*) circuit (Figure 4.5A). Representative (n = 1 of the 3 trials) Bode magnitude and phase plots are shown in Figure 4.5B-C, respectively, for three solution conditions including PBS, 0.001 M H₂O₂ in PBS and 0.1 M H₂O₂ in PBS. Randles-*CPE* fits using symmetry-based EIS overlap the experimental data as dashed and dotted lines. Note the decrease in oxide |Z| (Figure 4.5B) and Θ (Figure 4.5C) as H₂O₂ concentration increases.



Figure 4.5. (A) A Randles-*CPE* circuit consisting of a resistor R_p in parallel with a *CPE* element, and a second resistor, R_s , was used to fit EIS data and extract circuit elements. (B) A Bode phase angle plot shows data captured at -0.3 V in PBS, 0.1 M, and 0.001 M H₂O₂ solutions, as well as their Randles-*CPE* fits obtained using a symmetry-based EIS analysis method [38]. Note the decrease in phase angle with increasing concentrations of inflammatory species. (C) A Bode impedance plot at -0.3 V shows a decrease in oxide R_p with increasing solution concentrations. Data shown in (B-C) are representative (n = 1), though all EIS experiments were run in triplicate.

Average $(n = 3) \text{Log}R_p$ over stepwise-increased potentials in four different solutions are shown in Figure 4.6. During step polarization in PBS (Figure 4.6A), LogR_p starts comparatively low at 4.2 Ω cm². As potential increases so does the oxide R_p . Maximum Log R_p is achieved in PBS (6.4) Ω cm²) at -0.3 V before a slight dip at -0.1 V and plateau to about 5.7 Ω cm² for the remaining potentials. Generally, this pattern of (1) increasing $Log R_p$ with potential, followed by (2) a peak and/or plateau around the Ti-6Al-4V open circuit potential (ca. -0.3 V) and (3) a plateau continuing at more anodic potentials, repeats with increasing concentrations of hydrogen peroxide, but with lower plateau values. At cathodic potentials, as the solution concentration increases, $Log R_p$ decreases. At anodic potentials in the plateau region, the stepwise increase in potential has little effect on the oxide $Log R_p$. Instead, the H₂O₂ solution concentration dominates, lowering the plateau $Log R_p$. Thus, at potentials below the open circuit potential for Ti-6Al-4V (around -0.3 V vs. Ag/AgCl in PBS), a synergistic effect exists between cathodic activation and inflammatory species. A two-way ANOVA confirms that solution concentration (p = 0.000), potential (p = 0.000), and the concentration*potential interaction (p = 0.000) all significantly affect oxide $Log R_p$.

Plots of Log R_p vs. hydrogen peroxide solution concentration (Figure 4.6B) at -1 V, -0.5 V, and 0 V reveal a family of curves with a log-log or power law relationship ($R^2 = 0.99$). PBS-based Log R_p values are plotted on the far left for comparison. At -0.3 V (Figure 4.6C), the Log R_p values captured in PBS and the varying H₂O₂ concentrations at -0.3 V are all significantly different ($\alpha < 0.05$) except for the PBS and 0.001 M H₂O₂ groups.



Figure 4.6. (A) Step polarization of Ti-6Al-4V shows a synergistic effect of cathodic activation and solution concentration on $LogR_p$. Above Ti-6Al-4V OCP, $LogR_p$ remains constant with respect to potential. Instead, solution concentration is the primary factor degrading $LogR_p$; (B) At -1 V, -0.5 V, and 0 V, a log-log dependence between H₂O₂ solution concentration and $LogR_p$ is observed. (C) Pairwise comparison of the oxide $LogR_p$ in various solution concentrations at -0.3 V. All groups are significantly different except for PBS and 0.001 M H₂O₂.

4.3.3 Effect of Solution Chemistry on Oxide Semiconductor Behavior

Mott-Schottky plots (using Q^{-2} versus potential) for 0.1 M H₂O₂ and PBS (Figure 4.7A) show differences in semiconductor behavior. For PBS, Q^{-2} linearly increases from -1 V to -0.6 V before briefly plateauing until -0.2 V. Then, Q^{-2} linearly increases again from -0.2 V until 0.5 V. This plateau followed by a linear increase is characteristic of n-type semiconductors. In contrast, Q^{-2} in 0.1 M H₂O₂ (Figure 4.7A) decreases from -1 V to -0.4 V before plateauing until 0.1 V. Then, Q^{-2} begins to linearly increase with potential but at a comparatively lower slope than in PBS. Thus, in solutions with 0.1 M H₂O₂, we observe apparent p-type semiconductor behavior at cathodic potentials and n-type at anodic potentials.

When inflammatory solution concentration was decreased to 0.01 M H₂O₂, Q^{-2} again behaves differently (Figure 4.7B). From -1 V to -0.8 V, Q^{-2} briefly increases, before decreasing until -0.5 V. From -0.4 V until 0.6 V, Q^{-2} linearly increases. In 0.001 M H₂O₂ solution (Figure 4.7C), Q^{-2} behavior is similar to that in PBS. A brief linear increase occurs between -1 V and -0.6 V, before plateauing until -0.2 V. Q^{-2} linearly increases from -0.2 V until 0.5 V, characteristic of n-type semiconductor behavior.



Figure 4.7. Q^{-2} versus electrode potential for Ti-6Al-4V in PBS and (A) 0.1 M H₂O₂; (B) 0.01 M H₂O₂; (C) 0.001 M H₂O₂. Note the apparent transition from p-type to n-type semiconductor behavior as inflammatory solution concentration decreases. Experiments were run in triplicate (n = 3).

Plots of C^2 versus potential (Figure 4.8A-C, converted from the Q^2 plots in Figure 4.7) demonstrate n-type semiconductor behavior regardless of H₂O₂ solution concentration. From -1 V to approximately -0.1 V, C^2 increases at a relatively constant rate. At potentials above -0.1 V, C^2 continues to linearly increase, but at a higher rate than before. Note the flattening of the C^2 plots in 0.1 M and 0.01 M hydrogen peroxide compared to PBS (Figure 4.8A-B). In both these plots, C^2 starts higher and ends lower than the overlayed PBS group. In contrast, the 0.001 M H₂O₂ group in Figure 4.8C more closely resembles the PBS plot. Oxide defects increased in the presence of H₂O₂ compared to PBS (Figure 4.8D). Calculated defect densities and flat band potentials are reported in Table 4.1. Interestingly, flat-band potentials, and Log*R_p* plateau potentials are roughly co-located and the straight-line Mott-Schottky increases occur in the region where $LogR_p$ has plateaued.



Figure 4.8. Mott-Schottky plots for PBS and (A) 0.1 M H₂O₂; (B) 0.01 M H₂O₂; (C) 0.001 M H₂O₂. Oxides exhibit n-type semiconductor behavior regardless of solution concentration; (D) The number of oxide defects (N_D) increased in hydrogen peroxide containing solutions compared to PBS. Experiments were run in triplicate (n = 3). Mott-Schottky analysis and N_D were calculated from average C^{-2} values using Eq. (6).

Solution (M H2O2)	Flatband Potential (V _{FB}) (V vs. Ag/AgCl)	Defect Density (N_D) (cm ⁻³)
Phosphate Buffered Saline	-0.28	4.99 * 10 ¹⁷
0.001	-0.34	1.00 * 10 ¹⁸
0.01	-0.44	1.35 * 10 ¹⁸
0.1	-0.46	1.12 * 10 ¹⁸

Table 4.1. Calculated flatband potential (V_{FB}) and defect density (N_D) from Mott-Schottky analysis.

4.3.4 Effect of Solution Temperature on Oxide Impedance for 0.001 M H₂O₂

Increasing 0.001 M H₂O₂ solution temperature above 24 °C decreased Log R_p (Figure 4.9A). At -1 V, Log R_p is approximately 3 Ω cm² for each sample regardless of solution temperature. As potentials increase within this cathodic region, higher solution temperatures shift Log R_p to lower values. At anodic potentials above Ti-6Al-4V OCP (from -0.1 V to 0.5 V), potential has little effect on Log R_p . Instead, increasing solution temperature decreased the Log R_p plateau. In this anodic region, note the similar Log R_p magnitudes (6 Ω cm²) of samples in 24 °C and 37 °C solutions. When temperature was increased to 45 °C, Log R_p decreased to 4.5 Ω cm². At 55 °C, solution temperature resulted in a further decrease in Log R_p to 3.6 Ω cm². Thus, at more negative potentials, cathodic activation is the primary factor decreasing Log R_p . As potential increases towards Ti-6Al-4V OCP (or above the flatband potential), the effect of temperature grows until, at more positive potentials, it is the primary variable affecting Log R_p . At higher temperatures (45, 55 °C), the potential above which Log R_p stabilizes shifts more cathodically. While Log R_p plateaus around -0.2 V for 24 °C and 37 °C, the oxide film reaches its maximum $LogR_p$ at approximately -0.4 V and -0.6 V for 45 °C and 55 °C respectively.

Plots of $\text{Log}R_p$ at -1 V, -0.5 V, and 0 V (Figure 4.9B) reveal log-linear relationships between $\log R_p$ and solution temperature ($\mathbb{R}^2 = 0.94$, 0.82, and 0.92 respectively). Following a two-way ANOVA, a pairwise comparison at -0.3 V (Figure 4.9C) reveals significantly different $\text{Log}R_p$'s except for the 37 °C and 45 °C groups. Both solution temperature and potential had significant effects on $\text{Log}R_p$ (p = 0.000). Additionally, a significant interaction effect was present (p=0.000).

A Log-linear plot of $1/R_p$ vs. 1/T (Figure 4.9D) shows Arrhenius-like behavior which systematically decreases slope as potential increases. When these slopes are converted to activation energy, a decrease in *G* is observed at cathodic potentials (Figure 4.9E). This sigmoidal shape of *G* vs. *V* implies three separate potential regions (V < -0.6 V, -0.6 V < V < -0.3 V, and V > -0.3 V) may be involved.


Figure 4.9. The effect of 0.001 M H₂O₂/PBS solution temperature on Log R_p across the sampled range of electrode potentials (-1 V to 0.5 V). (A) Increasing solution temperature from 24 °C to 37, 45, and 55 °C decreased Log R_p . At negative potentials, both potential and temperature are driving forces lowering Log R_p . Above the plateau potential, solution temperature is the main factor affecting Log R_p . (B) Plots of Log R_p vs. solution temperature reveal a log-linear relationship at -1 V, -0.5 V, and 0 V. (C) A pairwise comparison of solution temperature and Log R_p at -0.3 V shows that all groups are significantly different from one another ($\alpha = 0.05$) except for 37 °C and 45 °C. (D) An Arrhenius plot of log₁₀(1/ R_p) vs. 1/*T* documents a systematic decrease in the slopes of fitted lines prior to a plateau at approximately -0.3 V. (E) A plot of the activation energy versus *V* identifies a sigmoidal effect of potential on *G*. Both experimentally derived values and the sigmoidal function (Eq. (12)) are shown. Electrochemical experiments were run in triplicate (n = 3).

4.3.5 Effect of Solution Temperature on Oxide Semiconductor Behavior

TiO₂ oxide in 0.001 M H₂O₂ solution behaved like an n-type semiconductor regardless of solution temperature (Figure 4.10). C^{-2} slightly increases from -1 V until -0.2 V. An inflection point, or elbow, exists at -0.2 V for samples in 24, 37, 45, and 55 °C. After this potential, from - 0.2 V until 0.5 V, C^{-2} increases. This is in contrast with higher H₂O₂ solution concentrations (Figure 4.7-4.8) which may affect oxide semiconductor function. Thus, while increasing solution

temperatures modified oxide $Log R_p$ (Figure 4.9), no functional changes within the oxide were observed from the Mott-Schottky analysis.



Figure 4.10. Increasing 0.001 M H₂O₂ solution temperature from 24 °C to 37, 45, and 55 °C had little effect on oxide semiconductor behavior. Note the increased variance for the 55 °C group. All sample oxides behaved like n-type semiconductors regardless of solution temperature. Electrochemical experiments were run in triplicate (n=3).

4.3.7 Empirical Equations for $LogR_p$ vs. [C], T and V

Log R_p from the above experiments over voltage (V), H₂O₂ concentration [C], and temperature (T) demonstrated highly systematic variations that can be interpreted using empirically-derived equations. First, from Figure 4.6B, there is a log-log (or power law) relationship between R_p and [C] and a linear relationship between Log R_p and V at T = 24 °C. By fitting regression lines to Figure 4.6B of the form

$$(7) LogR_p = A + BLog[C]$$

for each *V*, the constants *A* and *B* were determined and found to vary approximately linearly with voltage:

(8)
$$A = m_A V + b_A$$
 and $B = m_B V + b_B$

where *A* is the intercept and *B* is the slope of the log-log linear relationship. Plotting *A* and *B* versus *V* yields the slope and intercept for both *A* and *B* (m = slope and b = intercept). Substituting these results in, an equation was developed that can calculate Log R_p at T = 24 °C for any concentration, [*C*] and voltage, *V*:

(9)
$$LogR_p = m_A V + b_A + (m_B V + b_B) Log[C]$$

we report the coefficients, found by least squares fitting using Solver in Excel, in Table 4.2 [49].

Coeff	Value	
mA	1.52	
$m_{\rm B}$	-0.76	
b _A	3.09	
b_{B}	-1.34	

Table 4.2: Fitting coefficients for Eq. 9.

This empirical equation shows that for T = 24 °C, $LogR_p$ can be calculated for any composition and voltage between 0.1 M to 0.001 M H₂O₂ and -1 V and 0 V vs. Ag/AgCl and predicts the experimental data. To incorporate temperature, Figure 4.9D clearly shows an Arrhenius-like dependence of $Log(1/R_p)$ with 1/T. Thus, with Eq. 9 as the basis for behavior at T = 24 °C, one can use the Arrhenius equation to obtain $LogR_p$ at any other temperature:

(10)
$$LogR_p = [m_A V + b_A + (m_B V + b_B) Log[C]] + \frac{G}{R} \left[\frac{1}{T} - \frac{1}{297}\right]$$

or

$$(11) Log R_p^T = Log R_p^{297} + \frac{G(V)}{R} \left[\frac{1}{T} - \frac{1}{297} \right]$$

it should be noted that G, the activation energy barrier, is a voltage-dependent function (see Figure 4.9E). This function is sigmoidal in shape and can be fit by

(12)
$$G(V) = G_{Vo} + \Delta G \frac{e^{aV} \tau^a}{1 + e^{aV} \tau^a}$$

where G_{Vo} is the activation energy at V = -1 V and ΔG is the change in activation energy from -1 V. Fitting the *G* vs. *V* plots (using Solver in Excel) yields Table 4.3:

Table 4.3. Coefficients for equation 12 obtained by least-squares fitting.

Coeff	Value	Coeff	Value (J/mol)
α	14.72	Gvo	31,026
τ	1.60	ΔG	119,500

Thus, the combined effects of T, [C], and V on $Log R_p$ can be obtained from these empirically derived functional relationships and hold for the range of cathodic potentials from 0 V to -1 V,

the range of temperatures from 24 $^{\circ}$ C to 55 $^{\circ}$ C and the range of solution concentrations from 0.001 to 0.1 M H₂O₂.

4.4. Discussion

In this study, we assessed the effects of potential, solution concentration, and temperature on the Ti-6Al-4V oxide structure and impedance properties. We investigated both $LogR_p$ and C⁻² under conditions meant to represent physiological conditions, particularly when tribocorrosion may occur (e.g., cathodic potentials). We systematically measured the oxide impedance (R_p and CPEresponse) of as-polished Ti-6Al-4V surfaces using a step-potential symmetry-based EIS method to compare and relate R_p and C with experimental conditions. Our results showed large and systematic variations in both R_p , generally acknowledged to be a measure of corrosion resistance, and C^2 , a measure of oxide semiconducting response of the metal oxide film. Each impedance parameter provided important insights into the oxide film performance and how conditions like solution chemistry, potential, and temperature alter both properties. In addition, our results investigating the Ti-6Al-4V surface structure after β phase dissolution showed significant morphological changes in the oxide film. These changes are likely associated with the property changes observed on surfaces that were not yet selectively dissolved, may be driven by transport processes within and across the film, and reflect oxide internal structural changes that drive alterations in R_p and C.

We found systematic and synergistic effects of potential, solution concentration, and temperature on $\text{Log}R_p$. From our data, we derived empirical functions describing the combined effects of these environmental factors on the oxide film's polarization resistance. Similarly, C^{-2} was affected by solution concentration but was not profoundly affected by temperature. More

aggressive inflammatory solutions increased charge carrier density in the oxide and may have driven a change from n-type to p-type response (based on Q^{-2} versus V behavior, Figure 4.7A), although after conversion of Q to C, the slope no longer showed p-type behavior.

The empirical analysis of $LogR_p$ provides a potential guideline for developing accelerated testing conditions involving Ti-6Al-4V alloy corrosion processes, including tribocorrosion and mechanically assisted crevice corrosion. Since R_p is typically associated with the reciprocal of the rate of corrosion (e.g., Stern-Geary equation), using $1/R_p$ as a substitute for the rate allowed Arrhenius-like temperature-dependent behavior to be incorporated into the analysis and predictive equations. Thus, higher temperature conditions can be better related to body temperature (or room temperature) experiments.

Experiments in this work used a symmetry-based EIS method recently published that reduces the time needed to acquire spectra to as short as three minutes and relies on the fact that *CPE*-Randles responses are symmetrically distributed over Log of the frequency. Thus, capturing the upper half of the frequency response determines the low-frequency response as well. Such short-time impedance capture methods reduce the possibility of large changes in surface behavior during the test period (i.e., relatively constant electrochemical conditions are maintained). This allowed for both R_p and C to be simultaneously captured and compared.

Coupled responses of $\text{Log}R_p$ and C^2 were observed. Where $\text{Log}R_p$ increased with V, C^2 was at or below the flatband potential. $\text{Log}R_p$ rose and reached a plateau at roughly the flatband potential, and C^2 began to rise linearly with V, indicating typical n-type behavior. At these anodic potentials, $\text{Log}R_p$ stayed constant. These paired characteristic variations, clearly linked in the reported data, reflect the overall oxide film property response to voltage changes. The results of these experiments provide insight into how Ti-6Al-4V surfaces perform under the complex tribocorrosion and crevice conditions generated *in vivo*. It is well documented, for example, that tribological processes can both decrease the local surface potential and disrupt (or breach) the oxide film [37, 50]. However, what happens after or in regions adjacent to, but not directly participating in the tribocorrosion process? In the context of mechanically assisted crevice corrosion (MACC), the oxide re-passivation mechanism and its impact on local impedance characteristics is unclear and poorly understood. In this work, it appears that cathodic electrode potentials (that were applied directly here but can arise from tribocorrosion *in vivo*) have a profound effect on $LogR_p$. Similarly, inflammatory simulating conditions also impact $LogR_p$, lowering R_p by orders of magnitude and rendering the oxide film much more susceptible to corrosion attack.

It is important to note that corrosion of Ti-6Al-4V orthopedic devices rarely results in clinical failure. Indeed, this work focuses on devices and circumstances where a Ti-6Al-4V tribocorrosion condition (negative potentials) is present, such as in modular tapers or screw-countersink contacts. Modularity and screw-countersink combinations are ubiquitous in current total hip arthroplasty systems and fracture fixation/spinal implants, and retrieval studies document severe corrosion of Ti-6Al-4V interfaces [9, 36, 51]. Titanium and its alloys continue to be used in permanently implanted medical devices. Therefore, understanding how adverse electrochemical events affect the surface oxide film may provide valuable insight. A deeper understanding of the effects of cathodic activation and varying ROS concentrations may help generate more rigorous pre-clinical corrosion tests and inform improved device design processes. This work clearly shows the dependence of the impedance characteristics of Ti-6Al-4V on the solution and electrode potentials that are possible *in vivo*.

Throughout this study, we used two terminal frequencies when capturing impedance spectra. Under accelerated conditions (0.001 M 45 °C, 0.001 M 55 °C, 0.1 M, and 0.01 M), we acquired EIS from 10^4 Hz to 10^{-1} Hz. The inhibited remodeling of the oxide film allowed us to collect the crossover frequency, ω_x , when the derivative of the phase angle $d\Theta/d\omega = 0$ (the lower frequency cut-off required for the symmetry-based analysis). In more physiologically representative conditions, we needed an additional decade of low frequency data from 10^4 Hz to 10^{-2} Hz to acquire ω_x . These extra ten data points extended EIS capture time from approximately three to thirty minutes. Increased time in solution likely influenced the oxide films' remodeling. More time at neutral potentials relative to the Ti-6Al-4V OCP may promote hydration of the oxide film, increasing the measured polarization resistance.

Our aim in this study was to model the oxide film's repassivation mechanism following negative potential excursions. To address this aim, we systematically captured R_p and C starting from -1 V and increased potential. *In vivo*, this process likely occurs on the time scale of seconds. It is hypothesized that the accumulation of these cyclic, tribological potential drops, or the surface's electrochemical history, can permanently alter the oxide film's structure and function. Thus, while accelerated conditions (including temperatures of 45 and 55 °C and molarities of 0.1 M and 0.01 M) may never occur in the human body, the total experimental time needed to capture all EIS spectra more accurately depicts the *in vivo* mechanism. Finally, within a series of EIS data captured at similar terminal frequencies (10^{-2} or 10^{-1} Hz), the results of this study hold true. Ten-fold decreases in R_p are documented at various potentials for samples in PBS and 0.001 M solution. Between data captured out to 10^{-1} Hz, these differences between groups are similarly large.

This study builds on previous literature. In 2006, Chandresekaran et al. showed evidence of selective dissolution of the β phase using H₂O₂ and cathodic potentials [52]. Rodrigues, et al. (2009), first identified β dissolution in retrieved implants [9]. Prestat et al. utilized sustained cathodic activation, particularly at -0.4 V, to induce β dissolution [19]. Here, we used conditions similar to Prestat (0.1 M at -0.4 V) to generate selectively dissolved surfaces, studying the structural changes to the oxide on α phase crystals post-dissolution. Selective dissolution was presented in this work to help relate the structural changes arising from hypothesized in vivo corrosion conditions to the impedance properties of the oxide film. Additionally, this work builds off the studies of Ehrensberger et al. and Pan et al., who investigated titanium in simulated biological environments [47, 53]. While titanium and Ti-6Al-4V are different biomaterials, the protective oxides on both are primarily TiO2. In Mott-Schottky analysis of titanium stepwise impedance, Ehrensberger et al. report a V_{FB} of -0.27 V in PBS, close in magnitude to the -0.28 V in PBS we report here for Ti-6Al-4V V_{FB} in PBS [47]. In their Mott-Schottky analysis, they show two regions of linear increase for C^2 , with a linear increase in C^2 above the flat band potential. While an ideal n-type semiconductor typically has a region with a slope greater than zero above the flat band potential, in TiO₂ over Cp-Ti and now Ti-6Al-4V, we observe a second linearly increasing region at more negative potentials. This second potential region has a lower slope than data captured above the flatband potential, indicating a possible increase in lower-order oxide, including Ti₂O₃ and TiO, as well as the hydride TiH as the electrode potential becomes more negative. X-ray photoelectron spectroscopy (XPS) may be utilized to explore this hypothesized structure-property relationship, though this is beyond the scope of this study.

The most physiologically representative solution and temperature condition explored in this study was 37 °C 0.001 M H₂O₂, simulating adverse electrochemical conditions at body

temperature. Though we used H₂O₂ to simulate all ROS, this is far from a universal approach [18, 54-58]. At the 37 °C 0.001 M H₂O₂ temperature-solution combination, we documented several phenomena. In the anodic range, there is little difference in oxide R_p between samples in 37 °C 0.001 M H₂O₂ (Figure 4.9A) and samples in 24 °C PBS (Figure 4.6A). As the surface potential becomes more cathodic, a synergistic effect occurs. While cathodic activation decreases R_p regardless of solution type, the combination of cathodic activation and low ROS degrades R_p more than high ROS-containing solutions at positive potentials or cathodic activation alone. Structurally, these changes in oxide R_p may manifest as decreases in oxide film thickness and/or increases in anion vacancies. Using the defective oxide in Figure 4.3 as a guide, as well as the R_p vs. potential plot in Figure 4.6A, we illustrate the hypothesized structural changes to the oxide film in Figure 4.11.



Figure 4.11. Hypothesized structural changes to the oxide film when exposed to cathodic activation and reactive oxygen species; (A) Model of the hydrated TiO₂ oxide film in PBS; (B) Cathodic activation and (C) high solution concentrations of ROS generate vacancies within the film; (D) When combined, low ROS (e.g., 0.001 M H₂O₂) and cathodic activation induce more vacancies than either high ROS or negative potentials in isolation.

The current paradigm for both *in vitro* exploratory research and gathering pre-clinical data is to use solutions with neutral pHs and few additional oxidizers. Common solutions include Ringer's solution, PBS, and 0.9% NaCl. While these solutions may match the isotonic properties of the *in* vivo biology present at the device interface, several key variables that may affect corrosion in vivo are ignored. First, most severe corrosion of Ti-6Al-4V is observed in crevice environments. Within the crevice, a small volume with two opposing metal surfaces, changes to the physiological solution may have a greater effect than in the bulk solution. Consequences of mechanically assisted crevice corrosion include deaeration, the influx of chloride ions, the formation of oxidizing chemicals, and lowering of the solution pH. Additionally, leukocytic enzymes may be present. While elements of biology, tribocorrosion, and solution chemistry have been investigated in isolation, a combinatorial approach may be required to fully recapitulate the complex interactions that occur in vivo. In this study, we showed that variables directly related to these adverse electrochemical events dynamically affect the oxide, remodeling it in real time. Future work will further characterize the oxide after crevice corrosion damage modes and identify solution chemistries more representative of the biological milieu.

4.5. Conclusion

In this study, we show how adverse electrochemical events (inflammatory chemistry and cathodic activation) that may arise at the biology-device interface *in vivo* affect Ti-6Al-4V oxide structure and function *in vitro*. AFM images after sustained cathodic activation in inflammatory species show selective dissolution of the β phase and structural changes to the oxide domes. A fuzzy appearance in the oxide film overtop corroded samples suggests increased vacancies. Using stepwise impedance, we demonstrate a significant effect of solution concentration, voltage, and temperature on oxide polarization resistance (p=0.000). Additionally, Mott-Schottky analysis of the constant phase element response (Q^{-2}) reveals a change in the semiconductor behavior of the oxide film. While the film behaves like an n-type semiconductor function resembles p-type behavior at more cathodic potentials. These structural and functional data suggest a complex and rapidly evolving oxide film when subjected to cathodic potentials *in vivo*. Future work will investigate the characteristics of the oxide in crevice geometries and more complex solution chemistries.

4.6. Acknowledgements

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4.7. References

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Chapter 5

Increasing temperature accelerates Ti-6Al-4V oxide degradation and selective dissolution in H₂O₂-containing physiological solutions: An Arrhenius-based analysis

(In Submission)

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²The Clemson University-Medical University of South Carolina Bioengineering Program, Charleston, SC Abstract: Retrieval studies show severe Ti-6Al-4V corrosion within the modular taper junctions of orthopedic implants. While researchers successfully model aspects of the tribological behavior associated with this damage, a gap persists in our fundamental understanding of chemically induced corrosion. Additionally, previous pre-clinical tests fail to recapitulate adverse electrochemical events that occur at the device-biology interface. In this study, we investigated the temperature dependence of Ti-6Al-4V β phase dissolution, a key component of the *in vivo* corrosion mechanism. We hypothesized that solution temperature and H₂O₂ concentration would accelerate oxide degradation, systematically decreasing the experimental times needed to induce β dissolution in an Arrhenius-like fashion. First, we acquired electrochemical impedance spectra during active β dissolution at -0.4 V vs Ag/AgCl, showing significant decreases in oxide polarization resistance (R_p) both over time (p = 0.000) and as temperature increased (p = 0.000, 0.1 M, 0.05 M H₂O₂ solutions, 24 °C, 37 °C, 45 °C). Next, we selected scanning electron microscope imaging time points after the rapid decrease in R_p, to quantify the extent of selective dissolution. The characteristic time needed to induce β dissolution decreased in an Arrheniusdependent manner. Finally, we correlated our impedance results with image-based dissolution data, identifying three surface classes (undissolved, dissolving and fully dissolved) as the oxide properties changed under sustained cathodic activation. These results clearly indicate a concentration and temperature dependent structure-property relationship between the solution, the protective oxide film, and the substrate alloy, where an exponential decrease in R_p precedes selective dissolution.

Highlights:

- Increasing solution temperature increased the corrosion rate and decreased the experimental time needed to induce selective dissolution of the Ti-6Al-4V β phase.
- Oxide polarization resistance (Log₁₀R_p) significantly decreased (p = 0.000) as temperature increased.
- Correlation of the constant phase element parameter, Log₁₀(Q), and Log₁₀R_p with the corrosion rate, τ⁻¹, over time reveals a systematic progression from undissolved, to transition, and finally dissolved surface classes.
- The oxide properties of the surface classes (undissolved, transition, and dissolved) significantly differed from one another (p = 0.000). As the surface corroded, Log₁₀(Q) significantly increased and Log₁₀R_p significantly decreased (p = 0.000).
- Increasing H₂O₂ concentration significantly decreased Log₁₀R_p for undissolved and transition classes (p < 0.05). Once dissolved, Log₁₀(Q) became the oxide film property affected by solution concentration (p < 0.05).
- These results support the inclusion of cathodic activation and inflammatory simulating solutions in pre-clinical tests. Increasing solution temperature may decrease the experimental time needed to elucidate chemically induced corrosion damage modes observed on retrieved orthopedic devices.

Keywords: Ti-6Al-4V, Selective Dissolution, Arrhenius, Corrosion, Electrochemical Impedance Spectroscopy

5.1. Introduction

Ti-6Al-4V is widely used in orthopedics due to its excellent biocompatibility, mechanical properties, and corrosion resistance [1-5]. A two phase $\alpha+\beta$ alloy, applications include femoral stems, acetabular cups and tibial baseplates in total hip and total knee replacement systems [4, 6, 7]. *In vivo*, a thin 2-10 nm oxide film protects the Ti-6Al-4V alloy surface [8-12]. When chemically or mechanically destructive conditions disrupt the oxide, corrosion initiates. Though titanium alloy corrosion rarely results in clinical failure, retrieval studies document severe Ti-6Al-4V corrosion within the modular taper junctions of total hip replacement devices [13-20]. Reported damage modes include hydrogen embrittlement, the formation of large (> 100 µm) pits, direct conversion of the alloy to oxide, and selective dissolution of the alloy's β phase.

Researchers previously reproduced elements of β phase selective dissolution *in vitro* using negative (cathodic) potential excursions and inflammatory simulating solutions [21-30]. While the microstructural aspects of the dissolution mechanism are well defined, the structure-property relationship between the oxide film and the Ti-6Al-4V surface at the onset of β dissolution remains unclear. Additionally, the role of temperature in the corrosion kinetics, useful for accelerating testing conditions, remains unexplored.

Using scanning electron microscopy, the Ti-6Al-4V phases visibly contrast. The α phase appears globular and darker, while the β phase appears bright and vein-like (Figure 5.1A). This contrast under backscattered electron mode arises due to the distribution of elements within the phases: The α phase is aluminum rich with a hexagonally close packed crystal structure while the β phase is vanadium rich and body centered cubic. On retrieved Ti-6Al-4V surfaces, micrographs show preferential dissolution of the β phase at modular taper junctions (Figure 5.1B) and within cross sectioned pits (Figure 5.1C) [14, 31]. Where the bright vein-like structure used to be

present, dark voids appear. In addition, 200 μ m thick oxide films may form at the alloy interface. While preferential dissolution of the β phase initiates the corrosion attack, subsequent corrosion of the α phase occurs.



Figure 5.1. (A) Reference micrograph showing the Ti-6Al-4V α and β phases. (B) A micrograph of a retrieved Ti-6Al-4V modular body shows preferential dissolution of the β phase. (C) Within the cross section of a pit on a Ti-6Al-4V stem-neck taper, β dissolution initiates the corrosion mechanism, followed by corrosion of the α phase. The micrographs in (B) and (C) were reproduced with permission from Kurtz et al., Orthop. Clin. North Am. 2023, and Gilbert et al., JBMR-B, 2012 [14, 31].

The Arrhenius equation can be used to model temperature's effect on corrosion [32-41]. Previous studies identified an Arrhenius dependence between the preferential dissolution of the Ti-6Al-4V α phase and solution temperature [34]. Experiments were completed in 2 M HCl solution and electrolyte temperatures ranged from 28 to 43 °C. After 30 minutes of immersion under sustained cathodic potential, micrographs revealed dissolved α grains. From our group, we identified a temperature effect on β dissolution [25]. In 0.1 M H₂O₂/phosphate buffered saline (PBS) solution, increasing the temperature from 24 °C (room temperature) to 37 °C (physiological temperature) decreased the time needed to dissolve the β phase. However, the two temperatures we used were insufficient for a systematic analysis.

A gap persists in our ability to model chemically induced Ti-6Al-4V corrosion, including pitting, the formation of thick oxides, and hydrogen embrittlement [42]. Linking the accelerated corrosion rate of Ti-6Al-4V with temperature and solution may aid in developing pre-clinical device tests and serve as a framework for investigating other crevice corrosion damage modes. Additionally, while the microstructural and mechanistic aspects of selective dissolution are well defined, the temperature dependence of β dissolution has not been fully elucidated. In this study, we systematically investigated the effect of H_2O_2 solution temperature on Ti-6Al-4V β dissolution. We sampled three temperatures (24 °C, 37 °C and 45 °C) across two H₂O₂ solution chemistries (0.1 and 0.05 M H₂O₂). We hypothesize that increasing solution temperatures will accelerate oxide film degradation, decreasing the experimental time needed to induce β dissolution. We sought to answer the following research questions: (1) Will increasing solution temperature increase the rate of β dissolution? (2) Does a structure-property relationship exist between the oxide film and the underlying Ti-6Al-4V surface class? (3) Using an Arrhenius analysis, can accelerated corrosion conditions be related to more physiologically relevant conditions?

5.2. Methods

In this study, we first evaluated the effect of sustained cathodic activation on selective dissolution, holding samples at fixed potentials in $0.1 \text{ M H}_2\text{O}_2$ solution. Then, we captured the impedance of Ti-6Al-4V surfaces undergoing active selective dissolution at -0.4 V. Solution temperatures ranged from 24 °C to 45 °C. Next, we reran these experiments, selecting time points to stop the tests and image the sample surfaces. This general protocol of impedance capture followed by imaging was repeated for samples in 0.05 M H₂O₂ solution. After testing, we correlated the impedance data we captured in different solution concentrations over time with the

image-based data we gathered, identifying three visually and quantitatively different surface classes. Finally, using impedance and dissolution rates, we constructed Arrhenius plots.

5.2.1 Metallographic preparation

Ti-6Al-4V (ASTM-F136) samples were polished using emery paper ranging from 200-600 grit. A final mirror polish was applied with alumina/H₂O suspensions (1 and 0.3 μ m). An electrical connection was maintained between samples and external wires using carbon tape. Tape was used to isolate working electrode surface areas for electrochemical testing. The sample-wire interface was fixed using hot glue.

5.2.2 Evaluating the effect of sustained cathodic potential

Samples were potentiostatically held for 24 h in 0.1 M H₂O₂/phosphate buffered saline (PBS) solution. Bipotentiostats (Custom-made, Northwestern University Electronics Shop, 1988) were used. The electrochemical cell consisted of the Ti-6Al-4V working electrode, a carbon counter electrode and an Ag/AgCl reference electrode. A minimum of three ($n \ge 3$) experiments were conducted for potentials ranging from -1 V to 0.2 V. Post-test, samples were sonicated in 70% ethanol/30% deionized H₂O, air dried, and imaged using scanning electron microscopy (SEM, 5700N, Hitachi Inc., Tokyo, Japan). Backscattered electron (BSE) micrographs were captured at 5000x magnification. ImageJ was used to contrast threshold SEM micrographs, quantifying the extent of β dissolution according to our previously published protocol [25].

5.2.3 Monitoring oxide degradation over time

To isolate the effect of temperature on the dissolution rate, we proceeded with a fixed potential of -0.4 V for the remainder of the tests in this study [21]. First, we used electrochemical impedance spectroscopy (EIS, VersaSTAT 4 potentiostat) to monitor the oxide film during

active dissolution. A baseline EIS spectrum was captured (from 10^4 Hz to 0.1 Hz) following a 60 s measurement of the open circuit potential (OCP). Next, a second spectrum was captured at -0.4 V vs. the Ag/AgCl reference. Then, the sample was potentiostatically held at -0.4 V for 24 h. After each hour, EIS was captured vs. -0.4 V. Solution chemistries included 0.1 M and 0.05 M H₂O₂/PBS. Three temperatures were selected, sampling above (45 °C), below (24 °C) and at body temperature (37°C). Temperature was maintained using a hot plate (± 3 °C). A second beaker filled with DI H₂O was used to continuously monitor and maintain hot plate temperature, preventing active corrosion of the metal temperature sensor within the existing electrochemical cell.

To capture more of the oxide's degradation behavior in 0.1 M 45 °C H₂O₂ solution, additional EIS spectra were captured every 8 minutes for the first 3 h. These tests were stopped after approximately 6 h as it was well beyond the experimental time needed to induce β dissolution. EIS data captured from 10⁴ to 0.1 Hz over about 3 minutes were fit with a Randles constant phase element (CPE) circuit using phase angle symmetry (sbEIS) [43]. Plots of R_p over time were used to select preliminary time points for imaging. Generally, we picked a time point after the R_p plateaued. Additionally, plots of Log₁₀(Q⁻²) versus time were constructed. The constant phase element parameter, Q, may be directly related to the oxide film capacitance using the Brug equations [44, 45]. We used Q⁻² as a proxy for the Mott-Schottky behavior of the oxide film during active selective dissolution. The Mott-Schottky equation relates C⁻² to the number of charge carriers in the oxide. Here, the larger charge carrier density corresponds to smaller C⁻² and R_p.

Twice during data acquisition, the potentiostat failed to acquire an EIS spectrum, skipping from one -0.4 V potentiostatic hold to the next. As the surrounding data was otherwise unaffected, the

k-nearest neighbors algorithm was used to impute the missing data (k = 6). This method works by replacing the missing data point with the average of the *k* nearest data points calculated by Euclidian distance. Both imputed data points were one of 78 + EIS spectra (2 of the 500 total EIS spectra used in this work) and used to calculate the average Log₁₀R_p, and Log₁₀(Q⁻²) values. The imputed data fell within plateau regions and had little effect on the presented results.

5.2.4 Inducing β dissolution at various temperatures

Using bipotentiostats, Ti-6Al-4V samples were held at -0.4 V for various experimental times in 0.1 M and 0.05 M H₂O₂/PBS solutions. Additionally, we reproduced β dissolution using the temperatures used to capture the oxide behavior (24 °C, 37 °C, 45 °C). A complete list of the experiment factors including concentration, temperature, and imaging time may be found in Table 5.1. For each of the concentration-temperature combinations, and at each imaging time point, a minimum of three (n ≥ 3) tests were run. Post-test, samples were sonicated and 5k SEM BSE micrographs were captured. ImageJ contrast thresholding was used to determine the dissolved β (%).

Concentration (M)	Temp (°C)	Timepoint 1 (h)	Timepoint 2 (h)	Timepoint 3 (h)
0.1	24	6	9	24
0.1	37	4	5	7
0.1	45	0.5	2	4
0.05	24	12	24	48
0.05	37	6	12	24
0.05	45	4	9	16

Table 5.1. Experimental solution concentrations, temperatures, and imaging times.

5.2.5 Weibull Cumulative Distribution Fitting

Plots of β dissolution over time were constructed for both 0.1 M and 0.05 M H₂O₂ solutions. Each plot contained a series of data corresponding with the three temperatures sampled in this study. Data were fit with a Weibull cumulative distribution function (CDF, Eq. 1) and parameters were optimized using solver in excel, minimizing the square root of the residual sum of squares (Eq. 2):

$$f(t) = \left(1 - \exp\left[-\left(\frac{t}{\tau}\right)^{\gamma}\right]\right) * 100$$

$$error = \sqrt{\sum_{i=1}^{n} (y_i - f(t)_i)^2}$$
(2)
(1)

where f(t) is the predicted dissolved β (%), t is the time in hours, τ is the Weibull CDF scale parameter, γ is the shape parameter and y_i are the experimental values. Error was minimized using the individual experimental values rather than the averages for a single time point. The characteristic time, where $t = \tau$, is the time at which 63 % of β was dissolved for a solutiontemperature combination, i.e., where f(t) = 63 %.

5.2.6 Correlation of oxide impedance values and dissolution rate

To further analyze the oxide undergoing active dissolution we generated plots of R_p vs. Q for the six solution temperature-concentration combinations. This was done to demonstrate the relationship between these properties and to assess the predictive compacity of the CPE capacitance on R_p . Further correlation of the surface structure (i.e., the dissolution state) and oxide property behavior was implemented by defining three classes (undissolved, transition, dissolved) and labeling the data within 0.1 M and 0.05 M H₂O₂ R_p vs. Q plots. Data were sorted into classes using the time needed to induce 10% and 80% β dissolution (τ_{10} and τ_{80}) for a

particular temperature-solution concentration combination. τ_{10} and τ_{80} were calculated using Eq. 1. We selected these thresholds based off the calculated β dissolution values in initial and final micrographs over time. Data were assigned to one of three classes as follows:

Undissolved
$$< \tau_{10} < \text{Transition} < \tau_{80} < \text{Dissolved}$$
 (3)

Vertical dashed lines were manually overlayed in the plots to illustrate the approximate cutoffs where one class ended and the next began.

5.2.7 Arrhenius-based Analysis

To assess the effect of solution temperature on β dissolution, an Arrhenius-based analysis was implemented using τ^{-1} (acquired from fit Weibull CDF functions at f(t) = 63 %) as an approximation of the corrosion rate [46] and assuming a first order reaction with H₂O₂ concentration, [C]:

$$\frac{1}{\tau} = [C]Ae^{-\frac{E_a}{RT}} \tag{4}$$

where A is the pre-exponential factors, E_a is the activation energy, R is the universal gas constant, and T is the temperature in Kelvin. A $Log_{10}\tau^{-1}vs$. T⁻¹ Arrhenius plot was constructed for the experimental data collected in this study in 0.1 M and 0.05 M H₂O₂ solutions. Activation energies (E_a) were calculated by multiplying the slope of linearly regressed lines (- E_a/R) with the universal gas constant, R and with the Ln to Log₁₀ conversion factor (2.303).

5.2.8 Statistical Methods

A one-way analysis of variance (ANOVA) was used to assess the effect of sustained potential on β dissolution. Next, a two-way ANOVA was used to evaluate the effect of time (0-24 h) and temperature (24, 37, 45 °C) on Log₁₀R_p and Log₁₀(Q). For the 0.1 M H₂O₂ solution group, the

statistical comparison of temperatures was constrained to 24 °C and 37 °C and time was constrained to the first 6 h. Here, the limiting factor was the termination of tests post dissolution for the 0.1 M 45 °C group. A second two-way ANOVA assessed the effect of solution concentration (0.1, 0.05 M) and surface class (undissolved, transition, dissolved) on Log₁₀R_p and Log₁₀Q. A post-test Tukey's multiple comparison test was used to identify significant differences between groups, using $\alpha = 0.05$. Statistics were conducted in MATLAB (versions R2019b-R2022b). A minimum of three ($n \ge 3$) electrochemical tests were performed to generate data for each solution-temperature-time condition. Additionally, while we display average R_p vs. Q plots, unaveraged data from individual trials were labeled and used for statistical analysis. Finally, error bars on plotted charts represent the standard deviation of the data.

5.3. Results

5.3.1 The effect of sustained potential on β dissolution

SEM Micrographs (Figure 5.2) establish a range of cathodic potentials (-0.3 V to -0.7 V) where the β phase dissolves after 24 h in 0.1 M H₂O₂ solution. The α phase appears globular and grey, and the β phase looks like thin, long white lines surrounding the α crystals. When dissolved, the β appears as connected dark lines, or crevices. At -1.0 V (Figure 5.2A) and -0.8 V (Figure 5.2B), most of the β phase remains. Small black dots appear, indicating pit nucleation at the phase boundaries. At -0.8 V (Figure 5.2C), some of the β phase dissolved, manifesting as black lines. Pitting also occurred here. Micrographs at -0.7 V (Figure 5.2D), -0.4 V (Figure 5.2E) and -0.3 V (Figure 5.2F) showed high levels of β dissolution. At -0.1 V (Figure 5.2G) and +0.2 V (Figure 5.2H), the surface shows little visible corrosion. ImageJ analysis of the micrographs in Figure 5.2A to 5.2H quantifies the dissolved β at each potential (Figure 5.2I). Note the normal distribution-like appearance of the data. The cathodic range from -0.3 V to -0.7 V had significantly increased β dissolution compared to the other potentials (p < 0.05).



Figure 5.2. Micrographs of Ti-6Al-4V surfaces after 24 h in 24 °C, 0.1 M H₂O₂ solution at -1 V (A) and -0.9 V (B) show low levels of β dissolution. Small pits appear at the phase boundaries. At -0.8 V (C), the micrograph captures the surface in a transition from polished to dissolved. At -0.7 V (D), -0.4 V (E) and -0.3 V (F) a majority of the β phase is dissolved, a significant increase compared to the other potentials (p = 0.000). Micrographs for -0.1 V (G) and +0.2 V (H), respectively, show much less selective dissolution of the β phase. (I) Summary of the β phase dissolution (%) versus applied electrode potential (vs Ag/AgCl) over 24 h. Note the rise and fall

of dissolution over the potential range investigated. Potentiostatic experiments were run at least three times at each voltage ($n \ge 3$).

5.3.2 Representative EIS during active dissolution

The metal-oxide-solution interface may be modeled using the Randles CPE circuit (Figure 5.3A). Representative data (n = 1) captured after 3, 6, 9, and 12 h at -0.4 V in 24 °C 0.1 M H₂O₂ solution generally conform to the Randles CPE circuit model (Figure 5.3B-D). Note the rapid decrease in real and imaginary impedance from 3 h to 6 h in the Nyquist plot in Figure 5.3B. Bode magnitude (Figure 5.3C) and phase (Figure 5.3D) plots reveal a systematic decrease in both |Z| and Θ over time. Like the Nyquist plot, the largest change occurs between 3 and 6 h.



Figure 5.3. (A) Schematic of the Ti-6Al-4V oxide interface and corresponding Randles circuit model. Nyquist (B), Bode magnitude (C) and Bode phase (D) plots generally show Randles CPE behavior. Note the systematic decrease in impedance as the Ti-6Al-4V oxide is continuously exposed to -0.4 V in 24 °C 0.1 M H₂O₂ solution. Data are representative (n = 1).

5.3.3 The effect of temperature on impedance and β dissolution in 0.1 M H₂O₂

Plots of $Log_{10}R_p$ and $Log_{10}(Q^{-2})$ vs. time during sustained -0.4 V cathodic activation (Figure 5.4) show systematic behavior. First, the application of a -0.4 V hold at t = 0 h significantly decreased the $Log_{10}R_p$ from the baseline acquired vs. OCP (Figure 5.4A, top left, p < 0.05). As the sample is continuously held at -0.4 V, $Log_{10}R_p$ continues to decrease, before reaching a plateau. Visually, the rate of this decrease depends on the solution temperature. From 0 to 6 h, as temperature increases, the $dLog_{10}R_p/dt$ also increases (i.e., becomes steeper). Note the consistent gap between data captured in 24 and 37 °C solutions from 12 to 24 h. After 24 h, $Log_{10}R_p$ decreased to 2.3 Ω cm² (199 Ω cm²) for the 24 °C samples and 1.9 Ω cm² (79 Ω cm²) for the 37 °C samples.

EIS captured on a shorter timescale in 45 °C solution (one spectrum every eight minutes) follows a similar pattern: $Log_{10}R_p$ rapidly decreases before reaching a plateau (Figure 5.4B). In contrast with $Log_{10}R_p$, $Log_{10}(Q^{-2})$ (Figure 5.4C-D) continues to visually decrease with time, though this rate also changes. Time (0–6 h), temperature (24, 37 °C), and the temperature*time interaction all significantly affected $Log_{10}R_p$ and $Log_{10}(Q^{-2})$ (p = 0.000). Here, the comparatively shorter experimental time of the 45 °C tests (6 h vs. 24 h) constrained the statistical analysis.



Figure 5.4. In 0.1 M H₂O₂ solution and under sustained -0.4 V cathodic activation, $Log_{10}R_p$ (A-B) and $Log_{10}(Q^{-2})$ (C-D) systematically decrease with increased time and temperature. From 0-6 h, the slope visually increases as temperature increases (A). Note the two linear regions in $Log_{10}R_p$ before and after 1 h in 45 °C 1 M H₂O₂ solution (B). Experiments were run at least three times for each temperature condition (n > 3).

Using the $Log_{10}R_p$ plot in Figure 5.4A as a guide, Ti-6Al-4V samples were potentiostatically held at -0.4 V in 0.1 M H₂O₂ for different times and temperatures. In 24 °C solution, after 6 h the samples showed a small (<20 %) amount of β dissolution (Figure 5.5A). This is comparable to 37 °C and 45 °C at 4 h and 0.5 h, respectively (Figure 5.5D and 5.5G). β dissolution continued to progress, nearing complete dissolution at 12 h, 7 h, and 4 h for 24 °C, 37 °C, and 45 °C, respectively (Figure 5.5C, 5.5F, and 5.5I). The fastest progression of β dissolution occurred in 45 °C solution which achieved dissolution (91 % dissolved β) four times faster than 24 °C (Figure 5.5J). Note the increase in Weibull CDF slope as temperature increases.



Figure 5.5. Increasing 0.1 M H₂O₂ solution temperature increased the rate of β dissolution. Note the decrease in experimental time needed to induce dissolution as temperature increased from 24 °C (A-C) to 37 °C (D-F) and finally to 45 °C (G-I). Weibull CDF fits of the experimental data (J) show increasing slopes as the solution temperature increased.

5.3.4 Correlation of impedance and β dissolution in 0.1 M H₂O₂ 24 °C solution

A plot of R_p vs. time and β dissolution vs. time provides insight into the corrosion mechanism (Figure 5.6). Generally, a decrease in R_p precedes an increase in β dissolution. From 0-6 h, R_p rapidly decreases from 1.7 * 10⁴ to 1.6 * 10³ Ω cm². Around 12 h, R_p continues to decrease, but remains the same order of magnitude (10² Ω cm²) for the experiment's duration. Between 6 and 12 h, β dissolution increases from 19 % to 90 %. Thus, β visibly dissolves after the R_p decreases by an order of magnitude from the initial -0.4 V cathodic activation. However, dissolution initiation occurred prior to the R_p plateau. The fit Weibull CDF projects a measurable increase in β dissolution (from 0 % to 1 %) at 4 h. Simultaneously, R_p equals 3.0 * 10³ Ω cm². For a particular concentration-temperature combination, an R_p threshold may exist. Once R_p degrades past this value, β dissolution may initiate. Note the increased variance in the β dissolution at 9 h, indicative of the multiple surface classes (dissolved, transition, undissolved) documented at this time.



Figure 5.6. A dual y-axis plot of β dissolution (purple circles, right axis) and R_p (green circles, left axis) vs. time shows how oxide degradation precedes corrosion initiation in 24 °C 0.1 M H₂O₂ solution. A characteristic R_p threshold may exist for a particular concentration-temperature

combination. Averages represent four (n = 4) EIS trials and three (n = 3) BSE SEM micrographs captured after 6, 9, and 12 h, respectively.

5.3.5 The effect of temperature on impedance and β dissolution in 0.05 M H₂O₂

Decreasing solution concentration from 0.1 M to 0.05 M H₂O₂ yielded similar systematic differences in Log₁₀R_p and Log₁₀(Q⁻²) over time (Figure 5.7A and 5.7B). In the family of Log₁₀R_p vs time curves (Figure 5.7A), as the temperature increases from 24 °C to 45 °C, Log₁₀Rp decreases. Note the increasing negative slopes (dLog₁₀R_p/dt) from 0 to 6 h corresponding with increases in temperature. From 6 to 24 h, Log₁₀R_p continues to decrease, though at a reduced rate. This behavior, a rapid decrease followed by a long tail, repeats for 37 and 45 °C groups in the Log₁₀(Q⁻²) vs. time plot. In contrast, the 24 °C group exhibits a more linear decrease. These data suggest that as the surface transitions from undissolved to dissolved, structural changes occurring at the interface manifest as property changes in the CPE capacitance, Log₁₀(Q⁻²), and oxide polarization resistance, Log₁₀R_p. Statistical analysis reveals a significant effect of time (p = 0.000), temperature (p = 0.000) and time*temperature interaction (p > 0.001) on both Log₁₀Rp



Figure 5.7. In 0.05 M H₂O₂ solution, the oxide polarization resistance, $Log_{10}R_p$, (A) and CPE capacitance, $Log_{10}(Q^{-2})$, (B) decreased over 24 h when cathodically activated at -0.4 V. Increasing solution temperature from 24 °C to 37 °C and 45 °C yielded systematic decreases in both $Log_{10}Rp$ and $Log_{10}(Q^{-2})$. These changes support a structure-property relationship between the dissolving surface and the measured EIS circuit parameters. Experiments were run in triplicate (n = 3).

Micrographs captured at various time points in 0.05 M H₂O₂ solution under sustained -0.4 V cathodic activation show an increase in β dissolution as temperature increases from 24 °C to 45 °C (Figure 5.8). Time points selected after the rapid decline of R_p in Figure 5.7A show a common progression. First, pits nucleate in the β phase and at the α + β phase boundaries. Second, pit width grows and interconnects. The β phase is visibly present but no longer level with the surrounding α grains. Third, the β phase dissolves from the Ti-6Al-4V surface. Dark crevices replace the white, vein-like β phase. Throughout the process, small pits propagate in the α phase
but do not progress to the same extent as the β . As temperature increased, the time-scale of this process shortened. At 24 °C, micrographs capture the various surface classes at 12 h (Figure 5.8A), 24 h (Figure 5.8B) and 48 h (Figure 5.8C). Increasing the temperature to 37 °C halved the experimental time needed to dissolve the β phase. After 6 h, (Figure 5.8D) the surface appears undissolved, after 12 h (Figure 5.8E), the surface is transitioning, and after 24 h (Figure 5.8F), β is dissolved. At 45 °C, this process occurred from 4-16 h (Figure 5.8G-I).

Weibull CDF fits (Figure 5.8J) of the analyzed images quantify the visual changes in A-I. Weibull CDF slopes increase as temperature increases. Larger error bars at the intermediate time point indicate multiple surface classes (dissolved, transition and undissolved).



Figure 5.8. The Ti-6Al-4V β phase progresses from (1) undissolved to (2) a transition state and finally (3) complete dissolution after 48 h in 24 °C 0.05 M H₂O₂ solution (A-C); 24 h in 37 °C solution (D-F) and 16 h in 45 °C solution. Weibull CDF fits show increasing slopes as temperature increases (J). Experiments were run at least three times for each time-point temperature combination (n \geq 3).

5.3.6 Correlating impedance properties with temperature and surface classes

Parametric plots of Log₁₀R_p vs. Log₁₀(Q) document families of curves for 0.1 M H₂O₂ (Figure 5.9A) and 0.05 M H₂O₂ solutions (Figure 5.9B) that are very similar, correlating measured values of Q and R_p. These relationships do not appear to be strongly dependent on temperature, time or concentration, and mostly overlap. The curves show a direct link between the drop in R_p and the rise in Q such that one of these values can predict the other one's value regardless of the solution or temperature present. Additionally, there is some temperature effect. As temperature increases from 24 °C, the slope of the respective curve increases ($dLog_{10}R_p/dLog_{10}(Q)$). This behavior is especially noticeable around $Log_{10}R_p = 3 \ \Omega cm^2$ and $Log_{10}(Q) = -4 \ Scm^{-2}(s)^{\alpha}$. The data captured over 24 h (Figure 5.4 and Figure 5.7) progress in a time dependent fashion. As time increases (not shown here), $Log_{10}R_p$ decreases and $Log_{10}(Q)$ increases. Regression between R_p and Q ($R^2 =$ 0.80-0.89) suggests a non-linear relationship, though a linking between the two circuit parameters exists. For the 0.05 M 24 °C group (Figure 5.9B), the Log₁₀R_p-Log₁₀(Q) curve appears truncated. This is likely due to the lack of data points acquired from a dissolved surface. While β dissolution occurred at 24 h in 37 °C solution and 16 h in 48 °C (Figure 5.8F, I) 48 h elapsed before micrographs show β dissolution in room temperature solution (Figure 5.8C). Labeling the Log₁₀ R_p vs. Log₁₀(Q) plots using the β dissolution (%) present (synthesizing the data in Figs. 5.4, 5.5, 5.7 and 5.8) resulted in three areas corresponding approximately with the surface class present (Figure 5.9A and 5.9B). This behavior is reproduced in both 0.1 M H_2O_2

shifts from (1) undissolved (blue) to (2) a transition state (yellow) and finally to (3) dissolved (green). Manually placed dashed lines generally separate the three surface classes. In 0.1 M H₂O₂ (Figure 5.9A), these occur at -4.1 and -3.5 Scm⁻²(s)^{α}. In 0.05 M H₂O₂ (Figure 5.9B), thresholds

and 0.05 M H₂O₂ solutions. As Log₁₀R_p decreases and Log₁₀(Q) increases, the surface class

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are delineated at -4.1 and -3.4 $\text{Scm}^{-2}(s)^{\alpha}$. Thus, the CPE parameter Q may be a useful predictor of surface dissolution class independent of solution temperature or concentration.

Bar charts of the average $\text{Log}_{10}R_p$ (Figure 5.9C) and $\text{Log}_{10}(Q)$ (Figure 5.9D) for each surface class (undissolved, transition, dissolved) quantify the changes in the impedance parameter curves (Figure 5.10A-B). Note the decrease in $\text{Log}_{10}R_p$ and increase in $\text{Log}_{10}(Q)$ as the surface class progresses. Both Mean $\text{Log}_{10}R_p$ (p = 0.000) and $\text{Log}_{10}(Q)$ (p = 0.000) were significantly different for each surface class. Additionally, the effect of solution concentration was significant (p = 0.000 for $\text{Log}_{10}R_p$ and p = 0.000 for $\text{Log}_{10}(Q)$) and significant concentration*surface class interactions were present (p = 0.002 $\text{Log}_{10}R_p$ and p = 0.000 for $\text{Log}_{10}(Q)$). Significant differences (p < 0.05) in pairwise comparisons are indicated with an asterisk.



Figure 5.9. Synthesizing $Log_{10}R_p - Log_{10}(Q)$ curves with the β dissolution (%) present establishes three surface classes as $Log_{10}R_p$ decreases and $Log_{10}(Q)$ increases. This behavior repeats in both 0.1 M H₂O₂ (A) and 0.05 M H₂O₂ (B) solutions. A clear relationship exists between Q and R_p during active dissolution. Bar charts averaging the mean $Log_{10}R_p$ (C) and $Log_{10}(Q)$ (D) reveal significant differences depending on the surface class. As the surface becomes dissolved, $Log_{10}R_p$ significantly decreases (p = 0.000) and $Log_{10}(Q)$ significantly increases (p = 0.000). A minimum of 39 data points were used for each surface class and concentration combination (n ≥ 39, n = 500 total).

5.3.7 Arrhenius-based analysis of corrosion rate and impedance

An Arrhenius plot (Figure 5.10) identifies a linear relationship between the inverse of the characteristic times needed to induce 63 % β dissolution, τ^{-1} , and inverse temperature, T⁻¹. As the solution temperature increases, the rate of corrosion linearly increases (R² = 0.95 for 0.1 M H₂O₂, R² = 1 for 0.05 M H₂O₂). Similar slopes suggest that the frequency factor, A, governs differences in corrosion rate within the sampled variable space (0.1 M and 0.05 M; 24 °C, 37 °C and 45 °C) rather than changes in the activation energy. Calculated activation energies for 0.1 M and 0.05 M solutions were 46,000 and 42,000 J/Mol, respectively.



Figure 5.10. An Arrhenius plot using the inverse of the characteristic time, τ , shows a clear relationship between the corrosion rate, H₂O₂ solution concentration and temperature. As temperature increases, the corrosion rate increases. Linearly regressed lines to the experimental Log τ^{-1} values share similar slopes.

5.4. Discussion

In this study, we systematically evaluated the effect of solution H_2O_2 concentration and temperature on Ti-6Al-4V β dissolution. First, we identified a cathodic potential range from -0.3 V to -0.7 V where a synergistic effect between the negative potential and 0.1 M H₂O₂ solution increased β dissolution (p = 0.000). Second, we captured impedance during a constant -0.4 V activation of the surface at three temperatures. We used the resulting plots of R_p vs. time to identify time points to image the Ti-6Al-4V surface. Weibull CDF fits to the image-based data clearly show a decrease in time needed to induce β dissolution as the solution temperature increased or concentration increased. Collecting additional impedance data and images over time, we correlated the corrosion rate, quantified from the SEM micrographs, with the circuit element parameters, revealing a structure-property relationship between the oxide film and the underlying Ti-6Al-4V surface class. Decreases in R_p and increases in Q corresponded with the progression of the surface from undissolved to a transition state to fully dissolved. Finally, we used an Arrhenius based analysis to show a linear dependence between the inverse solution temperature and Log of the inverse dissolution rate (i.e., Arrhenius behavior). In totality, these results support our original hypothesis of a temperature dependent oxide degradation mechanism preceding β phase dissolution.

Several challenges persist in the *in vitro* modeling of mechanically assisted crevice corrosion (MACC) damage modes. While researchers successfully model aspects of wear and fretting, few tests successfully reproduce chemically induced corrosion [47-56]. It is unclear what physiologically representative conditions *in vitro* induce pitting, hydrogen embrittlement, and the growth of thick oxides consistent with the damage observed on Ti-6Al-4V retrievals. What is the role of the patient's biology? The effect of the crevice geometry? The components of a representative *in vivo* solution? These broad, fundamental questions remain unanswered. In

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addition, efforts to develop *in vitro* solutions that both accelerate corrosion and relate back to physiological solutions and degradation modes are limited.

While we use supraphysiological levels of H_2O_2 in this study, researchers reproduce elements of the device-biology interface by altering the pH, culturing phagocytes, and introducing proteins [26, 27, 57-61]. Retrieved cobalt chrome (CoCrMo) heads show evidence of etching adjacent to macrophages. When challenged with wear particles, the CoCrMo corrosion resistance lowers to a magnitude of $10^3 \ \Omega \text{cm}^2$ and capacitance increases, consistent with the EIS behavior and R_p magnitude we document in this study [59]. Additionally, the challenged macrophage condition decreased the reported open circuit potential to around -0.75 V, introducing an additional possible source of cathodic activation at the CoCrMo-Ti-6Al-4V modular taper junction. Activated macrophages cultured on CoCrMo discs show significant increases in molybdenum concentration when digested and compared with non-activated cells [58]. Thus, within modular taper junctions, cell activity during the initial inflammatory cascade and subsequent chronic inflammatory state may play a role in initiating crevice corrosion damage modes.

The crevice geometry, where retrieval studies document severe Ti-6Al-4V corrosion, remains poorly understood. The proximity of the interfaces within the crevice and the small solution volumes present are hypothesized to play key roles during MACC [62]. The small volume of ingressed solution within the crevice differs in composition from the bulk. A gradient between the crevice and the bulk drives ion transport. Attempts at replicating the crevice geometry and conditions *in vitro* fail to reproduce the damage observed on retrievals [63].

These gaps extend to pre-clinical device testing, where a lack of representative, standardized tests limit *in vivo* predictions. The existing ASTM standard (F746, Pitting or Crevice Corrosion of Metallic Surgical Implant Materials), useful for material selection, does not evaluate implant

design [42]. First, cyclically polarizing titanium alloys to + 0.8 V as the test recommends likely has little effect, as this potential falls within the Ti-6Al-4V passive region. Next, many modular junctions *in vivo* contain two metal surfaces, rather than the metal on polytetrafluoroethylene (PTFE) couple in the test. Finally, modular taper junctions *in vivo* experience cyclic loading as the patient moves, promoting MACC. For titanium biomaterials, a more representative crevice corrosion test likely includes elements of cathodic activation (either through fretting or potentiostatic applications) and inflammatory simulating solutions including reactive oxygen species or activated macrophages. Additionally, as we show here, increasing the electrolyte temperature may help to rapidly evaluate the effect of various oxidizers, acids, and corrosion debris, decreasing the experimental time needed to simulate the adverse electrochemical events that occur at device interfaces. This proposed high throughput analysis is based on the Arrhenius behavior with temperature, allowing for systematic links between accelerated corrosion at higher temperatures and decreased corrosion rates at physiological temperatures.

If we assume the rate of selective dissolution, R, is described by τ^{-1} from the Weibull CDF, and the reaction rate is based on 1st order chemical reaction rate theory, then:

$$R = \frac{1}{\tau} = \tau^{-1} = k[C]$$
(5)

where [C] is the concentration of H_2O_2 and k is the reaction rate constant which is temperature dependent according to the Arrhenius equation:

$$k = Ae^{\frac{E_a}{RT}}$$
(6)

where A is the frequency (or pre-exponential) factor, E_a is the activation energy, R is the ideal gas constant and T is the temperature. Combining these yields

$$\tau^{-1} = [C]Ae^{\frac{E_a}{RT}}$$
(7)

Taking the Log of both sides results in:

$$\log_{10} \tau^{-1} = \log_{10} [C] + \log A - \frac{2.303 E_a}{R} \frac{1}{T}$$
(8)

This equation shows a Log-Log relationship between τ^{-1} and [C], and a straight-line relationship between Log10 τ^{-1} and T⁻¹, the slope of which is 2.303 times the activation energy divided by the ideal gas constant, R. It should be noted that when [C] = 1, and T⁻¹ = 0, A = τ^{-1} which can be determined from the intercept of the lines shown in Figure 5.10. The slopes for the two concentrations are close to one-another at about 2200, which translates into an activation energy, E_a of about 42,000 J/molK. Figure 5.10 shows three temperatures and two concentrations where the τ^{-1} was determined. One can use these conditions to solve for LogA which ranges from 7.0 to 7.3 (for 0.05 M, 7.02, and for 0.1 M, 7.27). Figure 5.10 also shows the slope term to be similar for the two concentrations. Thus, this equation, with A and E_a known, can be used to estimate the time constant for dissolution for any combination of concentration and temperature. For example, using Log₁₀A of 7.1 and 2.303E_a/R = 2161, τ^{-1} for 1 mM would be about 740 h or 31 days. Such estimates make it possible to interpret the accelerated effects of H₂O₂ in physiologically representative conditions for Ti-6Al-4V.

In addition to the ability to combine temperature and concentration effects, estimating the time to induce selective dissolution, the correlation between R_p and Q for these samples is also important and revealing. It appears that significant changes in the passive oxide film precede selective dissolution. Indeed, monitoring of the oxide film may be a tool to assess how close to such conditions a surface is before dissolution commences. In addition, because R_p and Q are so

correlated, measurement of one of these two will allow for estimations of the other. This may be important in impedance acquisition methods where Q can be obtained from high frequency analysis at very short time intervals. Thus, monitoring of Q may be an excellent means of tracking rapid changes in impedance characteristics in electrode-electrolyte systems.

We experienced several limitations throughout this study. While imaging corroded samples during the transition time point (between τ_{10} and τ_{80}), we documented various surface classes. Some of the samples were truly in-between, evidenced by the micrographs in Figure 5.5B, 5.5E, and 5.5H. However, at these intermediate timepoints, we also observed dissolved and undissolved conditions. This variability is represented in the large standard deviations for these groups and suggests a stochastic mechanism. Probabilistic pit nucleation at the phase boundaries may depend on the surface area of the β phase, localized crystallographic defects, and the degraded structure of the oxide film overtop the Ti-6Al-4V substrate. Empirical data from this study and others shows that once pitting initiates, growth and dissolution proceeds in a more predictable and consistent manner [25].

This work focused on a single applied potential, -0.4 V vs Ag/AgCl to induce selective dissolution. It is clear that other potentials will alter the time course of selective dissolution as we have documented previously and will alter this analysis accordingly [24, 25].

Additionally, we previously investigated temperatures as high as 55 °C on the oxide film properties [24]. These tests required comparatively less experimental time than the 24-48 h trials we ran in this study. After multiple 24 h + trials at temperatures of 45 °C and above, the Ag/AgCl reference electrodes we used began to corrode and deposit on the Ti-6Al-4V surface. At higher than physiological temperatures, the electrical connection between the working electrode and the external wire often failed. Bubbles emitting from the carbon counter electrode accumulated over time, obscuring the working electrode surface area, and increasing the solution resistance. When these events occurred, we ran additional trials to replace the failed tests, measuring the potential of our references vs. a stable Ag/AgCl electrode. We additionally conducted several validation experiments to assess the internal reproducibility of our results. Avoiding these temperature-induced failures likely requires a testing setup less dependent on hot glue, wires, and tape.

The data generated in this study is well suited for the application of artificial intelligence. We establish a clear connection between the circuit parameters, R_p and Q, and the corresponding surface class. Unsupervised machine learning algorithms, including k-means clustering and non-negative matrix factorization, may accurately predict the surface classes from the EIS data alone. Labeling the EIS pairs with their ground truth (undissolved, transition, dissolved) allows for the training of neural network and support vector machine models. Future work will generate additional data to support machine learning analysis.

5.5. Conclusions

In this study, we investigated the effect of temperature on Ti-6Al-4V β phase selective dissolution. We showed systematic decreases in oxide R_p over time as the solution temperature (24 °C, 37 °C, 45 °C) increased (p = 0.000). Imaging the Ti-6Al-4V surface after the rapid degradation of R_p revealed an increase in corrosion rate, τ , dependent on the solution temperature. Correlation of the corrosion rate with the impedance data identified three surface classes with significantly different R_p and Q values (p = 0.000). This structure-property relationship between the oxide film and the underlying Ti-6Al-4V substrate may allow for rapid prediction of the surface class from impedance data using an artificial intelligence approach. Finally, an Arrhenius-based analysis identified a linear relationship between the solution

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temperature and the corrosion rate ($R^2 = 0.95$ for 0.1 M H₂O₂, $R^2 = 1$ for 0.05 M H₂O₂). The temperature-dependent nature of Ti-6Al-4V dissolution allows for rapid testing of implant designs and may decrease the experimental time needed to induce chemically induced corrosion damage modes during exploratory research.

5.6. Acknowledgements

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5.7. Data Availability

The data that support the findings of this study are available from the corresponding author,

Jeremy L. Gilbert, upon reasonable request.

5.8. References

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Chapter 6

Additively Manufactured Ti-29Nb-21Zr Shows Improved Oxide Passivation Resistance Versus Ti-6Al-4V in Inflammatory Simulating Solution

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Abstract: Retrieval studies in the past two decades show severe corrosion of titanium and its alloys in orthopedic implants. This damage is promoted by mechanically assisted crevice corrosion (MACC), particularly within modular titanium-titanium junctions. During MACC, titanium interfaces may be subject to negative potentials and reactive oxygen species (ROS), generated from cathodic activation and/or inflammation. Additive manufacturing (AM) may be able to produce new, corrosion-resistant titanium alloys and admixtures that are less susceptible to these adverse electrochemical events. In this study, we characterize the impedance and corrosion properties of three new AM titanium materials, including Ti-6Al-4V with added 1% nano-yttria stabilized ZrO₂, admixed Ti-29Nb-21Zr, and pre-alloyed Ti-29Nb-21Zr. We aim to elucidate how these materials perform when subjected to high ROS solutions. We include conventionally and additively manufactured Ti-6Al-4V in our study as comparison groups. A 0.1 M H₂O₂ phosphate-buffered saline (PBS) solution, simulating inflammatory conditions, significantly increased biomaterial OCP (-0.14 V vs Ag/AgCl) compared to PBS only (-0.38 V, p=0.000). During anodic polarization, Ti-6Al-4V passive current density more than doubled from $1.28*10^{-7}$ to $3.81*10^{-7}$ A/cm² when exposed to 0.1 M H₂O₂. In contrast, Ti-29Nb-21Zr passive current density remained relatively unchanged, slightly increasing from 7.49*10⁻⁸ in PBS to $9.31*10^{-8}$ in 0.1M H₂O₂. Ti-29Nb-21Zr oxide polarization resistance (R_p) was not affected by 0.1M H₂O₂, maintaining a high value (1.09 *10⁶ vs. 1.89*10⁶ Ω cm²), while Ti-6Al-4V in 0.1 M H₂O₂ solution had significantly diminished R_p (4.38*10⁶ in PBS vs. 7.24*10⁴ Ω cm² in H₂O₂). These results indicate that Ti-29Nb-21Zr has improved corrosion resistance in ROS containing solutions when compared with Ti-6Al-4V based biomaterials.

Graphical Abstract:



Highlights:

- Ti-29Nb-21Zr shows higher R_p in 0.1 M H₂O₂ compared to Ti-6Al-4V based biomaterials.
- Ti-29Nb-21Zr passive current density and R_p are not affected by immersion in 0.1 M H₂O₂ compared to phosphate buffered saline while Ti-6Al-4V is affected.
- Pre-alloying had little effect on the corrosion properties of Ti-29Nb-21Zr.

Keywords: Ti-6Al-4V, Ti-29Nb-21Zr, additive manufacturing, corrosion, biomaterial selection, orthopedic materials

6.1. Introduction

The two-phase $\alpha+\beta$ titanium alloy, Ti-6Al-4V, is widely used in the biomedical field due to its excellent biocompatibility, osseointegration, corrosion resistance, and mechanical properties [1-4]. *In vivo*, the biology-device interface subjects Ti-6Al-4V to chemically and mechanically destructive conditions [5-11]. Within the oral cavity, acidic drinks and foods may decrease the pH to less than 6—well below physiological levels—and pathobionts can induce inflammation [12, 13]. Additionally, diseases like periodontitis disturb the oral microbiome, promoting infection, acidity, and enhanced corrosion at the tissue-implant interface [14, 15].

Inflammatory conditions remain a concern in orthopedics, where severe corrosion of Ti-6Al-4V has been documented on retrieved orthopedic implants [16-21]. Micrographs of failed devices show large-scale pitting, the formation of hundreds of micron-thick oxides, hydrogen embrittlement, and selective dissolution [7, 11]. Mechanically assisted crevice corrosion (MACC) promotes this damage within the constricted modular taper microenvironment [5, 22]. While recent *in vitro* studies show that sustained cathodic activation and reactive oxygen species (ROS) induce selective dissolution of the Ti-6Al-4V β phase, crevice corrosion damage modes remain poorly understood. Additionally, fretting at the modular taper junction between Ti-6Al-4V stems and cobalt or ceramic heads is an ongoing concern [6, 23-29]. Thus, documented *in vivo* corrosion modes of Ti-6Al-4V raise questions about alternative titanium alloys and their performance in ROS containing solutions.

Additive manufacturing (AM) may be a way to generate new orthopedic devices and metallic biomaterials. Currently, AM metals in the human body are limited to Ti-6Al-4V, CoCrMo, 316L Stainless Steel and other alloys used in traditionally manufactured medical devices [30, 31]. In orthopedics and dentistry, AM Titanium devices are implanted with increasing frequency at the

point of care. Current *in vivo* applications include spinal cages, bone plates, acetabular shells, tibial trays, and dental implant screws. Extensive literature exists on the long-term effects of conventionally manufactured Ti-6Al-4V in the human body, and early reports from device registries suggest low revision rates for AM Ti-6Al-4V devices [32]. However, little is known about how AM titanium alloys will respond to long term implantation, particularly in the context of modular junctions where most corrosion of Ti-6Al-4V has been documented.

In medical device development, AM's ability to produce complex geometries, reduce material waste, and generate patient-specific devices are considerable advantages over traditional manufacturing [30, 33]. Powder bed fusion allows for the rapid development of new titanium alloys and admixtures, where powders of different compositions can be sintered together. The weight percentages of α and β stabilizers in powder metallurgy are customizable, and printing settings and post-print annealing can tune material properties including microstructure, corrosion resistance, density, porosity, and strength [30, 34, 35]. For patients undergoing a second or third revision surgery, or cancer patients suffering from bone loss, AM can produce devices to fit their specific needs, filling a clinical gap that off-the-shelf modular devices cannot.

Although Ti-6Al-4V device revision rates remain low in many orthopedic and dental applications, various β and near β titanium alloy alternatives have been developed [3, 36-38]. The rationale for replacing Ti-6Al-4V has historically centered on published literature of vanadium ion cytotoxicity at the device interface and generating an alloy with a lower modulus to mitigate stress shielding [39, 40]. While vanadium ion cytotoxicity has proven to be a non-issue, *in vitro* studies show that the Ti-6Al-4V α - β phase boundaries are susceptible to corrosion when exposed to cathodic activation and ROS [23, 41]. Thus, the equiaxed α + β microstructure, originally optimized for

fatigue crack initiation resistance, exhibits diminished corrosion resistance when subjected to adverse electrochemical conditions within the confines of a crevice [7, 11].

Modular implant designs, inherent in most total hip and knee replacement systems, promote negative potential excursions and ROS at device interfaces by creating localized environments where two surfaces are in proximity. Within the small volume of a crevice, conditions that might otherwise have little effect in the bulk solution can initiate an auto-catalytic cascade. Additionally, both cathodic activation and ROS are hypothesized components of the MACC mechanism. During MACC, excess free electrons generated by metal oxidation reactions decrease the potential of the electrode interface. Mechanically assisted corrosion (e.g., tribocorrosion) processes interrupt the passive oxide film, and subsequent oxide passivation can decrease Ti-6Al-4V potential to as low as -1V [42]. These cathodic excursions may be able to generate ROS at the metal surface independent of oxidative stress or the inflammatory cascade post implantation [43].

Compared with Ti-6Al-4V, the near β titanium alloy Ti-13Nb-13Zr (using niobium as a β stabilizer) exhibits improved corrosion performance in inflammatory simulating solutions [44]. Although Ti-13Nb-13Zr was designed as an orthopedic alloy, and has been used in permanently implanted medical devices, Ti-6Al-4V remains the predominant titanium medical alloy in the United States [37, 38]. It is unclear if AM Ti-6Al-4V, with a microstructure modified from the equiaxed, two phase $\alpha+\beta$ of conventionally manufactured Ti-6Al-4V, will be susceptible to crevice and tribological damage modes. With the rise of digital dentistry and as more AM orthopedic devices are placed into patients, creating new titanium alloys specifically designed to take advantage of AM may mitigate some of the tradeoffs between fatigue resistance, modulus, and electrochemical performance *in vivo*.

In this study, we investigate the fundamental corrosion and impedance properties of three candidate titanium biomaterials: AM Ti6Al4V with 1% nano-yttria stabilized zirconia (Ti-6Al-4V 1% nYSZ), admixed Ti-29Nb-21Zr (admix Ti-29Nb-21Zr), and pre-alloyed Ti-29Nb-21Zr (Ti-29Nb-21Zr). While Hattal et al. studied the microstructural and mechanical properties of Ti-6Al-4V 1% nYSZ, comparing as-built and heat-treated samples, the admixture's corrosion properties (along with the Ti-29Nb-21Zr biomaterials) remain unknown [45-47]. We aim to evaluate these new biomaterials in the context of high ROS solutions that may arise within modular junctions *in vivo* and compare them to conventional and additively manufactured Ti-6Al-4V. Using hydrogen peroxide—a chemical species generated by the immune system—as a proxy for all ROS, we determine the effect of a simulated inflammatory solution on open circuit potential (OCP) and anodic potentiodynamic polarization. We also use electrochemical impedance spectroscopy (EIS) to assess oxide polarization resistance in both normal and simulated inflammatory conditions. We hypothesize that admix and pre-alloyed Ti-29Nb-21Zr AM alloys will be less susceptible to simulated inflammatory conditions that Ti-6Al-4V based biomaterials.

6.2 Methods

6.2.1 Biomaterial Composition

In this study, the corrosion properties of five different alloys and admixtures are characterized. Three materials were Ti-6Al-4V based, including conventionally manufactured Ti-6Al-4V, AM-Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ. The remaining two alloys were admix Ti-29Nb-21Zr and Ti-29Nb-21Zr. For the sake of brevity, these biomaterials may be further abbreviated in figure axes as Ti64, AM Ti-64, Ti-64 1% nYSZ, admix TNZ, and TNZ, respectively. Mill-annealed Ti-6Al-4V ELI with an equiaxed α + β microstructure (ASTM F-136) and AM Ti-6Al-4V were selected as comparison alloys due to their current use *in vivo*, and the existing body of literature characterizing their corrosion behavior. AM samples and powders were supplied by Z3DLAB SAS (Paris, France).

Histograms of particle size were generated for each powder precursor. Scanning electron microscopy (SEM, SN3700, Hitachi Inc., Tokyo, Japan) was used to capture images of the powder. Resulting micrographs were subjected to measurements using Image Processing and Analysis in Java (Image J), a publicly available software package from the NIH. Energydispersive x-ray spectroscopy (EDS, Aztec, Oxford Instruments, Abingdon, UK) was used to confirm the elemental composition of as-received biomaterial powders and samples. Compositions from provided material data sheets are reported in Table 6.1. SEM and EDS maps of the as-received powders were captured at 500x.

6.2.2 Biomaterial Printing & Post-Processing

Prior to the selective laser melting-powder bed fusion (SLM-PBF) process, a 20 mm diameter x 4 mm thick disc form was generated in SOLIDWORKS 2021 and exported as an STL file. This file was then sliced in AutoFab Version 1.8. Samples were manufactured under a vacuum to prevent oxygen from spontaneously reacting with titanium powder particles and anodizing the as-built sample during printing. AM Ti-6Al-4V, Ti-6Al-4V 1% nYSZ, admix Ti-29Nb-21Zr, and Ti-29Nn-21Zr were additively manufactured on an SLM 125HL (SLM Solutions Group AG, Lübeck, Germany) machine. Printing parameters are reported in Table 6.2. Following the SLM-PBF manufacturing process, samples were stress relieved at 600 °C for 3 h, followed by air cooling.

6.2.3 Metallographic and Electrochemical Sample Preparation

As-received samples included AM Ti-6Al-4V, admix Ti-29Nb-21Zr, and Ti-29Nn-21Zr in disc form. Ti-6Al-4V 1% nYSZ was received as a cubic test coupon with approximately 20x10x60 mm dimensions. This test coupon was sliced using a Buehler circular diamond abrasive cut-off wheel (Lake Bluff, Illinois) into 20x10x5 mm samples to prepare for electrochemical testing. To ensure a flat surface for an electrical connection between a conductive wire and the sample, the support structures on as-received samples were abraded using a sanding belt.

Electrical connection between samples and wires was maintained using carbon tape and isolated from the electrolyte solution using epoxy resin (Cold Mounting JETSET Epoxy kit, METLAB, Niagara Falls, NY). The resin curing was performed over 24 h using a bottomed, cylindrical mold coated with PTFE spray-on lubricant. Each sample was removed from its mold once fully hardened.

Prior to each electrochemical test, samples were polished to a mirror finish. This multi-step process involved abrading the samples using 240, 320, 400, and 600 grit emery paper, followed by using a polishing disk with 1.0 µm and 0.3 µm alumina powders suspended in de-ionized water. To prepare for SEM imaging of the sample microstructure, a final polish was applied using a suspension of 40% H₂O₂ (9.8 M stock solution) and 60% non-crystalline colloidal silica. Sample microstructure was imaged in SEM backscatter electron mode (BSE) at 2000x magnification. To determine element distribution in the microstructure, EDS spectra were captured for the admix Ti-29Nb-21Zr for 1 h. Additional EDS were captured in secondary mode for as-built and stress relieved samples in triplicate. The average chemical composition (weight %) of the printed parts and 95% confidence intervals are reported in Table 6.3.

6.2.4 Electrochemical Testing

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Before each experiment, the exposed sample surface area was isolated using insulating adhesive tape. This division allowed for multiple experiments to be performed on a singular metal sample before re-polishing. Sample area was then measured and recorded before each experiment using a digital optical microscope (DOM, Keyence VHX-6000, Keyence Corp., Mahwah, NJ).

Electrochemical data was acquired using a VersaSTAT 4 (AMETEK, Berwyn, PA) and a Solartron 1280C (AMETEK, Berwyn, PA), both programmable single-channel potentiostats. Each sample was connected to a potentiostat in a three-electrode system. A carbon rod was used as the counter electrode, an Ag/AgCl wire was used as the reference electrode, and the sample, connected via conductive wire, was used as the working electrode. Tests were programmed in the VersaStudio software. Each trial began by monitoring open circuit potential (OCP) for 3600 s to assess the effect of adding 0.1 M H₂O₂ to the PBS solution. Next, electrochemical impedance spectroscopy was sampled at OCP from 10000 to 0.01 Hz. Finally, potential was anodically swept, beginning at -0.2 V below the previously measured OCP and finishing at 1 V vs. the Ag/AgCl reference electrode. Following electrochemical testing, the passive region of the anodic polarization data was individually fit using linear regression to find the passive current density. Impedance data were fit using phase angle symmetry, Randles-CPE circuit elements were extracted, and the area was normalized [48].

6.2.5 Statistical Methods

All electrochemical tests were run in triplicate (n=3). Significant differences in OCP, passive current density, CPE capacitance (Q), and oxide resistance (R_p) were assessed using a two-way analysis of variance (ANOVA) with biomaterial and solution type as factors. Passive current density and R_p were log₁₀ adjusted prior to the ANOVA. For all statistical tests in this work, an α level of 0.05 was used to assess significance, followed by a post-hoc Tukey's multiple

comparison test. Statistical analysis was conducted in MATLAB software versions R2019b, R2020b, and R2021b.

6.3. Results

6.3.1 Characterization of powders, as-built sample surfaces, and microstructure

AM Ti-6Al-4V powder beads (Fig. 6.1A) are pre-alloyed, spherical, and have minimal particles adhered to the surface. Note the small defects on the surface of particles larger than 20 μm. Particle diameters (Fig. 6.1E) ranged from 2-58 μm (Mean 13.5 μm). Micrographs of Ti-6Al-4V 1% nYSZ powder (Fig. 6.1B) show that it is an admixture of pre-alloyed Ti-6Al-4V powder and 1% nYSZ particles. The nano-ceramic appears as tiny particles on the surface of the comparatively larger powder beads. Particle diameter (Fig. 6.1F) ranged from 2-50 μm (Mean 15.1 μm). For the sake of comparative analysis, ceramic nYSZ particles were not included in this count as particle diameter size is visually smaller.

Micrographs of admix Ti-29Nb-21Zr (Fig. 6.1C) show particles of three different shapes and contrasts corresponding with the three different elements in the admixture. Spherical titanium particles appear the darkest, while the comparatively smaller spherical Zirconia particles are light grey. Cuboidal particles of niobium appear the brightest. Particle diameter (Fig. 6.1G) ranged from 2 to 42 μ m (Mean 9.64 μ m), and the micrograph visibly shows more particles than the other powders (Fig. 6.1A-B, Fig. 6.1D). ImageJ analysis (Fig. 6.1G) supports this visual assessment as both small particles (n = 116, diameter between 2 and 10 μ m) and total particles (n = 188) were the most out of the five powders analyzed. Finally, a micrograph of Ti-29NB-21Zr (Fig. 6.1D) shows a homogenous, pre-alloyed powder. The particle density documented in this micrograph is lower than the other three powders, and the histogram of particle diameter (Fig.

6.1H) reveals a right-skewed distribution. Particle diameter ranged from 2 to 42 μ m (Mean 7.14 μ m).



Figure 6.1. SEM Micrographs of (A) AM Ti-6Al-4V; (B) Ti-6Al-4V 1% nYSZ; (C) Admix Ti-29Nb-21Zr and (D) Ti-29Nb-21Zr powders. Note the difference in contrast of 1% nYSZ debris in (B) and the Ti, Nb, and Zr particles in (C). Histograms of (E) AM Ti-6Al-4V; (F) Ti-6Al-4V 1% nYSZ; (G) Admix Ti-29Nb-21Zr and (H) Ti-29Nb-21Zr show powder diameter distributions as well as particle counts within each micrograph. Micrographs are 500x BSE.

EDS mapping of AM Ti-6Al-4V powder (Fig. 6.2A) reveals pre-alloyed powder beads containing titanium, vanadium, and aluminum. Using x-ray mapping (false color maps), 1% nYSZ particles in Fig. 6.2B appear bright green in contrast to the blue Ti-6Al-4V. When magnification increases (Fig. 6.2C), EDS mapping documents the presence of ZrO₂ within the stabilized ceramic particles. Admix Ti-29Nb-21Zr powder (Fig. 6.2D) distinctly shows the elements of each Ti, Nb, and Zr particles. Spherical Ti and Zr are designated as purple and green, respectively, while cubic Nb appears orange in these false color EDS maps. When these elements are pre-alloyed, powder particles appear yellow in Fig. 6.2E. Note the purple ring on each yellow Ti-29Nb-21Zr particle caused by the angle of x-ray acquisition within the SEM.



Figure 6.2. SEM EDS documents the elemental composition of (A) AM Ti-6Al-4V; (B) Ti-6Al-4V 1% nYSZ; (C) 1% nYSZ: (D) Admix Ti-29Nb-21Zr and (E) Ti-29Nb-21Zr particles. Note the homogenous appearance of pre-alloyed particles in (A) and (E) compared with distinctly different colored particles of admixtures in (B) and (D). SEM micrographs are BSE with elemental map overlays at 500x magnification.

DOM images of as-built AM Ti-6Al-4V and admix Ti-29Nb-21Zr show square 5 mm x 5 mm (Fig. 6.3A) and 2.5 mm x 2.5 mm (Fig. 6.3D) islands. Note the diagonal scan path relative to the island borders on both as-built sample surfaces. At the intersection of AM Ti-6Al-4V islands (Fig. 6.3B), residual un-melted powder beads are present. Swirling melt patterns are visible where the laser rastered across the region. At the island borders, (Fig. 6.3C), voids are present with unmelted particle beads. The admix Ti-29Nb-21Zr island intersection (Fig. 6.3E) is similarly swirl-shaped and comparatively larger. The border between the two admix Ti-29Nb-21Zr islands (Fig. 6.3F) melds together with the edges of the laser spot's path across the surface visible as lines intersecting diagonally.



Figure 6.3. DOM images of the as-built surfaces for AM Ti-6Al-4V (A-C) and Admix Ti-29Nb-21Zr (D-F). Note the swirl pattern at the intersection of the islands in (B) and (E). AM Ti-6Al-4V borders in (C) contain voids where the Ti-6Al-4V powder did not infill and residual particle beads. In contrast, the admix Ti-29Nb-21Zr island borders (F) meet at a vertical line.

SEM BSE micrographs of the polished equiaxed Ti-6Al-4V (Fig. 6.4A) show a distinct twophase microstructure. The α phase is globular in appearance and darker in contrast to the intermittent and vein-like structure of β . The microstructure of stress-relieved AM Ti-6Al-4V (Fig. 6.4B) appears martensitic with a hatch-like pattern of small needles characteristic of the SLM-powder bed fusion manufacturing process. Prior β grain boundaries are also observed. Approximately 20 µm lamellar α grains appear darker in contrast than the rest of the surface and are interspersed throughout. Lamellar α grains in Ti-6Al-4V 1% nYSZ (Fig. 6.4C) vary in size, with the largest greater than 30 µm and the smallest less than 5 µm. Post-build and stressrelieved microstructures are similarly martensitic. Micrographs of admix Ti-29Nb-21Zr (Fig. 6.4D) reveal three distinctly contrasted regions corresponding with areas where Ti, Nb, and Zr particles rapidly melted and resolidified. The admixed alloy has a much more heterogeneous chemical distribution than represented in Fig. 6.4D, (see Fig. 6.5). BSE micrographs of the prealloyed Ti-29Nb-21Zr reveal a homogenous near β alloy with no distinguishable microstructure under normal polishing conditions.



Figure 6.4. BSE SEM micrographs of the following admixtures and alloys: (A) Ti-6Al-4V; (B) AM Ti-6Al-4V; (C) Ti-6Al-4V 1% nYSZ; (D) Admix Ti-29Nb-21Zr; and (E) Ti-29Nb-21Zr.

Micrographs show two phase microstructures for Ti-6Al-4V, AM Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ. Admix Ti-29Nb-21Zr (D) shows rapid melting and solidification of the distinct element particles observed in Fig. 6.1C. The microstructure of the near β alloy Ti-29Nb-21Zr (E) is indistinguishable under normal polishing conditions. Micrographs are 2000x magnification. SEM BSE micrographs of the polished admix Ti-29Nb-21Zr at higher magnifications of 60x (Fig. 6.5A) and 850x (Fig. 6.5B) reveal a heterogeneous microstructure with bright particles interspersed throughout. Note the swirling appearance of the microstructure in the bottom right of Figure 6.5A, and darker contrasted regions. SEM EDS (Fig. 6.5C) of the surface in Figure 6.5B and resulting false color maps (Fig. 6.5D-F) document several phenomena unique to the admixture. First, the bright particles in the BSE micrographs are remnants of the cuboidal niobium particles that have failed to melt completely. No titanium secondary x-rays were detected, and few zirconium secondary x-rays were acquired in these brightly contrasted regions. The point spectrum of regions one and two in Figure 6.5B identifies the elemental composition of these bright regions as 100% Niobium (Fig. 6.5G). Next, the darkest regions in both Figure 6.5A and Figure 6.5B are titanium-rich regions where titanium particle bead diffusion was concentrated during the rapid melting and re-solidification process. This observation of the variable concentration of titanium in the false map in Figure 6.5D overlaps the varying contrasted regions in Figure 6.5B. A point spectrum (spectrum four) acquired from this region shows an increase in titanium from 47.8 % (from the grey region in spectrum three) to 60.7%.



Figure 6.5. SEM BSE micrographs of admix Ti-29Nb-21Zr captured at (A) 60x and (B) 850x magnification. The locations of four elemental spectra acquisition points are denoted with

numbered diamonds. Capture resolution was selected based on micrograph features. Note the bright, dispersed niobium particles scattered throughout the heterogeneous microstructure. (C-F) EDS false map images visually show concentrated niobium particles within the microstructure, and titanium rich regions. Four spectra (G) were acquired, showing the various elemental distributions. The bright white particles in (A) and (B) were 100% niobium.

6.3.2. Effects of inflammatory species on open circuit potential

Open circuit potential (OCP) of Ti-6Al-4V in PBS was recorded as -0.450 V vs. an Ag/AgCl reference electrode (Fig. 6.6A). The addition of 0.1 M H₂O₂ increased OCP to -0.154 V. Both OCPs appear relatively stable after approximately 10 min and continued to slowly increase until 60 min. The OCPs for AM Ti-6Al-4V (Fig. 6.6B) in PBS and 0.1 M H₂O₂ after 60 min in solution were -0.358 V and -0.146 V, respectively. The rate of increase (dV/dt) was lower in magnitude than Ti-6Al-4V, and both OCPs ceased increasing after approximately 40 min. Both OCPs for Ti-6Al-4V (Fig. 6.6C) increased compared with either Ti-6Al-4V (Fig. 6.6A) or AM Ti-6Al-4V (Fig. 6.6B). Final recorded values were -0.243 V and -0.028 V for PBS and H₂O₂ respectively. After 60 min in solution, both OCPs continued to increase with a higher rate of change than Ti-6Al-4V (Fig. 6.6A).

The process of pre-alloying Ti-29Nb-21Zr had no effect on OCP in either PBS or 0.1 M H₂O₂. After 60 min, admix Ti-29Nb-21Zr OCP (Fig. 6.6D) was measured at -0.435 V and -0.174 V, while Ti-29Nb-21Zr (Fig. 6.6E) was recorded at -0.437 V and -0.191 V for PBS and H₂O₂ respectively. OCPs continued to increase for the 60 min data acquisition period. Averages of final OCP values (n=3) are shown in Figure 6.6F for each biomaterial and solution combination. There was a significant effect of solution on OCP (p = 0.000) and of biomaterial type on OCP (p = 0.000). Average Ti-6Al-4Z 1% nYSZ OCP was significantly higher than the other four

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biomaterials. Additionally, the average AM Ti-6Al-4V OCP was significantly higher than Ti-29Nb-21Zr.



Figure 6.6. OCP was measured in PBS and 0.1 M H₂O₂/PBS solution over 60 min for the following alloys and admixtures: (A) Ti-6Al-4V; (B) AM Ti-6Al-4V; (C) Ti-6Al-4V 1% nYSZ; (D) Admix Ti-29Nb-21Zr; and (E) Ti-29Nb-21Zr. Final OCP values (n=3) were averaged (Fig. 6.6F) and analyzed using a two-way ANOVA. The introduction of 0.1 M H₂O₂ significantly increased the OCP (p=0.000). OCPs for Ti-6Al-4Z 1% nYSZ were significantly higher than the other biomaterials (p=0.000). AM Ti-6Al-4V OCPs were also significantly increased compared to Ti-29Nb-21Zr.

6.3.3. Effects of inflammatory species on anodic polarization

The introduction of 0.1 M H₂O₂ solution increased the corrosion potential for all biomaterials. For Ti-6Al-4V (Fig. 6.7A), AM Ti-6Al-4V (Fig. 6.7B), and Ti-6Al-V 1% nYSZ (Fig. 6.7C),
passive current density also increased, indicated by the rightward translation of the H₂O₂ anodic polarization plots relative to the tests in PBS. No such shift occurred for admix Ti-29Nb-21Zr (Fig. 6.7D) and Ti-29Nb-21Zr (Fig. 6.7E) in 0.1 M H₂O₂. Note the development of an increase in the current density of the Ti-6Al-4V based biomaterials (Fig. 6.7A-C) around 0.7 V in 0.1 M H₂O₂. In contrast, the passive region of admix Ti-29Nb-21Zr and Ti-29Nb-21Zr extends to 1 V, the maximum value of anodic potentials sampled. Log-adjusted average (n=3) passive current densities are shown for each biomaterial in both PBS and 0.1 M H₂O₂ in Figure 6.7F. Both solution (p=0.000) and biomaterial type (p=0.006) significantly affected passive current density. Average passive current density of admix Ti-29Nb-21Zr was significantly lower than Ti-6Al-4V (p=0.006). Additionally, average passive current density of Ti-29Nb-21Zr was significantly lower than both Ti-6Al-4V and Ti-6Al-4V 1% nYSZ (p=0.006).



Figure 6.7. Representative anodic polarization plots of (A) Ti-6Al-4V; (B) AM Ti-6Al-4V; (C)

Ti-6Al-4V 1% nYSZ; (D) Admix Ti-29Zr-21Nb and (E) Ti-29Zr-21Nb in both PBS and 0.1M

 H_2O_2 solution. Note the shift in passive current density in Ti-6Al-4V based alloys in 0.1M H_2O_2 solution and evidence of the breakdown potential at 0.7 V. Average passive current density (F) of Ti-29Nb-21Zr was significantly lower than Ti-6Al-4V in 0.1M H_2O_2 and PBS solution (n=3) (p=0.011).

6.3.4 Effects of inflammatory species on electrochemical impedance

Bode magnitude plots $(Log|Z| \Omega cm^2 vs. Log(\omega) Hz)$ of biomaterials in both PBS and inflammatory solutions show predominately Randles-CPE behavior (see Fig. 6.8). Representative plots for both PBS and 0.1 M H₂O₂ solutions are shown for Ti-6Al-4V (Fig. 6.8A), AM Ti-6Al-4V (Fig. 6.8B), Ti-6Al-4V 1% nYSZ (Fig. 6.8C), admix Ti-29Nb-21Zr (Fig. 6.8D) and Ti-29Nb-21Zr (Fig. 6.8E). Generally, these data show similar high-frequency responses, regardless of solution, but have divergent behavior at low frequency, where the 0.1M H₂O₂ solution results in a lower impedance plateau for the Ti-6Al-4V alloys (Fig. 6.8A-8C), while having little effect on the Ti-29Nb-21Zr alloys. These results demonstrate that the R_p for the Ti-6Al-4V was significantly decreased in the H₂O₂ solutions compared to tests in PBS and that H₂O₂ solutions could not diminish the corrosion resistance of the Ti-29Nb-21Zr alloy samples.



Figure 6.8. Representative Bode impedance plots of (A) Ti-6Al-4V; (B) AM Ti-6Al-4V; (C) Ti-6Al-4V 1% nYSZ; (D) Admix Ti-29Nb-21Zr; and (E) Ti-29Nb-21Zr. Note how the 0.1 M spectra in (D) and (E) lack a second low-frequency elbow. Data shown are predominately Randles CPE-like (F).

Representative Bode phase plots (phase angle versus Log of the frequency, Fig. 6.9) correspond with the conditions and material combinations used to produce the Bode impedance plots in Figure 6.8. The variation in Ti-6Al-4V response to the different solutions is evident in these phase angle plots (Fig. 6.9A-6.9C). In contrast, the phase angle plots for the admix Ti-29Nb-21Zr (Fig. 6.9D) and Ti-29Nb-21Zr (Fig. 6.9E) show little difference between spectra captured in 0.1 M H₂O₂ and those captured in PBS. Note the slight differences in peak height in Figure 6.9D and the near identical peak heights in Figure 6.9E.

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Figure 6.9. Representative Bode phase plots of (A) Ti-6Al-4V; (B) AM Ti-6Al-4V; (C) Ti-6Al-4V 1% nYSZ; (D) Admix Ti-29Nb-21Zr; and (E) Ti-29Nb-21Zr. The entire phase angle spectrum was acquired in 0.1 M H₂O₂ solution for Ti-6Al-4V based biomaterials (A-C). Phase plots of (D) and (E) reveal little effect of inflammatory species on θ.

Nyquist plots of Z' and Z'' for Ti-6Al-4V (Fig. 6.10A) show a decrease in real and imaginary impedance magnitudes in 0.1 M H₂O₂ solution. This visual decrease in impedance is also documented for both AM Ti-6Al-4V (Fig. 6.10B) and Ti-6Al-4V with 1% nYSZ (Fig. 6.10C). The addition of 0.1 M H₂O₂ solution visually had little effect on either admix Ti-29Nb-21Zr (Fig. 6.10D) or Ti-29Nb-21Zr (Fig. 6.10E).



Figure 6.10. Nyquist plots of Z'' vs. Z' reveal a shift in real and imaginary impedance magnitudes for Ti-6Al-4V based biomaterials (A-C) upon the addition of 0.1 M H₂O₂ solution. Note the similarities in impedance magnitude for both admixed (D) and pre-alloyed (E) Ti-29Nb-21Zr regardless of solution chemistry. Plots are representative, and spectra continue past 10⁶ Z' for Admix Ti-29Nb-21Zr (D) and Ti-29Nb-21Zr (E). X-axes were shortened to aid in side-by-side comparison.

A summary of the Randles circuit elements, including $R_p R_s$, Q, and α , along with their standard deviations for each alloy type and solution combination, are reported in Table 6.4. These values were obtained from symmetry-based EIS analysis [48]. The introduction of 0.1 M H₂O₂ significantly decreased the oxide polarization resistance (p=0.000) by over a factor of 10 for Ti-6Al-4V, AM Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ (Fig. 6.11A). For admix Ti-29Nb-21Zr and Ti-29Nb-21Zr, 0.1 M H₂O₂ had little effect. R_p values for admix Ti-29Nb-21Zr were calculated as 2.4*10⁶ Ω cm² in PBS and 1.2*10⁶ Ω cm² in 0.1 M H₂O₂. For Ti-29Nb-21Zr, the measured value of R_p in 0.1 M H₂O₂ (1.8*10⁶ Ω cm²) was higher than in PBS (1.1*10⁶ Ω cm²) though their

orders of magnitude are equivalent. Across both solutions (average of Rp in PBS and 0.1 M H₂O₂), admix Ti-29Nb-21Zr and Ti-29Nb-21Zr had significantly higher polarization resistance compared to the Ti-6Al-4V biomaterials (p=0.000). A significant interaction effect of biomaterial and solution type (p=0.000) supports the finding that the 0.1 M H₂O₂ solution affected the Ti-29Nb-21Zr and Ti-6Al-4V based biomaterials differently. Within groups, there was no significant difference in R_p between admix Ti-29Nb-21Zr and Ti-29Nb-21Zr. Additionally, there was no significant difference in R_p amongst Ti-6Al-4V based biomaterials. The addition of 0.1 M H₂O₂ solution had little effect on the Log adjusted CPE capacitance $(Log(Q) (Scm^{-2}(s)^{\alpha}), Fig. 6.9B)$ for all five biomaterials. While oxide R_p decreased by a factor of at least 10 for the Ti-6Al-4V based biomaterials in inflammatory solutions, recorded Q were all in the same 10^{-4} Scm⁻²(s)^{α} range regardless of solution type (Fig. 6.11B). The mean capacitance (log-adjusted) of Ti-29Nb-21Zr was significantly lower than Ti-6Al-4V, AM Ti-6Al-4V and Ti-6Al-4V 1% nYSZ (p = 0.000). Additionally, admix Ti-29Nb-21Zr capacitance was significantly lower than Ti-6Al-4V 1% nYSZ (p=0.000). While there was no significant solution effect, there was a significant biomaterial-solution interaction (p = 0.023), indicating that the 0.1 M H₂O₂ solution affected the titanium biomaterials differently.



Figure 6.11. (A) Both solution (p=0.000) and biomaterial type (p=0.000) significantly affected R_p . Note the 10-fold decrease in R_p for Ti-6Al-4V, AM Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ compared to R_p in PBS. Inflammatory 0.1 M H₂O₂ solution had little effect on admix Ti-29Nb-21Zr and Ti-29Nb-21Zr. (B) Additionally, 0.1 M H₂O₂ had little effect on CPE capacitance magnitude.

6.4. Discussion

Several key results support our original hypothesis that Ti-29Nb-21Zr has improved corrosion resistance in inflammatory simulating solutions compared to Ti-6Al-4V based biomaterials. First, while we observe a decrease in OCP in 0.1 M H₂O₂ for all biomaterials tested, the Ti-29Nb-21Zr passive current density remains unchanged during anodic polarization. Next, Bode impedance and phase plots of Ti-29Nb-21Zr show few differences between PBS and 0.1 M H₂O₂ solutions, while Ti-6Al-4V alloy plots in 0.1 M H₂O₂ are visually distinct. Indeed, the presence of 0.1 M H₂O₂ decreased R_p for Ti-6Al-4V, AM Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ by over a

factor of 10 while admix Ti-29Nb-21Zr and Ti-29Nb-21Zr R_p remained relatively unchanged (see Table 6.4). Thus, we have a mix of quantitative (R_p and I_{pass}) and qualitative (Bode plots, Nyquist plots, and polarization plots) fundamental corrosion properties supporting our original hypothesis.

Ti-29Nb-21Zr is closest in elemental composition and weight percentage to the conventionally manufactured Ti-13Nb-13Zr biomaterial. This near β alloy was originally developed in the 1990s [36, 37]. While European manufacturers have adopted Ti-13Nb-13Zr for commercial and clinical use, Ti-6Al-4V remains the dominant biomedical alloy in the United States. Comprising the same elements in different weight percentages, Ti-29Nb-21Zr's impedance behavior in the presence of 0.1 M H₂O₂ is similar to reported results of Ti-13Nb-13Zr in inflammatory conditions. Assis et al. show that the R_p of Ti-13Nb-13Zr in minimal essential media (MEM) + 0.1 M H₂O₂ is almost identical to the R_p in MEM alone after both 15- and 125-day immersion [49]. Similarly, there was little effect on the short-term (0-10 days) impedance of Ti-13Nb-13Zr in Hank's solution + 0.1 M H₂O₂ compared to Hank's alone, though over longer periods (20-60 days), R_p in Hank's solution + 0.1 M H₂O₂ did decrease [44]. While other corrosion properties (e.g., OCP, polarization plots) differ from our results, this is to be expected with the various electrolyte solutions used.

SLM-PBF allows for new and rapid development of potential biomaterials that would not otherwise be producible using conventional manufacturing methods. In this study, we evaluate the fundamental corrosion properties of two admixtures, including Ti-6Al-4V 1% nYSZ and admix Ti-29Nb-21Zr. In the case of Ti-6Al-4V 1% nYSZ, ceramic ZrO₂ particles were combined with pre-alloyed Ti-6Al-4V powder. Similarly, admix Ti-29Nb-21Zr powder consisted of a mixture of three different particles (Ti, Nb, and Zr). The microstructures of these admixtures

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generated using SLM-PBF may be difficult to recapitulate using traditional manufacturing methods. Throughout this study, both admix Ti-29Nb-21Zr and Ti-29Nb-21Zr show similar OCPs, anodic polarization, and impedance responses. Thus, SLM-PBF of admixtures followed by characterization of fundamental corrosion properties may be a way to rapidly screen new biomaterial combinations prior to the more expensive pre-alloying process. Our work demonstrates this similarity for a single alloy. Further investigation of the relationship between admixtures and alloys is needed to confirm this behavior.

Recapitulating the *in vivo* interface, biology, and solution following device implantation remains a challenge. Modeling the crevice *in vitro*, where severe corrosion has been documented on retrievals, adds additional complexity [50, 51]. While we use supraphysiological levels of H₂O₂ as a proxy for all ROS throughout this study, this is far from a universal approach [52]. To reproduce inflammatory conditions, other researchers have cultured macrophages on titanium, stainless steel, and cobalt alloys. Using inductively coupled plasma mass spectroscopy, they document increased ion concentrations in the collected supernatant and in lysed macrophages after activation [53, 54]. When cultured in media with cobalt chrome alloy wear debris, macrophages may reduce oxide R_p and solution pH more than H₂O₂ containing solutions [55]. Interestingly, while H₂O₂ increases OCP, documented OCPs for cobalt chrome in the presence of macrophages and osteoblasts is as low as -0.7 V. No consensus exists on how to best model the *in vivo* solution. Accurately representing the *in vivo* inflammatory solution will likely require a combination of activated immune cells, ROS, and proteins.

Despite increased levels of H_2O_2 , the tests in this study still bear physiological relevance. H_2O_2 may be generated at implant surfaces *in vivo* from two potential sources. First, tribocorrosion between acetabular and femoral components induces large drops in surface potential [42]. These

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negative (cathodic) excursions can promote ROS directly on the surface-solution interface. Previous in vitro studies generate ROS on cobalt chrome surfaces during cathodic activation [43]. A second source of ROS is the patient's biology. Following arthroplasty, the body's inflammatory cascade initiates, recruiting macrophages and other immune cells directly at the sight of implantation [56]. These cells utilize respiratory burst reactions to convert oxygen into superoxide anions, subsequently reacting into a range of reactive oxygen species. At the bulk device-biology interface, these sources of ROS may have a negligible effect on corrosion, diluted by the surrounding physiological solution. However, most severe corrosion *in vivo* has been documented within modular taper junction crevices, where two opposing metal interfaces are separated by a small volume [57]. In this crevice microenvironment, an adhered macrophage or foreign body giant cell may secrete ROS onto the surface and generate solution chemistry with a far higher molarity than previously reported. Indeed, retrievals showing a ring of cells adjacent to a corroded femoral stem and etching trails the approximate width of immune cells in crosssectioned CoCrMo femoral heads support this hypothesis of cellular-induced corrosion [58, 59]. Additional ROS generation from adjacent tribology may accumulate in sufficient concentrations to initiate MACC and promote auto-catalytic corrosion behavior. Thus, supra-physiological in *vitro* tests may generate results directly related to physiologically relevant solution conditions. Curiously, both pre-alloyed and admixture Ti-29Nb-21Zr demonstrate significantly improved oxide polarization resistance compared to Ti-6Al-4V based biomaterials. While micrographs of the Ti-29Nb-21Zr show distinct, separately contrasted regions, these globular regions result from rapid melting and re-solidification of the separate elements within the admixture. In comparison, contrast within micrographs of traditionally manufactured mill annealed Ti-6AL-4V is indicative

of the α + β phases. Backscattered SEMs show dark aluminum rich, hexagonally-close-packed α phase grains, and bright blocky grains of body-centered-cubic β .

The near- β nature of both admix and pre-alloyed Ti-29Nb-21Zr may contribute to their improved corrosion resistance. Within retrievals of failed Ti-6Al-4V orthopedic implants, micrographs document deep pits within titanium-titanium component junctions. When these pits are cross-sectioned, they reveal selective dissolution of the Ti-6Al-4V β as the initiating step of a corrosion attack. Following the dissolution of the β , α is subsequently dissolved. Previous studies within our lab and others show that the combination of inflammatory species and cathodic activation can reproduce key characteristics of this damage *in vitro* [23, 28]. In these simulated crevice corrosion conditions, β dissolution begins as small pits at the phase boundaries between β and α before continuing over time until all β is dissolved from the surface. This preferential dissolution initiated at the phase boundaries indicates that the protective oxide structure over α may be differ from oxide over β . Interphase boundary regions contain greater disorder and crystallographic defects, which may further promote corrosion. The oxide covering near β Ti-29Nb-21Zr biomaterials is likely more stable and homogenous than the oxide passivating on two phase-titanium alloy biomaterials. However, further investigation is needed to support this hypothesis.

While promising in terms of the corrosion properties in ROS containing solutions, the tests performed in this study are not fully indicative of successful, long-term *in vivo* biomaterial performance. Inflammation at device interfaces is a complex, multiphysics problem involving the interaction of biology and corrosion. In this study, we investigate one aspect of the inflammatory cascade, (high ROS containing solutions) in isolation of other variables. Superoxide anions generated during oxygen reduction may react into other oxidizers and acids, creating a more corrosive solution within the crevice [56]. The patient's biology too plays a role.

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Phagocytic cells are hypothesized to engage in inflammatory cell induced corrosion. Recent studies link patient genotype to aseptic lymphocyte-dominated vasculitis association lesion (ALVAL) susceptibility [60]. Improving fatigue performance in additively manufactured titanium alloys (particularly in β alloys) remains an ongoing issue. Ti-6Al-4V implant fracture, though rare, is more commonplace than corrosion failure. Any improvements in corrosion performance must be corroborated with as good or better fatigue, mechanical, and wear performance. Failure to validate these properties may result in an admixture or alloy that promotes more clinical complications than it negates. Though these challenges are beyond the scope of this study, they are important considerations for any new metal biomaterial.

Characterizing the effects of tribology, sustained cathodic activation, and rapid remodeling of the oxide structure under adverse electrochemical events would provide additional insight into the long-term *in vivo* corrosion performance of the novel AM titanium biomaterials investigated in this work. Additionally, both printing parameters and post-build processing of AM Ti-6Al-4V show the ability to modify and fine-tune alloy microstructure [61-64]. Because mechanical and corrosion properties are functionally dependent on alloy microstructure, developing high throughput test methods that can evaluate and expose multiple AM alloys—or the same alloy with various microstructures—to adverse electrochemical events at once may aid in identifying new metallic biomaterials that do not fail when exposed to mechanically and chemically destructive conditions. Varying the fraction of AM Ti-6Al-4V β present and assessing the effect on selective dissolution would be of particular interest.

AM Ti-6Al-4V biomaterial OCP, corrosion current density, and impedance properties performed comparably to conventionally manufactured Ti-6Al-4V in both inflammatory and normal conditions. While this indicates identical elements and weight compositions, it raises several important questions about long-term clinical performance. In the United States, most AM Ti-6Al-4V devices have been approved for *in vivo* use through either the 510k or compassionate use pathways. The highly customizable geometry of AM promotes innovative Ti-6Al-4V device design, addressing clinical gaps at the point of care. However, the resulting microstructure of AM Ti-6Al-4V is highly sensitive to printing parameters and post-processing techniques. This has likely led to device manufacturers generating final microstructures far from the commonly accepted Ti-6Al-4V microstructure obtained from rod or bar stock. Indeed, these AM Ti-6Al-4V microstructures may additionally vary on a company-by-company basis, resulting in varying device corrosion properties.

While the tribocorrosion behavior of conventionally manufactured Ti-6Al-4V has been extensively investigated, crevice corrosion damage modes remain largely unexplored, poorly understood, and except for selective dissolution, un-replicated *in vitro*. Our OCP, anodic polarization, and impedance results support the hypothesis that the crevice corrosion damage modes affecting conventionally manufactured Ti-6Al-4V will also impact additively manufactured Ti-6Al-4V alloys. Because device manufacturers treat printing and post-build processes as intellectual property, the true corrosion properties of many AM Ti-6Al-4V devices remain unknown, along with their long-term clinical performance. Future work will explore the corrosion behavior of AM explants compared to both mill-annealed and as-built AM Ti-6Al-4V alloys.

6.5. Conclusions

In this study, we characterize the powder metallurgy and microstructure of Ti-6Al-4V and Ti-29Nb-21Zr metallic biomaterials and compare their oxide resistance in both physiological and inflammatory simulating solutions. The rapid melting and solidification of admix Ti-29Nb-21Zr particles generated a unique microstructure of heterogenous pools and unmelted Nb particles. This contrasts with the martensitic microstructures of AM Ti-6Al-4V and Ti-6Al-4V 1% nYSZ. The Ti-29-21Zr alloy microstructure was not visibly distinguishable using mechanical and chemical polishing. The 0.1 M H₂O₂ solutions significantly increased the OCP of all five metallic biomaterials evaluated in this study (p=0.000). Anodic polarization plots confirm this increase. We additionally documented shifts in passive currents for Ti-6Al-4V, AM-Ti-6Al-4V, and Ti-6Al-4V 1% nYSZ, whereas no shift occurred for admix Ti-29Nb-21Zr and Ti-29Nb-21Zr. Finally, we show significant increases in admix Ti-29Nb-21Zr and Ti-29Nb-21Zr R_p compared to Ti-6Al-4V based alloys in 0.1 M H₂O₂ and PBS solutions. Future work will continue to evaluate these new admixtures and alloys as candidate biomaterials.

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Biomaterial	Al (%)	V (%)	Nb (%)	Zr (%)	Ti (%)
Ti-6Al-4V	6	4	0	0	Balance
Ti-6Al-4V 1% nYSZ	6	4	0	1*	Balance
Admix Ti-29Zr-21Nb	0	0	28.9	20.35	Balance
Pre-alloyed Ti-29Zr-21Nb	0	0	28.9	20.35	Balance

Table 6.1. Chemical Composition (Weight %) of Biomaterial Powders (* - as ZrO₂)

Table 6.2. Process parameters used to fabricate AM Ti-6Al-4V, Ti-6Al-4V 1% nYSZ, admix Ti-

29Nb-21Zr, and Ti-29Nb-21Zr samples

Process Parameters	
Laser Power (W)	200
Laser spot diameter (µm)	80
Speed (mm/s)	700
Hatch spacing (mm)	0.1
Layer thickness (μm)	30

Table 6.3. Mean Chemical Composition (Weight %) of As-Built Samples and 95% Confidence

Intervals (± 2 *STD)

Biomaterial	Al (%) V (%)		Nb (%)	Zr (%)	Ti (%)
Ti-6Al-4V	6.1 ± 0.12	3.8 ± 0.23	0	0	Balance
Ti-6Al-4V 1% nYSZ	5.7 ± 0.20	3.8 ± 0.31	0	0.7 ± 0.00	Balance
Admix Ti-29Zr-21Nb	0	0	30.2 ± 0.72	22.4 ± 0.64	Balance
Pre-alloyed Ti-29Zr-21Nb	0	0	28.8 ± 1.68	22.1 ± 0.64	Balance

Table 6.4. Mean Q (Scm⁻²(s)^{α}), R_p (Ω cm²), R_s (Ω cm²) and α values, as well as calculated

standard deviations for each biomaterial.

Material	Soln.	$\begin{array}{c} Q\\ \mathrm{Scm}^{-2}(\mathrm{s})^{lpha} \end{array}$	<i>Std Dev</i> Scm ⁻² (s) ^α	$R_p \ \Omega \mathrm{cm}^2$	$\frac{Std Dev}{\Omega cm^2}$	R_s $\Omega m cm^2$	$\frac{Std Dev}{\Omega cm^2}$	α	Std Dev
Ti-6Al-4V	PBS	2.61E-05	4.1E-06	4.38E+06	4.1E+05	1.92E+01	4.6E+00	9.11E-01	1.1E-02
	H_2O_2	2.44E-05	2.9E-06	7.24E+04	1.7E+04	1.95E+01	2.2E+00	9.00E-01	1.7E-02
AM Ti-6Al-4V	PBS	2.38E-05	7.3E-06	4.57E+06	2.3E+06	1.35E+01	4.1E-01	8.87E-01	3.9E-02
	H ₂ O ₂	2.91E-05	8.5E-07	8.21E+04	2.5E+04	1.40E+01	3.8E+00	9.04E-01	6.0E-03
Ti-6Al-4V 1% nYSZ	PBS	3.24E-05	1.2E-06	2.11E+06	6.6E+05	2.12E+01	1.5E+00	8.81E-01	1.2E-02
	H_2O_2	3.11E-05	8.5E-06	1.19E+05	6.9E+04	3.65E+01	2.2E+01	8.85E-01	8.6E-03
Admix Ti-29Nb-21Zr	PBS	2.76E-05	2.4E-06	2.43E+06	3.3E+05	1.60E+01	4.6E+00	8.87E-01	4.4E-03
	H ₂ O ₂	1.70E-05	3.2E-06	1.24E+06	6.0E+05	1.99E+01	6.6E+00	9.45E-01	1.8E-02
Ti-29Nb-21Zr	PBS	1.84E-05	2.1E-06	1.09E+06	2.1E+05	1.38E+01	4.0E+00	9.50E-01	1.3E-16
	H ₂ O ₂	1.77E-05	2.4E-06	1.89E+06	1.0E+06	1.51E+01	2.0E+00	9.34E-01	6.1E-03

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Chapter 7

Oxide Degradation Precedes Additively Manufactured Ti-6Al-4V Selective Dissolution: An Unsupervised Machine Learning Correlation of Impedance and Dissolution Compared to Ti-29Nb-21Zr

(In Submission)

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Abstract: Additively manufactured (AM) Ti-6Al-4V devices are implanted with increasing frequency. While early registry data suggest favorable outcomes, the long-term corrosion behavior of AM Ti-6Al-4V remains unknown. Retrieval studies document various corrosion damage modes on conventionally manufactured Ti-6Al-4V devices, including selective dissolution of the alloy's β phase. Researchers reproduce this damage *in vitro* by combining negative potential excursions (i.e., cathodic activation) and inflammatory species. In this study, we investigate the effects of sustained cathodic activation and inflammatory simulating solutions on the impedance behavior and selective dissolution of AM Ti-6Al-4V. We hypothesize that these adverse electrochemical events will degrade the oxide film, altering the impedance response and subsequently promoting selective dissolution. First, we held AM Ti-6Al-4V samples at -0.4 V for 48 h in 0.1 M H₂O₂/phosphate buffered saline solution. Next, we acquired nearfield electrochemical impedance spectroscopy (EIS) data before and after dissolution. Finally, we captured micrographs and EIS during active corrosion for 24 h, elucidating the selective dissolution mechanism. Throughout, we used AM Ti-29Nb-21Zr as a comparison alloy. After 48 h of cathodic activation, AM Ti-6Al-4V selective dissolution occurred, while Ti-29Nb-21Zr remained uncorroded. Modifications to the AM Ti-6Al-4V oxide film manifested as changes to the constant phase element (CPE) and polarization resistance (R_p) parameters. The log-adjusted CPE capacitance, Q, significantly increased for dissolved samples from -4.75 to -3.84 (Scm⁻²(s)^{α}) (p = 0.000) and the CPE exponent, α significantly decreased from 0.90 to 0.84 (p = 0.000). Next, we identified a clear link between oxide film degradation and selective dissolution. A systematic decrease in oxide R_p (over 4 to around 2, p < 0.05) under sustained -0.4 V preceded pit nucleation and growth. Finally, using k-means clustering, we established a relationship between the AM Ti-6Al-4V CPE parameters and the surface's dissolution state.

These results link Ti-based implant corrosion susceptibility to potential and solution chemistry changes that may arise *in vivo*.

Dedication:

There are only a few mentors that have come close to, and none have exceeded, the impact Jim Anderson has had on my career. Starting with reading JBMR-A in the 1980's while in graduate school (Jim was editor even then), submitting work to JBMR-A over my career, to ultimately becoming Editor-in-Chief of JBMR-B, Jim has been there giving advice, providing references and recommendations and helping to promote me in my career. I dedicate this paper to Jim as a testament of his openness to my and many others' science and for his support for my career.

Jeremy L. Gilbert

Graphical Abstract:



1. Cathodic activation an inflammatory species degrade the oxide film 2. Pit nucleation initiates in the additively manufactured Ti-6Al-4V β phase

3. Pit width increases, and pits interconnect

Highlights:

- Sustained application of -0.4 V for 48 h in 0.1 M H₂O₂/PBS solutions selectively dissolves the AM Ti-6Al-4V β phase but does not affect Ti-29Nb-21Zr.
- AFM images show increased surface roughness for dissolved vs. polished samples and nearfield electrochemical impedance spectroscopy shows significant (p < 0.05) differences in the oxide polarization resistance, R_p, solution resistance, R_s, constant phase element capacitance Q, and constant phase element exponent α.
- The AM Ti-6Al-4V selective dissolution mechanism initiates with degradation of the passive oxide film. Oxide R_p, systematically decreases, and then plateaus. R_p decreases precede the nucleation and growth of pits.

• Cluster analysis-based response of constant phase element parameters Q and α may be predictive of the surface's dissolution state.

Keywords: Ti-6Al-4V, Ti-29Nb-21Zr, additive manufacturing, selective dissolution, k-means clustering

7.1. Introduction

Additively manufactured (AM) Ti-6Al-4V devices are implanted into patients with increasing frequency. AM is favored over conventional manufacturing for metallic medical devices due to its ability to produce complex geometries, create personalized devices, and improve osteointegration at the device-bone interface [1-5]. Orthopedic applications include tibial baseplates and acetabular cups within total knee and total hip replacement systems [6]. Early registry data on AM Ti-6Al-4V devices suggest clinical success with few revisions [7-9]. However, the long-term *in vivo* effects of AM Ti-6Al-4V remain unknown.

Conventionally manufactured Ti-6Al-4V is one of the most widely used medical alloys for permanently implanted medical devices in the United States [10]. In contrast with the various microstructures of AM Ti-6Al-4V, the mill annealed alloy contains two phases, $\alpha+\beta$, of differing crystal structures [11-14]. The α phase (hexagonally close packed) is aluminum rich while the β phase (body-centered cubic) contains a greater percentage of vanadium. Decades of clinical success, especially in total hip replacement surgeries where revision rates range in the single percentages after 15 years, promote continued usage, even as other metals are phased out. While cobalt chrome molybdenum use has been associated with both aseptic lymphocyte-dominant vasculitis-associated lesions (ALVAL) and adverse local tissue reactions (ALTR), corrosion failure associated with conventionally manufactured Ti-6Al-4V is rare within the literature [15-20].

Despite this clinical success, retrieval studies document Ti-6Al-4V device failure including severe corrosion within the modular taper junctions of total hip replacement systems [21-24]. Micrographs of device interfaces reveal chemically induced corrosion damage modes including the formation of hundreds of microns thick oxide films, pitting, hydrogen embrittlement and β

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phase selective dissolution. This damage propagates within device crevices, when two interfaces are near one another, and solution may ingress.

While most chemically induced Ti-6Al-4V corrosion damage modes remain poorly understood, various researchers have induced Ti-6Al-4V selective dissolution [25-32]. *In vitro*, cathodically activating samples in hydrogen peroxide containing solutions alters the oxide and accelerates the preferential dissolution of the β phase [33, 34]. Three techniques have been identified, including (1) anodically scanning from negative potentials at a fixed rate; (2) applying a transient cathodic hold for a short period of time followed by a recovery, and (3) constantly activating the surface at a fixed cathodic potential. All three methods rely on decreasing the Ti-6Al-4V surface potential below its open circuit potential, though the time spent in the cathodic region varies. Additionally, while Ti-6Al-4V may undergo preferential dissolution in reactive oxygen species (ROS) containing solutions, cathodic activation expedites the reaction.

Both ROS and cathodic activation, used to induce selective dissolution *in vitro*, are analogous to adverse electrochemical events that occur *in vivo*. In the human body, negative potential excursions occur during fretting when the protective oxide film is abraded. For Ti-6Al-4V devices, these drops may approach -1 V [35-37]. Inflammation following implantation promotes ROS at the device-biology interface [38]. Macrophages, lymphocytes, and proteins may adhere to the Ti-6Al-4V surface. When faced with a large foreign object, macrophages attempting to phagocytose the device can become frustrated, promoting foreign body giant cell formation (FBGC). These FBGCs can generate ROS, of which hydrogen peroxide is an intermediate species, in close proximity to the device. During the joint replacement procedure, a third source of hydrogen peroxide may be introduced. Physicians may clean the implant site with povidone-iodine and hydrogen peroxide prior to wound closure [39, 40].

In most patients, Ti-6Al-4V corrosion does not visibly occur and has little clinical impact. This is largely due to the nanometers thick TiO₂ oxide film that passivates on its surface. The intact film prevents active corrosion [41, 42]. In incidences of mechanically assisted crevice corrosion, this paradigm is subverted [43, 44]. Loading and motion of asperities at the device interface in combination with high ROS solutions interrupt or breach the oxide. The oxide's polarization resistance (R_p), inversely proportional to the rate of corrosion, decreases [45]. Researchers model the impedance of this complex device-oxide-solution interface using the Randles circuit containing R_p, a constant phase element (CPE) and a solution resistor, R_s [46-48]. In this conceptual model, the CPE replaces the capacitor, functionally reproducing the behavior of the oxide layer [49].

AM Ti-6Al-4V components within total joint replacement systems are likely exposed to similar adverse electrochemical events experienced by conventionally manufactured devices. Modular junctions as well as screw-countersink geometries are ubiquitous in modern implants, ensuring the continued existence of both crevices and articulating surfaces. In the absence of intended motion in implant design, (e.g., cobalt chrome liners and titanium shells in acetabular components of total hip replacements) fretting may still occur. In this study, we investigate how the martensitic microstructure of as-built AM Ti-6Al-4V reacts to the combination of cathodic activation and hydrogen peroxide. We use AM Ti-29Nb-21Zr, a near- β alloy with more corrosion resistant elements, as a comparison [50]. We hypothesize that negative potentials and ROS containing solutions will generate a defective oxide film, promoting selective dissolution of the AM Ti-6Al-4V β phase. We sought to answer the following research questions: first, can AM Ti-6Al-4V β selective dissolution be reproduced *in vitro* under conditions similar to that used for conventionally manufactured alloy? Next, how does the oxide structure and function change

after the surface is dissolved? Finally, what is the time course of the mechanism of AM Ti-6Al-4V selective dissolution, and how does the oxide impedance properties evolve during this process?

7.2. Materials and Methods

7.2.1 Biomaterial Printing and Post Processing

Cylindrical 20 mm x 4 mm AM Ti-6Al-4V and Ti-29Nb-21Zr samples were manufactured from powder precursors using selective laser melting-powder bed fusion (SLM-PBF, SLM 125HL, SLM Solutions Group AG, Lübeck, Germany). Powders and as-built samples were received from Z3DLAB SAS (Paris, France). Samples were stress relieved for 3 h at 600 °C and a belt sander was used to remove support structures. Further details of powder and as-built sample chemical composition, as well as sample printing parameters may be found in Kurtz et. al [48].

7.2.2 Metallographic Preparation and Baseline Imaging

Following heat treatment, samples were mechanically polished using emery paper. A final mirror finish was obtained using 1 and 0.3 µm alumina/deionized (DI) H₂O solutions, respectively. Scanning electron microscopy (SEM, SN3700, Hitachi Inc., Tokyo, Japan) and energy dispersive X-ray spectroscopy (EDS, Aztec, Oxford Instruments, Abingdon, UK) was used to confirm normal alloy chemistry at the working electrode interface. An additional polishing step was used to prepare samples for microstructural imaging, using a 40% H₂O₂ (9.8 M stock solution) and 60% non-crystalline colloidal silica suspension. This treatment alters the properties of the oxide film and was thus removed through repolishing prior to electrochemical testing. Baseline backscattered electron (BSE) micrographs were captured of the AM Ti-6Al-4V and Ti-29Nb-21Zr sample surfaces and powder precursors at 1.5k and 500x magnifications, respectively.

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Baseline atomic force microscopy (AFM, Dimension ICON AFM, Bruker, US) height and deflection images were captured at 1 µm x 1 µm magnification on AM Ti-6Al-4V samples.

7.2.3 Inducing Selective Dissolution

Working electrode surface areas (c.a. 0.20 cm^2) were isolated using non-conductive tape, allowing for repeated testing prior to repolishing. Electrical connection was maintained between the metal samples and an external wire using carbon tape. The three-electrode electrochemical cell was completed with a sintered Ag/AgCl reference electrode and a carbon rod counter electrode. AM Ti-6Al-4V and Ti-29Nb-21Zr samples (n = 3) were cathodically activated at -0.4 V for 48 h. The electrolyte solution used was 0.1 M H₂O₂ in phosphate buffered saline (PBS). Following cathodic activation, samples were sonicated, air dried, and imaged. Secondary (SE) and BSE micrographs were captured of working electrode surfaces at 1.5k magnification. To confirm the presence of selective dissolution on AM-Ti-6Al-4V samples and quantify the effects on the oxide film, AFM height and deflection images were captured at 50, 5, and 1 μ m².

7.2.4 Nearfield Electrochemical Impedance Spectroscopy

A custom 3D printed Polyethylene terephthalate glycol (PETG) fixture was used to capture nearfield electrochemical impedance spectroscopy on dissolved and control AM Ti-6Al-4V surfaces. The working electrode surface area (0.07065 cm²) was limited to the inner diameter of an O-ring (2 mm, outer diameter 4 mm, McMaster-Carr, Elmhurst, IL), creating a seal between the PETG fixture and the working electrode. A downwards force was manually applied to maintain this seal, and initial surface tension between the hydrophobic O-ring and the AM Ti-6Al-4V surface was disrupted using a 1 mL pipette tip. Due to the comparatively small size of the PETG fixture, a platinum wire was used as the counter electrode. Three spectra were

captured from three dissolved and three control samples (n = 9) in 0.1 M H₂O₂/PBS solution. The impedance response was acquired from 10^4 to 10^{-1} hz. Resulting data were fit with a Randles CPE circuit using phase angle symmetry and area normalized [51]. Plots were constructed of representative phase angle and impedance data (n = 1) as well as averages of the extracted circuit elements (R_p, R_s, the CPE exponent α , and the CPE capacitance Q).

7.2.5 Elucidating the Selective Dissolution Mechanism

To investigate the AM Ti-6Al-4V dissolution mechanism, samples were held at -0.4 V in 0.1 M H_2O_2/PBS solution for 6, 12, 18, and 24 h (n = 3 for each alloy). Electrochemical experiments were conducted in triplicate. Post test, SEM BSE micrographs were captured of the working electrode surface at 5k magnification. Using ImageJ (NIH), the number of dissolved pixels in a micrograph were calculated. This method assumes that the darkest pixels in a micrograph are voids where the β phase or prior β grains were present. The number of dissolved pixels was divided by the total number of pixels in the micrograph to generate a percentage.

To understand the oxide properties during this process, sample open circuit potential (OCP) was recorded for 60 s. A baseline EIS spectrum was acquired vs. the OCP, and a second spectrum was acquired immediately afterwards at -0.4 V. EIS spectra were then captured every hour for 24 h while the sample was continuously held at -0.4 V. The sampled frequency range was from 10^4 to 10^{-1} hz. Representative plots of AM Ti-6Al-4V impedance spectra at 6, 12, 18, and 24 h were generated. Average circuit element fits (R_p, R_s, Q, and α) for all spectra were plotted versus the average final EIS capture time for both AM Ti-6Al-4V and the comparison alloy Ti-29Nb-21Zr (n= 3 for each alloy and time point). Further plots of the CPE exponent α vs. CPE capacitance Q were generated, overlaying the CPE circuit elements acquired from before and after 48 h nEIS data (n = 9) with the average Q and α values captured during active selective dissolution. To

illustrate the path-dependent changes, a second plot was generated showing individual trials, as well as the CPE data collected during sustained cathodic activation of the Ti-29Nb-21Zr alloy.

7.2.6 K-means cluster primer and analysis

CPE parameter data from individual trials during active selective dissolution, as well as from control and dissolved nEIS spectra were collated into a 168 x 2 matrix. In this matrix, the first column was the CPE parameter, Q, and the second column was the corresponding CPE exponent, *α*. Unlike previous plots generated during the analysis of the selective dissolution mechanism (section 2.5), the labels for the data were removed (there was no distinguishing between the data captured from the 24 h sustained cathodic activation of AM Ti-6Al-4V or Ti-29Nb-21Zr, and the data extracted from nEIS spectra captured before and after 48 h of selective dissolution). K-means clustering was applied in MATLAB R2019b using the built in *kmeans* function, a part of the statistics and machine learning toolbox. Generally, k means clustering works as follows: (1) a value for k is selected, determining the number of cluster centers, or centroids; (2) centroid seeds (their initial starting coordinates) are randomly generated; (3) the squared Euclidean distance:

$$d^{2}(x,c) = (x-c)^{2}$$
(Eq. 1)

where d is the distance, x is the data and c is the centroid is calculated between all data points and each centroid; (4) data points are assigned to the closest centroid and the average is calculated; (5) the mean of the clusters becomes the new centroid coordinates and re-clustering occurs until the clusters remain the same; (6) Finally, the centroid seeds are regenerated and steps 2-5 are repeated for a predetermined number of iterations [52, 53]. The solution with the lowest sum of the squared Euclidean distance is output.

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From a visual observation of the unlabeled data, k = 3 was chosen. After 100 iterations, the function returned three centroid coordinates and class labels for the 168 data points, which were subsequently plotted. The experimental pipeline is shown in Figure 7.1.



Figure 7.1. Graphical representation of experimental pipeline. A total of 168 EIS spectra were acquired from: (1) dissolved AM Ti-6Al-4V (Ti-64) surfaces after 48 h in 0.1 M H₂O₂/PBS solution at -0.4 V (n = 9); (2) control (polished) AM Ti-6Al-4V surfaces (n = 9); (3) AM Ti-6Al-4V during sustained -0.4 V for 24 h (n = 75) and (4) Ti-29Nb-21Zr (TNZ) during sustained -0.4 V for 24 h (n = 75). EIS spectra were fit using phase angle symmetry with a Randles CPE circuit.

A 168 x 2 matrix of paired CPE circuit parameters Q and α was used as an input for k-means clustering. Outputs included centroid coordinates and class labels for each of the 168 CPE pairs.

7.2.7 Statistical Methods

Statistically significant differences in nEIS Randles circuit element properties between dissolved and polished AM Ti-6Al-4V groups (n = 9) were assessed using a two-sample t-test and an α significance level of 0.05. Differences in dissolution percent (n = 3) between dissolved samples after 6, 12, 18 and 24 h were evaluated using a one-way analysis of variance (ANOVA, α = 0.05) and post hoc Tukey's multiple comparison test. Additionally, impedance parameters R_p and Q varying with material and time were assessed with a two-way ANOVA and Tukey post-hoc testing. Error bars on plots are calculated standard deviation. Statistical Analysis was conducted in MATLAB versions R2019b and R2021b.

7.3. Results

7.3.1 Metallographic Characterization

A BSE SEM micrograph of the AM Ti-6Al-4V precursor powder shows spherical particles with a bimodal distribution in particle size (Figure 7.2A). In comparison, a micrograph of Ti-29Nb-21Zr particles (Figure 7.2B) documents a visual increase in particle density. Additionally, visually, there is increased variance in the particle diameters when compared with the Ti-6Al-4V powder in Figure 7.2A.

A BSE micrograph of the polished, stress relieved AM Ti-6Al-4V surface reveals a martensitic microstructure with acicular lathes of α , typical of the selective laser melting manufacturing process (Figure 7.2C). α lathes approximately 10-30 um in width are interspersed throughout. Microstructural features were not visible under normal polishing conditions for Ti-29Nb-21Zr

samples (Figure 7.2D). AFM height imaging (Figure 7.2E) of the polished AM Ti-6Al-4V surface shows visually discernable oxide domes approximately 40 nm in height. A deflection image (Figure 7.2F) of the same surface area shows the oxide domes more clearly.



Figure 7.2. Metallographic characterization of AM Ti-6Al-4V and Ti-29Nb-21Zr. 500x BSE micrographs of (A) AM Ti-6Al-4V and (B) Ti-29Nb-Zr precursor powders. 1.5k BSE micrographs of (C) AM Ti-6Al-4V and (D) Ti-29Nb-21Zr polished metal surfaces. Note the

martensitic AM Ti-6Al-4V microstructure. 1 µm x 1µm height (E) and deflection (F) images of the AM Ti-6Al-4V reveal discernable oxide domes.

7.3.2 Inducing Selective Dissolution In Vitro

After 48 h of sustained cathodic activation at -0.4 V in 0.1 M H₂O₂/PBS solution, SE and BSE micrographs of the AM Ti-6Al-4V surface show β phase selective dissolution (Figure 7.3A, B). Dark, curved, grooves on the AM Ti-6Al-4V surface indicate areas where prior β grains dissolved (Figure 7.3A). In the BSE micrograph (Figure 7.3B) dissolved β appears as dark voids. The Ti-29Nb-21Zr surface (Figure 7.3C, D) is comparatively less corroded and micrographs appear to have minimal differences in surface morphology with polished samples (Figure 7.2D). 50 µm AFM height (Figure 7.3E) and deflection (Figure 7.3H) images of the cathodically activated surface shows the topography of the corroded AM Ti-6Al-4V surface. Note the hatch like pattern and voids where the β phase was dissolved, consistent with the BSE micrographs in Figure 7.2A-B. At 5 µm (Figure 7.3F and 7.3I), oxide domes on the AM Ti-6Al-4V visually populate the roughened surface. At 1 micron (Figure 7.3G and 7.3J), the oxide is present but appears with greater resolution. The oxide dome structure over the dissolved surface resembles the polished surface. However, the domes cover a much rougher substrate following the corrosion attack.


Figure 7.3. 1.5k BSE and SE micrographs of cathodically activated AM Ti-6Al-4V (A, B) and Ti-29Nb-21Zr (C, D) surfaces. After 48 h, the combination of sustained -0.4 V and 0.1 M H_2O_2/PBS solution preferentially dissolved the AM Ti-6Al-4V β phase. Prior β grains appear as dark grooves in the metal surface. The Ti-29Nb-21Zr surface appears comparatively less

corroded. AFM images of the dissolved AM Ti-6Al-4V surface show different features at different magnifications. The 50 µm height (E) and deflection (H) images show the underlying selectively dissolved metal surface and structure. At 5 µm, the oxide film domes overtop of the corroded alloy come into focus (F, I). Finally, at 1 micron, oxide domes are visually discernable in both the height (G) and deflection imaging modes (J). These oxide domes are visually similar to those over polished surfaces though the measured height and deflection increased by an order of magnitude.

Representative Bode plots of nEIS spectra (n = 1 of 9) captured from dissolved and control (polished) surfaces show visually distinct features. The Bode |Z| magnitude plot (Figure 7.4A) shows a decrease in dissolved impedance at high frequencies (i.e., R_s), from 72 to 44 Ω cm². This decrease is likely caused by the comparatively larger surface area of the dissolved samples. Bode phase plots (Figure 7.4B) identify a shift to lower frequencies in the dissolved spectra peak. Randles circuit fits using phase angle symmetry align with the experimental data as dashed and dotted lines.

Following circuit fitting, shifts in the Bode phase plot may be quantified as changes to the oxide's CPE. Log adjusted Q, the CPE capacitance, significantly increased for dissolved samples from -4.75 to -3.84 (Scm⁻²(s)^{α}) (Figure 7.4C, p =0.000). The CPE exponent, α , significantly decreased from 0.90 to 0.84 (Figure 7.4F, p = 0.000). Significant differences were also documented in the oxide R_p (Figure 7.4D, p = 0.04), and the solution resistor R_s (Figure 7.4E, p = 0.04), though these changes are less visually identifiable. Plots display averages of 9 spectra for both dissolved and control samples.



Figure 7.4. Bode magnitude (A) and phase (B) plots of representative nEIS spectra. Note the leftward shift in the dissolved phase response. Average (n = 9) fitted circuit values for (C) Q; (D) R_p ; (E) R_s ; and (F) α . All circuit elements showed significant differences (p < 0.05) though only Q and α are visually perceptible from the Bode plots in A and B.

7.3.3 Elucidating the In Vitro Selective Dissolution Mechanism

Micrographs (BSE, 5k magnification) of AM Ti-6Al-4V captured at 6 h, 12 h, 18 h, and 24 h help visualize the *in vitro* selective dissolution mechanism (Figure 7.5A-C). Samples cathodically held at -0.4 V and immersed in 0.1 M H₂O₂/PBS solution show pit nucleation beginning at 12 h (Figure 7.5A). After 18 h (Figure 7.5B), the number of visible pits in the micrograph increases. At 24 h (Figure 7.5C), existing pit diameter increases, and adjacent pits begin to coalesce. The lathe-like α phase shows less evidence of pitting.

A clear coupled response exists between dissolved β phase (%) and oxide R_p (Figure 7.5D). The green circular data points correspond with oxide R_p and the purple diamonds represent the dissolved % calculated from the images in Figure 7.5A-C (6 h not shown). Following cathodic activation at -0.4 V, oxide R_p starts at 4.3 * 10⁴ Ω cm². After 6 h under sustained -0.4 V, R_p decreases to 1.6 * 10³ Ω cm². By 12 h, the oxide R_p has decreased by a further order of magnitude to 3.8 10² Ω cm². This drop in R_p coincides with an increase in dissolution. While the R_p maintains a 10² magnitude after 12 h, the dissolved % significantly increases from 0.77 % to 10.58 % at 24 h (p = 0.001).

Representative Bode phase (Figure 7.5E), impedance (Figure 7.5F), and Nyquist (Figure 7.5G) plots help to illustrate the evolution of the oxide impedance throughout the selective dissolution process. Note the decrease in |Z|, Θ , and -Z'' and Z' when comparing spectra captured at 6 and 12 h. All four variables remain constant after 12 h, consistent with the bottoming out and plateauing of R_p in Figure 7.5D. All electrochemical experiments were run in at least triplicate (n = 3)



Figure 7.5. SEM BSE Micrographs captured at 5K magnification show the selective dissolution mechanism over time. Pit nucleation begins at 12 h (A), the number of pits increases at 18 h (B) and the pits grow wider and begin to connect after 24 h (C). A coupled response exists between the dissolved % and oxide R_p (D), where a decrease and bottoming out in the oxide R_p precedes a significant increase in dissolution (p = 0.001). Representative Bode magnitude (E), phase (F) and Nyquist plots (G) help illustrate this impedance plateau. Note the decrease between spectra captured at 6 h and 12 h.

EIS spectra captured during active AM Ti-6Al-4V selective dissolution show increases in capacitance and decreases in polarization resistance over time. After 24 h at -0.4 V, $log_{10}R_p$ values decrease by three orders of magnitude from the baseline (Figure 7.6A). In comparison, Ti-29Nb-21Zr $log_{10}R_p$ remains stable (c.a., $log_{10}R_p=3.6 \ \Omega cm^2$) once potentiostatically held at -0.4 V. Post hoc analysis following a two way ANOVA revealed that the Ti-29Nb-21Zr $log_{10}R_p$ was significantly higher than the AM Ti-6Al-4V $log_{10}R_p$ over time (p = 0.000). The effect of time on $Log_{10}R_p$ was significant (p = 0.000), and a significant alloy*time interaction effect (p = 0.001) was present suggesting that the sustained cathodic activation in 0.1 M H₂O₂ affected the alloys' polarization resistances differently.

The AM Ti-6Al-4V CPE exponent α linearly decreases with time (Figure 7.6B). Over the first 18 h of the experiment, the AM Ti-6Al-4V CPE capacitance, Q, increases (Figure 7.6C). For the last 6 h, a plateau is reached. Average Q for AM Ti-6Al-4V was significantly higher than Ti-29Nb-21Zr (p = 0.000), time had a significant effect (p = 0.000) and a significant time*alloy interaction was present (p = 0.000). The inverse squared CPE capacitance Q⁻² (Figure 7.6D, a measure of the Mott-Schottky response of the oxide, which is inversely related to the semiconducting charge carrier density) is similar in its behavior over time as the log₁₀R_p, where a decrease in log₁₀Q⁻² precedes a plateau. Ti-29Nb-21Zr α , Q, and Q⁻² remained relatively unaffected by the combinatorial effect of cathodic activation and 0.1 M H₂O₂.



Figure 7.6. Average (n = 3) circuit element values after 24 h of sustained cathodic activation at - 0.4 V in 0.1 M H2O2/PBS solution. (A) log₁₀Rp; (B) α (C) log₁₀Q and (D) log₁₀Q⁻². Following a baseline EIS measurement vs. OCP, the AM Ti-6AL-4V impedance diverges from the comparatively stable Ti-29Nb-21Zr.

In Figure 7.6, R_p , Q and α each undergo systematic variations with time. The R_p decreases, Q increases and α decreases as exposure time increases and selective dissolution occurs. A plot of α vs. Log₁₀(Q) (Figure 7.7A) was constructed by overlaying circuit element values from control and dissolved nEIS spectra (Figure 7.4C and F) and EIS spectra acquired over time during active AM Ti-6Al-4V corrosion (Figure 7.6B-C). The plot identifies a Log-linear relationship between Q and α during selective dissolution (Figure 7.7A, $R^2 = 0.9476$). CPE values from control and aerated dissolved AM Ti-6AL-4V surfaces form visually distinct clusters. These clusters are intersected by the average CPE values acquired over time. Including the Ti-29Nb-21Zr CPE values from Figures 6B-C introduces a third cluster, directly adjacent, and in some cases

overlapping, the CPE values captured on polished AM Ti-6AL-4V samples (Figure 7.7B). Plotted data points from similar individual trials in Figure 7.6 are close in distance to one another, showing good reproducibility.



Figure 7.7. Plot of α vs. Log₁₀(Q) (A) overlaying data captured before and after selective dissolution (Figure 7.4) and during active dissolution (Figure 7.6) for AM Ti-6AL-4V. A linear relationship exists between Log₁₀(Q) and α during active dissolution, intersecting clusters of CPE values extracted from dissolved and control surfaces. Ti-29Nb-21Zr CPE values (B) from Figure

7.6 are close to the control AM Ti-6Al-4V cluster. Data points from similar trials closely align with one another, showing good reproducibility.

Looking at the plots in Figure 7.7, one can visually identify three groups at the locations of the control nEIS spectra, the transition between control and dissolved, and the terminal EIS data captured around hours 18-24 of active selective dissolution. Removing the labels from Figure 7.7B and applying the k-means clustering algorithm generates three centroids approximately at these locations (Figure 7.8). Classified data points next to the first centroid (top left) correspond with undissolved surface states for AM Ti-6Al-4V and Ti-29Nb-21Zr. The middle centroid generally corresponds with the transition between undissolved and dissolved surface states over 24 h for AM Ti-6Al-4V. Finally, the third cluster (bottom right) neatly captures the dissolved surface state. Dissolved nEIS spectra acquired on AM Ti-6AL-4V surfaces after 48 h are split between class 2 (5/9, 56%) and class 3 (4/9, 44%).



Figure 7.8. K-means clustering analysis of the α vs. log₁₀Q from Figure 7.7 reveals three classes corresponding with (1) undissolved surface states for AM Ti-6Al-4V and Ti-29Nb-21Zr; (2) The transition from dissolved to undissolved surface states and (3) dissolved AM Ti-6Al-4V surface states. Dissolved nEIS spectra are split between class two and class three.

A clear relationship exists between Log₁₀(Q) and Log₁₀R_p over time (Figure 7.9). Generally, as Log₁₀(Q) increases, polarization resistance decreases. A regressed line ($R^2 = 0.87$) supports a proportional relationship between the two variables. When the initial data point (top left, -4.75, 5.28) extracted from an EIS spectrum captured vs. OCP is removed, the R^2 of the remaining data points vs. the newly regressed line (not shown) increases to 0.90. In this case, the remaining data are all captured during active dissolution at a constant potential of -0.4 V. In the bottom right corner, the data begin to cluster, consistent with the plateauing of Log₁₀Rp and Log₁₀(Q) over time in Figure 7.6A and Figure 7.6C, respectively.



Figure 7.9. Plot of $Log_{10}(Q)$ vs. $Log_{10}Rp$ over time. As $Log_{10}Q$ increases, the $Log_{10}Rp$ decreases. Note the linear relationship ($R^2 = 0.8729$).

7.4. Discussion

In this study, we investigated the effects of sustained negative potentials and inflammatory species on AM Ti-6Al-4V, using Ti-29Nb-21Zr as a comparison alloy. First, we selectively dissolved the AM Ti-6Al-4V β phase over a period of 48 h, holding the potential at -0.4 V in 0.1 M H₂O₂/PBS solution. We documented a 10-fold increase in the measured height and deflection across the dissolved oxide surface. Next, we used nEIS to quantify the changes on the AM Ti-6Al-4V oxide before and after selective dissolution. We identified a shift in the phase angle response as a characteristic feature of dissolved surfaces. These changes manifested as a significant decrease in the CPE exponent α and a significant increase in the CPE capacitance Q (p = 0.000).

In the second part of this study, we elucidated the AM Ti-6AL-4V selective dissolution mechanism over time. Micrographs captured during the selective dissolution process revealed pit nucleation, followed by growth. A clear coupling existed between dissolution of the surface and the oxide R_p , where a decrease and bottoming out of R_p preceded active dissolution. While both resistive and capacitive properties of the AM Ti-6AL-4V oxide changed during this process, the Ti-29Nb-21Zr oxide remained stable. Finally, circuit element plots established a log-linear relationship where decreases in α corresponded with increases in Q ($R^2 = 0.9476$) and showed a power-law relationship between R_p and Q. In totality, these results support our initial hypothesis, suggesting that AM Ti-6Al-4V may be susceptible to damage modes documented on conventionally manufactured devices. The impedance data captured in this study are well suited for a machine learning (ML) approach, either through the development of a neural network or cluster-based analysis. It is important to note here that the application of ML in this context improves decision making rigor, allows for rapid classification, and provides additional insight into our data. From our application of the kmeans clustering algorithm in Figure 7.9, the dissolved nEIS spectra (captured on reaerated surfaces after 48 h of cathodic activation) fell between the borders of class two and class three. This split classification of the spectra, where 5/9 share CPE characteristics with those transitioning from uncorroded to dissolved, and 4/9 CPE parameters approximate dissolved surfaces undergoing continued cathodic activation, supports the hypothesis of electrochemical history. Compared to the dissolved samples in class 3, the 48 h nEIS group's Log₁₀Q decreased, and α increased. This suggests that once cathodic activation and inflammatory conditions cease, the oxide recovers to some degree. However, both the oxide and surface structure retain elements of this electrochemical excursion including structural features (selective dissolution) and changes to the oxide impedance properties. It is likely that these dissolution states may be accurately classified from the bode phase plots alone, negating the need for circuit fitting, though this is beyond the scope of this study.

The k-means clustering algorithm may fail to converge to a global minimum, a well-known limitation. During our 100 replications of the function, we identified two additional local minimums where the total sum of the squared Euclidean distance was slightly higher than the solution we present in this work (2.139 and 2.143 vs. 2.103). In general, these increases in variance resulted in a shift of the centroids, causing more of the 48 h nEIS spectra to fall within class two (7/9, 78%). While we opted to present the lowest variance model in this work, the degree to which these spectra fall into either class is unclear. The application of nonnegative

matrix factorization, while also susceptible to local minima, would provide an interval to delineate between the classes, allowing for a better quantification of the model's uncertainty [54].

Throughout, we used as-built AM Ti-6Al-4V samples following a 3 h 600 °C stress relieving heat treatment. It is likely that the microstructure of these samples differs from the final microstructure on permanently implanted medical devices. It is well documented in the literature that post-print heat treatments modify the microstructure of AM Ti-6Al-4V. Besides modifying the mechanical properties of the alloy, microstructural changes affect the oxide film and the alloy's resistance to corrosion. In a two-phase alloy, heat treatments may alter phase size and chemical composition. Additional mechanical processes (e.g., shot peening) may be applied to achieve properties comparable with conventionally manufactured Ti-6Al-4V. Because industry views these post processing techniques as intellectual property, recapitulating the exact surface microstructure of AM Ti-6Al-4V devices *in vitro* remains a challenge.

We used additively manufactured Ti-29Nb-21Zr as a comparison alloy. Generally, this alloy did not corrode to the same extent as AM Ti-6Al-4V. Previous studies establish increased Ti-29Nb-21Zr oxide R_p in the presence of 0.1M H₂O₂/PBS solution [50]. Additionally, the conventionally manufactured Ti-13Nb-13Zr, comprised of similar elements, shows improved corrosion resistance in inflammatory simulating conditions [55-57]. The addition of sustained cathodic activation at -0.4 V, while lowering the Ti-29Nb-21Zr oxide R_p from baseline, had little effect on the alloy's capacitance. This aligns with lack of visible changes to the oxide or working electrode surface following electrochemical testing. While the -0.4 V cathodic hold on AM Ti-6Al-4V represents a cathodic excursion from the open circuit potential in 0.1 M H2O2/PBS solution (c.a. -0.1 V), the Ti-29Nb-21Zr OCP (approximately -0.2 V) constitutes a smaller gap in potential.

When exposed to sustained mechanical abrasion, the Ti-29Nb-21Zr surface potential may decrease below the -1 V maximum documented for Ti-6Al-4V, and applying increasingly cathodic potentials may degrade the oxide R_p. Because our focus in this study was the AM Ti-6Al-4V dissolution mechanism, we did not pursue these hypotheses.

While conventionally manufactured Ti-6Al-4V remains an intuitive comparator, various studies have thoroughly characterized the selective dissolution mechanism for the mill annealed alloy [26-32]. β phase dissolution within conventionally manufactured Ti-6Al-4V initiates at the α/β phase-boundary as small pits. Under continuous exposure to cathodic activation in inflammatory simulating solutions, the remaining β phase dissolves from the surface, leaving voids where the β phase used to be. During the dissolution process, structural changes to the oxide film occur, resulting in a thinner oxide film over the β phase [32]. Cross sectional analysis reveals cracks greater than 10 μ m forming beneath the surface, along and besides the β phase. Finally, the conditions that dissolve the β phase may also degrade the α phase. Micrographs show missing α grains when exposed to $0.1 \text{ M H}_2\text{O}_2 + 0.16 \text{ mM FeCl}_3$ for five days [32]. The characteristics of this damage is consistent with micrographs of selective dissolution on retrieved Ti-6Al-4V devices. From this study, it is unclear whether corrosion to the AM Ti-6Al-4V α phase occurs. While the two-phase microstructure of conventionally manufactured Ti-6Al-4V is black and white under SEM BSE, visually distinguishing the AM Ti-6Al-4V phases from SEM micrographs remains a challenge. Electron backscatter diffraction may help visualize the extent of corrosion on different phases and will be considered in future work.

The experimental conditions used to simulate inflammatory conditions in this study are far from a universal approach. Various researchers have added hydrochloric acid to H₂O₂ containing solutions, decreasing the pH, cultured and activated macrophages, and investigated the

synergistic effect of commonly adhering proteins at the device interface [28, 33, 34, 58-60]. A truly representative *in vivo* solution may require elements of all these approaches. The biology-device interface is complex and highly dynamic both immediately post implantation and over the course of the device's life. Retrieval studies document the presence of adhered cells at modular taper junctions and chemically induced corrosion damage modes including columnar damage, pitting, and the generation of thick oxide films [61]. While this study represents a step in understanding how these damage modes occur on passive alloys during tribocorrosion processes (e.g., cathodic potential drops across the entire electrode), more work is required. A solution more representative of the biological milieu would likely provide increased insight into these poorly understood corrosion damage modes.

7.5. Conclusion

In this study, we investigated the combined effects of sustained cathodic activation and an inflammatory simulating solution on AM Ti-6Al-4V selective dissolution. We showed that after 48 h in 0.1 M H₂O₂/PBS solution, the AM Ti-6Al-4V β phase preferentially dissolves. Using nEIS, we linked these structural changes to property changes in the oxide's impedance, particularly the phase angle response. CPE capacitance, Q, significantly decreased for dissolved surfaces while the CPE exponent, α , significantly increased (p = 0.000). Next, we elucidated the selective dissolution mechanism, capturing micrographs and EIS spectra at various time points over 24 h. A systematic decrease in the oxide R_p preceded pit formation within the β phase and subsequent growth. When CPE parameters α and Q were plotted, a log-linear relationship was established over the course of active dissolution (R² = 0.9476). K-means clustering analysis shows that these parameters may be predicative of the surface's dissolution state. In totality,

these results support our hypothesis, suggesting that AM Ti-6Al-4V may be susceptible to corrosion damage modes documented on conventionally manufactured Ti-6Al-4V retrievals.

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7.7. References

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Chapter 8

Predicting Corrosion Damage in the Human Body Using Artificial Intelligence: In Vitro Progress and Future Applications

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Key Points:

- Artificial intelligence is currently used in the clinic to improve patient outcomes.
- While there have been some successes, artificial intelligence has not yet made advances in biomaterial corrosion research.
- Few studies implement artificial intelligence/machine learning to predict corrosion of orthopedic biomaterials; many studies investigate physiologically relevant corrosion damage modes in the context of marine, oil and gas, and aerospace.
- Artificial intelligence/machine learning models may be able to predict corrosion damage modes from both image and non-image data, as well as multi-dimensional variable spaces that may provide value to the study of orthopedic biomaterials.
- Implant registries and retrieval libraries are potentially rich information sources to build datasets that apply state-of-the-art machine learning models.

Synopsis: Artificial intelligence (AI) is used in the clinic to improve patient care. While the successes illustrate AI's impact, few studies have led to improved clinical outcomes. A gap in translational studies exists, beginning at the basic science level. In this review, we focus on how AI models implemented in non-orthopedic fields of corrosion science may apply to the study of orthopedic alloys. We first define and introduce fundamental AI concepts and models, as well as physiologically relevant corrosion damage modes. We then systematically review the

corrosion/AI literature. Finally, we identify several AI models that may be implemented to study fretting, crevice, and pitting corrosion of titanium and cobalt chrome alloys.

8.1. Introduction

8.1.1 Artificial Intelligence in Orthopedics

Artificial intelligence (AI) and machine learning (ML) are increasingly used in orthopedics to assess patient risk, improve diagnostic accuracy in radiographs and predict patient outcomes [1-5]. The transition to electronic health records following the American Recovery and Reinvestment Act in 2009 has exponentially increased the amount of digital medical data for each patient [6-8]. This data, along with biological samples, retrieved devices, images, and patient reported outcomes, may be leveraged in multi-modal machine learning models to improve clinical outcomes, and decrease patient complications [9].

The goal of AI in orthopedics is not to replace the surgeon or radiologist at the point of care; instead, it is a tool to ultimately improve the consistency and quality of treatment patients receive at a population health level. Indeed, one of the fundamental theorems in the field of bioinformatics—the study of biomedical data to improve human health—is that a person in combination with an information resource is more effective than that same person unassisted [10-13]. In orthopedics, that information resource may include machine learning models to predict either adverse events from a patient's electronic health record or hip osteoarthritis from x-ray images [2, 14, 15]. The current clinical applications and future implications of AI in orthopedics are well documented in the literature [3, 16-19]. Some potential areas where ML or AI may find crucial new information is in their application to implant registries and/or implant retrieval programs. Researchers could use this extensive information related to implant performance in tandem with AI to investigate orthopedic outcomes. However, translational science begins outside the clinic, and a gap exists in applying AI to orthopedic implants and biomaterials at a basic science level.

To date, the application of AI to metal orthopedic biomaterials is limited, especially in the subfield of corrosion. Despite few published studies, the intersection of AI and corrosion of orthopedic biomaterials has many clinical implications. Langton et al. (2022) conducted AI-based work relating metallic corrosion and debris generation in total hip replacement patients with measures of soft-tissue reactions. They implement genetic phenotyping and develop a machine learning algorithm that may be able to predict genetically predisposed patient populations that are more reactive to metal-derived degradation products [20]. This work clearly establishes a genetic link to a metal hypersensitivity reaction in a subgroup of the patient population for the first time.

Permanently implanted metal devices are the standard of care for many orthopedic procedures, including total hip and knee replacement surgeries. *In vivo*, many factors impact the survivorship of these metallic implants including infection, loosening, wear and corrosion [21-28]. Passive metals, including 316L stainless steel, CoCrMo, and titanium and its alloys, are among the most used in orthopedic devices due to the passive oxide film that forms on their surface [29-31]. When this 2-10 nanometer thick film is interrupted *in vivo*, corrosion occurs, and the resulting damage may be associated with clinical failure.

Retrieval studies in the past three decades reveal corrosion damage modes on CoCrMo and Ti-6A1-4V devices, including mechanically assisted corrosion, fretting corrosion, crevice corrosion, and pitting [25, 28, 29, 32, 33]. Developing *in vitro* AI models to detect, classify and predict these damage modes, and translating these results *in vivo* may increase implant longevity,

decrease revisions, and improve patient outcomes. While a wealth of information exists on the application of AI to the broader corrosion literature, few basic science studies use AI to predict or classify corrosion *in vivo or in vitro* in the context of orthopedic biomaterials. Analyzing AI models from the aerospace, oil and gas, and marine corrosion fields may provide insight into how these models might apply to metals used in the human body. In this review, we first define AI and commonly used AI models in corrosion science. Next, we briefly introduce corrosion damage modes relevant to orthopedic biomaterials, including fretting corrosion, crevice corrosion, and pitting. We then systematically analyze how researchers use AI to predict and classify each damage mode. Finally, we discuss how these AI models may be translated from the broader corrosion literature into orthopedics to improve patient outcomes.

8.1.2 AI Primer

Here we define fundamental artificial intelligence (AI) concepts and models that will be used throughout this review. AI uses computers to model intelligent behavior with minimal human intervention [34]. The application of AI is firmly entrenched in today's widespread technological landscape and is used in various industries, including finance, manufacturing, and medicine [35-37]. AI aims to make computers think and act like humans to solve complex problems. Machine learning (ML) is a crucial subset of AI and can automatically learn from previous data to gain knowledge from experience. ML models gradually improve their learning behavior to make predictions based on new, unseen data [38].

8.1.3 Model Learning

Machine learning can broadly be categorized as supervised, unsupervised, and reinforcement learning. In supervised learning, a computer algorithm is trained on an input dataset labeled to classify data and predict outcomes. The learning algorithm can develop an inferred function that can detect the underlying relationships between the input data and output labels to make predictions about unseen observations after encountering sufficient training data. Supervised learning is implemented for object classification, semantic segmentation, and time series prediction. Within biomedicine, supervised learning can leverage existing patient data with known outcomes to aid in future predictions.

In contrast, unsupervised learning is used to train models on unlabeled data to discern underlying patterns within the dataset. These features are otherwise difficult to determine and reliably identify from human intervention alone. The unsupervised learning model can group input data based on similarity instead of predicting continuous variable output values. Unsupervised learning applications include clustering, association, and complex data dimension reduction.

Reinforcement learning is a sub-domain of machine learning that enables an agent to learn how to take proper actions in an interactive environment to maximize cumulative rewards. The agent, also known as the decision maker, can perceive the surrounding environment through sensors and respond to achieve goals. While most supervised and unsupervised learning algorithms focus on minimizing model loss, reinforcement learning focuses on maximizing the total reward. At the intersection of supervised and unsupervised learning is semi-supervised learning which works with a small number of input data with labeled output and a large number of input data without labeled output. Out of all the machine learning techniques mentioned above, supervised learning is the most widely used in orthopedics.

8.1.4 Model Prediction, Regression, and Classification

We typically categorize supervised machine learning models depending on the type of "ground truth" they predict. Models that predict continuous numeric values or quantitative outputs are typically considered regression models, while those that predict a label or categorical output are considered classification. The differences between these two categories are shown in Figure 8.1. In addition, the techniques to determine the model's success differ. Classification prediction results may be evaluated by accuracy, precision, recall, confusion matrix, etc. In regression modeling, the mean absolute error (MAE), mean square error (MSE), and root mean square error (RMSE) are frequently used metrics to calculate the difference between the predicted and ground truth values.

8.1.5 Machine Learning Models: Artificial Neural Networks

Artificial neural networks (ANN), support vector machines (SVM), and decision trees (DT) are prominent ML algorithms for classification (Figure 8.1A) and regression (Figure 8.1B) prediction in the both the literature and in the clinic.



Figure 8.1. The plots of (A) classification and (B) regression modeling.

Artificial neural networks (ANN) are supervised ML algorithms that loosely imitate the biological neural circuit. In practice, this model is a cluster of connected artificial neurons that extracts features from raw input data. A neuron of ANN, much like a biological neuron, receives input and processes it to produce an output [39]. This artificial neuron uses a mathematical function known as the activation function to process the input. In a web of interconnected neurons, one neuron's output becomes another's input. Next, a backpropagation algorithm is applied to train the ANN [40]. The weights of activation functions are iteratively updated in backpropagation based on the loss function performance. Figure 8.2A shows a typical ANN comprising input, hidden, and output layers.

An ANN with multiple hidden layers is a deep neural network (DNN). DNNs became successful with tremendous growth in computing power and the accessibility of large amounts of data. The popularity of DNN played a significant role in the rise of Deep Learning (DL), a sub-discipline of machine learning [41]. Muti-layer perceptron networks (MPN), convolutional neural networks (CNN), and recurrent neural networks (RNN) are prominent deep learning algorithms utilized for processing data such as images, text, and audio. DL algorithms can understand complex features of massive data that are not apparent to human intuition. Computer vision, natural language processing, drug design, and bioinformatics are taking advantage of DL models for classification, regression, and cluster analysis [42-45]. In healthcare, DL has been employed in medical image classification to assist in disease diagnosis and research [46]. A fully trained DL model on orthopedic radiographs performed on par with human experts in identifying fractures [47].

8.1.6 Machine Learning Models: Support Vector Machines

Support vector machines are a popular ML algorithm for classification problems [48]. SVMs are linear classifiers that can be applied to nonlinear datasets. They use kernel functions, mathematical

formulations that convert input data into the required form, to map the nonlinear data onto a highdimensional feature space. As illustrated in Figure 8.2B, a hyperplane is generated within this feature space that assists in data classification. SVMs are known for their ability to generalize and escape local extrema. Due to these properties, SVMs have been applied for medical image classification, health monitoring, and disease prediction [49-51]. SVMs have also been used for several classification tasks to investigate osteoarthritis [16]. The SVM algorithm may be extended as Support Vector Regression (SVR) and Support Vector Clustering (SVC), which are used for regression and cluster analysis, respectively [52, 53].



Figure 8.2. (A) Structure of ANN, (B) Data classification using SVM, (C) Structure of DT algorithm, and (D) Cluster analysis through K-means clustering.

1.2.5 Machine Learning Models: Decision Trees

Many ML algorithms are considered black box models. The user has input and output details, but the model's inner mechanism is unknown. In contrast, decision tree algorithms (DTs) are intuitive, and the concepts underlying the family of algorithms are comparatively easier to understand. DTs are supervised ML algorithms and are widely used for data classification [54]. They break a complex decision-making process into a network of simpler decisions and have a hierarchical tree structure with nodes and branches, as illustrated in Figure 8.2C. The entire dataset enters the DT at the root node, traverses through decision nodes, and ends at leaf nodes. The nodes and branches are recursively built until all the data instances in a leaf node belong to the same category. Each decision node is a function of attributes that splits the data into smaller subsets. Although DTs are predominantly used for classification, they can solve regression problems. DT algorithms are utilized in healthcare for data mining, automated diagnosis, and medical image and data classification [55-58]. Within orthopedics, DTs are employed in spinal column injury cases to create homogeneous clusters of patients and study the actual effects of treatment [59].

8.1.7 Machine Learning Models: K-means Clustering

In contrast to classification algorithms that use predefined labels, clustering algorithms are unsupervised. K-means clustering is a prominent unsupervised ML algorithm for cluster analysis [60]. The algorithm starts by creating k random centroids that determine the number of clusters in the dataset. An instance of data is assigned to a cluster with the nearest centroid. Figure 8.2D shows the dataset separated into three clusters. The centroids are iteratively updated with the arithmetic

mean position, and the data is reassigned based on the updated centroids of clusters. K-means clustering does not require labeling of training data, guarantees convergence, and can handle big data [61]. One drawback of this algorithm is that input data representation and the random initialization of centroids influence the output. K-means clustering has been applied for knowledge discovery in healthcare, clustering of patient disease data, and medical image segmentation [62-64]. Previously, k-means clustering has been used to classify patient images of intertrochanteric fractures into five distinct fracture types [65].

8.1.8 Corrosion in the Human Body

Corrosion occurs at the biology-device interface *in-vivo* and is associated with clinical failure [29]. In the past three decades, retrieval studies have documented corrosion in the modular tapers of total hip replacement devices [22-24, 32, 33, 66-69]. The use of modular taper designs in orthopedic implants began in the 1980s and has continued to be a foundational design element in total hip implants. Within the taper region of a total hip replacement, the femoral head and neck of the stem form a crevice when assembled. Both the head and stem interfaces are in close proximity and create a small volume where physiological solution can be present. When a patient cyclically loads their implant (i.e., walking), asperities—high points that inevitably arise on manufactured metal surfaces—on the two interfaces may abrade the passive oxide film covering CoCrMo, Ti-alloys, and stainless-steel alloys, resulting in a high rate of corrosion at the metalsolution interface until the oxide film repassivates, typically within a few milliseconds. This cyclic abrasion is defined as fretting when sliding distances are $100 \,\mu\text{m}$ or less, and along with the synergistic effects of solution chemistry, pH, and cathodic activation (i.e., negative potentials that arise from oxide film disruption), is responsible for most severe corrosion documented *in* vivo [25, 70-74]. The combined phenomenon of wear and crevice corrosion is known as

mechanically assisted crevice corrosion, or tribocorrosion. It is hypothesized to promote an autocatalytic behavior, promoting further corrosion damage *in vivo* [25].

In this review, we separate MACC into mechanical (i.e., fretting) and chemical damage modes (crevice corrosion and pitting). Because few research articles exist on predicting corrosion damage modes in the context of orthopedic biomaterials, we broadened our literature review to include all fields of corrosion. We investigated the following research questions: First, how are researchers using AI to predict clinically relevant corrosion damage modes *in vitro*? Next, how can this *in vitro* benchwork be translated to improve clinical outcomes?

8.1.9 Fretting in vivo

Fretting corrosion damage (Figure 8.3A-D) has been documented at modular taper junctions and acetabular interfaces in orthopedic devices. This damage can generate metallic debris that may induce adverse local tissue responses and promote periprosthetic osteolysis or soft-tissue reactions, including pseudotumors, fluid cysts, and necrotic masses [75, 76]. Clinical failure may arise when fretting occurs in an aqueous environment *in vivo* in combination with cyclic loading. On retrieved devices, fretting corrosion damage can be classified using the Goldberg score [33], a visual assessment to quickly quantify the amount of corrosion on an orthopedic component. Devices' scores range from one to four depending on the presence and severity of wear debris, pitting and surface discoloration. The total corroded surface area of the device may also be used to distinguish between the various Goldberg scores. The mechanisms of fretting corrosion have been extensively modeled and explored *in vitro*, helping to improve pre-clinical orthopedic device tests [21, 71, 72, 77-79].



Figure 8.3. Digital optical images of fretting corrosion on (A) exterior femoral taper and (B) interior femoral head surfaces; (C) SEM backscattered electron micrograph of femoral taper. Note the accumulation of oxide (dark regions) between the machined metal (bright) ridges; (D) SEM micrograph of fretting scars on the interior taper of a femoral head. Reproduced from J.R. Goldberg et al., CORR 2002, with permission from Lippincott Williams & Wilkins.

8.1.10 Crevice Corrosion in vivo

While the wear damage modes associated with MACC (i.e., fretting) have been replicated *in vitro*, the mechanisms of crevice corrosion damage modes observed on orthopedic retrievals remain comparatively unexplored and unelucidated. Within the modular taper junctions of femoral heads and stems, the formation of thick oxide films, selective dissolution, and hydrogen embrittlement have been documented on Ti-6A1-4V interfaces [28, 32]. Additionally, columnar damage, selective dissolution, and phase boundary corrosion have all been observed on CoCrMo orthopedic devices [80].

Though tribology initially abrades the passive oxide film, promoting oxidation and redox reactions, it is hypothesized that alterations to the physiological solution and surface potential affect the development of these damage modes *in vivo*. Deaeration of the crevice, cathodic activation of the surface, and the generation of oxidizers at the solution-device interface may all be necessary to reproduce crevice corrosion damage modes [25]. Indeed, studies show that the combination of cathodic activation and inflammatory species induces selective dissolution of the Ti-6A1-4V β phase *in vitro* [81, 82]. Digital images of orthopedic devices and SEM micrographs showing various crevice corrosion damage modes can be seen in Figure 8.4A-D.



Figure 8.4. (A) Ti-6Al-4V modular taper sleeve showing severe crevice corrosion; (B-D) Micrographs of crevice corrosion damage modes on Ti-6Al-4V. Note the preferential dissolution of the Ti-6Al-4V β phase in (C) and the etching in (B) and (D). Apart from selective dissolution,

these damage modes have not been recapitulated *in vitro*. Images of the modular taper sleeve in (A) are reproduced from Rodrigues et al. JBMR-B 2009 with permission from Wiley & Sons.

8.1.11 Pitting in vivo

Pits have been documented on retrieved CoCrMo surfaces and are found within crevicecontaining regions like modular junctions or immediately adjacent to crevice-containing regions [29]. Pitting on Ti-6Al-4V *in vivo* (Figure 8.5A-D) was not considered possible until recently and has not been replicated *in vitro* to date [32]. Micrographs of Ti-6Al-4V femoral stems show pits 500 μ m wide. When cross-sectioned, these pits reveal selective dissolution of the Ti-6Al-4V β phase. Thus *in vivo* pitting on Ti-6Al-4V may be promoted by crevice corrosion conditions.


Figure 8.5. (A-D) SEM micrographs of various pitting morphologies on retrieved Ti-6Al-4V devices. Note the variability in pit diameter. To date, the mechanism of Ti-6Al-4V pitting has not been elucidated under physiologically representative conditions. The micrograph in (A) is reproduced from Gilbert et al. JBMR-B 2012 with permission from Wiley & Sons.

8.2. Methods

The Web of Science and Scopus databases were queried with the following topic search terms: "Fretting" AND "Artificial intelligence" OR "Fretting" AND "Machine Learning", "Crevice corrosion" AND "Artificial intelligence" OR "Crevice corrosion" AND "Machine Learning", and "Pitting corrosion" AND "Artificial intelligence" OR "Pitting corrosion" AND "Machine Learning". We selected these two databases and formed search terms to capture AI/ML manuscripts that relate to physiologically relevant damage modes, even if the application in the selected works were outside the scope of orthopedics. When needed, corrosion damage modes and AI were queried both separately and together with ML to increase search rigor. For example, in Scopus, we searched (1) "Fretting" AND "Artificial intelligence" OR "Fretting" AND "Machine Learning", (2) "Fretting" AND "Artificial intelligence", and (3) "Fretting" AND "Machine Learning" to capture all relevant research articles.

Research studies were excluded from the review if the title or abstract was not relevant to corrosion and AI (i.e., when querying "Fretting" AND "Artificial intelligence", we incidentally returned research articles that described fluorescence resonance energy transfer (FRET) and AI. These studies were excluded from the review). We additionally excluded non-English studies, duplicate research studies, and studies tangentially related to the corrosion damage modes we focused on. We included theses and conference proceedings that presented substantially more work when compared with similarly titled publications from the same authors. Finally, we

excluded patents. We performed our search on August 26, 2022. Database searches were augmented with relevant research articles, theses, and conference proceedings that were not indexed in either Web of Science or SCOPUS. In this systematic approach, we prioritized presenting the most up-to-date research, augmenting queried articles with relevant literature. Complete details of our systematic approach can be found in Figure 8.6.



Figure 8.6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing identification, screening, and eligibility processes involved in identifying relevant AI/Corrosion research studies.

8.2.1 Data Extraction

Three independent researchers manually extracted the following data from each research article: author, title, year published, biomaterial investigated, corrosion damage mode, *in vitro* vs. *in vivo*, model learning type, prediction type, and ML models used. One additional researcher reviewed the data reported in standard data extraction tables (Tables 8.1-8.3). Attention was paid to whether the ML model used supervised or unsupervised learning and whether the output prediction was calculated via regression or classification. Various studies we analyzed referred to subclassifications of ML models. For instance, investigators labeled the neural network model they used as feed-forward (FF-NN) or back-propagated (BP-NN). For homogeneity of nomenclature, we classified the ML model used in each research study with the broader umbrella term, in this case, artificial neural network (ANN).

After extracting the ML models from the "Pitting corrosion" AND "Artificial intelligence" Web of Science search, four models across the research articles were selected to define in the introduction, including neural networks, support vector machines, decision trees, and k-means clustering.

8.3. Results

8.3.1 Fretting

8.3.1.1 Fretting of Orthopedic Biomaterials

Of the three corrosion damage modes investigated in this review, fretting corrosion had the most existing AI/ML literature directly applicable to orthopedic devices. Here we contrast two retrieval analysis studies relevant to this review that were not returned in our database queries. Milimonfared et al. and Codirenzi et al. both use AI to classify fretting damage on femoral tapers, predicting the Goldberg score associated with the documented damage [83, 84]. Of the 138 stems Milimonfared et al. investigated, 39% were CoCr, 30% were stainless steel, and 23% were titanium or titanium alloys [85]. Tapers were imaged eight times to generate a dataset of 1104 images. After hyper-parameter tuning, their SVM accurately classified the Goldberg score of the modular taper with 85% accuracy. Codirenzi et al. trained a neural network on images generated from 725 retrieved femoral stems. Digital optical microscopy captured four images per stem, generating a data set of 2890 unique images. Of the stems analyzed, 47% were titanium, 46% were CoCr, and 7% were stainless steel. Classification accuracy of the 4 Goldberg scores was comparatively worse (48.21 %) than the SVM approach employed by Milimonfared et al. However, accuracy improved to 98% when the NN was tasked with differentiating between mild (Goldberg 1 & 2) and severe (Goldberg 3 & 4) fretting corrosion categories.

8.3.1.2 Fretting AI Models

Artificial neural networks were the most popular ML model implemented to evaluate fretting (n = 10/12, 83%). SVM was the second most used model (n = 3/12). It is important here to note that it is common for AI studies to implement multiple model types and compare their performance. While only one study investigating fretting corrosion implemented this approach (using both ANN and SVM), both pitting and crevice corrosion AI studies implemented multiple ML models with increased frequency.

Of the metals investigated, 25% (3/12) included at least one metallic biomaterial. Various steel grades were used as either counter or bearing surfaces in 75% (9/12) of fretting applications. All research was conducted *in vitro*, though three of the studies we analyzed were revision studies involving total hip replacement devices previously in patients. Every reported AI approach involved some aspect of supervised learning. A test dataset was generated with a ground truth and used to predict either a categorical or continuous outcome. 83% (n=10/12) regressed a continuous output while % (n = 2/12) predicted classification. Fretting volume loss was a commonly reported outcome for regression models, while all classification models predicted a Goldberg score. The complete details of the extracted data can be found in Table 8.1.

8.3.2 Crevice Corrosion AI Models

Queries for crevice corrosion and ML/AI returned five papers after screening and exclusion criteria were applied. Of the five studies reviewed, only one used an orthopedic biomaterial candidate (316L Stainless steel). While we have opted to include the Rosen et al. work in both Tables 8.2 and 8.3, as they study both pitting and crevice corrosion, we have made sure not to double-count it in our analysis or figures. All the crevice corrosion studies used supervised AI models, with 60% (n = 3/5) using regression-based models and 40% (n = 2/5) performing classification. AI models used included ANN (n = 3/5), decision trees (n = 1/5), KNN (n = 1/5) and gaussian processes (n = 1/5). All five studies were performed outside the context of orthopedic biomaterials. Predicted outcomes included the presence of crevice corrosion (n = 2/5) and various outputs related to the severity of crevice corrosion damage (material loss, corrosion rate, initiation and propagation of crevice corrosion). Full details of extracted data may be found in Table 8.2.

8.3.3 Pitting Corrosion AI Models

Pitting corrosion research accounted for 68% (n = 34/50) of the studies evaluated in this review. Common topic areas included pipeline corrosion, building corrosion, marine infrastructure, and environmental degradation. 12% (n = 4/34) of studies used a biomedical alloy, in this case, 316LStainless steel. However, every pitting corrosion study we investigated was conducted outside the scope of biomedicine. Many metals studied (e.g., API 5L X52 Steel) were targeted toward pipeline usage or the oil and gas industry.

Most (94%, n = 32/34) investigators implemented supervised machine learning models. Popular model types included ANN (59%, n = 20/34), SVM (50%, n = 17/34), decision trees (21%, n = 7/34) and K-NN (18%, n = 6/34). Two studies utilized unsupervised approaches, using the non-negative matrix factorization and the k-means algorithm for clustering, respectively. 56% of studies (n = 20/34) used classification models, while 44% (n = 15/34) regressed a continuous variable as their outcome. These values add to over 100% because one study implemented both regression and classification. This ratio was much higher than in fretting AI studies, where regression accounted for almost all models implemented. 47% (n = 16/34) of investigators applied more than one AI model in their study. Pitting potential (E_{pit}), the presence or grade of pitting on a surface, and pit depth were all common model predictions. Complete details of the extracted data relating to pitting corrosion may be found in Table 8.3. The number of studies examining each corrosion damage mode and a breakdown of common AI models implemented per corrosion damage mode can be seen in Figure 8.7A-B.



Figure 8.7. (A) The number of studies investigated in the review by corrosion damage mode; (B) A breakdown of the number of articles that implement a DT, ANN, or SVM AI model by corrosion damage mode.

8.4. Discussion

Of the 50 articles we systematically reviewed, seven involved orthopedic biomaterials. This comparative lack of studies related to orthopedics may be due to several factors. First, implementation of AI models often requires interdisciplinary collaboration between subject matter experts (biomaterials, orthopedics, corrosion, etc.) and those with domain expertise in AI/ML. However, expertise in one subject matter may not be enough to design an AI experiment, choose and implement a successful model, and disseminate that information clearly and concisely such that others can build off the study or implement the model onto a new dataset. Similarly, those with AI expertise may be far removed from the clinic, lacking the skills and knowledge to identify gaps in clinical care or identify target areas that AI can improve.

Clinicians and basic science researchers armed with a fundamental, if high-level, overview of AI paired with data scientists who appreciate the pain points in clinical care may be able to generate and implement AI models that can make an impact in the clinic. The NSF has recognized the importance of interdisciplinary collaborations, launching funding programs targeted towards implementing AI that can improve biomedicine or public health.

Our database searches returned more pitting corrosion studies than crevice corrosion or fretting corrosion. This is mainly because pitting is one of the primary mechanisms of material loss and failure for steel pipelines [86, 87]. While corrosion failure of a medical device may or may not induce clinical failure for a single patient, corrosion failure of a pipeline can cause multiple deaths and environmental consequences, with the societal cost estimated in the billions of dollars [86-89]. Additionally, access to real-world data is more readily available for oil and gas studies. Pipeline steel may be evaluated using a potentiostat, and corrosion damage can be reproduced in environments representative of the atmospheric or soil conditions the alloys interact with in real-world use. In contrast, collecting corrosion data *in vivo* is challenging, and recapitulating the complex factors at the device biology interface *in vitro* remains a gap.

Severe corrosion documented on orthopedic retrievals is associated with mechanically assisted crevice corrosion. For metals used in total hip arthroplasties, including titanium and cobalt chrome alloys, pitting is induced by a complex combination of solution chemistry, oxide structure and function, and the biology present at the metal interface [90]. Unlike steel alloys, including 316L, cobalt chrome and titanium alloy pitting cannot be reproduced *in vitro* by statically applying a specific breakdown or pitting potential. Many models exist for wear and tribocorrosion of titanium and cobalt chrome alloys. However, few *in vitro* tests exist that induce crevice corrosion damage modes, including hydrogen embrittlement, pitting, and oxide

accumulation. Indeed, the FDA identified the lack of effective pre-clinical crevice corrosion tests as a gap in a 2019 white paper [91]. Thus, a lack of AI implementation to crevice corrosion experiments in the context of biomaterials may be explained by the comparatively poor ability to reproduce crevice corrosion in the lab under physiologically relevant conditions.

While gaps exist in our ability to model clinically relevant corrosion damage modes outside the human body, several studies we examined in this review may provide insight into how to identify critical variable spaces for solution chemistries and potentials that more accurately model the biological milieu. Jimenez et al. implemented SVM and ANN models to predict the two-dimensional chloride solution concentration and temperature area that would induce pitting corrosion on 316L Stainless steel [92]. Jimenez et al. additionally predicted a variable space that would corrode austenitic stainless steel, training their model with four variables: chloride ion concentration, pH, critical pitting potential, and temperature [93, 94].

The current paradigm for generating pre-clinical data and material selection for orthopedic devices is to evaluate the corrosion properties of metal samples or devices in saline solutions. Though these electrolytes may match the isotonic properties of the *in vivo* environment, they fail to include the array of lymphocytes, macrophages, and proteins attracted to the device once implanted. When confronted with a foreign body (i.e., the implant), lymphocytes and macrophages can promote oxidizers, including hydrogen peroxide, hydroxide radicals peroxynitrites, hypochlorous acid, and hydrochloric acid at the device interface [90]. Fretting, a common phenomenon in modular taper designs, may provide an additional source of reactive oxygen species (ROS) [95]. What is currently being modeled with salt water is a multi-dimensional variable space, and our simplification of the *in vivo* solution presents a challenge when trying to understand the mechanisms of crevice corrosion damage modes *in vitro*. AI,

especially SVM and ANN models, may help elucidate the critical solution concentrations of ROS and pH necessary to induce crevice corrosion damage modes in vitro, reducing the experimental time and number of tests needed. Besides mechanistic understanding, a more representative testing solution would aid in detecting poor device designs prior to clinical use. The ability of AI to classify images of corrosion damage in vitro may have the potential to impact clinical care. In this study, we reviewed two retrieval programs that implemented AI models to classify fretting corrosion on femoral tapers. We additionally reviewed various in vitro models that classified corrosion damage modes from image-based data. One retrieval study used digital optical microscopy to generate their dataset, and the second study classified digital photographs of the taper surface [83-85]. This latter approach is closer to the original application of the Goldberg score, a method intended to classify modular taper corrosion damage based on a quick visual assessment [33]. While these orthopedic devices were removed from the patient and cleaned before imaging, the ability to classify the corrosion damage on a taper mid-revision may decrease the time needed for surgery and improve clinical outcomes. Mid-revision, the surgeon separates the femoral head from the femoral stem and must decide whether to replace just the head or both femoral components. Replacing the stem is an invasive process and can result in increased complications when patients have poor bone density and bone volume loss. Applying this classification model to photos of the taper would provide additional information to the surgeon, improving decision-making in the operating room.

Many studies we reviewed applied AI to classify and predict corrosion damage modes from nonimage-based data. Morizet et al. classified crevice corrosion from acoustic emission signals [96]. Rosen et al. predicted various stages of pitting, general, and crevice corrosion damage on 316L Stainless steel using features extracted from polarization scans [97]. Recent studies show that

corrosion damage modes on retrieved orthopedic devices have unique electrochemical impedance spectroscopy (EIS) signatures [98, 99]. With the miniaturization of potentiostats (pocket potentiostats), the near-field EIS method may be a way to classify corrosion damage modes in the absence of imaging, providing decision support to surgeons and researchers. However, further research is required. Future studies will build a dataset of near-field EIS signatures on retrievals before AI implementation.

8.5. Summary

In this review, we systematically evaluated the existing corrosion AI literature, looking for applications of AI/ML models on physiologically relevant corrosion damage modes. We identified several experimental designs that may be implemented on orthopedic biomaterials, including classifying pitting, fretting, and crevice corrosion damage modes from image and nonimage-based data as well as predicting critical variable conditions that promote corrosion. Understanding successful models in the broader corrosion literature may aid in developing basic science studies with translational potential.

8.6. Clinical Care Points

- AI is already being used in the clinic and can improve patient outcomes.
- While there have been some successes, there is a lack of translational studies beginning at a basic science level.
- The broader corrosion field has rapidly adopted AI models predicting corrosion damage modes relevant to orthopedics.
- Translating these models to investigate orthopedic alloys has the potential to improve pre-clinical device testing and provide decision support to clinicians.

• Fully delivering on the promise of AI in orthopedics may require increased collaboration and knowledge transfer between clinicians, basic science researchers, and data scientists.

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8.8. Tables

Table 8.1.	Extracted	data	from	fretting	corrosion	articles.
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Author	Title	Year Published	Material Investigated	Corrosion Damage	Experiment Mode (<i>in</i>	Supervised or unsupervised	Regression or classification?	ML Approach	Predicted Outcome
				Mode	vitro vs in vivo)	learning?			
Buck, J.A.[100]	Evaluation of machine learning tools for inspection of steam generator tube structures using pulsed eddy current	2017	Alloy-800 (iron nickel chromium alloy)	Fretting	in vitro	Supervised	Regression	SVM, ANN	Support structure hole size, tube off-centering in two dimensions (one dimension containing variable fret depth), and fret depth
Codirenzi, A.[83]	Large-scale analysis and automated detection of trunnion corrosion on hip arthroplasty devices	2022	CoCr, stainless steel, titanium	Fretting	Explant analysis	Supervised	Classification	ANN	No and mild corrosion to moderate and severe corrosion in correspondence with Goldberg score
Gorji, M.B.[101]	Machine learning predicts fretting and fatigue key mechanical properties	2022	C-Mn steel	Fretting	in vitro	Supervised	Regression	ANN	Crack lengths and corresponding stress intensity factors under partial slip conditions resulting in crack arrest
Haviez, L.[102]	Semi-physical neural network model for fretting wear estimation	2015	Two chromium- molybdenum stainless steels: one carburized stainless steel and one stainless steel with mass quenching	Fretting	in vitro	Supervised	Regression	ANN	Wear volume
Kolodziejczyk, T.[103]	Artificial intelligence as efficient technique for ball bearing fretting wear damage predication	2010	Chromium steel	Fretting	in vitro	Supervised	Regression	ANN	Wear volume
Anand Kumar, S.[104]	Prediction of fretting wear behavior of surface mechanical attrition treated Ti-6Al-4V using artificial neural network	2013	Treated and untreated Ti-6Al- 4V, alumina and steel counter bodies	Fretting	in vitro	Supervised	Regression	ANN	Tangential force coefficient, fretting wear volume, and wear rate
Milimonfared, R.[85]	Development and implementation of an artificial intelligence system for assessing corrosion damage at stem taper of hip replacement implants: A retrieval study	2019	CoCr, stainless steel, titanium	Fretting	Explant analysis	Supervised	Classification	SVM	Corrosion damage rate in correspondence with Goldberg scoring
Nowell, D.[105]	A machine learning approach to the prediction of fretting fatigue life	2020	Al 4%Cu alloy	Fretting	in vitro	Supervised	Regression	ANN	Total fretting fatigue life
Ozarde, A.P.[106]	Optimization of diesel engine's liner geometry to reduce head gasket's fretting damage	2021	Steel	Fretting	in vitro	Supervised	Regression	ANN	Ruiz parameters for fretting fatigue damage
Qureshi, W.[107]	Prediction of fretting wear in aero-engine spline couplings made of 42CrMo4	2016	42CrMo4	Fretting	in vitro	Supervised	Regression	ANN	Fretting wear
Sharma, M.[108]	Studies for wear property correlation for carbon fabric-reinforced PES composites	2011	PES composites 52100 steel ball	Fretting	in vitro	Supervised	Regression	ANN	Wear rate and coefficient of friction
Zhang, G.[109]	Predicting running-in wear volume with a SVMR-based model under a small amount of training samples	2018	1050 steel (pin) 52100 steel (disc)	Wear (Pin on disk model)	in vitro	Supervised	Regression	SVM	Wear volume

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Author	Title	Year Published	Material Investigated	Corrosion Damage Mode	Experiment Mode (in vitro vs. in vivo)	Supervised or unsupervised learning?	Regression or classification?	ML Approach	Predicted Outcome
Bansal, P.[110]	Physics-informed machine learning assisted uncertainty quantification for the corrosion of dissimilar material joints	2022	Fe-Al Joints	Galvanic, Crevice Corrosion	in vitro	Supervised	Regression	Gaussian process model with probabilistic confidence- based based adaptive sampling	Material loss
Kamrunnahar, M.[111]	Prediction of corrosion behavior of Alloy 22 using neural network as a data mining tool	2011	Alloy 22 (Ni -22Cr - 14Mo -3W)	General & crevice corrosion	in vitro	Supervised	Regression	ANN	Corrosion rate, crevice repassivation potential, impedance values
Morizet, N.[96]	Classification of acoustic emission signals using wavelets and Random Forests: Application to localized corrosion	2016	304 L Stainless steel	Crevice corrosion	in vitro	Supervised	Classification	Decision trees, KNN	Crevice corrosion or no corrosion classes
Rosen, E.M.[97]	Corrosion prediction from polarization scans using an artificial neural network integrated with an expert system	1992	Hastelloy C- 276, 316 Stainless steel,	Pitting, Crevice Corrosion, General Corrosion	in vitro	Supervised	Classification	ANN	Presence of pitting corrosion, crevice corrosion, and whether general corrosion should be considered.
Trasatti, S.P.[112]	Crevice corrosion: a neural network approach	1996	Various stainless steels	Crevice corrosion	in vitro	Supervised	Classification	Artificial neural network	Initiation and propagation of Crevice corrosion

 Table 8.2. Extracted data from crevice corrosion articles.

Author	Title	Year Published	Material Investigated	Corrosion Damage Mode	Experiment Mode (in vitro vs in	Supervised or unsupervised learning?	Regression or classification?	ML Approach	Predicted Outcome
Agrawal, R.[113]	The use of machine learning and metaheuristic algorithm for wear performance optimization of AISI 1040 steel and investigation of	2022	AISI 1040 Steel	Wear, Pitting	in vitro	Supervised	Regression	ANN	Process parameters, wear rate
Abuia	corrosion resistance	2021		Ditting	in vitro	Supopulsod	Classification		
S.K.[114]	learning framework for detecting pitting corrosion based on image segmentation	2021		Fitting	in vito	Supervised	Classification		
Ampazis, N.[115]	Prediction of Aircraft Aluminum Alloys Tensile Mechanical Properties Degradation Using Support Vector Machines	2010	AI 2024-13 Aluminum alloy	Pitting	in vitro	Supervised	Regression	SVM	Yield strength, Tensile strength, elongation to fracture, strain energy density
Ben Seghier, M.E.A[116]	Advanced intelligence frameworks for predicting maximum pitting corrosion depth in oil and gas pipelines	2021	Not specified, stainless steel	Pitting	in vitro	Supervised	Regression	ANN, Decision Tree, Multivariate Adaptive Regression Splines, Locally Weighted Polynomials, Kriging, Extreme Learning Machines	Maximum pitting corrosion depth
Boucherit, M.N.[117]	Pitting corrosion prediction from cathodic data: application of machine learning	2021	Carbon Steel	Pitting	in vitro	Supervised	Regression	ANN	Pitting Potential
Boucherit, M.N.[118]	Modelling input data interactions for the optimization of artificial neural networks used in the prediction of pitting corrosion	2019	0.2% Carbon Steel	Pitting	in vitro	Supervised	Regression	ANN	Pitting Potential
Boukhari, Y.[119]	Optimization of learning algorithms in the prediction of pitting corrosion	2018	0.18% Carbon Steel	Pitting	in vitro	Supervised	Regression	ANN, SVM, K- NN, Decision Tree	Pitting Potential
Boukhari, Y.[120]	Artificial Intelligence to Predict Inhibition Performance of Pitting Corrosion	2017	0.18% Carbon Steel	Pitting	in vitro	Supervised	Regression	ANN, SVM, K- NN, Decision Tree, KBP, LDA, Adaptive neuro-fuzzy inference systems	Pitting Potential
Chou, J. S.[121]	The use of artificial intelligence combiners for modeling steel pitting risk and corrosion rate	2017	Steel Rebar, 3C steel	Pitting	in vitro	Supervised	Regression	ANN, SVM, Decision Tree, Linear Regression	Pitting corrosion risk, corrosion rate
Enikeev, M.[122]	Machine learning in the problem of recognition of pitting corrosion on aluminum surfaces	2018	Aluminum	Pitting	in vitro	Supervised	Classification	SVM	Hydrogen bubble detection
Hoang, N.D.[123]	Image Processing- Based Pitting Corrosion Detection Using Metaheuristic Optimized Multilevel Image Thresholding and Machine- Learning Approaches.	2020	Not specified	Pitting	in vitro	Supervised	Classification	SVM, Decision Trees, ANN	Detection of pits in images

 Table 8.3. Extracted data from pitting corrosion articles.

Ji, J.[124]	Prediction of stress concentration factor of corrosion pits on buried pipes by least	2015	Not specified	Pitting	in vitro	Supervised	Regression	SVM	Stress concentration factor
	vector machine								
Jimenéz- Come, M.[92]	An automatic pitting corrosion detection approach for 316L stainless steel	2013	316L Stainless steel	Pitting	in vitro	Supervised	Classification	ANN, SVM, Decision Tree, KNN	Solution temperatures and concentrations that induce pitting corrosion
Jimenéz- Come, M.[93]	Pitting corrosion behavior of austenitic stainless steel using artificial intelligence techniques	2012	EN 1.4404 Stainless steel	Pitting	in vitro	Supervised	Classification	Decision Trees, Discriminant Analysis, KNN, ANN, SVM	Environmental factors affecting pitting corrosion
Jimenéz- Come, M.[94]	Pitting Corrosion Detection of Austenitic Stainless Steel EN 1.4404 in MgCl2 solutions using a Machine Learning Approach	2012	EN 1.4404 Stainless steel	Pitting	in vitro	Supervised	Classification	Decision Trees, Discriminant Analysis, KNN, ANN	Pitting corrosion under various environmental factors
Jimenéz- Come, M.[125]	A support vector machine-based ensemble algorithm for pitting corrosion modeling of EN 1.4404 stainless steel in sodium chloride solutions	2018	EN 1.4404 Stainless steel	Pitting	in vitro	Supervised	Classification	SVM	Environmental variable that promotes pitting corrosion or breakdown potential modelling
Kankar, P.K.[126]	Fault diagnosis of ball bearings using machine learning methods	2010	Ball bearings	Pitting	in vitro	Supervised	Classification	ANN, SVM	Bearing fault type
Kubisztal, J.[127]	Corrosion damage of 316L steel surface examined using statistical methods and artificial neural network	2020	316L Stainless steel	Pitting	in vitro	Supervised	Regression	ANN	Corrosion Degree
Li, Q.[128]	Determination of Corrosion Types from Electrochemical Noise by Gradient Boosting Decision Tree Method	2018	X65 Steel, 304 Stainless steel	Passivation, Uniform Corrosion, Pitting	in vitro	Supervised	Classification	Decision Tree	Corrosion Type
Li, X.[129]	A Novel Framework for Early Pitting Fault Diagnosis of Rotating Machinery Based on Dilated CNN Combined With Spatial Dropout	2021	Not specified; Gears	Pitting	in vitro	Supervised	Classification	ANN	Fault Diagnosis
Liu, K.C.[130]	On-stream inspection for pitting corrosion defect of pressure vessels for intelligent and safe manufacturing	2017	304 Stainless steel	Pitting	in vitro	Supervised	Binary Classification	Adaptive neuro-fuzzy inference systems	Presence of pitting Corrosion
Lu, H.[131]	A Feature Selection- Based Intelligent Framework for Predicting Maximum Depth of Corroded Pipeline Defects	2022	Not specified; Pipeline	Pitting	in vitro	Supervised	Regression	SVM, eight benchmark models	Pitting corrosion depth
Pidaparti, R.[132]	Neural network mapping of corrosion induced chemical elements degradation in aircraft aluminum	2007	Aluminum 2024-T3	Pitting	in vitro	Supervised	Regression	ANN	Degradation behavior due to metal corrosion
Pinto, G.[133]	Non-intrusive Internal Corrosion Characterization using the Potential Drop Technique for Electrical Mapping and Machine Learning	2022	AISI 304 steel	Pitting	in vitro	Supervised	Classification, Regression	KNN, SVM, Decision Trees, Gradient boosting, Extreme Gradient boosting, ANN	Damage depth, Damage Severity

Qu, Z.[134]	Pitting Judgment Model Based on Machine Learning and Feature Optimization Methods	2021	Pipeline steels	Pitting	in vitro	Supervised	Classification	SVM, Decision Trees, Naive Bayes, Gradient Boosting, KNN	Occurrence of pitting and the key factors that influence it
Rosen, E.[97]	Corrosion prediction from polarization scans using an artificial neural network with an integrated expert system	1992	Hastelloy C- 276, 316 Stainless steel,	Pitting, Crevice Corrosion, General Corrosion	in vitro	Supervised	Classification	ANN	Presence of pitting corrosion, crevice corrosion, and whether general corrosion should be considered.
Roy, N.[135]	Effect of heterogeneities on pitting potential of line pipe steels: An adaptive neuro-fuzzy approach	2018	Pipeline steels, API X60 Steel alloys	Pitting	in vitro	Supervised	Regression	Adaptive Neuro Fuzzy Inference System	Pitting Potential
Sanchez, G.[136]	Corrosion grade classification: a machine learning approach	2019	M4140 steel	Pitting, general corrosion	in vitro	Supervised	Classification	SVM, Bag-of- Features	Corrosion Grade
Shin, M.[137]	A study on the condition-based maintenance evaluation system of smart plant device using convolutional neural network	2020	Not specified	Pitting	in vitro	Supervised	Classification	ANN	Pitting Corrosion Grade
Takara, Y.[138]	Analysis of the elemental effects on the surface potential of aluminum alloy using machine learning	2022	Al-Mg-Si-Cu alloys	Pitting, selective dissolution	in vitro	Unsupervised	Classification	NMF	Compound class, Matrix Phase class
Urda, D.[139]	A Constructive Neural Network to Predict Pitting Corrosion Status of Stainless Steel	2013	316L Stainless steel	Pitting	in vitro	Supervised	Classification	ANN, LDA, KNN, SVM, Naïve Bayes	Pitting Corrosion status
Wei, X.[140]	Shear strength prediction of TCSWs with artificial pitting based on ANN	2021	Steel	Pitting	in vitro	Supervised	Regression	ANN	Shear Strength
Yajima, A.[141]	A clustering based method to evaluate soil corrosivity for pipeline external integrity management	2014	API 5L X52 Steel	Wall thickness as a proxy for pitting	in vitro	Unsupervised	Classification	k-means clustering, Gaussian mixture modeling	Soil corrosivity classes
Zhang, Y.[142]	Corrosion pitting damage detection of rolling bearings using data mining techniques	2015	Not specified, Rolling bearings	Pitting	in vitro	Supervised	Classification	Support Vector Data Descriptor, ANN, SVM	Fault Diagnosis

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Chapter 9

Deep Neural Network Predicts Ti-6Al-4V Dissolution State Using Near-Field Impedance Spectra

(In Submission)

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Abstract: Retrieval studies document Ti-6Al-4V selective dissolution within crevices of total hip replacement devices. A gap persists in the fundamental understanding of Ti-6Al-4V crevice corrosion in vivo and its impact on the local impedance. Previous studies use nearfield electrochemical impedance spectroscopy (nEIS) for characterization of retrieved CoCrMo surfaces and phase angle symmetry-based EIS (sbEIS) for rapid data acquisition. In this study, these methods combine with a deep neural network to characterize the changes in local impedance after selective dissolution. It was hypothesized that structural changes occurring during dissolution would manifest as property changes to the oxide film capacitance. First, after sustained cathodic activation, the Ti-6Al-4V β phase selectively dissolves from the surface. Next, nEIS acquires n = 100 control and n = 105 dissolved spectra. Over dissolved regions, oxide capacitance significantly increases (Log₁₀Q = -4.17 vs. -4.78 (Scm⁻²(s) $^{\alpha}$), p = 0.000). Using single frequency EIS (5000 Hz), a capacitance-based scanning impedance microscopy method differentiates dissolved regions from control within seconds. Finally, bode phase plots of the 205 control and dissolved nEIS spectra are input into a deep neural network. After training, the model predicts the surface state for previously unseen nEIS spectra with 96% accuracy.

Table of Contents Graphic:



Keywords: Selective dissolution, Ti-6Al-4V, Scanning Impedance Microscopy, Deep Neural

Network, Corrosion

9.1. Introduction

Titanium alloys are widely used in orthopedic applications. Ti-6Al-4V is particularly favored due to its corrosion resistance, promoted by a thin 2-10 nm oxide film passivating on its surface [1-3]. *In vivo*, the metal-oxide-solution interface is complex. Mechanical, chemical, and biological events degrade both the oxide film and the underlying metal surface [4-14]. Wear during cyclic loading of orthopedic devices abrades the Ti-6Al-4V oxide film [15, 16]. On a nanoscale, asperities sliding 100 μ m or less (i.e. fretting) within the crevice of femoral components can initiate mechanically assisted crevice corrosion (MACC), an autocatalytic mechanism that promotes destructive conditions within the confines of modular taper junctions [5, 14, 17-20].

Surface potential decreases during MACC cathodically activate the surface and may generate reactive oxygen species (ROS). Previous studies document potentials as negative as -1 V during fretting corrosion of Ti surfaces. A second source of ROS may arise from the biology [11]. Activated immune cells, including M1 macrophages and foreign body giant cells can adhere directly to the implant surface and secrete ROS. While the wear mechanisms that occur within the femoral trunnion have been explored in the scientific literature, a gap persists in our ability to model both chemically and biologically destructive corrosion damage modes [21-26]. A further gap exists in our fundamental understanding of the interaction between potentials and the passive oxide film's electrochemical behavior under varying solution conditions, and the effects of prior electrochemical damage on the impedance response of Ti-6Al-4V.

Previous studies use electrochemical impedance spectroscopy (EIS) to map fundamental structural and property relationships between the Ti-6Al-4V oxide film's impedance and its ability to prevent corrosion [27]. Defects generated in the Ti-6Al-4V oxide structure as it

remodels under cathodic activation, tribology, or corrosive solutions decrease the oxide's polarization resistance, promoting corrosion at the interface. From our group, we used EIS to document a synergistic effect between negative potential excursions (i.e., cathodic activation) and inflammatory species, decreasing oxide passivation resistance by a factor of 10⁵ [28]. Further elucidation of these structure-property relationships between the oxide film and degraded implant surfaces is critical to our ability to replicate chemically and biologically induced corrosion damage modes in the lab and to prevent them *in vivo*.

Recent developments in EIS techniques provide powerful insights into the metal-oxide interface. First, phase angle symmetry rapidly captures multiple impedance spectra in short time periods [29]. Next, nearfield EIS quantifies the impedance of both small areas (mm² to um² resolution) and different corrosion damage modes. While micro impedance is well established, a recent study applied this approach in an electrochemical-cell-in-a-pipette setup, evaluating the impedance of chemically and tribologically induced corrosion damage modes at the surface interface [30-32]. The application of nEIS in a retrieval study documented significant differences in the capacitive behavior of intergranular corrosion, phase boundary corrosion, and oxide debris regions from control surfaces [33]. They also report differences in the constant phase element exponent, α . Thus, phase angle symmetry, for the first time, allows for the design of high throughput impedance testing and nearfield EIS may be utilized to identify unique impedance characteristics, or "signatures", of various corrosion damage modes.

Artificial intelligence is currently used in orthopedics to identify and classify features in radiographs, predict patient outcomes, and assess patient risk [34-38]. While these case examples illustrate the impact AI can have at the point of care, few studies apply AI within the field of metallic biomaterial corrosion [39-41]. Previous research shows the promise of AI in classifying

the Goldberg score of retrieved femoral stems. Support vector machine and neural networks models achieved high accuracy with multiclassification (85%) and binary classification (98%) problems, respectively. The ability to classify damage on femoral stems may have clinical implications at the point of care. During revision surgeries of total hip arthroplasty devices, the clinician must make a real time decision whether to replace the femoral head and acetabular components, or to remove the stem as well. Extraction of a well-fixed stem is a time-consuming process and can impact revision outcomes. Additionally, replacing the stem in patients exhibiting bone loss may require a custom device. The ability to quickly predict the corrosion state of a femoral stem trunnion may have value as a decision support tool for surgeons, and act as an aid in surgical planning.

In this study, we combine phase angle symmetry, nearfield EIS and an AI approach to elucidate the differences between selectively dissolved and control areas of Ti-6AI-4V surfaces. We hypothesize that structural changes to the oxide film under cathodic activation and inflammatory species will manifest as functional changes to the oxide's impedance. First, we utilize nEIS and sbEIS to repeatedly capture impedance spectra on dissolved and control areas. Next, we capture nEIS across a dissolved surface at intervals of 1-3 mm. Additionally, we introduce an impedance microscopy method where we continuously capture the loss impedance (-Z'') at a fixed high frequency (e.g., 5000 Hz) within seconds, moving our electrochemical cell across a Ti-6AI-4V surface with both selectively dissolved and uncorroded control areas. Finally, we use nEIS spectra from selectively dissolved and control areas to train and test a deep neural network model. We sought to answer the following research questions: (1) are selectively dissolved and uncorroded control Ti-6AI-4V regions identifiable using nearfield EIS and (2) can a DNN predict surface dissolution state from the respective impedance spectra?

9.2. Methods

To address our research questions, we used various electrochemical experiments and techniques including: (1) the application of sustained cathodic activation to induce selective dissolution; (2) the repeated nEIS measurement over dissolved and control Ti-6Al-4V surfaces; (3) the acquisition of nEIS as we manually moved an electrochemical cell fixture (1-3 mm increments) over a control and dissolved surface and (4) the continuous capture of -Z" at a single high frequency as we moved the fixture across a control and dissolved surface. To assess the predictive capability of impedance, we used the spectra captured over dissolved and control areas as inputs to a deep neural network. This systematic approach is reported in the following methods.

9.2.1 Sample preparation

Ti-6Al-4V samples (ASTM F-136) were mechanically polished using increasingly fine grits of emery paper, starting with 240 grit, and ending with 600 grit. Next, samples were manually held on polishing wheels for approximately 15 minutes each. Alumina/deionized H₂O suspensions of 1 μm and 0.3 μm, respectively, were applied until a mirror finish was achieved. Prior to imaging the control Ti-6Al-4V microstructure, a further chemical-mechanical polish was applied using a 40% H₂O₂, 60% colloidal silica suspension. Scanning electron microscopy (SEM, Hitachi S-3700N, Hitachi Inc., Tokyo) images were captured in both backscattered electron (BSE) and secondary modes. Chemically polished Ti-6Al-4V surfaces were mechanically polished afterwards to return both the surface finish and oxide structure to the same starting state as Ti-6Al-4V samples that were selectively dissolved. Prior to inducing selective dissolution, electrical connection was maintained between the back of the sample and an external wire using copper or carbon tape. This wire-Ti-6Al-4V junction was protected from the electrolyte solution using hot

glue. Finally, individual surfaces on a Ti-6Al-4V discs were isolated using tape, and the nominal surface area was measured using digital optical microscopy (DOM, Keyence VHX-6000, Keyence Corp., Mahwah, NJ).

9.2.2 Inducing selective dissolution

Selective dissolution was induced on Ti-6Al-4V samples by cathodically activating the surface at -0.4 V for 24 h. The electrochemical cell consisted of a Ti-6Al-4V working electrode and a carbon rod counter electrode. Reference electrodes included sintered Ag/AgCl references, as well as silver wire references chlorinated in household bleach for at least 24 h. Reference electrode potential difference was evaluated versus a mother electrode prior to use to assure a common reference potential. A VersaSTAT4 (AMETEK, Berwyn, PA) was used. The electrolyte consisted of a 0.1 M H₂O₂/ Phosphate buffered saline (PBS) solution. Experiments were conducted at both 24 °C (room temperature) and 37 °C \pm 3°C (physiological temperature). Physiological solution temperature was maintained using an IKA C-Mag HS7 digital hot plate with an external temperature sensor. To prevent active corrosion of the metallic temperature sensor, and unintended Fenton reactions at the Ti-6Al-4V oxide-solution interface, a second beaker was placed on the hot plate, filled with DI H₂O to the same volume as the beaker containing the electrochemical cell. Both beakers were simultaneously covered with parafilm to ensure equal heating, and the final temperature of the electrolyte in the electrochemical cell was measured to ensure accuracy. After 24 h, samples were removed, sonicated in 70% ethanol/30% H₂O solution, and dried with a kim wipe. SEM BSE micrographs of dissolved surfaces were captured at 5000x magnification. Resulting images were analyzed for β dissolution using ImageJ contrast thresholding [28].

9.2.3 Additively manufacturing nEIS fixture

An nEIS fixture consisting of a 25 mm wide base and a 40 mm high solution chamber was manufactured using fused filament fabrication (Original Prusa i3S MK3 printer). The CAD file of the nEIS fixture was sliced, exported to G-code, and transferred to the printer using an SD card. Polyethylene terephthalate glycol (PETG) filament was used, and printing took approximately 1.5 h. Post print, support structures were removed and an O-ring (inner diameter = 2 mm, outer diameter = 4 mm, McMaster-Carr 9269K101) was inserted into the designated slot.

9.2.4 Repeated nEIS measurement over dissolved and control Ti-6Al-4V surfaces

nEIS spectra were repeatedly captured from dissolved (n = 105) and control (n = 100) regions. The PETG fixture was first clamped to the Ti-6Al-4V working electrode (Fig. 9.1A). The 0.07 cm² (3 mm diameter) opening (Fig. 9.1C) was then visually inspected for the presence of corrosion, to ensure accurate spectra labeling. Next, 0.1 M H₂O₂ solution was added to the fixture using a 10 ml Corning auto-pipette. Then, a 1 ml plastic pipette tip was inserted into the electrolyte solution within the PETG fixture, until the tip contacted the working electrode surface. This was done to assure solution contact with the working electrode by breaking any surface tension generated between the hydrophobic O-ring, PETG fixture, and the Ti-6Al-4V working electrode surface. A sintered Ag/AgCl reference electrode and Pt wire counter electrode were inserted into the open top of the PETG fixture, an alligator clip was connected to the Ti-6Al-4V working electrode, and potential was monitored to ensure a complete electrochemical cell (Fig. 9.1B). The open circuit potential was recorded for 10 s. Next, EIS was captured from 10^5 to 10^1 Hz, or until the cross over frequency, ω_x , corresponding with the maximum phase angle was recorded [29]. In cases where EIS capture did occur at frequencies lower than 10^1 Hz, due to not reaching ω_x , only a few additional points were needed. Following capture, EIS data were fit using the phase angle symmetry (sbEIS) method, with a Randles CPE circuit equivalent.

Fifteen EIS spectra were captured from each of the seven dissolved regions (n = 105, Fig. 9.1D). The nEIS PETG fixture was moved after an EIS spectrum was recorded to ensure that a unique spectrum was acquired. One hundred EIS spectra were captured on a separate polished Ti-6Al-4V disc. The nEIS fixture was moved several mm after each capture to ensure that a unique spectrum would be recorded. The full details of the nEIS PETG fixture, capture resolution, and electrochemical cell can be seen in Figure 9.1.



Figure 9.1. Digital image showing the nEIS PETG fixture clamped to the Ti-6Al-4V working electrode (A). The blue wire extending out the top of the fixture is the reference electrode, and the alligator clip attached to the base of the Ti-6Al-4V disc connects directly to the potentiostat. The electrochemical cell consisted of Pt wire counter, sintered Ag/AgCl reference, and Ti-6Al-4V working electrodes (B). The PETG fixture was designed for a 4 mm outer diameter O-ring insert to create a sealed and constant contact region with the working electrode (C). A cut-away view of the PETG fixture in contact with a corroded region on the Ti-6Al-4V disc is shown in (D). Graphics in (B-D) are not to scale.
9.2.5 Spatial nEIS acquisition

During spatial nEIS acquisition, full nEIS spectra were systematically acquired on dissolved and control areas. The log adjusted capacitance from these experiments was plotted vs. the position on the surface in mm.

The PETG fixture was manually moved across a selectively dissolved area in increments of 1-3 mm. Generally, acquisition began in a control area, moved across a dissolved area of the sample surface and ended in a second control area. EIS spectra (n=3) were captured from two areas in the first control region (6 total spectra), one area at the control-dissolved border, and two areas within the selectively dissolved region. This process was mirrored as the fixture continued to move left to right. Captured spectra were fit using sbEIS with a Randles CPE circuit model. The distance of the first control nEIS spectra was labeled as 0 mm, and the locations of the following nEIS spectra were marked with sharpie and measured on the sample (±1 mm) using a ruler. Following nEIS measurement, DOM images of the control-dissolved region were captured.

9.2.6 Spatial scanning with single frequency capture of loss impedance

Single frequency (5000 Hz) data of the loss impedance (-Z") were continuously captured while spatially moving the system from left to right. During capture, the nEIS fixture was first held over a control area for 30 s. Next, the fixture, including the electrochemical cell, was slowly moved 5 mm from control to selectively dissolved region and held there for 10 s. The fixture was then moved 5 mm again to a second control area for 10 s, before moving in the reverse direction, -5 mm back onto the dissolved region. Finally, the nEIS fixture was moved back to the original control region and held for 10 s. The PETG nEIS fixture was swept back and forth across the

dissolved region for four complete cycles. The resulting -Z" values were converted to the CPE capacitance Q using the following formula:

$$Q = -\sin(\alpha * \pi/2)/(\omega^{\alpha} * Z'')$$
⁽¹⁾

where α is determined from the average peak height for dissolved ($\alpha_{dissolved} = 0.86$) or control ($\alpha_{control} = 0.90$) regions calculated from experimental nEIS data (Fig. 9.6F), ω was the nEIS d $\Theta/d\log_{10}(\omega)$ frequency peak (5000 Hz), and Z'' is the impedance loss. Data at the two linear plateaus corresponding with dissolved and control regions were identified, labeled, and clustered.

9.2.7 Deep neural network model

A deep neural network (DNN) was used to predict the dissolution state of the Ti-6Al-4V surface. The DNN comprised of input, output, and hidden layers. Inputs consisted of the phase angle vs. frequency datasets obtained through repeated nEIS capture (detailed in section 2.5). Model output was a binary classification of control or dissolved (1 or 0). To measure model error, the output of the DNN model was compared against the ground truth using a loss function. During backpropagation, the error was fed back to the network and the model parameters, including the weights within the hidden layers were updated. Forward propagation, loss evaluation, back propagation, and parameters were iteratively and continuously updated until an acceptable loss was obtained.

The DNN model comprised of multiple hidden layers. Each hidden layer was an assembly of several neurons. A neuron may be defined as a function that takes input processes it and produces an output. The rectified linear units (ReLU) activation function was used within the hidden layer neurons. The ReLU function is expressed as follows:

$$ReLU(x) = \max(x, 0)$$

where x is the input of the layer. The max function returns x, if x is greater than zero, and zero, if x is less than or equal to zero. A sigmoid activation function was used for the output layer of the DNN model. The sigmoid function was calculated as follows:

$$S(x) = \frac{e^x}{e^x + 1}$$

where *x* is the input of the layer. The sigmoid functions output ranges from 0 to 1. For example, when x = 0, the sigmoid output is 0.5, indicating that both classes have equal probabilities. Our binary classification problem had only two output values 0 (control) and 1 (dissolved). Hence, the threshold 0.5 was used to convert the output of our sigmoid function to either 0 or 1.

The binary cross entropy function was applied to evaluate the loss of the DNN model. The loss function calculated the error by comparing the predicted output $p(y_i)$ with the ground truth y_i . The equation of binary cross entropy is:

$$H_p(p(y_i), y_i) = -\frac{1}{N} \sum_{i=1}^{N} y_i * \log(p(y_i)) + (1 - y_i) * \log(1 - p(y_i))$$

where *N* is number of samples.

Backpropagation fine-tuned the learning parameters (weights and biases) of the DNN model based on the loss obtained from the binary cross entropy loss function. The gradients of the loss with respect to the weights and biases were evaluated layer by layer starting from the output layer and consecutively working back to the input layer. Based on these gradients, the neural network adjusted the weights and bias of each layer using gradient descent algorithms. Gradient descent algorithm further uses learning rate that determines the step size of each iteration. This training process continued until the network output error decreased to an acceptable value. To evaluate the performance of the DNN model, we used the classification accuracy metric. Accuracy may be calculated as the ratio of total true predictions of the DNN model to the total predictions. A model of the neural network architecture can be seen in Figure 9.2.



Figure 9.2. Deep neural network approach. First, n = 105 dissolved and n = 100 control nEIS spectra were captured from Ti-6Al-4V samples. Next, these spectra were fit using sbEIS, and

capacitance was identified as a differentiating variable. The phase angle and frequency data from the nEIS spectra were used to train (n = 180) and test (n = 25) a DNN. Model prediction of the surface state (0 for control, 1 for dissolved) was compared with the ground truth.

Hyperparameter tuning is the process of selecting a set of optimal hyperparameters for the DNN model. Hyperparameters include the number of hidden layers, layer size (no. of neurons in each layer), batch size (number of samples), and learning rate. The five DNN models and their classification accuracies with different hyperparameter combinations are listed in Table 9.1. Among these five models, the first DNN model configuration achieved the best performance on the test cases with 0.96 classification accuracy.

Table 9.1. Hyperparameters of five DNN.

DNN Model Configuration	1	2	3	4	5
DNN Layer 1 (no. of neurons)	50	100	50	50	50
DNN Layer 2 (no. of neurons)	20	20	20	20	20
DNN Layer 3 (no. of neurons)	-	-	10	-	10
Learning Rate	0.001	0.001	0.001	0.0001	0.001
Batch Size	50	50	50	50	20
Accuracy	0.96	0.92	0.88	0.92	0.72

9.2.8 Statistical methods

Two-sample t-tests were used to assess the differences in $log_{10}(Q)$ (Fig. 9.6C) and the CPE exponent α (Fig. 9.6F) between n = 105 dissolved and n = 100 control nEIS spectra. A one-way analysis of variance (ANOVA) was used to determine significant differences in the spatially acquired nEIS (Fig. 9.5A) capacitance. Pairwise comparisons between control, border, and dissolved regions were conducted using a post hoc Tukey's multiple comparison test. Differences in capacitance following the continuous capture of loss impedance (Fig. 9.5F) were assessed using a two means t-test. Transient Z'' points captured while moving the PETG fixture between control and dissolved regions were removed and the remaining points were labeled as either 0 (control) or 1 (dissolved) and converted to CPE capacitance. The mean capacitance of a dissolved cluster (n = 338) was compared with the mean capacitance of a control cluster (n =417). An alpha rejection level of 0.05 was used for all statistical tests. A minimum of n = 6 data points were sampled from each population statistically analyzed in this work.

9.3. Results

9.3.1 Inducing selective dissolution

Cathodically activating Ti-6Al-4V samples at -0.4 V for 24 h in 37 °C or 24 °C 0.1 M H₂O₂ induced preferential dissolution of the Ti-6Al-4V β phase (Fig. 9.3). Reference secondary electron SEM micrographs (Fig. 9.3A) of the untreated surface show a uniform surface with the faint outline of the Ti-6Al-4V β phase. In backscatter electron mode (Fig. 9.3B), the two phases are easily distinguishable. Equiaxed globular α takes up more relative surface area and is darker in contrast to the vein-like interspersed β phase. The β phase appears light grey. On surfaces exposed to cathodic activation and inflammatory species, the β phase is preferentially leached (Fig. 9.3C-D). Note the dark crevices in Figure 9.3D where the β phase used to be and the beveled appearance of the remaining α at the phase boundaries.



Figure 9.3. Matched Secondary and BSE micrographs of control (A, B) and selectively dissolved (C, D) Ti-6Al-4V. Dark crevices appear on the Ti-6Al-4V surface in (C) and (D) where the β phase used to be. Digital images of the Ti-6Al-4V sample show seven separately selectively dissolved regions (Fig. 9.4A).

Digital optical microscopy (DOM, Fig. 9.4B) reveals a heterogenous surface. Though the entire surface appears selectively dissolved, indicated by the dark crevices surrounding the remaining globular α , various regions are shades of brown, blue, and purple. Note the nearfield EIS capture resolution, the circular area of the surface exposed to the electrochemical cell, overlayed on top of the DOM image. For the image in Figure 9.4B, the nEIS capture resolution is approximately 22% of the dissolved region. ImageJ contrast thresholding of BSE micrographs of the seven dissolved regions (Fig. 9.4C) confirms the visual analysis from the DOM. All seven surfaces exhibited at least 89% β dissolution. The maximum β dissolution measured was 100%.



Figure 9.4. Digital image (A) of the Ti-6Al-4V sample showing seven separately dissolved regions. DOM imaging (B) reveals a non-uniform surface and shows the 0.07 cm² spatial scale of the nEIS. ImageJ contrast thresholding (C) quantifies the level of β dissolution of the dissolved regions in image (A).

9.3.2 Repeated nEIS measurement over dissolved and control Ti-6Al-4V surfaces

Representative (n = 1) impedance spectra captured on dissolved and control areas are shown in Bode magnitude and phase plots (Fig. 9.5A-B). Note the similarity in |Z| at low frequencies for control and dissolved areas in Figure 9.5A. These values correspond with the predicted $R_s + R_p$ using phase angle symmetry. Bode phase plots (Fig. 9.5B) show a leftward shift in the peak of the dissolved spectra. Circuit elements extracted from control (n = 100) and dissolved (n = 105) spectra reveal several important characteristics (Fig. 9.5C-F). First, there is a significant increase in the log adjusted Q for dissolved regions (Fig. 9.5C, -4.17 (Scm⁻²(s)^{α})) compared to control regions (-4.78 (Scm⁻²(s)^{α}), p=0.000). This increase quantifies the leftward shift of the dissolved spectrum presented in the Bode phase plot in Figure 9.5B. Next, the magnitudes of R_p and R_s (Fig. 9.5D-E) are similar, indicating that changes in the capacitance are due to modifications in the oxide structure rather than changes to the electrochemical cell setup or solution chemistry. Finally, there is a significant decrease in the CPE exponent α for dissolved regions (0.86) compared to control regions (0.90, p = 0.000).



Figure 9.5. Bode magnitude (A) and phase (B) plots of representative EIS spectra for dissolved and control areas. Note the leftward shift in the dissolved phase angle peak in (B). Extracted Randles circuit element values Q (C); R_p (D); R_s (E); and α (F) for dissolved (n = 105) and control (n = 100 spectra) areas. Log adjusted Q for dissolved areas significantly increased (p = 0.000) and the constant phase element exponent, α , significantly decreased (p = 0.000).

9.3.3 Spatial measurement using nEIS of dissolved and control regions

Following spatial acquisition at 1-3 mm intervals across a dissolved Ti-6Al-4V surface, nEIS spectra (Fig. 9.6A, region 1 in Fig. 9.4A) show an increase in the log adjusted Q for selectively dissolved regions (Fig. 9.6B, p=0.000). At distances of 0 and 4 mm over control areas, log₁₀(Q) was recorded as -4.86 (Scm⁻²(s)^{α}) and -4.80 (Scm⁻²(s)^{α}) respectively. At the first border between control and dissolved regions (6 mm), log₁₀(Q) increased to -4.41 (Scm⁻²(s)^{α}). EIS spectra captured in the center of the dissolved region (9 mm, 11 mm) reveal a second increase in log₁₀(Q) to -4.24 (Scm⁻²(s)^{α}) and -4.16 (Scm⁻²(s)^{α}) respectively. This behavior was mirrored as EIS data were captured on the border and second control area. Log₁₀(Q) was lower on the second dissolved-control border at 13 mm and returned to -4.88 (Scm⁻²(s)^{α}) and -4.81 (Scm⁻²(s)^{α}) at 17 and 20 mm respectively. The differences in log adjusted Q between control, dissolved, and border areas were all statistically significant (p=0.000).



Figure 9.6. DOM images (A) of dissolved and control areas. Log adjusted capacitance (B) acquired at 1-3 mm intervals over the 20 mm scale bar in (A). Log₁₀Q over control, dissolved, and border regions are significantly different (p=0.000).

9.3.4 Continuous impedance loss capture at a single high frequency

Continuously acquiring impedance loss at a constant 5000 Hz frequency and rastering the nEIS electrochemical cell 10 mm across the Ti-6Al-4V sample shows an increase in the imaginary component of the impedance magnitude, Z'', over dissolved regions (Fig. 9.7A). This plot is of Z'' versus time as the electrochemical cell is translated over the surface from control regions to selectively dissolved regions, and back. Note the increase in Z'' from -105 Ω at 31 s to -35 Ω at 32 s in 0.1 M H₂O₂ electrolyte solution, corresponding with moving the nEIS electrochemical cell 5 mm from a control area to the center of a dissolved area. After capturing Z'' over the dissolved area for 10 s, moving the nEIS fixture another 5 mm to a second control area decreased Z'' at 42 s to -96 Ω . Rastering 5 mm back across the dissolved region, holding for 10 s, and

returning to the original control area at 62 s replicated the increase in Z'' over dissolved regions and subsequent decrease over control areas. Note, similar results (although shifted in value) were obtained when the solution was replaced with PBS. This rastering back and forth was repeated four times over 180 s, yielding similar characteristic increases in Z'' over dissolved regions (Fig. 9.7B). Converting Z'' to Q, and removing transient points captured during movement of the electrochemical cell shows two distinct linear regions, one corresponding with control areas and a second corresponding with dissolved areas (Fig. 9.7C). Plots of the Log₁₀(Q) values vs. their ground truth labels (Fig. 9.7D) reveals two clusters of data, the capacitance captured over control areas (labeled 0) at -4.3 (Scm⁻²(s)^{α}) and the capacitance over dissolved areas (labeled 1) at -3.8 (Scm⁻²(s)^{α}). The means capacitance of the dissolved cluster (n = 338) was significantly higher than the control cluster (n = 417, p=0.000).



Figure 9.7. Continuous capture of loss impedance at 5000 Hz shows an increase in Z'' when rastering across dissolved areas (A). This process was repeated four times with similar results (B). Converting the Z'' 0.1 M H₂O₂ values in (B) to CPE capacitance and area normalizing reveals two distinct linear regions corresponding with control and dissolved surfaces (C). Plotting the log adjusted Q vs. the ground truth label shows two clusters (D). The means of these clusters are significantly different (p = 0.000).

9.3.5 Deep Neural Network Dataset and Predictions

Plots of the Randles CPE exponent α versus Log₁₀Q show two clusters of data, corresponding with the ground truth labels (Figure 9.8A). Spectra captured over control regions are clustered around -4.8 Log₁₀(Q) and 0.9 α . In contrast, dissolved spectra CPE values have increased variance, though the resulting CPE variables are still visually distinguishable from the control cluster. A deep neural network trained with the phase angle and frequency dataset (n = 180), as well as a binary label (0 for control, 1 for dissolved) was able to predict the true class of unseen data with 96% (n = 24/25) accuracy (Figure 9.8B). It is important here to note that while we visually represent the EIS spectra in Figure 9.8B using the calculated CPE values and exponents, these data were not used to train the model. Instead, only the unfit EIS phase versus log ω spectra were needed for classification.



Figure 9.8. Ground truth labels for the EIS spectra used to train and test the deep neural network (A). Note the visually distinct clusters of control (n = 100) and dissolved data (n = 105). The EIS spectra associated with the data in (A) were randomly divided into training (n = 180) and testing (n = 25) data (B). A deep neural network was able to predict the class of previously unseen

testing data with 96% accuracy. Data inputs for the neural network were the phase angles and frequency captured during EIS and the output was a binary classification of the dissolution state of the Ti-6Al-4V surface, 0 for control or 1 for dissolved.

9.3.6 Assessing the Deep Neural Network's Generalizability

In this section, we present the results of two tests cases to assess the generalizability of the trained deep neural network. First, A DOM image (Fig. 9.9A) of a Ti-6Al-4V sample shows a dissolved area after 7 h of cathodic activation at -0.4 V in 0.1 M 37 °C H₂O₂ solution. Though the time exposed to inflammatory species and cathodic activation was lower than those in the training data set (24 h), the state of the surface is dissolved. EIS captured in control areas, border areas, and dissolved areas shows similar behavior to the linear acquisition in Figure 9.5B. Log adjusted Q starts off low, rises at the border regions between control and dissolved areas, and peaks in the dissolved area. As EIS were captured across the second border area (7 mm), and second control area (9-10 mm), this behavior is maintained. The trained deep neural network was able to successfully predict the true class of n = 7/8 of the points (or 21/24 individual impedance spectra) in Figure 9.9B from the associated phase angles and frequencies. It is important to note that this surface was (1) dissolved on a separate Ti-6Al-4V disc than the training data was captured from, and (2) none of these impedance spectra were used to train the neural network.



Figure 9.9. DOM images (A) show a selectively dissolved Ti-6Al-4V area after 7 h at -0.4 V in 37 °C 0.1 M H₂O₂ solution. Line scan impedance (B) measured across the 10 mm axis in (A) show an increase in log adjusted Q on both border and dissolved areas from the control areas, similar to the behavior of Q in Figure 9.5B. EIS spectra were captured in triplicate (n =3) for each point in (B). Error bars are plotted with the standard deviation though they are too small to appear here. The deep neural network trained in Figure 9.7 was able to successfully predict the labels of 7/8 points (87%).

A second generalizability test was performed on region five in Figure 9.4A. While dissolved impedance spectra were captured from this area using 0.1 M H₂O₂ to train the neural network in Figure 9.7, here, we linearly acquired nEIS of the region using a PBS electrolyte solution. A DOM image shows the 10 mm raster path of the line scan (Fig. 9.10A). Resulting Q values are low over control areas, increase over the border between dissolved and control areas and increase

again over dissolved areas. These characteristics are similar to the EIS line scans captured using $0.1M H_2O_2$ in Figure 9.5 and Figure 9.9. The deep neural network predicted 8/8 points (100%) and 24/24 EIS spectra (100%) correctly.



Figure 9.10. 10 mm raster path (A) of the EIS linescan across control and dissolved areas using PBS as an electrolyte. Resulting Q values (B) show an increase over dissolved regions. The neural network trained in Figure 9.7 was able to predict the dissolution state of the EIS spectra with 100% accuracy (n =8/8). EIS spectra were captured in triplicate (n = 3) at each distance. Error bars show the standard deviation.

9.4. Discussion

In this study, we used a combination of four approaches, including (1) nearfield EIS, (2) sbEIS, (3) high frequency Z" spatial scanning and (4) a deep neural network (based on phase versus log ω) to quantify and classify the impedance differences between selectively dissolved and control Ti-6Al-4V areas. This combination of impedance analysis and artificial intelligence methods demonstrates the potential for high speed measurement and classification of corrosion damage on alloy surfaces. While only two classes were identified and studied in this work (selectively dissolved and control surfaces), the possibility of adopting this approach for rapid analysis of damaged implant surfaces exists, or in other circumstances where variations in surface alloy impedance may reflect variations in surface quality. In particular, high frequency loss impedance measurements, which were chosen to be at 5000 Hz in this work, but could be at higher frequencies as well, may provide high speed and high throughput impedance based analysis for imaging and surface assessment. When used in combination with DNN methods, monitoring and determination of degradation classes, as well as high speed imaging based in impedance become possible.

The results presented in this study build off the existing body of literature. Prestat et al. document capacitive changes to the oxide film over time during active selective dissolution of the Ti-6Al-4V β phase [42]. They present a linear increase in oxide capacitance with respect to time, as the Ti-6Al-4V surface is exposed to oxidizing solutions, including PBS/ 0.1 M H₂O₂ and PBS/ 0.1 M H₂O₂ with the addition of 0.16 mM FeCl₃. When the Ti-6Al-4V surface is cathodically activated at -0.4 V in addition to the oxidizing solutions, the capacitance increases with a logarithmic relationship to the elapsed time. It is important to note here that while Prestat et al. are actively measuring the EIS of a corroding surface, we are capturing the nEIS of the surface after dissolution has been completed, and the oxide has re-aerated. Despite these experimental differences, we still identify a significant increase in the capacitance of dissolved surfaces compared to the control Ti-6Al-4V (p = 0.000). This suggests that changes in the capacitance are driven by modifications to the TiO₂ oxide structure during β dissolution, and that once modified, the oxide does not recover to the pre-dissolution state.

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These insights support the hypothesis of electrochemical history, where the oxide accumulates defects *in vivo* when exposed to adverse electrochemical events. It is unrealistic, for example, to expect the supraphysiological conditions $(0.1 \text{ M H}_2\text{O}_2, \text{ sustained cathodic activation at } -0.4 \text{ V})$ used in this work to occur at the biology-oxide-device interface in vivo. Retrieval studies document dissolved surface states, including the formation of thick oxide films, and pitting within the crevices of modular taper junctions where β dissolution appears as an initiating mechanism. The *in vitro* benchwork in this study, Prestat et al., and others, while accelerated to produce selective dissolution in a reasonable experimental time frame, supports a dissolution mechanism that is induced on a time scale of months or years rather than in the span of 24 h [43-48]. We hypothesize that as Ti-6Al-4V modular taper junctions are cyclically loaded *in vivo*, the cathodic activation of the surface induces defects in the oxide film. In combination with ROS generated from fretting or activated immune cells during inflammation, the number of defects may reach a threshold such that the passivation resistance of the TiO₂ oxide film may no longer be sufficient to prevent active dissolution initiating at the $\alpha + \beta$ phase boundaries. Indeed, it is not only the β phase that corrodes *in vivo*. Retrieval studies show evidence of chemically induced corrosion of the Ti-6Al-4V α phase and recently published *in vitro* studies show that α may be targeted for preferential dissolution [7, 9, 49]. More *in vitro* work is needed to confirm this hypothesized *in vivo* mechanism. Future studies will evaluate the cyclic effect of cathodic activation and inflammatory species on the oxide capacitance and passivation resistance. Functional changes in the oxide capacitance documented in this study are likely directly related to structural changes in the oxide film and/or topographic changes to the surface. Atomic force

microscopy of the oxide overtop titanium and its alloys reveals homogenous, closely packed domes [50]. When subjected to inflammatory species, these domes become fuzzy (when imaged

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in AFM), indicating defects in the oxide film [50, 51]. Additionally, FIB-SEM of dissolved and cross sectioned Ti-6Al-4V surfaces reveals structural differences in the oxide overtop α and the oxide overtop β [42]. While the oxide over top α remains closely packed, voids appear in the β oxide. A habit relationship likely exists between the oxide over alpha and the oxide over β , corresponding with the different elemental composition of the two phases (α is aluminum rich in contrast with the vanadium rich β phase). Additionally, the increase in defects due to the differing crystal structures (HCP, BCC) at the $\alpha + \beta$ phase boundaries may aid in initiating β dissolution in the presence of cathodic activation and inflammatory species.

In this work, me make several modifications to the nEIS method presented by Wiegand and Shenoy [30]. While their electrochemical-cell-in-a-pipette setup had a spatial resolution of 0.00196 cm², our electrolyte contact area with the working electrode was 0.07065 cm². Both the PETG filament diameter (1.5 mm), PRUSA printing resolution, and O-ring size limited are ability to recapitulate their nEIS capture resolution. Despite a larger spatial scale, our nEIS results support key findings from their study. Wiegand and Shenoy identify nEIS as a method to classify various corrosion damage modes based on their impedance "signature". They show significant increases in both α and Q corresponding with different classes of corrosion damage modes *in vitro* and *in vivo*. While this experiment was designed for binary classification between dissolved and non-dissolved surface states, we document significant changes to the CPE capacitance and exponent between dissolved and control surfaces (p = 0.000). Additionally, the Bode Phase plots of dissolved surfaces clearly show defining, "signature", characteristics allowing for visual classification, including a shifting to lower frequencies and decrease in peak height. We used a DNN model to predict the surface dissolution state of Ti-6Al-4V. While DNNs are a widely used approach within the broader corrosion literature, few studies to date have explored implementation in the field of orthopedic biomaterial corrosion [52]. Though the binary classification DNN architecture presented in this work may seem rudimentary, given that β dissolution may be visually assessed within seconds on a micrograph or a Bode plot, the results in this study demonstrate that nEIS may indeed be used to identify corrosion damage modes in the absence of traditional imaging methods. Additionally, we show how a DNN may predict the dissolution state from the captured EIS spectra, negating the need for circuit fitting.

Future studies will expand this AI approach for the classification of multiple corrosion damage modes, and the degrees of corrosion damage present. The DNN model presented here may struggle with multiclassification. Codirenzi et al. document a decrease in neural network model accuracy when switching from binary classification of modular taper Goldberg scores to multiclass classification [53]. While the original intentions of the Goldberg score may play a role in the poor neural network multiclass accuracy (the Goldberg score was intended for quick, visual classification within seconds, rather than complex computational analysis of features extraction from digital imaging), other investigators were able to circumvent this pitfall with a support vector machine (SVM) approach [41]. Thus, when this AI architecture is expanded for the classification of more than one corrosion damage mode, it may be important to consider other AI models.

Finally, we present a methodology for the identification of dissolved surface states using linear EIS. By capturing the Z" at a frequency close to the peak of the derivative of the phase angle with respect to the log of the frequency (in this case, 5000 Hz), we can calculate the CPE capacitance Q from a single point, negating the need to capture an entire, or partial EIS

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spectrum. This methodology allows for the rapid acquisition of capacitance data from a surface, and may be used for scanning impedance microscopy, where the PETG filament is rastered across the surface of a metallic biomaterial to identify dissolved regions. In combination with an AI approach, scanning impedance microscopy may be able to correctly classify corrosion damage modes in the time scale of seconds on metallic biomaterials. Further investigation is needed.

9.5. Conclusion

In this study, we used nearfield EIS, phase angle symmetry, and a deep neural network approach to identify property changes in the Ti-6Al-4V oxide film after selective dissolution of the Ti-6Al-4V β phase. We document significant increases in capacitance of dissolved areas, and significant decreases in the CPE exponent alpha compared to control areas (p = 0.000). Next, we present scanning impedance microscopy as a new method to rapidly identify corrosion damage modes on metallic surfaces. Constant acquisition of the impedance loss and subsequent conversion to CPE capacitance revealed a significant increase in dissolved Q, consistent with the nEIS results. Finally, we built a neural network architecture that can predict the dissolution state of the surface from the associated EIS spectra with 96% accuracy. Future work will expand this binary classification model to multiple corrosion damage modes.

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Chapter 10

Synthesis of Work

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Throughout this thesis, several themes emerge. First, the selective dissolution mechanisms for both AM and conventional Ti-6Al-4V share similar processes. For both, baseline R_p started at approximately $10^5 \Omega \text{cm}^2$. After 6 h of continuous activation at -0.4 V in 24 °C 0.1 M H₂O₂/PBS, the oxide degraded to $10^3 \Omega \text{cm}^2$. After 12 h under these electrochemical conditions, the conventional Ti-6Al-4V β phase dissolved. In contrast, at 12 h on the AM Ti-6Al-4V surface, visible pit nucleation began. Thus, under similar experimental conditions, micrographs show decreased β dissolution for the AM alloy, suggesting improved corrosion resistance. Next, degradation of the oxide is a key component of the dissolution mechanism. Prior to the 10^3 threshold, little dissolution occurs, regardless of alloy microstructure. We document most dissolution after this threshold, when LogR_p begins to plateau. Future work is required to validate these findings.

Empirically, our results show that different oxide properties dominate the impedance response for different surface classes. Increased oxide R_p may differentiate polished AM and conventional Ti-6Al-4V surfaces from those in transition or completely dissolved. However, most structural changes occur to the Ti-6Al-4V surface when the oxide is already degraded. For the transition and dissolved surface classes, the oxide's capacitive behavior, manifesting as the CPE parameter Q and the CPE exponent α , becomes a better predictor of dissolution severity.

Impedance monitoring suggests that selective dissolution is path independent. While increased solution concentrations and temperatures directly increase the corrosion kinetics, the initial oxide parameters associated with a polished surface, and the final parameters associated with a dissolved surface remain relatively fixed. Within our results, and for both AM and conventional Ti-6Al-4V, these R_p and Q couples exist at approximately ($10^5 \ \Omega cm^2$, $10^{-5} \ Scm^{-2}(s)^{\alpha}$) for polished surfaces and ($10^{2.5} \ \Omega cm^2$, $10^{-3.5} \ Scm^{-2}(s)^{\alpha}$) for dissolved surfaces. Additionally, while

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increasing the solution concentration and temperature visibly increased dR_p/dQ , the family of R_p and Q curves appear to overlay one another. This indicates that it is the structural changes to the surface as it undergoes dissolution that determines property changes within the impedance, rather than the electrolyte solution present. This observation is further supported by nEIS spectra captured in both PBS and 0.1 M H₂O₂. Our neural network accurately classified dissolved and polished surfaces using spectra captured in PBS when trained exclusively using data acquired in 0.1 M H₂O₂ electrolyte solution.

Throughout the various studies in this thesis, we identified a cathodic potential range (-0.3 V to - 1 V) critical to the dissolution mechanism. First, when applying a transient cathodic hold for 600 s, we documented little selective dissolution above -0.5 V. During our stepwise impedence methodology, -0.3 V represented a transition point. Below -0.3 V, R_p rapidly decreased. Above - 0.3 V, R_p was stable, plateauing at relatively fixed values dependent on the solution concentration. Under sustained cathodic activation for 24 h, potentials from -0.3 V to -0.8 V induced at least 50% β dissolution. Interestingly, little dissolution occurred at -0.9 V to -1 V, suggesting a limit on active corrosion at these potentials, despite the degraded oxide film. These negative potentials directly relate to the *in vivo* interface. During tribocorossion, the Ti-6Al-4V surface potential may decrease to as low as -1 V.

The cumulative research in this thesis incrementally moves the field forward. Bai et. al first induced β dissolution as a Ti-6Al-4V surface treatment. Prestat et. al thoroughly explored the microstructural aspects of selective dissolution, introducing a sustained cathodic activation methodology [1-3]. Here, we use Prestat's method of sustained cathodic activation to explore both AM and conventional Ti-6Al-4V dissolution mechanisms, relating the property changes occurring at the interface to the structural changes as the surface corrodes. Additionally, we

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investigated the effects of temperature on dissolution, building upon the work of Davenport et. al [4]. We show a clear temperature dependence of β dissolution, supporting their findings of an Arrhenius-like relationship between α dissolution and temperature in an HCl electrolyte. Finally, we implemented AI for the binary classification of selective dissolution. Our machine learning work builds off AI models and approaches used to classify Goldberg scores on orthopedic retrievals [5-7].

We document several important insights and introduce new methods of characterization and analysis. Using imageJ, we present a contrast thresholding method for quantifying β phase dissolution. This allowed us to improve the rigor of our study design, generating numeric cutoffs for surface classification. We introduce a new scanning impedance microscopy (SIM) method, rapidly capturing the impedance CPE parameter Q. SIM may be translated to retrieval analysis of corroded implants, generating maps of the device surface. Next, in various chapters throughout this thesis, we see a direct, if non-linear, relationship between R_p and Q. Because we can rapidly capture Q, relating the impedance properties allows for prediction of R_p, decreasing impedance acquisition time. Additionally, we applied machine learning for the accurate prediction of dissolved surfaces. This too, generates new research directions. Finally, we show how accelerated testing conditions may be related back to physiological conditions for Ti-6Al-4V.

These studies experienced several limitations. First, we used various concentrations of H₂O₂ as proxies for ROS produced at the device interface. Though H₂O₂ represents an intermediate ROS species, it may further react into hydroxyl radicals, hydroperoxyl radicals and hypochlorous acid. Additionally, it may engage in Fenton reactions, oxidizing Fe (II) to Fe (III). Next, the biological milieu at the device interface consists of more than just oxidizers and acids. Post implantation, the body recruits an array of cells including neutrophils, macrophages, foreign body giant cells and osteoclasts in an inflammatory response. Researchers document macrophage sized etching within modular taper junctions [8]. Additionally, lysed macrophages showed uptake of CoCrMo ions *in vitro* [9]. Finally, challenged macrophages on CoCrMo decreased the open circuit potential to around -800 mV, and significantly increased the corrosion rate (I_{corr}, p < 0.05) [10]. Clearly, the patient's biology plays a role in inducing corrosion *in vivo*. However, implementation of a cell culture-based methodology is beyond the aims of this thesis.

To simulate fretting potential drops at the device interface, we used potentiostatic holds below the Ti-6Al-4V open circuit potential. We used this substitution to (1) reduce the experimental time needed to induce β dissolution and (2) isolate the chemically induced corrosion mechanism from the plastic and elastic deformation caused by wear. True cathodic activation *in vivo* is likely cyclic, and intrinsically coupled with the oxide's repassivation following mechanical abrasion. Next, the crevice geometry, where two interfaces are near one another, plays a role. Empirically, and not shown here, we documented severe corrosion as solution ingressed between the nonconductive tape we used to isolate our working electrode area and the Ti-6Al-4V surface. Additionally, AM Ti-6Al-4V β dissolution appeared to initiate at the borders of the working electrode, occasionally corroding the artificial tape-metal crevice to such a degree that solution freely contacted most of the working electrode surface area. No study design is perfect, and despite these various limitations, we elucidated elements of the Ti-6Al-4V selective dissolution mechanism. We developed powerful testing methods and contributed new science to the study of titanium alloy corrosion.

Chapter 11

Conclusions

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Throughout, our results supported our aims and hypotheses. Here, for each aim, we report the key takeaways, new methodologies, and contributions to the literature.

11.1A: Determine the critical conditions needed to induce Ti-6Al-4V selective dissolution.

- Negative (cathodic) potentials and inflammatory species are critical to inducing Ti-6Al-4V β dissolution. While H₂O₂ solutions alone induce β dissolution, a 600 s transient potential decreased the experimental time needed.
- Mechanistically, pits nucleate within the β phase at the α/β phase boundaries. As dissolution progresses, the pits grow and become interconnected. Finally, all the β dissolves, leaving dark crevices on the surface.
- Both transient cathodic activation and inflammatory species significantly decreased oxide R_p from baseline by a factor of $10^2 \Omega cm^2$ (p < 0.05). When combined, the oxide R_p further decreased by an additional order of $10^3 \Omega cm^2$.

11.1B: Systematically evaluate the effects of cathodic potential, solution concentration, and temperature on the Ti-6Al-4V oxide film structure and properties.

- Atomic force microscopy images of the oxide film show structural changes after inducing β dissolution. The oxide over polished Ti-6Al-4V surfaces appears homogenous and closely packed. Once dissolved, the oxide appears fuzzy, suggesting increased defects.
- Inflammatory species and cathodic activation synergistically decreased oxide R_p over a -0.3 V to -1 V potential range. Additionally, As H₂O₂ concentration increased, oxide R_p decreased.

 High molarities of H₂O₂ (0.1 M) induced changes in the oxide semiconductor properties. At negative potentials (-1 V to -0.4 V), the oxide exhibits p-type behavior. As the solution concentration decreases, the oxide transitions to a p-type response.

11.1C: Investigate the effect of temperature on the selective dissolution mechanism.

- During sustained cathodic activation in 0.1 M and 0.05 M H₂O₂/PBS solutions, oxide R_p decreases prior to the initiation of selective dissolution. After a threshold around 10^3 Ωcm^2 , β dissolution initiates.
- Plots of Log₁₀(R_p) and Log₁₀(Q) reveal a family of closely overlapping curves, regardless of the electrolyte solution temperature (24, 37, and 45 °C). Using the dissolution % calculated from SEM micrographs, we identify three surface classes, undissolved, transition, and dissolved, dependent on the Log₁₀(R_p) and Log₁₀(Q) circuit parameters. As the surface dissolved, Log₁₀(R_p) significantly decreased and Log₁₀(Q) significantly increased (p = 0.000).
- An Arrhenius-like relationship between dissolution rate and solution temperature clearly exists. Similar slopes in 0.1 M and 0.05 M H₂O₂/PBS solutions suggest that increases in the corrosion kinetics are driven by increases in the frequency factor, rather than changes to the activation energy.

11.2A: Compare the fundamental corrosion properties of new, additively manufactured titanium biomaterials with Ti-6Al-4V.

• Microstructures of AM Ti-6Al-4V and AM Ti-6Al-4V 1% nYSZ appear martensitic, typical of the selective laser melting/powder bed fusion process. The admixed Ti-29Nb-
21Zr shows isolated pools of niobium where the powder beads failed to fully melt and mix.

- Both admixed and AM Ti-29Nb-21Zr show improved corrosion resistance in 0.1 M H₂O₂/PBS solution when compared with the Ti-6Al-4V based biomaterials. Ti-6Al-4V passive current density shifted upon the addition of 0.1 M H₂O₂. Next, during EIS acquisition, the Ti-6Al-4V biomaterial R_p decreased by a factor of 10. In contrast, both Ti-29Nb-21Zr biomaterials showed overlapping passive regions in PBS and 0.1 M H2O2/PBS solutions. Their oxide R_p's did not decrease, suggesting improved corrosion resistance.
- Few oxide and corrosion property differences were reported between the admixed and pre-alloyed Ti-29Nb-21Zr. This supports pre-alloying as a cost-effective method of assessing materials and element weight percentages prior to the more expensive alloying process.

11.2B: Assess the dissolution mechanism of AM Ti-6Al-4V.

- In this study, we showed that the AM Ti-6Al-4V β phase preferentially dissolves under similar conditions to the conventionally manufactured alloy (-0.4 V, 0.1 M H₂O₂/PBS solution). Additionally, we identify a similar dissolution mechanism. Oxide degradation preceded pit nucleation in the β phase. Under continuous cathodic activation, pits grew, and the surface level β dissolved.
- Unlike conventional Ti-6Al-4V, the structure of oxide domes over top polished and dissolved surfaces looked similar in AFM images. However, the deflection and height differences between the dissolved surface and the oxide supported a corroded, uneven surface.

- The unsupervised machine learning technique k-means clustering identified three classes in our data, generally associated with the surface dissolution state. Impedance captured on polished AM Ti-6Al-4V surfaces, and Ti-29Nb-21Zr during sustained cathodic activation populate one cluster. As the Ti-6Al-4V alloy is exposed to cathodic activation and inflammatory species, the CPE parameter, Q, increases and the CPE exponent α decreases. We labeled this middle group as the transition class. Finally, the dissolved impedance properties surround a cluster (bottom right) at Log₁₀(Q) = -3.6 Scm⁻²(s)^{α} and $\alpha = 0.83$.
- AM Ti-29Nb-21Zr corroded comparatively less than the AM Ti-6Al-4V. Micrographs show pits, but not to the same extent as the Ti-6Al-4V β dissolution after 24 h. Additionally, monitoring of the oxide properties over 24 h shows a relatively stable Log₁₀(R_p) and Log₁₀(Q). In contrast, the AM Ti-6Al-4V Log₁₀(R_p) decreases and the Log₁₀(Q) increases.

11.3A: Systematically review the corrosion-artificial intelligence (AI) literature.

- Few studies implement AI within the biomaterials-corrosion field. Most AI models within corrosion fall under oil and gas, aerospace, and marine corrosion domains. A gap exists in the application of AI at the basic science level within orthopedic biomaterial corrosion.
- Supervised machine learning models including artificial neural networks, decision trees, and support vector machines dominated model selection. Additionally, most studies focused on supervised machine learning, iteratively training models with data to predict a class or regress a value.

Most AI/Corrosion studies focused on pitting (n = 34). This was partially due to the prevalence of oil and gas research in our systematic review, where pits within pipeline steel have severe environmental and economic consequences. Crevice corrosion (n = 5), most relevant to the corrosion within modular tapers *in vivo*, remained comparatively unexplored.

11.3B: Predict selective dissolution using a deep neural network and near field impedance spectroscopy.

- Using nearfield electrochemical impedance spectroscopy (nEIS), we identify the CPE parameter, Q, and CPE exponent, α , as impedance properties predictive of selective dissolution. For dissolved surfaces, (much like the AM Ti-6Al-4V results) Log₁₀(Q) significantly increased (p = 0.000) and α significantly decreased (p = 0.000). Both parameters may be gleaned from Bode phase plots.
- Next, we introduced a new scanning impedance microscopy method to rapidly identify dissolved areas. Capturing the loss impedance at 5000 Hz, we show increases in the Log₁₀(Q) as we moved our electrochemical cell from polished to dissolved regions.
- Finally, we trained a neural network, using n = 180 dissolved and control nEIS Bode phase spectra as inputs. The trained model predicted the class (0 = polished, 1 = dissolved) for 25 previously unseen spectra with 96% accuracy. Further model validation was carried out using a selectively dissolved surface after 7 h of exposure to adverse electrochemical conditions (87% accuracy) and changing the electrolyte used for impedance capture to PBS (100%) accuracy.

Chapter 12

Future Work

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While we thought out and systematically evaluated the aims presented in this thesis, we tried many experimental designs that failed. However, some of the pilot tests we explored, but did not fully investigate, show promise for future work. First, we replaced the potentiostatic, cathodic hold with continuous fretting at 100 Hz. SEM BSE (Figure 12.1A) and secondary micrographs (Figure 12.1B) show dissolution adjacent to the fretting scar after approximately 24 h. Partial dissolution (Figure 12.1C, D) is visible within the bulk working electrode area, far away from the pin-on-disc contact region. Most severe corrosion (Figure 12.1B) occurs directly next to the fretting scar, likely in the crevice region formed by the pin.



Figure 12.1 Backscattered (A, C) and secondary (B, D) SEM micrographs of a Ti-6Al-4V sample after 24 h of 100 Hz pin-on-disc fretting. Images (A) and (B) show complete dissolution of the β phase directly next to the fretting scar. Partial dissolution (C-D) occurred at the borders of the working electrode surface.

The limitations of this pilot study are clear. We only ran n = 1 trials, limiting our analysis and conclusions. Next, 100 Hz is a much higher fretting frequency than what occurs *in vivo*. Finally, it is unclear if the hydrogen peroxide in the solution is driving the dissolution process or if it is the synergistic effect of H₂O₂ and cathodic activation. We know from our previous research that high molarities (1 - 3 M) of H₂O₂ alone will dissolve the β phase, and that cathodic activation will decrease the experimental time needed. Control studies examining each factor (fretting, H₂O₂) in isolation, would help to determine their effect on selective dissolution. ImageJ analysis could be used to quantify the extent of dissolution for samples exposed to H₂O₂ and those exposed to H₂O₂ and fretting, allowing for comparative analysis. Additionally, recording the electrode potential during fretting would provide additional evidence of a cathodic activation driven mechanism.

Next, we attempted to model the *in vivo* crevice geometry by mounting CoCrMo femoral heads on Ti-6Al-4V stem testing coupons. These components were previously used for cyclic fretting testing but generally showed little visual evidence of corrosion. Using an MTS, we cyclically loaded the modular taper junction with four kN of force for three million cycles at nine Hz (approximately five days of experimental time). After two pilot tests, we documented corrosion within the modular taper junction on the Ti-6Al-4V component. However, the electrolyte solution we used (0.1 M H₂O₂) corroded the bulk stem as well. Micrographs of the Ti-6Al-4V stem (Figure 12.2A) and trunnion (Figure 12.2B) show the accumulation of corrosion debris. Note the buildup between the trunnion grooves in Figure 12.2B, indicative of corrosion within the crevice. After sonicating the stem, secondary (Figure 12.2C) and backscattered (Figure 12.2D) micrographs show tunnel-like corrosion and interconnected pits. In Figure 12.2C, the bottoms of the tunnels look like dry, cracked, lake-beds.

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Figure 12.2 BSE images of a Ti-6Al-4V stem (A) and trunnion (B) prior to sonication after three million cycles of fretting in 0.1 M H₂O₂/PBS solution. Interconnected pits (C, D) form tunnels on the surface. N = 2 pilot studies were performed.

First, like our fretting experiment, additional trials are required to validate these preliminary findings. Next, our experimental design was fatally flawed. Our H₂O₂ solution concentration was too strong, corroding not only parts of the crevice underneath the CoCrMo femoral head, but the entire stem exposed to the electrolyte solution. Future experiments lowering the solution concentration may aid in synergistically corroding the working electrode area exposed to cyclic fretting, while leaving the bulk stem undissolved. Another potential solution to this problem is to drill a port within the CoCrMo head, exposing the crevice to oxidizers and acids while cyclically loading the head-stem junction in PBS.

We rely on EIS in many of the chapters in this thesis to quantify oxide film properties at the interface. Because fretting generates a current, capturing EIS during fretting is a challenge.

Capturing single frequency EIS during normal fretting conditions, Swaminathan reported data that approximates a Nyquist plot [11]. EIS Monitoring during fretting-induced selective dissolution remains a possible future research direction.

During our implementation of a neural network, we developed a new, rapid method for capturing impedance, converting the loss impedance at 5000 Hz to the constant phase element parameter Q. This scanning impedance microscopy (SIM) method shows promise for capturing localized impedance of large working electrode surface areas, producing impedance maps, and decreasing the experimental time needed for impedance capture. In this thesis, we apply SIM by rastering between dissolved and polished regions, showing a significant increase in Q over selectively dissolved areas (p = 0.000). Future studies may build off this methodology by capturing loss impedance systematically across a corroded device surface. Producing three dimensional plots of Q and the x-y coordinates of the loss impedance would provide unique insight into the corrosion damage modes documented on retrievals. Additionally, it is hypothesized that R_p and Q are related to one another. Here we show the potential for SIM to acquire Q thousands of times per second. If functionally related using a neural network, SIM may be used for near instantaneous impedance monitoring, a valuable tool for the broader corrosion field.

Finally, we show the promise of artificial intelligence for binary classification of dissolved and polished surfaces, using Bode phase spectra as inputs. *In vivo*, multiple corrosion damage modes may be present and overlap. Expanding our binary classification model to multiclassification would improve its usability for retrieval analysis. Additionally, incorporating damage severity, like the previous research that classifies the Goldberg score of devices, would provide insight at the point of care.

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12.1 References

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