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Philosophical perspectives on time in biology

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PHILOSOPHICAL PERSPECTIVES ON TIME IN BIOLOGY

by

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"Time is making fools of us again…"

- *Albus Dumbledore (Harry Potter and the Half-Blood Prince)*

DEDICATION

To my parents –

My mother for her loving heart and joie de vivre…

My father for his insightful mind and authenticity…

I have everything I need because of you.

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ABSTRACT

Although time is a central topic in philosophy, within the philosophy of science discussions of time in biology have largely been neglected. This dissertation argues for the philosophical importance of paying closer attention to the vastly different timescales at which biological phenomenon can be investigated and explained. The importance of timescales for four themes in philosophy of biology is examined: abstractions and manipulations of time in biological practice, metaphysical debates between the mechanistic and process ontology frameworks, the problem of synchronizing molecular clocks and fossil clocks, and reductionism in biology. This dissertation provides the first sustained philosophical examination of the role of time in biology.

The first chapter explores how researchers manage the complexities of multiple timescales by abstracting from time physically, procedurally, mathematically, and conceptually. Understanding how researchers abstract from time in their investigations is important for determining what phenomena might be obscured by such practices.

Chapter two turns to the debate in philosophy of biology between traditional mechanistic accounts and the new process ontology. While process ontology is an advance, insofar as it has the potential to bring temporal issues to the fore, it is better understood as an epistemological—not metaphysical—framework. A careful

consideration of timescales highlights how different metaphysical frameworks can be more epistemologically appropriate in different contexts.

The third chapter examines how molecular and fossil clocks are used to measure time in biology. In both cases, researchers use phenomena occurring at one timescale (e.g. DNA mutations) to measure durations across another scale (e.g., the evolutionary occurrence of a last common ancestor). Attempts to synchronize these clocks for key biological events in the deep past pose interesting methodological problems—and suggest new solutions—for how to deal with discordant and interdependent lines of evidence.

The final chapter considers the consequences of this analysis of time in biology for debates about reductionism. Reductionism has focused almost exclusively on spatial scales. This chapter shows how a consideration of temporal scales transforms philosophical debates about reductionism in biology and poses new challenges. This dissertation demonstrates the fertility of extending the philosophy of time into the philosophy of biology.

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INTRODUCTION

Discussions of time have a long and varied history in philosophy. These discussions have ranged from phenomenological accounts of the experience of time to accounts of the metaphysical nature of time itself to theoretical discussion of the role of time in science. Some of the philosophical discussions of time have become importantly integrated with discussions in theoretical physics. While time clearly plays an important role in the science of biology and in biological phenomena, there has been little philosophical exploration of time in the biological sciences. The aim of this dissertation is to initiate a discussion of time in biology. This dissertation will not be the final word on the nature of time in biology, instead it will serve as a beginning to a new arena of conversation.

Despite the lack of direct attention to time in biology, its importance has been noted by at least one of the most prominent figures in the history of biology. In 1956 J.B.S. Haldane, a key participant in the modern synthesis, published a paper called "Time in Biology". In this paper he foreshadows many of the themes taken up in this dissertation – including the importance of time for methodological choices, metaphysical frameworks, and reductionism. For example, Haldane declares that:

> "[M]any of the difficulties of biology arise from the need of thinking simultaneously in several time scales. If we think too exclusively on the molecular timescale we shall be led to mechanistic materialism. If we think too exclusively on the evolutionary scale we shall be led into an exaggerated teleology." (1956, p. 399)

Phenomena that are of interest to biologists occur on vastly different timescales, and Haldane insists that studying phenomena on different timescales will change how we

interpret the world. In his paper, Haldane examines different domains of biology (physiology, genetics, evolution, etc.) and declares that each different project in biology takes place on a different timescale, requires a different type of thought, and is based on a different set of facts. Despite this call from a prominent member of the field, issues of time and timescales have remained virtually unexplored in biology and philosophy of biology. Haldane's paper "Time in Biology" has barely been cited, and biology and the philosophy of biology have gone on without considering the roles that these different timescales play. It is one of my central theses that considerations of time and timescale should be important concerns for biologists and philosophers of biology, and an aim of this dissertation is to initiate a conversation about the role of different timescales in biology, and how these are treated by scientists.

The importance of timescales for four themes in philosophy of biology are examined: abstractions and manipulations of time in biological practice, metaphysical debates between the mechanistic and process ontology frameworks, the problem of synchronizing molecular clocks and fossil clocks, and reductionism in biology. Generally, when we measure a timescale we're talking about the amount of time taken for some phenomenon of interest to occur. So we say the average lifespan of a bowhead whale is 100-200 years, or a sodium-based action potential takes under one millisecond to travel the axon. The matter of "scale" has to do with how we frame the phenomenon in question. So the lifespan of a whale requires that we use a longer or larger scale (years), while the action potential requires that we use a smaller or shorter timescale. Biology is interested in phenomena that occur at vastly different timescales, and perhaps more

complexly, phenomena which are occurring simultaneously at multiple timescales. In order to study these different temporal systems biologists often alter the temporality of their research subjects. They do so either by imposing an external timescale onto the system or by artificially eliminating the temporal dynamics of the system, and sometimes both.

Researchers make these types of abstraction because we, as humans, have our own timescale. We are made up of many different biological processes that are occurring at different rates, and perhaps more importantly, our sensory systems are equipped to make observations of changes that occur in a certain temporal range. Our own perceptual processes privilege a particular timescale. To the human hiker the mountain is fixed and unchanging, but from the perspective of the planet Earth or the solar system, the mountain is a momentary manifestation in a continually changing system. Our natural perceptual biases drive much of our manipulations in science – we alter systems in order to bring them into a range that is perceptible to us. This holds for temporal manipulation. Since we cannot observe changes that are occurring too quickly or too slowly, biologists have found ways to artificially slow down or speed up systems of interest. The abstraction from some aspects of a system is inevitable in attempting to make the unobservable perceptible to humans. Yet, this will also often come with information loss of some type. Understanding how researchers abstract from time allows us to clearly see what kinds of information we might be losing or distorting in the process.

Chapter one of this dissertation will explore the kinds of abstraction that biologists make from time in biological research. I argue that biological methods abstract

from time in four ways: physically, procedurally, mathematically, and conceptually. On the one hand, biologists tend to make physical or procedural manipulations in order to slow down the timescales of biological systems moving more rapidly than ourselves. On the other hand, biologists tend to use mathematical extrapolation to artificially speed up systems that are moving much more slowly (i.e., have much longer timescales) than ourselves. The sustained examination of how time is treated in biological methods and representations shows how the dominance of frameworks that abstract from time has obscured some important aspects of biological phenomena.

When one begins to think about the temporality of living things, the necessity of change and process naturally comes to the fore. As Haldane writes, "if you prevent internal changes in many, but not all, living things, they die" (1956, p. 386). However, emphasizing this processual characteristic of living things runs counter to the traditional way of characterizing them in biological science. Life forms have often been defined by essential properties, if not their anatomy then their DNA sequences. What is more, much of biological science looks for uniquely definable features of living things or their parts (i.e. the distinctive shape of a protein or the distinctive diet of Pandas). This practice of defining entities and their properties is part of the "mechanistic" framework in biology, which ultimately tells us that entities are stable and finitely definable. The changing nature of living things and their deep interdependences challenge these metaphysical assumptions though they are common in biological science and the philosophy of biology. In their place, the suggestion is that we should use a new processual way of understanding the living world. Focusing on time alters the sorts of metaphysical

presuppositions that seem intuitive. If we continually abstract from time, static definable features seem most real. However, if we focus on temporality, it is change and process that seem most real. Chapter two will explore the differences between the processual and mechanistic metaphysical frameworks, as well as how these frameworks should be used in science.

While there is a common view that metaphysical presuppositions like these are not important for science, there is evidence from the history of science that suggests this is not the case. Instead, scientists often unconsciously let their metaphysical presuppositions guide their research endeavors. This is even clear in Haldane's comments quoted earlier about the dangers of being led towards a "mechanistic materialism" (1956). There is a deep relationship between the assumption that viewing biological entities as substances with fixed properties is acceptable, and the metaphysical assumption that the world is made of substances with fixed properties. Since much of the innovation in molecular biology has relied on this sort of substance-based ontology, it has also validated that metaphysical framework. I take this to be a deep explanation of why substance ontology came to dominate biology. As I argue in the first half of chapter two, taking internal timescales seriously means considering treating entities as processes. A processual ontology does not define entities in terms of essential properties, but rather in terms of how the entities are maintained and stabilized amidst constant change. This shift in perspective incorporates internal temporality into the way we define an entity, rather than abstracting from it.

However, as we see in the second half of chapter two, we need to practice caution, lest we allow one metaphysical framework to dominate biology to the exclusion of others (all the worse for the prospects of creative research projects). One can see this concern in Haldane's words when he follows his warning about being led to a mechanist materialism, with a warning of being led into an exaggerated teleology (1956). Focusing too exclusively on one perspective, can generate an overly confident acceptance of an exclusionary metaphysical framework. While there are extremely compelling reasons to use a processual ontological approach to frame some scientific projects, this does not mean that we ought to abandon the mechanistic framework. Since a choice between metaphysical frameworks will always be underdetermined by the available evidence, we should not ultimately base our methodological choices on exclusionary metaphysical frameworks, but rather adopt a more pragmatic approach to metaphysics. It is extremely important to understand how metaphysical presuppositions shape methodological choices, but this is because we do not want to be artificially limited by a framework that is underdetermined. Instead, we should allow multiple well-founded metaphysical frameworks to simultaneously guide scientific research. While the mechanistic framework might abstract from the temporality of biological systems, that doesn't mean it can never be a useful framework. In some contexts, this sort of abstraction might be fruitful. The view I argue for here is a type of metaphysical pluralism.

In evolutionary biology, we see quite vividly what happens when phenomena occurring on different timescales need be compared. In order to determine the structure of the phylogenetic tree or the relatedness of various species, we require the dating of

different divergence events in deep history. The measurement of time in the history of life on earth requires comparing the rate of change on different scales – for example, comparing events of DNA mutation to events of speciation which occur on vastly different timescales. As we will see in chapter three, researchers have developed both the fossil clock and the molecular clock for dating events in the deep past. An examination of these clocks will lead to a rejection of two common methodological presuppositions; specifically, the common assumptions that lines of evidence need to be independent to be epistemically useful and that discordant evidence cannot be jointly epistemically useful. Instead, I will argue for the importance of interdependent and discordant evidence in developing knowledge of the deep past. While we commonly hold that multiple lines of evidence are more useful when they agree tend when they are independent, I will argue that interdependent lines of evidence and discordant results can still be jointly epistemically useful, as is demonstrated in the case of the molecular and fossil clocks.

As matters of scale abound, so do questions of the possibility of their reduction to one another. While discussions of reductionism in biology have focused almost exclusively on matters of spatial scale, chapter four will consider reductionism with a focus on time and timescales. In the inferences of biologists interested in measuring time in the deep past we can see the idea that the temporal scales of biology are neatly reducible to one another. Specifically, if we want to measure time on the scale of evolution, we can measure the rate of change at the level of DNA (which is occurring at a much smaller scale). Chapter four will show how a focus on time can allow us to intervene on the existing debates surrounding reductionism in biology. As commonly

framed there are three different types of reduction: methodological, epistemological, and ontological. Insofar as time can be considered another sort of scale in biological science, we can consider temporal reduction along each of these three axes as well. Ultimately chapter four will argue that focusing on time lends further support to anti-reductionist ideas, while generally complicating the relationships between different types of reductionism.

Together, these chapters make the case for a requisite new attention to the role of time in biology, and open up new avenues for this conversation. The considerations raised here are also relevant to practicing biologists insofar as it has research implications, and to philosophers of biology insofar as there are important philosophical consequences. Even more broadly, these concerns connect with wider themes of interest in metaphysics, epistemology, and the philosophy of science.

CHAPTER ONE

PHILOSOPHICAL FOUNDATIONS FOR THE INTEGRATION OF TIME INTO THE PHILOSOPHY OF BIOLOGY

1.1 Introduction

While there are long and varied conversations about time in philosophy, this chapter will ground a new conversation about time in the context of biological science. The difference between the timescales of different biological entities seems to be one of the biggest differentiators between fields of biology. For example, while microbiology gets its name from the size of its subject matter, evolution can happen among things that are of a vast array of sizes. So both microbiology and evolutionary biology can be concerned with bacteria, but what differentiates them from each other is the timescale of focus. While biologists also differentiate fields by function (e.g. immunology vs. microbiology), timescales are of great importance in understanding the differences between biological systems. This chapter will explore the challenges that comes from the need to think simultaneously on multiple timescales. Ultimately, this chapter will provide an analysis of the role time plays in biological phenomena themselves, and an interpretation of the methods researchers have developed for dealing with the differences in timescale.

Section 1.2 will begin by exploring two important existing concepts of time in science. Specifically, I will discuss how absolute and relative conceptions of time are described in physics. This will be important since biologists make use of similar concepts. I will also discuss how research in neuroscience challenges the notion that

timescales are objective and independent features of phenomena, rather than artifacts of researcher intervention. Section 1.3 will examine the concept of a 'timescale' more fully. I will argue that we can differentiate between timescales that are internal to biological organisms and timescales that are external. This will lay the groundwork for understanding what it means to abstract from temporality. Section 1.4 will argue that biological researchers often abstract from time either by using a measure that is external to the system of interest or by suppressing the internal timescale altogether. I will discuss the unique role timescales play in living organism and examine the assumptions that common biological methods make about time. Section 1.5 will examine some of the methods biologists use for representing time in their diagrams, and how these too can abstract from internal timescales. Section 1.6 will offer two different examples of research paradigms that seek to incorporate internal timescales into the biological methodology. Specifically, I will examine new models for studying the rate of molecular change in evolution. Finally, I will conclude in section 1.7 by arguing that since time plays such an integral and unique role in biological phenomena, both biologists and philosophers of biology ought to be paying more direct attention to ideas about temporality.

1.2 Time in Science

While there is a rich history of discussions of time in physics, there are two concepts that come from the existing philosophy of science literature on time that will be particularly important for the discussion of time in biology. First, I will discuss how

physics conceives of the difference between absolute time and relative time. I will show that biologists often use a closely related distinction. Second, I will discuss an argument that has arisen in neuroscience that timescales are not as easily definable as researchers often assume. As the search for uniquely definable timescales is prevalent in biology, this discussion will help us understand how time is understood in biological science.

1.2.1 Absolute vs. Relative Time

Sir Isaac Newton founded classical mechanics on the idea that space and time are distinct, absolute, and static. He distinguished absolute time and absolute space from relative time and relative space. Absolute time is the idea that time remains unchanged by the activities of the world – time is an independent arena in which events and changes occur. However, there are various ways we measure time (and space) that may be affected by the goings on of the world, and these concepts are of relative time and space. This alternative view, originally articulated by Gottfried Wilhelm Leibniz and expressed clearly by Ernst Mach, is that time is not independent of change or process – if there was no change there would be no time. Each of these conceptions will be discussed briefly in turn.

The existence of absolute time and absolute space is the foundation for motion according to Newton. Physical bodies exist within time and space, and they can be said to move as they change position in absolute time and space. An object's trajectory in time can be represented by a linearly varying parameter which mathematically represents the march of the minutes on the face of a clock. Thus, we can understand motion as a

function according to time (i.e., a change in location over time). Similarly, velocity is the rate of change over time, and acceleration is the rate of change of velocity. What is notable about each of these mathematically well-defined concepts is that the rate of time itself is independent of the motion of any objects in question. Time marches, and rates of change or locations of objects can change within the boundaries of time – even if there were no objects (and therefore no change) there could still be time marching forward.

Newton acknowledged that measurement was of supreme importance. Since neither absolute time or space are sensible by humans, all measurement involves measuring relative time and space and making an inference to absolute time and space. Newton write of absolute time and space, "But since these parts of space cannot be seen and cannot be distinguished from one another by our senses, we use sensible measures in their stead" (Newton [1687] 2004, 66). Absolute time and space are necessary to determine the aim of measurement, but as a good empiricist, Newton does not see absolute time and space as empirically necessary for measurement. Better measures are those that make better approximations of absolute time or space, but all earthly measures capture merely relative time or space. This defense of absolute time and space are the backdrop that influenced Newton's thinking during the development of classical mechanics and the universal law of gravitation.

In Newton's *Scholium on Time, Space, Place and Motion* he argues from the practices of 17th century science to the existence of absolute time. While days were (and are) commonly assumed to be uniform in length, they actually vary by as much as 20 minutes over the course of a year. In the astronomy of Newton's time, complex

mathematics was developed to correct for this inaccuracy. Newton believes that while absolute time is what is calculated by using mathematical equations, this is clearly different from relative time measured using a rotation of the earth (or any other relative measure for that matter). Newton writes "The duration or perseverance of the existence of things remains the same, whether the motions are swift or slow, or none at all: and therefore duration ought to be distinguished from what are only sensible measures thereof; and from which we deduce it, by means of the astronomical equation" (Newton [1687] 1962, p. 8). This is not merely an appeal to scientific practice, but also a conceptual point. According to Newton, in order for time to make conceptual sense it cannot be merely relational[1].

In a famous set of correspondences Leibniz and Samuel Clarke (as a spokesperson for Newton) argued about relative versus absolute notions of time (Leibniz and Clarke [1715-1716] 2007). Leibniz argued against Newton's account of absolute time and space, while Clarke defended Newton's absolute space and time. Leibniz argues that space and time are not things, but rather sets of relations. He compares time and space to a genealogical tree – stating that the genealogical tree is not something that exists independent of, or prior to, its members. Rather a genealogical tree is a sort of system of relations that holds between different members of a family. Time and space then are systems of relations that hold between entities, but are not themselves something over and above those bodies and relations. In Leibniz, we see the first development of a relative notion of time.

[1] In other words, time itself cannot be so-called B-relations, but must be A-properties of which the B-relations are derivative. (McTaggart, 1908)

Perhaps the most succinct account of a relative notion of time comes from physicist and philosopher Ernst Mach when he says "time is an abstraction, at which we arrive by means of the change of things" ([1883] 2013, p. 224). The relational account of time tells us that time is a series of relations between things. We arrive at the abstract notion of time through the observation of changes in things. In other words, time is an inference from the observation of changes in the world to something like duration. We might compare this to a relative notion of space. If absolute space is the idea of a container in which things exist, then relative space is the idea that space is merely the relations between objects in the world.

While biologists have substantially different concerns that guide their different sorts of engagement with the concept of time, these two different ideas about time have been highly influential. For example, many biological graphs use time as the independent variable, meaning they measure quantities of interest over time. Doing so borrows the idea of measuring change over absolute time from Newton. This will be explored more in section 1.5, when we examine representations of time in biology. However, section 1.6 will highlight how some of the alternative methods in biology take time to be relative. We can see this when timescales are compared or measured, rather than treated as independent and objective. While biologists do not typically use this language about time being relative, there is at least some overlap that this project will highlight.

1.2.2 Non-objectivity of Timescales

Timescales are crucial concepts in biological science, but as noted earlier they have received almost no direct philosophical attention. One notable exception is the neurophysiologist Shimon Marom who published an article in 2010 calling for more consideration of the subject. The article, entitled "Neural Timescales or Lack Thereof" accomplished two main tasks: First, Marom catalogues a series of general difficulties that the life sciences face in dealing with time, and second, he scrutinizes the methodologies used in neuroscience across different levels of inquiry. Marom argues that there are two important commonalities in the methodologies of neuroscience operating from the behavioral scale to that of the single neuron: 1. They involve abstractions that obscure the general difficulties of understanding time in neural systems, and 2. Above certain lower limits, each system can be seen as temporally unbounded. While Marom focuses on neuroscience, many of his methodological points and concerns are transferable to our discussion of time in biology; specifically, the idea that some timescales are not objective or independent of observation and measurement will be a main theme of section 1.3.

Marom argues that the concept of a "timescale" is fundamental to science. A timescale can be roughly understood as the time within which some phenomenon of interest takes place. He further contends that by using this concept, scientists are implicitly assuming the timescale is inherent in the phenomenon: "it is assumed that these timescales are separable from each other in the boundaries, and that they are inherent to the observed system rather than reflecting the ways the observer chose to measure them" (2010, p. 17). According to Marom, the first problem arises because much of

neuroscience makes essential use of the concepts of timescales: either aiming to reveal them and using them as guides in search of mechanisms, or as the basis of models. By assuming the fundamentality of timescales without good evidence, neuroscience has put itself in a tricky situation – searching for a definitive timescale without good reason to suppose one exists. The second general problem with timescales is that they do not reveal themselves directly, but rather are inferred through indirect observations. The final general problem Marom points out is that the concept of a timescale gets significance only with reference to function. Establishing some timescale involves defining a functionally significant observable, which is not a fundamentally objective choice. These general difficulties are usually obscured by research techniques, and Marom aims to bring them back into focus through his discussion of specific practices in neuroscience.

The focus of his paper is the neuroscientific research on forgetting, and particularly the timescale of forgetting. Researchers have looked at forgetting on a variety of scales (behavioral, neural assemblies, single neurons, etc.), and findings have been importantly similar. In particular, research has shown that above a certain lower limit – there is no uniquely definable timescale of forgetting. Further, researchers have displayed a tendency to assume that what underlies the scale-free rate[2] at one particular level is a mechanism with a well-defined temporal scale at the next level down. As Marom writes, this tendency "reappears each time an underlying microscopic machinery is sought for, as

[2] Scaling is a relationship that variables such that they are self-similar, or in other words the relationship repeats itself at a variety of scales. Being self-similar means that, in these cases, the phenomenon in question will not depend on the parameter (Barenblatt 2003). Being scale-free refers to this relationship of repetition on multiple scales, such that the phenomenon does not depend on the scale chosen, and depends on the existence of a power-law relationship.

a possible explanation to a macroscopic time course" (2010, p. 18). This concern can be seen in the case of neuronal assemblies.

A neuronal assembly is a "group of cells that share similar static and dynamic response properties when activated through a specific subset of receptors" (Marom, 2010, p. 20). Neurons in an assembly respond to stimuli, or continue activity in the absence of stimuli, together. These synchronizations are observed through electroencephalograms (EEGs), magneto encephalograms (MEGs), functional magnetic resonance images (fMRIs), as well as micro-electrodes measuring single neurons in the assembly *in vivo* and *in vitro*. Ideally one would be able to directly observe the forgetting (or relaxation) rate of neural assemblies that underlie behavioral memories. However, no such work is currently possible. An important reason for this is that no mapping from behavioral memories to a particular neural assembly (or assemblies) has been found. In lieu of such direct studies, researches have looked to statistical quantification of neurological activity fluctuations. Fluctuation analysis is a method used to measure the self-affinity (i.e. self-similarity) of neuronal activity. What we want to know is if the activity of some neuronal assembly is long-range dependent (LRD) on the earlier activity. A phenomenon is considered LRD if the activity decays more slowly than exponential decay. In other words, if the activity displays self-affinity it will be seen as LRD on the earlier activity, and decay more slowly than exponential decay. According to Marom, assemblage patterns viewed using EEG, MEG, fMRI, and single neuronal measurement in vivo and in vitro all displayed scale-invariant fluctuations. This means that their decay can be described as following a power law distribution, which is slower than exponential decay.

There are two important things to note: the first is that developing these results relied upon several questionable assumptions. As Marom points out, performing fluctuation analysis relies on the assumption that the fluctuation-dissipation theorem applies generally to biological systems. The second thing to note is that the general reaction to the work is not to assume continued scale-invariance but to push one level down – to assume that beneath the scale-invariance displayed at the level of the neuronal assembly is a well-ordered temporal system at the level of the individual neuron. Thus the discovery that forgetting lacks a definitive timescale at the level of the neuronal assembly only fuels the search for uniquely definable timescales at the next level down.

Marom repeatedly underscores that work on timescales of forgetting uncovers complex temporal relations, and that uniquely defined timescales are unlikely to be found. One solution Marom proposes in the context of studying forgetting in protein dynamics comes through making better choices about the rate types we choose to use when building models. According to Marom, approaches come in two broad categories: constant-rates and scaled-rates.

> If one insists on using constant rates, the only way to enrich the temporal dynamics (without using an external modulator) is by subdividing x state to more distinct coupled entities. On the other hand, if one allows the reaction rate leading from $x \rightarrow y$ to change as a function of, for instance, time spent in x, options for complex temporal dynamics are unconstrained, without adding more states. (2010, p. 25)

The choices we make in our scientific methodology are not temporally benign. Marom keenly points out how the methods of neuroscience obscure temporal dynamics, but here he is suggesting a method for bringing back in some of the temporal complexity. We have many reasons to build models to reduce the complexity of living systems, and

increase our ability to understand and manipulate. However, scaled-rates models can include temporal dynamics when rates change as a function of time, which can allow researchers to increase their ability to understand the role time plays in a system. While the methods within and between neuroscience and biology vary, there is important overlap that allows this lesson to have implications for our discussion of time in biology. Biology, like neuroscience, often seeks to measure and define timescales. Likewise, then, concerns about the objectivity of timescales apply to biology as I will show in the next section.

1.3 Timescales in Biology

Before we focus on the way methodologies impact our understanding of time in biology, it is important to further elaborate the concept of a timescale. The timescale is obviously an important concept in biology, as it is in neuroscience. For starters, much scientific effort has been put into quantifying some particular timescales – the timescale for the existence of our species, the timescale for the existence of life on earth, the timescale for the development of a mouse, the timescale the conversion of ADP to APT, etc. Unlike function, however, the concept of a timescale has not received much direct attention in biology. Much of biology makes the unreflective assumption that time is external to biological systems. In other words, most biology is conducted under a framework that could be called "Newtonian" with respect to time. On this sort of understanding of time, a timescale is merely the objective amount of time taken up by some process of interest. This is made clear by the practice of using clocks in minutes,

hours, etc. to measure the timescales of biological phenomena. For example, it has often been asked what the reaction speed of some particular chemical or physiological process is, and the answer is determined in an absolute clock time unit.

This is not, however, universally the case in biology. Sometimes, biologists use measures like generations, or circadian rhythms, or even mutations to measure duration. When biologists measure in this way, they are using a time that is *internal* to the biological system. Such time would be relative to the ongoing process against which time is being measured (i.e., the generational cycle or the daily circadian cycle, etc.). On this sort of understanding, a timescale is not an absolute concept, but one relative to some perspective or reference frame. Of course biologists have not been actively debating these alternative ways of understanding time as philosophers and physicists have, but it might be worth considering whether there are good reasons to suspect one sort of measure to be preferable to another. Is this merely a context dependent decision? What sorts of context might call for one timescale measure over another? While answering these questions will be very difficult, this section will begin by arguing for the idea that biological phenomena have internal timescales, which are distinct from external timescales as measured by clock time in years, hours, etc. If internal timescales are important to the phenomena, then presumably they will be at times scientifically important.

1.3.1 Clock time vs. internal time

My cat and my plant seem to develop at different rates. The changes in my cat aren't perceptible to me, at least day to day. She looks basically the same to me every day. My plant, on the other hand, changes every day. I can see its stems form buds, and

the buds turn into leaves. Of course there are many rates within each of these entities, but I'm painting with a broad brush for the moment. My point is that each of these entities has a rate of its own at which its lifecycle is occurring. This means that we can differentiate between time that is external to a given biological entity, for example clock time (in minutes, hours, days, etc.) and internal time (circadian rhythms, life cycles, etc.).

I contend that biological entities have salient internal (or endogenous) timescales. By this I mean that there is, for example, a temporal scale (or scales) that are a part of my cat. She has her own lifespan, her own circadian rhythms, etc. When I say "internal" it is shorthand for "internal to a particular system of interest". Our ordinary ways of measuring time (hours, minutes, years, etc.) are all external to any given biological entity. So while earth years might be an internal measure if the system we are interested in is the solar system, this is not internal to any cat or tree. Thus when I say external I also mean external to a system of interest. This isn't meant to be a hard and fast distinction, but it is helpful to keep in mind that biological phenomena have internal timescales, which can be important to biological science.

This distinction seems to track two major ways time gets conceptualized in biology: clock time and generational or life-cycle time. The first, clock time, is external to the living organism. This is a system against which we measure living organisms. The second, the time of life-cycles or generations, is internal to the organism or at least internal to the continued lineage of which the organism is a part. What I have in mind here is not the measurement of a life-cycle against clock time (i.e., the life-cycle takes around 24 hours or 20 years, etc.) but rather the practice of measuring processes in the

time of the life-cycle or generation. When processes are measured in terms of the life-cycle or generation they are not assigned a unit in clock time, but are rather a percentage of a typical life-cycle spent in a particular developmental phase or that some event lasted some number of fruit-fly generations.

Consider, for example the common phrases “cat years” or “dog years”. These scales do not measure the life of a cat or dog in terms of rotations around the earth, but rather in terms of how much development a cat or dog undergoes in a period of time compared to a developing human (we will return to this example in section 1.6 with the examination of figure 1.2). There are, of course, complex interdependencies between some internal timescales in biological organisms and some external timescales (for example between circadian rhythms and the rotation of the earth). However, this does not undermine the distinction between internal and external time, but only makes the study thereof more complex. Clock-time, as we will see, is certainly the more popular way of understanding time in biological science. However, given the prevalence of internal timescales in biological phenomena it is worth discussing if the reliance on clock-time is always appropriate.

Another obvious overlap between biological phenomena and time is in circadian rhythms or other endogenous rhythms, which are studied in the field of chronobiology. Circadian rhythms are endogenously generated cycles (although they often take cues from external signals) that repeat approximately every 24 hours, or every day on earth. There are of course many other endogenous cycles that repeat every 28-ish days or every year, etc. Researchers are interested in the time that is internal to the organism: how the

organism keeps time, and what sorts of changes predictably occur according to these internal clocks. It is these areas of study that make the possibility of measuring time in biology from the internal perspective seem the most obvious. Chronobiology largely focuses on how different organisms keep time for themselves, using a variety of different internal signaling. In fact, the 2017 Nobel Prize in physiology or medicine was awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries of the physiology of circadian rhythms (The Nobel Assembly at Karolinska 2017). This research focuses on an external measure of time (days on earth) and how living organisms keep internal track of this cycle. This is not the only example of interdependence between external and internal timescales, and these sorts of relations between timescales makes studying biological temporality even more complex.

Timescales play an extremely important role in biology, not only as independent scales against which to measure phenomena of interest, but within living organisms themselves. This will be important in the next section as we examine how various research methods in biology abstract from internal timescales, and in section 1.6 as we examine how researchers put time back into biological research.

1.4 Manipulations of Time in the Biology Lab

I used to work in a neuropharmacology lab studying the effects of alcohol and methylphenidate on the action potentials in the brains of rats. Now, there were many things that were curious about this work, many of which are on the list of reasons I ended up in philosophy rather than as a practicing scientist. However, as I've been thinking

about time, I've realized that there were many things I took for granted as good laboratory practices that were abstracting in important ways from time. For example, we implanted electrodes in the brains of our rats in order to monitor the electrical response to different stimuli (light flashes or beep sounds). In order to check if the electrodes had been properly placed in the brains of the rats, we would euthanize the animals and preserve their brains. We would then physically inspect the preserved brains using anatomical markers to determine the location from which the electrical activity had been recorded. The inference from locations of the electrode in the preserved animal brain to the location of activity in the living brain abstracts away from the temporal aspect of the actual activity in the living brain. This represents a modern version of the common practice of examining the anatomy of deceased animals. This practice is supposed to tell us where in the brain certain functions are located, but it looks at the animal only out of time. The organisms are not actually frozen, but dynamic, and the functional property in question is importantly temporally extended. Many of the practices of biologists that modify time make assumptions about our ability to infer facts about the organism from a static picture – in the case of my rats, a literal static photograph. When I say scientific practices abstract from time, I mean that they take a process out of its normal temporal context and put it within another temporal context. We remove internal time from our research in biological science in two simple ways, either by imposing a particular timescale that is not endogenous to the system or eliminating temporal dynamics of a system all together (sometimes both). I am not trying to assume an association between

time and change, but at the very least preserved organisms are not living in time from an internal perspective, even if they continue to persist in clock time.

I argue there are at least four primary ways that the methods of biology abstract from the internal time of organisms: physically, procedurally, mathematically, and conceptually. Biologists physically alter time when they put samples on ice or examine deceased organisms. Biologists procedurally abstract away from time when they, for example, check with a system at particular static moments in time. This happens in a cellular growth assay when one checks the size of a cellular colony at particular times over the course of a few days. Biologists abstract from time mathematically when they represent dynamic properties of organisms or communities as static numbers. For example, fluctuation analysis, which is popular in many different life sciences, but is especially popular in biology as a method for calculating mutation rates. Fluctuation analysis involves assuming exponentially distributed division times which are not well supported by empirical findings (Ycart, 2013). Finally, scientists conceptually abstract from time when they emphasize or utilize concepts that lack temporality all together. In what follows, I will explore various common biological methodologies and discuss how they abstract away from time.

So called manipulability approaches to causation are popular among some scientists and philosophers. These approaches hold that causes are essentially devices for manipulating effects. If one thinks of manipulation as necessarily causal manipulation, there might be concern that the concerns I have over the 'manipulation' of time in biology are not actually instances of manipulation. However, whether one considers time

to actually be the relative succession of events (as Leibniz or Mach did) or considers all that we have empirical access to be the relative succession of events (as Newton did), if the relationship between successive events changes, we can consider that intervention to be a causal change in time. While I do not wish to necessarily endorse this way of thinking about causes or manipulations, even under this way of thinking we can consider what biologists do in certain cases to be a manipulation of time.

1.4.1 Physical

Many large-scale laboratories rely on packaged assays or kits to supply consistency and ease of operation. These assays are used for a variety of functions, but here we will focus on cellular proliferation assays. There are a number of reasons one might want to measure cell proliferation, including testing the effects of pharmacological agents or growth factors, assessing cytotoxicity or investigating circumstances of cell activation. Assays for measuring cell proliferation fall into four basic categories based on what is actually measured as an indicator of proliferation: DNA synthesis, metabolic activity, antigens associated with cell proliferation and ATP concentration. For example, Resazurin (or blue dye) and Tetrazolium reduction assays are used to measure the metabolic activity of the cells. These particular compounds permeate the cell membrane, and when they find themselves in a cell that is metabolically active, the cell will reduce these compounds. In the case of these specific compounds this will change their color, and the color of the media as a whole. The color of the sample is measured using spectrophotometry. If Resazurin and Tetrazolium were placed in a sample without living

cells (i.e. no metabolic activity present), these compounds would not be reduced and their color would not change. Each of the assays listed above is used to measure cellular proliferation work similarly in the sense that a compound is added to a sample, and that compound interacts in a measurable way with only the living cells of the sample.

One particularly product that is used to measure cellular proliferation is the "CellTiter-Glo® Assay". This assay is used to determine the number of living cells in a sample by measuring the presence of ATP, which is indicative of metabolic activity. Somewhat ironically, the assay requires lysis (splitting open, and killing) all of the cells in order to expose the ATP to the necessary reaction. Similar to spectrophotometry, this assay works by measuring light. In this case though, the reaction between the added reagent and the ATP in the (formerly) living cells forms a bioluminescent compound. The amount of light, measured using a luminometer, is considered directly proportional to the amount of ATP present, and accordingly the amount of (formerly) living cells.

Many biological techniques are similar in that they require the addition of a reagent. A reagent is just some compound that is added to a sample in order to reveal or make observable a trait of interest. In the simple case of microscopes, staining is required to make traits of microorganisms visible even under a magnified condition. This physically alters the natural temporality of the living system, and renders the scientist unable to capture or observe the temporal nature of the system in question. While these additions may be crucial for enabling the observation of some other properties of the phenomena of interest it is important to keep in mind the temporal altering of any such observation. While this may in some cases be a justified or benign modification, it is

important that it is not an overlooked or invisible one – for it is too often that invisible assumptions get science into trouble. Here we also see how two of the types of abstraction listed at the beginning of this section (physical and procedural) often come together. The addition of a reagent could be seen as either a physical or procedural abstraction depending on where the emphasis is placed; on the methodology, making it physical, or on the analysis, making it procedural.

So far the methods I have discussed are similar in the sense that they disrupt the sample enough that they are only used once. The addition of reagents that modify the sample precludes the recycling of the particular sample used in a spectrophotometer or a cellular proliferation assay. This is the underlying fact that has led me to classify these particular biological techniques as physical modifications to the temporal structure of their subjects.

1.4.2 Procedural

Several of the techniques discussed in 1.4.1 rely on spectrophotometry. A spectrophotometer is a tool that measures the amount of light that passes through a sample material indirectly measuring the amount of light absorbed by that sample. Since different molecules will absorb light at different rates, information about light absorption can be used to tell what is present in the sample. This tool is used in biology by applying different markers to samples and these markers can be used to show levels of protein or RNA expression among other properties. There is nothing spectacular or even particularly interesting about this method, but if we think carefully about what biologists

extrapolate from these results, we can understand the subtle way in which it abstracts from the temporal aspects of cellular life. Imagine a biologist using spectrophotometry to measure protein expression. From the spectrophotometry results, the scientist might infer their experimental condition led to increased expression of the relevant protein. However, protein expression and degradation are not fixed properties, but are continually occurring within a cell. The static nature of spectrophotometry obscures these facts. This is not to say there is anything wrong with spectrophotometry, but merely to point out that it obscures the temporal nature of the biological process it is used to study.

This sort of procedural abstraction through freezing or slowing time is not unique to spectrophotometry, but is extremely common in cellular and molecular biological techniques. Despite the fact that different sorts of cellular proliferation assays measure different markers of proliferation, they almost[3] all work similarly in the sense that they take a frozen picture of an active process and extrapolate a static property from the snapshot. This perpetuates an image of life as less dynamic than it really is. Accordingly, it is important for scientists to note what role time might play in the properties or functions they are studying. Depending on the importance of time, it may or may not be appropriate to make use of methods that obscure time in this particular way.

Another common example of a biological technique that relies on a similar abstraction is flow cytometry, a technique commonly used to sort and identify different cell types or other biomarkers. Flow cytometers use lasers, and measure the scatter created as the cell passes through the beam. Particularly the scatter shows differences

[3] I will discuss shortly a dynamic cellular proliferation assay. These are used much less commonly than those I'm considering here, but it is worth noting that they exist.

between cells of different size and granularity, which, when scatter plotted, can allow researchers to differentiate between most cell types. A typical flow cytometry protocol, as with many other lab protocols, requires scientists to prepare their samples on ice before using the instrument. The explicit purpose of putting samples on ice is to manipulate the timescale at which the sample is changing in order to maintain the overall viability of the cellular sample. Cooling a sample slows down the timescale, and heating a sample will speed up the timescale, and accordingly such procedures are obvious physical manipulations of time. Further, flow cytometry abstracts from time by extrapolating processual facts about cells from a snapshot. This is quite similar to the functioning of the previously discussed cell proliferation assays and spectrophotometry.

Techniques involved in the identification of the structure of various proteins or nucleic acids also abstract from time in important ways. For example, one of the most common and historically important methods for identifying the structure of a protein is X-ray crystallography. X-ray crystallography involves shining an x-ray beam onto a crystal of interest, and recording the refraction of beams on the other side. Doing this process repeatedly allows scientists to infer the structure of the crystal from the refraction data and some information about atomic structures. These x-ray observations require samples that have been specially prepared, or crystalized. While some substances crystalize naturally, in the study of most biochemical molecules or proteins crystallization must be forced artificially, usually through elaborate cooling or evaporation methods. Despite the knowledge that proteins do not exist in an unchanging conformation, in order to study their shape, scientists artificially augment the stability of these molecules. Shape

is often taken to be a key property of a molecule's ability to perform some biological function. In a dynamic and temporal biological system, these properties are temporal, and yet in our attempt to understand these important properties we abstract away from the importance of their temporality.

However, there are many techniques in biological science that can be used repetitively, yet still importantly obscure the temporality of the subject. For example, one extremely common method in microbiology is plate counting. After placing some bacteria or other sample onto a standard plate, one incubates the plate and later physically counts the number of visible colonies of the bacteria. One can count the number of colonies over a number of hours or days, and under a variety of control or experimental conditions. Even though the checks are performed at several different times, the checks themselves are static pictures of the dynamic system. The procedural abstraction is not generated necessarily by the physical destruction of the sample that is created by the addition of some reagents necessary for spectrophotometry or flow cytometry. Rather the procedural abstraction comes from the fact that, in experiments that rely on these procedures, the dynamics of the system under study are not monitored. Instead the methods check in on static moments of a dynamic system, and use that information to extrapolate to certain facts about the system as a whole.

The methods discussed in this section are similar in the sense that the procedure requires ignoring the internal temporal dynamics of a system of interest. X-ray crystallography and flow cytometry require taking a static snapshot of a moving system.

This is the underlying fact that has led me to classify these particular biological techniques as procedural abstractions from the temporality of their subjects.

1.4.3 Mathematical

The techniques I have focused on so far are used in molecular or microbiology, or even biochemistry. However, temporal abstractions are not unique to these subdomains of biology. For example, population ecology commonly uses the Malthusian growth model to understand how populations change over time. The Malthusian growth model states that populations will grow exponentially as long as the environment remains constant. In these sorts of models, time is entirely external to the organisms themselves, and could be understood as akin to Newtonian time. Despite the fact that populations and individuals both have internal timescales, these population models rely on external clock time.

One popular way to understand evolutionary systems to use Hardy–Weinberg based modeling techniques. These artificially simulate the behavior of sexually reproducing populations of varying sizes in response to different evolutionary forces. The Hardy-Weinberg principle states that genetic frequencies in a population will remain the same unless acted upon by an evolutionary force (including drift). The Hardy-Weinberg equations (when p and q are allele frequencies for a given trait: $p^2+2pq+q^2 = 1$) is a mathematical expression of this general principle. Without getting too caught up in explaining the complexities of how these models work, the basic point is that by using these sorts of assumptions and mathematical formulas, biologists can build models that

illustrate evolutionary change. These models are subsequently used to understand processes that generally are of a timescale far too long for us to directly observe. By abstracting away from the actual temporality of these systems, biologists are able to study how they change in a feasible period of time. Models have been increasing in popularity in biology, especially as computing power has enabled models to account for a larger number of variables, ostensibly increasing the similarity between models and the systems modeled. However, increasing the complexity of the model does not necessarily change the abstraction from time. For example, many biology models assume discrete generations, but these are rarely found in nature. Increasing the number of variables does nothing in particular to change this assumption. There would need to be more fundamental changes to the modeling methods in order to make the temporal assumptions more dynamic.

Biological methods modify time mathematically when they rely on different mathematical techniques that have built-in temporal assumptions[4]. Using the Hardy-Weinberg equation or the Malthusian Growth model imposes an artificial timescale onto a system that has a different internal timescale. These mathematical abstractions do not attempt to freeze or eliminate time from a system of interest, but rather they impose a particular external timescale onto a system with an internal timescale.

[4] Zollman and Huttegger (2012) argue that using evolutionary stable strategy (ESS) methodology can limit our ability to understand dynamical evolutionary activity. At least part of this could be explained by arguing that ESS methodology abstracts from time.

1.4.4 Conceptual

Conceptual abstraction from time involve researchers focusing on static aspects of a system or properties that can be understood statically. These abstractions do not come from particular practices or laboratory techniques, but rather large-scale conceptual framings that guide biological research. For example, we can think of the gene-centric biology as participating in a time-obscured view of biology. Much of biology has focused on identifying and cataloguing DNA sequences. As technology has improved, the sequencing or even modification DNA has become commonplace. DNA is clearly a massively powerful and important molecule in life on earth. However, the power ascribed to a static (or assumed-static) sequence of nucleotide base-pairs at minimum suppresses the temporal aspect of any living organism. While a sequence on its own might be eternal or unchanged, no living organism could ever be eternal or unchanged. Of course this does not deny the importance of DNA, or suggest that studying or modifying DNA sequences is a waste of time. However, it does make plausible the idea that other kinds of practices that do not abstract away from the temporal nature of life might be able to capture something left out of a gene-centered view. This is especially important given the funding and attention that gene centered research has received in the last 50 or so years. Perhaps if we take the temporal nature of biological systems seriously we might make technological or methodological advancements that facilitate research that does not obscure the temporal aspects of these systems, or dedicate funding towards research that is not gene-centered.

These conceptual abstractions have been facilitated by revolutionary biological laboratory techniques like the Polymerase Chain Reaction (PCR). PCR is a method of amplifying a piece of DNA by several orders of magnitude. This allows the DNA to be manipulated or sequenced with much more ease. Today, PCR is frequently used in a variety of clinical and research settings. PCR is one the techniques that have enabled a gene-centered biological science to flourish and be extremely fruitful. PCR itself does nothing in particular to manipulate time. Rather, it is our reliance on genetic information as being of primary importance that obscures the importance of time. As a technique for amplifying DNA and enabling sequencing or modification, PCR is extremely useful and accurate. The abstraction of time comes from the importance we place on the static information gained through PCR, and not any physical, procedural, or mathematical abstraction.

Another famous recent development in biology can be understood similarly. CRISPR (clustered regularly interspaced short palindromic repeats) Cas 9 (an enzyme) is a technology used to modify segments of DNA. This technology acts as a 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome allowing for bits of DNA to be added or removed. This technology is derived from an adaptive element of the prokaryotic immune system that confers resistance to foreign genetic elements such as those present within plasmids and phages. Essentially we have co-opted this immune strategy to use as a tool to edit the genome in vivo. This is an extremely accurate and powerful gene-editing technology. However, it allows biologists to place the same emphasis on static gene sequences that PCR does. What is important in

CRISPR is the static sequence, not the more dynamic features of cellular life. This technology itself does not manipulate or eliminate the internal timescale of the organism, but rather it is our reliance on genetic information as of primary importance that obscures time.

Biologists make conceptual abstractions from time when they emphasize aspects of a biological system that can be understood as static or eternal. Unlike the other modes of abstraction, conceptual abstractions do not do anything directly alter the internal timescale of the phenomena of interest, or augment the representation of the internal timescale. Yet there can still be an important loss in these cases. This loss can occur because minimizing the importance of internal timescales allows researchers to abstract from those internal timescales without concern. This is part of what causes us to not reflect on the role timescales might play in biology.

1.4.5 An Important Qualification

It is extremely important to note that the type of abstractions I have examined are not necessarily criticisms. Science is importantly built on a process of abstracting from irrelevant details in order to focus on the variables of importance. This is built into the way children are taught the "experimental method" in primary school where they are taught that scientists control or fix all extraneous conditions so that they can understand how the independent variable effects the dependent variable[5]. I do wish to suggest,

[5] Independent variable is the factor that scientists manipulate, the dependent variable is the variable scientists measure in order to test the effect of the independent variable on the dependent variable.

however, that there will be times when abstraction from time does obscure something important about the variable of interest to scientists. For example, the paradigm of studying anatomy in deceased animals can tell us something about the structure of an organism's body, but obscures important facts about the functional activity of the body in motion. Biologists often make the choice to abstract from time without reflecting on what this might obscure. What is important to understand is what we might be missing, and actively assess in what contexts or for what questions it is acceptable or unacceptable to abstract from the temporal aspects of the system.

1.5 Representations of Time in Biology

Scientists do not merely conduct experiments, they also create representations. Biologists can be seen abstracting from time not only in their methodologies, but also in their diagrams and other representation when reporting their results. The most obvious way this is done is by using time as one dimension on a graph, (i.e. making time the X axis). The Y axis is generally represents some variable of interest that changes over time. In these cases, they take some biological phenomenon with its own internal timescale and represent it in the time of a different system. However, this is not the only way biologists represent time. One can use time as both axes on a graph, or one can abandon the graph representation altogether. In this section I will explore how visual representation in biology represent temporality.

As we will see in chapter two, traditional mechanistic biology has difficulty accounting for the temporality of biological systems. While chapter two will focus on the

conceptual difficulties, we can also see the challenges in how mechanistic diagrams represent time. William Bechtel and colleagues specifically examined the representation of circadian rhythms, and uncovered the difficulty in representing time in traditional mechanistic diagrams. A mechanistic diagram is a visual representation of a step by step causal process. These diagrams can easily accommodate feedback loops or other causal differences in behavior. However, temporality is very difficult to represent in a mechanistic diagram, as Bechtel and colleagues note:

> Incorporating time is a challenge. The various activities occur at different times of day. The operation associated with each arrow takes time, and each cycle of activity that returns the mechanism to the same state takes approximately 24 hours, but nothing else about timing is shown. (2014, p. 4)

The problem here is that when mechanism and space are emphasized, as they often are in biology, the temporality gets suppressed. This is particularly problematic, and thus evident, in research on chronobiology, but it is true in many different areas of biology. Choices are constantly made about how to represent biological phenomenon, and these choices, more often than not, suppress or alter the temporality of the systems. There has not been an active debate over the representation of time in biology, but it might be worth having one, at the very least to grapple with the following questions: Are there practical or theoretical reasons to augment time in biological representations? What sorts of contexts might call for different types of temporal representations?

One interesting area of biology where this representation issue becomes tricky is developmental biology. Developmental biology studies the processes by which living organisms, specifically plants and animals, grow and mature. There are a great many interesting philosophical questions related to the field of developmental biology, and time

could likely be considered in relation to many of them. However, right now I will focus on the oft-used representations of developmental stages as an illustration of the challenges faced in incorporating temporality into biological representations. Consider the following typical image of embryogenesis:

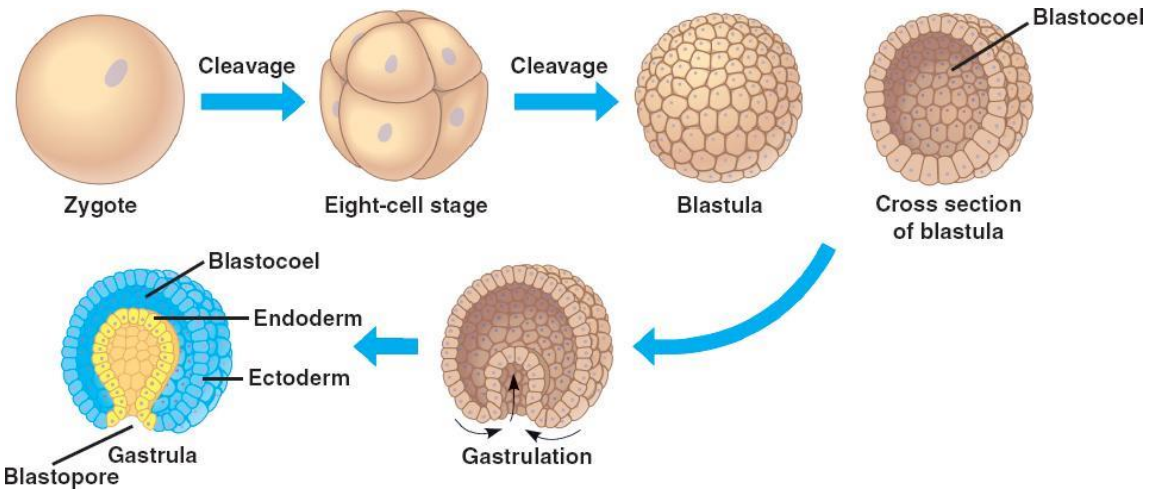

Figure 1. 1 Embryonic cleavage in animals. Showing the fate of different stages through developmental time.

This image is a typical illustration used to show how an animal develops starting from fertilization. We can tell from the arrows in these sorts of diagrams that time is passing in one direction as the zygote develops. However, as is typical in these images, nothing else about time is shown. Sometimes in these diagrams for particular animals one will see days or hour labels on the different stages, but that is the extent of the temporal information. Importantly this sort of representation suppresses any relational information about time between the different elements of developing zygote. Development can often be simplified as a uniform process, yet it is unlikely that the temporality of these systems is as simple as these representations make it seem. Perhaps development calls for a richer temporal representation. Especially given recent developments in visual technology, it is

certainly possible for more dynamic images to be included in scientific papers. If such images could portray richer or more representative information, they would be worth considering.

1.6 Alternative Methods

Section 1.4 detailed methods that abstract from the internal temporality of biological entities, and section 1.5 discussed difficulties in representing time in biology graphically. There are, however, many very interesting methods and modes of representation in biology that attempt to account for internal timescales. This section will examine a few examples to help shed light on what it might look like to incorporate temporality into biological methodologies.

One thing these methods will have in common is that they take the timescale itself to be the outcome of dynamic activity, interpreted as something to be measured and reported. While this might sound like a complicated practice, it is actually quite familiar if we consider the concept of "cat years". Since we know that humans and cats develop at different rates, many are interested in understanding how developmentally advanced a cat

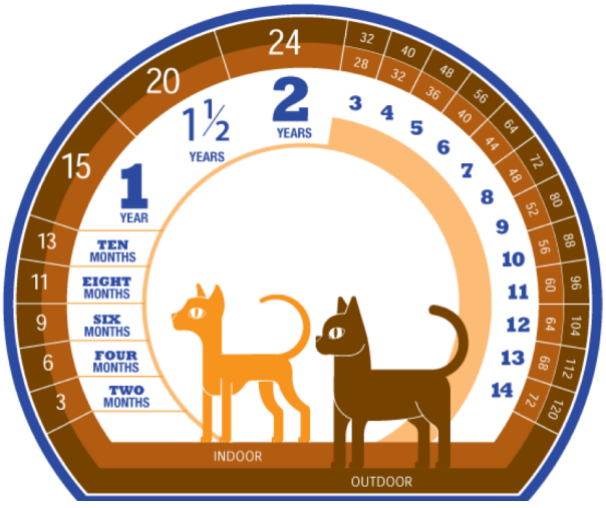

Figure 1. 2 Shows the developmental age of indoor (orange) vs. outdoor (brown) cats in human years, compared to amount of time the cat has spent on earth (blue).

is compared to a developing human. Humans don't merely live longer than cats, so it is not merely a matter of zooming in and out. Rather, the rate of development for a cat can vary. For example, cats develop much more quickly than humans in the beginning of their lifespans. We can also represent this rate variation in diagrams like figure 1.2. Here we see the internal timescale of human development compared to the amount of time a cat has spent on earth. So, for example, a one-year-old cat is about as developed as a 15-year-old human, and a two-year-old cat is about as developed as a 24-year-old human. Using this graphic, we can easily see that a cat's developmental rate slows compared to that of a human. The cat aged 15 human years in the first year on earth, but only nine human years in the second year on earth. If we were to impose a different scale, we would lose the ability to visualize the rate variation we see here. As we will see, scientists use a variety of techniques to reveal rates and timescales as something to measure and study, rather than something to hold fixed. These methods, unlike those discussed in section 1.4, all take the internal timescale of the biological phenomenon of interest as important for their research.

1.6.1 Modeling Rates of Molecular Evolution

Biologists often use molecular change to measure time. This will be discussed extensively in chapter three, but here I wish to briefly highlight a case of not merely using molecular change to measure external time, but rather developing a more complex model that takes an internal timescale as a key output. Evolutionary biologist Simon Ho and colleagues were among the first to discover that rates of DNA mutation depend on

timescales: on short scales, mutation rate estimates tend to be much quicker than on long scales (2005). When they calculated how quickly DNA mutations accumulated in birds and primates over just a few thousand years, they found the genomes were chock-full of small mutations. This indicated a briskly ticking evolutionary clock. But when they zoomed out and compared DNA sequences separated by millions of years, they found something very different. The evolutionary clock had slowed to a crawl. In an interview, Ho suggests that we think of this phenomenon like the stock market: day to day there are wild fluctuations, but if we zoom out it appears to be relatively stable, and can display predictable patterns (Arnold 2017). This result can have far reaching consequences, which Ho and colleagues recognized immediately: "Our results show that it is invalid to extrapolate molecular rates of change across different evolutionary timescales, which has important consequences for studies of populations, domestication, conservation genetics, and human evolution" (2005, p. 1)[6]. Their research threw into question the validity of results gained using the molecular clock.

However, Aris Katzourakis, a paleovirologist, eventually developed a mathematical model that can be used to account for the timescale dependence of the DNA mutation rate (known as the time-dependent rate phenomenon), providing biologists with much more accurate dates for evolutionary events. He was interested in viruses and recognized that if the viruses were evolving much more slowly than scientists

[6] The marked differences between mutation and substitution rates are taken by Ho and colleagues to pose a direct challenge to the neutral and nearly neutral hypothesis. In practice mutation rates are taken to be equal to or higher than substitution rates. Ho and colleagues investigate this assumption by looking at the rates of change of DNA across different timescales.

thought when the focus was on short timescales, it could imply that the viruses were much older than expected as well. The time-dependent rate phenomenon implies that the speed of an organism's evolution will depend on the time frame over which the observer is looking. Katzourakis used his work on viruses to develop a model which researchers can use to calculate by how much the rate will vary. Instead of taking the timescale for granted, the model these researchers built mathematically interpreted the relationship between total per-lineage substitutions and the evolutionary timescale. Katzourakis and colleagues chose to study foamy viruses because they have a unique history of co-speciation with mammalian hosts, which allowed them to incorporate timescales estimation and rate variation into their dating estimates (Aiewsakun & Katzourakis 2017). Katzourakis and colleagues estimated that foamy viruses emerged somewhere between 460 and 550 million years ago (much older than previously expected) (Aiewsakun & Katzourakis 2017).

Here we have an example of a researcher exchanging a focus solely on external timescales, for a method that incorporates internal timescales. This is not merely to be a more accurate representation of the system, but in order to generate more reliable knowledge. The timescale dependence of DNA mutation rates also highlights the conceptual importance of timescales and the importance of timescales to practicing researchers. Paying attention to time matters if we are to correctly understand evolutionary history.

1.7 Conclusion

Unlike debates about time in physics, different ideas about the nature of biological time have not been discussed by biologists or philosophers of biology. However, as we saw, time plays a key role in the biological sciences and in living systems themselves. This chapter has argued for the importance of internal timescales to biological science, and demonstrated how biologists often abstract from timescales. Since the concept of an internal timescale is relative to a system of interest, projects that focus on time as an independent or absolute variable inevitably abstract from internal timescales. We see this both in biological methodologies and in biological representations. This can lead to erroneous results, as shown in the previous section.

As I argued, in biological methodologies there are four different forms the abstractions from time tend to come in: physical, procedural, mathematical and conceptual. In representations, this is seen most prominently when time is represented on the x-axis of a graph as the independent variable. These abstractions are not made haphazardly, but follow predictable patterns based on timescale. On the one hand, biologists tend to make physical or procedural manipulations in order to slow down the timescales of biological systems moving more rapidly than ourselves. On the other hand, biologists tend to use mathematical extrapolation to artificially speed up systems that are moving much more slowly (i.e., have much longer timescales) than ourselves. Think back to the examples of physical and procedural manipulations of time. These examples largely had to do with cell cultures or individual living organisms, where the manipulations were aimed at slowing the system down in order to enable observation. On

the other hand, the examples of mathematical manipulation in models largely focused on extremely slow phenomena like evolution, which takes place over hundreds or thousands of years, and the manipulation is aimed at artificially speeding up such systems to enable observation within our own much shorter timescales. The manipulations of time by biologists are not haphazard then, but systematic in nature. They aim to bring systems of fundamentally different timescales to one more similar to ours. This is important because things of a similar timescale to ours are more comprehendible by us.

As has been demonstrated by this chapter, there are a variety of different abstractions from time occurring in biology without much philosophical reflection. This demonstrates the need for a more open conversation about time in biology. This conversation is necessary, for practical and theoretical reasons: both to inform future research projects and to understand the answers to philosophical questions. For example, highlighting the internal temporality of biological phenomena also highlights their fluidity. As we will see in the next chapter, this focus on time has much to contribute to debates in biological metaphysics between mechanists and process ontologists.

CHAPTER TWO

BIOLOGY AND PROCESS ONTOLOGY

2.1 Introduction

As noted in the introduction, J.B.S. Haldane warned us that "If we think too exclusively on the molecular timescale we shall be led to mechanistic materialism" (1956, p. 399). Many of the advances in modern biology have been at the molecular level, and some have begun to worry that we have been led to an overly mechanistic materialism. There has been a growing contingent of philosophers of biology arguing that a process ontology (which takes change as the default, and describes entities in terms of how they maintain stability) is better suited to describing the biological world than the traditional mechanistic ontology (which characterizes entities in terms of their stable properties). Further, there is some evidence that contemporary biologists increasingly see the need for different ontological concepts than traditionally allowed. Specifically, many biologists are beginning to use non-static ontological concepts that do not fit into the mechanistic framework. Just as time and space became linked in physics, biologists are beginning to understand that ontological concepts in biology are intertwined with time as well. This chapter will investigate the consequences of considering time for our metaphysical understanding of the biological world.

This chapter will begin with a broad account of the traditional mechanistic framework and the problems this framework is facing. Section 2.2 will also introduce the process framework which emphasizes how stability is generated and maintained. By conceiving of the world in terms of process, this framework removes the necessity of

defining discrete objects with definite properties. Section 2.2 will conclude with an explanation of how this alternative framework accounts for the problems faced by the mechanistic framework. Section 2.3 will discuss a variety of examples of processes in the natural world. This discussion will begin with the example of the role played by bacteria in human digestion. While this first example is very particular, the examples will progressively expand to a wider scope, demonstrating the prevalence of certain kinds of interactions in nature – specifically those that are problematic for mechanists to understand or describe. Section 2.4 will offer an interpretation of the examples that establishes they are best understood by a process ontology. This section will also argue that these ontological facts suggest the importance of a processual perspective for the science of biology. Sections 2.5 will address how researchers should treat metaphysical frameworks when designing projects through the use of cancer research as a case study. I will argue that researchers should ultimately take an agnostic attitude towards their metaphysical framework in order to ground a pluralism of productive projects. Part of the difficulty with the dominance of the mechanistic framework is that it precludes other sorts of metaphysical frameworks and projects. While the processual framework is promising in its ability to focus attention to temporality, it would be a mistake to adopt this new framework to the exclusion of all others.

2.2 Mechanism vs. Process

Many of the authors at the head of mechanistic philosophy do not take there to be a coherent 'mechanistic framework'. While it is certainly true that accounts of

mechanistic explanation vary, they do share a core conception of science and the natural world. Generally speaking, the mechanistic framework involves both developing an inventory of discrete entities, and analyzing their organization or behavior. In perhaps the most canonical text in the mechanistic philosophy of biology, Peter Machamer, Lindley Darden, and Carl F. Craver write, "Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (2000, p. 3). This core is a metaphysical framing that guides how those who subscribe to this view carve up the world. Often, this means they look for entities with particular properties that enable these entities to participate in certain activities.

I will rely on an oft-cited example to illustrate the concept of a mechanism in the biological sciences to illustrate how the framework works: Synaptic transmission – the transfer of neuronal depolarization from one neuron to another via a chemical signal. As typically understood, when the fluid inside of a neuron cell is negatively charged with respect to the fluid outside, the cell is in its resting state. Neurons 'activate' and neuronal signals are sent when the cells become 'depolarized', i.e., selective channels allow positive ions to enter the neuron. These signals travel down the neuron via diffusion aided by successive channel opening along the axon of the neuron. When the depolarization signal in the first neuron reaches the termination point, the positive ions will bind packaged vesicles within the neuron[7]. This binding process activates the vesicles and prompts the release of their chemical contents into the space between the two neurons (the synapse). The neurotransmitter will then diffuse across the synaptic

[7] This can also happen via signal cascade when the ion induces the production of other protein(s) that in turn attaches the vesicles. Either way, the result is the same.

space, eventually binding to and activating positive ion channels on the second neuron. The activation of these positive ion channels leads to the influx of positive ions into the second neuron. This influx begins the depolarization process in the second neuron. The transfer of a depolarization signal from one neuron to another is a characteristic mechanistic event. Machamer, Darden, and Craver (2000) use a standard textbook diagram to illustrate how the passing of this signal takes place (figure 2.1).

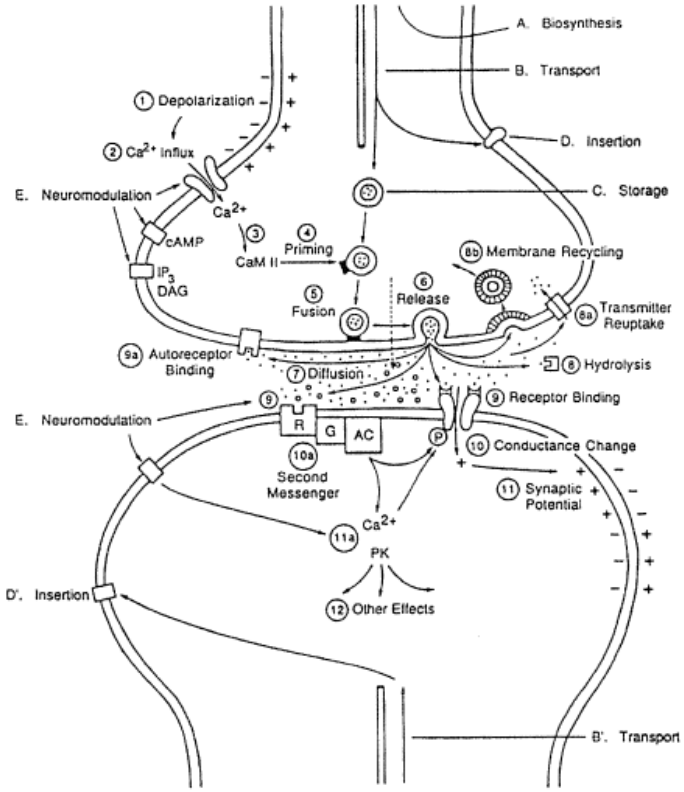

Fig. 4.8 A summary of some of the main biochemical mechanisms that have been identified at chemical synapses. A–E. Long-term steps in synthesis, transport, and storage of neurotransmitters and neuromodulators; insertion of membrane channel proteins and receptors; and neuromodulatory effects. ①–⑫. These summarize the more rapid steps involved in immediate signaling at the synapse. These steps are described in the text, and are further discussed for different types of synapses in Chapter 8. Abbrevations: IP_3, inositol triphosphate; CAM II, Ca/calmodulin-dependent protein kinase II; DAG, diacylglycerol; PK, protein kinase; R, receptor; G, G protein; AC, adenylate cyclase.

Figure 2. 1 Transmission at a neuronal synapse. As found in Machamer, Darden, and Craver (2000). Originally from Gordon M. Shepherd, *Neurobiology*, 3/e; 1994 by Oxford University Press, Inc.

While each step in the transmission event is complex and involves its own lower level mechanisms, there are distinct principles mechanistic descriptions follow that can be illustrated using this example. Descriptions of mechanisms all begin with initial conditions. In our example, these conditions include the

negative polarization found along neuronal membranes, and the presence of a variety of entities (ions, ion channels, vesicles of neurotransmitters, receptors, etc.). Descriptions of mechanisms also include termination conditions, or the state of interest that is reached via the mechanism. In this example, we wanted to understand how a second neuron could become activated in response to the activation of another separate neuron. Descriptions of mechanisms include descriptions of the activities that link these states together. In this case the transfer happens via a series of distinct actions, for example, the ions *moving into* the neuron, or the ions *binding* to the vesicles. Since the activation of the second neuron is the state of affairs researchers sought to understand, the process of synaptic transmission is taken to be causally explanatory. Finally, descriptions of mechanisms include a list of the entities or objects involved in the phenomenon. In the example, this list would include ions, ion channels, vesicles of neurotransmitters, receptors, etc. A completed mechanistic description would also include a description of the properties of these entities, specifically the properties that facilitate their participation in the activities of the mechanism. For example, the shape of the neurotransmitter and receptor would be matching in order to facilitate the binding event.

More abstractly, we can understand that people seeking to describe mechanisms have four desiderata. For purposes of clarity I will use roman numerals I-IV to refer to the desiderata of the mechanists, as follows:

I. Initial conditions

II. Termination conditions

III. Connecting activities

IV. List of relevant entities and their properties

Most mechanistic thinkers understand that these sorts of explanations involve idealizations, but the idealizations are taken to be relatively unimportant. This is described, for example, by Oppenheim and Putnam in their classic paper "The Unity of Science as a Working Hypothesis" (1958). According to Oppenheim and Putnam, many scientists hold some sort of framework "in a more or less vague manner and without very deep-going justification" (1958, p. 27-28). A sort of *ceteris paribus* clause is often implicit in mechanistic descriptions – so unimportant that it does not even need to be mentioned. The mechanistic framework is not merely a method for interpreting the activity of biological researchers, but also a way of understanding the natural world and of generating future expectations for the science. Accordingly, if we have an as-of-yet unexplained phenomenon of interest, researchers might use these desiderata to generate expectations about how to explain such a phenomenon or what they might look for in their experiments.

Although many authors have defended the notion that biology is dominated by mechanistic explanations (Bechtel and Richardson 2010; Bechtel and Abrahamsen 2005; Darden, Machamer, and Carver, 2000; Carver and Darden, 2013), there is some indication that defenders of mechanistic thinking have been under pressure to expand their theoretical framework in light of new developments in biological research (Bechtel and Abrahamsen 2010; Brigandt 2015; Kaplan 2015; Levy and Bechtel 2016). Mechanists have tried to expand the framework to account for temporal or non-mechanistic properties in biological phenomena, however it is clear that the framework is

incapable of making such an accommodation (without being transformed into something else entirely). There are at least five reasons, in the form of properties of biological phenomena, why biological science cannot meet the four criteria of the mechanists which were described above. While roman numerals I-IV to refer to the desiderata of the mechanists, I will use Arabic numerals 1-5 to refer to the properties of biological phenomena that challenge these desiderata. These reasons are found in the nature of biological phenomena. Specifically, biological phenomena that have the following properties:

1) Interchangeable parts or parts that change over time
2) Parts that are not discrete entities
3) Phenomena that appear to be caused by higher-order kinds of objects not definable in terms of any specific parts themselves
4) Mechanisms with porous boundaries
5) Context dependent functions

Each of these properties prohibits a description of some phenomenon in question from meeting the criteria of mechanistic description. Here I will explain in abstract terms how these properties of biological phenomena prevent someone interested in such phenomena from describing them mechanistically. In section 2.3, I will offer a series of examples of these properties being found in the biological world, and in section 2.4 I will explain how those phenomena fulfill these properties.

When the parts involved in some phenomenon are interchangeable or change over time, there are no essential parts. Accordingly, phenomena that have interchangeable

parts prevent one from enumerating the entities relevant to a given phenomenon. Different entities can play the same role in the phenomenon, and it is even possible that a role once played by entity A could be replaced without issue by entity B. This stands in defiance of desideratum IV, the requirement of listing the entities involved. Second, when the parts are not discrete objects, even if one could list them, they would not be able to list their essential properties, which might constantly change. Since such objects are not individually distinct, they cannot be described in such a way as to distinguish them uniquely. This means that such entities cannot be enumerated on a list of entities (desideratum IV) – at least not in such a way that sufficiently defines them. Third, if one were interested in a phenomenon that was (or at least appeared to be) caused by a higher-order phenomenon that is not itself definable in terms of parts, one would once again be faced with the problem of defining a list of relevant entities, because something (at least apparently) causally responsible for the phenomenon of interest is not itself definable in terms of definite parts. For example, movements of individual cars on a road often only appear explained by higher-order patterns of traffic flow that are not themselves explainable in terms of the movement of individual cars. Phenomena of this nature are difficult to explain for mechanists because they again violate desideratum IV: to list the entities involved in a phenomena of interest. When a phenomenon has porous boundaries, one will be unable to define at least the initial conditions (desideratum I), and likely the termination conditions as well (desideratum II). Porous boundaries simply refer to the idea that a system is not closed – it might be causally affected by a number of different entities or systems, such that one cannot draw closed boundaries around what is or is not

a part of the system generating the phenomenon of interest. Since the phenomenon in question has a sufficiently vast array of inputs (or at least potential inputs that it cannot be finitely characterized) it becomes empirically impossible to define the starting or ending points. Finally, functions that are context dependent prevent us from defining the parts, or at least the essential properties of the parts, in a supposed mechanism. Since the entities involved (or what role they play in the phenomenon of interest) will vary according to context, one cannot define them as mechanists' desire (desideratum IV).

Different mechanists have responded to these challenges in a number of different ways. Some have tried to save the mechanistic framework by changing the notion of the mechanism to fit the problematic cases (Bechtel and Abrahamsen 2010). Others have attempted to fit these cases into the existing frameworks (Carver and Darden 2013). Still others have used a combination of these two approaches (Levy and Bechtel 2016). The attention that these mechanists have shown to the problem of boundaries supports the idea that this is a challenge to the success of the framework, and not merely part of the idealizations necessary for scientific practice. These concerns have led some to argue that the mechanistic framework is fundamentally unable to adequately account for these properties. Thus, some have started to offer an alternative framework. For example, John Dupré has introduced what he calls a 'process ontology'. A process ontology is one that "should characterize entities in terms of how they emerge, are maintained and are stabilized" (Bapteste and Dupré, 2013). This sort of ontology does not characterize entities in terms of essential properties. Rather, a process framework gives us a different perspective spatially and temporally. This alternative framework dismisses the focus on

the now and the here that dominates the mechanistic framework, and extends our perspective over time and space. A process is not definable at a moment or a point but rather takes place over time, and through space. Most scientists or philosophers of science will readily tell you that the natural world does not work like a wristwatch or a steam engine. They might even say something like ‘nature doesn't have edges’ – if you look closely enough you won't discover clear boundaries between species or parts of the human body or trees in a forest or really anything else. Biological entities (cells, livers, trees, cats, humans) are just temporary manifestations in the continual motion of biological activity. Yet scientists will nonetheless revert to the mechanistic framework in their everyday work. This might be problematic because using the mechanistic framework can obscure certain parts of the phenomena, as we saw in chapter one.

Let me clarify how a process framework might work by addressing the five problems faced by mechanistic thinkers. If we focus on processes, we do not need to label essential parts, and accordingly, problems of type (1) do not arise. In a process, we do not concern ourselves with the objects that are generating the process as much as the overall process itself. This also applies to problems of type (2). There is no issue with the parts that generate some phenomenon themselves being processes. In fact, that even lends support to the idea of a process framework. Being unable to finitely establish discrete parts because the parts themselves are continually changing is precisely the type of state that provides evidence that objects are actually processes. Similarly, regarding problems of type (3). When investigating a phenomenon that is caused by some 'thing' that is itself only definable by some higher-order properties, one cannot list the objects involved in

generating the phenomenon because at least some of the causes are of a higher order. However, since a process ontologist does not require a list of entities, they can welcome multi-level causal accounts. These cases, while problematic for the mechanist, are exactly what the process ontologist relies on to support their ideas. They generate the supposition that all things are really fluctuating, and that stability is the illusion, rather than vice versa.

Problems (4) and (5) are also of a similar fundamental nature, however, they come from a top-down perspective on the phenomenon, rather than the bottom-up perspective of problems (1), (2), and (3). When a mechanism has porous boundaries, the problem is that the phenomenon of interest is contributed to by an array of factors that are not enumerable by scientists. This type of phenomenon of interest is similar to the parts that are not discrete entities (type 2), but discovered from a different perspective. Rather than parts with porous boundaries, so-to-speak, researchers discover that the phenomenon itself is not a discrete entity. Problem (5) examines functions rather than objects or parts. We might compare this most closely to problem (3). The same object can have different functions or can do different things when it is in a different environment. This is a problem for the mechanists because they want to be able to label (at least ideally) the things that are a part of a mechanism. Thus, when the role a given entity can play is not fixed, that is it changes, it is not definable as part of some mechanism.

What has been said so far is fairly preliminary. I have suggested that mechanists have certain sorts of desiderata they seek when describing or explaining the natural world. I have also provided some general reasons for thinking that the biological world

fails to meet their desiderata. Finally, I have sketched an alternative sort of framework that would not face the problems of the mechanists. However, I have yet to describe any examples from the natural world that resemble the abstract reasons I've given to reject the mechanistic framework. In the next section, I give exactly these sorts of cases. In addition to giving examples, I will argue that the situations described are systemic in the biological world by building examples that have an incrementally wider scope. Beginning with one very specific example, I will build out similar cases until it becomes clear that process is ubiquitous in the biological world.

2.3 Process in the Natural World

In this section I will offer examples of phenomena in the natural world that have the properties (1-5) discussed in section 2.2. I will begin with the example of human digestion, which is fairly limited in scope. I will eventually extend the example to consider the phenomenon of metabolism throughout living organisms, and argue that we have good reason to suspect the properties discussed will occur in most or all of these cases. The overall objective of this section is to offer evidence that there are a great many cases in nature that will be difficult for the mechanistic framework to fully capture.

2.3.1 Symbiosis in Human Digestion

Humans breakdown and uptake ingested nutrients through a process known as digestion. It has long been known that microbes found in healthy gastrointestinal (GI) tracks make important contributions to digestion. Scientists, following a mechanistic

formula, began looking for the parts that are essential to the phenomenon of digestion – they began looking for the essential species of bacteria involved. The picture these researchers seemed to have in mind is that human GI tracks provide some initial conditions, perhaps certain kinds of digestive tasks they are not very good at performing. Additionally, different bacterial species are presumed have different abilities to contribute to digestion, defined by their genetic code, that would be more or less helpful to humans. This picture relies on the idea that bacterial species and their genomes are fixed in a way similar to the human species and the human genome. In fact, after the sequencing of the human genome in 2001, some scientists argued that the achievement would remain incomplete until the collaborative role of the microbial flora within humans were fully understood (Davies 2002). There was a call for a "second human genome project" which would be "a comprehensive inventory of microbial genes and genomes in all four major sites of microbial colonization in the human body: mouth, gut, vagina, and skin" (Relman and Falkow 2001). Relying on a mechanistic framework, researchers assumed they could enumerate the properties of the entities involved in digestion, and sought to do just that by defining the bacterial species essential to the process.

Researchers used 16S rRNA analysis to identify the bacterial species present in the human GI track. 16S rRNA is a laboratory technique used to reveal the evolutionary history of prokaryotic ribosomes by relying on the 16S rRNA gene region's relatively slow rate of evolution. By performing such an analysis, scientists hope to discover the evolutionary history of the lineages of bacteria they are studying. Contrary to their expectations, however, standard 16S rRNA analysis revealed that different populations of

humans contained systematically different populations of microbes in their GI tracks. Scientists were surprised by this result because the seemingly different bacteria present in different GI tracks were all able to function normally. This meant that different organisms were able to make a functionally equivalent contribution to digestion, and this violated the desiderata of listing all of the relevant entities involved in generating the phenomenon in question.

However, the assumptions detailed above misunderstand the nature of bacterial species, and how bacteria are capable of relating to humans. Scientists who study bacteria have found that the traditional mechanistic concept of a genome (i.e., the one relied upon in the discovery of *the* human genome) does not adequately capture the nature of bacterial entities. The human genome is a list of all the genes that are found in an individual of the human species. While there are of course differences in the genomes of individual humans, these difference amount to less than 0.1% of the genome. This very small amount of variability allows scientists to define the list of genes shared by all humans. Bacteria, on the other hand, cannot be thought of this way. Compared to humans, bacterial genomes mutate at a very rapid rate, and more importantly, bacteria also engage in lateral gene transfer (LGT). LGT is a process through which one adult bacterium can transfer a portion of its genome to a neighboring adult bacterium. This violates the traditional model of vertical descent and allows genes from different species to be transferred freely. While the mechanistic framework operating in the background of their project generates the expectation that the bacterial partners in digestion could be

defined, bacteria cannot be understood as discrete entities in the ways researchers expected. In other words, these researchers faced problem (2), as defined on my list.

Rather than giving up, researchers developed new ways to understand bacterial species. Instead of relying on the static genome concept, microbiologists developed the concept of a pan-genome. The pan-genome is the set of all the genes contained in any individual of the species, and is made up of the core genome and the dispensable genome. As the names suggest, the core genome is made up of genes that most all members of the species have, and the dispensable genome contains the rest of the genes. One study investigated the genome of eight different strains of *Streptococcus agalactiae* (Tettelin, et al. 2005). These researchers were able to identify the core-genome for *S. agalactiae* with a relatively high degree of confidence, such that adding additional samples would not drastically change the finding (Tettelin, et al. 2005). However, using mathematical extrapolation the researchers concluded that new genes would be continually added to the list of dispensable genes even after hundreds or thousands of genomes for the species had been sequenced (Tettelin, et al. 2005). Another investigation of the publically available genomes of *Escherichia coli* bacteria revealed a pan-genome of about 16,000 genes (Lukjancenko Wassenaar and Ussery 2010). A typical *E. coli* bacterium contains about 5,000 genes, only about one-fifth of which are considered part of the "core-genome" for the species (Lukjancenko Wassenaar and Ussery 2010). The so-called dispensable genes account for about 80% of a given individual's genome, and about 90% of the pan-genome of the species (Lukjancenko Wassenaar and Ussery 2010). Unlike the human genome, bacterial species have genomes with high variability, and accordingly do not have

statically definable genomes – at least on the timescale relevant for use in research on the human GI tract. The new concept of the pan-genome is processual in nature as it defines bacterial species in terms of how they are maintained and stabilized, rather than in terms of facts about their stable states.

Since bacteria cannot be understood as having definable genomes, new methods of examining microbiomes were developed, including metagenomics analysis which is used to measure the total genetic material present in a sample that often consists of many individual organisms (of potentially differing varieties). Metagenomic analysis of samples from human GI tracks revealed that the total genetic material present among different individuals were actually very similar (Kav et al. 2012; Lozupone et al. 2008), despite the different lineages or "species" of bacteria present. It was really the metagenome of the whole microbe community that is constrained, and stabilized, by the environment of the GI tract, and not the species of bacteria. It is the metagenome as a whole that provides the resources necessary for humans to successfully perform digestion, rather than the particular types of bacterial species. Lineages (or "species") of bacteria are much less stable and more diverse, so varied constituent microbes can end up providing the stable metagenome required for human digestion.

So far I have highlighted how the mechanistic framework guides certain assumptions in scientific research about the digestive process, how these assumptions can fail, and how a processual framework could potentially resolve these problems. Next, I want to highlight how the temporality of biological entities plays a key role in this conflict. Humans and microbes are stable across different timescales. The human genome

is definable because it is changing slowly enough for us to consider it static. However, this is not the case for the genomes of bacteria. Accordingly, making an inference from the stability of the human genome to the stability of the bacterial genome turned out to be flawed[8]. In other words, the expectation that because humans have a stable genome, a stable GI track environment, and a plethora of microbes are found in the healthy GI, that there must be stable mechanistic parts that play a consistent role in the digestive process, turned out not to be a fair expectation. The standard mechanistic framework looks for entities to play an identifiable and consistent role in the execution of some function in a way that is not present in the case of the human GI tract. The idea that the output of the human gut microbiome could be stable, even though they contain widely varied parts, is not something that easily fits into the mechanistic framework. While the mechanists search for essential properties to define the 'part', a process ontologist would simply understand the microbiome functionally, that is, in terms of how it is maintained and stabilized. Since different biological entities occur at different timescales, they will look differentially stable or diffuse depending on the scale of observation. These remarks are only preliminary, but it is worth noting the relationship between the obscuring of the temporality of biological entities, and the assumptions of a mechanistic framework. Specifically, as Haldane warned, privileging one timescale might end up making only some stability apparent, while obscuring other important factors. This suggests that part of recognizing the internal timescales of living things might be moving away from the mechanistic framework. While the difficulties of understanding multiple timescales is

[8] Bapteste and Dupré (2013) extensively discuss the flaws in making inferences from the stability of one entity, or lack thereof, to the stability, or lack thereof, of another.

only part of the complexity in understanding digestion, it is still worth considering how a more robust understanding of process extended in time and across different timescales could impact this research. This section shows the importance of timescale and processual thinking in one quite specific scientific context (human digestion), but the next section will highlight how these same issues arise across the phylogenetic tree.

2.3.2 Symbiotic Metabolism Across the Phylogenetic Tree

Humans are not the only organisms that engage in digestion, and they are far from the only ones to receive essential contributions from microbial symbionts. Almost all animals get help from microbes in their digestive processes. In fact, scientists divided digestive strategies into two major groups: allo-enzymatic and auto-enzymatic. Allo-enzymatic digestion is carried out primarily by enzymes secreted from microbes inhabiting the GI tract of the animal, while auto-enzymatic digestion is carried out primarily by enzymes that the animals secrete themselves. Animals like cows, buffalo, rabbits, ostriches, and horses are allo-enzymatic digesters. Ruminants, like cows, famously have digestion pouches that house microbes, which carry out the fermentation of ingested material. This requires regurgitation and re-chewing multiple times in the digestion process. The fermentation in their foreguts is completed entirely by microbial symbionts. By contrast, animals like humans, cats, giant pandas, and most avian species (hawks, owls, toucans, sparrows, etc.) are auto-enzymatic digesters. Humans are members of the auto-enzymatic group, and like humans, most so-called auto-enzymatic digesters still host microbial symbionts. For example, many scientists believe that

microbial symbionts play an essential role in allowing Giant Pandas to survive on a diet of bamboo despite their evolutionary history as carnivores (Wei Wang and Wu 2015). There is also extensive evidence that microbes aid digestion in avian species, with the density of colonization of bacteria being particularly high in the hind gut (Waite and Taylor 2015). Bacteria in the GI of fish aid in the decomposition of nutrients, as well as provide the host with resources, such as enzymes, amino acids and vitamins (Sugita, et al. 1997). For example, researchers studying ayu, carp, channel catfish, Japanese eel and tilapia found that amylase produced by microbes in their guts played a major role in their digestion of starch (Sugita et al. 1997). While much more is known about digestive symbionts in species of interest to humans, such as ourselves, and those use in agriculture (cows, chickens, etc.) or laboratories (mice, rats, etc.), evidence suggests that all animals get some help from microbes in their digestive processes.

The above are all vertebrate examples, but invertebrates also have digestive bacterial symbionts. Even though bacteria are an important food source for sea cucumbers (Gao, Xu and Yang 2010), studies have also shown that endogenous bacteria release extracellular enzymes that aid in their digestive process (Zhang et al. 2012), and produce essential amino acids for their hosts (Phillips 1984). Termites depend on bacteria in their hindgut to breakdown the wood they ingest into usable nutrients (Brune and Ohkuma 2010). Bacteria have also been found to play a role in digestion in crabs. For example, in the Marsh Fiddler Crab bacteria in the hindgut secrete protease, glucosidase and chitinase enzymes which play a crucial role in the organism's breakdown of nutrients

(Gulmann 2004). The role bacteria play in digestion is not a development unique to some animals, but is found in animals of striking variety in both morphology and dietary habits.

Digestion is just a subset of the larger phenomenon of metabolism. Digestion is a specific process that takes place in animals with guts. While not all living things have guts, all living things metabolize. Some even consider metabolism and reproduction to be the two essential components of life itself. Plants use a variety of soil-dwelling microbes to help them absorb water and mineral nutrients (Kahn 2005). Famously, many plant have nodules on their roots that house bacteria. These bacteria fix atmospheric nitrogen into ammonia which plants are able to use in their amino acid and nucleic acid synthesis (Spaink 2000). Some bacteria also provide vitamin nutrients to their hosts; for example, algae species get vitamin B_{12} from a bacterial symbiont (Croft et al. 2005). At hydrothermal vents and other reducing habitats, chemoautotrophic bacteria and archaea serve as the base of the food chain for a diverse array of organisms. In such locations, energy does not come from the sun, but rather from sulfide, hydrogen, methane, or other chemical sources. Giant tube worms do not possess a mouth or a digestive track, but rather house large amounts of bacteria in their body tissue. These worms directly absorb nutrients produced by the bacteria in their tissue (Yong 2016). The phenomenon of chemotrophic bacteria being hosted in animals near hydrothermal vents is known to occur in at least seven different phyla (Dubilier, Bergin, and Lott 2008). The activities of these symbioses contribute to larger communities that include non-symbiotic animal and microbial species, but they all ultimately rely on the primary production from these chemoautotrophic bacteria. Since symbiotic digestive bacteria violates the desiderata of

mechanists, all of these examples support the idea that the mechanistic framework will be insufficient for biological science.

There is also evidence that the importance of bacteria to other forms of life has a long history. The fossil record provides evidence that some animal forms in the Ediacaran grazed on collections of bacteria on hard substrates (Fedonkin, Simonetta and Ivantsov 2007) and that burrowing animals originated only in association with microbial mats (Seilacher 1999). All sort of living organisms rely on microbes to perform functions essential to their continued life. The most interesting evidence comes from the origin of eukaryotic cells. All animals, plants, fungi, and algae belong to a group called eukaryotes, which are characterized by large complex cells with internal organelles. These organelles include the nucleus, which houses DNA, and the mitochondria. It has been hypothesized that mitochondria became part of eukaryotic cells through an endosymbiotic relationship when one smaller simpler cell engulfed another (Martin and Mentel 2010). While there are competing hypotheses about the nature of the cell that engulfed the other, scientists widely agree that the origin of the mitochondria necessitated an endosymbiosis (Lane and Martin 2010). Mitochondria perform some of the most important metabolic functions in eukaryotes. Mitochondria are responsible for the creation of most of the Adenosine triphosphate (ATP) in such cells, which is the primary molecule used to capture energy from the breakdown of food nutrients and used as fuel in cellular processes. For these reasons ATP is often called the currency of the cell. The mitochondria are essential to metabolic activity in all eukaryotic lifeforms, including plants, animals, and fungi. This symbiotic relationship has shaped a great deal of the metabolic activity of living

creatures. The point here is not about this particular symbiosis, but the importance and prevalence of symbiosis more generally.

While the symbiotic relationship of the mitochondria is not of the same nature as those discussed above, it ought to indicate the long and important evolutionary history of cooperative interaction for all living things. Bacteria and archaea have and continue to dominate the living world. While the questions we often ask are "why make use of bacterial partners" or "how does X organism come to interact with Y microbe", the better questions might be just the opposite. The interaction between different lifeforms is not a mystery but an explanation. This is because questions are generated when what is held as a background expectation is violated. When one expects organisms to be functionally independent, the observation that they are not generates questions. However, if we were to change our background assumptions to hold instead that cooperation and interdependence is to be expected, we would ask completely different questions; questions that our current background assumptions tell us are uninteresting. A similar line can be found in Doolittle and Booth (2017) who argue that "it's the song, and not the singer", the overall pattern and not the individual constituents, that are evolutionarily important. Perhaps it wasn't that complex lifeforms were looking for an easy way to perform some functions, but rather that certain innovations already existed in the living world, and those sorts of creatures that made good use of existing 'technology' through cooperation were able to thrive and become increasingly complex. It was the ability to work with different lifeforms that allowed the more complex life forms to form. Some have suggested that it was the metabolic powers of the mitochondria that enabled the

complexity of life to increase; the suggestion is that by increasing the capacity of cells to generate and store energy, the mitochondria enabled cells to synthesize increasingly large numbers of proteins (Lane and Martin 2010). While mitochondria do not represent an actively modulating part of the eukaryote, such a deep importance for symbiotic relationships indicates their prominence and frequency.

All of this is of interest because it suggests that mechanists might have a hard time describing the metabolic function in many sorts of living organisms past and present. Recall that the desiderata for mechanistic explanation include an enumeration of the parts involved in generating a given phenomenon of interest (desideratum IV). Bacteria are not the kind of thing that easily fits a mechanists' understanding of what it is to be a stable 'part'. Bacteria simply are not that kind of thing – at least at the timescale comparable to some other living things. Scientists interested in metabolism or digestion in any organism that uses a microbial symbiont will not be able to generate a list of stable entities that produce a stable phenomenon. Instead, they will have to accept an explanation in terms of how a metagenomic contribution is stabilized and maintained, and even the entities contributing to that metagenome are not the same. A mechanist might respond that the metagenome is the entity that belongs on their list of entities involved in digestion – they were simply mistaken about which object should go on the list, but the list remains. However, the metagenome does not have the sorts of stable properties that one usually associates with a discrete object, and is instead understood abstractly in terms of how it is maintained. While a mechanist could try to save their view

by adding such an 'object' to their inventory, the better path might be to admit that such objects are of a different nature.

2.3.3 Symbiosis as a Problematic Property for Mechanists

As we have seen, symbiotic relationships are common across the phylogenetic tree. Just as the bacterial partners in human digestion complicated the ability of mechanists to explain how digestion occurs, this ubiquity of symbiosis complicates the ability of the mechanistic framework to account for metabolic activity in any organism. Recall that the problem for mechanists include: (1) parts that change over time, (2) parts that are not discrete entities, (3) phenomena that appear to be caused by higher-order kinds of objects not definable in terms of any specific parts themselves, (4) phenomena with porous boundaries, and (5) context dependence. Trying to account for bacteria as part of a mechanism only is a problem that falls into category (2). This means that the cases I've discussed so far generate problems for mechanists because of the nature of the entities they wish to categorize as a static part. However, it is important to note that symbiosis can also highlight problems of each of the other four types.

As already seen, species of bacteria that serve as symbionts in a given animal are often interchangeable or even change over time. For example, after a human takes a course of antibiotics their GI track microbiome is decimated. When the microbiome is eventually replenished it is often colonized by different types of bacteria (Dudek-Wicher, Junka and Bartoszewicz 2018). Additionally, it has been documented in several species that as they grow and develop their microbiomes go through corresponding changes

(Waite and Taylor 2015). These cases are instances where symbiosis has parts that change over time, and thus highlight problems of type (1).

The metagenome of bacterial colonies is not definable in terms of discrete parts, and yet the metagenome plays an apparently causal role in digestion. While we cannot define the metagenome statically it makes a contribution to digestion. Without this contribution human digestion doesn't function normally. Furthermore, the metagenome seems to be somewhat self-stabilizing. In other words, the bacteria create their own environment, and this environment recruits bacteria that are capable of playing particular roles. The active recruitment of bacteria in various species means that the metagenome is also in some sense caused by the higher order object. For example, researchers speculate that recruitment plays a critical role in efficient colonization of the roots by the essential nitrogen fixing bacteria (Lakshmanan et al. 2012). Such recruitment activities represent problems of type (3).

Bacteria can also highlight problems of type (4) as gut bacteria do not stick to their role as digesters, but influence various other systems (and vice versa). For example, a short-chain fatty acid produced by gut bacterium stimulates insulin production in fruit flies, which increases growth rates while reducing sugar and lipid levels (Shin et al. 2011). Research on mammals shows that stress influences the composition of the gut microbiota and that communication between microbiota and the central nervous system (CNS) influences an individual's reactivity to stress (Foster and Neufeld 2013). Further, changes in microbiota have been shown to affect serotonergic and GABAergic signaling systems in the CNS (Foster and Neufeld 2013). As much as a third of the molecules

carried in an animal's blood have microbial origin (Nicholson, et al. 2012). This circulation distributes the products of the microbiome, allowing them to influence the physiology and functioning of distant organs (Nicholson, et al. 2012). This vast array of complex interactions demonstrates the difficulty or even impossibility of drawing definitive lines around any given phenomenon in nature, and thus illustrates problems of type (4).

Finally, bacteria can highlight problems of type (5). Microbes are neither inherently beneficial nor inherently harmful. Whether some particular bacterium is a pathogen or a symbiont has been shown to depend largely on context. Bacteria that are helpful in the human gut can be lethal if they make their way outside of the GI track (Gorbach 1996). Living organisms have found ways of stabilizing and maintaining their constantly fluctuating relationships with microbes. Traditional labels like 'mutualist' or 'pathogen' do not accurately represent fixed identities but are more like states of being (like being hungry or awake). This is even true of the billions-of-year-old relationship humans have with mitochondria. If a human suffers a physical injury, cellular damage can lead to the release of mitochondria into the body and blood. Researchers have shown that our body reacts to mitochondria's associated molecular patterns as if they were pathogens creating the sepsis-like state known as systemic inflammatory response syndrome (SIRS) (Zhang et al. 2010). Mitochondria are hugely beneficial when kept inside our cells, but SIRS can often be a lethal condition. Further, the particular sorts of symbionts organisms of the same species contain, depended on the particular history or context of their life (e.g. who their mother was, what they eat, where they've been, etc.).

In general symbiosis demonstrates each of the qualities that mechanists have trouble accounting for.

The larger point here is that this perspective on bacteria and microbes can be understood as suggesting the importance of context to biology. In other words, a focus on the ontology of the biological world reminds us of the importance of the complex interactions between an organism and its environment. It is a reminder to us that any apparent stability is maintained by a complicated and vast network. This perspective calls attention to the fact that picking out patterns or categories becomes a pragmatic question of what matters to the person looking. In most of the cases I've considered here, the system in question is an individual organism and its many microbial communities. It is important to remember that this system (already too complicated for the mechanist) does not occur in isolation but is itself nested within communities of other organisms that, in turn, coexist in and influence successively larger communities of microbes, fungi, plants, animals, and geographical units. While it may seem impossibly complex to honor this interconnectedness in scientific research, there are options available.

For example, a variety of studies have been done on mice who were genetically engineered to have a genetic mutation similar to that found in humans with Crohn's disease (Yong 2016). These rodents developed inflamed guts only if they had the genetic mutation *and* were exposed to an inflammatory toxin *and* had a normal set of gut bacteria. If they did not have normal GI bacteria or were not exposed to the toxin, the mice would continue to have healthy GI tracks. This complexity reveals that the disease is not one pathogen or one genetic variation but a process. Many scientists have sought to

understand the causes of inflammatory bowel disease (IBD) through identifying particular pathogens or genetic variations. However, scientists have discovered over 160 different gene variants associated with the condition, and been unable to identify any particular pathogen (Yong 2016). This study on genetically modified mice illustrates how one can study environmental influence and honor the processual nature of phenomena, at least in a limited way.

This section has explored the ways that the biological world presents challenges to being understood within the mechanistic framework. I have demonstrated that there are widespread phenomena surrounding metabolism that violate the mechanistic desiderata (I-IV). Many of these challenges result from the variety of temporal scales at which biological entities exist. While I have suggested that the process framework can offer some solutions to these problems, the next section will explore in more detail how researchers should treat these sorts of metaphysical frameworks in their work. Specifically, I will argue that since we cannot be certain that our current metaphysical frameworks are correct, we ought to take a pluralist approach by allowing many metaphysical frameworks to frame scientific research.

2.4 From Metaphysics to Methods

Metaphysical presuppositions guide scientific research. They do so by articulating an ontology for a particular domain of phenomena, that is, by making a claim about what sort of things there are and what they are fundamentally like. These ontological claims, in

turn, prescribe a particular methodology for how to go about investigating and explaining those kinds of things. There is thus what I call a move from metaphysics to methods.

A key question that has yet to be addressed is what sort of attitude researchers ought to take towards such metaphysical presuppositions. Scientific research cannot take place in a metaphysical vacuum; yet, there are better and worse attitudes one can take. On the one hand, there is an attitude I will call "unreflective trust". On this view, researchers accept a particular metaphysical framework uncritically, unaware of the nontrivial metaphysical choices that are being made. On the other hand, there is an attitude I will call "passionate affirmation". On this approach, researchers are fully aware of the substantive metaphysical choices being made, but nonetheless argue that theirs is the one correct metaphysical framework to adopt. In what follows, I argue that both of these attitudes are mistaken and prematurely restrict scientific research. I argue instead for an "agnostic" attitude towards the metaphysical presuppositions guiding research, focusing specifically on the example of cancer research. I defend this agnosticism on two grounds: first, the underdetermination of metaphysical frameworks by empirical research, and second, considerations of inductive risk, namely that when it comes to cancer research there are more than just epistemic consequences for making the wrong metaphysical choice. I conclude that one should instead allow for a pluralism of metaphysical frameworks to guide research.

In the context of cancer research, the “unreflective trust” view will be exemplified by the currently dominant mechanistic approach to cancer, while the “passionate affirmation” attitude will be illustrated by a new processualist approach to cancer. I will

argue as an alternative to both of these, that an "agnostic attitude" would be more appropriate because it can ground a methodological pluralism.

2.4.1 Mechanistic Cancer Research

The mechanistic metaphor has been deeply influential in biology, and cancer biology is no exception. For many years, scientists complained about the lack of mechanistic understanding of cancer itself and how the various treatments combat the disease. In 1971, when one of many large pushes was made for a "moonshot" for a cure for cancer, one cancer researcher said "An all-out effort at this time would be like trying to land a man on the moon without knowing Newton's laws of gravity" (Mukherjee 2012, p. 186). Reflecting on the state of cancer research at the end of the 1980s, Bruce Chabner, former director of the NCI's Division of Cancer Treatment, said

> It was as if the whole discipline of oncology, both prevention and cure, had bumped up against a fundamental limitation of knowledge. We were trying to combat cancer without understanding the cancer cell, which was like launching rockets without understanding the internal combustion engine. (Mukherjee 2012, p.304)

What these complaints have in common is that they are based on a mechanistic understanding of biology. Prior to this time, researchers had been content to test and use treatments for their outcomes only. Now these researchers were now telling us that we need to know more than just that a patient starts in the diseased state and ends in a healthy state or vice versa. Instead we need to understand the properties of the cancer and the treatments that allow them to successfully generate the non-cancerous healthy state. What scientists were in effect saying was that they needed to look for the mechanism

behind the success or failure of treatments, and the failure of the body to maintain a healthy state.

Not only did mechanism capture the minds of scientists, but it also captured the minds of many philosophers. Philosophers began to argue that mechanisms could be used as a framework for understanding all biological explanations and philosophical assumptions. In one of the first philosophical accounts of the way scientists explain disease, Paul Thagard argued that part of explaining disease is the search for mechanisms: "Medical researchers are similarly concerned with finding mechanisms that explain the occurrence of diseases, for therapeutic as well as theoretical purposes" (1999, p. 107). Thagard believes this search for mechanism characterized many sciences, arguing that different sciences, "employ different kinds of mechanisms in their explanations, but each involves a system of parts that change as the result of interactions among them that transmit force, motion, and energy" (1999, p. 107). Thagard even used the cancer research of the 1970s and 1980s as a successful example of this search for mechanisms (1999, p. 107-108). Perhaps the most influential work in the early years of the 'new mechanistic[9]' philosophy came from Machamer, Darden, and Craver (2000). They argue that biology (and perhaps even all science) should be understood as a search for mechanisms (Machamer, Darden, and Craver 2000). While many philosophers of biology have seen the mechanistic metaphor as merely an explanatory aid, the demand that we look for and discover mechanisms makes clear that mechanistic thinking is also a

[9] In contrast to the mechanistic philosophy of Descartes, the "new mechanical philosophy" emerged around the turn of the twenty-first century as a successor to the logical empiricist approach to philosophy of science. For more see Craver and Tabery, 2015.

metaphysical framework – it is a way of understanding the natural world and generating future expectations. Both mechanistic explanation and mechanistic philosophy more broadly, share the same assumption; they all implicitly assume the world is composed of stable entities and their activities. Further, mechanists assume that we can explain the activities of some entity based on its parts and properties. While biologists and philosophers of biology argued for the importance of mechanism to understand biology broadly, cancer biologists demanded a mechanistic understanding of carcinogenesis specifically.

The dominant theory of carcinogenesis, Somatic Mutation Theory (SMT), can be seen as an example of a mechanistic account that seeks to fill the gap pointed out by cancer researchers from the 1970s. SMT holds that cancer is caused by somatic mutations (i.e. changes to the DNA of the body that are not part of the germ line). The picture according to SMT says that when these mutations occur within particular cells they cause those cells to undergo aberrant proliferation. This aberrant proliferation is the cancer. While this deranged proliferation can manifest as a tumor or metastases, according to SMT, cancer just is abnormal cellular proliferation caused by DNA mutation. In SMT, the background expectation is for a system to stay unchanged and stable, cells are considered to be quiescent, and when an oncogenic driver mutation (or mutations) occurs it acts independently of context. This is an instance of the mechanistic framework providing metaphysical guidance to cancer scientists, instructing them to develop a theory of carcinogenesis that conceives of the disease in terms of fixed entities and their activities. While scientists may not have intentionally allowed their metaphysical

presuppositions to guide their scientific practices, the evidence suggests that they, in fact, looked for mechanisms behind cancer because they believed the world was fundamentally made of mechanisms. They developed their ontology for cancer not in isolation, but from their context deeply embedded in the mechanistic framework. It was because they believed the world was made of mechanisms that they saw their task as the search for them. This exemplifies the attitude of trust these researchers had in their metaphysical presuppositions.

This project was not entirely unsuccessful. SMT became popular because it was able to explain many of the observed characteristics of cancer. For instance, SMT was able to explain how cancer can be heritable. In the early 1970s, Dr. Alfred Knudson popularized his 'two-hit' hypothesis (Hino and Kobayashi 2017). Retinoblastoma is a type of cancer that originates from the retina (the very back of the eye), and it is the most common cancer in children. In response to the observed patterns of heritability in childhood Retinoblastoma Knudson hypothesized that these children were inheriting one mutated (i.e. non-functioning) copy of a gene, and all that was needed was one additional 'hit' (i.e. mutation) to cause cancer (Knudson 1971). The reasoning goes, if every normal cell has two copies of every gene, and one copy is mutated already, the probability of a random mutation causing both copies to be non-functional is greatly increased. Thus, if cancer is caused by mutations to DNA inside cells, one can easily explain how cancer can be heritable.

SMT was also able to explain how viruses can cause cancer. One of the early popular theories of carcinogenesis was the virus theory. This theory held that cancer was

caused by special kinds of viruses. The theory was supported by the discovery of the Epstein-Barr virus(EBV) and the hepatitis B virus (HBV) which cause cancer in humans, as well as Rous sarcoma virus (RSV) which causes sarcoma in chickens (Javier and Butel, 2008). However, it was eventually discovered that these viruses were not the proximal causes of cancer. In the case of HBV researchers found that it was the inflammation caused by the virus that actually caused the cancer (Javier and Butel 2008). For RSV, it was discovered that it caused cancer in chickens by inserting this message into the DNA of the cell itself. The virus is merely a messenger, and the cancer is manifest by the change to the genome (Javier and Butel 2008). Thus, SMT was an advance over the virus theory in that it can more accurately explain how viruses can cause cancer. SMT tells us that some viruses are capable of inserting their message into the host DNA, thereby altering the genome like inherited and random mutations.

Finally, SMT is able to explain the cancer-causing effects of generic mutagens. It was long observed by cancer researchers that chemicals and other agents that increased the mutation rates of DNA were carcinogens. The puzzle was how diverse agents like radiation, cigarette smoke, and various chemicals could all cause the same disease. Before SMT there was no general theory of cancer that was successfully able to incorporate all of these observations. SMT tells us that chemicals or other agents that increase the mutation rate of DNA, increase the chances that a mutation will occur in an oncogene(s) leading, eventually, to cancer (Mukherjee 2012). Thus, because it united the exogenous (chemicals and viruses) and endogenous (hereditary) known causes of cancer,

and offering a description of the roots of carcinogenesis, SMT became the dominant theory of cancer.

Like all theories, SMT has underlying metaphysical assumptions, and these assumptions seem to have been guided by a mechanistic understanding of the world. SMT is mechanistic in that it explains cancer by describing the initial conditions (normal DNA, normal cell), the termination conditions (abnormal cell, abnormal DNA), the entities that are involved, and the activities that connect these conditions. In other words, researchers assign an ontology of entities and activities to cancer, and explain the disease in terms of properties of the entities involved. Under this mechanistic approach, cancer is a cellular disease – cells and DNA are the entities involved in cancer. Cells that become disordered and grow out of control cause tumors and other malignant developments – this disordered growth is the activity of cancer. SMT tells us that mutations create the first cancerous cell(s) and the property of having mutated DNA is what causes the cell to engage in the deranged growth activity. More deeply, SMT assumes that questions about the nature of cancer will be answered at the level of the DNA, and will guide research programs that attack or investigate cancer at the cellular level. In other words, we need to continue to look for other properties of the entities involved in cancer in order to understand how cancer develops. SMT gives causal primacy to DNA and the cell. This is not a generic presupposition but reflects a very particular view about the nature of biological organisms as mechanistic. Finally, SMT also provides a temporal ordering to the events associated with cancer: regardless of whether a carcinogen (chemical, viral, etc.) was present, mutations to DNA occur before the cell begins to behave abnormally. It

is the abnormal behavior of the cell that ultimately forms the cancer. By describing cancer in terms of entities and activities, SMT fulfills the demands of the mechanistic metaphysical framework and the expectations of mechanistically minded scientists and philosophers.

Unfortunately, not all scientific observations fit nicely within SMT. For example, Brücher and Jamall (2016) observed that some mutations occur only after disordered cellular behavior has started. This contradicts the temporal ordering of SMT. SMT predicts mutations will occur before changes in cellular behavior, because mutations in DNA are believed to cause such disordered behavior. However, Bucher and Jamall argue that somatic mutations are epiphenomena that occur after carcinogenesis is well underway, and thus the mutations could not be the cause of the overall cellular behavior. In a related study, Sonenschein and Soto (2004) conducted a series of experiments to test the role of the tumor micro-environment on carcinogenesis. They found that in rats, epithelial tumor cells could reorganize into healthy cells when placed in a normal stroma (part of a tissue or organ that serves a structural or connective role). Similar results have been shown for recombining normal mammary epithelial cells with stroma that had been treated with a carcinogen (Barcellos-Hoff and Ravani 2000), and a healthy prostate cell line with a prostate cancer derived cell line (Barclay, et al. 2005). These results show carcinogenesis to be importantly dependent on the tumor microenvironment, rather than purely on DNA mutations. This conflicts with the mechanistic characterization of cancer as cell and DNA based that SMT offers. Both Bucher and Jamall, and Sonenschein and

Soto argue that the SMT picture of cancer suppresses the importance of cell-cell signaling and the microenvironment of a developing tumor.

2.4.2 Processual Cancer Research

In response to these discoveries, a growing group of scientists (e.g., Soto and Sonnenschein 2011) and philosophers (e.g., Bertloaso and Dupré 2018) have been arguing for the need to develop an alternative to the SMT cancer paradigm. More specifically, they argue for a theory that views cancer as a *process*. Soto and Sonnenschein (2011) have theorized that cancer is a tissue-based disease that occurs when the normal interactions of cells in a tissue are disrupted. The so-called "Tissue Organization Field Theory" (TOFT) differs from SMT not merely in this account of carcinogenesis, but also in its ontological and metaphysical presuppositions. TOFT asserts that the default state of cells is proliferation, not quiescence as it is according to SMT (Soto and Sonnenschein 2011). These scientific challenges undercut the SMT paradigm at the most fundamental level: its ontological picture of cancer. Armed with a new processual ontology for cancer, these researchers are arguing for new methodological choices in the field.

From a philosophical perspective, TOFT can been seen as guided by a processual metaphysical framework. Bertloaso and Dupré argue that cancer ought to be understood as part of a new processual ontology for biology. They argue that "the proper balance of cell types is not something that is achieved once and then maintained by inertia; its maintenance requires a continuous and dynamic set of activities" (2018, p. 324). They

assert that what scientists ought to focus on in studying cancer is the dynamic coupling between proliferation and differentiation that occurs in healthy tissue, and how this ebb and flow becomes disturbed in pathological contexts. Cancer is not a set of somatic mutations and deranged cell growth (i.e. the entities and activities of the mechanists), cancer is a complex process contributed to by a multitude of factors. On this processual view, the default of an individual cell is to grow, but cellular growth is usually constrained somehow. Thus, instead of asking what causes cancer, we ought to ask what prevents cancer? What prevents deranged cell growth? SMT cannot answer these questions because it assumes cells are quiescent by nature.

Interestingly, after researchers proposed TOFT, their views were not met with opposition, but accusations that their theory was not meaningfully different from SMT. Bedessem and Ruphy argued that "Since [TOFT] shares with SMT its vocabulary, its ontology and its methodology, it appears that a claim of incompatibility based on this metaphysical plan is not fully justified in the present state of the debate" (2015). These authors fail to see that TOFT is proposing the development of a new vocabulary and ontology, because the existing mechanistic vocabulary and ontology is so deeply entrenched. The mechanistic metaphysical framework holds such a strong hold on the scientific community that publishers will reject papers that do not use the mechanistic vocabulary, and will even explicitly demand that researchers specify a "mechanism" in order to be published. This publishing demand and an inability of peer researchers to see the deeper argument of TOFT is evidence that a deeper metaphysical framework is restricting the field. As I will argue below, the problem is not that the mechanists are

allowing metaphysics to guide their methods, but rather that the attitude they assume towards their preferred metaphysical framework is that it is the only possible option.

Bertloaso and Dupré believe that what SMT gets most fundamentally wrong is its mechanistic metaphysical view of the biological world, and explicitly reject this account. As they write:

> Overall, SMT is incapable of providing a satisfactory explanation of the characteristics of tumor cells, as well as the neoplastic process as a whole. In principle, SMT is not compatible with an explanation of cancer that construes it as an aberrant process of development, or as the disruption of the homeostatic mechanisms governing the normal proliferation of the cells. (2018, p. 328)

Instead they argue that explanations and investigations of cancer need to use methods and explanations that accommodate the metaphysically correct (processual) view of cancer. They explicitly suggest modeling explanations or "morphogenetic field" explanations as alternatives to mechanistic explanation that are compatible with a processual understanding of causation. The key point, however, is that explanations that have the wrong underlying metaphysical presuppositions cannot be used and will be fundamentally mistaken. Bertloaso and Dupré are arguing that an explanation is flawed because of its underlying ontology.

Collectively these scientists and philosophers can be understood as making an argument from metaphysics to methods as they are attacking scientific methods and explanatory frameworks on metaphysical grounds. Their argument runs as follows: If a set of methods requires that we presuppose the world to be a particular way, but we also know the world is not, actually, as it is supposed by this method, then we ought not use

these particular methods. And yet, inferences like this are commonly found in science, and in cancer research specifically.

Consider a historical case that is more removed from our present-day intuitions. For hundreds of years, doctors refused to operate on cancer, or only rarely performed operations to attempt to remove tumors. This was because the dominant theory was that of the Roman physician Claudius Galen. He had proposed around 160CE that cancer was 'trapped' black bile congealed into a mass (Mukherjee 2012). Galen had developed this theory based on the Greek anatomy of Hippocrates which said that the body was made up of four cardinal fluids. From this anatomical understanding, Galen abstracted that the tumor was a local manifestation of a systemic imbalance, an overgrowth of black bile. These beliefs about anatomy are an ontology – an understanding of what there is and what it's like. The physicians who believed in Galen's theory argued that the problem with simply removing a tumor was that it didn't treat the underlying problem, and that the excessive amounts of black bile circulating in the body would simply re-grow the tumor if the underlying problem remained untreated. Galen's theory of cancer was dominant for many hundreds of years, and was the reason doctors did not consider operating on cancer (Mukherjee, 2012). Their ontology, and its guiding metaphysical framework, shaped the methodological choices of hundreds of years' worth of physicians. It wasn't until anatomical studies failed to uncover any black bile in healthy subjects (Vesalius 1543) and dissected tumors were not black but a variety of colors (Baille 1793) that surgery was considered to remove tumors. This historical case clearly shows how metaphysics, ontology, and methods are entangled. An ontology is developed based on some

underlying metaphysical framework, and this in turn guides methodological choices, making some approaches seem promising and others impossible.

The situation we find ourselves in now closely resembles the moment that evidence against the ontology of the black bile theory of cancer began to emerge. We've discovered empirical evidence that contradicts the ontology of the predominant theory of cancer (SMT). We've discovered that mutations don't always occur before cancer develops and that cancer cells can be normalized by normal tissue. Researchers quickly recognized this contradicted the ontology of SMT. Accordingly, processualist philosophers and scientists are arguing for the need to revise our ontological picture of cancer, and to consider a change in the methods we use for studying and treating the disease. If the concepts underlying certain methods are faulty, it follows that we have good reasons to abandon not only the concepts, but also the methods, just as we had reason to abandon the prohibition on surgery as a treatment for cancer. The reasoning goes from a rejection of metaphysics to a rejection of methods.

2.4.3 Pluralism in Practice

Scientific research cannot take place in a metaphysical vacuum, as metaphysical frameworks are tied to methods through ontology, and methods rely on particular accounts of what there is in the world and what it's like. Although necessary, metaphysical frameworks can become an obstacle to scientific advancement when they prevent the use of innovative methods. This is seen in the case of the mechanists, who object to a different approach to cancer research on metaphysical grounds, and also in the

case of the Galenists, who refused to operate on tumors. These researchers unreflectively assumed that their current metaphysical framework was correct, to the detriment of progress. If they are not careful, processualists are in danger of placing this same methodological limitation on research. Through their attitude of passionate affirmation, processualists could limit research to only those methods that make use of their underlying processual metaphysical framework. Although it is important to use a metaphysical framework that is appropriate to the empirical evidence at hand, I argue in this section that the epistemic attitude we take towards such a metaphysical framework is equally important to scientific progress.

So far, I have illustrated the existing attitudes scientists and philosophers have taken to the role of metaphysical frameworks in cancer research. Mechanists unreflectively trust their metaphysical presuppositions, and generated a theory of carcinogenesis (SMT) based on their underlying metaphysical presuppositions. On the other hand, scientists and philosophers who encountered data that did not fit with SMT's mechanistic ontology developed a new ontology and metaphysical framework based on process. They argued that a theory of cancer ought to be derived from a processual framework, instead of a mechanistic one, because the processual framework is a more accurate metaphysical framework. Rather than an attitude of unreflective trust, these scientists and philosophers took an attitude of passionate affirmation towards their newly developed metaphysical framework. However, I believe that both of these attitudes towards the role of metaphysical frameworks in science are inappropriate. Given the pragmatic aims of science, and of cancer research in particular, I will argue, in this

section, that an agnostic attitude is more appropriate because it allows scientists and philosophers to make use of multiple frameworks, and this empirically constrained pluralism will increase our chances of success.

A conversation about methodologies should not be grounded on metaphysics, but rather ought to be grounded on pragmatic concerns for research success – especially in the context of cancer research. The reaction to the metaphysical presuppositions of scientific methods and explanations should not be prematurely restrictive. Rather, we ought to adopt a genuine pluralism about the metaphysical presuppositions allowable in science – especially when the potential upshot is a treatment or cure for one of the deadliest diseases in our society. Since our choice of metaphysical frameworks is underdetermined by empirical evidence, the problem with using only the mechanistic SMT is that it is metaphysically restrictive, and we ought to be using and testing more, not fewer, metaphysical conceptions of the world. Those interested in a processual account of cancer have given us good reason to explore new methods and explanations for cancer, but it would be premature to do away with substance-based ontological concepts entirely. Rather a response that does not limit methodological options is most appropriate. The pluralism that I am advocating for is a methodological pluralism. However, since methods, as we have seen, are based on metaphysical presuppositions, adopting a methodological pluralism requires that one has not restricted oneself to a single type of metaphysical framework. Thus, adopting a methodological pluralism, I contend, requires an agnostic attitude towards the metaphysical presuppositions.

Sometimes processualists claim to agree with this pluralist approach. Bertolaso and Dupré (2018), for example, explicitly argue for a pluralistic explanatory approach to cancer research. Dupré argues that a process ontology applied generally to biology provides deeper grounds for classificatory pluralism – that viewing the living world as a hierarchy of interlocking processes allows us to understand why there are many overlapping ways of dividing the natural world (Nicholson and Dupré 2018). He argues that "it is possible to see the processual character of biological entities as providing a deep explanation of why a multiplicity of ways of classifying such entities" (Nicholson and Dupré 2018). Yet there is an important difference between the pluralism needed to ground a variety of methodological choices that I am advancing and the classificatory pluralism Dupré is concerned with. Classificatory pluralism holds that there are many equally good ways of classifying the entities of the world, which can allow us to see genes, cells, organs, etc. as overlapping kinds. However, this pluralism says nothing of the metaphysical frameworks underlying such classifications. The pluralism called for by the complexities of cancer is not merely a classificatory pluralism, but a pluralism that validates the use of multiple methods, techniques and models, that have a variety of different underlying presuppositions in order to explain cancer in a variety of different ways. Some of these may be mechanistic, and call for a substance, not process, ontology. A classificatory pluralism, the sort of pluralism Dupré argues for, is supported by a process ontology, and might still presuppose a unified set of metaphysical presuppositions.

Therefore, the pluralism that is necessary is one of methodologies, not of classifications. A basic pessimistic meta-induction will tell us that our current scientific theories or metaphysical frameworks might turn out to be wrong (Chakravartty 2017). Using a variety of methods is the most appropriate response to our inability to know if our current theories are correct. The pluralism that I believe is necessary in the context of cancer research, has to do with allowing different approaches and methods to be taken in studying cancer. Further, since in the case of cancer there are high non-epistemic risks of harm and suffering if researchers are found to be in error – there is what Heather Douglas calls 'inductive risk' (2000). This inductive risk means that non-epistemic factors should be considered in making methodological choices. In this context, I believe that should mean preferring a methodological pluralism because it is more likely to find a successful treatment. In order to ground the use of many methods who's underlying metaphysical presuppositions might conflict, we need an agnostic attitude towards metaphysical frameworks[10].

Unfortunately, this sort of metaphysical pluralism is not permissible according to either the "unreflective trust", or the "passionate affirmation" attitudes towards metaphysical frameworks. These attitudes are grounded in a belief that *one* particular metaphysical framework is correct, and thus that this chosen metaphysical framework ought to guide all methodological choices. While Bertolaso and Dupré obviously understand the value of a pluralistic approach to cancer research, the arguments they offer

[10] Anya Plutynski (2018) argues for a pluralistic approach to cancer research, although on very different grounds. Plutynski argues that cancer research is problem (or puzzle) driven, which would ultimately be compatible with the sort of pluralism I'm interested in here.

are not, in fact, compatible with a requisite diversity of methods. The arguments that processualists offer in critique of the mechanistic approaches to cancer research are about their metaphysical inadequacy. Dupré argues that mechanistic approaches cannot be adequate "because it presupposes an ontology in which substances at least play a central role" (Nicholson and Dupré 2018, p. 29). Processualists argue that this reliance on a substance ontology limits the power of the framework. Their argument cannot be that all methodologies with any sort of metaphysical presuppositions can be used in researching cancer; instead, their argument must be that a variety of methods, all of which are compatible with their processual metaphysical framework, and an ontology that views cancer and biological entities as processes (not things), can be used in researching cancer. So while there are a variety of good reasons to take processual ontology seriously, and engage in processual research, we need to make sure we maintain an agnostic attitude towards the ultimate status of the framework.

Neither a mechanistic framework nor a processual framework on their own can ground a metaphysical pluralism that validates a wide array of scientific methods. The inability of a restrictive metaphysical framework to validate the use of certain methods is exactly what grounds the processualist critique of mechanistic explanations. Processualists argue that mechanistic research obscures some scientific possibilities because it cannot use processual concepts. Yet it seems the processualists have committed the same sin they accuse the mechanists of as they cut off avenues of research by advocating for a singular guiding metaphysical framework. Process ontology explicitly calls on us to use a particular (and in the view of those advocating it, the one

and only correct) metaphysical picture of the natural world. Far from giving us permission to use a variety of different concepts, the processual account demands that the concepts we use need to be of a quite particular nature. Instead, if one is interested in selecting methods one should argue for the importance of processual thinking on pragmatic (rather than metaphysical) grounds. A pragmatically motivated metaphysical pluralism would allow researchers to make use of different, potentially conflicting, guiding metaphysical frameworks in so far as they allow fruitful research projects.

Despite the fruitfulness of the substance ontology and the compelling arguments for a process ontology, the metaphysical debate is far from settled. Most simply perhaps, we can acknowledge that the present state of our scientific knowledge at any given moment underdetermines our choice of metaphysical frameworks. Even Dupré and Nicholson admit that there are "many reasons for thinking that the living world is a world of processes rather than a world of things, although we do not take this to demonstrate conclusively that the world is processual throughout" (2018, p. 4). If cancer is not processual throughout, but only in certain respects and degrees, then restricting ourselves from potentially fruitful avenues of research because they make different metaphysical assumptions is uncalled for. Given the moral consequences of this metaphysical choice, we ought to pursue as many empirically promising avenues, using as many different frameworks as we have good evidence to support, in order to increase our chances of finding success in reliable treatments for cancer.

While it is undeniably important that we recognize the long-ignored metaphysical foundations of our methods and explanations in science, this does not mean that we need

to base our decisions about methods solely on metaphysics. Instead, we need to adopt an agnostic attitude towards metaphysical frameworks. Given the difficulty of settling theoretical metaphysical debates, and the grave importance of advancing biomedical research to save lives, an open-minded approach to metaphysical frameworks that allows for pluralism of methodologies in practice is the best route forward. This will allow us to continue pursuing those successful portions of research guided by mechanistic assumptions, but will also make room for a processual approach to cancer research in other cases (or even some undiscussed alternative approach). Processualists are making great strides in advancing cancer research, and these new and exciting avenues of research should be pursued. However, attempting to generate methodological arguments from metaphysical grounds alone is incompatible with the sort pluralism that is arguably required for success. Since all of our modes of explanation and methodologies come with metaphysical presuppositions, if we wish to make an argument for explanatory or methodological pluralism, it cannot be based on a restrictive attitude towards metaphysical presuppositions. Instead, we should turn to the pragmatic aims of science to ground explanatory or methodological pluralism. The practical ability of different metaphysical presuppositions to guide novel research is paramount, especially in the life-threatening context of cancer, where there are large non-epistemic risks involved in our choices (Douglas 2000).

While this section has examined cancer research as a case study, these methodological considerations can be extended to scientific research more generally. Metaphysical frameworks will always be underdetermined by empirical research; thus we

cannot be justified in having the attitude of passionate affirmation. We can at best pursue a line of research based on a metaphysical framework with good evidence, while keeping ourselves open to the possibility of the failure, not only of the research project, but also of the framework more generally. Also, since there will sometimes be inductive risk involved in research choices, it is ultimately more risk avoidant to pursue lines of research based on multiple justified metaphysical frameworks.

2.5 Conclusion

This chapter has demonstrated a link between the metaphysical frameworks that researchers (consciously or unconsciously) hold, and their methods. Recall that when scientists set out to explain human digestion, they set out looking for certain kinds of objects – specifically parts with definable properties that play a particular role in the phenomenon in question. Scientists were doing this because they had something like the mechanistic framework in mind. In so far as researchers were to rely on mechanistic concepts to frame their research, they would be unable to adequately understand human digestion, because it has properties which defy the mechanistic desiderata. We have good reason to suspect that scientists who continue to take a mechanistic approach to phenomena that have one or more of the five properties discussed throughout this chapter will continue to have problems generating adequate explanations. In short, the metaphysical nature of the objects in the world can generate explanatory problems for mechanists because their approach makes use of ontological concepts that do not match the phenomena. Therefore, I have pointed out a few examples of scientific concepts that

are processual in nature such as the pan-genome for bacterial "species" and the metagenome of a sample. As we continue to develop new concepts and examine the world as we've found it, we need to remain open to processual ontological concepts that focus on how stabilization is maintained rather than on facts about stability.

In this chapter I have shown that these problems for mechanists are pervasive in phenomena in the biological world. Our ontology ought to respond to empirical demands – the cases I have discussed put pressure on the mechanistic ontological concept, and give us reason to think of the biological world in terms of a process ontology. Mechanistic frameworks are limited, and are systematically obscuring some specific insights that would be better revealed using another framework. If we can find ways to adopt a process ontology, we will broaden the scope of what our science is capable of understanding. Recall that before the development of metagenomic analysis, scientists believed that humans had substantial differences in the microbial flora found in their GI tracks. However, using a more sophisticated processual understanding of bacteria scientists were able to discover that despite superficial differences in lineage, the bacteria in human GI tracks actually constitute a relatively stable metagenome. Using their understanding of how bacteria are maintained and stabilized, scientists were able to better understand one phenomenon of interest: human digestion. The pervasiveness of interactivity in the natural world, suggests that a processual approach to nature more generally could illuminate many yet unexplained phenomena. In such cases, the mechanists are missing something important, and we have good reason to think they will continue to miss this important aspect of the world. Even if it were one of the most useful

frameworks to use, since, we've already spent a great deal of time looking at the world mechanistically, another framework might be worth exploring.

However, I have also pointed out that this move from metaphysics to methods is ultimately fraught. While there are good reasons to suspect the importance of a process framework, making decisions based on metaphysical presuppositions can ultimately limit scientific progress. Metaphysical frameworks will always be underdetermined by empirical research. Knowing this makes the risk of depending on only one framework unnecessary. Having an agnostic attitude towards a variety of well supported possible metaphysical framework allows multiple fruitful research programs to be perused side by side. The idea of this sort of pluralism has been defended (e.g. Feyerabend 1975), although it a very different context. While I have argued for the importance of paying attention to how metaphysics can shape and limit our research, my ultimate argument is not for one specific framework, but for a recognition of the overall role of metaphysics in scientific research.

The necessity of paying attention to our metaphysical frameworks in science is highlighted by thinking carefully about time in biology. The mechanistic metaphysical framework that has been dominant in biology for quite some time licenses the suppression of time as an aspect of biological systems. While this might be perfectly effective in some cases, another framework (like the process framework) that takes account of the role of timescales in biological entities can expose other limiting aspects of these systems. This chapter has explored how paying attention to time can shift the metaphysical framework that seems most fit to frame biological science. The next chapter

will examine cases in which biologists do not ignore or abstract from time, but rather where they directly try to measure it.

CHAPTER THREE

BIOLOGICAL CLOCKS AND THE USEFULNESS OF MULTIPLE LINES OF EVIDENCE

3.1 Introduction

Chapters one and two have given us a good sense of some of the ways biologists have obscured time in their research, but this chapter will focus on those parts of biology that seek to measure or reconstruct time. Part of understanding life on Earth is the development of a timeline that can tell us when and for how long dinosaurs roamed or when exactly the last common ancestor of humans and bonobos existed. As easy as these questions are to pose, they are extremely difficult to answer. One of the largest problems researchers face in trying to date events in the biological past is that there are no ready-made instruments or methods for measuring how long ago something happened. While we already have a unit of interest (year), and we know certain events happened in the past, researchers have needed to invent ways to measure how long ago the events happened. This chapter will explore how those methods work, as well as the ongoing process of refining them.

In this chapter I will explore two specific methods scientists have developed for telling time into the deep past: the molecular clock (which uses changes in nucleotide or amino acid sequence to tell time) and the biostratigraphic clock (which uses fossil features and stratigraphic placement to tell time). One challenge, however, is that these methods don't always agree (i.e. they are discordant). Sometimes the discrepancies are small but in other cases the disagreements can be quite large. Since both of these methods

have important limitations, scientists have started using them in conjunction with one another to develop even better date estimates. I will use key episodes in the development of dating methodology to highlight the epistemic features of using multiple lines of evidence; how can these clocks, despite their limitations, give us information about the deep past? Some have argued that discordant lines of evidence cannot be jointly epistemically useful (Stegenga 2009), and other have argued that different lines of evidence need to be independent in order to be jointly epistemically useful (Wylie 1999; Forber and Griffith 2011; Stegenga 2009). I will argue that discordant lines of evidence can jointly support a single hypothesis, and that interdependent lines of evidence can jointly increase the reliability of a particular hypothesis.

In section 3.2, I will describe the biostratigraphic clock (also known as the fossil clock), and section 3.3 will detail the development and function of molecular clocks. Section 3.4 will explain in detail how biostratigraphy has been used to calibrate molecular clocks, and how improving this process of calibration has been key to the improvement of molecular clock dating. Despite this close relationship, important differences between molecular clock estimates and biostratigraphic clock estimates remain. Section 3.5 will examine some of these discrepancies and the three predominant strategies for overcoming them. These methods are: first, using molecular clock estimates to revise how fossils are categorized and dated, second, changing how the fossil record is used to calibrate molecular clocks, or third, using an external arbiter to help guide dating decisions. Finally, section 3.6 will explore the consequences of this case study for existing debates about how multiple lines of evidence are epistemically useful. I will

argue that independence is not a prerequisite for the epistemic usefulness of multiple lines of evidence, and that discordant lines of evidence can be used to support the same hypothesis.

3.2 The Fossil Clock

Stratigraphy is the study of the layering (stratification) of different rock layers (strata). Biostratigraphy is a branch of stratigraphy that organizes strata based on the fossils they contain. In an important sense, biostratigraphy is considered an objective categorization based on the paleontological content of different layers of rock. However, the biostratigraphic clock is considered a relative-time clock because the ordering is not inherently linked to any numerical dates in particular. The biostratigraphic clock needs to be anchored to an absolute numerical time, in order to provide dating information beyond a sequential ordering.

Biostratigraphy is based on the idea that species have a "life-span". Ordinarily we think of the life span as the length of time an organism is alive. Similarly, for species, the "life span" is the length of time the species is in existence, the time from the appearance of the very first member of a species to the death of the very last member of the species. According to the law of superposition, lower layers of rock are older, and thus, the vertical layering of strata are considered evidence for the passing of geological time. Scientists call the vertical space in which fossils of a certain species are found its "range", which is taken to be representative of the life span of that species. The range for a species is defined in terms of two stratigraphic "horizons". A species is absent below the lower

horizon, but present above it. Similarly, a species is absent above the upper horizon, but present below it. Thus, the lower horizon contains the lowest occurrence (LO) of the species, which marks the oldest stratigraphic layer in which a species is present. Similarly, the upper horizon contains the highest occurrence (HO) of a species, which marks the youngest stratigraphic layer in which the same species is present.

The idea of "faunal succession" tells us that groups of organisms follow one another in a particular order in the fossil record, and was developed before the publication of the theory of evolution by natural selection. However, as the theory of evolution by natural selection explains the ordered organization of successive groups of species in successive layers of earth, it offered important explanation for faunal succession. The concept of faunal succession paired with the law of superposition (newer rock layers are found on top of older rock layers) provide for geoscientists the "arrow of time" (Gould 1987), that is, the sense of temporal ordering moving in a particular direction towards the present. However, biostratigraphy can only provide a relative ordering for the succession of different lifeforms on earth. Biostratigraphy must be linked to an absolute dating method to provide numerical dates for events in the deep biological past.

Some stratigraphic layers can be dated using radiometric dating tools. The materials that can be dated radiometrically are limited to zircon crystals (U-Pb) or potassium based minerals (Ar-Ar) from volcanic eruptions. Successive volcanic ash layers can bracket the ages for fossils contained in the layers between them. While biostratigraphy provides a relative dating for fossils, radiometric dating provides an

absolute numerical dating for rocks (Peppe and Deino, 2013). Radiometric dating compares the abundance of naturally occurring radiometric isotopes and their decay products. While all elements contain protons, neutrons, and electrons, only the number of protons is constant for a particular element). Isotopes are instances of the same element with different number of neutrons, and are defined by their atomic mass (the number of protons plus the number of neutrons). For example, carbon has six protons, but can have six (carbon 12), seven (carbon 13), or eight (carbon 14) neutrons. Some isotopes are unstable and will decay over time. For example, carbon 14 is unstable and will decay to nitrogen 14 (7 protons and 7 neutrons) over time (Peppe and Deino 2013). Scientists have found that the rate at which radioactive isotopes decay is unique and regular. As such the amount of time it takes for half of the unstable parent isotope to decay into the more stable daughter isotope is known as the half-life of an isotope. When the ratio of unstable isotope to daughter isotope is 1:1 scientists know that one half-life has passed. Different isotopes have different rates of decay (meaning isotopes are only useful for dating things in a particular age range), and are found in different kinds of rocks (meaning one cannot rely on the right kind of isotope always being in the right place). Accordingly, scientists use many different types of radiometric isotopes to date different sorts of rocks. While radiometric dating has many of its own complications, biostratigraphy often depends on radiometric dating for defining the age range of a particular fossil occurrence.

Geologists categorize geological zones using biostratigraphy in order to help them determine the relative age of different strata. Biostratigraphic zones (or ‘biozones’) are measured by their thickness and defined by aspects of their fossil content. Different types

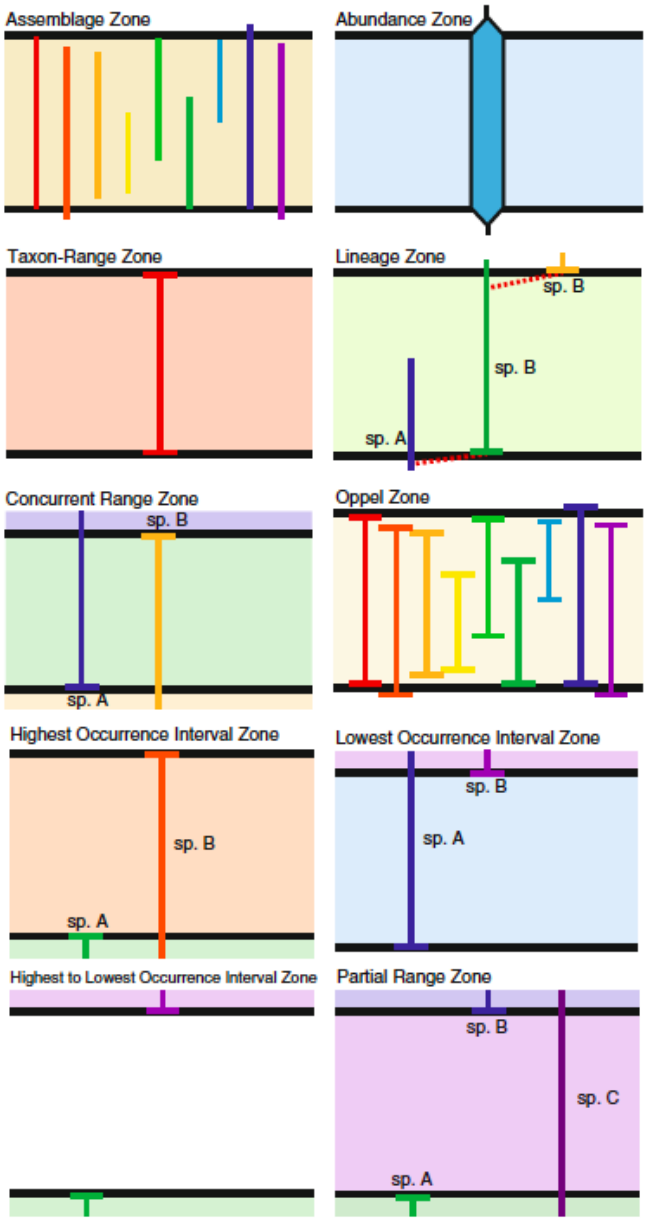

Figure 3. 1 Types of Biostratigraphic Zones (as found in Aubrey, 2014).

of biozones are shown in figure 3.1. While many biostratigraphic zones are marked by the LOs and HOs of specific species of taxa, there are other horizons that can also be used. For example, layers where the abundance of a species is considerably increased can be considered a different type of horizon in defining a biostratigraphic zone (top right in figure 3.1). Most simply, biostratigraphic zones can be defined by their boundaries or their content (including the occurrence(s) or relative abundance of different species).

Scientists extend biozones laterally through a process called 'biostratigraphic correlation'. If a scientist can identify the biohorizons (the surface along which there is a

distinctive change in the fossil occurrences) associated with biozones at distant locations that have been formally defined, then they may draw lines of correlation between them. This lateral extension is essential for determining if the presence of similar fossils is a marker of temporal similarity or not. Different types of biozones have different strengths and weaknesses, which make this lateral extension more or less reliable. Typically, concurrent-range zones (center left in figure 3.1) and taxon-range zones (second from top left in figure 3.1) are considered the most reliable for lateral extension because they are defined by both their content and their boundaries. However, as Aubry (2014) points out, these two ranges cannot be in immediate succession "but are necessarily separated by a highest occurrence interval zone, a highest to lowest occurrence interval zone, or a partial range zone, which are less reliable" (p. 98). Thus, researchers are inevitably forced to identify zones in ways that make their lateral extension more challenging.

There are a large variety of other problems with the lateral extension of biozones, making relative dating across geographic regions even more difficult. These difficulties include taxonomic factors surrounding the formation and preservation in the fossil record and the sampling thereof (anomalous occurrences, displacement, insufficient record or recovery, etc.) (Pearson 1998). There are also difficulties surrounding taxonomy (e.g. inconsistent identification). The Signor-Lipps effect explains how sampling bias can cause the disappearance of a species to appear gradual, when it, in fact, was not (Signor and Lipps 1982). While many had argued that the gradual decline of a species in the fossil record was evidence against a mass extinction event, the Signor-Lipps effect explains why this need not be the case (Signor and Lipps 1982). However, this also

places limitations on our ability to reconstruct the past, since the fossil record may ultimately be unable to record the difference between gradual and sudden extinction events (Forber and Griffith 2011, p. 12) Since, the absence of a fossil of a particular species might be due to the difficulties in fossil preservation, and not, in fact, indicative of the species absences from that temporal range, it becomes difficult to use fossils to infer precise temporal knowledge of the past. In general, these difficulties surrounding fossil formation and recovery become epistemic problems as fossil occurrences cannot always be taken as reliable signifiers of the historical events of speciation and extinction. Further, as the concept of a biozone is dependent on the taxonomic concepts in use, any uncertainty in our understanding of taxonomy will lead to uncertainty in our identification of biozones. A major source of difficulty then is the conflict between different understandings of the species concept that operate in different fields. Paleontologists working with the fossil record typically work with a typological (or morphological) concept of species, while biologists studying living groups typically rely on a population concept (McGowran 2005). There are great difficulties, in general, in defining the species concept. At least twenty different versions of the concept have been proposed by scientists and philosophers (Hey, 2001). Difficulties identifying and defining species may also become difficulties in identifying biohorizons and using them to infer temporal orderings.

The fossil record is notoriously incomplete. Fossils are the remains of formerly living organisms that have been preserved in the rock layers of the earth. Different features of organisms have different potential to survive as fossils depending on their

chemical structure and on the environment in which they find themselves upon their death. Sedimentation is neither continuous nor uniform, and not all rock deposits are equally good at preserving fossils. Thus, the probability of becoming a fossil is non-random; instead the fossil record is spatially and temporally biased. Further, the recovery of fossils is biased by exposure and access, as well as the interest of scientists in particular types of fossils. While fossil order can provide, at least to some degree, a relative ordering of species appearances, the calculation of absolute dates for particular fossil occurrences requires additional information and nontrivial inference. For example, surrounding rock layers can be dated radiometrically, and then scientists use that date to determine the age of the fossil. Sometimes dating the surrounding rock is not possible, and then scientists date the rock through stratigraphic correlation with other locations that can be radiometrically dated.

According to some, one of the main purposes of developing biostratigraphic units is to uncover the temporal significance of biohorizons. However, this is also one of the most difficult tasks facing biostratigraphy. Biostratigraphy is used as a check on the other forms of stratigraphy (e.g. magneto-stratigraphy and sequence stratigraphy) in the development of geochronology (the dating of rock formations and geological events). The LO and the HO of a species are, through this process, converted into events with dates (e.g. appearance and extinction). The chronology is an inference made from the biostratigraphic information, but is not itself objectively observable. For starters, it is almost certain that LO and HO do not correspond to the events of first appearance and extinction respectively, because of delayed LOs and premature HOs. Further, there is the

problem of whether the LO or HO of a species at distant locations correspond to the same time. This is called the problem of "diachrony" in geology. For example, researchers found that in marine samples *Globorotalia truncatulinoides* first occurs about 2.4 M between 20 º and 35º south latitude in the southwest Pacific, which is 0.5 million years earlier than in other locations (Dowsett, 1988). In this case, researchers argued that the temporal differences suggest that *G. truncatulinoides* originated in the south Pacific, and later migrated elsewhere (Dowsett, 1988). An alternative interpretation could have been that the gap of 0.5 million years is simply a mistake in the fossil record. It is important for researchers to sort out if observed diachrony is due to slow migration or to a gap in the record. Failure to distinguish between aberrations and accurate unexpected data can lead to poor correlations and incorrect dating.

3.3 Molecular Clocks

Historically, the phrase 'molecular clock' referred to what was believed to be a constant rate of molecular change that could be used to tell time. However, as researchers discovered that rates of molecular change are not constant even within particular species or lineages, 'molecular clock' came to refer to a method of analysis that is used to estimate evolutionary timescales using information about nucleotide sequences in DNA or amino acid sequences in proteins.

Emile Zuckerlandl and Linus Pauling (1962) were among the first scientists to develop the hypothesis that proteins undergo amino acid replacement at a consistent rate. Zuckerlandl and Pauling developed their hypothesis based on their analysis of globin

proteins from vertebrates. They used data from the amino acid sequence of globin proteins in horses compared to humans in order to estimate the divergence of humans and gorillas. The hypothesis of clocklike molecular evolution expanded rapidly after Zuckerlandl and Pauling's original publication. In the five years that followed other researchers reported similar relationships between amino acid substitution in fibrinopeptides (Doolittle and Blombäck 1964) and albumin (Sarich and Wilson 1967).

While the concept of the molecular evolutionary clock, as Zuckerlandl and Pauling named it in 1965, was greeted with skepticism by some scientists, the development of the "neutral theory" of molecular evolution gave a large boost to the development of molecular clocks. The neutral theory states that many mutations have no effect on the fitness of an individual organism, and thus they can be considered "neutral" from an evolutionary perspective. This occurs because many amino acids have similar enough biochemical properties that they can be substituted for one another without changing the properties of the protein. Similarly, in the case of DNA, single nucleotide changes to sequences are often synonymous and they will not ultimately lead to a change in the amino acid sequence of the protein. The neutral theory was proposed separately by Motoo Kimura (1968), and Jack King and Thomas Jukes (1969), who cited a wide range of evidence for their theory. Interestingly, one of the predictions of the neutral theory is constant rates of molecular evolution among lineages. The neutral theory and molecular clocks lent support to one another in their early days.

While some suspected that the neutral theory was an ad hoc attempt to save a theory of genotype frequency, its historical development shows how tied the theory has

always been to the molecular clock. Understanding how the concept of a molecular clock is tied to ideas about molecular chance can help us understand how some bias may be built into molecular clock models. Prior to the development of the neutral theory, panselectionism – the idea that natural selection is the dominant mechanism of biological evolution – was the predominant view among evolutionary scientists (Dietrich 1994, p. 21). Since selection was understood to be the leading evolutionary force, debates in biology were over things like the nature of genetic variation: would we expect to see more individuals that are homozygous (have two of the same copies of an allele) or heterozygous (have two different alleles at a given loci) (Dietrich 1994, p. 23). The debate at the time was between the so-called "classical" and "balance" positions regarding the nature of genetic variation. The classical position held that most loci would be homozygous due to purifying selection (selective removal of harmful alleles), while the balance position held that heterozygous genes would be more common due to balancing selection (a family of selective forces that maintain multiples alleles, for example frequency-dependent selection) (Dietrich 1994, p. 23). Many, including Richard Lewontin, saw the neutral theory as an extension of the classical position in the debate over genetic variation (Dietrich 1994, p. 24). The classical position needed a way to explain a series of experiments conducted by Jack Hubby in 1966, which found high levels of heterozygosity. The neutral theory could explain that heterozygous loci are caused by neutral polymorphisms rather than by balancing selection. One could then maintain that most selected loci would be homozygous due to purifying selection. However, Michael Dietrich argues that this is only half of the story of the development of

the neutral theory, and ignores the importance of molecular biology to its development. The other half of the story shows how the neutral theory has been linked to ideas of a molecular clock since its inception.

While Hubby's results came from the newly developed electrophoresis techniques and were predominantly used in the fields of population and evolutionary genetics, the field of molecular biology had also been rapidly developing since Watson and Crick's discovery of the double helix structure of DNA. For example, comparative studies of mammalian hemoglobin resulted in a high estimated rate of nucleotide substitution (one base-pair replacement every 1.8 years). Kimura's 1968 paper argued that the selective pressure on the population would need to be intolerably high, unless most of the mutations were neutral in natural selection (Dietrich 1994, p. 47-48). Kimura's argument from selective cost turned out to be mistaken[11], but King and Jukes justified the neutral theory on slightly different grounds. They argued directly from the constancy of the rate of molecular evolution to the neutral theory (Dietrich 1994, p. 50). According to the neutral theory, the rate of molecular change is independent of population size and the environment, and thus one would expect a constant rate. However, according to the selectionists the rate is not independent of population size and environmental effects, and thus they could not explain the observed rate constancy (Dietrich 1994, p. 52). The arguments for the importance of random genetic drift is deeply connected to results in molecular biology (Dietrich 1994). While the electrophoresis results put the need to explain heterozygosity at center stage in evolutionary genetics, the primary support for

[11] Kimura's cost of selection arguments received rebuttals from a variety of sources, including King and Jukes. See Stebbins and Lewontin (1972) and Maynard Smith (1968).

the neutral theory came from molecular biologists studying rates of molecular change. The neutral theory provides a mechanism for the molecular clock, and the development of this theory is inextricably linked to the initial observation of rate constancy that spawned the molecular clock. This deep historical tie between the neutral theory and the molecular clock can help us understand the interactions they share even today.

In the 1970s interest began to grow in mutations that were neither completely neutral nor deleterious nor beneficial. These so-called "nearly" neutral mutations were defined mathematically as those whose selection coefficient, *s*, was nearly equal to the reciprocal of the population size, $s \approx 1/N$ (Ohta and Gillespie 1996, p. 130). Highly deleterious mutations, $s \gg 1/N$, are driven out of a population by natural selection, and advantageous mutations were thought to be so rare as to make only a negligible contribution to the totality of substitutions. Tests, like the Ewens distribution test, were used to determine the agreement between the neutral theory and observed polymorphisms, mutation with $s \ll 1/N$ were treated as neutral, $s = 0$ (Ohta and Gillespie 1996, p. 130). If nearly neutral mutations, $s \approx 1/N$, were common in a population, there would be a negative correlation between the evolutionary rate and the population size (Ohta and Gillespie 1996, p. 131). This would contradict the independence from population size and environmental effects proposed by the neutral theory. Kimura and Ohta used the neutral theory to estimate the population sizes, between 10^4 and 10^5, that would be necessary to make the neutral theory true (1971). However, these estimates proved not to hold for actual populations (e.g. *D. willistoni* was estimated to have a population size of 10^9 (Ayala et al., 1972)). Tomoko Ohta proposed

the *nearly* neutral theory of molecular evolution in 1973 as a solution to this problem (Ohta and Gillespie 1996, p. 132). The nearly neutral theory modifies the neutral theory to account for the fact that some mutations are only driven from the population if their selection coefficient is greater than the inverse of the population, and thus accounted for the presence of nearly neutral mutations ($s \approx 1/N$). The story began as a change from selective mutations only to the acceptance of neutral mutation, has become a story that recognizes the larger variety of DNA changes.

In the 80s and 90s, scientists began to develop statistical tests for the clocklike evolution of genetic data (Ho 2015). Using these tests researchers began to observe that genetic changes did not, in fact, always occur at constant rates. Instead, rates were found to vary along a variety of different axes. So-called "lineage effects" result from the sorts of concerns that drove critiques of the neutral theory. Factors like generation time can lead different lineages to have different rates of molecular evolution (Lee and Ho 2016). "Site effects" refer to differing rates of evolution within lineages at different DNA sites. For example, functionally important genes often evolve at an extremely slow rate because new mutations can be extremely detrimental (Lee and Ho 2016). Nuclear DNA evolves more slowly than mitochondrial DNA in animals for reasons that are still poorly understood. Rates of molecular changes can also vary within a lineage depending on the time (or era) during which one observes such changes (Lee and Ho 2016). Even more complex are the interactions between all of these different types of rate variation. For example, site effects can interact with generation time effects when different genes have different patterns of rate variation across taxa (Lee and Ho 2016). Research into the

different causes of rate variation —including those discussed here, and others like body temperature or exposure to ultraviolet radiation— is still ongoing. Despite the fact that researchers no longer believe the original idea of invariant regularity in mutation rate, scientists have still sought to use molecular change to date events in the biological past.

Since pressure has been put on the idea of a unified rate of molecular evolution, scientists have developed a variety of different statistical techniques for their continued use in phylogenetic analyses. In contrast with the "strict" or "global" models which assume constant rates among all lineages, newer statistical models allow the evolutionary rates to vary among types of organisms. However, there are a variety of ways in which different models understand this rate variation. Figure 3.2 shows a simple way of understanding some differences in molecular clock models. In figure 3.2, the thickness of each line represents the magnitude of the rate of molecular change for that group of animals. Accordingly, we can see that in the strict clock all lineages are assumed to have the same rates of molecular change, as represented by lines of the same thickness.

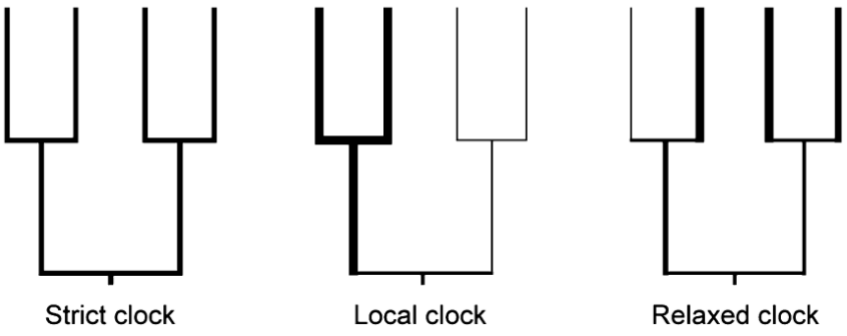

Figure 3. 2 Three different classes of molecular clocks, the thickness of each line represents the magnitude of the evolutionary rate along the branch (as found in Ho 2015)

Local clocks assume that the variation in rates among branches can be described using a few discrete rates. Since individuals sharing a common ancestor can be expected to share

many biological features with one another, scientists can expect they would also share a reasonable number of the traits that influence the rate of evolution. Rate-smoothing methods treat the rate of evolution as a heritable trait that can evolve over time for the same reason. However, these models include the assumption that rates would be similar, but not necessarily identical. Thus, they penalize large changes in evolutionary rates between neighboring branches in their models. Relaxed clocks on the other hand use an explicit model of rate variation without making any assumptions about the causes of this variation. In auto-correlated models (also known as rate change models), the rate is assumed to change gradually along branches of the phylogenetic tree. In uncorrelated models of rate change, there is no programed similarity between the rates along branches of the phylogenetic tree. Currently there is little biological information incorporated into these models of rate variation and as researchers understand rate variation it will be important to begin including such information in models (Ho 2015).

There is also a problem of information destruction in the use of molecular clocks. This can be seen most simply in the case of 'multiple hits' (Page and Holmes, 1998). Over a long enough period of time, many sites along a length of DNA or in a protein sequence will have undergone multiple mutations. However, it is not possible to detect more than one such change. Even if one assumes a constant rate change, the rate of change that we are able to observe would eventually level off because of this inability to observe multiple changes at the same locus. There are a variety of ways that multiple changes can be obscured when one observes particular extant lineages, as illustrated in figure 3.3. In figure 3.3a, we can see a single mutation is marked by a single difference

between the nodes of interest. However, figures 3.3b-f illustrate the various ways that multiples changes will not always be accessible simply by observing the nodes of

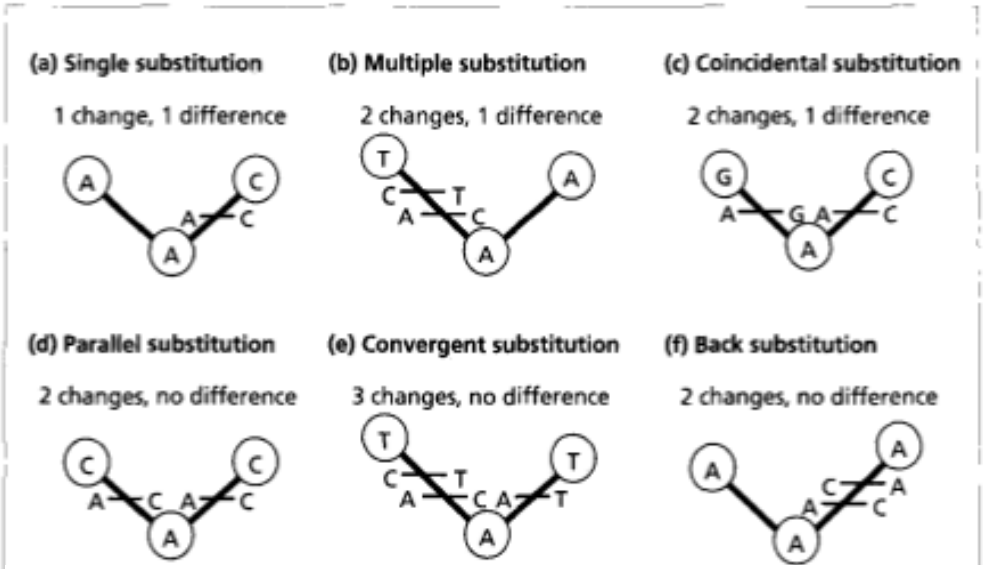

Figure 3. 3 a-c show DNA sequences changes over time lead to only one observed difference between extant lineages; figures d-f show three options for no observed differences (as found in Page and Holmes, 1998).

interest. For example, in figure 3.3b there have been two substitutions in one lineage, but there is still only one observable difference between the nodes of interest. At shorter times scales, observed variation and sequences can represent momentary changes that will eventually be lost as opposed to those changes that will eventually move to fixation. The inclusion of mutations that will not become fixed can lead to the calculation of a much higher evolutionary rate. In each of these cases, different natural processes lead to information loss – facts that researchers are unable to access, such as the real number of changes between two particular lineages.

Elliott Sober and Mike Steel conducted an analysis of how evolutionary processes destroy information over time (2014). While their research generally confirms the adage

that the evolutionary process destroys information over time, the picture they uncovered was a bit more complex than that. For example, selection for some particular allele makes it easy to drive that allele to fixation. Thus, when an allele has been selected for, the present proportion of the population that has that allele provides "scant" evidence of the past proportion of the population that had the allele (Sober and Steel 2014, p. 567). However, if the allele that has achieved fixation as the result of drift or the result of negative selection (i.e. selection against that allele), one could infer more about the prior status of the allele in the population (Sober and Steel 2014, p. 567). Not all evolutionary processes destroy information at the same rate, and accordingly understanding how information is preserved or destroyed by evolution is important for understanding how to date events in the deep past and infer the passage of time.

While molecular change can provide information about events in the biological past, as in the case of fossils, it is important to keep in mind the particular complication inherent in molecular information. As we saw with biostratigraphic clocks, there are unique difficulties that molecular clocks face in the quest to measure time in the deep past. Both of these clocks only provide a relative ordering of events, and must be tied to an absolute date in order to produce numerical date estimates. In biostratigraphy this is done by tying the fossil locations to rocks that are dated radiometrically. In the next section, we will see how molecular clocks are calibrated, most commonly by using the fossil record.

3.4 Calibration of Molecular Clocks

One important area of overlap between fossil clocks and molecular clocks comes through the process of calibration. Molecular clock models can provide a relative timescale for the divergence of different lineages, but it cannot provide the absolute dates for such divergences. When scientists use molecular clocks they need to be "calibrated", in other words, an absolute date needs to be assigned to one or more nodes of the phylogeny (Warnock 2015). If you fix a date for one event on the phylogenetic tree, this can act as a reference point for estimating the ages of the other nodes. For example, if one fixes the date for the split between mammals and birds, then using a calculated rate of molecular change, combined with data on observed changes between different lineages one can date other events in the phylogenetic tree (like the split between different mammal subgroups). The date that is used to fix the first point in the phylogeny can be obtained in a number of ways. Most frequently calibrations are based on the fossil record. For example, in a phylogeny of vertebrates modern birds must be at least as old as the most ancient fossil that can be robustly assigned to that group (Lee and Ho 2016). Less frequently, calibration is tied to well-dated geological or tectonic events like island formation or the separation of continents, which one has good reason to suppose effected the taxa in question (Warnock 2015). Finally, and least ideally, previous estimates that have been made using molecular clocks can be used to calibrate a new clock (Lee and Ho 2016). This is done when other calibrating information is not available and is called "secondary calibration" (Lee and Ho 2016). Since there is uncertainty associated with any of these dating methods, the calibration process for molecular clocks has been of

great debate among scientists. In this section, I will focus on the use of the fossil record in calibrations.

How the molecular clock is calibrated needs to account for uncertainty arising from the incompleteness and bias of the fossil record. Since the fossil record can never provide precise temporal information about the origins of a last common ancestor, models need to account for the uncertainty surrounding chosen calibration points. Originally "strict" or "global" molecular clocks required the assumption of a fixed date in the calibration of their clocks. However, newer versions of the molecular clock do not require this assumption. Instead scientists assume that the order in which organisms appear in the fossil record matches the order in which the corresponding branches of the tree of life emerged. These newer clocks require that calibration provides both minimum and maximum constraints, meaning a minimum date of the last common ancestor and a maximum date of the last common ancestor. Minimum constraints can be calculated from an individual fossil specimen. If one has a well-identified occurrence of a species or lineage of interest, and that occurrence can be robustly dated, this can be considered the minimum constraint. Since, at minimum the divergence event must have happened before the occurrences of the specimen in question, this constraint can be fairly well established. Unfortunately, minimum constraints cannot be used on their own, and maximum constraints are very difficult to calculate. For example, in much of the literature the mammal-bird split has been dated at 310±0 million years ago (Ma) (Graur and Martin 2004). Assuming this sort of precision in the date at both the minimum and maximum constraint, the divergence between primates and rodents, primates and artiodactyls, and

artiodactyls and rodents were found to be 95±7 Ma, 90±8 Ma, and 113±9 Ma respectively (Hedges, et al 1996). Researchers re-did these calculations using a more conservative estimated of 338-288 Ma for the date of the mammal-bird split. They found the dates of divergence to be 119±74 Ma, 117±67 Ma, and 145±85 Ma respectively (Graur and Martin 2004). Not only are these substantially different dates, they also do not support the hypothesis of the original authors —that the ordinal diversification of birds and mammals coincided with the Mesozoic continental break-up (Hedges, et al. 1996).

Some researchers have argued that one should use the first appearance of the descendants of the preceding divergent event to define the maximum constraint (Müller and Reisz 2005). However, this method has been critiqued by many authors including Benton and Donoghue (2007) and Hedges, Kumar, and Tuinen (2006). Hedges, Kumar, and Tuinen argue that anyone using such maximum constraints "will likely be underestimating times of divergence", placing them earlier than they actually occurred (2006, p.770). Benton and Donoghue (2007) propose instead that the maximum constraint can be estimated by tracing the fossil record back to a time when conditions were conducive to fossil preservation, yet no fossils resembling the lineage of interest have ever been found. This provides a much more conservative estimate of the maximum constraint, but still might result in what Hedges, Kumar, and Tuinen call "underestimating times of divergence". This is part of why many, including Benton and Donoghue (2007) have argued that the fossil record can only provide reliable minimum constraints for molecular clocks.

Beyond the difficulty in establishing minimum and maximum constraints, there is a difficulty in deciding how to model the probability distribution within those constraints. Researchers have used lognormal, exponential, and uniform distributions within the Bayesian model in molecular clock models (figure 3.4). The different shapes of the shaded grey area in Figure 3.4 represent different ways of understanding the probability that the divergence event occurred at a given point in time between the constraints (or before the minimum constraint). What is most important to recognize is that researchers have options about how to represent the relative probability

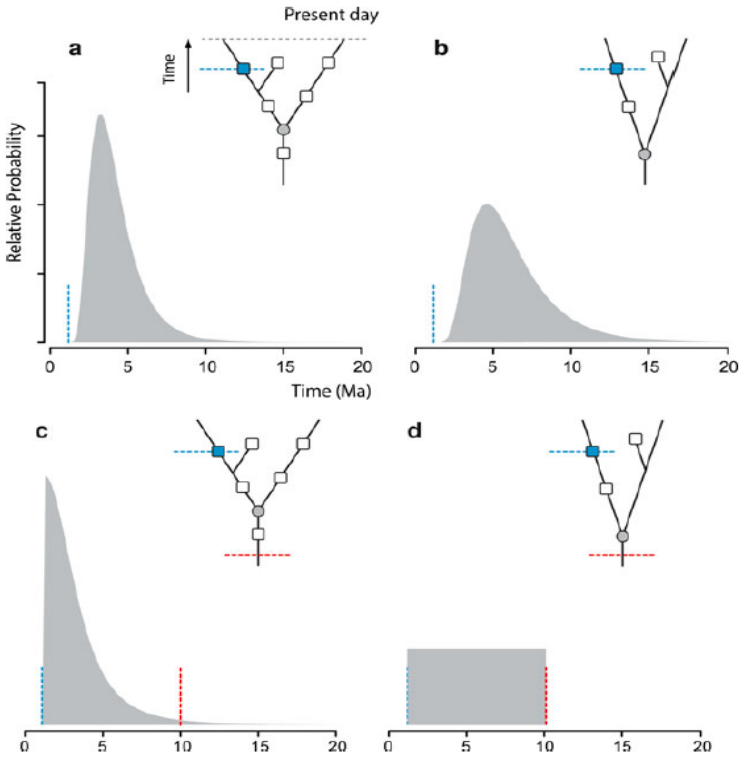

Figure 3. 4 Different calibration priors for Bayesian molecular clock analyses (as found in Warnock, 2014). A and B how different lognormal distributions, while C shows a skew-t distribution, and D shows a uniform distribution.

that the last common ancestor appeared at a given point in a temporal space. In the absence of clear evidence one might suppose it is equally likely that the last common ancestor appeared at any time within a particular range. This would mean choosing a uniform probability distribution, like the one seen in figure 3.4d. Normally, however there is at least some sort of evidence that makes it more likely for the last common ancestor to have appeared around a particular time. This leads researchers to model the probability that the last common ancestor appeared over a particular time period in non-uniform ways (as seen in figures 3.4 a, b, c). The distribution that is chosen is normally based on the fossil evidence. For example, if an organism has a robust fossil record, the first appearance in this record might be a fairly good approximation of the divergence of the species. In this case a distribution such as the one found in figure 3.4a might be appropriate. However, if there is a poor representation of a species in the fossil record, then a more diffuse representation of the probability distribution would be appropriate (e.g., the one seen in figure 3.4b). All of these choices are

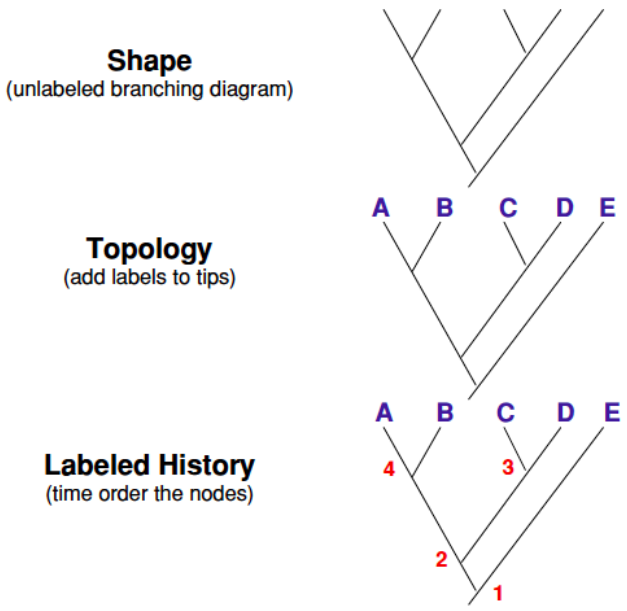

Figure 3. 5 Shows the differences between phylogenetic trees at different stages of development. Shape shows only a branching pattern; Topologies adds species labels to the tips; Labeled History includes tip labels and dates for branching events. (as found in Velasco 2008)

about creating a labeled history from a tree topology (see figure 3.5). However, important questions remain about the development of a tree topology generally.

Joel Velasco has argued that priors for phylogenetic tree models need to be made using the Yule birth-death process (2008). The Yule process is a particular version of a Markov process where there are only two state transition options from any given state – essentially a population can increase by one (birth), decrease by one (death), or stay the same (no transition). Velasco is interested in how we assign probabilities to shapes and topologies in ultimately generating labeled histories (figure 3.5). As figure 3.5 shows, the shape of a phylogeny is the unlabeled branching diagram, the topology includes labels added to the tips, and the labeled history includes a temporal ordering for the different branching events (i.e. nodes) in the diagram. Velasco points out that:

> Some shapes are consistent with more topologies than others; if each topology has an equal prior, not all shapes will be equally probable. Similarly, some topologies are consistent with more labeled histories than others so assigning equal priors to all topologies means that not all shapes nor all labeled histories will be equally probable. (2008, p. 460)

Almost all papers which use Bayesian methods use uniform distribution on tree topologies. However, Velasco shows by using a Yule birth-death process to model the

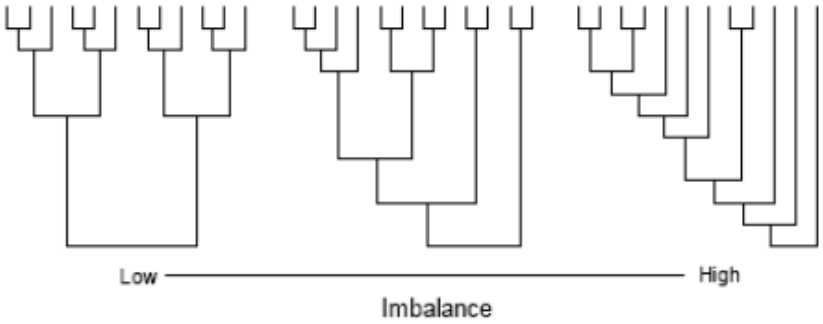

Figure 3. 6 Shows phylogenetic tree shape differences from balanced on the left to imbalanced on the right

probability of extinction and speciation that all *labeled histories* are equally probable (2008). This means that not all topologies or shapes will be equally probable. For example, well balanced trees will be more probable because there are more pathways to reach it compared to an unbalanced tree (Velasco, 2008). If taxa are evenly distributed among the clades, then the topology is balanced, but if some clades have many more taxa than other clades of equivalent rank, then a tree is considered unbalanced (see figure 3.6). Accordingly, it is important for researchers to pay attention to how their models distribute probability from shape to topology to labeled history, and that they make informed decision about the priors in their models instead of assuming uniform probability on any particular stage in tree development. Molecular clock models often build in assumptions about the probability of different shapes or topologies. If these models fail to account for Velasco's finding they might end up building biased models that generate predictably inaccurate labeled histories.

While some early molecular clock estimations were concordant with existent fossil date estimation, some large discrepancies between the evolutionary times estimated using the paleontological record and those made using molecular clocks have long been prominent (Donoghue and Benton 2007). This is partially because the early molecular clock models used fixed calibration points which lead to much older estimations. By assuming there was no uncertainty associated with the chosen single calibration point the assumption becomes that the lineage is *at least* as old as the oldest fossil record. This assumption pushes the calculated date backward, while not allowing uncertainty to provide a wider or more recent estimate (Graur and Martin 2004). One of the most

prominent examples of such a discrepancy was the difference in the estimation of the Cambrian explosion. The first appearance of most animal phyla in the fossil record (i.e. the Cambrian explosion) is estimated to be around 541 Ma, but early molecular clocks suggested an age more than twice that old (Hedges and Kumar 2003). While improvements have been made to the molecular clock, and there is less divergence between the two clocks, there is still substantial disagreement in a few prominent cases that will be discussed in the next section. As we will see, neither clock (molecular or biostratigraphic) has an a priori epistemic priority over the other. Rather through a process of iterative coherence, they are tested against one another, the source of error in a given case is clarified, and the methods subsequently improved.

3.5 Dating Discrepancies

Fossil occurrences reflect the time at which a population of organisms with a uniquely identifiable set of morphological characteristics reached a level of abundance and stability that some individuals became preserved and identified. Given the difficulty in reaching this threshold, the LO of a fossil is unlikely to represent the time at which organisms of that type began to differentiate themselves molecularly. This is not merely because the fossil is unlikely to be the first member of the new species, but also because molecular differentiation likely precedes morphological differentiation. The molecular clock will provide a date for when the organisms first became genetically identifiable, which is necessarily earlier. Thus, one might suspect that the discrepancies in dates for a given lineage are due, at least to a certain extent, to either misidentification of the fossil

record or lack of recoverable specimen in the fossil record. In some cases, what may have been molecularly a new lineage is identified morphologically as part of an older lineage, and in other cases, the new lineage existed at a time, but none of them became fossilized. These difficulties could explain some differences between molecular and biostratigraphic clock results. However, the observed discrepancies are larger than these complications can explain on their own. Accordingly, scientists have sought other means to resolve the apparent discrepancies between these two dating methods. Specifically, they use three methods for resolving the discrepancies: discrepancies can be resolved by using molecular clock estimates to revise how fossils are categorized and dated, by using an external arbiter to help guide dating decisions, or by changing how the fossil record is used to calibrate molecular clocks. An example of each of these three approaches will be discussed in what follows. While no single method has become the ultimate arbiter, they can be used comparatively to generate better methods, and more coherent dating estimates.

In the case of discrepancies in dating the divergences of animals from other life forms, scientists have used molecular clock estimates to revise how fossils are understood and categorized. As recently as 2016 molecular clock estimates of the divergence of most animals was over 100 million years before the first fossil records of these species. Animal fossils begin appearing fairly abruptly in the fossil record around 541 Ma, and by around 520 Ma virtually all animal phyla are present in the fossil record. However, molecular clocks consistently date Metazoan (multicellular animals) as originating between 850 and 650 Ma (Cunningham, Liu, Bengtson, and Donoghue 2016). Relaxed clock models have

been able to diminish these discrepancies, but they have not been eliminated. Some researchers have started arguing that if we revise our interpretation of the fossil record, we can resolve most of these apparent discrepancies. Cunningham, Liu, Bengtson, and Donoghue argue that that such revised analysis of the fossil record reveals that the so-called Cambrian Explosion was "neither Cambrian nor explosive" (2016). They argue that we have good evidence for the presence of animals by 565 Ma. This includes a variety of soft-bodied Ediacaran macrobiota: *Kimberella* between 558 Ma ± 0.3 Million years (Myr) and 555.3 Ma ± 0.3 Myr (Grazhdankin, 2004), *Dickinsonia* around 558 Ma ± 1 Myr (Grazhdankin, 2004), *Eoandromeda* around 551 Ma (Tang, et, al. 2011), and *Haootia* around 560 Ma (Liu, et al. 2014). While the status of these organisms as metazoans has been debated, Cunningham, et al. believe there is strong evidence that these four are good candidates for membership in the Metazoa.

Since the dating of evolutionary events (e.g. the splitting of branches) is strictly dependent on our taxonomic concepts, one way of reconciling discrepancies between molecular and biostratigraphic clocks is to revise our morphological taxonomic concepts in light of molecular data. For example, *Kimbrella* is a bilaterian found in rocks from the Ediacaran period in the White Sea of Russia. Many have argued that *Kimbrella* was a member of the Mollusk group because of its bilateral symmetry, anterior-posterior polarity, and foot and mantle like structures. Some researchers argue that this is enough evidence to suggest that *Kimbrella* was a member of the Metazoa broadly understood, which suggests that animals were indeed differentiating themselves before the Cambrian. These claims can bolster the molecular clock suggestion of older differentiation in

challenge to the idea of the Cambrian explosion. This argument represents one important way researchers have sought to reconcile the dating discrepancies between molecular clocks and biostratigraphy, namely by correcting the understanding of fossils, in particular their taxonomic categorization, in light of molecular data. While it can be hard to disentangle the motivation for claims that fossils belong to some particular category or another, the fact that molecular clocks would lead us to expect to find certain members of the animal group before the Cambrian period certainly provides some motivation for suspecting one might find such specimen. Cunningham and colleagues suspect that at least some of the claims for animal occurrence in the Neoproterozoic were made in response to the molecular clock findings (2016). If one believes that the molecular clock estimates are accurately dating the first appearances of animals before we have traditionally believed there to be fossil evidence for their existence, one response is to reevaluate the fossil record. This is precisely what is being done in all of the cases mentioned in the previous paragraph. This sort of reorganization of taxonomic identification represents one method for reconciling dating discrepancies.

Another method is to simply look to an outside source to help settle any discrepancies between molecular and biostratigraphic clocks. This approach is taken by researchers who have been looking for non-fossil evidence to support the idea that Metazoans differentiated before the Cambrian. While molecular clocks predict the differentiation of Sponges (a basal metazoan group) in the Cryogenian (720-635 Ma), fossils for this group only appear beginning in the Cambrian period. The molecule 24-isopropyl cholesterol (24-ipc) is known for appearing only in demosponges and

pelagophyte algae (Gold et al. 2016). Researchers consider the pre-Cambrian presence of 24-ipc to be an indication of early members of the Sponge group. Since the production of 24-ipc by pelagophyte algae can be linked to a gene duplication event that is not believed to have occurred until about 541 Ma, this leaves demosponges as the most likely producers of pre-Cambrian 24-ipc (Gold et al. 2016). However, this is not considered sufficient evidence by most to definitively indicate the presence of some member of the Sponge group. Still as part of an attempt to reconcile the differences between molecular clock and fossil records, looking for biomarkers provides an interesting alternative to traditional fossils.

A third method to resolve discrepancies is to use the fossil evidence to correct molecular clock models. The arguments over molecular clock calibration discussed in the previous section can be seen as a case where scientists are seeking to solve the discrepancies by changing how the fossil record is used to modify molecular clock estimates. One of the most common points of contention surrounds the split between birds and mammals (estimated to be about 310 Ma). Some paleontologists have argued that the fossil record is inadequate for dating this particular event (Reisz and Müller 2004). The mammal-bird split is considered a good calibration point because it represents a basic division of amniotes (vertebrates that either lay eggs on land or retain the eggs during gestation). According to Reisz and Müller, the 310Ma estimate is heavily based on a single set of fossil records from Joggins, Nova Scotia (2004). Yet they suggest that the best geological evidence dates this site at between 331 and 316 million years old, which is older than the commonly used age of the split. Reisz and Müller provide a method for

evaluating the quality of the fossil record for use in calibrating molecular clocks. They argue that calibration points need to be chosen based on: 1) the quality of the fossil record, 2) the temporal distribution of the taxa within the phylogeny, and 3) the temporal distribution of closely related taxa (2004). Their focus is on the paleontological record, and how to make appropriate use of this record in shaping molecular clock estimates. The attempts of researchers to incorporate more fossil evidence, and to incorporate that evidence with more accurate representations of the uncertainties surrounding the fossil record, is one way of using fossil evidence to revise molecular clock estimates.

The primary opponent of Reisz and Müller in the literature are biologists S. Blair Hedges and Sudhir Kumar. Hedges and Kumar argue that the insistence of Reisz and Müller on particular types of fossil calibrations is misguided. Most of the disagreement is over how to interpret the possibility of error in our current understanding of the fossil record. Hedges and Kumar argue that Reisz and Müller fail to appreciate the importance of ongoing activity in fossil discovery, and thus place too much importance on existing fossil evidence. What is interesting, in terms of understanding how dating discrepancies are reconciled, is the emphasis Hedges and Kumar place back on molecular evidence. Hedges and Kumar seem to favor the mammal-bird split primarily due to the robust availability of DNA sequence data (2004). Still, in order to make use of this DNA sequence data a calibration of some variety must take place. Privileging the disagreement over which method for settling dating discrepancies is more appropriate (using molecular clock estimates to revise how fossils are categorized and dated or changing how the fossil record is used to calibrate molecular clocks), fails to appreciate the importance of

iteration in gradually generating better clocks and better dating estimates. There are good ways of modifying molecular clocks in response to fossil findings and good ways to modify our understanding of the fossil record in response to molecular clock findings. It is through repeating this process that the overall reliability of dating estimates are increased. Since both methods are incomplete, there can be no single answer that gives one primacy over the other, and improving how the fossil record is used is an important step in this process.

While molecular clock models often select rate variation with little reference to biological evidence, there are some researchers who are trying to change this trend. Some scientists have begun developing a new method which can incorporate different modes of evidence into a single model called "Total Evidence Dating" (TED). TED involves incorporating a wide range of dating information into a unified statistical analysis. Researchers who undertook the TED project were particularly concerned with the phenomena that occupies center stage in the Hedges-Kumar vs. Reisz-Müller debate– the role that maximum calibration times play in generating overall dating estimates. Using their new models, Ronquist, Lartillot, and Phillips were able to show how adding or excluding different types of information changed the results of a model. They observed that "inadequate models of vague priors" lead to a phenomenon they call "deep root attraction" (DRA) – which results in dating divergence events further in the past (Ronquist, et al. 2016). However, they also observed that their TED approach could, under certain circumstances, display DRA. Ronquist and colleagues identify three primary causes of DRA: 1) inadequacy of morphological models, 2) failure to account for

diversified sampling, and 3) fossil sampling priors that do not incorporate enough background information (2016). In the first place, models that do not account for the dependencies between morphological characteristics can cause distorted tree topology and branch length estimates. Next, if tips are assumed to represent a complete sample of all lineages, branching event estimates are much older than if tips are assumed to represent either a random sample of historical linages or a maximally diverse sample. Finally, there is a complex relationship in including fossil data in models that can contribute to DRA, but generating informative priors can also help to combat DRA (Ronquist et al. 2016, p. 6-7). This result is important because it allows us to begin to understand some of the causes for the much older date estimates of molecular clocks. For example, they discovered that our assumptions about tip sampling (which answer questions like, are currently existent species a complete sample of historical lineages, or in what ways is our current sample (lineage tips) an incomplete sample of historical lineages?) have a massive effect on DRA (Ronquist, et al. 2016). Understanding how our modeling choices affect outcomes can allow researchers to make more informed choices about the priors they choose in their models.

It is important to note that only some of Ronquist and colleague's models used the Yule birth-death prior suggested by Velasco. They also used equal prior probability distributions for all topologies in certain analyses (Ronquist, et al. 2016). For example, in non-clock analyses of the phylogenetic tree, they used a uniform prior probability distribution for all topologies. In other cases, they compared a uniform tree prior to different types of birth-death tree priors. What is important to include in a model, and

how one can best include the necessary factors, are open questions that need to be investigated. In these cases of dating events in the deep past we can use our models to check and improve other models. For example, when Ronquist and colleagues were concerned to understand how their model worked and how different settings within their models would affect the output they chose to use an equal prior probability for all topologies (2016). This made it easy for them to compare the effects of varying different parameters, for example the type of input data, on the output of their model. Since their concern was not to generate a dating estimate or an accurate tree, it was acceptable for them to use the uniform prior. For dating, they compared a uniform tree prior to a birth-death prior (Ronquist et al. 2016). In a separate publication Ronquist and colleagues argue that there are three problems with the birth-death prior: first, that it assumes constant fossilization probability, second, that it is very sensitive to assumptions about lineage sampling, and finally, that more trees are unbalanced than are predicted by the birth-death model, which undermines the assumption of the models accuracy (2012). While for some investigations, Velasco showed how uniform priors can corrupt results, the corrosiveness of the assumptions depends on the purpose of the experiment. Since Ronquist and colleagues are concerned with understanding the functionality of their models, it is fair for them to make inaccurate assumptions, as long as in the final iteration of their models they incorporate more informative priors. Here we see an instance of the iterative process of building and correcting our dating tools, which is how scientists are able to improve the process and yield better overall results.

3.6 Philosophical Consequences

In the development of the methods for measuring time in the deep past we can see scientists defying some of the common adages about how to use evidence. It has seemed intuitive to many that multiple lines of evidence need to agree in order to provide increased support for a hypothesis. Yet as we have seen, sometimes in dating events in the deep past different date estimates can be taken to support the same hypothesis. A hypothesis need not always be a specific temporal estimate, but could also be a hypothesized method for generating the dating estimate. Some have also believed that different lines of evidence cannot be interdependent (at least in specific ways) if they are to provide increased support for a hypothesis. The thought seems to be that if evidence from two completely separate projects converge on the same hypothesis, then we can consider the evidence in favor of the hypothesis to be elevated. Yet again, in dating events in the deep past, our lines of evidence are deeply interdependent. However, it is not in spite of, but because of this interdependence that researchers increase their credence in their outputs. In what follows I will explore the challenge to the epistemic importance of the independence and the value of discordant evidence that can be found in the case of dating events in the deep past.

3.6.1 Independence

Philosophers commonly assert that different lines of evidence or techniques that lend support to a hypothesis must be "independent". This is not the same as statistical independence, but a richer epistemic and methodological independence. The literature

does not always make the nature of this demand for independence clear, and the correctness of this demand is often simply assumed without conceptual defense (Weber 2018). The most thorough examination of independence has been conducted by Alison Wylie (1999). Wylie argues that there are a few different senses of independence, and specifically that there seem to be two different axes along which she differentiates types of independences. In the first place, there are different ways hypotheses can be independent of theories and in the second place, there are different ways multiple lines of evidence supporting a theory can be independent of each other.

Along the first axis, Wylie distinguishes between so-called vertical and horizontal independence. Vertical independence exists between background assumptions used to interpret some set of data and the hypotheses the evidence is used to test. Wylie notes that "all evidence is theory-laden, but typically not by the same theories as archaeologists are intent on testing" (1999, p. 307). Separation between the hypothesis under examination and the background assumptions used in the experimental set up is not always possible, when it is found there is what Wylie calls vertical independence. Horizontal independence exists between different lines of evidence when they are based on different ranges of background theories. This is presumably the more important sense for those interested in the epistemic value of multiple lines of evidence. Of course, not all different ways of supporting a hypothesis are based on different background theories. For example, repetitions of the same experiment are often taken to lend additional support to a hypothesis, but cannot be based on different theoretical assumptions. When there is a

difference between the theories that lines of evidence are based on, they are considered horizontally independent.

Horizontal independence seems the be what many researchers find necessary for multiple lines of evidence to increase the support of a single hypothesis, yet this concept itself is vague. Wylie suggests three different ways different lines of evidence might be horizontally independent, or in other words three different ways of being based on different background theories. These are causal, inferential, and disciplinary independence. According to Wylie, causal independence is what distinguishes different physical systems – the ability of different lines of evidence to count in favor of a hypothesis "depends on the plausibility of the assumptions that these different trace-generating systems are causally independent in the sense that they do not interact in such a way as to ensure an artificial congruence in the signals they transmit" (1999, p. 309). There is some ambiguity in Wylie's description of causal independence – is the causal independence supposed to be between the causal process or mechanism that gives rise to the observable properties that are then detected or observed through different scientific processes? Or is the independence between the systems that observe the phenomenon of interest? For example, consider a microscope observing a cell. Is causal independence between the causal processes that give rise to different properties observable by different types of microscopes? Or is the causal independence between the ways different microscopes give rise to images of the cell? The ambiguity is found in what exactly Wylie means by "trace-generating system". While both of these are plausibly different types of independence, each of which could separately be on Wylie's list of types of

horizontal independence, the more important one for epistemic purposes is the later. One cannot reasonably expect that different properties of a phenomenon of interest are causally independent of one another. If the phenomenon is casually unified or at least interrelated this sort of independence would not be possible (e.g. in the example, the cell's different properties are interrelated). However, it might be epistemically beneficial if the systems of observation were causally independent in such a way that their methods for generating observations do not depend on the same causal pathways. In the case that different types of microscopes can be understood as relying on different lines of physical causation, they could not both malfunction in the same way, in effect, they could not both show some property of the cell falsely for the same causal reason.

According to Wylie, inferential independence is supposed to hold between the sets of background theories that are used to understand "the pathways by which signals are transmitted and received" (1999, p. 309). Here the separation is between the theories that allow for the interpretation of some data – this can become epistemically important because it can ensure that the support different lines of evidence show for the same hypothesis is not merely an artifact of dependence on the same background assumptions. This is similar to the importance of causal independence mentioned in the previous paragraph as both of these types of independence (causal and inferential) license joint inference because they decrease the probability of failure. According to Wylie, inferential independence is necessary in addition to causal independence to establish the epistemic importance of different lines of evidence. So in addition to being generated by different causal pathways (e.g., the observation of the phenomenon is conducted via different

causal systems), these different lines of evidence additionally need to depend on different background assumptions in order to be epistemically relevant.

Finally, Wylie asserts that disciplinary independence occurs when background theories that different lines of evidence rely on were developed by institutionally distinct disciplines (1999). Sometimes, disciplinary independence can be a guide to inferential independence, but not always. Similarly, it is often assumed that all three types of independence can be treated as one, but this is not always the case. Wylie argues that archeologists invoke all three of these types of independence in their arguments, and in practice can demonstrate how complex the relationship between lines of evidence can be.

The independence of different lines of evidence is important insofar as it increases the epistemic value of their total support for some hypothesis. Wylie writes:

> [T]wo lines of inquiry are necessary to determine epistemically relevant independence: one to establish the extent to which the processes responsible for ostensibly different records are, in fact, *causally independent* of one another; and another to determine the extent to which the background theories concerning these processes – the interpretative principles used to 'read' these records – are *conceptually independent* (1999, p. 312).

The implication here is that in order for different lines of evidence to be jointly epistemically relevant, researchers must establish these types of independence. While Wylie highlights the difficulties historical archeologists have in achieving these goals, she argues that there is no dispute that these are not only the goals, but the necessary steps to epistemically responsible science.

Another way of discussing the importance of multiple streams of evidence arises in the discussion of "consilience". Patrick Forber and Eric Griffith have argued that the consilience, or the "convergence of independent evidential inferences" (2011, p. 1), is "a,

if not the, primary measure of support for historical reconstructions of the deep past" (2011, p. 7). Forber and Griffith's notion of consilience requires the "independence" of multiple streams of evidence in order for them to be epistemically relevant. Adrian Currie (2018) provides an analysis of the specific sort of independence required for consilience using Wylie's interpretations of the different senses of independence. Currie argues that Forber and Griffith are relying on a particularly strong version of horizontal independence such that multiple lines of evidence must be based on substantially different background assumptions. Forber and Griffith write:

> For an isolated inferential path, each of these auxiliaries bears the full inferential load—the inferential chain is only as strong as its weakest link. Consilience of multiple independent inferences distributes the epistemic load across auxiliaries employed in multiple inferential paths. As the number of paths to the inferred aspect of the reconstruction increases, the inferential load on auxiliaries that appear in one path lessens insofar as different paths that rely on different auxiliaries converge on the same inferred value. Thus, the support accruing from consilience rises with increasing independence of the inferential paths. The independence between two inferential paths increases as the number of shared auxiliary hypotheses decreases (2011, p. 9)

The implication here is fairly clear: Forber and Griffith believe that horizontal inferential independence is the most important type of independence, and further that in in the ideal epistemic circumstance lines of evidence should be completely inferentially independent.

While these authors take some degree of independence between multiple lines of evidence to be an important condition for increasing the epistemic support for a particular hypothesis, the cases examined in this chapter on the dating of biological events in deep past reveal epistemic importance of interdependence. When scientists date events in the deep biological past they make use of multiple lines of evidence in order to increase the confidence in a given result. However, the way they rely on these lines of evidence to be

epistemically useful depends on the lines of evidence being interdependent rather than independent. It is exactly through the integration of different lines of evidence with one another iteratively that better and better methods are developed. Below, I will discuss how the lines of evidence involved in dating events in the deep past are interdependent in important ways, and how they can be jointly epistemically useful because of this interdependence.

First of all, the background theories the dating methods are based on depend on one another in important ways. The calculation of dates using molecular clocks depends on the calibration of the clock using biostratigraphy. It has been through increasing the nuance and complexity of the calibration process, or in other words improving the ways molecular clocks depend on biostratigraphy, that has increased epistemic confidence in the results from such calculations. Further, our understanding of the fossil record is dependent upon our taxonomic concepts, which are in turn at least partially dependent on molecular dating methods. As I highlighted in section 3.4, the way we understand phylogeny has been heavily influenced by molecular methods (Schwartz 2004). While the fossil record had been understood as indicating a very distinctive Cambrian "explosion", researchers have used molecular clock results to begin reinterpreting this supposed finding (Cunningham, Liu, Bengtson and Donoghue, 2016). Both the molecular clock and the fossil clock operate with background assumptions that are interdependent.

It also appears that fossil clocks and molecular clocks are causally interdependent. Recall that Wylie, defined causal independence as when different trace-generating systems "do not interact in such a way as to ensure an artificial congruence in the signals

they transmit" (1999, p. 309). One way to understand this is that if systems of observation are not dependent on the same causal pathways, one does not need to worry about them displaying similar results merely due to a similar mistake. While it can be hard to disentangle what degree of causal separation is important, there is at least some important ways in which fossil clocks and molecular clocks are causally related. For example, when the molecular clock models depend on biostratigraphic dates, they also depend on the physical systems that generated the fossil traces. More intimately the idea that the morphological and molecular taxanomic concepts are similar enough to compare depends on the idea that they are causally connected. As discussed, our dating methods are strictly dependent on our taxonomic concepts, but there are different ways of generating taxonomies. It is often presumed that molecular characteristics give rise to morphological characteristics such that the later depend on the former. If this is true, then there should be nice alignment between these different taxonomic concepts. However, this also would indicate a causal dependence between the systems that give rise to the traces in fossil and molecular clocks. This is not a pernicious dependence, but rather one that enables information to flow between the traces (fossils and molecules).

While one might argue that fossil clocks and molecular clocks might still be independent at least to some degree, it is clear that this is not what is epistemically important in these cases. While one might contend that there is no causal dependence between the trace generating systems in the fossil and molecular clock cases, what is clear is that what is epistemically relevant is the ways in which they are interdependent. It is the interdependence of these different dating methods that a richer and more

epistemically reliable picture is developed. More specifically, it is through increasing the depth and complexity of the ways in which they depend on one another, that they achieve more epistemic reliability. For example, consider the re-evaluation of the morphological concepts of phylogeny. Before we had a molecular concept of phylogeny or molecular dating, scientists relied on morphological similarity as a proxy for relatedness of fossil specimens. When molecular clocks suggested the presence of Metazoa before the Cambrian, researchers re-considered some of the evidence from the fossil record. They found that several species with robust presence in the pre-Cambrian fossil record (including *Kimbrella* as discussed in section 3.4) could be considered members of the Metazoa. However, these changes in the reading of the fossil record did not account for the entire difference between the molecular clock dating estimate and the biostratigraphic dating estimate of the first appearance of animals. Other methods were used to further reconsider the molecular dating estimates (including modeling techniques and calibration choices). It was not through agreement of multiple lines of evidence that the total evidence becomes strengthened, but rather through the iterative process of testing and revising of both the dating estimate and the testing methods that these scientists arrive at better supported hypotheses. While philosophers are correct to think that there is something important about the support of multiple lines of evidence, it is not necessarily important that those lines of evidence be independent. In fact, in this particular case it is necessary that lines of evidence are dependent on each other. The iteration of testing and the revision of methods and hypotheses is what appears to be essential in order to provide increased evidential support to some particular hypothesis. One might be concerned that

these interdependent lines of evidence might artificially converge. However, iteration can guard against artificial convergence through constant revision, as we will see in what follows. Perhaps then it is best to frame this conversation as an alternative reading of the importance of multiple lines of evidence; one that comes from the same impulse as the robustness literature, but offers a different interpretation of how evidence can compound in favor of a hypothesis.

Here I have in mind a process similar to that outlined by Hasok Chang in his book "Inventing Temperature" (2004). Through a detailed consideration of the historical case of temperature, this book develops a general theory of how concepts come to be scientifically measurable. This process is often called measurement standardization, and involves legislating the conditions for the application of a concept (Tal 2016). In the case of temperature this process came with several challenges. How can we invent a tool for measuring temperature, when we cannot know the temperature of any substance without such a tool? Against what will we check the accuracy of our temperature reading devices? In order to get a process of knowledge generation started, Chang argues that we "start by adopting an existing system of knowledge, with some respect for it but without any firm assurance that it is correct" (2004, p. 6). Based on this existing system of knowledge researchers launch new experiments, which will lead to "the refinement and even correction of the original system" (2004, p. 6). Initially, judgements of temperature (hot vs. cold) were made simply using the senses. In order to create a numerical scale on which to measure temperature researchers needed to introduce fixed points. This was done using a *thermoscope* – a tool that allows scientists to judge that two substances are

the same temperature without any sort of numerical scale. The idea of iteration in experimentation allows us to understand how this process escapes vicious circularity and makes discordant measurements useful. Chang writes: "empirical science requires observation based on theories, but empiricist philosophy demands that those theories should be justified by observation" (2004, p. 221). Scientists can often find themselves in a situation of circularity in justification when there is not independent access to a quantity of interest, one needs make some assumptions to get the discovery process started. The iterative process of revision ensures that the original, or any new assumptions, will constantly be rechecked and revised.

Researchers interested in dating events in evolutionary history face just this sort of problem: how can we judge the date of some event in the past, when no dates or dating methods have previously been established? Far from necessitating independence, the difficulty of developing a measurement system when what is to be measured is unknown, seems to necessitate using different lines of evidence *inter*dependently. This is what Chang observed in among the scientists who invented temperature, and what we see among those scientists who are endeavoring to invent a scale for time in the history of life on earth. The idea of iteration allows us to understand how a process of making different lines of evidence depend on each other can escape vicious circularity, and become epistemically reliable.

3.6.2 Discordant Evidence

Many believe that multiple lines of evidence can only be jointly epistemically valuable when they are in agreement, or correspondingly that discordant lines of evidence cannot be jointly epistemically valuable. Jacob Stegena, for example, argues that robustness is valuable only in "ideal evidential circumstances, when all available evidence is concordant" (2009, p. 652). While he acknowledges that the problem of discordance is not a knockdown objection to the idea of robustness (since it doesn't say that concordant lines of evidence cannot ever lend increased support to a hypothesis), he still insists that "discordance demonstrates an important constraint on the value of robustness" (2009, p. 655). According to Stegenga, one of the problems is that there is no principled way to assess or amalgamate multimodal evidence, which means that different lines of evidence cannot be integrated. Multiple lines of evidence that are discordant can still be valuable in some sense, according to Stegenga they just cannot support the same hypothesis. This, however, runs counter to what we observe in the case of dating events in evolutionary history: even when different lines of evidence give different dating estimates for some particular event, they can still be used to support the same general dating hypothesis (e.g. the hypothesis that mammalian and bird lineages diverged 310 ± 0 Ma). First, I will examine Stegenga's account of what makes discordant evidence problematic, and then will examine a case study in historical dating to show how, under certain circumstances, discordant evidence can be made epistemically useful.

Stegenga argues that there are two separate problems with discordant evidence. According to Stegenga, the problem of inconsistency occurs when one line of evidence

suggests "*x*" and another "¬*x*" (2009, p 654). On the other hand, the problem of incongruity occurs when experiments are conducted in "different languages" such that one suggests "*x*", another "*y*", and yet another "*z*" (2009, p 654). The difficulty for incongruent lines of evidence is that they depend on different background assumptions that must be translated and interpreted in order to be compared. The assumptions that will go into such a translation or comparison will be of varying degrees of plausibility from case to case. Thus, Stegenga worries: "if they are not plausible, then it is hard to see how multimodal evidence provides greater epistemic support to a hypothesis than a single mode of evidence does" (2009, p 654). Another element of Stegnega's problem with discordance is the degree of "intensity" of the disagreement. The argument here is that different types of experiments yield support of different strength for their conclusions. Stegenga uses the example of so-called "golden-event experiments" in physics which yield "intense" support for their conclusions. The problem is how one might compare such results to, for example, statistical experiments, which lend a different sort of partial support to their conclusions.

It is important to keep in mind that discordant lines of evidence are not necessarily incommensurable, but merely apparently conflicting. The problem is not that one cannot, through various methods, come to compare the results of these lines of evidence, but rather that these lines of evidence yield results that, when compared, seem to disagree with respect to a hypothesis of interest. Importantly, this sort of disagreement is what authors like Stegenga have in mind when they discuss discordance in the context of robustness. For example, Stegenga writes:

> I share the intuition that multimodal evidence does (often) provide greater epistemic support to a hypothesis than monomodal evidence does – at least when all independent techniques are concordant. Unfortunately, multimodal evidence, when available, is rarely concordant (2009, p. 655).

Here the emphasis is clearly on the agreement (or lack thereof) among different lines of evidence. The confusion comes from Stegenga's insistence that "robustness-style arguments presuppose a principled and systematic method of assessing and amalgamating multimodal evidence" (2009, p. 665). However, this is not what is observed, at least in the case of dating events in the deep biological past. There is no problem comparing the results from molecular and fossil clocks, but they are often found to disagree. The important phase of discovery comes as researchers try to discover the source of the disagreement and refine their methods in light of the new information. It is through the iterative process of figuring out how to assess and amalgamate multimodal evidence that discordant lines of evidence can come to be seen as jointly epistemically useful.

The case of dating events in the deep biological past involves making use of multiple lines of discordant evidence to support a single hypothesis. Researchers like Ronquist, Lartillot and Phillips who are working on Total Evidence Dating (TED) are interested in the prospect of making discordant lines of evidence jointly epistemically useful. TED involves the explicit coding of multiple lines of evidence – including fossil analysis and analysis of more recent taxa — and their incorporation into a large statistical model. TED combines molecular clock data with biostratigraphic information, and importantly allows researchers to explicitly code the uncertainty associated with each. On its own, molecular analysis reports a substantially different phylogenetic tree when compared to morphological analysis of the fossil record. As Ronquist, Lartillot and

Phillips see it, understanding the specific uncertainties surrounding each of these discordant lines of evidence can allow them to be jointly used in the production of a maximally reliable phylogenetic tree. Since each line of evidence, in this case molecular changes and the fossil record, have different types of bias and potential errors, researchers can use the discordant evidence in conjunction with one another as evidence. Importantly it is not the case that molecular clocks and biostratigraphic clocks are modified to artificially make concordant dating estimates or similar phylogenetic trees, their outputs remain discordant, yet these measures can still be jointly used to support a hypothesis through the process of discovery and revision. Here again we can see the importance of the iterative process described by Chang. Discordant lines of evidence can be taken to jointly support some hypothesis as part of this iterative process. As researchers interested in dating events in the deep past work on developing their methods, they look to each other. Microbiologists have become concerned with how to appropriately understand the fossil record, and biostratigraphers have become concerned with how we ought to understand phylogeny in light of molecular results.

Molecular and biostratigraphic clocks are discordant lines of evidence – they suggest different dates for important events in the biological past. Through a process of iterative testing and correction, scientists come to understand the errors and limitations in both of these methods. This is not merely a matter of statistically weighting the different lines of evidence. Rather comparison is used to find problematic assumptions within the methods that are subsequently revised. As the errors are understood, the seemingly discordant results can come to be jointly epistemically significant. This is because their

differences can help researchers better understand how their methods work. While the results are not reinterpreted or resolved to be concordant, the lines of evidence come to be understood as lending evidential support to the same hypothesis. The focus here is not on the outputs of the experiments or models per se, but on the greater system of iterative testing and revision. Through this process researchers are able to generate a more coherent picture, and this process makes essential use of discordant evidence in improving overall epistemic reliability.

3.7 Conclusion

This chapter has both characterized how scientists have developed measures for telling time in the deep past, and illuminated two issues with our understanding of scientific epistemology that arise from the investigation of the molecular and fossil clocks.

First, the ability of molecular clocks and fossil clocks to generate more robust support of a hypothesis rely on their interdependence, rather than their independence. As we saw, molecular clocks depend on dating estimates from fossil clocks for calibration. Molecular clocks get better as the methods for incorporating and interpreting fossil clocks get better. Further, fossil clocks depend on taxonomic concepts that are developed using molecular clocks. Integrating our understanding of molecular and morphological taxonomy leads to improvements of the fossil clock. These interdependencies are not epistemic weaknesses, but strengths.

Second, the dates provided by molecular clocks and biostratigraphic clocks are often discordant, and yet they are jointly epistemically useful. For example, many of the estimates generated by fossil and molecular clocks disagree, and yet in combination they are used to generate good epistemic estimates. According to the philosophical community then, it would seem that these multiple lines of evidence could not count together to provide evidence for a particular dating hypothesis. However, this is not what we have observed in the community of scientists who are interesting in dating these events in the history of evolution.

The issues that a focus on time reveals, when we examine biologists who are explicitly interested in measuring time, are quite different than those revealed in chapters one and two when the focus was on the abstractions biologists make from time. However even in these cases where the focus is explicitly on measuring time, we can see how a focus on external measures has impacted biological science. Specifically, the difference of timescales between molecular and evolutionary change, underlies many of the complications discussed in this chapter. From the difference between morphological and molecular taxonomic concepts to the problem of multiple hits, the difference of timescale produces many of the difficulties researchers face in telling time in the deep past. Examining how they overcome these difficulties highlights the epistemic innovations of scientists.

CHAPTER FOUR

TEMPORAL REDUCTION IN BIOLOGY

4.1 Introduction

The question of reductionism asks if the properties, explanations, objects, etc. of one domain can be constructed from, or explained by, the properties, explanations, objects etc. of some lower domain. For example, one might wonder if all explanations in biology could be reduced to explanations in terms of just physical particles. The discussions of reductionism have so far focused almost exclusively on matters of spatial scale. In biology this has meant a focus on the extent to which wholes are nothing but their parts or can be explained by nothing but their parts. However, as this dissertation has lent more attention to the role of time in biological science and biological entities, new perspectives on reductionism have arisen. This chapter will explore ideas about reductionism and time in two ways. First, I will explore some of the classic debates about reductionism with specific focus on the role that time plays in changing our understanding of the questions traditionally associated with reductionism. Second, I will consider a notion of temporal reductionism, or the idea that temporal properties, explanations, objects, etc. of one domain can be constructed from or explained by the properties, explanations, objects etc. of some lower domain.

Section 4.2 will begin by exploring the types of reductionism that have been commonly identified in the philosophy of biology: methodological, ontological, and epistemological. We will consider these different types of reductionism and their relations with each other, as well as addressing the connections to what has already been

said about the role of time in biology. While little has been said about time and reductionism, section 4.3 will examine those instances when philosophy of biology has directly addressed time and reductionism, and begin to expand upon these ideas. Section 4.4 will offer two case studies from biology that highlight the relationship between time and reductionism, and will examine attempts to understand protein structure in terms of linear amino acid sequences and network analyses in genetics. Given these considerations, section 4.5 will directly consider the philosophical prospects of temporal reduction, and argue that the role time plays in biology makes the project of reduction even more difficult than has already been recognized.

4.2 Reductionism in Biology

The modern philosophical debate about reductionism in philosophy of biology communities arguably got its start trying to apply Ernest Nagel's ([1961] 2010) classical model of theory reduction to biology. While theory reduction has an important historical place in the philosophy of biology, there are many different modern incarnations of the conversation. First, there are at least three different types of reduction: ontological, epistemological, and methodological (Sarkar 1992; Brigandt and Love 2017). Second, there are many areas in biology and in neuroscience where people are interested in the project of reducing one domain to another. For example, many believe that classical genetics can be reduced to molecular biology. There is important overlap between this division of types of reductionism, and the chapters of this dissertation. Speaking very generally, chapter one was methodological, chapter two was metaphysical, and chapter

three was epistemic. As we will see each of these overlaps will help us to understand reductionism in biology in new ways. We will begin by exploring how these three types of reduction are commonly understood.

4.2.1 Types of Reductionism in Biology

Ontological reductionism is the idea that biological entities are made of nothing but molecules and their interactions. This is not an explanatory thesis about how to explain biological entities in terms of molecules and their parts. Rather, ontological reductionism is about what biological things are made of. This view is essentially physicalism and is widely accepted in philosophy of biology communities. While many in other philosophical communities might be more open to or interested in the complexities between substance dualism and physicalism, this ontologically reductive view is often taken as given within philosophy of biology communities. As Alexander Rosenberg put it:

> [S]ubstance dualism about biology… [is] just not a live option. The only biologists who deny physicalism are an assortment of cranks and creationists to whom serious science pays no heed. We're all physicalists now. (2006, p. 4)

While there may, in fact, be a bit more room for debate than Rosenberg suggests, he is quite correct in pointing out that ontological reductionism is not a major arena for debate among contemporary philosophers of biology.

Methodological reductionism is the idea that biological entities are best studied at the lowest level possible (Andersen 2017). While methodological reductionism may often be motivated by an ontological reductionism, it does not follow from it. One could

maintain a methodological reductionism approach without being an ontological reductionist, or one could advocate a methodological pluralism despite being an ontological reductionist. While methodological reductionism is also not generally the focus of debate in philosophical communities, it is still worthy of consideration. In fact, there is important overlap here with my argument regarding the move from metaphysics to methods found in chapter two. The success of methodological reductionism, especially in molecular biology, is often seen as justification for other kinds of reductionism. I argued that metaphysical beliefs are often used inappropriately in making methodological choices.

Jason Robert (2004) uses the example of developmental biology to emphasize the flipside of this point arguing that although reductionist methods have proven useful in developmental biology, an inference to the idea that only molecular causes are explanatorily relevant is not licensed. Robert argues that, "The Devil is not in the details, but rather in the Gestalt" (2004, p. 130), by which he means to suggest that the focus should not be on the parts, but on the whole. While reductionist methods have been quite successful in developmental biology, Robert is concerned that we not take this methodological success as indicative of the nature of development. Instead he argues that, "development is a matter of contingent interactive processes between multiple components within hierarchical systems in specific (though variable) contexts" (2004, p. 130). This is a point that most developmental biologists would, in fact, accept as characterizing the nature of developing biological systems. Similar to my concerns in chapter two, Robert is worried about the unreflective relating of methods and

metaphysics – the assumption of a reductionist nature due to the success of reductionist methods. This argument from Robert – coupled with my arguments in chapter two – give us reason to think even more generally about the relationship between metaphysics and methods. The assumptions that are often made regarding this relationship are not as reliable as they seem. Recognizing that inference from one form of reductionism to another is not always reliable is especially important in holding separate the different forms of reductionism.

While methodological and metaphysical reductionism are important ideas, most of the debate surrounding reductionism in the philosophy of biology is about epistemological reductionism. Epistemological reduction is the idea that knowledge from one domain can be reduced to knowledge of another lower, or more fundamental, domain. Again, it is important to note that while epistemic reductionism might often be motivated by ontological or methodological reductionism, this relationship is not necessary. In other words, ontological reduction does not imply epistemic reductionism, and vice versa epistemic reductionism does not necessitate either methodological reductionism (as we will see in section 4.4) or metaphysical reductionism.

Accounts of epistemic reduction fall into two basic categories: theory reduction or explanatory reduction. Theory reduction was prominent in the conversations about reductionism that began in the 1960s. For example, Nagel thought of reduction as a logical relation between theories where the reducing theory T_A reduces the reduced theory T_B if the laws of T_B can be logically derived from T_A ([1961] 2010). You can apply this model to synchronic interlevel theory reduction, like that advocated for by

Oppenheim and Putman (1958), or to successive theory reduction. Attempts to concurrently relate parts and wholes is called synchronic theory reduction. Successive theory reduction, on the other hand, is a relationship between a theory and its successor, where by the former subsumes the later – in other words the new more general theory takes the old theory in as a special limiting case. This latter notion of successive theory reduction has also been called diachronic theory reduction, and is where an earlier theory can be understood as a reduction of a later theory. Some have argued that diachronic reduction is useful as a notion of theoretical progress (Nickles 1973). In general, theory reduction has encountered a number of problems in biology (e.g., Hull 1974, Kitcher 1984, Sarkar 1998, and Wimsatt 1976). As a result, most of the recent discussion on reductionism is focused on explanatory reduction, which will also be the focus here.

Reductive explanations can vary in scope, but typically focus is on the causal relationship between parts and wholes. There have been many different accounts of explanatory reduction, but Marie Kaiser (2015), for example, argues that three characteristics unite all reductive explanations: (1) being at a lower-level, (2) being internal, and (3) using parts-in-isolation. First, reductive explanation relies only on features that are at a lower level than the phenomenon being explained. Second, a reductive explanation appeals only to physical parts of the phenomenon or system of interest. Finally, to count as reductive, an explanation must represent each part involved in the explanation in isolation. In other words, the system should be near decomposable such that a part's functioning can be understood in isolation (Kaiser 2015, p. 221-236).

Using these criteria Kaiser argues for distinctions between reductionist explanations, part-whole explanations, and mechanistic explanations.

Given the emphasis on mechanistic accounts in chapter two it is important to take a moment here to examine both the areas of overlap and the differences between mechanistic and reductionist accounts of explanation. Kaiser distinguishes between them by arguing that mechanists require that the parts in an explanation be internal to the phenomenon of interest, but do not require that they are either lower-level or understood in isolation. However, this differs importantly from the characterization I offered in chapter two. In chapter two, I argued that it was essential for mechanists that at least some of the properties of the entities involved in a mechanism were understood essentially in isolation. Kaiser rules this out by saying that mechanists "do not restrict the kinds of organization of and interactions between parts that are allowed in mechanistic explanation to those that can be discovered by studying the components of a mechanism in isolation" (2015, p. 241). However, I argue that this line of reasoning confuses methodological reduction with epistemic reduction.

Kaiser is correct that the methodology of mechanists does not restrict them to studying the isolation of parts involved in a mechanism, however their explanatory demands do restrict the kinds of properties that can be attributed to parts of a mechanism. The ultimate epistemic demand seems to be that mechanistic explanations are reductive in some minimal sense. This demand gives rise, at least partially, to the difficulties mechanists have with processual phenomena, as we saw in chapter two. Since the components of an explanation are supposed to be internal, at a lower level, and

understandable in isolation (or in other words, reductive), mechanists have difficulty accounting for phenomena that violate these conditions. Recall that in chapter two, I argued that organisms which engage in metabolism across the tree of life will commonly have the kinds of properties that will be challenging for mechanists to account for, two of which (context dependence and multiple realizability) will be discussed next.

4.2.2 Objections to Reductionism in Biology

Two of the major objections to reductionism in biology have been context dependence (e.g. Hull 1974, Wimsatt 1979, or Gilbert and Sarkar 2000) and multiple realization (e.g. Hull 1974 or Kinkaid 1997). These are also two of the features that are challenging for mechanistic explanation in biology, as seen in chapter two. For example, bacteria that are helpful partners in digestion, but deadly when found outside of the G.I. tract have context dependent functions. In other words, their function (to aid in digestion or cause illness) depends on their surroundings. Further, the functional aspects of digestion for which we need bacterial assistance can be performed by multiple different types of bacteria which displays multiple realization. In other words, one function (digestion) can be fulfilled by many different parts (many different types of bacteria). The presentation of these as problems for reductionist explanation as well as mechanistic explanation lends further credence to the intimate relationship between mechanistic and reductionist explanation.

The first key challenge (context dependence) is that the effect of many molecular entities or mechanisms depends strongly on the context in which they occur. Such

phenomena are often referred to as 'one-many phenomena', because one entity or mechanism can be the cause or explanation for many different phenomena. The idea here is that the context the entity or mechanism finds itself in is what influences which particular phenomenon is caused. The second key challenge, multiple realization, is that the same higher level phenomenon can be produced by several different kinds of molecular configurations. Such phenomena are often called 'many-one phenomena', because many different molecular configurations can give rise to one type of phenomenon. Examples of these kinds of phenomena are common in the natural world. In chapter two, the context sensitive functionality of bacteria in the human body was an example of a one-many phenomena – the same bacteria that in one context can be helpful and in a different be near deadly. Digestive function was the primary example of a many-one phenomena; this single functionality can be realized by a great many different molecular configurations. Such phenomena pose challenges to reductionism because they do not allow for explanations using a fixed set of lower level entities or properties.

All explanations involve representation – they take the features of the system and symbolize them in miniature, mathematics, or other abstract symbolics. While some have argued that explanations are things (in other words, concrete causes in the world) (e.g. Craver 2014, Salmon 1989, or Strevens 2008), explanations are better conceived of as essentially including representations of the phenomena in question (Bokulich, 2018). In his account of reductive explanations Sahotra Sakar argues that different representational choices will lead to different types of reductive explanations (1998). Sarkar distinguishes between three different axes along which to characterize attempts at reductive

explanations (1998, p. 43-45). Sarkar's representational criteria are fundamentalism, abstract hierarchy, and spatial hierarchy. According to Sarkar, fundamentalism occurs when some feature of a system is explained by features from another realm than the system itself (as represented) (1998, p. 43). Abstract hierarchy occurs when the representation itself has an explicit hierarchy, and "the explanatory factors refer only to properties of entities at the lower levels of the hierarchy" (1998, p. 43). Finally, spatial hierarchy is the same as an abstract hierarchy, but it occurs in physical space, in other words, the entities that are evoked in the explanation are spatially contained within the explanans. Whether or not the two major problems for reductionism (one-many or many-one relations) occur depends, at least partially, on the representational choices that are made. How the system is represented will importantly change how the system is ultimately understood.

4.3 Temporal Reductionism in Biology

While it is clear from what has been said so far that the ideas raised by this dissertation through thinking carefully about the role of time in biology can intervene in important ways on existing discussions of reductionism in biology, much of the existing conversation on reductionism has not incorporated considerations of time. There are, however, a few areas where reductionism conversations have explicitly considered time. In discussing these, it is important to note that I am not interested in so-called diachronic reduction of one theory to a successive theory historically (e.g. Rosenberg 2006, Dupré

1993), but rather how the temporal dynamics of biological phenomena affect the ability to generate ontological, methodological, and epistemic reductions.

The traditional distinction between synchronic and diachronic reduction misses the possibility of temporal aspects within biological entities. Although not discussed, this was surprisingly foreshadowed in Nagel, when he says:

> The contrast between structure and function is evidently a contrast between the spatial organization of anatomically distinguishable parts of an organ and the temporal (or spatiotemporal) organization of changes in those parts. What is investigated under each term of the contrasting pair is a mode of organization or a type of order. In the one case the organization is primarily if not exclusively a spatial one, and the object of the investigation is to ascertain the spatial distribution of organic parts and the modes of their linkage. In the other case the organization has a temporal dimension, and the aim of the inquiry is to discover sequential and simultaneous orders of change in the spatially ordered and linked parts of organic bodies. (Nagel 1961, p. 426)

Nagel here is pointing out what has been a key idea of this dissertation, that biological entities have internal timescales that are inescapably apparent when we pay attention to their functionality. This was the foundation of the claims in chapter two, that paying attention to the temporality of biological entities highlighted their processual character. A similar foreshadowing can be seen in remarks made by Philip Kitcher on developmental biology, when he writes:

> Because developmental processes are complex and because changes in the timing of embryological events may produce a cascade of effects at several different levels, one sometimes uses descriptions at higher levels to explain what goes on [later] at a more fundamental level. (1984, p. 371)

Here Kitcher is also pointing to particular challenges for reductive explanation that are posed by the processual character of development. While ultimately I raised concerns about using metaphysical ideas to guide methodological choices, in so far as we are interested in metaphysical reductionism, this focus on temporality is quite informative.

The recognition of Nagel and Kitcher — examining the organization of changes in biological phenomenon will expose different aspects than merely examining their spatial arrangement— is quite similar to the arguments of the processualists detailed in chapter two.

More recently the importance of time for reductionism has been noted by Andreas Hütteman and Alan Love, who argue that temporality is, in fact, one aspect of what makes an explanation reductive. Following Nagel, they argue that any causal explanation will involve some element of temporal duration, and that this temporality is a unique mark of biological explanations (2011, p. 531). While physical explanations are often atemporal, biological explanations almost always involve a temporal aspect. Hüttemann and Love argue that temporally reductive explanations "explain the state of a compound of whole … in terms of states of the parts at earlier times" (2011, p. 533). Hüttemann and Love believe that temporality is an important, and frequently missed, dimension of reductive explanations that can be helpful to examine when looking at the success or failure of reductive explanations. In this argument from Hüttemann and Love we see the beginning of the idea of considering the role of time for reductionism, although this is not elaborated in sufficient detail. Their argument does not go far enough in accounting for the importance of time, but their argument does show how we can consider temporal reduction in the sense that I am interested in. This will be explored further in section 4.5.

Temporality also seems to play an oft-missed role in metaphysical arguments about reduction. Recall one example of a processual ontological concept from chapter two: the pan-genome of bacterial species. The genomes of each bacterium on their own

cannot define the species genome. Since the pan-genome is undergoing constant change, if one were to define the pan-genome at one moment in time, it would have already changed. Further, the pan-genome of a species will almost necessarily be too complex to predict without actually sequencing the genome of every individual member of the species. Accordingly, the concept of the pan-genome seems to fit Bedau's definition of a weakly emergent state (i.e. a state of a system that is definable only by simulation) (Bedau, 1997).

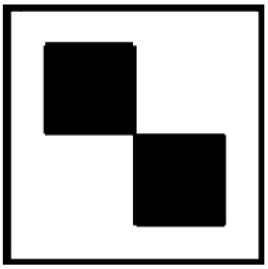

Figure 4. 1 Bow-tie shaped grid (as found in Humphreys 2008)

Paul Humphreys (2008) argues that Bedau's notion of weak emergence "has an essentially historical aspect". By this he means that there could be two systems with indistinguishable macrostates, and one could be weakly emergent due to its history, while the other could not be emergent at all. Consider a simple two-dimensional grid on which cells are either black or white. On this grid each cell state is updated at each step by a deterministic rule that is a function of the current state of the cell and its immediate neighbors. Humphreys offers a grid (figure 4.1) that makes the following pattern by following the rules after an indefinite number of steps. We can think of the property displayed by this large grid – the bow-tie shape – as weakly emergent. It is essentially true by definition that the system is too complex to predict without actually running through each intermediary step. However, Humphreys points out that if one were to instantaneously print exactly the same pattern using a rubber stamp, we would not consider that bow-tie shaped pattern as emergent. He concludes, "It is therefore

impossible to determine whether a pattern is emergent by looking only at synchronic relations between the pattern and the spatial array of elements that comprise that pattern" (2008, p. 434). Incorporating time into the understanding of an entity is, therefore, required to reveal uniquely emergent properties.

4.4 Two Case Studies on the Importance of Time for Reductionism

There are two key examples deployed in the literature that are worth discussion in the context of temporal reduction. First, there are attempts to reduce protein structure to the linear sequence of amino acids which are discussed by Hüttemann and Love (2011). Second is the discussion of temporal dynamics in activity networks by Green et al. (2018); each will be examined in turn. These examples are instructive for understanding how laboratory work in biology can be used to inform discussions of the role for time in reductionism.

First, I will consider the reduction of protein structure to amino acid sequence. Proteins are made up of amino acids. The first step in their construction involves the translations of DNA triplets into a sequence of amino acids that get linked together in a linear sequence. This linear sequence is called the "primary structure" of the protein. Proteins are also folded into local repetitive structures like α-helix or ß-sheets(secondary structure) and often these folds are further folded into a larger globular structure (tertiary structure) to create their ultimate functional conformation[1]. Many have argued that the three-dimensional protein structure is the result of the linear sequence of amino acids and

[1] Conformation is a technical term used in describing the shape of proteins.

their interactions alone (this is often called the "linear sequence hypothesis"). Francis Crick, for example, wrote: "It is of course possible that this is a special mechanism for folding up the chain, but the more likely hypothesis is that the *folding is simply a result of the order of the amino acids"* (1958, p. 144). While there is some evidence that the sequence of amino acids itself is important for the ultimate tertiary structure of the protein, there is also good evidence that it is not sufficient.

There are several reasons why it cannot merely be the linear sequence of amino acids that is responsible for the ultimate protein structure. For example, chaperone proteins (other fully formed proteins) guide the folding process in important ways (e.g. Frydman 2001). Also, protein structure is not a static achievement. Rather, the shape necessary for a protein to be functional is a dynamic oscillation between a few preferred states (Eisenmesser et al. 2005). Hüttemann and Love argue that temporality is important for understanding the usefulness of this sort of philosophical analysis to ongoing research projects (2011). Hüttemann and Love point out that researchers often make seemingly paradoxical statements about chaperone proteins falsifying the linear sequence hypothesis (2011, p. 541-542). This apparent conflict arises because of an ambiguity surrounding the temporality of the original claim. The linear sequence of amino acids cannot be part of a temporal (i.e., causal) reduction, however this does not conflict with the predictive value of the linear sequence of amino acids. They write:

> Robust inferences of three-dimensional conformation from linear sequence information are possible in the absence of details about the causal (temporal) process of protein folding in the cell, and researchers focused on the predictive construal need not deny that extrinsic molecular chaperones are necessary and specific causal factors for protein folding in vivo. (2011, p. 542)

Ultimately Hüttemann and Love view the temporality as a lenses through which we understand the practices of working scientists. Without understanding the role of time in reduction, one might misunderstand the difference between the metaphysically reductive claim and the predictively reductive claim about the linear sequence hypothesis. Not only is time playing a key role in the conceptual mistake which confuses whether or not the sequence of amino acids can be considered as reductive of protein structure, but temporality is key to the nature of the phenomenon itself. When we fail to consider time as one of the aspects in a conversation about reductionism, we will fail to understand distinctions such as this one made by Hüttemann and Love (2011).

Next, I will consider the temporal dynamics in activity networks. Most graph-theoretic studies of biological networks treat the system of interest as static, or at least the time of activities at different nodes is not differentiated. However, in real cells, different activities occur at different timescales and functioning is often dependent on order and timing. Thus, we have a question about how to build the temporality of biological systems into graph-theoretical models. Sara Green, et al. (2018) examined work done on protein-protein interactions during the cell cycle of yeast. Protein-protein interactions are assumed anytime two or more proteins are shown to be able to bind, which is indicative of their ability to interact in living cells. High-throughput studies of protein interactions are used to generate network analyses that can identify complexes of proteins that are expressed together. Using information about co-expression, researchers can come to understand how protein complexes are organized to perform cellular functions. The work that Green and colleagues consider comes specifically from the laboratory of de

Lichtenberg and colleagues who study *S. cerevisiae* (a particular yeast species). De Lichtenberg and colleagues integrated information obtained from static protein-protein interaction studies with time-series data about gene expression in order to develop a richer picture of the functional organization of proteins in the yeast cell cycle (2005).

By integrating the internal temporality of the system into their research methods, de Lichtenberg and colleagues were able to, among other new discoveries, identify new functional modules of the cell cycle. They found that Nis1p and Yol070p, two proteins whose functions were unidentified previously, were part of a Nucleosome/Bud formation module (de Lichtenberg, et al. 2005). De Lichtenberg and colleagues also discovered that protein complexes are assembled just in time for their use (2005). For example, the members of the pre-replication complex Orc1p and Orc6p are constitutively expressed, but different proteins are synthesized to bind with the Orc proteins at different phases of the cell cycle (de Lichtenberg, et al. 2005). Importantly, Green and colleagues point out that:

> Rather than beginning with a mechanism and determining its temporal patterns, as in more traditional mechanistic research, the strategy consists in building a system-wide representation of the time expression across the whole network which reveals how the nodes in a cluster relate temporally throughout the cell cycle. Moreover, this focus on the temporal dimension of the protein interaction network gives rise to a research strategy for discovering new mechanisms and their organization. (2018, p. 1764)

The focus for Green and colleagues is to motivate network analysis as an alternative to mechanistic explanation. This parallels the points I made in chapter two about the limitations of mechanistic explanation. Further, this pushes the idea that mechanistic explanations are reductionist in at least some important senses. We can, however, see in this analysis another important idea. Specifically, the work of de Lichtenberg and

colleagues is an example of non-reductionist research methodology serving an epistemically reductionist agenda. Methods that were reductionist, and failed to account for the temporality of the system, were not able to uncover the mechanisms, or ultimately reductionist explanations that became available using these methods. While one may assume that the incorporation of more information into our research methods will lead to more complicated epistemology, this will not always be the case (as is seen here). These examples again highlight the importance of understanding the complex relationship between reductionist methods, reductionist ontologies, and reductionist epistemology.

Rather than revealing one unified role for time, these cases reveal how incorporating temporality in our discussions of reductionism can expose new aspects of the reductionism debate.

4.5 Philosophical Issues of Temporal Reduction

So far we have considered the role that time can play in intervening in the existing conversations about reductionism. The temporal extendedness of biological entities means that certain sorts of methodological, epistemic, or ontological reduction obscure some aspects of those entities. We saw this in chapter one, and have applied many of these lessons so far in this chapter. There is, however, another way of understanding the role of time in reductionism – that is to consider directly whether we could or should be reductionist about time. We saw earlier that Hüttemann and Love argued that explanations need to include only statements about parts of a whole from an earlier time to be considered fully reductive. In this section, I will consider the prospects for

temporal reductionism — the idea that temporal properties, explanations, objects, etc. of one domain can be constructed from or explained by the properties, explanations, objects etc. of some lower domain. Temporal reductionism, like any reductionism, could come in metaphysical, epistemic, or methodological forms. While the idea of temporal reductionism has yet to receive any real attention, this section will argue it is a fruitful area for future research.

It is important to begin by merely understanding what each of these types of temporal reductionism would look like. A metaphysical reductionist account of time might say that some timescale (or duration) is made up of nothing but smaller units of time (e.g. an hour is made up of minutes). An explanatory reductionist about time might say that anything that happens at one timescale is explainable in terms of things that happen at a smaller timescale (e.g., some phenomenon that takes one hour is explainable in terms of phenomenon that take minutes or seconds). Finally, a methodological reductionist would say that phenomena are best studied in terms of the shortest timescale possible (e.g., a phenomenon that lasts one second is best studied by methods that investigate the phenomenon at the scale of milliseconds).

Biologists and philosophers of biology are almost certainly not interested in directly answering questions about a metaphysical reduction of time itself. Thus, one might suspect that this is not an important concept for a discussion of time in biology. However, as I argued in chapter two, our implicit metaphysical assumptions often guide our methodological choice. Thus understanding that there are different options for understanding the nature of time, and that reductionism is only one choice, can help

inform discussions of those aspects of temporal reductionism that are more directly applicable to biological science.

Given that biologists often treat time as an independent phenomenon that occurs at a continuous rate regardless of biological events, being a temporal reductionist might seem quite natural. If time is an independent phenomenon, then it seems quite natural to think of it simplistically as being uniquely and evenly divisible. This sort of metaphysical presupposition has often been taken to guide the inference to temporally reductive methods or explanations. However, much of this dissertation has made this sort of picture of time as an independent external phenomenon seem questionable. Chapter one argued that timescales should be thought of as internal or external to a system of interest. This means that timescales cannot be defined without reference to a particular system. Timescales like hours or years are external to biological systems and phenomena (at least most systems and phenomena of interest) and can be thought of in a sense as independent. However, these timescales are not independent of any system – they are not occurring at a constant rate regardless of the goings on of the world. They are rather constituted by changes occurring in the world, just changes that happen to be external to systems biologists are typically interested in studying. Again, it is not that biology can give answers about the metaphysical nature of time itself, but rather about the ways biology has of understanding or measuring time.

Consider the difficulties posed by timescales for how we are to understand the relationship between parts and wholes. There is, on the one hand, the timescale of the life of my cat, and on the other, the timescale on which various processes within her are

occurring. The reductionist would simply assert that the best methods are those that investigate on the scale of the latter, or that the best explanations will explain the former in terms of the latter. It is clear that we cannot solve the problems of biology by choosing one scale, but instead we will be forced to consider multiple timescales. Further, it isn't clear that the shorter scale will always be the best methodological or explanatory choice. The methods and explanations detailed extensively in chapter three depend on changes occurring in the world in such a way that makes studying or explaining only at the lowest scale seem improbable. The issue is a comparison of scales rather than a reduction of timescales.

Examples like the protein-protein interaction network analysis study and DNA mutation rate analysis also bring into question methodological and epistemic reductionism about time. For starters, the research by de Lichtenberg and colleagues represents a methodology that is not merely not spatially reductionist, but it is specifically designed to also not be temporally reductionist. These researchers integrated temporal information about when and for how long different proteins were expressed in order to generate their network analysis. The integration of temporal information into the methodology is an example of non-reductionist temporal methodology. This methodology was, however, attached to conclusions that were epistemically reductionist – emphasizing once again how these types of reductionism can come apart. Further, research into DNA mutation rate variation (discussed in chapters one and three) shows how we can have explanations that are not reductionist about time. As Simon Ho and colleagues showed, the rate at which DNA mutates varies depending on the timescale on

which one constructs the observation. This way of understanding DNA mutation rates explicitly includes the importance of timescales. Both of these examples mark cases where the reduction of temporality would mean a loss of information. While there are other cases where temporally reductionist methods and explanation have proven useful, these examples (and others like them) undermine the idea that temporally reductionist methodology and epistemology will be the only ultimately valuable methods and explanations in biology.

Reductionism has often been seen as a route to unity in the sciences – here I do not mean a specific reduction of one theory or explanation, but rather the global idea that reduction is the ultimate goal of science. The idea behind this goal can also be metaphysical, methodological, or explanatory. The most famous assertions of global reductionism in science are that of Nagel (who earlier was credited with inspiring much of the reductionist project in the philosophy of biology) and Carl Hempel. Both of these reductionist accounts are focused on the epistemological dimensions of science (Cat 2017). Most philosophers of biology accept a metaphysical reductionism asserting that the predominant remaining reductionist questions surround only methodology and epistemology. Since the physical world (usually understood spatially) is made up of nothing but physical material, everything that exists can be considered physically reducible. However, the reintroduction of time into the understanding of the biological world can make reductionism as a route to the unity of the sciences seem less promising. Since at least parts of this dissertation have questioned prospects for reductionism, that could be seen as a challenge to the idea of unity in the sciences.

4.6 Conclusion

One way to understand this dissertation is to see that each of the first three chapters focuses on one of the types of reductionism (methodological, ontological, or epistemological). This chapter is, in some ways then, a sort of synthesis of many of the major themes of this project. The methods and representations that were categorized as abstracting from time, could also be seen as reducing time. The mechanistic metaphysical framework can be seen as (at least) a temporally reductive framework. Finally, this chapter has shown how some methods or explanations that seem reductive might fail to be temporally reductive, and how a focus on temporality can help reveal some of the non-reductive qualities of biological entities.

CONCLUSION

Despite the lack of sufficient philosophical attention to the role of time in biology, there are numerous philosophical issues on which a more careful attention to time can shed new light. This dissertation has shown that a focus on time in biology exposes new features of debates about scientific metaphysics, epistemology, and scientific practice. While this has been under-appreciated, it should not come as a surprise, since this dissertation has shown the essential role of timescales in biological phenomena and in biology as a science. While it is of course necessary in scientific practice to abstract from the phenomena under consideration, the systematic obstruction of time has led to missed scientific opportunities and philosophical misunderstandings. This dissertation has exposed some of the specific consequences of this abstraction, but more generally exposed the practice of ignoring temporality, and thus made it possible for further consequences to be better understood.

The first chapter demonstrated four common ways in which biologists abstract from time: physically, procedurally, mathematically, and conceptually. This chapter argued that in some circumstances, in particular for research concerning the rate of DNA mutation, these sorts of abstractions can obscure relevant aspects of the phenomenon. In the case of DNA mutation, we saw that the timescale of observation changed the observed mutation rate. Chapter two argued that the newly proposed process ontology has the potential to bring temporal issues to the fore. However, chapter two also demonstrated how different metaphysical frameworks can be more epistemologically appropriate in different contexts, and argued for a metaphysical pluralism when choosing

frameworks to guide methodological choices. Chapter three examined how molecular and fossil clocks are used to measure time in biology. This chapter argued that attempts to synchronize biological clocks demonstrate how to make discordant and interdependent lines of evidence jointly epistemically useful. The final chapter argued that time can also change the way we understand the prospects for reductionism in biology. Biological science makes ineliminable use of multiple timescales, which, I argue, makes any form of reductionism (ontological, methodological, or epistemic) untenable. Focusing on the multiplicity of timescales which are all important for biological sciences lends new challenges to reductionism in biology.

One of the core themes of this dissertation has been the advocacy for pluralism in scientific research. In chapter two, I argued that restricting ourselves to one metaphysical framework would unduly limit our scientific prospects. So here I must add the same qualification for focusing on time. Part of what makes the processual framework promising in biology, is its ability to incorporate temporality into scientific explanation, however, temporality will not be an important part of every biological explanation. Any focus we choose can only reflect some aspect of the world, and will inevitably be flawed or miss something else important about the world. It is the practical aims as determined by those who make use of the concepts and frameworks in science that need to guide appropriate decisions about where to focus. An elevation map wouldn't be very helpful if you're looking for directions to the nearest grocery store, and a road map wouldn't help a hiker find the top of a mountain either. Similarly, whether or not it is appropriate to abstract from time ought to be a contextual and methodological decision. Yet this choice

is not arbitrary, since the success of a given representation is constrained by features of the world itself. My intention is not to banish mechanistic thinking, or other systems that abstract from time, but rather I advocate a pluralism about our scientific representations and conceptions of the world, such that a focus on time at different scales and to varying degrees will be one among many ways of examining the biological world.

We have also seen the conflict between what is accessible to study empirically and the phenomena itself. In chapter three we saw that even when time is the explicit focus of biology as a science, there are still important issues which arise to the differences between what is accessible as an object of empirical study, and that which we wish to know or explain. In this respect, time is not different from the other objects of scientific inquiry. In any area of science, there is always much to be gained by exposing the gap between what we seek to understand and what we have empirical access to. By focusing on the differences between what we want to know about time, and what is accessible to empirical study we can better understand the nature of measurement and the relationship between evidence and knowledge. It is through iterative comparison of methods (both of their results, and their internal assumptions) that we come to have better methods for generating evidence and better knowledge. This iterative process is what helps to close the gap.

Time can often have the feeling of being a constant force in the world, and most biologists have let this feeling guide the way they understand the role of time in biology. However, it is the job of science to help carry us beyond our limited perspectives, and towards a richer understanding of the world we live in. One could argue that what the

development of the theory of evolution required was a radical departure from our own temporal perspective. It seems prima facie obvious to me that species are not changing, but that is simply because of the timescale on which my perception takes place. Unfortunately, much of modern biological practice, as this dissertation has shown, is set up to restrict our ability to see outside of our own temporal perspective. If we naively allow our own temporal biases to guide biological practice, we might miss the kinds of ideas that are made manifest by consciously acknowledging the way we understand time and timescales. While it is hard for us to tell us what such an acknowledgement might expose, but there are certainly good reasons to think it will be an illuminating and fruitful endeavor.

In the end, we can see even more fully the wisdom in Haldane's warning. By ignoring the importance of the temporal aspect of biological science, we have limited our ability to understand biological entities and systems, and constrained the overall project of biology. Through a detailed examination of the role of time in biology, this dissertation has endeavored to free us from these constraints in order to allow us to operate from novel perspectives in our examinations of the natural world. We have seen this to be both of importance for scientific projects (e.g. understanding how DNA mutations rates vary according to the timescales of observation) and to philosophical debates (e.g. the mechanistic vs. process debate). There is much to gained through such investigations and by exposing the role of time in biological entities and biology as a science; we take the first steps towards new frontiers of understanding.

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