Medical Innovation: Using mechatronics engineering to reduce inequities in healthcare

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A thesis submitted for the degree of

Doctor of Philosophy

in

Bioengineering

at the

University of Canterbury

Christchurch, New Zealand

April 1, 2022

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Acronyms and abbreviations

2FA	Two-factor authentication
ACTIV	Actuated, closed-loop, time-series, inspiratory valve
ADC	Analogue to digital converter
APS	Artificial pancreas system
BG	Blood glucose
BOB	Blood opitical biosensor [CGM]
BOM	Bill of materials
CGM	Continuous glucose monitor
CPAP	Continuous positive airway pressure
COVID-19	Novel coronavirus disease
DC	Direct current
DHB	District Health Board
DIY	Do-it-yourself
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
EGP	Endogenous glucose production
FDA	Food and Drug Administration
FGM	Flash glucose monitor

FSM	Finite state machine
GDP	gross domestic product
GP	General practitioner
GUI	Graphical user interface
HEPA	High-efficiency particulate absorbing
HIV	Human immunodeficiency virus
I2C	Inter-intergrated circuit protocol
ICING2	Intensive control insulin-nutrition-glucose model system
ICU	Intensive care unit
IOT	Internet of things
ISO	The International Organization for Standardisation
LEAPS	Low-cost, equitable APS
LED	Light-emitting diode
MDI	Multiple daily injections
MMOIST	Model-based modified OGTT insulin sensitivity test
MIR	Mid infrared
NIR	Near infrared
NSIO	non-specific interoperability
NZ	New Zealand
OpenAPS	Open artificial pancreas system
OGTT	Oral glucose tolerance test
PANDA	PANDAPeep Gen2 Inline Valve — a DIY PEEP valve
PCB	Printed circuit board
PEEP	Positive, end-expiratory pressure
PIP	Peak inspiratory pressure
POC	Point of care

PPE	Personal protective equipment
PPG	Photoplethysmography
RT-CGM	Real-time continuous glucose monitor
RTC	Real-time clock
RRI	Responsible research and innovation
SD	Standard deviation
SIO	Specific interoperability
SMBG	Self-monitored blood glucose
SME	Small- and medium- sized enterprises
STAR	Stochastic targeted glycaemic control
SPI	Serial peripheral interface protocol
TAR	Time above range
TB	Tuberculosis
TBR	Time below range
TDD	Total daily dose
Tech-ISM	Framework for technology adoption
TIR	Time in range
UI	User interface
UK	United Kingdom
ULC	Ultra-low cost [insulin pump]
USA	United States of America
USD	USA dollars

Abstract

Medical device innovation provides access to healthcare. Innovations come about because of pressures, in particular financial pressures, and access to care. With increasing interoperability of devices, distinction is made between devices with specific interoperability (SIO) only able to communicate with a pre-determined range of other devices, and non-specific interoperability (NSIO). Devices with NSIO pose substantially greater potential benefits by allowing long-term system wide innovations.

Scales of innovation are discussed, where short-term innovations meet an immediate need, such as the inundation of intensive care units (ICUs) in the COVID-19 pandemic. Medium-term innovations see either incremental increase in efficiencies, or an increase in interoperability which enables subsequent innovation. Long-term innovations are disruptive, systemic changes, often enabled through the use of increasing interoperability. The uptake of innovation is often lacking, but through the use of a framework such as Tech-ISM the chance of adoption is increased. This framework sees establishment and fostering of close relationships with a range of end users, decision makers, and industry partners.

Diabetes technologies are presented as examples of innovation. Insulin pumps are an effective method of delivering insulin, and see considerable benefit in control. Widespread adoption of insulin pumps is posed through the development of an ultra-low cost (ULC) insulin pump, made possible by the separation of hardware and computation, and costing $12\times - 20\times$ less than currently-available devices, both for a traditional-style insulin pump, and also a novel spring-driven design.

Initial results show similar accuracy to current commercially-available insulin pumps, with a mean error of 0.64%, the same as the MiniMed™640G (Medtronic, Dublin, Ireland) for $1\ U$ boluses, and mean error of 0.06% for $10\ U$ boluses. Basal windows of 1 hour are similarly accurate, with 100% within $\pm15\%$, 92% within $\pm10\%$, and 84% within $\pm5\%$, again very similar to the MiniMed™640G. The ULC insulin pump is a solution to the economic infeasibility of insulin pumps for the majority of New Zealanders.

System-wide adoption of insulin pumps would see considerable economic benefit for New Zealand, in particular with a patch pump. Several possible adoption scenarios are presented. Annually, direct savings associated with less insulin use and current public investment in insulin pumps is expected to total \$6.6M - \$25.3M, indirect savings from reduction of expensive complications are expected to save \$2.5M - \$25.5M, with direct costs of \$0.8M - \$25.7M. Projections are for a total overall system saving of \$8.3M with no additional uptake of insulin pumps, but only replacing current insulin pumps with the ULC alternative, to \$25.0M with widespread adoption. These figures do not account for additional savings made possible through future long-term development of smart, automated healthcare systems.

A continuous glucose monitor (CGM) is a device that estimates blood glucose (BG) every 1-5 minutes, replacing discrete, invasive self-monitored blood glucose (SMBG) measurements as required four to ten per day currently for approximately 40,000 - 60,000 New Zealanders with diabetes who administer insulin. Current CGM use is limited, but relatively unknown, due to no public funding, with expert estimates at 2-8% prevalence among individuals with type-one diabetes. A low-cost alternative is presented in the form of the blood optical biosensor CGM (BOB CGM) at an annual cost $10 \times -20\times$ less expensive than current devices. Initial, un-calibrated results show promise, with 91% of BG results deemed clinically accurate, and a further 8% sufficiently accurate to not cause treatment error. Fundamentally, cost savings arise from allowing access to otherwise inaccessible data, and thus turning the current data monopoly into a data market. Substantial economic benefit is seen from direct savings from current monitoring of diabetes disease progressions with SMBG and glycated haemoglobin (HbA1c), and also indirect savings from earlier identification of worsening diabetes control. Various adoption scenarios are presented, with overall annual economic savings of $1.9M - $25.1M.

Another medical innovation is presented in the form of the actuated, closed-loop, time-series inspiratory valve (ACTIV) dual ventilation system. This innovation is a short-term example, developed under pressure of inundation of the healthcare system due to the novel coronavirus disease (COVID-19). The basic operating premise is ventilatory effort from a single mechanical ventilator is delivered first to one patient, and subsequent to a valve switching state, to a second patient. The system is a solution that addresses valid concern for multiple ventilation from a consensus of oversight bodies for ICU

treatment, in particular personalised therapy and monitoring, especially in the case of changing pathology. The system is designed to be low-cost, robust, portable, and readily manufactured in low-resource environments. Thus, it has an Arduino (Arduino, Massachusetts, USA) controller, and requires a 5.0 V power supply.

The system requires a flow and pressure sensor for detection of inspiration, and subsequent valve switching. A custom-made 3D-printed Venturi interfaced with simple electronics with an analogue $0.0 - 5.0\ V$ output signal is presented. The sensor is validated against data from mechanical ventilation devices to be accurate over the range of $5 - 75 L \cdot min^{-1}$, with a Pearson Correlation ≥ 0.95 for flow and pressure, typically ≥ 0.97 in 5 S bins at $f_s = 50\ Hz$. Additional components are a 3-D printed pressure drop device in the form of the PANDAPeep Gen2 Inline valve, and off-the-shelf one-way valves, airway filters, and 22 $mm\oslash$ tubing.

The switching ACTIV valve is another 3D-printed component, and uses a common HXT12K servo motor, or similar, for interoperability. The Arduino-based control system is a basic finite state machine (FSM) relying on low-pass filtered flow sensor data, implemented through a circular buffer, for state changes. These state changes, in combination with various necessary delays for safety, dictate the change of state of the ACTIV valve, and thus to which patient ventilation effort is delivered. An example of two considerably unbalance patients, with compliance $C_1 = 0.10\ L \cdot cmH_2O^{-1}$and $C_2 = 0.05\ L \cdot cmH_2O^{-1}$, being safely and efficiently balanced to achieve equal tidal volume is demonstrated to show individualised therapy and monitoring.

Without innovations such as the diabetes technologies and ACTIV system, care will become increasingly rationed. Rationing of diabetes devices with high effectiveness, but also high cost, is already seen in the lack of public funding for CGM devices, and funding for only 8-10% of individuals with type-one diabetes to access insulin pumps, despite significant proven benefits of both of these devices. Since 2000, increases in direct out-of-pocket expenditure have grown an average of 4.3% per annum, compared to median wage growth of 3.2%, and inflation of 2.6%. These trends show that the rationing of healthcare is being seen in a reduction of access to publicly-funded services. Given an average annual wage increase of only 1.6% for the lowest 20th centile, individuals who are least well off are less able to afford the required personal expenditure to attain the same access the healthcare. Therefore, access to healthcare is seeing worsening equity of access.

With increasing demand for healthcare, and a taxation base stagnant at best, relying only on intrinsic changes, New Zealand faces significant taxation increases, or drastic reductions in healthcare services. The alternative is to increase the efficiency of healthcare delivery methods, using extrinsic, disruptive changes. These changes are only made possible through innovation informed by strong clinical insight, developing mechatronic devices with broad, non-specific interoperability, if not open-source design. This approach provides equitable access to care, and provides the necessary framework for automation of healthcare services, including diagnostics, prognostics, and personalised care models under a one-method-fits all approach. This widespread technological innovation and adoption poses significant increase of access to care, combating current inequities.

Part I

Background and Context

Chapter 1

Introduction

Diabetes is a global health crisis, requiring a global response to combat. Current inequities of access to care are profound, with affected individuals in low- and low-middle-income countries suffering disproportionately, due to financial constraints preventing access [1, 2]. In high-middle- and high- income countries, there are worsening inequities of access to care and to outcomes, with individuals in minority indigenous groups and of low socio-economic status receiving worse care [3]. Subsequently, these groups see greater human and financial costs from diabetes, creating positive feedback of worsening outcomes including shorter life expectancy, worse quality of life, and lost productivity.

Technological innovations present solutions increasing access to care in New Zealand. Access to insulin pump and continuous glucose monitor (CGM) technologies enable better outcomes of care, with improved glycaemic control, higher patient satisfaction,

and higher adherence to prescribed protocols [4]. However, current access to devices is rationed to limit system financial costs [5]. Low-cost, highly-interoperable devices could provide widespread adoption, with decreasing complications with high human and social cost [6], and providing a foundation for future developments in automated, digital-twin driven healthcare delivery methods [7].

Similar inequities potential inequities of care arose due to the pandemic of the coronavirus disease (COVID-19). A significant shortfall in available ventilated intensive care unit (ICU) bedspaces was predicted, and subsequent care-rationing guidelines published [8]. Short-term innovations to meet this need were widespread, including conversations regarding ventilation of multiple patients from a single mechanical ventilator. However, the solutions proposed failed to address concerns raised by a consensus statement for multiple ICU oversight organisations [9]. A solution which diverted ventilation to one of two patients in a time-series manner would address these concerns [10, 11]. Design constraints include the ability for construction in resource-poor regions, portability, and robustness.

The research presented in this thesis investigates and presents medical innovations within the two identified areas. Background specific to medical device development is presented, discussing both drivers for innovation, and the economic context of growing inequities in healthcare expenditure in New Zealand, specifically in the context of diabetes. Low-cost, open-source, highly interoperable designs are presented for both an insulin pump and a CGM. Initial validation data from bench testing and early clinical results are presented. A critique of proposed methods for ventilating multiple patients from a

single ventilator provides context and justification of the actuated, closed-loop, time-series inspiratory valve (ACTIV) dual ventilation system. The innovation of the ACTIV system is subsequently presented, including design of specific subsystems and validation on a physical lung model.

1.1 <u>Preface</u>

This thesis is presented in three parts. *Part I* investigates the background of innovations in healthcare, particularly medical devices. *Part II* discusses the development of innovations in the context of providing equitable access to interoperable diabetes technologies, and *Part III* discusses the development of an acute innovation to meet high demand of mechanical ventilation during the COVID-19 pandemic. Specifically:

Part I — Background and Context presents the context of medical device innovation within healthcare.

CHAPTER 2 — MEDICAL INNOVATION discusses the drivers, time-scales, and uptake of medical device innovations.

Part II — Diabetes Technologies Discusses several innovations within diabetes technologies, both medium- and potential long- term.

Chapter 3 — Pressure for innovation presents the economic pressures for innovation in diabetes technologies.

Chapter 4 — One small driver for big change discusses the context, including economic considerations, and development of a low-cost, widely accessible insulin pump.

Chapter 5 — Continuous glucose monitors discusses the context and development of a low-cost, widely accessible continuous glucose monitor based on a novel light-based sensing methodology.

Chapter 6 — Coming full circle: Closing the loop discusses the integration of the sensor and insulin pump technology.

Part III — Dual Ventilation System discusses the development of an acute innovation to meet high demand of mechanical ventilation during the COVID-19 pandemic.

Chapter 7 — Caring is sharing? discusses the context and theory of series ventilation.

Chapter 8 — Main elements discusses the components of the series ventilation system.

Chapter 9 — ACTIV specifics — switch it up discusses the switching valve and control system which enable series ventilation.

CHAPTER 10 — COMBINED ACTIV SYSTEM discusses the system as a whole, and presents initial validation of the overall series dual ventilation system.

CHAPTER 11 — CONCLUSIONS AND FUTURE WORK discusses the continuation of work from this thesis.

Chapter 2

Medical innovation

Engineering innovation is vital to the continuation of growing efficiency and safety within the healthcare industry.

2.1   Drivers for innovation

Innovations occur because of stress. Financial stress to meet increases in demand outgrowing available resources, or health stress to provide currently unmeetable healthcare needs. Healthcare is expensive. An estimated 10% of global gross domestic product (GDP) is spent on health, or USD$8.3 trillion per annum [1]. In the COVID-19 pandemic, there has been considerable financial pressures, as well as pressure to provide healthcare to an increased number of individuals. While the financial pressures in most

high-income countries have been met with increased funding, the lack of ability to do so in other countries has prompted innovation of tools to meet the increased demand in health services.

GDP and overall healthcare have globally have seen similar growth since 2000, with healthcare having grown 1.8% more than GDP growth, on average, from the period of 2000-2002 to 2016-2018 [1]. Low and lower-middle income countries continue to see a lower per capita spending on healthcare. It is also a smaller portion of GDP in these countries, creating even greater inequitable global access to healthcare [1]. These inequities in access to healthcare translate directly to inequities in access to health outcomes.

While there has been an increase in spending from low and lower-middle income countries, as evidenced in an international increase in life expectancy [12], the portion of healthcare expenditure from out-of-pocket sources has remained high at over 40% of total health expenditure [1]. The self-funded nature of healthcare in these regions is an indication of the continuation of inequitable access to healthcare. Innovation is required to overcome financial inaccessibility to healthcare.

While it would be nice if all innovation was purely altruistic, financial reasons are most often the strongest for innovation in medicine. This issue is evident in the causal effect of medical company ownership by institutional investors on increasing the rate and success of innovation [13], and in the recognition within SMEs that "*research and innovation*

was generally understood to be a means towards increasing the company's success in economc terms" [14].

There are limitations to the strong financial drive for medical innovation. It is easy for SMEs to be limited in their scope of research by venture capitalists [15]. Dominant early customers may stifle further market growth [16]. It is important for innovative processes to not be stifled by financial reasons prior to adoption. These problems can be mitigated through use of proper market analysis, and ensuring a close working relationship between innovators and clinicians [17].

The importance of the relationship between industry and research institutions, such as universities has long been recognised [18]. Research and subsequent innovation supported by both public and private enterprises allows for greater risk in the development of the innovation [19]. Often industry partners will have more practical experience, and thus guide the innovation towards an outcome more likely to be adopted [20].

Recently, innovation processes have emerged seeking balance of commercial interests with other interests. Responsible Research and Innovation (RRI) is one such example, which recognises innovation driven by social and environmental benefits can subsequently create economic benefits [14, 21–23]. While the exact definition of RRI has many interpretations, the underlying principle is innovation is done for the benefit of society [24] in a sustainable manner. There is a low utilisation of the RRI approach, particularly among small- and medium- enterprises (SMEs) [14].

Innovation financed through public institutions is more often addressing societal need in a manner similar to RRI. However, there is growing economic pressure on universities to become entrepreneurial, typically best done in a close relationship with industry [25]. Doing so allows research institutions to translate research into innovative outcomes [25, 26], which if done in a manner aligned with RRI means economic success arises from, and after, social sustainability.

Recognising the necessity for innovation success to be measured more than only financially is well understood among Māori enterprise. The principle of tūhono describes the necessity for success to be beneficial in ways more than only economic [27]. This understanding of a wide range of measures of success is one reason a Māori-lead enterprise could present significant social benefit for New Zealand [28]. An example can be seen in the establishment of Ngāti Porou Hauora for the benefit of an isolated community [29].

2.1.1 Access to care

Access is also a strong driver of innovation in healthcare, for example access to healthcare enabled through access to data. For example, in the innovation of information systems, which typically increase productivity, and access to care through a wider range of healthcare delivery options. One example in New Zealand (NZ) is the development of the widespread information-sharing platform Health Connect South (Orion Health, Auckland, New Zealand). This technology has lead to information sharing throughout the South Island, connecting the information systems of five District Health Boards

(DHBs), covering approximately 20% of NZ's population. [30]. This innovation was driven by the need to increase access to health data, regardless of the medical facility to which the patient presented. Doing so has increased efficiency in automating data entry, decreasing duplicate investigations, and allowing technological familiarity for staff who work across multiple facilities or regions [31], subsequently increasing access to care.

There is inequitable access to healthcare throughout the world. Innovation allows for the development of low-cost alternatives for more widespread consumption of medical devices. While sophisticated devices with more complex and personalisable control algorithms provide a higher level of care, access to devices with basic function, and possibly more manual input, provide significant access to otherwise unobtainable care. For example, the FreeStyle Libre (Abbott Diabetes Care, California, United States of America (USA)) is a flash glucose monitor (FGM) similar to a continuous glucose monitor (CGM), except it requires manually querying with an external device. This added manual measurement requirement means the device is available for approximately half the price of real-time CGM (RT-CGM) devices.

In New Zealand, disparities in access to healthcare between ethnic groups as well as across the socio-economic spectrum are evident. Māori and Pasifika see a significantly higher mortality from preventable illness, with findings showing *"potentially avoidable causes of death make up over half of all Māori deaths and nearly half of all Pacifc deaths"* [32]. Socio-economic disparities also exist, with differences in life expectancy between the least and most deprived of 7.5 years for males and 6.1 years for females [33]. The trends in increasing life expectancy for the least deprived and minimal recent changes

for the most deprived signify that increases in healthcare spending are not providing for equitable access or healthcare, or to outcomes. Global inequities of access to healthcare have a strong historic foundation, and require global collaboration to address.

2.1.2   NON-SPECIFIC AND SPECIFIC INTEROPERABILITY

With the development of modern smartphones and similar devices, there is an expectation for devices to be interoperable [34]. This expectation is seen in the evolution of many medical devices into smart medical devices. For example, diabetes technologies as insulin pumps and CGMs have seen significantly higher levels of interoperability in the last 10 years [35]. Equally, other devices such as smart watches, have become medical sensors [34]. Therefore, new innovation is increasingly seeing the development of increasingly interoperable medical devices.

The level of interoperability of medical devices is variable. Many devices are increasingly locked-down to limit interoperability to a white-list of devices typically from the same company [36]. This list is primarily determined by financial partnerships[1] [37, 38], denoted specific interoperability (SIO).

Devices operating in conjunction with one another demonstrates interoperability. While there are valid concerns about cybersecurity to limit access to interoperability protocols

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[1]One such example of a financial relationship determining interoperability can be seen in between Tandem (Tandem Diabetes Care, California, USA) and DexCom (DexCom Inc., California, USA), where: *"Tandem will pay DexCom a technology license fee of \$3 million, reimburse DexCom's development, clinical and regulatory expenses, and upon commercialization of the combined system, Tandem will pay DexCom a royalty of \$100 for each CGM-enabled insulin pump sold."* [37]

[39], existing examples of safe interoperability clearly infers it can be done safely by any organisation with the appropriate framework and conceptual understanding of system components [40]. Thus, SIO is enforced via data obfuscation and legal action [41], limiting the possibilities of use for the data, and denying equitable access to the individual's own data, and to best care.

The development of open-source medical devices has recently grown significantly [42]. There was a substantial increase in short-term development of open-source projects during the initial phases of the COVID-19 pandemic [43–48]. This increase was accompanied by a marked increase in the public recognition of the potential offered by open-source innovation within healthcare. Innovations from the open-source community are inherently broadly interoperable, often by intentional design for non-specific interoperability (NSIO). Non-specific interoperability is where the communication protocols through which a device communicates are public and widely-accessible. For example the development of open-source sensors and actuators that are designed for use with any device, and where instructions for how to do so are made public [49, 50].

Even when there is not explicit ability for non-specific interoperabliity, individuals with diabetes are often personally or organisationally motivated to develop technical solutions to overcome the limitations of SIO [51, 52]. For example, the Tidepool platform allows querying a wide range of CGM devices, typically through reinterpritation of data stored on a cellphone [51, 53]. While this SIO-based NSIO enables analysis and sharing of data, there is a manual process associated with the upload process. Therefore, such platforms

do not enable real-time, automated insulin dose calculation or automated delivery, and are often too technologically difficult for many possible end users to use with confidence.

2.2   Scales of innovation

Innovations occur over differing time scales. Short-term innovations meet immediate needs, often in access. Medium-term innovations build upon current devices or systems with either explicit goals to extrinsically or intrinsically reshape how current care is delivered. Long-term innovations are systemic, and often introduce extrinsic, disruptive changes to healthcare technology, and/or delivery.

Short-term innovations are intended to directly replace or augment current devices to meet an immediate need. A significant amount of short-term innovations were completed in an open-source manner during the COVID-19 pandemic [43–48]. Innovations included devices to provide mechanical ventilation [54–61], other respiratory devices[50, 62], monitoring equipment [49, 63], PPE [64–66], and testing devices [67]. In addition to devices, there were some open-source system-level innovations [68–72].

Medium-term innovations often increase access, with inbuilt potential for future efficiencies. For example, the development of a device which serves a similar or identical role to a current device, with either added clinical use, increased interoperability, or lower cost and rapid deployment, all of which enable subsequent long-term extrinsic innovations. The value added is typically an incremental, intrinsic increase in produc-

tivity, or in the potential further innovation facilitated through interoperability. Within diabetes, effective medium-term innovations would see currently available devices such as insulin pumps and CGM devices made more accessible through more cost-effective design, and with increased, non-specific interoperability.

An example of a medium-term innovation within diabetes technologies is the MiaoMiao (MiaoMiao, Shanghai, China). This is a simple innovation that allows the FreeStyle Libre to send data to a mobile device over BlueTooth™, rather than being confined to the SIO of the dedicated reader or smartphone app [73]. The pressure for innovation of the Miaomiao reader was individuals wanting access to their own data. Other examples of short-term innovations within diabetes are lacking because there are no strong short-term pressures for innovation, in cost or significant access to healthcare issues.

Examples of current medium term innovations see increased miniaturisation, portability, and interoperability. The combinations of these changes to medical devices enables them to become part of a larger system [74–77]. Examples can be seen in wearable heartrate and oxygen saturation monitors [78–80], increasing availability of wearable ECG devices [81–84], and wearable bloodpressure monitors [85]. A specific example for diabetes is the open-source Nightscout software and movement, which increases interoperability and access to CGM data, and thus access to control. These devices have increasing access through a decreased cost, and a high level of interoperability with consumer electronics.

Long-term innovations are enabled by adoption of other technologies. They often involve systemic changes and/or the deployment of smart systems, technologies, or devices.

Long-term innovations are also often enabled through the gathering and analysis of data, which in turn are made accessible through interoperability. Long-term innovations often see changes in entire systems of care or care delivery, with substantial increased productivity as a result.

One example of a long-term innovation is the establishment of the STAR programme to control glycaemia within ICUs [86–94]. This innovation was only made possible through the acquisition of long-term BG and insulin data, and its analysis. These data enable the creation of world-leading digital twin models to personalise and optimise care. It also creates a platform for greater interoperability to further increase gains in quality of care and outcomes, beyond the extrinsic gains already achieved in ICU by the deployment of this smart technology system.

Within diabetes, a long-term innovation would see the development of a smart health system similar to STAR. Interconnected CGM devices and insulin pumps would combine to form closed-loop systems for individual patients, with the subsequent potential for innovation of a self-learning digital twin system, and later greater integration and optimisation of all diabetes care.

2.3   Innovation uptake

Despite being technologically sound, many healthcare innovations are not adopted. Barriers for adoption are largely based on the relationship between the clinician and both

the innovator and the innovation, as well as regulatory processes, and the lack of an understanding of the process which decides system-wide adoption of medical technologies. Funders, such as insurance companies or national health systems, create additional hurdles to adoption as their approval is necessary.

2.3.1 CLINICIAN-ENGINEER RELATIONSHIP

A lack of clear partnership is associated with failure of uptake. Development of medical devices without a clear route from '*bench to bedside*' through strategic partnerships is an unsustainable method [95]. If the development of device is secularly technological, extra temporal and financial costs are added in the iterative redevelopment for regulatory testing [96]. This added cost is avoided if there is a strong relationship and regular communication and adjustment of the innovative process throughout [17, 97]. Connectedness throughout the development process with the clinician who will be performing clinical testing for the regulatory process also enables a greater level of familiarity between the clinician and the device [97]. This familiarity also lends itself to a higher level of trust in the device, which is key for successful clinical adoption and uptake [98, 99].

As one of the end users, clinicians are vital to the successful adoption and widespread uptake of technological innovations. Successful adoption of innovation by clinicians requires the innovation and education around it to be presented in a manner they are readily able to understand [100], otherwise time pressures from increasing pressure will not be overcome [101]. Therefore, adoption is enabled through previous experience in

the general field of the innovation [17, 99], and the perception of benefit to patient and staff from the adoption [102, 103].

Technology is more readily adopted with advocacy from leadership. It is important both clinical and management leadership groups support uptake of the innovation [17, 103]. Furthermore, communication of ideas is best diffused through informal channels, particularly over the entire period over which the new innovation is implemented [17, 104]. Thus, the importance of a clinical champion is shown. A clinical champion enables the development of better-understood, easily-consumed educational material around the new innovation, as well as continuing education throughout the period of initial use [105]. They also provide a driver for change from within the organisation, including the mana to persuade others, all of which increase the innovation adoption [106].

The clinician-engineering relationship is also important in determining where innovation can have the greatest impact. This importance is recognised and realised in Māori enterprise through the use of whakawhanaungatanga: the development of relationships to the extent of those similar to familial [107]. This level of collaboration inherently enables the innovative process to produce a result addressing a real life unmet need, which is more likely to be adopted. Close relationships will all stakeholders see benefit to the innovation through more effective communication, and thus the barriers to adoptions and potential issues with the innovation are addressed earlier in the innovative process [17, 108].

2.3.2 REGULATORY

Sufficient oversight and prior approval is critical to maintaining a safe medical device industry. There is increasing recognition that as information systems mature, less importance is placed on obtaining data in the pre-market setting. There is a wide range of regulatory bodies and processes which oversee the medical device market [109], and exemptions are typically made for devices during their pre-market, initial clinical trial stages [110]. The regulatory process is the main challenge for open-source medical device adoption, because design is not always done in line with such processes, and relationships with clinicians are often lacking [42].

Obtaining access to clinical testing is essential for the regulatory process for any new medical device [110, 111]. The USA FDA is the agency with responsibility for regulating the medical device market in the United States of America. Devices such as insulin pumps are typically categorised as Class II devices, defined as posing a moderate risk of harm to the user [110]. While a complete pre-market approval, involving 'reasonable' scientific-based assurance of the safety and efficacy, is required for some Class II devices, most are subject to a lower threshold of assurance [110]. Clinical data demonstrating the efficacy and safety of the device in a clinical setting are required for a range of reasons, and any device deemed to have significant risk, must provide such data.

The acquisition of clinical data is another strong benefit from a close working relationship between innovator and clinician. Financial relationships are common between industry

and clinicians, with an estimated USD \$210 million paid to physician authors prior to 2013 by Medtronic Inc. — one of the largest current diabetes device companies — in relation to a bone-growth product, and there had been Medtronic recommendations against the publication of a complete list of adverse events [112]. The financial nature of these relationships brings into question the independence, and thus safety, of subsequent published data.

There are curiosities surrounding devices requiring regulatory approval and those which do not. For example, devices using light to approximately peripheral oxygen saturations levels and heart rate do not require FDA approval [113], but devices with the ability of electrocardiogram (ECG) detection do. ECG obtained solely at the wrist provides minimal further clinical insight than a heart rate obtained through the use of photoplethysmography [114], but because it is intended for use to provide medical recommendations [115], FDA approval is required [115].

2.4   Summary

Innovation in medicine is driven by various pressures, and influenced by financial interests. Publicly-funded innovations are not driven by the same pressures for strong direct financial returns as industry-led innovations, allowing for more risk, and greater potential societal and economic benefit. This societal benefit is the focus of innovation within sectors, which are not primarily financially driven, such as Māori enterprise or public good enterprises, for example Médecins Sans Frontières.

Innovations occur over differing time scales, with short-term innovations meeting immediate needs. Medium-term innovations see the development of similar devices, but with added incremental efficiencies, or increasing access to care or access to data. The increased access to data often enables subsequent long-term innovations, with a smaller number of high-level, systemic changes, altering the methodology of healthcare delivery.

Uptake of innovations is variable, but barriers and limitations can be mitigated. The depth and breadth of uptake can be increased by fostering key relationships with stakeholders including clinical and patient users, industry, and management. The role of the clinician-engineer relationship is particularly important to enabling uptake of medical devices. This relationship improves the design process, and is more likely to result in solutions trusted and understood by the clinician, which can in turn enable a smoother regulatory process.

Part II

Diabetes Technologies

Chapter 3

Pressure for innovation

Global diabetes spending accounted for an estimated USD\$760 billion in 2019 [116]. This value represents approximately 9% of entire healthcare spending. There is significant financial pressure for innovations to combat these rapidly-increasing costs. Significant disparity in diabetes-related healthcare expenditure is seen in high-income and low-income countries, with $38\times$ more per capita direct diabetic expenditure in high-income countries. Projections are for significant increases in expenditure due to diabetes in coming decades, with USD\$825 billion expected global direct diabetic expenditure by 2030 [116].

Developing countries are seeing a double burden of malnutrition. As life expectancies increase, and rapid globilisation disrupts traditional diets, the prevalence of chronic conditions, such as obesity and type-two diabetes, increases [2] alongside healthcare

problems such as severe malnourishment [117]. This increase is alongside healthcare problems traditionally seen only where access to healthcare is lacking in low-income countries. For example, while still seeing cases of extreme nutrition-based diseases such as kwashiorkor, obesity and type-two diabetes is also increasing in prevalence [118, 119]. These low income countries are attempting to manage increasing healthcare demand from a rising prevalence of type-two diabetes in the context of historic underfunding [120].

Increasing diabetes prevalence in developing countries also impacts the control of communicable diseases. The vascular and nervous damage increases susceptibility to other diseases, such as TB, malaria, HIV, and other infective processes [2, 121]. This co-prevalence represents additional costs caused by diabetes in healthcare systems struggling to meet demand. An estimated 77% of individuals with diabetes have unmet needs in low- and middle- income countries, in the form of diabetes being untested; tested, but not diagnosed; diagnosed, but untreated; or treated, but without adequate control [120]. All of these outcomes lead to significant complications and reduced life expectancy.

The increasing susceptibility of low-income populations to diabetes is foreshadowing of a ballooning expenditure. Already a larger rate of increase of prevalence of diabetes in low-income countries compared to high-income countries is evident [122]. This difference in rate is of particular concern in the context of substantial underdiagnosis of diabetes in these same countries, with estimates 83.3% of all undiagnosed cases of diabetes are in low- or low-middle- income countries, representing a possible half of individuals with diabetes in such countries [123]. These trends suggest already under-funded low-resource

countries face an insurmountable rising expenditure, whether public or private, to provide healthcare to individuals with diabetes.

One of the contributing factors to the increase in diabetes prevalence in low- and low-middle- income countries is the lack of historic investment in public health, and health education. Amount of time in education is the strongest predictor of health literacy [124, 125], and is typically low in developing countries [126]. This impact on health literacy is seen in health outcomes, with education a stronger predictor than wealth for all-cause mortality in low-income countries by a factor of two [126].

3.1   Diabetes in New Zealand

Diabetes spending within New Zealand has seen — and is projected to see — significant growth, placing increasing pressure on the healthcare system. A decreasing workforce supporting an ageing population, combined with a considerable increase in the prevalence, means gold-standard care will be unobtainable except for an increasingly select few. Public resources will be distributed among hundreds of thousands of sufferers beyond the approximate 250,000 with type-one or type-two diagnoses today [127]. Incremental, intrinsic changes to address the rising demand will not impact outcomes and costs faster than the growth in demand [128]. Therefore, extrinsic changes are required in order to avoid unaffordable healthcare expenditure to treat diabetes. These required innovations for extrinsic changes are able to be provided from the interface between medicine and engineering.

3.1.1   Systemic

There are currently an estimated 228,000 New Zealanders diagnosed with type-2 diabetes alone, with a projected growth of 70-90%, to approximately 400,000 people by 2040 [127]. Currently, approximately 1% of GDP is spent solely on treating diabetes and its complications, or $2.1 billion per annum [127]. Approximately 80% of this cost is paid for by the public health system [129, 130], an equivalent approximate cost of $460 per taxpayer per annum. This figure represents 4.4% of the total tax paid [131], or $8.3k per individual diagnosed with diabetes per annum.

Individuals with diabetes account for twice the health expenditure as those without [132]. With projections of an increase in prevalence from 4.7% to 6.6%-7.4%, the systemic costs of providing healthcare to the increased number of individuals with diabetes will increase significantly.

The projections are exclusive of individuals with as yet undiagnosed diabetes, where 7% of overweight New Zealanders are predicted to have diabetes, but no diagnosis [133]. Given an estimated 35% of New Zealand adults are overweight [134], it is can be approximated that there are an additional 100,000 individuals who have not been diagnosed with diabetes. The hidden potential future costs of these individuals because of the development of serious complications [6] will compound with the already predicted 60% increase in diabetic expenditure in New Zealand [127] to place extreme, unmeetable burden on the healthcare system.

There will not only be significantly more individuals diagnosed with diabetes, but there will also be an increase in the overall health expenditure due to each one. This increase in cost is because of a trend in earlier diagnoses of diabetes [135] — described as 'rising tide [136] — and thus a longer duration of poor glycaemic control. This increase in disease duration is associated with a higher incidence of complications throughout the duration of the disease.

In particular, with increasing duration of diabetes there is a near-exponential increase in risk of cardiovascular disease, particularly of severe cardiovascular disease [137, 138]. Furthermore, duration of disease is a strong independant predictor or diabetic foot amputation [139], retinopathy [140], infective processes requiring hospitalisation [141], and a lower quality of life in general [142]. All of these complications significantly reduce quality of life for individuals with diabetes, and increase the financial cost of diabetes, both directly through healthcare expenditure, and indirectly through lost of diabetes, and reduce quality of life for individuals Because the increase in incidence of complications is independent of age, the earlier ages of diagnosis will result in a higher rate of complications requiring increasingly complex and thus more expensive management. Therefore, there will be a significant increase in the overall healthcare costs associated with treating each individual with diabetes.

Therefore, the future of diabetes spending based on current projections is bleak. With increasing prevalence of diabetes and increasing financial cost per individual diagnosed, the expected cost per individual with diabetes will increase signinficantly [6, 127]. This increase in absolute cost in combination with a larger portion of the population of a

non-working age [143] means publicly-funded healthcare will be paid for by a decreasing portion of New Zealanders, necessitating either greater taxation, or substantially increased productivity, greater rationing of services, or some combination. Governmental forecasts predict a marked increase in financial requirement for healthcare, or naïvely hope that while they *"do not assume efficiency gains. However, … efficiency gains may not only be achievable, but large enough to compensate for any small drop in current consumption [of healthcare services] due to [decreased taxation income]"* [144].

Increases in efficiency can only come from extrinsic changes. To meet the projected increase in demand for diabetes health services, intrinsic changes would simply see an increase in current services proportional to the increase in demand. The increase in resourcing required for the combination of increasing prevalence and number of complications would far outgrow likely increases in GDP and taxation [127, 144]. An increase in efficiency would allow the predicted demand to be met with less additional funding, effectively increasing productivity. These extrinsic changes arise in the form of new technologies, clinical tools, and/or other healthcare innovations that are typically created from interdisciplinary development [145].

In addition to explicit expenses, there is also considerable systemic and personal loss from lost wages due to activity-impairing complications, and lost non-salary productivity due to the inability to perform activities, such as domestic cares or voluntary work [127, 146]. Lost personal wages are estimated to have an economic cost of $562M in 2020 ($2.4k per individual with diabetes), and increase 47% to $755M in 2040 ($1.9k per individual with diabetes), and the non-salary economic loss is predicted to increase from $334M

to \$506M in the same period (\$1.5k - 1.3k per individual with diabetes) [127]. The lost wages are accompanied by a loss of government revenue through income tax, from \$163M in 2020 to \$221M in 2040. Lost tax revenue because of disability from diabetes is equal to 8% of the current economic costs of diabetes [127].

One method used to reduce the cost of healthcare expenditure is by limiting its availability, and triaging access to those who benefit the most. This rationing of healthcare is a common practice in medicine, and has been of particular academic and public interest throughout the COVID-19 pandemic as health systems become inundated [147, 148]. There has been general agreement that the relatively widespread implicit rationing should be more made more explicit [149]. This conversation and awareness will become greater as countries with relatively widespread healthcare access face increases in demand outstripping increases in the ability to supply healthcare. Increasing rationing will see services becoming less available through universally-accessible healthcare systems, and an increase in the amount of self-funded healthcare, which would see a substantial increase in the current inequities in access to healthcare [150].

In New Zealand, for example, there are increasing conversations about access to insulin pumps and CGMs, the former of which is tightly rationed to approximately 10% of individuals with type-one diabetes, and less than 5% of the total population who manage their diabetes with insulin [5, 151, 152]. Continuous glucose monitors are currently not publicly-funded in New Zealand, and recent public campaigns have urged for funding to include CGMs for type-one diabetics [153, 154]. Citing a funding increase of \$200M across four years, this value would represent the ability to provide only approximately

38% of individuals with type-one diabetes with CGMs, or 4% of individuals diagnosed with type-one or type-two diabetes. This hypothetical spending would in itself be an example of significant rationing of healthcare, given Pharmac's mandate to "*make decisions on which medicines and medical devices are funded in order to get the best health outcomes from within the available funding*" [155].

3.1.2   Personal: A story of inequities

Systemic health costs from diabetes are growing, but so too are personal health costs. Private spending accounts for approximately 20% of total health expenditure in New Zealand [129], of which 12% - 15% is directly an out-of-pocket expense [130]. Personal expenditure within diabetes is most commonly seen in the primary sector [127]. Examples of personal healthcare expenditure for individuals with diabetes include primary care appointments, part-charges for subsidised medications, and BG testing if not fully funded.

Projections for out-of-pocket diabetes-related spending are expected to increase 3.0% per annum, rising almost 80% in the two decades to 2040 [127]. This considerable increase is similar to historic median wage growth, but two times the wage growth of the 20th centile [156]. Because these cost increases are expected to be seen at a primary healthcare level [127], where intervention has the greatest impact [6], this growth is a compounding factor in denying most vulnerable equitable access to preventable medicine. Thus, primary

healthcare is expected to become even more relatively unaffordable for New Zealand's poorest, and equitable access to healthcare less obtainable.

3.1.2.1 The only positive thing about inequity is the feedback loop

Personal expenditure on diabetes-related healthcare are greater for those with worse disease and more complications. For example, those treated with insulin will require several primary care appointments when insulin is initiated to ensure safe dosing [157]. Patients with more complications will have more indirect costs, such as transport and over-the-counter products for symptom management. Complications can often also impact employability or employment-based productivity, creating a personal positive feedback loop of loss. Subsequently, because of the hereditary association of type-two diabetes — be it genetic [158] or social [159] — this positive feedback loop of loss is also seen on a family scale.

Financially, inequity is increasing due to increases in out-of pocket spending. Accounting for private insurances and charitable spending, the most recent data from the Ministry of Health show out-of-pocket expenditure increased on average 4.3% per annum (albeit in 2012 when it was last reported) [129]. This increase in out-of-pocket expenditure is at a comparable level to an average inflation rate of 2.7% since 2000 [161]. However, as shown in Figure 3.1, this increase in out-of-pocket expenditure compares to an average median wage growth of 3.2% [162]. To exaggerate inequity further, the mean household income of the 20th centile (P20 from Table 9.1 of [156]) has risen on average only 1.5%
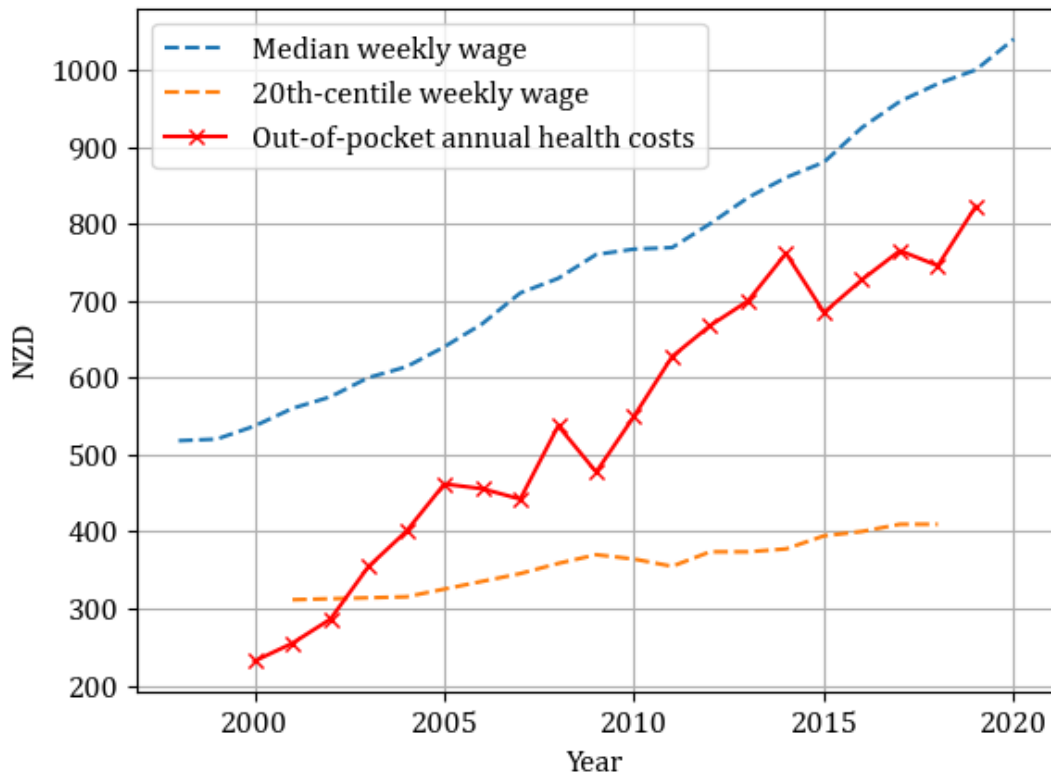
Figure 3.1: Historic average annual out-of-pocket health expenditure per capita [130], compared to median weekly wage [156, 160], and mean of 20th-centile weekly household income [156]. Out-of-pocket health expenses are exclusive of charitable and private insurance spending.

per annum. Thus, increasing personal diabetes costs are an increasingly regressive tax on New Zealand's poorest.

Forming a disproportionately high amount of the lower socioeconomic cohort [162], Māori have worse diabetes outcomes compared to their pākehā counterparts [3, 163]. One possible explanation is less equitable access to primary care [3], as evidenced in lower-income households having 25% fewer GP appointments relative to the portion who report being of 'poor health', than the NZ average [164]. Even accounting for government subsidy schemes, such as the community services card, a GP appointment costs up to $19.50. The average household in the lowest quintile in New Zealand has only $230 per week disposable income after housing [162]. **Visiting a general practitioner for the most vulnerable is as much a financial decision as a healthcare decision.**

The correlation between low socioeconomic status and poor health literacy is well established, with level of education being the strongest predictor of health literacy [124]. Those lacking in health literacy require strong advocacy to obtain the same level of care as those with high health literacy, from a personal acquaintance or a health professional for equitable access to outcomes [165]. Thus, significantly increasing workload for health professionals, means it will fall outside the healthcare sector to determine the level of care received, effectively rationing healthcare. When considering the future of rationed healthcare, those who do not understand and feel comfortable within the medical sector will be the least likely to engage, and thus the least likely to receive necessary care in a timely, more economically-efficient manner. This lower engagement will further lower

health literacy, which is almost hereditary in nature [166], creating a self-perpetuating disenfranchisement and reducing equity of access to care.

Diabetes prevalence is higher, age at diagnosis lower, and diabetes outcomes worse among Māori and Pasifika,[3, 127, 167]. Considering these ethnic groups also typically face greater socio-economic hardship[162], they have a double burden. Despite the now decades of discussion around diabetic inequalities and inequities [167–188], the trend of higher incidence and worse outcomes has persisted [189], an outcome being cited as 'inaction in the face of need' [3].

3.2   Summary

Among rising global healthcare expenditure, diabetes currently accounts for approximately 10%, with predictions this level of expenditure will increase on the basis of rising prevalence and an increase in the cost of treating each individual with diabetes. These trends are of particular concern in low- and low-middle income countries, where historic underinvestment in public health in combination with increasing access to poor diet is leading to faster increases in the rates of diabetes prevalence.

In New Zealand, the overall economic impact of diabetes is approximately 1% of GDP. Forecasts are for substantial increases in the medium-term future as prevalence and complications rise substantially. The human costs of diabetes are disproportionately paid for by Maori and New Zealand's poorest, with inequitable access to care and

outcome for these groups. Despite decades-long recognition of these inequities, little definitive progress has been made to combat them.

Increasing the efficiency of the healthcare system is necessary to avoid excessive ballooning of economic and human costs associated with diabetes. Continued intrinsic investment will become progressively less affordable in the context of lowering taxation relative to increasing numbers of superannuates and individuals with diabetes. More directly, intrinsic investment to keep pace with growing demand is already falling further behind actual economic growth, creating an increasingly regressive tax on over half the population.

Therefore, extrinsic changes are required, with a strong focus on equitable access to best care for all New Zealanders. These developments require strong engineering-clinician partnerships for the development of interoperable technologies subsequently enabling long-term development of smart digital health systems to manage diabetes, and to meed growing demand for healthcare in general.

Chapter 4

One small driver for big change

Delivery of insulin is a daily reality for tens of thousands of New Zealanders. It is essential for every single one of the 26,000 individuals with type-one diabetes, and for an estimated 38,000 of the individuals with type-two diabetes [190]. Insulin delivery is made more difficult because it is a small protein molecule, and such molecules are not well absorbed through gastrointestinal absorption, typically having a bioavailability of $\leq 1\%$ when administered orally [191]. While there are many attempts to overcome the barriers to less invasive delivery routes [192–195], insulin delivery remains almost entirely subcutaneous [196]. This delivery is typically achieved through use of a needle, either in a traditional needle and syringe arrangement, or from a pre-filled pen system, as shown in Figure 4.1. The pain and invasiveness are a primary reason that insulin therapy is not more widespread throughout individuals with type-two diabetes.forkin

Insulin Pen

Needle

Needle attachment point

Insulin reservoir

Expiration label

Cap

Insulin cartridge

Dose adjustment dial

Injection button
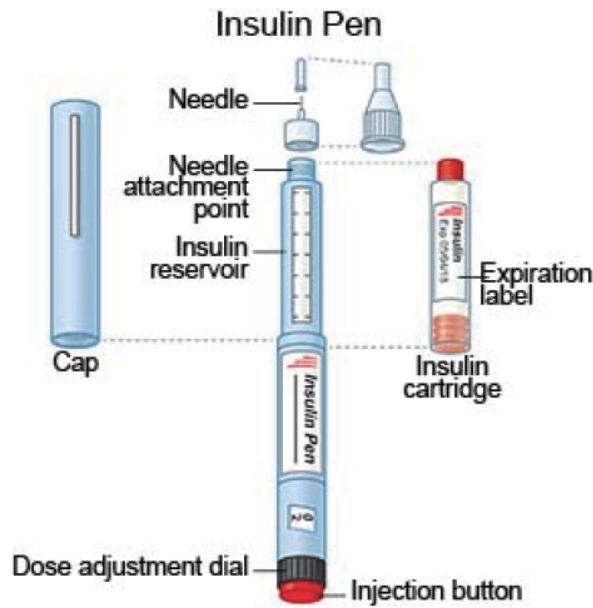
Figure 4.1: Example breakdown of a pre-filled pen device for the delivery of SC insulin.

An alternative method of SC insulin delivery is with an insulin pump. Insulin pumps are devices semi-permanently attached to the patient for a period of approximately three days. Over this time, they deliver insulin in a pseudo-continuous manner, providing a relatively constant infusion of insulin from the local subcutaneous space into which the insulin is delivered to the systemic blood volume. This constant infusion is achieved by multiple small deliveries every few minutes. Additional to the basal delivery, boluses are given on demand in an attempt to mimic endogenous periprandial secretions. Both basal delivery and boluses are achieved through the delivery of insulin, normally at relatively high concentration, from a reservoir within the pump through a plastic giving set to a site where plastic cannula is inserted into the subcutaneous space.

4.1 Treatment of DM

Insulin is used because it is the most effective medication to lower circulating blood glucose concentration [197]. Compliance and proper dosing face considerable challenges, largely because of the required subcutaneous administration route [198]. Insulin pumps mitigate a significant portion of the negative aspects of regular insulin administration via MDI. There is only one injection, which is associated with the insertion of the cannula and required only once every three days. As per Figure 4.1 this is in contrast to MDI, where once-daily injections of long-acting insulin are required, and additional injections of bolus insulin at meal times and/or whenever carbohydrates are consumed. With three main meals a day, four injections per day would be the minimum expected [199].

Problems associated with insulin delivery are depressingly yet unsurprisingly worse in developing countries. Without equitable access to pre-filled pen cartridges, refrigeration, or effective medicine education, experiences in India, for example, see severe, life-threatening complications associated with the delivery of the life-saving medication [200]. Poor compliance is also recognised in sub-Saharan Africa, with less than 80% self-reporting adherence to an insulin regime in Nigeria, and was found to be less than 70% in Ethiopia [201]. While this is in part due to pain and inconvenience, 41% of non-compliant diabetics cited high costs as the greatest impediment, and those who were employed spent a median 26% of their net income on insulin therapy [202]. With worsening incomes and pressures on medical industries during the COVID19 pandemic, these adherences are only expected to also worsen, and subsequently outcomes.
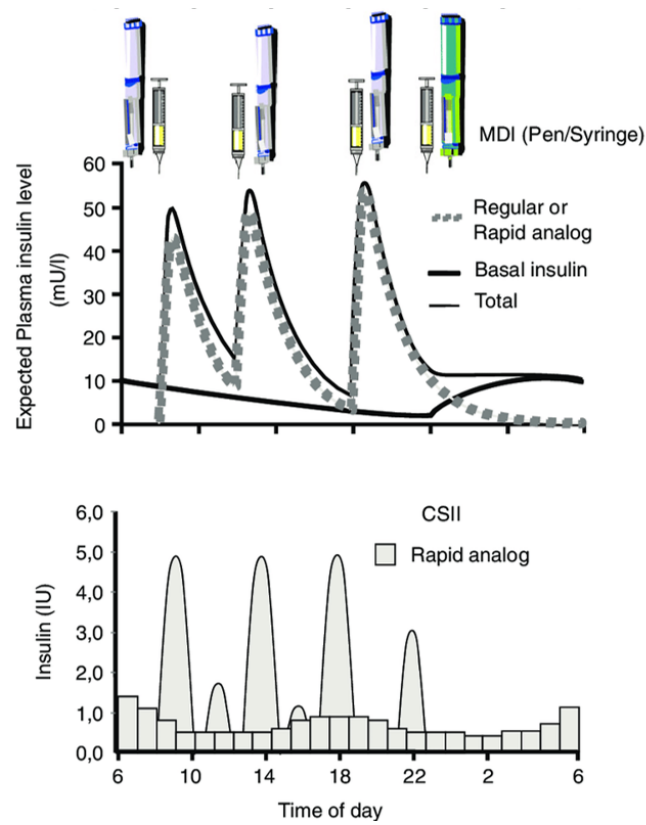
Figure 4.2: Examples of daily profiles comparing MDI with delivery via an insulin pump [199].

Like any disease process, it is vital that monitoring is done to track the progress of the disease. For both type-one and type-two diabetes, which are characterised by the body's inability to control circulating BG concentrations, it is therefore necessary to monitor circulating BG. This is done in two time-scales: discrete or short-term measurements to inform insulin administration dosing, and measurements to examine the long-term glycaemic control. It is possible to take individual glucose measurements at a fixed period, however this would be impractical for the patient, and also not capture all of the dynamic glucose changes required to fully represent glycaemic control.

In order to capture properties of both fasting BG and dynamic changes associated with carbohydrate consumption, a long-period moving average measurement is the most appropriate. Biochemical properties are able to be exploit to this end, in the form of a glycated haemoglobin measurement. Haemoglobin is in circulating blood alongside glucose molecules, and subsequently some of the haemoglobin molecules become glycated to form what is known as glycated haemoglobin (Hba1c). Therefore, the concentration of glycated haemoglobin relative to the concentration of total haemoglobin is directly proportional to the average blood glucose over the average lifespan of a haemoglobin molecule. The period over which Hba1c is recognised to represent average BG concentrations is two to three months, with three months being the most common. Given the testing of relative concentrations of Hba1c is relatively accessible through a standard venous blood test, it is commonly used to represent the level of glycaemic control. A low Hba1c measurement is synonymous with 'good' glycaemic control, and similarly a high Hba1c measurement with 'poor' glycaemic control. The measurement of Hba1c is

used to diagnose pre-diabetes and diabetes, and to inform clinical decisions around the level of intensity of treatment required.

4.1.1   T1D

Individuals with type-one diabetes die without regular insulin administration. Typically, a basal-bolus regime is used to meet the requirements of regular carbohydrate consumption. When an insulin pump is used, this regime is achieved in a manner similar to typical MDI regimes, with the continuous basal rate replacing the need for long-acting insulin administration. There are also varying types of insulin pump-based bolus delivery, with different time-varying profiles, such as square-wave, bimodal, or single injection[203, 204]. In New Zealand boluses are typically calculated and delivered manually, with the use of aids such as mobile device applications [205–207]. Insulin pumps have varying degrees of intelligence, where some will simply deliver the called-upon amount of insulin, but some have the ability for entry of carbohydrate mass per meal and will automatically calculate the dose.

The manual dose calculation raises several sources of error. There is obvious potential for human error [208], but also systemic errors. For example, the lack of regulation of online diabetic tools allows for significant error. For example, the majority of online tools which allow for the conversion of insulin units are incorrect [209].

In New Zealand, insulin pumps are almost solely used by individuals with type-one

diabetes, and there is no standard provision for prescription of a pump to an individual with type-two diabetes [152]. The current criteria are not only restrictive because they are clinically strict to ration healthcare services and reduce cost, but also logistically. The application must come from an appropriate specialist or nurse practitioner, and must qualify either under severe unexplained hypoglycaemia, or be believed to show considerable increase in glucose control. The full requirements are outlined in Table 4.1.

Because the medical and logistic requirements are relatively high, the portion of individuals with type-one diabetes with insulin pumps is low, compared to approximately 60% in the US [210]. In New Zealand, this limit is primarily done intentionally because of the cost of insulin pumps, and therefore these steps are an attempt to manage the total number of insulin pumps to sustainable levels. Hence, public funding is only available for individuals with diabetes who would receive the greatest benefit from a insulin pump [152].

Lowering the cost of insulin pumps would provide more individuals with type-one diabetes access. One study has shown by halving the cost of insulin pumps, the reduction in HbA1c required for prescription could be lowered from 10 $mmol \cdot mol^{-1}$ as per requirement (2).6 of Table 4.1 to just 3 $mmol \cdot mol^{-1}$ [211]. This lowering of the strict medical requirements would subsequently also remove some of the non-medical requirements, such as the necessity for a specific diabetic practitioner to complete the prescription.

Table 4.1: Requirements for a publicly-funded prescription for an insulin pump under either the severe hypoglcaemia or glycaemic control criteria, recreated from [212].

(1) Severe Unexplained Hypoglycaemia	
All of the following:	
1	Patient is continuing to derive benefit according to the treatment plan agreed at induction of at least a 50% reduction from baseline in hypoglycaemic events; and
2	HbA1c has not increased by more than 5 mmol/mol from baseline; and
3	Either:
3.1	It has been at least 4 years since the last insulin pump was received by the patient; or
3.2	The pump is due for replacement; and
4	Either:
4.1	Applicant is a relevant specialist; or
4.2	Applicant is a nurse practitioner working within their vocational scope.

(2) Glycaemic control	
All of the following:	
1	Patient has type 1 diabetes or has undergone a pancreatectomy or has cystic fibrosis-related diabetes; and
2	Has undertaken carbohydrate counting education (either a carbohydrate counting course or direct education from an appropriate health professional); and
3	Applicant is part of a multidisciplinary team experienced in the management of type 1 diabetes care; and
4	Has adhered to an intensive MDI regimen using analogue insulins for at least six months; and
5	Has unpredictable and significant variability in blood glucose including significant hypoglycaemia affecting the ability toreduce HbA1; and
6	In the opinion of the treating clinician, HbA1c could be reduced by at least 10 mmol/mol using insulin pump treatment; and
7	Has typical HbA1c results between the following range: equal to or greater than 65 mmol/mol and equal to or less than 90 mmol/mol; and
8	Has been evaluated by the multidisciplinary team for their suitability for insulin pump therapy; and
9	Either:
9.1	Applicant is a relevant specialist; or
9.2	Applicant is a nurse practitioner working within their vocational scope.

<div align="center">

Abbreviations:
HbA1c - Glycated haemoglobin
MDI - Multiple daily injections

</div>

Uptake among individuals with diabetes, in particular type-one, would be expected to be very high. Studies have shown up to 95% greater satisfaction with the use of insulin pumps over MDI [213–220]. Because of the wide range of analyses, it is expected this result is transferable to a large portion of the population. The possible exception is there who are comfortable in their routines, and stubborn to change. However, an overwhelming majority of individuals who are dependant on insulin have shown a preference of SC insulin delivery via an insulin pump, rather than MDI.

4.1.2   T2D

Because of concerns around the safety associated with the delivery of insulin, it is very rarely used as a first-line treatment for T2DM, and is typically only done in the presence of extremely poor diabetic control [221], typically very late in the course of the disease. This approach is used despite a long-standing recognition that the use of insulin in early or even pre-diabetes have significant impacts on the progression of the disease [6]. Even when insulin is prescribed, adherence is poor [222]. In New Zealand, insulin is prescribed initially in a low-dose basal formulation, which is then titrated up until a sufficient HbA1c is achieved. If it is not, bolus insulin is added on top of the basal insulin, effectively the same treatment as for individuals with type-one diabetes [157].

Challenges preventing widespread treatment of individuals with type-two diabetes with insulin arise because it is difficult to have a one-size fits all approach to care that is safe and effective, and adherence is strongly reliant on clinician-patient relationships, with

physician trust being the strongest indicator of good adherence [200, 223]. Treatment regimes must be personalised to accommodate personal physiological and psychosomatic factors to minimise risk of iatrogenic hypoglycaemia, while maximising potential glycaemic control from insulin administration [224].

In particular, despite being more accurate than even a trained clinician using a manually-filled syringe [225, 226], the risks of accidental overdose when using a pre-filled pen cartridge are significant when the dose must be manually calculated and delivered by the patient themselves [227]. Even patients who have been using insulin for an average of 15 years had only a self-reported 55% accuracy of always administering the correct dose [228]. These risks of hypoglycaemia mean patients are likely to intentionally under-dose to avoid it, which comes at considerable detriment to optimal glycaemic control, or requires a subsequent correction dose [218].

Because there is some endogenous insulin production in individuals with type-two diabetes, and thus there is not complete reliance on exogenous sources, insulin pump therapy is rare. Its role in hospitalised insulin-dependant individuals with type-two diabetes is increasingly recognised [229], a use which is extending further and further to out-of-hospital use also. A thorough meta analysis analysing the evidence for use of insulin pumps for individuals with type-two diabetes found a substantial relationship between their use and better outcomes [4] . While some studies only examined short-term use of insulin pump therapy, almost all studies examined found a considerable increase in glycaemic control. Very few were of sufficient length to definitively observe all of the long-term beneficial outcomes, including reduction in expensive long-term

complications, which are predicted to only be truly apparent after five to ten years' use [6].

Instead of acting solely as a direct replacement for delivery of SC insulin from pre-filled pens for those who currently are prescribed insulin, pumps pose significant further possibility. Initiating an individual with type-two diabetes on basal insulin — the first line of insulin management for these individuals [230] — is something general practitioners have mixed experiences and variable personal clinical preferences [231, 232]. This hesitancy, in the context of increasingly available oral anti-hyperglycaemic agents, has seen an increase in the threshold for initiation of basal insulin as indicated solely by very poor glycaemic control in the context of [157]: guidelines have increased from initiating solely on a HbA1c of $75 mmol \cdot mol^{-1}$ to $80 - 90 mmol \cdot mol^{-1}$ [233]

4.1.3   Who has them currently - and who doesn't?

Insulin pumps have been available via publicly-funded prescription since 2012. While there has been considerable increase in uptake in more recent years as shown in Figure 4.3, uptake is still reasonably low. Approximately 9-14% of individuals with type-one diabetes have access to publicly-funded insulin pumps [151], and there are additional self-funded insulin pumps in New Zealand. Estimates are total insulin pump numbers are currently 4,000 - 4,500 [234]. Thus, there are an estimated 350 - 860 additional pumps that are privately funded in New Zealand.
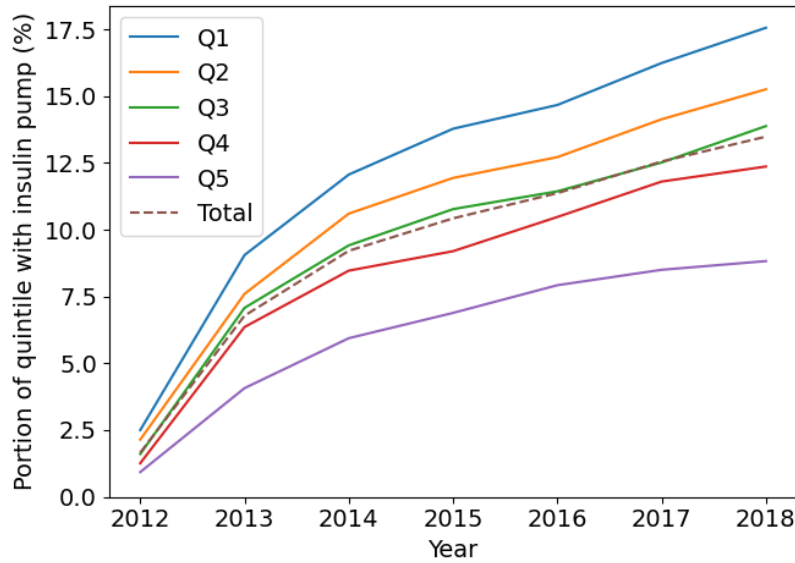
Figure 4.3: Portion of individuals with type-one diabetes with publicly-funded insulin pumps. Deprivation quintiles as per NZDep2006; 1 is the least deprived, and 5 is the most deprived, recreated from data from [151].

Like many aspects of diabetes care, there is inequitable access to care and outcomes in relation to insulin pump technology. In New Zealand, Māori and Pasifika are less likely to have insulin pumps, and less likely to have their insulin pump renewed [151], despite having worse outcomes [3]. The lack of access has been recognised for considerable time, and attempts to rectify it have not had any noticeable impact in recent years [151].

Currently, the biggest impediment to insulin pumps is cost. With wage growth of a quarter of New Zealanders less than inflation [156], and over a half less than the growth of out-of-pocket medical expenditure, medical care is becoming increasing inequitably accessible. Thus, socio-economically deprived groups are less likely to be able to access them privately. With 20th-centile median household incomes $230 after housing, the $10,000 upfront cost for a pump and $42 weekly cost for consumables simply make
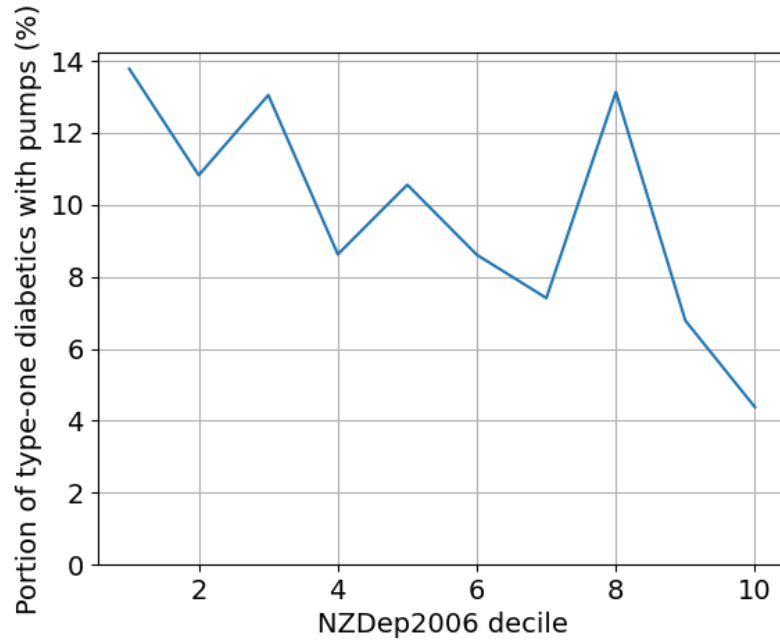
Figure 4.4: Pump prevalence showing only publicly-funded insulin pumps as a function of deprivation centile. 1 is the least deprived, and 10 is the most deprived, recreated from [151]

them unaffordable, and economically, perfectly inaccessible [156, 212]. While there is understandable logic in that people with lower income are less likely to be able to self-fund their own insulin pumps, the same cannot be said in the explanation of lower levels of publicly-funded insulin pumps in lower socio-economic populations [151]. In 2018, while there were similar numbers of individuals with type-one diabetes in the lowest deprivation quintile (most deprived) as the top quintile, (least deprived), there are less than 53% as many insulin pumps in the lowest deprivation deciles: 502 pumps among 2858 diabetics compared with 265 in 3002 [151].

4.1.4   Benefits

There is considerable benefit associated with insulin pump therapy over MDI. Advantages include safety, better glycaemic control, subsequent better health outcomes, and the opening up of a range of options for controllability through interoperability.

4.1.4.1   Control, short-acting basal

The control achieved with insulin pumps is better than with insulin delivered via MDI [214–220, 235–251]. There is a possible exception in the treatment of pregnant individuals with type-one diabetes [252], but across paediatric individuals with type-one diabetes, [235, 237, 246, 248], individuals with poorly controlled type-one diabetes [216, 243], individuals with recently-diagnosed type-two diabetes [213, 217, 239–241, 249, 250], and individuals with poorly-controlled type-two diabetes [214, 220, 251] a reduction in HbA1C is evident from use of insulin pump therapy over MDI. Therefore, access to insulin pumps represents access to best care for individuals with type-one or type-two diabetes. Currently, given the inequities in access to insulin pumps, there is considerable inequity in access to best care, and thus to outcomes.

One advantage is the use of rapid-acting insulin, rather than a long-acting insulin. In addition to being much lower cost [212], it also reduces the potential severity of hypoglycaemic episodes due to insulin overdose [4]. This reduction occus because rapid-acting insulin is most commonly used in insulin pumps [196], and has a peak duration

of 30 minutes - 1 hour, and an active duration of 2 - 4 hours [253]. This duration is compared to insulin glargine, which is commonly used in New Zealand for once-daily basal insulin support [230], and has a peak action time of 2-6 hours and duration of 18-26 hours [254]. Hypoglycaemic episode duration is reduced further when rapid-acting insulins are used, particularly in over-night episodes in paediatric patients [255].

Another benefit from insulin pump use is a lower totally daily dose (TDD) of insulin. In both type-one and type-two diabetes, insulin resistance occurs because of sustained hyperinsulinaemia [256]. Thus, a higher amount of insulin delivered is correlated to a higher insulin resistance, which is likely to result in higher circulating BG. The use of an insulin pump lowers TDD in individuals with type-one or type-two diabetes [4], thereby impeding disease progression and the number of complication with high human and financial cost.

4.1.4.2 Health outcomes

Long-term health outcomes see considerable benefit from the use of insulin pump therapy over MDI. These benefits arice from an increase in good glycaemic control, and the subsequent prevention of various disease pathologies arising because of long-term high circulating BG. These pathologies are typically are either due to long-term microvasculopathy and peripheral neuropathy [257, 258].

Diabetes seems to have become so common, even those suffering from it claim to be

of good health [259]. Perhaps, because it is a chronic disease, rather than acute, the life-limiting harm is not forefront of the patient's mind. During COVID-19 diabetes was shown to significantly increase the risk of severe sickness by $2\times$ and death by $3\times$ [260]. Because of the number and extent of systems impacted, outside the pandemic setting, the risk of death from coronary or other pathologies reduces life expectancy by up to five - ten years in all forms of diabetes [127, 261–264].

Quality of life is also considerably effected, with retinopathpy-related blindness, the 'salami' of successive limb amputations to treat infective processes [198], neuropathy, nephropathy, cognitive impairment and dementia [265]. Because of the prevalence it is easy to forget diabetes is a debilitating disease. There is considerable impact on quality of life years, with severe potential pathologies, including strokes, acute coronary syndromes, amputations, and blindness. Preventing the progression of the disease, or at least the development of complications, has far-reaching benefits for individuals and society.

4.2 Financial aspects

With the adoption of any medical technology, one of the most important discussions concerning the topic of widespread insulin pump adoption is the economic one. While thorough analyses have been performed elsewhere, in the UK for example, [266], similarly thorough analyses are completely lacking in the New Zealand context. An adoption-dependant analysis has allowed approximation of the overall costs and savings of various

aspects of widespread adoption of insulin pump and CGM technologies. Throughout this analysis, figures will pertain to adoption of insulin pumps for all individuals currently using insulin to treat diabetes in New Zealand, with realistic potential adoption scenarios discussed subsequently.

4.2.1 DIRECT SAVINGS

The reduction in spending due to changing insulin preparations associated with widespread insulin pump uptake are considerable. Delivery via an insulin pump sees smaller total daily doses of insulin used, from between 10-40% [4]. Across the population of individuals with diabetes this reduction is significant, and even more so considering the formulation changes from a 3 mL pre-filled syringe with single-use needles to glass 10 mL ampoules. A type-one diabetic uses a combination of long-acting and short-acting insulins, the most common long acting insulin being insulin Glargine [157]. In NZ, a pre-filled pen of 300 U Insulin Glargine currently costs \$18.90, compared to a 1000 U ampoule of human insulin at a cost of \$25.26 [212]. Using a conservative estimate of an average of 50 $U \cdot day^{-1}$ [4], transitioning to devices with a lower TDD of insulin would realise considerable cost savings.

The other direct saving resulting from adoption of a low-cost insulin pump is the saving associated with reduction in expense of current insulin pumps. Currently, 10-14% of type one diabetics administer via an insulin pump, at an expense of approximately

$5.1M - $8.0M per annum. The cost of purchasing the same number of ULC pumps is expected to be less than $0.6M - $0.9M.

4.2.2   Indirect savings

Considerable financial return from widespread insulin pump adoption would be seen by preventing the need for costly management of these complications in secondary care: surgeries, admissions, and acute presentations. It is projected the 57% of current diabetes spending which secondary care will be at a similar, if not slightly higher level in coming decades [127]. Better control would see fewer presentations to hospitals, and a reduction in cost for those presentations.

For a local case study, data from the Southern District Health Board from the year 2016/2017 are discussed [267]. One example of cost savings is in coronary artery disease admissions, for diabetics alone costing $3,860,997. A decrease in HbA1C of 11 mmol/mol sees approximately 10% reduction in coronary artery disease [3], a decrease which is attained with insulin pump therapy within the first year [4, 268]. Thus, a 10% reduction in incidence rate would see an average saving of approximately $386,000 across a population of 27,400 diabetics. Futhermore, individuals using insulin pump therapy to manage their diabetes often attain normoglycaemia, [4], and patients with a diagnosis of diabetes have more expensive admissions for coronary artery disease than those without. Therefore, attaining excellent control would see a reduction in cost associated with each admissions. Considering over 50% of individuals with type-two diabetes are

able to attain normoglycaemia with insulin pumps [213], it is expected that a reduction in cost of $875 per coronary artery disease admission for diabetic patients would be seen [267]. In total, a saving of 18% of cost associated with admission for coronary artery disease can be expected from population-wide insulin pump adoption.

Diabetic ketoacidosis among type-1 diabetics accounts for the majority of spending of admissions for primary complications [267]. Use of insulin pumps realises a reduction of approximately 15% [269]. This Reduction which would be seen directly in the expenditure, and correlate to $52,483.8 within the 320,000 entire population of Southland, or $768,171 nationally.

In the year reported, the Southland District Health Board had lower rates of diabetes in Māori and Pacific groups that the national average [270]. Considering these ethnic groups have worse diabetic control [3], and the worse the control the greater the decrease in HbA1C [4], it thus follows that these savings can be expected to be greater when extrapolated throughout NZ. Assuming similar expenditure on diabetes-related admissions throughout NZ, extrapolating to the entire population of New Zealand would see a reduction of secondary care spending of tens of millions of dollars, possible even hundreds.

There is considerable expense in the treatment of diabetic wounds - peripheral vascular and nervous damage result in long-festering wounds, particularly on the lower limbs. The damaged vasculature results in poor healing, thus drastically increasing risk of infection. If the infection becomes too severe, amputation is the required treatment to prevent systemic infection. It is not uncommon for subsequent amputations to be done

on the same limb in a progressive 'salami' manner [198]. At Auckland hospital between 2009 and 2014, the management of 265 wound episodes were examined, and a mean cost of $38,555 per was identified. Those patients who underwent major amputation, or a combination with other management were over twice as expensive [271]. The lower value is used for evaluation because of ambiguity in the reporting .

Achieving good glucose control sees a reduction in amputation by a factor of two [272]. With 793 amputations per year in New Zealand [273], a total annual cost of approximately $30.6M. This reduction is seen as soon as 3 years after intervention to improve glucose control. Halving the rate of amputations sees a direct reduction in expense to the tune of $15.3M per annum nationally.

Hypoglycaemic episodes are estimated to cost $2479 per admissions. With rates variable across age groups, there are approximately 3,200 occurences of hypoglycaemia requiring intervention from medical professionals per year in New Zealand. Insulin pumps have been shown to reduce the occurence by up to 32% in at-risk populations. Thus, insulin pumps would allow for a national saving of $1-5M per annum, nationally.

4.2.3   DIRECT COSTS

The direct costs associated with widespread insulin pump adoption lie primarily in the consumables. Pharmac is currently able to purchase infusion sets for $13 each, and reservoirs for $5 each [212]. Ignoring the significantly stronger purchasing power

Pharmac has because of the larger quantities sought, the cost for consumables comes to an annual cost of approximately $2150 per patient. These costs would be be considerable with mass adoption, but could be significantly lowered with the intended development of a patch pump, removing the need for an infusion set.

The cost of the purchase of the devices themselves can be estimated using a conservatively expensive estimate of $500 per device, and a lifespan of four years. This is very conservative given a current bill of materials (BOM) price of approximately $80 per device. This gives an annual cost of $125 per year per person. Therefore, a total price of approximately $2275 per patient per year is an estimate at overall direct cost of hardware for the ULC pump.

4.2.4   PRIMARY/EDUCATION COSTS

Insulin pump therapy works best with good patient education, and therefore the ability to correctly operate and debug the device [4]. Proper insulin pump education sees an additional considerable decrease in prevalence of hypoglycaemic episodes and a mild increase in insulin pump control [274]. Thus, there is a cost associated with initial education and coaching in how to most effectively use the device. Because of current pump requirements and their unique properties, device-specific education is required [4].

Throughout most of New Zealand there is currently access to public-funded annual diabetes reviews with a GP or nurse [275]. These reviews currently provide an opportunity

for a medication review, screening for complications, and assessing glycaemic control. Furthermore, NZ guidelines state that diabetics *"who require insulin will receive the initiation by trained healthcare professionals within a structured programme that, whenever possible, includes education in dose titration by the person with diabetes. People on insulin will know how to access timely expert help and support to manage their condition"* [275]. Thus, there is already considerable primary care resources devoted to individuals who treat their diabetes with insulin.

Higher saturation of insulin pumps will allow for significantly more effective delivery of education around them. With the current relatively low numbers of 4,000 - 4,500, it is inefficient to commit too many resources to the development of educational material. Similarly, fewer people will be trained in the use of the devices, and thus insulin pump reviews and clinician interacts specifically regarding insulin pumps are limited to only specialist endocrinologists or specifically-trained nurse practitioners. This necessity for specialist care inherently prevents equitable access for thus with impediments to specialist, such as rural communities [276, 277] and Māori [278]. As insulin pumps become significantly widespread, and, in particular, a single device, it becomes resource-efficient to spent greater time in developing tools for effective education in insulin pump use, even tailored for specific sub-populations. Furthermore, the number of clinicians familiar with insulin pump use and able to provide clinical reviews and coaching will increase significantly, as will their distribution throughout New Zealand.

Any additional primary care resources required to ensure proper use of insulin pumps will be substantially offset by significant increases in productivity. Having an interop-

erable (see Section: 4.3.1.1) device into which patients routinely enter their BG data and carbohydrate consumption with the native ability to record insulin administration information enables significant advances in diabetes care. Average BG is strongly correlated to HbA1c, and thus there will effectively be a digital HbA1c obtained without need for physical interaction with the healthcare system. Similarly, increasing insulin doses can be noted, which in turn allow for investigation as to the cause, and possible intervention if required. Such a system is an example of a long-term innovation to bring about the disruptive, extrinsic changes required in the healthcare system given demand for diabetes care significantly outgrowing GDP and wages.

Due to a lack of literature examining resource use of primary healthcare specific to insulin pumps [279], and even more so in the New Zealand context, it is difficult to put an economic cost to it. Qualitatively, it is apparent there is significant resource given to primary care of individuals with diabetes. Given the scale of mass adoption of insulin pumps, and particularly a single device with broad NSIO, it is expected that the development of robust systems and educational resources will result in a minimal net increase in primary healthcare resource use for the management of insulin pumps. Any such increase will be more than offset by the increase in productivity made possible through sophisticated digital health platforms.

4.2.5   TOTAL POTENTIAL COSTS

The approximate overall net cost per person adopting the pump is expected to be: a net gain of \$422 per annum for each individual who adopts a patch pump, or for a standard pump approximately a net cost of \$1090 per annum. Several possible adoption scenarios were examined for a more thorough investigation. These scenarios range from no additional adoption, to minimal adoption, moderate adoption, and generous adoption. Total costs associated with Sections 4.2.1 — 4.2.4 are presented for each adoption scenario in Table 4.2, or in full in Appendix A.1.1.

It is important to note the adoption scenarios presented in Table 4.2 assume there is no intelligent thought given into the selection of individuals to whom insulin pumps are provided, but instead they are effectively given randomly across the entire diabetic population. The use of research-informed systems for the prioritisation of specific sub-populations of diabetics would see considerably higher savings associated with the same adoption rates suggested in Table 4.2.

For example, in Southland 2016/2017 there were 6994 admissions involving patients with any diagnosis of diabetes associated with only 3615 diabetics, of which an estimated 20% had three or more admissions [267]. While it is arguably too late because there are already complications, one potential prioritisation scheme would be the prescription of an insulin pump to every individual who uses insulin to manage their type-one or type-two diabetes who presents to a hospital.

Table 4.2: Potential adoption scenarios for the ULC insulin pump. Scenario 1 represents no change in total insulin pump adoption, but assumes that only those who currently have pumps will adopt the ULC pump. Savings are represented as positive values, and costs as negative values. All values are in thousands of New Zealand Dollars. T1D — Individuals with type-one diabetes; T2D — Individuals with type-two diabetes

Scenario:		1	2	3	4
Type	Number	Adopters (%)	Adopters (%)	Adopters (%)	Adopters (%)
T1D	26000	3640 (14)	6500 (25)	13000 (50)	20800 (80)
T2D[A]	33800	0 (0)	3380 (10)	10140 (30)	16900 (50)
Saving (NZD, 000s)					
Direct savings:		$6,588	$10,096	$17,418	$ 25,251
Indirect savings:		$2,530	$ 6,760	$ 15,726	$ 25,538
Direct Costs:		-$795	-$5,371	-$15,095	-$25,772
Total[B]:		**$ 8,324**	**$11,485**	**$18,050**	**$25,017**
Infusions sets[C]:		*(-$1,714)*	*(-$ 11,584)*	*(-$32,557)*	*(-$55,586)*

[A] — Only individuals with type-two diabetes who are currently on insulin therapy are included.
[B] — Assuming complete patch pump adoption.
[C] — Infusion sets would be an additional added cost if there is no patch pump available.

Given historic low rates of pump ownership [151] and poor health outcomes [3], Māori have inequitable access to best healthcare and to outcomes. Therefore, an organisation or scheme led by Māori for the benefit of Māori should be established. The establishment of such an entity would allow for the development of specific solutions designed for uptake by being informed by those who need to uptake medical technologies the most. This aspect is further discussed in Section 4.3.4.2 These prioritisation schemes would

replace the current labour-intensive specialist-only special authority prescription that is currently in place in New Zealand.

4.3   ULC-Pump

An ultra-low cost insulin pump (ULC pump) is currently under development in the Centre for Bio-engineering at the University of Canterbury. This pump is the realisation of an insulin pump able to be manufactured in a very cost-effective manner, to allow for maximal uptake.

4.3.1   DESIGN PHILOSOPHY

This innovation is one come about from the pressure of need for wider access to insulin pumps, specifically ones with broad NSIO. It is a medium-term innovation, with a strong benefit in the cost reduction, and provides for significant further long-term innovation around a highly interconnected, automated healthcare system.

4.3.1.1   OPEN

There are recognised differing needs in insulin therapy and insulin pump technologies for several different subpopulations of individuals who are dependant on the use of insulin for management of diabetes: Groups with differing needs identified were individuals

with type-one diabetes, recently-diagnosed individuals with type-two diabetes, poorly-controlled individuals with type-two diabetes, and elderly and care-dependent diabetics [4]. Because of the currently locked-down nature of insulin pumps, where any software change requires additional regulatory approval [280], accommodating to all of these groups' needs is difficult. The UC ULC pump poses a solution able to circumvent these problems through use of interoperability and open access. Supposing a cellular phone or other Bluetooth™-capable device is used as the controlling computational device, it is then trivial to envisage the use of different mobile applications to be used during different disease pathologies, disease stages, or other indications of insulin pumps.

The continuation of this philosophy is the realisation of the democratisation of medicine: people should be in control of their own medical choices and data. The wider interoperability of the UC ULC pump inherent to devices with open-access designs means technologically-minded individuals or organisations are able to design their own solutions. This outcome is already seen in the OpenAPS project [52], which provides ability for otherwise uninteroperable devices to be used in a closed-loop fashion. Despite the need for a moderate-high level of technological literacy for development and initial adoption of the system, it is increasingly adoptable and adopted by individuals with diabetes [281]. This increasing adoption shows the ability of open-access technological development even when the hardware remains relatively rigidly clamped down by entities with financial interests to maintain the status quo. The development and widespread adoption of hardware designed with these specific uses and users, such as the OpenAPS project, in mind, poses widespread betterment of the international diabetic community.

The development of open-source medical equipment paves the way to increased inter-operability to benefit healthcare consumers. On the back of open-source software such as Python and its various scientific packages, Linux kernels, and various desktop environments [282], there is increasing recognition of the reliability of complex open-source devices [282–285]. There are considerable notable examples outside the medical industry of open source hardware which is holding its own with other stricter intellectual property competitors, such as Arduino [286], several cellphones [287–290], Raspberry Pi [291], and Prusa [292]. The popularity and reliability of these devices can be leveraged to transfer trust to open source medical devices specifically. The COVID-19 pandemic has also allowed greater development and adoption of open source medical hardware [293–296]. The lower costof these devices has not come at the expense of the value which is placed in them, compared to closed-source competitors [297]. The increasing trust in open-source medical devices would see lower-cost alternatives become increasingly accessible to consumers.

Aside from access to cost-effective hardware, the key advantage of open-source hardware is in its inherent interoperability. With the exception of exceptionally rare intentional locking down, open-source hardware, by design has broad NSIO. Thus, interfacing other interoperable hardware is typically trivial, requiring a simple reformatting to the format expected by the receiving hardware.

Therefore, the open-source future of medical hardware is enabling the realisation of the value of medical data in allowing any desired additional computation or communication of that data. It also returns the ownership of the data to the patient. If the patient

wishes to opt out of any data service they are able to do so, and there is no requirement for data to be used. In particular, this data sovereignty is of importance for Māori, and recognises the right of tino rangatiratanga.

There is a point of interoperability which yields wider adoption once sufficient market share is obtained. For example, as has been seen with charging ports of smart phones, where once there were dozens of manufacturer-specific charging ports [298], the majority of devices now have a common interface, and devices are even not supplied with charging hardware because interoperability removes the need for it. Similar interoperability in the medical device industry will see diminishing requirements for manufacturer-specific hardware to share data or control. This change will benefit patients and clinicians, and the medical industry as a whole. Increasing interoperability will allow for greater access to data, and thus analysis and development of tools to aid clinicians' decision making, as has been seen in the STAR programme [145]. The development of such tools enables better outcomes for patients, and a lighter workload for staff, both of which see reduction of hospital stay and associated financial cost.

Diabetes technologies are typically limited to the interoperability based on pre-manufacture decisions [36]. It is common for insulin pump manufacturers to incorporate interoperability with specific devices only: SIO. The insulin pumps subsidised within New Zealand [212] have very limited interoperability: the t:slim X2™(Tandem Diabetes Care, California, USA) is compatible with the G6 CGM System (Dexcom, California, USA), and the MiniMed™640G, (Medtronic, California, USA) and the MiniMed™770G (Medtronic, California, USA) are natively compatible with the Enlite™(Medtronic, Dublin, Ireland) or

Guardian™Sensor 3 (Medtronic, California, USA) CGM devices. This SIO prohibits consumers using cost-effective devices, rendering access to closed-loop control prohibitively expensive for most New Zealanders.

The ULC insulin pump is designed for maximum interoperability, allowing interfacing with any glucose monitoring or insulin control device. The opening of the interface is the main reason that considerable cost savings are allowed. This design approach is in line with making medicine accessible to the consumer in a way they prefer, and enables principles, such as indigenous peoples' data sovereignty to be realised. It also allows consumers to use their data for best control, in a manner best suited to their needs.

4.3.1.2   THE PIRATE'S PUMP [HACKABILITY]

The ULC pump is viable due to very low computation required. While insulin pumps are typically seen as complex, software-intensive embedded systems [4], this need is removed in the ULC pump. Instead, a strong focus is in design for communication and wide compatibility, and thus the device is intended to be operated from a mobile device/smart phone. This approach removes the need for extensive computational power, and sophisticated software development. Thus, the device can, in theory, be run from any mobile computing platform with appropriate connectivity capabilities. While an official supported mobile device application will be developed and distributed with the device, users will be able to decide how to control the insulin pump.

Security is a common conversation around medical devices, and is of greater concern in devices with inherent non-specific interoperability [299]. A device is intended to be controlled from another device, is inherently at risk of being controlled from *yet another* device. Modern cell phones support security features such as 2FA, biometric security, and native support of various cybersecurity algorithms [300, 301], which will be used to ensure the correct device is interacting with the ULC insulin pump. There are increasingly stronger lessons to be learnt from IOT development with rigid security protocols [302], which lend themselves to the development of medical devices. These lessons, alongside active discussions around the use of Bluetooth™, and specifically around its use in diabetes technologies [303] allow for development of safe, secure, and low-cost remotely driven insulin pumps.

The cybersecurity of digital health information is a point everyone asks. In New Zealand there exist systems for sharing health data [304], which integrate primary, secondary, and tertiary care facilities. There are more and more applications dependent on strict cybersecurity within and external to the medical device industry. These solutions will be eminently portable to the insulin pump, and the data obtained from it.

The one thing which makes an insulin pump an insulin pump, is the insulin. The technology contained within the insulin pump is extremely simple considering its price. However, if it is made more readily available it would have significantly more applications, particularly as a patch pump. One example is within palliative care, for administration of haloperidol and morphine for end of life cares. Currently, subcutaneous infusions are made possible through use of syringe drivers, such as the Niki T34 (InfuSystem,

(a)

(b)

Figure 4.5: Renderings of prototypes of the ULC pumps. (a) depicts the traditional, motor-driven pump, and (b) the mechanically-driving pump design.

Michigan, USA). These infusions are often low-dose medications which are diluted to volumes up to 34 mL to allow for convenient use in common syringes [305]. These syringe drivers are typically attached to a physical mount, and require an infusion set. A re-purposed insulin pump would enable the use of un- or minimally- diluted medications in a 3 mL reservoir, where, currently, supplier formulations for common medications in New Zealand are already of the appropriate concentration [306]. This application of the ULC pump would allow a smaller, lighter device, and, in the case of the patch pump, be significantly less restrictive, allowing greater dignity in dying.

4.3.2   ADDITIONAL DEVELOPMENTS BEYOND TYPICAL

The development of the ULC insulin pump is currently bimodal, with the development of a traditional pump alongside the development of a mechanically-driven pump. A typical insulin pump has a lead screw driven by a stepper or brushless DC motor, via some form
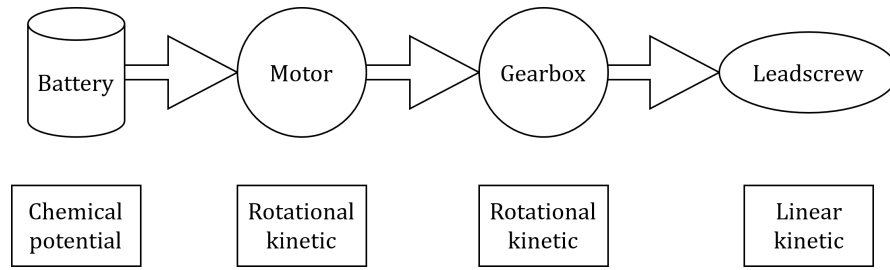
Figure 4.6: Energy transformations within a traditional insulin pump.

of advantageous rotation-to-rotation motion transmission. Therefore, the energy to drive the syringe plunger forward is ultimately produced from a battery, as shown in Figure 4.6. This power is typically obtained from very common batteries, such as AA [307], to ensure constant operation is readily available. Despite this solution, there is still concern for battery life and reliability [308], resulting in alternative solutions being sought [309]. Because of the inherent portability required for insulin pumps, power considerations will always be paramount.

There are some current, entirely mechanically-driven solutions. These solutions typically use the pressurisation of a reservoir with the insulin, and release insulin as either a constant infusion determined by mechanical properties, with the ability to bolus again entirely mechanically [310], or driven with the force of actuating two buttons [311]. These mechanical devices market themselves as a replacement for pre-filled pen injections, rather than as a complete insulin pump, largely because of their very limited control [4]. Because these devices are entirely mechanical, without electronics, there is no capability of communications, and thus no ability to be controlled by any other device, reducing current and future interoperability.

Along similar developmental lines, a mechanically-driven insulin pump was developed
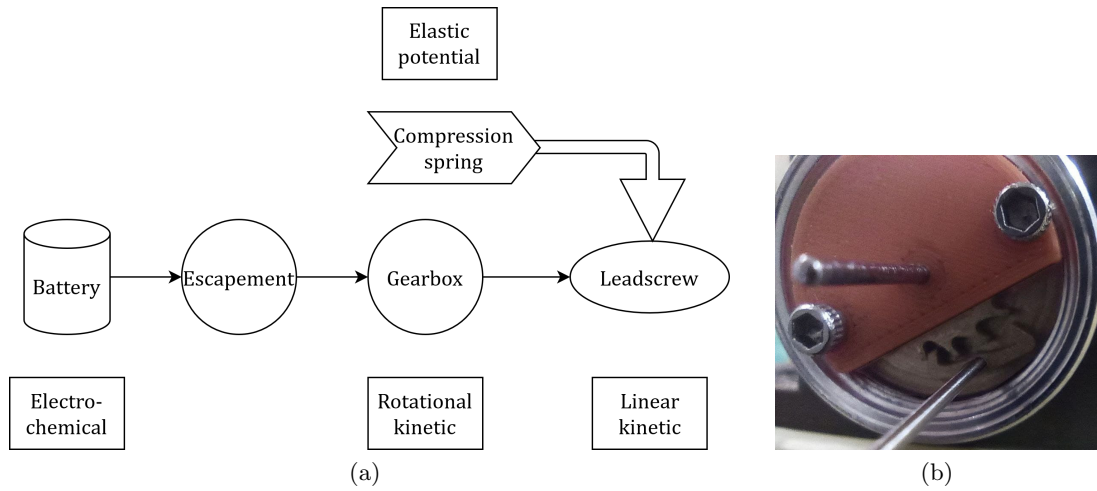
Figure 4.7: (a) Energy transformations of the novel mechanically-driven ULC pump. Thick arrows denote energy transformations associated directly with insulin delivery, whereas thin arrows denote control. (b) Picture of the escapement mechanism of the prototype.

[312]. This version of the ULC pump is in a similar format to a traditional insulin pump, but, instead of a battery, a compressed spring is used to provide the energy required for delivery, as shown in Figure 4.7. Without adequate control this pump would simply deliver the entire reservoir at once, and thus a clock-like escapement mechanism is used for control. This approach allows for design for a particular resolution through the use of a symmetrical lock, equidistant pallet type [313], and selection of the number of teeth on the escape wheel, motion transmission overall gear ratio, and lead screw pitch. Renderings of both pump designs are shown in Figure 4.5.

This clockwork pump has numerous advantages. Because there is no electromechanical need to provide the force required to administer the insulin, the required electrical power consumption is substantially lower, thus enabling a vastly extended battery life. The motor is often the most expensive single component of an insulin pump, and thus substantial cost is saved in its omission. Similarly, the potential life span of the device

Table 4.3: Testing results from the laboratory tests evaluating the ULC insulin pump's ability to deliver boluses compared against other devices currently available in New Zealand.

Pump System	1 U Bolus		10 U Bolus	
	Mean error (SD)	Within 15%	Mean error (SD)	Within 15%
MiniMed™640G	0.6% (2.6%)	100%	-0.7% (0.6%)	100%
Tandem t:slim™X2	1.9% (1.3%)	100%	-	-
Omnipod	0.0% (12.5%)	76.9%	0.3% (0.7%)	100%
ULC pump	-0.64% (2.6%)	100%	-0.06% (0.32%)	100%

is extended. The main challenges associated with the clockwork pump are managing friction, and manufacture of relatively small components. In the absence of a motor, the life-limiting factor is now the gradual increase of friction due to material fatigue, which can be mitigated through design and material selection. Managing mechanical tolerances is another difficulty, as with a shaft diameter of only 0.8 mm, the overall design tolerances are very small.

4.3.3   RESULTS

Bench testing of both insulin pump designs has successfully demonstrated the ability for the devices to deliver the correct amount of insulin. The appropriate testing standards state the need to be able to consistently deliver the correct amount of insulin when instructed with boluses of 1 U and 10 U, and a basal rate of 1 $U \cdot h^{-1}$ [314, 315]. As shown in Tables 4.3 and 4.4, the ULC insulin pumps perform at a similar, if not better, level to those currently available.

Table 4.4: Testing results from the laboratory tests evaluating the ULC insulin pump's ability to deliver a constant basal rate compared against other devices currently available in New Zealand.

Pump System	Individual 1-hour windows within:		
	±15%	±10%	±5%
MiniMed™640G	95.6%	93.1%	84.0%
Tandem t:slim™X2	99.8%	98.9%	91.4%
Omnipod	81.2%	71.2%	46.6%
ULC pump	100%	92.6%	84.0%

4.3.4   CRITICAL NEXT STEPS

With promising initial validation results, there is work that must be done in continuation of development of the technologies alongside work to prepare for widespread adoption. The pump is currently very much in a design for prototype stage, with very few considerations of ergonomic designs. However, current design is being undertaken to accommodate ergonomic and custom design in the future, with an emphasis on modular design allowing several smaller PCBs, for example.

4.3.4.1   THE PIRATE'S PUMP [PATCH]

One design outcome posing many significant benefits is the development of the patch pump. A patch pump removes the need for an infusion set, instead containing the cannula within it and simply injecting directly out of the bottom of the pump. Pump use relatively high among young adults [151], for whom physical body image is important to the extent of impacting their adherence [316]. The patch pump allows individuals who require insulin to feel more in control of their own illness, rather than current
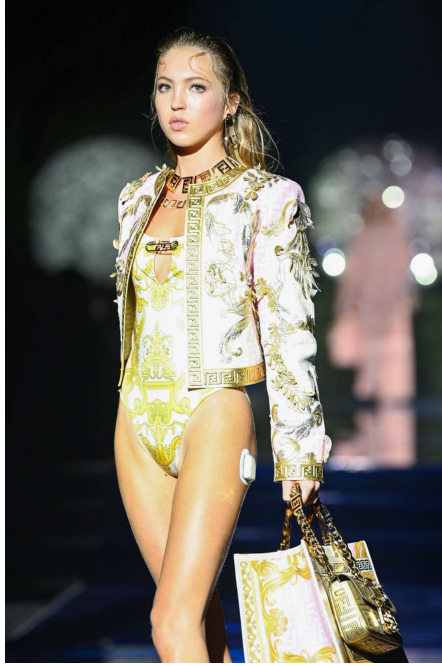
Figure 4.8: Lila Moss at Milan Fashion Week 2021 with an Omnipod™(Insulet Corporation, Massachusetts, USA) patch pump prominently on display.

perceptions around insulin delivery. Vial and syringe delivery in particular has a low perceived social acceptance [317], because individuals feel like they are being associated with "*intravenous drug addicts or severe illness*" [318].

Patch insulin pumps are becoming more and more common, with the most common — the OmniPod™(Insulet Corporation, Massachusetts, USA)[319] — having seen 24% year-on-year growth in sales [320], showing the increasing demand. Furthermore, they are starting to increasingly feature in popular culture, for example being made visible at the Milan Fashion Week as shown in Figure 4.8. Therefore, the patch pump design presents significant potential in enabling greater adherence, through higher levels of social acceptance of insulin delivery and reduced user costs. Development of a patch pump involves some mechanism of embedding the needle within the insulin pump.

Another substantial benefit of the patch pump is financial. Insulin pump consumables are expensive, at approximately \$2150 per person per annum [212] if publicly funded, or approximately an extra 15% more expensive if not. A patch pump removes the need for the infusion set entirely, which comprises 72% of the cost of insulin pump consumables. As discussed in Section 4.2.3, these costs are considerable when applied on scale, and thus the savings associated with adoption of the patch pump instead of a traditional pump are expected to be up to \$55M per annum, depending on adoption rates.

In addition to the patch pump, technological development continues around the custom application for mobile devices, further more extensive accuracy and lifespan testing, and ergonomic design.

4.3.4.2   ACTUALLY ENSURING UPTAKE

There are many technologically sound devices, which still lack appropriate medical uptake. There are a wide range of reasons for failure of uptake of sound medical device technology, which individually mitigating would be cumbersome. A better approach is to use a research-led framework that provides for the ability of innovation to be taken up, such as the Tech-ISM approach [17]. This framework breaks down the necessary aspects required for a medical technology specifically to be adopted to widespread market use as per an individual-centric approach as shown in Figure 4.9.

The Tech-ISM approach can be engaged throughout technological development through
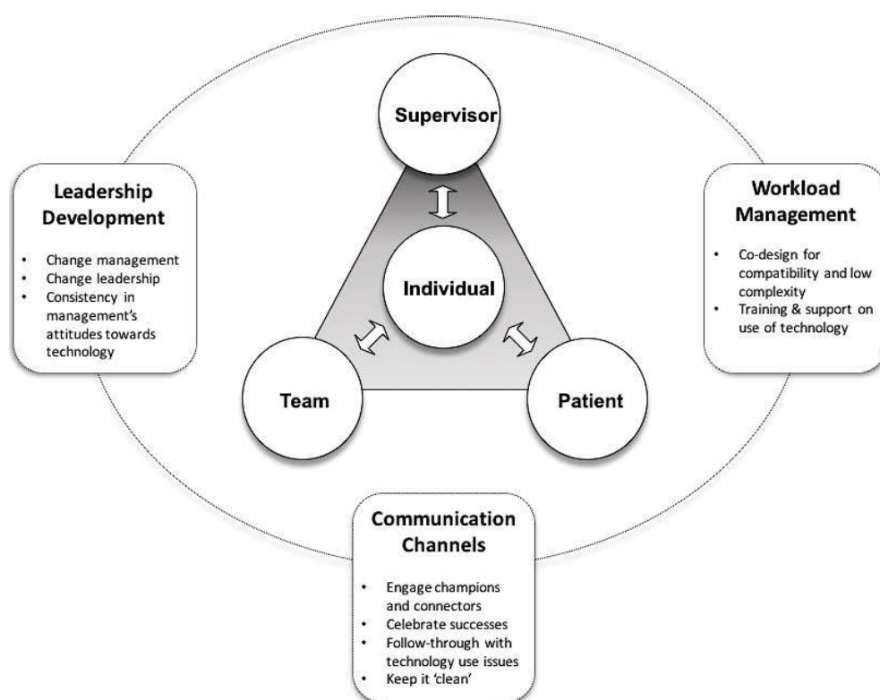
Figure 4.9: The Tech-ISM framework which enables adoption of technological innovations within medicine [17].

the use of champions and connections, and through design, specifically for uptake, rather than solely for the sake of the technology. In terms of the ULC insulin pumps, it means immediate future engagement with a very wide range of collaborators can help ensure the successful uptake of the innovation. It is key to develop these innovations in close partnership with the end users: diabetes clinicians, and individuals with diabetes. Specifically, the Tech-ISM framework will inform the immediate future of the device design in its social adoptability, particularly in groups currently under-represented in uptake and use of insulin pumps.

Māori and Pasifika, and people of greater socieo-economic deprivation, have fewer insulin-pumps [151]. The development of a Māori social entity with the aim of providing a meaningful working relationship to ensure design for adoption is critical. The process

of ergonomic design, mobile application development, and also the specific health practitioners involved in delivering insulin pumps to Māori, will have a substantial effect. Given the need for a collective, whānau-led approach, even in personalised healthcare [321], it is vital to engage at this level constantly throughout the continuing development of the ULC insulin pump and surrounding infrastructure technologies.

The mutual relationship with Māori is not solely for the benefit of Māori. The establishment of a close working relationship allows greater level of understanding of Māori culture and decision making processes by researchers. This allows researchers to identify and mitigate current biases in the delivery of healthcare to Māori. Doing so provides researchers the ability to engage in conversations with Māori in their own context. This exposure through close relationship enables future cultural safety which is vital to address current inequities in healthcare [322].

Another important relationship to develop is with the individuals and organisations who have the ability to actually decide to adopt the device. Thus, it requires starting early conversations with entities such as the Ministry of Health and DHBs (/HealthNZ). These early conversations allow meaningful understanding of the project to be conveyed throughout the continuation of it, and thus decisions-makers will be more optimally informed.

4.4   Summary

Insulin pumps are a means to bring about a substantial reduction in the human and financial cost of diabetes. In New Zealand there is limited access due to intentional rationing of healthcare, despite considerable benefits in their use for individuals with type-one or type-two diabetes. Financially, an ultra low-cost insulin pump poses potential tens of millions of dollars of systemic and personal savings, while increasing equitable access to healthcare and outcomes.

The ULC insulin pump is a medium-term innovation made possible by the separation of the hardware and the computational software. While the ULC pump is intended to be controlled by a mobile application for a cell phone, there is broad non-specific interoperability which allows control from any device capable of the appropriate communication and security protocols. The benefits of open-source devices with NSIO are also in future long-term innovations drastically increasing productivity through automation of healthcare delivery.

Measures to ensure a high uptake of the device include the adoption of the Tech-ISM framework. This framework involves the continuation of close working relationships with clinical, industry, health policy, and Māori partners.

Chapter 5

Continuous glucose monitors

Monitoring blood glucose levels is vital for any individual with diabetes. Diabetes is defined as a lack of ability to contol one's circulating BG. Therefore, the monitoring of BG is synonymous with monitoring the disease. The frequency of measurement is dependent on the specific indication.

5.1   Current blood glucose monitoring

The majority of current BG measurements in New Zealand, and the world, are made with invasive capillary measurements. Doing so is based on decades-old technology [323, 324], and requires puncturing the skin with some form of needle to subsequently absorb a small volume of blood onto a thin gold-plated membrane impregnated with

glucose oxidase. The glucose reaction with glucose oxidase creates an electrochemical reaction interpreted by basic electronics to approximate the glucose concentration [325]. Modern fabrication techniques have enabled widespread distribution of such devices, in the form of a point-of-care (POC) electronic glucose monitoring device into which single-use test strips are inserted. Testing with such a device in an out-of-hospital context is commonly referred to as self-monitored blood glucose (SMBG).

Individuals with diabetes who regularly check their blood sugar have a better quality of life [142]. However, SMBG testing is infrequently carried out as instructed, with poor compliance levels due to pain [326–328], perceived social stigma of performing medical procedures in public [329], and/or the inconveneince [330]. For example, if patients are suspecting nocturnal hypoglycaemia, they are recommended to set alarms at 3:00am, and perform a SMBG test every night at this time for several nights [157]. These instructions are, understandably, rarely followed. This lack of regular monitoring leads to delayed testing and insulin delivery, and can impact overall glycaemic control [329].

5.1.1 Glucose monitoring in type-one diabetes

For best glycaemic control, individuals with type-one diabetes must regularly test BG. Because these individuals have a complete lack of endogenous insulin secretion, they are fully reliant on exogenous insulin delivery. Determining insulin doses is multi-variate, but obtaining an accurate blood glucose measurement is vital for determining the appropriate insulin dose [331]. Therefore, individuals with type-one diabetes should test prior

to every administration of insulin, once a day for basal dose, after meals for a correction dose, before going to bed, before and/or after exercise, and any other time that they feel symptomatically hypoglycaemic or hyperglycaemic [332–335]. Thus, a thorough testing regime would see an individual with type-one diabetes test their BG up to eight times every day, but four is generally accepted as sufficient for good control [336, 337].

Children with type-one diabetes are particularly high risk for low adherence to invasive SMBG testing. Even enrolled into a trial specifically examining test regularity, compliance of only 10% is evident over just a 3 day period [338]. Children, especially young children, are one sub-population of individuals with diabetes who see the greatest benefit from regular glucose monitoring, because they have rapidly changing metabolisms, and are more susceptible to hypoglycaemia [339–341]. Fear of hypoglycaemia is a worry for children with type-one diabetes and their parents [342, 343]. These people are often diabetes-naïve, in particular to being in complete control of insulin dosing, at the expense of effective sleep and general mental health [344].

The lack of regular SMBG and subsequent suboptimal insulin dosing has serious implications in children and adolescents. Only 21% of adolescents with type-one diabetes achieve adequate long-term glycaemic control [345]. Because this lack of glycaemic control is at a period of continuing physiological development, there is greater potential for the lack of glycaemic control to have long-term health implications. Examples of long-term health conditions, which may arise subsequent to poorly-controlled adolescent type-one diabetes, include retinopathy, renal impairment, neuropathy, and cardiovascular disease [346–349]. They are also at greater risk of acute complications, such as

hypoglycaemia and diabetic ketoacidosis (DKA) [346]. Therefore, the lack of a modality for SMBG testing with high compliance in children and adolescents with type-one diabetes, as well as adults, has long-term implications for these individuals.

5.1.2   Glucose monitoring in type-two diabetes

The recommended frequency of SMBG for individuals with type-two diabetes is dependant on the extent of the disease and treatment. For individuals who are on intense, basal-bolus insulin administration regimes, testing should be as regular as for individuals with type one diabetes because of the necessity of accurate BG estimation to inform insulin dosing. Any time where hypoglycaemia or hyperglycaemia is suspected a BG measurement is required for potential correction of any therapeutic regime.

For individuals with type-two diabetes who are not at risk of hypoglycaemia — from insulin or oral anti-hyperglycaemic agents — testing of HbA1c is often used as the sole measurement of glycaemic control [157, 196]. As discussed in Section 4.1, haemoglobin is glycated at a rate directly proportional to the concentration of circulating glucose. Therefore, the concentration of glycated haemoglobin relative to the total concentration of haemoglobin is a surrogate for the time-averaged blood sugar level of the average lifetime of a haemoglobin molecule, which is two to three months [350].

In the early stages of type-two diabetes, blood sugar levels are generally well controlled, except forpostprandial. Thus, the utility of a single, discrete SMBG sample is minimal,

as testing would optimally be at the postprandial BG peak, which is very difficult to exactly predict. Thus, individuals with type-two diabetes who are not on insulin or sulfonylurea medications are not required to regularly test their BG concentrations, despite literature suggesting a benefit [351]. For all individuals with type-two diabetes, relative glycated haemoglobin concentrations are recommended to be tested every six months if adequate control is attained, and every three months otherwise [352]. The use of CGM data not only replaces HbA1c for monitioring disease progression, but also enhances it for example allowing specific analysis of peaks and plateaus of BG, or changing the period over which the low-pass filter is applied for more rapid determination of efficacy of treatment on glycaemic control [353].

However, for individuals with type-two diabetes who are not treated with insulin, there is a correlation with regular SMBG and a small increase in glycaemic control, but only if the SMBG results were used to inform clinical processes [354]. Even if they are completed, SMBG data are often inaccessible to clinicians for a variety of reasons, such as a lack of context to the individual BG measurement, a lack of time and date with the BG, or specific information around medication use and timing relative to the BG measurements [355]. Furthermore, the value of the BG may also be inaccessible, either through illegibility or incorrect nature of manually-recorded results, or because of simplistic interfaces on cost-effective, popular POC glucometer devices [356, 357]. These impediments to effective clinical use of BG data in the context of time-pressured primary appointments prevent maximising the efficiency in current healthcare delivery models.

One example of SMBG informing the clinical process is for medication dose adjustments. When initiating a sulfonylurea, it is necessary to use SMBG to ensure risk of hypoglycaemia is minimised. These medications increase endogenous insulin secretions, and thus dose-related hypoglycaemia is possible [358]. While the dose is still being adjusted, it is necessary to test BG before meals, and two hours postprandial [359]. These systems are still dependant on individuals proactively recording and presenting BG test results to the appropriate clinicians. Hence, there is very little to no automation in such processes, currently.

5.2   Current CGM use

A continuous glucose monitor is a device providing multiple glucose measurements. They are still invasive, with the insertion of a small filament into the interstitial space. Interstitial fluid is allowed to diffuse into the sensor at a rate assumed to be continuous [360]. The CGM samples the electrochemical output at regular intervals, at approximately $1 - 5\ min$. This increased frequency of data allows more complex decision making than a single discrete point, if for no other reason than the estimation real-time differential, allowing current insulin action to be approximated [361].

Because the device is implanted, albeit superficially, there are considerable biochemical challenges for longevity of the sensor. Thus, the section of the device that is directly connected to the filament must be regularly replaced, typically every 7-10 days [362–364]. Current CGM technologies are either real time CGMs (RT-CGM), which are constantly

communicating with a paired device, or flash glucose monitors (FGM). Flash glucose monitors require an external device to scan the implanted section of the device, either a proprietary companion device, or a third-party device. For example, the MiaoMiao (MiaoMiao, Shanghai, China) sensor is capable of querying the Freestyle Libre (Abbott Laboratories, Illinois, USA).

5.2.1 BENEFITS OF CGM

The use of continuous glucose monitoring devices is correlated with an increase in glycaemic control [365–369]. Contributing factors to this outcome are both an increase in compliance compared to SMBG [338], and also the increase in the amount of data available for informing insulin dose calculation [361, 370, 371]. The use of CGM is not only correlated with a decrease in average BG, but also with the decrease in prevalence of hypoglycaemic episodes [366, 367, 369, 372–375]. Continuous glucose monitoring is a technology which has bettered outcomes for individuals with type-one and type-two diabetes.

Individuals with a long history of type-one diabetes are at risk of being unaware of hypoglycaemic episodes, or hypo-unaware. This complication poses significant risks, as if individuals with low or lowering BG levels are unaware of mild hypoglycaemia, the risk of a severe hypoglycaemic episode increases, from which serious harm can result [375–378]. For example, if an individual is hypoglycaemic and driving, it is possible for them to have a seizure or lose consciousness, which has obvious extreme potential

harm for themselves and others. Therefore, individuals who are susceptible to being unaware of hypoglycaemia require diagnosis through SMBG, which if they are unaware is difficult to achieve unless prompted by other people. The use of a CGM mitigates unaware hypoglycaemic episodes [375–377], through the use of automatic notification of hypoglycaemia, and the subsequent prompting of treatment of hypoglycaemia when it is still mild.

Use of CGMs also allow for more convenient sharing of BG data. Sharing could be to healthcare provider such as a primary care facility or specialist endocrinologist, to family members such as parents of young children with type-one diabetes, or to a personal device to aid in decision making. Data sharing is enabled by the device manufacturer, which has several limitations in lack of widespread interoperability, as discussed in Section 5.2.2.1. This SIO is one of the primary reasons for the expense of diabetes technologies. In limiting the ability for data transfer, consumers of diabetes technologies are prescribed to a data monopoly, where they are forced to purchase specific devices to implement a closed-loop diabetes system.

The data sharing that is available is particularly beneficial for parents of individuals with diabetics, and has been shown to improve sleep, and provide an increased sense of hypoglycaemic-related security [379]. Other similar uses include for remote monitoring of insulin dose titration during initiation [380], or even providing a higher level of control during ICU admissions [381–383].

5.2.2 LIMITATIONS

There are some inherent errors associated with CGM use. Because the sensor is inserted into the interstitial space instead of directly sampling capillary blood, there is a time lag in CGM data due to the phase delay associated with chemical transport between blood and interstitial fluid. Thus, CGM data is also highly dependant on factors which impact the peripheral vasculature of the specific CGM insertion location [384]. Exercise, ambient temperature, tightness of clothing, medications, and disease processes all have the potential to cause sensor error. There is recognised drift error, as well as other dynamic properties which lead to inaccuracies of CGM measurements [385–389].

Because of the various sources of error associated with CGM use, almost all models require regular calibration. The calibration is typically done through the use of a standard invasive capillary SMBG measurement. Calibration is largely required due ot inherent sensor drift and other compounding errors [385, 386, 390]. Thus, while reducing the requirement for POC BG testing, they do not completely remove it. With increasing recognition that calibration is often not carried out by the CGM user in the manufacturer-recommend fashion, there is increasing acceptance this calibration is not required [391].

The greatest impediment to widespread CGM use is cost. There is currently no provision for public funding of CGM devices in New Zealand [212]. Thus, any New Zealander with diabetes who wishes to access use of a CGM must self-fund, or possibly crowd-fund [392].

The lack of public funding means there is limited information about CGM prevalence in New Zealand, as data are lacking on official governmental databases [270]. Estimates are that approximately 10% of individuals with type-one diabetes use continuous glucose monitoring, although best estimates are censored for commercial sensitivity [393]. The few New Zealanders who are able to self-fund a CGM often do not use it consistently due to budgetary constraints, instead opting to use the devices only when experiencing regular symptoms of dysglycaemia [394].

5.2.2.1   Locked out

There is a lack of interoperability in current CGMs. Most devices have a white-list of devices with which they are capable of operating with their specific software [395, 396]. This approach inherently limits the freedom of data and interoperability of devices. Therefore, the ability of users to readily access, and use their own health data in whatever manner they wish is inhibited. This lack of NSIO prevents equitable access to best care, because the use of algorithms or other computational aids requires specific hardware, which may be accessible only through purchase from the same companies.

Not only do medical device companies not design for interoperability, but they actively inhibit open-source solutions benefiting patients. For example, Abbott Diabetes Care Incorporated have taken legal action against the use of any piece of software that interacts with its own as part of the FreeStyle Libre FGM due to copyright that it owns on

the software [41]. This clearly demonstrates commercial interests ahead of users' data sovereignty and wellbeing.

There is limited market competition for CGM technologies. High requirements for proof of reliability for the regulatory process, and the high financial cost of development and testing remains a barrier to new competitors. Thus, the share of the market belonging to Abbott Laboratories (Illinois, USA), Medtronic Inc. (California, USA), and DexCom (California, USA) approaches 90%-100%. To at least some extent, their dominance continues because of the close relationship with insulin pump manufacturers, where Medtronic Inc. also manufacture insulin pumps, and subsequently any other competitor is disadvantaged. Such a market stifles innovative solutions at the ultimate cost of healthcare consumers.

5.3 Biomedical optic blood continuous glucose monitor

Light-based medical devices have been in use for a long time, most commonly photoplethysmography for the measurement of peripheral oxygen saturation [397]. The fundamental basis of this sensing methodology is the approximation of relative quantities of substances through the emission of specific wavelengths of light, and analysis of the subsequent absorption of various wavelengths [398]. Compared to blood-based analyses, light-based sensing has several advantages, most notably it is cost-effective through the use of re-usable robust sensor design. It is also non-invasive, so it is very

well tolerated as there is no pain associated with measurement [399]. It is also easily and robustly deployed, with minimal training required.

Light-based glucose sensing has seen measurable research interest, particularly in the mid 2000s [400–402]. This work generally focussed on NIR spectroscopy [401, 403, 404], and relied on large spectral generators and relatively complex instrumentation to isolate the desired wavelengths. These latter issues were problematic with respect to sensor accuracy, as well as cost. In particular, designs which are heavily dependant on broad-spectrum emissions are inherently difficult to miniaturise and make portable due to large power requirements and physical size. Therefore, despite validation of proof-of-concept designs, there are currently no commercially-available pulse glucometer devices [405].

Subsequent advances in silicon manufacturing processes have allowed an increase in access to narrow-spectrum LEDs in the NIR/MIR range have enabled novel LED-to-LED sensing for pulse glucometry. These devices are readily made miniature and portable with minimal additional design required [405]. Through the use of several relatively-discrete wavelength LEDs at wavelengths of 660 nm 850 nm, 940 nm, 1450 nm, and 1550 nm, which are used both as emitters and receivers, a miniature and portable design has been realised in the form of the biomedical optic blood (BOB) CGM. As can be seen in preliminary clinical validation testing presented in Figure 5.1, the results show the success of the overall design.

One uncertainty is around the requirement for calibration with the BOB CGM. With promising results, such as those presented in Figure 5.1, there has been minimal analysis
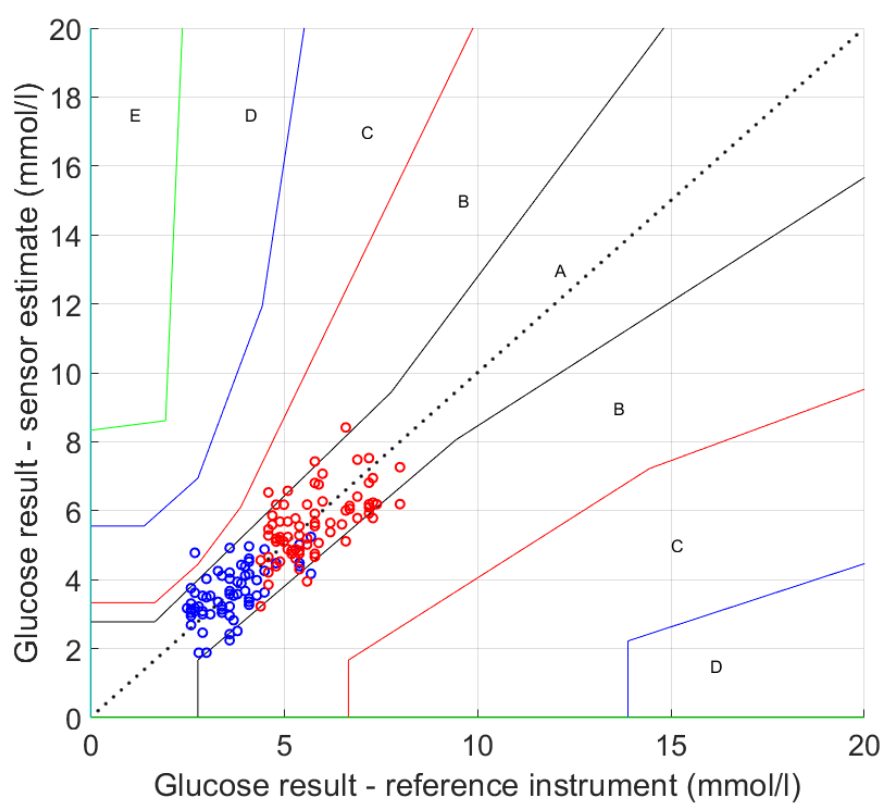
Figure 5.1: Clarke error grid [406] for the novel light-based pulse glucometer.

of BG concentrations in the lower or higher ranges. This result is compared against data from devices currently available in New Zealand in Table 5.1 Correctly identifying hypoglycaemia is vital, because this condition has the greatest potential immediate risk to the individual with diabetes [375, 376, 378, 407–410].

5.3.1　Benefits

With a relatively simple level of electronic design, but reliant on uncommon LEDs, the BOB CGM has a BOM of \$360 for one-off production, so \$1000 is a very conservative estimate of potential purchasing price considering manufacturing overheads. With an expected life span of five years, a cost of \$66M per annum would provide every single individual with diabetes in New Zealand their own testing device. The exact physical form of the device is not confirmed, but the dual development of a RT-CGM and a FGM device are both conceivable.

All of the benefits inherent to CGM devices would also be seen by widespread adoption of the BOB CGM, but additional benefits would be seen because of its different testing modality. Photoplethysmography (PPG) is pain free, instead PPG is used to derive pain indices [411–413]. This lack of pain provides benefit over traditional CGM devices [379, 414, 415], in particular with neonatal patients [416]. Furthermore, because there is no insertion required for reapplication of the device even in a RT-CGM configuration, there is no impediment to temporarily remove the device is seen for current RT-CGM devices, for example in relation to showering [417–419]. Removing the BOB-CGM is

Table 5.1: Comparison of the novel light-based pulse glucometer with other commercially available devices: The Enlite 2 (Medtronic Inc., California, USA), the FreeStyle Libre FGM (Abbott Diabetes Care Inc., California, USA), and the G6 (DexCom Inc., California, USA).

	% of time in subgrid					
Device	A	B	C	D	E	Ref
Enlite 2	86.1	13.3	0.1	0.5	0.0	[420]
FreeStyle Libre[A]	85.5	12.3		2.2		[384]
Dexcom G6	91.9	7.6		0.5		[414][B]
BOB CGM	90	9	1	0	0	[421]

[A] - Flash CGM.
[B] - Validation funded by manufacturing company.

not directly associated with having to subsequently reinsert the device, and while no device is attached the BOB-CGM could simply be held against the individual's skin to estimate BG, rather than test via SMBG. Thus, a higher level of adoption and a greater ease of use is expected with the BOB CGM.

The non-invasiveness of the BOB CGM should see greater acceptance of the device by Māori. In Te Ao Māori, the entire body is tapu, and thus greater consideration and respect is required for healthcare involving the use of any constituent of the body. Using light instead of drawing blood or inserting a device into the body is more acceptable, and while modern Māori are relatively pragmatic about invasive procedures, it is one less barrier to equitable access to healthcare.

The inherent NSIO of the BOB CGM leans itself to allowing the individual to make their own decisions about their data and healthcare. Data are able to be sent to any device that is able to be connected to the BOB CGM, and from their the individual using the device has ownership of their own data. Examples include sharing data to the parent of a individual with diabetes, to the individual's primary care physician, or to a secure database for subsequent automated analysis. This ownership allows realisation of tino rangitiratanga in Māori data sovereignty [422].

5.4   Economics

The single-use nature of test strips result in a relatively high expenditure associated with SMBG testing. Publicly-funded SMBG devices in New Zealand are $10 - $20 each, and the test strips are $0.21 each, and additional one-off costs for a device to break the skin. While these absolute values are relatively low, the scale of the disease means providing every individual with diabetes with a sensor is associated with a $1.0M per annum cost [212].

Across the diabetic population, there are 26,000 individuals with type-one diabetes in New Zealand. At an average of only 6 tests a day for these patients, estimated systemic costs are approximately $9.0M per annum. Similarly, for individuals with type-two diabetes who are dependant on insulin administration, again at 6 tests per day, an annual cost of $12.3M is seen. Individuals with type-two diabetes who are not on

insulin test an estimated average of 1.7 times per day (derived from [423], for an annual cost of $6.9M per annum.

The sum of these figures at $28.6M per annum, along with personal expenditure currently spent on CGM devices, form the potential direct savings associated with a low-cost CGM. Official figures from Pharmac show that the agency only spends $13.8M on all BG testing equipment [424]. This infers that there is considerable non-systemic expenditure towards BG testing. This is likely from several sources; partial or complete co-payment of the subsidised devices are expected to form considerable out-of-pocket expenditure. Further contributions are made to BG testing from health and disability allowances and private insurance spending. The large discrepancy between the Pharmac-funded contributions, and the financial cost of all tests carried out in New Zealand signify one area where inequitable access to healthcare is growing.

Continuous glucose monitoring is expensive. For an individual to use a CGM system constantly, there is a cost of $2500-$5000 per annum. These costs represent approximately 5% of the 2020 median NZ household income [156], making them unaffordable for the majority of New Zealanders with diabetes. An estimated 10% prevalence among individuals with type-one diabetes represents an approximate annual out-of-pocket expenditure of $6.5M - $13M, nationally.

While regular SMBG represents considerable expense in consumables, there is a net cost savings from high-intensity SMBG [425]. This saving arises because of the early detection of a lack of glycaemic control [426], allowing for medical intervention. Given

complication rates are proportional to the lack of glycaemic control [6], there is a lower complication rate associated with a higher incidence of adherence to SMBG protocols, and thus long-term cost savings, at an estimated 10-12% of overall healthcare costs for these individuals [354, 423, 425]. Given the reduction in general healthcare expenditure from frequent SMBG, indirect savings from the potential widespread uptake of low-cost CGMs are considerable, at approximately $300-$800 per individual with diabetes per annum. Direct and indirect cost savings, and direct costs associated with manufacture are presented in Table 5.2.

The cost associated with HbA1c testing is not insignificant. Blood tests are assumed to be relatively inexpensive because of their regularity, and, while a single HbA1c test is low-cost at $13.30 [427], an average of three tests per year, yields a population-wide cost of Hba1c testing for individuals with a diabetes diagnosis of $10M per annum.

However, it is recognised that many clinicians do not understand the physiological low-pass filter the HbA1c test represents, evidenced in multiple requests for Hba1c blood tests within a short duration. While NZ specific literature is lacking, an Indonesian study identified an incidence of 34.5% of tests being repeated within a period that was considered too soon [428]. Therefore, the actual cost of Hba1c throughout the overall diabetic population could be as high as $13M per annum, plus indirect costs, such as Vaccutainers™(BD, New Jersey, USA), and resource use of nurse, phlebotomist, and laboratory time. For the sake of cost analyses in Table 5.2, it is assumed clinicians only test when required, and 80% of the HbA1c test are replaced with CGM-based averages. More explicit discussion of the costs is presented in Appendix A.1.1.

Table 5.2: Potential adoption scenarios for the ULC CMG. Scenario 1 represents no change in total CGM, but assumes that only those who currently have CGMs will adopt the ULC CGM. Savings are represented as positive values, and costs as negative values. All values are in thousands of NZ dollars. T1D — Individuals with type-one diabetes; T2D — Individuals with type-two diabetes

Scenario:		1	2	3	4
Type	Number	Adopters (%)	Adopters (%)	Adopters (%)	Adopters (%)
T1D	26000	2600 (10)	5200 (20)	13000 (50)	20800 (80)
T2D$^{\mathbf{A}}$	33800	338 (1)	3380 (10)	15210 (45)	25350 (75)
T2D$^{\mathbf{B}}$	210000	1050 (0.5)	10500 (5)	52500 (25)	105000 (50)
Savings (000's)					
Direct savings:		$1,827	$5,529	$18,880	$32,161
Indirect savings:		$358	$ 3,579	$ 17,895	$ 35,790
Direct Costs:		-$178	-$3,951	-$19,359	-$36,969
Total:		**$1,867**	**$4,421**	**$14,237**	**$25,060**

$^{\mathbf{A}}$ — Individuals with type-two diabetes who administer insulin.
$^{\mathbf{B}}$ — Individuals with type-two diabetes who do not administer insulin.

5.5   Summary

Monitoring of glucose and glycaemic control is cumbersome and expensive. Therefore, it is not done as regularly as is required. This lack of monitoring has considerable implications for long-term outcomes, especially among children with type-one diabetes. Individuals with type-two diabetes are $10\times$ as numerous, and also suffering from the lack

of monitoring, particularly those dependant on exogenous insulin or who are otherwise at risk of hypoglycaemia.

Continuous glucose monitoring devices provide a potential solution for the lack of monitoring in the form of a temporarily-implanted device that detects the concentration of glucose in the interstitial fluid. There are considerable benefits to the use of CGMs, particularly in sub-populations of individuals with diabetes who typically see poor compliance. However, CGMs have limitations in accuracy and considerable expense, and are further limited by pre-determined financial relationships in the interoperability with various devices.

The ULC CGM is a solution to solve all of these limitations, showing excellent uncalibrated accuracy, and inherent interoperability through open design, both of which are provided for in a miniaturised, portable, and low-cost solution. The potential economic benefits are profound, with widespread adoption throughout all diabetics posing tens of millions of dollars per year of net savings, both systemically and personally. The true potential savings in terms of human and financial cost from the BOB CGM are those realised when it is used in conjunction with an insulin pump, such as the ULC insulin pump. Such as system would see the CGM provide regular estimations of BG concentration, subsequently used to determine insulin doses in an intelligent manner — an artificial pancreas.

Chapter 6

Coming full circle: Closing the loop

Closed-loop control refers to control systems which have some way of estimating the state of the system they are controlling [429, 430]. For diabetes technologies, closed-loop control refers to a system which includes an insulin pump, a CGM, and some sort of algorithm which determines the appropriate response to inputs. In reference to the organ which is typically responsible for glycaemic control, such a system is referred to as an artificial pancreas system (APS). In the absence of an automated closed-loop system the individual takes the place of the control system, placing burden to constantly be correct. Currently, even with high-fidelity CGM measurement, individuals are often unsure how their CGM data should inform their insulin therapy [431].

6.1   Low-cost realisation

A closed-loop control system for diabetes is possible through the use of BOB and the ULC pump. The most basic format this system could take is automating the standard calculation of insulin dose as a function of total carbohydrate consumption, a personal insulin-to-carb ratio, and a rough estimate for the total amount of systemic insulin [432]. With increasing experience in the diabetes physiological modelling field, advances for more complex predictive modelling are possible, to form a low-cost, equitable APS (LEAPS).

6.1.1   Personalisable - digital twins

The most important aspect of any closed-loop system is the ability to predict the future to accurately control it. For diabetes control this is done through predictive modelling [433]. The acquisition of real-time BG data via the BOB CGM, and exogenous insulin delivery through the ULC insulin pump makes many levels of analysis from any device possible.

The level of analysis providing the greatest level of clinical insight is the digital twin, or virtual patient model. A digital twin is a computer-based representation of the individual which allows analysis of potential scenarios and inputs [7, 434]. A digital twin in the context of diabetes enables stochastic modelling of potential responses to medications, and thus provides the optimal dose of insulin for best control while directly

accounting for intra-patient variability [7, 145, 433]. Thus, a digital twin must be an accurate personalised model of the patient, as well as able to directly manage variability in use to guide care.

The development of sophisticated digital twin software is made possible by the significant level of validation of the ICING-2 model, a compartment model deployed internationally in ICUs [86–94, 435]. Because the ICU is a highly-controlled environment, with exact nutrition information readily available, and the ability for intravenous medication delivery, these models require adapting to a less-controlled environment.

6.1.1.1 ICING-2 model adoption

While transferability to out-of-hospital contexts has been established [436–438], further development of the ICING-2 model system is required. To account for more complex meals and SC insulin delivery, the system is modified to include a gastrointestinal (GI) glucose model, and a SC insulin delivery model, to form the overall system depicted in Figure 6.1, presented in peer-reviewed format in Appendix A.2. The critical value to be determined is the insulin sensitivity, S_I, which specifies the action of insulin on lowering circulating BG for a given BG and circulating insulin concentration. To this end, the model system is presented primarily in the form of a short-term test for insulin sensitivity.

The GI model system uses a three-compartment non-linear model with compartments
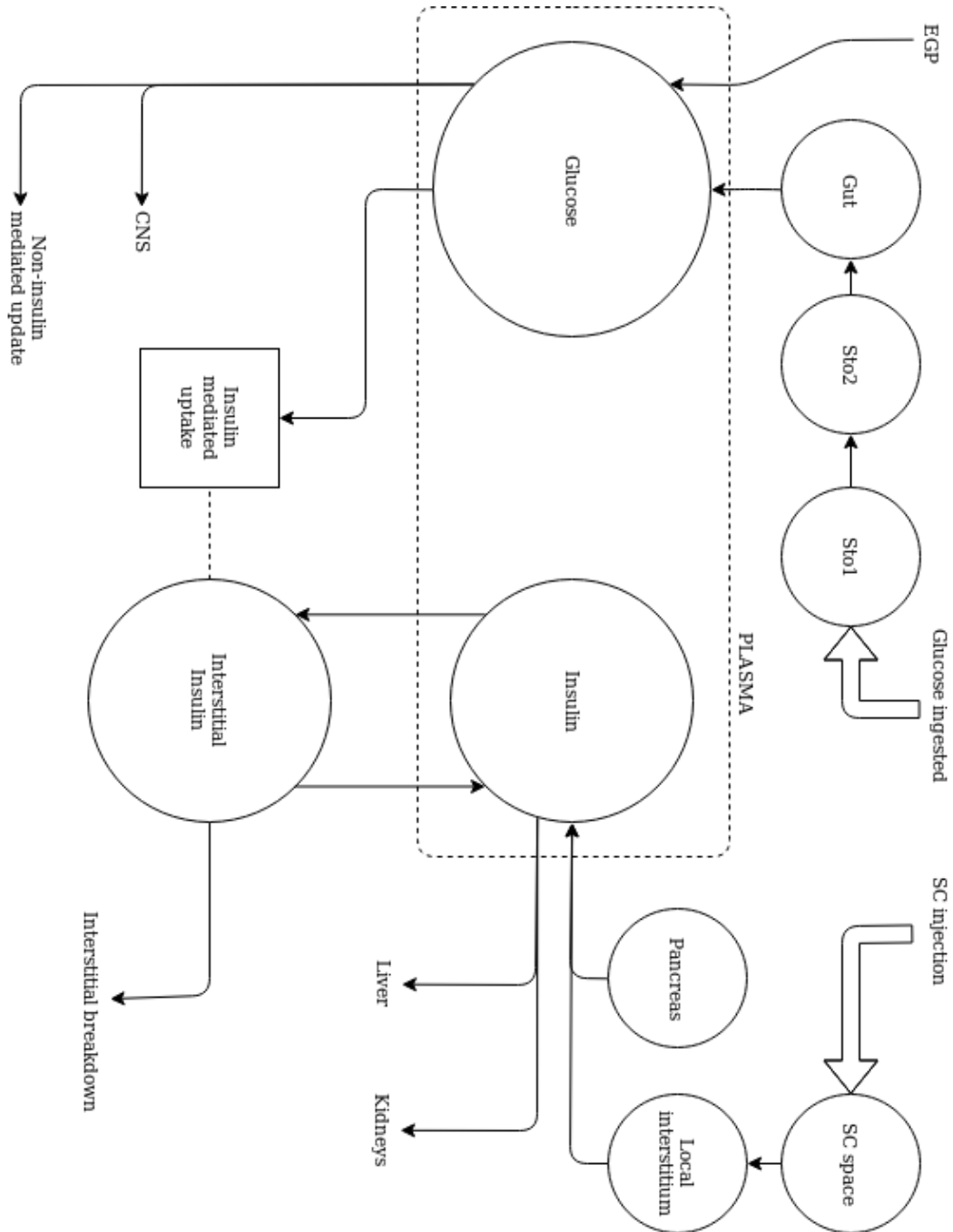
Figure 6.1: Compartment model representation of the overall system.

q_{sto1}, q_{sto2}, and q_{gut}, the value of which represents the amount of glucose in each respective compartment [439]. Specifically, q_{sto1} and q_{sto2} represent the solid and the liquid stages of the stomach respectively, and q_{gut} the glucose which has passed into the intestines. The model is defined per Equation 6.1

$$\dot{q}_{sto1}(t) = -k_{21} \cdot q_{sto1}(t) + D\delta(t)$$

$$\dot{q}_{sto2}(t) = -k_{empt}(q_{sto}) \cdot q_{sto2}(t) + k_{21} \cdot q_{sto1}(t)$$

$$\dot{q}_{gut}(t) = -k_{abs} \cdot q_{sto1}(t) + k_{empt} \cdot q_{sto2}(t)$$

$$Ra(t) = f \cdot k_{abs} \cdot q_{gut}(t)$$

$$(6.1)$$

In Equation Set 6.1, k_{21} is the rate constant of grinding, D the amount of glucose ingested, δ the dirac delta, k_{abs} the rate at which glucose is absorbed from the gut into the blood stream, Ra is the rate at which glucose appears in the blood stream, and f a scaling factor which accounts for incomplete absorption and first-pass hepatic clearance. The rate at which the stomach empties into the gut — k_{empt} — is a function of the total amount of remaining glucose in the two stomach compartments relative to D, and is defined by Equation Set 6.2:
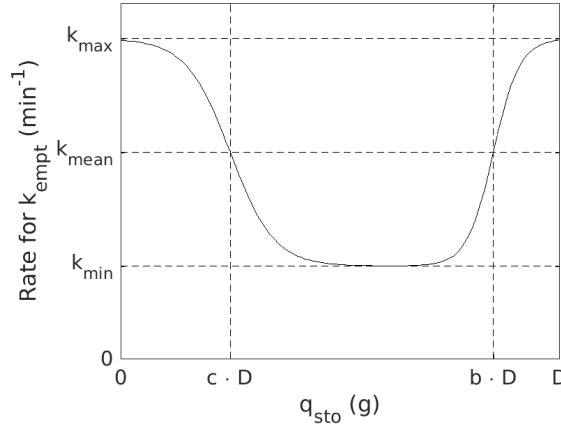
Figure 6.2: Depiction of k_{empt} as a function of q_{sto}, adapted from [439]

$$k_{empt}(q_{sto}) = k_{min} + \frac{k_{max} - k_{min}}{2} \cdot \{tanh\big[\alpha(q_{sto} - b \cdot D)\big]$$

$$- tanh\big[\beta(q_{sto} - c \cdot D)\big] + 2\}$$

$$q_{sto}(t) = q_{sto1}(t) + q_{sto2}(t) \tag{6.2}$$

$$\alpha = \frac{5}{2 \cdot D \cdot (1 - b)}$$

$$\beta = \frac{5}{2 \cdot D \cdot c}$$

The constants b and c are defined as the points at which k_{empt} intersects k_{mean}; the mean of k_{max} and k_{min}. The non-linear behaviour of Equation Set 6.2 can be seen graphically in Figure 6.2. Because the validation uses only glucose dissolved in liquid, the grinding constant $k_{21} = 1$ bypasses the solid phase.

Because the SC insulin used in insulin pumps is predominately monomeric preparation, the model is simplified from other insulin formulations [440] to only two compartments;

the subcutaneous space into which the insulin is injected — I_{SC} — and the local inter-stitium Q_{local}. It is important to note the local interstitium is a separate compartment from the interstitium within the glycaemic control model. There is a small amount of breakdown within the local interstitium prior to being absorbed into the bloodstream, but it is assumed the local interstitium is sufficiently small to be negligible in glucose uptake. Mathematically, the governing equations are defined:

$$\dot{I}_{SC}(t) = -k_2 \cdot I_{SC}(t) + \delta(t - T) \cdot I_{bolus}$$

$$\dot{Q}_{local}(t) = -k_3 \cdot Q_{local}(t) + k_2 \cdot I_{SC}(t) - k_{di} \cdot Q_{local}(t)$$

(6.3)

Where k_2 is the rate constant defining the diffusion from the SC space into the local interstitium, T the time the insulin is given relative to $t = 0$, I_{bolus} the amount of insulin injected, k_3 the rate constant defining the insulin being absorbed into the plasma, and k_{di} the breakdown of insulin in the local interstitium.

Both the oral glucose and SC insulin models are subsequently handled by the glycaemic control model [441]. The glycaemic control model as shown in Equations 6.4 – 6.6 takes into account glucose uptake both mediated by insulin and not, and insulin secretion and uptake. It incorporates compartments for plasma glucose, G, plasma insulin , I, and interstitial insulin, Q.

$$\dot{G}(t) = -p_g \cdot (G(t) - G_{fast}) - S_I \cdot G(t) \cdot Q(t)$$
$$- \frac{Ra(t) + EGP - CNS}{V_G} \tag{6.4}$$

$$\dot{I}(t) = - n_K \cdot I(t) - n_L \cdot \frac{I(t)}{1 + \alpha_I \cdot I(t)}$$
$$- n_I \cdot (I(t) - Q(t))$$
$$+ \frac{k_3 \cdot \dot{Q}_{local}(t) + (1 - x_L) \cdot u_{en}(G)}{V_I} \tag{6.5}$$

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_c \cdot \frac{Q(t)}{1 + \alpha_G \cdot Q(t)} \tag{6.6}$$

Where in Equation 6.4, p_g is the non-insulin mediated uptake, G_{fast} is the fasting BG, S_I is the insulin sensitivity, EGP is the endogenous glucose production, CNS the glucose consumption attributed to the central nervous system, and V_G the volume of distribution of glucose. EGP is iteratively solved such that at $G(t) = G_{fast}$, and with no exogenous glucose nor insulin, the system is in steady state. In Equation 6.5, n_K is the renal insulin clearance, n_L the hepatic insulin clearance rate, α_I the hepatic clearance saturation constant, n_I the trans-endothelial diffusion rate between the plasma and interstitial compartments, x_L the first pass constant as endogenous secretion, u_{en}, is secreted into the portal vein, and V_I the volume of distribution of insulin. In Equation 6.6, n_c is the insulin degradation rate, and α_g the insulin binding saturation constant.
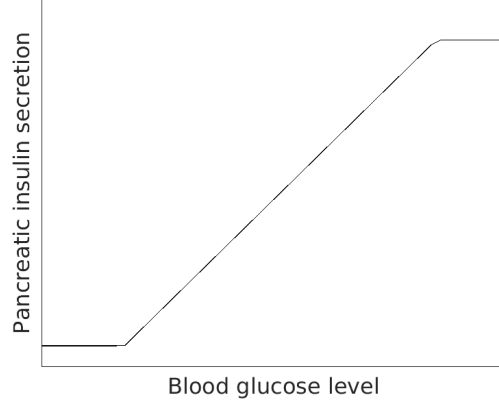
Figure 6.3: Endogenous pancreatic release as a function of the blood glucose level.

Endogenous insulin secretion by the pancreas is modelled as a simple limited, proportional response depicted in Figure 6.3, and defined in Eqation 6.7:

$$u_{en}(G) = \left\{ \begin{array}{ll} u_{min}, & \text{for } G(t) \leq G_{fast} \\ f(G), & \text{otherwise} \\ u_{max}, & \text{for } f(G) \geq u_{max} \end{array} \right\}, \tag{6.7}$$

$$f(G) = k_{sec} \cdot G(t) + k_{offset}$$

As C-peptide and insulin are secreted in equimolar quantities, the the rate of secretion of C-peptide can be directly ascertained from Equation 6.7.

Units and example values and for all above parameters can be seen in Table 6.1.

Therefore, the foundation for the development of the LEAPS digital twin platform to guide each individual with their treatment regime has been subject to over 10 years of

Table 6.1: Example of a parameter set used for the forward simulation of a digital twin. Sources: (1) - [439], (2) - [442], (3) - [441], (4) - [443], (5) - [444]. Note A: These are parameters which change as a function of carbohydrate intake. Note B: Measured. Note C: Solved for in steady state conditions.

Parameter	Value	Units	Source
Gut			
k_{21}	1.0	min^{-1}	A,(1)
D	35	g	A
k_{abs}	0.205	min^{-1}	(1)
b	0.85	-	(1)
c	0.25	-	(1)
k_{max}	0.043	min^{-1}	(1)
k_{min}	0.013	min^{-1}	(1)
SC Insulin			
k_2	0.0104	min^{-1}	(2)
k_3	0.60	min^{-1}	(2)
T	15	min	A
I_{bolus}	2000	mU	A
k_{di}	0.006	min^{-1}	(2)
ICING			
p_g	0.04	min^{-1}	(3)
G_{fast}	4.8	$mmol \cdot L^{-1}$	B
S_I	10.8×10^{-4}	$L \cdot (mU \cdot min)^{-1}$	(4)
EGP	0.96	$mmol \cdot min^{-1}$	C
CNS	0.30	$mmol \cdot min^{-1}$	(3)
V_G	12.2	L	(3)
n_K	0.060	min^{-1}	(3)
n_L	0.0324	min^{-1}	(3)
α_I	0.0017	$L \cdot mU^{-1}$	(3)
α_G	0.0154	$L \cdot mU^{-1}$	(3)
n_I	0.006	min^{-1}	(3)
x_L	0.67	-	(3)
n_c	0.032	min^{-1}	(3)
V_I	4.0	L	(3)
u_{min}	16.7	$mU \cdot min^{-1}$	(5)
u_{max}	267	$mU \cdot min^{-1}$	(5)
k_{sec}	14.9	$mU \cdot L \cdot (mmol \cdot min)^{-1}$	(5)
k_{offset}	-50	$mU \cdot min^{-1}$	(5)
Initial			
q_{sto1}	D	g	A
q_{sto2}	0	g	
q_{gut}	0	g	
I_{SC}	0	mU	
Q_{local}	0	mU	
G	G_{fast}	$mmol \cdot L^{-1}$	B
I	15	$mU \cdot L^{-1}$	B
Q	9	$mU \cdot L^{-1}$	C

Figure 6.4: Test protocol for the MMOIST

peer-reviewed clinical use and scrutiny. Through the widespread use of NSIO devices, such as the ULC pump and the BOB CGM, further development of a clinical-guiding protocol is made possible, similar to the current STAR protocol.

6.1.1.2   VALIDATION

The equation system presented in Section 6.1.1.1 was validated initially through *in silico* Monte Carlo analysis [445] to ensure safety of the *in vivo* validation. This validation took the form of a modified oral glucose tolerance test (OGTT), with approval for the University of Canterbury Ethics Committee: 2018/03, in full in Appendix A.2.1. The model-based, modified OGTT insulin sensitivity test (MMOIST) used a smaller amount

of glucose with only 35 g, and the administration of SC insulin after approximately two minutes. The glucose and insulin delivery and testing protocol are shown in Figure 6.4.

Results of initial validation included the steady-state calculation of $U_e n$, and fitting for n_L and x_l against the insulin data, and finally S_I against the insulin and glucose data using basic linear regressions, and values for example data are shown in Table 6.2. Results can be seen in Figure 6.5, and errors in Table 6.3

Table 6.2: Identified values for fitted parameters for the MMOIST.

Patient	Parameter		
	x_l	n_l (min^{-1})	S_I ($\times 10^{-4} L \cdot (mU \cdot L)^{-1}$)
22	0.233	0.405	10.6
30	0.411	0.232	11.1
1b	0.213	0.664	14.6

Table 6.3: Fitting errors for the MMOIST.

Patient	Parameter	
	Glucose RMSE ($mmol \cdot L^{-1}$) (%)	Insulin RMSE ($mU \cdot L^{-1}$) (%)
22	0.212 (2.6%)	4.28 (10.7%)
30	0.687 (9.1%)	6.49(24%)
1b	1.036 (13.6%)	4.44(32.8%)

RMSE — Root mean square error
Percentage error is MAPE — Mean absolute percentage error
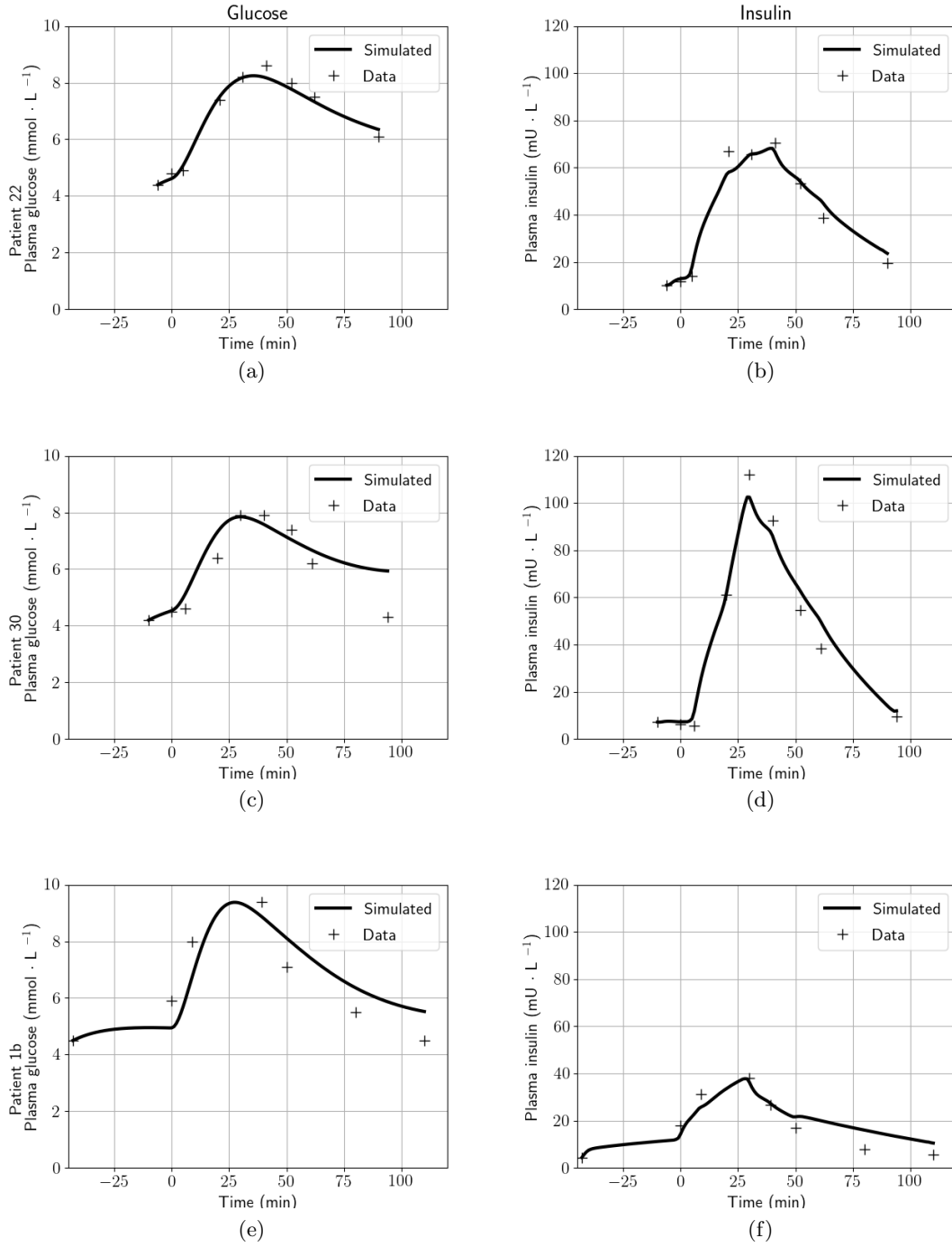
Figure 6.5: Example validation data from basic fitting of n_l, x_l, and S_I to data obtained from the MMOIST.

6.1.1.3 Current role

There has been no real experience in the deployment of digital twin technology for diabetes control in out-of-hospital environments. Some systems identify as digital twins, but lack the ability of identify andr/or manage intra-patient variability of glycaemic control, as well as the two-way data flow and command-control pathways, which also define a digital twin beyond the model-based approach to care [446, 447]. In a small validation study of one such system, a greater TIR was seen compared to a standard automatic closed-loop system. Early analysis of another digital twin deployment within individuals with type-two diabetes has shown significant increases in glycaemic control to the extent that there was a four-fold increase in the portion who attained HbA1c less than $48 mmol \cdot mol^{-1}$. Furthermore, subsequent to the 90-day trial 100% of participants who adhered to the trial saw a cessation of insulin delivery, and there was similarly large reductions in the use of many oral anti-hyperglycaemic medications.

Limitations of this particular study include no control group in the form of all of the interventions except the digital twin algorithm, such as: Health coach assistance, and *"physicians with access to daily CGM data titrated medications and monitored patient conditions"*, and the programme saw only 71% adherence [447].

Digital twins allow the use of less precise or accurate sensor data. This lower level of reliance on high-accuracy is achieved with stochastic, risk-based modelling. Provided the net effect from sources of error for the CGM measurement are understood, a erroneous

glucose data can be identified as incorrect in the context of previous inputs and/or a validated model [448, 449].

The gathering of glucose and insulin data is currently a *"major challenge in artificial pancreas development"* [36]. Therefore, development of digital twin software to aid the calculation of insulin dosing will not require extensive reformatting for interoperability. The NSIO inherent with open-source projects means that the BOB CGM and the ULC insulin pump will readily interact with other devices, removing limits on future innovations of a LEAPS. Less complex realisations of closed-loop control will be able to natively integrate the data obtained from the BOB and the ULC insulin pump, with some individuals with diabetes trusting less-controlling algorithms more [450], as seen, for example, with current DIY artificial pancreas solutions.

6.2   Benefits

Even individuals who have had type-one diabetes for some time are imperfect at calculating insulin doses. For example, any error in the total amount of carbohydrate consumed in a given meal creates a considerable source of insulin dose error [451]. Removing the dependency on the user to manually input data increases control because of a lack of transcribing error, but also in the increased frequency and decreased latency of data. An automated closed-loop system provides a level of safety and security because of the self-correcting nature of the system using feedback control. This behaviour outlines

the immediate, direct, and patient-specific benefit from a smart, highly interconnected healthcare delivery method.

6.2.1 Health

Closing the loop results in better glycaemic control [452–470]. There is conclusive evidence closed-loop insulin delivery is safe as seen in a reduction in hypoglycaemic episodes [452, 459, 471], and is linked to an overall increase in the portion of time in range (TIR) [452–459, 462–465, 468]. There are a variety of metrics used to analyse glycaemic control, enabled through the use of CGM over HbA1c, all of which show an improvement. Specifically, time below range [452, 453, 456, 457, 459, 460, 462, 468], time above range [463, 468], and mean BG [455, 458, 463, 464]. While a less responsive measure of glycaemic control, HbA1c also decreased with use of a closed-loop system [458, 459, 465].

A very significant market share of current closed-loop systems are the 2,300 DIY APS users [461]. These systems are open-source, community-led initiatives providing the ability to automate insulin delivery based on CGM measurements [472, 473]. Some require custom electronics as a workaround for SIO and outdated communication modalities [474], while others are controlled directly through a smartphone application [475, 476]. Commercially-available closed-loop solutions are available, and to-date currently do not perform as well as DIY solutions, with TIR $\geq$ 70%, compared to DIY solutions with TIR $\geq$ 80% [475, 476]. However, this difference in outcomes may be due to the higher level of self-motivation and understanding required for the implementation of a DIY

solution, although initial use of all types of closed-loop systems is self-selecting of the most motivated individuals with diabetes.

Commercially-available systems, such as the closed-loop 670G system (Medtronic, California, USA), and the Tandem Control-IQ system (Tandem Diabetes Care, California, USA), show promising results but relatively small market uptake [477]. These systems have minimal to no self-learning aspects, with focus around future prediction of hypoglycaemia, and avoidance by adjusting the basal insulin delivery rate [478]. Similar prediction-based avoidance of hyperglycaemia is carefully being delivered, but the greater inherent risks of overdosing insulin, compared to underdose, mean a higher threshold of assurance of safety is required [477]. These systems also require specific high-cost hardware, exacerbating inequities to healthcare.

Initial results suggest self-adapting closed-loop systems provide greater glycaemic control than static automatic closed-loop insulin delivery [446]. While there is increased personalisation, particularly within DIY closed-loop solutions [479], it is done manually using an empirical approach. A digital twin automates this personalisation process through the identification of model parameters [7].

Improved glycaemic control is not the only health benefit from use of an automated closed-loop system for insulin delivery. Psychological improvements are observed in the reduction of fear of hypoglycaemia, reduction in unawareness of hypoglycaemia, reduction in diabetes-related anxiety, and an overall improvement in the perceived quality of life [480, 481]. Finally, good control yields long-term health benefits.

6.2.1.1 Smart health

A highly interoperable system enables a substantial amount of further long-term, extrinsic innovation within diabetes. For example, within NZ, there are current inequities of access on the basis of geographical location alone [276]. The integration of CGM sensor data, particularly the broadly NSIO of the BOB CGM, would mitigate this inequity through remote monitoring. This integration and subsequent automation would have economic benefits in reducing healthcare resource dedicated to diabetes reviews, and indirect personal and systemic benefits by increasing general productivity by avoiding the need to travel and attend primary and specialist appointments.

Current monitoring of diabetes depends primarily on invasive glycated haemoglobin [352, 482]. Each HbA1c test requires patient and phlebotomist time and travel, laboratory resources, and a direct assay cost of \$13.30 [427]. Population-wide, this testing comprises significant overall direct and indirect cost solely to monitor disease progression.

While HbA1c is currently used to monitor the progress of type-two diabetes, it is not the best measurement of disease progression. In particular, it measures dysglycaemia, which is a symptom of the disease, as opposed to the original pathogenesis. It is more accurate to assess the individual's sensitivity to insulin [483]. This numeric quantity represents the change in circulating BG as a function of current BG, and the circulating insulin concentration. Current methods of quantifying insulin sensitivity are invasive, expensive due to requiring one-to-one doctor to patient ratio, and entail some risk [484, 485].

The euglycaemic clamp is often used, in which a constant rate of either insulin or glucose in infused intravenously, and similarly an infusion of glucose or insulin respectively is titrated such that steady state conditions are attained [486, 487]. With a larger amount of personalised data for carbohydrate consumption, exogenous insulin delivery, and BG concentrations, it is possible to estimate insulin sensitivity using a model-based analysis [445, 485, 488]. Monthly determination of insulin sensitivity, for community-based individuals with diabetes, would provide significant insight into each individual's disease progression, and could be readily integrated into current healthcare data sharing platforms. A further gain is the ability for these glycaemic control metrics to also explicitly account for insulin delivery and carbohydrate consumption.

Detecting changes in insulin sensitivity, rather than monitoring the symptoms, allows for earlier identification of worsening disease, and subsequent intervention, if required. Early intervention is correlated with reduced risk of complications from diabetes [6]. Monitoring these interventions is considerably more available and accurate using the NSIO of the BOB CGM, as data can be examined for any treatment-specific metric. This ability to monitor poses significant advantages over intermittent HbA1c representing implicit time-based BG average. Thus, CGM data and physiologic models allow determination of treatment-induced changes in metabolic status over periods of days, rather than the 2-3 months represented by HbA1c. Subsequently, the use of digital twins allows more rapid, targeted, and effective early intervention. Therefore, the widespread adoption of devices with broad NSIO increases equity of access to better healthcare, and subsequently better outcomes.

6.2.2 ECONOMIC

Economic benefits from the widespread use of digital twin closed-loop insulin delivery are widespread. There is a reduction in personal costs associated with primary care due to the automation, and the increase in glycaemic control reduces complications which require extensive management and reduce personal productivity. These complications also have considerable expense to the healthcare system [267]. Reducing the occurrence of these complications, in combination with reduced HbA1c testing, reduces system-wide financial strain. Clinicians see a marked increase in productivity associated with automation of monitoring disease progression and treatment changes.

Considerable potential savings are associated with making insulin delivery safely available to all community-based individuals with diabetes. Even individuals with pre-diabetes see benefit in reduction of progression to type-two diabetes [6]. The overall economic benefits of the adoption of a closed-loop insulin pump control system is an example of the long-term, disruptive change required to increase efficiency in the healthcare system.

6.3 Summary

Closed-loop control of an insulin pump using CGM data from can be automated. In the context of the BOB CGM and the ULC insulin pump, the inherent NSIO from their open-source design enables any closed-loop realisation. Extensive personalised stochas-

tic glycaemic modelling in the ICU provides a foundation for digital twin technology. Widespread rollout of such a digital twin would increase equity of access to best care and outcomes, as well as significant economic benefits for individuals, clinicians, and the health system.

Further systemic returns are possible in the widespread adoption of devices with broad non-specific interoperability. These devices enable development of smart, automated healthcare processes and systems, automating glycaemic reviews and prompting human input only when it is necessary. Monitoring of disease progression of type-one and type-two diabetes is more accurate by being able to continually measure blood glucose, rather than simply a biochemical marker used as a surrogate. Model-based analysis of such data allows for population-wide tracking of disease progression, which is currently unaffordable, unobtainable, and inequitable.

Part III

Dual Ventilation System

Chapter 7

Caring is sharing?

The COVID-19 pandemic considerably increased demand for acute and intensive care. The disease causes mild to severe respiratory symptoms, with 15% of the most unwell patients requiring hospitalisation [489], and 1-3% require invasive respiratory support using a mechanical ventilator in the intensive care unit (ICU) [490]. The scale of the disease puts considerable strain on ventilated bedspaces, to the extent the availability of ventilated bedspaces is an indicator for mortality [491]. Guidelines for rationing of ventilation become increasingly widespread [8].

This problem is considerably exacerbated in under-resourced regions, where ICU ventilated bedspaces are scarcer yet [492–494]. There has been considerable increase in mechanical ventilator production, as well as development of open-source, often low-cost, ventilator projects [56, 495–497] to combat this issue. However, ventilators remain
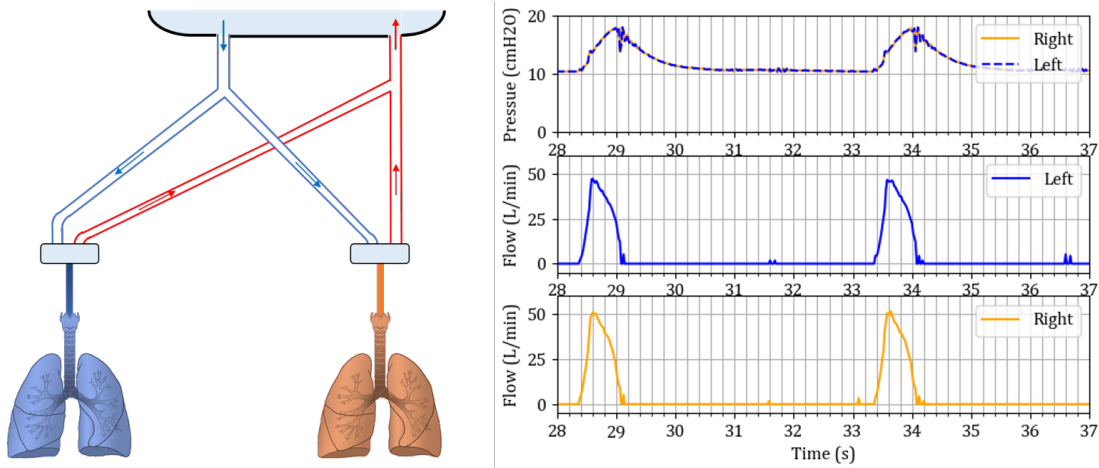
Figure 7.1: Ventilation delivered to two patients from a single ventilator in a parallel configuration. Inspiratory effort is delivered to both patients simultaneously. In this example both patients have equal lung characteristics.

scarce in developing countries, and many of the rapidly-produced projects see challenges in either lacking monitoring or customisation, and/or require components inaccessible in low-resource countries. Therefore, this pandemic has seen access to life-saving health-care become increasingly inequitable, a significant and growing issue in normal times, and one which can be addressed through innovation.

7.1   Multiple ventilation

One widely-discussed solution considered using a single mechanical ventilator for more than one patient [498–522]. There were several propositions for cost-effective, easy-to-manufacture systems, all but one of which were **parallel** solutions as shown in Figure 7.1. Parallel solutions use a passive valve to allow flow from the ventilator to simultaneously reach multiple patients, and additional external components to enable some level of

customisable ventilation therapy. Alongside clinical and technical discussions, the ethical dilemma was investigated, on the basis that it must improve net survivability [506].

Most ventilator multiplexing solutions were hindered by the lack of interoperability with standard medical hardware, the inability to detect changes in respiratory characteristics, such as compliance, and the resultant inability to customise therapy for each patient in real time. Due to these issues, several international intensive care organisations issued a consensus statement stating: "*sharing mechanical ventilators should not be attempted because it cannot be done safely with current equipment*" [9]. The justification behind this statement was the concerns around potential damage from differences in patient lung mechanics, damage resulting from pathology-related physiological changes, and the inability to safely monitor each patient individually.

There were a wide range in the complexity of proposed multiple ventilator therapy designs, which was typically proportional to the success of the design in addressing the points raised in the consensus statement. The most basic proposals for multiple-patient ventilation from a single mechanical ventilator were simply connecting multiple patients using basic, passive 'Y' valves, possibly 3D-printed [499]. Some form of increasing the target volumes or using pressure-controlled ventilation to achieve similar breath characteristics was proposed, without the ability to customise ventilation therapy [498, 501, 507, 517, 519, 521, 523]. Several designs recognised the need for customisable ventilation delivery, usually through the use of restrictive devices [510, 518, 519, 524]. Further approaches included explicit patient matching protocols [525, 526], which did not reduce debate [10].

Of designs enabling customisable therapy, few provided for true independent customisation to achieve individualised therapy robust to physiological changes in volume-control mode. Many systems introduced some form of variable resistance to the inspiratory circuit [510, 518], and many recognised the necessity of requirement of an inline PEEP valve, as well as a pressure regulating valve in the inspiratory circuit [504, 510]. However, none could address all concerns.

Some of the failings of systems include the inability to operate with ventilators requiring a fully-closed respiratory circuit [518]. The fact that resistance, and thus pressure drop, are a direct function of flow was another shortcoming [510, 519, 524]. Others required disassembling the respiratory circuit to individualise therapy [56]. Some complete systems were proposed, but involved extensive or difficult manufacturing, such as gluing a collapsible pressure vessel inside a fixed box to provide a capacitor-like barrier between patients, and the introduction of an additional fresh gas feed to fill the balloon [509].

A singularly common failing was the inability to individually monitor and treat each patient independently. The ventilator is obviously blind to the multiplexing, and thus it is not possible to use any of the measured or derived values for a given patient. Thuis, it was not possible to meet the key concern of individual patient matching.

Overall, it was recognised the necessity for customisable ventilation lay in the provision of the ability to regulate pressure in each patient's inspiratory circuit to regulate PIP, as well as PEEP [502, 504, 527]. The majority of propositions in how to achieve this goal involved the use of a shroud over a BVM-type PEEP valve, thereby forcing the PEEP
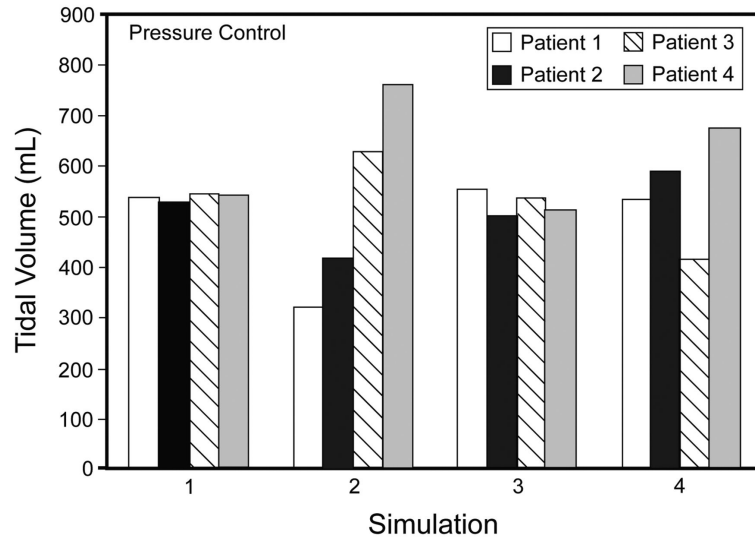
Figure 7.2: Laboratory-simulated results of 4-way shared ventilation in a parallal manner, adjusting the compliance of different patients and attempting to rectify the variations in tidal volume through the use of differing diameter ETTs, reproduced from [528].

valve to vent to a port of some sort as opposed to atmosphere. However, all classes of these devices however inherently leaked to atmosphere because of the threaded design, and had a non-zero minimum pressure drop, negating their use for this application. Thorough analysis concluded [527]:

- PEEP valves must be inline to allow for return of all delivered ventilatory volume to the ventilator, to allow for interoperability with devices that would otherwise fail.

- Pressure drop valves should be able to be readily adjusted without disassembly, and have a minimum pressure drop approaching 0 cmH_2IO.

- Supply chain issues prevented the use of off-the-shelf inline PEEP valves.

7.1.1   PATIENT MATCHING

Patient matching may also be required. The basis of matching is two patients with very similar lung characteristics will respond to ventilation therapy in very similar ways, and thus, similar ventilation outcomes will be obtained, allowing the same mechanical ventilation inputs. A large portion of the commentary emphasised the need for matching [503, 510, 523]. Some solutions relied on patient matching alone for balanced ventilation therapy [514, 523], and the subsequent necessity for *"monitoring of patients and shuffling when a mismatch arises"* [523].

Because of the large potential variations in tidal volume when patients are not matched, the recommendation was to only use patients who were *"well-matched in terms of mechanical properties and ventilatory requirements"* [510]. While it may be theoretically possible to use well-matched patients at a given time, it is not pragmatic in typical practic, let along a pandemic situation with ICU demand and workload significantly increased due to COVID-19 patients. In particular, with moderate variation in lung compliances, volumes of directly attached test and training lungs were found to vary significantly in volume [528], as shown in Figure 7.2. The risks of ventilating poorly-matched patients were recognised as potentially to likely fatal, as confirmed by simulation [503]. Therefore, it remains ill-advised to use matching alone with a basic 'Y' splitter only.

This unpredictability of patient-specific disease progressions means balancing delivery based on patient matching alone is not practically achievable. Equally, if an entire
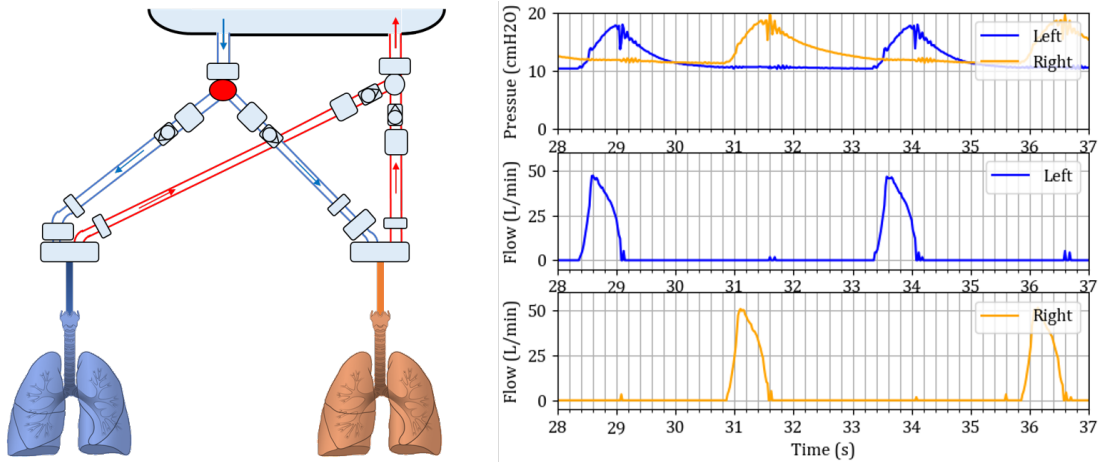
Figure 7.3: In-series ventilation as is made possible by the ACTIV system. Breath is delivered first to one patient and then the other.

intensive care unit was balanced properly, the nursing workload would more than double with the number of patients, which would be unsustainable. At minimum, if patients are matched, they must continue to be ventilated with matched patients, a significantly higher level of monitoring to determine when patients become mismatched. Without the use of dedicated external monitoring equipment, uncommon on a large-scale within ICUs, and expensive and difficult to procure during a pandemic, the burden of this increased monitoring falls directly on clinical staff. Hence, it is particularly pertinent no parallel ventilation system proposed a practical means of individual monitoring.

On top of these monitoring requirements, the constant 'shuffling' of patients is logistically and physically demanding. It would also be resource intensive in an already-stretched, overfull ICU, necessitating nursing time, as well as significant added ventilator circuits at each change. It is simply not practical to rely on patient-matching even in combination with pressure-regulating valves for ventilation balancing, and thus parallel ventilation of multiple patient is simply not safely, nor effectively, possible.

7.2   Series ventilation

A solution accomodateing all of the points of the consensus statement is the use of a
series ventilation approach, as depicted in Figure 7.3: Connect two patients using an
actuated switching valve, detect inspiration, and divert every second breath to a different
patient [10, 11]. This philosophy successfully mitigates the issues raised in the consensus
statement [9–11], as is presented in full in Appendix B.1. Series ventilation is manifested
in the Actuated, Closed-loop, Time-series Inspiratory Valve (ACTIV) system.

Customisable ventilation is achieved in the ACTIV system by inducing pressure drops
in the respiratory circuits, using in-line adjustable spring-loaded PEEP valves, as well as
other additional components, as shown in Figure 7.4. The use of four such valves – one
in each patient's inspiratory and expiratory circuits, creates a system able to provide
fully individualised ventilation for each patient. In addition to pressure drop valves,
a 3D-printed, servo motor operated switching valve is used to connect the inspiratory
system to one of the two respiratory circuits. Because equitable access to mechanical
ventilators is worse in resource-poor countries [492–494], a strong emphasis is placed in
this solution on the ability to produce the system in these constrained environments.
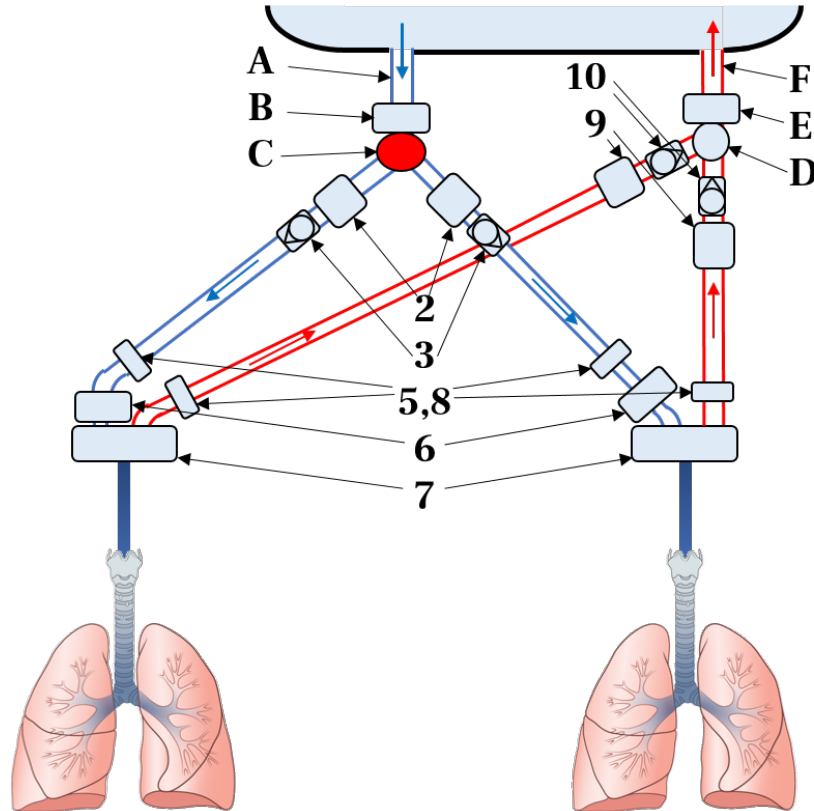
Figure 7.4: In-series ventilation set-up with two patients connected to a single ventilator, as per the ACTIV system. A&F)are short sections of hosing for convenience, B, 6, and E) are 3D-printed flow and pressure sensors, C) is the ACTIV switching valve which diverts ventilation to one of the two respiratory circuits. 2 & 9) are the PANDAPeep pressure drop valves, 3 & 10) are one-way valves, 5&8) HEPA filters, 7) Passive Y-valve as per standard respiratory circuit, and D) is an additional passive Y-valve.

7.3   <u>Summary</u>

Significant increased demand for mechanical ventilators within ICUs threatened to inundate healthcare systems, creating pressure for short-term innovation. Many solutions were proposed to achieve ventilation of multiple patients from a single mechanical ventilator, all but one in a parallel manner. This approach is difficult to provide safely for multiple patients for various monitoring and indivdiualisation of ventilation therapy.

A series ventilation system, containing an active switching valve, is proposed. This system requires design for manufacture in resource-constrained environments, and a number of subcomponents to be completely designed and validated, rather than purchased off-the-shelf.

Chapter 8

Main elements

The design requirements for the sub-components of the ACTIV system are very similar to the larger, overall system. The combination of specific measurement ranges, accessible manufacturing, and simple interface — both physical and electrical — defines the requirements for the design. Ideally, all of the physical components required to assemble a series ventilation system would be off-the-shelf. However, due to limited availability and the design requirements, specific designs for the PEEP valve, the flow and pressure sensor, and the switching valve are required.

Given the fragility of human airways and potential significant harm from high pressures and flows, the sensors and actuators are significantly different from those found in industry, for example. The order of magnitude of pressure measurements is in the range

of 10 kPa, compared to 1000 kPa which may be used to measure pressure in a bicycle tire: a pressure which would be fatal to humans.

Analogue voltage outputs are desirable in their ability to be interfaced a massive range of systems. A basic search for microcontrollers with ADC capability shows in excess of 70,000 possible components [529]. Furthermore, electronic circuits that do not contain any sort of logic controller are compatible. An analogue output format enables the interface with systems comprising analogue comparators and operational amplifiers, thus broadening accessibility.

The global increase in access to basic additive manufacturing in the form of 3D-printing has enabled accessible distributed manufacturing networks [530]. This access perfectly enables the creation of subcomponents for the ACTIV system, and therefore the sensor and actuator design must be able to be manufactured with 3D-printing. Design for 3D-printing, with relatively large minimum tolerances, up to 0.5 mm [531], and limited material selection options, has significant impact on the nature of the sensor. Bleeding-edge technology such as flexible graphene nanosheets [532] or microwave microfluidic [533] sensors are inaccessible, and require specialist equipment to manufacture. A Venturi-based sensor was selected because of the large gross critical dimensions ($\geq 10\ mm$) and subsequent reduction of reliance on precise manufacturing capabilities.

The design of the flow and pressure sensor, the characterisation of the inline PEEP valve, and a discussion of the off-the-shelf components is contained within this chapter.
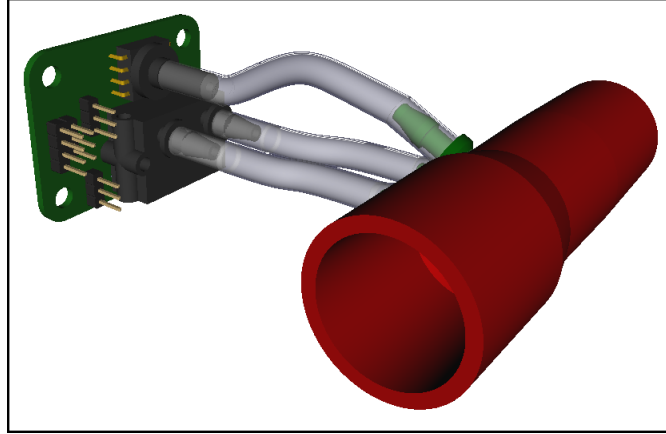
Figure 8.1: Fully assembled ACTIV flow and pressure sensor.

8.1 Sensor

For a closed-loop system to be effective, access to reliable flow and pressure data is vital. Because of the substantial increased demand on all respiratory therapy components, and their associated cost when in stock, a 3D-printed Venturi with both a differential pressure and absolute pressure sensor was used as the flow and pressure sensor [49]. The sensor, presented as a peer-reviewed article in Appendix B.2.2, was designed for cost-effectiveness, as well as good resolution in mid-range flows and high sensitivity in lower range flows to allow for effective computation of switching and control logic.

While the flow and pressure sensor is most critically used in the ACTIV system to provide closed-loop feedback to the control system, it also enables estimation of tidal volume delivered to each patient. It thus completes the requirement of standard ventilation systems to fully inform the clinician of the state of the system. As discussed further in Appendix B.2.2 [49], if the sensor is configured:
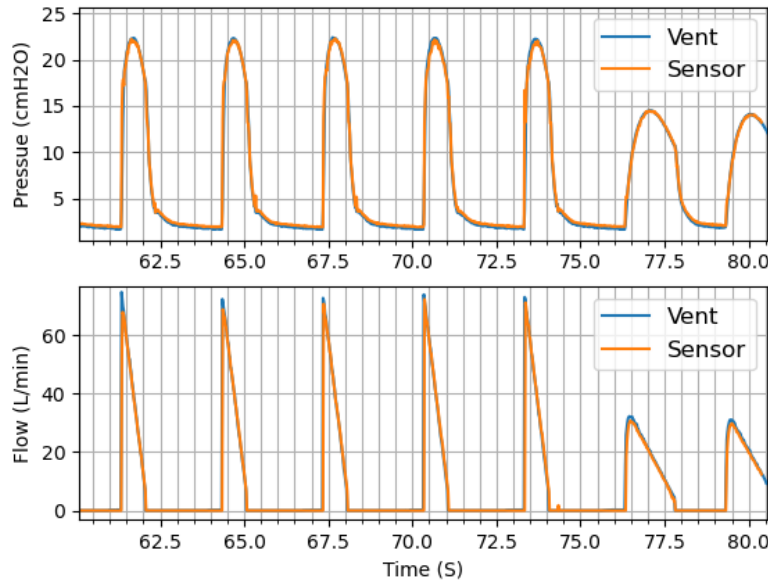
Figure 8.2: Example data snippet showing the sensor output against the ventilator (PB840) captured data. Note the data clipping at $75L \cdot min^{-1}$ for the sensor. The artefact after the flow returns to zero is from moving parts in the respiratory circuit. Clipping at the maximum flow can be seen in the second half of the data.

- With a $15 - 10 \ mm$ Venturi;

- Connected to a $125 \ Pa$ differential pressure sensor;

- With the sensor configured to linear operation mode;

- Operating at $V_{CC} = 5.0 \ V$; and

- Interfaced to a 10-bit ADC.

It is true:

- The device can be used for flows $5 - 75 \ L \cdot min^{-1}$ and pressures up to $6 \ kPa$ or $61.5 \ cmH_2O$

- $q \ [L \cdot min^{-1}] = 0.97 \times 6.27 \times \sqrt{38 \times \dfrac{ADC \ count}{1023} - 38}$

This sensor has been shown to be effective when compared to the data obtained by a mechanical ventilation device, as shown in Figures 8.2 and 8.3. Over the 80 seconds of experimentation from which the data within Figure 8.2 were obtained, while sampling at 50 Hz, the Pearson correlation in five-second bins was consistently $R^2 \geq 0.95$ for flow, and for 90% of the time $R^2 \geq 0.97$. The distance correlation was typically ≥ 0.95. A Bland-Altman plot [534] demonstrating the error can be seen in Figure 8.3. The points with significant error are due to the sample rate being relatively low relative to the gradient of the near-vertical increases in flow. These locations are shown at the start of inspiration in the earlier data of Figure 8.2. The pressure sensor performed similarly, with Pearson correlation typically $R^2 \geq 0.97$. Complete datasets are available at https://doi.org/10.17605/osf.io/ktxuh.

Over a total approximately 2 hours of experimentation, the device consistently had a Pearson correlation $R^2 \geq 0.9$, and more often than not $R^2 \geq 0.97$, as is shown in Figure 8.2. There was not a significant difference in correlation when comparing with data from either mechanical ventilator or the other. Given the devices are intended for use in mechanical ventilation or similar applications, validation against high-quality equipment controlling these circuits demonstrates the ability of the device to determine the state of the system, specifically the end inspiratory phase of the respiratory cycle, characterised by low flow, high pressure, and high volume.

Having access to a cost-effective, readily-assembled, well-characterised and validated device would enable considerable development of open source hardware. Throughout the COVID-19 pandemic many open-source hardware solutions were developed in the res-
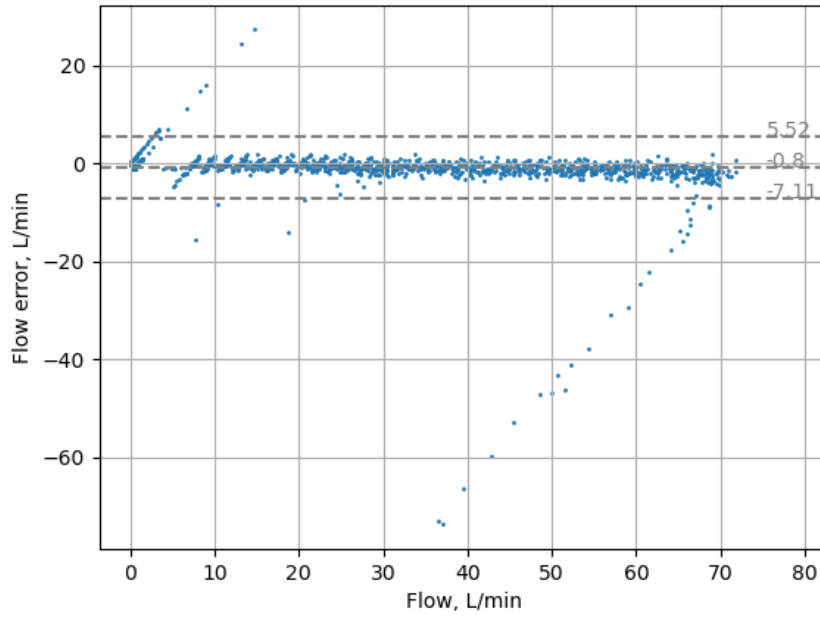
(a)
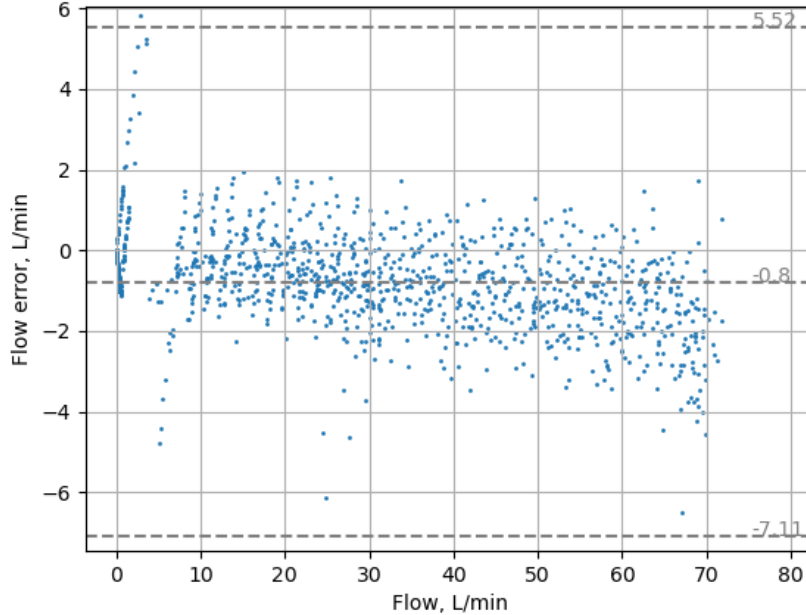
(b)

Figure 8.3: Bland-Altman plot demonstrating the error of the flow sensor across 80 seconds, $N = 4000$. The significant errors are due to sampling at a rate relatively low compared to the near-vertical increases in flow rate, and the smoothing which is done by the ventilator. (b) is cropped to depict only data within 2σ.

piratory therapy space, for example low-cost mechanical ventilators [56, 495–497]. An absent or expensive aspect of these designs was the ability to determine the characteristics of the respiratory therapy provided to each patient.

The ACTIV flow sensor provides this need in the form of flow and pressure data, from which many of the metrics and measurements required for a detailed understanding of the respiratory therapy can be gained. Being customisable and having multiple configurations, it also enables further development of other open source hardware, for example spirometers or peak flow meters. One hindrance to development of such technologies is flow sensors, particularly multi-use sensors, are too expensive to be accessible in low-resource regions. This design also addresses these issues.

8.1.1 ALTERNATE CONFIGURATIONS

The flow sensor is broadly customisable for use in specific applications. It works on the basis of a pressure decrease associated with increase in velocity through a constriction. From first principles, assuming laminar flow, the flow can be calculated:

$$q = c_d \frac{\pi}{4} D_2^2 \cdot \sqrt{\frac{2 \cdot \Delta P}{\rho \left(1 - d^4\right)}}$$

Where:

$$D_2 = 10 \ mm$$

$$d = \frac{D_2}{D_1} = \frac{10 \ mm}{15 \ mm}$$

$$\rho = 1.225 \ kg \cdot m^{-3} \ , \text{assumed to be constant}$$

$$c_d = \text{Discharge coefficient} \ = \ f(Re, q, d, etc.).$$

$$\text{Fitted in data} = 0.97$$

The high $c_d = 0.97$ value is also encompassing a linear scalar to fit the output of the sensor to the validation data. This value provided an acceptable fit to data for several Venturi/PCB combinations as shown in Section 8.2. Data are shown in full at https://doi.org/10.17605/osf.io/ktxuh.

With the differential flow sensor in linear mode:

$$\Delta P = \frac{190 \times V_{Analogue \ out}}{V_{CC}} - 38$$

[535]

Thus, assuming the operating voltage is $V_{CC} = 5.0 \ V$, and the sensor is connected to a device with a 10-bit ADC, such as an Arduino Nano, flow is defined:

$$q \ [L \cdot min^{-1}] = c_d \times 6.722 \times \sqrt{\Delta P}$$

For a 15-12 mm Venturi, replace the value of 6.722 with 11.284.

The pressure loss caused by the Venturi is minimal in the context of respiratory circuits. By modelling the Venturi as a cylinder with $d = 10 \ mm$, and $l = 70 \ mm$, the theoretical loss is $\leq 0.3 \ cmH_2O$ (30 Pa) at 60 $L \cdot min^{-1}$, and $\leq 0.005 \ cmH_2O$ (0.5 Pa) at 5 $L \cdot min^{-1}$.

8.1.1.1 Operational Range

The operational range of the flow sensor is presented in Table 8.1 for a variety of configurations. It is important to note that with the differential pressure sensor configured in linear operating mode, the resolution at the lower flows listed here is particularly poor. It is also possible for the Venturi to be connected to both a 125 Pa and a 500 Pa sensor allowing a significantly greater range.

The device presented in this document is the foundation for other devices, to be built upon as required for specific applications. It is simple to design a custom Venturi, or series of Venturis, which enable a more comprehensive analysis of a respiratory circuit.

Table 8.1: Operation ranges of the various configurations of the flow/differential pressure sensor. The combination of the 15-10 mm Venturi and the 125 Pa differential pressure sensor is the most used by the authors. Note: The operational range shown here is beyond the '100%' value specified by the manufacturer [535], but has shown to be relatively reliable.

		Pressure sensor:	
		125 Pa	500 Pa
	15-10 mm	$5 - 75 L \cdot min^{-1}$	$15 - 150 L \cdot min^{-1}$
Venturi:			
	15-12 mm	$12 - 125 L \cdot min^{-1}$	$25 - 250 L \cdot min^{-1}$

Similarly, it is possible to include another port to allow for flow to be determined in two

directions.

The pressure sensor range is $0 - 6.0\ kPa$, or $0 - 61.2\ cm\ H_2O$.

8.1.1.2   RESOLUTION

Table 8.2: Resolution of the flow sensor for a variety of configurations, all values in $L \cdot min^{-1}$ unless otherwise indicated. **with the differential pressure sensor configured in linear mode**, and with a **10-bit ADC**. The inter tenth-centile resolutions are shown.

		Pressure sensor			
		125 Pa		500 Pa	
	15-10 mm	Bot 10% (23.6)	.17	Bot 10% (46.8)	0.33
		Top 10% (71.4)	0.055	Top 10% (142)	0.11
Venturi					
	15-12 mm	Bot 10% (39.6)	0.28	Bot 10% (78.6)	0.56
		Top 10% (120)	0.093	Top 10% (238)	0.18

The resolution of a variety of configurations of sensors are shown in Table 8.2 Because

of the square root relationship, the resolution is very poor at low flows. For a better

resolution at lower flows, one could either investigate the use of the sensor in square root operating mode, or else using a tighter constriction in the Venturi.

While the resolution values presented in Table 8.2 are those associated with a 10-bit ADC, the resolution could be significantly increased with the use of a higher definition ADC, up to the 16-bit internal digital resolution of the component [535]. The validation has been performed with a 10-bit ADC to demonstrate effective and accurate sensing is achievable with accessible, cost-effective hardware such as that found on Arduino systems, but it could be expected that the resolution of the device with a 16-bit ADC would be $2^{16-10} = 64\times$ smaller than the values presented in Table 8.2.

The resolution of the pressure sensor appears to be limited only by the resolution of the ADC to which it is connected: for example a 10-bit ADC sees a resolution of $0.0064\ Pa$ or $6.5 \times 10^{-4}\ cm\ H_2O$.

8.2   PEEP valve

A common tool for more effective ventilatory therapy for intubated patients is the introduction of positive end-expiratory pressure (PEEP). PEEP provides mechanical splinting of large and small airways by keeping them more open throughout the entire respiratory cycle [536]. PEEP has the effect of lowering airway resistance and providing greater surface area for gas exchange, and is a crucial tool in the treatment of ventilated patients with COVID [490].
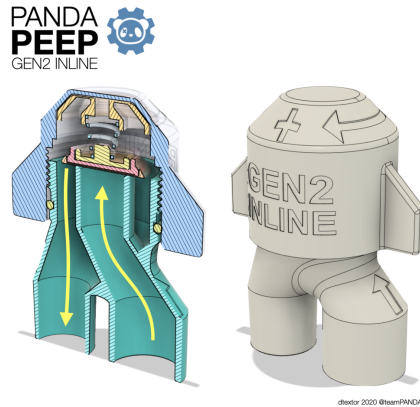
Figure 8.4:   PANDAPeep Gen2 Inline pressure drop valve.   Made with 3D-printed components and other common mechanical components.   Image from: https://www.thingiverse.com/thing:4316582.

Because of the use of a single expiratory port with the ACTIV system, it is critical there is some form of PEEP valve in the circuit between each patient and the passive 'Y' valve to provide individualised therapy. Thus, an inline PEEP valve must be used to allow capture of all expired gasses. This valve could consist a small shroud glued to a typical BVM-type PEEP valve [502]. However, this approach depends on gluing, and the availability of high-demand medical hardware, and has an undesirable non-zero minimum pressure drop.

The PANDAPeep Gen2 Inline[1] valve [537], as shown in Figure 8.4, was used: a 3D-printed PEEP valve with relatively common mechanical components. More critically, it is self-contained and can provide longevity and adequate sealing in an already-developed package.

In addition to its use as a PEEP valve, the PANDAPeep can also be used as a pressure

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[1]Used in this context under the CC BY-NC-SA 4.0 licence: https://creativecommons.org/licenses/by-nc-sa/4.0/.
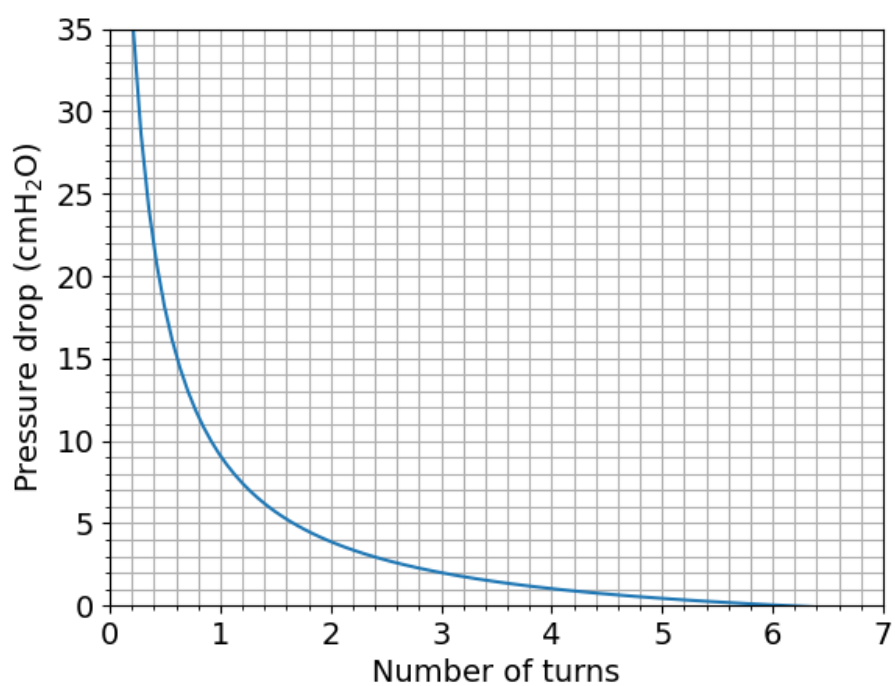
Figure 8.5: Approximation of the relationship between rotation **from fully closed** and pressure across the PANDAPeep Gen2 Inline valve. It is variable as a function of the exact assembly process and components used.

drop valve on the individual inspiratory respiratory circuits. This use provides protective pressure drops for patients with lower lung stiffness when the system is used with imperfectly-matched patients. In the metal spring configuration, the PANDA valves have proven reliable and adjustable for pressure drops between $0- \approx 35\ cmH_2O$, with no deterioration over several months of experimentation. Because of variability in assembly and components, there is no consistent transfer function between rotation of the cap and the pressure drop, but it is approximated in Figure 8.5. A large amount of the variation comes from the spring because it is a component defined by its use, rather than by a spring constant value.

Critical features of the operation of the PANDAPeep Gen2 Inline valve include:

1. With the metal spring configuration, as is recommended because of the longevity, it is possible to tighten the valve to the extent it is permanently closed at any realistic airway pressure. This issue can be seen in the vertical asymptote in Figure 8.5.

2. It is possible to undo the valve to the extent it does not provide any pressure drop, and the sealing disc is permanently disengaged from the inlet into the top of the valve. This state can be identified by a faint rattle when the valve is gently shaken.

3. The valve operates as a one-way valve because a reverse pressure gradient aids the mechanical sealing of the valve, inherent by design of the valve, but also convenient to prevent reversed expiratory flow. However, because of 2), it is possible the sealing surfaces of the valve are completely disengaged, in which case the pressure

differential will not result in sealing. Thus, unless there is absolutely no alternative, additional one-way valves must be used where indicated in Figure 7.4 throughout the ACTIV system.

4. As shown in Figure 8.5, as the valve is tightened towards being fully shut, there is a significant gradient in the change of pressure across the valve. Therefore, it is possible to mistakenly fully close the valve, or induce a pressure drop completely occluding ventilation. Hence, whenever a PANDA valve is adjusted, there **must be careful examination to ensure the circuit is not completely occluded**, be it through use of sensing, or physiological signs, such as patient chest rise and fall or auscultation.

8.3   Off-the-shelf components

Some components of the ACTIV system are readily sourced off-the-shelf. While these components are necessary, the exact brands and models specified here are not vital. Thus, they may be substituted for other components with the same overall behaviour/effect.

8.3.1   ONE-WAY VALVE

One-way valves are required in various places in the respiratory circuits to ensure proper operation. The Hudson RCI 1665 (Teleflex, PA, USA) was used in the ACTIV system,

and provides the basis for ensuring no cross-ventilation between the two patients. While it may be possible to introduce the use of a valve with a smaller resistance and thus forward pressure drop, it is vital the valve allows absolutely zero flow when a reverse pressure gradient is present.

8.3.2   FILTERS

The placement of filters in various places throughout the respiratory circuit provides multiple important clinical uses. Primarily, they remove any possible contamination from the manufacturing or assembly process, or other sources. They also remove the single point of failure for cross contamination between the two patients. Specifically,if a one-way valve fails there is still adequate filtration of both patients' inspired and expired air to mitigate cross contamination.

8.3.3   AIRWAY TUBING

Airway tubing is required beyond what is supplied in standard respiratory circuits. Hudson RCI Corr-A-Flex II (Teleflex, PA, USA) tubing was used as it provided flexibility of length. This sealed effectively with both commercial and 3D-printed 22 mm components, but lacked rigidity to easily disconnect multiple times. A smaller diameter tubing could be used, but would require adapters or redesign for interface with commercial and 3D-printed components. Furthermore, the added airway resistance associated with a smaller diameter hose should also be considered in the context of ventilator capac-

ity. However, these limitations are modest and do not exceed the limits of commercial ventilators.

8.4 Summary

A readily-assembled flow and pressure sensor forms the basis of the ACTIV system, and also allows for other low-cost respiratory innovation. The design of the sensor is well validated, and additional configurations are presented in Appendix B.2.2 [50]. Other required components of the ACTIV system are presented, including the open-source PANDA valve, and other common off-the-shelf respiratory components.

The components presented here support the key feature of the ACTIV system as a series ventilation system — the switching valve. Similar levels of design and validation are required for this valve, and the switching software supporting it.

Chapter 9

ACTIV specifics — switch it up

It is pivotal to have an active valve switching flow to one of two circuits to realise an in-series method of sharing a ventilator. In a similar manner to the flow and pressure sensor, the valve must be able to be manufactured using basic additive manufacturing techniques, such as single-material 3D-printing, be appropriate for low pressure and flow rates, and be widely compatible for customisation and use for other projects.

The hardware design was largely informed by these criteria, specifically the orientation of the sealing surfaces to allow for substantial o-ring capture. In order to provide a smooth plane for these to seal against, either horizontal or vertical alignment is required. This requirement dictates the gross structure of the valve, as does the necessity to mate with common airway components [538], for which 22 $mm\oslash$ interfaces were selected. This diameter also allowed maximal flow with minimal pressure loss.

To maximise compatibility, a servo motor was chosen as the actuator. The torque is critical, as with insufficient torque the sealing surfaces may not be properly engaged during actuation, causing undefined behaviour. Servo motors have a universal interface, and are commonly found on devices such as remote control vehicles, as well as within complex systems. They require only a pulse-width modulated signal to instruct an angular displacement.

The completed design and validation of the ACTIV valve is described here, as is the overall electrical and software interface of the greater ACTIV system.

9.1   Valve

Diversion of air to one of two respiratory circuits is achieved through use of the ACTIV valve [50], presented in peer-reviewed format in Appendix B.2.3. This valve operates in the relatively low physiological respiratory flow and pressure ranges, and natively allows external connection to medical devices, such as CPAP or mechanical ventilators. There are very few commercially-available valves able to connect to respiratory circuits without the need for complex adapters or extensive customisation. Outside of those designed for use within mechanical ventilators, there are few valves suitable directly for clinical applications or trials, none of which enable ventilation multiplexing.

The valve switches an inlet (from the ventilator) two either one of two outlets (to patients), using a basic wedge ('pie') which alternately occludes each outlet passage. The
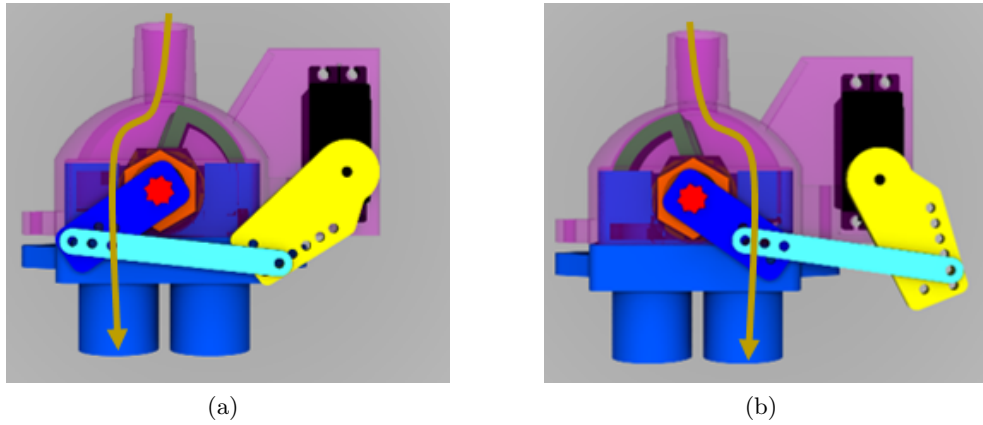
Figure 9.1: Depictions of the valve in the two operating positions.
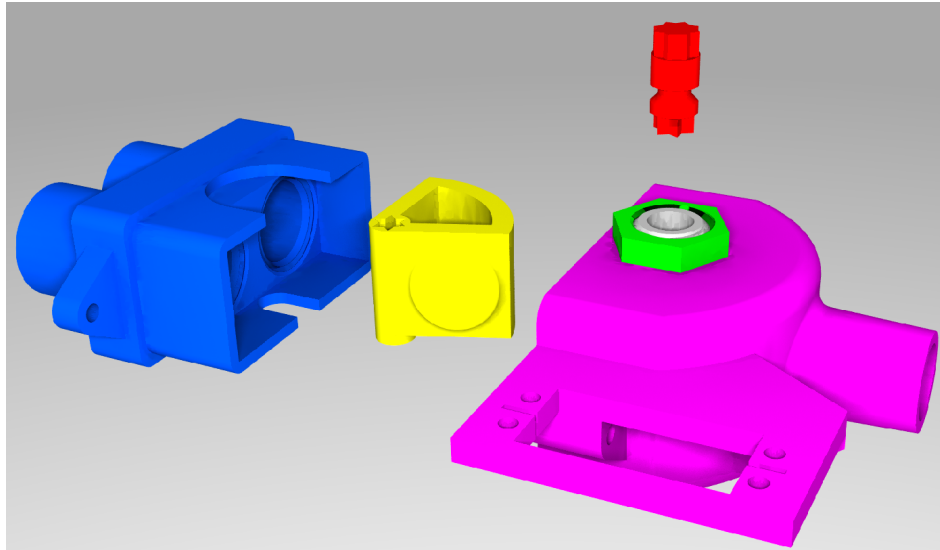
Figure 9.2: Partial exploded view of the valve. For a colour key see [50].

wedge has extrusions, which press against o-rings, sealing one of the output respiratory circuit outlets. This wedge is rotated from one position to the other using a servo motor, connected via a basic linkage, using 3D-printed bars. Therefore, the valve is able to be controlled by any device capable of powering and controlling a servo motor, such as an Arduino or a Raspberry Pi. An exploded view is shown in Figure 9.2.

The connectors of the valve conform to ISO 5356-1:2015 [539]. There is a combined

15mm socket/22mm cone (15F/22M) input, and 22mm socket output connectors. Adapters are very simply printed for interfacing with less common connectors.

The 3D-printed parts of the system can be sterilised with hydrogen peroxide, meaning the device can be reused between patients without deformation [540]. However, given the system excluding the servo is reasonably inexpensive, it is recommended the valve is not used across multiple patients, in a clinical setting to avoid cross-contamination risk.

The valve can be used for flows and pressures within common medical respiratory ranges. It is shown in Figure 9.2, and is:

- A 3/2-way valve
- Mostly 3D-printable
- Compatible with common respiratory circuits
- Sterilisable/Cheap if reusing the motor

9.2   Electrical System

The electrical system design for the ACTIV system was completed on the foundation of being portable, robust, and accessible. To this end, the system was designed on the basis of an Arduino Nano [286], as these devices are popular, cost-effective solutions for open-access electrical system solutions. The system is designed to operate with two Arduino Nanos, one to act as a controller for the entire system, and one to provide a graphical user interface to the clinician. Printed circuit boards have been designed

to allow easy use with few external components. The controller PCB requires a stable 5.0 V power supply, capable of delivering at least 3.0 A. There is bulk decoupling on the PCB, but fluctuations may interfere with stability of the measurement system.

9.2.1 CONTROLLER

The controlling Arduino Nano has a PCB design to allow interface with sensors, power systems, the servo motor, and basic debugging. A complete schematic can be found in Appendix B.2.4. The system has all analogue ports broken out for use with Venturi sensors. An optional potentiometer (≥ 10 $k\Omega$ recommended) enables basic tuning of the servo motors, but must be selected with the appropriate jumper on J2. Two outputs for servo motors are provided, only one of which is used – J12 by default, connected to digital pin 5 on the Ardiuno Nano.

Communication is over serial, in two modes: Instructions delivered via ASCII characters, or data in a binary format. Serial communications are required at a Baud rate of 115200, in a 8N1 format: 8 data bits, 1 stop bit, and no parity. There should be no end characters, for example carriage returns \r, or new line \n characters. A complete instruction set is presented in Appendix B.2.1.1, and is case sensitive. To properly communicate, the serial data to the GUI must be stopped with the s0 command. The data format expected by the Python software for analysis is as per the od command.

There are several broken-out peripherals not required by the ACTIV system, allowing

for further customisable use. Specifically, two SPI communication systems, I2C, two momentary push buttons, and all of the otherwise unused digital pins of the Arduino are provided

9.2.2   GUI

The interface PCB is another breakout board for an Arduino nano, and has a schematic presented in Appendix B.2.5. It enables:

- A screen with a parallel interface, such as the ILI9341 or UC8230.

- Serial communications with the control board.

- Three momentary push buttons for control. These buttons can be assembled directly on the PCB, but allowances have been made to interface with external buttons.

- Two status LEDS, which can be external, such as in a 3D-printed enclosure, if desired.

- Connections have been made with optional 0Ω resistors for SPI communication. However, populating these resistors to use SPI will use the ports on the Arduino Nano to which the buttons are currently routed. Cuttable jumpers exist on the PCB to allow for reword, as do currently open solder jumpers to allow rerouting to connect the push buttons to ports currently used as parallel communication to the screen.

The screen enables basic plotting of data, which is obtained, processed, and communicated from the controller Arduino Nano. There is also the ability to issue pre-determined instructions, as per Table B.2, to the controller to change settings which may be changed during operation of the system. The operating instructions and state diagram of the interface Arduino Nano are shown in Figure B.2.1.2. Again this subsystem is designed to be widely compatible to a number of applications, and is easily converted to other uses though software and solder jumper changes on the PCB.

9.3 Control system

The control system is based on a simple, robust, self-correcting, timed-loop, embedded operating system. It uses flow sensor data to change through states, as shown in Figure 9.3. All values are kept in raw digital output format without conversion to differential pressure or flow values. Because raw values are used, should the configuration change from the one presented as the recommended option in Section 8.1, it is necessary for the control system values to be altered to ensure proper operation. The appropriate configuration is defined:

- A $15 - 10\ mm$ Venturi;
- Connected to a 125 Pa differential pressure sensor;
- With the sensor configured to linear operation mode;
- Operating at $V_{CC} = 5.0\ V$; and
- Interfaced to a 10-bit ADC.

If the resolution of the ADC is changed, it is recommended that the resultant ADC values are up- or down- sampled to match the scale of the 10-bit ADC used with the Arduino Nano, i.e. scaled such that 0 V correlates to 0, and with a full span of $2^{10} = 1024$ counts. For the purposes of the control system this level of accuracy is more than sufficient, and allows easy interface with other devices.

9.3.1   FILTERING

The controller implements a basic circular buffer of length 10 for each of the flow and pressure inputs: one for the inspiratory sensor, one for each of the patient sensors, and one for the expiratory sensor. Raw ADC values are used without conversion to flow or pressure values. A low-pass filter is implemented using the integer mean of the circular buffer. Given a nominal loop period of $20ms$, the low-pass filter is thus a moving average of the most recent 0.2 s of sensor data. This rudimentary filter introduces stability to the system, ensuring only appropriate state changes are made, while allowing fast responses to appropriate inputs.

Because gradients are used in combination with values, gradients are estimated by calculating the difference between the maximum and minimum values of the sum of subsections of the circular buffer. Optimal sensitivity was found using sub-windows of size five, representing the difference between the average of the two halves of the circular buffer. The gradient approximation was not normalised for the length of time over which it was
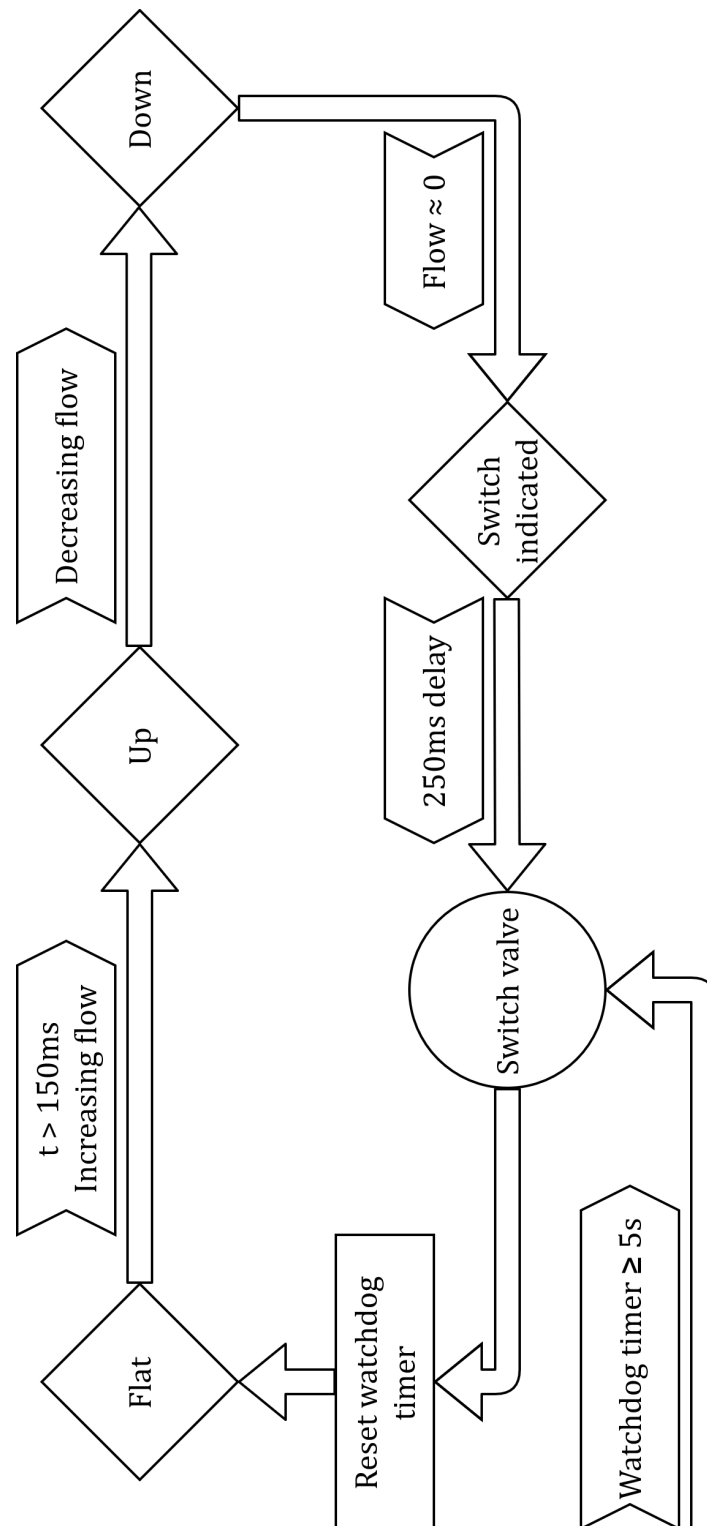
Figure 9.3: State machine implementation of the control system to determine when to switch the status of the valve.

sampled, but instead represented as the signed relative change in output of the ADC value.

9.3.2   CHANGING STATE

Any value between 150-250 was considered to be 'zero flow' for indicating the end of an inspiratory effort, and similarly a gradient approximation less that 10 was required. Increasing flow was defined as a gradient approximation of at least 25, and decreasing by less than -25. These these values were found to balance adequate sensitivity for low flow applications, while maintaining stability with large artefact variations from moving circuit components such as the PANDAPeep pressure-drop valves.

There are minimum times before which the state of the FSM does not change after switching has occurred[1]. These values are typically 150 ms, which in combination with 250 ms delay between a change in motor state being indicated and initiated provides sufficient time for artefact associated with moving components to settle, thus providing system stability.

The delay in switching provides deadtime in the respiratory circuit to allow for further expiration of the patient to whom inspiratory flow has most recently been delivered. The time is ideally manually set to a time allowing maximal uninterrupted expiration to occur, and the state switch is completed immediately prior to the subsequent ventilation

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[1]in this context occurred means after the software instruction for switching to begin, i.e. after the 250 ms delay indicated in Figure 9.3, but before switching has necssarily completed based on the position of the servo motor.

delivery. However, this exact time is a function of respiratory rate, servo motor limits, power supply, and lung compliance. Hence, a conservative default value of 250 ms is used, which can be adjusted during operation using the control and interface system in Section 9.2.2.

To ensure safe operation in the case of sensor failure, a watchdog timer is implemented with a default value of 5 s, corresponding to a respiratory rate of 12 min^{-1} total, or 6 min^{-1} per patient, which is clinically lower than likely desired. The value of the watchdog timer can be written in milliseconds over the serial communications interface using the `wXXXX` instruction, where `XXXX` is the number of milliseconds after which the switch state will change, regardless of sensor inputs. It is possible to use the watchdog timer as a mechanism for regular switching if the respiratory rate is strictly rigid, and there is sufficient agreement between the Arduino Nano RTC and the mechanical ventilator. This method is not recommended, and should only be attempted if there is no alternative.

As discussed in Section 9.3.1 all calculations completed for the control system are kept in raw ADC values to decrease computational demands. However, because of the non-linear relationship between differential pressure and flow as discussed in Appendix B.2.2 [49], the ADC differences and tolerances do not represent consistent physical flows. This has not created any observed problems in the reliability of the control system, but requires consideration if the system is adopted for other use.

9.4   <u>Summary</u>

A servo-actuated valve is presented for use within the ACTIV system. The valve lends itself to being interfaced with medical equipment standard for use with airway systems, with 22 mm $\oslash$ inlets and outlets. The servo is used to force a pie-shaped wedge to occlude one of the two outlets at any given time, and is reusable between several devices. The performance of the valve is shown to be adequate for the application, with minimal operational pressure loss through the open connection, and undetectable flow through the closed connection.

An Ardiuno Nano based control system sees the implementation of a finite state machine which changes state on the basis of inputs from the flow and pressure sensor connected to the inspiratory output of the mechanical ventilation device. The basis of the control system is to detect the end of the inspiratory period, and subsequently change the position of the ACTIV valve. These data are also shown on a basic screen in a manner with which clinicians are familiar, similar to a standard ventilator display.

Chapter 10

Combined ACTIV system

The assembly of the entire ACTIV system is trivial, as per Figure 10.1, and shown in Figure 10.2.

10.1 Validation method

To validate the system for use with patients, it is necessary to prove the validity in a more controlled environment. For this purpose, the ACTIV system is inserted into a ventilator circuit for two patients, as shown in Figure 10.1. The inspiratory output from an Evita Infinity V500 (Dräger, Germany) mechanical ventilation device connects to the ACTIV valve through a FPS [49]. The mechanical ventilator was set to pressure
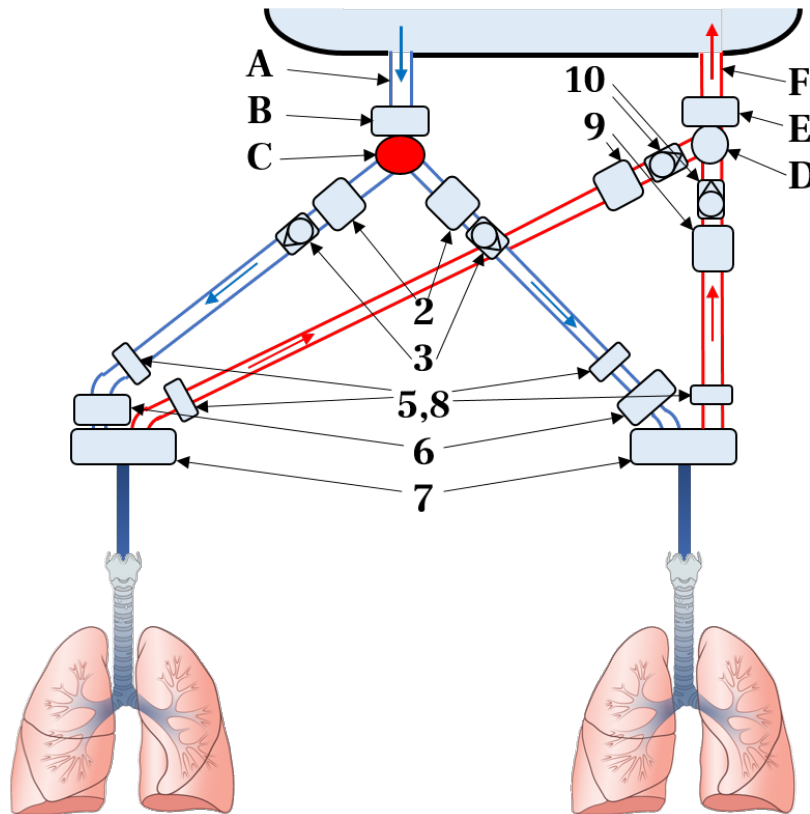
Figure 10.1: In-series ventilation set-up with two patients connected to a single ventilator, as per the ACTIV system. A&F)are short sections of hosing for convenience, B, 6, and E) are 3D-printed flow and pressure sensors, C) is the ACTIV switching valve which diverts ventilation to one of the two respiratory circuits. 2 & 9) are the PANDAPeep pressure drop valves, 3 & 10) are one-way valves, 5&8) HEPA filters, 7) Passive Y-valve as per standard respiratory circuit, and D) is an additional passive Y-valve.
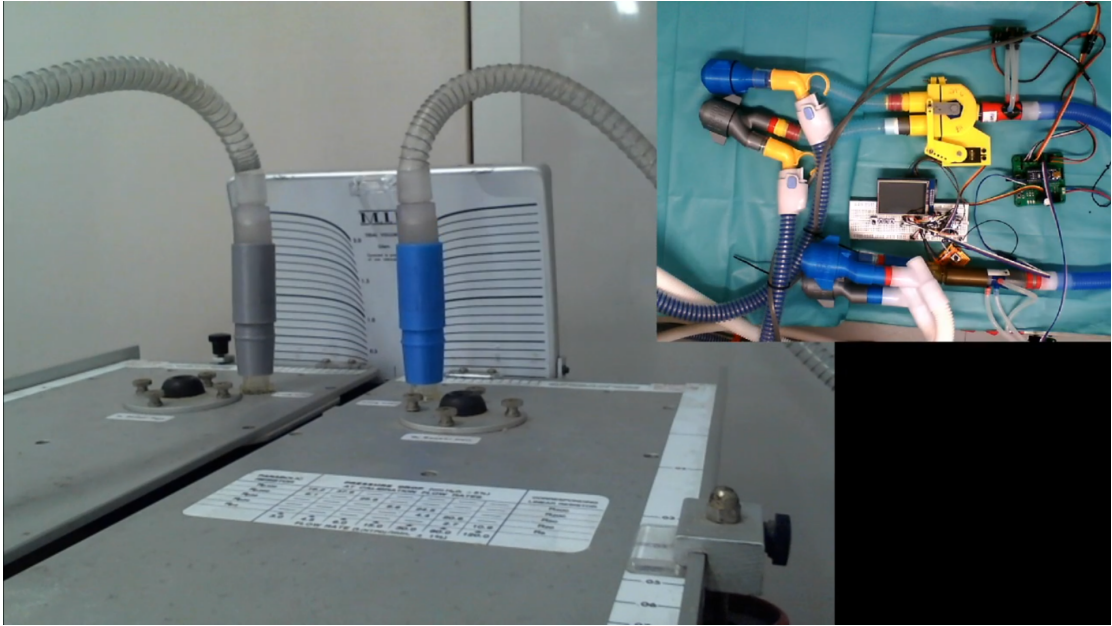
Figure 10.2: Image of the complete ACTIV setup, with colour-coordinated sides for convenience.

control mode, initially with a PIP of 18 cmH_2O, PEEP of 5 cmH_2O, RR of 24 min^1, and $t_i = 0.8\ s$.

10.1.1   BALANCING PROCESS

At $t = 62\ s$, the compliance of the arbitrarily 'Right' patient was decreased from 0.10 $L \cdot cmH_2O^{-1}$to 0.05 $L \cdot cmH_2O^{-1}$, to represent a pathological change, or difference between unmatched patients. This difference in compliance would represent a considerable problem for parallel ventilation systems because the unchanged, healthy patient would receive a greater respiratory effort, and thus potential hyperinflation injury [536]. In the case of the ACTIV system, this difference in compliance requires intervention in the form of adjusting pressures.

The balancing process is displayed graphically in Figure 10.3. The patient with decreased compliance, as identified by a decrease in volume with no changes to respiratory settings, will be referred to as the 'unhealthy' patient. The unchanged will be referred to as the 'healthy' patient. This process assumes the mechanical ventilator is operating in a pressure control mode, which is clinically very common [541]. The basic idea is for the ventilator pressure settings to have a PIP as desired for the unhealthy patient, and the PEEP for the healthy patient. The other pressures will be set through the use of external pressure-drop valves. The process is defined:

1. Ensure the need for balancing by determining there is no other reason for a perceived decrease in delivered volume to the patient, such as flow sensor error, airway obstruction, or airway disconnect.

2. To protect the healthy patient from hyperinflation injury, first induce an external pressure drop on the inspiratory side of the respiratory circuit by tightening the PANDApeep valve to decrease inspiratory pressure.

3. Increase the driving pressure on the ventilator, aiming to deliver the desired PIP to the unhealthy patient, while ensuring the healthy patient does not exceed safe pressures. If the pressure to the healthy patient reaches maximum allowable, return to Step 2.

4. Increase PEEP on the expiratory side of the unhealthy circuit, if desired, by tightening the PANDApeep valve to the desired setting to ensure adequate recruitment for just this patient, adding PEEP only to their circuit.

5. Confirm PIP, PEEP, and tidal volume for each patient are as clinically desired.

10.1.2 Data gathering

Data were gathered from two sources. The Evita® Infinity® V500 (Dräger, Germany) mechanical ventilator was queried via the serial communication port using CURESoft [542] at a frequency of 100.0 Hz, Data were directly obtained from the 3D-printed flow and pressure sensors [49] via an Arduino Nano (Arduino LLC, MA). The sensors were sampled at a nominal rate of 50 Hz. Data from the Mechanical Ventilator were down-sampled to match the flow and pressure sensor.

10.2 Results

Data were obtained from both the mechanical ventilator and the 3-D printed flow and pressure sensors. Complete datasets including Python scripts used for analysis are viewable at https://doi.org/10.17605/osf.io/ktxuh. Analysis included determining breath-by-breath determination of tidal volume, PEEP, and PIP. Methods for extracting these from the raw data can be seen in https://doi.org/10.17605/osf.io/ktxuh. An overview can be seen in Figure 10.4. The 'Healthy' lung is reported as the 'Left', and the less compliant 'Unhealthy' the right.

The process of Section 10.1.1 was followed, with the end point defined as equal tidal
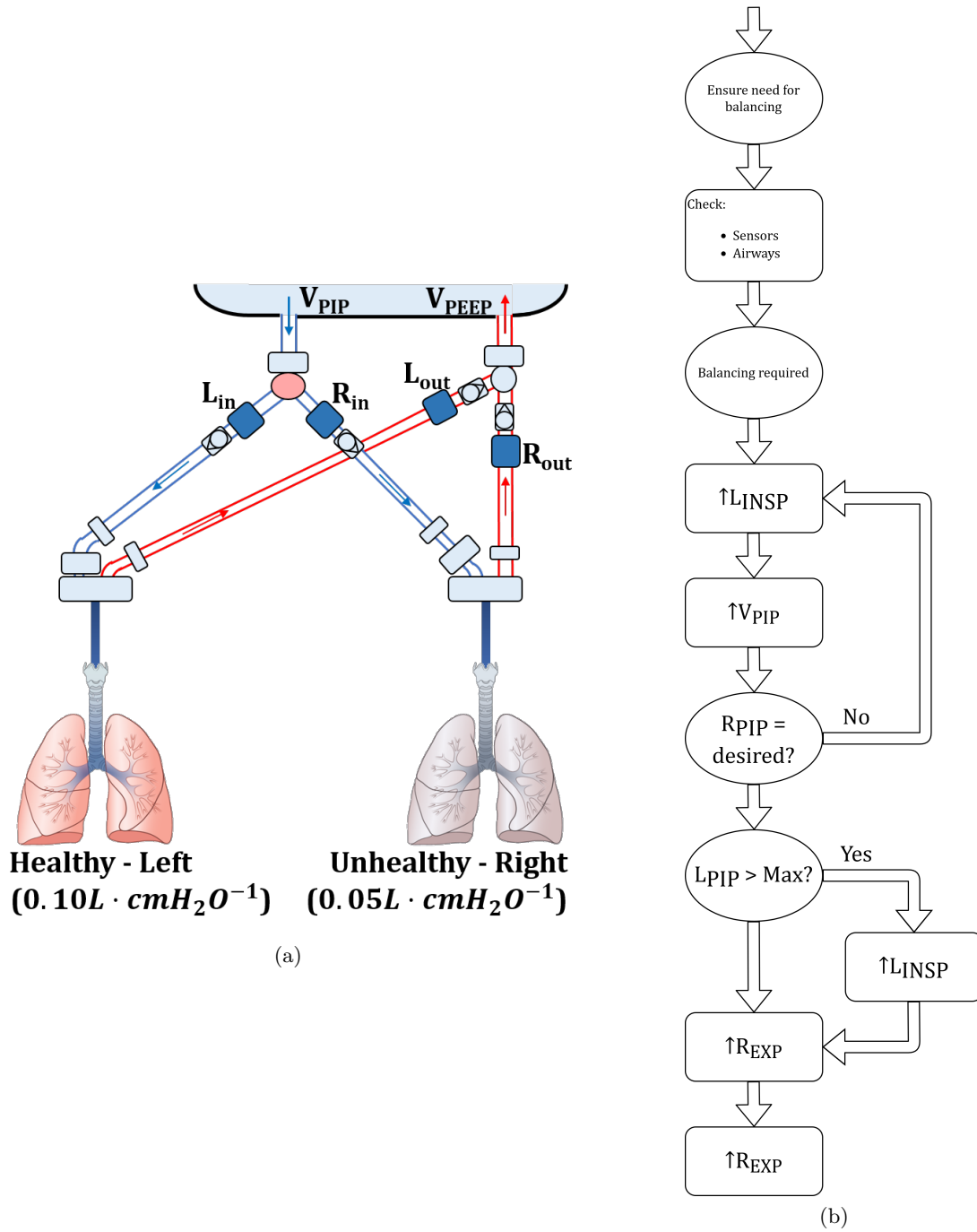
Figure 10.3: Procedure for balancing ventilation between a healthy and an unhealthy patient. (a) specifies the PANDAPeep valves for use during the process, which is shown in (b). Note ↑ indicates to tighten the corresponding valve, except in the case of V_{PIP} which is to increase the driving pressure of the ventilator.
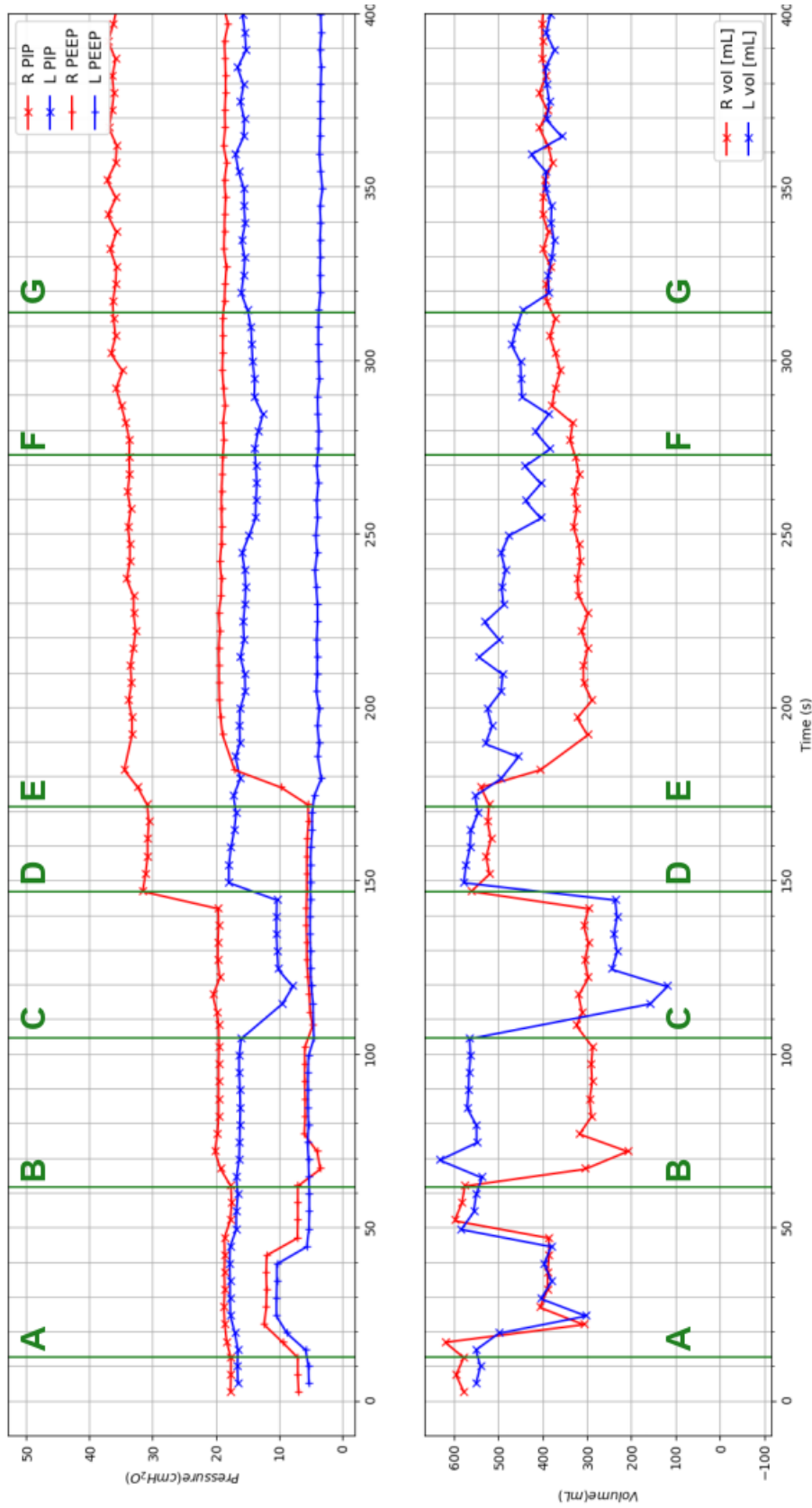
Figure 10.4: Breath characteristics from the two patients, as measured by the FPS at the 'patient'. A) represents a change in PEEP to align the data from the flow and pressure sensors with the mechanical ventilator. B) represents the physiological change of the left lung from $0.10\ L \cdot cmH_2O^{-1}$ to $0.05\ L \cdot cmH_2O^{-1}$ as per Section 10.1.1; C) is the protective introduction of an inspiratory pressure drop on the healthy lung as per Section 10.1.1;2; D) is the increase in driving pressure from the mechanical ventilator as per Section 10.1.1;3; E) is the introduction of external PEEP for the unhealthy lung; F) another small increase in driving pressure from the ventilator; and G) is another small increase in the pressure drop in the inspiratory circuit of the healthy lung. This balancing process is shown and discussed at https://www.youtube.com/watch?v=FqLRors0JA4.

volumes. This outcome was attained with the healthy patient have a PIP of 16 cmH_2O and a PEEP of 4 cmH_2O, and the unhealthy patient a PIP of 36 cmH_2O and PEEP of 19 cmH_2O. Initially, the ventilator settings were a PIP of 20 cmH_2O, and a PEEP of 4 cmH_2O. The healthy patient had an inspiratory pressure drop of 8 cmH_2O induced, and subsequently the PIP on the ventilator was increased also by 8 cmH_2O. This change was followed by adding another inspiratory pressure drop of 6 cmH_2O to the healthy patient, and an increase in ventilator driving pressure of 5 cmH_2O. An external PEEP of 14 cmH_2O was then induced for the unhealthy patient. Similar, smaller adjustments were continued until tidal volumes were equal at 400 mL.

10.3 Discussion

A safe, customisable method of providing respiratory therapy to two patients from one mechanical ventilator has been demonstrated. The device is cost-effective and accessible, providing a possible solution for chronically under-resourced regions, as they are seeing wider pandemic disease prevalence in the context of a pandemic. This technology is not a definitive solution, given personnel or other resources may be the limiting factor to providing care. However, it poses a potential solution to inequitable access to healthcare for some, by providing two patients respiratory therapy, instead of one.

The system has shown it is capable of delivering individualised ventilation therapy, with PIPs and PEEPs differing by at least 20 cmH_2O. The limitation of maximal pressure differences is the PANDAPeep valve used in this study, where control of the pressure drop

becomes too sensitive as the valve nears completely closed at approximately 30 cmH_2O. Therefore, with the addition of a sensor on each patient detecting flow and pressure, it is therefore possible for the system to provide individualised therapy and monitoring, fully addressing the concerns raised within the joint statement [9].

Even during high-prevalence outbreak events, there is still the standard background workload of non-COVID patients. Because clinicians are much more familiar with the respiratory demands and likely changes of these patients, it is recommended to use the ACTIV system with these patients. In the case of multiple ACTIV systems used within one department, it is recommended to have one ventilator spare to allow for debugging the ACTIV system, or to separate paired patients in case of drastic physiological changes in one. This clinical approach offers a factor of safety, while still offering a significant increase in mechanical ventilators.

The internal pressure and flow sensing, and the subsequent values generated by the mechanical ventilator are likely incorrect. This error is due to a number of factors, particularly the extra components in the circuit of which the mechanical ventilator is unaware in estimating circuit pressures and flows. For example, if a pressure drop is induced on the inspiratory breathing circuit of either patient, the driving pressure of the ventilator will over report the actual value.

A further implication of the impact on individual monitoring, is there is no ability to provide supplementary ventilatory support for spontaneous patient respirations, a natural evolution in ICU ventilation care. It is necessary for the trigger thresholds for
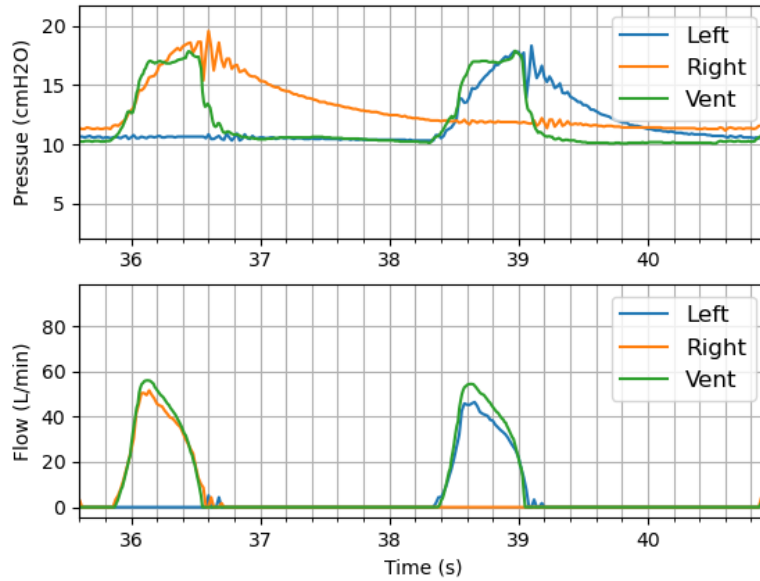
Figure 10.5: Example of incomplete expiration. The right lung is inflated, and slowly deflates until a breath delivered to the left lung at $t = 38.4s$, at which time expiration for the right lung pauses, until the left lung has also expired.

such events are set to the maximum possible values to minimise the probability of this happening. Failure to do so may result in erratic switching behaviour, and depriving one patient of oxygenation. Therefore, it is necessary to use the device on patients who are deeply sedated or paralyzed. Hence, it is recommended the ACTIV system is used on patients in the middle of their illness who are anticipated to remain sedated for some time to minimise the risk of attempted spontaneous respiration, while being past the more variable acute illness phase.

One factor affecting the sensing of the mechanical ventilator is incomplete expiration: Expiration for one patient may not be fully completed until after the complete inspiratory cycle of the second patient. The pressure downstream of the passive expiratory Y valve ('D' in Figure 10.1) is equal to the highest at any given time of the pressure at the

mouth of either patient, taking into account the position of the ACTIV valve, and any external pressure-drop valves. Thus, when breath is being delivered to a patient, the second patient will be unable to completely expire as the pressure downstream of the one-way valve in the expiratory circuit ('10' in Figure 10.1) will be greater than at the mouth, and therefore the one-way valve will remain closed. This issue can be graphically seen in Figure 10.5, where P_{Right} remains constant while P_{Left} is receiving expiratory effort, and is one of the primary factors impacting the mechanical ventilator's ability to accurately determine the tidal volume.

Depending on the make and model, mechanical ventilators will either strictly sample breath-to-breath, or else average over a number of breaths. In the former case, the lack of complete expiration will result in an under estimation of the tidal volume for the patient who does not fully expire, and and overestimation of the other patient. If the mechanical ventilator averages over several respiratory cycles, then neither patient will be have an accurate tidal volume recorded.

In the abscence of external pressure and flow sensors, it is possible to provide customised ventilation based solely on the metrics recorded by the ventilator. For this purpose it is recommended to have a relatively low respiration rate to allow for near-complete expiration, and ensuring accurate measurement by the mechanical ventilator. Unless the PANDAPeep valves are disengaged, tidal volumes, V_t, will be the only accurate measurement on the ventilator, and physiologic signs will need to be used to guide individualisation to therapy.

Development and validation was carried out primarily on the Evita Infinity V500, and
the Puritan Bennett 840 Ventilator System (Medtronic, Ireland). These devices were
used due to availability rather than any technical reason. There was minimal difference
between the two devices. It may be problematic with other mechanical ventilators if
there is some sort of pseudo intelligence that attempts to account for differences in
compliance automatically, or if there is some attempt to rectify the lack of delivered
volume in subsequent respirations. Ventilation devices requiring a characterisation of
the respiratory circuit will possibly fail due to the increased compliance associated with
the increase in deadspace of the system.

10.3.1   SAFETY CONSIDERATIONS

During the process of customising ventilation, as discussed in Section 10.1.1, it is neces-
sary to monitor the characteristics in each patient's respiratory circuit. An external tool
can be used, inserted as physically close to the patient as possible in the respiratory cir-
cuit. Equally, there is provision for monitoring using the ACTIV system provided there
is a FPS in each of the patient's respiratory circuit, and the external interface screen.
For instructions on how to use the interface to read each of the sensors see Appendix
B.2.1.2.

During the balancing process it is necessary to mitigate the risk of causing a hyperin-
flation injury to the healthy patient. This outcome is achieved by always inducing an
external inspiratory pressure drop for the healthy patient prior to increasing the driv-

ing pressure of the ventilator. This approach always protects the healthy patient with higher compliance.

The chance of cross ventilation from one patient to the other is minimal. The use of one-way valves ensures that flow is only in the direction in Figure 10.1, preventing expired gasses from reaching the inspiratory circuit of the other patient. In the case of failure of a one-way valve, there is considerable deadspace to overcome for the expired breath to reach the shared components of the system. Furthermore, the use of HEPA filters as per Figure 10.1 minimises any potential contamination in the unlikely event of a failure of a one-way valve, and considerable expired volume. These HEPA filters should be replaced as per manufacturer recommendations. The risk of cross contamination between the two patients attached to the ACTIV system is thus minimal.

Unlike some proposed dual ventilation systems [509], the ACTIV system does not have a pressure release valve. Thus, there is no ability for the system to self regulate. Safety is made possible due to the ACTIV system maintaining realistic physiological circuits, and thus allowing continuation of oversight from the mechanical ventilator.

In contrast, the ventilator may not alarm if the PANDAPeep valve is tightened to the point of closure. Through experimentation, this alarming has been dependant on the ventilator and exact ventilation settings used, as some will not alarm if every second breath is still able to be delivered. This variability highlights the importance of continuing vigilance in patient monitoring, be it through the flow and pressure sensors, other

external monitoring systems, or clinical signs, such as effective chest rise and fall, and auscultation.

10.3.2 OTHER CONSIDERATIONS

One important aspect of making this design available is the recognition of the clinician-engineer relationship. The nature of the manufacturing process lends itself to engineers, rather than clinicians, manufacturing the device, exacerbated further by the nature of clinician workload evident throughout the pandemic. The system requires 3D-printing and printed circuit board assembly to complete, technologies which are typically not inherently accessible to clinicians. Therefore, adoption of the device is simplified by the existence of an already strong clinician-engineer relationship.

While this device has been developed specifically with the COVID-19 pandemic in mind, there are other potential uses. Obviously, any environment in which the limiting factor is a low number of mechanical ventilators, the device may be used to provide ventilatory support to a second patient without a need another mechanical ventilator. It is necessary to consider the separate pathologies at play, and thus the suitability given the potential expected physiological changes to the respiratory system. Given the increased workload associated with COVID patients in additional positional treatments and PPE, there benefits from using the ACTIV system on non-COVID patients to remove further added workload. Furthermore, in accordance to the requirement of using the device on deeply-

sedated patients only, selecting patients with a better understood disease progression allows clinicians to more easily achieve this outcome.

Another application where the device may see beneficial outcomes is in delivering independent lung ventilation. For patients suffering severe unilateral lung pathology, for example unilateral trauma or severe lung resection, or during thoracic surgery. While very well-resourced centres have the option of using two separate ventilators to provide individual therapy, under-resourced centres would benefit from the ability to provide dual ventilation therapy. The validation studies performed on *dual test lung setups* are very similar to this clinical use. However, inspiration is delivered to one lung and then the other, rather than the standard synchronised method.

10.4   Summary

The complete ACTIV system has successfully demonstrated the ability to safely provide mechanical ventilation to two patients from a single ventilator. The system presented in this manuscript provides a safe and customisable method for emergency use at relatively low cost.

The safest way to ventilate two patients from a single ventilator is not to do it. The ACTIV system is the next best way.

Chapter 11

Conclusions and future work

11.1 Conclusions

Healthcare in New Zealand is not equitable. This thesis discusses the background of medical innovation, including the pressures and time scales of innovation. Diabetes care globally and specifically in New Zealand is discussed, in particular the increasing inequities of access to care subsequent to the increase in personal healthcare expenditure evident in New Zealand. Two specific examples of best-care diabetes technologies are discussed: the insulin pump and the continuous glucose monitor. Access these technologies is inequitable, and sees overall low prevalence within New Zealand in general because of their expense.

Insulin pumps are devices able to semi-continuously infuse insulin, avoiding the need

for multiple daily injections — the current norm — which are painful, prone to human error, and thus poorly complied with. A comprehensive financial analysis is completed, discussing the net economic benefit of widespread adoption of insulin pumps. It is demonstrated that a pump available for $500NZD per device would see a net saving of $25M per annum should such a pump be made in a patch pump format — without the need for infusion sets.

Initial results for two potential open-source pumps are presented, one of which is a novel-spring powered design. Results comparable to current commercially-available insulin pump systems are presented, providing a proof of concept. The key design philosophy of this pump are the separation of the hardware from the computation, allowing control to be based in a cellphone or other secure, mobile, Bluetooth™-capable device.

The use of continuous glucose monitors within individuals with both type-one and type-two diabetes is proven to have considerable advantages, from objective measures of diabetes control, to improving individuals' interactions with their healthcare in terms of compliance and quality of life over invasive SMBG. The limitations are in the prohibitive expense of current devices, at $2500 − $5000 per annum, and the intentional inability of current devices to operate in conjunction with the other diabetes technologies for financial gain. Because the cost is associated with the non-tangible data, by releasing access to data through open-source or open-access design, the cost is significantly reduced. Conceptually, this is the transformation of the current data monopoly to a data market, where an increase in accessibility sees a decrease in cost.

A novel CGM prototype is summarised, where non-invasive light-based technology is used to estimate BG without the need for breaking the skin. This technology has significant potential in longevity and expense, with a conservative $1000 per device for 2-5 years. The initial results show comparable results to regulatory tests of other current commercial competitors. A complete economic analysis demonstrates that widespread adoption would see potential annual reduction in diabetes BG related expenditure of $25M.

Further benefits are seen in the adoption of a BG sensing devices with broad NSIO. At a personal level, the ULC insulin pump and the BOB CGM form the basis of the LEAPS. This control system would use digital twin technology to provide personalised healthcare in a substantially more productive manner than is currently achieved. The basis of this technology is the ICING-2 model system, with over 16 years deployment experience within ICU. Systemically, there are significant potential benefits in the ability for remote monitoring of individuals' diabetes, enabling significant productivity advantages within the stretched healthcare system.

An example of a short-term innovation to meet unprecedented increase of demand on ICU resources is the ACTIV system. Faced with unmeetable requirements for ventilated bedspaces, the bioengineering community at large saw numerous projects for open-source ventilators, and systems increasing the potential use of individual ventilators for multiple projects. The multiple-patient ventilation systems considered and discussed used a parallel ventilation sharing scheme, where inspiratory effort is delivered to all

patients simultaneously. Such systems are difficult to make sufficiently safe for the potential benefits to outweigh the risks in a clinically-viable manner.

The ACTIV system is a series ventilation system, where an actuated valve is utilised to alternately connect the mechanical ventilation device to one of two breathing circuits, allowing every second breath to be diverted to a second patient. Detailed design of the entire ACTIV system is presented, as is bench testing of the system. The subcomponents of the overall ACTIV system are designed to be able to manufactured in resource-poor locations, able to operate in the necessary specific physiological conditions, and be readily interoperable both mechanically and electrically. The flow and pressure sensor and the 3/2 switching valve in particular are designed for general use, enabling research and further open-source development within respiratory systems.

Changing physiological conditions is the greatest risk when considering providing ventilator therapy to two patients from a single mechanical ventilation device. Changes in lung compliance has potentially fatal consequences if the two patients are not adequately separated, as is the case in parallel ventilation sharing. The ACTIV system mitigates this risk by providing personalisation of therapy through the use of inline pressure-drop valves, and several flow and pressure sensors. Substantially physiologically-different pseudo-patients are able to have appropriate personalised ventilator therapy delivered through the ACTIV system.

This thesis brings the application of clinically-guided mechatronics innovation to increase equity within healthcare.

11.2   Future work

The next steps are largely in the continuation of innovation for adoption of the technologies presented in this thesis.

11.2.1   DIABETES TECHNOLOGIES

With initial validation of both the ULC insulin pump and the BOB CGM complete, comprehensive clinical testing is required. This testing comes after further design for ergonomics, and mass manufacturing processes. Continuation of developments presented in Section 4.3.4 are vital: the development of the insulin pump as a patch pump in order to increase potential adoption, and significantly reduce economic cost of widespread insulin pump adoption.

The continuation of modelling the SC insulin and oral glucose in individuals both healthy and with type-two diabetes would enable development of a comprehensive digital twin model for the realisation of an automated closed-loop insulin delivery platform. These developments require the continuation of close clinical support from diabetes clinicians, without whom this work is not possible. Development of initial enterprises to support widespread adoption is required, including discussions with Māori enterprises, and system-wide decision makers such as the Ministry of Health. The establishment of these relationships will ensure the best opportunity for uptake of the philosophy and devices.

The completion of the digital twin model working with hardware with broad NSIO would see the ability of major disruptive innovation in the delivery of healthcare to individuals with diabetes. Significant increases in efficiencies of the medical industry are possible, with those who currently face the greatest inequities of access to benefit the most. There is considerable engineering to be done to achieve these goals, primarily at information system levels.

11.2.2 DUAL VENTILATION

The ACTIV system provides a working example for safe deployment of multiple ventilation. Work to form a more cohesive product would see greater potential adoption. For example, a single physical unit which integrates the various components of Chapters 8 and 9, with direct access only to pertinent airway connectors, and the PANDA valves for adjustment of pressures. This integration would form a more cohesive, and more readily-accepted product for adoption. Further testing to explicitly compare the ACTIV system with those discussed in Chapter 7 would provide a sound academic argument for use of the system. Development could also be seen in the integration of a more sophisticated electronic subsystem for interface, for example, a Raspberry Pi-controlled touch screen with increased monitoring capabilities. This increased sophistication allows for more explicit monitoring, while maintaining balance of accessibility

Further validation and a more sophisticated design would allow for potential clinical trials of the device with patients. Outside of the context of extreme demand for venti-

lated ICU bedspaces, these trials should involve the use of one patient, and one physical

test lung, to maximise safety. These trials would enable easier provision of the ACTIV

system in the case of future potentially-overwhelming demand of mechanical ventilators.

Part IV

End matter

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Appendix A

Diabetes technologies

A.1   Pump pictures

Figure A.1: Prototype of the motor-driven pump design.

Figure A.2: Prototype of the spring-driven pump design

Inputs

Type	Number	Adopt Pump	Total Pump	Adopt CGM	Total CGM		From below	
							Net Saved	**Net Per Person**
T1D	26000	0.25	6500	0.2	5200		**10,780,018**	**39.96**
T2D	33800	0.1	3380	0.15	5070			
T2D No Insulin	210000	0		0.05	10500			
Portion eligible adopters:	0.17							

Pump:	- 99,015.41 -	10.92
CGM:	10,879,032.99	523.79

Insulin dependent type 2 - there are 200,000 more who only test and *could* adopt this CGM

Non-insulin dependent type 2 who would want easier measurement for better outcomes and care

Number T2D on insulin = https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/diabetes/

0.1 min for adopt pump T1D and 0.05 T2D as minimum now using and 0.1 for CGM for all but no insulin T2D as minimum now using

Direct Savings (to patients and health systems)

Savings from moving to ActRapid from Glargine Insulin

	CURRENT					Adopting Pump			
Type	TDD (Units)	Cost / Unit	Cost / Year / Person	Total Cost / Year Currently	TDD Reduction (%) with Pump	Cost / Unit (now ActRapid)	Cost / Year / Person	Total Cost / Year Adopting Pump	Savings / Year	Savings / Year / Person
T1D	50	0.046	836.46	5,436,979.17	0.1	0.0270	443.97	2,885,790.38	2,551,188.79	392.49
T2D	50	0.063	1149.75	3,886,155.00	0.1	0.0270	443.97	1,500,611.00	2,385,544.01	705.78

Assumes T1D use 50% Glargine and 50% Regular Insulin, while T2D use all Glargine (typical)

https://www.tandfonline.com/doi/full/10.1185/03007995.2011.599838?casa_token=OJ7qwbcnnqUAAAAA%3A4Ao9rkaWBcXLdTl-

10% reduction of TDD with pumps is conservative

Savings from moving from CGM to Light CGM or test strips to Light CGM - only for those currently using CGM

	CURRENT			Adopting light based CGM			
Type	Fraction Using CGM Now	Cost / Year / Person	Current Test Cost / Year	Cost / Year / Person	Cost Using Light-based CGM	Savings / Year	Savings / Year/ Person
T1D on CGM	0.15	2,607.14	2,033,571.43	250.00	195,000.00	1,838,571.43	2,357.14
T2D on CGM	0.05	2,607.14	660,910.71	250.00	63,375.00	597,535.71	2,357.14
T1D Test Strips		730.00	3,226,600.00			3,226,600.00	730.00
T2D Test Strips		730.00	3,516,045.00			3,516,045.00	730.00
T2D No Ins Strips		182.50	1,916,250.00			1,916,250.00	182.50

Assuming those T2D not on insulin only measure 1x EVERY OTHER day so uts strip cost by 4x -- up to 10 +/-9 per week in active users IVh9mNBIBGhNU1Pj0sWyzBqXqOBcoQmCqA6CV_i3aJWbk-1z-V9vQkw9lcI

T2D testing 1x per day for 43% of population, so 1x per day for half is ok too: https://link.springer.com/article/10.1186/1756-0500-3-318

Savings for those already on Pumps (T1D only - assume all who have will adopt)

	CURRENT								
Type	Fraction Using Pump	Cost / Device	Cost / Year / Person (4 yr life)	Current Cost / Year		Cost / Device	Cost / Year / Person (4 yr life)	Cost / Year with Pump	Savings / Year	Savings / Year/ Person
T1D	0.0983	9,000.00	2,250.00	5,750,550.00		500	125.00	591,028.75	5,159,521.25	198.44

Users who transition	0.95

	Total Savings	Total Savings / Year/ Person
	21,191,256.19	7,653.50

PHARMAC reported cost of glucose strip testing is $1/test or $730 pear year, while CGM is $50-100 / week but $50 used here - CGMs are not subsidised

Assumes a Light based CGM lasts 2 years, so $500 cost is $250/year ... this is conservative

TDD reduction with pump REF = Freckman et al, Journal of Diabetes Science and Technology2021, Vol. 15(4) 901–915

Pump:	10,096,254.05
CGM:	11,095,002.14

Indirect Savings (to health system and patients) - where admissions or costs change with glycemic control - amputations and hypos to come

Coronary Artery Disease Costs

#Admissions / Year	Cost / Adm	Current Cost / Year	#Admissions / Year	Cost / Adm	Cost / Adm if reach normoglycemia	Current Cost / Year	Savings / Year	Savings / Year/ Person
5430	10,407.00	56,510,912.30	5340	10,407.00	8,657.00	54,805,221.68	1,705,690.62	172.64

Reduction in Admissions w 10 mmol/mol reduction	0.1	% reaching normoglycemia	0.5

10 mmol/mol reduction in HbA1c reduces complications and thus complexity and thus cost / admission by 10% -- Jansen et al in NZMJ = Ethnic inequity in diabetesoutcomes—inaction in theface of need

50% can attain normoglycaemia, Freckmann 2021 JDST - normoglycemia is 40mmol/mol and median NZ HbA1c is 8.1-9.0% or 65-70 mmol/mol (Freckman et al) --> *Thus, a 10 mmol/mol reduction is modest long term*

Diabetic Ketoacidosis Costs

#Admissions / Year	Cost / Adm	Current Cost / Year	#Admissions / Year	Cost / Adm	Current Cost / Year	Savings / Year	Savings / Year/ Person
1508	3,397.01	5,121,142.58	1451	3,397.01	4,929,099.73	192,042.85	19.44

Reduction in Admissions w 10 mmol/mol reduction	0.15

Coppell, K.J., Drabble, S.J., Cochrane, J.A., Stamm, R.A. and Sullivan, T.A., 2019. The cost of diabetes-related hospital care to the Southern District Health Board in 2016/17.

Reduction in ketoacidosis value = Karges, B. et al., (2017) Associated of inulin pump therapy vs insulin injection therapy ….. JAMA, 318(14):1358-1366.

Diabetic foot amputations

#Amputations/ Year	Cost / Amputations	Current Cost / Year	# / Year	Cost / Adm	Future Cost / Year	Savings / Year	Savings / Year/ Person
793	38,555.00	30,574,115.00	727	38,555.00	28,048,427.24	2,525,687.76	97.14

Reduction in Admissions w 10 mmol/mol reduction	0.5

Cost per amputation from Joret et al., 2016 in Journal of Vascular Surgery *The Financial burden of surgical and endovascular treatment of diabetic foot wounds*

Reduction Hazard ratio 2.76 per 1% HbA1C from Goldman et al., 2018 in J Am Coll Surg - *Glycemic Control and Risk of Amputation*

Number of national amputations from Gurney et al., 2018 in ANZ J Surg - *Regional variation in the risk of lower-limb amputation among patients with diabets in New Zealand*

Hypoglycaemic episodes

#Admissions / Year	Cost / Adm	Current Cost / Year	#Admissions / Year	Cost / Adm	Future Cost / Year	Savings / Year	Savings / Year/ Person
3200	2,000.00	6,400,000.00	3033	2,000.00	6,065,449.57	334,550.43	104.55

Reduction in Admissions w/ pump control: **0.32**

Price is mean from Coppell for T1D admits, similar to the `other specific complaint' category
Rate is based on 13.9/100 pt years from Karges et al., 2017 - it is children to young adults only

T2D other costs associated with admissions

Number	Current Cost / Year / Person	Current Cost / Year LESS Major Costs above (who are Group 4 mostly)	Current Cost / Year / Person	Future Cost / Year - those above	Savings / Year	Savings / Year/ Person
9880	3000.00	13,348,545.85	2550.00	11,346,263.97	2,002,281.88	202.66

Reduction in REMAINING Cost w/insulin pumps: **0.15**

T2D 10% reduction in total costs with intensive SMBG like our CGM allows: https://link.springer.com/article/10.1186/1756-0500-3-318 AND https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074758/
Current cost of $3000 is average yearly cost of Group2 and Group 3 T2D in PWC Report for NZ

T2D w no insuiln and high SMBG cost reductions

Number	Current Cost / Year / Person	Current Cost / Year LESS Major Costs above (who are Group 4 mostly)	Current Cost / Year / Person	Future Cost / Year - those above	Savings / Year	Savings / Year/ Person
10500	3000.00	35,790,308.49	2700.00	32,211,277.64	3,579,030.85	340.86

Reduction in REMAINING Cost w/ regular SMBG: **0.1**

T2D 10% reduction in total costs with intensive SMBG like our CGM allows: https://link.springer.com/article/10.1186/1756-0500-3-318 AND https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074758/
Current cost of $3000 is average yearly cost of Group2 and Group 3 T2D in PWC Report for NZ

Hypos T2D per year incidence is 11.5-11.8 per 100 patient years:: https://care.diabetesjournals.org/content/26/4/1176 -- Leese et al, Diabetes Care 2003 or 0.115 pear year per patie
Cost of ED admission $525 at Counties Manukau, and upward from there with complexity: https://www.countiesmanukau.health.nz/for-patients-and-visitors/do-you-have-to-pay/

	Total Savings	Total Savings / Year/ ALL DIABETICS who use either
	10,339,284	497.80

Pump: 6,760,254
CGM: 3,579,031

ED Cost can be $2929.50 for admissions on MDPI article on Sheet 3, but $525 is lower

Direct Costs to implement

	Num new users	Cost / Year / Person	Annual added cost			Total New Costs	Total New Costs / Year / Person
New Pump users:	7324					20,750,523.00	375.00
Portion patch pumps:	0.00				Pump:	16,955,523.00	
					CGM:	3,795,000.00	
Cost of consumables for traditional pumpers:	7324	2190	16,039,998.00				
Cost of consumables for patch pumps:	0	608	-				
Cost of Extra Pumps for New Users	7324	125.00	915,525.00				
Cost of extra CGMs for New Users	15180	250.00	3,795,000.00				

Current user costs accounted for above in net savings in each case, so these are just added new costs

Net per year

						Net Total / Year	Net Total / Person / Year who use insulin or CGM
						10,780,018	351.71

	Savings	Cost
Pump:	16,856,508	16,955,523.00
CGM:	14,674,033	3,795,000.00

A.2   Closed-loop

Model-based Modified OGTT Insulin Sensitivity Test Design

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Abstract: Type 2 diabetes mellitus requires early, accurate, and efficient monitoring for best treatment. Current common diagnosis tools either test late-appearing symptoms, are low resolution, or are expensive in cost and time. A system of physiological models for the oral ingestion of glucose, subcutaneous injection of insulin, and glycaemic control, are used to generate a quantitative test for insulin sensitivity. The proposed test uses $35g$ of oral glucose, 2.0 units of rapid-acting insulin, and both intra-venous and finger-prick blood samples for insulin, C-peptides, and blood glucose levels frequently over a 2-hour period. The test is developed *in silico* to enable early and repetitive monitoring of the pathogenesis of type 2 diabetes. In conjunction with emerging technologies in insulin sensing and needle-free delivery and monitoring devices, there is a pathway with this test to provide more effective, efficient early diagnosis of diabetes risk.

Keywords: chronic diabetes care, physiological model, insulin, insulin sensitivity, OGTT

1. INTRODUCTION

Identification and monitoring of disease pathogenesis is essential to guide physicians' treatment options. The disease process of type 2 diabetes mellitus (T2D) is a chronic condition requiring regular monitoring for most appropriate treatment. As well as the chronic nature of T2D, the scale of the disease is also a factor increasing the necessity of efficient, accurate monitoring. A meta study of 751 studies that considered 4.4 million people showed that from 1980 to 2014 there was a global increase from 4.3% to 9.0% in the incidence of T2D. The global trend was not seen to be slowing (NCD Risk Factor Collaboration et al., 2016).

The pathogenesis of the disease, as can be seen in Figure 1, deviates from normal glucose tolerance (NGT) with a decrease in insulin sensitivity. This change is masked in the glycaemic control by an increase in the amount of insulin secreted by the pancreas. This stage is known as pre-diabetes, or impaired glucose tolerance (IGT). Because of the compensation of the pancreas, this aspect is not detected in measuring gross ability to control blood glucose levels (BGLs). As the disease progresses, the ability of the pancreas to create and secrete insulin saturates, and then decreases (Clark et al., 2001) causing the inability to regulate glucose, at which point T2D can be diagnosed.

The most common tests currently used for T2D are based on the ability to control blood glucose: either fasting BGL, or HbA1c, which is in essence a low-pass filter of BGL. The nature of these tests are unable to obtain quantifiable results for insulin secretion nor sensitivity, which are the key early-changing metrices. A more comprehensive test which specifically examines the post-prandial glucose is the oral glucose tolerance test (OGTT). The OGTT typically
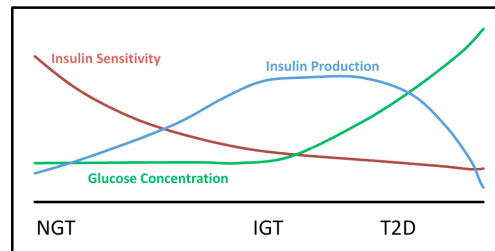
Fig. 1. Pathogenesis leading to type 2 diabetes mellitus (Docherty, 2011).

involves consuming 75g of liquid glucose, and taking blood glucose measurements at 0, 60, and 120 minutes. However, for early recognition of IGT as can be seen in Figure 1, either the insulin sensitivity or the amount of insulin secreted must be determined. Current common methods include giving the patient significant amounts of parenteral glucose or insulin, and then determining the rate of infusion of insulin or glucose, respectively, which results in a consistent BGL.

Insulin sensitivity is defined as the relative change of concentration of glucose due to uptake by skeletal muscle over a given time, for a given concentration of insulin.

Detection of pre-diabetes during the early IGT stage allows early treatment, which is achievable given a quantitative test for insulin sensitivity. For some time there has been evidence to suggest early treatment of pre-diabetics with insulin results in better outcomes, both in terms of cessation of the disease process and also reducing the inci-

dence of complications associated with diabetes (ORIGIN Trial Investigators and others, 2012).

To treat pre-diabetes, effective identification is required. The test protocol designed here attempts to create such a test to allow widespread testing at a minimal cost. Furthermore it would allow definitive information into the progression of the disease, leaving behind the contemporary 'yes-no-maybe' testing style most commonly used. The test proposed here is an oral glucose test with subcutaneous (SC) insulin. The addition of insulin provides a greater signal strength to distinguish between IGT with a low S_I, and IGT with a low endogenous insulin production, thus accurately diagnosing within pre-diabetes.

2. MODELLING

To model the entire system for the test, a gastrointestinal (GI) glucose model, a SC insulin delivery model, and glycaemic control model are combined. A graphical overview of this system can be seen in Figure A.1 — at the end of the paper for convenience.

2.1 GI modelling

The GI model system uses a three-compartment non-linear model with compartments q_{sto1}, q_{sto2}, and q_{gut}, the value of which represents the amount of glucose in each respective compartment (Dalla Man et al., 2006). Specifically, q_{sto1} and q_{sto2} represent the solid and the liquid stages of the stomach respectively, and q_{gut} the glucose which has passed into the intestines. The model is defined:

$$\begin{aligned}
\dot{q}_{sto1}(t) &= -k_{21} \cdot q_{sto1}(t) + D\delta(t) \\
\dot{q}_{sto2}(t) &= -k_{empt}(q_{sto}) \cdot q_{sto2}(t) + k_{21} \cdot q_{sto1}(t) \\
\dot{q}_{gut}(t) &= -k_{abs} \cdot q_{gut}(t) + k_{empt} \cdot q_{sto2}(t) \\
Ra(t) &= f \cdot k_{abs} \cdot q_{gut}(t)
\end{aligned} \tag{1}$$

In Equation Set 1, k_{21} is the rate constant of grinding, D the amount of glucose ingested, δ the dirac delta, k_{abs} the rate at which glucose is absorbed from the gut into the blood stream, Ra is the rate at which glucose appears in the blood stream, and f a scaling factor which accounts for incomplete absorption and first-pass hepatic clearance. The rate at which the stomach empties into the gut — k_{empt} — is a function of the total amount of remaining glucose in the two stomach compartments relative to D, defined:

$$\begin{aligned}
k_{empt}(q_{sto}) &= k_{min} + \frac{k_{max} - k_{min}}{2} \cdot \{tanh\big[\alpha(q_{sto} - b \cdot D)\big] \\
&\quad - tanh\big[\beta(q_{sto} - c \cdot D)\big] + 2\} \\
q_{sto}(t) &= q_{sto1}(t) + q_{sto2}(t) \\
\alpha &= \frac{5}{2 \cdot D \cdot (1 - b)} \\
\beta &= \frac{5}{2 \cdot D \cdot c}
\end{aligned} \tag{2}$$

The constants b and c are defined as the points at which k_{empt} intersects k_{mean}; the mean of k_{max} and k_{min}.

The non-linear behaviour of Equation Set 2 can be seen graphically in Figure 2. Because the test developed here uses only glucose dissolved in liquid, the grinding constant $k_{21} = 1$ bypasses the solid phase.
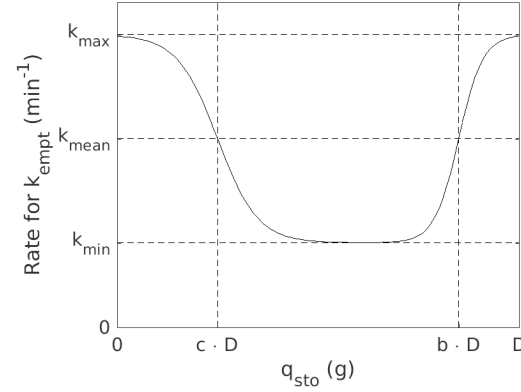
Fig. 2. Depiction of k_{empt} as a function of q_{sto}.

2.2 SC insulin model

Because the SC insulin used in the test is a monomeric preparation, the model is simplified from other insulin formulations (Wong et al., 2008) to only two compartments; the subcutaneous space into which the insulin is injected — I_{SC} — and the local interstitium Q_{local}. It is important to note the local interstitium is a separate compartment from the interstitium within the glycaemic control model. There is a small amount of breakdown within the local interstitium prior to being absorbed into the bloodstream, but it is assumed the local interstitium is sufficiently small to be negligible in glucose uptake. Mathematically, the governing equations are defined:

$$\begin{aligned}
\dot{I}_{SC}(t) &= -k_2 \cdot I_{SC}(t) + \delta(t - T) \cdot I_{bolus} \\
\dot{Q}_{local}(t) &= -k_3 \cdot Q_{local}(t) + k_2 \cdot I_{SC}(t) - k_{di} \cdot Q_{local}(t)
\end{aligned} \tag{3}$$

Where k_2 is the rate constant defining the diffusion from the SC space into the local interstitium, T the time the insulin is given relative to the start of the test, I_{bolus} the amount of insulin injected, k_3 the rate constant defining the insulin being absorbed into the plasma, and k_{di} the breakdown of insulin in the local interstitium.

2.3 Glycaemic control model

The inputs from both the oral glucose and SC insulin models are subsequently handled by the glycaemic control model (Lotz et al., 2008). The glycaemic control model as shown in Equations $4 - 6$ takes into account glucose uptake both mediated by insulin and not, and insulin secretion and uptake. It incorporates compartments for plasma glucose, G, plasma insulin, I, and interstitial insulin, Q, and is defined:

$$\dot{G}(t) = -p_g \cdot (G(t) - G_{fast}) - \frac{S_I \cdot G(t) \cdot Q(t)}{1 + \alpha_G \cdot Q(t)} + \frac{Ra(t) + EGP - CNS}{V_G} \quad (4)$$

$$\dot{I}(t) = -n_K \cdot I(t) - n_L \cdot \frac{I(t)}{1 + \alpha_I \cdot I(t)} - n_I \cdot (I(t) - Q(t)) + \frac{k_3 \cdot \dot{Q}_{local}(t) + (1 - x_L) \cdot u_{en}(G)}{V_I} \quad (5)$$

$$\dot{Q} = n_I \big(I(t) - Q(t) \big) - n_c \cdot Q(t) \quad (6)$$

Where in Equation 4, p_g is the non-insulin mediated uptake, G_{fast} is the fasting BGL, S_I is the insulin sensitivity, EGP is the endogenous glucose production, CNS the glucose consumption attributed to the central nervous system, and V_G the volume of distribution of glucose, and α_g the insulin binding saturation constant. EGP is iteratively solved such that at $G(t) = G_{fast}$, and with no exogenous glucose nor insulin, the system is in steady state. In Equation 5, n_K is the renal insulin clearance, n_L the hepatic insulin clearance rate, α_I the hepatic clearance saturation constant, n_I the trans-endothelial diffusion rate between the plasma and interstitial compartments, x_L the first pass constant as endogenous secretion, u_{en}, is secreted into the portal vein, and V_I the volume of distribution of insulin. In Equation 6 n_c is the insulin degradation rate.

Endogenous insulin secretion by the pancreas is modelled as a simple limited, proportional response depicted in Figure 3, and defined:

$$u_{en}(G) = \begin{cases} u_{min}, & \text{for } G(t) \leq G_{fast} \\ f(G), & \text{otherwise} \\ u_{max}, & \text{for } f(G) \geq u_{max} \end{cases}, \quad (7)$$

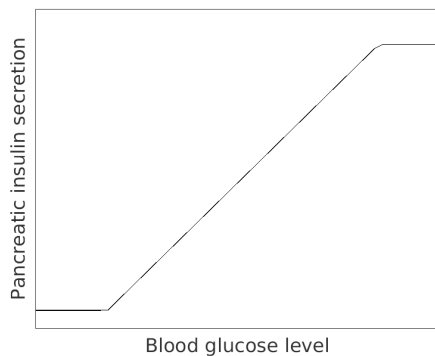$$f(G) = k_{sec} \cdot G(t) + k_{offset}$$

Fig. 3. Endogenous pancreatic release as a function of the blood glucose level.

As C-peptide and insulin are secreted in equimolar quantities, the the rate of secretion of C-peptide can be directly ascertained from Equation 7.

Units and example values parameters in Equations 1 - 7 can be seen in Table 1.

Table 1. Values used for the forward simulation of NGT, IGT, and T2D subjects. Sources: (1) - Dalla Man et al. (2006), (2) - Wong (2008), (3) - Lotz et al. (2008), (4) - Docherty (2011), (5) - Pretty (2012). Note A: Test design parameters. Note B: Measured. Note C: Solved for in steady state.

Parameter	Value	Units	Source
Gut			
k_{21}	1.0	min^{-1}	(1)
D	35	g	A
k_{abs}	0.205	min^{-1}	(1)
b	0.85	-	(1)
c	0.25	-	(1)
k_{max}	0.043	min^{-1}	(1)
k_{min}	0.013	min^{-1}	(1)
SC Insulin			
k_2	0.0104	min^{-1}	(2)
k_3	0.060	min^{-1}	(2)
T	15	min	A
I_{bolus}	2000	mU	A
k_{di}	0.006	min^{-1}	(2)
ICING			
p_g	0.04	min^{-1}	(3)
G_{fast}	4.8	$mmol \cdot L^{-1}$	B
S_I	10.8	$10^{-4} L \cdot (mU \cdot min)^{-1}$	(4)
	6.9	IGT	
	3.1	T2D	
EGP	0.96	$mmol \cdot min^{-1}$	C
CNS	0.30	$mmol \cdot min^{-1}$	(3)
V_G	12.2	L	(3)
α_G	0.0154	min^{-1}	(3)
n_K	0.060	min^{-1}	(3)
n_L	0.0324	min^{-1}	(3)
α_I	0.0017	$L \cdot mU^{-1}$	(3)
n_I	0.006	min^{-1}	(3)
x_L	0.67	-	(3)
n_c	0.032	min^{-1}	(3)
V_I	4.0	L	(3)
u_{min}	16.7	$mU \cdot min^{-1}$	(5)
u_{max}	267	$mU \cdot min^{-1}$	(5)
k_{sec}	14.9	$mU \cdot L \cdot (mmol \cdot min)^{-1}$	(5)
	25	IGT	
	4.1	T2D	
k_{offset}	-50	$mU \cdot min^{-1}$	(5)
	-75	IGT	
	-13	T2D	
Initial			
q_{sto1}	D	g	A
q_{sto2}	0	g	
q_{gut}	0	g	
I_{SC}	0	mU	
Q_{local}	0	mU	
G	G_{fast}	$mmol \cdot L^{-1}$	B
I	15	$mU \cdot L^{-1}$	B
Q	9	$mU \cdot L^{-1}$	C

3. RESULTS

Combining these models and using the parameters and typical parameter values defined in Table 1, a forward simulation can be carried out for the consumption of a sugary drink and the injection of small amount of SC insulin. The results of the simulation done using numerical integral methods can be seen in Figure 4. These are done with variance in the species with greatest clinical relevance for the pathogenesis of T2D.
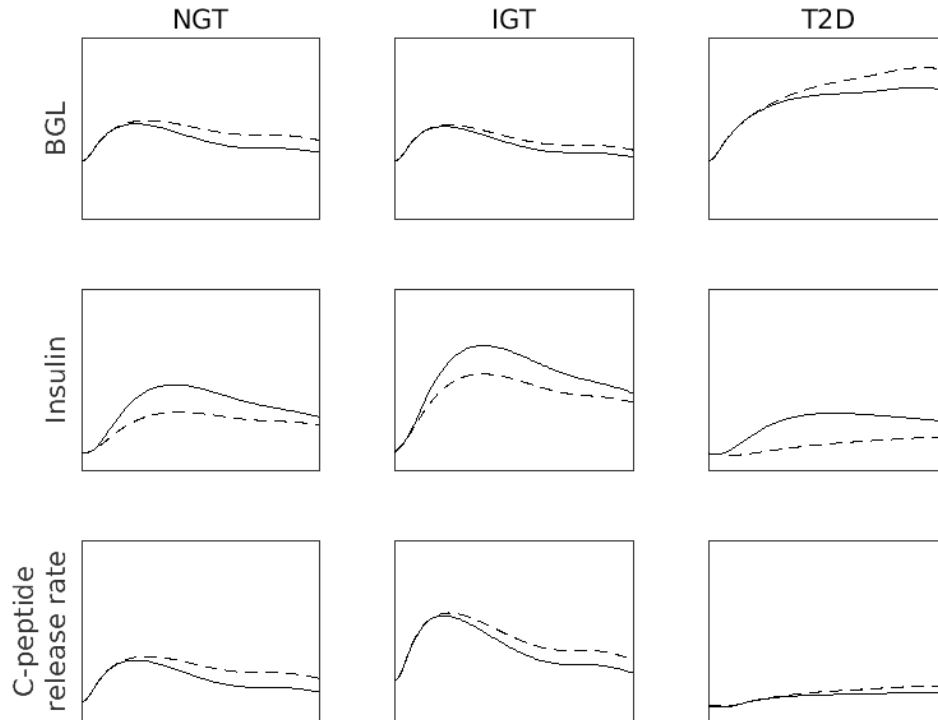
Fig. 4. Simulated comparison of the 35*g* OGTT (dashed line) with the modified test (solid line), in each of blood glucose levels, plasma insulin concentrations, and rate of C-peptide release as function of time, over a period of 120 minutes. The test is demonstrated for participants each with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes.

4. CLINICAL TRIAL

From analysis of literature for a range of parametric values a test for determining insulin sensitivity is proposed using the physiological model defined here. The test is similar to both the OGTT, and the more recently-developed DISTq (Docherty et al., 2013). The test differs from the OGTT in that instead of simply measuring BGL at time 0, 60, and 120 minutes, the BGL is done at a higher frequency throughout the 120 minutes, and insulin and C-peptides are also assayed. It differs from DISTq in that the glucose is delivered enterally and the insulin subcutaneously, and due to much slower appearance rates must therefore be conducted over a longer period of time.

Based on the results from forwards simulations such as those presented in Figure 4, an initial experimental test protocol was designed. This protocol involves ingesting 35*g* of dissolved glucose at time $t = 0$, followed 15 minutes later by a 2.0 units of rapid-acting monomeric insulin delivered via SC injection. Intra-venous blood species monitoring includes C-peptides taken intra-venously at $t = 0, 20, 40, 50, 60, 90, 120$, and point of care BGL tests at $t = -15, 0, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120$. This protocol has been selected because it allows the examination of variability of glucose and insulin appearances, in addition

to overall model validity. The data will also provide a proof-of-concept for the ability to quantify insulin sensitivity.

An application for a clinical trial to perform the test *in vivo* is currently before the University of Canterbury Human Ethics Committee. This will obtain data from up to 20 healthy subjects and 5 with an existing diagnosis of pre-diabetes or T2D. This will allow the results of the test to be demonstrated over a range of the pathogenesis of T2D. Information from this initial study will also future protocols with significant downsampling to be determined.

5. DISCUSSION

Figure 4 shows the *in silico* simulation responding appropriately to both the glucose and insulin. As true to Figure 1, the glucose-alone responses for both NGT and IGT are similar. However, the addition of the exogenous insulin has a greater impact with NGT, as there is still a higher insulin sensitivity compared to IGT. T2D sees a characteristically poor glucose response due to both low insulin sensitivity and secretion. As per Starling's curve (Clark et al., 2001), the insulin secretions in IGT are greater than NGT, and in T2D are very low. Overall, insulin secretion is lower for all stages of pathogenesis with the addition of exogenous

insulin. This outcome is not due to any explicit insulin suppression within the model, but instead because $u_{en}(G)$ is proportional to $G(t)$. Therefore the lowered BGL due to the action of the exogenous insulin implicitly suppresses the endogenous system. The expected C-peptide secretion rates echo this reduction of insulin secretion for each of NGT, IGT, and T2D.

By combining these models a system which estimates the principal physiological systems pertaining to glucose control, and which are affected by the pathogenesis of T2D, has been created. The individual models have all been validated independently and together through forward simulation provide results within the range of human variability, but have not been validated as one coherent system beyond *in silio* testing. Prior to the continuation of development and refinement of the test this will be done from the data obtained in the clinical trial.

There are some small, undeniable risks associated with delivering 2.0U of rapid-acting insulin. A Monte Carlo analysis has been completed over a range of reasonable physiological parameters which shows a low risk of hypoglycaemia associated with the trial. Furthermore, due to the high frequency of sampling, this will always be detected in the very early stages of hypoglycaemia.

Initially, the test will enable early diagnosis of IGT, at a resource cost somewhat greater than the OGTT. However, refinement resulting from initial trials is expected in the form of reduced sample points, confirmed safety, and a shorter test period. With advancements in insulin assay technology the cost will continue to decrease compared to the normal OGTT. The cost will only decrease with all of these refinements, and could conceivably become only slightly more expensive than the OGTT. These improvements will allow early and continuous monitoring of the disease process, and thus enable early treatment, improving patient outcomes at a lower cost to healthcare systems.

Beginning the development and refinement of this test now will allow for considerable advances with the development of other technologies. As point-of-care insulin sensing becomes more accessible (Malkoc et al., 2017), the test will be well poised to provide rapid quantifiable information about the pathogenesis of T2D. Another near-future technology which will empower the test is a needle-free insulin delivery mechanism (Ruddy et al., 2017). This would be especially powerful when combined with an automated, needle-free, point-of-care BGL sensor (Chang et al., 2015). Combining all of these technologies this test would potentially culminate into a fully-automated quantitative test for insulin sensitivity.

6. CONCLUSIONS

By combining GI, SC insulin, and internal insulin and glucose systems, a succinct model for type 2 diabetes has been developed. This system is powerful in its ability to aid both diagnosis and treatment of diabetes. The insulin sensitivity test developed will allow accurate and efficient monitoring of the pathogenesis of diabetes, and combines well with emerging technologies to further advantage it.

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Appendix A. GRAPHICAL DEPICTION OF THE MODEL SYSTEM
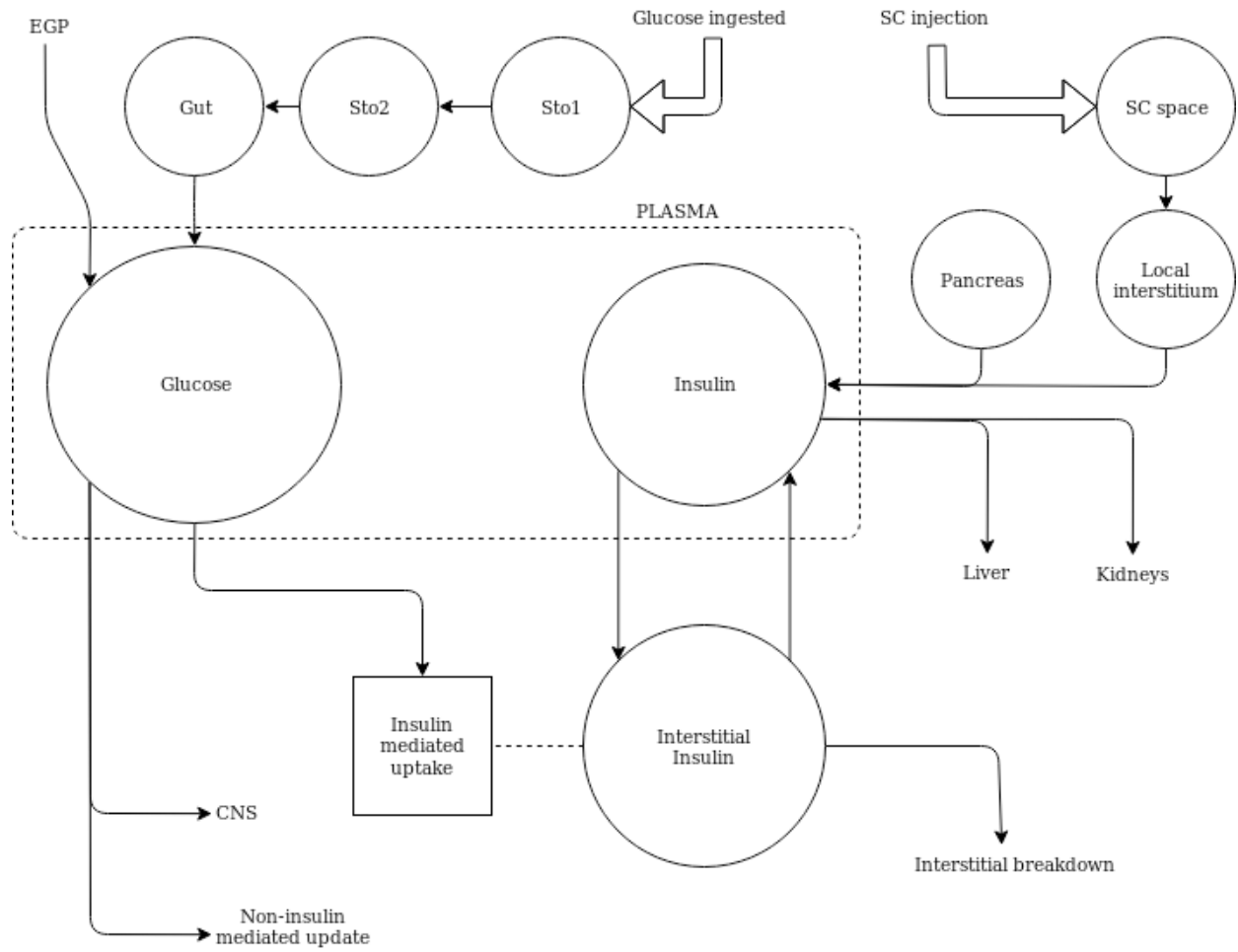
Fig. A.1. Overview of the computational models combined to form the system. Sto1, Sto2, and Gut compartments are controlled by the GI model, the SC space and local interstitium by the SC insulin model, and the glucose and both plasma and interstitial insulin compartments by the glycaemic control models.

A.2.1   APPROVED ETHICS CONFIRMATION AND INFORMATION SHEET

HUMAN ETHICS COMMITTEE

Secretary, Rebecca Robinson
Telephone: +64 03 369 4588, Extn 94588
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2018/03

30 April 2018

Lui Rivers Holder Pearson
Mechanical Engineering
UNIVERSITY OF CANTERBURY

Dear Lui

The Human Ethics Committee advises that your research proposal "Model-Based Modified OGTT for Insulin Sensitivity Test" has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your emails of 22nd February and 20th April 2018.

Best wishes for your project.

Yours sincerely

pp. R. Robinson

Professor Jane Maidment
Chair
University of Canterbury Human Ethics Committee

Telephone: +64 27 998 3298 (Lui Holder-Pearson)
                 +64 3 369 2182   (Geoff Chase)

Email: lui.holderpearson@pg.canterbury.ac.nz
            geoff.chase@canterbury.ac.nz

Model-based Modified OGTT Insulin Sensitivity Test

INFORMATION SHEET FOR PARTICIPANTS

My name is Lui Holder-Pearson, and I am working towards a PhD at the University of Canterbury within the Mechanical Engineering Department, and I would like to invite you to be a participant in my study to validate a novel medical test.

My aim is to develop a new, more accessible test for diagnosing diabetes and pre-diabetes within the umbrella of type 2 diabetes. This test is similar to the oral glucose tolerance test, in which the participant drinks a sugary drink and then has finger-prick blood samples done at 0, 60, and 120 minutes. My test is similar to this in that it involves drinking a sugary drink, but it is then followed shortly by having a small amount of insulin injected into the skin. To gather data, I will take blood samples to measure plasma insulin and C-peptide levels, as well as the finger-prick blood samples to determine blood sugar levels.

As is shown in the chart at the end of this page, the test specifically involves:

1. You will have the option of wearing up to three continuous glucose monitor (CGM) devices prior to the test. These are small devices which sit just on your stomach and have a tiny filament which sits under your skin, and are fully waterproof. If you are interested in this option, please see the additional CGM information sheet.

2. Prior to the test:

   • You will be required to fast for the 10 hours immediately prior to starting.

   • Your height, weight, and age will recorded, as will one finger-prick blood sample test 30-60 minutes prior to starting.

3. During the test you will be given:

   • a drink containing 35 grams of glucose dissolved in 200mL of water at the beginning of the test. This is equivalent to the amount of sugar in a 330mL can of Coke.

   • a dose of insulin into your abdomen fifteen minutes after the sugary drink. This will be delivered in the same manner as diabetics take their insulin. The amount of insulin will be 2.0 units, which is less than recommended for this amount of glucose. This will either be given through a needle-based delivery method, or with a needle free injection method.

4. The Monitoring throughout the test involves:

   • finger-prick blood tests will be done at time points 0, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120 minutes. A finger-prick test is where a very small needle is very

briefly inserted into the skin, which allows a drop of blood to be collect on the surface of the skin. A small piece of plastic is then inserted into the drop of blood to measure the sugar concentration. These tests will be done by me.

- blood samples taken through an intra-venous catheter;

  ◦ These will be taken at time points -30, 0, 5, 10, 20, 40, 50, 60, 90, and 120 minutes, for a total of ten small blood samples, each 8.0mL, will be drawn, totalling less that 100mL of blood over 120 minutes. For comparison, a standard blood donation is 470mL over a period less than 15 minutes.

  ◦ The intra-venous catheter for taking the blood samples will be inserted by an experienced clinician under the same same practice principles employed in hospitals. Similarly, the blood samples will be drawn only by an experienced clinician.

  ◦ The blood samples are sent to Canterbury Health Laboratories to be tested. The specific tests done are to determine the concentration of glucose, insulin, and C-peptide, which is a protein released when insulin is created by the body.

5. After the test is completed:

- you will be given a soft drink and a biscuit, and if you feel unwell you will be welcome to be continue being monitored for another hour.

- If you chose to have a CGM inserted it will be removed after the test has finished.

The test will be conducted under the medical direction of Dr Geoff Shaw MBChB, FANZCA, FCICM, Hon FIPENZ. In addition to being a senior consultant intensivist at Christchurch Hospital with over 30 years of practising experience, Dr Shaw is an academic with the Universities of Otago and Canterbury.

The test itself is conducted over a period of less than three hours, with up to an additional hour should you choose to opt into the continuous glucose monitoring aspect of the test.

There are some minor risks with the intra-venous catheter and finger-prick blood glucose tests; risks identical to the risks when donating blood. These risks are minor, and include irritation around the site of catheterisation and finger-prick tests, and a very minor risk of infection, although the procedures are conducted to the same level of sterility as used in hospitals. There is some pain associated with the insertion of the intra-venous catheter, and minor pain associated with the finger-prick blood tests.

Because you will be receiving insulin, there is a very small risk that you will experience the effects of having low blood sugar levels. Thes.e include sweating, mild shaking, dizziness, hunger, headache. This risk has been minimised because the amount of insulin being used is very low for the amount of sugar you are given, and the very frequent blood sugar testing will mean that it is detected early on. **If you feel unwell or, are concerned about this at any stage, please tell the researcher immediately. We will take immediate action to recognise and treat hypoglycaemia.**

Participation in the test is totally voluntary, and if at any point you want to stop the test for any reason you are free to do so any time you want, without penalty.

You will be assigned a number when undertaking the test, and all information will be stored against this number. Your identifying data will only be accessible by me and my supervisors.

The non-identifying data gathered from this study may be published in scientific journals, presented at conferences, and will be presented as a part of my PhD thesis which will be publicly available through the University of Canterbury library. Furthermore, the non-identifying data may be used for future projects within the bioengineering department of Mechanical Engineering, such as to validate other models pertaining to type 2 diabetes.

Data will be stored on an encrypted drive on a secure computer on the University of Canterbury campus. Data will be kept for 10 years and then destroyed.

If you have any questions about the study, please contact me (details above), or my senior supervisor Geoff Chase (details above).

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee, and participants should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz)

If you would like to take part in this study, please fill out the attached consent form.

Yours sincerely,

Lui Holder-Pearson

Model-based Modified OGTT Insulin Sensitivity Test

Test Protocol

Study time, minutes
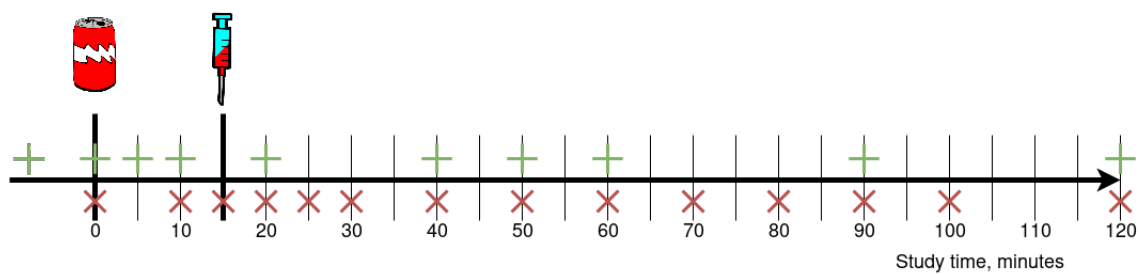
Key

35 grams glucose

2 units insulin

IV blood sample

finger-prick sample

Lui Holder-Pearson:
lui.holderpearson@pg.canterbury.ac.nz

Appendix B

ACTIV

B.1 ACTIV Introductory appendices

Table B.1: Specific reasons against the use of ventilators for multiple patients, and the safe mitigation of each reason. The wide range of valid criticisms from the consensus statement [9] are individually addressed in the context of a series ventilation approach. *VC* volume-controlled, *PC* pressure-controlled ventilation, *PEEP* positive end-expiratory pressure, *PIP* peak inspiratory pressure, V_t tidal volume. Recreated with permission from [11].

Consensus statement critique	Mitigation by use of serial ventilation approach

Volumes would go to the most compliant lung segments.	Serial breathing ventilates a single lung at a time, and thus, using a volume-controlled (VC) mode, lung compliances are not 'mixed' and do not create this same, critical problem. A pressure controlled (PC) mode will also be separated. Critically, in all modes, each lung responds individually to the inputs.
Positive end-expiratory pressure, which is of critical importance in these patients, would be impossible to manage.	PEEP can be individually set using PEEP valves on the expiratory circuit and putting PEEP = 0 on the ventilator. These valves are commonly available and some come with multiple settings. Thus, PEEP may also be individualised.

Monitoring patients and measuring pulmonary mechanics would be challenging, if not impossible.	Patients are split in serial breathing so inspiration does not overlap, and any monitoring present would monitor each inspiratory portion (at least) separately. Monitoring mechanics would depend on the ventilator interface and monitoring algorithms used, thus the displayed patient-specific parameters would be averaged. However, clinicians could still examine breath by breath waveforms or PV loops. PIP or Vt alarm limits could still be used as these are based on safety settings determined for a population of patients, rather than individual patients. Again, these outcomes are enabled by separating inspiration for both patients.
Alarm monitoring and management would not be feasible.	See above, again by separating patient inspiration segments in serial ventilation this issue is mitigated.

Individualised management for clinical improvement or deterioration would be impossible.

PC driving pressure and VC tidal volume would have to be the same as ventilators currently do not have the capability to enable alternating breath settings. Clinical judgement would determine which one of the ventilation is most appropriate for this situation. Where there are significant differences in compliance, a volumecontrolled mode may be preferable. However, PEEP would be individualised via separate PEEP valves. These PEEP valves could also be made active if desired, or set manually similarly to changing PEEP on a ventilator, but for each patient.

In the case of a cardiac arrest, ventilation to all patients would need to be stopped to allow the change to bag ventilation without aerosolizing the virus and exposing healthcare workers. This circumstance also would alter breath delivery dynamics to the other patients.

In this case, the patient still on the ventilator can be restored to a 1 patient, 1 ventilator standard use, after the other patient is disconnected.

Alternatively, a rubber bag (test lung) could be swapped in while the arrested patient is being hand ventilated during CPR. This would not involve having to make changes to the ventilator settings, which would create cognitive overload in the event of a cardiac arrest.

The added circuit volume defeats the operational self-test (the test fails). The clinician would be required to operate the ventilator without a successful test, adding to errors in the measurement.

Additional external monitoring would be required. The ventilator monitors the average pressures and volumes.

Self-testing can be carried out in the usual manner. There is no added circuit volume as individual breaths are within usual physiological limits and therefore not vulnerable to errors of extrapolation created by connecting patients in parallel.

In serial breathing, each breath would be presented. The clinician would have to know to identify each patient by examining their breathing directly, to know which waveform or PV loop corresponds to a particular patient.

Even if all patients connected to a single ventilator have the same clinical features at initiation, they could deteriorate and recover at different rates, and distribution of gas to each patient would be unequal and unmonitored. The sickest patient would get the smallest tidal volume and the improving patient would get the largest tidal volume.

Since each patient is separated, there is less need for matching compliance or resistance, the latter of which would be similar. Specifically, for the following: PC: driving pressure would have to be the same. However, a resistor with known pressure drop can be added to one of the two inspiratory circuits to reduce driving pressure for one patient. Tidal volume alarming would still be feasible and ventilator controlled to avoid injury or damage.

VC: tidal volume would be the same for both patients, where we would recommend setting tidal volume for the smaller of two patients in ml/kg; however, a vast difference could be problematic requiring some light matching by approximate size. PIP alarms and limits would still be applicable and ventilator controlled.

The greatest risks occur with sudden deterioration of a single patient (e.g. pneumothorax, kinked endotracheal tube), with the balance of ventilation distributed to the other patients.

Patients are ventilated separately so changes in patient condition, resulting in tidal volume changes (during PC) or peak pressure changes (during VC) would be notable on the monitor and ventilator set limits and alarms would still work be useful.

Finally, there are ethical issues. If the venti-
lator can be lifesaving for a single individual,
using it on more than one patient at a time
risks life-threatening treatment failure for all
of them.

The best way to ventilate 2 patients on 1 ven-
tilator is not to do it! Given the exigency of
no other alternative, we propose this method
is currently the next best way.

B.2 ACTIV components

B.2.1 USER INTERFACE

B.2.1.1 ACTIV CONTROLLER INSTRUCTION SET

Table B.2: Available instructions for the control module over serial.

Cmd		Example	Description
f		f5	[f]requency: Set the period of the software loop (ms). It is recommended to not change this unless experimentally.
p		p10	[p]rint period: Set how often output information is printed (multiples of loop period as defined above).
i		i0	[i]gnore pressure: Binary switch - if equal 1 will require pressure to be zero before switching.
w		w6000	set [w]atchdog: Watchdog timer value (ms).
s		s0	set [s]erial: Serial printing to the screen module (binary switch). NOTE: THIS WILL PREVENT OTHER FORM OF COMMUNICATION WITH THE CONTROL SYSTEM.
g		g0	[g]raphing source: Selects the sensor for the source of the [s]erial data printing to the screen module.

	0		Inspiratory
	1		Left
	2		Right
	3		Expiratory
d		d500	set [d]elay: Sets the delay between switch being indicated and actually switching (ms).
l		lc90	servo [l]imit: Sets the corresponding servo limit from 0-180. The closed limits must be less than the open limits.
	a		left closed
	b		left open
	c		right closed
	d		right open
t		t	[t]une servo: THIS STOPS FUNCTION OF THE CONTROL SYSTEM. Allows tuning of the servo motors only for experimental determination of the limtis of servo travel. Will use the in-built potentiometer on A7. Will end either on use of button on input pin 2 or automatically after 20s.
q		qw	[q]uery: Request one of the following values:

| | d | | [d]elay (ms): Delay after switching is indicated until switching is actually done. |
	w		[w]atchdog timer value (ms)
	i		[i]gnore pressure status (0/1)
	p		[p]rint period (multiples of loop period
	f		[f]requency of software loop: actually period (ms)
o		od	[o]utput settings: Specifies the format for data
	d		[d]ata: Prints buffered data without meta data. Use this output data for use with the provided analysis code.
	b		[b]asic: Prints last; mean; and variance of each sensor.
	v		[v]erbose: Prints the full buffers and min; mean; and max.
	l		[l]ong: Prints both basic and verbose.
	n		[n]one: No output printing.
?		?	Help: Shows available commands and sets output settings to [n]one.
[other]		e32	

B.2.1.2 GUI USE
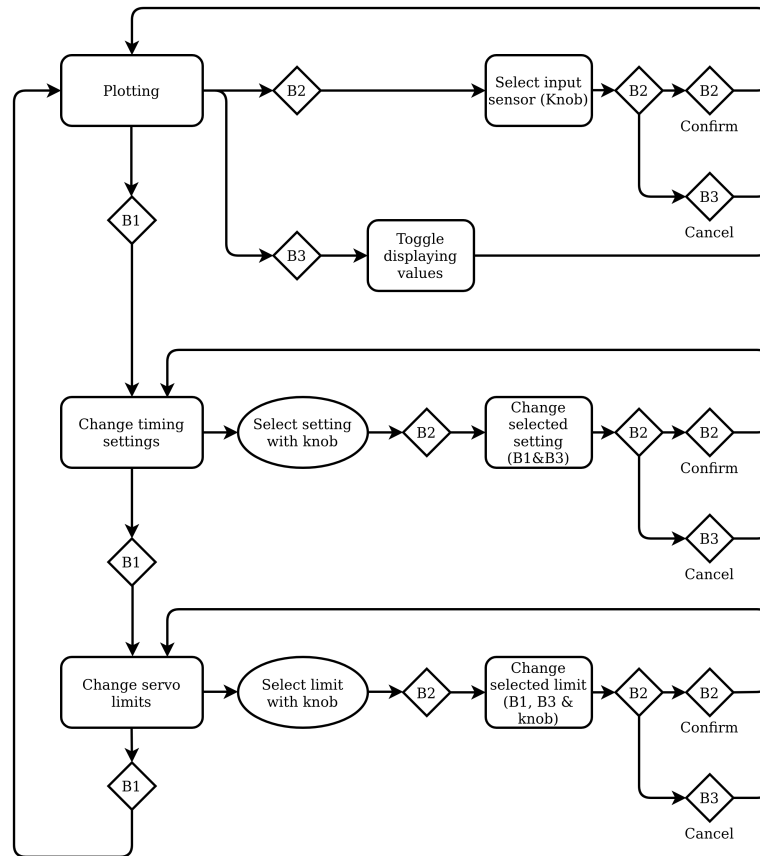
Figure B.1: State diagram and instructions for use of the interface for plotting and sending commands to the system controller.
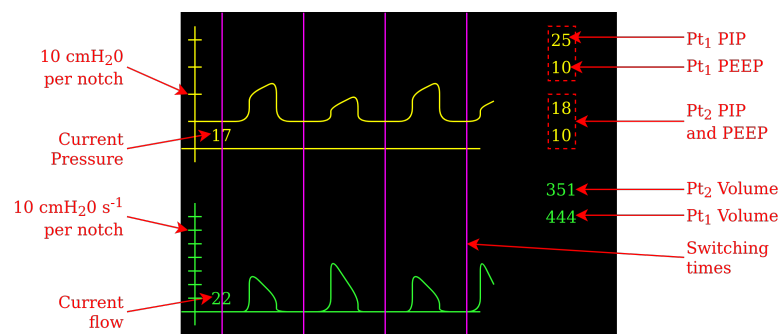

Figure B.2: Explanation of the screen layout when in plotting mode.

B.2.2 SENSOR PAPER

Physiologic-range flow and pressure sensor for respiratory systems

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ARTICLE INFO

ABSTRACT

A low-cost but reliable flow and pressure sensor is an impediment to development of medical equipment, and studies of human respiratory function, which is characterised by relatively low pressures and flows. A Venturi tube ($D_1 = 15\ mm$, $D_2 = 10\ mm$) connected to a differential pressure sensor (SDP816-125 Pa) allows accurate measurement of flow between $5 - 75\ L \cdot min^{-1}$, with Pearson Correlation over 4 min at 50 $Hz \geqslant 0.97$, and distance correlation $\geqslant 0.96$. The pressure measurement was similarly accurate using a MPVZ4006GW7U. Both sensors provide an analogue output from a 5.0 V supply, aiding compatibility and customisation. Each populated PCB costs approximately \$50USD, and each Venturi sensor costs approximately \$1USD. Multiple configurations exist, allowing flow rates up to 250 $L \cdot min^{-1}$, increased resolution for specific ranges, and different physical characteristics.

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Specifications table:

Hardware name	ACTIV flow and pressure sensor
Subject area	• Mechanical Engineering
	• Biomedical Engineering
	• Medical sensor
Hardware type	• Clinical Tool
	• Flow and pressure sensor
	• Ventilator or CPAP applicable
Open source license	Creative Commons Attribution-ShareAlike 4.0
Cost of hardware	\$50USD initially, ~\$1USD for sterilisable sensors
Source file repository	https://doi.org/10.17605/osf.io/bre5f or registered: https://doi.org/10.17605/osf.io/uce2h

1. Hardware in context

This device allows measurements of flow and pressure in physiological ranges for natural and assisted respiration. This relatively low range lends itself to respiratory research, and development of novel medical treatments without the necessity

for substantial cost associated with a traditional flow and pressure sensor. For example, an off-the-shelf product such as the Sensirion SFM3300-250 (Sensirion AG, Switzerland) is either US$41.80 for a single-use version, or US$179.20 for one which can be autoclaved. While the device presented here has a smaller range, and less precision across sections of the range, it provides an effective, low-cost foundation for respiratory research, as well as further development of other specific applications or requirements.

Having access to a cost-effective, readily-assembled device which is well characterised and validated would enable considerable development of open source hardware. During the COVID-19 pandemic many open-source hardware solutions were developed in the respiratory therapy space, for example mechanical ventilators [1–4]. An aspect that was absent or expensive in these designs was the ability to determine the characteristics of the respiratory therapy provided. The device presented in this paper provides for this in the form of flow and pressure data, from which many of the metrics and measurements required for a detailed understanding of the respiratory therapy can be gained. Being customisable and having multiple configurations, it also enables further development of other open source hardware, for example spirometers or peak flow meters. One hindrance to development of such technologies is that flow sensors, particularly multi-use ones, are too expensive to be accessible in low-resource regions.

2. Hardware description

The device[1] consists of a 3D-printed Venturi tube, both an absolute and differential pressure sensor, and some minimal electrical hardware for interfacing. The Venturi is designed to interface with standard respiratory circuits as specified by ISO 5356-1:2015 [5], with a combined 22 *mm* cone and 15 *mm* socket (22 M/15F) input, and a 22 *mm* socket (22F) output. Adapter designs are also provided for other common connections. The deadspace of the Venturi is approximately 10 *mL*. For applications where a smaller deadspace is desired, for example in the analysis of neonatal respiratory circuits, a Venturi with all passages narrower could be used, for example $7.5 - 5$ *mm*. This narrowing and reduced deadspace comes at the expense of an increase in added resistance in the circuit.

The electrical hardware is a single printed circuit board housing two sensors, an absolute pressure sensor and a differential pressure sensor for determining the flow. The sensors both operate from a 5.0 *V* power supply, and provide an analogue voltage output between $0 - 5$ *V*. Thus, they are very widely compatible with any device with an analogue to digital converter (ADC), such as Arduino or Raspberry Pi based systems.

The 3D-printed parts of the system can be sterilised with hydrogen peroxide, meaning the device can be reused between patients or subjects, if required. There should be minimal deformation to the Venturi [6]. It is also feasible to print multiple single-use Venturis, as each only uses approximately 15 *g* of filament and some hosing, thereby ensuring low costs.

The device provides a foundation for analysis of, and development of tools for respiratory circuits, such as mechanical ventilation. It is:

•	Low-cost	•	Widely compatible
•	Mostly 3-D printable	•	Reusable and sterilisable

3. Design files

3.1. Design files summary

The design files are all available at https://doi.org/10.17605/osf.io/bre5f. The file locations specified in Table 1 are relative to the base of this directory, as implemented in OSF's Components.

3.2. FreeCAD

Physical design was done in FreeCAD [7]. The holes for the barbs in the Venturi are slightly oval to account for deformation associated with 3D printing. This geometry has been shown to work in both PLA and PET-G with a tight seal, but with other materials or print orientations the deformation associated with gravity should be considered.

3.3. Printed circuit board design

The PCB was designed in KiCAD. Local library files are included for both the schematic and PCB footprints. The design is rudimentary, but has been shown to have acceptable noise characteristics from use (see Section 7.4 for data). While the PCB is designed to be connected with 2.54 *mm* pitch pin header connectors, it could be modified to accept any other required

---

[1] To avoid ambiguity, in this document *sensor* pertains solely to the electronic components capable of detecting absolute or relative pressure, and the physical 3-D printed tube will be referred to as the *Venturi*. The entire system is the *device*.

Table 1
Summary of critical design files.

Design filename	File type	License	Location of the file *Relative to base directory*
Production Files:			
venturi15–10 mm.stl	3D-printable	CC BY-SA 4.0	physical/renders
barb.stl	3D-printable	CC BY-SA 4.0	physical/renders
sensorComb1.0.zip	Contains Gerber and drill files	CC BY-SA 4.0	electrical/SensorComb/
dataLog.ino	Arduino project	CC BY-SA 4.0	software/dataLog
Source files:			
venturi15–10 mm.FCStd	FreeCAD	CC BY-SA 4.0	physical/
barb.FCStd	FreeCAD	CC BY-SA 4.0	physical/
SensorCombined.pro	KICAD project	CC BY-SA 4.0	electrical/SensorComb/

plug. The PCB is very basic, but has proven itself operational with complex devices. There is also the ability to have basic on-board analogue-realm filtering. This rudimentary design provides a proven foundation for more advanced configurations.

3.4. Software

There is minimal software included by a simplicity-focused design. Only a very simple Arduino code is included, which enables data recording over a serial port. The sample frequency is adjustable, and the time since the previous data point was read (real-time sample period) is also reported. For an example of a more comprehensive application see the ACTIV ventilation system (https://gitlab.com/luihp/activVent). This simplicity, again, creates a simple but robust platform upon which more complex applications can be developed if desired.

4. Bill of materials

The complete bill of materials can be found at https://doi.org/10.17605/osf.io/bre5f. Table 2 contains the critical components and subsystem totals for costing and ease of reference

5. Build instructions

There are six main steps for the construction of the device:

1. Determine the desired sensor and Venturi combination. Table 3 presents the range of possible combinations, and Table 4 the associated resolution.
2. Place an order for the PCBs and the appropriate sensors. Due to shipping this step is often the slowest process, with the rest being done in–house.
3. Print the correct Venturi; any layer height should be appropriate. Include at least three barbs, which are better with a layer height $\leqslant 0.10$ *mm*, for each flow and pressure sensor desired. The.stl files are in the correct orientation for printing, which can also be seen in Fig. 1. Support materials are not required..
4. Insert the barbs into the appropriate holes of the Venturi for connection to the sensors. This can require a reasonable amount of force to properly seat them (in the realm of $150 - 300$ *N* load axial to the barb).
5. Populate the PCB. Note, the only required components are highlighted in the BOM, or indicated in Fig. 3.
6. Connect:
   - The jumpers to select both the power supply, and the operating mode of the differential pressure sensor, as per Fig. 4.
   - Hosing onto the sensors, and then onto the barbs of the Venturi, as shown in Fig. 2. The 'High' pressure terminal of the differential sensor must connect to the input of the Venturi.
   - The PCB to an appropriate device. For example, an Adruino or Raspberry Pi.

6. Operation instructions

Once assembled, the device can be inserted into any respiratory circuit. Ensure that the flow is travelling from the 22 *mm* cone/15 *mm* socket (22 M/15F) input, to the 22 *mm* socket (22F) output, as indicated by the arrow on the external aspect of the Venturi. With the device electrically interfaced to the desired electronic hardware, including a $=5.0$ *V* power supply, the device can be sampled with an ADC as frequently as is desired for the application.

For operation of the device with the provided software, simply connect the analogue voltage outputs to appropriate inputs of an Arduino, by default flow (Fl) to `A0`, and pressure (Pr) to `A1`. Ensure that the serial terminal used is set to a baud rate of `115200`.

Device operation depends to a reasonable extent on non-turbulent flow. Turbulent flow is generally unlikely in respiratory circuits given the typical flow rates and pressures. However, as such, consideration should be given to the exact placement of the sensor within a respiratory or similar circuit. It is recommended to:

Table 2
Reduced bill of materials showing critical components only. Cost is in USD.

Component	Qty	Total Cost	Notes
Key components:			
Electrical Components:			
SDP816-125PA or SDP816-500PA	1	$30.69	Differential pressure/flow sensor
MPVZ4006GW7U	1	$15.36	Absolute pressure sensor
3D-printed parts:			PLA/PET-G recommended
venturi15–10 mm.stl	1	$0.41	
barb.stl	3	$0.05	
∼3.5–4 mm ID Tubing	0.3 m	$0.42	Silicone
System totals			
Populated PCB	1	$48.36	Including sensor cost
Sterilisable Venturi	1	$0.82	
Total device		$49.17	

Table 3
Operation ranges of the various configurations of the flow/differential pressure sensor. The combination of the 15–10 mm Venturi and the 125 Pa differential pressure sensor is the most used by the authors. Note: The operational range shown here is beyond the '100%' value specified by the manufacturer [8], but has shown to be relatively reliable.

|		Pressure sensor:	
		125 Pa	500 Pa
Venturi:	15–10 mm	$5 - 75 L \cdot min^{-1}$	$15 - 150 L \cdot min^{-1}$
	15–12 mm	$12 - 125 L \cdot min^{-1}$	$25 - 250 L \cdot min^{-1}$

Table 4
Resolution of the flow sensor for a variety of configurations, all values in $L \cdot min^{-1}$ unless otherwise indicated. **with the differential pressure sensor configured in linear mode**, and with a **10-bit ADC**. The inter tenth-centile resolutions are shown.

|		Pressure sensor			
		125 Pa		500 Pa	
Venturi	15–10 mm	Bot 10% (23.6)	.17	Bot 10% (46.8)	0.33
		Top 10% (71.4)	0.055	Top 10% (142)	0.11
	15–12 mm	Bot 10% (39.6)	0.28	Bot 10% (78.6)	0.56
		Top 10% (120)	0.093	Top 10% (238)	0.18

- Avoid placing the sensor immediately after a narrow constriction or a sharp corner.
- Avoid placing the sensor somewhere subject to a considerable amount of acceleration.

  Other operating considerations include:

- The length of tubing from the Venturi to the sensors should be minimised. A bracket is provided that enables the PCB to be attached directly to the Venturi or to another tubular part of the circuit, or if the tubing is sufficiently stiff, the PCB will often be fine suspended by the tubing, which will also isolate it from physical movement.
- While the MPVZ4006GW7U reports its voltage requirements as specifically within the 4.75–5.25 V range, there have been no issues running it from the 5.0 V regulator from the Arduino for the 400 + hours of testing and use of the device.
- **There is definite potential for aerosol- and saliva-based pathogens to contaminate this device. If it is being used across multiple subjects, it is strongly recommended to sterilise and/or utilise filters in the respiratory circuit to minimise any possible cross contamination.**
- **Another safety concern is the barb becoming dislodged from the Venturi,** causing a leak in the circuit. If being used as part of a critical respiratory circuit, for example on a ventilator, it is vital to:
  - Ensure the barbs are properly seated by firmly tapping them in the axial direction of the Venturi,
  - Possibly use tape between the barb and Venturi for added friction and vibration support,
  - Ensure, if available, the use of leak alarms with any connected respiratory devices.
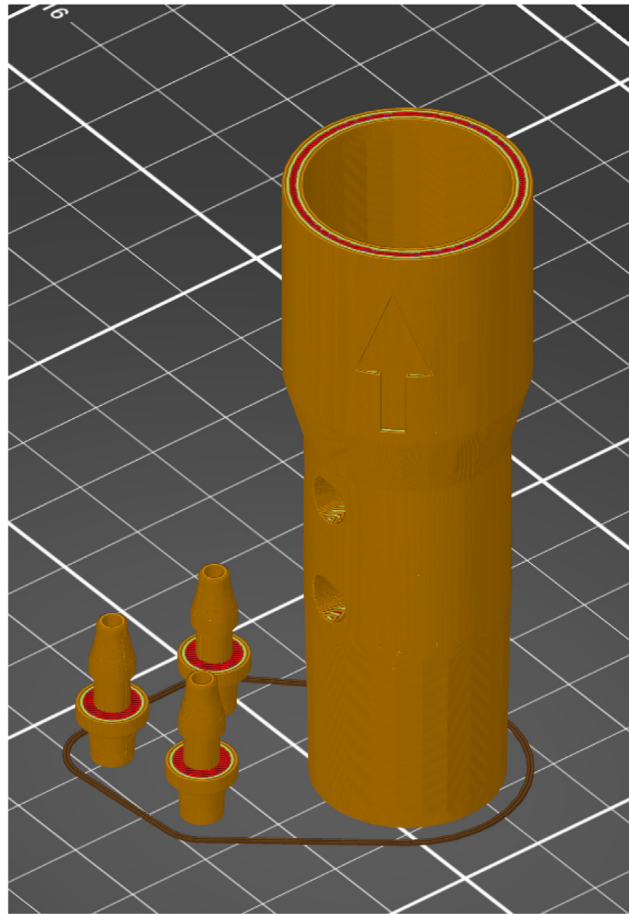
Fig. 1. Print orientation for the 3D-printed components.
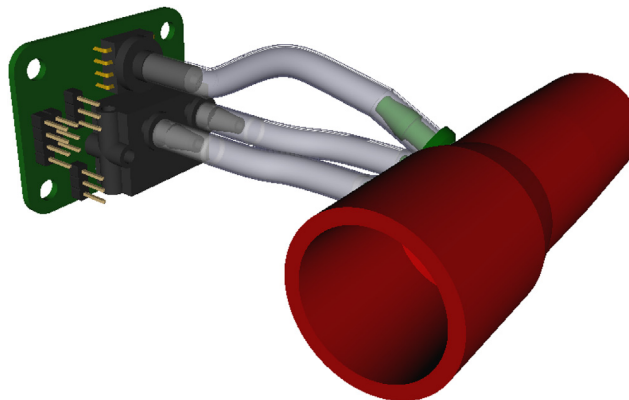
Fig. 2. Device depicted with hosing connecting the 3D-printed Venturi to the sensors.

(a)   (b)
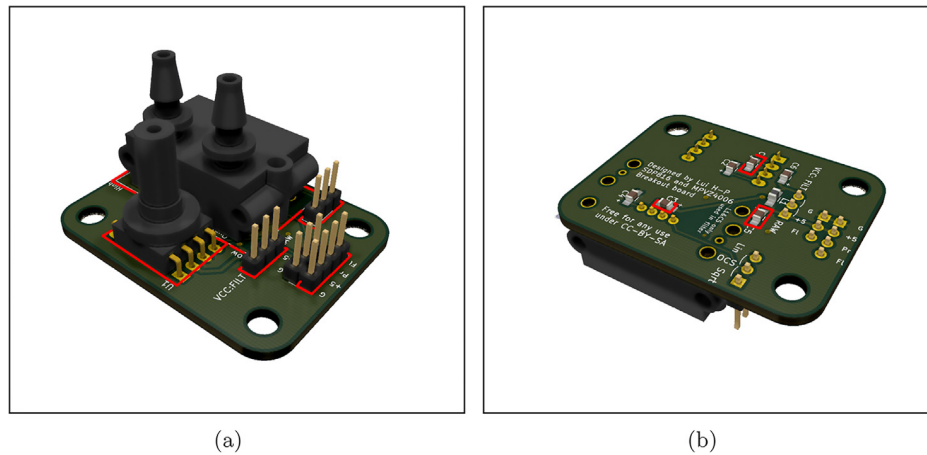
Fig. 3. Depictions of the sensor populated with all of the required components highlighted in red, (a) on the top of the printed circuit board, and (b) on the bottom. Note: On the top it is not necessary to populate the three-pin header immediately adjacent to the four-pin header. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
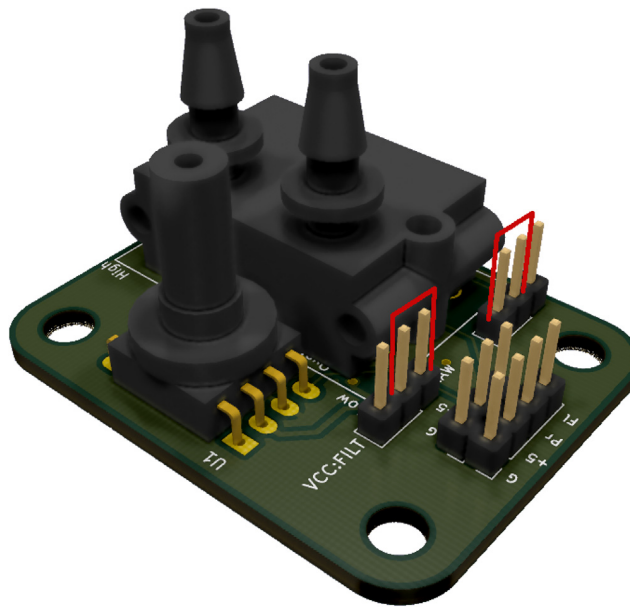
Fig. 4. Configuration used for validation, with the required jumpers shown in red. The one on the VCC header is to select the raw, unfiltered supply voltage, and the one on the right is to configure the SDP816-xxxPa to linear output mode. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

7. Validation and characterisation

In brief, for a system specifically defined as:

- Using the 15–10 mm Venturi;
- Connected to the 125 Pa differential sensor;
- with the sensor configured to linear operation mode;
- Operating at $V_{CC} = 5.0$ V; and
- Interfaced to a 10-bit ADC

It is true that:

- The device can be used for flows $5 - 75\ L \cdot min^{-1}$ and pressures up to 6 kPa or 61.5 cmH_2O
- $q\ [L \cdot min^{-1}] = 0.97 \times 6.27 \times \sqrt{38 \times \frac{ADC\ count}{1023} - 38}$

7.1. Characterisation

The flow sensor works on the basis of a pressure decrease associated with increase in velocity through a constriction. From first principles, assuming laminar flow, the flow can be calculated:

$$q = c_d \frac{\pi}{4} D_2^2 \cdot \sqrt{\frac{2 \cdot \Delta P}{\rho\ (1 - d^4)}}$$

Where:

$D_2 \quad = 10\ mm$

$d \quad = \frac{D_2}{D_1} = \frac{10\ mm}{15\ mm}$

$\rho \quad = 1.225\ kg \cdot m^{-3}$, assumed to be constant

$c_d \quad = $ Discharge coefficient $= f(Re, q, d, etc.).$
$\quad\quad$ Fitted in data $= 0.97$

The high $c_d = 0.97$ value is actually used as a linear scalar to fit the output of the sensor to the validation data. This value provided an acceptable fit to data for several Venturi/PCB combinations as shown in Section 7.4. Data are shown in full at https://osf.io/tj624/.

With the differential flow sensor in linear mode:

$$\Delta P = \frac{190 \times V_{Analogue\ out}}{V_{CC}} - 38$$

[8]

Thus, assuming the operating voltage is $V_{CC} = 5.0\ V$, and the sensor is connected to a device with a 10-bit ADC, such as an Arduino Nano, flow is defined:

$$q\ [L \cdot min^{-1}] = c_d \times 6.722 \times \sqrt{\Delta P}$$

For a 15–12 mm Venturi, replace the value of 6.722 with 11.284.

The pressure loss caused by the Venturi is minimal in the context of respiratory circuits. By modelling the Venturi as a cylinder with $d = 10\ mm$, and $l = 70\ mm$, the theoretical loss is $\leqslant 0.3\ cmH_2O$ (30 Pa) at $60\ L \cdot min^{-1}$, and $\leqslant 0.005\ cmH_2O$ (0.5 Pa) at $5\ L \cdot min^{-1}$.

7.2. Operational range

The operational range of the flow sensor is presented in Table 3 for a variety of configurations. It is important to note that with the differential pressure sensor configured in linear operating mode, the resolution at the lower flows listed here is particularly poor. It is also possible for the Venturi to be connected to both a 125 Pa and a 500 Pa sensor allowing a significantly greater range.

The device presented in this document is the foundation for other devices, to be built upon as required for specific applications. It is simple to design a custom Venturi, or series of Venturis, which enable a more comprehensive analysis of a respiratory circuit. Similarly, it is possible to include another port to allow for flow to be determined in two directions.

The pressure sensor range is $0 - 6.0\ kPa$, or $0 - 61.2\ cm\ H_2O$.

7.3. Resolution

The resolution of a variety of configurations of sensors are shown in Table 4 Because of the square root relationship, the resolution is very poor at low flows. For a better resolution at lower flows, one could either investigate the use of the sensor in square root operating mode, or else using a tighter constriction in the Venturi.

While the resolution values presented in Table 4 are those associated with a 10-bit ADC, the resolution could be significantly increased with the use of a higher definition ADC, up to the 16-bit internal digital resolution of the component [8]. The validation has been performed with a 10-bit ADC to demonstrate effective and accurate sensing is achievable with accessible, cost-effective hardware such as that found on Arduino systems, but it could be expected that the resolution of the device with a 16-bit ADC would be $2^{16-10} = 64\times$ smaller than the values presented in Table 4.

The resolution of the pressure sensor appears to be limited only by the resolution of the ADC to which it is connected: for example a 10-bit ADC sees a resolution of 0.0064 Pa or 6.5×10^{-4} $cm\ H_2O$.

7.4. Validation

The device was validated against the serial output data from both Puritan Bennett™ 840 (Medtronic, Ireland), and a Evita® Infinity® V500 (Dräger, Germany) mechanical ventilation devices. Several experiments were conducted, in which one device was used to detect the inspiratory flow from the ventilator, and another for the expiratory flow to the ventilator. A pair of devices were also used to examine the flow and pressure characteristics within the circuit. The circuit was driven by the mechanical ventilator, with settings in the following ranges:

Volume control	
Tidal volume: V_t	$200 - 1000\ mL$
Maximum inspiratory flow: Q_i	$20 - 80\ L \cdot min^{-1}$
Maximum inspiratory time: t_i	$0.3 - 1.5\ S$
Waveform	Trapezoid, square, triangular
Pressure control	
Inspiratory pressure: P_i	$4 - 20\ cmH_2O$
Inspiratory time: t_i	$0.3 - 1.5\ S$
General settings	
PEEP	$5 - 20\ cmH_2O$
Respiratory rate: RR	$10 - 45\ min^{-1}$

Therefore, the device has been validated within a range of oscillatory environments common within mechanical ventilation.

Over the 80 s of experimentation from which the data within Fig. 5 were obtained, while sampling at 50 Hz, the Pearson correlation was consistently $\geqslant 0.95$ for flow, commonly $\geqslant 0.97$. The distance correlation was typically $\geqslant 0.95$. A Bland–Altman plot [9] demonstrating the error can be seen in Fig. 6. The points with significant error are due to the sample rate being relatively low relative to the gradient of the near-vertical increases in flow. These are shown at the start of inspiration in the earlier data of Fig. 5. The pressure sensor performed similarly, with the Pearson correlation typically $\geqslant 0.97$. Complete datasets are available at https://osf.io/tj624/. Over the total approximate two hours of experimentation, the device consistently had a Pearson correlation $\geqslant 0.9$, and more often than not performed $\geqslant 0.97$ as is shown in Fig. 5. There was not a significant difference in correlation when comparing with data from either mechanical ventilator or the other. Given the devices are
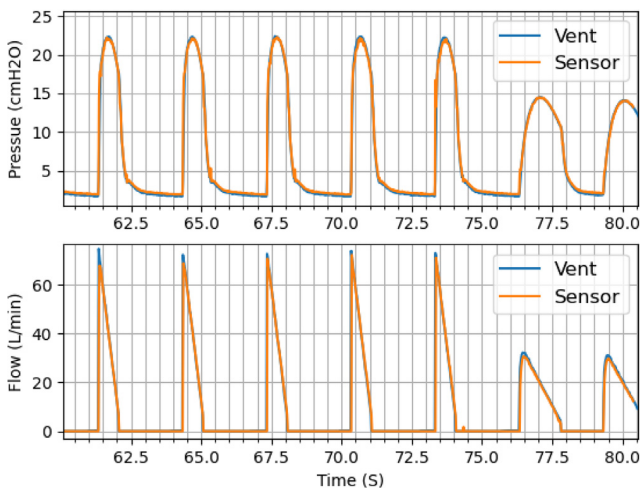
Fig. 5. Example data snippet showing the sensor output against the ventilator (PB840) captured data. Note the data clipping at $75L \cdot min^{-1}$ for the sensor. The artefact after the flow returns to zero is from moving parts in the respiratory circuit. Clipping at the maximum flow can be seen in the first half of the data.

(a)

(b)
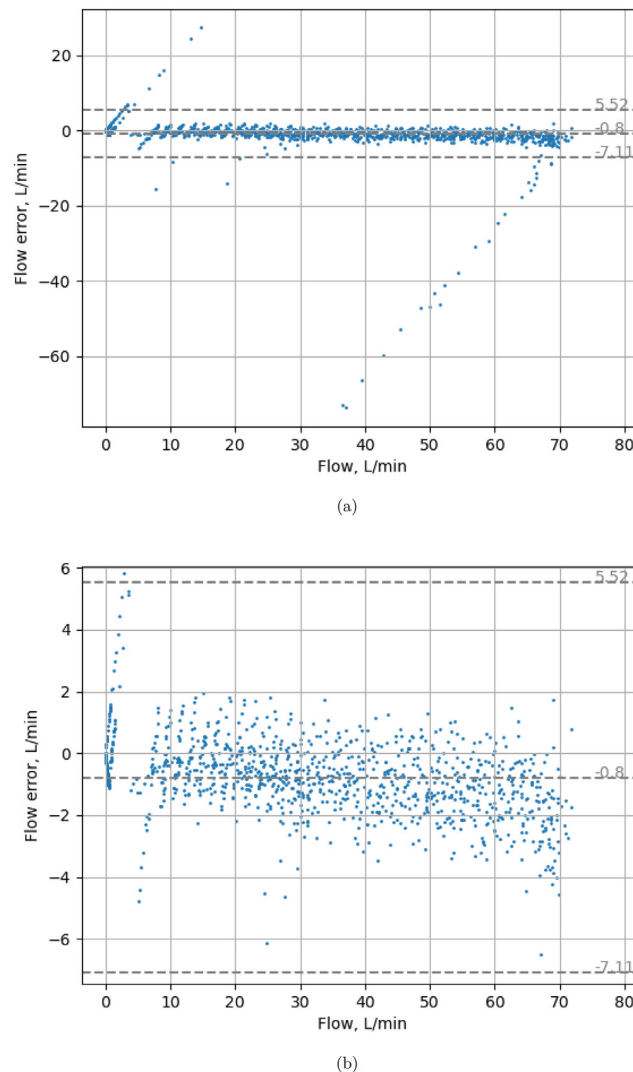
Fig. 6. Bland–Altman plot demonstrating the error of the flow sensor across 80 s, $N = 4000$. The significant errors are due to sampling at a rate relatively low compared to the near-vertical increases in flow rate. (b) is cropped to depict only data within 2σ.

intended for use in mechanical ventilation or similar applications, being validated against high-quality equipment which control these circuits demonstrates the ability of the device to determine the state of the system.

Venturis for validation were printed on the PRUSA MK3, PRUSA MK3S, and PRUSA MINI printers (PRUSA, Poland) at layer heights $0.05 - 0.2$ mm.

7.5. Calibration

The flow sensors have been shown to have a variability of less than 3% across combinations of sensors and Venturis. If available, calibration should be done against a device such as a mechanical ventilator, or a flow calibrator. If these devices are unavailable, a known volume can be passed through the flow sensor at a rate within the high-resolution range of the flow sensor, and the integration of the flow data should be equal to the known volume, where repetition of differing volumes and flow rates can provide robust calibration.

Human and animal rights

No human or animal studies were conducted in the design of this work.

Declaration of Competing Interest

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B.2.3 SENSOR PAPER

Physiologic-range three/two-way valve for respiratory circuits

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ARTICLE INFO

ABSTRACT

A 3D-printed three/two-way valve compatible with respiratory circuits is presented. It is actuated by a servo motor (HXT12K), which is able to be controlled by any PWM-capable micro controller. The valve sufficiently isolates respiratory circuits to deliver fully customisable mechanical ventilation breathing cycles, with differences in driving and end-expiratory pressures of up to 30 cmH_2O successfully demonstrated. It is suitable for multi-plexing ventilators for in-series breathing, or providing separate ventilation to each individual lung in a single patient. Each switching valve costs approximately $16USD, $10 of which is the servo motor which can be reused, allowing subsequent devices for only $6USD of 3D printing and common engineering components. The valve has proven reliable for at least 50,000 state changes over at least one month.

Specifications table:

Hardware name	*ACTIV Valve*
Subject area	• *Mechanical Engineering* • *Biomedical Engineering* • *Medical valve*
Hardware type	• *Clinical Tool* • *Flow diverter* • *Ventilator or CPAP applicable*
Open source license	Creative Commons Attribution-ShareAlike 4.0
Cost of hardware	$16USD initially, ≈$6USD if reusing servo
Source file repository	https://doi.org/10.17605/osf.io/ktxuh

1. Hardware in context

In the COVID-19 pandemic, there were numerous projects targeting the potential or realised need for more mechanical ventilators [1–4]. Where several open-source mechanical ventilator designs were being developed, most of these either were basic and did not allow for the monitoring and customisation with which clinicians are familiar with, and/or required expensive or inaccessible components. Another area investigated was the feasibility of ventilating multiple patients from a single ventilator [5,6]. A joint statement from the Society of Critical Care Medicine, American Association for Respiratory Care,

American Society of Anesthesiologists, Anesthesia Patient Safety Foundation, American Association of Critical-Care Nurses, and American College of Chest Physicians stated "*sharing mechanical ventilators should not be attempted because it cannot be done safely with current equipment*" [7]. A large number of reasons were given supporting this viewpoint, most of which addressed the lack of ability to monitor each patient, and to provide individualised care. [1]

The chief assumption made discussing treating multiple patients using a single mechanical ventilator was the principle of ventilating two or more patients in **parallel**: Connecting multiple patients using basic 'Y' valves, increasing the allowable or target volumes, and possibly use restrictive valves to allow *relative* customisation. The problems can be circumvented using a **series** ventilation approach as shown in Fig. 1: Connect two patients using actuated valves, detect inspiration, and divert every second breath to a different patient [8,9]. This philosophy successfully mitigates the issues raised in the joint statement [7–9], and is realised as the Actuated, Closed-loop, Time-series Inspiratory Valve (ACTIV) ventilation system. A series of 3D-printed Venturi-tubes are used to detect pressures and flows [10] within the system, and an Arduino-based controller is used to change the state of the valve presented in this document between the two states as shown in Fig. 2, delivering ventilatory effort to first one patient, and then the other. The resultant in-series ventilation effectively sees the inspiratory connection of the ventilator connected to one patient, and then the other after a breath has been delivered to the first patient. An example of a demonstration with two mechanical lungs using this device can be seen at: https://www.youtube.com/watch?v=j-HhQD3qVdA.

This valve operates in physiological ranges, and natively allows external connection to medical devices, such as CPAP or mechanical ventilators. There are very few commercially-available valves able to connect to respiratory circuits without the need for complex adapters or extensive customisation. Outside of those designed for use within mechanical ventilators, there are few valves suitable directly for clinical applications or trials, none of which enable ventilation multiplexing.

2. Hardware description

The valve switches an inlet (from the ventilator) two either one of two outlets (to patients), using a basic wedge ('pie') which alternately occludes each outlet passage. The wedge has extrusions which press against o-rings, sealing one of the output respiratory circuit outlets. This wedge is rotated from one position to the other using a servo motor, connected via a basic linkage, using 3D-printed bars. The valve is therefore able to be controlled by any device capable of powering and controlling a servo motor, such as an Arduino or a Raspberry Pi. An exploded view is shown in Fig. 3.

The connectors of the valve conform to ISO 5356-1:2015 [11]. There is a combined 15 mm socket/22 mm cone (15F/22 M) input, and 22 mm socket output connectors. Adapters are provided for interfacing with less common connectors.

The 3D-printed parts of the system can be sterilised with hydrogen peroxide, meaning the device can be reused between patients without deformation [12]. However, given the system excluding the servo is reasonably inexpensive, it is recommended the valve is not used across multiple patients, if used in a clinical setting to avoid cross-contamination risk.

The valve is able to be used for flows and pressures within common medical respiratory ranges. It is shown in Fig. 3, and is:

- A 3/2-way valve
- Mostly 3D-printable
- Compatible with common respiratory circuits
- Sterilisable/Cheap if reusing the motor

3. Design files

Design filename	File type	License	Location of the file *Relative to base directory*
outer.FCStd	FreeCAD	CC BY-SA 4.0	physical/
inner.FCStd	FreeCAD	CC BY-SA 4.0	physical/
nut.FCStd	FreeCAD	CC BY-SA 4.0	physical/
sleeve.FCStd	FreeCAD	CC BY-SA 4.0	physical/
shaft.FCStd	FreeCAD	CC BY-SA 4.0	physical/
pie.FCStd	FreeCAD	CC BY-SA 4.0	physical/
bar-shaft.FCStd	FreeCAD	CC BY-SA 4.0	physical/
bar-span.FCStd	FreeCAD	CC BY-SA 4.0	physical/
bar-motor.FCStd	FreeCAD	CC BY-SA 4.0	physical/
[all of above].stl	3D-printable	CC BY-SA 4.0	physical/renders
basicServ.ino	Arduino	CC BY-SA 4.0	software/basicServ

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[1] https://www.thingiverse.com/thing:4250354.
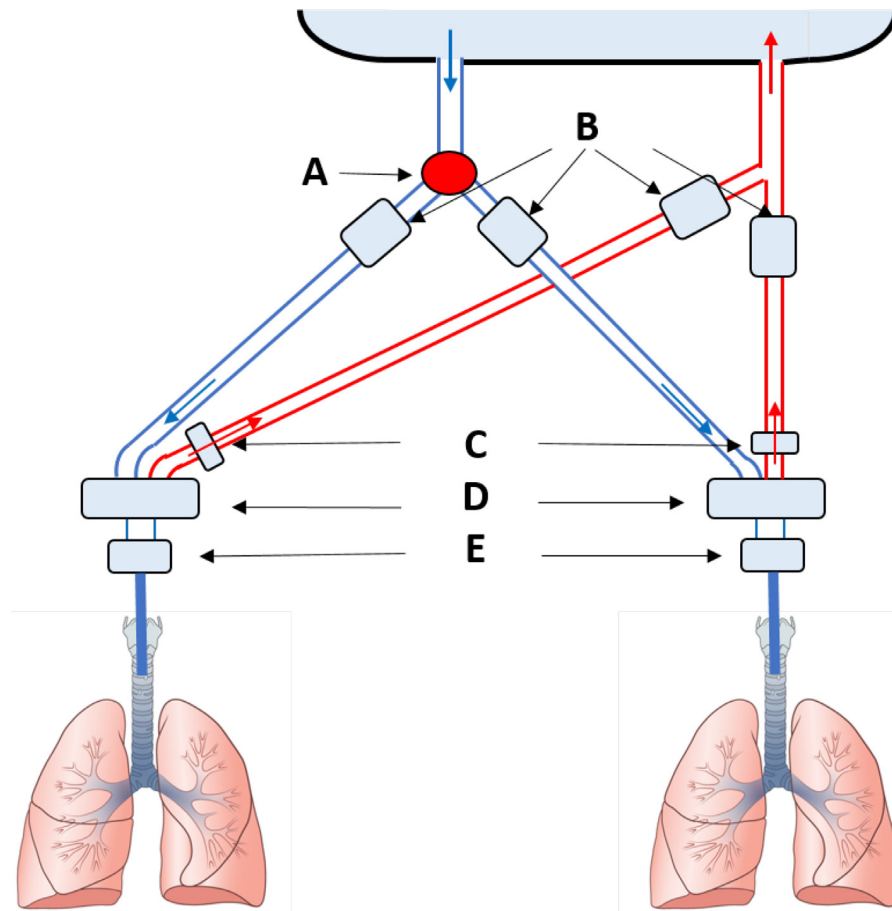
Fig. 1. In-series ventilation set-up with two patients connected to a single ventilator, as per the ACTIV system. A) An active switching valve, as that presented in this paper, B) One-way and variable pressure drop valves, such as the PANDAPeep valves, C) HEPA filters, D) Passive Y connectors, and E) Pressure and flow sensors. A comprehensive instruction set can be found at https://gitlab.com/luihp/activvent.

(a)   (b)
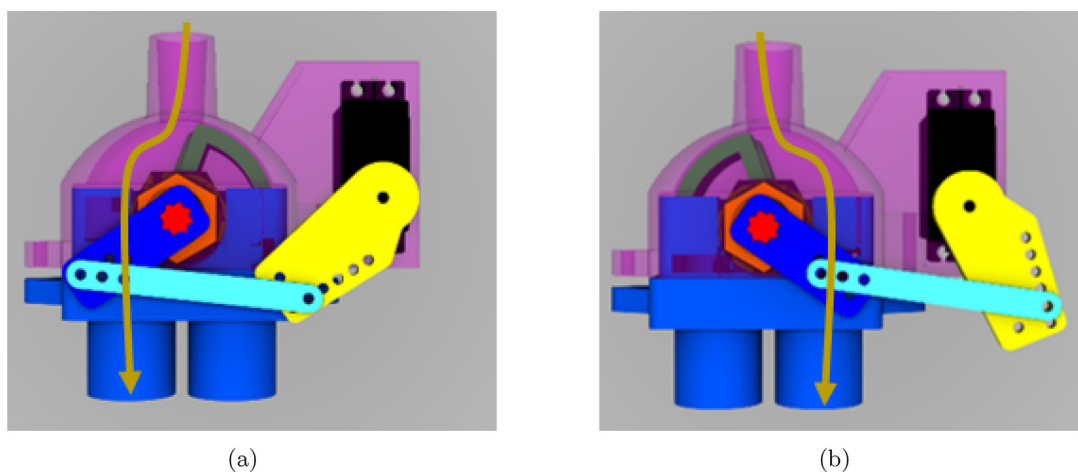
Fig. 2. Depictions of the valve in the two operating positions.
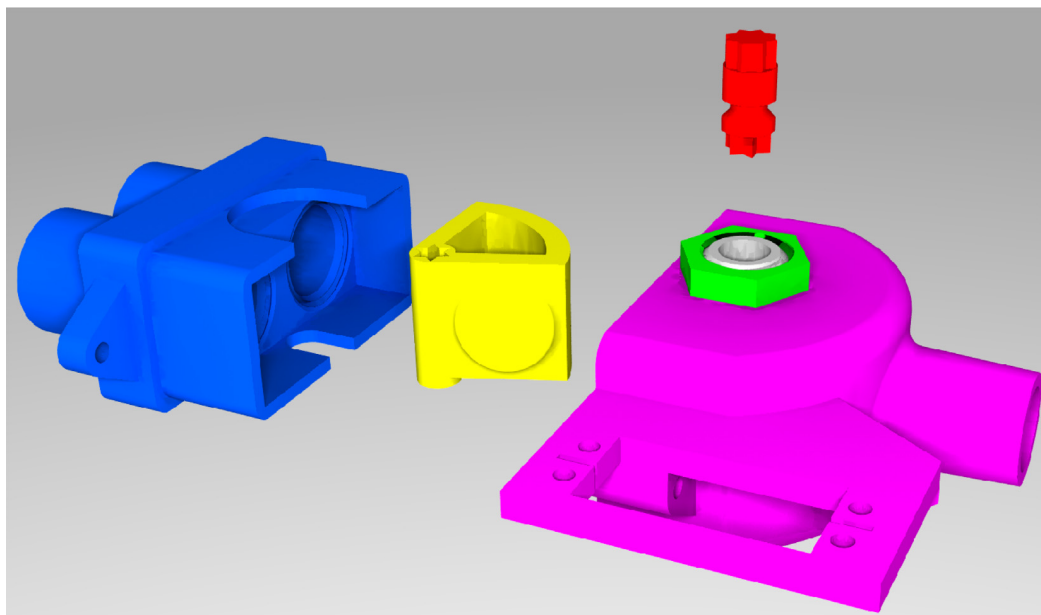
Fig. 3. Partial exploded view of the valve. For a colour key see Table 1.

The design files in full are available at https://doi.org/10.17605/osf.io/ktxuh. The file locations specified here are relative to the base of this project.

3.1. FreeCAD

Physical design was done in FreeCAD [13]. The geometry has been shown to work in both PLA and PET-G with a adequate sealing and operation, but for other materials or print orientations the valve should be comprehensively tested prior to use.

3.2. Software

There is minimal software included as only the hardware of the valve is presented here. An Arduino script which allows for determination of the servo limits of travel — `basicServ.ino` — is included only. For an example application with more complex software, see the complete ACTIV ventilation system (https://gitlab.com/luihp/activVent).

4. Bill of materials

See Table 1.

5. Build instructions

5.1. Printing

For the most part, the printing is self explanatory in terms of orientation. While minimising support is important, maintaining circular airway connectors was prioritised. Therefore, any part which attaches to another part and/or ventilator tubing should be printed in an orientation the preserves the circularity of the connector: i.e. the axis of the cylinder(s) is parallel to the vertical axis of the printer. Specific details are provided in Table 2, and an example printbed can be seen in Fig. 4. Note that the infill of the shaft, and at least part of the pie is required to be higher that usual for strength. Printing for development was done using the PRUSA MINI, PRUSA MK3S and PRUSA MK3 (PRUSA, Poland), using both PLA on a smooth spring steel print bed, and PET-G on a textured print bed. Printing was done with a layer height of 0.07—0.20 *mm*, with no observable change in performance.
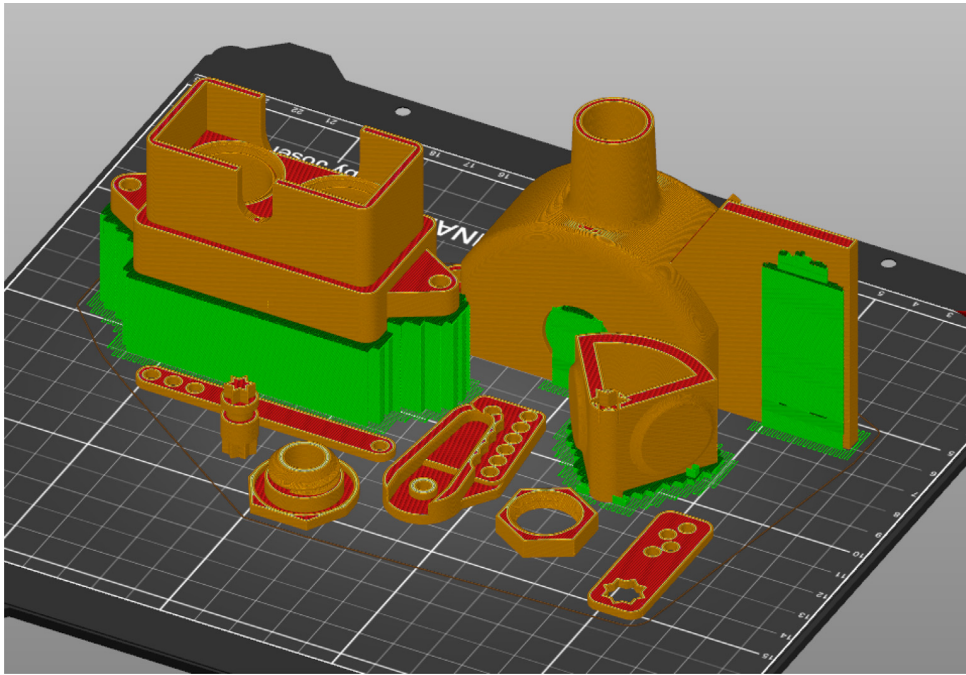
Table 1
Bill of materials, with **all values in USD**. Complete bill of materials with sources and more specific costing et cetera available at https://doi.org/10.17605/osf.io/ktxuh.

Part	Qty	Total Cost	Pro rata	Notes	
3D-printed parts:		$24.99		1 kg spool	
				Rendered colour:	Mass (g):
outer	1			Pink	58.66
inner	1			Blue	52.05
sleeve	1			Brown	3.21
shaft	1			Red	1.11
pie	1			Green	10.45
nut	1			Orange	1.61
barServo	1			Yellow	4.91
barLink	1			Cyan	1.65
barShaft	1			Dark blue	1.78
					Total Mass:
All printed parts:			$3.37		135.43
HX12K servo	1	$10.21	$10.21	11 kg · cm torque	
				180° range	
				$300° \cdot S^{-1}$ speed	
Servo arm	1			Supplied with above	
O-Rings:					
22×2	2	$0.68	$0.14	Pressed into wedges in inner	
18×2	1	$0.60	$0.60	Sleeve	
6×2	1	$1.68	$0.04	On shaft	
41×2	1	$1.06	$0.11	Between inner and outer	
Hardware:					
$M3 \times 40$ mm	2	$1.47	$0.30	Joining inner and outer	
$M3 \times 16$ mm	5	$2.03	$0.21	Attaching servo (4)	
				Joining barServo & barLink (1)	
$M3 \times 10$ mm	2	$0.82	$0.18	Joining barShaft & barLink(1)	
				Servo shaft connection (1)	
Standard M3 nuts	6	$0.47	$0.12		
Standard M3 washer	20	$0.55	$0.22		
M3 lock washer	7	$0.90	$0.63	All non-rotating connections	
M3 nylock nut	2	$0.87	$0.07	For bolts which connect bars	
Total:		$46.33	$16.27		

Table 2
Printing details for the parts required for the active valve.

Part	Orientation	Support	Notes
Outer	Connector up	Y	Support everywhere for servo mount.
Inner	Connectors down	Y	Should only have support on bed.
Sleeve	Large flat surface on bed.	N	–
Pie	Additional shaft down	Y	At least the cylinder of the shaft should have a medium infill ($\geqslant 50\%$) to reinforce the teeth that the shaft part contact. The orientation does result in quite a small area of the actual part on the print bed; only the circle of the shaft, and the support material.
Shaft	Axis up	N	Should be printed with high ($\geqslant 80\%$) infill.
Nut	Hex on bed.	N	–
BarServo	Flat surface on bed	N	–
BarLink	Flat surface on bed	N	–
BarShaft	Flat surface on bed	N	–

Fig. 4. Example print bed showing orientation and support materials in green.
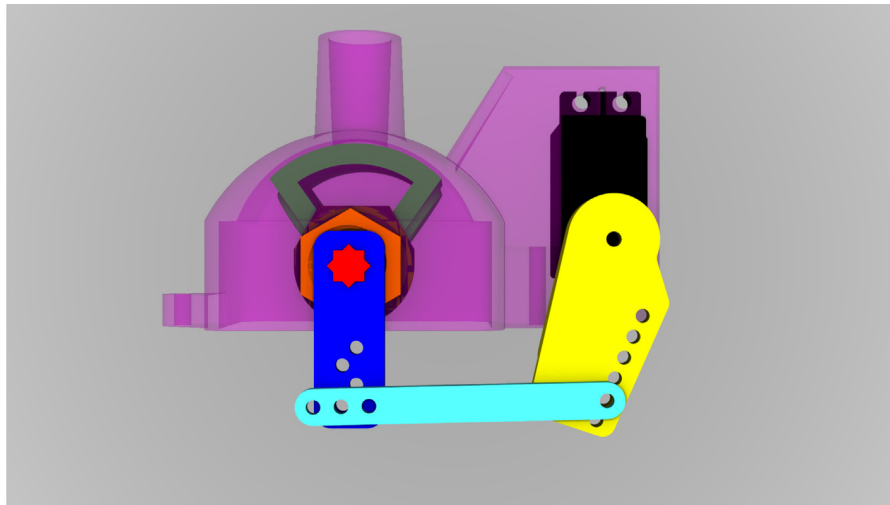
Fig. 5. View from above showing the recommended orientation of the for insertion of the shaft. The recommended hole alignment and orientation of the link, span, and servo bars is also demonstrated. See Table 1 for colour key.

5.2. Assembly

In addition to the 3D-printed parts, a small number of o-rings and some M3 nuts and bolts are required for assembly. This assembly assumes that all of the support material have been removed, and if required the surface in contact with the support material smoothed. Furthermore, depending on first layer height, there may be a slight brim around the very base of the part, which is particularly pertinent for inner and outer parts. A video showing the assembly can be seen at https://www.youtu-be.com/watch?v=cK5hVcv7b8M, and there are detailed pictures within Appendix A.

1. Fitting o-rings:
   (a) On sleeve: fit the 18x2mm o-ring over the sleeve and ensure it is bedded in the groove at the bottom of the thread.
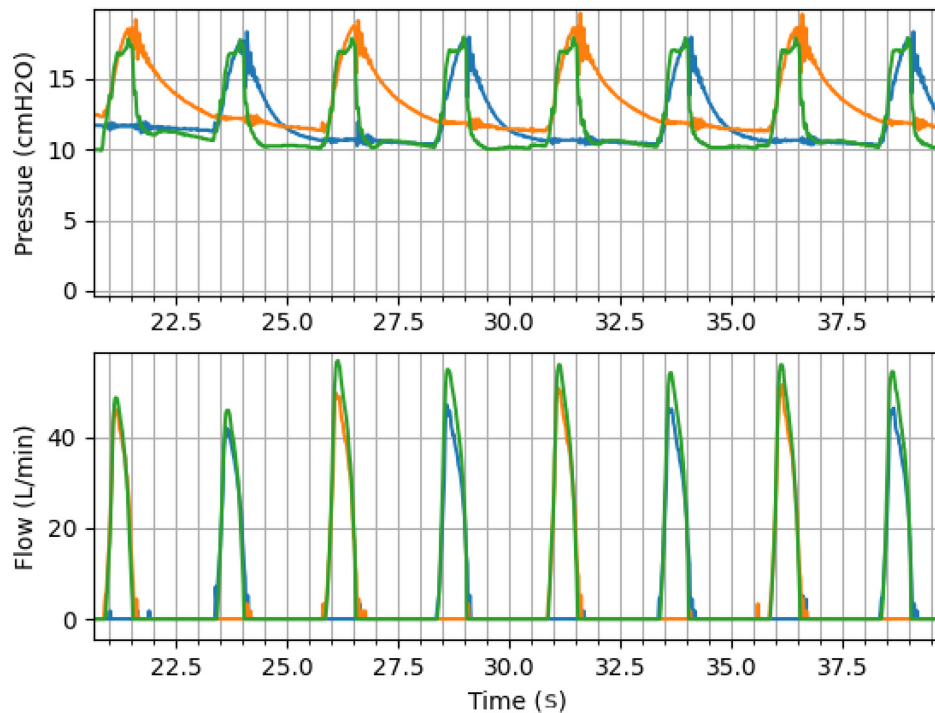
Fig. 6. Demonstration of the ability of the valve operation with identical respiratory loads. Data from each of the outlets (blue and orange) are shown against data from the Evita V500 (Dräger, Germany) (green), clipped $\geqslant 0 \; L \cdot min^{-1}$. The artefact after each inspiration is associated with physical movement within the respiratory circuits; the actuation of the valve, and also one-way vales oscillating.

    (b) On shaft: pull the 6×2 mm o-ring over the shaft, and fit it in the groove. If using tools to stretch it onto the shaft (it is quite difficult otherwise), ensure to not damage the o-ring with the tool. A flat-headed screw driver works quite well for this.

    (c) On the valve inner part:
- Fit the large ($\approx 41 \times 2$ mm) o-ring over the entire outside.
- Fit the 22×2 mm o-rings into the valve sealing surfaces. This is best done by sitting the o-ring on top of the groove in which it will be seated, and then pressing on two opposite points, and then the two points between the first two points (i.e. $0°$ and $180°$, and then $90°$ and $270°$). The o-ring should then be pressed fully all the way in, either by running something around the circumference, or by firmly pressing the associated face of the pie wedge into the o-ring.

2. Outer assembly:
    (a) Insert the sleeve from the inside upwards through the circular hole in the outer. While this hole has been stretched slightly to allow for asymmetry in the printing process, it may require slight trimming of the edge closest to the 22 mm male connector to allow the sleeve to fit. Only do this after a reasonable amount of effort - it is best that it is difficult to fit than to be trimmed as this provides the best sealing surface.
    (b) Fasten the nut onto the sleeve to finger tight. If tools are used with a large moment, there is risk of causing damage that is not evident from external inspection. After proper tightening, the bottom of the sleeve should be about flush with the extrusion on the inside of the outer.
    (c) Insert the pie into the outer. For orientation purpose, it is easiest to do this such that the pie is as close to halfway between the two limits of travel (i.e. the middle of the curved section of the pie should be visible through the 22 mmM/15 mmF connection). The cylindrical extrusion points down, away from the sleeve, and is caught but an extrusion on the inside of the outer part.
    (d) Insert the shaft. Ensure that the smaller, hexagonal shaft is inserted into the pie. In terms of rotational alignment, it is best that the bar which connects to the shaft is approximately opposite to the pie. i.e. when the pie is halfway between the two switching positions, the barShaft should be orthogonal to the edge of the outer, as shown by the dark-blue bar in Fig. 5. This is made easier if the barShaft is already fitted on to the shaft.
    With the shaft inserted, the pie should move freely: if not there may be residual support material at the top of the inside of the outer.

    (e) Attach the servo motor to outer. This is done with 4x M3x16mm bolts, and it is recommended to use lock washers and standard nuts. The servo is pressed up to the plate from underneath.

3. Insert the inner into the outer.
   (a) This can be a bit of a hard fit it there is extra material from the first layer on the outer. Running a blade lightly along the edge of the outer will remove the excessive material allowing easier insertion.
   (b) Insert two bolts (M3x40mm) through the aligned holes on the sides/wings, and fasten the two together quite tight. These will be tight enough such that the wings will flex/bend inwards towards each other.

4. Assemble drive mechanism.
   (a) If able, instruct the servo motor to go to the middle of its range of motion.
   (b) Connect the bars: barShaft to barLink with a M3 × 10 mm bolt, and barLink to barShaft with a M3 × 16 mm bolt. The configuration is dependant on exactly the orientation of the pie and the shaft, but testing has shown fourth hole on the servo bar, the middle hole of the link bar, and the third hole of the shaft bar. Further detail is shown in Fig. 14 in Appendix A.
   (c) When inserting bolts to join the bars, pass them from bottom to top and fasten with a nylock nut. This orientation will provide the best clearance when operating, and the nylock nut will resist being worked loose with during motion. 14b.
   (d) The servo bar should simply fit over the servo horn, and then be screwed down. An M3x10mm bolt should be used to fasten the barServo and the servo arm to the shaft of the servo motor. For orientation and range purposes, the horn may need to be refitted; to do this move this to one of its limits, and then orientate the horn such that it will provide the full range of motion necessary for the valve to operate. One way to do this is to rotate the servo by hand in the direction of moving the horn away from the rest of the valve until you reach the limit of the servo. The horn can now be removed, and replaced on the servo such that it points directly away from the shaft.

6. Operation instructions

The operation of the valve is relatively straight forward. The limits of travel will need to be determined prior to proper use. This can done simply through trial and error, determining the point of the duty cycle limits at which the pie properly seals against the inner part to form an adequate seal. The pinout for the servo motors is:

Orange:	PWM
Red:	+5 V
Brown:	GND

The operation of the valve is very easy, simply provide the signal to rotate the wedge to one limit, and then to the other at the desired time. For an example application see the ACTIV ventilator system https://gitlab.com/luihp/activvent.

Safety concerns to watch for:

- In testing the device, if the shaft has been printed with a less than 50% infill has snapped. It is crucial to avoid the possibility of this, because the failure is not visible without disassembling the device. It is recommended to print the shaft with at least 80% infill.
- While cross contamination is very unlikely if used with standard respiratory circuits due to the high deadspace, it is advised to use HEPA filters or equivalent/better, as well as one-way valves[2] on both of the output circuits. This filters should be changed as often as specified by the manufacturer.
- The valve should only be used upstream of potential contamination, or if downstream in the respiratory circuit it should either be used once and disposed/sterilised, and/or be protected by HEPA filters.
- While the valve has withstood rigorous testing, it is possible that failure of the device will not be evident externally, for example if the shaft snaps. It is therefore recommended that pressure and/or flow sensors are used to monitor both output respiratory circuits, such as the ACTIV flow and pressure sensor [10], to ensure continued correct operation of the device.
- Ensure, if available, the use of leak alarms with any connected respiratory devices.

7. Validation and characterization

The primary test system has successfully been used for approximately 72 h of testing, switching at least once every five seconds. The system has been proven reliable for over 50,000 state changes without any reliability issues. While the shelf life

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[2] While there is a one-way valve design included, they are not a particularly robust design, and should only be used if there is absolutely no other choice.
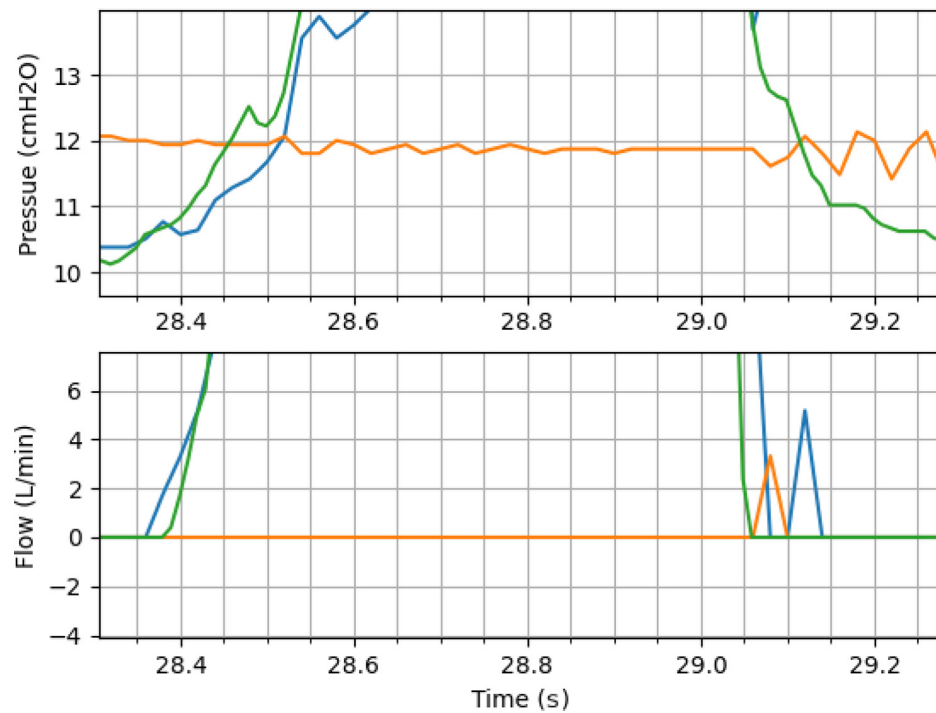
Fig. 7. Section of data more closely demonstrating the critical sealing characteristics: there is no increase in pressure in the orange path while a breath is being delivered to the blue path, and similarly there is no detectable flow through the closed outlet of the valve.
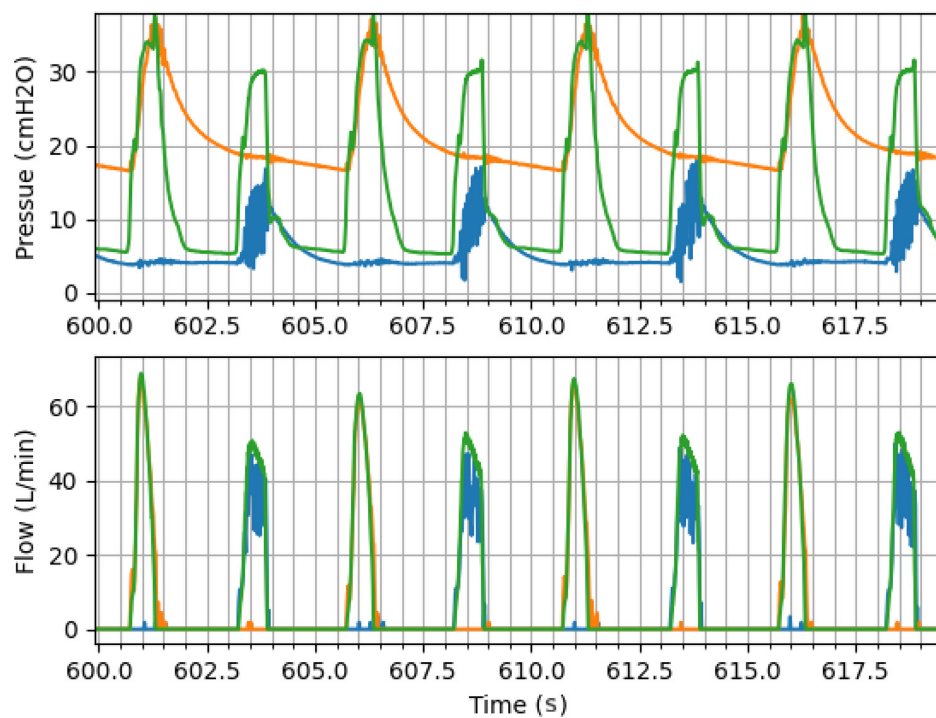
Fig. 8. Example of the closed characteristics with substantially differing ventilation parameters; the orange circuit has approximately 12 cmH_2O greater PEEP, and 20 cmH_2O extra driving pressure. The fluctuations in pressure and flow in the blue circuit are caused by oscillating pressure-drop valves within the circuit.

of the device has not been explicitly tested, the limiting consideration is the heat and humidity related degradation of the o-rings. Provided use mitigates potential contamination, the device has been shown to capable of intermittent use of at least a month. Usage beyond this should involve regular testing of the device to ensure continued operation.

The device:

- Has a deadspace of: 40 *mL*
- Has a switching time of: $\leqslant 0.5s$
- Is reliable for at least 50,000 switches

7.1. Validation

The device was validated as part of the ACTIV ventilation system[3] ∧,[4]. Complete datasets are available at https://doi.org/10.17605/osf.io/ktxuh.

The ACTIV ventilation system is a system in which connects to a mechanical ventilator, and diverts every second breath to a different respiratory circuit, allowing a single ventilator to provide respiration to two patients. The system consists of this valve, passive one-way and pressure drop valves[5], some sensors [10], and an Arduino-based controller. The data presented in Figs. 6–8 is extracted from the ACTIV system validated against an Evita V500 (Dräger, Germany). These data show:

1. The valve is able to be actuated within 0.5 *s*.
2. There is no detectable flow through the closed valve ($\leqslant 1\ L \cdot min^{-1}$ with $\Delta P \geqslant 34\ cmH_2O$).
3. There is minimal increase in pressure in the closed respiratory circuit ($\leqslant 0.2\ cmH_2O$ over 2 *s*).

Funding

Human and animal rights

No human or animal studies were conducted in the design of this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Additional building instructions

See Figs. 9–14.

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[3] https://gitlab.com/luihp/activvent
[4] An example can be seen at: https://www.youtube.com/watch?v=1pCCMqLMpSI
[5] PANDApeep valves: https://www.thingiverse.com/thing:4250354
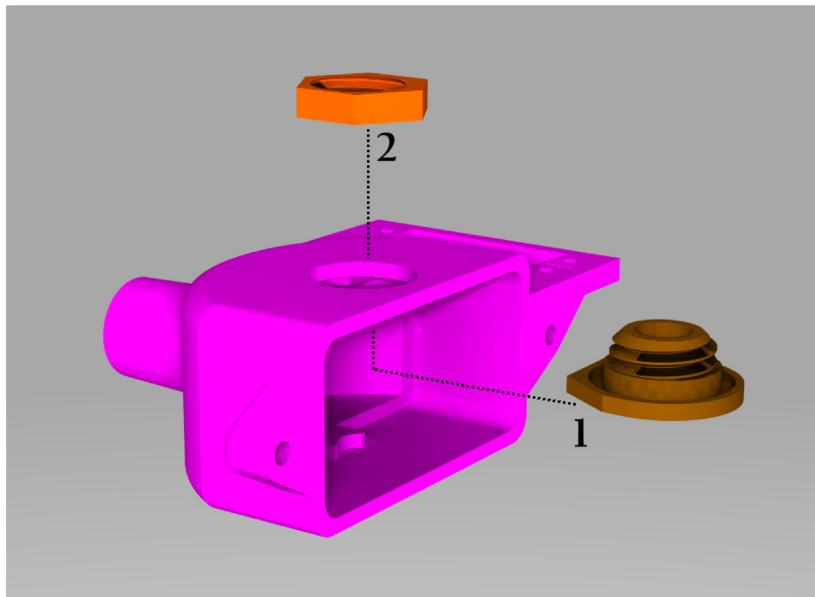
Fig. 9. Depiction of the insertion of the sleeve into the outer, and the nut to fasten, as per Section 5.2 2)a.
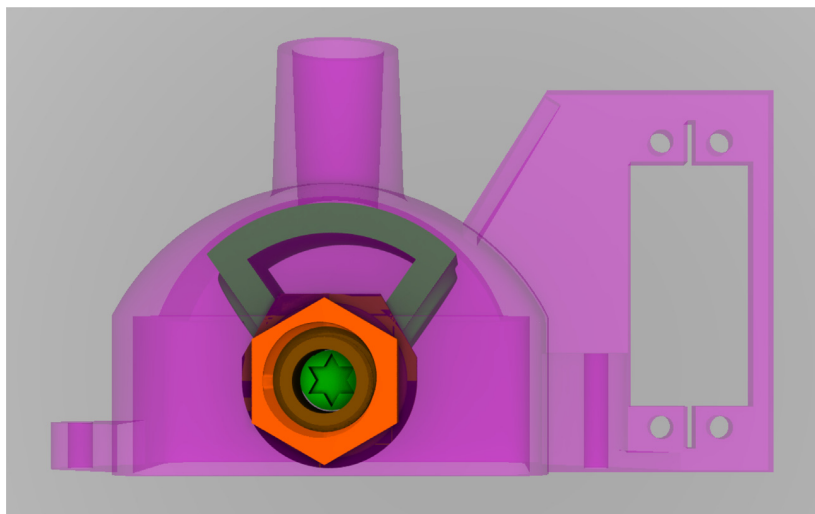
Fig. 10. The best orientation of the pie inside the outer as per Section 5.2 2)c, for best assembly of the shaft and drive mechanism. Note the orientation of the sleeve to mate with the inside of the outer.
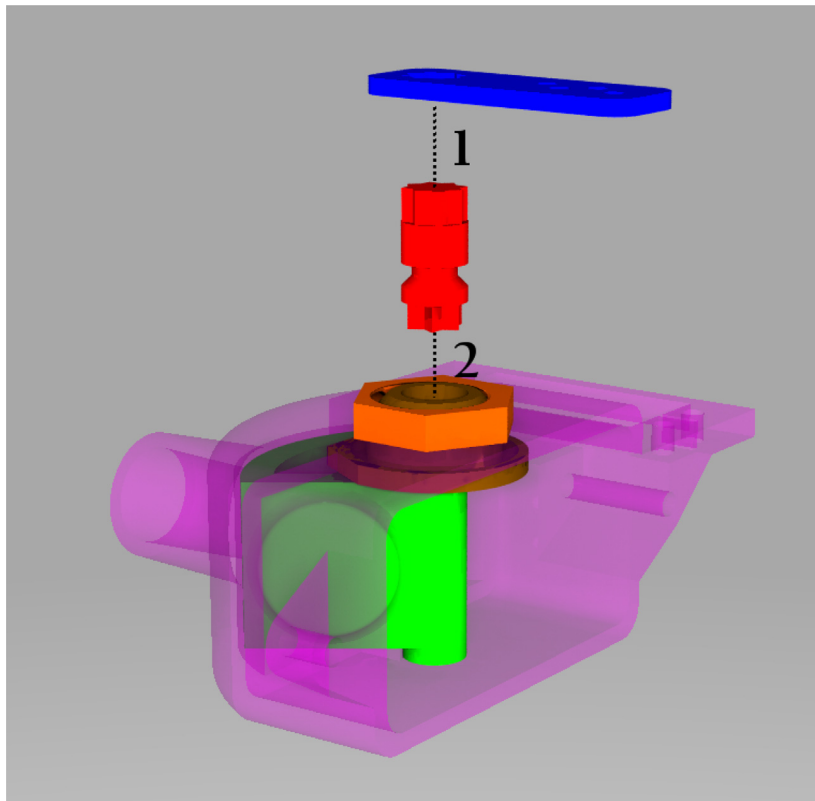
Fig. 11. Depiction of the insertion of the shaft into the pie for easiest orientation of the drive mechanism, as per Section 5.2 2)d.
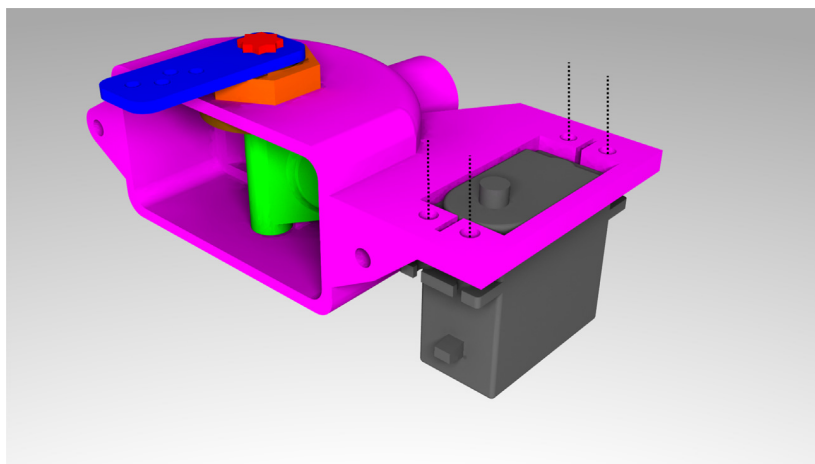
Fig. 12. Attachment of the servo motor to the outer, as per Section 5.2 2)e. Dotted lines indicate the location of the 4x M3×16 mm bolts with lock washers. The bolts from above give greater clearance for the rest of the drive mechanism, but can be difficult to handle the nuts on the other side.
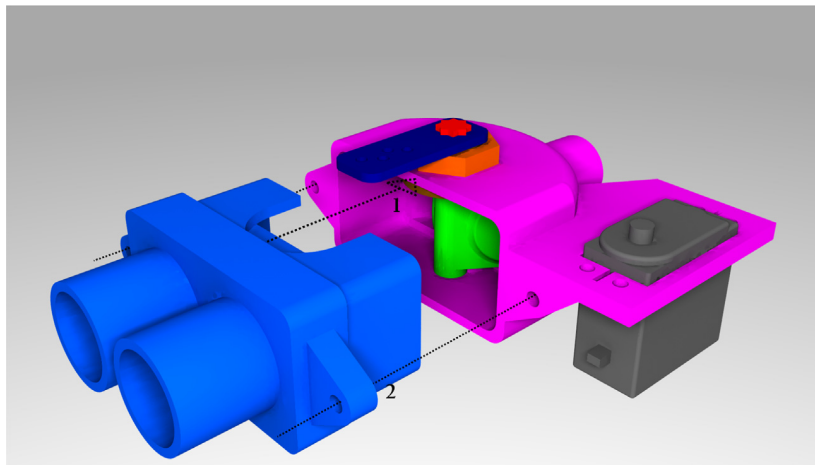
Fig. 13. Joining of the inner and the outer as per Section 5.2 3), and the location of the M3 × 40 mm bolts for 5.2)(b), with lock washers and standard nuts.
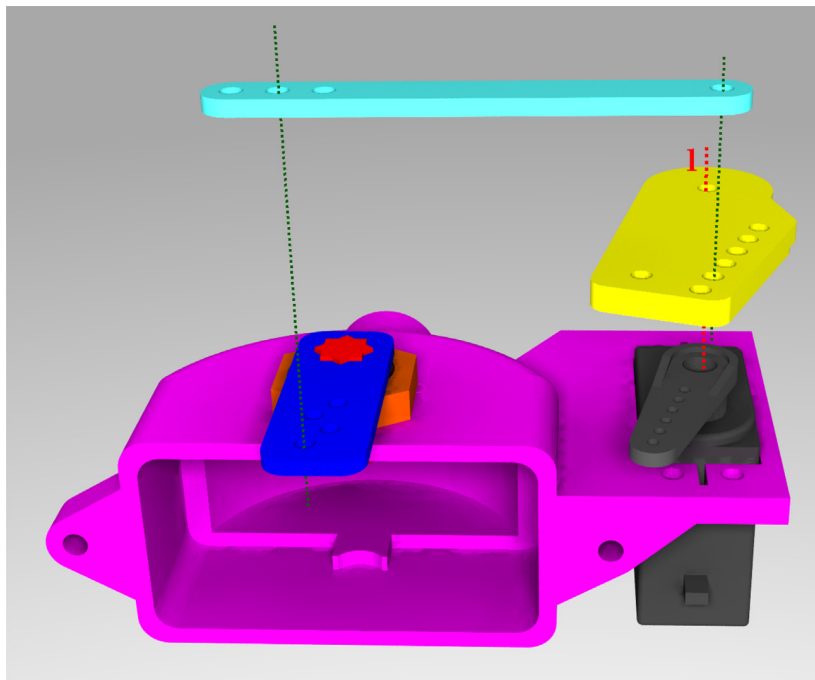
Fig. 14. Best orientation and layout of the bars for assembly as per Section 5.2 4)b. The servo should be in the middle of its possible range prior to completing this. First press the servo horn into and the barServo onto the servo motor in approximately this orientation, then fasten with a M3x10mm bolt into the servo shaft. Then, with washers and nylock nuts, connect the barLink to both barShaft and barServo as per the green lines. BarLink and barShaft (dark blue), are connected with an M3x10mm bolt, but barLink and barServo (yellow) are attached with an M3x16mm bolt, due to the thickness of barServo. Ensure the correct alignment of holes as indicated. It may be necessary to remove barShaft in order to insert the bolt from the underneat.

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H6 MountingHole
H5 MountingHole
H7 MountingHole
H8 MountingHole

These ones are the corners

Power

J1
Conn_01x02_Male VBatt
2
GND

SW3
SW_SPST
Vin VBatt
1 2

Vin VBatt +5V
C3 CP C1 CP C2 CP
GND GND GND

Connectors

Jumpers

Conn_01x03
3 pot
2 A7
1 A7analogIn
J2

Shield for Arduino Nano

P1
1(Tx) 1
0(Rx) 2
Reset 3
4
2 5
3 6
4 7
5(**) 8
6(**) 9
7 10
8 11
9(**) 12
10(**/SS) 13
11(**/MOSI) 14
12(MISO) 15
Digital
GND

P2
Vin +5V+3.3V
1
2
3 Reset
4
5 A7
6 A6
7 A5
8 A4
9 A3
10 A2
11 A1
12 A0
13 AREF
14
15 13(SCK)
Analog
GND

Servos

Conn_01x03
3 GND
2 Vin
1 6(**)
J13

Conn_01x03
3 GND
2 Vin
1 5(**)
J12

Communications

R1 A4 R2 A5
R R
+5V +5V

1(Tx) 4 J17
0(Rx) 3
2
GND 1
+5V
Conn_01x04_Male

GND +5V GND +5V
J10 Conn_01x06_Male
2 13(SCK)
3
4 12(MISO)
5 11(**/MOSI)
6 10(**/SS)
J11 Conn_01x06_Male
2 13(SCK)
3
4 12(MISO)
5 11(**/MOSI)
6 9(**)

Analog headers

A0 J3
1
+5V 2
GND 3
Conn_01x03

A1 J5
A0
1
+5V 2
GND 3
Conn_01x04

A2 J4
1
+5V 2
GND 3
Conn_01x03

A3 J14
A2
1
+5V 2
GND 3
Conn_01x04

A4 J6
1
+5V 2
GND 3
Conn_01x03

A5 J7
1
+5V 2
GND 3
Conn_01x03

A6 J8
1
+5V 2
GND 3
Conn_01x03

A7analogIn J9
1
+5V 2
GND 3
Conn_01x03

Buttons

+5V
RV1
R_POT 2pot
GND

J16
Conn_01x05_Male
1 2
2 3
3 8
4 4
5 7

+5V SW1
SW_Push 3
GND
R R7

+5V SW2
SW_Push 2
GND
R R8

Interface

D1 LED
R R3 7

D2 LED
R R4 8

D3 LED
R R6 4

GND

LEDs

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Physical I/O

SW1 SW_Push
R1 R
JP3 Jumper_2_Open — ardD2
JP4 Jumper_2_Bridged
butt1
J2 Conn_01x02_Male
GND

SW2 SW_Push
R2 R
JP5 Jumper_2_Open — ardD3
JP6 Jumper_2_Bridged
butt2
J3 Conn_01x02_Male
GND

SW3 SW_Push
R3 R
JP7 Jumper_2_Open — ardD4
JP8 Jumper_2_Bridged
butt3
J4 Conn_01x02_Male
GND

RV1 R_POT
+5V — GND
potIn

LEDs

D3 LED
R6 R
GND +5V

JP2 Jumper_2_Open
D2 LED
R5 R
GND led1
+5V
J7 Conn_01x03_Male
Can have LED on or of board,
Or can solder JP2 and use as GPIO

JP1 Jumper_2_Open
D1 LED
R4 R
GND led2
+5V
J6 Conn_01x03_Male
Can have LED on or of board,
Or can solder JP1 and use as GPIO

Arduino Nano

Arduino_Nano_v3.x
+3V3
+5V
VIN 30
3V3 17
+5V 27
RX 2 D0/RX
TX 1 D1/TX
RESET 28
RESET 3
ardD2 5 D2
ardD3 6 D3
ardD4 7 D4
D5 8
D6 9
ardD7 10 D7
AREF 18
S_CS — R7 R — R9 R
S_RESET — R11 R — ardD8 11 D8
R10 R — ardD9 12 D9
S_DC — butt1 13 D10
S_MOSI — R8 R — butt2 14 D11
S_MISO — butt3 15 D12
S_SCK — R12 R — ardD13 16 D13
A0 19 ardA0
A1 20 ardA1
A2 21 ardA2
A3 22 ardA3
A4 23 ardA4
A5 24 led1
A6 25 led2
A7 26 potIn
GND 4
GND 29
A2
GND

Parallel interface screen

Arduino_UNO_R3
A1
+3V3
+5V
VIN 8
3V3 4
+5V 5
D0/RX 15
D1/TX 16
RESET 3
ardD2 17 D2
ardD3 18 D3
IOREF 2
ardD4 19 D4
D5 20
ardD6 21 D6
AREF 30
ardD7 22 D7
ardD8 23 D8
ardD9 24 D9
A0 9 ardA0
A1 10 ardA1
A2 11 ardA2
A3 12 ardA3
D10 25
SDA/A4 13 ardA4
D11 26
SCL/A5 14
D12 27
D13 28
SDA/A4 31
SCL/A5 32
GND 29
GND 6
GND
GND

Serial comms

J1 Conn_01x04_Male
1 RX
2 TX
3
4 +5V
GND

SPI type screen

J5 Conn_01x14_Male
1 +5V
2 GND
3 S_CS
4 S_RESET
5 S_DC
6 S_MOSI
7 S_SCK
8 S_LED +5V
9 S_MISO
10 T_CLK
11 T_CS +5V
12 T_DIN
13 T_DO
14 T_IRQ

R17 R — S_CS — GND
R13 R — S_DC — GND
R14 R — S_SCK — GND
R15 R — S_MOSI — GND
R18 R — S_MISO — GND
R16 R — S_RESET — GND

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