The Machine in the Loop – Patient Empowered AI Implementation

Healthcare automation in the United States began to take off following the passage of the Health Insurance Portability Accountably Act (HIPAA) in 1996. Technological advances in records keeping have progressed markedly since HIPAA and fostered an ecosystem of digitally enabled medical care. Nearly every aspect of medical care has been revolutionized by computers and more recently by Artificial Intelligence (AI) and Machine Learning (ML). Yet what happens when the technologies that foster improved care are too expensive, take too long to come to market, are selective in their compatibility or all the above.

Type-1 Diabetes (T1D) is a chronic disease that has benefited greatly over the last century from advances in technology. In particular T1D patients have been the beneficiaries of advances in AI and ML technologies in ways that might significantly alter their quality of life. Nearly 1.6 million Americans are T1Ds among which 187,000 are children or adolescents. A century ago T1D was a fatal condition. Now T1D is a chronic disease managed with the aid of advanced biotechnologies.

T1Ds are faced with a dual set of challenges in managing their condition – hyperglycemia and hypoglycemia. When first diagnosed, most diabetics are hyperglycemic. Hyperglycemia is a condition in which there is an excessive amount of glucose (sugar) in the blood plasma of and can lead to a condition known as diabetic ketoacidosis (DKA). DKA is a life-threatening situation. Sustained elevated levels of glucose in a person's blood damages organs over time and can lead to organ and blood vessel damage among other long-term consequences. Prior to the invention of insulin hyperglycemia resulting in organ failure or DKA was assured for diagnosed T1Ds. The invention of Insulin by Frederick Banting, John MacLeod, James Collip and Charles Best altered the diagnosis of T1D from fatal to chronic, yet problems in the management of T1D remained. While insulin was critical for lowering blood glucose too much insulin resulted in another fatal condition, hypoglycemia. The management of T1D is a balance between too much and too little glucose in a person's blood.

When James Collip and Charles Best sold the first patent for Insulin to the University of Toronto they did so for a mere $1. At the time Insulin was primarily manufactured from pigs. However this changed in the 1980s when it was discovered that insulin could be synthesized within strains of E.coli bacteria. Today the average cost of insulin regularly exceeds $300-400 a vial. Moreover, different types of insulin have different effects on blood glucose levels. Some forms of insulin are engineered to be long acting and can be taken at specific times of the day to counteract the introduction of carbohydrates at meals and other forms of insulin are short acting and are given principally in response to or anticipation of the consumption of carbohydrates. Both forms of insulin, however, require patients to know their blood glucose levels.

When insulin was first invented glucose monitoring was practiced through basic urinalysis test that identified the presence of glucose in urine or through a form of lab analysis developed by Ivar Bang in 1913 that examined the constituent parts of blood. Despite these early methods of glucose analysis, the average person was unable to accurately measure their blood glucose outside of a hospital setting. It wasn't until the 1940s that Urine test strips could be used to identify different levels of glucose and give diabetics a reliable way to adjust insulin intake. Urinalysis was inexact and made the challenge of finding a balance between hyperglycemia and hypoglycemia a constant guessing game. In 1963 Ernie Adams developed the first blood glucose (Dextrostix) strip which would change in color intensity relative to the amount of glucose in the blood sample and in 1970 Anton H. Clemens developed the first glucometer which cost $650 ($4,551.61 today) that could read the Dextrostix and provide a more accurate assessment of the amount of glucose in a patient's blood.

Since the 1970s advances in glucometers have increased substantially and typically measure the electrical conductivity of blood with different concentrations of glucose to provide highly accurate readings. With this information patients were increasingly empowered to control their chronic disease. Yet, managing diabetes even with advanced insulin and a glucometer or a modern continuous glucose meter (CGM) requires constant attention. Early on scientists tried to reduce the patient's role in their care through the development of insulin pumps which would provide bolus (insulin given in response in the intake of carbohydrates) and basal (insulin given in small doses to offset minor fluctuations in blood glucose). The first insulin pump was invented not long after the first glucometer in 1974. The Biostator combined the monitoring of glucomters and the delivery of insulin. The drawback of the Biostator was that it was the size of a large microwave!

In 2016 the United States Food and Drug Administration (FDA) approved the first artificial pancreas, the MiniMed 670G closed loop continuous glucose monitor and insulin pump. The system comprised of two connected devices used algorithms to help manage the delivery of insulin to keep T1D patients within a desired blood glucose range. The cost of the system alone, not including the insulin or replacement sensors was $8,000 and had a lifespan of four years. It was expected that patients would acquire the device under insurance plans and remain with the device for the duration of that 4-year period or have to pay a premium to shift to new devices or services. Patients who elected to use the MiniMed 670G would be essentially locked into a single method of treatment regardless of new advances in technology. The device which is much smaller than the Biostator but still comes with enormous drawbacks. It uses tubes that run to the phone sized device which sits in a reservoir carried by the patient and connects to a proprietary CGM which also must be worn on the body. The data and decisions made by the device are FDA approved but the algorithms and controls are generally outside of the view of the patient, making the device a "black box" for patient care. Other constraints on the system limited the visibility of

the insulin delivery data and CGM data to the patient alone, a problem for caregivers and parents of T1Ds.

The rise of the artificial pancreas inserted a machine in the loop to manage the care of patients and limited the visibility of the patient into the decisions of that machine. While the balance between hyperglycemia and hypoglycemia was becoming better, the control of the patient over the processes was being shifted to algorithms beyond their control. The technology fostered improved care but was extremely expensive, took too long to come to market and locked patients into a market even if new and better treatments arose, and was selective in its compatibility.

Patients are never patient. When you or someone you love has a chronic disease every day can be a challenge. Waiting for scientists, technologists and doctors to come up with better methodologies of care, new drugs or technologies can seem like an eternity. In 2013 a group of patients and caregivers under the hashtag #wearenotwaiting got to work taking apart and analyzing the insulin pumps and CGMs of two of the major brands of insulin pumps and the major brand of CGM providers to develop a series of technologies to build a better, more reliable, open source artificial pancreas. The initial work on that eventually evolved into the Open Artificial Pancreas System (OpenAPS) began in 2013 when software engineer John Costik's four-year-old son was diagnosed with T1D. The Costiks like many parents in the early phase of chronic disease management discovered that they lost the ability to monitor their son's glucose levels when he went to school. At the time CGMs provided data only to a device carried by the patient. Costik developed a software which connected the CGM to a phone that would broadcast securely the CGM data securely to other accounts via "cloud." This initial project formed the foundation of what would become the NightScout Project. By opening up CGM data Costik set the stage for the inclusion of other forms of data that could help in the management of diabetes.

In 2015 Chris Hannemann, Ben West, Dana Lewis and Scott Leibrand began to contribute to NightScout and expand its capabilities. In particular they focused on life-saving alerts for hypoglycemia. The group then began work what would become a Do-It-Yourself-Pancreas-System (DIYPS) which connected the glucose measurements of the CGM and the insulin delivery mechanisms of Medtronic Insulin Pumps. The early DIYPS was a decision assist device that used clear algorithms to build models of insulin to carbohydrate ratios for patients. This eventually was modified into the OpenAPS project. The OpenAPS system has been designed with integrated safety protocols to be fault tolerant. This means it limits frequency of boluses and constrains basal rate injections to prevent the over introduction of insulin into patients. The algorithms that run OpenAPS are transparent and structured. The designers also hold conferences annual public to discuss the design and implementation of the algorithms. The software was open source and free and only required a small single board computer such as a Raspberry Pi ($35) or an Intel Edison ($50).

In late 2015 Pete Schwamb joined in the effort and designed a clone of the Carelink radio interface to a Bluetooth Low-Energy interface opening the devices up to communicate with mobile phones. This connection began to create what is often now referred to as a body area network. By setting and controlling frequencies and frequency strengths the devices are able to communicate. Working together they began solving the radio frequency issues that prevented communications between different types of devices. These issues required the group to work together across different specialties.

In late 2015 T1D patient Nate Racklyeft, who also happens to be an apple software engineer, began working in his free time to analyze the data being brought together by the diverse sources and slowly linked CGM, Insulin Pump, and Carbohydrate data. While he was working on these linking issues the rest of the team began further incorporating the data streams into NightScout. By early march 2016 Nate had completed his initial application and was "looping" all the data together to create a unified system with the potential for closed loop applications. Nate published his work and it immediately developed a loyal and devoted following. However, within a couple years management of the connections, design, maintenance, and upgrades of the software overwhelmed Nate. He eventually turned over control of the project to Pete Schwamb, Mark Wilson, and Chris Hannemann who along with other coders monitor and maintain the project on github.

The project has now expanded to cover both Medtronic and OmniPod brands of insulin pumps. At present the application is available on GitHub and requires interested users to go through a series of steps to use the application with their CGM and insulin pump. First users must become registered apple developers. Second they must download Apple's developer environment xCode. Third, they must download the software from github and "build" the application in xCode. Fourth they must deploy the application to their Apple iPhone. Fifth, they must purchase a Riley Link (a small single board computer like a Rasberry Pi with the necessary wireless communications antennas ~$150). Sixth, they must input all their relevant care information including basal and bolus limits, insulin to carb ratios and more into the built app on their phone. Seventh, they must connect their phone, the Riley Link, their pump, and their CGM. After all these steps are complete, they can choose to have open loop (the app issues consistent commands based on preassigned basal settings) or they can close their loop, let the algorithm establish basal rates based on the limits established by the patient.

The use of the open-source artificial pancreas comes with explicit and extremely clear disclaimers stating: "Important please understand that this project is highly experimental, it is not approved for therapy – You take full responsibility for building and running this system and do so at your own risk." The total cost of implementing this system beyond the cost of an Apple iPhone is $300 to start and $100 for every year afterwards. If used in tandem with the NightScout application individuals can build free hosted server instances for NightScout or pay ~$120 for paid hosting.

This lowers the cost of having an artificial pancreas from about $2,000/year to about $300/year an 85% savings.

Yet most patients who use the LoopKit as it is now called do not do so only because it is less expensive. The do it because it gives them better control over their diabetes, allows them to change between pump manufacturers and CGMs as those technologies improve and shrink in size. They also do it because LoopKit in combination with NightScout provides extremely detailed data useful for the management of T1D. For parents and caregivers, they can use LoopKit and NightScout to see forecasted blood glucose levels of their children at all hours of the day and night, they can see when boluses and carbohydrates are administered, and they can closely track changes in basal rates as determined by the application's embedded algorithms. NightScout in combination with LoopKit also enables trends visualization and reports, insulin pump reservoir status, and patient phone battery status remotely. And, unlike with conventional closed loop systems, they can monitor all this information at a distance if the patient's mobile phone has cellular coverage. Combined all these features empower patients, parents, and caregivers in ways not possible before. The level of control helps to reduce HBA1C (measure of blood health) and foster longer, healthier lives for patients with T1D.

The evolution of the LoopKit application from concept to implementation has not stopped and the teams that worked on NightScout, OpenAPS and LoopKit coordinated to form a 501(c)(3) nonprofit organization to shepherd the LoopKit and OpenAPS through FDA approval. It was announced in June 2021 that Tidepool Loop completed FDA 510(k) submission paving the way for LoopKit to be accessible to anyone with access to the Apple app store. LoopKit's implementation is designed to be open-source and accessible across platforms to enable patient choice in ways previously constrained by the market.

At the core of the innovation chain in modern augmented diabetes control is artificial intelligence and machine learning. While the present LoopKit algorithms are highly structured this is likely to change over time as algorithm validity and efficacy in the provision of care improves. It is conceivable that in the future increasingly complex algorithms will ingest a variety of enhanced biometric data from additional devices within the body area network including heart rate, pulse oxygenation, temperature, altitude and more to further refine insulin delivery methods in ways that take the present state of artificial pancreases to new levels that reduce the burden on patients and caregivers. In the future AI will tailor the delivery of insulin to the unique needs of patients based on the conditions the patient is experiencing. By fostering a multi-track of innovation that combines open-source community developed medical solutions, with non-profit research and development with, corporate innovation, the future of algorithmic diabetes management is promising.

The open-source development undertaken by the developers of OpenAPS, NightScout, and LoopKit is increasingly being discussed as a "patient centric" model that empowers patients with the aid of technology to make better, more affordable health decisions. This model however does challenge the established status quo of the FDA. It also undermines the business model of firms that must adhere to FDA regulations. There are several other concerns raised about the open-source movement. As cybersecurity concerns grow in intensity there are worries that the open-source non-verified development of biomedical technologies might lead to severe negative outcomes and even possibly patient death. NightScout and LoopKit also contain vast troves of data on patients. This data is highly personal and because it is managed individually without government oversight, it might be vulnerable to theft.

Discussion Question #1
As technologies become more democratized and the ability individuals or groups operating outside of normal regulatory and market constrains increase what is the role of the government in regulating unregulated – open-source advances in biomedical science? Should individuals like Nate Racklyeft be subject to the same laws and restrictions of commercial firms? Although LoopKit places clear disclaimers on its site, should its developers be subject to civil or criminal liability if an individual is harmed while using their code?

Discussion Question #2
The initial development of new applications for the management and control of diabetes was initiated by John Costik, the father of a new patient. Is it ethical to have parents, friends, or relatives "hacking" the biomedical equipment of their relations? When might it become ethical? Might it become ethical if there are concerns over cost, equipment reliability, equipment connectivity, patient safety, or equipment efficiency?

Discussion Question #3
None of the individuals in the OpenAPS, NightScout, or LoopKit projects sought to earn any profit from their efforts. If any of these individuals had sought to earn a profit from their efforts would it have made their hacking activities unethical or immoral? Would it change the way they are perceived legally?

Discussion Question #4
NightScout and LoopKit both required "hacking" the frequencies and functionalities of existing commercial products to achieve new functionalities not approved by the FDA. Is hacking the functionality of another firm's product to expand functionality ethical? Is it legal? If something goes wrong and a patient is injured because of modifications to the intended use of the commercial equipment certified by the FDA who is liable? Should the device manufacturer or the hackers be held responsible for modifications to the functionality of the biomedical device?

Discussion Question #5
What concerns or challenges might patients face when implementing AI functionality to supplant or supplement normal biological functions? What is the responsibility of the AI developer to ensure that the decisions that the AI makes are logical and coherent to the patient and caregivers? Who should verify the functionality and coherence of the AI, the government, an open-source community, or some other entity?

Discussion Question #6
Is it ethical for patients to circumvent regulated and legally established medical markets to secure special – unregulated care? Under what conditions might it be ethical for patients to circumvent regulated medical markets to secure care?

Reflecting on the Machine in the Loop

The history of NightScout, LoopKit, and OpenAPS is not hypothetical. Each of these projects are real and ongoing. These open-source products provide enhanced medical care opportunities to tens of thousands of people world-wide. Yet the development of these projects challenges the status quo of existing biomedical development processes. These advances are also hastening the day when the delineation between man and machine becomes fuzzy. The creation of smart body area networks fosters both excitement and trepidation.

When medical treatments and technologies combine outside of existing research institutions, biomedical and pharmaceutical firms, there is reasonable cause for concern. The history of medicine is replete with examples of fraudulent cures and remedies that have been hoisted on an unsuspecting public with significant negative consequences including death. The modern system of laws and regulations surrounding medical care, drug and software approvals is a direct result of the many harmful activities that took place in the past. In particular, laws and regulations ensure that medical care meets certain standards and does more good than harm. They also remediate the significant information disadvantage of the general public. Medical treatments and technologies are complex and knowing what is helpful and what is harmful is difficult to identify for non-specialists. Yet, at the same time the modern controls on medical care and its associated technologies dramatically slow lifesaving or quality of life improving technologies from reaching those who need them most.

Patients dying of a rare disease do not have the time to wait for certain experimental treatments and are often vulnerable and willing to try anything that might help them live. This vulnerability places them at a disadvantage to those who might take advantage of their condition for financial or personal gain. To combat this most research studies must undergo a process of institutional review with an oversight board. The practice of institutional review can often place constraints

on who can receive certain treatments and who cannot. Often these constraints can feel arbitrary and oppressive to those who are in desperate need of medical solutions.

Similarly, above T1Ds are faced with thousands of choices on a daily basis about how much insulin to administer, when to administer it, and what activities they can participate in. They are challenged by the high costs of insulin, testing strips, CGMS, insulin pumps, and all the other basic tools that help them live. When the Costiks confronted the challenge of viewing their son's glucose status while he was at school, they were attempting to solve a problem that was not unique to them and one that had already been identified by the CGM manufacturer. However, while they were unconstrained by law and regulation, the CGM manufacturer was required to ensure that the data that would be transmitted from the CGM remained secure and did not leak patient data.

The development of open-source technologies in the biomedical space raises a number of concerns about transparency, inequality, accountability, equity, and legitimacy. Addressing these issues below is a key challenge that scholars and practitioners face.

Transparency

Although the FDA approvals process might lack public transparency it forces drug manufacturers and technology developers to prove the efficacy of their products to the government. A failure to prove efficacy can result in drugs or technologies being rejected and delaying their arrival on the market and their availability to patients. The process of filing paperwork and presenting findings before a review board is meant to prevent new products or services from harming the very people they are meant to help. Yet the developers of OpenAPS, NightScout, and LoopKit would be correct in saying that their products are more transparent than those of private vendors because of their open-source nature. It is easy to view the LoopKit code on github and to watch its processes run in xCode. But while the code is transparent and available to all unlike those of private vendors it is not understood by all its users. Whereas when software is reviewed by the FDA it must go before a board of experts, the same is not true of these open-source applications. None of the developers of these applications was specifically trained to treat diabetes, rather they used their personal experiences to inform their software development and recognized their own limitations. But this poses a question, does that fact that these projects are open-source make them transparent? Do most T1Ds who use LoopKit actually go line by line to verify the code before they use to maintain their quality of life? The answer is no, most do not verify the code, nor would they be able to. They are relying on the good-faith and expertise of the community.

Accountability

As was discussed in the case above there are significant concerns over accountability. The developers of the open-source applications try to avoid accountability in the legal sense known as liability by putting big disclaimers on their websites. These disclaimers are meant to shift the

accountability from them as developers to those individuals who decide to use their applications to maintain their lives. This transfer of accountability is simply not possible for major medical software and pharmaceutical firms. They are accountable to their customers and can be held liable if their products result in harm. This difference in accountability is a major concern moving forward. The applications discussed above all have a loyal and devoted developer community and community of users willing to problem solve and accept the risks associated with the use of these applications, but as AI branches off into new fields and new user and developer communities a lack of accountability might create significant challenges.

Equity

Equity is a difficult point of discussion in relation to the cases above. It is clear that these applications lower the relative cost to users and therefore make quality diabetes management more affordable and therefore more equitable. Diabetes care generally lacks equity because good care and management of diabetes is generally reserved to those who can afford insulin, CGMs, and insulin pumps. Yet even if we focus on the fact that these applications make care more affordable and consequently more equitable there is a large gap in the knowledge available to individuals with T1D. Many patients simply do not know that these applications exist. Some of those who know that these applications exist are not technically savvy enough to implement these applications. These applications lower the cost care and increase the control of care to a subset of the T1D community who can already afford insulin, pumps, and CGMs. Their use of these open-source technologies reduces the market size and thus incentives of manufacturers to further expand and reduce costs on existing diabetes technologies.

Legitimacy

None of the developers of the applications in the case analysis above were registered biomedical firms and none filed the appropriate FDA paperwork. None of the developers had previously worked in biomedical settings prior to their work on these applications. Yet each were able to make substantial improvements to products already in existence. Does their lack of credentialing make them illegitimate? Does a lack of formal legitimacy impact the efficacy of their applications? Each of the developers had some personal or familial relation that spurred their desire to work on application development. Does this personal or familial relationship to T1Ds increase the legitimacy of the applications they created? None of the developers sought personal financial reward for their work, does this increase or decrease the legitimacy of their work?