Controlling the iPancreas

Professor Frank Doyle's group is at the forefront of the computational side of the field of systems biology, having developed groundbreaking artificial pancreas technology that is currently being tested on patients with Type 1 diabetes

To begin, could you explain how the Doyle Group came to pioneer the development of an artificial pancreas (AP)?

Our work on the AP goes back 20 years to the time I started as an Assistant Professor at Purdue University. One of my colleagues in the department and still a close friend, Professor Nicholas Peppas, knew of my interest in systems biology and my expertise in control systems, and suggested we team up to look at controlled drug delivery for Type 1 diabetes; that was the beginning of our group's journey down an exciting research path that has led to the current state of clinical testing and device prototyping.

How does the Artificial Pancreas System (APS©) establish communication between continuous glucose monitors and insulin pumps?

The APS functions as a communication layer to allow devices (computer algorithms (controllers), glucose sensors, and insulin pumps) to interoperate in a seamless manner. The key to versatility is a plug-and-play architecture. All components are connected to the APS Human Machine Interface, which is the main part of the software responsible for all communication, data transfer, data logging, and display. We utilise device-specific codes to 'hand shake' with the APS, thus enabling universal compatibility. In this manner, a closed-loop system may be implemented and tested with different devices. Furthermore, the controller component has the same modularity and can be realised using different control structures, from a simple proportional-integrative-derivative controller to more sophisticated model predictive algorithms. Approximately 400 subject trials have been conducted around the world using our APS software.

Were there any significant challenges thrown up during the testing of a prototype of the computerised artificial pancreas device in patients with Type 1 diabetes, and how were these overcome?

Two of the key challenges were the variability of the human body (not only hour-to-hour but also day-to-day), and the danger of overdosing with insulin, a potentially lethal drug. To address the insulin overdosing problem, we built a system that calculated the circulating insulin in the body, and set a specific safety bound on the total amount of insulin that would be delivered. This arose from a particular trial in which the algorithm was beginning to overdose the insulin based on a particularly aggressive controller tuning. The MD halted the trial, and we questioned him on his rationale. As a result, we built that medical understanding as a safety limiter explicitly into the algorithm. The second challenge, human variability, continues to be problematic – but one way we have addressed this is through the use of flexibly programmable 'zones' for the core algorithm in our study. In that manner, we can program an acceptable range of glucose, allowing for the intrinsic variability of both the human body and the glucose sensor. The controller accomplishes the medical objective of stabilising glucose levels, but does not try to over-compensate, leading to inevitable 'fighting' between the controller and the glucose level.

You have been awarded US $4.5 million from the National Institutes of Health (NIH) to further develop AP for testing in outpatient trials. At what stage are you with these trials? What is the anticipated timeline for transitioning the artificial pancreas technology into clinical practice?

Our timeline for completely automated outpatient trials in the US is approximately two years from now; however, we have leveraged that NIH study with funding from JDRF and, together with collaborators at UVA, Padova University, and Montpellier University, we have already done preliminary outpatient trials in Europe. The recent NIH grant will enable us to better characterise the variability in the human body, and will also enable us to build understanding of the behavioural dimensions of subjects using an artificial pancreas.

Could the AP be used to treat other pancreatic disorders?

The artificial pancreas technology we have developed has broader ramifications than Type 1 diabetes – in effect, it is a sophisticated paradigm for controller drug delivery. As such, it has relevance to blood pressure control, control of anaesthesia, as well as drug dosing for cancer and HIV. They key challenge is to customise the computational model for the patient (ie. how the drug interacts with the body); design the safety components (eg. limits on drug delivery); and establish the medical objectives for the controller target.

Automating insulin

The **Doyle Group** at the University of California, Santa Barbara is pioneering an artificial pancreas system, after 20 years of research into insulin delivery using an algorithm normally deployed in oil refineries

Control system approaches are instrumental in the field of systems biology, which involves the application of theoretical approaches and the integration of experimental and computational research. Developing control systems for medical applications to treat diseases such as diabetes poses particular challenges. Physiological systems involve a multitude of interacting subsystems and networks, with multiple feedforward and feedback loops, and interactions at many levels. The dynamics vary from one individual to another, as well as within the same individual over time. No two people are alike, and this is especially true at the molecular scale in the body. For example, across the spectrum of subjects with diabetes, there are significant variations in how the cells respond to insulin, as well as other hormones in the body. It is also true that different individuals with Type 1 diabetes have varying severities of the disease, due to factors including age, exercise, diet and stress.

MEDICALLY INSPIRED ENGINEERING

One research group based at the University of California, Santa Barbara is at the cutting edge of overcoming these challenges in medical systems biology and biomedical control systems. Led by Professor Frank Doyle, the group's studies are wide-ranging and include Alzheimer's disease, heat stroke, Post-traumatic Stress Disorder (PTSD) and diabetes. Their work on the regulation of insulin delivery is now converging on a prototype artificial pancreas device, which could revolutionise the lives of those with Type 1 diabetes.

DOYLE GROUP INVESTIGATIONS

The Doyle Group is uniquely interdisciplinary, matching medical doctors with control engineers: "While many groups have diverse team members, our group has medical doctors working together on algorithms, and engineers helping support clinical trials," Doyle enthuses. "The result is 'medically inspired engineering', which is crucial to advancing the technology for this challenging disease." The team's technical developments are many and varied, including: a method for hypoglycemia alarming; a zone model predictive control strategy; a safety mechanism to limit insulin overdosing; monitoring and telemedicine; schemes for improved day-to-day management of insulin dosing.

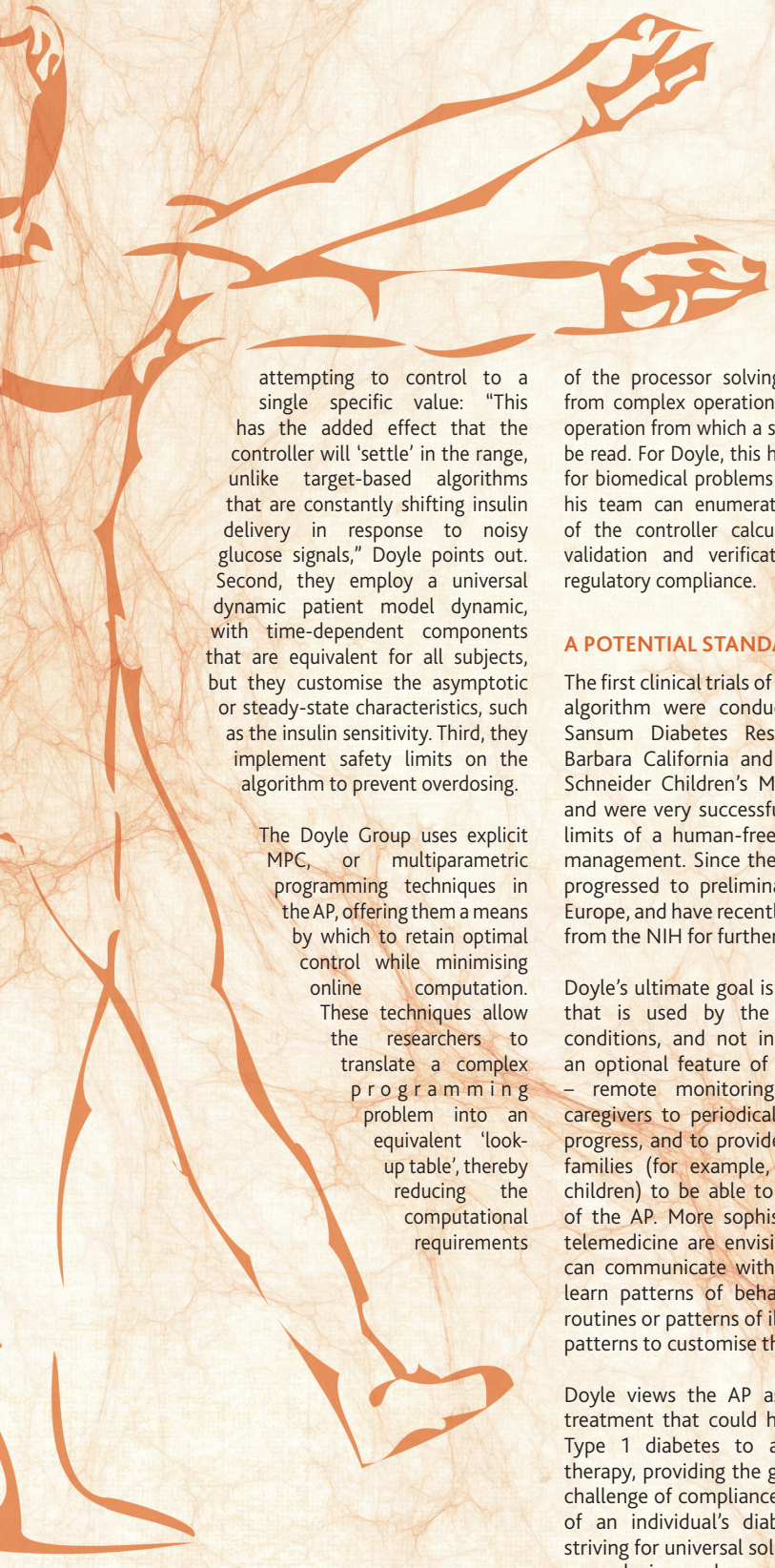
AUTOMATED ARTIFICIAL PANCREAS

Doyle's group is one of only a few in the world to demonstrate the feasibility of a completely automated artificial pancreas, with no patient input for meals. There is a wide variation in individuals' insulin pharmacokinetics; consequently, effective management of diabetes must take into consideration gender, age and body weight, as well as physical, psychological and hormonal stressors, which affect the need for insulin. For example, for patients with Type 1 diabetes, daily insulin requirements may need to be adjusted to compensate for stress; some are sensitive to stress and require increased insulin doses, while others do not. The difficulty in calculating such adjustments often results in poor blood glucose control.

The Artificial Pancreas System (APS) represents a candidate solution for this problem. The Doyle Group has designed personalised control algorithms within this system. The two key variables they aim to characterise are firstly how the body responds to insulin, and secondly, the interaction of meals and insulin: "These are the crucial 'gains' that affect how one designs a feedback controller for the APS, and how one tunes the controller to strike a compromise between over-delivery of insulin (very dangerous) and under-delivery of insulin (not therapeutic)," Doyle explains. However, there are no models that truly allow the prediction of how these quantities vary from individual to individual, so the researchers are using a combination of prior knowledge, including the patient's medical history, which contains parameters like total daily insulin utilised, to build customised models that are the heart of the control algorithm.

20 YEARS OF EXPERTISE IN MPC

At the core of Doyle's AP is an algorithm called model predictive control (MPC). His team was the first to publish this as a solution for the APS in 1996, although the core algorithm itself dates back over 40 years. Today, MPC can be found in everything from oil refineries to cars and aeroplanes, but the Doyle Group has adapted this powerful technology to the specific problem of insulin pump control. They have achieved this in a number of ways: first, by calculating insulin values that place a subject in an appropriate safe range, rather than



attempting to control to a single specific value: "This has the added effect that the controller will 'settle' in the range, unlike target-based algorithms that are constantly shifting insulin delivery in response to noisy glucose signals," Doyle points out. Second, they employ a universal dynamic patient model dynamic, with time-dependent components that are equivalent for all subjects, but they customise the asymptotic or steady-state characteristics, such as the insulin sensitivity. Third, they implement safety limits on the algorithm to prevent overdosing.

The Doyle Group uses explicit MPC, or multiparametric programming techniques in the AP, offering them a means by which to retain optimal control while minimising online computation. These techniques allow the researchers to translate a complex programming problem into an equivalent 'look-up table', thereby reducing the computational requirements of the processor solving the control algorithm from complex operations on a chip to a lookup operation from which a single value in a table can be read. For Doyle, this has particular significance for biomedical problems such as the AP, because his team can enumerate all possible solutions of the controller calculation, which facilitates validation and verification steps required for regulatory compliance.

A POTENTIAL STANDARD TREATMENT

The first clinical trials of Doyle's fully automated algorithm were conducted in April 2007 at Sansum Diabetes Research Institute, Santa Barbara California and then in July 2008 at Schneider Children's Medical Center in Israel, and were very successful in demonstrating the limits of a human-free algorithm for glucose management. Since then, the researchers have progressed to preliminary outpatient trials in Europe, and have recently been awarded funding from the NIH for further outpatient testing.

Doyle's ultimate goal is to deliver a technology that is used by the patient in free-living conditions, and not in a clinic. To that end, an optional feature of the AP is telemedicine – remote monitoring features that allow caregivers to periodically review the patients' progress, and to provide tools for the subjects' families (for example, the parents of young children) to be able to track the performance of the AP. More sophisticated applications of telemedicine are envisioned where the device can communicate with a remote database to learn patterns of behaviour such as exercise routines or patterns of illness, and exploit those patterns to customise the insulin therapy.

Doyle views the AP as a potential standard treatment that could help all individuals with Type 1 diabetes to automate their insulin therapy, providing the group can overcome the challenge of compliance, as well as the severity of an individual's diabetes: "We have been striving for universal solutions that will work for many devices and many subjects," he elucidates. "However, to achieve effective control, those universal solutions must be customised to the requirements and needs of the individual."

INTELLIGENCE

THE DOYLE GROUP

OBJECTIVES

The Doyle Group is one of the only groups in the world to demonstrate the feasibility of completely automated artificial pancreas (ie. without patient intervention at mealtimes). Its members are leveraging 20 years' expertise with MPC and chemical process control – powerful technologies that have been adapted to the specific problem of insulin pump control.

KEY COLLABORATORS

This project harnesses a unique multidisciplinary research team (MDs and engineers), co-located in Santa Barbara:

Dr Lois Jovanovic, MD, Sansum Diabetes Research Institute • **Dr Howard Zisser, MD**, Sansum Diabetes Research Institute **Dr Eyal Dassau**, UCSB • **Professor Dale Seborg**, UCSB

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FRANK DOYLE obtained his BS at Princeton (1985) and his MS at Cambridge University (1986) before completing a PhD at the California Institute of Technology (1991). Recent honours bestowed upon him include fellowship of the American Association for the Advancement of Science and the Institute of Electrical and Electronics Engineers. Professor Doyle's research interests include biosystems analysis, synthesis and control, with applications including drug delivery devices.