

People with diabetes cannot transfer the glucose in their bloodstream to various organs of the body for consumption or storage for later use. Blood glucose concentration (BGC) increases by absorbing carbohydrates in meals and converting them to glucose.

Blood glucose is consumed by the brain for energy, stored in the liver (as glycogen) for consumption when BGC drops to low levels a few hours after a meal, and transferred to muscle and fat cells for storage and utilization. The glucose transfer to liver, muscle, and adipose tissue can happen only if enabled by insulin. Insulin is produced and secreted by the pancreas, which also produces glucagon and digestive enzymes. Diabetes is an autoimmune disease where the cells producing insulin are compromised by the immune system. If most of these cells (beta cells in the islets of Langerhans of the pancreas) are destroyed such that no insulin is produced, insulin must be administered externally to regulate BGC. Type 1 diabetes (T1D) refers to people in this state. In type 2 diabetes (T2D), some beta cells are still functional, but the total amount of insulin produced is too low or the insulin produced cannot be used effectively. The treatment options for T2D include changes in lifestyle, the use of medicine to enhance insulin productivity or utilization efficiency, and insulin administration.

Glucose homeostasis is achieved by the release of appropriate amounts of insulin to lower BGC, release of glucagon (insulin release is stopped) to halt further glucose absorption to cells, and conversion of glycogen to glucose and its release to the bloodstream to prevent further drops in BGC. Maintaining the BGC within a narrow range is critical. Low BGC (hypoglycemia) causes a lack of energy in the brain, which compromises its operation and leads to dizziness, fainting, diabetic coma, or even death. High BGC (hyperglycemia) destroys the cardiovascular system, starting with the capillaries, leading to a lack of proper nutrition to various organs. High BGC also damages vision (retinopathy), the ability to sense by touch (neuropathy), renal functions (kidney failure), and delays wound healing.

The body has perfected a powerful multivariable control system that senses BGC levels and adjusts the doses of insulin and glucagon to keep BGC within the desired range, in spite of major disturbances such as meals, physical activities, and psychological stress. This control system breaks down if the beta cells are destroyed and insulin production is compromised. People with T1D administer three to five insulin injections daily or infuse basal and bolus insulin doses with insulin pumps to regulate their BGC in the target range (70–180 mg/dl). This manual glucose regulation is laborious, and many people with T1D experience hypoglycemia or hyperglycemia during their daily lives. The fear of hypoglycemia is a major concern in the minds of most people with T1D and their families, since it can be fatal if unnoticed and counteractions are not implemented. These can be as simple as drinking a glass of fruit juice or eating cookies; but such interventions may be delayed if

hypoglycemia occurs during sleep and is unnoticed. Hence, many families of young children must often sacrifice their sleep to monitor and prevent hypoglycemia.

THE ARTIFICIAL PANCREAS

Diabetes, in particular T1D, provides a challenging control problem. The complexity of glucose homeostasis, the nonlinearities and time-varying changes of BGC dynamics, the occurrence of nonstationary disturbances, time-varying delays in measurements and insulin infusion, and noisy data from sensors must be addressed in developing hypoglycemia alarm systems and artificial pancreas (AP) systems. The AP was conceived to automate the information collection, decision making, and insulin management of a person with T1D to maintain euglycemia, in spite of various daily disturbances. All AP systems have three basic components: *sensors*, *decision-making algorithms* (controllers), and *insulin infusion mechanisms* (such as insulin pumps). The types of sensors used determine the variables available to the control module. Since the first AP systems were conceived to automate the sequence of decisions and actions of the patient, the AP consisted of a glucose concentration sensor, a feedback control algorithm implemented on a computer, and an insulin pump. Closed-loop control of glucose concentration for people with T1D was first proposed over 40 years ago [1]. Dextrose (a sugar used as a meal) and insulin were fed directly to the venous system in clinical experiments that were conducted in hospital rooms. The results were very successful in regulating BGC. However, the first hybrid closed-loop control was approved for sale in the United States in 2017 [2]. Although this AP system seeks manual input entries for major disturbances to glucose homeostasis (such as meals) and reverts to manual control when faced with major challenges, it is a major achievement in the automation of insulin infusion based on closed-loop automatic control. Several different types of AP systems have been proposed to enhance the automation, use glucagon as a second manipulated variable, make use of wearable technologies to automate the detection of measurable disturbances (such as exercise and stress), and eliminate the manual announcement of meals.

One major obstacle in the transition from the hospital room to daily living environment was the time delays in receiving automated glucose concentration readings at a high frequency and delivering insulin via subcutaneous tissue rather than direct access to vasculature. Another challenge was the level of technologies to address these interactions of the AP with the human body and develop user-centric, reliable, and secure mobile devices.

Reviews of the literature provide detailed information about the progress in AP development, alternative technologies, and recent clinical studies [3]–[5]. A recent tutorial in *IEEE Control Systems Magazine* gives an account of the elements of an AP [6]. Four major sources of variations in BGC and daily concern are meals, exercise, sleep, and stress

The development of smartphones and advances in wireless communications enabled new generations of AP platforms on smartphones and currently on insulin pumps.

(MESS). Developments in several technologies were necessary to consider the development of fully automated AP systems that maintain BGC within the desired range, in spite of many manually unannounced MESS activities. Advances across several fronts enabled this achievement.

STRATEGIC INITIATIVES

The Juvenile Diabetes Research Foundation (JDRF) initiated an AP research consortium in 2006 and proposed an iterative road map to AP system development in 2009 that guided many AP research projects [7], [8]. During the same years, the Diabetes Technology Program of the National Institute of Diabetes and Digestive and Kidney Diseases provided significant investments to AP research. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the U.S. Food and Drug Administration (FDA), initiated public workshops to facilitate medical device innovation in the development of the AP beginning in 2010 [9]. Two annual international conference series, the Diabetes Technology Meeting and the Advanced Technologies and Treatments for Diabetes, brought academic researchers, FDA and National Institutes of Health representatives, and industry to provide a forum to report recent developments and discuss future research needs.

The fertile research environment created by the JDRF and NIDDK enabled many multidisciplinary teams to address various challenges, ranging from the development of better glucose sensors and insulin pumps to novel, model-based hypoglycemia prediction and automatic control algorithms. National and international collaborations of medical researchers, systems and control engineers, and device developers have accelerated research and development efforts, and major advances have been made in hardware, information processing, decision making, and automatic control.

ADVANCES IN HARDWARE AND COMMUNICATIONS

The technologies in the development of glucose sensors, wearable devices that report physiological information, wireless devices, and smartphones enabled various compact AP systems that can be used under free-living conditions. Early AP prototypes were implemented in laptop computers carried in backpacks. The development of smartphones and advances in wireless communications enabled new generations of AP platforms on smartphones and currently on insulin pumps. Cloud computing ushered in another wave of improvements by providing extensive

use of historical data, machine learning, and individualized advisory systems.

CURRENT RESEARCH CHALLENGES

While celebrating the success based on the contributions of many research groups and industrial research and development groups in achieving this milestone, several additional challenges must be addressed in developing the next-generation AP systems.

Meals, Exercise, Stress, and Sleep

MESS presents four major challenges to glucose homeostasis. The first-generation AP systems rely exclusively on glucose concentration information provided by a subcutaneous glucose sensor. Hence, control action can be made after sensing the changes in glucose concentrations. To introduce feedforward action, manual meal entries and manual adjustment of insulin infusion rates before starting physical activities are made. MESS represents measured (or measurable) disturbances. Automating the collection of data from sensors that can inform the presence of MESS factors before their impact on BGC will improve glucose control. This would necessitate a multivariable modeling and control framework, integrated with powerful machine learning and classification algorithms.

Faults and Failures in Hardware, Software, and Communications

Some hardware fault detection techniques have been incorporated in glucose sensors and insulin pumps. However, the techniques developed by the systems and control community can provide powerful fault detection and diagnosis and data reconciliation techniques that can enhance the AP and provide fault-tolerant control. Controller system performance assessment, recursive identification, and adaptive control contribute to control system designs that can improve AP performance.

Mass Transfer Limitations of Popular Glucose Measurement and Insulin Infusion Routes

The AP systems for use in daily living conditions necessitate medically safe and robust human-machine interfaces. Glucose measurements from blood vessels or insulin infusion to blood vessels are only done in clinical environments. Subcutaneous glucose sensors and insulin infusion to subcutaneous tissue have been widely used solutions to

provide medically acceptable and safe solutions. Both offer significant delay in data collection and control action due to mass transfer limitations. Several innovative solutions are being studied to reduce these delays and their effects.

ARTICLES IN THE SPECIAL ISSUE

The six articles in this special issue address some of the critical challenges:

- » “Glucose Sensor Dynamics and the Artificial Pancreas,” by Huyett, Dassau, Zisser, and Doyle, addresses the consequences of subcutaneous glucose sensor dynamics for measurement accuracy and controller performance.
- » “Insulin Estimation and Prediction,” by Bondia, Romero-Vivó, Ricarte, and Díez, presents the challenges of using population models for the estimation of insulin pharmacokinetics and advocates real-time state estimation and adaptation of pharmacokinetic parameters by using continuous glucose measurements and observer techniques for computing the blood insulin concentration to use in AP systems.
- » “The Artificial Pancreas and Meal Control,” by El Fathi, Smaoui, Gingras, Boulet, and Haidar, discusses the effects of meals (a major disturbance to glucose homeostasis) and control of post-meal glucose concentrations.
- » “Individualized Model Predictive Control for the Artificial Pancreas,” by Messori, Incremona, Cobelli, and Magni, proposes the adaptation of the model used in model predictive control by various individualization techniques that provide model updates and evaluate the effects of individualization with simulation studies.
- » “Multimodule, Multivariable Artificial Pancreas for Patients with Type 1 Diabetes,” by Turksoy, Littlejohn, and Cinar, presents a multimodule, multivariate, adaptive AP to mitigate several challenges simultaneously. Adaptive control tolerates unpredictable changes and external disturbances by quickly adjusting the controller parameters. Physiological variables provide additional information that enable feedforward action for measurable disturbances, such as exercise, and enhance fault detection and diagnosis activities.
- » “Overnight Hypoglycemia and Hyperglycemia Mitigation for Individuals with Type 1 Diabetes,” by Bequette, Cameron, Buckingham, Maahs, and Lum, presents various strategies for overnight hypoglycemia and hyperglycemia detection and mitigation, leveraging predictive low-glucose to suspend insulin infusion.

The landscape of AP development includes international large companies, start-ups, and do-it-yourself groups [10]. The motivation to develop better AP solutions is generating many alternatives and options that will benefit people

with T1D. Several research groups and companies are proposing novel AP control methods, new glucose sensors, the use of glucagon as a second manipulated variable to better mitigate hypoglycemia, predictive hypoglycemia warning systems, and algorithms to mitigate the effects of stress and sleep. The commercial launch of the hybrid closed-loop system is expected to accelerate additional AP configurations seeking FDA approval, and several large clinical studies are in progress. There is room for improvement in these techniques and devices, and the systems and control community is well positioned to make significant contributions in AP research and development.

AUTHOR INFORMATION

Ali Cinar (cinar@iit.edu) received the Ph.D. degree in chemical engineering from Texas A&M University, College Station. He is a professor of chemical engineering and biomedical engineering at the Illinois Institute of Technology, Chicago, and he has been the director of the Engineering Center for Diabetes Research and Education since 2004. His current research interests include agent-based techniques for the modeling, supervision, and control of complex and distributed systems; the modeling of diabetes; angiogenesis and tissue formation; and adaptive control techniques for artificial pancreas systems. He has published two books and more than 200 technical papers in refereed journals and conference proceedings. He is a Senior Member of the IEEE and a Fellow of the AIChE.

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