Closing the loop. The development of an artificial pancreas that automatically links devices to measure blood glucose levels (left) and deliver insulin (right) via advanced computer programs should help to reduce the burden of diabetes management on people with this disease.

(Image credit: Fang-Mei Liu, The Scientific Consulting Group, Inc.)
BIOENGINEERING APPROACHES FOR THE DEVELOPMENT OF AN ARTIFICIAL PANCREAS TO IMPROVE MANAGEMENT OF GLYCEMIA

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health
Large prospective clinical trials have established the long-term benefits of intensive blood glucose control in people with type 1 or type 2 diabetes. The research has shown that good blood glucose control is a key factor in lowering risk of many of the devastating long-term complications of diabetes, including blindness, kidney failure, and cardiovascular disease. For children and adults with type 1 diabetes, this has led to the widespread use of intensified insulin therapy to prevent or minimize the onset and progression of diabetes-related complications. However, the global application of this approach has been limited by a lack of technologies that would enable people with diabetes to easily and appropriately adjust delivery of insulin in response to minute-to-minute changes in circulating glucose. Currently, most people receiving insulin treatment for diabetes need to check their blood glucose levels several times a day with finger sticks and hand-held glucose meters, so that they can adjust their insulin doses to avoid extreme high and low glucose levels. For most insulin-treated people, this is very difficult. Not only is it uncomfortable, but more importantly, this approach cannot replicate the exquisitely precise and dynamic regulation of insulin levels achieved by the insulin-producing beta cells within the pancreatic islets. Instead, individuals only see brief snapshots of the pattern of glucose changes over a 24 hour period. Thus, despite a person’s best efforts, glucose levels can rise excessively (hyperglycemia)—particularly after meals—and at other times fall dangerously low (hypoglycemia), causing unconsciousness, seizures, and even death. Moreover, as the frequency of hypoglycemia increases, individuals lose the ability to perceive its warning symptoms, preventing them from taking corrective action by eating, a phenomenon called hypoglycemia unawareness. As a result, most people who need to treat their diabetes with insulin do not meet optimal targets for glucose levels, because their immediate fear of hypoglycemia outweighs their fear of future, long-term complications (see sidebar, “Hypoglycemia: An Achilles Heel in Therapy To Prevent Diabetes Complications”).

To improve insulin treatment and the care for people with diabetes, new methods of insulin delivery need to be developed and tested that more effectively simulate the functions of beta cells. There is a need for: 1) more accurate and rapid detection in real time of glucose levels throughout the day; 2) improved methods for rapidly translating real-time glucose measurements into adjustments in insulin delivery; 3) infusion devices that can deliver insulin more effectively, conveniently, and physiologically; and 4) improved insulin preparations that can more rapidly respond to changes in blood glucose.

Encouragingly, scientists, engineers, and patients have already taken the first steps toward the development of a mechanical “artificial pancreas.” Mechanical continuous glucose monitors (CGMs) are now being used clinically to give people with diabetes and parents of young children with the disease the ability to view real-time glucose levels, review trends and fluctuations in recent blood glucose levels, and receive alerts when blood glucose levels become too high or too low. These CGMs combine a continuous glucose sensor with a unit displaying glucose levels. The sensors are inserted...
Advances in diabetes technology are bringing hope for improved glycemic control. The top part of the figure shows wide swings in glucose levels over the course of 200 days in the life of an 8-year-old girl with type 1 diabetes a decade ago. The bottom part of the figure shows glucose levels from multiple days (differently colored lines) in a newly diagnosed youth with type 1 diabetes using a CGM, demonstrating comparatively reduced swings in glucose and infrequent dips into hypoglycemia (below the green shaded target range). (Top image courtesy of Drs. Jay Skyler and Norma Kenyon, University of Miami School of Medicine; bottom image courtesy of Dr. Bruce Buckingham, Stanford University School of Medicine.)

under the skin for up to 3 to 7 days and transmit readings of glucose levels in tissue fluid (called interstitial fluid)—an approximation of blood glucose levels—every 1 to 5 minutes to a receiver carried by the individual. Although currently approved glucose sensors remain less accurate than traditional blood glucose meters, they offer people with diabetes who use these new devices an opportunity to spend more time in the close to normal glucose range, without increasing the risk of brain injury from severe hypoglycemia. NIH-sponsored research is helping to accelerate validation of these devices—for example, the NIH-sponsored Diabetes Research in Children Network (DirecNet) is studying use of these sensors and their ability to improve management of type 1 diabetes in children. Thus, the availability of real-time continuous blood glucose monitoring represents a critical first step toward the development of a mechanical artificial pancreas.

Before a mechanical artificial pancreas can be fully realized, however, other important biological and engineering issues will need to be addressed. To more closely approximate the blood glucose lowering effect of pancreatic beta cells, a series of incremental steps will need to be introduced. These steps include the development of more accurate and robust glucose-sensing devices, improved methods of insulin delivery,
and the development of improved computer algorithms that appropriately translate glucose measurements into changes in the delivery of insulin, including its interruption—i.e., methods that can “close the loop” between glucose sensing and insulin delivery. Specifically, there is a need to produce smaller insulin infusion devices, optimize the site of insulin delivery in the body, develop more effective and rapidly-acting insulin preparations, and determine the benefit of combining insulin delivery with delivery of its counterbalancing hormone, glucagon, to reduce hypoglycemia. Amylin, a hormone co-secreted with insulin by beta cells, is also under study. Amylin has potent inhibitory effects on gastric emptying, appetite, and food intake in humans, and could be administered as part of an integrated closed-loop system for better control of post-prandial (meal-related) glucose excursions. Studies will also need to be done to assess the capacity of the artificial mechanical pancreas to improve overall metabolism, increase patient well-being, restore hypoglycemia awareness, and preserve existing pancreatic beta cell function. For example, DirecNet and another NIH-sponsored network, Type 1 Diabetes TrialNet, are collaborating to study use of a closed-loop system to initiate intensive metabolic control in people with new-onset type 1 diabetes.

Moreover, adoption and use of a new technology for diabetes treatment, such as an artificial pancreas, in real-life settings require behavior change and modification. Key factors, such as the extent to which people with diabetes accept a technology, use it appropriately, consider it as beneficial and convenient versus burdensome or intrusive, and identify its clinical benefits, are all equally important for success. The user interface requirements will also be different across the lifespan. For example, the way a technology is used may require different behavioral approaches when it is employed in different age groups, such as young children, adolescents, and adults. For a new technology to be successful and widely accepted, it should help individuals overcome problems related to diabetes self-management and reduce the burden of living with diabetes. The high prevalence of diabetes-related physical, cognitive, and psychological limitations and disabilities also necessitates that a technology address accessibility and universal design features. For example, a device should be easy to operate for people with visual impairments and require only basic levels of math

A closed-loop control system will rely on several key elements, including glucose sensors, insulin delivery devices, and a control algorithm reading sensor data and computing optimal insulin delivery. The control algorithm will be initialized by a screening procedure that will tailor the algorithm to each person’s specific parameters, and will be informed in real time by system observers – subroutines that estimate the state of a person’s glucose and insulin requirements, as well as behavioral specifics such as rest or physical activity. The system development and testing will be greatly facilitated by comprehensive in silico environment, which will permit efficient and cost-effective pre-clinical trials. The outcome of closed-loop control will be judged not only by metrics of average glycemia, such as HbA1c, but also by risk measures accounting for the expected reduction in hypoglycemia and hyperglycemia. (Image courtesy of Dr. Boris Kovatchev, University of Virginia.)
and reading skills. The successful adoption of devices may also facilitate their integration into telemedicine approaches to diabetes management, an important new area of study.

While scientists are vigorously pursuing this very encouraging therapeutic approach for diabetes treatment, there are likely to be certain limitations to a mechanical artificial pancreas. For example, there are many other factors besides glucose that modulate islet function that would not be recognized by a glucose-driven mechanical pancreas. Thus, a complementary strategy to pursue is to use bioengineering to develop cellular or molecular methods for replacing or regenerating pancreatic islets. Currently, islet transplantation is limited by the sparse supply of donor islets, as well as by the destructive immune response generated by transplanted beta cell antigens (autoimmunity) and foreign tissue (rejection). These barriers to islet transplantation may be overcome by: 1) genetic alteration of beta cells and/or optimization of immunobARRIER-encapsulation technologies so that the transplanted beta cells are not recognized by a person's immune system; 2) the generation of beta cells from stem cells or gene therapy; and 3) technologies that may facilitate the ex vivo expansion of generated cells and their long-term preservation. These approaches offer great promise in the future, although it will likely be many years before they can be applied clinically, particularly in children. A potential intermediate step could be a bioartificial pancreas involving combinations of biological and engineering approaches. For example, islet transplantation might be combined with a mechanical artificial pancreas to supplement insulin delivery and reduce hyperglycemic stress on marginally functioning islet transplants. The topic of islet replacement is covered in greater depth in “The Beta Cell” chapter.

Bioengineering has improved diabetes care today and offers considerable potential for the creation of an artificial mechanical pancreas for the treatment of diabetes in the future. This chapter describes research advances and opportunities that could make the achievement of this goal a reality in the next decade.
Introduction of Short-Term Continuous Glucose Monitoring into the Clinic: A major advance has been the development by industry of CGMs for use by people with diabetes. These needle-like percutaneous glucose sensors use an enzyme (glucose oxidase) coupled to electrochemical detectors to measure glucose levels. They are inserted under the skin by the user, operated for several days to one week, and then replaced. The combined number of users is estimated to have reached several hundred thousand and is still growing. In addition to facilitating self-monitoring of glucose levels by individuals, the most important lesson learned from the use of this glucose sensor technology is that blood glucose actually varies to a much greater extent during the course of the day than was previously thought, even in presumed well-controlled individuals. The sensors have also made possible research on, and initial clinical applications of, controllers, algorithms, and automated insulin delivery systems. Studies conducted by the NIH-supported DirecNet have investigated the capacity of current glucose monitoring technology to improve the management of type 1 diabetes in children. While there are still a number of caveats and limitations to current devices, such as the requirement to calibrate devices using finger sticks and the need to do so frequently, developments to date in continuous glucose monitoring technology have laid the groundwork for a new era of advances in therapies for diabetes.

Continuous Glucose Monitoring Enhances Intensive Insulin Treatment: Clinical studies have shown significant benefits of CGM use by people with diabetes. Recent clinical trials have focused on CGM use among adults and children already on intensive insulin therapy, and whether it can improve hemoglobin A1c (HbA1c) values and reduce time spent outside of normal blood glucose levels. These trials have shown that CGMs, when used near-daily, not only help people with type 1 diabetes get into control—which can have a significant positive impact on lowering the risk of complications—but also enable them to stay in control without increasing the near-term risk of hypoglycemia. Study results have also highlighted particular challenges that will need to be addressed in future research, including identifying barriers to CGM use in children and adolescents so that they may reap the full benefits of this technology.

Development of New Algorithms To Help “Close the Loop”: A key aspect of closing the loop between glucose sensing and insulin delivery in a mechanical artificial pancreas is the development of algorithms, special instruction sets for computers. In the case of the artificial pancreas, these sophisticated computer programs are needed to interpret continuous glucose sensor data and instruct the insulin pump to dose the proper amount of insulin, and also potentially direct glucagon delivery to help prevent hypoglycemia. Two primary algorithm approaches are under investigation: the classic proportional-integral-derivative (PID) algorithm, and model predictive control (MPC). These algorithms are already being tested in clinical trials of closed-loop blood glucose control in carefully controlled hospital settings, with encouraging results. The further development of these algorithms is essential for the rapid implementation of closed-loop glucose control.
Development of In Silico Models as a Resource for Pre-Clinical Testing: In 2008, the FDA accepted the use of an in silico, or computer-based, model of diabetes as a pre-clinical testing tool for closed-loop research. This and other optimized simulators will facilitate the development of new control algorithms by enabling researchers to test and refine artificial pancreas algorithms quickly. It will also allow for computer-based algorithm comparisons. Finally, in silico models may eliminate or minimize the need for testing in animal models, allowing investigators to focus instead on in-hospital human clinical trials, potentially saving time and money. This approach may also lead to a more expedited and better defined process of receiving regulatory approval for human trials of closed-loop systems. As the simulator is equipped with a wide array of tools for precise fine-tuning, it should help to bring promising algorithms closer to perfection in a shorter time frame.

HYPOGLYCEMIA: AN ACHILLES HEEL IN THERAPY TO PREVENT DIABETES COMPLICATIONS

Keeping blood glucose levels under control has important, proven health benefits for people with diabetes. Dramatic reductions in risk for eye, kidney, nerve, and cardiovascular complications are all possible with good control. Yet, current strategies to achieve this goal come with a serious risk: abnormally low blood glucose, or hypoglycemia. While usually mild and easily treatable, severe hypoglycemia can lead to seizures, coma, and even death. Therefore, researchers are focused on finding ways to prevent or reduce hypoglycemia in people with diabetes.

Intensive insulin therapy is the biggest culprit in hypoglycemia. Recommended for most people with type 1 diabetes and some with type 2 diabetes, this aggressive treatment strategy requires individuals to monitor blood glucose levels frequently throughout the day, and to balance food intake and exercise with frequent doses of insulin to maintain blood glucose levels in a healthy target range. If the amount of insulin administered exceeds the body’s needs, however, blood glucose levels can fall precipitously. Acute episodes of hypoglycemia are a major complication for people with type 1 diabetes. Events occur on average 2 to 4 times a week; a severe bout causing loss of consciousness is rarer, but, on average, can occur annually. It is estimated that 2 to 4 percent of people with type 1 diabetes die as a result of brain injury or arrhythmia due to a hypoglycemia event (13). Children are very vulnerable to hypoglycemia, especially at night. Although hypoglycemia is less frequent in people with type 2 diabetes, even among those treated with insulin, the risk of severe events progressively increases with disease duration. As a result, many people with diabetes who are treated with insulin have difficulty meeting target goals for blood.
glucose control, because their immediate fear of hypoglycemia overshadows their fear of future long-term complications.

The urgency of addressing hypoglycemia as a complication of intensive insulin therapy first became clear in the NIH-led Diabetes Control and Complications Trial (DCCT). This trial in people with type 1 diabetes showed for the first time that rigorous glycemic control, achieved through intensive insulin therapy, dramatically reduces the risk of developing long-term serious eye, kidney, and nerve complications of diabetes. Together with similar results observed for people with type 2 diabetes in the United Kingdom Prospective Diabetes Study, the DCCT findings led to current recommendations for blood glucose control in people with diabetes. However, the DCCT also reported a 3-fold higher rate of severe hypoglycemia in participants who were in the intensive insulin therapy arm of the trial, compared to those in the then-standard-treatment arm—revealing hypoglycemia as the “Achilles heel” of intensive insulin therapy. This vulnerability was reinforced recently by results from the NIH-led Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial. The ACCORD trial found that attempts to lower blood glucose levels to near normal levels (lower than current recommendations) in older people with longstanding type 2 diabetes using a variety of methods, including intensive use of insulin, resulted in a 3-fold higher rate of hypoglycemia in the intensively treated group than in the group receiving standard treatment.

Because of the tremendous long-term health benefits of good glucose control demonstrated by the DCCT, its follow-up study, and related studies, researchers are working vigorously to find ways to engineer blood glucose monitoring and insulin therapy so that people automatically get the right insulin dose at the right time—thus avoiding episodes of hypoglycemia. This highly anticipated artificial pancreas technology is discussed in the main chapter text. As this research moves forward, it is also important to study hypoglycemia and find ways to minimize it so that people with diabetes can reap the full benefits of good control now. For example, a key factor in severe hypoglycemia events is “hypoglycemia unawareness.” Individuals with this condition lose the ability to recognize impending hypoglycemia and take protective action, such as eating. Compounding this problem, repeated episodes of hypoglycemia attenuate the body’s ability to counteract falling blood glucose levels, leaving people more vulnerable to severe hypoglycemia. Elucidating how the body senses and defends itself against falling glucose levels—and how hypoglycemic episodes alter these behavioral and biological defenses—is thus critical not only for developing strategies that can limit acute hypoglycemia episodes, but also for reducing long-term risk of severe hypoglycemia. Scientists are making progress in this area. For example, a complex network of “glucose sensors” has been described in both the brain and tissues outside the brain, with those in the brain most likely playing the dominant role. Recent studies suggest that previous hypoglycemic episodes induce adaptations in brain glucose sensing via changes in neurotransmitters, cellular receptors, and the metabolic efficiency of glucose-sensing cells—thus revealing a number of potential therapeutic
targets for drugs to minimize hypoglycemia and potentially prevent development of hypoglycemia unawareness and defects in glucose counter-regulation.

Another problematic aspect of hypoglycemia is its effect on brain function and the potential for injury. In general, tasks that primarily involve higher cognitive processes, such as following directions for medication, are more sensitive to acute hypoglycemia than simple motor tasks, such as picking up a piece of paper. In more severe episodes, the insult to the brain can result in seizures, coma, and even death. New strategies to protect the brain from acute hypoglycemia-induced injury are essential for optimizing the benefits of insulin therapy. One prospect is “alternative fuels.” While glucose is its primary fuel source, the brain can utilize alternative fuels—such as the molecule acetate—to maintain its energy requirements. Exposure to prolonged fasting and/or repetitive episodes of hypoglycemia appears to enhance the brain’s ability to utilize alternative fuel sources. For example, researchers have found that brain uptake of acetate is increased in people with type 1 diabetes receiving intensive insulin therapy—suggesting that these individuals, by virtue of their increased exposure to hypoglycemia, develop an enhanced ability to use alternate fuels in the brain, increasing the appeal of this potential therapeutic approach. Moreover, alternate fuels might help by protecting the brain during acute hypoglycemia while at the same time not causing deleterious hyperglycemia.

In their ongoing battle to overcome hypoglycemia, scientists can draw on many recent advances. For example, studies have shown that islet transplantation—an experimental therapy currently being used to treat “brittle” type 1 diabetes—is highly effective in reducing severe hypoglycemia events, even in cases in which transplant recipients have subsequently lost their insulin independence. This beneficial effect of islet transplantation has also been shown for hypoglycemia awareness, which is restored after transplantation and sustained even if the transplant fails—observations that researchers can exploit in developing new therapies (see the chapters on “Type 1 Diabetes and Autoimmunity” and “The Beta Cell” for more information on islet transplantation and cell replacement therapies). Tools such as newly improved animal models, gene therapy, and selective gene “knockdowns” in brain cells provide an opportunity to answer questions about glucose sensing that could lead to ways to restore the body’s normal ability to counteract hypoglycemia. Studies of alternate brain fuels that could lead to new strategies to protect the brain from hypoglycemia will benefit from recent advances in brain imaging methods (fMRI, MR spectroscopy, PET). Combined with work on artificial pancreas technologies, these opportunities provide hope that people with diabetes will soon be able to treat their disease without the fear of hypoglycemia.
The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, anticipated current efforts to develop biomechanical approaches to insulin replacement and, ultimately, an artificial pancreas. To help speed progress, these efforts have been fostered through strategic planning processes for the Special Statutory Funding Program for Type 1 Diabetes Research and through the 2006 “Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan.” As opportunities to advance and refine glucose sensing, insulin delivery, algorithm development, and other key aspects of an effective closed-loop system for patients continue to evolve at a rapid pace, new directions for research have been identified to help guide these efforts.

**Glucose Sensors**

The unique advantage of the continuous glucose sensor is its potential value for directing insulin dosing and for hypoglycemia warning. In contrast to the intermittent information provided by finger stick glucose monitoring, continuous sensors can provide minute-by-minute glucose trend data. A reliable and accurate glucose sensor is key to the implementation of new therapies based on insulin delivery devices, automated control systems, and faster-acting insulins, and is absolutely essential to the safety of these therapies. For widespread acceptance, the sensor must be unobtrusive and user-friendly, require only occasional recalibration, and otherwise be generally suitable to a broad group of people with diabetes.

**Key Questions**

- Can accuracy and reliability of glucose sensors be improved?
- Can new glucose-sensing technologies be developed?
- Will the incorporation of nanotechnology strategies and the use of smart biomaterials be able to improve reliability and durability of sensors?
- Will it be possible to develop a reliable and durable implantable sensor?
- Will it be possible to develop new technologies/strategies for a noninvasive, reliable, low cost, continuous glucose sensor?
- Will universal design strategies for sensor development be applied to facilitate use by people with diabetes?

**Future Directions**

- Develop improved glucose sensors.

There is a need for a new generation of sensors that have sufficient overall reliability and safety to support more aggressive therapies and can be expected to be widely acceptable by people with diabetes. The sensors should be small, fully implantable for periods of months to years, require only occasional (weekly to monthly) recalibration, be accurate enough for insulin dosing and warning of hypoglycemia without the requirement for
confirmation by finger stick, be easily implanted and replaced, and be unobtrusive to the user. Research in the field of nanotechnology, and application of smart biomaterials to improve sensing sensitivity and accuracy and promote biocompatibility, may contribute to the development of more effective glucose sensors. It is important to facilitate the introduction and development of new glucose detection principles, such as optical, ultrasound, and magnetic-impedance-based detection. The development of non- or minimally-invasive glucose sensors that are specific, continuous, and reliable is a critical step in reaching the goal of an artificial mechanical pancreas.

- Validate glucose-sensing technologies.

Glucose sensors need to be tested extensively and remain accurate under a variety of conditions such as during exercise, sleep, hyperglycemia, and especially hypoglycemia. There is a need to develop an acceptable implantation approach, including establishing an appropriate implantation site, development of methods for implantation and replacement, and documentation of device biocompatibility. It is also important that the sensor responds more rapidly to changes in glucose, so that the time lag compared to blood measurements is sufficiently short. In parallel with glucose measurements, it may also be advantageous to continuously monitor certain physiologic variables such as heart rate, temperature, perfusion in the vicinity of the sensor, physical activity, gastric emptying, lactate, and insulin. Implanted telemetry devices that send sensor data to external receivers must be small, long-lived, and hermetic. New strategies for data management will be needed to distribute and use the continuous stream of information most effectively. Development and introduction of this type of glucose sensor system is critical because of its central importance to clinical implementation of new insulin replacement technologies and its potential for widespread acceptance by users.

- Translation.

The effective transfer of technology from the research stage through industrial development and on to clinical introduction requires special attention. It is also crucial that information from clinicians and users is rapidly fed back for incorporation in technology evolution. New and more thoughtful approaches to technology transfer may be needed. For example, application of universal design principles would stress making glucose-sensing devices usable by all patients, to the greatest extent possible, without the need for adaptation or specialized design at the user end. The issue of interoperability of the devices and the potential application of universal design strategies must be taken into consideration for better usability of the devices at the point of care, and for collection and transmission of data to health care providers—leading to more effective feedback and greater quality of care (see the “Telemedicine” topic in this chapter). Translation will also require diabetes health care providers to learn ways to use the output from these devices in a way that improves outcomes and enhances adherence to diabetes self-management issues.

Algorithm Development—In Silico/Simulation Models

People with diabetes face a life-long optimization problem: to maintain strict glycemic control without increasing their risk for hypoglycemia. The engineering challenge related to this problem is to design algorithms that use automated insulin delivery to exert optimal closed-loop control of glucose fluctuations. Fortunately, the mathematical modeling of glucose-insulin interaction is already one of the most advanced applications of quantitative science to medicine. Beginning with
the now classic Minimal Model of Glucose Kinetics (MMGK), a number of elaborate models have been developed. These models can be classified in three broad classes: (1) models to measure parameters that are not accessible by direct lab tests, such as MMGK assessing insulin sensitivity; (2) models to simulate, which enable in silico pre-clinical trials; and (3) models to control, which are used to empower algorithms such as MPC. Because computer simulation is a mainstream engineering tool, the recently developed first computer simulator capable of substituting for animal trials in certain pre-clinical experiments holds great promise to accelerate the development of closed-loop control systems and to optimize clinical trial design. Due to the complexity of glucose regulation, a person’s response to insulin can vary even under identical conditions. Thus, an additional requirement for a successful closed-loop control strategy is that it will have to be adaptive and to account for both changes in physiology and perturbations caused by a person’s behavior. The key to adaptation is system observation. An approach to closed-loop control of emerging importance is thus modular design, including not only control algorithms, but also automated observers, which estimate in real time the physiological, and possibly behavioral, states of the person. With this modular design in mind, several key questions emerge.

Key Questions

• What outcome measures are suitable for judging the effectiveness of closed-loop control in relatively short-duration clinical trials? What would be the “standard” performance criteria? What degree of control error is acceptable?
• What are the requirements for designing control modules?

• Can in silico models of human metabolism be improved by making them more powerful in terms of generating “virtual participants” for in silico trials? Can a rich tracer database on type 1 diabetes (adult and children) be developed? Can counterregulation and exercise be incorporated? Can a type 2 diabetes simulator be developed?
• What safety features can be incorporated into controllers?

Future Directions

➢ Using system biology approaches, develop a comprehensive computer simulation environment allowing for efficient and cost effective in silico experiments with diabetes treatments.

This should be a large-scale collaborative effort, with several centers contributing data and engineering expertise. Archival databases need to be scanned for useful information. However, for this effort to be successful, additional data collection is required to reconstruct critical elements of the human metabolic network, most notably hypoglycemic counter-regulation and the metabolic effects of physical activity.

➢ Develop effective closed-loop algorithms for clinical and outpatient use.

One size may not fit all in terms of algorithms for an artificial pancreas. Patient-to-patient variability and individual differences could render this difficult—thus, creating a generic, off-the-shelf algorithm might not be feasible. It might be necessary to develop a unique control for each individual, which would be time-consuming and costly. Current sensors are not
sufficiently accurate, and insulin delivery systems now in use do not deliver insulin rapidly enough or to the optimal site (the portal vein). Robustness of control is also yet to be achieved for everyday activities (e.g., exercise, stress, and meals). An approach to overcome this challenge could be to develop a standardized set of observation and control modules that can be assembled into individually-tailored algorithms, including, but not limited to, modules that direct:

- Detection of glucose sensor errors caused from lags in glucose transport between blood and interstitial fluid;
- Mitigation of time lags inherent with glucose sensor analyses and subcutaneous insulin delivery;
- Hypoglycemia prediction, alarms, and prevention via automated insulin pump control, including through automated, sensor-controlled interruption of insulin delivery.
- Overnight closed-loop control;
- Automated, sensor-controlled administration of small doses of glucagon during impending hypoglycemia;
- Bio-behavioral control combining steady-state closed-loop control with behavioral, user-initiated “open-loop control” of meals and physical activity. During open-loop control, the bioengineering system would assume an advisory role, providing information to the user;
- Control-to-range, which aims to prevent extreme glucose excursions, but not necessarily the maintenance of blood glucose level at a certain preset target.

A high degree of collaboration and coordination between multiple centers is necessary to develop such modules and requires a combination of modeling, in silico, and clinical studies. While it is envisioned that in silico trials may accelerate the development process, in silico experiments cannot serve as the definitive answer to the questions asked—rather, they may indicate which treatment scenarios are ineffective, and help with the selection of an algorithm for subsequent clinical studies. Clinical trials are required to provide definitive validation of all methods.

**Insulin—Improving Delivery and Formulation**

Since the discovery and preparation of insulin nearly a century ago, the attempt to mimic insulin’s real-life physiologic properties has been and remains a challenge. Exogenous insulin replacement therapy via injection or pump can be affected by modulating the insulin formulation per se, by changing the delivery route, and by adjusting the dosing scheme. Alternative insulin delivery technologies offer the potential to improve glycemic control without the cost, safety, and resource-availability limitations of cell- and gene-based therapies. A number of approaches aim to provide commercially available insulin more rapidly or less invasively than is achieved with current methods; this could be achieved through novel technologies for continuous infusion under the skin or into the abdominal cavity, as well as through pulmonary, oral, and transdermal routes to decrease the number of required daily injections. Several alternative delivery approaches require a novel device combined with uniquely formulated insulin. Each approach, whether applied externally or implanted, includes electromechanical devices with glucose sensors and delivery systems and/or glucose-responsive materials based on competitive glucose binding or enzyme-controlled mechanisms. Some approaches have even attempted to build the glucose-sensitivity directly into the insulin molecule to eliminate the need for devices altogether. Technical challenges in this field include
optimizing device material biocompatibility, improving the accuracy and increasing the rapidity of glucose-responsive action, eliminating the potential for unwanted delivery of excess insulin, and reducing the immunogenicity associated with alternative sites of administration and/or modification of the insulin molecule.

**Key Questions**

- Which insulin delivery approaches result in clinically relevant improvements and are acceptable to the user?
- How do market-specific cost constraints influence the optimization of novel delivery methods, devices, and insulins?
- What changes in insulin chemistry and/or physical properties would most likely improve its use in alternative delivery routes, devices, and/or materials?
- How can the potential risk of alternative delivery sites and insulin chemistries to produce unwanted metabolic, toxic, or immunogenic effects be quantified and reduced?
- How may the automated delivery of insulin counter-regulatory hormones such as glucagon be integrated into current or future closed-loop systems? What changes in glucagon chemistry and/or physical properties are needed to have more effective and stable glucagon formulations for delivery by pumps?

**Future Directions**

- Develop integrated insulin delivery systems that improve the quality of life.

Daily diabetes management should not be overwhelming or hugely time consuming to the individual. Devices should be user-friendly and any functions (checks, dosing adjustments, refills, recharging) handled quickly, accurately, and discreetly. The “patch pump” concept is emerging; however, cost margins currently limit widespread adoption. Integration of pumps with glucose-sensing devices will reduce the need to carry or insert multiple devices. Development of fully implantable devices will further minimize inconvenience and visibility as long as maintenance procedures are also kept to a minimum. In addition, fully implantable systems potentially offer alternative insulin delivery routes, such as the vasculature or the abdominal cavity.

- Develop failsafe devices or biomaterials that respond based on low glucose levels to release...
glucagon or other insulin-counteractive therapeutics to prevent hypoglycemia.

The major immediate clinical risk of state-of-the-art methods of insulin delivery is severe hypoglycemia due to the dangerous “dumping” of insulin from highly insulin-loaded materials and devices. Therefore, it is essential to develop approaches that link delivery of insulin and glucagon with devices that monitor glucose levels to reduce the excessive or inappropriate administration of insulin and to correct impeding hypoglycemia.

- **Reduce immune responses to facilitate alternative site and/or long-acting polymeric insulin delivery systems.**

One of the factors that can diminish the ability of insulin or insulin delivery devices or glucose sensors to act/operate effectively is the induction of immune responses. Thus, the development of new insulins or delivery and monitoring systems will require the development of materials that reduce the risk of immune reactions that could impair function over time.

- **Develop new insulins with increased stability at high concentrations and minimal, reproducible subcutaneous absorption delay time.**

Insulin preparations for subcutaneous administration typically contain six-molecule aggregates (hexamers) that cannot pass directly into the bloodstream. Observed delays in subcutaneous insulin absorption are attributed to the time it takes for insulin hexamers to dissolve, followed by diffusion-driven absorption. The rapid absorption with minimal delay times that is needed for optimal insulin delivery requires administration of highly concentrated insulin in monomeric form. Unfortunately, current commercial insulin preparations tend to multimerize and irreversibly aggregate at such high concentrations. New insulin formulations are needed.

- **Develop a family of non-toxic, non-antigenic, low molecular weight molecules that effectively and specifically bind glucose in the presence of serum components and across the physiological range of glucose concentrations, from hypoglycemic to hyperglycemic levels.**

Many novel glucose-responsive biomaterials and insulins function by competitively binding glucose molecules in the body, similarly to naturally occurring sugar-binding proteins called lectins. Early attempts at implementing safe lectin-like molecules for use in these systems have involved synthetic and chemically-engineered lectins, molecularly imprinted polymers, recombinant human proteins, and polynucleotide/peptide-based aptamers. Optimal materials need to be minimally cross-reactive with non-glucose molecules, responsive in the physiological range, and capable of being manufactured cost effectively in large quantities.

**Telemedicine**

The widespread adoption in everyday life of information and communication technology—e.g., the Internet, mobile phones, and personal digital assistants (PDAs)—is providing an excellent opportunity to improve the delivery of diabetes care and lower treatment costs by improving communication between patients, health care providers, and health care systems. This effort has been aimed at supporting the management of diabetes, mainly via electronic patient records, decision support systems, and telemedicine. Telemedicine is defined as the use of telecommunications to support health care. It includes timely transmission and remote interpretation of patient data for follow-up and preventive interventions.
over the Internet. Data are uploaded and instructions are downloaded by way of wireless or hardwired communication tools. Telemedicine has been demonstrated to be: 1) sound, in terms of accurately transmitting and processing data; 2) possibly effective, in terms of improved HbA1c levels; and 3) somewhat practical, in terms of being designated as legal, being considered as standard of care (rather than malpractice), and being reimbursed in fee-for-service but not capitated practice settings. Challenges to the practicality of telemedicine include concerns about the privacy and security of data that is housed on a Web site and linked to an electronic medical record with many portals where potentially illicit downloading can occur. Currently, little research is available as to the economic impact and longer-term benefit of telemedicine practices. Many outcome studies of telemedicine to date have significant limitations, including small sample size, lack of controls, or a lack of demonstration of long-term benefit. Carefully designed, robust studies of telemedicine are needed, as well as long-term studies to see whether potential benefits persist over time. Future research in information and communication technology for diabetes should concentrate on providing new sophisticated technological tools and instruments to increase the quality of telemedicine solutions, and, at the same time, properly modify the health care delivery process to more effectively exploit the opportunities provided by novel telecommunication systems.

**Key Questions**

- What are the best technological solutions (both hardware and decision-support software) to best enable telemedicine to be easily and effectively applied in clinical practice?

- What types of behavioral modification tools or incentives can be developed to facilitate communication and adherence to telemedicine-generated instructions?

- Can high blood glucose or low blood glucose alerts be sent automatically from a glucose meter to a health care provider by way of a Web server to elicit an immediate assistance response that could reduce emergency room visits?

- Can PDA applications (“apps”) for diabetes management, which track blood glucose, food intake, insulin, and exercise, improve outcomes?

- How can telemedicine platforms be integrated into an automated closed-loop system?

**Future Directions**

- Develop telemedicine approaches that can be incorporated as components and/or adjuvants of an artificial pancreas.

To accomplish this goal, a software developer should be designated specifically to work hand-in-hand with investigators. Telemedicine components could potentially provide two-way communication by the phone or Internet, algorithms to provide advice on diabetes management decisions, accelerometers to track physical activity that could be used in diabetes management decisions, and global positioning system (GPS) technology so that a person could be located if he or she needed assistance. These platforms could form the basis for a more effective and user-friendly artificial pancreas. If standards were established for meter, sensor, and
pump communications, it would allow consumers to choose the combination of sensor, meter, and pump that best fits their needs.

- **Determine whether online peer-to-peer management can improve diabetes outcomes.**

The value of online group “chat rooms,” mandatory interactions, and text messaging by patient leaders who have been successful in their diabetes management should be tested and evaluated as part of a telemedicine instrument to improve the management of diabetes. A “chat” with a mental health specialist could also be included at regular intervals; the benefits of such an addition should be evaluated as well. Adolescents, who are often the hardest age group in which to achieve good glucose results, are heavy users of social networking and text-paging. As peer support is important to adolescents, the use of these services may be extremely beneficial in this age group.

**Tissue Engineering for Replacement of Pancreatic Islets**

The prospect of replacing the beta cell deficit of both type 1 and type 2 diabetes with islet transplantation or beta cell regeneration has been a research focus for several decades. An important proof-of-principle has been established in humans receiving both pancreas and islet transplants. Normal control of blood glucose levels has been restored, but at the expense of the requirement for immunosuppressive therapy. Moreover, glucose control with islet transplants is usually lost within a few years due to loss of beta cells from immune injury and inadequate vascular perfusion. Tissue engineering approaches may help to overcome some of these challenges.

**Key Questions**

- Will the development of novel biomaterials contribute to more effective immunobarrier/encapsulation methods to establish and maintain a functional bioartificial pancreas using transplanted islets from different sources?
- What methods can be developed for effective vascularization of islets after implantation?

**Future Directions**

- **Improve perfusion of islet cells within a graft site.**

Because beta cells are metabolically very active, one of the key factors affecting long-term maintenance of insulin production from transplanted islets will likely be the establishment of an adequate blood vessel network to assure sufficient oxygenation and supply of nutrients to the cells. It would be ideal to find ways to restore vascularization in grafts to the same rich pattern of vessels found in islets within the pancreas. Work with tissue engineering and bioscaffolds holds promise in this area.

- **Develop new biomaterials and immunobarrier protection for transplanted islets.**

The concept of protecting transplanted islets from immune destruction with a barrier is more than 30 years old, but has proven challenging in practice. Biomaterials that have been used for these barriers include: alginate, agarose, polyethylene glycol (PEG), polytetrafluoroethylene (PTFE), chitosan, and others.
Configurations have included planar devices, hollow tubes, conformal coatings of islets, micro-gel beads, macrobeads, and gel slabs. While results obtained in rodents have been impressive, success has been limited in large animals and humans. Thus, work needs to be done to develop better biomaterials for this purpose. Some development and implantation options include islets in microcapsules (or more complex devices) placed in the abdominal cavity, and microcapsules or planar devices inserted in a subcutaneous site. For planar devices, challenges include the packing density of the islet cells, which must be optimized so that the surface area of the device is small enough for surgical implantation. Finding ways to optimize oxygen delivery to islets will also be important. Moreover, it is not clear how much selective permeability will be required to limit immune responses. Materials for sustained localized delivery of immunosuppressants to minimize risk of systemic effects while maximizing the potential to eliminate rejection should be developed. Another avenue is to optimize distribution and function of islet cell clusters by using matrices and other three-dimensional approaches made possible with bioengineering advances.

➢ Pursue approaches to scale up and commercialize production.

The success of these approaches will ultimately depend on a close interaction between the applied sciences and industry. Once technical obstacles have been adequately addressed, commercialization of this type of therapy will likely be more difficult than previous therapies. New and more thoughtful approaches to technology translation may be needed.

Impact of Closed-Loop Control on the Pathophysiology of Diabetes

Building on evidence that continuous glucose monitoring devices can be used successfully in the outpatient setting, research can now advance further toward the development of a mechanical artificial pancreas that can close the loop between glucose sensing/monitoring and insulin delivery. As this closed-loop research moves forward, studies need to be pursued not only on the efficacy of individual device technologies to control glucose levels, but also on how these technologies affect the overall pathophysiology of diabetes. For example, investigators have long pondered the importance of delivering insulin directly to the liver (a major target organ for insulin action) via the portal vein, instead of systemically, when considering open-loop and closed-loop control protocols. This more physiological route of delivery may help people with diabetes achieve blood glucose control without chronic systemic elevation of insulin levels (hyperinsulinemia) and its side effects, but there is currently insufficient long-term evidence demonstrating this potential benefit. It is anticipated that the institution of closed-loop control in type 1 diabetes would reverse hypoglycemia unawareness and prevent brain injury in young children, but there is currently insufficient long-term evidence demonstrating this as well. Another major challenge for closed-loop control is how to predict the insulin infusion rates necessary to normalize glycemia as rapidly as possible without producing hypoglycemia; new approaches are needed. Moreover, there is speculation that use of a closed-loop artificial pancreas would more effectively
preserve beta cell function in people with new-onset type 1 diabetes, thereby reducing daily insulin dose requirements and potentially restoring glucagon responses to hypoglycemia—a win/win combination. Studies testing this hypothesis could lead to changes in type 1 diabetes care at disease onset.

**Key Questions**

- Can an artificial mechanical pancreas or islet replacement restore glucose counter-regulation and hypoglycemia awareness and preserve brain function in people with type 1 diabetes, especially young children?
- Can early intensive insulin therapy increase beta cell survival and prevent the loss of the glucagon response to hypoglycemia in people with new-onset of type 1 diabetes?
- What are the short- and long-term consequences of the route of delivery of insulin on glycemic outcome, vascular complications, and body weight?
- Is glucose the only target that should be used in developing closed-loop systems? Should additional compounds be measured online, e.g., insulin, glucagon, other metabolites?
- Are the differences between systemic and portal administration significant enough to favor technologies (mechanical or cellular) that deliver insulin to the liver—its primary site of action?
- Can incorporation of automated glucagon delivery increase defenses against hypoglycemia without excessively raising blood glucose?

**Future Directions**

- **Determine the impact of an artificial mechanical pancreas on brain function, fuel metabolism, and structure, especially in children.**

The development of improved imaging methods to examine brain structure, function, connectivity, and fuel metabolism has opened the door to studies that can elucidate the effect(s) of treatment with an artificial mechanical and/or islet replacement therapy on brain function in people with diabetes. This is particularly important in young children who are more vulnerable to brain injury and cognitive deficits caused by severe hypoglycemia.

- **Determine if a closed-loop system artificial mechanical pancreas is sufficient to restore normal glucose counter-regulation and reverse hypoglycemia unawareness.**

Individuals currently receiving intensive insulin therapy and/or with long-standing type 1 diabetes lose their ability to activate hormonal defenses against hypoglycemia and to develop symptoms that tell them to take corrective action, namely, to eat. It is believed that a major clinical indication for closed-loop glucose control would be for treatment of these patients; however, studies are needed to see if closed-loop glucose control is sufficient or might be further enhanced by drugs shown to improve hypoglycemia defense mechanisms in animal models of diabetes.

- **Determine whether an artificial mechanical pancreas (or implanted engineered islets) can preserve beta cells and maintain alpha cell**
responses to hypoglycemia in type 1 diabetes if given early, when some insulin secretion is still present.

Multi-center clinical trials should be pursued to determine if closed-loop glucose control is able to preserve beta cell insulin secretion, insulin sensitivity, and glucagon release by alpha cells in people with recent onset of type 1 diabetes. However, this key outcome is likely to require additional medical therapy. Thus, drug interventions should be pursued in diabetic animal models aimed at promoting beta cell regeneration and the restoration of the glucagon response to hypoglycemia. One challenge that limits such studies is the current lack of methods to accurately assess beta cell mass in humans.

- **Determine whether insulin delivery via the portal vein will be more effective in achieving normoglycemia by reducing insulin resistance and enhancing portal sensing of glucose and gut peptides.**

There is increasing evidence that the portal circulation is a sensory locus in which portal glucose, and potentially portal GLP-1 and other gut peptides, may be detected. Thus, portal administration could in principle be advantageous in achieving long-term metabolic control, but there is currently insufficient evidence to show this. Long-term studies in large animals are needed in which insulin is delivered either intraportally or systemically using closed-loop control, which will mismatch systemic insulin levels. The impact of higher blood insulin levels produced by peripheral versus portal insulin delivery on insulin sensitivity, free fatty acid levels, gut hormones, and on body weight regulation will provide important information on the preferred route of insulin administration. This will be best accomplished in large experimental animal models of diabetes. Such data are important in the cost/benefit analysis regarding mechanical insulin infusion systems which allow for peripheral delivery versus cellular-based systems which will allow for portal delivery.

- **Develop methods to measure insulin levels in real time, to provide input to closed-loop feedback algorithms.**

Many private sector companies have developed micro methods for the measurements of metabolites and proteins (i.e., metabolomics and proteomics). These approaches have allowed for the measurement of many compounds in very small amounts of sample. It will be valuable to exploit these methods, which in many cases have been automated, to develop an online approach, which can provide additional information (e.g., plasma insulin) to the feedback algorithm so that it can then make more intelligent decisions regarding exogenous insulin infusion, and moment-to-moment estimations of in vivo insulin sensitivity. Collaborations should be developed between groups designing closed-loop artificial pancreas devices and experts in measuring proteins and metabolites from small samples in real time.

**Behavioral Aspects**

The public health benefits of bioengineering advances in health care are realized not only through development of accurate and clinically effective therapeutic technologies, but ultimately through the use of these devices by people with diabetes and their health care providers to improve health outcomes and quality of life. The full benefits of self-monitoring of blood glucose, and continuous glucose monitoring, in particular, have not been realized due to a need for improved individual, family, and provider awareness and skill in effective utilization of the information and data yielded. It is
essential for new technologies not only to incorporate a broad array of patient behavior dynamics and cognitive and psychological limitations in their design, but also to account for the impact of new technologies on an individual’s personal and social relationships, which, in turn, could affect his or her diabetes management. People with diabetes and their families are more likely to adopt innovations if they reduce disease burden, lead to better health outcomes, and improve quality of life.

Key Questions

- What are the challenges and benefits of new diabetes technologies for individuals with the disease, including physical (e.g., complexity of use, ease of availability), behavioral (e.g., cognitive load, adherence, time requirements), psychological (e.g., quality of life, fear of hypoglycemia), and social (vocational and family functioning) impacts?

- What factors contraindicate the use of specific diabetes technologies for individuals with diabetes (e.g., age, knowledge, psychological status, cognitive development, functional status, treatment regimen, type and stage of diabetes, and home environment and disease management support)? How can accessibility and usability be increased across populations?

- How can these technologies be more accessible to people from different backgrounds and those with educational, sensory, motor, and cognitive limitations? Has the human/technology interface been designed to be easy to use for people with limited literacy and numeracy skills?

- What are the most effective ways for health care providers to incorporate new technologies and the data they produce into practice?

Future Directions

- Quantify the broad-ranging impact of new diabetes technologies on people with diabetes.

Research needs to be pursued to account for impact of new technologies across multiple indices, such as behavioral, psychological, and social. For example, studies should be performed to assess how technologies affect the ability to carry out daily life activities including work, leisure, and self-care as normally as possible (functional outcomes). Investigators also need to determine how technologies can reduce the extent to which diabetes treatment and management interfere with a person’s life tasks, and whether technologies can positively affect a person’s mood and emotions. Data need to be obtained on how convenient it is for people with diabetes to fit a technology into daily life, and to enhance the range of options to fit individual needs and preferences. The impact of technologies on family and social outcomes (e.g., can use of diabetes technologies help relationships within a family and with friends, reduce family conflict, improve communication, and help build positive social support) should also be evaluated without the need for adaptation or specialized design at the user end.

- Increase accessibility and usability of technologies by people with diabetes-related (and non-diabetes-related) functional impairments and disabilities.

Research to address this issue should take into account visual impairment/blindness, fine motor skill.
impairment, mild cognitive impairment, and other motor/mobility deficits.

- **Increase adoption and effective use of technologies across the lifespan.**

Strategies are needed for bringing technologies that improve diabetes care into wider use. This can be enhanced by industry application of universal design principles to technology development. Studies will be needed to optimize patient, parent/caregiver, provider, and community-based education and training, including implementation of multi-modal training, use of educational guidelines in development of instructions and other educational materials for therapeutic devices, and testing of instruction for literacy and numeracy demands. An important aspect of future studies will be increasing the emphasis on understanding the benefits and limitations of the different technologies/therapeutic advances as applied to biological, psychological (cognitive and emotional), and interpersonal outcomes. Data will also be needed on how to best provide training for use of information gained from technologies in order to take action for self-management (e.g., problem-solving training for what to do with self-monitoring data). Finally, research should be pursued on tailoring of technologies for diabetes care across the lifespan.

- **Increase employment of generic new technologies to promote positive health behavior change in people with diabetes.**

Studies should be conducted on ways to capitalize on existing and general use technologies, such as smart phones and the Internet, in delivering primary psycho-behavioral interventions that can be used to initiate, prompt, track, and summarize behavior, and evaluate behavior change efforts in a larger population than previously accessible (see the “Telemedicine” topic in this chapter).

- **Develop more effective information and educational and training methods for health care providers in use of diabetes technological advancements.**

Studies should test best practices to increase caregiver awareness, correct execution, and consistent employment of different diabetes technologies that can improve health outcomes.

### Design of Clinical Trials and Clinical Outcomes

Planning for the design of clinical trials and framing of appropriate clinical outcomes needs to take into account currently available technologies (CGMs) and also anticipate the development of artificial mechanical pancreas technologies. Building on recent developments, scientists are poised to answer important clinical questions about the added value of CGMs in managing people who have type 2 diabetes, in whom much less is known, as well as important questions about the impact of glycemic variability—both low and high glucose—and not simply average glucose levels on the development or progression of diabetes complications. In the case of artificial pancreas technologies, once available, such devices will initially target a population with the greatest need and the potential for maximum benefit (e.g., people with brittle type 1 diabetes, those experiencing frequent hypoglycemic episodes or diabetic ketoacidosis, or those with hypoglycemia unawareness), and then lead to expanded testing in other populations, based upon the initial experiences. Other important aspects to take into consideration for clinical study design include enrollment criteria (such as degree of...
metabolic instability, age, presence of complications), study settings (highly controlled clinical environments or the less-controlled home setting), how to define hypoglycemia (severe clinical events, or time spent with blood glucose concentrations at less than 70 or less than 60 mg/dl on CGM) and glycemic variability, the relevant clinical end points (e.g., control of glucose levels, reduction in hypoglycemic episodes), and approaches to evaluating outcomes with different devices and systems.

**Key Questions**

- What are appropriate outcome measures (e.g., HbA1c, reduction in hypoglycemia, reduction in glycemic variability) for clinical trials of artificial mechanical pancreas technologies in people with type 1 or type 2 diabetes?
- Can CGM or an artificial mechanical pancreas be used successfully in insulin-requiring patients with type 2 diabetes to maintain HbA1c targets with less hypoglycemia?
- Can reduction of glycemic variability in people with type 2 diabetes who are insulin-dependent lead to improved outcomes, such as reduced diabetic nephropathy, reduction in cardiac arrhythmias in people at high risk for cardiac mortality, and/or reduction of systemic inflammation and oxidative stress?
- What is the value of CGM and/or closed-loop insulin delivery devices in the intensive care unit?
- Can an artificial mechanical pancreas prevent hypoglycemia and/or diabetic micro- and macrovascular complications?
- Should the measurement of vital signs such as heart rate, temperature, and breathing rate be monitored together with glucose monitoring in clinical studies to prevent hypoglycemia and excessive glycemic postprandial excursions?

**Future Directions**

- **Study the impact of closed-loop glucose control on exercise and nocturnal hypoglycemia.**

  Initial closed-loop studies should be aimed at preventing hypoglycemia during sleep by using the system to temporarily stop insulin delivery when hypoglycemia is projected. In addition, clinical trials are needed to test algorithms for closed-loop glucose control during exercise and to prevent hypoglycemia, which may occur many hours after a bout of exercise. Improved algorithms are also needed to optimize food intake and insulin delivery during and after exercise based on sensor and perhaps accelerometer or heart rate data. This would be a safe initial use of closed-loop technology.

- **Determine the efficacy of CGMs and eventually of closed-loop glucose control to improve disordered fuel metabolism and reduce hypoglycemia and diabetic complications in people with type 2 diabetes who require insulin treatment.**

  There has been very little experience in the use of CGMs and no experience using closed-loop technology in people with type 2 diabetes. Continuous glucose monitoring will provide, for the first time, the opportunity to measure glycemic variability and undetected hypoglycemic events during insulin treatment in people with type 2 diabetes, and the potential impact of these factors on cardiac arrhythmias that could potentially be fatal. Studies of the potential clinical value of closed-
loop glucose control in type 2 diabetes will need to take into account its impact on surrogate markers of cardiovascular disease, such as lipid metabolism and blood pressure, as well as cognitive function in this older population.

- **Determine whether closed-loop glucose control can preserve beta cell function in people with new-onset type 1 diabetes or with type 2 diabetes.**

At the time of onset of type 1 diabetes, the destruction of beta cells is incomplete, while in type 2 diabetes, progression of disease is largely influenced by the loss of beta cell function and mass over time. Controlled trials using closed-loop glucose control offer the potential to see if near normalization of glucose levels can protect islets from injury caused by high glucose levels and slow disease progression.

- **Conduct long-term studies of closed-loop glucose control in children and adolescents.**

Young children with type 1 diabetes are particularly susceptible to permanent neurologic damage as a result of severe hypoglycemic events. To minimize this possibility, glucose targets are set higher for children than adults. Unfortunately, elevations of glucose levels also appear to damage brain white and grey matter, which can impair memory and learning as well. The potential of closed-loop systems to reduce brain injury in young children with type 1 diabetes will need to be tested in long-term clinical trials.

- **Study use of continuous glucose monitoring and closed-loop insulin delivery systems in people with gastroparesis.**

People with diabetes who experience slow empting of food from the stomach caused by nerve damage from diabetic hyperglycemia have great difficulty controlling glucose levels because meal absorption is very variable. Continuous glucose monitoring, and particularly closed-loop glucose control, may be extremely beneficial in the management of individuals with gastroparesis, and could be used to modify insulin delivery to prevent early hypoglycemia following a meal and delayed hyperglycemia.

- **Study use of closed-loop technologies in the intensive care unit (ICU).**

The ICU is perhaps well-suited for initial closed-loop studies, as there is constant supervision. The development of accurate intravascular glucose sensors with rapid response times would be ideal for closed-loop management in the ICU because insulin is given intravenously, so there is little delay in the onset of insulin action, which is ideal for closed-loop control.

![Graph](https://example.com/graph.png)

Plasma glucose concentration during closed-loop insulin delivery and conventional pump therapy (continuous subcutaneous insulin infusion, CSII) in children and adolescents with type 1 diabetes (closed-loop starts at 20:00 on the x-axis). The plot figure shows that closed loop may increase time spent in target glucose levels range (between dashed lines), reducing extreme hypoglycemia/hyperglycemia fluctuations and time spent in hypoglycemia. (Reprinted from *The Lancet*, 375, Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, Kollman C, Hovorka T, Larsen AM, Nodale M, De PA, Wilinska ME, Acerini CL, and Dunger DB, Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial, 743-751, Copyright (2010), with permission from Elsevier.)
During the past three decades, a variety of technological advances have been introduced that have significantly improved the ability of people with diabetes and their physicians to treat diabetes with insulin, including home glucose monitoring devices that allow periodic measurements of blood levels; improved insulin formulations; portable insulin pumps that provide continuous insulin delivery in a more controlled manner; and, most recently, early-phase CGMs that rely on inserting glucose sensors under the skin. These advances, however, have only partially diminished wide swings in glucose levels that can harm the health of people with diabetes, from the severe falls in blood glucose that may cause unconsciousness and brain injury, to the high glucose levels that may lead to chronic complications such as kidney failure, blindness, nerve damage, amputations, and cardiovascular disease.

Moreover, the burden of care on people with diabetes and their families has been increased in many cases. The research directions outlined in this chapter will help guide the development of new technologies and studies in animals and humans with diabetes that can drive us toward the next step: an automated insulin delivery system using more rapidly acting insulin preparations, and driven by computer algorithms derived from continuous glucose measurements obtained with the use of more rapidly responsive and accurate glucose sensors. A system like this may also be remotely assessed/monitored and even adjusted through a telemedicine platform. Artificial pancreas technology is at a very early stage of development and will require a step-wise approach and new interdisciplinary scientific partnerships between bioengineers and basic and clinical scientists for its future success.