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The Artificial Pancreas: A Dynamic Challenge

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Abstract: **In patients with diabetes mellitus type 1, the pancreatic insulin production ceases, causing raise in blood glucose level (BGL) and potentially severe long-term complications. The "holy grail" of diabetes treatment is the artificial pancreas (AP), a closed-loop control system that regulates the user's BGL by infusing insulin, and possibly glucagon. Numerous attempts have been largely unsuccessful, mainly due to slow dynamics that make it difficult to avoid unwanted BGL excursions. System performance has been improved through improved sensor technology and faster-acting insulin types, but the risk of hypoglycemia is still significant unless the glucose setpoint is unnaturally high.**

We argue that this problem can be circumvented by choosing appropriate sites for glucose measurement and insulin infusion. While intravascular measurement and infusion provides the fastest dynamics and thus the best conditions for closed-loop control, it is only viable in inpatients mainly due to danger of infections and limited sensor durability. On the other extreme, state-of-the-art subcutaneous systems exhibit significant time delays and diffusion dynamics, yielding poor BGL control in the event of disturbances like meals and physical activity. Avoiding dangerous hypoglycemia therefore comes at the expense of daily episodes of elevated BGL (typically 10–15 mmol/L) that increase the risk of long-term complications. Furthermore, slow insulin uptake from subcutis remains as a major challenge. Hence we advocate the double intraperitoneal (IP) AP. Here, insulin is released into the abdominal cavity (peritoneum) through a semi-permanent port, which also allows access for IP glucose sensing. This improves both sensing and absorption dynamics. Thus the closed-loop control may be significantly tighter, allowing a setpoint closer to the healthy normal BGL of approximately 4.5 mmol/L whilst potentially improving system safety. These statements are supported by results from our own research and the literature.

Keywords: **Medical applications, artificial pancreas, dynamic modelling, time delay, time constants.**

1 INTRODUCTION

Diabetes mellitus involves defective regulation of blood glucose levels (BGL), which can lead to serious or fatal complication both in the short and the long term. The "holy grail" of diabetes treatment is the artificial pancreas (AP), a closed-loop system that monitors the glucose level and infuses insulin, and possibly glucagon, according to an appropriate control law to keep the user's BGL within appropriate limits. Numerous attempts have been largely unsuccessful, mainly due to slow open-loop system dynamics associated with the technology itself and the sites chosen for glucose measurement and insulin infusion, which limits the attainable closed-loop performance and robustness. Improved sensor technology and faster-acting insulin types have induced notable improvements in AP performance, and it now seems achievable to avoid most of the serious hyper- and hypoglycemic events through the use of a closed-loop system (Kropff et al. 2015b). However, there is an increasing understanding that a simple "time within range" consideration is insufficient as a treatment target, and that target ranges commonly applied are too wide, especially in the higher BGL range (DCCT/EDIC Research Group et al. 2015, Hu et al. 2015). On these grounds we claim that all in all there is no well-functioning AP as of yet.

In principle there are many ways to restore the glucose regulating function of a dysfunctional or missing pancreas. Complete organ transplantation is a given option, however with potentially severe consequences related to immune suppression and possible rejection of the transplanted organ (Redfield et al. 2015). Similar complications occur in methods based on implantation of pancreatic beta cells or stem cells (Johannesson et al. 2015, Soon-Shiong et al.

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1992). Further explorations of these treatment options are outside the scope of this paper.

The first experiments with an AP were performed in the early 1970's with a large device with significant limitations. However, the dream had been awakened, and a substantial and increasing number of clinical studies have been performed over the last decade. The theoretically ideal solution in which both glucose sensing and insulin infusion are performed intravascularly is infeasible in outpatients due to safety issues. Most studies are therefore based on subcutaneous (SC) continuous glucose monitoring (CGM) with enzymatic technology and SC insulin administration by use of insulin pumps. This "double SC approach" has certain physiological limitations that hamper the possibilities for a well-functioning robust AP able to maintain normal or close to normal BGL. In this paper we discuss these limitations and argue, based on basic concepts from control theory, that an AP in which both glucose measurement and insulin infusion take place in the peritoneal cavity, e.g. through a port similar to that used by Liebl et al. (2009), is a promising option.

The rest of this paper is organized as follows: Section 2 provides a brief discussion of the dynamics of an AP system in terms of its physical components and some basic notions that will be used in subsequent sections. Sections 3 and 4 describe the SC and IP routes of insulin infusion and glucose measurement in terms of dynamics and safety. Section 5 discusses the implications of the findings in terms of future AP systems and provides some concluding remarks.

2 ON DYNAMICS

For the purpose of a structured discussion, we will section the open-loop dynamics as follows (cf. Fig. 1):

Site dependent absorption dynamics – from insulin input to intravascular insulin concentration ($[I_{IV}]$),

Site independent physiological dynamics – from $[I_{IV}]$ to intravascular glucose concentration ($[G_{IV}]$),

Site dependent physiological sensing dynamics – from $[G_{IV}]$ to glucose concentration at the site of the sensor ($[G_{site}]$),

Glucose sensor dynamics – from $[G_{site}]$ to sensor output ($[G_{IV}]$), i.e. the dynamics associated with the sensor technology itself.

For the sake of completeness Fig. 1 also includes a block marked *meal digestion*, which represents the dynamics from meal input to blood glucose; here, R_a represents the rate of appearance of meal related glucose in the bloodstream. As this is not part of the control loop and we consider systems without meal announcement (feed-forward), this block will not be treated any further.

Some of the subsystems in Fig. 1 will be treated in more detail in later sections. Several of these systems are somewhat coupled, e.g. through nonlinear effects. However, this does not invalidate the general conclusions. The influence of insulin type and local factors like temperature and pressure are suggested by dashed lines.

2.1 Time delays, time constants, and bandwidth

Concepts such as *time delays*, *time constants* and *bandwidth* are essential for the following discussion. In order to make this text more accessible to a wide audience, we offer a brief explanation of these terms; see e.g. Åstrøm and Murray (2014) for an introduction to the subject.

Parts of this discussion strictly relates only to linear systems, while human insulin and glucose dynamics exhibit non-linear properties. The use of these notions in the present context is justified because the system in question is *predominantly linear* within its normal operating range, and thus can be well approximated by linear models (see e.g. Chee and Fernando (2007)).

A *time delay*, also known as *dead time*, is typically associated with a transportation mechanism (e.g. blood transport), and denotes the time that passes from a stimulus is applied to a system until the first trace of the incident is theoretically detectable at the system's output.

A *time constant* can be associated with e.g. diffusion through a semipermeable barrier (like a cell membrane) separating two compartments, and relates to the time it takes to re-establish an equilibrium following a sudden concentration gradient across the membrane.

The *bandwidth* of a system is the frequency of the fastest oscillating sine wave that can be fed into the system's input and subsequently be observed at its output without significant attenuation. The bandwidth of a system exhibiting a single time constant T [s] is normally defined as $\beta = 1/T$ [rad/s], so a larger time constant implies a lower bandwidth.

Whereas the effect of a time constant in principle can be cancelled to any desirable accuracy by filtering of the output signal, a time delay cannot be negated in real time because it requires the prediction of future signal levels. Time delays

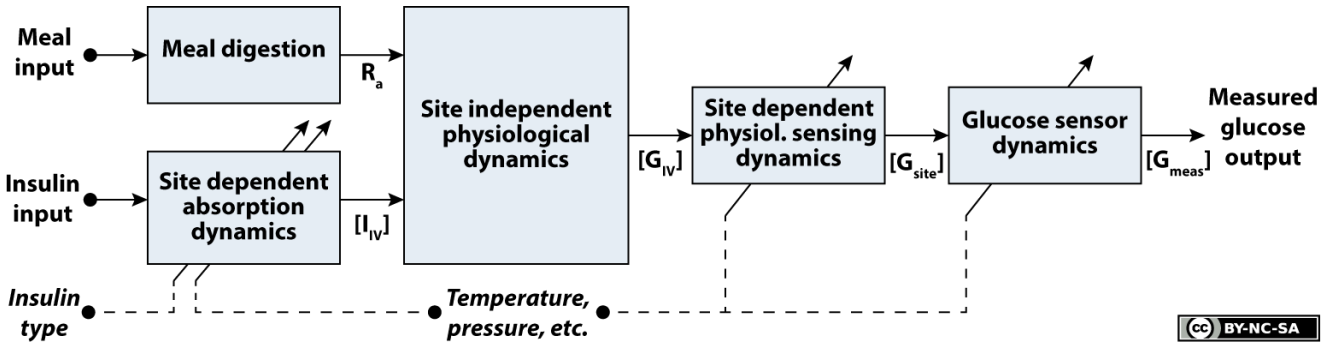

Fig. 1. Insulin and glucose dynamics split into different sections. This figure is licensed under a Creative Commons BY-NC-SA 4.0 license, hereafter abbreviated to CC BY-NC-SA.

and time constants limit the obtainable bandwidth (i.e. the usable frequency range) of a closed-loop system. In a system with multiple time delays and time constants it is the *total* of all time delays and the *larger* time constant(s) that constitute the limiting factors. It is therefore common to simplify the analysis by assuming that the system includes only one "equivalent" time constant and time delay, respectively.

Following from the preceding discussion, time constants and delays in the control loop limit how quickly a closed-loop AP system can respond in order to correct BGL deviations; the lower the closed-loop bandwidth, the larger the glucose fluctuations. This fact is at the core of this paper's message.

In AP research literature the importance of dynamics is appreciated, but distinctions are only occasionally made between notions like time delays and time constants; the terms are frequently used interchangeably with other terms like *time lag, latency*, *time to half-max* etc., and are sometimes used ambiguously. In this paper we use the term *latency* to collectively denote bandwidth-limiting effects, including quantities for which the cited publication does not indicate clearly if it is a time delay, a time constant or another related phenomenon that is reported.

3 INSULIN ADMINISTRATION

3.1 Site dependent absorption dynamics

Insulin can be infused or injected in different tissues. The pharmacokinetics of insulin is influenced by the site of insulin administration and the type, concentration and volume of the insulin solution, through the associated transportation, diffusion and biochemical processes. Attempts have been made to administer insulin both through inhalation and orally, with varying results (Sousa et al. 2015). However, infusion through syringes or catheters inserted in SC tissue is still the prevailing treatment solution. Among the more recent developments is that of faster-acting insulins. An overview of typical infusion insulin dynamics can be found in Evans et al. (2011) and Heise et al. (2015). The mathematical models of insulin dynamics have been reviewed by Wilinska et al. (2005).

3.2 Subcutaneous insulin delivery; I_{SC}

The present clinical gold standard of insulin delivery is continuous SC delivery of short-term acting insulin by a pump, or multiple daily SC injections of medium long-term and short-term acting insulin (Hirsch 2005, Pickup 2012). The duration of the effect of injected insulin mostly depends on the rate of absorption from the SC tissue to the circulation. This may take more than 24 hours for some insulins, and even for the most fast acting types 90–120 min are needed to reach maximum glucose-lowering effect (Heise et al. 2015). This differs considerably from the physiologic situation, where insulin released from the pancreas arrives in the circulation within minutes after the BGL is increased. Important is also the lasting glucose lowering effect, which may continue even after circulating insulin levels have normalized. Taken together, this means that a SC injection of the fastest acting insulin analogue will have a glucose lowering effect for as much as 4–5 hours after it has been delivered (Evans et al. 2011, Heise et al. 2015). Due to slow absorption the maximum insulin effect on BGL may be 1–3 hours after SC injections. For all practical purposes this means that the SC approach for insulin delivery is not compatible with a robust AP (Hovorka et al. 2006, Cobelli et al. 2011). Additionally, the insulin absorption rate and fraction of insulin absorbed are unpredictable due to changes to the local blood circulation and the tissue surrounding the infusion site.

3.3 Intraperitoneal insulin delivery; I_{IP}

Intraperitoneal insulin infusion (I_{IP}) has been applied with some success (Liebl et al. 2009, Renard et al. 2010). Physiologically, this option is quite appealing, and it has a fast dynamic effect. The pancreas secretes insulin to the liver via the portal vein, and a significant proportion of the insulin is absorbed by the liver ("first passage effect") within a few seconds after secretion before the rest enters the systemic circulation according to studies in animals (Matsuo et al. 2003, Micossi et al. 1986, Radziuk et al. 1994, Schade et al. 1979, Schade et al. 1980, Schade et al. 1981, Selam et al. 1990) and humans (Widerøe et al. 1996). I_{IP} gives close to physiological insulin levels both in the liver and other tissues (Nelson et al. 1982). The liver responds to this insulin stimulus by inhibiting its glucose production and storing glucose as glycogen, and thus causing a primary and fast BGL reduction. The insulin that is not absorbed by the liver enters the systemic circulation and causes an increase in glucose uptake in the various tissues, thereby leading to a secondary BGL response. The overall result is a glucose lowering effect that is almost comparable to intravenous infusion in terms of bandwidth, and with a latency comparable to that of the glucose increasing effect of food intake (Schade et al. 1979). Consequently, it is possible to counteract the trend of an increasing BGL with a faster and increased glucose lowering effect of a given amount of insulin without increasing the risk of subsequent hypoglycemia compared to the risk associated with I_{SC} delivery. This has a significant and desirable impact on the closed-loop control performance and reduces the dependence on feed-forward actions like meal announcements.

The practical implementation of I_{IP} can have at least two different forms, as illustrated in Fig. 2. The left part of the figure shows a partially implanted AP in which the insulin

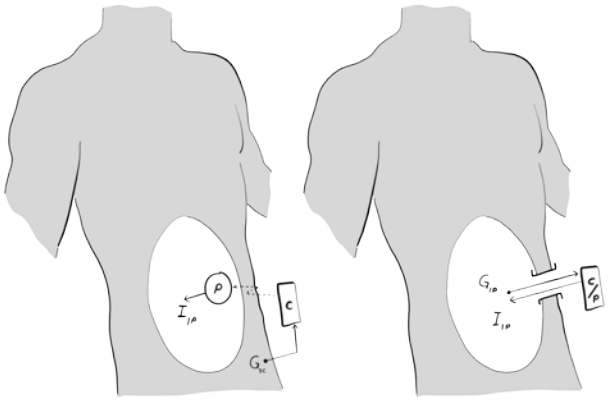

Fig. 2. Illustration of a partially implanted (left) and port-based (right) intraperitoneal AP. CC BY-NC-SA.

pump and reservoir (*P*) are connected wirelessly to an external control unit (*C*) with a subcutaneous glucose sensor. This resembles the system described e.g. by Lee et al. (2014). The right-hand figure illustrates the concept of a port-based intraperitoneal AP, in which a combined controller and hormone pump (*C/P*) resides externally to the body. Insulin infusion and glucose sensing are performed with slender and retractable components through a semi-permanent port through the abdominal wall. The size of the port has been exaggerated for clarity; the port can be similar to the DiaPort (Roche Diagnostics, Basel, Switzerland), adapted to accommodate the glucose sensing components.

3.4 Safety issues and comparison (I_{SC} vs. I_{IP})

Because of the slow uptake to the circulation, SC insulin delivery carries a particular risk of overdosing e.g. in conjunction with postprandially elevated BGL. By the time, the BGL has returned to the normoglycemic range, already delivered insulin may still be released from the SC tissue, reducing the BGL even further. This may lead to hypoglycemia. If this is treated with carbohydrate intake, one can easily induce over-treatment that brings BGL back into the hyperglycemic range. Large deviations from desirable glucose levels as well as adiposity due to increased overall caloric intake are potential results.

Suggested countermeasures include "insulin-on-board constraints" (Ellingsen et al. 2009) to prevent insulin overdosing, and feed-forward of meals, i.e. input/predictions from the user. However, relying on the user's meal prediction is in itself a large safety hazard in that the user may overestimate a meal, or the meal may be delayed or even cancelled completely. Both of these cases could end up with serious hypoglycemias.

The comparative benefit of the I_{IP} option is quite obvious: the amount of insulin that is infused in the patient but not yet distributed through circulation is reduced, and thus BGL oscillations can more easily be avoided.

Fault detection is another important issue with respect to safety of an AP. Information about faults is mainly derived by comparing CGM data with the expected response to the given insulin infusion. I_{IP} potentially involves less local tissue irritation, less clotting and more predictable insulin absorption compared to the I_{SC} route (Liebl et al. 2009, Renard et al. 2010, Schaepelynck Bélicar et al. 2003). Thus, one can expect faster detection of insulin infusion system failures, e.g. an obstruction of the infusion set.

One could argue that the faster insulin uptake from the IP infusion site to the blood stream (Schade et al. 1979, Schade et al. 1980) makes it more dangerous, because insulin delivered this way affects the BGL more rapidly and with a stronger peak effect. On the other hand, the faster effect allows for a higher closed-loop bandwidth, which in normal situations implies smaller transient BGL deviations and thus generally improves safety and robustness. The balance of these effects requires further investigation.

4 GLUCOSE MEASUREMENT

4.1 Glucose sensing dynamics

Glucose concentration can in principle be measured in all tissues. In order to be measureable, glucose in the blood must be transported through tissue and fluids by diffusion and/or active cellular transport mechanisms, and establish a representative concentration in the immediate vicinity of the sensing element. This constitutes what is denoted *site dependent physiological sensing dynamics* in Fig. 1 (Basu et al. 2013, Basu et al. 2015). In addition to this, the sensor technology has dynamical properties in and of itself, corresponding to the block named *glucose sensor dynamics* in the same figure. These phenomena arise from elements such as protective membranes through which the glucose must diffuse in order to reach the sensing element, and enzymatic and electrochemical reactions in the element. Further latency and discretization effects may be added by the associated software, which typically employs integration or filtering of the raw sensor signal over several minutes in order to suppress measurement noise.

4.2 Subcutaneous glucose measurement; G_{SC}

Commercially available CGM units employ sensors that are placed in SC tissue. The resulting *site dependent physiological sensing dynamics* from intravascular glucose to interstitial glucose surrounding the sensor includes a latency of at least 6–7 minutes (Basu et al. 2013, Basu et al. 2015). Local skin temperature may influence the local blood flow and there is also the effect of local pressure on the tissue restricting local blood circulation, both potentially changing the dynamics.

Most current sensors for CGM are enzyme-based with essentially unknown device specific *glucose sensor dynamics*. At present, most CGMs give glucose values that are averaged over 5 minutes, a figure that is not unlikely to improve as sensor technology is further refined. Burnett et al. (2014) identified the collective effect of *site dependent physiological sensing dynamics* and *glucose sensor dynamics*, and found a mean time delay and time constant for G_{SC} of as much as 1.4 min and 12.4 min, respectively.

Among the more practical drawbacks of current CGM technology are the limited lifetime of each sensor (usually in the range 6–8 days) and in particular the limited accuracy of glucose measurements in the low normal and normal range (Kropff et al. 2015a). Additionally, typical sensors need to be calibrated during normal operation at least two times daily to compensate for signal drift (Keenan et al. 2011).

4.3 Intraperitoneal glucose measurement; G_{IP}

The possibility of continuous IP glucose measurement has only been studied a few times in animals (Burnett et al. 2014, Clark et al. 1988, Clark et al. 1987, Fougner et al. submitted, Velho et al. 1989).

Our pilot animal studies (Fougner et al. submitted) show that the G_{IP} time delay is in the range 0–26 s (mean: 9.7 s), while the time constant was found to be 0.5–10.2 min (mean: 4.7 min) for the *site dependent physiological sensing dynamics* alone (i.e. after the sensor's intrinsic time constant had been compensated for). In comparison, Burnett et al. (2014) found

a mean time delay and time constant for G_{IP} of 0.68 min and 5.6 min, respectively; these numbers relate to the collective effect of the *site dependent physiological sensing dynamics* and the unknown *glucose sensor dynamics*, and are in general agreement with our findings. IP glucose sensing sites thus have substantially faster dynamics than SC sites.

At present, insulin absorption is a far more severe bottleneck than glucose sensing, but as faster insulins and faster infusion methods (e.g. I_{IP}) are adopted, the sensing (site dependent as well as sensor specific) dynamics will become increasingly important as a limiting factor.

4.4 Safety issues and comparison (G_{SC} vs. G_{IP})

Important properties of a closed-loop control system are the accuracy and reliability of sensor readings. Common glucose oxidase sensors used for SC measurement are frequently impaired by transient *pressure induced sensor attenuation* (PISA). This occurs in particular during night when the patient is lying on the sensor (Helton et al. 2011) and leads to decreased glucose readings. Recent miniaturization of sensors may have reduced this predominantly mechanical problem. Most sensor augmented insulin pump systems on the market incorporate an automatic shut-off algorithm that stops insulin delivery when BGL falls below a threshold to prevent hypoglycemia. However, pump shut-offs based on erroneously low sensor readings result in hyperglycemia (e.g. Baysal et al. (2014)).). As in the cases described above, large BGL oscillations may result.

Sensors located in the peritoneum are largely protected against externally induced mechanical stress. Depending on the sensing technology, this may reduce the problems of PISA and thus significantly improve the reliability of sensor readings. However, it may be difficult to control exactly where the tip of the catheter resides, and it can get stuck in the peritoneal wall or fatty tissue during insertion or later. This may affect the measurement dynamics as well as the insulin absorption in a yet unpredictable way. The possible influence of bowel and body movements and changing intra-abdominal pressure also needs to be established.

The body reacts to SC sensors with encapsulation, fouling and inflammation, impairing the sensor performance in an unpredictable manner (Helton et al. 2011). Experiences with IP implants have shown that the foreign body response is less acute in the peritoneal cavity (Haveman et al. 2010). This may translate to less dynamical changes in the case of IP sensing and consequently to more reliable sensor readings. One could also foresee a reduced need for sensor recalibrations.

Concerning sensor faults, physical redundancy is an obvious way to increase the system's reliability, but two or more SC sensors are inconvenient and not likely to be accepted by most patients (Doyle et al. 2014). A port to the peritoneal cavity, on the other hand, has the potential to allow the use of redundant sensors without the need for additional punctures.

Sensed glucose concentration may differ from actual BGL, a fault that can cause the whole AP to fail. It is therefore essential for a safe AP to detect deviations from normal behavior as soon as possible. Information about sensor faults is obtained by comparing CGM data with statistical knowledge or with expected glucose change for the given insulin infusion. Due to the faster glucose sensing dynamics (Burnett et al. 2014, Fougner et al. submitted), as well as faster insulin infusion dynamics, as described above, the IP approach is expected to allow earlier detection of both insulin infusion faults and sensor faults alike.

5 DISCUSSION

In addition to the benefits and drawbacks already mentioned related to glucose sensing and insulin infusion, there are a number of possible complications and uncertainties associated with IP access in general.

The higher degree of invasiveness of the IP route suggests an increased risk of serious infections. For a port based system, this risk will mainly be associated with the initial surgical procedure for establishing the port, as well as during subsequent use and maintenance e.g. during replacement of sensor or infusion tubing via the port. More superficial infections may occur at the skin-port interface. In the case of an implanted insulin pump, similar hazards are associated with the initial implantation, and also with subsequent re-filling of the insulin reservoir, which will take place with a syringe through the skin. More seriously, the inevitable need for eventually replacing defective componentry implies some degree of surgical procedure and the associated hazards. All in all it is very likely that the IP route will require more frequent visits to a hospital than the SC one, and in particular until the technology has matured. A port-based system in principle lends itself to more user "self-service" than the implanted alternative due to the easier access to internal components, but it remains to establish to what extent the different procedures can be performed outside of a hospital.

From a control perspective, the main hazard of an AP is hypoglycemia. The preceding sections point to challenges associated with using the subcutaneous tissue for glucose measurement and insulin infusion. It has been advocated that CGMs based on SC sensors perform adequately for use in a closed-loop system if sensor calibration and failure is handled properly (Keenan et al. 2011). However, the same authors point out that the BGL setpoint should be raised to 7.8 mmol/L at night to reduce the risk of hypoglycemia. This is significantly higher than the normal BGL in healthy subjects, and likely to be high enough to cause serious long-term physiological effects (DCCT/EDIC Research Group et al. 2015, Hu et al. 2015).

In contrast, the reduced latency associated with measurement and infusion in the peritoneum should allow for increased closed-loop bandwidth that would keep the actual BGL significantly closer to its setpoint. Consequently, this setpoint may be chosen to be closer to the steady-state level for healthy individuals, even during the night, without increased risk of inducing hypoglycemia. "Impaired fasting glucose" (IFG) level is defined as 5.6–6.9 mmol/L by the American Diabetes Association (2014) and 6.1–6.9 mmol/L by the World Health Organization (2006). It is challenging to define a normal fasting glucose level, but it must certainly be lower than the IFG level. We advocate that the appropriate goal setpoint for an IP AP should be as low as 4.5 mmol/L, with a safety constraint that BGL should never exit the range 4.0–

8.0 mmol/L. This ambitious goal seems to be compatible with the physiological realities of IP sensing and infusion dynamics, although it may take novel technology to achieve it in a practical system.

Several groups and studies have pointed to the benefits of the IP route, and a number of highly different technical solutions have been suggested for how to implement a double IP AP. Taylor et al. (2010) assessed a fully implantable, completely passive device in which the release of insulin was governed by the response of a glucose-sensitive material. The device quite successfully controlled the BGL of a rat model until the insulin reservoir was exhausted. Another fully implantable device conceived by Huyett et al. (2015) comprises a glucose sensor, a controller running a proportional-integral-derivative (PID) algorithm and an active insulin pump. *In silico* experiments indicated its ability to keep BGL within its desired range of 4.4–7.8 mmol/L without ever dropping below this range, which is compatible with the desired range advocated above.

While these and several of the I_{IP} studies suggest fully implanting the device in peritoneum, we believe that access through a peritoneal port is a superior option. This will reduce the need of higher concentration insulin (with its challenges) and simplify re-filling. Obviously, if insulin is infused in the peritoneum through a semi-permanent port, this access point lends itself to glucose measurements as well. Thus, all major components can be placed externally, allowing easy access for power supply, inspection and repair.

Apart from the significant dynamic benefits, the I_{IP} alternative has several other benefits of which some will only be evident in the long term and thus are only conjectures at present. These aspects are discussed briefly below.

There is some evidence that the higher and more physiologically appropriate ratio between insulin reaching the liver and that reaching peripheral tissues (Nelson et al. 1982) may allow for reduction in total insulin use, which may reduce the long-term risk of cardiovascular disease (Hopkins 2013).

One of the hormones that increase BGL is glucagon, which is produced in the pancreatic alpha cells and seems to be coupled in one way or another to the production of insulin. In fact glucagon is very important in counteracting hypoglycemia. The ability to produce glucagon seems to be significantly inhibited early in the lifetime of patients with Diabetes Mellitus type 1, and an artificial supply of this hormone is indeed included as a second control input in the so-called “bionic pancreas” or dual hormone AP (Russell et al. 2014). However, a major improvement of glucose control towards normoglycemia seems to improve the intrinsic production of glucagon in response to hypoglycemia, thereby opening the possibility of improving glucose homeostasis (Oskarsson et al. 2000). In this way, a well-functioning AP may also benefit from the body’s own guard and counteraction to avoid hypoglycemia, and thus facilitates the possibility to completely normalize glucose levels even without the use of exogenous glucagon infusion.

By conjecture, in the case of a dual hormone AP, an IP approach would probably also imply faster absorption of glucagon. The hormone would reach the liver at a higher concentration and have a more physiological distribution throughout the body as compared to the SC route, in much the same way as for insulin, thereby further facilitating improved glucose control.

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