



Metabolic modelling and the closed-loop insulin delivery problem

Garry Steil *, Kerstin Rebrin, John J. Mastrototaro

Medtronic MiniMed, Northridge, CA, USA

Abstract

The approach used by Medtronic MiniMed to close the insulin delivery loop using the subcutaneous site for both glucose sensing and insulin delivery relies on modeling insulin action and β -cell insulin secretion. This approach is contrasted with traditional control systems engineering.

© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Metabolic models; Closed-loop systems; Controllers; beta-Cell model; Artificial pancreas

Contents

1. Introduction	S183
2. Modeling and the closed-loop insulin delivery problem	S184
3. Is the β -cell a PID controller?	S185
4. Conclusion	S186
Acknowledgments	S186
References	S186

1. Introduction

Mathematical models aid in understanding and quantifying metabolic processes and have long been used as a starting point in the design of closed-loop control systems. Bergman’s “minimal model” dominates modeling as it pertains to assessing insulin sensitivity and glucose effectiveness, but more comprehensive models do exist [1]. Models describing carbohydrate absorption by the gut, insulin appearance after subcutaneous (sc) insulin delivery and the relationship between plasma and interstitial insulin and glucose also exist [1]. Many of these models were not derived with the intent of aiding in the design of

a closed-loop insulin delivery system – for example, the minimal model was derived with the objective of obtaining an estimate of insulin sensitivity from a frequently sampled intravenous glucose tolerance test – but they can be adapted for this task.

Using a model has historically been the starting point for designing a closed-loop control system. Classically, the models were low order systems of differential equations (2 or 3 equations) that, if possible, were transformed to a simpler algebraic form using the Laplace transform. Controllers were often derived based on terms proportional to the error (measured output minus target), the area under the curve of the error, and the rate-of-change of the error – the so-called PID

* Corresponding author. Address for correspondence: Correspondence to Dr. Garry M. Steil, Division of Research and Development, Medtronic MiniMed, 18000 Devonshire Street, Northridge, CA 91325, USA. Tel: +1 818-576-4330; Fax: +1 818-576-6206.

E-mail address: garry.steil@medtronic.com (G.M. Steil).

controllers, with the choice of controller determined in conjunction with the model [2].

With the advent of computers, higher order models were easily accommodated (4 or more differential equations) and a “state-variable” approach based on matrix differential equations was utilized. Control strategies became more complex – often utilizing one feedback gain for each state variable with the gain vector optimized by minimizing a cost function (typically sum square error weighted with a penalty for excessive control action). With still more powerful computers, the parameters used in the state equations came to be identified in “real time” – a process that resulted in adaptive control. Today, model predictive control (MPC) is more common. In this strategy, the difference between the model-prediction and measured output is not used to adapt change model parameters (they are fixed), but rather to calculate a sequence of control steps (control horizon) that optimize some cost-function over a future “prediction horizon”.

2. Modeling and the closed-loop insulin delivery problem

Common to all the control strategies described above, is the existence of an underlying model. Herein the previously non-overlapping worlds of the control systems engineer and physiologist converge. Theoretically, existing models of insulin action, rate of appearance of glucose following a meal, SC insulin absorption following SC insulin delivery, and putative delays in glucose sensing (Fig. 1, components in non-shaded area) can today be used to design a closed loop insulin delivery system (Fig. 1, components in

shaded area). Model equations for all the components have been proposed; however, no consensus model exists [1]. Nonetheless, the existing models can provide substantial insight in the control problem.

One aspect of metabolic modeling not captured in the scheme of Fig. 1 is model results related to the β -cell. Numerous model of glucose induced insulin secretion exist that describe insulin as the sum of different “phases” that react immediately to glucose, have a delayed reaction to glucose, and/or react to the rate-of-change of glucose [3]. The question thus arises as to whether these models might be adapted for use in the closed-loop insulin delivery algorithm. Differences exist, of course, between the control problem faced by the β -cell and that of the artificial closed-loop system with even the most abbreviated list including the delay in sc insulin absorption, the delay in ISF glucose sensing, and the lack of a direct portal effect of insulin to suppress hepatic glucose output. In addition, the β -cell likely benefits from neural signals and incretin factors – signals that allow the β -cell to release insulin in advance of an increase in blood glucose and may potentiate the insulin response. However, simple adjustments in the β -cell model response – for example, changing the amount of insulin given in the first and second phase response [4] – may allow the secretion model to be adapted for sc insulin delivery. Digital filtering techniques may be able to remove delays associated with sc-ISF glucose sensing [5]. And, the effects associated with cephalic phase insulin release and incretins may be added by having the subject inform the algorithm of an impending meal.

Although not all of these ideas have been tested, closed-loop experiments utilizing sc-glucose sensing

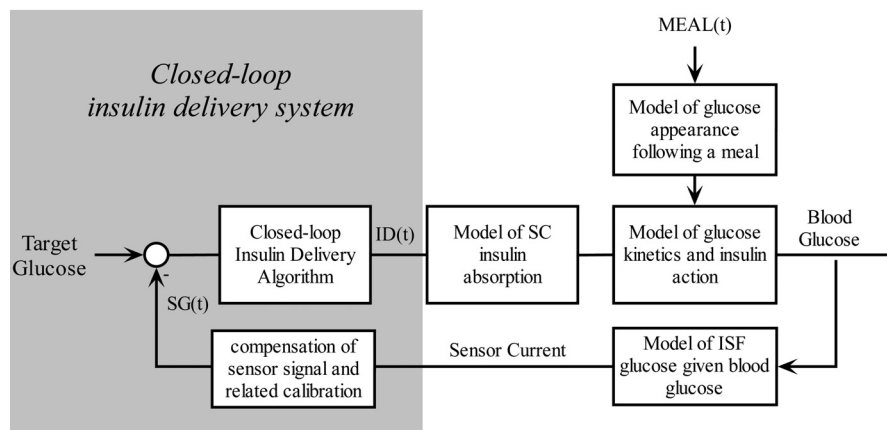


Fig. 1. Block diagram representing a closed loop control system (shaded area) interacting with models describing different components of the metabolic process to be controlled. Sensor current is assumed to be derived from the sc interstitial fluid (ISF), and insulin delivery (ID(t)) is likewise assumed to be subcutaneous.

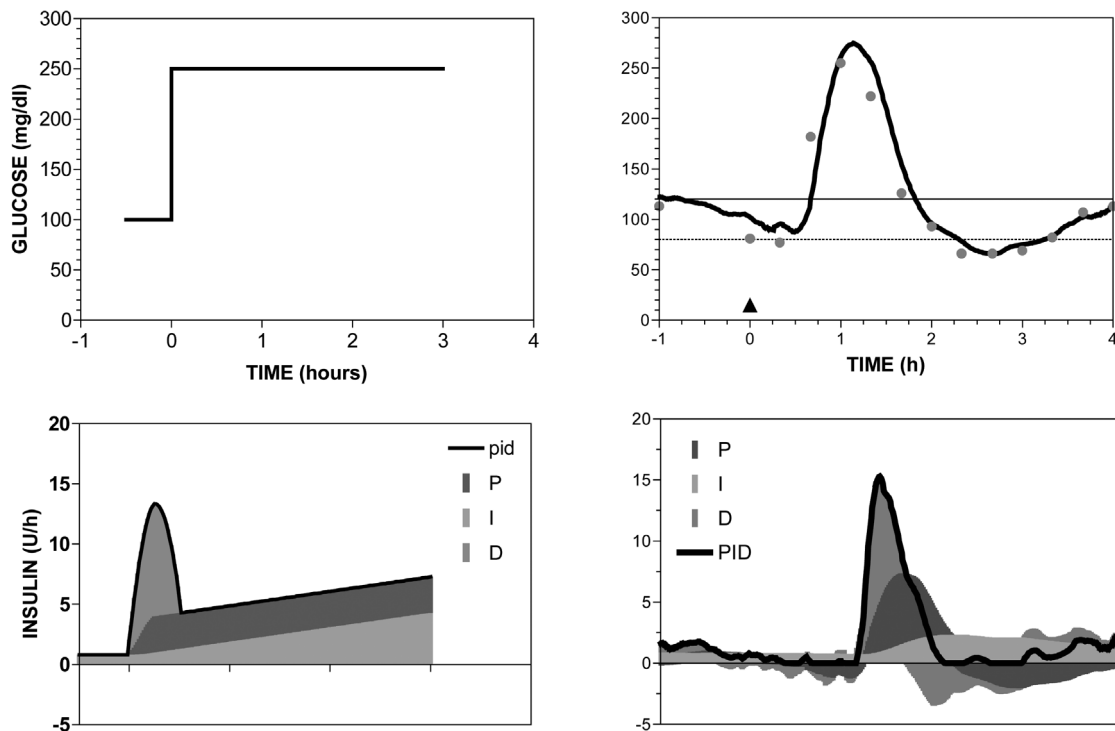


Fig. 2. Left panels show the three-components of the PID control during a simulated hyperglycemic clamp. Right panels show the same three-phase response during a closed-loop experiment performed in diabetic canines (adapted from [6]).

and sc-insulin delivery in animals have been encouraging [6] (studies in humans are ongoing). To date, studies have used a model of the β -cell that has 3 components: one proportional to glucose, one that slowly increments up or down in response to glucose, and one that reacts to the rate-of-change of glucose [3]. The three components sum to produce a response similar to that typically observed during a hyperglycemic clamp [4] (Fig. 2. left panels). The *rate-of-change* component rapidly delivers insulin during meal-induced increase in glucose, and suppresses delivery during periods where glucose is falling (Fig. 2, right panels) and the incremental component adjusts up or down depending on if glucose is above or below *target*.

3. Is the β -cell a PID controller?

While we have shown the 3-phase “ β -cell model” (Fig. 2) to describe the multiphasic insulin response to glucose during hyperglycemic clamps [3], it would be more commonly recognized in the engineering community as a classical “proportional-integral-derivative” controller [2]. Other models of β -cell secretion also exist, but most describe glucose stimulated insulin secretion as the sum of components that react either slowly to glucose (analogous to an integral or integral

with slow “leak”), immediately to glucose (analogous to a proportional response), and/or its rate of change (analogous to a derivative response; see reference [7] for discussion). This leads to the open question: is the β -cell behaving like the classical PID controller that is virtually ubiquitous in engineering applications?

An extension to this question would be to ask if any of the control strategies that followed PID might also benefit closed-loop insulin delivery. Can concepts such as state-feedback, adaptive control, or model predictive control, be utilized to improve on the control responses obtained with PID? The first two – state-feedback and adaptive control – likely have substantial overlap with putative β -cell behavior. For example, insulin concentration is widely believed to suppress insulin secretion (feedback of insulin concentration and/or effect is analogous to state-feedback), and the β -cell is commonly believed to adjust its gain to changes in a subject’s insulin sensitivity (a type of adaptive control). Model predictive control [8] is, however, unlikely to have an obvious analogy with the β -cell. Nonetheless, this does not necessarily indicate the controller will not perform better.

Model predictive control (MPC) is virtually guaranteed to improve the control performance criteria defined in the MPC cost function, provided the model

used to predict future glucose is in complete agreement with the actual response. That is, if the correlation between the subject's glucose response and the model predicted glucose response is perfect ($r^2 = 1$). At the opposing extreme, MPC can logically be expected to perform poorly if the predictive ability is 0 (i.e. if the model prediction is completely random). Between these two extreme r -values – neither of which is likely to be true – there should exist a correlation where MPC and a control strategy derived from the β -cell/classical control theory can be expected to perform similarly. What that r -value is remains to be determined.

4. Conclusion

The achievement of a completely automated closed-loop insulin delivery system for the treatment of type 1 diabetes will most assuredly benefit from a detailed understanding of the dynamics of insulin and glucose. These dynamics can best be understood through the use of metabolic models. Insight provided by the β -cell may also aid the process of designing a closed-loop algorithm. Control systems engineering and digital signal processing are also likely to play substantial roles, as will the ability to capitalize on the vast clinical knowledge of medical doctors treating patients. Finally, the knowledge and experience that individuals with diabetes have themselves acquired will be critical if the system is to achieve widespread use.

Acknowledgments

This work was supported by the National Institutes of Health grants RO1 DK 57210 (KR) and RO1 DK 64567 (GMS).

References

- [1] G.M. Steil, B. Clark, S. Kanderian, K. Rebrin, Modeling insulin action for development of a closed-loop artificial pancreas, *Diabetes Technol Ther* (2005) 94–108.
- [2] Ogata, K *Modern Control Engineering*, Edition 3 Prentice-Hall Upper Saddle River, NJ, 1997
- [3] G.M. Steil, K. Rebrin, R. Janowski, C. Darwin, M.F. Saad, Modeling beta-cell insulin secretion—implications for closed-loop glucose homeostasis, *Diabetes Technol Ther* (2003) 953–964.
- [4] G.M. Steil, A.E. Panteleon, K. Rebrin, Closed-loop insulin delivery—the path to physiological glucose control, *Adv Drug Deliv Rev* (2004) 125–144.
- [5] K. Rebrin, G.M. Steil, W.P. Van Antwerp, J.J. Mastrototaro, Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring, *Am J Physiol* (1999) E561–E571.
- [6] A.E. Panteleon, G.M. Steil, M. Loutseiko, K. Rebrin, Evaluation of the Effect of Gain on the Meal Response of an Automated Closed Loop Insulin Delivery System, *Diabetes* (2005).
- [7] G.M. Steil, C.M. Hwu, R. Janowski, F. Hariri, S. Jinagouda, C. Darwin et al., Evaluation of insulin sensitivity and beta-cell function indexes obtained from minimal model analysis of a meal tolerance test, *Diabetes* (2004) 1201–1207.
- [8] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, F.M. Orsini, et al., Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes, *Physiol Meas* (2004) 905–920.