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MEETING PROCEEDINGS

Update on Mathematical Modeling Research to Support the Development of Automated Insulin Delivery Systems

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Abstract

One year after its initial meeting, the Glycemia Modeling Working Group reconvened during the 2009 Diabetes Technology Meeting in San Francisco, CA. The discussion, involving 39 scientists, again focused on the need for individual investigators to have access to the clinical data required to develop and refine models of glucose metabolism, the need to understand the differences among the distinct models and control algorithms, and the significance of day-to-day subject variability. The key conclusion was that model-based comparisons of different control algorithms, or the models themselves, are limited by the inability to access individual model–patient parameters. It was widely agreed that these parameters, as opposed to the average parameters that are typically reported, are necessary to perform such comparisons. However, the prevailing view was that, if investigators were to make the parameters available, it would limit their ability (and that of their institution) to benefit from the invested work in developing their models. A general agreement was reached regarding the importance of each model having an insulin pharmacokinetic/pharmacodynamic profile that is not different from profiles reported in the literature (88% of the respondents agreed that the model should have similar curves or be analyzed separately) and the importance of capturing intraday variance in insulin sensitivity (91% of the respondents indicated that this could result in changes in fasting glucose of ≥15%, with 52% of the respondents believing that the variability could effect changes of ≥30%). Seventy-six percent of the participants indicated that high-fat meals were thought to effect changes in other model parameters in addition to gastric emptying. There was also widespread consensus as to how a closed-loop controller should respond to day-to-day changes in model parameters (with 76% of the participants indicating that fasting glucose should be within 15% of target, with 30% of the participants believing that it should be at target). The group was evenly divided as to whether the glucose sensor *per se* continues to be the major obstacle in achieving closed-loop control. Finally, virtually all participants agreed that a future two-day workshop should be organized to compare, contrast, and understand the differences among the different models and control algorithms.

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Abbreviations: (AR) autoregressive, (CGM) continuous glucose monitoring, (GMWG) Glycemia Modeling Working Group, (ISF) interstitial fluid, (MPC) model predictive control, (MVP) Medtronic Virtual Patient, (PK/PD) pharmacokinetic/pharmacodynamic, (UVA) University of Virginia

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Introduction

The Glycemia Modeling Working Group (GMWG) was originally formed in 2008 with the intent to document current practices in metabolic modeling for advancing closed-loop glucose control. The intent was to formulate a framework for the exchange of information and collaboration among research centers, to identify limitations of glycemia models, and to identify essential tasks that need to be accomplished in order to achieve a fully automated closed-loop glucose control system. The working group, which was then composed of 25 scientists representing many of the world leaders in glycemia modeling, was reconvened in 2009 with 39 scientists in attendance, including 14 of the original 25 participants. This report serves to update the progress achieved on the 2008 recommendations[1] and summarizes the topics discussed in the 2009 meeting. As with the 2008 report, we sought to document the collective efforts and view points of the world leaders in glycemia modeling, to increase awareness of the existing modeling challenges and opportunities, and to provide information to guide funding priorities and future solicitations.

Progress Achieved on the 2008 Recommendations

Briefly, the main conclusions and recommendations from the 2008 GMWG meeting were as follows:[1]

1. Physiological variance represents the single largest technical challenge to creating accurate simulation models.

2. A Web site describing the different models and data supporting them should be made publicly available, with funding agencies and journals requiring investigators to provide open access to both models and data.

3. Existing simulation models should be compared and contrasted using the same evaluation and validation criteria to better assess the state of the art, understand any inherent limitations in the models, and identify gaps in data and/or model capability.

Although it was generally agreed that an accurate description of physiological variances continue to be a major challenge and that models should be made public (see recommendations 1 and 2), modest progress was reported. Data for 30 subjects were made available for a model developed at the University of Virginia[2] (UVA; simulator; contact UVA Patent Foundation for details). The subjects—10 adults, 10 adolescents, and 10 children—were selected from a larger virtual population of 300 subjects (100 in each group) with the intent to describe a wide range of subjects, including both "average" and "extreme" subjects (with the extreme subjects used to assess the robustness of different control algorithms). Intraday variation in parameters was not included, as the developers do not believe appropriate data exist for their identification (personal communication from B. Kovatchev). Eighteen subjects were also identified for a model developed at Cambridge University, with a limited subset of subject data available from the developer under a research license agreement (personal communication from R. Hovorka). The Cambridge model includes intraday variation on selected model parameters (5% amplitude; 3-hour period[3]). Finally, intraday variances in parameters characterizing a model developed at Medtronic[4] were also described for 10 subjects (intraday variation in model parameters identified in three 6-hour windows). Nevertheless, given the importance placed on understanding how intrasubject variability might affect closed-loop control and the potential for models to aid in the development of effective control algorithms, these are small steps. Particularly disappointing is that no Web site was created describing the different models (part of recommendation 2), and no publication comparing different modeling approaches or identifying any limitations or gaps has appeared (recommendation 3).

The prevailing view as to why there was so little progress on model comparison was that the derivation and validation of the models, as well as the identification of the underlying parameters, represent a substantial amount of work by the individuals who developed them and that making such information freely available to other investigators or companies was an unrealistic objective. The models, associated simulation software, and any related control algorithms that might be derived from them are viewed as potential sources of revenue through intellectual property royalties and licensing agreements or as providing a competitive edge when applying for extramural funding. At issue is the ability to access individual parameter sets that comprise the average parameter values typically reported in publications. It was widely agreed that simulations performed using the average parameter values do not yield useful results when comparing models or evaluating control algorithms, although they may still serve in a more limited capacity.

Although it is becoming clear that individual investigators are unlikely to make their model parameters available, a positive outcome of the meeting was that virtually all the investigators embraced the idea of a subsequent Modeling Comparison Workshop in which different models would be compared and contrasted using common data sets and testing criteria.[1] Also, there was widespread agreement on what we would like to accomplish with the individual models—mainly achieve a better understanding of the strengths and weakness of each model when used to compare and evaluate different control algorithms. There was also substantial agreement on numerous aspects of how the control algorithm should be configured and introduced. We highlight these discussions next and return to the issue of how to compare models in our conclusion.

Specific Topics Discussed at the 2009 Glycemia Modeling Working Group Meeting

Similar to the 2008 GMWG meeting, a series of questions was used to guide the 2009 meeting. The questions and the participants' answers are provided in the **Appendix**. Not all responses add up to 39, as some participants left some questions blank and the answers from the authors were not tabulated. Some questions sought to survey opinions as to the state of glycemia monitoring, modeling, and control technologies (by definition questions that have no correct or incorrect answer), while other questions attempted to obtain answers that are not necessarily known but that could be easily verified using the different metabolic models. As the questions were largely predetermined by the authors, the following discussion undoubtedly reflects the authors' biases, with the hope that future meetings can mitigate this issue by having participants submit their own questions in advance. With this caveat in mind, the following summarizes the discussions and our analyses of the tabulated results.

Generally, the working group remained cautiously optimistic that glucose sensor technology is advancing, with ~19% (5/27) of the respondents believing that closed-loop control can be achieved with today's technology and an additional 41% (11/27) of the respondents believing that improvements in continuous glucose monitoring (CGM) calibration and filter routines will suffice. Approximately 60% of the respondents did not believe that interstitial fluid (ISF) glucose is substantially delayed compared with plasma glucose, but only 30% of the respondents believed that the maximum rate of change of ISF glucose is well characterized (with the average value reported by these individuals as 4 mg/dl/min). However, of those that believed the delay is ≤10–15 min, 50% believed that insulin can cause changes in the blood (i.e., plasma)-to-ISF glucose gradient. Also, 50% still indicated that the biggest impediment to the development of an artificial pancreas is the ability to reliably measure glucose. Of the 50% of the respondents who did not believe that glucose sensing is the problem, the predominant sentiment (60% [9/13] of the respondents) was that the absence of a high-fidelity predictive model is the main impediment. Surprisingly, only 4 of 26 respondents believed that a complete understanding of what the control strategy should be remains an open issue. Unfortunately, we did not survey these individuals as to what control strategy they believed should be used; however, given the number of respondents who indicated that the largest impediment was the lack of a high-fidelity predictive model suggests that most would favor some form of model predictive control (MPC).

Arguably, MPC should always be the preferred approach in instances where a model can be shown to reliably predict future values of the controlled variable (glucose). However, in cases where the model is less than perfect, it has been argued[5] that other control strategies may work equally well or better. The ability of a model to predict glucose excursions using meal and insulin information likely depends on the interday and/or intraday variability in the parameters of the model. This is consistent with the conclusion arrived at in the 2008 GMWG meeting[1] that physiological variance represents the single biggest technical challenge to creating accurate simulation models. In this year's meeting, we attempted to expand on this topic by quantifying the extent of the variance and discussing some of the underlying sources. Intraday variance in insulin sensitivity was thought to effect changes in fasting glucose of >15% in 21 of 23 respondents (91%), with 12 respondents (52%) believing the variability to be ≥30%. To counter these changes, respondents generally believed that basal rates either need to be adjusted by ≥30% (8 of 22 respondents) or somewhere between 15% and 30% (10 of 22 respondents). Exercise was widely believed to be one of the underlying factors responsible for changing insulin requirements, with 78% (18/23) of the respondents believing that exercise affects both the needed insulin amount and acting time (four additional respondents believed the interaction between exercise and model parameters to be more complex than simple changes in insulin magnitude and time of effect). Similarly, the effect of a high-fat meal was perceived to be more complex than putative changes in gastric emptying[6–9] by more than two-thirds of the respondents, with approximately one-half of the respondents believing that

metabolic parameters could be affected for ≥12 h after the meal. Almost 80% of the participants thought that a closed-loop control algorithm should be able to compensate for these changes with little (12 of 25 respondents) or no (7 of 25 respondents) error.

Interestingly, when asked about "insulin sensitivity factors" commonly used in open-loop therapy, there was no consensus whether a bolus is expected to effect a transient or steady state decrease in glucose given that the basal rate is appropriately adjusted to maintain glucose levels at a stable level (specified as 130 mg/dl in question 10). Essentially, the vast majority of respondents (82% [18/22]) indicated that the effect could not be classified as transient or fixed in all cases (of the 4 respondents who chose one of the two outcomes, the responses were equally divided). What makes the response interesting is that most models predict the response to be transient (KADIS[10,11] being a notable exception; see the discussion in reference 12). This is one of the few model characteristics that can be determined by examining the model equations alone. If it is true that, after the basal rate is adjusted to achieve stable glucose, administering a bolus of insulin can lead to a steady state decrease in blood glucose in some subjects—whereas in other subjects, the bolus has only a transient effect—then models need to be configured to capture this variability.

One of the more obvious differences among competing metabolic models is their order, which is defined as the number of differential equations used to describe changes in glucose. This was generally acknowledged to be a complex issue. Only 30% (8/26) of the respondents thought that, if open-loop profiles were equally well described by two models with different order, then simulated closed-loop profiles would be close; 65% (17/26) of the respondents indicated that the question could only be answered by an analysis of the different model structures. Observability analysis[13] applied to the linear components of the different models, or to linearized versions of nonlinear components, was discussed as a potential method to assess the need for high-order model terms. By definition, unobservable/near-unobservable model states (and associated model equations) have no/little effect on the model's output. What most respondents did agree was important is that the pharmacokinetic/pharmacodynamic (PK/PD) response obtained from a sample of virtual subjects should have peak concentration and effect times not statistically different from published values (46% [12/26] of the respondents) and that cases where the response differs by ≥3 standard deviations from the mean should be separately identified and analyzed (42% [11/26] of the respondents). The PK/PD profiles have been obtained clinically and characterized for virtually all insulin types and mixes,[14–17] by subject age,[18] and by the number of days of catheter use[19] (pump). One might argue that other key clinical observations should also be reproducible by model simulation. For example, one could ask whether the model's response to a short interruption in insulin delivery should also be similar to the response observed clinically,[20] as an interruption in pump delivery is putatively believed to be a first step in transitioning from open- to closed-loop control and is widely accepted to be critical to the overall safety of closed-loop devices.[21] Obtaining a given model's PK/PD profile, or its response to an interruption in pump insulin delivery, is relatively trivial if the model equations and parameters are known; however, the question remains as to who would do such simulations and how results that differ substantially from those observed in the clinical setting would be perceived, given that many clinical studies are now approved based on model simulations.[2]

As with the first GMWG meeting,[1] participants were careful to distinguish between models that are to be used for simulation and models that are to be used for control (see the discussion in the first GMCW report for definitions[1]). A class of data-driven models was also discussed at this year's meeting, with the primary question being whether the glucose system is stationary. This is an important consideration in establishing the ability of linear autoregressive (AR) models to improve short-term glucose prediction accuracy (i.e., glucose predictions in the 30–60 min window). On this item, the majority of the respondents were of the opinion that glucose signals are either not stationary (14 of 20 respondents) or, at best, weakly stationary (6 of 20 respondents). Generally, stable AR models are only representative of stationary processes, but it may be possible to mitigate the problem by detrending the signal—for example, by computing the difference between two consecutive data points—before developing an AR model. What is "at stake" is the ability to use these models to improve short-term predictions compared with other modeling approaches (e.g., Kalman filter[22]) or the first-order finite difference methods commonly used in existing CGM products (i.e., predictions based on the assumption that future values can be approximated by the most recent value *plus* the glucose rate of change *times* the desired future interval). Model-based approaches have substantial potential to improve hypoglycemic detection rates, although it is interesting to note that 40% of the respondents indicated that there is no real consensus on what constitutes a hypoglycemic event.

Conclusions

As in the first GMWG meeting,[1] there was widespread agreement on what the unanswered modeling questions are but substantially less agreement on how to answer the questions. The model-related questions and/or needs believed to be unanswered or unmet include the following:

1. The need for a mechanism that would allow investigators to simulate different models (see question 14 of the survey). The key question was how an investigator can validate a model before using it to make informed decisions regarding the choice of a control algorithm, optimal tuning of a given control algorithm, estimating the range of stability for control parameters, and assessing closed-loop stability as subject parameters change.
2. The need for models to include realistic interday and intraday variance in insulin requirements. This variance was generally believed to lead to substantial changes in the required basal rates (questions 6, 7, 10, and 11), with the effect of a high-fat meal and/or prior exercise possibly contributing to the variability (questions 12 and 13). The key question is of how to compare closed-loop simulations performed on models that do not include this variability with clinical studies in which the variability can be substantial.
3. Insulin PK/PD profiles associated with different models were widely thought to be an important model characteristic that could affect how different control algorithms perform (question 15). The key issue again being how to interpret closed-loop simulations on virtual subjects with PK/PD responses that are substantially different from published studies.
4. Continuous glucose monitoring accuracy was believed by at least one-half of the participants (questions 1 and 5) to still be the primary obstacle in achieving closed-loop control, with the inherent properties of ISF still needing to be resolved (questions 2 and 9) and the statistical properties of the glucose signal (i.e., mean, variance, and autocorrelation) still needing to be characterized (question 4). The key question was how to evaluate models for their ability to improve predictive alerts that warn subjects of impending hyperglycemic or hypoglycemic conditions (also ill defined; see question 3).

Questions identified at this year's meeting reflect many of the same issues discussed at the 2008 GMWG meeting. The need for investigators to have access to different models was identified at the 2008 meeting as a key recommendation but was generally accepted at this year's meeting to have been unrealistic. The need for models to reflect the variability in insulin requirements commonly observed in clinical practice[23,24] continues to be an issue. The issue as to whether a simulation model's insulin PK/PD profile needs to be similar to measured profiles[14–19] was a new argument this year, but it can be seen as a simple example of why individual investigators seek access to model parameters. The profile was widely viewed as an important consideration for designing a closed-loop algorithm (as also true for an open-loop algorithm). The PK/PD profiles can now be simulated for a limited set of patients identified with the Cambridge simulator,[3] as the developer of that model allows access to individual parameters under a research license agreement (personal communication from R. Hovorka). In addition, all subjects identified to date using the Medtronic Virtual Patient (MVP) model are now publicly available,[4] but this only includes 10 adult subjects studied under that company's closed-loop controller.[25] Similarly, a limited subset of patient parameters are available for the UVA simulator.[2]

The positive outcome of this year's meeting was that all the participants expressed interest in attending a new workshop devoted to presenting and discussing their models. David Klonoff (editor-in-chief of this journal and a key individual responsible for organizing the meeting) has written an article highlighting how such a workshop might be conducted.[26] Moreover, given the interest by the GMWG participants and the subsequent positive feedback from senior leadership in distinct organizations, the U.S. Army is considering sponsoring such an event for 2011. While many of the details obviously need to be finalized, one of the key ideas being considered is to make new data available for investigators to identify (i.e., customize) their models. This would eliminate the need for any of the investigators to divulge proprietary information and still enable a limited evaluation and comparison of the individual approaches using common data sets and testing metrics. Four data sets are recommended in the article written by Klonoff.[26] Although four data sets are unlikely to have the statistical power to detect differences in closed-loop simulation results, compared with one another or with results obtained in published clinical studies,[25,27–29] the approach should serve to delineate broad differences in how the models perform. It is also unlikely that models used for *simulation* can be identified from such data, as the models are typically of high order and may require glucose tracers to be identified.[1] While this would not allow the UVA simulator, by definition a *simulation* model, to be evaluated, it is likely that the Cambridge[3] and the KADIS[11] models could be identified by the developers of those models using their proprietary software, and anyone familiar

with systems identification could identify parameters for the MVP model. Noteworthy is that neither the KADIS nor the MVP model conveniently fit into the "models used for simulation/models used for control" categorization, with the KADIS model being something of a hybrid, allowing individual patients to be identified and simulations to be performed to optimize open-loop control,[10,11] and the MVP model used in a similar manner but with optimization done on closed-loop control.[30] Similarly, the low-order models used for *control*, for example, the glucose model[31] with multiple competing insulin/meal models used to effect control in the study by Hovorka and colleagues,[29] might be evaluated using such data (as could the internal models of virtually all the proposed MPC algorithms). Finally, all modeling approaches proposed for improving the prediction of glucose values from CGM data *per se* could be compared, e.g., the Wiener,[30] AR,[32] and Kalman[22] approaches.

In conclusion, the survey responses obtained at the 2009 GMWG meeting indicate a lack of consensus by many of the participants on multiple issues, suggesting that the approaches to glycemic modeling and control are still fluid. The GMWG continues to look for an approach to validate and compare models, with the objective being to highlight what the strengths of the different models are and elucidate gaps and/or weaknesses. Although we cannot disagree with the desire of individual investigators to keep the details of their models confidential, the authors of this report continue to advocate open collaboration between groups as well as the need for models to undergo independent validation before being used as the sole mechanism to make control algorithms decisions or determine the underlying stability and safe operating range of a given control algorithm. With these objectives in mind, a new workshop is being planned, the U.S. Army-sponsored Modeling Comparison Workshop, which will focus on comparing, contrasting, and understanding the differences among the different models and control algorithms. This workshop is planned for 2011.

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Disclosure:

Garry M. Steil is a former employee and holds stock in Medtronic MiniMed.

Disclaimer:

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or of the U.S. Department of Defense. This paper has been cleared for all audiences.

References:

1. Steil GM, Reifman J. Mathematical modeling research to support the development of automated insulin-delivery systems. J Diabetes Sci Technol. 2009;3(2):388–95.
2. Kovatchev BP, Breton M, Man CD, Cobelli C. *In silico* preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol. 2009;3(1):44–55.
3. Wilinska ME, Chassin LJ, Acerini CL, Allen JM, Dunger DB, Hovorka R. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. J Diabetes Sci Technol. 2010;4(1):132–44.

4. Kanderian SS, Weinzimer S, Voskanyan G, Steil GM. Identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. J Diabetes Sci Technol. 2009;3(5):1047–57.

5. Steil G, Rebrin K, Mastrototaro JJ. Metabolic modelling and the closed-loop insulin delivery problem. Diabetes Res Clin Pract. 2006;74 Suppl 2:S183–6.

6. Marciani L, Wickham M, Singh G, Bush D, Pick B, Cox E, Fillery-Travis A, Faulks R, Marsden C, Gowland PA, Spiller RC. Enhancement of intragastric acid stability of a fat emulsion meal delays gastric emptying and increases cholecystokinin release and gallbladder contraction. Am J Physiol Gastrointest Liver Physiol. 2007;292(6):G1607–13.

7. Lodefalk M, Aman J, Bang P. Effects of fat supplementation on glycaemic response and gastric emptying in adolescents with type 1 diabetes. Diabet Med. 2008;25(9):1030–5.

8. Gentilcore D, Chaikomin R, Jones KL, Russo A, Feinle-Bisset C, Wishart JM, Rayner CK, Horowitz M. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. J Clin Endocrinol Metab. 2006;91(6):2062–7.

9. Burge MR, Castillo KR, Schade DS. Meal composition is a determinant of lispro-induced hypoglycemia in IDDM. Diabetes Care. 1997;20(2):152–5.

10. Augstein P, Vogt L, Kohnert KD, Freyse EJ, Heinke P, Salzsieder E. Outpatient assessment of Karlsburg Diabetes Management System-based decision support. Diabetes Care. 2007;30(7):1704–8.

11. Salzsieder E, Augstein P, Vogt L, Kohnert KD, Heinke P, Freyse EJ, Azim Ahmed A, Metwali Z, Salman I, Attef O. Telemedicine-based KADIS combined with CGMS has high potential for improving outpatient diabetes care. J Diabetes Sci Technol. 2007;1(4):511–21.

12. Steil GM, Clark B, Kanderian S, Rebrin K. Modeling insulin action for development of a closed-loop artificial pancreas. Diabetes Technol Ther. 2005;7(1):94–108.

13. Ogata K. Modern control engineering. 3rd ed. Saddle River: Prentice-Hall; 1997.

14. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care. 1999;22(9):1501–6.

15. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. Diabetes. 1994;43(3):396–402.

16. Heise T, Weyer C, Serwas A, Heinrichs S, Osinga J, Roach P, Woodworth J, Gudat U, Heinemann L. Time-action profiles of novel premixed preparations of insulin lispro and NPL insulin. Diabetes Care. 1998;21(5):800–3.

17. Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G. Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects. Diabetes Care. 2003;26(7):2027–31.

18. Swan KL, Weinzimer SA, Dziura JD, Steil GM, Voskanyan GR, Steffen AT, Martin ML, Tamborlane WV. Effect of puberty on the pharmacodynamic and pharmacokinetic properties of insulin pump therapy in youth with type 1 diabetes. Diabetes Care. 2008;31(1):44–6.

19. Swan KL, Dziura JD, Steil GM, Voskanyan GR, Sikes KA, Steffen AT, Martin ML, Tamborlane WV, Weinzimer SA. Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. Diabetes Care. 2009;32(2):240–4.

20. Zisser H. Quantifying the impact of a short-interval interruption of insulin-pump infusion sets on glycemic excursions. Diabetes Care. 2008;31(2):238–9.

21. Cengiz E, Swan KL, Tamborlane WV, Steil GM, Steffen AT, Weinzimer SA. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. Diabetes Technol Ther. 2009;11(4):207–10.

22. Kuure-Kinsey M, Palerm CC, Bequette BW. A dual-rate Kalman filter for continuous glucose monitoring. Conf Proc IEEE Eng Med Biol Soc. 2006;1:63–6.

23. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. J Pediatr. 2004;145(3):380–4.

24. Klinkert C, Bachran R, Heidtmann B, Grabert M, Holl RW, DPV-Initiative. Age-specific characteristics of the basal insulin-rate for pediatric patients on CSII. Exp Clin Endocrinol Diabetes. 2008;116(2):118–22.

25. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes. 2006;55(12):3344–50.

26. Klonoff DC. The need for a glycemia modeling comparison workshop to facilitate development of an artificial pancreas. J Diabetes Sci Technol. 2010;4(1):1–3.

27. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care. 2008;31(5):934–9.

28. Clarke WL, Anderson S, Breton M, Patek S, Kashmer L, Kovatchev B. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. J Diabetes Sci Technol. 2009;3(5):1031–8.

29. Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, Kollman C, Hovorka T, Larsen AM, Nodale M, De Palma A, Wilinska ME, Acerini CL, Dunger DB. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010;375(9716):743–51.

30. Kanderian SS Jr, Steil GM. Apparatus and method for controlling insulin infusion with state variable feedback. U.S. Patent Application 20070173761.

31. Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. Am J Physiol Endocrinol Metab. 2002;282(5):E992-1007.

32. Gani A, Gribok AV, Rajaraman S, Ward WK, Reifman J. Predicting subcutaneous glucose concentration in humans: data-driven glucose modeling. IEEE Trans Biomed Eng. 2009;56(2):246–54.

Appendix: Meeting Survey with Responses Shown in Brackets

1) Can currently available continuous glucose monitoring (CGM) devices provide accurate inference of blood (i.e., plasma) glucose concentrations for the purpose of closed-loop control?

   a. [5] Yes, it is not a problem.

   b. [11] Accurate inference can only be achieved via calibration and postsignal processing techniques, which are still being researched.

   c. [11] The accuracy of the current available CGM devices must be improved before the devices are used for closed-loop control.

2) Subcutaneous interstitial fluid (ISF) glucose is typically:

   a. [9] Delayed by ≥15 min, and the plasma-to-ISF glucose gradient is increased by insulin.

   b. [7] Well-equilibrated with plasma glucose within 10–15 min, but changes in plasma insulin may lead to errors in sensor glucose of ≥10%.

   c. [7] Delays in ISF glucose and changes in the plasma-to-ISF glucose gradient do not lead to errors in glucose sensing of ≥5–10%, but errors in obtaining accurate reference glucose values, changes in sensor sensitivity, and other factors can still be a problem.

3) Is there a consensus of what constitutes hypo- and hyperglycemic episodes?

   a. [1] Yes (e.g., ____ consecutive minutes of CGM signals below/above a threshold ____ minutes apart from the previous episode).

   b. [11] No.

   c. [15] To some extent.

4) Is the maximum rate of increase/decrease of subcutaneous glucose levels well characterized?

   a. [8] Yes (e.g., +/- ____ $mg/dl^{-1}/min^{-1}$), 4 being the average answer.

   b. [8] No.

   c. [11] To some extent.

5) What is the biggest impediment for the development of an artificial pancreas?

   a. [9] Lack of high-fidelity predictive models.

   b. [4] Complete understanding of what the control strategies should be.

   c. [13] Unreliable measurements of glucose concentration levels.

6) With a fixed basal rate, changes in day-to-day insulin sensitivity result in morning fasting glucose that

   a. [2] Typically is within 15% if the subject has accurately administered insulin for all meals during the previous day and not eaten for 10 h.

   b. [9] Typically may be 15–30% different even if the subject has accurately administered insulin for all meals during the previous day and not eaten for 10 h.

   c. [12] May be ≥30% even if the subject has accurately administered insulin for all meals during the previous day and not eaten for 10 h.

7) Day-to-day changes in insulin sensitivity typically require

   a. [4] Changes in overnight basal rates of up to 15% to achieve target.

   b. [10] Changes in overnight basal rates of up to 15–30% to achieve target.

   c. [8] Changes in overnight basal rates of ≥30% to achieve target.

8) Closed-loop controllers should be

   a. [15] Designed to adapt to changes in the patient (or model parameters) automatically, with no physician-based adjustments.

   b. [5] Adjusted by physicians in much the same way that open-loop algorithms are adjusted, with more complicated self-tuning algorithms introduced at a later point.

   c. [8] The strategy that works best based on existing model simulations should be introduced first.

9) Are ISF glucose signals

   a. [0] Stationary.

   b. [6] Weakly stationary.

   c. [14] Not stationary.

10) Given a well-controlled individual with bedtime and morning glucose equal to 130 mg/dl and an insulin sensitivity factor of "1 U drop of glucose 30 mg/dl,"

   a. [2] A 1 U nighttime (10 PM) bolus of insulin is expected to temporarily lower blood glucose to 100 mg/dl, but morning glucose (10 h later) is expected to return to a value near 130 mg/dl. To effect a change in the morning value requires a change in overnight basal.

   b. [2] A 1 U nighttime bolus of insulin is expected to lower blood glucose by approximately 30 mg/dl, with morning glucose also lower by 30 mg/dl. No change in basal is required, as the subject is already stable at the existing basal rate.

   c. [18] Neither statement "a" nor "b" is true in all cases.

11) How well does a closed-loop controller need to adjust to changes in insulin sensitivity?

    a. [7] The controller should adapt to changes in sensitivity such that fasting glucose is at target when the sensor is correctly calibrated.

    b. [12] Fasting glucose should be within 15 mg/dl of target when the sensor is accurate. Target should be thought of as a "range," not a value.

    c. [6] Fasting glucose should be within 15–30 mg/dl of target when the sensor is accurate.

12) Exercise can

    a. [18] Change insulin requirements for 12–24 h after the exercise. Both the absolute amount needed and the rate at which insulin acts can change.

    b. [1] Change insulin requirements for 12–24 h after the exercise; however, only the absolute amount of insulin needed changes, with other metabolic parameters being largely unaffected.

    c. [0] Neither statement "a" nor "b" is true. The effect that exercise is expected to have on model parameters is minor.

    d. [4] Neither statement "a" nor "b" is true. The effect that exercise is expected to have on model parameters is much more complex.

13) A high-fat meal can

    a. [5] Affect gastric emptying but has little effect on other metabolic parameters, such as insulin sensitivity or endogenous glucose production.

    b. [10] Effect changes in metabolic parameters other than gastric emptying, with the effect lasting 12 h or more.

    c. [0] Neither statement "a" nor "b" is true. The effect of a high-fat meal on model parameters is minor.

    d. [6] Neither statement "a" nor "b" is true. The effect of a high-fat meal on model parameters is much more complex.

14) Given low- and high-order models with parameters chosen such that the 24 h open-loop predictions are within 10% at all time points, the closed-loop simulation results would be expected to be

    a. [8] Nearly similar.

    b. [1] Dramatically different, with one model predicting some controllers to be unstable and unsafe and the other models predicting the same controller to be both stable and safe.

    c. [17] Neither "a" nor "b" can be said to be true, with the answer depending on how the low- and high-order models are structured

15) Should a model composed of a population of "virtual subjects" generate pharmacokinetic/pharmacodynamic (PK/PD) responses not statistically different from those in the literature?

a. [12] Yes, the average time-to-peak concentration and peak effect should not be statistically different for measured values.

b. [3] No, the simulation model should represent extreme cases that can potentially be encountered in the real population.

d. [11] Both should be done, but patients whose PK/PD response are ≥3 standard deviations from the mean should be identified.