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MEETING PROCEEDINGS

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

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Abstract

The world leaders in glycemia modeling convened during the Eighth Annual Diabetes Technology Meeting in Bethesda, Maryland, on 14 November 2008, to discuss the current practices in mathematical modeling and make recommendations for its use in developing automated insulin-delivery systems. This report summarizes the collective views of the 25 participating experts in addressing the following four topics: current practices in modeling efforts for closed-loop control; framework for exchange of information and collaboration among research centers; major barriers for the development of accurate models; and key tasks for developing algorithms to build closed-loop control systems. Among the participants, the following main conclusions and recommendations were widely supported:

1. Physiologic variance represents the single largest technical challenge to creating accurate simulation models.
2. A Web site describing different models and the data supporting them should be made publically 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.

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Abbreviations: (AR) autoregressive, (DirecNet) Diabetes Research in Children Network, (GMWG) Glycemia Modeling Working Group, (ICU) intensive care unit, (JDRF) Juvenile Diabetes Research Foundation, (ODE) ordinary differential equation, (PK/PD) pharmacokinetic/pharmacodynamic, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

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Introduction

Together with continuous glucose monitoring devices and insulin-delivery pumps, algorithms for closed-loop control hold the key for the realization of an "artificial pancreas." Critical to the development of such algorithms is the availability of biomathematical models that can be used as part of the control algorithm and as a means for simulating and testing the composite system *in silico*. To discuss the current status of these applications and steps that could be taken to facilitate further developments, we formed the Glycemia Modeling Working Group (GMWG), which convened during the Eighth Annual Diabetes Technology Meeting in Bethesda, Maryland, on 14 November 2008. The GMWG brought together 25 scientists (see Acknowledgements), representing many of the world leaders in glycemia modeling. The following four topics were addressed:

- Current practices in modeling efforts for closed-loop control;
- Framework for exchange of information and collaboration among research centers;
- Major barriers for the development of accurate models; and
- Key tasks for developing algorithms to build closed-loop control systems.

This report summarizes the key findings and recommendations discussed at the GMWG meeting, including various different perspectives on each topic. Accordingly, this report serves three purposes: first, to relate concisely, in one document, the collective efforts and viewpoints of the world leaders in glycemia modeling; second, to increase awareness of both the challenges and the opportunities that lie within the realm of modeling; and third, to provide sufficient information to craft a science and technology pathway for guiding funding priorities and future solicitations.

Current Practices in Modeling Efforts for Closed-Loop Control

Historically, mathematical modeling has played a prominent role in the development and implementation of advanced control algorithms. Notable examples include the control of industrial processes, airplanes, and robots, where the underlying models are derived from first principles. For example, macroscopic conservation of mass, energy, and momentum is used for modeling thermal-hydraulics phenomena in nuclear power plants, and Newtonian mechanics is used to derive the underlying modeling equations governing robotic-arm motion. Unlike such first-principles models, the equations governing metabolic models are often data driven, and in cases where knowledge of the underlying physiological phenomena is limited, subjective determinations are often necessary. For example, equations representing insulin pharmacokinetic/pharmacodynamic (PK/PD) profiles are often obtained by examining different models, each having a different form or different number of compartments, and choosing a model based on which representation best fits the data.[1] The compartments are often interpreted as representative of concentrations in different tissue beds (e.g., muscle and liver), but for the most part, this is difficult to validate, as direct measurement of concentration in the interstitial fluid surrounding these tissues is difficult to obtain. In some cases, compartments are added that do not reflect a concentration *per se*, but rather a downstream intracellular signaling process. Again, a direct measure of the signal is often not available, and much of the reasoning behind the model remains speculative.

There was wide-scale agreement at the Workshop that models can serve two different purposes: (1) to simulate the response of humans to daily activities, exercise, and food and insulin intake and (2) to be included as part of the control algorithm *per se*. Generally, the simulation model can be expected to be a more complex, higher-order model and to have higher fidelity than the simpler models used for control. Simulation models should be expected to mimic the complexity and the dynamics of insulin–glucose interactions so as to provide valuable information about the effectiveness, safety, and limitations of various control algorithms over a wide range of scenarios, some of which would be difficult to perform in animals and impossible in humans. Recent examples of *simulation models* include those proposed by Chassin and colleagues,[2] Stocker and colleagues,[3] and Kovatchev and colleagues,[4] albeit numerous other models have also been proposed.[5] Each of the models uses different compartmental structures to describe subcutaneous insulin absorption into the bloodstream and its subsequent effects to lower glucose, how glucose is transported between different compartments, and the rate of appearance of glucose following meals. The primary differences among the formulations relate to the number of compartments (model order) and the

time course for insulin to exert its various effects. The model developed by Stocker and colleagues has the lowest order (three compartment insulin, one compartment glucose) but includes provisions for diurnal variation in model parameters.[6] None of the models proposed directly characterize the effect of exercise, although this has recently been introduced by Dalla Man and colleagues.[7] Noteworthy is that member organizations of the Juvenile Diabetes Research Foundation (JDRF) closed-loop consortium—described later under Framework for Exchange of Information and Collaboration Among Research Centers—have successfully used the University of Virginia simulator[4] to replace *in vivo* animal studies for regulatory approval (under a Food and Drug Administration Investigation Device Exemption).

Generally, models to be used as part of the controller can be similar to the higher-order model used for simulation purposes.[8] However, it is also common to linearize a higher-order model and reduce it to a lower order[9] or simply use a subset of the model components, such as the components related to the PK/PD response of the insulin being used.[10] Whatever the strategy, the *control model* should be of sufficient accuracy so that control actions based on the model predictions improve performance. While this may seem obvious, it is important to note that the control model need not be perfect to improve the overall system performance. Thus use of a lower-order model with population-average parameters rather than a more accurate higher-order model with patient-specific parameters can often improve control performance. Under these conditions, the simulation model allows the controller to be evaluated under conditions where the internal control model is not 100% predictive of the simulation model. Such simulations provide a rapid, cost-effective method of assessing controller safety in advance of performing human clinical trials.

One issue discussed at length at the Modeling Workshop was how to validate models. While many consider models to be validated only if they can be shown to match a set of measured observations over an envelope of initial states and operating conditions, others argued that models cannot be validated at all, only "invalidated." That is, it is only possible to identify the limits at which a given model "breaks." Related to this issue is the lack of any consensus metric to evaluate different glucose models. Although these issues are not unique to glucose modeling, we believe that it would be useful if the glucose modeling community were to establish "standard criteria" by which existing and future models could be assessed. Three criteria to assess simulation model validity might be as follows: first, show that the model fits existing closed-loop data; second, show that the model can predict clinical closed-loop results obtained on a population of subjects that is independent from the population used to construct the model; and third, show that, if the model is identified on a specific subject, it can predict glucose profiles under conditions different than those used to identify it. These criteria would remove models unable to fit existing closed-loop data, directly validate that the simulation model is sufficiently accurate for preclinical safety analysis (one possible intended use), and show that the model can optimize insulin-delivery algorithms for specific subjects or provide insight into how to correct an undesirable unanticipated closed-loop control response. Models in which the last criterion is validated should allow for their use in optimizing open-loop insulin-delivery algorithms as well as closed-loop ones. For example, to optimize the 24 h basal profile, determine the optimal insulin-on-board time profile, set insulin sensitivity factors, or adjust carbohydrate-to-insulin ratios.

Recommendations

Given the diversity of existing models and modeling techniques to simulate human responses and for inclusion in closed-loop control algorithms, it is timely to assess the advantages and limitations of each approach. A workshop should be organized to compare and contrast the distinct approaches using common data sets and established validity criteria for accepting or rejecting different models. The Workshop findings should be published in peer-reviewed papers to increase the awareness and stimulate research in any identified gaps.

Framework for Exchange of Information and Collaboration among Research Centers

Bringing the different components together for a successful closed-loop insulin-delivery system will require the convergence of different disciplines. Collaboration within a competitive environment is not easily accomplished, as competition for publications and grants can be seen as an inherent disincentive. Thus, unless appropriate, transparent, and financial or intellectual incentives are created, such collaboration is unlikely to occur, despite its potential to accelerate progress in developing the closed-loop system. With appropriate incentives, multigroup collaborations are, however, likely to be successful. An example of such a successful collaboration is the JDRF-sponsored six-member consortium that started in 2005 (expanded to seven sites in 2007; see the JDRF Web site for

additional information[11]). Individual groups are actively pursuing a variety of different control algorithms—predominantly model predictive control, either with[12] or without[8,9] a glucagon infusion arm, and a proportional-integral-derivative controller emulating the β cell.[10,13,14] Collaborations can also be initiated through interpersonal relationships, with many of the Workshop participants having already done so. The overwhelming consensus of the Workshop members was that such collaborations should be strongly encouraged by funding agencies and that the benefits of such collaborations would be even further increased if the protocols, data sets, models, and criteria for model assessment were made available to the entire community to share.

Sharing these research outcomes through Web-based public databases, open-source software, and open-access publishing has become a required, common practice in molecular, genomic, and computational biology research. For example, funding agencies, such as the National Institutes of Health, require that certain data be placed in public repositories, and most open-access journals require authors to make both data and software available as a prerequisite for publication.[15] Public access would not only allow for the expansion of the research community—for example, a data repository with glucose data for individuals with and without diabetes would lower the entry barrier for physical scientists with signal-processing, modeling, and control expertise—but would also transform how and what research is conducted. Moreover, it should optimize resource utilization and accelerate the development of an artificial pancreas by eliminating the need to replicate data and recreate or revalidate past models. This would shift focus to favor complementary data collection and alternative modeling techniques.

With a few exceptions, the incorporation of de-identified clinical data into large public Web-based databases has been limited, perhaps due to privacy concerns and/or lack of appropriate incentives. One notable exception is PhysioNet, which archives and provides free access to collections of physiologic time-series measurements and related open-source analysis software.[16,17] Another exception is the resource provided by the Diabetes Research in Children Network (DirecNet).[18] DirecNet consists of five clinical centers and a coordinating center, with the mission to investigate the potential use of glucose monitoring technology and its impact on the management of type 1 diabetes mellitus (T1DM) in children. The DirecNet Web site presently provides direct access to six separate studies containing time-series glucose data and related information for dozens of healthy and T1DM children ages 3–18 measured with different continuous glucose monitoring systems, both as inpatients and outpatients.

While the DirecNet Web site provides a valuable resource, additional public Web-based databases should be established to archive well-annotated clinical and animal-study data sets. Importantly, such sites ought to be maintained beyond the lifespan of the original grant for collection of the original study data.[15] While a detailed description of the data types required for archival is beyond the scope of this report, we recommend that the data sets contain not only time series of glucose data—and time series of other physiologic parameters—but also the timing of physical activities and the timing and type of insulin intake and the caloric content of meals. Ideally, this would include data from nondiabetes patients, patients with type 2 diabetes mellitus (T2DM), and those with T1DM, each obtained from inhomogeneous populations. The data could include tracer studies, studies on insulin PK/PD profiles and meal responses, and data assessing intra- and interday variance. Raw, unprocessed individual data should be archived to provide maximum flexibility to groups looking to perform independent analysis.

Another opportunity that could be provided is the option to share simulation models. This requires the full model structure to be disclosed, together with a database of parameters defining different subjects. Still another avenue for fruitful collaboration is through the adoption of common research protocols. These could include, at a minimum, reference meals with agreed-upon composition and timing. While not perfect, a common protocol should allow different closed-loop clinical studies to be compared more objectively, with only the underlying subject characteristics being different. Although accomplishing such meritorious goals will require incentives and the appropriate institutional review board approvals, the potential advantages for all parties involved—industry, government, and academia—would be substantial.

Recommendations

As a condition for funding, sponsoring agencies should require that investigators make the outcome of funded research publicly available. Likewise, journals should impose similar requirements as a condition for publishing. Specific request for proposals could be made for investigators to identify and generate the required data sets to build comprehensive models, and once the data are made available, different modeling groups could use the data to defend or reject existing models.

Major Barriers for the Development of Accurate Models

Two themes emerged from the discussion on this topic—the first being that variability represents the biggest challenge in creating an accurate model, and the second being that there are too little data addressing this issue. Variability in meal absorption and subcutaneous insulin absorption was highlighted as a primary concern, together with changes following exercise or in response to stress. To these, interday variability in insulin sensitivity and endogenous glucose production due to normal circadian rhythms could be added, as they are well-known to lead to multiple basal rates during the day in patients using insulin pumps.[19]

For models in which the glucose dynamics are described as a series of ordinary differential equations (ODEs), each characterized by parameters that reflect physiologic processes (e.g., insulin sensitivity), the primary obstacle is the inherent variability associated with each process itself. Although some variance may be overestimated by the methods used to assess it,[20] and some modeling strategies may be more robust to variance than others,[21,22] it is well accepted that patients with T1DM have highly variable meal and insulin responses and that ODE models are often used as the starting point for controller design. Generally, fixed overnight basal rates lead to widely varying morning glucose values, and the same meal given on consecutive days can result in widely different glucose excursions despite identical insulin boluses. Clearly, if a clinical study is conducted in which all the modeling "inputs" are controlled—for example, size and composition of meal and amount of insulin—and the glucose response varies 20–40% on consecutive days, a model that perfectly describes the response on the first day will necessarily be 20–40% wrong on the second day. Clinical studies assessing how high the variance is and its statistical and temporal properties are lacking. Once established, these variances should be incorporated into the simulation model formulation to better duplicate expected human responses.

That there is insufficient data to fully understand this variance is, we believe, largely because most modeling data have been derived from subjects with T2DM. For this patient population, most data have been acquired over short intervals (3–4 h) and under fasted conditions, for example, during intravenous glucose tolerance tests or euglycemic hyperinsulinemic clamps. The modeling focus on T2DM is justifiable, given that T2DM is characterized by defects in insulin-mediated peripheral glucose uptake and/or insulin suppression of endogenous glucose production. Nonetheless, short tests under fasted conditions do little to address intraday variability. Furthermore, it is unclear if the dynamics observed in these older, often obese, and insulin-resistant individuals with inherent defects in insulin sensitivity will mimic the dynamics in the T1DM population. Differences that do exist are likely to be substantially exacerbated when considering the dynamic responses observed in very young individuals with T1DM insofar as young children with T1DM may not have any of the underlying conditions associated with T2DM. These very young individuals are part of a population most likely to benefit from closed-loop glucose control, in that, diabetes is a progressive disease.

Another potential barrier to developing new metabolic models is the putative need to include glucose tracer data. Including a glucose tracer—typically an intravenous infusion of a negligible amount of labeled glucose—allows for the determination of whether changes in blood glucose are due to variations in glucose production or variations in glucose uptake by peripheral tissues. Given the choice between having a metabolic study with or without tracer data, virtually all modeling experts would choose to have the tracer. However, any absolute requirement to include tracers in future modeling studies may create an unrealistic burden, particularly in young children. Arguably, having a model describing the decrease in plasma glucose to an increase in subcutaneous insulin is sufficient for designing the insulin-delivery algorithm. What is important is that the model captures all the different dynamic components of the response. It is unclear, however, how knowing which dynamic component is related to endogenous glucose production and which is related to peripheral glucose uptake will affect the algorithm design.

Finally, it will be important to identify modeling strategies that are inherently less susceptible to the variability in insulin and glucose response curves, for example, data-driven autoregressive (AR) models. These models have been proposed for directly capturing the dynamics in a time series of glucose data, where the model parameters, i.e., the AR model coefficients, are obtained as those that best fit the glucose data.[21–23] Surprisingly, the AR coefficients seem to be invariant to interday and intersubject variances, leading to "universal" models that, once developed, accurately predict the glucose level of different individuals without any additional model fitting.[21,22] We would encourage research into these models, as they can be readily combined with many control algorithms.

Recommendations

New studies should be conducted to identify and acquire essential data for developing and validating new metabolic models for T1DM. The data should be sufficient to characterize variability in intra- and interday variability for both meal and insulin responses and to quantify age-related differences in model parameters. The need to include tracers should be carefully assessed in cases where the requirement may create an excessive burden.

Key Tasks for Developing Algorithms to Build Closed-Loop Control Systems

As might be expected in a modeling workshop, the vast majority of the participants were in agreement that having an agreed-upon simulation model is a high-priority task when developing a control system. The reason is well justified insofar as having a model allows for comparison and optimization of different control algorithms. Also, once a model exists, the stability of the controller can be determined *a priori* for defined ranges of model and control parameters. Having these ranges may become a requirement for safety analysis prior to clinical studies of new algorithms. As the safety of future clinical studies—and the ability to investigate promising new control algorithms—may become linked to a mathematical simulation model, it becomes critically important that the model be able to accurately predict clinical data. Recognizing this importance, the number one priority should be to establish a validated simulation model and make it publicly available. Key tasks to achieve this and other goals include the following:

- Creating a core data set for use in developing, evaluating, and validating new simulation models and making the data publicly available. The evaluation criteria could include, but need not be limited to, mean squared error, residual runs testing, fractional standard deviation of parameter estimates, and statistical tests verifying the significance of high-order model components (e.g., Akaike information criteria). Validation could include confirming that the simulation model can
  - Be configured to fit existing closed-loop data,
  - Predict clinical closed-loop results obtained on a population of subjects independent from the population used to construct it, and
  - Show that, if the model is identified on a specific subject, it can predict glucose profiles in that subject under conditions different from those used to identify the model parameters.
- Improving sensor signal processing to better account for signal delays, errors, and filtering.
- Including "hardware in the loop" to allow the simulation model to respond to known hardware failure modes.
- Introducing closed-loop algorithm technology in "stages," particularly if it is useful in accelerating regulatory approval.

Not reflected in these tasks is the discussion on what role, if any, animal studies should continue to have or what benefit might be achieved by studying closed-loop insulin delivery in an intensive care unit (ICU). Again, while not discussed at length, the ICU environment represents to many investigators an ideal environment to assess new control algorithms, as the ratio of doctors/nurses to patient is high and, as such, it provides a level of safety not present in other environments.

The creation of publically accessible data sets for model development and validation is, we believe, a worthy goal. However, thoughtful consideration will be required for determining what the "essential data" should be. Substantial data may already be available, for example, PK/PD profiles for pre- and postpuberty children[24] and for characterizing the variability between Day 1 and Day 3 of catheter insertion.[25] Agreement on what criteria a model may need to pass is likely to remain a contentious issue, but the existence of common data for evaluating different models is likely to aid in building consensus among different modeling groups and in providing confidence that the model can be used to define which control algorithms are ultimately tested clinically.

Undoubtedly, the performance of a closed-loop algorithm can be improved if signal-processing algorithms are better able to correct for the lag in interstitial fluid glucose and better able to predict future glucose values.[22] Much of the data required for this effort may also exist, albeit the glucose sensor data need to be provided in unfiltered form together with time-matched blood glucose values. Adding hardware failure modes to simulation results will be important, as neither the insulin catheter nor the glucose sensor is 100% fail proof. Finally, there is an emerging consensus that closed-loop strategies will need to be introduced in stages for regulatory approval to be obtained.

Recommendations

Progress on the realization of a closed-loop insulin-delivery system does not require simultaneous efforts in each of the tasks listed here. Considerable advances can be achieved if sponsoring organizations focused on addressing specific tasks and affording the entire community to share the outcomes of the funded effort.

Conclusions

This report attempts to summarize the perspectives of the world leaders in mathematical modeling research needed for closed-loop automation of insulin delivery in diabetes patients. While the authors made a conscious effort to report the collective views of the GMWG participants, inevitably our personal biases and experiences influenced our writing and are reflected throughout the document. Nonetheless, we hope that the research community at large can benefit from the findings summarized here. Furthermore, we hope that this report will increase awareness of both the challenges and opportunities that lie ahead for the development of models for closed-loop control of insulin delivery and that it provides sufficient information to craft a science and technology pathway for guiding funding priorities and future collaborations. We believe the following recommendations and conclusions were widely supported by the GMWG participants:

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

2. A Web site describing different models and the data supporting them should be made publically 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.

It was widely agreed upon that the underlying variability in the physiologic responses to insulin and meals represent the single largest technical challenge to creating accurate models. However, it is arguable that it is this variance that underlies the need for closed-loop control.

A consistent theme emerging from the Workshop was that data used to define a simulation model should be publically available for use in independently developing new models and comparing different models advocated by many groups. We believe this has potential to lead to a better consensus as to what the simulation model should look like. Absent such a consensus, many of the *in silico* results risk being dismissed as "model dependent." Together with a (yet to be defined) common set of evaluation and validation criteria, this has the potential to identify more transparently the strengths and limitations of each approach, leading to new specific research efforts to address the identified gaps.

A second theme that surfaced at the Workshop was that the simulation model should provide a means to compare control algorithms prior to performing clinical studies. To this end, the need to define measures of success for the *controller* was raised. Throughout this report, we attempted to focus on modeling issues and not on control algorithms. Nonetheless, one might argue that the two cannot be separated, as once a model is defined, it becomes a relatively simple task to show which control algorithm—open or closed—can be expected to best meet design criteria. Ultimately, the potential for a model to inform and guide new product development and define what may be the best strategy for delivering insulin cannot be dismissed. However, care will be needed to realize these benefits without pushing the envelope beyond what are, as yet, unknown limitations in a model's ability to predict clinical results. As the design and regulatory approval of new medical devices become more closely linked to mathematical simulation models, it will become imperative that such models be widely accepted to accurately reflect the underlying processes being modeled. Conversely, the existence of multiple competing models should not limit our ability to maximally benefit from simulations. We have argued throughout this report that open collaboration using Web-based data access will provide the best mechanism to advance the development and application of simulation models.

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