Modeling the Variability of Daily Life *In Silico*: Carbohydrate Counting Error, Insulin Dosing Error, and Meter Error in a T1DM Population

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Background

The use of clinical studies would be a very costly and difficult approach for assessing the effect of randomly varying real-life factors on glucose control for subjects with Type 1 diabetes (T1DM). The presence of multiple confounding variables makes it difficult to ascertain direct causal relationships between factors of interest and the clinical outcomes. The use of computer simulations provides the possibility of quantitatively controlling and isolating each factor, which may provide clearer visibility to the possible effects of each.

Methods and Protocols

Within the Diabetes Mellitus Metabolic Simulator[1,2] (DMMS.R, The Epsilon Group), we incorporated models of sensors and of common self-management patterns and lifestyle variabilities in a virtual population of 100 adults with Type 1 Diabetes Mellitus (T1DM). We defined two control arms – one to serve as a baseline from which to examine effects of variabilities applicable under SMBG-based management, and a second to do the same for those applicable under CGM-management.

SMBG-managed control arm:

- Meals: 3 per day, of 45, 60, and 75g carbohydrates, at 07:00, 12:00 and 18:00, respectively
- Basal insulin: Delivered continuously via a perfect pump, dosed on a subject-specific basis
- Meal Boluses: Delivered at start of meal, and dosed optimally for each subject.
- Postprandial corrections: 120 minutes postprandial with 180mg/dl threshold and 120mg/dl target. Dosed with simulated SMBG and optimal correction factors for each subject.
- Rescue carbs: 15g every 15 minutes when blood glucose < 60mg/dl

Lifestyle variations applied to the above, each in an independent arm of the study, were as follows:

- Carbohydrate estimation errors (carb est. errors). Modeled with a random distribution ranging from approximately -40% to 20% of actual meal size, consistent with the literature[3] (with negative values representing underestimation).
- Skipped postprandial corrections: 35% probability of skipping a correction following any given meal[7]
- BG guesses on postprandial corrections (Blind Bolusing): 35% probability of making a guess following a meal. Guessed values are represented by a bivariate normal distribution consistent with the literature[4]

CGM-managed control arm:

- Identical to SMBG-managed arm, but with CGM-alarm based corrections in place of the postprandial corrections. Simulated SMBG used for confirmation and dosing in response to simulated CGM's alarms

Lifestyle variations applied individually in independent CGM-managed arms were as follows:

- Carbohydrate estimation errors[3]
- For the alarm-based correction, use CGM readings only (no use of SMBG confirmation or dosing)

Additional arms were defined to demonstrate how effects could be examined in combination, and to show how the impact of a given lifestyle choice could be affected by the presence or absence of sensor errors.

Sensor Models

SMBG: Modeled to minimally satisfy the ISO 15197 2013 standard[5]. The fraction of measurements within the ranges specified by the standard will match the minimum tolerated by the standard.

CGM: Modeled to account for lags and noise[6], yielding a typical MARD (8.5%). The alarms are defined to occur when BG exceeds 180mg/dl, and will repeat every 30 minutes as long as BG remains over this level. A 120-minute minimum time between alarm-triggered boluses was enforced.

1.Dalla Man C, Rizza RA, Cobelli C., Meal Simulation Model of the Glucose-Insulin System. IEEE Trans Biomed Eng. 2007; 54(10):1740-1749.
2.Dalla Man, C., et al., The UVA/PADOVA Type 1 Diabetes Simulator: New Features. Journal of Diabetes Science and Technology, 2014. 8(1): 26-34.
3.Brazeau, A.S., et al., Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Research and Clinical Practice, 2013. 99(1):19-23.
4.Meltzer, L.J., et al., Blood Glucose Estimations in Adolescents With Type 1 Diabetes: Predictors of Accuracy and Error. Journal of Pediatric Psychology, 2003. 28(3): 203-211.
5.International Organization for Standardization, ISO 15197: In vitro diagnostic test systems—requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus (draft). 2011, International Organization for Standardization: Geneva.
6.Marc Breton, Ph.D. and Boris Kovatchev, Ph.D. Analysis, Modeling, and Simulation of the Accuracy of Continuous Glucose Sensors J Diabetes Sci Technol 2008; 2(5): 853-862
7.Yeaw, J., et al., Cost of self-monitoring of blood glucose in the United States among patients on an insulin regimen for diabetes. J Manag Care Pharm, 2012. 18(1): 21-32.

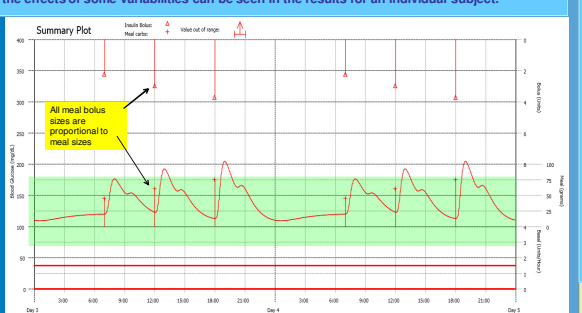
Results – Variability Modeling Verification

Simulated variabilities were verified by confirming (e.g.):

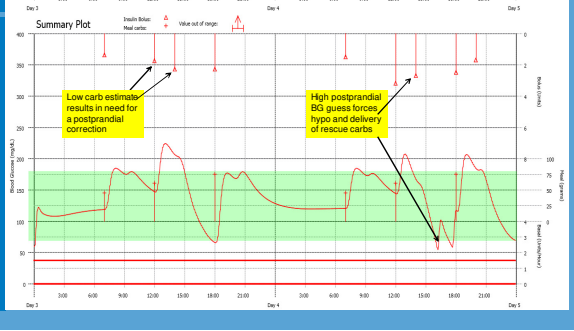
- Recorded data showed a distribution of meal bolus size inaccuracies consistent with the intended carb estimation error distribution.
- Recorded values for sensor data and postprandial corrections are consistent with intended modeling of blind bolusing.
- Recorded SMBG and CGM sensor data reflect intended error distributions

The figures below show how the effects of some variabilities can be seen in the results for an individual subject.

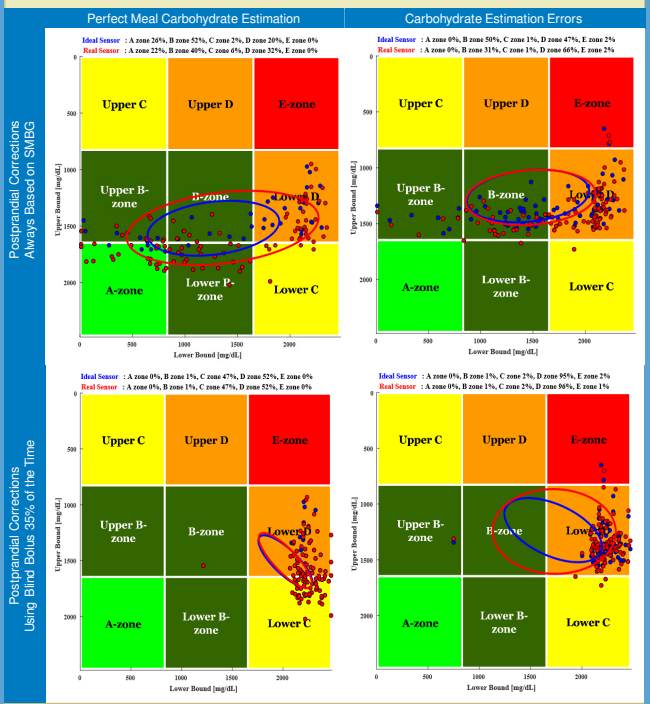
SMBG-Managed control with perfect carbohydrate estimation and perfect SMBG



Identical SMBG-managed control, but with carb estimation errors and blind bolusing for some postprandial corrections, using the same subject, meals, and perfect SMBG as above

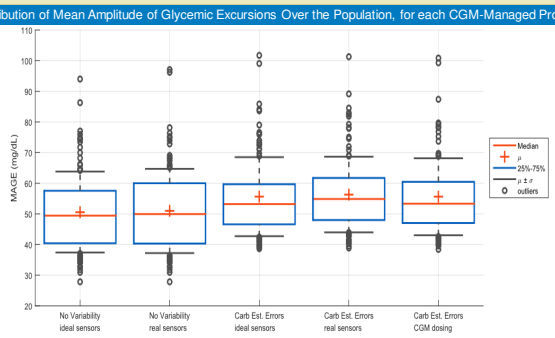


Results: SMBG-Managed Variability Effects



Results – CGM Managed Variability Effects

Distribution of Mean Amplitude of Glycemic Excursions Over the Population, for each CGM-Managed Protocol



Hypoglycemia and Hyperglycemia Population Statistics for each CGM-Managed Protocol

	Metric	No Variability Ideal Sensors	No Variability Real Sensors	Carb Est. Errors Ideal Sensors	Carb Est. Errors Real Sensors (CGM Alarms, SMBG Dosing)	Carb Est. Errors CGM Dosing
Number of subjects experiencing…	any BG < 60mg/dl	21	49	52	62	78
	any BG < 70mg/dl	38	58	72	78	88
	any BG > 200mg/dl	15	24	58	78	76
	any BG > 220mg/dl	5	12	19	24	26

Results – Discussion

Within the context of the SMBG-managed *in silico* protocols, the following effects were observed:

- Carb estimation errors cause a small increase in hypoglycemia, and a large increase in hyperglycemia. This likely results from the fact that the error distribution is designed to be biased toward underestimation.
- Using BG guesses in 35% of the postprandial corrections resulted in a dramatic increase in hypoglycemia, often necessitating the delivery of rescue carbs.
- Ideal SMBG readings show some benefit, but this is small compared to the impact of our carb estimation errors and blind bolusing, given the modeled magnitude of these variabilities. When carb estimation errors are present, there is some indication that ideal SMBG readings have a greater impact, probably because postprandial corrections are required less often if a perfect meal bolus is given. In particular, note the B zone percentage increase with ideal sensors vs. real sensors.

In the CGM-managed *in silico* protocols, the following were observed:

- Ideal sensors improve incidents of both hypoglycemia and hyperglycemia, even with no variability. This probably results from the fact that, with CGM alarms triggering doses, every CGM reading (updated each minute) has the potential to inappropriately trigger an insulin dose when sensor errors exist.
- With carb estimation errors, use of a CGM for dosing (instead of SMBG) did not meaningfully effect overall variability or hyperglycemia, but caused somewhat more hypoglycemia. This may be attributable to signal lag which predisposes the CGM to high readings at the time of postprandial dosing, when high BG levels may already be dropping.

Conclusions

In silico studies, performed with a flexible and easily configured simulation program such as the DMMS provide the ability to examine the effects of a wide range of random lifestyle variabilities on glucose control. These can be examined individually and in combination. Furthermore, their contributions to glucose control can be evaluated in the context of a variety of sensor options or treatment strategies, such as SMBG vs. CGM-based management. These studies can help to understand potential impacts of hypothetical protocols and behaviors, even in cases where corresponding clinical studies would represent unacceptable risk to the subjects.

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