Kurt Brendlinger - BGSuggest TDR

1. Introudction and scope of the document

The purpose of this document is to lay a basic foundation for a semi-automated fast-acting insulin dosage suggestion system, based on personal data collected by the Minimed Paradigm insulin pump and its associated blood glucose meter and/or continuous glucose monitoring system. By collecting and analyzing insulin dosages (including basal rates, food boluses and correction boluses), food intake, and other behavioral information from a specific user, the software (hereafter referred to as BGSuggest) will seek to suggest changes to the user's insulin regime in as focused a manner as possible.

It is anticipated that the software development will proceed in stages. In order to quickly produce results, a first tool will use aggregate information to make suggestions, in a brute-force approach which ignores some nuances (Phase I). While this tool may be effective at lowering average blood sugar rates, it is susceptible to the effects of localized events, including meal carbohydrate uncertainties, exercise, and fatty meals.

A second tool, aimed at evaluating data event-by-event, allows for more precise feedback. By analyzing data event-by-event, and incorporating meal carbohydrate estimate uncertainties, it would be able to suggest changes on an event-by-event basis, with appropriate uncertainties. The problem with this approach is that incorrect dosages can be blamed on any of three (or more) sources, and thus in a single event the data is under-constrained. The problem is resolved with three or more measurements; however, three accurate measurements within the same hour of the day is sometimes difficult, and the degree of uncertainty may be high. It is envisioned that the Phase II tool would leave these ambiguities unresolved, and up to the discretion of the user.

A third tool (Phase III) would attempt to solve this problem by attempting to minimize some converging test statistic through varying the three dosage variables (basal, bolus, sensitivity). To develop this tool, some studies using simulated data may be helpful.

Other related tools could be imagined, such as a tool to recognize trends in certain meal types (or even a particular food) and suggest changes to carbohydrate estimation. These tools would require a dedicated user whose blood sugar levels were already known to a fairly precise level, and whose carb counting techniques were well-honed.

Before Phase I can begin, however, a basis of plotting and visualization techniques, as well as a system of persistified data (ntuples) must be devised (Phase 0).

This document will also serve as a repository of information, researched and anecdotal, related to balancing an maintaining blood sugar rates.

2. Precisely Predicting Blood Sugar Rise and Fall

2.1. **Formalism for developing predictive techniques.** Predicting blood sugar trends can be an indespensible tool for improving blood sugar control. The medical dosage settings saved in the Medtronic insulin pump contain all the information needed to make such predictions, and the Bolus Wizard already uses some of this information to calculate boluses, corrections, and account for active insulin. Simply making this information more accessible to the user (and to the physician) can help make informed decisions on dosage changes.

The three main physiological quantities that must be medically controlled are sensitivity to insulin (S), insulin-carb ratio ($R_{\text{I-C}}$), and basal rate. All three can be related to absolute rise and fall of blood sugars. Converting all of these quantities into mg/dLunit equivalents is the first

step in developing predictive blood sugar level trends. Table 1 summarizes the quantities affecting blood sugar, and their relations.

TABLE 1. Relevant Quantities

Quantity	Abbrev.	Type	Unit	Conversion to mg/dL
Measured blood sugar	B_{meas} (or B)	Input/Output	mg/dL	-
Sensitivity	S	Physiological Response	$\frac{\text{mg/dL}}{U}$	-
Insulin	I_0	Input	U	$\Delta B_I = S \cdot I_0$
Insulin-Carb Ratio	$R_{\text{I-C}}$	Physiological Response	$\frac{\text{g}}{U}$	-
Active insulin time	t_A	Physiological Response	hours	-
Basal Rate	R_{Bas}	Physiological Process	$\frac{\text{mg/dL}}{h}$	$\Delta B_{\text{bas}} = R_{\text{Bas}} \cdot t$
Food (carbs)	C_0	Input	grams	$\Delta B_f = C_0 \cdot S/R_{\text{I-C}}$

2.1.1. *Time-dependent predictions.* Modeling insulin absorption rates is crucial. Minimed claims its formula is proprietary, however the formula can be determined using a few simple assumptions. In determining the time-dependent insulin absorption function, several conditions must be met:

(1) At $t = 0$, no insulin is being absorbed. Also the rate of absorption is zero.
(2) At infinite time, no more insulin will be absorbed.
(3) At $t = t_A$, all but 5% of the insulin is absorbed.

The last of these is chosen somewhat arbitrarily. The Minimed bolus wizard's "active insulin time" setting allows for seven options: 2-8 hours, in increments of 1 hour. It is not clear how Minimed defines active insulin time, but the third condition is seen as a reasonable approximation. In theory, one could determine this by reverse-engineering the "active insulin remaining" detail in the bolus wizard data.

Then, given these conditions, it takes a few guesses to arrive at a reasonable looking result. (Guess #1: a decaying exponential. Guess #2: something very close to a decaying exponential.) The formula is:

$$\frac{I(t)}{I_0} = 1 - 0.05^{\left(\frac{t}{t_A}\right)^2} = 1 - \exp\left(\ln(0.05) \cdot \left(\frac{t}{t_A}\right)^2\right) \tag{2.1}$$

where I_0 is the inital insulin bolus. Thus, $I(t)/I_0$ is the fractional amount of insulin absorbed at time t. Converting to ΔB_I by substituting in sensitivity, we can determine the blood sugar rise (fall) due to an insulin bolus:

$$\Delta B_I(t) = -S \cdot I_0 \left(1 - 0.05^{\left(\frac{t}{t_A}\right)^2}\right) \tag{2.2}$$

Taking derivatives of this:

$$\frac{\partial B_I}{\partial t} = -6SI_0 \frac{t}{t_A^2} 0.05^{\left(\frac{t}{t_A}\right)^2}, \quad \frac{\partial^2 B_I}{\partial t^2} = SI_0 \cdot 0.05^{\left(\frac{t}{t_A}\right)^2} \left(\frac{36t^2}{t_A^4} - \frac{6}{t_A^2}\right) \tag{2.3}$$

and setting the 2nd derivative to 0, we can get the maximum dB/dt, $t \sim \frac{t_A}{\sqrt{6}} = 1.63$ hours for $t_A = 4$ (at which point $dB/dt = 0.37I_0$ u/hr), 0.81 hours for $t_A = 2$. Fig. 1 shows the total absorption and dB/dt of a typical "4-hour" insulin bolus.

We can compare our absorption curves to the insulin absorption rates quoted in Medtronic's Paradigm Insulin Pump User Guide. Fig. 2 compares the formula obtained from first principles

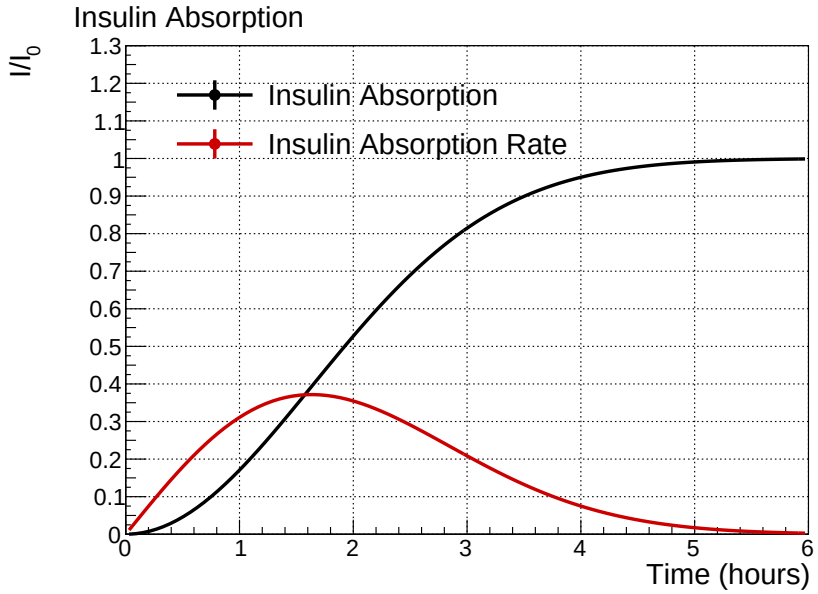

FIGURE 1. Insulin absorption curves. The red curve is the overall fractional absorption over time (I/I_0), and the black curve is dI/dt. The curve is plotted with $t_A = 4.0$, meaning that 95% of the insulin is absorbed after 4 hours.

with those used by Minimed (and apparently taken from Mudaliar et. al.). The result is a near-exact match.

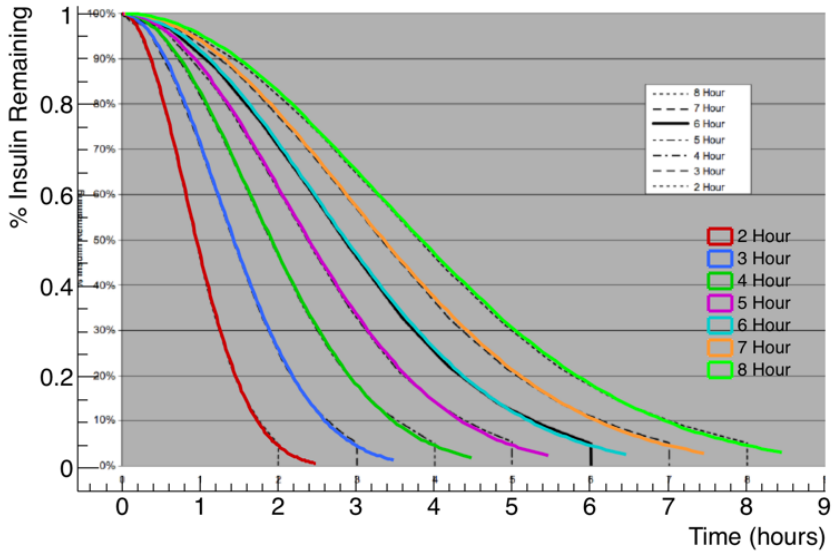

FIGURE 2. Absorption curves given different absorption rates. Formula reverse-engineered from Mudaliar and colleagues, Diabetes Care, Volume 22, Number 9, Sept. 1999, page 1501. Image taken from Medtronic Paradigm Insulin Pump User Guide.

Food absorption rates follow the same reasoning. Here, however, the t_A equivalent (call it t_C) varies according to the food's score on the glycemic index. Thus, we set $t_C = 2.0$ hours for simplicity (corresponding to a high-glycemic-index food). Thus:

$$B_C(t) = \frac{S}{R_{\text{I-C}}} \cdot C_0 \left(1 - 0.05^{\left(\frac{t}{t_C}\right)^2}\right) \tag{2.4}$$

Figure 3 shows what happens when you put all of this together.

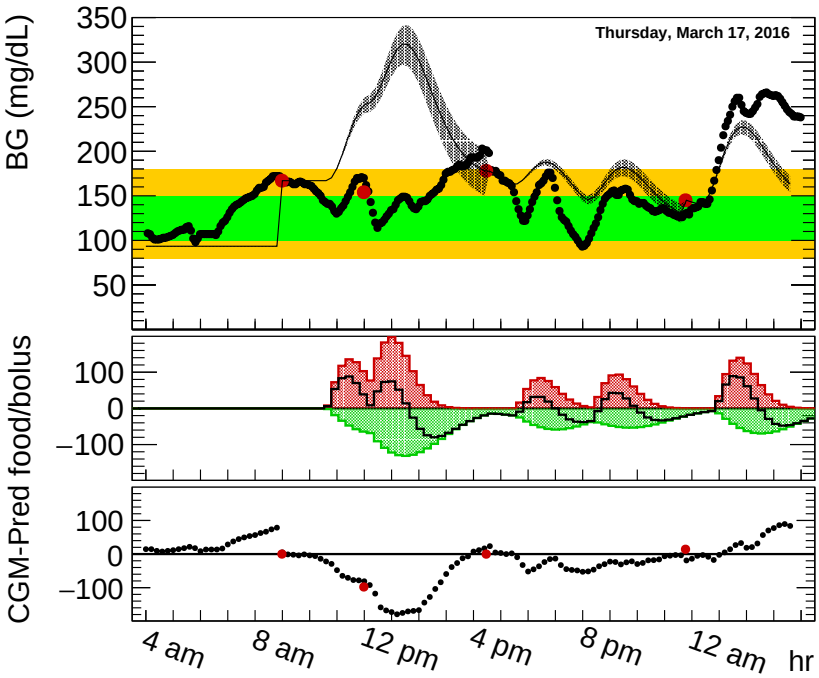

FIGURE 3. Prediction of a day's blood sugar, overlaid with CGM data.

3. Long-term trends

An important aspect of management is assessing long-term trends. Fig. 4 is a year-long review, which includes rolling 1-week averages, 4-week averages, and 17-week average BG. (17 weeks is roughly the lifetime of a red blood cell, and thus the 17-week average should give a fair comparison to HbA_{1c}.) In the figure, the HbA_{1c}axis has been calibrated to roughly match the 17-week average of this particular user (and not the $< BG > -\text{HbA}_{1c}$ conversion that the ADA publishes. The agreement between the 17-week average trend and the HbA_{1c}supports the assertion that the former can be used to track diabetes management as well.

3.0.2. *Relation between average glucose readings and HbA_{1c}.* There is some description in the literature about relating $\text{HbA}_{1c}$to average BS. [1] Based on this one text, the formula is below:

$$BS(\text{mg/dL}) = (35.6 \times \text{HbA}_{1c}) - 77.3$$

or, reframing in a way which emphasizes the target BG for achieving a $\text{HbA}_{1c}$of 7.0:

$$BS(\text{mg/dL}) = 35.6 \times (\text{HbA}_{1c} - 7) + 171.90$$

[1] See http://care.diabetesjournals.org/content/25/2/275.full

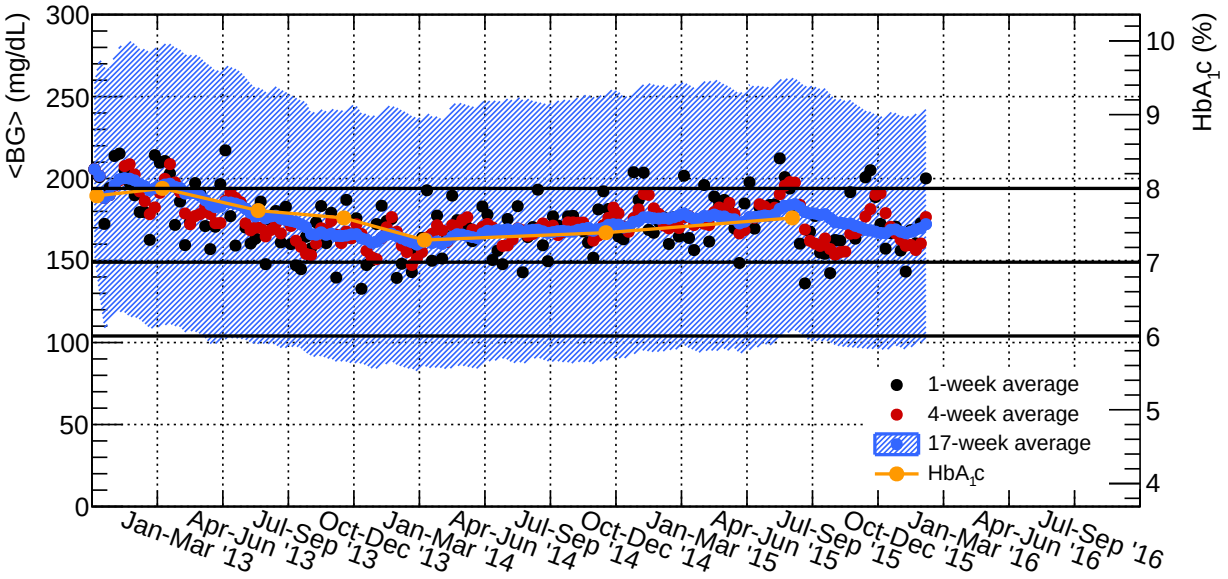

FIGURE 4. Year in review for the years 2013-2016. Detailed record-keeping began in May 2013. HbA_{1c}values are shown in orange. The solid lines emphasize the HbA_{1c}=6, 7, and 8 values.

The ADA has a much more pessimistic estimate[2]:

$$BS(\text{mg/dL}) = 28.71 \times (\text{HbA}_{1c} - 7) + 154.42$$

This number may depend on the nature of blood sugar measurement (relating to how long after eating each measurement is taken) - and thus might depend on one's personal habits. Trying to correlate my personal BS (taken from a 17-week rolling average) with my HbA_{1c}readings, the relationship is roughly

$$BS(\text{mg/dL}) = 45.0 \times (\text{HbA}_{1c} - 7) + 149.0$$

Below are some representative numbers, for the purposes of setting targets. Roughly speaking, it appears as if 1/4 of a point in $HbA_{1c}$is equivalent to 9 mg/dL (paper), 7 mg/dL (ADA), 11 mg/dL (personal).

HbA_{1c}	BS (Paper)	BS (ADA)	BS (Personal)
6.50	154.1	140.1	126.5
6.75	163.0	147.2	137.8
7.00	**171.9**	**154.4**	**149.0**
7.25	180.8	161.6	160.2
7.50	189.0	168.8	171.5
7.75	198.0	176.0	182.8
8.00	207.5	183.1	194.0
8.25	216.4	190.3	205.2
8.50	225.3	197.5	216.5

[2]http://care.diabetesjournals.org/content/31/8/1473.full.pdf

4. Simulated Data as a Learning Tool

Simulated blood sugar data can serve as a learning tool to illustrate common (or uncommon) scenarios encountered in diabetes management. It can also serve as a testing ground for honing diabetes software in the testing phase. The following section features illustrations suitable for understanding the effect of certain lifestyle choices on blood sugar levels.

4.1. **Quantifying the Advantages of Carb Intake Reduction and E.B..** Fig. 5 has some representative plots showing the potential gain of reducing carb intake, and bolusing before food intake (early bolus). The plots show the gains assuming perfect bolus estimates, however it should be noted that lowering carbohydrate intake can also reduce the potential for mis-estimation. Strict adhesion to a <65 grams per meal diet with heavy early-bolus could result in as much as a 1% improvement in HbA_{1c}

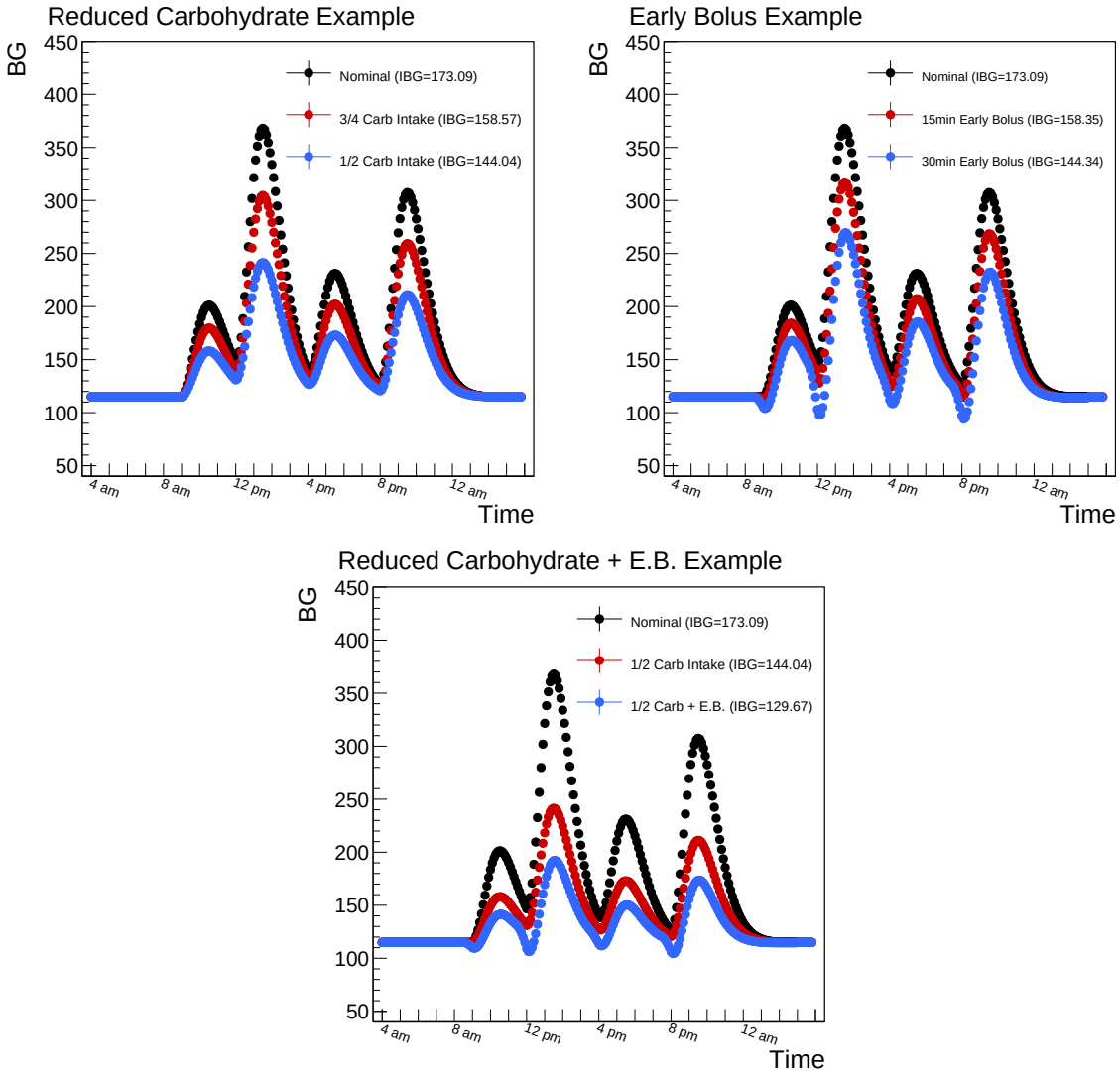

FIGURE 5. Left: The effects of multiplying carbohydrate intake by a factor of 3/4 and 1/2 on a nominal day's BG readings. Right: The effects of early bolus, by 15 minutes and 30 minutes. Bottom: Combining both methods. Plots are based on a 2-hour glucose absorption rate and a 4-hour insulin absorption rate. The nominal day consists of 45g at 9am, 130g at 12pm, 60g at 4pm and 100g at 8pm.

4.2. **The benefit to predictive plots.** The closed loop is far away.

One benefit of the predictive plots would be to determine when a CGM sensor was nearing its end of life. It is critical to know when a CGM is providing incorrect results. Noise studies can be used to determine this, but another input can be whether the CGM matches the predicted rise or fall of blood sugar. If the CGM reading differs from the prediction, it can point to a failing sensor (or it may be incomplete / incorrect information from the user). In this scenario, the software can ask the user whether they made a mistake in their reporting, whether the sensor might be failing, or whether a change in dose is required.

Even when the loop is closed, this type of software can be crucial to an effective, safe, and efficient system. Assuming the loop is closed using a combination of glucagon and insulin, predictions are indespensible to prevent alternating over-doses of the two enzymes.

4.3. **Suggestions for broader data input.** Allowing the user to input these quantities can help the software do a better job of predicting blood sugar levels:

- Estimated glycemic index (alternately, provide a drop-down list of foods)
- Time delay (positive or negative) between bolus and eating
- Excercize, including exact duration, and/or intensity.

4.4. **How the predictive plot macro works.** Rather than looking at raw BG readings, carb totals, and correction boluses, it would be easier to look at all of these quantities in their shared units: BG concentration. As described in the table 1, there are conversion factors to translate each quantity into a BG-equivalent. Of course, some of these conversions include "unknown" quantities - the very quantities we are trying to determine. Thus, the plot will represent a user's estimate, based on his settings.

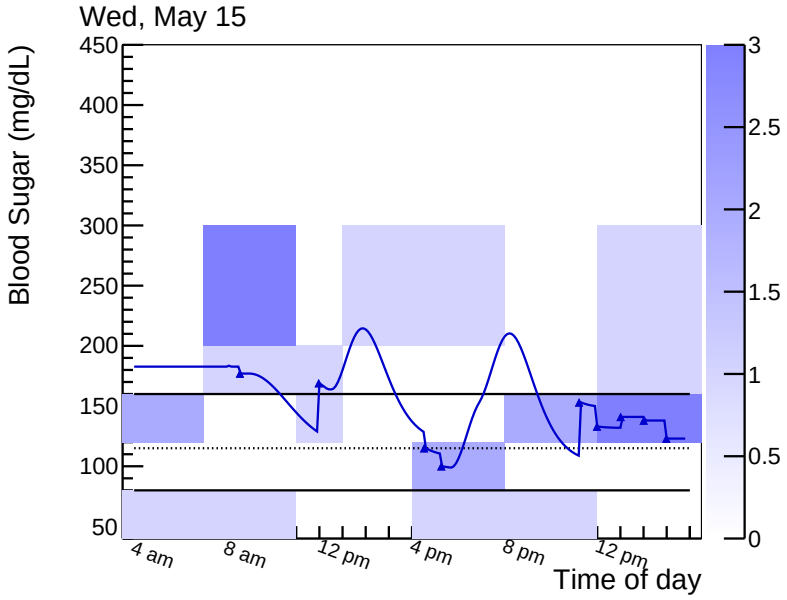

FIGURE 6. Predictive curve overlaid on top of BG measurements. The curve resets each time a new measurement is made. From the plot above, one can see problems with the morning regime, as well as the evening regime.

The plot macro (see fig. 6) uses 3 classes of information: BG measurements, food intake, and insulin dosages. Based on S, $R_{\text{I-C}}$ and t_A at the time of the event, it uses eq. 2.2 and 2.4 (or rather their derivatives) to estimate the BG evolution over time, given the user's inputs. When an additional BG measurement is made (it is taken to have 0 uncertainty), any discrepancy between the estimate and the new measurement is an indication of an incorrect dosage (whether caused by sensitivity S, food estimate C_0, basal rates, or insulin-to-carb ratio ($R_{\text{I-C}}$), or a combination of these. The discontinuity in the graph represents the magnitude of the discrepancy.

The usefulness of an isolated plot like this is limited. One cannot, given one measurement in time, determine which dose-related quantity (S, C_0, $R_{\text{I-C}}$, R_{Bas}) is incorrect. One can circumvent this problem in 2 ways: 1. Reduce the number of unknowns by refraining from eating, or not issuing a corrective bolus, and 2. Analyze data over multiple days, with different characteristics (more food / less food, etc).

It is also important to remember that a predictive curve which lines up exactly with the measured BG could be caused by the cancellation of 2 or more effects.

4.5. **Predictive plot macro and error bands.** More on this later.

5. Phase I Software

5.1. **Dedicated Event-by-event macros.** User-conducted studies are foreseen to play a large role in the Phase I software. The fasting basal rates and fixed carbohydrate meals are extremely valuable, and as such, making them easy for the user to execute is an important goal of the software.

For somewhat unrelated reasons, a skeleton of a user interface has been developed to help keep track of certain data. This user interface could allow the user to indicate when such a study (fixed carb or fasting basal) has been performed, rather than the software attempting to find these events on its own.

It is envisioned that in the Phase III version of the software will have the capacity to find these events, and other "accidental studies" unwittingly carried out by the user, and act on them. However, the aforementioned user-delimited studies will suffice; they are also safer, since the Phase III software would require the user to keep more detailed records.

6. Phase II Software

6.1. **Food uncertainties.** A crucial aspect of the Phase II software would be to incorporate carbohydrate uncertainties into the data model. Consider this scenario: each time a packaged, labeled food is consumed, the dosage is correct; however, each time an un-labeled meal is consumed, the insulin dosage is underestimated, leading to higher blood sugar levels. The Phase I software will suggest increasing bolus rates, and as a result the average blood sugar will decrease. However, well-labeled meals will now be consistently overestimated.

6.2. **The Event Data Model (EDM).** It is not altogether straightforward how to specify an "event" in this type of scenario. Several things could qualify as "events," in that they happen at a particular time: a glucose measurement, a meal, and a bolus. Sometimes these events occur simultaneously, and sometimes they do not. Some events, such as exercise and raised basal rates, occur over a fixed period of time. And the act of insulin absorption and carbohydrate metabolism evolve over a period of time.

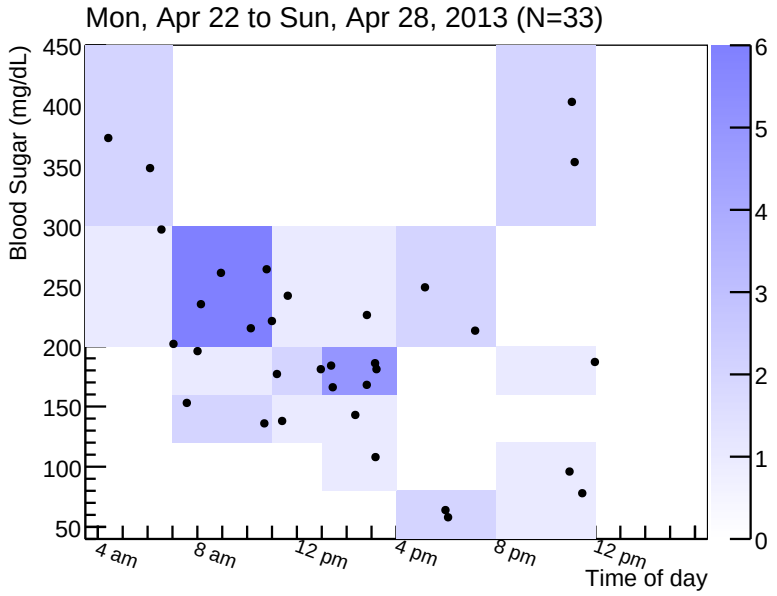

FIGURE 7. An example scatter plot, with a coarse binning underneath, highlighting general trends in blood sugar levels for one week. These plots are intended to catch large trends in insulin dosage response.

Since the goal of the software is to suggest changes in insulin dosages, it makes sense to build the event around the suggested change in dosage ("At this time, change your bolus rate from 15 g/unit to 18 g/unit").

7. Phase III Software

8. Pairing with dietary changes

It has been suggested that coupling an appropriate insulin regimen with dietary changes may significantly improve sugar control. ADA suggestions, along with a pre-prandial test of <130, a post-prandial target of <180 is desired. It is likely that this can only be achieved with significant dietary changes. These changes include (but are not limited to):

- Reducing total carb intake (weekly metric)
- Spreading carb intake over a longer period of time (coupled with an early bolus!)
- Surrounding oneself with low-carbohydrate food.

List of foods no longer desirable as a full meal:

- Spaghetti
- Rice
- Bread
- Cookies
- Ooh, cereal. Well well well.
- Basically anything above 50 (?) grams of carb - *unless* it is low on the glycemic index

Replacement options

- Dark chocolate
- Vegetables

A reasonable target might be to never be above 200 mg/dL. Particularly in the post-prandial period, from which I have managed to shift all testing. Other healthy habits:

- Drink lots of water
- Exercise
- Avoid stress
- Vitamins?

9. Additional Studies

9.1. **Fasting basal rates (Recurring).** This recurring study is an integral part of the Phase I

9.2. **Fixed-carbohydrate meals (Recurring).** This study is also important to phase I. The goal is to consume a meal with a fixed, 0-uncertainty number of carbohydrates.

9.3. **Clean Correction Bolus studies.** Correcting a large BG deviation (300+) can give an excellent handle on insulin sensitivity, a key number that affects the correction estimates of both R_{Bas} and $R_{\text{I-C}}$. (Must assume a reasonably accurate basal rate.) The sensitivity is essential for setting error bars on BG extrapolation curves.

9.4. **Effect of coffee on blood sugar levels.** It is hypothesized that coffee intake should be accompanied by an insulin bolus, though there is insufficient data to corroborate this. A study is suggested which probes the effect of coffee, on an empty stomach, during a period with well-known stable basal rates.

9.5. **Effects of fatty foods.**

9.6. **Effect of alcohol.**

10. Personal Insulin Dose Changes

10.1. **Notes.** Important note: the process of correcting insulin doses is highly sensitive to the sensitivity number, S. Note that it figures in to carb ratios, insulin, basal rates and correction boluses. Thus, if S is underestimated while trying to change basal rates, the magnitude of the change in basal rate will be overestimated.

One way to probe S is to have a clean, non-food correction bolus after a high (say 300+) glucose reading. The subsequent measurement is influenced almost entirely by the correction bolus, and can be used as a data point for that 3-hour period.

The "1500 rule" (as described in the literature, applying to fast-acting insulin) is supposed to relate daily insulin totals to sensitivity, i.e. $S = 1500/T$. I am not sure whether this is based off a 2000 calorie diet, and whether or not eating more changes this value. In any case, my daily totals range from 30-50, so sensitivity, accordingly, seems to be anywhere from 30 to 50. Or 65, who knows?

10.2. **Evolution of Carb Ratios.** Where * means "actually starts 1/2 hour earlier."

10.3. **Log of changes.** Started Wednesday, June 12, 2013.

10.4. **Specific food successes.**

2013/6/25 - Frozen Pizza	120 g, plus 4 hours at 130%. 127 mg/dL in morning.

TABLE 2. Carb Ratios

Date	12am				4am				8am				12pm				4pm				8pm			11pm
2013/01/01	18								16*				15					16						
2013/06/12	18							16					14*					16						
2013/06/20	16							16					14*					16					15	
2013/10/18	16							16					14*			16		16					15	
2014/05/22	16							16					19*			19		19					19	
2014/05/23	16							16					16*			16		16					16	
2014/05/27	16							16					17*			19		20					18	
2014/05/28	16							16					17*			19		23					18	
2015/xx/xx	19							16					17*			19		23					18	
2015/03/01	20							16					17*			19		23					20	

TABLE 3. Sensitivity

Date	12am			3am			6am			9am			12pm			3pm			6pm			9pm			11pm
2013/01/01	60				60			40					35				35				40			60	
2013/06/12	60				60			40					35				50				40			60	
2013/06/12	60			60			45			45			45			50			45			60			
2013/06/13	60			60			65			65			50			50			45			60			
2013/10/18	60			60			65			65			50*			50			45			60			
2014/05/22	60			60			65			65			65*			65			65			60			

TABLE 4. Basal Rates

Date	12am				4am				8am				12pm				4pm				8pm			11pm
2013/06/12	.8		.8		.9		.9		.9		.9		.9		.85		.85		.9		.9		.9	
2014/03/30	.8		.8		.9		.9		.9		.9		.9		.85	.75	.75		.8		.9		.9	
2014/05/22	.8		.7		.7		.7		.9		.9		.9		.85	.75	.75		.8		.9		.9	
2014/05/26	.8		.75		.75		.75		.9		.9		.9		.85	.75	.75		.8		.9		.9	
2014/12/05	.8		.75		.75		.75		.9		.9		.9		.85	.7	.7		.7		.9		.9	
2015/01/09	.7		.65		.65		.65		.9		.9		.9		.85	.7	.7		.7		.9		.9	
2015/03/01	.55		.5		.5		.5		.9		.9		.9		.85	.7	.7		.7		.9		.9	
2015/03/01	.75		.75		.75		.75		.9		.9		.9		.85	.7	.7		.7		.9		.9	
2015/07/20	.70		.70		.70		.70		.9		.9		.9		.85	.7	.7		.7		.9		.9	

2013/6/12	Increased basal 0.1 u/hr, 8am-12pm (from 0.8 to 0.9). Actual estimate was 1 u/hr. Need to increase in steps if not effective. **Hindsight: estimate was too high due to low sensitivity!** Decreased lunchtime C from 15 to 14 g/u carb ratio. May not be enough. (May also be estimating food poorly.) Careful - sensitivity! Changed sensitivity from 35 to 50 from 2pm-8pm, based on lows in the afternoon. This was the exact estimate.
2013/6/13	Increased sensitivity to 65 in the morning, due to constant, high-significance lows.
2013/6/20	Decreased carb:insulin ratio due to high reading with some cereal.
2013/10/18	Increased carb:insulin ratio in the afternoon (3pm) due to persistent low readings. Sensitivity change at 11:30am instead of 12pm to make it relevant for lunchtime boluses.
2014/03/30	Decreased basal 0.1 u/hr between 3pm and 8pm, due to frequent lows (and a particular event in week 64 - 50 points in 2 hours). Other possible explanation: longer insulin act time?
2014/05/22 2014/05/22	Increased carb/insulin ratio in the afternoon and evening due to persistent lows. May have been too extreme - will see. Decreased basal at night, after a precision measurement and some other lows.
2014/05/26	Increased basal slightly as a tweak to the previous change
2014/05/27	Increased carb:insulin ratio in the afternoon, after a very clean food event. (Estimate is 23 - changed to 20 at 5pm, with smoothness in between)
2014/05/28	Increased carb:insulin ratio in the afternoon, further. (Another low.)
2015/01/09	Decreased basal at night (85% of nominal) due to night lows. Started in Denmark.
2015/01/22	Decreased basal at night (-0.05 per hour) due to night lows. Noticed the other night...
2015/03/01	Decreased basal at night (85% of nominal) due to night lows. Noticed the other night...
2015/03/01	Decreased basal at night (Shaved of 0.05) due to night lows. Problem for a while - maybe the heat?