Insulin Wizard smart phone app

[Background for those who don't know about diabetes mellitus]

When blood sugar (glucose) is high, the kidneys remove it to the bladder (to mitigate damage to the body), resulting in frequent urination. Diabetes means "passing [urine] like a siphon", and mellitus means "honey sweet." High blood sugar is usually brought down by insulin produced by the beta cells in the islets (hence 'insulin') of Langerhans in the pancreas.

Type 1 (insulin dependent) diabetes, by contrast, involves no physiologic defect, apart from a lack of insulin production in the pancreas. This lack is brought on by an event: the body's autoimmune response to a virus that, in turn, attacks the pancreas' insulin making beta cells. The incidence of these events follows Poisson frequency statistics; with a peak of around 12 years (making for most new cases in the young) and a distribution tail extending out to about 50 years (I was 39 when I got it).

In type 2 (non-insulin dependent) diabetes, blood glucose is high because of underlying metabolic conditions (such as insulin resistance, pancreatic insufficiency, inadequate liver and kidney function, etc.) that make the usual physiologic control inadequate. This degradation is exacerbated by body mass and comes on over time, making it more common with age and in the overweight.

[The glucose control problem: high and low glucose bad. Keeping glucose steady is hard.]

Replacing the lack of endogenous insulin production in Type 1 diabetes (to the same effect) is difficult in practice. You don't want high glucose levels (hyperglycemia) because that brings on complications (eye, kidney & nerve damage). But neither do you want low glucose levels (hypoglycemia) because when the brain lacks its fuel source its functioning degenerates into a drunk-like condition that can result in accidents. Getting the insulin dose right requires tailoring the insulin action profile, knowing insulin quantity and timing, with insulin need, which varies over time and with meal content.

[First protocol: Regular 4 X / day]

At first (from 1922), the only insulin available was "Regular" insulin from pigs and cows. It required 3 to 4 injections per day because Regular insulin only lasts about 6 hours. In 1936, a method to extend its action with protamine was developed; yielding NPH, which lasts about 12 hours. Regular human insulin became available after a biosynthetic process to produce it was developed in 1978, and it lasts for slightly less time than non-human does.

[Next: Split / Mixed NPH and Regular 2 X / day]

Physicians seized on these two forms of insulin to control glucose with the "Split / Mixed" regimen, which combined Regular and NPH in one shot in the morning (the Regular covering breakfast and the NPH lunch), and evening (the Regular covering dinner and the NPH overnight need). This regimen, while efficient in terms of number of injections per day, wasn't much, if any, better at balancing glucose. This is because the NPH component was inefficient at handling lunch [lasting too long], and the dinner NPH dose was inefficient at covering overnight need (which is the basic amount the body needs absent food) [because it started too soon and didn't last long enough]. Moreover, the other three components had to cover both this underlying basic need *and* the meal they covered, which made doses difficult to calculate. For this reason doses were adjusted empirically to meals <u>fixed in size</u> from day to day, with variety achieved through food equivalent "exchanges."

[Now, a physiologic approach: Basal / Bolus]

The complications (of high and low glucose) common with the Split / Mixed regimen lead to a desire to tighten glucose control by taking advantage of insight into the normal physiologic production of insulin; which involves a component for continuous background (basal) insulin and another component for (bolus) insulin released for everything eaten. The new regimen used for tight control became known as the "Basal / Bolus" regimen, initially with basal insulin need covered by morning and evening injections of NPH or, later, an even newer, long acting (18-24 hour) insulin, and bolus need for food covered by Regular (or, later, newer, even faster 4 hour) insulin taken with each meal.

[Variations on Basal / Bolus, w/ NPH & Regular 4+ X / day]

Early "Basal / Bolus" implementations continued to combine the overnight NPH dose with the bolus for dinner [saving an injection at the cost of appropriate morning basal coverage], while others did move this NPH dose to bedtime. The morning Split / Mixed NPH dose was reduced (sometimes to the same NPH dose as was taken overnight) with breakfast and lunch both covered by injections of Regular.

[Further refinement of Basal / Bolus for preprandiai glucose]

With the Regular dose adapted to and taken with the meal it would cover (allowing variation in meal size and timing), further adjustment for the pre-prandial (before eating) glucose level (to correct for any error in the previous meal's bolus) became possible, and was integrated into the Basal / Bolus regimen over time. But even with regimens that adjusted mealtime boluses for the glucose level, concern for overnight hypoglycemia still caused reluctance to compensate for high glucose levels at bedtime.

[Proof tight glucose control is important]

With Basal / Bolus still less common than Split / Mixed about 27 years ago, the NIDDK (part of the National Institutes of Health) began a Diabetes Control and Complications Trial (DCCT), to see if and what sort of tight control might be effective in reducing complications. The results of that trial were announced in 1993: that "tight control" made a significant difference in high glucose complications, but at the cost of three times more hypoglycemia. While every DCCT center (there were 23 in the US and Canada) used their 3-4 glucose tests and 3-4 injections per day differently, I am aware of no analysis of DCCT data intended to investigate which of these various center's implementations were better and worse; either in minimizing glucose highs, or lows. But ever since 1993, "tight control", with 3-4 glucose tests and injections per day has been preferred for Type-1 diabetes, provided the patient was up to the extra effort (injections, glucose tests, carb estimation & calculations).

[A better way to implement the basal in Basal / Bolus: an insulin pump]

Insulin pumps provide an alternative to manual injections, using fast acting insulin for both basal and bolus. Boluses with a pump are the same as with an injection, but using essentially continuous infusion for basal need can potentially tailor the rate better than is possible with two, or even three NPH injections per day. Moreover, unlike with NPH injections, with pumps basal infusion can be adjusted on the fly, should, for example, unexpected exercise arise. Pumps are known for their better glucose control, but this is so in part because with a pump, management is inherently Basal /

Bolus.

[My (somewhat biased) opinion of what drives research in glucose control]

I believe much of the difficulty eliminating hypoglycemia derives from the fact that the insights leading to new treatments has been driven by medical observation and understanding, whereas the underlying technical issue of glucose control is really an engineering matter. Moreover, the medical profession has not been inclined to use mathematical physiologic models. Many physicians consider that such models are too complex, and that parameter variation from patient to patient makes them impractical in any event.

[My experience]

Around 1990, after 6 years of Split / Mixed (briefly, at frost), then basic Basal / Bolus control, I was experiencing slight to mild hypoglycemia a couple of times a week, and severe hypoglycemia at the rate of a few times a decade. While typical for Type 1 patients at the time, this was unacceptable to my wife (and me), and I sat down to see if I could get things right applying control system insights and mathematical models I had learned studying Cybernetics in and after graduate school.

[My improvements]

The first thing I realized was that the Basal dose would confound Bolus calculations if it contributed at all to the mealtime Bolus dose by either exceeding or being deficient in the amount needed to maintain blood glucose absolutely constant absent any food at all. At the time, this was not a concern to be found in descriptions of the Basal / Bolus regimen, though it is possible some researchers dealing with insulin pumps may have been discussing it. At any rate, I know of no one who spoke of actually fasting 18+ hours to establish the Basal dose empirically back then.

Once I had separated the Basal factor from the Bolus factor, I experimented to see how much one unit of insulin lowered blood glucose. I would skip lunch and look for high afternoon glucose long after the rise from breakfast had finished. Then I took a known bolus, and watched glucose fall over time. This gave me my true insulin sensitivity (total glucose drop per unit insulin) as well as the time course of insulin action. Now I knew how much to adjust a Bolus should glucose not be normal before a meal. It helped at the time that there was a meter that provided as many tests as desired, as often as every 5 minutes, with a reusable sensor (the 30 \ 30 from Lilly).

Then I experimented to see how much a given amount of carbohydrate would raise glucose (glucose to carb ratio), as well as the time course of this carb action. I finally published this in **Medical Informatics** in 1997 as Minimal model of food absorption in the gut. Combining this glucose to carb ratio with Insulin sensitivity, I had the insulin to carb ratio I needed to adjust Bolus doses to meals. Meantime, I noticed that while food was generally absorbed within a couple of hours, the Regular Insulin that was used for prandial need at that time was hardly half used up at that point. So I proposed testing glucose 2-3 hours after the meal Bolus, when the food was mostly absorbed, but half the Bolus was still "on board", at which point the time course of insulin action I had determined could be used to predict what lay ahead.

If glucose was predicted to fall much below normal when the bolus was used up, that deficit could be used with the glucose to carb ratio (determined above) to calculate how much of a carb snack was needed. And the time course of insulin action could be used to estimate how long it would take before glucose fell below a given critical threshold (such as 50-60 mg/dl), letting patients know how long they had to eat that snack (while still competent). Ideally, the snack would be sized well enough that glucose would be normal at the next meal.

If glucose was predicted to be above normal when the bolus was finally used up, the excess glucose could be accommodated with a supplemental bolus immediately. This supplement might not be used up by the next meal, but with careful logging every bolus would be adjusted not only for the pre-prandial glucose level, but for any "on board" insulin. Ideally, at the next meal the supplement needed for high pre-prandial glucose would be matched by the insulin on board, and the bolus could be calculated as though glucose were normal. Indeed, it wouldn't strictly be necessary to test before eating with this protocol, which would use the same number of glucose tests per day. I also published this in **Medical Informatics** in 1997; as Controlling blood glucose: insights from an engineering control systems perspective.

[Adoption of these improvements since the DCCT]

Unfortunately, **Medical Informatics** is not a clinical journal, and little note was taken of either of my papers, though the concepts and model ratios I described in them gradually came to be recognized and adopted, especially after the DCCT results were released. The DCCT provided an impetus for attitudes toward models to shift, especially with regard to glucose control. Throughout the rest of the 1990's, and especially 2000's, carb counting, together with the patient's insulin to carb ratio, was used to adapt the bolus to the meal with more mathematical precision than was possible with the old food exchanges. Then the pre-prandial glucose measurement was incorporated into the bolus, using the Insulin to glucose (insulin sensitivity) ratio. Finally the glucose to carb ratio was seen as useful when glucose was low to determine how much carb was needed to raise glucose a given amount.

I patented much of my model-based technique in 1996, especially the model-based control system strategy of measuring glucose a few hours after the bolus, which measurement was then used to predict future glucose during the period the on board insulin was used up, from which prediction patients could both preclude hypoglycemia (if the prediction indicated it), and ensure effectively normal glucose at the next meal (should the prediction be for normal or higher glucose then).

I wrote a program for the Palm Pilot that incorporated all these aids, such that all a patient had to do was enter the pre-prandial glucose and the carb content of the meal (having entered boluses previously), and it would calculate the appropriate bolus. Then it would set a timer for the post-prandial glucose measurement, and when that value was entered, it would estimate the ultimate glucose value and advise whether to take supplemental insulin, or how much carb to eat before so much time had elapsed, all based on the insulin on board. I presented this at the ADA Scientific Sessions in 2000, and it attracted some attention, though still with a "while it works for you, it may not work for others" concern in the minds of many. No doubt they couldn't quite believe my claim to have reduced the frequency of both mild and severe hypoglycemia by a factor of nearly 100.

[Improvements incorporated into pumps]

But then in 2004 MiniMed incorporated on board insulin action, as well as carbohydrate based bolus calculation with adjustment for pre-prandial glucose, into its insulin pump as a "Bolus Wizard®". This proved enormously popular with pump users and was quickly copied by other pump makers. I didn't have the resources to hire a patent lawyer to see if they had infringed my patent, but a researcher I knew at MiniMed told me their lawyers had asked him about me because of my patent, so they certainly knew what they had to work around in their implementation. The Bolus Wizard did not go so far as to predict hypoglycemia the way I did, and it's possible they omitted this precisely because that was the core of my patent, and my patent agent went to greater lengths to cover that in the claims than the on board insulin calculation, etc.

The Bolus Wizard (and imitators) soon had an impact on pump sales. Whereas most patients originally went for an insulin pump because of its reputation for better glucose control, after the Wizard made its appearance they began to go for a pump because of this built-in assistance with carbohydrate counting, glucose level bolus adjustment, and Insulin on board calculation and adjustment. Animas, for example, incorporated a food carbohydrate database into its pump. With such pumps, now all patients have to do is go to the trouble of adjusting their Basal insulin profile to start with, then simply measure glucose as needed, and the pump will tell them how much insulin to take and when.

[Where pumps currently fall short]

The books I've read on pump use (Walsh, Pumping Insulin and Scheiner, Think Like a Pancreas) go to some trouble to have patients determine their basal need empirically while fasting, explaining how to do it in 6 hour intervals, but neither Medtronic nor Animas so much as mention the possibility. As far as pump makers are concerned, basal insulin is something for patients to deal with in consultation with their physicians. Unfortunately, my 1990 realization that basal had to be determined absent any food at all has still not become a well known, standard practice.

Pump makers don't make establishing the basal dose easy, either. Animas limits the number of different levels during the day to 12, and Minimed doesn't even mention their maximum number of basal levels in 24 hours, though their examples indicate it may be fewer than Animas. No where that I've seen does anyone suggest fasting 18+ hours to make sure it's right, nor to use a continuous sensor.

When you consider that Basal is the only insulin component that pumps handle better than manual injections, I find it surprising that no pump maker has ever funded a study of what Basal insulin profiles look like in different patient populations, or how much improvement getting Basal down right provides. The only study I'm aware of was by Scheiner, q.v. above, and he didn't use a continuous sensor or have his subjects fast all day long.

It may be because of my patent, but no pump (that I know of) tells patients about impending hypoglycemia should the bolus have been too large for the meal. Curiously, both Medtronic and Animas both deliberately ignore any excess of Insulin On Board over the correction needed for a post-prandial glucose level that's above normal. An example (6, p.195) in the Medtronic Revel User Guide recommends a dose that could result in an ultimate glucose of 60 mg/dl (and only that high because the target was 120mg/dl) that is dangerously low. Any more IOB in this example and the pump could recommend enough insulin to render the user unconscious.

In addition to these areas that were covered in my Controlling blood glucose paper, there are additional areas where model based control can improve insulin estimates, especially when continuous glucose sensors are available. My Minimal model paper can be used with continuous glucose to estimate the model's parameters for the meal, minimizing Carb On Board errors at the two hour after bolus correction point. In addition, even with manual glucose, using both pre- and post-prandial glucose values over time the Insulin Sensitivity value can be adaptively refined to improve model estimates that use this parameter. Using known low glucose carb corrections, such as with glucose tabs, the glucose to carb ratio can be refined with "learning" algorithms as well.

[Where does this leave all those who can't afford a pump?]

While the built in assistance in pumps today is great, it is not strictly necessary to have a pump to achieve glucose control without hypoglycemia; you just need the same sort of assistance found in, e.g., the Bolus Wizard®, provided by a smart phone app. As mentioned, the only difference between manual and pump insulin administration is the slightly less precise tailoring of basal insulin using NPH and the other long acting insulins available today.

[Food and Drug Administration Requirements]

While there are a number of apps available for diabetes, they tend to be for logging or diet, not control. One reason for this is the requirement of FDA approval for anything that provides advice on insulin administration. Pump makers had to get approval, and what advice they provide does not even involve much, just Insulin On Board and insulin / carb / glucose ratios that had become generally accepted by 2000. Getting basal right probably won't be an issue with the FDA, but predicting hypoglycemia, especially estimating how long it will be until it comes, will require clinical trials, certainly to demonstrate that post-prandial glucose can be used in this way safely. Otherwise, modeling meals and predicting the time course of their effect on glucose, as well as adaptive determination of model parameters, will certainly need to be proven to their satisfaction as well.

[What is needed?]

Much more is needed than merely programming a smart phone app. The published methods of determining basal insulin need must be distilled into something that can be worked into an easy to use graphic interface, both for those with a continuous glucose sensor, and those with the usual meter test strips. Sufficient test subjects need to be found to see if and how well this works for various kinds of patients (young, old, sophisticated, and barely able to use a web browser). Same thing for determining the Insulin On Board / Insulin Sensitivity factor with the experiment mentioned above. And again for determining the glucose to carb ratio experimentally with a glucose tab.

The operational Insulin Wizard app needs to be well designed according to the user interface standard for the smart phone system, be it iOS, Android or something else. Wireless communication should be implemented with those meters (and pumps) that support it, and the glucose, carb and insulin values that go into and come out of the app should be logged to a file that can be uploaded to the user's PC, where the sort of analysis software available for meters and pumps can use it for further analysis. The app should be reasonably intuitive in its operation, and involve minimal effort.

Then a real clinical trial will have to be conducted that will pass muster with the FDA. It will have to involve sufficient patients to establish the population range for which it will work, and run for long enough to ensure that a comprehensive set of glucose, carb and IOB situations has been encountered in the trial, and handled both appropriately and well.

[The upshot]

When this has been done I anticipate that the study will show that the 100 to 1 reduction in the frequency of hypoglycemia I achieved personally (doing much of the math in my head, without an app to sound a check now alarm) can be achieved using my post-prandial model-based control strategy by almost anyone, at the same time as average glucose, hyperglycemia and HbA1c are reduced, showing that the DCCT presumption that these two conflict is not true when an engineering approach to glucose control is utilized.