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Outcome-Driven Personalized Treatment Design for Managing Diabetes

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Abstract. Diabetes affects 422 million people globally, costing over $825 billion per year. In the United States, about 30.3 million live with the illness. Current diabetes management focuses on close monitoring of a patient's blood glucose level, while the clinician experiments with dosing strategy based on clinical guidelines and his or her own experience. In this work, we propose a model for designing a personalized treatment plan tailored specifically to the patient's unique dose-effect characteristics. Such a plan is more effective and efficient—for both treatment outcome and treatment cost—than current trial-and-error approaches. Our approach incorporates two key mathematical innovations. First, we develop a predictive dose-effect model that uses fluid dynamics, a compartmental model of partial differential equations, constrained least-square optimization, and statistical smoothing. The model leverages a patient's routine self-monitoring of blood glucose and prescribed medication to establish a direct relationship between drug dosage and drug effect. This answers a fundamental century-long puzzle on how to predict dose effect without using invasive procedures to measure drug concentration in the body. Second, a multiobjective mixed-integer programming model incorporates this personalized dose-effect knowledge along with clinical constraints and produces optimized plans that provide better glycemic control while using less drug. This is an added benefit because diabetes is costly to treat as it progresses and requires continuous intervention. Implemented at Grady Memorial Hospital, our system reduces the hospital cost by $39,500 per patient for pregnancy cases where a mother suffers from gestational diabetes. This is a decrease of more than fourfold in the overall hospital costs for such cases. For type 2 diabetes, which accounts for about 90%–95% of all diagnosed cases of diabetes in adults, our approach leads to improved blood glucose control using less medication, resulting in about 39% savings ($40,880 per patient) in medical costs for these patients. Our mathematical model is the first that (1) characterizes personalized dose response for oral antidiabetic drugs; and (2) optimizes outcome and dosing strategy through mathematical programming.

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Keywords: diabetes • outcome-based personalized treatment plan • pharmacokinetics and pharmacodynamics • dose response • predictive analytics • mathematical programming • mixed-integer programming • treatment-planning optimization

Challenges and Objectives

More than 100 million U.S. adults are now living with diabetes or prediabetes, according to a recent report (Centers for Disease Control and Prevention 2017). The report finds that as of 2015, a total of 30.3 million Americans—9.4% of the U.S. population—have diabetes. Another 84.1 million have prediabetes, a condition that, if not treated, often leads to type 2 diabetes within five years. Globally, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 (World Health Organization 2016), costing over $825 billion dollars per year (NCD Risk Factor Collaboration 2016). This surge in diabetes has made it one of the most common diseases that doctors treat.

Type 2 diabetes accounts for about 90%–95% of all diagnosed cases of diabetes in adults (Menke et al. 2015). In these cases, the patient's pancreas still produces insulin, but the body does not produce enough or is not able to effectively use it. The management of type 2 diabetes is often through a combination of treatments, including diet control, exercise, self-monitoring of blood glucose, and, in some cases, oral drugs or insulin. Treatment is often ad hoc and can be complicated, especially for patients with multiple health conditions.

Through trial and error, clinicians experiment using various doses and medications. Clinical guidelines often describe titration (i.e., a dosing-experiment period) as a process to gradually increase the patient's dose every three days or one week until the patient's blood glucose becomes stable. This may take six to eight weeks (or longer) for a diabetes patient using an oral antidiabetes drug.

In gestational diabetes mellitus (GDM), the management focuses on close monitoring of a patient's blood glucose level, while the clinician experiments with dosing strategy based on some clinical guidelines and his or her own experience (Jovanovic and Pettitt 2001, Alwan et al. 2009, World Health Organization 2013). However, conflicts in guidelines and wide variations in practice often result in inappropriate care (Jovanovic-Peterson et al. 1989, Panel 2004, Hawkins et al. 2009, Jacqueminet and Jannot-Lamotte 2010, Kim 2010). Women with GDM and elevated glucose levels are at higher risk of maternal and fetal complications during pregnancy and birth, including shoulder dystocia, birth injuries, hypoglycemia, respiratory distress syndrome, cesarean section, preeclampsia, and fetal overgrowth (Metzger et al. 2008). It may also trigger the occurrence of type 2 diabetes in mothers after pregnancy (Bellamy et al. 2009). In the United States, GDM affects up to 7% of all pregnancies, resulting in over 200,000 cases annually (Hillier et al. 2008), and incurs approximately $636 million of annual treatment cost (Chen et al. 2009).

To ensure treatment success, diabetes management often requires the monitoring of blood glucose levels up to four times a day (Beckmann et al. 2013). Dietary control and physical activities are the most common interventions. If they fail to control the blood glucose level, more effective insulin therapies will be prescribed (Todorova et al. 2007). Oral hypoglycemic agents (OHAs) are commonly used for treating type 2 diabetic patients. Although not approved by the Food and Drug Administration for treating pregnant women, OHAs are also common GDM drugs because of their ease of use and low cost. Glibenclamide-glyburide, which we use in this study, has been proven to be an effective alternative to insulin for achieving adequate glycemic control (Kimber-Trojnar et al. 2008).

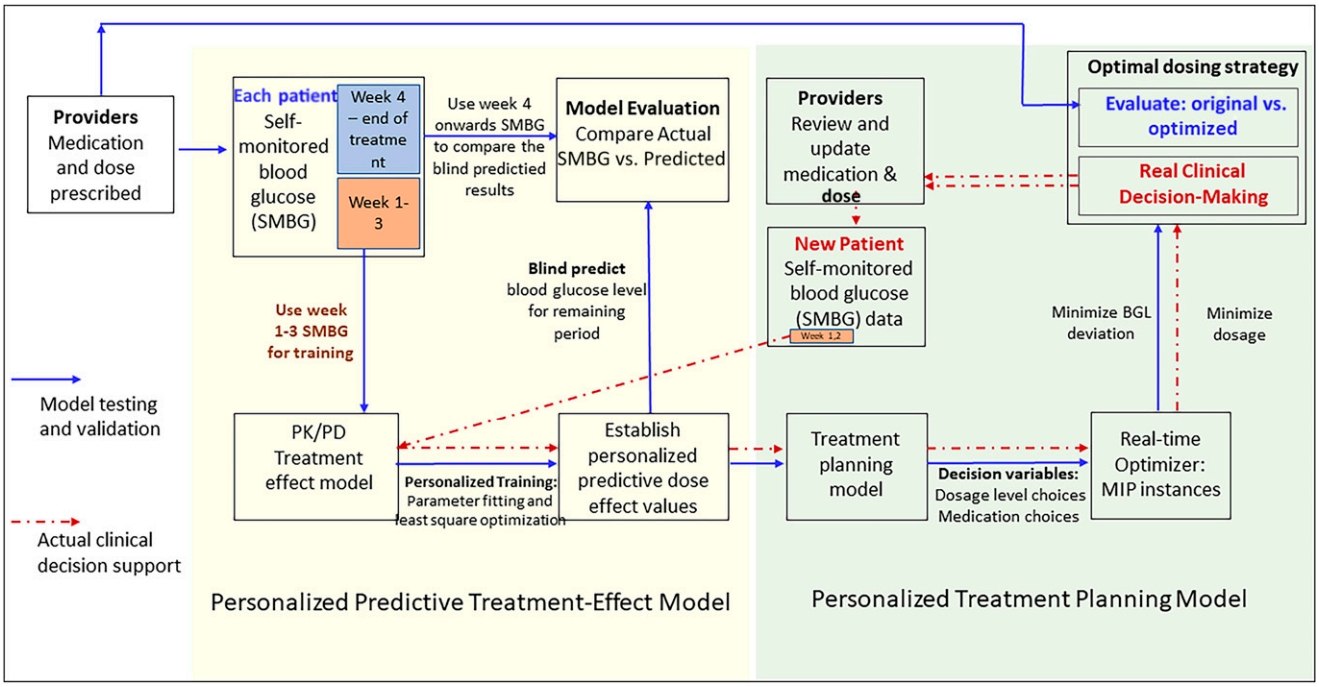
A major challenge in diabetes management is that patients have different dose-response and disease-progression characteristics. Hence, a personalized treatment plan tailored specifically to the patient's unique dose-effect characteristics will be more effective and efficient—for both treatment outcome and treatment cost—than current trial-and-error approaches. This is particularly critical because treatment expenses have been increasing, whereas insurance coverage for diabetes-related medications and supplies has been declining.

Among drug-effect mathematical models, predictive models, such as mechanism-based models, are often better than descriptive models because predictive models can be used to fit historical data to identify response patterns and to accurately predict the levels of future effects (Miyazaki et al. 2001, Landersdorfer and Jusko 2008). Both are key to determining the best course of treatment. Unfortunately, although most mechanism-based models can capture the entire dynamic insulin–glucose system well, they require continuous measurement of blood glucose and drug concentrations in body fluids, thus making them impractical for routine clinical use (Bergman et al. 1979, De Winter et al. 2006, Cobelli et al. 2009, Wang et al. 2014). Furthermore, although the use of mathematical models in all phases of preclinical and clinical drug development has proven to be beneficial (Palmer et al. 2000, 2004), little research has been done to apply those concepts in clinical therapy.

In this work, we address the twofold dosing challenge in diabetes management by designing a novel outcome-based decision-support tool that couples a predictive treatment-effect model with a treatment-planning optimization model. Our combined model has four distinct features. First, the new treatment-effect model is a mechanism-based pharmacokinetic (i.e., the movement of drugs within the body) and pharmacodynamic (i.e., the effects of drugs and the mechanism of their action) model, which we refer to as a PK/PD model, that captures the underlying glucose dynamics and personalized drug effects of each patient; this establishes a predictive estimate of drug-dose and glucose-response characteristics. Second, the model captures disease progression over the entire treatment horizon. This is crucial to ensuring that the patient has good glycemic control, which is of particular importance for safe delivery in GDM patients. Third, personalized dose response and disease progression are obtained by fitting the treatment-effect model using only drug dosage and self-monitored blood glucose levels (SMBGs), which the patients themselves record. These data are readily available, and thus our approach is implementable under current clinical and patient practice (with no additional requirements). Last, and most importantly, the predictive treatment-effect model is fitted for each individual patient to obtain a personalized dose response and disease progression. This predictive information is then incorporated into a mixed-integer-program treatment model that optimizes the glycemic control and drug dosage for the entire treatment period.

In implementing this approach for gestational diabetes patients at Grady, we found that the resulting personalized treatment plan returns better glycemic control while using less medication. The treatment success reduces the risk for cesarean sections (C-sections) and the need for admission of the newborn to the neonatal unit.

Figure 1. (Color online) The Schematic Workflow and Interplay of the Predictive Treatment-Effect and the Personalized Treatment-Planning Models



Note. BGL, blood glucose level; MIP, mixed-integer program; PD, pharmacodynamic; PK, pharmacokinetic.

Methods and Study Design

Figure 1 shows the data and process flows of our study design and analytic schema. It highlights the interplay between the predictive treatment-effect model and the personalized treatment-planning model within an evidence-based clinical decision framework. The predictive pharmacological-based treatment-effect model, which we describe in Appendix A, involves fluid dynamics, a compartmental model, statistics, and nonlinear programming optimization. It seeks to establish drug-dose blood glucose response using partial information collected during the dosing-experiment period. The personalized treatment-planning model, which we describe in *The Treatment-Planning Model* subsection and in detail in Appendix B, takes the predicted dose-response knowledge as input and utilizes mixed-integer programming with multiple objectives to design the best course of treatment.

In Figure 1, the solid arrows show the model-testing and validation pathways. Specifically, this entails a retrospective study with patients who have received diabetic treatment. For each patient in the training set, an estimation of parameters is first performed by using part of the patient's dosing-experiment data. The resulting treatment-effect model is used to predict the dose effect for the entire treatment duration. Two validations are then performed: (1) compare these predicted values against the actual blood glucose level based on the prescribed clinical dosage; and (2) incorporate the predicted drug-effect knowledge into the personalized treatment-planning system. The resulting plan is then compared with the original clinical plan.

The dotted arrows illustrate the clinical decision pathways. New patients coming in for diabetic treatment receive an initial diagnosis and treatment regimen. Data from the dosing experiment are used to establish the drug-effect response, and this information is used to design the personalized treatment. The resulting optimized plan facilitates the provider's clinical decision making.

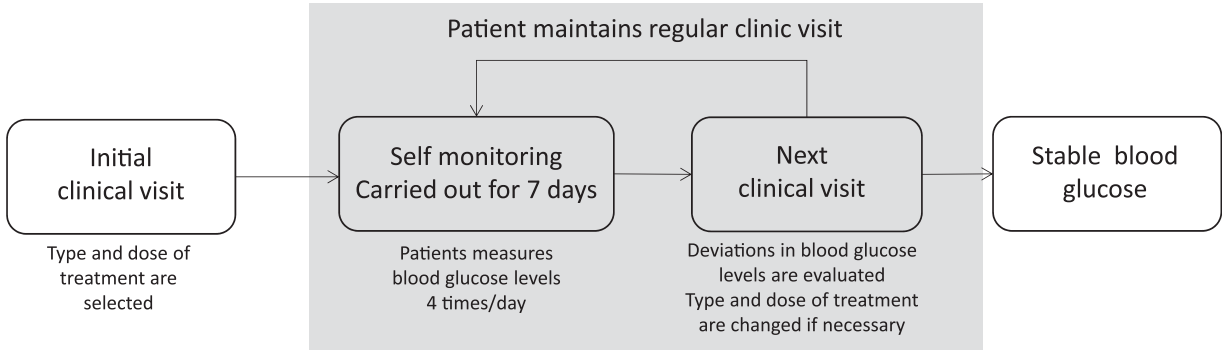
We designed our modeling framework for diabetes patients; however, the design schema is generalizable to other types of diseases.

We describe our predictive treatment-effect model in Appendix A and our multiobjective treatment-planning model in Appendix B. The appendices include the equations, parameters, and decision variables we used. Below, we summarize the information in each appendix.

The Predictive Treatment-Effect Model

A basic fact of clinical pharmacology is that the intensity of pharmacological effects relates directly to the concentration of a drug at the effect site (Derendorf and Meibohm 1999). Pharmacokinetic (PK) models characterize the time course of drug concentration in the body fluids. In the simplest one-compartment model, plasma drug concentration is a function of the dose and

Figure 2. The Decision Process for Diabetes Management



Note. For gestational diabetes patients, the treatment will be completed upon delivery; patients who develop type 2 diabetes and require continued management are an exception.

the elimination rate of the drug; see Equation (A.1). The area under the concentration-time curve (AUC) is the integration of Equation (A.1) from zero to infinity, which represents the total drug exposure over time.

Pharmacodynamics (PD) models characterize the relationship between drug concentration and drug effect. The effect of a drug present at the site of action is a function of the concentration of the drug at the site, the potency of the drug in the system, and its efficacy; see Equation (A.2).

The drug-effect model, which we show in Equation (A.6), gives the predicted blood glucose level over time by using antidiabetic drugs, which is a function of AUC. The calculation of AUC requires continuous measurement of drug concentration, which is impractical in daily diabetes management.

Our Innovation. We introduce a predictive dose-effect model by replacing *AUC* with drug dosage. By doing so, we overcome the calculation of *AUC* and establish a direct relationship between drug dosage and drug effect. *This answers a fundamental century-long puzzle on how one can predict the dose effect without measuring the drug concentration in the body fluids.* Moreover, all parameters are patient-specific and can be specialized for each patient. As a result, we obtain a treatment-effect model that characterizes personalized drug response and disease progression by using only daily blood glucose records and dosage information. In Appendix A, we describe the full predictive treatment-effect model.

The Treatment Planning Model

The management of diabetes starts with the diagnosis (for gestational diabetes, usually at weeks 24–28 and ending after the delivery). An initial plan is determined when a diagnosis is made and is set by determining the type and dose of treatment. Decisions on whether to maintain or switch treatment types or dose are made at subsequent clinical visits until the desired blood glucose level is maintained (or until delivery in cases of gestational diabetes). Decisions are made after assessing the impact of prior treatment according to the self-monitored blood glucose data (Figure 2). There are three types of treatment for diabetes: (1) diet control only, (2) OHA therapy with diet control, and (3) insulin therapy with diet control. In this study, we only consider the first two methods because insulin therapy is not prescribed for our patients.

The dosing strategy of diabetes currently relies heavily on the results from clinical trials. However, clinical trials often address the (trial) patient population for whom the intervention is appropriate, instead of individual patient characteristics. Clinical trials also seldom observe health outcomes over long periods and less frequently consider the long-term economic impact of the interventions (Panel 2004).

A Novel Approach. Our model aims to address these two shortcomings. First, we fit our PK/PD predictive treatment-effect model to each specific patient by using his or her own SMBGs so that the parameters obtained reflect the patient's own personalized dose response and disease progression. Second, we incorporate such personalized information into a mixed-integer program to optimize the glycemic control, while simultaneously minimizing the drug dosage. Although OHAs are commonly used for treating gestational diabetes, they are not formally approved. Minimizing dosage thus serves to improve safety for these patients.

We use mixed-integer programming to design the treatment-planning model. The objective function is a combination of health outcome and treatment cost. Because diabetic treatment aims to maintain the blood glucose level within a recommended range, we minimize the sum of the deviation of glucose level from the upper and lower bounds over the entire treatment horizon. In terms of costs and side effects, we minimize the total amount of the drug used. The model optimizes

the medication regimen for the entire treatment duration with a specific treatment(s) selected for each week. Because OHAs are usually in the form of pills, drug dosage in our model is restricted to discrete levels. Dosage level 0 implies that the patient is on diet control only, and no drug is administered. The model includes the PK/PD predictive treatment effect (calculated and personalized for each patient using his or her dosing-experiment data), which estimates the change of blood glucose level at different phases and times as a result of the drug effect, as Equation (A.11) predicts.

Clinical practice advises that the dosage level should not fluctuate too much from one visit to the next. Because no national standard exists to control the fluctuation, it can be physician-dependent. In practice, clinicians always start with "diet control only" at the start of the visit. We comply with this practice by setting the initial treatment at the start to no dosage. In Appendix B, we describe the full treatment-planning model.

Results and Findings

We use a group of diabetic patients to train and establish our predictive treatment-effect model parameters. We then apply our model individually to an independent set of 200 patients to gauge its predictive performance. We note that this is a personalized predictive model; that is, each patient's predicted dose response is established based on his or her data.

Table 1 summarizes the statistics of these patients; 57% are African-American and 43% are Caucasian-American. Furthermore, 21% have a history of gestational diabetes; 21% have a history of type 2 diabetes; 28% are obese; 7% have hypotension; and one patient is blind.

Determining Personalized Predictive Treatment-Effect Parameters

We first present the personalized predictive treatment-effect results. For each patient, we use the initial 30% (first two to three weeks during the dosing-experiment period) of SMBG and dosage data to establish the personalized least-square estimator of parameters for the treatment effect in Equation (A.11). For each patient, there are four sets of SMBGs, corresponding to four phases of monitoring per day: before breakfast, after breakfast, after lunch, and after dinner.

We develop an efficient gradient descent method to obtain the optimal parameters β^* in Equation (C.1). Because the least-square optimization is nonconvex in the corresponding parameters, the gradient descent algorithm cannot guarantee the global optimality of the solution. As a result, different choices of the initial value of β can lead to different estimations. To avoid local optima and ensure the quality of the solution, we run the algorithm multiple times with different initial values and choose the one with the minimum estimation error. Different initial values are chosen according to the population mean and variance of these parameters in the literature (Holford and Sheiner 1982) because we assume that the value of these parameters for each patient will not differ very much from the population mean. Mathematically, the gradient descent requires an initial value to start. Clinically, the choice can be interpreted as an initial guess of the patient's response characteristics.

Once we fit the data, we then generate predicted glucose levels for the entire duration. We compare the predicted values to actual values collected by patients. Moving averages are often used to uncover trends in time series (Brockwell and Davis 2006); therefore, we use them to compare the actual data versus the predicted values. Figure 3 shows the predicted glucose level trend (solid curve) versus the actual trend (dotted curve). Specifically, the solid curve is based on training during the first 14 days. After day 14, the established parameters are used to predict the future glucose trend by using the prescribed dosing. In Appendix C, we describe the full process for estimating the model parameters, including the equations, test data, and estimated performance.

Designing Personalized Optimal Treatment Plans

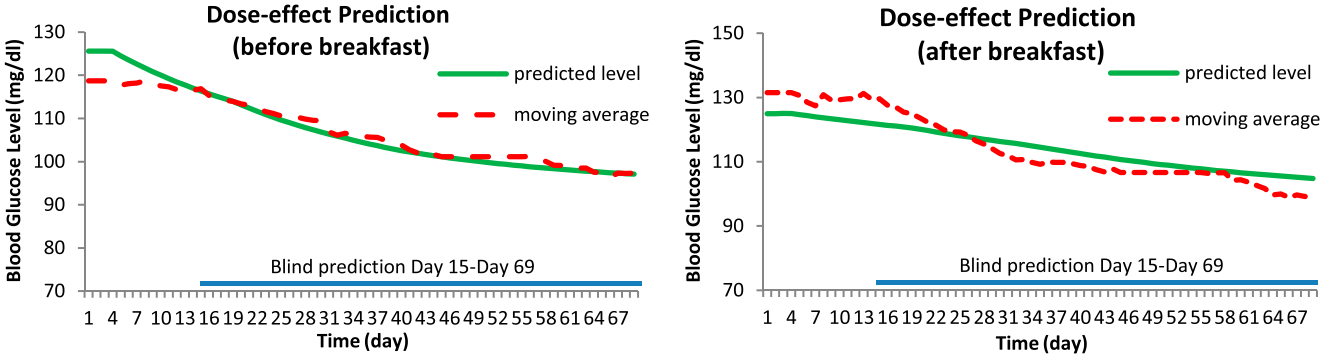
The parameters estimated for predicting treatment effect for each patient are entered into the mixed-integer programming-based treatment-planning model to generate a personalized dosing strategy based on the patient's dose-response information; see Figure 4.

The upper-bound target blood glucose levels are 95 milligrams per deciliter (mg/dl) before breakfast and 120 mg/dl after meals. The lower-bound baseline blood glucose levels are 60 mg/dl for all four phases

Table 1. Classification of the Data by Age, Height, Weight, Body Mass Index, and Length of Treatment Until Steady Stage Is Reached

	Age (years)	Height (inches)	Weight (pounds)	Body mass index ($kg \cdot m^{-2}$)	Length of treatment (days)
Minimum	20	59	122	22.7	26
Maximum	41	70	260	50.8	153
Mean	33.7	62.9	184.5	32.8	79.5
Median	34.5	62	181.5	33.2	68.5
Standard deviation	5.3	3.0	38.6	6.5	38.8

Figure 3. (Color online) The Prediction Results of the Dose-Effect Trend Using Self-Monitored Blood Glucose Data for Patient 5



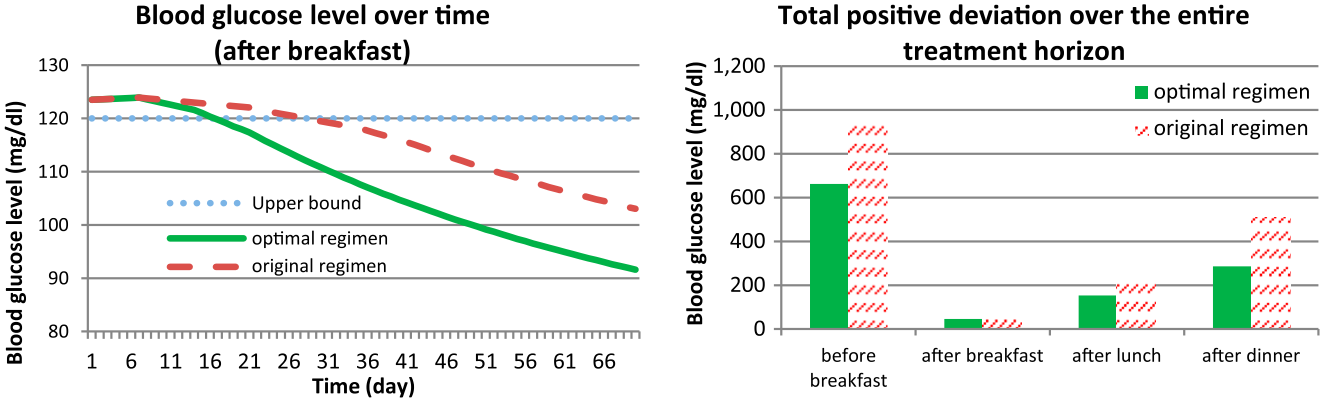
Notes. Parameters were trained and estimated using the first 14 days of dosing and self-monitored blood glucose. Blind prediction was then performed and compared with recorded SMBG. Our predictive model (solid curve) approximates well the trend of blood glucose level over the entire treatment horizon (dotted curve).

to avoid hyperglycemia. Among the two objectives, health outcome is more important than drug cost in managing diabetes, especially for gestational diabetes, because a high blood glucose level relates to complications in delivery, and the price of the oral antidiabetic drug (e.g., glyburide) is inexpensive and affordable. So we set the cost of positive deviation $C_+ = 20$, the cost of negative deviation $C_- = 10$, and the cost of drug $C(i) = i$, $i = 0,...,16$, where i corresponds to dosage level $1.25*i$ mg. The choice of cost coefficients reflects the importance of each objective. Guided by our clinical team, our selection places more emphasis on the positive deviation than the negative deviation.

We solve the mixed-integer program instance of each patient using an in-house system, MIPSOL. In 93% of the patients, the optimized dosing strategy results in smaller (or the same) total positive deviation value in all four phases compared with the original treatment plan. We could not draw any conclusions for the remaining 7% because a large amount of SMBG data are missing. Among these 93%, 11.7% of the optimized plans are identical to the original plans. The remaining 88.3% all experience reductions in blood glucose with the optimized plans, although they are using fewer drugs. This shows that the dosing regimen obtained from our model can provide better glycemic control with lower required dosages.

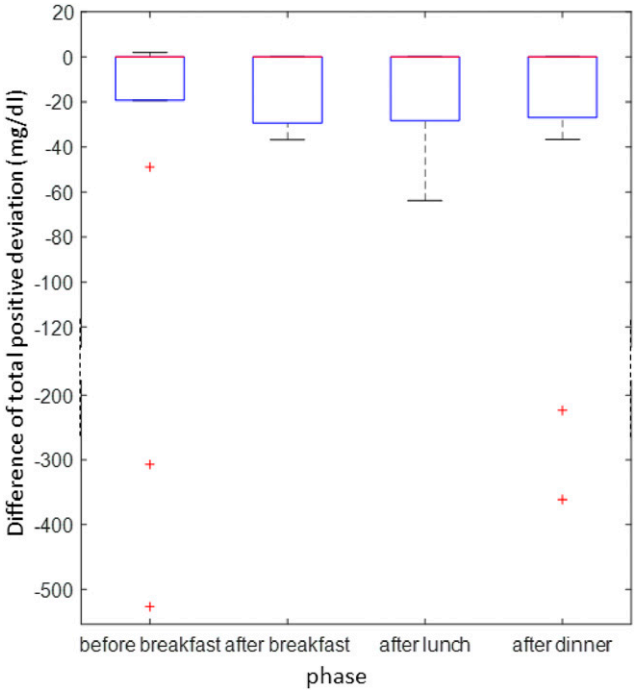
Figure 4 contrasts the optimal regimen to the original regimen for Patient 5. The graph on the left compares the blood glucose levels over the entire treatment horizon, showing that the optimal regimen achieves uniformly lower blood glucose levels than the original regimen. The graph on the right shows the total positive deviation among all four phases over the entire treatment period, indicating a better overall glycemic control for the optimized plan. These improved patterns are observed among 93% of all cases. Figure 5 shows the net reduction in the total positive deviation of the optimal plans among all patients.

Figure 4. (Color online) Contrast of the Optimal Regimen to the Original Regimen for Patient 5



Notes. The graph on the left compares the after-breakfast blood glucose level over the entire treatment horizon, showing that the optimal regimen (solid) achieves uniformly lower blood glucose level than the original clinical regimen (dashed). The graph on the right shows the total positive deviation among all four phases over the entire treatment horizon, optimal (solid) vs. original plan (dashed); note the reduction in positive deviation, indicating a better overall glycemic control for the optimal regimen.

Figure 5. (Color online) The Net Total Positive Deviation Reduction When We Compare the Optimized Regimen to the Original Regimen



Notes. Our comparison covers all four phases over the entire treatment horizon and 200 patients. The results indicate a better overall glycemic control for the optimized regimen. Some patients achieve very large net reduction (represented by the isolated +).

We also observe that the treatment plan from our model tends to prescribe a higher dose early in the program; we see no change in dosage after week 3; this contrasts to six to eight weeks (or sometimes months) for the current clinical practice. The dosing-experiment period is thus significantly shortened, and the maintenance dosage level is achieved quickly. This demonstrates that the predictive treatment-effect model enables clinicians to prescribe higher doses early in the program without concerns about overdosing. This is in agreement with recommendations to quickly increase the dose of an oral hypoglycemic agent until an adequate glycemic control is achieved or a response is not observed (Frey et al. 2003). *Our model pinpoints precisely when and what dosage the clinicians should prescribe.*

Clinical Decision Making for the General Diabetic Population

The real-time clinical decision support system enables clinicians to tailor treatment design to the needs of patients. It shortens the dosing-experiment period and helps clinicians make better treatment decisions.

At Grady, a high percentage of the gestational diabetic patients are overweight and diabetic. The treatment success of these patients reduces the risk for C-section and the need to admit the newborn to the neonatal unit. The elimination of these high-cost risks saves approximately $39,500 per patient, more than a fourfold decrease in the overall hospital costs. It also reduces the need for long-term care for the babies, thus generating additional savings. For patients with type 2 diabetes, it offers good glucose level maintenance, thus reducing diabetic-related complications. The age-adjusted lifetime medical cost for a diabetic patient is estimated to be $105,000, of which 53% is spent on complications due to poor glucose maintenance. Factoring this globally, the savings could be very significant to the world economy. Most importantly, the model tailors treatment to the dose-response effect for each individual patient, allowing better individual outcomes. This, in turn, improves overall patient health and safety in drug usage.

The drug-effect outcome-based personalized treatment-planning framework is applicable to any diabetes-management analysis. In addition to using it at Grady Memorial Hospital, we are now conducting two diabetic studies: (1) investigating the effect of glibenclamide dose escalation on blood glucose and insulin in patients with poorly controlled type 2 diabetes; and (2) investigating practice variance and best practices among more than 800 clinical sites with 377,118 diabetic patients who have multiple chronic health conditions and optimizing individual treatments to produce the best outcomes.

Scientific Advances and Impact

This study establishes a predictive drug-effect-based personalized treatment-planning framework that improves the treatment outcome for diabetic patients. First, a predictive pharmacokinetic and pharmacodynamics model is designed to uncover drug effect based on analysis of antidiabetic drug dosage and the blood glucose level recorded in the dosing-experiment period of each patient. This personalized evidence is then utilized within a treatment plan optimization model to generate an optimal dosing strategy. This work offers unique mathematical and clinical advances on multiple fronts.

Mathematical and Operations Research Advances

- The predictive treatment-effect modeling framework includes fluid dynamics, a compartmental model, a constrained nonlinear programming model, and statistical smoothing for establishing the direct drug-dose drug-effect relationship. The model describes the movement of drugs within the body, the effects of drugs, and the mechanisms of their actions. Although the model is powerful, it presents theoretical and computational challenges. We establish solution strategies to make it practical for actual usage in a clinical setting.
- The complexity of our predictive treatment-effect mathematical models is evident. Our model answers

a century-old challenge: How can one predict dose effect based on available noninvasive measurements? Although the complex clinical pharmacology of drug-concentration drug-effect relationship in Equation (A.2) was first established in 1910, it took over nine decades for researchers to compensate for the lack of knowledge of "concentration of drug" by replacing it with "continuous measurement of drug concentration." Such measurements remain impractical for actual daily diabetes management. Our mathematical and computational model is the first that establishes a *direct relationship* between drug dosage and drug effect. Furthermore, it requires only the knowledge of medication and prescribed dosage from the doctor and the daily self-monitoring glucose data. The latter is collected via a home glucose meter that is routinely used by diabetes patients. The resulting predictive treatment-effect model characterizes personalized drug response and disease progression. It can also be used within a treatment-planning framework.

- The multiobjective mixed-integer programming treatment-planning model offers a flexible modeling environment, adapting to individual patients. It incorporates the predictive treatment-effect model output, captures the disease progression over the entire treatment horizon, and ensures that the patient has good glycemic control. The model optimizes the treatment outcome (glycemic control) and safety (drug dosage). The resulting personalized treatment plan, stipulating the medication and dosage for each week for the entire treatment horizon, offers better glycemic control while using less medication for patients. To the best of our knowledge, this is the first predictive personalized treatment-planning model that optimizes dosing and quality of outcome. The modeling framework is generalizable to other diseases. It can also be adapted to the specific needs of patients and can incorporate drug interactions and minimize adverse effects.
- This real-time clinical decision tool combines multidisciplinary mathematics and operations research tools: (1) a fluid dynamics compartmental model, constrained nonlinear programming, and statistics for establishing the predictive treatment effect; and (2) mixed-integer programming optimization to develop a personalized treatment plan. The predictive treatment effect model can effectively handle missing data and can generate dose-response characteristics in real time utilizing our in-house nonlinear solver. We caution that our solver obtained only local optimal solutions for these difficult quadratic constrained programming instances. Different initial values are chosen according to the population mean and variance of these parameter in the literature. We repeated the solution process multiple times to determine the best local optimum as our parameter estimator. We found that the quality of the first solution is comparable to and has only marginal differences to later solutions.

Clinical and Translational Advances

In the United States, half of the adults (age 20 or older) have diabetes (30.3 million) or prediabetes (84.1 million), racking up an estimated $327 billion in costs in 2017 (American Diabetes Association 2018). Globally, an estimated 422 million adults were living with diabetes in 2014. It is one of the most common diseases that internists and other medical specialists treat. Treatment is ad hoc and can be complicated, especially for patients with multiple health conditions. As we state above, a personalized treatment plan tailored specifically to the patient's unique dose-effect characteristics is more effective and efficient for both treatment outcome and treatment cost. This is particularly critical with mounting treatment expenses while coverage for diabetes-related medications and supplies has been on the decline.

- The clinical usage of our system offers improved outcome and cost savings. Gestational diabetes can lead to 34% higher maternity costs and complications. It results in higher rates of emergency C-sections (1.75 times), higher rates of infant neonatal-unit admission (3.14 times), and 34% higher costs of care (Gillespie et al. 2013). Implemented at Grady Memorial Hospital, our system helps reduce the hospital cost by $39,500 per delivery, more than fourfold decrease in the overall hospital costs. Grady delivers about 3,000 newborns annually, and many of their mothers are overweight and suffer from diabetes; thus, the cumulative savings are substantial.
- For type 2 diabetes patients, the age–gender weighted average of the lifetime medical costs adjusted to net present value is approximately $105,000, of which 53% is due to treating diabetic complications (Zhuo et al. 2013).
- Grady has an unusual burden with only 8% of its patients privately insured. Reduction in hospital cost translates to reductions in Medicaid and Medicare expenses, which are significant for a leading safety-net hospital in a state that did not expand Medicaid coverage under the Affordable Care Act. There is also savings in the reduction of long-term care requirements for the babies.
- The adaptive system reduces practice variance and empowers objective clinical decision making. Currently, the treatment of diabetes relies heavily on clinicians' experiences. This data-driven model, which uses personal self-monitoring glucose data, provides a clinician with good insights on a patient's personalized drug

response and potentially guides the clinician's decision making during the treatment. This decision support tool also allows continuous learning of evidence for each patient as new treatment outcomes are recorded.

- Scientifically, our clinical decision framework has four important distinctions. First, the PK/PD predictive treatment-effect model establishes a direct relationship between drug dosage and drug effect (the amount of decrease in blood glucose level); it is the first model that overcomes the obstacle of many existing models, which require continuous measurement of insulin or drug concentration in the blood. Second, in contrast to traditional PK/PD models that are used in drug development, we fit the model for each individual patient to characterize and predict the personalized dose response and disease progression over the entire treatment horizon. Third, our model uses only drug dosage and self-monitored blood glucose levels that are recorded by patients themselves at home. Since the 1990s, diabetics have routinely collected daily blood glucose for self-monitoring. The digital era has enabled providers to more easily collect and maintain these data in their patients' records. Hence, our model can be disseminated and implemented within current clinical and patient practices (without extra resource requirements). Last and most importantly, such personalized predictive information is utilized in a novel treatment-plan optimization model to generate personalized dosing strategy that optimizes glycemic control and drug dosage. This is crucial to ensure that the patient has good glycemic control for safe delivery. The resulting personalized treatment plan shortens the dosing-experiment period, it empowers clinicians to quickly identify and achieve the maintenance dose, and it eliminates subjective trial-and-error planning. The resulting treatment plans provide better glycemic control while using less drug. This is an added benefit because diabetes progresses and requires continuous intervention; thus, it is costly to treat. The financial burden is further amplified with coverage for diabetes-related medications and supplies being in decline.
- Our model is generalizable. We have begun a larger clinical implementation that involves over 300,000 diabetic patients to further explore and validate our model. We caution that clinical trials must be carried out to document the potential gain in outcome for broad dissemination and adoption.

Acknowledgments

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Appendix A. The Predictive Treatment-Effect Model

A basic fact of clinical pharmacology is that the intensity of pharmacological effects relates directly to the concentration of a drug at the effect site (Derendorf and Meibohm 1999). Pharmacokinetic models characterize the time course of drug concentration in the body fluids. The simplest one-compartment model is particularly useful for the analysis of drugs that distribute rapidly throughout the body. According to first-order kinetics, the plasma drug concentration after a rapid intravenous injection is given by

$$C(t) = \frac{D}{V} e^{-k_{el} \cdot t}, \tag{A.1}$$

where $C(t)$ is the plasma drug concentration at time t, D is the injected dose, and k_{el} is the first-order elimination rate constant for the drug. V is the volume of distribution, which has no direct physiologic meaning but is an indication of the extent of drug distribution in the body (Gibaldi and Perrier 1975). The area under the concentration-time curve is the integration of Equation (A.1) from zero to infinity. It represents the total drug exposure over time and is used in computing the average drug concentration over a period of time.

Pharmacodynamics models characterize the relationship between drug concentration and drug effect. The effect of a drug present at the site of action is determined by that drug's binding with a receptor, and the most commonly used model is the sigmoid E_{max} model (Hill 1913), which is of the form:

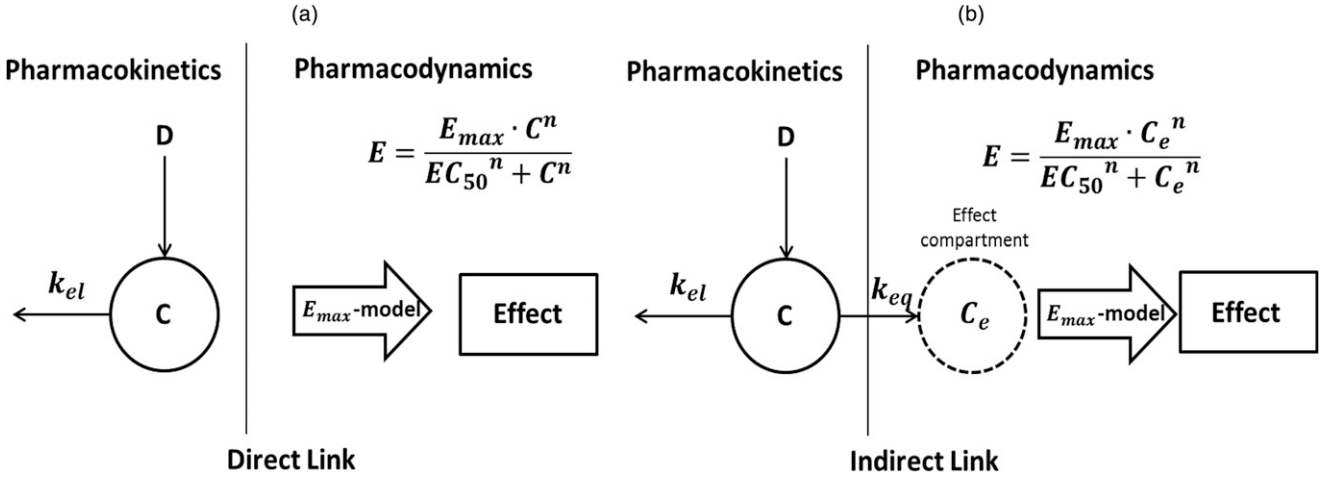
$$E = \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}, \tag{A.2}$$

where E_{max} is the maximum effect, C is the concentration of the drug at the effect site, EC_{50} is the concentration that produces half of the maximal effect, and n is the shape factor. Here, EC_{50} characterizes the potency of the drug in the system, and E_{max} reflects its efficacy. Although the shape factor n is derived from receptor theory as the number of molecules interacting with a receptor and can provide better data fits, it is rarely used in practice (Derendorf and Meibohm 1999).

Drug concentration C at the effect site in Equation (A.2) is not the same as in Equation (A.1), which is measured in plasma. The relationship between plasma and effect-site concentration may either be constant or change over time. For direct-link models, equilibrium between both concentrations is assumed to be achieved rapidly; thus, their ratio is a constant [Figure A.1(a)]. For indirect-link models, however, there is a temporal dissociation between the time course of concentration and effect, which is most likely caused by the distributional delay between the concentrations in plasma and at the effect site. A general approach to characterize this delay is the effect compartment model first introduced by Holford and Sheiner (Sheiner et al. 1979, Holford and Sheiner 1982). A hypothetical effect compartment is attached to the pharmacokinetic model to describe the concentration at the effect site [Figure A.1(b)].

Let C_p denote the concentration in plasma and C_e the concentration in the effect compartment, and assume that the

Figure A.1. The Direct-Link and Indirect-Link Models, Which Are Based on the Work of Derendorf and Meibohm (1999)



Notes. The models calculate the effect-site drug concentration C in the drug effect E_{max} model in two ways. In (a), the direct-link model uses plasma drug concentration C_p as C. In (b), the indirect-link model uses effect-compartment drug concentration, $\boldsymbol{C_e = C_p \cdot (1 - e^{-k_{eq} \cdot t})}$, as C.

drug influx into the effect compartment follows a first-order process; then, we have

$$\frac{dC_e}{dt} = k_{eq} \cdot (C_p - C_e), \tag{A.3}$$

where k_{eq} is the equilibration rate constant. Solving this differential equation, we have

$$C_e(t) = C_p(t) \cdot (1 - e^{-k_{eq} \cdot t}). \tag{A.4}$$

The drug-concentration drug-effect relationship, which we show in Equation (A.2), was first established in 1910 (Hill 1910). Frey et al. compensated for the lack of concentration using the area under the curve (Frey et al. 2003).

In particular, Frey et al. proposed a mixture model capturing both disease progression and drug effect of the diabetes treatment. In their model, the fasting plasma glucose level (FPG) for a patient taking an antidiabetic drug can be represented by

$$FPG(t) = Base + S(t) - \ E(t), \tag{A.5}$$

where $FPG(t)$ is the fasting plasma glucose at time t, $Base$ is the predicted baseline level, $S(t)$ is the disease progression model, and $E(t)$ the drug-effect model. Because diabetes is a progressive disease, Frey et al. (2003) used $S(t) = \alpha \cdot t$ (Chan and Holford 2001), which means constant rate progression.

The drug-effect model, $E(t)$, gives the predicted decrease of blood glucose level at time t by using antidiabetic drugs. Drug concentration C is replaced with AUC in Equation (A.2) and incorporated the effect compartment model in Equation (1.4):

$$E(t) = \frac{E_{max} \times AUC \times (1 - e^{-k_{eq} \cdot t})}{AUC \times (1 - e^{-k_{eq} \cdot t}) + AUC_{50}}. \tag{A.6}$$

The calculation of AUC requires continuous measurement of drug concentration, which is impractical in daily diabetes management.

Our Innovation

We introduce a predictive dose-effect model by replacing AUC with drug dosage D. By doing so, we overcome the calculation of AUC and establish a direct relationship between drug dosage and drug effect. *This answers a fundamental century-long puzzle on how one can predict the dose effect without measuring the drug concentration in the body fluids.* Moreover, although Equation (A.5) is a population PK/PD model proposed by Frey et al. (2003) to measure the long-term hypoglycemic effect of gliclazide, all parameters are patient-specific and can be specialized for each patient. As a result, we obtain a treatment-effect model that characterizes personalized drug response and disease progression by using only daily blood glucose records and dosage information.

Most drugs are administered periodically with sufficient frequency to maintain the presence of drug in the body. For drugs given in a fixed dose at a constant dosing interval, they accumulate in the body until a steady-state plasma level is achieved. At steady state, the drug concentration at any time during any dosing interval will be identical to the concentration at the same time during any other dosing interval (Gibaldi and Perrier 1975) (Figure A.2). We use this fact to establish the relationship between AUC and dosage D. Suppose a drug is administered at dose D with dosing interval τ for N intervals, then the drug concentration at time $N \cdot \tau + t$ will be

$$C_N(t) = \frac{D}{V} e^{-k_{el} \cdot t} \cdot \sum_{n=0}^{N} e^{-n \cdot k_{el} \cdot \tau} = \frac{D}{V} e^{-k_{el} \cdot t} \cdot \frac{(1 - e^{-(N+1) \cdot k_{el} \cdot \tau})}{(1 - e^{-k_{el} \cdot \tau})}. \tag{A.7}$$

Therefore, at steady state, the drug concentration at any time t is given by

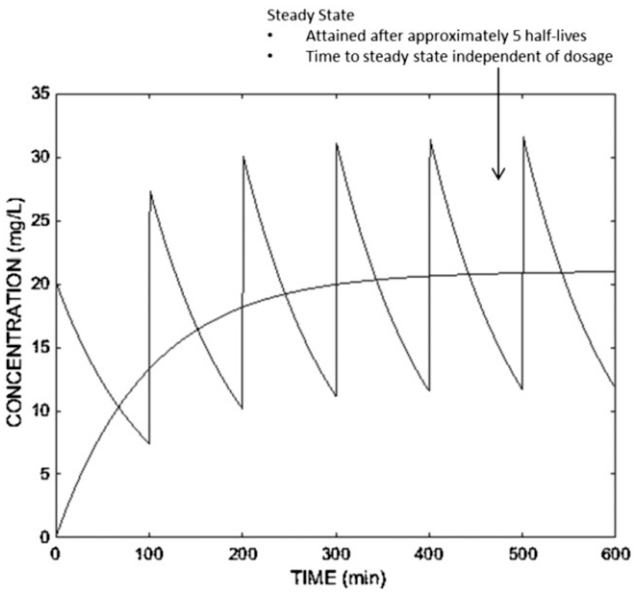
$$C_{ss}(t) = \lim_{N \to \infty} C_N(t) = \frac{D}{V} \cdot \frac{e^{-k_{el} \cdot t}}{(1 - e^{-k_{el} \cdot \tau})}, \quad t \in [0, \tau). \tag{A.8}$$

By Equation (A.8), we have the following relationship:

$$AUC_1^{0-\infty} = \int_0^{\infty} C(t)dt = \frac{D}{V \cdot k_{el}} = \int_0^{\tau} C_{ss}(t)dt = AUC_{ss}{}^{0-\tau}. \tag{A.9}$$

Therefore, AUC during any dosing interval at steady state is the same as the overall AUC after the first dose and

Figure A.2. The Time Course of Drug Concentration After Multiple Intravenous Dosings



Notes. Here, drug dosage $D = 200$ mg; the volume of distribution $V = 10$ l; the first-order elimination rate constant for the drug $k_{el} = 0.1$ min^{-1}; and the dosing interval $\tau = 100$ minutes. Because no absorption time is considered, the drug concentration will spike suddenly at the time of each drug administration.

$AUC_{ss}^{0-\tau} = \frac{D}{V \cdot k_{el}}$. By substituting $AUC_{ss}^{0-\tau}$ with $\frac{D}{V \cdot k_{el}}$ in (A.6), we have

$$E(t) = E_{max} \times \frac{\frac{D}{V \cdot k_{el}} \times (1 - e^{-k_{eq} \cdot t})}{\frac{D}{V \cdot k_{el}} \times (1 - e^{-k_{eq} \cdot t}) + AUC_{50}} = E_{max} \times \frac{D \cdot R_d \cdot (1 - e^{-k_{eq} \cdot t})}{1 + D \cdot R_d \cdot (1 - e^{-k_{eq} \cdot t})}. \quad \text{(A.10)}$$

Here, for model simplicity, we combine pharmacokinetic parameters into $R_d = \frac{1}{V \cdot k_{el} \cdot AUC_{50}}$ (mg^{-1}). It can be used to describe the drug sensitivity of a patient. When all other parameters are fixed, patients with larger R_d will have larger drug effect, indicating that these patients tend to have better treatment outcome.

Finally, we derive the blood glucose level BGL on day t as

$$BGL(\boldsymbol{\beta}, t) = Base + \alpha \cdot t - E_{max} \cdot \frac{D \cdot R_d \cdot (1 - e^{-k_{eq} \cdot t})}{1 + D \cdot R_d \cdot (1 - e^{-k_{eq} \cdot t})}, \quad \text{(A.11)}$$

where $\beta = (Base, \alpha, E_{\max}, R_d, k_{eq})$ are the parameters to be estimated for each individual patient.

Appendix B. The Multiobjective Treatment-Planning Model

We first introduce the parameters and decision variables used in our treatment optimization model.

The treatment-planning model can be formulated as

$$\text{(MIP) Min} \sum_m \sum_w \sum_t f_1(m,w,t) + \sum_w \sum_i f_2(w,i)$$
$$\text{s.t. } f_1(m,w,t) = C_+ \cdot p(m,w,t) + C_- \cdot n(m,w,t), \quad \forall\ m = 1\ldots4, w = 1\ldots W, t = 1\ldots7 \quad \text{(B.1)}$$
$$f_2(w,i) = C(i) \cdot x(w,i), \quad \forall\ w = 1,\ldots W,\ i = 0,\ldots,L \quad \text{(B.2)}$$

Indices	
w	Index for week, $w = 1,...,W$
m	Index for phase of daily blood glucose level, $m = 1,...4$ (before breakfast, after breakfast, after lunch, after dinner)
t	Index for days during a week, $t = 1,...7$
i	Drug dosage level, $i = 0,...L$
Parameters	
$g(m, w, t, i)$	Treatment effect for dosage level i at week w, day t, and phase m
C_+	Cost or penalty of positive deviation of blood glucose level from upper-bound level
C_-	Cost or penalty of negative deviation of blood glucose level from lower-bound level
$C(i)$	Cost of drug at dosage level i
W	Total number of weeks
L	Total number of dosage levels (assume that dosage level increases 1.25 mg per level)
k_+	Maximum positive dosage-level change between two consecutive decisions
k_-	Maximum negative dosage-level change between two consecutive decisions
$T(m)$	Upper bound of blood glucose level for phase m
$B(m)$	Lower bound of blood glucose level for phase m
$Base(m)$	Predicted blood glucose baseline for phase m, output from the predictive model
Decision variables	
$x(w, i)$	Binary decision variable, which takes a value of 1 if dosage level i is applied for week w, 0 otherwise.
$s(m, w, t)$	Blood glucose level at week w, day t, phase m.
$p(m, w, t)$	Positive deviation of blood glucose level from upper bound at week w, day t, phase m
$n(m, w, t)$	Negative deviation of blood glucose level from lower bound at week w, day t, phase m

$$\sum_i x(w,i) = 1, \quad \forall\ w = 1\ldots W \quad \text{(B.3)}$$
$$s(m,w,t) = s(m,w,t-1) + \sum_i g(m,w,t-1,i) \cdot x(w,i), \quad \forall\ m = 1\ldots4, w = 1\ldots W, t = 1\ldots7 \quad \text{(B.4)}$$
$$s(m,0,0) = Base(m), \forall\ m = 1\ldots4 \quad \text{(B.5)}$$
$$p(m,w,t) \geq s(m,w,t) - T(m), \quad \forall\ m = 1\ldots4, w = 0\ldots W, t = 1\ldots7$$
$$n(m,w,t) \geq B(m) - s(m,w,t), \quad \forall\ m = 1\ldots4, w = 0\ldots W, t = 1\ldots7 \quad \text{(B.6)}$$
$$x(w-1,i) + \sum_{j<i-k_-} x(w,j) + \sum_{j>i+k_+} x(w,j) \leq 1, \quad \forall\ w = 1,\ldots W,\ i = 0,\ldots,L \quad \text{(B.7)}$$
$$s \geq 0, p \geq 0, n \geq 0, x \in B^{W \times L},\ \ x(0,0) = 1. \quad \text{(B.8)}$$

The objective function of this mixed-integer program is a combination of health outcome, Equation (B.1), and treatment cost, Equation (B.2). Because diabetic treatment aims to maintain the blood glucose level within the recommended range, Equation (B.1) minimizes the sum of deviation of glucose level from the upper and lower bounds over the entire treatment horizon calculated by Equation (B.6). In terms of cost and side effect, Equation (B.2) minimizes the total amount of drug used. Constraint (B.3) ensures that a treatment is selected for each week. Because OHAs are

mostly in the form of pills, drug dosage in our model is restricted to discrete levels. Dosage level 0 implies that the patient is on diet control only and no drug is administered. Constraints (B.4) and (B.5) estimate the change of blood glucose level as a result of the drug effect, as predicted by Equation (A.11). Specifically,

$$g(m,w,t,i) = \alpha(m) - E_{\max}(m)\cdot\frac{D_i\cdot R_d(m)\cdot k_{eq}(m)\cdot e^{-k_{eq}(m)\cdot(7w+t)}}{1+D_i\cdot R_d(m)\cdot(1-e^{-k_{eq}(m)\cdot(7w+t)})}, \tag{B.9}$$

where D_i is the i-th dosage level and parameters $\beta = (Base, \alpha, E_{\max}, R_d, k_{eq})$ are estimated from SMBGs of phase m. Constraint (B.7) follows clinical practice that the dosage level should not fluctuate too much from one visit to the next. Because no national standard exists regarding the choice, the fluctuation allowed can be physician-dependent. In practice, clinicians always start with "diet control only" at the start of the visit. We comply with this practice by setting the initial treatment at week 0 to no dosage—that is, $x(0,0) = 1$.

Appendix C. Establishing the Predictive Treatment-Effect Parameters

For each patient, we use the initial 30% (during the dosing-experiment period) of SMBGs and dosage data to establish the personalized least-square estimator of parameters for the treatment effect in Equation (A.11). Each patient has four sets of SMBGs corresponding to four phases of monitoring per day: before breakfast (BB), after breakfast (AB), after lunch (AL), and after dinner (AD). Let $\{l_1, l_2, \ldots, l_T\}$denote the blood glucose level recorded at one of the phases from day 1 to day T; then, we obtain parameter β for that phase by solving the nonnegative least-square problem:

$$\boldsymbol{\beta}^* = \underset{\beta\geq 0}{\operatorname{argmin}}\ Err(\boldsymbol{\beta}) = \underset{\beta\geq 0}{\operatorname{argmin}} \sum_{t=1}^{T}(l_t - BGL(\boldsymbol{\beta},t))^2. \tag{C.1}$$

As the dosage level keeps changing during the treatment, dosage D in Equation (A.11) depends on time t. To address this issue, we calculate the blood glucose level by the first-order approximation:

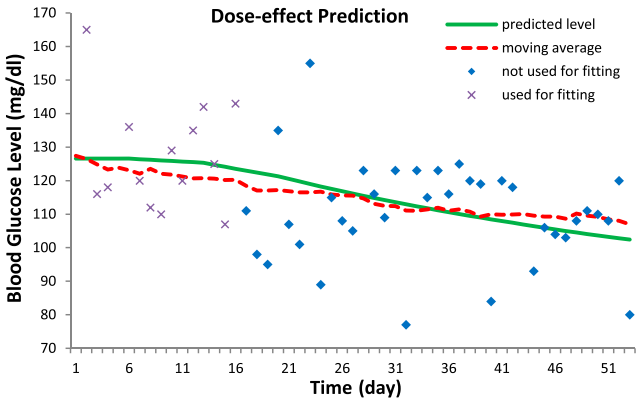
$$\begin{aligned} BGL(\boldsymbol{\beta},t+1) &\approx BGL(\boldsymbol{\beta},t) + \frac{\partial BGL}{\partial t}(\boldsymbol{\beta},t)\times 1 \\ &= BGL(\boldsymbol{\beta},0) + \sum_{s=0}^{t}\frac{\partial BGL}{\partial s}(\boldsymbol{\beta},s) \\ &= BGL(\boldsymbol{\beta},0) + \alpha\cdot t - \sum_{s=0}^{t} E_{\max}\cdot\frac{D(s)\cdot R_d\cdot k_{eq}\cdot e^{-k_{eq}\cdot s}}{1+D(s)\cdot R_d\cdot(1-e^{-k_{eq}\cdot s})}. \end{aligned} \tag{C.2}$$

Patients sometimes forget to record their glucose level. Equation (C.2) calculates $BGL(\beta, t)$ on those days; however, they are not included in the summation in Equation (C.1) because l_t values are missing.

We develop an efficient gradient descent method to obtain the optimal parameters β^* in Equation (C.1). Because the least-square optimization is nonconvex in the corresponding parameters, the gradient descent algorithm cannot guarantee the global optimality of the solution. As a result, different choices of the initial value of β can lead to different estimations. To avoid local optima and ensure the quality of the solution, we run the algorithm multiple times with different initial values and choose the one with the minimum estimation error. Different initial values are chosen according to the population mean and variance of these parameters in the literature (Holford and Sheiner 1982) because we assume that the value of these parameters for each patient will not differ very much from the population mean. Empirically, we obtain the range of parameters: $Base = 90 \pm 10$ mg·dl^{-1} for phase AB and $Base = 130 \pm 10$ mg·dl^{-1} for others; $\alpha = 0.005 \pm 0.001$ mg·dl^{-1}·day^{-1}, $E_{\max} = 90 \pm 10$ mg·dl^{-1}, $R_d = 0.2 \pm 0.1$ mg^{-1}, and $k_{eq} = 0.05 \pm 0.01$ day^{-1}. These choices consistently reflect the clinician's initial judgement on the patient's status. Mathematically, the gradient descent requires an initial value to start. Clinically, the choice can be interpreted as an initial guess of the patient's response characteristics.

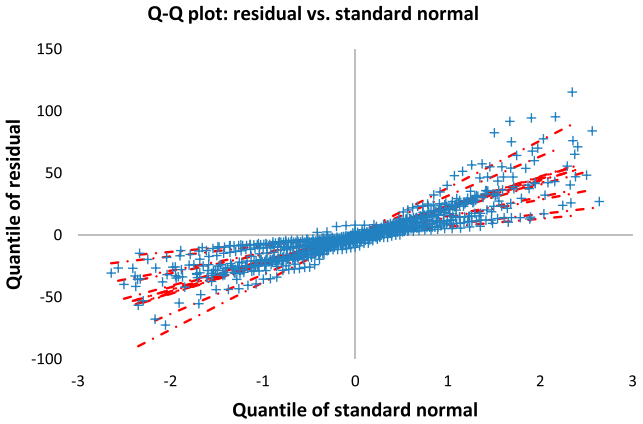
Once we fit the data, we then generate predicted glucose levels for the entire duration and compare them to the actual values. Moving averages are often used to uncover trends in time series (Brockwell and Davis 2006); therefore, we use them to compare the actual data versus the predicted values using window size 15. Specifically, we use 15 data points to calculate each point of the moving average. Figure C.1 illustrates the results for a patient. Specifically, the "X" values are actual SMBG data from the first 14 days. They are input into our treatment-effect model to establish the predicted drug effect (solid). The squares denote the actual SMBG values for the remaining treatment period not used for training. The moving average of all SMBG data ("X" and squares) for this patient is represented by the dotted line. We observe that our predictive model (solid curve) approximates well the blood glucose level trend over the entire treatment horizon (dotted curve). Furthermore, Figure C.2 suggests that the fitting residual (for all patients) is both close to normally distributed and close to stationary in time. This indicates that the model predicts well.

Figure C.1. (Color online) Prediction of the Drug-Effect Trends Using Self-Monitored Blood Glucose Data Obtained During the Dosing-Experiment Period



Notes. Specifically, each "X" is an SMBG data point from the first 14 days (dosing-experiment period). They are input into our treatment-effect model to establish the predicted drug effect (solid curve). The squares denote the actual SMBG values for the remaining treatment period (not used in training). The moving average of all SMBG data for this patient is represented by the dotted curve. Our predictive model (solid curve) provides a good approximation of the trend of blood glucose levels over the entire treatment horizon.

Figure C.2. (Color online) Least-Square Residual Values of All Patients vs. the Standard Normal Distribution



Note. Q-Q, quantile-quantile.

Hence, the SMBGs can be seen as a stationary time series with time-independent noise, and statistically the least square estimator β^* is the maximum-likelihood estimator.

This shows that our model gives good predictions on the drug effect and disease progression using data collected during the first few weeks of treatment. We observe consistently good-quality performance in the resulting predictive dose–glucose effect trend for all four phases (BB, AB, AL, and AD) for 93% of the 200 patient cases. In 7% of the cases, we have insufficient patient data to evaluate the performance.

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