Preprints of the 21st IFAC World Congress (Virtual)
Berlin, Germany, July 12-17, 2020

# Virtual Patients: An Enabling Technology for Multivariable Control of Biomedical Systems ⋆

**Mudassir M. Rashid** * **Sediqeh Samadi** * **Mert Sevil** **
**Nicole Hobbs** ** **Minsun Park** *** **Laurie Quinn** ***
**Ali Cinar** *,**,****

* *Department of Chemical and Biological Engineering, Illinois Institute of Technology, Chicago, IL 60616 USA.*
** *Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL 60616 USA*
*** *College of Nursing, University of Illinois at Chicago, Chicago, IL 60616 USA*
**** *(Corresponding author e-mail: cinar@iit.edu)*

**Abstract:** This paper presents the development of virtual patients to enable the simulation evaluation and assessment of multivariable control algorithms for biomedical systems. The virtual patients are generated by fitting the parameters of the models to clinical experimental data, followed by the estimation of the multivariate distribution of the actual patient parameters. The estimated multivariate distribution is then incorporated with constraints to ensure the sampling of synthetic virtual patients conforms to the actual patient parameter bounds. The sampled synthetic virtual patients are analyzed through multivariate statistical techniques and data clustering algorithms to prune out virtual subjects with similar characteristics or unrealistic dynamics, yielding a virtual patient population that is diverse and with individually distinct characteristics. The generated virtual patient population is used to evaluate multivariable nonlinear and adaptive control algorithms for insulin dosing in people with Type 1 diabetes.

*Keywords:* Biomedical system modeling and simulation, Multivariable control of biological systems, Metabolic and physiological model, Artificial pancreas, Model identification and validation

## 1. INTRODUCTION

Multivariable predictive control is becoming increasingly prevalent in biomedical systems. The significance of transitioning from the traditional monitoring of a single physiological variable of interest to the broad multivariable assessment of the inherent physiological state of a patient is widely recognized. However, the adoption of multivariable technologies and advanced predictive control algorithms in medical applications is relatively restrained, despite extensive research and development. The limited application of multivariable control techniques in medicine is related to the complex nature of the physiological response to controlled drug infusion, the difficulty in quantifying the transient responses, and the stringent requirements for patient safety.

Physiological and metabolic systems represent a complex system with nonlinear interdependencies among multiple pathways and processes, with effects characterized by distinct magnitudes and time-scales. The physiological and metabolic dynamics can vary substantially among patients, depending on genetic traits, behavioral tendencies, and concurrent disturbances. Because of the complex nonlinear and multivariable interactions in biological systems, the control algorithms developed for medical applications require extensive testing to validate safety and efficacy. Mathematical modeling and simulation of dynamic physiological and metabolic behaviors across a diverse population of patients can contribute to the development and application of multivariable control algorithms in biomedical systems (Resalat et al., 2019; Visentin et al., 2018).

The closed-loop control of glucose concentrations in people with Type 1 diabetes (T1D) is a complex multivariable control problem (Oviedo et al., 2017; Bequette, 2012). The difficulties involved in continuous infusion of insulin for the regulation of glucose concentrations relate to the myriad disturbances perturbing the glucose dynamics, patient variability, and accurate measurement and assessment of the physiological state (Balakrishnan et al., 2013; Ackerman et al., 1965). A number of studies in the literature report the implementation of predictive control algorithms for glucose control. Many of the existing control algorithms are single-loop systems for the controlled infusion of insulin in response to measurements of the glucose concentration.

⋆ This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grants DP3 DK101075-01 and DP3 DK101077-01, and the Juvenile Diabetes Research Foundation (JDRF) grant A18-0036-001 made possible through collaboration between the JDRF and The Leona M. and Harry B. Helmsley Charitable Trust.

A few recent insulin dosing algorithms comprise of more complex multivariable control architectures that integrate the assessment of the state of the patient through additional measurements such as heart rate, skin temperature, and accelerometer readings (Fig. 1). Translating these advanced multivariable control systems from the clinical setting to an outpatient free-living environment can be accelerated through virtual models of the patients (Messori et al., 2019; Boiroux et al., 2016; Dalla Man et al., 2007; Visentin et al., 2016; Makroglou et al., 2006; Haidar et al., 2013; Chassin et al., 2004).

Comprehensive integrated metabolic and physiological models are essential to allow the early and efficient assessment of the multivariable controller performance. Motivated by the need, this paper proposes an approach for the development of a virtual patient population, which serves as a foundation for the design and assessment of multivariable controllers for insulin infusion. In this regard, important properties of the virtual simulation platform and the virtual patient population, such as scalability, interoperability, expansibility, and fidelity, are addressed. This paper also elucidates the approach for developing the virtual patients and ensuring the conformity of the virtual patient populations to the actual population of people with T1D.

## 2. OVERVIEW OF SIMULATOR MODELS

A new multivariable simulator called mGIPsim (multivariable Glucose Insulin Physiological Variable Simulator) was developed (Fig. 1). The simulator is introduced elsewhere (Rashid et al., 2019). The simulator involves the integrated physiologic and metabolic simulation of a cohort of virtual subjects with T1D. Enabling this comprehensive simulation is a physiological model that is integrated with Hovorka's glucose-insulin model to instigate both immediate and long-lasting variations in the glucose-insulin dynamics in response to physical activity (Hovorka et al., 2004). User-defined scenarios for meals, administered insulin, and physical activity are used in the proposed multivariable simulator to generate heart rate, energy expenditure, skin temperature, and accelerometer readings in addition to insulin and glucose concentrations. Clinical experimental data are used to determine the virtual subject population.

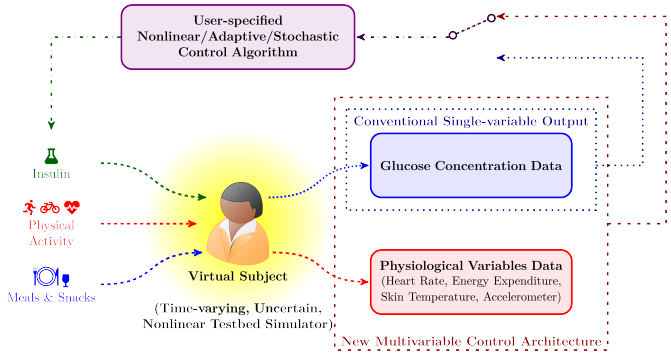


Fig. 1. Illustration of the use of synthetic virtual subjects for the assessment of nonlinear/adaptive/stochastic control algorithms through either the (blue) single-variable or (blue + red) multivariable control architectures.

### 2.1 Models

Several mathematical models are developed and used to generate various simulator output variables based on meal, insulin, and physical activity. Some model parameters are subject-specific to capture the inter-subject variability. The models are briefly described in this subsection to enhance the description of the capabilities and capacity of the multivariable simulator. A detailed description and analysis of the models is reported in Rashid et al. (2019).

*Glucose-Insulin Model* The glycemic model simulates the glucose variations in response to meals, administered insulin, and physical activity. The effects of physical activity are explicitly considered in the glycemic dynamics described by an extended version of Hovorka's glucose-insulin model. The original Hovorka's model consists of a glucose subsystem, an insulin subsystem, and an insulin action subsystem. In the proposed model, physical activity instigates immediate changes in the glucose disposal and long-lasting variations in the insulin action on glucose distribution, disposal, and endogenous glucose production. The driving force for the changes in the glucose-insulin dynamics is the elevated heart rate during exercise, which increases the glucose uptake from the plasma compartment to the muscles and tissues and also increases the glucose disposal from the working muscles. The glucose disposal rate increases with both immediate effect and long-lasting changes in insulin sensitivity. The new model explicitly considering the effects of physical activity on glucose-insulin dynamics improves glucose prediction accuracy compared to the reference model.

*Physiological Heart Rate Model* A dynamic physiological model characterizing the heart rate as a function of exercise intensity is used to compute the heart rate in the simulator. The heart rate during exercise is described by three different components that are combined to contribute the overall dynamics, including a fast component related to increased oxygen requirement of the exercising muscles, a slow component concerning the removal of accumulated lactate through supplied oxygen, and a metabolic component for the increase in demand of oxygen due to elevated core body temperature. A number of parameters in the physiological model are subject-specific, including demographic information such as body weight, resting heart rate, maximum heart rate, and maximum intensity achieved during the Bruce protocol test. The data spanning the exercise sessions and including a cool-down period beyond the termination of exercise is considered for optimizing the model parameters to specific patients.

*Energy Expenditure Model* Experiments are conducted for energy expenditure measurement using the COSMED K5 wearable metabolic system (COSMED, Italy) during treadmill and stationary bike exercises at different intensities and protocols. The data are used to develop a model to predict the energy expenditure in metabolic equivalents (MET). The mechanical work rate is computed from the exercise intensity information and the computed power is translated to energy expenditure estimates through a first-order filter with a subject-specific time constant to capture the transient behavior of the energy expenditure dynamics.

*Skin Temperature Model* Skin temperature, affected by exercise, is modeled by assuming a temperature gradient from the core body to the skin temperature with physical activity as the source of increased metabolism or heat generation. The skin temperature depends on the exercise intensity and other factors reflecting the environment and ambient conditions (for instance, wind speed or humidity). A partial differential equation model of heat convection with time and distance dependencies relates the core body temperature to the skin temperature dynamics. The effect of exercise is integrated as the source of metabolic heat generation in the core body. The model parameters include the thermal conductivity and the distance from core body to skin.

Details of the models are reported in Rashid et al. (2019).

### *2.2 Parameter Estimation*

The proposed exercise-glucose-insulin model is personalized to 18 subjects with T1D by identifying the subject-specific values for the identifiable model parameters. The model parameters are estimated using the clinical experimental data and by using Bayesian parameter estimation involving the Markov chain Monte Carlo (MCMC) approach that leverages the model and exploits the prior knowledge available in earlier literature studies. The maximum a posteriori estimation problem is expressed by

$$x^* = \arg\min_x P\left(x \mid f(\cdot), D\right) \tag{1}$$

$$= \arg\min_x \frac{P\left(f(\cdot), D \mid x\right) P(x)}{\int P\left(f(\cdot), D \mid x'\right) P(x')\,\mathrm{d}x'} \tag{2}$$

$$= \arg\min_x P\left(f(\cdot), D \mid x\right) P(x) \tag{3}$$

where the optimum parameter values, $x^*$, are found such that the posterior probability, $P\left(x \mid f(\cdot), D\right)$, is maximized. Further, $P\left(f(\cdot), D \mid x\right)$ is the likelihood of the parameters $x$ given the model $f(\cdot)$ and the clinical experimental data $D$, with $P(x)$ denoting the prior distribution of the parameters. Eq. 2 is formulated from Bayes' rule and Eq. 3 is obtained after discarding the normalization constant that does not affect the Bayesian optimization.

The Bayesian optimization approach relies on the cascaded Goodman and Weare affine invariant ensemble MCMC sampler where an ensemble of chains is generated to search for model parameters. The parameter estimation for each subject is obtained from the posterior probability distribution of the subject-specific parameters after running one million iterations of the ensemble MCMC sampler for the model. The first 30% of the samples are discarded as the initial burn-in period.

## 3. VIRTUAL PATIENTS

In this section, the generation of the virtual patient parameters is discussed.

### *3.1 Generation of Virtual Patients*

Virtual patients are generated by sampling of the distribution of the actual patient parameters. Given the set of actual patient parameters $\left\{x^{(1)}, x^{(2)}, ..., x^{(m)}\right\}$, the distribution of the actual patient parameters is approximated as a multivariate Gaussian distribution of the form

$$p(x; \mu, \Sigma) = \frac{1}{(2\pi)^{\frac{n}{2}} |\Sigma|^{\frac{1}{2}}} \exp\left(-\frac{1}{2}(x-\mu)^T \Sigma^{-1} (x-\mu)\right) \tag{4}$$

with the parameters

$$\mu = \frac{1}{m}\sum_{i=1}^{m} x^{(i)}$$

$$\Sigma = \frac{1}{m}\sum_{i=1}^{m} \left(x^{(i)} - \mu\right)\left(x^{(i)} - \mu\right)^T$$

where $\mu$ and $\Sigma$ denote the mean and covariance of the multivariate Gaussian distribution. Currently the distribution of the actual patient parameters is approximated as a Gaussian distribution, though future work may consider the approximation as a multivariate Gaussian mixture model to characterize subpopulations within the overall population of people with T1D. The estimated distribution is used to sample synthetic virtual subjects representative of the actual patient population.

The virtual patients are sampled from a truncated multivariate Gaussian distribution defined as

$$p(x; \mu, \Sigma, x_{\min}, x_{\max}) = \frac{\exp\left(-\frac{1}{2}(x-\mu)^T \Sigma^{-1} (x-\mu)\right)}{\int_{x_{\min}}^{x_{\max}} \exp\left(-\frac{1}{2}(x-\mu)^T \Sigma^{-1} (x-\mu)\right)\mathrm{d}x} \tag{5}$$

with $p(x; \mu, \Sigma, x_{\min}, x_{\max})$ for $x < x_{\min}$ and $x > x_{\max}$, where $x_{\min}$ and $x_{\max}$ denote the minimum and maximum bound constraints for the parameter values.

Generating variates from the truncated Gaussian multivariate distribution can be conducted through either rejection or Gibbs sampling. Rejection sampling is straightforward and involves drawing samples from the unconstrained distribution shown in Eq. 4 and to accept only those samples that are within the support region, thus rejecting the samples violating the bound constraints. However, rejection sampling can be inefficient for large dimensional spaces and limited supports by tight bound constraints, thus increasing the rejection rate. Another approach for generating random samples from a truncated multivariate Gaussian distribution is to use the Gibbs sampler, a MCMC technique that, given sufficient sampling, converges to a stationary target distribution. The advantage of Gibbs sampling is that it accepts all drawn samples without the limitations of an acceptance rate.

### *3.2 Enforcing Conformity of Virtual Patients*

The approximation of the actual patient population and the subsequent random sampling of synthetic virtual subjects may result in virtual subjects that are similar in their parameter values or the output prediction responses, and a few virtual subjects may be distant from the mean of the actual patient population. Therefore, the unrealistic virtual patients or the less plausible realizations of the synthetic virtual patients must be eliminated.

*Low-Probability Virtual Patients* Some synthetic virtual patient parameters may be far from the mean of the actual patient population. These virtual patients can be eliminated from the virtual patient population by evaluating the probability of the virtual patients as

$$\arg\max_{\mathbb{J}_{n_1}} \prod_{j \in \mathbb{J}_{n_1}} P\left(x_j \mid \mu, \Sigma\right) \tag{6}$$

where $n_1 > 0$ is the number of retained subjects, and $\mathbb{J}_{n_1}$ denotes the set of retained virtual subjects as a subset of the full set of synthetic virtual subjects $\mathbb{J}_n$, that is $\mathbb{J}_{n_1} \subset \mathbb{J}_n$.

The Mahalanobis distance may also be used to find the virtual subjects that are highly-probable since it considers the correlation in the data through the use of the inverse of the variance-covariance matrix of the actual patient population. The Mahalanobis distance is given by

$$d_j = \sqrt{\left(x_j - \mu\right)^T \Sigma^{-1} \left(x_j - \mu\right)} \tag{7}$$

and the set of virtual subjects that has lower Mahalanobis distances can be retained to form the virtual patient population as

$$\arg\min_{\mathbb{J}_{n_2}} \sum_{j \in \mathbb{J}_{n_2}} d_j \tag{8}$$

where $\mathbb{J}_{n_2} \subset \mathbb{J}_n$ is the set of retained virtual subjects as a subset of the full set of synthetic virtual subjects. However, the computation of the covariance matrix may be non-ideal, especially when the actual patient parameter values contain much redundant or correlated information, or multicollinearity, which may result in a noninvertible nearly singular covariance matrix. This is likely in the covariance of the actual patient population since the parameter values of a subject are likely to be highly correlated due to the same underlying physiologic or metabolic conditions affecting several parameter values. Another drawback of the calculation of the covariance matrix is that the number of actual patients has to be greater than the number of parameters, which may not necessarily hold in biological systems where recruiting patients for experiments may be expensive and time-consuming. To overcome this drawback, a subset of meaningful and identifiable parameters may be selected from the total set of parameters to compute the inverse covariance matrix.

A more robust approach to overcoming the drawbacks of computing the inverse of the covariance matrix is to use feature reduction methods like principal component analysis (PCA). Then the Mahalanobis distance can be readily computed using the latent variables (or principal components) instead of the original parameter values. Moreover, the analysis is also simplified as the principal components are orthogonal (uncorrelated).

PCA effectively handles high-dimensional, noisy, and correlated data by generating an orthonormal basis that maximizes the variance explained by the projection of the actual patient parameters on the lower dimensional space. This reduces the original parameter space from a high dimensional space to a lower dimensional subspace and extracts the significant features from the data set. PCA can be used to decompose the matrix of parameter values $X \in \mathbb{R}^{n \times k}$ (where $n$ is the number of actual patients and $k$ is the number of parameters) as the sum of the outer product of vectors $t_i$ and $p_i$ plus the residual matrix, $E$, as

$$X = TP^T + E = \sum_{i=1}^{a} t_i p_i + E \tag{9}$$

where $t_i$ denotes the score vectors that form the projections of the original parameter space to the subspace, and $p_i$ denotes the orthonormal loading vectors containing information about relations among the parameters. The projection also reduces the original set of parameter values to a smaller number of latent variables, that is $a < k$, while the residual matrix may remove noise resulting from the numerical optimization of the models to clinical experiment data.

The Hotelling's $\mathrm{T}^2$ and squared prediction error (SPE) statistics and their control limits can be used to identify the virtual patients that are outliers relative to the actual patient data. The Hotelling's $\mathrm{T}^2$ statistic is given by

$$\mathrm{T}_k^2 = t_k^T \Lambda t_k \tag{10}$$

where $\Lambda$ is the diagonal matrix of the inverse of the eigenvalues associated with the retained principal components and the SPE statistic is given by

$$\mathrm{SPE}_k = x_k^T \left(\mathrm{I} - PP^T\right) x_k \tag{11}$$

The control limits for the Hotelling's $\mathrm{T}^2$ and SPE statistics can be calculated as

$$\mathrm{T}_{a,n,\alpha}^2 = \frac{a\left(n-1\right)}{n-a} F_{a,n-a,\alpha} \tag{12}$$

and

$$\mathrm{SPE}_\alpha = g\chi_h^2 \tag{13}$$

with $g = b/2a$ and $h = 2a^2/b$ where $a$ and $b$ are the estimated mean and variance of the SPE statistic. Determining the contributions of individual variables to the $\mathrm{T}^2$ and SPE indexes can reveal variables or phenomena that are the likely causes of the deviations from expected trends. The projected data can be clustered to identify cohorts of subjects. The virtual subjects that have high Hotelling's $\mathrm{T}^2$ and SPE statistics compared to the actual patient population data can be pruned as those synthetic virtual patients are not representative of the actual patient population.

*Cluster Analysis for Uniqueness* Beyond the elimination of the virtual patients that are unlikely to occur in the actual patient population, it is also desired for the virtual patients to possess distinct and individual dynamics. The similar virtual patients can be identified through cluster analysis. It should be noted that the similarity of the parameter values is not exclusively the main criteria as virtual patients with distinct parameter values may also have similar responses due to the complex nonlinear relationships among the parameters.

To determine the similarity of the virtual patients, we use an agglomeration hierarchical clustering algorithm. The clustering algorithm is based on a predefined distance (or similarity) metric. The clusters of virtual subjects are formed by grouping subjects with similar parameter values or glucose-insulin dynamics together, while subjects with distinctly different parameter values or dynamics are placed in distinct clusters. This unsupervised approach unveils naturally occurring subgroups within the virtual patient population, without requiring labeled training data.

The agglomeration hierarchical clustering algorithm is summarized as follows:

(1) Compute distances between each pair of virtual subjects ($x_i$ and $x_j$) as $d\left(x_i, x_j\right) = \left\|x_i - x_j\right\|_2$, which yields a metric for the pairwise similarity between virtual subjects. Consider each subject as a distinct cluster.
(2) Form a binary cluster from either the two most similar subjects or clusters. For a binary cluster of:
   - subjects, the distance metric is:
   $$d\left(x_i, x_j\right) = \left\|x_i - x_j\right\|_2$$
   - existing clusters, the linkage metric is:
   $$l\left(A, B\right) = \frac{1}{n_A \cdot n_B} \sum_{a \in A} \sum_{b \in B} d\left(a, b\right)$$
   where the two existing clusters are denoted $A$ and $B$ with associated virtual subject parameters $a$ and $b$.
(3) Recompute the distances between newly formed cluster and the remaining subjects or clusters.
(4) Return to Step 2, or terminate if all virtual subjects are included in one main cluster, and form the dendrogram.
(5) Specify the level of the hierarchy and assign the virtual subjects below the specified level to specific clusters.

Following the clustering, only one unique virtual subject from each cluster is selected for inclusion in the final virtual patient population.

## 4. RESULTS

Given the glucose data, input variables including meal, insulin, and heart rate information, and the prior distribution of the parameters, the generated posterior distributions of subject-specific model parameters are used to obtain the parameter estimates and the corresponding confidence intervals. Table 1 summarizes the results of fitting the new proposed model and the reference model to the clinical experimental data. Fig. 2 shows the output predictions of the glucose values given the known meal, insulin, and physical activity inputs with model parameters optimized for the original Hovorka's model and the proposed extended Hovorka's model. The improvement of the proposed extended model is statistically significant relative to the original Hovorka's model with p-values $< 1 \times 10^{-3}$ for one-sided t-test to evaluate reduction in prediction error.

A virtual patient population is generated from the distribution of the actual patient population, and the outliers and unlikely virtual patients are excluded, as are virtual patients with similar characteristics. The virtual patient population is simulated under the same simulation scenario to demonstrate the diversity of the virtual patients (Fig. 3). The results demonstrate that the diversity of the actual patient population is well characterized by the virtual patient population. The virtual patients are valuable for testing novel nonlinear/adaptive/stochastic control algorithms in a simulation virtual setting to evaluate its efficacy.

Table 1. Comparison of predictive performances between proposed exercise-glucose-insulin model and reference glucose-insulin model. RMSE: root-mean-square error, MAE: mean absolute error.

| | RMSE (Mean±SD) | MAE (Mean±SD) |
|---|---|---|
| Proposed model | $18.65 \pm 4.89$ | $14.50 \pm 3.55$ |
| Reference model | $22.39 \pm 6.00$ | $17.34 \pm 4.61$ |

## 5. CONCLUSION

The problem of developing virtual patients for enabling the simulation evaluation and assessment of multivariable control algorithms for biomedical systems is addressed. The virtual patients are generated by fitting the parameters of the models to clinical experimental data, followed by the estimation of the constrained multivariate distribution of the actual patient parameters. The sampled synthetic virtual patients are analyzed through multivariate statistical and clustering algorithms to eliminate virtual subjects with similar characteristics or unrealistic dynamics. A diverse virtual patient population is generated for evaluating multivariable control algorithms for insulin dosing in people with T1D in a virtual simulation environment.

## REFERENCES

Ackerman, E., Gatewood, L.C., Rosevear, J.W., and Molnar, G.D. (1965). Model studies of blood-glucose regulation. *Bull. Math. Biol.*, 27(1), 21–37.

Balakrishnan, N.P., Samavedham, L., and Rangaiah, G.P. (2013). Personalized hybrid models for exercise, meal, and insulin interventions in type 1 diabetic children and adolescents. *Ind. Eng. Chem. Res.*, 52(36), 13020–13033.

Bequette, B.W. (2012). Challenges and recent progress in the development of a closed-loop artificial pancreas. *Annu. Rev. Control*, 36(2), 255–266.

Boiroux, D., Hagdrup, M., Mahmoudi, Z., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2016). Model identification using continuous glucose monitoring data for type 1 diabetes. *IFAC-PapersOnLine*, 49(7), 759–764.

Chassin, L.J., Wilinska, M.E., and Hovorka, R. (2004). Evaluation of glucose controllers in virtual environment: methodology and sample application. *Artif. Intell. Med.*, 32(3), 171–181.

Dalla Man, C., Rizza, R.A., and Cobelli, C. (2007). Meal simulation model of the glucose-insulin system. *IEEE Trans. Biomed. Eng.*, 54(10), 1740–1749.

Haidar, A., Wilinska, M.E., Graveston, J.A., and Hovorka, R. (2013). Stochastic virtual population of subjects with type 1 diabetes for the assessment of closed-loop glucose controllers. *IEEE Trans. Biomed. Eng.*, 60(12), 3524–3533.

Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Federici, M.O., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol. Meas.*, 25(4), 905.

Makroglou, A., Li, J., and Kuang, Y. (2006). Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview. *Appl. Numer. Math.*, 56(3-4), 559–573.

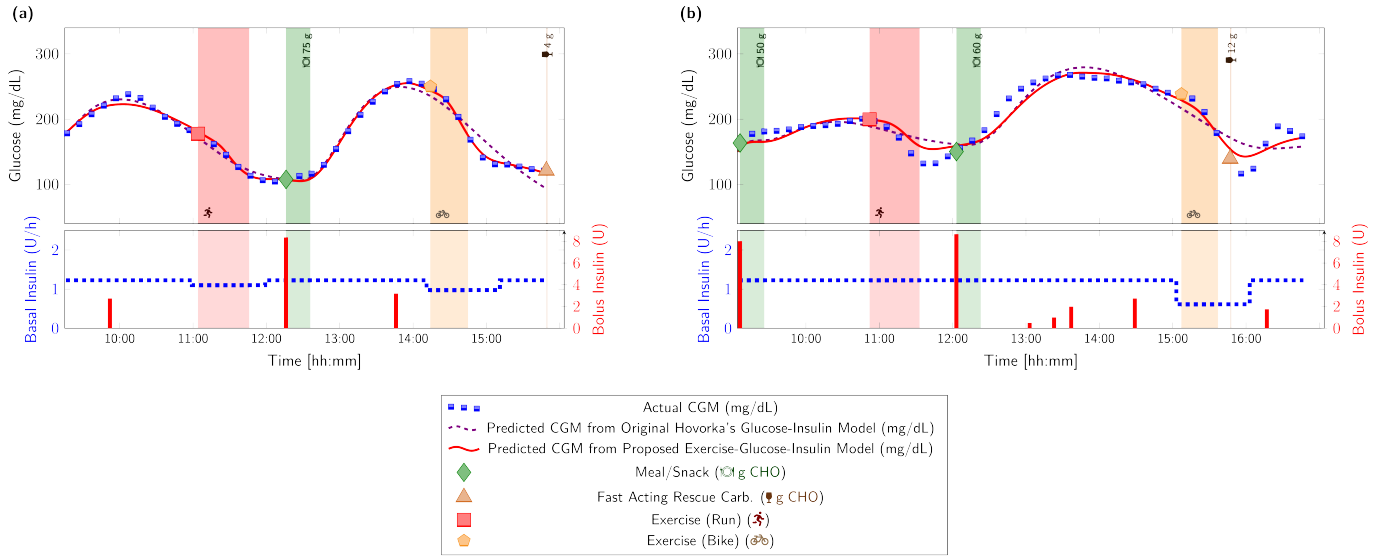


Fig. 2. Parameter optimization results using real clinical data for a select subject with T1D.

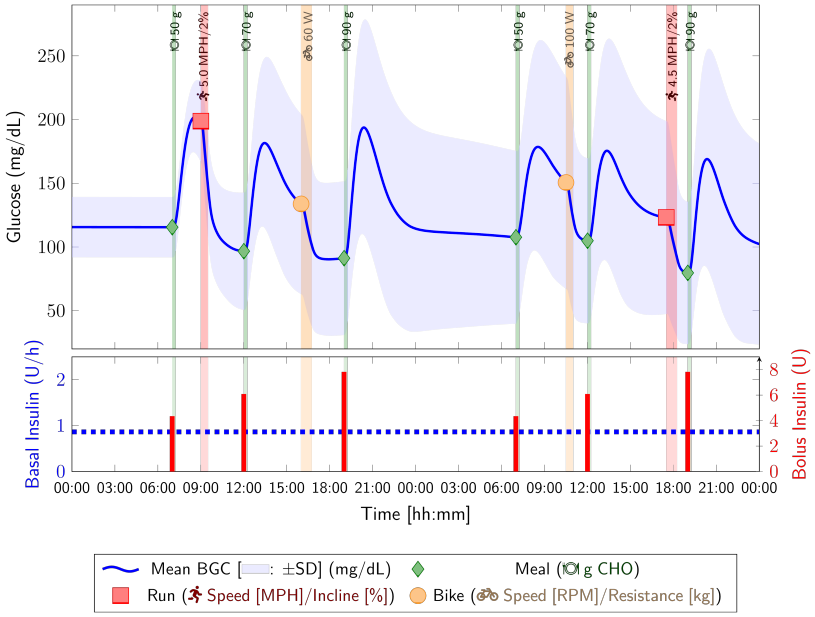


Fig. 3. Simulation results for the virtual subjects with T1D. The shaded area spans the standard deviation (SD) for the glucose dynamics of the virtual subjects. The multivariable simulation generates the glucose data, as well as the heart rate, energy expenditure, skin temperature, and accelerometer data, in response to meals, infused insulin, and physical activity (running and bicycling).

Messori, M., Toffanin, C., Del Favero, S., De Nicolao, G., Cobelli, C., and Magni, L. (2019). Model individualization for artificial pancreas. *Comput. Methods Programs Biomed.*, 171, 133–140.

Oviedo, S., Vehí, J., Calm, R., and Armengol, J. (2017). A review of personalized blood glucose prediction strategies for t1dm patients. *Int. J. Numer. Methods Biomed. Eng.*, 33(6).

Rashid, M., Samadi, S., Sevil, M., Hajizadeh, I., Kolodziej, P., Hobbs, N., Maloney, Z., Brandt, R., Feng, J., Park, M., Quinn, L., and Cinar, A. (2019). Simulation software for assessment of nonlinear and adaptive multivariable control algorithms: Glucose–insulin dynamics in type 1 diabetes. *Comput. Chem. Eng.*, 130, 106565.

Resalat, N., El Youssef, J., Tyler, N., Castle, J., and Jacobs, P.G. (2019). A statistical virtual patient population for the glucoregulatory system in type 1 diabetes with integrated exercise model. *PLOS ONE*, 14(7), 1–17.

Visentin, R., Dalla Man, C., and Cobelli, C. (2016). One-day bayesian cloning of type 1 diabetes subjects: Toward a single-day UVA/Padova type 1 diabetes simulator. *IEEE Trans. Biomed. Eng.*, 63(11), 2416–2424.

Visentin, R., Campos-Náñez, E., Schiavon, M., Lv, D., Vettoretti, M., Breton, M., Kovatchev, B.P., Dalla Man, C., and Cobelli, C. (2018). The UVA/Padova type 1 diabetes simulator goes from single meal to single day. *J. Diabetes Sci. Technol.*, 12(2), 273–281.