Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Rapid Model Identification for Online Glucose Prediction of New Subjects With Type 1 Diabetes Using Model Migration Method

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Abstract: Online prediction of glucose concentration is of importance for blood glucose control in diabetes. For conventional modeling methods, model identification has to be repeated with sufficient data collected for each subject. This may cause repetitive cost and burden for patients and clinician and requires a lot of modeling efforts. Here, a rapid model development strategy is proposed using the idea of model migration for new subjects. First, a base model is obtained which can be empirically identified from any subject or constructed by priori knowledge. Then parameters of inputs in the base model are properly revised based on a small amount of data from new subjects. These issues are investigated by developing auto-regressive models with exogenous inputs (ARX) based on thirty *in silico* subjects. Some important issues relating to model adjustment performance are also checked, referring to the data used for model parameter adjustment and the interaction of two inputs, etc. The rapid modeling method is compared with subject-dependent models developed based on a large number of data with respect to on-line short-term (30min) glucose prediction accuracy.

Keywords: rapid model identification, autoregressive with exogenous inputs (ARX), model migration, Type 1 diabetes mellitus (T1DM), glucose prediction.

1. INTRODUCTION

Characterized by the inability of the body to regulate blood glucose concentration, Type I diabetes mellitus (T1DM) has been recognized as one of the most serious diseases in the world. Due to autoimmune destruction of the pancreatic β-cells, people with T1DM may not maintain their blood glucose concentration within a normal range (e.g., 70-120 mg/dL before meal and less than 160 mg/dL after meal) without appropriate treatment with exogenous insulin. The research of artificial pancreas has changed the traditional treatment way of diabetes mellitus and brought hope to the diabetes subjects. Glucose monitoring and prediction are the basis and key in artificial pancreas. Online glucose prediction has been an important issue in blood glucose control in diabetes. Therefore, the identification of simple, accurate glucose prediction models has been drawing increasing attention. Many empirical (or "data-driven") modelling techniques have been developed and successfully applied to glucose prediction (Zanderigo F et al., 2007; Reifman J et al., 2007; Finan D.A. et al., 2009).

In general, the existing dynamic empirical models can be divided into two types, linear models and nonlinear models, as summarized by Finan and colleagues (Finan D.A. et al., 2009). Linear model that represented by autoregressive (AR) and autoregressive with exogenous inputs (ARX) have received a wide range of applications due to their simple model structure and calculation. For AR modelling, only CGM data are employed in the model and future glucose concentrations are simply expressed as linear combinations of recent glucose measurements. The ARX models are an extension of AR models that reflect the relationship between glucose and exogenous inputs by including inputs signals into the model structure, e.g., insulin delivery and meal carbohydrate (CHO) estimates. For different subjects, their glucose levels may response differently to the exogenous inputs, revealing their different physiological reactions and life styles. Difference between subjects may make the existing ARX prediction model developed from one subject invalid for new subjects. The conventional modelling methods are to re-conduct clinical trials, re-collect modelling data, and re-identify new prediction models for new subjects. Subject-specific ARX models (Finan D.A. et al., 2009 and Zhao et al., 2011, 2012) have been developed and evaluated for *in silico* and clinical subjects. The effects of key design issues, such as the degree of input excitation, model orders and prediction horizons, have also been checked.

In contrast to the widespread development of personalized glucose prediction models, there is a limited body of work concerning the analysis of inter-subject variability for glucose prediction. In particular, Gani et al. (2010) and Zhao et al. (2013) have mentioned and verified the concept of a *universal* or *global* AR model of glucose prediction for T1DM. The model can be identified based on glucose data for a single subject and then used to make short-term (30-min-ahead) glucose predictions for other subjects without any need of model customization. Their results indicated that the predictive capability of the AR models (i.e., glucose autocorrelation) was not affected by inter-subject differences. However, for the development of glucose prediction model, exogenous inputs are very important factors, which are also the basis for the practical application of glucose control. Zhao et al. (2013, 2014) have pointed out that ARX prediction models were not global when two exogenous inputs, insulin

delivery and meal CHO estimates, were included in the model structure. This well supports the fact that different subjects may give different glucose responses to exogenous inputs due to diverse physique, changes of life styles or physiological function. Based on the above discussion, to get an accurate ARX prediction model, conventional methods require repetitive model development for different subjects with a large number of data, which may cause burden for patients and clinicians and also may be inefficient, time-consuming and uneconomical.

In this paper, a rapid model development strategy is proposed using model migration method for new subjects with type 1 diabetes. First, the existing model describing the old subject is defined as a base model and the model to be identified for a new subject is defined as a new model. The base model can be obtained by empirical modelling for one subject with a large number of data or can be a mechanistic model obtained by solid first-principle knowledge and good understanding of subjects. In the current research, we focus on empirical model development using measurement data. Considering that responses to exogenous inputs may change across different subjects due to their different excitations, parameters of the base model are properly revised so that the updated model can be used for a new subject. Of particular interest, are first what and how much data are required for model migration so that more information can be extracted; second how to determine adjusting step and adjusting direction to capture the difference between the new subject and the base model. These issues are investigated by developing ARX models based on thirty *in silico* subjects using University of Virginia/University of Padova (UVA/Padova) metabolic simulator. The rapid modeling method is compared with subject-dependent model for on-line short-term (0-60min) glucose prediction.

2. METHODOLOGY

2.1 Standard ARX Prediction Models

In this paper, ARX modelling technique based on least squares (LS) algorithm (Ljung, 1999) is used to develop empirical prediction models. The general form of the LS-based ARX model used in this paper can be described as,

$$A(q^{-1})g_k = B(q^{-1})i_{k-k_{ins}} + C(q^{-1})m_{k-k_{meal}} + \beta + \varepsilon_k \qquad (1)$$

where g_k denotes glucose concentration at sampling time k. $i_{k-k_{ins}}$ and $m_{k-k_{meal}}$ are bolus insulin and meal CHOs consumed at sampling time $k-k_{ins}$ and $k-k_{meal}$ respectively. Bolus insulin and meal CHOs are considered as two exogenous inputs while basal insulin that stays invariables is left out in the ARX model for simplicity. k_{ins} and k_{meal}, which can be different for different subjects, are the input time delays. β is a constant bias term and ε_k is random disturbance at time k. $A(q^{-1})$, $B(q^{-1})$ and $C(q^{-1})$ represent the coefficients of glucose concentration, bolus insulin and CHOs respectively which can be identified by LS algebra (Ljung, 1999). q^{-1} is the backward shift operator, i.e., $q^{-1}g_k \equiv g_{k-1}$. For example, if the order of the $A(q^{-1})$ polynomial is n, then $A(q^{-1})$ can be described as,

$$A(q^{-1}) = a_0 + a_1 q^{-1} + a_2 q^{-2} + \cdots + a_n q^{-n} \qquad (2)$$

2.2 Rapid Model Development using Model Migration

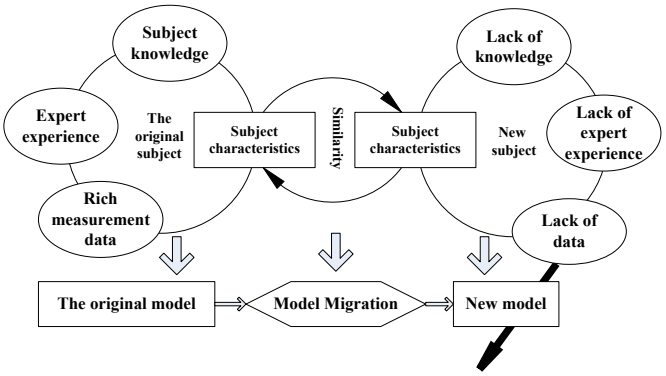

Fig. 1. The illustration of model migration method

For model migration, the foundation is first to detect how different or similar two subjects are and what kind of difference they have. As mentioned before, despite that different subjects may response differently to the exogenous inputs, certain glucose dynamics remain the same. Previous work (Zhao et al., 2013) have demonstrated that an AR prediction model developed for data from one subject is also valid for other subjects without any customization. That is, they revealed that glucose autocorrelations are similar across subjects. Therefore, the glucose dynamics of each subject can be separated into subject-dependent part and subject-independent part in the present work. Correspondingly, the model parameters of historical glucose data (i.e., $A(q^{-1})$) in ARX model are the same for different subjects. However, the model parameters of exogenous inputs (i.e., $B(q^{-1})$ and $C(q^{-1})$) plus bias term (β) in ARX model may be different, whose sizes directly reflect the response magnitudes. Based on the above analysis, the idea of model migration as shown in Figure 1 can be used to rapidly develop the prediction model for new subjects by proper model parameter adjustment. Clearly, analysis of these common glucose dynamics and taking advantage of the existing prediction model for one subject can allow fewer data and minimal priori knowledge to be required and make the model development for new subjects more efficient and economical. By model migration, it is hoped that the proposed rapid modelling method can present similar prediction accuracy in comparison with subject-dependent modelling method but cost less modelling burden.

The general idea of rapid prediction model development is described as below. First, a base model is available which can be empirically identified from any subject or constructed by priori knowledge of one subject. In the present work, LS algebra is used to develop ARX prediction model for one subject based on a large number of data, including both glucose data and two exogenous inputs. In general, the existing base model is good for glucose prediction for the

current subject but fails to get satisfying prediction accuracy for the other subjects although they have the same model structure. To customize this base model so that it can be used for glucose prediction for new subjects, model parameters for $B(q^{-1})$ and $C(q^{-1})$) plus bias term (β) in Eq. (1) should be adjusted based on only a small number of data from new subjects. In fact, the differences between subjects indicate that prediction relationship of the new subject is simply a shift and re-scale of that for the old subject, then the new model can be described as a slope and bias correction (SBC) to the base model.

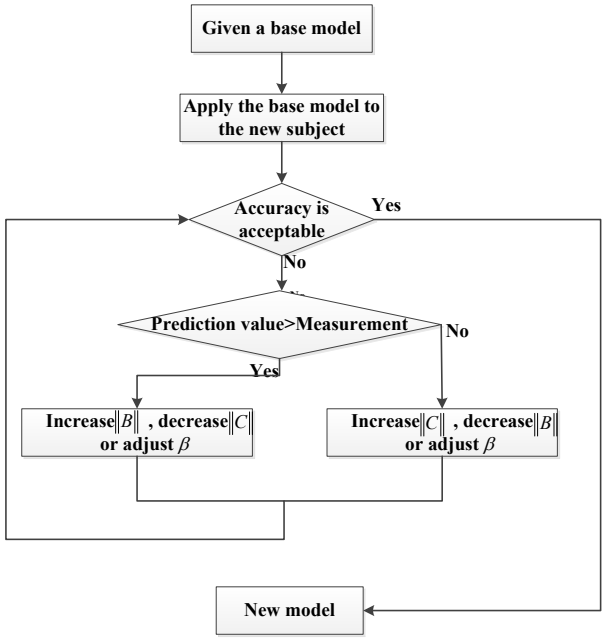

Fig. 2. The flowchart of new model development for new subjects

The flowchart of model parameter adjustment procedure is shown in Figure 2. The specific rapid modeling procedure is described as below.

(1), The base model is obtained by ordinary LS algebra based on a larger number of glucose and exogenous input data, which is described as shown in Eq. (1). The two inputs and bias term have different influences on glucose level. In general, insulin can decrease glucose level while meal will increase glucose level. The bias will compensate for the left prediction ability.

(2), The difference of input excitations between the old subject and a new subject should be evaluated so as to determine the adjustment direction of model parameters. For the new subject, only a small number of measurement data are available. In general, the available new data should cover information of inputs and their influences on glucose level so that the difference of input excitation between the old subject and the new subject can be captured and used to guide model parameter adjustment. First, the base model is directly applied to the new subject for glucose prediction with a small number of data with no customization. The predicted glucose values are indicated as $\hat{\mathbf{Y}}(N\times 1)$ and the measured glucose values are described as $\mathbf{Y}(N\times 1)$ where N is used to indicate the number of predicted glucose samples as well as that of measured glucose samples.

(3), The average values ($mean(\hat{\mathbf{Y}})$ and $mean(\mathbf{Y})$) are used to compare the predictions and measurements. The prediction errors are calculated as the difference between predicted and measured glucose values. Starting from the base model shown in Eq. (1), the specific adjustment action can be taken based on analysis of prediction errors:

(i) If $mean(\hat{\mathbf{Y}}) > mean(\mathbf{Y})$, which may result from the fact that the parameter of insulin in base model is comparatively smaller than the real value for the new subject or the parameter of meal in base model is comparatively larger than the real value for the new subject or the bias term is positively larger, increase the absolute parameter value of insulin ($\|B_{ins}\|$) or decrease the absolute parameter value of meal ($\|B_{meal}\|$) with the predefined step size so as to reduce the predicted glucose values;

(ii) If $mean(\hat{\mathbf{Y}}) < mean(\mathbf{Y})$, which may be caused by the oversized parameter of insulin, the undersized parameter of meal or the positively smaller bias term in base model than the real value for the new subject, decrease the absolute parameter value of insulin ($\|B_{ins}\|$) or increase the absolute parameter value of meal ($\|B_{meal}\|$) with the predefined step size so as to increase the predicted glucose values;

(iii) If $mean(\hat{\mathbf{Y}}) = mean(\mathbf{Y})$, no model adjustment is needed.

During the model parameter adjustment, the other model parameters should stay invariable when one parameter is adjusted. The model parameter of insulin is first regulated with the predefined step size until prediction errors can not be further reduced; then keep it invariable and regulate the model parameter of meal CHOs until prediction error can not be reduced. Also, the above regulation should be iteratively implemented as shown in Figure 2 for the two inputs until the convergence requirement is met which is in general set to be the improvement of prediction accuracy.

In general, a smaller step size means more steps are required to reach the target but the corrected parameter value may be more close to the real value. In contrast, a larger step size means fewer steps are required to reach the target value but the corrected parameter value is easy to go far from the real parameter value. Therefore, the step size reflects the compromise between model accuracy and adjustment complexity. A larger step size can be chosen at the beginning of adjustment process and then a smaller step size should be used when the parameter is around the target as indicated by the improvement of prediction accuracy.

2.3 Prediction Performance Evaluation

In order to evaluate the feasibility of developing a new model for new subjects using model migration, two approaches are considered and compared:

a) *Model migration with a small number of data (MM)*: The new prediction model is obtained by model parameter adjustment based on a base model for one old subject. After model migration, this updated model is then used to make glucose predictions for the new subjects.
b) *Subject-dependent model development with a large number of data (SM)*: A large number of data are used for new model development for new subjects using standard LS algebra without using the information from base model. The new identified model is then used to make glucose predictions for the new subjects.

For ARX modelling, the exogenous inputs are transformed using two different second-order transfer functions (Grosman et al., 2010), producing time-smoothed inputs. In this way, the effects of the two inputs can be separated to a certain extent, which facilitates the model identification.

We want to check whether an ARX prediction model can be rapidly obtained by simple model parameter adjustment based on a smaller number of data and whether it is comparable to the subject-dependent models developed from a larger number of data. In order to evaluate the glucose prediction performance, three metrics are used: 1). Root-mean-square error (RMSE (mg/dL)) (Gani A et al., 2010) which is a frequently used measure of the differences between values predicted by a model or an estimator and the values actually observed. 2). Rate Error Grid Analysis (R-EGA) (Kovatchev et al., 2004) which assesses the prediction ability to capture the direction and rate of glucose fluctuations. It has a clinical meaning similar to the original EGA (Clarke and Kovatchev, 2008). 3). Time lag which is defined as the time difference between a measured hyperglycaemia/hypoglycaemia episode and a predicted one. Also, sensitivity (Eren-Oruklu et al., 2010) of a method to predict abnormal glucose event is calculated to evaluate the prediction performance.

3. SIMULATION AND DISCUSSION

As a proof-of-concept study, the simulated data are generated from the FDA-accepted University of Virginia/University of Padova (UVA/Padova) metabolic simulator with a 5 min sampling interval (Kovatchev et al., 2009). It includes a three-meal scenario for breakfast, lunch, and dinner taken at approximately 7:00, 12:00, and 18:00 with 40g, 85g, and 60g CHOs, respectively. Three cases are considered to assess the performance of the model migration method:

Case I: Bolus insulin was given simultaneously with CHOs based on the "optimal" subcutaneous (SQ) insulin bolus.

Case II: Bolus insulin was given half an hour later after meal was taken based on the "optimal" subcutaneous (SQ) insulin bolus.

Case III: Bolus insulin was given an hour later after meal was taken based on the "optimal" subcutaneous (SQ) insulin bolus.

Thirty *in silico* subjects are chosen as representatives and four days of data are simulated for each subject. Thirty min ahead glucose prediction is used to evaluate prediction performance. A preliminary investigation is made for subject-dependent ARX models where the model orders and time delays for two different inputs are determined to achieve the best accuracy. Based on the results, the model orders for glucose, insulin and meals are set equal to 7, 1, and 1 sample, respectively. The input time delays of both bolus insulin and meal CHOs are set to be 5, which means $k_{ins} = 5$ and $k_{meal} = 5$. The base model is then developed using LS algorithm for one *in silico* subject which is chosen randomly.

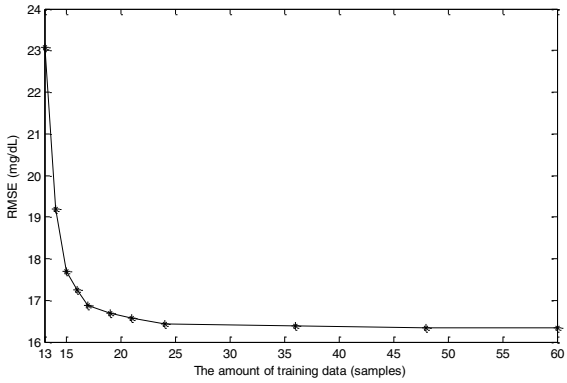

Fig. 3. The effect of the amount of training data on prediction performance for model migration method evaluated by average of RMSE values for 30 *in silico* subjects and Case II

For each new subject, rapid model development is performed. Based on the adjustment strategy described in subsection 2.2, new prediction model is rapidly identified for the new subject. The new model is then applied to the other data of the new subject to evaluate the prediction accuracy. Figure 3 shows the influence of the amount of training data (N_{tr}) on the prediction accuracy for Case II where the new model is developed and then tested based on data from the same case. For 30 min ahead glucose prediction, RMSE index is used to evaluate the prediction accuracy and its average is calculated for 30 *in silico* subjects and one day of testing data. When N_{tr}=13, only one 30min-ahead glucose prediction value is available for model parameter adjustment. With the increase of the amount of training data, the prediction accuracy is improved since more glucose prediction values are available for model migration. However, after N_{tr}=24 samples (two hours), the prediction accuracy almost stays invariable based on the RMSE metric. The difference between the case using N_{tr}=24 and the other cases using a larger N_{tr} is not statistically different based on a paired *t*-test (α=0.05) (Montgomery and Runger, 2006). For Case I and Case III, the same conclusion can be drawn. Therefore, for the subsequent rapid model development, a value of N_{tr}=24 is used from which 12 prediction samples are available to guide the adjustment of model parameters.

Using models developed based on training data from Case II, comparisons of the measured and predicted glucose profiles are shown in Figure 4 for model migration method and subject-dependent modelling method. These results are for two different subjects and one day of testing data from

Case II. In general, the evolving glucose trends are captured by both methods and the difference of prediction accuracy is not statistically significant based on a paired *t*-test (α=0.05) (Montgomery and Runger, 2006).

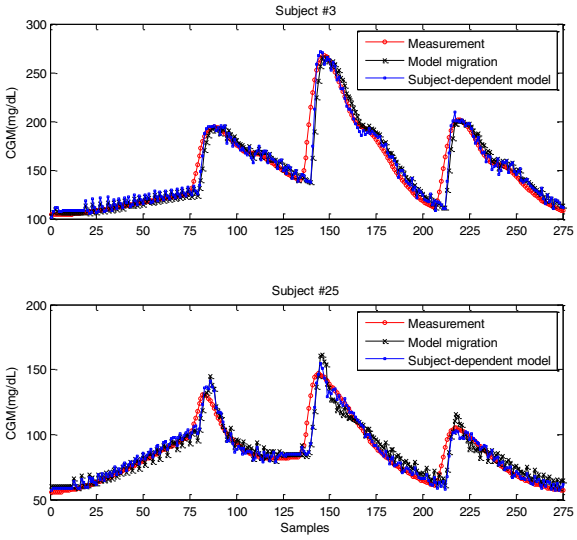

Fig. 4. Comparison of representative measured and 30 min predicted glucose profiles for Subjects #3 (top) and #25 (bottom) and Case II based on model migration method and subject-dependent modelling method

Table 1 and Table 2 summarize the model prediction accuracy of two different methods for 30 *in silico* subjects and 30 min ahead predictions. Three metrics, RMSE (mg/dL), R-EGA (%) in zone A, and time lag of hyper/hypo alarms plus sensitivity, are used to evaluate the prediction performance. For model development, three cases are considered where measurement data from Case I, II and III are chosen as training data respectively. Then the developed models are tested based on one-day data from Case II. In this way, the model generalization ability can be studied. For model migration method, 24 samples (two hour) from each case are used as training data for model adjustment. For subject-dependent modelling method, three days of simulated data covering 864 samples from each case are used as training data. Clearly, the number of data used for model migration method is much smaller than that used for subject-dependent modelling method. For both methods, the testing results using models from Cases II and III indicate good prediction generalization ability for Case II. Also two methods in general show comparable prediction accuracy for Cases II and III although the proposed model migration method may give slightly lower accuracy. However, when the models are developed from Case I and then tested for Case II, the proposed model migration method shows much better prediction results than subject-dependent modelling method as indicated by RMSE index and Sensitivity. For subject-dependent modelling method, the testing results indicate that it may not present good generalization ability from Case I to Case II.

In order to analyze the difference between two methods for Case I, predicted profiles are compared with measured profiles for Subjects #2 and #29 and one day of testing data as shown in Figure 5. The models are developed based on training data from Case I and then tested for data from Case II. For subject-dependent modelling method, the predicted profiles are quite different from measured glucose values, failing to capture the true glucose trends. In particular, the predictions are especially bad around the glucose peaks. It reveals that input parameters of subject-dependent models which reflect the glucose response to inputs in Case II are not suitable to reflect the glucose dynamics in Case I.

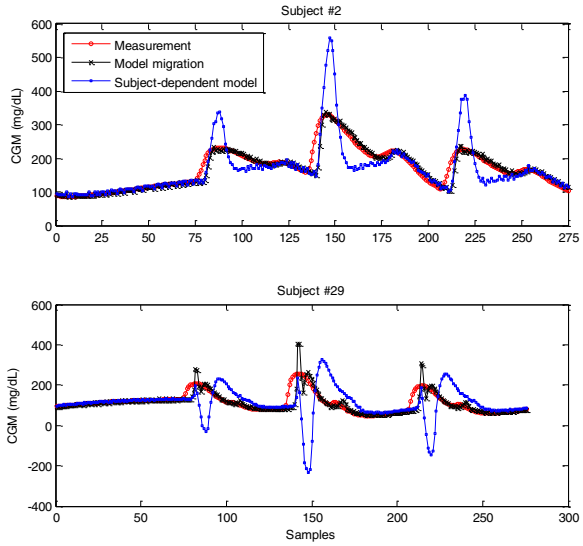

Fig. 5. Comparison of representative measured and 30 min predicted glucose profiles for Subjects #2 (top) and #29 (bottom) and Case I based on model migration method and subject-dependent modelling method

Based on the results, subject-dependent modelling method may not present good generalization ability when the conditions for training data and testing data are different. That is, the model parameters may overfit to the training case but fail to reveal the response relationship in testing case. In contrast, the proposed model migration method shows good generalization ability. It may result from the fact that the parameters are obtained by simple adjustment based on a small number of training data which thus may overcome the overfitting problem to a certain extent.

4. CONCLUSIONS

In this paper, a rapid and economic modeling method is developed using the idea of model migration. Starting from a base model for one old subject and a small number of data for new subjects, the input parameters of base model are properly adjusted to capture the difference between the old subject and new subjects. A new prediction model is thus readily obtained and used for online short-term ahead glucose prediction in type 1 diabetes mellitus. The results indicate that the prediction accuracy of the rapid modeling method is comparable to that for subject-dependent modeling method for some cases. Also, model migration method presents better generalization ability. The proposed method can be regarded as an effective and economic modeling method instead of repetitive subject-dependent modeling method. Besides, these

promising analyses results encourage extensions of this research methodology for the specific purpose of glucose control in future.

ACKNOWLEDGEMENTS

This work is supported by the National Natural Science Foundation of China (No. 61273166), Program for New Century Excellent Talents in University (NCET-12-0492), Zhejiang Provincial Natural Science Foundation of China (LR13F030001) and Specialized Research Fund for the Doctoral Program of Higher Education of China (20120101120182).

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Table 1. Prediction accuracy for thirty *in silico* subjects and 30 min glucose predictions using model migration method (mean ± standard deviation)

Case No. For training data	RMSE (mg/dL)	R-EGA (% in zone A)	Time Lag for hyper event (samples)	Sensitivity for hyper event (%)	Time Lag for hypo event (samples)	Sensitivity for hypo event (%)
Case I	16.59±10.47	79.53±2.40	3.12±0.90	77	4.76±1.65	79
Case II	16.42±10.35	79.60±2.39	3.12±0.90	76	4.76±1.65	79
Case III	16.48±10.33	79.60±2.44	2.94±0.80	78	4.76±1.65	79

Table 2. Prediction accuracy for thirty *in silico* subjects and 30 min glucose predictions using Subject-dependent standard modeling method (mean ± standard deviation)

Case No. For training data	RMSE (mg/dL)	R-EGA (% in zone A)	Time Lag for hyper event (samples)	Sensitivity for hyper event (%)	Time Lag for hypo event (samples)	Sensitivity for hypo event (%)
Case I	28.14±24.78	79.70±10.92	2.79±0.62	63	3.48±2.06	70
Case II	14.17±8.61	77.70±10.50	2.38±1.12	85	4.10±2.36	82
Case III	14.90±9.09	76.01±10.58	2.58±1.09	83	5.20±0.84	82