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Effect of Intra-Patient Variability on Personalized Parameters of Glucose-Insulin Dynamic Models for Exercise, Meal, and Insulin Interventions

Naviyn P Balakrishnan*, Lakshminarayanan Samavedham **, Gade P Rangaiah ***

, **, * Department of Chemical and Biomolecular Engineering, National University of Singapore, Singapore*
** (e-mail: naviyn@ nus.edu.sg); ** (e-mail: chels@nus.edu.sg); *** (*Phone: +65 6516 2187; *e-mail: chegpr@ nus.edu.sg)*

Abstract: The objective of this paper is to study the effect of intra-patient variations on the personalized parameters of the modified exercise minimal model by re-estimating them from the clinical data measured after several days of first estimation. Clinical data of eight type 1 diabetic children and adolescents have been used for this purpose. For the first estimation of 6 estimable parameters, clinical data collected during one of the visits have been employed. Subsequent re-estimation of parameters is accomplished using the second clinical visit data, which was collected after 7-35 days from the first visit. The results of re-estimation indicate that the estimable parameters corresponding to glucose-insulin compartments and meal absorption model are greatly affected by intra-patient variability in most of the patients, while the 2 estimable parameters corresponding to exercise compartments are least affected by intra-patient variations in 6 out of 8 patients.

Keywords: Parameter Estimation, Parameter Identification, Model reduction, Validation, Statistical Analysis, Uncertainty

1. INTRODUCTION

Inter- and Intra-patient variations in the glucose homeo-stasis emphasize the need for development of personalized models in diabetics. Since diabetes is a lifestyle disease, factors like exercise and meal play a major role in determining the blood glucose (G) levels of patients. Personalized models incorporating these lifestyle interventions along with the insulin interventions will be useful in devising optimal patient specific treatment strategies that can prevent various short and long term complications in diabetics. This indeed will transform the conventional reactive treatment practices towards a proactive mode.

Many glucose prediction models have been developed since early 1960s. These models can be broadly classified as mechanistic or knowledge driven models and empirical or data driven models. A comprehensive review of both the classes of G prediction models developed for type 1 diabetics (T1Ds) can be seen in Balakrishnan et al. (2011). There is also a special class of models which involve both the mechanistic and data driven models, known as hybrid models (Balakrishnan et al., 2012, Balakrishnan, 2013, Mougiakakou et al., 2006, Zarkogianni et al., 2011).

Most of the available mechanistic glucose-insulin dynamic models have considered only meal and insulin interventions in them. There are also few models which included the exercise effect on glucose-insulin dynamics (Kim et al., 2007, Lenart and Parker, 2002, Roy and Parker, 2007). The exercise effect models of Kim et al. (2007) and Lenart and Parker (2000) are too complex to be tailored as patient specific models. Moreover, these two models were only validated for healthy subjects. Although the minimal exercise model of Roy and Parker (2007) was validated for T1Ds, the model did not consider the cohorts of children and adolescents where the T1D population is prevalent. Further, it follows a one-size-fits-all assumption for the parameters related to glucose and insulin compartments. In other words, full minimal exercise model was not estimated and validated using the meal, insulin and exercise data of diabetics. One common aspect in all the exercise effect models is that the exercise intensity in these models is quantified using a measure called percentage oxygen consumption ($PVO_2^{\max}$). Measurement of $PVO_2^{\max}$ requires sophisticated devices like treadmills and electronic bicycles, which are not affordable in the day-to-day life settings of diabetics. This shows the need for alternative exercise markers in these models.

In order to overcome the above mentioned issues, in one of our research articles, we have identified, estimated and validated personalized mechanistic and hybrid models for exercise, meal, and insulin interventions in T1D children and adolescents (Balakrishnan, 2013). Rate of Perceived Exertion (RPE) has been used as an alternative exercise marker. The cross validation results in our recent work indicated that the personalized mechanistic models are not good in predicting the glucose dynamics after 7-35 days of first estimation. We have not re-estimated the mechanistic models to study the consequences of intra-patient variability on the first estimates of parameters. Hence, the major objective of this paper is to investigate the influence of intra-patient variability on the personalized parameters of the modified exercise minimal model, which we have identified and validated recently (Balakrishnan, 2013). Clinical data of eight T1Ds have been used from the public access database, DirecNet (2005). There were two clinical visits where each visit lasted from lunch till dinner; the

meals were given as in home settings and exercise was performed at around 4:00 pm. Exercise sessions lasted for a period of 75 min in 4 phases with 5 min resting period in between each phase. *G* readings were recorded for every 5 minutes using Continuous Glucose Monitoring Sensors (CGMS). A basic difference between both the visits was that the basal insulin supply was stopped during exercise in one of the visits and continued during exercise in the other visit. The details of meal, insulin, exercise and *G* data can be found in the Excel sheets of DirecNet study's (2005) website.

2. RESEARCH DESIGN AND METHODS

Overall methodology can be divided into two major parts: first estimation and re-estimation. Sub-section 2.1 outlines various steps involved in the first estimation of personalized parameters and sub-section 2.2 explains the steps in the re-estimation of model parameters.

2.1 First Estimation of Personalized Models

The first part of methodology involves identification and estimation of personalized parameters of glucose-insulin dynamic model using the clinical data of the first clinical visit. In our recent work (Balakrishnan, 2013), we have accomplished a similar objective for 34 T1Ds by using 80% data obtained from one clinical visit, while the remaining 20% data of the same visit were used for same day validation. In this sub-section, we have followed the same procedures to estimate patient-specific parameters of 8 T1Ds using the 100% data of the first clinical visit. An outline of the steps involved in this process is discussed in sub-sections 2.1.1 – 2.1.3. A detailed explanation on this can be found in our work (Balakrishnan, 2013).

2.1.1 Modified Exercise Minimal Model

The original exercise minimal model of Roy and Parker (2007) involves nine compartments, whose mathematical representation and the nominal parameter values of the original model can be found in the cited paper. The important modifications on this original model are:

[A] Introduction of RPE as Exercise Marker: Roy and Parker (2007) employed $PVO_2^{\max}$ as a marker to quantify the exercise intensity. However, as mentioned in the introduction part of this paper, measurement of $PVO_2^{\max}$ is not affordable in the routine life settings. RPE can be seen as a potential alternative which can be measured via simple speech tests. The validity of RPE in children and adolescents using pictorial scales has been tested successfully in the literature (Roemmich et al., 2006, Utter et al., 2002). We have modeled the linear relationship between RPE and $PVO_2^{\max}$ using the data from Roemmich et al. (2006), as:

$$PVO_2^{\max} = \begin{cases} 1(\%RPE) + 13.1; \text{ (Girl)} \\ 1.2(\%RPE) + 9.6; \text{(Boy)} \end{cases} \quad (1)$$

The intercept values in equation (1) show that the basal PVO_2^{max} values vary according to the gender. Hence, the 8% basal PVO_2^{max} value used in Roy and Parker's model (2007) will be replaced by gender specific basal values (given by the intercepts of equation (1)). More detailed explanation on this linear relationship can be found in our work (Balakrishnan, 2013).

[B] Meal and Insulin Absorption Models: The meal absorption dynamics of the modified exercise minimal model is explained by Hovorka's meal absorption model (Hovorka et al., 2004), which models the pre-intestinal and intestinal carbohydrate absorption using a single lumped analytical equation. On the other hand, the total insulin absorption in a day is given by the sum of basal and bolus insulin doses. Since the basal insulin supply in DirecNet exercise patients was via insulin pumps, there was a continuous availability of exogenous insulin in plasma throughout the day. In the case of bolus insulin, the absorption kinetics is described by Berger's kinetic model (Berger and Rodbard, 1989, Nucci and Cobelli, 2000).

2.1.2 A Priori Identifiability Analysis

Identifiability analysis has often been seen as a pre-requisite for parameter estimation, which helps in identifying the subset of estimable parameters in a model structure based on the scaled sensitivity matrix of measured state. Yao et al.'s (2003) methodology of a *priori* identifiability analysis is employed here. The modified exercise minimal model has 16 parameters in it, including the 3 parameters of Hovorka's meal absorption model. This can be represented as:

$$\theta = \begin{bmatrix} p_1 & p_2 & p_3 & p_4 & V_G & n & t_{max,G} & f \\ T_1 & k & a_1 & a_2 & a_3 & a_4 & a_5 & a_6 \end{bmatrix} \quad (2)$$

In the current system, $G(t)$ is the only measured state, and hence, the scaled sensitivity matrix (G_{ss}) is given by:

$$G_{ss} = \theta \frac{\partial G}{\partial \theta} = \begin{bmatrix} p_1 \frac{\partial G}{\partial p_1}\Big|_{t=0} & p_2 \frac{\partial G}{\partial p_2}\Big|_{t=0} & \cdots & a_6 \frac{\partial G}{\partial a_6}\Big|_{t=0} \\ p_1 \frac{\partial G}{\partial p_1}\Big|_{t=5} & p_2 \frac{\partial G}{\partial p_2}\Big|_{t=5} & \cdots & a_6 \frac{\partial G}{\partial a_6}\Big|_{t=5} \\ \vdots & \vdots & \cdots & \vdots \\ p_1 \frac{\partial G}{\partial p_1}\Big|_{t=t_f} & p_2 \frac{\partial G}{\partial p_2}\Big|_{t=t_f} & \cdots & a_6 \frac{\partial G}{\partial a_6}\Big|_{t=t_f} \end{bmatrix} \quad (3)$$

Parameters are ranked iteratively based on the largest column sum of the scaled sensitivity matrix. Details of steps involved in iterative ranking of parameters can be found in Yao et al. (2003). Once the ranking of all model parameters is over, the percentage contribution of each ranked parameter is calculated based on the column sum. A cut-off limit of 95% has been set to select the possible subset of estimable parameters, which is denoted as θ_{est}.

2.1.3 Parameter Estimation and Uncertainty Calculation

The parameters identified in sub-section 2.1.2 are estimated using the clinical data of 8 DirecNet children and adolescents. 100% of clinical data collected during one of the visit days have been used for first estimation. The objective is to minimize the mean squared error (Skrovseth et al.) between the clinical data and model predicted values, which can be formulated as:

$$\underset{\theta}{Min}\ MSE = \sum_{i=1}^{ns} \frac{(G_{\text{real}}(i) - G_{\text{pred}}(i))^2\Big|_{t_i = t_{\text{ns}}}}{ns - np} \qquad (4)$$

$$s.t.\ \theta_{\text{est}} > 0$$

where *ns* and *np* are the total number of samples and number of estimable parameters, respectively. Parameter estimation is performed using fmincon solver in Matlab. Multistart optimization has been employed, which estimates parameters for 25 random initial guesses. The lowest MSE found is likely to be the global optimal solution, and so the corresponding parameter estimates are selected. Statistical significance and precision of the obtained point estimates have been evaluated by calculating confidence intervals (CIs) of each personalized parameter in θ_{est} using the k^{th} diagonal term in the covariance matrix (V_{kk}) and t-test. The uncertainty in estimated parameters (as $\Delta\theta_{\text{est}}$) can be computed as:

$$\Delta\theta_{\text{est}} = \sqrt{V_{\text{kk}}} * t_{1\text{-}\alpha/2} * (ns - np)$$

$$\text{where, } V_{\text{kk}} = \left[\left(G_{sens,\theta_{\text{est}}} \right)^T \left(G_{sens,\theta_{\text{est}}} \right) \right]^{-1} \qquad (5)$$

$G_{\text{sens},\theta\text{est}}$ in equation (5) refers to the sensitivity matrix of the measured state variable with respect to the estimable parameters in θ_{est}.

2.2 Re-estimation of Personalized Models

The personalized models are simulated for input conditions of second visit day using the point estimates obtained in sub-section 2.1. The resulting *G* predictions are compared with the real *G* values to check the validity of the first estimated parameters in predicting G dynamics after several days from their initial estimation. Also, the clinical data of the second day visit have been used to re-estimate the model parameters using multistart optimization approach for 25 different initial guesses. In a similar manner as that of first estimation, MSE and uncertainty values are calculated for re-estimation. The re-estimation is performed to understand if there are any intra-patient variations in the personalized parameter estimates after few days from the first estimation.

3. RESULTS AND DISCUSSION

3.1 A priori Identifiability Analysis

A priori identifiability analysis has revealed that the cumulative sum of 6 out of 16 parameters show a contribution of up to 96% (which is just above the cut-off percentage); while the remaining 10 parameters have shown only 4% contribution. Among the 6 estimable parameters, 2 of them are related to insulin and glucose distribution volumes (p_4 and V_G, respectively), 1 parameter is related to meal absorption dynamics ($t_{\text{max,G}}$), 2 of them are related to exercise effect compartments (a_3, and a_4) and 1 parameter is related to insulin disappearance (p_2) in remote compartment. Inverse of insulin distribution volume has been found to be the most estimable parameter with a contribution of about 57%, followed by $t_{\text{max, G}}$, V_G, a_3, a_4, and p_2. These are identified as the estimable parameters (θ_{est}) of the modified exercise model and they are estimated for each patient as personalized parameters. Hence, this analysis has reduced the model from its original 16 parameters to 6 parameters. A detailed description on the individual percentage contribution of the 6 parameters can be seen in our upcoming paper (Balakrishnan, 2013)

3.2 Estimation of Personalized Parameters

The six estimable parameters are estimated for each patient using multistart optimization approach with 25 different initial guesses. The lowest MSE values corresponding to the best parameter estimates appeared at least thrice (among 25 solutions) in 8 patients, and are illustrated in Fig. 1, which shows that the CGMS data of Patients 23 and 31 fits well to the model with a relatively low MSE of 17.3 $(\text{mg/dl})^2$, and 17.2 $(\text{mg/dl})^2$, respectively; whereas model for patient 29 shows a relatively high MSE value among the 8 patients tested. However, qualitative comparison of *G* plots in Fig. 2 shows that the fitted model of patient 29 captures the actual trends in a more or less similar manner as that of patients 23 and 31. One reason for high MSE value in patient 29 could be the fewer number of samples (as MSE value is dependent on the sample size). Although minor deviations from the actual blood glucose values are observed in all these patients, the fitted trends are closer to the actual trends in almost all these patients (see Fig. 2). One of the major reasons for the minor deviations might be the measurement errors prevalent in CGMS sensors.

The point estimates corresponding to the least MSE values of first estimation are illustrated in Fig. 3 (black circles with error bars denoting uncertainty). The point estimates of parameters vary from patient to patient, thereby confirming the inter-patient variability. Further, these estimates (black circles in Fig. 3) are almost the same as those of the estimates obtained for 80% of data in our recent work (Balakrishnan, 2013), whilst there are deviations in the $\Delta\theta_{\text{est}}$ values when compared to those of estimation with 80% data. Mostly, the precision of parameter estimates has been improved in case of using 100% data for estimation, as there is a drop in $\Delta\theta_{\text{est}}$ values.

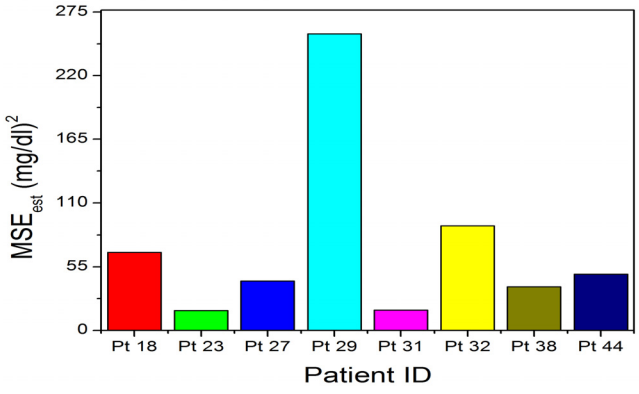

Fig. 1 Lowest MSE values (obtained after first estimation) corresponding to the best point estimates

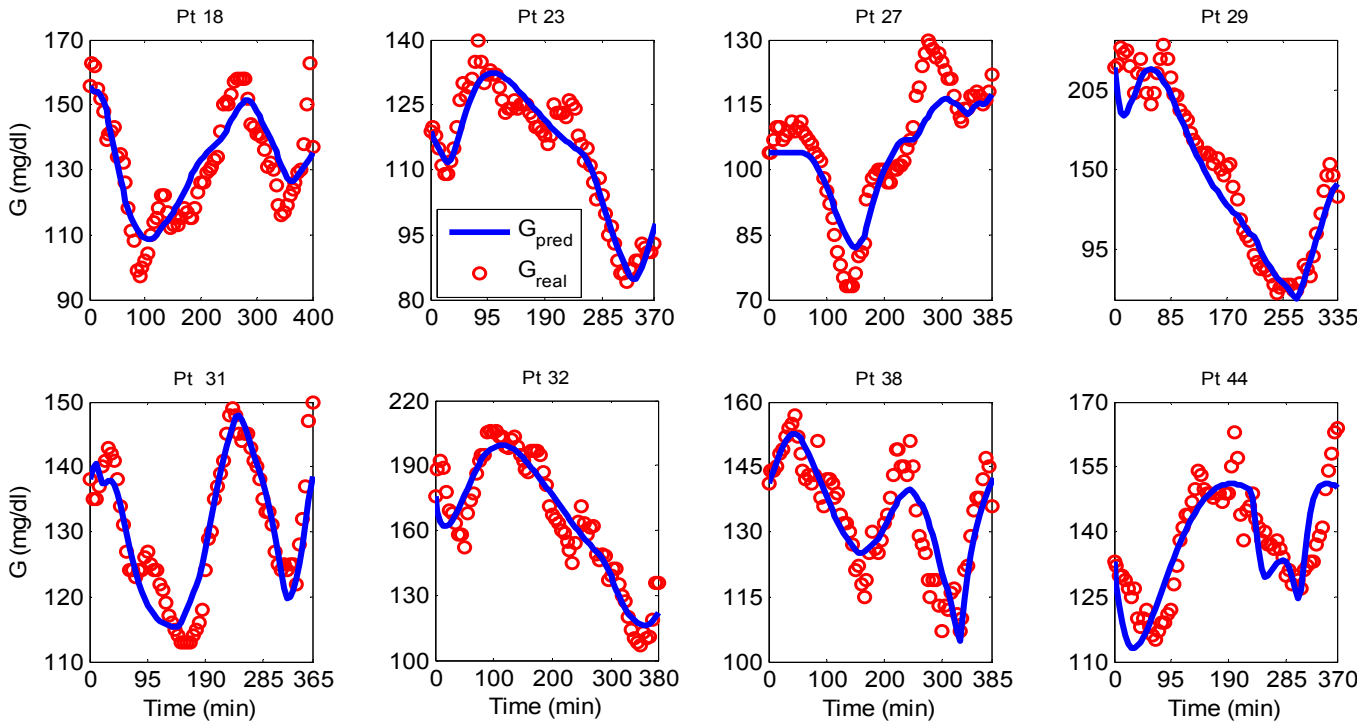

Fig. 2 Comparison between the actual and model fitted *G* trends after first parameter estimation

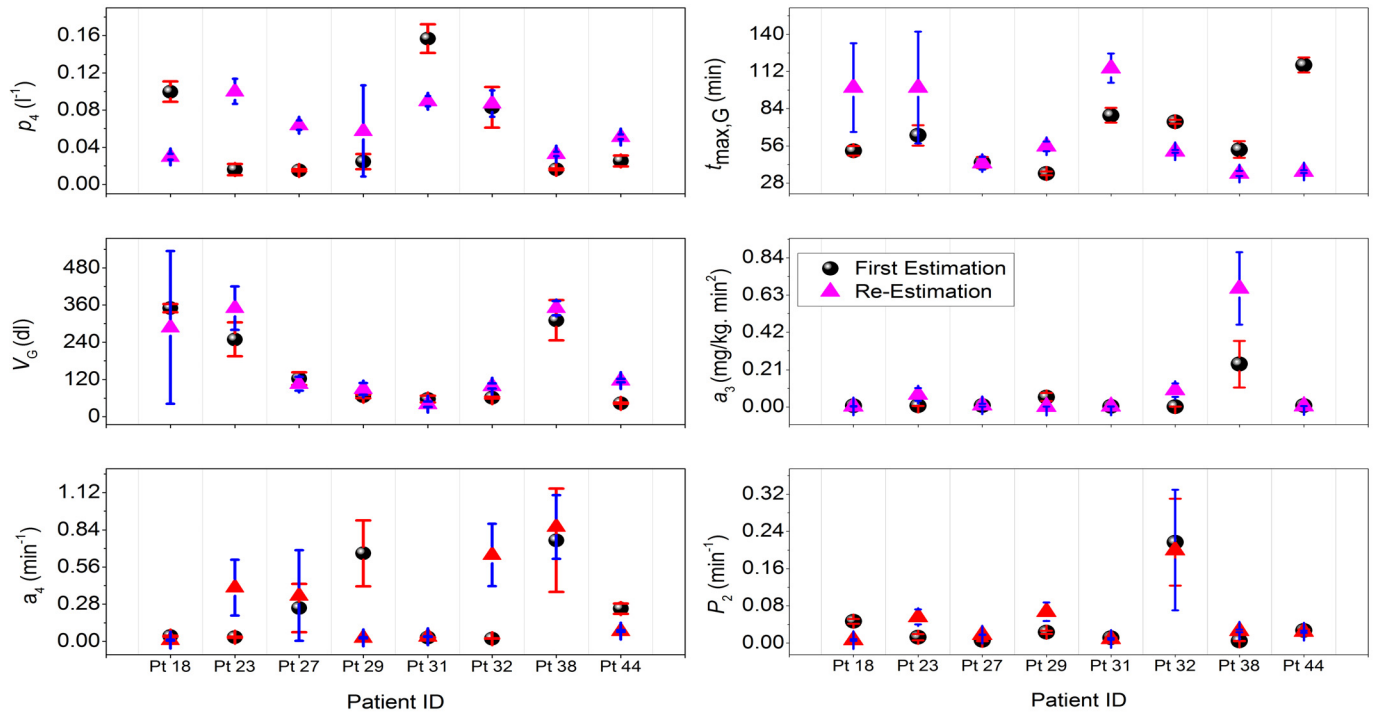

Fig. 3 Personalized point estimates after first estimation (circles) and re-estimation (triangles) of estimated parameters with CIs (capped lines: red lines denote the CIs of parameters after first estimation; blue lines represent the CIs of re-estimated parameters)

3.3 Re-estimation of Personalized Models

3.3.1 Simulation using first estimates

Simulation of personalized models (with the parameters estimated using first clinical visit data) for the input conditions of second clinical visit has revealed higher MSE values, ranging from 750 $(mg/dl)^2$ - 4000 $(mg/dl)^2$, in 7 out of 8 patients (see red dashed bars in Fig. 5). This is also reflected in the *G* dynamics (shown as blue dashed lines in Fig. 4), where huge deviations of predicted values from the actual values are observed. Despite these deviations, the crests and troughs (i.e., trends) of these predictions in majority of the patients (except exercise and post exercise phases of Patients 23 and 44) follow the same pattern as those of the real trends (represented as green circles in Fig. 4). This

shows that the dynamics are captured well but with poor accuracy in predicted *G* values. Such poor prediction is due to the gap between the two clinical visits, which is 7 - 35 days for patients in the DirecNet exercise cohort (2005). Hence, it is evident that the point estimates of personalized parameters obtained after first estimation are not valid to accurately predict the *G* values after a number of days. This reveals the need for frequent re-estimation of parameters for accurate prediction of *G* values along with the trends.

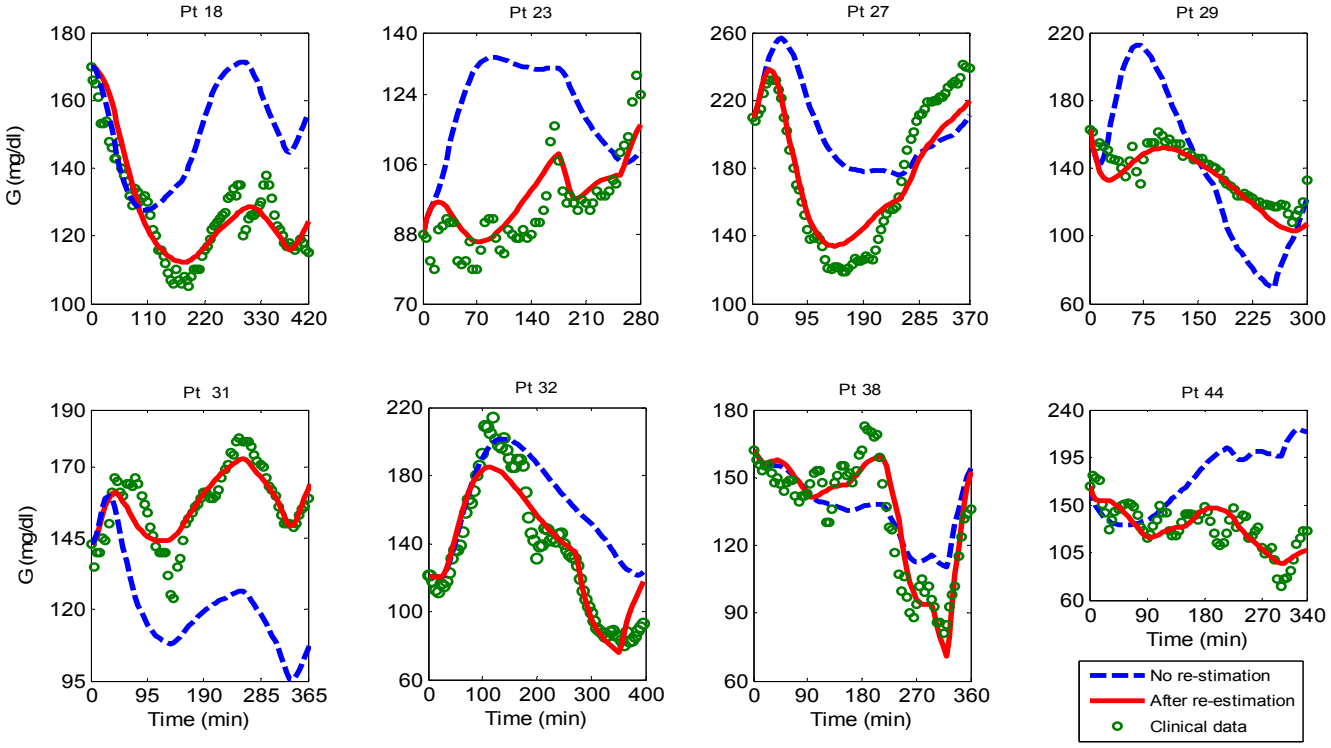

Fig. 4 Comparison between the actual *G* (circles), model predicted *G* using first estimates (blue dashed lines) and model fitted *G* after re-estimation (red continuous lines)

3.3.2 Re-estimation of personalized models

Owing to the inaccurate predictions by the personalized models in the sub-section 3.3.1, the 6 estimable parameters are re-estimated using the second clinical visit data. The lowest MSE value corresponding to the best point estimates (among the 25 estimates) obtained for 8 patients are shown in black bars in Fig. 5. In all these patients, MSE values corresponding to the re-estimation are very much lower than those obtained without re-estimation (Fig. 5). This can also be observed from the qualitative comparison plots of 8 patients in Fig. 4, which show that the fitted *G* trends after re-estimation (red continuous lines) is closer to the real trends (green circles) than the trends predicted with first estimates (blue dashed lines). Although the fitted *G* values after re-estimation are not completely devoid of deviations from the real values, these deviations are significantly lower when compared to that of the predictions without re-estimation.

The point estimates along with the CIs after re-estimation are illustrated as triangles with blue error bars in Fig. 3. The percentage change in the estimates of each parameter for all the 8 patients are shown in Fig. 6. Comparing the point estimates obtained after and before re-estimation, it can be inferred that there are significant changes (in most of the patients) in the point estimates of p_4, $t_{max,}$G, V_G and p_2, which shows that there is significant effect of intra-patient variability on the parameters related to glucose-insulin compartments and meal absorption model. This can also be understood by the percentage change plot in Fig. 6. In case of the two exercise compartment related parameters (a_3 and a_4), there is almost no or small change in their point estimates obtained for 6 out of 8 patients (except patients 23 and 32). It can also be inferred from Fig. 3 that re-estimation in some patients has increased the width of CIs (especially parameters p_4, $t_{max,}$G, VG).

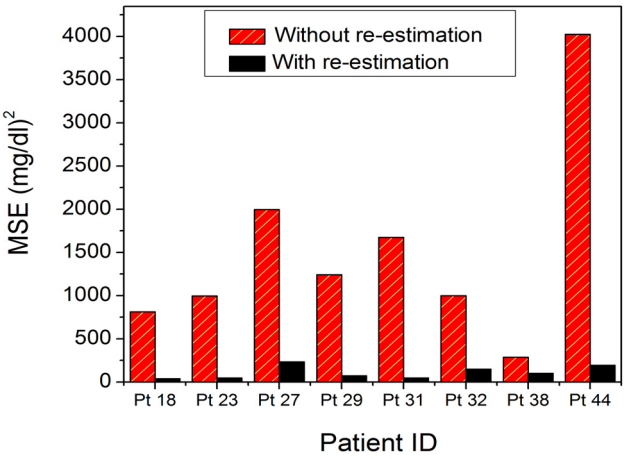

Fig. 5 MSE values calculated based on model predictions with and without re-estimation

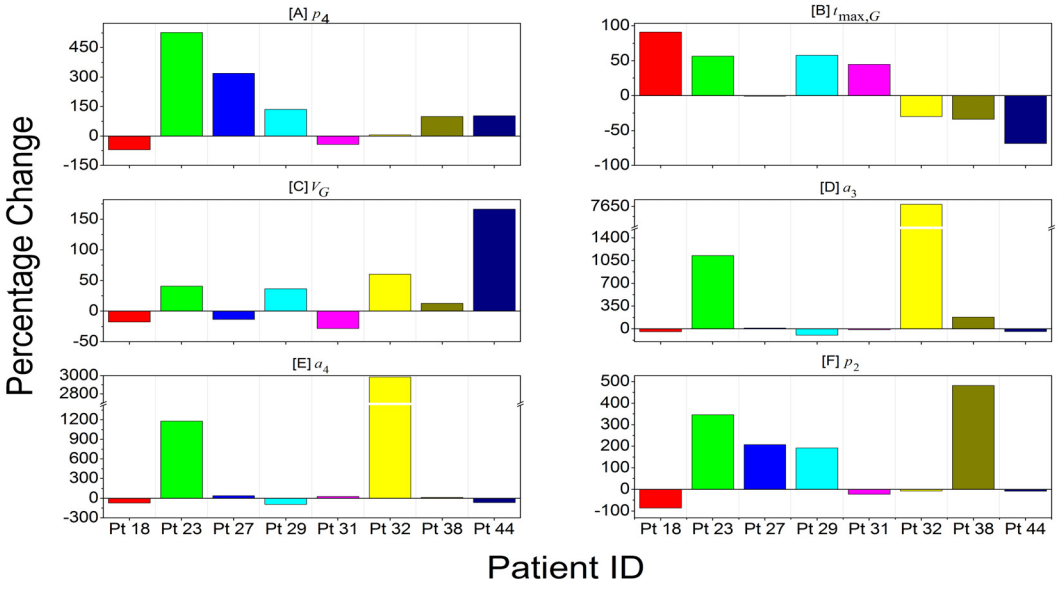

Fig. 6 Intra-patient variability based on percentage change in point estimates of personalized parameters after re-estimation

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