

Observer Based Plasma Glucose Prediction in Type I Diabetes

F. Ståhl and R. Johansson

Abstract—Recent years’ progress in the development of Continuous Glucose Monitors (CGM) has made rich well-sampled glucose data readily available. Reliable, frequent measurements are of utmost importance for the emerging closed-loop control of diabetic plasma glucose. However, these sensors do not measure the variable of primary interest - plasma glucose, but a delayed signal - the interstitial glucose. To overcome this difficulty this paper presents a novel model, merging a black-box model of the glucose dynamics together with a CGM sensor model. Using an observer the plasma glucose level is estimated and predicted. The outlined scheme was evaluated on one patient, with a significant sensor delay, from a clinical trial of the DIAdvisor European FP7-project. Using the raw signal from the CGM device together with meal and insulin infusion data predictions for 20, 40 and 60 min were produced for a breakfast meal. Results: RMSE of the prediction error was smaller than 26 mg/dl for validation data even for the longest prediction horizon and no points in the C/D/E zones in the pCGA evaluation. The model clearly outperformed the CGMS and the results indicate that the method could be used successfully.

I. INTRODUCTION

Diabetes mellitus is a chronic disease characterized by the inability of the organism to autonomously regulate the blood glucose level due to insulin deficiency or resistance. Health damages caused by impaired glucose fluctuations are various and serious and could be prevented by keeping as tight glucose control as possible. In recent years closed-loop glucose control has received a lot of attention, see e.g. [1]. The feedback channels considered for such control are the recently developed CGM systems. These systems do not provide direct information about the variable of interest - plasma glucose, but measure the interstitial glucose, thus creating a delay in the feedback loop. Apart from reliable measurements an accurate simulation model of the glucose-insulin system during meals and normal daily life is of major importance for the purpose of control design and implementation, e.g. in a Model Predictive Control (MPC) approach.

The purpose of this paper is to make predictions of future plasma glucose evolutions based on Continuous Glucose Measurements (CGM) and a modeling approach outlined below. The main novelty is the use of an observer to assess the plasma glucose value. Previous attempts at model-based prediction can be found in e.g. [2], [3], [4], [5]. For prediction

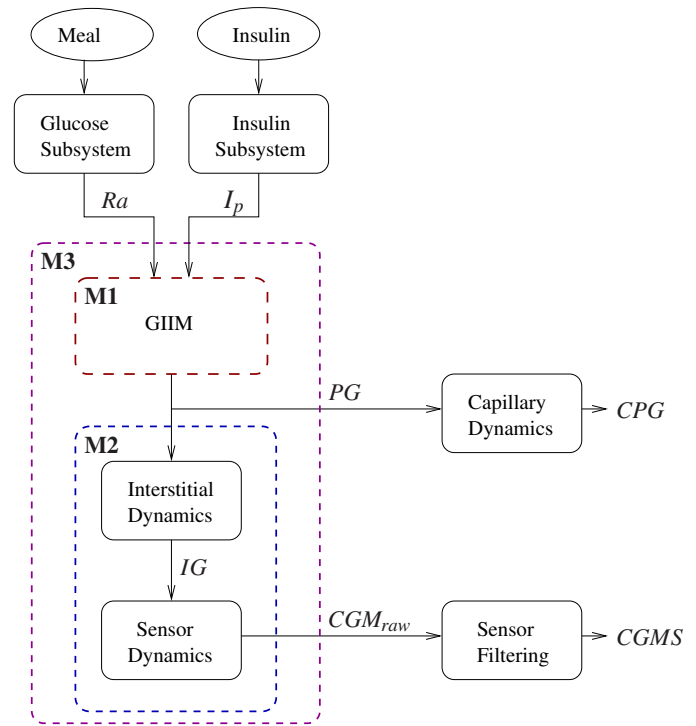


Fig. 1. Overview of the modeling approach. Notation: Plasma Glucose PG , Capillary Plasma Glucose CPG , Plasma Insulin I_p , Rate of Glucose Appearance following a meal R_a .

based on CGM time series analysis, see for example [6].

The modeling approach is based on a framework depicted in Fig. 1. The modeling consists of a number of modules; each representing one part of the overall glucose dynamics. Due to the lack of data, empirical identification of each module is difficult, resulting in merged models or that assumptions have to be made on intermediate model levels. A nice summary of PK models for insulin diffusion following a subcutaneous injection is found in [7]. Modeling the digestion process and the flux of glucose from the gut from a meal has been initiated in [8]. The module called Glucose-Insulin Interaction Model (GIIM) has received a lot of attention both from physiological modeling point of view, [9], [10], and using black-box approaches [2], [3], [4], [5]. The capillary and sensor characteristics of the finger-stick measurement sensors are generally disregarded (and the delay is indicated to be small [11]). The interstitial and CGM sensor dynamics have been investigated assuming a first-order diffusion model [12] and [13]. In [13], the plasma glucose level is recovered from

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the CGM signal using deconvolution and in [14] an early attempt at observer based estimation was presented. However, so far (to the best of the authors' knowledge) no attempts have been made on merging them all the modules together for the purpose of plasma glucose prediction.

In this paper, two parts of the total model are addressed: the GIIM and the interstitial and sensor dynamics (here treated as one model, see [15] for a brief discussion on the contribution of each term to the delay). Each model is identified separately and thereafter merged together into one single grey-box model, and using an observer the plasma glucose evolution is predicted ahead using the raw sensor output.

II. GLUCOSE AND INSULIN DISPERSION SUBMODELS

To retrieve the intermediate signals R_a and I_p models from the literature [7], [8] was applied using average population parameters.

III. GIIM MODELING - M1

Denoting the plasma glucose PG and raw CGM signal CGM_{raw} :

$$\gamma = \begin{bmatrix} y \\ z \end{bmatrix} = \begin{bmatrix} PG \\ CGM_{raw} \end{bmatrix} \quad (1)$$

and the filtered inputs $u = [I_p \ R_a]^T$ the GIIM is modeled with a discrete-time state space model \mathbf{M}_1 .

$$x_{k+1} = A_1 x_k + B_1 u_k + \omega_k \quad (2)$$

$$y_k = C_1 x_k + v_k \quad (3)$$

where ω is process noise and v is the fingerstick measurements noise with covariances:

$$E \left\{ \begin{pmatrix} \omega \\ v \end{pmatrix} \begin{pmatrix} \omega \\ v \end{pmatrix}^T \right\} = \begin{bmatrix} Q_1 & 0 \\ 0 & R_1 \end{bmatrix} \quad (4)$$

The order is determined using the Akaike criterion, [16].

IV. INTERSTITIAL AND SENSOR MODEL - M2

The dynamics between blood glucose and interstitial glucose, as measured by the sensor, is modeled as an ARX-process.

$$A(z) \cdot z(k) = B(z) \cdot y(k-d) + e(k) \quad (5)$$

where A , B are polynomials of the zero-order-hold operator z , d is a delay, and $e(k)$ is the CGM measurement noise. The model orders n_A , n_B and d evaluated for values according to Table I are determined using the MDL criterion. The choice of evaluated model orders covers the compartment model suggested in [17].

TABLE I
EVALUATED MODEL ORDERS

Parameter	Value
n_A	1-2
n_B	1-2
d	5-20 min

V. MODEL MERGING - M3

Converting the sensor ARX model into a state-space model $\mathbf{M}_2 : \{A_2, B_2, C_2\}$ with process and measurement noises Q_2 and R_2 , the GIIM and sensor models are merged into one model $\mathbf{M}_3 : \{A_3, B_3, C_3\}$ with the augmented state vector ξ and the output γ .

$$\begin{aligned} A_3 &= \begin{bmatrix} A_1 & 0_{[n_{A_1} \times n_{A_2}]} \\ B_2 \cdot C_1 & A_2 \end{bmatrix}, & B_3 &= \begin{bmatrix} B_1 \\ 0_{[n_{A_2} \times 2]} \end{bmatrix} \\ C_{33} &= \begin{bmatrix} C_{31} \\ C_{32} \end{bmatrix} = \begin{bmatrix} C_1 & 0_{[1 \times n_{C_2}]} \\ 0_{[1 \times n_{C_1}]} & C_2 \end{bmatrix} \\ Q_3 &= \begin{bmatrix} Q_1 & 0 \\ 0 & Q_2 \end{bmatrix}, & R_3 &= \begin{bmatrix} R_1 & 0 \\ 0 & R_2 \end{bmatrix} \end{aligned}$$

VI. STATE ESTIMATION AND SENSOR FUSION

Data is available on different rates from the two measurement devices, and at least from the finger-stick measurements, in a non-equidistant manner. Thus, combinatorially there are 3 (4) possibilities; (1) data from both, (2) Data from HemoCue and (3) Data from the CGM sensor, ((4) No data). This calls for having three different systems to switch in between - each with a specific observer. Solving the Riccati equation for the three systems $\mathbf{M}_{31} : \{A_3, B_3, C_{31}\}$, $\mathbf{M}_{32} : \{A_3, B_3, C_{32}\}$, $\mathbf{M}_{33} : \{A_3, B_3, C_{33}\}$ three corresponding stationary Kalman gains K_i $i \in \{1, 2, 3\}$ are retrieved.

$$P_i = A_3 P_i A_3^T + Q_i \quad (6)$$

$$K_i = A_3^T P_i C_i (C_i P_i C_i^T + R_i)^{-1} \quad (7)$$

where Q_i is the covariance of the process noise and R_i is the measurement covariance in the i :th system.

The boolean variables δ_1 and δ_2 are used to keep track of which signal that is present in the feedback. Using these switching variables the measurement update and the prediction update can be written in compact notation:

$$\Delta = \begin{bmatrix} \delta_1 & 0 \\ 0 & \delta_2 \end{bmatrix} \quad (8)$$

$$K_{12} = [K_1 \ K_2] \quad (9)$$

$$\delta_{max} = \max(1 - \delta_1, 1 - \delta_2) \quad (10)$$

$$K = \delta_{max} \cdot K_{12} + (1 - \delta_{max}) \cdot K_3 \quad (11)$$

$$\xi_{k+1} = A_3 \xi_k + K \cdot \Delta \cdot (\gamma_k - C_3 \xi_k) \quad (12)$$

$$\gamma_k = C_3 \xi_k \quad (13)$$

The covariance of the process and measurement noises determine the characteristics of the filter, but are unknown. The accuracy of the finger-stick HemoCue glucose monitor has been studied in [18], which indicate a standard deviation in the area of 10-15 mg/dl when compared to a state of the art laboratory device (Yellow Spring Instrument). The study indicates a linear relationship between noise and glucose level, which is common for glucose meters. No information on the measurement noise of the relatively new Abbott CGM system has been found, but a standard deviation of 20 mg/dl

is not an unrealistic assumption. Also for CGM systems a proportional increase in noise level to the glucose level is found. Current evaluation methods to assess the performance of CGM systems is based on comparing the CGM signal to a blood glucose reference. As the previous discussion shows, the signal to reference deviation incorporates deviation due to the time lag between the signals and does not accurately capture the stochastic variation in the CGM signal. Recent developments in CGM error assessment aims to quantize these error dynamics, but do not address the estimate of CGM variation per se [19]. In this paper the initial guess for noise level standard deviation was chosen to correspond to 15 mg/dl for the HemoCue device and 20 mg/dl for Abbott CGM. The measurement errors were considered to be uncorrelated.

Given the initial guesses \hat{Q}_0 and \hat{R}_0 can be iteratively estimated by first calculating the state estimation sequence $\hat{\Xi}_N = [\hat{\xi}_1 \dots \hat{\xi}_N]$ and the estimation error sequence $\hat{W}_N = [\hat{w}_1 \dots \hat{w}_N]$ from the estimation data $\{Y_N, U_N, \hat{\Xi}_0\}$ [?].

$$\hat{\Xi}_{N+1} = A\hat{\Xi}_N + BU_N + K(Y_N - C\hat{\Xi}_N) \quad (14)$$

$$\hat{W}_N = C\hat{\Xi}_N - Y_N \quad (15)$$

Thereafter the covariance estimates

$$S = E\{(\hat{\xi} - \xi)(\hat{\xi} - \xi)^T\}, \quad R = E\{\hat{w}\hat{w}^T\} \quad (16)$$

are determined. Given that the sequence is stationary $\lim_{N \rightarrow \infty} S_N = S$ and $\lim_{N \rightarrow \infty} R_N = R$. Now $\{A, B, C\}$ may be re-estimated again by recognizing that

$$\hat{\xi}_{k+1} = (A - KC)\hat{\xi}_k + [B \quad K][u_k \quad \gamma_k]^T \quad (17)$$

$$\hat{w}_k - \gamma_k = -C\hat{\xi}_k \quad (18)$$

Finally

$$\hat{Q} = S_N - AS_NA^T - KR_NK^T \quad (19)$$

$$\hat{R} = CS_NC^T - R_N \quad (20)$$

Note that this computation may result in sign-indefinite solutions [16].

VII. DATA

The approach outlined was evaluated on data collected within the European FP7 project DIAdvisor at the Montpellier University Hospital. The study was conducted in-hospital during a three-day visit. Standard meals were served for breakfast (08:00), lunch (13:00) and dinner (19:00), the amount of carbohydrates included being about 45, 70 and 70 grams, respectively. No specific intervention on the usual diabetes treatment was scheduled during the study since a truthful picture of normal blood glucose fluctuation and insulin-glucose interaction was pursued. The patients, thus, adapted their insulin therapy according to meter-provided glucose measurements as they used to do. For a first assessment of the approach outlined in this paper 1 patient was chosen from the total data set of 30 patients based on data completeness and the distinct delay in CGM sensor response to glucose fluctuations. Estimating the delay using the method outlined in [20] the longest delay was found to be 25 min, and these patient data were chosen for evaluation.

A. Signals

Data collection consisted of CGMS measurements obtained with the Abbott FreeStyle NavigatorTM, fingerstick measurements with a personal glucose meter (HemoCueTM, average 38 measurements/day), and carbohydrate intake and insulin administration reported in a personal patient logbook. The HemoCue measurements were interpolated using a shape preserving interpolation method (pchip in Matlab) to retrieve an equidistant sampled signal.

Apart from the CGMS signal (10 min sampling rate) an intermediate signal CGM_{raw} from the glucose sensor was collected (1 min sample rate). The signal was normalized to the same amplitude as the plasma glucose data, and was used in the identification instead of the final CGM signal CGMS. By using the raw signal, any calibration error in the CGM signal will not affect the result.

B. Estimation and Validation

The overnight data between the first and the second day were used together with breakfast meal data from the second day for estimation. It was decided to use overnight data together with meal data in order to have a data set with sufficient amount of excitation. Using meal data alone is problematic since both inputs act simultaneously during these circumstances. An assessment of the importance of input excitation to identification using simulated diabetic data sets is made in [21]. The first and third days' breakfasts were used for cross validation. Additionally, to challenge the predictor all HemoCue measurements were removed from the validation data sets.

VIII. EVALUATION CRITERIA

To evaluate the predictive performance of the model 20, 40 and 60 minute predictions were considered. The correspondence to the reference HemoCue measurements were assessed using the Clarke Pointwise Error Grid Analysis (pCGA) [22], RMSE and maximum absolute error. The performance was compared to the CGM signal's ability to measure the plasma glucose.

IX. RESULTS

First the GIIM M_1 was identified. Using the interpolated HemoCue data and the meal and insulin submodels to retrieve the filtered inputs a second-order state-space model was identified using the N4SID command of the System Identification Toolbox in Matlab [23]. The model was stable and responded qualitatively correctly to input (not shown). The interstitial mode M_2 was thereafter identified from the interpolated plasma glucose data and the raw CGM signal. The model order chosen according to the MDL criteria was $n_A = 2$, $n_B = 1$ and $d = 1$. Converting the M_2 model to state space format, the merged model M_3 was retrieved.

Since only CGM data were available in the validation data ($\delta_1 = 0$), no need for designing K_1 nor K_3 existed.

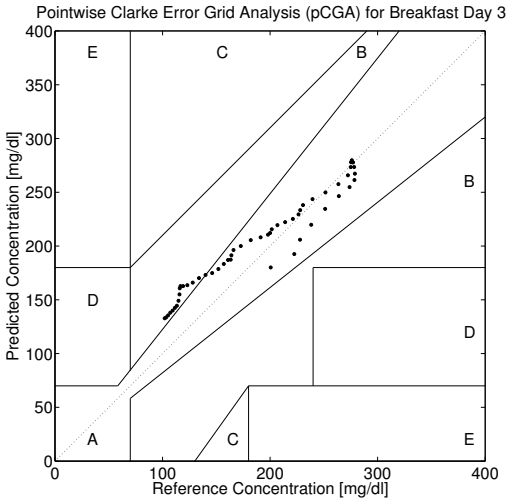


Fig. 2. Example of Clarke Error Grid Diagram, 40 min prediction Day 3.

Using the initial guess for Q and R produced noisy predictions. The attempt to estimate the noise characteristics from the estimation data broke down into non-positive definite covariance matrices. Instead, Q and R were chosen to strike a sound balance between signal smoothness and responsiveness to model-to-feedback mismatch.

In Fig. 3, the 20, 40 and 60 minutes predictions together with normalized CGM raw signal and the CGMS can be seen, and in Fig. IX an example of pCGA can be seen. All performance metrics have been summarized in Table II.

TABLE II
PERFORMANCE EVALUATION FOR THE M_3 PREDICTOR AND THE CGMS ON VALIDATION DATA.

Pred. Horizon	pCGA[%]			RMSE [mg/dl]	max e [mg/dl]
	A	B	CDE		
20	84.2	15.8	0	19.1	42
40	84.9	15.1	0	19.5	46
60	83.7	16.3	0	21.1	45
CGMS	45.9	51.6	2.5	46.5	90

X. DISCUSSION

A. Error Analysis

To determine the source of the prediction error the simulation errors of the sensor model and of the GIIM model were investigated separately. In Fig. 4 the simulation error between the simulated raw CGM signal and the true signal can be seen. The error distribution is clearly non-gaussian. This could be explained by time-varying dynamics, and in [6] a recursive sensor model is used to handle such occurrences. However, the evaluated time periods are short, and applying the model over the entire data record gives a more even distribution (Fig. 6). Given a tolerance interval of ± 20 mg/dl, corresponding to the CGA A zone for a 100 mg/dl plasma glucose value, the model error can be considered acceptable.

The simulation error of the GIIM can be seen in Fig. 5. The contribution is significantly larger. For breakfast day one the model overestimates the glucose drop after the peak. On day

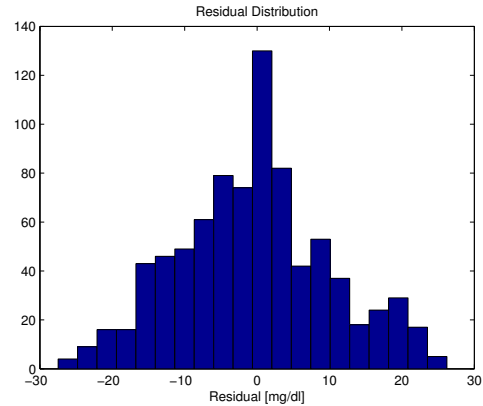


Fig. 6. Distribution of simulation error of the sensor model over the entire data record.

three on the other hand the model underestimates the same drop. Given that these are infinite-horizon prediction without any measurement feedback, a maximum error in the magnitude of 40 mg/dl should be considered to be a very good result. In fact, the error is almost within the CGA A zone at all times.

Looking at the predictions in Fig. 3, the behavior of the prediction error can be understood from the error contribution from the sensor model, sensor errors and the GIIM. As the prediction horizon increases, the GIIM error becomes more and more dominant.

B. Glucose and Insulin Submodels

Major sources of uncertainty are the intermediate inputs R_a and I_p and the assumptions made to retrieve them. Unfortunately these obstacles are hard to come by. Neither the rate of glucose appearance following a meal nor the plasma insulin level are normally available for measurement. Estimates of R_a have been made in [8] and require a tracer based experiment. I_p can be obtained from lab assays of blood samples. Obviously such arrangements cannot be expected in a normal day setting. Further work to assess the intra- and inter-individual variations of these processes, and on mitigations to handle these principle obstacles, is needed.

C. GIIM Modeling

In this modeling approach the glucose and insulin interaction was considered to be linear, whereas many models inhibit nonlinearities [10]. As indicated by the results improvements can be made in the GIIM and glucose and insulin dispersion models.

D. IG Dynamics

These dynamics were assumed to be time invariant, and homogeneous in direction and magnitude of glucose change and glucose level. The assumption of independence of the sign of the glucose change has been shown to be questionable, see [20], where statistically significant differences in response time depending on the direction of glucose change are presented. However, in this study no such differences could be observed.

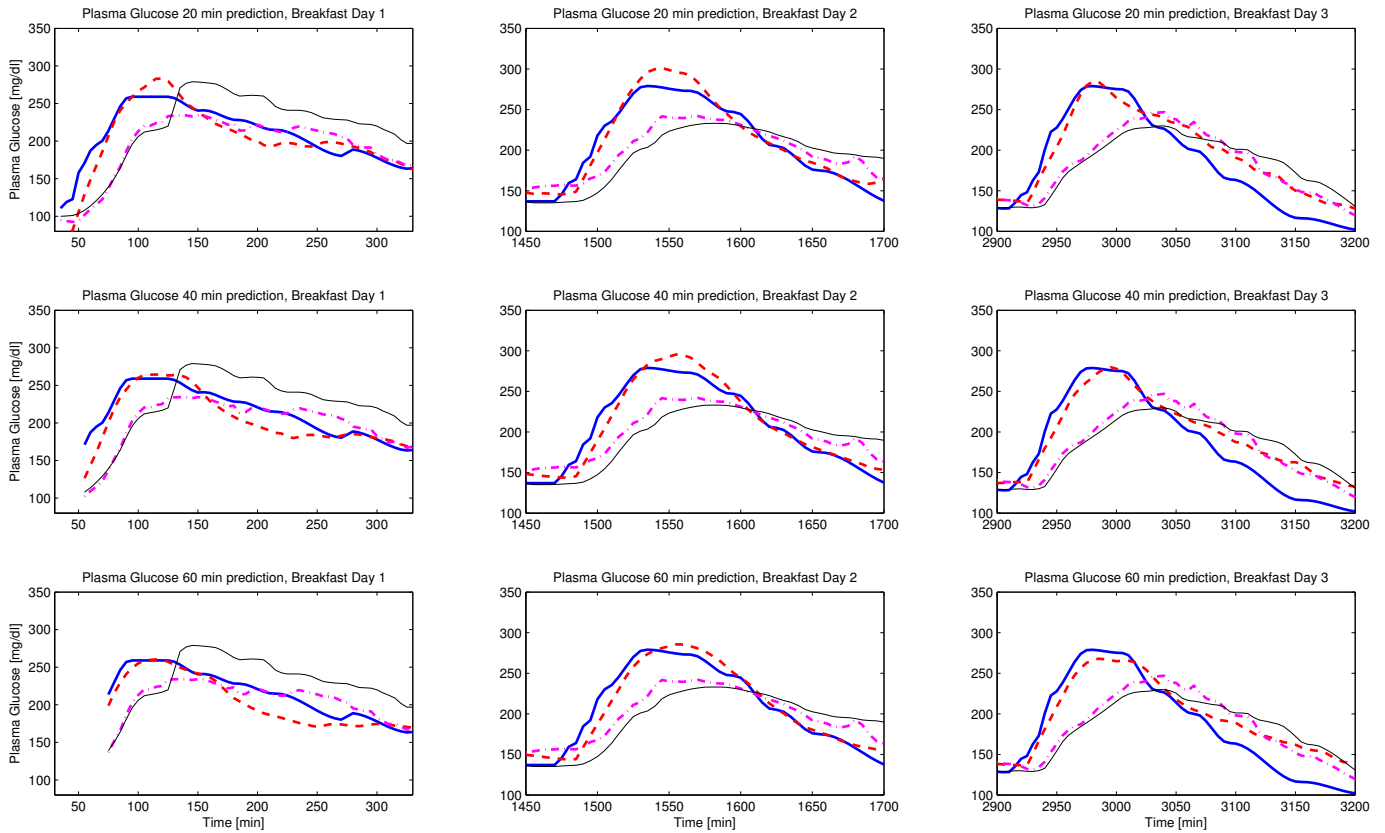


Fig. 3. Plasma glucose predictions. Interpolated HemoCue measurements (thick solid blue), CGMS (solid black), CGM_{raw} (dash dotted magenta) and M3 predictions (dashed red) for estimation data (middle plot) and validation data (left and right plots).

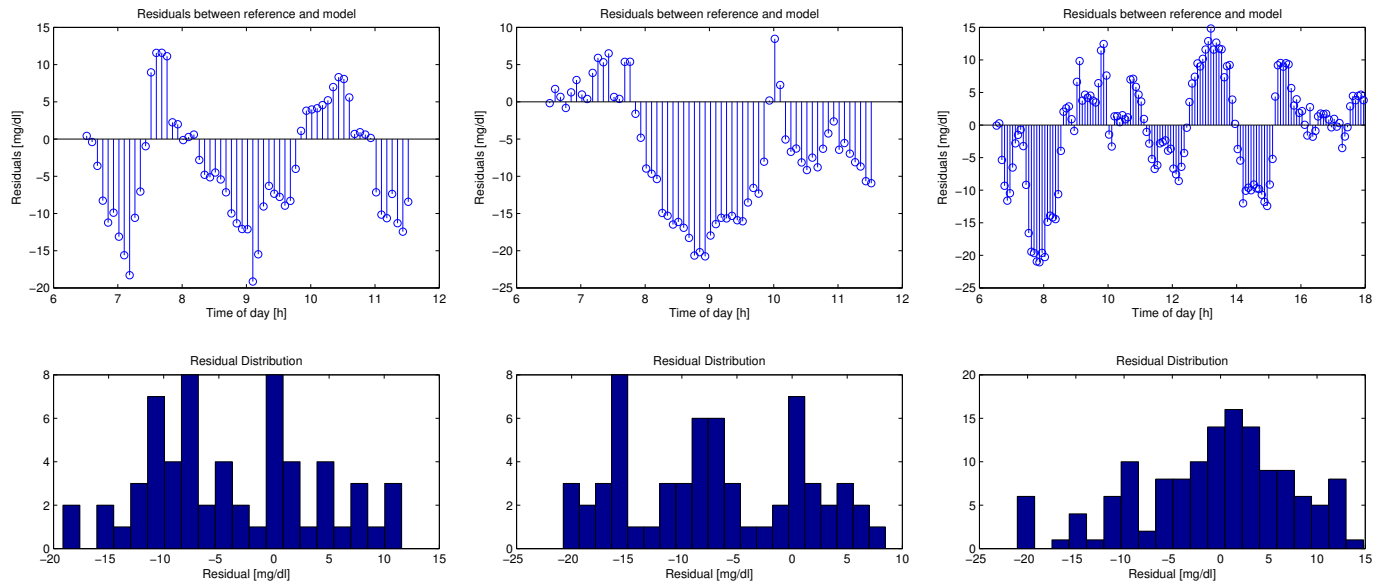


Fig. 4. Simulation error of the simulated raw CGM signal z_k given plasma glucose y_k using the sensor model M_2 .

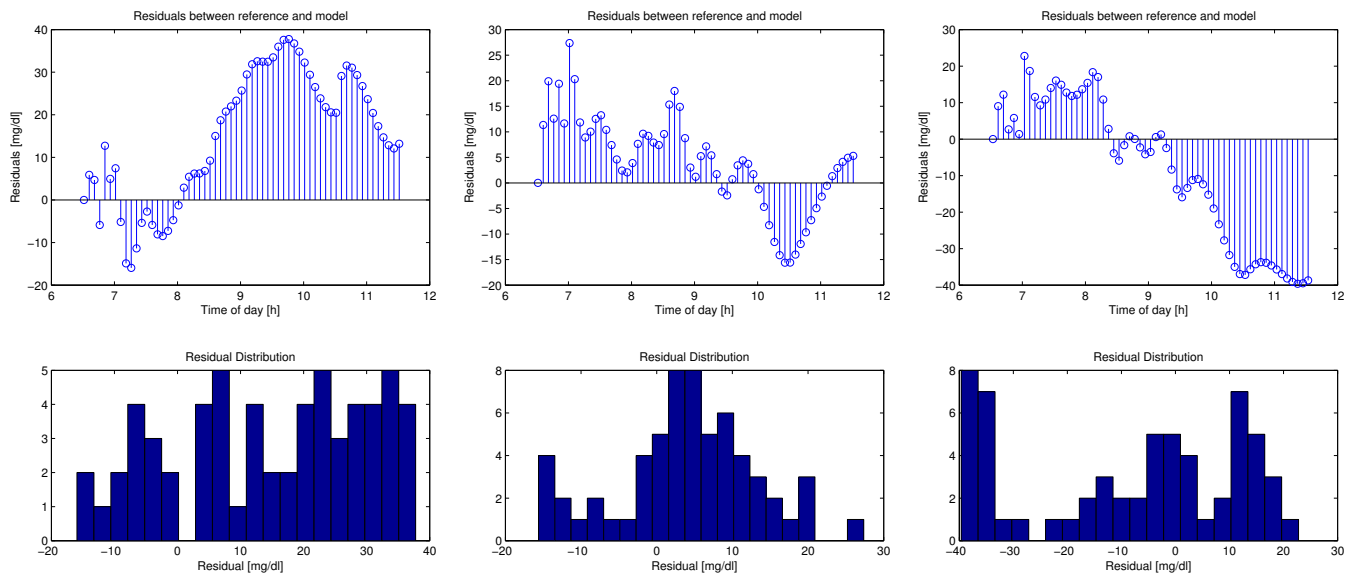


Fig. 5. Simulation error of plasma glucose y_k given inputs u_k using M_1 .

XI. CONCLUSIONS

The comparison of the merged prediction to the CGM signal clearly shows that merged model manages to significantly reduce the delay that otherwise is present when only relying on the CGM signal to estimate the plasma glucose. Furthermore, the results indicate that the underlying GIIM model seems to with acceptable accuracy describe the combined impact of a breakfast and the subsequent insulin injection. To summarize this study indicates that a merged model incorporating a plasma glucose observer could be a powerful tool in the struggle for normoglycemia in millions of diabetic patients.

XII. ACKNOWLEDGMENT

Further work on glucose prediction and glucose control will be pursued in the European FP7 IST-216592 DIAdvisorTM ICT project [24].

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