MPC Model Individualization in Free-Living Conditions: A Proof-of-Concept Case Study

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Abstract: In the last years, Model Predictive Control (MPC) proved to be one of the most promising approaches for an Artificial Pancreas (AP), a device for closed-loop blood glucose control in subjects affected by Type 1 Diabetes (T1D). MPC performance is highly influenced by the quality of the model used for prediction. Moreover, the inter-patient variability characterising subjects with T1D increases the need of patient-tailored models. Recently, promising results have been obtained in silico using the UVA/Padova simulator in Soru et al. (2012) and Messori et al. (2016) where different individualization techniques have been studied and compared to the "average" model of the UVA/Padova adult population showing significant improvements in term of prediction ability. The aim of this paper is to verify the applicability of the technique described in Soru et al. (2012) and extend it to be used on free-living data collected without ad hoc clinical protocols. Data were collected during a 1 month trial in free-living conditions (Renard et al. (2016)). In this proof-of-concept case study, individualized models obtained with different identification parameters are compared with the "average" model that was used to synthetize the MPC controller used during that trial. The individualized models show superior prediction performance and prove robustness to non-optimal algorithm initialization in a selected test-case.

Keywords: Identification and validation, artificial pancreas, clinical trial, type 1 diabetes, personalized model for control

1. INTRODUCTION

Type 1 Diabetes (T1D) is an autoimmune disease characterized by the destruction of pancreatic β-cells that are responsible for the production of insulin. As a consequence, T1D results in high Blood Glucose (BG) level, BG $>$ 180 mg/dl, known as hyperglycemia. Subjects with T1D need exogenous insulin administration to maintain the BG level in the acceptable range [70-180 mg/dl]; their goal is to minimize diabetes complications related to hyperglycemia and simultaneously avoid hypoglycemia (BG $<$ 70 mg/dl). In the last 10 years, the availability of pump for continuous subcutaneous insulin infusion (CSII) and the increased accuracy of Continuous Glucose Monitor (CGM) sensors, together with the large effort to improve control algorithms, brought to reality the long dreamed of Artificial Pancreas (AP), a device for automatic glycemic regulation (Cobelli et al., 2011; Thabit and Hovorka, 2016). In particular, in the last two years a number of clinical studies have shown the efficacy of AP prototypes when used in free-living conditions lasting 1-6 months (Thabit et al., 2015; Kropff et al., 2015; Renard et al., 2016; Anderson et al., 2016; Bergenstal et al., 2016). Model Predictive Control (MPC), one of the most promising control techniques for an AP, is based on a glucose-insulin model to predict the glycemic trend and react in advance to its changes, so that patient BG can be kept in the safe range. Therefore, the control performance is highly influenced by the quality of the model and the inter-patient variability characterizing subjects with T1D enhances the need of patient-tailored models. Recently, new identification techniques have been investigated to this purpose, but this remains an open problem. For reasons of space a comprehensive literature review can not be given here. We refer the interested reader to Zarkogianni et al. (2015).

Promising results have been obtained on this topic by our group in silico, i.e. using the UVA/Padova simulator (Kovatchev et al. (2009); Dalla Man et al. (2014)) to account for the inter-patient variability, the simulator offers 100 vectors of model parameters, the so called "virtual patients". The average parameters vector describes the so called "average patient". In Messori et al. (2016) different individualization techniques have been studied in silico and compared to the linearization of the average virtual patient. In silico data were collected during closed-loop simulations of clinical protocols designed to produce a sufficient input-output excitation without compromising the patient safety. One of the methods proposed in Messori et al. (2016), the non-parametric technique, was tested in Del Favero et al. (2011) on real data collected during controlled trials on hospitalized patients. Despite the short duration of the dataset (less than 24h), the results were promising and outperforming traditional system identification strategies such as Prediction Error Methods. Furthermore we proposed the Impulse-Response (IR) technique

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(Soru et al. (2012)) that showed very interesting results in closed-loop in in silico subjects.

In this paper, we consider the last method and extend its use to the closed-loop in free-living conditions (Renard et al., 2016), described in section 3.1. This set-up is particularly challenging because the identification of reliable models on real-data is more difficult than on simulated data. Moreover free-living conditions are much more challenging than the highly controlled experimental conditions of in-hospital studies, due to the many confounding factors affecting blood glucose in real-life, such as physical exercise and differences in daily activities. Technical issues affecting the AP prototype and human errors on patient-provided information further complicate this set-up.

In this proof-of-concept case study, we consider a single patient and show the improved prediction capabilities of the patient-tailored model with respect to the average model, currently used in the MPC controller during the recent trials. First, we focus on a short (1 day) "clean" data portion, manually selected by visual inspection among those free from technical issues of the AP system including infusion set failures and possible errors on patient provided information. Then, we face the challenge of assessing model prediction on the entire trial data (1 month) without any manual ad-hoc exclusion.

2. MODEL IDENTIFICATION: THE MODIFIED IMPULSE RESPONSE METHOD

The measurable inputs of the patient model are the injected insulin, $i(t)$, and the assumed carbohydrates content, $m(t)$. The model output is the glucose concentration measured by the CGM sensor, $CGM(t)$. Denoting with $I(s)$, $M(s)$ and $CGM(s)$ the Laplace transformations of inputs and output, the model has the following structure:

$$CGM(s) = G_i(s)I(s) + G_m(s)M(s) + E(s)$$

where $G_i(s)$ and $G_m(s)$ are transfer functions to be estimated from the data and $E(s)$ is the Laplace transformation of the residual error $e(t)$. Besides insulin and meal, a number of other unmeasurable factors affect blood glucose concentration, first and foremost physical exercise, but also stress, illness, menstrual cycle, etc. The effect of these unmeasured factors and other unmodeled dynamics is partially accounted for by assuming $e(t)$ to be a coloured noise, i.e. assuming that $e(t)$ is correlated with the past errors $e(t-1), e(t-2), \ldots$. Also the spectral characterization of the error has to be estimated from the data.

2.1 Model Identification: Input-Output relation

Due to the impossibility of performing extensive and potentially dangerous experiments on subjects, the identification technique described in Soru et al. (2012) exploits the simulator for a preliminary analysis in order to identify the $G_i(s)$ and $G_m(s)$ of the average in silico patient (Av) of the UVA/Padova simulator (Dalla Man et al. (2014)). Consequently, they are adapted to the specific patient by minimizing the sum of squares of the difference between actual CGM and the simulated one.
In particular, the transfer functions were determined by impulse response experiments on the Av patient by starting from basal conditions. They can be defined as

$$\begin{aligned} G_i(s) &= \frac{\mu_i}{(1+sT_{i1})(1+sT_{i2})(1+sT_{i3})(1+sT_{i4})} \\ G_m(s) &= \frac{\mu_m}{(1+sT_{m1})(1+sT_{m2})(1+sT_{m3})} \end{aligned} \quad (1)$$

since a fourth-order all-pole transfer function $G_i(s)$ gave a flexible, yet parsimonious, description of the observed insulin impulse response, while a third-order all-pole transfer function $G_m(s)$ was adequate for the meal response.
These transfer functions have to be tailored to the patient, so the identification phase was performed by estimating the vector θ of the individual parameter values:

$$\theta = \begin{bmatrix} \theta_i \\ \theta_m \end{bmatrix}, \theta_i = \begin{bmatrix} \mu_i \\ T_{i1} \\ T_{i2} \\ T_{i3} \\ T_{i4} \end{bmatrix}, \theta_m = \begin{bmatrix} \mu_m \\ T_{m1} \\ T_{m2} \\ T_{m3} \end{bmatrix}$$

The procedure tries to optimize the Sum of Squares Residuals (SSR) computed as differences between the observed CGM data (CGM) and the CGM obtained by running a simulation using the model ($\widehat{CGM}$):

$$SSR(\theta) = \sum_{t=1}^{N} CGM(t) - \widehat{CGM}(t,\theta) \quad (2)$$

The residuals are a non linear function of the model parameters, so an iterative non linear least squares algorithm is needed and the adopted initialization affect the final result. We explore two different initializations in order to obtain the best performance: the first one, already described in Soru et al. (2012), uses all the parameters estimated for the Av patient (θ^{Av}) as initial values, while the second one uses only the time constants of the Av patient and uses some available clinical parameters to adapt the two gains μ_i and μ_m in order to define the initialisation vector (θ^{Cp}). In particular, the Correction Factor (CF) is defined as the ratio between the ΔG obtained by administrating I units of insulin and the insulin amount I itself, so:

$$\frac{\Delta G_I}{I} = CF$$

and a natural initialization for μ_i is $\mu_i = CF$. Given the Carbohydrate Ratio (CR) defined as the ratio between the meal amount (m) and the insulin bolus (b) to compensate it,

$$\frac{m(t)}{b(t)} = CR$$

it is easy to obtain that the meal gain can be initialized as $\mu_m = \frac{CF}{CR}$. In this work, both initializations are taken into account.
Given the required computational load, the optimization problem has been divided in two parts. The first one has the goal to optimize the parameters θ_i by keeping fixed θ_m to the one chosen as initialization value:

$$\theta_{i1}^{*} = \arg\min_{\theta_i} \quad SSR(\theta_i)$$

with $\theta_i^{init} \in \{\theta^{Av}, \theta^{Cp}\}$. This is a reasonable choice because the meal response is a reasonably reliable estimation of the patient response in both cases, θ_m^{Av} and θ_m^{Cp}. In the second part, the insulin parameters are initialized to θ_{i1}^{*} and the entire θ, meaning both θ_i and θ_m, is estimated in order to obtain its most accurate estimation:

$$\theta^{*} = \arg\min_{\theta} \quad SSR(\theta)$$

with $\theta_i^{init2} = \theta_{i1}^{*}$, $\theta_m^{init2} \in \{\theta^{Av}, \theta^{Cp}\}$ and $\theta^{*} = [\theta_{i2}^{*} \ \theta_{m2}^{*}]'$.

Moreover, it is well-known from physiology that the insulin response is affected by absorption delays. This a priori information has been introduced in the model as a pure delay of τ minutes in $G_i(s)$, so that

$$G_i^d(s) = e^{-\tau s} \cdot G_i(s) \quad (3)$$

$G_i^d(s)$ represents the transfer function between $CGM(t)$ and $i(t)$, while now $G_i(s)$ represents the transfer function between $CGM(t)$ and $i(t-\tau)$. During the identification phase, the optimization problem is then fed with the delayed insulin signal. In this work, models without and with delays of different magnitudes are investigated.

2.2 Model identification: stochastic part

After the estimation of $G_i(s)$ and $G_m(s)$ for maximizing the simulation accuracy, we identify the stochastic part of the model by describing the residual error $e(t)$ as an AR process of order n:

$$e(t) = a_1 e(t-1) + \cdots + a_n e(t-n) + \epsilon(t)$$

with $\epsilon(t)$ a zero-mean mean white noise with variance λ. The parameters $a_1, \ldots, a_n$ and λ are estimated from the data by minimizing the 1 steps ahead prediction. The complexity of the AR model is fixed a priori and chosen by trial and error to $n=5$.

3. DATA

3.1 Experimental set-up

In 2015, 20 patients have been enrolled in a 1-month trial aimed to test the day-and-night use of an AP system in free-living conditions (Renard et al., 2016). The patients worn the AP prototype consisting of an suitably modified android smartphone (the DiAs platform, Keith-Hynes et al. (2014)), communicating wirelessly with the G4 Platinum CGM system, Dexcom Inc. and the AccuCheck Spirit Combo insulin pump, Roche Diagnostic. The computational unit run the MPC controller described in Toffanin et al. (2013). Carbohydrates ingested at meal time or for snack and those used to treat hypoglycemic episodes were manually entered by the patient into the system. Capillary blood glucose measurements, obtained by pricking patient's finger (Self-Monitoring Blood Glucose measurements, SMBG) were performed for CGM calibration, at meal and to confirm hypo or hyperglycemia detected by the CGM sensor.
In this proof-of-concept we consider 1 patient on the 20 involved in the trial.

It should be noted that this prototype was not specifically designed to collect data for model identification, posing a number of technical issues regarding device synchronization, completeness of stored data and reliability of patient's provided information. Furthermore, a few malfunctions occurred during the trial hampering the reliability of the associated data portions. Hence, a careful data selection phase has been performed before the model identification.

3.2 Data Preprocessing

Current CGM sensors have to be calibrated two times/day by using SMBG measurements to produce reliable glucose readings. Imperfect calibration induces a systematic distortion in CGM measurements as illustrated in Figure 1 and modeled in Facchinetti et al. (2015). Denoting with $CGM_{\text{b.p.}}(t)$ the CGM before preprocessing, a simplified version of the model in Facchinetti et al. (2015) is:

$$CGM_{\text{b.p.}}(t) = \alpha g(t) + \beta + \gamma t + e(t)$$

where $g(t)$ is the true glucose concentration $e(t)$ is a colored noise and α, β, γ are the "decalibration" model parameters. These parameters abruptly change every time a calibration is performed.

Apparently, this distortion can affect the estimate of model coefficients and introduce spurious jumps and additional dynamics. To mitigate these artifacts, we employ a pre-processing algorithm known as "retrofitting" (Del Favero et al., 2014), that retrospectively corrects this calibration-induced distortion by leveraging on the other SMBG measurements collected during the trial. Here we only illustrate the effect of the algorithm with Figure 1, while we refer the interested reader to the original manuscript for more details.

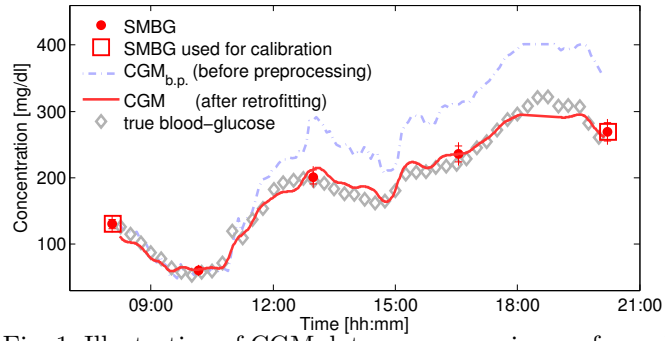

Fig. 1. Illustration of CGM data pre-processing performed by the retrofitting algorithm, taken from Del Favero et al. (to appear). Due errors and uncertainty in the calibration process the CGM measurement (dashed blue line) overestimates the true blood glucose (gray diamond, not available in our dataset). The retrofitting algorithm, leveraging on a few SMBG measurements collected during the trial (red dots), compensates for calibration error and the output of the method (red solid line) is closer to the true glucose concentration.

Let us remark that in this work $CGM(t)$ always refers to the CGM trace *after* the preprocessing by retrofitting. Furthermore, it should be noted that the retrofitting algorithm improves the accuracy of the CGM, but it does not solve the issue of data reliability previously mentioned (e.g. due to AP malfunctioning or human errors on patient-provided data). As such, the extraction of a "clean" data portion remains of interest even when this preprocessing is performed.

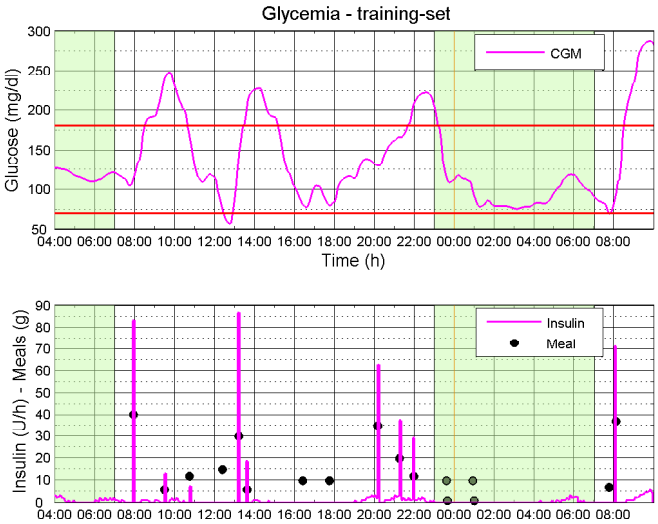

Fig. 2. The **training-set** containing the data used for identification. On the top panel the output signal, on the bottom panel the input signals.

3.3 Final Datasets

The final datasets consists of 3 signals: $CGM(t)$, the system output, obtained by preprocessing the trace collected by the sensor with the retrofitting algorithm described above; the injected insulin $i(t)$, recorded by the system; the carbohydrates assumption $m(t)$, inserted manually by the patient.

Three datasets were selected: the **training-set**, containing 30 hours of data picked up randomly among the available ones; **test-set A**, a 1-day dataset, completely disjoint the training-set and carefully selected in order to contain only complete and reliable data; **test-set B** the entire 1-month dataset containing all data from the trial for the selected patient. It is important to note that the **test-set B** is really challenging because it includes all the problems experienced during the whole trial.

As an example, the training-set is depicted in Figure 2.

4. PERFORMANCE METRICS

To assess the efficacy of an identified model we compare the model predictions of future CGM against its actual values $CGM(t)$ on the test-sets previously mentioned. Various Prediction Horizon (PH) are considered.

In details, let us denote with $\widehat{CGM}(t|t-PH)$ the PH-steps ahead prediction of a model, i.e. the prediction obtained by exploiting past glucose values up time t - PH, $CGM(t-PH)$, $CGM(t-PH-1)$, ... and inputs up to time t, $i(t)$, $i(t-1)$, ..., $m(t)$, $m(t-1)$, ... Furthermore, let us denote with $PH=+\infty$ the glucose simulation, i.e. the output of the model when fed with the inputs $i(t)$, $i(t-1)$, ..., $m(t)$, $m(t-1)$, ... without taking advantage of any of the measure outputs.

The signal $\widehat{CGM}(t|t-PH)$ and CGM are compared using the metrics listed below. The starting point is Root Mean Square Error (RMSE) defined as:

$$RMSE(PH)=\frac{1}{N}||CGM(t)-\widehat{CGM}(t|t-PH)||.$$

where we denote with $||x(t)||$ the l_2 norm of the signal $x(t)$, namely $\sqrt{\Sigma_{t=1}^{N}x(t)^2}$, N being the length of the dataset. RMSE assesses the variance of the prediction error: the larger it is, the poorer is the prediction. Instead of presenting this absolute quantity, we report two normalized versions commonly used in system identification (Cescon and Johansson, 2009; Finan et al., 2009).

Metric 1: FIT.
Defined as

$$FIT(PH)=100*\left(1-\frac{||\widehat{CGM}(t|t-PH)-CGM(t)||}{||CGM(t)-\overline{CGM}(t)||}\right)$$

where $\overline{CGM}(t)$ is the sample mean of the glucose signal. FIT is equal to 100% if and only if $CGM(t)=\overline{CGM}(t)$ $\forall t=1,...,N$ (perfect prediction), and smaller than 100% otherwise. Note that FIT can become negative if the RMSE is larger than the sample variance of the signal.

Metric 2: Coefficient of Determination (COD).
Defined as

$$COD(PH)=100*\left(1-\frac{||\widehat{CGM}(t|t-PH)-CGM(t)||^2}{||CGM(t)-\overline{CGM}(t)||^2}\right)$$

Similarly to FIT, COD is equal to 100% for perfect predictions and smaller than 100% and possibly negative otherwise.

Metric 3: Pearson's correlation coefficient ρ.
Defined as

$$\rho(PH)=\frac{\sum_{t=PH}^{t_{max}}(CGM(t)-\overline{CGM})(\widehat{CGM}(t|t-PH)-\overline{\widehat{CGM}}(t|t-PH))}{||CGM(t)-\overline{CGM}||\cdot||\widehat{CGM}(t|t-PH)-\overline{\widehat{CGM}}(t|t-PH)||}$$

with $\overline{\widehat{CGM}}(t|t-PH)$ being the sample mean of the predicted CGM.

All the metrics mentioned above are function of the prediction horizon PH. Since we aim to use the identified model in our MPC controller (Toffanin et al. (2013)), that computes model predictions with sample time of $T_s=5$ minutes up to 60 minutes (PH=12), we consider $PH=[T_s,2T_s...,12T_s,+\infty]=[5,10,...,60,+\infty]$ min. Furthermore, the average value of each metric for the considered PHs was used as main outcome to evaluate the models.

5. RESULTS

We identified 10 models using all the possible combinations of the initialisations, $\theta_i^{init}\in\{\theta^{Av},\theta^{Cp}\}$, and delays, $\tau\in\{0,15,...,60\}$ as reported in Table 1.
The performance metrics evaluating the identified models

Model	Parameters		
	μ_i^0	μ_m^0	τ
M1	μ_i^{Av}	μ_m^{Av}	0
M2	μ_i^{Av}	μ_m^{Av}	15
M3	μ_i^{Av}	μ_m^{Av}	30
M4	μ_i^{Av}	μ_m^{Av}	45
M5	μ_i^{Av}	μ_m^{Av}	60
M6	μ_i^{Id}	μ_m^{Id}	0
M7	μ_i^{Id}	μ_m^{Id}	15
M8	μ_i^{Id}	μ_m^{Id}	30
M9	μ_i^{Id}	μ_m^{Id}	45
M10	μ_i^{Id}	μ_m^{Id}	60

Table 1. List of all considered models.

on **test-set A** and **test-set B** are reported in Table 2 and in Table 3 respectively; in both tables the performance of the average in silico model (Av) is also reported for comparison with the patient-tailored models.

Model	$\overline{\text{FIT}}$	$\overline{\text{COD}}$	$\overline{\rho}$
M1	51.96	74.71	0.86
M2	52.65	75.25	0.87
M3	52.89	75.32	0.87
M4	55.01	76.6	0.87
M5	55.5	77.29	0.88
M6	52.25	74.8	0.86
M7	53.72	76.51	0.88
M8	52.67	74.67	0.87
M9	**55.63**	**77.88**	**0.88**
M10	54.96	77.05	0.88
Av	**39.83**	**59.38**	**0.82**

Table 2. Performance metrics of the identified models for patient 1 on **test-set A**.

Model	$\overline{\text{FIT}}$	$\overline{\text{COD}}$	$\overline{\rho}$
M1	40.92	53.84	0.76
M2	33.37	41.88	0.7
M3	42.29	54.55	0.76
M4	38.72	49.61	0.74
M5	**48.18**	**63.42**	**0.81**
M6	39.16	51.27	0.74
M7	40.40	53.16	0.74
M8	36.48	46.98	0.72
M9	40.98	53.27	0.75
M10	44.88	59.77	0.78
Av	**31.12**	**45.46**	**0.74**

Table 3. Performance metrics of the identified models for patient 1 on **test-set B**.

It is evident that the technique is robust to non-optimal algorithm initialization and wrong insulin delay estimation. The best patient-tailored model is M9 for **test-set**

A, that uses the clinical patient information as initial condition and assumes the insulin delay $\tau = 45$ minutes. The improvements of M9 respect to the Av model are of 40% in term of FIT, 31% in term of COD and 7% in term of ρ. Figure 3 reports the performance metrics as a function of PH, the predictions FIT (a), COD (b) and ρ (c), respectively, for all the considered models with the **test-set A**. The figure clearly shows that the performance of the individualized models initially decreases as the Av model (see $PH < 6$), but afterwards reaches a stable value (e.g. around 40 for the FIT) whereas of the Av model continues to decrease.

If the entire trial is considered (**test-set B**), the best patient-tailored model is M5, which uses the clinical patient information for initializations and assumes an insulin delay $\tau = 60$ minutes. The improvements of M5 with respect to the Av model are of 55% in term of FIT, 40% in term of COD and 9% in term of ρ. Figure 4 reports the performance metrics as a function of PH, the predictions FIT (a), COD (b) and ρ (c), respectively, for all the considered models with **test-set B**. The improvements of the individualized models is less evident, since the decreasing trends are similar. This is probably due to the larger impact of the many confounding factors and technical issues. In general, both initializations show a good performance with a preference for the clinical one that includes additional information about the patient; the introduction of an a priori insulin delay τ seems to improve the prediction ability of the model, particularly with a value between 45 and 60 minutes.

6. CONCLUSION

In this proof-of-concept case study, the technique described in Soru et al. (2012) has been extended to be used on free-living data collected without ad-hoc clinical protocols. The data used in this work were collected during a 1 month AP trial in free-living conditions (Renard et al. (2016)). The individualized models are compared with the "average" model used to synthetize the MPC controller employed in the trial. The patient-tailored models show a performance improvement and prove to be robust to non-optimal algorithm initialization in two test-sets.

The main limitation of this contribution is that it focuses only on a single patient, but the good results obtained by considering the entire month, where the patient habits have widely changed, represent an important starting point for future application.

Future works will include the evaluation of the individualization techniques on the entire dataset of 20 patients. Furthermore we will work to the application of these techniques to adapt the patient-tailored model so that the model follows the patient response changes over time.

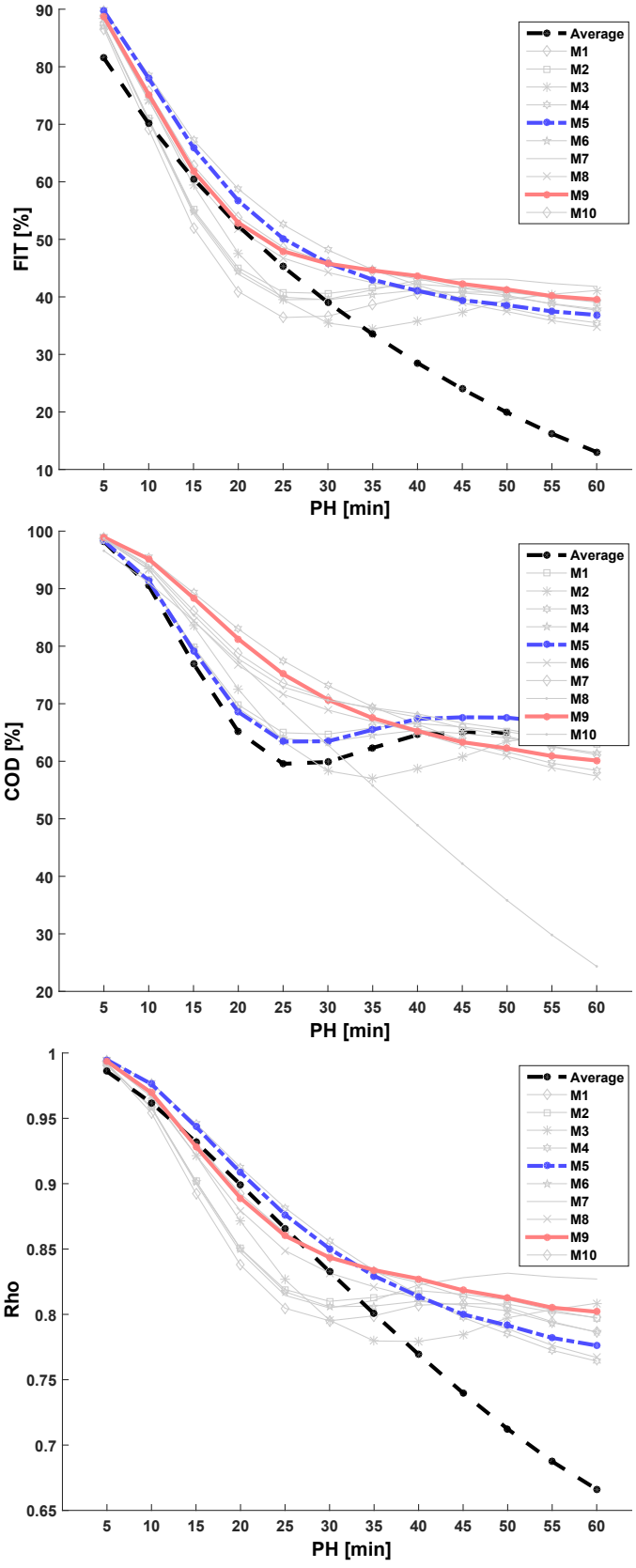

Fig. 3. A comparison of the prediction performance of the proposed technique compared to the average patient of the in silico population in term of FIT (a), COD (b) and ρ (c) on **test-set A**.

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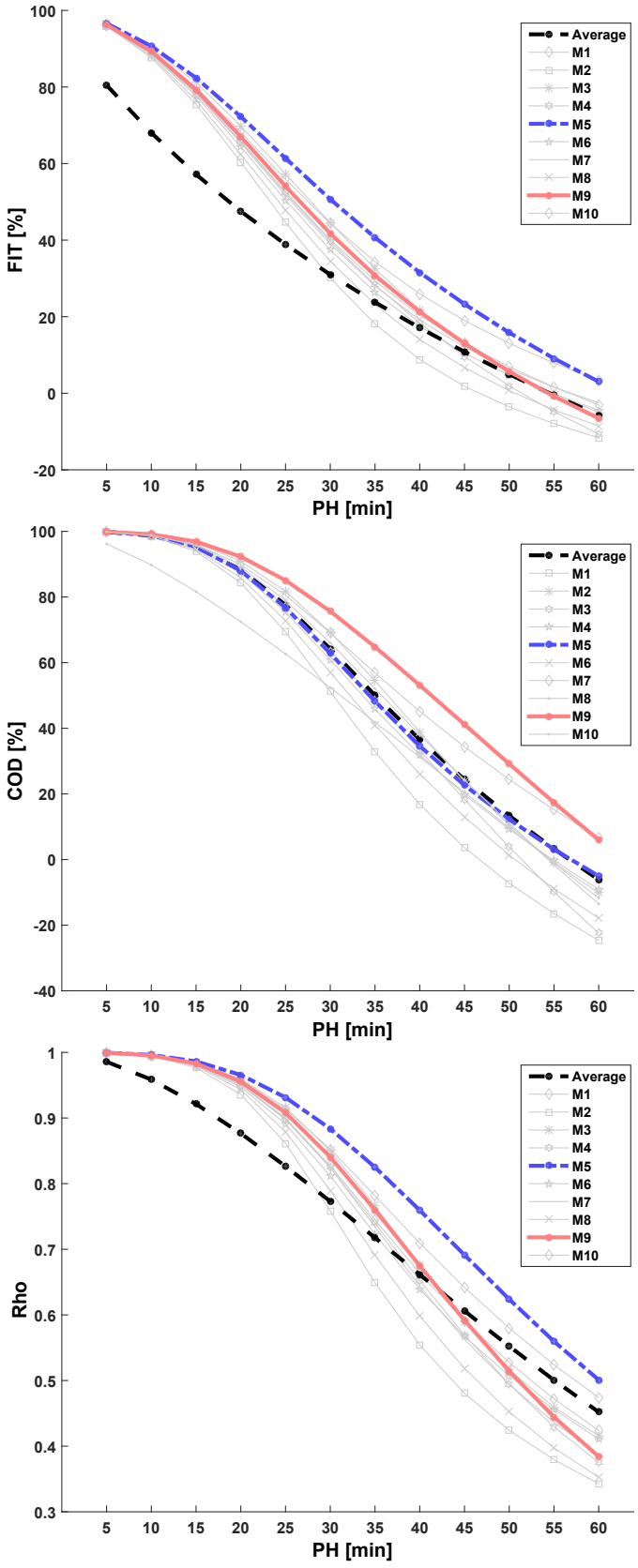

Fig. 4. A comparison of the prediction performance of the proposed technique compared to the average patient of the in silico population in term of FIT (a), COD (b) and ρ (c) on **test-set B**.

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