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A nonparametric approach for model individualization in an artificial pancreas ⋆

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Abstract: The identification of patient-tailored linear time invariant glucose-insulin models is investigated for type 1 diabetic patients, that are characterized by a substantial inter-subject variability. The individualized linear models are identified by considering a novel kernel-based nonparametric approach and are compared with a linear time invariant average model in terms of prediction performance by means of the coefficient of determination, fit, positive and negative max errors, and root mean squared error. Model identification and validation are based on in-silico data collected from the adult virtual population of the UVA/Padova simulator. The data generation involves a protocol designed to produce a sufficient input excitation without compromising patient safety, compatible also with real life scenarios. The identified models are exploited to synthesize an individualized Model Predictive Controller (MPC) for each patient, which is used in an Artificial Pancreas to maintain the blood glucose concentration within an euglycemic range. The MPC used in several clinical studies, synthesized on the basis of a non-individualized average linear time invariant model, is also considered as reference. The closed-loop control performance is evaluated in an in-silico study on the adult virtual population of the UVA/Padova simulator in a perturbed scenario, in which the MPC is blind to random variations of insulin sensitivity in each virtual patient.

Keywords: Artificial pancreas, Nonparametric identification, Predictive control, Linear systems, Biomedical control, Biomedical systems.

1. INTRODUCTION

People affected by Type 1 Diabetes Mellitus (T1DM) are dependent on exogenous insulin administrations to maintain the blood glucose (BG) concentration within an euglycemic range because of the destruction of the pancreas beta-cells, which are responsible for insulin secretion. Since manual insulin administration is very difficult and burdensome for the patient, there is great interest towards the development of an automatic system called artificial pancreas (AP), which consists of a subcutaneous (sc) glucose sensor, (CGM, Continuous Glucose Monitor), a sc insulin pump, and a control algorithm. Several research projects on AP were supported by the Juvenile Diabetes Research Foundation, the European Commission, and the National Institutes of Health (see Bequette (2012), Cobelli et al. (2009), El-Khatib et al. (2010), Hovorka et al. (2010), and Weinzimer et al. (2008)). One of the most promising control techniques for an AP is Model Predictive Control (MPC), which synthesizes a controller on the basis of a process model. MPC for AP has been successfully tested in-silico (see Hovorka et al. (2004), Dua et al. (2006), Wilinska et al. (2009), Magni et al. (2007), Magni et al. (2009), Patek et al. (2012), Soru et al. (2012), Toffanin et al. (2013), Messori et al. (2014), Grosman et al. (2010), Lee et al. (2009), Cameron et al. (2011), and Schmidt et al. (2013)), in-vivo in hospitalized volunteers (see Murphy et al. (2011), El-Khatib et al. (2010), Breton et al. (2012), Luijf et al. (2013), and Zisser et al. (2014)), and outside the hospital (see Leelarathna et al. (2014), Hovorka et al. (2014), Thabit et al. (2014), Kovatchev et al. (2014), Russel et al. (2014), Del Favero et al. (2014), and Del Favero et al. (2015)).

Since diabetic patients are characterized by a substantial inter-subject variability, the development of individualized control strategies promises to bring a significant improvement. The aim of this study is to identify an individualized glucose-insulin model usable to synthesize a patient-tailored MPC. A linear approximation of glucose-insulin interaction is adequate to capture the essential dynamics to design an effective and safe MPC control, while guaranteeing reduced complexity and low computational burden in the MPC implementation, as shown in Del Favero et al. (2014) and other references therein. The model is derived from an individualized predictor of future glucose values identified through a nonparametric (NP) approach based on kernel-based regression (see Pillonetto et al. (2010) and Pillonetto et al. (2011)). This NP approach has proved to be more effective in this application than standard identification techniques (PEM, Prediction Error Methods), Del Favero et al. (2011).

Both identification and validation are based on in-silico data collected from the adult virtual population of the UVA/Padova simulator (see Dalla Man et al. (2014)). The

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data cover a 3-day closed-loop (CL) identification protocol where the patient BG is controlled by the MPC proposed in Toffanin et al. (2013), synthesized on the basis of an average linear time invariant model (A-MPC) and currently used in several clinical trials. The protocol was designed to produce a sufficient input excitation without compromising patient safety and is compatible also with real life settings. A-MPC is also used for the in-silico generation of the validation data, which involves a 3-day CL protocol reproducing a standard real life scenario. The validation performance is evaluated by means of the coefficient of determination (COD), FIT, positive and negative max errors (PME and NME, respectively), and root mean squared error (RMSE). The identified models are compared to the average linear time invariant model used to synthesize the A-MPC.

The MPC synthesized with the individualized models (I-MPC) and the A-MPC are compared in terms of CL control performance in an in-silico study on the adult virtual population of the UVA/Padova simulator in a perturbed scenario, where the controller is blind to random variations of insulin sensitivity in each virtual patient.

2. NON-PARAMETRIC APPROACH

This Section reports a concise description of the NP identification approach, for sake of simplicity presented for a single input. Details of the multi-input formulation, needed for our application, can be found in Pillonetto et al. (2011). The aim is to obtain a linear dynamical model of the form

$$y(t) = \sum_{k=1}^{\infty} q(k)u(t-k) + \sum_{k=0}^{\infty} w(k)e(t-k) \qquad (1)$$

where u and y are the model input and output, respectively, and e is a white noise signal.

2.1 Linear predictor estimation

Let consider a generic linear one-step ahead predictor of the form

$$\hat{y}(t) = \sum_{k=1}^{\infty} f(k)y(t-k) + \sum_{k=1}^{\infty} g(k)u(t-k) \qquad (2)$$

where $\hat{y}$ is the predicted output, and f and g are the output and input discrete impulse responses, respectively, which have to be estimated from noisy measurements. The estimation of the unknown impulse responses can be performed by solving an optimization problem in an infinite-dimensional functional space given by a reproducing kernel Hilbert space (RKHS). The kernel of the RKHS should reflect the properties of the functions to be estimated and its choice is a key point in the NP approaches. In this study, the chosen kernel K is the stable spline kernel (SSK) proposed in Pillonetto et al. (2010), where the generic impulse response f_{SSK} to identify is seen as a realization of a zero-mean Gaussian random process whose covariance can be written as

$$Cov(f_{SSK}(k), f_{SSK}(l)) = \lambda^2 K(k,l) = \lambda^2 \left(\frac{e^{-\beta(k+l)} e^{-\beta \max(k,l)}}{2} - \frac{e^{-3\beta \max(k,l)}}{6} \right) \qquad (3)$$

with $k, l = 1, 2, \ldots, \infty$, $\beta > 0$, and $\lambda > 0$. As explained in Pillonetto et al. (2011), by defining K_f and K_g the SSK of f and g, respectively, and letting $\mathscr{H}_f$ and $\mathscr{H}_g$ denote the RKHS of deterministic functions on $\mathbb{N}$ associated with K_f and K_g (with norms denoted by $\|\cdot\|_{\mathscr{H}_f}$ and $\|\cdot\|_{\mathscr{H}_g}$), the stable spline estimators $\hat{f}$, $\hat{g}$ of f, g are obtained from the solution of the following Tikhonov-type variational problem:

$$(\hat{f}, \hat{g}) = \arg \min_{h_f \in \mathscr{H}_f,\, h_g \in \mathscr{H}_g} \left\{ \|y^+ - Ah_f - Bh_g\|^2 + \gamma_f \|h_f\|^2_{\mathscr{H}_f} + \gamma_g \|h_g\|^2_{\mathscr{H}_g} \right\} \qquad (4)$$

$$[A]_{ji} = y(j-i), \quad [B]_{ji} = u(j-i)$$
$$i = 1, 2, \ldots, \infty, \quad j = 1, 2, \ldots, n$$
$$y^+ = [y_1 \; y_2 \; \ldots \; y_n]^T$$

where $\|\cdot\|$ is the Euclidean norm, $\gamma_f = \sigma^2/\lambda_f^2$, $\gamma_g = \sigma^2/\lambda_g^2$, and n is the number of future samples to consider during the identification procedure. In view of (3), the covariances of the impulse responses f and g include the parameters β_f and β_g, respectively. Here β_f, β_g, γ_f, γ_g, and σ are *hyperparameters*, that have to be properly tuned prior to the solution of the Tikhonov problem (4). By assuming known hyperparameters, the solution of (4) is given by

$$\hat{f} = \lambda_f^2 K_f A^T \phi$$
$$\hat{g} = \lambda_g^2 K_g B^T \phi$$
$$\phi = (\lambda_f^2 A K_f A^T + \lambda_g^2 B K_g B^T + \sigma^2 I_n)^{-1} y^+$$

where I_n is the $n \times n$ identity matrix.

2.2 Hyperparameter estimation

By letting ζ denote the hyperparameters vector, as explained by Pillonetto et al. (2011), the maximum (marginal) likelihood estimate $\hat{\zeta}$ of ζ is given by

$$\hat{\zeta} = \arg \min_{\zeta} J(y^+, \zeta)$$
$$J(y^+, \zeta) = \frac{1}{2} \ln(\det[2\pi V[y^+]]) + \frac{1}{2} (y^+)^T (V[y^+])^{-1} y^+$$
$$V[y^+] = \lambda_f^2 A K_f A^T + \lambda_g^2 B K_g B^T + \sigma^2 I_n$$

where J is the opposite log-marginal likelihood of y^+.

2.3 Linear model

By considering the predictor (2), estimated by solving (4), it holds that

$$y(t) = \hat{y}(t) + e(t)$$

and the input-output form of (1) can be approximated as

$$y(t) = \frac{\sum_{k=1}^{p} g(k) z^{-k}}{1 - \sum_{k=1}^{p} f(k) z^{-k}} u(t) + \frac{1}{1 - \sum_{k=1}^{p} f(k) z^{-k}} e(t)$$

where the Z-transform formalism has been used. The approximation consists in truncating the summations to p, a tunable parameter that however can be arbitrarily large. The Z-transforms of q and w of (1) are given by

$$Q(z) = \frac{\sum_{k=1}^{p} g(k) z^{-k}}{1 - \sum_{k=1}^{p} f(k) z^{-k}}, \quad W(z) = \frac{1}{1 - \sum_{k=1}^{p} f(k) z^{-k}}$$

and admit a minimal realization of dimension p.

3. GLUCOSE-INSULIN MODELS

For each virtual patient a linear one-step ahead predictor is derived having the form

$$\hat{c}(t) = \sum_{k=1}^{p} \left(f(k)c(t-k) + g_1(k)i(t-k) + g_2(k)m(t-k) \right) \tag{5}$$

where the infused insulin $i(k)$ and the carbohydrates intake $m(k)$ are the inputs, and the prediction $\hat{c}(k)$ of the CGM measurement $c(k)$ of subcutaneous glucose is the output. From this predictor, the following model is derived:

$$c(k) = Q_{im}(z)[i(k) \;\; m(k)]^T + W(z)e(k) \tag{6}$$

with

$$Q_{im}(z) = \begin{bmatrix} \dfrac{\sum_{k=1}^{p} g_1(k)z^{-k}}{1 - \sum_{k=1}^{p} f(k)z^{-k}} & \dfrac{\sum_{k=1}^{p} g_2(k)z^{-k}}{1 - \sum_{k=1}^{p} f(k)z^{-k}} \end{bmatrix}$$

Its minimal state-space realization can be conveniently used in the MPC algorithm.

3.1 Identification

The training set is generated in-silico with a 3-day protocol composed by three meals per day (breakfast, lunch, and dinner) with additional snacks in each day that are controlled without announcement (see Soru et al. (2012) for details about meal announcements). Data are generated in CL with A-MPC on the adult population of the UVA/Padova simulator. This protocol is designed to produce a sufficient input excitation without compromising patient safety and can be proposed also in real life settings, where the identification data would be collected in clinical experiments.
By following the approach described in Section 2, a linear predictor having the form (5) is identified for each virtual patient by using $c(k)$ as system output (noisy CGM traces are generated with the sensor noise model described in Toffanin et al. (2013)), and $i(k)$ and $m(k)$ as system inputs. The order of the minimal realization of the identified models can vary depending on the patients characteristics.

3.2 Validation

Similarly to the training set, the test set is generated in-silico by considering a 3-day CL protocol in which the meal amounts and times are changed so as to represent a real life scenario. The identified models are validated in simulation by considering the inputs $i(k)$ and $m(k)$ and by setting $e(k) = 0 \; \forall k$ (i.e. $W(z)$ is not excited). This correspond to test model prediction over an infinite prediction horizon.
The model predictions are evaluated through the following performance indices:

$$\text{COD} = 100 \left(1 - \frac{\|c(k) - I_g(k)\|_2^2}{\|I_g(k) - \bar{I}_g\|_2^2} \right)$$
$$\text{FIT} = 100 \left(1 - \frac{\|c(k) - I_g(k)\|_2}{\|I_g(k) - \bar{I}_g\|_2} \right)$$
$$\text{PME} = \max\left\{ \max\left(c(k) - I_g(k) \right), 0 \right\}$$
$$\text{NME} = \min\left\{ \min\left(c(k) - I_g(k) \right), 0 \right\}$$
$$\text{RMSE} = \sqrt{\frac{\|c(k) - I_g(k)\|_2^2}{N_s}}$$

where $I_g(k)$ is the interstitial glucose simulated by the non-linear virtual patient model of the UVA/Padova simulator, $\bar{I}_g$ is its average, and N_s is the total number of samples considered in the validation protocol. Table 1 shows a comparison of the mean prediction performance achieved on the adult population by the identified NP models and by the average model used to synthesize A-MPC. The gain achieved by the NP models is evident.

Table 1. Prediction performance indices on the adult population of the UVA/Padova simulator (mean ± SD)

	Average Model	NP Models
COD	−238.98 (±389.31)	87.04 (±7.98)
FIT	−62.26(±87.43)	65.53 (±10.44)
PME	59.15 (±43.57)	22.05 (±6.32)
NME	−71.68 (±75.81)	−10.13 (±5.01)
RMSE	39.82 (±29.73)	8.08 (±2.40)

Fig. 1 shows simulations performed on the validation protocol with the average patient, i.e. a patient whose parameters are the average values of 100 virtual patients of the adult population. The simulations provided by the corresponding identified NP model and by the model linearized around the basal equilibrium are also reported. One can note that the NP model is able to reproduce better the glucose excursions of the virtual patients especially far from the basal value (e.g. where glycemia peaks occur due to the meal intake). Consider also that the average patient is a favorable case of study for the average linear model, that has been obtained by linearizing exactly this patient. On the contrary, it is just a representative case for the NP techniques.

4. INDIVIDUALIZED MPC CONTROLLER

Based on the MPC algorithm presented in Toffanin et al. (2013), the I-MPC is obtained for each patient using the linear model derived by the minimal state space realization of (6). Moreover, the cost function to be minimized is tuned directly on the identified model.

4.1 Controller calibration

First define the cost function

$$J(x(k), i(\cdot), k) = \sum_{j=0}^{\text{PH}-1} \left(q_c(c(k+j) - y_0(k+j))^2 \right. \\ \left. + (i(k+j) - i_0(k+j))^2 \right) + \|x(k+N)\|_P^2 \tag{7}$$

where $i(k)$ is the insulin to be infused at each time k, $x(k)$ the NP model state, PH the prediction horizon, $i_0(k)$ the insulin suggested by the patient conventional therapy, $y_0(k)$ the glucose set-point, P the solution of the discrete time Riccati equation, and q_c a parameter that quantifies the controller aggressiveness. The latter is tuned through a calibration procedure driven by the following minimization problem:

$$\hat{q}_c = \arg\min_{q_c} \left\{ \|[X_{CVGA} \;\; Y_{CVGA}]\|_2 + \left(\log_{10}(q_c) - \xi \right)^2 \right\}$$
$$q_c^o = \min\{\max\{\hat{q}_c, \overline{q}_l\}, \overline{q}_h\} \tag{8}$$

where q_c^o is the optimized q_c, $\overline{q}_l$ and $\overline{q}_h$ are minimum and maximum allowed values, respectively, ξ is a parameter, and X_{CVGA} and Y_{CVGA} are the coordinates on the Control Variability Grid Analysis (CVGA) introduced in Magni et al. (2008) and refined in Soru et al. (2012). The calibration cost of (8) is composed by two terms. The aim of the first one is to obtain a q_c^o value that is able to maintain the patient BG as close as possible to 110 mg/dl, that corresponds to the left corner of the CVGA (an example of which is shown in Fig. 4). The second is used to bias the $\log_{10}(q_c^o)$ value to $\xi \in [\log_{10}(\overline{q}_l) \;\; \log_{10}(\overline{q}_h)]$. High ξ values will make I-MPC an aggressive controller while

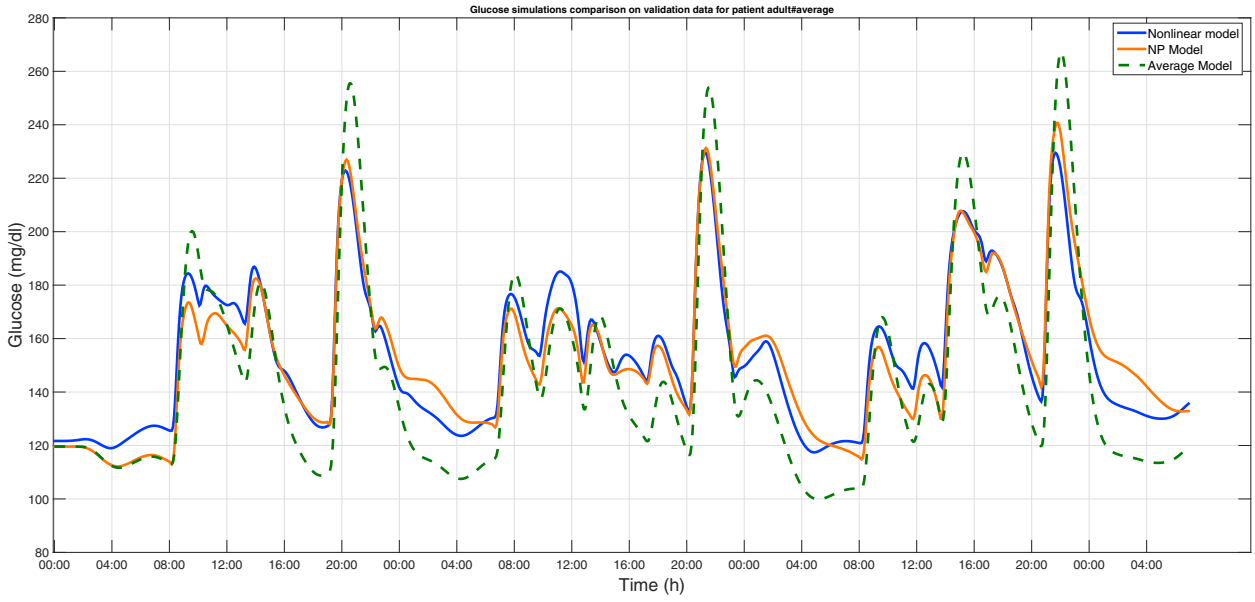

Fig. 1. Glucose simulations on the validation protocol: comparison with the average adult virtual patient. The simulations are generated by the nonlinear model (blue solid line), by the identified NP model (orange solid line), and by the linearized model around the basal equilibrium (green dashed line). The latter is used to synthesize A-MPC.

low ξ values will make I-MPC more conservative. The problem (8) is minimized in a protocol that is composed by three meals and one night and is simulated in CL with the I-MPC on the identified NP model (i.e. the virtual patient and the controller share the same linear identified NP model). This procedure is entirely performed automatically by a trial and error approach and can be exploited to find the optimal q_c^o value. In order to synthesize a conservative I-MPC for each patient, ξ has been imposed close to $\log_{10}(\overline{q}_m)$. This choice is motivated by the higher average PME achieved during the validation protocol with respect to the average NME (as shown in Table 1), which reveals the tendency of the identified NP models to slightly overestimate the actual patient glycaemia.

It is worth to emphasize that the presented calibration procedure is different with respect to that described in Soru et al. (2012), where the calibrations were performed on the nonlinear models of the adult virtual population and, in order to obtain an estimate of the optimal q_c^o for the real patient, a regression model based on clinical parameters was identified. In this study, the calibration is performed directly on the identified NP linear model and the derived optimal q_c^o value is used for the considered diabetic patient.

5. SIMULATION RESULTS

I-MPC and A-MPC were simulated in CL with a perturbed simulation protocol on the adult population of the UVA/Padova simulator. In order to evaluate the robustness in presence of model uncertainties, the controller is blind to a random ±25% variation of the patients insulin sensitivity. The considered simulation protocol is depicted in Fig. 2, the postprandial periods are defined as 4 hour time intervals after each meal and the night period begins at 23:00 and lasts 8 hours. If glycemia falls below 65 mg/dl, the protocol imposes 16 g of carbohydrates administration, called hypo treatment (HT). Two consecutive HT are separated by at least 30 min.

The CL control performance was evaluated by means of the average glucose (A), the glucose standard deviation (SD), the time spent within [70 180] mg/dl or time in target (Tt), the time spent within [80 140] mg/dl or time in tight target (Ttt), the time spent above 180 mg/dl or time above target (Ta), the time spent below 70 mg/dl or time below target (Tb), the time spent below 50 mg/dl or time in hypo (Th), the number of HT (# HT), and the number of patients with at least one HT (# pats with HT). Table 2 shows the control performance achieved by I-MPC and A-MPC on the perturbed simulation protocol of Fig. 2. The O, N, and PP columns represent the outcome indices computed during the overall (O) scenario, during the night (N), and by considering the CL postprandial (PP) periods, respectively. The p–values used to evaluate the statistical significance of the indices differences are shown in Table 2, with * representing p–value < 0.05, ** representing p–value < 0.03, and *** representing p–value < 0.001. p–values calculation is performed with the paired t-test

Table 2. MPC CL performance achieved with the perturbed simulation protocol. * represents p–value < 0.05, ** p–value < 0.03 and *** p–value < 0.001

		O	N	PP
A (mg/dl)	I-MPC	136.74***	114.14***	150.10
	A-MPC	140.55	120.99	149.25
SD (mg/dl)	I-MPC	26.56***	6.44	23.98
	A-MPC	25.22	7.57	24.67
Tt (%)	I-MPC	87.17	99.73	79.99
	A-MPC	87.04	99.63	79.69
Ttt (%)	I-MPC	58.43**	96.26*	39.30
	A-MPC	55.50	94.39	38.08
Ta (%)	I-MPC	12.15	0.15	19.35
	A-MPC	12.25	0.22	19.13
Tb (%)	I-MPC	0.67	0.12	0.65
	A-MPC	0.71	0.15	1.17
Th (%)	I-MPC	0.11	0.00	0.15
	A-MPC	0.10	0.00	0.21
#HT	I-MPC	45	1	30
	A-MPC	49	1	41
# pats with HT	I-MPC	7	1	7
	A-MPC	9	1	7

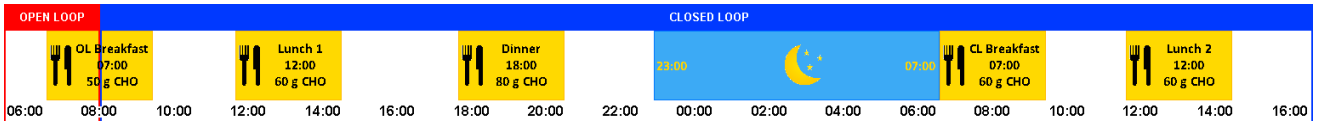

Fig. 2. Simulation protocol composed by 5 meals (4 CL meals), and one CL night.

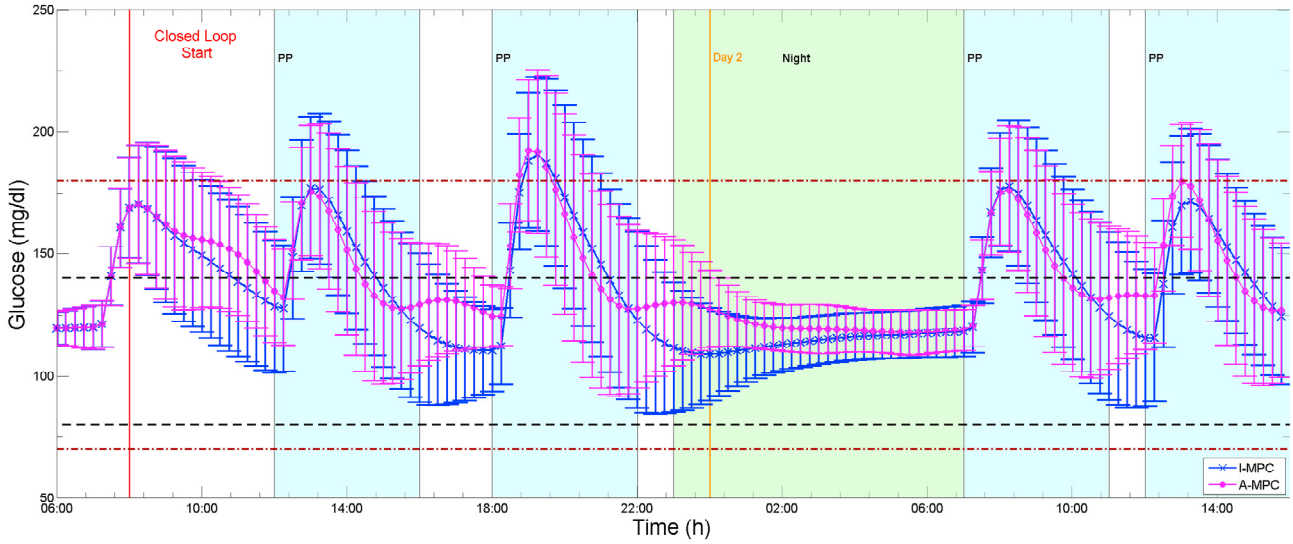

Fig. 3. Blood glucose time courses achieved on the perturbed simulation protocol with I-MPC and A-MPC in terms of mean (central solid line) and standard deviations (vertical bars). CL start is represented by the solid red vertical line. The dashed black and the dot dashed brown lines represent tight target range ([80 140] mg/dl) and the target range ([70 180] mg/dl), respectively. PP represents a CL postprandial period.

if the distributions are normally distributed or with the Wilcoxon signed-rank test if at least one of the distribution is not normally distributed. Lilliefors test is used to check the normality.

I-MPC is able to significantly reduce the average glucose, to increase the Tt, to significantly increase the Ttt and to reduce Tb and Ta at the same time. Th is slightly increased during the O period, but the # HT are reduced during both O and PP periods. The glucose SD is significantly increased during the O period and is reduced during N and PP. It is interesting to note that all the HT events are concentrated in less than 10 patients with both the controllers. Figures 3 and 4 show the blood glucose time courses and the CVGA achieved with I-MPC and A-MPC on the perturbed simulation protocol. I-MPC moves the majority of the CVGA points towards the B-zone and achieves a better glucose control after each meal.

6. CONCLUSION

The presented NP approach was able to identify effective patient-tailored linear time invariant glucose-insulin models. The CL control performance was improved and the individualized models identification was based on a protocol studied to produce a sufficient input excitation without compromising patient safety. Thanks to the compatibility of the identification protocol with real life scenarios, the presented identification method can be used in-vivo, where data coming from clinical experiments can be used to synthesize an individualized MPC for AP. Furthermore, in order to find the optimal tuning, the individualized MPC cost function is automatically calibrated by a trial and error approach on the identified NP model.

A possible future improvement of this work could address the addition of high frequency poles as prior information for the NP identification. The modified prior could reduce the glucose over- and underestimation of the identified models especially during the postprandial excursions, where the fastest model dynamics are excited, thus further improving the resulting CL control performance.

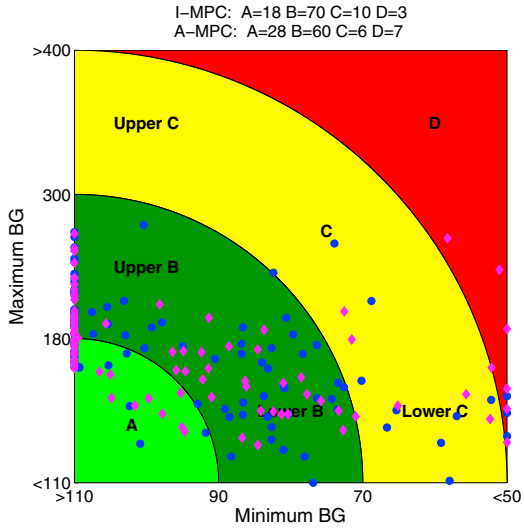

Fig. 4. Control Variability Grid Analysis achieved with I-MPC (blue circles) and A-MPC (magenta diamonds) on the perturbed simulation protocol.

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