Model-based Healthcare Applications at Óbuda University

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Abstract— **Following the tradition established at previous IEEE INES conferences, this paper presents the results achieved by the Physiological Controls Group of Óbuda University in the field of physiological control last year (2013). The application target was focused on diabetes (artificial pancreas), tumor (antiangiogenic therapy), and hemodialysis (control of peristaltic pumps).**

I. INTRODUCTION

Physiological control studies and applies identification and control strategies in order to understand and help automated treatment of various diseases or injuries of the human body. As a particular field of biomedical engineering [1], nowadays the key target of physiological control is to efficiently create and support personalized solutions for disease management in a model-based way. The aim of the recently established Physiological Controls Group of the Óbuda University is to develop solutions in the mentioned area working together in control applications with the Department of Control Engineering and Information Technology of the Budapest University of Technology and Economics and the Semmelweis University from Budapest.

The article briefly summarizes the newest (last year, 2013) results obtained in the field, following the tradition established at the previous IEEE INES 2011-2013 conferences [2-4]. Control results in three different fields are presented:

- cancer, where the uncontrolled growth of abnormal cells [5] are proposed to be handled by control engineering methods. As a result, not only the tumor volume can be minimized, but also the dosage of the inhibitor creating a cost-efficient therapy. For this our idea follows robust control methodology.

- diabetes mellitus, where the problem of artificial pancreas [6] is investigated. Newest results in robust control are presented in order to deal with high uncertainties caused by imprecise descriptions of the glucose metabolism.

- hemodialysis, where direct blood particle separation is done with external devices, i.e. peristaltic pumps maintain the fluid flows [7]. However, the transfer depends on their loaded tube segment; hence, the fluid balance should be controlled.

II. ROBUST CONTROL DEVELOPMENT FOR CANCER TREATMENT

P. Hahnfeldt et al. created a dynamic model for tumor growth for antiangiogenic therapy [8]. The aim of antiangiogenic therapy is to prevent tumors from forming new blood vessels, because without angiogenesis tumor growth is inhibited [9]. The original model was modified; the simplified model takes into account continuous infusion therapy [10]. Fig. 1 presents the simulated tumor growth with and without antiangiogenic therapy. Without treatment the growing tumor size reaches lethal state (17340 mm^3), while with antiangiogenic therapy the tumor size can be reduced.

Hence, robust control strategy has been investigated. The proposed control structure is presented in Fig. 2. K is the two-degrees of freedom controller which consists of two parts: K_r is the feedforward branch and K_y is the feedback branch. Multiplicative uncertainty (G_{unc}) has been taken into account in order to handle differences between the nominal model and the real system.
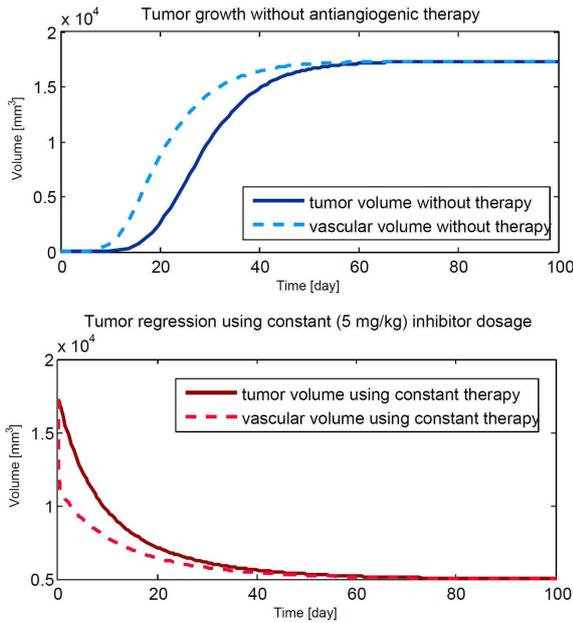
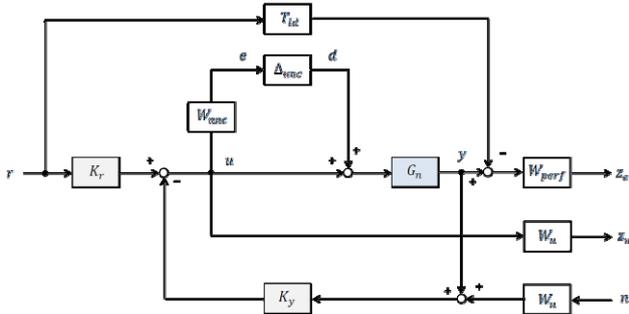Figure 1. Simulation results of with and without therapy case.

Figure 2. The closed-loop interconnection structure for controller design

W_n stands for sensor noise weighting function, W_u for the control input one, while T_{id} represents the transfer function for the ideal system. W_{perf} represents the performance weighting function [11].
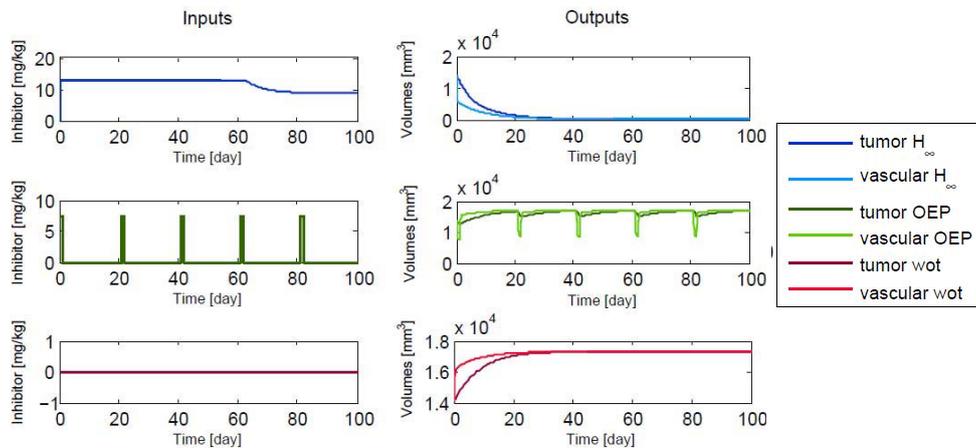
The results (Fig. 3 and Fig. 4) have shown that the designed H_∞ controller can handle the sensor noise in a robust way until 15%. We have simulated and compared the changes in three different cases. The first case was a therapy when the inhibitor was administered by the H_∞ controller. In the second case the therapy was based on the Hungarian OEP protocol for antiangiogenic monotherapy [12]. The third case was the simulation without therapy.

One can see that intermittent dosing used by the chemotherapy protocol is not effective. The tumor volume reduced slightly as a result of one-day dose, but between the treatment phases, tumor grows back again. At the end of the whole treatment period, there is no large difference between the therapy with OEP protocol and the case without therapy.

III. ROBUST CONTROL FRAMEWORK FOR TYPE 1 DIABETES

Although model predictive control (MPC) is one of the most effective method in individual based therapies of diabetes, in practice the controlled process can deviate from the nominal model. Hence, robust methods are required in order to satisfy general requirements (e.g. avoiding hypoglycemia) under unexpected situations or extreme conditions.

Our approach focuses on Linear Parameter Varying (LPV) method [13] making direct nonlinear control possible. In the last period, we have examined whether the capabilities of a robust LPV controller could be extended by additional constraints. Investigations have been done for the well-known model of [14].
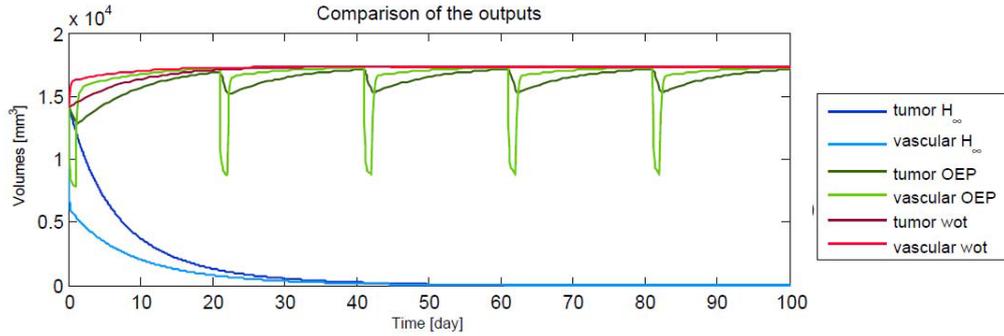
Figure 3. Comparison of input and output signals of the systems in the mentioned cases: *(i)*, *(ii)* and *(iii)*

Figure 4. Comparison of changes in tumor volume after making the diagnosis (14137 mm^3) in three different cases:
a) therapy using the controller which was designed with Robust Control method
b) therapy based on the Hungarian OEP protocol for antiangiogenic monotherapy
c) without therapy

There are two main sources of uncertainty: parameter inaccuracy and scheduling parameter inaccuracy. Fig. 5 captures the control structure taken into account. Measurement noise and the parameter inaccuracies were randomized and the aim of our research was to examine control quality in case of unannounced meals or high amount of carbohydrate (CHO) intakes.

An example of virtual patient simulation is shown in Fig. 6. Three different protocols have been taken into account: classical 150 g CHO, 215 g CHO and irregular and inexactly determined (±20 g CHO) meal intake. Overall summary of the investigations have been presented on the well-known literature metric of control variability grid analysis (CVGA) (Figs. 7-8).

One can see that robustness is achieved even in extreme conditions, demonstrating the effectiveness of the methodology avoiding hypoglycaemia as well.
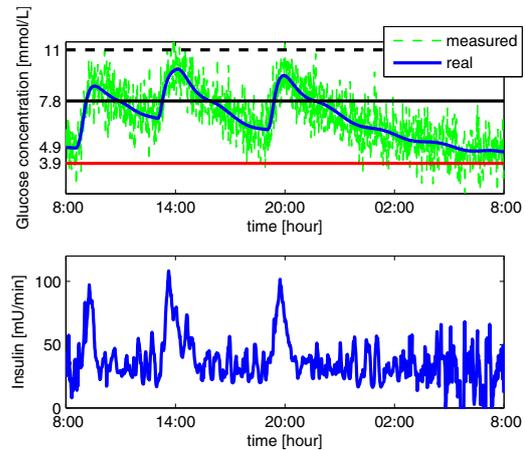

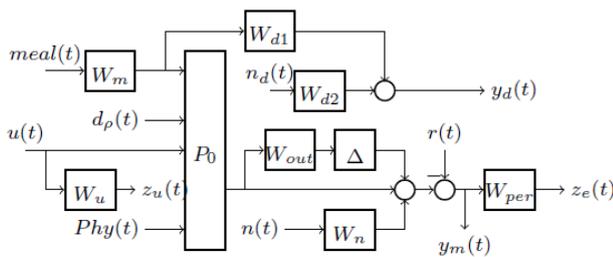Figure 6. Example for Virtual Patient (VP) simulation

Figure 5. Control structure for type 1 diabetes investigations

IV. AUTOMATIC CONTROL OF PERISTALTIC PUMPS

The transfer volume of peristaltic pumps depends mainly on their loaded tube segment. Due to the deviation of production their transfer volume can differ by $\pm10\%$ that is important from the patient point of view. As a result, fluid flow should be controlled automatically. The system contains a hanged bag above the peristaltic pump's level (with the solution to be transported), the peristaltic pump and a vessel collecting the transported fluid.
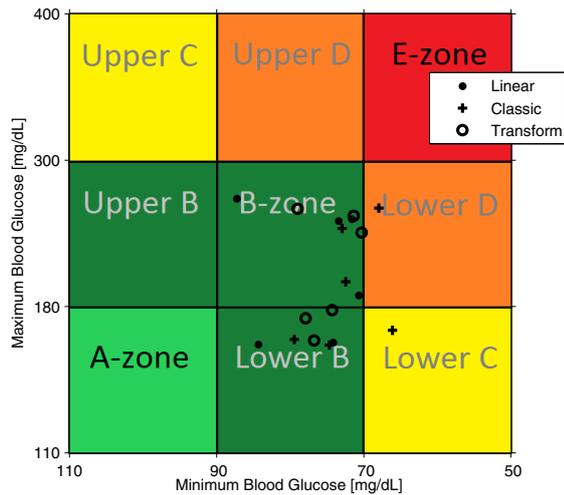
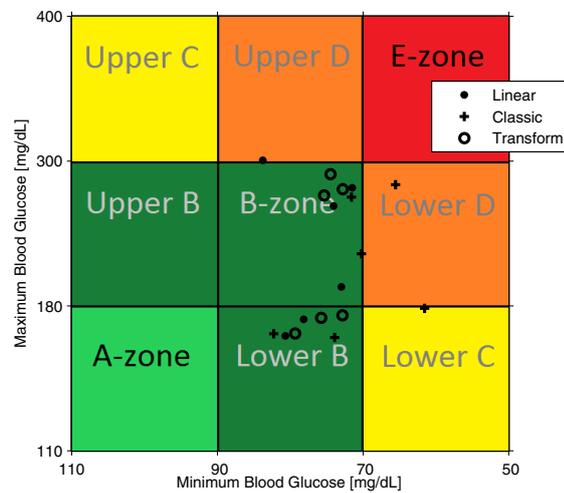Figure 7. CVGA of all LPV controllers for 150 g of daily carbohydrate intake

Figure 8. CVGA of all LPV controllers for (2) meal intake protocol

First system identification was necessary in order to determine the transfer function of the considered plant. Different methods have been used and compared: ARX, ARMAX, Box-Jenkins and output error (OE).
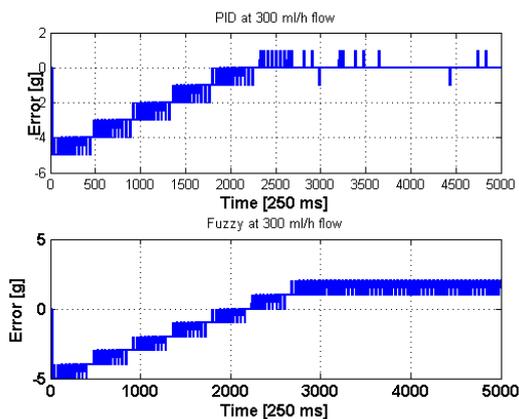

Figure 9. System error from settling time point of view (At 300 ml/h, -10% slope error, 20 g offset error)

Two control methodologies have been examined: classical PID and fuzzy rule-based ones. Three scenarios were taken into account with different fluid flows: one with medium low flow (300 ml/h), one with medium flow (1500 ml/h) and one with highest flow (3000 ml/h). Control quality from settling time, accuracy and overshoot can be seen in Fig. 9, Fig. 10 and Fig. 11.

Due to similar results obtained, PID controller was applied for the real system (Fig. 12). It can be seen that desired performance was achieved.
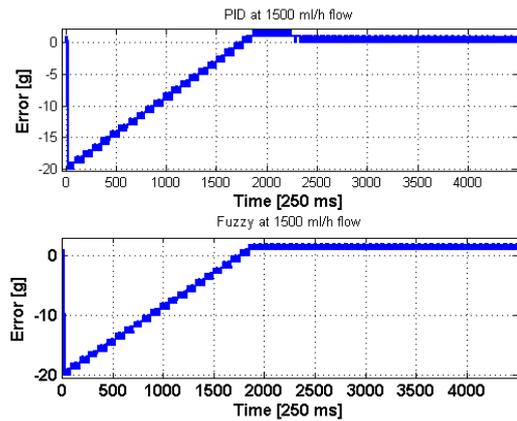

Figure 10. System error from overshot point of view (At 1500 ml/h, -10% slope error, 20 g offset error)
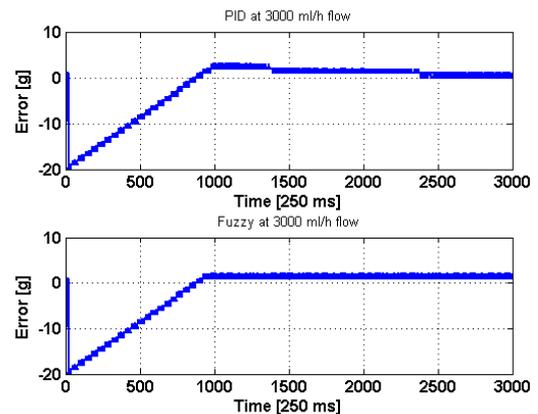

Figure 11. System error at in accuracy examination (At 3000 ml/h, -10% slope error, 20 g offset error)
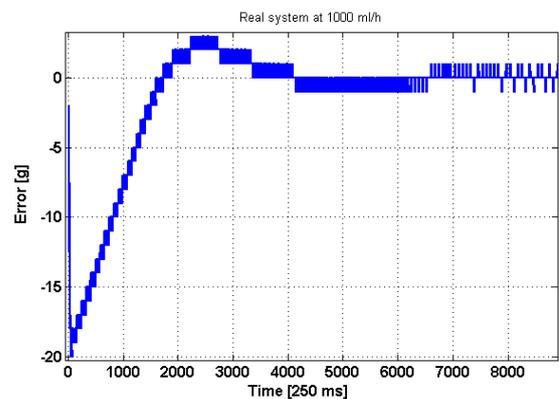

Figure 12. System error in the real system (At 1000 ml/h, -5% slope error 20 g offset error)

V. CONCLUSIONS

The paper summarized the latest research results in the field of physiological modeling and control carried out by Physiological Controls Group of the Óbuda University.

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