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Theoretical blood glucose control in hyper- and hypoglycemic and exercise scenarios by means of an H_∞ algorithm

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A B S T R A C T

Artificial Endocrine Pancreas (AEP) is one of the most optimistic approaches in Type 1 Diabetes Mellitus (T1DM) treatment due to the novel technological advances in continuous glucose monitoring, exogenous insulin delivery, and their proofs in clinical assessments. The main goal of AEP is to replace the pancreatic insulin secretion in the blood glucose regulation loop by means of an automatic exogenous insulin infusion. The joint element between glucose sensing and insulin delivering actions is an automatic algorithm-based decision. In this contribution, there is an H_∞ control algorithm to compute the insulin infusion rate during hyperglycemia, exercise and nocturnal hypoglycemia. In order to mimic the insulin release pattern of a healthy pancreas, a frequency restriction in the insulin infusion pattern generated by controller was considered in the design. The inclusion of mathematical models of relations between glucose and chosen biosignals in the control loop generates an adequate insulin infusion pattern to compensate blood glucose variations during each metabolic scenario. The proposed automatic algorithm for decision shows good performance in controlling glycemia in metabolic scenarios, avoiding long-term hyperglycemia as well as glycemic disturbances during exercise and nocturnal hypoglycemia, guaranteeing insulin infusion with a delivery pattern closer to that generated by a healthy pancreas.

1. Introduction

Type 1 Diabetes Mellitus (T1DM) is a metabolic disease caused by the auto-immune destruction of pancreatic $\beta-$cells, resulting in an insignificant release of insulin into the blood stream. The developed treatments around T1DM have been addressed to satisfy the insulin requirements, mainly through the re-establishment of insulin delivery function, as pancreatic islet transplantation (Morath and Zeier, 2009; James et al., 2000), or by the substitution of the secretory function by means of an external mechanism, like insulin infusion (Pickup and Keen, 2002; Lenhard and Reeves, 2001). In both options, the aim is to ensure enough insulin to metabolize blood glucose (Korenman, 2000).

Since insulin was synthesized, daily insulin injections have become the most accessible and popular treatment of T1DM; nevertheless, the successful substitution of the pancreatic insulin release has required extensive work regarding the solution of its essential problem: *supplying the required insulin amount to compensate blood glucose variations*. Many advances have been addressed to develop suitable technology for insulin infusion and glucose measurement (Lenhard and Reeves, 2001; Mastrototaro, 2000). The efforts to improve external infusion therapy have resulted in the so-called Artificial Endocrine Pancreas (AEP). Such device attempts to integrate continuous insulin infusion and continuous glucose monitoring with an automatic algorithm (Bequette, 2005), which computes the required infusion rate. That means, the AEP might be the promising evolution of the classic insulin infusion injections towards a real automatic insulin delivery closer to pancreatic insulin release.

The AEP seeks to incorporate the physiological loop of glucose regulation that determines pancreatic insulin delivery due to variations of blood glucose concentration, promoting or inhibiting insulin delivery to maintain glucose within its physiological range. Clinical trials on the use of Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) suggest an improvement in glycemia management in T1DM (Pickup and Keen, 2002; Kaufman et al., 2001); however, the integration of the essential parts of the AEP (insulin pump, glucose sensor and algorithm) is in its early stages. A recent study has reported experimental closed-loop data employing intravenous subcutaneous glucose sensors, implanted externally with insulin pumps, and a PID (Proportional, Integral and Derivative) control scheme as automatic algorithm for decision (Steil et al., 2004). A couple of years later, a similar contribution has been

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reported in human T1DM patients (Steil et al., 2006). In spite of these early advances, there are many issues to tackle towards the integration of the AEP; in fact, the advances, challenges and main problems to integrate the AEP have been clearly outlined recently (Klonoff, 2007). In case of glucose sensing and insulin delivery the problems are in designing a suitable way of insulin infusion, trying to mimic the pancreatic release, and the precise measurement of glucose concentration reducing complications (rejection, fibrosis, inflammation, etc.), respectively. Regarding automatic algorithm, its aim is to compute a continuously auto-adjustable insulin infusion rate depending on the measurements of the current blood glucose concentration value and metabolic condition of the patient. A very concise review about the closed-loop algorithms for glycemic control in T1DM can be found in Youssef et al. (2009).

The first attempt to automatize the decision was proposed in early 60 s (Kadish, 1964). In this approach a basic *on-off* scheme was used, i.e. an established (and fixed) insulin amount was delivered if blood glucose level was above the euglycemic range (70–120 mg/dl) and it was inhibited if the blood glucose was within the euglycemic range; although this scheme has a very basic sense of automatization, it did not determine the required insulin amount for a specific blood glucose concentration. After that, traditional techniques of classic control (Gopakumaran et al., 2005) were applied to obtain control laws based on simple mathematical models of glucose metabolism (Bergman et al., 1981). In fact, traditional control schemes PI (Proportional-Integral), PD (Proportional-Derivative) and PID have been used in the first attempts to integrate the AEP (Steil et al., 2004, 2006; Stuart et al., 2008). Understanding the control problem to determine the pancreatic insulin delivery has required the use of advanced control techniques. Along this line, some algorithms based on nonlinear model predictive control (Hovorka et al., 2004; Hovorka, 2006) and those based on mathematical compartmental models of glucose metabolism (Parker and Doyle, 2000; Ruiz-Velázquez et al., 2004; Femat et al., 2009). Since hyperglycemia due to ingesta is the most common symptom in T1DM, all these control approaches have been designed to avoid high blood glucose concentration. Nevertheless, in order to reach an acceptable glycemia control, more metabolic states must be considered in the decision process. Two of the typical metabolic scenarios of a T1DM patient are exercise and recurrent hypoglycemia induced by the insulin treatment. The necessity of having an adequate automatic algorithm considering such metabolic scenarios is the main motivation of our contribution. We propose the design of a control algorithm based on H_∞ theory that takes into account exercise and hypoglycemia, as well as hyperglycemia. Moreover, a restriction in the insulin infusion rate computed by the algorithm was imposed in order to mimic the delivery pattern generated by a healthy pancreas.

2. Biosignals in algorithm-based decision control

Basal carbohydrate metabolism is altered if there are changes in requirements or disposal of energy. Although the source of such changes can be different physiological functions, the direct effect derives from variations in blood glucose concentration. In a control system where the controlled signal is the blood glucose concentration, such variations can be considered as disturbances. So, the aim is to design an automatic algorithm able to reach the control objective even though disturbances (from different sources) in the blood glucose concentration. We consider three main sources of disturbances: (i) energy excess due to ingesta (typical hyperglycemic scenario), (ii) energy requirement due to physical exercise, and (iii) energy depletion due to hypoglycemic scenarios. In this section, a mathematical model of each disturbance source is presented. These models are obtained from the relations of blood glucose concentration and three indicative biosignals in each scenario: (i) insulin in hyperglycemia, (ii) lactate in exercise, and (iii) adrenaline in hypoglycemia, as it is shown in diagram of Fig. 1. Next, the modelling methodology and the obtaining of each disturbance model are presented.

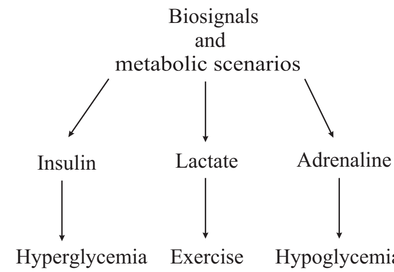

Fig. 1. Diagram of biosignals and associated metabolic scenarios.

2.1. Modelling methodology: ARX technique

The ARX (AutoRegressive with eXternal input) is a modelling technique of System Identification Theory used to propose mathematical models from measured data of the system stimulus (input) and response (output) (Ljung, 1999). The input data can be represented by the set $\{u(1),u(2),\ldots,u(kT),\ldots,u(NT)\}$, where $u(kT)\in\mathbf{R}$, $k\in\{1,2,\ldots,N\}$ and $N\in\mathbf{N}$. N is the total number of measured data taken at each sample time T. Likewise, the set of output data is given by: $\{y(1),y(2),\ldots,y(kT),\ldots,y(NT)\}$, where $y(kT)\in\mathbf{R}$. The input and output data sets form the general set of measured data:

$$M^N=(u(1),y(1)),(u(2),y(2)),\ldots,(u(kT),y(kT)),\ldots,(u(NT),y(NT)) \tag{1}$$

Because M^N is a set of discrete data, the common form to approach the system behavior is by means of a difference equation:

$$y(k)=-a_1y(k-1)-\cdots-a_ny(k-n)+b_1u(k-1)+\cdots+b_nu(k-n) \tag{2}$$

where $a_1,\ldots,a_n,b_1,\ldots,b_n\in\mathbf{R}$, $n\in\mathbf{N}$, and k stands for a discrete time moment. Eq. (2) can be written as: $y(k)=\phi(k)^T\theta$ where $\theta=[a_1 \ \cdots \ a_n \quad b_1 \ \cdots \ b_n]$ is the parameter vector and

$$\varphi(k)=\begin{bmatrix} -y(n) & \ldots & -y(1) & u(n) & \ldots & u(1)\\ -y(n+1) & \ldots & -y(2) & u(n+1) & \ldots & u(n)\\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots\\ -y(N-1) & \ldots & -y(N-n) & u(N-1) & \ldots & u(N-n)\end{bmatrix} \tag{3}$$

The parameter vector θ can be estimated by the Least Square Method, minimizing the estimation equation $V_N(\theta,M^N) = \sum_{k=1}^{N}(y(k)-\hat{y}(k,\theta))^2$. The θ value satisfying $V_N(\theta,M^N)$ is the estimated $\hat{\theta}_N$given by:

$$\hat{\theta}_N=\left[\sum_{k=1}^{N}\varphi(k)\varphi(k)^T\right]^{-1}\sum_{k=1}^{N}\varphi(k)y(k) \tag{4}$$

Once the parameter vector is estimated, z–transform $(Z\{y(k-1)\}=z^{-1}Y(z))$ can be applied to Eq. (2) in order to obtain the discrete transfer function:

$$G(z)=\frac{B(z)}{A(z)} \tag{5}$$

where $A(z)=1+a_1z^{-1}+\cdots+a_pz^{-p}$ and $B(z)=b_1z^{-1}+\cdots+b_qz^{-q}$. Eq. (5) can be transformed in a continuous transfer function by