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# Nonlinear Modeling of the Insulin-Glucose Dynamic Relationship in Dogs

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*Abstract:* **Using experimental time-series measurements of spontaneous variations of plasma glucose and insulin in dogs, we have derived a nonlinear model of the dynamic relationship between spontaneous insulin variations (input) and glucose variations (output) employing our modeling methodology based on Laguerre-Volterra networks [1]. The obtained model is put in a block-structured form that is readily interpretable in a physiological context, since it is comprised of two parallel branches corresponding to the two primary effects of insulin on plasma glucose levels: the reduction of glucose levels (glucolepsis) and the generation of new glucose (glucogenesis).**
**Each branch of the model (glucolepsis and glucogenesis) is composed of a linear filter receiving the insulin input, followed by a static nonlinearity that transforms the output of the filter into the glucoleptic or glucogenic component of the observed plasma glucose level. It must be emphasized that the obtained model form is derived from the data (empirical or inductive modeling) and is not postulated *a priori* as in previous parametric modeling studies of this system. Although the presented results are preliminary, they seem to support the efficacy of this approach.**
*Keywords-* **Nonlinear modeling, Insulin- Glucose dynamics, Laguerre-Volterra network.**

## INTRODUCTION

The multiple metabolic effects of insulin have been the subject of intensive study for many years. In particular, the effect of insulin and its possible deficiency on the level of plasma glucose has been studied extensively in the context of diabetes mellitus and the treatment of Type I diabetic patients with insulin injections. The recent development of continuous glucose monitors and insulin micropumps has further stimulated the long-held interest in an "artificial pancreas". The latter requires a thorough understanding of the dynamic insulin-glucose relationship and reliable means that can be used to control the release of insulin in order to maintain fairly steady glucose levels in the blood. Such models can be used also for improved diagnostic purposes in a clinical context.

The requisite mathematical model of the insulin-glucose relationship must be dynamic, since the physiological processes involved are dynamic (i.e., the present value of blood glucose depends on a whole epoch of insulin values extending over 3 to 4 hours into the past, and not simply the present value of insulin). Furthermore, it has been found that the underlying physiological processes are nonlinear and nonstationary, rendering the modeling problem rather formidable.

The contribution of this paper is in proposing an effective modeling approach to this purpose and in demonstrating the efficacy of this approach with experimental data from dogs.

## METHODOLOGY

Experimental data of plasma glucose and insulin were collected in dogs every 3 minutes over a 10-hour period (200 time-series samples). The data were collected under conditions of spontaneous activity and, therefore, represent normal spontaneous variations during closed-loop operation (i.e., there are no insulin or glucose injections).

The time-series data were analyzed using our nonlinear modeling methodology termed the "Laguerre-Volterra Network" (LVN), where the insulin signal of spontaneous variations is viewed as the input and the glucose signal is viewed as the output. The LVN approach yields a nonlinear dynamic model of the input-output relationship in a "black-box" context. Therefore, it does not require model postulates and yields models that are "true to the data" (inductive or empirical modeling). For details of this methodology, the reader is referred to [1].

The obtained nonlinear dynamic model is put in a modular form that is readily interpretable in a physiological context. This modular form follows the modeling concept of "principal dynamic modes" [2] and is isomorphic to the LVN model. It must be emphasized again that this modular model form flows form the data and it is not postulated *a priori*. The results are presented in the following section.

## RESULTS

The obtained modular (block-structured) model of the insulin-glucose system is shown in Figure 1. It is comprised of two parallel branches, each composed of a cascade of a linear filter followed by a static nonlinearity. The specific form of the obtained model components indicates that the two branches correspond to the two primary effects of insulin on plasma glucose levels. Namely, the upper branch describes the nonlinear dynamics of the physiological processes causing reduction of glucose levels due to facilitated diffusion of glucose through the cell membrane and enhanced rate of glycogen synthesis in the cell (glucolepsis) and the lower branch describes the processes of generation and release in the blood of new glucose by the liver and other organs (glucogenesis).

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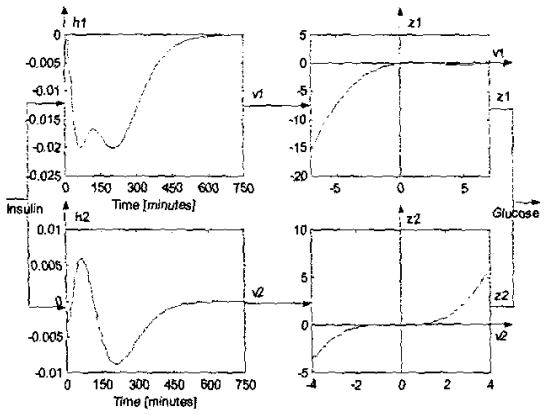


Figure 1: The insulin-glucose model is composed of the glucoleptic component (upper branch) and the glucogenic component (lower branch). Each branch is a cascade of a linear filter followed by a astatic nonlinearity (see text).

The nonlinearity of the glucoleptic component of the model (upper branch) exhibits rectifying characteristics that assure the reduction of plasma glucose in response to a positive deflection of plasma insulin from the baseline value (basal level) but no change in glucose for a negative deflection of plasma insulin from the basal level. Furthermore, the glucoleptic nonlinearity shows a supralinear (cubic) dependence of glucose reduction on the magnitude of the plasma insulin action represented by the glucoleptic state variable $v_1$. The latter exhibits maximum responsivity to insulin changes occurring about 1 hour and 3.5 hours prior to present time(as indicated by the first and second troughs of the impulse response function of the glucoleptic filter). The dynamic effects of the glucoleptic component appear to diminish about 6 hours after the stimulating onset of a change in plasma insulin.

The nonlinearity of the glucogenic component of the model (lower branch) exhibits a "dead zone" demarcating the values of the glucogenic state variable $v_2$ for which no new glucose release is initiated by catabolism of glycogen and amino acids in the liver and muscle, or by breakdown of triglycerides in adipose tissue (and subsequent catabolism of glycerol in the liver). Outside this "dead zone", the glucogenic response is supralinear (cubic) and bi-directional (i.e., significant negative or positive deflections of $v_2$ form baseline values will cause more than proportional negative or positive changes in the glucogenic responses, respectively). The "dead zone" is somewhat broader towards the negative side, implying a higher threshold for counter glucogenesis. The form of the impulse response function of the glucogenic filter indicates a latency of about 20 minutes and a peak of glucogenic response about 60 minutes after the onset of the stimulating change in plasma insulin. The glucogenic response is reversed about 2 hours later leading to a reduction of plasma glucose (counter regulation) that peaks about 3.5 hours after the stimulus onset. The latter peak coincides temporally with second trough of the glucoleptic impulse response.

This model allows the quantitative prediction of the plasma glucose for given plasma insulin variations over several hours. Note that the effect of the latter appears to last for about 6 hours. Therefore, this model can be used for studies of regulation and diagnostic purposes.

## CONCLUSION

The presented model of spontaneous insulin-glucose variations may offer the means for improved diagnosis and treatment of diabetes.

In terms of regulation of plasma glucose as the ultimate goal of an "artificial pancreas" (i.e., closed-loop system of insulin infusion), it must be noted that the system (and model) dynamics will be somewhat different when the input is externally injected insulin (instead of spontaneous variations of plasma insulin, as in our study). However, the proposed methodology can be used for this purpose. The obtained nonlinear dynamic model shows that closed-loop control requires extremely sophisticated control strategy based on such a reliable model. Simplistic types of control (without reliable model reference) may lead to disastrous results endangering the patients' lives.

With regard to improved diagnostic methods, the obtained model can be used to determine the "glucose effectiveness" and the "insulin sensitivity" of the subject in a reliable and accurate manner. It may also disclose additional physiological deficiencies or abnormalities, especially if the modeling effort is extended to include additional physiological variables of interest (e.g., free fatty acids).

## REFERENCES

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