THE MODELING OF THE INSULIN EXOCYTOSIS AFTER A GLYCEMIC STIMULUS

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ABSTRACT
The modern medicine frequently appeals to the latest news in engineering, informatics or mathematics. One of the challenges is related to the modeling of some phenomena inside the human body that can be valuable instruments for diagnosis and patients monitoring.

The contribution of this paper offers a digital model for the cellular exocytosis and a global model for the in vivo monitoring of insulin concentration after a glycemic stimulus.

The glucose concentration from the human body is regulated by the beta cells activity, via the insulin hormone released into the bloodstream. The insulin exocytosis in 7 steps is modeled as a digital system, expressed as an organigram. The entire physiological behavior is modeled at macro-level, in order to offer a useful tool for diagnosis of diabetes. A simple method for the model parameters extraction, besides to their diagnostic meaning, is provided.

KEY WORDS
Nonlinear systems, cellular organigram, invasive methods and macro-bio-modeling.

1. Introduction

The glucose concentration in the bloodstream is regulated by the pancreas endocrine function. Here are involved the beta cells, with the insulin secretion duty.

Insulin is an animal and a human hormone released by pancreas after meals, whose secretion activates the myocyte, hepatocyte and adipocyte cells to store the glucose in excess into glycogen or fats, [1]. In this way, the additional glucose after meal decreases toward the basal value, encountered before the external glycemic stimulation, [2]. Based on this natural phenomenon, a special experiment is proposed.

In our tests on humans, the insulin level is monitored after a glycemic peak, intravenous administrated, in order to avoid any variations from co-lateral causes (duodenal secretion, delay in absorption, others hormonal interferences, etc). The glucose pathway into the beta cell is a key problem for the insulin secretion and for diabetes diagnosis. Starting from cellular level, a global experimental setup is described, finishing with a mathematical model capable to offer useful parameters in the diabetes diagnosis.

2. Glucose, insulin and beta cell

Glucose is a fuel for the living matter, [3-4]. Its molecule belongs to the hexoses group, being a monosaccharide that contains six carbon atoms (C₆H₁₂O₆), with the molecular mass 180.18g/mol. Glucose is also an aldehyde that contains the -CHO group. The spatial distribution of the glucose molecule presents the pyranose ring, which is formed by 5 carbons plus one oxygen atoms. In this ring each carbon atom is bounded to hydroxyl and to hydrogen side groups, excepting the fifth atom that is linked to the sixth carbon out of this ring. A higher glucose concentration into the bloodstream triggers the insulin secretion, by some specialized beta cells from pancreas.

Insulin is a poly-peptide composed by 51 amino-acid residues with a molecular weight of 5808 Da, [5]. This hormone acts to regulate the glucose metabolism in the body. In diabetes the insulin secretion is poorly. Therefore, the identification and the succession of the insulin exocytosis steps offer much more control in a deficiency secretory disease.

Pancreas has a total mass about 100g. It contains beta-insulin-secretary cells in the Langerhans islets dispersed in the entire organ that doesn’t reach more than 1-2g. Every islet comprises 2500…3000 beta cells, [6]. Therefore the quantity of insulin released in the bloodstream is proportional with the healthy endocrine pancreas mass. In diabetes, different failure mechanisms arise that diminish the insulin secretion. Versus the degree of the disease, 30% up to 60 % and more of the total insulin-secretary cells are damaged.

3. The logic blocks modeling

An experimental setup based on the stimulus-effect action on beta cell is considered. This is possible on this kind of cells too, because beta cells are excitable cells, like neurons or myocytes, releasing an insulin signal at output port, when is excited by an incident stimulus represented by glucose.
On a trial of 10 healthy persons, the glycemia and insulinemia were monitored before and after a glycemic stimulation.

In basal conditions, without glucose stimulation, the fluctuations of the insulinemia concentration are alternating from 10 to 17 µU/ml (1µU/ml = 6 pico-mol/l for insulin) during 20 minutes. The glycemia level is maintaining in the range of 80 - 100 mg/dl.

The applied limit glycemic stimulus was intravenous i.v. administrated, per 1 minute. As a reply, the glycemia increases to 170 - 250 mg/dl while the insulinemia signal varied from 10 to 55µU/ml in the next 5 minutes. The limit stimulus consists in a maximum glucose dose. It is considered as a limit because a higher glucose dose has the same reply in insulinemia.

This peak of insulinemia after a limit glycemic stimulus could be a powerful tool in the diabetes diagnosis, expressing the total beta pancreatic active mass.

For a better understanding of the experiment, a correlation between stimulus – the extracellular e.c. glucose – and the reply effect – the insulin exocytosis – has to be put in agreement by an electronic model of the endocrine systems with internal feedback, fig. 1.

The extra cellular e.c. detector of a beta cell is representing by a trans-membranar protein, GLUT2 that also assists the glucose intracellular i.c. transport inside the cell. A high level of glucose into the bloodstream leads to an increased insulinemia releasing, which decreases by a negative feed-back the glycemia level. This first simple model with one feed-back loop is developed in this paper, in order to put in a first correspondence all the stages of the signaling path-ways during the glycemic stimulation.

The most suitable model for the beta-cell electrophysiology must closely follow the real behavior of the cell at an input stimulus. Here the stimulus is the glicemic signal that initiates the insulin releasing in 7 steps.

The first step consists in the extra cellular e.c. glucose detection with the GLUT2 receptors. The same receptors act as carrier protein for the glucose penetration inside the cell. The input signal of the system is the e.c. glucose concentration versus time, g(t), fig. 2. The detector is GLUT2 and the glucose suffers a facilitated diffusion in the intracellular i.c. domain.

The second step is the glycolysis, which consists in the glucose oxidation under the glucokinase action. This enzyme from citozol leads either to lactate under aerobic conditions, or to pyruvate under anaerobic conditions. For instance the aerobic glycolysis of the glucose involves: glucose, P - Phosphorus, ADP - the Adenosine-Di-Phosphate, NAD⁺ - the Nicotinamide adenine dinucleotide coenzyme and the products are: ATP - the Adenosine-Tri-Phosphate, pyruvate and hydrogen ions. The produced ATP molecules are stored in the mitochondria organelle, like in a storage device, fig. 2.

But the maximum administrated dose of glucose produces an excess of ATP. The ATP is crowding into mitochondria and conducts to the forth step: the K⁺ channels closing. Similarly, this step occurs in the nervous cells too, due to the gradient of the potassium ions, [7]. This stage that is encountered in nervous cells too, enforces the relationship among the excitable cells.
Before this step the transmembranar potential is maintained at a Resting Potential, RP = -70mV for beta cell. The influx of K⁺ ions changes the transmembranar potential to the Action Potential value, AP = -30mV, [6]. In this way, the chemical signal of glucose, converted in ATP, is transformed now into an electrical stimulus – the action potential, AP.

In the fifth step, the action potential AP is propagating along the insulator bilipidic membrane till the Ca²⁺ channels. The electrical lost along membrane are almost zero due to the high isolator properties of the membrane.

The AP arrives to the Ca²⁺ channels in the sixth step. Under this electrical field gradient, many Ca²⁺ ions come into the cytoplasm. This can activate the insulin vesicles exocytosis during the seventh step. The insulin is released near a capillary vicinity into the bloodstream. A part of insulin acts on some hepatocyte receptors producing the glucose consuming. But a part of insulin, paracrine acts onto the insulinic receptors of the beta cell itself, fig. 2.

The entire auto-signaling system was highlighted on the IRS1 way ("Insulin Receptor Substrate 1"), fig. 2.

The above organigram stands for a useful tool in the diabetes cause establishing: the damaged processes at cellular level are more visible at each step.

4. Experimental results

The time evolution of the insulin blood concentration, after a glycemic peak stimulus, is valuable in the diabetes prognostic. In this paragraph it is described the insulin concentration versus time after a limit dose of glucose i.v. administrated, for two investigated persons: a healthy patient 41 years, 71kg and a patient with type 2 diabetes 63 years, 95kg.

![Figure 3. The experimental insulinemia measured at humans in two cases versus time](image)

In the first stage, the glycemia is recorded in basal conditions after a minimum 12 hours alimentary repose. Then, a limit dose of glucose is i.v. administrated during one minute. The glycemia and insulinemia is recorded at 1min, in order to observe the first phase of the insulin secretion, in the next 30 min.

For normal patients is observed an increasing of the insulin concentration from ~ 10µU/ml up to 55µU/ml in the next 3 to 10min - the "early phase", [8]. For diabetic patients, the insulin peak reaches lower values 42µU/ml or less, being in a direct correspondence with the insulin-secretory total active mass from pancreas.

A mathematical model is proposed to describe the dependence insulin concentration - time.

This model is accompanied by a set of model parameters, which will procure a diagnosis significance, easy to be correlated with the insulin secretion among those steps. The measured insulinemia versus time is presented in fig. 3.

5. A mathematical model

A mathematical model of the insulin concentration versus time is proposed. The experimental results from fig. 3 suggest a function that is equal with the insulin concentration in basal condition at t=0, which is the experimental beginning time. The function must admit a maximum, so a first order derivative zeroing and must admit a horizontal asymptote.

The shape of the measured insulin concentration i, into the bloodstream versus the variable time t, suggest the following fitting model:

\[
\begin{align*}
    i(t) &= \begin{cases} 
    i_0, & \text{for } t < 0 \\
    i_0 + \frac{s \cdot t}{1 + r \cdot t^2}, & \text{for } t \geq 0
\end{cases}
\end{align*}
\]

(1)

where the model parameters have the following meaning: \(i_0\) is the insulin concentration in basal conditions, \(s\) is the entrance slope of the curve \(i(t)\) during the rising regime; \(r\) is the recovery coefficient that depicts the fastness recovering, after the peak reaching.

All the parameters \(i_0\), \(s\) and \(r\) are reals and positives. The insulin concentration is expressed in µU/ml, the time is expressed in minutes, the entrance slope is important for \(t>0\) but \(t\to0\) and is expressed in min⁻¹ and the recovery coefficient must be expressed in min⁻² accordingly with (1). The first order derivative for \(t > 0\) is:

\[
\frac{di}{dt} = \frac{s \cdot (1 - r \cdot t^2)}{1 + r \cdot t^2}
\]

(2)

The first order derivative is positive for \(0 < t < 1/\sqrt{r}\) and negative for \(t > 1/\sqrt{r}\), hence the curve \(i(t)\) is increasing below \(1/\sqrt{r}\) and decreasing after \(1/\sqrt{r}\). The proposed
model monotony fulfils the experimental curve shape. By zeroing the first order derivative, the following insulinic peak results:

\[ i_{\text{peak}} = i_0 + \frac{s}{2\sqrt{r}} \text{ for } t_{\text{peak}} = \frac{1}{\sqrt{r}} \]  

(3)

Also, the horizontal asymptote occurs: \( i = i_0 \) for \( t \to \infty \)  

(4)

Using the equations (3), (4) the model parameters \( i_0, s \) and \( r \) are computed. The extraction of these parameters can be easily optimized by the regression curves method. However, the equations (3), (4) provides the initial values for iterations. For the experimental curves from fig. 3, the following parameters results:

- \( s=22.5\text{min}^{-1}, r=0.0625\text{min}^{-2}, i_0=12 \), for the normal patient;
- \( s=16\text{min}^{-1}, r=0.07\text{min}^{-2}, i_0=10 \), for the patient with diabetes.

After the regression curves method, the model parameters become:

- \( s=22.124\text{min}^{-1}, r=0.0671\text{min}^{-2}, i_0=12 \), for the normal patient;
- \( s=14.76\text{min}^{-1}, r=0.098\text{min}^{-2}, i_0=10 \), for the patient with diabetes.

6. Conclusion

The paper has a double scope: to presents the glucose properties and its enzymatic mechanisms inside the bloodstream and to model the beta cell functionality at micro and macro level, as an interdisciplinary application of the bioscience. Both presentations are related by a main phenomenon that governs the energetic reasons in the living beings: the glucose metabolic pathway. A first model in the beta cell physiology emphasizes the internal feed-back of these cells that produces insulin and detects insulin, too. The second model proposed in this paper establishes a cyber model for the insulin releasing steps from the beta cells. All biological organelles find out some dual digital system. This correspondence makes from beta cell an engineering system.

Based on some experimental data, a mathematical model was developed, in order to describe the insulin blood concentration versus time, after a maximal glycemic stimulus. The resulted peak of insulinemia can be a powerful tool in the diabetes diagnosis, expressing the total beta pancreatic active mass, which decreases in diabetes.

This model represents the starting point for the insulin secretor cells damaging arisen at different steps of the diabetes evolution.

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References