Modeling the Dynamics of Insulin-Glucose Subsystem Using a Multi-agent Approach Based on Knowledge Communication

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Abstract — Mathematical analytical modeling and computer simulation of the physiological system is a complex problem with a great number of variables and equations. The objective of the present research is to describe the insulin-glucose subsystem using multi-agent modeling based on intelligence agents. Such an approach makes the modeling process easy and clear; moreover, new agents can easily be added to the investigations.

Keywords - multiagent paradigm; compartments; normoglycemia; insulin-glucose system; physiology.

I. INTRODUCTION

Expert systems have emerged as developed methods of artificial intelligence in the eighties of the last century. The most-widely used definition of an expert system is the one which defines an expert system as a computer program that uses the procedures for requesting a solution to non-algorithmic problems, or, in other words, problems requiring the participation of experts in the field (experts) in order to benefit from their knowledge or expertise. At the moment, expert systems are these computer programs which perform complex tasks with high requirements on intellectual capacity, and manipulate large amounts of input data. The basic features distinguishing expert systems from other computer programs are as follows:

- the use of knowledge instead of the data. It is stored separately and independently from the rest of the executive system.
- the knowledge base is created and stored in a symbolic form. Any kind of inference is conducted on the basis of the symbolic computations that can be compared to the manipulation of human natural language. A symbolic representation of knowledge is understood as all kinds of rules, semantic networks.
- the reasoning often involves drawing conclusions from the so-called meta-knowledge and are used for learning mechanisms - possessed knowledge becomes enlarged (generalization) with a new phenomenon or is updated in the form of a replacement of the wrong rules with the valid rules; such systems are also able to justify given answers corresponding to explanations of a deductive process.

Extended possibilities of expert systems in the fields of the knowledge-acquirement speed, the analysis of the potential solutions to a problem and the decision concerning a definitive answer, led to the development of multi-agent systems. The main difference between systems and multi-agent systems is based on the indirect contact of expert systems with the environment. Input does not come from sensors, but from an additional agent which is usually human. Multi-agent systems are complex systems, from communication and cooperation among agents themselves to pursuit of a common objective. This design allows troubleshooting of a diffuse character or computationally complex one. When teaching multi-agent systems, the concept of agent is presented as an autonomous object with the initiative of action based on the observation of the environment in which it is located. It also has the ability to use the resources of this environment, and the motivation is to solve the problem posed in front of it. This definition forces the agent to know sensor inputs through which it can receive signals from the environment, and effectors which will be able to influence the surrounding environment. The most important task of the agent is to decide which of the possible courses of action is the best at the time of knowledge about the problem to achieve this goal.

This branch of science concerns the resolution of the nature diagnostic problems and therapeutic nature using a large base of knowledge and a broad spectrum of causes and effect relationships between different states of health of the patient and the interaction between different treatments [1][2][3] which should simultaneously be performed as part of the patients' overall treatment plan. This rather specific branch of science is based on expert knowledge - here the doctor is a good candidate to use artificial intelligence systems. These systems are an addition to proper disease diagnosis, correct diagnosis, and proper treatment process in order to overcome the disease or reduce complications of the disease. Examples of medical problems should also mention the following: databases of patients, search for medical knowledge, support for medical decisions, evaluation of the efficacy, etc. At the same time, the use of multi-agent systems is implemented in order to eliminate the drawbacks of the previous solutions in medical systems that showed a limited autonomy, limited interaction with the environment and a smaller store of knowledge to solve a problem. The new directions of research focus, for example, on the treatment of advanced stage by many physicians at the same

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time. See [4][5][6][7][8]. The examples of the use of these systems in order to improve the quality of treatment can be found in many works. They can also be used as part of the healthcare system, ranging from sending ambulances to optimize the route, choosing a hospital that is best equipped with the apparatus necessary for the patient transported, to supporting drug treatment and analysis of its implications.

More information on the application of multi-agent systems in medicine and related sciences can be found in publications [9][10][11]. In the publication [12], multi-agent systems have been subjected to critical analysis as a result of which it is possible to define the areas of application describing artificial intelligence systems and limitations that must be taken into consideration in order to benefit from these opportunities.

II. THE USE OF MULTI-AGENT SYSTEM IN PHARMACOKINETICS

A. Compartments theory

A separate group of medical problems are the methods of description, analysis and prediction of the dynamics of the selected substances in a human body. The most common methods used for the description and analysis of these phenomena are based on differential equations, whose construction and analysis are based on major or minor assumptions and approximations. One of the said methods is described by using a compartments model, as illustrated in Fig.1. On the basis of such a model, the appropriate equations describing the dynamics of the system created are built. The modeling assumes the existence of so-called compartments in the body where a uniform concentration of the substance to be analyzed is located.

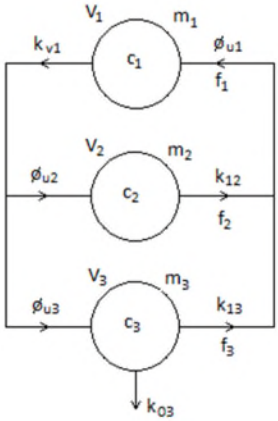

Figure 1. An example of a compartment model (the model has three compartments here).

In some models, the number of compartments may be higher due to an attempt to approach mathematical description of transport of the substance in the body to real physiological value, and fostering real pharmacokinetics of the substance. In the description, the multi-compartments model is a particularly useful application of matrix (1) which, in the final finished form, allows the calculation of each point of the interest stream.

However, it should be emphasized that a task of this type is difficult, or, at least, problematic.

$$\frac{d\boldsymbol{m}(t)}{dt} = \boldsymbol{A}\boldsymbol{m}(t) + \boldsymbol{F}\boldsymbol{d}(t) \quad (1)$$

satisfying the initial conditions:

$$\boldsymbol{m}(t=0) = \boldsymbol{m}(0) \quad (2)$$

Finally, it can be shown that the solution is determined by the formula:

$$\boldsymbol{m}(t) = e^{\boldsymbol{A}t}\boldsymbol{m}(0) + \int_0^t e^{\boldsymbol{A}(t-\tau)}\,\boldsymbol{F}\boldsymbol{d}(\tau)d\tau \quad (3)$$

Given the complexity of physiological systems, one often seeks to get a quantitative result rather than qualitative.

B. The compartment model in terms of multi-agent paradigm

In this view, the agent is to be understood as any clearance reflecting the specified area of the body which changes the concentration of the test substance. The agent's behavior is defined by the function describing the distribution of substances seen as a change in its output stream φ_{01}. If the agent represents a compartment through which a certain amount of the tested substance flows, then this agent (its behavior) is defined by an appropriate transmittance reflecting changes in the output to changes in the agent at the entrance agent – Fig. 2.

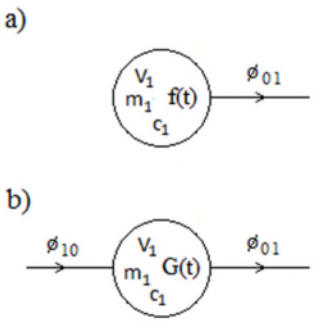

Figure 2. Agent concept diagram representing the compartment:
a) the agent as the source of the substance,
b) the agent intermediary in the flow of the substance.

The description of one compartment agent model means determining the flux distribution function φ_{01} and the time step t defining the rate of change of the flux. In addition, one must declare the initial conditions - in this case the level of drug concentration c(0) at t = 0. The initial level determines the value at which the stream will begin to change over time. Because the function is defined as the behavior of the agent, it will show the direction and the rate of change. The flow of the elimination of substances is given by:

$$\varphi_{01} = f(t) = k_{01}m_1(t) \quad (4)$$

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and, by using the formula for the change of mass over time:

$$\frac{dm_1(t)}{dt} = -k_{01}m_1(t) \quad (5)$$

We obtain the function to determine changes in the weight of the agent:

$$m_1(t) = m_1(0)e^{-k_{01}t} \quad (6)$$

where $m_1(0)$ represents the mass of a drug at time t = 0.

Therefore, the effluent of the agent can be represented as:

$$\varphi_{01}(t) = k_{01}m_1(t) = k_{01}m_1(0)e^{-k_{01}t} \quad (7)$$

One can also specify the variation of weight of the $U_{01}(t)$ excreted with the agent in the process of elimination:

$$U_{01}(t) = \int_0^t \phi_{01}dt = m(0)(1 - e^{-k_{01}t}) \quad (8)$$

For the purposes of multi-agent simulation environment, the time t is a discrete time in which the agent generates a "signal" for the appropriate behavior.

$$t_{\kappa+1} = t_\kappa + \Delta t \quad (9)$$

where Δt is the time step increment function describing the agent behavior.

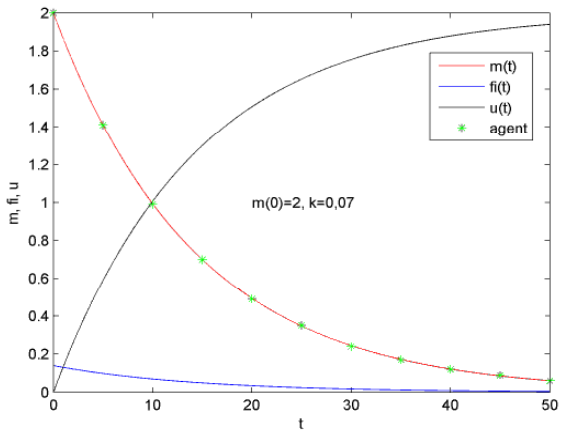

Figure 3. Simulation graphs for the equations (6) (7) (8) and the value generated by the agent.

III. THE OVERALL CONCEPT OF MULTI-AGENT MODEL

A. *Multi-agent concept*

The section below will focus on the concept of a multi-agent system where the work is aimed at the restoration of glucose homeostasis. The amount of glucose supplied from the gastrointestinal tract into the blood depends on the amount, composition and frequency of meals. On the other hand, the energy demand of tissues and organs is variable. The concentration of glucose in the blood of a healthy individual is maintained within relatively narrow limits of about 4.5 - 9.0 mmol/L (81 - 162 mg/dL). Mechanisms of preventing glucose concentration decline in the blood as well as its excessive growth are extremely important for the proper functioning of the body. These mechanisms act on the substrate, hormonal, and nervous system.

The principle of the mechanism of the substrate is directly controlled by the change of glucose in tissues depending on the flow to the cells, or the availability of the other substrates.

As a part of the hormonal control, the most important hormone lowering blood glucose – insulin – should be considered. The effect of insulin in the liver mainly involves stimulation of glycogen synthesis, and inhibition of gluconeogenesis. The insulin found in muscle and fat will affect the glucose transporter proteins across cell membranes stimulating glucose uptake by these tissues as well as stimulating glucose oxidation and glycogen synthesis [13]. The indirect effects of insulin uptake, oxidation and size of the glycogen involves its rate inhibiting effects of lipolysis and oxidation of fats [14][15]. The nervous control of blood glucose is mediated by two branches of the autonomic nervous system. The parasympathetic nervous system stimulates glycogen synthesis in the liver and secretion of insulin, contributing in this way to lower blood glucose.

The activation of this system is associated with the consumption of a meal (olfactory stimuli, taste), and the presence of food in the gastrointestinal tract.

Based on the above-described three ways of adjusting the level of glucose in the blood, we propose a multi-agent model that reflects, as much as possible, the mechanism of action and structures responsible for normoglycemia. Considering the above, we propose a layered multi-agent model which closes an appropriate regulatory mechanism in each layer.

The proposed model consists of three layers – Fig. 4:

- layer 1 - base layer where the agents representing the cell are located. This layer reflects the basic building block of individual cell structure of the body's organs. This layer processes occur on/in a cell scale . Layer 1 can be called the cells layer.
- layer 2 - layer of organs, which enables communication between them through biochemical signals. It is the layer of the actual process of normoglycemia. Layer 2 can be called the physiological layer.
- layer 3 - layer representing the selected areas of the brain directly related to the stabilization process of glucose. This layer simulates the processes involving information flow control of the glucose and insulin dynamics in the blood, and provides the opportunity to simulate the psychological stimuli that affect blood sugar levels. Layer 3 can be called the psychological layer.

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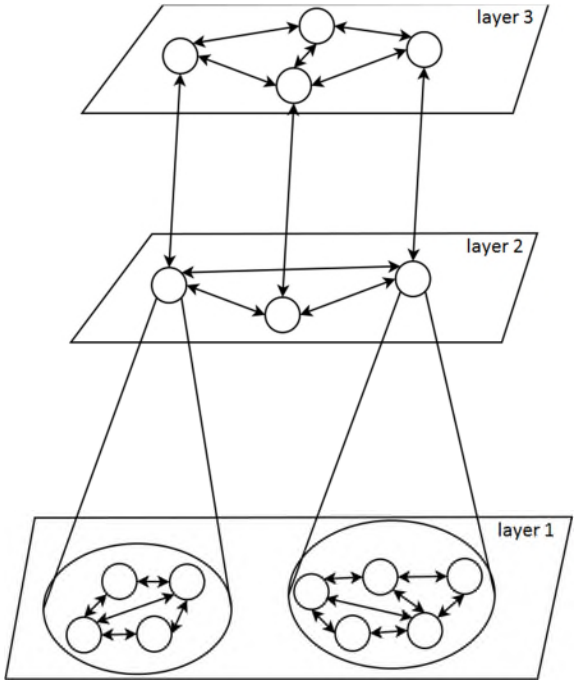

Figure 4. The idea of layered multi-agent model.

In the described approach, the emphasis is on the modeling of organs which play an active role in glucose homeostasis.

It should be stipulated that having this layer representing the single-cell level create the opportunities for simulation also in the cellular scale and molecular - if incorporated into the cell interaction and exchange between biochemical information.

Adopted layers number 2 and 3 are constructed in accordance with the agents representing organs involved in normoglycemia, and the environment fuzzy logic programming language to build a simple knowledge base. The multi-agent environment is built on the basis of the JADE environment and programming language Java. The agents act as the appropriate organ (pancreas, liver, adipose tissue, gastrointestinal tract as a source of food, and insulin-independent mechanism for glucose utilization). Each agent is assigned its own task, in the form of behavior described by using the tool, or knowledge base. The first description applies to a situation in which the agent is the source medium, i.e. food in the form of glucose. Then the agent is treated as the one producing its own interior medium which then goes into the environment common to all agents. Specific interactions between agents are shown in Fig. 5. This approach allows to make more complex and advanced analysis than the models based on differential equations. The use of this type of multi-agent model has many advantages over analytical methods:

- Rules can be easily modified
- The objective function and the definitions of limitations may be more complex
- The attributes of individual organs / agents can be easily defined
- More opportunities to analyze simulation results.

Such agents are obtained by subtracting from the differential equation members who bring changes representing the response of the organ increases or decreases in glucose and / or insulin to the equation. Fig. 6 presents a concept for the equation based on Hardy-Stolwijk to show a method of identifying agents that are presented in Fig. 5.

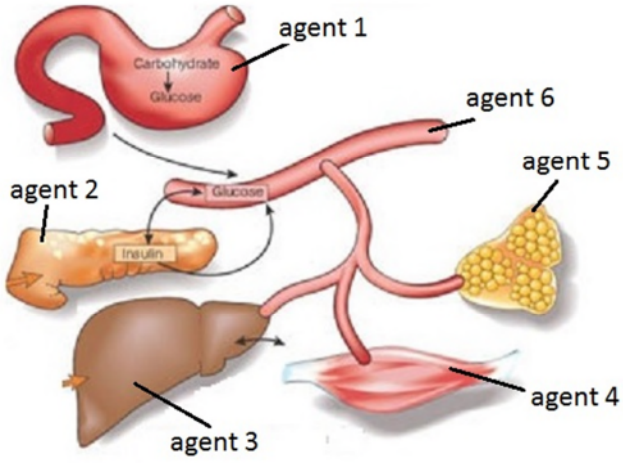

Figure 5. A schema connection beetwean agents-organ.

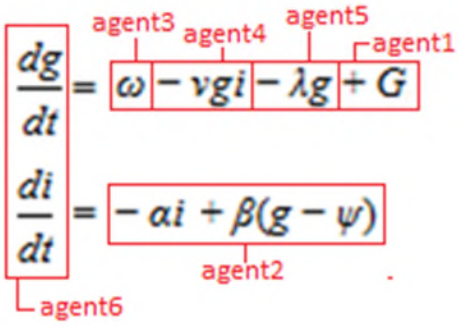

Figure 6. Equation of Stolwijk-Hardy model used to separate the functional parts of multi-agent system.

B. *Agent dynamic models based on fuzzy logic rules*

Each agent of glucose-insulin model answers to its behavior and products the output according to its inner state. For instance, the agent representation of Stolwijk&Hardy model gives the members of the right side of the equations an output of the agent. These members have parameters (alfa, beta, etc.) whose values depend on the case modeled (healthy, or ill man). Moreover, during the simulation, we have the same values of these parameters that produce the linear response and not always are realistic (the STELLA model is used for this correction).

We propose generating the appropriate output using fuzzy rule bases that can produce any complex nonlinear

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function. Moreover, such an approach can be easily accepted by a medic due to their simplicity and clearness.

The simplest way to provide fuzzy rule base is illustrated in the example of member ϑgi of Stolwijk&Hardy model. Agent 4 is response to this output.

If parameter $\vartheta = Const$, we can use the member ϑgi as the simplest output. In other cases, we have to use "If" condition, or rule (for instance, in the cases of healthy man, or type-II diabetes one). In a more complex behavior, we have to construct the set of rules (rule base).

The fuzzy rule base considers all variables as fuzzy sets with appropriate membership functions. Moreover, we can perfectly avoid now the parameter ϑ, which is not easy to understand for a medic.

Let us consider the fuzzy sets for variables insulin i and glucose g. After normalization, the membership functions for these variables can be shown as in Fig.7.

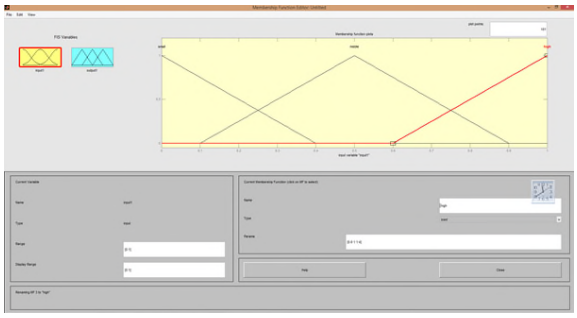

Figure 7. Membership funcitons of variables insulin and glugose (normalized).

The rules can be formed in Mamdani or Taskagi-Sugeno manner. In Mamdani model, we use fuzzy sets both in premise and conclusion of the rules. Fig. 8 shows the variables connection.

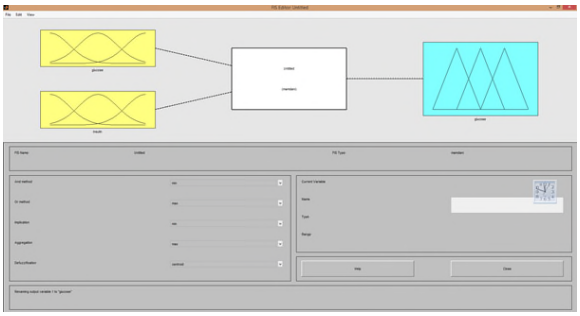

Figure 8. Structure of agent's rules.

Therefore, in our case, we could create 9 rules for fuzzy sets of variables insulin i and glucose g with 3 membership functions. The rules have the following form:

If Insulin is Small **and** Glucose is High **then** Glucose is Middle.

The set of rules for agent 4 is shown in Fig. 9.

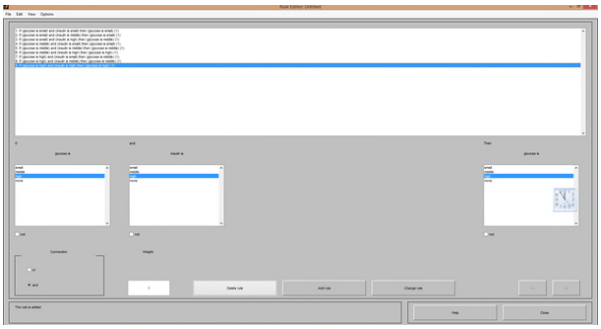

Figure 9. A set of rules for agent 4.

The Mamdani style inference is shown in Figure 10.

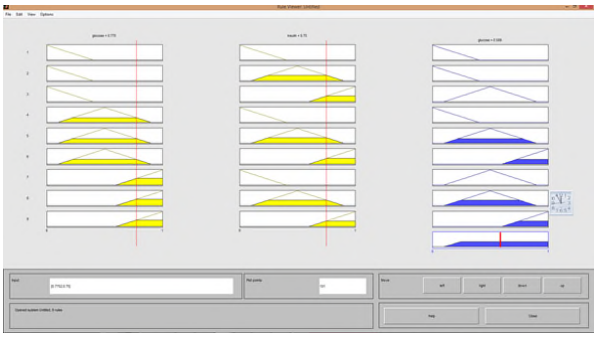

Figure 10. Inference engine of Mamdani model.

The function of agent output is shown in Figure 11.

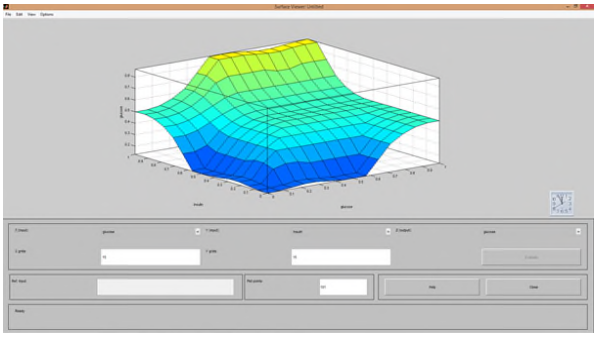

Figure 11. Surface of rule base mapping.

The advantages of the approach above include easiness and clearness for agent output description (we connect only semantic variables like insulin i and glucose g without additional coefficients like ϑ) on one hand, and complex nonlinear behavior of the agent, on the other.

IV. RESULTS

Thanks to our proven analytical methods for solving the equations in Fig. 6, we achieve an objective method for determining the benefit of the resulting simulation based on a the multi-agent system. In order to verify the correct operation of multi-agent system, it was asked to write the software multi-agent system in JAVA with using JADE multi-agent environment. As a result of the development of

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the agents that have been implemented in philosophy according to Fig. 5, simulation results such as shown in Fig. 12 were obtained.

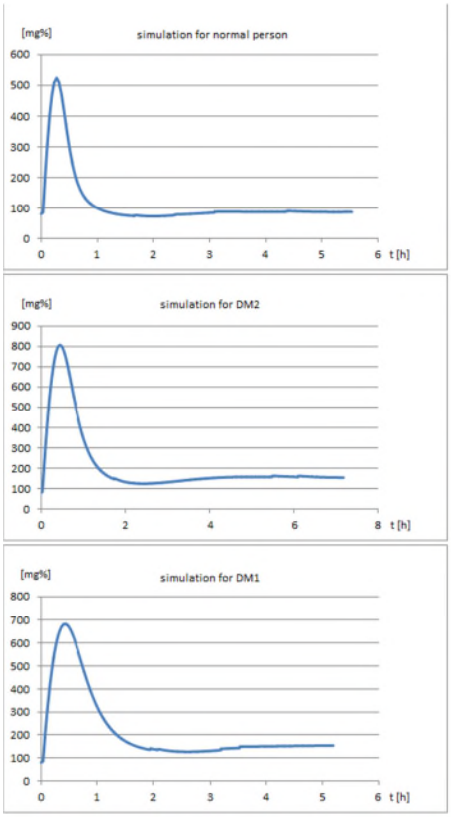

Figure 12. The results created based on work of multi-agent system.

V. CONCLUSION AND FUTURE WORK

The agent approach allowed us to modify the dynamic model of insulin-glucose system in the direction of modeling of inner behavior of each agent and communication with each other. Such modeling gives the possibility to address more complex behavior (not only with coefficients in the equations like in Fig. 6 but using fuzzy relations between parameters).

With the presented approach, we obtained satisfactory results that coincide with the results obtained from the simulation of the analytical equations. The use of fuzzy logic allows to dispense with rigidly assigned coefficients (parameters) models, allowing a more flexible approach. One can take into account many factors that can shape the response to individual agents to changes in their environment, through which this study should understand the changes in insulin sensitivity, body weight changes, efficiency of secretion of insulin, glucose half-life, e.g. Our next efforts will be directed towards the communication among agents for exchange of information about current states and to take a common decision.

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