# Agent-Based Modelling And Simulation Of Insulin-Glucose Subsystem

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*Abstract*— **Mathematical analytical modeling and computer simulation of the physiological system is a complex problem with great number of variables and equations. The objective of this research is to describe the insulin-glucose subsystem using multi-agent modeling based on intelligence agents. Such an approach makes the modeling process easier and clearer to understand; moreover, new agents can be added or removed more easily to any investigations. The Stolwijk-Hardy mathematical model is used in two ways firstly by simulating the analytical model and secondly by dividing up the same model into several agents in a multiagent system. In the proposed approach a multi-agent system was used to build a model for glycemic homeostasis. Agents were used to represent the selected elements of the human body that play an active part in this process. The experiments conducted show that the multi-agent model has good temporal stability with the implemented behaviors, and good reproducibility and stability of the results. It has also shown that no matter what the order of communication between agents, the value of the result of the simulation was not affected. The results obtained from using the framework of multi-agent system actions were consistent with the results obtained with insulin-glucose models using analytical modeling.**

**Keywords:** ***multi-agent system; normoglycemia; diabetes mellitus; Stolwijk-Hardy model.***

## I. INTRODUCTION

The purpose of modeling is to obtain an understanding of the actual functioning of biological systems using mathematical models that describe and simulate all or some of the essential features of the biological object. Models may be a useful tool in the structuring of research or for the investigation of relationships between the different parts of biological systems in silico. System models are used to identify key elements in a biological system and to integrate different types of information. In addition, hypotheses about a system can be tested in order to afford a better understanding. The human body can be modelled as an open (biological) system. In the perceived model in this work, we have used differential equations and various methods taken from the artificial intelligence (AI) domain (e.g., fuzzy logic). The ultimate goal is to understand how this system works. We can focus on some of the subsystems or just one of them (see Figure 1. Not only are we looking for a model that helps us to understand how the human body works, but this study also allows us to carry out different virtual experiments.

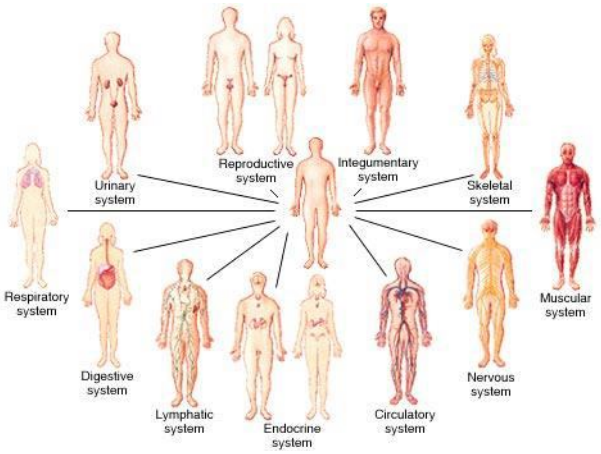


Figure 1. Subsystems of human body.

The main objective of this paper is to show how biological systems can be modeled and analyzed at different levels of complexity with the use of multi-agent systems. We also used a compartment model description in which the agent could be understood as a compartment (i.e., a separate area of the body)[1]. In this paper, we compare the Stolwijk-Hardy model by simulating the analytical model and by dividing the same model into parts in where each part is implemented into an agent as its behavior. The authors are inclined to believe that the multi-agent systems presented in this paper are easier to use and better illustrate the processes that occur in the phenomenon of glucose homeostasis. In addition, the proposed solution enables a comparison of a model description using different simulation environment, in this case by using MATLAB and implemented as a multi-agent system. Furthermore, they provide an easy way to deduce which element of the model represents the body and how it affects the studied process. The authors are aware that this work and the presented model does not reflect all the processes that are actively involved in the metabolism of carbohydrates. It should also be noted that the presented approach largely reflects the processes in a qualitative rather than a quantitative way. Section 2 is devoted to the multiagents systems in medicine. In Section 3 will introduce the main concept of agent-based modelling and briefly describes an implementation of this concept. Section 4

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describes results between differential model and our model. The last one, Section 5, describes conclusion of this work.

## II. MULTIAGENT SYSTEMS IN MEDICINE.

In computer science, an intelligent agent (IA) is a software agent that exhibits some form of artificial intelligence to assist the user; it acts on their behalf in performing repetitive computer-related tasks. Some scientists characterize agents as initiative and reactive objects, whilst others emphasize, for example, self-learning and communication abilities. In our opinion, the most unifying property of agent models is their decentralization. A good discussion on multi-agent systems can be found in [2][3][4].

The use of multi-agent systems in medicine is related to the resolution of problems of a diagnostic and therapeutic nature. In particular, they feature a large knowledge base and a broad spectrum of cause-and-effect relationships between different states of health in patients and the interaction between treatments [5][6][7], which should simultaneously be taken into account when treating these patients. This rather specific branch of science, which is based on expert knowledge (i.e., the physician) is a good candidate for the use of artificial intelligence systems. These systems would be in addition to traditional methods used to gain a correct disease diagnosis. Likewise, they would be used to carry out the treatment process in order to overcome the disease or reduce complications arising from the disease and for the treatment of advanced stages of disease by many physicians at the same time. For further details, see the following studies [8][9][10][11].

Past study in the area has presented a multi-agent system designed to simulate the tissue at a cellular level [12]. This simulation is designed to help in the understanding of the mechanisms that operate within the cell, and is expected to contribute to our understanding of the development of cancer cells. In this work, the authors have assumed that the most faithful reproduction of biological mechanisms rest in the cell and that by taking this into account, we can assess the impact of external factors on its operations. Another study has described physiological process, namely glucose homeostasis using a multi-agent system [13]. This approach uses a negotiation mechanism between two member regulators: the first portion represents glucose-monitoring for providing nutrition from outside – in this case, in an attempt to reduce the level of glucose in the blood. The second part of his act regulates glucose levels based on the information associated with physical activity - that is to say, its purpose is to maintain glucose levels by lowering insulin levels. Multi-agent systems are also used for the extraction of data from the genotype, even when the data are incomplete [14]. The system also allows data to be managed from different "computing places" and for decisions to be generated that relate to the progression analysis.

## III. THE OVERALL CONCEPT OF A MULTI-AGENT MODEL

Below, we describe the concept of a multi-agent system in which the aim is to restore 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 by tissues and organs is variable. The concentration of glucose in the blood of a healthy man is maintained within relatively narrow limits of about 4.5 - 9.0 mmol/l (81 - 162 mg/dl). Mechanisms to prevent the lowering of glucose concentration in the blood as well as its excessive growth are extremely important for the proper functioning of the body.

One kind of control mechanism is the hormonal control patch. This mechanism should take into account the most important hormone that lowers blood glucose: insulin. The effect of insulin in the liver mainly involves the stimulation of glycogen synthesis and the inhibition of gluconeogenesis. Muscle and fat insulin affect the glucose transporter proteins across cell membranes, stimulating the uptake of glucose by these tissues, as well as stimulating glucose oxidation and glycogen synthesis [15]. An indirect effect of insulin uptake, oxidation and size of glycogen is the rate it inhibits the effects of lipolysis and the oxidation of fats.

The proposed model consists of three layers:

- Layer 1 - base layer, where agents represent the cell. This layer reflects the basic building blocks of the individual cell structure of the body's organs. This layer also scales the processes of the cell. Layer 1 can be called the cell's layer.
- Layer 2 - layer organ, which enables communication between the layers through biochemical signals. This is the layer at which the actual process of normoglycemia takes place. Layer 2 can also be called the physiological layer.
- Layer 3 - layer representing the selected areas of the brain that are directly involved in the process of the stabilization of nerve glucose. This layer simulates the processes related to the information flow control dynamics of glucose and insulin in the blood and makes it possible to simulate the psychological stimuli that affect blood sugar levels. Layer 3 can be called a psychological layer.

A multi-agent environment is built using the JAVA Agent Development Framework (JADE) [17]. Agents act as the appropriate organ (i.e., pancreas, liver, adipose tissue, the gastrointestinal tract as a source of food, and the kidney as a simple mechanism for glucose utilization). Each agent is assigned its own task in the form of the 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. This is then treated as an agent that produces its own interior medium, which feeds into the environment that is common to all agents. The second situation applies when the agent mediates a medium; for example, the agent represents the circulatory system, which flows from one side (glucose) to another agent. Specific interactions between agents are shown (in Figure 2). This approach allowed us to carry out a more complex and sophisticated analysis than would have been the case with a model based on differential equations [17].

The use of this type of multi-agent model has many advantages over analytical methods:

- The interactions in the model are clearly described.

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- 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 more easily defined.
- There are more opportunities to analyze simulation results.

We can also benefit from a new description of glucose metabolism, where each agent represents one organ (see Figure 2). Agents 1 to 5 ask agent 6 for the level of glucose in the blood and check their own knowledge base of what the answer should be. Agent 7 represents an insulin infusion dose. Each of the agents is from a child class and are developed to be able to simulate each vital organ. In the body of each of the agents are coded functions that describe how the authority operates, based on equations formulated by Stolwijk-Hardy (see Figure 3); thus, each of the agents is part of the above equation. This model is characterized by relatively simple mathematical form and however, can generate the results reflecting several important physiological processes occurring during changes in blood

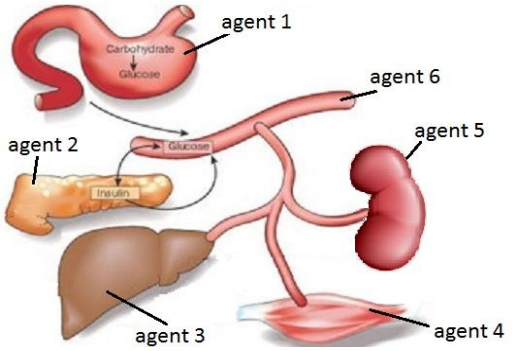


Figure 2. A schema connection between agent and organ.

glucose. Firstly, the increase in postprandial glucose levels is fast - until it reaches a maximum in 30-60 minutes. Secondly, the function of the violence changes after approx. 3 h after eating a meal appears reactive hypoglycemia. This

$$\frac{dg}{dt} = \omega - \nu g i - \lambda g - \mu(g - \Theta) + G$$

agent 3 agent 4 agent 4 agent 5 agent 1

$$\frac{di}{dt} = -\alpha i + \beta(g - \psi) + I$$

agent 3 agent 2 agent 7

agent 6

Figure 3. The Stolwijk-Hardy model.

model takes into account the additional ways of glucose utilization, and its internal production from a glucagon is given constant function ω (endogenous glucose flux). Using a description of the agent, without the need for the formulation of formal numerical coefficients, it is possible to formulate a solid adaptation of a mathematical model to identify actual changes in glucose-insulin levels.

We can describe five types of agents (see Figure 4):

1. The first type (AK) - blood agent (agent 6). This agent is of a higher order, and affects the behavior of other agents. It stores information related to the value of the levels of glucose and insulin, and provides updated information about the level of the individual agents, i.e., bodies. In this paper, this agent is also the environment in which other agents exist. Because of its function, only this agent has the ability to send information to other agents.
2. The second type (AO) – body agent (agents 2, 3, 4, and 5). This type of agent performs specialized functions that depend on the type of body to which it responds. Once implemented, this agent simulates the behavior of the dynamic processes that occur in the real organ. Through two-way communication with a blood agent, this type of agent is able to interpret process and generate feedback, which is then sent to the blood agent.
3. The third type (AKO) - cell agent (agent that exists inside of agent 2). This agent is the lowest type in the described solution. Its function is solely to generate information relevant to the cell. This agent is the simplest of them all: it exhibits two types of behavior, one of which is to be purely reactive. More specifically, it is responsible for generating a value, which is then sent to the master agent. The cell agent is only compatible with the master agent, and only interacts with this type of agent. The cell agent is questioned by an agent of the parent and its reaction to this question is to send the relevant information.
4. The fourth type - dosing agent (agent 1, 7). In this example, there are two agents in this category. The first represents the dosage of insulin infusion in an extravascular and active form. In terms of a simulation model, it is only used for the modeling of a person suffering from diabetes type one. The second type of dosing agent is one that simulates the supply of glucose from the gastrointestinal tract. It can therefore be concluded that this agent represents the entire digestive system through its provision of blood glucose.
5. The fifth type - GUI agent. This is a special agent, which has been developed exclusively for the visualization of the internal states of agents of the first and second type. It is represented by a user interface that allows specific, essential parameters to be set for the simulation.

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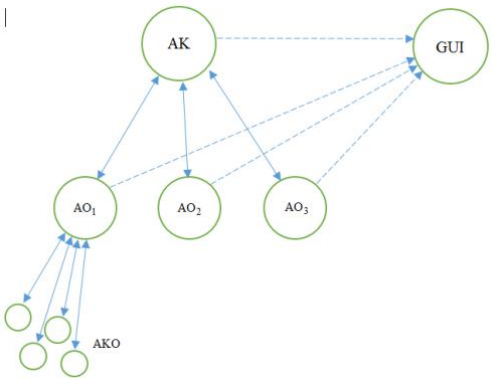


Figure 4. The Stolwijk-Hardy model.

The blood agent, which is a parent agent, representing authority, sends information about the current value of glucose and insulin to agents via an approximate circulation loop. This is characterized by the passing of blood through the capillary network of the stomach, duodenum, and small intestine and colon, followed by the pancreas, before dropping into the portal vein and the liver. Thus, the flow of information between the agents is based on this circulation loop. The blood agent sends information to other agents in the following order: digestive agent, pancreas agent, liver agent, kidneys agent, and finally, the muscle agent.

## IV. EXPERIMENTAL RESULTS

We designed a series of four experiments aimed at gaining knowledge about the temporal stability of the model, and the stability of the generated results. We also sought to determine the convergence of the results with the results of the method of analysis of differential equations carried out using MATLAB in experiment 4. The analytical model for multi-agent model was used as a reference and results were compared with it.

### *A. Experiment 1*

The first experiment was carried out to determine the temporal stability of the performance of individual agent's behavior for the different numbers of behaviors implemented and the number of agents that communicate with each other. The purpose of this experiment was to determine the temporal stability of a different number of agents' behaviors. Several variants of the experiment were designed:

- One agent
  - Simulation of one behavior.
  - Simulation of two behaviors.
  - Simulation of three behaviors.
  - Simulation of four behaviors.
- Implementation of two agents and, for each one, the agents used to carry out communication with a second agent.
- Implementation of three agents and, for each one, the behaviors used for communicating with other agents.

Each of the experiments was carried out using a specific run-time behavior (jade.core.behaviours.TickerBehaviour) - values were taken from the set [10ms, 20ms, 50ms, 100ms, 250ms, 500ms, 1000ms, 1500ms]. Each of the experiments was performed through 100 cycles. The experiment showed that the best stability was obtained by implementing each of the behaviors of an agent in a separate thread. Particularly good stability was preserved for the following times: 10ms, 20ms and 50ms.

### *B. Experiment 2*

The second experiment was designed to check the influence of the communication sequence between the blood agent and other agents on the generated simulation results. This experiment aimed to examine whether or not the sequence of communication between the agent and other blood agents was significant. Simulations were performed for three types of simulated "patient" properties: a healthy patient (i.e., classed as normal), with type 2 diabetes (DM2) and type 1 diabetes with insulin dose (DM1). The simulation was carried out with a dose of glucose measuring 75g and an absorption time of 15 min. For DM1, the simulation used an infusion of Regular insulin. The simulation time for a healthy person and DM2 amounted to four hours, and for a person with DM1, 12 hours. For the purposes of this experiment the following defined order of communication was used:

- K1: digestive, pancreas, liver, muscle, kidneys, insulin.
- K2: digestive, liver, pancreas, muscle, kidneys, insulin.
- K3: muscle, kidneys, liver, pancreas, digestive, insulin.
- K4: pancreas, kidneys, liver, muscle, digestive, insulin.

Figure 5. Definition of measurement points.

In order to determine the repeatability of solutions, we performed an experiment that simulated each of these instances in strictly defined points in time. Three characteristic points of comparison are given in (see Figure 5):

- Point A (upper left) - Its coordinates determine the occurrence of the maximum value for a specific time moment
- Point B (middle) - shows the value of the test function at a time of two hours
- Point C (lower left) - represents the value of the function under examination at the end of the simulation time.

The results are shown on Table I. The experiment shows that the order of communication between agents does not affect the results.

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TABLE I. ORDERING OF AGENTS.

| | Healthy person | | |
|---|---|---|---|
| *K1* | 370,6 ± 1,55 | 53,7 ± 0,24 | 59,0 ± 0,18 |
| *K2* | 370,9 ± 1,77 | 53,7 ± 0,12 | 59,0 ± 0,18 |
| *K3* | 366,9 ± 0,15 | 53,5 ± 0,36 | 58,9 ± 0,13 |
| *K4* | 366,8 ± 0,02 | 53,7 ± 0,09 | 58,9 ± 0,01 |
| | | | |
| **DM2** | | | |
| *K1* | 493,6 ± 1,51 | 201,5 ± 0,46 | 110,4 ± 0,18 |
| *K2* | 493,6 ± 1,44 | 201,9 ± 0,29 | 110,5 ± 0,25 |
| *K3* | 491,6 ± 0,01 | 201,6 ± 0,35 | 110,2 ± 0,27 |
| *K4* | 491,6 ± 0,01 | 201,5 ± 0,53 | 110,4 ± 0,00 |
| | | | |
| **DM1** | | | |
| *K1* | 460,9 ± 1,53 | 141,4 ± 0,53 | 122,1 ± 0,01 |
| *K2* | 461,1 ± 1,92 | 141,7 ± 0,27 | 122,2 ± 0,18 |
| *K3* | 457,9 ± 1,23 | 140,9 ± 0,55 | 122,1 ± 0,17 |
| *K4* | 458,2 ± 0,43 | 141,3 ± 0,41 | 122,1 ± 0,00 |

### C. *Experiment 3*

The third experiment was carried out in order to check the repeatability of the generated simulation results. In other words, we want to check whether or not our simulation will always generate the same results. The test points are the same as those used in experiment 2. This experiment was conducted using three cases (i.e., a normal, DM2, and DM1 person). In all, ten simulations were generated for each case and, in each case, they were subjected to a statistical analysis in order to determine the mean value and standard deviation. As Table II shows, the results are very stable; they have a small standard deviation.

TABLE II. RESULTS OF EXPERIMENT.

| | A | B | C |
|---|---|---|---|
| ***Normal*** | 370,6 ± 1,55 | 53,7 ± 0,24 | 59,0 ± 0,18 |
| ***DM2*** | 493,6 ± 1,51 | 201,5 ± 0,46 | 110,4 ± 0,18 |
| ***DM1*** | 460, 9± 1,53 | 141,4 ± 0,53 | 122,1 ± 0,01 |

### D. *Experiment 4*

The fourth experiment was based on a comparison of the results obtained from the analytical model (see Figure 3) and our proposed multi-agent model. The experiment was performed for the same dose of glucose (75g), and in the case of a patient with type 1 diabetes, using the same dose and type of insulin (Regular). Curves were obtained for each of the cases: normal, DM1, and DM2. These were obtained from a simulation of the analytical model using MATLAB and the proposed multi-agent system (see Figure 6). The same three points (A, B, C) were used to compare the results from the analytical model in MATLAB and the proposed multi-agent system. In this comparison, the results show that they are similar to each other (see Table III).

TABLE III. RESULTS OF MODELING.

| **(Multi-agent system)** | **A** | **B** | **C** |
|---|---|---|---|
| ***Normal*** | 370,6 | 53,7 | 59,0 |
| ***DM2*** | 493,6 | 201,5 | 110,4 |
| ***DM1*** | 460,9 | 141,4 | 122,1 |

| **(MATLAB)** | **A** | **B** | **C** |
|---|---|---|---|
| ***Normal*** | 382,2 | 52,6 | 57,4 |
| ***DM2*** | 572,3 | 265,0 | 102,5 |
| ***DM1*** | 531,3 | 223,4 | 129,1 |

## V. CONCLUSION

The main objective of the research is to show, in what way, biological systems can be modelled and analysed in various scales of complexity, with the use of advanced programming tools such as multiagent systems. Moreover, the following paper presents the way of transformation from the compartmental description to the description of physiological subsystem, using the multiagent description. According to the authors, the description presented in this paper is easier to use, better illustrates processes taking place in homeostatic phenomena of glucose and furthermore, it allows for an easy deduction which element of a model represents given organ and how it influences examined process. The authors are fully aware that the following research and presented model do not reflect all the processes actively participating in the process of carbohydrate metabolism. It should be mentioned here that presented approach reflects processes in mainly qualitative, not quantitative way. This paper presents a model of glucose homeostasis, which is based on a multi-agent programming paradigm. Using the Stolwijk-Hardy model, a model of multi-agent was used to develop a new tool that allowed us to simulate and analyze the phenomena associated with the regulation of sugar levels in the blood. The experiments carried out show that the multi-agent model has good temporal stability, especially in the short term. In addition, the results are highly reproducible. Our study has also shown that the order of communication between agents does not affect the value of the result of the simulation. The final

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experiment confirmed the equivalence of the results obtained from the analytical model and the multi-agent model. A discrepancy is visible at some points; we believe that this is a result of the different modes of the model's operation. Thus, during this period of time, there are different dynamics for changes in glucose levels.

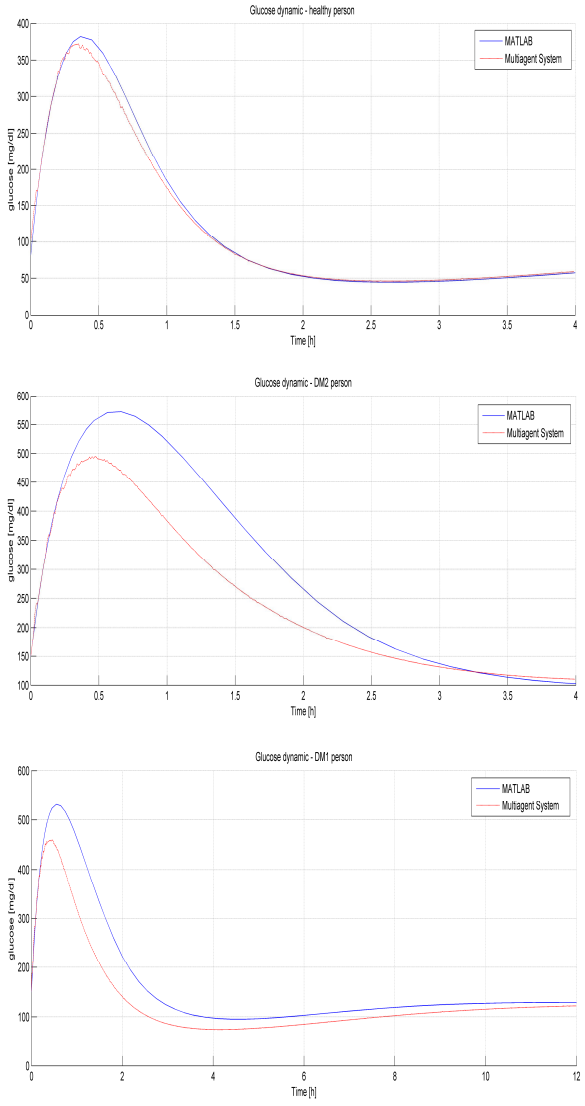


Figure 6. Solutions – validated data from the Multi-agent System and MATLAB.

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