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Mathematical Model and Simulation for the Mechanism of Glucose Uptake in the Cells

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ABSTRACT

Glucose uptake in the cells involves complex mechanism including interactions among proteins regulated by insulin. This mechanism is supported by several proteins that assist in translocating glucose transporter 4 to the cell membrane, facilitating glucose uptake. The main mechanism is illustrated in the insulin signaling pathway, which is complex and challenging to interpret intuitively. In this study, we propose a mathematical model to represent the underlying phenomena, enhancing interpretability and enabling effective simulation for numerical purposes. Investigating the behavior of the model through numerical simulations and dynamics within parameters and initial conditions are included in the analysis. To achieve the objectives, we formulate the mechanism by incorporating kinetic reactions involving proteins, enzymes under non-conserved complex C_i, based on the kinetic laws underlying the system. Several databases are employed during the model formulation process, providing critical information on the proteins, enzymes, and reactions involved in the system. A system of ordinary differential equations (ODEs) under the assumption of non-conservative complexes C_i provides a systematic explanation. Dynamic and numerical simulation results indicate that the graphical profiles of all variables remain stable.

Keywords: Modeling mathematics; uptake-glucose mechanism; ODEs; non-conserved C_i; Dynamical analysis; Numerical analysis

NTRODUCTION

Daily glucose uptake into the cell plays a crucial role to maintain the homeostasis of glucose in blood [1]. Homeostasis of blood glucose levels and optimal daily glucose absorption as an energy source for cells greatly influences the quality of an individual's metabolism, thereby preventing the expression of metabolic diseases such as T2DM. In contrary, impaired glucose absorption can cause blood toxicity, poor body metabolism, T2DM gene expression, and the emergence of other complications [2]. Homeostasis is also reciprocally connected to insulin performance [3]. The role of insulin is crucial in the regulation of glucose homeostasis. Insulin as a protein regulator is responsible in

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controlling GLUT4 translocation to obtain optimal blood glucose absorption [4], [5]. GLUT4 is a protein which acts a gate for glucose to enter into the cell. Hence, GLUT4 must be able to translocate to the cell membrane perfectly through protein-protein interaction regulated by insulin. The translocation purpose involves complex reactions, with several regulatory proteins and enzymes acting as catalysts for the reactions [6]. Investigating the phenomena remains challenging in order to elucidate the insulin signaling pathway described within the system (see in https://www.kegg.jp/pathway/map04910). The pathway determines the types of kinetic reactions among proteins. Within the GLUT4 system remain unclear [3], so, there are challenges in uncovering mechanisms. Several studies have attempted to address the issue. One of which reveal protein interactions from the perspective of mathematical models, both at the molecular interaction level and in terms of protein-protein interactions [7],[8],[9], in which the study theoretically explained in [10],[11]. Relevant to the effort, several databases provide information on the molecular interactions and networks, including biochemical GLUT4 pathways, gene functions, and chemical substances. The Kyoto Encyclopedia of Genes and Genomes (KEGG.jp) https://www.kegg.jp/ and the Search tool for the retrieval of interacting genes/proteins (STRING-db.org) database, https://string-db.org/, support actual explanations for a functional protein associations networks based on the latest discoveries and score of interactions, including GLUT4 pathway. For the next investigation purpose, the Biological General Repository for interaction Datasets (BioGRID) https://thebiogrid.org/ is focused on experimental validation for protein-protein interactions (PPIs). Otherwise, the database so called the Intact https://www.ebi.ac.uk/intact provides a system to track enzymes interacting with proteins in different biological processes. In line with this, the database of Interacting proteins (DIP) https://dip.doe-mbi.ucla.edu/dip/Main.cgi determines interactions between proteins. The Molecular Interaction Database (MINT) which accessible in https://mint.bio.uniroma2.it specializes in experimentally verified protein-protein interactions, particularly for enzymes and their role in signaling and metabolic processes. Suplementary databases that support the investigation are Biophysical Interactions of Complex Proteins (BioPlex) a free access database in https://bioplex.hms.harvard.edu/ as a systematically profiling protein interactions in the multiple cell line, Human Reference Interactome (HuRI) http://www.interactome-atlas.org/ the curated binary protein interactions from the scientific literature that is of comparable quality to interactions identified in systematic screens at CCSB, and Human Protein Reference Database (HPRD) http://www.hprd.org/. The databases are highly recommended for uncovering mechanisms at the protein-protein interaction level. Recent studies, by leveraging these databases, have successfully analyzed GLUT4 translocation, demonstrating its role in improving insulin sensitivity, maintaining glucose homeostasis in the blood, and preventing the occurrence of diabetes [12] and other diseases.

Given the critical importance of understanding normal glucose uptake, this study aims to elucidate the process from a mathematical modeling perspective. Starting with the premise that glucose uptake is closely associated with GLUT4 translocation, we investigate the specific pathway involved. Our analysis incorporates insights from previous research addressing this issue [7],[8],[9] and integrates relevant theoretical frameworks to provide a comprehensive understanding of the mechanism [10]. We focused on a normal mechanism of GLUT4 translocation; in which insulin secreted by the pancreas through the secretory system must binds to the insulin receptor (INSR) on the surface of the cell membrane through a phosphorylation process at the tyrosine kinase level [13]. Subsequently, the INSR is phosphorylated and undergoes an

autophosphorylation reaction on the insulin receptor substrate (IRS) [14]. This process allows IRS to associate with the regulatory subunit of phosphatidylinositol-3-kinase (PI3K). For the next, PI3K activates protein kinase-1 (PDK1) that depends on 3-phosphoinositide and activating Akt. Finally, Akt activation results in the translocation of GLUT4 vesicles from intracellular pool to the plasma membrane. This normal process allows GLUT4 to carry out its duties as a gateway for glucose to enter the cells. Based on this, it can be concluded that GLUT4 translocation is further viewed as a complex system, involving a complex interaction among proteins, including specific pathways, enzymes and reactions. The presence of mathematical modeling leads to systematic understanding which will ultimately lead to predictions and inventions.

Mathematical modeling principles begin by defining proteins or metabolites as model variables, enzymes as model parameters, and the interactions between proteins as kinetic reactions which catalyzed by enzymes [15]. In this study, we define variables of the model, namely insulin (INS), insulin receptor (INSR), insulin receptor substrate-1(IRS1), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), 3-phosphoinositide dependent protein kinase-1 (PDK1), and RAC serine/threonine-protein kinase (AKT). We represent the enzymatic reaction under the assumption that the kinetic reactions subject to the laws of mass action and mass balance laws [16], [9], [17]. In order to identify and analyze reactions types which are playing such as a key role in modeling, we based on Kyoto Encyclopedia of Genes and Genomes (KEGG.jp) [18] and String. dB [19]. Specifically, KEGG provides collection of molecular information, proteins data, pathways, functions, and high experimental results [20]. On the other hand, String database can be used to examine protein-protein interaction within GLUT4 pathway, functional analysis, the score trust of reaction between two proteins, and organism [21]. These two databases also confirm each other for identification and analysis of protein-protein reactions in the complex system. Through both databases, genomic information can be explored as a first step in mathematical modeling. We formulate the system of ordinary differential equations (ODEs) based on the kinetic reaction in each couple of proteins from the GLUT4 mechanism which can be found in insulin signaling pathway. The system of ODEs describes the rate of change in the concentration of proteins or substrates interacting with each other over time. For the next, numerical simulations and dynamic analysis are required to elucidate the whole mechanism [22], [23], [15]. The simulation of the model is directed to obtain predicted behavior for all protein concentration using parameters from secondary reaction rate enzymes data. The system of ODEs and their simulations serve as a bridge to enhance understanding of the underlying problems, while also paving the way for further analysis and the development of practical innovations.

The rest of this paper is organized as follows: in section 2, we review some papers and some theoretical background relating with insulin signaling pathway, laws for protein-protein interactions i.e laws of mass action and kinetic reaction. We also studied Kegg database to elucidate all proteins involved in the pathway. In this section we also explain our methodology, i.e analysis of the kinetic type of all reactions involved and identification of the trust score of the reaction types through string database. This analysis is required to arrange the kinetic reaction as a guidance in formulating the system of ODEs. In Section 3, we explain our step by step of ODEs development, analysis of the model behavior, numerical computation through Runge Kutta and Heun methods, and we highlight the discussions based on our work. Finally, Section 4 is the conclusion of our work.

METHODS

In formulating a mathematical model, some important points should be followed. First, we analyze the pathway for the mechanism of activation of (GLUT4). We identify interactions among proteins including: (1) interaction between Insulin and INSR, (2) interaction between INSR and IRS1, (3) interaction between IRS1 and PI3K, (4) interaction between PI3K and PIP3 - Interaction between PIP3 and PDK1, (5) interaction between PDK1 and AKT. Second, we identify the types of interactions (bindings, activation, inhibition) through Kegg.jp and Strings. dB that are available for free access. Third, we arrange all kinetic reactions using the law of mass action, the law of mass balance. Fourth, we convert kinetic reactions into a system of ordinary Differential Equations. Fifth, we calculate the function C_i as a parameter of the research variable that appear in the ODEs. Finally, we are substituting C_i into the ordinary differential equation model. Numerical simulation and dynamic analysis are then directed to obtain the graphic of every variable involved. To see the behavior of the ODEs, we explain through dynamic and numerical computation. Based on both methods, we describe initial assumptions regarding changes in the concentration of each variable and their stability from time to time.

RESULTS AND DISCUSSION

In this section, we explain our detail framework to obtain system of ODEs for GLUT4 translocation in protein-protein interaction perspective. We show dynamic and numerical computation in order to have the initial insight related to the behavior of the model we have formulated.

Mathematical Modeling

Mathematical modeling is a process of translating a real problem into differential equations. The modeling can be implemented in biological systems such as signaling processes regulated by regulatory proteins, so we can have useful insight from the phenomenon [9],[8]. Mathematical model can be integrated with experimental data, so it can then be used to analyze the behavior of the model and validation purpose of the model. We raise the mathematical modeling in the mechanism of glucose uptake and express it into a system of ordinary differential equations (ODEs). This model describes the kinetic reactions of protein-protein interactions within the mechanism which is depicted in GLUT4 pathway. We consider mass balance and mass action principles which are essential in development of kinetic reactions [8].

We focused on figures which illustrate the interaction among proteins for a mechanism of GLUT4 translocation. The identification of protein-protein interactions performed step-by-step for every couple protein start from INS to the Akt. we also examined confidence scores of all parameters involved in the interactions through STRING data base. Each reaction section has a confidence score confirming the validity of the relationship or interaction between two proteins according to the metabolic map depicted on the KEGG database.

The protein interaction scores that we obtained from STRING is displayed in Table 1:

Tabel 1. Protein Interaction Scores from STRING

Gene	Interaction	Confidence Score
$INS \rightarrow INSR$	Activation	0.999
$INSR \rightarrow IRS1$	Phosphorylation	0.999
$IRS1 \rightarrow PI3K$	Activation	0.999
$PI3K \rightarrow PIP3$	Activation	-
$PIP3 \rightarrow PDK1$	Activation	-
$PIP3K \rightarrow PDK1$	Activation	0.977
$PDK1 \rightarrow AKT$	Phosphorylation	0.997

The confidence score is also used as a basis for identifying all kinetic reactions between consecutive pairs of proteins. The confidence limits for the confidence score are 0.15 - 0.39 as low confidence, 0.4 - 0.69 as medium confidence, 0.7 - 0.89 as high confidence, and < 0.9 is higher confidence respectively. We use the confidence score from this string as a guide to confirm the type of interaction for each pair of proteins expressed in the pathway so that we can construct the appropriate kinetic reaction. Based on the kinetic reactions as follow:

$$x_i + x_{i+1} \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} C_i \overset{k_{i+1}}{\rightharpoonup} x_{i+1} + x_i \qquad (1)$$

Where $x_1, x_2, x_3, \ldots, x_{18}$ are concentrations of INSR, C_1, pINSR, IRS1, C_2, pIRS1, P13K, C_3, pP13K, PIP2, C_4, PIP3, PDK1, C_5, pPDK1, AKT, C_6, and pAKT respectively. Map flow for models is

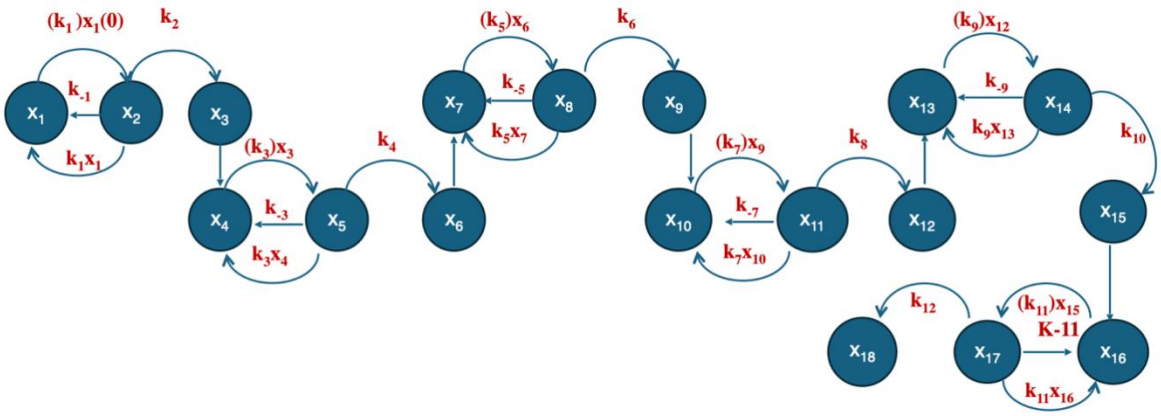


Figure 1. Compartment of the mechanism for all variable of the Model

Meanwhile, the initial concentration for all protein involved in the ODEs are denoted as $x_{1,0}, x_{2,0}, \ldots, x_{12,0}$ respectively. The ODEs for kinetic reaction in equations (2) are displayed as follow the models equation in

$$
\begin{aligned}
\frac{dx_1}{dt} &= -k_1 x_1 (INS_T - x_2) + k_{-1} x_2 \\
\frac{dx_2}{dt} &= -(k_{-1} + k_2) x_2 + k_1 x_1 (INS_T - x_2) \\
\frac{dx_3}{dt} &= (k_2) x_2 \\
\frac{dx_4}{dt} &= -k_3 x_4 (x_3 - x_5) + k_{-3} x_5 \\
\frac{dx_5}{dt} &= -(k_{-3} + k_4) x_5 + k_3 x_4 (x_3 - x_5) \\
\frac{dx_6}{dt} &= (k_4) x_5 \\
\frac{dx_7}{dt} &= -k_5 x_7 (x_6 - x_8) + k_{-5} x_8 \\
\frac{dx_8}{dt} &= -(k_{-5} + k_6) x_8 + k_5 x_7 (x_6 - x_8) \\
\frac{dx_9}{dt} &= (k_6) x_8 \\
\frac{dx_{10}}{dt} &= -k_7 x_{10} (x_9 - x_{11}) + k_{-7} x_{11} \\
\frac{dx_{11}}{dt} &= -(k_{-7} + k_8) x_{11} + k_7 x_{10} (x_9 - x_{11}) \\
\frac{dx_{12}}{dt} &= (k_8) x_{11} \\
\frac{dx_{13}}{dt} &= -k_9 x_{13} (x_{12} - x_{14}) + k_{-9} x_{14} \\
\frac{dx_{14}}{dt} &= -(k_{-9} + k_{10}) x_{14} + k_9 x_{13} (x_{12} - x_{14}) \\
\frac{dx_{15}}{dt} &= (k_{10}) x_{14} \\
\frac{dx_{16}}{dt} &= -k_{11} x_{16} (x_{15} - x_{17}) + k_{-11} x_{17} \\
\frac{dx_{17}}{dt} &= -(k_{-11} + k_{12}) x_{17} + k_{11} x_{16} (x_{15} - x_{17}) \\
\frac{dx_{18}}{dt} &= (k_{12}) x_{17}
\end{aligned}
\tag{2}
$$

The parameters are obtained from the brannmark model under normal condition[21]. For the next, we investigate the behavior of the model through dynamical and numerical analysis. The dynamic analysis aims to look at the behavior model around a fixed point and the results show indications of a stable model. On the other hand, numerical calculations via the Runge-Kutta method show that the proteins involved in the GLUT4 translocation mechanism interact with each other. The following sections describe the objectives.

Dynamic Analysis of ODEs

Equilibrium Points

In this section, we considered analysing the behaviour of proteins x_i in equation (2) around their fixed points. We assumed that the equilibrium points of the system are obtained when $\frac{dx_i}{dt} = 0$, in which the change in the concentration of all metabolites involved in the system are assumed constant, indicating that the system is in a steady state. If $N(t)$ is considered as constant, that is $N(t) = N^*$ and since one has $N(t) = \sum_{i=1}^{13} x_i$. By these assumptions, an equilibrium point from (2) is computed using the values of

$x_i, \forall\, i = 1,2,\dots,17$. i.e: $x_1 = x_1(0)$, $x_2 = 0$, $x_3 = x_3(0)$, $x_4 = 0$, $x_5 = x_5(0)$, $x_6 = 0$, $x_7 = x_7(0)$, $x_8 = 0$, $x_9 = x_9(0)$, $x_{10} = 0$, $x_{11} = x_{11}(0)$, $x_{12} = x_{12}(0) = 0$, $x_{13} = x_{13}(0)$, $x_{14} = 0$, $x_{15} = x_{15}(0)$, $x_{16} = 0$ and $x_{17} = x_{17}(0)$. Therefore, the equilibrium point is:

$$E = \left(x_{10}(0), 0, x_3(0), 0, x_5(0), 0, x_7(0), 0, x_9(0), 0, x_{11}(0), 0, x_{13}(0), 0, x_{15}(0), 0, x_{17}(0)\right)$$

Stability Analysis

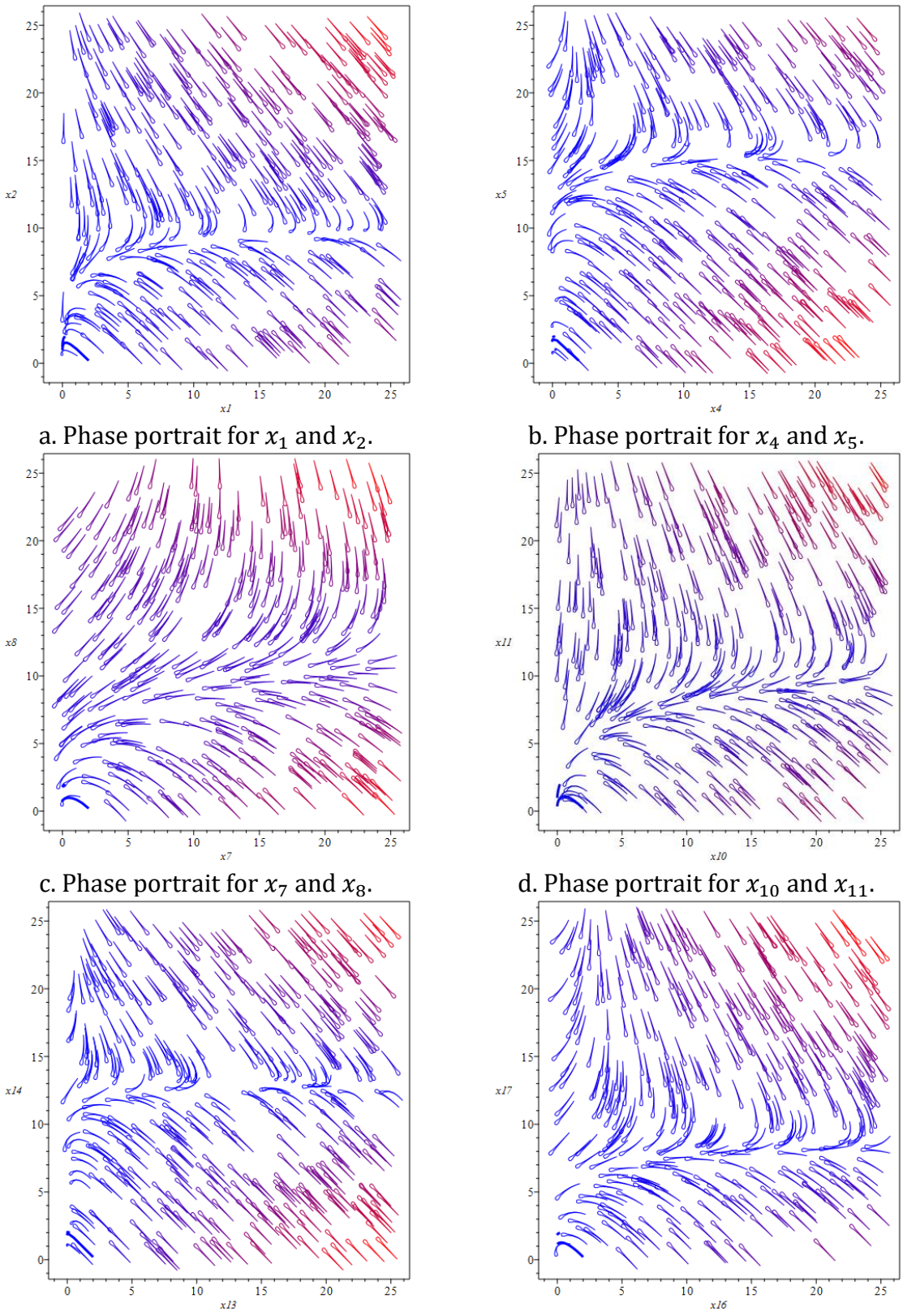
The interaction model insulin signaling pathway is nonlinear. Therefore, the stability of the equilibrium points can be determined by linearizing the system using the Jacobian matrix , which is given as follows:

$$J = \begin{pmatrix}
J_{1,1} & J_{1,2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
J_{2,1} & J_{2,2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & J_{3,2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & J_{4,3} & J_{4,4} & J_{4,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & J_{5,3} & J_{5,4} & J_{5,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & J_{6,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & J_{7,6} & J_{7,7} & J_{7,8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & J_{8,6} & J_{8,7} & J_{8,8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{9,8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{10,9} & J_{10,10} & J_{10,11} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{11,9} & J_{11,10} & J_{11,11} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{12,11} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{13,12} & J_{13,13} & J_{13,14} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{14,12} & J_{14,13} & J_{14,14} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{15,14} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{16,15} & J_{16,16} & J_{16,17} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{17,15} & J_{17,16} & J_{17,17}
\end{pmatrix}$$

The stability of the point E_0 Can be determined by substituting the equilibrium point into equation \eqref{matk.1}. So that becomes

$J_{1,1} = -(k_1 + k_2)$ $J_{1,2} = -k_1 x_{1,0}$ $J_{2,1} = -k_1$ $J_{2,2} = -k_1 x_{1,0}$
$J_{4,3} = -k_2$ $J_{4,4} = -(k_{-3} + k_4)$ $J_{4,5} = -k_3$ $J_{5,3} = -k_{-3}$
$J_{4,5} = -\left(k_3 x_{3,0}\right)$ $J_{5,5} = -k_1 x_{1,0}$ $J_{6,5} = -k_1$ $J_{7,6} = -k_1 x_{1,0}$
$J_{7,7} = -k_{-5}$ $J_{7,8} = -(k_{-3} + k_4)$ $J_{8,6} = -k_3$ $J_{8,7} = -k_{-3}$
$J_{8,8} = -k_7 x_{7,0}$ $J_{9,8} = -k_1 x_{1,0}$ $J_{10,9} = -k_1$ $J_{10,10} = -k_1 x_{1,0}$
$J_{10,11} = -(k_{-9} + k_{10})$ $J_{11,9} = -(k_{-3} + k_4)$ $J_{11,10} = -k_3$ $J_{11,11} = -k_{-3}$
$J_{12,11} = -k_{10}$ $J_{13,12} = -k_1 x_{1,0}$ $J_{13,13} = -k_1$ $J_{13,14} = -k_1 x_{1,0}$
$J_{14,12} = -\left(k_{11} x_{11,0}\right)$ $J_{14,13} = -(k_{-3} + k_4)$ $J_{14,14} = -k_3$ $J_{15,14} = -k_{-3}$
$J_{16,15} = -(k_1 + k_2)$ $J_{16,16} = -k_1 x_{1,0}$ $J_{16,17} = -k_1$ $J_{17,15} = -k_1 x_{1,0}$
$J_{17,16} = -k_2$ $J_{17,17} = -(k_{-3} + k_4)$

The eigenvalues indicate that $\lambda < 0$, indicating that the equilibrium point E_0 is asymptotically stable



a. Phase portrait for x_1 and x_2.

b. Phase portrait for x_4 and x_5.

c. Phase portrait for x_7 and x_8.

d. Phase portrait for x_{10} and x_{11}.

e. Phase portrait for x_{13} and x_{14}.

f. Phase portrait for x_{16} and x_{17}.

Figure 2. Phase portrait of mathematical models

Based on Figure 2. Above, the phase portrait results show that the direction is towards the fixed point E_0. So from this it can be concluded that the model is asymptotically stable.

Numerical Solution

In this section, We used Runge-Kutta and Heun methods with parameters k_i and all initial value given in table parameters. We need to know the trend of each variable as one of our measures of the validity of the model we have built.

Tabel 2. Parameters values and initial value.

Notation	Description	Unit	Value
k_1	Rate contantas of phosphorylation x_1	$\mu M min^{-1}$	0.6331
k_{-1}	Rate contantas of phosphorylation x_2	$\mu M min^{-1}$	0.03683
k_2	rate constants enzyme concentration x_3	$\mu M min^{-1}$	0.8768
k_3	Rate contantas of phosphorylation x_3	$\mu M min^{-1}$	0.5471
k_{-3}	Rate contantas of phosphorylation x_4	$\mu M min^{-1}$	0.2671
k_4	rate constants enzyme concentration x_5	$\mu M min^{-1}$	0.1377
k_5	Rate contantas of phosphorylation x_5	$\mu M min^{-1}$	0.09876
k_{-5}	Rate contantas of phosphorylation x_6	$\mu M min^{-1}$	0.5361
k_6	rate constants enzyme concentration x_7	$\mu M min^{-1}$	0.05506
k_7	Rate contantas of phosphorylation x_7	$\mu M min^{-1}$	0.08575
k_{-7}	Rate contantas of phosphorylation x_8	$\mu M min^{-1}$	0.04441
k_8	rate constants enzyme concentration x_9	$\mu M min^{-1}$	0.4146
k_9	Rate contantas of phosphorylation x_9	$\mu M min^{-1}$	0.5361
k_{-9}	Rate contantas of phosphorylation x_{10}	$\mu M min^{-1}$	0.1298
k_{10}	rate constants enzyme concentration x_{11}	$\mu M min^{-1}$	0.04441
k_{11}	Rate contantas of phosphorylation x_{11}	$\mu M min^{-1}$	0.05506
k_{-11}	Rate contantas of phosphorylation x_{12}	$\mu M min^{-1}$	0.09876
k_{12}	rate constants enzyme concentration x_{13}	$\mu M min^{-1}$	0.0018
INS_T	Initial value x_1	$\mu M min^{-1}$	10

The graphic profile of the model for each protein concentration with Runge Kutta order-4 can be seen on figure 3.

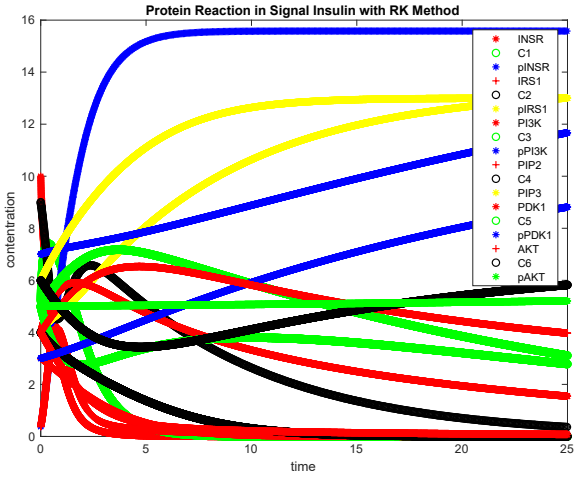


Figure 3. Numerical Simulation with Runge-Kutta Method

From Figure 3 the interaction occurs in protein. Insulin interacts with insulin receptors on the surface of target cells, such as muscle, liver, and adipose tissue cells. The insulin receptor is a transmembrane protein that has an extracellular domain that binds insulin and an intracellular domain that is involved in signal transduction. After insulin binds to the insulin receptor, a conformational change occurs in the receptor which activates intracellular tyrosine kinase activity. Activation of the insulin receptor causes phosphorylation of several substrate proteins in the cell, including itself (autophosphorylation) and other proteins. This phosphorylation activates specific signaling pathways that lead to specific cellular responses. Phosphorylation of substrate proteins activates intracellular signaling pathways, such as the insulin receptor substrate (IRS) and phosphatidylinositol 3-kinase (PI3K) pathways, which in turn results in cellular responses such as translocation of GLUT4 to the cell membrane to take up glucose.

Insulin-protein interaction is a highly regulated and well-coordinated process that plays an important role in regulating body metabolism and maintaining blood glucose homeostasis. Disturbances in this interaction can cause various metabolic disorders, including diabetes mellitus.

CONCLUSIONS

This study presents a mathematical model describing the translocation of GLUT4 as the mechanism underlying normal glucose uptake. The mechanism is formulated as a system of ordinary differential equations (ODEs), providing a scientific framework to facilitate the understanding of glucose uptake in cells under non-conservative C_i. The enzymatic reactions within the system are derived based on trust scores from the STRING database, and compared against KEGG pathway data.

The model's behavior was investigated using two complementary approaches: dynamic analysis and numerical simulations. Experimental results demonstrate that the stability of the dynamic and numerical computations validates the proposed model as a reliable representation of the mechanism.

The formulated mathematical model is anticipated to serve as a reference for future experimental designs, particularly in exploring specific enzyme data and protein-protein interactions. For further development, integrating the ODE system and simulations with

real experimental data will enhance the model's predictive accuracy in describing glucose uptake. Additionally, the model offers the potential for standardization in systems biology through implementation in Biological Markup Language (SBML) for broader applications and accessibility.

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