Simulation of a Mathematical Model of Proteins Interaction on GLUT4 Translocation

Ari Kusumastuti, Mohammad Isa Irawan*, Kistosil Fahim, Nurul Anggraeni Hidayati, Anindita Sharkar

***Abstract*—Glucose is the energy source of cells. Glucose absorption into muscle cells is regulated by Insulin by involving the interaction of several proteins in a specific system. The system works for the translocation of GLUT4 to the cell membrane. GLUT4 is a transporter protein owned by every muscle cell, as an entry gate for glucose and an Insulin partner in maintaining homeostasis of blood glucose levels. After the Insulin activation occurs in the Insulin Receptor Substrate (IRS), it is followed by the activation of several proteins to regulate GLUT4 translocation, namely IRS, phosphatidylinositol 3-kinase (P13K), 3-phosphoinositide-dependent protein kinase-1 (PDK1/2) and serine/threonine-protein kinase (AKT). This study describes these processes in a mathematical model as a system of ordinary differential equations. The specific process modeled is the Insulin signal pathway that regulates GLUT4 translocation, which can be accessed on Kegg.jp. Moreover, string.db.org analysis results are used as a reference to prove the type of protein interaction. The formulated model is directed to coherently explain the flux changes of each protein involved in the system and stimulate easily. The simulation provides an overview of the protein dynamics in the system over time. Finally, the mathematical models and simulations will complement the basic understanding of the effect of glucose absorption on the translocation of GLUT4.**

***Index Terms*—Insulin-signaling Pathway, Protein Interactions, GLUT4, IRS, P13K, PDK1/2, AKT, Protein Dynamics, Mathematical Model, Simulations.**

I. Introduction

SPECIFIC cellular processes within cells involve complex protein-protein interactions (PPI) [1]. This interaction occurs in a complex system involving interrelated pathways that influence each other. The complex glucose uptake system involves complicated protein-protein interactions in a specific pathway to activate GLUT4 proteins from the cytosol into the cell membrane [2][1]. For example, proteins involved in the GLUT4 translocation process involve IRS, P13K, PDK1/2, and Akt proteins that act on complex insulin signaling pathways [3][4]. The research provides a comprehensive overview of the regulation and translocation of GLUT4, emphasizing the importance of this process in glucose metabolism. The paper explores the intricate signaling pathways, protein kinases, lipid rafts, and advanced imaging techniques involved in understanding GLUT4 translocation. Active insulin IRS1 regulates the translocation of GLUT4 to the surface of the cell membrane; then this protein will carry out successive critical processes involving regulatory proteins with different interaction characteristics. Successively, the two process steps can be described as follows: The first stage is the occurrence of phosphorylation by Insulin, which encourages the separation of the IRS from the insulin receptor. Second, IRS will activate P13K so that PIP3 is produced through PIP2 phosphorylation. PIP3 will then activate PDK1 through a binding reaction. Finally, activation of PDK1 will be followed by the activation of AKT through phosphorylation at the Threonin level [5]. The protein interactions process is easier to explain using a mathematical model[6]. Mathematical models are built based on the pathway presented on the kegg.jp website [4]. The pathway describes protein-protein interactions in complex pathways and is interrelated with other pathways. In KEGG, one can trace the sequence of protein-protein interactions in carrying out cell-specific tasks, for example, insulin signaling in the GLUT4 translocation process [7]. The pathway is the KEGG database containing graphical representations of cellular processes, such as metabolism, membrane transport, signal transduction, and cell cycle [8]. All candidate proteins' interactions are expressed in kinetic reactions [9], which are regulated by enzymes that act as catalysts [10]. The following modeling stage analyzes the kinetic reactions of each interaction of two proteins sequentially in the system. The second step is transforming all the kinetic reactions into time-dependent ordinary differential equations through rigorous algebraic processes. This modeling rule takes into account the law of mass action, the direction of the mass balance of the proteins in the system [11][12][13]. Mathematical models of kinetic reactions reveal the rate of change in the concentrations of proteins or substrates that interact with each other over time. The formed mathematical model is simulated using parameters from several studies to obtain predictions of the interaction and regulatory mechanisms. The previous research about insulin signaling in the GLUT4 translocation process [14] incorporates various components and processes involved in insulin signaling, such as the insulin receptor, insulin-sensitive glucose transporter (GLUT4), and downstream signaling molecules like protein kinase B (Akt) and glycogen synthase kinase 3 (GSK3). The benefit of this model is that it can simulate the signaling and metabolic responses to different conditions, such as variations in insulin levels, glucose levels, or the presence of specific molecular inhibitors or activators. [15] combines mathematical equations and biophysical models to simulate the interactions between insulin, insulin receptors, signaling pathways, and GLUT4 vesicles. The process begins by collecting experimental data on insulin signaling and GLUT4 translocation, such as protein-protein interactions, phosphorylation events, and membrane trafficking dynamics.

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This data is then used to develop mathematical equations and algorithms that describe the underlying biological processes. [16] compares different mathematical models and their kinetic realizations, which represent the dynamic interactions and reactions involved in insulin signaling. These models are based on a variety of experimental data, biochemical reactions, and signaling pathways. The comparing result is used to identify the strengths, weaknesses, and limitations of each kinetic realization and provide insights into the understanding of insulin signaling.

A. Insulin

Insulin was originally a peptide hormone secreted by the β cells of the Langer-Hans Pancreas. Insulin coded by the arm chromosome 117 is short and is synthesized by β cells from the pancreatic islets of Langerhans as proinsulin. Proinsulin is synthesized in the ribosome-rough endoplasmic reticulum as pre-proinsulin. Pre-proinsulin is formed through signal peptide synthesis. The release of the signal peptide will assemble proinsulin in the endoplasmic reticulum. After binding and phosphorylation with the insulin receptor, Insulin will be activated at the insulin receptor substrate (IRS) level as active insulin [17][18]. This process transforms the hormone proinsulin into active Insulin in the form of IRS protein. This active Insulin is then tasked with regulating essential cell processes, such as GLUT4 translocation. Based on this, Insulin functions as a regulator of blood glucose levels are crucial. Furthermore, Insulin plays a vital role in regulating glucose absorption into cells, activating proteins that support cell function, and regulating glucose storage in the liver and muscles as a food reserve [18].

B. Insulin Receptor Substrate (IRS)

The IRS proteins are a family of cytoplasmic adapter proteins that transmit signals from insulin receptors and IGF-1 to elicit cellular responses [19]. The insulin receptor has a heterotetramer structure consisting of the 2α and 2β glycoprotein subunits linked by disulfide bonds and located in the cell membrane. IRS-1 is the first member of the family to be identified as a 185 kD phosphoprotein in response to insulin stimulation. IRS-2 was discovered as an alternative insulin receptor substrate. IRS-1 and IRS-2 are significant mediators of insulin-dependent mitogenesis and regulation of glucose metabolism in most cells[20]. IRS proteins regulate the growth of organisms. These proteins do not contain intrinsic enzymatic activity, and they mediate IR/IGF-IR signaling through their function as scaffolding proteins to regulate signaling complexes. The IRS protein functions to activate upstream receptors via the PH and PTB domains located at the N-terminus. An essential role of IRS in the regulation of metabolism is the amplification of PI3K signaling to activate serine-threonine kinase AKT. The IRS protein contains several consensus PI3K-binding motifs that recruit and activate PI3K via the SH2 domain in the p85 subunit [19]. Furthermore, the naming of IRS is based on the function and sensitivity of this protein binding, which mainly regulates certain types of disease [19][21].

C. Phosphatidylinositol-3-kinase (PI3K)

Phosphatidylinositol 3-kinase (PI3K) is suspected as an essential protein that helps translocate glucose 4 (GLUT4). After insulin activation occurs through tyrosine phosphorylation on the IRS intracellular substrate, it will be followed by the binding of the src-homology-2 protein domain (SH2) by IRS, which includes the enzyme phosphatidylinositol-3-kinase (PI3K). Typically, this binding leads to a phosphorylation reaction of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce the lipid second messenger phosphatidylinositol (3,4,5)-triphosphate (PIP3), which in turn recruits Akt to the plasma membrane via phosphorylation. The pathway connecting IRS signaling to P13K and Akt is essential downstream signaling in GLUT4 translocation [22]. The Phosphatidylinositol 3-kinase P13K and AKT pathways are then activated by various cellular stimuli, including the role of phosphorus [23]. In the recruitment and signaling process of Akt, the successful phosphorylation of lipids in the cell membrane is very important [24]. Interestingly, the P13K protein and its lipid products are key proteins in successfully recruiting and activating Akt at the upstream level. This can be achieved by the ability of P13K to bind to the growth protein receptor known as the PDGF protein [25].

D. The 3-phosphoinositide-dependent protein kinase-1 (PDK1)

PDK1 regulates phosphorylation at the kinase level, regulates the activity of insulin groups, and is responsible for activating the protein Akt [26][27]. PDK1 also participates with other proteins in carrying out the GLUT4 translocation mission for glucose uptake. Phosphoinositide-dependent protein kinase 1 (PDK1) can phosphorylate AKT1 at T308, which is required for AKT activity. PDK1 is also needed to activate the phosphorylation loop of a family of protein kinases, including protein kinases stimulated by growth hormone[25].

E. Akt1/2

Akt is a key protein in pathophysiology. Failure of Akt function will affect the emergence of insulin resistance, inflammation, and diabetes mellitus. Downstream activation of Akt is closely related to cellular transformation and insulin response. Akt is activated depending on the P13K [25]. Akt The Akt protein consists of 3 types, namely Akt1, Akt2, and Akt3. This classification is based on the function and location where this Akt works. One of the tasks of Akt1 is responsible for protein synthesis. Meanwhile, Akt2 controls glucose homeostasis in blood and GLUT4 translocation to cell membranes [5]. Akt1/2 is important in translocating GLUT4 to the cell surface [5]. Akt is the only protein kinase family that can bind to PIP3, so that it becomes a target for PDK1. Akt is in charge of controlling the main signaling and governing several downstream cellular targets and functions. [25].

F. Glucose Transporter-4 (GLUT4)

GLUT is a specific protein that is the glucose gateway to enter cells [28]. GLUT works by being regulated by Insulin

and assisted by P13K protein [29]. GLUT is spread throughout the network, and its name is based on which network the GLUT protein is stored in. GLUT classification is based on the area of glucose absorption task that must be carried out. GLUT1 helps the absorption of glucose in the brain and erythrocytes. GLUT2 is found in the liver, pancreas, intestine, and kidney cells. GLUT3 specifically works in the brain; meanwhile, GLUT4 in skeletal muscle, brain, heart, and adipose tissue [30]. GLUT4 is distinctive compared to other GLUT families in terms of its dynamic cycle in adipocytes and muscle cells[5]. GLUT4 helps the process of glucose metabolism through stimulation by Insulin or stimulation by muscle contraction. Therefore the failure of insulin stimulation and insulin signaling will have an impact on T2DM [5].

G. Kinetic Reaction

The kinetic reaction is a chemistry that discusses the rate of reaction and the factors that affect the rate of the reaction. Furthermore, enzyme kinetics is the kinetic reactions catalyzed by enzymes. In theory, the rate (speed) of the reaction is expressed as the change in the concentration of the reactant or product of the reaction (product) over a unit of time. An example of a kinetic reaction is as follows:

$$A + B \rightarrow P + B \tag{1}$$

A is the substrate, B is the enzyme, and P is the two-step product. The first B combines with A, predicts that the change in reaction rate is linear with the change in A. Breaks down into products P releases B:

$$A + B \rightleftharpoons_{k_2}^{k_1} C \rightarrow^{k_3} P + E \tag{2}$$

Enzyme-catalyzed reactions use reactants and produce products that are the same as uncatalyzed reactions. Enzymes do not change the equilibrium position between substrate and product. In the case of relatively low enzyme concentration and substrate concentration, the reaction rate will increase linearly with the addition of substrate concentration. Whereas in the case of high substrate concentrations, the reaction rate will reach a maximum, resulting in a saturation condition. If the law of mass action is applied to the reaction mechanism 2, the following differential equation is obtained:

$$\frac{dA}{dt} = k_2 C - k_1 AB \tag{3}$$

$$\frac{dB}{dt} = (k_2 + k_3)C - k_1 AB \tag{4}$$

$$\frac{dC}{dt} = k_1 AB - (k_2 + k_3)C \tag{5}$$

$$\frac{dP}{dt} = k_3 C \tag{6}$$

from the equation 5 and 6 obtained $\frac{dB}{dt} + \frac{dC}{dt} = 0$, so $B + C = B_0$, in this case B_0 is the total amount of enzyme available.

II. Methods

The proposed method to further validate the mathematical model is as follows:

1) Data collection: Data related to the insulin signaling pathway from Kegg.jp, including protein-protein interactions and kinetics based on string.db.org analysis, and the effect of insulin on glut4 translocation and glucose uptake.
2) Model formulation: Using the collected data, develop a set of ordinary differential equations (ODEs) that describe the kinetic reactions of protein-protein interactions in the insulin signaling pathway. Incorporate the principles of mass balance and mass action to transform the kinetic reactions into a mathematical model.
3) Computational processes: Implement the mathematical model into a computational framework.
4) Simulation: Interpret the simulated results obtained from the mathematical model.
5) Evaluation: Evaluate the model's sensitivity to parameter changes, and assess the model's predictability under different conditions to ensure its reliability.

By following this proposed method, the mathematical model describing the insulin signaling pathway and its regulation of glut4 translocation and glucose uptake can be further validated and enhanced.

III. Mathematical Models

Mathematical models are mathematical equations to facilitate understanding of phenomena, for example, signaling processes regulated by the interaction of regulatory proteins [31][13]. Furthermore, the mathematical model that has been formulated can be integrated with computational processes, simulation, and model validation using experimental data. Mathematical modeling of a signaling pathway is generally expressed in ordinary differential equations that describe the kinetic reactions of protein-protein interactions. The principle of mass balance and mass action is concerned with transforming kinetic reactions into this mathematical model [31]. The mathematical model formed is an assumption model, so experimental data is needed to test the model's reliability [31]. The mathematical model in this study is based on the insulin signal pathway, which regulates GLUT4 translocation and Yol insulin signaling; we can see the interaction of IRS1 to AKT as follows: Figure 1 shows the process of insulin

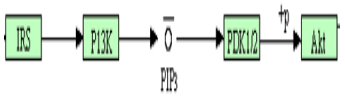


Fig. 1: IRS1 interaction pathway with PI3K-AKT on the insulin signaling pathway

interaction (INS) connected with insulin receptors (INSR). Identification of interactions between proteins will be carried out in stages. The parameter used is the trust score of the interaction relationship between the substrates obtained from the STRING software [32]. The confidence score is the estimated probability of a predicted link or interaction between the two enzymes in the metabolism map in the KEGG database [4]. The interaction score of the insulin protein with the insulin

receptor is obtained as follows:

TABLE I: Protein interaction score from STRING [32]

Protein	Interaction Type	Trust score	Information
$IRS1 \rightarrow PI3K$	Activation	0.999	IRS1 activates PI3K
$PI3K \rightarrow PIP3$	Activation	-	PI3K activates PIP3
$PIP3 \rightarrow PDK1$	Activation	-	PIP3 activates PDK1
$PI3K \rightarrow PDK1$	Activation	0.977	PI3K activates PDK1
$PDK1 \rightarrow AKT$	Phosphorylation	0.995	PDK1 activates AKT

Based on the identification of gene interactions previously stated, that Insulin activates INSR. The interaction of INS and INSR can be described in the kinetic reaction equation as follows:

$$IRS1 + PI3K \rightleftharpoons^{k_1}_{k_2} C_1 \rightarrow^{k_3} IRS1 + pPI3K \quad (7)$$

$$pPI3K + PIP2 \rightleftharpoons^{k_4}_{k_5} C_2 \rightarrow^{k_6} pPI3K + PIP3 \quad (8)$$

$$PIP3 + PDK1 \rightleftharpoons^{k_7}_{k_8} C_3 \rightarrow^{k_9} PIP3 + pPDK1 \quad (9)$$

$$pPDK1 + AKt \rightleftharpoons^{k_{10}}_{k_{11}} C_4 \rightarrow^{k_{12}} pPDK1 + AKt \quad (10)$$

The interaction equation 7 shows that $IRS1$ activates $PI3K$. The interaction equation 8 shows that $PI3K$ interacts with $PIP2$ and is phosphorylated into $PIP3$. The Equation 9 shows that $PIP3$ interacts and activates $PDK1$. Futhermore, equation 10 shows that $PDK1$ interacts and activates AKT. Application of the law of mass action and the law of mass balance results in a system of ordinary differential equations that govern the following reactions [13]: Berikut adalah sistem persamaan yang sudah dibagi menjadi dua baris untuk beberapa persamaan yang panjang:

$$\begin{aligned}
\frac{d[IRS1]}{dt} &= (k_2+k_3)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K),\\
\frac{d[PI3K]}{dt} &= (k_2)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K),\\
\frac{d[pPI3K]}{dt} &= \frac{k_3}{2}(IRS1_0 - IRS1) + \frac{k_5+k_6}{2}(pPI3K_0 - pPI3K)\\
&\quad - \frac{k_4}{2}(PIP2)(pPI3K),\\
\frac{d[PIP2]}{dt} &= (k_5)(pPI3K_0 - pPI3K) - k_4(PIP2)(pPI3K),\\
\frac{d[PIP3]}{dt} &= \frac{k_6}{2}(pPI3K_0 - pPI3K) + \frac{k_8+k_9}{2}(PIP3_0 - PIP3)\\
&\quad - \frac{k_7}{2}(PIP3)(PDK1),\\
\frac{d[PDK1]}{dt} &= (k_8)(PIP3_0 - PIP3) - k_7(PIP3)(PDK1),\\
\frac{d[pPDK1]}{dt} &= \frac{k_9}{2}(PIP3_0 - PIP3) + \frac{k_{11}+k_{12}}{2}(pPDK1_0 - pPDK1)\\
&\quad - \frac{k_{10}}{2}(pPDK1)(AKT),\\
\frac{d[AKT]}{dt} &= (k_{11})(pPDK1_0 - pPDK1) - k_{10}(pPDK1)(AKT),\\
\frac{d[pAKT]}{dt} &= (k_{12})(pPDK1_0 - pPDK1).
\end{aligned} \quad (11)$$

IV. Dynamic Analysis

In this section, we will study the characteristics of systems of equations 11. Dynamic analysis of the system of equations includes the equilibrium point and local stability analysis.

A. Equilibrum Point

The system equilibrium point is obtained when:

$$\frac{dIRS1}{dt} = \frac{dPI3K}{dt} = \frac{dpPI3K}{dt} = \frac{dPIP2}{dt} = \frac{dPIP3}{dt} = \frac{dPDK1}{dt} = \frac{dpPDK1}{dt} = \frac{dAKT}{dt} = 0$$

so that the system of equations 11 becomes

$$\begin{aligned}
(k_2+k_3)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K) &= 0,\\
(k_2)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K) &= 0,\\
\frac{k_3}{2}(IRS1_0 - IRS1) + \frac{k_5+k_6}{2}(pPI3K_0 - pPI3K)&\\
- \frac{k_4}{2}(PIP2)(pPI3K) &= 0,\\
(k_5)(pPI3K_0 - pPI3K) - k_4(PIP2)(pPI3K) &= 0,\\
\frac{k_6}{2}(pPI3K_0 - pPI3K) + \frac{k_8+k_9}{2}(PIP3_0 - PIP3)&\\
- \frac{k_7}{2}(PIP3)(PDK1) &= 0,\\
(k_8)(PIP3_0 - PIP3) - k_7(PIP3)(PDK1) &= 0,\\
\frac{k_9}{2}(PIP3_0 - PIP3) + \frac{k_{11}+k_{12}}{2}(pPDK1_0 - pPDK1)&\\
- \frac{k_{10}}{2}(pPDK1)(AKT) &= 0,\\
(k_{11})(pPDK1_0 - pPDK1) - k_{10}(pPDK1)(AKT) &= 0.
\end{aligned} \quad (12)$$

Based on equation 12, obtained solutions $IRS1 = IRS1_0$, $PI3K = 0$, $pPI3K = pPI3K_0$, $PIP2 = 0$, $PIP3 = PIP3_0$, $PDK1 = 0$, $pPDK1 = pPDK1_0$ and $AKT = 0$. So the equilibrium point of the system of equations is $E_0 = (IRS1_0, 0, pPI3K_0, 0, PIP3_0, 0, pPDK1_0, 0)$.

B. Stability Analysis

The interaction model on IRS1, PI3K, and AKT is a nonlinear system; therefore, the stability of the equilibrium point is obtained by linearizing the system with the Jacobi matrix [33] as follows:

$$J = \begin{pmatrix}
J_{1,1} & J_{1,2} & 0 & 0 & 0 & 0 & 0 & 0\\
J_{2,1} & J_{2,2} & 0 & 0 & 0 & 0 & 0 & 0\\
J_{3,1} & 0 & J_{3,3} & J_{3,4} & 0 & 0 & 0 & 0\\
0 & 0 & J_{4,3} & J_{4,4} & 0 & 0 & 0 & 0\\
0 & 0 & J_{5,3} & 0 & J_{5,5} & J_{5,6} & 0 & 0\\
0 & 0 & 0 & 0 & J_{6,5} & J_{6,6} & 0 & 0\\
0 & 0 & 0 & 0 & J_{7,5} & 0 & J_{7,7} & J_{7,8}\\
0 & 0 & 0 & 0 & 0 & 0 & J_{8,7} & J_{8,8}
\end{pmatrix}. \quad (13)$$

in this case

$J_{1,1} = -(k_2+k_3) - k_1(PI3K)$ $J_{1,2} = -k_1(IRS1)$ $J_{2,1} = -(k_2) - k_1(PI3K)$

$J_{2,2} = -k_1(IRS1)$ $J_{3,1} = -\frac{k_3}{2}$ $J_{3,3} = -\frac{(k_5+k_6)}{2} - \frac{k_4}{2}(PIP2)$

$J_{3,4} = -\frac{k_4}{2}(pPI3K)$ $J_{4,3} = -k_5 - k_4(PIP2)$ $J_{4,4} = -k_4(pPI3K)$

$J_{5,3} = -\frac{k_6}{2}$ $J_{5,5} = -\frac{(k_8+k_9)}{2} - \frac{k_7}{2}(PDK1)$ $J_{5,6} = -\frac{k_7}{2}(PIP3)$

$J_{6,5} = -(k_8) - k_7(PDK1)$ $J_{6,6} = -k_7(PIP3)$ $J_{7,5} = -\frac{k_9}{2}$

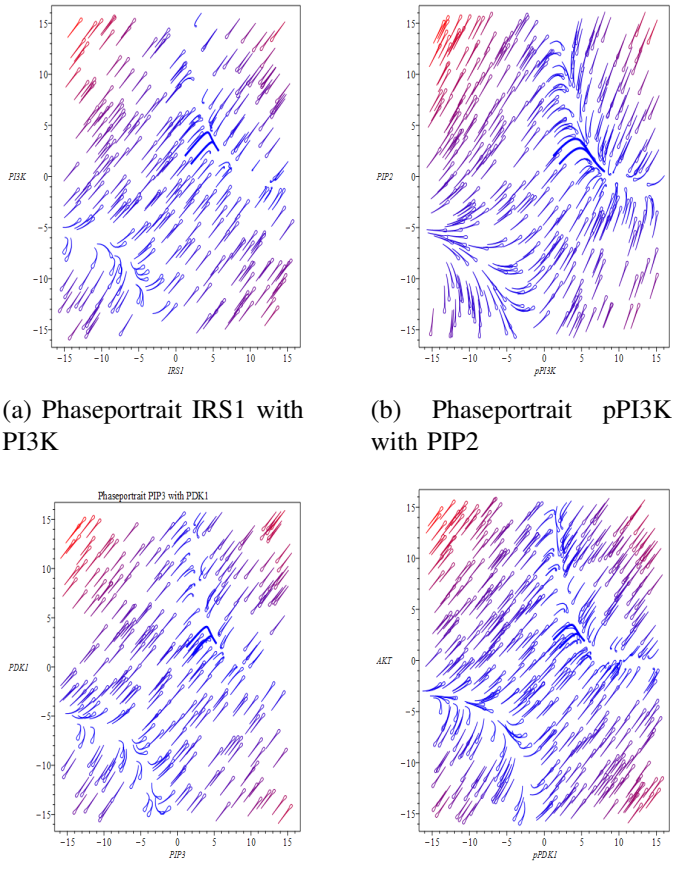
$J_{7,7} = -\frac{(k_{11}+k_{12})}{2} - \frac{k_{10}}{2}(AKT)$ $J_{7,8} = -\frac{k_{10}}{2}(pPDK1)$ $J_{8,7} = -k_{11} - k_{10}(AKT)$

$J_{8,8} = -k_{10}(pPDK1)$

The stability at point $E_0 = (IRS1_0, 0, pPI3K_0, 0, PIP3_0, 0, pPDK1_0, 0)$ can be found by substituting the equilibrium point into 13. The eigenvalues obtained from the matrix are:

$$\lambda = \begin{pmatrix} -\frac{k_4 pPI3K0}{2} - \frac{k_5}{4} - \frac{k_6}{4} \\ -\frac{k_4 pPI3K0}{2} - \frac{k_5}{4} - \frac{k_6}{4} \\ -\frac{k_{10} pPDK10}{2} - \frac{k_{11}}{4} - \frac{k_{12}}{4} \\ -\frac{k_{10} pPDK10}{2} - \frac{k_{11}}{4} - \frac{k_{12}}{4} \\ -\frac{k_7 PIP30}{2} - \frac{k_8}{4} - \frac{k_9}{4} \\ -\frac{k_7 PIP30}{2} - \frac{k_8}{4} - \frac{k_9}{4} \\ -\frac{k_1 IRS10}{2} - \frac{k_2}{2} - \frac{k_3}{2} \\ -\frac{k_1 IRS10}{2} - \frac{k_2}{2} - \frac{k_3}{2} \end{pmatrix}$$

the eigenvalues show that $\lambda < 0$, so the equilibrium point E_0 is asymptotically stable. The phase portraits of the system of equations are shown in Figure 2.



(a) Phaseportrait IRS1 with PI3K

(b) Phaseportrait pPI3K with PIP2

(c) Phaseportrait PIP3 with PDK1

(d) Phaseportrait pPDK1 with AKT

Fig. 2: Phase portrait of Proteins Interaction

In the phase portrait 2, the stability of a fixed point refers to the behavior of nearby trajectories around that point. A fixed point is considered stable if trajectories close to it converge toward the fixed point over time. Stable fixed points are typically represented by closed orbits or spirals in a phase portrait 2, indicating that trajectories tend to oscillate or evolve towards the fixed point without diverging. The stability of a fixed point is crucial in determining the long-term behavior of protein dynamics, providing insights into its overall behavior and equilibrium states.

V. Discrete Equation Models

This section discusses the discrete form for the mathematical model of the equation 11using the 1st order forward difference finite difference method. The 1st order finite difference form is as follows:

$$\frac{F^{n+1} - F^n}{dt}$$

so that when applied to the system of equations 11 for the time derivative, the system of equations 11 becomes:

$$\begin{aligned}
\frac{d[IRS1]}{dt} &= (k_2 + k_3)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K), \\
\frac{d[PI3K]}{dt} &= (k_2)(IRS1_0 - IRS1) - k_1(IRS1)(PI3K), \\
\frac{d[pPI3K]}{dt} &= \frac{k_3}{2}(IRS1_0 - IRS1) + \frac{k_5 + k_6}{2}(pPI3K_0 - pPI3K) \\
&\quad - \frac{k_4}{2}(PIP2)(pPI3K), \\
\frac{d[PIP2]}{dt} &= (k_5)(pPI3K_0 - pPI3K) - k_4(PIP2)(pPI3K), \\
\frac{d[PIP3]}{dt} &= \frac{k_6}{2}(pPI3K_0 - pPI3K) + \frac{k_8 + k_9}{2}(PIP3_0 - PIP3) \\
&\quad - \frac{k_7}{2}(PIP3)(PDK1), \\
\frac{d[PDK1]}{dt} &= (k_8)(PIP3_0 - PIP3) - k_7(PIP3)(PDK1), \\
\frac{d[pPDK1]}{dt} &= \frac{k_9}{2}(PIP3_0 - PIP3) + \frac{k_{11} + k_{12}}{2}(pPDK1_0 - pPDK1) \\
&\quad - \frac{k_{10}}{2}(pPDK1)(AKT), \\
\frac{d[AKT]}{dt} &= (k_{11})(pPDK1_0 - pPDK1) - k_{10}(pPDK1)(AKT), \\
\frac{d[pAKT]}{dt} &= (k_{12})(pPDK1_0 - pPDK1).
\end{aligned} \tag{14}$$

Equation 14 can be simulated as shown 3. The parameters used are $k_1 = 0.124273, k_2 = 0.396235, k_3 = 0.05$, and $IRS0 = 10$ with Initial Value $IRS1(0) = 0, PI3K(0) = 0.0009, pPI3K(0) = 0.0009$, $PIP2(0) = 0.0009, PIP3(0) = 0.0009, PDK1(0) = 0.0009, pPDK1(0) = 0.0009, AKT(0) = 0.0009$ and $pAKT(0) = 0$. IRS1 is a diffuse IRS in skeletal muscle. Phosphorylated IRS binds to specific src-homology-2 domain proteins (SH2), namely phosphatidylinositol-3-kinase (PI3K) and phosphotyrosine phosphatase (SHPTP2), and proteins that are not enzymes but can link IRS-1 with intracellular signals. PI3K will result in the translocation of glucose proteins, glycogen, lipids, and protein synthesis. PI3K works via serine and threonine kinases, namely AKt. Figure 3 shows the simulation results of the IRS1-AKT interaction under normal circumstances.

VI. Conclusion

The results of this study obtained the conclusion that

1) A mathematical model formulated from the interactions of IRS1, PI3K, PIP2, PIP3, PDK1, and AKT in the KEGG pathway based on kinetic reactions in the form

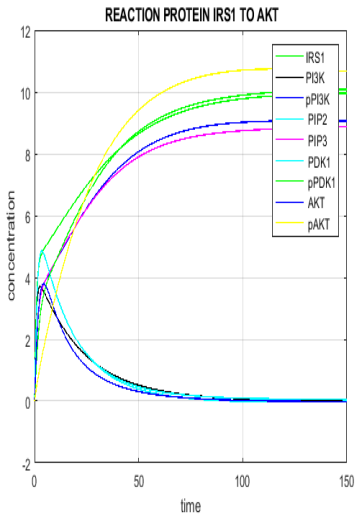


Fig. 3: Numerical Simulation

of ordinary differential equations shown in the equation 11,

2) The fixed point analysis and eigenvalues of this model show stable results, so it is hoped that it may become a useful tool for designing research experiments on GLUT-4 translocation. In addition, it can be developed to design and develop mechanisms for controlling glycemia,
3) The simulation results show that glut4 translocation smoothly runs when there are no obstacles or resistance occurs. as can be seen in the IRS1 graph, which interacts through PI3K, PIP2, PIP3, PDK1, and AKT, showing pAKT phosphorylation that corresponds to IRS1.

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