A Dynamic of PI3K/AKT Pathways in Acute Myeloid Leukemia

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A Dynamic of PI3K/AKT Pathways in Acute Myeloid Leukemia

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Abstract— **Acute Myeloid Leukemia (AML) is a malignant hematopoietic disorder characterized by uncontrolled proliferation of immature myeloid cells. In the AML cases, the phosphoinositide 3-kinases (PI3K)/AKT signaling pathways are frequently activated and strongly contributes to proliferation and survival of these cells. In this paper, a mathematical model of the PI3K/AKT signaling pathways in AML is constructed to study the dynamics of the proteins in these pathways. The model is a 5-dimensional system of the first order ODE that describes the interaction of the proteins in AML. The interactions between those components are assumed to follow biochemical reactions, which is modeled by Hill's equation. From the numerical simulations, there are three potential components target in PI3K/AKT pathways to therapy in the treatment of AML patient.**

Keywords— **PI3K/AKT pathways; AML; ODE system; Hill's Equation; Numerical simulations.**

I. Introduction

Acute Myeloid Leukemia (AML) is a[3]ematological malignancy originating in the bone marrow. It is characterized by the infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system [1], [2]. The AML is the most co[3]mon malignancy of hematological system, illustrated by the accumulation of acquired somatic genetic alterations in hematopoietic progenitor cells. This alteration modifies the normal mechanisms of cells proliferation, self-re[17]al, and differentiation [3], [4]. Based on the validated cytogenetics and molecular abnormalities, The National Comprehensive Cancer Network (NC[23] classifies patients into three risk categories, which are a[22]ter risk, intermediate risk, and poor risk. Patients with the NPM1 mutation in the absence FLT3-[1]D and CEPBA mutations are classified as favorable risk and patients with FLT3-ITD mutated CN-AML and with P53 mutatio[4]s are classified as poor risk [5]. Untreated AML patient leading to fatal infection, bleeding or organ infiltration within 1-year diagnosis, but often within weeks to months [9]. The standard therapeutic strategy in a patient with AML are chemotherapy, irradiation, and hematopoietic stem cell transplantation (HSCT) [2], [5]–[7]. The main objective of those treatments is inducing remission and preventing the relapse [8]. In recent years, despite the potential gain of HSCT, the post-transplantation outcome remains dismal, especially those with high-risk category [7]. Currently, t[20] development of the new therapies has been challenging to further improve the clinical outcome of AML, such as cytotoxic agent, small molecule inhibitor, and targeted therapies [6].

During the last decade, the PI3K/AKT signaling pathway[16] has been studied extensively in human diseases. This [4]athway plays a significant role in a number of cellular functions, including differenti[4]on, apoptosis and cell cycle progression [9], [10]. Aberrant PI3K/Akt [1]tivation is reported in 50-80 % of AML cases [9]. The PI3K/AKT/mTOR network is activated in AML cells through a variety of mechanisms including upstream oncogenes such as FLT3-ITD, KIT,

NRAS, and KRAS, or autocrine/paracrine growth factors such as VEGF, IGF-1. It can also be activated by altered expression of p110d or phosphorylation of PTEN of pathway components, and microenvironmental signals including chemokines and adhesion molecules [11],[12]. The AKT activation is associated with significantly elevated levels of phosphorylation FOXO3a in AML blast cells, suppression its normal function in induction apoptosis and cell cycle regulation [3],[11],[13]. Normally, FOXO3a transcriptionally activates several genes as the target. The FOXO3a binds to the promoter of apoptosis-inducing genes, such as Bim, FasL, and TRAIL, and to the promoter of cell cycle inhibitors, such as p27 and p21. The FOXO3a also activates the autophagy gene Gabarapl1, ATG12, etc [14], [15]. Researchers show that phosphorylation of FOXO3a is an adverse prognostic factor in AML associated with increased proliferation and overall survival [13], [15].

Kadia et all construct a mathematical modeling of cancer, the dynamics of cervical cancer and HPV infection in a cellular level [16]. These models are cellular level modeling, that studies the interactions between cells. For modeling in biopathways, the model of PI3K/AKT/mTOR pathway has been conducted in [17]. The modeling of the interaction protein-protein in cell repair regulation also has been constructed in [18]. However, such models have not specifically studied a specific diseases. In a previous work, Adi et al in [19] has been studied the mathematical model of PI3K/AKT signaling pathway in AKT phosphorylation. The model has not included the FOXO3a protein that have been known as prognostic factor in AML. This model also does not follow the Hill's equation that describes the substrate-enzyme interaction that has multiple ligand binding sites. In this paper, we construct a mathematical model of PI3K/AKT pathway in AML that consider FOXO3a, the most important downstream pathway of AKT. With a deeper understanding of these signaling pathways, the important parameters that play a role in the development of AML will be identified. Furthermore, a strategy can be determined in the treatment of AML disease through targeted therapy. For the model, the Michaelis Menten kinetics and Hill's equation in some components of biochemical reactions are used.

II. Model Development

The mathematical model is constructed by extending the AKT phosphorylation model in [19]. The extension model is defined by adding FOXO3a, which is a potential downstream pathway of AKT in the leukemic progression. Figure 1 shows the simplification of the complex network diagram of PI3K/AKT signaling pathways that drives the AML cells. Our model is focused to discuss the activities of five proteins in PI3K/AKT pathways that have been observed to be significant players in AML cells. We assume that the interactions of the protein follow the Michaelis Menten and Hill's equation. The mutation of the growth regulatory genes such as FLT3-ITD is common in AML cases and resulting in the activation of PI3K. The activation of PI3K then catalyzes the phosphorylation of phosphatidylinositol bisphosphate (PIP2) which can be phosphorylated at the D3 position of the inositol ring on extracellular stimulation, resulting in the formation of phosphatidylinositol trisphosphate (PIP3). In this model, the formation is grouped as a single process, called the PI3K level and denoted by k_0. This formation can be reserved primary by tumor suppressor PTEN that catalyzes PIP3 dephosphorylation into PIP2. The PIP3 dephosphorylation is assumed follows the Hills Equation with coefficient 4. It is according to the fact that PIP3 has four binding sites of PH domain, that is with PTEN, SHIP1, InsP4, and AKT [2].

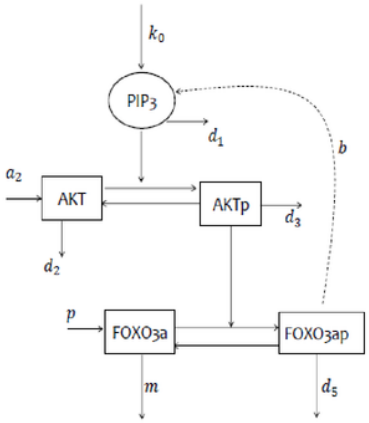


Fig. 1: Simplified diagram of PI3K/AKT/FOXO3a pathway.

Inactive AKT binds PIP3 which enables 3-phosphoinositide-dependent kinase-1 (PDK1) to phosphorylate AKT at Thr308. For full activation, AKT is also phosphorylated at Ser473 by mTORC2. PDK1 and mTORC2 are grouped as a single enzyme catalyzing the phosphorylation (activation) of AKT. Activated AKT is regulated by protein phosphatase 2A (PP2A) and pleckstrin homology domain leucine-rich repeat protein phosphatase (PHLPP). The phosphate PP2A preferentially dephosphorylates AKT on the Thr308 site, while PHLPP specifically dephosphorylates AKT on Ser473 site. In this model, the two phosphatases are grouped into a single enzyme catalyzing the dephosphorylation of AKT. According to the fact that AKT has two binding sites, so this protein activity is assumed follows Hills equation with the coefficient 2. In the next downstream pathways, the activated AKT phosphorylates and inhibits the forkhead transcription factor, FOXO3a. FOXO3a phosphorylation promotes its translocation from the nucleus to the cytoplasm. Phosphorylation by AKTp on Thr 24, Ser 256, and Ser 318 inhibits FOXO3a activities by increasing nuclear export and

this in turn increases proliferation. The FOXO3a in the cytoplasm, denoted by FOXO3ap, is the interaction with the 14-3-3 nuclear export protein. This interaction preventing nuclear reimport by concealing nuclear localization signals and promotes the FOXO3ap degradation by the proteasome [13], [14]. In this model, the growth of FOXO3a is assumed follows the logistic model as well as the translocation and relocation of the cytoplasm and nucleus by phosphorylation and dephosphorylation. According to the fact that FOXO3a has three binding sites, so the Hills equation with coefficient 3 is used. The FOXO3ap enhances the expression and phosphorylation of RTKs that could in turn activate and sustain this pathways [4]. Thus, FOXO3a indirectly interacts and enhances PIP3 activity resulting in a positive feedback loop. The reactivation or dephosphorylation FOXO3a, which is mediated by PP2A, promotes the relocation to the nucleus. Based on the diagram in Figure 1, a mathematical model is defined as in (1)-(5):

$$\frac{dx_1}{dt} = k_0 + bx_5 - \frac{k_1 x_1^4}{K_1^4 + x_1^4} - d_1 x_1 \quad (1)$$

$$\frac{dx_2}{dt} = a_2 - \frac{k_2 x_1 x_2^2}{K_2^2 + x_2^2} + \frac{k_3 x_3^2}{K_3^2 + x_3^2} - d_2 x_2 \quad (2)$$

$$\frac{dx_3}{dt} = \frac{k_2 x_1 x_2^2}{K_2^2 + x_2^2} - \frac{k_3 x_3^2}{K_3^2 + x_3^2} - d_3 x_3 \quad (3)$$

$$\frac{dx_4}{dt} = x_4(p - mx_4) - \frac{k_4 x_3 x_4^3}{K_4^3 + x_4^3} + \frac{k_5 x_5^3}{K_5^3 + x_5^3} \quad (4)$$

$$\frac{dx_5}{dt} = \frac{k_4 x_3 x_4^3}{K_4^3 + x_4^3} - \frac{k_5 x_5^3}{K_5^3 + x_5^3} - d_5 x_5 \quad (5)$$

where the variables in the system of ODEs are defined in Table I.

The numerical simulation will be run in two different situations based on the existence of the FOXO3a translocation from the nucleus to the cytoplasm as a Normal cell or AML cell to understand the dynamics of AKT/FOXO pathways. In Normal cell, the activities of AKTp does not induce the translocation of FOXO3a from the nucleus to the cytoplasm. In the AML cell, aberrant PI3K/AKT signaling pathway results in phosphorylation of FOXO3a leading to cytoplasmic mislocalization and consequent degradation of this proteins [15].

TABLE I
VARIABLE DESCRIPTION

Variable	Description
x_1	Concentration of PIP3
x_2	Concentration of AKT
x_3	Concentration of AKTp
x_4	Concentration of FOXO3a
x_5	Concentration of FOXO3ap

The situation of Normal and AML Cells are distinguished based on differences in some parameter values. First, the constant rate of PIP3 dephosphorylation in AML cells is lower than normal cells as a result of various abnormal mechanisms in the PI3K signal upstream pathway, for example, PTEN deletion [10]. Secondly, the value of dephosphorylation rate of AKT in AML cells is smaller than the one in the normal cells. This is due the fact that in AML, there is a decresion level of PP2A, a protein phosphatase that plays a role in the dephosphorylation of AKTp [10]. Furthermore, in normal cells, it is assumed that AKTp does not induce the translocation of FOXO3a from the nucleus to the cytoplasm so that the parameter value of phosphorylation of FOXO3a is tending to zero. The last difference is that the rate of dephosphorylation of FOXO3ap in AML is smaller than in normal cells. This is due to the degradation of FOXO3ap in AML cells in the cytoplasm [14], [15].

III. PROTEIN DYNAMICS

In this section, the numerical results of System (1) – (5) is simulated by employed the Runge-Kutta method order 4 to provide the integration in some cases depend on the parameter values. The parameter values used in the system are based on the clinical data that can be obtained in some medical literature as in Table II and Table III.

TABLE II
INITIAL CONCENTRATION OF THE MOLECULAR COMPONENT

Protein	Concentration (μM)	References
PI3K	0.01 – 0.1	[19]
PIP3	0.7 – 0.8	[19]
AKT	0.01 – 1.2	[20]
PP2A	0.004 – 0.15	[19]
FOXO3a	0.01 – 1.4	Assumed

TABLE IIIPARAMETER VALUES AND KINETIC RATES BEING USED

Parameter	Description	Unit	Value	References
k_0	PI3K level	μM	0.01 – 0.1	[19]
b	Increase activation PIP3 by FOXO3ap	min^{-1}	0.0083	*
k_1	Constant rate of PIP3 dephosphorylation	$\mu M min^{-1}$	0.0006 – 0.21	[19]
d_1	PIP3 degradation	min^{-1}	0.001 – 0.01	[20]
a_2	AKT production rate	min^{-1}	0.036 – 0.108	[19], [20]
k_2	Constant rate of AKT phosphorylation	$\mu M min^{-1}$	1 – 20	[19]
k_3	Constant rates of AKTp dephosphorylation by PP2A	$\mu M min^{-1}$	0.36 – 13.5	[19], [20]
d_2	AKT degradation rate	min^{-1}	0.063 – 0.08	[19]
d_3	AKTp degradation rate	min^{-1}	0.0008 – 0.1	[19], [20]
p	FOXO3a production rate	$\mu M min^{-1}$	0.002 – 0.5	*
m	FOXO3a degradation rate	$\mu M min^{-1}$	0.004 – 0.28	*
k_4	Constant rate of FOXO3a phosphorylation	$\mu M min^{-1}$	0 – 0.33	*
k_5	Constant rate of FOXO3a dephosphorylation	$\mu M min^{-1}$	0.000167 – 0.06	*
d_5	Constant rate of FOXO3ap phosphorylation	$\mu M min^{-1}$	0.033 – 0.125	*
K_1	Michaelis constant of PIP3 dephosphorylation	μM	0.01 – 0.1	[18]
K_2	Michaelis constant of AKT phosphorylation	μM	0.1	[18]
K_3	Michaelis constant of AKTp dephosphorylation	μM	0.08 – 0.12	[20]
K_4	Michaelis constant of FOXO3a phosphorylation	μM	0.1	*
K_5	Michaelis constant of FOXO3ap dephosphorylation	μM	0.1	*

*Parameters value are assumed to be the same as others transcription factor such as MDM2 in [20]

Table II and Table III show the kinetic rates and the initial concentration levels of the various proteins in PI3K and AKT pathways. For AML cells the parameter values are $k_0 = 0.01; b = 0.0083;\ k_1 = 0.005; K_1 = 0.2;\ a_2 = 0.09;\ k_2 = 1; d_1 = 0.0083;\ K_2 = 0.1;\ k_3 = 0.36;\ K_3 = 0.2;\ d_2 = 0.08;\ d_3 = 0.1; p = 0.3; m = 0.25; k_4 = 0.3; K_4 = 0.1;\ k_5 = 0.1;\ K_5 = 0.1$, and $d_5 = 0.1$. For normal cells, similar parameter values are used, except $k_1 = 0.017; k_3 = 0.67;\ k_4 = 0.001$, dan $k_5 = 0.033$.

Figure 2 left, shows that existence of the FOXO3a phosphorylation plays a role in the increasing of FOXO3ap concentration. The presence of inactive FOXO3a in the cytoplasm, FOXO3ap in our model, means that the apoptosis mechanism is not working properly so that there is no cell death. The FOXO3ap also enhances proliferation cell, lead accumulation of abnormal cell because they don't stop growing when they should. The lifespan of the white blood cell in a myeloid lineage is about 3 - 12 days [21]. Therefore, they should be apoptosis between 3 - 12 day characterized by low-level FOXO3ap after that time, which does not occur in the AML cell. It can be seen that FOXO3ap reaches a peak in 100 minutes then decreases and oscillates to a certain level (see Figure 3 left).

The increasing concentration of the FOXO3ap would affect the decreasing concentration of FOXO3a. It is illustrated in Figure 2 left, the FOXO3a concentration initially increases and peaks within 38 minutes. Moreover, the FOXO3a concentration immediately decreases and oscillates in low concentration with small amplitude, see Figure 3 right. The oscillation indicates that cell cycle and proliferation continue to occur and there is no maturation of these cells. The behavior of FOXO3a

can be used to identify the existence of AML disease. Under the normal condition, the concentration of FOXO3a transcription factor in the nucleus much higher than those in the cytoplasm, FOXO3ap, see Figure 2 right.

The concentration of FOXO3a in the normal cell reaches the maximal level in short time. The increasing of FOXO3a is followed by the slightly increasing of FOXO3ap in much lower concentration. It indicates that FOXO3a is not translocated to the cytoplasm. It shows that FOXO3a promotes apoptosis and cell cycle regulation as well. Thus the balancing of cell cycle regulation can be well preserved. We note that if the constant rate of FOXO3a phosphorylation set to be zero, the concentration of FOXO3ap will be zero (not shown in the figure). In addition, from the simulation, it is known that FOXO3a and FOXO3ap in the normal cell do not oscillate as in AML cell, see Figure 4. It indicates that FOXO3a works properly in cell cycle regulation and apoptosis.

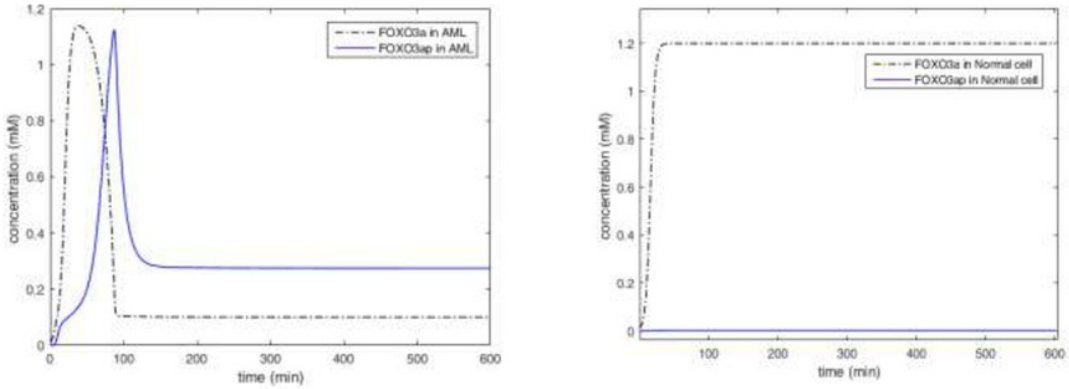


Fig. 2: Dynamic of FOXO3a and FOXO3ap concentration in AML cell (left) and in the normal cell (right)

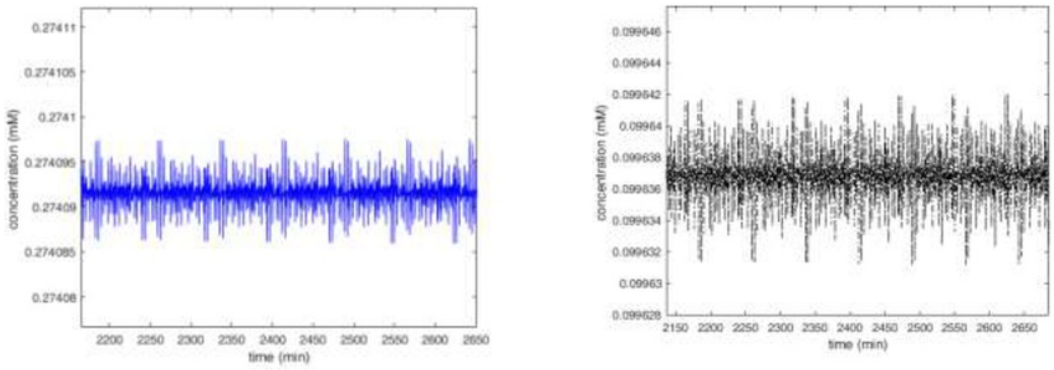
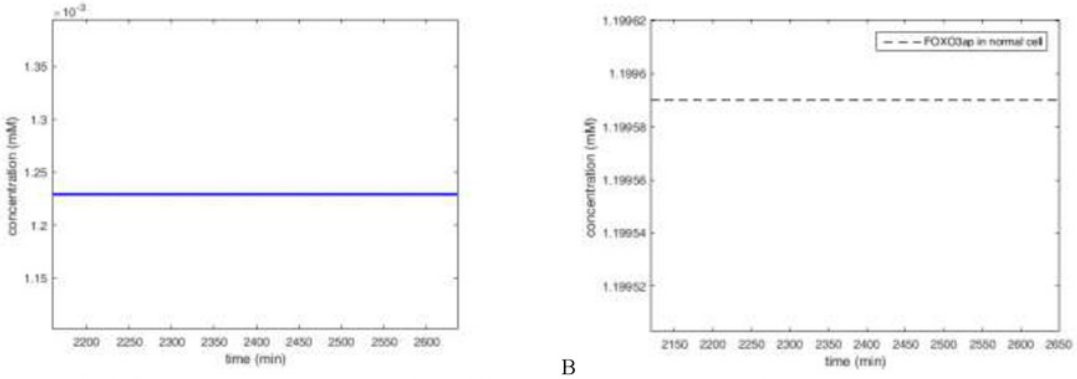


Fig. 3: The FOXO3ap (left) and FOXO3a (right) concentration in AML cell. FOXO3ap is decreased and then oscillate around 0.274 micromolar, while FOXO3a oscillate around 0.0996 micromolar

Next, we will see the effect of phosphorylation of FOXO3a on the other proteins, such as PIP3, AKT, and AKTp. Figure 5 and Figure 6 show the comparison of PIP3, AKT, and AKTp concentration in the normal cell and AML cell. It can be seen that in the longtime behavior, the concentration of PIP3 and AKTp in the AML cells are higher than in the normal cells, while AKT in the AML cells is lower than in the normal cells. In the AML cells, the concentration of PIP3 is gradually increasing and oscillates at a certain level as a respond of FOXO3a phosphorylation. The PIP3 concentration reaches the maximum level and remains at that level for a long time and oscillation with small amplitude, see Figure 5 top-right. Figure 5 bottom-right illustrates the concentration of PIP3 in the normal cells are at a low level without oscillation.

Figure 6 shows the differences between AKT and AKTp behavior in the normal cell and AKT and AKTp in the AML cell, respectively. Under normal conditions, when the levels of PIP3 decrease, the AKT activity is attenuated by dephosphorylation by phosphatase.



B

Fig. 4: The FOXO3ap (left) and FOXO3a (right) concentration in the normal cell.

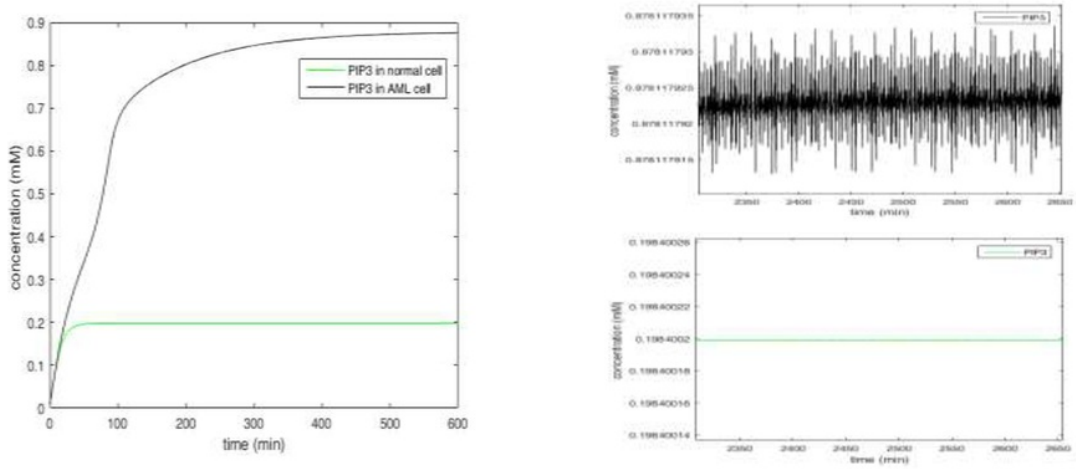


Fig. 5: Dynamics of PIP3 in the normal cell and AML cell

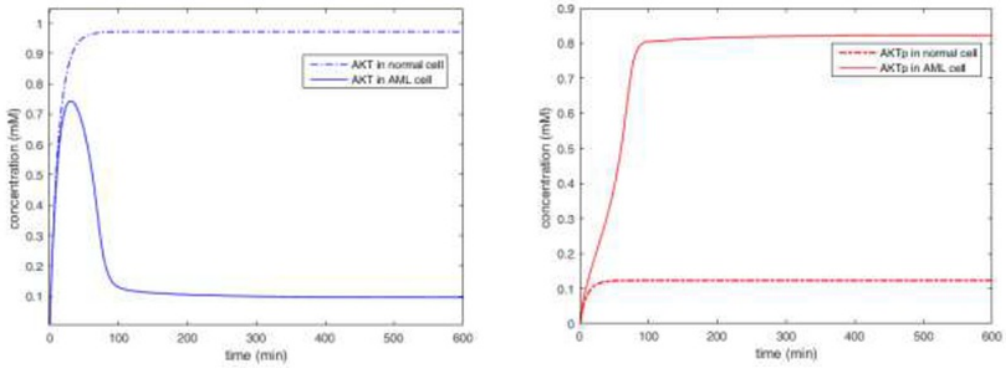


Fig. 6: Dynamics of AKT and AKTp normal and AML cell

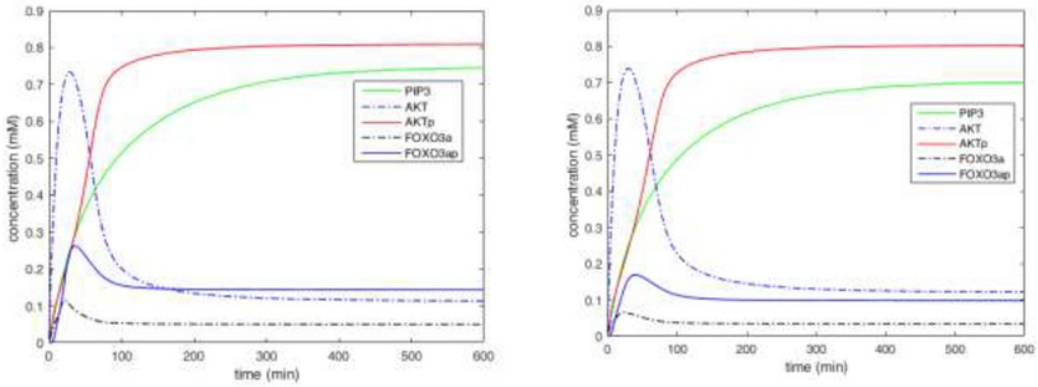


Fig. 7: Dynamics of PIP3, AKT, AKTp, FOXO3a, and FOXO3ap in the AML cell with increasing rate of FOXO3a phosphorylation from 1.0 to 2.0.

Figure 6 left shows the AKT in AML cell subsequently sustained at lower concentrations than in normal cell. In the AML cell, as the result of FOXO3a translocation from the nucleus to the cytoplasm, the concentration level of AKT decrease quickly, while AKTp immediately increases and remain at a certain level. Figure 6 right shows that the AKTp in AML cell subsequently sustained at a higher concentration than in the normal cell. Figure 7 is tested the model by increasing the constant rate of FOXO3a phosphorylation from 1 to 2 while keeping all other parameter values the same as in Figure 2. The effect of this increase is that the greater the rate of FOXO3a phosphorylation the concentrations of FOXO3a and FOXO3ap are lower. This condition is due to the greater value of FOXO3a phosphorylation rate will accelerate the translocation of FOXO3a from the nucleus to the cytoplasm and lead to proteasome degradation. The increase of FOXO3a phosphorylation rate does not extremely affect the dynamics of AKT and AKTp, while the PIP3 concentration slightly lower.

IV. Remarks and Discussions

As shown in the numerical simulation, the key components in driven AML cell are high levels of PIP3, AKTp, and FOXO3ap, ie inactive FOXO3a in the cytoplasm. These results suggest that these three components are potential targets for AML therapy, of course with due regard to the other proteins that mediated protein interactions. For example, the parameter values associated with FOXO3a are taken from proteins that have a similar function with FOXO3a, such as MDM2. It could be very useful for determining reasonable ranges for the rate of various biochemical reactions involved. As more medical fact is known about the PI3K/AKT signaling pathways in AML.

The model may be needed to be modified. It is possible that other equations representing rates of change of other proteins or other signaling pathways that integrated with PI3K/AKT pathways may have to be added to the system. Mathematical analysis of the model may also be useful in understanding protein interactions in this pathway. On the future work, we will analyze mathematically the dynamic of the system and study the bifurcation related to the variation of its parameter values.

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