# RIWAYAT KORESPONDENSI ARTIKEL DI JURNAL OF APPLIED MATHEMATICS (JAM) (PENERBIT HINDAWI) 

1. Artikel di submid melalui sistem OJS pada 28 Juni 2018

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Dear Dr.Adi

The Fesearch Acticle Bled "A Dynamic of P13K_AKT Pathways in Acute Myeloid Leukemia ;'by Yudi Adt Fajar Ads-Kusumo, Lina Aryati and Mardiah Harciantj has been received and assigned the number 2983138

All suthors will recelve a copy of al the correapondences regarting this manuscript
Thark you for submitting your work to Journal of Appliod Mathamatics

Best regards
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2. Pada 16 Juli 2018 Editor meminta mnyertakan ID ORCID
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Dear Dr. Ad
This is regording your manuscipt illed "A Dynemic of PI3KIAKT Pathwsys in Acule Myeloid Leukertian "in Joumal of Appled Moshematics. Plesse register an ID with Open Researcher and Contributor ID (ORCID) and lirk it to your Manuscript Tracking System (MTS) account, as we need to incinde authors' ORCID. IDs in the articie metadata that we subrilt to various indexing -services

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3. Hasil review dengan kategori revisi Mayor diperoleh pada 1 Oktober 2018

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Dear Dr Ads,
The revised version of Research Article 29e313B tifod 'A Dinamic Model of Pl3W/AKT Pathways in Acuta Myeloid Leukerria * by YodiAcli, Fajar Adi-Kusumo Lina Aryati a Mardiah Hardiartil has been recelved. The editar assigned to hande the review process of your manuscript wili infarm you as soon as a decision is reached

Thank you for submiting your work to Jeurnal of Applied Mathomatics
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Maryam Hazem
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Dear Editor:
Thank you for the opportunity to revise our manuscript, A Dynamics of PI3K/AKT Pathways in Acute Myeloid Leukemia. We thank the review panel for their critical but insightful comments. Addressing those comments resulted in an improved paper. We thank all reviewers for their kind words and positive comments on our paper.

In the table below, we document how we have addressed the comments from the three reviewers. We do hope that you will find the revisions meet the quality standard required by the journal.

Thank you for your consideration.
Sincerely,
Yudi Ari Adi.

## REVIEW \#1

| No. | The reviewer's comments | Our responses |
| :---: | :---: | :---: |
| 1 | The title looks incomplete and/or unclear. It should rather read like Dynamics of PI3K/AKT pathways in Acute Myeloid Leukemia or A Dynamic Model of PI3K/AKT pathways in Acute Myeloid Leukemia | We have changed the title to A Dynamic Model of PI3K/AKT Pathways in Acute Myeloid Leukemia |
| 2 | The grammar and typography in the article need to be improved. | We have improved the Grammar and typography. <br> In page 1 , last line, we have changed <br> "Untreated AML patient leading to fatal infection, bleeding or organ infiltration within 1-year diagnosis, ..." to <br> "Untreated AML patient results in fatal infection, bleeding or organ infiltration within 1-year of diagnosis, ..." <br> In page 2, second paragraph, line 11, we have changed "suppression" to "supressing" <br> In page 2, third paragraph, line 5 , we have changed "... <br> there no..." to "...there are no known..." <br> In page 3 , first paragraph, line 2 , we have changed "... <br> extension..." to "...extended..." <br> In page 3, first paragraph, line 14 , we have changed <br> "...reserved..." to "...reversed..." <br> In page 4, we have not changed "...coefficient 3..." to "...a cubic of power...", because <br> for the Hill's Equation $\frac{X^{n}}{K^{n}+X^{n}}$, the exponent $n$, called the Hill coeficient, so we use the term coefficient instead of a power |


| 3 | There exists some dimensional inconsistencies in the model. For instance $k 0$ is said to have units $\mu M$ <br> which is inconsistent with the expected dimension ( $\mu \mathrm{M} / \mathrm{min}$ ) of $\frac{d x_{1}}{d t}$. Considering the dimensions of $k 4$ and $K 4$, the term $\frac{k_{3} x_{3}^{2}}{K_{3}^{2}+x_{3}^{2}}$ will have dimension of $(\mu M)^{2} \mathrm{~min}^{-1}$, which is inconsistent with that of $\frac{d x_{4}}{d t}$. If the dimensions of the parameters are correct, then the model needs to be reformulated. Authors should consider the definitions and/or units given to the parameters in $T a$ ble 2. | According to the references, some dimensions of the parameters presented in table 2 are incorrect. Therefore, we make corrections as follows |
| :---: | :---: | :---: |
|  |  | We also correct description $d_{5}$, " Constant rate of FOXO3a dephosphorylation" to "FOXO3ap degradation rate". The complete of Tabel 2 is presented in the paper. |
| 4 | Authors should consider doing some basic mathematical analysis of the model, like biological and mathematical and/or possessedness of the model before the simulation. This is agreed on by authors in the conclusions section. | The model is not sufficiently accessible to allow us to conduct the mathematical analysis. It is due to the complexity of the model. The complexity comes from the use of the Hill's equation with coefficients according to the number of protein binding sites. For example, PIP3 has four binding sites so that the reaction will follow the Hill's equation with a coefficient four. We obtained a $26^{\text {th }}$ degree polynomial equation when trying to analyze the model, so we couldn't find the solution. Furthermore, we can't analyze the positivity and stability of the model. Mathematical analysis can be obtained if we reduce or simplify some of the interaction terms, for example by reducing the Hill's coefficient or if the model does not follow the Hill's equation. <br> In this paper, we want to show the dynamics of the protein with a model which the biochemical reaction follows the Hill's equation. Therefore, in this paper, we are only limited to providing numerical simulations and no theoretical analysis. <br> We added a statement at the begining of section Result and Discussions in page 5 as follows. <br> "The model equations (1) - (5) is not sufficiently accessible to allow us to conduct the mathematical analysis. Therefore, in this paper, we only provide numerical simulations." |

## REVIEW \#2

| No. | The reviewer's comments | Our responses |
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| 1 | In page 2 , third paragraph, line 10 , change "Adi et al in [1] has been studied ....." to "Adi et al in [1] studied ......" <br> In page 2, third paragraph, line 11, change "The model has not included .." to "The model did not include .." <br> In page 3, line 5, change "Our model is focused to discuss ....." to "Our model is focused on discussing ....." | In page 2, third paragraph, line 10, We have changed "Adi et al in [1] has been studied ....." to "Adi et al in [1] studied ......" <br> In page 2, third paragraph, line 11, We have changed "The model has not included .." to "The model did not include .." <br> In page 3, line 5, We have changed "Our model is focused to discuss ....." to "Our model is focused on discussing ....." |

## REVIEW \#3

| No. | The reviewer's comments | Our responses |
| :--- | :--- | :--- |
| 1 | $\begin{array}{l}\text { Introduction and model formulation } \\ \text { parts are satisfactory }\end{array}$ | Thank you |
| 2 | $\begin{array}{l}\text { Section of the analytical solution of } \\ \text { the model is missing; the following } \\ \text { should be included } \\ \text { i) Boundedness of the model } \\ \text { ii) Positivity } \\ \text { iii) Stability analysis of the model } \\ \text { Note: however in the conclusion } \\ \text { part, the authors recommended } \\ \text { these aspects will be captured in } \\ \text { future work. }\end{array}$ | $\begin{array}{l}\text { The model is not sufficiently accessible to allow us to } \\ \text { conduct the mathematical analysis. It is due to the } \\ \text { complexity of the model. The complexity comes from } \\ \text { the use of the Hill's equation with coefficients } \\ \text { according to the number of protein binding sites. For } \\ \text { example, PIP3 has four binding sites so that the } \\ \text { reaction will follow the Hill's equation with a } \\ \text { coefficient four. We obtained a 26t degree polynomial } \\ \text { equation when trying to analyze the model, so we } \\ \text { couldn't find the solution. Furthermore, we can't } \\ \text { analyze the positivity and stability of the model. } \\ \text { Mathematical analysis can be obtained if we reduce or } \\ \text { simplify some of the interaction terms, for example by }\end{array}$ |
| reducing the Hill's coefficient or if the model does not |  |  |
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| In this paper, we want to show the dynamics of the |  |  |
| protein with a model which the biochemical reaction |  |  |
| follows the Hill's equation. Therefore, in this paper, we |  |  |
| are only limited to providing numerical simulations. |  |  |$\}$


|  | as per Table 2. For example, K1, <br> K3 and K5, the author should <br> explain why? | between 0.08-0.4. The range of parameter value of $k_{5}$ <br> should be written 0.000297 - 2.92. The value of the <br> $K_{5}$ parameter is obtained from the assumption as given <br> in the description at the bottom of the table and is <br> appropriate. This range of parameter values is taken <br> from Adi-Kusumo and Wiraya [2], Karabekmez [10] <br> and from Wee and Aguda [21]. We have added Wee <br> and Aguda in the references [21]. |
| :--- | :--- | :--- |
| 4 | The author refers to the wrong <br> figure that Figure 3a instead of <br> Figure 2a in page 6 "It can be seen <br> that FOXO3ap reaches a peak in <br> 100 minutes then decreases and <br> oscillates to a certain level (see <br> Figure 3a)." | We have reffered to the right figure. |
| 5 | The caption of figure two is placed <br> in the wrong place. The caption <br> should be below the figure | We have placed the caption in the right place. |
| 6 | In page 7, the figure which justifies <br> "We note that if the constant ate of <br> FOXO3a phosphorylation set to be <br> zero, the concentration of <br> FOXO3ap will be zero (not shown <br> in the figure)." Should be included | We have added Figure 2c to justify the statement |
| 7 | There are no explanations for the <br> figure 3, the explanation should be <br> given | We have rewritten this part to provide explanation in <br> first paragraph, page 8. |

5. Permintaan revisi minor pada 29 Oktober 2018 dan hasil revisi dikirim pada 2 November 2018
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Dear Dr Ads
The revised version of Research Atticle 2983138 stied 'A Dynamic Model of PI3KIAKT Pathways in Accise Myeloid Leukamia" by Yudi Adi. Fajar Adi-Kuisumo, Lina Aryati a Mardiah Handianti has been rocolved. The odtor assignod to handle the reviow proceas of your manuscript will inform you as soon as a dechion is reached

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Best regarda.
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Tue, Nov 6, 2018, 11:16 AM
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Dear Dr.Ad.

This is to confinm the recsipt of the slectronic files of Ressarch Article 2983138 stifed "A Dynamic Model of PI3KIAKT Pasnways in Acute Myeloid Leulcemia "by Yud Fajar Ad-Kusumo, Lina Aryati and Mardiah Handlans. We will check all the uploaded fles and contact you z anything else is needed.

Thank you for your cooperation.
Best regards.
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Maryam Hazem
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7. Artikel dinyatakan diterima pada $\mathbf{5}$ November 2018 dan permintaan biaya untuk open akses jurnal

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Dear Dr Adi
The review process of Research Article 2963138 thied 'A Dynarnic Model of P1KKJAKT Pathways in Acute Myeloid Leukenia " by Yudi Ads. Fajar Aui Kunums, Lina Acyati and Mardiah Hardiant submimed to Journal of Appled Mathematics has been completed I ain pleased to infoma you that your manuscript has nolim been accepted for publication in the joumal.

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9. Pemberitahuan artikel dipublikasikan pada 14 November 2018

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Dear Dr, Adi,
I am pleased to let you know that your erticle has been published in lis fral form in "Joumat of Applied Mathematics.
Yudi Art Adl 'A Dynamic Madel of PLFKAKT Pathways in Acute Myoloid Leukomia," Joumal of Applied Mathomatics, vol. 2018, Article iD 2983130. 9 pagss, 2018

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