Applied Mathematics E-Notes, 22(2022), 362-370 ©
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ISSN 1607-2510

An Algebraic Mathematical Model For Non-Competitive Enzyme Inhibitors With Slow And Fast Subsystems*

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Received 12 July 2021

Abstract

In biological systems, mathematical modeling plays an important role for the characterization of the binding behavior of the biochemical enzyme inhibitors to the target molecule. Dynamic mathematical models of biological investigation efficiently serve with reasonable and optimal outcomes. The role of such models usually need some techniques to attain the reduction in model parameters. This study presents model techniques that are very useful for model reduction and split the model equations into slow and fast subsystems. They are Quasi-Equilibrium Approximation (QEA) and Quasi Steady-State Approximation (QSSA). For identifying analytical approximate solutions in non-competitive enzyme inhibitors , these techniques play a crucial role for simplifying the model equations and suggest the appropriate reduction approaches. This study was primarily used to understand the slow and fast subsystems in order to reduce the number of variables and parameters. Moreover, the analytical solution for biochemical inhibitor system has been exhaustively discussed which avoid linearization and physically unrealistic assumptions.

1 Introduction

Enzymes are catalysts mostly proteins and their major role in biological systems is to increase the rate of reaction without itself being consumed by the process. Each enzyme has high specificity for at least one reaction, and subsequently accelerate the reaction by millions of times. Substances that reduce the activity of an enzyme-catalysed reaction are known as inhibitors. Basically, inhibitors are low molecular weight compounds form an enzyme-inhibitor complex when bind with the enzyme, thereby reducing or completely inhibiting the catalytic activity of the enzyme and hence reducing the rate of reaction [4]. Despite the fact that catalysts are significant forever, however high enzyme activity can also give rise to some abnormal conditions and may lead to certain diseases. Hence, overactive enzymes are attractive targets for outgrowth of inhibitor molecules to relieve disease conditions. Manipulation of enzyme catalysis with inhibitors is hypercritical for prevention of infectious diseases, treatment of hypertension, control of inflammatory response and more. Besides inhibitors are acting as therapeutic agents, these also play crucial roles in biological and clinical research [2, 10]. The entry of substrate to the particular active site of enzyme can be choked by binding of an inhibitor molecule to that site. Alternatively, sometimes inhibitors not only bind to the active site of enzyme but can also bind to a site other than the active site and develop a conformational change that stops the entry of substrate to the active site. Inhibitors take measures directly or indirectly affecting the catalytic properties of the active site. They are involved with catalytic and enzymatic reactions. Moreover, this inhibition can be reversible or irreversible. Reversible enzyme inhibition can be competitive, uncompetitive or non-competitive, each affecting K_m (Michaeli's constant) and V_{max} (maximum velocity) in a specific fashion [20]. In the current study, a non-competitive inhibition will be discussed using basic mathematical tools.

Non-competitive inhibition is a common type of reversible inhibition. This inhibition is also called mixed inhibition. The inhibitor binds to the enzyme at a site other than the active site, either to the free enzyme or ES complex, see Figure 1. A mathematical model has been established to analyze enzymatic reactions of

*Mathematics Subject Classifications: 92BXX; 92CXX; 92B10; 92C40.
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cellular metabolism that have a special interest with biotechnology [9]. Fang, X. established a mathematical model of enzymatic inhibition that is used to simulate two separate inhibition mechanisms for the growth of M.Tuberculosis cells in an *in-vitro* environment [6]. The kinetic dynamics in heterogeneous enzymatic hydrolysis of Cellulose were studied [8] and kinetic equations for reversible enzyme reactions with some analytical approximate solutions were also established [14]. An algebraic model for the kinetics of covalent enzyme inhibition at low substrate concentration has been formulated in this direction as well [18].

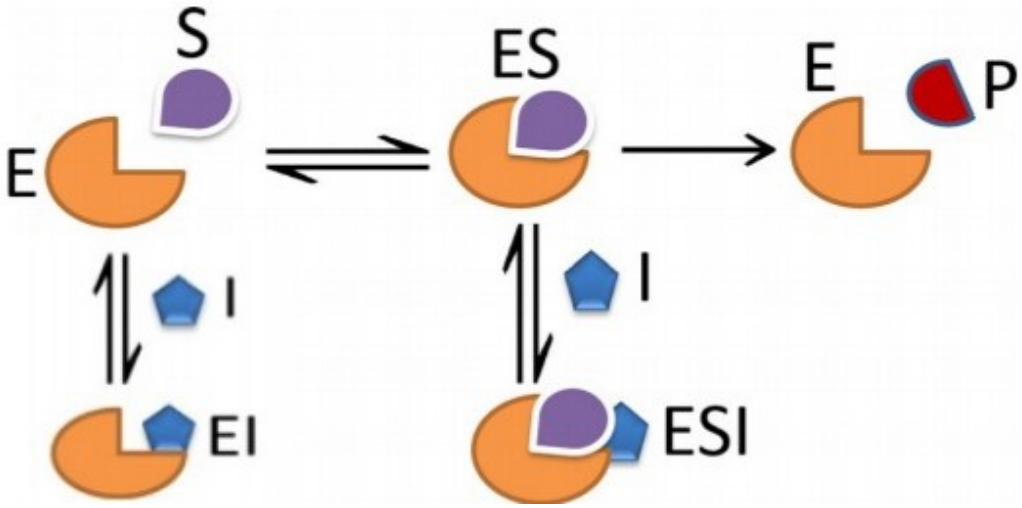

Figure 1: Non-Competitive Inhibition [1].

Model reduction is a strategy for diminishing the computational intricacy of mathematical models in numerical simulations. The model reduction process approximates the original model with a model of reduced complexity, i.e, model reduction is a change on the original system to another system in which the new model contains a fewer variables than the original one. The process of model reduction is applicable in case the saturation is cumbersome and the results can not be established analytically. However, reduction only leads to an approximate version of the original model.

Solving the complex enzymatic reactions is a cumbersome task and hence some well known methods have been applied in order to describe their dynamics. Assorting the model equations of enzymatic reactions into the slow and fast subsystems play an important role to describing the model dynamics for biological systems [1, 11]. In the current study, the major problem is to identify the slow and fast reactions for non-competitive enzyme inhibitor system and the equations have been divided into slow and fast subsystems by two well-known methods ; quasi-equilibrium approximation (QEA) and quasi steady-state approximation (QSSA). These two approaches can be applied in biological systems, in order to reduce variables and parameters for such systems [22, 23]. These techniques play a major role in model reduction. Initially the quasi-steady-state approach was first suggested by Briggs and Haldane (1925) [12] and this approach will became a good technique of model reductions and model analysis for biochemical reactions. Quasi Steady State Approximation provides a great step in systems biology. The suggested technique can be applicable for non linear models to assort such systems into slow and fast subsystems. Moreover, QSSA is also used to identify analytical approximate solutions and is also used to report the mechanisms of miRNA signaling and genetic pathways [17]. There are some appropriated results that give a significant step forwards to comprehend the model reduction methods and their applications in biochemical reaction networks and system biology. The most important and exciting computational methods and tools available for systems biology were developed and these developing accessibility of large amounts of data will permit models to be tested very finely [3]. There is one more important method known as RCW (Rahmanzadeh-Cah-White) that is used for solving the Classical Blasius Equation and is governing equation of boundary layer problem. In this method (RCW),

the solution of the problem is considered as the sum of the Fourier series and a polynomial of degree 4 [21]. Moreover, a mathematical model has been established which gives an approximate analytical solution using homotopy perturbation method [24]. In this study, we have applied these methods on non-competitive enzyme inhibition. At the end, the suggested approaches are very efficient to reduce the number of variables and also to find analytical approximate solutions. There are few more important techniques that have been used for model reduction in systems biology [19, 15, 5].

2 Materials and Methods

Let E, S and I respectively denote the enzyme, substrate and inhibitor. Also, the complex intermediate species are EI, ES and ESI with respect to the rate constants k_i; $(i = 1, 2, 3, ..., 7)$. In order to establish efficient and better method to understand the dynamics of non-competitive inhibition, a mathematical approach has been adapted to study the behavior over fast and slow subsystems. Consider a system of n reversible enzymatic reactions given below [11]:

$$\sum_{j=1}^{m} a_{ij}x_j \underset{k_{i+}}{\overset{k_{i-}}{\rightleftharpoons}} \sum_{j=1}^{m} b_{ij}x_j, \quad i = 1, 2, ..., n,$$

where x_j signify the concentrations of chemical components (metabolites), n their numbers, a_{ij} and b_{ij} are stoichiometric coefficients, k_i^+ and k_i^- are reaction constants and m the number of reactions in the system. The mathematical description of the dynamics of above enzymatic reactions is performed by means of a system of differential equations :

$$\frac{dx}{dt} = \sum_{j=1}^{r} c_{ij}v_j,$$

where $x \in R^m$, v_j represents the activities of the enzymes participating in the metabolic pathway analysed, t the time. The coefficients $c_{ij} = b_{ij} - a_{ij}$ are the elements of the stoichiometric matrix. The stoichiometric matrix contains an information on the structural network, i.e; "topology" of the enzyme system [11].

In order to define the method, we simply divide a set of variables $x(t)$ into two sets, slow species set $x_s(t)$ and fast species set $x_f(t)$. Further the differential equations can be divided into two subsystems:

Slow subsystem:

$$\frac{dx_s}{dt} = g_s(x_s(t), x_f(t), k).$$

Fast subsystem:

$$\frac{dx_f}{dt} = \frac{1}{\epsilon}g_f(g_s(t), g_f(t), k),$$

where $x \in R^m$, $x_s \in R^{m_1}$, $x_f \in R^{m_2}$, $k \in R^n$ and $m = m_1 + m_2$.

Furthermore, a slow manifold of the system can also be calculated from the algebraic equations,

$$g_f(x_s(t), x_f(t)) = 0$$

when

$$\epsilon \to 0.$$

As long as the QEA is a model reduction method and minimizes the number of parameters and variables, however, this method gives idea that fast reactions accomplish equilibrium immediately as compared to slow reactions.

Khoshnow [16] described a system of differential equations of chemical reaction as:

$$\frac{dx}{dt} = \sum_{s,slow} R_s(x, k)\gamma_s + \frac{1}{\epsilon}\sum_{f,fast} R_f(x, k, t)\gamma_f, \tag{1}$$

where ϵ is a small parameter $(0 < \epsilon \ll 1)$; γ_s and γ_f are stoichiometric vectors ; R_s and R_f are reaction rates. Therefore, the fast subsystem takes the following form:

$$\frac{dx}{dt} = \frac{1}{\epsilon} \sum_{f,fast} R_f(x,k,t)\gamma_f.$$

Moreover, quasi-equilibrium manifold can also be calculated by using the following algebraic equations:

$$\sum_{f,fast} R_f(x,k,t)\gamma_f. = 0, \tag{2}$$

$$h^i(x) = b_i, \text{ for } 1 \le i \le k+p. \tag{3}$$

Equation (3) is called linear conservation laws [1, 15]. More information about proposed techniques for chemical and biological models can be explored from these references [1, 7]. The Kinetic reactions of non-competitive enzyme inhibition are given by [20]:

$$\begin{cases} E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_3}{\longmapsto} E + P, \\ E + I \underset{k_5}{\overset{k_4}{\rightleftharpoons}} EI, \\ ES + I \underset{k_7}{\overset{k_6}{\rightleftharpoons}} ESI. \end{cases} \tag{4}$$

The concentration of the reactants in equation (4) are denoted by

$$E = [E],\ S = [S],\ I = [I],\ P = [P],\ C_1 = [ES],\ C_2 = [EI],\ C_3 = [ESI].$$

The model differential equations based on the law of mass action are given by

$$\frac{dS}{dt} = -k_1ES + k_2C_1, \tag{5}$$

$$\frac{dE}{dt} = -k_1ES + k_2C_1 + k_3C_1 - k_4EI + k_5C_2, \tag{6}$$

$$\frac{dC_1}{dt} = k_1ES - k_2C_1 - k_3C_1 - k_6C_1I + k_7C_3, \tag{7}$$

$$\frac{dC_2}{dt} = k_4EI - k_5C_2, \tag{8}$$

$$\frac{dC_3}{dt} = k_6C_1I - k_7C_3, \tag{9}$$

$$\frac{dI}{dt} = -k_4EI + k_5C_2 - k_6C_1I + k_7C_3, \tag{10}$$

$$\frac{dP}{dt} = k_3C_1. \tag{11}$$

Consider the following initial conditions

$$E(0) = e_0,\quad S(0) = s_0,\quad I(0) = i_0,\quad \text{and}\quad C_1(0) = C_2(0) = C_3(0) = P(0) = 0.$$

The model has the following conservation equations:

$$\begin{aligned} C_1 + C_3 + S + P &= s_0, \\ I + C_2 + C_3 &= i_0, \\ C_1 + C_2 + C_3 + E &= e_0. \end{aligned}$$

By substituting the conservation laws into above system of differential equations (5)–(11), the kinetic equations take the form:

$$\frac{dS}{dt} = -k_1 S(e_0 - i_0 + I - C_1) + k_2 C_1, \tag{12}$$

$$\frac{dI}{dt} = -k_4 I(e_0 - i_0 + I - C_1) + k_5(S + PC_1 + i_0 - s_0 - I) - k_6 I C_1 + k_7(s_0 - S - C_1 - P), \tag{13}$$

$$\frac{dC_1}{dt} = k_1 S(e_0 - i_0 + I - C_1) - (k_2 + k_3 + k_6 I)C_1 + k_7(s_0 - S - C_1 - P), \tag{14}$$

$$\frac{dP}{dt} = k_3 C_1. \tag{15}$$

By introducing the following new variables:

$$\tau = k_1 e_0 t, \quad u = \frac{I}{i_0}, \quad v = \frac{S}{s_0}, \quad w = \frac{C_1}{e_0} \quad \text{and} \quad x = \frac{P}{e_0}.$$

Therefore, the above system of equations (12)–(15) takes the form (see appendix) :

$$\frac{dv}{d\tau} = (w - 1) + \alpha_1(1 - u) + \alpha_2 w, \tag{16}$$

$$\frac{du}{d\tau} = \eta(v - 1) + \epsilon\eta(x + w) + \alpha_7 u(w - 1) + \xi u(1 + u) + \alpha_9(1 - u) + \alpha_4 uw, \tag{17}$$

$$\epsilon\frac{dw}{d\tau} = v(1 - w) - \alpha_1 v(1 - u) + \epsilon[\alpha_3 w + \alpha_4\alpha_1 uw + \alpha_5(w + x)] + \alpha_5(1 - v), \tag{18}$$

$$\frac{dx}{d\tau} = \alpha_{11} w. \tag{19}$$

with initial conditions $u(0) = 1$, $v(0) = 1$, $w(0) = 0$ and $x(0) = 0$. It is clear that the above system of equations (16)–(19) can be presented in the slow and fast forms. Therefore, we can use QSSA when $\epsilon \to 0$, then the equations take the form

$$\frac{dv}{dt} = (w - 1) + \alpha_1(1 - u) + \alpha_2 w, \tag{20}$$

$$\frac{du}{dt} = \eta(v - 1) + \epsilon\eta(x + w) + \alpha_7 u(w - 1) + \xi u(1 + u) + \alpha_9(1 - u) + \alpha_4 uw, \tag{21}$$

$$0 = v(1 - w) - \alpha_1 v(1 - u) + \epsilon[\alpha_3 w + \alpha_4\alpha_1 uw + \alpha_5(w + x)] + \alpha_5(1 - v), \tag{22}$$

$$\frac{dx}{dt} = \alpha_{11} w. \tag{23}$$

Equation (22) can be solved for w in terms of u and v, we have

$$w = \frac{v + \alpha_5(1 - v) - \alpha_1 v(1 - u)}{v}. \tag{24}$$

Thus, the approximate solution for equations (16)–(19) and the manifold M_0 are relatively close. The slow manifold M_0 is given by

$$M_0 = \left\{(u, v, x) : u, v, x \in [0, 1]; w = \frac{v + \alpha_5(1 - v) - \alpha_1 v(1 - u)}{v}\right\}.$$

By substituting equation (24) into equations (20), (21) and (23), the following differential equation close to the manifold M_0 are obtained.

$$\frac{dv}{d\tau} = \beta\frac{1 - v}{v} - \kappa(1 - u) + \lambda,$$

$$\frac{du}{d\tau} = \eta(v - 1) + \xi u(1 - u) + (\gamma + \mu u)(1 - u) + (\upsilon + \sigma u)(\frac{1 - v}{v}) + \alpha_4 u + \epsilon\eta(1 + x),$$

$$\frac{dx}{d\tau} = \alpha_{11}\left\{\frac{v + \alpha_5(1 - v) - \alpha_1 v(1 - u}{v}\right\}.$$

Using the technique of QEA for chemical reactions (4), we assume the (2) reaction of the given system of equations, i.e,

$$E + I \underset{k_5}{\overset{k_4}{\rightleftharpoons}} EI,$$

goes equilibrium very quickly:

$$k_4 = \frac{k^+}{\epsilon}, \quad k_5 = \frac{k^-}{\epsilon}, \quad k^+ = \frac{k_4 e_0}{i_0} \quad \text{and} \quad k^- = \frac{k_5 e_0}{i_0}.$$

This means k_4 and k_5 are large constants in comparison with k_1 and k_2. Thus, equations (5)–(11) take the form of equation (1)

$$\begin{aligned}
\frac{dS}{dt} &= g_{s_1}(S, E, C_1), \\
\frac{dE}{dt} &= g_{s_1}(S, E, C_1) + g_{s_2}(C_1) + \frac{1}{\epsilon} g_f(E, I, C_2), \\
\frac{dI}{dt} &= \frac{1}{\epsilon} g_f(E, I, C_2) + g_{s_3}(I, C_1, C_3), \\
\frac{dC_1}{dt} &= -g_{s_1}(S, E, C_1) - g_{s_2}(C_1) + g_{s_3}(I, C_1, C_3), \\
\frac{dC_2}{dt} &= -\frac{1}{\epsilon} g_f(E, I, C_2), \\
\frac{dC_3}{dt} &= -g_{s_3}(C_1, C_3, I), \\
\frac{dP}{dt} &= g_{s_2}(C_1).
\end{aligned}$$

where $g_{s_1}(S, E, C_1) = -k_1 ES + k_2 C_1$, $g_{s_2}(C_1) = k_3 C_1$, $g_{s_3}(I, C_1, C_3) = (-k_6 C_1 I + k_7 C_3)$ and $g_f(E, I, C_2) = -k^+ EI + k^- C_2$ when $\epsilon \to 0$, we can apply the Quasi- equilibrium approximation.

As a result, the model has two slow variables $b_1(C_2, E) = C_2 + E$ and $b_2(I, C_2) = I - C_2$. The slow manifold is calculated from non-linear equation $g_f(E, I, C_2) = 0$. This is given by

$$M_0 = \left\{ (E, I, C_2) \in R^2 : I = \frac{k^- C_2}{k^+ E} \right\}.$$

After fixing the slow variables b_1 and b_2, we have the following equations

$$-k^+ EI + k^- C_2 = 0,$$

$$C_2 + E = 0,$$

$$I - C_2 = 0.$$

The following quadratic equation for C_2 is obtained:

$$k^+ C_2^2 - (k^+ b_1 - k^+ b_2 - k^-) C_2 - k^+ b_1 b_2 = 0. \tag{25}$$

Equation (25) can be solved analytically for C_2. We obtain

$$C_2(b_1, b_2) = \frac{1}{2k^+} \left\{ (k^+ b_1 - k^+ b_2 - k^-) \pm \sqrt[2]{(k^+ b_1 - k^+ b_2 - k^-)^2 + 4k^+ k^+ b_1 b_2} \right\}$$

or,

$$C_2(b_1, b_2) = \frac{1}{2} \left\{ (b_1 - b_2 - \frac{k^-}{k^+}) - \sqrt[2]{(b_1 - b_2 - \frac{k^-}{k^+})^2 + 4 b_1 b_2} \right\}.$$

We select a negative sign in order to have positive concentrations of I, E and C_2. If $b_1 \to 0$ and $b_2 \to 0$, then $C_2 \to 0$. Moreover, the variables E and I were computed and are given by

$$E(b_1, b_2) = b_1 - \frac{1}{2}\left\{(b_1 - b_2 - \frac{k^-}{k^+}) - \sqrt[2]{(b_1 - b_2 - \frac{k^-}{k^+})^2 + 4b_1 b_2}\right\},$$

$$I(b_1, b_2) = b_2 - \frac{1}{2}\left\{(b_1 - b_2 - \frac{k^-}{k^+}) - \sqrt[2]{(b_1 - b_2 - \frac{k^-}{k^+})^2 + 4b_1 b_2}\right\}.$$

3 Discussion and Conclusion

A mathematical model has been established that describes the approximate analytical solutions for non-competitive enzyme inhibition to the system of a simple enzymatic reactions. Rate equations are in general non-linear functions of chemical components (x) and the parameters (p_k). In the present scenario, the differential equations become also non linear and the solution of the equations can not be obtained in a closed analytical form. So, in order to deal with such equations we employed two simple techniques; quasi-steady state approximation and quasi- equilibrium approach. The proposed techniques show a principal role for analyzing complex problem in systems biology. These techniques allowed us to divide the whole system of equations into slow and fast sub-system and were later used to calculate slow manifolds. The rationale behind the current study was to understand the techniques that reduces the number of variables and parameters in order to find analytical approximate solutions. The number of parameters are reduced by the fast subsystem. This solution procedure can be easily extended to all kinds of enzymatic reaction models including enzyme inhibitors. Such techniques can also help us to modify some existing results on heat and mass transport in cancerous tumors under local therapy[13]. This study can also be used to calculate some approximate solutions of non-linear enzymatic reaction models.

Acknowledgment. The authors are highly grateful to the reviewers whose comments helped us to improve the quality of the manuscript.

References

[1] A. Akgul, S. H. A. Khoshnaw and A. S. Abdalrahman , Mathematical modeling for enzyme inhibitors with slow and fast subsystems, Arab Journal of Basic and Applied Sciences, 27(2020), 442–449.

[2] F. Alam, Z. Shafique, S. T. Amjad and M. H. Hassan Bin Asad, Enzyme inhibitors from natural sources with antidiabetic activity: A review, Phytotherapy Research, 33(2018), 41–54.

[3] E. Bartocci and P. Lio, Computational modeling, formal analysis, and tools for systems biology, PLOS Computational Biology, 12(2016), e1004591.

[4] A. Cornish-Bowden, Enzyme kinetics from a metabolic perespective, Biochem. Soc. Trans., 27(1999), 281–284.

[5] J. Eilertsen and S. Santiago, The quasi-steady-state approximations revisited: Timescales, small parameters, singularities, and normal forms in enzyme kinetics, Mathematical Biosciences, 325(2020), 108339.

[6] X. Fang, W. Anders and R. Jaques, A systems biology framework for modeling metabolic enzyme inhibition of Mycobacterium tuberculosis, BMC Systemic Biology, 3(2009).

[7] C. L. Frenzen and P. K. Maini, Enzyme kinetics for a two-step enzyme reaction with comparable initial enzyme-substrate ratios, Journal of Mathematical Biology, 26(1988), 689–703.

[8] Q. Gan, S. J. Allen and G. Taylor, Kinetic dynamics in heterogeneous enzymatic hydrolysis of cellulose: An overview, an experimental study and mathematical modeling, Process Biochemistry, 38(2003), 1003–1018.

[9] A. K. Gombert and N. Jens, Mathematical modeling of metabolism, Current Opinion in Biotechnology, 11(2000), 180–186.

[10] K. Hamden, K. Mnafgui, Z. Amri, A. Aloulou and A. Elfeki, Inhibition of key digestive enzymes related to diabetes and hyperlipidemia and protection of liver-kidney functions by trigonelline in diabetic rats, Scientia Pharmaceautica, 81(2012), 233–246.

[11] R. Heinrich, S. M. Rapoport and T. A. Rapoport, Metabolic regulations and mathematical modeling, Prog. Biophys. Molec. Biol., 32(1977), 1–82.

[12] J. Keener and J. Sneyd, Interdisciplinary Applied Mathematics, Mathematical Physiology I. Cellular Physiology. 2^{nd} edition, Springer volume 8/I (2009).

[13] M. A. Khanday and K. Nazir, Mathematical and numerical analysis of thermal distribution in cancerous tissues under the local heat therapy, International Journal of Biomathematics, 10(2017), 1750099.

[14] S. H. A. Khoshnaw, Iterative approximate solutions of kinetic equations for reversible enzyme reactions, Natural Science, 5(2013), 740–755.

[15] S. H. A. Khoshnaw, Model Reduction in Biochemical Reaction Networks (PhD Thesis). University of Leicester, Leicester (2015).

[16] S. H. A. Khoshnaw, Reduction of a kinetic model of active export of importins, Discrete Contin. Dyn. Syst., (2015), 705–722.

[17] S. H. A. Khoshnaw and H. Rasool, Mathematical modeling for complex biochemical networks and identification of fast and slow reactions, The international conference on mathematical and related sciences, Antalya Springer, (2019), 55–69.

[18] P. Kuzmic, J. Soloweij and B. W. Murray, An algebraic model for the kinetics of covalent enzyme inhibition at low substrate concentrations, Analytical Biochemistry, 484(2015), 82–90.

[19] A. Meena, A. Eswari and L. Rajendran, Mathematical modeling of enzyme kinetics reaction mechanisms and analytical solutions of non-linear equations, J. Math Chem., 48(2010), 179–186.

[20] L. A. Moran, H. Robert, S. Gray and P. Marc, Principles of Biochemistry, 5th ed. Pearson (2012).

[21] M. Rahmanzadeh, A. Tahereh and A. Meysam, The development and application of the RCW method for the solution of the Blasius problem, Journal of Applied and Computational Mechanics, 6(2020), 105–111.

[22] S. Schnell and P. K. Maini, Enzyme kinetics far from the standard quasi-steady-state and equilibrium approximations, Mathematical and computer modeling, 35(2002), 137–144.

[23] L. A. Segel and S. Marshaal, The quasi-steady-state assumption: A case study in perturbation, SIAM Review, 31(1989), 446–477.

[24] M. C. Sharmila, T. Parveen and L. Rajendran, Mathematical modeling and analysis of nonlinear enzyme catalyzed reaction processes, Journal of Theoretical Chemistry, (2013), 1–7.

4 Appendix

$\epsilon = \frac{e_0}{s_0}$, $\alpha_1 = \frac{i_0}{e_0}$, $\alpha_2 = \frac{k_2}{k_1 s_0}$,

$\alpha_3 = -\frac{k_2+k_3}{k_1 e_0}$, $\alpha_4 = -\frac{k_6}{k_1}$, $\alpha_5 = \frac{k_7}{k_1 e_0}$,

$\alpha_7 = \frac{k_4}{k_1}$, $\alpha_8 = \frac{k_5}{k_1 i_0}$, $\alpha_9 = \frac{k_5}{k_1 e_0}$,

$\alpha_{10} = \frac{k_7}{k_1 i_0}$, $\alpha_{11} = \frac{k_3}{k_1 e_0}$.

$\xi = \alpha_1 \alpha_7$, $\eta = \frac{\alpha_8 - \alpha_{10}}{\epsilon}$, $\gamma = (\alpha_9 - \epsilon\eta\alpha_1)$,

$\mu = -\alpha_1(\alpha_7 + \alpha_4)$, $\nu = \epsilon\eta\alpha_5$, $\sigma = \alpha_5(\alpha_7 + \alpha_4)$,

$\lambda = \alpha_2$, $\kappa = \alpha_1\alpha_2$.