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SLOW AND FAST SUBSYSTEMS FOR COMPLEX UNCOMPETITIVE INHIBITOR MECHANISMS

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Abstract: To fully understand intricate enzyme reaction models, one must explore beyond the confines of chemical and biological tools and look toward mathematical modeling and model reduction techniques. Mathematical modeling and model reduction techniques have the potential to provide a vast array of analysis tools for such models. This piece of work entails a review and discussion of a complex noncompetitive inhibitor model. This model is composed of seven non-linear differential equations with constant rates. We propose two efficient model reduction techniques: quasi- steady-state approximation (QSSA) and quasi-equilibrium approximation (QEA). By utilizing the suggested methods, the model equations are segregated into slow and fast subsystems, leading to the attainment of reduced models and slow manifolds with fewer variables and parameters. The outcomes manifest some analytical approximate solutions for the proposed model and establish a profound agreement between model dynamics for both the original and the reduced models. Observing that the reduced models can accurately identify certain critical model parameters is intriguing.

Keywords: *Mathematical modeling, enzymatic reactions, slow and fast sub- systems, model reductions*

1. Introduction

A molecule that hinders the activity of an enzyme is referred to as an enzyme inhibitor. An enzyme is a protein molecule that catalyzes biological reactions. These molecules can function as activators or inhibitors, regulating numerous biological processes. Enzymes interact with substrates to produce products. Enzyme inhibition can be categorized into two types: reversible and irreversible inhibitors. The three types of reversible enzyme inhibition are competitive, noncompetitive, and uncompetitive [1].

Mathematical modeling is an essential tool in the scientific method, where mathematical statements (or models) are used to create hypotheses and predictions. Several classical works have investigated models of biochemistry differential equation systems. Authors have sought models for biochemical reaction networks, such as model reductions, quasi-equilibrium manifold approximations, total quasi-steady- state approximations, model reductions in chemical dynamics, slow invariant manifolds, singular perturbations, thermodynamic estimates, and reaction graph analysis. Additionally, mathematical modeling techniques have been applied to enzyme inhibitors with slow and fast subsystems [2–7].

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Various mathematical models exist, including dynamical systems, statistical models, and differential equations. The conversion of a concept to a theoretical model and then a quantitative model can be achieved in multiple ways. A theoretical model is a visual representation of the concept using boxes and arrows in a model diagram. The concept of chemical kinetics modeling is utilized to convert physical reality into a mathematical description. Real-world problems can also be expressed using mathematical equations [8–18].

In systems biology, a mathematical model is an intellectual tool used to describe and analyze models. Chemical reactions are often complex, and the fundamental characteristics of the reaction mechanism must be known to simplify the complexity of a complex reaction. Model reduction techniques are necessary to create such models. The first theories of complex chemical reactions coincided with the development of model reduction approaches. Model reduction involves transforming one system into another with fewer variables and parameters. Quasi-steady-state approximation (QSSA) and quasi-equilibrium approximation (QEA) are two useful approximation tools in the study of biochemical kinetics. These methods are focused on nonlinear differential equation systems, where one or more dependent variables can be considered in a steady state with respect to the instantaneous values of the other dependent variables following an initial fast transient [9, 20].

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The written work comprises several valuable contributions. Firstly, we delve into and examine a multifaceted model of uncompetitive inhibitor reactions, which is comprised of seven nonlinear differential equations featuring constant rates. We then proceed to employ two efficacious techniques for model reduction, namely the quasi- steady-state approximation (QSSA) and quasi-equilibrium approximation (QEA). Furthermore, we have made another significant contribution by dividing the model equations into slow and fast subsystems. Additionally, the original model equations can be suitably abridged, leading to the acquisition of slow manifolds with a fewer number of variables and parameters. Ultimately, we identify certain critical parameters of the model based on the reduced models that can help facilitate further research and enhancements.

2. Chemical Reaction Kinetics

One of the most significant technique theories for modeling is the concept of chemical kinetic theory. Model states, parameters, and equations are significant assumptions for building such models. This is because it helps to examine mathematical modeling effectively and conveniently. The generally reversible chemical reaction equations can be expressed as follow:

$$\sum_{i=1}^{n} a_i A_i \underset{k_j^b}{\overset{k_j^f}{\rightleftharpoons}} \sum_{i=1}^{n} b_i B_i \ , \qquad (1)$$

where k_j^f and k_j^b are chemical reaction constants, the real numbers a_i and b_i stand for the stoichiometric coefficients of the corresponding species (reactants and products), species A_i and B_i are the i^{th} reactant or product. Let R^b and R^f are denoted for backward and forward rates respectively then the reaction speed of each elementary step R_j for $j = 1, 2, \dots, m$ can be expressed as follows:

$$W_j = R_j^f - R_j^b \ . \qquad (2)$$

Using mass action law, the reaction rates for equation 1 are given below:

$$R_j^f = k_j^f \prod C_{Ai}^{ai}$$

$$R_j^b = k_j^b \prod C_{Bi}^{bi},$$

where A_i and B_i are the reactants and products species and their concentration are C_{Ai}, C_{Bi}. Finally, the model of kinetic differential equations with constant rates are expressed below:

$$\frac{dc}{dt} = \sum_{j=1}^{m} \gamma_j W_j(C), \qquad (3)$$

where $\gamma_j = b_{ij} - a_{ij}$ for $i = 1, 2, \dots, n$ and $j = 1, 2, \dots, m$ are stoichiometric vectors.

3. Model Reduction Techniques

Model reduction techniques in systems of complex chemical reactions are employed to simplify the mathematical representation of the reaction network while preserving the essential behavior of the system. These techniques aim to reduce computational complexity and facilitate analysis and simulation of the chemical kinetics. Here are some commonly used models' reduction techniques in systems of complex chemical reactions:

Quasi-Steady-State Approximation (QSSA): This technique assumes that certain species in the reaction network reach a quasi-steady state, meaning their concentrations change relatively slowly compared to other species. By applying the QSSA, the rate equations for these quasi-steady-state species can be simplified or eliminated, reducing the dimensionality of the system.

Partial Equilibrium Approximation: In systems with fast and slow reactions, the partial equilibrium approximation assumes that some reactions reach equilibrium much faster than others. By assuming rapid equilibration for these reactions, the equilibrium concentrations of the involved species can be calculated independently of the rest of the system, allowing for further simplification.

Species Lumping's: Species lumping involves grouping together similar or unimportant species into lumped species, reducing the total number of species in the system. This is often done based on chemical similarities or through the use of empirical grouping rules. Lumping reduces the dimensionality of the system and simplifies the reaction network.

Reaction Lumping's: Similarly, to species lumping, reaction lumping involves combining multiple elementary reactions into lumped reactions. This is typically done by identifying reactions with similar rate-controlling steps or by lumping re- actions that have negligible contributions to the overall system behavior. Reaction lumping reduces the number of reactions in the system and simplifies the kinetics.

Time-Scale Separation: If the reaction network exhibits distinct time scales, it may be possible to simplify the system by assuming that some reactions are much faster or slower compared to others. This allows for approximations such as assuming steady-state or equilibrium conditions for certain species or reactions, leading to a reduced model.

Principal Component Analysis (PCA): PCA is a statistical technique used to identify dominant modes of variation in a high-dimensional dataset. In the context of chemical kinetics, PCA can be employed to identify the most important reaction pathways or species in the system. By focusing on the dominant modes, a reduced model can be constructed that captures the essential behavior of the system.

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These model reduction techniques are often combined or adapted based on the specific characteristics of the chemical system and the objectives of the analysis. The goal is to strike a balance between computational efficiency and accuracy, enabling the study and understanding of complex chemical kinetics in a more tractable manner. The art of reducing models in intricate chemical reaction systems is a widely recognized technique to decrease the quantity of constituents such as variables and parameters. Although simplified, the dynamics of these models should still exhibit a resemblance to their original counterparts. The categorization of model equations into their slow and rapid subsystems plays a pivotal role in elucidating the model dynamics [2, 21].

The objective of this endeavor is to partition the structure of intricate uncompetitive inhibitor mechanisms into sluggish and speedy subsystems through the implementation of the quasi-steady-state approximation (QSSA) and quasi-equilibrium approximation (QEA) techniques. Subsequently, the reduced models and slow manifolds are generated with a reduced number of parameters and variables. The approximated analytical solutions for the proposed model demonstrate an excellent correspondence between the model dynamics for both the original and the reduced models. The quasi-steady-state approximation technique has undergone numerous revisions over the course of the previous century. In the analysis of biochemical kinetics, the quasi-steady-state approximation technique is a vital approximation method that can be employed to categorize nonlinear models into slow and fast subsystems, as well as to derive some analytical approximation solutions [7, 9, 22]. Following this method, the variable set $C(t)$ is divided into two groups: the group of slow variables $C^S(t)$ and the group of fast variables $C^f(t)$. Then kinetic equation 3 can be split into slow and fast subsystems:

$$\frac{dC^s}{dt} = W^s(C^s(t), C^f(t), \kappa), \tag{4}$$

$$\frac{dC^f}{dt} = \frac{1}{\epsilon} W^f(C^s(t), C^f(t), \kappa), \tag{5}$$

where equations 4 and 5 are slow and fast subsystems respectively, C^s, C^f are groups of slow and fast variables (basics). Based on the Tikhonov theorem, the standard singular perturbation can be applied on the fast subsystem and we can analyze fast subsystem 5. The slow manifold occurs if we have a stable dynamic of fast variables under given values of slow concentrations [23, 26]. The attractive slow manifold of the system can be calculated from algebraic equation

$$W^f(C^s(t), C^f(t), \kappa) = 0,$$

when $\epsilon \to 0$. As a result, the new system has fewer variables (species concentration) and parameters (chemical reaction constants). The concept of quasi-equilibrium approximation (QEA) is an effective technique of model reduction to reduce the number of variables and parameters. According to this concept, fast reactions reach equilibrium very quickly compared to a set of slow reactions. We can write the initial system 3 as follows:

$$\frac{dc}{dt} = \sum_{s,slow} \gamma^s W^s(C, \kappa, t) + \frac{1}{\epsilon} \sum_{f,fast} \gamma^f W^f(C, \kappa, t), \tag{6}$$

where W^s and W^f are reaction rate functions, whereas γ^s and γ^f are stoichiometric vectors and ϵ is a small parameter. Then, the fast subsystem can be stated as:

$$\frac{dc}{dt} = \frac{1}{\epsilon} \sum_{f,fast} \gamma^f W^f(C, \kappa, t), \tag{7}$$

By using the algebraic equations $\sum_{f,fast} \gamma^f W^f(C, \kappa, t) = 0$, when $\epsilon \to 0$ we can calculate the quasi-equilibrium manifold μ_0. For further information about the approaches described and their use in biological and chemical models see [9, 24–26].

4. Reversible Uncompetitive Reaction Mechanisms

Uncompetitive inhibition occurs when an enzyme inhibitor binds only to the complex generated between the enzyme and the substrate. We can now derive a substrate inhibition equation. For substrate S, enzyme E has two binding sites which are a catalytic site that generates the product P and a non-catalytic site that produces the product at a slower rate. We can write the reaction scheme as follows [27]

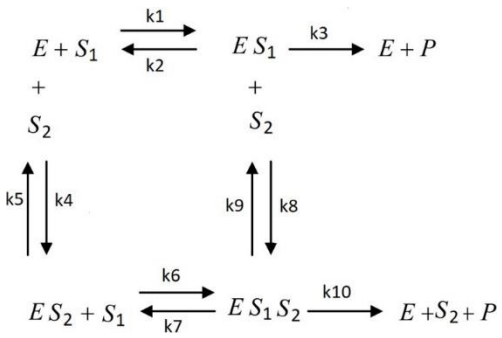

Figure 1. Chemical Reaction Networks for Uncompetitive Inhibitor Mechanisms.

The substrates bound to the catalytic and non-catalytic sites are denoted by ES1 and ES2, respectively, and two substrate molecules attached to both the catalytic and non-catalytic sites are denoted by ES1S2, and k_i for $i = 1, 2, \ldots, 10$ are model parameters. By taking the above assumptions, the mathematical model reactions and their reaction rates are shown below:

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$$
\begin{aligned}
&E + S_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES_1 \overset{k_3}{\rightarrow} E + P,\\
&E + S_2 \underset{k_5}{\overset{k_4}{\rightleftharpoons}} ES_2,\\
&ES_2 + S_1 \underset{k_7}{\overset{k_6}{\rightleftharpoons}} ES_1S_2,\\
&ES_1 + S_2 \underset{k_9}{\overset{k_8}{\rightleftharpoons}} ES_1S_2,\\
&ES_1S_2 \overset{k_{10}}{\rightarrow} E + S_2 + P.
\end{aligned} \tag{8}
$$

Let concentrations of the reactants in 8 denoted by lowercase letters as:

$s_1 = [S_1],\ s_2 = [S_2],\ e = [E],\ c_1 = [ES_1],\ c_2 = [ES_2],\ c_3 = [ES_1S_2]$ and $p = [P]$,

where [ ] denotes concentration and $k_i,\ i = 1, 2, \cdots, 10$ are called the rate constants.

Then the Law of Mass Action applied to 8 leads to one equation for each reactant and hence the system of nonlinear reaction equations,

$$
\begin{aligned}
\frac{de}{dt} &= -k_1 e s_1 + (k_2 + k_3)c_1 - k_4 e s_2 + k_5 c_2 + k_{10} c_3\\
\frac{ds_1}{dt} &= -k_1 e s_1 + k_2 c_1 - k_6 s_1 c_2 + k_7 c_3\\
\frac{ds_2}{dt} &= -k_4 e s_2 + k_5 c_2 - k_8 c_1 s_2 + k_9 c_3 + k_{10} c_3\\
\frac{dc_1}{dt} &= k_1 e s_1 - k_2 c_1 - k_3 c_1 - k_8 s_2 c_1 + k_9 c_3\\
\frac{dc_2}{dt} &= k_1 e s_2 - k_5 c_2 - k_6 c_2 s_1 + k_7 c_3\\
\frac{dc_3}{dt} &= k_1 s_1 s_2 - k_7 c_3 + k_8 c_1 s_2 - k_9 c_3 - k_{10} c_3\\
\frac{dp}{dt} &= k_3 c_1 + k_{10} c_3
\end{aligned} \tag{1}
$$

The model initial conditions are $e(0) = e_0,\ s_1(0) = s_1^0,\ s_2(0) = s_2^0$ and

$c_1(0) = c_2(0) = c_3(0) = p\ (0) = 0$. Based on the proposed simple enzymatic reactions, there were a very important assumption that the total amount of enzyme is much smaller than the amount of substrate, $[E] \ll [S1]$. Therefore, we can define a very small parameter based on the given condition, $\epsilon = \frac{e_0}{s_1^0}$.

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

5. Quasi Steady State Approximation

The system 9 has the following conservation laws:

$$e + c_1 + c_2 + c_3 = e_0,\ \ s_2 + c_2 + c_3 = s_2^0,\ \ s_1 + c_1 + c_3 + p = s_1^0. \quad (10)$$

By substituting the conservation laws 10 into the system 9, and we can eliminate the variables s_2, c_2 and p from the system 9, and then by introducing the following new variables:

$$\tau = k_1 e_0,\ \ u_1 = \frac{e}{e_0},\ \ u_2 = \frac{s_1}{s_1^0},\ \ w_1 = \frac{c_1}{e_0},\ \ w_2 = \frac{c_3}{e_0}.$$

The system (9) takes the following form:

$$\frac{du_1}{d\tau}\epsilon = -u_1u_2 + (\alpha_1 + \alpha_2)w_1 - \alpha_3u_1\big(\alpha_4 - \epsilon(1 - u_1 - w_1)\big) + \alpha_5(1 - u_1 - w_1 - w_2) + \alpha_6w_2, \quad (11a)$$

$$\frac{du_2}{d\tau} = -u_1u_2 + \alpha_1w_1 - \alpha_7u_2(1 - u_1 - w_1 - w_2) + \alpha_8w_2, \quad (11b)$$

$$\frac{dw_1}{d\tau}\epsilon_1 = u_1u_2 + \alpha_1w_1 - \alpha_2w_1 - \alpha_9w_1(\alpha_4 - \epsilon_1 + \epsilon_1u_1 + \epsilon_1w_1) + \alpha_{10}w_2, \quad (11c)$$

$$\frac{dw_2}{d\tau}\epsilon_1 = \alpha_7u_2(1 - u_1 - w_1 - w_2) - \alpha_8w_2 + \alpha_9w_1(\alpha_4 - \epsilon_1 + \epsilon_1u_1 + \epsilon_1w_1) - \alpha_{10}w_2 - \alpha_6w_2, \quad (11d)$$

where

$$\alpha_1 = \frac{k_2}{k_1s_1^0},\ \ \alpha_2 = \frac{k_3}{k_1s_1^0},\ \ \alpha_3 = \frac{k_4}{k_1},\ \ \alpha_4 = \frac{s_2^0}{s_1^0},\ \ \alpha_5 = \frac{k_5}{k_1s_1^0},\ \ \alpha_6 = \frac{k_{10}}{k_1s_1^0},$$
$$\alpha_7 = \frac{k_6}{k_1},\ \ \alpha_8 = \frac{k_7}{k_1s_1^0},\ \ \alpha_9 = \frac{k_8}{k_1},\ \ \alpha_{10} = \frac{k_9}{k_1s_1^0},$$

with initial conditions $u_1(0) = 1, u_2(0) = 1$ and $w_1(0) = w_2(0) = 0$. Equation $11b$ is the slow form while equations $11a, 11c$ and $11d$ are fast. Now by using quasi steady-state approximation (QSSA) when $\epsilon_1 \to 0$, then sub-equations $11a,\ 11b, 11c$ and $11d$ take the form:

$$0 = -u_1u_2 + (\alpha_1 + \alpha_2)w_1 - \alpha_3u_1\alpha_4 + \alpha_5(1 - u_1 - w_1 - w_2) + \alpha_6w_2, \quad (12a)$$
$$0 = u_1u_2 + \alpha_1w_1 - \alpha_2w_1 - \alpha_9\alpha_4w_1 + \alpha_{10}w_2, \quad (12b)$$
$$0 = \alpha_7u_2(1 - u_1 - w_1 - w_2) - \alpha_8w_2 + \alpha_9\alpha_4w_1 - \alpha_{10}w_2 - \alpha_6w_2, \quad (12c)$$
$$\frac{du_2}{d\tau} = -u_1u_2 + \alpha_1w_1 - \alpha_7u_2(1 - u_1 - w_1 - w_2) + \alpha_8. \quad (12d)$$

After solving equations $12a$,$12b$ and $12c$ for u_1, w1 and w_2 in terms of u_2:

$$u_1 = \frac{\beta_1 + \beta_2 + \beta_3u_2}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2}$$

$$w_1 = \frac{u2(\beta4 + \beta5u2)}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2} \quad (13)$$

$$w_2 = \frac{u2(\beta8 + \beta9u2)}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2}$$

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

where

$\beta_1 = \alpha_5(\alpha_1\alpha_6 + \alpha_2\alpha_6 + \alpha_1\alpha_8 + \alpha_2\alpha_8 + \alpha_1\alpha_{10} + \alpha_2\alpha_{10}),$

$\beta_2 = \alpha_4\alpha_5(\alpha_6 + \alpha_8),$

$\beta_3 = \alpha_7\big(\alpha_6(\alpha_1 + \alpha_2 + \alpha_4\alpha_9) + \alpha_{10}(\alpha_1 + \alpha_2)\big),$

$\beta_4 = \alpha_5(\alpha_6 + \alpha_8 + \alpha_{10}) + \alpha_3\alpha_4\alpha_7\alpha_{10},$

$\beta_5 = \alpha_7(\alpha_6 + \alpha_{10}),$

$\beta_6 = \alpha_3\alpha_2\alpha_9(\alpha_6 + \alpha_9),$

$\beta_7 = \alpha_3\alpha_4\big(\alpha_6(\alpha_1 + \alpha_2)\alpha_8(\alpha_1 + \alpha_2)\alpha_{10}(\alpha_1 + \alpha_2) + \alpha_4\alpha_5\alpha_9(\alpha_6 + \alpha_8)\big),$

$\beta_8 = \alpha_4\alpha_9(\alpha_5 + \alpha_3\alpha_4\alpha_7) + \alpha_3\alpha_4\alpha_7(\alpha_1 + \alpha_2),$

$\beta_9 = \alpha_4\alpha_7\alpha_9,$

$\beta_{10} = \alpha_4\alpha_8\alpha_9.$

As a result, the approximate solution of the system 11 comes close enough to the manifold μ_0, which is defined as follows:

$$\mu_0 = \{(u_1, u_2, w_1, w_2): u_2 \in [0,1]\},$$

where

$$u_1 = \frac{\beta_1 + \beta_2 + \beta_3 u_2}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2},$$

$$w_1 = \frac{u2(\beta_4 + \beta_5 u_2)}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2}, \tag{14}$$

$$w_2 = \frac{u2(\beta_8 + \beta_9 u_2)}{\beta_1 + \beta_6 + (\beta_3 + \beta_4 + \beta_8 + \beta_{10})u_2 + (\beta_5 + \beta_9)u_2^2},$$

By substituting 13 into $12d$, we get the reduced differential equation below, which is close to the manifold μ_0.

$$\frac{du_2}{d\tau} = \frac{\rho_1 u_2 - \rho_2 u_2^2}{\rho_3 + \rho_4 u_2 + \rho_5 u_2^2},$$

where

$\rho_1 = \beta_2 - \beta_1 + \alpha_1\beta_4 + \alpha_7\beta_6 - \alpha_8\beta_8,$
$\rho_2 = \beta_3 - \alpha_1\beta_5 - \alpha_8\beta_9 + \alpha_7\beta_{10},$
$\rho_3 = \beta_1 + \beta_6,$
$\rho_4 = \beta_3 + \beta_4 + \beta_8 + \beta_{10}$
$\rho_5 = \beta_5 + \beta_9.$

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

6. Quasi Equilibrium Approximation

In order to simplify model equations and obtain some analytical solutions, we can use the second method defined as quasi-equilibrium approximation (QEA) for chemical reaction 8. We can take two separate assumptions for fast reactions, as shown below. For first assumption we suppose that the first reaction

$$E + S_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES_1$$

becomes quasi-equilibrium when the equilibrium is fast i.e. the parameters can be taken as $k_1 = \frac{1}{\epsilon}k_1'$ and $k_2 = \frac{1}{\epsilon}k_2'$ where $\epsilon = \frac{e_0}{s_0}$ this means that $k_1' = \epsilon k_1$ and $k_2' = \epsilon k_2$. Then, the system 9 takes the following form:

$$\begin{aligned}
\frac{de}{dt} &= -\frac{1}{\epsilon}H^f(e,s_1,c_1,t) + H_1^s(c_1,t) + H_2^s(e,s_2,c_2,t) + H_3^s(c_3,t),\\
\frac{ds_1}{dt} &= -\frac{1}{\epsilon}H^f(e,s_1,c_1,t) + H_4^s(s_1,c_2,c_3,t),\\
\frac{ds_2}{dt} &= H_2^s(e,s_2,c_2,t) + H_3^s(c_3,t) + H_5^s(s_2,c_1,,c_3,t),\\
\frac{dc_1}{dt} &= \frac{1}{\epsilon}H^f(e,s_1,c_1,t) - H_1^s(c_1,t) + H_5^s(s_2,c_1,,c_3,t)\\
\frac{dc_2}{dt} &= -H_2^s(e,s_2,c_2,t) + H_4^s(s_1,c_2,c_3,t),\\
\frac{dc_3}{dt} &= -H_4^s(s_1,c_2,c_3,t) - H_5^s(s_2,c_1,,c_3,t) - H_3^s(c_3,t),\\
\frac{dp}{dt} &= H_1^s(c_1,t) + H_3^s(c_3,t),
\end{aligned} \tag{15}$$

where

$H^f(e,s_1,c_1,t) = k_1' es_1 - k_1'c_1, H_1^s(c_1,t) = k_3c_1,$

$H_2^s(e,s_2,c_2,t) = -k_4es_2 + k_5c_2,\ H_3^s(c_3,t) = -k_4es_2 + k_5c_2,$

$H_4^s(s_1,c_2,c_3,t) = -k_6s_1c_2 + k_7c_3,$

$H_5^s(s_2,c_1,c_3,t) = -k_8c_1s_2 + k_9c_3.$

Now, we can apply the quasi-equilibrium approximation (QEA) when $\epsilon \to 0$. It's clear that the fast reaction involves three species, S, E, and ES, while other chemical reaction components are not considered in the quasi-equilibrium manifold (QEM) analysis. According to conservation laws of fast reactions, we obtain two slow variable which defined as:

$$\eta_1(e,c_1) = e + c_1, \quad \eta_2(s_1,c_1) = s_1 + c_1. \tag{16}$$

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

The slow variable η_1 is the total amount of enzyme and η_2 is the sum of the free substrate and the complex of enzyme–substrate. After solving the algebraic equation $H^f(e, s_1, c_1, t) = 0$ we can compute the slow manifold μ_0 for as follows:

$$\mu_0 = \left\{(e, s_1, c_1) \in \mathbb{R}^3 : s_1 = \frac{k_2' c_1}{k_1' e}\right\}. \tag{17}$$

After finding e and s1 from 16 then substituting into algebraic equation $H^f(e, s_1, c_1, t) = 0$, we get the following quadratic equation:

$$k_1' c_1^2 - (k_1'\eta_1 + k_1'\eta_2 + k_2')c_1 + k_1'\eta_1\eta_2 = 0. \tag{18}$$

Now, equation 18 can be solved for c_1 as follows:

$$c_1(\eta_1, \eta_2) = \frac{1}{2}\left[(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}) \pm \left(\left(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}\right)^2 - 4\eta_1\eta_2\right)^{\frac{1}{2}}\right]. \tag{19}$$

The solution for *s* and *e* are

$$s_1(\eta_1, \eta_2) = \eta_2 - \frac{1}{2}\left[\left(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}\right) \pm \left(\left(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}\right)^2 - 4\eta_1\eta_2\right)^{\frac{1}{2}}\right], \tag{20}$$

$$e(\eta_1, \eta_2) = \eta_1 - \frac{1}{2}\left[\left(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}\right) \pm \left(\left(\eta_1 + \eta_2 + \frac{k_1'}{k_2'}\right)^2 - 4\eta_1\eta_2\right)^{\frac{1}{2}}\right]. \tag{21}$$

For the second assumption, we suppose that $E + S_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES_1$ and $ES_2 + S_1 \underset{k_7}{\overset{k_6}{\rightleftharpoons}} ES_1S_2$ are only two fast reversible reactions in the model network become quasi-equilibrium when the equilibrium is fast. Let $k_1 = \frac{1}{\epsilon}k_1'$, $k_2 = \frac{1}{\epsilon}k_2'$, $k_6 = \frac{1}{\epsilon}k_6'$ and $k_7 = \frac{1}{\epsilon}k_7'$ where $\epsilon = \frac{e_0}{s_0}$ this means that $k_1' = \epsilon k_1, k_2' = \epsilon k_2, k_6' = \epsilon k_6$ and $k_7' = \epsilon k_7$.

Then, the system 9 takes the following form:

$$\begin{aligned}
\frac{de}{dt} &= -\frac{1}{\epsilon}H_1^f(e, s_1, c_1, t) + H_1^s(c_1, t) - \frac{1}{\epsilon}H_2^f(e, s_2, c_2, t) + H_2^s(c_3, t),\\
\frac{ds_1}{dt} &= -\frac{1}{\epsilon}H_2^f(e, s_2, c_2, t) - H_4^s(s_2, c_1, c_3, t) + H_2^s(c_3, t),\\
\frac{ds_2}{dt} &= -\frac{1}{\epsilon}H_2^f(e, s_2, c_2, t) + H_3^s(c_3, t) + H_5^s(s_2, c_1, , c_3, t),\\
\frac{dc_1}{dt} &= \frac{1}{\epsilon}H_1^f(e, s_1, c_1, t) - H_1^s(c_1, t) + H_4^s(s_2, c_1, , c_3, t),\\
\frac{dc_2}{dt} &= \frac{1}{\epsilon}H_2^f(e, s_2, c_2, t) - H_3^s(s_1, c_2, c_3, t),\\
\frac{dc_3}{dt} &= H_3^s(s_1, c_2, c_3, t) - H_4^s(s_2, c_1, , c_3, t) - H_1^s(c_1, t),\\
\frac{dp}{dt} &= H_1^s(c_1, t) + H_2^s(c_3, t),
\end{aligned} \tag{22}$$

where $H_1^f(e, s_1, c_1, t) = k_1' e s_1 - k_2' c_1$, $H_2^f(e, s_2, c_2, t) = k_4' e s_2 - k_5' c_2$, $H_1^s(c_1, t) = k_3 c_1$, $H_2^s(c_3, t) = k_{10} c_3, H_3^s(s_1, c_2, c_3, t) = k_6 c_2 - k_7 c_3$ and $H_4^s(s_2, c_1, , c_3, t) = k_8 s_2 c_1 - k_9 c_3$.

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

Now, we can apply the quasi-equilibrium approximation (QEA) when $\epsilon \to 0$. The fast reaction involves four species, E, S_1, S_2, ES_1, and ES_2, while other chemical reaction components are not considered in the quasi-equilibrium manifold (QEM) analysis. Hence, we obtain three slow variables $\eta_1(e, c_1, c_2) = e + c_1 + c_2$, $\eta_2(s_1, c_1) = s_1 + c_1$ and $\eta_3(s_2, c_2) = s_2 + c_2$. The slow manifold is determined after solving the algebraic equation ${H_1}^f(e, s_1, c_1, t) = 0$ and $H_2^f(e, s_2, c_2, t) = 0$:

$$\mu_0 = \left\{(e, s_1, c_1, c_2) \in \mathbb{R}^3 : s_1 = \frac{k_2' c_1}{k_1' e}, \quad s_2 = \frac{k_5' c_2}{k_4' e}\right\}. \tag{23}$$

By using an assumption that $[S_1] \gg [C_1]$ this means that $\eta_2 \gg C_1$, we get the following equation:

$$\begin{aligned} \left(1 + \frac{\eta_1}{\eta_2} + \frac{k_2'}{k_1' \eta_2}\right) c_1 + c_2 &= \eta_1 + O\left(\frac{c_1 c_2}{\eta_2}\right), \\ \left(\frac{\eta_3}{\eta_2} + \frac{\eta_1}{\eta_2} + \frac{k_5'}{k_4' \eta_2}\right) c_2 &= \frac{\eta_1 \eta_3}{\eta_2} + O\left(\frac{c_1 c_2}{\eta_2}\right). \end{aligned} \tag{25}$$

The approximation solution of c_1 and c_2 become:

$$\begin{aligned} c_1(\eta_1, \eta_2) &\approx \frac{\eta_1 \eta_2 (\eta_1 + k_6')}{(\eta_1 + \eta_3 + k_6')(\eta_1 + \eta_2 + k_7')}, \\ c_{21}(\eta_1, \eta_3) &\approx \frac{\eta_1 \eta_3}{(\eta_1 + \eta_3 + k_6')}. \end{aligned} \tag{26}$$

Where $k_6' = \frac{k_5'}{k_4'}$ and $k_7' = \frac{k_2'}{k_1'}$. Furthermore, other variables $e, s_1 and\ s_2$ are obtained as follows:

$$\begin{aligned} e(\eta_1, \eta_2, \eta_3) &= \frac{\eta_1 (\eta_1 + k_6')(\eta_1 + k_7')}{(\eta_1 + \eta_3 + k_6')(\eta_1 + \eta_2 + k_7')}, \\ s_1(\eta_1, \eta_2, \eta_3) &= \eta_2 - \frac{\eta_1 \eta_2 (\eta_1 + k_6')}{(\eta_1 + \eta_3 + k_6')(\eta_1 + \eta_2 + k_7')}, \\ s_2(\eta_1, \eta_2, \eta_3) &= \frac{\eta_1 (\eta_3 + k_6')}{(\eta_1 + \eta_3 + k_6')}. \end{aligned} \tag{27}$$

7. Conclusions

For intricate kinetic systems, reductions in modeling can play a significant role in obtaining analytical approximations. In this manuscript, we have implemented two model reduction techniques on the intricate model of uncompetitive inhibitor mechanisms. Both methodologies are instrumental in reducing the model into a more concise form in terms of parameters and variables. Firstly, we utilized the quasi-steady-state approximation (QSSA), which allowed us to calculate slow manifolds by partitioning the original model equations into slow and fast subsystems. The fast subsystems can be efficiently analyzed. Secondly, we employed the quasi- equilibrium approximation (QEA) to classify the reaction rates into slow and fast reactions, which enabled us to investigate the concentrations of species involved in fast reactions. Then, the fast reactions were studied and simplified. Therefore, the proposed model reduction techniques in this study can be further improved and applied to a wide range of complex mechanisms in systems biology.

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Malaysian Journal of Science 42(2): 22-32 (June 2023)

6. References

Akgu¨l, A., 2019. Reproducing kernel Hilbert space method based on reproducing kernel functions for investigating boundary layer flow of a Powell–Eyring non-Newtonian fluid. Journal of Taibah University for Science, 13(1), pp.858- 863.

Akgu¨l, A., Khoshnaw, S.H. and Abdalrahman, A.S., 2020. Mathematical mod- eling for enzyme inhibitors with slow and fast subsystems. Arab Journal of Basic and Applied Sciences, 27(1), pp.442-449.

Ali, R., Akgu¨l, A. and Asjad, M.I., 2020. Power law memory of natural con- vection flow of hybrid nanofluids with constant proportional Caputo fractional derivative due to pressure gradient. Pramana, 94(1), pp.1-11.

Asjad, M.I., Ikram, M.D. and Akgu¨l, A., 2020. Analysis of MHD viscous fluid flow through porous medium with novel power law fractional differential oper- ator. Physica Scripta, 95(11), p.115209.

Bilal, S., Shah, I.A., Akgu¨l, A., Tekin, M.T., Botmart, T. and Yahia, I.S., 2022. A comprehensive mathematical structuring of magnetically effected Sutterby fluid flow immersed in dually stratified medium under boundary layer approximations over a linearly stretched surface. Alexandria Engineering Journal, 61(12), pp.11889-11898.

Bowen, J.R., Acrivos, A. and Oppenheim, A.K., 1963. Singular perturbation refinement to quasi-steady state approximation in chemical kinetics. Chemical Engineering Science, 18(3), pp.177-188.

Dangelmayr, G. and Kirby, M., 2003. Mathematical modeling: a comprehensive introduction.

Frenzen, C.L. and Maini, P.K., 1988. Enzyme kinetics for a two-step enzymic reaction with comparable initial enzyme-substrate ratios. Journal of mathematical biology, 26(6), pp.689-703.

Gorban, A.N. and Shahzad, M., 2011. The michaelis-menten-stueckelberg theorem. Entropy, 13(5), pp.966-1019.

Gorban, A.N., 2018. Model reduction in chemical dynamics: slow invariant manifolds, singular perturbations, thermodynamic estimates, and analysis of reaction graph. Current Opinion in Chemical Engineering, 21, pp.48-59.

Hashemi, M.S., Inc, M., Kilic, B. and Akgu¨l, A., 2016. On solitons and invariant solutions of the Magneto-electro-elastic circular rod. Waves in Random and Complex Media, 26(3), pp.259-271.

Heineken, F.G., Tsuchiya, H.M. and Aris, R., 1967. On the mathematical status of the pseudo-steady state hypothesis of biochemical kinetics. Mathematical biosciences, 1(1), pp.95-113.

Khoshnaw, S.H., 2015. Reduction of a kinetic model of active export of importins. In Conference Publications (Vol. 2015, No. special, p. 705). American Institute of Mathematical Sciences.

Khoshnaw, S. H. A. (2015). Model reductions in biochemical reaction networks [PhD thesis] UK: University of Leicester.

Khoshnaw, S.H. and Rasool, H.M., 2019, April. Mathematical Modelling for complex biochemical networks and identification of fast and slow reactions. In The international conference on mathematical and related sciences (pp. 55-69). Springer, Cham.

Murray, J.D., 2002. Mathematical biology: I. An introduction.

Qureshi, Z.A., Bilal, S., Khan, U., Akgu¨l, A., Sultana, M., Botmart, T., Zahran, H.Y. and Yahia, I.S., 2022. Mathematical analysis about influence of Lorentz force and interfacial nano layers on nanofluids flow through orthogonal porous surfaces with injection of SWCNTs. Alexandria Engineering Journal, 61(12), pp.12925-12941.

Shahzad, M., Arif, H., Gulistan, M., and Sajid, M. (2015). Initially Approximated Quasi Equilibrium Manifold. Journal of the Chemical Society of Pakistan, 37(2).

Shahzad, M., Sultan, F., Wahab, A., Faizullah, F., and Ur Rahman, G. (2016). Slow Manifolds in Chemical Kinetics. Journal of the Chemical Society of Pak- istan, 38(5).

Shahzad, M. and Sultan, F., 2018. Complex reactions and dynamics: advanced chemical kinetics. InTech, Rijeka.

Shahzad, M., Sultan, F., Haq, I., Ali, M. and Khan, W.A., 2019. C-matrix and invariants in chemical kinetics: a mathematical concept. Pramana, 92(4), pp.1-8.

Shahzad, A., Imran, M., Tahir, M., Khan, S.A., Akgu¨l, A., Abdullaev, S., Park, C., Zahran, H.Y. and Yahia, I.S., 2023. Brownian motion and ther- mophoretic diffusion impact on Darcy-Forchheimer flow of bioconvective mi cropolar nanofluid between double disks with Cattaneo-Christov heat flux. Alexandria Engineering Journal, 62, pp.1-15

Schnell, S. and Maini, P.K., 2002. Enzyme kinetics far from the standard quasi-steady-state and equilibrium

DOI:https//doi.org/10.22452/mjs.vol42no2.4
Malaysian Journal of Science 42(2): 22-32 (June 2023)

approximations. Mathematical and Computer Modelling, 35(1-2), pp.137-144.

Segel, L.A. and Slemrod, M., 1989. The quasi-steady-state assumption: a case study in perturbation. SIAM review, 31(3), pp.446-477.

Tzafriri, A.R. and Edelman, E.R., 2004. The total quasi-steady-state approximation is valid for reversible enzyme kinetics. Journal of theoretical biology, 226(3), pp.303-313.

Whiteley, C.G., 2000. Enzyme kinetics: partial and complete uncompetitive inhibition. Biochemical Education, 28(3), pp.144-147.

Yoshino, M. and Murakami, K., 2015. Analysis of the substrate inhibition of complete and partial types. Springerplus, 4(1), pp.1-8.

DOI:https//doi.org/10.22452/mjs.vol42no2.4
Malaysian Journal of Science 42(2): 22-32 (June 2023)