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A mathematical model of enzymatic reactions with Bi-Bi random mechanism and its applications

Vinh Q. Mai[1, *], Dat T. Nguyen[1]

1. Division of Applied Mathematics, Thu Dau Mot University, Binh Duong Province, Vietnam

*Corresponding author email: vinhmq@tdmu.edu.vn

Abstract

Enzymes are biodegradable catalysts naturally present in living organisms, and they are able to accelerate biochemical reactions in the metabolism process. A wide range of applications of enzymes has been developed in biotechnology, industry, medicine, pharmaceuticals, food processing, biofuels, and so on. In this paper, we develop a novel mathematical model describing the enzymatic reactions with Bi-Bi random mechanism. The model consists of a coupled system of nonlinear ordinary differential equations for the species of interest. Using nondimensionalization analysis, a formula for the product formation rate for this mechanism is obtained in a straightforward manner. In order to obtain insights into the model behaviors, we use Python software to obtain numerical solutions for the model. Some discussions on the numerical results is provided. Finally, an application of the model to the phosphorylation of glucose by *glucokinase* enzyme is briefly discussed.

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1 Introduction

Enzymes are biological catalysts that are naturally present in most living organisms. The active sites of an enzyme can accommodate substances and catalyze the reactions to produce new compounds. An individual enzyme is typically able to catalyze a few specific reactions. The molecular weight of an enzyme ranges from 10,000 - 2,000,000 Dalton which is much larger than that of their substrates [1, 3, 5, 10, 22].

Enzymes are capable of greatly accelerating biochemical reaction rates even when the enzyme is at very low concentrations. Especially, enzymes are not consumed during the reactions, and this is one of the commercial advantages of enzymes. In order for a reaction to take place, an amount of activation energy is needed irrespective of whether the reaction consumes or releases energy. Enzymes speed up reactions by reducing the required activation energy [1, 5]. They play an important role because of their ability to catalyze biochemical reactions at typical biological temperatures and pH levels in metabolism. Enzyme-catalyzed reactions take place at much faster rates than reactions without enzyme [10, 17].

As aforementioned, enzymes offer a variety of benefits. Nowadays, scientific and technological advances facilitate the study of enzymes and their applications [15]. New enzymes are being extracted and studied increasingly. A variety of applications of enzymes have been investigated and developed in biotechnology, industry, medicine [4, 9, 14], pharmaceuticals, food processing, biofuels, and so on [2]. The kinetic mechanism of an enzyme must first be understood before developing its applications. Mathematical models are also helpful tools to help gain insights into the mechanism of action of an enzym besides experimental studies.

The Michaelis-Menten formula for the product formation rate of enzymatic reactions is derived from a simple model for the kinetic mechanism of an enzyme, and it is a widely used tool in studying the kinetic mechanism of enzymes [22]. Hence, it is worth formulating such a product formation rate formula for enzymatic reactions with Bi-Bi random mechanism.

In the current study, we shall develop a mathematical model describing a system of enzymatic reactions with a Bi-Bi random mechanism. A nondimesionalization analysis will yield a product formation rate formula in a transparent manner, and this will be the first-ever established formula to our best knowledge. The model will be used to model the phosphorylation of glucose by *glucokinase*.

The rest of this paper is organized as follows. In Section 2, we describe the formulation of the mathematical model. The nondimensionalization analysis of the model is described in Section 3. Section 4 presents numerical solutions for the model, and we shortly discuss an application of the model to the phosphorylation of glucose by *glucokinase* in Section 5. Finally, we provide some concluding remarks in Section 6.

2 The mathematical model

In this section, we develop and analyze a minimal model that describes enzymatic reactions obeying the Bi-Bi random mechanism. We begin by describing the kinetic mechanism that model is based on.

2.1 The kinetic mechanism

Figure 1 graphically depicts the enzymatic reactions for the Bi-Bi random mechanism. In the model, the enzyme molecule has two binding sites for the substrates. The binding of each substrate molecule is random. Once a substrates-enzyme complex ES_1S_2 is formed, the enzyme molecule catalyzes the complex to form and release two product molecules and one free enzyme molecule.

NOMENCLATURE

$[X]$ – the concentration of a species X; a function of time (mM)
E – a molecule of the enzyme
S_1 – a molecule of the substrate S_1
S_2 – a molecule of the substrate S_2
P_1 – a molecule of the product P_1
P_2 – a molecule of the product P_2
ES_1 – an enzyme-substrate complex
ES_2 – an enzyme-substrate complex
ES_1S_2 – an enzyme-substrate complex
k_0 – catalytic rate for the enzyme acting on the substrate molecules S_1 and S_2 (s^{-1})
k_1 – adsorption rate of substrate molecules S_1 to free enzyme molecules E or complexes ES_2 $(mM^{-1}s^{-1})$
k_{-1} – desorption rate of substrate molecules S_1 from enzyme-substrate complexes ES_1, ES_1S_2 (s^{-1})
k_2 – adsorption rate of substrate molecules S_2 to free enzyme molecules E or complexes ES_1 $(mM^{-1}s^{-1})$
k_{-2} – desorption rate of substrate molecules S_2 from enzyme-substrate complexes ES_2, ES_1S_2 (s^{-1})

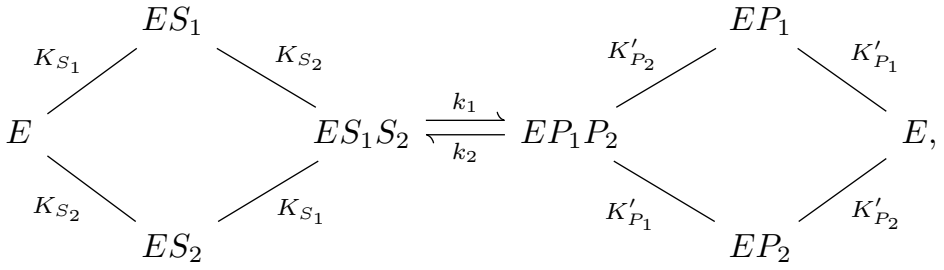

Figure 1: Scheme of the Bi-Bi ramdom mechanism. Here E represents an enzym molecule; S_1 and S_2 denote substrate molecules, and P_1, P_2 represent product molecules, respectively. Furthermore, K_X , K'_X are the dissociation constants for $X = S_1, S_2, P_1, P_2$ in each part, respectively. Finally, k_1 and k_2 are the reaction rates of the reversible reaction.

However, in the current study, we consider the simplified process presented in Figure 2.

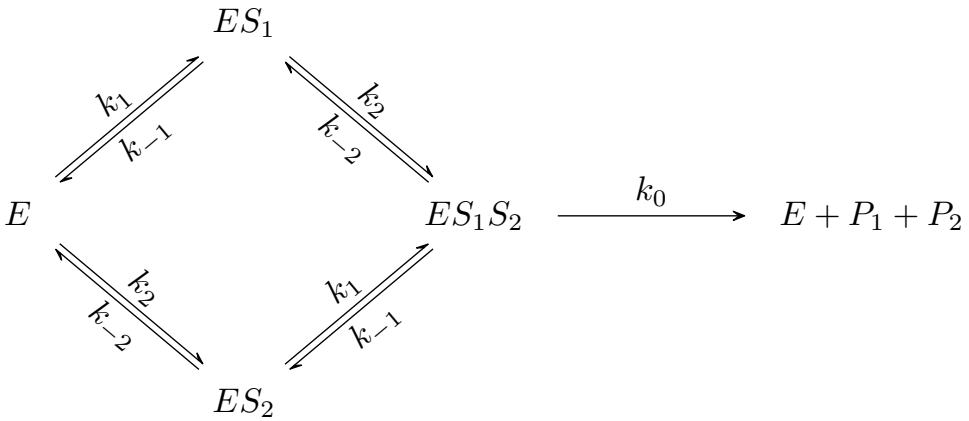

Figure 2: Scheme of the simplified Bi-Bi ramdom mechanism. Here E represents an enzyme molecule; S_1 and S_2 denote substrate molecules, and P_1, P_2 represent product molecules, respectively. Furthermore, k_1 and k_{-1} are the forward and reverse rate constants for S_1, respectively. The forward and reverse rate constants for S_2 are k_2 and k_{-2}, respectively. Finally, k_0 is the catalytic constant.

This simplified scheme is depicted graphically in Figure 3.

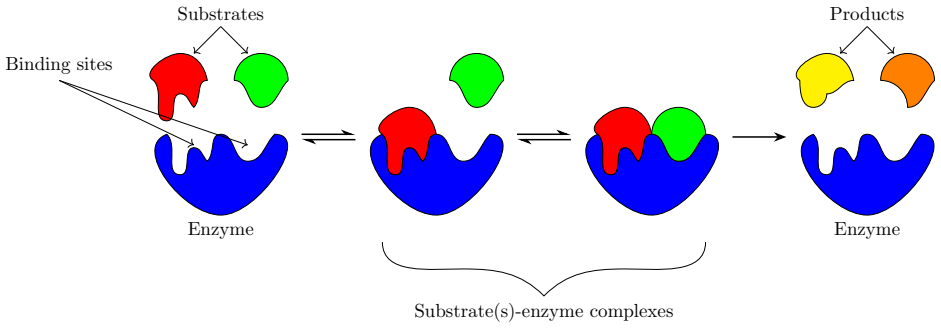

Figure 3: Diagram of the simplified Bi-Bi ramdom mechanism.

The chemical reactions for the model are

$$\begin{aligned}
&S_1 + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES_1 \\
&S_2 + E \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ES_2, \\
&ES_2 + S_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES_1S_2, \\
&S_2 + ES_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ES_1S_2, \\
&ES_1S_2 \xrightarrow{k_0} E + P_1 + P_2,
\end{aligned} \tag{2.1}$$

where here E denotes an enzyme molecule; S_1 and S_2 represent substrate molecules, and P_1, P_2 denote product molecules, respectively. The complexes ES_1, ES_2, and ES_1S_2 have the obvious interpretation; see Figure 1. A double arrow represents a reversible reaction, so each single arrow of double arrows represents a reaction. Furthermore, k_0 (s^{-1}) is the catalytic constant for enzyme, k_1 $(mM^{-1}s^{-1})$, k_2 $(mM^{-1}s^{-1})$ are the forward rate constants for the binding of substrates S_1 and S_2 to their binding sites, respectively. Finally, k_{-1} (s^{-1}), k_{-2} (s^{-1}) are the reverse rate constants for the dissociation of substrates S_1 and s_2 from their binding sites, respectively. We assume that the binding rate constants of the substrate S_1 (k_1) to free enzyme E and enzyme-substrate complex ES_2 are the same. The same assumptions are applied for the rest of model parameters k_{-1}, k_2, and k_{-2}.

2.2 Modeling assumptions

Here we list our modeling assumptions.

(a) The mixture of substrate and enzyme is well-stirred. This implies that diffusive effects in the reaction process can be neglected, and that the concentrations of the various species in the mixture can be described by functions of time only. This further implies that the evolution of the system can be modeled by a coupled system of nonlinear ordinary differential equations, and that a partial differential equations model is not required [7, 11, 12].

(b) We assume mass action kinetics throughout; this implies that the rate of a reaction is taken to be proportional to the product of the concentrations of the reactants. We emphasize here that more complex formulas, such as the Michaelis–Menten formula for the rate of product formation in an enzyme-catalyzed reaction, are derivable from more fundamental mass action considerations under simplifying assumptions [11, 12, 22, 23].

(c) The binding of one substrate does not affect the affinity of the binding sites for other substrates.

2.3 The model equations

Applying the law of mass action in the usual way, the corresponding ordinary differential equations of the model are given by

$$\begin{aligned}
\frac{d[E]}{dt} &= -k_1[E][S_1] - k_2[E][S_2] + k_{-1}[ES_1] + k_{-2}[ES_2] + k_0[ES_1S_2],\\
\frac{d[S_1]}{dt} &= -k_1[E][S_1] - k_1[ES_2][S_1] + k_{-1}[ES_1] + k_{-1}[ES_1S_2],\\
\frac{d[S_2]}{dt} &= -k_2[E][S_2] - k_2[ES_1][S_2] + k_{-2}[ES_2] + k_{-2}[ES_1S_2],\\
\frac{d[ES_1]}{dt} &= -k_{-1}[ES_1] - k_2[ES_1][S_2] + k_1[E][S_1] + k_{-2}[ES_1S_2],\\
\frac{d[ES_2]}{dt} &= -k_{-2}[ES_2] - k_1[ES_2][S_1] + k_2[E][S_2] + k_{-1}[ES_1S_2],\\
\frac{d[ES_1S_2]}{dt} &= -(k_{-2} + k_{-1} + k_0)[ES_1S_2] + k_2[ES_1][S_2] + k_1[ES_2][S_1],\\
\frac{d[P_1]}{dt} &= k_0[ES_1S_2],\\
\frac{d[P_2]}{dt} &= k_0[ES_1S_2],
\end{aligned} \tag{2.2}$$

where $[X]$ (mM) is a function of time that represents the concentration of a species X.

It is not necessary to discuss all of these equations here. However, we do briefly discuss two of them to illustrate how these model equations are constructed. We begin by considering the equation for S_1. This is given by

$$\frac{d[S_1]}{dt} = \overbrace{-k_1[E][S_1]}^{\mathcal{A}}\overbrace{-k_1[ES_2][S_1]}^{\mathcal{B}} + \overbrace{k_{-1}[ES_1]}^{\mathcal{C}} + \overbrace{k_{-1}[ES_1S_2]}^{\mathcal{D}},$$

where

- $\mathcal{A}$ - this term accounts for the reduction in concentration of S_1 due to enzyme binding.
- $\mathcal{B}$ - the reduction in concentration of S_1 due to enzyme-substrate complex binding.
- $\mathcal{C}$ - the increase in concentration of S_1 due to enzyme unbinding from the complex ES_1.
- $\mathcal{D}$ - the increase in concentration of S_1 due to substrate unbinding from the complex ES_1S_2.

Next consider the equation for the enzyme E, given by

$$\frac{d[E]}{dt} = \overbrace{-k_1[E][S_1]}^{\alpha}\overbrace{-k_2[E][S_2]}^{\beta} + \overbrace{k_0[ES_1S_2]}^{\gamma} + \overbrace{k_{-1}[ES_1]}^{\delta} + \overbrace{k_{-2}[ES_2]}^{\epsilon},$$

where

- α - this term accounts for the reduction in concentration of E due to enzyme binding to the substrate S_1.
- β - the reduction in concentration of E due to enzyme binding to the substrate S_2.
- γ - the increase in concentration of E due to enzyme catalyzing the complex ES_1S_2 and releasing the products P_1 and P_2 then.
- δ - the increase in concentration of E due to enzyme unbinding from the complex ES_1.
- ϵ - the increase in concentration of E due to enzyme unbinding from the complex ES_2.

The remaining equations listed in (2.2) are interpreted similarly.

The model equations are solved subject to the initial conditions

$$\begin{aligned} &[E](0) = e_0, \quad [S_1](0) = s_{10}, \quad [S_2](0) = s_{20}, \quad [P_1](0) = 0, \\ &[ES_1](0) = 0, \quad [ES_2](0) = 0, \quad [ES_1S_2](0) = 0, \quad [P_2](0) = 0, \end{aligned} \tag{2.3}$$

where e_0, s_{10}, and s_{20} are the constant initial concentrations of enzyme and substrates, respectively. In (2.2), it is clear that

$$\frac{d[E]}{dt} + \frac{d[ES_1]}{dt} + \frac{d[ES_2]}{dt} + \frac{d[ES_1S_2]}{dt} = 0. \tag{2.4}$$

Integrating (2.4) gives

$$[E] + [ES_1] + [ES_2] + [ES_1S_2] = e_0, \tag{2.5}$$

which corresponds to the conservation of enzyme. Similarly, we have

$$\frac{d[ES_1]}{dt} + \frac{d[ES_1S_2]}{dt}\frac{d[S_1]}{dt} + \frac{d[P_1]}{dt} = 0, \tag{2.6}$$

and integrating (2.6) gives

$$[ES_1] + [ES_1S_2] + [S_1] + [P_1] = s_{10}, \tag{2.7}$$

which corresponds to the conservation of substrate S_1. Finally, the conservation of substrate S_2 is given by

$$[ES_2] + [ES_1S_2] + [S_2] + [P_2] = s_{20}. \tag{2.8}$$

3 Nondimensionalization analysis

We nondimensionalize the equations by introducing the dimensionless quantities

$$\begin{aligned} &e = \frac{[E]}{e_0}, && c_1 = \frac{[ES_1]}{e_0}, && c_2 = \frac{[ES_2]}{e_0}, && c_3 = \frac{[ES_1S_2]}{e_0}, \\ &s_1 = \frac{[S_1]}{s_{10}}, && p_1 = \frac{[P_1]}{s_{10}}, && s_2 = \frac{[S_2]}{s_{20}}, && p_2 = \frac{[P_2]}{s_{20}}, \\ &\tau = e_0 k_1 t, \end{aligned}$$

to obtain the dimensionless equations

$$\frac{ds_1}{d\tau} = \hat{k}_{-1}(c_1 + c_3) - (1 - c_1 - c_3)s_1, \tag{3.1a}$$

$$\delta\frac{ds_2}{d\tau} = \hat{k}_{-2}(c_2 + c_3) - (1 - c_2 - c_3)\delta\hat{k}_2 s_2, \tag{3.1b}$$

$$\epsilon\frac{dc_1}{d\tau} = (1 - c_2 - c_3)s_1 + \hat{k}_{-2}c_3 - \left(s_1 + \hat{k}_{-1} + \delta\hat{k}_2 s_2\right)c_1, \tag{3.1c}$$

$$\epsilon\frac{dc_2}{d\tau} = (1 - c_1 - c_3)\delta\hat{k}_2 s_2 + \hat{k}_{-1}c_3 - (s_1 + \hat{k}_{-2} + \delta\hat{k}_2 s_2)c_2, \tag{3.1d}$$

$$\epsilon\frac{dc_3}{d\tau} = \delta\hat{k}_2 c_1 s_2 + c_2 s_1 - (\hat{k}_{-2} + \hat{k}_{-1} + \hat{k}_0)c_3, \tag{3.1e}$$

$$\frac{dp_1}{d\tau} = \hat{k}_0 c_3, \tag{3.1f}$$

$$\delta\frac{dp_2}{d\tau} = \hat{k}_0 c_3, \tag{3.1g}$$

where

$$\epsilon = \frac{e_0}{s_{10}}, \qquad \delta = \frac{s_{20}}{s_{10}}, \qquad \hat{k}_0 = \frac{k_0}{k_1 s_{10}},$$
$$\hat{k}_{-1} = \frac{k_{-1}}{k_1 s_{10}}, \qquad \hat{k}_2 = \frac{k_2}{k_1}, \qquad \hat{k}_{-2} = \frac{k_{-2}}{k_1 s_{10}}.$$

We have omitted the equation for e here since this can be determined from the dimensionless form for (2.5), given by

$$e + c_1 + c_2 + c_3 = 1.$$

It should be noted that the initial concentration s_{10} is assumed to be less than the s_{20} without loss of generality.

Under typical conditions, the initial concentration of substrates are much larger than the enzyme concentration, so that $e_0 \ll s_{10}$, or $\varepsilon \ll 1$. Taking the limit $\varepsilon \to 0$ in the equations (3.1), we obtain at leading order that (for $\tau = O(1)$)

$$c_3 = \delta \hat{k}_2 s_1 s_2 \frac{\alpha}{\beta + \gamma + \varphi},$$

where

$$\alpha = s_1 + \hat{k}_{-1} + \hat{k}_{-2} + \delta \hat{k}_2 s_2,$$
$$\beta = (s_1 + \hat{k}_{-1} + \hat{k}_0)\delta \hat{k}_2 s_2 (\hat{k}_{-2} + \delta \hat{k}_2 s_2),$$
$$\gamma = (\delta \hat{k}_2 s_2 + \hat{k}_{-2} + \hat{k}_0) s_1 (s_1 + \hat{k}_{-1}),$$
$$\varphi = (\hat{k}_{-2} + \hat{k}_{-1} + \hat{k}_0)(s_1 + \hat{k}_{-1})(\hat{k}_{-2} + \delta \hat{k}_2 s_2).$$

Substituting these expressions into (3.1f) gives

$$\frac{dp_1}{d\tau} = \hat{k}_0 \delta \hat{k}_2 s_1 s_2 \frac{\alpha}{\beta + \gamma + \varphi}, \tag{3.2}$$

and reverting to dimensional variables gives

$$v = \frac{d[P_1]}{dt} = s_{10} e_0 k_1 \frac{dp_1}{d\tau},$$

which leads to

$$v = \frac{d[P_1]}{dt} = V_{\max} \frac{\mu}{\sigma + \psi + \omega}, \tag{3.3}$$

where

$$\mu = k_1 k_2 [S_1][S_2](k_1[S_1] + k_2[S_2] + k_{-1} + k_{-2}),$$
$$\sigma = (k_1[S_1] + k_{-1} + k_0) k_2 [S_2](k_2[S_2] + k_{-2}),$$
$$\psi = (k_2[S_2] + k_{-2} + k_0) k_1 [S_1](k_1[S_1] + k_{-1}),$$
$$\omega = (k_{-2} + k_{-1} + k_0)(k_1[S_1] + k_{-1})(k_2[S_2] + k_{-2}),$$

and $V_{\max} = k_0 e_0$ is the maximal velocity of product formation.

Letting $[S_2] \to \infty$ in (3.3) gives

$$v \to V_{\max} \frac{[S_1]}{[S_1] + K_{M,S_1}}, \tag{3.4}$$

where $K_{M,S_1} = (k_{-1} + k_0)/k_1$ is the Michealis-Menten constant of enzyme for the substrate S_1. The right-hand site expression is the well-known formula of velocity of product formation for univariate enzyme reaction [18, 22].

The surface shown in Figure 4 illustrates the product formation rate of enzyme. It is seen that the higher the initial concentrations of substrates are, the higher the rate of product formation is. However, if the initial concentrations of substrates are sufficiently high, the rate of product formation approaches the maximal rate $V_{\max}$, which is consistent with the formula (3.4) for sufficiently high $[S_1]$.

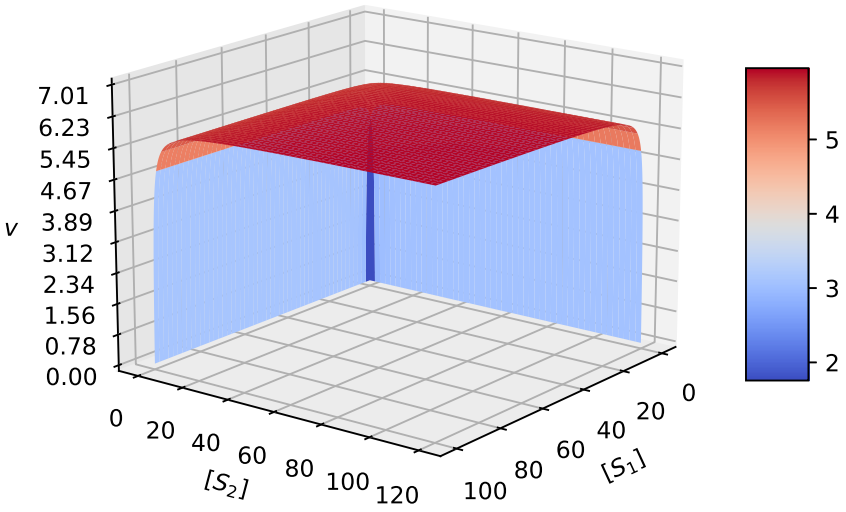

Figure 4: Plot of product formation rate as a function of $[S_1]$ and $[S_2]$ as given by equation (3.3). The parameter used here are given by $e_0 = 3\ mM$, $k_0 = 2.0\ s^{-1}$, $k_1 = 5.0\ mM^{-1}s^{-1}$, $k_{-1} = 0.1\ s^{-1}$, $k_2 = 4.0\ mM^{-1}s^{-1}$, $k_{-2} = 0.2\ s^{-1}$, and $V_{\max} = 6\ mMs^{-1}$.

4 Numerical solutions

The system of differential equations was numerically integrated using the `odeint` solver, the SciPy, and Numpy libraries. SciPy is an open source Python library that contains numerical routines for applications in science and engineering. The numerical solutions of the model were visualized by the `matplotlib` library. The initial conditions used here are given by

$$
\begin{aligned}
&[E](t=0) = 3.0\ mM, && [S_1](t=0) = 5.0\ mM,\\
&[S_2](t=0) = 6.0\ mM, && [ES_1](t=0) = 0.0\ mM,\\
&[ES_2](t=0) = 0.0\ mM, && [ES_1S_2](t=0) = 0.0\ mM,\\
&[P_1](t=0) = 0.0\ mM, && [P_2](t=0) = 0.0\ mM,
\end{aligned}
$$

and the values of model parameters are set as follows

$$\begin{aligned} &k_0 = 2.0\ s^{-1}, \\ &k_1 = 5.0\ mM^{-1}s^{-1}, \quad k_{-1} = 0.1\ s^{-1}, \\ &k_2 = 4.0\ mM^{-1}s^{-1}, \quad k_{-2} = 0.2\ s^{-1}. \end{aligned}$$

In Figure 5, we plot the numerical solutions of the model corresponding to the initial conditions and the parameter values aforementioned. Each line corresponds to the concentration of one species in the mixture with respect to time t. Below, we give some discussions on these numerical results.

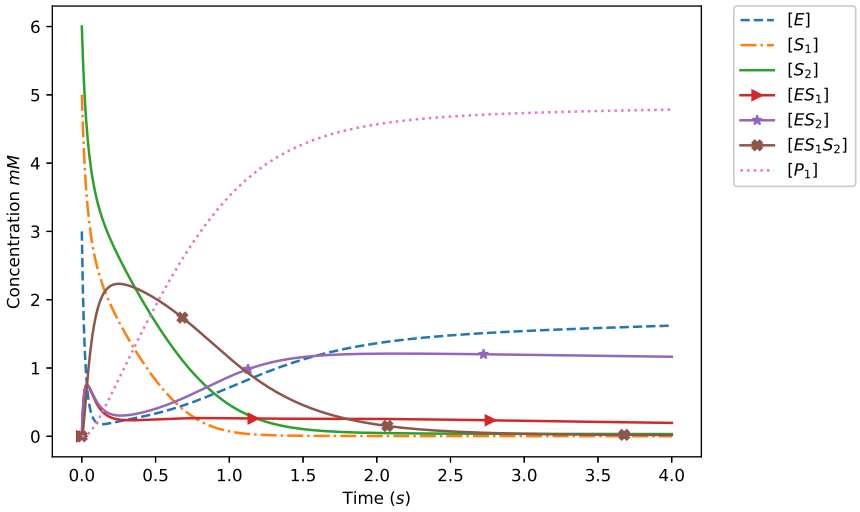

Figure 5: Numerical solutions of the model. Each line represents the concentration of one species in the mixture with respect to t. The values of model parameters are referred to the main text.

- The line ----- represents the concentration of enzyme during the process. In the first stage, the concentration of enzyme drops rapidly due to the binding of substrates to form substrate-enzyme complexes ES_1 and ES_2. As time goes on, the substrates-enzyme complex appears and the enzyme converts the substrates to the products. This reduces the concentrations of the substrates and makes the increase in the concentrations of products continuously. The concentration of the enzyme goes up and reaches a steady level at the end of the process. It should be noted that the steady concentration of the enzyme is lower than its initial concentration since the concentration of S_2 is not depleted.
- The line -·-·- describes the concentration of the substrate S_1. The concentration decreases rapidly and tends to be depleted at the end of the process. This happens because the substrate is completely converted to the product P_1.
- The line ——— displays to the concentration of the substrate S_2. It can be seen that the concentration goes down rapidly in the early stage because of the binding of the substrate to the enzyme. In the end, the concentration of the substrate goes to a steady level. This is because the concentration of S_2 is greater than that of S_1 and once the substrate S_1 is depleted, the enzyme can not convert S_2 to the product P_2.
- The line —▶— describes the concentration of the substrate-enzyme complex ES_1. The concentration increases rapidly and drops down quickly then.This agrees with the nature of the process. That is the substrate S_1 quickly binds to free enzyme molecules to form the substrate-enzyme complex ES_1. Then the substrate S_2 molecules bind to these complexes

to form complexes ES_1S_2, or the substrate molecule S_1 unbind from the complex ES_1. We can see that the concentration of ES_1 tends to zero since the substrate S_1 is completely converted to the product P_1 in the end.

- The line corresponds to the concentration of ES_2. The concentration goes up rapidly and goes down quickly then. In the end, the concentration reaches a steady level. It is clear that the concentration is lower than the initial concentration of the substrate S_2. This is in line with the nature of the process since the concentration of S_2 is higher than that of S_1.
- The line represents the concentration of the complex ES_1S_2. The rapid increase in the concentration is due to the binding of the substrates S_1 and S_2 to the enzyme E to form the substrates-enzyme complex ES_1S_2. The concentration, then, quickly decreases because the enzyme catalyzes the complex to form the products P_1 and P_2, and release them later. The concentration goes to zero at the end of the process since the substrate S_1 is completely converted to the product P_1.
- The line shows the concentration of the product P_1. At the early stage, the rapid increase in the concentration is due to the enzyme catalyzing the complex ES_1S_2 to form the products P_1 and P_2. The concentration approaches that of S_1 at the end of the process since the substrate S_1 is completely catalyzed to the product P_1. This is in line with the fact that the conversion of the complex ES_1ES_2 to the products P_1 and P_2 is an irreversible reaction.

Note that the concentration of P_2 is the same as that of P_1. So we omitted it here.

5 Model and glucose phosphorylation by glucokinase

Here, we shall consider a potential application of the model to a real system. The system is the phosphorylation of glucose by the enzyme *Hexokinase IV* which is the first step of the glucose glycolysis.

The production of energy in a cell is achieved via glucose glycolysis in which the first step is the transformation of glucose into glucose-6-phosphate. This is the phosphorylation of glucose that is catalyzed by an enzyme called *hexokinase*. Four isozymes of hexokinase are found in mammalian tissue [8, 21], and these are usually referred to as *hexokinase I*, *II*, *III*, and *IV* (*glucokinase*).

The model we have just developed may be applicable to a *glucokinase* system. The *glucokinase* molecule in question is a *glucokinase* enzyme molecule with two binding sites, one for ATP and another for glucose. The products of the phosphorylation are ADP and glucose-6-phosphate. The enzyme obeys a Bi-Bi random mechanism [6, 13, 16, 24, 25].

To successfully model the phosphorylation of glucose catalyzed by the enzyme, the mixture of species has to satisfy the model assumptions. Then, the glucokinase enzyme plays the role of the enzyme E in the model. The reactant ATP is the substrate S_1; glucose (G) corresponds to the substrate S_2; E^{ATP}, E_G, and E_G^{ATP} are ES_1, ES_2, and ES_1S_2 complexes, respectively. The products P_1 and P_2 are ADP and glucose-6-phosphate, respectively.

6 Conclusions

In this paper, we have developed a mathematical model for the enzymatic reactions with Bi-Bi random mechanism. Using nondimensionalization analysis, a formula of the rate of product formation was formulated in a transparent manner. The model behaviors were investigated using Python software to numerically integrate the model. Furthermore, the model was seen to model the phosphorylation of glucose by *glucokinase*. This application may show the model may

be applicable for realistic enzymes.

Although the mathematical model in the current study is detailed, there is scope for improvement and future work. For example, one avenue for future research is to analyze the equilibrium and stability of the model. Also, the model may be potentially solved by using the Lie algebra method [19], and the analytical solutions of the model may be helpful in estimating the model parameters. This provides another interesting topic for future study. For biological systems, model parameters are often time-dependent, so the analytical solutions of the model are of importance for unpicking the behavior insights of the system [20].

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Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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