Applying singular perturbation to the stochastic model of the Michaelis-Menten mechanism

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Abstract: We apply singular perturbation to the chemical master equation of the Michaelis-Menten mechanism. Singular perturbation is used to simplify the model and derive a lower dimensional approximation.

Keywords: *Michaelis-Menten mechanism, chemical master equation, singular perturbation method*

1 Introduction

Enzymatic reactions in intracellular environments are always faster than other protein interactions. Such biological systems exhibit dynamical stiffness as they have rate constants that vary several orders of magnitudes which result in different dynamics over different time scales. One of the most well-known enzymatic reactions is the so-called Michaelis-Menten (MM) mechanism [1, 2, 3] which is an irreversible conversion of the substrate, S, into a product, D, through the formation of an intermediate species named complex, C, catalyzed by the enzyme, E. This mechanism which exists in a closed and finite system is formed by three basic reactions:

$$E + S \underset{\kappa_{-1}}{\overset{\kappa_1}{\rightleftharpoons}} C \xrightarrow{\kappa_2} E + D \tag{1}$$
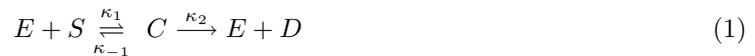
Here, κ_1, κ_2 and κ_{-1} are the forward and backward rate constants which show the description of reactions' kinetics. Furthermore, the MM constant which governs the reactions is defined as $\kappa_m = \frac{\kappa_{-1} + \kappa_2}{\kappa_1}$. In this paper, we specifically assume: (1) the values of κ_2 and κ_{-1} are always much larger than κ_1 in the system such that the parameter $\frac{1}{\kappa_m}$ always less than a small parameter ϵ (which will be defined in section (2)); (2) the number of molecules of the substrate, x_1, is always much smaller than κ_m. Therefore, we know that the population of C is small at any time in the system.

We rename the four molecular species, S, C, E and D in the MM mechanism as S_1, S_2, S_3 and S_4 respectively and let x_i, for $i = 1, ..., 4$, be random variables which denote the number of S_i molecules in the system. Since the system is closed, one has the following mass conservation laws:

$$x_{e_0} = x_2 + x_3 \quad \text{and} \quad x_{s_0} = x_1 + x_2 + x_4$$

where the system initially have x_{e_0} copies of enzyme, x_{s_0} copies of the substrate and zero copy of complex or product. Hence, it is sufficient to include x_1 and x_2 only in the modelling.

As a consequence, we can represent the dynamics of species S_1 and S_2 in a stochastic model with the so-called chemical master equation (CME):

$$\begin{aligned}
\frac{dP(x_1, x_2; t)}{dt} &= \sum_{j \in M_1} \alpha_j(x_1 - v_j^1, x_2) P(x_1 - v_j^1, x_2; t) - \alpha_j(x_1, x_2) P(x_1, x_2; t) \\
&+ \sum_{j \in M_2} \beta_j(x_1, x_2 - v_j^2) P(x_1, x_2 - v_j^2; t) - \beta_j(x_1, x_2) P(x_1, x_2; t) \\
&= ((A_1 + A_2)P)(x_1, x_2; t).
\end{aligned} \tag{2}$$

The formulation of this CME (2) is different with the standard modelling which based on the reactions (1) directly. Here, we redefine the reactions in MM mechanism according to the molecular species, that is, $M_1 = \{r_1, r_2\}$ is the set of reactions involving the substrate where

    i. $r_1 : S_1 \to \emptyset$ represents the decay of S_1 with propensity function $\alpha_1(x_1, x_2) = \kappa_1(x_{e_0} - x_2)x_1$, and

ii. $r_2 : \emptyset \to S_1$ is the production of S_1 with propensity function $\alpha_2(x_1, x_2) = \kappa_{-1} x_2$.

The set $M_2 = \{r_3, r_4\}$, on the other hand, is the set of reactions involving the complex, that is,

i. $r_3 : S_2 \to \emptyset$ is the decay of S_2 with propensity function $\beta_1(x_1, x_2) = (\kappa_2 + \kappa_{-1}) x_2$, and

ii. $r_4 : \emptyset \to S_2$ is the production of S_2 with propensity function $\beta_2(x_1, x_2) = \kappa_1(x_{e_0} - x_2) x_1$.

The stoichiometric vector v_j^i which associated with these propensity functions defines the way the state changes when the reaction occurs. In summary, we assume that the reactions involving both the fast and slow species can be treated separately. We conjecture that this model is an accurate description of the chemistry in many cases. In particular one can show that the expectations are preserved.

Here, we classify the chemical species in the system into two distinct subgroups: the fast and the slow species. We define the fast species to be any species whose molecular level always approach a stable value in a rate faster than all other species; Slow species, on the contrary, is any species which evolves slowly to its stationary state. Mathematically, we look to the eigenvalues of propensity matrices to recognize the characteristic of each species. For species S_i whose propensity matrix A_i possesses larger eigenvalues than other species is classified as fast species, and vice versa. Hence, complex which involving in reactions with larger propensities (that contribute to the larger eigenvalues in its propensity matrix) is the fast species; The substrate, on the contrary, is the slow species in the MM mechanism.

2 Singular perturbation method

As the MM mechanism involves two time scales with rate constants that vary several order of magnitudes, the fraction of the propensities of slow and fast species is expected to be of order $O\left(\frac{1}{\epsilon}\right)$ for $\epsilon \in (0, 1)$. Segel et al. [5] has defined this small parameter as

$$\epsilon = \frac{x_{e_0}}{x_{s_0} + \kappa_m}. \tag{3}$$

This system is singularly perturbed that the solution cannot be approximated by simply setting the parameter $\epsilon = 0$ as the formulation for regular perturbation problem. The boundary layer phenomenon exists here so that the approximation fails in a short interval of time at the beginning. In dealing with such cases, the problem domain is divided into two subdomains. In one of these domains (outer region, $t > 0$), the solution can be approximated by setting the parameter $\epsilon = 0$. The other domain where the approximation fails near $t = 0^+$, a new time variable τ is introduced to enlarge the boundary layer of $O(\epsilon)$ thickness into semi-infinite interval $\tau > 0$ and thus disclosing the boundary layer jump in this domain [4]. The solution in the boundary layer can then be well approximated by treating the newly formulated problem as a regular perturbation problem. Finally, an approximated solution for the whole domain of the system is yielded by matching both set of solutions at the edge of boundary layer.

2.1 Outer solution

In order to see the clear appearance of the small parameter ϵ in the CME, we introduce a scaled variable $T = \frac{t}{t_s}$ by defining a slow timescale $t_s = \frac{x_{s_0} + \kappa_m}{\kappa_2 x_{e_0}}$ for the decay of substrate in the outer region [5]. Then, by using the chain rule, equation (2) is reformulated as

$$
\begin{aligned}
\frac{d\hat{P}(x_1, x_2; T)}{dT} &= \sum_{j \in M_1} \hat{\alpha}_j(x_1 - v_j^1, x_2) \hat{P}(x_1 - v_j^1, x_2; T) - \hat{\alpha}_j(x_1, x_2) \hat{P}(x_1, x_2; T) \\
&+ \frac{1}{\epsilon} \sum_{j \in M_2} \hat{\beta}_j(x_1, x_2 - v_j^2) \hat{P}(x_1, x_2 - v_j^2; T) - \hat{\beta}_j(x_1, x_2) \hat{P}(x_1, x_2; T)
\end{aligned}
\tag{4}
$$

where the propensity functions are $\hat{\alpha}_1 = \frac{\kappa_1 (x_{s_0} + \kappa_m)(x_{e_0} - x_2) x_1}{\kappa_2 x_{e_0}}$, $\hat{\alpha}_2 = \frac{\kappa_{-1}(x_{s_0} + \kappa_m) x_2}{\kappa_2 x_{e_0}}$, $\hat{\beta}_1 = \frac{(\kappa_2 + \kappa_{-1}) x_2}{\kappa_2}$ and $\hat{\beta}_2 = \frac{\kappa_1(x_{e_0} - x_2) x_1}{\kappa_2}$ with the reaction's stoichiometric vectors $v_1^1 = [-1, 0]^T$, $v_2^1 = [1, 0]^T$, $v_1^2 = [0, -1]^T$ and $v_2^2 = [0, 1]^T$.

As $\epsilon \to 0$, the CME (4) degenerates to

$$\tilde{A}_2(x_1)\tilde{P}(\cdot|x_1) = 0, \tag{5}$$

where the propensity function of $\tilde{A}_2$ is $\hat{\beta}_j(x_1, x_2)$ at fixed x_1 for $j \geq 1$. This means the probability distribution of the complex, $\tilde{P}(x_2|x_1)$ is approximated by a stationary distribution in the outer region. Therefore, the reactions of the substrate will be the major concern in this domain. Summing equation (4) over x_1, we obtain the following CME solely in terms of x_1:

$$\frac{d\tilde{P}(x_1; T)}{dT} = \sum_{j \in M_1} \gamma_j(x_1 - v_j^1)\tilde{P}(x_1 - v_j^1; T)\gamma_j(x_1)\tilde{P}(x_1; T) \tag{6}$$

with the propensity function

$$\begin{aligned} \gamma_j(x_1) &= \sum_{x_2} \hat{\alpha}_j(x_1, x_2)\hat{P}(x_1, x_2; T) \\ &\approx \hat{\alpha}_j(x_1, \hat{E}[x_2|x_1]). \end{aligned} \tag{7}$$

The functional $\gamma_j(x_1)$ in (7) is the conditional expectation of the functional $\hat{\alpha}_j(x_1, x_2)$ where the expected value $\hat{E}[x_2|x_1]$ can be found from equation (5). This system is known as reduced or degenerate system where the CME (6) has lower dimension in comparison to the original system (4). Here, we use $\tilde{P}$ instead of $\hat{P}$ to show that the subsystems (5) and (6) which derived when $\epsilon = 0$ is different from the original perturbed stochastic system (4).

2.2 Inner solution

The solution obtained via the reduced system is incorrect when $t \approx 0$, thus a scaled time variable $\tau = \frac{t}{t_c}$ is introduced to magnify the boundary layer and study the singular limit as $\epsilon \to 0$. By modifying the fast timescale t_c suggested by Segel et al. [5], t_c is set as

$$t_c = \frac{1}{\kappa_1 (x_{s_0} + \kappa_m)}.$$

Subsequently, an equivalent form of CME (2) can be expressed in the τ term as:

$$\begin{aligned} \frac{d\check{P}(x_1, x_2; \tau)}{d\tau} = {}&\epsilon \sum_{j \in M_1} \check{\alpha}_j(x_1 - v_j^1, x_2)\check{P}(x_1 - v_j^1, x_2; \tau) - \check{\alpha}_j(x_1, x_2)\check{P}(x_1, x_2; \tau) \\ &+ \sum_{j \in M_2} \check{\beta}_j(x_1, x_2 - v_j^2)\check{P}(x_1, x_2 - v_j^2; \tau) - \check{\beta}_j(x_1, x_2)\check{P}(x_1, x_2; \tau) \end{aligned} \tag{8}$$

where the propensities functions are $\check{\alpha}_1 = \frac{(x_{e_0} - x_2)x_1}{x_{e_0}}$, $\check{\alpha}_2 = \frac{\kappa_{-1}x_2}{\kappa_1 x_{e_0}}$, $\check{\beta}_1 = \frac{\kappa_m x_2}{x_{s_0} + \kappa_m}$ and $\check{\beta}_2 = \frac{(x_{e_0} - x_2)x_1}{x_{s_0} + \kappa_m}$.

This CME (8) can be treated as common regular perturbation problem, that is, as $\epsilon \to 0$, the first term of the right hand side of equation (8) is omitted, so the CME has a simpler form

$$\frac{d\bar{P}(x_1, x_2; \tau)}{d\tau} = \sum_{j \in M_2} \check{\beta}_j(x_1, x_2 - v_j^2)\bar{P}(x_1, x_2 - v_j^2; \tau) - \check{\beta}_j(x_1, x_2)\bar{P}(x_1, x_2; \tau) \tag{9}$$

with fixed $x_1 = x_{s_0}$ as

$$\frac{d\check{P}(x_1; \tau)}{d\tau} = 0$$

when $\epsilon = 0$, so the molecular level of x_1 will always remain at the initial level, x_{s_0}.

Here, we use $\bar{P}(x_1, x_2; \tau)$ to replace the $\check{P}(x_1, x_2; \tau)$ in order to show the difference between the probability distributions of perturbed (8) and unperturbed (9) systems.
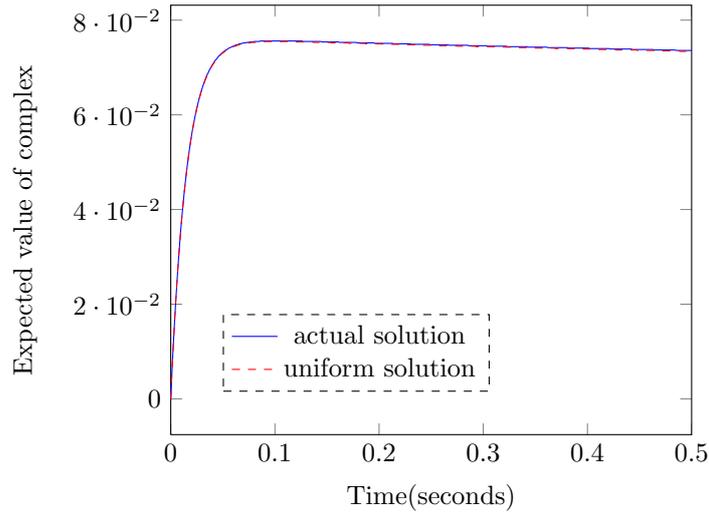
Figure 1: The computed expected value of complex with $E_0 = 10$, $S_0 = 50$, $\kappa_1 = 0.01$, $\kappa_2 = 30$ and $\kappa_{-1} = 35$.
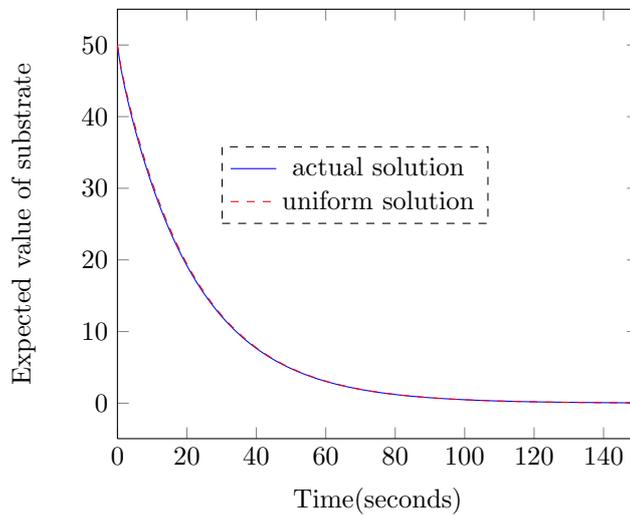

Figure 2: The computed expected value of substrate with $E_0 = 10$, $S_0 = 50$, $\kappa_1 = 0.01$, $\kappa_2 = 30$ and $\kappa_{-1} = 35$.

2.3 Matching and uniform approximation

We compute the expected values of complex and substrate in both inner and outer regions, we conjecture that these solutions have a unique common limit at the edge of boundary layer. Consider now $\epsilon \to 0$, $\tau \to \infty$ and $T \to 0$ respectively, the common limit of the inner and outer solutions is defined as

$$\lim_{\epsilon \to 0}[\tilde{E}[X_i; T]|_{T=0}] = \lim_{\epsilon \to 0}[\check{E}[X_i; \tau]|_{\tau=\infty}] = \omega$$

for $i = 1, 2$ and some positive constant ω. In other words, the inner and outer solutions are matched if in the limit of $\epsilon \to 0$, the expected value in inner region as $\tau \to \infty$ is equal to the expected value in outer region as $T \to 0$.

Finally, add the inner and outer solutions together and subtract their common limit:

$$u\left(E[X_i; t]\right) = \tilde{E}[X_i; t/t_s] + \check{E}[X_i; t/t_c] - \omega$$

This is the so-called uniform approximation for singular perturbation method which would be valid throughout the time $t \in [0, t_{end}]$.

3 Discussion

The CME in this paper is formulated based on a conjecture that the reactions involving both the fast and slow species can be treated separately. The MM system is computed in two approaches: (1) solve the CME (2), and (2) apply singular perturbation method to the stochastic model and solve the lower dimensional CMEs. The singular perturbation method has provided a good approximation to the multiple time scales system as shown in the Figure 1 and Figure 2 where the maximum relative error for the expected values of complex and substrate are 0.002 and 0.01 respectively. The singular perturbation method is very promising that by splitting the problem domain according to the different time scales and applying perturbation techniques to each subdomain, the computations on lower dimension CMEs in the subdomains allow us to deal with higher dimensional stochastic problems.

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