

A note on the kinetics of suicide substrates

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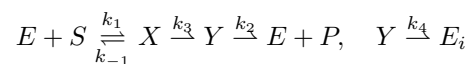
Abstract

We determine the limit sets of a system modelling suicide substrate kinetics, and show that a result by Tatsunami et al., derived under additional quasi-steady state assumptions, holds generally.

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1 Introduction

A system of biochemical reactions is called a suicide substrate system if it involves a substrate capable of inactivating the enzyme. Suicide substrates are of interest because they make inactivation of specific enzymes possible. The suicide substrate mechanism to be investigated in the present note involves substrate S , enzyme E , intermediate complexes X , Y , inactivated complex E_i and product P . The reaction scheme is as follows.



This system is a modification of the Michaelis-Menten system (see Michaelis and Menten [5], Segel and Slemrod [7], Heinrich and Schuster [4]). There are two complexes, viz. enzyme-substrate complex X and enzyme-product complex Y , and formation of the second complex as well as formation of product is irreversible. Moreover, the enzyme-product complex may change irreversibly

into an inert state E_i . Mass action kinetics and stoichiometry lead to the four-dimensional differential equation

$$(1) \quad \begin{aligned} \dot{s} &= -k_1(e_0 - x - y - e_i)s + k_{-1}x \\ \dot{x} &= k_1(e_0 - x - y - e_i)s - (k_{-1} + k_2)x \\ \dot{y} &= k_2x - (k_3 + k_4)y \\ \dot{e}_i &= k_4y \end{aligned}$$

with relevant initial conditions $s(0) = s_0 > 0$, $x(0) = y(0) = e_i(0) = 0$ (and $e(0) = e_0 > 0$, $p(0) = 0$). This system was discussed, among others, by Waley [9], Tatsunami et al. [8], and Burke et al. [2]. The biologically relevant questions are: Will all of the substrate be converted in the process, and will all of the enzyme be inactivated? Tatsunami et al. assumed quasi-steady state for both complexes X and Y , and then applied the customary QSS reduction method to obtain a two-dimensional system. They concluded that under this condition all of the substrate will be converted if and only if

$$(2) \quad k_4s_0 \leq (k_3 + k_4)e_0,$$

while all enzyme will be inactivated if and only if the reverse inequality holds. Burke et al. employed a more intricate analysis, involving scaling procedures and discussed the short-time and long-time dynamics of the system under the assumption of a small parameter introduced by Segel and Slemrod [7]. Essentially the same derivation is also presented in Murray [6], Subsection 6.4.

In the present note we will show that the result by Tatsunami et al. [8] holds true without any quasi-steady state hypothesis, and without invoking any assumption on small parameters. The main result will be stated precisely in the following section, and the proof will be given in the Appendix.

2 Main result

The crucial observation is that the four-dimensional system (1) admits the linear first integral

$$\phi = s + x + y + \frac{k_3 + k_4}{k_4}e_i,$$

as is easily verified. This first integral is not induced by stoichiometry and seemingly was not noticed in [8], [2] and [6]. Thus one obtains reduction to a three-dimensional system

$$(3) \quad \begin{aligned} \dot{s} &= -k_1\left(e_0 - x - y - \frac{k_4}{k_3+k_4}(s_0 - s - x - y)\right)s + k_{-1}x \\ \dot{x} &= k_1\left(e_0 - x - y - \frac{k_4}{k_3+k_4}(s_0 - s - x - y)\right)s - (k_{-1} + k_2)x \\ \dot{y} &= k_2x - (k_3 + k_4)y. \end{aligned}$$

For this system singular perturbation methods do not seem helpful and actually their applicability seems questionable (see the arguments in [3]). However, a qualitative analysis will provide a complete understanding of the system's long-time behavior.

Theorem 1. (a) *System (3) always admits the stationary point $P_1 = (0, 0, 0)$ in the positive orthant $\mathbb{P} = \{(s, x, y) : s \geq 0, x \geq 0, y \geq 0\}$. There is a second stationary point in \mathbb{P} , viz. $P_2 = (s_0 - \frac{k_3+k_4}{k_4}e_0, 0, 0)$ if and only if condition (2) does not hold.*

(b) *Every solution starting in \mathbb{P} converges to P_1 as $t \rightarrow \infty$ if and only if condition (2) is satisfied.*

If $k_4s_0 > (k_3 + k_4)e_0$ then every solution starting in \mathbb{P} but not on the line $Z := \{(s, x, y) : s = x = 0\}$ converges to P_2 as $t \rightarrow \infty$. Solutions starting on Z converge to P_1 as $t \rightarrow \infty$.

We briefly note the biological interpretation: Our analysis supports the conclusion of Tatsunami et al. [8]: All substrate is converted (thus $s \rightarrow 0$ as $t \rightarrow \infty$) if and only if $k_4s_0 \leq (k_3 + k_4)e_0$. In this case $e_i \rightarrow \frac{k_4}{k_3+k_4}s_0$ as $t \rightarrow \infty$. On the other hand, all enzyme is transformed to inert state (thus $e_i \rightarrow e_0$ as $t \rightarrow \infty$) if and only if $k_4s_0 \geq (k_3 + k_4)e_0$, and in this case $s \rightarrow s_0 - \frac{k_3+k_4}{k_4}e_0$ as $t \rightarrow \infty$. However, we show that this result holds for arbitrary rate constants and initial concentrations, without any quasi-steady state assumptions or restrictions. Therefore it reflects a universal property of the reaction scheme.

One should clarify why the analysis by Tatsunami et al. [8] arrives at the same result. This is due to the correspondence between stationary points of the full system and of the reduced system in [8], which is a general feature of the standard QSS reduction method. In the particular scenario under consideration there is also a simultaneous stability exchange for stationary points in the full and the reduced system.

3 Appendix: Proof

(i) Part (a) follows from a straightforward computation.

(ii) The limit sets of system (3) in the positive orthant \mathbb{P} can be determined from the following observation: The function $\psi(s, x, y) := s + x + y$ has Lie derivative (orbital derivative) equal to $-(k_3 + k_4)y$, and therefore ψ is a Lyapunov function on the positive orthant. This shows that solutions are confined to compact sets

$$\{(s, x, y) \in \mathbb{P} : \psi(s, x, y) \leq \text{const.}\}$$

and in particular all limit sets in \mathbb{P} are nonempty and connected. By LaSalle's criterion (see e.g. Amann [1], Theorem 18.3 and Corollary 18.4), all limit sets are contained in the subset Y given by $y = 0$. Next we use the fact that limit sets are also invariant sets, and consider solutions

$$\begin{pmatrix} \sigma(t) \\ \xi(t) \\ 0 \end{pmatrix}$$

of (3) that remain in Y for all t . Substitution into the third entry of the

differential equation yields $\xi = 0$, and furthermore $\dot{\xi} = 0$ implies the identity

$$k_1 \left(e_0 \frac{k_4}{k_3 + k_4} (s_0 - \sigma(t)) \right) \cdot \sigma(t) = 0.$$

Therefore σ is constant and equal to the entry of a stationary point in \mathbb{P} . By connectedness, every limit set is either equal to $\{P_1\}$ or to $\{P_2\}$, and this implies that every solution converges to a stationary point. If condition (2) holds then P_1 is the only stationary point in \mathbb{P} , and therefore every solution in \mathbb{P} converges to P_1 .

(iii) We assume from now on that (2) does not hold, and investigate the stability of P_1 . The Jacobian at P_1 is given by

$$\begin{pmatrix} \alpha & k_{-1} & 0 \\ -\alpha & -(k_{-1} + k_2) & 0 \\ 0 & k_2 & -(k_3 + k_4) \end{pmatrix}$$

with $\alpha := -k_1 e_0 + \frac{k_1 k_4}{k_3 + k_4} s_0 > 0$, since (2) does not hold. The negative eigenvalue $-(k_3 + k_4)$ of this matrix can be read off directly; the corresponding eigenspace is just the axis Z . There remain the eigenvalues of

$$B := \begin{pmatrix} \alpha & k_{-1} \\ -\alpha & -(k_{-1} + k_2) \end{pmatrix}$$

with $\alpha > 0$. Since the determinant of B is negative, B has real eigenvalues of opposite signs. Let β be the negative eigenvalue of B , and

$$v = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix}$$

a corresponding eigenvector of the Jacobian. Then the equations

$$\begin{pmatrix} \alpha & k_{-1} \\ -\alpha & -(k_{-1} + k_2) \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \beta \begin{pmatrix} v_1 \\ v_2 \end{pmatrix}$$

show that v_1 and v_2 are both nonzero and have different signs. To summarize: The stable subspace W of the Jacobian at P_1 has dimension two and is spanned by

$$\begin{pmatrix} v_1 \\ v_2 \\ 0 \end{pmatrix} \text{ and } \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}.$$

(iv) By the stable manifold theorem (see e.g. Amann [1], Proposition 19.10 and Theorem 19.11), there is a neighborhood \tilde{U} of 0 in \mathbb{R}^3 and a two-dimensional submanifold $M \subseteq \tilde{U}$ with $0 \in M$, tangent to W in 0, with the property that every solution converging to P_1 as $t \rightarrow \infty$ has non-empty intersection with M . Since the axis Z defined by $s = x = 0$ is obviously an invariant set of (3), and every solution starting on Z converges to P_1 as $t \rightarrow \infty$, this axis is contained

both in W and (locally) in M . Moreover one has $W \cap \mathbb{P} = Z$, since v_1 and v_2 have different signs. Now an elementary argument shows that there is a neighborhood $U \subseteq \bar{U}$ of 0 such that

$$U \cap M \cap \mathbb{P} = Z \cap U.$$

(v) From (iv) one sees that every solution in \mathbb{P} which converges to P_1 as $t \rightarrow \infty$ is contained in the axis Z . Since every solution in $\mathbb{P} \setminus Z$ converges to some stationary point, the only remaining possibility is convergence to P_2 , as asserted.

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