International Electronic Journal of Pure and Applied Mathematics

Volume 6 No. 1 2013, 31-40
ISSN: 1314-0744
url: http://www.e.ijpam.eu
doi: http://dx.doi.org/10.12732/iejpam.v6i1.2

ON THE EXISTENCE FOR AN ENZYME REACTION MODEL

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Abstract: In this paper we discuss existence for a mathematical model of the enzyme reaction process described by a reaction-diffusion equation under initial and boundary conditions. Some existence conditions which guarantee solvability are considered. A unique exponentially asymptotically stable solution of the considered problem is shown. Uniqueness and ununiqueness are discussed as well.

AMS Subject Classification: 35K20, 35B35, 35K57
Key Words: enzyme kinetics, stability, asymptotically stable solution, uniqueness, ununiqueness, exponentially asymptotically stable solution, steady-state solution

1. Introduction

In this paper we consider a mathematical model in the chemistry concerning dynamics of the enzyme processes. The reaction scheme for free enzyme E and substrate

Received: November 14, 2012

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concentration S can be expressed by

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P \ ,$$

where ES is the enzyme-substrate complex and P is the reaction product (see, e.g. [4], [5], [8], [9]). The constants k_1, k_{-1} and k_2 represent the various rates of reaction.

The rate of change of substrate concentration $S = S(t, x)$ at time t and position x is equal to the sum of the rates due to the reaction and diffusion. Accept further $u = S$. Thus the enzyme dynamics can be described by the parabolic PDE,

$$u_t - \nabla \cdot (D\nabla u) = q(t, x, u), \quad (t, x) \in \mathbb{R}_+ \times \Omega, \tag{1}$$

called also reaction-diffusion equation, with initial and boundary data

$$\begin{aligned} &(a) \quad Bu = h(t, x), \quad t > 0, \quad x \in \partial\Omega, \\ &(b) \quad u(0, x) = u_0(x), \quad x \in \Omega, \end{aligned} \tag{2}$$

respectively, where the boundary condition (2)(a), and the initial condition (2)(b) are given preliminarily. The initial and boundary value problem denote by IBVP for short. Here $B \equiv \alpha_0(x)\partial/\partial\nu + \beta_0(x)$ is referred to as the boundary operator, i.e.

$$\alpha_0(x)\frac{\partial u}{\partial \nu} + \beta_0(x)u = h(t, x), \quad t > 0, \quad x \in \partial\Omega,$$

where Ω is a bounded domain with sufficiently smooth boundary $\partial\Omega$, $\alpha_0 \geq 0$, $\beta_0 \geq 0$, and $\alpha_0 + \beta_0 > 0$ on $\partial\Omega$. The function $D(x)$ is called the diffusion coefficient in the chemical diffusion processes, the term $\nabla \cdot (D\nabla u)$ in (1), represents the rate of change due to the diffusion and $q(t, x, u)$ is the rate of change due to the reaction. The reaction function q is the density per unit volume and per unit time formed through the process of reaction or interaction (see, e.g. [8], [9]).

Assume that the functions α_0, β_0, h are Hölder continuous in $\bar{\Omega}$, $\partial/\partial\nu$ is considered as the outward normal derivative on $\partial\Omega$, and $\nu = \nu(x)$ is a normal vector pointing outward from $x \in \partial\Omega$. Actually the reaction term depends on both S and E.

The reaction process from the substrate S to the product P goes in two steps. The first represents a reversible binding to an enzyme, and the second dissociates the complex ES into the product with release of the enzyme. The reaction diffusion dynamics takes place in a finite dimensional medium Ω. The substrate concentration is governed by (2), and then $q(u) \equiv -\sigma u(1 + au)^{-1}$, where σ and a are positive constants.

If a competitive inhibitor (substrate inhibitor) is taken into account, then a special reaction rate can be described by $q(u) \equiv -\sigma u(1 + au + bu^2)^{-1}$ (σ, a, b are real constants).

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It is known that the uniqueness of a steady-state solution is not always guaranteed (see, e.g. [9]). Our goal is to establish some existence, uniqueness and stability conditions as for this purpose construct some inequalities including the steady states and reaction. The nonuniqueness is discussed as well.

We note that there exist in chemistry mathematical models of different type with delay and whose properties are considered in [8] (see, e.g. [6]).

2. Preliminaries

Let the number $T > 0$ be fixed, and let $\Omega \subset \mathbb{R}^3$ be some domain in the class $C^{2+\alpha}$. Denote by $Q_T \equiv (0,T) \times \Omega$, $\Gamma_T \equiv (0,T) \times \partial\Omega$, $u_t = \partial u/\partial t, u_{x_i} = \partial u/\partial x_i, u_{x_i x_j} = \partial^2 u/\partial x_i \partial x_j$.

Consider the most general IBVP:

$$\begin{aligned} &(a) \quad u_t - Lu = q(u) \quad \text{for } (t,x) \in Q_T, \\ &(b) \quad Bu = h(x) \quad \text{on } \Gamma_T, \\ &(c) \quad u(0,x) = u_0(x) \quad \text{in } \bar{\Omega}, \end{aligned} \tag{3}$$

where the reaction function $q(u) \equiv -\sigma u(1 + au)^{-1}$, $a, \sigma \in \mathbb{R}$, and the operator

$$Lu \equiv \sum_{i,j=1}^{n} a_{ij}(x) u_{x_i x_j} + \sum_{j=1}^{n} b_j(x) u_{x_j}$$

is uniformly elliptic in the sense that the matrix $\{a_{ij}(x)\}$ is positive definite in $\bar{\Omega}$. As an example we can let $Lu = \nabla \cdot (D\nabla u)$ as it is in (1). Assume that the coefficients of L are Hölder continuous in $\bar{\Omega}$. The boundary operator B is defined by $Bu \equiv \partial u/\partial \nu + \beta_0(x)u$, where $\beta_0(x)$ is a nonnegative function in $C^{1+\theta}(\partial\Omega)$ $(0 < \theta < 1)$ and not identically zero on $\partial\Omega$; $\partial/\partial\nu$ is the outward normal derivative on $\partial\Omega$. The functions $u_0(x)$ and $h(x)$ are always assumed to be nonnegative and $u_0 \in C^2(\bar{\Omega})$, $h \in C^{1+\theta}(\partial\Omega)$ $(0 < \theta < 1)$.

The function $u \in C^{1,2}(Q_T)$ is called a solution of IBVP if it satisfies (3).

The function $u \in C^{1,2}(Q_T)$ is called an upper solution of IBVP if

$$\begin{aligned} &(a) \quad u_t - Lu \geq q(u) \quad \text{for } (t,x) \in Q_T \\ &(b) \quad Bu \geq h(x) \quad \text{on } \Gamma_T \\ &(c) \quad u(0,x) \geq u_0(x) \quad \text{in } \bar{\Omega}. \end{aligned}$$

A lower solution is defined analogously by reversing the above inequalities.

The function $u_s(x)$ is called steady-state solution of (3) if it is a solution of the elliptic boundary-value problem:

$$\begin{aligned} -Lu = q(u) \qquad & \text{in } \Omega, \\ Bu = h(x) \qquad & \text{on } \partial\Omega, \end{aligned} \tag{4}$$

where L and B are the same operators as in (3).

There are different mathematical models describing enzyme reaction processes which can be seen in [2], [4], [8], [9]. Some numerical methods in the general cases are offered in [1], [7].

First we consider the enzyme-substrate reaction scheme in case when the effect of inhibition is neglected. Then the Michaelis-Menton hypothesis leads to the IBVP

$$\begin{aligned} &(a)\ \ u_t - D\nabla^2 u = q(u) \quad \text{in } \ Q_T, \\ &(b)\ \ Bu = h(x) \qquad \text{on } \ \Gamma_T, \\ &(c)\ \ u(0,x) = u_0(x) \quad \text{in } \ \Omega, \end{aligned} \tag{5}$$

where $q = -\sigma u(1+au)^{-1}$, a, σ are positive constants. Obviously, $q(0) = 0$ in this case, and $q(u) \leq 0$, $\forall u \geq 0$. Then in accordance with the stated criterion in [8] every positive constant $\rho > 0$ satisfying the conditions

$$q(\rho) \leq 0, \quad \rho \geq \frac{h(t,x)}{\beta_0(x)}, \quad \rho \geq u_0(x) \tag{6}$$

is an upper nonnegative solution of (5) provided that $\beta_0 > 0$ on Γ_T, that is, $\tilde{u} = \rho$. Also if the function q belongs to the class C^1 in the sector $\langle 0, \tilde{u} \rangle$, and if

$$q(0) \geq 0, \quad h(t,x) \geq 0, \quad u_0(x) \geq 0, \tag{7}$$

then there exists a unique solution $u(t,x)$ of (5) such that $0 \leq u(t,x) \leq \tilde{u}$ in $\overline{Q}_T$. Furthermore, if the condition (6) be satisfied, then $\tilde{u} = \rho$, and $0 \leq u(t,x) \leq \rho$ in $\overline{Q}_T$. In our case the condition (7) hold since obviously $q(0) = 0$.

Consider the following linear IBVP:

$$\begin{aligned} &(a)\ \ v_t - D\nabla^2 v + c_0 v = q_0(t,x) \quad \text{in } \ Q_T, \\ &(b)\ \ Bv = h(x) \qquad \text{on } \ \Gamma_T, \\ &(c)\ \ v(0,x) = v_0(x) \quad \text{in } \ \Omega, \end{aligned} \tag{8}$$

where c_0 =const can be defined as an upper bound of $(-\partial q_0/\partial v)$ over the sector $\langle 0, \tilde{u} \rangle$, and $v_0, q_0, h \geq 0$. Following the linear theory it follows that a unique nonnegative solution to (8) exists.

In case when $\beta_0 = 0$ on some subset of Γ_T, then there exists nonconstant upper solution of (8).

Let $\beta_0 = c_0 = q_0 = 0$, then there exists a nonnegative solution $\overline{z} = \overline{z}(t,x)$ of (8) which is at the same time a nonnegative upper solution to (5).

Now we should focus our attention on the derivative of q in (5),

$$q'(u) = -\sigma(1+au)^{-2} \geq -\sigma, \quad \text{for} \quad u \geq 0,$$

therefore $0 > q'(u) \geq -\sigma$. Then there is a solution $\underline{z}$ of (8) corresponding to $c_0 = \sigma$, $q_0 = 0$. Thus it turns out that there exists a lower solution $\underline{z}$ to (5), and also a solution u of (5) such that $\underline{z} \leq u \leq \overline{z}$. Whence it follows the existence and uniqueness for the problem (5), (a), (b), (c).

Remark. Let the boundary condition (8) (b) be changed by

$$(b') \quad v(t,x) = h(x) \qquad \text{on} \ \ \Gamma_T.$$

Thus we consider the Dirichlet problem with the same inhomogeneous data $h(x)$ for (8). Next assume that the coefficients of the elliptic operator L are continuous functions w.r.t. $x \in D_T$. Then there exists a unique solution of the Dirichlet problem (8), (a), (b'), (c) (see, e.g. [3]). So we denote this solution by w. In case that $c_0 \geq 0$, the function w should be upper solution of the quasilinear Dirichlet problem (5), (a), (b'), (c), and in addition if $h, u_0 \geq 0$ then the same problem has a solution $u = u(t,x)$, $0 \leq u \leq w$. Thus we may state that the problem (5), (a), (b'), (c) has a unique solution.

3. The Steady-State Problem

Consider the steady-state problem (4) with

$$q(u) = \frac{-\sigma u}{1+au} \tag{9}$$

where $a, \sigma > 0$. In the case when $\beta_0 > 0$, then the upper solution can be chosen as a number defined by $\rho \geq h/\beta_0$. Note that $q'(u) \leq 0 \ \forall u \geq 0$, hence from Theorem 7.2 in [8] obtain the existence and uniqueness for the steady-state problem (4), i.e., there exists a unique steady-state solution $v = v(t,x)$, $0 \leq v \leq \rho$. In the case when β_0 is not strictly positive, there exists an upper solution $\overline{v}$ as a solution at the same time to the problem

$$\begin{aligned} -\nabla^2 v + c_0 v = q_0(x) \ \ \text{in} \ \ \Omega, \\ Bv = h(x) \ \ \text{on} \ \ \partial\Omega, \end{aligned} \tag{10}$$

with $c_0 = q_0 = 0$; here in general case both h and q_0 are nonnegative functions, and $c_0 \in \mathbb{R}$. Using the same argument as in [8] we state that there exists a lower solution $\underline{v}$, hence we state that a steady-state solution v to the problem (4), exists and $0 < \underline{v} \le v \le \overline{v}$ in Ω.

Furthermore, consider the linear problem

$$\begin{aligned} &(L - c_0 + \lambda r)\Phi = 0 \qquad &&\text{in } \Omega, \\ &B\Phi = 0 &&\text{on } \partial\Omega, \end{aligned} \tag{11}$$

where $c_0 = c_0(x)$ and $r = r(x)$ belong to $C(\Omega)$.

Denote by λ_0 the principal eigenvalue of the eigenvalue problem (11) corresponding to $r = 1$ and $c_0 = 0$. It is known that $\lambda_0 > 0$ and the corresponding eigenfunction $\Phi_0(x)$ is positive in $\bar{\Omega}$. In what follows we assume that $\Phi_0(x)$ is normalized by $\max\{\Phi_0(x) : \ x \in \bar{\Omega}\} = 1$.

There exists a result (Theorem 3.2, Section 5 in [8]) that a given steady-state solution $u_s(x)$ for the particular case of enzyme reaction model is asymptotically stable if $q_u(u_s) < \lambda_0$ and is unstable if $q_u(u_s) > \lambda_0$. Then the solutions of (4) belong to the class $C^\alpha(\bar{\Omega}) \cap C^2(\Omega)$.

The steady-state solution u_s to (3) is said to be stable if given any constant $\varepsilon > 0$ there exists $\delta > 0$ such that

(i) $|u(t,x) - u_s(x)| < \varepsilon$ in Q_T whenever $|u_0(x) - u_s(x)| < \delta$ in Ω, where $u(t,x)$ is the solution of (3).

If in addition,

(ii) $\lim\limits_{t\to\infty} |u(t,x) - u_s(x)| = 0$ in $\bar{\Omega}$ then u_s is said to be asymptotically stable.

The steady-state solution $u_s(x)$ is called unstable if it is not stable.

A steady-state solution is said to be exponentially asymptotically stable if both conditions (i) and (ii) hold and convergence in (ii) is in exponential order, i.e. this is the case when there exist positive constants ρ and α such that $|u(t,x) - u_s(x)| \le \rho e^{-\alpha t}$ $(t > 0,\ x \in \bar{\Omega})$, whenever it holds at $t = 0$.

The set of initial functions $u_0(x)$ whose corresponding solutions $u(t,x)$ satisfy the inequality (i) and (ii) in the last definition stated above is called the stability region of u_s. If this is true for all initial functions then u_s is globally asymptotically stable.

It is known that two different cases of stability exist:

The first is that if $q(0)$ and h are identically zero, and β_0 is not identically zero, and if there exists stability then we say that there is stability of a uniform steady-state solution.

The second is that if $q(0)$ and h are not both identically zero and if there exists stability then we say that there is stability of a nonuniform steady-state solution.

Here, we focus our attention on the second case. The nonuniform steady-state solution will be called steady-state solution for simplicity.

A pair of upper and lower solutions of (1) is called ordered if $\tilde{u} \geq \hat{u}$ in the corresponding closed domain where they exist. For $\tilde{u}$ and $\hat{u}$ define a sector $\langle \hat{u}, \tilde{u} \rangle$, that is, all functions u of the corresponding functional class such that $\hat{u} \leq u \leq \tilde{u}$.

A sector $\langle v, w \rangle$ between two functions $v, w \in C(\bar{\Omega})$ with $v \leq w$ is called an invariant set of (3) if for any $u_0 \in \langle v, w \rangle$ the corresponding solution $u(t, x)$ of (1) remains in $\langle v, w \rangle$ for all $t > 0$.

Lemma 1. *Assume that there is a bounded nonnegative function in* Ω $\underline{c}(x) \geq \sigma$ $\forall x \in \Omega$. *Then* $q(u)$ *in the form (9) satisfies the one-sided Lipschitz condition*

$$q(u_1) - q(u_2) \geq -\underline{c}(x)(u_1 - u_2) \quad \text{for} \quad \hat{u} \leq u_2 \leq u_1 \leq \tilde{u}.$$

The proof is trivial.

The following hypothesis concerns the multiplier $\underline{c}(x)$ in Lemma 1.

H1. Assume that $\underline{c}(x) \geq \sigma$, $\forall x \in \Omega$, $q(0) \geq 0$ and $h(x) > 0$ $(x \in \partial\Omega)$.

Since only positive solutions of the model under consideration are of interest we state an existence and uniqueness result for those solutions.

Theorem 1. (see Chapter 3, [8]) *Let* $\tilde{u}$ *be a positive upper solution of (4) and let* $q(u)$ *be one-sided Lipschitzian and H1 hold. Then (4) has at least one solution* u_s *in* $\langle 0, \tilde{u} \rangle$ *which is either positive or zero. It is positive when either* $q(0)$ *or* $h(x)$ *is not identically zero. Moreover,* u_s *is the unique solution in* $\langle 0, \tilde{u} \rangle$ *if* β_0 *is not identically zero, and the inequality* $q(u_1) \leq q(u_2)$ *for* $\hat{u} \leq u_2 \leq u_1 \leq \tilde{u}$ *holds with* $\hat{u} = 0$.

The following statement gives a sufficient condition for the stability of u_s for arbitrary $q(u)$.

Theorem 2. (see Chapter 5, [8]) *Let* u_s *be a given steady-state solution of (3) with* $T = \infty$. *If there exist constants* ρ_i, α_i *with* $\rho_i \geq 0$, $0 \leq \alpha_i \leq \lambda_0$ $(i = 1, 2)$, *such that*

$$\begin{aligned} &(a) \quad q(u_s + \eta) - q(u_s) \leq (\lambda_0 - \alpha_1)\eta \quad \text{for} \quad 0 \leq \eta \leq \rho_1 \quad (x \in \Omega) \\ &(b) \quad q(u_s) - q(u_s - \eta) \leq (\lambda_0 - \alpha_2)\eta \quad \text{for} \quad 0 \leq \eta \leq \rho_2 \quad (x \in \Omega) \end{aligned} \tag{12}$$

then problem (3) has a unique solution u *such that*

$$u_s(x) - \rho_2 e^{-\alpha_2 t}\Phi_0(x) \leq u(t, x) + \rho_1 e^{-\alpha_1 t}\Phi_0(x) \quad (t > 0,\ x \in \bar{\Omega}) \tag{13}$$

whenever it holds at $t = 0$.

Assume that a steady-state solution of (3) exists. Then require the following conditions:

H2. There exist $\alpha_1,\ \rho_1 \geq 0$, such that

$$\frac{\sigma}{\lambda_0 - \alpha_1} \leq \frac{(1 + a u_s)\eta}{\|u_s\|_\infty}, \tag{14}$$

where $\lambda_0 > \alpha_1$, $0 \le \eta \le \rho_1$.

H3. There exist $\alpha_2,\ \rho_2 \ge 0$, such that

$$\frac{\sigma}{\lambda_0 - \alpha_2} \le \frac{(1 + a(u_s - \eta))\eta}{\|u_s\|_\infty}, \tag{15}$$

where $\lambda_0 > \alpha_2$, $0 \le \eta \le \rho_2$.

Here $u_s(x)$ is the steady-state solution of (3); $\|\cdot\|_\infty$ is the standard supremum norm.

Remark. In the case when $\rho_1 = \rho_2$, $\alpha_2 \ge \alpha_1$, one may require only the assumption H3 to be satisfied.

4. Main Results

4.1. Existence and Uniqueness

Let $u_s(x)$ be a unique and positive steady-state solution of (3). Then we state that:

Proposition 1. *Let the assumptions H1, H2 be satisfied. Then the relation (12) (a) holds with* $0 \le \alpha_1 < \lambda_0$.

Proof. The proof follows from

$$(\lambda_0 - \alpha_1)\eta \ge \frac{\sigma\|u_s\|_\infty}{1 + au_s} \ge \frac{\sigma u_s}{1 + au_s} \ge -\frac{\sigma(u_s + \eta)}{1 + a(u_s + \eta)} + \frac{\sigma u_s}{1 + au_s}\ .$$

Proposition 2. *Let the assumptions H1, H3 be satisfied. Then the relation (12) (b) holds with* $0 \le \alpha_2 < \lambda_0$.

Proof. The proof follows by the same arguments used in the proof of Proposition 1, i.e.

$$\eta(\lambda_0 - \alpha_2) \ge \frac{\sigma\|u_s\|_\infty}{1 + (u_s - \eta)} \ge \frac{\sigma u_s}{1 + a(u_s - \eta)} \ge \frac{\sigma(u_s - \eta)}{1 + a(u_s - \eta)}$$
$$\ge -\frac{\sigma u_s}{1 + au_s} + \frac{\sigma(u_s - \eta)}{1 + a(u_s - \eta)}\ .$$

The main result follows by Proposition 1 and 2.

Theorem 3. *Suppose that:*

1) $\hat{u} = 0$, $\tilde{u} > 0$ *are the lower and upper solutions, respectively, and H1 hold.*

2) β_0 *is not identically zero.*

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Then there exists a unique positive solution of (4) in $\langle 0, \tilde{u} \rangle$.

Proof. The conditions 1) and 2) assure validity of Theorem 1, and $q(u_1) \leq q(u_2)$ for $\hat{u} = 0 \leq u_2 \leq u_1 \leq \tilde{u}$ which leads to uniqueness of the solution of (3). □

We need the above stated result in order to assure the existence of a unique positive solution of (4) which on the other hand appears as a steady-state solution for (3).

Theorem 4. *Let* $u_s(x)$ *be a steady-state solution of (3) such that H1-H3 hold. Then the problem (3) has a unique solution* $u(t,x)$ *that is exponentially asymptotically stable.*

Proof. The result follows from Proposition 1 and 2 and Theorem 2. It follows from (13) that

$$|u_s(x) - u(t,x)| \leq \rho_2 e^{-\alpha_2 t}\Phi(x) + \rho_1 e^{-\alpha_1 t}\Phi(x) \leq\leq \rho e^{-\alpha t} \quad (t > 0, \; x \in \bar{\Omega}),$$

where $\rho = \max\{\rho_1, \rho_2\}$, $\sup_{\bar{\Omega}} \Phi_0(x) = 1$, $\alpha = \min\{\alpha_1, \alpha_2\}$. □

4.2. A General Case of Nonuniqueness

Next we take a reaction function $q(u)$ in the form

$$q(u) = \frac{-\sigma u}{\varphi(u)}, \quad \varphi(u) > 0,$$

where the function $\varphi(z)/z$ is Hölder continuous, i.e.

$$|\varphi(u)/u - \varphi(v)/v| \leq A|u-v|^{\alpha}, \quad 0 < \alpha < 1, \quad \forall\, u, v \in J, \quad u \geq v > 0.$$

Here $J = \langle \hat{u}, \tilde{u} \rangle$ is a sector, and φ satisfies in addition,

$$\varphi(z) \geq z, \quad \forall z \geq 0, \quad \text{and} \quad \underline{c}(x) \geq \sigma > 0 \quad \text{in} \quad \Omega.$$

Then having in mind Theorem 6.1, Chapter 1 in [8] we state that if there exist a constant σ_0 and positive numbers σ_1, $\gamma < 1$ such that

$$q(z) \equiv \frac{-\sigma z}{\varphi(z)} \geq -\sigma_0 z + \sigma_1 z^{\gamma}, \quad z \geq 0,$$

and the condition

$$u - v \geq \frac{u}{\varphi(u)} - \frac{v}{\varphi(v)},$$

then there exists a positive number T^* such that for any $T < T^*$ ($\forall t \in [t_0, T]$) (3) has a trivial solution $u_1 = 0$ and infinitely many other solutions.

Acknowledgments

The present investigation was supported by BG 051PO001-3.3.06.

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