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Stability of the bicarbonate system in the blood

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ABSTRACT

In this paper, we describe a mathematical model about the reaction–diffusion kinetics of bicarbonate system, which it plays a key role in regulating blood pH. It is very important to know the determinants of blood pH in both experimental and theoretical studies, in order to help to investigate the hidden mechanism of acid–base disorders in the clinical setting. We explore the dynamics of the bicarbonate system under the closed condition. This condition yields that the total amount of carbon dioxide is conserved and the difference in concentrations between anions and cations is conserved. For the stability of the model, we hypothesize that the amount of initial concentrations perturbed around an equilibrium point is less than a certain constant depending on a rate constant. With an application of Liapunov's method, we prove that the model in the form of reaction–diffusion system is globally stable under the hypothesis. We also provide the blood pH profile, which is computed in our model with the experimentally observed rate constants.

1. Introduction

The primary systems that regulate blood pH are the chemical acid–base buffer systems of the body fluids; the respiratory center; the kidneys. These mechanisms help the body-pH balance so effectively that they can control body-pH to vary slightly within a normal range in physiologic status. The normal range of pH in the blood plasma is 7.40 ± 0.02 (clinical normal range 7.35–7.45). Among three mechanisms, the bicarbonate system is the main physiological buffer, because the H_2CO_3 of blood plasma is in equilibrium with a large reserve capacity of gaseous carbon dioxide $CO_2(g)$ in the air space of the lungs [17].

The relationship among the elements of the bicarbonate system is described in the classical formulation by Henderson–Hasselbalch (1908) that aids in understanding pH regulation of body fluids [21]. For normal plasma at 37 °C, it takes the following form

$$\mathrm{pH} = \mathrm{pK}' + \log_{10} \frac{[\mathrm{HCO}_3^-]}{[\mathrm{CO}_2(\mathrm{d})]}, \tag{1}$$

where by Henry's law, dissolved carbon dioxide $CO_2(d)$ is equal to $\alpha \times PCO_2$ with $\alpha = 0.0306$ M per mmHg. The partial pressure of carbon dioxide PCO_2 is measured in millimeters of mercury and HCO_3^- is measured in millimoles per liter. The constant K′ is defined as $\mathrm{K}' = \frac{[\mathrm{H}^+][\mathrm{HCO}_3^-]}{[\mathrm{CO}_2(\mathrm{d})]} = 10^{-6.103}$ (thus $\mathrm{pK}' = 6.103$) and is said to be an equilibrium constant. We note that $[CO_2(d)]$ is regulated by lung and $[HCO_3^-]$ is regulated by kidney. When pH is equal to 7.4, the ratio $[HCO_3^-]/[CO_2(d)]$ is approximately 20/1. Acid–base disorders are classified both by the direction of the pH change and by the underlying cause.

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Acidosis is defined as an arterial blood pH < 7.35; alkalosis indicates that an arterial blood pH > 7.45. Acid–base balance disturbances that result from a change in the $[HCO_3^-]$ are termed metabolic acid–base disorders, whereas those that result from a change in the PCO_2 are termed respiratory acid–base disorders.

The analysis of acid–base balance in the clinical setting has been intensively studied for the practice of critical care medicine. Considering clinical implications, Kellum revealed three independent variables that regulate pH in blood plasma as: carbon dioxide, relative electrolyte concentrations, and total weak acid concentrations [12]. Gilfix et al. [8] evaluated the clinical application of Stewart model, which is based on quantitative physical chemical principles. Four systems, which determine H^+, are identified as follows. The first system is the difference in concentration between strong anions and cations and the second is PCO_2, which is tightly regulated by the ventilatory system. The third system is the concentration of weak acids; serum proteins and the fourth system is the presence of other acids or bases that are not normally present in significant quantities. Local or regional acid–base balance has been incompletely understood. The human respiratory system—the main controller of carbon dioxide transport has been monitored and has been modeled [1]. These studies showed that decreased blood flow increases CO_2 storage in the pulmonary blood (high PCO_2; factor 2) and H^+ as a counteract (acidosis), and then the respiratory center stimulated by acidosis increases the ventilation rate to increase blood pH by means of increasing clearance of CO_2 by lungs (respiratory compensation). This is an example of acid–base balance mechanism in the closed condition.

On the other hand, acid–base balance mechanism is also studied in the open condition. In the paper [19], it has been observed that exercising muscles may produce a large amount of lactic acid (extra acid out of bicarbonate buffer; factor 4) so that it can induce acidosis, and this acidic change can also stimulate the respiratory center to increase the ventilation rate for respiratory compensation as above. The mentioned studies can be examples of metabolic acidosis with respiratory compensation. The compensation mechanism under the open condition has more complexity than that under the closed condition. Consequently, it is hard to observe that the compensated pH is achieved only by respiration. The combination of several changes, for example, the combination of an initial pH disturbance and compensatory change can be one of factors to analyze acid–base balance in the clinical settings through the mathematical model. The present work focuses on the long time evolution of the mechanisms of the bicarbonate reaction, under the open condition, responsible for systematic acid–base balance in the blood. Our developed model aims to predict stability or instability of the bicarbonate system under this condition.

An outline of the paper is as follows. Section 2 describes the experimental background of the bicarbonate buffer system. The motivation and the result of this study are explained from the physiological point of view. In Section 3, a comprehensive mathematical model incorporating reaction–diffusion effect is described. In Section 4, we restate the main result with calculations to reduce the system of equations. Section 5 discusses the dynamics of kinetics differential equations, such as equilibrium solutions and stability. Section 6 proves the stability of the system of reaction–diffusion equations.

2. Experimental motivation and main result

The bicarbonate buffer system that plays a key role in regulating blood pH is

$$\begin{aligned} &H^+ + HCO_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} H_2CO_3, \\ &H_2CO_3 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} CO_2(d) + H_2O. \end{aligned} \tag{2}$$

The first step is an ionic reaction and proceeds very fast. Without a catalytic dehydration of H_2CO_3 the second step is slower and can be observed [16]. When the blood reaches the lungs, $CO_2(d)$ in the plasma at a partial pressure of 46 mmHg equilibrates with the lower CO_2 tension of the alveoli (40 mmHg) to bring the arterial PCO_2 to 40 mmHg [18]. Most of CO_2 is present as $CO_2(d)$ and very little as H_2CO_3. The ratio of $CO_2(d)$ to H_2CO_3 in the plasma is approximately 700 to 1 [18]. At 37 °C, the half-time of the uncatalyzed CO_2–HCO_3^- reaction under physiological conditions with sufficient buffer power in reacting solution to hold pH relatively constant is less than 3.5 sec [4].

In the theoretical studies, analysis of pH changes in blood has been partly obtained by focusing on gas exchange [1,3,6,10,11]. The importance of these studies can be found in the fact that the respiratory system is one of the two main control systems that maintains a constant pH environment in the body. In order to reach a deeper understanding of CO_2 transfer, several mathematical models have been constructed with a set of ordinary differential equations. For example, Geers and Gros [6], a theoretical model represents CO_2 diffusion into blood with plasma and erythrocytes. It predicted the complex interdependence of reactions and transport processes involved in CO_2 exchange. A buffering mechanism through hemoglobin has been investigated for finding the functions of the regulation of ventilation [1]. Their studies focused on how diffusion and blood flow are related with the reaction in the theoretical model.

All of the previous models predicted local and regional acid–base balance in the theoretical setting. Some of them analyzed the acid–base balance through theoretical models, incorporating the spatial effect of diffusion during the bicarbonate reactions. K. Uchida et al. [20] questioned what the effect of diffusion process in acid–base balance is: the pH change is accelerated and determined only by the diffusion process of CO_2 within a layer of hemoglobin solution. They found that the

Table 1
At 37 °C, the reaction constants and initial values used in the simulations.

Constants/inital values	Value	Reference
k_1	89 M^{-1} sec^{-1}	[10]
k_2	0.03 sec^{-1}	
k_3	49.6 sec^{-1}	[7]
k_4	0.145 sec^{-1}	[7]
$[H^+]$	48 nM/l	pH = 7.316
$[HCO_3^-]$	30 mM/l	
$[H_2CO_3]$	0.0026 mM/l	
$[CO_2(d)]$	1.836 mM/l	$PCO_2 = 60$ mmHg

pH rise observed in the CO_2 diffusion out of the layer was slower than the pH fall caused by inward diffusion. As experimental results, the diffusion coefficients of CO_2 and $[HCO_3^-]$ of 100% hemolysate were 0.34×10^{-5} and 0.14×10^{-5} cm^2/sec, respectively.

The motivation behind developing our model is to explore a complicated mechanism of acid–base regulation, considering the bicarbonate buffer reactions with diffusion in the general domain, instead of the local and regional domain. The model consists of four chemical concentrations $[H^+]$, $[HCO_3^-]$, $[H_2CO_3]$, $[CO_2(d)]$ with six rate constants as variables and parameters. Our assumption is that the chemical reactions occur under the closed condition. More precisely, it is assumed that the total amount of $[CO_2(d)]$ is conserved by mass action law and the difference between the concentrations of cations and anions is constant by law of conservation of charges. The resulting system of reaction–diffusion equations is formulated by mass action law. This approach allows us to both qualitatively and quantitatively deal with the model that describes the chemical reactions with diffusion. Compared to the previous models in the form of ordinary differential equations, our model, established partial differential equations, makes it possible to predict the evolution and the spatial effect of the dynamic behavior. The kinetic parts of our model are similar to those of the previous one, except the local compartment, such as erythrocytes [6]. In their model, the elements of the reaction are $[H^+]$, $[HCO_3^-]$, and $[CO_2(d)]$, which are slightly different from the elements of our model. Stability analysis of the developed model is carried out with the theory of partial differential equations.

The parameters in the reactions are defined and are quantitatively illustrated with the relations to the directions of reactions as follows. The forward (backward) velocity constants are denoted by k_1, k_3 (k_2, k_4). For the second reaction, the average value of the constant k_4/k_3 is 1/440 [4]. Table 1 lists the values for all the constants and parameters used in the simulation of our model. The constant k_2 is computed optimally with the experimental result described before.

Our aim of the current work is to analyze whether our model is stable or not stable depending on reaction kinetics. Our analytical treatment allows us to get two main results of the model. First, without diffusion, under the specific condition for a rate constant, each concentration approaches its equilibrium concentration that we calculated explicitly. The specific condition that we imposed is that amount of initial concentrations, which is perturbed around the equilibrium concentrations, is strictly less than a certain constant depending on the velocity constant k_1. Secondly, with diffusion effect, we obtain the same result as before. In the case of non-diffusion, the theoretical finding agrees very nicely with the numerical simulations of the model. The simulations is calculated by using Matlab solver ode23s with an appropriate choice of parameters and initial values illustrated in Table 1. Initial concentrations is chosen in the set of values that satisfy the specific condition. The initial values are chosen slightly outside of the normal range of acid–base balance; they represent acute respiratory acidosis according to Fig. 51-1 in [21] (p. 591) or Fig. 32-15 in [2].

Figs. 1 (a) and (b) show the equilibrium state of $[CO_2(d)]$ and PCO_2 in short time. In (c), pH is computed directly by taking logarithm of the concentration hydrogen ion that we solved numerically, whereas in (d) blood pH computed by the Henderson–Hasselbalch equations is implemented with the numerical solutions $[HCO_3^-]$ and $[CO_2(d)]$. The difference between them probably came from the equilibrium constant fixed to 6.103. The second graph was able to reach up to the equilibrium state with the value 7.317 and went up only the value of 0.001. From the explicit formula that we suggest for the equilibrium point, we find that the equilibrium constant K', as shown in (1), is closely related to rate constants. In other words, the constant $K' = u_1^\infty u_2^\infty / u_4^\infty$ is equal to the ratio k_2k_4/k_1k_3 (u_i^∞ will be discussed in the next section). With a choice of the parameter values in Table 1, the value of pK′ is computed as 6.18, which is close to the value 6.103 as shown in Henderson–Hasselbalch equation.

Our findings show that the regulation of the bicarbonate system through the reaction–diffusion process under the closed condition is very quickly achieved the equilibrium. This current theoretical work gives us the new insights into the physiological mechanisms, and the prospects of the future experimental and clinical studies. Moreover, this result can be applied to other problems containing diffusion phenomena with very similar diffusion rates in any one-dimensional space. Our finding might be observed in experimental study. We thus propose to test how effectively the velocity constants are involved in the change of the equilibrium constant K' in experiments.

Our assumption—the closed condition make it difficult to apply to the case where patients have a failure in respiratory center or where patients have the presence of other acids or bases in significant quantities. The latter case can be produced from certain poison, such as methyl alcohol, or salicylates. The limitations of the current study might be illustrated; (1) in vivo is not fully replaced by in vitro; (2) other chemical buffer reaction mechanisms, such as Hb^-/HHb, $HPO_4^=/H_2PO_4$,

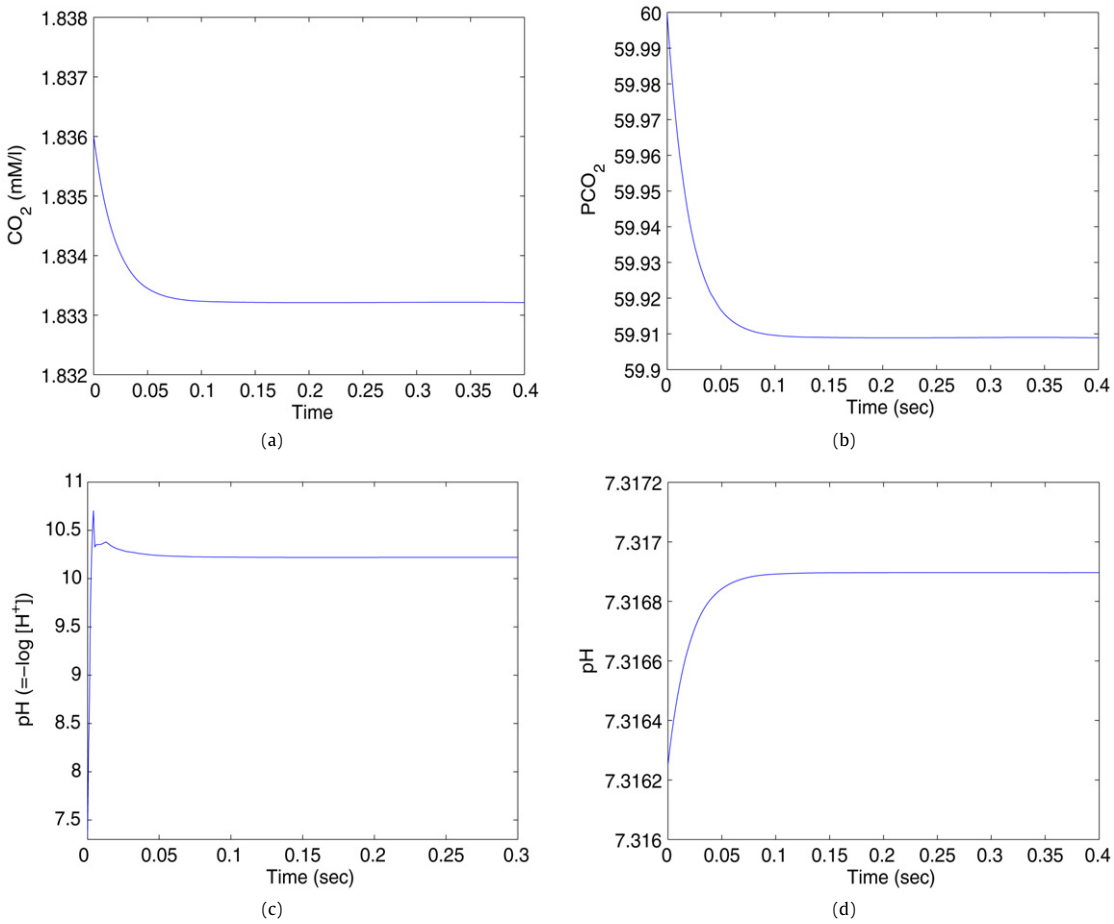

Fig. 1. (a) Computed evolution of CO_2. (b) Computed evolution of PCO_2. (c) Blood pH ($= -\log_{10}[H^+]$). (d) Blood pH by Henderson–Hasselbalch equation with computed $[HCO_3^-]$ and $[CO_2]$.

are not involved. We thus suggest that the future work should provide a more developed model containing other several chemical buffers under the open condition. It is needed to discuss the regulation mechanism of the bicarbonate system in a specific clinical setting.

3. Model description

This section develops a new model incorporated reaction–diffusion effect in the bicarbonate buffer system that we mentioned earlier. The purpose of the present model is to describe the pH related to the bicarbonate reactions in the closed condition. Brief explanation of model procedure is described below.

Suppose we have a complex chemical reaction containing N chemical species $X_1, X_1, \ldots, X_N$. Assume that M reaction steps are taking place as follows:

$$\sum_{i=1}^{N} \alpha(i,j) X_i \xrightarrow{k_j} \sum_{i=1}^{N} \beta(i,j) X_i \quad (j = 1, \ldots, M). \tag{3}$$

Here the positive values of k_j are the reaction rate constants, and the nonnegative integers $\alpha(i,j)$, and $\beta(i,j)$ are the stoichiometric coefficients.

The reaction (3) is said to be mass conserving if there exist positive real numbers θ_i $(i = 1, \ldots, N)$ for which

$$\sum_{i=1}^{N} \alpha(i,j)\theta_i = \sum_{i=1}^{N} \beta(i,j)\theta_i \quad (j = 1, \ldots, M).$$

We define the concentrations of species $x_i \equiv [X_i]$ as dependent variables and time as an independent variable. The mass action type model of the reaction (3) is formulated as

$$\frac{dx_i}{dt} = \sum_{j=1}^{M} \big(\beta(i,j) - \alpha(i,j)\big) k_j \prod_{p=1}^{N} x_p^{\alpha(p,j)} \quad (i = 1, \ldots, N).$$

Based on mass action law, we present a working model including diffusion phenomena for the chemical reactions (2). The model consists of four chemical concentrations. We define variables u_i $(i = 1, \ldots, 4)$ as $u_1 \equiv [H^+]$, $u_2 \equiv [HCO_3^-]$, $u_3 \equiv [H_2CO_3]$, $u_4 \equiv [CO_2(d)]$. With spatial coordinate x, the system of reaction–diffusion equations for the concentrations $u_i(x,t)$ is

$$\begin{aligned}
\frac{\partial u_1}{\partial t} &= D_1 \frac{\partial^2 u_1}{\partial x^2} + k_2 u_3 - k_1 u_1 u_2,\\
\frac{\partial u_2}{\partial t} &= D_2 \frac{\partial^2 u_2}{\partial x^2} + k_2 u_3 - k_1 u_1 u_2,\\
\frac{\partial u_3}{\partial t} &= D_3 \frac{\partial^2 u_3}{\partial x^2} + k_1 u_1 u_2 + k_4 u_4 - (k_2 + k_3) u_3,\\
\frac{\partial u_4}{\partial t} &= D_4 \frac{\partial^2 u_4}{\partial x^2} + k_3 u_3 - k_4 u_4,
\end{aligned} \tag{4}$$

where D_i $(i = 1, \ldots, 4)$ are the diffusion coefficients of u_i, respectively. It is assumed that all the diffusion coefficients are equal: $D_1 = \cdots = D_4$.

It is assumed that the nonnegative initial conditions

$$u_i(x,0) = g_i(x) \quad (i = 1, \ldots, 4)$$

are given and $g_i(x) \in L^1(U)$.

The carbonate system in natural water has been analyzed with a set of differential equation (Li and Wright [13]). This model consists of six chemical species ($[CO_2]$, $[H_2CO_3]$, $[HCO_3^-]$, $[CO_3^=]$, $[H^+]$), which they participate in five chemical reactions. Due to all species are in natural waters, they are subjected to both advection and diffusion influences. They proved a global existence and uniform boundedness of the solutions to the carbonate system of parabolic partial differential equations (Li and Wright [14]).

4. Main theorem

Before we present the main theorem, we make an important observation from our model under non-diffusive influence. For the state equations, we find equations

$$\frac{\partial(u_2 + u_3 + u_4)}{\partial t} = 0, \qquad \frac{\partial(u_2 - u_1)}{\partial t} = 0.$$

The positive constants C_1 and C_2 are given by

$$\begin{aligned}
C_1 &= u_2(t) + u_3(t) + u_4(t),\\
C_2 &= u_2(t) - u_1(t)
\end{aligned} \tag{5}$$

for all $t \geqslant 0$. Here C_1 states that the total mass of carbon is conserved and C_2 states that difference in concentrations of ion and proton is conserved. We naturally assume that for the state equations

$$\begin{aligned}
C_1 &= u_{2,0} + u_{3,0} + u_{4,0},\\
C_2 &= u_{2,0} - u_{1,0}.
\end{aligned} \tag{6}$$

For the reaction–diffusion system (4), the two constants are given by the average of corresponding initial conditions

$$\begin{aligned}
C_1 &= \frac{1}{|U|} \int_U \big[g_2(x) + g_3(x) + g_4(x)\big]\, dx,\\
C_2 &= \frac{1}{|U|} \int_U \big[g_2(x) - g_1(x)\big]\, dx.
\end{aligned} \tag{7}$$

We introduce new variables z_1, z_2, z_3 such that

$$z_1 = u_3 + u_4, \qquad z_2 = u_4,$$

which reduce the system (4) to the two-dimensional system of the equations. Applying (7) to (4) and denoting $D_i = D$ yield a set of the equations

$$\frac{\partial z_1}{\partial t} = D\frac{\partial^2 z_1}{\partial x^2} - \big[k_1(2C_1 - C_2) + k_2\big]z_1 + k_2 z_2 + k_1 z_1^2 + k_1 C_1(C_1 - C_2),$$
$$\frac{\partial z_2}{\partial t} = D\frac{\partial^2 z_2}{\partial x^2} + k_3 z_1 - (k_3 + k_4)z_2.$$

This system can be simplified by introducing the dimensionless variable $\tilde{x} = \frac{1}{\sqrt{D}}x$. Dropping the tilde, it becomes

$$\frac{\partial z_1}{\partial t} = \frac{\partial^2 z_1}{\partial x^2} - \big[k_1(2C_1 - C_2) + k_2\big]z_1 + k_2 z_2 + k_1 z_1^2 + k_1 C_1(C_1 - C_2),$$
$$\frac{\partial z_2}{\partial t} = \frac{\partial^2 z_2}{\partial x^2} + k_3 z_1 - (k_3 + k_4)z_2 \tag{8}$$

with the initial conditions $z_1(x, 0) = g_3 + g_4$, $z_2(x, 0) = g_4$.

We now state the main result for the stability analysis of this initial value problem. Here, we denote the equilibrium point by z_i^∞ $(i = 1, 2)$, which these values are explicitly given in terms of C_1, C_2 in the next section.

Theorem 1. *Let $z_1(x, t)$, $z_2(x, t)$ be the solutions of the initial value problem* (8)*. Assume a vector $\mathbf{y} = (y_1, y_2) \in R^3$ such that $z_1 = y_1 + z_1^\infty$, $z_2 = y_2 + z_2^\infty$.*

Suppose that

$$\big|\mathbf{y}(\cdot, 0)\big| < \sigma/k_1$$

with $\sigma = \min\{|\lambda_1|, |\lambda_2|\}$, λ_i the eigenvalues of A, satisfying the following equation

$$\frac{\partial \mathbf{y}}{\partial t} = \Delta\mathbf{y} + A\mathbf{y} + f(\mathbf{y}), \tag{9}$$

where the matrix $A = \begin{bmatrix} -[k_1(2u_2^\infty - C_2) + k_2] & k_2 \\ k_3 & -(k_3 + k_4) \end{bmatrix}$ and the function $f(\mathbf{y}) = [k_1 y_1^2, 0]^T$.

Then

$$\lim_{t\to\infty} z_1(x, t) = z_1^\infty, \qquad \lim_{t\to\infty} z_2(x, t) = z_2^\infty.$$

As a result, it has been shown that using two conditions for C_1 and C_2,

$$u_1(x, t) \to C_1 - C_2 - z_1^\infty = u_1^\infty,$$
$$u_2(x, t) \to C_1 - z_1^\infty = u_2^\infty,$$
$$u_3(x, t) \to z_1^\infty - z_2^\infty = u_3^\infty,$$
$$u_4(x, t) \to z_2^\infty = u_4^\infty$$

as time goes to infinity.

5. The kinetics differential equations

Analysis of the model without diffusion is carried out by finding equilibrium points to the state system. This section formulates a stable equilibrium solution in terms of C_1 and C_2 and investigates the stability of the state equations model.

5.1. Equilibrium solutions

The state equations become

$$\frac{du_1}{dt} = k_2 u_3 - k_1 u_1 u_2,$$
$$\frac{du_2}{dt} = k_2 u_3 - k_1 u_1 u_2,$$
$$\frac{du_3}{dt} = k_1 u_1 u_2 + k_4 u_4 - (k_2 + k_3)u_3,$$
$$\frac{du_4}{dt} = k_3 u_3 - k_4 u_4. \tag{10}$$

To formulate the equilibrium solutions to the system (4) (or (8)), let us write the equilibrium points as $E_0 = (u_1^\infty, u_2^\infty, u_3^\infty, u_4^\infty)$ to the system of equations.

The equilibrium point is

$$u_2^\infty = \frac{1}{2}\left[\left(C_2 - \frac{1}{d}\right) + \sqrt{\left(C_2 - \frac{1}{d}\right)^2 + \frac{4C_1}{d}}\right], \tag{11}$$

which is stable, where $d = \frac{k_1}{k_2}(1 + \frac{k_3}{k_4})$. We skip the details for calculations.

Consequently, using (5) we find one positive equilibrium point E_0 in terms of u_2^∞:

$$E_0 = \left(u_2^\infty - C_2, u_2^\infty, \frac{k_1}{k_2}(u_2^\infty - C_2)u_2^\infty, \frac{k_1 k_3}{k_2 k_4}(u_2^\infty - C_2)u_2^\infty\right).$$

These points can be rewritten for the reduced system

$$\begin{aligned} \frac{dz_1}{dt} &= -\big[k_1(2C_1 - C_2) + k_2\big]z_1 + k_2 z_2 + k_1 z_1^2 + k_1 C_1(C_1 - C_2), \\ \frac{dz_2}{dt} &= k_3 z_1 - (k_3 + k_4)z_2. \end{aligned} \tag{12}$$

The equilibrium points are defined as $z_1^\infty = u_3^\infty + u_4^\infty$, $z_2^\infty = u_4^\infty$. We thus have the following result.

Proposition 1. *There exists a unique stable equilibrium point to Eqs.* (12) (*or* (10)).

5.2. Stability

We prove the stability of the equilibrium solutions to the reduced system (12). The idea of proof is based on an earlier result (Lim [15]) regarding the general chemical reaction $X_1 + X_2 \leftrightharpoons X_3$. We will utilize the Liapunov function [9, p. 293] to derive the global stability for the ordinary differential equations model.

Theorem 2. *Assume that z_1, z_2 are the solutions of the initial value problem* (12). *Assume a vector $\mathbf{y} = (y_1, y_2) \in R^2$ such that $z_1 = y_1 + z_1^\infty$, $z_2 = y_2 + z_2^\infty$.*

Assume that

$$\big|\mathbf{y}(0)\big| < \sigma/k_1$$

with $\sigma = \min\{|\lambda_1|, |\lambda_2|\}$, λ_i the eigenvalues of A, satisfying the following equation

$$\frac{d\mathbf{y}}{dt} = A\mathbf{y} + f(\mathbf{y}), \tag{13}$$

where A and f are the same as before.

Then

$$\lim_{t\to\infty} z_1(t) = z_1^\infty, \qquad \lim_{t\to\infty} z_2(t) = z_2^\infty.$$

Proof. We outlines our proof as follows. We first perturb the equilibrium point of (12) and find the linear part of the new system, called a matrix A. We observe that A has negative eigenvalues and prove that by applying Liapunov's method, the diagonalized system is stable.

We introduce new variables y_i $(i = 1, 2)$ to perturb the equilibrium point in the system (12) with

$$z_1 = y_1 + z_1^\infty, \qquad z_2 = y_2 + z_2^\infty.$$

Thus a new system takes the form of the equations

$$\begin{aligned} \frac{dy_1}{dt} &= -\big[2k_1\big(C_1 - z_1^\infty\big) - k_1 C_2 + k_2\big]y_1 + k_2 y_2 + k_1 y_1^2 = -\big[k_1\big(2u_2^\infty - C_2\big) + k_2\big]y_1 + k_2 y_2 + k_1 y_1^2, \\ \frac{dy_2}{dt} &= k_3 y_1 - (k_3 + k_4)y_2. \end{aligned} \tag{14}$$

The condition $C_1 = u_2^\infty + z_1^\infty$ is used to derive the first equation.

Finally we rewrite the system in the form of matrix equations

$$\frac{d\mathbf{y}}{dt} = A\mathbf{y} + f(\mathbf{y}), \tag{15}$$

where the matrix $A = \begin{bmatrix} -[k_1(2u_2^\infty - C_2) + k_2] & k_2 \\ k_3 & -(k_3 + k_4) \end{bmatrix}$ and the function $f(\mathbf{y}) = [k_1 y_1^2, 0]^T$. We note that the system is asymptotically stable if all eigenvalues of A have negative real parts.

We begin the stability analysis by checking that all eigenvalues of A have negative real parts.

The characteristic equation to the matrix A is

$$h(\lambda) = \lambda^2 + E\lambda + F = 0,$$

where $E(= -\operatorname{tr}(A)) = k_1(2u_2^\infty - C_2) + k_2 + k_3 + k_4$, and $F(= \det(A)) = k_1(2u_2^\infty - C_2)(k_1(k_3 + k_4) + k_2k_4)$. We observe that the constants E and F are positive provided that the inequality $2u_2^\infty - C_2 > 0$. It is easy to check that since $C_2 \leqslant 2C_1$. Thus, the equation has negative real parts of all the roots and then all the eigenvalues of A have negative real parts. We note that A is diagonally dominant and thus A is nonsingular.

To diagonalize the system (15) we change the variable $\mathbf{y} = P\tilde{\mathbf{y}}$. We drop the tilde and obtain a new equation

$$\frac{d\mathbf{y}}{dt} = P^T AP\mathbf{y} + g(\mathbf{y}), \tag{16}$$

where $P^T AP = \operatorname{diag}(\lambda_1, \lambda_2)$, $P^T = P^{-1}$ and $g(\mathbf{y}) = P^T f(P\mathbf{y})$.

Thus the system above can be expressed in the form of

$$\begin{bmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{bmatrix} = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} + k_1 \begin{bmatrix} p_{11}y_p^2 \\ p_{12}y_p^2 \end{bmatrix}. \tag{17}$$

Define a positive definite function $V : U \subset R^2 \to R$ as

$$V(\mathbf{y}) = y_1^2 + y_2^2.$$

We claim that V is a Liapunov function.

To show that $\frac{dV}{dt} < 0$, we compute

$$\begin{aligned} \frac{dV}{dt} &= 2\big[y_1\big(\lambda_1 y_1 + k_1 p_{11} y_p^2\big) + y_2\big(\lambda_2 y_2 + k_1 p_{12} y_p^2\big)\big] = 2\big(\lambda_1 y_1^2 + \lambda_2 y_2^2\big) + 2k_1(p_{11}y_1 + p_{12}y_2)^3 \\ &\leqslant -2\sigma\big(y_1^2 + y_2^2\big) + 2k_1\big(y_1^2 + y_2^2\big)^{3/2} = -2\sigma\big(y_1^2 + y_2^2\big)\left(1 - \frac{k_1|\mathbf{y}|}{\sigma}\right) < 0, \end{aligned} \tag{18}$$

where $\sigma = \min\{|\lambda_1|, |\lambda_2|\}$, provided $|\mathbf{y}| < \sigma/k_1$. Here the first inequality is obtained by applying Minkowski's inequality.

More precisely,

$$(p_{11}y_1 + p_{12}y_2)^3 \leqslant \big(p_{11}^2 + p_{12}^2\big)^{3/2}\big(y_1^2 + y_2^2\big)^{3/2} = \big(y_1^2 + y_2^2\big)^{3/2}$$

since P is an orthogonal matrix.

Thus we conclude that $y_1 \to 0$ and $y_2 \to 0$ as $t \to \infty$. That is,

$$z_1 \to z_1^\infty, \qquad z_2 \to z_2^\infty,$$

as $t \to \infty$, where z_1^∞, z_2^∞ are shown before. □

6. Stability of the reaction–diffusion equations

Proof of Theorem 1. It is enough to prove that the reaction–diffusion system corresponding to (17) is stable for all times.

The reaction–diffusion system takes the form of

$$\begin{aligned} \frac{\partial y_1}{\partial t} &= \frac{\partial^2 y_1}{\partial x^2} + \lambda_1 y_1 + k_1 p_{11} y_p^2, \\ \frac{\partial y_2}{\partial t} &= \frac{\partial^2 y_2}{\partial x^2} + \lambda_2 y_2 + k_1 p_{12} y_p^2 \end{aligned} \tag{19}$$

in a domain $\Omega = U \times [0, \infty)$. Here the values λ_i $(i = 1, 2)$ are eigenvalues of the matrix A, as shown in (15), and the variable y_p and constants p_{11}, p_{12} are defined in the previous proof. The nonnegative initial conditions are given by $g_i(x) = y_i(x, 0)$ $(i = 1, 2)$ and $g_i \in L^1(U)$.

We use the same positive definite function $V(\mathbf{y}) = y_1^2 + y_2^2$, as shown in the previous proof.

We first show that

$$V_t \leqslant V_{xx} - mV \quad (m > 0). \tag{20}$$

Direct calculations yield

$$\begin{aligned} V_x &= 2[y_1\partial_x y_1 + y_2\partial_x y_2], \\ V_{xx} &= 2\big[(\partial_x y_1)^2 + (\partial_x y_2)^2 + y_1\partial_{xx}y_1 + y_2\partial_{xx}y_2\big]. \end{aligned}$$

Using these equations, we obtain

$$\begin{aligned} V_t &= 2\big[y_1\big(\partial_{xx}y_1 + \lambda_1 y_1 + k_1 p_{11} y_p^2\big) + y_2\big(\partial_{xx}y_2 + \lambda_2 y_2 + k_1 p_{12} y_p^2\big)\big] \\ &= V_{xx} - 2\big[(\partial_x y_1)^2 + (\partial_x y_2)^2\big] + 2\big(\lambda_1 y_1^2 + \lambda_2 y_2^2\big) + 2k_1 y_p^3 \\ &\leqslant V_{xx} - mV, \end{aligned}$$

where $m = 2\sigma\big(1 - \frac{k_1|\mathbf{y}(\cdot,0)|}{\sigma}\big) > 0$ provided $|\mathbf{y}(\cdot,0)| < \sigma/k_1$. The last inequality is obtained from the result in the proof of Theorem 2.

Now, applying the Weak Maximum Principle [5, p. 369], we have

$$0 \leqslant V \leqslant C,$$

where $C = \max V$ on the parabolic boundary $\Gamma_t = \bar{U}_T - U_T$ with $U_T = U \times (0, T]$.

Remembering $m > 0$, we see that in shorter periods of time, $V_t \leqslant V_{xx}$.

Thus,

$$V(x,t) < \big\|V(\cdot,0)\big\|_{L^\infty} < \left(\frac{\sigma}{k_1}\right)^2.$$

Since $V = |\mathbf{y}|^2$, we have $|\mathbf{y}(x,t)| < \sigma/k_1$ for all $t \geqslant 0$.

Let $\tilde{V} = e^{mt}V$. Then we see that $\tilde{V}$ satisfies $\tilde{V}_t \leqslant \tilde{V}_{xx}$ by (20). Thus we have $e^{mt}V \leqslant (\frac{\sigma}{k_1})^2$, which leads to $V \leqslant e^{-mt}(\frac{\sigma}{k_1})^2 \to 0$, as $t \to \infty$. Consequently, $y_1(x,t)$ and $y_2(x,t)$ converge to zero as $t \to \infty$. Hence our assertion is proven. □

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References

[1] T. Aittokallio, M. Gyllenberg, O. Polo, J. Toivonen, A. Virkki, Model-based analysis of mechanisms responsible for sleep-induced carbaon dioxide differences, Bull. Math. Biol. 68 (2006) 315–341.
[2] C.A. Burtis, E.R. Ashwood, Tietz Textbook of Clinical Chemistry, third ed., W.B. Saunders Company, Pittsburgh, 1998.
[3] A. Bidani, E.D. Crandall, R.E. Forster, Analysis of postcapillary pH changes in blood in vivo after gas exchange, J. Appl. Physiol. 44 (1978) 770–781.
[4] S.J. Dodgson, R.E. Tashian, G. Gros, N.D. Carter, The Carbonic Anhydrases: Cellular Physiology and Molecular Genetics, Plenum Press, New York, 1991.
[5] L.C. Evans, Partial Differential Equations, Amer. Math. Soc., 2002.
[6] C. Geers, G. Gros, Carbon dioxide transport and carbonic anhydrase in blood in muscle, Physiol. Rev. 80 (2000) 681–715.
[7] L.C. Garg, T.H. Maren, Rates of hydration of carbon-dioxide and dehydration of carbonic-acid at 37 degrees, Biochim. Biophys. Acta 161 (1972) 70–76.
[8] B.M. Gilfix, M. Bique, S. Magder, A physical chemical approach to the analysis of acid–base balance in the clinical setting, J. Crit. Care 7 (1993) 187–197.
[9] J.K. Hale, Ordinary Differential Equations, Wiley, New York, 1969.
[10] E.P. Hill, G.G. Power, L.D. Longo, A mathematical model of carbon dioxide transfer in the placenta and its interaction with oxygen, Am. J. Physiol. 224 (1973) 283–299.
[11] E.P. Hill, G.G. Power, L.D. Longo, Mathematical simulation of pulmonary O_2 and CO_2 exchange, Am. J. Physiol. 224 (1973) 904–917.
[12] J.A. Kellum, Determinants of blood pH in health and disease, Crit. Care 4 (2000) 6–14.
[13] C. Li, E.S. Wright, Modelling chemical reactions in rivers: A three component system, Discrete Contin. Dyn. Syst. 7 (2001) 377–384.
[14] C. Li, E.S. Wright, Global existence of solutions to a reaction–diffusion system based upon carbonate reaction kinetics, Commun. Pure Appl. Anal. 1 (2002) 77–84.
[15] J. Lim, Stability of solutions to a reaction–diffusion system based upon chemical reaction kinetics, J. Math. Chem. 43 (2008) 1134–1140.
[16] B. Morelli, Fast mixing flow system: Kinetics of carbonic-acid dehydration in aqueous acid solutions between 20- and 40-degrees-C, Anal. Chim. Acta 106 (1979) 73–79.
[17] D.L. Nelson, M.M. Cox, Lehninger Principles of Biochemistry, W.H. Freeman, New York, 2000.
[18] H.E. Spiegel, Clinical Biochemistry: Contemporary Theories and Techniques, vol. 1, Academic Press, New York, 1981.
[19] K. Sahlin, A. Alvestrand, R. Brandt, E. Hultman, Intracellular pH and bicarbonate concentration in human muscle during recovery from exercise, J. Appl. Physiol. 45 (1978) 474–480.
[20] K. Uchida, M. Mochizuki, K. Niizeki, Diffusion coefficients of CO2 molecule and bicarbonate ion in hemoglobin solution measured by fluorescence technique, J. Physiol. 33 (1983) 619–634.
[21] J.D. Wilson, E. Braunwald, K.J. Isselbacher, R.G. Petersdorf, J.B. Martin, A.S. Fauci, R.K. Root, Harrison's Principles of Internal Medicine, twelfth ed., McGraw–Hill, New York, 1991.