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Mathematical Modeling of Metabolic Processes in a Living Organism in Relation to Nutrition

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Summary: The paper is devoted to the mathematical modeling of metabolism and nutrition based on enzyme-kinetics reactions described by Michaelis-Menten equations. Proposed are simple models of metabolic processes in a living system which explain certain effects related to various regimes of nutrition and fasting.

Keywords: Metabolic Processes, Enzyme-kinetics Reactions, Michaelis-Menten Equations.

1. INTRODUCTION AND MOTIVATION

The food substances entering a living organism gradually undergo biochemical changes during digestion and metabolic processes. It is characteristic for biochemical processes that enzymes play an important role as catalists.

Biochemical processes involving enzymes can be effectively described mathematically by systems of nonlinear differential equations. The basic model of enzyme kinetics is proposed by Michaelis and Menten [3]. A substrate S converts into a product P in the presence of an enzyme E. Thereby S and E bind into an enzyme-substrate complex C, which then dissolves into P and E. Schematically,

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E \qquad (1)$$

where k_1, k_{-1} and k_2 are coefficients of proportionality. The first process – the binding of S and E into the complex C – is reversible, the production of P is irreversible. According to the Mass Action Law, the rate of a reaction is proportional to the product of the

concentrations of the reactants. The corresponding system of ordinary differential equations is, see e.g. [6]:

$$\begin{aligned} ds/dt &= -k_1 es + k_{-1} c \\ dc/dt &= k_1 es - (k_{-1} + k_2) c \\ de/dt &= -k_1 es + (k_{-1} + k_2) c \\ dp/dt &= k_2 c \end{aligned} \tag{2}$$

wherein $s = [S]$, $e = [E]$, $c = [C]$, $p = [P]$ are the concentrations involved and the initial conditions are

$$s(0) = s_0,\ c(0) = c_0,\ e(0) = e_0,\ p(0) = 0. \tag{3}$$

The equation for p is uncoupled, so we shall further concentrate on the system of the first three coupled equations. Using the following nondimensionalization, cf. [6],

$$\begin{aligned} &\tau = k_1 e_0 t,\ u(\tau) = s(t)/s_0,\ \upsilon(\tau) = c(t)/e_0, \\ &w(\tau) = e(t)/e_0,\ \lambda = k_{-1}/(k_1 s_0), \\ &K = (k_{-1} + k_2)/(k_1 s_0),\ \varepsilon = e_0/s_0 \end{aligned} \tag{4}$$

we obtain the system

$$\begin{aligned} u' &= -uw + \lambda\upsilon \\ \varepsilon\upsilon' &= uw - K\upsilon \\ \varepsilon w' &= -uw + K\upsilon \end{aligned} \tag{5}$$

with initial conditions

$$u(0) = 1,\ \upsilon(0) = 0,\ w(0) = 1. \tag{6}$$

Typically we have $\varepsilon \in \left[10^{-7}, 10^{-2}\right]$, which makes system (5) stiff. Namely, the substrate variable (u) changes near 0 much slower than the enzyme (υ) and complex variables (w) change. We can exclude one of the variables υ or w from system (5), reducing thus the

number of equations from 3 to 2. However, even the reduced system cannot be solved in a closed form, see [6]. Therefore we need to make use of numerical methods, see Figs. 1 and 2.

Remark. As well-known, the solution for s in (2) can be approximated by the solution σ of the simple DE $d\sigma / dt = k_2 e_0 \sigma / (s_0 k + \sigma)$. However, we shall not be able to use such an approximation, as we shall need to supply (2) by additional nonlinear terms.

In an organism the enzymes themselves are a product of biochemical reactions. This observation lies at the basis of the proposed models. The concentration of enzymes in the organism changes: namely the concentration diminishes because of a natural wash-out of enzymes and increases due to a reproduction of enzymes. The corresponding models are considered in Section 3. In Section 4 the results of numerical experiments with the proposed models are presented.

2. ASSUMPTIONS OF THE MODEL

In the present work we propose a global mathematical model of the metabolic processes in a living organism under the following assumptions, cf. [2]:

1. All substances entering the organism (food, water, oxygen etc.) are considered as substrates, involved in subsequent processes catalized by the enzymes present in the organism.

2. Theoretically all enzyme-catalytic reactions can be described mathematically using Michaelis-Menten equations involving specific parameters. However, the mathematical description of even a small number of reactions leads to a complex mathematical system of nonlinear differential equations, which cannot be solved analytically and whose numerical study is tedious. In order to keep the mathematical model as simple as possible, we unify the biochemical reactions in large groups under certain characteristic properties. For instance, in the model proposed no substantial distinction is made between catabolic and anabolic processes and between digestic and metabolic processes – all these processes are considered from the point of view of enzyme kinetic.

3. The role of enzymes in biochemical processes is twofold. From one side, enzymes are catalysts of these processes needed for the production of certain products. On the other side, enzymes are themselves products of the metabolism. As a consequence, the biochemical processes can be conditionally subdivided into two large groups. In the first one we classify catabolic enzyme-catalytic reactions which are not directly involved in the production of enzymes; typically here belong reactions, partaking in digestion and lower metabolic cycles. In the second group we classify anabolic reactions responsible for the production of new enzymes.

4. For simplicity we can assume that catabolic reactions take place mainly in the extracellular part of the organism and that their main purpose is the breakdown of the nutrient substances up to amino acids. On the other side anabolic reactions occur mainly in the citoplasm of the cells leading to the synthesis of amino acids up to proteins. We can consider the extracellular and the intracellular parts of the organism as two separate compartments arriving thus to a two-compartmental model.

5. In an organism, the concentration of enzymes (both in bound and free form) undergoes changes. One reason is the outflow of enzymes with the excrements of the organism. We thus introduce a wash-out function γe in the equation for e as follows:

$$\begin{aligned} ds/dt &= -k_1 es + k_{-1} c \\ dc/dt &= k_1 es - (k_{-1} + k_2) c \\ de/dt &= -k_1 es + (k_{-1} + k_2) c - \gamma e \\ dp/dt &= k_2 c \end{aligned} \tag{7}$$

where the initial conditions are again (3) and $\gamma \geq 0$ is a wash-out constant.

Using formulae (4) together with $\delta = \gamma / (k_1 s_0)$ we obtain the system

$$\begin{aligned} u' &= -uw + \lambda \upsilon \\ \varepsilon \upsilon' &= uw - K\upsilon \\ \varepsilon w' &= -uw + K\upsilon - \delta w \end{aligned} \tag{8}$$

with initial conditions (6). Figs. 3 and 4 visualize the numerical solutions to (7), resp. (8).

3. MODELS WITH TWO TYPES OF SUBSTRATES

In what follows we mathematically describe the simultaneous transformation of two different types of nutrient substrates *S* and *R*. We assume that the enzyme *E* stands for the set of all enzymes necessary for the transformation of *S* and *R* and that *E* is partially reproduced from the substrates *S*, *R* in the sense that certain components of *S* and *R* are used for the production of new enzymes. The nutrients (substrates) are differentiated as follows: substrates *S* do not directly contribute to the formation of proteins, whereas substrates *R* are easily converted to proteins and effectively contribute to the reproduction of enzymes needed for the biochemical activity in the organism. Amino acids belong to group *R*. The corresponding enzyme-kinetic can be schematically described in two possible ways.

Variant 1. Here it is assumed that the nutrients *S* and *R* are partially transformed into enzymes according to the following scheme

$$\begin{aligned} S+E &\underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \overset{k_2}{\rightarrow} (1-\alpha)Q_1+\alpha E+E \\ R+E &\underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} RE \overset{k_4}{\rightarrow} (1-\beta)Q_2+\beta E+E \end{aligned} \tag{9}$$

where $0 \le \alpha < \beta \le 1$. In particular, if $\alpha = 0$, $\beta = 1$, (9) obtains the form

$$\begin{aligned} S+E &\underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} SE \overset{k_2}{\rightarrow} Q+E \\ R+E &\underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} RE \overset{k_4}{\rightarrow} E+E=2E \end{aligned} \tag{10}$$

We shall assume that nutrients both of types *S* and *R* are entering the organism, which will be reflected by means of functions $U_s = U_s(t)$, $U_r = U_r(t)$.

The scheme (9) leads to the following system of differential equations:

$$\begin{aligned}
ds/dt &= -k_1 se + k_{-1} c_s + U_s \\
dr/dt &= -k_3 re + k_{-3} c_r + U_r \\
dc_s/dt &= k_1 se - (k_{-1} + k_2) c_s \\
dc_r/dt &= k_3 re - (k_{-3} + k_4) c_r \\
de/dt &= -k_1 se + (k_{-1} + (1+\alpha) k_2) c_s - \\
&\quad -k_3 re + (k_{-3} + (1+\beta) k_4) c_r - \gamma e
\end{aligned} \tag{11}$$

wherein s = [*S*], r = [*R*], e = [*E*], c_s = [*C*], c_r = [*RE*] are the concentrations of the corresponding substances in (9) and the functions $U_s = U_s(t)$, $U_r = U_r(t)$ present the (rate of) introduction of nutrients in the organism. The saturation of the enzyme *E* in the left-hand side of the equation for *de*/*dt* in (11) is limited again by the wash-out function γe. The initial conditions are

$$s(0) = s_0,\ r(0) = r_0,\ c_s(0) = c_r(0) = 0,\ e(0) = e_0.$$

Numerical solutions to (11) are given on Figs. 5 and 6.

Variant 2. Here we assume that the nutrient *S* is partially transformed into nutrient *R* and then *R* is partially transformed into enzyme.

$$\begin{aligned}
&S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} (1-\alpha) Q_1 + \alpha R + E \\
&R + E \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} RE \xrightarrow{k_4} (1-\beta) Q_2 + \beta E + E
\end{aligned} \tag{12}$$

This scheme leads to the following system of ODE's:

$$
\begin{aligned}
ds/dt &= -k_1 se + k_{-1} c_s + U_s \\
dr/dt &= -k_3 re + k_{-3} c_r + \alpha k_2 c_s + U_r \\
dc_s/dt &= k_1 se - \left(k_{-1} + k_2\right) c_s \\
dc_r/dt &= k_3 re - \left(k_{-3} + k_4\right) c_r \\
de/dt &= -k_1 se + \left(k_{-1} + k_2\right) c_s - \\
&\quad - k_3 re + \left(k_{-3} + \left(1+\beta\right) k_4\right) c_r - \gamma e
\end{aligned}
\tag{13}
$$

The meaning of the functions $U_s = U_s(t)$, $U_r = U_r(t)$, γe as well as the initial conditions are same in (11). Numerical solutions to (13) are visualized on Fig. 7 and Fig. 8.

4. COMMENTS ON THE NUMERICAL EXPERIMENTS

For the numerical solution we use an Euler method and a uniform mesh which is smaller in the boundary layer, e.g. the stepsize is h = 0.007 for the first 150 points starting from 0, and then it becomes larger, h = 0.05. It has been shown [1, 5], that by means of such a simple mesh one can achieve same uniform error (accuracy) as more sophisticated meshes can produce.

Fig. 1 presents the solution to (2) with the following values for the parameters and initial data:

$$k_1 = 5,\ k_{-1} = 1,\ k_2 = 4,\ s_0 = 10/3,\ e_0 = 1. \tag{14}$$

Fig. 2 presents the solution to (5) corresponding to the above data transformed by (4). Figs. 3 and 4 visualize the solutions to (7) and (8) respectively using data (14) with γ = 0.5. The wash-out effect of the parameter γ (with respect to the enzyme) is clearly observed.

To visualize the solutions to the next two models (11) and (13) we use the following values for the parameters and the initial data:

$$k_1 = 5,\ k_{-1} = 1,\ k_2 = 4,\ k_3 = 5,$$
$$k_{-3} = 1,\ k_4 = 4,\ \alpha = 0.2,\ \beta = 0.5, \qquad (15)$$
$$\gamma = 0.3,\ s_0 = 10/3,\ r_0 = 2,\ e_0 = 1.$$

Fig. 5 presents graphically the solutions of (11) within $U_s(t) = U_r(t) = 0$. The next Fig. 6 visualizes the outputs to (11) with

$$U_s(t) = \{3,\ 4 \le t \le 5;\ 0,\ \text{otherwise}\};$$
$$U_r(t) = \{2,\ 2 \le t \le 3;\ 0,\ \text{otherwise}\}. \qquad (16)$$

Figs. 7 and 8 present the solutions to (13) using data (15); on Fig. 7 we have $U_s(t) = U_r(t) = 0$, Fig. 8 uses $U_s(t)$ and $U_r(t)$ from (16). A possible purpose of any nutrition regime (diet) could be to keep the enzyme concentration above a certain limit. Thus the substrate intake function $U_s(t)$ plays the role of control variable. We may formulate various optimization or control problems like keeping *e* above a certain level, minimizing the quantity of food (the integral of $U_s(t)$).

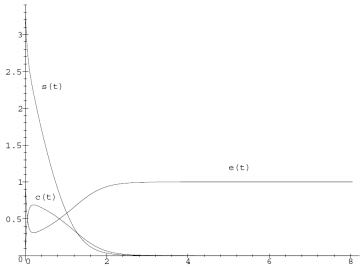

Fig. 1. Solution to (2) using data (14)

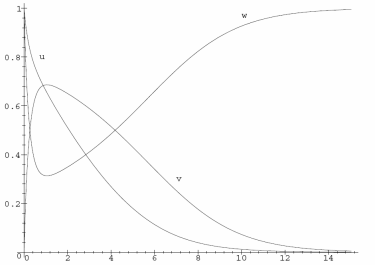

Fig. 2. Solution to (5) using data (14)

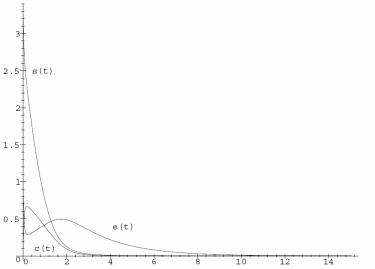

Fig. 3. Solution to (7) using data (14) and $\gamma = 0.5$

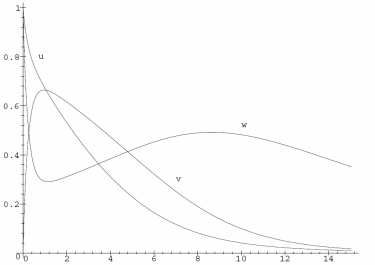

Fig. 4. Solution to (8) using data (14) and $\gamma = 0.5$

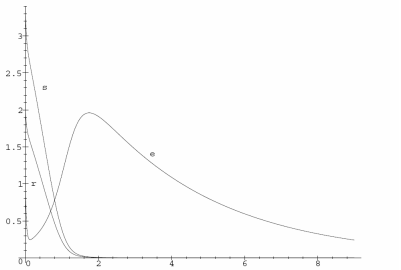

Fig. 5. Solution to (11) using data (15) within α = 0.2, β = 0.5, γ = 0.3 and $U_s(t) = U_r(t) = 0$

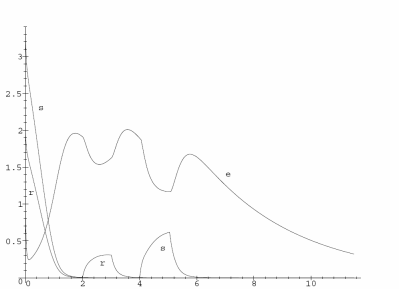

Fig. 6. Solution to (11) using data (15) within α = 0.2, β = 0.5, γ = 0.3 and $U_s(t)$, $U_r(t)$ from (16)

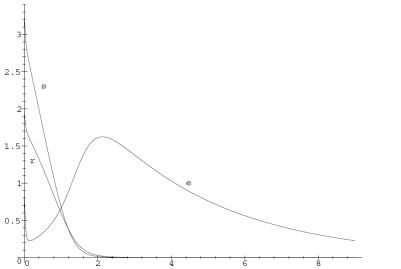

Fig. 7. Solution to (13) using data (15) within α = 0.2, β = 0.5, γ = 0.3 and $U_s(t) = U_r(t) = 0$

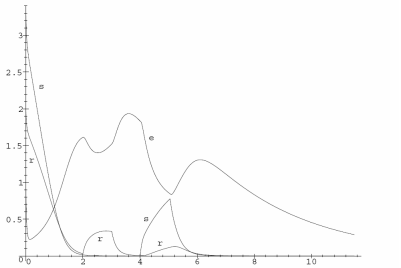

Fig. 8. Solution to (13) using data (15) within α = 0.2, β = 0.5, γ = 0.3 and $U_s(t)$, $U_r(t)$ from (16)

5. CONCLUSION

We present and numerically study two enzyme-kinetic models with the purpose to model basic metabolic activity of an organism. It is observed that different types of substrates contribute differently to the (re)production of enzymes.

There is a strong feedback expressed in a stimulating effect on the concentration of enzymes when the substrate exhibits a restoration quality (α close to 1), or in an inhibiting effect whenever the substrate does not possess such qualities (α close to 0). The effectiveness of the above mentioned feedback is checked in the proposed model by the numerical simulation of various types of diets (that is various regimes of nutrition and fasting). It is well-known that well-expressed symptomatic phenomena can be observed under various types of diets, such as a slow restoration of the metabolic activity of the organism after a prolonged fasting, a possibility for poisoning when consuming certain types of food after fasting, etc. The inability of the metabolic system to process the nutrient substrates can be interpreted as poisoning of the organism due to the lack of suitable enzymes needed to catabolize the incoming nutrients.

The numerical experiments with the proposed models suggest that they can be used for checking various hypotheses related to dieting, for an alternative model see [4]. We hope that on the base of the above models more sophisticated models involving certain specific metabolic circles can be developed.

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