

# Decomposition of enzyme kinetics equations

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**Abstract.** The problem of singularly perturbed differential systems decomposition by the method of integral manifolds is studied and the application of the method to the problems of kinetics is considered.

## 1. Introduction

The main object of our consideration is the following system of differential equations:

$$\dot{x} = f(x, y, t, \varepsilon), \quad (1)$$

$$\varepsilon \dot{y} = g(x, y, t, \varepsilon), \quad (2)$$

where  $x$  and  $f$  are vectors in Euclidean spaces  $R^m$ ,  $y$  and  $g$  are vectors in  $R^n$ ,  $t \in R$ , and  $\varepsilon$  is a small positive parameter.

The goals of the paper are to construct a transformation reducing (1)-(2) to the system

$$\dot{v} = \varphi(v, t, \varepsilon), \quad \varepsilon \dot{z} = \eta(v, z, t, \varepsilon),$$

and to discuss some applications to the problems of enzyme kinetics.

This approach was suggested in [5] and it has been successfully used to solve a number of problems in control theory. However, in the general case, the construction of a splitting transformation is not a simple task. The transformation uses functions that describe slow and fast integral manifolds. With the construction of slow integral manifolds, the situation is sufficiently studied. After the first paper [6], in which the slow integral manifold was constructed as an asymptotic expansion in powers of a small parameter, this approach was used by many authors (see, for example, the book [4] and references therein).

## 2. Splitting transformation

Our main goal is the constructing of the transformation

$$x = v + \varepsilon H(v, z, t, \varepsilon), \quad (3)$$

$$y = z + h(x, t, \varepsilon), \quad (4)$$

which reduces the original system (1), (2) to the form

$$\dot{v} = \varphi(v, t, \varepsilon), \quad (5)$$

$$\varepsilon \dot{z} = \eta(v, z, t, \varepsilon). \quad (6)$$

Let  $(x(t), y(t))$  be a solution to (1), (2) with an initial condition  $x(t_0) = x_0, y(t_0) = y_0$ . There exists a solution  $(v(t), z(t))$  of (5), (6) with the initial condition  $v(t_0) = v_0, z(t_0) = z_0$ , such that

$$x(t) = v(t) + \varepsilon H(v(t), z(t), t, \varepsilon), \quad y(t) = z(t) + h(x(t), t, \varepsilon). \quad (7)$$

It is sufficient to show that (7) takes place under  $t = t_0$ . Setting  $t = t_0$  in (7) we obtain

$$x_0 = v_0 + \varepsilon H(v_0, z_0, t_0, \varepsilon), \quad y_0 = z_0 + h(x_0, t_0, \varepsilon),$$

and, therefore,  $z_0 = y_0 - h(x_0, t_0, \varepsilon)$ .

For  $v_0$  we have the equation

$$v_0 = x_0 - H(v_0, z_0, t_0, \varepsilon) = V(v_0), \quad (8)$$

which has the unique solution for any  $x_0 \in R^m$  and fixed  $z_0$  and  $t_0$ , where

$$\|z_0\| = \|y_0 - h(x_0, t_0, \varepsilon)\| \leq \rho_2$$

for some  $\rho_2$ .

If some natural assumptions are hold, then there exist such numbers  $\varepsilon_2$  and  $\rho_2$  that for all  $\varepsilon \in (0, \varepsilon_2]$  any solution  $x = x(t, \varepsilon), y = y(t, \varepsilon)$  of system (1), (2) with the initial condition  $x(t_0, \varepsilon) = x_0, y(t_0, \varepsilon) = y_0$ , where  $\|y_0 - h(x_0, t_0, \varepsilon)\| \leq \rho_2$ , can be represented in form of (7). This means that in the  $\rho_2$ -neighbourhood of the slow integral manifold  $y = h(x, t, \varepsilon)$  of system (1), (2) can be reduced to the form (5), (6) by the splitting transformation (3), (4). Thus, system (1), (2) was split into two subsystems, the first of which is independent and contains a small parameter in a regular manner. Note that the initial value  $v_0$  can be calculated from (8) in a form of an asymptotic expansion:

$$v_0 = v_{00} + \varepsilon v_{01} + \varepsilon^2 v_{02} + \dots$$

For example,  $v_{00} = z_0, v_{01} = -H(x_0, z_{00}, t_0, 0)$ , where  $z_{00} = y_0 - h(x_0, t_0)$ .

Note that there exist positive numbers  $a$  and  $b$  such that

$$\begin{aligned} \|H(v, z, t, \varepsilon)\| &\leq a\|z\|, \\ \|H(v, z, t, \varepsilon) - H(v, \bar{z}, t, \varepsilon)\| &\leq b\|z - \bar{z}\|, \\ \|H(v, z, t, \varepsilon) - H(\bar{v}, z, t, \varepsilon)\| &\leq b\|z\|\|v - \bar{v}\|. \end{aligned} \quad (9)$$

It is important to underline that there exists number  $K, K > 1$  such that

$$\|z(t, \varepsilon)\| \leq K \exp(-\gamma t/\varepsilon) \|z_0\|, \quad t \geq 0. \quad (10)$$

This means: the solution  $x = x(t, \varepsilon), y = y(t, \varepsilon)$  of the original system (1)-(2) that satisfied the initial condition  $x(0, \varepsilon) = x_0, y(t_0, \varepsilon) = y_0$  can be represented as

$$\begin{aligned} x(t, \varepsilon) &= v(t, \varepsilon) + \varepsilon \varphi_1(t, \varepsilon), \\ y(t, \varepsilon) &= \bar{y}(t, \varepsilon) + \varphi_2(t, \varepsilon). \end{aligned} \quad (11)$$

Thus, this solution is represented as a sum of solution which lies on the slow integral manifold, i.e.

$$x = x(t, \varepsilon) = v(t, \varepsilon), \quad y(t, \varepsilon) = h(v(t, \varepsilon), t, \varepsilon),$$

and exponentially decreasing functions

$$\begin{aligned} \varepsilon \varphi_1(t, \varepsilon) &= \varepsilon H(v(t, \varepsilon), z(t, \varepsilon), t, \varepsilon), \\ \varphi_2(t, \varepsilon) &= z(t, \varepsilon) + h(v(t, \varepsilon), t, \varepsilon) + \varepsilon H(v(t, \varepsilon), z(t, \varepsilon), t, \varepsilon), t, \varepsilon) - h(v(t, \varepsilon), t, \varepsilon). \end{aligned}$$

### 3. Systems that are linear with respect to fast variables

Consider the differential system

$$\dot{x} = \zeta(x, t, \varepsilon) + F(x, t, \varepsilon)y, \tag{12}$$

$$\varepsilon \dot{y} = \xi(x, t, \varepsilon) + G(x, t, \varepsilon)y, \tag{13}$$

where  $x \in R^m$ ,  $y \in R^n$ ,  $t \in R$ .

Such systems are typical of enzyme kinetics [1].

We assume that the eigenvalues  $\lambda_i(x, t)$  of the matrix  $G(x, t, 0)$  have the property  $Re\lambda_i(x, t) \leq -2\gamma < 0$ , in  $t \in \mathbb{R}, x \in \mathbb{R}^m$ , and that the matrix- and vector-functions  $\zeta, \xi, F$  and  $G$  are continuous and bounded as well as their partial derivatives with respect to the arguments  $t \in \mathbb{R}, x \in \mathbb{R}^m, \varepsilon \in [0, \varepsilon_0]$ . When these assumptions hold, the system (12)-(13) has a slow integral manifold

$$y = h(x, t, \varepsilon) = h_0(x, t) + \varepsilon h_1(x, t) + \dots$$

Noting that

$$\frac{dy}{dt} = \frac{\partial h}{\partial t} + \frac{\partial h}{\partial x}(\zeta + Fh),$$

or using the first of (12)-(13)), the functions  $h_i$  can be derived from the second of (12)-(13)

$$\varepsilon \frac{\partial h}{\partial t} + \varepsilon \frac{\partial h}{\partial x}(\zeta + Fh) = \xi + Gh.$$

Suppose that the following representations take place

$$F(x, t, \varepsilon) = \sum_{j \geq 0} \varepsilon^j F_j(x, t), \quad G(x, t, \varepsilon) = \sum_{j \geq 0} \varepsilon^j G_j(x, t),$$

$$\zeta(x, t, \varepsilon) = \sum_{j \geq 0} \varepsilon^j \zeta_j(x, t), \quad \xi(x, t, \varepsilon) = \sum_{j \geq 0} \varepsilon^j \xi_j(x, t).$$

Here,  $G_0 = G_0(x, t)$  plays the role of matrix  $B(x, t)$ . The formulae for the coefficients of asymptotic expansions of slow integral manifold  $h = h(x, t, \varepsilon)$  take the form

$$\begin{aligned} h_0 &= G_0^{-1} \xi_0, \\ h_k &= G_0^{-1} \left[ \frac{\partial h_{k-1}}{\partial t} + \sum_{p=0}^{k-1} \frac{\partial h_p}{\partial x} (\zeta_{k-1-p} + \sum_{j=0}^{k-1-p} F_j h_{k-p-1-j}) \right. \\ &\quad \left. - \xi_k - \sum_{j=1}^k G_j h_{k-j} \right], \quad k \geq 1. \end{aligned} \tag{14}$$

The invariance equation for the fast integral manifold  $H = H(v, z, t, \varepsilon)$  in this case takes the form

$$\begin{aligned} \varepsilon \frac{\partial H}{\partial t} + \varepsilon \frac{\partial H}{\partial v} [\zeta(v, t, \varepsilon) + F(v, t, \varepsilon)h(v, t, \varepsilon)] + \frac{\partial H}{\partial z} [G(v + \varepsilon H, t, \varepsilon) \\ - \varepsilon \frac{\partial h}{\partial x}(v + \varepsilon H, t, \varepsilon)F(v + \varepsilon H, t, \varepsilon)]z = \zeta(v + \varepsilon H, t, \varepsilon) - \zeta(v, t, \varepsilon) \\ + F(v + \varepsilon H, t, \varepsilon)(z + h(v + \varepsilon H, t, \varepsilon)) - F(v, t, \varepsilon)h(v, t, \varepsilon). \end{aligned}$$

Setting  $\varepsilon = 0$ , we obtain

$$\frac{\partial H_0}{\partial z} G_0(v, t)z = F_0(v, t)z.$$

It is possible to represent  $H_0(v, t, z)$  in the form  $H_0(v, z, t) = D_0(v, t)z$ , where matrix  $D_0(v, t)$  satisfies the equation

$$D_0(v, t)G_0(v, t) = F_0(v, t),$$

and, therefore,

$$H_0(v, z, t) = F_0(v, t)G_0^{-1}(v, t)z.$$

Neglecting terms of order  $o(\varepsilon)$ , we use the transformation

$$x = v + \varepsilon H_0(v, z, t), \quad y = z + h_0(x, t) + \varepsilon h_1(x, t) \tag{15}$$

to reduce system (12) to a nonlinear block-triangular form:

$$\begin{aligned} \dot{v} &= \zeta_0(v, t) + F_0(v, t)h_0(v, t) + \varepsilon[\zeta_1(v, t) \\ &+ F_0(v, t)h_1(x, t) + F_1(v, t)h_0(v, t)] + O(\varepsilon^2), \\ \varepsilon \dot{z} &= [G_0(v, t) + \varepsilon(G_1(v, t) + \frac{\partial G_0}{\partial x}(v, t)H_0(v, z, t) \\ &- \frac{\partial h_0}{\partial x}(v, t)F_0(v, t))]z + O(\varepsilon^2). \end{aligned} \tag{16}$$

#### 4. Equations of enzyme kinetics

##### 4.1. General equations

Consider the differential system

$$\begin{aligned} \dot{x} &= \zeta(x) + F(x)y, \\ \varepsilon \dot{y} &= \xi(x) + G(x)y, \end{aligned} \tag{17}$$

where  $x \in R^m$ ,  $y \in R^n$ ,  $t \in R$ , which appears under the modelling of enzyme kinetics systems [1, 2, 3]. Let the initial value conditions are

$$x(0) = x_0, \quad y(0) = y_0.$$

This system may be reduced to the form

$$\dot{v} = \zeta(v) + F(v)h(v, \varepsilon), \tag{18}$$

$$\varepsilon \dot{z} = [G(v + \varepsilon H) - \varepsilon \frac{\partial h}{\partial x}(v + \varepsilon H)]z \tag{19}$$

by the transformation

$$x = v + \varepsilon H(v, z, \varepsilon), \tag{20}$$

$$y = z + h(x, \varepsilon). \tag{21}$$

Here,

$$h(x, \varepsilon) = h_0(x) + \varepsilon h_1(x) + O(\varepsilon^2), \tag{22}$$

$$H(v, z, \varepsilon) = H_0(v, z) + O(\varepsilon), \tag{23}$$

where

$$h_0(x) = -G^{-1}(x)\xi(x), \quad h_1(x) = G^{-1}(x)[\frac{\partial h_0}{\partial x}(\zeta(x) + F(x)h_0(x)) - \xi(x) - G(x)h_0(x)], \tag{24}$$

$$H_0(v, z) = F(v)G^{-1}(v)z. \tag{25}$$

Corresponding initial value conditions take the form

$$v(0) = v_0 = x_0 - \varepsilon F(x_0)G^{-1}(x_0)[y_0 + G^{-1}(x_0)\xi(x_0)] + O(\varepsilon^2),$$

$$z(0) = z_0 = y_0 + G^{-1}(x_0)\xi(x_0) - \varepsilon h_1(x_0) + O(\varepsilon^2).$$

Note that for dimensionless models of enzyme kinetics the initial values of slow variables are equal to unity and the initial values of fast variables are equal to zero, i.e.  $x_0 = \text{colon}(1, 1, \dots, 1)$  and  $y_0$  is the zero vector,  $y_0 = 0$  [2, 3]. This means that

$$v(0) = v_0 = x_0 - \varepsilon F(x_0)G^{-2}(x_0)\xi(x_0)] + O(\varepsilon^2), \tag{26}$$

$$z(0) = z_0 = G^{-1}(x_0)\xi(x_0) - \varepsilon h_1(x_0) + O(\varepsilon^2) \tag{27}$$

where  $x_0 = \text{colon}(1, 1, \dots, 1)$ .

Results of this section together with representation (7) or (11) means that the original dynamical model (17) of some enzyme system with the initial conditions

$$x(0) = x_0 = \text{colon}(1, 1, \dots, 1), \quad y(0) = 0$$

may be reduced to the dynamical model of lower dimension

$$\dot{v} = \zeta(v) + F(v)h(v, \varepsilon), \quad v(0) = v_0 = x_0 - \varepsilon F(x_0)G^{-2}(x_0)\xi(x_0)] + O(\varepsilon^2), \tag{28}$$

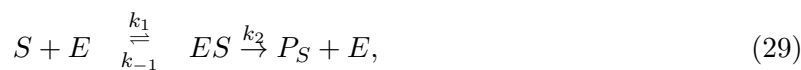
without singular perturbation. For the original variables  $x$  and  $y$  the following presentation may be used

$$x = v(t, \varepsilon), y = h(v(t, \varepsilon), \varepsilon).$$

It is important to emphasize that the reduced model is effectively constructed with any degree of accuracy and reflects the behavior of the original model both qualitatively and quantitatively.

#### 4.2. Enzyme-Substrate-Inhibitor System

We consider a enzyme–substrate reaction [2] as an example of system with two slow and two fast variables. The reaction consists of an enzyme  $E$  with a single reaction site (many enzymes have several such sites) for which two substrates compete and form one of two complexes. These break down to give two products and the original enzyme. When one substrate combines with the enzyme it means, in effect, that it is inhibiting the other substrate’s reaction with that enzyme. The reactions can be written schematically as



where  $S$  and  $I$  are the two substrates, which compete for the same enzyme  $E$ , and  $P_S$  and  $P_I$  are the products of two enzyme-substrate reactions.

When two substrates are competing for the same enzyme site, the reaction system (29) and (30) is said to be *fully competitive*. In such reactions one or other of the substrates can be singled out for its reaction rate to be measured by an experiment (see more details in [2]). The one so singled out is called the *substrate* and the other the *inhibitor*. We choose the inhibitor to be  $I$  and its reaction to be (30).

Applying the law of mass action to (29), (30) gives the kinetic equations for the concentrations of the reactants. Since we shall be interested primarily in the rates of the reactions of  $S$  and  $I$ ,

we do not need the equations for the products; only the rate constants  $k_2$  and  $k_4$  in (29), (30) are involved. Thus we need only consider the kinetic equations for the substrate, inhibitor, and enzyme complex whose concentrations as functions of time  $t$  are denoted by

$$\begin{aligned} s(t) &= [S], \quad i(t) = [I], \quad e(t) = [E], \\ c_s(t) &= [ES], \quad c_i(t) = [EI]. \end{aligned} \quad (31)$$

The kinetic equations for the concentrations for the reactions (29), (30), see [2], are

$$\frac{ds}{dt} = -k_1 s e + k_{-1} c_s, \quad (32)$$

$$\frac{dc_s}{dt} = k_1 s e - (k_{-1} + k_2) c_s, \quad (33)$$

$$\frac{di}{dt} = -k_3 i e + k_{-3} c_i, \quad (34)$$

$$\frac{dc_i}{dt} = k_3 i e - (k_{-3} + k_4) c_i \quad (35)$$

$$\frac{de}{dt} = -k_1 s e - k_3 i e + (k_{-1} + k_2) c_s + (k_{-3} + k_4) c_i. \quad (36)$$

Appropriate initial conditions for equations (32)–(36) are that there are no enzyme complexes initially but  $s$ ,  $i$ , and  $e$  are prescribed, that is

$$s(0) = s_0, \quad i(0) = i_0, \quad e(0) = e_0, \quad c_s(0) = c_i(0) = 0. \quad (37)$$

The conservation equation for the enzyme  $e$  is obtained immediately by adding (33), (35), (36) and using the initial conditions (37) to get

$$\frac{d}{dt}(c_s + c_i + e) = 0 \Rightarrow c_s + c_i + e = e_0. \quad (38)$$

Eliminating  $e$  from (32)–(36) by using (38) gives four equations for  $s$ ,  $i$ ,  $c_s$  and  $c_i$ . We now introduce nondimensional variables and parameters by

$$\begin{aligned} x_1(\tau) &= \frac{s(t)}{s_0}, \quad x_2(\tau) = \frac{i(t)}{i_0}, \quad y_1(\tau) = \frac{c_s(t)}{e_0}, \quad y_2(\tau) = \frac{c_i(t)}{e_0}, \\ \tau &= k_1 e_0 t, \quad \varepsilon = \frac{e_0}{s_0}, \quad \beta = \frac{i_0}{s_0}, \quad \gamma = \frac{k_3}{k_1}, \end{aligned} \quad (39)$$

$$K_s = \frac{k_{-1} + k_2}{k_1 s_0}, \quad K_i = \frac{k_{-3} + k_4}{k_3 i_0}, \quad L_s = \frac{k_2}{k_1 s_0}, \quad L_i = \frac{k_4}{k_3 i_0}.$$

Then the four equations for  $s$ ,  $i$ ,  $c_s$  and  $c_i$  become the four dimensionless equations

$$\frac{dx_1}{d\tau} = -x_1 + (x_1 + K_s - L_s)y_1 + x_1 y_2 = f_1(x_1, x_2, y_1, y_2), \quad (40)$$

$$\frac{dx_2}{d\tau} = \gamma[-x_2 + x_2 y_1 + (x_2 + K_i - L_i)y_2] = f_2(x_1, x_2, y_1, y_2), \quad (41)$$

$$\varepsilon \frac{dy_1}{d\tau} = x_1 - (x_1 + K_s)y_1 - x_1 y_2 = g_1(x_1, x_2, y_1, y_2), \quad (42)$$

$$\varepsilon \frac{dy_2}{d\tau} = \beta\gamma[x_2 - x_2 y_1 - (x_2 + K_i)y_2] = g_2(x_1, x_2, y_1, y_2), \quad (43)$$

with initial conditions

$$x_1(0) = x_2(0) = 1, y_1(0) = y_2(0) = 0. \quad (44)$$

We use the results of the previous section to calculate the approximate two-dimensional slow invariant manifold and the equation that describes the flow on this manifold with the assumption that  $0 < \varepsilon \ll 1$ .

The degenerate system is

$$\frac{dx_1}{d\tau} = -x_1 + (x_1 + K_s - L_s)y_1 + x_1y_2, \quad (45)$$

$$\frac{dx_2}{d\tau} = \gamma[-x_2 + x_2y_1 + (x_2 + K_i - L_i)y_2], \quad (46)$$

$$0 = x_1 - (x_1 + K_s)y_1 - x_1y_2, \quad (47)$$

$$0 = \beta\gamma[x_2 - x_2y_1 - (x_2 + K_i)y_2], \quad (48)$$

The last two equations give the unique solution

$$y_1 = \bar{h}_0(x_1, x_2) = K_i x_1 / \Delta,$$

$$y_2 = \bar{\bar{h}}_0(x_1, x_2) = K_s x_2 / \Delta.$$

Here  $\Delta\beta\gamma$  is the determinant of the Jacobian matrix

$$B(x_1, x_2) = \begin{pmatrix} \frac{\partial g_1}{\partial y_1} & \frac{\partial g_1}{\partial y_2} \\ \frac{\partial g_2}{\partial y_1} & \frac{\partial g_2}{\partial y_2} \end{pmatrix} = \begin{pmatrix} -x_1 - K_s & -x_1 \\ -\beta\gamma x_2 & -\beta\gamma(x_2 + K_i) \end{pmatrix},$$

where  $\Delta = K_s x_2 + K_i x_1 + K_s K_i$ . The slow surface is stable since the  $-\text{tr} B(x_1, x_2)$  and  $\det B(x_1, x_2)$  are positive.

where

$$P = (K_i L_s - \gamma K_s L_i)x_2 + K_i^2 L_s,$$

$$Q = -(K_i L_s - \gamma K_s L_i)x_1 + \gamma K_s^2 L_i.$$

Consequently, the first order approximation to the flow on the slow invariant manifold is

$$\frac{dx_1}{d\tau} = \frac{K_i}{\Delta} \left[ -L_s x_1 + \frac{\varepsilon K_s}{\beta\gamma\Delta^3} (\beta\gamma[K_i x_1 + (K_s - L_s)(x_2 + K_i)]P x_1 + L_s Q x_1 x_2) \right] + O(\varepsilon^2),$$

$$\frac{dx_2}{d\tau} = \frac{\gamma K_s}{\Delta} \left[ -L_i x_2 + \frac{\varepsilon K_i}{\beta\gamma\Delta^3} (\beta\gamma x_1 x_2 L_i P + [K_s x_2 + (K_i - L_i)(x_1 + K_s)]Q x_2) \right] + O(\varepsilon^2),$$

where the manifold is given by

$$y_1 = \frac{K_i x_1}{\Delta} + \varepsilon \frac{K_i K_s}{\beta\gamma\Delta^4} [\beta\gamma(x_2 + K_i)P x_1 - x_1 x_2 Q] + O(\varepsilon^2),$$

$$y_2 = \frac{K_s x_2}{\Delta} + \varepsilon \frac{K_i K_s}{\beta\gamma\Delta^4} [-\beta\gamma x_1 x_2 P + (x_1 + K_s)x_2 Q] + O(\varepsilon^2).$$

## 5. Conclusion

The focus of this paper is the effective separation of slow and fast dynamics. The decomposition method begins by removing the slow variable from the fast equation, then an additional change of variables is applied to remove the fast variables from the slow equation, this results in a nonlinear block-triangular form.

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