Asymptotic expansions of solutions in the model of virus dynamics with immune response

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Abstract. This paper deals with the model of virus dynamics with immune response. Consisting of three integro–differential equations with partial derivatives with two small parameters the singularly perturbed system describes the model. By Vasil’eva–Tikhonov boundary function method, asymptotic expansions of the solutions of the initial boundary value problem are constructed.

1. Introduction
It is well–known that an extremely slow biological evolution process proceeds against the background of much faster interactions of different nature. As a result, models of evolution biology have several time scales. To model such processes with several time scales, systems of differential equations with a small parameter for a part of the derivatives are usually used. These systems are called singularly perturbed systems of differential equations. Numerical analysis of such systems involves a large amount of computation because there are variables that vary with appreciably different velocities.

For the first time, the analysis of singularly perturbed systems was carried out in the works of Tikhonov (see, for example, [1]). In these works, in particular, the passage to the limit of the solution to a degenerate problem in a system with several small parameters multiplying derivatives is justified. In her works ([2, 3, 4]), Vasil’eva developed the boundary functions method for ordinary singularly perturbed equations. The approach discussed allows us to construct approximate solutions with a high degree of accuracy. For integro–differential equations, a boundary layer phenomenon was considered for the first time in [5]. The goal of the paper is to build asymptotic expansions of the solution to the initial boundary value problem for the model of virus dynamics with immune response. The model describes the interaction of three population: healthy (uninfected) cells, infected cells, and cytotoxic T–lymphocytes (CTL).

Virus particles attach to a host cell and inject the genetic material into the cell. The immune system attacks a virus to stop its growth or to kill it at all. The cell–mediated response is composed of killer T–cells (also called cytotoxic T–lymphocytes, CTL). The immune cells multiply rapidly to kill off the pathogen. Killer T–cells fight infected cells. CTL response is generally considered to be the most effective response of the immune system.

2. Model
Let us consider the model of the virus dynamics with the specific immune response [6]:

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2. Model
Let us consider the model of the virus dynamics with the specific immune response [6]:
\[
\frac{du(t)}{dt} = b - \left( c + \int_{0}^{+\infty} \beta(s)v(t,s)ds \right) u(t),
\]
\[
\frac{\partial z(t, s)}{\partial t} = qv(t, s) + \gamma z(t, s) \left( 1 - \frac{z(t, s)}{p} \right),
\]
\[
\frac{\partial v(t, s)}{\partial t} = \mu \frac{\partial^2 v(t, s)}{\partial s^2} - mv(t, s) + \beta(s)u(t)v(t, s) - \xi v(t, s)z(t, s),
\]

with boundary and initial conditions:

\[
u(0) = u^0, \quad z(0, s) = z^0(s), \quad v(0, s) = v^0(s), \quad \frac{\partial v}{\partial t} (t, 0) = 0, \quad v(t, +\infty) = 0.
\]

Each virus phenotype is described by the set of parameters, and all possible values of these parameters form a phenotype space, which is assumed to be a one-dimensional and continuous: 
\( s \in [0, +\infty) \) (s is a dimensionless quantity). Variables \( v(t, s) \), cell/mm³, and \( z(t, s) \), cell/mm³, are the population density of infected cells of phenotype \( s \) at a time \( t \), \( \text{day} \), and the population density of CTL-cells, able to kill infected cells of phenotype \( s \) at a time \( t \), respectively. Uninfected target cells with concentration \( u(t) \), cell/mm³, are produced at constant rate \( b \), cell/(mm³·day), and have a natural death at a rate \( c \), 1/day. Uninfected cells become infected at a rate \( \beta \), mm³/(virion · day). The quantity \( +\infty \int_{0}^{\beta(s)v(t,s)ds} \) is called the infective force. Infected cells die naturally at a rate \( m \), 1/day, and are eliminated by CTL response at a rate \( \xi \), mm³/(virion · day). The activation term of CTL response is assumed to be proportional to \( v(t, s) \) with a coefficient \( q \), 1/day, since the number of infected cells should not be zero to activate the growth of \( z(t, s) \). After the activation of CTL response, the activated cells will multiply by cloning (the so-called clonal expansion). To model this phenomenon, a logistic term is employed. The dispersion with the coefficient \( \mu \), 1/day, defines the random mutations.

Since \( v(t, s) \) is a distribution, it is natural to assume that \( v(t, +\infty) = 0 \). The boundary condition at \( s = 0 \) is the non-flux condition for convenience. It is assumed that a host is already infected by a virus.

Without loss of generality, for simplicity, we assume that only \( \beta \) depends on \( s \) and that \( m, \xi \), \( q \), \( \gamma \) are constant and have common values for all phenotypes. Although the model is stated for \( s \in [0, +\infty) \), the parameter \( s \) is usually assumed to belong a finite interval \( [0, \ell] \), and the boundary condition is replaced by the condition \( \frac{\partial v}{\partial s} (t, \ell) = 0 \).

With the following changes of variables and parameters,

\[
t \rightarrow t\mu, \quad u \rightarrow \frac{cu}{b}, \quad v \rightarrow \frac{qv}{p\gamma}, \quad z \rightarrow \frac{z}{p}, \quad \beta \rightarrow \frac{p\gamma\beta}{cq}, \quad m \rightarrow \frac{m\mu}{\xi}, \quad \xi \rightarrow \frac{p\xi}{\mu},
\]
\[
\xi \rightarrow \frac{p\xi}{\mu}, \quad u^0 \rightarrow \frac{cu^0}{b}, \quad v^0 \rightarrow \frac{qv^0}{p\gamma}, \quad z^0 \rightarrow \frac{z^0}{p},
\]
\[
\varepsilon = \frac{\mu}{c}, \quad \theta = \frac{e}{\gamma}, \quad d = \frac{bq}{p\gamma\mu},
\]

the system (1) is transformed to the following form:
\[\varepsilon \frac{du(t)}{dt} = 1 - \left(1 + \int_0^\ell \beta(s)v(t, s)ds\right)u(t),\]
\[\varepsilon \theta \frac{\partial z(t, s)}{\partial t} = v(t, s) + z(t, s)\left(1 - z(t, s)\right),\]
\[\partial v(t, s) \partial t = \frac{\partial^2 v(t, s)}{\partial s^2} - mv(t, s) + d\beta(s)u(t)v(t, s) - \xi v(t, s)z(t, s)\]

with boundary and initial conditions

\[u(0) = u^0, \quad z(0, s) = z^0(s), \quad v(0, s) = v^0(s), \quad \frac{\partial v}{\partial t}(t, 0) = 0, \quad \frac{\partial v}{\partial s}(t, \ell) = 0.\]

The parameter \(\mu\) is proportional to the mutation probability. For HIV \(\mu\) does not exceed \(10^{-9} - 10^{-7}\) 1/day. HIV is one of the most rapidly mutating RNA–viruses so that \(\varepsilon\) is substantially smaller for more slowly mutating RNA–viruses. As \(\varepsilon \ll \gamma\), then \(\theta \ll 1\). Thereby a system (3) is a singularly perturbed system with two small parameters. As a result, it has three time scales. It should be noted that a system with several time scales was considered in the original work [1].

3. Constructing an asymptotic expansion

Let us find the solution to the problem (3), (4) in the form of asymptotic expansions in powers of small parameters \(\varepsilon, \theta\). In accordance with the boundary functions method [4], such a solution can be sought as a sum of a regular series and boundary layer series of two types:

\[u(t, \varepsilon, \theta) = \bar{u}(t, \varepsilon, \theta) + \Pi_1u(\tau_1, \varepsilon, \theta) + \Pi_2u(\tau_2, \varepsilon, \theta),\]
\[y(t, s, \varepsilon, \theta) = \bar{y}(t, s, \varepsilon, \theta) + \Pi_1y(\tau_1, s, \varepsilon, \theta) + \Pi_2y(\tau_2, s, \varepsilon, \theta),\]

where

\[\bar{u}(t, \varepsilon, \theta) = \sum_{k,l=0}^\infty u_{kl}(t)\varepsilon^k\theta^l, \quad \bar{y}(t, s, \varepsilon, \theta) = \sum_{k,l=0}^\infty y_{kl}(t, s)\varepsilon^k\theta^l\]

are the regular parts of the asymptotic expansions,

\[\Pi_1u(\tau_j, \varepsilon, \theta) = \sum_{k,l=0}^\infty \Pi_{k,l}^ju(\tau_j)\varepsilon^k\theta^l, \quad \Pi_2y(\tau_j, s, \varepsilon, \theta) = \sum_{k,l=0}^\infty \Pi_{k,l}^jy(\tau_j, s)\varepsilon^k\theta^l, \quad j = 1, 2\]

are the boundary-layer parts, \(\tau_1 = t/(\varepsilon\theta)\) and \(\tau_2 = t/\varepsilon\) are the boundary-layer variables. Hereinafter, \(y\) denotes the aggregate of \(z\) and \(v\), i.e., \(y = \{z, v\}\).

Formally substituting series (5) into equations (3) and conditions (4) and equating the regular and the boundary-layer parts of each of two types separately (taking into account that \(\varepsilon \theta d/dt = d/d\tau_1, \varepsilon d/dt = d/d\tau_2\)), we get the equations.
\[
\frac{d\bar{u}}{dt} = 1 - \left(1 + \int_0^\ell \bar{v} ds\right) \bar{u},
\]

\[
\frac{d\Pi^1 u}{d\tau_1} = - \left(1 + \int_0^\ell \beta (\bar{v} + \Pi^1 v + \Pi^2 v) ds\right) \Pi^1 u - (\bar{u} + \Pi^2 u) \int_0^\ell \beta \Pi^1 v ds \theta,
\]

\[
\frac{d\Pi^2 u}{d\tau_2} = - \left(1 + \int_0^\ell \beta (\bar{v} + \Pi^2 v) ds\right) \Pi^2 u - \bar{u} \int_0^\ell \beta \Pi^2 v ds,
\]

\[
\varepsilon \theta \frac{\partial \bar{z}}{\partial t} = \bar{v} + \bar{z} (1 - \bar{z}),
\]

\[
\frac{\partial \Pi^1 z}{\partial \tau_1} = (1 - 2 \bar{z} - 2 \Pi^2 z - \Pi^1 z) \Pi^1 z,
\]

\[
\theta \frac{\partial \Pi^2 z}{\partial \tau_2} = (1 - 2 \bar{z} - \Pi^2 z) \Pi^2 z,
\]

\[
\frac{\partial \bar{v}}{\partial t} = \frac{\partial^2 \bar{v}}{\partial s^2} - m\bar{v} + d\beta \bar{u} \bar{v} - \xi \bar{v} \bar{z},
\]

\[
\frac{\partial \Pi^1 v}{\partial \tau_1} = \left[-m \Pi^1 v + \left(d \beta (\bar{u} + \Pi^1 u + \Pi^2 u) - \xi (\bar{v} + \Pi^1 z + \Pi^2 z)\right) \Pi^1 v + \Pi^2 v + \frac{\partial^2 \Pi^1 v}{\partial s^2}\right] \varepsilon \theta,
\]

\[
\frac{\partial \Pi^2 v}{\partial \tau_2} = \left[-m \Pi^2 v + \left(d \beta (\bar{u} + \Pi^2 u) - \xi (\bar{v} + \Pi^2 z)\right) \Pi^2 v + \frac{\partial^2 \Pi^2 v}{\partial s^2}\right] \theta,
\]

\[
\bar{u}(0, \varepsilon, \theta) + \Pi^1 u(0, \varepsilon, \theta) + \Pi^2 u(0, \varepsilon, \theta) = u^0(0),
\]

\[
\bar{z}(0, s, \varepsilon, \theta) + \Pi^1 z(0, s, \varepsilon, \theta) + \Pi^2 z(0, s, \varepsilon, \theta) = z^0(s),
\]

\[
\bar{v}(0, s, \varepsilon, \theta) + \Pi^1 v(0, s, \varepsilon, \theta) + \Pi^2 v(0, s, \varepsilon, \theta) = v^0(s),
\]

\[
\frac{\partial \bar{v}}{\partial s}(t, 0, \varepsilon, \theta) = 0, \quad \frac{\partial \Pi^1 v}{\partial s}(\tau_1, 0, \varepsilon, \theta) = 0, \quad \frac{\partial \Pi^2 v}{\partial s}(\tau_2, 0, \varepsilon, \theta) = 0,
\]

\[
\bar{v}(t, \ell, \varepsilon, \theta) = 0, \quad \Pi^1 v(\tau_1, \ell, \varepsilon, \theta) = 0, \quad \Pi^2 v(\tau_2, \ell, \varepsilon, \theta) = 0.
\]

4. Zeroth–order approximation

Let us look at the zeroth–order approximation more closely. Setting \(\varepsilon = 0\) and \(\theta = 0\) in equations (6) and conditions (7), we obtain

\[
u_{00}(t) = \frac{1}{1 + \int_0^\ell \beta(s) v_{00}(t, s) ds},
\]

\[
\frac{d\Pi^1_{00} u(\tau_1)}{d\tau_1} = 0,
\]
\[
\frac{d\Pi_{00}^2 v(\tau_2)}{d\tau_2} = - \left( 1 + \int_0^\ell \beta(s) \left( v_{00}(0, s) + \Pi_{00}^2 v(\tau_2, s) \right) ds \right) \Pi_{00}^2 v(\tau_2) - u_{00}(0) \int_0^\ell \beta(s) \Pi_{00}^2 v(\tau_2, s) ds, \\
0 = v_{00}(t, s) + z_{00}(t, s) \left( 1 - z_{00}(t, s) \right), \\
\frac{\partial \Pi_{00}^1 z(\tau_1, s)}{\partial \tau_1} = \left( 1 - 2z_{00}(0, s) - 2\Pi_{00}^2 z(0, s) - \Pi_{00}^1 z(\tau_1, s) \right) \Pi_{00}^1 z(\tau_1, s), \\
0 = \left( 1 - 2z_{00}(0, s) - \Pi_{00}^2 z(\tau_2, s) \right) \Pi_{00}^2 z(\tau_2, s), \\
\frac{\partial v_{00}(t, s)}{\partial t} = \frac{\partial^2 v_{00}(t, s)}{\partial s^2} - mv_{00}(t, s) + d\beta(s)u_{00}(t)v_{00}(t, s) - \xi v_{00}(t, s)z_{00}(t, s), \\
\frac{\partial \Pi_{00}^1 v(\tau_1, s)}{\partial \tau_1} = 0, \\
\frac{\partial \Pi_{00}^2 v(\tau_2, s)}{\partial \tau_2} = 0,
\]

\[
u_{00}(0) + \Pi_{00}^1 u(0) + \Pi_{00}^2 u(0) = u^0, \\
z_{00}(0, s) + \Pi_{00}^1 z(0, s) + \Pi_{00}^2 z(0, s) = z^0(s), \\
v_{00}(0, s) + \Pi_{00}^1 v(0, s) + \Pi_{00}^2 v(0, s) = v^0(s), \\
\frac{\partial v_{00}}{\partial s}(t, 0) = 0, \quad \frac{\partial \Pi_{00}^1 v}{\partial s}(\tau_1, 0) = 0, \quad \frac{\partial \Pi_{00}^2 v}{\partial s}(\tau_2, 0) = 0, \\
v_{00}(t, \ell) = 0, \quad \Pi_{00}^1 v(\tau_1, \ell) = 0, \quad \Pi_{00}^2 v(\tau_2, \ell) = 0.
\]

In addition, the functions of the boundary layer must satisfy the following conditions:

\[
\Pi_{kl}^j u(+\infty) = 0, \quad j = 1, 2, \quad k, l = 0, \infty,
\]

\[
\Pi_{kl}^j y(+\infty, s) = 0, \quad \forall s \in [0, \ell], \quad j = 1, 2, \quad k, l = 0, \infty.
\]

Hence, \(\Pi_{00}^1 u = 0\), \(\Pi_{00}^j v = 0\), \(j = 1, 2\), \(\Pi_{00}^2 z = 0\). The fact that the slow variable \(v\) in the zeroth-order approximation has no boundary layer is a characteristic feature of this kind of problems.

From the fourth equation, one can find \(z_{00} = \left(1 + \sqrt{1 + 4v_{00}}\right)/2\). For the first-order associated system

\[
\frac{\partial \hat{z}}{\partial \tau_1} = v + \hat{z}(1 - \hat{z}),
\]

where \(v\) enters as a parameter, only one of the roots, namely \(z_{00} = \left(1 + \sqrt{1 + 4v_{00}}\right)/2\), is the asymptotically stable (in the sense of Lyapunov) stationary point (see, for example, [1]).

Now \(v_{00}(t, s)\) can be found from the integro-differential equation

\[
\frac{\partial v_{00}}{\partial t} = \frac{\partial^2 v_{00}}{\partial s^2} - mv_{00} + \frac{d\beta v_{00}}{\ell} - \frac{\xi v_{00}(1 + \sqrt{1 + 4v_{00}})}{2},
\]

using the initial boundary conditions \(v_{00}(0, s) = v^0(s) - \Pi_{00}^1 v(0, s) + \Pi_{00}^2 v(0, s) = v^0(s)\), \(\frac{\partial v_{00}}{\partial s}(t, 0) = 0\) and \(v_{00}(t, \ell) = 0\). The existence and uniqueness of the solution to this problem can be proved by the approach proposed in [7].
functions. The approximate solution is found in the form of series in powers of small parameters. The approach discussed is based on the Tikhonov–Vasil’eva method of boundary problem for the model of the virus dynamics with the immune response is proposed. The

5. Conclusions
In this paper, a procedure for finding an approximate solution to the initial boundary value problem for the model of the virus dynamics with the immune response is proposed. The model can be transformed to a singularly perturbed integro–differential system with two small parameters. The approach discussed is based on the Tikhonov–Vasil’eva method of boundary functions. The approximate solution is found in the form of series in powers of small parameters.

\[
\Pi_{00}^2 u(\tau_2) \text{ is the solution to the Cauchy problem}
\]

\[
\frac{d\Pi_{00}^2 u}{d\tau_2} = - \left( 1 + \int_0^\ell \beta(s)v^0(s)ds \right) \Pi_{00}^2 u,
\]

i.e., \( \Pi_{00}^2 u(\tau_2) = (u^0 - 1/A) \exp(-A\tau_2) \), where \( A = 1 + \int_0^\ell \beta(s)v^0(s)ds \).

\[
\Pi_{00}^1 z(\tau_1, s) \text{ is the solution to the Cauchy problem for the Bernoulli equation}
\]

\[
\frac{\partial \Pi_{00}^1 z}{\partial \tau_1} = - \left( \sqrt{1 + 4v^0(s)} + \Pi_{00}^1 z \right) \Pi_{00}^1 z,
\]

i.e., \( \Pi_{00}^1 z(\tau_1, s) = \frac{B_1}{B_2 \exp(B_1 t_{\tau_1}) - 1} \), where \( B_1 = B_1(s) = \sqrt{1 + 4v^0(s)} \), \( B_2 = B_2(s) = \frac{2z^0(s) - 1 + \sqrt{1 + 4v^0(s)}}{2z^0(s) - 1 - \sqrt{1 + 4v^0(s)}} \).

Thus, the zeroth–order approximation of the solution to the problem (3), (4) has the form

\[
\Pi_{00}^1 z(0, s) = z^0(s) - \left( 1 + \sqrt{1 + 4v^0(s)} \right)/2,
\]

i.e., \( \Pi_{00}^1 z(\tau_1, s) = \frac{B_1}{B_2 \exp(B_1 t_{\tau_1}) - 1} \), where \( B_1 = B_1(s) = \sqrt{1 + 4v^0(s)} \), \( B_2 = B_2(s) = \frac{2z^0(s) - 1 + \sqrt{1 + 4v^0(s)}}{2z^0(s) - 1 - \sqrt{1 + 4v^0(s)}} \).

The asymptotic character of the expansions is justified as described in [8]–[11] or by approach discussed in [12].

To construct more accurate approximations of the solution, it is necessary to use higher order asymptotic expansions. Expanding \( \Pi(\tau_1 \varepsilon, \varepsilon, \theta), \frac{d\Pi(\tau_1 \varepsilon, s, \varepsilon, \theta)}{dt}, \frac{d\Pi(\tau_2 \varepsilon, s, \varepsilon, \theta)}{dt}, \Pi_1^2 u(\tau_1 \theta, \varepsilon, \theta), \Pi_2^2 y(\tau_1 \theta, s, \varepsilon, \theta) \) in powers of \( \varepsilon, \theta \) and substituting the resulting expansions into the equations of system (6) and conditions (7), we equate the coefficients multiplying equal powers of \( \varepsilon \) and \( \theta \) to find the \( kl \)-th terms of the asymptotic expansion. We can expand the regular parts of the functions in Taylor series around \( t = 0 \) and then replace \( t \) by \( \tau_1 \varepsilon \theta \) or \( \tau_2 \varepsilon \). The boundary–layer functions can be expanded in Taylor series around \( \tau_2 = 0 \) and, then, \( \tau_2 \) can be replaced by \( \tau_1 \theta \).
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