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Passage to the limit for models of viral dynamics with random mutations

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Passage to the limit for models of viral dynamics with random mutations

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Abstract. Models of viral dynamics are considered in this paper. These models describe different mechanisms of mutations and are formulated in the form of the systems of singularly perturbed partial integro-differential equations with two small parameters multiplying derivatives. The possibility of the passage to the limit of the solution to a degenerate problem is justified.

1. Introduction
Mathematical modeling of biological processes leads, as a rule, to the appearance of singularly perturbed equations. The reason for this is the extreme complexity of biological systems. In addition, such models should take into account the processes occurring on incommensurable time scales. For example, the process of biological evolution is extremely slow, while the interactions of a different nature that accompany it are significantly faster.

In this paper, three models of viral dynamics with different mechanisms of viral mutation are considered. These models describe the population dynamics of healthy (uninfected) cells, infected cells and free virus particles (virions). Due to the significant difference in the life-cycle duration of the above-mentioned populations, the models can be written in the form of singularly perturbed systems of partial integro-differential equations. For a singularly perturbed system of ordinary differential equations, Tikhonov's theorem is effective [1]. This theorem states that the passage to the limit of the solution to a degenerate problem in a system with several small parameters multiplying derivatives is justified. Some types of singularly perturbed equations were considered in the papers [2]-[5]. In this paper, the system size reduction of the models of viral dynamics is carried out, that allows to restrict ourselves to the study of a single equation.

2. Models
Let us consider the next models of viral dynamics with random mutations.
    Model I:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \int_\Omega p_1(s,r)\alpha(r)x(t)v(t,r)\,dr - m(s)y(t,s),$$

$$\frac{\partial v(t,s)}{\partial t} = k(s)y(t,s) - c(s)v(t,s).$$

Model II:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \alpha(s)x(t)v(t,s) - m(s)y(t,s),$$

$$\frac{\partial v(t,s)}{\partial t} = \int_\Omega p_2(s,r)k(r)y(t,r)\,dr - c(s)v(t,s).$$

Model III:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \alpha(s)x(t)v(t,s) - m(s)y(t,s) - \gamma\left(y(t,s) - \int_\Omega p_3(s,r)y(t,r)\,dr\right),$$

$$\frac{\partial v(t,s)}{\partial t} = k(s)y(t,s) - c(s)v(t,s).$$

In these models $x(t)$ is the concentration of uninfected (susceptible) cells at the time t, $y(t,s)$, $v(t,s)$ are the density distributions of infected target cells (CD4+ cells, or T helper cells, or Th-cells) and free virus particles respectively in a one-dimensional phenotype space $s \in \Omega$ at the time t. The uninfected cells susceptible to the virus are produced at a constant rate b and die of natural reasons unrelated to the virus infection at a rate $\sigma x(t)$, $\sigma > 0$. The factors α, m, k and c are characteristics of the virus phenotype, and hence, they are functions of the variable s or r.

In model I framework it is assumed that a mutation occur in the process of cell infection. Function $p_1(s,r)$ describes the probability that the infected by virus of phenotype r cell produces exclusively virus of phenotype s. Model II postulates that mutations occur in the process of viral production by the cell. Function $p_2(s,r)$ describes the probability that a virion produced by the infected by the virion with phenotype r cell is of phenotype s. Finally, in the model III framework it is assumed that a cell, infected with viral phenotype r, after some moment switches to production of the virus of phenotype s instead of phenotype r with a probability given by function $p_3(s,r)$, and positive constant γ is the rate of such a mutation.

If the integral kernel $p(s,r)$ is represented by the Gaussian distribution $p(s,r) = \frac{1}{\mu\sqrt{\pi}}\exp(-\frac{(s-r)^2}{\mu^2})$ with small variance μ, then

$$\int_\Omega p(s,r)u(t,r)\,dr \approx u(t,s) + \mu\frac{\partial^2 u(t,s)}{\partial s^2}.$$

Then the models can be formulated as the system of partial integro-differential equations.

Model I:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \alpha(s)x(t)v(t,s) - m(s)y(t,s) + \mu x(t)\frac{\partial^2 \alpha(s)v(t,s)}{\partial s^2},$$

$$\frac{\partial v(t,s)}{\partial t} = k(s)y(t,s) - c(s)v(t,s).$$

Model II:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \alpha(s)x(t)v(t,s) - m(s)y(t,s),$$

$$\frac{\partial v(t,s)}{\partial t} = k(s)y(t,s) - c(s)v(t,s) + \mu\frac{\partial^2 k(s)y(t,s)}{\partial s^2}.$$

Model III:

$$\frac{dx(t)}{dt} = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t,s)ds,$$

$$\frac{\partial y(t,s)}{\partial t} = \alpha(s)x(t)v(t,s) - m(s)y(t,s) + \mu\gamma\frac{\partial^2 y(t,s)}{\partial s^2},$$

$$\frac{\partial v(t,s)}{\partial t} = k(s)y(t,s) - c(s)v(t,s).$$

3. Reduction
Following, for example [6], let us introduce the dimensionless variables and parameters

$$t = T\bar{t}, \ s = S\bar{s}, \ x(t) = X\bar{x}(\bar{t}), \ y(t,s) = Y(\bar{s})\bar{y}(\bar{t},\bar{s}), \ v(t,s) = V(\bar{s})\bar{v}(\bar{t},\bar{s}), \tag{1}$$

$$T = \frac{1}{\mu m_0}, \ S = 1, \ X = \frac{b}{\sigma}, \ V = \frac{k_0}{c_0}Y = \frac{k_0}{c_0}\frac{b}{m_0}, \ Y = \frac{b}{m_0}, \tag{2}$$

where m_0, k_0, c_0 are $m(s)$, $k(s)$, $c(s)$ of the wild (initial or any fixed) strain. T is measured in the units of time, while X, Y and V are in the units of concentrations of target cells and free virus.

Substituting of (1) and(2) in to Model I yields

$$\mu\frac{m_0}{\sigma}\frac{d\bar{x}(\bar{t})}{d\bar{t}} = 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})\,d\bar{s},$$

$$\mu\frac{m_0}{m(\bar{s})}\frac{\partial\bar{y}(\bar{t},\bar{s})}{\partial\bar{t}} = \int_\Omega p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{r})\,d\bar{r} - \bar{y}(\bar{t},\bar{s}),$$

$$\mu\frac{m_0}{c(\bar{s})}\frac{\partial\bar{v}(\bar{t},\bar{s})}{\partial\bar{t}} = \bar{y}(\bar{t},\bar{s}) - \bar{v}(\bar{t},\bar{s}),$$

where $R_0(\bar{s}) = b\alpha(s)k(s)/(\sigma m(s)c(s))$ is the basic reproduction ratio.

Denoting $\bar{m}(\bar{s}) = m(s)/m_0$, $\varepsilon = \mu m_0/\sigma$ $\nu = \sigma/c_0$, we get singularly perturbed system with two small parameters:

$$\varepsilon \frac{d\bar{x}(\bar{t})}{d\bar{t}} = 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{s}) \, d\bar{s},$$

$$\frac{\partial \bar{y}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu} \left(\int_\Omega p_1(\bar{s}, \bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{r}) \, d\bar{r} - \bar{y}(\bar{t}, \bar{s}) \right),$$

$$\varepsilon\nu \frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{c(\bar{s})}{c_0} (\bar{y}(\bar{t}, \bar{s}) - \bar{v}(\bar{t}, \bar{s})).$$

Setting $\nu = 0$, we obtain the so-called first-order degenerate system

$$\varepsilon \frac{d\bar{x}(\bar{t})}{d\bar{t}} = 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{s}) \, d\bar{s},$$

$$\frac{\partial \bar{y}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu} \left(\int_\Omega p_1(\bar{s}, \bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{r}) \, d\bar{r} - \bar{y}(\bar{t}, \bar{s}) \right),$$

$$0 = \frac{c(\bar{s})}{c_0} (\bar{y}(\bar{t}, \bar{s}) - \bar{v}(\bar{t}, \bar{s})).$$

The third equation is algebraic and has root $\bar{v} = \bar{y}$. For the first-order associated equation

$$\frac{\partial \hat{v}(\tau, \bar{s})}{\partial \tau} = \frac{c(\bar{s})}{c_0} (\hat{v}(\tau, \bar{s}) - \bar{y}),$$

where $\bar{y}$ enters as a parameter, the root $\hat{v} = \varphi(\bar{y}) = \bar{y}$ is the asymptotically stable (in the sense of Lyapunov) stationary point.

Let us add the initial conditions $\bar{x}(0) = x^0$, $\bar{y}(0, \bar{s}) = y^0(\bar{s})$ and $\bar{v}(0, \bar{s}) = v^0(\bar{s})$. At the initial value of the parameter $\bar{y}$, i.e., at $\bar{y} = y^0(\bar{s})$, the first-order associated equation with the initial condition $\bar{v}(0, \bar{s}) = v^0(\bar{s})$ has a unique solution $\hat{v} = y^0(\bar{s}) + \left(v^0(\bar{s}) - y^0(\bar{s}) \right) \exp\left(-\frac{c(\bar{s})}{c_0}\tau \right)$, and $\hat{v}(\tau, \bar{s}) \to \varphi(y^0(\bar{s})) = y^0(\bar{s})$ as $\tau \to +\infty$ $\forall \bar{s} \in \Omega$. Thereby the initial point $v^0(\bar{s})$ of the first-order associated equation belongs to the domain of attraction of the stable stationary point $\varphi(y^0(\bar{s}))$. Thus, for sufficiently small ν, the singularly perturbed system with two small parameters has a unique solution $\bar{x}(\bar{t}, \varepsilon, \nu)$, $\bar{y}(\bar{t}, \bar{s}, \varepsilon, \nu)$ and $\bar{v}(\bar{t}, \bar{s}, \varepsilon, \nu)$, and, for some t_1, the following limiting equalities hold:

$$\bar{x}(\bar{t}, \varepsilon, \nu) \to \bar{x}_0(\bar{t}, \varepsilon) \; \forall \bar{t} \in [0, t_1] \; \forall \bar{s} \in \Omega,$$

$$\bar{y}(\bar{t}, \bar{s}, \varepsilon, \nu) \to \bar{y}_0(\bar{t}, \bar{s}, \varepsilon) \; \forall \bar{t} \in [0, t_1] \; \forall \bar{s} \in \Omega,$$

$$\bar{v}(\bar{t}, \bar{s}, \varepsilon, \nu) \to \varphi(\bar{y}_0(\bar{t}, \bar{s}, \varepsilon)) \; \forall \bar{t} \in (0, t_1] \; \forall \bar{s} \in \Omega,$$

as $\nu \to +\infty$, where $\bar{x}_0(\bar{t}, \varepsilon)$, $\bar{y}_0(\bar{t}, \bar{s}, \varepsilon)$ are the solutions to the first-order degenerate system. Note that the third limiting equality holds for $t \neq 0$, as the solution $\bar{v} = \varphi(\bar{y})$ of the first-order degenerate system, generally speaking, does not satisfy initial condition for this variable $(\bar{v}(0, \bar{s}) \neq \varphi(\bar{y}(0, \bar{s})))$. The boundary layer phenomenon occurs [7]. The first order associated equation is also called the boundary layer equation.

Then let us $\varepsilon = 0$. We obtain the second-order degenerate system

$$\begin{aligned}
0 &= 1 - \bar{x}(\bar{t}) - \int_{\Omega} R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})\,d\bar{s}, \\
\frac{\partial \bar{y}(\bar{t},\bar{s})}{\partial \bar{t}} &= \frac{\bar{m}(\bar{s})}{\mu}\left(\int_{\Omega} p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{r})\,d\bar{r} - \bar{y}(\bar{t},\bar{s})\right), \\
0 &= \frac{c(\bar{s})}{c_0}\left(\bar{y}(\bar{t},\bar{s}) - \bar{v}(\bar{t},\bar{s})\right),
\end{aligned}$$

first equation in which is algebraic with respect to $\bar{x}$ and has a root $\bar{x} = \Psi(\bar{v}) = \left(1 + \int_{\Omega} R_0(\bar{s})\bar{v}(\bar{t},\bar{s})\,d\bar{s}\right)^{-1}$. This root is the asymptotically stable (in the sense of Lyapunov) stationary point of the second-order associated equation

$$\frac{\hat{x}(\tau)}{d\tau} = -\left(1 + \int_{\Omega} R_0(\bar{s})\bar{v}(\bar{t},\bar{s})\,d\bar{s}\right)\hat{x}(\tau) + 1.$$

The latter equation with the initial condition $\bar{x}(0) = x^0$ at the initial value of the parameter $\bar{v}$ $\bar{v} = v^0(\bar{s})$ has a unique solution $\hat{x}(\tau) = \left(x^0 - 1/f\right)\exp(-f\tau) + 1/f$, where $1/f = \Psi(v^0(\bar{s})) = 1 + \int_{\Omega} R_0(\bar{s})v^0(\bar{s})\,d\bar{s}$, for all $\tau \geq 0$, and $\hat{x}(\tau) \to \Psi(v^0(\bar{s}))$ as $\tau \to +\infty$. Thus, the initial point x^0 of the second-order associated equation belongs to the domain of attraction of the stable stationary point. Consequently, for some t_2

$$\begin{aligned}
\bar{x}_0(\bar{t},\varepsilon) &\to \Psi(\bar{y}_{00}(\bar{t},\bar{s}))\ \forall \bar{t}\in(0,t_2]\ \forall \bar{s}\in\Omega, \\
\bar{y}_0\bar{t},\bar{s},\varepsilon) &\to \bar{y}_{00}(\bar{t},\bar{s})\ \forall \bar{t}\in[0,t_2]\ \forall \bar{s}\in\Omega, \\
\bar{v}_0(\bar{t},\bar{s},\varepsilon) &\to \varphi(\bar{y}_{00}(\bar{t},\bar{s}))\ \forall \bar{t}\in(0,t_2]\ \forall \bar{s}\in\Omega,
\end{aligned}$$

as $\varepsilon \to +\infty$, where $\bar{y}_00(\bar{t},\bar{s})$ is the solutions to the second-order degenerate system.

Finally, we obtain single integro-differential equation

$$\frac{\partial \bar{y}(\bar{t},\bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu}\left(\frac{\int_{\Omega} p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r}}{1 + \int_{\Omega} R_0(\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r}} - \bar{y}(\bar{t},\bar{s})\right).$$

If the kernel $p_1(s,r)$ is can be represented by a normal distribution with a small standard deviation, then

$$\begin{aligned}
\frac{\partial \bar{y}(\bar{t},\bar{s})}{\partial \bar{t}} &= \frac{\bar{m}(\bar{s})}{\mu}\frac{(R_0(\bar{s})-1)\bar{y}(\bar{t},\bar{s})}{1 + \int_{\Omega} R_0(\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r}}\left(1 - \frac{\int_{\Omega} R_0(\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r}}{R_0(\bar{s})-1}\right) \\
&+ \frac{\bar{m}(\bar{s})}{1 + \int_{\Omega} R_0(\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r}}\frac{\partial^2 R_0(\bar{s})\bar{y}(\bar{t},\bar{s})}{\partial \bar{s}^2}.
\end{aligned}$$

Model II with dimensionless variables and parameters is also a singularly perturbed system with two small parameters:

$$\begin{aligned}
\varepsilon\frac{d\bar{x}(\bar{t})}{d\bar{t}} &= 1 - \bar{x}(\bar{t}) - \int_{\Omega} R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})d\bar{s}, \\
\varepsilon\theta\frac{\partial \bar{y}(\bar{t},\bar{s})}{\partial \bar{t}} &= \bar{m}(\bar{s})\left(R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s}) - \bar{y}(\bar{t},\bar{s})\right), \\
\frac{\partial \bar{v}(\bar{t},\bar{s})}{\partial \bar{t}} &= \frac{\bar{c}(\bar{s})}{\mu}\left(\int_{\Omega} \bar{p}_2(\bar{s},\bar{r})\bar{y}(\bar{t},\bar{r})\,d\bar{r} - \bar{v}(\bar{t},\bar{s})\right),
\end{aligned}$$

where $\bar{c}(\bar{s}) = c(s)/m_0$, $\bar{p}_2(\bar{s}, \bar{r}) = p_2(\bar{s}, \bar{r})m(\bar{s})k(\bar{r})/(k(\bar{s})m(\bar{r}))$, $\theta = \sigma/m_0$.

Assuming that $\varepsilon = 0$ and $\theta = 0$, we get equalities

$$\bar{x}(\bar{t}) = \frac{1}{1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}}, \qquad R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{s}) = \bar{y}(\bar{t}, \bar{s}).$$

Thus

$$\bar{y}(\bar{t}, \bar{s}) = \frac{R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})}{1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}}.$$

As a result, the Model II can be reduced to a single integro-differential equation

$$\frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{c}(\bar{s})}{\mu} \left(\frac{\int_\Omega \bar{p}_2(\bar{s}, \bar{r})R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}}{1 + \int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}} - \bar{v}(\bar{t}, \bar{s}) \right),$$

or, in the case of the normal distribution with a small standard deviation,

$$\frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{c}(\bar{s})}{\mu} \frac{(R_0(\bar{s}) - 1)\bar{v}(\bar{t}, \bar{s})}{1 + \int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}} \left(1 - \frac{\int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}}{R_0(\bar{s}) - 1} \right)$$
$$+ \frac{\bar{c}(\bar{s})}{1 + \int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}} \frac{\partial^2 R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})}{\partial \bar{s}^2}.$$

Dimensionless Model III has the form

$$\varepsilon \frac{d\bar{x}(\bar{t})}{d\bar{t}} = 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(s)\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{s}) d\bar{s},$$
$$\frac{\partial \bar{y}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu} (R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t}, \bar{s}) - \bar{y}(\bar{t}, \bar{s})) - \frac{\bar{\gamma}}{\mu} \left(\bar{y}(\bar{t}, \bar{s}) - \int_\Omega \bar{p}_3(\bar{s}, \bar{r})\bar{y}(\bar{t}, \bar{r})\, d\bar{r} \right),$$
$$\varepsilon \nu \frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{c(\bar{s})}{c_0} (\bar{y}(\bar{t}, \bar{s}) - \bar{v}(\bar{t}, \bar{s})).$$

Here $\bar{p}_3(\bar{s}, \bar{r}) = p_3(\bar{s}, \bar{r})m(\bar{s})/m(\bar{r})$, $\bar{\gamma} = \gamma/m_0$.

If $\nu = 0$ and $\varepsilon = 0$, the next equalities yield:

$$\bar{y}(\bar{t}, \bar{s}) = \bar{v}(\bar{t}, \bar{s}), \qquad \bar{x}(\bar{t}) = \frac{1}{1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}}.$$

Model III also reduced to a single integro-differential equation

$$\frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu} \frac{(R_0(\bar{s}) - 1)\bar{v}(\bar{t}, \bar{s})}{1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}} \left(1 - \frac{\int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}}{R_0(\bar{s}) - 1} \right)$$
$$- \frac{\bar{\gamma}}{\mu} \left(\bar{v}(\bar{t}, \bar{s}) - \int_\Omega \bar{p}_3(\bar{s}, \bar{r})\bar{v}(\bar{t}, \bar{r})\, dr \right).$$

If the kernel $\bar{p}_3(\bar{s}, \bar{r})$ is represented by a normal distribution with a small standard deviation, then this equation has the form

$$\frac{\partial \bar{v}(\bar{t}, \bar{s})}{\partial \bar{t}} = \frac{\bar{m}(\bar{s})}{\mu} \frac{(R_0(\bar{s}) - 1)\bar{v}(\bar{t}, \bar{s})}{1 + \int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}} \left(1 - \frac{\int_\Omega R_0(\bar{r})\bar{v}(\bar{t}, \bar{r})\, d\bar{r}}{R_0(\bar{s}) - 1} \right) + \bar{\gamma} \frac{\partial^2 \bar{v}(\bar{t}, \bar{s})}{\partial \bar{s}^2}.$$

4. Admissibility of the passage to the limit

In [8] the theorem, that connects the solutions of the singularly perturbed system of partial integro-differential equations with one small parameter, is proved. Let us generalize this theorem to the case of Model I and III (for Model II this can be done in a similar way).

Let us consider the singularly perturbed system of integro-differential equations with two small parameters

$$
\begin{aligned}
\varepsilon \frac{dx}{dt} &= f(x, \int_\Omega g(s,v)ds) \\
\varepsilon \nu \frac{\partial v}{\partial t} &= h(y,v) \\
\frac{\partial y}{\partial t} &= w(s,x,y,v, \int_\Omega q(s,r,y,v)dr)
\end{aligned}
\tag{3}
$$

with the initial conditions

$$
x(0) = x^0, \ v(0,s) = v^0(s), \ y(0,s) = y^0(s),
\tag{4}
$$

where $x, v, y \in R$, ε, ν are the small positive parameters.

We assume that system (3) satisfies the following conditions.

i). The functions $f(x,z_1)$, $g(s,v)$, $h(y,v)$, $w(s,x,y,v,z_2)$ and $q(s,r,y,v)$ together with their partial derivatives with respect to all variables, are uniformly continuous and bounded in the respective domains $D_1 = \{|x| \leq a, \ |z_1| \leq b_1\}$, $D_2 = \{s \in \Omega, \ |v| \leq c\}$, $D_3 = \{|y| \leq d, \ |v| \leq c\}$, $D_4 = \{s \in \Omega, \ |x| \leq a, \ |y| \leq d, \ |v| \leq c, \ |z_2| \leq b_2\}$, $D_5 = \{s, r \in \Omega, \ |y| \leq d, \ |v| \leq c\}$.

ii). The equation $h(y,v) = 0$ has an isolated root $v = \varphi(y)$ in the domain $\{|y| \leq d\}$ and in this domain function $v = \varphi(y)$ is continuously differentiable.

iii). The inequality $h_v(y,\varphi(y)) \leq -\alpha < 0$ holds for $|y| \leq d$. This condition implies, that the stationary point $\hat{v} = \varphi(y)$ of the first-order associated equation

$$
\frac{\partial \hat{v}}{\partial \tau} = h(y,\hat{v}),
\tag{5}
$$

which contains y as a parameter, is Lyapunov asymptotically stable as $\tau \to +\infty$ uniformly with respect to y , $|y| \leq d$.

iv). There exist a solution $\hat{v} = \hat{v}(\tau,s)$ of the problem

$$
\frac{\partial \hat{v}}{\partial \tau} = h(y^0(s),\hat{v}), \ \hat{v}(0,s) = z^0(s),
\tag{6}
$$

for $\tau \geq 0$, $\forall s \in \Omega$. Further, this solution tends to the stationary point $\varphi(y^0(s))$ as $\tau \to +\infty$ $\forall s \in \Omega$, i.e. $v^0(s)$ belongs to the domain of attraction of the stable stationary point $\varphi(y^0(s))$.

v). The equation $f(x,z_1) = 0$ has an isolated root $x = \psi(z_1)$ in the domain $|x| \leq a$ and in this domain function $x = \psi(z_1)$ is continuously differentiable.

vi). The inequality $f_x(\psi(z_1),z_1) \leq -\beta < 0$ $(z_1 = \int_\Omega g(s,\varphi(y))ds)$ holds for $|y| \leq d$, i.e. the stationary point $\hat{x} = \psi(z_1)$ of the second-order associated equation

$$
\frac{d\hat{x}}{d\tau} = f(\hat{x}, \int_\Omega g(s,\varphi(y))ds),
\tag{7}
$$

which contains y as a parameter, is Lyapunov asymptotically stable as $\tau \to +\infty$ uniformly with respect to y , $|y| \leq d$.

vii) There exist a solution $\hat{x}(\tau)$ of the problem

$$\frac{d\hat{x}}{d\tau} = f(\hat{x}, \int_{\Omega} g(s, \varphi(y^0(s)))ds), \ \hat{x} = x^0 \tag{8}$$

for $\tau \geq 0$. Further, this solution tends to the stationary point $\psi(\int_{\Omega} g(s, \varphi(y^0(s)))ds)$ as $\tau \to +\infty$, i.e. x^0 belongs to the domain of attraction of the stable stationary point.

viii) The truncated system

$$
\begin{aligned}
\frac{\partial y}{\partial t} &= w(s, \psi(z_1), y, \varphi(y), \int_{\Omega} q(s, r, y, \varphi(y))dr), \\
x &= \psi(z_1), \\
v &= \varphi(y), \\
z_1 &= \int_{\Omega} g(s, \varphi(y))ds
\end{aligned} \tag{9}
$$

with initial condition

$$y(0, s) = y^0(s) \tag{10}$$

has a unique solution $\bar{y}(t, s)$, $\bar{x}(t) = \psi(\int_{\Omega} g(s, \varphi(\bar{y}(t, s)))ds)$, $\bar{v}(t, s) = \varphi(\bar{y}(t, s))$.

Theorem. *If conditions i-viii are satisfied, then, for sufficiently small ε, ν, for some $T > 0$ problem (3), (4) has a unique solution $x(t, \varepsilon, \nu)$, $v(t, s, \varepsilon, \nu)$, $y(t, s, \varepsilon, \nu)$ which is related to the solution $\bar{x}(t)$, $\bar{v}(t, s)$, $\bar{y}(t, s)$ of the truncated problem (9), (10) by the limit formulas*

$$
\begin{aligned}
\lim_{\varepsilon \to +0, \nu \to +0} x(t, \varepsilon, \nu) &= \bar{x}(t) = \psi(\int_{\Omega} g(s, \varphi(\bar{y}(t, s)))ds), \ 0 < t \leq T, \\
\lim_{\varepsilon \to +0, \nu \to +0} v(t, s, \varepsilon, \nu) &= \bar{v}(t, s) = \varphi(\bar{y}(t, s)), \ 0 < t \leq T, \ s \in \Omega, \\
\lim_{\varepsilon \to +0, \nu \to +0} y(t, s, \varepsilon, \nu) &= \bar{y}(t, s), \ 0 \leq t \leq T, \ s \in \Omega.
\end{aligned}
$$

5. Conclusion

In this paper, we considered three models of viral dynamics with different mechanisms of viral mutation, which describe the population dynamics of uninfected cells, infected cells and free virus particles. Based on Tikhonov's theorem time scale separation procedure made it possible to reduce the original systems of three integro-differential equations to a single one. The latter becomes significant in the numerical simulation of such systems because of their extreme complexity. Since in evolutionary biology mathematical models are usually formulated as partial integro-differential equations, the same concept can be applied to ones as well.

6. References

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