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STABILITY OF A STOCHASTIC MODEL FOR HIV-1 DYNAMICS WITHIN A HOST

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ABSTRACT. We consider a stochastically perturbed Nowak-May model of virus dynamics within a host. Using the direct Lyapunov method, we found sufficient conditions for the stability in probability of equilibrium states of this model.

Key words: Virus dynamics, stochastic model, direct Lyapunov method, Lyapunov function, equilibrium state.

1. BACKGROUND

Processes in biology are extremely complex and involve a large number of factors; impacts of these factors are often not known in details. Moreover, details of the interactions between the major agents are usually also known with a large degree of uncertainty. In the mathematical modelling framework, these complexity and uncertainty can be to some extent captured by a reasonably simple low-dimensional mathematical model, where the impacts of multiple uncertain factors are imitated by stochastic perturbations.

In this notice, we consider a stochastically perturbed model of virus dynamics within a host; the deterministic version of this model was suggested by Nowak and May [7] in order to describe the dynamics of HIV-1 in vivo. Our objective is to establish sufficient conditions of the stability in probability [9] for equilibrium states of this model. To address this problem, we apply the direct Lyapunov method.

The Nowak-May model of virus dynamics comprises three variable quantities, namely concentrations of the susceptible target cells, $x(t)$, the infected cells, $y(t)$, and free virus particles, $v(t)$, respectively. The model postulates that there is a constant influx of the susceptible target cells with a rate λ, that the susceptible cells are infected by free virus particles with a bilinear incidence rate $\beta x(t)v(t)$, and that the infected cells produce free virus particles with a rate $ky(t)$; average life spans of the susceptible cells (in absence of the virus), the infected cells and free virus particles are $1/m$, $1/a$ and $1/u$, respectively. Under these assumptions,

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the model is represented by the following system of ordinary differential equations:

$$
\begin{aligned}
\dot{x}(t) =& \lambda - mx(t) - \beta x(t)v(t),\\
\dot{y}(t) =& \beta x(t)v(t) - ay(t),\\
\dot{v}(t) =& ky(t) - uv(t).
\end{aligned} \tag{1.1}
$$

Equilibrium states of this model satisfy the following system of algebraic equations:

$$
\begin{aligned}
\lambda =& mx + \beta xv,\\
ay =& \beta xv,\\
ky =& uv.
\end{aligned} \tag{1.2}
$$

It is easy to see that the model can have at most two equilibrium states, namely an infection-free equilibrium state $E_0 = (x_0, y_0, z_0)$, where

$$
x_0 = \frac{\lambda}{m}, \qquad y_0 = 0, \qquad v_0 = 0, \tag{1.3}
$$

and a positive equilibrium state $E^* = (x^*, y^*, v^*)$, where

$$
x^* = \frac{au}{k\beta}, \qquad y^* = \frac{\lambda}{a} - \frac{mu}{k\beta}, \qquad v^* = \frac{\lambda k}{au} - \frac{m}{\beta}. \tag{1.4}
$$

The positive equilibrium state E^* exists if the condition

$$
R_0 = \frac{\lambda k \beta}{amu} > 1, \tag{1.5}
$$

where R_0 is the basic reproduction number of virus, holds.

The properties of the Nowak-May model are well studied. Specifically, it was proved that if $R_0 \le 1$ holds, then the infection free equilibrium E_0 (which is the only equilibrium state of the model in this case) is globally asymptotically stable, whereas if $R_0 > 1$ holds, then E_0 is a saddle point, and the positive equilibrium state E^* exists and is globally asymptotically stable (in R^3_+, as x-axis is an invariant set of the model and the stable manifold of E_0) [5, 6].

2. A stochastically perturbed model

Let us now assume that system (1.1) is stochastically perturbed by white noises, and that magnitudes of perturbations are proportional to the deviation of a current state $(x(t), y(t), v(t))$ from an equilibrium point. Thus, for the positive equilibrium state E^*, the stochastically perturbed system takes the form

$$
\begin{aligned}
\dot{x}(t) =& \lambda - mx(t) - \beta x(t)v(t) + \sigma_1(x(t) - x^*)\dot{w}_1(t),\\
\dot{y}(t) =& \beta x(t)v(t) - ay(t) + \sigma_2(y(t) - y^*)\dot{w}_2(t),\\
\dot{v}(t) =& ky(t) - uv(t) + \sigma_3(v(t) - v^*)\dot{w}_3(t),
\end{aligned} \tag{2.1}
$$

where σ_1, σ_2, σ_3 are positive constants, and $w_1(t)$, $w_2(t)$, $w_3(t)$ are mutually independent Wiener processes. An advantage of this approach is that for the stochastic perturbations of such a type the equilibrium point (x^*, y^*, v^*) of system (2.1) coincides with the equilibrium point E^* of system (1.1). Stochastic perturbations of this form were proposed in [1] for ordinary differential equations and later this idea was successfully applied to finite difference equations with discrete and continuous time [8], and for partial differential equations [2].

The technique which we use further in this paper for the analysis of system (2.1) is similar to that in [1, 2, 8, 9]. A substitution

$$x(t) = x_1(t) + x^*, \qquad y(t) = x_2(t) + y^*, \qquad v(t) = x_3(t) + v^*$$

transforms system (2.1) to the form

$$\begin{aligned}\dot{x}_1(t) =& \lambda - m(x_1(t) + x^*) - \beta(x_1(t) + x^*)(x_3(t) + v^*) + \sigma_1 x_1(t)\dot{w}_1(t),\\ \dot{x}_2(t) =& \beta(x_1(t) + x^*)(x_3(t) + v^*) - a(x_2(t) + y^*) + \sigma_2 x_2(t)\dot{w}_2(t),\\ \dot{x}_3(t) =& k(x_2(t) + y^*) - u(x_3(t) + v^*) + \sigma_3 x_3(t)\dot{w}_3(t),\end{aligned}$$

or, using (1.2), to the form

$$\begin{aligned}\dot{x}_1(t) =& -(m + \beta v^*)x_1(t) - \beta x^* x_3(t) - \beta x_1(t)x_3(t) + \sigma_1 x_1(t)\dot{w}_1(t),\\ \dot{x}_2(t) =& \beta(v^* x_1(t) + x^* x_3(t) + x_1(t)x_3(t)) - a x_2(t) + \sigma_2 x_2(t)\dot{w}_2(t),\\ \dot{x}_3(t) =& k x_2(t) - u x_3(t) + \sigma_3 x_3(t)\dot{w}_3(t).\end{aligned} \tag{2.2}$$

The origin of the system (2.2) phase space corresponds to the positive equilibrium state E^* of system (2.1) and is an equilibrium state of this system. Our objective is to establish the stability of the origin.

Further we will also consider the linear part of system (2.2) in the form

$$\begin{aligned}\dot{y}_1(t) =& -(m + \beta v^*)y_1(t) - \beta x^* y_3(t) + \sigma_1 y_1(t)\dot{w}_1(t),\\ \dot{y}_2(t) =& \beta(v^* y_1(t) + x^* y_3(t)) - a y_2(t) + \sigma_2 y_2(t)\dot{w}_2(t),\\ \dot{y}_3(t) =& k y_2(t) - u y_3(t) + \sigma_3 y_3(t)\dot{w}_3(t).\end{aligned} \tag{2.3}$$

Note that the order of nonlinearity of the system (2.2) is higher than one, and hence sufficient conditions for the asymptotic mean square stability of the trivial solution of the system (2.3) are, at the same time, the sufficient conditions for the stability in probability for the trivial solution of system (2.2) [9].

3. Stability for the positive equilibrium state E^*

In order to establish conditions for the stability of positive equilibrium state E^*, we represent the linear system (2.3) in the matrix form

$$\dot{y}(t) = Ay(t) + B(y(t))\dot{w}(t); \tag{3.1}$$

here

$$y(t) = \begin{pmatrix} y_1(t) \\ y_2(t) \\ y_3(t) \end{pmatrix}, \quad A = \begin{pmatrix} -(m+\beta v^*) & 0 & -\beta x^* \\ \beta v^* & -a & \beta x^* \\ 0 & k & -u \end{pmatrix},$$

$$B(y(t)) = \begin{pmatrix} \sigma_1 y_1(t) & 0 & 0 \\ 0 & \sigma_2 y_2(t) & 0 \\ 0 & 0 & \sigma_3 y_3(t) \end{pmatrix}, \quad w(t) = \begin{pmatrix} w_1(t) \\ w_2(t) \\ *[4pt] w_3(t) \end{pmatrix}.$$

It is easy to see that, if $v^* > 0$ (that is, if $R_0 > 1$) holds, then matrix A satisfies the Routh-Hurwitz criterion for stability (see [3], p. 197). Indeed, for coefficients of the characteristic equation

$$\lambda^3 - S_1\lambda^2 + S_2\lambda - S_3 = 0,$$

the inequalities

$$\begin{aligned} S_1 &= \mathrm{tr}A = -(m+\beta v^* + a + u) < 0, \\ S_2 &= (m+\beta v^*)(a+u) > 0, \\ S_3 &= \det A = -au\beta v^* < 0, \\ S_3 &> S_1 S_2 \end{aligned}$$

hold (we used equalities (1.2) here). Therefore, for a positive definite matrix

$$Q = \begin{pmatrix} q_1 & 0 & 0 \\ 0 & q_2 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \qquad q_1 > 0, \qquad q_2 > 0,$$

there exists a positive definite solution $P = \|p_{ij}\|$ of the Lyapunov matrix equation

$$A'P + PA = -Q. \tag{3.2}$$

Remark 3.1 The diagonal elements p_{ii}, $i = 1, 2, 3$, of the solution P to the matrix equation (3.2) are defined [9] as

$$p_{ii} = \frac{1}{2\Delta_3} \sum_{r=0}^{2} \gamma_i^{(r)} \Delta_{1,r+1}. \tag{3.3}$$

Here

$$\Delta_3 = \begin{vmatrix} -S_1 & -S_3 & 0 \\ 1 & S_2 & 0 \\ 0 & -S_1 & -S_3 \end{vmatrix} = (S_1S_2 - S_3)S_3 > 0$$

is the determinant of Hurwitz matrix; $\Delta_{1,r+1}$ is the algebraic adjunct of the element of the first line and $(r+1)$-th column of the determinant Δ_3, that is, $\Delta_{11} = -S_2S_3$, $\Delta_{12} = S_3$ and $\Delta_{13} = -S_1$, and $\gamma_i^{(r)}$ are defined by the identity

$$\sum_{k=1}^{3} q_k D_{ik}(\lambda) D_{ik}(-\lambda) \equiv \sum_{r=0}^{2} \gamma_i^{(r)} \lambda^{2(2-r)}, \tag{3.4}$$

where q_i are the elements of the matrix Q, that is, $q_1 > 0$, $q_2 > 0$ and $q_3 = 1$, and $D_{ik}(\lambda)$ are the algebraic adjuncts of the determinant

$$D(\lambda) = \begin{vmatrix} a_{11}-\lambda & a_{12} & a_{13} \\ a_{21} & a_{22}-\lambda & a_{23} \\ a_{31} & a_{32} & a_{33}-\lambda \end{vmatrix}.$$

From (3.3), (3.4) it follows that the diagonal elements of the solution P of the matrix equation (3.2) can be represented in the form

$$p_{ii} = p_{ii}^{(1)} q_1 + p_{ii}^{(2)} q_2 + p_{ii}^{(3)}, \qquad i = 1,2,3. \tag{3.5}$$

Sufficient stability conditions for the trivial solution of system (2.3) are given by following Theorem:

Theorem 3.1 . Let σ_i, $i = 1,2,3$, satisfy the conditions

$$\sigma_1^2 < \left(p_{11}^{(1)}\right)^{-1}, \qquad \sigma_2^2 < \left(p_{22}^{(2)} + \frac{\sigma_1^2 p_{11}^{(2)} p_{22}^{(1)}}{1-\sigma_1^2 p_{11}^{(1)}}\right)^{-1},$$

$$\sigma_3^2 < \left(p_{33}^{(3)} + \frac{\sigma_1^2 p_{33}^{(1)}\left[\sigma_2^2 p_{11}^{(2)} p_{22}^{(3)} + p_{11}^{(3)}\left(1-\sigma_2^2 p_{22}^{(2)}\right)\right]}{\left(1-\sigma_1^2 p_{11}^{(1)}\right)\left(1-\sigma_2^2 p_{22}^{(2)}\right) - \sigma_1^2\sigma_2^2 p_{11}^{(2)} p_{22}^{(1)}} + \frac{\sigma_2^2 p_{33}^{(2)}\left[\sigma_1^2 p_{11}^{(3)} p_{22}^{(1)} + p_{22}^{(3)}\left(1-\sigma_1^2 p_{11}^{(1)}\right)\right]}{\left(1-\sigma_1^2 p_{11}^{(1)}\right)\left(1-\sigma_2^2 p_{22}^{(2)}\right) - \sigma_1^2\sigma_2^2 p_{11}^{(2)} p_{22}^{(1)}}\right)^{-1}. \tag{3.6}$$

Then the trivial solution of system (2.3) is asymptotically mean square stable.

Proof. Let L be the generator [4] of the equation (3.1), $P = \|p_{ij}\|$ be the solution of the matrix equation (3.2), and $V = y'Py$. Then

$$\begin{aligned} LV =& y'(t)(A'P + PA)y(t) + \sum_{i=1}^{3} \sigma_i^2 p_{ii} y_i^2(t) \\ =& (-q_1 + \sigma_1^2 p_{11}) y_1^2(t) + (-q_2 + \sigma_2^2 p_{22}) y_2^2(t) + (-1 + \sigma_3^2 p_{33}) y_3^2(t), \end{aligned}$$

and hence the sufficient conditions for the asymptotic mean square stability of the trivial solution of equation (3.1) are (see [9])

$$\sigma_1^2 p_{11} < q_1, \qquad \sigma_2^2 p_{22} < q_2, \qquad \sigma_3^2 p_{33} < 1. \tag{3.7}$$

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Using (3.5), we can rewrite conditions (3.7) in the form

$$\sigma_1^2\left(p_{11}^{(1)}q_1+p_{11}^{(2)}q_2+p_{11}^{(3)}\right)<q_1, \tag{3.8}$$

$$\sigma_2^2\left(p_{22}^{(1)}q_1+p_{22}^{(2)}q_2+p_{22}^{(3)}\right)<q_2, \tag{3.9}$$

$$\sigma_3^2\left(p_{33}^{(1)}q_1+p_{33}^{(2)}q_2+p_{33}^{(3)}\right)<1. \tag{3.10}$$

It is easy to see that Theorem hypotheses (3.6) imply that (3.8)–(3.10) hold for some positive q_1 and q_2. Indeed, combining inequalities (3.8) and (3.9), we get

$$0<\frac{\sigma_2^2\left(p_{22}^{(1)}q_1+p_{22}^{(3)}\right)}{1-\sigma_2^2p_{22}^{(2)}}<q_2<\frac{\left(1-\sigma_1^2p_{11}^{(1)}\right)q_1-\sigma_1^2p_{11}^{(3)}}{\sigma_1^2p_{11}^{(2)}}. \tag{3.11}$$

Hence, if there exists $q_1>0$ such that the inequality

$$0<\frac{\sigma_2^2\left(p_{22}^{(1)}q_1+p_{22}^{(3)}\right)}{1-\sigma_2^2p_{22}^{(2)}}<\frac{\left(1-\sigma_1^2p_{11}^{(1)}\right)q_1-\sigma_1^2p_{11}^{(3)}}{\sigma_1^2p_{11}^{(2)}} \tag{3.12}$$

holds, then there also exists $q_2>0$ such that (3.11) holds. Furthermore, from (3.12) it follows that

$$q_1>\frac{\sigma_1^2\left[\sigma_2^2p_{11}^{(2)}p_{22}^{(3)}+p_{11}^{(3)}\left(1-\sigma_2^2p_{22}^{(2)}\right)\right]}{\left(1-\sigma_1^2p_{11}^{(1)}\right)\left(1-\sigma_2^2p_{22}^{(2)}\right)-\sigma_1^2\sigma_2^2p_{11}^{(2)}p_{22}^{(1)}}. \tag{3.13}$$

Likewise, inequalities (3.8) and (3.9) yield

$$0<\frac{\sigma_1^2\left(p_{11}^{(2)}q_2+p_{11}^{(3)}\right)}{1-\sigma_1^2p_{11}^{(1)}}<q_1<\frac{\left(1-\sigma_2^2p_{22}^{(2)}\right)q_2-\sigma_2^2p_{22}^{(3)}}{\sigma_2^2p_{22}^{(1)}}, \tag{3.14}$$

and hence the existence of $q_2>0$, such that the inequality

$$0<\frac{\sigma_1^2\left(p_{11}^{(2)}q_2+p_{11}^{(3)}\right)}{1-\sigma_1^2p_{11}^{(1)}}<\frac{\left(1-\sigma_2^2p_{22}^{(2)}\right)q_2-\sigma_2^2p_{22}^{(3)}}{\sigma_2^2p_{22}^{(1)}} \tag{3.15}$$

holds, also ensures the existence of $q_1>0$ such that (3.14) holds. Moreover, from (3.15), it follows that

$$q_2>\frac{\sigma_2^2\left[\sigma_1^2p_{11}^{(3)}p_{22}^{(1)}+p_{22}^{(3)}\left(1-\sigma_1^2p_{11}^{(1)}\right)\right]}{\left(1-\sigma_1^2p_{11}^{(1)}\right)\left(1-\sigma_2^2p_{22}^{(2)}\right)-\sigma_1^2\sigma_2^2p_{11}^{(2)}p_{22}^{(1)}}. \tag{3.16}$$

Theorem hypothesis, and specifically the first and the second inequa-lities in (3.6), guaranties that the right hand parts in (3.13) and (3.16) are positive. Furthermore, by (3.13), (3.16) and the third condition in (3.6), inequality (3.10) holds as well. That is, Theorem hypothesis (3.6) ensure the existence of $q_1 > 0$ and $q_2 > 0$ such that conditions (3.8)–(3.10) hold, and, thereby, the asymptotic mean square stability of the trivial solution of linear equation (2.3). The proof is now completed.

Corollary 3.1 Under Theorem 2.1 hypothesis, the trivial solution of nonlinear system (2.2), or, what is the same, of the positive equilibrium state E^* of system (2.1), is stable in probability.

The proof follows from [9], since the order of nonlinearity of system (2.2) is higher than one.

Remark 3.2 Note that if all conditions (3.6) do not hold then the trivial solution of system (2.3) cannot be asymptotically mean square stable [9].

4. Stability of the infection-free equilibrium E_0

For the infection-free equilibrium state E_0, systems (2.1), (2.2) and (2.3), respectively, have the forms

$$\begin{aligned} \dot{x}(t) &= \lambda - mx(t) - \beta x(t)v(t) + \sigma_1(x(t) - x_0)\dot{w}_1(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t) + \sigma_2 y(t)\dot{w}_2(t), \\ \dot{v}(t) &= ky(t) - uv(t) + \sigma_3 v(t)\dot{w}_3(t); \end{aligned} \tag{4.1}$$

$$\begin{aligned} \dot{x}_1(t) &= -mx_1(t) - \beta x_0 x_3(t) - \beta x_1(t)x_3(t) + \sigma_1 x_1(t)\dot{w}_1(t), \\ \dot{x}_2(t) &= \beta(x_0 x_3(t) + x_1(t)x_3(t)) - ax_2(t) + \sigma_2 x_2(t)\dot{w}_2(t), \\ \dot{x}_3(t) &= kx_2(t) - ux_3(t) + \sigma_3 x_3(t)\dot{w}_3(t), \end{aligned} \tag{4.2}$$

and

$$\begin{aligned} \dot{y}_1(t) &= -my_1(t) - \beta x_0 y_3(t) + \sigma_1 y_1(t)\dot{w}_1(t), \\ \dot{y}_2(t) &= -ay_2(t) + \beta x_0 y_3(t) + \sigma_2 y_2(t)\dot{w}_2(t), \\ \dot{y}_3(t) &= ky_2(t) - uy_3(t) + \sigma_3 y_3(t)\dot{w}_3(t). \end{aligned} \tag{4.3}$$

For these systems, conditions for the asymptotic mean square stability of the trivial solution of system (4.3) at the same time are the conditions for the stability in probability of the trivial solution of system (4.2) and for the stability in probability of the infection-free equilibrium state E_0 of system (4.1).

Conditions of the stability are given by following Theorem:

Theorem 4.1 Let $R_0 < 1$ holds, and σ_i, $i = 1, 2, 3$, satisfy the conditions

$$\delta_1 < m, \qquad \delta_2 < \frac{|\mathrm{tr}(A)|\det(A)}{A_2}, \qquad \delta_3 < \frac{|\mathrm{tr}(A)|\det(A) - A_2\delta_2}{A_1 - |\mathrm{tr}(A)|\delta_2}, \tag{4.4}$$

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where

$$\delta_i = \frac{1}{2}\sigma_i^2, \qquad i = 1, 2, 3,$$

$$A = \begin{pmatrix} -a & \beta x_0 \\ k & -u \end{pmatrix}, \qquad \mathrm{tr}(A) = -(a+u) < 0,$$

$$\det(A) = au - k\beta x_0 = au - k\beta\lambda m^{-1} = au(1 - R_0) > 0,$$

$$A_1 = \det(A) + a^2, \qquad A_2 = \det(A) + u^2.$$

Then the trivial solution of the system (4.3) is asymptotically mean square stable.

Proof. We note that the second and the third equations of (4.3) are independent of $y_1(t)$, and hence the system of two equation $(y_2(t), y_3(t))$ can be considered separately. Sufficient conditions for the asymptotic mean square stability of the trivial solutions for systems of such a type are well known (for instance, see [9]). Theorem hypothesis (4.4) ensures that these conditions are held. The conditions (4.4) also imply the stability in probability of the equilibrium point (1.3) of the system (4.1).

5. Conclusion

The concept of stochastic modelling allows to capture, to some extent, the complexity of biological processes and to imitate the impacts of unavoidable in the real life uncertainties. This consideration motivates the growing interest to stochastic modelling in mathematical biology. In this paper, we considered a stochastic version of the Nowak-May model of virus dynamics within a host, which was originally suggested to describe HIV-1 dynamics. Using the direct Lyapunov method, we found sufficient conditions for the stability in probability for the equilibrium states of this model.

It is noteworthy that the approach used in this paper can be applied to a wider variety of the stochastic models.

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