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A permanence theorem for a mathematical model for dynamics of pathogens and cells in vivo using elementary methods

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An elementary proof of permanence for a simple mathematical model proposed by Nowak and Bangham. In many papers, permanence property is proved by theorems established by the general theory of dynamical system. In this paper, we present an elementary proof only using differential inequalities and the theory of linear differential equations with constant coefficients.

Keywords: Permanence, dynamical system, pathogen

1 Introduction

Infectious diseases have been studied using ordinary differential equation models. For studying the state of diseases, it is important to know whether the disease dies out or persists. For many models, if the basic reproductive rate R_0 is less than 1, the boundary equilibrium is globally asymptotically stable. On the other hand if R_0 is greater than 1, the boundary equilibrium becomes unstable and the interior equilibrium becomes asymptotically stable. But in general, the global property of the interior equilibrium is very difficult to study.

A system is called permanent if all variables are greater than some positive value which is independent of the initial values after sufficiently long time. For permanence of ordinary differential equation, many researches have done ([1], [4]). The expository paper [3] reviews the contents of these papers.

For a very simple model presented by Nowak-Bangham [2], it is possible to prove permanence if $R_0 > 1$ using theorems in [1],[4]. But the model is very simple and such theorems are not simple, and are proved using deep techniques of dynamical system, it is desirable to prove the permanence of this model not using these theorems. In this note, we present an elementary proof of the permanence of Nowak-Bangham model only using differential inequalities and the theory of linear ordinary differential equations with constant coefficients. In this note, we do not use general methods of dynamical system theory, and treat each variable separately. The authors think that the method in this note gives a help to understand permanence of ordinary differential equations.

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2 Simple pathogen model

We consider the following system of ordinary differential equation describing interaction between pathogens and cells in vivo [2].

$$\frac{dx}{dt} = \lambda - dx - \beta xp \quad (1)$$

$$\frac{dy}{dt} = \beta xp - ay \quad (2)$$

$$\frac{dp}{dt} = by - cp. \quad (3)$$

The variable x denotes the density of uninfected cells, y denotes that of infected cells, and p denotes that of pathogens. Uninfected cells are produced at the constant rate λ and die at rate d. Uninfected cells are infected by pathogens at rate βp. Infected cells die at rate a. At lysis, b/a pathogens per an infected cell are released.

This equation has two equilibria. One is the boundary equilibrium $X_1 = (\bar{x}, 0, 0)$ and and other is the interior equilibrium (x^*, y^*, p^*), where $\bar{x} = \lambda/d$. Let $R_0 = (\beta\lambda b)/(dac)$. Then R_0 is a basic reproduction rate. If $R_0 < 1$ then X_1 is globally asymptotically stable, and the disease dies out. This is shown using Lyapunov function and La Sard invariance principle. If $R_0 > 1$ then X_1 becomes unstable and X_2 is locally asymptotically stable. But the global asymptotical stability of X_2 is not known yet.

For the proof of main theorem, we need the first two lemmas.

Lemma 2.1 *If $x(0) \geq 0$, then $x(t) > 0$ for every $t > 0$. If $y(0) \geq 0$, $p(0) \geq 0$ and moreover if one of them is positive, $y(t) > 0$ and $p(t) > 0$ for every $t > 0$.*

Lemma 2.2 *There exists a positive constant M such that for every initial value $(x(0), y(0), p(0))$ there exists a positive constant T_1 such that $x(t) \leq M$, $y(t) \leq M$ and $p(t) \leq M$ hold for $t \geq T_1$.*

Proof From the equations (1), (2) and (3), we have

$$\begin{aligned} & \frac{d}{dt}\left(x + y + \frac{a}{2b}p\right) \\ = \;& \lambda - dx - \frac{a}{2}y - \frac{c}{2b}p \\ \geq \;& \lambda - \min\left(d, \frac{a}{2}, \frac{c}{a}\right)\left(x + y + \frac{a}{2b}p\right). \end{aligned}$$

Then we come to the conclusion.

We call the permanence property holds for a variable if there exists a positive constant T such that the variable is greater than some positive constant which is independent of the initial values for $t \geq T$.

The permanence property for x holds for every parameter value.

Lemma 2.3 *We put $x_0 = \lambda/(d + 2\beta M)$. There exists a positive constant T_2 which is greater that T_1 such that we have $x(t) \geq x_0$ for every $t \geq T_2$.*

Proof By Lemma 2.2, for $t \geq T_1$ we have

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xp \\ &\geq \lambda - (d + \beta M)x \end{aligned}$$

Since $\lambda/(d + 2\beta M) < \lambda/(d + \beta M)$, there exists a T_2 such that $x(t) \geq \lambda/(d + 2\beta M)$ for $t \geq T_2$. Of course, we can assume $T_2 > T_1$.

If the permanence property holds for p, then it holds also for y.

Lemma 2.4 *We assume that there exists a positive constant T_3 which is greater than T_2 such that $p(t) \geq p_0 > 0$ for $t \geq T_3$. We put $T_4 = T_3 + (\log 2)/a$. Then $y(t) \geq (p_0 x_0)/(2a)$ for $t \geq T_4$.*

Proof For $t \geq T_4$ we have

$$\begin{aligned} y(t) &= e^{-at}y(T_3) + e^{-at}\int_{T_3}^{t} e^{as}p(s)x(s)\,ds \\ &\geq e^{-at}y(T_3) + e^{-at}\int_{T_3}^{t} e^{as}p_0x_0\,ds \\ &\geq \frac{p_0x_0(1 - e^{-a(t-T_3)})}{a} \\ &\geq \frac{p_0x_0(1 - e^{-a(T_4-T_3)})}{a} = \frac{p_0x_0}{2a} > 0. \end{aligned}$$

From now, we assume that $R_0 > 1$. Then we can take $\tilde{x}$ such that $0 < \tilde{x} < \bar{x}$ and $ac - \beta\tilde{x}b < 0$. We take $\varepsilon > 0$ such that we have $\tilde{x} < \lambda/(\beta\varepsilon + d)$, and fix it.

Lemma 2.5 *Let δ and M be constants such that $0 < \delta < \varepsilon$ and $M > 0$. We put $D = \{(u_1, u_2) | 0 \leq u_1 \leq M,\ \delta \leq u_2 \leq \varepsilon\}$. We consider the following system of linear differential equations with constant coefficients:*

$$\begin{aligned} \frac{du_1}{dt} &= -au_1 + \beta\tilde{x}u_2 \\ \frac{du_2}{dt} &= bu_1 - cu_2, \end{aligned}$$

with the initial condition $(u_1(0), u_2(0)) \in D$. Then there exists a constant $T^* > 0$ which is independent of the initial values such that $u_2(t) \geq \varepsilon$ for every $t \geq T^*$.

Proof Let

$$A = \begin{bmatrix} -a & \beta\tilde{x} \\ b & -c \end{bmatrix}.$$

The characteristic equation of A has two solutions $\Lambda_1 < 0$ and $\Lambda_2 > 0$. We note $\Lambda_1 < -a, -c$. Let

$\mathbf{p}_1 = \begin{bmatrix} p_{11} \\ p_{21} \end{bmatrix}$ and $\mathbf{p}_2 = \begin{bmatrix} p_{12} \\ p_{22} \end{bmatrix}$ be the eigenvectors associated with eigenvalues Λ_1 and Λ_2 respectively. Then we can assume that $p_{11} < 0$, $p_{21} > 0$, $p_{12} > 0$ and $p_{22} > 0$. We put $P = [\mathbf{p}_1 \quad \mathbf{p}_2]$ and express P^{-1} as

$$P^{-1} = \begin{bmatrix} q_{11} & q_{12} \\ q_{21} & q_{22} \end{bmatrix}.$$

Then we have $q_{11} < 0$, $q_{12} > 0$, $q_{21} > 0$ and $q_{22} > 0$. If we put $\begin{bmatrix} c_1 \\ c_2 \end{bmatrix} = P^{-1} \begin{bmatrix} u_1(0) \\ u_2(0) \end{bmatrix}$, we have $\begin{bmatrix} u_1(t) \\ u_2(t) \end{bmatrix} = P \begin{bmatrix} c_1 e^{\Lambda_1 t} \\ c_2 e^{\Lambda_2 t} \end{bmatrix}$. Since $c_1 = q_{11}u_1(0) + q_{12}u_2(0)$ and $c_2 = q_{21}u_1(0) + q_{22}u_2(0)$, we have $c_2 \geq q_{22}\delta$ and $0 \leq |c_1| \leq |q_{11}|M + q_{21}\varepsilon$. Then we have

$$\begin{aligned} u_2(t) &= c_1 p_{21} e^{\Lambda_1 t} + c_2 p_{22} e^{\Lambda_2 t} \\ &\geq p_{22} q_{22} \delta e^{\Lambda_2 t} - (|q_{11}|M + q_{12}\varepsilon) p_{21} e^{\Lambda_1 t}. \end{aligned}$$

We take $T^* > 0$ such that $(|q_{11}|M + q_{12}\varepsilon)p_{21}e^{\Lambda_1 T^*} \leq 1$ and $p_{22}q_{22}\delta e^{\Lambda_2 T^*} \geq \varepsilon + 1$. Then we have $u_2(t) \geq \varepsilon$ for $t \geq T^*$. The choice of T^* is independent of the initial values.

When $p(t)$ is small, the solution approaches the boundary flow. Even though $R_0 > 1$, $(\bar{x}, 0, 0)$ is globally asymptotically stable in $\{(x,y,p) | x \geq 0,\ y = 0,\ p = 0\}$.

Lemma 2.6 *We assume that* $p(t^*) \leq \varepsilon$. *Then there exists a constant* $T_5 > 0$ *such that* $x(t^* + T_5) \geq \tilde{x}$ *if* $p(t) < \varepsilon$ *for* $t^* \leq t \leq t^* + T_5$. *Moreover If* $p(t) < \varepsilon$ *for* $t^* + T_5 \leq t \leq t^{**} + T_5 + T_{**}$, *where* T_{**} *is an arbitrary positive number, we have* $x(t) \geq \tilde{x}$ *for* $t^* + T_5 \leq t \leq t^* + T_5 + T_{**}$.

Proof We consider the differential equation

$$\frac{du}{dt} = \lambda - (d + \beta\varepsilon)u$$

with initial condition $u(0) = x_0$. Then $u(t)$ is monotonously increasing for $t > 0$ and there exists a unique T_5 such that $u(T_5) = \tilde{x}$. For the original equation, if $p(t) < \varepsilon$ for $t^* \leq t \leq t^* + T_5$, by the comparison theorem, $x(t) \geq \tilde{x}$.

The proof of the second statement is similar.

Lemma 2.7 *Let* $p(t^*) = \varepsilon$, *and* T *be a positive number. Then* $p(t) \geq \varepsilon e^{-cT}$ *for* $t^* \leq t \leq t^* + T$.

Proof This follows from the differential inequality $\frac{dp}{dt} \geq -cp$.

Using these lemmas, we can prove the permanence of the original system.

Theorem 2.8 *The system (3) is permanent: For the system (3), there exists a positive* $\bar{\varepsilon}$ *such that*

$$\liminf_{t\to\infty} x(t) \geq \bar{\varepsilon}, \quad \liminf_{t\to\infty} y(t) \geq \bar{\varepsilon}, \quad \liminf_{t\to\infty} p(t) \geq \bar{\varepsilon}.$$

Proof If there exists a $t^* \geq 0$ such that $p(t) \geq \varepsilon$ for every $t \geq t^*$, by Lemma 2.4 the system (3) is permanent.

If $p(t^{**}) \leq \varepsilon$ and $p(t) < \varepsilon$ for every $t \geq t^{**}$, by Lemma 2.5 and Lemma 2.6 a contradiction occurs.

Suppose that there exist s and r such that $s < r$ and $p(s) = \varepsilon$, $p(r) = \varepsilon$ and $p(t) < \varepsilon$ for $s < t < r$. Let T_5 be as in Lemma 2.6. We assume that $r \leq s + T_5$. By Lemma 2.7, $p(t) \geq \varepsilon e^{-cT_5}$ for $s \leq t \leq r$. We assume that $s + T_5 < r$. For $s + T_5 \leq t \leq r$, we have $x(t) \geq \tilde{x}$, and $p(s + T_5) \geq \varepsilon e^{-cT_5}$. We take $\delta = \varepsilon e^{-cT_5}$ in Lemma 2.5. By Lemma 2.5 and the comparison theorem, we have $r \leq s + T_5 + T^*$. By Lemma 2.7, we have $p(t) \geq \varepsilon e^{-c(T_5 + T^*)}$ for $s \leq t \leq r$.

We can conclude that $\liminf_{t\to\infty} p(t) \geq \varepsilon e^{-c(T_5+T^*)}$ in any case. We get conclusion by Lemma 2.6 and Lemma 2.4.

Remark 2.1 *We note that the lower bound* $\bar{\varepsilon}$ *can be calculated explicitly from the coefficients.*

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