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.

2 Simple pathogen model

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

\[
\begin{align*}
\frac{dx}{dt} &= \lambda - dx - \beta xp \\
\frac{dy}{dt} &= \beta xp - ay \\
\frac{dp}{dt} &= by - cp.
\end{align*}
\]

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 \( \lambda \) and die at rate \( d \). Uninfected cells are infected by pathogens at rate \( \beta p \). 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 $R_0 = (\beta \lambda b)/(d \alpha c)$. 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

\[
\frac{dx}{dt} = \lambda - dx - \frac{a}{2}y - \frac{c}{2b}p \\
\geq \lambda - \min\left(\frac{a}{2}, \frac{c}{2b}\right)\left(x + y + \frac{a}{2b}p\right).
\]

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 than $T_1$ 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

\[
\frac{dx}{dt} = \lambda - dx - \beta xp \\
\geq \lambda - (d + \beta M)x.
\]

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

\[
y(t) = e^{-at}y(T_3) + e^{-at}\int_{T_3}^{t} e^{as}p(s)x(s)ds \\
\geq e^{-at}y(T_3) + e^{-at}\int_{T_3}^{t} e^{as}p_0 x_0 ds \\
\geq \frac{p_0 x_0 (1 - e^{-a(t-T_3)})}{a} \\
\geq \frac{p_0 x_0 (1 - e^{-a(T_4-T_3)})}{a} = \frac{p_0 x_0}{2a} > 0.
\]

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 $\tilde{x} < \lambda/(\beta \epsilon + d)$, and fix it.

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

\[
\frac{du_1}{dt} = -au_1 + \beta \tilde{x}u_2 \\
\frac{du_2}{dt} = bu_1 - cu_2,
\]

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
Then we assume that $p(t^{**}) = \varepsilon$ 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, $p(t) \geq e^{-cT_{5}}$ for $s \leq t 

lim \inf_{t \to \infty} x(t) \geq \varepsilon$, $\lim \inf_{t \to \infty} y(t) \geq \varepsilon$, $\lim \inf_{t \to \infty} p(t) \geq \varepsilon$.

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.

Then we have $u_{2}(t) = c_{1}p_{21}e^{\Lambda_{1}t} + c_{2}p_{22}e^{\Lambda_{2}t}$

$\geq p_{22}q_{22}\delta e^{\Lambda_{2}t} - (|q_{11}|M + q_{12}\varepsilon)p_{21}e^{\Lambda_{1}t}$.

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 $Q > 1$, $(\bar{x}, 0, 0)$ 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 $x(t^{*} + T_{5}) \geq \bar{x}$ if $p(t) < \varepsilon$ for $t^{*} \leq t \leq t^{*} + T_{5}$. Moreover if $p(t) < \varepsilon$ for $t^{*} + T_{5} \leq t \leq t^{*} + T_{5} + T_{\ldots}$, where $T_{\ldots}$ is an arbitrary positive number, we have $x(t) \geq \bar{x}$ for $t^{*} + T_{5} \leq t \leq t^{*} + T_{5} + T_{\ldots}$.

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 $u(T_{5}) = \bar{x}$. For the original equation, if $p(t) < \varepsilon$ for $t^{*} \leq t \leq t^{*} + T_{5}$, by the comparison theorem, $x(t) \geq \bar{x}$.

The proof of the second statement is similar.

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

Proof This follows from the differential inequality

$$\frac{dp}{dt} \geq -cp.$$