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FINITE-TIME PERTURBATIONS OF DYNAMICAL SYSTEMS AND APPLICATIONS TO TUMOR THERAPY

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Abstract. We study finite-time perturbations of dynamical systems. We prove that finite-time perturbed dynamical systems are asymptotically equivalent to unperturbed dynamical systems. And so the asymptotical behavior of finite-time perturbed systems can be studied by unperturbed systems. As an example, we study a system perturbed by drug treatments.

1. Introduction.

Most of perturbed velocity fields in the study of dynamical systems are defined for all times, and they always remain close to the unperturbed velocity fields. However, in many models of practical problems, the perturbations or forcing terms are effective only over a period of finite-time interval. There are few literatures which are concerned about finite-time vector fields. In Sandstede et al [1], they extended Melnikov theory to a perturbed vector field defined over a sufficiently large finite-time interval, but still require the perturbed vector field remains close to the unperturbed vector field. There are quite a few articles which studied finite-time stability [2] [3] [4], but obviously the systems they considered are non-Lipschitzian dynamics. In the present paper, we are still working within the category of Lipschitzian dynamics. We require that perturbed vector fields are defined on fixed finite-time intervals and bounded. Our this study is motivated by a type of modeling of drug treatments.

When people have nausea and vomiting during certain healthy conditions and see doctors, doctors usually give a medicine, called metoclopramide. After taking metoclopramide, the symptom of nausea and vomiting will become light, and patients will feel much better. However, after taking metoclopramide 24 hours, the symptom of nausea and vomiting will come back. Maybe in the different status of the symptom when it come back. Mathematically speaking, there is a system that describes the dynamics of nausea and vomiting. If we do not put an outside forcing term, drug treatments, the system will eventually go to an equilibrium state over a long-time period. As we give an outside forcing term, drug treatments, the system will be changed. However, the efficacy of drug treatments only lasts a finite-time period. Comparing with the long-time period of reaching an equilibrium state of the system, the finite-time period of drug treatments is not negligible, but also not

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sufficiently large. Therefore, in this interesting case, we take it as a fixed finite-time period, and call the outside forcing term during the fixed finite-time period a finite-time perturbation.

In section 2, we study some asymptotical behavior of finite-time perturbed systems. We prove that finite-time perturbed dynamical systems are asymptotically equivalent to unperturbed dynamical systems. For illustration, we have given two examples. In section 3, we study a tumor ecology model perturbed by virotherapy. There seems some interesting mathematical problems related finite-time perturbations, and we therefore list some open problems in section 4.

2. **Finite-time perturbations.**

Consider a nonlinear system of differential equations

$$\dot{x} = f(x),$$

where $f : E \to R^n$ and E is an open subset of R^n. A finite-time perturbation $p(t, x)$ is a velocity field which is defined on $R \times E$ with a finite-time support set. Namely, there is a positive finite number T, $p(t, x) = 0$ when $|t| \geq T$. Therefore, the perturbed system we are considering is given by

$$\dot{y} = f(y) + p(t, y).$$

Lemma 2.1. *Let $b(t,x)$ be a $C^1(R \times R)$ and $b(t,x)=0$ when $t \geq 0$, $b(t,x)$ be Lipschitzian when $t \leq 0$. Then the following two initial value problems have the same values of solutions when $t \geq 0$,*

$$\begin{cases} \dot{x} & = 0 \\ x(0) & = c, \end{cases}$$

and

$$\begin{cases} \dot{x} & = b(t, x) \\ x(0) & = c. \end{cases}$$

Proof. It is obvious that the first initial value problem has a constant solution, $x(t) = c$. The second initial value problem is equivalent to the following integral equation problem.

$$y(t) = y(0) + \int_0^t b(s, y(s))ds,$$

and $t \in I$, where I is an interval which contains 0 point. Since $b(t, y) = 0$ when $t \geq 0$, we have, when $t \geq 0$,

$$y(t) = y(0) = c.$$

Therefore, the solution of the second initial value problem should be constant c when $t \geq 0$ if it has a solution. From the basic theorem of existence and uniqueness of solutions of initial value problems, we know the second problem has a unique solution $y(t)$. Thus, both solutions of these two initial value problems are the same constant when $t \geq 0$. □

The asymptotical theorem is presented in a general compact manifold, but it is easy to see it also holds in any open subset of R^n [5].

Theorem 2.2. *Let M be a compact manifold and let $f \in C^1(M)$, $p \in C^1(R \times M)$. If $p(t, x)$ is Lipschitzian and bounded, and $p(t, x) = 0$ when $t \geq T$ or $t \leq -T$, then the following two systems are asymptotically equivalent,*

$$\dot{x} = f(x), \tag{1}$$

and

$$\dot{x} = f(x) + p(t, x). \tag{2}$$

Proof. Consider the initial value problem

$$\begin{cases} \dot{x} & = f(x) \\ x(0) & = x_0, \end{cases}$$

By Chillingworth's theorem [6], there exists a unique solution $u(t)$ defined for all $t \in R$, satisfies $u(0) = x(0) = x_0$. Now, we consider the initial value problem

$$\begin{cases} \dot{y} & = f(y) + p(t, y) \\ y(T) & = u(T). \end{cases}$$

From Chillingworth's theorem or generalized version of it, there exists a unique solution $v(t)$ defined for all $t \in R$, and $v(T) = u(T)$. Apply the Lemma 2.1, we have, when $t \geq T$,

$$u(t) = v(t).$$

Of course, we have

$$lim_{t\to\infty} \parallel u(t) - v(t) \parallel = 0.$$

If the initial value problem

$$\begin{cases} \dot{y} & = f(y) + p(t, y) \\ y(0) & = y_0 \end{cases}$$

has the solution $\overline{v(t)}$, we then consider the initial value problem

$$\begin{cases} \dot{x} & = f(x) \\ x(T) & = y_0. \end{cases}$$

By Chillingworth's theorem, this initial value problem has the solution $\overline{u(t)}$ over R. And from Lemma 2.1, when $t \geq T$, we have $\overline{u(t)} = \overline{v(t)}$. Naturally,

$$lim_{t\to\infty} \parallel \overline{u(t)} - \overline{v(t)} \parallel = 0.$$

Therefore, these two systems (1) and (2) are asymptotically equivalent. □

Theorem 2.3. *Under the same conditions as stated in theorem 2.2, for any solution of (1) and any solution of (2), if they have the same initial values, $x(0) = y(0)$, we have, for $t > 0$,*

$$\parallel x(t) - y(t) \parallel \leq MTe^{\delta t};$$

and for $t < 0$,

$$\parallel x(t) - y(t) \parallel \leq MTe^{-\delta t},$$

where M and δ are positive finite numbers.

Proof. By integration, we have

$$x(t) = x(0) + \int_0^t f(x(s))ds$$

and

$$y(t) = y(0) + \int_0^t (f(y(s)) + p(s, y(s)))ds.$$

Taking the difference, we have, when $t > 0$,

$$\begin{aligned}
\| x(t) - y(t) \| &= \| \int_0^t (f(x(s)) - f(y(s)))ds - \int_0^t p(s, y(s))ds \| \\
&\leq \| \int_0^t (f(x(s)) - f(y(s)))ds \| + \| \int_0^t p(s, y(s))ds \| \\
&\leq \| \int_0^t (f(x(s)) - f(y(s)))ds \| + \| \int_0^T p(s, y(s))ds \| \\
&\leq MT + \int_0^t \| f(x(s)) - f(y(s)) \| ds \\
&\leq MT + \int_0^t \delta \| x(s) - y(s) \| ds \\
&\leq MT + \delta \int_0^t \| x(s) - y(s) \| ds
\end{aligned}$$

where M is a bound of $p(t, x)$, $p(t, x) \leq M$; and δ is a constant from Lipschitz condition. We now apply Gronwall inequality [7], and get

$$\| x(t) - y(t) \| \leq MTe^{\delta t}.$$

When $t < 0$, we can go through the similar process to get

$$\| x(t) - y(t) \| \leq MTe^{-\delta t}.$$

□

Theorem 2.4. *Let $f \in C^1(E)$ and $p \in C^1 \in (R \times E)$, where E is an open set of R^n; f and p are Lipschitzian. Further more, suppose p is bounded and $p(t, x) = 0$ when $t \geq T$. If the system*

$$\dot{x} = f(x) \tag{3}$$

has a periodic solution with period τ, then the system (4) perturbed by $p(t, x)$:

$$\dot{y} = f(y) + p(t, y) \tag{4}$$

has a quasi-periodic solution with the same period τ. That is, after the time interval T or backward the time interval T ago, a trajectory of the dynamical system (4) will fall in a periodic cycle.

Proof. Denote the periodic solution of the dynamical system (3) which passes through the point x_0 by $\phi(t, x_0)$. We now consider the initial value problem

$$\begin{cases} \dot{y} &= f(y) + p(t, y) \\ y(T) &= x_0. \end{cases}$$

By the basic theorem of existence and uniqueness on initial value problems, we know that there is a solution of this initial value problem, say $\varphi(t)$, satisfies $\varphi(T) = x_0$. From the lemma (2.1), we see that when $t > T$, the trajectory of the dynamic system (4), or the solution of the initial value problem, will fall in a cycle. Actually, $\varphi(t) = \phi(t, x_0)$ when $t > T$.

For the backward case, it can be explained similarly. □

Remark 1. Actually, if $\dot{x} = f(x)$ has a periodic solution $\phi(t)$, then along each point Q at the trajectory of $\phi(t)$ there is a solution of $\dot{x} = f(x) + p(t, x)$ that passes through the point Q at time T and then follows the trajectory of $\phi(t)$. Look at example 1.

Example 1. Consider the harmonic equation $\ddot{x} + x = 0$ which is equivalent the following vector form equations

$$\begin{cases} \dot{x_1} &= x_2 \\ \dot{x_2} &= -x_1. \end{cases}$$

We know it has periodic solutions; and they are cycles around the origin. Now let's consider a finite-time perturbation defined by a smooth function $\eta(t)$:

$$\begin{cases} \dot{y_1} &= \eta(t)y_1 + y_2 \\ \dot{y_2} &= -y_1 + \eta(t)y_2. \end{cases}$$

The function $\eta(t)$ is defined as follows. Set,

$$\xi(t) = \begin{cases} e^{-\frac{1}{t}}, & \text{if } t > 0, \\ 0, & \text{if } t \le 0; \end{cases}$$

then, define

$$\eta(t) = \frac{\xi(T^2 - t^2)}{\xi(T^2 - t^2) + \xi(t^2 - 1)}.$$

It is easy to see that the function $\eta(t)$ is smooth and satisfies

$$\begin{cases} \eta(t) = 1, & \text{if } |t| \le 1 \\ 0 < \eta(t) < 1, & \text{if } 1 < |t| < T \\ \eta(t) = 0, & \text{if } |t| \ge T \\ \eta(-t) = \eta(t), & \text{for all } t \in R. \end{cases}$$

In order to get solutions of the perturbed system, we use variation of constants. For harmonic system, $x_1 = sint$ and $x_2 = cost$ is a solution. Suppose that $y_1 = c(t)sint$ and $y_2 = c(t)cost$ is a solution of the perturbed system, then substitute them into the equations, we get $c(t) = e^{\int_0^t \eta(s)ds}$, therefore, $y_1 = sinte^{\int_0^t \eta(s)ds}$ and $y_2 = coste^{\int_0^t \eta(s)ds}$ is a solution of the perturbed system. Now, let the system starts at point (a, b), that is $y_1(0) = a$ and $y_2(0) = b$, the trajectory is given by

$$\begin{cases} \dot{y_1} &= (bsint + acost)e^{\int_0^t \eta(s)ds} \\ \dot{y_2} &= (bcost - asint)e^{\int_0^t \eta(s)ds}. \end{cases}$$

We see from the point (a, b) the trajectory spirals out $\frac{T}{\pi}180°$ degree and then follows the circle Γ centered at the origin with radius $\sqrt{a^2 + b^2}e^{\int_0^T \eta(s)ds}$.

Now, we also can see that from each point at the circle Γ there is a trajectory (solution) that starts at a certain point of the circle γ centered at the origin with radius $\sqrt{a^2 + b^2}$. In this case, the perturbation just shift the trajectories from one circle to another circle during finite-time interval.

Example 2. Let's take an unperturbed system as a linear system for the sake of simplicity,

$$\dot{x} = \begin{pmatrix} -2 & 3 \\ 0 & -1 \end{pmatrix} x.$$

It is easy to get the general solution is given by

$$\begin{cases} x_1 &= 3c_1e^{-t} + c_2e^{-2t} \\ x_2 &= c_1e^{-1}. \end{cases}$$

Because the two eigenvalues are negative, the origin is asymptotically stable.

We now perturb it by a finite-time perturbation $\eta(t)$ as in example 1, that is

$$\dot{y} = \begin{pmatrix} -2 & 3 \\ 0 & -1 \end{pmatrix} y + \eta(t) y.$$

We use the variation of constants, and get

$$\begin{cases} y_1 &= (3c_1 e^{-t} + c_2 e^{-2t}) e^{\int_0^t (\eta(t))ds} \\ y_2 &= c_1 e^{-t} e^{\int_0^t (\eta(t))ds}. \end{cases}$$

We can see that the solutions are just the solutions of unperturbed system multiplied by a factor $e^{\int_0^t (\eta(t))ds}$ caused by perturbations; and the origin is still asymptotically stable.

From our theorem 2.2, theorem 2.4 and the above two examples, we can conclude that the asymptotical behavior of a dynamical system perturbed by a finite-time perturbation can be derived from the corresponding unperturbed dynamical system. For example, in order to find the equilibrium states of a dynamical system perturbed by a finite-time perturbation, we could simply look for the equilibrium states of the corresponding unperturbed system. If the equilibrium states of the corresponding unperturbed system are not solutions of the perturbed system, we simply define that the equilibrium states of a dynamical system perturbed by a finite-time perturbation are the equilibrium solutions of the corresponding unperturbed system. This definition is reasonable because any equilibrium state can not be reached within a finite-time period.

3. **A model of tumor ecology perturbed by drug treatments.** In paper [8], we developed a mathematical model for virotherapy of brain tumor, glioma. From the perspective of ecology, we here simplify that model, and study the ecology but perturbed by drug treatment, pre-administration of cyclophosphamide. We consider a tumor as a complex where several cell species interact. The cell populations in our model include: tumor cell population, innate immune cell population, infected tumor cell population, and free virus population. We consider virus as a semi-species, and we then also model free virus in the population level. Since interaction among these different species, the population dynamics of each species is affected. There are five main interactions in our model include: infection of tumor cells by free virus, stimulation of innate immune system, immune response of innate immune cell to infection, immune response of innate immune cells to free virus, free virus from bursting. We also take necrotic cells into account since model variables will be densities of each cell population. In order to change the dynamics of the whole complex, we perturb the system by immune suppressive drug cyclophosphamide. The model equations are given by:

$$\frac{dx_1}{dt} = \lambda x_1 - \beta x_1 x_4, \tag{5}$$

$$\frac{dx_2}{dt} = \beta x_1 x_4 - k x_2 x_3 - \delta x_2, \tag{6}$$

$$\frac{dx_3}{dt} = s x_2 x_3 - c x_3 - p(t) x_3, \tag{7}$$

$$\frac{dx_4}{dt} = b\delta x_2 - k_0 x_3 x_4 - \gamma x_4, \tag{8}$$

$$\frac{dx_5}{dt} = k x_2 x_3 + \delta x_2 - \mu x_5. \tag{9}$$

x_1 is number density of tumor cell population, x_2 is number density of infected tumor cell population, x_3 is number density of innate immune cell population, x_4 is number density of free virus population, and x_5 is number density of necrotic cell population. All values of parameters can be found in paper [8]. We know that the number density of cells within tumor is a constant, approximately is $\theta = 10^6$ per cubic millimeter [9]. The virus particle in our model is mutation of herpes simplex virus which has a negligible size comparing with cell size, we therefore take

$$x_1 + x_2 + x_3 + x_5 = \theta. \tag{10}$$

The perturbation is $p(t)x_3$ which is product of the concentration of cyclophosphamide and the number density of innate immune cell population. Because the effective of cyclophosphamide only last five days, it is taken as the following function.

$$P(t) = \begin{cases} 8.5 \times 10^{-2} & \text{if } 0 \le t \le 72, \\ \frac{8.5\times10^{-2}}{48}(120 - t) & \text{if } 72 \le t \le 120, \\ 0 & \text{if } t \ge 120 \end{cases} \tag{11}$$

where the unit of $P(t)$ is 1/hour.

This is a finite-time perturbation problem. We here first to study their equilibrium states. As the asymptotical theorem 2.2 states, we just need to find the critical points of the unperturbed system:

$$\frac{dx_1}{dt} = \lambda x_1 - \beta x_1 x_4, \tag{12}$$

$$\frac{dx_2}{dt} = \beta x_1 x_4 - k x_2 x_3 - \delta x_2, \tag{13}$$

$$\frac{dx_3}{dt} = s x_2 x_3 - c x_3, \tag{14}$$

$$\frac{dx_4}{dt} = b\delta x_2 - k_0 x_3 x_4 - \gamma x_4. \tag{15}$$

We now consider the ecology of the tumor, the interactions among different cell populations within the tumor, and we do not consider the spatial growth of the tumor explicitly. Therefore, we also drop out the equation (9), and do not take the combined density to be a constant (10) into account.

We solve the system

$$\begin{aligned} &\lambda x_1 - \beta x_1 x_4 = 0 \\ &\beta x_1 x_4 - k x_2 x_3 - \delta x_2 = 0 \\ &s x_2 x_3 - c x_3 = 0 \\ &b\delta x_2 - k_0 x_3 x_4 - \gamma x_4 = 0. \end{aligned}$$

And get four equilibrium states for system (5)-(8)

$$(0,0,0,0), \quad (0, \frac{c}{s}, -\frac{\delta}{k}, \frac{bck\delta}{s(k\gamma - k_0\delta)}), \quad (\frac{\gamma}{b\beta}, \frac{\lambda\gamma}{b\beta\delta}, 0, \frac{\lambda}{\beta})$$

and

$$(\frac{bc^2k\beta\delta + ck_0 s\lambda\delta - cks\lambda\gamma}{k_0 s^2 \lambda^2}, \frac{c}{s}, \frac{bc\beta\delta - s\lambda\gamma}{k_0 s\lambda}, \frac{\lambda}{\beta}).$$

The Jacobian at point x is computed as

$$J(x)=\begin{pmatrix}\lambda-\beta x_4 & 0 & 0 & -\beta x_1\\ \beta x_4 & -kx_3-\delta & -kx_2 & \beta x_1\\ 0 & sx_3 & sx_2-c & 0\\ 0 & b\delta & -k_0x_4 & -k_0x_3-\gamma\end{pmatrix}$$

At the equilibrium state $E_1=(0,0,0,0)$, we have

$$J(E_1)=\begin{pmatrix}\lambda & 0 & 0 & 0\\ 0 & -\delta & 0 & 0\\ 0 & 0 & -c & 0\\ 0 & 0 & 0 & -\gamma\end{pmatrix}.$$

The eigenvalue thus are λ, $-\delta$, $-c$ and $-\gamma$. Because all parameters are positive [8], the equilibrium state E_1 is hyperbolic and unstable for the linearization system at E_1, and according the Hartman-Grobman Theorem [6] it is unstable for system (12)-(15). Therefore, according to the asymptotical theorem 2.2, E_1, as an equilibrium state of the system (5)-(9), is unstable.

At the equilibrium state $E_2=(0,\frac{c}{s},-\frac{\delta}{k},\frac{bck\delta}{s(k\gamma-k_0\delta)})$, the Jacobian is given by

$$J(E_2)=\begin{pmatrix}\lambda-\frac{bck\beta\delta}{s(k\gamma-k_0\delta)} & 0 & 0 & 0\\ \frac{bck\beta\delta}{s(k\gamma-k_0\delta)} & 0 & -\frac{ck}{s} & 0\\ 0 & -\frac{s\delta}{k} & 0 & 0\\ 0 & b\delta & \frac{bckk_0\delta}{s(k\gamma-k_0\delta)} & \frac{k_0\delta}{k}-\gamma\end{pmatrix}.$$

The eigenvalues are $\lambda-\frac{bck\beta\delta}{s(k\gamma-k_0\delta)}$, $\frac{k_0\delta}{k}-\gamma$, $\sqrt{c\delta}$ and $-\sqrt{c\delta}$. Because $\sqrt{c\delta}$ is always a positive number, E_2 is unstable for the system (12)-(15). According the asymptotical theorem 2.2, E_2 is also unstable for the system (5)-(9). Since the second coordinate of the equilibrium state always is negative, we will not pay much attention to this equilibrium state.

At the equilibrium state $E_3=(\frac{\gamma}{b\beta},\frac{\lambda\gamma}{b\beta\delta},0,\frac{\lambda}{\beta})$, the Jacobian is

$$J(E_3)=\begin{pmatrix}0 & 0 & 0 & -\frac{\gamma}{b}\\ \lambda & -\delta & -\frac{k\lambda\gamma}{b\beta\delta} & \frac{\gamma}{b}\\ 0 & 0 & \frac{s\lambda\gamma}{b\beta\delta}-c & 0\\ 0 & b\delta & -\frac{k_0\lambda}{\beta} & -\gamma\end{pmatrix}.$$

The characteristic polynomial is given by

$$(\zeta+c-\frac{s\lambda\gamma}{b\beta\delta})[\zeta^3+(\gamma+\delta)\zeta^2+2\gamma\delta\zeta+\lambda\gamma\delta]=0.$$

Let's denote the eigenvalues by $\zeta_i,\ \ i=1,2,3,4$, and $\zeta_1=\frac{s\lambda\gamma-bc\beta\delta}{b\beta\delta}$. In order to get the sign of the eigenvalues, we apply Hurwitz's Criterion [10] into

$$\zeta^3+(\gamma+\delta)\zeta^2+2\gamma\delta\zeta+\lambda\gamma\delta=0.$$

We see that $D_0=1>0$, $D_1=\gamma+\delta>0$; and

$$D_2=\begin{vmatrix}\gamma+\delta & 1\\ \lambda\gamma\delta & 2\gamma\delta\end{vmatrix}>0,\quad D_3=\begin{vmatrix}\gamma+\delta & 1 & 0\\ \lambda\gamma\delta & 2\gamma\delta & \gamma+\delta\\ 0 & 0 & \lambda\gamma\delta\end{vmatrix}>0$$

if and only if

$$\gamma+\delta>\frac{\lambda}{2}.$$

Therefore, when $\gamma+\delta>\frac{\lambda}{2}$ and $\frac{s\lambda\gamma}{b\beta\delta}<c$, the four eigenvalues all have negative real parts or negative, E_3 is stable. If $\gamma+\delta=\frac{\lambda}{2}$, we have a pair of purely imaginary eigenvalues, $\zeta_2=\sqrt{2\gamma\delta}i$, $\zeta_3=-\sqrt{2\gamma\delta}i$ and ζ_4 is negative. In this case when $\frac{s\lambda\gamma}{b\beta\delta}>c$, E is unstable; when $\frac{s\lambda\gamma}{b\beta\delta}<c$, we have a 2-dimensional local center manifold and 2-dimensional stable manifold. If $\gamma+\delta<\frac{\lambda}{2}$, there will be an eigenvalue with positive real part, and so E_3 is unstable.

According to the parameter's values in paper [8], $\lambda=2\times10^{-2}$, $\gamma=2.5\times10^{-2}$ and $\delta=\frac{1}{18}$, we know that the eigenvalues ζ_2, ζ_3 and ζ_4 all have the negative real parts. As to eigenvalue ζ_1, it is negative even for a very large burst size $b\le 4500$. The involved parameters values are $\beta=\frac{7}{10}\times10^{-9}$, $s=5.6\times10^{-7}$ and $c=1.7\times10^{-3}$. Overall, E_3 is an asymptotical stable equilibrium point of the system (12)-(15), therefore according the asymptotical theorem 2.2, E_3 is an asymptotical stable non-trivial boundary equilibrium state of the perturbed system (5)-(9).

The equilibrium state $E_4=(\frac{bc^2k\beta\delta+ck_0s\lambda\delta-cks\lambda\gamma}{k_0s^2\lambda^2},\frac{c}{s},\frac{bc\beta\delta-s\lambda\gamma}{k_0s\lambda},\frac{\lambda}{\beta})$, is an interior critical point since each coordinate is positive with the parameter's value given in paper [8]. More interestingly, when the burst size b is any value which's greater than 42, the third coordinate of E_4 will always be positive. The value of burst size b does not affect the first coordinate of E_4. The Jacobian at E_4 is given by

$$J(E_4)=\begin{pmatrix} 0 & 0 & 0 & -\frac{bc^2k\beta^2\delta+ck_0s\beta\lambda\delta-cks\beta\lambda\gamma}{k_0s^2\lambda^2} \\ \lambda & -k\frac{bc\beta\delta-s\lambda\gamma}{k_0s\lambda}-\delta & -\frac{ck}{s} & \frac{bc^2k\beta^2\delta+ck_0s\beta\lambda\delta-cks\beta\lambda\gamma}{k_0s^2\lambda^2} \\ 0 & \frac{bc\beta\delta-s\lambda\gamma}{k_0\lambda} & 0 & 0 \\ 0 & b\delta & -\frac{k_0\lambda}{\beta} & -\frac{bc\beta\delta-s\lambda\gamma}{s\lambda}-\gamma \end{pmatrix}.$$

Denote the characteristic polynomial by

$$Q(z)=\alpha_0z^4+\alpha_1z^3+\alpha_2z^2+\alpha_3z+\alpha_4, \tag{16}$$

then after a tedious computation, we have $\alpha_0=1$, $\alpha_2=0$,

$$\alpha_1=\delta+\frac{bc\beta\delta}{s\lambda}+\frac{bck\beta\delta}{k_0s\lambda}-\frac{k\gamma}{k_0},$$

$$\alpha_3=\frac{2b^2c^3k\beta^2\delta^2}{k_0s^2\lambda^2}+\frac{b^2c^2k\beta^2\delta^2}{k_0s^2\lambda}+\frac{bc^2\beta\delta^2}{s\lambda}+\frac{bc\beta\delta^2}{s}+\frac{ck\gamma^2}{k_0}-\frac{3bc^2k\beta\gamma\delta}{k_0s\lambda}-\frac{bck\beta\gamma\delta}{k_0s}-c\gamma\delta,$$

$$\alpha_4=\frac{2bc^2k\beta\gamma\delta}{k_0s}+c\lambda\gamma\delta-\frac{b^2c^3k\beta^2\delta^2}{k_0s^2\lambda}-\frac{bc^2\beta\delta^2}{s}-\frac{ck\lambda\gamma^2}{k_0}.$$

According to Hurwitz's Criterion, all the roots of the characteristic polynomial (16) have negative real parts if and only if

$$\alpha_0>0,\quad D_1=\alpha_1>0,\quad D_2=\begin{vmatrix}\alpha_1 & \alpha_0\\ \alpha_3 & \alpha_2\end{vmatrix}>0,$$

and

$$D_3=\begin{vmatrix}\alpha_1 & \alpha_0 & 0\\ \alpha_3 & \alpha_2 & \alpha_1\\ 0 & \alpha_4 & \alpha_3\end{vmatrix}>0,\quad D_4=\begin{vmatrix}\alpha_1 & \alpha_0 & 0 & 0\\ \alpha_3 & \alpha_2 & \alpha_1 & \alpha_0\\ 0 & \alpha_4 & \alpha_3 & \alpha_2\\ 0 & 0 & 0 & \alpha_4\end{vmatrix}>0.$$

However, we see

$$D_3=\begin{vmatrix}\alpha_1 & \alpha_0 & 0\\ \alpha_3 & \alpha_2 & \alpha_1\\ 0 & \alpha_4 & \alpha_3\end{vmatrix}=\begin{vmatrix}\alpha_1 & 1 & 0\\ \alpha_3 & 0 & \alpha_1\\ 0 & 0 & \alpha_3\end{vmatrix}=-\alpha_3^2<0.$$

Therefore, not all the roots of the characteristic polynomial have negative real parts.

We also claim that the characteristic polynomial has no zero root or purely imaginary root, namely, E_4 is a hyperbolic equilibrium point. After we substitute the parameter's values, we see that $\alpha_4 < 0$ even in large range of the parameter's values. So, zero is not a root of the characteristic polynomial (16). If the characteristic polynomial (16) have purely imaginary roots, say bi, then it must be true that $\alpha_1^2\alpha_4 + \alpha_3^2 = 0$. But, this is not the case. Therefore, we conclude that E_4 is unstable.

In conclusion, the equilibrium states E_1, E_2 and E_4 are unstable, E_3 is stable. The system does not posses any stable interior equilibrium point. Drug treatments, finite-time perturbations, can not change the stability of equilibrium states.

4. **Open problems related finite-time perturbations of dynamical systems.** As motivations of finite-time perturbations, we would like to compare the effective of different finite-time perturbations, or different drug treatments. That requires to study the behavior of solutions over the finite-time intervals during the perturbations. We therefore post some open problems related finite-time perturbations.

- Consider the two systems $\dot{x} = f(x) + p_1(t, x)$ and $\dot{x} = f(x) + p_2(t, x)$, and start from the same initial value $x(0) = x_0$, how to compare the solutions $x_1(t)$ and $x_2(t)$ during the finite-time interval T ? Where $x_i(t)$ is the solution of $\dot{x} = f(x) + p_i(t, x)$, $i = 1, 2$, with the initial value $x(0) = x_0$.
- Consider a system $\dot{x} = f(x)$ with periodic solutions, when perturb it by a finite-time perturbation $p(t, x)$, how to extend the Melnikov function for the perturbed system $\dot{x} = f(x) + p(t, x)$?
- If we denote the flow defined by the dynamical system $\dot{x} = f(x)$ with the starting point x_0 by $\Phi(t, x_0)$, and that by the finite-time perturbed dynamical system $\dot{x} = f(x) + p(t, x)$ by $\Phi_p(t, x_0)$, it is obvious that, for $t > T$,

  $$\Phi(t, \Phi_p(T, x_0)) = \Phi_p(t, x_0).$$

  However, for local stable and unstable manifolds S and U, how to define the global stable and unstable manifolds ? Or, how to modify the the following definitions for finite-time perturbed systems ?

  $$W^s = \bigcup_{0 \leq t} \Phi_p(t, S)$$

  and

  $$W^u = \bigcup_{0 \leq t} \Phi_p(t, U)$$

  Or, generally, how to develop or apply stable manifold theory to compare the local behavior of the finite-time perturbed dynamical systems ?

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