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碩士學位 請求論文

Oscillators involving two species

두 종류의 인자를 포함하는 진동모형

2008 年

誠信女子大學校 教育大學院

教育學科 數學教育專攻

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2008 年

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논 문 개 요

생물학적 체계는 화학반응에 기초한 고도의 복합적 집합체로서 굉장히 복잡함에도 불구하고 동시에 매우 효율적인 방법으로 규칙적이고 간결하게 구성된다. 생물 내부에서 일어나는 신진 대사 및 정보 처리 과정과 같은 생명 활동은 예외없이 화학 반응을 그 기반으로 하고 세포 분열, 호르몬 분비, 심장 박동과 같은 생명 활동은 언제나 광범위한 주기를 가진다.

이 연구 논문에서는 이러한 생물학적 체계의 진동하는 과정을 다루고자 한다. 생의학 과학에서 이러한 진동은 공통적이며 다방면에 걸쳐 다양한 환경에서 나타나고, 수 초에서 수 시간, 수 일, 수 주까지의 다양한 주기를 갖게 된다. 생물학적 진동의 주제는 매우 크기 때문에 생물학적 진동을 포함하는 다수 영역의 최근 연구로부터 몇가지 간단한 모형을 분석하고 이를 다른 상황에의 수학적 모델링 아이디어로 확장하고자 한다. 따라서 이 연구 논문에서는 2종 진동자에 관한 미분방정식 체계와 유용한 몇몇 제어 매커니즘과 모형들을 분석하고 이를 가지고 주기적 행동과 관련된 실질적이고 구체적인 생물학적 현상에 적용하고자 한다.

차　례

I Introduction

Although living biological systems are immensely complex, they are at the same time highly ordered and compactly put together in a remarkably efficient way. Such systems concisely store the information and means of generating the mechanisms required for repetitive cellular reproduction, organisation, control and so on. This thesis is mainly concerned with oscillatory processes. In the biomedical sciences these are common, appear in widely varying contexts and can have periods from a few seconds to hours to days and even weeks. We consider some in detail in this thesis, but mention here a few others from the large number of areas of current research involving biological oscillators.

The periodic pacemaker in the heart is, of course, an important example. which is an excellent introduction to mathematical models in physiology in general, covering a wide spectrum of topics. There is the now classical work of Hodgkin and Huxley(1952) on nerve action potentials, which are the electrical impulses which propagate along a nerve fibre. This is now a highly developed mathematical biology area. Under certain circumstances such nerve fibres exhibit regular periodic firing. Breathing is a prime example of another physiological oscillator, here the period is of the order a second. There are many others, such as certain neural activity in the brain, where the cycles have very small periods. A different kind of oscillator is that observed in the glycolytic pathway. Glycolysis is the process that breaks down glucose to provide the energy for cellular metabolism; oscillations with periods of several minutes are observed in the concentrations of certain chemicals in the process. The book on biochemical oscillations and cellular rhythms by Goldbeter(1996) gives a thorough and extensive discussion of this as well as other phenomena; he also discusses the molecular basis for chaotic behaviour. Blood testosterone levels in man are often observed to oscillate with periods of the order of 2-3 hours.

At certain stages in the life cycle of the cellular slime mould, Dictyostelium discoideum, the cells emit the chemical cycle-AMP periodically, with a period of a few minutes. This important topic has been extensively studied theoretically and experimentally. Othmer and Schaap (1999) give an extensive review which covers the major aspects of this important area of signal transduction and the properties of this slime mould in general. They particularly deals with such spatial wave phenomena associated with this slime mould. The process of regular cell division in Dictyostelium, where the period is measured in hours, indicates a governing biological oscillator of some kind. Since the subject of biological oscillators is now so large, it is quite impossible to give a remotely comprehensive coverage of the field here. Instead we concentrate on a few general results and some useful simple models which highlight different concepts. We also discuss some of the areas and mechanisms of practical importance and current interest. A knowledge of these is essential in extending the mathematical modeling ideas to other situations.

The history of oscillating reactions really dates from Lotka(1910) who put forward a theoretical reaction which exhibits damped oscillations. Later Lotka (1920, 1925) proposed the reaction mechanism which now carries the Lotka-Volterra label. Experimentally oscillations were found by Bray (1921) in the hydrogen peroxide-iodate ion reaction where temporal oscillations were observed in the concentrations of iodine and rate of oxygen evolution. He specifically referred to Lotka's early paper. This interesting and important work was dismissed and widely disbelieved since, among other criticisms, it was mistakenly thought that it violated the second law of thermodynamics. It doesn't of course since the oscillations eventually die out, but they only do so slowly. The next major discovery of an oscillating reaction was made by Belousov (1951, 1959), the study of which was continued by Zhabotinskii (1964) and now known as the Belousov-Zhabotinskii reaction. There are now many reactions which are known to admit periodic behaviour.

In the rest of this thesis we comment generally about differential equation systems for oscillators and describe some special control mechanisms, models which have proved particularly useful for demonstrating typical and unusual behaviour of oscillators. They are reasonable starting points for modelling real and specific biological phenomena associated with periodic behaviour.

II Preliminaries

The models for oscillators which we are concerned with here all give rise to systems of ordinary differential equations for the concentration vector $\mathbf{u}(t)$; namely,

$$\frac{d\mathbf{u}}{dt} = \mathbf{F}(\mathbf{u}) \tag{1}$$

where $\mathbf{F}$ describes the nonlinear reaction kinetics, or underlying biological oscillator mechanism. The mathematical literature on nonlinear oscillations is large and daunting, but much of it is not of relevance to real biological modelling. Even though quite old, a good practical review from a mathematical biology point of view, is given by Howard (1979). Mostly we are interested here in periodic solutions of (1) such that

$$\mathbf{u}(t + T) = \mathbf{u}(t) \tag{2}$$

where $T > 0$ is the period. In the phase space of concentrations this solution trajectory is a simple closed orbit, γ say. If $\mathbf{u}_0(t)$ is a limit cycle solution then it is asymptotically stable (globally) if any perturbation from $\mathbf{u}_0(t)$, or

γ, eventually tends to zero as $t \to \infty$. It is always the case with realistic, qualitative as well as quantitative, biological models that the differential equations involve parameters, generically denoted by λ, say. The behavior of the solutions $\mathbf{u}(t;\lambda)$ varies with the values or ranges of the parameters. Generally steady state solutions of (1), that is, solutions of $\mathbf{F}(\mathbf{u}) = 0$, are stable to small perturbations if λ is in a certain range, and become unstable when λ passes through a critical value , a bifurcation point. When the model involves only two dependent variables the analysis of (1) can be carried out completely in the phase plane. For higher-order systems the theory is certainly not complete and each case usually has to be studied individually. A major exception is provided by the *Hopf bifurcation theorem* , the results for which strictly hold near the bifurcation values. A basic, useful and easily applied result of the Hopf theorem is the following.

Let us suppose that $\mathbf{u} = 0$ is a steady state of (1) and that a linearization about it gives a simple complex conjugate pair of eigenvalues $\alpha(\lambda) = Re\,\alpha \pm i\,Im\,\alpha$. Now suppose this pair of eigenvalues has the largest real part of all the eigenvalues and is such that in a small neighborhood of a bifurcation value λ_c,

(1) $\text{Re}\ \alpha < 0 \ \ if \ \ \lambda < \lambda_c$,

(2) $\text{Re}\ \alpha = 0 \ \ and \ \ \text{Im}\ \alpha \neq 0 \ \ if \ \ \lambda = \lambda_c$

(3) $\text{Re}\ \alpha > 0 \ \ if \ \ \lambda > \lambda_c$

Then, in a small neighborhood of λ_c, $\lambda > \lambda_c$ the steady state is unstable by growing oscillations and, at least, a small amplitude limit cycle periodic solution exists about $\mathbf{u} = 0$. Furthermore the period of this limit cycle solution is given by $2\pi/T_0$ where $T_0 = \text{Im}\ [\alpha(\lambda_c)]$. The value λ_c is a Hopf bifurcation value. The theorem says nothing about the stability of such limit cycle solutions although in practice with real biological systems they usually are when numerically simulated.

In this paper we study system (1) with two dimensional vector $\mathbf{u} = (u, v)$, that is,

$$\begin{aligned} \frac{du}{dt} &= f(u, v) \\ \frac{dv}{dt} &= g(u, v), \end{aligned} \tag{3}$$

where f and g are nonlinear. Steady state solutions $(\bar{u}, \bar{v})$ of the two species system (3) are given by

$$f(\bar{u}, \bar{v}) = g(\bar{u}, \bar{v}) = 0, \tag{4}$$

of which only the positive solutions are of interest.

Definition II.1. The *phase plane* of the system (3) means the two dimensional plane with u-axis and v-axis. In the phase plane we plot the null clines $f(u, v) = 0$, $g(u, v) = 0$, and other information regarding the relationship between the values of $u(t)$ and $v(t)$.

Remark II.1. Realistic systems of the form (3) must have some enclosing domain in the phase plane with boundary B, that is, a confined set, such that

$$\mathbf{n} \cdot \frac{d\mathbf{u}}{dt} < 0 \quad \text{for} \quad u \quad \text{on } B, \tag{5}$$

where $\mathbf{n}$ is the outward unit normal vector to the boundary B.

Definition II.2. A *cycle or periodic orbit* of the system (3) means any closed solution curve of (3) which is not an equilibrium point of (3). A *limit cycle* of the system (3) is the periodic solution which is the set of points

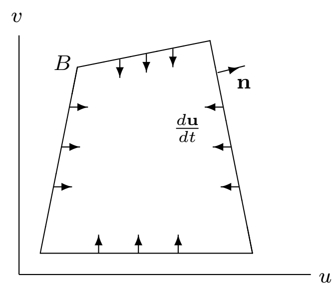

Figure 1: An example of a confined set in the phase plane for the system (3)

$P_{(u_0,v_0)}$ such that

$$P_{(u_0,v_0)} = \lim_{n\to\infty} (u(t_n), v(t_n))$$

for the solution $(u(t), v(t))$ of the system (3) for arbitrary initial point (u_0, v_0) inside the confined set, and any sequence $t_n \to \infty$ as $n \to \infty$.

Theorem 1. *If the system* (1) *possesses a confined set enclosing a unique steady-state which is unstable spiral or node then the trajectory tends to a limit cycle solution as* $t \to \infty$.

If the unique steady-state is a saddle point a limit cycle cannot exists.

Proof. This is a simple application of the *Poincaré-Bendixson Theorem.* Refer, for example, Jordan and Smith (1999). □

We investigate in this paper under which the conditions the two-species models of interacting populations can exhibit limit cycle periodic oscillations. We derive some general results as regards the qualitative character of the reaction kinetics which may exhibit such periodic solutions.

Linearizing about $(\bar{u}, \bar{v})$ we have

$$\begin{pmatrix} \frac{d(u-\bar{u})}{dt} \\ \frac{d(v-\bar{v})}{dt} \end{pmatrix} = A \begin{pmatrix} u - \bar{u} \\ v - \bar{v} \end{pmatrix}, \quad \mathbf{A} = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}_{\bar{u},\bar{v}} \tag{6}$$

The matrix A is called the stability matrix or community matrix in interaction population terms.

The linear stability of $(\bar{u}, \bar{v})$ is determined by the eigenvalues λ of the stability matrix A, given by

$$\begin{aligned} |A - \lambda I| = 0 \quad &\Longrightarrow \quad \lambda^2 - (\operatorname{tr} A)\lambda + |A| = 0. \\ &\Longrightarrow \quad \lambda = \frac{1}{2}\{\operatorname{tr} A \pm [(\operatorname{tr} A)^2 - 4|A|]^{1/2}\}. \end{aligned} \tag{7}$$

Necessary and sufficient conditions for stability are

$$\operatorname{tr} A = f_u + g_v < 0, \quad |A| = f_u g_v - f_v g_u > 0, \tag{8}$$

where here, and in what follows unless stated otherwise, the derivatives are evaluated at the steady state $(\bar{u}, \bar{v})$.

For an unstable node or spiral to occur, we require

$$\operatorname{tr} A > 0, |A| > 0, \quad (\operatorname{tr} A)^2 \left\{ \begin{array}{c} > \\ < \end{array} \right. 4|A| \quad \Longrightarrow \quad \text{unstable} \left\{ \begin{array}{l} \text{node} \\ \text{spiral} \end{array} \right. \tag{9}$$

III Main Results

The concept of a sequence of linked reactions is a useful one and various modifications have been suggested. In one, which has been widely used and studied, the number of reactions has been increased generally to n and the feedback function made more more general and hence widely applicable. In a suitable nondimensional form the system when $n = 2$ is

$$\begin{aligned} \frac{du}{dt} &= h(v) - k_1\,u \\ \frac{dv}{dt} &= u - k_2\,v, \end{aligned} \tag{10}$$

where the k_1, $k_2 > 0$ and $h(v)$, which is always positive, is the nonlinear feedback function. If $h(v)$ is an increasing function of v, $h'(v) > 0$, (10) represents a *positive feedback* loop, while if $h(v)$ is a monotonic decreasing function of u, $h'(v) < 0$, the system represents a *negative feedback* loop or *feedback inhibition.* Positive feedback loops are not common metabolic control mechanisms, whereas negative ones are; for example, Tyson and Othmer (1978) and Goldbeter (1996). Yagil (1971) suggested specific forms for $h(v)$

for several biochemical situations. steady state solutions of (10) are given by

$$\begin{aligned} h(v) &= k_1\, u \\ u &= k_2\, v \end{aligned} \tag{11}$$

Theorem 2. *For the system* (10) *assume that* $h(v) >$, $h'(v) < 0$, *and*

$$U > \frac{h(0)}{k_1}, \quad V > \frac{U}{k_2} \tag{12}$$

Then the set B *consisting of the lines* $u = 0$, $v = 0$, $u = U$, *and* $v = V$ *is a confined set on which* (5) *is satisfied.*

Proof. Note that along the lines $u = 0$ and $u = U$ on the boundary B, we have that $\mathbf{n} = (-1, 0)$ and $\mathbf{n} = (1, 0)$, respectively, and along the lines $v = 0$ and $v = V$ on the boundary B, we have that $\mathbf{n} = (0, -1)$ and $\mathbf{n} = (0, 1)$, respectively.

Using the outward normal vectors $\mathbf{n}$ obtained above it is proved that on the boundaries $\mathbf{n} \cdot \frac{d\mathbf{u}}{dt} < 0$ as shown in the following.

$$u = 0, \quad \mathbf{n}\cdot\frac{d\mathbf{u}}{dt} = (-1, 0)\cdot(\frac{du}{dt}, \frac{dv}{dt}) = -\frac{du}{dt} = -(h(v) - k_1 \cdot 0) < 0 \quad \text{for all } v \geq 0.$$

$$u = U, \quad \mathbf{n}\cdot\frac{d\mathbf{u}}{dt} = (1, 0)\cdot(\frac{du}{dt}, \frac{dv}{dt}) = \frac{du}{dt} = h(v) - k_1 U < 0 \quad \text{for all } 0 \leq v \leq V,$$

because that $h(v)$ is a decreasing function and $U > \frac{h(0)}{k_1}$ from the condition in the statement of the present theorem.

$$v = 0, \quad \mathbf{n} \cdot \frac{d\mathbf{u}}{dt} = (0, -1) \cdot (\frac{du}{dt}, \frac{dv}{dt}) = -\frac{dv}{dt} = -(u - k_2 \cdot 0) < 0 \quad \text{for all } u > 0.$$

$$v = V, \quad \mathbf{n} \cdot \frac{d\mathbf{u}}{dt} = (0, 1) \cdot (\frac{du}{dt}, \frac{dv}{dt}) = \frac{dv}{dt} = u - k_2 V < 0 \quad \text{for all } 0 < u \leq U,$$

because that $V > \frac{U}{k_2}$ from the condition in the statement of the present theorem. □

Theorem 3. *The system* (10) *cannot admit limit cycle oscillations under the same condition as in* Theorem 2.

Proof. Let us denote $(\bar{u}, \bar{v})$ the unique solution of the equations (11), that is

$$\begin{aligned} h(\bar{v}) &= k_1 \bar{u} \\ \bar{u} &= k_2 \bar{v} \end{aligned}$$

From the conditions that h is a decreasing function and that

$$U > \frac{h(0)}{k_1}, \quad V > \frac{U}{k_2}$$

we have that

$$0 < \bar{u} = \frac{h(\bar{v})}{k_1} < \frac{h(0)}{k_1} < U$$

and

$$0 < \bar{v} = \frac{\bar{u}}{k_2} < \frac{U}{k_2} < V.$$

Thus $(\bar{u}, \bar{v})$ becomes a unique steady-state of the system (3) inside the confined set B.

Linearizing the system (10) about $(\bar{u}, \bar{v})$ we have

$$\begin{pmatrix} \frac{d(u-\bar{u})}{dt} \\ \frac{d(v-\bar{v})}{dt} \end{pmatrix} = A \begin{pmatrix} u - \bar{u} \\ v - \bar{v} \end{pmatrix}, \quad \mathbf{A} = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}_{\bar{u},\bar{v}} = \begin{pmatrix} -k_1 & h'(\bar{v}) \\ 1 & -k_2 \end{pmatrix} \quad (13)$$

Thus we see that the stability condition (8) is satisfied

$$\operatorname{tr} A = -k_1 - k_2 < 0, \quad |A| = f_u g_v - f_v g_u = k_1 k_2 - h'(\bar{v}) > 0,$$

and so $(\bar{u}, \bar{v})$ is a stable steady-state inside the confined set. Therefore every trajectory converges to $(\bar{u}, \bar{v})$ as $t \to \infty$, and there exists no oscillations for the system (10). □

Now we turn to the general cases in which the system (3) may possesses oscillation solutions. Let us assume that the kinetics $f(u, v)$ and $g(u, v)$ are such that (5) has a confined set in the positive quadrant. Then, as stated in Theorem 1, by the Poincare-Bendixson theorem, limit cycle solutions exist if $(\bar{u}, \bar{v})$ is an unstable spiral or node, but not if it is a saddle point.

We remind the linearlizaton of the system (3)

$$\begin{pmatrix} \frac{d(u-\bar{u})}{dt} \\ \frac{d(v-\bar{v})}{dt} \end{pmatrix} = A \begin{pmatrix} u-\bar{u} \\ v-\bar{v} \end{pmatrix}, \quad \mathbf{A} = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}_{\bar{u},\bar{v}} \tag{14}$$

and that the linear stability of $(\bar{u}, \bar{v})$ is determined by the eigenvalues λ of the stability matrix A, given by

$$\begin{aligned} |A - \lambda I| = 0 \quad &\Longrightarrow \quad \lambda^2 - (\operatorname{tr} A)\lambda + |A| = 0. \\ &\Longrightarrow \quad \lambda = \frac{1}{2}\{\operatorname{tr} A \pm [(\operatorname{tr} A)^2 - 4|A|]^{1/2}\}. \end{aligned} \tag{15}$$

For an unstable node or spiral to occur, we require

$$\operatorname{tr} A > 0, |A| > 0, \quad (\operatorname{tr} A)^2 \left\{ \begin{array}{c} > \\ < \end{array} \right. 4|A| \quad \Longrightarrow \quad \text{unstable} \left\{ \begin{array}{l} \text{node} \\ \text{spiral} \end{array} \right. \tag{16}$$

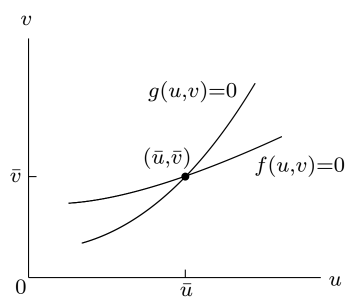

Figure 2: An example location of null clines of the system (3)

We consider the kinetic functions f and g with the null clines as illustrated in Figure 2. To proceed further we need to know individually the signs of f_u, f_v, g_u and g_v at the steady state. On each of $f = 0$ and $g = 0$ the gradient $dv/du > 0$ with $dv/du]_{g=0} > dv/du]_{f=0}$, so

$$\left.\frac{dv}{du}\right]_{g=0} = -\frac{g_u}{g_v} > \left.\frac{dv}{du}\right]_{f=0} = -\frac{f_u}{f_v} > 0.$$

Since $dv/du > 0$ it also means that at $(\bar{u}, \bar{v})$, f_u and f_v have different signs, as do g_u and g_v. Hence with Figure 2 there are 4 possibilities as illustrated in Figure 3. These imply that the elements in the matrix A in (6) have the following signs,

$$\mathbf{A} = \begin{pmatrix} - & + \\ + & - \end{pmatrix} \text{ or } \begin{pmatrix} - & + \\ - & + \end{pmatrix} \text{ or } \begin{pmatrix} + & - \\ + & - \end{pmatrix} \text{ or } \begin{pmatrix} + & - \\ - & + \end{pmatrix} \quad (17)$$

Theorem 4. *In each of the cases* Figure 3 (a) *and* (d) *the system* (3) *does not have any limit cycle solution.*

Proof. To get the sign of f_u at $(\bar{u}, \bar{v})$ in Figure 3 (a) we note that as we move along a line parallel to the u-axis though $(\bar{u}, \bar{v})$, f decreases since $f > 0$ on the lower u-side and $f < 0$ on the higher u-side. hence $f_u < 0$. Similarly we

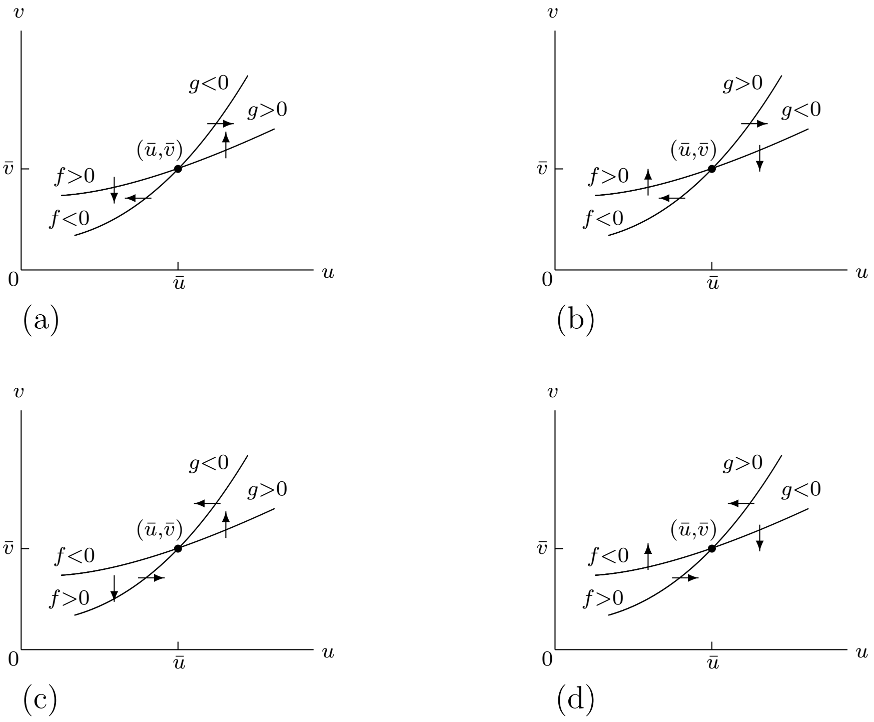

Figure 3: An example location of null clines of the system (3)

see that $g_v < 0$. Hence in the case Figure 3 (a) we have

$$\operatorname{tr} A = f_u + g_v < 0$$

and so the condition (9) is not satisfied.

In the case Figure 3 (d) at the steady state $(\bar{u}, \bar{v})$ we have that $f_v < 0$ and $g_v > 0$, so $f_v\, g_v < 0$. And also on each of $f = 0$ and $g = 0$ the gradient $dv/du > 0$ with $dv/du]_{g=0} > dv/du]_{f=0}$, so

$$\begin{aligned} \left.\frac{dv}{du}\right]_{g=0} = -\frac{g_u}{g_v} &> \left.\frac{dv}{du}\right]_{f=0} = -\frac{f_u}{f_v} > 0 \\ \Longrightarrow\quad -\frac{g_u}{g_v}\cdot(f_v\, g_v) &< -\frac{f_u}{f_v}\cdot(f_v\, g_v) < 0, \\ \Longrightarrow\quad |A| &= f_u g_v - f_v g_u < 0, \end{aligned}$$

Hence $(\bar{u}, \bar{v})$ is a saddle point and so there be no limit cycle solution enclosing $(\bar{u}, \bar{v})$ by Theorem 1. $\square$

Theorem 5. *In each of the cases* Figure 3 (b) *and* (c) *the system* (3) *possesses a limit cycle solution provided that* $\operatorname{tr} A > 0$.

Proof. In each cases of Figure 3 (b) and (c) at the steady state $(\bar{u}, \bar{v})$ we have that f_v and g_v have same sign, so $f_v\, g_v > 0$. And also on each of $f = 0$

and $g = 0$ the gradient $dv/du > 0$ with $dv/du]_{g=0} > dv/du]_{f=0}$, so

$$\left.\frac{dv}{du}\right]_{g=0} = -\frac{g_u}{g_v} > \left.\frac{dv}{du}\right]_{f=0} = -\frac{f_u}{f_v} > 0$$

$$\Longrightarrow \quad -\frac{g_u}{g_v} \cdot (f_v\, g_v) > -\frac{f_u}{f_v} \cdot (f_v\, g_v) > 0,$$

$$\Longrightarrow \quad |A| = f_u g_v - f_v g_u > 0.$$

Hence if $\operatorname{tr} A > 0$ we conclude that the system (3) possesses a limit cycle solution by Theorem 1. $\square$

IV Applications

An example of two species system with oscillation solutions

Let us consider an activator-inhibitor system proposed by Gierer and Meinhardt(1972).

$$\begin{aligned} \frac{du}{dt} &= a - bu + \tfrac{u^2}{v(1+Ku^2)} \\ \frac{dv}{dt} &= u^2 - v, \end{aligned} \tag{18}$$

where a, b, c, and K are all positive constant. (refer page 206)

u is an activator of v if $g_u > 0$ while v is an inhibitor of u if $f_v < 0$.

For any $\varepsilon > 0$ if $v(t) \geq \epsilon$ then $\frac{u^2}{v(1+Ku^2)} \leq \frac{1}{\epsilon K}$. Hence $u(t) \leq U = \frac{1}{b}\left(a + \frac{1}{\epsilon K}\right)$ for $t \geq 0$ provided $u(0) \leq U$. And $v(t) \leq U^2$ for $t \geq 0$ provided $v(0) \leq U^2$. And if $u(t) = 0$ then $\frac{dv}{dt} < 0$. Therefore the set B consisting of the lines $u = 0$, $v = \varepsilon$, $u = U$, $v = U^2$ is a cofined set for the system (18). And the unique steady-state inside B is $(\bar{u}, \bar{v}) = (\bar{u},\, \bar{u}^2)$ where $\bar{u}$ satisfies the qubic equation

$$(a - b\bar{u})(1 + K\bar{u}^2) + 1 = 0.$$

The null clines in the phase plane near the steady-state is the form of Figure 2.

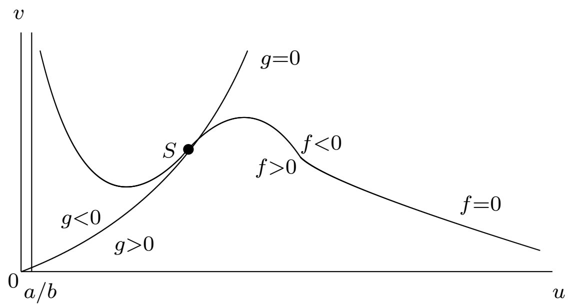

Figure 4: Tyoical null clines for the activator-inhibitor model (18)

$$\mathbf{A} = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} = \begin{pmatrix} -b + \frac{2uv(1+Ku^2)-2Ku^3v}{v^2(1+Ku^2)^2} & \frac{-u^2}{v^2(1+Ku^2)} \\ 2u & -1 \end{pmatrix} \tag{19}$$

$$= \begin{pmatrix} -b + \frac{2u}{v(1+Ku^2)^2} & \frac{-u^2}{v^2(1+Ku^2)} \\ 2u & -1 \end{pmatrix} \tag{20}$$

If $-b + \frac{2u}{v(1+Ku^2)^2} > 0$ is satisfied the stability matrix is of the form Figure 3 (b) with the signs

$$\mathbf{A} = \begin{pmatrix} + & - \\ + & - \end{pmatrix}. \tag{21}$$

Finally under the condition

$$\mathrm{tr}\, A = -b + \frac{2u}{v(1+Ku^2)^2} - 1 > 0$$

the system (18) possesses a lomit cycle solution near the unstable steady-state $(\bar{u}, \bar{v})$ by Theorem 4.

References

[1] A. Gierer and H.Meinhardt A theory of biological pattern formation. *Kybernetik*, 12:30-39, 1972.

[2] A. Goldbeter. Biochemical Oscillations and Cellular Rhythms. The molecular bases of periodic and chaotic behaviour.*Cambridge University Press, Cambridge,*1996.

[3] A.J. Lotka. Contribution to the theory of periodic reactions. *J.Phys. Chem.*, 14:271-274, 1910.

[4] A.J.Lotka. Undamped oscillations derived from the law of mass action. *J. Amer.Chem. Soc.*, 42:1595-1599, 1920.

[5] A.J.Lotka. Elements of Physical Biology. Williams and Wilkins, Baltimore, 1925.

[6] A.L Hodgkin and A.F.Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)* , 117:500-544,1952.

[7] A.M. Zhabotinskii. Periodic processes of the oxidation of malonic acid in solution (Study of the kinetics of Belousov's reaction). *Biofizika*, 9:306-311, 1964.

[8] B.P.Belousov.An oscillating reaction and its mechanism.In Sborn. *referat.radiat.med.(Collection of abstracts on radiation medicine)*, page 145. Medgiz,Moscow, 1959.

[9] B.P.Belousov. A periodic reaction and its mechanism. In R.J. Field and M. Burger, editors, 1951 *Oscillations and Travelling Waves in Chemical System,*,1951, (from his archives (in Russian)), pages 605-613.John Wiley,New York, 1985.

[10] D.W.Jordan and P.Smith. Nonlinear Ordinary Differential Equations. *Oxford University Press, Oxford, third edition*,1999.

[11] G.Yagil and E. Yagil. On the relation between effector concentration and the rate of induced enzyme synthesis. *Biophys.J.*, 11:11-27, 1971.

[12] H.G. Othmer and P.Schaap. Oscillatory cAMPsignalling in the development of Dictyostelium discoideum. *Comments Theor. Biol.*, 5:175-282, 1999.

[13] J.J. Tyson and H.G. Othmer. The dynamics of feedback control circuits in biochemical pathways. *Prog. Theor.Biol.*, 5:1-62,1978.

[14] L.N.Howard. Nonlinear oscillations. *Amer.Math Soc.Lect.Notes in Appl.Math.*, 17:1-67, 1979.

[15] W.C.Bray. A periodic reaction in homogeneous solution and its relation to catalysis. *J.Amer.Chem.Soc.*, 43:1262-1267, 1921.

ABSTRACT

Although living biological systems with the aggregate which establishes in chemical reaction are immensely complex, they are at the same time highly ordered and compactly put together in a remarkably efficient way. Metabolism which happens from the living thing inside and life activity like information processing process are based on chemical reaction without exception. The life activity like cell division, hormone production and heart beat always has period. This thesis is mainly concerned with oscillatory processes. In the biomedical sciences these are common, appear in widely varying contexts and can have periods from a few seconds to hours to days and even weeks. Since the subject of biological oscillators is so large, concentrate on a few general results and some useful simple models from the areas of current research involving biological oscillators. In this thesis we comment generally about differential equation systems for oscillators and describe some special control mechanisms, useful models for demonstrating typical and unusual behaviour of oscillators. They are reasonable starting points for modeling real and specific biological phenomena associated with periodic.