

**Mathematical Modelling  
In  
Biological Science**

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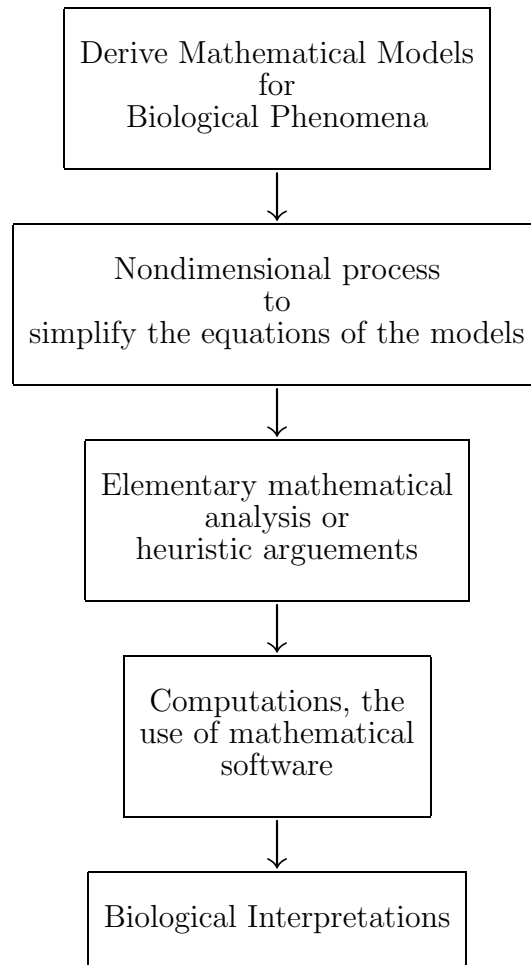


# Introduction

In this lecture note we shall discuss the mathematical modelling in Biological Science. Especially we shall restrict our attentions to the following topics:

1. Continuous population models for single species, delay models in population biology and physiology.
2. Continuous models for inter acting populations: predator-prey model, competition models, mutualism or symbiosis.
3. Chemical reaction Kinetics: Michaelis-Menten theory for enzyme-substrate Kinetics.
4. Biological Oscillators: Feedback and control mechanisms, Hodgkin-Huxley theory for nerve membrane: FitzHugh-Nagumo model.
5. Belousov-Zhabotinski Reactions.
6. Reaction Diffusion, Chemotaxis and Non-local Mechanisms.
7. Biological waves for single species model and multiple-species model.
8. Pattern formation Theory.

In each topics, we shall derive the biological models, then we do the non-dimensional analysis to reduce the model to a simple model with fewer parameters. We shall only do the elementary analysis, for example, the linearized stability analysis or heuristic argument for the models. Finally we shall show the reader the computation results. Basically we shall show the readers how to use the mathematical software, like Matlab, Mathematica, xtp to realize the biological phenomena. The models will be nonlinear and each topics are of difficult mathematics, a challenge for students to do and explore. We shall present the important references for each topics.

**Scheme :**

# Chapter 1

## Continuous population model for single species

### 1.1 Logistic equation

The simplest population model of single species is the Malthusim model. Let  $N(t)$  be the population density of the species at time  $t$ . Assume the rate of change of the population is proportional to the current population, i.e.

$$\frac{dN}{dt} = rN, \quad N(0) = N_0, \quad r > 0 \quad (1.1)$$

Then obviously  $N(t) = N_0 e^{rt} \rightarrow \infty$  as  $t \rightarrow \infty$ .  $r$  is called the intrinsic growth rate of the species. Model (1.1) is called the Malthusim model. It is used for the growth of species, like bacteria in a nutrient-unlimited supplied environment. In 1848 Verhulst introduced the following logistic equation:

$$\begin{aligned} \frac{dN}{dt} &= rN - bN^2 \\ N(0) &= N_0 \end{aligned} \quad (1.2)$$

In (1.2) the interspecific competition between the members of the species in the population is considered. It can be rewritten as

$$\begin{aligned} \frac{dN}{dt} &= rN \left(1 - \frac{N}{K}\right) \\ N(0) &= N_0 \end{aligned} \quad (1.3)$$

Then for any  $N_0 > 0$ ,  $N(t) \rightarrow K$  as  $t \rightarrow \infty$ .  $K$  is called "carrying capacity" of the environment. Although (1.3) can be solved directly by separation of variables,

$$N(t) = \frac{N_0 K e^{rt}}{K + N_0 (e^{rt} - 1)},$$

, it is easy to see that if  $N(t) < K/2$  then  $N''(t) > 0$  while  $N(t) > K/2$  implies  $N''(t) < 0$ . Hence the solution  $N(t)$  has a typical sigmoid character with inflection point at  $t_0$  where  $N(t_0) = K/2$ , which is commonly observed. Sometimes the inflection point is at  $t_0$ ,  $N(t_0) = \theta K$ ,  $0 < \theta \leq 1$ , then we consider the following model due to Gilpin:

$$\frac{dN}{dt} = rN \left(1 - \left(\frac{N}{K}\right)^\theta\right) \quad (1.4)$$

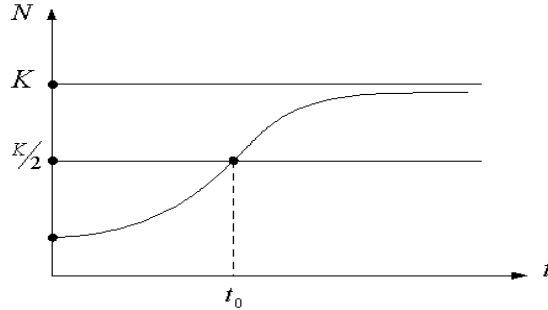


Fig.1.1

## 1.2 Delayed logistic equation

In 1950 ecologist Hutchinson proposed a delayed logistic equation in the following form

$$\frac{1}{N} \frac{dN}{dt} = r \left( 1 - \frac{N(t-T)}{K} \right) \quad (1.5)$$

i.e. the per capita growth rate depends on the population  $N(t-T)$  at  $t-T$  time.

### Scaling:

Let  $\tau = t/T$  and  $x(\tau) = \frac{N(t)}{K} = \frac{N(T\tau)}{K}$ . Then (1.5) becomes

$$\begin{aligned} \frac{dx}{d\tau} &= \frac{T}{K} r N(t) \left( 1 - \frac{N(t-T)}{K} \right) \\ &= Trx(\tau) (1 - x(\tau-1)) \end{aligned} \quad (1.6)$$

Let  $\alpha = Tr$  and  $y(\tau) = x(\tau) - 1$ . Then we have

$$\frac{dy}{d\tau} = -\alpha y(\tau-1) (1 + y(\tau)) \quad (1.7)$$

From (1.6),  $x(\tau) \equiv 1$  is a steady state and the linearized equation about the steady state  $x(\tau) \equiv 1$  is

$$\frac{dy}{d\tau} = -\alpha y(\tau-1) \quad (1.8)$$

Let

$$y(\tau) = e^{\lambda\tau} \quad (1.9)$$

and substitutes (1.9) into (1.8), then we have

$$\lambda e^{\lambda} = -\alpha \quad (1.10)$$

The transcendental equation (1.10) has infinitely many roots  $\lambda$ . In A5 of the book [H], the result due to Hayes was presented.



**Theorem 1.1** All roots of the equation  $(z + a)e^z + b = 0$  where  $a, b \in \mathbb{R}$ , have negative real parts if and only if

$$\begin{aligned} a &> -1 \\ a + b &> 0 \\ b &< \xi \sin \xi - a \cos \xi \end{aligned}$$

where  $\xi$  is the root of  $\xi = -a \tan \xi$ ,  $0 < \xi < \pi$  if  $a \neq 0$  and  $\xi = \pi/2$  if  $a = 0$ .

**Lemma 1.3** ([H]p.255) Equation (1.7) has a Hopf bifurcation at  $\alpha = \pi/2$ .

For  $\alpha > \pi/2$ , Jones introduced the idea of finding a cone and a map from cone into itself, and applied a fixed point theorem of cone to prove the existence of periodic solutions. The reader may check the details in p.254-260 of [H].

### 1.3 Time-delay models from physiology

Conceptually simple feedback mechanisms are believed to be fundamental for the control of a large number of different physiological processes. The simplest negative feedback described by ordinary differential equation

$$\frac{dx}{dt} = \lambda - rx$$

In physiological situations, time lags are often important and  $\lambda$  and/or  $r$  are not constants, but are some appropriate functions of  $x(t)$  and/or  $x(t - \tau)$ .

#### Delay Models in Physiology : Dynamic Diseases

##### Cheyne-Stokes respiration:

Cheyne-Stokes respiration is a human respiratory illness manifested by an alteration in the regular breathing pattern which directly related to the breath volume-ventilation  $V$ . Let the level of arterial carbon dioxide ( $CO_2$ ),  $c(t)$ , is monitored by receptors which determine the level of ventilation. It is believed that these  $CO_2$ -sensitive receptors are situated in the brainstem so there is an inherent time lag  $T$ , in the overall control system for breathing levels. We assume the dependence of the ventilation  $V$  on  $c$  is a Hill's function

$$V = V_{max} \frac{c^m(t - T)}{a^m + c^m(t - T)}, \quad m > 0.$$

We also assume that the removal of  $CO_2$  from the blood is proportional to the product of the ventilation and the level of  $CO_2$  in the blood. Let  $p$  be the constant production rate of  $CO_2$  in the body. Then the dynamics of the  $CO_2$  level is modelled by

$$\begin{aligned} \frac{dc}{dt} &= p - bc(t) \cdot V_{max} \frac{c^m(t - T)}{a^m + c^m(t - T)} \\ x &= \frac{c}{a}, \quad t^* = \frac{pt}{a}, \quad T^* = \frac{pT}{a}, \quad \alpha = \frac{abV_{max}}{p}, \quad V^* = \frac{V}{V_{max}} \end{aligned}$$

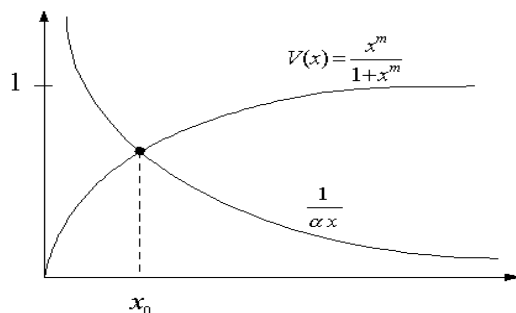
The model becomes (drop \*)

$$\begin{aligned} x'(t) &= 1 - \alpha x(t)V(x(t - T)) \\ &= 1 - \alpha x(t) \frac{x^m(t - T)}{1 + x^m(t - T)} \end{aligned}$$

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Steady state:

$$1 - \alpha x_0 V(x_0) = 0 \quad \text{or} \quad V(x_0) = \frac{1}{\alpha x_0}$$



Linearized equation:

$$\begin{aligned} u &= x - x_0 & V_0 &= V(x_0), & V'_0 &= \frac{dV}{dx}(x_0) \\ u' &= -\alpha u V_0 - \alpha x_0 V'_0 u(t-T) \end{aligned}$$

Stability analysis:

$$\begin{aligned} u(t) &= e^{\lambda t} \Rightarrow \lambda e^{\lambda t} = -\alpha e^{\lambda t} V_0 - \alpha x_0 V'_0 e^{\lambda(t-T)} \\ \lambda &= -\alpha V_0 - \alpha x_0 V'_0 e^{-\lambda T} \end{aligned}$$

Let

$$A = \alpha V_0, \quad B = \alpha x_0 V'_0$$

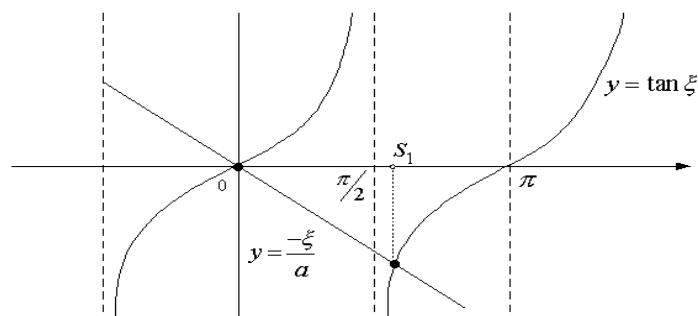
then

$$\lambda = -A - B e^{-\lambda T} \quad \text{or} \quad (\lambda + A) e^{\lambda T} + B = 0 \quad (1.11)$$

Set  $z = \lambda T$  then  $(\frac{z}{T} + A) e^z + B = 0$  or  $(z + a) e^z + b = 0$ , where  $a = AT, b = BT$ .  
By Hayes Theorem and  $a > 0, b > 0$ , the steady state  $x_0$  is stable if and only if

$$b < \xi \sin \xi - a \cos \xi$$

where  $\xi$  is the root of  $\xi = -a \tan \xi, 0 < \xi < \pi$ .



Let  $T$  be a bifurcation parameter. Set  $\lambda = \mu + i\omega$ . Then (1.11) becomes

$$\begin{aligned}\mu &= -A - Be^{-\mu T} \cos \omega T \\ \omega &= Be^{-\mu T} \sin \omega T\end{aligned}\tag{1.12}$$

We are interested in the Hopf bifurcation, i.e., the real part  $\mu = 0$ . If  $\mu = 0$  then (1.12) gives, with  $s = \omega T$ ,

$$\tan s = -\frac{s}{AT} \quad \pi/2 < s < \pi.$$

Let  $\mu = 0$  and  $s = s_1$  then

$$\begin{aligned}0 &= -A - B \cos s_1, \\ s_1 &= BT \sin s_1.\end{aligned}$$

This implies

$$BT = \left[ (AT)^2 + s_1^2 \right]^{\frac{1}{2}}.$$

When  $T = 0$  we have  $\mu = -A - B < 0$ . Increase  $T$  from  $T = 0$  to  $T$  satisfies

$$BT < \left[ (AT)^2 + s_1^2 \right]^{\frac{1}{2}},\tag{1.13}$$

$$\tan s_1 = -\frac{s_1}{AT}.$$

We note that if (1.13) holds then  $Re\lambda = \mu < 0$  i.e. the steady state is stable. In terms of the original dimensionless variables from (1.13) the conditions are

$$\alpha x_0 V_0' T < \left[ (\alpha V_0 T)^2 + s_1^2 \right]^{\frac{1}{2}},\tag{1.14}$$

$$\tan s_1 = -\frac{s_1}{\alpha V_0 T}.$$

The actual parameters for normal humans have been obtained by Mackey and Glass [MG], They are

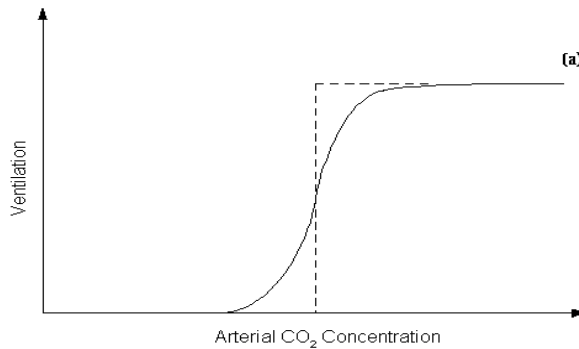
$$\begin{aligned}x_0 &= 40 \text{ mmHg}, \quad p = 6 \text{ mmHg/min}, \quad V_0 = 7.44 \text{ litre/min}, \\ V_0' &= 4 \text{ litre/min mmHg}, \quad T = 0.25 \text{ min}, \\ \alpha &= 80 \text{ litre/min}.\end{aligned}$$

The solution of the second equation in (1.13) is  $s_1 \approx \pi/2$  and

$$\alpha V_0 T = \frac{T}{x_0} = 0.0375.$$

Hence  $s_1 \gg \alpha V_0 T$  and from (1.14) it follows that the inequality is approximately

$$V_0' < \frac{\pi}{2\alpha x_0 T}$$



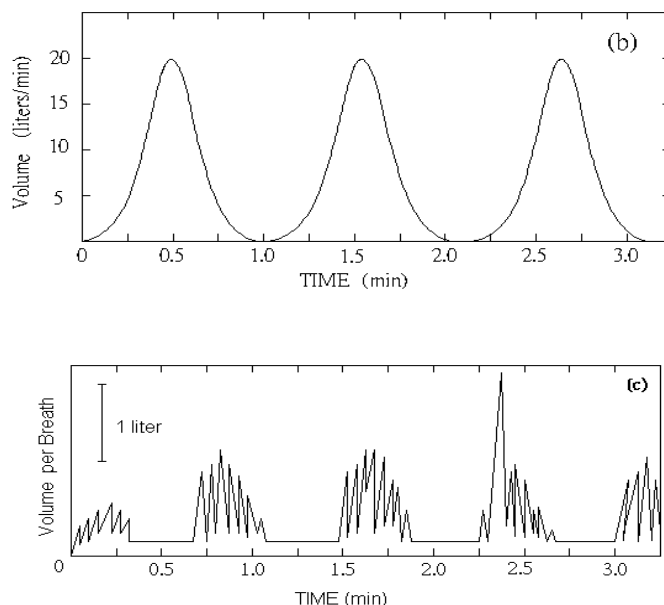


Fig. 1.2. (a) Schematic picture of the ventilatory control function. (b) Oscillatory behavior of the ventilation obtained by integrating equation for parameters in which the ventilation is oscillatory because of instabilities in the negative-feedback control loop. (c) Ventilation during Cheyne-Stokes respiration. Panels (b) and (c) are from Mackey and Glass (1977).

These observations are of interest when considering a breathing pattern known as *Cheyne-Stokes respiration* (see figure 1.2(c)), in which there is a regular waxing and waning of ventilation. Cheyne-Stokes respiration often occurs in the pathological condition of congestive heart failure (associated with increased circulatory time  $\tau$  from the lungs to the chemosensitive centers in the brain stem regulating ventilation), in obese individuals (increased  $\tau$ ), and it has been reported after neural brain-stem lesion (associated with increased sensitivity of the ventilatory  $CO_2$  response function, i.e., an elevated  $x^*$ ). Cheyne-Stokes respiration has been induced in normal dogs via an increase in  $\tau$  with the addition of an arterial extension, thereby increasing the circulatory time.

In normal individuals, Cheyne-Stokes respiration occurs at high altitude, particularly during sleep. This phenomenon is the cause of the frequently reported inability to sleep soundly during the first few nights following movement to a high altitude from a low altitude. In such circumstances, both  $O_2$  and  $CO_2$  blood gas concentrations are believed to play a role. The low  $O_2$  stimulates hyperventilation, which lowers  $CO_2$  to the lower asymptote of the  $CO_2$  control curve. Ventilation is then sharply reduced or zero until either an increase of  $CO_2$  or a decrease of  $O_2$  stimulates a resumption of ventilation.

### Regulation of hematopoiesis:

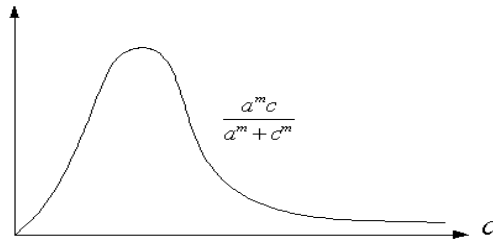
The formation of blood cells in the body, for example white and red blood cells, platelets produced in the bone marrow is considered. Let  $c(t)$  be the concentration of cells (the population species) in the circulating blood; the units of  $c$  are, say,

cells/mm<sup>3</sup>. We assume that the cells are lost at a rate proportional to their concentration, that is like  $gc$ , which the parameter  $g$  has dimensions (day)<sup>-1</sup>. After the reduction in cells in the blood stream there is about a 6 day delay before the marrow releases further cells to replenish the deficiency. We thus assume that the flux  $\lambda$  of cells into the blood stream depends on the cell concentration at an earlier time, namely  $c(t - T)$ , where  $T$  is the delay. Such assumptions suggest a model equation of the form

$$\frac{dc(t)}{dt} = \lambda(c(t - T)) - gc(t). \quad (1.15)$$

Mackey and Glass (1977) [MG] proposed two possible forms for the function  $(c(t - T))$ . The one we consider gives

$$\frac{dc}{dt} = \frac{\lambda a^m c(t - T)}{a^m + c^m} - gc, \quad (1.16)$$



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## Chapter 2

# Continuous Models for Interacting Populations

In this chapter we shall introduce the predator-prey models, competition models and mutualist models.

### 2.1 Predator-Prey models

Let  $x(t)$  be the population density of prey,  $y(t)$  be the population density of predator at time  $t$ . The general model for predator-prey interaction is following

$$\begin{aligned}\frac{dx}{dt} &= xf(x, y) \\ \frac{dy}{dt} &= yg(x, y) \\ x(0) &> 0, \quad y(0) > 0\end{aligned}$$

where  $f(x, y)$  and  $g(x, y)$  satisfy

$$\frac{\partial f}{\partial y} \leq 0, \quad \frac{\partial g}{\partial x} \geq 0.$$

In 1926 Volterra first proposed a simple model for the predation of one species by another to explain the oscillatory levels of certain fish catches in the Adriatic. The model is

$$\begin{aligned}\frac{dx}{dt} &= x(a - by) \\ \frac{dy}{dt} &= y(cx - d)\end{aligned}\tag{2.1}$$

The model (2.1) is known as Lotka-Volterra model since the same equations were also derived by Lotka, a chemist, from the autocatalysis in chemical reaction.

As a first step in analysing (2.1) we non-dimensionalize the system by

$$u(\tau) = \frac{cx(t)}{d}, \quad v(\tau) = \frac{by(t)}{a}, \quad \tau = at, \quad \alpha = b/a$$

and (2.1) becomes

$$\begin{aligned}\frac{du}{d\tau} &= u(1 - v) \\ \frac{dv}{d\tau} &= \alpha v(u - 1)\end{aligned}\tag{2.2}$$

$u(0) > 0, v(0) > 0$

In the  $uv$  phase plane, we have

$$\frac{dv}{du} = \alpha \frac{v(u-1)}{u(1-v)}$$

or

$$\frac{v-1}{v} dv + \alpha \frac{u-1}{u} du = 0 \quad (2.3)$$

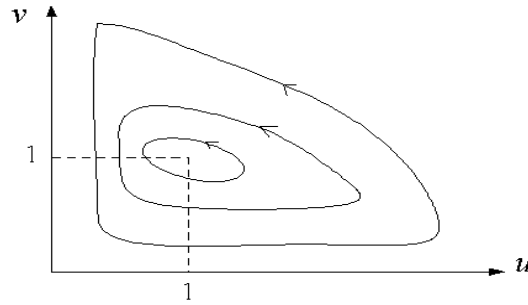
Integrate (2.3) we obtain

$$V(u, v) = \int_1^v \frac{\xi-1}{\xi} d\xi + \alpha \int_1^u \frac{\eta-1}{\eta} d\eta \equiv \text{const} \quad (2.4)$$

or

$$v-1 - \ln v + \alpha(u-1 - \ln u) \equiv H$$

Then each solution of (2.2) is a periodic solution and we obtain a series of "neutrally" stable closed curves in  $u-v$  plane.



**Fig.2.1**

If we assume the prey grows logistically with carrying capacity  $K$  in the absence of predation, then the model takes the form

$$\begin{cases} \frac{dx}{dt} = rx \left(1 - \frac{x}{K}\right) - bxy, \\ \frac{dy}{dt} = y(cx - d). \end{cases} \quad (2.5)$$

Let  $\tau = rt$ ,  $u = x/K$ ,  $v = \frac{b}{\gamma}y$ ,  $\beta = \frac{d}{c}$ ,  $\alpha = \frac{c}{\gamma}$ . Then (2.5) becomes

$$\begin{aligned} \frac{du}{dt} &= u(1-u-v), \\ \frac{dv}{dt} &= \alpha v(u-\beta). \end{aligned} \quad (2.6)$$

It can be shown that if  $\beta > 1$  then the solution of (2.6) satisfies  $(u(t), v(t)) \rightarrow (1, 0)$  as  $t \rightarrow \infty$ . On the other hand if  $0 < \beta < 1$ , then  $(u(t), v(t)) \rightarrow (\beta, 1-\beta)$  as  $t \rightarrow \infty$ . (We may employ  $V(u, v)$  as a Lyapunov function).



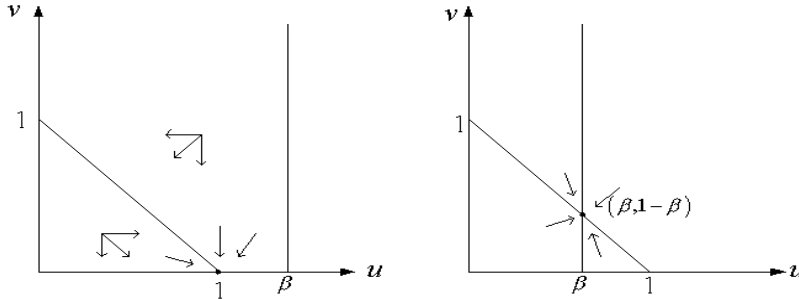


Fig.2.2

## 2.2 Realistic Predator-Prey Model

Consider the following Gause-type predator-prey system:

$$\begin{aligned} \frac{dx}{dt} &= xg(x) - p(x)y \\ \frac{dy}{dt} &= (cp(x) - q(x))y \end{aligned} \tag{2.7}$$

where  $x = x(t)$ ,  $y = y(t)$  are density of prey and predator respectively. The function  $g(x)$  satisfies

**(H1)**  $g(0) > 0, g(K) = 0$  for some  $K > 0$  and  $(x - K)g(x) < 0$  for all  $x \neq K$ .

For example  $g(x) = r(1 - \frac{x}{K}), g(x) = r(1 - (\frac{x}{K})^\theta)$ . The functional response  $p(x)$  satisfies

**(H2)**  $p(0) = 0, p'(x) > 0 \forall x \geq 0$ .

The death rate  $q(x)$  satisfies

**(H3)**  $q(x) > 0, q' \leq 0, x \geq 0$ .

The constant  $c$  is called the conversion rate. There are three types of functional responses,

- (i)  $p(x) = kx$  — Type I,
- (ii)  $p(x) = \frac{mx}{a+x}$  — Type II,
- (iii)  $p(x) = \frac{mx^n}{a+x^n}$  — Type III,

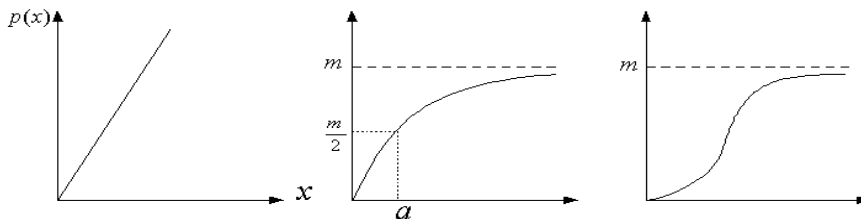


Fig.2.3

Type I is the Lotka-Volterra type. Type II is called Holling's type II functional response or Michaelis-Menten type with maximal growth rate  $m$  and half saturation constant  $a$ . Type III is also called the learning functional response since the curve  $p(x)$  is a sigmoid type curve with an inflection point.

Stability of the equilibria:

There are three equilibria:  $(0, 0)$ ,  $(K, 0)$ ,  $(x^*, y^*)$ .

The Jacobian of the system (2.7) is

$$J(x, y) = \begin{bmatrix} xg_x(x) + g(x) - yp_x(x) & , -p(x) \\ cyp_x(x) & cp(x) - q(x) \end{bmatrix}.$$

Then

$$J(0, 0) = \begin{bmatrix} g(0) & 0 \\ 0 & -q(0) \end{bmatrix}$$

Since  $g(0) > 0$ , the equilibrium  $(0, 0)$  is a saddle point with stable manifold  $\{(x, y) : x = 0, y \geq 0\}$  and unstable manifold  $\{(x, y) : y = 0, x \geq 0\}$ .

The Jacobian matrix at  $(K, 0)$  is

$$J(K, 0) = \begin{bmatrix} Kg_x(K) & , -p(K) \\ 0 & , cp(K) - q(K) \end{bmatrix}$$

Since  $g_x(K) < 0$ ,  $(K, 0)$  is stable if and only if  $cp(K) - q(K) < 0$ .

The Jacobian at interior equilibrium  $(x^*, y^*)$  is

$$J(x^*, y^*) = \begin{bmatrix} H(x^*) & -p(x^*) \\ y^*p_x(x^*) & , 0 \end{bmatrix}$$

where

$$H(x^*) = x^*g_x(x^*) + g(x^*) - \frac{x^*g(x^*)p_x(x^*)}{p(x^*)}. \quad (2.8)$$

Since the eigenvalues of  $J(x^*, y^*)$  are given by

$$\frac{H(x^*)}{2} \pm \frac{[H^2(x^*) - 4y^*p(x^*)p_x(x^*)]^{1/2}}{2}.$$

It is clear that the sign of the real parts of these eigenvalues coincide with the sign of  $H(x^*)$ .

From this we may come to the following conclusions, again utilizing  $y^* = \frac{x^*g(x^*)}{p(x^*)}$ ,

$$H(x^*)^2 - 4x^*p(x^*)p_x(x^*) < 0(> 0) \Rightarrow (x^*, y^*) \text{ is a spiral (node)}. \quad (2.9)$$

Further

$$H(x^*) < 0(> 0) \Rightarrow (x^*, y^*) \text{ is stable (unstable)}.$$

The prey isocline is  $y = \frac{xg(x)}{p(x)}$  and the predator isocline is  $x = x^*$ . From (2.8)

$$\begin{aligned} \frac{H(x^*)}{x^*g(x^*)} &= \frac{g_x(x^*)}{g(x^*)} + \frac{1}{x^*} - \frac{p_x(x^*)}{p(x^*)} \\ &= \frac{d}{dx} \ln \left[ \frac{xg(x)}{p(x)} \right] \Big|_{x=x^*}. \end{aligned}$$

Then the stability criterion (2.9) becomes

$$\frac{d}{dx} \ln \left[ \frac{xg(x)}{p(x)} \right] \Big|_{x=x^*} < 0(> 0) \Rightarrow (x^*, y^*) \text{ is stable (unstable)} \quad (2.10)$$

Then (2.10) is equivalent to the prey isocline

$$y = \frac{xg(x)}{p(x)} \text{ is decreasing (increasing) at } x^* \Rightarrow (x^*, y^*) \text{ is stable (unstable).}$$

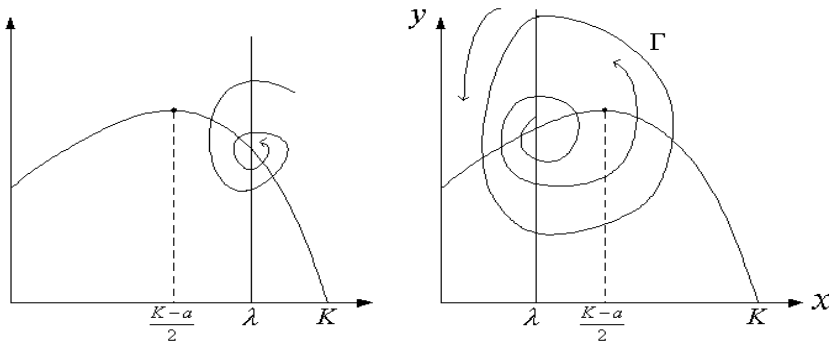
**Example:**[HHW] [C]

$$\begin{aligned} x' &= rx \left(1 - \frac{x}{K}\right) - \frac{mx}{a+x}y \\ y' &= \left(\frac{mx}{a+x} - d\right)y \\ x(0) &> 0, \quad y(0) > 0 \end{aligned} \tag{2.11}$$

From [HHW] and [C] we have the following results.

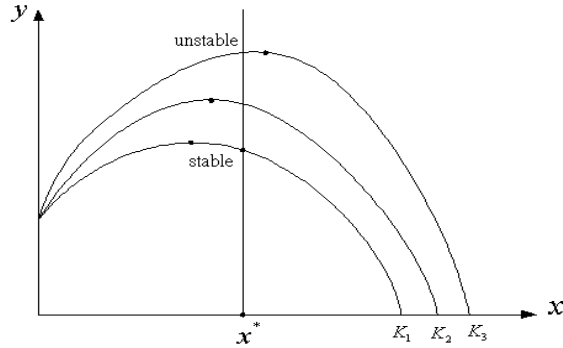
**Theorem 2.1:**

- (i) If  $0 < K < \lambda = \frac{a}{\left(\frac{m}{d}\right)-1}$  then the solution of (2.11) satisfy  $\lim_{t \rightarrow \infty} x(t) = x^* = \lambda$  and  $\lim_{t \rightarrow \infty} y(t) = y^*$ .
- (ii) If  $K > \lambda$  then there is a unique limit cycle  $\Gamma$  which is globally orbitally stable.



**Fig.2.4**

**Remark:** "Paradox of enrichment" Rosenzweig [R]. The system (2.11) exhibits the well-known "paradox of enrichment" which states that according to model (2.11), enriching a predator-prey system (increasing the carrying capacity  $K$ ) will cause an increase in the equilibrium density of the predator but not in that of prey, and will destabilize the positive equilibrium (the positive steady state changes from stable to unstable as  $K$  increase) and thus increase the possibility of stochastic extinction of predator. Unfortunately numerous field observations provide contrary to this "paradox of enrichment". What often observed in nature is that fertilization does increase the prey density, does not destabilize a stable steady state and fails to increase the amplitude of oscillations in systems that already cycle.



In the following we construct a Lyapunov function  $V(x, y)$  for the system (2.7) to prove the global stability for the local stable equilibrium  $(x^*, y^*)$  under the condition that the lines  $x = x^*$  and  $y = y^*$  separate the prey isocline  $y = \frac{xg(x)}{p(x)}$  into two disjoint parts.

**Theorem 2.2:** [Hsu 1978] *If  $\left(\frac{xg(x)}{p(x)} - y^*\right)(x - x^*) \leq 0$  for all  $x \geq 0$  then  $(x^*, y^*)$  is globally stable in the 1st quadrant.*

**Proof:** Construct Lyapunov function

$$V(x, y) = \int_{x^*}^x \frac{cp(\xi) - q(\xi)}{p(\xi)} d\xi + \int_{y^*}^y \frac{\eta - y^*}{\eta} d\eta \quad (2.12)$$

on  $G = \{(x, y) : x > 0, y > 0\}$ . Then the time derivative computed along the solution of (2.7) is

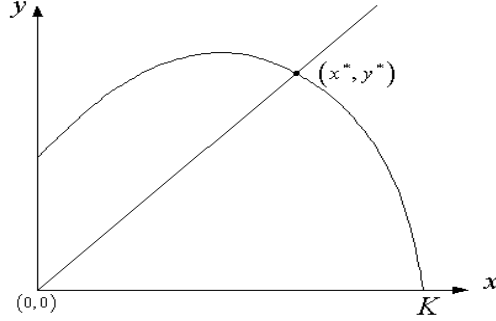
$$\dot{V} = (cp(x) - q(x)) \left( \frac{xg(x)}{p(x)} - y^* \right) \leq 0 \quad \text{on } G.$$

Let  $E = \{(x, y) \in \bar{G} : V(x, y) = 0\}$ . Then  $E = \left\{ (x, y) : \frac{xg(x)}{p(x)} = y^*, y \geq 0 \right\}$ , and the largest invariant set  $M$  in  $E$  is  $\{(x^*, y^*)\}$ . Hence the theorem follows directly from LaSalle's Invariance Principle [H].

There are two types of "ratio-dependence" models.

**Example** [Hsu & Hwang] Holling-Tanner model

$$\begin{aligned} x' &= rx \left( 1 - \frac{x}{K} \right) - \frac{mx}{a+x} y \\ y' &= \delta y \left( 1 - \frac{y}{hx} \right) \\ x(0) &> 0, y(0) > 0 \end{aligned} \quad (2.13)$$



**Fig.2.5**

Consider the nondimensional system of (2.13)

$$\begin{aligned} \frac{dx}{dt} &= x(1-x) - \frac{x}{a+x}y = f(x, y) \\ \frac{dy}{dt} &= y(\delta - \beta\frac{y}{x}) = g(x, y) \end{aligned} \tag{2.14}$$

It is easy to verify  $E^* = (x^*, y^*)$  is locally asymptotically stable if  $P(x^*) > 0$  where

$$P(x) = 2x^2 + (a + \delta - 1)x + a\delta$$

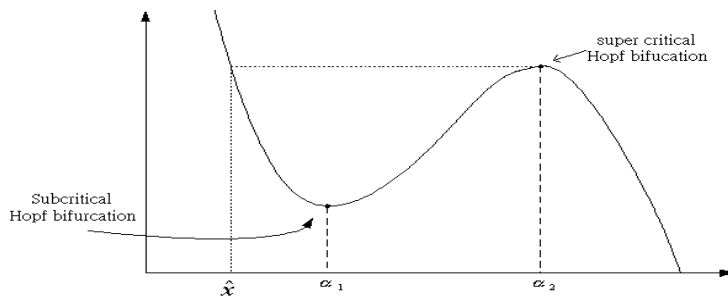
and  $E^*$  is an unstable focus or node if  $P(x^*) < 0$ . In [HH1] the author prove the global stability of  $E^*$  by application Dulac's criterion. To show the uniqueness of limit cycle, we convert the system (2.14) into a Gause-type predator-prey system by the transformation  $(x, y) \rightarrow (x, u)$  where  $u = yl(x), l(x) = (\frac{1-x}{x})^\delta$ . Then (2.14) becomes

$$\begin{aligned} \frac{dx}{dt} &= x(1-x) - \frac{x}{a+x} \frac{u}{l(x)}, \\ \frac{du}{dt} &= \frac{u^2 \beta}{xl(x)(1-x)(a+x)} \left(x + \frac{a}{x^*}\right) (x - x^*). \end{aligned} \tag{2.15}$$

The isocline  $u = h(x) = (1-x)(a+x)l(x)$  satisfies

$$h'(x) = -\frac{l(x)}{x}P(x)$$

The graph of  $h(x)$  is Fig.2.6.



**Fig.2.6**

If  $x^* < \hat{x}$  then we construct a Lyapunov function like (2.12) to show that  $(x^*, y^*)$  is global stable. For  $\alpha_1 < x^* < \alpha_2$ ,  $(x^*, y^*)$  is unstable and by Poincaré-Bendixson Theorem there exists a limit cycle. The problem of uniqueness of limit cycle was studied in [HH2].

For  $x^* > \alpha_2$ ,  $E^*$  is global stable. For  $\hat{x} < x^* < \alpha_1$ , there may exist limit cycles even  $E^*$  is stable due to the subcritical Hopf bifurcation.

**Example:** [HHK]

$$\begin{aligned} x' &= rx \left(1 - \frac{x}{K}\right) - \frac{c\left(\frac{x}{y}\right)}{a + \left(\frac{x}{y}\right)} y = rx \left(1 - \frac{x}{K}\right) - \frac{cxy}{ay+x} = F_1(x, y) \\ y' &= \left[ \frac{m\left(\frac{x}{y}\right)}{a + \left(\frac{x}{y}\right)} - d \right] y = \left( \frac{mx}{ay+x} - d \right) y = F_2(x, y) \end{aligned} \quad (2.16)$$

This model demonstrates the possibilities of simultaneous extinction of predator and prey and the outcomes depending on the initial populations.

We note that  $(0, 0)$  is also an equilibrium of (2.16) for

$$\lim_{(x,y) \rightarrow (0,0)} F_1(x, y) = \lim_{(x,y) \rightarrow (0,0)} F_2(x, y) = 0$$

With the scaling

$$t \rightarrow rt, \quad x \rightarrow x/K, \quad y \rightarrow \frac{my}{K},$$

(2.16) is converted into

$$\begin{aligned} x'(t) &= x(1-x) - \frac{sxy}{x+y} \\ y'(t) &= \delta y \left(-r + \frac{x}{x+y}\right) \end{aligned} \quad (2.17)$$

where  $s = \frac{c}{ma}$ ,  $\delta = \frac{f}{a}$ ,  $\frac{d}{f}$ .

Consider the change of variables  $(x, y) \rightarrow (u, y)$ ,  $u = \frac{x}{y}$ , then (2.17) is reduced to the following Gause-type predator-prey system

$$\begin{aligned} u'(t) &= g(u) - \varphi(u)y \\ y'(t) &= \psi(u)y \end{aligned} \quad (2.18)$$

where

$$\begin{aligned} g(u) &= u(A + Bu)/(1 + u), \\ \varphi(u) &= u^2, \\ \psi(u) &= \delta \left( \frac{u}{u+1} - r \right) \\ A &= 1 + \delta r - s, \quad B = 1 + \delta r - \delta. \end{aligned}$$

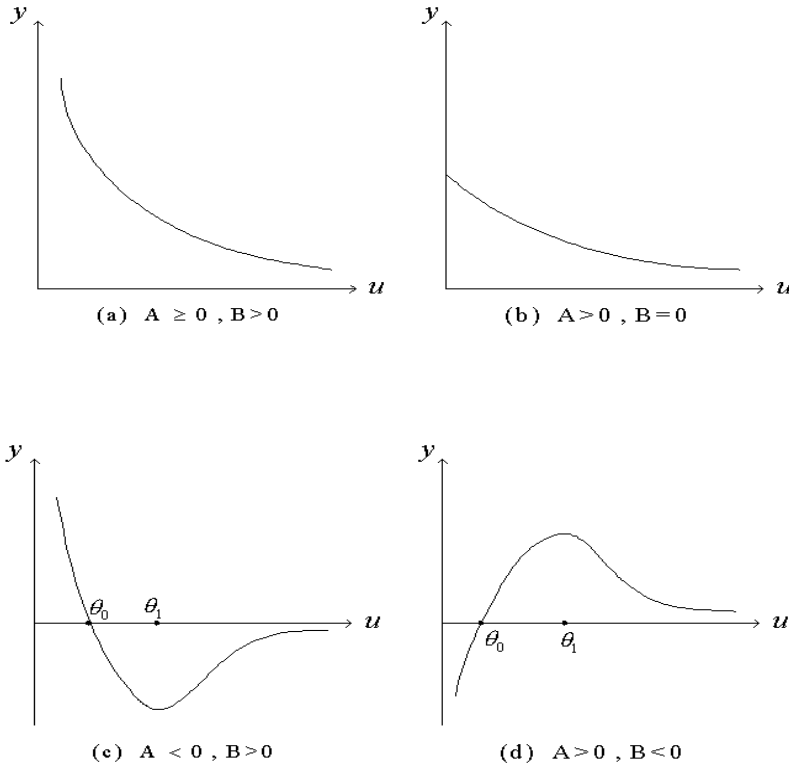
(2.18) can also be rewritten as

$$\begin{aligned} u'(t) &= \varphi(u) (h(u) - y) \\ y'(t) &= \psi(u)y \end{aligned} \quad (2.19)$$

we see that the prey isocline of (2.18) is given by

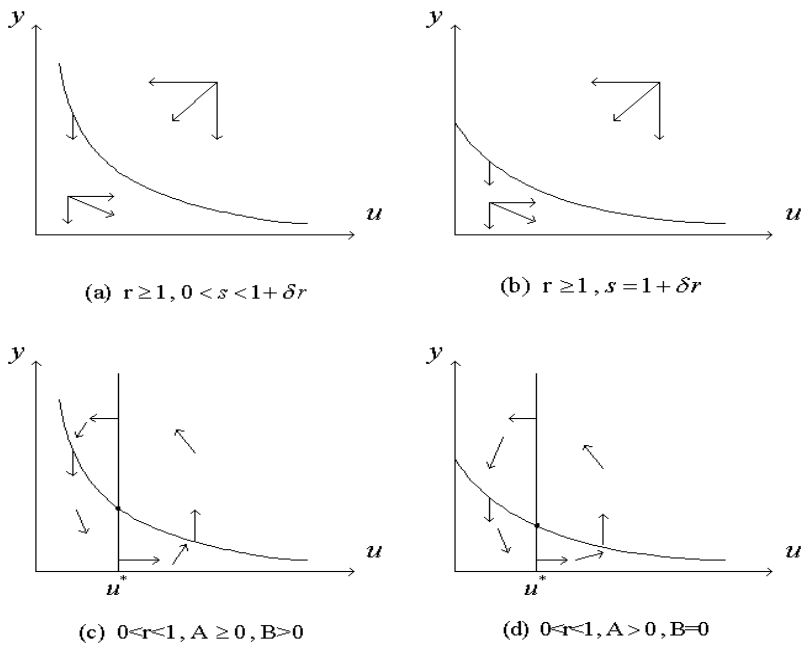
$$y = \frac{g(u)}{\varphi(u)} = h(u) = \frac{A + Bu}{u(u+1)}.$$

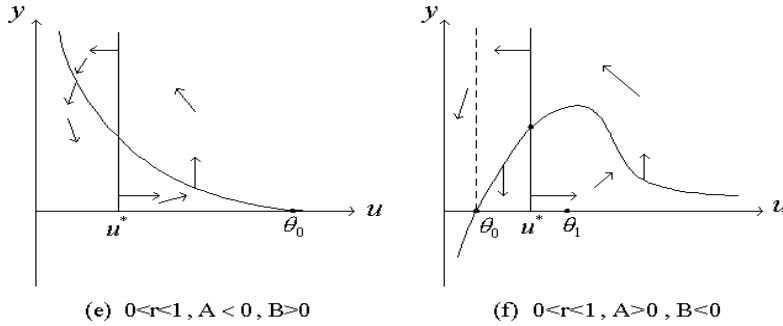
There are several cases for the shapes of prey-isoclines for different  $A$  and  $B$ . (See Fig. 2.7)



**Fig.2.7: Scenarios of the shape of  $y = h(u)$ .**

The direction field for (2.19) under various conditions is shown as in Fig. 2.8.

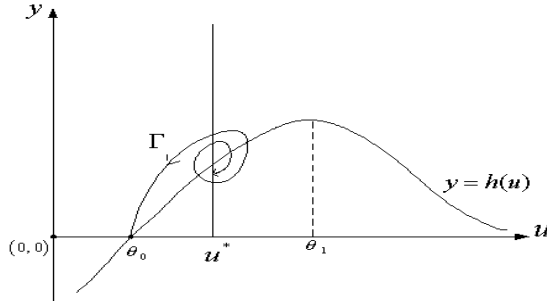




**Fig.2.8:** The direction field chart for system (2.19) under various conditions.

The most interesting cases are the case  $0 < r < 1, A > 0, B < 0$  in Fig. 2.8(f). For  $\theta_0 < u^* < \theta_1$ , there are two possible cases:

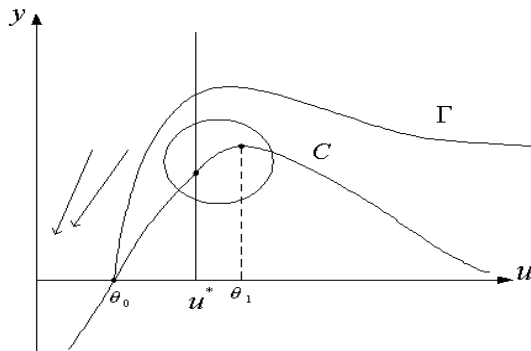
- (i) The stable manifold  $\Gamma$  of equilibrium  $E_1 = (\theta_0, 0)$  of the system (2.18) intersect prey-isocline  $y = h(u)$ . Then  $\Gamma$  connects to the equilibrium  $E^* = (u^*, y^*)$  (See Fig. 2.9)



**Fig.2.9**

In this case, it can be shown that  $\lim_{t \rightarrow \infty} (u(t), y(t)) = (0, 0)$  as  $t \rightarrow \infty$  for  $(u(0), y(0)) \notin \Gamma$

- (ii) The stable manifold  $\Gamma$  does not intersect the prey-isocline  $y = h(u)$

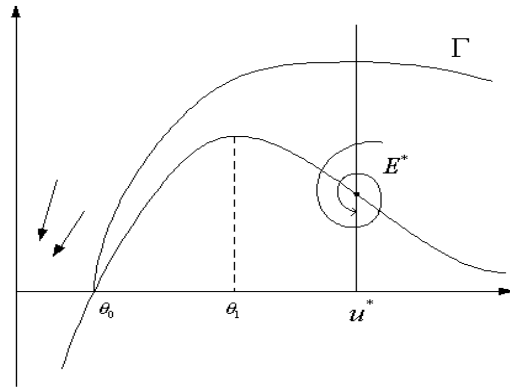




**Fig.2.10**

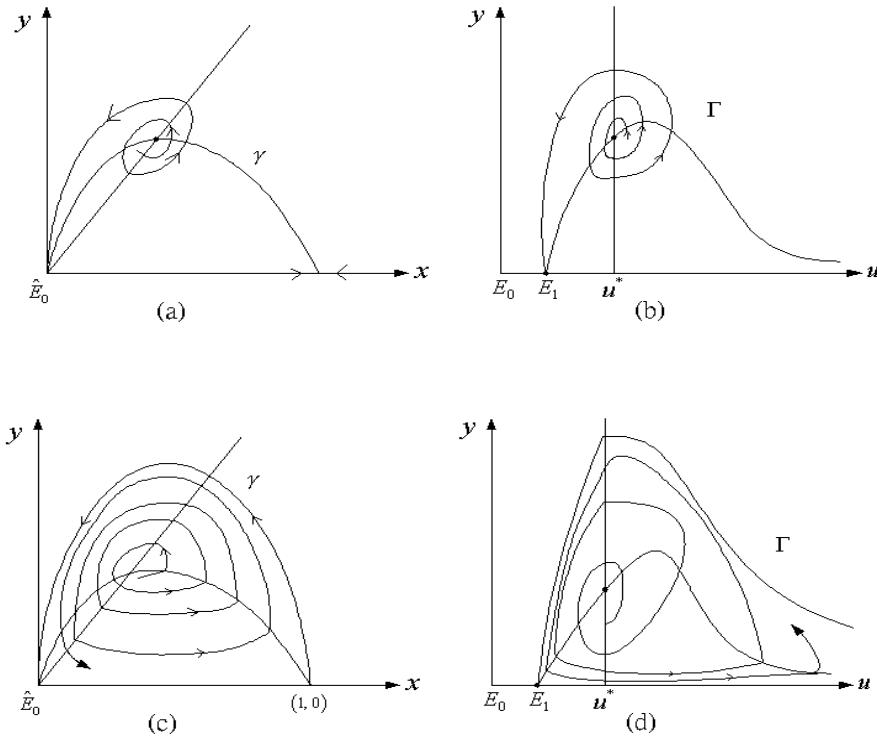
Then  $\lim_{t \rightarrow \infty} (u(t), y(t)) = (0, 0)$  if  $(u(0), y(0))$  is above  $\Gamma$  and there exists a unique limit cycle  $C$  below  $\Gamma$  and  $\lim_{t \rightarrow \infty} \text{dist}((u(t), y(t)), \Gamma) = 0$  provided  $(u(0), y(0)) \neq E^*$  and  $(u(0), y(0))$  below  $\Gamma$ . (See Fig. 2.10)

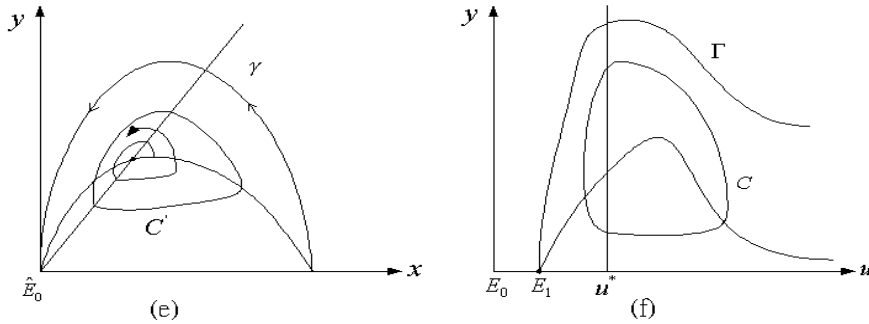
For  $u^* > \theta_1$ , then  $\Gamma$  does not intersect  $y = h(u)$ . If  $(u(0), y(0))$  is above  $\Gamma$  then  $(u(t), y(t)) \rightarrow (0, 0)$  as  $t \rightarrow \infty$ . If  $(u(0), y(0))$  is below  $\Gamma$  then  $(u(t), y(t)) \rightarrow E^*$  as  $t \rightarrow \infty$ . (See Fig. 2.11)



**Fig.2.11**

If we return to original variables, then the dynamical behavior of the solutions are show in Fig. 2.12.





**Fig.2.12:** Figures 2.12(a,b) illustrate the case when origin is the global attractor. Figures 2.12(c,d) illustrate the case when a heteroclinic cycle is the global attractor. Figures 2.12(e,f) illustrate the case when a limit cycle is the global attractor.

Open problems:

The prey-dependent model (2.11) and ratio-dependent model (2.16) are two extreme cases for predator-prey models. Some ecologists propose the following model

$$\begin{cases} x' = rx \left(1 - \frac{x}{K}\right) - \frac{c\left(\frac{x}{y^r}\right)}{a + \left(\frac{x}{y^r}\right)} y \\ y' = \left(\frac{m\left(\frac{x}{y^r}\right)}{a + \left(\frac{x}{y^r}\right)} - d\right) y \\ x(0) > 0, \quad y(0) > 0 \end{cases} \quad (2.20)$$

For  $r = 0$ , we have system (2.11) which behavior of the solutions are independent of initial populations and conversion rate  $c$ , depend on carrying capacity  $K$ . On the other hand, for  $r = 1$ , the ratio-dependent system (2.16) which behavior of solutions depends on initial population and  $c$ , independent of  $K$ . Treat  $\gamma$ ,  $0 < \gamma < 1$  as a bifurcation parameter, it is interesting to see how the behavior changes for the system (2.20), when does the bifurcation occurs.

## 2.3 Competition Models

The general  $n$ -species competition model is described by the following systems

$$\begin{aligned} x_1' &= x_1 f_1(x_1, \dots, x_n) \\ &\vdots \\ x_n' &= x_n f_n(x_1, \dots, x_n) \\ x_i(0) &> 0, \quad i = 1, 2, \dots, n \end{aligned} \quad (2.21)$$

where  $f_i(x_1, \dots, x_n)$  satisfies

$$\frac{\partial f_i}{\partial x_j} \leq 0, \quad j \neq i.$$

In this section we first consider two-species competition model

$$\begin{aligned}x'_1 &= x_1 f_1(x_1, x_2) & \frac{\partial f_1}{\partial x_2} &\leq 0, & \frac{\partial f_2}{\partial x_1} &\leq 0 \\x'_2 &= x_2 f_2(x_1, x_2)\end{aligned}\tag{2.22}$$

Lotka-Volterra two-species competition model:

$$\begin{aligned}\frac{dx_1}{dt} &= r_1 x_1 \left(1 - \frac{x_1}{K_1}\right) - \alpha_1 x_1 x_2 \\ \frac{dx_2}{dt} &= r_2 x_2 \left(1 - \frac{x_2}{K_2}\right) - \alpha_2 x_1 x_2\end{aligned}\tag{2.23}$$

There are equilibria:  $E_0 = (0, 0)$ ,  $E_1 = (K_1, 0)$  and  $E_2 = (0, K_2)$ . The interior equilibrium at  $E^* = (x_1^*, x_2^*)$  exists under following case (iii) and (iv). The varational matrix  $E(x_1, x_2)$  is

$$A(x_1, x_2) = \begin{bmatrix} \gamma_1 \left(1 - \frac{x_1}{K_1}\right) - \alpha_1 x_2 - \frac{\gamma_1}{K_1} x_1, & -\alpha_1 x_1 \\ -\alpha_2 x_2, & \gamma_2 \left(1 - \frac{x_2}{K_2}\right) - \alpha_2 x_1 - \frac{\gamma_2}{K_2} x_2 \end{bmatrix}$$

At  $E_0$ ,

$$A(0, 0) = \begin{bmatrix} \gamma_1 & 0 \\ 0 & \gamma_2 \end{bmatrix}$$

$E_0$  is a source or a repeller.

At  $E_1 = (K_1, 0)$

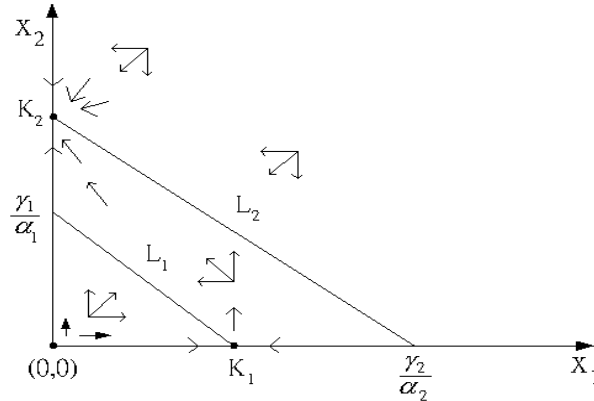
$$A(K_1, 0) = \begin{bmatrix} -\gamma_1, & -\alpha_1 K_1 \\ 0, & \gamma_2 - \alpha_2 K_1 \end{bmatrix}$$

At  $E_2 = (0, K_2)$

$$A(0, K_2) = \begin{bmatrix} \gamma_1 - \alpha_1 K_2, & 0 \\ -\alpha_2 K_2, & 0 \end{bmatrix}$$

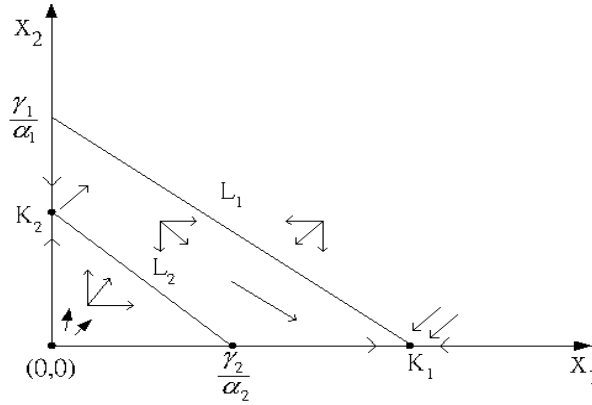
There are four cases according to the position of isoclines  $L_1 : \gamma_1 \left(1 - \frac{x_1}{K_1}\right) - \alpha_1 x_2 = 0$  and  $L_2 : \gamma_2 \left(1 - \frac{x_2}{K_2}\right) - \alpha_2 x_1 = 0$ :

(i) Extinction case: species  $y$  wins



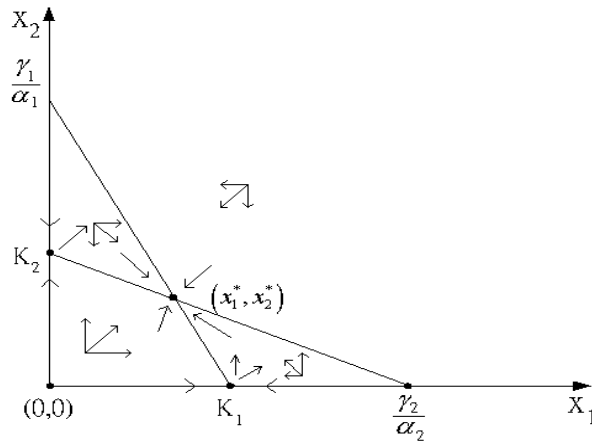
In this case  $E_2 = (0, K_2)$  is a stable node,  $E_1 = (K_1, 0)$  is a saddle point and  $E_0 = (0, 0)$  is an unstable node. It can be show that  $\lim_{t \rightarrow \infty} (x_1(t), x_2(t)) = (0, K_2)$ .

(ii) Extinction case: species  $x_1$  win.



In this case  $E_1 = (K_1, 0)$  is a stable node,  $E_2 = (0, K_2)$  is a saddle point and  $E_0 = (0, 0)$  is an unstable node. It can be shown  $\lim_{t \rightarrow \infty} (x_1(t), x_2(t)) = (K_1, 0)$ .

(iii) Coexistence case:



In this case  $E_1 = (K_1, 0)$  and  $E_2 = (0, K_2)$  are saddle point,  $E_0 = (0, 0)$  is an unstable node. It can be shown  $\lim_{t \rightarrow \infty} (x_1(t), x_2(t)) = (x_1^*, x_2^*)$ .

The variational matrix for  $E^*$  is

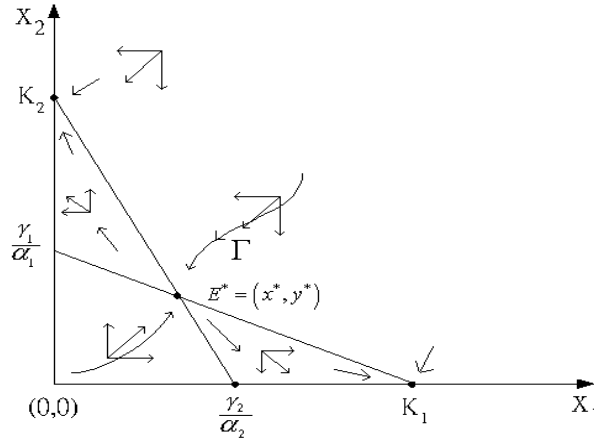
$$A(x_1^*, x_2^*) = \begin{bmatrix} -\frac{\gamma_1}{K_1} x_1^* & -\alpha_1 x_1^* \\ -\alpha_2 x_2^* & -\frac{\gamma_2}{K_2} x_2^* \end{bmatrix}$$

The characteristic polynomial of  $A(x^*, y^*)$  is

$$\lambda_2 + \left( \frac{\gamma_1}{K_1} x_1^* + \frac{\gamma_2}{K_2} x_2^* \right) \lambda + x_1^* x_2^* \left( \frac{\gamma_1 \gamma_2}{K_1 K_2} - \alpha_1 \alpha_2 \right) = 0$$

Since  $\frac{\gamma_2}{\alpha_2} > K_1$ ,  $\frac{\gamma_1}{\alpha_1} > K_2$ , it follows that  $E^* = (x_1^*, x_2^*)$  is a stable node.

(iv) Bistable case:

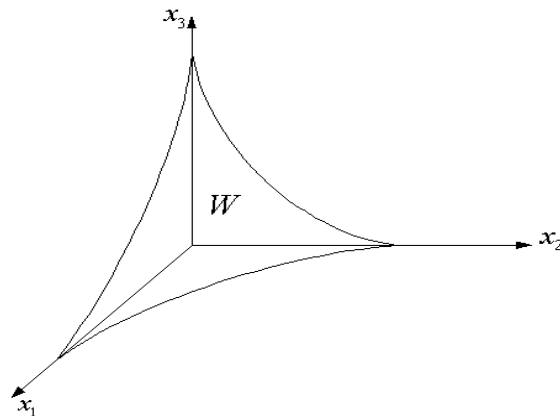


In this case  $E_1 = (K_1, 0)$  and  $E_2 = (0, K_2)$  are stable nodes.  $E_0 = (0, 0)$  is an unstable node.

And from  $E_1 > \frac{\gamma_2}{\alpha_2}$ ,  $K_2 > \frac{\gamma_1}{\alpha_1}$ , it follows that  $E^* = (x_1^*, x_2^*)$  is a saddle point. It can be shown that there exists a one-dimensional stable manifold  $\Gamma$  of  $E^* = (x_1^*, x_2^*)$  such that every trajectory with initial condition on the left(right) hand of  $\Gamma$  converges to  $(0, K_2)$  ( $(K_1, 0)$ ).

**Remark 3.1:** We apply isocline analysis and Poincaré-Bendixon theorem to obtain the global behavior of the solutions in case (i)–(iv). This technique is frequently used in the cases of resource-based two species competition model in chemostat.

**Remark 3.2:** For the general  $n$ -species system (3.1), M. Hirsch [Hirsch] showed that there exists a "carrying" simplex  $W$  which is the boundary of repeller of origin and is homeomorphic to a  $n$ -simplex, such that the  $\omega$ -limit set of each trajectory lies on  $W$ .

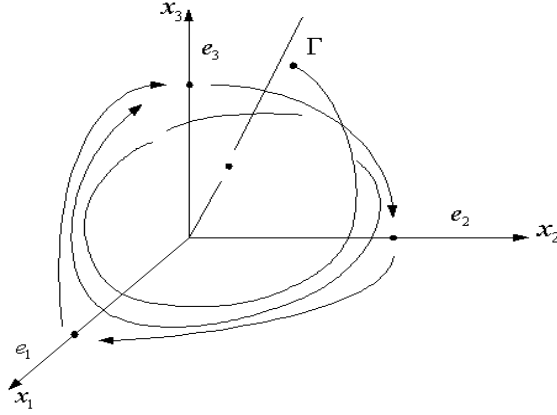


**Remark 3.3:** For  $n = 3$ , M. Hirsch [Hirsch] and Smith [S] showed that Poincaré-Bendixon Theorems holds and every periodic orbit "enclose" an equilibrium.

**Remark 3.4:** May-Leonard model of Three competing species [May][SSW][Hsu]. Consider

$$\begin{aligned} x'_1 &= x_1(1 - x_1 - \alpha x_2 - \beta x_3) \\ x'_2 &= x_2(1 - \beta x_1 - x_2 - \alpha x_3) \\ x'_3 &= x_3(1 - \alpha x_1 - \beta x_2 - x_3) \end{aligned} \tag{2.24}$$

under the assumption  $0 < \alpha < 1 < \beta$ ,  $\alpha + \beta > 2$ , then there exists a unique interior equilibrium  $P = \frac{1}{1+\alpha+\beta}(1, 1, 1)$  which is a saddle point with one-dimensional stable manifold  $\Gamma$  and the solutions with  $x_0 = (x_1(0), x_2(0), x_3(0)) \in \Gamma$  exhibits nonperiodic oscillations. Specifically, the  $\omega$ -limit set  $\omega(x_0) = O_{123}$ , where the orbit  $O_3$  on  $x_1x_2$  plane connecting  $e_2 = (0, 1, 0)$  to  $e_1 = (1, 0, 0)$  and orbit  $O_2$  on  $x_1x_3$  plane connecting  $e_1 = (1, 0, 0)$  to  $e_3 = (0, 0, 1)$  and orbit  $O_1$  on  $x_2x_3$  plane connecting  $e_3$  to  $e_2$ .



**Remark 3.5:** Smale [[S], P.71] show that for  $n \geq 4$ , given only dynamical system on  $n$ -simplex (including chaotic dynamics), we are able to construct an  $n$ -dimensional competitive system. Hence for  $n \geq 4$ , we anticipate a complicated behavior of the solutions.

**Remark 3.6:** We say the following system

$$x'_i = x_i f_i(x_1, x_2, x_3, \dots, x_n), \quad i = 1, 2, \dots, n \tag{2.25}$$

is a cooperative system (or mutualist system) if  $\frac{\partial f_i}{\partial x_j} \geq 0$  for all  $j \neq i$ . We note that the competitive system (3.1) is the "reverse" time system of (3.5). One nice thing of cooperative system is the property of monotonicity, i.e.,  $\vec{x}(0) \geq \vec{y}(0)$  implies  $\vec{x}(t) \geq \vec{y}(t)$  for all  $t \geq 0$ , where  $x(t), y(t)$  are solutions of (3.5). The monotonicity can be obtained by Kamke's Theorem [C]. For two species competition model

$$\begin{aligned} x'_1 &= x_1 f_1(x_1, x_2) \\ x'_2 &= x_2 f_2(x_1, x_2) \end{aligned} \tag{2.26}$$

we also have the monotonicity property. Define  $a = (a_1, a_2) \leq_K b = (b_1, b_2)$  if and only if  $a_1 \leq b_1, a_2 \geq b_2$ . Then it can be shown that  $\vec{x}(0) \leq_K \vec{y}(0)$  implies  $\vec{x}(t) \leq_K \vec{y}(t)$  for all  $t \geq 0$ .

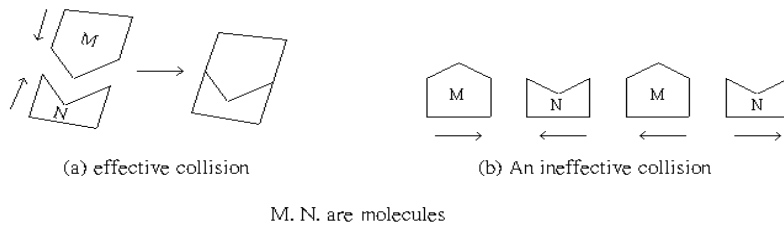
## Chapter 3

# Chemical Reaction Kinetics

### 3.1 Enzyme Kinetics

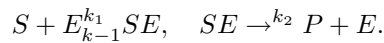
#### Law of Mass Action:

The rate of a reaction is proportional to the product of the concentrations of the reactants.



**Fig.3.1**

Consider one of the most basic enzymatic reactions, proposed by Michaelis and Menten (1913) involving a substrate (molecule)  $S$  reacting with an enzyme  $E$  to form a complex  $SE$  which in turn is converted into a product  $P$ . Schematically we have



Let

$$s = [S], e = [E], c = [SE], p = [P]$$

where  $[ ]$  denotes concentration. By Law of mass action, we have the system of nonlinear equations

$$\begin{aligned} \frac{ds}{dt} &= -k_1 es + k_{-1} c, & \frac{de}{dt} &= -k_1 es + (k_{-1} + k_2) c, \\ \frac{dc}{dt} &= k_1 es - (k_{-1} + k_2) c, & \frac{dp}{dt} &= k_2 c, \end{aligned} \quad (3.1)$$

$$s(0) = s_0, \quad e(0) = e_0, \quad c(0) = c_0, \quad p(0) = p_0.$$

From (3.1), we have

$$\frac{de}{dt} + \frac{dc}{dt} = 0 \quad \text{or} \quad e(t) + c(t) \equiv e_0 \quad (3.2)$$

By (3.2) we have

$$\begin{aligned}\frac{ds}{dt} &= -k_1 e_0 s + (k_1 s + k_{-1}) c, \\ \frac{dc}{dt} &= k_1 e_0 s - (k_1 s + k_{-1} + k_2) c, \\ s(0) &= s_0, \quad c(0) = 0\end{aligned}\tag{3.3}$$

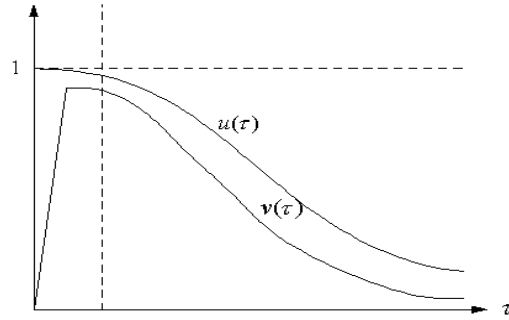
With the nondimensionalization

$$\begin{aligned}\tau &= k_1 e_0 t, \quad u(\tau) = \frac{s(t)}{s_0}, \quad v(\tau) = \frac{c(t)}{e_0} \\ \lambda &= \frac{k_2}{k_1 s_0}, \quad K = \frac{k_{-1} + k_2}{k_1 s_0}, \quad \varepsilon = \frac{e_0}{s_0}\end{aligned}\tag{3.4}$$

the system (3.3) become

$$\begin{aligned}\frac{du}{d\tau} &= -u + (u + K - \lambda) v \\ \varepsilon \frac{dv}{d\tau} &= u - (u + K) v \\ u(0) &= 1, \quad v(0) = 0\end{aligned}\tag{3.5}$$

where  $0 < \varepsilon \ll 1$  and from (3.4),  $K > \lambda$ .



**Fig.3.2**

Here  $v(\tau)$  changes rapidly in dimensionless time  $\tau = O(\varepsilon)$ . After that  $v(\tau)$  is essentially in a steady state, or  $\varepsilon \frac{dv}{d\tau} \approx 0$ , i.e., the  $v$ -reaction is so fast it is more or less in equilibrium at all times. This is Michaelis and Menten's pseudo-steady state hypothesis. In the following we introduce method of singular perturbation for system (3.5).

Singular Perturbation: Initial Value Problem

Consider the following system

$$\begin{aligned}\frac{dx}{dt} &= f(x, y) \\ \varepsilon \frac{dy}{dt} &= g(x, y), \quad 0 < |\varepsilon| \ll 1 \\ x(0, \varepsilon) &= x_0, \quad y(0, \varepsilon) = y_0\end{aligned}\tag{3.6}$$



If we set  $\epsilon = 0$  in (3.6), then

$$\begin{aligned} \frac{dx}{dt} &= f(x, y), \quad x(0) = x_0 \\ 0 &= g(x, y) \end{aligned} \tag{3.7}$$

Assume  $g(x, y) = 0$  can be solved as

$$y = \varphi(x) \tag{3.8}$$

Substitute (3.8) into (3.7), then we have

$$\begin{aligned} \frac{dx}{dt} &= f(x, \varphi(x)) \\ x(0) &= x_0 \end{aligned} \tag{3.9}$$

Let  $X_0(t)$ ,  $0 \leq t \leq 1$  be the unique solution of (3.9) and  $Y_0(t) = \varphi(X_0(t))$ . In general  $Y_0(0) \neq y_0$ . Assume the following hypothesis:

There exists  $K > 0$  such that for  $0 \leq t \leq 1$

$$\left[ \frac{\partial g}{\partial y} \right] \bigg|_{\substack{x = X_0(t) \\ y = Y_0(t)}} \leq -K(H) \text{ and } \left[ \frac{\partial g}{\partial y} \right] \bigg|_{\substack{x = X_0(t) \\ y = \lambda}} \leq -K \text{ for all}$$

$\lambda$  lying between  $Y(0)$  and  $y_0$ . We shall prove that

$$\lim_{\epsilon \downarrow 0} x(t, \epsilon) = X_0(t), \quad \lim_{\epsilon \downarrow 0} y(t, \epsilon) = Y_0(t)$$

Uniformly on  $0 < t \leq 1$ . Since  $Y_0(0) \neq y_0$ , we expect  $Y_0(t)$  to be non-uniformly valid at  $t = 0$ . Introduce a new variable, the stretch variable  $\xi = t/\epsilon$  and write

$$\begin{aligned} x(t, \epsilon) &= X(t, \epsilon) + u(\xi, \epsilon) \\ y(t, \epsilon) &= Y(t, \epsilon) + v(\xi, \epsilon) \end{aligned} \tag{3.10}$$

where  $X(t, \epsilon)$ ,  $Y(t, \epsilon)$  are called "outer solutions" and  $u(\xi, \epsilon)$ ,  $v(\xi, \epsilon)$  are called "inner solutions". There is a matching condition between inner and outer solutions,

$$\lim_{\xi \uparrow \infty} u(\xi, \epsilon) = 0 \quad \lim_{\xi \uparrow \infty} v(\xi, \epsilon) = 0 \tag{3.11}$$

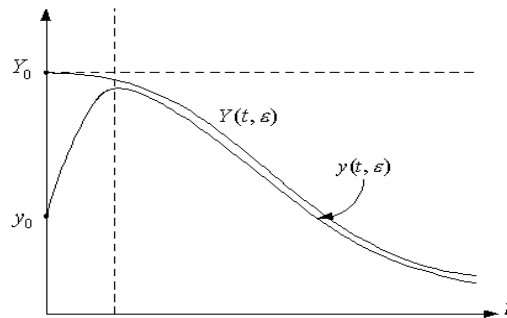


Fig.3.3

Step 1: Finding outer solutions  $X(t, \epsilon)$  and  $Y(t, \epsilon)$ .

Let

$$X(t, \epsilon) = \sum_{n=0}^{\infty} \epsilon^n X_n(t), \quad Y(t, \epsilon) = \sum_{n=0}^{\infty} \epsilon^n Y_n(t). \quad (3.12)$$

Do the regular perturbation for system (3.6), i.e. substitute (3.12) into (3.6) and compare  $\epsilon^n$ -term for  $n = 0, 1, 2, \dots$ . Compute

$$\begin{aligned} f(X(t, \epsilon), Y(t, \epsilon)) &= f\left(\sum \epsilon^n X_n, \sum \epsilon^n Y_n\right) \\ &= f(X_0, Y_0) + \epsilon \left[ \left(\frac{\partial f}{\partial x}\right)_{X_0, Y_0} X_1 + \left(\frac{\partial f}{\partial y}\right)_{X_0, Y_0} Y_1 \right] + O(\epsilon^2), \\ g(X(t, \epsilon), Y(t, \epsilon)) &= g\left(\sum \epsilon^n X_n, \sum \epsilon^n Y_n\right) \\ &= g(X_0, Y_0) + \epsilon \left[ \left(\frac{\partial g}{\partial x}\right)_{X_0, Y_0} X_1 + \left(\frac{\partial g}{\partial y}\right)_{X_0, Y_0} Y_1 \right] + O(\epsilon^2) \end{aligned} \quad (3.13)$$

The comparison of  $\epsilon^2$  term by substituting (3.11) into (3.6) yields

$O(1)$

$$\begin{aligned} \frac{dX_0}{dt} &= f(X_0, Y_0) \\ &= g(X_0, Y_0) \end{aligned} \quad (3.14)$$

$O(\epsilon)$

$$\begin{aligned} \frac{dX_1}{dt} &= \left(\frac{\partial f}{\partial x}\right)_{X_0, Y_0} X_1 + \left(\frac{\partial f}{\partial y}\right)_{X_0, Y_0} Y_1 \\ 0 &= \left(\frac{\partial g}{\partial x}\right)_{X_0, Y_0} X_1 + \left(\frac{\partial g}{\partial y}\right)_{X_0, Y_0} Y_1 - \frac{dY_0}{dt} \end{aligned} \quad (3.15)$$

In (3.14)  $X_0(t), Y_0(t)$  satisfy

$$\begin{aligned} Y_0(t) &= \varphi(X_0(t)), \\ \frac{dX_0}{dt} &= f(X_0, \varphi(X_0)), \\ X_0(0) &= x_0. \end{aligned} \quad (3.16)$$

From (3.15), we obtain

$$Y_1(t) = \left[ \frac{dY_0}{dt} - \left(\frac{\partial g}{\partial x}\right)_{X_0, Y_0} X_1 \right] \bigg/ \left(\frac{\partial g}{\partial y}\right)_{X_0, Y_0}, \quad (3.17)$$

and  $X_1(t)$  satisfies

$$\begin{aligned} \frac{dX_1}{dt} &= \psi_1(t)X_1 + \mu_1(t) \\ X_1(0) &= 0 \end{aligned} \quad (3.18)$$

where

$$\begin{aligned}\psi_1(t) &= \left( \frac{\partial f}{\partial x} \right)_{X_0, Y_0} - \frac{\left( \frac{\partial f}{\partial y} \right) \left( \frac{\partial g}{\partial x} \right)}{\left( \frac{\partial g}{\partial y} \right)} \Big|_{X_0, Y_0} , \\ \mu_1(t) &= \frac{\left( \frac{\partial g}{\partial y} \right)_{X_0, Y_0} \frac{dY_0}{dt}}{\left( \frac{\partial g}{\partial y} \right)_{X_0, Y_0}} .\end{aligned}$$

Inductively we shall have for  $i = 2, 3, \dots$

$$\begin{aligned}Y_i(t) &= \alpha_i(t) + \beta_i(t)X_i(t) \\ \frac{dX_i}{dt} &= \psi_i(t)X_i + \mu_i(t), \\ X_i(0) &= 0.\end{aligned}\tag{3.19}$$

for  $x(0, \epsilon) = X(0, \epsilon) = x_0 = \sum_{i=1}^{\infty} X_i(0)\epsilon^n$  it follows that  $X_0(0) = x_0$  and  $X_i(0) = 0$  for  $i = 1, 2, \dots$

Step 2: Inner expansion at singular layer near  $t = 0$ .

From (3.6) and (3.10),  $\xi = t/\epsilon$ , we have

$$\begin{aligned}\frac{du}{d\xi} &= \frac{d}{d\xi} (x(\epsilon\xi, \epsilon) - X(\epsilon\xi, \epsilon)) \\ &= \epsilon f(X(\xi\epsilon, \epsilon) + u(\xi, \epsilon), Y(\xi\epsilon, \epsilon) + v(\xi, \epsilon)) \\ &\quad - \epsilon f(X(\xi\epsilon, \epsilon), Y(\xi\epsilon, \epsilon)) \\ \frac{dv}{d\xi} &= g(X(\xi\epsilon, \epsilon) + u(\xi, \epsilon), Y(\xi\epsilon, \epsilon) + v(\xi, \epsilon)) \\ &\quad - g(X(\xi\epsilon, \epsilon), Y(\xi\epsilon, \epsilon)) \\ u(0, \epsilon) &= x(0, \epsilon) - X(0, \epsilon) = 0 \\ v(0, \epsilon) &= y_0 - Y(0, \epsilon) \neq 0\end{aligned}\tag{3.20}$$

Let

$$u(\xi, \epsilon) = \sum_{n=0}^{\infty} u_n(\xi)\epsilon^n, \quad v(\xi, \epsilon) = \sum_{n=0}^{\infty} v_n(\xi)\epsilon^n.\tag{3.21}$$

Expand (3.20) in power series in  $\epsilon$  by (3.21) and compare the coefficients on both sides of (3.20), we have set  $\epsilon = 0$ , we obtain

O(1)

$$\begin{cases} \frac{du_0}{d\xi} = 0 \\ u_0(0) = 0 \end{cases} \Rightarrow u_0(\xi) \equiv 0\tag{3.22}$$

and

$$\begin{cases} \frac{dV_0}{d\xi} = g(X_0(0), Y_0(0) + V_0(\xi)) - g(X_0(0), Y_0(0)) \\ \quad \equiv^{M.V.T} V_0(\xi)G(V_0(\xi)) \\ V_0(0) = y_0 - Y_0(0) \quad (\text{Boundary layer jump}) \end{cases} \quad (3.23)$$

From hypothesis (H),  $G(V_0(\xi)) \leq -K < 0$ ,  $|V_0(\xi)|$  initially decreases and  $|V_0(\xi)| \leq |V_0(0)|e^{-K\xi}$  for  $\xi > 0$  small.

O(1):

$$\begin{cases} \frac{du_1}{d\xi} = f[X_0(0), Y_0(0) + V_0(\xi)] - f(X_0(0), Y_0(0)) \\ \quad \equiv V_0(\xi)F(V_0(\xi)) \\ u_1(0) = 0 \end{cases} \quad (3.24)$$

Once  $V_0(\xi)$  is solved by (3.23), we solve (3.24) and obtain

$$u_1(\xi) = \int_{\infty}^{\xi} v_0(s)F(v_0(s)) ds$$

by the matching condition (3.11)  $u_1(\infty) = 0$ .

Hence

$$\begin{aligned} x(t, \epsilon) &\sim X_0(t) + \epsilon[X_1(t) + u_1(t/\epsilon)] + O(\epsilon)^2 \\ y(t, \epsilon) &\sim Y_0(t) + v_0(t/\epsilon) + O(\epsilon) \end{aligned}$$

Now we go back to the Michaelis-Menten Kinetics

$$\begin{aligned} \frac{dx}{dt} &= f(x, y) = -x + (x + K - \lambda)y, \quad K > 0, \lambda > 0 \\ \epsilon \frac{dy}{dt} &= g(x, y) = x - (x + K)y \end{aligned} \quad (3.25)$$

Let

$$\begin{aligned} x(t, \epsilon) &= X(t, \epsilon) + u(\xi, \epsilon) = \sum_{n=0}^{\infty} \epsilon^n X_n(t) + \sum_{n=0}^{\infty} \epsilon^n u_n(t) \\ y(t, \epsilon) &= Y(t, \epsilon) + v(\xi, \epsilon) = \sum_{n=0}^{\infty} \epsilon^n Y_n(t) + \sum_{n=0}^{\infty} \epsilon^n v_n(t) \end{aligned}$$

Then from (3.16)

$$Y_0(t) = \varphi(X_0(t)) = \frac{X_0(t)}{X_0(t) + K} \quad (3.26)$$

where  $X_0(t)$  satisfies

$$\begin{cases} \frac{dx}{dt} = -x + (x + K - \lambda) \frac{x}{x+K} = \frac{-\lambda x}{x+K} \\ x(0) = x_0 = 1 \end{cases}$$

Then  $X_0(t)$  satisfies

$$X_0(t) + K \ln X_0(t) = 1 - \lambda t \quad (3.27)$$

From (3.23) we obtain

$$\begin{aligned}\frac{dV_0}{d\xi} &= [x_0 - (x_0 + K)(Y_0(0) + v_0(\xi))] - [x_0 - (x_0 + K)Y_0(0)] \\ &= -(x_0 + K)v_0(\xi) \\ v_0(0) &= y_0 - Y_0(0), \quad x_0 = 1, y_0 = 0\end{aligned}$$

and

$$\begin{aligned}v_0(\xi) &= \left(y_0 - \frac{x_0}{x_0 + K}\right) e^{-(x_0 + K)\xi} \\ &= \left(\frac{-1}{1 + K}\right) e^{-(1 + K)\xi}\end{aligned}$$

Hence

$$y(t, \epsilon) \sim \frac{x_0(t)}{x_0(t) + K} + \left(\frac{-1}{1 + K}\right) e^{-(1 + K)\xi(t/\epsilon)}.$$

From (3.24)

$$\begin{aligned}\frac{du_1}{d\xi} &= f(x_0(0), Y_0(0) + V_0(\xi)) - f(X_0(0), Y_0(0)) \\ &= (1 + K - \lambda)v_0(\xi) = \frac{\lambda - (1 + K)}{1 + K} e^{-(1 + K)\xi} \\ u_1(\infty) &= 0, \\ u_1(\xi) &= ((1 + K) - \lambda) e^{-(1 + K)\xi}\end{aligned}$$

## 3.2 Autocatalysis

Autocatalysis is the process where by a chemical is involved in its own production.

**Example:**  $A + X \xrightleftharpoons[k_{-1}]{k_1} 2X$

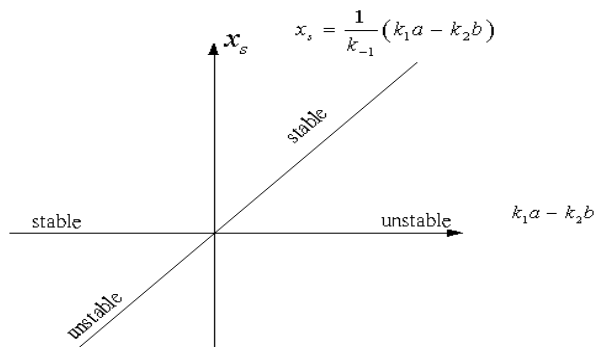
Suppose  $A$  is maintained at constant concentration, by the law of mass action we have

$$\frac{dx}{dt} = k_1 ax - k_{-1} x^2 \quad (3.28)$$

where  $x = [X]$ ,  $a \equiv [A]$ . The autocatalysis reaction exhibits a strong feedback with the "product" inhibiting the reaction rate.

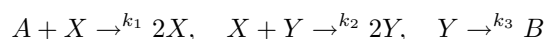
**Example:**  $A + X \xrightleftharpoons[k_{-1}]{k_1} 2X, B + X \xrightarrow{k_2} C$ .  $X$  is used up in the production of  $C$ .

$$\begin{aligned}\frac{dx}{dt} &= k_1 ax - k_{-1} x^2 - k_2 bx \\ &= (k_1 a - k_2 b)x - k_{-1} x^2\end{aligned} \quad (3.29)$$



**Fig.3.4: Bifurcation diagram**

**Example:** Lotka-Volterra equation



$$\begin{cases} \frac{dx}{dt} = k_1 a x - k_2 x y \\ \frac{dy}{dt} = k_2 x y - k_3 y \end{cases} \quad (3.30)$$

Under the scalig

$$u = \frac{k_2 x}{k_3}, \quad v = \frac{k_2 y}{k_1 a}, \quad \tau = k_1 a t, \quad \alpha = \frac{k_3}{k_1 a}$$

becomes

$$\begin{aligned} \frac{du}{d\tau} &= u(1 - v) \\ \frac{dv}{d\tau} &= \alpha v(u - 1) \end{aligned} \quad (3.31)$$

In almost all biological process we do not know the detailed biochemical reactions that are taking place. However we often do know the qualitative effect of varying a known reactant.

#### Activation and Inhibition:

For a general system

$$\frac{du}{dt} = f(u, v), \quad \frac{dv}{dt} = g(u, v) \quad (3.32)$$

$u$  is an activator of  $v$  if  $\frac{\partial g}{\partial u} > 0$  while  $v$  is an inhibitor of  $u$  if  $\frac{\partial f}{\partial v} < 0$ .

**Example:** Thomas mechanisms

It is based on a specific reaction involving the substrate oxygen ( $v$ ) and uric acid ( $u$ ) which react in the presence of the enzyme uricase. The dimensionless equations are

$$\begin{aligned}\frac{du}{dt} &= a - u - \rho R(u, v) = f(u, v) \\ \frac{dv}{dt} &= \alpha(b - v) - \rho R(u, v) = g(u, v) \\ R(u, v) &= \frac{uv}{1+u+Ku^2}\end{aligned}\tag{3.33}$$

where  $a, b, \alpha, \rho$  and  $K$  are positive constants. We note that the term  $R(u, v)$  exhibits substrate inhibition. Given  $v$ ,  $R(u, v)$  is linear in  $u$  for  $u$  small and  $R(u, v)$  decrease in  $u$  for large  $u$ . The parameter  $K$  measures the severity of inhibition,  $R(u, v)$ , as a function of  $u$ , reach maximum at  $u = \frac{1}{\sqrt{K}}$ .

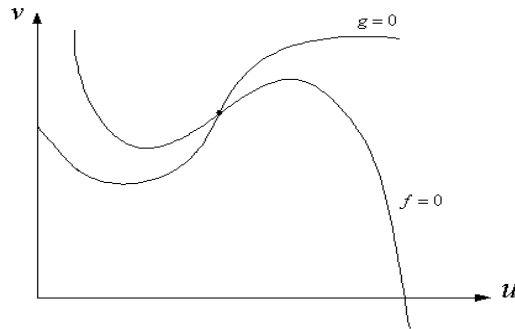


Fig.3.5

**Example:** (Gierer and Meinhardt) Activator-inhibitor system

$$\begin{aligned}\frac{du}{dt} &= a - bu + \frac{u^2}{v(K+u^2)} = f(u, v) \\ \frac{dv}{dt} &= u^2 - v = g(u, v)\end{aligned}\tag{3.34}$$

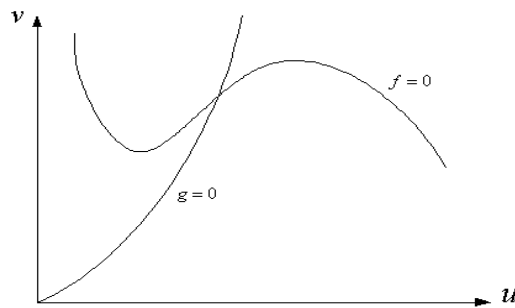


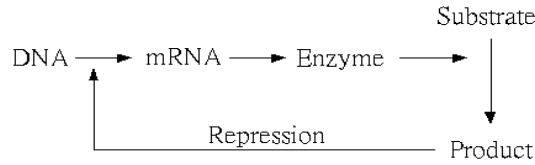
Fig.3.6

### 3.3 Biological Oscillators: Monotone cyclic feedback systems

In this section we shall consider the biological model in the form of the system of ordinary differential equations

$$\frac{d\vec{u}}{dt} = \vec{f}(\vec{u}). \quad (3.35)$$

where  $\vec{u} = \vec{u}(t)$  is the concentration vector.  $\vec{f}$  describes the nonlinear reaction kinetics or underlying biological oscillator mechanism. We are interested in finding periodic solution  $u(t)$ . In the following we consider a mathematical model concerning the feedback control mechanisms of certain metabolites repressing the enzymes which are essential for their own synthesis. This is done by inhibiting the transcription of the molecule DNA to messenger RNA (mRNA) which is the template which makes enzyme. Goodwin (1965) proposed a simple model for this process which is schematically in following figure.



**Fig.3.7**

Let  $M, E, P$  be the concentration of mRNA, the enzyme and the product of the reaction of the enzyme and a substrate assumed to be available at a constant level. The equations are

$$\begin{aligned} \frac{dM}{dt} &= \frac{V}{K+P^m} - \alpha M \\ \frac{dE}{dt} &= bM - cE \\ \frac{dP}{dt} &= dE - eP \end{aligned} \quad (3.36)$$

For general feedback control system, a suitable nondimensional form is given as following:

$$\begin{aligned} \frac{du_1}{dt} &= f(u_n) - k_1 u_1 \\ \frac{du_i}{dt} &= u_{i-1} - k_i u_i, \quad i = 2, 3, \dots, n \end{aligned} \quad (3.37)$$

where  $k_i > 0, i = 2, 3, \dots, n$  and  $f(u) > 0, \forall u$ , is the nonlinear feedback function. If  $f'(u) > 0, \forall u > 0$  the system represents a positive feedback loop while if  $f'(u) < 0$ , for all  $u \geq 0$ , the system represents a negative feedback system loop or feedback inhibition. Positive feedback loops are not common metabolic control mechanisms where as negative one are (See Tyson and Othmer (1978)).

Steady state solutions of (3.37) are give by

$$\begin{aligned} f(u_n) &= k_1 k_2 \dots k_n u_n, \quad u_{n-1} = k u_n \\ u_1 &= k_2 k_2 \dots k_n u_n. \end{aligned}$$



With positive feedback functions  $f(u)$ , multiple steady states are possible whereas with feedback inhibition there is always a unique steady state.

For the more important negative feedback system (3.37), it is quite simple to determine a bounded domain  $\Omega$  satisfying  $\vec{n} \cdot \frac{d\vec{u}}{dt} < 0$  for  $\vec{u} \in \partial\Omega$ , i.e., the trajectory with initial condition in  $\Omega$  stays in  $\Omega$  for  $t \geq 0$ . Consider first the two species case of (3.37), namely

$$\begin{aligned} \frac{du_1}{dt} &= f(u_2) - k_1 u_1 \\ \frac{du_2}{dt} &= u_1 - k_2 u_2 \end{aligned}$$

where  $f(u_2) > 0$  and  $f'(u_2) < 0$ . Consider first the rectangular domain bounded by  $u_1 = 0, u_2 = 0, U_1 = U_1$  and  $u_2 = U_2$  where  $U_1$  and  $U_2$  are to be determined. On the boundaries

$$\begin{aligned} u_1 = 0, \quad \vec{u} \cdot \frac{d\vec{u}}{dt} &= -\frac{du_1}{dt} = -f(u_2) < 0 \quad \text{for all } u_2 \geq 0, \\ u_2 = 0, \quad \vec{u} \cdot \frac{d\vec{u}}{dt} &= -\frac{du_2}{dt} = -f(u_1) < 0 \quad \text{for } u_1 > 0, \\ u_1 = U_1, \quad \vec{u} \cdot \frac{d\vec{u}}{dt} &= -f(u_2) - k_1 U_1 < 0 \\ \text{if } U_1 &> \frac{f(u_2)}{k_1} \quad \text{for all } 0 \leq u_2 \\ U_1 &> \frac{f(0)}{k_1} \end{aligned}$$

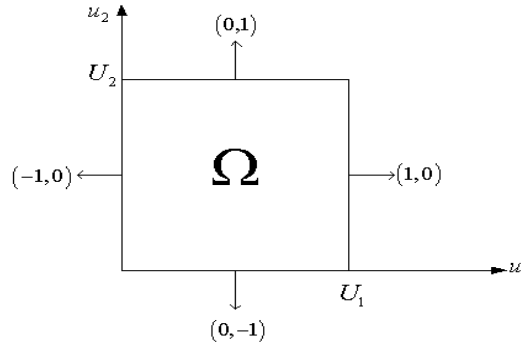


Fig.3.8

$$\begin{aligned} u_2 = U_2, \quad \vec{u} \cdot \frac{d\vec{u}}{dt} &= u_1 - k_2 U_2 < 0 \\ \text{if } U_2 &> \frac{u_1}{k_2} \quad \text{for } 0 < u_1 \end{aligned}$$

If we choose  $U_1, U_2$  to satisfy the inequalities

$$U_1 > \frac{f(0)}{k_1}, \quad U_2 > \frac{U_1}{k_2}$$

then the bounded region  $\Omega$  is positively invariant under the system (3.37). We note that the unique steady state  $(u_1^*, u_2^*)$  lies in  $\Omega$ .

Similarly for  $n$ -species negative feedback loop, we can construct a positively invariant, bounded region  $\Omega$  given by  $\Omega = \{(u_1, \dots, u_n) : 0 \leq u_i \leq U_i, i = 1, \dots, n\}$  where  $U_i, i = 1, \dots, n$  satisfy

$$U_1 > \frac{f(0)}{k_1}, \quad U_2 > \frac{U_1}{k_2}, \quad \dots, \quad U_n > \frac{U_1}{k_1 k_2 \dots k_n}.$$

For the large time behavior of (3.37), Mallet-Paret and H. Smidth [?] studied the general monotone cyclic feedback systems of the following form

$$x'_i = f_i(x_i, x_{i-1}), \quad i = 1, 2, \dots, n \quad (3.38)$$

where we agree to interpret  $x_0$  as  $x_n$ . In the cyclic system (3.38) our key assumption is

$$\delta_i \frac{\partial f_i}{\partial x_{i-1}}(x_i, x_{i-1}) > 0 \text{ for all } x_i, x_{i-1} > 0 \quad (3.39)$$

for some  $\delta^i \in \{-1, +1\}$ . Thus  $\delta_i$  describes whether the effect of  $x_{i-1}$  is to inhibit the growth of  $x_i$  ( $\delta_i = -1$ ) or to augment its growth ( $\delta_i = +1$ ). The product

$$\Delta = \delta_1 \delta_2 \dots \delta_n \quad (3.40)$$

characterizes the entire system as one with negative feedback ( $\Delta = -1$ ) or positive feedback ( $\Delta = +1$ ). We term such a system, of the form (3.38) satisfying (3.39), a monotone cyclic feedback system. In [MS] the authors proved that the Poincaré-Bendixson theorem holds for monotone cyclic feedback systems. In particular, the omega-limit set of any bounded orbit of a monotone cyclic feedback system can be embedded in  $R^2$  and must, in fact, be the type encountered in two-dimensional systems: either a single equilibrium, a single nonconstant periodic solution, or a structure consisting of a set of equilibria together with homoclinic and heteroclinic orbits connecting these equilibria. In a general sense "chaos" is ruled out. The authors use an integer valued Lyapunov function  $N$  as a principal tool. Interested readers should consult [?].

Besides the single-loop feedback system (3.37), we give the following systems as examples of (3.38).

**Example:** Simple Biochemical Control Circuit

$$\begin{aligned} y'_1 &= f(y_n) - \frac{\alpha_1 y_1}{b_1 + y_1} \\ y'_i &= \frac{\beta_i y_{i-1}}{a_i + y_{i-1}} - \frac{\alpha_i y_i}{b_i + y_i}, \quad 2 \leq i \leq n. \end{aligned} \quad (3.41)$$

**Example:** ([] Banks and Mahaffy) Multigene model with negative feedback

$$\begin{aligned}
 y'_1 &= f_1(w_m) - \alpha_1 y_1 \\
 y'_i &= \beta_i y_{i-1} - \alpha_i y_i, \quad 2 \leq i \leq p \\
 z'_1 &= f_2(y_p) - \gamma_1 z_1 \\
 z'_j &= \eta_j z_{j-1} - \gamma_j z_j, \quad 2 \leq j \leq l \\
 w'_1 &= f_3(z_l) - \delta_1 w^1 \\
 w'_k &= \xi_k w_{k-1} - \delta_1 w^k, \quad 2 \leq k \leq m
 \end{aligned} \tag{3.42}$$

where  $\alpha_i, \beta_i, \gamma_j, \eta_j, \xi_k, \delta_k > 0$  and  $f_1, f_2, f_3$  satisfies negative feedback assumption  $f'_i(u) < 0$  for  $u \geq 0, i = 1, 2, 3$ . This example displace the "three-gene". Readers may imagine there are  $n$  genes where the end product of  $q^{\text{th}}$  gene inhibits the transcription of mRNA associated with  $(q + 1)$ st gene. Delays are sometimes introduced in the first terms of the right side of (3.42). One could also replace the linear terms in (3.42) by Michaelis-Menten nonlinearities as in (3.41). We note that J. Mallet-Paret and G. Sell [JDE 1996] proved the Poincaré-Bendixson Theorem for the following Monotone cyclic feedback system with delay:

$$x'_i(t) = f_i(x_i(t), x_{i-1}(t - \beta^i)) \tag{3.43}$$

### 3.4 Biological Oscillators: Belousov-Zhabotinskii reaction

In 1951 Belousov found oscillations in the ratio of concentration of the catalyst in the oxidation of citric acid by bromate. The study of this reaction was continued by Zhabotinskii (1964) and is now known as the Belousov-Zhabotinskii reaction or simply the BZ reaction. When the details of this important reaction and some of its dramatic oscillatory and wave-like properties reached the West in 1970, it provoked widespread interest and research. Now BZ reaction is considered the prototype chemical oscillator in both theoretical and experimental sense. Here we briefly describe the key steps in the reaction by the Field-Noyes model. The basic mechanism consists of the oxidation of malonic acid, in an acid medium, by bromate ions,  $\text{BrO}_3^-$ , and catalyzed by cerium, which as two state  $\text{Ce}^{3+}$  and  $\text{Ce}^{4+}$ .

Sustained periodic oscillation are observed in the cerium ions. With other metal ion catalysts and appropriate dyes, for example, iron  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$  and phenanthroline, the regular periodic colour change is visually dramatic, oscillating between a reddish-orange to blue. See the following figure Fig. 3.9.

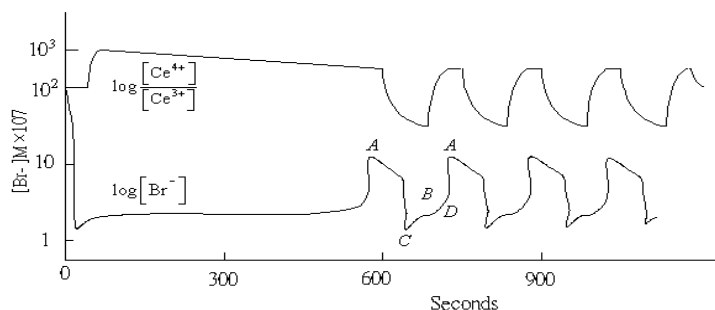
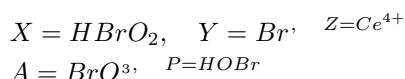


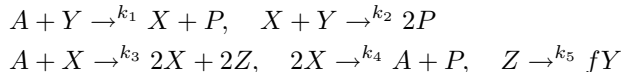
Fig.3.9

In Fig. 3.9. we can see the relaxation oscillations which will be discussed latter.

Next we discuss Field-Noyes model or FN model. The key chemical elements in 5-reaction FN model are



and the model reactions can be approximated by the sequence



where the rate constants  $k_1 \dots k_5$  are known and  $f$  is a stoichiometric factor,  $f \approx 0.5$ . We assume the concentration  $[A]$  of the bromate ion to be constant. Using the Law of Mass Action, we obtain

$$\begin{aligned} \frac{dx}{dt} &= k_1 ay - k_2 xy + k_3 ax - k_4 x^2 \\ \frac{dy}{dt} &= -k_1 ay - k_2 xy + fk_5 z \\ \frac{dz}{dt} &= 2k_3 ax - k_5 z \end{aligned}$$

This oscillator system is sometimes referred to as the "Oregonator" since it exhibits limit cycle oscillations and research by Field et al was done at the University of Oregon. Following Tyson (1985), introduce

$$\begin{aligned} x^* &= \frac{x}{x_0}, & y^* &= \frac{y}{y_0}, & z^* &= \frac{z}{z_0}, & t^* &= \frac{t}{t_0} \\ x_0 &= \frac{k_3 a}{k_4} \approx 1.2 \times 10^{-7} M, & y_0 &= \frac{k_3 a}{k_2} \approx 6 \times 10^{-7} M, \\ z_0 &= \frac{2(k_3 a)^2}{k_4 k_5} \approx 5 \times 10^{-3} M, & t_0 &= \frac{1}{k_5} \approx 50 s \\ \epsilon &= \frac{k_5}{k_3 a} \approx 5 \times 10^{-5}, & \delta &= \frac{k_4 k_5}{k_2 k_3 a} \approx 2 \times 10^{-4} \\ q &= \frac{k_1 k_4}{k_2 k_3} \approx 8 \times 10^{-4}, & f &\approx 0.5 \end{aligned} \tag{3.44}$$

### 3.4. BIOLOGICAL OSCILLATORS: BELOUSOV-ZHABOTINSKII REACTION 39

Then above system is converted into following non-dimensional equations

$$\begin{aligned}\epsilon \frac{dx}{dt} &= qy - xy + x(1 - x) \\ \delta \frac{dy}{dt} &= -qy - xy + 2fz \\ \frac{dz}{dt} &= x - z\end{aligned}\tag{3.45}$$

The equilibrium of (3.45) are  $(0, 0, 0)$  and  $(x_s, y_s, z_s)$  where  $z_s = x_s, y_s = \frac{2fx_s}{q+x_s}, 2x_s = (1 - 2f - q) + ((1 - 2f - q)^2 + 4q(1 + 2f))^{1/2}$ . It is easy to verify that  $(0, 0, 0)$  is always linearly unstable. If we linearize (3.45) about the positive steady state  $(x_s, y_s, z_s)$ , the eigenvalue  $\lambda$  satisfies

$$|A - \lambda I| = \begin{vmatrix} \frac{1-2x_s-y_s}{\epsilon} - \lambda & \frac{q-x_s}{\epsilon} & 0 \\ -\frac{y_s}{\delta} & -\frac{x_s+q}{\delta} - \lambda & \frac{2f}{\delta} \\ 1 & 0 & -1 - \lambda \end{vmatrix}$$

or

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0$$

where

$$\begin{aligned}A &= 1 + \frac{q + x_s}{\delta} + \frac{E}{\epsilon} > 0 \\ E + 2x_s + y_s - 1 &= \frac{x_s^2 + q(x_s + 2f)}{q + x_s} > 0 \\ B &= \frac{q + x_s}{\delta} + \frac{E}{\epsilon} + \frac{(q + x_s)E + y_s(q - x_s)}{\epsilon\delta} \\ C &= \frac{x_s^2 + q(2f + 1)}{\epsilon\delta} > 0\end{aligned}$$

From Routh-Hurwitz criterion  $(x_s, y_s, z_s)$  is locally stable if and only if  $A > 0, B > 0, C > 0$  and  $AB > C$ . To find a positively invariant box  $\Omega = \{(x, y, z) : x_1 \leq x \leq x_2, y_1 \leq y \leq y_2, z_1 \leq z \leq z_2\}$  enclosing  $(x_s, y_s, z_s)$ , we need to verify

$$\vec{n} \cdot \frac{d\vec{r}}{dt} < 0 \quad \text{on} \quad S = \partial\Omega$$

where  $\vec{r}$  is the vector field of (3.45) and  $\vec{n}$  is the unit outward normal vector. On the plane  $x = x_1, \vec{n} = (-1, 0, 0)$ ,

$$\vec{n} \cdot \frac{d\vec{r}}{dt} = -\frac{dx}{dt} \Big|_{x=x_1} < 0 \implies qy - xy + x - x^2 \Big|_{x=x_1} > 0.$$

Since  $0 < q \ll 1$ , we assume  $x_1 = O(q)$  then  $y(q - x_1) + x_1 - x_1^2 \approx y(q - x_1) + x_1 > 0$  for all  $y_1 \leq y \leq y_2$ .

So we choose  $x_1 = q < x_s$ , then

$$\vec{n} \cdot \frac{d\vec{r}}{dt} \Big|_{x=x_1=q} = -\frac{q(1-q)}{\epsilon} < 0 \quad \text{if} \quad q < 1.$$

On  $x = x_2, \vec{n} = \vec{i} = (1, 0, 0)$

$$\vec{n} \cdot \frac{d\vec{r}}{dt} \Big|_{x=x_2} = \frac{dx}{dt} \Big|_{x=x_2} < 0 \implies [y(q - x) + x - x^2]_{x=x_2} < 0$$

Choose  $x_2 = 1$ , then  $x_1 = q < x_s < x_2 = 1$  and

$$\vec{n} \cdot \frac{d\vec{r}}{dt} \Big|_{x=1} = y(q-1) < 0 \quad \text{for all } y_1 \leq y \leq y_2.$$

Consider the planes  $z = z_1$  and  $z = z_2$  where  $z_1 < z_s < z_2$ . On  $z = z_1$ ,  $\vec{n} = -\vec{k} = (0, 0, -1)$ ,

$$\vec{n} \cdot \frac{d\vec{r}}{dt} \Big|_{z=z_1} = -\frac{dz}{dt} \Big|_{z=z_1} = -(x - z_1) < 0$$

we choose  $z_1 = q$ . On  $z = z_2$ ,  $\vec{n} = \vec{k} = (0, 0, 1)$ ,

$$\vec{n} \cdot \frac{d\vec{r}}{dt} \Big|_{z=z_2} < 0 \implies (x - z_2) < 0 \quad x_1 \leq x \leq x_2.$$

we choose  $z_2 = 1$ . Finally consider the planes  $y = y_1$  and  $y = y_2$ ,  $y_1 < y_s < y_2$ .

On  $y = y_1$ ,  $\vec{n} = -\vec{j} = (0, -1, 0)$ , then

$$\vec{n} \cdot \frac{d\vec{r}}{dt} = [y(q+x) - 2fz]_{y=y_1} < 0$$

or

$$y_1 < \frac{2fz}{q+x} \quad \text{for all } q \leq x \leq 1, q \leq z \leq 1.$$

We choose  $y_1 = \frac{2fq}{q+1}$ . When  $y = y_2$ ,  $\vec{n} = \vec{j}$ , we need

$$\vec{j} \cdot \frac{d\vec{r}}{dt} \Big|_{y=y_2} < 0 \implies 2fz - y(q+x) \Big|_{y=y_2} < 0$$

or

$$y_2 > \frac{2fz}{q+x} \quad \text{for } q \leq x \leq 1, q \leq z \leq 1.$$

Take

$$y_2 = \frac{2f}{2q} = \frac{f}{q}$$

Hence  $\Omega = \left\{ (x, y, z) : q < x < 1, \frac{2fq}{1+q} < y < \frac{f}{q}, q < z < 1 \right\}$  is positively invariant.

Hastings and Murray (1975) have given a rigorous proof tracing the trajectory from a compact region in  $\Omega$  into itself and using Brouwer fixed point theorem to show the existence of limit cycle. The proof was rather complicated. Here we present another proof. The Jacobian matrix of the vector field at a point  $(x, y, z)$  is given by

$$J = \begin{pmatrix} \frac{1-y-2x}{\epsilon} & \frac{q-x}{\delta} & 0 \\ -y/\delta & -\frac{x+q}{\delta} & \frac{2f}{\delta} \\ 1 & 0 & -1 \end{pmatrix} \quad (3.46)$$

The signs of entries of matrix  $J$  is

$$\begin{pmatrix} * & - & 0 \\ - & * & + \\ + & 0 & * \end{pmatrix}$$

Consider the come  $K_m = \{(x, y, z) \in R^3 : x \geq 0, y \geq 0, z \geq 0\}$ .

Let  $P = \text{diag}(1, 1, -1)$  and  $\begin{pmatrix} \bar{x} \\ \bar{y} \\ \bar{z} \end{pmatrix} = P \begin{pmatrix} x \\ y \\ z \end{pmatrix}$ , i.e.,  $\bar{x} = x, \bar{y} = y, \bar{z} = -z$ .

Then the system (3.46) is converted into a competitive system on  $K_m$ :

$$\begin{aligned} \epsilon \bar{x}' &= q\bar{y} - \bar{x}\bar{y} + \bar{x}(1 - \bar{x}) = f_1(\bar{x}, \bar{y}, \bar{z}), \\ \delta \bar{y}' &= -q\bar{y} - \bar{x}\bar{y} - 2f\bar{z} = f_2(\bar{x}, \bar{y}, \bar{z}), \\ \bar{z}' &= -(\bar{x} + \bar{z}) = f_3(\bar{x}, \bar{y}, \bar{z}). \end{aligned} \tag{3.47}$$

We note that on  $K_m$ ,  $\frac{\partial f_1}{\partial \bar{y}} = q - \bar{x} < 0$ ,  $\frac{\partial f_1}{\partial \bar{z}} = 0$ ,  $\frac{\partial f_2}{\partial \bar{x}} = -\bar{y} < 0$ ,  $\frac{\partial f_2}{\partial \bar{z}} = -2f < 0$ ,  $\frac{\partial f_3}{\partial \bar{x}} = -\delta < 0$ ,  $\frac{\partial f_3}{\partial \bar{z}} = 0$ . The positive equilibrium  $E_s = (x_s, y_s, z_s)$  of (3.46) is either asymptotically stable or unstable. Since the determinant  $J$  at  $E_s$  is

$$\det(J) = C = \frac{x_s^2 + q(2f + 1)}{\epsilon\delta} > 0$$

,  $E_s$  have one-dimensional stable manifold  $\Gamma$  provided  $E_s$  is unstable.

From the Poincaré-Bendixson Theorem for 3-dimensional competitive system, we have the following theorem.

**Theorem 3.1:** *Suppose  $E_s$  is hyperbolic and unstable for (3.46). Then the stable manifold  $\Gamma$  of  $E_s$ , is one dimensional. For any  $P \in \Gamma$ , the  $\omega$ -limit set  $\omega(P)$  is a non-trivial periodic orbit in  $\Omega$ .*





# Chapter 4

## Nerve Conduction

In this chapter we shall derive the famous Hodgkin-Huxley model (1952) for which they were awarded the Nobel Prize in physiology and medicine in 1963. Hodgkin-Huxley model is too complicated to do mathematical analysis, people instead study the FitzHugh-Nagumo equations and their variants which extracts the essential behavior of the Hodgkin-Huxley fast-slow phase-plane and presents it in a simplified form.

### 4.1 Electrical Circuit model of the cell membrane

We may view the cell membrane as a capacitor for its separating charge. The capacitance  $C_m$  is defined as

$$C_m = \frac{Q}{V} \quad (4.1)$$

where  $Q$  is the charge across the capacitor and  $V$  is the voltage potential necessary to hold that charge. From standard electrostatics (Coulomb's law), one can derive the fact that for two parallel conducting plates separated by an insulator of thickness  $d$ , the capacitance is

$$C_m = \frac{k\epsilon_0}{d} \quad (4.2)$$

where  $k$  is the dielectric constant for the insulator and  $\epsilon_0$  is the permittivity of free space. For membrane  $C_m \approx 1.0\mu F/cm^2$ ,  $\epsilon_0 = (10^{-9}/(36\pi)) F/m$ , hence it follows that  $k \approx 8.5$ .

A simple electric circuit model of cell membrane is shown in Fig.4.1

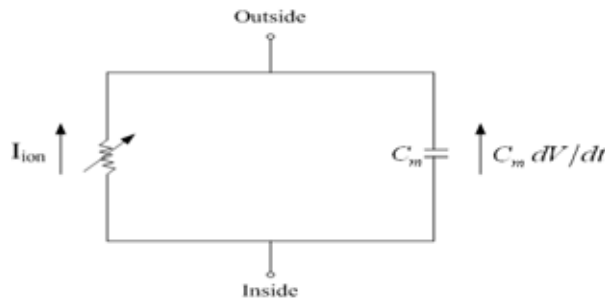


Fig.4.1 Electrical circuit model of the cell membrane.

It is assumed that the membrane acts like a capacitor in parallel with a resistor. Since the current  $I$  is defined as  $\frac{dq}{dt}$ , from (4.1) the capacitive current is  $C_m \frac{dV}{dt}$ .

There can be no net buildup of charge on either side of the membrane, the sum of the ionic and capacitive currents must be zero and so

$$C_m \frac{dV}{dt} + I_{ion}(V, t) = 0 \quad (4.3)$$

Where  $V = V_i - V_e$ ,  $V_i$  and  $V_e$  are internal and external potential of the membrane respectively.

Potential difference across the cell membrane causes ionic currents to flow through channels in the cell membrane. Regulation of this membrane potential by control of ionic channels is the most important for cellular functions. Many cells, such as neurons and muscle cells, use the membrane potential as a signal and thus the operation of the nervous system and muscle contraction are both dependent on the generation and propagation of electrical signal.

To understand electrical signaling in cells, it is helpful (and not too inaccurate) to divide all cell types into two groups: excitable cells and nonexcitable cells. Many cells maintain a stable equilibrium potential. For some, if currents are applied to the cell for a short period of time, the potential returns directly to its equilibrium value after the applied current is removed. Such cells are called nonexcitable, typical examples of which are the epithelial cells that line the walls of the gut. Photoreceptors are also nonexcitable, although in their case, membrane potential plays an extremely important signaling role nonetheless.

However, there are cells for which, if the applied current is sufficiently strong, the membrane potential goes through a large excursion, called an *action potential*, before eventually returning to rest. Such cells are called *excitable*. Excitable cells include cardiac cells, smooth and skeletal muscle cells, secretory cells, and most neurons. The most obvious advantage of excitability is that an excitable cell either responds in full to a stimulus or not at all, and thus a stimulus of sufficient amplitude may be reliably distinguished from background noise. In this way, noise is filtered out, and a signal is reliably transmitted.

There are many examples of excitability that occur in nature. A simple example of an excitable system is a household match. The chemical components of the match head are stable to small fluctuations in temperature, but a sufficiently large temperature fluctuation, caused, for example, by friction between the head and a rough surface, triggers the abrupt oxidation of these chemicals with a dramatic release of heat and light. The fuse of a stick of dynamite is a one dimensional continuous version of an excitable medium, and a field of dry grass is its two-dimensional version. Both of these spatially extended systems admit the possibility of wave propagation. The field of grass has one additional feature that the match and dynamite fuse fail to have, and that is recovery. While it is not very rapid by physiological standards, given a few months of growth, a burned-over field of grass will regrow enough fuel so that another fire may spread across it.

Although the generation and propagation of signals have been extensively studied by physiologists for at least the past 100 years, the most important landmark in these studies is the work of Allan Hodgkin and Andrew Huxley, who developed the first quantitative model of the propagation of an electrical signal along a squid giant axon (deemed "giant" because of the size of the axon, *not* the size of the squid). Their model was originally used to explain the action potential in the long giant axon of a squid nerve cell, but the ideas have since been extended and applied to a wide variety of excitable cells. Hodgkin-Huxley theory is remarkable, not only for its influence on electrophysiology, but also for its influence, after some filtering,

on applied mathematics. FitzHugh (in particular) showed how the essentials of the excitable process could be distilled into a simpler model upon which mathematical analysis could make some progress, Because this simplified model turned out to be of such great theoretical interest, it contributed enormously to the formation of a new field of applied mathematics, the study of excitable systems, a field that continues to stimulate a vast amount of research.

Because of the central importance of cellular electrical activity in physiology, because of the importance of the Hodgkin-Huxley model in the study of electrical activity, and because it forms the basis for the study of excitability, it is no exaggeration to say that the Hodgkin-Huxley model is the most important model in all of the physiological literature.

Hodgkin and Huxley developed the first quantitative model of the propagation of an electrical signal along a squid giant axon. In the squid giant axon, as in many neural cells, the principal ionic currents are the sodium ( $Na^+$ ) current and the potassium ( $K^+$ ) current. Although there are other ionic currents, like the chloride current ( $cl^-$ ),  $H-H$  theory assume they are small and lumped together into a current called the leakage current. Equation (4.3) becomes

$$C_m \frac{dV}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{app}. \quad (4.4)$$

where

$$g_{Na} = \frac{I_{Na}}{V - V_{Na}} \quad (\text{Compare with}) \quad R = \frac{V}{I},$$

$g_{Na} = \frac{1}{R}$  is the membrane conductance with respect to ionic flow  $Na^+$ . Similarly for  $g_K$  and  $g_L$ . We may rewrite (4.4) as

$$C_m \frac{dV}{dt} = -g_{eff}(V - V_{eq}) + I_{app}$$

where  $g_{eff} = g_{Na} + g_K + g_L$ ,  $V_{eq} = (g_{Na}V_{Na} + g_KV_K + g_LV_L) / g_{eff}$ ,  $V_{eq}$  is the membrane resting potential and is a balance between the reversal potentials for three ionic currents. In fact, at rest, sodium and leakage conductance are small compared to potassium conductance, so that the resting potential is closed to potassium equilibrium potential.

Next we want to find the conductance  $g_{Na}$  and  $g_K$  as a function of voltage  $V$  and time  $t$ . Hodgkin and Huxley used the voltage clamp to measure the transient transmembrane current. In Fig.4.2, they found that when the voltage was stepped up and held fixed at a high level, the total ionic current was initial inward, but at later time an outward current developed. They argue that the initial inward current is carried almost entirely by  $Na^+$  ions, while the outward current that develops latter is carried largely by  $K^+$  ions. Let's denote the  $Na^+$  currents for two cases of normal extra cellular  $Na^+$  and zero extracellular  $Na^+$  by  $I'_{Na}$  and  $I^2_{Na}$  respectively ( $I_{Na} = I'_{Na} + I^2_{Na}$  and

$$I'_{Na} / I^2_{Na} \equiv K \equiv \text{constant}.$$

Since  $I_{ion} = I_{Na} + I_K$ ,  $I'_K = I^2_K$ , it follows that  $I'_{ion} - I'_{Na} = I^2_{ion} - I^2_{Na}$  ( $I'_K = I^2_K$ ) and thus

$$I'_{Na} = \frac{K}{K-1}(I'_{ion} - I^2_{ion})$$

$$\left( I'_{ion} - I^2_{ion} = I'_{Na} - I^2_{Na} = I'_{Na} - \frac{1}{K}I'_{Na} = \frac{K-1}{K}I'_{Na} \right)$$

and

$$I'_K = \frac{I'_{ion} - KI_{ion}^2}{1 - K}$$

$$\begin{aligned} I'_K &= I'_{ion} - I'_{Na} = I'_{ion} - \frac{K}{K-1} (I'_{ion} - I_{ion}^2) \\ &= \frac{KI_{ion}^2 - I'_{ion}}{K-1}. \end{aligned}$$

Hence given measurements of the total ionic currents in two cases, and given the ratio  $K$  of the  $Na^+$  currents, it is possible to determine the complete time courses of both the  $Na^+$  and  $K^+$  currents. Finally we obtain the conductance

$$g_{Na} = \frac{I_{Na}}{V - V_{Na}}, \quad g_K = \frac{I_K}{V - V_K}$$

Samples of Hodgkin and Huxley's data are shown in Fig.4.3. The plots show ionic conductances as a function of time following a step increase or decrease in membrane potential.

From the experimental data, it is reasonable to expect  $g_K$  obeys some differential equation

$$\frac{dg_K}{dt} = f(\nu, t)$$

where  $\nu = V - V_{eq}$ . However, for  $g_K$  to have the required sigmoidal increase and exponential decrease. Hodgkin and Huxley wrote

$$g_K = \bar{g}_K n^4 \tag{4.5}$$

for some constant  $\bar{g}_K$ . The variable  $n$  obeys

$$\tau_n(\nu) \frac{dn}{dt} = n_\infty(\nu) - n \tag{4.6}$$

for some functions  $\tau_n(\nu)$  and  $n_\infty(\nu)$  must be determined from the experimental data. (4.6) can be written in the form

$$\frac{dn}{dt} = \alpha_n \nu (1 - n) - \beta_n(\nu) n \quad (4.7)$$

where

$$n_\infty(\nu) = \frac{\alpha_n(\nu)}{\alpha_n(\nu) + \beta_n(\nu)},$$

$$\tau_n(\nu) = \frac{1}{\alpha_n(\nu) + \beta_n(\nu)}.$$

Solve (4.6) with  $n(0) = 0$ , we have

$$n(t) = n_\infty(\nu_0) \left[ 1 - \exp\left(\frac{-t}{\tau_n(\nu_0)}\right) \right] \quad (4.8)$$

which satisfies  $\lim_{t \rightarrow \infty} n(t) = n_\infty(\nu_0)$ .

To match the data of  $g_K$  which has sigmoidal increase and exponential decrease. In response to a step decrease in  $\nu$  from  $\nu_0$  to 0 say, the solution for  $n$  is

$$n(t) = n_\infty(\nu_0) \exp\left(\frac{-t}{\tau_n(\nu_0)}\right) \quad (4.9)$$

Now we describe how the function  $n_\infty$  and  $\tau_n$  are determined from experimental data. For any given voltage step, the time constant  $\tau_n$ ,  $n$  can be determined by fitting (4.8) (Fig.4.4) to the experimental data. By this procedure one can determine  $\tau_n$  and  $n_\infty$  at a discrete set of  $\nu$ , those values used in experiments.

The sodium conductance

Hodgkin and Huxley proposed that the sodium conductance is of the form

$$g_{Na}(\nu) = g_{\bar{Na}} m^3 h$$

and they fit the time-dependent behavior of  $m$  and  $h$  to exponentials with dynamics

$$\frac{dw}{dt} = \alpha_w(1 - w) - \beta_w w$$

where  $w = m$  or  $h$ .

Because  $m$  is small at rest and increases, it is called to sodium activation, and because  $h$  shut down or inactivates, the sodium current, it is called sodium inactivation. As we did in data fitting for  $g_K$ , we fit the data in Fig.4.3c to determine the unknown function  $\alpha_w(V)$  and  $\beta_w(V)$ ,  $w = m$  or  $h$ .

### Summary of the equations

In summary, the Hodgkin-Huxley equations for the space clamped axon are

$$C_m \frac{d\nu}{dt} = -\bar{g}_K n^4 (\nu - \nu_K) - g_{\bar{Na}} m^3 h (\nu - \nu_{Na}) - \bar{g}_L (\nu - \nu_L) + I_{app}, \quad (4.10)$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m, \quad (4.11)$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n, \quad (4.12)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h. \quad (4.13)$$

The specific functions  $\alpha$  and  $\beta$  proposed by Hodgkin and Huxley were, in units of  $(ms)^{-1}$ ,

$$\alpha_m = 0.1 \frac{25 - \nu}{\exp\left(\frac{25 - \nu}{10}\right) - 1}, \quad (4.14)$$

$$\beta_m = 4 \exp\left(\frac{-\nu}{18}\right), \quad (4.15)$$

$$\alpha_h = 0.07 \exp\left(\frac{-\nu}{20}\right), \quad (4.16)$$

$$\beta_h = \frac{1}{\exp\left(\frac{30 - \nu}{10}\right) + 1}, \quad (4.17)$$

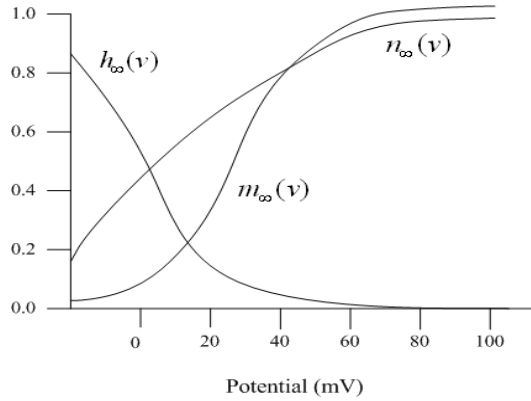
$$\alpha_n = 0.01 \frac{10 - \nu}{\exp\left(\frac{10 - \nu}{10}\right) - 1}, \quad (4.18)$$

$$\beta_n = 0.125 \exp\left(\frac{-\nu}{80}\right). \quad (4.19)$$

For these expressions, the potential  $\nu$  is the deviation from rest ( $V = V_{eq} + \nu$ ), measured in units of  $mV$ , current density is in units of  $/cm^2$ , conductances are in units of  $mS/cm^2$ , and capacitance is in units of  $/cm^2$ . The remaining constants are

$$g_{\bar{N}a} = 120, \quad g_{\bar{K}} = 36, \quad g_{\bar{L}} = 0.3, \quad (4.20)$$

with (adjusted) equilibrium potentials  $\nu_{Na} = 115$ ,  $\nu_K = -12$  and  $\nu_L = 10.6$ . In Fig.4.5 are shown the steady-state functions, and the time constants are shown in Fig.4.6.



**Fig.4.5** Steady-state functions  $m_{\infty}(\nu)$ ,  $n_{\infty}(\nu)$  and  $h_{\infty}(\nu)$

#### FitzHugh-Nagumo equation

In 1960, Nagumo, a Japanese electrical engineering, built the following circuit (See Fig.4.6) using a tunnel diode as a nonlinear element

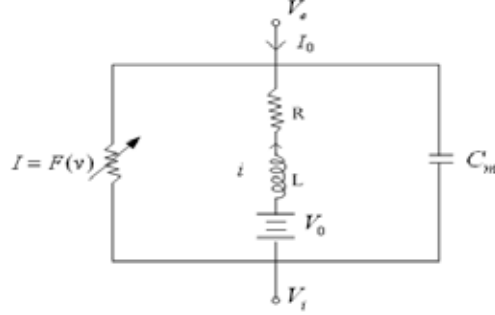


Fig.4.6

where  $I_0$  is an applied external current,  $i = i(\tau)$  the current through the resistor with resistance  $R$  and inductor with inductance  $L$ ,  $V = V_i - V_e$  is the membrane potential,  $\tau$  is the dimensional time.

Let the function  $F(V)$  be of the "cubic" shape having three zeros of which the smallest  $V = 0$  and the largest  $V = V_1 > 0$  are stable state of the differential equation  $\frac{dV}{d\tau} = -F(V)$ , by Kirchoff's law we have the following equations

$$C_m \frac{dV}{d\tau} + F(v) + i(\tau) + I_0 = 0 \quad (\text{current})$$

$$L \frac{di}{dt} + R_i = V - V_0 \quad (\text{potential})$$

Introduce the following scaling:

$$R_1 = \frac{1}{F'(0)} > 0, \quad v = \frac{V}{V_1}, \quad W = \frac{R_1 i}{V_1},$$

$$t = \frac{R_1}{L} \tau \quad \text{and} \quad f(v) = \frac{-R_1}{V_1} F(v V_1)$$

then we have

$$\begin{cases} \epsilon \frac{dv}{dt} = f(v) - W - W_0 \\ \frac{dW}{dt} = v - rW - v_0 \end{cases}$$

where  $0 < \epsilon = \frac{R_1^2 C_m}{L} \ll 1$ ,  $W_0 = \frac{R_1 I_0}{V_1}$ ,  $v_0 = \frac{V_0}{V_1}$  and  $r = \frac{R}{R_1}$ .

If  $f(v) = Av(v - \alpha)(1 - v)$ ,  $0 < v < 1$  then above system gives the FitzHugh-Nagumo model. Another form of  $f(v)$  given by Mckean (1970) is

$$f(v) = H(v - \alpha) - v = \begin{cases} 1 - v, & v > \alpha \\ -v, & v < \alpha. \end{cases}$$

An important variant of FitzHugh-Nagumo equation is the Van-der Pol equation

$$\begin{cases} C_m \frac{dv}{d\tau} + F(v) + i = -I_0 \\ L \frac{di}{d\tau} + R_i = V - V_0 \end{cases}$$

If  $R = 0$  then  $\frac{di}{d\tau} = \frac{V}{L} - \frac{V_0}{L}$  and it follows that

$$C_m \frac{d^2 v}{d\tau^2} + F'(v) \frac{dv}{d\tau} + \frac{di}{d\tau} = 0$$

or

$$C_m \frac{d^2v}{d\tau^2} + F'(v) \frac{dv}{d\tau} + \frac{v}{L} = \frac{V_0}{L}$$

Set  $F(v) = A \left( \frac{v^3}{3} - v \right)$  and from the rescaling, we obtain Van der Pol equation

$$v'' + a(v^2 - 1)v' + v = 0$$



## Chapter 5

# Reaction diffusion equations

### 5.1 Simple random walk and derivation of the diffusion equation

Consider one-dimensional random walk. Suppose a particle moves randomly back and forward along a line in a fixed step  $\Delta x$  that are taken in a fixed time  $\Delta t$ . Let  $p(m, n)$  be the probability that a particle reaches a point  $m$  space steps to the right (i.e.  $x = m\Delta x$ ) after  $n$  time steps (i.e. after a time  $n\Delta t$ ), where  $n \in \mathbb{Z}^+$  and  $-n \leq m \leq n$ . Let us suppose that to reach  $m\Delta x$  it has moved  $a$  steps to the right and  $b$  to the left. Then

$$m = a - b, \quad a + b = n$$

Then  $a = \frac{n+m}{2}$ ,  $b = n - a$ .

The number of possible paths that a particle can reach this point  $x = m\Delta x$  is

$$\frac{n!}{a!b!} = \frac{n!}{a!(n-a)!} \equiv C_a^n$$

The total number of possible  $n$ -step paths is  $2^n$  and so the probability  $p(m, n)$  is

$$p(m, n) = \frac{1}{2^n} \frac{n!}{a!(n-a)!}, \quad a = \frac{n+m}{2}$$

$n + m$  is even.

Note that from binomial theorem

$$\sum_{m=-n}^n p(m, n) = \sum_{a=0}^n C_a^n \left(\frac{1}{2}\right)^{n-a} \left(\frac{1}{2}\right)^a = 1$$

$p(m, n)$  is the binomial distribution.

From Stirling's formula

$$n! \sim (2\pi n)^{\frac{1}{2}} n^n e^{-n}, \quad \text{as } n \rightarrow \infty,$$

$$p(m, n) \sim \left[\frac{2}{\pi n}\right]^{\frac{1}{2}} \exp\left[-\frac{m^2}{2n}\right], \quad m \gg 1, \quad n \gg 1. \quad (\text{Exercises})$$

Set

$$m\Delta x = x, \quad n\Delta t = t$$

with  $x, t$  fixed and  $m \rightarrow \infty$ ,  $n \rightarrow \infty$ ,  $\Delta x \rightarrow 0$ ,  $\Delta t \rightarrow 0$ . Then  $p(m, n) \rightarrow 0$  as  $m, n \rightarrow \infty$  and it is not the quantity of interest. Let  $u = \frac{p}{2\Delta x}$ . Then  $u2\Delta x$  is the

probability of find a particle in the interval  $(x, x + \Delta x)$  at time  $t$ . With  $m = \frac{x}{\Delta x}$ ,  $n = \frac{t}{\Delta t}$ ,

$$u = \frac{p\left(\frac{x}{\Delta x}, \frac{t}{\Delta t}\right)}{2\Delta x} \left[ \frac{\Delta t}{(2\pi \cdot t \cdot |\Delta x|^2)} \right]^{\frac{1}{2}} \exp\left[ \frac{x^2 \Delta t}{2t(\Delta x)^2} \right].$$

If we assume

$$\lim_{\substack{\Delta x \rightarrow 0 \\ \Delta t \rightarrow 0}} \frac{(\Delta x)^2}{2\Delta t} \rightarrow D$$

then

$$u(x, t) = \lim_{\substack{\Delta x \rightarrow 0 \\ \Delta t \rightarrow 0}} \frac{p\left(\frac{x}{\Delta x}, \frac{t}{\Delta t}\right)}{2\Delta x} = \left(\frac{1}{4\pi Dt}\right)^{\frac{1}{2}} \exp\left(-\frac{x^2}{4Dt}\right). \quad (5.1)$$

$D$  is the diffusion coefficient. It is a measure of how effectively the particles disperse from a high to a low density. For example in blood, haemoglobin molecules has diffusion coefficient of order  $10^{-7} \text{cm}^2/\text{sec}$  while for oxygen in blood is of order of  $10^{-5} \text{cm}^2/\text{sec}$ .

Now we consider the classical approach to diffusion, namely, Fickian diffusion. Let  $J$  be the flux of material (cells, chemical etc). Then  $J$  is proportional to the gradient of the concentration of the materials. That is

$$J \propto -\frac{\partial c}{\partial x} \quad \text{or} \quad J = -D \frac{\partial c}{\partial x}$$

where  $c(x, t)$  is the concentration of the species and  $D$  is the diffusivity. The minus sign indicates the diffusion transports matter from a high to a low concentration. Consider a small region  $x_0 < x < x_1 = x_0 + \Delta x$ . Then

$$\frac{\partial}{\partial t} \int_{x_0}^{x_1} c(x, t) dx = J(x_0, t) - J(x_1, t).$$

If  $\Delta x \rightarrow 0$  then we obtain

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = \frac{\partial \left(D \frac{\partial c}{\partial x}\right)}{\partial x}.$$

If  $D$  is a constant then

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (5.2)$$

Let  $c(x, 0) = Q\delta(x)$  then the solution of PDE

$$c(x, t) = \frac{Q}{2(\pi Dt)^{\frac{1}{2}}} e^{-\frac{x^2}{4Dt}}$$

If  $Q = 1$  then we obtain the same result as (5.1) from a random walk.

Now we relate the random walk to the diffusion equation (5.2). Let  $p(x, t)$  be the probability that a particle released at  $x = 0$  at  $t = 0$  reach  $x$  in time  $t$ . At time  $t - \Delta t$  the particle was at  $x - \Delta x$  or  $x + \Delta x$ . Thus if  $\alpha$  and  $\beta$  are the probability that a particle will move to the right or left

$$\begin{aligned} p(x, t) &= \alpha p(x - \Delta x, t - \Delta t) + \beta p(x + \Delta x, t - \Delta t) \\ \alpha + \beta &= 1 \end{aligned}$$

If  $\alpha = \beta = \frac{1}{2}$  i.e. the random walk is isotropic (no bias) then Taylor expansion at  $(x, t)$  yields

$$\frac{\partial p}{\partial t} = \frac{(\Delta x)^2}{2\Delta t} \frac{\partial^2 p}{\partial x^2} + \left(\frac{\Delta t}{2}\right) \frac{\partial^2 p}{\partial t^2} + \dots$$

Now let  $\Delta x \rightarrow 0$  and  $\Delta t \rightarrow 0$  s.t

$$\lim_{\substack{\Delta x \rightarrow 0 \\ \Delta t \rightarrow 0}} \frac{(\Delta x)^2}{2\Delta t} = D$$

we get

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2}$$

## 5.2 Reaction diffusion equations

Consider diffusion in three space dimensions. Let  $S$  be an arbitrary surface enclosing a volume  $V$ . Then we have rate of change of amount in  $V$  equals to rate of flow of material across  $S$  into  $V$  plus the material created in  $V$ .

$$\frac{\partial}{\partial t} \int_V c(x, t) dV = - \int_S J \cdot ds + \int_V f \cdot dV$$

By divergence Theorem

$$\int_V \left[ \frac{\partial c}{\partial t} + D \cdot J - f(c, x, t) \right] dv = 0.$$

Since  $V$  is arbitrary, we obtain the reaction diffusion equation

$$\frac{\partial c}{\partial t} + \nabla \cdot J = f(c, x, t) \quad (5.3)$$

Now  $J = -D\nabla c$  then (5.3) becomes

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + f \quad (5.4)$$

The system of reaction-diffusion equation is

$$\frac{\partial \vec{u}}{\partial t} = \vec{f} + \nabla \cdot (D\nabla \vec{u})$$

where  $D$  is a matrix of diffusives and  $u(x, t) \in R^k$ .

## 5.3 Chemotaxis

A large number of insects and animals rely on an acute sense of smell for conveying information between members of the species. Chemicals which are involved in this process are called *pheromones*. For example, the female silk moth *Bombyx mori* exudes a pheromone, called bombykol, as a sex attractant for the male, which has a remarkably efficient antenna filter to measure the bombykol concentration, and it moves in the direction of increasing concentration. The modelling problem here is a fascinating and formidable one (Murray 1977). The acute sense of smell of many

deep sea fish is particularly important for communication and predation. Other than for territorial demarcation the simplest important exploitation of pheromone release is the directed movement it can generate in the population. Here we model this chemically directed movement, that is *chemotaxis*, which, unlike diffusion, directs the motion *up* a concentration gradient.

It is not only in animal and insect ecology that chemotaxis is important. It can be equally crucial in biological processes where there are numerous examples. For example when a bacterial infection invades the body it may be attacked by movement of cells towards the source as a result of chemotaxis. Convincing evidence suggests that leukocyte cells in the blood move towards a region of bacterial inflammation, to counter it, by moving up a chemical gradient caused by the infection (see, for example, Lauffenburger and Keller 1979, Tranquillo and Lauffenburger 1986, 1988, Alt and Lauffenburger 1987).

A widely studied chemotactic phenomenon is that exhibited by the slime mold *Dictyostelium discoideum* where single-cell amoebae move towards regions of relatively high concentrations of a chemical called cyclic-AMP which is produced by the amoebae themselves. Interesting wave-like movement and spatial patterning are observed experimentally. A discussion of the phenomenon and some of the mathematical models which have been proposed together with some analysis are given, for example, in the book by Segel (1984). The kinetics involved have been modelled by several authors. As more was found out about the biological system the models changed. Recently new, more complex and more biologically realistic models have been proposed by Martiel and Goldbeter (1987) and Monk and Othmer (1989). Both of these new models exhibit oscillatory behaviour.

Let us suppose that the presence of a gradient in an attractant,  $a(x, t)$ , gives rise to a movement, of the cells say, up the gradient. The flux of cells will increase with the number of cells,  $n(x, t)$ , present. Thus we may reasonably take as the chemotactic flux

$$\mathbf{J} = n\chi(a)\nabla a, \quad (5.5)$$

where  $\chi(a)$  is a function of the attractant concentration. In the general conservation equation for  $n(x, t)$ , namely

$$\frac{\partial n}{\partial t} + \nabla \cdot \mathbf{J} = f(n),$$

where  $f(n)$  represents the growth term for the cells, the flux

$$\mathbf{J} = \mathbf{J}_{\text{diffusion}} + \mathbf{J}_{\text{chemotaxis}}$$

where the diffusion contribution is from (5.4) with the chemotaxis flux from (5.5). Thus the *reaction (or population) diffusion-chemotaxis equation* is

$$\frac{\partial n}{\partial t} = f(n) - \nabla \cdot n\chi(a)\nabla a + \nabla \cdot D\nabla n. \quad (5.6)$$

where  $D$  is the diffusion coefficient of the cells.

Since the attractant  $a(x, t)$  is a chemical it also diffuses and is produced, by the amoebae for example, so we need a further equation for  $a(x, t)$ . Typically

$$\frac{\partial a}{\partial t} = g(a, n) + \nabla \cdot D_a \nabla a, \quad (5.7)$$

where  $D_a$  is the diffusion coefficient of  $a$  and  $g(a, n)$  is the kinetics/source term, which may depend on  $n$  and  $a$ . Normally we would expect  $D_a > D$ . If several

species or cell types all respond to the attractant the governing equation for the species vector is an obvious generalization of (9.28) to a vector form with  $\chi(a)$  probably different for each species.

In the slime mold model of Keller and Segel (1971),  $g(a, n) = hn - ka$  where  $h, k$  are positive constants. Here  $hn$  represents the spontaneous production of the attractant and is proportional to the number of amoebae  $n$ , while  $-ka$  represents decay of attractant activity: that is there is an exponential decay if the attractant is not produced by the cells.

One simple version of the model has  $f(n) = 0$ : that is the amoebae production rate is negligible. This is the case during pattern formation phase in the mold's life cycle. The chemotactic term  $\chi(a)$  is taken to be a positive constant  $\chi_0$ . The form of this term in any case is speculative. With constant diffusion coefficients, together with the above linear form for  $g(a, n)$ , the model in one space dimension becomes the nonlinear system

$$\begin{aligned}\frac{\partial n}{\partial t} &= D \frac{\partial^2 n}{\partial x^2} - \chi_0 \frac{\partial}{\partial x} \left( \frac{\partial a}{\partial x} \right), \\ \frac{\partial a}{\partial t} &= hn - ka + D_a \frac{\partial^2 a}{\partial x^2}\end{aligned}\tag{5.8}$$

Other forms have been proposed for the chemotactic factor  $\chi(a)$ . For example

$$\chi(a) = \frac{\chi_0}{a}, \quad \chi(a) = \frac{\chi_0 K}{(K + a)^2}, \quad \chi_0 > 0, \quad K > 0\tag{5.9}$$

which are known respectively as the log law and receptor law. In there, as  $a$  decreases the chemotactic effect increases.



# Appendix A

Let  $m = (m_1, m_2, \dots, m_n)$  where  $m_i \in \{0, 1\}$  and

$$K_m = \{x \in R^n : (-1)^{m_i} x_i \geq 0, 1 \leq i \leq n\}.$$

$K_m$  is a cone in  $R^n$  and it generates a partial order  $\leq_m$  defined by  $x \leq_m y$  if and only if  $y - x \in K_m$ . Equivalently  $x_i \leq y_i$  for those  $i$  for which  $m_i = 0$  and  $y_i \leq x_i$  for those  $i$  for which  $m_i = 1$ . Let  $P$  be the diagonal matrix defined by  $P = \text{diag}((-1)^{m_1}, \dots, (-1)^{m_n})$ . Obviously  $P = P^{-1}$  and  $x \leq_m y$  if and only if  $Px \leq Py$ . The domain  $D$  is said to be  $P_m$ -convex if  $tx + (1-t)y \in D$  whenever  $x, y \in D$ ,  $0 < t < 1$  and  $x \leq_m y$ . We say  $x' = f(x)$  is cooperative with respect to  $K_m$  provided  $D$  is  $P_m$ -convex and

$$(-1)^{m_i+m_j} \frac{\partial f_i}{\partial x_j}(x) \geq 0, \quad i \neq j, x \in D. \quad (\text{A.1})$$

It is competitive with respect to  $K_m$  if

$$(-1)^{m_i+m_j} \frac{\partial f_i}{\partial x_j}(x) \leq 0, \quad i \neq j, x \in D. \quad (\text{A.2})$$

**Proposition A.1:** *Let  $D$  be  $P_m$ -convex and  $f$  is continuously differentiable vector field on  $D$  such that (A.1) holds. If  $x \leq_m y$ ,  $t > 0$  and the flow  $\varphi_t(x)$  and  $\varphi_t(y)$  are defined, then  $\varphi_t(x) \leq_m \varphi_t(y)$ . If (A.2) holds then similar conclusions are valid for  $t > 0$ .*

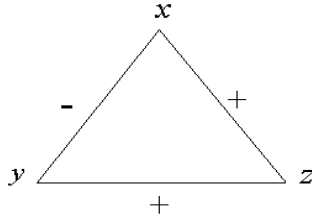
**Proof:** Let  $g(y) = Pf(Py)$ ,  $y \in PD$ . Then vector field  $g$  generates a flow  $\psi_t$  defined by  $\psi_t(y) = P\varphi_t(Py)$ . Since  $g_i(y) = (-1)^{m_i} f_i(Py)$ ,  $\frac{\partial g_i}{\partial y_j}(y) = (-1)^{m_i+m_j} \frac{\partial f_i}{\partial x_j}(Py) \geq 0$  by (A.1). If  $x \leq_m y$ , it follows that  $Px \geq Py$  then by Prop 1.1[],  $\psi_t(Px) \leq \psi_t(Py)$ . This implies  $\varphi_t(x) \leq_m \varphi_t(y)$  as asserted. The other assertions follows similarly.

Proposition A.1 suggests an algorithm for determining whether a given system  $x' = f(x)$  is cooperative or competitive in a domain  $D$  with respect to one of the cones  $K_m$ . First we check the off-diagonal elements of the Jacobian matrix are sign-stable in  $D$ . This means that each  $i \neq j$  either (a)  $\frac{\partial f_i}{\partial x_j}(x) \geq 0$  for all  $x \in D$  or (b)  $\frac{\partial f_i}{\partial x_j}(x) \leq 0$  for all  $x \in D$ . Assuming this test is passed, then the Jacobian matrix must be tested for sign-symmetry:  $\frac{\partial f_i}{\partial x_j}(x) \frac{\partial f_j}{\partial x_i}(y) \geq 0$  for all  $x \neq j, x, y \in D$ . If this test is satisfied, then for each  $i < j$  set  $s_{ij} = 0$  if  $\frac{\partial f_i}{\partial x_j}(x) + \frac{\partial f_j}{\partial x_i}(x) > 0$  for some  $x \in D$ .  $s_{ij} = 1$  if  $\frac{\partial f_i}{\partial x_j}(x) + \frac{\partial f_j}{\partial x_i}(x) < 0$  for some  $x \in D$ . Now consider the system of  $n(n-1)/2$

$$m_i + m_j = s_{ij} \pmod{2}, \quad i < j$$

Solve  $m$  and we find the cone  $K_m$ . Consider the graph  $G$  with vertices  $\{1, 2, \dots, n\}$  where an undirected edge connects vertices  $i$  and  $j$  if  $\frac{\partial f_i}{\partial x_j}(x)$  or  $\frac{\partial f_j}{\partial x_i}(x)$  does not vanish identically in  $D$ . Attach a sign  $+$  or  $-$  to the edge. Then  $x' = f(x)$  is cooperative in  $D$  with respect some cone  $K_m$  if and only if every closed loop in  $G$  the number of edges with  $-$  signs is even. It is competitive if every loop in  $G$  has an odd number of edges with  $-$  signs.

For system (3.45), from (3.46), the graph is



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Consider FN model (3.45)

$$\begin{aligned}\epsilon \frac{dx}{dt} &= qy - xy + x(1 - x) \\ \delta \frac{dy}{dt} &= -qy - xy + 2fz \\ \frac{dz}{dt} &= x - z\end{aligned}\tag{3.45}$$

with dimensionless parameters given by (3.44). Note that  $\epsilon \ll \delta$  and we set  $\epsilon \frac{dx}{dt} \approx 0$ . This gives

$$x = x(y) = \frac{(1 - y) + [(1 - y)^2 + 4qy]^{\frac{1}{2}}}{2}\tag{A.3}$$

Then (3.45) is reduced to

$$\begin{aligned}\delta \frac{dy}{dt} &= 2fz - y[x(y) + q] \\ \frac{dz}{dt} &= x(y) - z\end{aligned}\tag{A.4}$$

From (3.48) with  $q \ll 1$ , the  $z$ -nullcline of (3.49) is

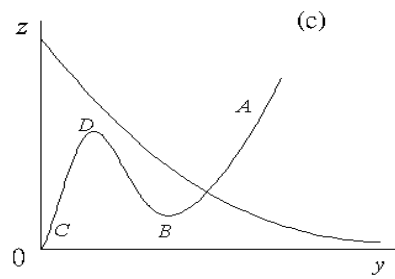
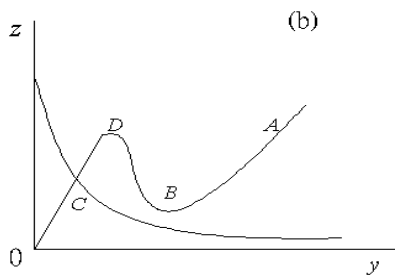
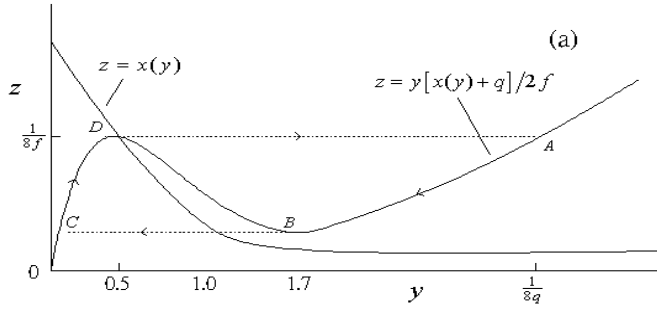
$$z = x(y) \approx \begin{cases} 1 - y & \text{for } q \ll 1 - y \leq 1 \\ \frac{qy}{y-1} & \text{for } q \ll y - 1. \end{cases}\tag{A.5}$$

Then  $y$ -nullcline is

$$z = \frac{y[x(y) + q]}{2f} \approx \begin{cases} \frac{y(1-y)}{2f} & \text{for } q \ll 1 - y \ll 1 \\ \frac{y[\frac{qy}{y-1} + q]}{2f} & q \ll y - 1 \\ \frac{qy}{f} & y \gg 1 \end{cases}\tag{A.6}$$

Then we have the following figures of relaxation oscillation.







# Bibliography

- [C] K. S. Cheng: Uniqueness of limit cycle of a predator-prey system, SIAM J. Math. Analysis (1981).
- [Co] Coppel: Stability and Asymptotic Behavior of Differential Equations, Heath, Boston 1965.
- [H] J. Hale: Functional Differential Equations.
- [H1] J. Hale: Ordinary differential equations.
- [HH1] S. B. Hsu and T. W. Hwang: Global stability for a class of Predator-Prey System, SIAM J. Appl. Math, 1995 p.763-783.
- [HH2] S. B. Hsu and T. W. Hwang: Uniqueness of limit cycles for a predator-prey system of Holling and Lesile type, Canadian Applied Math. Quarterly (1998) Vol.6, No.2, p.91-117.
- [HHK] S. B. Hsu, T. W. Hwang, Y. Kuang: Global Analysis of the Michaelis-Menten type ratio-dependence predator-prey system, J. Math. Biology, 42(2001) 489-506.
- [HHW] Hsu Hubbell Waltman: Competing of predators, SIAM J. Appl. Math. (1978) p.617-625.
- [Hirsch 1] Hirsch: Systems of differential equations which are competitive or cooperative I. limit sets, SIAM J. Appl. Math(1982) 167-179.
- [Hirsch 2] Hirsch: Systems of differential equations which are competitive or cooperative III. Competing species, Nonlinearity (1988) 51-71.
- [Hsu] S. B. Hsu: Limiting behavior of competing species, SIAM J. Applied Math. 1978, p.760-763.
- [M] ] J. Murray: Mathematical Biology.
- [MG] Mackey and Glass: Oscillations and chaos in physiological control systems, Science 197, 287-289(1977).
- [R] Rosenzweig: Paradox of enrichment: destabilization of exploitation systems in ecological time, Science 171 (1969) p.385.
- [S] H. Smith: Monotone Dynamical System.