2020 Summer School Lecture Notes
Dynamical and Quantitative Biology

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Contents

Chapter 1

Introduction

1.1 Dynamic vs. Informatic Approach to Modeling in Biology

1.1.1 Bioinformatics is data-driven

The goal of bioinformatics is "finding certain signatures" in the data. In the old time, when the data is very reproducible, e.g., planet motions, one simply looks for a mathematical function to "fit the data". In biology, almost all data are with significant variations. In this case, one tries to find a "statistical model" to fit the data: sample mean, standard deviation, linear regrssions, clustering, etc.

1.1.2 Dynamics is the logic of rational thinking

A physical approach to a system means "dynamical", and a mathematical approach to a process means quantitative. Hence the title. It embidies a very old Chinese saying: "qian yin hou guo", *e.g.,* a causal relation.

1.2 A Collection of Familiar Terms with More Precise Meanings

There is no doubt we all agree that "mathematics" is a tool. But it is a language as well; this is widely appreciated. But actually, it is also a *culture*. One does not hear this last point often; but actually it is a core of *Theoretial Physics*. *Applied Mathematics* is mainly about models of the real world, but theoretical physics provide representations of the Reality. In the theoretical physics thinking, one can understand the real world via purely mathematical deduction.

Let us give some examples: In high school, we did "bullet out of a gun".

More importantly, theoretical physics provided a *computational framework* that is not based on data; but based on mechanisms! This mode of operator is very different from "modeling". In the latter, its success is ultimately measured by fitting the reality. The theoretical physics approach is intimately related to the so called *mechanistic modeling*. Let us explain their relationship:

Equation of motion, which can be further divided into *kinematics* and *dynamics*, and constitutive equations; also called material property. Here are three examples.

1.2.1 Mechanis (lixue)

Since mechanics is the oldest paradigm for doing a mechanistic modeling, and it was the birth place of differential equations, we shall carry out a careful analysis of "what is mechanics".

The concept of point masses; instantaneous velocity and acceleration, forces, etc. The concept of point mass is actually very abstract. It does not even have a size. Note that

$$ma = \frac{\mathrm{d}^2 x}{\mathrm{d}t^2} = F,$$

is actually completely useless, if one does not have F as a function of x.

Let us recall that the accleration of a point mass on earth is $g = 9.8m/s^2$, a constant. Then

$$\begin{aligned}
&\frac{\mathrm{d}^2 x(t)}{\mathrm{d}t^2} = g, \\
&v(t) = \frac{\mathrm{d}x(t)}{\mathrm{d}t} = gt + v(0), \\
&x(t) = \frac{1}{2} g t^2 + v(0)t + x(0).
\end{aligned}$$

The significance of this? The concept of the "center of mass". Furthermore, in believing this paradigm, solid mechanics, fluid mechanics, and molecular dynamics of a protein. These are in fact the vast fields of several engineering.

1.2.2 Biochemistry (shenwu huaxue)

Chemical reaction can be expressed as

$$X \underset{J_{-1}}{\overset{J_{+1}}{\rightleftharpoons}} Y,$$

which is called reversible unimolecular reaction(s), or conformational change. It means that X and Y are isomers. The differenece is in the arrangement of the atoms within. And

$$A + B \underset{J_{-2}}{\overset{J_{+2}}{\rightleftharpoons}} C,$$

is call molecular association and dissociation. If A is a protein and B is a small molecule, it is also called binding.

In terms of the concepts of concentration and *instantaneous rate* of a reaction R, we have

$$-\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \frac{\mathrm{d}y(t)}{\mathrm{d}t} = J_{+1} - J_{-1},$$

and

$$-\frac{\mathrm{d}a(t)}{\mathrm{d}t} = -\frac{\mathrm{d}b(t)}{\mathrm{d}t} = \frac{\mathrm{d}c(t)}{\mathrm{d}t} = J_{+2} - J_{-2},$$

respectively. This equation is basd on counting; it cannot be wrong! But it is also useless, just as $F = ma$! To be useful, one needs to have J's as functions of the concentrations. One widely used is the *law of mass action*, which states that the instantaneous rate of a chemical reaction is proportional to the product of the masses of the reactants. See the equation below Eq. 1.12. The proportinal constant is called a *rate constant*, usually written as lower case ks:

$$X \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} Y, \quad A + B \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} C,$$

with

$$J_{+1}(x) = k_{+1}x,\ J_{-1}(y) = k_{-1}y, \quad J_{+2}(a,b) = k_{+2}ab,\ J_{-2}(c) = k_{-2}c.$$

We then have two of differential equations for the unimolecular reaction

$$-\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \frac{\mathrm{d}y(t)}{\mathrm{d}t} = k_{+1}x - k_{-1}y, \tag{1.1}$$

and for the association-dissociation reaction

$$-\frac{\mathrm{d}a(t)}{\mathrm{d}t} = -\frac{\mathrm{d}b(t)}{\mathrm{d}t} = \frac{\mathrm{d}c(t)}{\mathrm{d}t} = k_{+2}a(t)b(t) - k_{-2}c(t). \tag{1.2}$$

1.2.3 Detailed mathematical analysis of Eq. 1.1

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= k_{+1}x - k_{-1}\big(x_0 + y_0 - x\big) \\ &= -k_{-1}(x_0 + y_0) + \big(k_{+1} + k_{-1}\big)x.\end{aligned}$$

Therefore,

$$x^* = \frac{k_{-1}}{k_{+1} + k_{-1}}\Big(x_0 + y_0\Big).$$

$$y^* = x_0 + y_0 - x^* = \frac{k_{+1}}{k_{+1} + k_{-1}}\Big(x_0 + y_0\Big)$$

$$\boxed{x(t) = (x_0 - x^*)e^{-(k_{+1}+k_{-1})t} + x^*}$$

$$\boxed{y(t) = (y_0 - y^*)e^{-(k_{+1}+k_{-1})t} + y^*}$$

1.2.4 Detailed mathematical analysis of Eq. 1.2

$$\frac{c^*}{a^* b^*} = \frac{k_{+2}}{k_{-2}} \equiv K_a \equiv \frac{1}{K_d}.$$

$$\frac{c^*}{(a_0 - c^*)(b_0 - c^*)} = K_a.$$

$$\boxed{\left(c^*\right)^2 - \left(a_0 + b_0 + K_a^{-1}\right) c^* + a_0 b_0 = 0.}$$

1.2.5 Infectious disease epidemics (chuanranbing liuxing xue)

$$S + I \underset{R_{-1}}{\overset{R_{+1}}{\rightleftharpoons}} 2I, \quad I \xrightarrow{R_2} R.$$

1.3 Four Different Types of Mathematical Models

With all the above discussions in mind, we see that there are two types of modeling, *mechanistic* and *informatics*, and using two types of mathematics: *deterministic* and *stochastic*. $2 \times 2 = 4$. Mechanistic model is also called dynamics model, kinetic model, differential equation based model, etc.

1.4 Dynamic Models

Experimental biology follows a reductionistic approach in which modular, functional mechanisms are elucidated one piece at a time. But life is a complex phenomenon at every level, from cells to organisms, to populations, due to interactions among multiple, heterogeneous components. Therefore, in all area of biology, mathematical models provide the means for putting the pieces together.

Dynamic models describe how a system's properties, in a simplified representation, change over time. Dynamic models have a unique role in science: It is the only method that is able to definitively provide a *sufficient condition* for an observed phenomenon or phenomena. In modern biology, this is called a *mechanism*. It establishes a causal relation with certainty.

There are two types of models: "data-driven" descriptive models and mechanistic models. One of the best known data-driven descriptive models is perhaps Kepler's three laws of planetary motion. Most current statistical models obtained from "big data" belong to this category. Even when these models can provide accurate predictions, it does not tell us why the data behave the way they are — a fundamental element of what we call "understanding". In contrast, a mechanistic model

A dynamic model has two essential components: *state variables* and *dynamic equations*. One should visualize a dynamics as a "point" $\vec{x} = (x_1, x_2, \cdots, x_n)$ moving in a n-dimensional space as a function of time. One of the most important assumptions in a dynamic model is that the state of the system at time $t + \Delta t$ is completely determined by the state of the system at time t: $\vec{x}(t) \to \vec{x}(t + \Delta t)$.

A significant portion of the equations in biology are simply "counting the numbers", or density. This is discussed in the textbook as "Bathtub models", or I would like to call it "balance checkbooks":

$$\frac{dW(t)}{dt} = I(t) - O(t),$$

where $W(t)$ is the amount of water in the bathtub, $I(t)$ and $O(t)$ are the inflow and outflow rates, e.g., the amount of water going into and coming out the bathtub *per unit time*. In the

banking language: $W(t)$ is the amount of money in the account, $I(t)$ is the rate of deposite, and $O(t)$ is the rate of expanse.

1.5 Simple Models with a Few Equations

One important application of mathematical modeling is in population dynamics. This can be about populations of biological organisms, chemical species inside a test tube, or sociological and economical agents. As long as one has the notion of different "individuals", there is the concept of a "population".

Just as the bathtub problem, population dynamics usually starts with an equation like this:

$$\text{rate of population increase} = \text{birth rate} - \text{death rate} + \text{immigration rate}. \tag{1.3}$$

If we use $x(t)$ to denote the population at time t, then the above equation becomes

$$\frac{dx}{dt} = x\Big(b(x) - d(x)\Big) + i(x), \tag{1.4}$$

in which b and d are the *per capita* birth and death rates, respectively. Note that one of the most important aspects of birth and death is that if $x = 0$, then there will be no possibility of further birth or death. Without immigration, an extinct population will remain extinct. The immigration term $i(x)$, however, has a very different feature: It needs not to be zero when $x = 0$.

Consider a population with many subpopulations $\vec{x} = (x_1, x_2, \cdots, x_n)$, all $x_i \geq 0$. In the absence of immigration, if we denote $r_i(\vec{x}) = b_i(\vec{x}) - d(\vec{x})$, then

$$\frac{dx_i}{dt} = x_i r_i(\vec{x}), \tag{1.5}$$

and the per capita growth rate for the entire population, which is also the mean per capita growth rate,

$$\overline{r} = \frac{\dfrac{d}{dt}\displaystyle\sum_{i=1}^{n} x_i}{\displaystyle\sum_{i=1}^{n} x_i} = \frac{\displaystyle\sum_{i=1}^{n} \frac{dx_i}{dt}}{\displaystyle\sum_{i=1}^{n} x_i} = \frac{\displaystyle\sum_{i=1}^{n} x_i(t) r_i}{\displaystyle\sum_{i=1}^{n} x_i(t)}, \quad x_i \geq 0. \tag{1.6}$$

Then,

$$\frac{d\overline{r}(\vec{x})}{dt} = \left[\frac{\sum_{i=1}^{n} x_i r_i^2}{\sum_{i=1}^{n} x_i} - \left(\frac{\sum_{i=1}^{n} x_i r_i}{\sum_{i=1}^{n} x_i}\right)^2\right] + \frac{\sum_{i,j=1}^{n} x_i x_j r_j \left(\frac{\partial r_i}{\partial x_j}\right)}{\sum_{i=1}^{n} x_i}. \tag{1.7}$$

We shall particularly be interested in the case of $r_i(\vec{x}) = r_i$: All per capita growth rates are constants independent of $\vec{x}$. Then the term inside $[\cdots]$ on the right-hand-side is never negative:

$$\frac{\sum_{i=1}^{n} x_i r_i^2}{\sum_{i=1}^{n} x_i} - \left(\frac{\sum_{i=1}^{n} x_i r_i}{\sum_{i=1}^{n} x_i}\right)^2 = \frac{\sum_{i=1}^{n} x_i \Big(r_i - \overline{r}\Big)^2}{\sum_{i=1}^{n} x_i} \geq 0. \tag{1.8}$$

In fact, it is actually the variance of r_i among the different subpopulations. Therefore, it is always positive if there are variations amoug r_i. This mathematical result is a part of the ideas of both Adam Smith, on economics, and Charles Darwin, on the natural selection. In fact, the term $[\cdots]$ in Eq. (1.7) has been identified by R. A. Fisher, the British statistician and evolutionary biologist, as the "growth of fitness due to natural selection".[1] And here is a quote from Smith's *magnum opus* "An Inquiry into the Nature and Causes of the Wealth of Nations" (1776):

> "As every individual, therefore, endeavours as much as he can both to employ his capital in the support of domestic industry, and so to direct that industry that its produce may be of the greatest value; every individual necessarily labours to render the annual revenue of the society as great as he can. He generally, indeed, neither intends to promote the public interest, nor knows how much he is promoting it. By preferring the support of domestic to that of foreign industry, he intends only his own security; and by directing that industry in such a manner as its produce may be of the greatest value, he intends only his own gain, and he is in this, as in many other eases, led by an invisible hand to promote an end which was no part of his intention. Nor is it always the worse for the society that it was no part of it. By pursuing his own interest he frequently promotes that of the society more effectually than when he really intends to promote it. I have never known much good done by those who affected to trade for the public good. It is an affectation, indeed, not very common among merchants, and very few words need be employed in dissuading them from it."

With non-constant $r_i(\vec{x})$, Eq. 1.7 can be written as:

$$\boxed{\frac{d}{dt}\left(\frac{\sum_{i=1}^n x_i r_i}{\sum_{i=1}^n x_i}\right) - \frac{\sum_{i=1}^n x_i \frac{dr_i(\vec{x})}{dt}}{\sum_{i=1}^n x_i} = \frac{\sum_{i=1}^n x_i \Big(r_i - \overline{r}\Big)^2}{\sum_{i=1}^n x_i}}\,. \tag{1.9}$$

This equation can be phrased as "the change in the per capita growth rate of an entire population is never less than the average change in per capita growth rate of the subpopulations".[2] Eq. 1.7 also shows that $d\overline{r}/dt$ could be negative if the last term on the right-hand-side is large and negative. Therefore, it is interesting to investigate under what circumstances it is positive or negative.

First, we note that if all r_i are constant, independent of $\vec{x}$, then this last term is zero since $\big(\partial r_i/\partial x_j\big) = 0$.

Second, if r_i is a linear function of $\vec{x}$: $r_i(\vec{x}) = \sum_{k=1}^n w_{ik}x_k$. Furthermore, one can always decompose a matrix into a symmetric and an anti-symmetric parts: $w_{ij} = w_{ij}^S + w_{ij}^A$.

[1] Edwards, A.W.F (1994) The fundamental theorem of natural selection. *Biol. Rev.* 69, 443–474.

[2] Price, G.R. (1972) Fishers fundamental theorem made clear. *Ann. Hum. Genet. Lond.* 36, 129–140.

Then

$$\begin{aligned}
\frac{\sum_{i,j=1}^n x_i x_j r_j \left(\frac{\partial r_i}{\partial x_j}\right)}{\sum_{i=1}^n x_i} &= \frac{\sum_{i,j,k=1}^n x_i w_{ij} x_j w_{jk} x_k}{\sum_{i=1}^n x_i} \\
&= \frac{\sum_{i,j,k=1}^n x_i w_{ij}^S x_j w_{jk}^S x_k}{\sum_{i=1}^n x_i} + \frac{\sum_{i,j,k=1}^n x_i w_{ij}^A x_j w_{jk}^A x_k}{\sum_{i=1}^n x_i} \\
&= \frac{\sum_{j=1}^n x_j \Big(\sum_{i=1}^n x_i w_{ij}^S\Big)^2}{\sum_{i=1}^n x_i} - \frac{\sum_{j=1}^n x_j \Big(\sum_{i=1}^n x_i w_{ij}^A\Big)^2}{\sum_{i=1}^n x_i}. \qquad (1.10)
\end{aligned}$$

Hence, a symmtric interaction between subpopulations i and j increases the $\overline{r}$, and an anti-symmetric interaction between subpopulations i and j decreases the $\overline{r}$. Competition and symbiosis are the former type, and predator and prey are the latter type.

1.6 Complex Dynamics Such as a Single Protein in Water

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http://www.youtube.com/watch?v=iaHHgEoa2c8
http://www.youtube.com/watch?v=gFcp2Xpd29I
http://www.youtube.com/watch?v=Y79Xl0LfYI4
```

1.7 Michaelis-Menten Enzyme Kinetics

$$S + E \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} SE \xrightarrow{k_2} P + E \qquad (1.11)$$

The *law of mass action* from chemical reaction theory states that a chemcial reaction like

$$n_1 X_1 + n_2 X_2 + \cdots n_\nu X_\nu \xrightarrow{k} m_1 Y_1 + m_2 Y_2 + \cdots m_\mu X_\mu \qquad (1.12)$$

has a rate *constant* k, and the rate of reaction J, e.g., number of chemical reaction (1.12) per unit time:

$$J = k x_1^{n_1} x_2^{n_2} \cdots x_\nu^{n_\nu},$$

where x_k is the concentration of chemical species X_k among the reactants. Then

$$\frac{dx_k}{dt} = -n_k J,\ k = 1, 2, \cdots, \nu;$$

and

$$\frac{dy_k}{dt} = m_k J,\ k = 1, 2, \cdots, \mu,$$

where y_k is the concentration of chemical species Y_k among the products.

Applying the law of mass action to Eq. (1.11), we have

$$\frac{ds}{dt} = k_{-1}c - k_1 es, \tag{1.13a}$$

$$\frac{de}{dt} = (k_{-1} + k_2)c - k_1 es, \tag{1.13b}$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2)c, \tag{1.13c}$$

$$\frac{dp}{dt} = k_2 c. \tag{1.13d}$$

The initial conditions are

$$s(0) = s_0,\ e(0) = e_0,\ c(0) = p(0) = 0. \tag{1.13e}$$

We observe that $\frac{dc}{dt} + \frac{de}{dt} = 0$ and $\frac{ds}{dt} + \frac{dc}{dt} + \frac{dp}{dt} = 0$. This can be understood by going through the biochemical reaction "mechanism" and recognize that the total enzyme e_0 and total substrates s_0 are conserved. Substituting equations

$$c + e = e_0,\ \ s + c + p = s_0$$

into Eq. (1.13), and eliminating e and p, we have

$$\frac{ds}{dt} = k_{-1}c - k_1 e_0 s + k_1 cs, \tag{1.14a}$$

$$\frac{dc}{dt} = k_1 e_0 s - k_1 cs - (k_{-1} + k_2)c \tag{1.14b}$$

$$s(0) = s_0,\ c(0) = 0. \tag{1.14c}$$

Steady-state approximation:

$$\frac{dc}{dt} = 0,$$

$$k_1 e_0 s - k_1 cs - (k_{-1} + k_2)c = 0,$$

$$c = \frac{k_1 e_0 s}{k_1 s + (k_{-1} + k_2)} = \frac{e_0 s}{s + K_M} \tag{1.15}$$

where $K_M = \frac{k_{-1}+k_2}{k_1}$. Therefore,

$$\begin{aligned} \frac{\mathrm{d}s}{\mathrm{d}t} &= k_{-1}c - k_1 e_0 s + k_1 cs \\ &= \left[\frac{k_{-1} + k_1 s}{s + K_M} - k_1\right] e_0 s \\ &= \left[\frac{k_{-1} + k_1 s - k_1 s - K_M k_1}{s + K_M}\right] e_0 s \\ &= -\frac{V_{max} s}{s + K_M}, \end{aligned} \tag{1.16}$$

in which $V_{max} = k_2 e_0$.

Non-dimensionalization. The two equations in (1.18) are not yet ready to be analyzed computationally. Note that since a computation has to have all the parameters in the equations assigned with numerical values, explore the general behavior of a system differential equations involves many calculations for differet parameter values. Thus the fewer the parameter, the better. The system (1.18) seems to have four parameters: k_1, k_{-1}, k_2, e_0, and s_0. But actually, it has less.

Note that the one does not have to use the standard unit, such as molar, for the concentrations s and c, nor standard unit for time, such as second, for t. Rather, one can try to use some "internal units". First, we note that k_{-1} must have "dimension" of [time]$^{-1}$ since $k_{-1}c \sim \frac{ds}{dt}$ which is [concentration][time]$^{-1}$. Similarly, k_1 has a dimension of [concentration]$^{-1}$[time]$^{-1}$, thus $k_1 e_0$ has a dimension of [time]$^{-1}$. Now let us introduce "non-dimensionalized variables"

$$u = \frac{s}{s_0}, v = \frac{c}{e_0}, \text{ and } \tau = k_1 e_0 t \tag{1.17}$$

Then, (1.18) becomes

$$\begin{aligned} \frac{du}{d\tau} &= \left(\frac{k_{-1}}{k_1 s_0}\right) v - u + uv, && \text{(1.18a)} \\ \left(\frac{e_0}{s_0}\right)\frac{dv}{d\tau} &= u - uv - \left(\frac{k_{-1}+k_2}{k_1 s_0}\right) v, && \text{(1.18b)} \\ & u(0) = 1,\ v(0) = 0. && \text{(1.18c)} \end{aligned}$$

in which combined parameters $e_0/s_0 = \epsilon$, $k_2/(k_1 s_0) = \lambda$ and $(k_{-1} + k_2)/(k_1 s_0) = K$ are all dimensionless. We finally arrive at

$$\begin{aligned} \frac{du}{d\tau} &= -u + (u + K - \lambda)v, && \text{(1.19a)} \\ \epsilon\frac{dv}{d\tau} &= u - \big(u + K\big)v, && \text{(1.19b)} \\ & u(0) = 1,\ v(0) = 0. && \text{(1.19c)} \end{aligned}$$

It has only three parameters!

One of the important features of enzyme reaction systems inside a cell is that $e_0 \ll s_0$. That is $\epsilon \ll 1$.

Chapter 2

Radioactive decay and exponential random time

2.1 Random variables, probability density function, etc.

A random variable X taking a real value has a probability density function (pdf) $f_X(x)$:

$$\int_{-\infty}^{\infty} f_X(x)dx = 1. \tag{2.1}$$

The meaning of the $f_X(x)$ is this

$$\Pr\{x < X \leq x + \mathrm{d}x\} = f_X(x)\mathrm{d}x. \tag{2.2}$$

Then, the cumulative distribution of X:

$$F_X(x) = \Pr\{X \leq x\} = \int_{-\infty}^{x} f_X(z)dz, \text{ and } f_X(x) = \frac{dF_X(x)}{dx}. \tag{2.3}$$

The mean (or expected value) and variance of X are

$$\langle X \rangle = E[X] = \int_{-\infty}^{\infty} x f_X(x)dx, \tag{2.4}$$

$$\mathrm{Var}[X] = \int_{-\infty}^{\infty} \big(x - \mu\big)^2 f_X(x)dx. \tag{2.5}$$

in which we have denoted $E[X]$ by μ. Two most important examples of random variables taking real values are "exponential" and "normal", also called Gaussian.

Learn to use `rnorm( )`, `rexp( )`, `hist( )`, and `nls(log(hdata[,2]) ~ a-b*hdata[,1]^2, s` in which `hdata` contains the density function obtained from `hist`.

The pdf of a function of a random variable X. Let us have a random variable X with pdf $f_X(x)$. Now consider a differentiable, monotonic increasing function $g(\cdot)$ and let $Y = g(X)$. So Y is also a random variable. What is the distribution of Y? We note that

$$\Pr\{Y < y\} = \Pr\{X < g^{-1}(y)\}, \text{ i.e., } F_Y(y) = F_X\Big[g^{-1}(y)\Big]. \tag{2.6}$$

Therefore,

$$f_Y(y) = \frac{d}{dy}\Pr\big\{Y < y\big\} = \frac{d}{dy}\int_{-\infty}^{g^{-1}(y)} f_X(x)dx = f_X\Big(g^{-1}(y)\Big)\frac{d}{dy}\Big(g^{-1}(y)\Big). \tag{2.7}$$

Eq. (2.7) should be remembered as

$$f_Y(y)dy = f_X(x)dx, \text{ in which } x = g^{-1}(y) \text{ or } y = g(x). \tag{2.8}$$

There is a clear graphical interpretation of the formulae (2.6) and (2.8).

2.2 Exponential distribution

The simplest linear ordinary differential equation

$$\frac{dx}{dt} = -rx \tag{2.9}$$

is widely taught as a model for radioactive decay problem. More precisely, consider a block of radioactive material, the $x(t)$ is the remaining radioactive material at time t:

$$x(t) = x(0)e^{-rt}. \tag{2.10}$$

The parameter r is the "rate of decay" per atom.

If all the atoms in the block are identical and independent, then $x(t)$ can also be interpreted as the probability of a single atom in the population still not decayed at time t:

$$p(t) = e^{-rt}. \tag{2.11}$$

Sometime, this is called "survival probability" in the population dynamics.

However, a more careful inspection of the decays of individual atoms, one realizes that the occurrence of the "event", i.e., a click in a Geiger counter, is random. The time when an atom decay, T is a random variable with a probability density function $f_T(t)$:

$$f_T(t)dt = \Pr\{t < T \le t + dt\}, \quad (t \le 0) \tag{2.12}$$

which reads "$f_T(t)dt$ is the probability of random time T being in the interval $(t, t + dt]$. Then, at time t, the probability the atom is still no decayed, i.e., $T > t$, is the survival probability:

$$p(t) = \Pr\{T > t\} = \int_t^\infty f_T(s)ds. \tag{2.13}$$

We therefore have

$$f_T(t) = -\frac{dp(t)}{dt} = re^{-rt}. \tag{2.14}$$

The random time T has an exponential distribution. Its mean value, also called expected value, is

$$\langle T \rangle = \int_0^\infty t f_T(t) dt = \frac{1}{r}. \tag{2.15}$$

In fact, there is a variance in the random time T:

$$Var[T] = \langle T^2 \rangle - \langle T \rangle^2 = \left(\frac{1}{r}\right)^2. \tag{2.16}$$

2.3 The minimum of n identical, independent distribution

Why is the exponential distribution so prevalent in nature? To answer this question, let us consider the following problem: T_1 and T_2 are two independnet distributions for two random times T_1 and T_2. We are interested in the

$$T^* = \min\left\{T_1, T_2\right\}. \tag{2.17}$$

And we have

$$\Pr\{T^* > t\} = \Pr\{T_1 > t, T_2 > t\} = \Pr\{T_1 > t\} \Pr\{T_2 > t\}. \tag{2.18}$$

This is because the *multiplication rule* of two independent random events: The joint probability is the product of the probabilities. Therefore, if one has n identical and independently distributed random times $T_1, T_2, \cdots, T_n$, then their minimum T^* has a distribution

$$\Pr\left\{T^* > t\right\} = \Pr\{T_1 > t\} \cdots \Pr\{T_n > t\} = \Big(\varphi_T(t)\Big)^n, \tag{2.19}$$

in which $\varphi_T(t) = \Pr\{T > t\}$ is a monotonically decreasing function with $\varphi_T(0) = 1$ and $\varphi_T(\infty) = 0$. Therefore, if $\varphi_T'(0) = r \neq 0$ and n is very large, we have

$$\lim_{n\to\infty} \left[\varphi_T\left(\frac{t}{n}\right)\right]^n = \lim_{n\to\infty} \left[1 + \varphi_T'(0)\left(\frac{t}{n}\right)\right]^n = e^{-rt}. \tag{2.20}$$

Why is there a $1/n$ on the left-hand-side of Eq. (2.20)? This is because with larger and larger n, the mean time for T^* is getting smaller and smaller. In fact, it scales as $1/n$. If we had not introduced the $1/n$, the limit of $\big(\varphi_T(t)\big)^n$ would be 0 for all $t > 0$.

n exponential iid. In statistics, "iid" stands for "identical and independently distributed". If we consider n idential, independent atoms, each with an exponential waiting time e^{-rt}, then the time for the first decay, $T^* = \min\{T_i, 1 \leq i \leq n\}$ follows the distribution

$$\Pr\{T^* > t\} = \Pr\{T_1 > t, \cdots, T_n > t\} = \Big(\Pr\{T > t\}\Big)^n = e^{-nrt}. \tag{2.21}$$

Note we have used the fact that all T_i are independent. Therefore, the rate for one decay from n atoms is nr.

Exponential time is memoryless. Two measurements of T, one starts at $t = 0$, another starts at $t = t_0$, will give identical result:

$$\frac{\Pr\{T > t_0 + t\}}{\Pr\{T > t_0\}} = \frac{e^{-r(t_0+t)}}{e^{-rt_0}} = e^{-rt}. \tag{2.22}$$

2.4 Dynamics of a decreasing population

We can now re-interpret the equation in (2.9):

$$dp(t) = -rp(t)dt. \tag{2.23}$$

In an infinitesimal time interval $(t, t + dt]$, the change in the survival probability of a single atom is $rp(t)dt$.

Now consider a population of identical, independently distributed (iid) atoms. Let $p_n(t)$ be the probability of having n radioactive atoms. There are two events that change the $p_n(t)$:

> (a) A decay of one of $n + 1$ radioactive atoms. This increases $p_n(t)$ while decreases $p_{n+1}(t)$; the rate is $(n + 1)r$.
>
> (b) A decay of one of n radioactive atoms. This decreases $p_n(t)$ while increases $pn - 1(t)$. The rate is nr.

Therefore, considering each event can ocurr in the infinitesimal time interval $(t, t + dt]$, we have

$$dp_n(t) = (n + 1)rp_{n+1}(t)dt - nrp_n(t)dt. \tag{2.24}$$

We now consider a population with N total individuals at $t = 0$. The individuals are identical and independent, with individual "death rate", i.e., death rate per capita, r.

To characterize the dynamics of population, $X(t)$, X takes values $0, 1, 2, \cdots, N$, one no longer can say that at time t, the $X(t)$ is such and such. However, one can predict at time t, the *probabilitity of* $X(t) = n$:

$$p_n(t) = \Pr\{X(t) = n\}. \tag{2.25}$$

The $p_n(t)$ satisfies the system of differential equations

$$\frac{d}{dt}p_n(t) = r(n + 1)p_{n+1}(t) - rnp_n(t). \tag{2.26}$$

2.5 Mean value of the population dynamics

If the population $X_n(t)$ is random with distribution $p_n(t)$, then its mean value is

$$\langle X(t)\rangle = \sum_{i=0} n \Pr\{X(t) = n\} = \sum_{i=0} np_n(t). \tag{2.27}$$

Then we have

$$\begin{aligned}
\frac{d}{dt}\langle X(t)\rangle &= \sum_{n=0} n\frac{dp_n(t)}{dt} \\
&= \sum_{n=0} n\left(r(n+1)p_{n+1}(t) - rnp_n(t)\right) \\
&= r\sum_{n=0} n(n+1)p_{n+1}(t) - r\sum_{n=0} n^2 p_n(t) \\
&= r\sum_{n=0}(n+1)^2 p_{n+1}(t) - r\sum_{n=0}(n+1)p_{n+1}(t) - r\sum_{n=0} n^2 p_n(t) \\
&= -r\sum_{n=0}(n+1)p_{n+1}(t) \\
&= -r\langle X(t)\rangle.
\end{aligned}$$

This is the true meaning of equation (2.9).

Chapter 3

Discrete-time dynamics

Not all dynamics requite a continuous counting of time. In fact, any realistic measurements of any biological phenomenon are in discrete time. We now concern ourselves with *dynamics with discrete time*. For population dynamics without immigration, these dynamics has the form

$$N_{t+1} = N_t F\big(N_t\big) = f\big(N_t\big). \tag{3.1}$$

The simplest example of such dynamics is a linear system with $F(N) =$ a constant; the best-known example of such nonlinear dynamics is the logistic growth with $F(N) = r\big(1 - N/K\big)$. Interestingly, this is not really the discrete-time counterpart of the logistic differential equation. A more faithful discrete time version of logistic differential equation is $\widetilde{F}(N) = \frac{r}{1+N/K}$.

Now if we compare such dynamics with an ordinary differential equation (ODE) $dx/dt = f(x)$, and remember that one can study the ODE in terms of its *distribution*:

$$\frac{\partial \rho(x,t)}{\partial t} = -\frac{\partial}{\partial x}\Big(f(x)\rho(x,t)\Big), \tag{3.2}$$

then one expects that there is also "another equation" for the same dynamics in Eqn. (3.1). Note that Eqn. (3.2) is a map of $\rho(x,t)$ to $\rho(x,t+dt)$, which is interpreted as distribution changing with time. Therefore, we similarly have

$$\rho(y,t+1) = \int_{-\infty}^{\infty} \rho(x,t)K(x,y)dx. \tag{3.3}$$

For each y, if $K(y,x)$ is only concentrated at one point, then we say the dynamics is "deterministic". If there is a spread, we say the dynamics is "stochastic". if for a given x to which therer are more than one y, then we say the dynamics is "many-to-one".

The most important properties of $K(x,y)$ are ≥ 0, and

$$\int_{-\infty}^{\infty} K(x,y)dy = 1 \ \ \forall x. \tag{3.4}$$

Then, for any normalized $\rho(x,t)$:

$$\int_{-\infty}^{\infty}\rho(y,t+1)dy=\int_{-\infty}^{\infty}dy\int_{-\infty}^{\infty}\rho(x,t)K(x,y)dx=\int_{-\infty}^{\infty}\rho(x,t)dx\int_{-\infty}^{\infty}K(x,y)dy$$

$$=\int_{-\infty}^{\infty}\rho(x,t)dx=1. \tag{3.5}$$

A linear dynamics is "one-to-one". The logistic map is "two-to-one", but the $\widetilde{F}(N)$ is one-to-one. A stochastic dynamics can be "one-to-many". One of the most important features of the "1-to-1" dynamics is that one knows *exactly where the dynamics is coming from and where it goes.* All other cases, there are some uncertainties, either in the past or in the future.

We want to introduce a mathmatical representation of the above idea. The mathematics is not very hard, but somewhat unfamiliar. It only involves calculus!

The idea is related to the notion of "entropy" — a very elusive concept. But don't be discouraged; very few people really understand it anyway. Maybe mathematics can help us to understand it better.

We start with Eqn. (3.3). Let us consider a functional

$$H\big[\rho(x,t)\big]=\int_{-\infty}^{\infty}\rho(x,t)\ln\left(\frac{\rho(x,t)}{\rho^*(x)}\right)dx, \tag{3.6}$$

in which we assume that

$$\rho^*(x)=\int_{-\infty}^{\infty}\rho^*(y)K(y,x)dy. \tag{3.7}$$

Note that this is called a "functional" with "al" at the end: It is a function of a function: For each function $\rho(x,t)$, Eqn. (3.6) returns a single scalar number. The $\rho^*(x)$ is considered known.

We now first show that $H\big[\rho(x,t)\big]\geq 0$ for any normalized $\rho(x,t)$, $\rho^*(x)\geq 0$:

$$\begin{aligned}
H\big[\rho(x,t)\big] &= \int_{-\infty}^{\infty}\rho(x,t)\ln\left(\frac{\rho(x,t)}{\rho^*(x)}\right)dx\\
&= -\int_{-\infty}^{\infty}\rho(x,t)\ln\left(\frac{\rho^*(x)}{\rho(x,t)}\right)dx\\
&\geq -\int_{-\infty}^{\infty}\rho(x,t)\left(\frac{\rho^*(x)}{\rho(x,t)}-1\right)dx\\
&\geq -\int_{-\infty}^{\infty}\Big(\rho^*(x)-\rho(x,t)\Big)dx\\
&\geq -\int_{-\infty}^{\infty}\rho^*(x)dx+\int_{-\infty}^{\infty}\rho(x,t)dx \;=\; 0.
\end{aligned}$$

More importantly even we don't have $\rho^*(x)$, let us consider two sequences of $\rho(x,t)$ and $\hat{\rho}(x,t)$, started respectively with normalized $\rho(x,0)$ and $\hat{\rho}(x,0)$

$$H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] = \int_{-\infty}^{\infty} \rho(x,t)\ln\left(\frac{\rho(x,t)}{\hat{\rho}(x,t)}\right)dx \;\geq\; 0. \tag{3.8}$$

Now we consider

$$\begin{aligned}
& H\Big[\rho(x,t+1)\Big\|\hat{\rho}(x,t+1)\Big] - H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] \\
= & \int_{-\infty}^{\infty} \rho(y,t+1)\ln\left(\frac{\rho(y,t+1)}{\hat{\rho}(y,t+1)}\right)dy - \int_{-\infty}^{\infty} \rho(x,t)\ln\left(\frac{\rho(x,t)}{\hat{\rho}(x,t)}\right)dx \\
= & \int_{-\infty}^{\infty} dx\;\rho(x,t)\left\{\left[\int_{-\infty}^{\infty} dy K(x,y)\ln\left(\frac{\rho(y,t+1)}{\hat{\rho}(y,t+1)}\right)\right] - \ln\left(\frac{\rho(x,t)}{\hat{\rho}(x,t)}\right)\right\} \\
= & \int_{-\infty}^{\infty} dx\;\rho(x,t)\left\{\int_{-\infty}^{\infty} dy K(x,y)\left[\ln\left(\frac{\rho(y,t+1)}{\hat{\rho}(y,t+1)}\right) - \ln\left(\frac{\rho(x,t)}{\hat{\rho}(x,t)}\right)\right]\right\} \\
= & \int_{-\infty}^{\infty} dx\;\rho(x,t)\left\{\int_{-\infty}^{\infty} dy K(x,y)\ln\left(\frac{\rho(y,t+1)\hat{\rho}(x,t)}{\hat{\rho}(y,t+1)\rho(x,t)}\right)\right\}
\end{aligned}$$

$$\begin{aligned}
\leq & \int_{-\infty}^{\infty} dx\;\rho(x,t)\left\{\int_{-\infty}^{\infty} dy K(x,y)\left(\frac{\rho(y,t+1)\hat{\rho}(x,t)}{\hat{\rho}(y,t+1)\rho(x,t)} - 1\right)\right\} \\
= & \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} \rho(x,t)K(x,y)dx\left(\frac{\rho(y,t+1)\hat{\rho}(x,t)}{\hat{\rho}(y,t+1)\rho(x,t)} - 1\right) \\
= & \int_{-\infty}^{\infty} dy\left(\frac{\rho(y,t+1)}{\hat{\rho}(y,t+1)}\right)\int_{-\infty}^{\infty} \hat{\rho}(x,t)K(x,y)dx - \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} \rho(x,t)K(x,y)dx \\
= & \int_{-\infty}^{\infty} dy\left(\frac{\rho(y,t+1)}{\hat{\rho}(y,t+1)}\right)\hat{\rho}(y,t+1) - \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} \rho(x,t)K(x,y)dx \\
= & \int_{-\infty}^{\infty} dy\;\rho(y,t+1) - \int_{-\infty}^{\infty} dy\;\rho(y,t+1) \;=\; 1-1 \;=\; 0.
\end{aligned}$$

So we have shown that

$$H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] - H\Big[\rho(x,t+1)\Big\|\hat{\rho}(x,t+1)\Big] \leq 0. \tag{3.9}$$

Now, if the dynamics is one-to-one, then one can introduce a $K^{-1}(x,y)$ such that

$$\rho(y,t) = \int_{-\infty}^{\infty} \rho(x,t+1)K^{-1}(x,y)dx. \tag{3.10}$$

Then, all the above mathematics can be repeated, and one has

$$H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] - H\Big[\rho(x,t+1)\Big\|\hat{\rho}(x,t+1)\Big] \geq 0. \tag{3.11}$$

Now combining Eqns. (3.9) and (3.11), we have

$$H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] - H\Big[\rho(x,t+1)\Big\|\hat{\rho}(x,t+1)\Big] = 0, \tag{3.12}$$

or

$$H\Big[\rho(x,t)\Big\|\hat{\rho}(x,t)\Big] = \text{const.} \tag{3.13}$$

What is the significance of this mathematical result? Especially to biological dynamics?

Chapter 4

Birth, death, and population dynamics

In ordinary differential equations, $dx/dt = rx$ with a positive r or a negative r are solved in a same manner. The negative r problem is known as radioactive decay; and a positive r is about the growth of a population and the cumulation of bank interests. In the last section, however, we have seen that the negative r problem is actually related to an exponentially distributed time. Can we also applied the same discussion above to a growing population? Is the dynamics of a popultion with death rate d_1 and birth rate b_1, $b_1 - d_1 = r$ the same as another population with b_2, d_2 and $b_2 - d_2 = r$?

Certainly, the exponential time problem, with distribution $f_T(t) = re^{-rt}$, does not make any sense if the r is negative! However, the idea of an exponential time for ***an event*** of birth rather than death, can still apply.

To have a better understanding of "births" as a sequence of birthing events with random time, let us consider the following problem.

4.1 Rare event and exponential waiting time

We consider a repeated event that ocurrs at a random time. This can be births, or deaths, or arriving at a shop, or a molecular reaction. We assume that the events follows three assumptions:

> (i) the event occurrence is homogeneous in time, with number of events per unit time being r. r is the rate of the occuring events.
>
> (ii) the occurrences of the events in disjointed intervale $[t_1, t_2]$ and $[t_2, t_3]$ are independent;
>
> (ii) in an infinitesimal time interval $[t, t + dt]$, the probability of two events occur is negligible, i.e., on the order of $o(dt)$.

These three assumptions lead to the following equation:

$$P(t + dt) = P(t)\left(1 - rdt + o(dt)\right). \tag{4.1}$$

Therefore,

$$P(t+dt) - P(t) = -rP(t)dt + o(dt), \tag{4.2}$$

taking the limit $dt \to 0$, we have

$$\frac{d}{dt}P(t) = -rP(t). \tag{4.3}$$

We note that decay of a block of radioactive material is not homogeneous in time.

4.2 General birth and death dynamics of a single population

$$0 \underset{w_1}{\overset{u_0}{\rightleftharpoons}} 1 \cdots \underset{w_{n-1}}{\overset{}{\rightleftharpoons}} n-1 \underset{w_n}{\overset{u_{n-1}}{\rightleftharpoons}} n \underset{w_{n+1}}{\overset{u_n}{\rightleftharpoons}} n+1 \overset{u_{n+1}}{\rightleftharpoons} \cdots \tag{4.4}$$

in which u_ℓ and w_ℓ are the birth and death rates with population ℓ. They are <u>not</u> rate per capita. They are the rates for increasing one individual and decrease one individual, respectively.

Let us consider the simplest case of with birth and death rates, per capita, b and d. Then one has $u_n = nb$ and $w_n = nd$. Let $X(t)$ be the population in numbers, and $p_n(t) = \Pr\{X(t) = n\}$ be the probability of having n individuals in the population at time t. Then

$$\frac{d}{dt}p_n(t) = (n-1)bp_{n-1} - (nb+nd)p_n + (n+1)dp_{n+1}, \quad (n \geq 0). \tag{4.5}$$

$$\begin{aligned}
\frac{d}{dt}\langle X(t)\rangle &= \frac{d}{dt}\left(\sum_{n=0}^{\infty} np_n(t)\right) \\
&= \sum_{n=0}^{\infty}(n-1)^2 bp_{n-1} - n^2(b+d)p_n + (n+1)^2 dp_{n+1} \\
&\quad + \sum_{n=1}^{\infty}(n-1)bp_{n-1} - \sum_{n=0}^{\infty}(n+1)dp_{n+1} \\
&= \sum_{n=1}^{\infty}(n-1)bp_{n-1} - \sum_{n=0}^{\infty}(n+1)dp_{n+1} \\
&= (b-d)\langle X(t)\rangle.
\end{aligned} \tag{4.6}$$

Indeed, the dynamics for the mean $\langle X(t)\rangle$ depends only one the difference of $b-d$. However, one can also compute the variance of $X(t)$:

$$Var[X(t)] = \langle X^2(t)\rangle - \langle X(t)\rangle^2, \tag{4.7}$$

in which

$$\langle X^2(t)\rangle = \sum_{n=0}^{\infty} n^2 p_n(t). \tag{4.8}$$

Then,

$$\begin{aligned}
\frac{d}{dt}\langle X^2(t)\rangle &= \frac{d}{dt}\sum_{n=0}^{\infty} n^2 p_n(t) \\
&= \sum_{n=0}^{\infty} b\left[n^2(n-1)p_{n-1} - n^3 p_n\right] + d\left[n^2(n+1)p_{n+1} - n^2 p_n\right] \\
&= \sum_{n=0}^{\infty} b\left[n^2(n-1)p_{n-1} - n(n+1)^2 p_n + (2n+1)np_n\right] \\
&\qquad + d\left[n^2(n+1)p_{n+1} - n(n-1)^2 p_n - (2n-1)np_n\right] \\
&= \sum_{n=0}^{\infty} \left[b(2n+1)n - d(2n-1)n\right] p_n \\
&= 2b\langle X^2(t)\rangle + b\langle X(t)\rangle - 2d\langle X^2\rangle + d\langle X(t)\rangle. \qquad (4.9)
\end{aligned}$$

$$\begin{aligned}
\frac{d}{dt}Var[X(t)] &= \frac{d}{dt}\left[\langle X^2(t)\rangle - \langle X(t)\rangle^2\right] \\
&= 2(b-d)\langle X^2(t)\rangle + (b+d)\langle X(t)\rangle - 2\langle X(t)\rangle(b-d)\langle X(t)\rangle \\
&= 2(b-d)\, Var[X(t)] + (b+d)\langle X(t)\rangle. \qquad (4.10)
\end{aligned}$$

The differential equation for $Var[X(t)]$,

$$\frac{d}{dt}Var[X(t)] = 2(b-d)Var[X(t)] + (b+d)\langle X(t)\rangle, \tag{4.11}$$

is a linear, constant coefficient, inhomogeneous, first-order ordinary differential equation. Its solution can be obtained using the procedure in Sec. 4.3. Therefore, the mean and the variance of the population $X(t)$ are

$$\langle X(t)\rangle = X_o e^{(b-d)t}, \tag{4.12}$$

$$Var[X(t)] = X_o\left(\frac{b+d}{b-d}\right)e^{(b-d)t}\left(e^{(b-d)t} - 1\right). \tag{4.13}$$

The relative variance

$$\frac{Var[X(t)]}{\langle X(t)\rangle^2} = \frac{1}{X_o}\left(\frac{b+d}{b-d}\right)\left(1 - e^{-(b-d)t}\right). \tag{4.14}$$

We see that for the same *net growth rate* $r = b - d$, larger the $b + d$, larger the variance. In a realistic population dynamics, the different rates of birth and death, b and d, matter; not just their difference $r = b - d$.

4.3 Solving a linear inhomogeneous equation

$$\frac{dx}{dt} = -rx + g(t). \tag{4.15}$$

First, one obtains the *general solution* to the homogeneous equation, $x_{ho}(t) = Ae^{-rt}$. To obtain a *paticular solution* to the inhomogeneous equation, one apply the *method of variation of parameters* by consider

$$x_{inh}(t) = A(t)e^{-rt}. \tag{4.16}$$

Substituting this into Eq. (4.15), we have

$$\begin{aligned} A'(t)e^{-rt} - rA(t)e^{-rt} &= -rA(t)e^{-rt} + g(t); \\ A'(t)e^{-rt} &= g(t); \\ A'(t) &= g(t)e^{rt}; \\ A(t) &= \int_0^t g(s)e^{rs}ds; \end{aligned}$$

Hence, the general solution to Eq. (4.15) is

$$x(t) = x_{ho}(t) + x_{inh}(t) = \left(x(0) + \int_0^t g(s)e^{rs}ds\right)e^{-rt}. \tag{4.17}$$

4.4 Time inhomogeneous dynamics with random $\xi(t)$

Let us now assume that there are complex sources contributing to the growth dynamics in Eqn. (4.15). We shall model the $g(t)$ in Eqn. (4.15) as a piecewise constant "random" function $\xi(t)$, over each short δ time interval and taking values, independently, from a distribution f_ξ with zero mean:

$$x(t) = e^{-rt}\left(x(0) + \int_0^t e^{rs}\xi(s)ds\right). \tag{4.18}$$

We have

$$\big\langle x(t)\big\rangle = x(0)e^{-rt} + e^{-rt}\int_0^t e^{rs}\big\langle\xi(s)\big\rangle ds = x(0)e^{-rt}. \tag{4.19}$$

More interestingly,

$$\begin{aligned} Var\big[x(t)\big] &= \sum_{k=1}^{t/\delta} Var[\xi] \left(\int_{(k-1)\delta}^{k\delta} e^{-rs} ds \right)^2 \\ &= Var\big[\xi\big] \sum_{k=1}^{t/\delta} \left(\frac{e^{-r(k-1)\delta} - e^{-rk\delta}}{r} \right)^2 \\ &= \left(\frac{1 - e^{-r\delta}}{r^2 \left(1 + e^{-r\delta}\right)} \right) \left(1 - e^{-2rt}\right) \; Var[\xi] \\ &\approx \left(1 - e^{-2rt}\right) Var[\xi] \begin{cases} \frac{\delta}{2r} & r\delta \ll 1 \\ \frac{1}{r^2} & r\delta \gg 1 \end{cases} \end{aligned} \tag{4.20}$$

Finally, the relative "error"

$$\frac{\sqrt{Var\big[x(t)\big]}}{\big\langle x(t) \big\rangle} = \left(\frac{1 - e^{-r\delta}}{r^2 \left(1 + e^{-r\delta}\right)} \right)^{\frac{1}{2}} \left(\frac{\sqrt{1 - e^{-2rt}}}{e^{-rt}} \right) \; \frac{\sqrt{Var[\xi]}}{x(0)}. \tag{4.21}$$

And for large time $rt \gg 1$, we have a *stationary stochastic dynamics* $x(t)$ fluctuating around $x = 0$ with variance

$$Var\Big[x^{stationary}(t)\Big] = \left(\frac{1 - e^{-r\delta}}{r^2 \left(1 + e^{-r\delta}\right)} \right) Var[\xi]. \tag{4.22}$$

Chapter 5

Population dynamics with multi-stability

5.1 Population growth with predation

We are now consider a classic problem in population dynamics: a logistic growing population encounters a predation:

$$\frac{dX}{d\tau} = \widehat{r}X\left(1 - \frac{X}{\widehat{K}}\right) - \frac{BX^2}{A^2 + X^2}. \tag{5.1}$$

It is easy to check that the parameters A and $\widehat{K}$ have the same dimensions as X, $\widehat{r}$ has dimension [time]$^{-1}$, and B has the dimension of [X][time]$^{-1}$. $\widehat{r}$ is the per capita growth rate when there is no intra-population interaction; $\widehat{K}$ is the carrying capacity; A is a measure of a threshold at which the predation becomes significant; and B is amount of predator.

Before proceeding with analyses or computations, it is almost obligatory to simplify the equation through *non-dimensionalization* with

$$x = \frac{X}{A},\ r = \frac{A\widehat{r}}{B},\ q = \frac{\widehat{K}}{A},\ t = \frac{B\tau}{A}. \tag{5.2}$$

Substituting the those in (5.2) into (5.1), we have

$$\frac{dx}{dt} = b(x) - d(x) = rx\left(1 - \frac{x}{q}\right) - \frac{x^2}{1 + x^2}. \tag{5.3}$$

Let the right-hand-side of (5.3)

$$f(x; r, q) = rx\left(1 - \frac{x}{q}\right) - \frac{x^2}{1 + x^2}.$$

The roots of $f(x)$, the function on the right-hand-side of the ordinary differential equation (5.3), is a very important quantity for the population dynamics described by an ODE: they are the steady states of the dynamical system. In other words, if a system starts exactly at a steady state, the $\frac{dx}{dt} = 0$, hence $x(t) = x(0)$ forever!

For certain parameters, the system in (5.3) can have four steady states. For example, when $r = \frac{1}{2}$ and $q = 10$. The four steady states are at 0, 0.67, 2, and 7.3. The zerro steady state $x = 0$ should always be there for a reasonable population dynamics: In the absence of immigration, if there is no one there at time zero, it will have nobody for all time later.

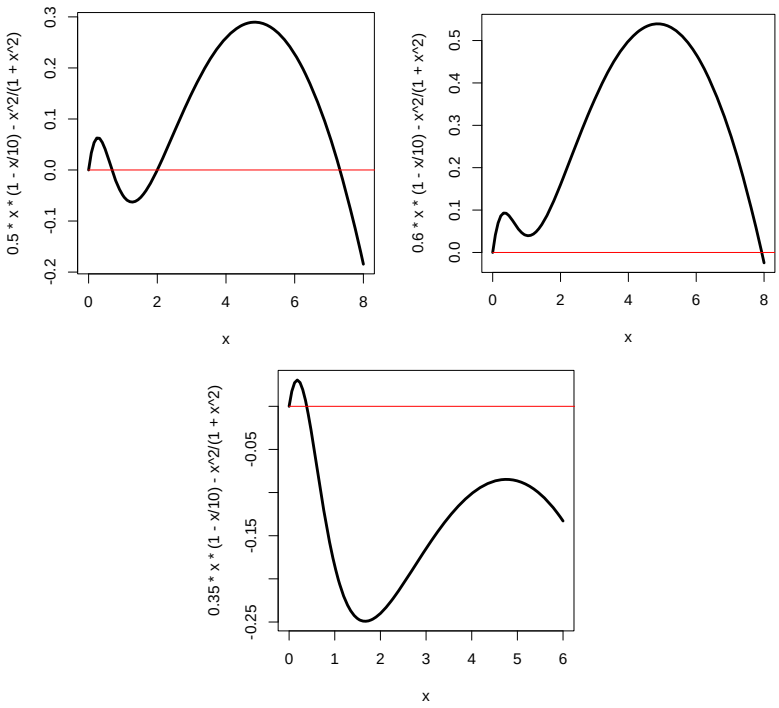

Figure 5.1: The right-hand-side of the differential equation in (5.3), $f(x, r, q)$, with $q = 10$, and $r = 0.5$, 0.6, and 0.35. We observe that they corresponding to respectively, in addition to a steady state at $x = 0$, "three steady states", "one steady state", and "one, another steady state".

Using the R command `curve(y(x),x0,x1,lwd=3)`, Fig. 5.1 shows the functions $f(x; 0.5, 10)$, $f(x; 0.6, 10)$, and $f(x; 0.35, 10)$. We note that the number of roots of $f(x)$ changes with different r.

5.2 The Schlögl chemical bistability

Let us consider a biochemical reaction system that involves *autocatalysis*, or positive feedback, known as the Schlögl model:

$$A + 2X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3X, \quad B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} X. \tag{5.4}$$

The ordinary differential equation (ODE) according to the law of mass action is

$$\frac{dx}{dt} = k_1 a x^2 - k_2 x^3 + k_3 b - k_4 x, \tag{5.5a}$$

$$\frac{da}{dt} = -k_1 a x^2 + k_2 x^3, \tag{5.5b}$$

$$\frac{db}{dt} = -k_3 b + k_4 x. \tag{5.5c}$$

We note that combining the two reversible reactions in (5.4) yields an overall transformation between A and B: $A \rightleftharpoons B$.

A closed biochemical system. What is the steady state of the biochemical dynamics in (5.4)? Letting the right-hand-side of Eq. (5.5) to be zero, we have

$$-k_3 b + k_4 x = -k_1 a x^2 + k_2 x^3 = k_1 a x^2 - k_2 x^3 + k_3 b - k_4 x = 0. \tag{5.6}$$

This yields

$$\frac{x^*}{b^*} = \frac{k_3}{k_4}, \ \frac{a^*}{x^*} = \frac{k_2}{k_1}, \implies \frac{a^*}{b^*} = \frac{k_2 k_3}{k_1 k_4}. \tag{5.7}$$

This is in fact well-known in chemistry: Neglecting all the intermediates:

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \cdots \underset{k_3}{\overset{k_4}{\rightleftharpoons}} B,$$

the chemcial equilibrium concentrations of A and B:

$$\left(\frac{[A]}{[B]}\right)^{eq} = \frac{k_2 k_3}{k_1 k_4}. \tag{5.8}$$

Note that in a chemical or biochemical equilibrium, there is no net flux in each and every reaction.

The equilibrium relations in (5.7) determine the ratio of equilibrium concentrations, but not their actual values. They have to be determined by the initial concentrations of the participating chemical species.

In a closed biochemical reaction system, no matter how many different biocheimical species involved in how many complex biochemical reactions, in the long time the system will reach a chemical equilibrium.

An open biochemical system. Now consider a single living cell, as those in a cell culture in a biomedical laboratory, as a complex biochemical reaction system. The "A" and "B" in (5.4) can be glucose ($C_6H_{12}O_6$) and CO_2+H_2O. The X can be all the important biochemicals inside a single cell: vitamins, proteins, and DNA. Then the most important aspect in a cell culture is to constantly change the "cell culture medium", that is to keep the A and B out of their equilibrium.

In fact, from the stand point of cell biochemistry, it is reasonable to simply assume that the concentrations of A and B are at some constant level of a and b, fixed; not changing with time at all. Such a device in a biomedical laboratory is called a "chemostat".

Let us now consider some numbers: If we have $k_1 = 3$, $k_2 = 0.6$, both in the unit of $(\text{mM})^{-2}\text{sec}^{-1}$, and $k_3 = 0.25$, $k_4 = 2.95$ both in the unit of sec^{-1}, then $([A]/[B])^{eq} = 0.6 \times 0.25/(3 \times 2.95) = \frac{1}{59}$. Fig. 5.2 shows the steady state of the biochemical system with fixed concentrations of a and b for A and B.

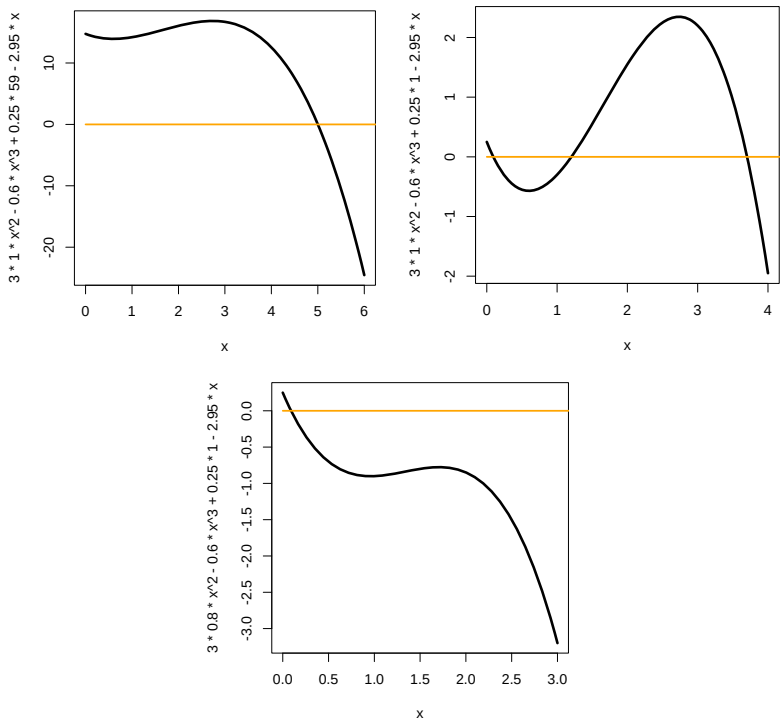

Figure 5.2: The right-hand-side of the differential equation in (5.5a) with various fixed values of a and b. Left panel: $a = 1$ and $b = 59$ give an equilibrium steady state in which $x^{eq} = 5$. Middle panel: $a = 1$ and $b = 1$ yield a bistable system with two stable steady states. Right panel: $a = 0.8$ and $b = 1$, again a single steady state; the another one this time.

5.3 Local stability analysis

Are all the steady states the same in Fig. 5.1, or in Fig. 5.2? There are stable and unstable steady states. In fact, one can re-write the right-hand-side of the ODE as

$$\frac{dx}{dt} = f(x) = -\frac{dU(x)}{dx} \text{ in which } U(x) = -\int_0^x f(z)dz. \tag{5.9}$$

Then, a stable steady state of the ODE is represented by a minimum of the $U(x)$, and an unstable steady state of the ODE is represented by a maximum of the $U(x)$. The dynamics

described by the differential equation can be visualized as a "down-hill" movement on a "energy landscape".

Both Figs. (5.1) and (5.2) show that the number of steady states of a differential equation can change with the parameters. One can in fact plot the steady state(s) of an ODE as a multi-valued function of a parameter.

5.4 Multivalued scalar functions

In the section, we carry out, hopefully a thorough, analysis of a multivalued scalar function: first with a single independent variable, $u(q)$, and then with two variables $u(q, r)$.

A multivalued scalar function usually is defined as the roots to an algebraic equation with a parameter or several parameters, like $f(u; q) = 0$ or $f(u; q, r) = 0$. Assuming the $f(u; q)$ is smooth and differentiable with respect to both u and q, then in calculus we have learned that the root to equation $f(u; q) = 0$ is a continuous curve in the (u, q) plane. Taking q as the abscissa and u as the ordinate, this curve in general can have zero, one, or more u values for each q.

Single variable $f(u; q) = 0 \Rightarrow u(q)$. If $f(u; q)$ is linear function of u, then:

$$\begin{aligned} f(u; q) &= a(q)u + b(q) = 0; \\ u &= -\frac{b(q)}{a(q)}, \text{ for } q \text{ with } a(q) \neq 0. \end{aligned}$$

In fact, at q where $a(q) = 0$, the root u simply tends to positive or negative infinity. Including the positive and negative infinity, there is one and only one u for each q. There could be several q's with a same u, however. One of the simple examples is $f(u; q) = \sin q - (\cos q)u = 0$; then $u = \tan q$.

What happens if the function $f(u; q)$ is a nonlinear function of u? In R, the command

```
> library(rootSolve)
> uniroot.all(function(x) 0.5*x*(1-x/10)-x^2/(1+x^2),
                          lower=-1,upper=8)
```

yields

```
[1] -2.062765e-05  6.833736e-01  2.000000e+00  7.316625e+00
```

which should be compared with the left panel of Fig. 5.1. Now, by using a for-loop, we can have

```
> rval <- seq( from=0.35, to=0.65, by=0.003 )
> xss <- matrix (ncol=3, nrow=101)
> for (i in 1:101) { xss[i] <- uniroot.all ( function(x)
                              rvalue[i]*x*(1-x/10)-x^2/(1+x^2),
                              lower=0.01, upper=8 )
```

```
                    }
> x1 <- matrix (ncol=2,nrow=101)
> x1[,1] = rval; x2= x1; x3 = x2
> for (i in 1:100) { x1[i,2]=xss[i,1]
                     x2[i,2]=xss[i,2]
                     x3[i,2]=xss[i,3]
                    }
```

Fig. 5.4 shows the multiple values of the roots to algebraic equation $rx(1-x/10)-x^2/(1+x^2) = 0$ for the value of $r \in [0.35, 0.65]$. This figure should be compared with all three panels in Fig. 5.1. One of the most striking features of Fig. 5.4 is the "abrupt appearance or disappearance" of a pair of roots, "out of blue". This corresponds to a pair of roots "becoming complex" so they no longer exist in the real space with $x \in \mathbb{R}$.

Two-variable $f(u;\alpha,\beta) = 0 \Rightarrow u(\alpha,\beta)$. We note that the rhs of Eq. (5.3) has actually two parameters r and q. Therefore, the roots of $f(u;q,r)$ are actually a scalar, multivalued function of two independent variables. The curve in Fig. 5.4 then becomes a multi-layered surface in a three-dimensional real space. Searching the words "catastrophe" with "Rene Thom" on the web and looking for images, your will see how such a surface has a very novel feature: Treating q and r as independent variables and $u(q,r)$ as a multi-layered surface, there are regions in (q,r) plane that correspond to a single layer of u, while other regions that have three layers. At the boundary of these two regions the u has exactly two values.

One would like to be able to locate this boundary. Let us now solve this very intriguing math problem. It requires some skill in your calculus. Using again the rhs of (5.3) as an example. We already knew that it always has a root $x = 0$. So the remaining problem is to find the other, possibly three, roots from

$$f(u;\alpha,\beta) = \alpha(\beta - u) - \frac{u}{1+u^2} = 0, \tag{5.10}$$

in which $\alpha = r/q$ and $\beta = q$. This change of notations simplifies a little bit of the algebra. Fig. 5.5A shows the root of the equation as a function of β, for several different α.

The situation with exactly two roots is a critical case. It occurs when $f(u;\alpha,\beta)$ is tangent to the $f = 0$ axis, say at $x = \xi$. So both $f(\xi) = 0$ and $f'(\xi) = 0$ at ξ:

$$\alpha(\beta - \xi) - \frac{\xi}{1+\xi^2} = 0, \quad -\alpha - \frac{1-\xi^2}{(1+\xi^2)^2} = 0. \tag{5.11}$$

If we eliminate the ξ from this pair of equations, we establish a relation between α and β, which gives the boundary for the region in which the system has three roots.

Unfortunately, the elimination of ξ from Eq. (5.11) is not a simple task! However, we note that we can obtain the following two equations from Eq. (5.11)

$$\alpha = \frac{\xi^2 - 1}{(1+\xi^2)^2}, \quad \beta = \frac{2\xi^3}{\xi^2 - 1}, \quad 1 \le \xi \le \infty. \tag{5.12}$$

Recall that if both α and β can be expressed in terms of a parameter ξ, then Eq. (5.12) is known as a *parametric equation* for the curve $\beta(\alpha)$. A well-known example is $x = R\cos t$ and $y = R\sin t$ actually define a circle $x^2 + y^2 = R^2$. Fig. 5.5B shows the function α vs. β: α increases with ξ for $\xi \in \left[1, \sqrt{3}\right]$, then decreases with $\xi > \sqrt{3}$. There is a cusp at $\xi = \sqrt{3}$.

One can understand the cusp qualitatively by simply considering the multi-layered surface $u(\alpha, \beta)$ defined by Eq. (5.10).

5.5 Nonlinear bifurcation

We now return to the ODE in (5.3). Note that all the discussion below applies equally well to One of the most striking features of Fig. 5.4 is the "abrupt appearance or disappearance" of a pair of roots, "out of blue". This corresponds to a pair of roots "becoming complex" so they no longer exist in the real space with $x \in \mathbb{R}$. the ODE in (5.5a) with constant a and b.

In nonlinear dynamical systems theory, the phenomenon of "abrupt appearance or disappearance" of a pair of steady states, "out of blue", is called a "saddle-node bifurcation". It indicates certain qualitative change in the dynamics. A plot of steady states as a multi-valued function of a parameter, such as shown in Figs. 5.4 and 5.5A, are called *bifurcation diagram*. Then in the case of two parameters, the behavior of the red, orange and green curves in Fig. 5.5A is known as *catastrophe*. It involves two saddle-node bifurcation events.

Saddle-node, transcritical, and pitchfork bifurcations. The canonical forms are

$$\frac{dx}{dt} = \mu - x^2, \Rightarrow x^{ss} = \begin{cases} -\sqrt{\mu} & \text{non-existent when } \mu \le 0, \text{ unstable when } \mu \ge 0 \\ \sqrt{\mu} & \text{non-existent when } \mu \le 0, \text{ stable when } \mu \ge 0 \end{cases} \tag{5.13}$$

$$\frac{dx}{dt} = \mu x - x^2, \Rightarrow x^{ss} = \begin{cases} 0 & \text{stable when } \mu < 0 \text{ and unstable when } \mu > 0 \\ \mu & \text{unstable when } \mu < 0 \text{ and stable when } \mu > 0 \end{cases} \tag{5.14}$$

and

$$\frac{dx}{dt} = \mu x - x^3, \Rightarrow x^{ss} = \begin{cases} 0 & \text{stable when } \mu < 0 \text{ and unstable when } \mu > 0 \\ \pm\sqrt{\mu} & \text{non-existent when } \mu < 0, \text{ stable when } \mu > 0 \end{cases} \tag{5.15}$$

with bifurcation diagrams as shown in Fig. 5.6A, B, and C.

XPPAUT. XPPAUT is a computer program particularly designed to analyze ordinary differential equations and bifurcations, developed single-handedly by Professor G. Bard Ermentrout of University of Pittsburgh:

`http://www.math.pitt.edu/~bard/xpp/xpp.htm`

Fig. 5.7 are two examples generated by XPPAUT.

Supercritical, subcritical, and structural stability. What is the relation between an ODE $\frac{dx}{dt} = f(x)$ and $\frac{dx}{dt} = -f(x)$? All the arrows in Fig. 5.6 change directions, all the solid lines and dash lines switch, and all the filled circle and open circle exchange. The pitchfork bifurcation in this case is called a *subcritical pitchfork* bifurcation.

Both transcritical and pitchfork bifurcations are *structurally unstable*; saddle-node bifurcation, however, is *structurally stable*. The distinction between "structurally stable phenomenon" and "structurally unstable phenomenon" is very important in biological modeling.

Here is an example: Consider both logistic population growth

$$\frac{dX}{dt} = rX\left(1 - \frac{X}{K}\right) \quad \text{and} \quad \frac{dX}{dt} = rX\left(1 - \frac{X}{K}\right) + \epsilon,$$

where the positive ϵ represent a very small rate of immigration. There is a transcritical bifurcation in the first model at $K = 0$. The two steady states of the second model are

$$X_{1,2}^{ss} = \frac{K \pm \sqrt{K^2 + 4K\epsilon/r}}{2},$$

in which the positive and negative branches no longer interset for any K value. The transcritical bifurcation phenomenon disappeared! From a biological standpoint, of course, the negative K and negative X^{ss} have no meaning. But as we shall show later in stochastic population dynamics, there is a real significance of $\epsilon > 0$, no matter how small.

Waddington's epigenetic landscape.

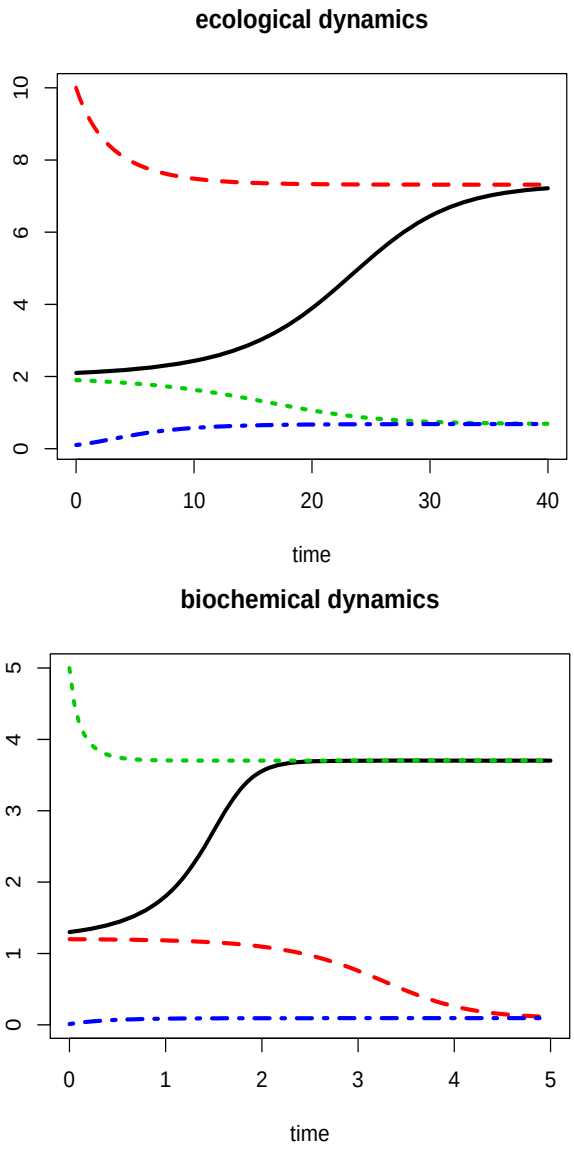

Figure 5.3: Let panel: solutions to the ODE in Eq. (5.3) with $q = 10$ and $r = 0.5$; right panel: solutions to the ODE in (5.5a) with $a = b = 1$, and other parameters $k_1 = 3, k_2 = 0.6, k_3 = 0.25, k_4 = 2.95$. Both ecological dynamics and biochemical dynamics exhibit *bistability*: Depending on the initial state of a system, its ultimate fates can be very different. The unstable steady state is often called a "threshold".

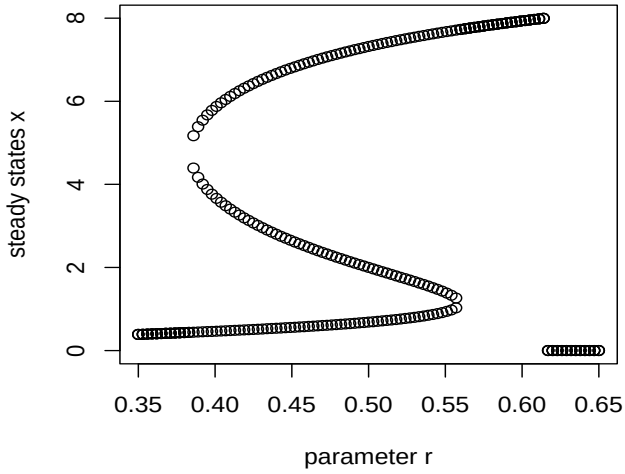

Figure 5.4: The steady states of the nonlinear ODE (5.3), which are the roots of its rhs $f(x, r, q) = rx(1 - \frac{x}{q}) - \frac{x^2}{1+x^2} = 0$, with $q = 10$ and $r \in [0.35, 0.65]$. It shows that the ODE can have either 1, or 2, or 3 steady states depending upon the value of r. Such a plot is called a *bifurcation diagram*.

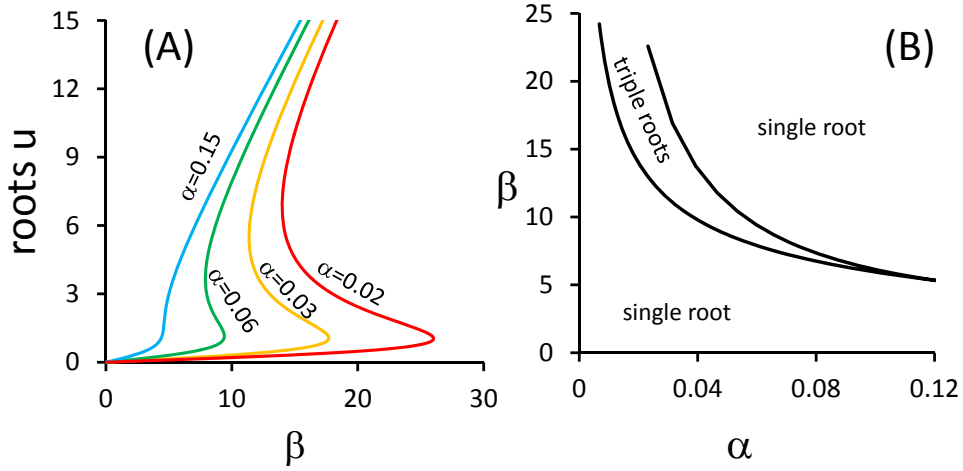

Figure 5.5: (A) Roots to (5.10) as a function of β, according to $\beta = u + (u/\alpha)/(1 + u^2)$, with $\alpha = 0.02, 0.03, 0.06$, and 0.15. (B) The regions of parameter space (α, β) in which $f(u; \alpha, \beta)$ has a single root and has three roots. The region for triple roots has a cusp at $\alpha = \frac{1}{8} = 0.125$ and $\beta = 3\sqrt{3} = 5.2$.

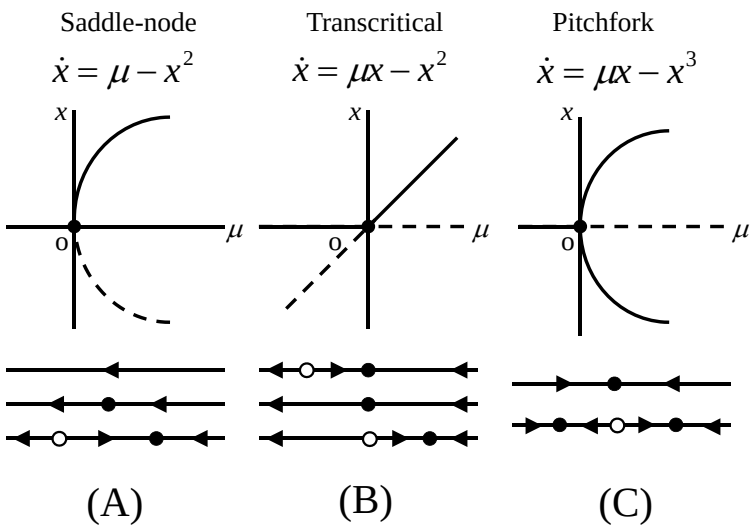

Figure 5.6: Bifurcation diagrams and corresponding vector fields before, during, and after bifurcations. An arrow along a line indicates the directions of a vector field, while an open circle and a filled circle represent a unstable and a stable fixed point, respectively. (A) Saddle-node (out-of-blue) bifurcation has a pair of stable and unstable fixed points simultaneously appear. (B) Transcritical bifurcation does not change the number of fixed points, rather there is a switch of stability. (C) Pitchfork bifurcation turns a stable fixed point into a unstable one surrounded by a pair of stable fixed points. All bifurcations shown here are "local", which means that a vector field has an infinitesimal local change at the critical bifurcation point when $\mu = 0$.

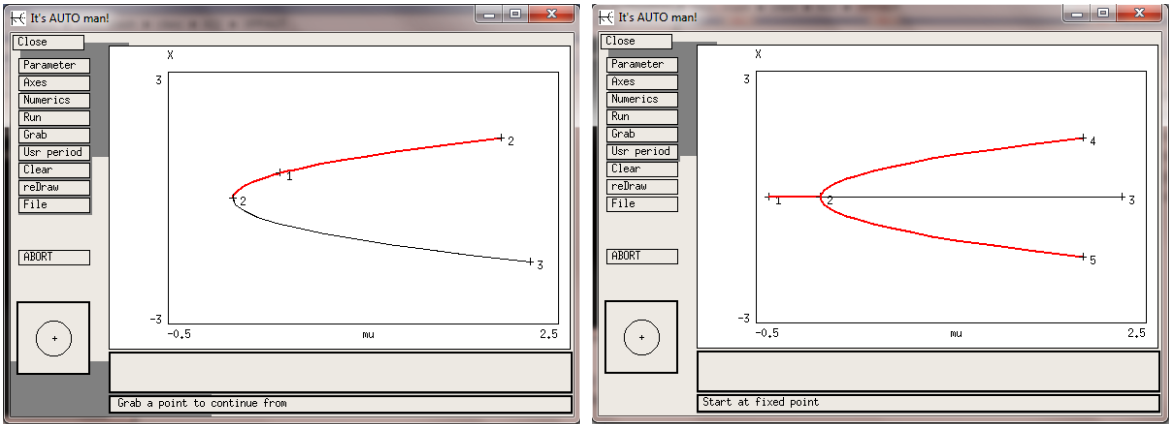

Figure 5.7: Two views of saddle-node and pitchfork bifurcation diagrams, generated by XPPAUT, for the differential equations in (5.13) and (5.15). The red lines represent stable fixed point, and the gray lines represent unstable fixed point.

Chapter 6

Chemical reaction: A nonlinear bifurcation in molecular mechanics

6.1 Newtonian mechanics and the concept of energy

The concept of center-of-mass. It is the concept of *center-of-mass* that allows Newtonian mechanics being able to be applied to a wide variety of scenarios, to complex objects.

The concept of mechanical energy. We start with Newton's second law of motion:

$$m\frac{d^2x}{dt^2} = F(x). \tag{6.1}$$

If one introduces a *potential of force*

$$U(x) = -\int_{x_0}^{x} F(y)dy, \tag{6.2}$$

then one has

$$\frac{dU(x)}{dx} = -F(x), \tag{6.3}$$

and

$$\boxed{\frac{m}{2}\left(\frac{dx}{dt}\right)^2 + U(x) = \text{constat}}, \tag{6.4}$$

in which the term $\frac{1}{2}mv^2$, called by Gottfried Leibniz as *vis viva*, is now called *kinetic energy*. Here is an excerpt from wikipedia on "Energy":

> The word energy derives from Greek $\epsilon\nu\acute{\epsilon}\rho\gamma\epsilon\iota\alpha\zeta$ (energeia), which possibly appears for the first time in the work of Aristotle in the 4th century BC.
>
> The concept of energy emerged out of the idea of *vis viva* (living force), which Leibniz defined as the product of the mass of an object and its velocity squared; he believed that total vis viva was conserved. To account for slowing due to

friction, Leibniz theorized that thermal energy consisted of the random motion of the constituent parts of matter, a view shared by Isaac Newton, although it would be more than a century until this was generally accepted. In 1807, Thomas Young was possibly the first to use the term "energy" instead of vis viva, in its modern sense. Gustave-Gaspard Coriolis described "kinetic energy" in 1829 in its modern sense, and in 1853, William Rankine coined the term "potential energy". It was argued for some years whether energy was a substance (the caloric) or merely a physical quantity, such as momentum.

It has to wait for Einstein's theory that unifies *energy* and *mass*: $E = mc^2$.

Energy conservation to include heat. In Eq. 6.4, the force from $-\frac{dU}{dx}$ is called conservative since kinetic energy and potential energy can forever convert back-and-forth. This is not the case if there is an energy dissipation due to frictional force. A frictional force is proportional to the velocity of a moving object:

$$m\frac{d^2x}{dt^2} = -\frac{dU(x)}{dt} - \eta\frac{dx}{dt}, \tag{6.5}$$

the last term no the right-hand-side is a frictional force. It is equal to zero if velocity $\frac{dx}{dt} = 0$.

Now parallel to the deviation of Eq. 6.4, we now have

$$\frac{d}{dt}\left[\frac{m}{2}\left(\frac{dx}{dt}\right)^2 + U(x)\right] = -\eta\left(\frac{dx}{dt}\right)^2. \tag{6.6}$$

The right-hand-side is the instantaneous rate of *heat energy* produced, which is equal to the rate of energy decreasing in the mechanical system. The total mechanical energy (= kinetic + potential) is no longer conserved in this system with friction. However, counting the rate of heat $\frac{dQ}{dt}$:

$$\frac{d}{dt}\left[\frac{m}{2}\left(\frac{dx}{dt}\right)^2 + U(x)\right] = -\frac{dQ}{dt} \quad \Leftrightarrow \quad \frac{d}{dt}\left[\frac{m}{2}\left(\frac{dx}{dt}\right)^2 + U(x) + Q\right] = 0. \tag{6.7}$$

The total energy conservation, including mechanical and thermal, is again regained.

6.2 Simple harmonic oscillator with damping

Let us now consider a Newtonian mechanical system with a point mass at x, which is attached to a Hookean spring with re-storing force $-kx$ and a frictional force $-\eta\frac{dx}{dt}$. Then according Newton's second law of motion:

$$m\frac{d^2x}{dt^2} = \text{total force} = -\underbrace{kx}_{elastic} - \underbrace{\eta\frac{dx}{dt}}_{frictional}. \tag{6.8}$$

The standard way to solve this linear, constant coefficient equation (6.8) is to assume the general solution with the form e^{rt}. Then we obtain the characteristic polynomial for r:

$$mr^2 + \eta r + k = 0, \tag{6.9}$$

whose two roots are

$$r_{1,2} = \frac{-\eta \pm \sqrt{\eta^2 - 4mk}}{2m}. \tag{6.10}$$

The general solution to Eq. 6.8 is

$$x(t) = c_1 e^{r_1 t} + c_2 e^{r_2 t}. \tag{6.11}$$

We see that that if $\eta \neq 0$ (η has to be positive from the physical requirement), then with increasing t, $x(t)$ in (6.11) tends to zero.

However, depending on whether $\eta^2 \geq 4mk$ or $\eta < 4mk$, the $x(t)$ approaches to zero either monotonically or oscillatorily with frequence $\sqrt{4mk - \eta^2}$. The latter corresponds to Eq. 6.9 having a pair of complex roots.

Heavily overdamped system. When $\eta^2 \gg 4mk$, the mechanical system is called heavily *overdamped*. In this case, one can approximate the two roots in (6.10). We use the important formula

$$(1+s)^{1/2} \approx 1 + \frac{s}{2} - \frac{s^2}{8} + \cdots \tag{6.12}$$

for small s. Then

$$\begin{aligned} r_{1,2} &= \frac{-\eta \pm \sqrt{\eta^2 - 4mk}}{2m} = \frac{-\eta \pm \eta\sqrt{1 - 4mk/\eta^2}}{2m} \\ &\approx \frac{-\eta \pm \eta\big(1 - 2mk/\eta^2 - 2m^2k^2/\eta^4\big)}{2m} \\ &= \begin{cases} -k/\eta \left(1 + mk/\eta^2\right) & \approx -\frac{k}{\eta} \\ -\eta/m \left(1 - mk/\eta^2 - m^2k^2/\eta^4\right) & \approx -\frac{\eta}{m} \end{cases} \end{aligned}$$

Both r_1 and r_2 are negative. Since $\eta^2 \gg 4mk$, $|r_2| \gg |r_1|$. Therefore, an overdamped system has a very rapid acceleration phase in which "inertia balancing friction", e.g., $m\ddot{x} = -\eta\dot{x}$, and a relatively slow motion in which "friction balances elasticity", i.e., $\eta\dot{x} = -kx$.

Significantly underdamped system. What happens if $\eta^2 \ll 4mk$? In this case, we have

$$\begin{aligned} r_{1,2} &= \frac{-\eta \pm \sqrt{\eta^2 - 4mk}}{2m} = \frac{-\eta \pm i\sqrt{4mk}\sqrt{1 - \eta^2/(4mk)}}{2m} \\ &\approx -\frac{\eta}{2m} \pm i\sqrt{\frac{k}{m}}. \end{aligned}$$

We have a decaying oscillation with frequency $\omega = \sqrt{k/m}$ and a much slower decaying rate $\eta/(2m) \ll \omega$. On the fast time scale, the inertia balances the elasticity: $m\ddot{x} = -kx$, just like a Harmonic oscillation without damping.

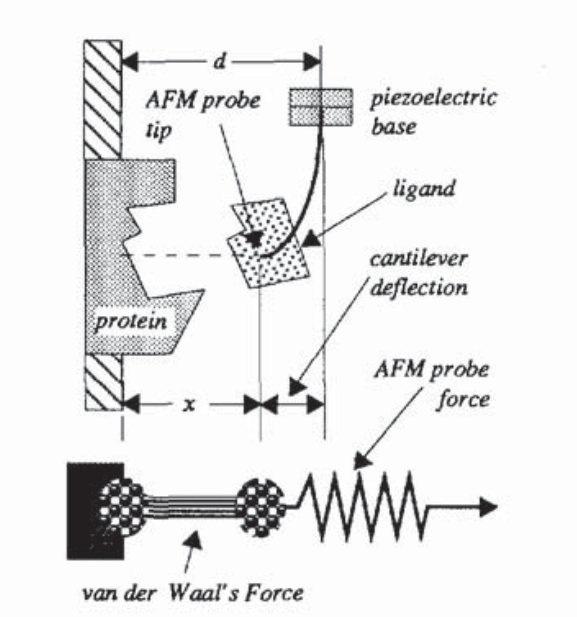

Figure 6.1: Upper pannel: A schematic overview of protein-ligand complex separation with the AFM. Lower pannel: One-dimensional model. The position of the ligand will be denoted by x.

6.3 Mechanical modeling of biomolecular transitions

In this section, we shall develop a mathematical model for the phenomenon of "forced biomolecular 'bond' rupture" first observed by Florin, Moy and Gaub in 1994. Their experimental observations were published in Science.[1] However, their "interpretations" were quite erroneous.

The problem, even though it is on a single biological molecule (a protein) and its natural partner (called a ligand) in water, is a very ideal Newtonian mechanical system. One can develop a mechanistic model (or theory) based two laws: Newton's law of motion and van der Waals' formula for the force between two molecules, together with a list of further assumptions.

We model the external force exerted by a cantilever from an atomic force microscope (AMF) as a linear, harmonic spring:

$$m\frac{d^2x}{dt} = -F_{int}(x) + k(d-x) - \eta\frac{dx}{dt}, \tag{6.13}$$

in which x is the distance between the center-of-mass of the ligand to the center-of-mass of the protein, which is assumed to be fixed.[2] m is the mass of the ligand, η is its frictional coefficient in water, $k(x - x_0)$ represents the force exerted by the AFM cantilever, with d

[1] Florin, E.L., Moy, V.T. and Gaub, H.E. (1994) Adhesion between individual ligand receptor pair. *Science* 264 415–417.

[2] This immediately gives the insight that the internal structure of the protein can change under the pulling.

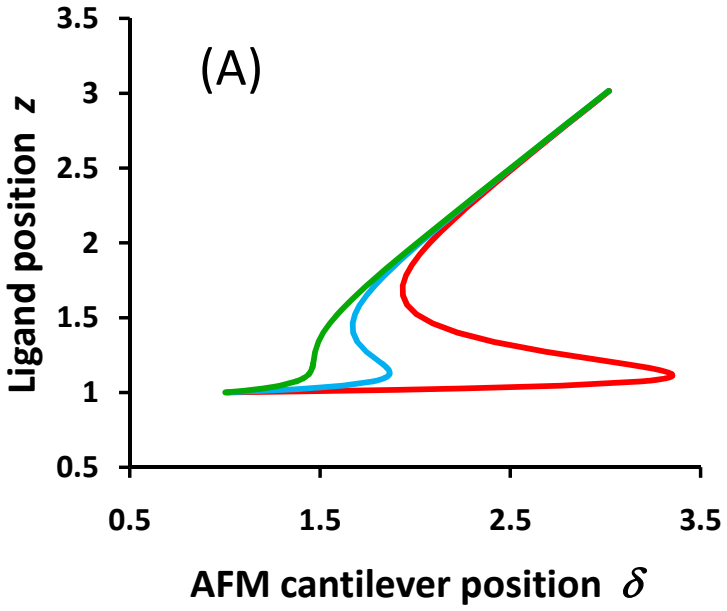

Figure 6.2: Mechanical equilibrium position of the ligand, z, as a function of δ, the position of the base of the cantilever, with several different αs, the stiffness of the cantilever. $z = 1$ is the equilibrium position of the ligand in the absent of the AFM force. Red: $\alpha = 0.1$; blue: $\alpha = 0.3$, and green: $\alpha = 0.7$.

being the position of the base of the cantilever. $F_{int}(x)$ is the interaction force between the ligand and the protein, it has the celebrated van der Waals potential $U_{vdw}(x)$

$$F_{int}(x) = \frac{dU_{vdw}(x)}{dx}, \quad U_{vdw}(x) = -U_0 \left[2 \left(\frac{x_0}{x} \right)^6 - \left(\frac{x_0}{x} \right)^{12} \right]. \tag{6.14}$$

Because water is a rather viscous medium, we further assume that (1) the mechanical system is *overdamped*, i.e., we can neglect the mass term. Therefore, Eq. (6.13) can be simplified into

$$\eta \frac{dx}{dt} = -F_{int}(x) + k(d - x). \tag{6.15}$$

We now ask the question: When d is slowly increased, i.e., the AFM is pulling the ligand away from the protein, how does the position of the ligand change?

This is in fact a static, force balance problem: $F_{int}(x) = k(d - x)$. That is,

$$\frac{U_0}{x_0} \left[12 \left(\frac{x_0}{x} \right)^7 - 12 \left(\frac{x_0}{x} \right)^{13} \right] = k(d - x). \tag{6.16}$$

The solution x to the equation, as a function of d, is the answer to our question.

But if our meassurement for x is precisely the distance between the center-of-masses, then it does not matter. However, in real world experiments, this is nearly impossible. So there will be consequences.

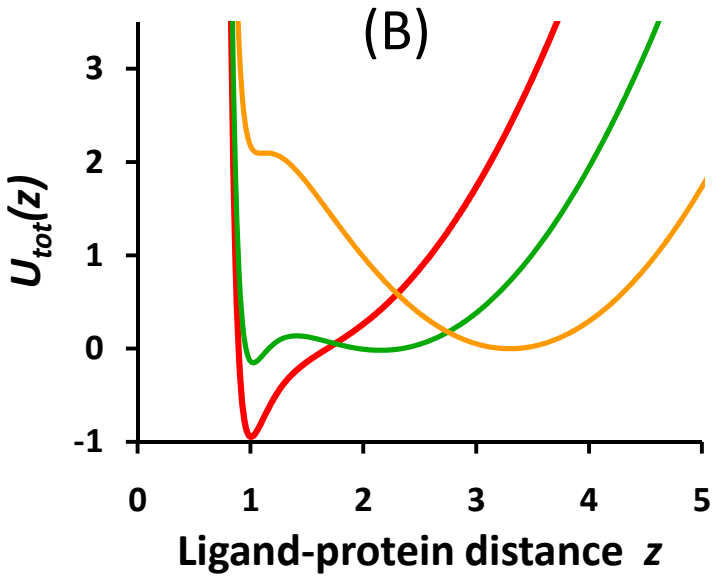

Figure 6.3: Total mechanical energy, $U_{tot}(z)$, as a function of the ligand-protein (center of masses) distance z for several different values of δs. Red: $\delta = 1.3$, green: $\delta = 2.2$, and orange: $\delta = 3.3$. All with $\alpha = 0.1$, correspond to the red curve in Fig. 1.

There are many parameters in the equation. But they can be *grouped* together:

$$z = x/x_0, \quad \delta = d/x_0, \quad \text{and} \quad \alpha = kx_0^2/(12U_0),$$

then,

$$\boxed{z^{-7} - z^{-13} = \alpha\,(\delta - z)}\,. \tag{6.17}$$

Note that all three quantities, z, δ, and α are *dimensionless*. non-dimensionalization is a very useful way to simplify mathematical models without involving any approximation. It uses the internal scales as units for physical quantities in a model.

This equation can not be solved in a closed form for $z(\delta)$. However, one can obtain a parametric equation for the function:

$$z = \left(\frac{1 \pm \sqrt{1-4\xi}}{2}\right)^{-\frac{1}{6}}, \quad \delta = z + \frac{\xi}{\alpha z}, \quad \xi \in \left[-\infty, \frac{1}{4}\right]. \tag{6.18}$$

Fig. 1 shows several z as functions of δ with different α's. We see with increasing α, i.e., the spring becoming more stiff, the "sluggish" behavior disappears.

One can also understand the behavior in the figure in terms of the "potential energy function":

$$\eta \frac{dx}{dt} = -\frac{dU_{tot}}{dx}, \tag{6.19}$$

where

$$U_{tot}(x) = U_{vdw}(x) + \frac{1}{2}k(x-d)^2 = -U_0\left[2\left(\frac{x_0}{x}\right)^6 - \left(\frac{x_0}{x}\right)^{12}\right] + \frac{1}{2}k(x-d)^2. \tag{6.20}$$

In non-dimensionalized form, it is

$$\frac{U_{tot}(z)}{U_0} = -\left[2\left(\frac{1}{z}\right)^6 - \left(\frac{1}{z}\right)^{12}\right] + 6\alpha(z-\delta)^2. \tag{6.21}$$

Fig. 2 shows the total potential energy function $U_{tot}(z)$ for three different values of δ.

Chapter 7

Nonlinear dynamics of two interacting populations

7.1 The Lotka-Volterra predator prey model

Let $N(t)$ be the population density of a prey, and $P(t)$ be the population of a predatory. The prey has its own growth rate a in the absence of predator; and the predator has its own negative growth rate $-d$ in the absence of prey, which is its essential food source. Then we have

$$\frac{dN(t)}{dt} = N(a - bP), \quad \frac{dP(t)}{dt} = P(cN - d). \tag{7.1}$$

Introducing non-dimensionalized variables

$$u(t) = \frac{cN(t)}{d},\ v(t) = \frac{bP(t)}{a},\ \tau = at,\ \alpha = \frac{d}{a},$$

we have

$$\frac{du}{d\tau} = u(1 - v), \quad \frac{dv}{d\tau} = \alpha v(u - 1). \tag{7.2}$$

Putting the pair of nonlinear ordinary differential equations into R, we see that $u(\tau)$ and $v(\tau)$ are both oscillatory as functions of time. In fact, in the (u, v) *phase space*, the $u(\tau)$ and $v(\tau)$ form closed orbits, with different intial data, as shown in Fig. 7.2.

Lotka's original chemical reaction dynamics. A. J. Lotka's original work, published in the *Proceedings of the National Academey of Sciences of the USA*, vol. 6, pp. 410–415, in 1920, entitled "Analytical note on certain rhythmic relations in organic systems", is a mathematical model for nonlinear chemica oscillations. In fact, consider the autocatalytic reaction system:

$$A + X \xrightarrow{k_1} 2X,\ \ Y + X \xrightarrow{k_2} (\nu + 1)Y,\ \ Y \xrightarrow{k_3} B. \tag{7.3}$$

It dynamics is described by the law of mass action:

$$\frac{dx}{dt} = k_1 c_A x - k_2 xy, \quad \frac{dy}{dt} = \nu k_2 xy - k_3 y. \tag{7.4}$$

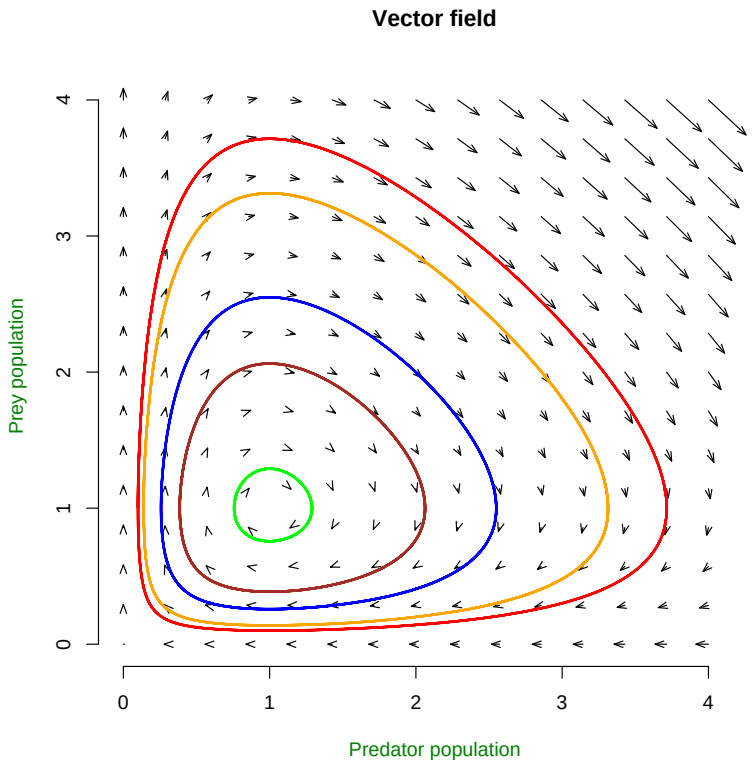

Figure 7.1: Predator-prey dynamics, as described by the differential equation (7.2), with various initial values and $\alpha = 1$: Red: $u = 1, v = 0.1$, orange: $u = 2, v = 0.2$, blue: $u = v = 2$, brown: $u = v = 1.7$, and green $u = v = 1.2$.

So compared with (7.2) we have $a = k_1 c_A$, $b = k_2$, $c = \nu k_2$, and $d = k_3$.

Can we obtained the closed orbit in Fig. 7.2 from solving the differential equations? The answer is yes. From Eqn. (7.2) we have

$$\frac{du}{dv} = \frac{u(1-v)}{\alpha v(u-1)}. \tag{7.5}$$

The solution to this equation is actually

$$\begin{aligned} \alpha\left(\frac{u-1}{u}\right) du &= \frac{(1-v)}{v}\, dv, \\ \alpha\int\left(1-\frac{1}{u}\right) du &= \int\left(\frac{1}{v}-1\right) dv, \end{aligned}$$

$$\alpha u + v - \ln\left(u^{\alpha} v\right) = C, \tag{7.6}$$

where C is a constant of integration. Now we consider a two-variable function $H(u, v) = \alpha u + v - \ln\left(u^{\alpha} v\right)$. It can be shown that $H(u, v)$ has its minimum at $u = v = 1$, and the

surface has a curvature matrix

$$\begin{pmatrix} \dfrac{\partial^2 H}{\partial u^2} & \dfrac{\partial^2 H}{\partial u \partial v} \\ \dfrac{\partial^2 H}{\partial v \partial u} & \dfrac{\partial^2 H}{\partial v^2} \end{pmatrix} = \begin{pmatrix} \alpha/u^2 & 0 \\ 0 & 1/v^2 \end{pmatrix}, \tag{7.7}$$

which is positive definite. That means the surface $H(u, v)$ is "bowl like". the the solution in Fig. 7.2 are the contour curves of $H(u, v) = C$.

7.2 Linear analysis and matrix exponential

7.3 Competition dynamics

Consider two competing populations N_1 and N_2:

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1} - b_{12}\frac{N_2}{K_1}\right), \tag{7.8}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_2}{K_2} - b_{21}\frac{N_1}{K_2}\right). \tag{7.9}$$

We introduce nondimensionalized variables:

$$x_1 = \frac{N_1}{K_1}, \;\; x_2 = \frac{N_2}{K_2}, \;\; \tau = r_1 t, \tag{7.10}$$

and

$$r = \frac{r_2}{r_1}, \;\; \beta_{12} = b_{12}\frac{K_2}{K_1}, \;\; \beta_{21} = b_{21}\frac{K_1}{K_2}. \tag{7.11}$$

Then,

$$\frac{dx_1}{d\tau} = x_1(1 - x_1 - \beta_{12}x_2) = f(x_1, x_2), \tag{7.12}$$

$$\frac{dx_2}{d\tau} = r x_2(1 - x_2 - \beta_{21}x_1) = g(x_1, x_2). \tag{7.13}$$

Drawing null clines, it is easy to see that $\big(x_1^* = x_2^* = 0\big)$, $\big(x_1^* = 1, x_2^* = 0\big)$, $\big(x_1^* = 0, x_2^* = 1\big)$, and

$$\left(x_1^* = \frac{1 - \beta_{12}}{1 - \beta_{12}\beta_{21}}, \; x_2^* = \frac{1 - \beta_{21}}{1 - \beta_{12}\beta_{21}}\right),$$

are four fixed points. Furthermore, the last fixed point is in the positve quardrant if both $\beta_{12}, \beta_{21} < 1$, or both $\beta_{12}, \beta_{21} > 1$. In other words, if one of the β's is greater than 1, and the other less than 1, then there is no fixed point in the first quardrant.

We now carry out linear stability analysis. We are interested in the Jacobian matrix:

$$A = \begin{pmatrix} \frac{\partial f}{\partial x_1} & \frac{\partial f}{\partial x_2} \\ \frac{\partial g}{\partial x_1} & \frac{\partial g}{\partial x_2} \end{pmatrix}_{(x_1^*, x_2^*)} = \begin{pmatrix} 1 - 2x_1 - \beta_{12} x_2 & -\beta_{12} x_1 \\ -r\beta_{21} x_2 & r(1 - 2x_2 - \beta_{21} x_1) \end{pmatrix}_{(x_1^*, x_2^*)}. \quad (7.14)$$

Now applying this to the four fixed points.

At (0.0) we have $\lambda_1 = 1$, $\lambda_2 = r$. It is unstable.

At $(1, 0)$, we have $\lambda_1 = -1$, $\lambda_2 = r(1 - \beta_{21})$. Therefore, it is stable if $\beta_{21} > 1$ and unstable if $\beta_{21} < 1$.

Then at $(0, 1)$ we have a similar result: it is stable if $\beta_{12} > 1$ and unstable if $\beta_{12} < 1$.

Finally, for the positive fixed point:

$$A = \left(1 - \beta_{12}\beta_{21}\right)^{-1} \begin{pmatrix} \beta_{12} - 1 & \beta_{12}(\beta_{12} - 1) \\ r\beta_{21}(\beta_{21} - 1) & r(\beta_{21} - 1) \end{pmatrix} \quad (7.15)$$

We see that its trace

$$\text{Tr}[A] = \beta_{12} - 1 + r(\beta_{21} - 1), \quad (7.16)$$

and its determinant

$$\det[A] = r(1 - \beta_{12}\beta_{21})^{-1}(\beta_{12} - 1)(\beta_{21} - 1). \quad (7.17)$$

Therefore, if both $\beta_{12}, \beta_{21} > 1$, then $\text{Tr}[A] > 0$ and $\det[A] < 0$. Thus the positive fixed point is a saddle.

If both $\beta_{12}, \beta_{21} < 1$, then $\text{Tr}[A] < 0$ and $\det[A] > 0$, and the positive fixed point is stable.

A large β means strong competition; a smaller β means weaker competition. Therefore, only when the two populations have equal balanced strength, there is the possibility for co-existence. Then both are strong competitors, the initial situation matters.

7.4 The Morris-Lecar model for excitable dynamics

We now study another planar system, the Morris-Lecar model for excitable, membrane electrochemical dynamics. ML model is a simplified version of the Hodgkin-Huxley (HH) model originally developed in 1950s. The latter is a system of four ordinary differential equations for $(V, n, m, h)(t)$. In contrast, the ML model is

$$C\frac{dV}{dt} = -g_{Ca} m^*(V)(V - V_{Ca}) - g_K w(t)(V - V_K) - g_L(V - V_L), \quad (7.18a)$$

$$\frac{dw}{dt} = -\frac{w - w^*(V)}{\tau_w(V)}, \quad (7.18b)$$

in whivh

$$m^*(V) = 0.5\left(1+\tanh\left(\frac{V-v_1}{v_2}\right)\right), \tag{7.18c}$$

$$w^*(V) = 0.5\left(1+\tanh\left(\frac{V-v_3}{v_4}\right)\right), \tag{7.18d}$$

$$\tau_w(V) = \tau^*\cosh^{-1}\left(\frac{V-v_3}{2v_4}\right). \tag{7.18e}$$

In physiological applications, this model was developed for the dynamics with an interplay between calcium ions and potassium ions in muscles. Note that one can re-write the Eq. (7.18b) as

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

with

$$\alpha_w(V) = \frac{w^*(V)}{\tau(V)} \text{ and } \beta_w(V) = \tau_w^{-1}(V).$$

The implicit assumption of using $m^*(V)$ in (7.18a) rather than a dynamic equation for $m(t)$ is that calcium dynamics is extremely fast on the time scale considered in Eq. (7.18).

We shall analyzing the ML equations with the following two sets of parameters:

Table I.

Parameter	C	g_{Ca}	g_K	g_L	V_{ca}	V_K	V_L	$(\tau^*)^{-1}$	I_{ext}	v_1	v_2	v_3	v_4
Set 1	20	4.4	8	2	120	-84	-60	0.04	90	-1.2	18	2	30
Set 2	20	5.5	8	2	120	-84	-60	0.22	90	-1.2	18	2	30

7.5 The Schnakenberg chemical oscillation

Known as the Schnakenberg model:

$$A \xrightarrow{k_1} X, \quad X+2Y \xrightarrow{k_2} 3Y, \quad Y \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} B. \tag{7.19}$$

According to the Law of Mass Action:

$$\frac{dc_X}{d\tau} = k_1c_A - k_2c_Xc_Y^2, \quad \frac{dc_Y}{d\tau} = k_2c_Xc_Y^2 - k_3c_Y + k_{-3}c_B. \tag{7.20}$$

After non-dimensionalization:

$$x = \sqrt{\frac{k_2}{k_3}}c_X, \;\; y = \sqrt{\frac{k_2}{k_3}}c_Y, \;\; t = k_3\tau, \;\; a = \frac{k_1}{k_3}\sqrt{\frac{k_2}{k_3}}c_A, \;\; b = \frac{k_{-3}}{k_3}\sqrt{\frac{k_2}{k_3}}c_B,$$

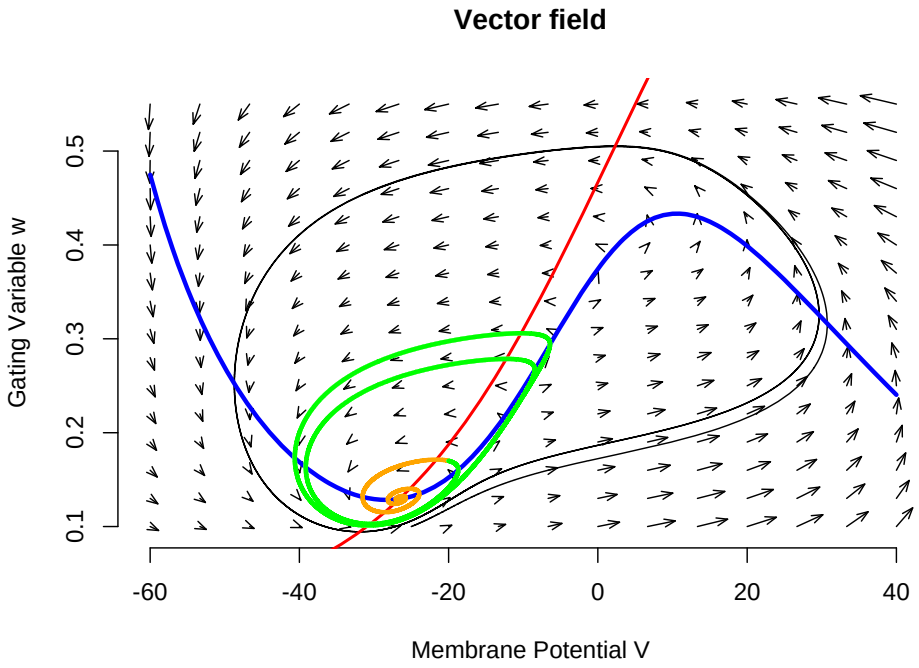

Figure 7.2: Phase portrait of the Morris-Lecar excitable membrane dynamics, described by the system (7.18) with the first set of parameters in Table I. Red line is the nullcline for $\frac{dw}{dt} = 0$ and the blue line is the nullcline for $\frac{dV}{dt} = 0$. Their intersection is a stable fixed point, a spiral as illustrated by the orange trajectory. The black trajectory also indicates there is a stable limit cycle. Between the stable fixed point and stable limit cycle, there is a unstable limit cycle as shown by the green trajectory. The green trajectory is obtained by solving the system (7.18) with $t \to -\infty$.

we have

$$\frac{dx}{dt} = a - xy^2 = f(x,y), \quad \frac{dy}{dt} = b - y + xy^2 = g(x,y). \tag{7.21}$$

Planar system (7.21) has a single, positive steady state:

$$x^* = \frac{a}{(1+b)^2}, \quad y^* = a + b,$$

at which, the Jacobian matrix

$$A = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}_{(x^*,y^*)} = \begin{pmatrix} -(y^*)^2 & -2x^*y^* \\ (y^*)^2 & -1 + 2x^*y^* \end{pmatrix}$$

with determinanat and trace

$$\det(A) = (a+b)^2, \quad \text{tr}(A) = \frac{a - b - (a+b)^3}{a+b}.$$

When $\text{tr}(A) = 0$, fixed point changes from stable to unstable. This is called a *Hopf bifurcation*. The Jacobian matrix actually provides a "frequency" for the spiral. The two eigenvalues are

$$\lambda_{1,2} = \frac{1}{2}\left(\text{tr}(A) \pm \sqrt{\text{tr}^2(A) - 4\,\det(A)}\right)$$

whose imaginary part, at the critical condition of Hopf bifurcation is $\det(A) = (a+b)^2$.

7.6 Hopf bifurcation

7.7 Bifurcation and structural stability

Chapter 8

Dynamics of gene regulatory networks

In modern cell biology, a key word is "regulation".

8.1 Simple Goodwin's model with feedback

Following the *central dogma of molecular biology* first stated by Francis Crick in 1958,[1] Dr. Brian Carey Goodwin (1931–2009) developed a mathematical model for gene expression as early as 1965. It deals with three types of biochemical species: an mRNA (X), a protein as an enzyme (Y), and a metabolite (Z) whose formation is catalyzed by the enzyme:

$$\frac{dx}{dt} = f(z) - d_1 x, \quad f(z) = \frac{V}{K + z^m} \tag{8.1a}$$

$$\frac{dy}{dt} = k_1 x - d_2 y, \tag{8.1b}$$

$$\frac{dz}{dt} = k_2 y - d_3 z. \tag{8.1c}$$

In the system of equations (8.1), the synthesis of mRNA (X) is regulated by the "end product", the metabolite Z, with a negative feedback: If z increases, the rate of X synthesis $f(z)$ decreases. Other forms of $f(z)$ have also been studied. For example $f(z) = \frac{a+z^m}{1+z^m}$ with $0 < a < 1$ represents a positive feedback.

One of the important features of biochemistry inside a living cell is that all biochemical materials are *continuously* been degradated, e.g, decomposed. A constant level of a particular biochemical is only maintained with a continuous synthesis and degradation. d_1, d_2, and d_3 represent the degradation rates for mRNA, protein, and metabolite.

As we shall see, Goodwin's model is still very influential in the current studies of the dynamics of gene regulations.

[1] Crick, F. H. C. (1958) On protein synthesis. *Symp. Soc. Exp. Biol.* 12, 139–163.

8.2 Self-regulating gene network

To understand epi-genetic differences of genomically identical cells, self-regulating gene network has received tremendous attentions in recent years. In its simplest form, it has a transcription factor (TF) binding to DNA step, two possible TF synthesis steps, and a TF degradation step:

$$\text{DNA} \ + m \ \text{TF} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \text{DNA} \cdot \text{TF}_m \ , \tag{8.2a}$$

$$\text{amino acids} \ + \ \text{DNA} \xrightarrow{g_0} \ \text{TF} \ + \ \text{DNA}, \tag{8.2b}$$

$$\text{amino acids} \ + \ \text{DNA} \cdot \text{TF}_m \xrightarrow{g_1} \ \text{TF} \ + \ \text{DNA} \cdot \text{TF}_m \ , \tag{8.2c}$$

$$\text{TF} \xrightarrow{d} \ \text{amino acids} \ . \tag{8.2d}$$

If $g_0 < g_1$, we say the gene expression has a positive feedback; if $g_0 > g_1$, we say the gene expression has a negative feedback.

In the simplest form, the mathematical model for the biochemical system in (8.2) is a planar system. We use X to denote the probability of the DNA with mTF bound, thus $(1 - X)$ for the probability of the DNA without TF, and Y as the concentation of the TF:

$$\frac{dX}{d\tau} = \alpha Y^m (1 - X) - \beta X, \ \ \frac{dY}{d\tau} = g_0 a (1 - X) + g_1 a X - dY, \tag{8.3}$$

in which a stands collectively for the concentration of amino acids, which is assumed to be a constant.

Now, with non-dimensionalization:

$$x = X, \ y = \frac{Y}{g_1 a}, \ t = \tau \ d, \ g = \frac{g_0}{g_1}, \ \omega = \frac{\beta}{d}, \ \theta = \left(\frac{\alpha}{\beta}\right) \left(g_1 a\right)^m,$$

we have

$$\frac{dx}{dt} = \omega \Big[\theta y^m (1 - x) - x\Big] = f(x, y), \ \ \frac{dy}{dt} = g + (1 - g)x - y = h(x, y). \tag{8.4}$$

Very large $\omega \gg 1$. If the FT unbinding to DNA is much more rapid than its own degradation, i.e., $\omega = \frac{\beta}{d} \gg 1$, then $x(t)$ reaches its quasi-steady state quickly while y barely changes:

$$x(y) = \frac{\theta y^m}{1 + \theta y^m}.$$

Therefore, substituting this into the second equation in (8.4),

$$\frac{dy}{dt} = \frac{g + \theta y^m}{1 + \theta y^m} - y. \tag{8.5}$$

Very small $\omega \ll 1$. If the FT unbinding to DNA is much slower than its own degradation, i.e., $\omega = \frac{\beta}{d} \ll 1$, then this time $y(t)$ reaches its quasi-steady state quickly while x barely changes:

$$y(x) = g + (1 - g)x.$$

Substututing this into the first equation in (8.4), we have

$$\frac{dx}{dt} = \omega\Big\{\theta\big[g + (1-g)x\big]^m(1-x) - x\Big\}. \tag{8.6}$$

8.3 A gene network as a clock

We now consider again a system of gene regulatory network in which there are three-step relay: TF-1 is the repressor for gene expression of TF-2, which in turn is the repressor for gene expression of TF-3, which in turn is the repressor for gene expression of TF-1.

We shall use m_i and p_i for the concentrations of mRNA and protein of FT-i:

$$\frac{dm_i}{dt} = f\big(p_{i-1}\big) - m_i, \quad f(p) = \alpha_0 + \frac{\alpha_1}{1+p^n}, \tag{8.7a}$$

$$\frac{dp_i}{dt} = -\beta\big(p_i - m_i\big), \tag{8.7b}$$

in which $i = 1, 2, 3$ and $p_0 = p_3$. That is, the $(i-1)^{th}$ protein inhibits the synthesis of i^{th} mRNA. This model is known as *repressilator*, e.g, repression-driven oscillator. It is a successful stroy of several independent engineering studies in 2000: A single pair of (m, p) developed by Becskei and Serrano, two pairs of (m, p) giving rise to bistability investigated by Gardner, Cantor, and Collins, and three pairs of (m, p), as in an oscillatory system (8.7) by Elowitz and Leibler.

The steady state of the three systems with one, two, and three pairs of (m, p) can be obtained as the roots to

$$\underbrace{f\big(f\big(f}_{k}(x)\big)\big) - x = 0, \tag{8.8}$$

in which $k = 1, 2, 3$. Note that $f(x)$ is a monotonically decreasing function of x. Hence $f(f(f(x)))$ is also a monotonically decreasing function of x. This implies there is only a single root to Eq. (8.8). It is the same root as $f(x) = x$:

$$\big(x - \alpha_0\big)\big(1 + x^n\big) - \alpha_1 = 0. \tag{8.9}$$

On the other hand, the function $f(f(x))$ is actually a monotonic increasing function of x.

Fig. 8.1 shows that $f(x)$, $f(f(x))$ and $f(f(f(x)))$ all intersect with x at a same x^*. The system with two pairs of (m, p) are two genes with mutual repression. It actually constitutes a positve feedback, as shown by the red curve in Fig. 8.1.

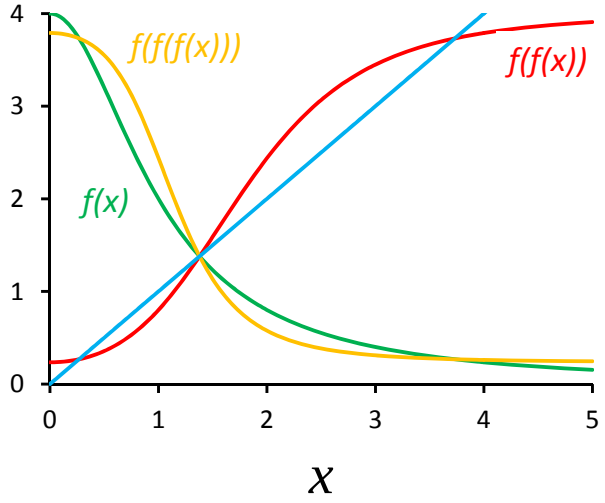

Figure 8.1: $f(x) = x$, $f(f(x)) = x$, and $f(f(f(x))) = x$ all have a same root. However, $f(f(x)) = x$ has two additional roots. Parameters $\alpha = 4$ and $m = 2$.

Chapter 9

A mathematical theory of conservative ecology

The populations of biological species and organisms, or even the biochemical species inside a living cell, usually are not at constant levels. Ecological conservation(s) should be understood as a phenomenon among inter-related species, with a conservation of certain quantities that are combinations of the participating populations. To see how this works, one of the good examples is the Lotka-Volterra predation-prey dynamics, in which the dynamics populations of prey and predator, $(u(t), v(t))$, satisfy $H(u, v) = \alpha(u - \ln u) + (v - \ln v) =$ const.

A mathematical theory of conservation ecology, therefore, is to discover and to define these hidden relations and their manifestations. In this chapter, we shall outline the fundamentals of this approach.

9.1 H-function, geometric shape of invariant manifold, and external parameters

Two essential notions of a "state". In the very detailed dynamical perspective, a (micro-)state is determined by the dynamics variables. So a single point in the phase space is considered a representation of the system, which is continuously changing with time.

In a long-time, stationary perspective, a (steady-)state is an entire, ergodic invariant manifold. The dynamics proceeds continously on the manifold.

9.2 Extending the conservation law to a broad context

9.3 From extensive quantity h to intensive quantity θ

The analysis carried out in the previous sections requires the invariant manifold to be ergodic under the dynamics. For a complex dynamical system, the H-function is not single

valued, rather, there are a set of conserved quantities $\vec{h} = \big(h_1, h_2, \cdots, h_K\big)$. The the geometric characterization $\mathcal{A} = \mathcal{A}\big(\vec{h}, \alpha\big)$.

In many ecological problems, however, the complete list of conserved quantities is difficult to obtain. In this case, a changing of perspective from extensive quantity to intensive quantity solves the problem of non-ergodicity. Coming with this change, however, is an introduction of *uncertainty*: The theory of probability enters into the deterministic dynamical systems theory.

9.4 Changing the dimensionality and Gibbs paradox

We now discuss one of the most important concepts in the theory of ecological conservation: the notion of ***chemical potential***. We again consider a predator-prey system which consists of n-pair of predator and prey, each and every one follows the same dynamic equation (7.2). This is a *reducible* dynamical system of $2n$-dimensions.

It is easy to show that the total H-function is

$$H_n(x_1, y_1, x_2, y_2, \cdots, x_n, y_n) = \sum_{i=1}^{n} H_1(x_i, y_i), \tag{9.1a}$$

in which

$$H_1(x, y) = \alpha\big(x - \ln x\big) + \big(y - \ln y\big). \tag{9.1b}$$

There is a very important, distinct feature in this system: A given H_n can in fact correspond to many different possibility of H_1, H_2, $\cdots$, each one of them are conserved in the dynamics. Such dynamical system is known as *non-ergodic*. Therefore, treating n as an external variable, the meaning of

$$\begin{aligned} & \mathcal{A}_{n+1} - \mathcal{A}_n \\ = \; & \Big[H_{n+1}\big(x_1, y_1, x_2, y_2, \cdots, x_n, y_n, x_{n+1}, y_{n+1}\big) - H_n\big(x_1, y_1, x_2, y_2, \cdots, x_n, y_n\big)\Big]_{h,\alpha} \end{aligned} \tag{9.2}$$

requires a careful analysis. One way to carry out this analysis is to change from a constant h, an extensive quantity, perspective to a constant θ, an intensive quantity, perspective.

9.5 Chemical potential in reaction systems

Let us start with arguably the simplest chemical reaction

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C + D. \tag{9.3}$$

We have, according to the Law of Mass Action:

$$-\frac{dc_A}{dt} = -\frac{dc_B}{dt} = \frac{dc_C}{dt} = \frac{dc_D}{dt} = k_+ c_A c_B - k_- c_C c_D. \tag{9.4}$$

In chemistry, the chemical potential of a chemical specie X in a reaction system is defined as

$$\mu_X = \mu_X^o + k_B T \ln c_X.$$

It has two parts: the first part, μ_X^o, is solely determined by the nature of chemical structure of a chemical species. It is related to something called "the internal energy". The second part is related to the amount of the chemical in a system. k_B is kown as the Boltzmann constant: $1.3806488 \times 10^{-23}$ m^2 kg s^{-2} K^{-1}, T is temperature in Kelvin.

The chemical potential of the right-hand-side of reaction (9.3) is $\mu_A + \mu_B$; and the chemical potential of the right-hand-side of the reaction is $\mu_C + \mu_D$. In a chemcial equilibrium, one has

$$\mu_A + \mu_B = \mu_C + \mu_D. \tag{9.5}$$

This leads to

$$\mu_A^o + \mu_B^o - \mu_C^o - \mu_D^o = k_B T \ln \left(\frac{c_C^{eq} c_D^{eq}}{c_A^{eq} c_B^{eq}} \right). \tag{9.6}$$

From the dynamic equation in (9.4), however, we have

$$\left(\frac{c_C^{eq} c_D^{eq}}{c_A^{eq} c_B^{eq}} \right) = \frac{k_+}{k_-}. \tag{9.7}$$

Putting these together, we have the chemical potential difference across the reaction (9.3)

$$\Delta\mu = \mu_A + \mu_B - \mu_C - \mu_D = k_B T \ln \left(\frac{k_+ c_A c_B}{k_- c_C c_D} \right). \tag{9.8}$$

Now consider a chemical reaction as (9.3) in a controlled test tube, where all the four chemcial species are activated being maintained by an experimenter. Then The reaction flux, i.e., the *net* number of reactions per unit time, from the left to the right, is

$$J = k_+ c_A c_B - k_- c_C c_D. \tag{9.9}$$

When $\Delta\mu > 0$, $J > 0$; when $\Delta\mu < 0$, $J < 0$. More importantly,

$$J \times \Delta\mu = \Big(k_+ c_A c_B - k_- c_C c_D \Big) k_B T \ln \left(\frac{k_+ c_A c_B}{k_- c_C c_D} \right) \geq 0. \tag{9.10}$$

always. It equals to zero if and only if the chemical reaction is at chemical equilibrium. What is the meaning of the term $J \times \Delta\mu$? Why is it never negative?

This is related to the First and Second Laws of thermodynamics. $J \times \Delta\mu$ in fact is the amount of work the experimentor has to do in order to keep the concentrations of c_A, c_B, c_C, and c_D. This amount of work is released as heat in the chemical reaction. The reason why it is always positive is the Second Law of Thermodynamics: you can turn chemical and biochemical energy into heat, but you can not turn 100% heat into chemical energy with a single temperature bath (Lord Kelvin's statement).

Reactions with multiple steps. If a raction has intermediate steps:

$$A + B \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} X_1 \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} X_2 + Y_2 + Z_2 \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} \cdots \underset{k_{-n}}{\overset{k_{+n}}{\rightleftharpoons}} C + D. \tag{9.11}$$

It can be easily shown that

$$\Delta\mu = k_B T \ln\left(\frac{k_{+1}k_{+2}\cdots k_{+n}c_A c_B}{k_{-1}k_{-2}\cdots k_{-n}c_C c_D}\right). \tag{9.12}$$

9.6 The energy expanditure in cellular signaling

All biological organism require"food" in the form of chemicals. How are the various types of food used in a biological system, more specifically on a cellular level? According to the current biology, there are three major "energy sinks" at the cellular level: (i) biosynthesis, (ii) powering mechanical movements, and (iii) sustaining ionic and chemical gradients. Note that these three ways of using energy are very classic; well established in 18th and 19th centuries. How about "information processing"? Does information processing require energy expenditure?

In current cell biology, *information processing* is known as "regulations" and "signalings".

Reversible enzyme kinetics. Let us again consider an enzmatic reaction:

$$E + S \underset{k_{-1}}{\overset{\hat{k}_{+1}}{\rightleftharpoons}} ES \underset{\hat{k}_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} E + P. \tag{9.13}$$

Now consider this is a single-enzyme system in terms of Markov probability $p_0(t)$ and $p_1(t)$ for the states E, and ES at time t:

$$\frac{dp_0}{dt} = k_{+2}p_1 - \big(k_{-2} + k_{+1}\big)p_0 + k_{-1}p_1, \tag{9.14a}$$

$$\frac{dp_1}{dt} = k_{+1}p_0 - \big(k_{-1} + k_{+2}\big)p_1 + k_{-2}p_0, \tag{9.14b}$$

in which we introduced two new notations $k_{+1} = \hat{k_1}c_S$ and $k_{-2} = \hat{k}_{-2}c_P$. c_A and c_B are assumed to be constant in a living steady state.

Now let us solve the steady state probabilities p_0^{ss} and p_1^{ss} from (9.14), and more importantly the steady state flux from $S \to P$:

$$p_0^{ss} = \frac{k_{-1} + k_{+2}}{k_{+1} + k_{-1} + k_{+2} + k_{-2}},$$

$$p_1^{ss} = \frac{k_{+1} + k_{-2}}{k_{+1} + k_{-1} + k_{+2} + k_{-2}},$$

$$J^{ss}_{S\to P} = p_0^{ss}k_{+1} - p_1^{ss}k_{-1} = p_1^{ss}k_{+2} - p_0^{ss}k_{-2}$$

$$= \frac{k_{+1}k_{+2} - k_{-1}k_{-2}}{k_{+1} + k_{-1} + k_{+2} + k_{-2}} = \frac{\hat{k}_{+1}k_{+2}c_S - k_{-1}\hat{k}_{-2}c_P}{\hat{k}_{+1}c_S + k_{-1} + k_{+2} + \hat{k}_{-2}c_P}. \tag{9.15}$$

Eq. (9.15) can be written as

$$J^{ss}_{S\to P} = \frac{V_f \dfrac{c_S}{K_{MS}} - V_r \dfrac{c_P}{K_{MP}}}{1 + \dfrac{c_S}{K_{MS}} + \dfrac{c_P}{K_{MP}}}. \tag{9.16}$$

with

$$K_{MS} = \frac{k_{-1} + k_{+2}}{\hat{k}_{+1}},\ K_{MP} = \frac{k_{-1} + k_{+2}}{\hat{k}_{-2}},\ V_f = k_{+2},\ V_r = k_{-1}.$$

Eq. (9.16) is known as Briggs-Haldane's theory of reversible enzyme. When $k_{-2} = 0$, it is reduced to the Michaelis-Menten kinetics with linear relationship between $\left(J^{ss}\right)^{-1}$ and c_S^{-1}.

$$J^{ss}_{S\to P} = \frac{V_f c_S}{K_{MS} + c_S}.$$

Three-state enzyme cycle. We now consider a more complex enzymatic reaction:

$$E + A \underset{k_{-1}}{\overset{\hat{k}_{+1}}{\rightleftharpoons}} EA_1 \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} EA_2 \underset{\hat{k}_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} E + B. \tag{9.17}$$

Now consider this is a single-enzyme system in terms of Markov probability $p_0(t)$, $p_1(t)$ and $p_2(t)$ for the states E, ES_1 and ES_2 at time t:

$$\frac{dp_0}{dt} = k_{+3}p_2 - \big(k_{-3} + k_{+1}\big)p_0 + k_{-1}p_1, \tag{9.18a}$$

$$\frac{dp_1}{dt} = k_{+1}p_0 - \big(k_{-1} + k_{+2}\big)p_1 + k_{-2}p_2, \tag{9.18b}$$

$$\frac{dp_2}{dt} = k_{+2}p_1 - \big(k_{-2} + k_{+3}\big)p_2 + k_{-3}p_0, \tag{9.18c}$$

in which we introduced two new notations $k_{+1} = \hat{k_1}c_A$ and $k_{-3} = \hat{k}_{-3}c_B$. c_A and c_B are assumed to be constant in a living steady state.

Now let us solve the steady state probabilities p_0^{ss}, p_1^{ss}, and p_2^{ss} from (9.18), and more importantly the steady state flux from $A \to B$:

$$J^{ss}_{A\to B} = \frac{k_1k_2k_3 - k_{-1}k_{-2}k_{-3}}{\left\{ \begin{array}{l} k_{+1}k_{+2} + k_{-1}k_{-3} + k_{+2}k_{-3} + k_{+2}k_{+3} + k_{-2}k_{-1} + k_{+3}k_{-1} \\ +k_{+3}k_{+1} + k_{-3}k_{-2} + k_{+1}k_{-2} \end{array} \right\}} \tag{9.19}$$

$$= \frac{\hat{k}_1k_2k_3c_A - k_{-1}k_{-2}\hat{k}_{-3}c_B}{\{\cdots\ \cdots\}}. \tag{9.20}$$

We now use the result in (9.20) to study a class of enzyme also known as molecular motors.

Phosphorylation-dephosphorylation signaling. We now turn our attention to phosphorylation signaling in cell biology. In particular, we shall discuss phosphorylation-dephosphorylation mechanism for cellular biochemical signaling.

$$E + ATP + K \underset{\beta_1}{\overset{\alpha_1}{\rightleftharpoons}} E^* + ADP + K, \tag{9.21a}$$

$$E^* + P \underset{\beta_2}{\overset{\alpha_2}{\rightleftharpoons}} E + Pi + P, \tag{9.21b}$$

in which E^* is the phosphorylated form of enzyme E; K stands for a protein kinase, and P stands for a phosphatase.

If one combines the two reactions in (9.21), then

$$ATP \underset{\beta_1}{\overset{\alpha_1}{\rightleftharpoons}} \cdots \underset{\alpha_2}{\overset{\beta_2}{\rightleftharpoons}} ADP + Pi,$$

the chemical potential difference for ATP hydrolysis is

$$\Delta\mu = k_B T \ln\left(\frac{\alpha_1\alpha_2 c_{ATP}}{\beta_1\beta_2 c_{ADP}c_{Pi}}\right).$$

According to the Law of Mass Action, we have

$$-\frac{dc_E}{dt} = \frac{dc_{E^*}}{dt} = \alpha_1 c_{ATP}c_E c_K - \beta_1 c_{ADP}c_{E^*}c_K - \alpha_2 c_{E^*}c_P + \beta_2 c_{Pi}c_E c_P. \tag{9.22}$$

Therefore, in the steady state, the fraction of E in the phosphorylated E^* state is

$$\begin{aligned}\left(\frac{c_{E^*}}{c_E + c_{E^*}}\right)^{ss} &= \frac{\alpha_1 c_{ATP}c_K + \beta_2 c_{Pi}c_P}{\alpha_1 c_{ATP}c_K + \beta_2 c_{Pi}c_P + \alpha_2 c_P + \beta_1 c_{ADP}c_K} \\ &= \frac{\theta_1\left(\dfrac{c_K}{c_P}\right) + \theta_2}{\theta_1\left(\dfrac{c_K}{c_P}\right) + \theta_2 + \dfrac{\theta_1}{\theta_2}\left(\dfrac{c_K}{c_P}\right)e^{-\Delta\mu/(k_B T)} + 1}\end{aligned} \tag{9.23}$$

in which parameters

$$\theta_1 = \frac{\alpha_1 c_{ATP}}{\alpha_2} \text{ and } \theta_2 = \frac{\beta_2 c_{Pi}}{\alpha_2}.$$

Fig. 9.1 shows the fraction of phosphorylated E^* as a function of $\theta_1(c_K/c_P)$ with various values of ATP hydrolysis $\Delta\mu$. With small $\Delta\mu$, the upsteam kinase can no longer signal the phosphorylation the down-stream substrate enzyme.

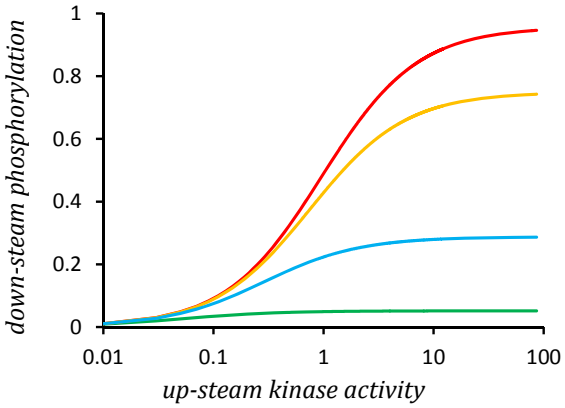

Figure 9.1: Down-stream fraction of steady state phosphorylation, $\frac{c_{E^*}}{c_E+c_{E^*}}$, as a function of the up-steam kinase activity, $\frac{\theta_1 c_K}{c_P}$. Different curves are for different values of ATP hydrolysis chemical potential $\frac{\Delta\mu}{k_B T}$: 10 (red), 8 (orange), 6 (blue), and 4 (green). Parameter $\theta_2 = 0.001$.

Chapter 10

Stochastic birth-and-death process

10.1 Steady state of birth-and-death process

The general dynamics for the probability distribution of a birth-and-death process is

$$\frac{d}{dt}p_n(t) = u_{n-1}p_{n-1} - (w_n + u_n)\,p_n + w_{n+1}p_{n+1}. \tag{10.1}$$

The stationary solution to the equation is

$$\begin{aligned}\frac{p_n^s}{p_0^s} &= \frac{p_n^s}{p_{n-1}^s} \times \frac{p_{n-1}^s}{p_{n-2}^s} \times \cdots \times \frac{p_1^s}{p_0^s} \\ &= \frac{u_{n-1}}{w_n} \times \frac{u_{n-2}}{w_{n-1}} \times \cdots \times \frac{u_0}{w_1} \\ &= \exp\left\{\sum_{m=1}^{n} \ln \frac{u_{m-1}}{w_m}\right\}. \end{aligned} \tag{10.2}$$

We now introduce continuous variable $x = n/b$, and similarly $m/b = z$. Then the sum in Eq. (10.2) can be written as an integral, through a Riemann integral: patition, sum, taking limit. First, let us denote

$$\lim_{b\to\infty} \frac{u_{bz-1}}{w_{bz}} = \frac{u(z)}{w(z)}. \tag{10.3}$$

Then the sum

$$\sum_{m=1}^{n} \ln \frac{u_{m-1}}{w_m} = b\int_0^x dx \ln \frac{u(z)}{w(z)}, \quad dx = \frac{1}{b}. \tag{10.4}$$

Now let us consider birth and death rates according to the ecological model given in Eq. (5.1):

$$u_n = rn, \quad w_n = \frac{rn^2}{q} + \frac{an^2}{b^2+n^2}. \tag{10.5}$$

Then

$$\begin{aligned}\frac{u(x)}{w(x)} &= \lim_{b\to\infty} \frac{rbx}{\frac{r(bx)^2}{q} + \frac{a(bx)^2}{b^2+(bx)^2}} \\ &= \lim_{b\to\infty} \frac{rb}{\frac{rb^2x}{q} + \frac{ax}{1+x^2}} = \lim_{b\to\infty} \frac{\alpha\beta}{\alpha x + \frac{x}{1+x^2}} \end{aligned} \tag{10.6}$$

Then, the probability density function for the continuous population x,

$$\begin{aligned} f(x) = \lim_{b\to\infty} p_{xb}^s &= A\exp\left\{b\int_0^x dv \ln \frac{\alpha\beta(1+v^2)}{\alpha v(1+v^2)+v}\right\} \\ &= A\exp\left\{b\int_0^x dv \left[\ln\beta + \ln(1+v^2) - \ln v - \ln\left(\sigma^2+v^2\right)\right]\right\} \\ &= A\exp\left(-b\phi(x)\right), \end{aligned} \tag{10.7}$$

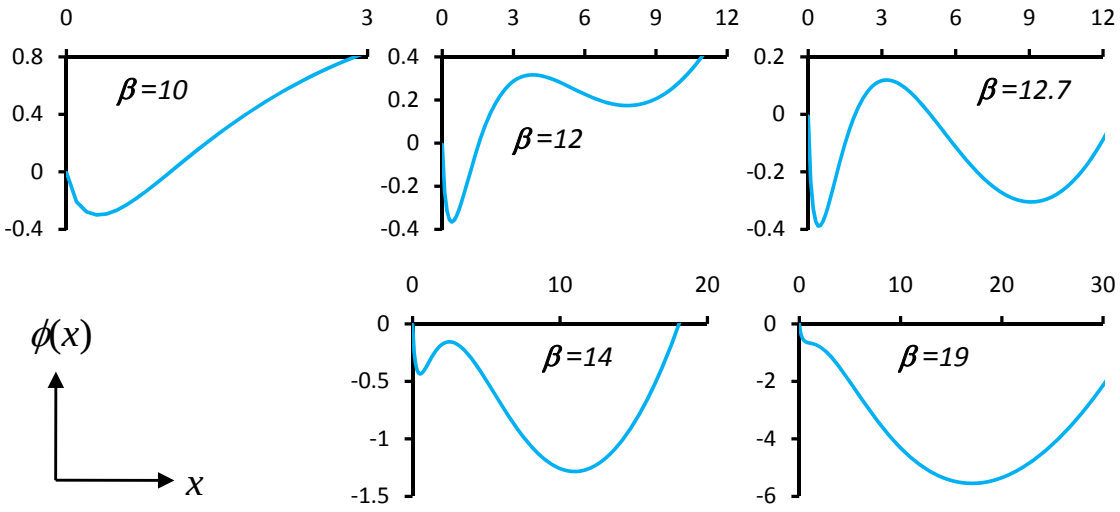

Figure 10.1: $\phi(x)$ given by Eq. (10.8) with different values of β and $\alpha = 0.03$, corresponding to $\sigma = 5.86$.

in which $\sigma^2 = \frac{1+\alpha}{\alpha}$, A is a constant, and

$$\phi(x) = x \ln\left(\frac{\sigma^2 + x^2}{1 + x^2}\right) + 2\sigma \arctan\left(\frac{x}{\sigma}\right) + x \ln\left(\frac{x}{\beta}\right) - 2 \arctan x - x. \tag{10.8}$$

10.2 Relation between deterministic and stochastic steady states and time scales

Fig. 10.1 shows that $\phi(x)$ for $\alpha = 0.03$ and $\beta = 10, 12, 12.7, 14$ and 19. Comparing Figs. **??** and 10.1, it seems that the minima of $\phi(x)$ are located at the steady state of ordinary differential equation (**??**). This turns out to be exactly true: The minima of $\phi(x)$ are located exactly at the stable steady states of the ODE; and the maxima are located at the unstable steady states of the ODE. To show that we only have to carry out the derivative

$$\frac{d\phi(x)}{dx} = -\ln \frac{\alpha\beta(1 + x^2)}{\alpha x(1 + x^2) + x} = -\ln \frac{b(x)}{d(x)}. \tag{10.9}$$

Therefore, steady states x^s where $b(x^s) = d(x^s)$ is also the place $\frac{d}{dx}\phi(x^s) = 0$.

We note that with $b \to \infty$, the probability density function $f(x) \to \delta(x - x^*)$ where x^* is the global minimum of $\phi(x)$. The global minimum will have probability 1 while all the local minima have probability 0. A local minimum is called a metastable state.

The concept of Lyapunov property. If for a deterministic dynamics $\dot{x} = f(x)$ a function $L(x)$ satisfies

$$\frac{d}{dt}L\left(x(t)\right) \leq 0, \tag{10.10}$$

then we say function $L(x)$ has Lyapunov property with respect to the dynamics. $\phi(x)$ has Lyapunov property with respect to the ODE $\dot{x} = b(x) - d(x)$:

$$\frac{d}{dt}\phi\left(x(t)\right) = \left(\frac{d\phi(x)}{dx}\right)\frac{dx}{dt} = -\ln\left(\frac{b(x)}{d(x)}\right) \times \left(b(x) - d(x)\right) \leq 0. \tag{10.11}$$

In an evolutionary time scale, ODE's $t = \infty$ is very short. For any finite b, i.e., finite population, its dynamics is stochastic and in a correspondingly long time, $\sim e^{cb}$ $(c > 0)$ the dynamics will have finite probabilities near both stable steady state. This is represented by the $e^{-b\phi(x)}$. However, in order for such a stationary distribution to emerge, the dynamics has to be in the two regines back and forth many times. This is a time scale beyond the infinite of the ODE dynamics. We shall call this "evolutionary time scale".

Some philosophical implications. Deterministic dynamics is the cornerstone of Newtonian theory of our physical world. Simple differential equations have stable steady states. The dynamics is usually "converging" to stable steady states; depending on the initial condition.

However, as we have shown, this coverging dynamic view is only valid on a very short time scale. In a much longer "evolutionary" time scale, the dynamics will be "diverging". For highly nonlinear systems, there are many many stable attractors, and the "evolutionary dynamics" is stochastic and jumps among all the different attractors. Deterministic dynamics is *intra-attractoral* while the stochastic evolutionary dynamics is *inter-attractoral*. They are on a completely different time scale.

10.3 Two stochastic dynamics with idential macroscopic ODE

This section is required for 523, but optional for 423.

We now discussion how different two stochastic systems can be, even though they have idential macroscopic dynamics. We use the logistic growth model as an example:

$$\frac{dn}{dt} = rn\left(1 - \frac{n}{q}\right), \tag{10.12}$$

We shall interpret the Eq. (10.12) as

(i) birth rate rn and death rate rn^2/q; and

(ii) death rate zero while the percapita birth rate $r(1 - n/q)$ decreases with n.

Again, we introduce continuous variable $x = n/q$: Then the macroscopic ODE is

$$\frac{dx}{dt} = rx(1 - x). \tag{10.13}$$

Linear growth rate and quadratic death rate. $u_n = rn$ and $w_n = rn^2/q$. Then we have

$$\frac{d}{dt}p_n(t) = r(n-1)p_{n-1} - rn\left(1+\frac{n}{q}\right)p_n + \frac{r(n+1)^2}{q}p_{n+1}. \tag{10.14}$$

In the limit of $n, q \to \infty$ and $n/q = x$:

$$\begin{aligned} \ln f^s(x) &= -\int_0^x dz \ln\left(\frac{rqz}{rqz^2}\right) + \text{Const.} \\ &= x\ln x - x + \text{Const.} \end{aligned} \tag{10.15}$$

This function has a single minimum at $x = 1$, corresponds to the stable steady state of Eq. (10.13).

Pure birth process with decreasing birth rate. $u_n = rn(1-n/q)$ and $w_n = 0$. Then,

$$\frac{d}{dt}p_n(t) = r(n-1)\left(1+\frac{n-1}{q}\right)p_{n-1} - rn\left(1+\frac{n}{q}\right)p_n. \tag{10.16}$$

The long time dynamics $n = q$ is an absorbing state. The stationary distribution is $p_n^s = \delta_{n,q}$. That is, $x = 1$ is an absorbing state of the system with stationary distribution $f^s(x) = \delta(x-1)$.

One can, however, compute the so-called quasi-stationary distribution, i.e., the distribution among the population that has not been absorbed:

$$\ln f^{qs}(x) = \ln x + \ln(1-x) + \text{const.} \tag{10.17}$$

10.4 Scaling of population size and "large-system limit"

In the light of all the discussions on discrete, random events involved in the birth and death of individuals in a population, we need to have a more precise description of how to "justify" the continuous differential equations in the previous sections. One of the natural way to do this is to introduce a new variable $x = n/b$, or $\widehat{x} = n/q$. Note that with a very large given b (or q), the quantities like x tends to continuous variables. The differential equation (**??**) appears independent of b.

It is also becomes clear that the dynamics described by the differential equation is *not* the dynamics of the mean value *per se*. It is the dynamics of an infinitely large population with x being a *population density*. x is an intensive quantity in the ODE (**??**), not an extensive quantity as n in Eq. (**??**).

Chapter 11

Numerical methods

11.1 Euler's method

11.2 Runge-Kutta method

11.3 von Neumann rejection method for random number generation

[1]

11.4 Tau-leaping

11.5 First-reaction and next-reaction methods

[2]

[1] Chen, Y. (2005) Another look at rejection samplingthrough importance sampling. *Statistics & Probability Letters*, 72, 277–283.

[2] Gibson, M. A. and Bruck, J. (2000) Efficient exact stochastic simulation of chemical systems with many species and many channels. *Journal of Physical Chemistry A*, 104, 1876–1889.

Chapter 12

Reaction-Diffusion Equation, Traveling Wave and Pattern Formation

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} - \beta u + (1+\beta)u^2 - u^3, \quad (\beta < 1) \tag{12.1}$$

with boundary conditions

$$u(-\infty) = 0, \quad u(\infty) = 1. \tag{12.2}$$

The nonlinear equation has an exact solution

$$u(x,t) = \frac{\beta \exp\left(\lambda_1 \xi_1\right) + \exp\left(\lambda_2 \xi_2\right)}{1 + \exp\left(\lambda_1 \xi_1\right) + \exp\left(\lambda_2 \xi_2\right)}, \tag{12.3a}$$

in which

$$\xi_i = x - c_i t + \phi_i, \tag{12.3b}$$

$$c_i = \sqrt{2}\big(1+\beta\big) - 3\lambda_i, \ \ i = 1, 2, \tag{12.3c}$$

$$\lambda_1 = \frac{\beta}{\sqrt{2}}, \quad \lambda_2 = \frac{1}{\sqrt{2}}. \tag{12.3d}$$

The solution is obtained as follows. Let us introduce a transformation

$$u(x,t) = \mu \frac{w_x}{w + \sigma}, \quad (\mu \neq 0) \tag{12.4}$$

where σ is a constant. Substituting this into the original equation, we have, since constant σ is arbitrary:

$$w_{xx} = w_{xxx} - \beta w_x, \tag{12.5}$$

$$w_t = 3w_{xx} - (1+\beta)\mu w_x, \tag{12.6}$$

$$\mu = \pm\sqrt{2}. \tag{12.7}$$

[1]

[1] Petrovskii, S. and Li, B.-L. (2003) An exactly solvable model of population dynamics with density-dependent migrations and the Allee effect. *Mathematical Biosciences*, 186, 79–91.

Chapter 13

Rare event and catastrophe

We have shown that a birth-and-death model with birth rate u_n and death rate w_n corresponds to, as the stochastic counterpart, of ordinary differential equation $\dot{x} = b(x) - d(x)$, with $b(x) \leftrightarrow u_n$ and $d(x) \leftrightarrow w_n$. And a fixed point for $\dot{x}$ is when $u_n = w_n$.

The fundamentally new phenomenon in this context is the "barrier crossing" which is absolutely impossible in an ordinary differential equation system. To investigate this new phenomenon, we consider a model of the model — a random walk with a drift. We consider the discrete time and process with rightward $p_n = p$ and leftward $q_n = q = 1 - p$. We ask a new question: What is the mean time from one place to another?

First we have the probability at position n at time m, $P_n(m)$, satisfying the equation

$$P_n(m+1) = pP_{n-1}(m) + qP_{n+1}(m). \tag{13.1}$$

In fact, tihs is the discrete version of the partial differential equation

$$\frac{\partial f(x,t)}{\partial t} = D\frac{\partial^2 f(x,t)}{\partial x^2} - V\frac{\partial f(x,t)}{\partial x}, \tag{13.2}$$

in which $D = \frac{(\Delta x)^2}{2\Delta t}$ and $V = \frac{(p-q)\Delta x}{\Delta t}$.

The mean time from position n to another position, T_n, satisfies

$$T_n = qT_{n-1} + pT_{n+1} + 1. \tag{13.3}$$

Let us consider the end point is N. This is famously known as "the gambler's ruin problem".

Then we have

$$T_N = 0, \text{ and } T_0 = T_1. \tag{13.4}$$

How do we solve the general solution for T_n? Again, it is an inhomogeneous llinear difference equation. The solution to the homogeneous problem is λ^n:

$$\lambda^n = q\lambda^{n-1} + p\lambda^{n+1}.$$

This yields $\lambda_1 = 1$ and $\lambda_2 = \frac{q}{p}$. To find a particular solution to the inhomogeneous equation, we try $T_n = an$:

$$an = qa(n-1) + pa(n+1) + 1 \implies a = \frac{1}{q-p}, \text{ if } p \neq q. \tag{13.5}$$

$\big($Note that if $p = q = \frac{1}{2}$, then the particular solution is $-n^2$.$\big)$ Therefore, the general solution to (13.3) is

$$T_n = a_1 + a_2 \left(\frac{q}{p}\right)^n + \frac{n}{q-p}. \tag{13.6}$$

Applying the boundary conditions in (13.4) we have

$$a_1 = \frac{N}{p-q} + \frac{p}{(p-q)^2}\left(\frac{q}{p}\right)^N, \quad a_2 = -\frac{p}{(p-q)^2}.$$

Therefore,

$$T_n = \frac{N-n}{p-q} + \frac{p}{(p-q)^2}\left[\left(\frac{q}{p}\right)^N - \left(\frac{q}{p}\right)^n\right], \quad \big(0 \leq n \leq N\big) \tag{13.7}$$

Let us now discuss the solution in (13.7). First, if $p > q$, then for large n and N, the terms in the $[\cdots] \approx 0$, and we have $T_n \approx \frac{N-n}{p-q}$ — distance divided by the velocity. However, when $p < q$:

$$T_{n\to N} \approx \frac{p}{(p-q)^2}\left(\frac{q}{p}\right)^N \sim e^{N\ln(q/p)}$$

is actually independent of initial position n, and it is exponentially large with respect to N.

Catastrophe in bistable system is induced by a changing "environment"; but the rare events in bistable system are spontaneous.