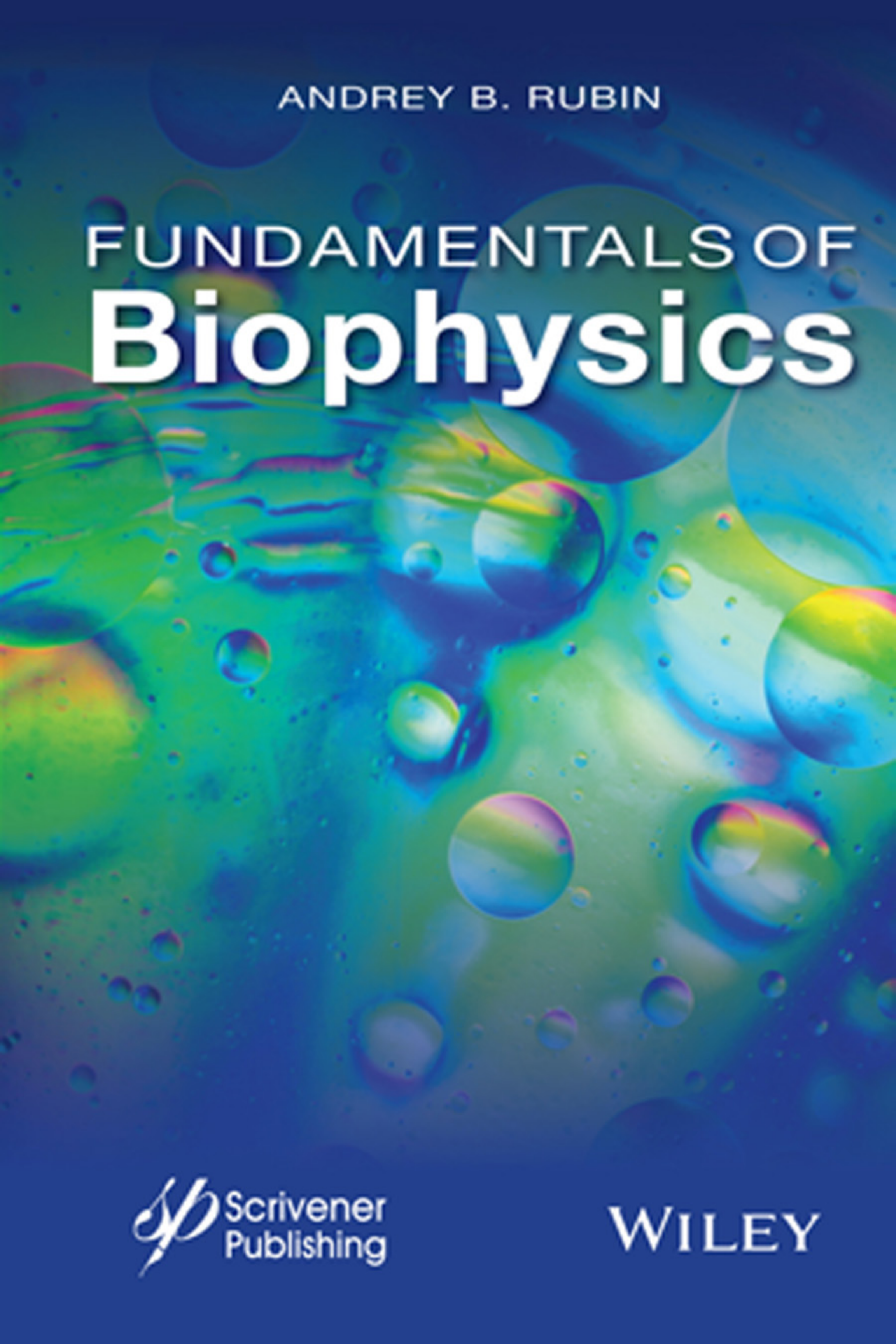

ANDREY B. RUBIN

FUNDAMENTALS OF Biophysics

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Scrivener Publishing
100 Cummings Center, Suite 541J
Beverly, MA 01915-6106

Publishers at Scrivener
Martin Scrivener (martin@scrivenerpublishing.com)
Phillip Carmical (pcarmical@scrivenerpublishing.com)

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Cover design by Kris Hackerott

Library of Congress Cataloging-in-Publication Data:

ISBN 978-1-118-84245-4

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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Preface

It is generally accepted that in the twenty-first century biology will occupy one of the leading places in science. Biology will make an important contribution not only to our fundamental knowledge but also to the development of medicine, ecology, generation of new living species. Many problems in biology which are of interdisciplinary complex character lie at the boundaries between different sciences. To solve such problems it is necessary to apply ideas and methods of other exact sciences and first of all physics, mathematics, chemistry, and physical chemistry. It is by close cooperation between biology and other exact sciences that the development of biophysics as an independent boundary science has become possible.

In this book the main ideas of modern biophysics are presented in the form accessible to wide circles of readers. Biophysics (biological physics) is a science about physical and physico-chemical mechanisms of interactions which lie in the basis of biological processes. Physical properties of biopolymers and kinetics of cell metabolic reactions are responsible for molecular characteristics of biological processes. A biomacromolecule as the main structure element in a cell is considered in biophysics as a peculiar molecular machine where energy is transformed and conversed from one type of energy into another. It is pertinent to recall what Bruce Alberts, a well known American biologist, said about a cell. He wrote that "the entire cell can be viewed as a factory that contains an elaborate network of interlocking assembly lines, each of which is composed of a set of large protein machines" (Cell, 1998, vol. 92, pp. 291-294).

The real understanding of how these protein machines operate demands the knowledge of not only atomic equilibrium structure but also our understanding of kinetic and energy characteristics of intermediate transformations. In the post-genome sequencing era the first priority is given to the mechanisms of intramolecular mobility of macromolecular complexes as the base of their activity. Such an approach corresponds to the biophysical concept of directed electron-conformational interactions when energy transformation and reaction product generation become a result of internal interaction between separate parts within the whole macromolecular complex. In other words, this is the concept of a "physical machine" put forward in 1970-1980s by D.S.Chernavsky, L.A.Blumenfeld, and M.V.Volkelshtein.

In theoretical biophysics, generalized kinetic and physical models of interactions allow to describe different biological phenomena. However the analysis of such models clearly demonstrates that different biological processes can very often be similar with respect to their molecular mechanisms. For example, mechanisms of primary photobiological processes (photosynthesis, visual reception), enzyme catalysis in the enzyme active center, and ion transfer through membrane channels are governed by similar physical principles. It follows that educational programs on biology at universities should necessarily include ideas of physics, mathematics and physical chemistry, thus illustrating their efficiency in solving biological problems. Biophysics bears the main responsibility to show an important role of regular application of ideas from exact sciences in studying biological processes.

The great experience gained at Moscow State University has shown that this requirement is satisfied when teaching of biophysics is carried on within a logically combined independent general course on biophysics. Such a lecture course on biophysics is given both to biology and physics undergraduates as well as to bachelors of medicine and agriculture. It is useful for scientists working in other fields who want to study biological problems using methods of exact sciences.

In this book the main ideas and concepts of theoretical biophysics (kinetics and thermodynamics of biological processes, molecular biophysics) are presented in a concise and simple form. It makes the base for the biophysical analysis of some important processes (membrane processes, primary photobiological processes and enzyme reactions) analyzed in the book. The material is quite understandable and accessible to specialists of different profiles and background. It is useful for the subsequent profound studying of biophysics using special literature sources for the application of the biophysical approach in different fields of biology.

1

Dynamic Properties of Biological Processes

Biological Kinetics. Intricate network of various reactions, specifically organized in time and space, underlie both cell exchange processes with the environment and internal metabolism. In biological systems, components interact continuously with each other, which for the most part specifies the nature of dynamic behavior of intact biological systems, mechanisms of their self-control and governing named kinetics of biological processes. As a result of such processes, concentrations of different substances, the number of individual cells and the biomass of organisms change; the other values may also vary, for instance the transmembrane potential in the cell. Upon description of the kinetics in biological systems, the basic initial prerequisites are generally the same as in chemical kinetics.

It is believed that changes of variables at every time moment can be described using corresponding differential equations. In addition to variable values, a kinetic system has a set of specific parameters that remain unchanged during its examination and characterize the conditions of reactions (temperature, humidity, pH, and electrostatic conductivity). As a rule, the constant values of the reaction rates are determined by such parameters.

Let us analyze an elementary example of closed cell population in which multiplication and death occur concurrently and which are abundant in nutrients. The questions arise: how is the number of cells changed in such a system with time, and can a stationary state eventually form in it when the number of cells remains the same? This kinetic problem may be solved with the use of differential equations. Let at moment t the concentration of cells in the environment be *N*. The rate of the cell concentration changes in the environment $\frac{dN}{dt}$ is the net sum of their multiplication rate (v_{mitipl}) and death rate (v_{death}).

$$\frac{dN}{dt} = v_{\text{multipl}} - v_{\text{death}}.$$

In an ordinary case, the multiplication rate, which is the increase in the cell concentration per time unit, is proportional to their number at every moment, i.e.

$$V_{\text{multipl}} = k_1 N,$$

where k_1 is the proportionality constant dependent on the environmental conditions (temperature, the presence of nutrients, etc.)

Correspondingly

$$V_{\text{death}} = k_2 N,$$

where k_2 is the constant determining the intensity of processes of cell death. Hence it follows that

$$\frac{dN}{dt} = k_1 N - k_2 N = kN, \tag{1.1}$$

where $k = k_1 - k_2$.

By solving the above equation we will see how the cell concentration is changed with time in the environment $N = N(t)$. By integrating Eq. (1.1) we get

$$\int \frac{dN}{N} = \int k dt \,;$$

$$\ln N = kt + c;$$

$$N = N_0 e^{kt}, \tag{1.2}$$

where N_0 is the cell concentration at zero time $t = 0$ of the examining the system.

It can be seen that depending on the ratio of the death rate constant (k_2) and multiplication rate constant (k_1) the destiny of this closed population will be different. If $k_1 > k_2$, $k > 0$, the system will give rise to the unlimited growth of the cell number.

$N(t) \rightarrow \infty$ at $t \rightarrow \infty$.

If $k_1 < k_2$, the population will dye out with time

$N(t) \rightarrow \infty$ at $t \rightarrow \infty$.

And only in a particular case when $k_1 = k_2$ the number of cells will remain constant

$N = N_0$.

Another example of the model of the population growth in the environment with a limited amount of nutrients is the known equation of a logistic curve. The Verhulst equation is as follows

$$\frac{dN}{dt} = k_1 N \left(\frac{N_{\max} - N}{N_{\max}} \right). \tag{1.3}$$

Here $N_{\max}$ is the maximal population number possible under such conditions. Curve $N = N(t)$ described by the above equation is shown in Fig. 1.1. At the initial period of growth, when $N \ll N_{\max}$ the curve is exponential. Then, after the inflection, the slope gradually decreases and the curve approaches the upper asymptote $N = N_{\max}$, i.e. the maximal attainable level under such conditions.

But as compared to the typical chemical kinetics, the biological kinetics has the following specificity.

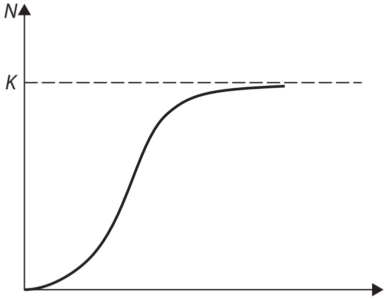

Figure 1.1 Logistic curve.

1. The variables can be not only substance concentrations but also other values.
2. The variables change not only in time but also in space (diffusion of reagents across biomembranes).
3. A biological system is heterogeneous in space and the conditions of the reagent interaction can vary in different sites of the system).
4. There exist special mechanisms of self-regulation functioning by the feedback principle.
5. The power of the polynomial in the right-hand side of the differential equation is not always dependent on the reaction order.

As a rule, a hydrodynamic model of a vessel connected with liquid inflow and outflow fluxes passing simultaneously, is taken as a simple model of an open system. The liquid levels in the vessel are dependent on the rates of liquid inflow and outflow fluxes. When the rates are the same, the liquid level would remain constant and a stationary state forms in the system. A change in the rate of at least one flow would cause a corresponding shift in the stationary level of the liquid in the vessel.

The Feedback Principle. Let us provide our hydrodynamic model with a special device that can increase or decrease the rate of liquid outflow upon rotation of the faucet at the outlet of the vessel depending on the liquid level changes. Such a system is shown in Figure 1.2. An electromotor rotates the stopcock according to the signal received from the photocell. The electric current generated in the photocell is governed by the level

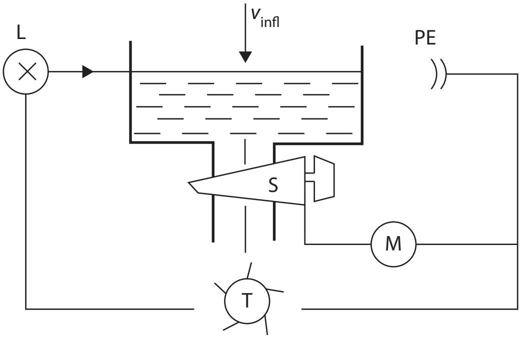

Figure 1.2 Hydrodynamic model of a feedback system. L, lamp; PE, photocell; S, stopcock; M, electromotor; T, turbine.

of light absorption that changes parallel to the liquid level in the vessel. The photocell lamp and the electromotor are power supplied from a small turbine whose blades are rotated by the water outflow. In this model the feedback principle maintains to a certain extent the liquid level upon varying the water inflow as a result of self-regulation. In biological systems, the feedback principle is used to regulate many enzyme reactions where the activity of enzymes varies depending on the reagent concentration or external conditions. As a result the concentration of reaction products remains constant. Biological systems may have different stationary regimes depending on the values of controlling parameters. It is also possible that fluctuations at the stationary states appear when concentrations of intermediate substances change in time at regular intervals and fixed frequency. Finally, under certain combinations of chemical reactions and diffusion processes proceeding concurrently, a special type of three-dimensional structure may appear in the originally homogeneous system.

The cardinal problem for biophysicists is to obtain characteristics of various dynamic regimes in complicated systems and to study conditions and parameters when they are realized in living cells. This can be done by studying the properties of stationary regimes, their stability and transition to a stationary state.

Elementary Model of Open System. Let us analyze an elementary model of an open system which exchanges substances a and b with the environment, coupled to the reversible first order reaction of transformations $a \rightleftarrows b$. In Fig.1.3, a and b are concentration variables within the system; A and B are constant concentrations of the same substances in the external vessels; and k_1, k_{+2}, k_{-2}, and k_3 are rate constants of the processes.

Though being very simple, the model reflects the basic features of metabolic processes in a cell. The supply of the substrate and the release of metabolites into the environment are triggered by the reactions $A \rightarrow a$, $b \rightarrow B$, and the transformation $a \rightleftarrows b$ corresponds to the processes of cell

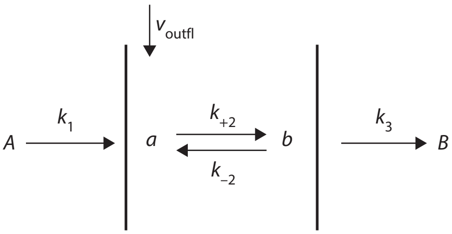

Figure 1.3 Open system: a model of metabolic processes in a cell.

metabolism. For example, glucose and oxygen as substrates for respiration are supplied to a cell at stage $A \to a$; stage $b \to B$ corresponds to the release of CO_2 and H_2O to the outside of the cell, and the entire metabolic respiratory cycle of the glucose molecule transformation can be described by reaction $a \rightleftarrows b$. The rate constant values are naturally phenomenological and generalized and therefore cannot be attributed to any particular biochemical stage. However, as we have seen, even such an utterly simplified model reveals basic features of a combination of metabolic reactions of a cell as an open system.

The kinetic equations for this system are as follows:

$$\frac{da}{dt} = k_1(A-a) + k_{-2}b - k_{+2}a = f_1(a,b),$$

$$\frac{db}{dt} = k_{+2}a - k_{-2}b - k_3(b-B) = f_2(a,b). \tag{1.4}$$

Inasmuch as at a stationary state, variables (a, b) are constant, then

$$\frac{da}{dt} = 0 \text{ and } \frac{db}{dt} = 0.$$

Let us equate the right-hand side of eq. (1.4) to zero:

$$\frac{da}{dt} = f_1(a,b) = 0; \ \frac{db}{dt} = f_2(a,b) = 0. \tag{1.5}$$

We get the system of algebraic equations:

$$\begin{cases} -(k_1 + k_{+2})a + k_{-2}b + k_1A = 0, \\ k_{+2}a - (k_{-2} + k_3)b + k_3B = 0, \end{cases} \tag{1.6}$$

from which stationary values $\overline{a}$ and $\overline{b}$ are known:

$$\overline{a} = \frac{Ak_1(k_{-2} + k_3) + k_3k_{-2}B}{k_1k_{-2} + k_1k_3 + k_{+2}k_3}; \ \overline{b} = \frac{k_3(k_1 + k_{+2})B + k_1k_{+2}A}{k_1k_{-2} + k_1k_3 + k_{+2}k_3}. \tag{1.7}$$

The above values do not depend on the initial conditions, i.e. on the initial values $a = a_o$ and $b = b_o$ at time $t = 0$ but depend only on the constant values and substance concentrations in the external vessels *A* and *B*. This means that whatever the initial state of the system is, the only stationary regime with $a = \overline{a}$, $b = \overline{b}$ will be finally formed. The system of differential equations (1.4) is solvable if dependences $a = a(t)$ and $b = b(t)$ are defined explicitly and it is ascertained how variable concentrations change with time. The solution will be

$$a(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t},$$

$$a(t) = c_1 \chi_1 e^{\lambda_1 t} + c_2 \chi_2 e^{\lambda_2 t}, \qquad (1.8)$$

where c_1 and c_2 are constants dependent on the initial conditions.

At $t = 0$, $a_o = c_1 + c_2$, $b_o = c_1 \chi_2 + c_2 \chi_2$, i.e.

$$c_1 = \frac{a_o \chi_2 - b_o}{\chi_2 - \chi_1}, \qquad (1.9)$$

$$c_2 = \frac{b_o - a_o \chi_2}{\chi_2 - \chi_1}.$$

The values λ_1 and λ_2 are exponential indices determined from the characteristic equation

$$\begin{vmatrix} -(k_1 + k_{+2}) - \lambda & k_{-2} \\ k_{+2} & -(k_{-2} + k_3) - \lambda \end{vmatrix} = 0,$$

or $\lambda^2 + \lambda(k_1 + k_{+2} + k_{-2} + k_3) + (k_1 k_{-2} + k_1 k_3 + k_{+2} k_3) = 0$.

The values χ_1 and χ_2 are estimated from the equation for the distribution coefficients

$$k_{-2}\chi^2 + (-k_1 - k_{+2} + k_{-2} + k_3)\chi - k_{+2} = 0.$$

If $t \to \infty$, then $e^{-\lambda_1 t} \to 0, e^{-\lambda_2 t} \to 0$, i.e. $a \to \overline{a}$ and $b \to \overline{b}$. This shows that finally the system attains a stationary state independent of the initial conditions $a = a_o$ and $b = b_o$. This is the so-called property of equifinality of stationary states that is inherent to open systems and frequently observed in biological processes. Although the initial conditions do not affect the

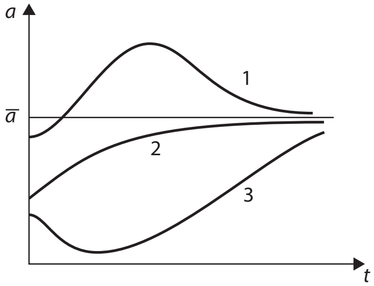

Figure 1.4 Transition curves $a(t)$ for scheme 2: 1, overshoot; 2, monotonous; 3, false start.

values of a and b, they determine a specific shape of the curves of changes in $a(t)$ and $b(t)$ and the kinetics of the transition of the system from the starting point $a = a_0$, $b = b_0$ at $t = 0$ to the stationary state $a = \bar{a}$, $b = \bar{b}$ at $t \to \infty$. Figure 1.4 demonstrates several types of such transition curves $a(t)$.

Similar shapes of the curves were traced, for example, in physiological studies of the respiration rate under different initial conditions. It should be understood that the shape of the curves depends on the initial conditions and constant k_1, k_{+2}, k_{-2}, k_3, A, and B values and can be changed due to their combinations. Examination of a simple system (1.4) shows that analytical solutions are rather bulky and are specified by a great number of parameters. It is clear that at a great number of variables, it is not only difficult to obtain such solutions but also to determine how the kinetic behavior of the system depends on its parameters. Let us pay attention to the fact that equations (1.4) have only linear members in their right-hand sides with unknown variables to the first power. However as a rule in biological systems, many processes are non-linear. Thus, the rate of the simplest second-order bimolecular reaction is described mathematically as the product of reagent concentrations, i.e. in a model of such reactions the right-hand sides of equations include non-linear members. In this case, the search for the accurate analytical solutions runs into serious mathematical difficulties and at times is not possible at all.

Qualitative Analysis of the Model. The basic approach in the contemporary kinetics and mathematical modeling of biological processes is to refuse the search for exact analytical solutions of differential equations. The idea is to get qualitative characteristics of the dynamic behavior of the system: its various stable and unstable stationary states, transitions between them, oscillatory regimes, qualitative dependence of the system behavior on critical values of the parameters. Many of these problems may be solved using methods of the qualitative theory of differential equations which allow disclosing essential general properties of the model without explicit calculation of the unknown functions. The most essential feature of a stationary state is its stability. The stability of the system depends on its ability to return spontaneously to the initial stationary state after the introduction of external disturbances that deviate the system from the initial stationary point.

Stationary Point Stability. Let us take the simplest open system $A \xrightarrow{v_{\text{infl}}} |a| \xrightarrow{v_{\text{outfl}}}$, to which substance a is supplied from an external source at a constant rate $v_o = v_{\text{infl}} = \text{const.}$

The kinetic equation is

$$\frac{da}{dt} = v_{\text{infl}} - v_{\text{outfl}} = v_0 - ka = f(a)\,, \tag{1.11}$$

where k is the rate constant v_{outfl}. The solution of this equation is very simple. But let us determine the value of stationary point $a = \bar{a}$ and estimate its stability graphically without considering the analytical solution of equation (1.11). It is evident that the stationary state $\frac{da}{dt} = 0$ in eq. (1.11) is established at such a value of $a = \bar{a}$ when the inflow and outflow rates become equal ($v_{\text{infl}} = v_{\text{outfl}}$).

Figure 1.5 shows the dependence of rates $v_{\text{infl}} = v_{\text{o}}$ and $v_{\text{outfl}} = ka$ on the a value. The plots of v_{infl} and v_{outfl} are straight lines intersecting at the point where $v_{\text{infl}} = v_{\text{outfl}}$, i.e. at the stationary point $a = \bar{a}$.

Let us see whether this point is a stationary one. Assume that incident disturbance occurred in the stationary-state system $a = \bar{a}$ that results in

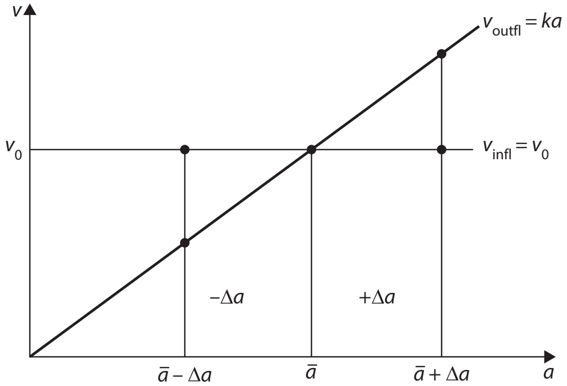

Figure 1.5 Dependence of inflow (v_{infl}) and outflow (v_{outfl}) rates on value a.

raising the stationary concentration of a by Δa and thus deviating the system from point $\bar{a}$ to the nearby point $\bar{a}$ $+\Delta a$. In the new perturbed state where $a = \bar{a} + \Delta a$, the v_{infl} and v_{outfl} values are not equal any longer and consequently the concentration of $\bar{a} + \Delta a$ begins changing. As seen from the figure, at point $\bar{a} + \Delta a$ the ratio of v_{infl} and v_{outfl} is such that $v_{\text{outfl}} > v_{\text{o}}$. Thus the concentration of $a(\bar{a}+\Delta a)$ in the system should decrease spontaneously along with the inflow rate $v_{\text{infl}} = ka$ until the rates v_{infl} and v_{outfl} become equal again when $a = \bar{a}$.

It is obvious that a similar situation will be if the incidental shift from point $a = \bar{a}$ would result in a decrease in stationary concentration a that causes the transition of the system to point $\bar{a} - \Delta a$. As far as in this case $v_{\text{infl}} = v_{\text{o}}$, the $\bar{a} - \Delta a$ value and the outflow rate would grow until v_{outfl} becomes equal to v_{o} so that the system returns to the initial state $a = \bar{a}$. So, accidental deviations from the stationary point ($\pm\Delta a$) are compensated by the system itself which just means that the system is in a stable stationary state.

The Criterion of Stability. There is an easy analytical method for determining the stationary state stability, and we will use it to examine models of biological processes with two equations.

Let us take an elementary mathematical model with a simple first-order differential equation:

$$\frac{da}{dt} = f(a), \tag{1.12}$$

where the right-hand side $f(a) = v_{\text{infl}} - v_{\text{outfl}}$ may have different form. Let the system have a stationary point $a = \bar{a}$, where $\left.\frac{da}{dt}\right|_{a=\bar{a}} = 0$ and as a result $f(\bar{a}) = 0$. We will see how the stability of point $a = \bar{a}$ is associated with the properties of function $f(a)$. We set deflection $\xi = \Delta a$ close to the stationary point $a = \bar{a}$ so that

$$\xi = a - \bar{a} \tag{1.13}$$

is a low value

$$\left|\frac{\xi}{\bar{a}}\right| = \left|\frac{a-\bar{a}}{\bar{a}}\right| << 1.$$

Let us substitute $a = \bar{a} + \xi$ from eq. (1.13) into eq. (1.12). We obtain:

$$\frac{d(\bar{a}+\xi)}{dt} = \frac{d\xi}{dt} = f(\bar{a}+\xi)\,. \tag{1.14}$$

Then we expand function $f(\bar{a}+\xi)$ in the Taylor series near point $\bar{a}$:

$$\frac{d\xi}{dt} = f(\bar{a}+\xi) = f(\bar{a}) + \left(\frac{df}{da}\right)_{a=\bar{a}} \xi + \frac{1}{2}\left(\frac{d^2 f}{da^2}\right)_{a=\bar{a}} \xi^2 + \dots \quad (1.15)$$

At the stationary point $f(\bar{a}) = 0$, so restricting ourselves to the first-order values, we obtain

$$\frac{d\xi}{dt} = f'(a)\big|_{\bar{a}}\, \xi . \quad (1.16)$$

This equation determines the time-dependent behavior of disturbance ξ introduced near the stationary point. From eq. (1.16) it follows that the change of $\xi = \xi(t)$ can be written as

$$\xi = \xi_o e^{f_a'(\bar{a})t} , \quad (1.17)$$

where ξ_o is the magnitude of the initial deviation at $t = 0$. It is clear that if $f_a'(\bar{a}) < 0$, then $\xi \rightarrow \infty$, at $t \rightarrow \infty$, that is the deviation disappear with time so that the system returns to the stationary point $\bar{a}$ which accordingly is stable. On the contrary, at the unstable state $\bar{a}$ the magnitude of the initial deviation increases with time as determined by the inequality $f_a'(\bar{a}) > 0$. In this case, it follows from eq. (1.17) that $\xi \rightarrow \infty$ at $t \rightarrow \infty$. So, at the stationary point the sign of the derivative of the right-hand side of the differential equation shows the type of stability of the stationary state. It may be easily checked that for system (1.11) $f_a'(\bar{a}) = -k < 0$ at point $\bar{a}$, i.e. at any $a = \bar{a}$ the stationary state is stable.

Several Stationary Points. Reactions of the second and higher orders can occur in a complicated system. In this case, equation $f(\bar{a}) = 0$ for determining the stationary point coordinates will have several roots, which is consistent with the fact that our system has several stationary states.

Let us analyze the model of a flow-through cultivator where concentration c is changed due to bacterial cell reproduction (γc^2), their death ($-\beta c$) and the adjusted constant rate v_o of inflow from the outside that can be altered when required. The model is as follows:

$$\frac{dc}{dt} = v_o - \beta c + \gamma c^2 = f(c) . \quad (1.18)$$

For simplicity, we take γ = 1. By equating $f(\overline{c})$ to zero, we find that there are two stationary points in the system:

$$\overline{c}_1 = \frac{\beta}{2} + \sqrt{\frac{\beta^2}{4} - v_0} \quad \text{and}$$

$$\overline{c}_2 = \frac{\beta}{2} - \sqrt{\frac{\beta^2}{4} - v_0} \tag{1.19}$$

Point $\overline{c}_1$ is not stable since the following equation is valid:

$$f'_{\overline{c}_1}(c) = 2\overline{c}_1 - \beta = 2\sqrt{\frac{\beta^2}{4} - v_0} > 0,$$

while on the contrary, point $\overline{c}_2$ is stable:

$$f'_{\overline{c}_2}(c) = 2\overline{c}_2 - \beta = -2\sqrt{\frac{\beta^2}{4} - v_0} < 0.$$

It is remarkable that the number of stationary points depends on the magnitude of v_0. As seen from eq. (1.19) while at $v_0 < \frac{\beta^2}{4}$ two stationary states $\overline{c}_1$ and $\overline{c}_2$ exist, at $v_0 > \frac{\beta^2}{4}$ there can be only one stationary state $\overline{c}_1 = \overline{c}_2 = \frac{\beta}{2}$. At $v_0 > \frac{\beta^2}{4}$ there are no stationary states at all, because $\overline{c}_1$ and $\overline{c}_2$ turn to be imaginary numbers which is not possible. So, by varying v_0 we alter not only the coordinates of the stationary points, but can also change their number. The value of $v_0 = \frac{\beta^2}{4}$, such that the number of stationary states changes or, as shown below, the type of their stability changes, is called a bifurcational value. In this case the v_0 parameter is a controlling one.

Reduction of the Number of Equations. As seen, some essential properties of stationary states can be revealed by studying the properties of the right-hand sides of differential equations without obtaining their accurate analytical solution. However such an approach yields good results when the models examined consist of a small number of equations (mostly of