

Chapter 1

Models of population dynamics and their applications in genetics

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1.1. Introduction

Population dynamics is the study of changes in the number and composition of individuals in a population, and the factors that influence those changes. Although the first population models appeared in demography and later in ecology and epidemiology, they have become increasingly important in almost all branches of biology. Methods of population dynamics are applied in ecology, epidemiology and infectious diseases, genetics, physiology, immunology and cancer growth. The rapidly developing techniques of molecular biology and genetics produce large quantities of data, that demand mathematical analysis and modelling. Using mathematical models one can analyse populations at various levels, including cells, genes, and biomolecules. Nowadays mathematical modelling of population dynamics is a central topic in theoretical biology and some biologists find that mathematical models are absolutely essential for research in modern biology. Mathematics provide a broad spectrum of methods to study population dynamics. The models use all types of differential equations, probability theory, dynamical systems, discrete mathematics and also very complicated systems which include age, stage or size structures.

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Modern genetics use a wide spectrum of mathematical models which describe the gene distribution in evolving populations, changes in a single genome or biochemical processes regulated by genes. Though genetics concerns small biological objects, the methods and models of the traditional population dynamics can be successfully applied to study genetic problems. On the other hand some genetics models are completely original, e.g. such as the Wright-Fisher and Moran models, and they initiate intensive development of the population dynamics.

Since a population is usually heterogeneous it is important to divide the population into homogeneous groups according to some significant parameters such as age, size, maturity or proliferative state of cells and study interactions between such groups. Models of this type are called *structured* and they describe the time evolution of the distribution of the population according to the fixed parameters. Structured model appeared for the first time in demography, where they described the age structure of human populations, but now they are used in all fields of biology. There are hundreds of articles and several books and collections of articles devoted to structured population models (see e.g. [4, 12, 13, 15, 33, 51, 73, 82]).

The aim of these lectures is to give a survey of mathematical models and methods of population dynamics. Some models are general, e.g. the age structured model can be applied to human population as well as to a cell population but others will concern specific populations e.g. the population of erythrocytes. The main subject will be structured populations but our aim is not to give a comprehensive review of this subject matter or even a selected part of it. We dedicate this article to students who can feel completely lost in enormous numbers of models and results concerning this subject. We want to show that most of models can be easily derived if we know only a few basic models and some general roles of investigation of the problem. Since a good model should give clearly formulated conclusions we show that our models really have this property. Most of them have asynchronous exponential growth — the behaviour having a simple biological interpretation. But since reality is not so simple we also explain when we can expect other behaviour. In order to achieve such aims we arrange the material according to mathematical structure. We consider continuous time models and discrete time models which usually describe the relations between consecutive generations. We also distinguish models according to the type of structure (discrete or continuous). We divide the lecture into four parts considering one type of models in one part. The theory of structured models is preceded by a section devoted to the history

of mathematical modelling. In this section we present “classic models”, but these models are still living and can be used as starting points in the investigations of complex phenomena. If we know the properties of a simplified model we can predict what can happen in the complex version. We will finish with a short conclusion section which provides possible directions of future investigations. Models connected with genetics play the crucial role in our presentation, although we do not collect them in one or two sections. We consider here the Penna model and models describing telomere shortening, distribution of genes in a genome, stochastic gene expression and the cell cycle.

1.2. History of mathematical modelling in biology

In many studies the history of mathematical modelling in biology usually begins in 1202. In that year Fibonacci in the book *Liber Abaci* introduced the sequence, further named after him, to describe the growth of a rabbit population. But the real history is a bit different. First, this sequence was known and used by Indian mathematicians in 500 B.C. Second, more interesting and surely more important from the view of modern science was Ulpian’s table of life expectancies [21, 49] which dates from about 220 A.D. In some sense Ulpian’s table can be treated as the first age structured model because it is possible to deduce from this table the age distribution of the Roman population.

Until the XX century demography was the only part of life sciences which used mathematics. We mention here a few names connected with these investigations. E. Halley, the most known as the astronomer, published in 1693 two articles [27, 28] on life annuities based on the mortality tables for the city of Breslau. This work was highly influential on the development of life insurance. In 1798 T. Malthus claimed in his book [48] that the human population will grow exponentially, i.e. according to the equation $N'(t) = \lambda N(t)$. Here and further $N'(t)$ denotes the derivative dN/dt . It is interesting that the old Malthusian model works properly not only in a biological laboratory. In some periods of time the world population really grew exponentially. For example, according to data taken from [37] in years 1950-1985 this growth was almost exponential and the doubling time $T = \ln 2/\lambda$ was about 36 years, but now the growth rate is a half of that one.

B. Gompertz in [25] improved in 1825 the Malthus model and proposed that the number of individuals at time t satisfies the following differential

equation

$$N'(t) = \lambda N(t) \log(N(t)/K). \quad (1.1)$$

P. F. Verhulst [77] proposed in 1838 a similar model

$$N'(t) = \lambda(1 - N(t)/K)N(t). \quad (1.2)$$

Both models are based on the assumptions that the available resources are limited, per capita birth and mortality rates depends on the population size and there is an optimal population size K . They are simple modifications of the Malthus model. The constant *per capita growth rate* λ in the Malthus model was replaced with the growth rates which depends on the population size: $f(N) = \lambda \log(N/K)$ in the Gompertz one and $f(N) = \lambda(1 - N/K)$ in the Verhulst one. If the initial size of the population is less than K , then the population grows and converges to its maximal size K . But in some situations such as an invasion on a new territory or sudden changes in the environment the initial size can be greater than K and then the population decreases and also converges to its equilibrium K . The Verhulst model is very popular and (1.2) is called the *logistic equation*.

W. C. Allee [2] observed that the reproduction and survival of individuals decrease for smaller populations and it can lead to the extinction of the population. This phenomenon is called the *Allee effect* and the reason is that small density of the population has a negative influence on the reproduction and survival of an individual. Moreover, the small genetic diversity in such a population also gives a negative effect on its survival and adaptability. The Allee effect can be added to the Verhulst model by modifying its growth rate. Since the Allee effect decreases with the growth of the population size, the simplest way is to subtract from the growth rate the term $A/(1 + BN)$ and, as a result, the size of the population can be described by the equation

$$N'(t) = \lambda \left(1 - \frac{N(t)}{K} - \frac{A}{1 + BN(t)} \right) N(t). \quad (1.3)$$

The real progress in the development of mathematical models in biology began in the 1920's. In that time V. Volterra [78, 79] studied the question: why did a complete closure of fisheries during the First World War cause an increase in predatory fish and a decrease in prey fish in the Adriatic Sea? He proposed a model which describes the relation between the number of prey $N_1(t)$ and predators $N_2(t)$. This model consists of the following system of

differential equations

$$\begin{cases} N_1'(t) = (\varepsilon_1 - \gamma_1 N_2(t))N_1(t), \\ N_2'(t) = (-\varepsilon_2 + \gamma_2 N_1(t))N_2(t). \end{cases} \quad (1.4)$$

A similar model was proposed independently by A. J. Lotka [45] and it is today known as the Lotka–Volterra prey–predator model. The system has one positive equilibrium (K_1, K_2) , $K_1 = \frac{\varepsilon_2}{\gamma_2}$, $K_2 = \frac{\varepsilon_1}{\gamma_1}$ and other solutions are periodic functions with some period T dependent on the initial data. But even more interesting property of the model is that the mean values of the number of prey and predators are constants:

$$\frac{1}{T} \int_0^T N_i(t) dt = K_i. \quad (1.5)$$

Observe, that from (1.5) it follows that if both prey and predators are fished then $\varepsilon_1' < \varepsilon_1$ i $-\varepsilon_2' < -\varepsilon_2$ and

$$K_1' = \frac{\varepsilon_2'}{\gamma_2} > \frac{\varepsilon_2}{\gamma_2} = K_1,$$

$$K_2' = \frac{\varepsilon_1'}{\gamma_1} < \frac{\varepsilon_1}{\gamma_1} = K_2,$$

where $'$ corresponds to the model including fishing. It means that if both populations are fished then the mean size of the population of prey grows and the population of predators decreases. The opposite process took place during the First World War. The Lotka–Volterra model was generalized in many ways. One of them was the Kolmogorov model [39] given by the system of equations

$$\begin{cases} N_1'(t) = \varepsilon_1(N_1(t))N_1(t) - \nu(N_1(t))N_2(t), \\ N_2'(t) = \varepsilon_2(N_1(t))N_2(t). \end{cases}, \quad (1.6)$$

where ε_1 is a decreasing function, ε_2 is an increasing function and ν is a positive function. If we choose properly functions ε_1 , ε_2 , and ν then the system has a limit cycle. We recall that the *limit cycle* is a periodic solution such that the graphs of other solutions in phase space spiral into its graph as $t \rightarrow \infty$. This property is very interesting from both mathematical and biological point of view. It denotes that there exists one periodic solution and the system is not sensitive on small perturbations – after sufficiently large time the size of the coexisting prey and predator populations will return to the periodic state. The book [69] contains an interesting collection

of papers from those time concerning ecology. Prey-predator models are still intensively investigated (see [40]).

The second big impulse in the development of mathematical models in biology were A. G. McKendrick works. He created with W. O. Kermack the mathematical theory of epidemics with the famous SIR model [36]. In this model the population is split into three groups whose numbers are denoted by S - susceptible, I - infected, and R - resistant (or removed). The model based on the following assumptions:

- 1) a susceptible individual who becomes infected goes immediately to the second group I and it can transmit the disease,
- 2) an infected individual can become resistant by recovery or quarantine and it become permanently immune; we include in the resistant group the dead individuals,
- 3) we neglect all demographic processes, the total number of individuals $N = S + I + R$ is constant,
- 4) the disease is transmitted directly, i.e. there is no intermediate host, e.g. mosquito for malaria,
- 5) the population is homogeneous — with the same probability each infected individual can infect a susceptible one.

The model is the following

$$\begin{cases} S'(t) = -\alpha S(t)I(t), \\ I'(t) = \alpha S(t)I(t) - \beta I(t), \\ R'(t) = \beta I(t), \end{cases} \quad (1.7)$$

where α is the rate at which a susceptible individual become infected by an infected one and β is the recovery (removal) rate. From the model it follows that there is no epidemic outbreak if and only if $S(0) \leq \frac{\beta}{\alpha}$. It is a practical information because it tells us how many people should be vaccinated to prevent the epidemic outbreak.

McKendrick [50] also introduced in 1926 a model which consists of a partial differential equation and a boundary integral condition and describes the age distribution of a population. This model will be discussed in details in Section 1.6. It should be noted that a similar model was introduced earlier by Sharpe and Lotka [68]. The Sharp-Lotka-McKendrick model is one of the earliest models of the structured population dynamics. From now we restrict ourselves to structured models. Readers interested in other applications of mathematics in biology, especially ordinary differential equations

are referred to the books by Murray [54], Thieme [72], Hofbauer and Sigmund [31], Brauer and Castillo-Chavez [11], and Farkas [18].

In these lectures we present only selected models from genetics and we restrict ourselves only to deterministic ones. The systematic study of mathematical theories of population genetics can be found in the books by Crow and Kimura [14], Ewens [19], Fisher [20], Hartl and Clark [29], Kimura [38], Moran [53], Nagylaki [55]. An overview of stochastic models in genetics can also be found in Blythe and McKane [8].

1.3. Discrete models

In this section we consider the simplest structured models where both time and the structure are discrete. Such models are called the *Leslie models* [43]. The population is divided into n subpopulations, but sometimes it is convenient to consider infinite number of subpopulations. We consider disjoint generations of individuals. The time is discrete and is identified with generations, so the k -th generation lives at time k . We should underline that the word “generation” used here has a general meaning and only in particular cases it is a real generation. We assume that an individual from the j -th subpopulation “produces” with probability $p_{i,j}$ a new individual in the i -th subpopulation. Let x_i^k be the number of individuals in the subpopulation i in the k -th generation. Let P be the matrix with entries p_{ij} , and let $\mathbf{x}^k = [x_1^k, \dots, x_n^k]$ be the vector-column of the age distribution in the population at time k . Then

$$\mathbf{x}^{k+1} = P\mathbf{x}^k. \quad (1.8)$$

We should underline that $[x_1^k, \dots, x_n^k]$ do not need to be a probability vector and the sum $N^k = x_1^k + \dots + x_n^k$ can depend on k . Here N^k is the population size in the k -th generation.

Example 1.1 (Discrete age structured model). *Here a generation is the set of individuals at a given time k , e.g. a year. Let the i -th subpopulation consists of individuals with age $i \leq a < i + 1$. Then $p_{j+1,j} = 1 - \mu_j$, where μ_j is the death rate at age j and $p_{0,j} = b_j$, where b_j is the birth rate at age j . In other cases $p_{i,j} = 0$.*

Example 1.2 (Space structured model). *As before a generation is the set of all individuals at a given time k and a subpopulation consists of all*

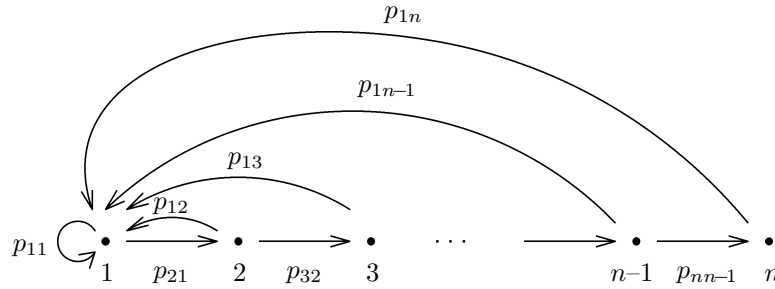


Fig. 1.1. The diagram of connections in the age structured model. Here $p_{j+1,j} = 1 - \mu_j$ and $p_{1,j} = b_j$, where μ_j is the death rate and b_j is the birth rate at age j .

individuals living in a given region. It is sensible to assume that in this model $p_{i,j} > 0$ for all i, j .

Example 1.3 (Telomere shortening).

The ends of chromosomes, called telomeres, shorten when a cell divides. When they reach a critical length no further divisions occur. The simplified model of telomere loss is the following. Assume that the length of a telomere is an integer from the interval 0 to n . The i -th subpopulation consists of cells with a given telomere of the length i . We assume that a cell from the i -th subpopulation can die with probability μ_i or divide and its daughter cell can have the telomere with the length i with probability a_i or $i - 1$ with probability $1 - a_i$. The cells which belong to 0-th subpopulation cannot divide and they finally die. Let $r_i = 2a_i(1 - \mu_i)$ and $d_i = 2(1 - a_i)(1 - \mu_i)$. The mean number of descendants of a cell from the i -th subpopulation in the same subpopulation is r_i and in the $(i - 1)$ -th subpopulation is d_i . In

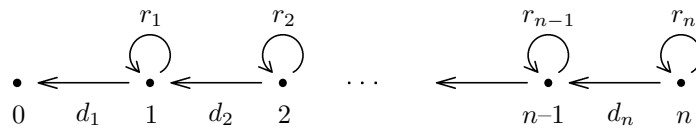


Fig. 1.2. The diagram of connections in the telomere shortening. In this case $p_{i,i} = r_i$ and $p_{i-1,i} = d_i$.

this case the matrix P is the following

$$P = \begin{bmatrix} 0 & d_1 & 0 & \cdots & 0 \\ 0 & r_1 & d_2 & \ddots & 0 \\ 0 & 0 & r_2 & \ddots & \ddots \\ \vdots & \ddots & \ddots & \ddots & d_n \\ 0 & 0 & \cdots & 0 & r_n \end{bmatrix}.$$

The behaviour of the vector \mathbf{x}^k when time k goes to infinity is described by the following theorem.

Theorem 1.1 (Perron). *Assume that the matrix P has the non-negative entries and for some positive integer r the matrix P^r has all positive entries. Then there exist a constant $\lambda > 0$ and sequences $\mathbf{x}^* = (x_1^*, \dots, x_n^*)$ and $\mathbf{y}^* = (y_1^*, \dots, y_n^*)$ with positive terms such that for each $\mathbf{x} \in \mathbb{R}^n$ we have*

$$\lim_{k \rightarrow \infty} \lambda^{-k} P^k \mathbf{x} = \mathbf{x}^* \langle \mathbf{y}^*, \mathbf{x} \rangle, \quad (1.9)$$

where $\langle \cdot, \cdot \rangle$ is the scalar product in \mathbb{R}^n .

For the proof see [70] Proposition I.2.3.

If condition (1.9) holds then we say that the population has *asynchronous exponential growth*. Let us explain the meaning of this notion. The vector \mathbf{x}^* can be chosen in such a way that $x_1^* + \cdots + x_n^* = 1$. The vector $\mathbf{p}^k = (p_1^k, \dots, p_n^k)$, where

$$p_i^k = \frac{(P^k x)_i}{\sum_{j=1}^n (P^k x)_j} \quad (1.10)$$

describes the probability distribution of the population in the k -th generation. From (1.9) it follows immediately that

$$\lim_{k \rightarrow \infty} \mathbf{p}^k = \mathbf{x}^*. \quad (1.11)$$

It means that independently on the initial distribution \mathbf{p}^0 the long-time distribution is almost \mathbf{x}^* (asynchronous growth). Moreover, the exponential growth means here that the total number of individuals grows asymptotically like a geometric progression with common ratio λ .

In order to apply Theorem 1.1 we should check that for some r the matrix P^r has all positive entries. This is equivalent to the following condition:

(c-d) for each i and j there exists a sequence i_0, i_1, \dots, i_r such that $i_0 = j$, $i_r = i$ and

$$p_{i_r i_{r-1}} \cdots p_{i_2 i_1} p_{i_1 i_0} > 0. \quad (1.12)$$

Condition (1.12) denotes that if we start from the j -th subpopulation we can reach the i -th subpopulation in r steps going on the oriented graph from the diagram of the connections between subpopulations.

Let us return to our examples. In the space structure model (see Example 1.2) all entries of P are positive and consequently the population has the asynchronous exponential growth. More interesting situation appears in the age structured model (see Example 1.1). If we assume that $b_j > 0$ for all $j = 1, 2, \dots, n$ then using the diagram of the connections one can check that the matrix P^n has all positive entries and we have the asynchronous exponential growth. But usually younger individuals cannot have offspring so we cannot assume that all b_j are positive. It turns out that it is sufficient to assume that $b_n > 0$ and $b_{n-1} > 0$. Then we can check that the matrix P^{n^2} has all positive entries. In some species of insects the life cycle can be constant and long. Thus we do not have the asynchronous exponential growth which can help the species to survive. For example, *the Magicicada* goes through a 17- or occasionally 13-year life cycle [24]. The predators are not able to adjust to this type of life cycle of cicadas. In the telomere shortening model (Example 1.3) we do not have the asynchronous exponential growth but the population has the *asynchronous polynomial exponential growth*. It means that for each \mathbf{x} there exist constants $c_i(\mathbf{x})$ such that

$$x_i^k \approx k^{n-i} \lambda^k c_i(\mathbf{x}) \quad (1.13)$$

for large k .

We can also consider nonlinear Leslie models. Such models are defined by the formula $\mathbf{x}^{k+1} = \mathbf{f}(\mathbf{x}^k)$, where the function \mathbf{f} is defined on a subset D of \mathbb{R}_+^n which is invariant with respect to \mathbf{f} , i.e. $\mathbf{f}(D) \subset D$. The theory of such models is difficult and, in practise, each model is treated independently. We can study here classical questions such as stability, the existence of a limit cycle and also newer problems such as invariant measures and chaos. We give here only some examples which show how general assumptions concerning the population can be included in previous models.

Example 1.4 (age structured model with limited resources). *Now we include in the age structured model (see Example 1.1) the assumption*

on the limited resources which appears in the Verhulst model. Let $x(a, t)$ be the number of individuals with age a at time t , where both time and age are positive integers. Let $N(t) = \sum_{a=1}^{\infty} x(a, t)$ be the total number of individuals at time t . We can assume that the mortality rate μ depends on the age of an individual and the size of the whole population at given time, i.e. $\mu = \mu(a, N(t))$, $0 \leq \mu \leq 1$. We also assume that $b = b(a, N(t))$ is the mean number of children at time t of an individual with age a . For example, if we forget about the Allee effect we can take $\mu = (1 - N(t)/N_{\max})$ and $b = (1 - N(t)/N_{\max})p(a)$, where N_{\max} is the maximum size of the population and $p(a)$ is the mean number of children in the best conditions. The general model is described by the following equations:

$$\begin{aligned} N(t) &= \sum_{a=1}^{\infty} x(t, a), \\ x(t+1, a+1) &= (1 - \mu(a, N(t)))x(t, a), \quad \text{for } a \geq 1, \\ x(t, 1) &= \sum_{a=1}^{\infty} b(a, N(t))x(t, a). \end{aligned} \quad (1.14)$$

If we assume that the maximum age is a_{\max} , then the infinity in the system (1.14) should be replaced by a_{\max} and we should also assume that $\mu(a_{\max}, N) = 1$.

Example 1.5 (Penna model). *T. J. P. Penna [58] introduced a bitstring model for biological ageing which has been successfully applied to study various problems of genetics and demography. We present an analytical version of this model restricted to asexual reproduction [3]. In the Penna model it is assumed that each individual has its own maximum life span m . Let $x(t, a, m)$ be the number of individuals at time t with age a and with maximum life span m . Then the model is described by the system of equations:*

$$\begin{aligned} N(t) &= \sum_{m=1}^{\infty} \sum_{a=1}^m x(t, a, m), \\ x(t+1, a+1, m) &= (1 - \mu(a, m, N(t)))x(t, a, m), \quad \text{for } a < m, \\ x(t+1, a+1, m) &= 0, \quad \text{for } a \geq m, \\ x(t, 1, m) &= \sum_{m'=1}^{\infty} \sum_{a=1}^{m'} b(a, m, m', N(t))x(t, a, m'). \end{aligned} \quad (1.15)$$

As in the previous model μ is the death rate, and $b(a, m, m', N)$ is the mean number of children with the maximum life span m of an individual with age

a and maximum life span m' . In [3] it is assumed that $\mu = (1 - N(t)/N_{\max})$ and $b = (1 - N(t)/N_{\max})p(m, m')$, where N_{\max} is the maximum size of the population and $p(m, m')$ is the birth matrix $p(m, m')$, i.e. $p(m, m')$ is the probability that a parent with maximum life span m' gives birth to a child with maximum life span m .

1.4. Time continuous discrete structure models

Now we consider models in which time has the ordinary physical meaning and the population is divided into a finite or infinite number of subpopulations. Models of this type appear in many applications. They can describe, for example, the migration of animals, birth and death processes, distribution of genes (we give examples in this section) and spreading diseases in heterogeneous populations (see [72] Chapter 24). The general scheme for such models is the following. In time interval from t to $t + \Delta t$ an individual from the subpopulation j can:

- (a) “move” with probability $p_{ij}\Delta t + o(\Delta t)$ to the subpopulation i ,
- (b) “produce” with probability $b_{ij}\Delta t + o(\Delta t)$ a new individual in the subpopulation i ,
- (c) die with probability $d_j\Delta t + o(\Delta t)$.

Let $x_i(t)$ be the number of individuals in the subpopulation i at time t . Then

$$x'_i(t) = \sum_{j=1}^n q_{ij}x_j(t), \quad \text{for } i = 1, \dots, n, \quad (1.16)$$

where $q_{ij} = b_{ij} + p_{ij}$ for $i \neq j$ and

$$q_{ii} = b_{ii} - d_i - \sum_{\substack{j=1 \\ j \neq i}}^n p_{ji}.$$

For $i \neq j$ we have $q_{ij} \geq 0$. If we consider only finite number of subpopulations then we can formulate a continuous version of the Perron theorem.

We need the following condition:

(c-c) for $i \neq j$ there exists a sequence (i_1, i_2, \dots, i_m) such that $i_1 = i$, $i_m = j$ and $q_{i_r+1, i_r} > 0$ for $r = 0, 1, \dots, m - 1$.

Theorem 1.2. *If $n < \infty$ and condition (c-c) holds then there exist a constant λ and sequences $\mathbf{x}^* = (x_1^*, \dots, x_n^*)$, $\mathbf{y}^* = (y_1^*, \dots, y_n^*)$ with positive*

terms such that for each solution $\mathbf{x}(t)$ we have

$$\lim_{t \rightarrow \infty} e^{-\lambda t} \mathbf{x}(t) = \mathbf{x}^* \langle \mathbf{y}^*, \mathbf{x}(0) \rangle. \quad (1.17)$$

For the proof see [72] Theorem A.45. The formula (1.17) can be written in the following way

$$\mathbf{x}(t) \approx C e^{\lambda t} \mathbf{x}^*$$

and also in this case we say that the population has an *exponential asynchronous growth*.

The condition (c-c) is weaker than (d-c) one. It is sufficient to check that all subpopulations are connected by oriented paths. For example, the system

$$\begin{cases} x_1' = b_1 x_n - a_1 x_1, \\ x_i' = b_i x_{i-1} - a_i x_i, \quad \text{for } i = 2, \dots, n, \end{cases} \quad (1.18)$$

where $b_i > 0$ for $1 \leq i \leq n$, satisfies this condition.

Now, we present models with infinite number of subpopulations.

Example 1.6 (Birth-death process). We consider a population of cells. This population is divided into subpopulations in such a way that the i -th subpopulation, $i \geq 0$, consists of cells which contains i copies of a given gen. The length of live of a cell of the type i has exponential distribution with expected value $1/\lambda_i$. Cells of the type i can mutate in the time interval $(t, t + \Delta t)$ to the type $i + 1$ with probability $b_i \Delta t + o(t)$ and to the type $i - 1$ with probability $d_i \Delta t + o(t)$. Let $x_i(t)$ be the number of cells in the i -th subpopulation. Then

$$x_i'(t) = -a_i x_i(t) + b_{i-1} x_{i-1}(t) + d_{i+1} x_{i+1}(t), \quad i \geq 0,$$

where $a_i = \lambda_i + b_i + d_i$ and $b_{-1} = 0$, $d_0 = 0$.

Example 1.7 (Paralog families). Now we present a model of the evolution of paralog families in a genome [67]. Two genes present in the same genome are said to be paralogs if they are genetically identical. It is not a precise definition of paralogs but it is sufficient for our purposes. We are interested in the size distribution of paralogous gene families in a genome. We divide genes into classes. The i -th class consists of all i -element paralog families. Let x_i be a number of families in the i -th class. Basing on experimental data Słonimski et al. [71] suggested that

$$x_i \sim \frac{1}{2^{i_i}}, \quad i = 2, 3, \dots,$$

but Huynen and van Nimwegen [32] claimed that

$$x_i \sim i^{-\alpha}, \quad i = 1, 2, 3, \dots,$$

where $\alpha \in (2, 3)$ decreases if the total number of genes increases. It is very difficult to decide which formula is correct if we study only experimental data because we can only compare first few elements of both sequences. We construct a simple model of the evolution of paralog families which can help to solve this problem.

The model is based on three fundamental evolutionary events: gene loss, duplication and accumulated change called for simplicity mutation. A single gene during time interval of length Δt can be:

- duplicated with probability $d\Delta t + o(\Delta t)$ and duplication of it in a family of the i -th class moves this family to the $(i + 1)$ -th class,
- removed from the genome with probability $r\Delta t + o(\Delta t)$. For $i > 1$, removal of a gene from a family of the i -th class moves this family to the $(i - 1)$ -th class; removal of a gene from one-element family results in elimination of this family from the genome. A removed gene is eliminated permanently from the pool of all genes.
- changed with probability $m\Delta t + o(\Delta t)$ and the gene starts a new one-element family and it is removed from the family to which it belonged.

It is assumed that $\lim_{\Delta t \rightarrow 0} \frac{o(\Delta t)}{\Delta t} = 0$. Moreover, we assume that all elementary events are independent of each other. Let $s_i(t)$ be the number of i -element families in our model at the time t . It follows from the description of our model that

$$s_1'(t) = -(d + r)s_1(t) + 2(2m + r)s_2(t) + m \sum_{k=3}^{\infty} k s_k(t), \quad (1.19)$$

$$s_i'(t) = d(i - 1)s_{i-1}(t) - (d + r + m)is_i(t) + (r + m)(i + 1)s_{i+1}(t) \quad (1.20)$$

for $i \geq 2$. Let $s(t) = \sum_{i=1}^{\infty} s_i(t)$ be the total number of families. Then the sequence $(p_i(t))$, where $p_i(t) = s_i(t)/s(t)$ is the size distribution of paralogous gene families in a genome at time t .

In order to study properties of system (1.19)–(1.20) we need to introduce some mathematical notions. Let X be the space of sequences (x_i) which satisfies the condition $\sum_{i=1}^{\infty} i|x_i| < \infty$. The main result of the paper [67] is the following.

Theorem 1.3. *There exists a sequence $(s_i^*) \in X$ such that for every solution $(s_i(t))$ of (1.19) and (1.20) with $(s_i(0)) \in X$ we have*

$$\lim_{t \rightarrow \infty} e^{(r-d)t} s_i(t) = C s_i^* \quad (1.21)$$

for every $i = 1, 2, \dots$ and C dependent only on the sequence $(s_i(0))$. Moreover if $d = r$ then

$$\lim_{t \rightarrow \infty} s_i(t) = C \frac{\alpha^i}{i}, \quad (1.22)$$

where $\alpha = \frac{r}{r+m}$.

In the case when $d = r$ the total number of genes in a genome is constant. It means that the genome is in a stable state. In this case the distribution of paralog families is similar to that stated in Słonimski's conjecture, both distributions are the same if $r = d = m$.

Now we give a sketch of the proof of Theorem 1.3. First, we notice that since the system (1.19) and (1.20) contains infinite number of equations we should formally define its solutions and prove their existence and uniqueness. Moreover we cannot apply the Perron theorem to show the exponential asynchronous growth of the population. Instead of it we apply the lower function theorem of Lasota and Yorke to prove this result. First, we change variables. Let

$$y_i(t) = e^{(r-d)t} i s_i(t). \quad (1.23)$$

Then

$$y_1' = -(2d+m)y_1 + (m+r)y_2 + \sum_{k=1}^{\infty} m y_k, \quad (1.24)$$

$$y_i' = -(d+r+m + \frac{d-r}{i}) i y_i + d i y_{i-1} + (r+m) i y_{i+1} \quad (1.25)$$

for $i \geq 2$. The system (1.24) and (1.25) generates a stochastic semigroup on l^1 , where l^1 denote the space of absolutely summable sequences. We recall that a linear mapping $P : l^1 \rightarrow l^1$ is called a *stochastic* or *Markov operator* if $P(D) \subset D$, where

$$D = \left\{ x \in l^1 : x_i \geq 0 \text{ for all } i \geq 1 \text{ and } \sum_{i=1}^{\infty} x_i = 1 \right\}.$$

A family $\{P(t)\}_{t \geq 0}$ of stochastic operators which satisfies conditions:

- (a) $P(0) = \text{Id}$,

- (b) $P(t+s) = P(t)P(s)$ for $s, t \geq 0$,
 (c) for each $x \in l^1$ the function $t \mapsto P(t)x$ is continuous with respect to the l^1 norm

is called a *stochastic* or *Markov semigroup*. The system (1.24) and (1.25) can be written in the following way:

$$y'(t) = Qy(t), \quad (1.26)$$

where $Q = (q_{i,j})_{i,j \geq 1}$. The matrix Q is a *Kolmogorov* matrix. It means that it has the following properties:

- (i) $q_{i,j} \geq 0$ for $i \neq j$,
 (ii) $\sum_{i=1}^{\infty} q_{i,j} = 0$ for $j \geq 1$.

We also denote by Q the operator $x \mapsto Qx$ with the domain $D(Q) = \{x \in l^1 : Qx \in l^1\}$. The operator Q generates a stochastic semigroup. This result can be obtained from the following theorem.

Theorem 1.4. *Let the matrix Q satisfies conditions (i) and (ii). Let $Q^* = (q_{i,j}^*)_{i,j \geq 1}$, where $q_{i,j}^* = q_{j,i}$ for $i, j \geq 1$ and let θ be a positive constant. Then the operator Q generates a stochastic semigroup $\{P(t)\}_{t \geq 0}$ on l^1 if and only if there is no non-zero solution of the equation $Q^*x = \theta x$, where $x \in l^\infty$.*

Recall that l^∞ is the space of bounded sequences. The proof of Theorem 1.4 can be found in [56] Corollary 2.7.3, [9] Proposition 8.3.22, [30] Theorem 23.12.6.

The semigroup $\{P(t)\}_{t \geq 0}$ is called a *semigroup generated* by equation (1.26). We also say in this case that the operator (matrix) Q generates the semigroup $\{P(t)\}_{t \geq 0}$. If $y^0 \in l^1$, then the function $y(t) = P(t)y^0$ is called the solution of (1.26) with the initial condition $y(0) = y^0$. The substitution (1.23) defines us the solution of the system (1.19)–(1.20).

The formula (1.21) can be obtained using some result concerning asymptotic stability of stochastic semigroups. A stochastic semigroup is called *asymptotically stable* if there exists $x^* \in D$ with $P(t)x^* = x^*$ for $t > 0$ and such that for every $x \in D$ $\lim_{t \rightarrow \infty} \|P(t)x - x^*\| = 0$. Our semigroup is asymptotically stable and the proof of this result is based on the following Lasota-Yorke theorem [42]:

Theorem 1.5. *Let $\{P(t)\}_{t \geq 0}$ be a stochastic semigroup on l^1 . If there exists $h \in l^1$, $h \geq 0$ and $h \neq 0$ such that*

$$\lim_{t \rightarrow \infty} \|(P(t)x - h)^-\| = 0 \quad (1.27)$$

for every $x \in D$, then the semigroup is asymptotically stable.

Here we use the notation $x_i^- = 0$ if $x_i \geq 0$ and $x_i^- = -x_i$ if $x_i < 0$. The proof of asymptotic stability of our semigroup by using the Lasota-Yorke theorem is very simple so we give it here. Let $y(0) \in D$ and $m > 0$. Then $y(t) \in D$ and since $\sum_{i=1}^{\infty} y_i(t) = 1$ from (1.24) it follows that

$$y_1'(t) \geq -(2d + m)y_1(t) + m.$$

This implies that

$$\liminf_{t \rightarrow \infty} y_1(t) \geq \frac{m}{2d + m}.$$

Let $h = (\frac{m}{2d + m}, 0, 0, \dots)$. Then h satisfies (1.27). From Theorem 1.5 it follows that the semigroup generated by the system (1.24) and (1.25) is asymptotically stable.

Remark 1.1. In the next two part of our lectures we will use stochastic operators and semigroups defined on the space $L^1 = L^1(X, \Sigma, m)$, where X is any set, Σ is a σ -algebra of subsets of X and m is a measure defined on Σ . A linear mapping $P : L^1 \rightarrow L^1$, is called a *stochastic* or *Markov operator* if $P(D) \subset D$, where D is the set of densities, i.e.

$$D = \{f \in L^1 : f \geq 0 \text{ and } \int_X f(x) m(dx) = 1\}.$$

We define a stochastic semigroup on L^1 and asymptotic stability as in the case l^1 . The Lasota-Yorke lower function theorem remains true in L^1 .

Theorem 1.2 does not hold for positive semigroups on the space l^1 . But for stochastic semigroups we have the following result.

Theorem 1.6. Let $\{P(t)\}_{t \geq 0}$ be a stochastic semigroup on l^1 generated by the matrix Q . If condition (c-c) holds then we have the following alternative:
 (a) if the semigroup $\{P(t)\}_{t \geq 0}$ have an invariant density, then it is asymptotically stable,
 (b) if the semigroup $\{P(t)\}_{t \geq 0}$ have no invariant density, then for each $x \in l^1$ and $i \in \mathbb{N}$ we have

$$\lim_{t \rightarrow \infty} (P(t)x)_i = 0. \quad (1.28)$$

Theorem 1.6 follows from some general results of the theory of Markov operators, namely, part (a) from [59] Theorem 2 and part (b) from [62] Theorem 2.

The property (b) is called *sweeping*. Theorem 1.6 can be a useful tool to study the long time behaviour of stochastic semigroups. Usually, it is easy to check condition (c-c) and sometimes it is also easy to find an invariant density x^* or check that it does not exist, because it is a solution of the equation $Qx^* = 0$.

Example 1.8 (Birth-death process – asymptotics). *We consider the birth-death process given by the equation*

$$x'_i(t) = -a_i x_i(t) + b_{i-1} x_{i-1}(t) + d_{i+1} x_{i+1}(t), \quad i \geq 0,$$

where $a_i = b_i + d_i$ and $b_{-1} = 0, d_0 = 0$. The matrix Q corresponding to this equation is a Kolmogorov matrix. If we assume that the birth sequence b_i do not grow too quickly, for example $b_i \leq \alpha i + \beta$ for all i and some α and β , then using Theorem 1.4 one can check that the matrix Q generates a stochastic semigroup. The sequence (x_i^*) which satisfies equation $Qx^* = 0$ is given by the recurrent formula

$$x_{i+1}^* = \frac{b_i + d_i}{d_{i+1}} x_i^* - \frac{b_{i-1}}{d_{i+1}} x_{i-1}^*.$$

If for example $b_i = b$ and $d_i = d$, then one can easily check that

$$x_i^* = c_1 + c_2 \left(\frac{b}{d}\right)^i,$$

where c_1 and c_2 are some constants. It means that the sequence (x_i^*) is a density if and only if $b < d$ and

$$x_i^* = \frac{d-b}{d} \left(\frac{b}{d}\right)^i.$$

1.5. Continuous structure generation models

Now we consider the case when the individual is characterized by one parameter or by a vector of parameters x but time changes in a discrete way. We study the distribution of the population with respect to the parameter x . We want to describe how this distribution changes in consecutive generations of individuals. We begin with a model of the cell cycle.

Example 1.9 (Cell cycle model). *The cell cycle is the series of events that take place in a cell leading to its replication. Usually the cell cycle is divided into four phases. The first one is the growth phase G_1 with the synthesis of various enzymes. Duration of the phase G_1 is highly variable even for cell from one species. DNA synthesis takes place in the second*

phase S . In the next phase G_2 significant protein synthesis occurs, which is required during the process of mitosis. The last phase M consists of nuclear division and cytoplasmic division. Looking from mathematical point of view we can simplify the model considering only two phases: $A = G_1$ which a random duration t_A and B which consists of the phases S , G_2 , and M . The duration t_B of the phase B is almost constant. There are several models of the cell cycle. Let us mention models by Lasota and Mackey [41] and Tyson and Hannsgen [76]. We present here the Tyrcha model [75] which generalizes the earlier mentioned models.

In the model of the cell cycle the crucial role play a parameter x which describes the state of a cell but nobody knows what exactly should be x . It can be size, or contents of genetic material, or amount of *mitogen* (a hypothetical substance responsible for the cell division). We call x the maturity. Let $\varphi(x)$ be the rate of entering the phase B . Let $x(t)$ be the maturity of a cell at time (age) t . The length t_A of the phase A is random and given by formula

$$\text{Prob}(t \leq t_A \leq t + \Delta t \mid t_A \geq t) \cong \varphi(x(t))\Delta t.$$

Let $g(x)$ be the growth rate, i.e. the maturity x grows according to the equation

$$\frac{dx}{dt} = g(x). \quad (1.29)$$

Let $\pi(t, x_0)$ be the size of a cell at time t if its initial size were x_0 , i.e. $\pi(t, x_0)$ is the solution of (1.29) at time t if it started from x_0 . Let $F(t) = \text{Prob}(t_A \geq t)$. Then

$$\frac{F(t) - F(t + \Delta t)}{F(t)} \cong \varphi(\pi(t, x_0))\Delta t.$$

From this equation we obtain

$$F'(t) = -F(t)\varphi(\pi(t, x_0))$$

and after simple calculations we get

$$F(t) = \exp\left\{-\int_0^t \varphi(\pi(s, x_0)) ds\right\}. \quad (1.30)$$

For $y \geq x_0$ we define $t(x_0, y)$ as such a t that $\pi(t, x_0) = y$. Since

$$\frac{\partial t}{\partial y} \cdot g(\pi(t, x_0)) = 1$$

we receive

$$\frac{\partial t}{\partial y} = \frac{1}{g(y)}$$

and

$$\frac{\partial}{\partial y} \left(\int_0^{t(x_0, y)} \varphi(\pi(s, x_0)) ds \right) = \frac{\varphi(y)}{g(y)}.$$

Let Y be the size of the cell at time t_A . Then

$$\begin{aligned} \text{Prob}(Y \geq y) &= \text{Prob}(\pi(t, x_0) \geq y) = \exp \left\{ - \int_0^{t(x_0, y)} \varphi(\pi(s, x_0)) ds \right\} \\ &= \exp \left(- \int_{x_0}^y \frac{\varphi(r)}{g(r)} dr \right) = \exp(Q(x_0) - Q(y)), \end{aligned}$$

where $Q(y) = \int_0^y \frac{\varphi(r)}{g(r)} dr$. Let ξ be a random variable with exponential distribution: $\text{Prob}(\xi \geq x) = e^{-x}$. Then

$$\begin{aligned} \text{Prob} \left(Q^{-1}(Q(x_0) + \xi) \geq y \right) &= \text{Prob} \left(Q(x_0) + \xi \geq Q(y) \right) \\ &= \text{Prob} \left(\xi \geq Q(y) - Q(x_0) \right) \\ &= \exp(Q(x_0) - Q(y)) = \text{Prob}(Y \geq y). \end{aligned}$$

From this it follows that the maturity of the cell at the moment of entering the phase B is given by the random variable $Q^{-1}(Q(x_0) + \xi)$ and the initial size of a daughter cell is

$$\gamma \left(Q^{-1}(Q(x_0) + \xi) \right),$$

where $\gamma(y) = \frac{1}{2} \pi(t_B, y)$. If X_n is the initial size of cell in the n -th generation then

$$X_{n+1} = \gamma \left(Q^{-1}(Q(X_n) + \xi_n) \right), \quad (1.31)$$

where (ξ_n) is a sequence of independent random variables with exponential distribution. If f_n is the density of the distribution function of X_n then $f_{n+1} = Pf_n$, where

$$Pf(x) = - \int_0^{\lambda(x)} \frac{\partial}{\partial x} \left\{ H \left(Q(\lambda(x)) - Q(y) \right) \right\} f(y) dy, \quad (1.32)$$

$H(x) = e^{-x}$ and λ is the inverse function for γ .

The asymptotic properties of the operator P depend on the function $\alpha(x) = Q(\lambda(x)) - Q(x)$. We have

- (a) If $\alpha(x) > 1$ for sufficiently large x , then P is *asymptotically stable*, i.e. there exists a density f^* such that

$$\lim_{n \rightarrow \infty} \|P^n f - f^*\| = 0 \quad \text{for } f \in D.$$

- (b) If $\alpha(x) \leq 1$ for sufficiently large x , then P is *sweeping* or *zero type*, i.e.

$$\lim_{n \rightarrow \infty} \int_0^c P^n f(x) dx = 0 \quad \text{for } f \in D \text{ and } c > 0.$$

- (c) If $\inf \alpha(x) > -\infty$, then the operator P is *completely mixing*, i.e.

$$\lim_{n \rightarrow \infty} \|P^n f - P^n g\| = 0 \quad \text{for } f, g \in D.$$

The results were proved, respectively, (a) in [22], (b) in [46], and (c) in [61].

Now we go to a general situation. Many biological processes can be modelled by means of randomly perturbed dynamical systems. The relation between the distribution of a parameter (size, maturity, etc.) in two successive generations is given by

$$X_{n+1} = S(X_n, \xi_{n+1}), \quad (1.33)$$

where $(\xi_n)_{n=1}^{\infty}$ is a sequence of independent random variables (or elements) with the same distribution, and the initial value of the system X_0 is independent of the sequence $(\xi_n)_{n=1}^{\infty}$. Studying systems of the form (1.33) we are often interested in the behaviour of the sequence of the measures (μ_n) defined by

$$\mu_n(A) = \text{Prob}(X_n \in A). \quad (1.34)$$

The evolution of these measures can be described by a Markov operator P given by $\mu_{n+1} = P\mu_n$. The operator P is defined on the space of probability measures. Let m be a given measure in the phase space (i.e. in the space of parameters). Assume that the distribution ν_y of the random variable $S(y, \xi_n)$ is absolutely continuous with respect to m and let $k(x, y)$ be the density of ν_y . Assume that the measure μ_n is absolutely continuous with respect to the measure m and let f_n be the density $\frac{d\mu_n}{dm}$. Then the measure μ_{n+1} has a density $f_{n+1} = Pf_n$, where the operator P is given by the formula

$$Pf(x) = \int k(x, y)f(y) m(dy).$$

1.6. Continuous time-structure models

In this section we present models in which both the time and the structure is continuous. In such models an individual is described by a parameter $x \in \mathbb{R}^n$ (age, size, maturity etc.). We are interested in finding the distribution of the parameter x at time t . This distribution is described by a density function $u(t, x)$, exactly

$$\int_A u(t, x) dx$$

is the number of individuals (or biomass) with the parameter x in set A . It should be underline that u is not a density in the probabilistic sense because the integral of $u(t, x)$ over the whole phase space is not one and this integral can change with time.

It is a large class of various models of this type and it is rather difficult to give a unified description of them. We begin with some examples and then we will try to present a general approach to these models.

Example 1.10 (Age structured model). *In the age structure McKendrick model there is only one parameter – the age of an individual a , which belongs to the interval $[0, c)$, where c a positive number or infinity. We assume that in the time interval $[t, t + \Delta t]$ an individual with age a can*

- (a) *with probability $b(t, a)\Delta t + o(\Delta t)$ “produce” a new individual. This assumption leads to following integral equation*

$$u(t, 0) = \int_0^c b(t, a)u(t, a) da,$$

- (b) *with probability $\mu(t, a)\Delta t + o(\Delta t)$ die.*

From condition (b) it follows that

$$u(t + \Delta t, a + \Delta t) - u(t, a) = -\mu(t, a)u(t, a)\Delta t + o(\Delta t).$$

If we pass with Δt to 0 we obtain a partial differential equation which is written below. We should also add an initial condition and, as a result, the whole model consists of three equations:

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} = -\mu(t, a)u, \quad (1.35)$$

$$u(t, 0) = \int_0^c b(t, a)u(t, a) da, \quad (1.36)$$

$$u(0, a) = u_0(a). \quad (1.37)$$

Let $N(t) = \int_0^c u(t, a) da$ be the total number of individuals at time t . Then the function $p(t, a) = \frac{u(t, a)}{N(t)}$ is the probability density of the age distribution at time t . The function $p(t, a)$ is called the *age profile*.

The following theorem describes the long time behaviour of the solutions of (1.35). We consider the case $c < \infty$. We precede the formulation of the theorem by some condition. We will assume that the initial function $u(0, a)$ satisfies the following condition:

$$\int_0^c \int_0^{c-a} u(0, a+t)b(t, a+t) dt da > 0. \quad (1.38)$$

Condition (1.38) denotes that the initial distribution of the population is chosen in such a way that not everybody is beyond child-bearing age.

Theorem 1.7 (Ergodicity, Norton(1928)). *Assume that μ and b are continuous functions and that there exist $a_0 \in (0, c)$, $\varepsilon > 0$ and $\delta > 0$ such that $b(t, a) > \varepsilon$ for $a \in (a_0 - \delta, a_0 + \delta)$ and $t \geq 0$. Let u, \bar{u} be the solutions with the initial conditions $u(0, a), \bar{u}(0, a)$ satisfying (1.38). Then*

$$\lim_{t \rightarrow \infty} \frac{\bar{p}(t, a)}{p(t, a)} = 1.$$

In the formulation of Theorem 1.7 the birth and death rates can depend on time and profiles can also depend on time. More precise information about long time behaviour can be obtained if we assume that the birth and death rates do not depend on time or they are periodic functions (see corollaries below).

Corollary 1.1 (Asynchronous exponential growth). *If b and d are independent on t , then there exist a constant $\lambda \in \mathbb{R}$ and a function $p_*(a)$ independent of a solution u and a constant C dependent on u such that*

$$\lim_{t \rightarrow \infty} e^{-\lambda t} N(t) = C \quad \text{and} \quad \lim_{t \rightarrow \infty} p(t, a) = p_*(a).$$

Corollary 1.2 (Periodic case). *If b and d are periodic functions of t with period T , then there exist a constant $\lambda \in \mathbb{R}$ and a function $p_*(t, a)$ periodic with respect to t with period T such that for each solution u there exists a constant C which satisfy*

$$\lim_{t \rightarrow \infty} \frac{u(t, a)}{e^{\lambda t} p_*(t, a)} = C.$$

Theorem 1.7 and Corollaries 1.1 and 1.2 were generalized in [34], [35], [65]. In these papers it is considered a population divided into n subpopulations. These subpopulations can be different phenotypes, or demographically distinct populations, or with $n = 2$ a two sex population, etc. We assume that for each i and j an individual from the i -th subpopulation can have descendants in the j -th subpopulation and consider an age structured model. Let $u_i(t, a)$ describes the age distribution in the i -th subpopulation. Then the functions $u_i(t, a)$ satisfy a system of partial differential equations of the first order with boundary-initial conditions. In this case one can prove that for two solutions u and \bar{u} there exists a constant $c > 0$ such that

$$\lim_{t \rightarrow \infty} \frac{\bar{u}_i(t, a)}{u_i(t, a)} = c.$$

Moreover, if the rates of death, birth and transition between subpopulations are periodic with the same period T or do not depend on time then Corollaries 1.1 and 1.2 also hold.

Let us return back to the McKendrick model. Assume that the birth and death rates do not depend on time, i.e. $\mu(t, a) = \mu(a)$ and $b(t, a) = b(a)$. We want to find the growth rate and the age profile for large time. If $u(t, a) = e^{\lambda t} p(a)$ is the solution of the McKendrick system then

$$\lambda p(a) + p'(a) = -\mu(a)p(a), \quad (1.39)$$

$$p(0) = \int_0^c b(a)p(a) da. \quad (1.40)$$

From (1.39) we get

$$\begin{aligned} p(a) &= p(0) \exp \left\{ - \int_0^a (\lambda + \mu(s)) ds \right\} \\ &= p(0) e^{-\lambda a} \exp \left\{ - \int_0^a \mu(s) ds \right\}. \end{aligned} \quad (1.41)$$

Let

$$\varphi(\lambda) = \int_0^c b(a) e^{-\lambda a} \exp \left\{ - \int_0^a \mu(s) ds \right\} da. \quad (1.42)$$

Then condition (1.40) holds if and only if $\varphi(\lambda) = 1$. It is easy to check that $\varphi(-\infty) = +\infty$, $\varphi(+\infty) = 0$ and $\varphi'(\lambda) < 0$ for all $\lambda \in \mathbb{R}$. This implies that there exists a unique $\lambda_0 \in \mathbb{R}$ such that $\varphi(\lambda_0) = 1$. Since

$$p(a) = p(0) e^{-\lambda_0 a - \int_0^a \mu(s) ds}.$$

and since the function $p(a)$ is a probability density, i.e. $\int_0^c p(a) da = 1$, we have

$$p(a) = e^{-\lambda_0 a - \int_0^a \mu(s) ds} \left(\int_0^c e^{-\lambda_0 a - \int_0^a \mu(s) ds} da \right)^{-1}.$$

Let T be the length of the life of an individual. Then T is a random variable. The function $F(a) = P(T \geq a)$ is the probability of being still alive at age a and this function is called the *survival function*. Now, we find the survival function. Since

$$P(T \in [a, a + \Delta a] | T \geq a) = \mu(a)\Delta a + o(\Delta a)$$

we have

$$\frac{F(a) - F(a + \Delta a)}{\Delta a} = -\mu(a) + o(1)$$

and, consequently,

$$\frac{F'(a)}{F(a)} = -\mu(a).$$

It means that

$$F(a) = \exp \left(- \int_0^a \mu(s) ds \right)$$

and we can write the age profile $p(a)$ in the following way

$$p(a) = e^{-\lambda_0 a} F(a) \left(\int_0^c e^{-\lambda_0 a} F(a) da \right)^{-1}.$$

Now, we return back to the beginning of our lectures, namely, to Ulpian's table. Let us assume that we are able to collect data concerning the distribution of the duration of life in a population. Having these data we are able to calculate the survival function F . The question is: how to find Ulpian's table? Ulpian's table gives us the information on the expected remaining life. Let $\varphi_a(x)$ be the probability that *remaining life* at age a is at least x . Then

$$\varphi_a(x) = P(T \geq a + x | T \geq a) = \frac{P(T \geq a + x)}{P(T \geq a)} = \frac{F(a + x)}{F(a)}.$$

It means that the *expected remaining life* at age a is given by the formula

$$D(a) = - \int_0^c x \varphi_a'(x) dx = \int_0^c \varphi_a(x) dx = \int_0^c \frac{F(a + x)}{F(a)} dx.$$

Now we present another age structured model which is interesting both from biological point of view because it concerns specific but important

medical problem, and also from mathematical point of view because the model contains a nontrivial boundary condition and leads to an interesting delay differential equation.

Example 1.11 (Erythrocytes dynamics). *Now we presented a model of the red blood cells dynamics by Ważewska–Czyżewska and Lasota [80]. We start from the necessary biological information. Red blood cells, like other blood cell, are produced in the bone marrow in a process called haematopoiesis from the same cells called committed stem cells in about 7 days. Healthy erythrocytes live about 120 days before they are degraded. The production of them is stimulated by the hormone erythropoietin and the production system try to keep the number of cells on a constant level.*

Now we formulate the model. Let $n(t, a)$ be the age distribution of red cells at time t . Then $N(t) = \int_0^\infty n(t, a) da$ is the total number of red cells at time t and $p(t) = n(t, 0)$ is the production of new cells in a unit time. Let h be the time for the production of a mature erythrocytes. The degree of arousal of the system can be characterized by the function

$$S(t) = \frac{p'(t)}{p(t)}.$$

We assume that the change of the number of red cells in the blood circulation causes arousal of the system in the following way

$$S(t) = -\frac{d}{dt}\gamma N(t-h).$$

It means that

$$\frac{p'(t)}{p(t)} = -\frac{d}{dt}\gamma N(t-h)$$

and, consequently,

$$p(t) = \rho e^{-\gamma N(t-h)}. \quad (1.43)$$

The constant ρ can be interpreted as the demand of the organism for oxygen. If $\mu(t, a)$ is the rate of degradation of cells then analogously to the McKendrick model we receive the equation

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(t, a)n. \quad (1.44)$$

Taking into account equation (1.43) and the initial condition the whole model is the following

$$\begin{aligned}\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= -\mu(t, a)n, \\ n(t, 0) &= \rho e^{-\gamma N(t-h)}, \\ n(0, a) &= n_0(a).\end{aligned}$$

We can also consider a simplified model. Let us assume that

$$\mu = \frac{1}{N(t)} \int_0^\infty \mu(t, a)n(t, a) da$$

do not depend on time. The constant μ is called the coefficient of destruction. Integrating both sides of (1.44) over a we get

$$N'(t) + n(t, \infty) - n(t, 0) = -\mu N(t)$$

and assuming that $n(t, \infty) = 0$ and using (1.43) we obtain

$$N'(t) = -\mu N(t) + \rho e^{-\gamma N(t-h)}. \quad (1.45)$$

Using computer simulations it is rather easy to find solutions of this equation for different coefficient h , γ , and ρ and compare the results with empirical data. The paper [80] contains conclusions concerning the course of the diseases under different parameters and the medical treatment of them. Since for some parameters equation (1.44) has periodic solutions the model confirmed the existence of periodic blood diseases and that this periodicity is a property of the system and does not follow from the daily or another typical rhythm of life [23].

Example 1.12 (Size structured model). *Now we consider a model of a cellular population which was introduced for the first time probably by Bell and Anderson [7] and was studied and generalized in many papers (see e.g. [17], [26], [51], [66], [81]). In this model a cell is characterized by its size x , a number from the interval $[a, 1]$, $0 < a < 1$. We assume that the death and the division rates are $d(x)$ and $b(x)$, respectively. We also assume that if x is the size of the mother cell then after division the size of the daughter cells is $x/2$. It is obvious that $b(x) = 0$ for $x < 2a$ and we need to assume that*

$$\int_a^1 b(x) dx = \infty.$$

This condition guarantees us that the size of any cell cannot be greater than 1. Observe that the lost of cells with size $\leq m$ in the time interval of the length Δt is

$$\Delta t \int_0^m (d(x) + b(x))u(t, x) dx + o(\Delta t)$$

and the number of the new cells with size $\leq m$ in this time interval is given by

$$\Delta t \int_0^{2m} 2b(r)u(t, r) dr + o(\Delta t).$$

Moreover we assume that a cell grows according to the equation $x' = g(x)$. It means that the cells with size $\leq m$ at time t will have size $\leq m + g(m)\Delta t + o(\Delta t)$ at time $t + \Delta t$. Combining these three elements we obtain

$$\begin{aligned} & \int_0^{m+g(m)\Delta t} u(t + \Delta t, x) dx - \int_0^m u(t, x) dx \\ &= -\Delta t \int_0^m (d(x) + b(x))u(t, x) dx \\ & \quad + \Delta t \int_0^{2m} 2b(r)u(t, r) dr + o(\Delta t). \end{aligned} \quad (1.46)$$

Dividing both sides of (1.46) by Δt and letting $\Delta t \rightarrow 0$ we receive

$$\begin{aligned} \int_0^m \frac{\partial}{\partial t} u(t, x) dx + g(m)u(t, m) &= - \int_0^m (d(x) + b(x))u(t, x) dx \\ & \quad + \int_0^{2m} 2b(r)u(t, r) dr. \end{aligned}$$

Differentiating both sides of the last equation with respect to m we finally obtain

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} (g(x)u(t, x)) = -(d(x) + b(x))u(t, x) + 4b(2x)u(t, 2x). \quad (1.47)$$

The full model consists of equation (1.47) and the following boundary and initial conditions

$$u(t, a) = 0, \quad (1.48)$$

$$u(0, x) = v(x). \quad (1.49)$$

Examples 1.10 and 1.12 show that though both models are based on similar biological assumptions they lead to different mathematical objects. Our aim is to give a unified approach to structured models. We start with

the *continuity equation*. Consider a structured model without mortality and proliferation. Let $x \in G \subset \mathbb{R}^n$ be a parameter which characterizes any individual. We assume that the parameter x changes according to the equation

$$x'(t) = g(t, x(t)). \quad (1.50)$$

If $u(t, x)$ is the distribution of x then u satisfies the following equation

$$\frac{\partial u(t, x)}{\partial t} + \operatorname{div}(g(t, x)u(t, x)) = 0, \quad (1.51)$$

where

$$\operatorname{div}(g(t, x)u(t, x)) = \sum_{i=1}^n \frac{\partial}{\partial x_i} (g(t, x)u(t, x)). \quad (1.52)$$

Proof. Given a domain $D \subset G$ with the smooth boundary S , consider the fluxes into the set D in the time interval of the length Δt :

$$I(\Delta t) = \int_D u(t + \Delta t, x) dx - \int_D u(t, x) dx. \quad (1.53)$$

Since the fluxes are through the surface S and since the speed at which individuals cross the surface is $-n(x) \cdot g(t, x)$, where $n(x)$ is the outward-pointing unit normal vector to S , we have

$$I(\Delta t) = -\Delta t \int_S (n(x) \cdot g(t, x)u(t, x)) d\sigma(x) + o(\Delta t). \quad (1.54)$$

According to the Gauss-Ostrogradski theorem we have

$$\int_S (n(x) \cdot g(t, x)u(t, x)) d\sigma(x) = \int_D \operatorname{div}(g(t, x)u(t, x)) dx. \quad (1.55)$$

Equations (1.53), (1.54) and (1.55) imply (1.51). \square

Now we introduce the *general reproduction operator*. We assume that an individual with the parameter x has k descendants and that $\mathcal{P}_k(x, A)$ is the probability that any of its descendant has the parameter in the set $A \subset G$ at the birth. For example, if x is the age then $\mathcal{P}_k(x, A) = \mathbf{1}_A(0)$. If x is the size then

$$\mathcal{P}_2(x, A) = \begin{cases} 1, & \text{if } x/2 \in A, \\ 0, & \text{if } x/2 \notin A. \end{cases}$$

Let $b_k(x)\Delta t$ be the probability that an individual with parameter x has k descendants in time interval $[t, t + \Delta t]$. We set

$$\mathcal{P}(x, A) = \sum_{k=1}^{\infty} k b_k(x) \mathcal{P}_k(x, A).$$

Then $\mathcal{P}(x, A)\Delta t$ is the probability that an individual with parameter x has a descendant in the set A . We also assume that $\mu(t, x)$ is the death rate which includes both the real death and the lost of cells during the process of division.

Now we introduce the *Kolmogorov's backward equation* corresponding to our model. Denote by $m_{t,x}$ the measure which describes the distribution of the parameter x at time t if at the initial time 0 we have one individual with parameter x . Let

$$u(t, x) = \int_G f(y) m_{t,x}(dy)$$

for a smooth function g . Then the function u satisfies the Kolmogorov's backward equation

$$\frac{\partial u}{\partial t} = -\mu u + \underbrace{\sum_{i=1}^n g_i \frac{\partial u}{\partial x_i} + \int_G u(t, y) \mathcal{P}(x, dy)}_{\mathcal{A}^* u} \quad (1.56)$$

and $u(0, x) = f(x)$. Set

$$Sf(x) = \int_G f(y) \mathcal{P}(x, dy).$$

Then the equation (1.56) can be written in the following way

$$\frac{\partial u}{\partial t} = -\mu u + \sum_{i=1}^n g_i \frac{\partial u}{\partial x_i} + Su. \quad (1.57)$$

The equation describing the evolution of the densities of the distributions of the parameter x in the population is conjugated to equation (1.56) and is called the *Kolmogorov's forward (Fokker-Planck) equation*:

$$\frac{\partial u}{\partial t} = Au. \quad (1.58)$$

But the question is: does there exist a linear operator \mathcal{A} defined on a dense subspace of $L^1(G)$ such that \mathcal{A}^* is given by formula (1.56)?

Example 1.13. If there exists a linear bounded operator $P : L^1(G) \rightarrow L^1(G)$ such that $P^* = S$, then

$$\mathcal{A}f = -\mu f - \operatorname{div}(gf) + Pf.$$

The sufficient condition for the existence of the operator P is the following:

(C) if $l(B) = 0$, then $\mathcal{P}(x, B) = 0$ for almost all x , where l denotes the Lebesgue measure and B is any Borel set. Indeed, from (C) it follows that for each density f the measure m given by the formula

$$m(B) = \int_G f(x)\mathcal{P}(x, B) dx, \quad \text{for Borel sets } B,$$

is absolutely continuous with respect to the Lebesgue measure and $m(G) = 1$. From this it follows that the Radon-Nikodym derivative $\frac{dm}{dx}$ exists and it is a density. The operator P is given by the formula $Pf = \frac{dm}{dx}$. For example, in the size structured population model we have

$$\mathcal{P}(x, A) = \begin{cases} 2b(x), & \text{if } x/2 \in A, \\ 0, & \text{if } x/2 \notin A. \end{cases}$$

Then the transition function \mathcal{P} satisfies (C) and the operator P is given by the formula $Pf(x) = 4b(2x)f(2x)$.

Example 1.14. In the age structure McKendrick model the transition function is the following $\mathcal{P}(x, A) = 2b(x)\mathbf{1}_A(0)$. This transition function does not fulfil condition (C) and the operator P does not exist. But in this case we can assume that

$$\mathcal{A}f(a) = -\mu(a)f(a) - f'(a)$$

and the domain of the operator \mathcal{A} is the following

$$D(\mathcal{A}) = \{f \in L^1 : f' \in L^1, f(0) = \int_0^c 2b(a)f(a) da\}.$$

Simple calculations show that

$$\mathcal{A}^*f(a) = -\mu(a)f(a) + f'(a) + 2b(a)f(0).$$

It means that

$$Sf(a) = 2b(a)f(0) = \int f(x)\mathcal{P}(a, dx).$$

Thus we obtain the proper Kolmogorov's backward equation:

$$\frac{\partial}{\partial t}u(t, a) = -\mu(a)u(t, a) + \frac{\partial}{\partial a}u(t, a) + 2b(a)u(t, 0).$$

In general, the long time behaviour of linear continuous structured models is similar to that in the McKendrick model – they usually have asynchronous exponential growth. We illustrate it considering the size structured model.

Theorem 1.8. *If $g(2x) \neq 2g(x)$ at least for one $x \in [a, 1]$, then there exist $\lambda \in \mathbf{R}$ and positive functions f_* and w such that*

$$e^{-\lambda t}u(t, \cdot) \rightarrow f_* \int_a^1 u(0, x)w(x) dx \quad \text{in } L^1(a, 1).$$

Proof. [Sketch of the proof] We repeat some steps in the proof of a more general result from the paper [66]. Equation (1.47) can be written as an evolution equation $u'(t) = Au$. First we show that A is an infinitesimal generator of a continuous semigroup $\{T(t)\}_{t \geq 0}$ of linear operators on $L^1(a, 1)$. Then we prove that there exist $\lambda \in \mathbb{R}$ and continuous and positive functions v and w such that $Av = \lambda v$ and $A^*w = \lambda w$. From this it follows that the semigroup $\{P(t)\}_{t \geq 0}$ given by $P(t) = e^{-\lambda t}T(t)$ is a stochastic semigroup on the space $L^1(X, \Sigma, m)$, where m is a Borel measure on the interval $[a, 1]$ given by $m(B) = \int_B w(x) dx$. Moreover, for some $c > 0$ the function $f_* = cv$ is an invariant density with respect to $\{P(t)\}_{t \geq 0}$. Finally, from Theorem 1.9 (see below) we conclude that this semigroup is asymptotically stable. Since the Lebesgue measure and the measure m are equivalent we obtain that $e^{-\lambda t}u(t, \cdot)$ converges to $f_*\Phi(u(0, \cdot))$ in $L^1(a, 1)$, where $\Phi(g) := \int_a^1 g(x)w(x) dx$. \square

In the proof of Theorem 1.8 we use some general result concerning stochastic semigroups. We recall it now. A stochastic semigroup $\{P(t)\}_{t \geq 0}$ is called *partially integral* if there exist $t_0 > 0$ and a measurable non-negative function $q(x, y)$ such that

$$\int_X \int_X q(x, y) m(dx) m(dy) > 0 \quad (1.59)$$

and

$$P(t_0)f(x) \geq \int_X q(x, y)f(y) m(dy) \quad \text{for every } f \in D. \quad (1.60)$$

Theorem 1.9 ([59]). *Let $\{P(t)\}_{t \geq 0}$ be a partially integral stochastic semigroup. Assume that the semigroup $\{P(t)\}_{t \geq 0}$ has the only one invariant density f_* . If $f_* > 0$ a.e., then the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable.*

The general scheme described above includes a large family of structured models. The parameters can be also the space position, maturity, contents of genetic material etc., and we can consider models which includes more parameters: e.g. age-size, space-maturity structured models. But there are a lot of models which are outside of this scheme. Now we give some examples.

Example 1.15 (Simple Cell Cycle Model). *We consider a model of the cell cycle given by Rubinow [60]. In this model the state of a cell in the cell cycle is described by a parameter called maturity $0 \leq x \leq 1$. It is assumed that the parameter x grows according to the equation*

$$x' = g(x)$$

and the cell divides at maturity 1 and new born cells have maturity 0. Let $u(t, x)$ be the density of the population with respect to x . We also assume that the mortality rate is $\mu(x)$. The density $u(t, x)$ satisfies the following initial-boundary problem

$$\begin{aligned} \frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} (g(x)u(t, x)) &= -\mu(x)u(t, x), \\ g(0)u(t, 0) &= 2g(1)u(t, 1), \\ u(0, x) &= u_0(x). \end{aligned}$$

Although the model is similar to the age structured model it cannot be treated by our general scheme because we cannot find the proper transition function \mathcal{P} for it.

Example 1.16 (continuous Penna model). *Now we present a continuous version of the Penna model [1]. In this model both time and age variables are nonnegative real numbers. Each individual is described by its age and its own maximum life span m . Let $u(t, a, m)$ be the density of a and m at time t . Then the model is described by the system of equations:*

$$\begin{aligned} N(t) &= \int_0^\infty \int_0^m u(t, a, m), \\ \frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} &= -\mu(a, m, N(t))u(t, a, m), \quad \text{for } a < m, \\ u(t, a, m) &= 0, \quad \text{for } a \geq m, \\ u(t, 0, m) &= \int_0^\infty \int_0^{m'} b(a, m, m', N(t))u(t, a, m') da dm'. \end{aligned} \tag{1.61}$$

As in Example 1.5, μ is the death rate. If the size of the population is N then the probability that a parent with maximum life span m' and age a gives birth to a child with maximum life span $m \in (m_1, m_2)$ in the time interval of the length Δt is

$$\Delta t \int_{m_1}^{m_2} b(a, m, m', N) dm.$$

In [1] it is assumed that like in the Penna model we have $\mu = (1 - N(t)/N_{\max})$ and $b = (1 - N(t)/N_{\max})p(m, m')$, where N_{\max} is the maximum size of the population and $p(m, m')$ is the birth function. The operator $Pf(m) = \int_0^\infty f(m') dm'$ can be called the mutation operator.

In some models we consider both continuous and discrete parameters. For example in tumour growth models we consider cells in a few different states connected with malignant progression but we are interested in the space distribution of them. A similar situation appears in epidemiology if we consider models with the space or age distribution of susceptible, infected, and resistant people [33]. In such a situation we consider different densities u_1, \dots, u_n for different classes of individuals. Now we present another model of this type.

Example 1.17 (The age structured model with telomere loss).

In [5] the authors consider an age structured cell population model in which the population is split into $N + 1$ subpopulations according to the telomere state. The biological aspects of telomere shortening were discussed in Example 1.3. We are interested in the age distribution $u_i(t, a)$ of cells in the i -th subpopulation, $i = 0, 1, \dots, N$. The functions u_0, \dots, u_N satisfies the following system of $(N + 1)$ partial differential equations with $(N + 1)$ boundary and initials conditions:

$$\frac{\partial}{\partial t} u_j(t, a) + \frac{\partial}{\partial a} u_j(t, a) = -(b_j(a) + \mu_i(a))u_j(t, a), \quad (1.62)$$

$$u_j(t, 0) = 2 \sum_{k=j}^N p_{jk} \int_0^\infty b_k(a) u(t, a) da, \quad (1.63)$$

$$u_j(0, a) = v_j(a). \quad (1.64)$$

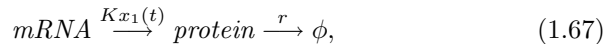
Here b_i, μ_i are the birth and death rates in the i -th telomere state and p_{jk} represents the probability for a cell in the k -th telomere state to produce by division a cell in the j -th telomere state. We assume that $p_{jk} = 0$ if $k < j$, which means that the daughter cell is in a lower state than the mother cell.

As in Example 1.3 we do not have here the asynchronous exponential growth but the population has the asynchronous polynomial exponential growth.

Example 1.18 (Stochastic gene expression). Now we present a simple model of gene expression introduced in the paper by Lipniacki et al. [44] and we give also some analytic results concerning this model received in the paper [10]. We consider the process of the regulation of a single gene. The model involves three processes: allele activation/inactivation, mRNA transcription/decay, and protein translation/decay. A gene can be in an active (denoted by A) or inactive state (denoted by I) and it can be transformed into an active state or into an inactive state, with intensities q_0 and q_1 , respectively. The rates q_0 and q_1 depend on the number of mRNA molecules $x_1(t)$ and on the number of protein molecules $x_2(t)$. If the gene is active then mRNA transcript molecules are synthesized at the rate R . The protein translation proceeds with the rate $Kx_1(t)$, where K is a constant. In addition, mRNA and protein molecules undergo the process of degradation. The mRNA and protein degradation rate are m and r , respectively. The reactions described above may be summarized as follows:



and



where ϕ stands for degradation of gene products. The state of the system is described by the triple $(x_1(t), x_2(t), \gamma(t))$, where $\gamma(t)$ is a random variables with values 1 if the gene is in the active state and 0 in the inactive state. The functions $x_1(t)$ and $x_2(t)$ satisfy the following equations

$$\frac{dx_1}{dt} = H\gamma(t) - mx_1, \quad (1.68)$$

$$\frac{dx_2}{dt} = Kx_1 - rx_2. \quad (1.69)$$

The switching function $\gamma(t)$ is a stochastic process with values in the set $\{0, 1\}$ and this process depends on the functions $x_1(t)$ and $x_2(t)$.

Equations (1.68) - (1.69) generate stochastic trajectories, which can be described as piecewise deterministic, time-continuous Markov process

$$p(t) = (x_1(t), x_2(t), \gamma(t)) = (x(t), \gamma(t)), \quad t \geq 0. \quad (1.70)$$

We introduce partial density functions of this process $u_i(t, x_1, x_2)$ by

$$\Pr\{x(t) \in B, \gamma(t) = i\} = \iint_B u_i(x_1, x_2, t) dx_1 dx_2, \quad i = 0, 1$$

where B is a Borel subset of $\mathbb{R}^+ \times \mathbb{R}^+$. The functions satisfy the following Fokker-Planck system:

$$\begin{aligned} \frac{\partial u_0}{\partial t} + \frac{\partial}{\partial x_1}(-mx_1u_0) + \frac{\partial}{\partial x_2}((Kx_1 - rx_2)u_0) &= q_1u_1 - q_0u_0, \\ \frac{\partial u_1}{\partial t} + \frac{\partial}{\partial x_1}((R - mx_1)u_1) + \frac{\partial}{\partial x_2}((Kx_1 - rx_2)u_1) &= q_0u_0 - q_1u_1, \end{aligned} \tag{1.71}$$

where $q_0 = q_0(x_1, x_2)$ and $q_1 = q_1(x_1, x_2)$ are given non-negative continuous functions defined on the rectangle $\mathcal{K} = [0, R/m] \times [0, KR/Mr]$. Next, we construct a stochastic semigroup $\{P(t)\}_{t \geq 0}$ on the space $L^1(\mathcal{S})$, $\mathcal{S} = \mathcal{K} \times \{0, 1\}$, related to the Fokker-Planck system of equations for the densities of the process. The semigroup $\{P(t)\}_{t \geq 0}$ is defined by $P(t)f(x_1, x_2, i) = u_i(t, x_1, x_2)$, where (u_1, u_2) is the solution of the system (1.71) with the initial conditions: $u_0(0, x_1, x_2) = f(x_1, x_2, 0)$ and $u_1(0, x_1, x_2) = f(x_1, x_2, 1)$. The main result of the paper [10] is the asymptotic stability of the semigroup $\{P(t)\}_{t \geq 0}$. The proof of this result is based on the following theorem.

Theorem 1.10. *Let \mathcal{S} be a compact metric space and Σ be the σ -algebra of Borel sets. Let $\{P(t)\}_{t \geq 0}$ be a Markov semigroup which satisfies conditions:*

- (a) *for every $f \in D$ we have $\int_0^\infty P(t)f dt > 0$ a.e.,*
- (b) *for every $q_0 \in \mathcal{S}$ there exist $\kappa > 0$, $t > 0$, and a measurable function $\eta \geq 0$ such that $\int \eta dm > 0$ and*

$$P(t)f(p) \geq \eta(p) \int_{B(q_0, \kappa)} f(q) m(dq) \tag{1.72}$$

for $p \in \mathcal{S}$, where $B(q_0, \kappa)$ is the open ball with centre q_0 and radius κ ,
Then the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable.

Theorem 1.10 is a simple consequence of Theorem 1.9 and Theorem 2 [62].

Till now we have discussed rather simple structured models. Now we present a more advanced model [47] to show various problems which can appear in building models and in their investigations.

Example 1.19 (Two-phase model of the cell cycle [47]). *Now we assume like in Example 1.9 that a cell can be in the resting phase A which duration is random or in the proliferating phase which duration is*

constant τ . The state of a cell is characterized by one parameter m called maturity. Denote by $p(t, m, a)$ and $n(t, m, a)$ the maturity-age distribution of proliferating and resting cells, respectively. The maturity m grows according to the equation

$$m' = V(m).$$

Let $\gamma(m)$ and $\delta(m)$ denote the death rates in phases A and B. Let $N(t, m) = \int n(t, m, a) da$, and $\bar{N}(t) = \int N(t, m) dm$. Then $\bar{N}(t)$ is the total number of cells in the resting phase and we can assume that $\bar{N}(t)$ characterizes the state of the whole population. We assume that the rate of entering of the proliferating phase β depends on the maturity of a cell and the state of the whole population, i.e. $\beta = \beta(\bar{N}, m)$. Let $h(m)$ be the maturity of the mother cell at cytokinesis if its daughter cells at birth have the maturity m . The whole model consists of two partial differential equations

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial(Vp)}{\partial m} = -\gamma p, \quad (1.73)$$

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \frac{\partial(Vn)}{\partial m} = -(\delta + \beta)n \quad (1.74)$$

and two boundary conditions

$$p(t, m, 0) = \beta(\bar{N}(t), m)N(t, m), \quad (1.75)$$

$$n(t, m, 0) = 2p(t, h(m), \tau)h'(m). \quad (1.76)$$

The system (1.73) and (1.74) provides conservation equations for $p(t, m, a)$ and $n(t, m, a)$ and can be derived in the same way as the continuity equation. Equations (1.75) and (1.76) describe the cellular flux between phases. Integrating both sides of (1.73) and (1.74) over the age variable a and using conditions (1.75) and (1.76) one can derive equations for the functions $N(t, m)$ and $P(t, m) = \int p(t, m, a) da$. To make the presentation more transparent, we assume additionally that δ, γ and β do not depend on m . Let $m(t)$ be the solution of the equation $m' = V(m)$ satisfying the initial condition $m(0) = m_0$ and let $g(m_0) = m(-\tau)$, $k(m) = g(h(m))$. Then

$$\begin{aligned} \frac{\partial N}{\partial t} + \frac{\partial(VN)}{\partial m} = & -(\delta + \beta(\bar{N}))N \\ & + 2e^{-\gamma\tau}\beta(\bar{N}(t-\tau))k'(m)N(t-\tau, k(m)). \end{aligned} \quad (1.77)$$

Equation (1.77) is rather difficult to study because it is a partial differential equation in which there is an explicit temporal retardation as well as

a nonlocal dependence in the maturation variable due to cell replication. Integrating both sides of (1.77) over m we obtain

$$\bar{N}'(t) = -(\delta + \beta(\bar{N}))\bar{N} + 2e^{-\gamma\tau}\beta(\bar{N}(t - \tau))\bar{N}(t - \tau). \quad (1.78)$$

In [47] it is proved the following result.

Theorem 1.11. *Assume that the delay equation (1.78) has a constant solution $\bar{N}_0 > 0$ and \bar{N}_0 is globally asymptotically stable. If*

$$(\delta + \beta(\bar{N}_0)) \log k'(0) < V'(0) \quad (1.79)$$

then there exists a stationary solution $N_0(m)$ of equation (1.77) and for every solution $N(t, m)$ of it we have

$$\lim_{t \rightarrow \infty} \int |N(t, m) - N_0(m)| dm = 0. \quad (1.80)$$

Condition (1.79) has an interesting biological interpretation. It shows that the stability of the population depends on the dynamics of low mature (small) cells. The term $k'(0)$ describes the relation between the maturation of the mother and daughter cells. If m is the maturation of a small mother cell at the moment of entering the proliferating phase, then the maturation of a new-born daughter cell is $m/k'(0)$. The term $c = \delta + \beta(N_0)$ is the rate of leaving of the resting phase (by being lost or by entering the proliferating phase). Since $V'(0)$ is the rate at which small cells mature, condition (1.79) means that the maturation of a big part of small cells will increase in the next generation.

1.7. Conclusion

In this lecture we presented some number of different types of structured models which we divided into four different classes according to the type of structure and time (discrete and continuous). The most advanced models are continuous time-structure models. They are usually described by one or by a system of partial differential equations (transport equations) with specific reproductions terms (non-local operators or integral boundary conditions). Advanced structured models contain also time delay (e.g. the delay connected with the cell cycle, reproduction process, etc.), nonlinear terms connected with limited resources or second order terms connected with stochastic movement of individuals or stochastic noise if, for example, a parameter is some phenotype property and evolution is influenced by mutation.

We restrict our mathematical results to study simple asymptotic properties of models as asynchronous exponential growth and asymptotic stability. But our models can have more complicated behaviour which can be studied using theoretical methods of dynamical systems. We can investigate such properties of models as the existence of a limit cycle, bifurcation, existence of invariant measures and chaos. It is hardly known that solutions of simple linear partial differential equations behave in a chaotic way. The following equation with the initial condition:

$$\begin{aligned}\frac{\partial u}{\partial t} + x \frac{\partial u}{\partial x} &= \lambda u, \\ u(0, x) &= v(x)\end{aligned}$$

defines a dynamical system on the space $X = C[0, 1]$ given by

$$S^t v(x) = u(t, x) = e^{\lambda t} v(e^{-t} x),$$

which is chaotic, practically in each sense of the meaning of this word. For example, for $\lambda > 0$ there exists a Gaussian measure with the support X invariant under $\{S^t\}_{t \geq 0}$ and the system is mixing [63] (see also a review [64]). This implies the topological chaos: the existence of dense trajectories (topological transitivity) and instability of trajectories. The topological chaos was also proved for the birth-death-type model [6].

In structured population models we mainly investigate the long time behaviour of densities. As we show in these lectures there are a lot of results concerning asymptotic stability and asynchronous exponential growth, but there are no results concerning chaotic behaviour on the set of densities. One of the reasons for the lack of such results is that there are no good mathematical tools to investigate this problem. Methods of studying chaos based on the paper [16] do not work in this case because they are strictly connected with dynamical systems acting on the whole linear spaces. Methods based on invariant measures seem to be too difficult in these models.

Another interesting problem is formation of spatial aggregates as a result of interaction between individuals. This phenomenon concerns a variety of biological species, from colonies of bacteria, swarms of larvae, or adult insects to fish schools, bird flocks etc. Numerous mathematical models have been proposed for these processes, e.g. [52, 57], but the problem of spatial heterogeneity is still far away from the real solution. The explanation, originally proposed by Turing [74] and developed in many papers, that diffusion can destabilise homogeneous distribution to produce pattern is often treated by biologists as a mathematical trick but not the real reason. Models based on interaction between individuals such as chemotaxis for simple

organisms and social actions of animals should better explain the behaviour of the whole population. Unfortunately it is not easy to build such models and very difficult to deduce from them qualitative and quantitative results which can be compared with biological observations.

There are also a lot of open problems in population genetics. Most of them are connected with stochastic models which are not discussed in these lectures, but also the models discussed in these lectures needs further investigations. For example, according to my knowledge, the Penna model (see Example 1.5) was not too intensively mathematically investigated. It would be interesting to show the existence and stability of a stationary distribution in this model and compare it with the age distribution in the human population. The models involving telomere loss (Examples 1.3 and 1.17) need future modifications which should include the recent knowledge concerning this subject. Also the model concerning the evolution of paralog families (Example 1.7) needs modifications and further studies. Genome evolution is a very complicated stochastic process which involves many events in addition to the ones considered in this model. We also ignore the possibility of dependence of rates of elementary events on the gene length, its location in the genome, genome size or the functional importance of a given gene.

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