Chapter 5  
The Lasota–Ważewska Equation

Polish scientists, the hematologist Maria Ważewska-Czyżewska and the mathematician Andrzej Lasota, formulated a mathematical model of the red blood cell system dynamics, known today as the Lasota–Ważewska equation, in an article published in *Applied Mathematics* (annals of the Polish Mathematical Society) in the year 1976. Their main goal was to provide a model that, with the possible low number of constants having a specified biological meaning, would allow to predict changes in the number of blood cells in the bloodstream. The basic idea was to associate some known equation of population dynamics taking into account the age structure of the population, with a properly constructed feedback in the form of an integral equation with a delayed argument. By doing so, they obtained a model that in many cases provides solutions corresponding to biological and medical experimental data, and which became the inspiration for studies on many issues in the field of pure mathematics and biomathematics (Rudnicki 2007).

5.1 McKendrick–Von Foerster Equation

The above-mentioned equation used by M. Ważewska-Czyżewska and A. Lasota in their model is the equation that was first proposed by Sharpe and Lotka (1911) (see Rudnicki 2014, p. 216), then by McKendrick (1926) and Von Foerster (1959). This is an equation describing the age distribution of the population over time. A. G. McKendrick used it to model the human population attacked by epidemics, while H. Von Foerster considered it in the context of hematological experimental data. In literature, it is called the “McKendrick” equation, or often the “Von Foerster” equation. We are going to use the name “McKendrick–Von Foerster” equation. It is one of the oldest of the so-called structural models (Rudnicki 2014, p. 216), (Murray 2006, p. 39), i.e. taking into account the natural structure for the studied population, e.g. age, spatial, maturity, size, etc.
We have mentioned that A. G. McKendrick used the equation to model dynamics of human population attacked by epidemics, in particular he was studied the variability of the population age distribution. Humankind has been affected significantly by infectious diseases throughout its known history (Thieme 2003, p. 283), (Rudnicki 2014, p. 84). Around 430 B.C. unknown epidemic contribute to the fall of Athens. The Plague of Justynian attacked the Byzantine and Sasanian empires, as well as the port cities around the whole Mediterranean Sea in 541-542 A.D. and returning until 750, killing around 25–100 millions people. The Black Death caused decease of up to 75–200 millions people in Eurasia and North Africa. In 1347–1351 around 1/4 of Europe population has fallen because of this pandemic. The history of mankind know more such examples. Infectious diseases (HIV, Ebola, Malaria, lassa, hanta, dengue viruses and yellow fever) causes still a continuing threat. Currently we are witnessing coronavirus SARS-CoV-2 pandemic. We can observe that population dynamics models are now intensively applied in order to predict this pandemic behaviour (see e.g. Peng et al. 2020; Luo et al. 2020; Khan and Atangana 2020; Kucharski et al. 2020; Prem et al. 2020; Cherniha and Davydovych 2020).

Knowledge of the structure and principles of the McKendrick–Von Foerster equation is important for understanding the models analyzed later in this book, therefore, we are going to derive this equation now (see Ważewska-Czyżewska and Lasota 1976; Rudnicki 2014). It is worth referring to the source papers of Sharpe and Lotka (1911), McKendrick (1926), and Von Foerster (1959).

Let us denote the density function of the age distribution for red blood cells population by \( n(t, a) \), satisfying the condition

\[
\int_0^\infty n(t, a) da = N(t), \tag{5.1}
\]

where \( N(t) \) is a total number of blood cells in the bloodstream at time \( t \). In other words, the function \( n(t, a) \) determines the number of blood cells in age \( a \) for a given time \( t \). Blood cells that were at age \( a \) at time \( t \), are at age \( a + \Delta t \) at time \( t + \Delta t \), therefore, the difference

\[
n(t, a) - n(t + \Delta t, a + \Delta t), \tag{5.2}
\]

gives the number of blood cells at age \( a \) that died within the time interval \((t, t + \Delta t)\). The limit

\[
i(t, a) = \lim_{\Delta t \to \infty} \frac{n(t, a) - n(t + \Delta t, a + \Delta t)}{\Delta t} \tag{5.3}
\]

denotes the destruction intensity of blood cells at age \( a \) and at time \( t \). The quotient

\[
\lambda(t, a) = \frac{i(t, a)}{n(t, a)} \tag{5.4}
\]
is called **coefficient of destruction** and it determines the probability that a blood cell which in time \( t \) is at age \( a \) will die within a period of time \( (t, t + \Delta t) \). From (5.3) and (5.4) we obtain

\[
\lim_{\Delta t \to \infty} \frac{n(t, a) - n(t + \Delta t, a + \Delta t)}{\Delta t} = \lambda(t, a)n(t, a).
\]

Assuming now that there are partial derivatives of the function \( n(t, a) \), the formula (5.5) can be written in a form of partial equation

\[
\frac{\partial n(t, a)}{\partial t} + \frac{\partial n(t, a)}{\partial a} = -\lambda(t, a)n(t, a).
\]

The Eq. (5.6) is the McKendrick–Von Foerster equation we are looking for. As can be seen from the presented formulation, it is a consequence of only the destruction coefficient \( \lambda \). Von Foerster (1959, p. 393) characterizes this coefficient as the sum of “intrinsic loss” caused by aging of population elements and “environmental loss” resulting from their interaction with the external environment.

To solve the Eq. (5.6), one must know the initial condition

\[
n(0, a) = v(a),
\]

i.e. the age distribution \( v(a) \) at time \( t = 0 \) and the boundary condition

\[
n(t, 0) = p(t),
\]

interpreted as the blood cell production \( p(t) \) at time \( t \) (see Ważewska-Czyżewska and Lasota 1976, p. 25). The Eq. (5.6) with conditions (5.7) and (5.8) is an example of “self-regulating” mechanism, as McKendrick emphasized in his work (1926, p. 124).

### 5.1.1 Method of Characteristics

Equation (5.6) can be solved using method of characteristics (Murray 2006, p. 41), (Rudnicki 2014, p. 209), (Pelczar and Szarski 1987, p. 253). Family of characteristics are solutions of equation

\[
\dot{a} = 1,
\]

so they are straight lines (see Fig. 5.1)

\[
a = \begin{cases} 
  t + a_0 & \text{dla } a > t, \\
  t - t_0 & \text{dla } a < t,
\end{cases}
\]
where \( a_0 \) is the individual’s initial age at time \( t = 0 \), and \( t_0 \) is the time (moment) at which the individual was born. Solution of the partial equation (5.6) is “strew” on characteristics by solutions of the equation

\[
\dot{n} = -\lambda \cdot n, \tag{5.11}
\]

By making an appropriate calculations, one can write this in the following form (see e.g. Murray 2006, p. 41)

\[
n(t, a) = v(a - t) \exp\{-\int_{a-t}^{a} \lambda(r)dr\}, \quad a \geq t \tag{5.12}
\]

\[
n(t, a) = f(t - a) \exp\{-\int_{0}^{a} \lambda(r)dr\}, \quad a \leq t \tag{5.13}
\]

### 5.1.2 Method of Straight Lines

For Eq. (5.6), which is a linear partial differential equation, it is possible to determine the exact solution. This is not always easy in the case of more complex nonlinear partial equations. In addition, when the characteristics are not straight lines, but take the form of some non-linear functions, the use of formulas obtained by the characteristics method for numerical calculations can be troublesome. We will now present a method that provides approximate solutions, sometimes called the “method of straight lines”. It is based on converting a partial differential equation into a system of ordinary differential equations. The number of these equations is equal to the number of discretization points of the spatial variable (i.e. the variable \( a \) in the case of Eq. (5.6)). An important advantage of the method of straight lines is its easiness to use in numerical calculations. When we replace Eq. (5.6) with a system of a finite
number of ordinary differential equations, then from the infinite-dimensional system we obtain its finite-dimensional approximation.

We will now use the method of straight lines to solve the Eq. (5.6) numerically.

### 5.1.2.1 Preparation of Numerical Calculations

We discretize a spatial variable (see Fig. 5.2)

\[ a_i = i \cdot s, \quad i = 0, 1, 2, 3, \ldots, M \rightarrow +\infty \]

and denote

\[ n(t, a_i) = n_i(t), \quad n(t, 0) = n_0(t) = p(t). \]

We approximate the derivative of the function \( n(t, a_i) \) over the variable \( a \)

\[ \frac{\partial n(t, a_i)}{\partial a} \approx \frac{n_i(t) - n_{i-1}(t)}{s} \]

and from the Eq. (5.6) we obtain

\[ \dot{n}_i(t) + \frac{n_i(t) - n_{i-1}(t)}{s} = -\lambda_i(t) \cdot n_i(t), \quad i = 1, 2, \ldots, M \rightarrow +\infty \]

and further

\[ \dot{n}_i(t) = -\left(\lambda_i(t) + \frac{1}{s}\right)n_i(t) + \frac{1}{s}n_{i-1}(t), \quad i = 1, 2, \ldots, M \rightarrow +\infty. \quad (5.14) \]

**Fig. 5.2** Scheme of the method of straight lines. For given, in points of discretization, values of initial condition (red circles on \( a \) axis) and for given boundary condition (blue circles on \( t \) axis) we calculate approximate values of \( n(t, a) \) in points marked with black dots.
We write the Eq. (5.14) in the following form

\[
\begin{align*}
\dot{n}_1(t) &= -(\lambda_1(t) + \frac{1}{s})n_1(t) + \frac{1}{s}n_0(t), \\ 
\dot{n}_2(t) &= -(\lambda_2(t) + \frac{1}{s})n_2(t) + \frac{1}{s}n_1(t), \\ 
\dot{n}_3(t) &= -(\lambda_3(t) + \frac{1}{s})n_3(t) + \frac{1}{s}n_2(t), \\ 
&\vdots \\ 
\dot{n}_M(t) &= -(\lambda_M(t) + \frac{1}{s})n_M(t) + \frac{1}{s}n_{M-1}(t)
\end{align*}
\]

and go to the matrix notation

\[
\begin{bmatrix}
\dot{n}_1(t) \\
\dot{n}_2(t) \\
\dot{n}_3(t) \\
\vdots \\
\dot{n}_M(t)
\end{bmatrix} = 
\begin{bmatrix}
-\lambda_1 - \frac{1}{s} & 0 & 0 & 0 & 0 \\
\frac{1}{s} & -\lambda_2 - \frac{1}{s} & 0 & 0 & 0 \\
0 & \frac{1}{s} & -\lambda_3 - \frac{1}{s} & 0 & 0 \\
0 & 0 & \ddots & \ddots & 0 \\
0 & 0 & 0 & \frac{1}{s} & -\lambda_M - \frac{1}{s}
\end{bmatrix}
\begin{bmatrix}
n_1(t) \\
n_2(t) \\
n_3(t) \\
\vdots \\
n_M(t)
\end{bmatrix} + 
\begin{bmatrix}
\frac{1}{s}n_0(t) \\
0 \\
0 \\
\vdots \\
0
\end{bmatrix},
\]

go zapisujemy

\[
\dot{n}(t) = An(t) + Bp(t), \quad n(t) = \begin{bmatrix} n_1(t) \\ n_2(t) \\ n_3(t) \\ \vdots \\ n_M(t) \end{bmatrix} \in \mathbb{R}^M,
\]

gdzie

\[
A = \begin{bmatrix}
-\lambda_1 - \frac{1}{s} & 0 & 0 & 0 & 0 \\
\frac{1}{s} & -\lambda_2 - \frac{1}{s} & 0 & 0 & 0 \\
0 & \frac{1}{s} & -\lambda_3 - \frac{1}{s} & 0 & 0 \\
0 & 0 & \ddots & \ddots & 0 \\
0 & 0 & 0 & \frac{1}{s} & -\lambda_M - \frac{1}{s}
\end{bmatrix}_{M \times M},
\]

\[
\lambda_i(t) = \lambda(t, a_i), \quad B = \begin{bmatrix}
\frac{1}{s} \\
0 \\
0 \\
\vdots \\
0
\end{bmatrix} \in \mathbb{R}^M.
\]

Now we discretize the variable \( t \) (time)

\[
t = t_k = k \cdot \tau, \quad k = 0, 1, 2, 3, \ldots, N \to +\infty
\]
and denote

\[ n(t_k) = n[k] = \begin{bmatrix} n_1[k] \\ n_2[k] \\ \vdots \\ n_M[k] \end{bmatrix} \in \mathbb{R}^M, \quad \lambda_i(t_k) = \lambda_i(k \cdot \tau). \]

We approximate the derivative of \( n \) over the variable \( t \)

\[ \dot{n}(t) \approx \frac{n(t) - n(t - \tau)}{\tau} = \frac{n[k] - n[k - 1]}{\tau} \]

and we have

\[ \frac{n[k] - n[k - 1]}{\tau} = An[k] + B p[k], \]

\[ n[k] - \tau A n[k] = n[k - 1] + \tau B p[k], \]

\[ n[k] = [I - \tau A]^{-1} n[k - 1] + [I - \tau A]^{-1} \tau B p[k], \]

\[ n[k] = [I - \tau A]^{-1} [n[k - 1] + \tau B p[k]], \quad k = 1, 2, \ldots, N \to +\infty \quad (5.16) \]

Solving numerically the Eq. (5.16) we find approximate solution of the Eq. (5.6).

Asymptotic stability of the recurrence system (5.16) is a necessary condition of correctness of numerical calculations.

### 5.1.2.2 Asymptotic Stability of the Recurrence Scheme (5.16)

The system (5.16) is asymptotically stable if and only if all eigenvalues of the matrix \([I - \tau A]^{-1}\) have modules smaller than 1, i.e. \(|\mu_i([I - \tau A]^{-1})| < 1, \forall i\), where \(\mu_i\) denotes eigenvalues.

Let us consider the (triangular) matrix

\[ I - \tau A = I - \tau \cdot \begin{bmatrix} -(\lambda + \frac{1}{s}) & 0 & 0 \\ \frac{1}{s} & \ddots & 0 \\ 0 & \ddots & 0 \\ 0 & \frac{1}{s} & -(\lambda + \frac{1}{s}) \end{bmatrix} = \]

\[ \begin{bmatrix} 1 + \tau(\lambda + \frac{1}{s}) & 0 & 0 \\ -\frac{\tau}{s} & \ddots & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & 1 + \tau(\lambda + \frac{1}{s}) \end{bmatrix} \]
5.2 Lasota–Ważewska Feedback

The originality of the Lasota–Ważewska model lies in the combination of the McKendrick–Von Foerster equation (5.6) with appropriately chosen feedback, with a delayed argument representing the \( p(t) \) function of erythrocyte production. It is possible that this is the only equation of hematopoietic system dynamics in which the dependence on blood cell production was derived mathematically (relationships as such are very often determined on the basis of experimental data). We will now derive the production function found by Ważewska-Czyżewska and Lasota (1976, p. 26) (see also Rudnicki 2014, p. 219).
5.2 Lasota–Ważewska Feedback

Fig. 5.4 Solution of the Eq. (5.6) on characteristics ((a) (b)): $a = t$ ((c) (d)): $a = t + 3$ ((e) (f)): $a = t - 4$. Green lines—method of characteristics, blue—method of straight lines. In figures (a), (c), (e), variables $t$ and $a$ discretization step is 0.25, and the integral of the square error respectively 0.0014, 0.0004 and 0.0003. In figures (b), (d), (f) discretization step is 0.125, the integral of the square error respectively 0.001, 0.0003 and 0.0002.
The increase in blood cell production per unit of time is described by the derivative \( p'(t) \), therefore

\[
S(t) = \frac{p'(t)}{p(t)}
\]  

(5.17)
denotes a unit increase of production, which we will call the degree of system stimulation. At equilibrium conditions \( S(t) = 0 \). The changing in the amount of erythrocytes in the bloodstream stimulates or stops their production (see Chap. 2). The system response (e.g. in the form of an increase in the number of red blood cells after their previous decrease) appears after the time needed to transform the undifferentiated bone marrow cell into a mature erythrocyte. M. Ważewska-Czyżewska and A. Lasota assumed (in order to obtain possibly simple model) that the degree of system stimulation is proportional to the change in the total number of blood cells in the bloodstream, i.e.

\[
S(t) = -\gamma \frac{d}{dt} N(t - h),
\]  

(5.18)

where \( \gamma \) is a proportionality coefficient and \( h \) denotes a hematopoietic system delay of reaction (this is the time needed to develop mature erythrocyte—see remarks in Chap. 2.4). Thus, it can be seen that the loss of blood cells corresponds to the increase in the system stimulation and the increase in its inhibition. From formulas (5.17) and (5.18), we have

\[
\frac{p'(t)}{p(t)} = -\gamma N'(t - h),
\]  

(5.19)

then after integration we receive

\[
p(t) = \rho \cdot e^{-\gamma N(t-h)},
\]  

(5.20)

where \( \rho \) is an integration constant. Figure 5.5 presents the function \( p(N_h) = \rho \cdot e^{-\gamma N_h} \), \( N_h \equiv N(t - h) \) for parameters corresponding to the state of healthy human body, i.e. \( \sigma = 0.01 \text{ day}^{-1} \), \( \gamma = 0.0015 \text{ ml}^{-1} \), \( \rho = 724.5 \text{ ml/day} \) (see Ważewska-Czyżewska and Lasota 1976, p. 32), (see Ważewska-Czyżewska 1983, p. 160,161). It can be seen that the function has a monotonically decreasing character. When the number of blood cells \( N_h \equiv N(t - h) \) drops below the normal level \( N = 2300 \text{ ml} \), the intensity of blood cell production increases, after a delay time \( h \), and when the number of blood cells returns to normal level, the production intensity decreases.

Putting together now (5.1), (5.6), (5.8) and (5.20) we obtain the Lasota–Ważewska equation describing dynamics of red blood cells system

\[
\begin{align*}
\frac{\partial n(t, a)}{\partial t} + \frac{\partial n(t, a)}{\partial a} &= -\lambda(t, a) \cdot n(t, a), \\
n(t, 0) &= p(t) = \rho \cdot e^{-\gamma \int_0^\infty n(t-h, a) \, da}.
\end{align*}
\]  

(5.21)
5.2 Lasota–Ważewska Feedback

In the foregoing part, we provided an interpretation of the destruction coefficient \( \lambda \), which denotes the probability that the blood cell, which at time \( t \) is at the age \( a \) will die in the time interval \( (t, t + \Delta t) \). The meaning of the coefficient \( \gamma \) results from the formula (5.18). It determines the excitation degree \( S(t) \) of the system caused by a unit change in the number of blood cells per unit of time. The \( \rho \) coefficient characterizes requirement of the body for an oxygen. The higher the demand, the higher the \( \rho \). The \( h \) delay determines the time needed for the production of mature erythrocytes. The lengths of this time specified in literature are provided in Sect. 2.4.

5.3 Reduced Lasota–Ważewska Model

Partial differential equations modelling the dynamics of hematopoiesis can be reduced to the corresponding differential equations with delayed argument (see Ważewska-Czyżewska and Lasota 1976; Ważewska-Czyżewska 1983; Mackey and Milton 1990). As a result of the reduction, from the model taking into account the structure of e.g. the age of blood cells (i.e. such as the Lasota–Ważewska equation), we obtain a model describing the change in their total quantity (Ważewska-Czyżewska and Lasota 1976, p. 31) and (Rudnicki 2014, p. 219)). Mathematical information on differential equations with delayed argument can be found, among others, in books by Hale and Verduyn Lunel (1993) or Rudnicki (2014). Let us introduce the coefficient

![Graph](image-url)

**Fig. 5.5** Function \( p(N_h) = \rho \cdot e^{-\gamma N_h} \), \( N_h \equiv N(t - h) \) describing production of erythrocytes found by M. Ważewsk-Czyżewska and A. Lasota. Here, for parameters corresponding to the state of healthy human body, i.e. \( \sigma = 0.01 \text{ day}^{-1}, \gamma = 0.0015 \text{ ml}^{-1}, \rho = 724.5 \text{ ml/day} \)
\[
\sigma = \frac{1}{N(t)} \int_0^\infty \lambda(t, a)n(t, a)da = \frac{\int_0^\infty \lambda(t, a)n(t, a)da}{\int_0^\infty n(t, a)da} .
\] (5.22)

In numerator we have the number of blood cells destroyed per unit of time, in denominator, the total number of blood cells, therefore \(\sigma\) means a probability of blood cell destruction per unit of time. From the Eq. (5.22) results, that \(\sigma\) depends of \(t\), however we will assume, that it is constant. Such simplification is made in order to formulate a model easier for mathematical analysis (see Rudnicki 2014, p. 205). Now integrating the Eq. (5.6), with respect to \(a\) in the interval \([0, \infty)\) we obtain

\[
\int_0^\infty \frac{\partial}{\partial t} n(t, a)da + \int_0^\infty \frac{\partial}{\partial a} n(t, a)da = \int_0^\infty \lambda(t, a)n(t, a)da.
\] (5.23)

Taking into consideration, that \(N(t) = \int_0^\infty n(t, a)da\), then the first component can be written as \(N'(t)\). Making natural biological assumption, that \(\lim_{a \to \infty} n(t, a) = 0\), then the second component is \(-n(t, 0) = -p(t) = -\rho e^{-\gamma N(t-h)}\). From the Eq. (5.22) the third component can be replaced by the expression \(-\sigma N(t)\). Therefore (5.23) takes the form

\[
\frac{dN(t)}{dt} = -\sigma N(t) + \rho e^{-\gamma N(t-h)}.
\] (5.24)

It is the so-called the reduced Lasota–Ważewska equation. We have already given the interpretation of all constants present in this equation.

Equation (5.24) can be written in the general form (see Ważewska-Czyżewska 1983, p. 157 and further)

\[
\frac{dN(t)}{dt} = -D(t) + P(t),
\] (5.25)

where \(D(t)\) denotes level of blood cells destruction at time \(t\), and \(P(t)\) level of their production at time \(t\). In the considered case \(D(t) = \sigma N(t)\), \(P(t) = \rho e^{-\gamma N(t-h)}\).

### 5.3.1 Mackey–Glass Equation

Mackey and Glass (1977), in their model of changes in the amount of circulating red blood cells in the bloodstream, proposed a bit different form of production function

\[
\frac{dN(t)}{dt} = -\sigma N(t) + \frac{\beta_0 t^n}{\theta^n + N_h^n}, \quad N_h \equiv N(t-h).
\] (5.26)

It has however the same monotonically decreasing character as the function obtained by M. Ważewska-Czyżewska and A. Lasota (compare Figs. 5.5 and 5.6). Information how it was formulated can be found in an article by Mackey (1978) and in a book.
5.3 Reduced Lasota–Ważewska Model

Fig. 5.6 Nonlinearity determining the production function in the Mackey–Glass equation (5.26)

by Ważewska-Czyżewska (1983, p. 159). The biological interpretation of the $\beta_0$ constant from the Eq. (5.26) corresponds to the interpretation of the constant $\rho$ from the Eq. (5.24), and the interpretation of $\theta$ corresponds to the interpretation of $\gamma$.

The dynamics of the hematopoietic system have been considered by many authors. There is a lot of models in the literature distinct in terms of mathematical construction and bio-medical conditions taken into consideration. E.g. papers of (Ackleh et al. 2006; Adimy and Crauste 2009, 2003; Adimy et al. 2005a, c; Bernard et al. 2003) concern structural models, while e.g. works of (Adimy et al. 2006a, 2005b, 2006b; Crauste 2006; Adimy et al. 2008) concern models in a form of delay equations. The content presented in this book in Chaps. 2 and 5 has been presented in detail so that the reader can find significant differences between existing models of hematopoiesis and the model considered in this monograph in the next Chap. 6.