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Fluctuations in circulating cell numbers following chemotherapy or bone marrow transplant

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Abstract. We study the effect of noise on the behaviour of a dynamic cell population model in which cell replication and maturation take place simultaneously. We assume that the maximum proliferative potential v fluctuates uniformly about a mean value of $\bar{v}$, and show that a decrease in $\bar{v}$ and/or the input flux u_{in} into the population can lead to an increase in the variance in the cellular efflux u_f. We draw a qualitative correspondence between this behaviour and the commonly observed increase in the variance of circulating blood cell numbers following chemotherapy and radiotherapy, both of which lead to a decrease in $\bar{v}$ and u_{in}, and bone marrow transplant which probably corresponds to a decrease in u_{in}.

Key words: Fluctuations – Stochastic PDEs – Blood cell maturation – Chemotherapy – Bone marrow transplant

1 Introduction

Many biological populations are *age structured* in that the recruitment of new individuals into the population depends on the density of a cohort of older individuals, e.g. all populations of replicating and maturing cells. Models of these age structured cellular populations are most naturally framed in terms of first order partial differential equations ("transport-like" equations) that are nonlinear because of dependencies of birth and/or death rates on cell population number (cf. Metz and Diekmann 1986 for an excellent survey of general age structured population models). However, these age structured cell replication models have never, to our knowledge, considered the effect of parametric fluctuations on the eventual solution behaviour of the model.

An assessment of the effects of parametric fluctuations in such models becomes of more than academic interest when one considers the nature of the recovery phase of patients following chemotherapy and/or bone marrow transplant (Prof. B. Cooper, personal communication). Though there seems to be no published literature in this area, the anecdotal evidence indicates the following pattern. Typically, following chemotherapy and/or bone marrow transplant the circulating numbers

of platelets and white blood cells fall to extremely low levels (often less than 1% of normal) and remain there for a period of days, displaying low level fluctuations. Then during a recovery phase these cell numbers gradually rise, first showing a waxing and then a waning in their variance as the mean values increase. The maximal variance occurs during this (hopefully) transient phase. In examining the recovery data from a number of patients post chemotherapy or bone marrow transplant (kindly provided by Prof. Cooper) we have noted precisely this same qualitative pattern. It is unfortunate that there is, at this time, neither any well documented presentation of this phenomena nor any characterization of the statistics (mean and variance) of peripheral blood cell counts in time series from normal individuals. We present the results of this paper in a hope that it will motivate clinical and experimental hematologists to examine the nature of blood cell fluctuations in both health and disease.

The plan of the paper is as follows. Section 2 presents a simple cellular replication-maturation model. In Sect. 3 we discuss the behaviour of the system in the absence of noise, while Sect. 4 considers the effects of noise on the model system. Finally, in Sect. 5 we discuss the significance of the results of Sect. 4 with respect to the effects of either chemotherapy or radiotherapy on fluctuations in the numbers of circulating hematopoietic cells.

2 A simple biological example

2.1 Physiological considerations

It is generally accepted that there is a population of pluripotential stem cells (PPSC) within the bone marrow that give rise to primitive stem cells committed to the production of erythrocytes, platelets, white blood cells, and lymphocytes. The committed stem cells for the erythroid series (CSC-E) are assayed in vitro by the primitive and mature burst forming units (BFU-E) and colony forming units (CFU-E). The committed stem cells for the white blood cells (CSC-GM) have the colony forming units/granulocyte-macrophage (CFU-C) as their in vitro analogs (Quesenberry 1990).

Within the erythroid system there is a well established long range negative feedback humoral control mediated by erythropoietin. A fall in the number of circulating red blood cells is followed by a decrease in tissue pO_2 levels. This, in turn, stimulates the production and release of renal erythropoietin whose action is to increase the flux of cells from the PPSC into the CSC-E and/or the proliferative rate within he CSC-E. A similar control mechanism, mediated by the regulator granulocyte-macrophage colony stimulating factor (GM-CSF), operates for the white blood cells.

In addition to these long range control mechanisms there are local regulatory mechanisms that exercise control over the proliferative rates within the PPSC, the CSC-E, and the CSC-G such that the proliferative rate is maximal at low cell numbers and monotonically decreases as cell numbers rise.

2.2 The model

From these comments we may now turn to a mathematical formulation of a model for a renewing and maturing cellular population. A similar model has previously

appeared (Lasota et al. 1981; Loskot et al. 1991), which is an extension of the Burns and Tannock (1970) cell cycle model (cf. Smith and Martin 1973).

We characterize every cell of the population by two internal variables: a, the age of the cell in the cell cycle, and m, the maturation level of the cell. At birth, cells have age $a = 0$ and their age increases with a unitary velocity $V_a = 1$ until cell division occurs at age $a = a_D$. In terms of maturation, cells are assumed to first become identifiable members of the population under consideration at a maturation level $m = m_0$. These cells mature at a velocity V_m until they reach the maturation level $m = m_1$ of a totally mature cell. During this entire process of maturation, the cells proliferate. It is important to emphasize that this process explicitly allows cellular movement through the cell cycle to proceed hand in hand with cellular maturation. The sufficiency of this hypothesis to explain existing granulopoietic and erythroid precursor cell kinetic data in humans, rats, and guinea pigs has been demonstrated by Mackey and Dörmer (1981, 1982).

We denote the number of cells of age a and maturation level m at time t by $n(t, m, a)$. Though the partial differential equation governing the evolution of this quantity is well known (cf. Metz and Diekmann 1986), from the outset we consider the age integrated quantity

$$N(t, m) = \int_0^{a_D} n(t, m, a)da\,,$$

which is the total number of cells of all ages with maturation level m at time t. Assuming that the proliferation rate of cells of maturation level m depends on the number $N(t, m)$ through a Verhulst type law (Mackey 1978; Mackey and Milton 1990), and that V_m is independent of the maturation level m, N satisfies the partial differential equation

$$\frac{\partial N}{\partial t} + V_m \frac{\partial N}{\partial m} = vN(1 - BN)\,, \quad N \in [0, B^{-1}]\,. \tag{1}$$

B and v are nonnegative constants characterizing the Verhulst replication law. v will be called the *maximal proliferative potential*, and B^{-1} is the maximum value of N.

Some of the parameters appearing in the model are superfluous and may be eliminated by a judicious choice of variables. To this end we introduce

$$u = BN\,, \quad u \in [0, 1] \tag{2}$$

and define a dimensionless maturation variable x by

$$x = \frac{m - m_0}{m_1 - m_0}\,, \quad x \in [0, 1] \tag{3}$$

where m_0 and m_1 are the initial and final maturation levels respectively. Then we have a maturation velocity c of the normalized maturation variable x given by

$$c = \frac{dx}{dt} = \frac{V_m}{m_1 - m_0}\,. \tag{4}$$

With these conventions, (1) becomes

$$\frac{\partial u}{\partial t} + c\frac{\partial u}{\partial x} = vu(1 - u)\,. \tag{5}$$

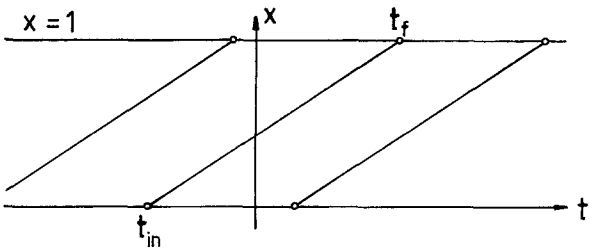

Fig. 1. Trajectories of three different cohorts corresponding to different t_{in}

To complete this model of blood cell production, (5) must be considered as a boundary value problem. This is a consequence of the physiological fact that new cells continuously enter the population at the initial maturation value m_0 ($x \equiv 0$) with a cell number $N(t, m_0)$, so the behaviour of the population for $t > T$ is completely determined if the boundary values

$$u(t, x = 0) = u_{in}(t) \tag{6}$$

are given for all times $t > T - c^{-1}$ with a finite advance of c^{-1}, as one can observe from the corresponding characteristics (cf. Fig. 1).

Equations (5) and (6) describe the behaviour of the cell population in the case of a constant proliferative potential v. We obtain a partial differential equation perturbed by noise if we assume that this coefficient is subject to fluctuations. (A previous paper (Mackey and Schwegler 1993) has considered the effects of fluctuations on the solution behaviour of (5) viewed as an initial value problem.) We assume that these fluctuations enter the system in such a way that a symmetrically distributed stochastic fluctuation ($d\xi/dt$) is added to v so the effective proliferative potential is $v + (d\xi/dt)$ with mean value v.

3 Behaviour of the system in the absence of noise

In the absence of fluctuations, the partial differential equation (5) is easily solved using the method of characteristics. The ordinary differential equations for the characteristics are simply

$$\frac{dx}{dt} = c \tag{7}$$

and

$$\frac{du}{dt} = vu(1 - u)\,. \tag{8}$$

Using well known procedures, we arrive at the solution

$$u(t, x) = \frac{u_{in}\left(t - \frac{x}{c}\right) e^{vx/c}}{1 + u_{in}\left(t - \frac{x}{c}\right)[e^{vx/c} - 1]} \tag{9}$$

for $t \in (-\infty, \infty)$ and $x \in [0, 1]$ since at $x = 1$ (corresponding to $m = m_1$) the cells are fully mature and leave the system.

We stress that the characteristics, (7) and (8), can be interpreted as governing the evolution of cell numbers u with time through the maturation space x for a

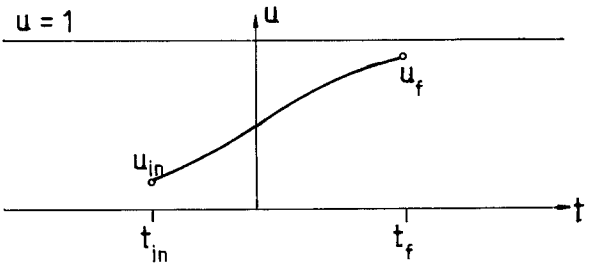

Fig. 2. Growth of the cell number in a cohort during the time span $t_{in} \leqq t \leqq t_f$

cohort of cells that entered at time t_{in} with maturation $x(t_{in}) = 0$ and cell number $u(t_{in}) = u_{in}$. Along the cohort trajectories, $u(t)$ increases monotonically as shown in Fig. 2.

4 The effects of noise

We now examine the effect of perturbing the proliferative potential v with a stochastic white noise $d\xi/dt$ so the characteristic equation (8) becomes a stochastic differential equation

$$\frac{du}{u(1-u)} = vdt + d\xi\,. \tag{10}$$

Defining a new variable

$$v = \frac{u}{1-u}, \quad v \in [0,\ \infty)\,, \tag{11}$$

(10) becomes

$$\frac{dv}{v} = vdt + d\xi\,, \tag{12}$$

which is easily integrated using either the Ito or Stratonovich calculus (both give the same results) to obtain

$$\ln\left[\frac{v(t)}{v(t_{in})}\right] = v(t - t_{in}) + \xi(t) - \xi(t_{in})\,, \tag{13}$$

Defining

$$w(t) \equiv \xi(t) - \xi(t_{in})\,, \tag{14}$$

(13) can be rewritten as

$$v(t) = v(t_{in})e^{v(t-t_{in})}e^{w(t)}\,, \tag{15}$$

with a corresponding formula for $u(t)$

$$u(t) = \frac{u(t_{in})e^{v(t-t_{in})}e^{w(t)}}{1 + u(t_{in})[e^{v(t-t_{in})}e^{w(t)} - 1]}\,. \tag{16}$$

Eliminating t_{in} through the relation $x = c(t - t_{in})$, we finally arrive at the field solution $u(t, x)$ of the boundary value problem with noise (9)

$$u(t, x) = \frac{u_{in}\left(t - \dfrac{x}{c}\right)e^{vx/c}e^{w(t)}}{1 + u_{in}\left(t - \dfrac{x}{c}\right)[e^{vx/c}e^{w(t)} - 1]}\,. \tag{17}$$

We assume, for simplicity, that the random variable $w(t)$ defined in (14) is uniformly distributed with mean of zero and a band width of $2\Delta w$. Thus the density g of w is

$$g(w) = \begin{cases} \dfrac{1}{2\Delta w} & -\Delta w \leqq w \leqq \Delta w \\ 0 & \text{otherwise}. \end{cases}$$

In the limit $t - t_{in} \to \infty$, the exponential $e^{v(t-t_{in})}$ would dominate all other terms so $v(t) \to \infty$ and $u(t) \to 1$ for the path of each cohort, and the influence of the perturbation of the proliferative potential v would disappear. This disappearance of the effects of the fluctuations in the $t - t_{in} \to \infty$ limit does not occur in the physiologically realistic case when maturation terminates at $x = 1$. Therefore we next calculate the mean cell number and its variance when $x = 1$.

In reality the maturation and proliferation processes within a given cohort terminate at t_f with a maturity level of $x = 1$ and a corresponding cell number $u(t, 1)$ give by

$$u(t, 1) = \frac{u_{in}\left(t - \dfrac{1}{c}\right) e^{v/c} e^{w(t)}}{1 + u_{in}\left(t - \dfrac{1}{c}\right)[e^{v/c} e^{w(t)} - 1]}. \tag{18}$$

From the assumptions concerning the stochastic process w, the mean value of u is given by

$$\langle u(t, 1)\rangle = \frac{1}{2\Delta w} \int_{-\Delta w}^{\Delta w} u(t, 1) dw \tag{19}$$

where $u(t, 1)$ is given by (18). A straightforward integration gives

$$\begin{aligned} \langle u(t, 1)\rangle &= \frac{1}{2\Delta w} \ln\left[\frac{1 + v_f^o(t) e^{\Delta w}}{1 + v_f^o(t) e^{-\Delta w}}\right] \\ &\simeq \frac{v_f^o(t)}{1 + v_f^o(t)} + \frac{(\Delta w)^2}{6} \frac{v_f^o(t)(1 + v_f^o(t))}{[1 + v_f^o(t)]^3} + \mathcal{O}((\Delta w)^4), \end{aligned} \tag{20}$$

where $v_f^o(t) \equiv v^o(t, 1)$ is the final value of v *in the absence of noise*,

$$v_f^o(t) = v_{in}\left(t - \frac{1}{c}\right) e^{v/c}. \tag{21}$$

The first term in the second line of (20) is the final value $u_f^o(t)$ *without noise* and the second term is a shift of the mean value due to the effect of the noise. This shift is positive if the noiseless solution $v_f^o(t) < 1$, corresponding to a noiseless cell number $u_f^o(t) < \frac{1}{2}$. Otherwise, it is negative.

The variance $\sigma_u^2(t, 1) = \langle u^2(t, 1)\rangle - \langle u(t, 1)\rangle^2$ can be calculated in a similar manner. First we obtain

$$\langle u^2(t, 1)\rangle = \langle u(t, 1)\rangle + \frac{1}{2\Delta w}\left\{\frac{1}{1 + v_f^o(t) e^{\Delta w}} - \frac{1}{1 + v_f^o(t) e^{-\Delta w}}\right\}, \tag{22}$$

and after an expansion

$$\sigma_u^2(t, 1) = \frac{(\Delta w)^2}{3} \frac{[v_f^o(t)]^2}{[1 + v_f^o(t)]^4} + \mathcal{O}((\Delta w)^4) . \tag{23}$$

The variance $\sigma_u^2(t, 1)$ has a maximum value of $(\Delta w)^2/48$ for $v_f^o(t) = 1$ corresponding to $u_f^o(t) = \frac{1}{2}$. Hereafter, we assume that the values $u_{in}(t) \equiv u(t, x = 0)$ which determine the boundary value problem are constant at least over time intervals which are long compared to the lifetime c^{-1}, so

$$v_{in} = \frac{u_{in}}{1 - u_{in}} \tag{24}$$

is also constant.

In this circumstance, by (17) the cell numbers $u(t, x)$ and thus also $u(t, 1)$ depend on time t only through the stochastic process $w(t)$. Without noise, the solution would be stationary and therefore u_f^o and v_f^o in (20) through (23) are constant:

$$\begin{aligned} v_f^o &= v_{in} e^{\nu/c} \\ u_f^o &= \frac{v_{in} e^{\nu/c}}{1 + v_{in} e^{\nu/c}} = \frac{u_{in} e^{\nu/c}}{1 + u_{in}[e^{\nu/c} - 1]} . \end{aligned} \tag{25}$$

To summarize the results of this section, it is sufficient to highlight the central results embodied in (20) and (23) which give, respectively, the mean and variance of the cell numbers leaving the replicating population. These are of practical importance since they are potentially observable quantities, and in the next section we consider how these might vary in two physiological circumstances.

5 Physiological and clinical implications

To examine the physiological implications of the results of the previous section, we assume that in the normal state the physiological system utilizes its proliferative power in an optimal fashion defined below. We consider the situation corresponding to cohorts who start their maturation at $x = 0$ with the same incoming cell number u_{in} independent of the initial time t_{in}. Thus all of these cohorts have the same behaviour between the initial time t_{in} and the final time t_f, described by Verhulst growth according to equation (16). For simplicity we use a representative Verhulst curve such that

$$t_M \equiv t\left(u = \frac{1}{2}\right) = 0 .$$

(cf. Fig. 3a). Thus

$$u(t) = \frac{e^{\nu t}}{1 + e^{\nu t}} . \tag{26}$$

We say that the physiological system uses its proliferative potentials in an optimal way if, for the representative choice (26), the time interval $t_f - t_{in}$ is symmetric with

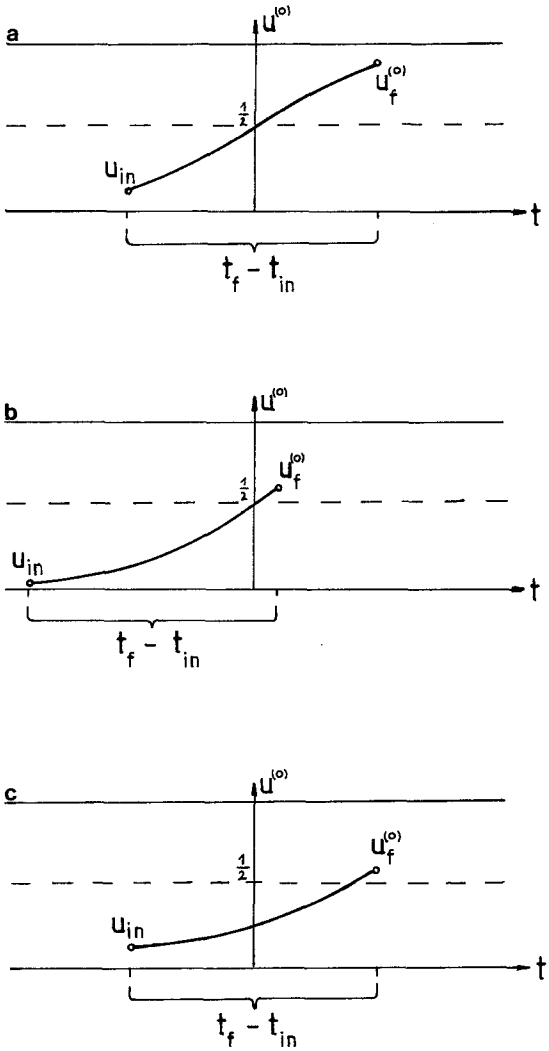

Fig. 3. Growth of a cohort: **a** under normal conditions in which the maximal proliferative power is utilized; **b** when, due to treatment, the initial cell number u_{in} has decreased and v is unchanged; and **c** when the proliferative potential v has been decreased by treatment but u_{in} is normal

respect to $t_M = 0$. This assumption implies that

$$t_{in} = -\frac{\alpha}{v}, \qquad t_f = \frac{\alpha}{v}, \qquad t_f - t_{in} = \frac{2\alpha}{v}, \tag{27}$$

where α is an undetermined parameter which describes the lifetime in terms of the proliferative potential v. Since $t_f - t_{in} = c^{-1}$ we have

$$\frac{v}{c} = 2\alpha\,. \tag{28}$$

It follows from this assumption that the initial cell number u_{in} of a cohort is

$$u_{in} = \frac{1}{1 + e^{\alpha}} \tag{29}$$

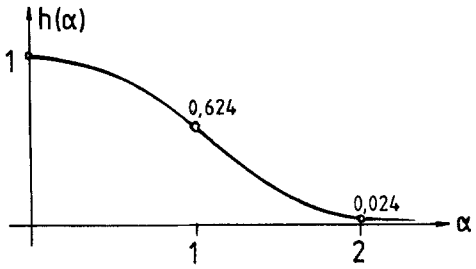

Fig. 4. The graph of $h(\alpha)$ (32) characterizing the relative strength of the final variance as a function of the lifetime parameter α

since $v_{in} = e^{-\alpha}$. Without noise, the final cell number u_f^o is

$$u_f^o = 1 - u_{in} = \frac{1}{1 + e^{-\alpha}} \tag{30}$$

and $v_f^o = e^{\alpha}$.

Now consider the effects of the noise. With noise, the Verhulst curve is stochastically modified and thus u_f is statistically distributed. It has a slightly shifted mean value given by

$$u_f = u_f^o + \frac{(\Delta w)^2}{6} \frac{e^{\alpha}(1 - e^{\alpha})}{(1 + e^{\alpha})^3}. \tag{31}$$

To illustrate this effect, for $\alpha = 1$ we have

$$u_{in} \simeq 0.27\,, \qquad v_f^o \simeq 2.7\,, \qquad u_f^o \simeq 0.73$$

and the second term in (31) is $0.09\ (\Delta w)^2/6$. Further, the final cell number has a variance given by

$$\sigma_f^2 = \frac{(\Delta w)^2}{3} \frac{e^{2\alpha}}{(1 + e^{\alpha})^4} = \frac{(\Delta w)^2}{48} h(\alpha)\,, \tag{32}$$

(cf. Fig. 4). Thus for sufficiently long lifetimes $t_f - t_{in} = 2\alpha/v$ we will see negligible fluctuations in the cell numbers in the final state.

Using this model to consider the potential influences of chemotherapy, radiotherapy, and/or bone marrow transplant is quite instructive. Thus let us assume that with these treatments the cell replication process is influenced in such a way that either:

(1) The initial cell density is decreased; or
(2) The proliferative potential v is decreased.

We consider both of these possibilities within the context of our previous analysis and discussion.

5.1 Decrease in initial cell number

If the initial cell number u_{in} is decreased and the proliferation potential v remains unchanged, then after the finite lifetime a decreased final cell number u_f^o is also the result according to (25) (see also Fig. 3b). Moreover, the variance σ_f^2 of the

fluctuations about u_f^o also changes, and with decreasing u_f^o the variance *increases* as a consequence of the treatment. The extreme case, in which the variance is maximal, occurs when $u_f^o = \frac{1}{2}$ corresponding[1] to $v_f^o = 1$, and a maximal variance of $(\Delta w)^2/48$. This is to be compared with the values presented in Fig. 4 where we have such smaller values of the variance in the untreated system for sufficiently large α, e.g. $h(\alpha = 2) = 0.024$.

5.2 Decreased proliferative potential

If the proliferative potential v is decreased with u_{in} unchanged, then there will be a decreased final cell number u_f^o (see Fig. 3c) which is once again associated with an increased variance σ_f^2 of the fluctuations about u_f^o. In the worst case when $u_f^o = \frac{1}{2}$, corresponding to $v_f^o = 1$, the variance can again reach its maximal value of $(\Delta w)^2/48$.

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References

1. Burns, F. J., Tannock, I. F.: On the existence of a G_0 phase in the cell cycle. Cell Tissue Kinet. **19**, 321–334 (1970)
2. Lasota, A., Loskot, K., Mackey, M. C.: Stability properties of proliferatively coupled cell replication models. Acta Biotheor. **39**, 1–14 (1991)
3. Lasota, A., Mackey, M. C., Wazewska-Czyzewksa, M.: Minimizing therapeutically induced anemia. J. Math. Biol. **19**, 43–62 (1981)
4. Mackey, M. C.: Unified hypothesis for the origin of aplastic anemia and periodic hematopoiesis. Blood **51**, 941–956 (1978)
5. Mackey, M. C.: Dynamic haematological disorders of stem cell origin. In: Biophysical and Biochemical Information Transfer in Recognition, pp. 373–409, Vassileva-Popova, J. G., Jensen, E. V. (eds.) New York: Plenum Press (1979)
6. Mackey, M. C., Dörmer, P.: Enigmatic hemopoiesis. In: Biomathematics and Cell Kinetics, pp. 87–103. Rotenberg, M. (ed.). North Holland: Elsevier (1981)
7. Mackey, M. C., Dörmer, P.: Continuous maturation of proliferating erythroid precursors. Cell Tissue Kinet. **15**, 381–392 (1982)
8. Mackey, M. C., Milton, J. G.: Feedback, delays and the origin of blood cell dynamics. Comm. Theor. Biol. **1**, 299–327 (1990)
9. Mackey, M. C., Schwegler, H.: Ensemble and trajectory statistics in a nonlinear partial differential equation. J. Stat. Phys. **70** 281–295 (1993)
10. Metz, J. A. J., Diekmann, O. (eds.): The Dynamics of Physiologically Structured Populations. New York: Springer Berlin Heidelberg, 1986
11. Quesenberry, P. J.: Hemopoietic stems cells, progenitor cells, and growth factors. In: Hematology, pp. 129–147, Williams, W. J., Beutler, E., Erslev, A. J., Lichtman, M. A. (eds.) New York: McGraw Hill, 1990
12. Smith, J. A., Martin, L.: Do cells cycle? Proc. Natl. Acad. Sci. U.S.A. **70**, 1263–1267 (1973)

[1] In this case, the deviation of the mean $\langle u_f \rangle$ from u_f^o is exactly zero.