THE MINIMAL, PHASE-TRANSITION MODEL FOR THE CELL-NUMBER MAINTENANCE BY THE HYPERPLASIA-EXTENDED HOMEORHESIS

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ABSTRACT

Oncogenic hyperplasia is the first and inevitable stage of formation of a (solid) tumor. This stage is also the core of many other proliferative diseases. The present work proposes the first *minimal* model that combines homeorhesis with oncogenic hyperplasia where the latter is regarded as a genotoxically activated homeorhetic dysfunction. This dysfunction is specified as the transitions of the fluid of cells from a fluid, homeorhetic state to a solid, hyperplastic-tumor state, and back. The key part of the model is a nonlinear reaction-diffusion equation (RDE) where the biochemical-reaction rate is generalized to the one in the well-known Schlögl physical theory of the non-equilibrium phase transitions. A rigorous analysis of the stability and qualitative aspects of the model, where possible, are presented in detail. This is related to the spatially homogeneous case, i.e. when the above RDE is reduced to a nonlinear ordinary differential equation. The mentioned genotoxic activation is treated as a prevention of the quiescent G0-stage of the cell cycle implemented with the threshold mechanism that employs the critical concentration of the cellular fluid and the nonquiescent-cell-duplication time. The continuous tumor morphogeny is described as a time-space-dependent cellular-fluid concentration. There are no sharp boundaries (i.e. no concentration jumps exist) between the domains of the homeorhesis- and tumor-cell populations. No presumption on the shape of a tumor is used. To estimate a tumor in specific quantities, the model provides the time-dependent tumor locus, volume, and boundary that also points out the tumor shape and size. The above features are indispensable in the quantitative development of antiproliferative drugs or therapies and strategies to prevent oncogenic hyperplasia in cancer and other proliferative diseases. The work proposes an analytical-numerical method for solving the aforementioned RDE. A few topics for future research are suggested.

Key words: cell, cancer, oncogenic hyperplasia, homeorhesis, formation and disintegration of tumor gradual process, concentration, genotoxicity, cell cycle, morphogeny, reaction-diffusion equation Schlögl's nonstationary phase transition

1. INTRODUCTION

In multicellular organisms, one of the fundamental tasks resolved by homeosta-

sis (Cannon, 1929) or, more generally, homeorhesis (Waddington, 1957) is the maintenance of the numbers of all types cells at physiologically acceptable levels.

The biological cell is the least structural aggregate of living matter capable of functioning as an independent unit. A living particle (e.g., a cell, or an animal, or a human being, a social group or a part of ecological system) is, by definition, always changing in time, moving along some defined time path, from an initial stage (such as the fertilized egg) through various larval stages to adulthood, and finally to senescence. The regulation that occurs in such a system is a regulation, not necessarily back to a static stable equilibrium, as in homeostasis, but to a more general stable mode which lies on some future stretch of the time path. The appropriate notion describing this process is *homeorhesis*. It was introduced by Waddington (1957, p. 32) (see also Waddington, 1968, p. 526). Loosely speaking, homeorhesis is a self-regulating process by which living systems tend to maintain the stability of their internal environment while adjusting *dynamical* conditions that are optimal for survival. If homeorhesis is successful, life continues; if unsuccessful, disaster or death occurs. The stability attained is actually a dynamic equilibrium, in which continuous changes take place. Any system in dynamic equilibrium tends to reach a steady state, a dynamic long-lasting balance. One of the key mechanisms here is clock-like, nearly periodic self-sustained oscillations (e.g., Yates and Iberall, 1982, Point 16-18 on p. 431; see also Chen and Aihara, 2002, for examples of specific models). In other words, homeorhesis is the *time*-dependent extension of homeostasis. Homeostasis is generally a *spatially inhomogeneous*, x-dependent state. However, the homeorhetic equilibrium is dynamic rather than static. In these terms, homeostasis is the time-independent homeorhesis.

The cell-number maintenance is commonly considered in connection with populations of cells, or cellular fluids, at habitual, fluid-phase concentrations. Extreme-concentration states of cellular fluids, such as amorphous solid phases, can also be the case in organisms. One example is tumors (e.g., Franks and Teich, Eds., 1997). The connection of homeostasis, or more generally, homeorhesis (see Section 3) to the transitions of cellular fluids from fluid to solid states (or back) remains unclear.

Development of a tumor, or oncogeny, comprises a few well known stages such as hyperplasia, dysplasia, *in situ* growth, angiogenesis and invasion (e.g., see the figure “Five stages of tumor” in the article “Tumour”, Encyclopædia Britannica Online, 2003, for a concise summary). It is well known that tumors at the latter, malignant stages (angiogenesis or invasion) are especially difficult to eliminate or suppress. “Cancer remains a disease of high unmet clinical need where life expectancy can often be short. In 1999, there were over 12 million new cases of cancer diagnosed and 7 million deaths” (Hughes, 2001). Unluckily, “killing the last cancer cell without killing the host is an objective that has not yet been reached” (Israel, 1996, p. 379). Moreover, the disease can be made even worse by iatrogenic (Gove, 1993, the middle column on p. 1119), i.e. physician-induced, effects resulting from the above all-cancer-cell-killing strategy pursued without a proper *system* analysis.

In order to help to develop better clinical strategies the present work focuses on oncogenic hyperplasia, the first and therefore inevitable stage in development of any (solid) tumor. Oncogenic hyperplasia is also implicated in many other proliferative

diseases, for instance: vascular proliferative diseases (atherosclerosis and coronary restenosis); gastrointestinal polyps (especially in the rectum and colon; e.g., pedunculated tumors); endocrine proliferative diseases (hyperparathyroidism, hypoglycemia in infants, and congenital adrenal hyperplasia); proliferative dermatoses (infantile eczema and lichenification); megakaryocytic or platelet hyperplasia; hyperplasia of cardiac muscle; hyperplastic lesions of the larynx; ductal, prostatic, intimal, endometrial, and lymphoid hyperplasias. Oncogenic hyperplasia is a process that is gradual in both space and time, in which quantitative changes in the cell-population characteristics result in qualitative differences. It is not possible to investigate this process with common tools. Indeed, biomedical experiments or animal models are inherently fragmentary and quantitatively unspecific. There is no equipment capable of providing cell population data that are continuous in both space and time. Hyperplastic lesions (if not pathological) are deeply presymptomatic, subclinical, and difficult to detect. The only way to overcome the above difficulties is to apply predictive mathematical models and related software. These are the tools that would also enable an improved understanding of the fundamental stage of oncogeny and would thereby contribute to its prevention. The latter is in principle the most efficient approach: "Prevention is always preferable to cure" (V. R. Potter, 1945). The enormous importance of oncogeny and cancer prevention has already been recognized even at the level of establishing dedicated institutions (e.g., see "Institute for Cancer Prevention. Prevention is the Best Cure" at http: //www.ifcp.us and "American Health Foundation: Research" at http://www.ahf.org /research/). However, such prevention has not yet become an everyday practice. More research and development remain to be done in the field. This requires the combined efforts across a wide range of disciplines including biology. The present work is a step in this direction.

Oncogenic hyperplasia is regarded as a process caused by either *genotoxicity* of cells (e.g., Trosko *et al.*, 1990, p. 241), i.e. their undesirable genetic mutations (Bishop, 1991; DePinho, 2000; Campbell and Farrell, 2003, Sect. 11.8; Lichtenstein and Potapova, 2003), or as a homeorhetic (in particular, homeostatic) dysfunction (e.g., Potter, 1945; Iversen, 1965). Importantly, these factors are not mutually exclusive. Indeed, hyperplasia is affected by nonmutational, epigenetic processes which may "masquerade as mutations" (e.g., see Kerbel et al., 1984, p. 89; see also Franks and Teich, Eds., 1997, Sect. 2.7.2, Chs. 9 and 10). Additionally, neither of the above factors on its own can completely explain hyperplasia (e.g., Trosko *et al.*, 1990, Sect. "Introduction"). This also means that "cancer research should no longer try to find the cause of cancer within one cell, but start to study the information and the transfer of information between cells" (Iversen, 1965, p. 104).

In line with the above vision, the present work develops a model for the cell-number maintenance by homeorhesis in conjunction with the genotoxically activated dysfunction shown by oncogenic hyperplasia. The model derivation follows the ideas suggested more than 65 years ago by Rashevsky (1938, pp. 134-135): "In biology, like in other natural sciences, we find that in spite of the tremendous variety and complexity of the phenomena observed, certain uniformities become apparent upon closer examination. The existence of such uniformities, of such a *unity in diversity* is one of the prerequisites for the possibility of existence of any exact sci-

ence". The "unity in diversity" can be regarded as one of the core principles of *systems biology*, a very young but rapidly developing science (e.g., Pennisi, 2003; Kitano, 2002). The present work attempts to reach an "exact science" by means of a fairly specific approach to Rashevsky's "unity in diversity". The derivation of the model deliberately involves the *mathematically simplest* assumptions, dependences and steps. It takes into account a limited number of necessary effects and parameters. In so doing, the two factors leading to hyperplasia, homeorhetic dysfunction and cell genotoxicity, are combined in unambiguous and clear terms. Some of the results in this work were previously reported by Koptioug and Mamontov (2004) and Koptioug (*et al.*, 2004).

The work focuses on the concentration of cells rather than their number for the following reason. The homeorhetic maintenance of the cell number deals with the number $N(t,X(t))$ of the cells at time point t in bounded or unbounded domain $X(t) \in \mathbb{R}^3$, $\mathbb{R} \in (-\infty,\infty)$. If one attempts to describe function $N(t,\cdot)$, the resulting models will generally be enormously cumbersome since this function is not a function of points in $\mathbb{R}^3$ but a function of *sets* of these points. The problem is, however, easily eliminated by introduction of the notion of concentration (or volumetric density of the number) of the cells. Indeed, number $N(t,X(t))$ is expressed as follows

$$N(t,X(t)) = \int_{X(t)} n(t,x)\,dx \tag{1.1}$$

where $n(t,x)$ is the concentration of the cells at moment t and at point $x \in X(t)$. Representation (1.1) completely describes function $N(t,\cdot)$ with function $n(t,\cdot)$, i.e. the function of sets is reduced to a function of the points in these sets. This advantage allows one to study the homeostatic maintenance of number $N(t,X(t))$ by means of modelling concentration $n(t,x)$. The latter is a much less complex task. Subsequently, the present work focuses on the maintenance of the concentration.

The structure of the work can be well characterized with the following main topics of the sections and appendixes:

- volume scaling and the scaled concentration (Section 2);
- the ideal-homeorhesis model (Section 3);
- the scaled concentration in regeneration and inflammation at ideal homeorhesis (Section 4);
- oncogenic hyperplasia as a homeorhetic dysfunction (Section 5);
- the hyperplastic-tumor/nonquiescent-cell asymptote (Section 6);
- the core phase-transition-endowed model for the hyperplasia-extended homeorhesis (Section 7);
- the summary for the core-model analytical analysis in the particular case of homeostasis (Section 8);
- the birth, life, and death of oncogenic hyperplasia (Section 9);
- the diffusion generalization of the core model to morphogeny: the PhasTraM model (Section 10);
- a discussion, concluding remarks and directions for future research (Section 11);
- the fundamental role of a point hyperplastic tumor in oncogeny and its definition in physical terms (Appendix A);

- the relation of the core and minimal models to Schlögl's theory of non-equilibrium phase transitions of the first and second orders (Appendix B); a good introduction to this theory can be found in Haken (1977, Sect. 9.3);
- the time-slice method for solving the Cauchy problem for the PhasTraM reaction-diffusion equation (Appendix C).

The work considers a cell population as a cellular fluid suspended in the extracellular fluid (a water-like molecular/ionic fluid). A particular case of the extracellular fluid is the interstitial one, the fluid component of the extracellular matrix.

2. VOLUME SCALING AND SCALED CONCENTRATION

Since the volume of a cell is generally not negligible, the work applies the *volume-scaling method* (VSM) (see Appendix A.2; see also Mamontov and Willander, 2003a, Sects. 2–3; Mamontov, 2005, Sects. 2–6). According to VSM, the effect of the fluid-particle volume is accounted for in terms of the scaled concentration, m, of the cellular fluid and the fraction, F, of the physical-space volume in which the cells are free to move. These quantities are related as follows (cf., Remark A.3)

$$m = n/F \tag{2.1}$$

(Line 1 of Table 2 for m). The present work deals with fluids which include two components (see the end of Section 1), cellular and extracellular, and, thus $L=2$ (see the text above (A.4)). Let ϕ and υ be the fraction of the volume occupied by the bodies of the extracellular-fluid particles (cf., Line 2 of Table 1) and the volume of a cell (cf., Line 3 of Table 1), respectively. Then (see also Line 1 of Table 1 for ζ), expression (A.4) at $L=2$ becomes $F = 1 - \zeta^{-1}(\phi + \upsilon n)$ or, equivalently,

$$F = v(n_T - n) \tag{2.2}$$

where

$$0 \le n < n_T \tag{2.3}$$

$$n_T = f/v, \tag{2.4}$$

$$v = \upsilon/\zeta, \tag{2.5}$$

$$f = 1 - \phi/\zeta, \tag{2.6}$$

(see Lines 4, 3 and 2 of Table 2 for n_T, v and f respectively). Subsequently, (2.1) becomes

$$m = n/[v(n_T - n)] \tag{2.7}$$

or, equivalently,

$$n = [vm/(1+vm)]\, n_T. \tag{2.8}$$

REMARK 2.1. Relation (2.7) (or (2.8)) establishes a one-to-one correspondence between the scaled concentration, m, and the concentration, n (cf., Remark A.3). For this reason, a VSM-based model can be formulated and solved for m and, after the solution is obtained, n is evaluated by (2.8).

It follows from (2.7) and (2.8) that

m and n are coupled by the linear homogeneous relation $m \approx n/(v\, n_T)$
under the *far-from-tumor* (FFT) *condition* $n \ll n_T$ (or $vm \ll 1$). (2.9)

Note that the concentration value, analogous to the hyperplastic-tumor concentration n_T in (2.7), is also used by other authors (e.g., De Angelis and Preziosi, 2000, parameter u_M on p. 392). The scaled concentration, m, can have any value in the interval $[0, \infty)$. Equality (2.7) shows that, in contrast to the concentration, n, the scaled concentration m need not be limited from above.

REMARK 2.2. The present work considers only the *hyperplastic* stage of oncogeny. To enable it to model the *dysplastic* stage, one has to take into account the time-space dependence of cell volume υ (see (2.5) and Line 3 of Table 1). For each of the above stages, the time-space Cauchy problem, i.e. the one in the entire physical space $\mathbb{R}^3$, can be adequate. To allow for an *in-situ-growing* tumor, one has to consider an oncogeny model on a semi-bounded or bounded domain rather than on $\mathbb{R}^3$. In so doing, the corresponding boundary conditions have to be involved. The *angiogenesis* stage of oncogeny makes it necessary to take into account the (t,x)-dependence of parameter ζ (see (2.5), (2.6), Line 1 of Table 1 and the text below (A.5)) since ζ becomes affected by the volume fraction occupied by the blood-vessel system in a tumor. In the case of the *invasion* stage of oncogeny, the model is to be applied to different space regions connected with blood vessels. This corresponds to the most general settings of the model.

The model for m, which includes the hyperplasia-homeorhesis competition, is derived in Section 7.

3. THE IDEAL-HOMEORHESIS MODEL

The notion of homeorhesis is discussed in the second paragraph of Section 1. Specific examples of homeorhetic behavior can be found in Haus and Smolensky (1999). The meaning of homeorhesis points out the following. Let

$$n_H \in (0, n_T) \tag{3.1}$$

be the homeorhetic value of concentration n (see Line 4 of Table 1). Then the property below holds

the (t,x)-dependent concentration n_H does not explicitly depend
on n and is sufficiently smooth and uniformly separated
from n_T for *all* (t,x) where it is defined. (3.2)

In view of (2.7), the value of scaled concentration m corresponding to n_H is (see (see Line 5 of Table 2)

$$m_H = n_H/[v(n_T - n_H)]. \tag{3.3}$$

Property (3.2) means that the quantity m_H does not explicitly depend on m, depends on (t,x), is of the same smoothness as n_H, and is uniformly bounded for all (t,x)

where it is defined. These features are used, for instance, in (3.4), (6.1), (7.1), (7.14), (7.18), (7.19), and (7.29) below.

The *simplest* spatially homogeneous model describing the maintenance of homeorhetic, generally (t,x)-dependent value m_H (i.e. the time convergence of scaled m to m_H) is the ordinary differential equation (ODE)

$$\partial(m - m_H)/\partial t = -a(m - m_H), \qquad t > 0, \tag{3.4}$$

where $a > 0$ does not explicitly depend on m. The initial condition is

$$\lim_{t\downarrow 0} m = m_0(x), \qquad x \in \mathbb{R}^3, \tag{3.5}$$

where $m_0(\cdot)$ (see Line 6 of Table 2) is obtained from the initial-concentration function $n_0(\cdot)$ of x (see Line 5 of Table 1), i.e. (see (2.7))

$$m_0(x) = n_0(x)/\{v[n_T - n_0(x)]\}, \qquad x \in \mathbb{R}^3, \tag{3.6}$$

$$\lim_{t\downarrow 0} n = n_0(x) \in [0, n_T), \qquad x \in \mathbb{R}^3. \tag{3.7}$$

The position vector x is a parameter in ODE (3.4).

The initial condition (3.7) means that the cellular fluid achieves the concentration value n_0 by time $t = 0$ in the course of the previous development, i.e. for $t < 0$. Thus, the function $n_0(\cdot)$ is not predicted by the present model. It is merely used as one of the input parameters (cf., Line 5 of Table 1). The output characteristics of the model are, according to the text in Section 1 on (1.1), the cellular-fluid concentration n dependent on (t,x) and with the values corresponding to (2.3).

Equation (3.4) is, under the FFT condition in (2.9) (see also (3.3)), representable as $\partial n/\partial t = -a(n - n_H) + \partial n_H/\partial t$. Subsequently, the positive parameter a can be interpreted as the inverse of the lifetime $\eta > 0$ of the ideal-homeorhesis cells in the *ideal* state (see Line 6 of Table 1) as follows (see Line 7 of Table 2)

$$a = 1/\eta \tag{3.8}$$

The term “ideal” is used for the reasons explained the text below (5.1).

4. SCALED CONCENTRATION AT REGENERATION AND INFLAMMATION IN THE IDEAL-HOMEOSTASIS CASE

This section considers certain distinguishing behaviors of the scaled concentration m at the cell regeneration and inflammation in the ideal-homeostasis case, i.e. when the ideal homeorhesis (cf., Section 3) is independent of t, $\partial m_H/\partial t \equiv 0$. For simplicity, it is assumed that a is also independent of t.

The cellular fluid when $m < m_H$ can be exemplified with a *regeneration* of the cells resulting from an injury. In this case, solutions of ODE (3.4) are monotonically increasing, tend to asymptote $m = m_H$, and are strictly concave (e.g., see Hazewinkel, Ed., 1988b, pp. 294 and 415 for the definition of *concave* and *strictly concave* functions). The concavity points out that m tends to m_H rather fast.

The opposite case, i.e. when m exceeds the homeostatic value m_H, i.e. $m > m_H$, corresponds to an abnormal accumulation of the cells. This accumulation usually results from an inflammation. The latter is characterized by such hallmarks

as capillary dilatation and the infiltration of the cellular-fluid environment by macrophages, lymphocytes, and plasma cells (i.e. mature antibody-producing B lymphocytes). Inflammatory cells release a variety of potentially harmful and genotoxic substances (such as oxygen, interleukines, interferons, colony-stimulating factors, tumor necrosis factors, and growth factors) which are chemical signals (or messengers; see Bullough, 1962, p. 332) in the form of the molecules or macromolecules (usually, polypeptides) known as cytokines. They affect cells by promoting their mitosis (i.e. division) or suppressing their apoptosis (i.e. programmed death), thereby increasing concentration $m > m_H$. Thus, the cytokines mentioned above form a *positive feedback* and, for this reason, can briefly be termed the *positive* cytokines. The cells in the fluid at $m > m_H$ can be regarded as the inflamed cells.

In addition to the positive cytokines, free radical scavengers as well as differentiation and inhibitory factors are also generated. The influence of these cytokines upon cells is opposite to that of positive cytokines. Namely, they affect cells by suppressing their mitosis (e.g., in a similar way to the mitosis chalones introduced by Bullough, 1962, p. 332) or promoting their apoptosis, thereby decreasing concentration m. The cytokines of this group form a *negative feedback* and, thus, can briefly be termed the *negative* cytokines. Examples of the latter are reported, for instance, by Lavagna (*et al.*, 1999) and Freeman (2000, pp. 316-317).

The net effect of the above phenomena *in vivo* depends on the balance of the positive and negative feedbacks. At inflammation $m > m_H$, solutions of ODE (3.4) are monotonically decreasing, tend to asymptote $m = m_H$ (similar to the behavior in the above regeneration case of $m < m_H$), and strictly convex (e.g., see Hazewinkel, Ed., 1988b, p. 415 for the definition of *convex* and *strictly convex* functions). Thus, the solutions tend to m_H rather fast. Here the negative feedback dominates over the positive feedback. This picture corresponds to an *acute* inflammation.

A chronic inflammation is long-lasting. Subsequently, one can expect that reducing m approaches m_H very slowly and hence is strictly concave during a noticeable time. However, after m crosses an inflexion value, it becomes strictly convex tending to m_H much faster and thereby manifesting an acute inflammation. The reduction of m means that the negative feedback dominates over the positive one but this dominance is less pronounced in the concavity interval than in the convexity one. The problem of the ideal-homeorhesis ODE (3.4) where a is t *-independent* is that it alone can not describe the concavity manifesting a chronic inflammation.

5. ONCOGENIC HYPERPLASIA AS A HOMEORHETIC DYSFUNCTION

The aforementioned drawback of equation (3.4) is not the only one. Indeed, ODE (3.4) is the simplest version of the so-called *evolution equations with convergence* (e.g., Demidovič, 1967, Ch. IV, §16). An equation of this type is by definition the equation that has an unique, generally t -dependent solution which is *uniformly* bounded for *all* $t \in (-\infty, \infty)$ and any other solution of the equation converges to this solution. The latter is called the steady-state solution. In other words, the steady-state solution is the global attractor. Models of this type are highly re-

levant to homeorhesis (cf., Section 3). However, the evolution with the globally attracting steady state does not take into account the cases when at least one solution grows unlimitedly.

In particular, ODE (3.4) cannot allow for unlimited growth

$$\lim_{t\to\infty} m = \infty . \tag{5.1}$$

This equation is equivalent to the formation of a point hyperplastic tumor because of (2.8), (2.2), and Definition A.2. Along with this, the relation is also equivalent to a *nonstationary* (and hence non-equilibrium) phase transition of the cellular fluid to a solid state because of Remark A.2. The phase-transition paradigm endows the oncogenic hyperplasia with a sharp physical reading. This interpretation underlies the present work that deals with hyperplastic tumors only (cf., Remark 2.2).

Hyperplasia is related to homeorhesis since it can be regarded as a homeostatic and hence homeorhetic dysfunction. Indeed, the section "Carcinogenesis, a multistage process leading to homeostatic dysfunction" of Trosko (*et al.*, 1990) includes in depth discussion on this topic (see also the corresponding references therein). In the present treatment, the above dysfunction can be described with equation (5.1) if it is combined with the ideal-homeorhesis model (3.4). The latter, in the light of (5.1), describes the *ideal* state of the cellular fluid. This also explains the term "ideal" in the text on (3.8). The subsequent question is how to endow ODE (3.4) with option (5.1).

6. THE HYPERPLASTIC-TUMOR/NONQUIESCENT-CELL ASYMPTOTE

The *simplest* model similar to (3.4) which takes into account (5.1) is obviously

$$\partial(m - m_H)/dt = b(m - m_H), \qquad t > 0, \tag{6.1}$$

where $b > 0$ does not explicitly depend on m. Since b is positive, ODE (6.1) (or, more generally, (7.18) below) is, in the hyperplastic-tumor limit case (5.1), the *hyperplastic-tumor* asymptote. It is defined for all $m \geq 0$ and is also the infinite-m (cf., (5.1)) asymptote that corresponds to the *nonquiescent* (NQ) cells, i.e. the ones which do not enter the quiescent nondividing $G0$ stage. Subsequently, we term ODE (6.1) (and its generalization (7.18)) the *hyperplastic-tumor/nonquiescent-cell* (HT/NQ) *asymptote*. One can estimate parameter b in (6.1) as follows

$$b = \ln 2/\theta \tag{6.2}$$

where term $\theta > 0$ (see Line 8 of Table 2) is explained in the remark below.

REMARK 6.1. Equation (6.1) is, under the FFT condition in (2.9) (see also (3.3)), representable as $\partial(n - n_H)/\partial t = b(n - n_H)$. Subsequently, θ in (6.2) can be interpreted as the HT/NQ-cell duplication time (i.e. the time from the birth of a cell to the moment of its division into two new cells (see Line 7 of Table 1)) under the FFT condition.

The cell-duplication time θ depends on the type of the cells. It is usually between a few tens of minutes and a few tens of hours. For embryonic cells of vinegar

flies (also called fruit flies), θ is about 11 minutes.

It is well known (e.g., Campbell and Farrell, 2003, p. 272) that the cell duplication of the eukaryotic cells consists of four stages, the $G1$, S, $G2$, and M stages. The S and M "follow canonical steps that vary little from cell to cell" (Massagué, 2004, p. 298). The durations of these stages are nonzero, $\theta_S, \theta_M > 0$. In contrast to this, the $G1$ and $G2$ stages "are largely dependent on cell type and context" (Massagué, 2004, p. 298). The durations of these stages can be zero (Massagué, 2004, p. 299 and Fig. 1), $\theta_{G1}, \theta_{G2} \geq 0$. Thus, the HT/NQ-cell duplication time θ is expressed as follows

$$\theta = \theta_{G1} + \theta_S + \theta_{G2} + \theta_M. \tag{6.3}$$

In general, changes in θ (e.g., down to the values not less than $\theta_S + \theta_M$) depend on various *genotoxic* biological signals (e.g., Massagué, 2004; Kitazono *et al.*, 1999).

Quantitative approaches (e.g., Ubezio, 2004) can help to develop models for θ.

7. THE CORE PHASE-TRANSITION-ENDOWED MODEL FOR THE HYPERPLASIA-EXTENDED HOMEORHESIS

Equation (6.1) radically differs from equation (3.4) because of the opposite signs on the right-hand sides. The *simplest* way to endow (3.4) with the capabilities of (6.1) is an interpolation between the *negative* constant $-a$ and the positive constant b. The *simplest*, linear interpolation results in the following combination of (3.4) and (6.1) $\partial(m - m_H)/dt = P[-a(m - m_H)] + (1 - P)[b(m - m_H)]$ or

$$\partial(m - m_H)/\partial t = [-aP + b(1 - P)](m - m_H), \qquad t > 0, \tag{7.1}$$

where

$$0 \leq P \leq 1. \tag{7.2}$$

Equation (7.1) is the very one that couples ideal homeostasis (3.4) with the hyperplasia option (6.1) (or (5.1)) that presents the homeostatic dysfunction. The right-hand side of equation (7.1) is the biochemical-reaction term for the scaled concentration m.

Relation (7.2) allows one to interpret P as some probability. Due to the nature of the form of the right-hand side of (7.1), P is the probability that the cellular-fluid is involved only in the homeostatic convergence of m to finite m_H whereas $1 - P$ is the probability that the cellular-fluid is involved only in the unlimited growth of m to infinity, i.e. in hyperplasia (5.1) or, equivalently, in the aforementioned phase transition. Since the probabilities P and $1 - P$ are *complementary*, ODE (7.1) allows for that the homeostatic convergence and hyperplasia constitute an *alternative*.

It is convenient to parametrize probabilities P and $1 - P$ with the probability ratio

$$Q = (1 - P)/P \tag{7.3}$$

in the following way

$$P = 1/(1 + Q), \qquad 1 - P = Q/(1 + Q), \tag{7.4}$$

where, in view of (7.2),

$$Q \in [0, \infty). \tag{7.5}$$

The meaning of P and $1-P$ (see the text between (7.2) and (7.3)) implies that

$$\lim_{m \to 0} Q = 0, \qquad Q \sim m, \qquad \lim_{m \to \infty} Q = \infty. \tag{7.6}$$

Indeed, ratio (7.3) is expected to be proportional to the growing quantity, i.e. (see (5.1)) m. This leads to the second relation in (7.6). At zero m, there is no hyperplasia. This is expressed with the first relation in (7.6). Finally, in case of (5.1), the hyperplasia probability $1-P$ strongly dominates over the homeorhetic-convergence probability P. This is specifically formulated with the third relation in (7.6).

The *simplest* m-dependence of Q which agrees with both (7.5) and (7.6) is

$$Q = m/m_* \tag{7.7}$$

where the value $m_* > 0$ of m is called the *median* value (cf., Line 9 of Table 2) because of issues explained in Remark 7.1 below. The form (7.7) is assumed in what follows. In spite of the simplicity of expression (7.7), this expression endows the present approach with *nonstationary-phase-transition* capabilities and (see Remark B.2 in Appendix B) turns out to be highly relevant.

In case of (7.7), the probabilities (7.4) become

$$P = P(m) = m_*/(m + m_*), \qquad 1-P = 1-P(m) = m/(m + m_*). \tag{7.8}$$

REMARK 7.1. If one regards scaled concentration of the cellular fluid as the value of a stationary stochastic process with the stationary random variable then the following interpretation is applicable.

Let the stationary random variable for the process be $\boldsymbol{m}(\cdot)$. Its values are described with $\boldsymbol{m}(\xi)$ where $\xi \in \Xi$ is the elementary event and Ξ is the space of elementary events. It follows from (7.8) that probability density ρ of random variable $\boldsymbol{m}(\cdot)$ is

$$\rho(m) = m_*/(m + m_*)^2, \qquad m \in [0, \infty). \tag{7.9}$$

Interestingly, this density is the *simplest* rational member (Lachenbruch and Brogan, 1971, (1)) of the Lachenbruch–Brogan probability-density family (Lachenbruch and Brogan, 1971, (3)). The median of the probability distribution corresponding to density (7.9) is m_*. This explains the above term "median value" for m_* (see the text below (7.7)). No moments of probability density (7.9) exist (Lachenbruch and Brogan, 1971). This feature is relevant in the case under consideration, i.e. when the density describes the stationary (scaled) concentration of the cellular fluid. Indeed, would the expectation (i.e. the first moment) exist, then it would be difficult to interpret this concentration value since both the homeorhetic convergence to m_H and oncogenic hyperplasia, i.e. growth to infinity, are *in principle equally represented processes*. The latter feature agrees well with the non-existence of the expectation.

Another value of m used in this work is m_C introduced with relations

$$m_* = (b/a)\, m_C, \tag{7.10}$$

$$m_C \in [m_H, \infty). \tag{7.11}$$

For the reasons explained in Section 8.1 below, we term value m_C of m the *critical* value (cf., Line 10 of Table 2). Value m_C derived below (see (7.22)) determines the corresponding, critical value n_C of n (see Line 10 of Table 2) as follows (see (2.8))

$$n_C = [v m_C/(1+v m_C)]\, n_T. \tag{7.12}$$

Relation

$$n_C \in [n_H, n_T) \tag{7.13}$$

stems from (7.11) and (7.12).

In view of (7.8) and (7.10), ODE (7.1) is equivalent to

$$\frac{\partial(m-m_H)}{\partial t} = \frac{ab(m-m_C)}{am+bm_C}(m-m_H), \qquad t>0. \tag{7.14}$$

Thus, dependence (7.7) allows one not only to combine homeostasis (see (3.4)) with hyperplasia (see (6.1)) resulting in the nonstationary-phase-transition (7.14) but also to provide a profound nonlinearity of the right-hand side of (7.14) in m.

The behavior of m where the cell apoptosis or cell mitosis is dominating is determined by the condition $dm/dt<0$ or $dm/dt>0$ respectively. In terms of ODE (7.14), these modes are described by the inequalities

$(m-m_H)(m-m_C)<0$, the cell-death-dominating behavior, (7.15)

$(m-m_H)(m-m_C)>0$, the cell-proliferation-dominating behavior. (7.16)

Both ODEs (3.4) and (6.1) can be derived from ODE (7.14). Indeed, in the limit case when $m_C \to \infty$ and

$$\lim_{m_C\to\infty} bm_C = \infty, \tag{7.17}$$

(7.14) becomes (3.4). The m_C-aware generalization of (6.1) stemming from (7.14) is

$$\partial(m-m_H)/\partial t = b\{m - m_H - [1+(b/a)]m_C\}, \qquad t>0,$$
in the limit case when $m \to \infty$. (7.18)

In the opposite limit case, i.e. when $m \to 0$, equation (7.14) leads to the following linear in m asymptotic representation

$$\partial(m-m_H)/\partial t = -a\{[1+(1+(a/b))(m_H/m_C)]m - m_H\}, \qquad t>0,$$
in the limit case when $m \to 0$. (7.19)

REMARK 7.2. One can easily check that the linear asymptotes on the right-hand sides of (7.18) and (7.19) intersect each other at $m=(b/a)m_C$ or, in view of (7.10), at $m=m_*$. This is a highly remarkable fact since the asymptotes explicitly depend on m_H whereas the median picture for m_* (see Remark 7.1) does not involve m_H at all. (The asymptote value at the intersection point is $-b(m_H+m_C)$.)

The above mentioned fact emphasizes the inherently consistent nature of model (7.14). Moreover, the feature of m_* to be the median of the probability distribution

corresponding to (7.9) is represented in terms of ODE (7.14) with the fact that the value $m = m_*$ subdivides the m-axis into two parts corresponding to the decreasing and increasing linear asymptotes. Subsequently, m_* is, on a par with m_H and m_C, a characteristic value of m inherent in ODE (7.14).

One can show that the right-hand side of ODE (7.14), as a function of m, reaches the global (for $m \in [0,\infty)$) minimum if and only if $m = m_i$ where

$$m_i = [\sqrt{(a+b)\, m_C (a m_H + b m_C)} - b m_C]/a . \tag{7.20}$$

It can be easily checked that

$$m_H < m_i < m_C, \qquad \lim_{m_C \downarrow m_H} m_i = m_H, \qquad \lim_{m_C \to \infty} m_i = \infty . \tag{7.21}$$

The above facts enable one to derive an explicit expression for the critical scaled concentration m_C. The derivation presented below is based on the analogous meanings of the minimum-point value m_i (see (7.20)) and median value m_* (see (7.10)).

It follows from the meaning of m_i that this value corresponds to the global minimum in m of the right-hand side of (7.14). If this right-hand side is schematically represented with the two linear asymptotes, as it is discussed in Remark 7.2, then the global-minimum value is the one for their intersection point, i.e. the median value m_*. Remark 7.2 also explains why this value is an inherent characteristic of ODE (7.14). Subsequently, one arrives to the equality $m_* = m_i$ that, by virtue of (7.10) and (7.20), is equivalent to the following

$$m_C = \frac{c(1+c)}{3-c} m_H \tag{7.22}$$

where

$$c = a/b . \tag{7.23}$$

Relations (7.11) and (7.22) point out that

$$c \in [1,3). \tag{7.24}$$

The expression for m_* (see (7.10)) and m_i (see (7.20)) corresponding to (7.23) and (7.22) is $m_* = m_i = m_C/c$. When c increases in the interval (7.24), i.e. from 1 to 3, the critical concentration m_C, as a function of c (see (7.22)), strictly monotonically increases from m_H to infinity. Also note that this function meets requirement (7.17). Subsequently, infinite m_C corresponds to the ideal homeorhesis (see Section 3). Relation (7.24) is, according to the proposed model, the necessary and sufficient condition for a cell to be duplicating.

The cell-duplicability condition (7.24) poses bounds on the cell-cycle time θ. Indeed, as it follows from (3.8) and (6.2),

$$c = \theta/(\ln 2\, \eta) \tag{7.25}$$

or, for the eukaryotic cells (6.3), $c = (\theta_{G1} + \theta_S + \theta_{G2} + \theta_M)/(\ln 2\, \eta)$. Hence (7.24) is transformed into the relation

$$1 \le (\theta_{G1} + \theta_S + \theta_{G2} + \theta_M)/(\ln 2\, \eta) < 3 . \tag{7.26}$$

Note that, in view of (7.22) and (7.25),

parameter m_C is a strictly monotonically increasing function of time ratio c (see (7.25)) or the HT/NQ-cell duplication time θ. (7.27)

Inequalities (7.26) imply

$$0 \le (\theta_{G1} + \theta_{G2}) / (\theta_S + \theta_M) < 2. \tag{7.28}$$

Remarkably, this fully agrees with the Katzung data (Katzung, 2001, p. 926; see also Antipas *et al.*, 2004, p. 1495): $\theta_{G1} = 0.4\,\theta$, $\theta_S = 0.39\,\theta$, $\theta_{G2} = 0.19\,\theta$, and $\theta_M = 0.02\,\theta$. In this case, $(\theta_{G1} + \theta_{G2}) / (\theta_S + \theta_M) = 1.439$ (cf., (7.28)). The authors of the present work are not aware of any published experimental results which do not satisfy condition (7.28). This enables one to formulate the following hypothesis.

HYPOTHESIS 7.1. Relation (7.28) is a quantitative law valid for any HT/NQ cells.

In view of (7.23) and (3.8), ODE (7.14) is equivalent to equation

$$\frac{\partial (m - m_H)}{\partial t} = \frac{1}{\eta} \frac{m - m_C}{cm + m_C} (m - m_H), \qquad t > 0. \tag{7.29}$$

Compared to the form (7.14), the advantage of (7.29) is that, owing to (7.25) and (7.22), it is written in terms of the time quantities η and θ which are among the model input parameters. We also stress that ODE (7.29) is the first description for a combination of homeorhesis and oncogenic hyperplasia which is the *minimal* model. The latter means that any simplification of the model leads to either quite particular cases (e.g., see Sections 3 and 8) or a destruction of the model. Thus, ODE (7.29) is the *core* description to be used in any subsequent modelling the mentioned combination. The above derivation is summarized as follows.

REMARK 7.3. The *core* phase-transition-endowed model of the maintenance of the cell number (see (1.1)) by the oncogenic-hyperplasia-extended homeorhesis describes the time dependence of the cellular-fluid concentration n in (1.1) with the dedicated ODE, and includes the following relations:

- equality (2.8) which expresses the concentration n in terms of the scaled concentration m according to Remark 2.1;
- nonlinear ODE (7.29) for the scaled concentration m;
- relations (7.25), (7.22) for the time ratio c and the critical concentration m_C;
- initial condition (3.5), (3.6) for ODE (7.29); equality (3.6) expresses the initial function $m_0(\cdot)$ in (3.5) for the scaled concentration $m(t, \cdot)$ in terms of the initial function $n_0(\cdot)$ in (3.7) for the concentration $n(t, \cdot)$.

The model input parameters are listed in Lines 1–7 of Table 1. In Section 10 the model is used as the core for the *diffusion*-aware description of m.

8. SUMMARY FOR THE CORE-MODEL ANALYTICAL ANALYSIS IN THE PARTICULAR CASE OF HOMEOSTASIS

Since the parameters η, θ, and m_H (as well as c and m_C because of (7.25)

and (7.22)), depend on t, ODE (7.29) can not be analyzed fully analytically in the general case. However, this analysis is possible in the particular case of homeostasis, namely, when homeorhesis is simplified to homeostasis by means of condition $\partial m_H/\partial t \equiv 0$ and, moreover, both η and θ (and thus c and m_C) are independent of t. The analysis is summarized in this section.

We first note that, in the present case, there can exist the unique value of m such that it is not an equilibrium point of equation (7.29) and is the ordinate of the inflexion points of the solution of the initial-value problem (7.29), (3.5). One can show that this value exists if and only if $m_i \le m_0 < m_C$ where m_i is described with (7.20) and has features (7.21). Moreover, if the value exists, it is m_i and the abscissa t_i corresponding to ordinate m_i is a function of $m_0(\cdot)$. Additionally, the space position x, is non-negative, i.e. $t_i \ge 0$, and gives $\lim_{m_0(\cdot)\uparrow m_C} t_i = \infty$. One can point out the following three states:

- the *generic* state; the state when $m_C > m_H$ in (7.11) is fixed;
- the *ideal* state; the limit state when m_C tends to the *upper* bound of the interval in (7.11), i.e. $m_C \to \infty$; this state is the *best* one for the host of the cells;
- the *brink* state; the state when m_C is equal to the *lower* bound of the interval in (7.11), i.e. $m_C = m_H$; this state is the *worst* one for the host of the cells.

Since (7.17) is valid (because of (7.22) and (7.23)) and (3.8) holds, the ideal state is presented with the model in Section 3. The only equilibrium point of ODE (3.4) is m_H, and it is exponentially stable in the large, i.e. for *all* $m \ge 0$ (see also the text on (7.15) and (7.16)).

Sections 8.1 and 8.2 consider the generic and brink states, respectively.

8.1. The generic state

At the generic state of the cellular fluid, the solution of the initial-value problem (7.29), (3.5) is defined for all $t \ge 0$ and is described as an implicit function of t in the following way (see also Dwight, 1961, integrals 160.01 and 160.11)

$$m \equiv m_0, \qquad t \ge 0, \qquad \text{if } m_0 \equiv m_H \text{ or } m_0 \equiv m_C,$$

$$[(m-m_H)/(m_0-m_H)]^{-\eta\frac{cm_H+m_C}{m_C-m_H}}\,[(m-m_C)/(m_0-m_C)]^{\eta\frac{cm_C+m_C}{m_C-m_H}} = \exp(t),$$

$$t \ge 0, \qquad \text{if } m_0 \ne m_H \text{ and } m_0 \ne m_C.$$

The summary of the time behavior of m is presented in Figure 1. There are the following three mutually exclusive cases of the generic state (the drawings mentioned in the list below are those shown in Figure 1):

- the *homeorhesis domain* when $0 < m < m_C$ (e.g., see (a)–(e)); it comprises (cf., Section 4) the *regeneration subdomain* $0 < m < m_H$ (e.g., see (a)) and the *inflammation subdomain* $m_H < m < m_C$ (e.g., see (c)–(e)) separated from each other by the (stationary) *homeorhesis point* $m \equiv m_H$ (see (b)); the regeneration subdomain corresponds to (7.16); the inflammation subdomain corresponds to (7.15); the latter subdomain includes the *acute-inflammation region* $m_H < m$

$< m_i$ (e.g., see (c) and (ê) and the *chronic-inflammation region* $m_i < m < m_C$ (e.g., see (e)) separated from each other by value (7.20) (see (d));
- the (stationary) *critical point* $m \equiv m_C$;
- the *oncogenic-hyperplasia domain* when $m_C < m < \infty$; this domain corresponds to (7.16).

Value m_C, the upper bound of the chronic-inflammation region, is in the present work called critical because it separates the homeorhesis and oncogenic-hyperplasia domains from each other (see (f) in Figure 1). Notably, the immediate proximity of these domains agrees with the fact that the development of cancer is usually attributed to inflammation. This idea was suggested as early as about AD 200 by the Greco-Roman physician Galen of Pergamum (AD 129 – c. 216).

We also note that in the homeorhesis domain, ODE (7.29) has the only equilibrium point $m \equiv m_H$ and this point is exponentially stable. The homeorhesis-domain features are expected in a normal host of the cells.

The critical point $m \equiv m_C$ (see (f) in Figure 1), is the case if and only if $m_0 \equiv m_C$. If the latter identity holds, point $m \equiv m_C$ is an *unstable* (see (1) and (2) in Figure 1) equilibrium point of ODE (7.29). Due to the instability, it would be difficult (if possible at all) to experimentally detect value m_C.

The oncogenic-hyperplasia domain is highly unfavorable to a host of the cells. Solution m of initial-value problem (7.29), (3.5) is in this domain (see (g) in Figure 1), if and only if m_0 is in the domain. In this case, m strictly monotonically increases from m_0 up to infinity, complying with (5.1) and being strictly convex. In other words, inequality $m_C < m$ activates the behavior that, in the limit case (5.1), results in the HT/NQ asymptote (6.1). This leads to the issues in the remark below.

REMARK 8.1. The *biological* meaning of the critical scaled concentration m_C (see (7.11)) can be formulated in the following way:

$$\text{the cells are the HT/NQ ones if and only if } m_C < m. \tag{8.1}$$

Equivalently, the reduction of m_C below m (at fixed m_H) prevents the cells from entering the quiescent, $G0$ stage. The m-dependent values c_m and θ_m of c and θ (see (7.22) and (7.25)) corresponding to the $G0$-stage threshold $m_C = m$ are determined from the equalities

$$c_m(1 + c_m)/(3 - c_m) = m/m_H, \qquad c_m = \theta_m/(\ln 2\, \eta). \tag{8.2}$$

The threshold picture for the $G0$-stage (de)activation is similar to that of the threshold-activation approach of Beltrami and Jetsy (1995) and agrees with the well-known vision discussed by Malumbers and Barbacid (2001, the box on p. 224).

According to our expression (7.22), the sub-m reduction of m_C can be achieved only by decreasing the time ratio c (see (7.25)). The latter can in turn be implemented only by lowering the HT/NQ-cell-duplication time θ since lifetime η in (7.25) is a quantity related to the ideal state (see the beginning of Section 8). The question is if there are any human-biology mechanisms that inhibit the $G0$ stage by a *simultaneous* reduction of the duplication time θ.

The answer is affirmative: these mechanisms do exist. One of them is related

to serum. For instance, Ohtsubo and Roberts (1993, the "Control" part of Figure 2.(d)) report that θ is inversely proportional to the serum concentration in the *in-vitro* NQ-cell measurements. When this concentration tends to zero, θ increases unlimitedly but, what is more important, θ decreases when the concentration increases. Serum is known as a medium containing various mitogenic cytokines.

Another group of the above mechanisms is inherently associated with the D-type cyclins (e.g., Kitazono, *et al.*, 1999). Overexpression of these cyclins (e.g., Sherr, 1995, p. 187; Kitazono, *et al.*, 1999, the section "D cyclins"; Hatzimanikatis *et al.*, 1999, p. 635) shortens θ (in particular, by reduction of θ_{G1} in (6.3)) and weakens the $G0$-stage effect thereby switching the cells to the (almost-)NQ behavior.

The above two pathways are not necessarily independent. Indeed, "the D cyclins are unique in that they respond to external signals. This gives them a special role as cell division initiators." (Kitazono, *et al.*, 1999, the section "D cyclins"). "The fundamental role of D-type cyclins is to integrate extracellular signals" such as automitogens (AMGs), autocrine mitogenic cytokines, "with the cell cycle machinery." (Sherr, 1995, p. 187). Subsequently, the amplification effect of serum on the D-cyclin activities has already been confirmed (e.g., Sherr, 1995, p. 187). This, in conjunction with the above facts, points out that the D cyclins can reduce the $G0$-stage effect and also endow the cells with the full NQ properties. Moreover, the "special role" of the D cyclins that they are directly influenced by intercellular signals opens up possibilities to discover AMG- or AMG-receptor-deactivating therapies or drugs for prevention or cure of oncogenic hyperplasias.

The brink state is a limit case of the generic state. This is discussed below.

8.2. The brink state

At the brink state, i.e. when $m_C = m_H$, the only equilibrium point of ODE (7.29) is $m \equiv m_H = m_C$. It is semi-stable, more precisely, exponentially stable from below and unstable from above. Because of the instability, it can be difficult to experimentally detect it. Figure 2 shows the time-dependences of m in the brink state.

The state is called the brink one since the line (b) in Figure 2 can be regarded as the "brink" line in the following sense. A sudden deviation of m up from this line attracts m away from the line (see (2) in Figure 2) whereas an opposite deviation does not prevent the attraction of m to the line (see (1) in Figure 1). This behavior can be recognized as an extremely particular example of bifurcation, the concept employed in an enormously wide range of mathematical problems (e.g., see Hazewinkel, Ed., 1988a, pp. 387-389 on bifurcation). The brink state is the most dangerous for a host of the cells.

9. BIRTH, LIFE, AND DEATH OF ONCOGENIC HYPERPLASIA

In model (7.29) analyzed in Section 8, the value m_C need not be independent of time t. This dependence is accounted in what follows.

It stems from ODE (7.29) that

$$\left.\frac{d^2m}{dt^2}\right|_{m=m_C} = -\frac{1}{\eta}\frac{m_C - m_H}{(c+1)m_C}\cdot\frac{dm_C}{dt} = -\frac{1}{\eta}\frac{(c_m+1)^2-4}{c(c_m+1)^2}\cdot\frac{dm_C}{dt}. \qquad (9.1)$$

The time intervals where m_C varies very slow and very fast compared to m can alternate (e.g., see Figure 3). This behavior of m_C is specified below.

Assume that $m_H|_{t=0} < m_o < m_C|_{t=0}$ (see (a) in Figure 3), i.e. at the initial moment an inflammation is the case (cf., the inflammation subdomain in Figure 1). Subsequently, m is in the homeorhesis domain. Assume as well that, in accordance with (7.27), due to a genotoxic reduction of θ and hence c (see (7.27) and Remark 8.1), m_C rapidly drops below m (see (1) in Figure 3). In view of (9.1), the point of the intersection of m_C and m (see (b) in Figure 3) is the point of a *local minimum* of m, and (since m is, in its neighborhood, strictly convex) corresponds to the acute-inflammation region (cf., (c) or (ê) in Figure 1). Note that the intersection point corresponds the threshold values (8.2).

If the above low value of θ (and c) remains (almost) unchanged for a while, then, by virtue of (8.1), the cells do not enter the quiescent $G0$ stage and, thus, oncogenic hyperplasia begins (see (c) in Figure 3). At the same time, it manifests the inflammation intensification from acute to chronic. Thus, the above intersection point is the birth of the hyperplasia and the beginning of the acute-to-chronic transition. Note that an *inherent* connection of oncogenic hyperplasia to chronic inflammation is well known from experiments (e.g., Kawai et al., 1994; Keenan et al., 1989, and the references therein).

Let θ and, thus (see (7.25)), c be pushed up sufficiently high to make (see (7.22)) m_C higher than m (see (2) in Figure 3). This can result from the immune surveillance (e.g., Franks and Teich, Eds., 1997, Sect. 16.3.1; Life, Death and the Immune System, 1993), pharmaco- or radiotherapy-action, or other relevant factors (e.g., see Remark 8.1) . Subsequently (see (8.1)), the cells are no longer prevented from entering the $G0$ stage. In this case, the point of the intersection of m_C and m (see (d) in Figure 3) is, due to (9.1), the point of a *local maximum* of m (since m is, in its neighborhood, strictly concave). It corresponds to the chronic-inflammation region (cf., (e) in Figure 1). This point is the death of oncogenic hyperplasia and the beginning of the inflammation relaxation from chronic to acute (see (e) in Figure 3). This scenario corresponds to sufficiently high θ (or c). If, on the contrary, the increased value of θ is not high enough and hence m_C is boosted insufficiently (see the dotted line in Figure 3), oncogenic hyperplasia will continue (see (ĉ) in Figure 3) resulting in a tumor. This allows for the well-known robustness of cancer (e.g., Kitano, 2003).

If the above high value of θ (or c) and, thus, of $m_C > m_H$ remains (almost) unchanged for a long time, the tumor, i.e. the accumulated cell lump, of concentration m is disintegrated, bringing m to homeorhetic value m_H. This happens since the $G0$ stage is active at $m_C > m_H$ (see above). After that, due to the next genotoxic "attack" (i.e. reduction of θ) m_C can be reduced, oncogenic hyperplasia can begin again, and so forth. (These repeated processes are not shown in Figure 3.)

The above picture shows how the core model allows for the genotoxic, θ-lowering activation of the hyperplasia resulting in its homeorhesis-dysfunction character.

REMARK 9.1. Every intensification of inflammation from acute to chronic is, in the dynamical terms, oncogenic hyperplasia. Each time when the latter ends, the accompanying chronic inflammation achieves a local maximum in time. If chronic inflammation does not achieve this maximum, oncogenic hyperplasia does not end.

The core model in Remark 7.3 is, similar to any other model, nothing but a hypothesis that has to be verified experimentally. The verification should, first of all, include a detailed description and operation guidance for the corresponding measurement equipment that would enable one to validate the model precisely in *the very same sharp, unambiguous, and time-space dependent terms* which the model is formulated in. The model is ready for verification since it does not contradict any qualitative aspect of homeorhesis, oncogenic hyperplasia, or the cell cycle.

10. THE DIFFUSION GENERALIZATION OF THE CORE MODEL TO MORPHOGENY: THE PHASTRAM MODEL

Morphogeny, a process of formation of a tissue, organ, tumor, or other similar body is not only inhomogeneous in space but also includes diffusion of species. The simplest way to correspondingly extend the core model (see Remark 7.3) is involvement of the reaction-*diffusion* approach applying it to the simplest domain, i.e. the entire physical space $\mathbb{R}^3$ (see the text above (1.1)). The reaction-diffusion treatment of morphogenesis and self-organization in biology was pioneered by Rashevsky (1940a, 1940b, 1940c) (see also Turing, 1952, 1992, as well as Levin and Segel, 1985, for a survey).

According to the above recipe, one takes into account the corresponding diffusion term (cf., Burton, 1966; De Angelis and Preziosi, 2000; Pettet *et al.*, 2001; Akabani *et al.*, 2002; Ferreira *et al.*, 2002; Kar *et al.*, 2002; Jiang *et al.*, 2002). This extends ODE (7.29) to the following reaction-diffusion equation (RDE)

$$\frac{\partial (m - m_H)}{\partial t} = \nabla^{\mathrm{T}}[D \nabla (m - m_H)] + \frac{1}{\eta} \frac{m - m_C}{cm + m_C} (m - m_H), \qquad x \in \mathbb{R}^3,\ t > 0, \quad (10.1)$$

where $D > 0$ is the diffusion parameter of the cellular fluid (e.g., see (10.4) below) and column ∇ is the Hamilton differential expression in the entries of vector x, i.e. $\nabla = (\partial/\partial x_1, \partial/\partial x_2, \partial/\partial x_3)^{\mathrm{T}}$. The familiar initial condition (3.5) is also the one for RDE (10.1).

Cells are enormously big and heavy compared to elementary particles (cf., Mamontov and Willander, 2003a). Subsequently, the *shifted* (and hence, generally non-equilibrium) Maxwell–Boltzmann (shifted-MB) statistics may be valid for cells even at high values of m (Mamontov and Willander, 2003a). Indeed, in the shifted-MB case, m is coupled with the cellular-fluid chemical potential μ with the well-known relation (e.g., Mamontov and Willander, 2003a, Sect. 3) $m = \mathrm{N} \exp[\mu/(KT)]$ where (e.g., Mamontov and Willander, 2003a, (9))

$$\mathrm{N} = (2s + 1)\left(h^{-1}\sqrt{2\pi KTM}\right)^3 \quad (10.2)$$

is the characteristic scaled concentration of the cellular fluid (see Line 13 of Table

2), s is the quantum-spin number of a cell (see Line 8 of Table 1), h is the Planck constant ($h \approx 6.626 \cdot 10^{-34}\,\mathrm{J \cdot s}$), K is the Boltzmann constant ($K \approx 1.38 \cdot 10^{-23}\,\mathrm{J \cdot K^{-1}}$), $T > 0$ is the absolute temperature of the cellular-fluid host (see Line 9 of Table 1), $M > 0$ is the mass of a cell (cf., Line 10 of Table 1). The validity criterion for the shifted-MB statistics is the inequality (e.g., Mamontov and Willander, 2003a, (12))

$$m/\mathrm{N} \le \pi^{-3}\,(\approx 1/31). \tag{10.3}$$

For cells, it holds up to very high m since the cell mass M in (10.2) is usually very high. (Note that the mass of a red blood cell in human blood exceeds the electron mass by 10^{17} (!) times (e.g., Mamontov and Willander, 2003a, Sect. 4 and Table 1)). The corresponding relaxation time τ of the cell momentum (see Line 11 of Table 1) is independent of m and hence the resulting diffusion parameter (e.g., Mamontov and Willander, 2002, (19))

$$D = KT\,(\tau/M) \tag{10.4}$$

in (10.1) is also m-independent. It is shown (Mamontov and Willander, 2002, (20)) that

$$\tau \ge [h/(4\pi)]\,[1/(KT)]. \tag{10.5}$$

Since, at the hyperplastic stage of oncogeny, both M and τ in (10.4) do not depend of x either, D is independent of x. Due to the latter, RDE (10.1) is equivalent to

$$\frac{\partial (m - m_H)}{\partial t} = D\,\nabla^{\mathrm{T}}\nabla (m - m_H) + \frac{1}{\eta}\,\frac{m - m_C}{cm + m_C}\,(m - m_H), \quad x \in \mathbb{R}^3,\ t > 0. \tag{10.6}$$

REMARK 10.1. The shifted-MB statistics implies that the cells are *mutually non-interacting*. If the cell-involving reactions (cf., the last term on the right-hand side of (10.1)) are present, then the mutual non-interaction is, strictly speaking, not the case. Subsequently, the above statistics (and the corresponding, concentration-independent diffusion parameter D) is at best an approximation.

Since the x-domain in (10.6) (or (10.1)) is the entire space, the solution of (10.6) is sought as the solution of the corresponding *Cauchy* problem (10.6), (3.5).

REMARK 10.2. The reaction-diffusion version of the core model (see Remark 7.3) is the model for the **phas**e-**tra**nsition-endowed **m**aintenance (PhasTraM) of the cell number (see (1.1)) by the oncogenic-hyperplasia-extended homeostasis. The PhasTraM model describes the time-space dependence of the cellular-fluid concentration n in (1.1) with the dedicated nonstationary RDE whereas the above core model describes n with the related ODE. The PhasTraM model includes the relations below:

- equality (2.8); it expresses the concentration n in terms of the scaled concentration m according to Remark 2.1; note that, if necessary, the following can be applied; *volume* $V(t)$ of a tumor is determined in terms of n, namely, $V(t) = \int_{\Upsilon(t)} dx$ where $\Upsilon(t) = \{x \in \mathbb{R}^3 : n(t,x) \ge n_C(t,x)\}$ is the tumor *locus* (empty if there is no tumor) and n_C is described with (7.12); if $\Upsilon(t) \ne \varnothing$, i.e. a tumor is formed, its *shape* and *size* are pointed out by boundary $\partial\Upsilon(t)$;
- nonlinear RDE (10.6) for the scaled concentration m;

- relations (7.25) and (7.22) for the time ratio c and critical concentration m_C;
- initial condition (3.5), (3.6) for RDE (10.6); equality (3.6) expresses the initial-value function $m_0(\cdot)$ of the scaled concentration m (see (3.5)) in terms of the initial-value function $n_0(\cdot)$ in (3.7) for concentration n.

In the entire physical space $\mathbb{R}^3$, the PhasTraM model describes m with the Cauchy problem (10.6), (3.5).

The above term "phase-transition" is due to the fact that the PhasTraM model is inherently associated with Schlögl's theory of non-equilibrium phase transitions of both the first and second orders. This is explained in Appendix B in more detail.

REMARK 10.3. The PhasTraM model (see Remark 10.2) generalizes the core model (see Remark 7.3) to the Schlögl-type spatial inhomogeneity thereby granting the cellular-fluid morphogenicity. The latter includes the *self-consistent continuous* formation of the solid-phase regions, i.e. tumors, in the fluid and the *coexistence and evolution* of different physical phases in different space regions. If a tumor is formed, the PhasTraM model describes the dynamics of the tumor shape and size.

The fluid-solid Schlögl-type phase-transition nature of the PhasTraM model is one of the next steps in development of the biomedicine-related *bistable* approaches exemplified with the well-known Hodgkin–Huxley (HH) model (e.g., Hazewinkel, 1988a, p. 292). It was proposed in 1952 to describe the electrical activity of nerve cells rather than formation of a tumor. In contrast to single nonlinear RDE (10.6) in the PhasTraM model, the HH model includes at least *four* nonlinear equations where one equation is also a nonlinear RDE. This points out a substantially higher complexity of the HH approach. At any rate, an interpretation of the HH model in terms of a genotoxically-activated tumor formation would facilitate its application to oncogeny.

The overall spatial inhomogeneity of the PhasTraM model is explicit when the Cauchy problem (10.6), (3.5) in the PhasTraM model (see Remark 10.2) can be solved analytically. The latter can be done for the ideal state and the (t,x)-independent η. In this case, the *nonlinear* RDE (10.6) becomes the *linear* RDE

$$\partial(m-m_H)/\partial t = D\,\nabla^{\mathrm{T}}\nabla(m-m_H) - (1/\eta)(m-m_H), \quad x\in\mathbb{R}^3,\ t>0. \quad (10.7)$$

Its solution with initial condition (3.5) is

$$m(t,x) = m_H(t,x) + \left[\int_{\mathbb{R}^3}\Phi(t,x-y)\,m_0(y)\,dy - m_H(t,x)\right]\exp(-t/\eta),$$
$$x\in\mathbb{R}^3,\ t\geq 0, \text{ at the ideal state,} \quad (10.8)$$

where $\Phi(t,z) = (4\pi Dt)^{-3/2}\exp[-z^{\mathrm{T}}z/(4Dt)]$, $z\in\mathbb{R}^3$, $t>0$. The term $\Phi(t,x-y)$ in (10.8), as a function of (t,x) at every fixed $y\in\mathbb{R}^3$, presents the diffusion Gaussian "bell" in x centered at y. This "bell" affecting the first term in the brackets in (10.8) determines the spatial inhomogeneity and, thus, the morphogenic aspects of the cellular-fluid time-evolution $m - m_H(t,x)\to 0$ at the ideal state (see the list below (2.42)). In other words, expression (10.8) extends the ideal-state model (3.4), (3.5) to the general, spatially inhomogeneous case.

Obviously, the corresponding extensions of the core description (7.29), (3.5), (3.6) by the PhasTraM model are also available even if the model cannot be solved analytically, for example, at more complex states such as those in Sections 8.1 and 8.2. Indeed, the nonlinear RDE (10.6) differs from the linear RDE (10.7) in that the coefficient in front of $m - m_H(t,x)$ depends on m. However, if one replaces m in this coefficient with the initial value $m_o(x)$ thereby *linearizing* (10.6) (that results in (C.1)), then the corresponding solution $\overline{m}(t,x)$ (i.e. the one of the Cauchy problem (C.1), (3.5)) is (e.g., Freidlin and Wentzell, 1998, p. 38)

$$\overline{m}(t,x) = m_H(t,x) + \left[\int_{\mathbb{R}^3} \Phi(t,x-y)\, m_0(y)\, dy - m_H(t,x)\right] \times \exp\left\{\int_0^t \frac{1}{\eta(s,x)} \frac{m_0(x) - m_C(s,x)}{c(s,x)m_0(x) + m_C(s,x)}\, ds\right\}, \quad x \in \mathbb{R}^3,\ t > 0. \quad (10.9)$$

It approximately describes $m(t,x)$ including the development of the above diffusion Gaussian "bell" when the cellular fluid is not in the ideal state (cf., (10.8)). Loosely speaking, those fragments of surface $\overline{m}(t,x)$ which are stimulated by the switching of $m_C(t,x)$ to sufficiently low values (see Figure 3) form (islands of) a tumor whereas the rest of surface $\overline{m}(t,x)$ (i.e. its parts for which the low values of $m_C(t,x)$ are still sufficiently high) relax to homeorhetic concentration $m_H(t,x)$.
Expression (10.9) arises in the considerations leading to the analytical-numerical *time-slice method* for numerical solving the Cauchy problem (10.6), (3.5). This method is proposed in Appendix C which also notes that the accuracy of formula (10.9) is not very high. Subsequently, (10.9) can serve only as a semi-qualitative estimation. A more accurate picture can be obtained by the time-slice technique.

11. DISCUSSION, CONCLUDING REMARKS AND DIRECTIONS FOR FUTURE RESEARCH

Modern biomedicine is mainly devoted to an enormous number of observations and measurements on living matter. In spite of that the settings of these observations and measurements are highly specialized and quite particular, the corresponding data provide an important insight into various *fragments* of life processes. However, the fragmentary paradigm inherent in the biomedical facts cannot resolve the gradual time-space dynamics of homeorhesis and oncogenic hyperplasia. A possible way to repair this mismatch is Rashevsky's "unity in diversity" (see Section 1). It can be approached, for example, by the related mathematical-physics models.

There is a considerable progress achieved in this direction. For instance, some results on the topic are presented by Lopez (*et al.*, 1999) in terms of the tumor growth resisted by drugs. One of the key issues according to (Lopez *et al.*, 1999, p. 13028) is: "The assumptions and definitions underlying the model-based approach are potentially testable, and this may allow for clearer quantification and interpretation of the complex concepts of synergism... for *in vivo* tumor models". Related results were reported by other authors such as Sherratt (1993), Stöcker and Curci (1998), Bellomo and De Angelis (1998), Tan and Chen (1998), Bellomo (*et*

al., 1999), Bellomo and Preziosi (2000), Chaplain (*et al.*, 2001), Ferreira (*et al.*, 2002), Bellomo (*et al.*, 2003). The review paper of Vicini (*et al.*, 2002) provides a deep insight into the crucial role of mathematical modelling in various fields of biomedicine.

The above development can be regarded as a response to the following note on cancer (Hughes, 2001): "For such a complex disease, it is essential that we tackle it with diverse thinking and practice." The present work is a step toward the "unity in diversity" and is in line with systems biology (e.g., Pennisi, 2003; Kitano, 2002). The main outcome is the PhasTraM model described in Remark 10.2. Certain aspects of cell biology are elucidated by other results such as Hypothesis 7.1 (stemming from the discussion on (7.28)) and Remark 9.1.

The PhasTraM model is the first *minimal* model (see the text below (7.29)) that combines homeorhesis with oncogenic hyperplasia where the latter is regarded as a genotoxically activated homeorhetic dysfunction. This dysfunction presents transitions of the cellular fluid from a fluid, homeorhetic state to a solid, hyperplastic-tumor state, and back. The key part of the model is RDE (10.6) where the biochemical-reaction rate enables the above transition generalizing the well-known Schlögl physical theory of the non-equilibrium phase transitions (cf., Table 4). The feature of the PhasTraM model to be the minimal model presumes further extensions, for instance, to the *generalized*-kinetics theory developed by Bellomo (*et al.*, 2003a, 2003b) (see also Willander *et al.*, 2004). The above genotoxic activation is treated by means of the critical concentration (see (7.12) and (7.22)) and the nonquiescent-cell-duplication time (see θ in Remark 6.1, (7.25), and Remark 8.1). The model can describe both formation and disintegration of a tumor, and even a sequence of the formation/disintegration events.

The PhasTraM model includes a limited number of carefully selected input parameters listed in Table 1. Each of them has a specific biological, biophysical, or physical meaning. A determination of the key input parameters is considered by Mamontov (*et al.*, 2005) who also generalizes the model to the action of the anti-AMG or anti-AMG-receptor drugs (see Remark 8.1 on AMGs). Preliminary results on this action were reported by Koptioug (*et al.*, 2004). When the input parameters are properly determined, the model predictive capabilities can be used in development of the quantitative measures for prevention of oncogenic hyperplasia in cancer and other proliferative diseases (e.g., listed in Section 1).

The key output characteristic of the PhasTraM model is the cellular-fluid concentration n as a time-space-inhomogeneous function, $n = n(t, x)$. It is continuously differentiable and, thus, describes the transitions of the fluid from the homeorhesis state to the solid, tumor state in a *smooth* way. There are no sharp boundaries, i.e. the *ideal* jumps (of zero length in space) of the cell concentration, between the domains of the homeorhesis- and tumor-cell populations. This agrees with what is known in biomedicine. The concentrations changes from the normal to tumor values without discontinuities. Moreover, the above ideal concentration jumps are unphysical. If, however, there is a need to estimate the geometric features of a tumor (if it is formed) in specific quantities, the PhasTraM model provides (see Remark 10.2) the *time-dependent* tumor locus $\Upsilon(t)$, boundary $\partial\Upsilon(t)$, volume $V(t)$, as well as the

tumor shape and size in terms of $\partial\Upsilon(t)$.

In the literature, there are many other models which describe oncogeny by means of RDEs. The main distinguishing features of the PhasTraM model are the following.

- In contrast to, for instance, Pettet (*et al.*, 2001) and Ferreira (*et al.*, 2002), the PhasTraM model does not idealize the homeostasis-cell/tumor-cell system to a system of exactly two strongly different phases with a sharp boundary separating a solid tumor from the surrounding normal cells.
- The PhasTraM model does not assume the shape of a tumor to be of any specific (e.g., spherical) form, and does not tie down a growth of the tumor to an enlargement of the spatially homogeneous single-phase, solid spheroid (cf., Marušić *et al.*, 1994a, 1994b; Ward and King, 1997; Pettet *et al.*, 2001; Ward and King, 2003); notably, these assumptions are not used by Ferreira (*et al.*, 2002) where the model can generate a variety of the tumor shapes.
- The PhasTraM model does not artificially subdivide the cells into the ones that are normal and tumoral (cf., Sherratt, 1993) or living and dead (cf., Ward and King, 1997).
- The PhasTraM model in the case when all the input parameters (see Table 1) are available includes only *one* RDE, (10.6) in contrast to, for instance, Ward and King (1997); Jiang (*et al.*, 2002), and Ferreira (*et al.*, 2002).
- The input parameters of the PhasTraM model are both time- and space-dependent but not limited to any particular forms of these dependences in contrast to, for instance, Akabani (*et al.*, 2002) or Kar (*et al.*, 2002).
- The PhasTraM provides the explicit connection (e.g., see above) of the cell-population behavior to an intracellular phenomena, namely, the activation/deactivation of the $G0$-stage of the cell cycle. All the referred works, except Pettet (*et al.*, 2001), do not include a *cell-cycle-based* genotoxic activation of oncogeny. None of them stresses the homeorhesis mode, thereby leaving the homeorhetic-dysfunction facet of oncogeny (e.g., Trosko *et al.*, 1990) beyond the analysis.
- The PhasTraM model describes hyperplasia, the first stage of oncogeny (and the core of many other proliferative diseases (see Section 1). This offers the possibility of *consistent* modelling of other stages of oncogeny (cf., Remark 2.2).

We suggest four directions for future work on the PhasTraM model.

- Experimental testing the model. The testing should be done in terms of the key output parameter, i.e. the above mentioned cell concentration n. The corresponding measurement technique must provide the *gradual time-space* dependence $n = n(t,x)$ either *in-vivo* or in those *in-vitro* settings which were certified for a complete compliance with the related *in-vivo* environment (e.g., certified *three*-dimensional (3D) *in-vitro* experiments). A discussion of the 3D *in-vitro* methods can be found in Abbot (2003). An example of the methods able to measure the cell concentration is the ultrasound backscattering which has already been tested for cells (e.g., Sennaoui *et al.*, 1997), the cell-size particles (e.g., Panetta *et al.*, 2003), and the molecule-size particles (e.g., Baucke *et al.*, 2004).
- Interpretation of the model in terms of the cell-AMG interactions (see Remark

8.1 on AMG), determination of the key input parameters including the measurement-technique issues, and incorporation of a description for the action of the AMG- or AMGR-deactivating drugs into the model. The first step in this direction is the results of Koptioug (*et al.*, 2004) further extended by Mamontov (*et al.*, 2005). The main purpose of the above drugs is to increase the HT/NQ-cell duplication time θ (see (6.3)) thereby boosting m_C (see (7.22) and Remark 8.1) by means of c (see (7.25)).

- Analysis of the *cumulative* effect of the AMG-based drugs and radiotherapy on formation and disintegration of a tumor. As it is shown by Mamontov (*et al.*, 2005), if the concentration rate due to the radiotherapy-caused cell death is $-rm$ where $r = r(t,x) \geq 0$, then the PhasTraM RDE (10.6) is generalized to

$$\frac{\partial (m - m_H)}{\partial t} = D \nabla^{\mathrm{T}} \nabla (m - m_H) + \frac{1 - r\eta c}{\eta} \frac{m - \dfrac{1 + r\eta}{1 - r\eta c} m_C}{cm + m_C} (m - m_H),$$

$$x \in \mathbb{R}^3, \; t > 0. \quad (11.1)$$

  It points out that radiotherapy increases the threshold for m (see Remark 8.1) in $(1 + r\eta)/(1 - r\eta c) \geq 1$ times compared to m_C. This in particular improves the aforementioned drug action. Equation (11.1) is the very one that can underlie the cumulative-effect analysis.
- Incorporation of a description for explaining the nonquiescent-cell-duplication time θ (e.g., see above) into the PhasTraM model. There are the recent works that can serve as a good starting point (e.g., Hatzimanikatis et al, 1999; Steuer, 2004; Novák and Tyson, 2004).
- Extension of the above cell-AMG system to the case when the cells and AMGs are described with a nonlinear RDE and a generalized kinetic equation, respectively. The generalized-kinetics theory (e.g., Bellomo *et al.*, 2003a) can better allow for the cytokine-relevant scales of the AMG-related phenomena and is more flexible to endow the models with features of "physical biology" Yates (1979).

All the above developments can open a way to such innovative practical tools as early-diagnostics techniques, therapies or drugs for prevention of oncogenic hyperplasia or disintegration of tumors.

APPENDIX A. THE FUNDAMENTAL ROLE OF A POINT HYPERPLASTIC TUMOR IN ONCOGENY AND ITS DEFINITION IN PHYSICAL TERMS

Different sciences can define the same object in different ways. Here is an example of a tumor definition common in medicine.

DEFINITION A.1. (Franks and Teich, Eds., 1997, the first paragraph of Sect. 1.5) "It is not possible to define a tumor cell in absolute way. Tumors are usually recognized by the fact that the cells have shown abnormal growth, so that a reasonably acceptable definition is that tumor cells differ from normal cells in that they are no longer responsive to normal growth-controlling mechanisms. Since there are almost

certainly many different factors involved, the altered cells may still respond to some but not to others. A further complication is that some tumor cells, especially soon after the cells have been transformed from the normal, may not be growing at all. In the present state of knowledge any definition must be 'operational'."

A few factors in this description attract attention. *Firstly*, a tumor cannot be defined in unambiguous way by just listing its features. *Secondly*, in contrast to normal cells, tumor cells do not respond to normal growth-controlling mechanisms and, as a result, grow abnormally. *Thirdly*, this nonresponsiveness is not a distinguishing feature since some tumor cells may respond to the above mechanism whereas some nontumor cells may be nonresponsive. *Fourthly*, the abnormal growth is not a distinguishing feature either since some tumor cells may not be growing at all, at least for a rather long time. *Fifthly*, the definition of a tumor must be "operational" where the meaning of the latter term is not disclosed thereby leaving a freedom to multiple and, in fact, arbitrary meanings. The five listed singular features of Definition A.1 open a way to the alternative definitions (hopefully "operational"). We suggest one of them below. It is related to the simplest, point hyperplastic tumors.

A.1. Point hyperplastic tumor as the fundamental stage of oncogeny

A point hyperplastic tumor is the first and hence inevitable stage of oncogeny.

REMARK A.1. A hyperplastic tumor is usually a very small, point-like "clump" (cf., Franks and Teich, Eds., 1997, the right column on p. 24) or "lump" (cf., Franks and Teich, Eds. 1997, the left column on p. 330) which are the "dense packing" (e.g., Franks and Teich, Eds., 1997, the right column on p. 361) of tumor cells or the structures where tumor cells are "closely packed" (e.g., Franks and Teich, Eds., 1997, the right column on p. 10). Note, however, that a pathological hyperplastic lesion can sometimes be on the order of centimeters in size.

All (solid) tumors grow from respective hyperplastic "seeds". In this respect, a hyperplastic tumor is the simplest but fundamental stage of oncogeny.

Hyperplasia presents an *increase in the number of cells within a given zone in the course of time*. In general, hyperplasia arises to meet special needs of the body and subside once these needs are met. Hyperplasias are the result of the sustained impact over time of stimulatory influences together with a loss of growth-inhibitory factors that are normally found within or around cells. As long as the loss of inhibition of cell growth is temporary, the capacity for enhanced cell proliferation when necessary has obvious advantages (cf., the regeneration subdomain in Section 8.1). However, if normal cells perform mutational transformations, they can permanently lose their ability to respond to growth-inhibitory factors. The corresponding hyperplasia becomes oncogenic, capable of resulting in a hyperplastic tumor.

A.2. The definition of a point hyperplastic tumor in terms of the volume-scaling method

Within a given zone, i.e. a *bounded* space domain, say, X of volume $V(X)$ which is *finite* due to boundedness of X, an increase of the cell number, say,

$N(t,X)$ is equivalent to an increase in the *average* cell-number *volumetric* density, or the *average* cell concentration,

$$\boldsymbol{n}(t,X) = N(t,X)/V(X). \tag{A.1}$$

In other words,

hyperplasia in X is an increase in concentration (A.1) with time. (A.2)

Since a typical volume of a cell is on the order of tens of cubic micrometers, domain X is microscopic at the very beginning of hyperplasia when it starts to grow from one cell or a few cells. Subsequently, definition (A.2) must be extended to microscopic domain X as well, including the case when it comprises a single cell and, for completeness, even a single *volumeless* particle, i.e. a space point. Indeed, multicomponent fluids are associated with different species (e.g., see the L-component relation (A.4) below), in particular, quite small molecules and, in some cases, also the electrons which are of zero volumes. Luckily, the concentration can be defined rigorously not only as the above nonlocal, integral term $\boldsymbol{n}(t,X)$ but also as a local quantity, the concentration $n = n(t,x)$, i.e. the one associated with arbitrary point x in X. Owing to that, one can define the *point hyperplasia* in the following way

hyperplasia at point x in X is an increase in $n(t,x)$ with time. (A.3)

Compared to (A.2), definition (A.3) is more general since concentration $n(t,x)$ determines number $\boldsymbol{n}(t,X)$ in (A.1), namely, $\boldsymbol{n}(t,X) = \int_X n(t,x)dx/V(X)$.

The above features (A.1)–(A.3) are valid for any hyperplasia, normal or oncogenic. Coming back to a hyperplastic tumor, we note its features in Remark A.1. They mean that the corresponding tumor cells present a community where each cell does not have a room sufficient for normal motion because the volume is (to a considerable extent) occupied by the very bodies of the cells and perhaps other obstacles different from these bodies. Loosely speaking, normal motion of the cells is blocked. Still the cell volume or concentration as well as the influence of the obstacles may vary in time. Physically, a hyperplastic tumor is, in a sharp contrast to normal hyperplasia, a *cluster* (ordered or disordered) of cells (cf., the entry "Presentation" in the article "Cancer", Encyclopædia Britannica Online, 2003). Let us consider this clustering in specific terms, for instance, those typical in common statistical mechanics.

To do that, we consider the L-component fluid ($L \geq 1$) of particles (such as cells or molecules) and denote the concentration of the i th component at time-space point (t,x) with $n_i(t,x)$, $i = 1,...,L$. Let $\upsilon_i(t,x)$ be the volume of the particle in the i th fluid component. Let also $\zeta(t,x) \in (0,1]$ be the ratio of the fraction of the volume occupied by the bodies of the fluid particles to the fraction of the volume unavailable for the particle motion at point (t,x). Then, according to the volume scaling method, or VSM (see the text above (2.1)), quantity

$$F(t,x) = 1 - [\zeta(t,x)]^{-1} \sum_{i=1}^{L} \upsilon_i(t,x)\, n_i(t,x) \tag{A.4}$$

is the *fraction* of the space volume which is available for motion of the fluid particles at point (t,x). Quantity $\zeta(t,x)$ is due to the aforementioned obstacles. More

precisely, it can be a manifestation of various physical or geometrical effects. For instance, it can result from the repulsive interparticle forces. Another example concerning purely geometrical issues (Mamontov and Willander, 2001, p. 217) shows that, if $L = 1$, then $\zeta(t,x) \approx 0.7547$ for the hard spheres occupying the entire physical space. Unlike this, one can apply the approximate value

$$\zeta(t,x) = 1 \tag{A.5}$$

to a fluid formed by highly elastic and freely moving particles (such as red blood cells in blood). In case of a cellular fluid in mammalian tissues, the extracellular matrix contributes to $\zeta(t,x)$. In case of the tumor cells at the angiogenesis stage of oncogeny, $\zeta(t,x)$ is affected by the volume fraction occupied by the blood vessels in the tumor (cf., the data in Table 1 of Akabani *et al.*, 2002).

Fraction (A.4) enables one to easily describe the clustering (see the text between (A.3) and (A.4)) at point x and in the time limit with relation

$$\lim_{t \to \infty} F(t,x) = 0. \tag{A.6}$$

Accordingly, we can modify definition (A.3) to allow for the tumor case as follows.

DEFINITION A.2. A *point hyperplastic tumor* (or a point cluster) is formed at a space point x in the course of oncogeny when the limit relation (A.6) holds.

The notion of a point hyperplastic tumor is a rigorous description of the *clustering* aspect of what is usually known as “small clumps of tumor cells” (Franks and Teich, Eds., 1997, the right column on p. 24).

REMARK A.2. It is well-known that a tumor presents an utmost-concentration, an amorphous-solid-like state of the population of the tumor cells. Definition A.2 formulates that in a concise and unambiguous way. Physically, the populations of tumor cells and nontumor cells present two qualitatively different phases of matter, namely, a high-concentration, solid phase and a low-concentration, fluid phase.

Note, however, that not every system loosely understood in biomedicine as a cluster of cells is a tumor. For instance, mesenchymal tissue is made up of clusters of cells (grouped together but not closely adhered to one another). These normal, nontumor clusters usually do not have the “utmost-concentration” property (A.6) (see also (A.4)). Thus, condition (A.6) is the distinguishing feature of a tumor.

We also stress that expression (A.4) explicitly shows that the fraction $F(t,x)$ depends on all the tissue components at point (t,x). This, in conjunction with (A.6), agrees with the well-known idea (e.g., Franks and Teich, Eds., 1997, the right column on p. 8): “The developed tumor usually consists of a mixed population of cells, which may differ in structure, function, growth potential, resistance to drugs or X-rays, and ability to invade and metastize.”.

REMARK A.3. A dynamic model developed consistently need not involve the assumption that the particle volumes are zero, i.e. $\upsilon_i(t,x) \equiv 0$, $i = 1,\ldots,L$, or, equivalently, $F(t,x) \equiv 1$. However, even if a dynamic model is developed under this assumption, then it can, in the first approximation, be generalized to the nonzero-volume case as follows. According to the VSM, one replaces the concentrations

$n_i(t,x)$ in the model with the *scaled* concentrations $m_i(t,x)$ and complements the model with the corresponding equations, i.e.

$$m_i(t,x) = n_i(t,x)/F(t,x), \qquad i = 1,\ldots,L. \tag{A.7}$$

Importantly, equations (A.4) and (A.7) establish a one-to-one correspondence between $m_1(t,x),\ldots,m_L(t,x)$ and $n_1(t,x),\ldots,n_L(t,x)$.

The recipe in Remark A.3 radically improves the adequacy of even very simple models. We illustrate that in Section 11 and Appendix B.

APPENDIX B. RELATION OF THE CORE AND MINIMAL MODELS TO SHLÖGL'S THEORY OF NON-EQUILIBRIUM PHASE TRANSITIONS OF THE FIRST AND SECOND ORDERS

The treatment in Section 8 enables one to completely analyze the t -dependence of the concentration n, an output characteristic of the core model (see Remark 7.3). This is summarized in Table 3 in terms of (see (3.3) and (7.12))

$$n_C \equiv n_T, \qquad \text{at the ideal state,} \tag{B.1}$$

$$n_C \equiv n_H, \qquad \text{at the brink state,} \tag{B.2}$$

under the assumptions that n_H (i.e. (see (3.3)) m_H), n_C (i.e. (see (7.12)) m_C and (7.22) c), and η are independent of time t .

REMARK B.1. Table 3 presents the simplest picture of hyperplasia-extended homeorhesis. This description is reasonable and expected *in-vivo*.

Importantly, the time dependence of n in Table 3 at $n_C \in (n_H, n_T)$ is *qualitatively* the same as that stressed by Schlögl (1971, $0 \le x \le x_3$ in Fig. 3 where x, $x = x_1$, $x = x_2$ and $x = x_3$ correspond to n, $n = n_H$, $n = n_C$ and $n = n_T$, respectively). Moreover, the proposed phase-transition-aware core model (see Remark 7.3) is of the Schlögl type.

Indeed, substituting (2.7), (3.3) and (7.12) into (7.29), one obtains the following ODE for n

$$\partial n/\partial t = \varphi(n), \qquad t > 0, \tag{B.3}$$

where (cf., Line 12 of Table 2)

$$\varphi(n) = -\frac{1}{\eta}\,\frac{n_T\,(n-n_H)(n-n_C)(n-n_T)}{(n_T-n_H)[c(n_T-n_C)n + n_C(n_T-n)]}. \tag{B.4}$$

The corresponding initial condition is (3.7). At the generic state, function (B.4) has *two* (exponentially) *stable* roots (see Lines 1 and 5 of Table 3) separated by *one unstable* root (see Line 3 of Table 3). This is qualitatively the very same picture as that described by Schlögl (1972, the text between (10.2) and (10.3)) in connection with a *first*-order non-equilibrium (and, thus, nonstationary) phase transition (NEPT) (see also (9.35) and Sect. 9.3 of Haken, 1977, or (11.47) and Sect. 12.C of Reichl, 1998). Subsequently, according to Schlögl's theory (1972, Sect. 3), dependence (B.4) in the generic state corresponds to the above transition that is noted in Line

1 of Table 4.

Function φ at the ideal or brink state is a particular case of (B.4). Indeed, expression (B.4) in the case of (B.1) becomes

$$\varphi(n) = -[(1/\eta)/(n_T - n_H)](n - n_H)(n_T - n), \quad \text{at the ideal state.} \quad \text{(B.5)}$$

This function has *one* (exponentially) *stable* root (see Line 1 of Table 3) and *one unstable* root (see Line 5 of Table 3) that corresponds to Schlögl's picture of a *second*-order NEPT (see Schlögl, 1972, Sect. 2; Haken, 1977, the text on (9.8), (9.9) and (9.14); Gardiner, 1994, Sect. 8.3.3). This is noted in Line 2 of Table 4.

In the case of (B.2), expression (B.4) becomes

$$\varphi(n) = -\frac{1}{\eta}\frac{n_T(n - n_H)^2(n - n_T)}{(n_T - n_H)[c(n_T - n_H)n + n_H(n_T - n)]}, \quad \text{at the brink state.} \quad \text{(B.6)}$$

This function has *one* (exponentially) *stable* root (see Line 5 of Table 3) and *one unstable* root (see Line 1 of Table 3) that, similarly to the ideal state (see above), qualitatively corresponds to the aforementioned Schlögl picture of a *second*-order NEPT. This is highlighted in Line 3 of Table 4. Note that the roots which are stable and unstable in case of (B.6) are, on the contrary, unstable and stable, respectively, in case of (B.5).

Thus, the initial-value problem (B.3), (B.4), (3.7) which is equivalent to the core model (see Remark 7.3) includes *both* first- *and* second-order-NEPT readings developed by Schlögl. This is summarized in Table 4.

Remarkably, all the above advantages are achieved owing solely to Definition A.2 (rather than Definition A.1) and VSM, in particular, Remark A.3.

REMARK B.2. Physically, hyperplasia can be regarded as a first- or second-order NEPT. Each of them is described with Schlögl's theory. The fact that the Schlögl-type core model (see Remark 7.3) originates from the interpolation (7.1), (7.2) (resulting from its particular cases (3.4) and (6.1)) confirms that this interpolation is highly relevant and viable.

Another advantage of the present model is emphasized in the following remark.

REMARK B.3. Schlögl (1972) applies a quadratic and cubic dependences for function φ in his theories of NEPTs of a first and second orders respectively. Our function (B.4) not only allows for both the Schlögl theories but also is less schematic than the above quadratic and cubic dependences. For instance, Schlögl's cubic dependence is noted as a considerable problem (e.g., Haken, 1977, the discussion on p. 291 on the dependence (9.136)). In contrast to this, function (B.4) follows from the interpolation stressed in Remark B.2.

The corresponding diffusion-aware generalization is associated with RDE (10.6). Indeed, this equation under condition (2.7) is a RDE of the Schlögl type (Schlögl, 1972, Sect. 3) (see also Haken, 1977, Sect. 9.3). Indeed, substitution of (2.7) into (10.6) and allowing for (2.2) and (7.12) gives RDE

$$\partial n/\partial t = D\nabla^{\mathrm{T}}\nabla n + [2D/(n_T - n)](\nabla n)^{\mathrm{T}}(\nabla n) + \varphi(n)\big|_{n=n_C},$$

$$x \in \mathbb{R}^3,\ t > 0, \quad \text{(B.7)}$$

where $\varphi(n)$ is analyzed above (see the text on (B.4)–(B.6)). In view of the features of φ and the transitions in Table 4, RDE (B.7) (equivalent to (10.6)), includes *both* first- *and* second-order-NEPTs developed by Schlögl. If, in any of the cases (B.4)–(B.6), one neglects the *second* term on the right-hand side of RDE (B.7), then RDE (B.7) is the well-known Schlögl RDE (see Schlögl, 1972, (4.1) or Haken, 1977, (9.28) for a first-order NEPT; Gardiner, 1994, (8.3.63) for a second-order NEPT) modified with (7.12). The neglected term results from allowing for the nonzero volume υ of a cell by means of (2.4) and (2.5).

The Schlögl RDE for a first- or second-order NEPT is well known in physics and chemistry as one of the key models. The literature on this topic includes hundreds of works. To mention a few, we point out Albano (*et al.*, 1984) and Reichl (1998, Sect. 12.C). It is, however, much less known in biomedicine. The present work is the first one where the Schlögl-type model is proposed for the hyperplasia-extended homeostasis and, moreover, homeorhesis.

APPENDIX C. THE TIME-SLICE METHOD FOR SOLVING THE CAUCHY PROBLEM FOR THE PHASTRAM RDE

Problem (10.6), (3.5) is the Cauchy one and therefore is formulated in the entire space $\mathbb{R}^3$. The latter feature noticeably complicates a numerical solving. The corresponding purely numerical techniques (such as the finite-difference or finite-element methods) are quite time-consuming. The multiple analysis, the core of computer-assisted research and design, requires much longer computing time. Along with this, it is desirable to implement this analysis on common computers, those of modest computing capabilities, such as notebooks. There are many users interested in a mobile and affordable computing: students, teachers, biomedical researchers, and engineers at the pharmaceutical industry, among others.

The above issues draw attention to *analytical-numerical* approaches (e.g., Mamontov and Willander, 2001, Ch. 8) rather than the purely numerical ones. An example is considered in the present appendix that proposes the analytical-numerical method to solve the Cauchy problem (10.6), (3.5).

As it is noted in the text above (10.9), if one replaces m in the coefficient in front of $m - m_H(t)$ in RDE (10.6) with initial value $m_o(x)$, the resulting version of (10.6) is

$$\partial[\overline{m} - m_H(t,x)]/\partial t = D\,\nabla^{\mathrm{T}}\nabla[\overline{m} - m_H(t,x)]$$
$$+ \frac{1}{\eta(t,x)}\,\frac{m_0(x) - m_C(t,x)}{c(t,x)\,m_0(x) + m_C(t,x)}\,[\overline{m} - m_H(t,x)], \quad x \in \mathbb{R}^3,\ t > 0, \quad \text{(C.1)}$$

where, according to Mamontov (*et al.*, 2005), parameters η, c (see (7.25)), and m_C (see (7.22)) generally depend on (t,x), i.e. $\eta = \eta(t,x)$,

$$c(t,x) = \theta(t,x)/[\ln 2\ \eta(t,x)] \in [1,3), \quad m_C(t,x) = \frac{c(t,x)\,[1 + c(t,x)]}{3 - c(t,x)}\,m_H(t,x).$$

This equation is *linear in* $\overline{m}$. By analogy with the linear RDE (10.7) and its solution (10.8) with initial condition (3.5), expression (10.9) is the *linearization*-based approximation to the solution of the Cauchy problem (C.1), (3.5) for *all* $t > 0$. Along with this, as it is well known, linearizations of nonlinear evolution equations are generally inaccurate. For this reason, approximation (10.9) is noted as semi-qualitative (see the paragraph above Remark 10.3).

To eliminate the mentioned difficulties, one can apply the time linearization to (10.6) in a sequence of reasonably small intervals $(t_{k-1}, t_k]$ where $t_k > t_{k-1}$, $k = 1,2,\ldots$ This leads to the following sequence of approximations

$$\partial[\overline{m}_k - m_H(t,x)]/\partial t = D\,\nabla^{\mathrm{T}}\nabla[\overline{m}_k - m_H(t,x)] + [\eta(t,x)]^{-1}$$

$$\times \frac{[\overline{m}_{k-1}(t_{k-1},x) - m_C(t,x)][\overline{m}_k - m_H(t,x)]}{c(t,x)\,\overline{m}_{k-1}(t_{k-1},x) + m_C(t,x)}, \quad t \in (t_{k-1}, t_k],\ x \in \mathbb{R}^3,\ k = 1,2,\ldots \tag{C.2}$$

where the (t,x)-domain $(t_{k-1}, t_k] \times \mathbb{R}^3$ can be regarded as a *time slice* of the entire space $\mathbb{R}^3$. The corresponding initial conditions are

$$\lim_{t \downarrow t_{k-1}} \overline{m}_k(t,x) = \overline{m}_{k-1}(t_{k-1},x),\ \overline{m}_0(t,x) \equiv m_0(x),\ x \in \mathbb{R}^3,\ k = 1,2,\ldots \tag{C.3}$$

Functions $\overline{m}_k(\cdot,\cdot)$ in (C.2) or (C.3) are approximations on the time slice $(t_{k-1}, t_k] \times \mathbb{R}^3$ for solution $m(\cdot,\cdot)$ of the Cauchy problem (10.6), (3.5). If scalars

$$G_k(t_{k-1},t,x) = \exp\left[\int_{t_{k-1}}^{t} \frac{1}{\eta(s,x)} \frac{\overline{m}_{k-1}(t_{k-1},x) - m_C(s,x)}{c(s,x)\,\overline{m}_{k-1}(t_{k-1},x) + m_C(s,x)}\,ds\right],$$

$$(t,x) \in (t_{k-1}, t_k] \times \mathbb{R}^3,\ k = 1,2,\ldots, \tag{C.4}$$

are independent of x, then (e.g., Freidlin and Wentzell, 1998, p. 38) the solutions of the initial-value problems in (C.2), (C.3) are

$$\overline{m}_k(t,x) = m_H(t,x) + F_k(t_{k-1},t,x)\,G_k(t_{k-1},t,x),$$

$$(t,x) \in (t_{k-1}, t_k] \times \mathbb{R}^3,\ k = 1,2,\ldots, \tag{C.5}$$

where

$$F_k(t_{k-1},t,x) = \int_{\mathbb{R}^3} \Phi(t - t_{k-1}, x - y)\,\overline{m}_{k-1}(t_{k-1},y)\,dy - m_H(t,x),$$

$$(t,x) \in (t_{k-1}, t_k] \times \mathbb{R}^3,\ k = 1,2,\ldots. \tag{C.6}$$

(see the text below (10.8)) for function Φ). However, the scalars (C.4) generally depend on x. Thus, one has to take into account not only the above linearization error associated with the time-slice Cauchy problems (C.2), (C.4) but also the error caused by the spatial inhomogeneity. For this reason, we will find out what the corresponding error is and how it can be reduced. The expression for the error is derived below.

Since the scalars (C.6) are the solutions of the Cauchy problems

$$\partial F/\partial t = D\,\nabla^{\mathrm{T}}\nabla F, \qquad (t,x) \in (t_{k-1}, \infty) \times \mathbb{R}^3,\ k = 1,2,\ldots,$$

$$\lim_{t\downarrow t_{k-1}} F = \overline{m}_{k-1}(t_{k-1},x) - m_H(t_{k-1},x), \qquad x\in\mathbb{R}^3,\ k=1,2,\dots\ ,$$

the approximations (C.5) can be expressed as

$$\frac{\partial \overline{m}_k}{\partial t} = D\,\nabla^{\mathrm{T}}\nabla\overline{m}_k + \frac{1}{\eta(t,x)}\,\frac{\overline{m}_k - m_C(t,x)}{c(t,x)\,\overline{m}_k + m_C(t,x)}\,[\overline{m}_k - m_H(t,x)] - E_k(t,t_{k-1},x),$$

$$t\in(t_{k-1},t_k],\ x\in\mathbb{R}^3,\ k=1,2,\dots\ , \qquad \text{(C.7)}$$

where the approximation error $E_k(t,t_{k-1},x)$ on the kth time slice is

$$E_k(t,t_{k-1},x) = \frac{[\overline{m}_k - m_H(t,x)]}{\eta(t,x)}\left[\frac{\overline{m}_k - m_C(t,x)}{c(t,x)\,\overline{m}_k + m_C(t,x)} - \frac{\overline{m}_{k-1}(t_{k-1},x) - m_C(t,x)}{c(t,x)\,\overline{m}_{k-1}(t_{k-1},x) + m_C(t,x)}\right]$$

$$+ D\left\{F_k(t_{k-1},t,x)\,\nabla^{\mathrm{T}}\nabla G_k(t_{k-1},t,x) + 2\,[\nabla F_k(t_{k-1},t,x)]^{\mathrm{T}}\,\nabla G_k(t_{k-1},t,x)\right\},$$

$$t\in(t_{k-1},t_k],\ x\in\mathbb{R}^3,\ k=1,2,\dots\ , \qquad \text{(C.8)}$$

and the initial conditions are described with (C.3). On the right-hand side of (C.8), the first term is the error due to the linearization at the time slice whereas the second term is the error due to the x-dependence of (C.4). If $E_k(t,t_{k-1},x)\equiv 0$, $k=1,2,\dots$, then the entire set of problems (C.7), (C.3) coincides with problem (10.6), (3.5). The way to making $E_k(t,t_{k-1},x)$ smaller is noted below.

It follows from (C.3) and (C.4) that $E_k(t,t_{k-1},x) = O(t-t_{k-1})$, $t\in(t_{k-1},t_k]$, $x\in\mathbb{R}^3$, $k=1,2,\dots$ Subsequently, the approximation error $E_k(t,t_{k-1},x)$ on the kth time slice can be reduced by decreasing the slice duration $h_k = t_k - t_{k-1}$ (or the time-discretization-step length). This points out that *analytical* results (C.5) which can generally be implemented *numerically* do present an approximate *method* to solve the Cauchy problem (10.6), (3.5) where η, c, and m_C depend on (t,x). We term this *analytical-numerical* method the *time-slice method*. A practical technique to estimate $E_k(t,t_{k-1},x)$ and to provide an automatic choice of h_k depending on k is developed by Psiuk-Maksymowicz and Mamontov (2005) who also report the corresponding numerical-simulation results.

Compared to purely numerical techniques, the key advantage of the proposed analytical-numerical method is that an *explicit* analytical expression (C.5) can be implemented without numerically solving a system of nonlinear equations for m at the time-space-discretization point. Thus, the amount of computations and robustness of the algorithms are expected to be less and higher, respectively.

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Table 1. Input parameters of the PhasTraM model (see Remark 10.2) including those of the core model (see Remark 7.3)

	Parameter	Meaning of parameter	Interval of values
1	ζ	ratio of the fraction of the volume occupied by the bodies of the cellular and extracellular fluids to the fraction of the volume unavailable for motion of the cells	$(0,1]$
2	ϕ	fraction of the volume occupied by the bodies of the extracellular-fluid particles	$(0,\zeta)$
3	υ	volume of a cell	$(0,\infty)$
4	n_H	homeorhetic (homeostatic, if it is t -independent) value of n; $n_H = n_H(t,x)$ in Section 3 and below it	(3.1)
5	$n_0(\cdot)$	initial function for n, i.e. the one providing the value of n at the initial time point $t = 0$	(3.7)
6	η	ideal-homeorhesis lifetime of a cell under the FFT condition in (2.9); generally $\eta = \eta(t,x)$	$(0,\infty)$
7	θ	duplication time of a cell at the HT/NQ asymptote (6.1) under the FFT condition in (2.9) (see Remark 6.1); generally $\theta = \theta(t,x)$	$(0,\infty)$
8	s	quantum-spin number of a cell; a cell is considered as a composon since it is a highly complex system	$[0,\infty)$
9	T	absolute temperature of the cellular fluid; is assumed to be equal to that of the host	$(0,\infty)$ and (10.2), (10.3)
10	M	mass of a cell	$(0,\infty)$
11	τ	relaxation time of the momentum of a cell in the cellular fluid due to the collisions of the cell with the extracellular fluid	(10.5)

Table 2. The main auxiliary parameters and functions of the PhasTraM model (see Remark 10.2) including those of the core model (see Remark 7.3)

	Parameter	Meaning of parameter or function	Interval of values
1	m	scaled concentration (2.7) of the cellular fluid (see also the shifted-MB-statistics-validity criterion (10.3))	$[0,\infty)$
2	f	(2.6); see Lines 1 and 2 of Table 1 for ζ and ϕ in (2.6) respectively	$(0,1]$
3	v	(2.5); see Lines 1 and 3 of Table 1 for ζ and υ in (2.5) respectively	$(0,\infty)$
4	n_T	(2.4); see Lines 1 and 2 of this table for f and v in (2.4); by virtue of (2.2) and Definition A.2, n_H is the value of the cellular-fluid concentration n at the hyperplastic-tumor state	$(0,\infty)$
5	m_H	(3.3); homeorhetic (homeostatic, if it is t -independent) value of m (see Line 1 of this table)	$[0,\infty)$
6	m_0	(3.6); initial value of m, i.e. its value at the initial time point $t=0$ (cf., (3.5)); m_0 is a function, $m_0(\cdot)$	$[0,\infty)$
7	a	(3.8)	$(0,\infty)$
8	b	(6.2)	$(0,\infty)$
9	m_*	(7.10); the median value of m; the median of the distribution corresponding to density (7.9)	$(0,\infty)$
10	n_C	(7.12); critical value of n	(7.13)
11	m_C	(7.22); the critical value of m	(7.11)
12	φ	(B.4); the biochemical-reaction-rate function of n in ODE (B.3)	$(-\infty,\infty)$
13	N	(10.2); characteristic scaled concentration of the cellular fluid	$(0,\infty)$
14	D	(10.4); diffusion parameter of the cellular fluid	(10.5)

Table 3. Behavior of the cellular-fluid concentration n according to the core model (see Remark 7.3) when all the parameters in ODE (B.3), (B.4) are independent of t

	Point or domain of the *generic* state	Time behavior of the cellular-fluid concentration n	Condition for n_0 *equivalent* to the behavior in the column to the left
1	Homeorhesis point	$n \equiv n_H$; this state is unstable from above at the brink state (B.2)	$n_0 = n_H$
2	Homeorhesis domain	Concentration n tends from n_0 to n_H strictly monotonically	$0 \le n_0 < n_C$
3	Critical point	$n \equiv n_C$; this state is unstable at $n_H < n_C$ and unstable from above in case of (B.2)	$n_0 = n_C$
4	Hyperplastic domain	Concentration n strictly monotonically increases from n_0 to n_T and exponentially tends to n_T	$n_C < n_0 < n_T$
5	Hyperplastic-tumor point	$n \equiv n_T$; this state is unstable from below at the ideal state (B.1)	$n_0 = n_T$

Table 4. Unification of Schlögl's theories of first- and second-order non-equilibrium phase transitions by function φ (see (B.4)) in the cases considered in Table 3.

	State of the cellular fluid	Expression for φ	Roots of function φ	Phase transition
1	Generic	(B.4)	$0 < n_H < n_C < n_T$: $n = n_H$ – stable, $n = n_C$ – unstable, $n = n_T$ – stable	first-order
2	Ideal (see (B.1))	(B.5), the case of (B.4) when $n_C \uparrow n_T$	$0 < n_H < n_C = n_T$: $n = n_H$ – stable, $n = n_C = n_T$ – unstable	second-order
3	Brink (see (B.2))	(B.6), the case of (B.4) when $n_C \downarrow n_H$	$0 < n_H = n_C < n_T$: $n = n_H = n_C$ – semistable (stable from below, unstable from above), $n = n_T$ – stable	second-order

Image of Figure 1

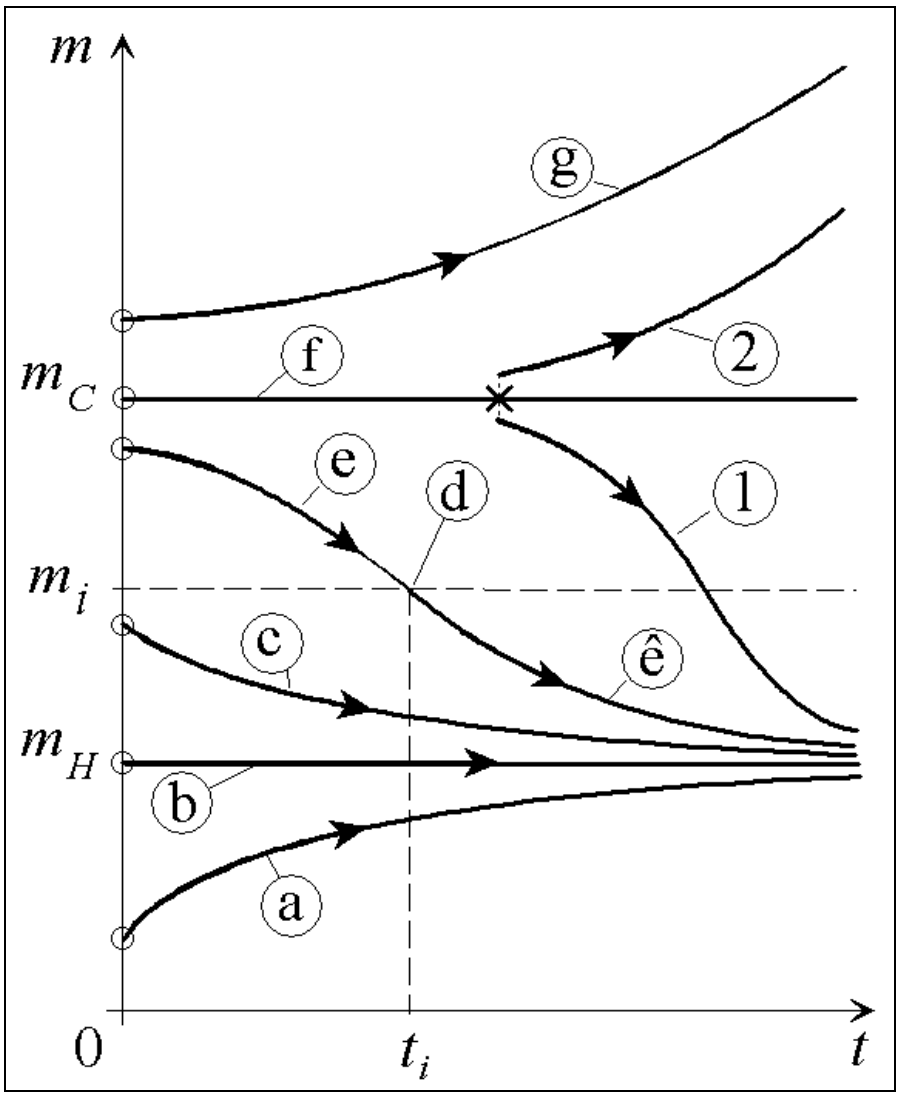

Figure 1

Image of Figure 2

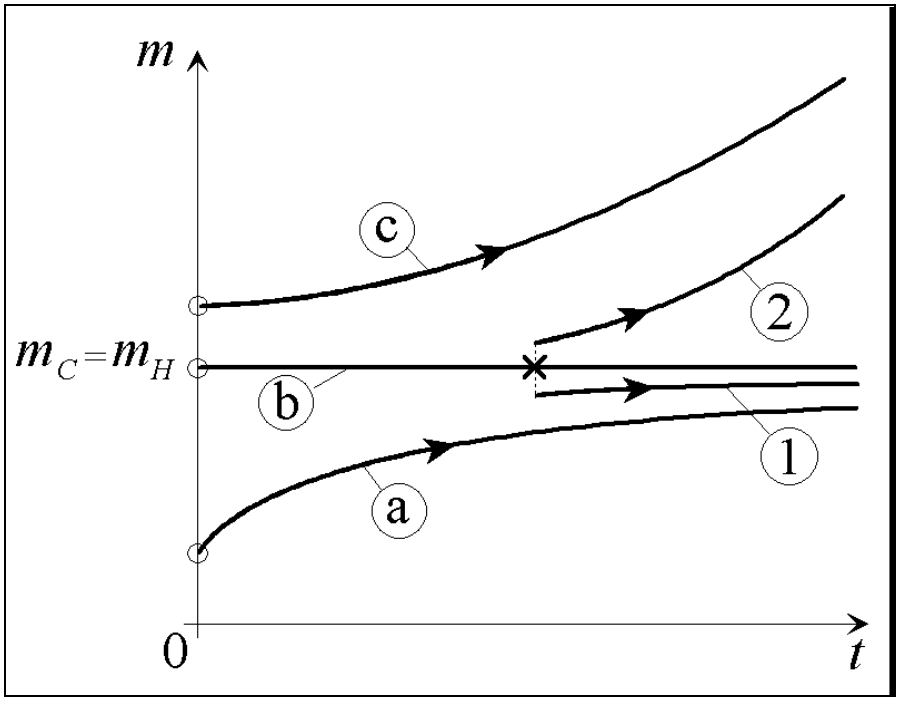

Figure 2

Image of Figure 3

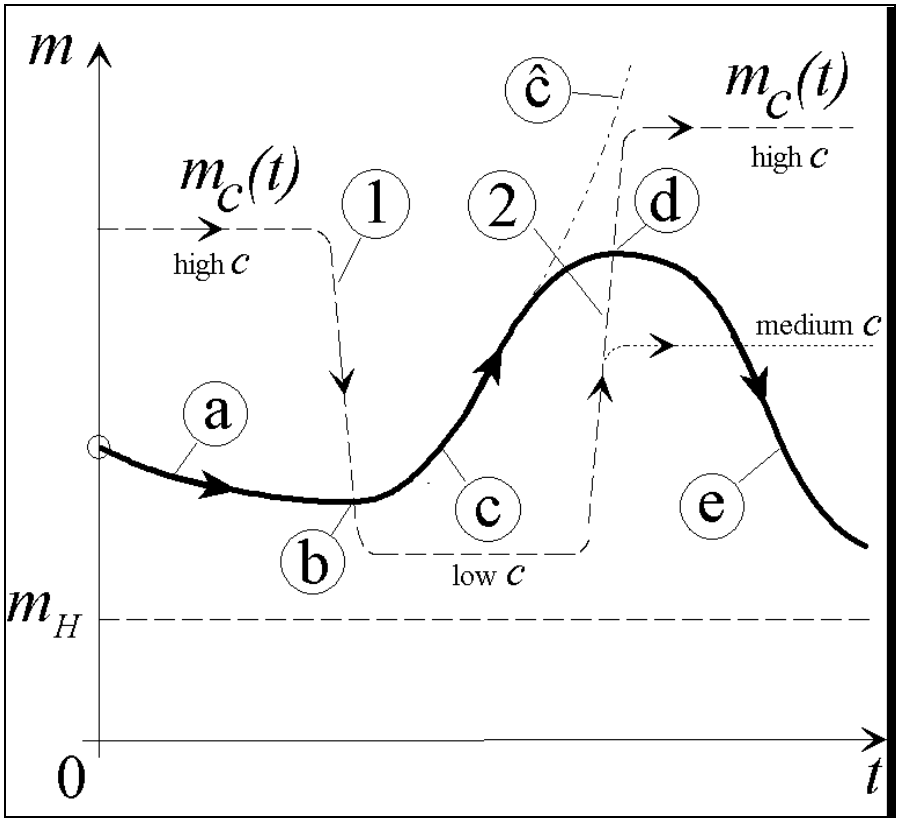

Figure 3

Figure Captions

Figure 1. Qualitative t -dependences of solutions of equation (7.29) at the generic state (see Section 8.1) when all parameters of the equation are independent of t . The signs "○" denote the corresponding values of m_0.

The domains of the generic state are exemplified and specified with the following curves and points: **(a)–(e)** — the homeorhesis domain, $m \in (0, m_C)$; **(f)** — the critical point $m \equiv m_C$ which is the unstable equilibrium point of ODE (7.29); the instability (in the case of a sudden deviation of m from m_C at the point denoted with the sign "×") is outlined with options **(1)** and **(2)**; **(g)** — the oncogenic-hyperplasia domain $m \in (m_C, \infty)$.

The homeorhesis-domain subdomains are exemplified and specified with the following curves and points: **(a)** — the regeneration subdomain, $m \in (0, m_H)$; **(b)** — the homeorhesis point $m \equiv m_H$ which is the exponentially stable equilibrium point of ODE (7.29); **(c)–(e)** — the inflammation subdomain, $m \in (m_H, m_C)$.

The inflammation-subdomain regions are exemplified and specified with the following curves and points: **(c)** and **(ê)** — the acute-inflammation region, $m \in (m_H, m_i)$; **(d)** — the inflexion point $(t_i(m_o), m_i)$ (see (7.20) for m_i); **(e)** — the chronic-inflammation region, $m \in (m_i, m_C)$, entering the acute-inflammation region with behavior **(ê)**.

Figure 2. Qualitative t -dependences of solutions of equation (7.29) at the brink state (see Section 8.2) (i.e. at $m_C = m_H$) when all parameters of the equation are independent of t . The signs "○" denote the corresponding values of m_0.

The domains of brink state are exemplified and specified with the following curves and points: **(a)** — the regeneration domain, $0 < m < m_H = m_C$; **(b)** — the point which is both the homeorhesis one and the critical one, i.e. $m \equiv m_H = m_C$; it is the semi-stable equilibrium point of ODE (7.29); specifically, it is asymptotically stable from below and unstable from above; this feature (in the case of a sudden deviation of m from line $m \equiv m_H = m_C$ at the point denoted with the sign "×") is outlined with options **(1)** and **(2)**; **(c)** — the oncogenic-hyperplasia domain, $m_H = m_C < m < \infty$.

Figure 3. Qualitative t -dependence of solutions of equation (7.29) and critical scaled concentration m_C at the generic state according to the scenario described in Section 9. The values of c are coupled with those of m_C with equality (7.22). The sign "○" denotes the initial value m_0 of m.

The generic state is exemplified and specified with the following curves and points: **(a)** — the inflammation subdomain of the homeorhesis domain at the generic state (similar to **(c)–(e)** in Figure 1) where *inflammation relaxes from chronic to acute*; **(b)** — the point of the intersection of the decreasing m and m_C; it is the point of a local minimum of m and corresponds to acute inflammation (since m is strictly convex); the point indicates both the *birth of hyperplasia* and the *beginning of the inflammation intensification from acute to chronic*; **(c)** — the oncogenic-hyperplasia domain (similar to **(g)** in Figure 1) where *inflammation intensifies from acute to chronic*; **(ĉ)** — the version of the behavior **(c)** of m corresponding to the dotted-line version of the behavior of m_C; **(d)** — the point of the intersection of the increasing m and m_C; it is the point of a local maximum of m and (since m is strictly concave) corresponds to chronic inflammation; the point indicates both the *death of hyperplasia* and the *peak of chronic inflammation*, i.e. the *beginning of the inflammation relaxation from chronic to acute*; **(e)** — the inflammation behavior similar to that in the above case **(a)**; **(1)** — a fast decrease in m_C due to the genotoxic events decreasing c via decrease in θ (see (7.25)); **(2)** — a fast and *high* (or *medium* — the dotted line) increase in m_C due to the immune surveillance, pharmacotherapeutic actions, radiotherapy, or other relevant factors that increase c by increasing θ. Remark 9.1 stresses certain features of the above behavior.