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MATHEMATICAL MODELS OF TUMOR GROWTH SYSTEMS

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Abstract. We study a class of parabolic-ODE systems modeling tumor growth, its mathematical modeling and the global in time existence of the solution obtained by the method of Lyapunov functions.

Keywords: tumor growth modeling, mean field theory, parabolic-ODE system, global-in-time existence, chemotaxis

MSC 2010: 35K57

1. Introduction

The process of tumor growth is observed both in upper and lower levels of cells, that is organs, tissues, cells, sub-cells, organelles, proteins, and DNA's. Besides, there are several stages such as mutation, invasion, angiogenesis, metastasis, and so forth. Two aspects are thus noted in tumor growth, that is the hierarchy of materials and the stage of events. Mathematical models using partial and ordinary differential equations may be, in both contexts, meso-scaled. These models take the role in the collaboration between mathematics and medicine, for example, hybrid simulation using discrete and continuous models [3], [4], [26]. The meso-scopic modeling is to be balanced between coarsing and precision processes and also between the first principles and experimental data. There may be two approaches, top down and bottom up modelings. In the top down modeling, one picks up key factors following several insights obtained by in vitro-in vivo experiments to make up a system of equations. In the bottom up modeling, on the other hand, one uses integrated pathways and the mean field theory.

Here is an example of the top down modeling of cell biology [13] concerning chemotactic features of cellular slime molds:

$$
\begin{aligned}
u_t &= \nabla \cdot (d_1(u,v)\nabla u) - \nabla \cdot (d_2(u,v)\nabla v), \\
v_t &= d_v \Delta v - k_1 v w + k_{-1} p + f(v)u, \\
w_t &= d_w \Delta w - k_1 v w + (k_{-1} + k_2) p + g(v,w)u, \\
p_t &= d_p \Delta p + k_1 v w - (k_{-1} + k_2) p,
\end{aligned} \tag{1}
$$

where $u = u(x,t)$, $v = v(x,t)$, $w = w(x,t)$, and $p = p(x,t)$ stand for the density of cellular slime molds, the concentrations of chemical substances, enzymes, and complices, respectively. The effect of diffusion to each component, u, v, w, and p is thus counted, while the last terms on the right-hand side of the first, the second and the third equation totally indicate the self-interaction between the chemotactic profile of u toward v and the creations of (v,w) by u. The rest factor is the ODE part of the last three equations,

$$
\begin{aligned}
v_t &= -k_1 v w + k_{-1} p, \\
w_t &= -k_1 v w + (k_{-1} + k_2) p, \\
p_t &= k_1 v w - (k_{-1} + k_2) p
\end{aligned}
$$

describing the chemical reaction between v, w, and p. More precisely, this chemical reaction is coarsed as

$$
V + W \underset{(k_{-1})}{\overset{(k_1)}{\rightleftarrows}} P \xrightarrow{(k_2)} W + (\text{a product}) \tag{2}
$$

where Michaelis-Menten's enzyme kinetics is used for further simplication, assuming quasi-staticity, $k_1 v w - (k_{-1} + k_2) p = 0$ and material closedness, $w + p = c$. System (1) is then reduced to

$$
\begin{aligned}
u_t &= \nabla \cdot (d_1(u,v)\nabla u) - \nabla \cdot (d_2(u,v)\nabla v), \\
v_t &= d_v \Delta v - k(v)v + f(v)u
\end{aligned} \tag{3}
$$

using

$$
k(v) = \frac{c k_1 k_2}{(k_{-1} + k_2) + k_1 v}.
$$

Later, [21] assumed that $d_1(u,v)$, $k(v)$, $f(v)$ are constant and $d_2(u,v) = u\chi'(v)$. It is

$$
\begin{aligned}
u_t &= d_u \Delta u - \nabla \cdot (u \nabla \chi(v)), \\
v_t &= d_v \Delta v - b_1 v + b_2 u
\end{aligned} \tag{4}
$$

where $\chi'(v)$ stands for the sensitivity function. Then a simplified system was introduced by [6], [12] using the constant sensitivity function and the parabolic-elliptic system

$$
\begin{aligned}
u_t &= \nabla \cdot (\nabla u - u \nabla v), \\
-\Delta v &= u - \frac{1}{|\Omega|} \int_\Omega u \qquad \text{in } \Omega \times (0,T), \\
\frac{\partial u}{\partial \nu} - u \frac{\partial v}{\partial \nu} &= \frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T), \\
\int_\Omega v &= 0,
\end{aligned} \tag{5}
$$

where $\Omega \subset \mathbb{R}^N$ is a bounded domain with smooth boundary $\partial\Omega$ and ν is the outer normal vector.

At this stage, conversely, we observe several key factors of (5) from the macroscopic point of view. In fact, the first equation indicates mass conservation

$$u_t = -\nabla \cdot j \tag{6}$$

with

$$j = -\nabla u + u \nabla v \tag{7}$$

standing for the flux of u. Thus the null flux boundary condition is imposed in (5) which guarantees the total mass conservation

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega u = 0.$$

In the flux j of (7), the chemical v stands for the carrier of the cells u. The diffusion $-\nabla u$ is thus competing the chemotaxis $u \nabla v$ following the phenomenological relation. The second equation of (5), on the other hand, describes a coarsed process of the creation of the chemical potential ∇v from the particle density u using the Poisson equation. System (5) is provided also with a kinetic-transport profile. In fact, Newton's equation of motion

$$\frac{\mathrm{d}x}{\mathrm{d}t} = v, \qquad m \frac{\mathrm{d}v}{\mathrm{d}t} = F \tag{8}$$

is a characteristic equation of the transport equation

$$\frac{\partial \varrho}{\partial t} + \nabla_x (v \cdot \varrho) + \frac{F}{m} \cdot \nabla_v \varrho = 0 \tag{9}$$

so that if $(x, v) = (x(t), v(t))$ and $\varrho = \varrho(x, v, t)$ are solutions to (8) and (9), respectively, then it holds that

$$\frac{\mathrm{d}}{\mathrm{d}t}\varrho(x(t), v(t), t) = 0$$

and hence $\varrho(x, v, t)\,\mathrm{d}x\,\mathrm{d}v$ is regarded as a particle density in the x-v space with

$$u(x,t) = \int \varrho(x, v, t)\,\mathrm{d}v,$$
$$V(x,t) = \frac{1}{u(x,t)}\int \varrho(x, v, t)v\,\mathrm{d}v$$

standing for the particle density and the mean velocity. Mass conservation (6) thus reads

$$\frac{\partial u}{\partial t} + \nabla\cdot(uV) = 0,$$

and, therefore, (7) implies

$$V = -u^{-1}j, \qquad j = -\nabla\log u + \nabla v.$$

We have, actually, several bottom up modelings and system (5) is nothing but a Smoluchowski-Poisson equation formulated in the transport and kinetic theories. In the transport theory used in semi-conductor physics and high-molecular chemistry, a master equation concerning the particle density p,

$$\begin{aligned} p_t(x, t \mid x_1, t_1) = & -\int \mathrm{d}x' W(x \to x')p(x, t \mid x_1, t_1) \\ & + \int \mathrm{d}x' W(x' \to x)p(x', t \mid x_1, t_1), \end{aligned}$$

is used following Chapman-Kolmogorov's relation. Then the Kramers-Moyal expansion

$$p_t(x, t \mid x_1, t_1) = \sum_{k=1}^{\infty}\frac{1}{k!}(-\partial_x)^k C_k(x)p(x, t \mid x_1, t_1),$$
$$C_k(x) = \int W(x \to x + y)y^k\,\mathrm{d}y = \lim_{\Delta t\to 0}\frac{1}{\Delta t}\big\langle[x(t + \Delta t) - x(t)]^k\big\rangle_{x(t)=x}$$

arises with Taylor's expansion formula where the Langevin equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = v, \qquad m\frac{\mathrm{d}v}{\mathrm{d}t} = -m\gamma v + R(t) + mF(x)$$

determines the moments C_k, $k = 0, 1, 2$. The Kramers equation

$$\frac{\partial}{\partial t}P(x, v, t \mid x_1, v_1, t_1) = \Big[-\frac{\partial}{\partial x}v + \frac{\partial}{\partial v}(-F(x) + \gamma v) + \frac{D}{m^2}\frac{\partial^2}{\partial v^2}\Big]P(x, v, t \mid x_1, v_1, t)$$

thus comes which takes two adiabatic limits, the Fokker-Planck equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial v}\Big[- F + \gamma v + \frac{D}{m^2}\frac{\partial}{\partial v}\Big]p$$

and the Smoluchowski equation

$$\frac{\partial f}{\partial t} = \frac{1}{\gamma m}\frac{\partial}{\partial x}\Big(- Kf + kT\frac{\partial f}{\partial x}\Big)$$

according to the typical status of (x, v). In the kinetic theory used in astrophysics, on the other hand, the Smoluchowski-Poisson equation is derived as a fluid dynamical limit of the mean field of many self-interacting particles. It uses the kinetic equation for the particle density $f = f(x, v, t)$,

$$f_t + v \cdot \nabla_x f - \nabla\varphi \cdot \nabla_v f = -\nabla_v \cdot j$$

where $-\nabla_v \cdot j$ and φ stand for the general dissipation flux and the potential. Then this j is prescribed by the local maximum entropy production principle so that for each (x, t), f maximizes the local entropy

$$S(x, t) = \int_{\mathbb{R}^N} s(f(x, v, t))\,\mathrm{d}v$$

under the constraint of the particle density homogeneous in the velocity and the pressure:

$$\mu(x, t) = \int_{\mathbb{R}^N} f(x, v, t)\,\mathrm{d}v,$$
$$p(x, t) = \frac{1}{n}\int_{\mathbb{R}^N} |v|^2 f(x, v, t)\,\mathrm{d}v.$$

Averaging f over the velocities $v \in \mathbb{R}^N$ and passing to the limit of large friction or large time imply

$$\mu_t = \nabla[D_* \cdot (\nabla p + \mu\nabla\varphi)],$$
$$\Delta\varphi = \mu,$$
$$p = p(\mu, \theta)$$

where μ and p stand for the particle density and the pressure, respectively. Here the entropy function $s(f)$ is selected subject to the law of partition of macroscopic states of particles into mesoscopic states. Thus the entropies of Boltzmann, Fermi-Dirac, Bose-Einstein, Rény-Tsallis, and so forth arise, while the temperature θ is determined according to the emsembles. Thus $\theta > 0$ is a constant in the canonical setting, while θ is a function of t prescribed by the total energy

$$E = \frac{n}{2}\int_\Omega p\,\mathrm{d}x + \frac{1}{2}\int_\Omega \mu\varphi\,\mathrm{d}x$$

in the micro-canonical setting. The Smoluchowski-Poisson equation then arises with the Boltzmann entropy and the canonical setting [5]. The structure of dual variation and scaling invariance in two-space dimension are due to the above described microscopic profiles, which results in the quantized blowup mechanism [29], [30].

We have described the concept of bottom up and top down modelings. The purpose of the present paper is, actually, two-fold; to approach the events of tumor growth both from mathematical modeling and mathematical analysis. The author expresses his sincere thanks to the referee for several remarks on the references.

2. Mean field approximation

There are several methods how to derive the diffusion equation and its relatives, such as the Smoluchowski equation as a mean field limit of the microscopic state describing the motion of particles. Among them, transport theory uses the master equation concerning mass conservation under the presence of jump processes. We may have two cases, the velocity jump and the space jump [23]. Here [24] is devoted to the latter case assuming that a particle walks on the lattice

$$\mathcal{Z} = \{\dots, -n-1, -n, -n+1, \dots, -1, 0, +1, \dots, n-1, n, n+1, \dots, \}$$

with the probabilities $T_n^{\pm}$ for the transient $n \mapsto n \pm 1$. If $p_n(t)$ denotes the particle density at the site n and the time t, then the master equation arises as

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = T_{n-1}^{+} p_{n-1} + T_{n+1}^{-} p_{n+1} - (T_n^{+} + T_n^{-}) p_n. \tag{10}$$

In the context of biology, it may be reasonable to assume some species to control the transient probability $T_n^{\pm}$. Several cases are proposed concerning the strategy of these control species [22], [20]. In the barrier model, one assumes

$$T_n^{\pm} = T_{n\pm 1/2} = T((n \pm 1/2)\Delta x, t). \tag{11}$$

Since the mean waiting time is given by $(T_n^{+} + T_n^{-})^{-1}$ the constant waiting time

$$T_n^{+} + T_n^{-} = 2\lambda \tag{12}$$

is consistent with (11) if $\pm$ sign is not exclusive. Using the renormalized barrier

$$T_n^{\pm} = \frac{2\lambda T_{n\pm\frac{1}{2}}}{T_{n+\frac{1}{2}} + T_{n-\frac{1}{2}}}$$

and the mean field limit $T_{n\pm1/2} = T((n \pm 1/2)\Delta x, t)$, we obtain the Smoluchowski equation

$$p_t = D\nabla \cdot (\nabla p - p\nabla \log T)$$

as $\Delta x \downarrow 0$ with

$$\lambda(\Delta x)^2 = D, \tag{13}$$

see [24]. Here we note that this D is consistent with the diffusion coefficient prescribed by Einstein's formula

$$\tau = \frac{(\Delta x)^2}{2ND}, \tag{14}$$

where τ, Δx, N, and D are the mean waiting time, the mean jump length, the space dimension, and the diffusion coefficient, respectively. In fact, the right-hand side of (12) is replaced by

$$2N\lambda = \frac{1}{\tau}$$

in N-dimension, and then (13) implies (14).

We may use the master equation concerning the particle density $q(x,t)$ defined for all $x \in \mathbb{R}^N$ and $t > 0$. Let $T(x,t;\omega)$ be the transient probability of the particle toward $\omega \in S^{N-1}$ during the calculation time Δt, where $S^{N-1} = \{\omega \in \mathbb{R}^N : \ |\omega| = 1\}$. In the simplest case when the particle takes the constant jump length Δx, the master equation arises with

$$\begin{aligned} q(x,t+\Delta t) - q(x,t) = &\int_{S^{N-1}} T(x+\omega\Delta x, t; -\omega) q(x+\omega\Delta x, t)\,\mathrm{d}\omega \\ &- \int_{S^{N-1}} T(x,t;\omega)\,\mathrm{d}\omega \cdot q(x,t) \end{aligned} \tag{15}$$

and the mean waiting time τ is reformulated by

$$\frac{1}{\Delta t}\int_{S^{N-1}} T(x,t;\omega)\,\mathrm{d}\omega = \tau^{-1}. \tag{16}$$

We assume that the right-hand side of (16) is independent of (x,t) and define the diffusion coefficient D by (14). In the simplest case when $T(x,t;\omega)$ is a constant denoted by T, it follows from (14) and (16) that

$$\frac{T}{\Delta t}|S^{N-1}| = \frac{2ND}{(\Delta x)^2}.$$

Then the master equation (15) is reduced to

$$\frac{1}{\Delta t}\{q(x,t+\Delta t)-q(x,t)\} = \frac{T}{\Delta t}\int_{S^{N-1}} q(x+\omega\Delta x,t)-q(x,t)\,\mathrm{d}\omega \tag{17}$$
$$= \frac{2ND}{|S^{N-1}|(\Delta x)^2}\int_{S^{N-1}} q(x+\omega\Delta x,t)-q(x,t)\,\mathrm{d}\omega$$

and an elementary calculation implies

$$\frac{\partial q}{\partial t} = D\Delta q \tag{18}$$

as the mean field limit of $\Delta t \downarrow 0$ and $\Delta x \downarrow 0$ of (17). From this formulation we know how to select parameters in the Monte Carlo simulation to (18). The Smoluchowski equation is derived similarly using the renormalized barrier which realizes the constant waiting time. In fact we assume

$$T(x,t;\omega) = cT\Big(x+\frac{\Delta x}{2}\omega,t\Big)$$

in (15) and take the constant c such that the mean waiting time τ is a constant:

$$\frac{1}{\Delta t}\int_{S^{N-1}} T(x,t;\omega)\,\mathrm{d}\omega = \frac{c}{\Delta t}\int_{S^{N-1}} T\Big(x+\frac{\Delta x}{2}\omega,t\Big)\,\mathrm{d}\omega = \tau^{-1},$$

which means

$$T(x,t;\omega) = \frac{\Delta t}{\tau}\cdot\frac{T\left(x+\frac{1}{2}\Delta x\omega,t\right)}{\int_{S^{N-1}} T\left(x+\frac{1}{2}\Delta x\omega',t\right)\,\mathrm{d}\omega'}. \tag{19}$$

Then, see [11], the master equation (15), Einstein's formula (14), and the transient probability (19) imply the Smoluchowski equation

$$\frac{\partial q}{\partial t} = D\nabla\cdot(\nabla q - q\nabla\log T). \tag{20}$$

Complicated chemical reactions inside cells are modeled by a set of ordinary differential equations on the macro-scopic level. Then these integrated pathways are taken for the Monte-Carlo simulation using compartment systems. An imortant observation here is that the chemical reaction is thus influenced by collisions of particles. Two particles walking on lattices of their own, however, will not meet and in this sense using particle densities defined continuously in space and time may be suitable for the bottom up modeling influenced by the process of chemical reaction. The consistency with the first principles involving physical constants such as the

diffusion, the chemical rate, and so forth, is then realizable. Let $q = q(x,t)$ be the particle density defined for all $x \in \mathbb{R}^N$ and $t > 0$. Taking the fundamental process $A + B \to C$ (k), we adopt the ansatz different from the traditional Smoluchowski-Debye's one [11], that is, this chemical reaction thus occurs if and only if a pair of A-B particles is in the distance R. We call this R the reaction radius where the reaction probability at each collision of A-B particles is denoted by P_r. Given an A-particle, the number of B-particles with the distance of reaction radius is equal to $n_B = [B]N_a v$, where $[B]$ is the concentration of B-partices, N_a is the Avogadro number, and $v = \omega_N R^N$ with ω_N denoting the volume of the N-dimensional unit ball. If Q_A and n_{jA} denote the number of A-particles in the vessel and the number of jumps of each A-particle per unit time, then

$$\frac{\mathrm{d}Q_{A,A\to B}}{\mathrm{d}t} = -P_r Q_A n_{jA} n_B$$

stands for the change rate of the number of A-particles reacting to B-particles. Letting V be the volume of the vessel and $[A]_{A\to B} = Q_{A,A\to B}/V$, it holds that

$$\frac{\mathrm{d}[A]_{A\to B}}{\mathrm{d}t} = -P_r N_a v n_{jA}[A][B]$$

due to $Q_A = [A]N_a V$. The relation

$$\frac{\mathrm{d}[A]_{B\to A}}{\mathrm{d}t} = -P_r N_a v n_{jB}[A][B]$$

is obtained similarly, and hence

$$\frac{\mathrm{d}[A]}{\mathrm{d}t} = -P_r N_a v (n_{jA} + n_{jB})[A][B], \tag{21}$$

where n_{jB} is the number of jumps of a B-particle per unit time. Comparing (21) with the phenomenological equation

$$\frac{\mathrm{d}[A]}{\mathrm{d}t} = -k[A][B],$$

recall the reaction rate k, we obtain Ichikawa's formula [11]

$$k = P_r N_a v (n_{jA} + n_{jB}). \tag{22}$$

We assume that the jump length Δx and the calculation time Δt are common for A and B-particles. If τ_A and τ_B denote the mean waiting times of A and B-particles, respectively, we have

$$n_{jA} = \tau_A^{-1} = \gamma^{-1}\frac{2ND_A}{\Delta t},$$
$$n_{jB} = \tau_B^{-1} = \gamma^{-1}\frac{2ND_B}{\Delta t}$$

using the discretization ratio $\gamma = (\Delta x)^2/\Delta t$ where D_A and D_B are the diffusion coefficients of A and B-particles, respectively. Hence it follows that

$$\frac{P_r}{\gamma \Delta t} = \frac{k}{2NN_a} \cdot \frac{1}{v} \cdot (D_A + D_B)^{-1} \tag{23}$$

with the right-hand side determined by physical constants. The master equation now arises as

$$\begin{aligned} q_A(x, t + \Delta t) - q_A(x, t) = &\int_{S^{N-1}} T_A(x + \omega \Delta x, t; -\omega) q_A(x + \omega \Delta x, t) \, \mathrm{d}\omega \\ &- \int_{S^{N-1}} T_A(x, t; \omega) \, \mathrm{d}\omega \cdot q_A(x, t) - P_r \int_{B(x,R)} q_B(y, t) \, \mathrm{d}y \cdot q_A(x, t), \end{aligned}$$

which leads to the limit system of equations

$$\begin{aligned} \frac{\partial q_A}{\partial t} &= D_A \Delta q_A - \frac{k_{A,B}}{v} \int_{B(\cdot,R)} q_B \, \mathrm{d}y \cdot q_A, \\ \frac{\partial q_B}{\partial t} &= D_B \Delta q_B - \frac{k_{A,B}}{v} \int_{B(\cdot,R)} q_A \, \mathrm{d}y \cdot q_B, \end{aligned} \tag{24}$$

recall that v denotes the volume of $B(\cdot, R)$, in the case that the transient probabilities T_A and T_B are constants, where

$$k_{A,B} = \frac{\gamma k}{2nN_a} (D_A + D_B)^{-1}.$$

Mathematical study of this new system will be a problem in future but several interesting features such as mushy interfaces are expected.

3. Smoluchowski-ODE system

Several tumor growth models are formulated by the Smoluchowski-ODE system regarding the multi-scaleness of the event. First, we recall the auxiliary model proposed by [24] other than (20). The response function $T = T(w)$ is thus formulated by the equilibrium of the ligand-receptor polymerization process

$$R + w \underset{(k_{-1})}{\overset{(k_1)}{\rightleftharpoons}} [Rw]. \tag{25}$$

Using the polymerization rate $\gamma = k_{-1}/k_1$ and the total number of receptors β we obtain

$$T(w) = \frac{\beta w}{\gamma + w}.$$

Next, the control species is not supposed to diffuse and the ODE models are adopted. Typical examples are

1. linear growth: $\dfrac{\partial w}{\partial t} = p - \mu w$
2. exponential growth: $\dfrac{\partial w}{\partial t} = (p - \mu)w$
3. saturated growth: $\dfrac{\partial w}{\partial t} = \dfrac{pw}{1+\nu w} - \mu w + \gamma \dfrac{p}{1+p}$

where $\mu, \nu, \gamma \geqslant 0$ are constants.

Some of these models are formulated by the parabolic-ODE system in the form of

$$
\begin{aligned}
q_t &= \nabla \cdot (\nabla q - q \nabla \varphi(v)), \\
v_t &= q \qquad \text{in } \Omega \times (0,T), \\
\frac{\partial q}{\partial \nu} &= 0 \qquad \text{on } \partial\Omega \times (0,T), \\
q\big|_{t=0} &= q_0, \quad v\big|_{t=0} = v_0 \qquad \text{in } \Omega,
\end{aligned}
\tag{26}
$$

where $\Omega \subset \mathbb{R}^N$ is a bounded domain with smooth boundary $\partial\Omega$, ν is the outer unit normal vector, $q_0 = q_0(x) > 0$ and $v_0 = v_0(x)$ are smooth functions of $x \in \overline{\Omega}$, and $\varphi\colon\ \mathbb{R} \to \mathbb{R}$ is a smooth function. Imposing

$$
\frac{\partial v_0}{\partial \nu} = 0 \qquad \text{on } \partial\Omega
$$

on the inititial value, we replace the boundary condition by the zero flux condition

$$
\frac{\partial q}{\partial \nu} - q \frac{\partial \varphi(v)}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T).
$$

Actually, several mathematical models proposed recently in connection with their chemical factors take the form of (26). Among others, [24] modeled the effect of chemotaxis as

$$
\begin{aligned}
p_t &= \nabla \cdot (D \nabla p - p \chi'(w) \nabla w), \\
w_t &= g(p, w).
\end{aligned}
\tag{27}
$$

Here, p and w are due to the conditional probability and the density of the control species associated with the decision of the walkers, respectively, $D > 0$ is the diffusion constant, χ' the chemotactic sensitivity, and g the chemical growth rate, and several behaviours of the solution globally in time are expected. The taxis is positive and negative according as $\chi'(w) > 0$ and $\chi'(w) < 0$, respectively, which causes the fundamental effects on the behavior of the density p. The chemical growth rate $g =$

$g(p,w)$, on the other hand, takes various forms; linear, exponential, and saturating. System (26) can represent several important cases of them:

1. $g(p,w) = (p-\mu)w$, $w > 0 \Rightarrow v = \log w$, $q = p - \mu$, $\varphi(v) = \chi(\mathrm{e}^v)$.
2. $g(p,w) = p(\mu - w)$, $w < \mu \Rightarrow v = -\log(\mu - w)$, $q = p$, $\varphi(v) = \chi(\mu - \mathrm{e}^{-v})$.
3. $g(p,w) = -pw$, $w > 0 \Rightarrow v = -\log w$, $q = p$, $\varphi(v) = \chi(\mathrm{e}^{-v})$.

Examples of the sensitivity function proposed by [18] consistent with these growth rates are the following:

1. $\chi'(w) = \dfrac{a(\beta-\alpha)}{(w+\alpha)(w+\beta)}$, $g(p,w) = pw$, $w > 0$: $\varphi(v) = a \log \dfrac{\mathrm{e}^v + \alpha}{\mathrm{e}^v + \beta}$.
2. $\chi'(w) = \dfrac{a(\beta-\alpha)}{(w+\alpha)(w+\beta)}$, $g(p,w) = -pw$, $w > 0$: $\varphi(v) = a \log \dfrac{\mathrm{e}^{-v} + \alpha}{\mathrm{e}^{-v} + \beta}$.

Sleeman and Levine [28] apply the model to explain the mechanism of tumor angiogenesis as a top down model.

Henceforth

$$
\begin{gathered}
q_0, v_0 \in C^{2+\alpha}(\overline{\Omega}), \\
\frac{\partial q_0}{\partial \nu} = \frac{\partial v_0}{\partial \nu} = 0 \qquad \text{on} \quad \partial\Omega, \\
\varphi \in C^3(\mathbb{R}), \quad \varphi' \leqslant 0, \quad \varphi'' \geqslant 0
\end{gathered} \tag{28}
$$

is assumed with $0 < \alpha < 1$. The key assumption here is the third relation which is actually the case of $v_0 \geqslant \frac{1}{2}\log(\alpha\beta)$ and $v_0 \leqslant \frac{1}{2}\log(\alpha\beta)$ in the first and the second of the above examples, respectively. There are other examples of the sensitivitiy function proposed by [24] which satisfy (28), see [31].

System (26) with (28) is equivalent to the one studied by [7],

$$
\begin{aligned}
& n_t = \nabla \cdot (\nabla n - n\chi'(c)\nabla c), \ n > 0, \\
& c_t = -cn, \ c > 0 \qquad \text{in } \Omega \times (0,T), \qquad (29) \\
& \frac{\partial n}{\partial \nu} - \chi'(c)\frac{\partial c}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T), \qquad (30)
\end{aligned}
$$

where $\chi = \chi(c)$ is a C^2-function satisfying

$$
\chi'(c) > 0, \qquad c\chi''(c) + \chi'(c) > 0. \tag{31}
$$

In fact, putting $v = -\log c$ and $q = n$, we obtain (26) for $\varphi = \varphi(v)$ defined by

$$
\varphi(v) = \chi(c), \qquad v = -\log c.
$$

Then, (31) means (28). In [7], the global in time existence of a weak solution with the convergence

$$q(\cdot,t) \to \overline{q}_0 \equiv \frac{1}{|\Omega|}\int_\Omega q_0(x)\,\mathrm{d}x \tag{32}$$

as $t \uparrow +\infty$ is asserted (see also [8]). Such a property is proven rigorously when the space-dimension is one, using the continuous embedding due to [19],

$$L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^2(\Omega)) \hookrightarrow L^4(0,T;L^\infty(\Omega)). \tag{33}$$

This mathematical result is actually a counterpart of the one obtained by [32] which says that if $\varphi(v) = v$, we have both global and blowup in finite time solutions depending on their initial data. We note that this $\varphi(v) = v$ does not satisfy $\varphi'(v) \leqslant 0$. Our arguments are also valid for the system

$$\begin{gathered} q_t = \nabla\cdot(\nabla q - q\nabla\varphi(v,w)), \\ v_t = q, \quad w_t = q \qquad \text{in } \Omega\times(0,T), \\ \frac{\partial q}{\partial \nu} = 0 \qquad \text{on } \partial\Omega\times(0,T), \\ q\big|_{t=0} = q_0, \quad v\big|_{t=0} = v_0 \quad w\big|_{t=0} = w_0 \qquad \text{in } \Omega. \end{gathered} \tag{34}$$

Here we impose the compatibility condition

$$\frac{\partial v_0}{\partial \nu} = \frac{\partial w_0}{\partial \nu} = 0 \qquad \text{on } \partial\Omega$$

which replaces the boundary condition by the zero flux condition

$$\frac{\partial q}{\partial \nu} - q\,\frac{\partial \varphi(v,w)}{\partial \nu} = 0 \qquad \text{on } \partial\Omega\times(0,T).$$

Then we obtain similar results, assuming

$$\begin{gathered} q_0, v_0, w_0 \in C^{2+\alpha}(\overline{\Omega}), \\ \varphi = \varphi(u,v) \in C^3(\mathbb{R}\times\mathbb{R}), \\ \varphi_v,\ \varphi_w \leqslant 0,\ \varphi_{vv},\ \varphi_{ww} \geqslant 0,\ \varphi_{vw} = 0. \end{gathered} \tag{35}$$

System (34) can describe other models associated with the angiogenesis. The first example is in [1] modeling the tumor induced angiogenesis using the endotherial cell

density per unit area n, the TAF (tumor angiogenic factors) concentration f, and the matrix macromolecule fibronectin concentration c, that is,

$$
\begin{aligned}
n_t &= D\Delta n - \nabla\cdot(\chi'(c)n\nabla c) - \varrho_0\nabla\cdot(n\nabla f),\\
f_t &= \beta n - \mu n f,\\
c_t &= -\gamma n c,
\end{aligned}
\tag{36}
$$

where

$$
\chi'(c) = \frac{\chi_0}{1+\alpha c}
\tag{37}
$$

and D, ϱ_0, β, μ, γ, χ_0, α are positive constants. We can write (36) as

$$
\begin{gathered}
n_t = \nabla\cdot(D\nabla n - n\nabla\log\Phi(c) - n\nabla\log\Psi(f)),\\
f_t = \beta n - \mu n f,\\
c_t = -\gamma n c \qquad \text{in } \Omega\times(0,T),\\
(D\nabla n - n\nabla\log\Phi(c) - n\nabla\log\Psi(f))\cdot\nu = 0 \qquad \text{on } \partial\Omega\times(0,T),\\
n\big|_{t=0} = n_0 > 0,\quad f\big|_{t=0} = f_0 > 0,\quad c\big|_{t=0} = c_0 > 0 \qquad \text{in } \Omega
\end{gathered}
\tag{38}
$$

with initial and boundary conditions where $\Phi, \Psi\colon\ \mathbb{R}\to\mathbb{R}$ are smooth positive functions. Assuming

$$
\begin{gathered}
f_0 > \frac{\beta}{\mu} \qquad \text{in } \Omega,\\
\frac{\partial p_0}{\partial\nu} = \frac{\partial c_0}{\partial\nu} = \frac{\partial f_0}{\partial\nu} = 0 \qquad \text{on } \partial\Omega,
\end{gathered}
\tag{39}
$$

we put $\tau = Dt$, $q = n$, $v = -(D/\gamma)\log c$, $w = -(D/\mu)\log(\mu f - \beta)$, and

$$
\begin{aligned}
\varphi(v,w) &= \log\tilde{\Phi}(v) + \log\tilde{\Psi}(w),\\
\tilde{\Phi}(v) &= \Phi(\mathrm{e}^{-\gamma v/D})^{1/D},\\
\tilde{\Psi}(w) &= \Psi(\mu^{-1}(\beta + \mathrm{e}^{-\mu w/D}))^{1/D}.
\end{aligned}
$$

Then we obtain (34) by virtue of (38), writing t for τ, and are able to confirm all the assumptions required for $\varphi = \varphi(v,w)$. The same treatment is possible for the other model of angiogenesis appearing in [2], that is

$$
\Phi(c) = \mathrm{e}^{\varphi_0 c}, \qquad \Psi(f) = \mathrm{e}^{\varrho_0 f}.
$$

These models of angiogenesis are derived from the top down modeling, counting the effects of angiogenesis, chemotaxis, and haptotaxis to adjust the experimental data. The existence of the global in time solution to (36)–(37) is studied by [14], [15], [17]. For any space dimension, the global in time solution exists if the initial data has the form $n_0(x) = k_0 + n_1(x)$ for a sufficiently large constant $k_0 > 0$ and a smooth function $n_1 = n_1(x)$ satisfying $\int_\Omega n_1(x)\,\mathrm{d}x = 0$. The models [24] with the sensitivity and the growth functions as in (28) are studied by Kubo-Suzuki [16] and they show the existence of the global in time solution for any space dimension. Applying the same approach to (36)–(37) Kubo-Hoshino-Suzuki [14] showed that these tumor growth models can be treated consistently. In the reverse case of (39),

$$0 < f_0 < \frac{\beta}{\mu},$$

we obtain a priori bounds of the solution to this system for any space dimension under the assumption

$$(\beta - \mu f_0)^{\gamma/\beta} \ll c_0,$$

and this provides the global in time solution converging to the stationary solution, see [10].

System (26) is written as an evolution equation with strong dissipation, that is

$$\begin{aligned} v_{tt} &= \Delta v_t - \nabla \cdot (v_t \nabla \varphi(v)) \qquad \text{in } \Omega \times (0,T), \\ \frac{\partial v}{\partial \nu} &= 0 \qquad \text{on } \partial\Omega \times (0,T). \end{aligned}$$

This formulation was used by [18] where the existence of blowup and global in time solutions is studied, and later [32], [16] followed it. In particular, if the nonlinearity $\varphi = \varphi(v)$ is sufficiently mild, that is, provided with the boundedness including higher order derivatives, the global in time solution exists provided that, for example, $q_0(x) = \gamma + q_1(x)$, $\gamma \gg 1$, $q_1 = q_1(x)$ is smooth, and $\int_\Omega q_1(x)\,\mathrm{d}x = 0$. There is also an approach by the comparison principle, and [10] studied the case that some a priori bounds of the solution arise from this principle, which results in the asymptotic stability of the stationary solution. There may be another point of view to regard (26) as a reduction of the full-system of chemotaxis, e.g.,

$$\begin{aligned} u_t &= \nabla \cdot (\nabla u - u \nabla v), \\ \tau v_t - \Delta v &= u - \frac{1}{|\Omega|} \int_\Omega u \qquad \text{in } \Omega \times (0,T), \\ \frac{\partial u}{\partial \nu} - u \frac{\partial v}{\partial \nu} &= \frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T), \\ \int_\Omega v &= 0. \end{aligned} \tag{40}$$

In fact, the Smoluchowski-Poisson equation (5) is the case of $\tau = 0$ in (40), while a variant of (26) will arise with $\varphi(v) = v$ if the diffusion $-\Delta v$ of v is ignored in the second equation of (40). The lack of the elliptic regularity in the second equation, however, makes the q-component unstable even if the interaction is self-repulsive when the first equation is replaced by

$$u_t = \nabla \cdot (\nabla u + u \nabla v).$$

The case $\varphi(v) = -v$ of (26) is actually studied by this method, where a global in time solution is obtained using the Lyapunov function in the case of one-space dimension, see [25]. In [31], this argument combined with crucial estimates derived from the comparison principle is applied.

Lemma 1. *The function*

$$L = L(t) = \int_\Omega q(\log q - 1) - \frac{1}{2}\varphi'(v)|\nabla v|^2 \, \mathrm{d}x$$

is a Lyapunov function to (26).

Local in time wellposedness, however, is not restricted to the case of one-space dimension, and, for example, we have the following theorem.

Theorem 2 [31]**.** *Under the assumption* (28)*, there exists a unique solution* $q = q(x,t)$*,* $v = v(x,t) \in C^{2+\alpha,1+\frac{\alpha}{2}}(\overline{\Omega} \times [0,T])$ *to* (26) *such that* $q = q(x,t) > 0$ *provided that* T *is sufficiently small.*

Then we obtain the following theorem.

Theorem 3 [31]**.** *In the case of one-space dimension, the solution in the previous theorem exists for any* $T > 0$*. Given* $t_k \uparrow +\infty$ *and* $\delta > 0$*, furthermore, we have* $t_k' \in (t_k - \delta, t_k + \delta)$ *such that*

$$q(\cdot, t_k') \to \overline{q}_0 \tag{41}$$

uniformly on $\overline{\Omega}$*.*

Differently from the elliptic-parabolic system, see [27], the possibility of the oscillation of $q(\cdot,t)$ as $t \uparrow +\infty$ is not yet excluded because of the ODE part. Even if this oscillation is actually the case, none of its biological meaning is certain to our knowledge. It is, however, true that some numerical computations become rather unstable in the q-component. Results similar to Theorems 2 and 3 are valid for (34) which are applicable to the Anderson-Chaplain-Pitcairn models [1], [2] of angiogeneis.

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