Chapter 2
Amounting the Balance

Three factors: cell deformation, ECM degradation, and adhesion regulation arise at sub-cell level in the early stage of invasion of cancer cells. To understand the relations between them, the study of cell biology on proteins is integrated into mathematical models. Here we focus on *invadopodia*, formed on the surface of malignant tumor cells when they gain motility. Invadopodia are spiky, contain a lot of MT1-MMPs inside, and act as drills toward ECM. *Actin* inside a cell, on the other hand, takes two phases, F (solid) and G (liquid). The F-actin forms a network which casts a skeleton of the cell. Finally, a positive feedback loop is observed concerning up-regulation of MMPs. Our idea is to create in silico invadopodia using the above feedback loop and the switching fluctuations. Here we present the most fundamental tool of mathematical modeling, amounting the balance.

2.1 Keller-Segel Model

Mathematical formulas are used to describe several phenomena. For example, if $u = u(t)$ stands for the total amount of some species, then

$$u_t = \alpha$$

means that it is produced at the amount of α per unit time. The formula

$$u_t = ku,$$

is derived from $\alpha = ku$ which describes the case that this u produces itself with the rate k per unit time (Fig. 2.1). The negative sign arises similarly, that is,

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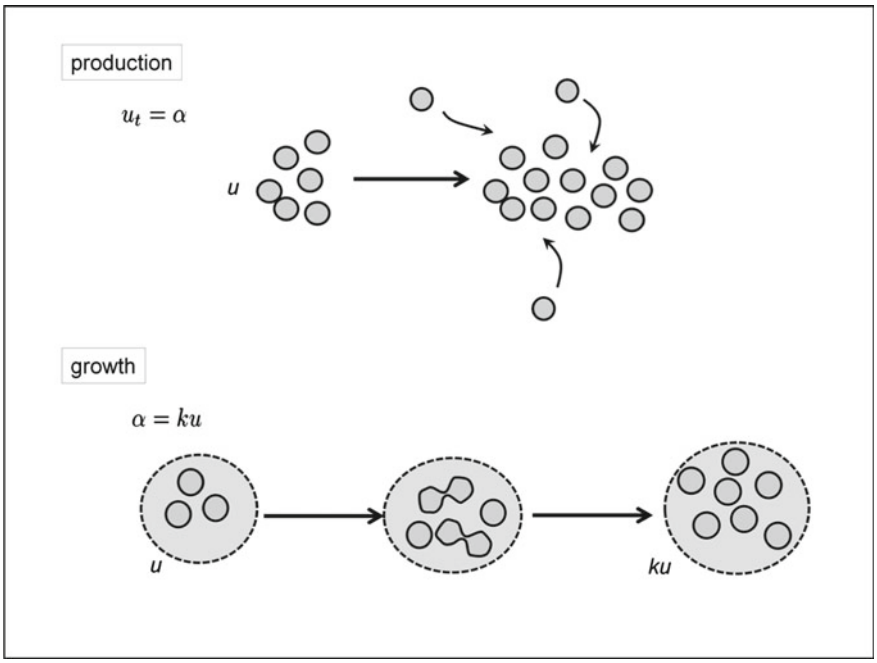

Fig. 2.1 Top down modeling (1)

$$v_t = -\beta$$

and

$$v_t = -\ell v.$$

If $u = u(x, t)$ denotes the density of some material at the position $x = (x_1, \ldots, x_n)$ and the time t, then

$$u_t = -\nabla \cdot j \tag{2.1}$$

formalizes the law of mass conservation, where j stands for the flux of u and

$$\nabla = \begin{pmatrix} \partial/\partial x_1 \\ \cdot \\ \cdot \\ \cdot \\ \partial/\partial x_n \end{pmatrix}$$

denotes the gradient operator (Fig. 2.2). Equation (2.1) arises together with the divergence formula,

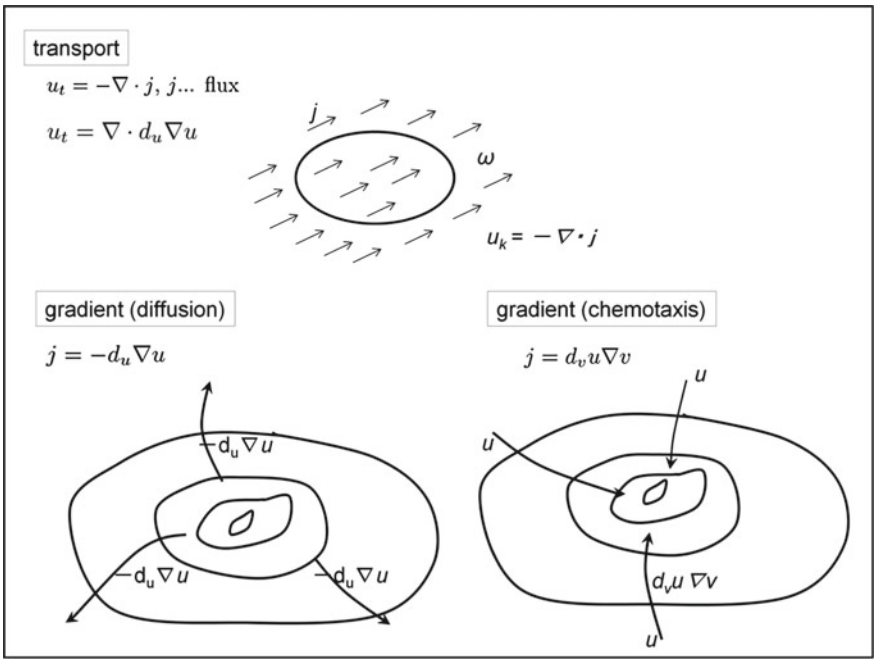

Fig. 2.2 Top down modeling (2)

$$\frac{d}{dt}\int_{\omega} u\, dx = -\int_{\partial\omega} \nu \cdot j dS, \tag{2.2}$$

where ω is a domain with smooth boundary $\partial\omega$, and ν and dS denote the outer unit normal vector and surface element, respectively. The vector field $\nabla\varphi$ generated by the scalar field $\varphi = \varphi(x)$ points in direction where φ increases most and the length equal to its inclination. Equality (2.2) indicates the mass inside ω is lost with the amount of the outer normal component of j on $\partial\omega$.

From a microscopic point of view, Newton's equations of motion

$$\frac{dx}{dt} = v, \qquad m\frac{dv}{dt} = F \tag{2.3}$$

represent the characteristic equations of the transport equation

$$\frac{\partial\rho}{\partial t} + \nabla_x \rho \cdot v + \frac{F}{m} \cdot \nabla_v \rho = 0. \tag{2.4}$$

If $(x, v) = (x(t), v(t))$ and $\rho = \rho(x, v, t)$ are solutions to (2.3) and (2.4), respectively, then it holds that

$$\frac{d}{dt}\rho(x(t), v(t), t) = 0$$

and hence $\rho(x, v, t)dxdv$ is regarded as a particle density in the (x, v)-space. The particle density and mean velocity are given by

$$u(x,t) = \int \rho(x, v, t)dv$$

and

$$V(x,t) = \frac{1}{u(x,t)} \int \rho(x, v, t)vdv,$$

respectively.

The above j is sometimes associated with the gradient of a scalar field. If $j = -d_u \nabla u$, then $u = u(x, t)$ is subject to diffusion and (2.1) reads

$$u_t = \nabla \cdot d_u \nabla u,$$

where $d_u > 0$ denotes the diffusion coefficient. If u is subject to chemotaxis, we take $j = d_v u \nabla v$, with $v = v(x, t)$ standing for the chemical concentration attractive to u. This means that u is carried toward the area where v takes higher concentration. This case is called positive chemotaxis.

These factors are sufficient for understanding the Keller-Segel model [66] dealing with the aggregation of cells of cellular slime molds, that is,

$$\begin{aligned}
&u_t = \nabla \cdot (d_1(u, v)\nabla u) - \nabla \cdot (d_2(u, v)\nabla v),\\
&v_t = d_v \Delta v - k_1 vw + k_{-1} p + f(v)u,\\
&w_t = d_w \Delta w - k_1 vw + (k_{-1} + k_2)p + g(v, w)u,\\
&p_t = d_p \Delta p + k_1 vw - (k_{-1} + k_2)p \qquad \text{in } \Omega \times (0, T)
\end{aligned} \tag{2.5}$$

with

$$\begin{aligned}
&d_1(u, v)\frac{\partial u}{\partial \nu} - d_2(u, v)\frac{\partial v}{\partial \nu} = 0,\\
&\frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} = \frac{\partial p}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T)
\end{aligned} \tag{2.6}$$

where $\Omega \subset \mathbf{R}^N$ is a bounded domain with smooth boundary $\partial\Omega$. Here, $u = u(x, t)$, $v = v(x, t)$, $w = w(x, t)$, and $p = p(x, t)$ denote the density of the cellular slime mold, concentration of the chemical material, that of enzyme, and that of the complexes produced by v and w, respectively (Fig. 2.3). The nonlinearities $d_1(u, v)$, $d_2(u, v)$, $f(v)$, and $g(v, w)$ are introduced on biological grounds; a more quantitive based on biological experiments will be used if necessary.

Hence the first equation of (2.5) combined with the first boundary condition of (2.6) governs the transport of u with the null-flux boundary condition,

$$u_t = -\nabla \cdot j, \quad \nu \cdot j|_{\partial\Omega} = 0,$$

$u = u(x,t)$ cellular slime molds
$v = v(x,t)$ chemical
$w = w(x,t)$ enzyme
$p = p(x,t)$ complex

1. transport, gradient
(a) diffusion u, v, w, p
(b) chemotaxis $v \to u$

2. production $u \to (v, w)$

3. chemical reaction v, w, p

$$V + W \underset{\leftarrow (k_{-1})}{\overset{(k_1) \rightarrow}{}} P \overset{(k_2)}{\rightarrow} W + A$$

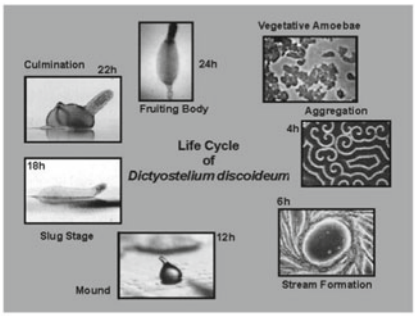

Fig. 2.3 Dd - KS model http://www.zi.biologie.uni-muenchen.de/zoologie/diicty/dicty.html

where $j = -d_1(u, v)\nabla u + d_2(u, v)\nabla v$ stands for the flux of $u = u(x, t)$, composed of the diffusion and chemotaxis terms, $-d_1(u, v)\nabla u$ and $d_2(u, v)\nabla v$, respectively: (Fig. 2.2). The chemical materials v, w, and p are subject to the diffusion,

$$v_t = d_v \Delta v, \quad w_t = d_w \Delta w, \quad p_t = d_p \Delta p,$$

while the productions of v and w per unit time are propotional to u:

$$v_t = f(v)u, \quad w_t = g(v, w)u.$$

We are thus led to the system of ordinary differential equations

$$\begin{aligned} v_t &= -k_1 vw + k_{-1} p, \\ w_t &= -k_1 vw + (k_{-1} + k_2) p, \\ p_t &= k_1 vw - (k_{-1} + k_2) p, \end{aligned} \tag{2.7}$$

representing the mass action law for the chemical reaction

$$V + W \underset{\leftarrow (k_{-1})}{\overset{(k_1) \rightarrow}{}} P \overset{(k_2)}{\rightarrow} W + A. \tag{2.8}$$

We observe, however, several interactions through the organic hierarchy in the life, that is, individuals, organs, issues, cells, organelles, and molecular with different time scales. Othmer and Stevens [101] used functional relations, ordinary differential equations, and partial differential equations, to describe the signaling sensitivity, chemical reaction, and material transport, repectively. This model is applicable to several situations involving tissue, cell, sub-cell, and molecule levels, but, originally, describes the movement of one particle subject to a reinforced random walk (see Sect. 3.1). It takes the form of the Smoluchowski-ODE system

$$\begin{aligned} p_t &= \nabla \cdot (D\nabla p - p\chi'(w)\nabla w), \\ w_t &= g(p, w) \qquad\qquad \text{in } \Omega \times (0, T) \end{aligned} \tag{2.9}$$

with

$$D\frac{\partial p}{\partial \nu} - p\chi'(w)\frac{\partial w}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T) \tag{2.10}$$

where p, w, D, χ', and g denote the existence probability, control species density, diffusion coefficient, chemotactic sensitivity, and growth factor, respectively (Fig. 2.4). The first equation of (2.9) is a generalization of the Smoluchowski equation and

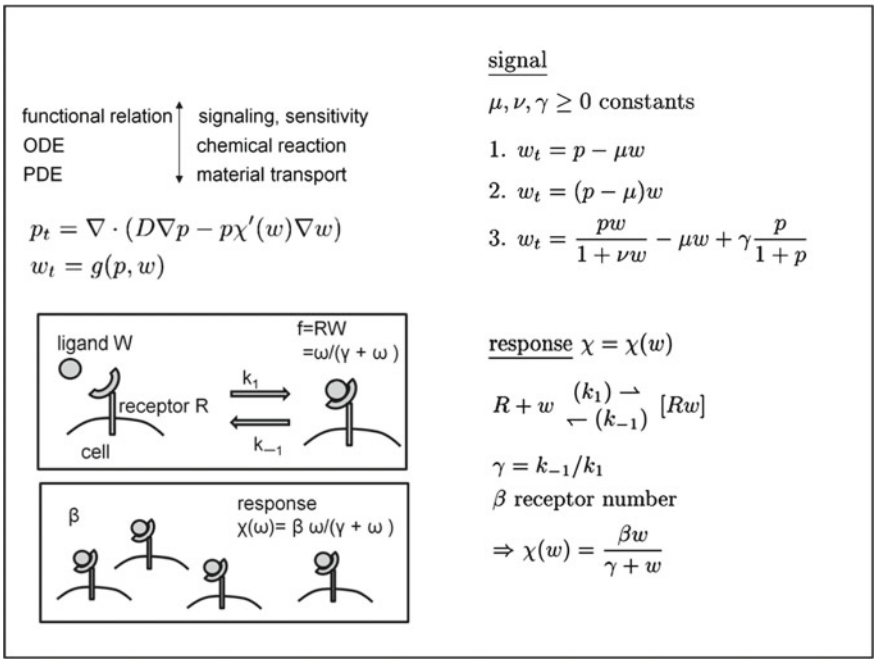

Fig. 2.4 Multi-scale model

(2.10) represents the null-flux condition. In the next chapter we shall see that it is based on modeling the movement of many particles.

The second equation of (2.9) is an ordinary differential equation. It governs the signaling process in accordance with the following functions:

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

It is assumed that the control species w is subject to the process of ligand-receptor coupling

$$R + W \to F \ \ (k_1), \quad F \to R + W \ \ (k_{-1}).$$

It follows that

$$\begin{aligned} \frac{dr}{dt} &= -k_1 r w + k_{-1} f, \\ \frac{dw}{dt} &= -k_1 r w + k_{-1} f, \\ \frac{df}{dt} &= k_1 r w - k_{-1} f, \end{aligned}$$

where $r = [R]$, $w = [W]$, and $f = [F]$.

We have the total mass conservation $r + f = c$ and also $rw = \gamma f$ in the stationary state, where $\gamma = k_{-1}/k_1$ is the equilibrium constant. Putting $c = 1$, we obtain

$$f = \frac{w}{\gamma + w}.$$

Letting β be the receptor number, we now assume that

$$\chi(w) = \frac{\beta w}{\gamma + w},$$

that is, the sensitivity function $\chi = \chi(w)$ is proportional to the value of f.

2.2 Invasion Model

The Chaplain-Anderson model [18] concerning the invasion of cancer cells at the tissue level is formulated by

$$\begin{aligned} n_t &= d_n \Delta n - \gamma \nabla \cdot (n \nabla c), \\ c_t &= -\delta f c, \\ f_t &= d_f \Delta f + \alpha n - \beta f \qquad \text{in } \Omega \times (0, T), \end{aligned} \tag{2.11}$$

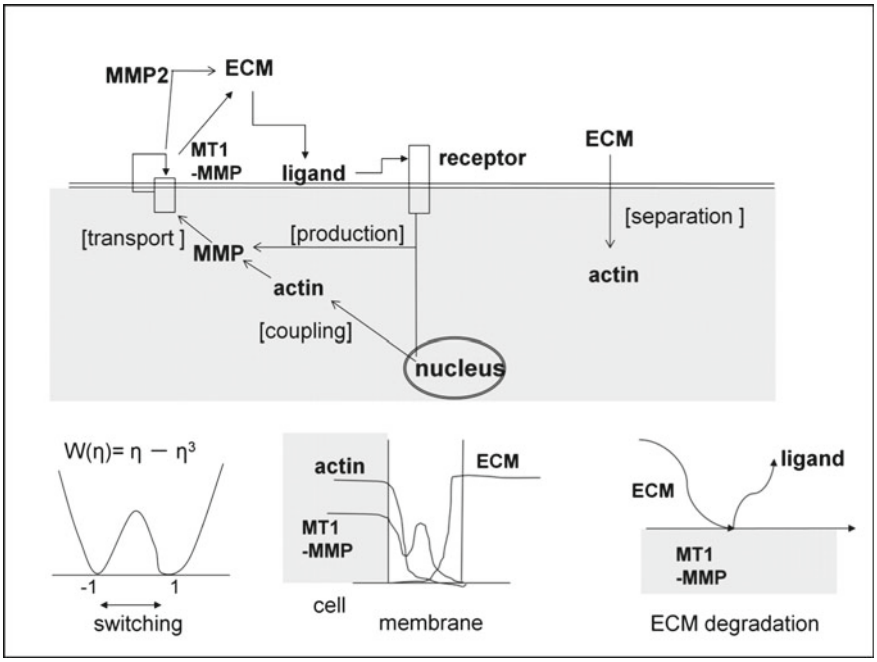

Fig. 2.5 Sub-cell model of invasion

with

$$d_n \frac{\partial n}{\partial \nu} - \gamma n \frac{\partial c}{\partial \nu} = \frac{\partial f}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T). \tag{2.12}$$

Here, $d_n, \gamma, \delta, d_f, \alpha$, and β are positive constants, and n, c, and f denote the density of cells, that of ECM, and the concentration of MMP, respectively. In accordance with the Keller-Segel model (2.5), the chemical reaction is reduce to ODE. It is thus a multi-scale model and (n, c) is subject to the Smoluchowski ODE system (2.9) with (2.10). The unknown variable f stands for the concentration of enzyme, subject to diffusion, production by n, and self-decay.

More precisely, in the first equation of (2.11), the first term on the right-hand side describes the diffusive property of cancer cells at the tissue level. Then its second term reflects a feature called *haptotaxis*, which means that the cancer cells invade the ECM territory. Hence a linear haptotactic sensitivity is assumed. The second equation of (2.11) models the mass action associated with the ECM degradation by MMPs. The third equation of (2.11) describes the secretory and decay properties of MMPs produced by cancer cells.

A cell level model is used in [109]. First, the chemical reaction between f and c is considered. Using the density of ECM fragment, denoted by c_*, we take

$$
\begin{aligned}
c_t &= -\kappa_c c f, \\
c_{*t} &= d_{c_*} \Delta c_* + \kappa_c c f - \lambda_{c_*} c_* \qquad \text{in } \Omega \times (0, T)
\end{aligned} \tag{2.13}
$$

with

$$
\frac{\partial c_*}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T), \tag{2.14}
$$

because c_* is secretory. Here, κ_c, d_{c_*}, and λ_{c_*} are the reaction rate of $C + F \to C_*$, diffusion coefficient, and decay rate of c_*, respectively. Below we use similar notations. From the feedback loop, binding to the receptor of c_* provides the production of MMPs f and also the regulation of actin n inside the cell. These processes may be described by

$$
\begin{aligned}
n_t &= d_n \Delta n - \gamma_n \nabla \cdot (n \nabla c_*), \\
f_t &= d_f \Delta f + \kappa_f c_* - \lambda_f f \qquad \text{in } \Omega \times (0, T),
\end{aligned} \tag{2.15}
$$

with

$$
d_n \frac{\partial n}{\partial \nu} - \gamma_n n \frac{\partial c_*}{\partial \nu} = \frac{\partial f}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T). \tag{2.16}
$$

There is, however, transport of f via n, which can be modeled by modifying the second equation of (2.15) and the corresponding boundary condition of (2.16) to

$$
f_t = d_f \Delta f + \kappa_f c_* - \lambda_f f + \gamma_f \nabla \cdot (f \nabla n) \quad \text{in } \Omega \times (0, T)
$$

and

$$
d_f \frac{\partial f}{\partial \nu} + \gamma_f f \frac{\partial n}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T),
$$

respectively. Thus n pushes f to the plasma membrane (see Fig. 2.5). Finally, since the events inside and outside the cell must be distinguished, we add the factor that ECM is repulsive to actin. This factor is treated by replacing the first equation of (2.15) by

$$
n_t = d_n \Delta n + \nabla \cdot (n \nabla \chi(c)) - \gamma_n \nabla \cdot (n \nabla c_*).
$$

Here, $\chi = \chi(c)$ is a suitable monotonically increasing function satisfying $\chi(c_k) = \infty$ with $0 < c_k - c_0 \ll 1$, where c_0 is a constant initially distributed for the value c outside the cell.

Thus we end up with the system

$$
\begin{aligned}
n_t &= d_n \Delta n + \nabla \cdot (n \nabla \chi(c)) - \gamma_n \nabla \cdot (n \nabla c_*), \\
c_t &= -\kappa_c c f, \\
c_{*t} &= d_{c_*} \Delta c_* + \kappa_c c f - \lambda_{c_*} c_*, \\
f_t &= d_f \Delta f + \kappa_f c_* - \beta f + \gamma_f \nabla \cdot (f \nabla n),
\end{aligned} \tag{2.17}
$$

where d_n, d_{c_*}, d_f, γ_n, γ_f, κ_c, κ_f, and λ_{c_*} are constants (Fig. 2.5). The flux of n is now given by

$$j = -d_n \nabla n - n \nabla \chi(c) + \gamma_n n \nabla c_*,$$

involving diffusion, separation of n and c, and upregulate signaling from c_*. Then the boundary condition is given by

$$j \cdot \nu = \frac{\partial c_*}{\partial \nu} = \frac{\partial f}{\partial \nu} = 0.$$

The positive feedback loop model (2.17), however, does not cause the localization in space-time of the variables, n, f, and c. Since our motivation is to produce in silico invadopodia, here we assume that the fluctuation of the ECM degradation rate κ_c exhibits several peaks on the plasma membrane. In Fig. 2.5, the Allen-Cahn dynamics is used to describe such fluctuation, which, however, is not essential (see [109]).

In any case we obtain in silico invadopodia. Then the simulations of modified models, made by cutting some pathways, clarify the role of two feedback loops (Fig. 2.6), that is, ECM fragments to MMPs directly, and ECM fragments to MMP's indirectly via actin. Thus there are direct upregulation of f by c_* and also regulation of n by c_* inducing the transport of f. Numerical simulations then suggest that these feeback loops act as peaking and expansion of the plasma membrane, respectively.

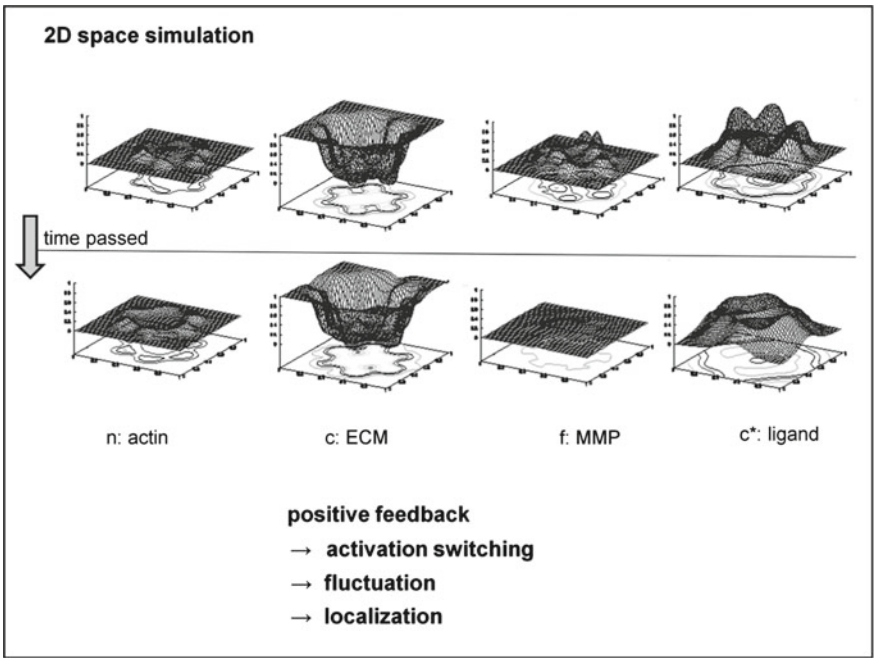

Fig. 2.6 In silico invadopodia

In spite of the presence of the phase separation term $n\nabla\chi(c)$ in the first equation of (2.17), in numerical simulations there arise the case that the region $n > 0$ becomes disconnected. Since the events taking place inside and outside the cell are different, treating the plasma membrane as a free boundary may be reasonable [37].

The plasma membrane can be represented by the level set like

$$\Gamma_t = \{x \in \Omega \mid \psi(x,t) = 0\}.$$

Here $\Omega \subset \mathbf{R}^N$ is the domain indicating the cancer cell and its enviroment, with smooth boundary $\partial\Omega$. The free boundary Γ_t is defined as the zero set of $\psi = \psi(x,t)$, assumed to be smooth. The interior and exterior the cell are denoted by ω_n^t and ω_c^t, respectively. Thus it follows that

$$\overline{\omega_n^t} \subset \Omega, \quad \partial\omega_n^t = \Gamma_t, \quad \omega_c^t = \Omega \setminus \overline{\omega_n^t}.$$

The velocity of the motion of Γ_t is the vector $v = v(x,t)$. This $v = v(x,t)$ is the gradient of the signal inside the cell denoted by σ. It is the driving force for the motion of the plasma membrane. Hence,

$$\psi_t + v \cdot \nabla\psi = 0, \quad v = \gamma_n \nabla\sigma \tag{2.18}$$

which implies

$$\frac{d}{dt}\psi(x(t),t) = \psi_t(x(t),t) + \frac{dx(t)}{dt} \cdot \nabla\psi(x(t),t) = 0$$

for $x = x(t)$ subject to

$$\frac{dx}{dt} = v(x,t).$$

The second idea is to restrict c_* and σ outside and inside the cell, respectively. Thus σ, n, and f are defined inside the cell, ω_n^t. There we assume that

$$\begin{aligned} n_t &= -\gamma_n \nabla \cdot (n\nabla\sigma), \\ f_t &= d_f \Delta f + \kappa_f \sigma + \gamma_f \nabla \cdot (f\nabla n) - \lambda_f f, \\ \sigma_t &= d_\sigma \Delta\sigma - \lambda_\sigma \sigma \qquad \text{in } \bigcup_{0<t<T} \omega_n^t \times \{t\}, \end{aligned} \tag{2.19}$$

with

$$\begin{aligned} & d_f \frac{\partial f}{\partial \nu} + \gamma_f f \frac{\partial n}{\partial \nu} + f v \cdot \nu = 0, \\ & \sigma = c_* \qquad \text{on } \bigcup_{0<t<T} \Gamma_t \times \{t\}, \end{aligned} \tag{2.20}$$

recalling (2.17) (Fig. 2.7).

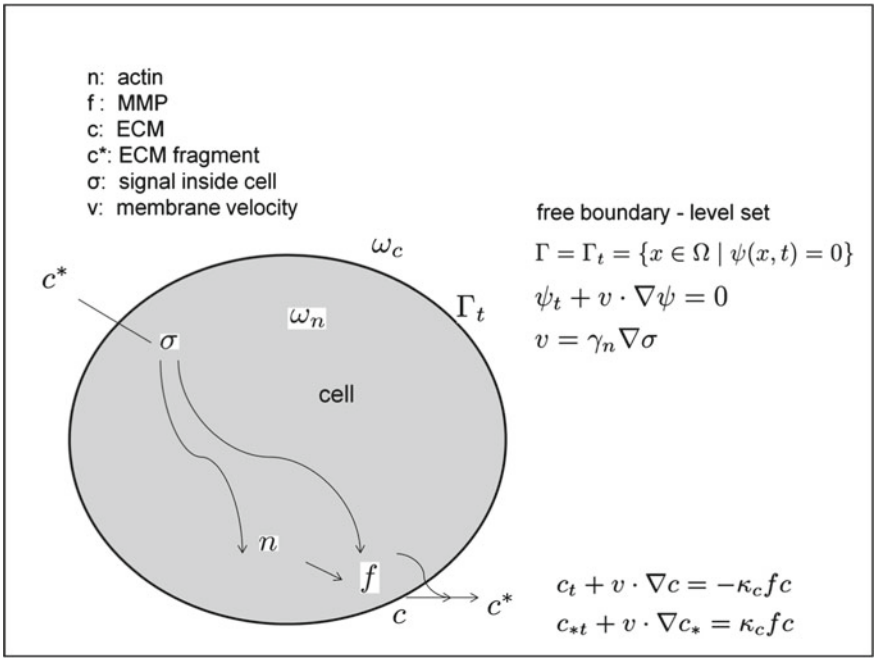

Fig. 2.7 Individual cell model

Hence the diffusion term of the first equation of (2.19) is dropped, which implies that

$$n_t = -\nabla \cdot nv \tag{2.21}$$

inside the cell. Then the total mass conservation of actin,

$$\frac{d}{dt}\int_{\omega_n^t} n\,dx = \int_{\omega_n^t} n_t\,dx + \int_{\partial\omega_n^t} nv \cdot \nu\,dS = 0$$

follows from the Liouville's formula for the first volume variation.

Given $v = v(x,t)$, the first equation of (2.18) is solved by the characteristic curve. Thus if the solution

$$\frac{dy}{dt} = v(y,t), \quad y|_{t=s} = x$$

is denoted by $y = U(t,s)x$, we have

$$\frac{d}{dt}\psi(U(t,0)x,t) = 0.$$

Here we emphasize the group property of the propagator $\{U(t,s)\}$, described by

$$U(t,\tau)\circ U(\tau,s)=U(t,s),\quad U(t,t)=\mathrm{Id}.$$

It follows that

$$\psi(x,t)=\psi_0(U(0,t)x),$$

where $\psi_0=\psi(\cdot,0)$. Equation (2.21) is solved similarly. In fact, it reads,

$$n_t+v\cdot\nabla n+n\nabla\cdot v=0$$

and then it follows that

$$\frac{d}{dt}n(U(t,0)x,t)=-n(U(t,0)x,t)(\nabla\cdot v)(U(t,0)x,t).$$

We thus obtain

$$n(U(t,0)x,t)=n_0(x)\exp\left(-\int_0^t(\nabla\cdot v)(U(t',0)x,t')dt'\right)$$

by the method of variation of constants, and therefore,

$$n(x,t)=n_0(U(0,t)x)\exp\left(-\int_0^t(\nabla\cdot v)(U(t',t)x,t')dt'\right),\tag{2.22}$$

where $n_0=n(\cdot,0)$.

The second equation of (2.19) is involved by the conservation law,

$$\tilde{f}_t=-\nabla\cdot j,\quad j=-d_f\nabla f-\gamma_f f\nabla n.$$

Then the boundary condition for f of (2.20) guarantees the total mass conservation of $\tilde{f}$, in the sense that

$$\frac{d}{dt}\int_{\omega_n^t}\tilde{f}\,dx=\int_{\partial\omega_n^t}\left(-\nu\cdot j+fv\cdot\nu\right)dS=0,$$

again by Liouville's formula for the first volume variation, where dS denotes the surface element.

The chemical reaction $c+f\to c_*$ is supposed to take place only on the boundary Γ_t. Using the material derivative

$$\frac{D}{Dt}=\frac{\partial}{\partial t}+v\cdot\nabla,$$

we obtain

$$\begin{aligned} &c_t + v \cdot \nabla c = -\kappa_c f c, \\ &c_{*t} + v \cdot \nabla c_* = \kappa_c f c \qquad \text{on} \bigcup_{0<t<T} \Gamma_t \times \{t\}. \end{aligned} \tag{2.23}$$

Then, similarly to (2.22), it follows that

$$\begin{aligned} c(x,t) &= c_0(U(0,t)x) \exp\left(-\kappa_c \int_0^t f(U(t',t)x,t')dt'\right), \\ c_*(x,t) &= c_{*0}(U(0,t)x) \exp\left(\kappa_c \int_0^t f(U(t',t)x,t')dt'\right) \text{ on } \bigcup_{0<t<T} \Gamma_t \times \{t\} \end{aligned}$$

and total mass conservation holds in the sense that

$$\frac{D}{Dt}(c + c_*) = 0.$$

Outside the cell, we only use the diffusion and decay of c_*. Since its values on the free boundary are determined by the second equation in (2.23), we take

$$c_{*t} = d_{c_*} \Delta c_* - \lambda_{c_*} c_* \quad \text{in} \bigcup_{0<t<T} \omega_c^t \times \{t\}, \tag{2.24}$$

with

$$\frac{\partial c_*}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T). \tag{2.25}$$

The model is now built up with (2.18), (2.19), (2.20), (2.23), (2.24), and (2.25). Then we obtain

$$\begin{aligned} \frac{d}{dt}\int_{\Gamma_t} c_* \, dS &= \int_{\Gamma_*} (c_{*t} + (\nabla \cdot c_* \nu) v \cdot \nu) \, dS \qquad (2.26) \\ &= \int_{\Gamma_t} \left(c_{*t} + [(\nabla \cdot \nu) c_* + \frac{\partial c_*}{\partial \nu}] v \cdot \nu\right) dS \\ &= \int_{\Gamma_t} \left(\kappa_c f c - v_\tau \frac{\partial c_*}{\partial \tau} + (\nabla \cdot \nu) c_* v \cdot \nu\right) dS, \qquad (2.27) \end{aligned}$$

by Liouville's formula for the first area variation. Here, the outer normal vector ν is taken, regarding $\omega_c = \omega_c^t$ as the interior. If $\omega_n = \omega_n^t$ has a peak denoted by Q, then $\nabla \cdot \nu < 0$ there. In the case that v is orthogonal to $\partial\omega_n$, the production of c_* is large at Q.

This model has the advantage of allowing simulations for many cells provided with the adhesion regulation (Fig. 2.8) see [37].

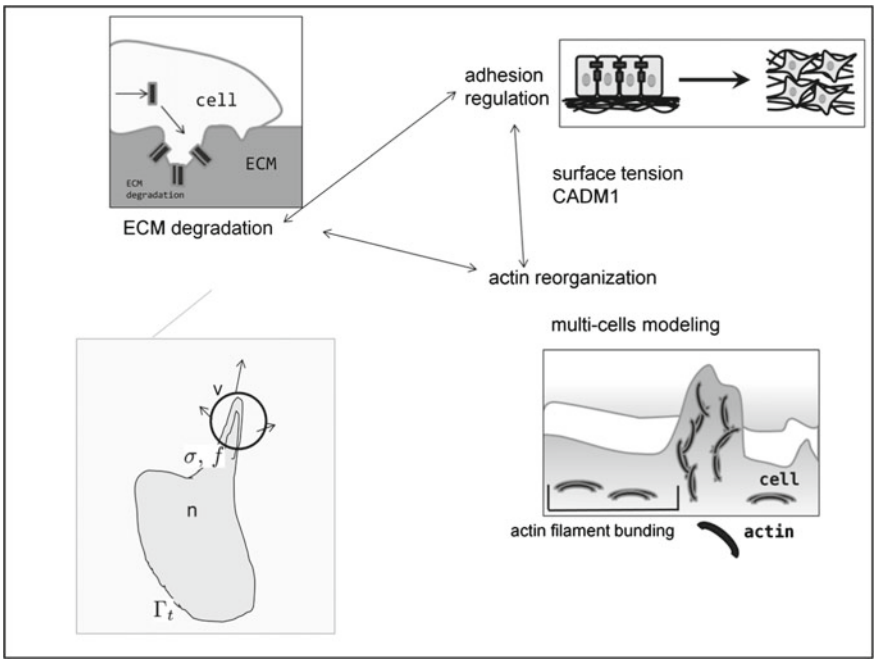

Fig. 2.8 Cell deformation

2.3 Smoluchowski-ODE Systems

Here we examine the mathematical validity of the multi-scale model described above, taking the simple form

$$\begin{aligned} &q_t = \nabla \cdot (\nabla q - q\nabla\varphi(v)),\ v_t = q && \text{in } \Omega \times (0,T), \\ &\tfrac{\partial q}{\partial \nu} - q\tfrac{\partial}{\partial \nu}\varphi(v) = 0 && \text{on } \partial\Omega \times (0,T), \\ &q|_{t=0} = q_0(x) \geq 0,\ v|_{t=0} = v_0(x) && \text{in } \Omega, \end{aligned} \tag{2.28}$$

where $\Omega \subset \mathbf{R}^N$ is a bounded domain with smooth boundary $\partial\Omega$, ν is the unit outer normal vector, $q_0 = q_0(x) > 0$ and $v_0 = v_0(x)$ are smooth functions of $x \in \overline{\Omega}$, and $\varphi : \mathbf{R} \to \mathbf{R}$ is a smooth function. Below we examine several multi-scale models of (2.9)–(2.10) via (2.28).

Imposing the condition

$$\frac{\partial v_0}{\partial \nu} = 0 \quad \text{on } \partial\Omega \tag{2.29}$$

to the initial value, we can replace the boundary condition by

$$\frac{\partial q}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0, T). \tag{2.30}$$

In fact, (2.30) and (2.29) imply that

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

because $v_t = q$, and then it follows that

$$\frac{\partial q}{\partial \nu} - q\frac{\partial \varphi(v)}{\partial \nu} = \frac{\partial q}{\partial \nu} - q\varphi'(v)\frac{\partial v}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, T). \tag{2.31}$$

Conversely, (2.31) and (2.29) imply that

$$\frac{\partial q}{\partial \nu}(\cdot, t) - [q\varphi'(v)](\cdot, t)\int_0^t \frac{\partial q}{\partial \nu}(\cdot, t')dt' = 0 \quad \text{on } \partial\Omega \times (0, T), \tag{2.32}$$

because

$$v(x, t) = v_0(x) + \int_0^t q(x, t')dt'. \tag{2.33}$$

Hence, (2.30) holds.

System (2.28) may look restrictive, compared with a variety of (2.9)–(2.10). For example, problem (2.1) of [150] with $\chi(w) = \log w$ and $g(p, w) = \beta p - \mu w$ does not reduce to (2.28). Some cases, however, are still reducible to (2.28). First,

$$w_t = g(p, w)$$

is transformed to

$$v_t = q$$

for $g(p, w)$ given by the expressions below, where $\mu > 0$ is a constant:

$$\begin{aligned} g(p, w) &= (p - \mu)w, \ w > 0 \quad &\Rightarrow \quad v &= \log w, \ q = p - \mu, \\ g(p, w) &= p(\mu - w), \ w < \mu \quad &\Rightarrow \quad v &= -\log(\mu - w), \ q = p, \\ g(p, w) &= -pw, \ w > 0 \quad &\Rightarrow \quad v &= -\log w, \ q = p. \end{aligned}$$

The model (2.9)–(2.10), used in [72–75], is thus reduced to (2.28) in the following cases:

$$\begin{aligned} &\chi'(w) = \frac{a(\beta - \alpha)}{(w + \alpha)(w + \beta)}, \quad g(p, w) = pw, \quad w > 0 \\ &\Rightarrow \quad \varphi(v) = a \log \frac{e^v + \alpha}{e^v + \beta}, \end{aligned} \tag{2.34}$$

$$\chi'(w) = \frac{a(\beta-\alpha)}{(w+\alpha)(w+\beta)}, \quad g(p,w) = -pw, \quad w > 0$$
$$\Rightarrow \quad \varphi(v) = a \log \frac{e^{-v}+\alpha}{e^{-v}+\beta}. \tag{2.35}$$

The case of negative chemotaxis,

$$\varphi \in C^3(\mathbf{R}), \quad \varphi' \le 0 \le \varphi''. \tag{2.36}$$

is obtained for $\alpha \ge \beta, v \ge \frac{1}{2}\log(\alpha\beta)$ and $\beta \le \alpha, v \le \frac{1}{2}\log(\alpha\beta)$ in (2.34) and (2.35), respectively. The other examples used by [101] are the following, where $a > 0$ is a constant:

$$\begin{aligned}
&\chi'(w) = a < 0, \quad g(p,w) = p(\mu - w), \quad w < \mu,\\
&\chi'(w) = -a/w, \quad g(p,w) = p(\mu - w), \quad v \ge -\log\mu,\\
&\chi'(w) = -a/(1+w)^2, \quad g(p,w) = pw, \quad w > 0, \quad v \ge 0,\\
&\chi'(w) = a, \quad g(p,w) = -pw, \quad w > 0,\\
&\chi'(w) = a/w, \quad g(p,w) = -pw, \quad w > 0,\\
&\chi'(w) = a/(1+w)^2, \quad g(p,w) = -pw, \quad w > 0, \quad v \ge 0.
\end{aligned}$$

Furthermore, system (2.28) with (2.36) is equivalent to the one studied by [22], that is,

$$\begin{aligned}
&n_t = \nabla\cdot(\nabla n - n\chi'(c)\nabla c), \ n > 0,\\
&c_t = -cn, \ c > 0 && \text{in } \Omega\times(0,T),\\
&\frac{\partial n}{\partial \nu} - \chi'(c)\frac{\partial c}{\partial \nu} = 0 && \text{on } \partial\Omega\times(0,T),
\end{aligned} \tag{2.37}$$

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

$$\chi'(c) \ge 0, \qquad c\chi''(c) + \chi'(c) \ge 0. \tag{2.38}$$

In fact, putting $v = -\log c$ and $q = n$, we obtain (2.28), for $\varphi = \varphi(v)$ where

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

Then (2.38) coincides with (2.36) (see also [23]).

In the next section we show the global-in-time existence of the solution to (2.28) and its ergodic property in the case where the space dimension is one. The argument follows [106] for $\varphi(v) = -v$, using the continuous embedding of [81], namely,

$$L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^2(\Omega)) \hookrightarrow L^4(0,T;L^\infty(\Omega)). \tag{2.39}$$

This result is a counterpart of the one obtained in [150] 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 $\varphi(v) = v$ does not satisfy $\varphi' \le 0$.

The above property is valid also to the system

$$\begin{aligned} &q_t = \nabla \cdot (\nabla q - q\nabla\varphi(v,w)), && \\ &v_t = q, \quad w_t = q && \text{in } \Omega \times (0,T), \\ &\tfrac{\partial q}{\partial \nu} = 0 && \text{on } \partial\Omega \times (0,T), \\ &q|_{t=0} = q_0, \quad v|_{t=0} = v_0, \quad w|_{t=0} = w_0 && \text{in } \Omega. \end{aligned} \tag{2.40}$$

Here we impose the compatibility condition

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

which replaces the boundary condition by the zero-flux condition

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

Then we obtain a similar result, assuming

$$\begin{aligned} &\varphi = \varphi(v,w) \in C^3(\mathbf{R} \times \mathbf{R}), \\ &\varphi_v,\ \varphi_w \le 0,\ \varphi_{vv},\ \varphi_{ww} \ge 0,\ \varphi_{vw} = 0. \end{aligned} \tag{2.41}$$

System (2.40) can describe several models.

The first example, found in [4], is modeling tumour induced angiogenesis. The variables in it are the endothelial cell density per unit area, denoted by n, the TAF (tumour angiogenesis factors) concentration f, and the matrix macromolecule fibronectin concentration c. Thus we have

$$\begin{aligned} &n_t = D\Delta n - \nabla \cdot (\chi'(c) n \nabla c) - \rho_0 \nabla \cdot (n \nabla f), \\ &f_t = \beta n - \mu n f, \\ &c_t = -\gamma n c, \end{aligned} \tag{2.42}$$

with

$$\chi'(c) = \frac{\chi_0}{1 + \alpha c} \tag{2.43}$$

where $D, \rho_0, \beta, \mu, \gamma, \chi_0, \alpha > 0$ are constants. We can write (2.42) with initial and boundary conditions as

$$
\begin{aligned}
&n_t = \nabla \cdot (D\nabla n - n\nabla \log \Phi(c) - n\nabla \log \Psi(f)),\\
&f_t = \beta n - \mu n f,\ c_t = -\gamma n c && \text{in } \Omega \times (0,T),\\
&(D\nabla n - n\nabla \log \Phi(c) - n\nabla \log \Psi(f)) \cdot \nu = 0 && \text{on } \partial\Omega \times (0,T),\\
&n|_{t=0} = n_0 > 0,\quad f|_{t=0} = f_0 > 0,\quad c|_{t=0} = c_0 > 0 && \text{in } \Omega. \qquad (2.44)
\end{aligned}
$$

Here, $\Phi, \Psi : \mathbf{R} \to \mathbf{R}$ are smooth positive functions satisfying

$$\chi(c) = \log \Phi(c), \quad \rho_0 f = \log \Psi(f).$$

Assuming

$$
\begin{aligned}
&f_0 > \frac{\beta}{\mu} && \text{in } \Omega,\\
&\frac{\partial n_0}{\partial \nu} = \frac{\partial c_0}{\partial \nu} = \frac{\partial f_0}{\partial \nu} = 0 && \text{on } \partial\Omega, \qquad (2.45)
\end{aligned}
$$

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

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

Then we obtain (2.40) from (2.44), writing t for τ, and are able to verify all the assumptions required for $\varphi = \varphi(v,w)$.

The same treatment is possible for the other model of angiogenesis used in [5], that is,

$$\Phi(c) = e^{\varphi_0 c}, \qquad \Psi(f) = e^{\rho_0 f}.$$

These models of angiogenesis are derived from several formulas in Sect. 2.1, accounting for the effects of angiogenesis, chemotaxis, and haptotaxis to fit the experimental data.

The system (2.28) is equivalent to the evolution equation with strong dissipation

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

This formulation is used to study the blowup and global-in-time solutions in [74, 80, 150]. For example, if the nonlinearity $\varphi = \varphi(v)$ is assumed to be bounded together with higher-order derivatives and to satisfy

$$\lim_{v \uparrow +\infty} \varphi'(v) = 0,$$

then a global-in-time solution exists, provided that

$$q_0(x) = \gamma + q_1(x), \quad \gamma \gg 1, \quad \int_\Omega q_1(x)\, dx = 0.$$

A similar result holds also for (2.42)–(2.43) (see [72, 73, 75]). Some models of [101] are reduced to taking $\varphi = \varphi(v, w)$ as in (2.34)–(2.35); these cases are studied by [74].

In the counterpart of (2.45),

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

there are a priori bounds of the solution to problem (2.42)–(2.43) under the assumption of

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

Then a global-in-time solution exists and it converges to the stationary solution, by the comparison principle [35].

2.4 Smoluchowski-Poisson Systems

The chemical process (2.8) is sometimes replaced by the Michaelis-Menten process. It arises when one assumes that (w, p) is in the quasi-stationary state. Using the conservation of total mass $(w + p)_t = 0$, it is formulated as

$$k_1 v w - (k_{-1} + k_2) p = 0, \quad w + p = c, \tag{2.46}$$

where c is a constant. Then it holds that

$$w = \frac{(k_-1 + k_2)c}{k_1 v + k_{-1} + k_2}, \quad p = \frac{c k_1 v}{k_1 v + k_{-1} + k_2},$$

and hence

$$-k_1 v w + k_{-1} p = -\frac{c k_1 k_2}{k_1 v + k_{-1} + k_2} v.$$

Equation (2.7) thus reduces to

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

and then the Keller-Segel system (2.5)–(2.6) implies

$$\begin{aligned} u_t &= \nabla \cdot (d_1(u,v)\nabla u) - \nabla \cdot (d_2(u,v)\nabla v), \\ v_t &= d_v \Delta v - k(v)v + f(v)u \qquad \text{in } \Omega \times (0,T), \end{aligned} \tag{2.47}$$

with

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T). \tag{2.48}$$

Nanjundiah [95] considered the case where $d_1(u,v)$, $k(v)$, and $f(v)$ are constants, and $d_2(u,v) = u\chi'(v)$ in (2.47)–(2.48) which leads to the problem

$$\begin{aligned} u_t &= d_u \Delta u - \nabla \cdot (u \nabla \chi(v)), \\ v_t &= d_v \Delta v - b_1 v + b_2 u \qquad \text{in } \Omega \times (0,T), \\ \frac{\partial u}{\partial \nu} &= \frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T). \end{aligned} \tag{2.49}$$

Here $\chi'(v)$ stands for the chemotactic sensitivity and henceforth $\chi = \chi(v)$ is called the sensitivity function.

Reducing the second equation to an ODE, we get the Smoluchowski-ODE system studied in (2.3),

$$\begin{aligned} q_t &= \nabla \cdot (\nabla q - q \nabla \varphi(v)) \\ v_t &= q \qquad \text{in } \Omega \times (0,T) \\ \frac{\partial q}{\partial \nu} - q \frac{\partial \varphi(v)}{\partial \nu} &= 0 \qquad \text{on } \partial\Omega \times (0,T). \end{aligned} \tag{2.50}$$

An asymptotic analysis, on the other hand, produces the simplified system for the linear sensitivity function $\chi(v) = \chi v$, the Smoluchowski-Poisson equation [20, 56]:

$$\begin{aligned} u_t &= \nabla \cdot (\nabla u - u \nabla v), \\ -\Delta v &= u - \frac{1}{|\Omega|} \int_\Omega u \, dx \qquad \text{in } \Omega \times (0,T), \quad \int_\Omega v = 0, \\ \frac{\partial u}{\partial \nu} - u \frac{\partial v}{\partial \nu} &= \frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega \times (0,T). \end{aligned} \tag{2.51}$$

Still we can observe several mesoscopic key factors in (2.51) used for the original top-down modeling.

In fact, the first equation represents mass conservation law (2.15),

$$u_t = -\nabla \cdot j \tag{2.52}$$

with the flux of u defined by

$$j = -\nabla u + u \nabla v. \tag{2.53}$$

The null-flux boundary condition is imposed in (2.51), which guarantees the conservation of the total mass:

$$\frac{d}{dt}\int_\Omega u\,dx = 0. \tag{2.54}$$

In (2.53) the chemical substance v stands for the carrier of the cells u. The diffusion $-\nabla u$ is thus competing the chemotaxis $u\nabla v$ according to the phenomenological relation. The second equation of (2.51), on the other hand, describes a coarsed process of generation of the chemical potential ∇v from the particle density u using the Poisson equation. These features of (2.51) reflect several principles used in the bottom-up modeling. System (2.51) is actually obtained also by bottom-up modeling based on the movements of particles described in Sects. 3.1 and 3.2. The conservation law (2.52) thus reads

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

with the transport velocity

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

The Poisson part

$$-\Delta v = u - \frac{1}{|\Omega|}\int_\Omega u\,dx \ \text{ in } \Omega, \quad \frac{\partial v}{\partial \nu} = 0 \ \text{ on } \partial\Omega, \quad \int_\Omega v\,dx = 0, \tag{2.55}$$

is uniquely solvable, which may be written as $v = (-\Delta)^{-1}u$ for simplicity. The strong maximum principle, on the other hand, guarantees that $u > 0$ in $\overline{\Omega}\times(0,T)$, provided that $u_0 \geq 0$ is not identically 0. Writing the Smoluchowski part as

$$u_t = \nabla\cdot u\nabla(\log u - v), \quad \left(\frac{\partial u}{\partial \nu} - u\frac{\partial v}{\partial \nu}\right)\Big|_{\partial\Omega} = 0, \tag{2.56}$$

we obtain

$$\int_\Omega u_t(\log u - v)\,dx = -\int_\Omega u|\nabla(\log u - v)|^2\,dx, \tag{2.57}$$

with the left-hand side equal to

$$\frac{d}{dt}\left\{\int_\Omega u(\log u - 1)\,dx - \frac{1}{2}\left\langle(-\Delta)^{-1}u, u\right\rangle\right\}.$$

This variational structure is physically justified by the fact that

$$\mathcal{F}(u) = \int_\Omega u(\log u - 1)\,dx - \frac{1}{2}\left\langle(-\Delta)^{-1}u, u\right\rangle$$

represents the Helmholtz free energy.

Using this model, it is rigorously shown in [56] that chemotaxis can serve as the main mechanism for the onset of self-organization of the *Dictyostelium discoideum* (Dd amoebae). Later studies are concerned with the blowup threshold [10, 36, 89, 90, 92, 118, 125], formation of collapse singularity [43, 117], mass quantization [43, 122, 128], sub-collapses which results in type II blowup rates [43, 94, 115], and the free energy transmission of the blowup solution [122, 123], while the blowup threshold does not arise for the full parabolic-parabolic system [11] (see [61, 145] for a related model).

Turning to the mesoscopic modeling, the phase field model arises with the chemical potential

$$\mu = \delta\mathcal{F}(\varphi),$$

where $\mathcal{F} = \mathcal{F}(\varphi)$ stands for the free energy $\mathcal{F} = \mathcal{F}(\varphi)$ defined by the order parameter $\varphi = \varphi(x)$. These equations are classified into models (A), (B), and (C) [40, 45]. The order parameter, $\varphi = \varphi(x, t)$, $(x, t) \in \Omega \times (0, T)$, represents the state of the material, while $\mathcal{F} = \mathcal{F}(\varphi)$ is a quantity determined by φ. Hence the system moves toward equilibrium: $\mathcal{F}(\varphi)$ decreases and attains a local minimum at the equilibrium. The chemical potential $\delta\mathcal{F}(\varphi)$ is defined by

$$\langle \psi, \delta\mathcal{F}(\varphi)\rangle = \frac{d}{ds}\mathcal{F}(\varphi + s\psi)\Big|_{s=0}, \tag{2.58}$$

where the pairing $\langle\ ,\ \rangle$ is usually identified with the L^2 inner product.

The model (A) equation is formulated by

$$\varphi_t = -K\delta\mathcal{F}(\varphi) \qquad \text{in } \Omega \times (0, T),$$

where K is a positive quantity, possibly associated with φ. Then it holds that

$$\frac{d}{dt}\mathcal{F}(\varphi) = -\int_\Omega K\delta\mathcal{F}(\varphi)^2 \le 0.$$

The model (B) equation takes the form

$$\begin{aligned} &\varphi_t = \nabla\cdot(K\nabla\delta\mathcal{F}(\varphi)) && \text{in } \Omega \times (0, T),\\ &K\frac{\partial}{\partial\nu}\delta\mathcal{F}(\varphi) = 0 && \text{on } \partial\Omega \times (0, T). \end{aligned}$$

In this case we obtain

$$\begin{aligned} &\frac{d}{dt}\int_\Omega \varphi\, dx = \int_{\partial\Omega} K\frac{\partial}{\partial\nu}\delta\mathcal{F}(\varphi)\, dS = 0,\\ &\frac{d}{dt}\mathcal{F}(\varphi) = -\int_\Omega K\,|\nabla\delta\mathcal{F}(\varphi)|^2\, dx \le 0. \end{aligned}$$

The equations of models (A) and (B) describe thermodynamically closed and thermodynamically-materially closed systems, respectively. Neither of them admits non-trivial periodic-in-time solutions.

The stationary state is actually defined by the vanishing of the free-energy consumption, that is,

$$\frac{d}{ds}\mathcal{F}(\varphi + s\psi)\Big|_{s=0} = 0, \quad \forall \psi, \tag{2.59}$$

and

$$\frac{d}{ds}\mathcal{F}(\varphi + s\psi)\Big|_{s=0} = 0, \quad \forall \psi, \quad \int_\Omega \psi \, dx = 0, \quad \int_\Omega \varphi \, dx = \lambda, \tag{2.60}$$

respectively, in model (A) and (B) equations, where λ is a constant prescribed by the initial value. The linearized stability of the stationary state φ means, similarly, that

$$Q(\psi, \psi) \equiv \frac{1}{2}\frac{d^2}{ds^2}\mathcal{F}(\varphi + s\psi)\Big|_{s=0} > 0, \quad \forall \psi \neq 0$$

and

$$Q(\psi, \psi) > 0 \quad \forall \psi \neq 0, \quad \int_\Omega \psi \, dx = 0$$

for the model (A) and (B) equations, respectively.

The Smoluchowski-Poisson equation (2.51) is the model (B) equation associated with the Helmholtz free energy. First, the Smoluchowski part describes mass conservation (2.52) with the flux given by (2.53). The chemotactic sensitivity v, on the other hand, is the solution to the Poisson part (2.55). Since $u = u(x, t)$ represents particle distribution function, this $v = v(x, t)$ acts as a potential of attractive chemotaxis. Here, (2.55) is equivalent to

$$v = \int_\Omega G(\cdot, x')u(x') \, dx' \tag{2.61}$$

with $G = G(x, x')$ denoting the Green function. Since

$$G(x, x') \approx \Gamma(x - x')$$

with

$$\Gamma(x) = \begin{cases} \dfrac{1}{4\pi} \cdot \dfrac{1}{|x|}, & N = 3 \\ \dfrac{1}{2\pi} \log \dfrac{1}{|x|}, & N = 2, \end{cases}$$

Eq. (2.55) may be regarded as the formation of gravitational field created by the particle density. The inner (potential) energy of this system, therefore, is defined by

$$E = -\frac{1}{2}\iint_{\Omega\times\Omega} G(x,x')u(x)u(x')\,dxdx'.$$

Here we take the minus sign because of the self-attractivity of gravitation. The factor $\frac{1}{2}$ appears as usual because Newton's third law of action-reaction induces the symmetry of the kernel in (2.61),

$$G(x',x) = G(x,x'), \tag{2.62}$$

Since u is the particle density, on the other hand, we introduce the entropy by

$$S = -\int_\Omega u(\log u - 1)\,dx.$$

Under the normalization $T = 1$, the Helmholtz free energy $F = E - TS$ thus takes the form

$$\mathcal{F}(u) = \int_\Omega u(\log u - 1) - \frac{1}{2}\iint_{\Omega\times\Omega} G(x,x')u(x)u(x')\,dxdx'. \tag{2.63}$$

The Smoluchowski-Poisson equation is an adiabatic limit of a kinetic equation with fluctuation and friction (see [143, 144] for more details). Equation (2.51) actually describes the motion of the mean field of many self-attracting particles subject to the second law of thermodynamics. Hence one has the decrease of free energy besides the total mass conservation (2.54). The phenomenological formulation of model (B) equation is consistent with the mesoscopic approach using kinetic equation in this case. In fact, the first variation $\delta\mathcal{F}(u)$ of $\mathcal{F}(u)$ is defined by

$$\langle w, \delta\mathcal{F}(u)\rangle = \frac{d}{ds}\mathcal{F}(u+sw)\bigg|_{s=0}.$$

Identifying again this pairing $\langle\ ,\ \rangle$ with the L^2 inner product, we obtain

$$\delta\mathcal{F}(u) = \log u - v, \quad v = \int_\Omega G(\cdot,x')u(x')\,dx'.$$

Thus (2.56) reads

$$\begin{aligned} &u_t = \nabla\cdot(u\nabla\delta\mathcal{F}(u)) && \text{in } \Omega\times(0,T),\\ &u\frac{\partial}{\partial\nu}\delta\mathcal{F}(u) = 0 && \text{on } \partial\Omega\times(0,T). \end{aligned} \tag{2.64}$$

This is a form of the model (B) equation derived from the free energy $\mathcal{F} = \mathcal{F}(u)$. Consequently,

$$\begin{aligned} &\frac{d}{dt}\int_\Omega u\,dx = -\int_{\partial\Omega} u\frac{\partial}{\partial\nu}\delta\mathcal{F}(u)\,dS = 0,\\ &\frac{d}{dt}\mathcal{F}(u) = -\int_\Omega u\,|\nabla\delta\mathcal{F}(u)|^2\,dx \le 0. \end{aligned} \tag{2.65}$$

The second inequality in (2.65) means the decrease of free energy, while the first equality, combined with $u = u(x,t) \ge 0$, assures the total mass conservation

$$\lambda \equiv \|u_0\|_1 = \|u(\cdot,t)\|_1\,, \qquad t \in [0, T_{\max}). \tag{2.66}$$

Relation (2.66) leads to the selection of the space dimension $N = 2$ for the formation of collapses, using dimensional analysis [20].

The stationary problem (2.60), on the other hand, is given by

$$\log u - v = \text{constant}, \quad v = (-\Delta)^{-1}u, \quad \int_\Omega u\,dx = \lambda, \tag{2.67}$$

where $v = (-\Delta)^{-1}u$ indicates (2.61). Then it holds that

$$-\Delta v = \lambda\left(\frac{e^v}{\int_\Omega e^v} - \frac{1}{|\Omega|}\right) \text{ in } \Omega, \quad \frac{\partial v}{\partial\nu} = 0 \text{ on } \partial\Omega, \quad \int_\Omega v\,dx = 0, \tag{2.68}$$

since

$$u = \frac{\lambda e^v}{\int_\Omega e^v dx}, \quad v = (-\Delta)^{-1}u.$$

The profile of the solution in (2.68) by [116] suggests the quantized blowup mechanism for (2.51). Later, this property was studied by many authors (see [122, 125, 128] and the references therein). See also Sect. 4.5.

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