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Self-Consistent Diffusive Kinetics and Dissipative Structures in a Distributed Cell System

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By analogy with a problem on the kinetics of the last stages of solid supersaturated solution decay, considered in Ref. 1, the problem on the kinetics of cell population development in the nutrient solution is formulated. The state of the system is described by the cell size distribution function and the concentration of nutrient in the solution. The stability of spatially homogeneous cell distribution is analyzed. Bifurcation, connected with the origin of nonhomogeneous spatial distribution of cells and nutrient, is discovered. Dissipative structures arising near the point of first bifurcation are found.

KEY WORDS: Cell population; spatial distribution; bifurcation.

1. INTRODUCTION

One of the most interesting results of I. M. Lifshitz, connected with the problems of the statistical physics, is the development of the theory of the last stages of solid solutions diffusional decay.[1] Physical peculiarity of this problem consists in the consideration of self-consistent evolution of an ensemble of objects; in Ref. 1 these objects are the grains of a new phase, which effectively interact through the solution. The state of the grain ensemble is described by the size distribution function whose form essentially depends on the law of a single grain growth. In its turn, the single grain rate of growth is considered as a definite function of the nutrient concentration in the solution. And the state of the solution is described by some balance equation, which takes into account a supersaturation of the solution and content of the substance in the grains of a new phase. The latter is defined by the cell size distribution function.

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Formally, a similar situation arises when one describes the evolution of a cell system in the nutrient solution. This analogy becomes clearly expressed in the case, when the state of the single cell may be uniquely defined by the radius. Such a system essentially differs from an ensemble of grains, because (1) there are processes of cell death and division, and (2) the rate of cell growth is a positive value, i.e., there is no process analogous to the dissolving of the grains of small radius.

When considering the process of coalescence,[1] evolution of an ensemble of voids and vacancies in the crystal,[2] kinetics of the new phase nucleation,[3] evolution of a system of dislocation loops in a crystal under an applied load,[4] and similar processes, one usually restricts oneself with the investigation of a spatially homogeneous situation. In the present paper an assumption about nonhomogeneous spatial distribution of cells and nutrient is essentially used. Then the processes of diffusion which can lead to the origin of a spatial structure become important.

2. EVOLUTION OF SPATIALLY NONHOMOGENEOUS CELL SYSTEM

Consider the ensemble of cells suspended in a nutrient solution. The number of cells is believed to be sufficiently large to introduce the distribution function in some parameters, particularly in cell sizes. At the same time the number of cells per unit volume is believed to be sufficiently small to neglect the direct interaction between the cells. Further, we shall consider the case when the concentration of substrate absorbed by the cells is small enough. In this case the cell growth rate depends on the value of this concentration like in the coalescence problem.[5] This means that there is an indirect interaction between the cells through the solution.

Let us introduce the cell size distribution function $f(R, \mathbf{x}, t)$, where R is the cell radius and $\mathbf{x}$ is the spatial coordinate. The full number of cells $N(t)$ in such a system equals to

$$N(t) = \int_V d\mathbf{x} \int_0^\infty f(R, \mathbf{x}, t)\, dR \tag{1}$$

where V is the system volume.

The evolution of the function $f(R, \mathbf{x}, t)$ is described by the continuity equation in the space of variables R and $\mathbf{x}$ taking into account the spatial diffusion of cells and substrate:

$$\frac{\partial f}{\partial t} + \frac{\partial}{\partial R}(vf) = -\frac{1}{\tau} f + D_c \Delta f - v(R)\, w(R)\, f(R, \mathbf{x}, t) + 2\sqrt[3]{2}\, v(\sqrt[3]{2}\, R)\, w(\sqrt[3]{2}\, R)\, f(\sqrt[3]{2}\, R, \mathbf{x}, t) \tag{2}$$

where $v(R) \equiv dR/dt$ is the growth rate of the cell of radius R; τ is the characteristic time of cell death; D_c is the coefficient of cell diffusion; $w(R)$ is the conditional probability of the division of the cells of radii R, i.e., the probability that a cell of radius R will be divided in the interval $(R, R + dR)$. The function $w(R)$ is connected with the absolute probability of the division $\varphi(R)$ as $w(R) = \varphi(R)/\{1 - \int_0^R \varphi(x)\,dx\}$, $\int_0^\infty \varphi(x)\,dx = 1$. Further we shall consider $D_c = \text{constant}$ independent on the cell size R.

In the case of small concentration c, the rate of growth takes the form[5]

$$v(R, c) = c(t)u(R) \tag{3}$$

where $u(R)$ is some function of radius taking into account the diffusive mechanism of substrate supply to the cells. The examples of functions $u(R)$ are given in Refs. 5, 7, and 8.

The equation describing the evolution of the function $c(t)$, similar to that in the coalescence problem, is the balance equation for the substance in the solution:

$$\frac{\partial c}{\partial t} = D_s \Delta c - \int_0^\infty \gamma(R, c) f(R, \mathbf{x}, t)\,dR \tag{4}$$

where D_s is the coefficient of substrate diffusion; $\gamma(R, c)$ in the simplest case equals $\gamma_0 R^2 v(R, c)$, where $\gamma_0 = \text{const}$.[5] The integral term in (4) describes the intensity of substrate absorption by the cells.

We shall find the solution of Eq. (2) in the form which allows the separation of variables:[6,9]

$$f(R, \mathbf{x}, t) = \xi(R)\,\eta(\mathbf{x}, t) \tag{5}$$

with the boundary conditions in the form

$$\left.\frac{\partial f}{\partial n}\right|_s = 0, \qquad c|_s = c_s \tag{6}$$

where s is the outside surface of the system, $\partial f/\partial n$ is the normal derivative at this surface.

Equations (2)–(4) with boundary conditions (6) and corresponding initial conditions completely describe the behavior of the cells–solution system. Substituting (5) into (2) and (4) we obtain the following set of equations:

$$\frac{\partial \eta}{\partial t} = \lambda c(\mathbf{x}, t)\eta - \frac{1}{\tau}\eta + D_c \Delta \eta \tag{7}$$

$$\frac{\partial}{\partial R}(u\xi) = -\lambda\xi - u(R)\, w(R)\, \xi(R) + 2\sqrt[3]{2}\, u(\sqrt[3]{2}\, R)\, w(\sqrt[3]{2}\, R)\, \xi(\sqrt[3]{2}\, R) \tag{8}$$

$$\frac{\partial c}{\partial t} = D_s \Delta c - \gamma_0 \eta(\mathbf{x}, t)\, c(\mathbf{x}, t) \int_0^\infty R^2 u(R)\, \xi(R)\, dR \tag{9}$$

where λ is the integration constant.

Equation (8) is autonomous and can be solved independently. As shown before,[6] the solution of this equation can be simply obtained in the case when the minimum size of the divided cells R_3 is greater than the maximum size of the cells being born $R_2 = R_4/\sqrt[3]{2}$. In this case[6]

$$\xi(R) = \frac{2}{u(R)} \exp\left[-\lambda \int_{R_2}^{R} \frac{dx}{u(x)}\right] \times \int_{R_3}^{\sqrt[3]{2}\,R} \varphi(r) \exp\left[-\lambda \int_{r/\sqrt[3]{2}}^{r} \frac{dx}{u(x)}\right] dr \qquad (R_1 < R < R_2) \tag{10}$$

$$\xi(R) = \frac{1}{u(R)} \exp\left[-\lambda \int_{R_2}^{R} \frac{dx}{u(x)}\right] \qquad (R_2 < R < R_3) \tag{11}$$

$$\xi(R) = \frac{1}{u(R)} \exp\left[-\lambda \int_{R_2}^{R} \frac{dx}{u(x)}\right]\left[1 - \int_{R_3}^{R} \varphi(x)\, dx\right] \qquad (R_3 < R < R_4) \tag{12}$$

taking into account that a mother cell of radius R is divided into two daughter cells of radii $R/\sqrt[3]{2}$. The cells are divided in the interval (R_3, R_4) are born in the interval (R_1, R_2). Parameter λ can be found from the boundary condition at the point R_2[6,10]:

$$\frac{1}{2} = \int_{R_3}^{R_4} \varphi(r) \exp\left[-\lambda \int_{r/\sqrt[3]{2}}^{r} \frac{dx}{u(x)}\right] dr \tag{13}$$

Particularly, in the case of the exponential law of a single cell growth, $u(R) = vR$, the parameter λ has the following spectrum:

$$\lambda_\kappa = 3v + i3v \frac{2\pi\kappa}{\ln 2}, \qquad \kappa = 0, \pm 1, \pm 2, \ldots \tag{14}$$

When the probability of cell division has the form $\varphi(R) = \delta(R - R_f)$, this spectrum is

$$\lambda_\kappa = \frac{\ln 2}{P} + i\frac{2\pi\kappa}{P}, \qquad P = \int_{R_f/\sqrt[3]{2}}^{R_f} \frac{dx}{u(x)}, \qquad \kappa = 0, \pm 1, \pm 2, \ldots \tag{15}$$

We used the complex parameter λ of the form (14) and (15) for consideration of the stationary regime establishment in a homogeneous system.[6] Now we shall consider only the real values of parameter λ, because of (7) is a nonlinear equation for real values.

Equations (10)–(13) completely define the behavior of the function $\xi(R)$ in the whole interval (R_1, R_4). Substituting $\xi(R)$ into Eq. (9), we obtain the following set of equations:

$$\begin{aligned} \frac{\partial \eta}{\partial t} &= D_c \Delta \eta - \frac{1}{\tau}\eta + \lambda c \eta \\ \frac{\partial c}{\partial t} &= D_s \Delta c - ac\eta \end{aligned} \tag{16}$$

where we introduced the notation $a = \gamma_0 \int_{R_1}^{R_4} R^2 u(R)\, \xi(R)\, dR$.

The boundary conditions for system (16) have the form (6). The function $\eta(\mathbf{x}, t)$ is a spatial cell density when there is the normalizing condition $\int_{R_1}^{R_4} \xi(R)\, dR = 1$.

3. BIFURCATION OF THE HOMOGENEOUS STATIONARY REGIME

Consider the one-dimensional problem, assuming the cells are contained between two parallel plates with coordinates $x = 0$ and $x = L$. Let us introduce the dimensionless variables

$$r = x/(D_s\tau)^{1/2}, \qquad y = a\tau\eta, \qquad z = \lambda\tau c, \qquad \theta = t/\tau, \qquad \varepsilon = D_c/D_s \tag{17}$$

One can consider the cell diffusion coefficient to be much less than the nutrient diffusion coefficient, i.e., $\varepsilon \ll 1$. Using the dimensionless variables set, (16) takes the form

$$\begin{aligned} \frac{\partial y}{\partial \theta} &= \varepsilon \Delta_{rr} y + yz - y \\ \frac{\partial z}{\partial \theta} &= \Delta_{rr} z - yz \end{aligned} \tag{18}$$

The boundary conditions corresponding to (6) have the form

$$\left.\frac{\partial y}{\partial r}\right|_0 = \left.\frac{\partial y}{\partial r}\right|_{L/(D_s\tau)^{1/2}} = 0, \qquad z(0) = z[L/(D_s\tau)^{1/2}] = \lambda\tau c_s \tag{19}$$

This problem allows a homogeneous stationary solution

$$y = 0, \qquad z = \lambda\tau c_s \tag{20}$$

To carry out the linear stability analysis of this solution, let us introduce the variables $y_1(r, \theta) = y(r, \theta)$, $z_1(r, \theta) = z(r, \theta) - \lambda\tau c_s$, where $|z_1(r, \theta)| \ll \lambda\tau c_s$. Then

$$\begin{aligned} \frac{\partial y_1}{\partial \theta} &= \varepsilon \frac{\partial^2 y_1}{\partial r^2} - y_1 + \lambda\tau c_s y_1 \\ \frac{\partial z_1}{\partial \theta} &= \frac{\partial^2 z_1}{\partial r^2} - \lambda\tau c_s y_1 \end{aligned} \tag{21}$$

Function $y_1(r, \theta)$ has to be a nonnegative value. The solution of (21) for a homogeneous deviation $y_1(r, 0) = y_0 = \text{const}$ can be presented as

$$y_1(r, \theta) = y_0 e^{\sigma\theta} \tag{22}$$

where

$$\sigma = \lambda\tau c_s - 1 \tag{23}$$

Homogeneous distribution (20) is stable at $\sigma < 0$. At $\sigma > 0$ distribution (20) loses its stability. If we take c_s as the bifurcation parameter, it can be easily shown that the first bifurcation of solution (20) takes place at the critical value

$$c_s^{\text{cr}} = 1/\lambda\tau \tag{24}$$

Consider the behavior of the solution near the bifurcation point. Let us introduce the dimensionless parameter μ:

$$\mu = (c_s - c_s^{\text{cr}})/c_s^{\text{cr}} = \lambda\tau c_s - 1 \ll 1 \tag{25}$$

Let us describe the arising dissipative structure. We shall find the solution of (18) in the form of the power-series expansion in μ:

$$\begin{pmatrix} y(r, \theta) \\ z(r, \theta) \end{pmatrix} = \begin{pmatrix} y^{(0)} \\ z^{(0)} \end{pmatrix} + \mu \begin{pmatrix} y^{(1)} \\ z^{(1)} \end{pmatrix} + \mu^2 \begin{pmatrix} y^{(2)} \\ z^{(2)} \end{pmatrix} + \cdots \tag{26}$$

When $\mu \to 0$, this series has to converge to homogeneous solution (20), therefore

$$y^{(0)} = 0, \qquad z^{(0)} = \lambda\tau c_s^{\text{cr}} = 1 \tag{27}$$

For the first-order terms in μ, we shall obtain the following equations:

$$\begin{aligned} \frac{\varepsilon}{\mu} \frac{d^2 y^{(1)}}{dr^2} + y^{(1)} z^{(1)} &= 0 \\ \frac{d^2 z^{(1)}}{dr^2} - y^{(1)} &= 0 \end{aligned} \tag{28}$$

One can see that the behavior of the solution of these equations essentially depends on the value of the ratio ε/μ. In the case $\mu/\varepsilon \ll 1$, Eqs. (28) are simplified

$$\frac{d^2y^{(1)}}{dr^2} = 0, \qquad \frac{d^2z^{(1)}}{dr^2} - y^{(1)} = 0 \tag{29}$$

Whence, taking into account the boundary conditions, we find in zero μ/ε order

$$y^{(1)} = \alpha = \text{const} \tag{30}$$

$$z^{(1)} = 1 + \frac{\alpha r}{2}\left[r - \frac{L}{(D_s\tau)^{1/2}}\right] \tag{31}$$

Constant α can be found in the next μ/ε order. It is easy to show that

$$\alpha = 12D_s\tau/L^2 \tag{32}$$

Turning to the initial variables, we finally obtain

$$\eta(x) = 12\frac{\lambda\tau D_s}{aL^2}\left(c_s - \frac{1}{\lambda\tau}\right) \tag{33}$$

$$c(x) = c_s + 6\left(c_s - \frac{1}{\lambda\tau}\right)\left(\frac{x^2}{L^2} - \frac{x}{L}\right) \tag{34}$$

The correction to (33) and (34) at $\varepsilon \ll 1$ has an order of μ^2/ε. In the vicinity of the point $c_s = c_s^{\text{cr}}$ the solution is defined both for $c_s > c_s^{\text{cr}}$ and for $c_s < c_s^{\text{cr}}$. However, the stationary structures (33) and (34) arising in the vicinity of the bifurcation point are stable only at the supercritical branch ($c_s > c_s^{\text{cr}}$) and unstable at the subcritical one.

Let us consider now the case $\varepsilon/\mu \ll 1$. As it is known,[11] the solution of the equation with the small coefficient at the higher-order derivative has to be found separately far from the boundary and in the boundary layer. Far from the boundary, at distances $\delta r \gg (\varepsilon/\eta)^{1/2}$, one can make regular expansion of the functions $y^{(1)}(r)$ and $z^{(1)}(r)$ in the powers of μ, which gives the solution of the form

$$y^{(1)}(r) = 0, \qquad z^{(1)}(r) = \beta = \text{const} \tag{35}$$

in this region.

This solution satisfies the boundary conditions at $\beta = 1$, and coincides with the homogeneous solution (20), which is defined in the whole region $(0, L/(D_s\tau)^{1/2})$. However, as follows from (24), such a homogeneous

solution becomes unstable at $\mu > 0$ even in the case $\varepsilon \to 0$. Therefore, in the boundary layer the solution must differ from (35).

In the vicinity of the boundary one has to take into account the term $(\varepsilon/\mu)(d^2y^{(1)}/dr^2)$, because of the large gradient of the function $y^{(1)}(r)$ in this region. The derivatives of the functions $y^{(1)}(r)$ and $z^{(1)}(r)$ have the same order of magnitude, and this means that $d^2z^{(1)}/dr^2$ is also large. So in zero ε/μ order equations (28) in the boundary layer are simplified:

$$\frac{\varepsilon}{\mu}\frac{d^2y^{(1)}}{dr^2} + y^{(1)}z^{(1)} = 0 \tag{36}$$

$$\frac{d^2z^{(1)}}{dr^2} = 0 \tag{37}$$

Designate the solutions of Eqs. (36) and (37) as $y_0^{(1)}$ and $z_0^{(1)}$. From the second equation we obtain

$$z_0^{(1)} = 1 - Mr, \qquad M = \text{const} \tag{38}$$

Substituting (38) into (36) we obtain Airy's equation

$$\frac{d^2}{dr^2}\, y_0^{(1)} + (1 - Mr)\frac{\mu}{\varepsilon}\, y_0^{(1)} = 0 \tag{39}$$

For large values of r, the solution of Eq. (39) has to transform to solution (35). Therefore, as a solution of (39), one has to take Airy's function $\mathrm{Ai}(x)$, which exponentially damps at $r > 0$:

$$y_0^{(1)}(r) = k\ \mathrm{Ai}\left\{\left(\frac{\mu M}{\varepsilon}\right)^{1/3}\left(r - \frac{1}{M}\right)\right\}, \qquad k = \text{const} \tag{40}$$

where k is an amplitude of the distribution function.

Function $y_0^{(1)}(r)$ describes the spatial density of cells, and thus it has to be a nonnegative value. Therefore, taking into account boundary condition (19), the point $r = 0$ must correspond to the first maximum of oscillations of function (40). Let x_0 is coordinate of the first maximum of Airy's function. Then the magnitude of M can be obtained from the condition

$$M = \left(-\frac{1}{x_0}\right)^{3/2}\left(\frac{\mu}{\varepsilon}\right)^{1/2}$$

Because of $x_0 \approx -1$, $M \approx (\mu/\varepsilon)^{1/2}$.

For obtaining the coefficient k, let us consider the solution of the second equation of (28):

$$z^{(1)}(r) = \int_0^r \int_0^\zeta y_0^{(1)}(\zeta_1)\, d\zeta_1\, d\zeta + 1 - Mr \tag{41}$$

Since for large r solution (41) must turn to (35), the following conditions,

$$\lim_{r\to\infty} z^{(1)}(r) = \beta, \qquad \lim_{r\to\infty} \frac{dz^{(1)}(r)}{dr} = 0 \tag{42}$$

must be satisfied. The second of these conditions defines the value of the constant k:

$$k = \frac{3(\mu/\varepsilon)^{1/3} M^{4/3}}{1 + 3\int_{x_0}^0 \mathrm{Ai}(\xi)\, d\xi} \tag{43}$$

From the first condition of (42) one can obtain parameter β:

$$\beta = 1 + \frac{3}{x_0} \frac{\int_{x_0}^\infty x\, \mathrm{Ai}(x)\, dx}{1 + 3\int_{x_0}^0 \mathrm{Ai}(x)\, dx} \tag{44}$$

Since $x_0 < 0$, we obtain $\beta < 1$.

Similarly, one can obtain the solution near the boundary $r = L/(D_s\tau)^{1/2}$. For this purpose it is sufficient to introduce new variable $r_1 = L/(D_s\tau)^{1/2} - r$ instead of r.

Thus, two situations may arise. In the case $\mu/\varepsilon \ll 1$, when the deviation from the critical concentration c_s^{cr} is small, the stationary nonhomogeneous distribution of the form (34) arises in the system. In the zeroth order in μ/ε, the cell density in this case will be spatially homogeneous. In the case $\varepsilon/\mu \ll 1$, when the diffusion coefficients for cells and nutrient strongly differ from each other, cell concentration differs from zero only in the boundary layer of size of $(\varepsilon/\mu)^{1/2}$. In this layer the spatial cell distribution is described by the Airy's function of the form (42).

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