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CELLS AND ATTRACTANT MASSES RELATED BY CHEMOTACTIC AGGREGATION

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Abstract. The active role played by chemotactic current density of the migrating cells in order to overcome its diffusion current, leads to a spatially - non-homogeneous and time - persistent distribution of the cells. We show that independently of the initial attractant concentration, its quantity tends exponentially to the concentration of cells as the system approaches a steady state.

Introduction

There is evidence that the sensing of chemical concentration gradients is essential to many single cell living organisms, insects and even cells in growing multicellular animals. Conveyance of information between members of a species is often based on their ability to release and sense the presence of special chemicals called pheromones. The presence of pheromones can lead to a direct movement of cells in the direction of, or against a concentration gradient of the pheromone. This may result in a process in which the cells move from regions where their concentration is lower to regions where it is higher. Such a process, which is contrary to common diffusion due to thermal motion, is referred as a *chemotaxis*. Chemotaxis is also crucial in biological processes of higher animals. For example, a bacterial infection generates chemicals in its vicinity, to which leukocyte cells in the blood are attracted in the direction of the concentration gradient of the chemical.

Chemotactic processes are successfully modeled mathematically using coupled nonlinear differential equations [1]. Recent models, intended to be biologically realistic, have numerous parameters and are so complicated that it is difficult to assume their value. Most of results obtained from such models are numerical [2-4]. In this work we analyze the simple chemotactic model of Keller and Segel [5], which contains a few essential and measurable parameters and gives insight into the phenomena which govern cell aggregation. In the Keller-Segel model there is no cell generation, i.e. the number of cells is considered to be constant. The concentrations of cells and of the attractant are characterized by their densities, and both the cells and the attractant can flow along a single line. The rate of change of the attractant and of the cell concentrations are nonlinear functions of the concentrations of the cells and of the attractant. The process that occur will be described by equations which depend on the coordinate $\vec{r}$ and the time t.

The aim of what follows is to show that among the solutions of the equations mentioned always exists the steady state solution.

Basic equations

We consider the density of the cells $\alpha(\vec{r},t)$ and of the attractant $\nu(\vec{r},t)$ as functions of an arbitrary point in space and time, characterized by the position vector $\vec{r}$ and time *t*. The attractant is a chemical, which is produced by the cell at a given rate.

The cell and attractant flows are described by current density vectors, $\vec{J}(\vec{r},t)$ and $\vec{J}_\alpha(\vec{r},t)$, respectively, which give the direction of the flow and the quantity that passes per unit time through a unit area perpendicular to the flow direction. The cell current density $\vec{J}(\vec{r},t)$ is composed of two parts: the diffusion current density $\vec{J}_\nu(\vec{r},t)$, due to the concentration gradient $\nabla\nu$, and the chemotactic current density, $\vec{J}_c(\vec{r},t)$, due to the gradient $\nabla\alpha$ of the attractant. Hence

$$\vec{J}(\vec{r},t)=\vec{J}_\nu(\vec{r},t)+\vec{J}_c(\vec{r},t) \tag{1}$$

The attractant current density $\vec{J}_\alpha(\vec{r},t)$ is purely due to diffusion. The diffusion current densities are assumed to have the form

$$\vec{J}_\nu(\vec{r},t)=-D_\nu\nabla\nu(\vec{r},t) \tag{2}$$

and

$$\vec{J}_\alpha(\vec{r},t)=-D_\alpha\nabla\alpha(\vec{r},t) \tag{3}$$

with D_V the cell diffusion coefficient and D_α the attractant diffusion coefficient, which are taken as positive and independent of the space and time coordinates. These are the usual diffusion equations, which express the fact that in a very good approximation a density gradient produces a flow which is linearly proportional to that gradient.

The chemotactic current density is assumed to be given by

$$\vec{J}_c(\vec{r},t)=\nu(\vec{r},t)\cdot\chi[\alpha(\vec{r},t)]\cdot\nabla\alpha(\vec{r},t) \tag{4}$$

where $\chi[\alpha(\vec{r},t)]$ is the chemotactic coefficient, which is also taken positive. Since the cells are producing the attractant, the attractant current is proportional to the cell density $\nu(\vec{r},t)$.

Notice the difference in sign between the diffusion currents and the chemotactic current: whereas diffusion always carriers material from regions of higher to

those of lower concentrations, the chemotactic current does the opposite. The chemotactic flux is generated by the self - propelling motion of the energy consuming biological activity of living organisms, as contrasted with the passive diffusion currents of the cells and the chemicals. For the chemical - in this case attractant - diffusion is a process which is always observed and is due to the random, thermally excited, motion of the molecules, coupled with their mutual repulsion at small distances.

The rate of change of $\nu(\vec{r},t)$ is due to a generation of new cells, plus an outflux of $\vec{J}(\vec{r},t)$, hence the cell density and cell current density are related by so-called continuity equation

$$\frac{\partial \nu(\vec{r},t)}{\partial t} = g_V[\alpha(\vec{r},t),\nu(\vec{r},t)] - \nabla \cdot \vec{J}(\vec{r},t) \tag{5}$$

where g_V is a cell generation rate function, which depends in general on both the cell and the attractant concentrations. From now on, we omit the arguments $\vec{r}$ and *t*, to simplify the notation. Using Equations (1) and (2) the continuity equation for $\nu(\vec{r},t)$ becomes

$$\frac{\partial \nu}{\partial t} = g_V(\alpha,\nu) - \nabla \cdot [D_V \nabla \nu - \nu \cdot \chi(\alpha) \cdot \nabla \alpha] \tag{6}$$

The continuity equation for the attractant is given, using (3), by

$$\frac{\partial \alpha}{\partial t} = g_\alpha(\alpha,\nu) + \nabla \cdot (D_\alpha \nabla \alpha) \tag{7}$$

where g_α is a cell generation rate (also called “source”) function for the chemical attractant.

The normal passive diffusion processes in Equations (6) and (7) have homogenizing effect on the densities, whereas the chemotactic process, given in (6) by the term with the negative sign, tends to make the cell density spatially inhomogeneous. It is mainly this inhomogeneous steady state that are important for biological processes.

In the following we derive a general time - dependent property of the system which will be summarized by Equations (12) and (13). The boundary condition, that the boundary surface S enclosing the volume *V* is impenetrable to the attractant, is expressed by

$$\hat{n} \cdot \vec{J}_\alpha(S) = 0 \tag{8}$$

Using Equation (3) this yields the Neumann boundary condition

$$\left(\hat{n}\cdot\nabla\alpha\right)_S = 0 \tag{9}$$

where $\hat{n}$ is a unit vector perpendicular to S and pointing towards the exterior at the point under consideration.

We assume that S is impenetrable not only to the attractant, but also to the cells: hence

$$\hat{n}\cdot\vec{J}(S) = \hat{n}\cdot\left(-D_\nu\nabla\nu + \nu\chi(\alpha)\nabla\alpha\right)_S = 0 \tag{10}$$

Using Equation (9) we arrive at the Neumann boundary condition for the cells:

$$\left(\hat{n}\cdot\nabla\nu\right)_S = 0 \tag{11}$$

Integrating (6) and (7) over the volume *V*, using the divergence theorem and applying the boundary conditions (9) and (11), leads to

$$\frac{\partial M}{\partial t} = \int_V dV g_\nu(\alpha,\nu), \quad \frac{\partial A}{\partial t} = \int_V dV g_\alpha(\alpha,\nu) \tag{12}$$

where *M* and *A* are the total masses of cells and attractant in *V* defined by

$$M = \int_V dV\nu(\vec{r}), \quad A = \int_V dV\alpha(\vec{r}) \tag{13}$$

The steady state of the system is defined by $\partial\nu/\partial t = 0$ and $\partial\alpha/\partial t = 0$. In this state *M* and *A* are constant in time and we show that in the Keller-Segel model they are proportional to each other.

The Keller-Segel model. This model for chemotaxis consists of neglecting the cell production source, i.e. setting

$$g_\nu(\alpha,\nu) = 0 \tag{14}$$

and modeling the attractant source term in (7) by

$$g_\alpha(\alpha,\nu) = h_\nu\cdot\nu - h_\alpha\cdot\alpha \tag{15}$$

with h_ν and h_α positive constant. In this simple model there is a linear competition between attractant production $h_\nu\cdot\nu$ by the cell and spontaneous attractant decay $-h_\alpha\cdot\alpha$. The diffusion coefficients D_ν and D_α are assumed to be constant, as is the chemotactic coefficient of the attractant, $\chi(\alpha) = \chi_0$, with χ_0 constant. In this approximation the continuity equations (6), (7) can be written in terms of scaled variables and coordinates in the unit less form

$$\frac{1}{D}\cdot\frac{\partial n}{\partial \tau}=\nabla\cdot\left(\nabla n-n\nabla\alpha\right) \tag{16}$$

and

$$\frac{\partial n}{\partial \tau}=\nabla^2 a-a+n \tag{17}$$

The new unit less quantities are defined by

$$n\left(\vec{\xi},\tau\right)=\frac{\chi_0 h_v}{D_v h_\alpha}\cdot v\left(\vec{r},t\right),\quad a\left(\vec{\xi},\tau\right)=\frac{\chi_0}{D_v}\cdot\alpha\left(\vec{r},t\right)$$

$$D=\frac{D_v}{D_\alpha},\quad \tau=h_\alpha\cdot t,\quad \vec{\xi}=\sqrt{\frac{h_\alpha}{D_\alpha}}\cdot\vec{r} \tag{18}$$

The operator ∇ now represents differentiation with respect to the vector $\vec{\xi}$. The scaled Equations (16) and (17) depend on the single physical constant *D*, the ratio of the diffusion coefficients. The scaled steady state equations obtained from (16) and (17) setting $\partial n/\partial\tau=0$ and $\partial a/\partial\tau=0$, contain no physical constants; thus they are universal in the sense that their solutions are valid for any combination of biological parameters.

Since in this model the cell generation source term is zero, the total mass *M* of cells is conserved. We define the scaled total mass of cells and attractant by

$$G_n(\tau)=\int_V dV n\left[\vec{\xi}(\vec{r}),\tau\right],\quad G_\alpha(\tau)=\int_V dV a\left[\vec{\xi}(\vec{r}),\tau\right] \tag{19}$$

Integrating Equation (17) over the volume, using divergence theorem and the Neumann conditions leads to the equation

$$\frac{\partial G_\alpha}{\partial\tau}+G_\alpha=G_n \tag{20}$$

Since the total cell mass *M*, and hence G_n, is constant in time, $G_\alpha(\tau)$ is given by

$$G_\alpha(\tau)=\left[G_\alpha(0)-G_n\right]\cdot\exp(-\tau)+G_n \tag{21}$$

From Equation (21) it follows that, independently of the initial attractant concentration, G_α tends exponentially to G_n as the system approaches a steady state. Using (13) and (18) we obtain for steady state the relation

$$A = \frac{h_\nu}{h_\alpha} \cdot M \tag{22}$$

where A and M are the total masses of attractant and cells, respectively.

Conclusions

When the cells and the attractant are restricted to a limited volume, a spatially inhomogeneous aggregation of the cells and of the attractant may result. We show that in the steady state the total mass of the attractant is always proportional to the total mass of the cells, hence constant.

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