Eur. Phys. J. B **11**, 187–192 (1999)

THE EUROPEAN PHYSICAL JOURNAL B

EDP Sciences

Nematic liquid crystals formed by living amoeboid cells*

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Received 7 September 1998 and Received in final form 4 March 1999

Abstract. Interacting cells have the ability to form liquid crystal phases: (i) A cluster of a polar nematic liquid crystal is formed by cells which emit molecules for attracting other cells and (ii) an apolar nematic liquid crystal is formed by elongated cells which have an anisotropic steric repulsion. The angle distribution function is predicted by using the characteristics of an automatic controller where the extracellular guiding field is approximated by two-dimensional mean-field. The nematic liquid crystal state is quite well described by the model.

PACS. 87.19.Rr Mechanical properties of tissues and organs – 87.19.St Movement and locomotion

Introduction

A living cell is an open system with a flow of energy passing through it. The energy flow creates the conditions for strong deviations from thermodynamic equilibrium [1]. This results in the phenomenon of self-organization, the parameters of which are set by genetic, as well as, epigenetic constrains and opens up the possibility of the autonomous pattern formation, as revealed in the fundamental contributions by Turing [2]. In the first part of this paper, the self-organization of amoeboid cells is explained and in the second part, the liquid crystal phases which are created by migrating and interacting amoeboid cells.

Self-organized machines

The important elements of an amoeboid cell, like a granulocyte (one type of white blood cells), that create migration are the plasma membrane and the appropriate chemistry. This is demonstrated by making cytokineplasts which are the purified cellular amoeboid motors [3,4]. The involved cellular signal chain is in short [5]: The first intracellular signal created by the membrane-bound receptors activated by kinesis stimulating molecules of the extracellular space. The second intracellular signal (composed of molecules like inositol triphosphate, diacylglycerol, Ca^{++}, ...) created by a chemical amplification process. One receptor activates many membrane-bound G-proteins. The membrane-bound G-protein-phospholipase-C complex hydrolyzes many lipid (phosphatidylinositol) molecules of the plasma membrane. The water soluble molecules inositol triphosphat open calcium stores and ion channels. The cellular reaction units (adhesion proteins, actin, myosin, ...) is activated by the second intracellular signal molecules. Diffusion processes in the signal chain are overwhelmed by a positive feedback which is basically the supply of fresh receptors induced by the second intracellular signal [6] and, hence, the formation of a spatial-temporal pattern of the second intracellular signal molecules is possible. The different machine types of amoeboid cells are created by the spontaneously formed spatial-temporal pattern [4]: (i) the machine cycle is given by the temporal pattern [6] and (ii) the different cellular machine types by the spatial pattern [4].

The action of a cell can be compared with that of a laser. The second intracellular messenger molecules which are responsible for the cellular action, are created by means of the cellular chemical amplification chain starting with the activated membrane-bound receptors. One could say that the cellular chemical amplification chain pumps second intracellular molecules [4]: For weak pumping, the action of the muscle proteins is weak and random and "no" cellular action is expected (= inactivated cellular state). But for strong pumping the action of the muscle proteins is strong and coherent even when the pumping is random and, thus, a coherent cellular action is expected (= activated cellular state). A part of this self-organization concept is already verified by experiments [4,6]. The different experimentally found self-organized cellular machines can be interpreted as the modes of the spatial pattern of the second intracellular messenger. Details of the function and morphology of some amoeboid cells is given *e.g.* in reference [7]: (i) In the isotropic mode, the cell body is surrounded by oriented and coherently working muscle proteins (leading front) but no direction is preferred. No cell migration or cell orientation is expected as actually

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observed for many cell types. The cells in the isotropic mode have the ability to make adherence to a substrate. (ii) The polar mode is very often observed in amoeboid cells. The oriented and coherently working muscle proteins are located at one side of the cell body. The cells have the ability of migration: The cells perform random movement in the absence of an extracellular guiding signal and directed movement under the influence of an extracellular guiding signal like a concentration gradient (chemotaxis) or an electric field (galvanotaxis) [8,9]. (iii) In the bipolar mode, the oriented and coherently working muscle proteins are located at two opposing sides of the cell body. The cells have the ability to orient their long axis: The cellular rotation is random in the absence of an extracellular guiding signal but anisotropic in the presence of an extracellular guiding signal like an electric field, a bent surface, a periodically stretched surface, etc. [8,10].

The polar and bipolar mode of the amoeboid cells act as an automatic controller since the orientation of the modes can be altered by a weak extracellular guiding signal in such a way as to minimize the deviation between the actual angle and the desired one. The rate equation for the orientation angles are stochastic differential equations (Langevin equations) due to stochastic processes in the cellular signal transduction chain:

$$\frac{\mathrm{d}\varphi}{\mathrm{d}t} = -k_1\, E_1(signal) \sin\varphi + \Gamma_1(t) \tag{1}$$

$$\frac{\mathrm{d}\Theta}{\mathrm{d}t} = -k_2\, E_2(signal) \sin 2\Theta + \Gamma_2(t). \tag{2}$$

The direction of migration, φ, is measured in respect to the direction of the extracellular guiding signal. The orientation angle, Θ, is measured in respect to the perpendicular direction of the extracellular guiding signal. The cellular signal transformer is described by the unknown functions, $E_1(signal)$ and $E_2(signal)$ and the cellular reaction unit by k_1 and k_2. The stochastic part of the machine equations, $\Gamma(t)$, is approximated by a white noise of the strength q ($\langle\Gamma\rangle = 0$, $\langle\Gamma(t)\,\Gamma(t')\rangle = q\,\delta(t-t')$). Due to the stochastic machine equations, the behavior of a single cell can not be predicted. Therefore, the Langevin equations are transformed into Fokker-Planck equations [11] which describe the probability of finding a cell under a certain angle (for mathematical details see Ref. [9]):

$$\frac{\partial f_1(\varphi,t)}{\partial t} = \frac{\partial}{\partial\varphi}\left(k_1\, E_1(signal)\, \sin\varphi + \frac{q_1}{2}\,\frac{\partial}{\partial\varphi}\right) f_1(\varphi,t) \tag{3}$$

$$\frac{\partial f_2(\Theta,t)}{\partial t} = \frac{\partial}{\partial\Theta}\left(k_2\, E_2(signal)\, \sin 2\Theta + \frac{q_2}{2}\,\frac{\partial}{\partial\Theta}\right) f_2(\Theta,t). \tag{4}$$

It is important to realize that the steady state angle distribution functions of living cells (system far from thermodynamic equilibrium) have the same mathematical structure as the Boltzmann distribution which describes the fluctuations of a system at thermal equilibrium.

$$f_1(\varphi) = f_{10}\, \exp\left(\frac{2\,k_1\, E_1(signal)}{q_1}\, \cos\varphi\right) \tag{5}$$

$$f_2(\Theta) = f_{20}\, \exp\left(\frac{k_2\, E_2(signal)}{q_2}\, \cos 2\Theta\right). \tag{6}$$

The argument of the exponential function of the angle distribution functions is the so-called generating function [12] which characterizes the cellular automatic controllers. One obtains a generating function for the directed migration process and another one for the cell orientation process. The angle distribution function, $f_1(\varphi)$ and $f_2(\Theta)$ can be determined experimentally under the condition of a constant guiding signal. This means E_1 and E_2 are constant. The predicted angle dependence are verified for different cell types and different extracellular guiding signals like electric field, concentration gradient, etc. [10].

The unknown functions E_1 and E_2 of the cellular signal transformer can be determined experimentally if the above mentioned experiments are repeated for different strength of the guiding signal. The experimentally determined value of the generating function (without the angle dependence) can be plotted versus the strength of the applied guiding signal. The unknown functions, $E_1(signal)$ and $E_2(signal)$, are approximated by power laws. From the symmetry of the system one expects in the case of directed migration an odd power and an even power for cell orientation. The following results are verified by experiments: (i) The cellular signal transformer of the polar mode which is responsible for directed migration, determines the strength of the guiding signal in a linear fashion ($E_1 \propto signal$, the predicted odd power is one) [9]. (ii) The cellular signal transformer of the bipolar mode which is responsible for cell orientation, determines the square of the strength of the guiding signal ($E_2 \propto signal^2$, the predicted even power is two) [10]. In addition, the cells in the polar mode try to orient themselves parallel to the guiding signal. This means the cells try to maximize their interaction with the extracellular guiding field. But, the cells in the bipolar mode try to orient themselves perpendicular to the guiding signal. This means that the cells try to minimize their interaction with the extracellular guiding signal. Next, interacting and migrating amoeboid cells are considered. One expects that the cells form condensed phases in analogy to interacting molecules.

Polar nematic liquid crystal

First, amoeboid cells in a polar mode are regarded. *E.g.* granulocytes is one type of white blood cells of the immune system of mammalian which form the first line of defense against invaded microorganisms. These cells form the desired polar mode when they are exposed to blood plasma and then they have the ability of directed migration (chemotaxis and galvanotaxis). One migrating cell can interact with another migrating cell by means of the

feedback system of the cellular signal chain: The vesicle fusion process supplies, on one hand, the plasma membrane with fresh receptors but, on the other hand, other cells can be attracted *via* chemotaxis if the fused vesicles release chemoattractant molecules into the extracellular space. The chemoattractant is cAMP in the case of staffed amoeboid slime mold cells but still unknown in the case of granulocytes kept at low calcium concentrations.

The expected cell-cell interaction can be determined by measuring the pair correlation function measured at low cell density [13]: (i) At high calcium concentration (2.5 mM), granulocytes show no interaction except steric repulsion. (ii) At low calcium concentration ($<$ 0.1 mM), granulocytes show cell-cell attraction in addition to the steric repulsion. The cell-cell attraction acts only over small distances which are in the order of the size of a cell (≈ 20 μm).

Granulocytes at low calcium concentration attract each other and form clusters containing actively moving cells. The following results were obtained [13]: (i) The migrating cells are oriented towards the clusters center. (ii) The cluster formation is a function of the mean cell density. (iii) No clusters were observed for small cell densities, ρ_1 ($<$ 150 - 300 cells/mm^2). (iv) Clusters were formed for large cell densities, ρ_1 ($>$ 150 - 300 cells/mm^2) and in the steady state the mean cluster size was a function of the mean cell density.

The cluster growth, $\mathrm{d}n/\mathrm{d}t$, is simplified by a mean-field model

$$\frac{\mathrm{d}n}{\mathrm{d}t} = a_+ \rho\, n - a_- \sqrt{n}. \tag{7}$$

The first term describes the chemotaxis induced flux of attracted cells. It is proportional to the cell density, ρ, in the vicinity of a cluster and to the concentration gradient of the chemoattractant which is produced by the n cells of the cluster. An adiabatic process is assumed: the diffusion of the small sized chemoattractant molecules is fast compared with the migrating cells. The second term describes the loss process. Only cells at the boundary can leave a dense packed cluster. Thus, the loss term should be proportional to $n^{1/2}$ since the circumference of a cluster is proportional to $n^{1/2}$. This simple droplet model describes quite well the static and dynamic properties of a cluster. More details are given in reference [13].

The cluster formation starts with two opposing granulocytes which are forced to stop and emitted chemical signal that attract further cells. In large sized clusters, the center cell is frequently forced to leave the polar mode into the immobile isotropic mode where the cell body is surrounded by an isotropic distributed leading front. The cluster formation can be initiated by another cell type like a monocyte (another white blood cell type). Monocytes on a glass surface form the immobile isotropic mode and attract mobile granulocytes which are in a polar mode. But, with increasing cluster size, the migrating granulocytes push each other and squeeze-out the immobile monocyte.

The cells in such a dense packed cluster form a polar nematic liquid crystal: The position of the cells shows no order like in a liquid, but the cells are oriented towards the center of the cluster and show, thus, an orientational order. The cluster with its oriented cells is a metastable state since the mean concentration of the chemotactic molecules increases in time and, thus, the concentration gradient of chemotactic molecules decreases in time. One observes that the clusters disappear after one to two hours.

Apolar nematic liquid crystal

Second, amoeboid cells in a bipolar mode are regarded. *E.g.* melanocytes are one type of cell in the skin which produce and distribute the color pigment melanin *via* dendrites. Cultured human melanocytes form the desired bipolar mode with two opposing dendrites when they are exposed to a melanocytes medium [14]. The cell body of different melanocytes attract each other probably *via* chemotaxis, as discussed above, but the dendrites repel each other. The orientation of the dendrites occurs during a periodic retraction and elongation process in such a way that each dendrite has a minimum of contact with the surrounding cells [14]. Each cell maximizes its free space. At low cell density, the dendrites have practically no interaction and the elongated melanocytes are randomly oriented. But at high cell density, the dendrites have a strong interaction and the elongated melanocytes are anisotropic oriented. The migrating cells with their periodically elongating dendrites form a nematic liquid crystal state which we will investigate in detail. Other amoeboid cell types like fibroblasts [15,16], osteoblasts, adipocytes, etc. form at large cell density an apolar nematic liquid crystal.

A suspension of cultured melanocytes was spread out on a flat surface in different concentrations. The cells, being of spherical shape in the suspension, come down onto the substrate and start to develop their dendrites. They stay in this shape and crawl around on the surface. After a couple of days a steady state is reached that clearly shows orientational long range order over almost the whole chamber (2.5 cm$\times$5 cm). To get the orientational distribution function we used a precision motorized $x-y$ stage on a CCD-camera equipped microscope and scanned an area of several mm^2 using a 10 $\times$ magnification lens. We developed an image processing algorithm for automatically finding the position of the cell body and the orientation of the dendrites based on two images of the same area that were taken at different illumination settings. The results are shown in Figure 1. The algorithm handles more than 90% of all cases in the correct way and produces no data for the cells it cannot deal with. The center of the cell body and the orientation of the two opposing dendrites in respect to a fixed coordinate system are determined. The measured orientation angles, Θ, for one cell density are collected in a angle distribution function, $f(\Theta)$. The measured data fit quite well the predicted distribution function (Eq. (6)) as shown in Figure 2 where the angle-free part of the generating function $V(= k_2E_2/q_2)$ is the only fitting parameter. The angle distribution function has, obviously, the same structures as those of cells of the bipolar mode exposed to an extracellular guiding field. This experimental result is interpreted such that the elongated

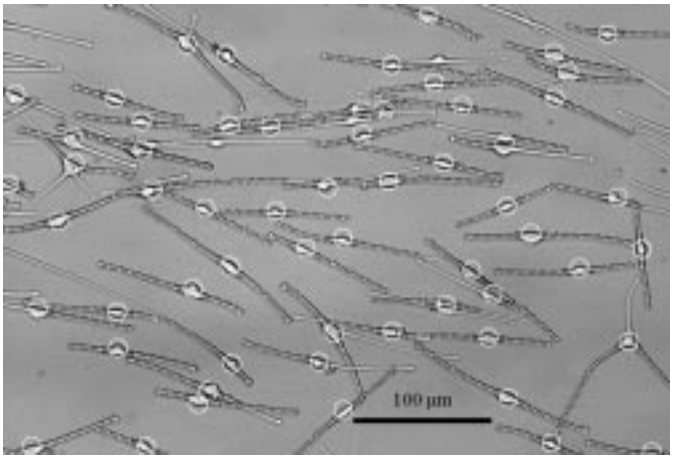

Fig. 1. Human melanocytes on a glass surface. Image processing algorithm: We use a two step approach by first finding the cell body (circles) and then the dendrites that belong to that cell. Some cells show three or more dendrites. In this case the algorithm finds those two dendrites that form an angle close to 180°. The algorithm is not able to handle all problems that are encountered but has proven to be correct in more than 90% of all cases.

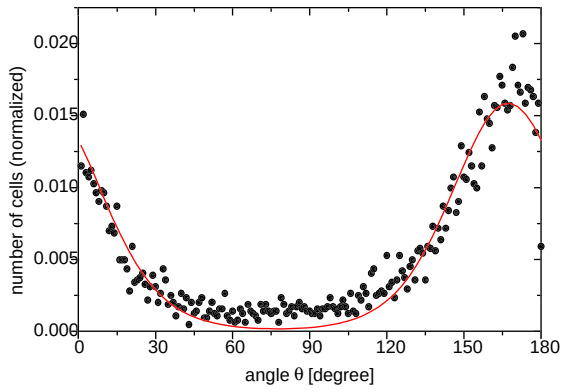

Fig. 2. Angle distribution function for an ensemble of 6431 melanocytes at a density of 159 cells per mm^2. This leads to an order parameter of 0.57. The points are fitted by the predicted function (Eq. (6)) where $V(= k_2\, E_2(signal)/q_2)$ (Eqs. (8–10)) was used as fitting parameter.

cells see a mean field which is produced by all the surrounding cells. The interaction potential of one cell with its neighboring cells (the angle dependent part of the generating potential) is proportional to $\cos 2\Theta$. This means one has a quadratic potential for small angles. Next, the angle free part of the generating function is investigated.

The strength of the interaction potential will be approached by a mean field. There exist basically two mean field approaches for nematics formed by elongated molecules: the Onsager theory and the Maier-Saupe theory.

(i) The Onsager theory is based on the steric repulsion of rigid long rods which cannot penetrate each other. The nematic phase is predicted for high rod concentration. The predicted nematic order parameter just at the transition is quite high (≈ 0.84). Thus, the Onsager theory leads to a rather sudden transition between a strongly ordered nematic and a completely disordered, isotropic phase. The apolar nematic phase formed by an aqueous suspension of tobacco mosaic viruses is quite well described by the Onsager theory. But the Onsager theory failed to explain the apolar nematic state formed by amoeboid cells like melanocytes since the sudden change of the apolar order parameter at the nematic-isotropic state transition is very small as it is demonstrated below. In addition the Onsager theory predicts an angle distribution function with an rectangular appearance. Thus, besides $\cos 2\Theta$ one expects higher order terms like $\cos 4\Theta$, $\cos 6\Theta$, etc. But experimentally it is found that the $\cos 2\Theta$ term makes the main contribution. The other terms can be neglected. The orientation of amoeboid cells is also modeled by Edelstein-Keshet and Ermentrout [17] in analogy to the Onsager theory (anisotropic steric repulsion). But, their predictions are not yet compared with experimental results.

(ii) The Maier-Saupe theory is based on a soft anisotropic interaction potential which is produced by flexible elongated molecules. The nematic phase is predicted for low enough temperature. The nematic order parameter just at the transition is medium (≈ 0.44). In the case of small elongated molecules the temperature dependence of the apolar order parameter is quite well described by the Maier-Saupe theory. Here, the Maier-Saupe theory is used to describe the extracellular guiding field which is produced by the oriented elongated amoeboid cells of the surrounding.

The extracellular guiding field E_2 is approached by a mean field where one cell is considered in the field produced by all the other cells: (i) the strength of the field, E_2, or the curvature of the interaction potential should be proportional to the cell density, ρ. A strong interaction is expected for dense packed cells and a weak interaction for loose packed cells. (ii) the strength of the field E_2 or the curvature of the interaction potential should be proportional to the mean apolar orientation, $S(= \langle \cos 2\Theta \rangle)$, of the surrounding cells. A strong interaction is expected for highly ordered cells and a weak interaction for lowly ordered cells.

$$E_2 = a_2\, \rho\, S + \cdots \tag{8}$$

Only the first non-trivial term of a Taylor series is considered. The extracellular guiding field is calibrated by the coefficient a_2. Now, the fitting parameter, V, of the angle distribution function can be expressed by the mean field as

$$V = A_2\, \rho\, S + \cdots \tag{9}$$

with

$$A_2 = \frac{a_2\, k_2}{q_2}\,. \tag{10}$$

The assumed mean field can be tested by plotting V/ρ as a function of ρ. A straight line is predicted (Eq. (9)) and

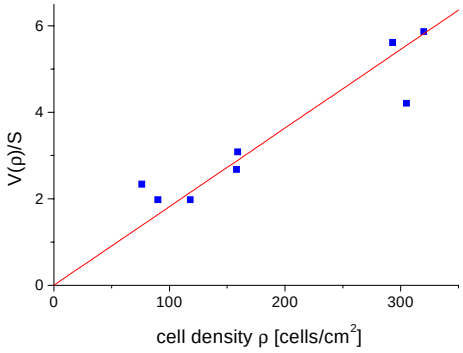

Fig. 3. The ratio of the strength, V, of the extracellular guiding field (see Fig. 2) and the order parameter, S, (determined by the distribution function) is plotted versus the cell density. The dots are fitted by the predicted straight line with $1/A_2 = 55$ cells/mm^2.

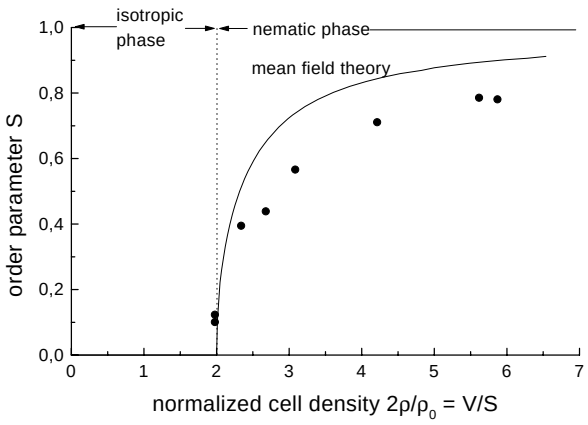

Fig. 4. Order parameter S as a function of the strength of the extracellular guiding field divided by the order parameter (=normalized cell density). Dots are experimental values adjusted with A_2 (from Fig. 3). The line is a fit-free prediction.

actually observed (Fig. 3). This graph demonstrates that the mean field is proportional to the cell density, as well as, to the mean cell orientation. A_2 is the fitting parameter ($1/A_2 = 55$ cells/mm^2).

State diagram

Next, the order parameter, S, is predicted as a function of the cell density. Note, it is a fit-free calculation since A_2, which characterize the strength of the mean field, and the cellular sensitivity as a whole (Eq. (10)), is already determined by Figure 3. The calculation of the apolar order parameter, $S\,(=\langle\cos 2\Theta\rangle)$, leads to the following self-consistent equation which defines the state of the nematic liquid crystal:

$$S(\rho) = \frac{\int_0^{2\pi} \cos 2\Theta\, \mathrm{e}^{V(S(\rho))\,\cos 2\Theta} \mathrm{d}\Theta}{\int_0^{2\pi} \mathrm{e}^{V(S(\rho))\,\cos 2\Theta}\, \mathrm{d}\Theta}\,. \qquad (11)$$

The integrals can be solved analytically and one obtains (modified Bessel functions, I_0 and I_1)

$$S(\rho) = \frac{I_1\left(\frac{2\,\rho\,S}{\rho_0}\right)}{I_0\left(\frac{2\,\rho\,S}{\rho_0}\right)}\,. \qquad (12)$$

The threshold density, ρ_0, is defined by A_2 as

$$A_2\,\rho_0 = 2. \qquad (13)$$

The theoretical predictions, as well as, the experimental results are shown in Figure 4. For low cell density ρ ($< \rho_0$), the order parameter is zero as actually observed. For large cell density ρ ($> \rho_0$), the order parameter increases with increasing cell density as predicted, but the measured order parameter is systematically too small. Some melanocytes form more than two dendrites (see Fig. 1) and, thus, disturb locally the nematic order. One expects in addition an isotropic distribution in the angle distribution function which can actually be seen in Figure 3.

Let us assume that the anisotropic steric interaction is the dominant part of the mean field. If this is true, then the threshold cell density, ρ_0, predicted by the length of the long cellular axis ($\approx$ 100 μm) is $\approx$ 100 cells/mm^2. This value is in accordance with ρ_0 ($=$ 110 cells/mm^2) determined directly from A_2.

Melanocytes were placed on a flat glass surface and the elongated cells formed at high enough cell density an apolar nematic liquid crystal state. The question is whether the cells form a two dimensional or a three dimensional nematic liquid crystal. The state is quasi two dimensional since the dendrites do not stay in one plane: Some dendrites cross each other and go thus in the third dimension. The extension into the third dimension is very small, in the order of 20 μm.

Melanocytes form an apolar nematic liquid crystal. No order is observed in the center of mass of the cells. But, the elongated cells are oriented. In the twenties of this century Friedel [19] concluded that the orientational order is of long range order due to the existence of orientational point defects (disclination). Similar point defects were found in an apolar nematic liquid crystals formed by amoeboid cells [20].

Uniaxial apolar nematic liquid crystal

The last question is whether an uniaxial nematic liquid crystal can be produced. A nematic liquid crystal, formed by elongated molecules, can be oriented by specially treated glass plates. A similar method works for an apolar nematic liquid crystal formed by amoeboid cells. The direction of the mean orientation of the liquid crystalline state is described by the director. It is important to realize that the director of the liquid crystalline state can be oriented by a very weak extracellular signal. Tiny

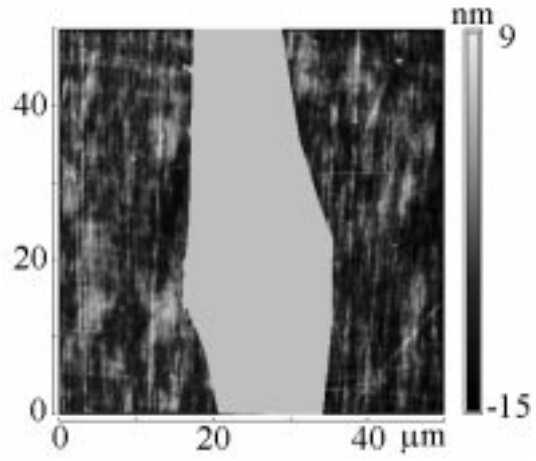

Fig. 5. AFM microscopic picture of the substrate which orient elongated melanocytes. The gray area is a projected melanocyte.

parallel scratches in the substrate (Fig. 5) produce an uniaxial single nematic liquid crystal. The interaction of an external signal with the nematic liquid crystal is at least 1000 times stronger than the interaction with a single cell. Thus, the formation of building a liquid crystal state has a clear physiological advantage for the cells, in that the ensemble react much more sensibly to external signals than a single cell does.

Outlook

Our results show that applying liquid crystal concepts to biological systems prove to be very helpful in getting descriptions for these systems that focus the vast number of biochemical pathways into simple but meaningful variables, thus giving models that are easier to interpret and are more powerful for making general predictions.

The process by which migrating cells exchange information constitutes one of the most intriguing areas of life sciences and physics. An individual cell transmits signals and guides its migration and orientation according to the signals it receives, these messages being chemical, sterical or electrical in nature. The physical process of reducing a gas containing freely moving molecules to a liquid form is understood to a large extent and the mean behavior of a given molecule in the interaction field of the other moving molecules may be determined by Boltzmann statistics. Identical principle are used to reduce freely migrating cells to a condensed state. The mean behavior of a given cell in the interacting field of other cells can be described in terms of its automatic controller. The self-organization, involved in morphogenesis, organogenesis and wound healing, takes in a new light.

This work was supported by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie

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