

Automatic Control and Directed Cell Movement

Novel Approach for Understanding Chemotaxis, Galvanotaxis, Galvanotropism

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It is shown that chemotaxis, galvanotaxis, galvanotropism, etc. are functions of cells having a goal-seeking system. Even when the involved physicochemical signals are unknown, the cellular system can be treated phenomenologically like an automatic controller having a closed-loop feedback system. The model is verified by means of galvanotaxis and chemotaxis data of human granulocytes. The galvanotaxis and chemotaxis coefficient quantifying the cellular sensitivity can be predicted from the coefficient which characterizes the deterministic part of the signal transduction/response system of the cell divided by the coefficient which characterizes the noise strength in the cellular signal transduction/response system. The model is not restricted to directed movement of granulocytes. It is very general and can be applied to any cell type for directed phenomena like chemotaxis, galvanotaxis, phototaxis, magnetotaxis, directed growth, etc. The virus-disturbed directed migration of granulocytes is discussed and it is shown that the virus alters the deterministic part of the cellular controller.

Introduction

During the past the live sciences have flourished with the growth of knowledge of the chemistry of living matter. Increasingly, however, the live sciences are dependent on the physical sciences for a deeper and more quantitative understanding of important biological and medical problems and for the development of successful solutions to these problems.

An important concept in understanding biological phenomena at various levels of complexity is cybernetics, also known as the theory of automatic control [1]. It is a basis for the quantitative understanding of biological regulatory systems. Nearly every macroscopic and microscopic process in living organisms requires the action of principles of feedback and control [1]. The modeling of biological systems *via* automatic control allows the incorporation of effects of secondary factors for which a detailed knowledge is missing.

The theory of automatic controls is widely used in physiology and neurophysiology [2]. Consider the following examples: The neuromuscular control of the eye in tracking and focusing. The neuromuscular control of light flux by the iris of the eye. The neuromuscular control of the blood pressure.

Glucose concentration, hydrogen concentration, ionic strength, and erythrocyte concentration in the blood are maintained very constant. In fact, the very existence of living organisms is based upon the existence of networks of sensing, feedback and control systems. The failure of these systems can lead to disease and death. In fact, feedback and control systems are as essential in biological systems as they are in modern technological society.

The subject of interest here is a system out of the living moving world having a network of sensing, feedback and control system – the protection of eukaryotic cells: Polymorphonuclear leukocytes (= granulocytes) are attracted by sites of inflammation to combat invading microorganisms [3]. Here it will be shown that the mechanism to account for the fact that these cells move toward the vicinity of the sites of infection, is an automatic controller. The direction determining field is created by the infected cells.

The field may be chemical in nature and the resulting directed locomotion is then called chemotaxis. The peptides, in which the initial part of the molecules is a formylmethionyl moiety form a class of molecules which allows the granulocytes to distinguish between prokaryotic and eukaryotic cells [3, 4]. This is because the proteins of the prokaryotic cells start with formylmethionyl (f-Met-...) and those of eukaryotic cells with any amino acid [5].

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The field may also be electrical in nature: the resulting directed locomotion is then called galvano-taxis. For instance, when a cell is lysed, ions inside and outside the cell diffuse to establish a concentration equilibrium. This diffusion process is an inverse function of the size of the ions. The different diffusion coefficients of the ions involved result in the separation of small and large ions, and a diffusion potential is created [6].

A few words about directed movement would be useful. It is quantified by the mean displacement, $\langle x \rangle$, of the cells in the direction of the polar field (e.g. electric field, concentration gradient, etc.) and the mean displacement, is expressed by the mean drift velocity, $\langle v_{\parallel} \rangle$, parallel to the polar field times the observation time, t .

$$\langle x \rangle = \langle v_{\parallel} \rangle \cdot t. \quad (1)$$

The translational movement in a polar field requires two components of the cellular response: the track velocity, $v_c(t)$, and direction of migration, $\Phi(t)$.

$$v_{\parallel}(t) = v_c(t) \cdot \cos \Phi(t). \quad (2)$$

One might well expect that these two parameters, $v_c(t)$ and $\Phi(t)$, would depend on each other. But they are independent of each other since the average drift velocity, $\langle v_{\parallel} \rangle$, is equal to the average track velocity, $\langle v_c \rangle$, times the average of $\cos \Phi$.

$$\langle v_{\parallel} \rangle = \langle v_c \rangle \cdot \langle \cos \Phi \rangle. \quad (3)$$

This holds at least for human granulocytes [6–8], human monocytes [9], somitic fibroblasts [10] and neural crest cells [11].

Here, it will be shown that the goal-seeking system of cells like granulocytes can be described in the framework of an automatic controller.

Automatic Control

The hallmarks of automatic control are first an element which measures the output of the biological system; second, a means of comparing that output with the desired output; third, a means of feeding back this information into the input in such a way as to minimize the deviation of the output from the desired level (Fig. 1).

The cell must have the ability to measure its orientation (= physical state) in respect to the applied polar field (e.g. electric field or concentration gradient). This actual state is compared with the desired one – e.g. to be parallel to the polar field

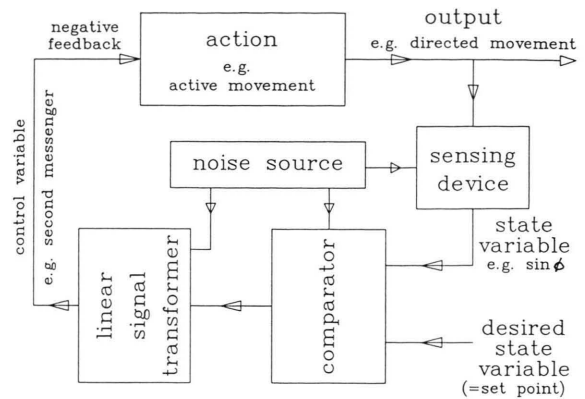


Fig. 1. Schematic representation of an automatic controller.

vector. The information leaving the comparator creates an intracellular signal which induces the cell to rotate in such a way to approach the desired orientation. Hence, a deterministic torque, $\Gamma(E; \Phi)$, is introduced depending on the applied field strength and on the cellular orientation in respect to the applied field strength. The noise in the signal transduction/response system is assumed to create a stochastic virtual torque, $\Gamma_N(t)$. The rate equation for the angle of migration is then

$$\frac{d\Phi}{dt} = -\Gamma(E; \Phi) + \Gamma_N(t). \quad (4)$$

For simplicity, a δ -correlated white noise source with the strength q is assumed ($\langle \Gamma(t) \rangle = 0$)

$$\langle \Gamma_N(t) \cdot \Gamma_N(t') \rangle = q \cdot \delta(t - t'). \quad (5)$$

The reader, unexperienced with stochastic differential equations, is referred to text books of Risken [12] and Haken [13].

Two different types of controllers are discussed: the proportional and the integral controller.

Proportional controller

The cellular response is proportional to the received signal (= actual state minus desired one). In order to approximate the deterministic torque, $\Gamma(E; \Phi)$, it is common to begin with a very general equation such as an infinite series. The symmetry requirements for the directed movement restrict the possible series and the number of terms in the chosen series. The physical state is unchanged if the coordinate system is rotated by $n \cdot 360$ degrees (n = integer) and the torque changes sign if the

coordinate system is reflected at a mirror which is parallel to the polar field. One well known series that meets these symmetry requirements is the Fourier Series. One can immediately eliminate half of the series by applying the symmetry restriction. Thus, one finds

$$\Gamma(E; \Phi) = c_1 \sin \Phi + c_2 \sin 2\Phi + \dots \quad (6)$$

The coefficients, c_1 , and c_2 have the following meaning: (i) c_1 , describes the directed (or polar) movement or growth, *e.g.* chemotaxis, galvanotaxis, galvanotropism, *etc.* (ii) The coefficient, c_2 , describes the bidirectional or apolar movement or growth, *e.g.* contact guidance [14, 15].

The coefficient c_1 is a function of the applied polar field. In the case of a proportional controller it is expected that c_1 is proportional to the applied electric field, E (galvanotaxis), and to the gradient of the chemical activity of the chemotactic molecule, $\text{grad} \ln [c]$ (chemotaxis).

$$c_1 = k_{PG} \cdot E \quad (7)$$

$$c_1 = k_{PC} \cdot \text{grad} \ln [c]. \quad (8)$$

The deterministic part of the automatic proportional controller is determined by k_{PG} or k_{PC} . We will give experimental evidence that large parts of the directed movement and growth can be described in the framework of a proportional controller.

Integral controller

The cellular response is proportional to the received integrated signal. The deterministic virtual torque of the integral controller reads then

$$\Gamma(E; \Phi) = k_I \cdot \Delta t \int \sin \Phi \cdot dt. \quad (9)$$

The integration takes place over the characteristic time Δt . The coefficient k_I characterizes the deterministic part of the integral controller and it could be a function of the applied field strength.

The rate equation for the proportional-integral controller reads then

$$\frac{d^2 \Phi}{dt^2} = -c_1 \cdot \cos \Phi \cdot \frac{d\Phi}{dt} - k_I \cdot \sin \Phi + \Gamma_N(t). \quad (10)$$

Experimental Results

Proportional controller

The predictions of the automatic proportional controller are based on drastic simplifications: It is

assumed (i) that only a single term in the Fourier Series with its infinite number of terms is important (Eqn. (6)) and (ii) that this single term is proportional to the applied polar field strength (Eqn. (7) or (8)). The verification of the model is based upon data from the galvanotactic and chemotactic response of granulocytes. The experiments have already been described and published in [6, 8] (galvanotaxis) and [15, 16] (chemotaxis). In addition to the published data also source data were used. The model is partially tested for other cell types as spermatozooids (galvanotaxis, chemotaxis) [17, 18], growing spores (galvanotropism) [19], neural crest cells (galvanotaxis) [11], and fibroblasts (galvanotaxis) [10].

Generating function and angle distribution density

In our used model the angle of migration is a stochastic variable, since the noise induced torque, $\Gamma_N(t)$, is a stochastic quantity. Therefore we may ask what the probability is to find the cellular response angle in the interval, $(\Phi; \Phi + d\Phi)$. Because Φ is a continuous variable we may ask for the probability density, $f(\Phi)$. The probability density times the size of the interval $d\Phi$ is the probability of finding the cell in the interval, $(\Phi; \Phi + d\Phi)$.

The stationary solution of the angle distribution density is in the case of a proportional controller [12, 13]

$$f(\Phi) = N \cdot e^{V(\Phi)}, \quad (11)$$

$$V(\Phi) = \frac{2}{q} \cdot \int_0^\Phi c_1 \cdot \sin \Phi' \cdot d\Phi'. \quad (12)$$

N is determined by the normalization ($\int f(\Phi) d\Phi = 1$). $V(\Phi)$ is the generating function.

By means of the generating function, it will be shown that only the first term of the infinite Fourier Series (Eqn. (6)) is important in the case of the directed movement or growth. A plot of the data, $\ln f(\Phi)$ vs. $\cos \Phi$ should give a straight line. (The slope of the line is a_1 .) Such straight line behaviour is found for galvanotaxis of granulocytes [6, 8] of neural crest cells [11] and of somitic fibroblasts [10], for chemotaxis of granulocytes [6, 15], for necrotaxis of granulocytes and monocytes [9], and for galvanotropism of fungal hyphae [19].

In summary, the basic term which describes directed movements or growth is the term $c_1 \cdot \sin \Phi$ of the infinite Fourier Series. Next, the coefficient c_1 will be examined.

Angle autocorrelation function

The stochastic differential equation of the proportional controller can be solved. The angle autocorrelation function $\langle \Phi(t_1) \cdot \Phi(t_2) \rangle$ is just a function of the time difference $t_1 - t_2$ [12, 13] for small angles of migration and large times t_1 and t_2

$$\langle \Phi(t_1) \cdot \Phi(t_2) \rangle = \frac{q}{2 \cdot c_1} e^{-c_1 \cdot |t_1 - t_2|}. \quad (13)$$

In the case of a linear response one expects that c_1 is proportional to E or $\text{grad} \ln[c]$.

The angle autocorrelation function can be determined from the spatial trajectories of the cells. A typical example is shown for migrating granulocytes exposed to an electric field (Fig. 2). The characteristic time $\tau = c_1^{-1}$ is a function of the exposed field strength as predicted (Eqn. (7)) (see Fig. 3). The slope yields the coefficient $k_{PG} = -0.22 \text{ mm} \cdot \text{V}^{-1} \cdot \text{s}^{-1}$. This coefficient quantifies the deterministic part of the proportional controller.

Dose-response curve and angle distribution density

The linear response of the proportional controller can also be shown by investigating the field dependence of a_1 since a_1 is proportional to c_1 and to E (or $\text{grad} \ln[c]$) see Eqn. (12)). K_G is the galvano-taxis coefficient.

$$a_1 = \frac{2}{q} \cdot c_1 = K_G \cdot E. \quad (14)$$

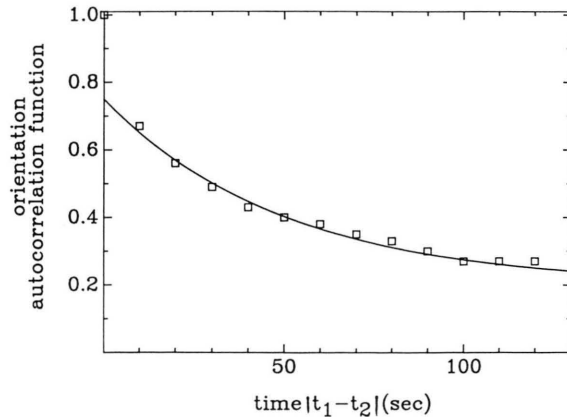


Fig. 2. Angle autocorrelation function $\langle \Phi(t_1) \cdot \Phi(t_2) \rangle$ as a function of time $|t_1 - t_2|$ for human granulocytes exposed to an electric field ($0.15 \text{ V} \cdot \text{mm}^{-1}$) [8]. The drop at $|t_1 - t_2| = 0$ is due to the uncertainty in the determination of the center of gravity of the cell. The fitted exponential function yields a characteristic time of 50 s.

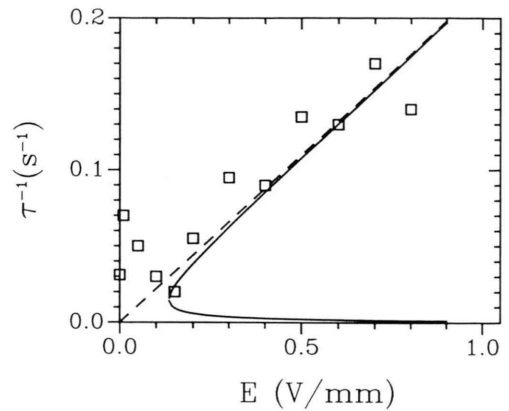


Fig. 3. The inverse of the characteristic time as a function of the applied electric field is shown. The values (open squares) are determined from the decay of the angle autocorrelation function of granulocytes exposed to different electric field strengths [8]. The dashed line is a theoretical prediction of the proportional controller (Eqn. (14)). The slope of the straight lines yields the coefficient, $k_{PG} (= K_G \cdot q/2)$ to $-0.22 \text{ mm} \cdot \text{V}^{-1} \cdot \text{s}^{-1}$. This coefficient characterizes the deterministic part of the proportional controller. The lines are predictions of the proportional-integral controller ($k_{PG} = -0.22 \text{ mm} \cdot \text{V}^{-1} \cdot \text{s}^{-1}$ and $k_I = 0.0002 \text{ s}^{-2}$). The oscillatory state is expected for $E < 0.13 \text{ V} \cdot \text{mm}^{-1}$.

The coefficient a_1 can be determined either from the magnitude of the angle autocorrelation function or from the generating function of the angle distribution (Fig. 4) or from the dose-response curve.

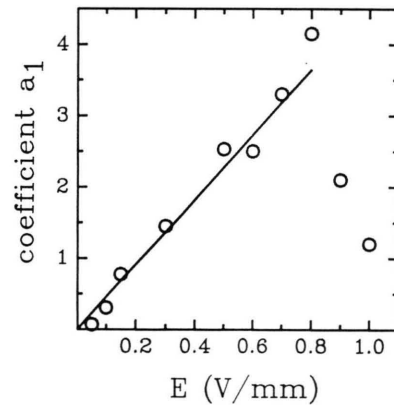


Fig. 4. The coefficient a_1 for human granulocytes as a function of the applied electric field E is shown. The coefficient a_1 is obtained from the measured angle distribution density [8]. The straight line is the theoretical prediction for a proportional controller (= linear response). The slope of the straight line yields the galvano-taxis coefficient ($K_G^{-1} = -0.2 \text{ V} \cdot \text{mm}^{-1}$).

The galvanotaxis dose-response curve (= average of $\cos \Phi$ vs. E) can be predicted as [10, 15, 18]

$$\langle \cos \Phi \rangle = \frac{I_1(a_1)}{I_0(a_1)} \quad (15)$$

where $I_1(a_1)$ and $I_0(a_1)$ are hyperbolic Bessel functions.

The signal transduction/response system is linear if the whole galvanotaxis dose-response curve can be fitted by a single parameter – the galvanotaxis coefficient. This holds for human granulocytes ($K_G^{-1} = -0.22 \text{ V} \cdot \text{mm}^{-1}$ for $E < 0.8 \text{ V} \cdot \text{mm}^{-1}$) [6, 8]. The inverse of the galvanotaxis coefficient K_G^{-1} derived directly from the trajectories (angle autocorrelation function) are -0.19 and $-0.18 \text{ V} \cdot \text{mm}^{-1}$ for $E = 0.5$ and $0.8 \text{ V} \cdot \text{mm}^{-1}$, respectively. A proof for the quality of the used model is the accordance of the galvanotaxis coefficients derived from different experimental data.

The linear response also holds in the case of chemotaxis of granulocytes as long as the mean concentration of the chemotactic compound is constant [15, 18]. A linear response is observed from spermatozooids (galvanotaxis) [17, 18], and (chemotaxis) [17] and of small growing spores (galvanotropism) [19].

In summary, the automatic proportional controller is justified for different polar fields, different cell functions and different cell types.

Proportional-integral controller

The experimental proof for the integral controller is weak. The prediction of the proportional-integral controller are [12]: (i) In the case of a large polar field ($c_1^2 > 4 \cdot k_1$) there exist two characteristic times. Actually the angle autocorrelation function decays in time with two different time constants (granulocytes [8], monocytes [9]). The short one is quite well explained by the proportional controller (see Fig. 3). The slow process could be explained in the framework of the proportional integral controller. (ii) The model predicts an oscillatory state for small polar fields ($c_1^2 < 4 \cdot k_1$). Actually at random walk a characteristic time of less than a minute is determined (granulocytes [15, 18]) and this characteristic is interpreted as the duration of the internal clock of the cell. More experimental material is necessary to proof the existence of the integral controller.

Discussion

Steering and automatic control

The directed movement can be divided into two independent processes – one for the translation and one for the rotation – since the track velocity and the angle of migration are two independent variables.

The rate equation for the translation can be described in the framework of a steerer (= controller without feedback) since the percentage of receptors loaded with chemokinetic molecules is proportional to the mean track velocity [15, 18, 20–22]. The cell has a device for measuring the mean concentration of chemokinetic molecules. The result is a driving force. The rate equation for the rotation can be described in the framework of an automatic controller as already shown.

The concept of a steerer and of a controller is a phenomenological description. Consequently it does not need details of the cellular machinery.

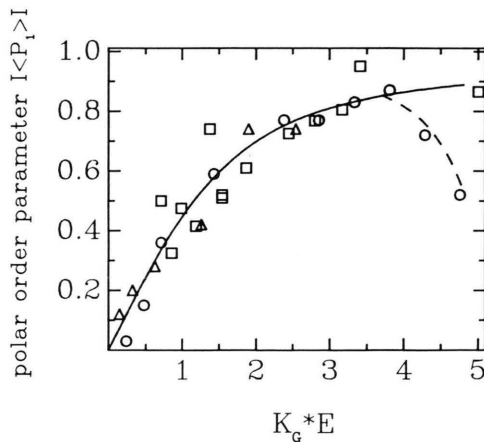


Fig. 5. The absolute value of the polar order parameter is shown as a function of the applied electric field. The electric field strength is given in a normalized scale, $K_G \cdot E$, which is a dimensionless quantity. The line is the theoretical prediction for a proportional controller (= linear response). The open circles were obtained from granulocytes directed by an electric field ($K_G^{-1} = -0.22 \text{ V} \cdot \text{mm}^{-1}$) [8]. The open squares were obtained from growing spores (*Neurospora crassa*) directed by an electric field ($K_G^{-1} = -2 \text{ V} \cdot \text{mm}^{-1}$) [17]. The linear response becomes non-linear if either the electric field is too high, as shown for granulocytes, or the dimension of the cell is too large. In the case of *Neurospora crassa* the grow process became non-linear for $E^2 \cdot l > 0.44 \text{ V}^2 \cdot \text{mm}^{-1}$ [19]. The open triangles were obtained from bracken spermatozooids ($K_G^{-1} = 0.024 \text{ V} \cdot \text{mm}^{-1}$) [17].

One expects that it holds for many cell types and many cell functions. For example the dose-response curve for different phenomena of different cell types can be described by one universal curve. To do this it is necessary to use dimensionless units of the different polar field strengths. The galvanotaxis of human granulocytes [8], the directed growth of spores in an electric field [19], and the galvanotaxis of spermatozooids [17, 18] are shown in one figure (Fig. 5). The common of these different cells and phenomena is the existence of a proportional controller: (i) The cells have a device for measuring their orientation in respect to the polar field. (ii) Their signal transduction/response system works linear. (iii) There exists a noise source in the signal transduction/response system.

As pointed out, the phenomenological descriptions needs no details of the cellular machinery. This fact is very well demonstrated by the investigated cells. The translatory cellular machinery is surely different for granulocytes and spermatozooids since granulocytes with their amoeboid movement, crawl on a surface and spermatozooids swim in an aqueous phase driven by flagellates. The process of the directed movement is surely different from the one of the directed growth.

Galvanotaxis coefficient

The galvanotaxis coefficient quantifies the cellular sensitivity to an electric field. K_G is the ratio of the coefficient, k_{PG} , which characterizes the deterministic part of the proportional controller, and of $q/2$, which characterizes the noise in the proportional controller. The cell measures the polar field in units of K_G^{-1} since $K_G \cdot E$ is dimensionless. The cell reacts very sensitive to electric fields if its electric field standard is small. A sensitive responding cell is expected if the deterministic part of the proportional controller works well ($= k_{PG}$ large) and if the noise in the controller is small.

Chemotaxis coefficient

A common rule in thermodynamics can be used to combine the chemotactic and the galvanotactic response: the electric potential ϕ is replaced by the chemical activity $\ln[c]$ of the chemotactic molecule [23]. This rule holds in general for cells like spermatozooids [17]. It holds for cells like granulocytes as long as their mean concentration is a constant

[15]. In general, the chemotaxis coefficient, K_{CT} , is a function of the mean concentration of the chemotactic molecule.

The concentration dependence of K_{CT} can be predicted if the molecular model of the chemokinetic response of granulocytes is enlarged [18, 20, 24]. If the difference of the number of occupied receptors of two spatially separated measuring devices is regarded as the primary cellular signal, then the chemotaxis coefficient should have the following concentration dependence [18]

$$K_{CT} = K_{CT}^0 \cdot \frac{K_R \cdot [c]}{([c] + K_R)^2}, \quad (16)$$

where K_R is the equilibrium binding constant of the membrane-bound receptor with the chemotactic molecule. The predicted concentration dependence is actually found for granulocytes as shown in Fig. 6. The bell-shaped curve is predicted by Eqn. (16) where $K_R (= 6.6 \mu\text{M f-Met-Met-Met})$ and $K_{CT}^0 (= 9 \text{ mm})$ are fitting parameters. K_R – determined in an additional experiment – is several μM .

The chemotaxis coefficient is obviously composed of two parts: One quantifies the recognition process and the other one the signal transduction/response system of the cell. This interpretation is obviously correct since the chemotaxis coefficient for another chemotactic molecule can be predicted

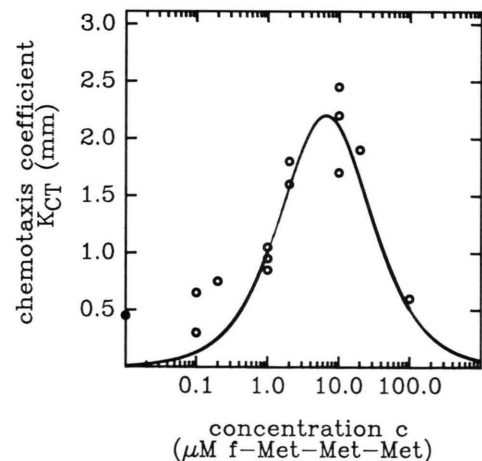


Fig. 6. Chemotaxis coefficient, K_{CT} , as a function of the mean concentration of the chemotactic molecule f-Met-Met-Met. The data of ref. [37] were used. The solid line is a fit of Eqn. (16) to the data with $K_{CT}^0 = 9 \text{ mm}$ and $K_R = 6.6 \mu\text{M f-Met-Met-Met}$.

if the mean concentration, $[c]$, and the equilibrium binding constant are known. The calculated chemotaxis coefficient is between 0.5 and 1.3 mm (5 nM f-Met-Leu-Phe, K_R between 0.5 and 1 nM, and $K_{CT}^0 = 9$ mm). The accordance with the direct measured chemotaxis coefficient ($= 1.5$ mm) is quite well.

Patlach-Keller-Segel model

A few words to the Patlach-Keller-Segel model of the directed movement [25, 26]. There the basic assumption is, that the mean drift velocity, $\langle v_{||} \rangle$, is proportional to $d[c]/dx$

$$\langle v_{||} \rangle = \chi_{CT} \cdot \frac{d[c]}{dx}. \quad (17)$$

χ_{CT} is a coefficient characterizing the chemotactic response. This model is only an approximation which holds for small concentration gradients since $\langle v_{||} \rangle$ increases in the same way as $d[c]/dx$. It cannot predict the observed saturation in the chemotactic response ($\langle v_{||} \rangle \rightarrow \langle v_c \rangle$ for $d[c]/dx \rightarrow \infty$). Eqn. (17) can be compared with our results

$$\chi_{CT} = \frac{1}{2} \cdot \langle v_c \rangle \cdot K_{CT}^0 \cdot \frac{K_R}{([c] + K_R)^2}. \quad (18)$$

Virus disturbed automatic proportional controller

A diminished directed reaction is expected in the case of a disturbed automatic controller. Here it will be shown that virus treated cells like granulocytes have a disturbed controller. This disturbance is of great clinical importance.

A few words about virus-induced disturbances would be useful. Invasion of a tissue by pathogenic bacteria results in the production of an inflammatory exudate which in the early phase consists of an abundant number of granulocytes. By contrast most virus-induced tissue lesions are characterized histologically by a mononuclear inflammatory cell exudate with only few or no granulocytes [27]. As an example, the Echo virus, type 9, strain A. Barty induced non-purulent murine polymyositis [28]. This enterovirus originally isolated from a patient suffering from aseptic meningitis, was investigated *in vitro*. The movement of granulocytes in a concentration gradient is disturbed by this virus, whereas other cell functions like phagocytosis and intracellular killing of staphylococci, remain intact [29]. In the following the automatic controller of

granulocytes under the influence of Echo 9 virus is investigated (source data of ref. [16] are used).

The directed migration of granulocytes is influenced by the virus. As mentioned above, the directed migration is the product of the mean track velocity, $\langle v_c \rangle$, and the polar order parameter, $\langle P_1 \rangle$ ($= \langle \cos \Phi \rangle$). The track velocity of the virus-treated cells is unaffected by the virus. Or – in other words – the steering process involved in the chemokinetic response, is not disturbed by the virus. But the automatic controller responsible for the directed movement, is altered by the virus since the polar order parameter, $\langle P_1 \rangle$, is influenced.

The steady state polar order parameter is zero in the case of virus-treated cells. At a constant viral dose, $[a_{virus}]$, the polar order parameter decays exponentially with time to zero [16].

$$\langle P_1(t) \rangle = \langle P_1 \rangle_o \cdot e^{-\frac{t}{\tau_{virus}}} \quad (19)$$

$\langle P_1 \rangle_o$ is the polar order parameter before the cells were exposed to the virus. The lifetime, τ_{virus} , of the ordered state is a function of the viral dose $[a_{virus}]$ and a law similar to the Weber-Fechner law was found [16]

$$\left(\frac{\tau_{virus}^o}{\tau_{virus}} \right)^2 = \ln [a_{virus}] - \ln [a_{virus}^o] \quad (20)$$

with $\tau_{virus}^o = 2.55$ h and $[a_{virus}^o] = 0.8$ plaque-forming units (pfu) per cell. There is no disturbance in the directed movement for sufficient small viral dose ($[a_{virus}] < [a_{virus}^o]$). Above the threshold viral dose, $[a_{virus}^o]$, the disordered state of the cell ($\langle P_1 \rangle = 0$) is the stable state. Next, the signal transduction/response system will be investigated.

The originally homogeneous cell population of migrating granulocytes splits into two subpopulations after virus treatment [16, 29, 30]. The cells of one subpopulation still exhibit the directed response of control cells ($\langle P_1 \rangle_I = \langle P_1 \rangle_o$) and the cells of the other subpopulation have totally lost their directed response ($\langle P_1 \rangle_{II} = 0$).

A similar observation is obtained from the angle autocorrelation function. The coefficient k_{PC} which characterizes the deterministic part of the proportional controller is determined from the decay of the angle autocorrelation function. k_{PC} is $0.08 \text{ mm} \cdot \text{s}^{-1}$ ($dc/dx = 10 \text{ nM} \cdot \text{mm}^{-1}$ and $c = 5 \text{ nM}$ f-Met-Leu-Phe) for the control cells. The angle autocorrelation function of virus-treated cell

(20 pfu, 1 h virus exposure ($\langle P_1 \rangle \sim 0.2$), $dc/dx = 10 \text{ nM} \cdot \text{mm}^{-1}$ and $c = 5 \text{ nM}$ f-Met-Leu-Phe) is identical with that one of control cells but not exposed to a concentration gradient. Consequently, k_{PC} , is zero for virus-treated cells since c_1 does not depend on the polar field. This means the deterministic part of the signal transduction/response system is disturbed by the virus.

The order-disorder transition of granulocytes was investigated *in vitro* with the Echo 9 virus. Other viruses, *e.g.* influenza [31–33], measles [34], *Herpes simplex* [35] and hepatitis virus [36] also induce disturbances of the chemotactic response of human granulocytes and/or monocytes under *in vivo* and *in vitro* conditions. Obviously, different types of viruses can disturb the data-processing system of human leukocytes. The next question is whether the order-disorder transition is restricted to leukocytes. It is known that the rhythm of *in vitro* beating heart cells can be disturbed by viruses. Coxsackie B virus can be accompanied by dysfunction of the heart – disturbance of the rhythm and a dilatation of the heart [27]. This dysfunction

can be explained by virus-induced disturbances of an automatic controller.

Conclusion

The theory of the automatic control is an important concept in understanding biological phenomena. This study wants to place the directed phenomena as chemotaxis, galvanotaxis, directed growth, *etc.* in a better perspective. The phenomenological description of biological systems by its control system allows the modelling of biological systems even when a detailed knowledge is missing. Other biological phenomena where feedback and control are essential, can be investigated in a similar way. The development of successful solutions to these problems on the basis of automatic controllers are in progress.

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