Brownian Motion and the Temperament of Living Cells

Roumen Tsekov1**, Marga C. Lensen2

1 Department of Physical Chemistry, University of Sofia, 1164 Sofia, Bulgaria
2 Institut für Chemie, Technische Universität Berlin, 10623 Berlin, Germany

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The migration of living cells usually obeys the laws of Brownian motion. While the latter is due to the thermal motion of the surrounding matter, the locomotion of cells is generally associated with their vitality. We study what drives cell migration and how to model memory effects in the Brownian motion of cells. The concept of temperament is introduced as an effective biophysical parameter driving the motion of living biological entities in analogy with the physical parameter of temperature, which dictates the movement of lifeless physical objects.

The locomemory of cells is also studied via the generalized Langevin equation. We explore the possibility of describing cell locomemory via the Brownian self-similarity concept. An heuristic expression for the diffusion coefficient of cells on structured surfaces is derived.

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Tissue cells (e.g. fibroblasts) are anchorage-dependent, implying that they need an interface to adhere to. If a substrate with sufficient rigidity is not available, these cells are not viable, even in the presence of extracellular matrix proteins. Successful initial adhesion is followed by cell spreading and eventually active migration, involving intricate mechanotransduction and biochemical signalling processes. Consequently, cell migration is dependent on physical, chemical and mechanical cues, and others. This has inspired many researchers over the years to predict and control cell migration, for example, by administering increasing concentrations of nutrients to lure cells in a certain direction, which is denoted chemotaxis,[1] or directing them to move up a gradient of substrate elasticity, a process called durotaxis.[2–3]

Controlling cell migration is a very important task in the biomedical field and in tissue engineering, since it determines, for example, the eventual integration of implants and plays an important role in cancer metastasis, where individual cells come loose from the tumour tissue and go out to settle at another suitable interface (e.g. in arteries). We have analyzed the motility of single cells cultured on polymeric gel substrates, i.e. hydrogels, with variable rigidities. Our preliminary unpublished results show that both the mean square displacement and the average speed are larger on stiffer gels, while the mean square displacement scales linearly with time, implying Brownian motion. In addition, the persistence (the angle of directional movement between subsequent steps) appears to be larger on the softest gel, an observation that could, however, be affected inherently by the slower speed. Thus, it seems that cell motility and active migration are correlated to the substrate stiffness,[2,3] besides other factors such as the ones mentioned above. Nevertheless, from single-cell observations, it becomes clear that cells are individual entities and do not all behave identically, whereas the chemical or mechanical cues are supposedly homogeneous and act upon all cells similarly. We are interested in unraveling the other driving forces that dictate cellular behavior and finding out more about the individual cell characteristics. In a sense, we are searching for the biophysical factors besides the well-known chemical and mechanical parameters that dictate cell behavior in a certain situation. In addition, by looking at a statistically relevant number of single cells and analyzing how their behavior might deviate more or less from the average, we take into account the individuality of living cells.

Cell migration is usually described as Brownian motion,[4–8] and non-Markovian effects are accounted for[9–14] as well. The general theory of Brownian motion is well developed in physics.[15–17] Starting from Newtonian mechanics, one can derive a generalized Langevin equation describing the stochastic dynamics of a Brownian particle.[18] An important result is the fluctuation-dissipation theorem, which relates friction and stochastic forces in such a way that the temperature of the system remains constant. Although the theory of Brownian motion has already been applied to biological systems,[19,20] there are still open questions. For instance, the Brownian motion of particles is driven by thermal fluctuations in the surrounding matter, whereas the cells possess an inherent vital power. Hence, the thermal fluctuations are not the driving force of cell migration. It is clear nowadays that cells are active Brownian particles.[21–24] In this

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**Corresponding author. Email: tsekov@chem.uni-sofia.bg

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Letter, we study what drives cell migration and how to model memory effects in the Brownian motion of cells. We introduce the concept of temperament as an effective biophysical parameter driving the motion of living biological entities in analogy to the physical parameter of temperature, which dictates the movement of lifeless physical objects. We also explore the possibility of describing cell locomotion via the Brownian self-similarity concept.[25,26]

In general, the dynamics of physical systems are Hamiltonian. Although the cells are alive, they can also be considered as physical objects[27] and can be described via a Liouville operator \( i\hat{L} \). Hence, the evolution of the mass center of the cell \( r(t) \) can be expressed as

\[
r(t) = \exp(i\hat{L}t)r,
\]

where \( r \equiv r(0) \) is the initial point. Thus, the cell and its interactions with the environment are completely defined by the Liouville operator, which accounts for all physical and chemical effects. Though it is impossible to write a detailed expression for \( i\hat{L} \), one can perform a general analysis without specification of the Liouville operator. Following the classical Mori–Zwanzig approach[16,17] the exponential operator in Eq. (1) can be expressed in an alternative way,

\[
\exp(i\hat{L}t) = \exp[(1 - \hat{P})i\hat{L}t] - \int_0^t \exp(i\hat{L}s)\hat{P}i\hat{L} \cdot \exp[(1 - \hat{P})i\hat{L}(t - s)]ds,
\]

where \( \hat{P} \) is an arbitrary projection operator satisfying the general definition \( \hat{P}^2 = \hat{P} \). A possible expression is

\[
\hat{P}r = \frac{v\langle vr \rangle}{\langle v^2 \rangle},
\]

where \( v = \dot{r}(0) = i\hat{L}r \) is the cell initial velocity. The projection operator (3) maps the coordinate space onto the velocity space of the cell. The brackets (\( \langle \rangle \)) indicate an empirical statistical average, which can differ from the usually employed equilibrium ensemble average. Thus, \( \langle v^2 \rangle \) is the stationary non-equilibrium dispersion of cell velocity and reflects the cell vitality.

Using Eqs. (1) and (2), one can express the cell acceleration in the form

\[
\ddot{r} = \exp[(1 - \hat{P})i\hat{L}t]i\hat{L}v - \int_0^t \exp(i\hat{L}s)\hat{P}i\hat{L} \cdot \exp[(1 - \hat{P})i\hat{L}(t - s)]i\hat{L}vds.
\]

Now introducing the stochastic Langevin force \( f(t) \equiv m\exp[(1 - \hat{P})i\hat{L}t]i\hat{Lv} \), Eq. (4) acquires the form of a generalized Langevin equation[17]

\[
m\ddot{r} + \frac{1}{m\langle v^2 \rangle} \int_0^t C_\eta(t - s)\dot{r}(s)ds = f,
\]

where \( m \) is the cell mass. This equation describes a non-Markovian behavior, and the stochastic force autocorrelation function \( C_\eta \equiv \langle f(t)f(s) \rangle \) plays the role of a memory kernel.

The simplest description of the Brownian motion of a cell is a Markovian one, where the friction force is instantaneous and the stochastic cell dynamics obey the ordinary Langevin equation[13]

\[
m\ddot{r} + b\dot{r} = f,
\]

where \( b \) is the cell friction coefficient. If the cells do not perform active swimming,[11] then the friction coefficient can be estimated in liquids by the Stokes formula \( b = 6\pi\eta R \), where \( \eta \) is the viscosity and \( R \) the cell radius.[28,29] Now comparing Eqs. (5) and (6) yields an expression for the Langevin force autocorrelation function

\[
C_\eta = 2m\langle v^2 \rangle b\delta(t - s),
\]

which is a white noise with a constant spectral density. Equation (7) is the so-called second fluctuation-dissipation theorem. In the usual thermal Brownian motion, the velocity dispersion of a Brownian particle is proportional to the system temperature \( \langle v^2 \rangle = k_B T/m \), and the Langevin force autocorrelation function acquires the classical form \( C_\eta = 2k_B T b\delta(t - s) \). In the case of cell Brownian motion, \( \langle v^2 \rangle \) is not determined by the temperature and depends on the living power of the cell. For the sake of convenience, here we will introduce an analogue of the thermodynamic temperature for living objects, \( \theta \equiv m\langle v^2 \rangle \), which we call temperament. This is a measure of the living power of the cells, reflecting the cells' more intensive aspiration to move. The \( \theta \) temperament is energy, and is conceivably proportional to the amount of energy stored as ATP in cells.

In the general case, cell migration can also be affected by external forces \( F \), which can cause, for instance, chemotaxis[1] and durotaxis.[2,3] In this case, the existing gradient of the surface properties forces the cells to migrate. Of course, due to the random movement, the experience of the cells is in fact a directed active Brownian motion. The force balance of the cell in this case reads

\[
m\ddot{r} + b\dot{r} = f + F.
\]

Taking an average value of this equation and remembering that the fluctuation force possesses a zero mean value, one can obtain an equation for the mean displacement \( \langle r(t) \rangle \) of the cell,

\[
m\langle \ddot{r} \rangle + b\langle \dot{r} \rangle = F.
\]
Usually, the friction force is much larger than the cell acceleration, and in this case Eq. (9) reduces to \( \langle \dot{r} \rangle = F/b \). If the external force is constant in time, one can derive the relation for the cell mean displacement \( \langle r \rangle = Ft/b \), which depends linearly on time. Hence, if several cells are monitored, one can calculate their average displacement, and by plotting it versus time obtain the \( F/b \) ratio from the slope of the linear fit. Thus if the external force is known, one is able to experimentally determine the friction coefficient \( b \), which is an interesting characteristic of cell motion. This depends on how the cells interact with the surrounding matter. In practice, apart from the gravitational force in sedimentation, the \( F \) force is unknown in chemotaxis and durotaxis. For this reason, the decay of the velocity autocorrelation function of the cell migration is typically used to extract the friction coefficient \( b \).

Now subtracting Eq. (9) from Eq. (8) yields an equation for the cell position fluctuations,

\[
m(\ddot{r} - \langle \ddot{r} \rangle) + b(\dot{r} - \langle \dot{r} \rangle) = f. \tag{10}
\]

This equation corresponds to pure Brownian motion, and for this reason the dispersion of the cell position is given by \( \langle r^2 \rangle - \langle r \rangle^2 = 2Dt \). Hence, plotting this linear relation from experimental measurements, one is able to obtain the cell diffusion constant \( D \) as well. According to Eq. (7), it is given by the ratio of the temperamant and friction coefficient, \( D = \theta/b \). Since the friction coefficient \( b \) can be calculated independently from the mean displacement, the temperament of a cell \( \theta = bD \) can be estimated from these two experimentally measured coefficients.\cite{28} Thus, one can calculate this very interesting characteristic of cell activity. It is exciting to compare the temperament of different types of cells.

The temperament is related to the entropy production \( \dot{S} \) in cells, which according to non-equilibrium thermodynamics, depends on thermodynamic flows \( \{x_k\} \) and forces \( \{f_k\} \),

\[
\dot{S} = \sum_k (\partial S/\partial x_k) \dot{x}_k = \sum_k f_k \dot{x}_k = \sum_k \sum_n L_{kn} \dot{x}_n \dot{x}_k. \tag{11}
\]

The last expression is valid for linear non-equilibrium thermodynamics, where \( \{L_{kn}\} \) is the symmetric matrix of kinetic coefficients. In the case of cell motion, one of the generalized flows is obviously the cell velocity \( v \equiv \dot{x}_1 \). The coefficient \( L_{11} = b/T \) equals the friction coefficient divided by the temperature, since the translation is a vector process, \( L_{1n\neq1} = 0 \), due to the Curie principle. Thus, the temperament \( \theta = m\langle \dot{x}_1^2 \rangle \) can be expressed as

\[
\theta = T(\langle \dot{S} \rangle - \langle \dot{S}_{-1} \rangle)m/b, \tag{12}
\]

where \( \langle \dot{S}_{-1} \rangle = \sum_{k\neq1} \sum_{n\neq1} L_{kn} \langle \dot{x}_n \dot{x}_k \rangle \) is the average entropy production due to all other activities of the cell, excluding cell migration. Equation (12) suggests proportionality between the temperamant and temperature. This could also be used to calculate the cell entropy production, which is further related to specific biophysical processes. If the cell is not alive, \( \langle x_k f_n \rangle = k_B \delta_{kn} \) according to the equipartition theorem, and during the momentum relaxation time \( m/b \) the cell will produce kinetic entropy equal to the Boltzmann constant \( k_B \). Hence, in this case the temperament will coincide with the thermodynamic temperature \( \theta = k_B T \) and the cell will move as a usual Brownian particle. If the cell is alive, it will produce much more kinetic entropy to compensate for the active entropy flow from the environment and to keep the stationary state of life. Hence, the temperament will be much higher than \( k_B T \), which will be reflected by more intensive Brownian motion and a higher diffusion constant \( D \).\cite{30}

An interesting aspect of cell migration is the Brownian motion of cells attached on structured surfaces. In this case, the cells experience a periodic potential \( U \), which modulates their motion. The corresponding Langevin equation reads

\[
m\ddot{r} + br = f - \partial_r U. \tag{13}
\]

Usually, the friction on a surface is much stronger than that in the bulk and for this reason the inertial effects in Eq. (13) can be neglected. Thus, following Eq. (7), the probability density \( \rho(r,t) \) to find the cell at point \( r \) at the moment \( t \) obeys the Smoluchowski equation

\[
\partial_t \rho = \partial_r \cdot (\rho \partial_r U + \theta \partial_r \rho)/b, \tag{14}
\]

where the temperament plays the role of an effective temperature. The term \( \theta \rho \) represents the osmotic pressure of the living cell and, hence, the temperamant \( \theta \) can be conveniently measured by osmotic experiments as well. In this respect, an interesting question arises here: what is the osmotic pressure of fish in an aquarium? Hence, the temperament can also be attributed to animals, people, etc. The stationary distribution, provided by Eq. (14), is a Boltzmann-like probability density \( \rho_{ST} \sim \exp(-U/\theta) \). In the case of gravity with \( U = mgz \), Eq. (14) describes the barometric distribution of cells with stationary probability density \( \rho_{ST} = (mg/\theta) \exp(-mgz/\theta) \), while small vibrations of an adsorbed cell are described by a harmonic potential \( U = m\omega^2 x^2/2 \) and probability density \( \rho_{ST} = \sqrt{m\omega^2/2\pi\theta} \exp(-m\omega^2 x^2/2\theta) \).

In the field of a periodic potential \( U \), the cell undergoes a continuous Brownian motion with an effective diffusion coefficient calculated from Eq. (14).\cite{31,32}

\[
D_{eff} = D/\langle \exp(-U/\theta) \rangle \langle \exp(U/\theta) \rangle, \tag{15}
\]
where the brackets ( ) indicate the spatial geometric average along the surface. For instance, in the case of a cosine potential \( U = A\cos(qr) \), explicit calculation is possible and the effective diffusion coefficient acquires the form

\[
D_{\text{eff}} = D/I_0^2(A/\theta),
\]

(16)

where \( I_0 \) is the modified Bessel function of the first kind and zeroth order. If the height of the potential barrier \( 2A \) is much smaller than the temperament \( \theta \), then the effective diffusion coefficient will reduce to the one on a non-structured surface \( D \). In the opposite case of strong barriers, Eq. (16) is approximated well by the Arrhenius-like dependence,

\[
D_{\text{eff}} = 2\pi(A/b)\exp(-2A/\theta).
\]

(17)

Hence, the temperament is essential for the description of cell motion in potential landscapes, which is usually the case in practice. The direct parallel between the temperament and temperature allows the employment of many well-known results from the statistical mechanics for the description of phenomena related to living objects. A similar approach accounting for the effective quantum temperature is used in chemical kinetics and catalysis.\[^{[33]}\]

From Eq. (13), one can derive in a standard way the Klein–Kramers equation describing the evolution of the probability density \( W(v,r,t) \) in the cell phase-space,

\[
\frac{\partial}{\partial t} W + v \cdot \nabla W - \nabla U \cdot \nabla W/m = b \Theta_v (vW + \theta \partial_r W/m)/m.
\]

(18)

It provides the Maxwell–Boltzmann-like distribution \( W_{\text{eq}} \sim \exp[-(mv^2/2 + U)/\theta] \) as the equilibrium solution. The Smoluchowski equation (14) can be derived from Eq. (18) in the case of large friction. In the case of a free cell, Eq. (18) can be integrated directly along the cell coordinate \( r \) to obtain the Fokker–Planck equation for the probability density \( w(v,t) \) in the cell velocity space,

\[
\frac{\partial}{\partial t} w = b \partial_v (vw + \theta \partial_r w/m)/m.
\]

(19)

This equation shows that the cell velocity is an Ornstein–Uhlenbeck process.

Due to the active locomotion of the cells, the fluctuation Langevin force \( f \) is strongly related to the cell vitality. For the problem demonstrated above, the simple white noise model is very useful, but does not take into account the memory effects, which are important in the living world. According to Eq. (5), the memory function of the Brownian motion is determined by the Langevin force autocorrelation function, which is a manifestation of the fluctuation-dissipation theorem. Since the Langevin force is not correlated to the initial cell velocity, \( \langle f(t)v \rangle = 0 \), it is straightforward to derive from Eq. (5) an integro-differential equation for the cell velocity autocorrelation function \( C_{vv}(t) \equiv \langle v(t)v \rangle \),

\[
m\theta \dot{C}_{vv}(t) + \int_0^t C_{vv}(t-s)C_{vv}(s)ds = 0.
\]

(20)

Using standard Laplace transformation, this equation can be transformed to

\[
\frac{\tilde{C}_{vv}(p)}{D} = \frac{1}{mp/b + \tilde{C}_{\Pi}(p)/b\theta},
\]

(21)

where \( p \) is the Laplace transform variable. As is seen, Eq. (21) relates the memory function to the Laplace spectral density of the cell velocity fluctuations. A useful idea to close the problem is to supply an additional relationship between these two quantities, which is the essence of the concept of Brownian self-similarity.\[^{[25]}\]

In Ref. [34] we proposed the similarity between the Laplace spectral densities of the Langevin force and Brownian particle velocity as a model of hydrodynamic fluctuations. According to this concept, the form of the Langevin force autocorrelation function spectral density is the same as that of \( \tilde{C}_{vv} \) in Eq. (21),

\[
\frac{\tilde{C}_{\Pi}(p)}{b\theta} = \frac{1}{\tau + \tilde{C}_{\Pi}(p)/b\theta}.
\]

(22)

Here, the new parameter \( \tau \) is the correlation time of \( f \) and Eq. (22) provides the standard white noise expression \( \tilde{C}_{\Pi}(p) = b\theta \) if \( \tau = 0 \). In general, the solution of Eq. (22) reads

\[
\tilde{C}_{\Pi} = b\theta [\sqrt{1 + (p\tau/2)^2} - p\tau/2],
\]

\[
\tilde{C}_{\Pi} = b\theta J_1(2\theta/\tau)/\tau,
\]

(23)

where \( J_1 \) is the Bessel function of the first kind and first order. The plot of this Langevin force autocorrelation function in Fig. 1 exhibits an oscillatory behavior corresponding to a sequence of correlations and anticorrelations. Another interesting property of the Langevin force autocorrelation function (23) is the long-time tail, where the amplitude of \( \tilde{C}_{\Pi} \) decays in time as \( 1/t^{3/2} \). The Langevin force also possesses a finite dispersion \( C_{\Pi}(0) = b\theta/\tau \).

Substituting Eq. (23) in Eq. (21) leads to an expression for the Laplace spectral density of the cell velocity autocorrelation function,

\[
\tilde{C}_{vv}(p) = D/[mp/b + \sqrt{1 + (p\tau/2)^2} - p\tau/2].
\]

(24)

This is the so-called Rubin model,\[^{[35]}\] known from the physics of chains of oscillators. Unfortunately, it is impossible to invert the Laplace image (24) in general, but there are some particular cases where
analytical expressions are obtained. If the cell relaxation time $m/b$ is much larger than the correlation time of the Langevin force $\tau$, Eq. (24) will reduce to the standard exponentially decaying function $C_{vv} = (\theta/m) \exp(-bt/m)$. If these two time constants are equal, then the velocity autocorrelation function $C_{vv} = D J_1(2bt/m)/t$ will coincide with the Langevin force autocorrelation function (23). This case corresponds to Brownian particles driven by similar objects. From these perspective cells, which dissipate energy mainly inside, we have the velocity autocorrelation function $C_{vv}$, like that in Fig. 1. The remaining heat into the cells is a requirement to keep the temperament constant in the case of an absent external energy flow. If $\tau = 2m/b$, then the inverse Laplace image of Eq. (24) is another oscillatory-decaying function $C_{vv} = (\theta/m) J_0(bt/m)$, where $J_0$ is the Bessel function of first kind and zeroth order. Finally, if the correlation time of the Langevin force is infinite, then the cell velocity is completely correlated at any time, $C_{vv} = \theta/m$.

The Brownian motion was originally discovered by colloidal particles, and later it was realized that Brownian motion is a universal movement of matter. For this reason, our application to cell motion starts from the first principles to convince the reader that cells should also follow Brownian motion dynamics. Therefore, there is no room for any doubt in the applicability of the Brownian motion model to living cells, and the only new specific parameter introduced is the cell velocity dispersion being directly proportional to the temperament. The observed deviations from the Einstein law are suitable, however, for the Gaussian white noise model, and can be resolved by proper modeling of the memory function in Eq. (5). Such an example is given. Even in the exact generalized Langevin equation (5), the problem for the value of the temperament is central. This is the cell property, and the effect of the environment is to contribute a negligible addition $k_\text{B}T$ to the temperament $\theta$. More essential in a structured environment is the modulation of the friction coefficient $b$ and the effective periodic potential $U$ via surface topography, stiffness, etc. These effects are very interesting for theoretical modeling or experimental measurement, but out of the scope of the present study. For illustration, we have mentioned the simplest case of spherical cells, where $b$ is given by the Stokes law, and estimated the corresponding values of temperament from already published data.

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