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From Maxwell's demon to the self-organization of mass transfer processes in living systems

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Abstract. As a result of cyclic interactions with their environment, microparticles are often drawn into a directed, stochastically determined motion and subsequently arrange themselves into dynamical structures. In the present review, the possibility of a directed motion of microparticles in the presence of weak, asymmetric, periodic governing fields is analyzed. The minimum energy requirement for changing from random walk to directed motion is estimated. Applications to regulatory processes in biosystems, such as the virus – bacterium interaction and intercellular movement of chemotaxis bacteria, vesicles, enzymes, and ions, are discussed and certain high-technology uses of these effects considered.

1. Introduction

The spectre of Maxwell's demon (1871), sorting out Brownian particles — that is, separating the fast from the slow — has been haunting scientists for over a hundred years. Several generations of physicists exorcised this demon from science. Restrictions were considered that prevent the microparticle, irrespective of its characteristics, from directionalizing its random path without supply of energy from outside; the growth of entropy in the demon – microparticle system was analyzed [1 – 3], as were the implications of the uncertainty principle [4 – 6], the impossibility of registering the direction of impacts under conditions of temperature equilibrium, etc. [7 – 9]. Nevertheless, interest in this problem persists. The revised formulation of the issue runs as follows: what is the minimum energy cost of vectorization of random walk of microparticles?

Directed movement of microparticles in the flow of protoplasm in living cells was observed as early as 225 years ago by Corti [10], and has been studied closely ever since. This phenomenon can be seen through an optical microscope in fungi and giant plant cells like *Acetabularia, Nitella*, etc., and sometimes even with the naked eye, as in the case of *Physarum polycephalum* [11, 12].

Thermal motion of microparticles was detected by J Ingenhausz as early as 1785, some 150 years after A Leeuwenhoek had laid the foundations of optical microscopy. Leeuwenhoek himself observed the motion of live bacteria, spermatozoa and protozoa, which very much resembled the movement observed later by Ingenhausz with inanimate objects: crushed charcoal particles floating on the surface of alcohol. However, the phenomenon of thermal motion was named after the British botanist Robert Brown, who in 1828 published his observations of the motion of small particles like pollen, dust and soot suspended in water [13]. In the early 1970s H Berg of Harvard University used a tracking microscope in the 'Lagrangian frame' to monitor experimentally the three-dimensional path of an individual bacterium; he demonstrated that this path is stochastic in the isotropic field of an attractant, and short spells of calm drift alternate with tumblings [14 – 17].

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Particles of size 10^{-8} to 10^{-6} m — for example, soot or dust suspended in a liquid — exhibit stochastic movement driven by collisions both with the molecules of the liquid and between the particles themselves ('the billiards model'). Brownian motion was described theoretically in 1905 by A Einstein and M Smoluchowski [18 – 20]. In 1908 this theory was augmented by P Langevin [21]. He postulated two components of the force acting on the Brownian particles. One is the force resulting from the high-frequency impacts of the molecules of the environment that change the direction of motion of the particle. Averaged over a finite time, this force is equal to zero. The other component is the force related to the viscosity of the medium, which fluctuates with a low frequency.

These two forces are independent, and their effect on the motion of particles is additive. This, however, is only true in the first approximation. If the parameters of the environment change, this may change the shape of the particles — they may become 'looser' or 'denser', thus affecting both the viscosity of the medium and the dynamics of their own motion. The theory of Brownian motion has been continuously modified ever since so as to include its different manifestations [22 – 24]. Three types of interactions between microparticles and environment may be distinguished, depending on which of the partners plays the active role in the interaction.

1.1 Active environment and passive microparticles

In this case the medium governs the object, and the motion of the object is caused by fluctuations of the medium (the Langevin model). Inhomogeneity of the space distribution of particles is an indicator of inhomogeneity of fluctuations of the medium [21]. This model, however, is not always able to account for the diversity and abundance of structures arising on account of the inhomogeneity of space distribution of moving microparticles [23 – 26, 28 – 31]. This version of interaction is close to the model proposed 45 years ago by Turing [27].

1.2 Active microparticles and passive environment

In this case the object has an inherent program of self-motion. In a homogeneous medium such particles may form heterogeneous clusters because the cycles of their genetic programs of motion are synchronized. This model is different from both the Turing and the Langevin models, and belongs to the class of models of objects with an innate 'biological clock'. The mobility of microparticles is then associated with their 'internal time' — that is, their age. For example, structures made up of mobile cells in many regimes of collisions of bacterial population waves can only be explained by introducing parameters related to the genetic features of self-motion of the objects [28 – 34].

1.3 Active microparticles and active environment

This situation corresponds to a closed cycle of interaction between equal partners, the microparticles and the environment, and is the most general of all. This behavior is determined by the interplay of the time evolution of the internal genetic program of motion of the objects themselves, and variations of the manifold environment [23, 24, 35].

Observe that often (but not always) in the cycle of interaction 'microparticles $\leftrightarrow$ environment' it does not matter which branch of the cycle is assumed to be active: this may have no effect on the final experimentally observed moving structure comprised of microparticles. Over a relatively large range of variations, similar results can be obtained either through genetic changes of the mobility of microparticles, or by varying the parameters of the environment.

1.4 Thermal noise in biosystems as a prerequisite to their functioning

Man-made machines and mechanisms become more and more complicated as the number of degrees of freedom increases. In engineering, thermal noise is regarded as a nuisance, as something that destroys coherence. By contrast, thermal noise in biological systems is a useful phenomenon and serves two purposes: the search of partners for molecular interactions, and adaptive variability. The presence of weak fields at all levels of cellular organization — from protozoa to humans — separates microparticles with different physicochemical properties moving chaotically at temperatures $T \sim 300$ K. In the case of biochemical interactions the stage of search and sorting in such systems occurs in terms of energy expenditure practically 'for free', at the expense of thermal motion, whereas intentional selection would require extra energy. Besides, the phase trajectories describing the motion of microparticles in living systems normally have the form of strange attractors [36 – 38]. As the external conditions change, thermal noise facilitates switching from one trajectory to another. In such a case the phase trajectories can be steered and stabilized with short periodical inputs. Such correction is often referred to as 'the butterfly effect' [39].

Further on we are going to illustrate the above concise statements with physical models (Section 2). Then we shall estimate the lowest energy cost of conversion of stochastic Brownian motion into directed motion under the action of the arising weak fields of various natures (Section 3). We shall show that the conversion of stochastic mobility of microparticles into directed motion takes place inside living cells (Section 4). Finally, we are going to formulate the immediate tasks of future biological studies, and consider the use of similar methods of controlling the stochastic mobility in new high-technology applications (Section 5).

2. Separation of the mixture of microparticles by modulation of Brownian mobility

2.1 Separation using external asymmetrical oscillating fields

Assume that we have a vessel containing a homogeneous mixture of two types of microparticles, A and B, possessing different properties. Let, for example, particles of type A carry an electric charge, and particles of type B be neutral while being heavier. Then we may cause the mixture of particles $A + B$ separate by applying electric and ultrasonic fields to our container. Separation may also be caused by applying one particular field if the particles of types A and B exhibit different susceptibilities to a field of this kind. Now what is the role of Brownian motion in the processes of separation? Seemingly adverse, since it stirs the particles thus obstructing their separation. However, this is not always the case. In some situations, Brownian mobility will facilitate separation. If the applied field reduces the hydrodynamic Stokes radius for particles of type A, and increases the same for particles of type B, then the particles of type A will be accelerated, and those of type B retarded by the thermal field. In such a case the movement of particles will be vectorized by

the concerted action of two forces — the 'pulling' and 'pushing' forces, with participation of the Brownian component of motion. Numerous separating systems of such a kind have been proposed [40–42].

The main idea is quite simple. The differential form of the diffusion expression for the motion of Brownian particles under the action of fluctuations is

$$\frac{\partial P(x,t)}{\partial t} = D\frac{\partial^2 P(x,t)}{\partial x^2} - \frac{\partial}{\partial x}\left[\frac{1}{\gamma}P(x,t)\frac{\mathrm{d}U(x)}{\mathrm{d}x}\right], \qquad (1)$$

where $P(x,t)$ is the probability of the space-time concentration of particles given in space by the Boltzmann distribution $P(x) = P_0 \exp[-U(x)/(kT)]$; $U(x)$ is the potential energy; k is the Boltzmann constant; T is the temperature; γ is the resistance of the medium (viscosity); and D is the diffusion coefficient. If we discard the second term on the right-hand side of Eqn (1), this expression becomes the classical Fokker–Planck–Kolmogorov operator of Brownian motion [43, 44]. Such a reduction of Eqn (1) would require assuming that the quantity D is not constant — D will become a function $D = f(U,x)$. The presence of the second term on the right-hand side allows D to be regarded as a constant. The sign of the second term depends on the sign of $\mathrm{d}U(x)/\mathrm{d}x$. If $[\mathrm{d}U(x)/\mathrm{d}x] < 0$, the term is 'retarding', and 'accelerating' if $[\mathrm{d}U(x)/\mathrm{d}x] > 0$. If function $U(x)$ is periodic and asymmetrical, then Brownian particles will accelerate or slow down so as to restore the symmetry, and their motion will become directional.

As an example of a practical separator, let us consider a system devised by French researchers [41]. It is based on the combination of asymmetrical periodic space potentials occurring across spatial maze-sieves, whose entrances are filled with Brownian particles. A time sequence of asymmetrical U-shaped voltage pulses is applied to the walls of labyrinths. In space, such pulses create a sawtooth potential (Fig. 1a). The vessel was made by printed circuit technology. The labyrinths have a herringbone shape (Fig. 1b). Brownian particles were represented by polystyrene latex spheres 0.1 to 0.5 micrometers in diameter. Electrolyte was selected, and measures taken to prevent decomposition of water. The observed effect consisted in that the particles were decelerated by the field, separated, and moved from one trap to the next in the direction of the x axis.

The mean velocity of directed motion of microparticles was shown to be given by

$$\bar{v} = \frac{pL}{\tau_{\mathrm{off}} + \tau_{\mathrm{on}}}, \qquad (2)$$

$$P = \frac{1}{2}\left[\exp\left(-\frac{\alpha^2}{4D\tau_{\mathrm{off}}}\right)\right], \qquad (3)$$

where $p \leqslant P$, P is the probability of occurrence of particles in the successive traps, τ_{off} and τ_{on} are the time intervals for which the change of the sawtooth electric field is on and off, respectively, α is the effective cross section of the channel between traps. The latter parameter takes account of three-dimensional effects related to the finite depth of the vessel and the shape of the electrodes. Falling into the region where the density of the lines of force of the field is the highest, the particles are retarded and polarized. For particles of the size 0.25, 0.4 and 1 micrometer, the value of α is, respectively, 19, 18 and 14 micrometers. The quantity D is the diffusion

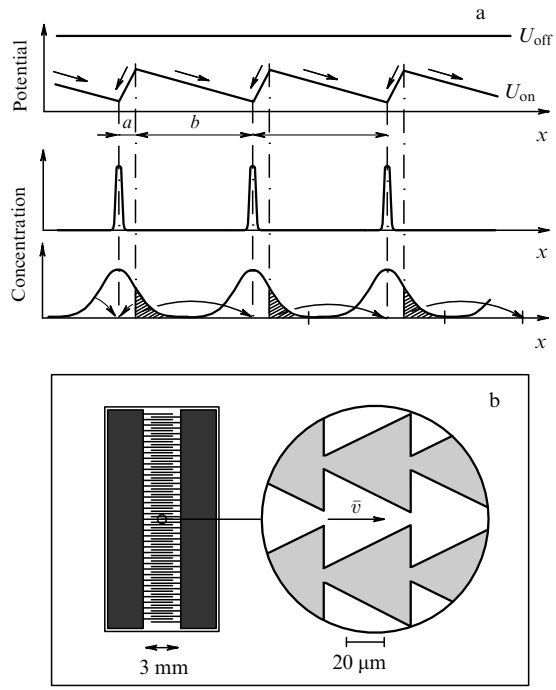

Figure 1. Realization of device for separating Brownian microparticles, based on a spatially asymmetrical periodical electric field [41]. The field is created by switching on and off the potential at the electrodes — the 'herringbone' walls of the vessel: (a) field potential (upper graph) and consecutive changes in concentration of microparticles (middle and bottom graphs). The field concentrates the particles by decelerating their thermal motion during the 'on' interval (middle graph). Thermal motion of particles during the 'off' interval smears the distribution of microparticles, thus ensuring their directional motion (lower graph); (b) construction of the device (left) and enlarged fragment showing the herringbone-shaped walls (right). Arrow indicates the direction of motion of microparticles.

constant; L is the period of the electrode grid, $L = 50$ μm. The variation of τ_{off} from 10 to 120 seconds with fixed τ_{on} (about 30 seconds) ensured directional motion of the particles in all cases, and the mean velocity of macroscopic displacement of particles was $\bar{v} = 0.2$ μm s^{-1}. In this model, the geometry of the space is rigidly controlled, being predetermined by the geometry of the electrodes and the sawtooth shape of the potentials.

In another study [42], the field was also established with a sawtooth-shaped space potential, whereas the second component was represented by a simple cyclic chemical reaction with the addition of the enzyme and the eventual formation of the Michaelis complex that played the role of the Brownian particle. The directed motion of the complex in the electric field was due to the change in the hydrodynamic Stokes radius of the microparticle upon attachment of the enzyme. The presence of the enzyme makes the reaction asymmetrical. The asymmetry of the reaction combines with the asymmetry of the oscillating electric field, which causes directional movement of particles. The direction of motion of complexes is determined by the phasing of the periodic asymmetry of the electric field and the stage of the periodic chemical reaction.

Now the question is whether such systems with directional movement of Brownian particles are capable of doing work.

One can show [42, 45] that the force developed by such a Brownian motor is

$$|F_{\max}| \leqslant \frac{\Delta U}{(1-\alpha)L}\,, \tag{4}$$

where ΔU is the conversion of the potential energy, α is the asymmetry indicator ($\alpha = (b-a)/(b+a)$; see Fig. 1a), and L is the pitch of the grid ('herringbone' in Fig. 1b). This force is tiny — from 0.5 to 1.5 pN (piconewton). If there are many such elements, however, the total force may be substantial. This principle underlies the operation of muscle [46]. Muscle contraction involves two processes: the kinetics of a chemical reaction localized at every point of space (the asymmetry of molecular transition constants in the branches of enzymatic cycle of pulling bridges), and the asymmetry of the potential distribution along the fibrillary proteins (actin and myosin). If the operation of such a system had been based on fluctuations alone, without the input of energy created by the asymmetry of the potential, its efficiency would have been very low. Owing to ATP hydrolysis, there is a periodic asymmetric potential that gives direction to the motion, and transforms the random movement of protein filaments of actin and myosin sliding with respect to one another into a coherent motion [46].

2.2 Directed motion of Brownian particles as a result of their 'loosening'/'compaction'. Taxis of bacterial viruses

In this case, the field change is set by the concentration potential. The second element is represented by microparticles of variable geometry themselves that possess a set of conformation states. We have considered this situation using the example of directed motion of bacterial viruses towards a bacterium [47]. A bacterium periodically expels the products of its metabolism into the environment. Their concentration in space obeys the Boltzmann distribution. Interaction of the metabolite with the polar elements of the virus (its fibrils) results in a change in the spatial geometry of the virus, and a change in the hydrodynamic Stokes radius (Fig. 2). The probability of forming a complex with the metabolite $p_i(x,t)$ or its disintegration $p_j(x,t)$ depends on the direction of movement of the virus in space, and is described by the diffusion-reaction equation [42], while the equation of motion of viruses is similar to Eqn (1):

$$\frac{\partial\phi(x,t)}{\partial t} = D\frac{\partial^2\phi(x,t)}{\partial x} - \frac{\partial}{\partial x}\left[\chi\phi(x,t)\frac{\mathrm{d}B(x,t)}{\mathrm{d}x}\right], \tag{5}$$

where D is the Brownian diffusion of viruses, $\phi(x,t)$ is the concentration of viruses, $B(x,t)$ is the concentration of metabolite ejected by bacteria, χ is the chemotaxis susceptibility of viruses (the sensitivity of the hydrodynamic radius), $\mathrm{d}B/\mathrm{d}x$ is the spatial gradient of metabolite (the concentration field) that governs the mobility of viruses. If this gradient is asymmetrical, then we have a 'pulling' component, since the probabilities of forward and back motion are not the same, $|p_i(x,t)| \neq |p_j(x,t)|$. This ensures directional motion of viruses towards the bacterium. A similar control system exists inside living cells [48] (see Section 5). The mobility of macromolecules having a set of conformation states is controlled by sorbents (ions or cations) that occupy the active sites of macromolecules and change their hydrodynamic radius.

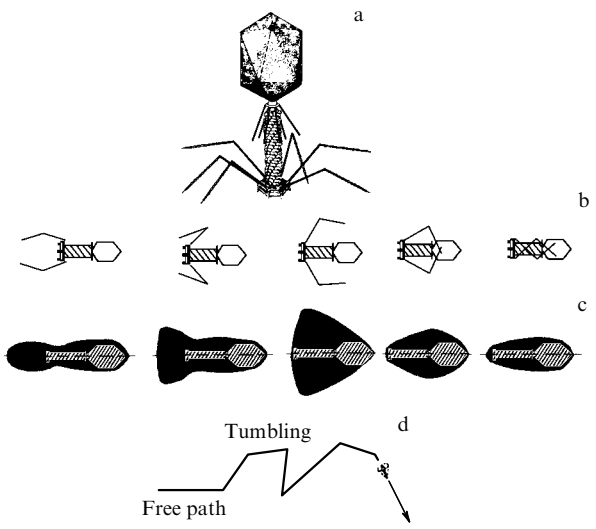

Figure 2. Bacteriophage T4 (bacterial virus) as an example of a particle with variable geometry; the size of the particle is approximately 10^{-7} m. The end fibrils of the bacteriophage spread out as the temperature increases and the metabolites are attached, and change the hydrodynamic profile and Stokes radius of the particle. The stochastic motion of bacteriophages becomes stochastic-directional, controlled by the concentration gradient of metabolites ejected by bacteria: (a) a model of bacteriophage reconstructed from aspect electron microphotographs; (b) a different arrangement of fibrils with respect to the body of the bacteriophage as the metabolites are attached; (c) hydrodynamic profiles of the bacteriophage as determined by the disposition of fibrils; (d) the path of motion of bacteriophage. As the gradient of metabolite increases closer to the bacterium, the number of tumblings per unit free path becomes smaller, so that the approach to the bacterium is faster. The corresponding change of profile is shown in diagram (c) from left to right.

2.3 Separation on account of change of internal pace on the scale of a 'biological clock'

In this case the capabilities of an asymmetric separating system are inherent in the microparticle itself. Its mobility is controlled by an internal 'biological clock'. In Ref. [32] we considered the case of the diffusion mobility of a population of fissile microorganisms whose mobility depends on their age. The model with a 'biological clock' is obtained by adding a diffusion term (depending on the density of population) to the equation of dynamics of the population age distribution:

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial \tau} = -m(\tau)n + \operatorname{div}\left[D\operatorname{grad}(n)\right], \tag{6}$$

where t is the external time; τ is the internal time (age); x, y are the coordinates; $n(t,\tau,x,y)$ is the age distribution of the population, $m(\tau)$ is the mortality rate; and D is the coefficient of spatial diffusion of species.

Equation (6) must satisfy the following initial and boundary conditions:

$$n(t,0,x,y) = \int_{-\infty}^{\infty} b(\tau)n(t,\tau,x,y)\,\mathrm{d}\tau\,, \tag{7}$$

$$n(0,\tau,x,y) = \varphi(\tau,x,y)\,, \tag{8}$$

where $b(\tau)$ is the birth rate in the population; and $\varphi(\tau,x,y)$ is the initial spatial distribution with respect to age.

Now let us consider the evolution of population that initially is pointwise and coeval:

$$\varphi(\tau,x,y) = N_0\delta(x,y)\delta(\tau-\tau_0)\,, \tag{9}$$

where N_0 is the initial population, and δ is the delta-function. From experiments we know that in many cases the movement

of species depends on both their number and age [49]. The diffusion coefficient increases with the size of population, and the motion is activated in a certain age interval — that is, during a certain phase of development. Given this, the space-inhomogeneous distributions in the population increase. Figure 3 shows an example of spatial evolution of the initially coeval population under the assumption that motion of the species occurs when their total density at a given point is greater than a certain critical value N_{cr}, and the age of the species does not exceed τ_{cr}. In this case $\mathfrak{R} = \mathrm{div}[D\,\mathrm{grad}(n)]$ is

$$\mathfrak{R} = \theta(N - N_{cr})\theta(\tau_{cr} - \tau)\,, \quad N = \int_0^\infty n(\tau, x, y)\,\mathrm{d}\tau\,, \qquad (10)$$

where θ is Heaviside's step function. This model and numerical experiment account for the mechanism of space-inhomogeneous changes as encountered in certain population and demographic problems involving population waves [18, 74–78]. The model is basically simple: $\mathfrak{R} = f(N, \tau)$. The function f has two thresholds: N_{cr}, τ_{cr}. As the population grows through multiplication and reaches the threshold N_{cr}, the species start moving in space (x, y), and the density of population decreases rapidly over the time $\tau - \tau_{cr}$; then the process repeats. The quantity $\mathfrak{R}$ then changes in jumps:

$$\mathfrak{R} = 1 \quad \text{for} \quad t \leqslant \tau_{cr} - \tau\,,$$
$$\mathfrak{R} = 0 \quad \text{for} \quad t > \tau_{cr} - \tau\,, \qquad (11)$$

The overall pattern of Eqn (11) is the same for any law of population growth — for example,

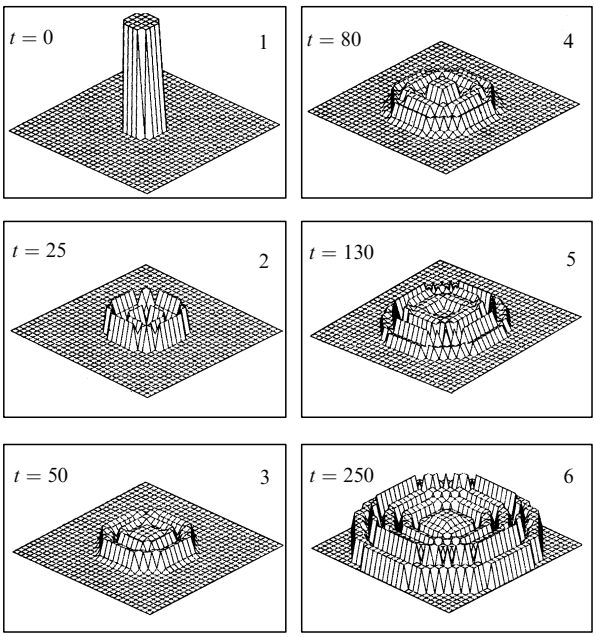

Figure 3. Consequent stages of propagation on the plane of an initially pointwise and coeval population of microorganisms. Their mobility only increases over a certain interval of their biological age. The short period of mobility compared with the life span results in rings of concentrations instead of a bell-shaped 'spreading' distribution typical of Brownian motion. Time in arbitrary units is indicated in the upper left corner of each frame, counted from the inoculation of the initial pointwise population (frame 1).

$$N = (N_{cr} - N_0)\left[1 - \exp\left(-\frac{t}{\tau_{cr}}\right)\right]\exp\left(-\frac{t}{\tau_{cr} - \tau}\right). \qquad (12)$$

The sequence of jumps of the diffusion coefficient $\mathfrak{R} = 0$ and $\mathfrak{R} = 1$ remains a periodical function with the time period τ.

3. Minimum energy price for directionality of motion

3.1 'Price of action'

Is there a minimum amount of energy required for a microparticle to make one directional step, and what is the main charge in terms of energy for processing information in asymmetric-potential systems of moving microparticles? Let us confine our discussion to a brief summary of recent results.

The processes in a cell — as compared with the processes in modern electronic systems — are in most cases very slow, the characteristic times ranging from 0.1 to 0.01 seconds. The masses of moving particles are relatively large, 10^{-18} to 10^{-12} grams. This does not apply to the processes of photosynthesis, where the characteristic times are measured in picoseconds. Photosynthesis involves high-energy light quanta and electron quantum transitions, and has nothing to do with Brownian processes. In drawing a comparison between different biosystems, the 'price of action' (the energy times the time) is usually measured in Planck's constants $h = 6.626 \times 10^{-34}$ J s, or in kTt, where k is Boltzmann's constant (1.380×10^{-23} J K^{-1}), T is the temperature in kelvins, t is the time in seconds. The lower limit of the energy spent on one unordered step of a Brownian particle is $kT \ln 2 = 0.7kT$ [50–55].

If the time reaching the target by the particle is not limited, there is no minimum additional energy E — a premium to thermal energy that has to be paid for this operation [50–52]:

$$E \sim \ln\left(\frac{n\tau_n}{m\tau_m}\right), \qquad (13)$$

where n and m are the numbers of steps forward and back, and τ_n, τ_m are the respective time constants. Thermal fluctuations are sufficient for slow drift. Then, however, we shall not be able to predict when the microparticle meets the target. Only be the mean probable time of encounter according to the Einstein–Smoluchowski formula [20] can be predicted. Additional energy is required when there is a time limit, and random walk has to be converted into directed motion. The main energy cost is then determined by the 'price of control' — the change in the number of turns in the paths of particles. The old path must be forgotten before the new one is taken.

3.2 'Price of control'

In order to remember the vector of the current 'impact' of the molecules of the environment, the microparticle must first 'forget' information about the results of previous interactions. Naturally, if the memory of the microparticle is not limited, it will continue to store information about interactions with the medium by acquiring sorbents and changing its physical parameters — for example, volume. Then the entropy of the memory of the particle will increase, with a simultaneous decrease in the entropy of the environment. The

microparticle will make its target on one branch of the cycle of the 'environment ↔ particle' energy exchange.

Assume that the volume of the particle increases when a sorbent becomes attached to the particle. The particle is an ordered part of the 'environment ↔ particle' system. Since its volume has increased, the order in the system as a whole would seem to increase too, which means that the entropy decreases. However, the sorbent and the particle had all this time been part of the system, so whence comes the energy for reducing the entropy of the system? No energy came from outside. The answer is simple. In this case we are dealing with the redistribution of energy which has already been in the system, and had been used for creating the stressed structure of the particles at the time of their synthesis ('structural energy'). If we include the structural energy in the energy balance of the 'environment ↔ particle' system, we can demonstrate that the entropy of the system always increases. At the first stage of sorption of the molecule, the structural energy may increase or decrease (depending on the construction of the particle) through the increase or decrease in the entropy of the environment alone (but not of the system). At the second stage, when the initial volume of the particle is restored, it is only the part of the energy stored in the stressed structure that is returned to the system. The other part of the energy is spent on removal of sorbent, transformed into heat, and dissipated. To significantly affect the path of the particle, the reaction of creation/destruction of a complex with the sorbent must be asymmetrical, and must be biased towards the formation of complex. In other words, the particle must 'remember' its new state for at least a few (say ten) steps.

Let us illustrate this with a simple example [9]. Assume that each molecule of sorbent from the environment upon attachment to the particle changes its volume by ΔV. This causes dissipation of an energy quantum $h\nu_1$, which raises the entropy of the environment S_{en} by

$$\Delta S_{\text{en}} = \frac{h\nu_1}{T_0} = kb\,, \tag{14}$$

where T_0 is the temperature of the environment,

$$\frac{h\nu_1}{kT_0} = b > 1\,. \tag{15}$$

Assume that the entropy of the whole system has initially been

$$S_0 = k \ln P_0\,, \tag{16}$$

where P_0 is the thermodynamic probability of the state of the system. Upon attachment of the sorbent to the particle, the disorder of the environment decreases by a certain amount P. The overall entropy balance is

$$\Delta S = k\left[b - \ln\left(\frac{P}{P_0}\right)\right] > 0\,, \tag{17}$$

since $b > 1$ and $(P/P_0) \ll 1$, and the total entropy of the system increases. If the volume of the particle increases, it slows down. If the environment hosts two sources of different types of molecules, one increasing the volume of the particle and the other decreasing, the particle will control its motion by moving towards one source and receding from the other. Each step of selection of path between tumblings will require, however, an additional energy $\Delta S_{\text{en}} = 2kb$. Each degree of freedom of control of the particle will give rise to an appropriate increase in the entropy of the environment

$$\Delta S_{\text{en}} = nkb\,, \tag{18}$$

where n is the number of degrees of freedom, $b = h\nu/(kT)$. It is easy to show that such particle will operate in the framework of a Carnot cycle [9]. Conversion of random walk into directional motion is always accompanied with the appropriate increase in the entropy of the system as a whole. The lower limit of energy expense for one unordered step is $k \ln 2$. In case of α conformation states (degrees of freedom) of the microparticle and q subdivisions in each, the minimum energy expenditure is

$$\alpha k \ln q \tag{19}$$

or $\alpha k \ln 2$ when there are two subdivisions. As follows from Eqn (18) and (19), the total minimum expenditure for one cycle, evaluated through the entropy increase ΔS, is

$$\Delta S = k(nb + \alpha \ln q)\,, \tag{20}$$

where $b = h\nu/(kT)$. The first term in Eqn (20) relates to the direct cycle of conformation change (for example, complex formation with sorbent — that is, memorization of information), whereas the second term corresponds to the reverse cycle (complex destruction, or obliteration of information). If $n = \alpha$, and there are two subdivisions in each conformation state, then

$$\Delta S = k(nb + n \ln 2) = n(A + B)\,, \tag{21}$$

where $A = h\nu/T$, $B = k \ln 2 = 0.7k$. Usually, $B > A$.

In this way, the local change of direction of motion of particles in a living cell with the memory capacity (retention of sorbent) for ten steps requires about $10 \times 0.7kT$ of free energy per each degree of freedom of movement. If the motion is controlled in three dimensions, the minimum energy expenditure will be $\sim 20kT$. If the target has to be reached in about 0.1 s, then the minimum 'price of action' is $\sim 10^{13}h$, where h is Planck's constant. The rate of tumblings over the length of this path will be ten times lower, and the gain in speed with which the target is reached will be in the 10 to 100 range. The actual energy cost of directed movement of particles to the source of sorbent molecules is usually much higher, and is determined by the binding constant between sorbent and particle. This value is $10^{-19} - 10^{-20}$ J grad^{-1}, or $10^2 - 10^3 kT$.

It is necessary to emphasise once again that the conversion of random walk into directional motion in biological systems is always accompanied with an increase in entropy of the system as a whole, and may only occur in systems receiving external energy or in nonequilibrium systems with stored energy available. Technological cloning of biological systems has no chance of beating the laws of thermodynamics and constructing a *perpetuum mobile*.

3.3 From macrosystems to microsystems

Figure 4a shows one of the well-known macroscopic systems based on the fluctuations of parameters of the environment. This toy, known as 'the dunking bird', was very popular in the late 1950s. The body of the bird is a glass tube topped with a

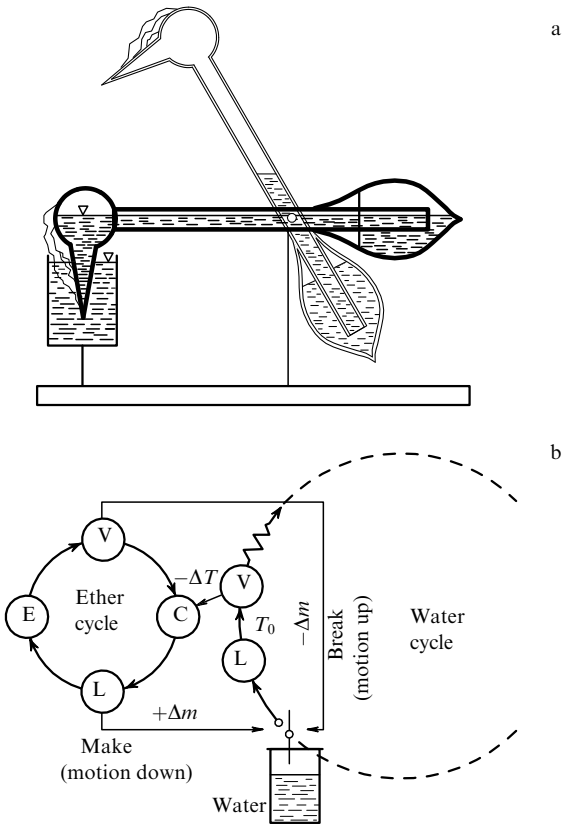

Figure 4. Example of pendulum macrosystem based on two coupled cycles, internal and external: (a) two extreme states of the macrosystem; (b) principle of operation. Abbreviations: L — liquid, V — vapor, E — evaporation, C — condensation, T_0 — ambient temperature, Δm — mass of ether transferred in the 'ether cycle' as the temperature varies (see text).

small beaked sphere, and the bottom end is contains ether. You start the motion by wetting the head and placing a glass of water before the bird. The bird then tilts forward and starts to oscillate, dunking its head into the water and then swinging back.

This motion is caused by the periodically arising asymmetry of behavior of ether vapor in the macrosystem: in the head of the bird and in its bottom part. When you wet the bird's head, its temperature drops by evaporation, and becomes lower than ambient. This effect is usually augmented by lining the head with cotton wool or any other porous material. As the temperature decreases, the pressure of ether vapor in the head falls, and liquid ether is sucked from the bottom into the head. The weight shifts upwards, and the bird tilts forward. Two processes start when the body assumes the horizontal position. Firstly, the bird dunks its head in the water, and the cotton tuft on its head is soaked again. Secondly, the saturated vapor and liquid ether from the top and bottom parts mix, and the pressures are equalized. Liquid ether returns to the bottom part by gravity, and the bird rights itself. Obviously, the bird oscillates because, like a macroscopic machine, it has two cycles of behavior coupled through the feedback: the internal cycle — the phase transition of ether (vapor/liquid), and the external cycle — the phase transition of water (vapor/liquid) (Fig. 4b).

This system will continue working until it comes into equilibrium with the environment — that is, either there is no more water in the glass, or the ambient humidity reaches saturation and the water no longer evaporates from the bird's head [58].

There are dozens of oscillating technical devices that use fluctuations of temperature, humidity, pressure, air movements, and concentrations of chemical reactants. For instance, the barometric clock of the English inventor Cox (late 19th century) is based on the Torricelli's experiments with mercury barometer. Variations of atmospheric pressure would wind this clock for 7 days. Another example is an even more ancient watch made by Pierre Jacques Drouse (mid-1700s) which used temperature fluctuations that caused deformation of bimetallic (steel/copper) strip [58].

Calculations prove, however, that even though such macroscopic devices work for free (taking advantage of fluctuations of the environment), the cost of manufacture keeps their efficiency below 3%. To illustrate this point, recall that a day's wind of a standard watch requires about 0.4 J, or 5×10^{-6} J per second. In other words, the power of the clockwork mechanism is 5×10^{-9} kW. Assuming that the manufacturing cost of the winding mechanism based, for example, on thermal expansion is just 0.05 US dollars, a 1 kW power plant consisting of many such devices connected in parallel would cost 10 million dollars. Obviously, mass production of such expensive motors is absolutely infeasible.

However, biological systems based on the principle of self-assembly may be quite useful and energy-advantageous for many purposes. For example, on the level of the biological microscopic scale of 0.1 to 50 A, any molecule of globular protein contains about 5000 atoms, which at this level may be regarded as micropendulums powered by fluctuations. The swing with respect to covalent bonds in the polypeptide skeleton covers angles from 20 to 60°. As a rule, these movements are not concerted, but they may be synchronized by periodical reactions of ATP decomposition or pH fluctuations.

The low-frequency dynamics of dilute solutions of linear polymers are well studied [59]. Fluctuations of atoms in the bulk of the protein do not exceed 0.5 A, but on the surface may be as large as 2 A and more, with the characteristic times of 10^{-9} to 10^{-3} s. If the fluctuations had been 'frozen', the energy barrier, for example, in the myoglobin molecule for capture of oxygen would have been more than 100 kcal mol^{-1}. Due to fluctuations, the barrier is almost 20 times lower. Because of this, the myoglobin molecule realizes its affinity for oxygen spending as little as 8.5 kcal mol^{-1} [60–62]. Similar environment-controlled conformation transitions based on Brownian motion underlie the performance of almost all kinds of biosystems.

4. There is no stochastic motion inside living cells

4.1. Processes that change the integral diffusion laws in a living cell

Some recent publications [63–66] discuss the inapplicability of both the Einstein–Smoluchowski equation [20]

$$\langle \bar{x}^2 \rangle = Dt\,, \tag{22}$$

and Fick's law [67]

$$i = \frac{\mathrm{d}C}{\mathrm{d}t} = D\,\mathrm{grad}C\,. \tag{23}$$

to the description of thermal and concentration motion of microparticles in living cells. In these expressions x is the linear displacement of the Brownian particle, D — the diffusion coefficient, t — the time, i — the flow of microparticles, and C — their concentration.

As already noted, the control of movement of Brownian microparticles in living cells depends on the supply of energy from the rupture of macroergic bonds of ATP compounds in cyclic reactions, or on energy storage by deposition of ions. This makes the systems inside living cells nonequilibrium [68 – 72]. The values of transmembrane potentials change, thus creating asymmetric fields of force inside the cell. Force fields transform the stochastic motion of microparticles into directional movement, and separate microparticles according to their physico-chemical properties. The contraction structures inside the cells work as pumps under the action of these fields [48].

The change of force fields determined by cyclic intracellular processes (changing the rate of the 'biological clock') depends on the external fields. We have demonstrated that this effect is easily observed at early stages of embryogenesis by monitoring the change of frequency of the transmembrane potential in the Fourier space of any cell in the pool of dividing cells [35]. The early stages of embryo development are characterized by synchronous division of cells. When the number of cells becomes as large as 500 to 10 000, the Fourier spectrum expands, and the fission falls out of synchronism. Similar processes are observed in models of neural networks [73 – 75].

It is worth noting that transitions between different types of motion in living cells

'stochastic → stochastic-directional → directional (ballistic)'

are associated not only with the increased energy requirements, but also with the change in the characteristic scale of motion. The linear model of motion of a particle in a thermal field, described by the Ornstein – Uhlenbeck model [76], corresponds to classical Newtonian dynamics. In the asymptotic Einstein – Smoluchowski model (22) which introduces the diffusion constant $D = x^2/t$, the characteristic time is proportional not to $\langle x \rangle$, but rather to $\langle \bar{x}^2 \rangle$ — that is, to the area, and the velocities on the time scale in the limit of small t vary as $t^{-1/2}$. Physically, switching from a line to a surface means that the continuous Brownian trajectories are not defined with certainty at any point. The characteristic dimensionality in the case of stochastic-directional movement lies somewhere between 1 and 2.

Such a description corresponds neither to a deterministic linear path as defined by Newton's ballistic expression, nor to an area-like formula for entirely random walk in Einstein's limit. This intermediate description allows for variations in the concentrations of moving particles, as in the case of flocks or Levy's jumps [77 – 79].

In some cases such motion of microparticles may lead to the formation of fractal clusters [80, 81]. Such transitions from stochastic to fractal structures are most vividly manifested in the experiment with the movement of a bacterial population [82 – 86]. In other words, we have the following correspondence:

stochastic → stochastic-directional → directional motion, that is,

$$x^2 \to x^R \to x^1 ,$$

where $2 > R > 1$; and x is the displacement of particles.

4.2 Biophysics plus biochemistry

Advances in biochemistry, cell biology and molecular genetics over the past 20 – 25 years cast some doubt on the idea that a detailed treatment of vectorization of Brownian motion in weak fields is important for understanding the processes inside the living cell. How and why could biochemists thrive without such a detailed treatment of Brownian motion?

The fact is that a special language was invented in terms of enzymes (catalysts), which included the diffusion operator of Brownian motion $\partial/\partial t = D\partial^2/\partial x^2$ (the operator in the Fokker – Planck – Kolmogorov equation [25, 31]) as part of the operating principle of an enzyme.

In 1957 – 1961, the Enzyme Committee of the International Biochemical Union developed a unified classification and nomenclature of enzymes, which divided all the then known enzymes into six classes. Subsequently, the taxonomy of enzymes expanded, and new branches appeared on the 'family tree'. The six main branches of this tree, however, remained [87, 88]. What are the functions performed by enzymes? Their main function is intensification (catalysis), which directs conversion of reaction substrates into products. If we write in a generalized form a simple chemical reaction of the form

$$AB \underset{2}{\overset{1}{\leftrightarrow}} A^+ + B^- , \tag{24}$$

where AB is the substrate, A^+ and B^- the products of the reaction, we note that such a reaction is usually time and space symmetrical and therefore reversible. The chemical constants for the forward and back reactions in time are equal: $K_{12} = K_{21}$. In space, the concentrations of ions A^+ and B^- are given by the Maxwell – Boltzmann distribution

$$[A^+](x) = \left\langle [A^+] \exp \frac{[U(x)]}{kT} \right\rangle ,$$
$$[B^-](x) = \left\langle [B^-] \exp \frac{[-U(x)]}{kT} \right\rangle , \tag{25}$$

where the angle brackets indicate averaging over one period of change of the potential energy $U(x)$ over which the reaction takes place; k is the Boltzmann constant, and T is the temperature. If the potential is spatially symmetrical, expression (25) becomes the concentration formulation of Eqn (24), when the reaction is only time-dependent and does not depend on the coordinates:

$$[AB] = K\langle [A^+][B^-] \rangle , \tag{26}$$

where K is a constant coefficient. Obviously, there are ways to upset such an equilibrium both in time and in space — for example, by changing, as already indicated, the spatial symmetry of the potential energy $U(x)$. Biochemistry knows methods for time-domain control of the reaction equilibrium. By convention, they may be divided into three categories.

1. Modification of one (or both) of the products at the reaction point. This can be done by attaching the product to the catalyst — enzyme E (the operation of gluing) — for example, with the formation of an EA complex (Michaelis complex). In this case the way back to reconstruction of the substrate from the products is obstructed — that is, $K_{12} > K_{21}$, or, in terms of probabilities, $p_{12} > p_{21}$ (such enzymes include liase, ligase, isomerase).

2. Modification of the process of decomposition of substrate AB itself by using 'scissor' enzymes that cut the

substrate AB apart at certain bonds but do not sew the products A and B back together. Then there is only direction 1 in reaction (24), and $K_{12} > K_{21} = 0$, or $p_{12} > p_{21} = 0$ (hydrolase enzyme).

3. Modification or withdrawal of one (or both) of the products from the reaction point, thus making the reaction asymmetrical (cut, move and paste at some other point). In other words, in this case we have 'scissors' with the operations of moving and gluing (as described in paragraphs 1 and 2 above). The transfer of reaction products, however, calls for the involvement of Brownian motion, or directional motion with energy expenditure, or both at the same time. Enzymes of this third group (transferase) catalyze the transfer of a chemical group from one molecule to another. Essentially, the transferase class involves the operator of motion with all its modifications.

Which language is better adapted for describing the processes inside the cell — the language of enzymatic reactions or the language with explicit physical operators of modification of Brownian motion in space? This question is rather similar to asking which is more convenient, hieroglyphic or alphabetical writing. By choosing the hieroglyphs that denote words or even concepts we compress the volume of the record at the initial stages of development; but with the advancement of knowledge, however, we have to increase the number of ideograms, which eventually leads to a cumbersome notation. By contrast, with an alphabet we have longer records at the initial stage of development of ideas; however, the records for complicated interactions later will be more concise. This means that there is no universal answer to the question. Following Kolmogorov [89, 90], the complexity of description can be measured in the bits of program which translates a given sequence $\{y_i\}$ into $\{x_i\}$, where $\{y_i\}$ is the description of a manifold of kinetics in terms of a manifold of ferments, and $\{x_i\}$ is the description of the same manifold of kinetics in terms of equilibrium constants and operators of motion. If the length of sequence $\{x_i\}$ is N, and that of $\{y_i\}$ is M, then the two descriptions are equivalent as long as

$$N \log M = M \log N \tag{27}$$

since the lengths of the programs are the same. For a particular problem, however, this symmetry may be upset one way or the other.

At first sight, this distinction between descriptions is not too important. In recent years, however, the focus of attention has been on the study of cellular morphogenesis — that is, formation of space structures, as well as on the influence of cosmophysical factors and weak fields of different natures on living organisms [24, 91]. The study of these mechanisms requires monitoring the change in spatial mobility. Because of this, such processes cannot be described in terms of enzymatic reactions without involvement of control over motion of enzymes and their complexes.

5. Spheres of application

The results described above have many applications in fundamental science and in high technology. The principle of Brownian mobility controlled by weak asymmetric fields underlies many biological processes involving fibrillary components. Involvement of ATP ensures control of thermal Brownian motion on the periodical lattice. Hydrolysis of ATP gives direction and periodicity of stops on the macroscopic scale, while thermal Brownian mobility ensures movement on the microscopic scale. The fibril along which the enzyme motor (microparticle) moves displays periodicity and spatial asymmetry determined by the genetic nature of these structures. The macroscopic pitch of the fibril's lattice determines the speed of motion of the enzyme. One may assume that hydrolysis of ATP is the source of 'color' for thermal 'white noise' [44] that moves the element of the system over fixed spatial potentials, whereas the element itself may occur in two or more different states. ATP hydrolysis induces thermal transitions between these states. Moving enzyme on the fibrillary structure and Brownian particles passing through the sieve have many things in common.

In Section 2.1 we discussed the model with space-asymmetric electrodes and space-asymmetric potential that periodically changed the direction of motion of Brownian microparticles between 'on' and 'off' levels. Observe that the scale of velocities 10^{-7} m s^{-1} in this model is lower than in real biological systems. However, the pitch of the printed lattice (maze) in this model ($L = 50$ micrometers) was quite large compared with the pitch in biological fibrillary systems. For example, the pitch of the filamentary tubulin protein is 8 nm. The corresponding velocity would then be 10^{-4} m s^{-1}, which in order of magnitude agrees with experimental observations.

Molecular machines constructed from fibrillary proteins, such as kinesin, actin or myosin, are many microns long. Under the action of asymmetric fields, microparticles like vesicles or chromosomes can be transported inside the cell along these lines. The dynamics of these processes are not yet completely understood: the observed crystallized fibrillary structure like the filaments of muscular myosin occur in a stable state, whereas the study of their kinetics requires nanometric resolution in real time.

In addition, to ensure directional motion it is not quite necessary to use the relatively 'rigid' periodical space structures (fibrils, maze lattices, sieves). They may be simulated with an oscillating field creating a periodical accelerating/retarding force. Directed motion and separation of particles can also be observed when the amplitude of the sawtooth space potential is modulated. This may be accomplished by switching two different space-biased asymmetric periodic potentials, which is equivalent to the situation when the Brownian particles themselves have different internal states, each of which corresponds to different asymmetric potentials of the environment.

Obviously, the movement of ions (Na^+, K^+, Ca^{2+}, Mg^{2+}, etc.) through channels in cellular membranes may give rise to weak electromagnetic fields. For example, the act of excitation of a neuron is associated with entry of Na^+ ions into the cell, and the egress of K^+ ions. The electric tension across the membrane then changes by approximately 80 – 100 mV (from −60 to +40 mV). Each individual channel in the membrane of the cell is an electric conductor carrying ions. A field must be generated near this conductor. Mediators modulate the operation of such channels in the range from 0.5 to 30 Hz, which is integrally manifested, for example, as electroencephalogram (EEG) wave patterns. Fields from such local sources ought to create dynamic mosaic fields on the cellular membranes. This composite coarse-grain membrane potential ('colored noise') is necessary for the control functions. It modulates the magnitude of the fine-grain thermal equilibrium ('white noise'). When the noise is 'colored', the average flow of microparticles in the neighborhood of the membrane

loses its stochasticity, becomes stochastic-directional, and ought to exhibit separation of particles with reliably distinct values of maxima.

Figure 5a shows what might be called an 'alphabet' of four field patterns. The distribution of rings of field strength need not necessarily be uniform. This distribution will depend on modulation of the flow of ions through channels. The width of the rings and the intervals between them may obey any law. By way of example, we have selected four laws: sinusoidal, waning from the center ($\exp(-x)$), waxing from the center ($1-\exp(-x)$), and an Archimedean spiral. Figure 5b shows the patterns of composite field produced by two local fields of adjacent conductor channels shown in Fig. 5a as a function of distance between the channels. The pattern is axially symmetrical (see Fig. 5b), but there is a wealth of cluster field structures.

Especially interesting, however, is the situation when two adjacent channels generate fields of a different configuration. Then the composite field pattern is transformed and leads to asymmetry in the distribution of clusters. An example is shown in Fig. 5c: a collection of asymmetric patterns obtained by combining the fields shown in Fig. 5a. It is possible that the control of mobility in the neighborhood of membranes in living cells is accomplished in this manner, although this hypothesis has yet to be verified.

It would be interesting to note that the operation of superposition of fields itself is irreversible. Whatever the logic (AND, OR, EXCLUSIVE OR) used for the summation of fields, this operation will inevitably lead to the loss of information on account of the impossibility of uniquely reconstructing the initial fields from the resulting field. To make the operation of superposition reversible, the system must remember the original patterns of the source fields. The movable microparticles that change their kinetic parameters under the action of fields — for example, their velocity and direction of motion — may serve as such a memory. Mixtures of microparticles that separate in different ways under the action of fields, may store the patterns of the source fields in their heterogeneous concentration. Then the superposition of fields becomes reversible, the original fields being remembered in the dynamic structures.

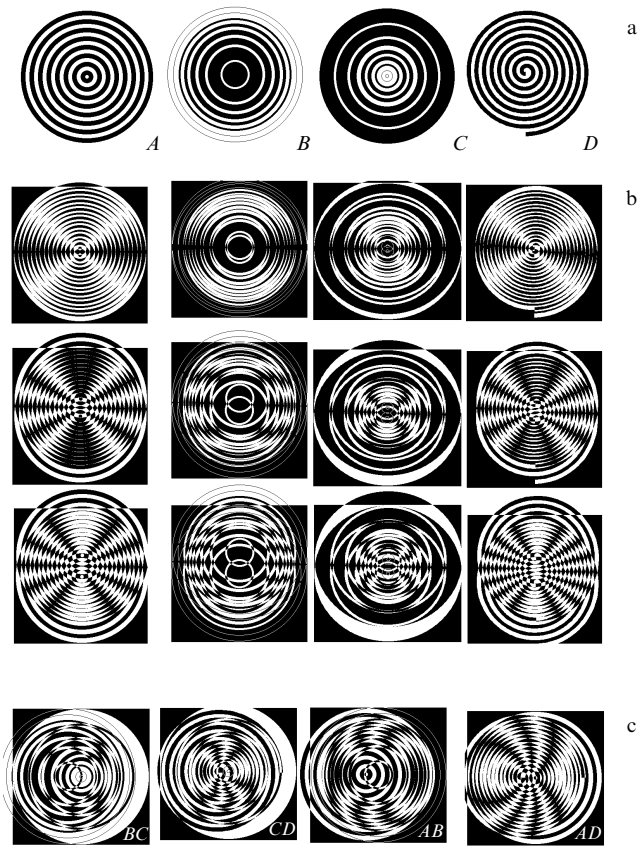

Figure 5. Field patterns obtained by superposition of fields with the EXCLUSIVE OR operator: (a) The starting kit of four different field patterns (ABCD alphabet); (b) symmetrical patterns obtained by superposition of fields of the same type from the initial alphabet, depending on the amount of shift (vertical files); (c) asymmetrical patterns (mutants), obtained by superposition of different fields from the initial alphabet.

It is possible that such mechanisms of dynamic memory exist inside the cells. The memory element may be the cytoskeleton of the cell. The intercellular paths in neural networks are established in the dynamic regime through assembly/disassembly of cytoskeleton made out of polymerizing protein filaments [92]. At the level of bacterial communities, such dynamic memory may be represented by the colony structure. It 'develops' and 'fixes' the concentration field of attractants and repellents. The concentration fields of attractants and repellents strongly affect the propagation of bacterial population waves, and the spatial patterns of the resulting colonies [23 – 28, 75, 93].

Biophysical investigation of the kinetics of interaction 'microparticles ↔ environment' is necessary for the development of biotechnology, whose principles of self-organization are currently used for producing biological materials, sensors, and even entire biological systems [94]. It is not by accident that the new (though perhaps not too elegant) term 'intellectual materials' appeared in the early 1990s. It refers to composite materials for prostheses of body parts, biochips for computers, new methods for controlling the cooperative mobility of sophisticated molecular complexes through modification of the medium and the object itself. The first international conference on intellectual materials was held in March 1992 in Oiso (Japan). The discussion centered around composite materials capable, by modification of the environment, of programmed (reversible or irreversible) change in shape, color, and other physical parameters. This capability is established in the material by creating structural heterogeneity in the course of its assembly, and is realized in the kinetic cycle of interaction with the environment. A widely known example of such a material is the spin glass, or such biological materials as rhodopsins. Man-made heterogeneous structures can be not only fixed to appropriate supports, but also movable. In this connection we could mention the rapidly developing branch of pharmacology dealing with the development of transport capsules (vesicles) for medicines, genetic correctors [95], or gases [96]. The 20th International congress on artificial cells, blood substitutes and immobilized biotechnology took place in Beijing in September 1997. A change in physico-chemical parameters is programmed in the capsule so as to ensure its movement towards the target, to the place where the contents of the capsule must be delivered and discharged.

In this respect a bacterium is also a kind of movable self-guided module, a natural 'biochip' less than 10 micrometers in size, which combines in one 'housing' the propelling system, sensors, logical devices and actuators, whereas a bacterial virus is a composite heterogeneous macromolecular complex lacking the systems of metabolism and directional motion,

but possessing a set of conformation states, reception and identification systems used in looking for the target. Separate and joint studies of the mobility of such systems will help draw the line between active live particles and passive particles. In a asymmetric environment the latter are also capable of directional motion.

Future technologies based on controlled Brownian motion using weak asymmetrical fields may be capable of creating entirely new ways of delivery of active compounds within a organism. For example, a large container might be loaded with the product needed by the cells of an organism, and move along large blood or lymph vessels, while microcapsules-carriers shuttle between container and cells, door-to-door delivering the contents of the container to tissues and organs. Such 'micromachine technology' is already being developed [97], and the first relatively simple systems are already available — such as the gas transport plasma blood substitutes [98]. The idea is that the particles of perfluorocarbon 0.07 – 0.1 μm across carry oxygen from erythrocytes remaining after the loss of blood to the tissues. The red cell in arterial blood, about a hundred times bigger than the particle of the emulsion, serves as the container loaded with oxygen. Circulating in the pulsating hydrodynamic blood flows between erythrocytes and tissues, and forming string-of-pearls structures, particles of perfluorocarbon relay oxygen from erythrocytes to the walls of blood vessel, from where it diffuses into the tissue.

In conclusion, we would like to observe that the applications discussed above are the subject of immediate experimental studies, and the basis of new technologies of the 21st century.

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