BIOPHYSICS AND BIOCHEMISTRY

Physicochemical Simulation of Cell-Cell Commutation

S. V. Stovbun and A. A. Skoblin

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Strings, anisometric structures with length-diameter ratio of 10^1-10^5 are formed in some homochiral solutions at a concentration of 10^{-3}-10^{-2} M. We studied macroscopic properties of strings (strength, charge at the ends, *etc*.) and showed that these strings can provide a power commutation of cells. The strength and electrostatic driving force of the strings are sufficient to transport cells with a velocity of ~1 cm/sec. The formation of strings is a mechanism of directional and error-resistant information exchange and for intercellular distances it is faster and more efficient by substance utilization than the diffusion mechanism. This suggests that strings or similar objects, including cytonemes, play an important role in various aspects of cell-cell commutation.

Key Words: *anisometry; strings; chirality; cell-cell commutation*

Contact interaction between the cells via nanotubes, or cytonemes was described in 2004 [5] and later was found in many cell types (Fig. 1). Cytonemes are extremely anisometric objects with a diameter (d) up to 100-200 nm and length (L) up to 100 μ, so that the anisotropy parameter L/d is typically equal to 10^3-10^5. Strings are structures geometrically close to cytonemes. They are observed during solidification of low-concentration (10^{-2}-10^{-3} M) homochiral solutions of some low-molecular-weight organic compounds [2-4]. In this case, strings can be regarded as the most adequate modern physicochemical model of cytonemes.

Here we studied macroscopic properties of strings in model solutions, which is important for understanding of the mechanism underlying cell-cell commutation via cytonemes.

MATERIALS AND METHODS

Light microscopy of strings formed in liquid model solutions and in xerogels obtained by evaporation of the solvent from the corresponding solutions was performed; we measured and analyzed string parameters: length, diameter, degree of deviation from linearity, distance between the strings, *etc*. We also filmed the process of string formation and evaluated the speed of this process.

RESULTS

The results were compared with previously established facts. The framework of solidified homochiral solution is presented by randomly filling strings, extremely anisometric objects less than a micron in diameter (d) and a length (L) of several millimeters or centimeters: L/d~(10^3-10^5) (Fig. 2).

The formation of strings is a rapid process, its speed is not less than 2 cm/sec by cinephotomicrography data. Evaluation of the speed (v) of *de novo* string formation on elementary helical generator with a radius (r) ~5 Å and a pitch (h) ~r, so that the helix consists of a single twisted stack of molecules, yields [2] (D, diffusion coefficient; n, the number of chiral molecules in unit volume; a, molecular size): v~($D\,a^2hn$)/r~1 cm/sec, which corresponds to the experimental result.

N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, Moscow, Russia. ***Address for correspondence:*** s.stovbun@chph.ras.ru. S. V. Stovbun

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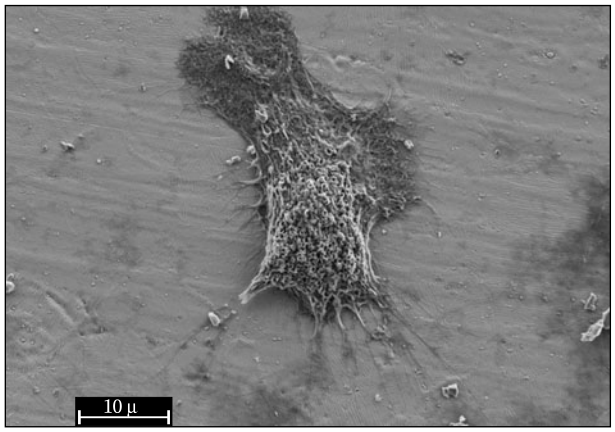

Fig. 1. HeLa cell.

This indicates that the forming string is an extremely thin, almost one-dimensional object. This string will be called elementary.

On the other hand, if nd^2/kT~1 (d~ea is dipole moment of the molecule, e is electron charge, k is Boltzmann's constant, T is temperature), cooperative effects may occur in the solution. Energy calculation of the dipole-dipole interaction shows that in this case dipole moments of the molecules has to be oriented in different directions in the string and in the surrounding mesophase to minimize free energy [1]. This triggers the mechanism of the radial assembly of a string virtually of any length (up to fraction of a centimeter) at diffuse times t_{SD}~$h^2/6D$~10^{-8} sec, where h~10^{-6} cm, cross-section diameter of the region from which diffusion of molecules occurs is case of radial assembly of the string.

Solidification of the solution occurs within several hours (up to days) due slow thickening of the strings. It is reversible with respect to temperature and easily disturbed by mechanical action (stirring, shaking). The rates of direct and inverse processes depend on environmental characteristics acidity, polarizability, *etc*. Microcrystalline nucleus is often a point of initial string formation, and the direction is determined by boundary conditions. Thus, in the capillary strings are formed along the axis (Fig. 3).

When the ends of strings formed from a single nucleus are at a distance R^*~50 μ, they deviate from each other by l^*~10 μ, that is naturally interpreted as electrostatic repulsion. Quantitative assessment leads to the following statements [2]:

- substance in the phase of strings is a pyroelectric with a dipole moment directed along the string axis;
- surface charge density at the ends of the string approximately corresponds to one electron charge per molecule;
- material of strings is saturated with defects similarly to isometric materials, and its Young's modulus E_d is ~10^{11}dynes/cm^2.

The characteristic distance over which the strings are bent strongly, is tens of microns, which is two orders of magnitude larger than the diameter, that is, strings are rather rigid formations. Elastic energy of string bending is estimated at approximately 10^{-4} eV per atom [2], which is three orders of magnitude less than typical energy of the molecules in the string. This does not contradict the formulated concepts of the string as a dense defect-saturated condensed phase.

These properties of strings enable us to simulate physical and chemical mechanisms underlying cell-cell commutations via cytonemes.

Intercellular and intracellular environment are enantiomerically pure for the majority of chiral compounds located therein. This suggests that in this environment chiral anisometric objects (strings) capable for intercellular commutation are formed.

Fig. 2. Chaotic system of strings in an isometric sample with typical dimensions of several centimeters. ×100.

Fig. 3. Discrete set of strings formed in a capillary with a diameter of 300 μ. ×200.

Cells can control the speed and direction of the string formation by changing the physicochemical parameters of medium.

The strings can act as an essential element of power commutation, providing electrostatic capture and subsequent transport of the cell.

Let us evaluate the efficiency of the capture. End face of a string with a diameter d is a flat site with area $S\sim d^2$ and the charge $Q\sim(er^{*-2}S)$, where r^* is the distance between the charges at the end, corresponding to the size of the molecule. The charge at the end face of the string induces the charge of the same magnitude, but opposite sign on the object interacting with the string. If the distance to this object is less than the diameter of the string, strength of their interaction is $F\sim Q^2/S$. It enables to transport a cell diameter of D^* with the speed V in a liquid medium with viscosity η, overcoming the viscous force $F_{visc}\sim\eta D^*V$. Hence the velocity V becomes:

$$V<V_S=(e^2d^2)/(r^{*4}D^*\eta). \quad \textbf{(1)}$$

For a thin string of diameter $d\sim10^{-7}$ cm and the large distance between the charges at the end $r^*\sim5\times10^{-8}$ cm, transporting a large cell diameter of $D^*\sim10^{-3}$ cm in a medium with typical viscosity $h\sim10^{-2}$ g/cm×sec, evaluation **(1)** gives a very large limiting velocity: $V_S\sim10^3$ cm/sec. This means that even a thin string can effectively capture the cell providing its transportation at a speed of some centimeters per second which is high speed for microbiological objects. The upper speed limit should be sought by considering the cell motion with regard to its deformation and destruction of the lipid bilayer.

Let us evaluate the limitation on the speed of cell transportation V following from the string strength at break. During transportation, the viscous drag force $F_{visc}\sim\eta D^*V$ is balanced by the pulling force: $F_n\sim\sigma d^2$, where σ is tension of the string material. It should not exceed the material strength at break $[\sigma]$: $\sigma<[\sigma]$ whence it follows that:

$$V<[V]=([\sigma]d^2)/(D^*\eta) \quad \textbf{(2)}.$$

If $[\sigma]\sim5\times10^9$dyn/cm^2, which corresponds to many polymers such as nylon, then for the thin string with the diameter $(d)\sim10^{-7}$ cm and a large cell with the diameter $(D^*)\sim10^{-3}$ cm the limiting **(2)** yields: [V]~5 cm/sec. Thus, even a thin string is strong enough to provide transportation of large cell at speeds up to 5 cm/sec. Let us consider the cell-cell information exchange. In the literature it is usually described within the diffusion paradigm, whence time t_D of interaction between the two cells at a distance L is: $t_D\sim L^2/D$. Time of signal transmission through the formation of a string t_S is determined by the speed of its formation: $t_S\sim L/v\sim(Lr)/(Da^2hn)$, if the string grows along the generator. If, however, the radial assembly of the string occurs in the cooperative field, then the formation time of a string is $t_{SD}\sim10^{-8}$s.

Let us consider the thin string, when $h\sim r$, $N_m=a^{-3}$. Then, if the string grows by the generator, the condition in which the string mechanism is faster than diffusion one ($t_S<t_D$), takes the following form:

$$L>L^*=a(N_m/n). \quad \textbf{(3)}$$

Because $(N_m/n)\sim(10^2\text{-}10^3)$, then $L^*=(10^{-5}\text{-}10^{-4})$ cm. Thus, the information exchange through the formation of thin strings is a faster mechanism, than diffuse one with characteristic intercellular distances of $(10^{-4}\text{-}10^{-3})$ cm and more.

If the radial assembly of the string occurs, the string mechanism for information exchange is faster than diffuse at distances greater than 10^{-6} cm.

Let us compare the diffuse and string mechanisms for the information exchange regarding consumption of substance. The object of diameter D^* can receive the diffuse signal at a distance L from the source, if the concentration of emitted molecules near the source is high enough to ensure the minimum number necessary for the registration $n_D\sim(10^1\text{-}10^2)$ in the volume of a sphere of diameter D^*, as at $n_D\sim1$ the signal is below the detection limit. To do this, the source of diffusion should emit at least N_D molecules, where $N_D=[4\pi L^3]/[(4/3)\pi(D^*/2)^3]n_D=24(L/D^*)^3n_D$. At the same time, $N_S\sim(\pi d^2/4)La^{-3}$ molecules are required to form a string of diameter d and length L. Therefore, the condition in which the exchange of signals via string formation uses less substance than the diffuse mechanism ($N_S<N_D$), takes the form:

$$L>L^{**}=d(D^*/a)^{3/2}\,(32n_D)^{-1/2}. \quad \textbf{(4)}$$

Since for cells $D^*\sim(10^{-4}\text{-}10^{-3})$ cm, then $L^{**}=3(10^{-4}\text{-}10^{-2})$ cm.

This analysis allows the following conclusions.

Strings are an effective tool of cell power commutation. The strength and electrostatic driving force of the strings are very high, which enables even extremely thin strings to transport large cells at a speed of several centimeters per second.

The formation of strings is the efficient mechanism of intercellular exchange of information which is directional and virtually error-resistant. At distances greater than $L^*=(10^{-5}\text{-}10^{-4})$ cm (or 10^{-6} cm at the radial assembly of strings), it takes less time than the diffuse mechanism. At distances greater than $L^{**}=3(10^{-4}\text{-}10^{-2})$ cm, it requires less material, than the diffuse mechanism.

Physical and chemical simulation suggests that strings or similar objects, including cytonemes, are of great concern in various aspects of cell-cell commutation.

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