CONCEPTUAL APPROACH TO THE DESCRIPTION OF BIOLOGICAL SIGNALS

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ABSTRACT

An attempt has been made to introduce the conception of biological signals in cellular systems apart from physical signals. We discuss their nature and suggest a model of such signals based on the concept of blot: in complex interacting biological systems (cells and tissues) interaction is also transferred by complex systems, which we call blots. The question of ground state existence in blots is also addressed, and method of quantitative information transfer is suggested based on Kolmogorov complexity formulation. Finally, we discuss role of the fundamental physical constants in biological interactions and necessity for introduction of the biological constants.

1. Physical and biological signaling

Physical signals measured directly in physically observable quantities are familiar to the community. However, these signals are not the only way for information to be transferred inside e.g. cells and tissues. Biological signals in cells and tissues have no absolute value, and their meaning depends on the state of both communicating units.

Microvesicles and liposomes recently have been shown to be an extremely important mechanism for information transfer between cells and tissues[1–3]. Microvesicles, for example, could carry onco-RNA from cancer cells to healthy regions[4]. Being just a small membrane vesicle they nevertheless carry information and act as a purely biological signals. Information transfer by biological signals is quite different from the usual physical signaling picture. The concept of biological signal is not a new concept, but there is still no strict definition suggested and no universal model is available. We discuss a possible way to clarify the concept.

3. Biological interactions in cells and tissues

The biological interaction concept is extremely broad concept, and it is used in a huge variety of contexts, so we limit ourselves to the interactions between cells and tissues which cannot be described in terms of purely physical or chemical signals. Approaches to the modeling of biological signals also

vary significantly, including rule-based approach[5] and methods of systems biology[6].

Cells in organisms interact and communicate in a highly complex and organized fashion. Cellular molecular organization is definitely not random, and its internal order could be represented as a hierarchically organized network. Most cellular functions are related to groups of several functional molecules, not just to a single particular substance, i.e. cell could be modeled as a tightly interconnected modular network. Cell-to-cell interactions also are known to possess highly-ordered network character[7]. What is more, cellular migration dynamics relevant to tissue repair, morphogenesis and tumor metastasis definitively has collective nature[8]: the traction force distribution near the leading shows non-gaussian behavior and cannot be approximated as a leading-cell induced effect. Quantitative investigation of these interactions is just starting to appear, shifting from population-average measurements to single-cell analysis, which points out significant cell-to-cell variability[9]. Biological systems are complex and are unlikely to be made up of identical structural units: diversity among individuals arises as a stabilizing mechanism. Interplay between nonlinearity, nonequilibrium and stochasticity determines dynamics at the levels of single cells and their inner compartments. These developments require shift from descriptive to quantitative treatment, i.e. introduction of metrological basis to the biological sciences is needed in order to obtain accurate quantitative data which could then be interpreted in an unambiguous way, as "there can be no exact science without exact data"[10].

From these facts we note that biological signals reach far beyond simple physical mechanisms, and conceptually new approach should be developed to understand and model these signals. We suggest the concept of blot as a model for biological signals: blot is defined as a mediator of biological interaction. The definition presented that way is not strict, but it allows us to state what sort of phenomena we are trying catch. In the following we discuss several aspects of the concept, putting emphasis on the properties of blot.

4. Water as a transferring medium and its ground state

Water is the most important medium for biological signal transfer in cells and tissues. There are two aspects related to the introduction of blot concept. First, macroscopic behavior of water on the characterstic cellular length scale is different from the bulk phase. Second, water has no absolute ground state as manifested by the significant residual entropy of ice at 0. The latter fact is especially important in emphasizing the dynamic nature of water-based systems and interactions. Hydrogen-bond network in water serves as a medium for transferring signals and also determines function of biological

molecules.

On the cell-sized scale (about 10-50 μm) water behaves in an unusual way: if capillary water flow is laminar, cell-sized water flow is more likely to be a droplet-based. These cell-sized water droplets probably constitute the basic building blocks of liquid water at that length scale, as there is no way to imagine how capillary flow could be spontaneously disintegrated into droplets. The first step to better understand cell-to-cell interactions then should be related to the cell-sized water droplet dynamics and interaction analysis. While there is now a plenty of ways to perform the measurements themselves, there is nevertheless lack of biological standards: we have no "standard biological cell", standard measure of the interaction strength between different cells, etc. There is a growing necessity to provide strict standardized fundamental definitions, interactions and constants as it is done in physics and chemistry for biology to become much more quantitative science then it is now. The vast amount of available experimental data cannot be processed in an appropriate manner as there are no standards relative to which measurements are made. Currently, in many cases, we can say that the concepts of control and reaction rates require more precise in comparison with existing definitions. Therefore, the increasing complexity of these systems require the standard biological measures to be global enough to capture that complexity and yet to have a particular degree of specificity in order to remain meaningful to the description of systems of interest.

5. Blot-blot interaction and entropy transfer

We begin our discussion with the analysis of entropy-driven interactions acting in cellular structures, considering the depletion interaction and the hydrophobic effect[11,12]. Osmotic phenomena also have entropic nature. From the thermodynamical viewpoint every spontaneous process is associated with the net entropy growth, and solvent-solute interactions important to biomolecules immersed in cellular water are also driven by entropy. Conformation of polymers and shape of the colloidal particles in water environment is also determined by the entropic forces[13]. Hydrophobic effect determines vast amount of biologically relevant processes including protein folding and lipid bilayer dynamics in cell membranes.

The key concept behind the entropy-driven interactions lies pretty straightforward in the growth of total entropy of the system. It should be noted that in general no fundamental field could be associated with the entropic forces. To put in another way, if these forces have no potential it's impossible to model them using, for instance, conventional Hamiltonian formalism and the only way to

make quantitative investigation is to use thermodynamical methodology. Molecular dynamics simulation usually indicate the correct in terms of entropy growth interaction of the solvent molecular ensembles and colloidal particles, but no mechanistic analytic treatment is available for these forces.

Hierarchical and network organization are intrinsic to cells, so it would be natural to use these terms in order to clarify their structural complexity. Entropic forces provide basis for the cell functioning and intercellular interactions. The underlying mechanism between cell-to-cell communication is now well-understood, but little is known on the mechanism behind intercellular interaction in a sense of cell measuring another cell and cell-tissue mutual measurement. In order to introduce strictly defined biological measures of these interactions there is a need to treat the entropic forces in a strict and deterministic manner. Recent developments suggest that entropic forces are causal in a sense of connection between adaptive behavior and entropy maximization[14]. Another major point is the usage of multiscale entropy method[15] to describe the complexity of biological signals. The point is that biological signals are neither stochastic nor absolutely organized, and cannot be described as one of these extremes.

While there is probably no way to treat the entropic forces using physical potentials, it's possible to model them as a consequence of semiempirical hierarchical potentials describing the interaction between adjacent levels of organization. If the physical potentials are clearly symmetric in terms of pairwise interactions, hierarchical potentials don't have to keep that property. The only way to apply analytic mechanistic formalism to describe these processes irreversible in a sense of thermodynamic spontaneity is to introduce asymmetric interaction potentials between objects of adjacent levels of organization. In this case there is an inequality between direct and reverse paths system can take, i.e. direct moving from the initial configuration X_i to the final configuration X_f is preferred over the reverse path due to the asymmetry of the driving force arising from the asymmetric potential acting between the levels organization. What is more, the definition of entropy for description of biological signals should be made in Kolmogorov complexity (also known as descriptive complexity, Kolmogorov–Chaitin complexity, algorithmic entropy, or program-size complexity) as it allows for high-level abstraction and quantitative estimations.

6. Biological interactions and fundamental constants

Cell-to-cell and blot-to-blot interaction should be distinguished according to their biological or purely physical nature: some effects may be related to regulatory molecules transport through the

intercellular connectors like plasmodesmata, tunneling nanotubes or septal pores[16]. However, some effect may be purely physical in nature and entropy-driven, as depletion interaction is one of the key driving forces leading to the colloidal structure organization inside cells. Protein folding and cell compartment organization in general is related to the so-called hydrophobic interaction being totally entropic in nature[17]. Osmotic potential resulting from differences in concentration profile of various ionic substances in cells is another example of physical effect having enormous impact on the functions and interaction of the particular cell. Indeed, if we are to understand the way how cells communicate and sense each other and such purely external physical quantities as the temperature and the pressure, there is a need to introduce strict biological standard measures.

CONCLUSION

We have made an attempt to introduce the concept of blot as a model of biological signal in cellular systems. Despite the broadness of the definition of blot as a biological interaction mediator, it provides the basis for further development of the conceptual models capable of incorporating the complexity of biological systems.

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