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Can subcellular organization be explained only by physical principles?

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In a recent forum article, Dan Needleman and Jan Brugues argue that, despite the astonishing advances in cell biology, a fundamental understanding of even the most well-studied subcellular biological processes is lacking.[1] This lack of understanding is evidenced by our inability to make precise predictions of subcellular and cellular behaviors. They suggest that to achieve such an understanding, we need to apply a combination of quantitative experiments with new theoretical concepts and determine the physical principles of subcellular biological organization.[1] We discuss these issues and suggest that, besides biophysics, we need strong theoretical inputs from biocommunication theory in order to understand all the core agents of the cellular life and subcellular organization.

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Despite huge sums of the money spent on drug research since the mid-1950s, Dan Needleman and Jan Brugues in their forum article conclude that success rates are not satisfactory and that the balance of financial input and progress in the development of new drugs is not evident.[1,2] In contrast, physical areas such as materials science, mechanical engineering and solid-state physics are achieving an understanding which allows good predictions to be made. This advance has led to remarkable improvements in performance and a dramatic reduction in cost in a range of applications. If available, such predictive theories in cell biology would not only support drug development, diagnostics and prognostics, but also empower synthetic biology and help better mechanistic understanding of evolutionary processes.

Needleman and Brugues ask in their forum article what may be the reasons for our inability to make better predictions in subcellular biology? One possible reason is the very high complexity and dynamicity of subcellular structures and assemblies, including the dynamic cytoskeleton and membraneous systems, and the complex networks of cytosolic proteins which underlie metabolism, secretion, signaling, motility, division and gene expression. Additionally, there is a lack of predictive theories on subcellular organization.

Why is the predictive power of cell biology so weak? What are the alternatives to existing practice in research and development? Needleman and Brugues[1] suggest that a possible remedy could be a focus on the physical properties of the different substances at the subcellular level, a better overview of the whole cell through more detailed investigations of the subcellular parts and their physical properties. Until recently, advances in material physics have had no broad impact on the understanding of subcellular organization, but this is now changing because of attempts to integrate and incorporate established principles from soft condensed matter physics into a range of subcellular structures, especially by using polymer physics in the understanding of nuclear organization and membrane mechanics.

As the authors of the forum article note, however, there is a crucial difference between the synthetic analogs of subcellular structures and the subcellular parts that consume energy to perform biotic reactions; between "active" energy-consuming molecules that behave and their "passive" counterparts in abiotic and inert matter.[1] Whereas the "active" molecules are self-organizing; the "passive" particles, which spontaneously form structures, are self-assembling. The self-organizing nature of "active" matter is different from that of non-equilibrium steady-state structures. Dan Needleman and Jan Brugues focus

on discovering the general principles of the "behaviors of active matter."[1]

The crucial question for Needleman and Brugues therefore is this: will it be possible to develop physical principles of subcellular organization to help establish predictive theories of cell biology? And will theories of "active matter" contribute to this process? The first step is the development of predictive theories for particular systems, the second to compare different systems, and the last to develop generalities.

The current intensive efforts to understand self-organization of "active matter" in the opinion of Needleman and Brugues have focused on (1) collections of cytoskeletal filaments which underlie cellular motilities and cell divisions, (2) experiments on mixtures of cytoskeletal filaments, molecular motors and other components, and (3) the 2 main theoretical approaches which describe self-organization of cytoskeletal systems, i.e. microscopic descriptions of interactions between cytoskeletal filaments and generic descriptions of variables such as mass and momentum densities and filament orientations. Both descriptions concern the active nature of the cytoskeleton which results from continuous consumption of energy. This should lead to a direct connection between large-scale behaviors of the cytoskeleton and its molecular constituents but is hindered by poor knowledge about the actual microscopic behavior of the molecular constituents or the rules of interactions between cytoskeletal filaments. Therefore it is difficult to construct realistic microscopic theories. Second, generic descriptions based on coarse-grained variables of the system are limited because of the large numbers of phenomenological parameters. Additionally, the finite size of the systems, and the incorporation of non-linear terms which are necessary because of forces outside the system, may limit the predictive power of such explanations.

Until now, the 3 approaches described above have not been fully integrated. Needleman and Brugues are convinced[1] that further quantitative measurements and experiments on cell biological structures will allow direct tests of the validity of system theories and that the harmonious alliance of the 3 approaches will result in truly predictive theories of biology.

In contrast to the authors of this forum article, we propose a more solution-orientated perspective. When we look at the sharp contrast between financial impact on drug research and development of successful applications from the methodological perspective, it is important to clarify the theoretical concepts that are behind every research program. In the twentieth century, all attempts to find successful translation rules from the language of observation and its description to the language of theory, and vice versa, failed.[3] There is obviously an unbridgeable gap between the language we use in description of observations and the language in which we construct scientific theories. In this respect, the suggestion of formulating theoretical descriptions in terms of phenomenological parameters that can be traced back to microscopic parameters[1] would feed back weaknesses of the theoretical concept directly to the microscopic parameters.

Are subcellular structures systems? When we speak about cells, tissues, organs and organisms, we speak about phenomena which can be observed, described, investigated, and tested in reproducible experiments. We can term them "systems," but cells are cells and systems are explanatory tools in a systems theoretical perspective. Whereas cells are phenomena which can be described through multiple perspectives, a system is a term within an artificial scientific theory. If we term cells as systems, we do not talk any further about cells but of systems, in a systems theoretical perspective. There is a price to pay: if we term cells as systems then we confuse a central term of a scientific model of explanation with an ontological entity. As recently noted, living organisms are not systems but historical products within a coherent evolutionary framework history,[4] with essential context-dependent impact on epigenetic formatting and transgenerational modifications of genome expression.[5,6]

Additionally, it is important to be aware that systems theory is based on a mathematical theory of language.[7] If we take cell-cell communication as an example, we find abilities that cannot be described sufficiently by mathematical theories of language such as de novo generation of behavioral patterns for unpredictable changes in environmental circumstances[8] which is based on the ability to modify genetic content or the modification of epigenetic markings' translational pattern and gene regulation.

If we want to develop a more efficient take on cytoskeletal structures and membranous motilities, we should integrate current knowledge about the evolution of eukaryotic complexity. An abundance of non-coding RNAs regulates gene expression, transcription, translation, repair and epigenetic markings.[9] The role of these non-coding RNAs is crucial for almost all cellular processes, as these are highly dynamic hierarchical networks.[10-13] Many of them are known to be infection-derived.[14] For example, the persistent viruses are forming counter-regulating modules such as toxin/antitoxin, restriction/modification, and insertion/deletion modules.[15,16] Mobile genetic elements, most of them remnants of former viral infections, play decisive roles in adaptational and regulatory processes.[17] All these modules interact in a network-like manner. Importantly, investigation of these biological agents as "active matter" excludes the investigation of sociological behaviors. Signaling is not just one competence of many but rather the essential competence of cells. If signaling in all contexts functions faithfully, then the functionality of cellular interacting compartments is guaranteed. If signaling processes are disturbed, deformed or damaged, then the function of interactional cell processes will be in question. The same holds true not only for subcellular structures but also for all cells, organs, and organisms, in all domains of life.[3]

Although self-organization seems to be an appropriate description of active molecules or "active matter," the underlying features are not well explained. Signaling means the organization is a prerequisite for coordinated behavior of subcellular structures which are rather complex hierarchically organized constructions.[18] This means active parts of the cells must be able to generate molecules that serve as signals in a spatio-temporal well-ordered network to generate meaning, i.e., semantics,

represented as a function of the receiving cells. If these signaling networks are out of the syntactic order, then confused meaning will arrive at the recipient cell. As a result, no coordination in behavior can take place among subcellular structures.

Can we reduce the human language to the exchange of vocals through air molecules? Can we extract the meaning of human utterances from the analysis of physical motion patterns of oxygen molecules? If so, it would mean that the meaning of language signs is inherent in syntax. However, according to empirical knowledge, the meaning of sentences is determined by their contextual use, i.e. pragmatics, not syntax.[8] If we want to describe self-organization we will find that it does not emerge from available chemical molecules following physicochemical principles, but is rather the result of successful biocommunication processes between competent living agents.[19]

Living agents are more than just "active matter." They represent identity (self/non-self), and form groups that integrate members and exclude non-members. Through signaling in sign processes they can form all the complexities we know, using a limited number of signs with a limited number of syntactic (combinatorial), pragmatic (context-dependent) and semantic (content-specific) rules. But rules are not laws. Whereas natural laws are strictly valid for all entities, rules – albeit rather conservative – can be changed according to need. All these parts are absent in inanimate nature or "passive matter." To reduce the behavioral patterns of living agents such as cells, tissues, organs and organisms to terms of physics cannot lead to theoretical concepts that explain astonishing capabilities such as biocommunication.[3,20] Cell-to-cell communication can be measured quantitatively and analyzed via statistics, but these approaches cannot explain equal understanding of 2 participants represented by common coordinated behavior.[3,18]

Because cell-to-cell communication depends on shared rules to use signs according to contextual needs, physical principles are not an appropriate tool for a better understanding of biological processes and subcellular organization. It will not by itself lead to a reduction of costs via predictions in pharmaceutical research. The bottom-up explanatory models of subsystems and the combined understanding of cellular systems on the basis of their physical principles have been a core concept of molecular biology and systems biology for more than half a century. Yet it is not part of the solution to find a better understanding and facilitate more successful research in cell biology and the pharmaceutical industry. Rather, we should look at new paradigms for investigating cell biology and subcellular organization such as top-down approaches which consider the competencies of complex cells, tissues, organs and organisms in their real-life contexts.[21-23] These features and abilities are absent at the purely physical level; nor can they be explained by physics alone. For example, take the evolution of the placenta. If we investigated this on the subcellular organization level with pure physics, we would have no opportunity to reconstruct or even to understand the evolution of the complex organ which is a crucial precondition for the evolutionary success story of mammals. Since we know the role of endogenous retroviruses, which incorporate complete gene-blocks into host organisms and change genetic identity and phenotypes in single infection events, we can coherently reconstruct the evolutionary history of the mammalian placenta with the syncytin complex.[24] Therefore, to avoid an imbalance between the money spent on drug research and the latter's success rates,[1,2] we need strong theoretical inputs from biocommunication theory to provide an overview of all the core agents of the cellular life and subcellular organization.[18]

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No potential conflicts of interest were disclosed.

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