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Could New Paradigms of System Theory Help with the Understanding of Molecular Interactions Inside a Cell?

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Abstract This review describes the viewpoint of new system theory paradigms that the metabolic and signal pathways substantiate non-linear dynamic processes which are responsible for asymptotic stability of intracellular systems. Observed spatial objects, not pathways themselves, are the elementary asymptotically stable objects to be studied. This approach is supported by generalized stochastic system theory, how to extract individual trajectories of the multi-fractal system – the biological stochastic attractor. Described representation is based on experiment observation with all its practical limits.

Keywords Theory Of Systems, Systems Biology, Decomposition, Synthesis

1. Introduction

Data obtained in measurement of chemical or physical parameters in molecular biology are often treated as given values provided with uncertainty measures – standard deviations or error bars. Behind the creation of these datasets there is extensive data manipulation in many senses determines the presented values. Current movement towards standardization of biological experiments description is definitely and inevitable steps in current data boom caused mainly by general accessibility of –omic technologies[1]. However, in scientific papers significant derivation from standard experimentation are still to be expected. In the standardization of data representation substantial problems coming from the fact that data are significantly instrument -dependent both in the actual technical set up of the instrument and on the technical set up of the biochemical and physico-chemical experiment; and from data handling approaches which are not standardized either in mathematical principles or in actual provision.

The understanding of cellular instrumental data as stochastic system may lead to principally different approach to data transformation which is not conform with standard terms used in data transformation[2]. Stochastic system is a system which not always gives the same output for given input. The origin of stochastic behaviour is given by our inability to observe and measure exact values of all system attributes with infinite accuracy[3] ,[4],[5]. It has been demonstrated in many cases that biological systems behave as stochastic systems[6],[7],[8]. Random inputs, time delays, noise from different source and of different character, various biochemical and physico -chemical manipulation with the sample are additional sources of stochasticity. Finally, the separation and detection system brings noise of generally uneven character.

Difficulties in finding the correspondence between the experiment and the model based predictions of molecular biology lead towards the definition of integrative biology with greater emphasis on the process of developing such models[9]. This inevitably leads to inclusion of modelling experiments on the basis of its description as stochastic system as legitimate way of description of biochemical experiment. The advantage of this approach is the naturaleness with which the characteristics of the biological model and that of the experiment itself may be integrated [10],[11],[12]. Nevertheless, it would be clearly missing the target of creation of bio-molecular models if the two complementary models, model of technical experiment and model of experiment, would not be dissected.

Both, inter cellular behaviour and cell fate estimators are the outputs expected from the molecular biology and systems biology, respectively, in the near future. Therefore, general mathematical systems theory is required to construct robust abstract models for experiments in silico.

The cell state may be ultimately characterized by state of metabolic and signaling pathways, and by state of cellular structures. These two parameters complement each other. The pathways and metabolite transformations define and maintain the cellular structures. The current state of knowledge, does not allow to devise state of pathways from

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observation of structures and vice versa. Both phenomena are being observed experimentally in many routine experiments.

Any metabolite analysis contains the element of metabolite profiling and targeted analysis. It is always more than one class of compounds present in targeted analysis. There is never a complete metabolite profile. One realistic approach towards objective analysis of the experiment is to determine evolution of information fluxes assessed by the experiment in time: Representation of information content of each time-step portrait. This representation is also in relation to dynamic biological system state in time of measurement. It is the map of information content in actual point in state space. Such detailed analysis is extremely computationally intensive, however, it might be of high value for rapid diagnostic in medicine, biotechnology, and any other discipline utilizing cell biology results.

2. Systems Theory and Systems Biology

Contemporary paradigms of real systems assume that any natural or artificial process under study fulfills the general set of nature laws. Those laws are a priori stochastic (probabilistic) descriptions, where a deterministic case is just a special case of stochasticity (with the probabilities equal to one). The stochastic behavior is given by our inability to measure (observe) exact values of all system attributes with infinite accuracy. All individual objects of interest are ordered to the proper subtraction of general laws, usually just by parameterization. It is necessary to mention that any thought construction above the object behavior never works with the real object itself, only with the abstract object. Thus, the abstract objects in every single theory are created as more or less homomorphic models of the real objects.

Every model is created for a reason. One of the most justified purpose is to discover (literally emphasize) congruent description (and parameterization) of known general law in the given case of study. This process verifies or rejects both the generality of the law in nature observation and hypothesis of exact instance of this law in the object of interest. The situation that rejects generality demands modification of paradigms and it is not considered in this article. On the other hand, the exact instance should be verified statistically by huge amount of measurements (observations) and their fits to the model.

However, even the measured data were obtained by measurement device which was designed according to some model of physical (chemical, biological, mathematical) process of the measure and they are always quantized in the value domain. It is done by analog/digital converters on the input of (control, storage and processing) computers and at many other instances which reflect primarily our inability to measure with infinitesimal accuracy and precision. Therefore, all possible datasets are already models according to the theory of systems. Moreover, proper description of the mathematical space results in description of the abstract model.

The term of systems theory arose from the cybernetics, and it is also often considered as the synonym for such branch of science. However, the cybernetics is not focused only on the theory of systems. Norbert Wiener (1894-1964), the father of the cybernetics, used the description of control and communication in living organisms and machines. The part of living organisms is usually forgotten. Thus, the cybernetics is used to be considered as a purely technical field, unfortunately for the molecular biology.

During the history, there were developed two basic approaches from the systems theory how to describe biomolecular or any system as its mathematical model.

2.1. Decomposition Approach

Decomposition (analytical) approach assume that the investigated system could be divided into subsystems, which are investigated independently. This decomposition approach suppose that properties as well as behavior of the whole system should be deduced from the properties of its subsystems. In molecular biology, it is necessary to choose certain level of decomposition which leads to the key subsystem of interest reason. Decomposition represent organizational or a logical hierarchical structure of a system. Decomposition approach was defined by Rene Descartes [13] using three simple steps (Decompose, Investigate, Deduce).

2.2. Synthetic Approach

At the basic level, the stone or the human being are both composed from the exactly same kind of elementary particles. Even the best description of the particles properties, will not tell us anything about the structure of human DNA. The situation is given by the fact, that the decomposition itself can not take into account also the interactions between all components (the description of electron-proton interactions only is still not enough).

The other approach supposes that the complicated system is more then just the sum of its subsystems. This definition of synthetic approach was probably first time formulated by Aristoteles. The synthetic approach is the process of understanding how subsystems influence one another within a whole. The system has structure, behavior, interconnectivity, and functions. Therefore, the system as a whole determines how the subsystems behave.

For complementary sake, the synthetic approach is also sometimes described as scientific holism. A primary term of holon is defined as something, that is simultaneously a whole and a part. Exampli gratia, the lymphocyte is a system, consisting of individual cooperating organelles, from the point of view of cytologist. However, the lymphocyte is just a component of the immune system, from the point of view of physiologist. The scientific holism also presume the principle of stochasticity.

The property that the whole is more than the sum of its

parts, is also often called the emergence property, and we might therefore talk about emergence systems.

2.3. How to Describe the Investigated Biological System

One way, how to describe the real system, is to use the input-output modeling. This type of description is quite often in the molecular biology. Tis model uses the ordinary differential equations (ODEs), like in the photosynthesis, or transfer functions, like in the fluorescence.. Unfortunately, the ODEs suffer for several disadvantages. First of all, there were not designed for the inclusion of oriented relations. Next, they are continuous (however, there exists also difference equations), they are deterministic (there exist also attempts of stochastic ODEs). Moreover, ODEs suppose the sufficient amount of the interaction carrier plus temporal and spatial availability of the carriers. This assumptions are not valid[14].

We are not able and we never will be able to measure continuously. Every single measurement is represented by discrete events, discrete in time (sampling) and quantity (quantization, like digital levels of A/D converters). Living cells are complex (and emergence) system, which consist of other 'holons' (nucleus, membranes, organelles). Such components of the cellular subsystems communicate using small signalling and/or functional molecules (metabolites). The key issue is that there is only limited finite amount of such molecules in each cell. Metabolites have to move through spatial distances between the subsystems. This communication space is full of other molecules with different attributes (size, shape, reactivity). Also the metabolites themselves differ by same kinds of attributes. This fact means that the available space of interactions is not continuous and does not have integer dimension. The inner cellular dimension is multi-fractal (set of finite fractal-like subsets[15],[16],[17]). Therefore, the mentioned limitations produce the probabilistic behaviour of the interactions.

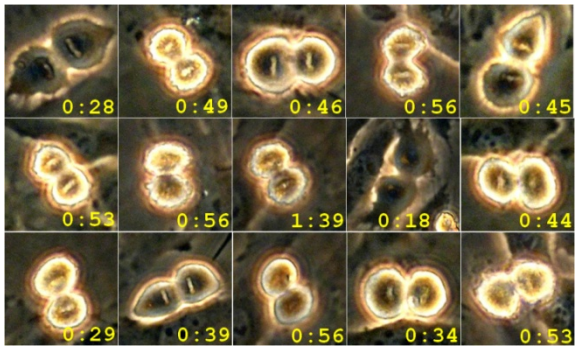

Figure 1. The examples of cell divisions of HeLa cells (Helacyton gartleri, genetic chimera of papillomaviru HPV18 and cervical human cancer cells[18],[19],[20]). The images captures the moments, when it is clearly visible the moment of two new daughter cells. The time of the beginning of the division to the captured moment is represented in the format of hour:minutes. The events are very similar, however the trajectories, realized by the cell system, are different. The images were captured byt the invert phase contrast microscopy. The typical size of the cells is 25 micrometers

More advanced description is the modelling of states which respects also the structure of the systems (the placement of the subsystems and the interactions between them). The behaviour of the system is described as time evolution (trajectory) in the state space. Then the set of trajectories, which gives similar outputs, is some event of the system. The events are what we do observe on the living organisms.

The cell division as the basic observed event is the trajectory (from preprophase to telophase), it is a set of states. We can not suppose that each division equals to exactly the same set of states. Division as an event can be represented by many possible trajectories[7],[8],[14],[15],[16] (Fig.1.). The system may never reach the same state again and even then it behaves very similarly. That is possible only if the states are grouped in the state space. The state groups are described as the zones of attraction and they represent the events. We are not able to measure or even define all state variables. What we are able to define is the causal decomposition to the events[8].

2.4. New Paradigms

Unfortunately, the decomposition and synthetic approaches had not gained corresponding position in the science. That was the main reason, why new paradigms of systems theory were arose[3],[4],[5]. The goal was to find an abstract system which would be sufficiently general as to cover any real problem and, at the same time, sufficiently specialized, as to enable to find an adequate physical realization to any theoretically given abstract system.

Thus the system is defined as such isolated, in other words, the inputs and outputs are just elements (sub-systems) of the system. The inner variables are the only system variables which are not accessible to measurement. The properties of any part of the system are conditional and are generally lost when the part of the system is transferred to another environment.

The structure of the system is given by the causal relations. Therefore, the physical realization is fulfilled. The elations are oriented, and the orientation is given by the causality. This causal relations might be conditional, and therefore the system is stochastic (where deterministic case is just a special case of stochasticity).

System trajectory is time ordered Cartesian product (mapping) of sets of system attributes. System event is a selected set of trajectories. System is defined as a set of all events. The sequential decomposition of the system trajectory is the tool how to determine the structure of the system. Stochasticity is defined as causal probabilities. Division as an event can be represented by many possible trajectories. The system may never reach the same state again and even then it behaves very similarly. That is possible only if the states are grouped in the state space. The state groups are described as the zones of attraction.

2.5. System Biology

During the conferences about system biology, molecular biology, or biophysics, it is quite common to discuss the advantages and disadvantages of decomposition and synthetic approach, of differential equations and state space. The new paradigms offers a solid mathematical theory to describe (also) the biological systems. Even more, A comprehensive abstract model of measured data is necessary for consequential processing or analysis. The reason of mathematically described data model is to encapsulate behaviour hypothesis into appropriate mathematical space. Layout of the possible domain values ensures that created behaviour models also fulfil the mathematical presumptions of data model. Furthermore, outputs of the processing and analysis are therefore also consistent with the theory of abstract systems.

One of the most important event in the living organisms is the cell division, the trajectory from preprophase to telophase. What we are observing are the events. We are not able to define them accurately as the states. Unfortunately, often we are not even able to determine all necessary state variables. Such situation is given by the stochasticity of the investigated systems. Proliferation of living cells is hard to describe as simple switching from state to state. It is not possible to presume, that the each division is represented by the same set of states. Division as an event may be represented by many different trajectories. Living cells are rarely returning back to the same state, however there are many slightly different states, representing exactly the same events (mitosis, interphase, tumor growth). At the end, the all end in the state of thermodynamic equilibrium (apotheosis, the cell death, terminal attractor). All observations can be explained only if the states are somehow clustered in the state space. Such clusters are usually described as the zones of attraction and are related to the events. The states of the systems are oscillating around the zones of attractions and the switching between the zones (events) is probabilistic and causal.

Besides, the decomposition[8] of the cell to the organelles and molecules has to be done according to the causal relationships (living cells represents physically real system). Nowadays, are the causal relations described as metabolomic pathways, usually deterministic, without taking into account the limits leading to the stochasticity. Decomposition based directly on the causal relations goes much further. Obviously, even the hierarchy of the relations defines the structure on the corresponding level of details. This is done because the relations might exists only between the subsystems. Thus, the analytical hierarchical decomposition will result, while the relations (of synthetic approach) and orientation of the relation are considered. Moreover, the decomposition is defined by the relations. That is the main reason, why the inputs and outputs are defined as the causal subsystems. Causal systems is therefore defined only by the set of all subsystems and by the set of all relations.

3. Conclusions

Overall, there is already a mathematical description how to determine the structure of a system on several level of details, and simultaneously how to describe its behavior via events. Moreover, such descriptions are consistent together, that was the biggest problem of every system theory and especially of the systems biology, till now. There is also automatically solved the question what is more appropriate, the model build top-down (system decomposed into subsystems) or model build bottom-up (subsystems joined into system). Finally, both models have to be equivalent (ideally isomorphically). The question, where to start, in other words, if to do the decomposition or synthesis, is just a question of taste and requirements of the model creators. The consensus about general approach to modeling systems in molecular and cellular biology is still missing. The cybernetics and biologist do not meet each other quite often. However, it will be a clear waste to discard mathematically robust theory, which is already available, for description of the complex systems like the living cells interior.

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