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On the Role of Synthetic and Systems Biology in Biological Studies

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The classical study of biological problems through a molecular approach implies that global properties of living systems are a reliable image of molecular events taking place within the cell. This is the view of molecular biology that implicitly assumes that the global properties of living systems can be understood from the properties of a number of isolated protein and nucleic acid molecules. In other words the aim of molecular biology is to understand the global properties of living systems from the individual properties of different types of molecules, namely proteins and nucleic acids.

An important idea that has recently emerged in scientific literature is that the fundamental biological properties of living systems cannot, in most cases, be defined at the individual macromolecular level but at the level of *systems of biomolecules* in interaction. It is from the interactions between the elements of such systems that novel properties emerge that are not the properties of individual, isolated macromolecules but properties of a *system* that possesses its own laws.

In opposition to this modern view, the classical reductionist approach does not rely upon firm epistemological grounds. The knowledge of the structure and function of macromolecules is necessary but not sufficient to understand the internal logic of the living world for the supramolecular organization of the eukaryotic cell plays an essential role in the expression of biological functions. There is little doubt that this approach has allowed a large number of important discoveries. It has appeared, however, that a deep knowledge of the molecular structure, synthesis and expression of nucleic acids and proteins is not sufficient *per se* to allow the understanding of the internal logic of most biological events. The basic idea that has emerged in recent years is that the fundamental biological properties cannot be defined at the individual macromolecular level but at the level of *systems* of biomolecules in interaction. It is from the interactions between the elements of such systems that *novel* properties emerge that are not properties of individual, isolated, macromolecules but properties of a new system that possesses its own laws.

In this perspective, it is the *network* of chemical reactions which constitutes a *system* and plays a major part in understanding the succession of events occurring in the living cell. What is the most important in such a system is not the properties of individual macromolecules but the properties of *sub-systems* of chemical reactions catalysed by these macromolecules. In this vision of biological problems, it is the topology and the physical properties of many connected networks that constitute a simplified image of living systems. It thus appears that the main task of biologists working on these biological systems is to explain, on a physical basis, how chemical reactions can display periodic, or chaotic, dynamics, how these multimolecular systems can convert chemical energy into movements, how matter can be transferred from place to place against concentration gradients etc…

Perhaps the best illustration of this idea comes from the chemiosmotic theory which offers a physical explanation of the energy storage under the form of adenosine triphosphate (ATP) in mitochondria and chloroplasts. For many years biochemists have tried to isolate a molecule that could have been responsible for the phosphorylation of adenosine diphosphate (ADP) into adenosine triphosphate (ATP). In fact this putative molecule did not exist. An enzyme, however, was discovered that catalysed the reverse process i.e. the hydrolysis of ATP into ADP and phosphate. Mitchell was then able to show that ATP synthesis can take place in mitochondria for it is coupled with a vectorial event, namely proton transfer across the inner mitochondrial membrane. It then appears that the same enzyme that catalyses ATP hydrolysis *in vitro* could catalyse its synthesis *in vivo* if anchored in the mitochondrial membrane.

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The basic idea which is at the very basis of this kind of approach is to view biological problems as some kind of sophisticated physical problems. It is sensible to consider that the properties of such a system cannot be reduced to the individual properties of the elements of the system itself. Hence, what is important in this system is its topology and dynamics.

In order to understand the organization of these systems one has to use the mathematical language which is essential to define and describe their properties. In fact the properties of such systems are, to a large extent, dependant upon the *relationships* between the various elements that constitute a network. It then appears that these *mathematical relationships* that define a network are more important than the individual properties of macromolecules involved in this network.

There is little doubt that this new vision of living organisms, considered as *systems*, will provide, and is already providing, new illuminating explanations of biological processes.

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