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Guest Editorial

Highlight: Molecular Machines

The term ‘molecular machines’ has become popular during the past few years. In a seminal article in the journal *Cell* entitled ‘The cell as a collection of protein machines: preparing the next generation of molecular biologists’, Bruce Alberts described his excitement for these, I quote, ‘ingenious, elegant, marvelous’ protein assemblies, for ‘the sophistication of these remarkable devices’ (Alberts, 1998).

In the Mosbach Symposium 2005, we wanted to share this excitement by hearing about such protein assemblies, many of them of stunning complexity, themselves parts of larger works of the cell. Certainly the symposium was also thought to help prepare young scientists for the art of studying these structures, taking them apart, putting them together again and understanding their ways of operation, and to express the conviction to the younger generation that quantitative biology is an essential ingredient of our science, as well as the use of a wide spectrum of technologies, beyond handling recombinant DNA.

A selection of the molecular machines functioning in different areas of cellular metabolism was dealt with in the Symposium. These ranged from chromatin structure and function, and components involved in transcription and translation, to chaperone machines with a role in folding, unfolding, degradation and intracellular translocation. Bacteriophages were presented as nanomachines that inject DNA into host cells, and kinesins and related proteins as nanomotors that endow cells with structural dynamics. Molecular machines that carry out most intricate enzymatic processes were discussed, such as the conversion of pyruvate to acetyl-CoA, or oxidative phoshorylation and photosynthesis, reactions comprising a multiplicity of steps and moving parts.

The intellectual pleasure of reading printed versions of several of these lectures in this issue comes from admiring the amazing and sophisticated variety of nature’s designs and, on the other hand, from recognizing the common principles and simplicity behind the various supramolecular assemblies and their dynamics. In this way it becomes beautifully clear how the structure and function of these machines are two sides of the one coin.

At the same time, however, we have to realize that viewing complex macromolecular assemblies as ‘machines’ is entirely inappropriate. Upon wondering and pondering about how similar dynamic protein structures are to products of machines engineered by humans, we tend to be oblivious to our genetics and evolutionary biology. Bruce Albert writes: ‘And to what extent has the design of present day protein machines been constrained by the long evolutionary pathway through which the function evolved, rather than being optimally engineered for the function at hand?’ The vast majority of biologists believe that these ‘machines’ are not made by optimizing a design. Rather, we are convinced that they are the products of aeons of evolutionary processes. Francois Jacob made this clear almost 30 years ago: nature is not an engineer; she is a tinkerer (Jacob, 1977). Molecular machines, although it often may seem so, are not made with a blueprint at hand. Yet, biochemists and molecular biologists (and many scientists of other disciplines) are used to thinking as an engineer, more precisely a reverse engineer. They are eager to ‘detect the blueprints of construction’. But there are no blueprints; the workshop of the tinkerer is a collection of millions of bits and pieces that are combined, and odds and ends are used over and over again to yield something that works better.

The apparent similarities of creations by engineers and tinkerers raise a fundamental scientific challenge: understanding the laws of nature that unite evolved and designed systems. Or in other words: understanding the work of a tinkerer not only by using equipment designed by engineers, such as diffractometers, NMR spectrometers, glass electrodes and microscopes, but also by searching for the blueprint. ‘Nothing in biology makes sense except in the light of evolution’: we know that Dobzhansky (1973) must be right. But our mind, despite being a product of tinkering, itself strangely wants us to think like engineers.

Somehow we are hesitant to accept the principle of biological construction by random mutation and selection. One explanation for this phenomenon may be that the evolutionary strategy does not work at the level of the individual, but only at the level of a population. And we do not have the patience to wait for this to happen.

On behalf of the organizers

Walter Neupert
Adolf-Butenandt-Institut der Universität München
Physiologische Chemie
Butenandtstr. 5, Gebäude B
D-81377 München
Germany
e-mail: neupert@med.uni-muenchen.de
http://www.adolfbutenandtinstitut.de/

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