Editorial:

Mathematical and Theoretical Biology for Systems Biology, and then … *vice versa*.

Systems Biology has two roots (Westerhoff & Palsson, 2004). The better known resides in molecular biology, grew to functional genomics and then became top-down, genome-wide systems biology. The less-publicized root resides in theoretical and mathematical biology, with topics such as non-equilibrium thermodynamics, self-organization, kinetic modelling, metabolic control analysis, flux analysis and biochemical systems theory, culminating in genome-wide versions thereof. It is anticipated that from these roots a Biology of unprecedented strength and quality will emerge, which ends the deadlocks of functional genomics drowning in its oceans of data and of mathematical biology escaping reality.

Much of the growth in systems biology has bypassed Mathematical and Theoretical Biology. Only at the recent ESMTB meeting in Dresden did the surge in Systems Biology activity seen in molecular cell biology, begin to be mirrored by a similar surge in mathematical biology. Until then, the more theoretical activities in Systems Biology involved engineers much more than mathematicians. Why has this been the case?

Systems Biology

Systems Biology is well-defined and broad at the same time, not unlike Mathematical Biology. It is the science that studies how functional biological properties arise in the interactions of components [Alberghina & Westerhoff, 2005; www.systembiology.net]. As such it may link molecules with cells, but also elephants to ecosystems. The new properties can only arise if the interactions are nonlinear, in spatial, temporal or the chemical dimensions and therewith Systems Biology is a nonlinear science. It is also a molecular or, at least, concrete science however, as it addresses the *actual* mechanisms by which true function arises, rather than virtual mechanisms. This is reinforced by the wealth of experimental data and possibilities offered by functional genomics.

Mathematical Biology to descend from the Olympus?

Stereo-typical mathematicians do not like biology, nor do they like chemistry. They have learned to accept physics, and indeed the real-world side topic in their studies has always been physics, never biology. This has been because physics was reductionist, reducing problems to simpler ones that could actually be solved mathematically. Biology was considered impure, a large number of special cases, where no analytical solution would be possible because it was too complex, too nonlinear.

Mathematical biologists included mathematicians that went one step further: they did venture into biology. Yet, many of them kept searching for general mathematical principles in highly idealised or simplified caricature models, thereby foregoing the essence of systems biology. They did not wish to descend to the details of molecular biology and to its nonlinearities. Attention focussed on developing general theories such as those connected to evolution, avoiding the issue of what is ‘Life’ here and now.

Mathematics in cell biology, be it enzyme kinetics, metabolic control analysis, or computational systems biology, therefore came almost exclusively from non mathematicians. Likewise, mathematical systems biology with its emphasis on understanding real systems in terms of real molecular or component properties, may be left to the more applied scientists, such as biochemists and engineers.

This would be bad both for systems biology and for mathematical and theoretical biology. Systems Biology would suffer because the mathematics would not be quite as good and efficient as possible. Mathematical Biology would suffer because it would miss a tremendous number of highly interesting problems, a possibility to develop a new branch of itself, and the accompanying possibility to grow into a mainstream Life Sciences, with associated funding. For the sake of both Systems Biology and Mathematical Biology, the latter should descend from the Olympus.

ESMTB and Systems Biology

Our society may wish to help mathematical biology descend to the reality of systems biology. Yes, there are details, 120 000 of them perhaps, but this in itself is a mathematical challenge. It is a challenge also because it is not just 120 000, but it is the 120 000 that enable Life. It is a challenge to discover what Life is in this sense, and for this we need mathematics. One may need to accept that one often has to deal with the mathematics of many special cases, although generality is still to be discovered. After all these 120 000 sample the space that spans Life.

With systems biology, mathematical biology has a brilliant future, if it does the above. In the same way that physics stimulated the creation of mathematical physics, systems biology may now get mathematical systems biology on the go. Mathematical biologists should accept that biologists driven by strong motivation and inspiration have often already accomplished part of what needs to be achieved theoretically. However, the way in which this was done may not have been formally rigorous. Mathematical biologists should now engage in improving and re-formalizing the existing work, with the expectation of thereby making new discoveries, through generalizations or even through specializations. Subsequently, the mathematical biologists will find their own ways to then lead systems biology to new discoveries.

Mathematical biology and the silicon cell

An extreme case of detail laden biology is the silicon cell program, where the idea is that computer replicas be made of intracellular pathways and, ultimately, whole living organisms (www.siliconcell.net). There is a remarkable importance of detail and special case here. Each enzyme is a special case with specific parameter values which have to be encoded in the computer program. Sophisticated mathematics should help in solving and analyzing the resulting systems which are simultaneously stiff in the dimensions of space, time and chemistry. Making a precise computer replica of a living cell, and subsequently of the human being itself, is one of the greatest scientific and humanistic challenges. The mathematical difficulties are enormous, especially when one realizes that the replica needs to be made understandable by formalization and the subsequent discovery of understandable principles and rules. Likewise, the mathematical remunerations are enormous: once we have a mathematical replica of Life, Life itself is open to all the mathematical and indeed philosophical/theoretical examinations one would wish to engage in. Computational Biology will be more realistic than computational physics and will provide an interesting challenge for the development of new mathematics.

Conclusion

There is a bonanza of new mathematical biology to be discovered in systems biology. I hope that as many bright mathematical and theoretical biologists as possible will engage in this challenge.

Hans V. Westerhoff
Vice-president of the European Society for Mathematical and Theoretical Biology
AstraZeneca Chair of Systems Biology at the University of Manchester
Chairs of Molecular Cell Physiology and Mathematical Biochemistry at the BioCentre Amsterdam

1. Westerhoff HV and Palsson B.O. (2004) Nature Biotechnol. 22, 1249- 1252
2. Alberghina L. & Westerhoff H.V. (2005) Systems Biology: Perspectives and Definitions, Springer, Berlin