EDITORIAL

On the virtues and dangers of models

DOI:10.1111/j.1574-6976.2010.00256.x

The recently elected Miss Switzerland got herself into trouble when she was asked what she was doing in her life and she casually replied that she was a biology student. As a matter of fact, her jobs as a model and shop assistant leave her little time for studying biology, although she apparently has done some distance learning of biology with the help of a British institution that offers such courses. But the public extrapolated her statement to imply that she was a university student and that her major was biology. When after further questioning the situation was eventually clarified, there was a public outcry that she had been untruthful. As a model, she ought to value truth more than anything else, people said. But was all this debate the model's fault? Or was her statement simply stretched too far by the public? I would argue that models have all sorts of virtues (otherwise they would not be models) but what makes models potentially dangerous is what you project into them, beyond their real values.

Biology and the specialization with which we are concerned here – microbiology – provide plenty of examples of how models become problematic when extrapolated too far. What elevates an experimental system to a model system? One of the most important features of a good model is that it should allow reliable predictions to be made. Likewise, an organism under study may be upgraded to a model organism if its properties are well known to the scientific community and if it is sufficiently well behaved so that researchers feel that they can predict the outcome of experiments with some confidence. Of course, a model should set an example. It should be representative of a group of organisms. In bacterial molecular genetics, for instance, two model organisms emerged some 50–60 years ago and they continue to serve as models: *Escherichia coli* and *Bacillus subtilis*. What we learn from textbooks about molecular genetics of bacteria is based to a large extent on just these two model organisms. No doubt, the fundamental mechanisms of DNA replication, transcription and translation are conserved across the bacterial kingdom, so it would seem fair to extrapolate these mechanisms from *E. coli* and *B. subtilis* to bacteria in general. But where do the generalities end? Textbooks usually do not tell us.

If we take conjugation as an example, the F plasmid of *E. coli* is inevitable as a paradigm of DNA transfer by cell–cell contact. The F plasmid model shows how a donor gives a plasmid to a recipient and still keeps the plasmid, that is via replication during transfer. The F plasmid model also provides an excellent view of the interactions that can take place between the plasmid and the *E. coli* chromosome (via transposition and other types of recombination) and explains how pieces of chromosomal DNA can be transferred from a donor to a recipient in conjugation. The same principles probably apply to conjugative plasmids of Gram-negative bacteria in general. But how about Hfr strains, which transfer chromosomal genes at frequencies of up to 10^{-1} per donor? In fact, it appears that Hfr formation is a unique property of F in *E. coli* and closely related enteric bacteria because F, unlike other plasmids, is tolerated as a chromosomally integrated replicon for an extended period of time. While some textbooks are careful to point out that Hfr strains specifically arise in *E. coli* carrying F, other books convey the impression that Hfr formation is a general consequence of an interaction between a conjugative plasmid and a bacterial chromosome. If this were the case, events of horizontal transfer of chromosomal genes in bacteria might be even more frequent than they are already because of other transfer mechanisms.

The notion that long-term regulation of bacterial gene expression is achieved through the control of transcription – with the aid of proteins such as sigma factors, transcriptional repressors and activators – is stated more or less explicitly in most textbooks and the *E. coli lac* operon, another inevitable paradigm, serves to explain the mechanisms. The fact that, with few exceptions, bacterial genomes contain numerous genes for transcriptional regulators seems in agreement with this general concept of pre-eminent transcriptional control. An underlying idea is, of course, that bacterial mRNAs are short-lived and rapidly turned over. But is this generally true? The trouble is that very few mRNA stability measurements have been performed outside enteric bacteria and *Bacillus*. Furthermore, these fast-growing bacteria are routinely cultivated in nutrient-rich media. Under such conditions of abundant energy supply, it makes sense for the model organisms to synthesize mRNAs and to degrade them rapidly, in response to environmental stimuli. By contrast, in natural environments, the vast majority of bacteria grow much more slowly and the energy supply tends to be limited. Under these conditions, one could imagine that it would be energetically more favourable for bacteria to produce a range of relatively stable mRNAs and to regulate gene expression post-transcriptionally, for example with the help of small RNAs. There is emerging evidence that small RNAs can indeed act as regulators of vital

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metabolic functions in some 'nonmodel' bacteria, even in the long term. Thus, it would be reasonable to specify the experimental conditions to which transcriptional models of bacterial gene regulation apply.

Diauxie, first observed and characterized in *E. coli* and *B. subtilis* by Jacques Monod (Monod, 1942), is a popular model picturing how bacteria establish the order in which they utilize nutrients: fast food first – meaning that a substrate which promotes fast growth is utilized before another substrate which leads to slower growth. However, as Monod's original work shows, diauxic growth is by no means a standard behaviour, even in the model organisms. Many combinations of two substrates do not result in diauxie. Textbooks do not point this out. Worse, some of them give the impression that the mechanisms causing diauxie in *E. coli* – cAMP-dependent regulation of transcription and inducer exclusion – are generally responsible for sequential utilization of nutrients in bacteria. This causes a dilemma: it is difficult to see how the same mechanisms would operate in bacteria that are metabolically more versatile than enteric bacteria. The recent review by Rojo (2010) illustrates very well that the versatile pseudomonads use a totally different set of mechanisms to establish their food preference.

Science like fashion needs good models. They should seduce. But we should be careful not to overinterpret what they say.

Acknowledgements

I thank Thomas Egli for drawing my attention to Monod's PhD thesis and Antoine Danchin and Michael Galperin for valuable comments on the manuscript.

References

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