Synthetic biology's flywheel

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The invention of the steam engine triggered the industrial revolution. However, the first commercial engines of the early eighteenth century produced only linear movements, parallel to the movement of the piston in the cylinder. They were therefore only suitable for a few limited applications. It was the invention of the crank to convert a linear movement into a circular one, coupled with the flywheel to preserve energy and feed it back to the piston, that made the steam engine suitable for transportation and a huge range of other applications.

Synthetic biologists might face the same problem—how to convert one type of action into another—if the field wants to live up to its promise of solving the many social and environmental problems that plague humanity: the sustainable production of energy and biofuels, low-cost production of drugs, bioremediation of polluted habitats, biodegradable packaging, and so on. Engineers assume that they can treat cells as programmable factories using a set of standardized devices analogous to the transistors and integrated circuits used in electronic engineering. However, the analogy between electronic and biological engineering does not easily translate into practice, because adding genetic circuits to a cell has a considerable impact on how it manages its fluxes of matter and energy. For the biological engineers, the challenge is to come up with the equivalent of a flywheel that connects nonlinear, 'digital' regulatory networks to the cell's linear, 'analogue' physiology.

This challenge reflects the epistemological shift from physiology to molecular biology. In fact, Jacques Monod's PhD thesis in bacterial physiology, in which he described bacterial cell growth as a function of nutrients and established a hyperbolic relationship between growth rate and carbon supply, is one of the founding works of molecular biology, but it also marked the

end of physiological studies. Biologists were no longer interested in the 'linearity' of cell growth; instead, they focused their attention on the seemingly more fascinating nonlinear regulation of gene expression.

Yet cell growth requires that cells gain matter and energy from some eventually limited source and adjust their metabolism and biosynthesis accordingly. Experimental observations show that these adjustments take place in a linear way and that they affect at least three types of cellular function: a fixed set of growth-rate independent housekeeping functions; the transcription–translation apparatus dominated by the ribosome that expands with growth; and other growth-rate-dependent functions (Scott *et al*, 2010).

This has direct implications for synthetic biology and many of its potential applications. Engineering cells that probe the environment for specific chemicals—such as detecting explosives in mine fields—should not be a major challenge for synthetic biology, because it only involves modification of nonlinear sensory and regulatory networks and because there is little energy required to generate bioluminescence or another signal to indicate the presence of explosives. But using the cell as a factory to produce chemicals from antibiotics to biofuels is a completely different challenge. It involves re-engineering whole metabolic pathways to redirect the flow of energy and matter, and inevitably affects many cellular functions from growth to protein synthesis to cell division. This is obviously not achieved by adding a few regulatory elements; it means that biological engineers have to identify and manipulate the cellular equivalent of the flywheel and crank that links regulatory with physiological functions. Personally, I believe that the translational machinery is a crucial element: it not only expands when the cell grows, but also provides the synthetic capacity to quickly produce new proteins for other cellular functions.

How else can we couple the nonlinear organization of the genetic network with linear physiology? Victor de Lorenzo and co-workers use a Boolean formalism and qualitative computation of general fluxes that might be able to identify bottlenecks and high-level organizational elements of regulatory circuits (Silva-Rocha *et al*, 2011). Beyond such theoretical and computational approaches, we also need to start experimental investigations of cell physiology. We should, for instance, analyse the important role of the few crucial elements at the top of the hierarchy of regulatory cascades, such as small regulatory RNAs or cyclic AMP (cAMP) and the catabolic regulatory proteins that use it. Although cAMP is involved in controlling carbohydrate fluxes in *Escherichia coli*, where it was originally discovered, its targets are completely different in *Pseudomonas putida*. Yet, the enzymes that generate cAMP are remarkably similar in both organisms. This shows that their features are a functional yet abstract property—similar to the arrangement of materials that defines the shape and characteristics of a boat, independently of the nature of said materials. cAMP represents information that organizes the coupling between the qualitative local organization of entities that vary from organism to organism and quantitative global physiology. Once we start looking, we will find more of these links between regulation and physiology: synthetic biology will need to understand these to achieve its goals.

REFERENCES

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