UNDER THE LENS

Cells and computers, better together

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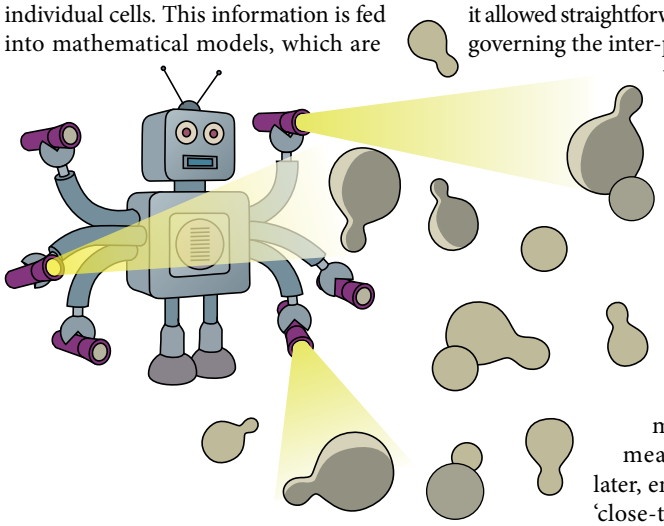
This month's Under the Lens discusses the potential of in silico feedback control applied to individual microbial cells, highlighting its use for study of single-cell dynamics and patterning behaviours.

Many of biology's most pressing challenges — such as the study of disease progression, tissue formation or the ecology of microbial communities — are predicated upon our understanding of complex cell–cell and cell–environment interactions. However, when parts of a biological system are isolated for in vitro analysis (for instance, on a microscope slide), it is challenging to mimic the complexity of these natural interactions that are foundational to many behaviours. Researchers have begun to address this context gap by implementing single-cell feedback control techniques in silico (that is, using a computer) to artificially realize interactions within and between populations of cells[1].

Single-cell in silico feedback control systems bring together emerging techniques from microscopy, control engineering and artificial intelligence. As data are acquired, automated image segmentation and analysis tools quantify the dynamic behaviour of individual cells. This information is fed into mathematical models, which are in turn used to select the subsequent level of an input (often light intensity in optogenetic systems) required to drive each cell towards a desired future state. Calculated input signals are delivered to individual cells using precise spatial control of light intensity, achieved with microscope setups that may be built around modified data projectors[1] or micromirror arrays[2]. This measure–calculate–actuate cycle can be iterated on a timescale of minutes or less, implementing 'closed-loop' feedback control of dynamic processes such as transcription and translation within many cells simultaneously.

In a recent study, Perkins et al.[3] used single-cell feedback control of an optogenetic transcription regulator (with fluorescent output) to investigate synthetic circuits for pattern formation. *Saccharomyces cerevisiae* cells in a 2D monolayer were assigned to 16 groups, each of which represented a patch of a four-by-four checkerboard. Patterning was established through lateral inhibition between neighbouring patches — this was enacted by 'virtual' (rather than biochemical) signalling between patches, mediated by dynamic computational control of light stimulus. The power of the authors' virtual implementation was that it allowed straightforward tuning of parameters governing the inter-patch signalling relation: this enabled them to validate theoretical predictions regarding how complex population-wide patterning could arise from 'localized' interactions between individual patches. Whereas traditional microscopy experiments are often set up to measure first and analyse later, emerging techniques that 'close-the-loop' with real-time in silico feedback control open the door to new approaches for the study of complex multicellular systems. Furthermore, by implementing key regulatory functions in silico, it is possible to quickly prototype and test engineered biological systems that exhibit sophisticated behaviours and that can operate over large spatio-temporal scales. Recent studies have highlighted the power of this approach in applications including pattern formation[3] and regulating the dynamics and cell-to-cell variability of gene expression[1] in bacteria and yeast, as well as in situ control of cells within higher organisms[4]. Building on this work, experimental approaches that interface cells and computers will extend our ability to, for example, probe dynamic behaviours of microbial gene regulatory networks[5], analyse interactions between members of multi-species communities and biofilms, and understand how the variability within a population of microorganisms is entwined with its response to stresses such as antibiotics[1].

Future developments are likely to extend the technical capabilities of single-cell measurement and actuation, which, combined with new image processing and control algorithms, will enable increasingly powerful in silico control of in vitro biology.



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