

MEETING REPORT

Microbial signaling and systems biology

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Abstract

A report of the symposium on Signaling and Systems Biology held during the Society for General Microbiology Spring Meeting, 29-30 March 2010, Edinburgh, UK.

A two-day symposium on signaling and systems biology held recently in Edinburgh was attended by more than 1,000 microbiologists and covered both bacteria and eukaryotic systems. Systems biology means different things to different people. To some, the desire to generate integrated views of biological systems is reflected in a drive to define global-interaction networks based on synthetic genetic interactions, transcriptomic datasets, proteomics, protein-protein interaction data, metabolomics, glycomics, and/or some other form of 'omics'. To others, systems biology is more about the mathematical modeling of local (relatively small-scale) systems or processes to be able to predict with reasonable accuracy the dynamic behaviors of these processes or to reveal novel emergent properties.

Most systems-biology sessions held during microbiology meetings emphasize the 'omics' view. So it was good to enjoy a systems-biology symposium where the focus was on the modeling of dynamic responses, of stochastic single-cell behavior and of population heterogeneity. A broad range of topics, combined with the fact that many of the issues addressed by speakers were of broad relevance to other experimental systems, meant that attendees were able to compare and contrast diverse systems with their own system of choice. This report describes some of the highlights in discussions of the impact of randomness on cellular behavior, modeling of cell behavior, phagocytosis, and the development of new tools.

The impact of stochasticity upon molecular and cellular behaviors

The issue of molecular decision-making was addressed in the context of the phage lambda life cycle by Ido Golding

(Baylor College of Medicine, Houston, USA). Golding's group is interested in how a single phage takes decisions at critical points during the life cycle. For example, how do the physiology of the host cell and the multiplicity of infection influence the decision of a single phage to enter lysogeny or trigger the lytic cycle? Golding and colleagues' elegant approach exploits fluorescence microscopy of living cells to monitor infection by individual lambda phages and the resulting fate of the *Escherichia coli* host. They have combined this with mathematical modeling to test specific hypotheses that might account for the impact of specific parameters upon the decision to embark upon lysis or lysogeny. This work is providing important new insights into the relative importance of hidden variables and stochasticity in generating the biological noise that is observed experimentally in this system.

Andrzej Kierzek (University of Surrey, Guildford, UK) also discussed the impact of stochasticity, but in the context of the behavioral switching of bacterial populations in response to metabolic stimuli or stresses via two-component signaling. Stochastic switching can lead to phenotypic heterogeneity within isogenic cellular populations, and this could underpin the heterogeneous responses of some bacterial pathogens to particular host niches. Kierzek's simulations of two-component signaling accurately reflect the biphasic nature of an experimental bacterial population responding via two-component signaling. His modeling suggests that stochasticity arises through the low abundance of the histidine kinase, and that this switch behavior is reinforced and fixed by the autoregulatory feedback loop within the two-component system.

The impact of stochasticity on another biological system was highlighted in a talk by Gero Steinberg (University of Exeter, UK). The system under study was the bidirectional transport of vesicles along fungal hyphae via cytoskeletal motors on microtubule tracks. Steinberg's question related to the mechanisms by which the motor protein dynein picks up its cargo close to the hyphal tip before retrograde transport of this cargo back down the hypha. Steinberg's accurate quantification and modeling of transport dynamics for single dynein complexes yielded a fascinating conclusion: dynein accumulates at the microtubule ends and picks up the cargo in a stochastic way. In order to do this efficiently and prevent organelles falling off the microtubules and being lost, motor protein numbers are kept high by the stochastic

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accumulation of dynein and by a phosphorylation-dependent anchorage of motors. This finding expands previous models that assumed that the cargo-dynein interaction at the tip would be regulated and deterministic. Instead, regulation appears only to promote efficient endosome-to-dynein loading rather than driving the process *per se*. This unexpected observation provided one of the clearest examples in this symposium of the value of modeling approaches to dyed-in-the-wool molecular biologists.

Modeling of cellular behaviors

The *Saccharomyces cerevisiae* mating response provides a well studied example of regulation via a mitogen-activated protein kinase (MAPK) signaling pathway. The question addressed by Peter Swain (University of Edinburgh, UK) was to what extent does the Ste5 scaffold protein influence the sensitivity of MAPK signaling in response to the yeast alpha-factor mating pheromone? Swain has combined mathematical modeling with experimental dissection of the pathway to show that the tight transition in the dose-response curve for alpha-factor is enhanced by the Ste5 scaffold, via multiple Ste5 dephosphorylation events that promote the release of Fus3 (the yeast MAPK) from the scaffold. Swain also argued that, in general, hyperphosphorylation of unstructured protein domains might promote greater rigidity in these structures, thereby providing a general mechanism through which molecular switches or thresholds could be tightened. According to this view, protein phosphorylation could provide a means of controlling the sensitivity of cellular decisions to external inputs.

The establishment of cell polarity is important in a range of biological processes and KC Huang (Stanford University, Stanford, USA) is investigating the relationship of protein localization to cell polarity by asking how *E. coli* cells indicate their midline using rapid oscillations of Min proteins between the poles of the cell (the Min proteins are required for the correct positioning of the septum at cell division). Huang described how his team's mathematical model of the Min system can accurately reflect the observed oscillations in rod-shaped, round, and branched cells, suggesting that such oscillations may provide a general mechanism by which proteins can localize in response to features of cell geometry to define the planes of DNA replication and cell division.

Staying with the theme of cell division, Fred Cross (Rockefeller University, New York, USA) discussed the roles of cyclins during cell-cycle progression in budding yeast, and in his SGM Prize Medal Lecture, Paul Nurse (Rockefeller University, New York City, USA) discussed the analogous issue in fission yeast. They both reasoned that while contemporary cell cycles are controlled by the

temporal cycling of cyclin-dependent kinases (CDKs) with qualitative differences in substrate specificity, the ancient cell cycle might have been regulated through quantitative differences in the levels of an ancient CDK. According to this argument, a ratchet arrangement might have led to the activation of sequential events in the ancient cell cycle, each step in the cell cycle being triggered at a higher threshold concentration of this CDK. These two groups have produced evidence to support this hypothesis by managing to generate mutants that display reasonably normal cell-cycle progression while depending on only a single cyclin. Furthermore, cell-cycle progression could be manipulated by titrating the levels of this cyclin. By constructing a minimal cell-cycle oscillator dependent on the activity of a single cyclin-CDK, these groups have effectively used synthetic biology to test their hypothesis about fundamental aspects of cell-cycle regulation.

The metabolic switch from primary to secondary metabolism in the bacterium *Streptomyces* is fundamentally important to the production of many clinically relevant antibiotics. On one hand, Colin Smith (University of Surrey, Guildford, UK) and colleagues are combining transcriptomics, chromatin immunoprecipitation and microarray (ChIP-chip), and metabolic modeling to investigate how signaling networks control the physiological and metabolic changes at this transition. Their analysis of differentially affected metabolites (ADAM) has highlighted the Pho regulon as possibly playing a key regulatory role in this transition. On the other hand, Leena Nieminen (Strathclyde University, Glasgow, UK) described a discrete-continuum hybrid mathematical model of filamentous growth and pellet formation for *Streptomyces*, which she and colleagues are developing with a view to understanding the transition from primary to secondary metabolism in industrial-scale fermentations.

Cellular behavior during phagocytosis

The detection and phagocytosis of microbial pathogens by macrophages and neutrophils involves the integration of complex cellular systems and so lends itself well to a systems-biology approach. Robert Insall (CR-UK Beatson Institute for Cancer Research, Glasgow, UK) presented apparently heretical views on mechanisms of chemotaxis and cell movement, which relates to the initial detection and hunting down of microbial cells by host innate immune defenses. Insall suggested that chemotactic signals act by modulating the behavior of autonomously generated pseudopods rather than by causing their formation. He argued that this 'pseudopod-centered' view, which contrasts with the prevailing 'signal-centered' view, is supported by his empirical modeling of pseudopod emergence and by the lack of success of efforts to identify mutants that can detect attractants and

can migrate, but cannot connect the two and migrate towards the stimulus. In Insall's computational model, the host cells can undergo chemotaxis without needing receptor adaptation.

Having hunted down the microbial pathogen, the next step is for the macrophage to phagocytose the microbial invader. The team led by Brian Robertson and Robert Endres (Imperial College London, UK) is applying mathematical modeling alongside molecular and cellular approaches to increase our understanding of the early stages of phagocytosis. Their work has highlighted the extent to which biophysical forces can account for the rates of particle engulfment by innate immune cells, and the dependence of these processes upon the size, shape and elasticity of the particles being phagocytosed. Smaller particles seem able to be engulfed via passive mechanisms driven by biophysical forces, but energy-driven actin polymerization accelerates this process and is apparently required for the uptake of larger particles.

Thierry Soldati (University of Geneva, Switzerland) presented a strong case for the use of the social amoeba *Dictyostelium discoideum* as a model system for the phagocytosis and infection of macrophages by mycobacteria, because of its genetic, molecular and biochemical tractability. According to Soldati, many of the features of the *D. discoideum*-*Mycobacterium marinum* interactions he is studying recapitulate the infection of phagocytes by *M. tuberculosis*, the cause of human tuberculosis, in terms of phagocytic entry, genesis of a replication vacuole and cell-to-cell dissemination. Soldati argued that this model is proving useful for the dissection of conserved mechanisms of mycobacterial virulence and host resistance.

Cool tools and applications

Many new tools are applied to the quantification of single-cell or molecule behaviors. These included the elegant quantification of the transport dynamics for single dynein complexes (discussed above). Also, Holger Kress (Yale University, New Haven, USA) described a new technology that combines the use of holographic optical tweezers with chemically loaded poly(lactic-co-glycolic) acid particles. This powerful approach can be used to probe the influence of chemical gradients on chemotaxis, phagocytosis and development.

John McKinney (Swiss Federal Institute of Technology, Lausanne, Switzerland) described a powerful combination of microscopy and microfluidics to temporally track

and quantify the responses of single cells to environmental insults. This approach has been extended to allow relatively high-throughput screens for mutants with defects in specific responses. McKinney's group has used this approach to show that the ability of some cells ('persisters') to survive treatments with antibiotics such as isoniazid does not correlate with unbalanced cell growth, slow growth or the depletion of mycolic acids in the cell wall. They are now investigating whether pulsatile expression of catalase G relates inversely to the ability of individual cells to survive the antibiotic. By advancing our understanding of antibiotic persistence, these quantitative approaches will hopefully lead to significant improvements in antibiotic-based therapies.

Vanessa Sperandio (University of Texas South Western Medical Center, Dallas, USA) further highlighted the potentially high impact of detailed quantitative molecular dissection of pathogen-related processes. Having revealed the importance of cross-kingdom communication for the virulence of bacterial pathogens, her group is developing novel and effective antibiotics that target this communication. These antibiotics block evolutionarily conserved QseC signaling processes which mediate responses to host epinephrine (adrenaline).

The scheduling of this interesting and diverse symposium during a major microbiology conference helped disseminate systems-biology ideas amongst researchers in virology, bacteriology, mycology and parasitology. While these communities are relatively receptive to quantitative experimental approaches, many remain to be convinced that predictive mathematical modeling could be a valuable weapon in their scientific armory alongside their reductionist and genomic experimental tools. Hopefully this symposium, which beautifully illustrated the scientific and potential medical impacts of microbial systems biology, will have helped to temper their doubts.

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