

NEWS AND VIEWS

Physics takes another stab at biological design principles

Daniil Zhuravel and Mads Kærn

Ottawa Institute of Systems Biology, Department of Cellular & Molecular Medicine, Department of Physics, University of Ottawa, Ottawa, Canada

Molecular Systems Biology 13 December 2005; doi:10.1038/msb4100037

Physicists taking a first principle approach to biological research are making discoveries with broad implications for systems biology.

In an era when high-throughput, hypothesis-free science makes most of the noise, pioneering physicists are stirring things up by taking a first principle approach to investigate how noise in gene expression impacts living organisms. They use statistical laws of physics to tackle complex biological problems and make fundamental discoveries that change the way we think about biological systems.

Recent years have seen remarkable progress in our understanding of the origins and consequences of stochasticity in gene expression (for recent reviews, see Kaern *et al.*, 2005; Raser and O'Shea, 2005). These advances have been driven mainly by the formulation of biological hypotheses using stochastic process and dynamical systems theory. Experiments have confirmed that the fundamental statistical mechanical $1/\Omega$ scaling of relative fluctuation amplitude (i.e., the noise) and system size Ω (i.e., the number of molecules) imposes a fundamental limit on the precision of gene expression (Elowitz *et al.*, 2002), and that population variability in the expression of single genes depends on DNA-encoded parameters in accordance with relationships predicted by stochastic theory (Ozbudak *et al.*, 2002; Blake *et al.*, 2003; Raser and O'Shea, 2004). Additionally, as predicted by theoretical physicists decades ago (Horsthemker and Lefever, 1984), it has been shown experimentally that increased noise in a transcriptional regulator can cause the emergence of distinct cellular expression states (Blake *et al.*, 2003) and that noisy gene expression can drive stochastic switching between such states (see e.g., Becskei *et al.*, 2001; Isaacs *et al.*, 2003; Ozbudak *et al.*, 2004; Acar *et al.*, 2005; Weinberger *et al.*, 2005).

Although the implications of these fundamental discoveries have yet to be fully realized, they have already contributed to an ongoing change in the perception of biological systems and function—the concept of a deterministic relationship between genotype, environmental cues and cellular phenotype, a contrivance of experimental necessity and convenience, is being dismantled. It is now more generally accepted that living organisms are not regulated with clockwork precision and that epigenetic phenotypic variation among supposedly identical individuals plays a more prominent role in key areas like development and disease than previously anticipated.

Inherently stochastic effects, such as limited precision in gene expression and random switching between phenotypic

states, may also have had a profound impact on evolution. On the one hand, as stochastic effects deteriorate the fidelity of regulatory signals, the minimization of noise generation and optimization of functional robustness to intrinsic and extrinsic fluctuations are important determinants of organismal fitness. In both cases, physics has contributed profoundly to contemporary research. For example, the demonstration that selective pressures have acted to minimize fluctuations in the expression of essential genes (Fraser *et al.*, 2004) is based on a statistical mechanical model, and many biological design principles used to ensure functional robustness (for reviews, see Kitano 2004; Stelling *et al.*, 2004) have analogies in dynamical systems and control theory. On the other hand, stochastic effects provide mechanisms for phenotypic diversification that can increase the probability of survival during times of stress. Physicists are also in this case among those setting the agenda.

As discussed above, gene expression noise can induce transitions between distinct expression states without genetic mutations. Such epigenetic stochastic phenotypic switching is believed, for example, to be an important factor in the persistence of bacterial infections following antibiotic treatment. In a recent investigation (Kussell and Leibler, 2005), researchers at Rockefeller University's Laboratory of Living Matter and Center for Studies in Physics and Biology took the investigation stochastic phenotypic switching to a new level. Using phenomenological modeling, they evaluated conditions where stochastic phenotypic switching should confer a selective advantage compared with that occurring as a response to environmental cues. The premises of their first principle model are minimal: cells switch phenotype at a rate that is either independent of the environment (stochastic switching) or strongly influenced by it (responsive switching), and multiply at a rate that depends on the environment and the phenotypic state of the cells. Responsive switching requires the expression of a sensing machinery that is associated with a specific 'sensing cost', whereas the alternative strategy, stochastic switching, is characterized by a 'diversity cost' due to the production of poorly adapted individuals. Based on calculations of Lyapunov exponents, the authors are able to conclude that a stochastic switching mechanism is superior to a sensor-response mechanism if the environment changes infrequently. Hence, in an unpredictable environment where organisms are confronted with rare changes, a stochastic switching design principle will be selected over one that is

responsive as an energy efficient means of 'bet-hedging' (Kussell and Leibler, 2005).

The findings by Kussell and Leibler raise the question of how evolution has acted upon DNA-encoded parameters and the wiring of regulatory networks to take full advantage of noisy gene expression for phenotypic diversification. In this case, physical analysis may be used to provide insight into the link between gene expression noise, stochastic phenotypic switching and regulatory network design. A clear example is a recent investigation of the galactose utilization system of yeast *Saccharomyces cerevisiae*. This network, which is traditionally viewed as providing responsive phenotypic switch, contains three nested feedback loops of which two are positive and one is negative. Its primary function is mediated by the positive feedback loops, which upregulate the expression of genes required for galactose utilization when this sugar is present in the environment. However, the negative feedback loop counteracts one of the positive feedback loops yielding an overall network design that seems counterproductive from a deterministic point of view. To investigate this further, researchers in the Department of Physics at MIT conducted an analysis based on the traditional physical concepts of potential energy landscapes, energetic barriers and escape times (Acar *et al.*, 2005). As predicted by this analysis, it was demonstrated experimentally that the negative feedback loop architecture increases the rate at which cells stochastically switch between expression states, suggesting that the function of the negative feedback is to prevent cells from being trapped in suboptimal phenotypic states. Hence, physical theory enables a formal analysis that successfully links network topology and design to biological function.

Perhaps the most significant result of the above-mentioned investigations, as well as studies not mentioned in this brief commentary, is that they clearly demonstrate how physics-based theory can be used to make fundamental discoveries when applied to complex biological problems. As demonstrated on numerous occasions (for recent examples, see Brandman *et al.*, 2005; Dekel *et al.*, 2005), such first principle approaches hold the promise of providing the fundamental understanding of biological network function and design required to interpret and rationalize data generated by high-throughput experiments.

References

- Acar M, Becskei A, van Oudenaarden A (2005) Enhancement of cellular memory by reducing stochastic transitions. *Nature* **435**: 228–232
- Becskei A, Seraphin B, Serrano L (2001) Positive feedback in eukaryotic gene networks: cell differentiation by graded to binary response conversion. *EMBO J* **20**: 2528–2535
- Blake WJ, Kaern M, Cantor CR, Collins JJ (2003) Noise in eukaryotic gene expression. *Nature* **422**: 633–637
- Brandman O, Ferrell Jr JE, Li R, Meyer T (2005) Interlinked fast and slow positive feedback loops drive reliable cell decisions. *Science* **310**: 496–498
- Dekel E, Mangan S, Alon U (2005) Environmental selection of the feed-forward loop circuit in gene-regulation networks. *Phys Biol* **2**: 81–88
- Elowitz MB, Levine AJ, Siggia ED, Swain PS (2002) Stochastic gene expression in single cells. *Science* **297**: 1183–1186
- Fraser HB, Hirsh AE, Giaever G, Kumm J, Eisen MB (2004) Noise minimization in eukaryotic gene expression. *PLoS Biol* **2**: 834–838
- Horsthemker W, Lefever R (1984) *Noise-induced Transitions. Theory and Applications in Physics, Chemistry, and Biology*. Berlin: Springer Verlag
- Isaacs FJ, Hasty J, Cantor CR, Collins JJ (2003) Prediction and measurement of an autoregulatory genetic module. *Proc Natl Acad Sci USA* **100**: 7714–7719
- Kaern M, Elston TC, Blake WJ, Collins JJ (2005) Stochasticity in gene expression: from theories to phenotypes. *Nat Rev Genet* **6**: 451–464
- Kitano H (2004) Biological robustness. *Nat Rev Genet* **5**: 826–837
- Kussell E, Leibler S (2005) Phenotypic diversity, population growth, and information in fluctuating environments. *Science* **309**: 2075–2078
- Ozbudak EM, Thattai M, Kurtser I, Grossman AD, van Oudenaarden A (2002) Regulation of noise in the expression of a single gene. *Nat Genet* **31**: 69–73
- Ozbudak EM, Thattai M, Lim HN, Shraiman BI, van Oudenaarden A (2004) Multistability in the lactose utilization network of *Escherichia coli*. *Nature* **427**: 737–740
- Raser JM, O'Shea EK (2004) Control of stochasticity in eukaryotic gene expression. *Science* **304**: 1811–1814
- Raser JM, O'Shea EK (2005) Noise in gene expression: origins, consequences, and control. *Science* **309**: 2010–2013
- Stelling J, Sauer U, Szallasi Z, Doyle III FJ, Doyle J (2004) Robustness of cellular functions. *Cell* **118**: 675–685
- Weinberger LS, Burnett JC, Toettcher JE, Arkin AP, Schaffer DV (2005) Stochastic gene expression in a lentiviral positive-feedback loop: HIV-1 Tat fluctuations drive phenotypic diversity. *Cell* **122**: 169–182