Genome Biology

Meeting report

Biology inspires engineering

Reine Byun and Attila Becskei

Address: Institute of Molecular Biology, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland.

Correspondence: Attila Becskei. Email: attila.becskei@molbio.uzh.ch

Abstract
A report of the Cold Spring Harbor Laboratory/Wellcome Trust Meeting on Engineering Principles in Biology, Cambridge, UK, 14-16 October 2009.

Engineering has predominantly interacted with physics, while biology has played the second fiddle for a long time, even if biologically inspired contrivances, such as aircraft imitating bird flight, can be traced back as far as Classical Antiquity. A rapid intensification of the interplay between engineering and biology occurred in the second half of the 20th century, as evidenced by magnetic resonance imaging (MRI), the artificial heart pacemaker, and production of human recombinant insulin. The fifth annual meeting of Engineering Principles in Biology held recently in Hinxton, on the outskirts of Cambridge, presented engineering successes inspired by biology and explored the principles that have been extracted from the workings of living organisms to aid engineering, especially biomedical engineering. The most frequently recurring principles were optimal design, economy in design, and the harnessing of and coping with the variability inherent in biological systems.

Optimal design of structures

Robert Full (University of California, Berkeley, USA) opened the meeting with a discussion of his research in neuromechanical systems biology. By integrating disciplines encompassing biology, engineering and physics, he and his team have built models based on the locomotion of animals ranging from cockroaches to geckos. Stability analysis of these models revealed that mechanical features of the animals alone are sufficient to stabilize the moving body against perturbations due to destabilizing forces or the unevenness of the environment. Neuronal feedbacks are required only for complex locomotive actions. This research inspired the engineering of robots that can climb trees or overcome obstacles such as mud lakes by rotational paddling movements.

The importance of inherent mechanics over control was echoed in the presentation by Raymond Goldstein (University of Cambridge, UK) who has studied the synchronous flagella-driven swimming of the colonial alga *Volvox*. Despite the lack of a nervous system, coordinated movement of the spherical colonies can be attained by the hydrodynamical forces of the whirling water, which is set in motion by rotation of neighboring colonies.

Optimal design is not restricted to the realm of organisms but is also the coveted goal of macro-molecular engineering. Lisa Hall (University of Cambridge, UK) explained how glucose oxidase can be used as a biosensor for monitoring blood glucose levels, which could improve the treatment of diabetes. The enzymatic oxidation of glucose produces an electron that can be directed to an electrode, generating a signal for each glucose molecule oxidized. However, the normal cellular glycosylation of the enzyme efficiently prevents the electron from erroneously jumping out of the protein, whereas just the opposite is required for biosensor design. Deglycosylation and optimal geometric alignment of the enzyme with the electrode were able to maximize electron transfer and signal generation.

Economy in design

The principle of economy in design resonates across disciplines. This is not surprising given that engineering and organisms face the same constraints. The primary aim of engineering is to invent objects or functions for human use, and only economical design makes their widespread use possible. Organisms are subject to similar restrictions as a result of the energy requirements for exploring new efficient designs during evolution - given that energy resources are limited. Seth Grant (Wellcome Trust Sanger Institute, Hinxton, UK) suggested that evolution heavily recycles molecules. Proteomic analysis of the mammalian neuronal synapse revealed that 25% of the synaptic proteins are conserved in as simple an organism as yeast. In yeast, orthologs of synaptic signal transducers function in the transmission of environmental signals such as pheromones. According to Ralph Greenspan (Neurosciences Institute, San Diego, USA), such similarity in proteins possibly explains why a large number of behaviors share similar phenomenology and neurochemical control mechanisms despite the lack of similarity of nervous systems between simple and complex animals.

Simon Laughlin (University of Cambridge, UK) pointed out that the nervous system consumes the most energy per mass of any organ in an animal and that signal transmission in the nervous system faces energetic and geometric constraints. For example, a graded (analog) response in the neuronal body has a higher information-processing capacity than a binary (digital, spiking) response in the axons even though they have similar energy costs. On the other hand, signals are more efficiently propagated to large distances using binary encoding. Comparison of related insect species revealed that evolution has promoted the formation of economical cellular structures and nervous system networks.

Addressing the question of improvements in DNA microarray technology, Olgica Milenkovic (University of Illinois, Urbana-Champaigne, USA) proposed that economy in signal processing, or 'compressed sensing', can improve design. The idea of compressed sensing builds on the supposition that most sampled signals are zero or negligibly small. For example, the olfactory system uses compressed sensing to distinguish roughly 10,000 different odors. Instead of assigning each odor a unique receptor, the olfactory system uses a small collection of combinatorial testing sensors, as each smell consists of a limited number of basic odors. Milenkovic showed that understanding how to encode information in a compressed way can help to find suitable probe sequences and design microarrays for detecting microorganisms in an environmental sample. Using these principles, a large number of DNA targets (microorganisms) can be detected with the minimum number of spots on the microarray.

Phenotypic and genetic variation

In classical engineering, variability is simply a nuisance. In contrast, architectural (genetic) and functional (phenotypic) variations can often be harnessed in biological applications. Dan Valente (Cold Spring Harbor Laboratory, Cold Spring Harbor, USA) described how genetic variability can be used to identify new genes. He and his colleagues developed a novel screen for genes involved in memory by imposing artificial selection on a fruitfly population for a memory phenotype. Statistical analysis of the genotypes of the organisms with improved memory helped to identify genetic interactions and new genes underlying memory.

Stem cells are now at the forefront of biomedical engineering aimed at the regeneration of tissues of multiple cell types. A central question in stem-cell research is how to derive multiple distinct stable phenotypes from the same genotype. Illustrating the problem, Alfonso Martinez-Arias (University of Cambridge, UK) showed that one of the key regulators of stem-cell development, the homeodomain transcription factor Nanog, displays two expression states in a stem-cell population. When an individual cell expresses high levels of Nanog, it remains pluripotent. However, such cells can switch back to a low expression state, from which the cells can either return to the high-Nanog state or differentiate into a specific cell type.

Marie Csete (Emory University, Atlanta, USA) discussed the fact that the engineering of tissues derived from adult multipotent stem cells and induced pluripotent stem cells will have to cope with the effects of aging, and that this will require many different approaches, as alteration of a single pathway has only partial effects. For example, she reported that overexpression of the antioxidant enzyme superoxidase dismutase 2 (SOD2 or MnSOD) in myoblasts helped to preserve the integrity of mitochondrial DNA and myoblast *in vitro* differentiation capacity with aging. However, muscle mass was not increased in aged SOD2-overexpressing transgenic mice.

One of us (AB) explained how chromosomal epigenetic processes can stabilize cell phenotypes. Binding of eukaryotic transcription factors - activators and repressors - to DNA leads to recruitment of enzymes of opposing functions that induce structural changes in chromatin constituting an 'epigenetic code'. A mathematical model of these epigenetic processes revealed that the resulting gene expression can be both monostable (graded) and bistable (switch-like), depending on the spatial distribution of repressor-binding sites. The transitions between the two states are triggered by stochastic processes.

Analytical insight into the mathematics of stochastic processes is limited. Mustafa Khammash (University of California Santa Barbara, USA) presented a new approach for solving master equations even for time transients by considering transitions between molecular concentrations only in the realistic range of concentrations. Johan Paulsson (Harvard University, Boston, USA) combined information theory with mathematics of stochastic processes that enables the inference of noise even from indirect measurements when the details of intervening processes remain poorly characterized.

In precise developmental processes random noise can be detrimental. Julian Lewis (Cancer Research UK London Research Institute, London, UK) presented work on the cellular timers that control the number and length of the embryonic somites that give rise to the segmented structure of the vertebrate anterior-posterior axis. One somite is produced during each cycle of oscillating expression of the *Her1* and *Her7* genes, which are regulated by the Notch signaling pathway. In zebrafish, the oscillations in individual cells are quite noisy but the Notch-mediated cell-cell communication between neighboring cells synchronizes the oscillations. The oscillation in *Her1* and *Her7* expression is driven by a transcriptional negative feedback loop. The period of the oscillations, and hence the length of individual somites, are determined by the delay due to transcriptional elongation and translation. Frank Doyle

(University of California, Santa Barbara, USA) discussed examples where synchronization can attain unusually high degrees of precision and robustness. In coral reproduction, global cues in the environment (sunlight and moonlight) combined with local coupling (hormones) lead to the precisely timed annual event of all corals in an entire bay spawning during the same 30-minute period.

Putting things together

John Doyle (California Institute of Technology, Pasadena, USA) emphasized the importance of understanding complex systems in terms of layers. Different layers are characterized by different trade-off strategies. Some layers face strong energy constraints while others face noise. Different design and control strategies will be required for each layer.

It is difficult to predict the future of biological engineering. Engineering of molecular biosensors is already moving out of its infancy. The engineering of cells and tissues and their interface with mechanical-electrical devices has just started. Currently available devices may provide interesting foresights: dynamic heart pacemakers sense blood oxygen, body temperature and messengers such as adrenaline, and use this information to calculate the frequency of the heartbeat so that the adjusted heartbeat rate meets the exerted physical effort. In a similar vein, cells can be connected to or rewired by synthetic elements to sense and perform relevant calculations in the brain or other tissues so that the desired outputs are attained. There was a feeling that the time has arrived to systematically explore the possibilities and principles of connecting these very different things.

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