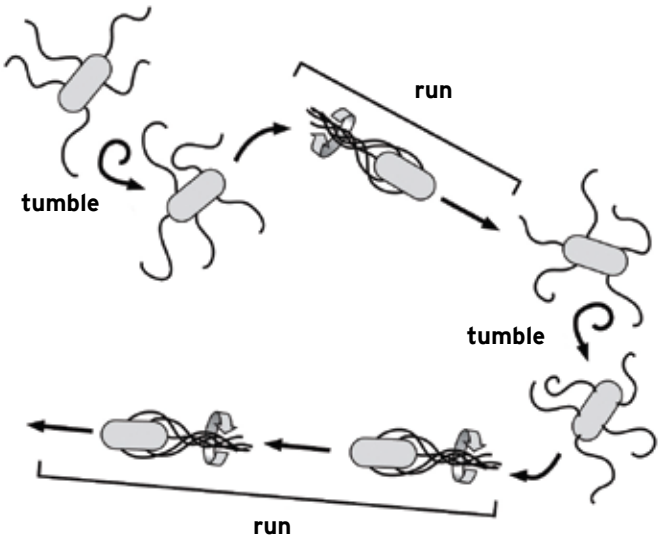
Redesigning a Bacterium Control System

Systems Engineering for Biology

"Systems biology" and "synthetic biology" are two major growth areas within biology. For these efforts to be successful in the long run, a systems engineering framework for biological circuit design must be built. Recent successes in building synthetic circuits that provide novel biological function (such as an oscillator or a programmable switch) demonstrate that the basic technology is at hand. However, initial attempts to systemize synthetic biology have not yet succeeded in building working systems from libraries of standard parts. The challenge lies in exploiting the modulator of molecular biology while at the same time gaining enough insight into the fundamental processes to understand key issues in building larger and larger systems from individual components.

Target Problem: Bacterial Chemotaxis

Chemotaxis is the process by which bacteria and other microorganisms sense chemical signals in the environment and adjust their motion to either move toward the signal (chemoattractants) or away from the signal (chemorepellants). The chemotaxis system in E. coli consists of a sensing system that detects the presence of nutrients, an actuation system that propels the organism in its environment, and control circuitry that determines how the cell moves in the presence of chemicals that stimulate the sensing system. Each of these subsystems is implemented via proteins inside the cell, with communication, computation, and control intermingled through the various molecular reactions that occur. Many chemotaxis mechanisms are stochastic in nature, with biased random motions causing the average behavior to be either positive, negative, or neutral (in the absence of stimuli).



Physical Biology of the Cell

Scientists are able to genetically modify microbiological organisms so that they produce certain chemicals or change their behavior. Can we redesign the control systems in bacteria (including implementation!) so that we can program their behaviors in response to external stimuli? Possible applications include new types of medical treatments, new methods for environmental remediation, and in vivo sensing systems. Initial demonstrations have successfully modified the sensing system, but true reprogramming would include systematic methods for designing the control system to have specified closed-loop properties, including stability, performance, and robustness.

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Chemotaxis Control System

The components that implement chemotaxis are becoming increasingly well understood. For example, flagellar motors have been imaged in detail (Figure 1), showing the incredible structure present in these systems. The cryo-electron micrograph in the top figure shows the molecular components of the motor, with the components labeled in the lower figure. The motor sits between the outer and inner membranes (OM, IM) and consists of a rotor stator and other elements.

The basic control circuitry (Figure 2) consists of membrane-bound proteins for sensing chemical signals (ligands) external to the cell, signal transduction pathways that communicate the presence or absence of ligands, and feedback regulation mechanisms that modify the sensitivity of the sensor and act as a form of integral feedback. The effect of this sensing and control system is to modulate the flagella such that they spin either clockwise or counterclockwise, resulting in either tumbling or nontumbling motion. Dynamical models have been developed that describe the various processes present in chemotaxis and give insight into the system-level properties.

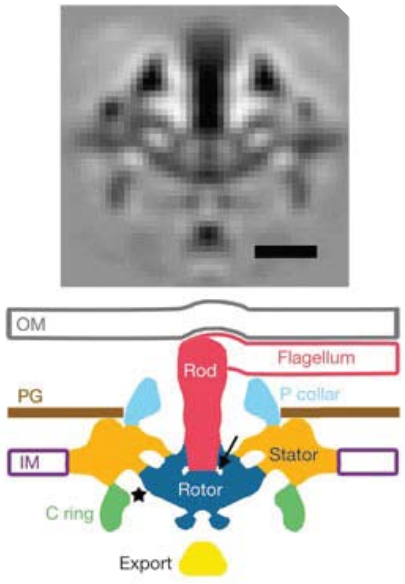

Figure 1: Detailed image of the flagellar motors

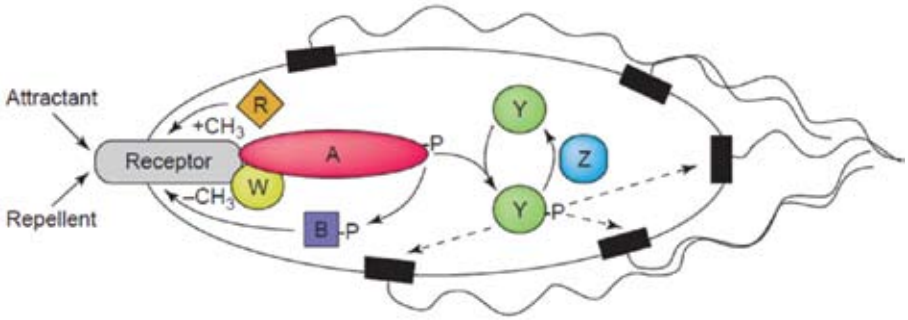

Figure 2: Basic control circuitry

Design Specification and Properties

We seek to design a control circuit that can be inserted into a bacterium and that will modify its behavior so that the bacterium can be used to deliver a drug to a specific area in an organism. The condition the bacterium responds to should be substantially more specific than current drug treatments, targeting a very localized area in the body or an organ, for example. The drugs that are released can either be synthesized within the bacterium or stored in some inert form and released at an appropriate time and location.

Rather than just experimenting with existing cellular organisms and genetic mutations, the circuitry used to accomplish this task should be designed in the usual engineering sense. This includes developing a model that predicts the behavior of the control circuit in the system and can be used to iterate on the design before synthesizing the DNA that encodes the circuit. Current technology already allows simple biological circuits to be built and inserted into bacterium, and there have been many genetic engineering demonstrations to modify the behavior of existing systems. The goal in this grand challenge is to move from a culture of experimentation and invention to one of systematic modeling, analysis, and design.

And there's much more!

Bacterial chemotaxis is just one of many interesting processes implemented using biomolecular feedback systems.

For further information: Nature special issue on synthetic biology, http://www.nature.com/nature/journal/v438/n7067/index.html; Registry of Standard Biological Parts, http://parts.mit.edu/