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BOURNS A265

Design Principles of Protein Switches, Genetic Circuits, and the Genetic Code.

The complexity of biological systems arises from the web of relationships between biological macromolecules, metabolites and signaling molecules. We seek to understand Nature's design principles and exploit them for establishing new relationships. We have created enzymes that behave as switches in which catalytic activity is turned on by biological molecules of our choosing. Our protein switch design algorithm views all natural proteins as an extensive parts list of potential input and output modules from which to build switches. We employ directed evolution algorithms to recombine these modules in ways such that communication is established between previously unrelated functions. We have used this approach to create protein switches that selectively render cancer cells susceptible to drug treatment. In addition, we have established design principles for building genetic circuits that are externally tunable from outside the cell. We have employed bacteria that harbor such circuits, together with a new mutagenesis technique called comprehensive codon mutagenesis, to extensively explore the fitness landscape of an antibiotic resistance protein. Our results indicate that the genetic code is arranged to facilitate evolution by making beneficial mutations more likely. We propose that the genetic code's architecture results in part from selective pressure for the evolvability of proteins.

