Toward the Design Principles of Molecular Machines

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Life is Fundamentally Out of Equilibrium

From the largest mammals down to unicellular organisms, living things manifest orderly structures, processes, and flows that are inconsistent with a state of thermal equilibrium [1]. Cells, the micron-scale structural units of life, maintain out-of-equilibrium conditions of chemical concentrations, charge and molecular distributions, and unequal pressures [2,3]. This ubiquity of out-of-equilibrium states flies in the face of the Second Law of thermodynamics, which pushes towards increased entropy in the absence of coordinated free energy input.

Life Stays Out of Equilibrium Using Molecular Machines

Cells rely heavily on many types of molecular machines—macromolecular complexes that convert between different forms of energy—to achieve various tasks that create and maintain low-entropy structure. The

These so-called fluctuation theorems relate reversibility to work and free energy changes. More general nonequilibrium between the adjacent metastable states, giving maximal force

Sufficiently slow processes remain near equilibrium, and provide a universal near-equilibrium result for irreversibility for a given amount of energy dissipation [34]. For a simple model of energy storage, irreversibility can be significantly increased above the near-equilibrium result by coupling storage of moderate-sized energy packets with moderate mechanical motion [36], suggesting the energy and length scales of molecular machines may be constrained by a requirement for forward progress [37].

FUTURE PROSPECTS

Stochastic Driving

Much of the theory above focuses on deterministic driving of a system, where a control parameter follows a fixed temporal schedule. Biomolecular machines do not typically experience an experimentalist deterministically changing a control parameter – instead they operate autonomously, responding to the stochastic fluctuations of coupled nonequilibrium systems. Recent research [38,39] has opened new vistas on the physical principles governing autonomous molecular machines driven by stochastic protocols.

Fundamental Understanding of Constraints for Biology

Although molecular machines are built and operate inside living cells, they are subject to physical constraints. In this article, we have outlined how molecular machines operate out of equilibrium to overcome viscous forces in the face of fluctuations. We also describe recent developments for efficient system control and generation of irreversible dynamics. This emerging understanding of the statistical physics of driven microscopic processes points toward general principles for molecular machine operation.

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