Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies

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Recommended and a commentary by Steve Berry, University of Chicago

In 1997, C. Jarzynski published a paper ("Nonequilibrium Equality for Free Energy Differences," Phys. Rev. Lett. 78, 2690-2693 (1997)) that caused a considerable stir. This paper showed how changes in free energies between two equilibrium states could be determined, not just limited, from a set of measurements of finite-time processes. The essential new step here is averaging not the work done but its exponential, in units of kT.

The principal next step in this development was the paper by G.E. Crooks, "Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences," (Phys. Rev. E 60, 2721-2726 (1999)). This paper shows a remarkable property of fluctuations in nonequilibrium systems. Specifically, this paper relates the probability distributions of fluctuations for forward and reverse processes between a given pair of end points, for processes occurring in finite time. Previous theoretical studies had related the forward and reverse fluctuations for reversible processes. These were interesting advances, certainly, but did not carry the surprise that Crooks' theorem has. To those of us trained in classical thermodynamics, it is not the least bit obvious that the fluctuations of an irreversible process should be related in any straightforward way to those of the irreversible process in the opposite direction.

Now we come to the recent advance, an experimental single-molecule study by Collin et al., which motivates this commentary "Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies" D. Collin, F. Ritort, C. Jarzynski, S. B. Smith, I. Tinoco Jr. and C. Bustamante Nature 437 (8), 231-234 (2005). This paper demonstrates with several unambiguous experiments how it is possible to extract thermodynamic information, specifically free energy changes, from sets of data taken from single-molecule, nonequilibrium processes. The heart of the method is, as the title indicates, the Crooks fluctuation theorem. This theorem shows a striking relation between the probability distributions of the work fluctuations in forward and backward processes, whether or not they are close to equilibrium. The experiments in this paper were done mostly as single-molecule pulling of a specific RNA and a single-base mutant of that molecule. In particular, although the work distributions for the forward and backward pulling processes have very different shapes, the points of crossing of the pairs of distributions were virtually independent of the force imposed. This point of crossing of the distributions is the point at which, according to the Crooks theorem, one can extract the free energy. The paper opens an exciting way to carry out a wide variety of thermodynamic determinations, especially of biomolecules, from single-molecule experiments. The only apparent limitation seems now to be that if the forward and backward processes are very far from equilibrium, the work distributions for forward and backward processes may get so far apart that it becomes difficult to distinguish where they cross, simply because the crossing for such cases could be well out in the tails of the distributions. The cases reported, even those fairly far from equilibrium, did not encounter this difficulty, so one can be optimistic that this will be a useful way to study biomolecules and other polymers.