

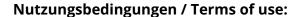


## Analysis of reversible two-state systems under force

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simple analytical results for the distribution and moments of the transition force. However, the irreversible model is a first-order approximation which is only valid very far from equilibrium, or under specific irreversible circumstances. Furthermore, the irreversible model has led many to conclude that force spectra that deviate from linearity unequivocally represent multiple energy barriers along the intermolecular reaction coordinate.

We show that irreversible first-passage analysis, which fails for two-state systems, can be replaced by analyzing the conditional single-passage time between the two states. We find simple solutions for the forward and time-reversed distributions of the transition force, and the isothermal work, which analytically satisfy the fluctuation theorem. We also define how stochastic force trajectories should be measured when multiple forward-reverse events occur. By accounting for reversibility, we show that both the distribution and the first moment of the rupture force significantly differ from the irreversible model and clearly connect with the equilibrium regime. We find that the resulting spectrum of rupture forces is not monotonic with log of the loading rate, but follows at least two major regimes - a linear-response and a dynamic response - with the linear regime tending to the equilibrium free energy change. We validate our analytical results with simulations and experimental data on bond rupture and protein unfolding.

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The dissociation of inter- and intra-molecular bonds by force is a process that occurs regularly in biological machinery and many cellular events. Forcing such transitions in a controlled environment has also emerged as a modern practice in the laboratory for studies of the physical principles of bond lifetimes and protein unfolding. It is commonly assumed that force-driven dissociation is irreversible, which leads to the analysis of first-passage statistics and results in