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PHYSICAL BIOLOGY

A fresh eye on nonequilibrium systems

A noninvasive probe reveals nonequilibrium behavior in systems at steady state

By **Jean-Francois Rupprecht**^{1} *and* **Jacques Prost**^{1,2,3}
Mechanobiology Institute, National University of Singapore, 117411 Singapore. ^{2}*Laboratoire Physico Chimie Curie, Institut Curie, PSL Research University, CNRS, 75005 Paris, France.* ^{3}*Sorbonne Universities, UPMC Univ Paris 06, CNRS, Laboratoire Physico Chimie Curie, 75005 Paris, France. Email: jacques.prost@curie.fr*

According to the physicist Richard Feynman, a system is in equilibrium when "all the fast things have happened but the slow things have not" (*1*). This definition really applies to a system at steady state, which can either be in thermodynamic equilibrium or in a nonequilibrium steady state. Most systems in nature are not in equilibrium; they exchange fluxes of matter or energy with their surroundings or undergo chemical reactions. When the fast "things" have happened but the slow ones have not, such systems are in a nonequilibrium steady state. The properties of nonequilibrium steady states are currently under intense theoretical investigation, and their similarities and differences with thermodynamic equilibrium states are starting to emerge (*2*). On page 604 of this issue, Battle *et al*. (*3*) propose a new way of probing the nonequilibrium nature of an apparent steady state and demonstrate how such nonequilibrium dynamics can be identified.

Being able to characterize the nature of nonequilibrium steady states is critical because it is not possible to use standard thermodynamic concepts to study them. However, it can be difficult to determine whether the observed dynamics differ from that expected for a system at thermal equilibrium. In cellular processes, for example, it is often unclear whether particular stochastic fluctuations of cellular components (e.g., proteins, membranes, organelles) are driven by thermal or non-thermal processes. This is important because, in contrast to thermal noise, non-thermal noise can generate a spontaneous motion even in the absence of an external driving force (*4*). This possibility is well illustrated by the Feynman-Smoluchowski ratchet, where a paddle and a pawl are connected by an axle on which a ratchet is fixed (*1*). When the whole system is kept at a uniform temperature, no net motion is possible: Perpetual motion at thermal equilibrium does not exist. As soon as the paddle and the pawl are exposed to different temperatures, the ratchet can rectify noise, and the axle can rotate and perform useful work—for instance, lifting a weight. Similar concepts apply to isothermal molecular motors that play a fundamental role in biology. In that case, the energy is derived from chemical reactions (*5*).

Until now, there was essentially only one method for determining whether a steady state is at equilibrium or not. This method relies on the conventional fluctuation dissipation theorem (FDT). In the context of

Einstein's seminal paper on the Brownian motion of a small particle in a fluid (*6*), the FDT takes the form of a proportionality relation between the diffusion coefficient of the particle at rest and the dissipative frictional force that an operator would need to balance in order to pull the particle in a particular direction. In a more general context, the FDT states that the time derivative of the two-point correlation function— a measure of the intensity of spontaneous fluctuations—is proportional to the response function, which quantifies the mean reaction exerted by the environment due to an external perturbation. In both contexts, the proportionality factor provides a measure of the temperature of the system. In general, one can define a frequency-dependent effective temperature, $T_{\mathrm{eff}}(w)$. For a system in thermodynamic equilibrium, $T_{\mathrm{eff}}(w)$ is constant and equal to the sample temperature; any deviation indicates that the system is out of equilibrium. The simplest violation concerns systems for which the proportionality relation still holds, but where the extracted temperature differs from that of the surrounding passive material. More pronounced deviations have been observed in living sound-detecting cells (hair cells) (*7*). The effective temperature is found to be negative at low frequency, to diverge at a characteristic frequency, and to become positive at high frequency. In contrast, as one should expect, dead cells, which are at thermal equilibrium, exhibit a constant effective temperature that is equal to the temperature of the sample.

In other cases, the situation is more complex. For instance, it has taken decades to pinpoint the out-of-equilibrium nature of red blood cell membranes. Initial indications of the out-of-equilibrium nature of these fluctuations were obtained by reducing the adenosine triphosphate (ATP) content of the cells. Although suggestive of the violation of the FDT, this method did not provide a definitive demonstration, because ATP could also influence purely passive properties, such as membrane elasticity. More recent work showing an unequivocal violation of the FDT finally provided a solution to this long-standing problem (*8*). Despite these successes, searching for FDT violations as a method to identify nonequilibrium steady states suffers from several drawbacks. First, this method requires that two separate measures of the correlation function and of the response function be available. Second, the measure of the response function is intrinsically invasive, because it relies on the application of controlled external perturbations. Furthermore, it is not always easy to guarantee that the measurements are made within the linear response regime—that is, involving small perturbations.

Other proposed methods have, until now, failed to be convincing as effective tools for characterizing nonequilibrium steady states. Higher-order time-correlation functions can reveal out-of-equilibrium conditions (*9*) but have not been fully exploited yet because of technical challenges. The existence of non-Gaussian distribution fluctuations has been associated in the literature with a nonequilibrium steady state. However, equilibrium systems can exhibit non-Gaussian fluctuations—e.g., in the presence of anharmonic potentials (*10*)—and nonequilibrium systems can exhibit Gaussian fluctuations (see the analysis presented in the supplemental materials of Battle *et al.*).

Battle *et al.* use the knowledge that fluxes between any microstate defining a system are pairwise balanced at equilibrium, as proposed by Boltzmann. The critical step was to define such a microstate at an intermediate spatiotemporal scale that is sufficiently small to observe a large number of transitions, while sufficiently large to be compatible with the time resolution of the experiment. The averaged flux between microstates is represented as a vector within a phase space plot. Within this phase space, at equilibrium there can be neither a flux loop nor a vortex involving three or more states, as a direct consequence of Boltzmann's condition for equilibrium. Conversely, if loops or vortices are observed, then the system is necessarily out of equilibrium.

A simple theoretical example is considered by the authors, which enables a direct comparison of equilibrium and nonequilibrium situations. The system consists of two elastically coupled Brownian particles in contact with two reservoirs generating Brownian noise at two prescribed temperatures. A prominent vortex appears when the two temperatures differ. More elaborate biological examples such as the beating of the *Chlamydomonas reinhardtii* flagellum or of the primary cilia of epithelial cells are also described by the authors. Battle *et al.*'s new insight also lies in designing an efficient bootstrap allowing for the correct use of experimental data.

In contrast to previous methods, the technique developed by Battle *et al.* requires neither the invasive injection of probes nor external perturbations of the system under study. Instead, it relies only on the observation of spontaneous fluctuations of the system itself using simple time-resolved imaging. The method is not limited to mechanical degrees of freedoms such as flagellar position, but can be extended to chemical or electrical variables, such as electron currents or calcium concentration. Its main limitation stems from the fact that systems in nonequilibrium steady states, and which thus break detailed balance at the microscopic scale, might, in some circumstances, restore detailed balance at a larger scale (*11*). Whether the theoretical system of (*11*) can be experimentally relevant or not is still an open question. The flux method presented by Battle *et al.* has the potential to become a standard tool not only in biological physics, but also more generally in the study of fluctuating systems.

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