Similarly, new dating results reported by Reichow *et al.* on page 1846 of this issue (*6*) document the subsurface extent of the Siberian Traps nearly 1000 km westward from the previously known limits of the province. The authors have analyzed drill-core samples from the West Siberian Basin (WSB). The new dating provides the first definitive evidence linking them to the same magmatic event.

Using the ^{40}Ar/^{39}Ar method, Reichow *et al.* (*6*) show that the WSB lavas are indistinguishable in age from those to the east, previously dated at 250 million years by similar methods (*7*). The new results suggest a total areal extent of 3.9×10^6 km^2 for the Siberian Traps. The total volume of magma represented by this enlarged province is difficult to estimate, but 2×10^6 to 3×10^6 km^3 is probable, clearly qualifying the Siberian Traps as the largest (by volume) known continental flood basalt province.

The WSB underwent rifting during the late Paleozoic or early Mesozoic (about 300 to 200 million years ago), bearing out the general relationship between extension and flood volcanism. Unfortunately, as in many other cases, existing data appear equivocal on the crucial question of whether extension began before or after the onset of volcanism. Establishing the relative ages of these events should now become a priority.

Upward revision of the dimensions of flood volcanic provinces will doubtless continue as research progresses. Recent work (*8*) shows that magmatism of essentially the same age as the Siberian Traps occurred as far south as central Kazakhstan, and a swath of contemporary magmatic activity may even extend semicontinuously from there to south of Lake Baikal. These complexes appear to represent the roots of silicic volcanic centers, whose explosive eruptions would have provided a mechanism for transporting volcanogenic gases into the upper atmosphere.

These increasing size estimates have important implications for the environmental consequences of flood volcanic events. The more voluminous a magma system is, the more likely it is to generate large quantities of climate-modifying gases such as CO_2 and SO_2. The amounts of such gases actually delivered to the atmosphere by flood volcanism remain difficult to quantify, but there is little doubt that the effects could be significant. The synchrony between flood volcanic events and mass extinctions in the geologic record has been noted for years. For the three biggest events (the Siberian, CAMP, and Deccan traps), a temporal correlation with the most severe extinctions at the end of the Permian, Triassic, and Cretaceous periods, respectively, is firmly established.

The empirical connection between major flood volcanism and severe mass extinctions is all the more intriguing in light of hints of evidence of large meteor impacts coincident with these events. The evidence is strongest at the end of the Cretaceous. The latest hint suggests that CAMP and the extinction at the end of the Triassic may have been coincident with an impact (*9*), although the impact evidence in this case is permissive rather than indicative.

To some Earth scientists, the need for a geophysically plausible unifying theory linking all three phenomena is already clear. Others still consider the evidence for impacts coincident with major extinctions too weak, except at the end of the Cretaceous. But few would dispute that proving the existence of an impact is far more challenging than documenting a flood basalt event: It is difficult to hide millions of cubic kilometers of lavas—even, as shown by Reichow *et al.* (*6*), when they are buried beneath 2 km or more of sediments in Siberia.

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PERSPECTIVES: STATISTICAL MECHANICS

Far from Equilibrium

David A. Egolf

For more than a hundred years, equilibrium statistical mechanics has elucidated the behavior of matter in all its phases. The theory tells us which phase we should expect for our experimental conditions, what characterizes the transitions between phases as conditions are varied, and how these transitions are "universal," such that almost all of the details of the specific experiment are irrelevant (*1*).

Much of the world around us, however, including life itself, is not in equilibrium. Scientists have successfully extended equilibrium statistical mechanics into "near"-equilibrium situations, such that the deviations from equilibrium can be described by linear equations. But theories of the behavior of systems far from equilibrium have been few and far between. On page 1832 of this issue, Liphardt *et al.* (*2*) provide the first experimental test of a remarkable connection (*3*, *4*) between an equilibrium property, the free energy, and a series of measurements performed far from equilibrium.

The free energy is of central importance in statistical mechanics and thermodynamics (*1*). The equilibrium phase of a system corresponds to the absolute minimum of the free energy, and the height of the free-energy barrier between two configurations determines the size of the fluctuation (and thus the amount of time) needed for the system to change from one configuration to the other. For large, complex molecules such as proteins, an understanding of the free-energy landscape (which describes the free energy of all possible configurations of the system) is crucial for determining folding pathways, the topology of the folded state, and the biological utility of the protein [see for example (*5*)].

Unfortunately, the free energy of a state (relative to an arbitrary reference state) is often difficult to determine. The free-energy difference between two thermal states is the work needed to move infinitely slowly (and hence reversibly) between the two states. In practice, the speed at which one can move quasi-reversibly along some reaction coordinate is determined by the relaxation time of the system, that is, the time it takes to reequilibrate as the experimental conditions are changed. If relaxation times are long, the determination of the free-energy differences of a large number of states becomes a daunting task.

In 1997, Jarzynski (*3*, *4*) developed a method for circumventing the difficulties of long relaxation times. He derived an exact relation between free-energy differences and appropriately weighted averages

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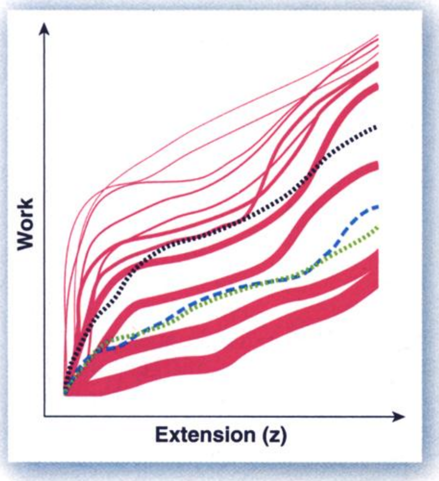

Unfolding an RNA molecule. This figure is schematic and not based on real data. Dashed blue line: free energy as a function of extension *z* from the reversible work. Solid red curves: many different trials of unfolding at nonequilibrium rates; line thicknesses represent the relative weightings necessary to satisfy Jarzynski's equality. Dotted green line: free energy determined with Jarzynski's equality. Dotted black line: equally weighted average of the nonequilibrium work.

of the work measured for many repetitions of a nonequilibrium process. The second law of thermodynamics guarantees that an equally weighted average of the work will yield a result larger than the free-energy difference. But Jarzynski showed that when the average taken over an infinite number of trials is Boltzmann-weighted according to the work required for each repetition, the result will always be the free-energy difference ΔF. This relation holds even for processes arbitrarily far from equilibrium.

Liphardt *et al.* (*2*) tested Jarzynski's equality by comparing the work performed in the reversible and irreversible mechanical unfolding of a single RNA molecule. They performed a delicate experiment in which small beads were attached to the ends of a single strand of RNA. The bead at one end was held in an optical trap, which allowed the force (and, thus, by integration, the work) to be measured. The bead at the other end was held by a micropipette attached to a piezoelectric device, allowing the position of this bead to be controlled by changing the voltage in the device. The position *z* of the second bead relative to an arbitrary position—a measure of the extent that the molecule has been unfolded—was used as the sole control parameter, giving a one-dimensional free-energy landscape as a function of *z*.

The researchers performed alternating trials of slower pulls (the quasi-reversible case) and pulls that were an order of magnitude faster (the nonequilibrium case). They found that the slower pulls were indeed approximately reversible. Repeated measurements yielded almost a single curve of work as a function of position *z* of the second bead (shown schematically in the figure as a dashed blue line). For faster pulling speeds, the work required to unfold the molecule as a function of *z* varied widely from trial to trial (solid red lines). The molecule does not have time to equilibrate during pulling, and the amount of work required therefore depends on the detailed microscopic configuration of the molecule. Small differences grow as the molecule is pulled at a nonreversible rate that prevents the various trials from settling into the common, equilibrium state.

Some individual trials actually require less work than the reversible case, but the majority require more work. In agreement with the second law of thermodynamics, the equally weighted average (dotted black line) is always larger than the reversible work. But when Liphardt *et al.* applied the weighting of the trials prescribed by Jarzynski, they found that the weighted average (dotted green line) agreed to within experimental error with the reversible work. Their results provide the first experimental demonstration that Jarzynski's equality is valuable not only as a theoretical construct but also as a practical (albeit technically challenging) method for mapping out free energy landscapes.

The Jarzynski equality is one of only a small number of relations between equilibrium properties and measurements made arbitrarily far from equilibrium, despite the prevalence of far-from-equilibrium processes in everyday life. As more relations are discovered or new uses of the known relations are developed [see for example (*6*)], we will continue to move closer to an understanding of these important and complicated nonequilibrium systems.

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PERSPECTIVES: IMMUNOLOGY

T Cell Activation in Six Dimensions

Ulrich H. von Andrian

Immunologists are elucidating how the immune systems of higher animals retain specific memories of antigens that they have encountered in the past. A central player in the maintenance of immunological memory is the T lymphocyte, which originates in the thymus as a thymocyte. Thymocytes must assemble T cell receptors (TCRs) that recognize self major histocompatibility complex (MHC) molecules but not the self antigens that the MHC presents. Those thymocytes whose TCRs do not match these positive and negative selection criteria are eliminated.

T cells that survive thymic selection enter the bloodstream as so-called naïve T cells and begin a restless survey of the body for antigens that can stimulate their TCRs. For T cell activation to occur, antigen must be encountered in the context of both self MHC and costimulatory molecules on mature dendritic cells (DCs), which reside in organized lymphoid tissues such as lymph nodes. After leaving the thymus, naïve T cells continuously recirculate between the blood and lymphoid organs but do not enter other tissues (*1, 2*). The critical events in this homing process—in particular, the adhesive and signaling interactions between circulating T cells and vascular endothelial cells—are well characterized. However, what happens to T cells in the thymus before their entry into the blood, and then after they exit the circulation and enter the lymph nodes, remains a mystery. Three elegant fluorescence microscopy studies reported in this issue shed new light, quite literally, on the dynamics and topography of T cells in living lymph nodes (*3, 4*) and in thymic organ cultures (*5*).

Miller *et al.* on page 1869 (*3*) and Stoll *et al.* on page 1873 (*4*) image fluorescently labeled T cells in explanted mouse lymph nodes. Given that these lentil-shaped organs measure ~1 mm in diameter, these studies are a technical tour de force. Normal lymph nodes have several distinct layers: They are covered by a fibrous capsule, which encloses the subcapsular sinus, a

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