Mesoscopic non-equilibrium thermodynamics

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Summary. Autonomous microsystems, such as biomolecules, molecular motors, nanomotors, and active particles, are functionally dependent on nanoscale energy conversion mechanisms. The non-equilibrium processes taking place in those systems are strongly influenced by the presence of fluctuations. Contributions to the free energy that vanish in the infinite particle number limit cannot be neglected and may exert an important influence in the dynamics of the system. We show that, in spite of these features, non-equilibrium thermodynamics applies. A rigorous theoretical foundation that accounts for the statistical nature of mesoscale systems over short time scales, "mesoscopic non-equilibrium thermodynamics", is currently being developed and offers a promising framework for interpreting future experiments in chemistry and biochemistry. [**Contrib Sci** 11(2): 147-151 (2015)]

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Non-equilibrium thermodynamics

Irreversible processes taking place in large-scale systems are well described by non-equilibrium thermodynamics [1]. The theory applies to a general description of these systems but ignores their molecular nature and assumes that they behave as a continuum medium. Earlier efforts to develop this theory started from the concept of local equilibrium states. Although a system may not be in equilibrium, individual pieces of it can be. For instance, imagine stirring a cocktail with a swizzle stick. The equilibrium is disturbed by the motion of the stick but can still be found if one looks closely at small pockets of fluid, which retain their internal coherence. These small regions are able to reach equilibrium if the forces acting on the system are not too large and if its properties do not change by large amounts over small distances. Concepts such as temperature and entropy apply to these islands of equilibrium, although their numerical

values may vary from island to island. For instance, when the ends of a metal bar are heated, heat flows through the bar toward the other end. The temperature difference between the ends of the bar acts as a force driving the heat flow, or flux, along the bar. A similar phenomenon occurs with a drop of ink in water. The difference in the ink concentration is the driving force that makes the ink invade the host liquid until it becomes uniformly colored. These forces are linear: the heat flux is proportional to the temperature difference and the particle flux to the concentration difference. This proportionality holds even when the forces acting on the system are strong. Also, in many turbulent flows, the internal stresses in the fluid are proportional to the velocity gradients. For these cases, Lars Onsager (1903–1976) and others formulated a theory of non-equilibrium thermodynamics and showed that the second law of thermodynamics continues to apply [2].

Under these conditions, the description of the system does not depend on its size, and scaling up the size does not lead to new behaviors. Irreversible processes taking place in a small vessel or in an industrial plant can therefore be analyzed using the same conceptual framework. But when scaling down the size of the system, its molecular nature becomes manifest; coarse-graining is no longer valid due to fluctuations in the quantities used in its description. A very different scenario is then reached, in which non-equilibrium thermodynamics only describe the evolution of the mean values of those quantities but does not completely characterize their actual values. In systems such as small clusters and biomolecules, fluctuations that are small in large-scale systems can be so large that they become the dominant factor in their evolution. The so-called mesostructures, defined as entities with sizes in between those of particles and objects, are examples of small systems undergoing assembly, impingement, and pattern formation processes in which fluctuations may play a very important role. Knowledge of the functionality of molecular motors (the small engines present in many biological systems) and the ability to manipulate matter at small scales to improve its performance—which constitutes the basic objective of nanoscience and nanotechnology—require a thermodynamic characterization of the system [3].

Non-equilibrium thermodynamics is restricted to the linear domain of fluxes and thermodynamic forces [1]; consequently, it is unable to completely characterize nonlinear transformations, in particular activated processes such as chemical reactions, nucleation, or self-assembly processes and, in general, abrupt changes in the state of a system described by a nonlinear equation.

How small is "small"?

With the development of experimental techniques, such as the X-ray laser, that are able to describe processes taking place over very short time scales (of the order of the femtosecond) [4], it has become possible to describe intimate mechanisms in proteins, biomolecules, molecular motors, self-assembled structures, and nanocolloids. But to reach this limit raises the question: is thermodynamics, originally formulated to deal with macroscopic systems containing a large number of molecules, even valid at these small observational scales?

Thermodynamics applies to infinite systems containing an infinite number of particles with a constant density—a situation referred to as the thermodynamic limit [5]. Basic concepts, such as heat, temperature, entropy, free energy, and thermodynamic principles, have been proposed for systems that fulfill this limit. Non-equilibrium thermodynamics also considers these concepts and assimilates the system into a continuum medium without molecular structure. In this description, the volume elements are considered thermodynamic systems since they still contain a large number of particles.

In many cases, the system is characterized in terms of its size. Macroscopic systems that fulfill the thermodynamic limit obey the laws of thermodynamics and can thus be studied using a thermodynamics approach. One would then be tempted to think that small-scale systems should obey other types of laws. But a classification based on size can be incomplete or even misleading. When one talks of small systems a key question arises: how small is "small?"

Small-scale systems can be better described through the extensivity (a mathematical property) of the relevant variables. Consider a system with a given free energy resulting from the contribution of the different degrees of freedom. A reduction of the size of the system entails a diminution of the number of degrees of freedom. The thermodynamic description of small systems exhibits peculiar features, as pointed out in the classical book by Terrell Leslie Hill (1917–2014) *Thermodynamics of small systems* [5]. Since in those systems the number of particles is not infinite, the free energy may contain contributions not present when the number of particles becomes very large. For example, in a small cluster composed of N particles, the free energy F contains, in addition to the volume term, a surface contribution proportional to $N^{2/3}$. It can be expressed as $F = Nf(T,P) + N^{2/3}g(T,P)$, where f is the free energy per unit volume and g is a function of the temperature T and the pressure P. When the number of particles is very large

and the system becomes of macroscopic size, the surface contribution is negligible and the free energy is simply Nf.

Far-from-equilibrium microsystems

The evolution of the state of a system is the result of the actuation of two competing factors. The presence of external forces, or imposed gradients of the relevant quantities, drives the system from an initial equilibrium state to a non-equilibrium state. Collisions between particles tend to restore the initial equilibrium situation. A force applied at the ends of a RNA molecule progressively breaks down the bonds of the molecule such that it adopts different conformations [6]. The addition of one of the components of a biochemical cycle alters the chemical equilibrium of a system, removing the state leading to a stationary state [7]. When the force applied is very intense and the collisions are unable to restore the initial equilibrium conditions, is it possible to thermodynamically describe this system?

An analysis based on the solution of the Boltzmann equation for reactive gases by means of a Chapmann-Enskog expansion [8] enables one to describe the transition from equilibrium to non-equilibrium states. The law of mass action, the expression of entropy production as the product of the reaction rate and the affinity, and the detailed-balance principle cease to be valid when the system is very far from equilibrium.

But there are cases in which the departures from equilibrium are less drastic. Application of a temperature difference at the ends of a metal bar induces a heat flux along the bar that is linear with respect to the temperature gradient. This linearity holds even for very large gradients. Experiments performed in a nanomotor that moves along a carbon nanotube under the influence of a temperature difference generated by an external current [9] have shown that, in spite of the very large gradients coming into play, of the order of 1 K/nm, the driving force is still linear along the gradient. This phenomenon also occurs regarding the orientation of non-polar molecules by means of a thermal gradient [10].

Quantities such as the temperature or the pressure of a system that are directly related to the collisions between the constituent particles relax very fast whereas the density associated with conformational changes involving many particles relax much slower. Molecular dynamic simulations have shown that temperature relaxation in a protein, determined from the average kinetic energy of the constituent atoms, takes place in the range of tens of picoseconds [11]. Thus, although the system is very small, of nanometric size, because it contains a sufficiently large number of particles it reaches local equilibrium very rapidly, which allows its thermodynamic description.

The transition towards non-equilibrium states relies on the nature of the irreversible process that takes place. A fluid at rest starts to move under the action of a pressure difference although the perturbation caused by that difference may be very small. By contrast, a chemical reaction needs a minimum amount of energy to proceed. Whereas the linear approximation is valid for many transport processes, such as heat conduction and mass diffusion, even in the presence of large gradients [12], it is not appropriate for activated processes in which the system immediately enters the nonlinear domain. Non-equilibrium thermodynamics does not provides a complete description of activated processes. But, is there a general framework within which both types of processes can be treated?

Mesoscopic non-equilibrium thermo-dynamics

When the system is very small, the chaotic jumble of molecular motions that dictates its behavior causes the system's properties to vary wildly over short distances and time intervals. Processes taking place in small systems, such as the condensation of water vapor and the transport of ions through a protein channel in a cell membrane, are dominated by such fluctuations, during which temperature and entropy cease to be well-defined quantities. Does the failure of the non-equilibrium thermodynamics theory in these instances imply the failure of the second law?

We have shown that many of the problems are eliminated with a change of perspective [13]. Our perception of abruptness depends on the time scale we use to observe the respective processes. If we analyze one of the seemingly instantaneous chemical processes in slow motion, we would see a gradual transformation, as if we were watching a pat of butter melting in the sun. When the process is viewed frame by frame, the changes are not abrupt. The trick is to track the intermediate stages of the reaction using a new set of variables beyond those of classical thermodynamics (Fig. 1). Within this expanded framework, the system remains in local thermodynamic equilibrium throughout the process. These additional variables enrich the behavior of the system. They define a landscape of energy that the system rambles through
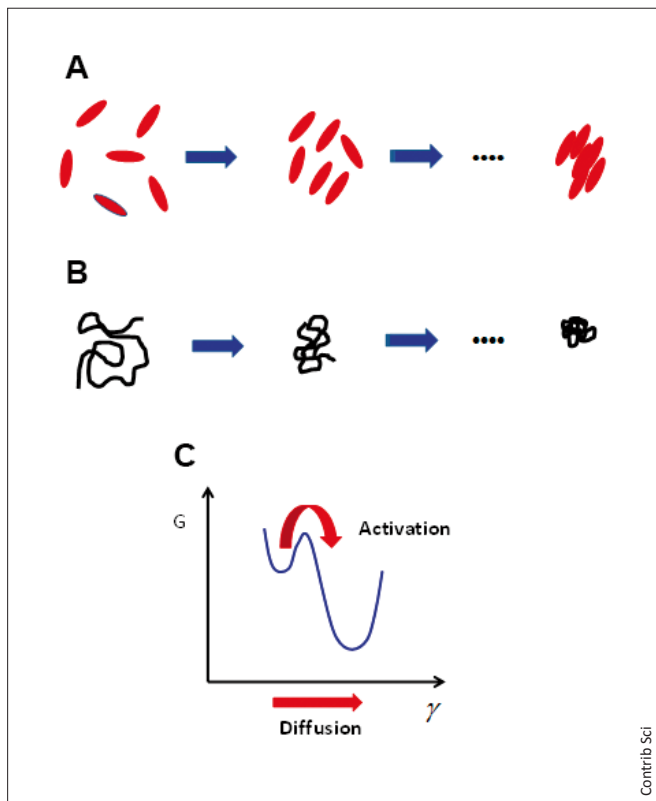
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Fig. 1. Activated process of a non-linear nature can be treated using a mesoscopic non-equilibrium thermodynamics approach. (**A**) Self-assembly. (**B**) Protein folding. (**C**) Over short-time scales, the transition can be viewed as diffusion through a potential barrier G that depends on an internal coordinate.

like a backpacker in the mountains. Valleys correspond to a dip in energy, sometimes involving molecular chaos, other times molecular order. The system can settle into one valley and then be kicked by external forces into another. If it is in the grasp of chaos, it can break away from disorder and find order, or vice-versa.

Important biochemical reactions that require microseconds to milliseconds to run to completion are composed of more elementary steps on the sub-nanosecond scale. Ultrafast events, on the time scale of femtoseconds to picoseconds, occur in photo-initiated reactions, such as photosynthesis, vision, and DNA repair, and as fluctuations during slower reactions, which effectively pre-sample the relevant energy landscape.

Next, consider the problem of fluctuations. Does thermodynamics fail when systems are excessively small? A simple example shows that the answer is no. If we toss a coin only a few times, it could be that, by chance, we get a series of heads. But if we flip the coin many times, the result

reliably approaches an average. Nature flips coins quite often. A few particles moving around in a container collide only occasionally and can maintain large velocity differences among themselves. But even in a seemingly small system, the number of particles is much larger, so collisions are much more frequent and the speed of the particles is brought down to an average (if slightly fluctuating) value. Although a few isolated events may show completely unpredictable behavior, a multitude of events shows a certain regularity. Therefore, quantities such as density can fluctuate but remain predictable overall. For this reason, the second law continues to rule over the world of the small.

In general, the reduction of the observational time and length scales of a system usually entails an increase in the number of non-equilibrated degrees of freedom [13]. Those degrees of freedom may, for example, represent the position and velocity of a single particle, the orientation of a magnetic moment, the size of a macromolecule, the number of particles that integrate self-assembled structures, or any internal coordinate or order parameter whose values define the state of the system in a phase space. The characterization at the mesoscopic level of the state of the system follows from the knowledge of the probability distribution defined in that space.

To bring the system to a state characterized by a given value of the coordinates, we need to exert a certain amount of work, which is related to the different thermodynamic potentials by imposing the constraints that define those potentials. For instance, for the case of constant temperature, volume, and number of particles, the minimum work corresponds to the Helmholtz free energy.

The theory assumes local equilibrium in the space of the degrees of freedom, with a probability distribution that undergoes a diffusion process in the space of the internal degrees of freedom. The probability current is obtained from the entropy production in the coordinate space, which follows from the Gibbs entropy—in the same way as Fick's law is obtained in non-equilibrium thermodynamics [1]. The kinetic equation for the evolution of the probability density follows from the probability conservation law after substituting the obtained expression for the diffusion current.

Mesoscopic non-equilibrium thermodynamics provides a simple and direct method to determine the dynamics of a system from its equilibrium properties, obtained from the equilibrium probability density. It has been used to analyze the many different non-equilibrium processes taking place in small-scale systems. In particular, the theory has been used to study nucleation and self-assembly processes [14], transport

through ion channels with the presence of entropic forces [15], polymer crystallization in the presence of gradients [16], active transport in biological membranes [17], diffusion in confined systems [18], and near-field thermodynamics [19]. The formulation of the theory and its applications are described in [10,20].

Competing interests. None declared.

References

1. Barreiro A, Rurali R, Hernández ER, Moser J, Pichler T, Forró L, Bachtold A (2008) Subnanometer motion of cargoes driven by thermal gradients along carbon nanotubes. Science 320:775-778 doi:10.1126/science.1155559

2. Callen HB (1985) Thermodynamics and an Introduction to Thermostatistics. John Wiley and Sons, New York

3. de Groot SR, Mazur P (1984) Non-equilibrium thermodynamics. Dover, New York

4. Hill TL (1989) Free energy transduction and biochemical cycle kinetics. Dover, New York

5. Hill TL (1994) Thermodynamics of small systems. Ed. Dover, New York doi:10.1007/978-1-4612-3558-3

6. Kjelstrup S, Rubi JM, Bedeaux D (2005) Active transport: a kinetic description based on thermodynamic grounds. J Theor Biol 234:7-12 doi:10.1016/j.jtbi.2004.11.001

7. Latella I, Pérez-Madrid A, Lapas LC, Rubi JM (2014) Near-field thermodynamics: Useful work, efficiency, and energy harvesting. J Appl Phys 115:124307 doi:10.1063/1.4869744

8. Lervik A, Bresme F, Kjelstrup S, Bedeaux D, Rubi JM (2010) Heat transfer in protein-water interfaces. Phys Chem Chem Phys 12:1610-1617 doi:10.1039/b918607g

9. Paul Sherrer Institute (2009) Ultrafast phenomena at the nanoscale: Science opportunities at the SwissFEL X-ray Laser. PSI Bericht 09-10 B.D. Patterson (ed)

10. Reguera D, Rubi JM, Vilar JMG (2005) The mesoscopic dynamics of thermodynamic systems. J Phys Chem B 109:21502-21515 doi:10.1021/jp052904i

11. Reguera D, Luque A, Burada,PS, Schmid G, Rubi JM, Hänggi P (2012) Entropic splitter for particle separation. Phys Rev Lett 108:020604(1-4) doi:10.1103/PhysRevLett.108.020604

12. Reguera D, Rubi JM (2001) Kinetic equations for diffusion in the presence of entropic barriers. Phys Rev E 64:061106 (1-8) doi:10.1103/PhysRevE.64.061106

13. Reguera D, Rubi JM (2001) Non-equilibrium translational-rotational effects in nucleation. J Chem Phys 115:7100-7106

14. Reguera D, Rubi JM (2003) Nucleation in inhomogeneous media. II. Nucleation in a shear flow. J Chem Phys 119:9888-9893 doi:10.1063/1.1614777

15. Römer F, Bresme F, Muscatello J, Bedeaux D, Rubi JM (2012) Thermomolecular orientation of nonpolar fluids. Phys Rev Lett 108:105901(1-4) doi:10.1103/PhysRevLett.108.105901

16. Ross J, Mazur P (1961) Some deductions from a formal statistical mechanical theory of chemical kinetics. J Chem Phys 35:19-28 doi:10.1063/1.1731889

17. Rubi JM (2008) The long arm of the second law. Sci Am 299:62-67 doi:10.1038/scientificamerican1108-62

18. Rubi JM, Bedeaux D, Kjelstrup S (2006) Thermodynamics for single-molecule stretching experiments. J Phys Chem B 110:12733-12737

19. Santamaria-Holek I, Reguera D, Rubi JM (2013) Carbon-nanotube-based motor driven by a thermal gradient. J Phys Chem C Phys 117(6):3109-3113 doi:10.1021/jp311028e

20. Vilar JMG, Rubi JM (2001) Thermodynamics "beyond" local equilibrium. Proc Nat Acad Sci 98:11081-11084 doi:10.1073/pnas.191360398