

Dissipative adaptation in driven self-assembly

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In a collection of assembling particles that is allowed to reach thermal equilibrium, the energy of a given microscopic arrangement and the probability of observing the system in that arrangement obey a simple exponential relationship known as the Boltzmann distribution. Once the same thermally fluctuating particles are driven away from equilibrium by forces that do work on the system over time, however, it becomes significantly more challenging to relate the likelihood of a given outcome to familiar thermodynamic quantities. Nonetheless, it has long been appreciated that developing a sound and general understanding of the thermodynamics of such non-equilibrium scenarios could ultimately enable us to control and imitate the marvellous successes that living things achieve in driven self-assembly. Here, I suggest that such a theoretical understanding may at last be emerging, and trace its development from historic first steps to more recent discoveries. Focusing on these newer results, I propose that they imply a general thermodynamic mechanism for self-organization via dissipation of absorbed work that may be applicable in a broad class of driven many-body systems.

Generally, the first step in trying to build something is having a pretty specific idea of what you want it to look like: we need blueprints because building materials do not normally arrange themselves in useful ways spontaneously, and so we have to implement some plan for forcing them into the right shape.

From such a perspective, it is quite difficult to make full sense of the molecular architecture of living things. Of course, striking examples of cellular components that resemble human-made tools in their structure¹, and that require exquisitely reliable spatial organization on the nanoscale to function^{1–3}, do exist. Still, many of the building blocks of life do not snap together neatly like Lego bricks⁴; instead, the biological world provides an endless array of cases where functional outcomes are achieved with extreme effectiveness using components that are constantly being rearranged by the fluctuating noisiness of individual collisions and reactions. Life manages to squeeze exquisite reliability in behaviour on large scales from a jittery herd of individual molecules, without always needing to put each atom in its place, and we might therefore feel encouraged to attempt something similar in our own feats of engineering.

The challenge is that living things always operate far from equilibrium, where theoretical foundations have historically been thin on the ground. As a result, it has long remained an open question whether general physical principles can make a fundamental contribution to our understanding of subcellular organization. The principal goal of this Perspective is to discuss new ideas on non-equilibrium statistical mechanics that may begin to light the way towards achieving some of this desired insight into the behaviour of fluctuating, many-body assemblies. I will begin by reviewing the classic contributions to this line of thinking. Subsequently, I will outline more recently developed theoretical ideas in the field, and sketch the main argument for a hypothesized mechanism of driven self-organization called dissipative adaptation. The closing discussion will focus on how several recent experiments can be understood in terms of such a mechanism, and try to provide an outlook for the future impact of these findings on how we think about nanoscale design.

Time, symmetry and dissipative structures

When a system is left unperturbed for a long time in contact with a heat reservoir at temperature T , we say that it has reached thermal

equilibrium. Under such conditions, it is generally assumed that microscopic arrangements j and k having energies E_j and E_k , respectively, will be visited with a relative probability (p) given by the Boltzmann distribution (Fig. 1a):

$$\frac{p(j)}{p(k)} = \exp\left[-\frac{E_j - E_k}{k_B T}\right] \quad (1)$$

where k_B is the Boltzmann constant. If we subject our system to driving forces that can do work over time (Fig. 1b), matters become considerably more complicated, as now the probability of the system being found in a given state depends not only on the availability of thermal energy from the bath, but also on the particular ways that the drive pushes on each possible sequence of arrangements i, j, k , and so on. Handling this new subtlety requires an additional physical principle, known as the time-reversal symmetry of particle mechanics. In classical physics, this symmetry amounts to the requirement that if a dynamical trajectory $\gamma \equiv [x(t), v(t)]$ for a given system with position variables $x(t)$ and velocity variables $v(t)$ is permissible according to the equations of motion over some time period τ , then so must its 'time-reversed movie' $\gamma^* \equiv [x(\tau - t), -v(\tau - t)]$ with all the particles running backwards along the same tracks through space⁵.

Lars Onsager made the first major theoretical step forward when he recognized the impact of time-reversal symmetry on a simple, but general class of non-equilibrium systems⁶. Onsager assumed that the dynamics of all macroscopic coordinates were governed by a linear system of differential equations relating the force on one coordinate to the degree of displacement from equilibrium in all other coordinates. He was able to show that the phenomenological parameters of these equations had to obey certain 'reciprocal relations' to be consistent with time reversibility, essentially requiring an equal and opposite reaction for every action. For example, in an electrochemical circuit, the Onsager relations would dictate a fixed relationship between the magnitude of electrical current that can be driven by a chemical potential difference and the rate of chemical reaction flux that can be driven by an applied voltage.

Owing to their simplicity and great generality, the Onsager relations have been widely applied, yet it was perhaps one of their least practical implications, discovered by Ilya Prigogine in his study of non-equilibrium steady states, that would be the most abidingly fascinating.

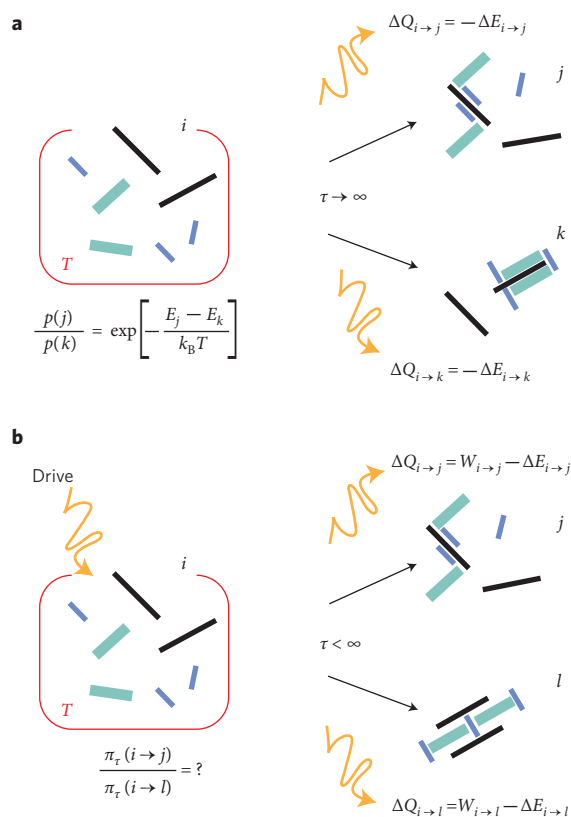


Figure 1 | Assembly probability in the presence of thermal fluctuations.

a, In the classic scenario of equilibrium statistical mechanics, a system held in contact with a thermal reservoir at temperature T for a long time τ loses all memory of its starting state i and, as a consequence, the relative probabilities (p) of microscopic states j and k are a simple exponential function of these states' respective energies. Because of conservation of energy, the heat released into the bath (ΔQ) during a transition from one state to another is equal and opposite to the change in internal energy (ΔE) that occurs during this process. **b**, When an external drive is introduced and the system is observed for a finite time, the probability of finding the system in a given state generally depends both on the initial condition and on exactly how the system was driven. The challenge of non-equilibrium statistical mechanics is to try to express this probability distribution in terms of thermodynamic quantities, which now include not only the internal energy of the final states, but also the work done by the drive during transitions between states. For a single realization of the same experiment, the heat (ΔQ) is a fluctuating stochastic variable that is determined by the difference between the work done by the drive (W) and the change in internal energy (ΔE) that occurs during the process of driving.

A steady state comes about when an external drive is used to sustain a constant flow through a system so that various macroscopic observables converge on steady, out-of-equilibrium values. According to the second law of thermodynamics, any such current through a system in a reservoir must necessarily lead to a positive rate of reservoir entropy increase in the steady state (for example, a constant electrical current through a resistor leads to a steady rate of heat dissipation in the surroundings). What Prigogine realized was that Onsager's reciprocal relations could be used to derive an expression for this rate of entropy production^{6,7}. More significantly, the resulting equation also established that the steady state reached by the system is a unique condition in which the total rate of entropy production is minimized.

Prigogine's minimum entropy production principle generated considerable excitement initially, for it enabled prediction of the long-time behaviour of a system by optimizing one collective thermodynamic property of the end state. Prigogine and others^{7,8}

were particularly eager to explore how this line of thinking could help in making sense of biological organization, proposing that many of the properties of living things might be explainable as 'dissipative structures' that arise from a general thermodynamic tendency to reduce the rate of entropy production.

Ultimately, however, the non-equilibrium world proved to be more diverse and complex than Prigogine's elegant principle could fully capture. Many driven systems (particularly living ones) operate in the nonlinear-response regime where the Prigoginian formula generally breaks down⁷. To make further progress, it turns out to be necessary to recognize that the statistical behaviour of non-equilibrium systems cannot be understood in terms of the local properties of individual microstates at one moment in time, but rather must be expressed through comparisons between dynamical trajectories.

Extending the second law

In 1999, Gavin Crooks combined time-reversal symmetry and energy conservation⁹ to derive an exact expression for the relative likelihoods of different dynamical paths that a thermally fluctuating system could take:

$$\frac{\pi(\gamma)}{\pi^*(\gamma^*)} = \exp\left[\frac{\Delta Q(\gamma)}{k_B T}\right] \quad (2)$$

This equation states that a microtrajectory γ is more likely than its time-reversed movie by an exponential factor of the positive amount of the heat that is released into the surrounding thermal reservoir while the forward path is being traversed (Fig. 2). The exciting thing here is that this relation holds even when an arbitrarily time-varying external field is being used to drive the system over the course of the whole trajectory, so long as the time variation is run backwards (*) for computation of the reverse trajectory's probability. The heat $\Delta Q(\gamma)$ thus is generally made up of two contributions: the internal energy change ΔE of the system from start to finish, and the work W performed by the applied field over the course of the whole process.

Talk of microtrajectories is highly abstract, and it is important to flesh out the concrete implications^{10–18} of a general statement such as equation (2). Certainly the most famous of these is the equality derived by Chris Jarzynski in 1997¹⁰, relating the probability distribution of non-equilibrium values of work done on an initially equilibrated system to the equilibrium free energy difference obtained when the work is done infinitely slowly.

More recently, equation (2) was used to derive an extension of the second law of thermodynamics that offers some helpful intuitions for understanding the thermodynamic constraints on far-from-equilibrium behaviour¹⁹. In a general experimental scenario, we start and end out of equilibrium, and are interested in the rates of interconversion between different coarse-grained states X , X' , and so on defined by some features of the system we can monitor. Each such state is expected to have some internal entropy S_{int}^X (which summarizes the fact that lots of microscopic arrangements of the system will all look to us like they are in state X), and also some average internal energy $\langle E \rangle_X$. If we start at X and apply an arbitrary external forcing field to the system (such as light oscillating at a particular frequency), then we can define the probability for transitions between states in a finite time τ as $\pi_\tau(X \rightarrow X')$, and write

$$\langle W \rangle_{X \rightarrow X'} - \langle \Delta E \rangle_{X \rightarrow X'} + T \Delta S_{\text{int}} \geq k_B T \ln \left[\frac{\pi_\tau(X \rightarrow X')}{\pi_\tau^*(X' \rightarrow X)} \right] \quad (3)$$

where $\langle \dots \rangle_{X \rightarrow X'}$ is averaging over repeated measurements of a transition from X to X' . We have long known that the world's total entropy is supposed to increase, yet here we have a more precise statement: the more statistically irreversible a spontaneous process is (that is, the more likely you are to go from X to X' than the reverse, under

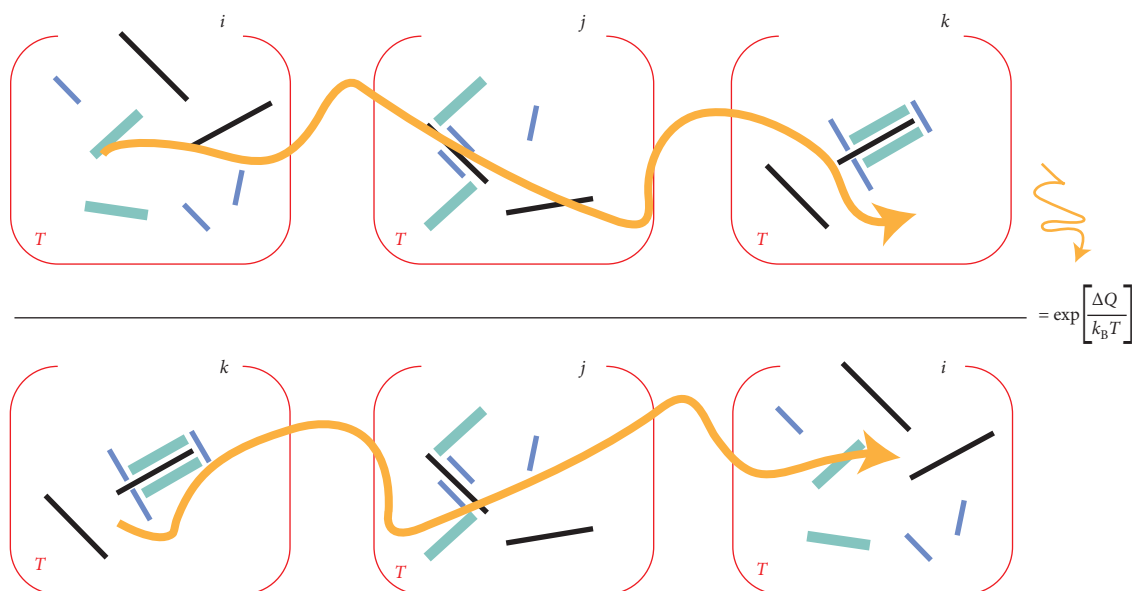


Figure 2 | Dynamical irreversibility and heat production. The probability of observing a specific sequence of configurations for a system driven with a particular pattern of time-varying field (large arrows) while in contact with a heat reservoir has a set ratio to the probability of observing the time-reversed sequence of events under a time-reversed drive. In particular, these two probabilities differ by an exponential factor of the heat released into the reservoir (ΔQ ; small arrow) when the system is driven according to the pattern corresponding to the ratio's numerator.

a given set of arbitrary non-equilibrium driving conditions), the greater the minimum amount of total entropy increase required. Two contributions to this entropy rise ($\langle \Delta E \rangle_{X \rightarrow X'} - T \Delta S_{\text{int}}$) are familiar, and together remind us of the role of free energy in describing equilibria. What is new here is that we now can see that on average any additional irreversibility beyond the contribution of this equilibrium-like term must be paid for by extra work. Put another way, greater irreversibility must be powered by more of the work done on the system being dissipated rather than stored in the system.

In many specific cases, the inescapable relationship between dissipation and irreversibility has been appreciated for a long time. Whether in Ralph Landauer's derivation²⁰ of the minimum heat required to accompany erasure of information in a computer, or in the general intuition that biochemical reactions can be made more irreversible through the coupling to directional, dissipative fluxes from sources (such as adenosine triphosphate (ATP)) to sinks (such as adenosine diphosphate (ADP))¹, we see the same principle rearing its head. What is potentially liberating about this more general formulation, however, is that it is no longer necessary to break the process of interest apart into local equilibria; this grants us a new freedom that is especially valuable when modelling complex systems such as live cells or many-body nanoscale assemblies, where we are invariably ignorant about most of the microscopic details.

To underline this point, this extended second law was applied to the study of self-replication¹⁹, pointing out that the statistical irreversibility of exponential growth implies thermodynamic constraints for the fuelling of systems that make copies of themselves. Similar kinds of reasoning can inform our thinking about guided nanoassembly as well. For example, without the need for a more detailed model of how a system of interest 'works', we now can say that the extra energy expended on dissipated work during the construction of a given assemblage of matter determines the maximum durability that this target structure can have in the presence of thermal fluctuations at the same temperature; once we know how fast it was assembled and how much dissipation was catalysed during that process, we can immediately estimate a timescale on which the structure is likely to fall apart spontaneously under the same conditions. Flipping things around, one can also say that at fixed yield and durability of product, accelerating a process of assembly should cost more in dissipated work.

Dissipative adaptation

To tackle the more significant challenge of predicting the path of arbitrary non-equilibrium evolution by using thermodynamics, we need to return to equation (2) and analyse it in a different light. It helps to appreciate some of this equation's most interesting consequences if we can rearrange it to compare outcomes of some process in which matter is driven by an arbitrary forcing field or externally imposed current in the presence of thermal fluctuations. By summing over different possible microtrajectories and their associated probabilities, we obtain

$$\frac{\pi_{\tau}(i \rightarrow j)}{\pi_{\tau}(i \rightarrow k)} = e^{-\Delta E_{jk}/(k_B T)} \frac{\pi_{\tau}^*(j^* \rightarrow i^*)}{\pi_{\tau}^*(k^* \rightarrow i^*)} \frac{\langle e^{-W/(k_B T)} \rangle_{i \rightarrow k}}{\langle e^{-W/(k_B T)} \rangle_{i \rightarrow j}} \quad (4)$$

where the angled brackets denote a weighted average over all microtrajectories with fixed start (i) and end (j, k) points. The effect of the leading factor of $e^{-\Delta E_{jk}/(k_B T)}$ on the right-hand side in equation (4) has an obvious meaning: it is what will allow us to recover the Boltzmann distribution if we have no external drive ($W = 0$) and wait a long time to equilibrate ($\pi_{\infty}^*(j^* \rightarrow i^*)/\pi_{\infty}^*(k^* \rightarrow i^*) = 1$). Moving forward, we will compare states assumed to have the same energy so that the non-equilibrium effects come to the fore.

The second factor on the right-hand side of equation (4) tells us that not all pairs of states are equally accessible to each other on a finite timescale: sometimes, j is a more likely outcome than k because exchange between i and j is a generally faster process than exchange between i and k due to the positioning of kinetic barriers. What is important to consider, however, is that if the states i, j, k , and so on represent the different possible arrangements of a system made up of many distinct particles, then the combinatorial space of possible arrangements for these particles is inconceivably vast, so much so that we would expect a still vast and diverse set of states j, j', j'' , and so on to exist that all have equal kinetic access to i , that is, for which $\pi_{\tau}^*(j^* \rightarrow i^*) = \pi_{\tau}^*(j'^* \rightarrow i^*) = \dots$

From this high altitude, such a notion should properly be understood as a speculative hypothesis that must be tested empirically in particular systems. If we entertain the notion for the moment however, a rather exciting consequence jumps up, for within our vast and diverse set of equally kinetically accessible states, the ones most

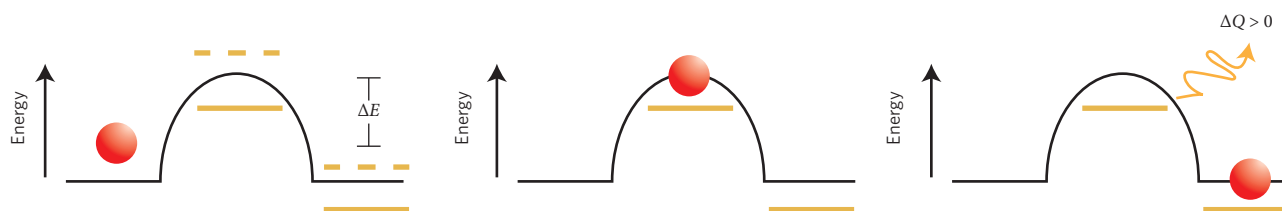


Figure 3 | Driven barrier hopping. Left: In this simple barrier-hopping model, a particle experiencing thermal fluctuations sits in an energy landscape that is driven so that the right state and transition state energies oscillate sinusoidally in sync over time (maximum and minimum values shown in yellow). Middle: The particle is most likely to make a hop at a point in time when the oscillation in the barrier height caused by the drive momentarily lowers the activation energy for the transition. Right: The drive in this system has been contrived to keep the barrier height for the leftward hop fixed over time, which means that the drive preferentially accelerates jumps to the right. This statistical irreversibility immediately implies that the energy of the right-side state will be lower than that of the left-side state at the moment of a typical rightward jump, so that positive heat is dissipated into the surrounding reservoir ($\Delta Q > 0$). Thus, irreversibility and heat dissipation go hand in hand.

likely to be outcomes of our particular scenario of driven evolution will have special histories of reliably high work absorption, meaning that all of the likely stochastic paths carrying the system from i to j have exceptionally positive values for W .

From this hypothesis, we can flesh out some intriguing implications. What we have to remember is that once we have chosen our external drive, different configurations of the system are not going to be equally competent to absorb work from that drive. For example, if we choose to impose an optical²¹ stimulus of a certain frequency, the spectrum of frequencies for linear-response oscillations about any local energy minimum will be a collective function of the full arrangement of all particles in the system, and the possibility of resonating with this drive (and thus absorbing and dissipating more work energy) will be intimately linked to the particular shape that the ensemble of particles has adopted. Accordingly, a structure that is chosen from a vast and diverse set for its likely history of atypically high work absorption may generally be the end product of antecedent structures that exhibited a well-matched relationship to the particular driving environment that enabled them to catalyse the absorption and dissipation of work with exceptional effectiveness.

The physical intuition behind this general expectation turns out to be surprisingly simple: the absorption of energy from a drive allows the system configuration to traverse activation barriers too high to jump rapidly by thermal fluctuation alone, and if this energy is dissipated after the jump, then it is not available to help the system go back the way it came (Fig. 3). Thus, while any given change in shape for the system is mostly random, the most durable and irreversible of these shifts in configuration occur when the system happens to be momentarily better at absorbing and dissipating work. With the passage of time, the ‘memory’ of these less erasable changes accumulates preferentially, and the system increasingly adopts shapes that resemble those in its history where dissipation occurred. Looking backward at the likely history of a product of this non-equilibrium process, the structure will appear to us like it has self-organized into a state that is ‘well adapted’ to the environmental conditions. This is the phenomenon of dissipative adaptation.

It is instructive to consider how this physical mechanism plays out in a clear and accessible case, such as that of the mechanically agitated self-replicating amyloid fibres studied by Carnall and colleagues²². The authors synthesized building blocks for dithiol macrocycles ligated to peptide tails. By vigorously shaking these components over the course of days, they were able to observe the self-catalysed growth of particular fibrillar species made of stacked macrocycles. In this case, the basic mechanism proposed was that the slower linear growth of fibrils was accelerated through mechanical perturbation, which increased the number of exposed end-points by breaking fibrils. Since longer fibrils are more ‘competent’ to absorb work and snap, but shorter ones polymerize in less time, a balance was struck that favoured the exponential growth of fibres of finite length. This may explain why it was found that

shaking enabled hexamer growth to compete with the normally faster heptamer growth, since heptamers were less competent to snap under shear.

The previous example considers how absorption and dissipation of work can power the growth of many copies of a self-replicating entity. However, the argument for dissipative adaptation in principle extends to a much more general class of cases, where the system as a whole could converge on a non-equilibrium state whose formation is not brought about in any discernible way by many separate, localized events of self-amplification by individual components. Of course, we would expect the space of such adapted states with exceptional work histories to itself be extremely diverse in its microscopic details. In striking analogy to the way things work in a directed evolution experiment used to engineer biomolecules with chosen properties^{23–25}, each repetition of the same experiment is expected to yield a product unique in many of its aspects. The hypothesis we are advancing, however, is that the whole vast and diverse ensemble of likely outcomes must have particular physical properties in common that emanate from their comparable histories of work absorption. Thus, the intriguing possibility is that a general thermodynamic tendency of driven many-body systems may enable us to use external fields to influence certain emergent features of the collective behaviour in the ‘particle herd’ while leaving most of the system’s individual degrees of freedom free to fluctuate.

The search for a general phenomenon

The plausibility argument we have made for dissipative adaptation is expressed in general terms, and there is still much to be understood about the more specific physical circumstances where the phenomenon is most likely to be observed. We can, however, take encouragement from several recent experimental studies.

Perhaps surprisingly, one of the clearest cases pointing to the possibility of dissipative adaptation was recently characterized in a macroscopic system²⁶. When conducting beads are immersed in oil and subjected to a strong external voltage drop from an electrode overhead, they spontaneously collect into visually striking, dynamic, branched structures that are maintained by the out-of-equilibrium flow of current through the system²⁷. Experimenters tracked the time evolution of the dissipation rate in a collection of 40 beads and found that, when initialized in a random arrangement, the cluster had a general tendency to relax to a branched steady state characterized by more rapid dissipation²⁶. The patterns of spatial organization the beads adopt turn out to be matched to the boundary conditions of the container to reduce the overall electrical resistance of the collective.

If self-organization of this kind is possible on the macroscale, then how much more so on the nanoscale, where strong fluctuations and large numbers of particles allow a vast range of possible combinations of building blocks to be explored. In a study²¹ conducted by Ito *et al.*, silver nanoparticles were allowed to assemble

spontaneously in the presence of an externally applied laser-light field, and their optical properties were assayed. The silver nanoparticles were shown to aggregate into 50–100-nm-sized clumps of different shapes and orientations that depended on the frequency and polarization of the light field. Strikingly, the measured surface plasmon resonance spectrum of this ensemble of particles was found to deviate significantly from that of individual separate particles, suggesting it arose from collective interactions among the particles dependent on their relative positions and orientations. More specifically, the spectrum was red-shifted towards the 1,064 nm wavelength of the driving field in which the particles had assembled. These observations could be construed to offer tentative support for the dissipative adaptation hypothesis, and underline how such a thermodynamic understanding may help in devising new methods for guiding processes of self-assembly on the nanoscale.

It may be, though, that the most intriguing opportunities for the discovery of dissipative adaptation lie in systems where we have not yet thought to look for it, and in which its signatures might be hiding in plain sight. Multi-protein mixtures containing ATP- or GTPase molecular machines hold great promise in this respect, since they couple interparticle interactions to conformational changes driven by discrete events of chemical dissipation through hydrolysis of triphosphates^{28,29}. For example, a past work by Schaller and co-workers reported²⁸ an impressive array of spatial patterns in the collective dynamics of actin filaments skating across a surface studded with immobilized myosin motors. One cannot help noticing in this system that the dynamical attractors it exhibits involve whole ‘herds’ of filaments co-orienting and flowing in concerted spiralling motions, a condition of organization that one might guess reduces the load on each motor and thus perhaps accelerates the global rate of consumption of ATP. Time will tell whether these and other patterned motions of macromolecules can be explained in part by the type of thermodynamic reasoning considered here.

Aftermath

At this point, dissipative adaptation should seem like too simple an idea to be true, not least because the reality is more complicated (even in principle) than the account of things we have managed to give within the confines of this Perspective. For one thing, our discussion has trod rather lightly over the (addressable) issue of rare trajectories that dissipate much less than average, which are known to come to the fore in a confounding way when we try to compute exponential averages like in equation (4). Even more significantly, we must acknowledge that it is not always the case that a history of absorbing and dissipating work from a drive corresponds to a continuing ability to do so in the present moment; sometimes the likeliest outcome of a non-equilibrium process is a pile of broken shards rather than a resonantly vibrating goblet, which means we cannot generally assume that dissipation rates must always increase over time — indeed, in the case of the near-equilibrium linear-response regime, dissipative adaptation reduces to the requirement that there be extra entropy production during relaxation to the steady state, so that Prigogine’s condition of minimum entropy production holds at the end of the process.

All this being said, the fundamental physical intuitions we should take forward as we refresh our thinking about driven self-assembly are that irreversibility carries a cost in dissipated work energy, and that when irreversible changes in shape occur ‘by accident,’ it means the system must have ‘accidentally’ adopted a shape that allowed it to pay this cost. Whether we are trying to build novel nanosized tools, or just pondering the intricate pageant put on by the cell’s molecular actors, this is a notion that may one day make life simpler.

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