

Cytoskeletal filaments are capable of self-assembly in the absence of externally supplied chemical energy, but the rapid turnover rates essential for their biological function require a constant flux of ATP or GTP hydrolysis. The same is true for protein assemblies employed in the formation of vesicles from cellular membranes, which rely on ATP-hydrolyzing enzymes to rapidly disassemble upon completion of the process. Recent observations suggest that the nucleolus, p granules and other mebraneless organelles may also demand dissipation of chemical energy to maintain their fluidity. We present a minimal model to study the relationships among dissipation, binding energy and rates of turnover or disassembly in a self-limiting assembly process with active monomer removal. After confirming that significant kinetic acceleration can be obtained under physiological parameters without melting the structure, we identify a new signature of far-from-equilibrium dynamics in the fluctuations of the assembled phase.

Kirschner and Mitchison pointed out in the 1980’s that GTP hydrolysis in microtubules is responsible for the amazingly high rate of monomer exchange of cytoskeletal components with the surrounding solvent [7]. A quick calculation with the measured association rates and binding energies shows that the dissociation rates at thermal equilibrium would be far too slow to support the massive structural rearrangements that take place over the course of the cell cycle. The large difference in chemical potential between the GTP and GDP pools in the cytosol allows the microtubule polymerization reaction to break detailed balance, speeding up the dynamics while maintaining the strength and stiffness demanded by the biological function of these structures.

Over the past decade, it has become clear that microtubules are not unique in this regard. The coupling of nucleotide hydrolysis to disassembly is a generic feature shared by a variety of intracellular structures, which rely on these detailed-balance-breaking chemical fluxes to enable rapid responses to biochemical signals without sacrificing mechanical integrity. Recent studies have established the Hsp70 family of chaperone proteins as an all-purpose ATP-powered disassemblase, responsible for the rapid disassembly of disordered aggregates as well as of the protein coats that regulate vesicle formation in eukaryotic cells [2] [4] [18]. Phase-separated intracellular droplets and granules appear to be fluidized by similar mechanisms [11], and even the structure of interphase chromatins seems to be set by the competition between equilibrium phase separation and active disassembly [12].

These discoveries make it increasingly urgent to convert our intuition that dissipation accelerates dynamics into a precise physical principle [5]. Doing this requires answering at least three questions. First of all, statistical mechanics tells us that only the ratios of kinetic rates are controlled by detailed balance, not the absolute rates themselves. So the connection between breaking detailed balance and increasing speed relies on some prior assumptions about the rates, which should be spelled out explicitly. Secondly, increasing the temperature is a simple way of accelerating kinetics without breaking detailed balance. How does the effect of active disassembly differ from mere thermal acceleration? Finally, many driven structures in the cell qualitatively resemble equilibrium models, and the paradigm of equilibrium phase separation has indeed been successfully used to describe much of the phenomenology of intracellular droplets [3] as well as much smaller protein aggregates [11]. Does active disassembly merely speed up the dynamics while leaving the other properties of the steady state untouched, or can we find measurable signatures of dissipation if we know what to look for?

To address these questions, we developed the simplified model of chemically driven disassembly illustrated in Figure 1 loosely based on the dynamics of endocytic protein coats [2]. We considered a solution of proteins that can exist in two distinct conformational states with identical internal free energy: “active” and “inactive.” Active proteins, at concentration $c_A$, stochastically bind to and dissociate from the assembled portion of the structure with binding energy $\Delta G = Jm$, where $m \in [0,1]$ is the fraction of the $N$ binding sites of the fully assembled structure that are currently occupied. These proteins bind to available sites at a rate $k_{on} = c_A k$ per site, and dissociate at a rate $k_{off} = k e^{-\beta \Delta G}$ where $\beta = 1/k_B T$ is the inverse thermal energy scale. Inactive proteins at concentration $c_I$ can also enter the binding sites with the same rate law $k_{on} = c_I k$, but they do not interact with the existing structure, and leave the site at a rate $k_{off} = k$. This choice of rates implicitly sets the units of concentration such that $c_I = 1$ is the (unattainably large) value at which the non-interacting proteins would occupy half of the available sites, without the help of any inter-particle forces.

These proteins also interact with a chemical fuel source. For concreteness, we assume that ATP binding stabilizes the active conformation and ADP the inactive conformation, and that these molecules are present at
high enough concentration that the proteins are always bound to one or the other. The populations of the two states in solution rapidly equilibrate due to catalyzed exchange of ATP/ADP with the surrounding reservoir, where the concentrations are clamped at fixed values of [ATP] and [ADP] by an external chemostat:

$$\frac{c_l}{c_A} = \frac{[ADP]}{[ATP]}$$

(1)

Bound proteins can spontaneously switch to the inactive conformation at a rate $k_I$ per protein, hydrolyzing the bound ATP molecule in the process. The hydrolysis reaction carries a free energy change of $\Delta G_{\text{hyd}} = \Delta G_0 - k_B T \ln [P_i]$, where $[P_i]$ is the molar concentration of inorganic phosphate, and $\Delta G_0$ is the magnitude of the free energy change when $[P_i] = 1$ M. Thermodynamic consistency now links the rate $k_A$ of switching back to the active conformation to $k_I$ by the relation:

$$\frac{k_A}{k_I} = e^{\beta (\Delta G - \Delta G_{\text{hyd}})}.$$  

(2)

If the ATP and ADP concentrations are held out of equilibrium, as in the cytosol, then a net probability current is set up around the cycle illustrated in Figure 1. Equation (1) allows us to express the size of the departure from detailed balance in terms of the chemical potential difference $\Delta \mu$ between the two nucleotide reservoirs:

$$\Delta \mu = k_B T \ln \frac{c_A}{c_l} + \Delta G_{\text{hyd}}.$$  

(3)

When $\Delta \mu = 0$, the system will relax to a state of thermal equilibrium that obeys detailed balance. Nonzero values of $\Delta \mu$ allow for continuous assembly-disassembly cycles in the steady state, driven by the work of the chemostat that maintains the fixed concentrations of ATP and ADP.

We proceeded to answer the first question, by identifying a natural constraint that would link acceleration to detailed balance breaking. In many biochemical contexts, the rate of arrival of new monomers is controlled by the time $\tau_D \sim (a D c)^{-1}$ required to diffuse with diffusion coefficient $D$ to an open site of linear size $a$ on the structure. Since the diffusion coefficient $D \sim 1/6 \pi \eta a$ depends mainly on the size of the particle and the viscosity $\eta$ of the medium, it is not easily tuned by evolution, and can be regarded as a constant for the purpose of evaluating trade-offs. Under this constraint, it makes sense to choose our units of time such that $k_A^{\text{on}} = c_A$. The binding energy $\Delta G$, on the other hand, depends sensitively on the detailed features of the binding surface, and is readily tunable by point mutations. The immediate consequence of this constraint is an exponential suppression of the dissociation rate $k_A^{\text{off}} = e^{-\beta \Delta G}$ of active monomers.

A trivial way of avoiding this slowdown without breaking detailed balance would be to increase $c_I$ or $k_I$, so that most of the particles in the structure are inactive, with fixed dissociation rate $k_I^{\text{off}} = 1$. But since the inactive particles are non-interacting, this would no longer represent a true self-assembly process, but a transient density fluctuation in a concentrated solution of freely diffusing particles. We will therefore restrict our attention to the regime $c_I, k_I \ll 1$, so that inactive monomers dissociate from the lattice much faster than they are added from the solvent or created from active monomers in the structure. To ensure that both these conditions are fulfilled, we held $c_I$ and $k_I$ fixed at values much smaller than 1 while varying the other parameters in the calculations below.

With the assumption of diffusion-limited association providing the link between detailed balance and kinetics, we proceeded to quantify the speed limits of thermal equilibrium: What is the maximum local turnover rate $k_m$ (including dissociation via the inactive state) at fixed $k, c_I, k_I$ in thermal equilibrium? And what is the time scale for large-scale structural rearrangement under these conditions? To answer these questions, we obtained a closed set of dynamical equations for the structure occupancy $m$ by computing the mean waiting time for dissociation via the inactive state $[14]$. The occupancy can increase by an increment $\Delta m = 1/N$ with Poisson rate

$$w_+(m) = c_A [1 + e^{-\beta \Delta \mu} q(m)]$$

(4)

and can decrease by $1/N$ with rate

$$w_-(m) = e^{-\beta J m} [1 + q(m)]$$

(5)

FIG. 1. Color online. Model of chemically driven self-assembly process. Circles represent active monomers, and squares represent inactive monomers with much weaker binding affinity. When the protein is in the structure, it can catalyze the hydrolysis of an ATP molecule to ADP, which is coupled to the protein’s internal conformation in such a way as to force it into the inactive state. When the protein leaves the structure, it can exchange the ADP molecule with the solvent and return to the active state. The units of time have been chosen so that $k = 1$. 

The distribution relaxes under these dynamics to a detailed balance. Above the critical coupling, the system exhibits a first-order phase transition between a disassembled state and an assembled state, when the system assembles to the disassembled state, when the system transitions to the inactive state becomes more and more irreversible.

The probability of finding the system at a given occupancy evolves according to the Master equation

\[
\frac{\partial p(m)}{\partial t} = w_+(m)p(m - \Delta m) + w_-(m)p(m + \Delta m) - [w_+(m) + w_-(m)]p(m).
\]

The distribution relaxes under these dynamics to a steady state defined by

\[
p_{ss}(m)w_+(m) = p_{ss}(m + \Delta m)w_-(m + \Delta m).
\]

In the limit of large \(N\), the steady-state distribution scales as \(p_{ss}(m) \propto e^{-Nf(m)}\), and Equation (8) can be rewritten in terms of \(f(m)\) as

\[
\frac{df}{dm} = \ln \frac{w_-(m)}{w_+(m)}.
\]

Integrating this expression yields

\[
f(m) = f_{eq}(m) + \frac{1}{\beta J} \left( \text{Li}_2 \left[ -k_f(e^{-\beta \Delta G_{\text{hyd}}} + e^{-\beta \Delta \mu})e^{\beta J m} \right] - \text{Li}_2 \left[ -k_f(e^{-\beta \Delta G_{\text{hyd}}} + 1)e^{\beta J m} \right] + N \right),
\]

where the first term is the equilibrium free energy for a fully coupled Ising model:

\[
f_{eq}(m) = m \ln m + (1 - m) \ln(1 - m) - m \ln c_A - \frac{\beta J}{2} m^2
\]

and the second is expressed in terms of the dilogarithm function

\[
\text{Li}_2(z) \equiv \sum_{k=1}^{\infty} \frac{z^k}{k^2}.
\]

For large \(N\), the probability \(p_{ss}(m)\) concentrates on the occupancy fraction \(m^*\) that minimizes \(f(m)\), whose shape is illustrated in Figures 3 and 4. In the absence of a chemical driving force, minimizing Equation (11) generates the usual phase diagram of the Ising model, shown in the first panel of Figure 2. The equilibrium phase diagram provides the final piece of information for answering our first question about the constraints that follow from detailed balance. Above the critical coupling \(J_c = 4k_B T\), the system exhibits a first-order phase transition between a disassembled \(m^* \approx 0\) phase and an assembled \(m^* \approx 1\) phase at a threshold concentration \(c_A = e^{-\beta J/2}\). To satisfy detailed balance \((\Delta \mu = 0)\) without melting the structure, we must therefore choose a \(\Delta G_{\text{hyd}}\) that satisfies:

\[
\beta \Delta G_{\text{hyd}} = \ln \frac{c_I}{c_A} < \frac{\beta J}{2} + \ln c_I.
\]

This result generates our desired upper bound on the total dissociation rate per particle in the assembled phase

\[
k^{\text{off}} = e^{-\beta J(1 + q)} < e^{-\beta J} + c_I e^{-\beta J/2}.
\]

If \(J\) is set to the reasonably large value of \(10k_B T\) and \(c_I \ll 1\) is 0.0001, then \(k^{\text{off}}\) is 20,000 times slower than the rate \(k^{\text{off}} = 1\) for a free particle to diffuse out of the site. This effect is magnified when we consider the mean first passage time \(\tau_{\text{diss}}\) for the global transition from the assembled to the disassembled state, when the system is taken across the phase boundary by an infinitesimal change in one of the parameters [19]:

\[
\tau_{\text{diss}} = \sum_{m=m_0}^{m^*} \sum_{m'=m}^{m^*} \frac{p_{ss}(m')}{p_{ss}(m)w_-(m)} \sim e^{N(f(m^*) - f(m'))}.
\]

Here \(m^*\) is the location of the largest value of \(f(m)\) between its two local minima, and the approximation holds in the limit of large \(N\). As illustrated in Figure 3, the factor of \(N\) in the exponent rapidly brings \(\tau_{\text{diss}}\) to astronomical values. At the moderate coupling \(J = 6k_B T\), where \(k^{\text{off}}\) is only three orders of magnitude slower than \(k^{\text{off}}\), the disassembly rate \(1/\tau_{\text{diss}}\) for \(N = 100\) is already 8 orders of magnitude below this basic rate.

Accelerating the dynamics beyond these limits requires increasing the irreversibility \(\Delta G_{\text{hyd}}\) of the transition to the inactive state, without decreasing the ratio of active to inactive proteins \(c_A/c_I\) in solution. And Equation (3) implies that this necessarily breaks detailed balance, creating a nonzero chemical potential difference \(\Delta \mu > 0\) between the ATP and ADP reservoirs. As shown in Figure 2, a moderate increase in \(\Delta G_{\text{hyd}}\) to \(2.5k_B T\) with
FIG. 3. Top left: Turnover rate $k_{\text{off}}$ in assembled phase as a function of $\Delta \mu$ for $\beta J = 6, 8, 10, 12, 14$. The concentration $c_A$ is tuned to the coexistence point, with $c_I = 0.0001$. Bottom left: Effective free energy landscape $f(m)$ along the $\beta J = 6$ trace of the first plot, with $\beta \Delta \mu$ ranging from 0 to 15. Top right: Stochastic trajectories for lattice of size $N = 100$, with $c_A$ tuned to coexistence at $\beta J = 6$ and $\beta \Delta \Delta_{\text{hyd}} = 2.5$. Black trace is obtained with active disassembly pathway deactivated ($k_I = 0$), and gray trace is taken from driven system with $k_I = 0.01$ (gray). Bottom right: Mean time $\tau_{\text{diss}}$ for switching from high to low $m$ states as a function of $J$ under the same conditions. Black circles are for $k_I = 0$, and gray squares have $k_I = 0.01$.

$c_I = 0.0001$ leaves the phase diagram almost unchanged, while Figure 3 shows that the disassembly time $\tau_{\text{diss}}$ decreases by 4 orders of magnitude. This figure also shows how $k_{\text{off}}$ grows as $\Delta \mu$ increases. The effect is particularly dramatic for $J$ above about 10 $k_B T$, where the equilibrium turnover rate is vanishingly small, but suddenly increases and saturates to $k_{\text{off}} \approx k_I = 0.01$ when $\Delta \mu$ crosses a $J$-dependent threshold. This happens when the inactivation reaction becomes effectively irreversible, so every hydrolysis event leads to ejection from the structure. Notably, the physiological value of $\Delta \mu \sim 15 k_B T$ is sufficient to maximally accelerate even structures with $J = 14 k_B T$, which is very large for a non-covalent interaction.

It is possible to achieve this accelerated $k_{\text{off}}$ or this vastly reduced $\tau_{\text{diss}}$ at a given coupling energy $J$ by simply raising the temperature, without any dissipation of chemical energy. The novel feature of the driven model is not the acceleration itself, but the achievement of faster kinetics without melting the structure. In the undriven dynamics with the inactivation pathway turned off ($k_I = 0$), the temperature only appears in the combination $\beta J$, and so we can visualize the effect of changing the temperature in the plot of $\tau_{\text{diss}}$ vs. $J$ by simply rescaling the $J$ axis. Since the slope of the driven dynamics is less than half that of the undriven dynamics, the temperature would have to be more than doubled in order to achieve the same disassembly time. Raising the temperature to $T' = 2T$ also increases the critical coupling to $J_c = 4k_B T' = 8k_B T$, and destroys the sharp transition between assembled and disassembled phases for lower values of $J$. But in Figure 2, we saw that the critical coupling for the driven system in fact remains very close to that of the undriven system at the original temperature. The ATP-fueled disassembly pathway thus opens up a new regime that is not accessible under the constraints of detailed balance, combining high-temperature kinetics with low-temperature phase behavior.

But the similarity of the driven and undriven phase diagrams at $\Delta G_{\text{hyd}} = 2.5 k_B T$ led to our final question: is kinetic acceleration the only significant effect of the nonequilibrium driving force, or are there static features of the steady-state distribution that reveal the presence of chemical fluxes? We found that a dramatic signature does emerges for stronger driving forces, and have plotted the phase diagram and $f(m)$ for the physiologically realistic value $\Delta G_{\text{hyd}} = 15 k_B T$ in Figure 4. A new intermediate phase emerges, separated by sharp transitions from $m^* = 0$ and $m^* = 1$ regimes. Using Equations 5 and 6, we find that the transition to the inactive conformation becomes effectively irreversible when $e^{-\beta \Delta G_{\text{hyd}}} \ll e^{-\beta J_{m} / k_I}$. In this regime, almost every such transition ends in dissociation from the lattice, so the dissociation rate through this pathway is equal to the inactivation rate $k_I$. If it is also the case that $k_I \gg e^{-J_{m}}$, then this is the dominant pathway for dissociation, and we can write

$$w_-(m) \approx mk_I$$

These same requirements guarantee that

$$w_+(m) \approx (1 - m)c_A$$

as long as $c_I < c_A$. The $m$-dependence of both of these rates is identical to that of the undriven dynamics in the absence of inter-particle coupling ($J = 0$), whose free energy landscape is illustrated by the blue dashed line in Figure 4, regardless of the actual value of $J$. If this regime includes the unique point where $w_- = w_+$, then this point becomes a local maximum of the steady-state distribution, which can be located anywhere between 0 and 1 (depending on the values of $k_I$ and $c_A$). This allows the system to be stable in a partially occupied state even at high values of $J$, something that is impossible in the absence of driving. Furthermore, the fluctuations around this maximum take on a distinctive form, since they are entirely determined by entropic effects. We find that the mean $m^*$ and variance $\sigma^2$ of the steady-state distribution are related in the $N \rightarrow \infty$ limit by

$$N\sigma^2 = m^*(1 - m^*)$$

which depends only on $N$ and not on any of the other parameters of the model.
FIG. 4. Top: Steady-state occupancy $m^*$ as a function of $J$ and $c_A$ with $\beta \Delta G_{\text{hyd}} = 10$, $k_I = 0.01$ and $c_I = 0.0001$. Bottom: Effective free energy $f(m)$ at the coexistence point indicated by the star in the top panel. The gray solid line is the actual $f(m)$, which matches $f_{eq}(m)$ for the given $J, c_A$ values (red dash-dot line) near $m = 0$, and matches the purely entropic $J = 0$ behavior of $f_{eq}(m)$ (blue dashed line) above $m = 0.5$.

Near $m = 0$, however, the assumption $k_I \gg e^{-Jm}$ is bound to fail. We have already required that $k_I \ll 1$, but $e^{-Jm}$ approaches 1 as $m \to 0$ for any value of $J$. This guarantees that the behavior near $m = 0$ will be nearly identical to that of the undriven system with $k_I = 0$, as illustrated in Figure 4. So even though the partially assembled phase locally shows no signs of cooperativity in the behavior of the mean and variance of $m$, there is still a sharp transition to a fully disassembled $m^* \approx 0$ phase at sufficiently high values of $J$. We expect that a similar novel phase should exist also in more complex models of driven self-assembly. Whenever the driven disassembly process removes particles so reliably as to be insensitive to the strength of their bond with their neighbors, the steady-state statistics above the initial nucleation threshold should be entirely dominated by entropic effects.

In conclusion, our toy model of driven disassembly has provided preliminary answers to our three original questions: diffusion-limited association links speed to dissipation, the driven steady state under these conditions combines high-temperature kinetics with low-temperature phase behavior, and large enough chemical driving forces generate a clear statistical signature in the steady-state occupancy distribution. Similar observations have been made in different contexts, including the vast world of dynamic structures in active materials driven by mechanical forces [4, 8, 13, 16, 17], and the various forms of kinetic proofreading [10, 15]. Our model represents a distinct class of systems that relies on purely chemical forces to accelerate the response of self-assembled structures. We hope that further study of this biologically ubiquitous framework will contribute to the discovery of unifying principles linking speed, resilience and dissipation in all of these diverse settings.

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