

Dissipation rates from experimental uncertainty

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Active matter and driven systems exhibit statistical fluctuations in density and particle positions that are an indirect indicator of dissipation across length and time scales. Here, we quantitatively relate these fluctuations to a thermodynamic speed limit that constrains the rates of heat and entropy production in nonequilibrium processes. By reparametrizing the speed limit set by the Fisher information, we show how to infer these dissipation rates from directly observable or controllable quantities. This approach can use available experimental data as input and avoid the need for analytically solvable microscopic models or full time-dependent probability distributions. The heat rate we predict agrees with experimental measurements for a pulled Brownian particle and a microtubule active gel, which validates the approach and suggests potential for the design of experiments.

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Introduction. Dissipation rates determine the efficiency of biological processes [1,2] and are now an important feature in designing active synthetic materials that function [3–10]. For example, active cytoskeletal materials sustain self-organized flows by consuming chemical energy and dissipating heat at picowatt rates [11]. It recently became possible to measure these rates with advances in picocalorimetry [12] and to directly observe active materials in the liquid phase with high-resolution electron microscopy [13]. These techniques are able to resolve dissipative degrees of freedom and beginning to provide a better understanding of how chemical energy propagates up length and timescales. However, these measurements are often interpreted with empirical models of the kinetics, which can have large uncertainties, missing parameters, and modeling assumptions that may be unjustified for active materials (e.g., well-mixed chemical kinetics, modeling only rate limiting reactions) [14]. Model-free approaches to predict dissipation rates from available experimental data could guide this experimentation on functional materials and their design [15–17].

Surveying stochastic thermodynamics [18], the thermodynamic speed limit [19] set by the Fisher information [20–22] $I_F = \tau^{-2}$ has potential for estimating dissipation rates. While not yet experimentally tested, this single timescale upper bounds the rate of heat, entropy production, dissipated work, and chemical work [19,23–25]. For example, a system that dissipates energy as heat with a rate $\dot{Q}$ [26] and is subject to energy fluctuations with a standard deviation $\Delta\epsilon$ has the speed

limit [19]

$$\tau_Q^{-1} := \frac{|\dot{Q}|}{\Delta\epsilon} \leq \sqrt{I_F} =: \tau^{-1}, \quad (1)$$

even if work is done on or by the system [27]. Speed limits on dissipation rates are now known in quantum [28–30], classical deterministic [31,32], and stochastic [19,33–35] dynamics. Alternative approaches to infer dissipation, such as the dissipation-time uncertainty relation [36] or the thermodynamic uncertainty relation [37–44] and its extensions [45,46] estimate dissipation through the statistics of currents [47]. Others use optimization methods and transition rates [48,49], waiting times [48,50], variances [51,52], partial information, and coarse graining [53,54]. However, these approaches give lower bounds on entropy production rates that are not necessarily explicit functions of easily measurable observables or estimates of the energy dissipated as heat. By contrast, estimates of the Fisher information in Eq. (1) could give upper bounds on the maximum rate of dissipation of entropy and heat. Equation (1) is also unique in that it can be combined with the quantum time-energy uncertainty relation [55] to bound the dynamical observables of open quantum systems [56].

In this Letter, we establish a method for predicting the rates of nonequilibrium observables from experimental data through the thermodynamic speed limit in Eq. (1). The Fisher information in this inequality is crucial in that it enables the use of uncertainty measurements as input. Both the classical and quantum Fisher information are an important part of the statistical design of experiments on systems ranging from chemical reactions and biological populations to dark matter [57]; by measuring experimental errors, one can use the Fisher information (matrix) to predict *a priori* the minimum error of any measured quantity [58]. In this context, the Fisher information predicts the minimum error in an observable before the measurement, which can then be used to assess the measurement sensitivity to control variables, minimize errors,

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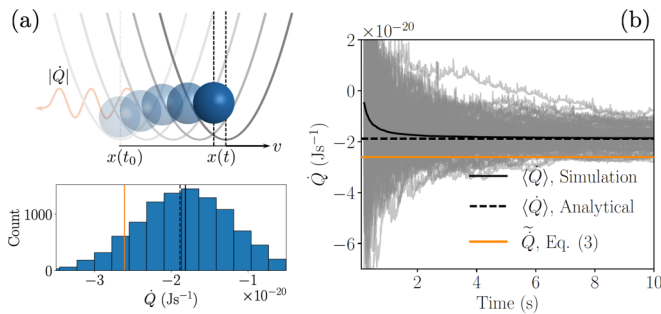


FIG. 1. (a) A Brownian particle dissipates energy as heat when pulled through a viscous medium. At $t = t_0$, the particle is at the trap center $x(t_0)$. Translating the trap through space forces the average particle position to be higher on the potential. During the process, heat is dissipated at a rate $|\dot{Q}|$ into the environment. (b) Histogram of the heat dissipated to the environment from a simulation of the overdamped Langevin dynamics for 10 000 noise realizations at $t = 4$ s (see Sec. 2 in the SM [59]). The housekeeping heat rate from Eq. (3) (orange) agrees with the sample mean from the simulations (black solid line) and the analytical mean (black dotted line).

and improve precision. Here, we establish a similar method for inferring dissipation rates, transforming the coordinates of the Fisher information so that we can use available measurements of positions, concentrations, and control variables [11]. The predictions of this method confirm experimentally measured dissipation rates in several examples, including the heat dissipated by active cytoskeleton materials composed of kinesin motors and microtubules [11] recently measured with picrocalorimetry [12].

Predicting dissipated heat by transforming the speed limit. To illustrate the approach, we first determine the net heat rate $|\dot{Q}|$ when dragging an optically trapped colloidal particle at a speed $|v|$ through a viscous medium at a temperature T , Fig. 1. Over time, the particle position fluctuates with a standard deviation σ_x that converges to a finite value at nonequilibrium steady state. At this steady state, we consider the situation in which the true position distribution is unknown but one can make a sufficient number of measurements of the particle position to estimate the first couple of statistical parameters. For example, by repeatedly measuring the spatial location of the particle, one can use an estimator to get an empirical standard deviation $\Delta\hat{x} = \sigma_x \pm |\varepsilon|$ with measurement error ε . We will denote the estimators of these directly measured variables $\hat{\theta}$ to distinguish them from the true values θ and from predictions of these variables $\tilde{\theta}$.

At first glance, determining the speed limit τ^{-1} set by the Fisher information seems to require the probability distribution $\rho(x, t)$ from experiments or a microscopic model for the dynamics of the particle. The measured positions x_i depend on the unknown distribution $\rho(x, t)$ moving through space at an unknown intrinsic rate $r = -\partial_t \ln \rho(x, t)$ —a nonzero quantity in the laboratory frame at nonequilibrium steady state. The Fisher information that sets the speed limit in Eq. (1) is the variance $\tau^{-2} = \Delta r^2$. This fact means we can estimate it by propagating the uncertainty in the particle position (see Sec. 1 in the Supplemental Material (SM) Ref. [59]).

To relate the speed limit to a measurable variance, we recognize that the rate $\hat{r}$ is a function $\hat{r} = f(\hat{x})$ of the position

measurements. Since the fluctuations in position $\Delta\hat{x}$ propagate [60] to $\Delta\hat{r}$, the speed limit is

$$\tilde{\tau}^{-1} := \Delta\hat{r} = \frac{\Delta\hat{x}}{|\partial_f \hat{x}|} + \mathcal{O}(\Delta\hat{x}^2). \quad (2)$$

Rearranging to $\Delta\hat{x}^2 = (\partial_f \hat{x}) \tilde{\tau}^{-2} (\partial_f \hat{x})$, we can see that the uncertainty in position is also a coordinate transformation of the Fisher information. Through this coordinate transformation, we also see that a direct measurement of $\Delta\hat{x}$ could serve as an indirect measurement $\tilde{\tau}^{-1} = \Delta\hat{r}$ of the true speed limit. If we have the function f , we can use measurements of $\Delta\hat{x}^2$ to estimate the speed limit.

Regression techniques are one means of finding the function and its derivatives in Eq. (2) when the dynamics of the distribution $\rho(x, t)$ are unknown. We hypothesize the relationship between the rate $\hat{r} = f(\hat{x})$ [23] and chosen observable $\hat{x}$, and minimize the mean squared error to find the optimal parameters and the derivatives [61]. For example, if hypothesize a linear relationship $f(\hat{x}) = a + b\hat{x}$, we see that we need a and b , which appears to require measurements of $\hat{r}$ or $\rho(x, t)$. However, because we have chosen $\hat{r}$ as our regression variable, the optimal slope is actually computable $b_{\text{opt}} = \partial_{\hat{x}} f = v/\Delta\hat{x}^2$ (Sec. 2 in the SM [59]). Therefore, combining an optimized regression hypothesis with Eq. (2) gives the speed limit $\tilde{\tau}^{-1} = |v|/\Delta\hat{x}$ in terms of the pulling speed and sample standard deviation $\Delta\hat{x}$. The sample standard deviation is generally easier to estimate than the full distribution, so this speed limit estimate requires less data and less computational effort than sampling the full distribution over time.

From measurements of the position fluctuations, we can also use the speed limit to predict the heat rate (Sec. 3 in the SM [59]) and other nonequilibrium observables. Notice that we can isolate the heat rate in Eq. (1): $|\dot{Q}| = \tau_Q^{-1} \Delta\epsilon$. We similarly find the measured heat rate $\tilde{Q}$ using Eq. (2) and estimate $\tilde{\tau}_Q^{-1} \Delta\epsilon \approx \tilde{\tau}^{-1} \Delta\epsilon$. For the pulled particle, the heat rate at nonequilibrium steady state,

$$|\tilde{Q}| = \tilde{\tau}_Q^{-1} \Delta\epsilon \approx |v| \Delta\epsilon / \Delta\hat{x}, \quad (3)$$

is in terms of known quantities from the experimental setup: the pulling speed and the uncertainties in the particle position and energy. In the laboratory frame, this heat rate is the housekeeping contribution that maintains the nonequilibrium steady state [26].

Equation (3) gives predictions of the heat rate using available experimental parameters. Take a particle of radius $1 \mu\text{m}$ being pulled at a speed [62] $|v| = 1 \mu\text{m s}^{-1}$ through water. If we measure the standard deviations from experiments, the heat rate follows from Eq. (3) without any additional assumptions. However, provided the surrounding medium is at thermal equilibrium, the standard deviation in position is known [63] to be $\Delta\hat{x} \approx \sigma_x = \sqrt{k_B T / k_f} = 78.32 \text{ nm}$ (errors can be of order $\pm 2 \text{ nm}$ [62]), and the standard deviation in energy is $\Delta\epsilon \approx k_B T / 2$. We take the trap to be harmonic with a force constant $k_f = 6.67 \times 10^{-7} \text{ N m}^{-1}$ and the surrounding medium to be water with a viscosity $\eta = 10^{-3} \text{ Pa s}$ at 296.5 K [64]. Using only these experimental values, the heat rate from Eq. (3) is $|\tilde{Q}| = \frac{1}{2} |v| \sqrt{k_f / \beta} = 2.61 \times 10^{-20} \text{ W}$.

To confirm this value, we chose physical models for the dynamics of the particle at the same experimental conditions.

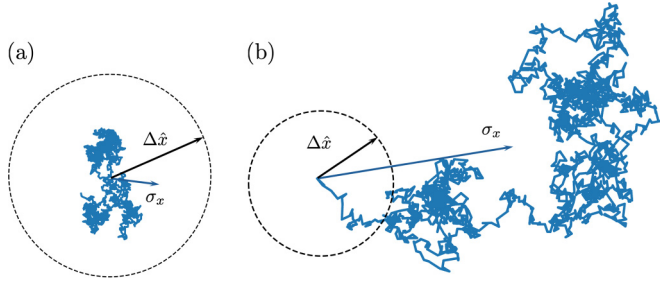


FIG. 2. Illustration showing the measured fluctuations $\Delta\hat{x}$ compared to the intrinsic fluctuations σ_x of a particle undergoing Brownian motion. (a) A higher uncertainty $\Delta\hat{x}$ than the true position fluctuations σ_x . (b) A lower measured uncertainty than the true position fluctuations.

We numerically simulated a particle undergoing Brownian dynamics and, over time, measured the particle position (Fig. 2) relative to the trap center in the laboratory frame [65,66]. As shown in Fig. 1, the housekeeping heat rate from Eq. (3) agrees well with the average over noise realizations from our numerical simulations 1.85×10^{-20} W. It also agrees well with an analytical prediction [62] for the heat rate $|\langle\dot{Q}\rangle| = v^2/\gamma = 1.885 \times 10^{-20}$ W (Sec. 2 in the SM [59]).

As this example highlights, the coordinate transformation of the Fisher information [67], together with a regression hypothesis for the relationship between r and $\hat{x}$, can bypass the need for the full probability distribution of a dynamical model. This observation motivates the derivation of a more general method for measuring this speed limit by transforming the Fisher information into the variance of other measurable quantities.

Thermodynamic speed limits from experimental uncertainty. The method here relates the variance $\tilde{\tau}^{-2} = \Delta\hat{r}^2$ to the variance $\Delta\hat{x}^2$. It is similar to the propagation of errors in that it also approximates an unknown probability distribution with its mean and variance. If we used the propagation of errors, we would model these measured quantities as random variables with means μ and covariances $(C_X)_{ij} = \text{cov}(X_i, X_j)$. We would express m functions of $Y = f(X)$ in terms of n measured quantities X by Taylor expanding

$$f_i(X) = f_i(\mu) + \nabla f_i^\top|_{X=\mu}(X - \mu) + \mathcal{E} \quad (4)$$

with the gradient $\nabla f_i = (\partial_{X_1} f_i, \partial_{X_2} f_i, \dots)^\top$ and error $\mathcal{E}$. Then, taking the error to be uncorrelated with the inputs X_i , we would propagate the covariances between elements of X to the covariances of f ,

$$C_Y = \nabla f^\top C_X \nabla f + \sigma_{\mathcal{E}}^2, \quad (5)$$

to the covariances $(C_Y)_{kl} = \text{cov}(f_k, f_l)$ with the Jacobian ∇f [68]. However, applying standard error propagation depends on knowledge of the functions and their derivatives, which, in our case, means finding the dynamics of an unknown distribution.

We avoid this issue with error propagation by instead making a regression hypothesis for a single function r and using the fact that the Fisher information is its variance Δr^2 . There are two immediate advantages of this approach. First, instead of the vector Y in Eq. (4) we have the scalar $\hat{r}$, and

instead of the covariance matrix C_Y in Eq. (5) we have the speed limit estimate $\Delta\hat{r}^2$. Second, by choosing the regression of the function r , the gradients/slopes are directly proportional to the covariances $c := \text{cov}(r, X)$. These covariances are rates of physical quantities [19]; for example, the heat rate is $\dot{Q} = -\text{cov}(r, \epsilon)$. Another example was our choice of $f(\hat{x}) = a_{\text{opt}} + b_{\text{opt}}\hat{x}$ for the pulled particle. In that case, the Jacobian from $\hat{x}$ to $\hat{r}$ is the optimal slope $|\partial_{\hat{x}} f| = b_{\text{opt}} = |\partial_t \langle \hat{x} \rangle| / \Delta\hat{x}^2 = |v| / \Delta\hat{x}^2$.

Using a linear regression hypothesis, Fisher information transforms as

$$\tilde{\tau}^{-2} = \Delta\hat{r}^2 = c^\top C_X c. \quad (6)$$

In the single variable case, the Fisher information $I_F(\theta) = (\partial_\theta f(\theta))^2 I_F(f(\theta))$ depends on parameter $I_F(\theta)$, and transforms to a function of that parameter $I_F(f(\theta))$. Here, the consequence of this equality is that correlations between measured variables C_X and measurable rates in c give an estimate of the speed limit $\tilde{\tau}^{-1}$. In other words, our main result is that the Fisher information can be transformed into (co)variances of measurable and more readily computable variables (without the full probability distribution over time) and estimate nonequilibrium rates.

Inferring the speed limit from data. We are free to choose the input (co)variances for the speed limit based on experimental convenience and the data that is available. As with any estimate, these choices must be made judiciously. The input variables should be those that are dissipative and have a finite variance; measuring only fluctuations in variables that are uncorrelated with dissipative degrees of freedom could not give accurate estimates of the speed limit (Sec. 3 in the SM [59]).

Another consideration is that the true relationship between r and measured variables X may be nonlinear. When the distribution is Gaussian, the dragged colloidal particle is an example of the case in which r is a linear function of positions. However, the dynamics may not be Brownian, the distribution may not be Gaussian, or the distribution may not be known analytically. Even if the true relationship is nonlinear, one can still minimize the error of a linear model, determine the parameters, and make an optimal prediction $\tilde{\tau}^{-1}$ of the true speed limit τ^{-1} with experimental data. One could also instead choose a model that is quadratic in $\hat{x}$ (and linear in the parameters), $f = a_{\text{opt}} + b_{\text{opt}}\hat{x} + c_{\text{opt}}\hat{x}^2$. In this case, the variance is $\Delta\hat{r}^2 = b_{\text{opt}}^2 \Delta\hat{x}^2 + c_{\text{opt}}^2 \Delta(\hat{x}^2)^2$.

Regression lowers the speed limit. Linear regression on r systematically lowers the speed limit. Let's compare the difference between the true speed limit $\tau^{-1} = \Delta r$ and the estimated speed limit $\tilde{\tau}^{-1} = \Delta\hat{r}^2$ from the linear approximation $\hat{r} = a + b\hat{x}$. With the optimal parameter b_{opt} , the true fluctuations in r are larger than those in the linear approximation

$$\Delta r^2 - \Delta\hat{r}^2 = \langle r^2 \rangle - b_{\text{opt}}^2 \Delta\hat{x}^2 = \Delta r^2 - \frac{\text{cov}(r, \hat{x})^2}{\Delta\hat{x}^2} \geq 0, \quad (7)$$

which follows from the Cauchy-Schwarz inequality. Therefore, neglecting experimental errors in $\Delta\hat{x}$, the estimate of the speed limit $\tilde{\tau}^{-1} = \Delta\hat{r}$ is systematically lower $\tau^{-1} \geq \tilde{\tau}^{-1}$. If r is in fact a linear function $\hat{r} = a + b\hat{x}$, then this inequality will saturate.

Prediction of energy dissipation rates for active gels. As another example, we compared the predicted heat rate with experimental measurements for microtubule active gels. In these active materials, kinesin motors cross-link microtubule pairs. The forward motion of the motors is driven by the chemical energy from ATP hydrolysis, which also releases energy as heat and sustains self-organized flows at longer length and time scales. The first picocalorimetry measurements [12] suggest the energy efficiency of these materials is low: the minority of the input chemical energy propagating to productive emergent flows and the majority dissipated away as waste heat [11].

Using the concentrations of chemical species in our main result, Eq. (6), the predicted heat rate

$$|\tilde{Q}| = |\partial_c \hat{r}| \Delta \hat{c} \Delta \hat{e} = \frac{|d_r \hat{c}|}{\Delta \hat{c}} \Delta \hat{e} \quad (8)$$

is in terms of $|d_r \hat{c}|$ the average rate of ATP hydrolysis and the standard deviations in concentration and energy. The rate of ATP hydrolysis depends on the initial concentrations of kinesin, microtubule, ATP, and rate constants (Sec. 4 in the SM [59]). This rate can be determined with a previously parametrized model or without a model from the numerical derivative of concentration measurements. Here, we use measured rate constants and a kinetic model for ATP hydrolysis that were reported previously [11].

To predict the heat rate with Eq. (8), we can use either measurements or estimates of the concentration and energy fluctuations. Since there are not direct measurements of the energy fluctuations, we estimate these values from available information. The active material is in a buffer solution of 1% 35 kDa polyethylene glycol in room temperature water at a pH of 6.8 (Sec. 4 in the SM [59]). A single molecule undergoes about $10^{13} - 10^{14}$ collisions per second, exchanging an average energy on the order of $k_B T$ at a rate of 10^{-8} W. In Ref. [11], the heat rate measurements are on the order of 1000 s, so we estimate $\Delta \hat{e} = 10^{-8} \text{ W} \times 1000 \text{ s} = 10^{-5} \text{ J}$. This estimate agrees with the uncertainty of the measured heat rate, which are on the order of 100 nW with fluctuations are on the order of 10–15 nW when the gel was prepared with and without the pyruvate kinase-based ATP regeneration system.

Pipetting error is likely the dominant source of error in these measurements [11], and data is not currently available for $\Delta \hat{c}$, so we instead estimate the standard deviation using experimental error. The total sample volume is 0.5 μL and the initial ATP concentration varies from 1.5 to 1500 μM . Propagating the 5% error in dose volume $\Delta \hat{c} = \hat{c} V^{-1} \Delta V$, the uncertainty in concentration is on the order of 1 μM for ATP concentrations in the range 12.5–190 μM . Other potential sources of uncertainty are the pipetting protocol and fitted rate constants, which could also be accounted for using Eq. (6).

While less data is available for these estimates, they illustrate the flexibility of this method and the ability to use information on hand. With these estimated inputs, the heat rate predicted with Eq. (8) agrees well with picocalorimetry measurements [11]. Figure 3 shows the estimated heat dissipation rate as a function of ATP concentration with all other concentrations fixed. Both the measured and estimated

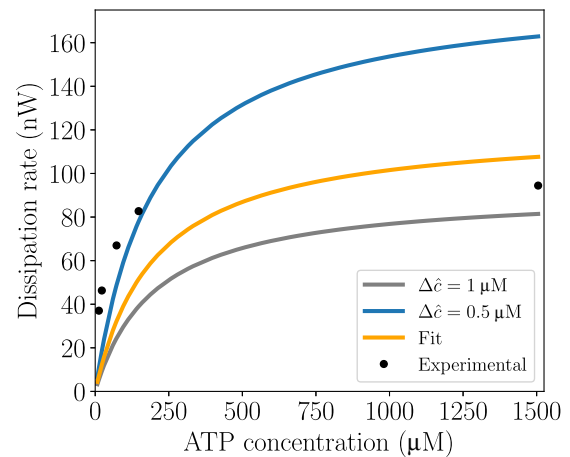


FIG. 3. Comparison of predicted heat rate with experimental measurement. Averaged dissipation rate versus ATP concentration with $[K401] = 210 \text{ nm}$, $[MT] = 16 \mu\text{M}$. We use $\Delta \hat{e} = 10^{-8} \text{ W} \times 1000 \text{ s} = 10^{-5} \text{ J}$ and the rate constants $k_{D,ATP} = 96.4 \mu\text{M}$, $k_{D,MT} = 17.4 \mu\text{M}$, and $k_{cat} = 44 \text{ s}^{-1}$. The fit (orange) is the chemical kinetics model to the data (black points) from Ref. [11].

dissipation rates increase with the initial ATP concentration. Using a standard deviation for concentration $\Delta \hat{c}$ of 0.5 or 1 μM , the predicted heat rate is less than a factor of two of the experimental values. For low ATP concentrations, the prediction with $\Delta \hat{c} = 0.5 \mu\text{M}$ agrees better with the measured data than the direct fit with a chemical kinetics model [11].

Conclusions. Fisher information is widely used in the statistical design of experiments: with known experimental errors, one can predict *a priori* the minimum error in a measured quantity. By leveraging its appearance in the thermodynamic speed limit, we have shown that it has a similar use in predicting dissipation rates. There is freedom to choose convenient transformations of the speed limit, together with statistical regression hypotheses, to make these predictions. A single speed—the square root of the Fisher information—bounds multiple dissipation rates, so we expect the results here to produce estimates of other physical observables. These predictions could be useful in determining the sensitivity of measurements to experimental control variables, and in determining the experimental uncertainty needed for accurate measurements of dissipation rates. Used in these ways, the thermodynamic speed limit set by the Fisher information and the transformation to more convenient variables is a potentially efficient method to guide both the design of experiments and synthetic active materials. Since these speed limit predictions of dissipation rates can be independent of an underlying microscopic model for the dynamics and the distance from thermal equilibrium, they hold across the length and time scales relevant for active materials.

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