Dynamic hysteresis in a one-dimensional Ising model: Application to allosteric proteins

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We solve exactly the problem of dynamic hysteresis for a finite one-dimensional Ising model at low temperature. We find that the area of the hysteresis loop, as the field is varied periodically, scales as the square root of the field frequency for a large range of frequencies. Below a critical frequency there is a correction to the scaling law, resulting in a linear relationship between hysteresis area and frequency. The one-dimensional Ising model provides a simplified description of switchlike behavior in allosteric proteins, such as hemoglobin. Thus our analysis predicts the switching dynamics of allosteric proteins when they are exposed to a ligand concentration which changes with time. Many allosteric proteins bind a regulator that is maintained at a nonequilibrium concentration by active signal transduction processes. In the light of our analysis, we discuss to what extent allosteric proteins can respond to changes in regulator concentration caused by an upstream signaling event, while remaining insensitive to the intrinsic nonequilibrium fluctuations in regulator level which occur in the absence of a signal.

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I. INTRODUCTION

Information processing in living cells is carried out by networks of interacting proteins. The computational capacity of such webs relies on certain network components acting as logical switches, so that their interactions with other components can be turned on and off. It has been suggested that allosteric proteins, which can flip between active and inactive conformations according to the concentration of regulator ligands, form an important class of protein switches [1]. Allostery has been extensively studied, and classic models [2,3] describe a sigmoidal activity curve as a function of ligand concentration, indicating that modest changes in the steady-state level of a regulator can be sufficient to effect a switch. The dynamics of switching, by contrast, has received little theoretical attention. Yet it is important to understand how allosteric proteins respond to changing conditions, in order to establish the speed at which information can be processed and to evaluate the robustness of switch states to intrinsic fluctuations in regulator concentration.

Many allosteric proteins, especially those that occur in signal transduction pathways, respond to a regulator ligand that is activated by a nonequilibrium process. The canonical example is a regulator that is activated by phosphorylation [4]. Phosphorylation is usually achieved by transferring a phosphoryl group from an ATP molecule to the regulator. The production of ATP costs energy and phosphorylated regulators usually dephosphorylate spontaneously, so the concentration of active regulators is far from equilibrium. In order to understand how switches can robustly respond to changes in regulator concentration while filtering out nonequilibrium concentration fluctuations that may be large, we must introduce a framework to describe the dynamics of a protein switch.

The counterparts of protein switches in electronic devices are flip-flops and memory bits, and it is in this context that the dynamics of switching has previously been investigated. When, for example, a magnetic field is varied from a negative to a positive value, there is a delay before a ferromagnetic domain switches from its metastable negatively magnetized state to a globally stable positively magnetized state. The length of the delay depends on the rate at which the field increases. This phenomenon is known as dynamic hysteresis [5], and it occurs in addition to any static hysteresis the system may possess.

The mean-field Ising model at a temperature below the critical temperature is suitable for analyzing this situation. Over a range of field values close to zero the magnetization is double valued and, because stochastic fluctuations are neglected, there is a static hysteresis in the system. When an oscillating external field is applied, the way that the system switches between negatively and positively magnetized states can be analyzed by considering the dynamical response to the change in the Landau free energy [6,7]. Forcing the system at frequency Ω leads to the equation

$$\dot{m} = (km - m^3) + A \sin \Omega t = -h(m) + A \sin \Omega t, \qquad (1)$$

where m is magnetization and $h(m)$ is the applied field that would give rise to magnetization m in the steady state. Dynamic hysteresis leads to an increase in the field value at which switching occurs and to a corresponding increase in the hysteresis area A from its static value A_0. Jung *et al.* [6] showed that close to the critical temperature, the additional area scales with frequency according to $A(\Omega) - A_0 \sim \Omega^{2/3}$.

Conformational transitions in allosteric proteins can be modeled using a one-dimensional nearest-neighbor Ising model [8]. It is our aim to investigate dynamic hysteresis in this situation. In contrast to the mean-field case, static hysteresis is absent in the one-dimensional (1D) Ising model: the magnetization approaches a step function as $T \to 0$ [9]. Nevertheless, dynamic hysteresis still occurs: when the field is varied at a nonzero rate, the magnetization lags behind the field (see Fig. 1).

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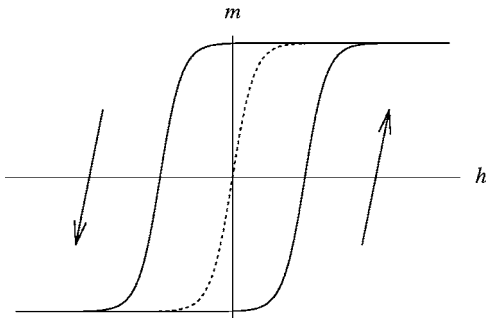

FIG. 1. Dynamic hysteresis in the 1D Ising model. The dotted line shows the magnetization $\langle s \rangle$ as a function of a static field h. If the field is varied at a nonzero rate (arrows), the magnetization lags behind the field, causing a hysteresis loop.

Analogously to Eq. (1), the forced one-dimensional Ising magnet for $T \to 0$ may be modeled by the differential equation

$$\dot{m} = -h(m) + A \sin \Omega t,$$

$$m(h) = \begin{cases} 1, & h \geqslant 0, \\ -1, & h \leqslant 0. \end{cases} \tag{2}$$

This equation bears a resemblance to a class of nonlinear ordinary differential equations of the form

$$\dot{m} = -m|m|^a + A \sin \Omega t, \tag{3}$$

for which dynamic hysteresis has been investigated by Goldsztein *et al.* [10]. The hysteresis area was found to scale as

$$A(\Omega) \sim \Omega^{(a+2)/(2a+1)}. \tag{4}$$

Equation (2) corresponds to Eq. (3) in the limit $a \to \infty$. We therefore expect, from Eq. (4), that in the one-dimensional Ising model, the hysteresis area scales with the square root of the driving frequency:

$$A(\Omega) \sim \Omega^{1/2}. \tag{5}$$

Testing this prediction forms the basis of this paper. In Sec. II we introduce the Ising model of allosteric proteins as a motivation to investigate dynamic hysteresis for a finite one-dimensional Ising model. In Secs. III and IV we determine the hysteresis curve for the one-dimensional Ising model and present numerical results. These show that the square-root scaling law predicted by Eq. (5) is valid for a range of frequencies, but breaks down below a critical frequency. In Sec. V we discuss the implication of these results for allosteric proteins.

II. ISING MODEL FOR ALLOSTERIC PROTEINS

An allosteric protein, or protein complex, is one in which there are indirect interactions between two or more binding sites [4]. The classic example is hemoglobin, which consists of four subunits (or protomers), each of which can bind an oxygen molecule [11]. The binding of oxygen to one site increases the affinity of oxygen for the other sites via a conformational change. This cooperativity leads to a sigmoidal binding curve, which is essential for the function of the molecule.

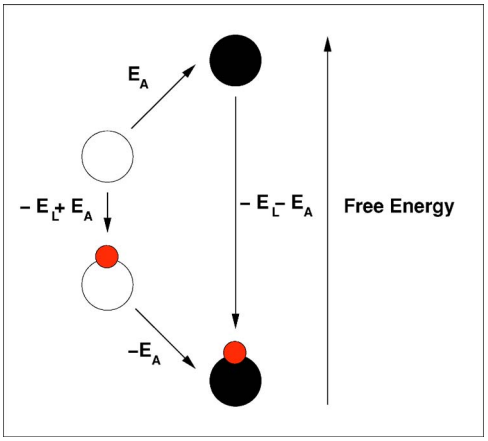

FIG. 2. A receptor can exist in two conformations: inactive (white) and active (black). When no ligand is bound, the energy of the inactive state is lower than that of the active state by E_A. Conversely, ligand binding stabilizes the inactive state, relative to the active state, by E_A. Ligand concentration c is assumed to be proportional to $\exp(E_L/k_B T)$ [16].

The original model of cooperativity [2] stressed the requirement of protomer *symmetry* for the proper function of cooperative proteins. This allowed a simple calculation of protein complex binding states, with the result that the cooperativity depended on only two parameters: the difference in ligand affinity for the two protein conformations and the relative free energies of the two conformations in the absence of ligand.

An especially important class of allosteric proteins is made up of regulatory enzymes. The affinity of an allosteric enzyme for its substrate is affected by whether or not a small ligand molecule is bound at a different site on the protein. This indirect interaction between distinct binding sites is responsible for the performance of the enzyme's regulatory function. Frequently, the activity of a protein complex may be regulated by the binding of more than one regulatory ligand. An example is the C-ring of the bacterial flagellar motor, which contains a binding site for the regulator CheY-p on each of about 30 copies of the protein FliM [8]. The whole complex appears to change conformation at a characteristic ligand concentration, causing the motor to switch abruptly from counterclockwise to clockwise rotation [12]. There are also examples of ion channels, motor proteins, and proteases that may work in a similar way [13–15]. In many of these examples, the protein complex is made up of a ring of protomers.

It must be assumed that the indirect interactions between binding sites in allosteric proteins are mediated by some kind of conformational change of the protein, which is affected by the presence or absence of the regulating ligand. Figure 2 shows a protein with two conformational states: active and inactive. The protein can make rapid stochastic transitions between the states, and the equilibrium probability of the two states is determined by their relative free energies. The binding of a regulatory ligand stabilizes one of the states (here

assumed to be the active state), enhancing its likelihood of occurrence.

The Hamiltonian for an ensemble of isolated, ligand-regulated proteins is

$$H = \sum_{i=1}^{N} -E_A B_i(c,s_i)s_i, \tag{6}$$

where $s_i=1$ (-1) denotes that protein i is active (inactive), $B_i=1$ (-1) corresponds to a liganded (unliganded) protein, and E_A is the energy difference between the active and inactive conformation. This is equivalent to the Hamiltonian of a paramagnet in a random δ-distributed field. The probability that ligand is bound to a protein clearly depends on the concentration c of ligands in solution. Less evidently, it also depends on the activity s_i of the protein. This is because thermodynamic consistency implies that ligand binds more strongly to the state which it stabilizes, leading to a coupling between the binding state and conformation. Thus the probability distribution of B_i depends on both c and s_i. In the magnetic analogy, the mean field varies with the concentration, and additionally there is coupling between spin and field.

The cooperative allostery of an oligomeric protein complex is modeled by introducing a coupling energy between neighboring protomers, making it favorable for them to be in the same conformation [8,16,17]. Many cooperative protein complexes, such as the C-ring, are rotationally symmetric and composed of identical elements [18]. Therefore we make the assumption that the coupling energy is not dependent on the position of the protomer in the ring. Furthermore, it is assumed that the coupling energy depends only on the conformation of the protomer with respect to its neighbors. This is because a sharp switchlike activity curve, as observed for the C-ring, is, in general, not observed if the coupling energy is a function of both protomer conformation and binding state [19].

Taking the coupling energy between neighboring subunits to be $-J/2$ if they are in like conformations and $+J/2$ otherwise gives

$$H = \sum_{i=1}^{N} -\frac{J}{2}s_i s_{i+1} - \frac{E_A}{2}B_i(c,s_i)s_i, \tag{7}$$

where i is now the spatial index of the protomer. In the case of a one-dimensional ring, which we shall examine here, periodic boundary conditions are imposed.

The coupling favors the occurrence of domains in which contiguous protomers have the same state. The protein ring behaves as a switch when the probabilities of the two extreme configurations, in which every protomer is active or all are inactive, outweigh the likelihood of any other configuration. For large rings, $N \gg 1$, this occurs when

$$J > J_c = k_B T \ln N, \tag{8}$$

because the occurrence of multiple domains, which is entropically favored, is then suppressed by the energetic penalty associated with the domain boundaries. It has also been shown [8] that the coupling energy J must be larger than the ligand binding energy E_A if the ring is to adopt a coherent state. Under these conditions, the ring spends the majority of time as a single domain—all active or all inactive. It is for this parameter constraint (large J), for which the activity (magnetization) as a function of concentration (field) approaches a step function, that we investigate the properties of dynamic hysteresis.

III. ANALYTICAL SOLUTION

A. Simplified model

In order to calculate the dynamic hysteresis curve, a number of simplifications were made to the model specified by Eq. (7). The random ligand field was replaced by a mean field h that acts *independently* of the protomer activity. The region analyzed was around $\Sigma_i B_i=0$, where half of the protomers are liganded on average. In this case h is small and the protein ring can switch in either direction. This region has biological relevance since a switch can be effected by a small change in the ligand concentration. It was also assumed that h could be varied linearly around the regime of interest, which corresponds to a linear variation of the concentration c if spin-field coupling is neglected.

In principle, the method used to find the hysteresis behavior of the Ising ring could apply to any arbitrary variation of field h in time. The rate of change of $h=\Sigma_i B_i/N$ with time can be calculated by solving the chemical kinetic equations for the binding state of the protein ring given the variation of ligand concentration in time. For a linear increase of ligand concentration from below K_d $(h<0)$ to above K_d $(h>0)$, a linear increase in effective ligand field h is a good approximation.

These simplifications permit a mapping to the standard one-dimensional, nearest-neighbor Ising magnet:

$$H = \sum_{i=1}^{N} -\frac{J}{2}s_i s_{i+1} - h(t)s_i. \tag{9}$$

B. Average time to switch

We consider the dynamics of switching in a field $h(t)$ that increases linearly in time at rate Ω. How does the magnetization switch from $\langle s\rangle=-1$ to $\langle s\rangle=+1$? First a single spin flips sign, nucleating a positively magnetized domain. Then the boundaries of this domain will diffuse, until the domain either vanishes or grows to encompass the whole ring. For strong coupling satisfying Eq. (8) the probability that more than two domains occur simultaneously is negligible [8], so the nucleation and growth of a single positively magnetized domain is the dominant mechanism of switching.

We assume that each spin flips at a maximum rate ω and that the rate is slowed by a Boltzmann factor if a flip is energetically unfavorable (the Metropolis method [20]). The rate of nucleation of a positively magnetized domain is therefore

$$r_{\mathrm{nucl}}(t) = N\omega e^{-2J+2h(t)}, \quad h>0. \tag{10}$$

The subsequent diffusion of the domain boundaries can be analyzed as a random walk between partially absorbing bar-

riers [21,22]. The domain grows by one site with probability p and shrinks with probability q, where according to detailed balance

$$q/p = e^{-2h(t)}. \tag{11}$$

Let g_k be the probability that a domain which has attained size k subsequently grows to size N, before it shrinks to size zero. This probability satisfies the master equation

$$\frac{dg_k}{dt} = pg_{k+1} + qg_{k-1} - (p+q)g_k. \tag{12}$$

Consider the biologically relevant case where the time scale for protein conformational change is much slower than the rate of change of ligand binding [23]. Then, if a switch has been initiated, the ligand binding state will be effectively constant until the switch is complete, so $dg_k/dt \approx 0$.

Equation (12) therefore has the general solution

$$g_k = A + B(q/p)^k. \tag{13}$$

The constants A and B are specified by the boundary conditions, which are determined by the geometry of the ring. When $k=1$, the domain can grow if either of two adjacent spins flip sign, but can shrink only by the flipping of a single spin. All three flipping events are energetically favorable if $h>0$ and $J>h$, and so occur with equal probability. Thus

$$g_1 = \frac{2}{3}g_2. \tag{14}$$

A similar condition at $k=N-1$ leads to

$$g_{N-1} = \frac{1}{1+2(q/p)} + \frac{2}{1+2(q/p)}g_{N-2}. \tag{15}$$

Together, Eqs. (13)–(15) yield the probability $p_{\mathrm{grow}}=g_1$ that a newly nucleated domain grows to encompass the whole ring:

$$p_{\mathrm{grow}} = \frac{2[1-(q/p)]}{3-2(q/p)+(q/p)^{N-2}[1-2(q/p)]}.$$

The instantaneous rate at which the Ising ring switches magnetization is then

$$r_{\mathrm{switch}}(t) = r_{\mathrm{nucl}}(t)p_{\mathrm{grow}}(t). \tag{16}$$

We consider a linearly increasing field $h(t)=\Omega t$. For small h, Eq. (16) can be expanded as

$$r_{\mathrm{switch}}(t) \approx 2\omega e^{-2J}(1+N\Omega t), \quad \Omega t, \quad N^{-1} \ll 1. \tag{17}$$

The mean time $\langle t_{\mathrm{switch}}\rangle$ at which a switch occurs can then be found. Let $P(t)$ be the probability that a switch has not occurred at time t. Then

$$\dot{P} = -r_{\mathrm{switch}}(t)P \rightarrow P = \exp\left(-\int r_{\mathrm{switch}}(t)dt\right), \tag{18}$$

$$\langle t_{\mathrm{switch}}\rangle = \frac{\int tP(t)r_{\mathrm{switch}}(t)dt.}{\int P(t)r_{\mathrm{switch}}(t)dt}. \tag{19}$$

Equations (17)–(19) give the average time to switch as

$$\langle t_{\mathrm{switch}}\rangle = \sqrt{\frac{\tau\pi}{2\Omega N}}\,\mathrm{erfc}\left(\sqrt{\frac{1}{2\Omega N\tau}}\right)e^{(2\Omega N\tau)^{-1}}, \tag{20}$$

with $\tau=(2\omega e^{-2J})^{-1}$. Thus the average field $\langle h_{\mathrm{switch}}\rangle = \Omega\langle t_{\mathrm{switch}}\rangle$ at which the switch occurs varies as $\sqrt{\Omega}$, and so does the hysteresis area.

This main scaling result is accompanied by a correction that becomes important below a critical rate Ω_c given by

$$\Omega_c \sim \frac{1}{2N\tau}. \tag{21}$$

For $\Omega<\Omega_c$,

$$\mathrm{erfc}\left(\sqrt{\frac{\Omega_c}{\Omega}}\right)e^{\Omega_c/\Omega} \sim \sqrt{\Omega}, \tag{22}$$

and there is therefore a linear scaling between $\langle h_{\mathrm{switch}}\rangle$ and Ω.

Because we have assumed strong coupling and Eq. (8) specifies a lower limit on the value of J, we can rewrite Eq. (21) as

$$\Omega_c < \frac{\omega}{N^3}. \tag{23}$$

Thus the way that $\langle h_{\mathrm{switch}}\rangle$ scales with Ω depends strongly on the size of the ring. Small rings respond linearly up to $\Omega_c \sim \omega$, while large rings respond with a square-root scaling law at much lower rates of increase of field. Thus one prediction of the model which could be tested experimentally is that that the critical frequency at which the scaling behavior changes is sensitive to the size of the protein ring.

Our calculation shows that the known result $A \sim \Omega^{1/2}$ is recovered in the thermodynamic limit $N \rightarrow \infty$. What is new and interesting is that a finite-size Ising ring displays a different scaling relation $A \sim \Omega$ for $\Omega < \Omega_c$.

What is the physical mechanism that causes this change in scaling? For $\Omega \rightarrow 0$ there are many switch initiations at an almost constant field. Therefore the switch probability is almost constant and one would expect the switching to follow Poisson statistics. The average switch time is then constant, giving a linear relationship between Ω and $h=\Omega\langle t\rangle$.

For larger Ω the situation is different. In this case, the field increases appreciably between switch initiations. The probability of a successful switch and the probability of a switch initiation are no longer constant. This leads to non-Poissonian switching and therefore a crossover in scaling from $h \sim \Omega$ to $h \sim \sqrt{\Omega}$. The crossover is modulated by N [Eq. (17)], because there are N switch initiation attempts per time step.

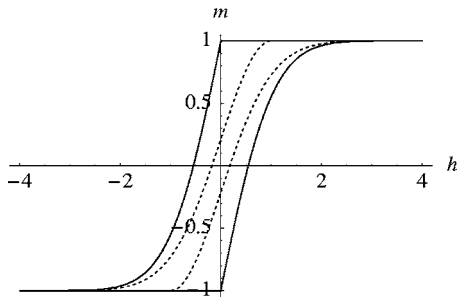

FIG. 3. Hysteresis curve predicted by Eqs. (25) (solid line) and (26) (dotted line). All parameters were set equal to 1, so the axes are arbitrary.

C. Shape of the hysteresis curve

The shape of the hysteresis curve can also be calculated. The average magnetization at time t is

$$\langle s(t)\rangle = -1 + 2\int_0^t P(t')r_{\text{switch}}(t')dt', \tag{24}$$

which, from Eq. (18), gives

$$\langle s(t)\rangle = 1 - 2\exp\left(-\frac{t(2+\Omega Nt)}{2\tau}\right). \tag{25}$$

The curve has a cusp at $h(t)=0$, due to the assumption that the Ising ring is initially in the $\langle s\rangle=-1$ state and the field starts at $h=0$. We can instead consider increasing the field from an initially negative value, for which the approximation of Eq. (17) gives a switch rate of zero. Then

$$\langle s(t)\rangle = -1 + 2\int_{-1/N\Omega}^t P(t')r_{\text{flip}}(t')dt'. \tag{26}$$

The two hysteresis curves are shown in Fig. 3.

IV. NUMERICAL RESULTS

Previous numerical studies of dynamic hysteresis in the one-dimensional Ising model [24] have confirmed the scaling law $\langle h_{\text{switch}}\rangle \sim \sqrt{\Omega}$, but did not report the different scaling in slowly varying fields predicted by Eq. (20). We therefore carried out Monte Carlo simulations to test the predicted correction to the scaling law. The simulations were performed on an Ising ring of $N=30$ sites and J was varied in the range $(5-7)k_BT$, where switching should occur according to Eq. (8). The time step Δt of the simulation corresponded to the inverse flipping rate $1/\omega$ of individual spins. Each time step, N spins were selected at random and flipped according to the Metropolis probability, and the field was incremented by $\Delta h=\Omega\Delta t$. The initial condition was $\langle s\rangle=-1$ and $h=0$.

Figure 4 displays the average field at which the ring switched as a function of the rate of increase of field. The data accord well with the prediction for $\langle h_{\text{switch}}\rangle$ from Eq. (20), shown as a solid line. The predicted square-root scaling in rapidly varying fields and linear scaling at slower rates of change are both apparent.

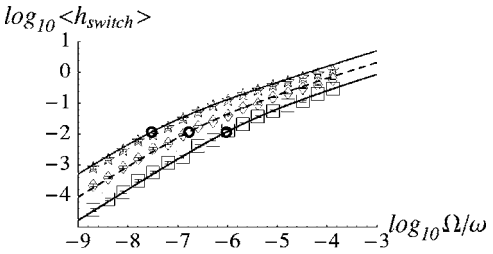

FIG. 4. Average field at which a switch occurs. Numerical data for $J/k_BT=5$ (squares), 6 (diamonds), and 7 (stars) are shown, together with the corresponding prediction of Eq. (20). Other parameters: $N=32$, $\omega=10^4\ \text{s}^{-1}$. The scaling crossovers [Eq. (21)] are shown as circles.

We carefully checked that the assumption used in calculating the switching field was valid. For every simulation run, the maximum number of domains during a switch was recorded. The maximum number of domains was found to be 2 (with very rare exceptions), implying that our assumption of one-domain switching was reasonable.

The prediction for the switching field, Eq. (20), was also investigated for various N. N was varied from 8 to 1024, ensuring $J>\ln N$, and the scaling prediction was found to hold. For large N, the crossover frequency becomes very small and the Metropolis method computationally expensive. However, there is no reason that the crossover should not be observed for any finite N.

The variance in the value of the field at which switching takes place can also be analytically determined by calculating $\langle h^2\rangle=\Omega^2\langle t^2\rangle$, as in Eq. (19). Figure 5 indicates that the variability in the simulated data agrees well with the predicted variance.

The expression for the hysteresis curve, Eq. (25), can be inverted to determine the average field at which the probability that the ring has switched is one-half, so that $\langle s\rangle=0$. This gives

$$h_{\text{switch}}(\Omega) = \frac{1}{N}[-1 + \sqrt{1 + 2\ln(2)N\tau\Omega}]. \tag{27}$$

This prediction is compared with numerical results from the simulation in Fig. 6.

The simulations show excellent agreement with our analysis of switching in a finite, one-dimensional Ising magnet, which we have argued represents a simplified model of

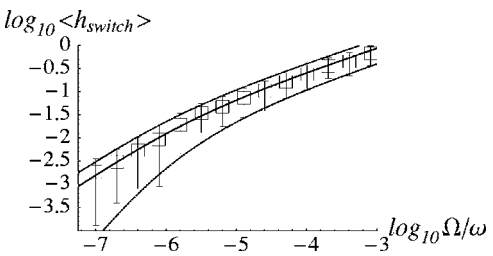

FIG. 5. Variability in the field at which a switch occurs (error bars) for $J=5k_BT$, together with the analytic prediction for the variance (dotted lines). Other parameters as in Fig. 4.

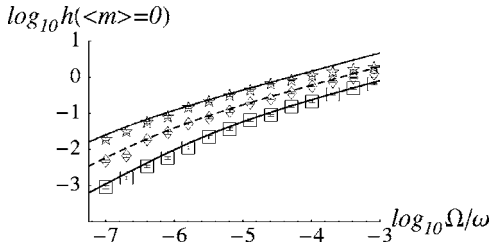

FIG. 6. Field at which $\langle s\rangle=0$, as a function of the rate of increase of field. Numerical data for $J/k_BT=5$ (squares), 6 (diamonds), and 7 (stars) are shown, together with the corresponding analytic result from Eq. (27). The fit is less good at large values of Ω where the expansion of Eq. (17) breaks down.

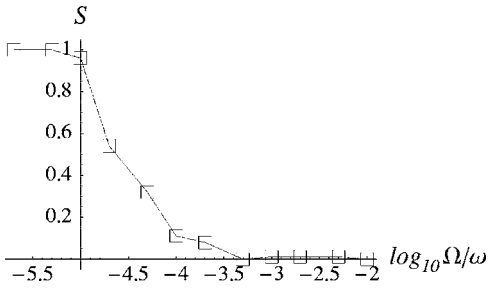

FIG. 7. Filtering properties of an Ising ring in a sinusoidally varying field. The frequency selectivity S, defined as the fraction of field oscillations that cause a switch, is shown as a function of oscillation frequency Ω. Parameters: $N=30$, $J=7k_BT$.

allosteric proteins. The question of how well the results apply to the complete model, in which random fields and spin-field coupling are incorporated, is discussed below.

V. DISCUSSION

According to the canonical models of allostery [2,3], the principal advantage conferred by cooperative interactions within a ringlike protein is a heightened sensitivity of response to regulating ligand. When the coupling between protomers is high, $J\gg J_c$, a modest change in the ambient ligand concentration is enough to switch the ring from the fully inactive to the fully active state. Indeed, the sensitivity to a change in concentration can be as much as N times greater than that of a noncooperative system [2,8]. While the sharpness of the response permits the activity to be switched on or off when the regulating signal passes a threshold level, the high sensitivity is potentially problematic. Might it not render the protein switch susceptible to fluctuations in regulator concentration which inevitably occur, even when the mean level of the regulator is not changing with time? The activity curves predicted by the canonical models certainly suggest that such fluctuations might cause unwanted switching between active and inactive states. In order to effect a switch with the minimum of effort, it is advantageous to maintain the ligand concentration close to K_d, so that a tiny change in concentration can cause the ring to switch. However, if the ligand concentration is close to K_d, small *fluctuations* rather than *signals* may switch the protein ring.

Our analysis of switching dynamics indicates that dynamic hysteresis mitigates this problem. Cooperative protein rings respond much more slowly to changing levels of ligand than their noncooperative counterparts. The scaling behavior of Eq. (20) indicates that a concentration fluctuation of frequency Ω must last for a time of order $\sqrt{\tau/\Omega N}$ before a protein ring switches conformation. In effect, this means that the protein ring is resilient to fluctuations whose frequency is faster than $\Omega_{\text{cutoff}}\sim N/\tau$. To illustrate this point, the response of an Ising ring to an oscillating field is shown in Fig. 7, where it can be seen that high-frequency oscillations with $\Omega>\Omega_{\text{cutoff}}$ have little effect. Because $\tau=\exp(2J)/\omega$, the cutoff frequency becomes arbitrarily small as the strength of the coupling is increased. Contrast this resilient behavior to the more fragile response of a noncooperative system, where fluctuations have negligible effect only if their time scale is faster than the typical ligand detachment time [25]. Cooperativity is thus a simple, robust way of filtering out noise in the concentration of the regulator, which helps to explain how proteins can work effectively in a noisy environment [26,27].

The C-ring in the bacterial flagellar motor provides a concrete example of this resilience to fluctuations. Studies of individual motors [12] indicate that the C-ring switches from a conformation that drives the flagellum counterclockwise to one that drives it clockwise, over a narrow range of concentration of the regulator CheY-p. In the middle of this range, at [CheY-p]=3 μM, the motor switches stochastically between the two directionalities at a rate of about once per second. The regulator CheY-p itself is produced by a signal transduction pathway, in response to extracellular stimuli. Because this pathway involves high amplification [28] and bearing in mind that there are only a few thousand copies of CheY-p in the cell [29], the noise in the CheY-p level is likely to be considerable. The time scale of these nonequilibrium concentration fluctuations depends on the transduction machinery and thus cannot readily be predicted. We therefore consider whether the switch is susceptible to the fluctuations that are typically observed experimentally, which occur on the time scale of milliseconds [12].

We can estimate the cutoff frequency $\Omega_{\text{cutoff}}\sim N/\tau$ by noting that the Ising model of allostery predicts that the stochastic switching rate at [CheY-p]=3 μM is approximately τ^{-1} [8]. Thus we conclude that the C-ring is insensitive to fluctuations whose frequency exceeds $\Omega_{\text{cutoff}}\sim 30\ \text{s}^{-1}$, and it is not much affected by the noise in the concentration of CheY-p.

Our analysis implies that mathematical models in which only average activity curves of cooperative proteins are used [30,31] miss many of the important details of the dynamics of switching between conformational states. Cooperative allosteric proteins might be even better at filtering fluctuations than our analysis of the one-dimensional Ising model indicates. The coupling between the protomer conformation and the probability that ligand is bound results in a positive feedback. At the average switching concentration an inactive ring has fewer ligands bound than an active ring. Consequently, a switch from the inactive to the active state requires additional ligand to bind and therefore cannot occur rapidly

unless the ligand concentration is raised well beyond the average switching concentration.

There is however a dilemma: Switches with $J \gg J_c$ are extremely robust with respect to to ligand fluctuations. However, they are also slow to switch in response to a change in the mean ligand concentration: The switch time increases exponentially with J. If a protein ring is to respond quickly to changes in regulator level, the coupling energy must be close to J_c. A smaller J necessarily makes the ring susceptible to ligand fluctuations.

Our analysis suggests that protein rings are either designed to be robust to fluctuations or to respond quickly to changes. Since different biological functions call for different computational requirements, we may expect to find fast switches or robust switches, depending on which feature is more important.

[1] M. Eigen, Nobel Symp. **5**, 333 (1967).
[2] J. Monod, J. Wyman, and J. P. Changeux, J. Mol. Biol. **12**, 88 (1965).
[3] D. E. Koshland, G. Némethy, and D. Filmer, Biochemistry **5**, 365 (1966).
[4] B. Alberts *et al.*, *Molecular Biology of the Cell*, 3rd ed. (Garland, New York, 1994).
[5] B. K. Chakrabarti and M. Acharyya, Rev. Mod. Phys. **71**, 847 (1999).
[6] P. Jung, G. Gray, R. Roy, and P. Mandel, Phys. Rev. Lett. **65**, 1873 (1990).
[7] J. Zemmouri, B. Ségard, W. Sergent, and B. Macke, Phys. Rev. Lett. **70**, 1135 (1993).
[8] T. A. J. Duke, N. Le Novère, and D. Bray, J. Mol. Biol. **308**, 541 (2001).
[9] J. M. Yeomans, *Statistical Mechanics of Phase Transitions* (Oxford University Press, Oxford, 1992).
[10] G. H. Goldsztein, F. Broner, and S. H. Strogatz, SIAM J. Appl. Math. **57**, 1163 (1997).
[11] L. Stryer, *Biochemistry*, 4th ed. (Freeman, San Francisco, 1995).
[12] P. Cluzel, M. Surette, and S. Leibler, Science **287**, 1652 (2000).
[13] R. D. Vale, J. Cell Biol. **150**, F13 (2000).
[14] V. Ruta *et al.*, Nature (London) **422**, 180 (2003).
[15] D. Bray and T. A. J. Duke, Annu. Rev. Biophys. Biomol. Struct. **33**, 53 (2004).
[16] J. P. Changeux, J. Thiery, Y. Tung, and C. Kittel, Proc. Natl. Acad. Sci. U.S.A. **57**, 335 (1967).
[17] Y. Shi and T. Duke, Phys. Rev. E **58**, 6399 (1998).
[18] D. S. Goodsell and A. J. Olson, Annu. Rev. Biophys. Biomol. Struct. **29**, 105 (2000).
[19] I. Graham (unpublished).
[20] J. J. Binney *et al.*, *The Theory of Critical Phenomena* (Oxford University Press, Oxford, 1992).
[21] G. R. Grimmett and D. R. Stirzaker, *Probability and Random Processes*, 2nd ed. (Oxford Science, Oxford, 1992).
[22] C. W. Gardiner, *Handbook of Stochastic Methods*, 2nd ed. (Springer-Verlag, Berlin, 1996).
[23] J. Howard, *Mechanics of Motor Proteins and the Cytoskeleton* (Sinauer, Sunderland, Mass., 2001).
[24] M. Acharyya and B. K. Chakrabarti, Phys. Rev. B **52**, 6550 (1995).
[25] M. Samoilov, A. Arkin, and J. Ross, J. Chem. Phys. **106**, 10205 (2002).
[26] H. H. McAdams and A. Arkin, Trends Genet. **15**, 65 (1999).
[27] J. M. G. Vilar, H. Y. Kueh, N. Barkai, and S. Leibler, Proc. Natl. Acad. Sci. U.S.A. **99**, 5988 (2002).
[28] V. Sourjik and H. C. Berg, Proc. Natl. Acad. Sci. U.S.A. **99**, 123 (2002).
[29] B. E. Scharf, K. A. Fahrner, and H. C. Berg, J. Bacteriol. **180**, 5123 (1998).
[30] J. D. Murray, *Mathematical Biology I: An Introduction*, 3rd ed. (Springer, Berlin, 2002).
[31] S. H. Strogatz, *Nonlinear Dynamics and Chaos* (Perseus, Cambridge, Mass., 1994).