Dynamics of neural networks relevant to properties of proteins

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We studied how the dynamics of Hopfield neural networks depend on computational and physical properties of the network. The dynamics of the network was characterized by the distribution of first passage times (FPT) between the states. The FPT distributions depended on the updating scheme, temperature, connectivity range, and number of stored memories. The FTP distributions were different for synchronous and asynchronous updating, and were more physically consistent for the synchronous than for the asynchronous updating scheme. Neural networks and proteins share common features such as many degrees of freedom, conflicting constraints on energy minimization, and energy functions with many local minima. Thus the general lessons learned here on how the dynamics of neural networks depends on their physical properties may be relevant in understanding how the dynamics of proteins is influenced by similar physical properties. [S1063-651X(97)13307-4]

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I. INTRODUCTION

Proteins are linear polymers of heterogenous amino acid units that fold into three-dimensional conformational structures. The dynamic motions of these structures play an important role in how proteins react with ligands and function as enzymes to catalyze biochemical reactions [1]. Proteins [2–5] share a number of structural and dynamical features with other complex systems such as spin glasses [6] and neural networks [7]. All these systems have many degrees of freedom. They have conflicting constraints on the minimization of energy, so that there is a complicated energy function with many local minima rather than one well-defined energy minimum. Since proteins share these characteristics with these other systems, we can use simulations of neural networks as a simplified way of studying some of the general structural and dynamical properties that have revelance to proteins.

In previous work we proposed that neural networks may be an efficient computational method to compute molecular dynamics [3]. Before this idea can be tested in detail, we first need to understand the dynamic properties of neural networks better. Much is known about the energy structure of neural networks, and whether a given set of initial conditions converges to a desired memory in the long term. However, much less is known about the dynamics of how such networks reach those memories, and how the dynamics is influenced by the computational properties of the updating method and the physical properties of the network. Thus this present work is an exploration of those dynamic properties of neural networks. The dynamic properties analyzed here are motivated by their relationship to issues in protein dynamics, but this present work is not intended to tie the dynamics of neural networks to specific details of protein dynamics.

In this work we determined how the dynamics of neural networks of the Hopfield type [8] depends on the updating scheme, temperature dependence, degree of locality of connections between elements, and number of memories. We used the distribution of first passage times (FPT's) to characterize the dynamics of the network. Our use of networks with two stored memories was motivated by our interest in ion channel proteins which have two distinct conformational states, open and closed to the flow of ions. The FTP distribution of an individual ion channel protein can be determined from the open and closed time intervals measured in our patch clamp experiments.

II. NEURAL NETWORK MODEL

The network we studied was of Hopfield type [8], and had $N=100$ nodes. The values of the nodes were $S_i=\pm 1$. There were two memories stored $p=2$—analogous to the open and closed states of the ion channel protein. Each memory $\vec{\xi^{\mu}}$ consisted of the set of N nodes ξ_i^{μ} which were given values at random so that the two memories are orthogonal. The connection matrix J was constructed by using the Hebbian algorithm [9]

$$J_{ij}=\frac{1}{N}\sum_{\mu=1}^{p}\xi_i^{\mu}\xi_j^{\mu}. \tag{1}$$

The state of the network corresponding to the open (1) or closed (2) state of the ion channel was defined by the largest overlap

$$m^{\mu}(t)=\frac{1}{N}\sum_{i=1}^{N}\xi_i^{\mu}S_i(t), \tag{2}$$

where $S_i(t)$ are the values of the nodes of the network at time t, $\mu=1$ (open), and $\mu=2$ (closed). When the state with the largest overlap changed from $1\rightarrow 2$ or from $2\rightarrow 1$, the network passed through the boundary between the two states. The first passage times were defined as the number of consecutive time steps spent in each state. The dynamics of the network was determined by the probability that a given neuron assumes a new state, which is given by

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$$\Pr(S_i = \pm 1) = \frac{1}{1+\exp(-2\beta h_i)}, \tag{3}$$

where

$$h_i(t) = \sum_{j=1}^{N} J_{ij} S_j(t), \tag{4}$$

and $\beta = 1/kT$.

III. RESULTS

The dynamics of the model was studied (i) using different updating schemes, (ii) in different temperature regimes, (iii) with different degrees of locality of connection lengths, and (iv) with different numbers of stored memories. In this section we will report the results obtained, and discuss their relevance to protein dynamics.

A. FPT distributions for different updating schemes

We found that the updating scheme can have a crucial affect on FPT distributions. These results have important implications for the dynamics computed by neural networks and by other simulations as well, such as molecular dynamics. It raises the question as to whether some dynamical properties computed by such simulations are artifacts of the updating scheme used.

There are two major ways that the values of the nodes of the network can be updated: *Synchronous updating*—all the elements are updated in every time step. *Asynchronous updating*—one randomly chosen element is updated at every time step. We also devised updating schemes that are intermediate between synchronous and asynchronous updating. In these schemes a set of n nodes were updated at each time step. The n nodes chosen for updating were either chosen at random from the N nodes or were a set of n contiguous nodes. The fraction of nodes $a = n/N$ upadated at each time step was varied over the range $a = 1$, for synchronous updating, to $a = 1/N$, for asynchronous updating.

The FPT distribution depended on the updating scheme. As shown in Fig. 1, at high temperature, as the updating scheme was varied from synchronous ($a = 1$) to asynchronous updating ($a = 1/N$), the FPT distribution varied continuously from a single exponential, to a power law with an exponential tail, to a power law. These results can be understood in the following way. The configuration of the network is defined by the set of values $S_i(t)$ of the nodes at a given time t. The configuration of the network at the next time step $t+1$ is given by

$$\vec{S}(t+1) = \hat{P}(t)\vec{S}(t). \tag{5}$$

The properties of $\hat{P}$ depend on physical properties of the system and the updating scheme. In the case of synchronous updating, all the values of the nodes can change at each time step, and thus any element of $\hat{P}$ can have a nonzero value. However, in the case of asynchronous updating the value of only one node can change at each time step, so that only the elements adjacent to the diagonal can be nonzero. A minimum of N time steps is thus required to change the values of all N nodes.

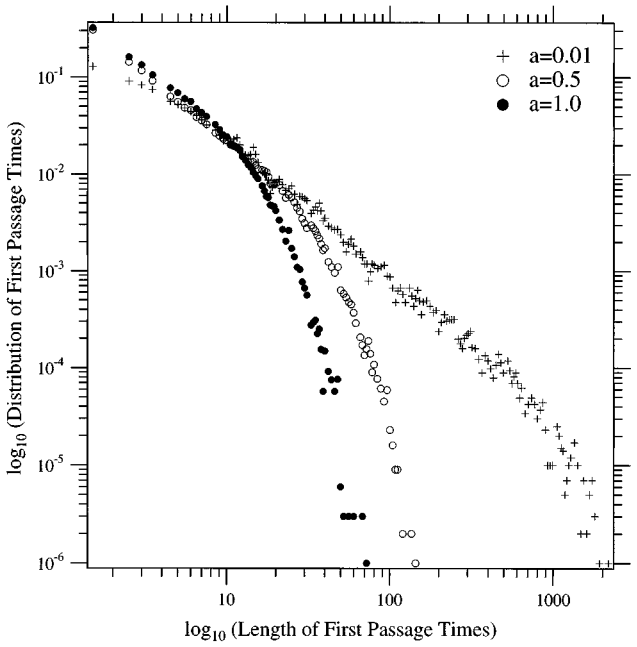

FIG. 1. As the updating was varied from synchronous ($a = 1.0$) to asynchronous ($a = 0.01$), the distribution of first passage times varied from a single exponential, to a power law with an exponential tail, to a power law. These simulations were performed for $\beta = 1$.

The evolution of the network in time can be represented as the motion of a point in a finite region of an N-dimensional space whose coordinates are given by the values $S_i(t)$ of nodes. The motion of this point in N-dimensional space has a random component determined by the temperature, and may have an additional component at each location driven by the connection strengths and the values of the nodes. The FPT distribution for such a random walk in a finite region of an N-dimensional space is a power law at short times and a single exponential at longer times [10,11]. The transition between these two regimes occurs at the time expected for the random walker to reach the boundary of the region. The matrix $\hat{P}$ determines the number of available pathways of reaching a new configuration $\vec{S}(t+\tau)$ at time $t+\tau$ from an earlier configuration $\vec{S}(t)$ at time t.

For synchronous updating, at high temperature, the point representing the network soon reaches the boundary of the finite region, and thus the FPT distribution is dominated by a single exponential component. However, for asynchronous updating, the large number of zero elements in $\hat{P}$ means that there are additional constraints in motion of the point representing the evolution of the network. It takes much longer for the point to reach the boundary of the configurational space, and hence the FPT distribution is a power law. Those restrictions in the motion of the point in the configurational space introduce additional constraints into the dynamics that are due to the updating scheme and are not physically meaningful. In essence, updating isolated nodes generates local, physically distinct regions, and the complexity introduced by such special regions leads to a power-law FPT distribution.

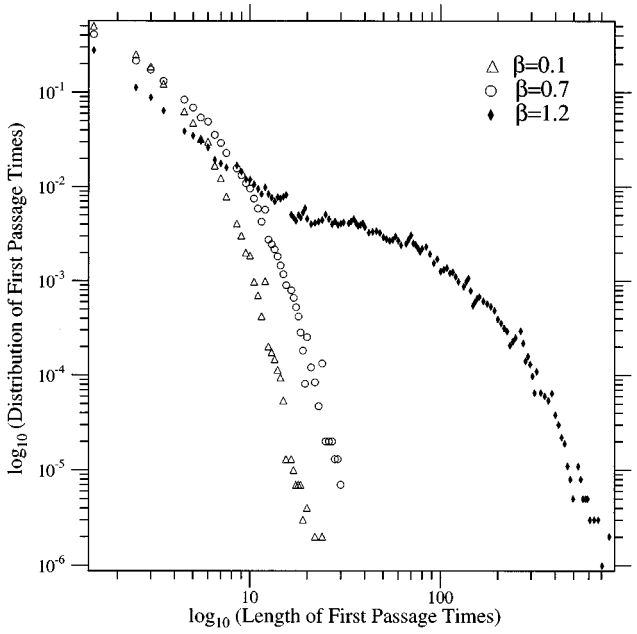

FIG. 2. Synchronous updating: Distribution of first passage times between the two memories in the neural network. High temperature ($\beta=0.1$), medium temperature ($\beta=0.7$), and low temperature ($\beta=1.3$). As the temperature decreases, the distribution changes from a single exponential to a power law with an exponential tail. This is consistent with the dynamics expected of a neural network.

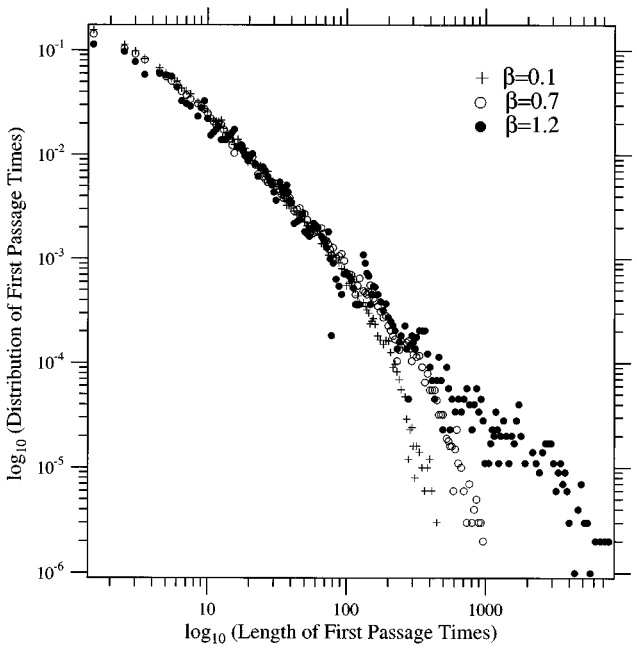

FIG. 3. Asynchronous updating: Distribution of first passage times between the two memories in the neural network computed by asynchronous updating. High temperature ($\beta=0.1$), medium temperature ($\beta=0.7$), and low temperature ($\beta=1.2$). The distribution is a power law over most of its range at all temperatures. This form may represent an artifact of the asynchronous updating.

B. FTP distributions for both updating schemes in different temperature regimes

For a synchronous updating, as shown in Fig. 2, at high temperature (low β), the FPT distribution is a single exponential. At lower temperature (higher β), the FPT distribution changes to a power law with a single exponential tail. For asynchronous updating, as shown in Fig. 3, the distribution is a power law at both high and low temperatures, over most of its range.

These results can be understood in terms of the random walk of the point in a finite N-dimensional region representing the evolution of the network. As noted in Sec. III A, the FPT distribution for such a walk is a power law at short times and a single exponential at long times, with the transition between the two regimes determined by the expected time to reach the boundary of the region.

For synchronous updating, at high temperature, the noise levels are much above the energy surface of the network. The configuration of the network performs an unrestricted random walk at high enough energy to reach the edge of the configurational space in short enough time to make the distribution of first passage times a single exponential. At lower temperature, the random walk is slower; it takes longer to reach the edge of the configurational space, and thus the distribution of first passage times consists of a power law with an exponential tail.

For asynchronous updating, at both high and low temperatures, the distribution of first passage times is the same power law. Since only one node is updated at a time, the network can only pass through a limited number of points adjacent in the configurational space at all temperatures. Thus the random walk is constrained; it takes much longer to reach the edge of the configurational space, and thus the distribution of first passage times is dominated by the power-law component.

The FPT distributions found from the synchronous updating are consistent with the physical characteristics expected from such networks [7,12]. For example, at high temperature (low β) the network freely wanders over the energy surface, producing a single exponential distribution. As the temperature is lowered there is a spin-glass phase where the network encounters many local minima and wanders between them. The heat energy is of the same order as the energy of the network. This produces constraints on the walk among these minima which leads to the power-law component in the distribution of first passage times. As the temperature is lowered further the network reaches one stable configuration, corresponding to one memory, and there is not enough heat for it to switch out of that memory. This behavior is also consistent with the physical properties derived from the T-α (temperature–storage-capacity) phase diagram [7]. As the temperature is lowered (in the limit of a few memories) the network passes from an ergodic phase where it passes through the entire configurational space, to a spin-glass phase where it passes through many local minima, to a stable state where the network converges to the minimum of a true memory. Moreover, we also found that the single exponential rate constant at high temperature had the expected physical characteristics of an Arrhenius ($e^{-E/kT}$) temperature dependence as shown in Fig. 4, where E is a constant. However, none of those physically consistent properties of the temperature dependence were found in the results of the asynchronous updating. In this case the power-law form of the FPT distribution appears to arise from the constraints

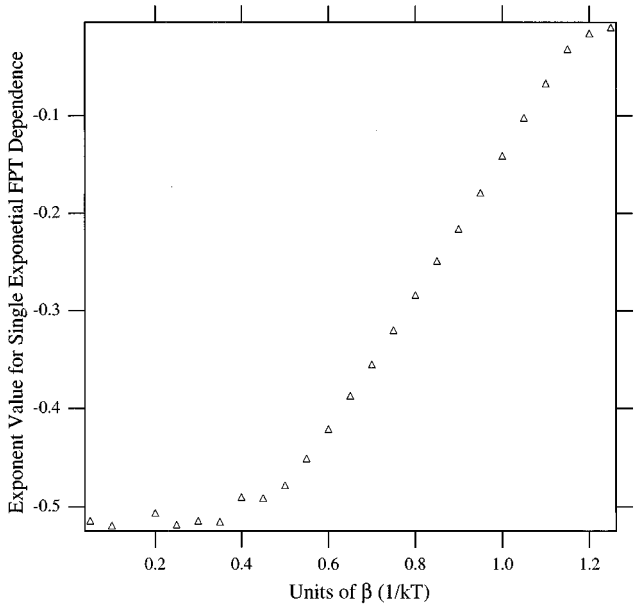

FIG. 4. For the single exponential distributions computed by synchronous updating, the variations of the logarithm of the rate constant for switching states is a linear function of $1/T$, and thus has the expected Arrhenius behavior proportional to $e^{-E/kT}$ when E is a constant.

introduced by the updating scheme, rather than representing the physical properties of the network.

C. FPT distributions for local and global connectivity

We also tested the dependence of the FPT distributions on different degrees of locality of connections between the elements. The network we studied for those cases was one dimensional. We defined

$$r_{ij}=|i-j|. \tag{6}$$

The local field was then calculated according to the equation

$$h_i(t)=\sum_{j:r_{ij}<r_{\max}} J_{ij}S_j(t), \tag{7}$$

where $r_{\max}$ determines the radius of the maximum interaction length. Connections were rescaled to have the same probability distributions as in Eq. (3) for the same values of β.

In the case of synchronous updating, shown in Fig. 5, for $\beta=1$ and when the connections are of a very short length, $r_{\max}\to 0$, the distribution is single exponential. With an increasing length of the connections, as $r_{\max}$ increases, the distribution stays exponential over most of its range; the slope of the distribution, however, decreases noticeably with the increasing $r_{\max}$ to the point it saturates. In the limit of high temperature ($\beta\to 0$) the FPT distributions for all values of $r_{\max}$ tend toward each other, and become a single exponential. In the low-temperature limit the distributions tend to a power law.

On the other hand, in the case of asynchronous updating, shown in Fig. 6, the FPT distributions at the same temperature do not depend on different values of $r_{\max}$ ($\beta=$const). This result again leads to the conclusion that the asynchronous updating scheme suppresses the physically meaningful dynamics of the modeled system.

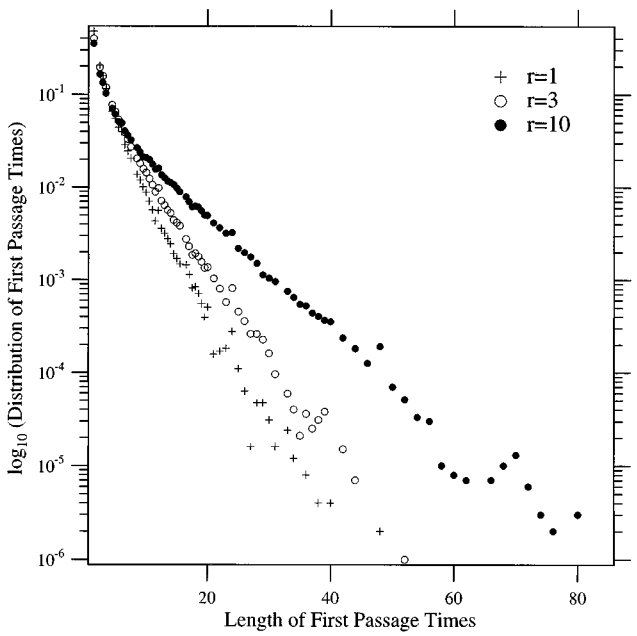

FIG. 5. Distribution of first passage times for different radii of the connection length ($r=3$, 10, and 20) for a synchronous updating scheme. These simulations were performed for $\beta=1$.

D. FPT distributions in the case of multiple stored memories

We also studied FPT distributions when more than two memories were stored, for local and gobal connectivity and both updating schemes. The characteristics of the FPT distributions did not change with different numbers of stored memories. This is the result expected because the temperature was sufficiently high to escape from any one memory,

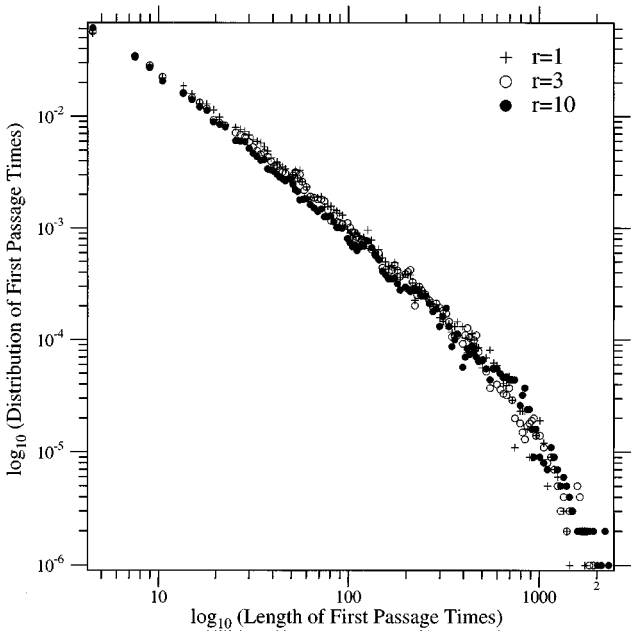

FIG. 6. Distribution of first passage times for different radii of the connection length ($r=1$, 3, 10, and 20) for an asynchronous updating scheme. These simulations were performed for $\beta=1$.

and the number of memories was small enough so that they did not interfere with each other.

IV. RELEVANCE OF THE DYNAMICAL PROPERTIES OF THE NEURAL NETWORKS TO PROTEINS

Neural networks share many properties in common with complex biomolecules, such as many degrees of freedom, conflicting constraints on the minimization of energy, and an energy function with many local minima. This does not necessarily mean that we can construct a neural network whose detailed dynamics matches that of a specific protein. However, by constructing neural networks with properties corresponding to different physical properties of proteins, we can study how those properties effect the dynamics of the neural network. This may be useful in understanding how those physical properties effect the dynamics of the protein. For example, important issues in the molecular dynamics of proteins include how the dynamics computed depends on the updating scheme, the temperature, the range of the forces within the molecule, and the number of the stable conformational shapes. We studied here how the corresponding features of the updating, the temperature, the degree of locality, and the number of memories effects the dynamics of neural networks.

Our results may be useful in interpreting some features of protein dynamics. For example, the open and closed time distributions of ion channels measured in patch clamp experiments is the distribution of first passage times out of the conformational states that are open and closed to the flow of ions through the ion channel protein. Experimentally, it has been found that different ion channels have different dwell time distributions that range from single exponentials to power laws [13]. The mechanisms that produce these different types of distributions may be similar to the mechanisms that produce similar distributions in the neural network dynamics. For example, power-law distributions found for potassium channels in *neuroblastoma x glioma* cells [14] may correspond to high-energy barriers between open and closed conformational states at physiological temperatures. On the other hand, the single exponential distributions found for potassium channels in *hyppocampal neurons* [15] may arise from low-energy barriers between the open and closed conformational states.

V. CONCLUSIONS

We determined how the dynamics of neural networks depend on different physical properties of the network. Neural networks and proteins share common features such as many degrees of freedom, conflicting constraints on energy minimization, and energy functions with many local minima. Thus the results found here on how the dynamics of neural networks depends on their physical properties may be relevant in understanding how the dynamics of proteins is influenced by similar physical properties. Since we are particularly interested in ion channel proteins which have two states that can be opened or closed to the flow of ions across the cell membrane, we studied the dynamical properties of Hopfield neural networks with two stored memories.

The effects of the updating scheme, temperature dependence, and degree of locality of connections were determined by analyzing the first passage time (FPT) distributions of the network. Low-energy barriers produced single exponential FTP distributions. High energy barriers produced more power-law FTP distributions. The slope of the FPT distributions depended on the range of the interactions.

An unexpected and important result was that the dynamics of the network was different for synchronous and asynchronous updating. The results of the synchronous updating were more consistent with the physical properties expected for these networks such as their temperature dependence. This suggests that synchronous updating in molecular-dynamics simulations of proteins may be more physically meaningful than asynchronously updating the position and velocity of one atom at a time.

ACKNOWLEDGMENT

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