Statistical properties predicted by the ball and chain model of channel inactivation

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ABSTRACT It has been proposed that part of a voltage gated channel is a tethered ball and that inactivation occurs when this wandering ball binds to a site in the channel. In order to be able to quantitatively test this model by comparison to experiments we developed analytical solutions and numerical simulations of the distribution of times it takes the ball to reach the binding site when the motion of the ball is random and when it is also influenced by a directed force. If the motion of the ball is one-dimensional, at long times this distribution is a single exponential with a rate constant that is inversely proportional to the square of the length of the chain and does not depend on the starting position of the ball. This dependence on the chain length is not significantly altered if there are short range electrical forces between the ball and its binding site. These predictions suggest that to confirm the validity of this model additional experiments should be done to more precisely determine the form of this distribution and its dependence on the length of the chain.

INTRODUCTION

Ion channels are proteins that span the lipid cell membrane. Each channel has multiple conformational shapes. Some of these shapes have a central pore that is open to the passage of ions, while others are closed. Channels spontaneously fluctuate between open and closed states. In a voltage gated channel, a change in the applied voltage to a new value causes a dramatic shift in the ratio of the time spent in the open and closed states, which is called "activation." However, some voltage gated channels "inactivate," the open/closed time ratio slowly returns to its original value, even though the voltage is maintained at its new value.

Armstrong and Benzanilla (1977) proposed that in a sodium channel the change in voltage activates one part of the channel so that it is more likely to be open and that inactivation occurs when another part of the channel, a "ball" tethered on a "chain," binds to a site that blocks ion conduction through the channel. This model is supported by the results of Hoshi et al. (1990) and Zagotta et al. (1991) who measured the changes in the inactivation of mutant *Shaker* potassium channels that had substitutions or deletions of amino acid residues in the putative ball and chain regions. They identified the ball as the first 20 amino acid residues at the amino terminal end of the channel and the chain as the next sequence of ~60 residues.

The properties of the ball and chain determine the distribution of the intervals of time that it takes the ball to reach its binding site. If the ball can only bind when the channel is open, then this distribution corresponds to the distribution of the duration of the open → inactivated transitions which could be experimentally measured from single channel recordings. Thus, it should be possible to test if this model is true by quantitatively comparing the model with the data. However, the quantitative form and properties of the distribution predicted by this model have not been described. In this paper we use analytical and numerical methods to derive the distribution predicted by this model. To test the validity of the ball and chain model, these results suggest new experiments should be done to more precisely determine the form of this distribution and its dependence on the length of the chain, such as single channel studies of deletion mutations.

THE MOTION OF THE BALL AS A RANDOM WALK

The properties of the ball and chain have not been fully described. Thus, we are forced to make some assumptions in order to formulate a quantitative description of this model. One advantage of a quantitative formulation of a model is that it forces one to explicitly delineate the characteristics of the model. Since this is the first study to quantify this model, we cautiously use the simplest assumptions.

When the change in voltage activates the channel, the ball will be in some starting position away from the binding site. The ball will move because it is at a temperature greater than zero and because it is driven by collisions with water, ions and other molecules. Thus, it will move in some random way. The ball can occupy any position in space. However, we can simplify this motion so that the ball occupies only certain positions on a grid, and it hops from one position on the grid to another adjacent position at discrete steps in time. This is called a random walk model. Läuger (1988) had used a related type of random walk model to describe the internal motions of a blocking group within the channel protein that opened and closed the channel.

The chain will limit the motion of the ball. We assume that the chain limits the range of the ball and that the chain does not exert any forces on the ball to alter its random walk. The shape of the channel protein, the location of the attachment of the chain, and the length of

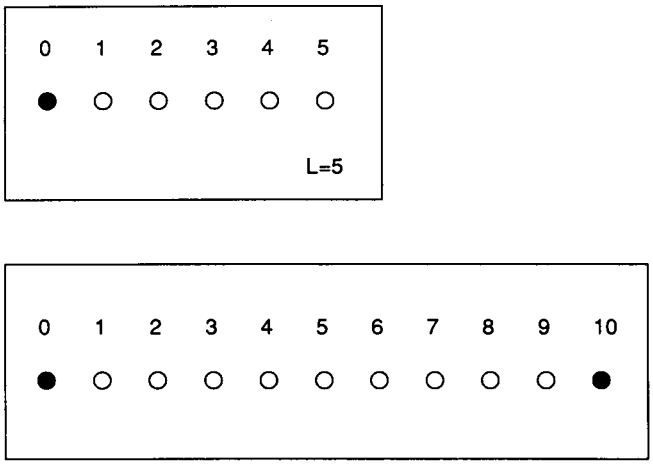

FIGURE 1 It has been proposed that part of a channel is a ball tethered to chain. Inactivation occurs when the wandering ball reaches a binding site in the channel. To calculate, $f(t)$, the probability density function of the intervals of time that it takes the ball to reach the binding site we model its motion as a random walk. Here, the random walk is illustrated in one dimension. (*Top*) The tethering chain limits the range of the ball to a distance $X = L$ from the binding site. The ball starts at a position $X = S$. At each time step the ball moves, with equal probability, to the right or to the left. The random walk terminates when the ball reaches the binding site at $X = 0$. The time it takes the ball to reach the binding site is equal to the number of steps in the walk. In this illustration $L = 5$. We calculated the probability density function, $f(t)$, for different values of S and L. (*Bottom*) It is easier to calculate some of the properties of the original random walk by transforming it into the equivalent random walk shown here where the ball starts at position $X = S$, and terminates either at the binding sites $X = 0$ or $X = B = 2L$.

the chain will determine the space available for the motion of the ball.

One position on the grid corresponds to the binding site and another to the starting position of the ball. We calculate the probability density function of the number of steps required for the ball to go from its starting position to the binding site. That is, we find how often the random walk to the binding site takes a given number of steps.

The space available for the motion of the ball is a three-dimensional space with a complex boundary. Since this full three-dimensional problem is very difficult, we first consider the motion of the ball in a one-dimensional space where the random walk can be solved exactly. Then we use numerical solutions to study the effect of forces such as electrostatic interactions between the ball and the binding site. Finally, we describe some properties of the fully three-dimensional solution.

ANALYTICAL SOLUTIONS OF THE ONE-DIMENSIONAL RANDOM WALK

First, we consider a random walk in one-dimension. We describe the motion of the ball through space as a discrete motion between points on a line, as shown in Fig. 1. The binding site is at position $X = 0$ and the starting position of the ball is at position $X = S$. Since the ball is tethered by its chain, it must remain within a certain distance, L, of the binding site which determines the length of the grid. The ball changes its position, X, at discrete times Δt. At each time step the ball moves one unit on the grid. If $X < L$, then there is equal probability that the next position of the ball is one unit to the right or one unit to the left. If $X = L$, the ball is at the end of the chain and since it can go no further, the next position must be $X = L - 1$. The walk ends the first time that $X = 0$. This is technically known as the first passage time of a random walk from starting position $X = S$ with an absorbing boundary at $X = 0$ and a reflecting boundary at $X = L$. The total number of steps in each walk is n and thus its duration is given by $t = n\Delta t$. We want to determine the distribution function $f(t)$, the probability that the duration of a walk is greater than t and less than $t + dt$.

As illustrated in the bottom of Fig. 1, this random walk is equivalent to a random walk on a grid of length $2L$, which terminates at either at $X = 0$ or $X = 2L$. That is, instead of changing direction at $X = L$, we pass on through to $X = L + 1$. In either case, we are $L - 1$ steps away from and heading toward the termination point. This problem was first proposed by Christian Huygens in 1657 and solved by Jacob Bernoulli in 1713 (Montroll and Shlesinger, 1984) and is known as the "gambler's ruin" problem (Feller, 1968). Early probability theory was motivated by gambling problems and it was not until nearly 200 yr later that this problem was first identified with a random walk. The gambler starts with a fortune, S, and bets against a bank with resources, $B - S$. The gambler's funds are given by X. Each step in the random walk corresponds to a bet of one unit. The gambler and the bank have equal probability of winning each bet. If the gambler wins the bet then $X = X + 1$, and if the gambler loses the bet then $X = X - 1$. The game terminates when $X = 0$ and the gambler is ruined, or when $X = B$ and the bank is ruined. Feller (1968, p. 353) shows that the probability density function that the gambler is ruined on the mth bet is given by:

$$g(m; B, S) = \frac{1}{B} \sum_{i=1}^{i<B} \cos^{m-1}\left(\frac{\pi i}{B}\right) \sin\left(\frac{\pi i}{B}\right) \sin\left(\frac{\pi i S}{B}\right). \quad (1)$$

Thus, $f(t)$, the probability that the walk to the binding site takes t steps is given by setting

$$m = t \quad (2)$$

$$B = 2L, \quad \text{and} \quad (3)$$

$$f(t) = g(m; B, S) + g(m; B, B - S). \quad (4)$$

Fig. 2 shows the distribution $f(t)$ when the ball starts at different starting positions $X = S$ on a grid of length $L = 16$ calculated from Eqs. 1–4. These solutions have different forms depending on the starting position of the

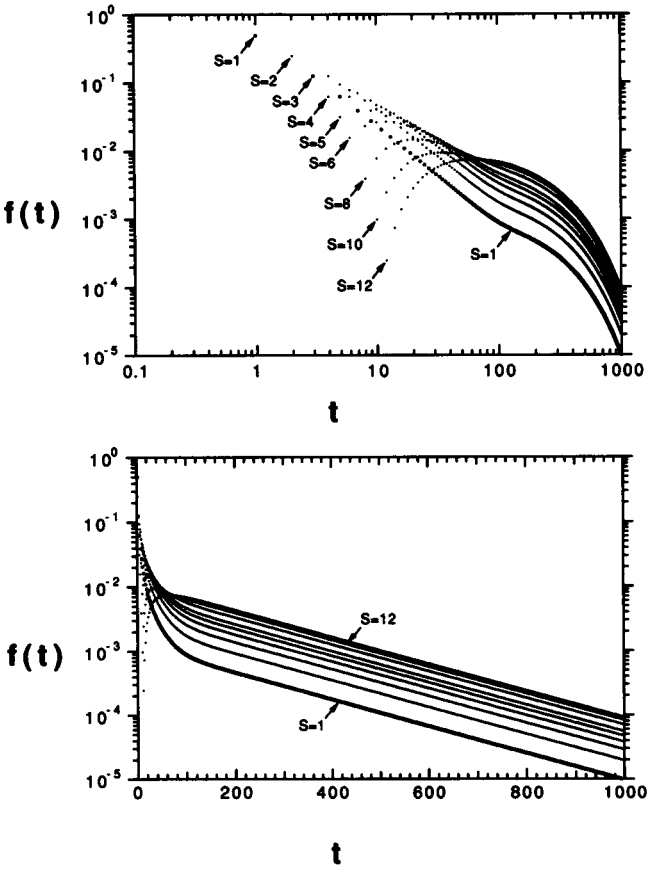

FIGURE 2 Full logarithmic plot (*top*) and semi-logarithmic plot (*bottom*) of the distribution $f(t)$ of times t it takes the ball starting in position $X = S$ to reach the binding site at $X = 0$ on a grid of length $L = 16$. These results were calculated from the analytic solution Eqs. 1–4.

ball and the duration of the walk. To understand the different time regimes, note that the average distance the ball moves is equal to the square root of the number of steps, that is, it is equal to $(t)^{1/2}$ (Feynman et al., 1963, pp. 6-5). Hence, the average time for the ball to move a distance d is equal to d^2. There are two regimes: (*a*) *Short times.* If the ball starts at position $X = S$, it can reach the binding site at $X = 0$ only after S steps and thus $f(t) = 0$, for $t < S$. The distribution $f(t)$ will rise to a maximum at the average time for the ball to reach $X = 0$, which occurs at $t \approx S^2$. When the ball starts near the binding site, the distribution $f(t)$ has the power law form $f(t) \propto t^{-3/2}$. This was demonstrated for the case $S = 1$ by Millhauser et al. (1988). (*b*) *Long times.* The average time for the ball to reach the end of the grid is $t \approx (L - S)^2$. An upper bound on this time is the time it takes the ball to diffuse a distance equal to the maximum extension of the chain, which is L_{max}^2/D, where D is the diffusion coefficient of the ball. In any protein, the maximum extension per residue is approximately 3.5 Å (Creighton, 1984, p. 171), and thus $L_{max} \approx 210$ Å. The diffusion coefficient of a 20 amino acid ball will be $\sim 1/\sqrt{20}$ the diffusion coefficient of one residue which is approximately 10^{-5} cm^2/s (Creighton, 1984, p. 184), and thus $D \approx 2 \times 10^{-6}$ cm^2/s. Hence, the long time regime is reached at ~0.002 ms. This brief time is much shorter than the resolution time of the patch clamp recordings. Thus, we concentrate our analysis on this long time regime because it corresponds to the time regime that will be sampled in the single channel or whole cell experiments.

At long times, the distribution $f(t)$ has the single exponential form $f(t) \propto \exp(-kt)$. The value of the rate constant k can be derived from Eqs. 1–4. As noted by Feller for large m, the value of the first term $i = 1$ in the sum is much greater than the sum of the remaining terms. When $B \gg 1$, then

$$f(t) \propto \cos^{m-1}\left(\frac{\pi}{B}\right) \approx \left[1 - \left(\frac{\pi^2}{2B^2}\right)\right]^{m-1} \qquad (5)$$

and since $m = t \gg 1$, and $t - 1 \approx t$, we find that

$$\ln f(t) \approx \text{const.} + t \ln\left(1 - \frac{\pi^2}{2B^2}\right) \approx -kt$$

$$\text{where} \quad k = \frac{\pi^2}{2B^2}. \qquad (6)$$

Eq. 6 demonstrates that the limiting form of $f(t)$ is indeed a single exponential, and using $B = 2L$, we find that the rate constant, k, is given by

$$k = \frac{\pi^2}{8L^2}. \qquad (7)$$

The rate constant k is inversely proportional to the square of the length L of the chain. Note however, that it does not depend on the starting position of the ball. This is because at long times the ball walks over the entire grid many times before reaching the binding site and thus the memory of its starting position is lost while the length of the grid is the essential parameter in determining the distribution $f(t)$.

NUMERICAL SIMULATIONS OF THE ONE-DIMENSIONAL RANDOM WALK

The techniques used to derive the analytical solution above cannot be extended to walks where there are forces on the ball or to walks in higher dimensions. Thus, we are forced to use numerical simulations in order to evaluate the distribution $f(t)$ in these cases.

First, we numerically simulated the one-dimensional random walk in Microsoft QuickBASIC and WaveMetrics Igor on Macintosh IIx and IIfx microcomputers. For each case (S, L) with starting position S and grid length L, 10,000 to 100,000 random walks were calculated. The distributions $f(t)$ calculated from these numerical simulations matched the analytical solution described in the previous section. Since the experimental data may typically have 10,000 events, we present in Figs. 3 and 4,

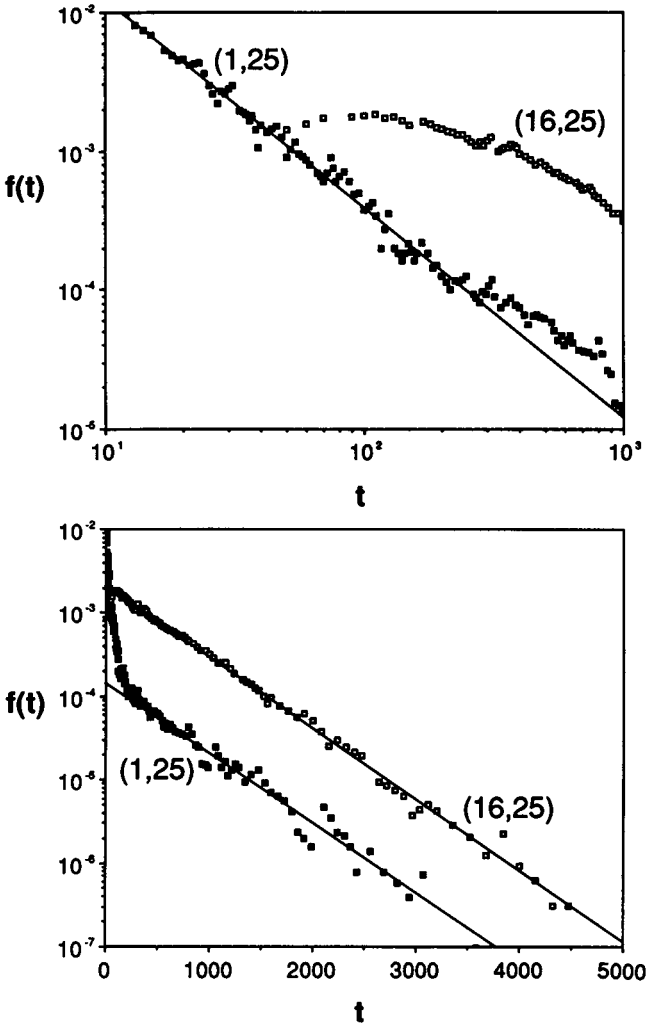

FIGURE 3 Simulations of 10,000 random walks in one dimension were used to determine the distribution $f(t)$ shown in the full logarithmic plot (*top*) and semi-logarithmic plot (*bottom*). The results are labeled by (S, L) indicating the starting position S and the length of the grid. In this plot the length of the grid was $L = 25$, and the ball was started either at $S = 1$, the first position away from the binding site, or at position $S = 16$. (*Top*) At short times when the ball starts at $S = 1$ very close to the binding site, $f(t)$ is a straight line, indicating that is a power law of the form t^{-a}. (*Bottom*) At longer times, or when the ball starts at $S = 16$ further form the binding site, $f(t)$ is a single exponential of the form e^{-kt}. The rate constant, k, is the slope of the line. Since both lines have the same slope, the rate constant, k, does not depend on the starting position of the ball.

the distributions $f(t)$ determined from the numerical simulations of 10,000 walks to provide a realistic impression of the analysis of such experimental data.

Fig. 3 shows the distribution $f(t)$ from random walks on a grid of length $L = 25$ starting either at $S = 1$, the first position away from the binding site, or starting from $S = 16$. At short times, as shown in the top of Fig. 3, when the starting position is $S = 1$, the distribution $f(t)$ is a straight line on a log-log plot and thus it is power law of the form $f(t) \propto t^{-a}$. Fitting this data, we found that $a = 1.51$ compared to its predicted value of 1.50 (Millhauser et al., 1988). At long times, as shown in the bottom of Fig. 3, the distribution $f(t)$ is a straight line on a semi-log plot, and thus it is a single exponential of the form $f(t) \propto \exp(-kt)$. One can see that the lines for both $S = 1$ and $S = 16$ have the same slope and thus the rate constant, k, does not depend on the starting position of the ball. Fitting this data, we found that $k = 1.95 \times 10^{-3}$ compared with its value of 1.97×10^{-3} predicted from Eq. 7.

Fig. 4 shows the distribution $f(t)$ at long times when the starting position $S = 15$ on grids of length $L = 16$, 20, and 30. At long times the distribution $f(t)$ is a straight line on these semi-log plots and the slope of that line, the rate constant, depends on the length L of the grid. The rate constant is smaller when the chain is longer. Fitting this data, we found that $k \propto 1/L^{2.00}$ compared with its value of $1/L^{2.00}$ predicted from Eq. 7.

NUMERICAL SIMULATIONS OF THE ONE-DIMENSIONAL RANDOM WALK WITH FORCES ACTING ON THE BALL

Experiments with mutant channels show that the inactivation rate is sensitive to the charges of the amino residues on the ball (Hoshi et al., 1990, Zagotta et al., 1991). Thus, electrostatic interactions between the ball and its binding site, or between the ball and the electric field across the membrane, may be important in the motion of the ball and thus effect the distribution $f(t)$. As shown above, a central property of the random walk ball and chain model is the prediction that at long times the distribution $f(t)$ is a single exponential with rate constant k that is proportional to $1/L^2$. We used numerical simula-

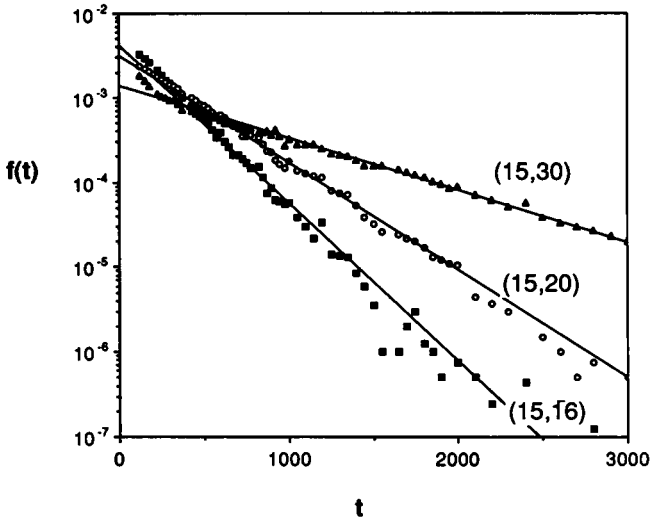

FIGURE 4 The distributions $f(t)$ determined from 10,000 random walks are shown for different values of (S, L) where S is the starting position and L is the length. The straight lines on this semi-logarithmic plot, indicate that $f(t)$ has the single exponential form e^{-kt}. The rate constant, k, is inversely proportional to the square of the length of the chain that tethers the ball.

tions to determine how this dependence is altered by directed forces on the ball.

In the random walk described above the probability, p_-, that the next position of the ball will be closer to the binding site equals the probability, p_+, that it will be further from the binding site. We now introduce a force by choosing $p_- \neq p_+$ while satisfying the constraint $p_- + p_+ = 1$. This additional bias at each time step corresponds to a net velocity on the ball. We studied the effects of both short range and long range forces. (*a*) *Long range, constant velocity.* At each position X we set $p_+ = 0.55$ for a repulsive force or $p_+ = 0.45$ for an attractive force between the ball and its binding site. In both cases we found that at long times the distribution was still a single exponential, that is $f(t) \propto \exp(-kt)$. The repulsive force causes the ball to spend more time at the far end of the grid away from the binding site. Without this repulsion $k \propto 1/L^2$. The additional time spent at the far end of the grid increases the dependence of k on L. Fitting our data, we found that $k \propto 1/L^{4.9}$ when $p_+ = 0.55$. The attractive force causes the ball to spend more time near the binding site thus reducing the influence of the length of the grid. Fitting our data we found that $k \propto 1/L^{0.9}$ when $p_+ = 0.45$. Such a long range constant velocity drift would result if the ball reached a limiting velocity as the result of a balance between viscous drag and a constant acceleration. Such an acceleration could be supplied by the constant electrical field imposed across the membrane. However, in solution, such fields are likely to be reduced by the screening effect of mobile ions. Thus, we also studied the effects of short range fields.

(*b*) *Short range.* We studied two examples of short range forces. First, a charge distribution screened by the ions in solution would yield an additional component to $\Delta p_+(X)$ that decays exponentially in X. Second, an electric dipole which induces an acceleration, $a(X)$, proportional to $1/X^3$. The additional component to the probability, $\Delta p_+(X)$ is proportional to the velocity, $v(X)$. Since, $a(X) = dv(X)/dt = [dv(X)/dX][dX/dt] = vdv(X)/dX$, then $\Delta p_+(X) \propto X^{-2}$. In both cases we found that, at long times, the distribution was still a single exponential, that is $f(t) \propto \exp(-kt)$. The forces only weakly affected the dependence of the rate constant k on L. That is, the force is significant over a small part of the grid and thus it acts like an energy barrier which changes the probability of getting through to the binding site. These forces only alter the dependence of k on L in that they are proportionally more significant for shorter grids. For example, repulsive forces with significant range of a few grid points with amplitude $\Delta p_+ = 0.3$, lead to $k \propto 1/L^{1.6}$.

EXTENSION TO TWO AND THREE DIMENSIONS

There are no known analytic methods to determine the properties of the distribution $f(t)$ for two- and three-dimensional walks where the boundary is arbitrarily shaped (Gerstein and Mandelbrot, 1964). Numerical solutions are also difficult because many different combinations of boundary conditions and starting locations must be explored over a large grid. However, using analytic arguments and numerical simulations we can say something about the form of the solution.

The random walk problem can be reformulated as a diffusion problem (Feller, 1968, p. 356). At long times, the solution will be dominated by the term with the smallest eigenvalue which has the form $f(t) \propto \exp(-\lambda^2 t)$ (Carslaw and Jaeger, 1959). Thus, we expect that at long times the distribution $f(t)$ will be a single exponential of the form $\exp(-kt)$ where $k = \lambda^2$. The correct boundary condition is that the entire boundary is reflecting except for the local absorbing site where the ball binds to the channel. However, if the entire boundary were spherical and absorbing, then $k \propto 1/L^2$. If this were the case, the two- and three-dimensional solution would have the same form as the one-dimensional solution. We expect that the eigenvalues of the correct boundary will have a different dependence on L. The additional reflections should increase the steepness of the dependence on L. Thus, as a lower bound we expect that $k \propto 1/L^2$. Our simulations of random walks on orthogonal grids in one, two, and three dimensions showed that k varied as $1/L^2$, $1/L^{2.4}$, and $1/L^{3.2}$, respectively. Hence, we conjecture that in D dimensions, at long times, the distribution $f(t)$ will be a single exponential and the rate constant of that exponential will have a dependence on the linear size L of the region that is in between $1/L^2$ and $1/L^{D+1}$.

COMPARISON WITH EXPERIMENTAL DATA

We can present only a tentative comparison between the quantitative predictions of the ball and chain model and the experimental data because some of the relevant experimental values have not yet been measured or measured with sufficient precision. An important goal of this paper is to describe the further experiments that need to be done to quantitatively test the validity of the ball and chain interpretation. The missing data that is most needed is: (*a*) the form of the distribution of the open → inactivated times. Is it a single exponential or a more complex form? The form of this distribution can tell us how far from the binding site the ball starts its walk. (*b*) How does this distribution change as a function of major deletions in the chain region. If it is a single exponential, what is the dependence of its rate constant on the length of the chain? The largest possible deletions of the chain are needed to determine the dependence on chain length with precision. This dependence can tell us if the ball moves at random or if its motion is significantly influenced by other forces.

The only tentative comparison we can make with the existing data is that the data of Hoshi et al. (1990, Fig. 3

C) indicates the distribution $f(t)$ is approximately a single exponential and that its rate constant, $k \propto 1/L^5$, where L is the length of the chain. Note that this relationship is not very precise because it is based only on mutations deleting 14, 8, and 6 amino acid residues from a chain that is 60 residues long. The one-dimensional random walk model makes the following predictions. If the walk is random with no directed forces then $k \propto 1/L^2$. Short range forces between the ball and the rest of the channel molecule cannot produce such a steep dependence on L as $1/L^5$. Only if there is a long range force and only if it is repulsive will the rate constant k have such a steep dependence on L. Electrical forces between distant components would be reduced by mobile charges in solution so it is not clear what physical mechanism would produce such a long range force. Although the result is less certain in two and three dimensions, it appears that rate constant of random walks in two and three dimensions is less steep than $1/L^4$, unless there are long range repulsive forces on the ball.

DISCUSSION

It has been proposed that inactivation in a voltage sensitive channel occurs when a tethered ball binds at a site blocking the mouth of the channel. We derived the quantitative form of the distribution of times it takes the ball to reach its binding site. These results suggest additional experiments to determine if the ball and chain picture is valid. They also suggest additional theoretical studies to further refine these predictions.

If the ball binds when the channel is open, then $f(t)$, the distribution of times it takes the ball to reach the binding site, corresponds to the distribution of open → inactivated times, measured in single channel experiments as the distribution of burst durations. It also corresponds to the decay curve of the current measured in whole cell recordings. The distribution $f(t)$ predicted by the ball and chain model can only be determined analytically when the motion of the ball is random and restricted to one dimension. We also used numerical simulations to determine the properties of $f(t)$ when there are short and long range forces on the ball in addition to its random motion.

The form of $f(t)$ for motion in one dimension is complex and depends on the starting position of the ball. At very short times, if the ball starts near the binding site, the distribution has the power law from $f(t) \propto t^{-3/2}$. If the ball starts far from the binding site, $f(t)$ rises to a maximum without this initial power law. Thus, if $f(t)$ can be measured with sufficient precision from single channel or whole cell experiments, then its form at short time can reveal the initial position of the ball when the channel is activated by the change in voltage. However, based on the length of the chain and the diffusion coefficient of the ball, we estimate that the time scale of these measurements will be ~0.002 ms, which may be beyond the resolution of patch clamp or whole cell recordings. The meaning of the very low value found for this short time scale is not clear. If the ball can bind so rapidly then sometimes inactivation would occur so fast that it would appear that the channel was never activated, and this is not observed. On the other hand, this estimate may be too short if there is an additional rate limiting step due to the chemical reaction of the ball attaching to the binding site.

At long times, the distribution has the exponential form $f(t) \propto \exp(-kt)$. The effective length of the chain will depend on the type of protein structure (β-sheet, α-helix, 3_{10} helix, etc.). Since we do not know the type of protein structure of the chain we cannot determine the absolute value of the rate constant k. If the type of protein structure varies along the chain, then the dependence of the rate constant k on the length of the chain will be complex. However, if the structure within the chain is all of one type, we can determine the type of dependence of the rate constant k on the length L of the chain. We showed that if the motion of the ball is random and restricted to one dimension, then the rate constant $k \propto L^{-2}$. This relationship is not altered much if there are short range forces, such as electrostatic forces, between the ball and the rest of the channel. This prediction could be tested by measuring the rate constant $k(L)$ in mutant channels with deletions of different numbers of amino acid residues in the chain region. If this model is correct then a plot of $\log k(L)$ vs. $\log L$ would have a slope equal to -2.

Analysis of the experimental data of Hoshi et al. (1990) yields $k \propto L^{-5}$. The relationship however cannot be determined precisely because it was based on deletions of only a small number of amino acid residues. We showed that such a steep dependence on L could only result from a long range repulsive force. Such a force could not likely be generated by charges within the channel because their effect at long distances would be reduced by ions in solution. One candidate for such a long range force is the voltage applied across the membrane. However, this seems to be ruled out by the observation that the inactivation does not depend on voltage (Hoshi et al., 1990; Zagotta et al., 1991). A long range force might also be imposed on the ball if the "chain" is actually a rigid structure that can exert mechanical forces on the ball and thus inactivation would be due to sticks, springs, and a ball rather than a chain and a ball. The important implications of the dependence of k on L strongly suggest that additional experiments to more precisely determine this relationship be done by measuring the rate constant of inactivation when larger regions of the chain have been deleted.

At long times, we also showed that the rate constant, k, does not depend on the starting position of the ball. Thus, the currents measured from repeated single channel experiments, or whole cell recordings with many channels, where the ball starts at different positions, can

be averaged together and will still yield a single exponential with the rate constant k.

Because of the much greater difficulties in predicting the distribution, $f(t)$, when the motion of the ball is in three dimensions, we have concentrated here on studying the motion of the ball in one dimension and presented much more limited results on motion in two and three dimensions. Time consuming three-dimensional numerical simulations with complex boundary conditions and many different starting positions for the ball are needed to refine the results presented here.

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