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# Fractal model of ion-channel kinetics

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**Markov models with discrete states, such as closed ⇄ closed ⇄ open have been widely used to model the kinetics of ion channels in the cell membrane. In these models the transition probabilities per unit time (the kinetic rate constants) are independent of the time scale on which they are measured. However, in many physical systems, a property, $L$, depends on the scale, $\epsilon$, at which it is measured such that $L(\epsilon) \propto \epsilon^{1-D}$ where $D$ is the fractal dimension. Such systems are said to be 'fractal'. Based on the assumption that the kinetic rates are given by $k(t) \propto t^{1-D}$ we derive a fractal model of ion-channel kinetics. This fractal model has fewer adjustable parameters, is more consistent with the dynamics of protein conformations, and fits the single-channel recordings from the corneal endothelium better than the discrete-state Markov model.**

## Introduction

Ion channels gate the flow of ions across the cell membrane. Typically, there are a few such channels per square micron of cell surface. Thus, when a small, micron-sized, piece of cell membrane is sealed within a micropipette, the picoamp currents due to ions moving through an open channel can be measured. With this patch clamp technique it is possible to determine the durations of the opening and closing of individual channels and thereby measure the kinetics of the channel. These channels have been widely modeled as consisting of a small number of discrete states, such as closed ⇄ closed ⇄ open, and the transition probabilities between the states represented by a Markov process. In such a model, the transition probabilities per unit time, that is, the kinetic rate constants, are constants.

However, in many physical systems the value, $L$, measured for a property often varies with the scale, $\epsilon$, at which $L$ is measured such that $L(\epsilon) = A\epsilon^{1-D}$, where $D$ is the fractal dimension [1]. For example, as the scale of a map becomes finer one detects more of the irregularities of a coastline so that its measured length increases. Such a scaling has been observed in the perimeters of clouds [2], the branching of the bronchi in the lungs [3], the energy of earthquakes [4], and in many other cases. This concept of 'fractals' was organized and developed by Benoit Mandelbrot [1] and has been applied to many different phenomena in many different scientific fields.

If such a fractal scaling also applies to the current flow through an ion channel, then as we observe the current at higher frequency resolution we will observe the channel fluctuating open and closed at a higher rate. We can formulate a model

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of a channel with fractal kinetics by saying that it has two states;

$$\text{closed} \underset{k_c}{\overset{k_o}{\rightleftharpoons}} \text{open}$$

but that the kinetic rate constants $k_o$ and $k_c$, rather than being constants (as in a Markov model), are actually functions of the time scale, $t$, at which they are observed such that $k_o(t) = At^{1-D}$ and $k_c(t) = A't^{1-D'}$. Over a short time range, the channel will look locally like a two-state Markov process, with effective rate constant $k_{eff}$, but over a longer time range $k_{eff}$ is a function of $t$. We will discuss the closed-time durations. The equations for the open times are analogous with $k_o$ replaced by $k_c$.

As shown below for a two-state process, $dP(t)/P(t) = -k_o(t)dt$, where $P(t)$ is the probability that the channel remains closed for the duration $[0, t]$ and the probability density of the closed durations $f(t) = d/dt[1 - P(t)]$. Thus, in this case $k_o(t) = -d/dt[\ln P(t)]$ and so it is reasonable to define $k_{eff} \equiv -d/dt[\ln P(t)]$ for a channel of any type. Colquhoun and Hawkes [5–7] derived $f(t)$ for channels with multiple discrete states. For a two-state closed $\rightleftarrows$ open channel $f(t) = \alpha \exp(-\alpha t)$, while for the three-state closed $\rightleftarrows$ closed $\rightleftarrows$ open channel $f(t) = B \exp(-\beta t) + C \exp(-\gamma t)$.

Shown in Fig. 1 are three typical examples of plots of log $k_{eff}$ vs. log $t$ for three different models:

(a) a two-state Markov model

$$\text{closed} \underset{k_c}{\overset{k_o}{\rightleftharpoons}} \text{open}$$

with $k_o = 6.25$ Hz and $k_c = 25$ Hz;

(b) a three-state Markov model

$$\text{closed} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \text{closed} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \text{open}$$

with $k_{12} = k_{21} = 2.5$ Hz, $k_{23} = 25$ Hz, and $k_{32} = 100$ Hz; and

(c) a fractal model

$$\text{closed} \underset{k_c}{\overset{k_o}{\rightleftharpoons}} \text{open}$$

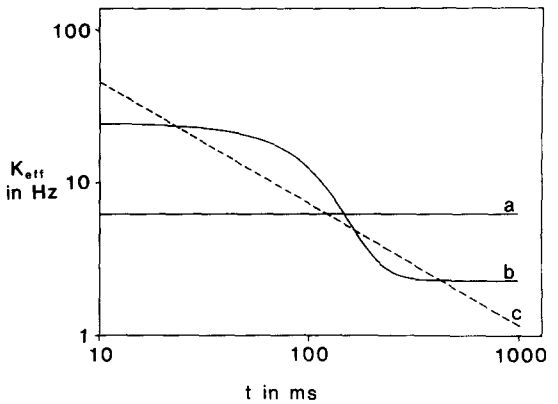


Fig. 1. Effective rate constant $k_{eff}$ evaluated at time scale, $t$, for three channels with three different types of kinetics: (a) a Markov two discrete state closed $\rightleftarrows$ open channel model; (b) a Markov three discrete state closed $\rightleftarrows$ closed $\rightleftarrows$ open channel model; and (c) a channel model with fractal kinetics. The values of the kinetic rate constants for these three models are given in the text.

with $k_o = At^{1-D}$ and $k_c = A't^{1-D'}$ where $A = 1.15$ $Hz^{0.2}$ and $D = 1.8$.

In the analysis of experimental data, information about the channel kinetics is limited to the range of effective times whose lower bound is set by the frequency response of the patch clamp amplifier and whose upper bound is set by the duration of the patch. If there are multiple discrete Markov states whose time constants are within this range then we will observe plateaux on this plot. We must be able to observe these plateaux to confirm the existence of the multiple discrete states. If the kinetics of the channel are fractal (or if there are many closely spaced states) such plateaux will not be observed. This provides a clear way to test the data from a channel to determine whether it can be represented by a small number of discrete states.

To derive the probability, $f(t)$, that a channel with fractal kinetics is closed for duration, $t$, we start with the formulation used by Colquhoun and Hawkes [8] for a discrete state channel. Let $P(t)$ be the probability that the channel is closed during the interval $[0, t]$. The probability that the channel remains closed over the interval $[0, t + \Delta t]$ is thus equal to the probability that the channel is closed on the interval $[0, t]$ times the probability it does not open during the interval $[t, t + \Delta t]$. Since the probability that the channel will open during

any time interval $\Delta t$ is equal to $k_o \Delta t$, the probability that the channel does not open during an interval of duration $\Delta t$ is equal to $1 - k_o \Delta t$. Thus, $P(t + \Delta t) = P(t)[1 - k_o \Delta t]$. In the limit $\Delta t \to dt$ and $\Delta P = P(t + \Delta t) - P(t) \to dP$, this equation becomes $\int dP/P = -\int k_o dt$, so that $P(t) = \exp(-k_o t)$. When the channel is fractal, $k_o$ is no longer a constant, but $k_o(t) = At^{1-D}$. The integral equation now becomes $\int dP/P = -\int At^{1-D}\, dt$, and $P(t) = \exp\{-[A/(2-D)]t^{2-D}\}$. The restriction that $k_o(t)$ be a constant or monotonically decreasing with $t$ requires that $D \geq 1$. The restriction that $P(0) = 1$ requires that $D < 2$. Thus, the fractal dimension $D$ is limited to the range $1 \leq D < 2$.

Since $P(t)$ is the probability than the channel is closed on the interval [0,t] then $1 - P(t)$ is the probability that the channel is closed for a duration greater than $t$. Thus, the probability density $f(t)$ that the channel is closed for duration $t$ is given by $f(t) = d/dt[1 - P(t)]$. Thus, for the channel with fractal kinetics

$$f(t) = At^{1-D} \exp\{-[A/(2-D)]t^{2-D}\}.$$

Note that the fractal dimension model is a generalization of the model based on discrete Markov processes and includes the two-state Markov model as a special case. When $D = 1$ in the equation above then, $f(t) = A \exp(-At)$, the well-known form for a two-state Markov process. The fractal model can be interpreted either as a continuous process or an infinite number of Markov processes.

The same functional form for $P(t)$ for the channel with fractal kinetics has appeared in other contexts. It was proposed by Kohlrausch in 1864

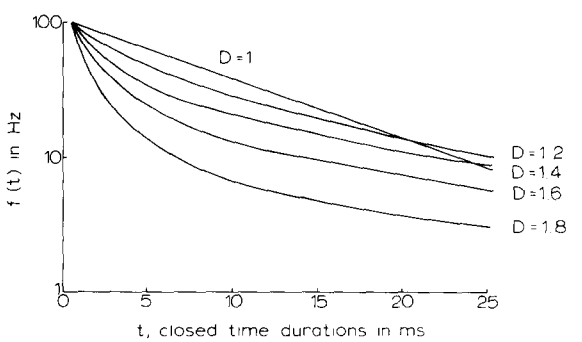


Fig. 2. The probability distribution of the durations of the closed times predicted by the fractal model of channel kinetics for some values of the fractal dimension, $D$.

to describe mechanical creep and was used by Williams and Watts in 1970 to describe dielectric relaxation in polymers, and is known as the stretched-exponential or Williams-Watts Law [9]. The relevance of the work done in these other systems to understanding the dynamics of the ion channel protein will be discussed below.

In Fig. 2, $\log[f(t)]$ vs. $t$ for various values of $D$ is shown for a channel model with fractal kinetics. If the experimental data has the fractal form shown in Fig. 2, then to fit such data with a Markov state model requires one to postulate the existence of multiple states. For example, the curves in Fig. 2 could be fit by the multiple state model closed $\rightleftarrows$ closed $\rightleftarrows$ open with $f(t) = B \exp(-\beta t) + C \exp(-\gamma t)$ where $B$ and $\beta$ are adjusted to fit the curve at short time scales and $C$ and $\gamma$ are adjusted to fit the curve at long time scales. However, no Markov discrete state model could fit such data for all times because for a channel with fractal kinetics, $d\{\log[f(t)]\}/dt \to 0$ as $t \to \infty$, so that slope of $\log[f(t)]$ is always less steep than that of any discrete state Markov process. Thus, if a Markov model with discrete states were to be fit to the data from a channel with fractal kinetics, as the channel is observed for longer and longer times, then more and more discrete states would have to be postulated to fit the experimental data.

We analyzed experimental data from single channel recordings to determine if these channels are best represented by the models with fractal dimensions or by models with multiple discrete states.

In analyzing the data recorded from a single channel, $f(t)$ is not known analytically, and so we developed two different procedures to determine $k_{\text{eff}}$, both based on the essential idea upon which the definition of $k_{\text{eff}}$ was based, namely, that it is the effective rate constant measured at a time scale $t$.

We used the analog/digital converter on our PDP 11/34 minicomputer to sample a single channel recording at different sampling frequencies, that is we sample the signal at different time intervals, $t_s$. Then for each sampling rate we plot the logarithm of the number of closed durations between $t$ and $t + \Delta t$ vs. the duration of the closed times. Since, $f(t) \propto \exp(-k_{\text{eff}} t)$, the slope of each such histogram, obtained from a least-

squares fit, then determines $k_{eff}$. Because we want to evaluate $k_{eff}$ over only a small range of the time scale, for each histogram, we should use as small a range of duration of closed times as possible. That is, for each histogram we choose the first three bins of the closed time duration frequency histogram. Thus, we determine $k_{eff}$ as a function of the time scale $t_s$.

Alternatively, we can take a data record sampled at any one sampling rate and evaluate several frequency histograms of the closed time durations by using different bin sizes $t_b$ for each histogram. That is, in each histogram we plot the logarithm of the number of closed durations between $t$ and $t + t_b$ vs. the duration of the closed times. For each histogram we ignore the lowest time bin (which includes all the events $t \ll t_b$ that happen much faster than our time scale of interest) and we ignore the longest time bins (which include all the events $t \gg t_b$ that happen at time scales much longer than our time scale of interest). Over a limited range of times (typically we chose $t_b \leq t \leq 4t_b$) the slope, obtained from a least-squares fit, determines $k_{eff}$. Thus, we determine $k_{eff}$ as a function of the time scale $t_b$.

Single-channel recordings up to 2.5 min long were made from a 70 pS channel in the rabbit corneal endothelium [10,11]. The records from two different patches were digitized at 5 kHz, 1.7 kHz, 500 Hz, and 170 Hz. At each sampling rate 20 000 points were digitized. The kinetic rate constants were determined by both measuring the closed time durations and the use of higher-order correlation functions [12,13]. Both methods yielded similar values. The entire record from one of these patches was also digitized at 5 kHz, printed on a chart recorder and the durations of 1465 closed times measured manually. Then the frequency histogram of these closed times was evaluated by using bin sizes of 2, 4, 8, 16, 32, 64, 128, and 256 ms. For each histogram the slope of $\ln[f(t)]$ vs. $t$ on the 2nd to 4th bins was used to determine $k_{eff}$.

As shown in Fig. 3, there are no plateaux that would indicate multiple discrete closed states; rather, the data are well fit by straight lines, indicating that the channels can be well represented by a model with fractal kinetics. The fractal dimensions as determined by varying the data sampling rate ($t_s$) were found to be $D = 1.74 \pm 0.03$ ($r = 0.996$) and $D = 1.83 \pm 0.11$ ($r = 0.965$). For the first channel, the sampling of a larger amount of data with different bin sizes ($t_b$) yielded $D = 1.79 \pm 0.01$ ($r = 0.999$).

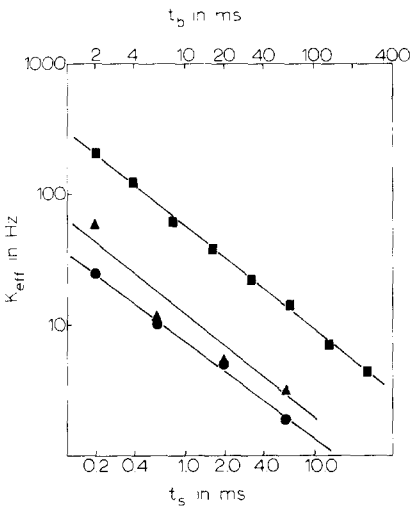


Fig. 3. Experimentally determined effective kinetic rate constnat, $k_{eff}$ as a function of the time-scale used to measure $k_{eff}$. Data are from a 70 pS channel in the rabbit corneal endothelium. The time scales were determined by sampling the single-channel record at different frequencies, that is, at intervals $t_s$ (●, ▲), or by evaluating frequency histograms for the durations of the closed times by using different bin sizes, $t_b$ (■). The linearity of the data suggests that these channels are better represented as having fractal kinetics rather than multiple discrete states.

We now compare the predictions made by the fractal model of channel kinetics to the observed distribution of the closed time durations. The number of closed time durations actually observed in an experimental record is equal to the probability of those closed time durations, $f(t)$, multiplied by the total number of events, $N_T$. Note that $f(t)$ as derived above depends only on the values of $A$ and $D$. From the slope and intercept of the least-squares fit of log $k_{eff}$ vs. log $t_b$ in Fig. 3 we found that $D = 1.79$ and $A = 1.49$ Hz$^{0.21}$ for that channel. Thus $f(t)$ is already completely determined for this data set without any other adjustable parameters. If $N_T$ could be accurately determined from the data then the fractal dimensional model would predict the observed frequency histogram of the duration of closed events with no adjustable parameters. (This contrasts sharply with the dis-

crete multiple state models, which would now try to fit the observed frequency histogram and the 'bursts' with many adjustable parameters to determine the four, or more, kinetic rate constants needed to specify $f(t) = B \exp(-\beta t) + C \exp(-\gamma t) + \ldots.$) In the fractal kinetic model, the channel fluctuates open and closed faster at shorter time scales. Thus, a single channel recording system with limited frequency response will miss many of these rapid events. The fraction of events actually recorded will equal $P(t_r) = \exp\{-[A/(2-D)]t_r^{2-D}\}$ where $t_r$ is the fastest time that can be resolved. For $D = 1.79$, $A = 1.49$ Hz$^{0.21}$, and $t_r = 4 \cdot 10^{-4}$ s, then $P(t_r) = 0.25$, meaning that only about 1 closing in 4 was actually observed. Because it is difficult to determine $N_T$ accurately, we have made it an adjustable parameter to be able to fit the distribution $f(t)$ predicted by the fractal kinetic model to the observed closed time durations. This parameter will shift the closed time duration histogram up or down, but will not alter its shape.

The experimentally observed frequency distribution of closed time durations and that predicted by the fractal kinetic model are shown in Fig. 4. Over closed-time durations that cover over three orders of magnitude, from 1 to 1200 ms, the fractal model matches the data quite well. (The fit could be improved by changing the values of $A$ and $D$ slightly, but we have not presented that plot because the point here is not curve fitting, but testing the hypothesis that the fractal model whose parameters are determined by the scaling law shown in Fig. 3 from log $k_{eff}$ vs. log $t_b$ can be used to determine the frequency histogram $f(t)$ shown in Fig. 4.) We are impressed by just how well the fractal kinetic model is able to explain the observed closed time durations over such a long range of closed times. Until now, it has always been a puzzle why longer closed durations seemed to appear in the data records at rates far beyond what was expected and so there has been a need to postulate the existence of multiple states connected by rate constants having different time

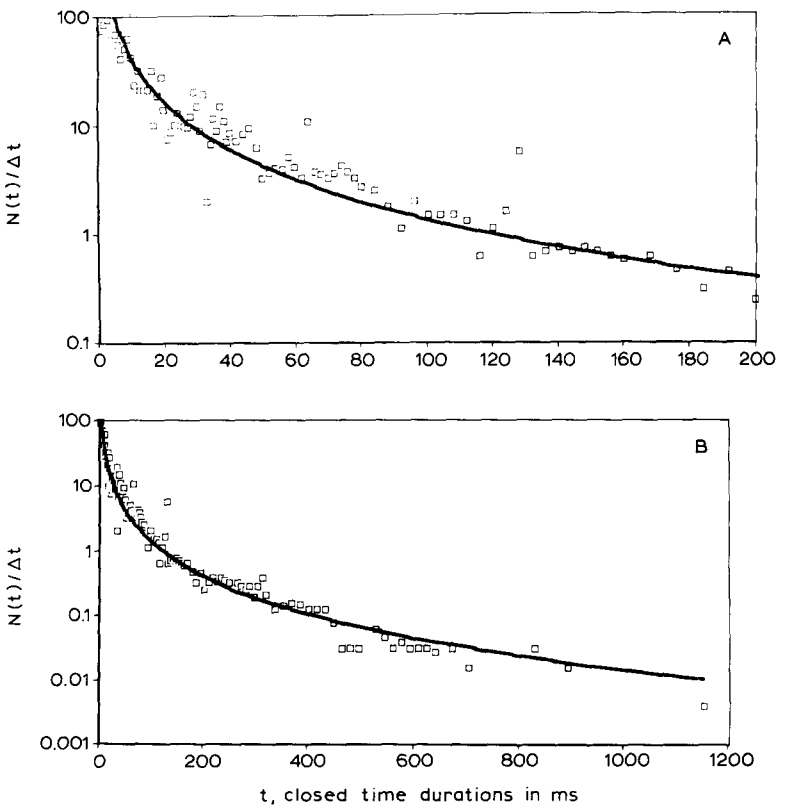


Fig. 4. Frequency histogram of the duration of closed times recorded from the corneal endothelium. Over both short (A) and long (B) closed-time durations, the experimental data (□) are compared to the prediction (–) from the fractal model of channel kinetics.

scales in order to explain such results. On the other hand, in the fractal model, both the short and long closed-time durations are seen as a simple manifestation of a single process, the fractal scaling of the channel kinetics.

The fit of four kinetic models to the experimental histograms of closed time durations was evaluated. The parameters of each model were determined by using the steepest descent method to minimize the sum of the squares of the residuals between the values predicted by each model and the experimental data [16]. The minimum sums of the squares of the residuals were found to be: 127 for the Markov closed ⇄ open model, 35 for the Markov closed ⇄ closed ⇄ open model, 24 for the Markov closed ⇄ closed ⇄ closed ⇄ open model, and 26 for the fractal closed ⇄ open model. To compare these residuals we used an $F$-test, where $F$ is the ratio of the residuals of any two models and the number of degrees of freedom is the number of data points (123) minus one [17,18]. The Markov closed ⇄ closed ⇄ closed ⇄ open model was a significantly better fit ($P \leq 0.025$) than the Markov closed ⇄ closed ⇄ open model, and the latter was a highly significantly better fit ($P \leqslant 10^{-10}$) than the Markov closed ⇄ open model. The fractal model was a highly significantly better fit ($P \leq 10^{-13}$) than the Markov closed ⇄ open model and also a significantly better fit ($P \leq 0.05$) than the Markov closed ⇄ closed ⇄ open model. In fact, the fractal model and the Markov closed ⇄ closed ⇄ closed ⇄ open model are equally good fits to the experimental data ($P \leq 0.67$).

These models are compared in Fig. 5. On this semi-logarithmic plot each discrete closed Markov state is represented as a straight line. Thus, if the data had a series of straight lines joined at obvious breaks then the multiple discrete Markov states could be unambiguously and accurately identified. However, as seen in Figs. 4 and 5, this is not the case. Rather, the experimental data is a smooth continuous curve without such distinctive breaks. The multistate Markov models approximate this curve by a series of short, almost straight line segments equal to the number of closed states. In fact, any smooth curve can be approximated by enough line segments of arbitrary shape. That is, even a completely invalid theory can be fit to

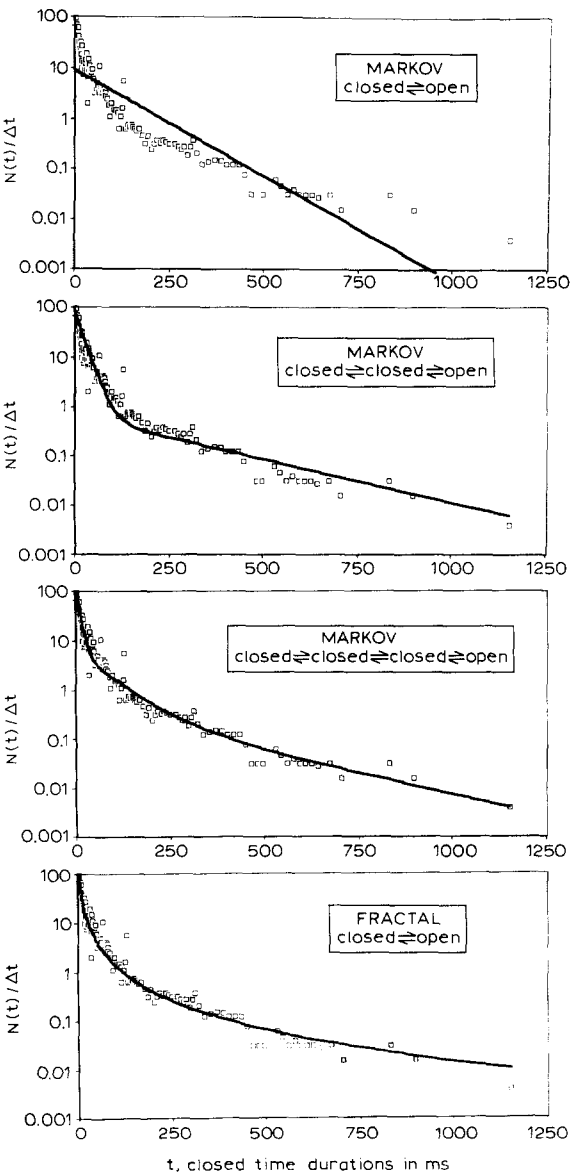


Fig. 5. Frequency histogram of the duration of closed times from the corneal endothelium (□) is compared to four theoretical models (−): Markov closed ⇄ open, Markov closed ⇄ closed ⇄ open, Markov closed ⇄ closed ⇄ closed ⇄ open, and the fractal model.

experimental data if we fit the theory over only small lines segments with each line segment having a different set of parameters. If both valid and invalid theories can fit the experimental data, how are we to choose the correct theory? One, often successful answer is Occam's razor (named after

William of Occam, a 14th century English scholastic); namely, that the simplest theory that fits the data is likely to be the valid one. The smooth curve predicted by the fractal model with two parameters fits the smooth curve of the experimental data as well as the Markov closed ⇄ closed ⇄ closed ⇄ open model with five parameters. As the number of closed states required by the Markov models to fit the smooth experimental data increases, our confidence in the reality of any of these states decreases.

We have also analyzed the frequency of the durations of the channel open times. The open times were also fractal with dimensions $D = 1.71 \pm 0.06$ ($r = 0.986$) and $D = 1.58 \pm 0.05$ ($r = 0.983$).

In a Markov process the transition probability per unit time (the kinetic rate constant $k$) depends only on the state of the channel. Thus a model of ion channel kinetics based on discrete Markov states requires that: (1) the ion channel has no intermediate states and (2) that it has exactly the same conformation when it returns to the same Markov state. Both of these assumptions are not consistent with the dynamics of protein conformations. Proteins are complex structures, with motions and conformational dynamics over many time scales; for example, $10^{-11}$ to $10^{-9}$ s (bound water relaxation), $10^{-9}$ to $10^{-8}$ s (local motions), $10^{-7}$ to $10^{-2}$ s (isomerization processes), and $1-10^{2}$ s (folding-unfolding transitions, 'breathing' modes) [15]. Thus, many intermediate conformations of the protein exist. Because some of these processes occur over long time scales, the ion channel has some 'memory' of its previous states and will be in a slightly different conformation every time it is in its 'open' or 'closed' states.

The fractal model of ion-channel kinetics described above is a first step in formulating a quantitative model of how such protein processes would be reflected in the single-channel recordings. In the fractal model, the transition probability per unit time depends both on the state of the channel and how long the channel has remained in that state, namely the transition probability per unit time $k \propto t^{1-D}$. This functional form is consistent with the theories developed to understand the kinetics of the relaxation of polymers and defects in glasses [9,14]. Although no theory now exists to derive this relationship for protein structure, the results from these other fields can be used to suggest a qualitative understanding of such fractal behavior. The protein channel has structure at many levels: side-chains, amino-acid residues, regions, and monomers. It is as if the gating of the channel is an overall property of the conformational dynamics of the channel protein and thus depends on many different processes that extend over many time scales from $10^{-11}$ to $10^{2}$ s, rather than depending on a single conformational change due to a single mechanism over a single time scale. After an open channel closes, there will be many dynamic relaxation processes over many time scales as these many units relax to the new protein state. Soon after the channel has closed, there have been few such motions and so it can more easily switch back to its open state. However, the longer the channel remains closed, the more the conformation of the protein has relaxed to the new state, and so the harder it is, and therefore the less likely it is, to return to the open state.

In conclusion, we have shwn how to test single-channel data to determine if it is better represented by discrete multiple states or fractal dimension kinetics by plotting log $k_{\text{eff}}$ vs. log $t$, where $k_{\text{eff}}$ is the kinetic rate constant measured over a time scale, $t$. If such a plot shows plateaux where $k_{\text{eff}}$ remains constant over a range of time scales, then the channel is best represented by a model consisting of multiple discrete states (for example, closed ⇄ closed ⇄ open). If such a plot shows a straight line, then $k_{\text{eff}} \propto t^{1-D}$ and the channel is best represented by fractal kinetics of dimension $D$. We also derived the distribution of closed time durations $f(t)$ for the channel with fractal kinetics. The analysis of single channel records from the corneal endothelium shows that these channels are well represented by a channel model with fractal kinetics.

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