

## Topical Review

### Fluctuations and Fractal Noise in Biological Membranes

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**Abstract.** Our understanding of cell structure and function derives from applications of a variety of physical and life science disciplines, methods and models to an important physiological process, namely, the exchange and transport of ions and molecules across biological membranes. We know that ion transport through membranes arises from a diversity of interrelated and interactive physical and chemical phenomena over a wide range of spatial and temporal scales. Among these phenomena common to all cellular structure and function include metabolism, kinetics of molecules, chemically mediated alteration of cell membrane electrical potential, membrane ion conductance, electrical signal propagation, and modulation by chemo- and mechanoreceptive mechanisms. This review focuses on the unique information contained in fluctuations in electrical properties associated with cell membrane ion transport.

**Key words:** Brownian motion — Cell membrane electrical properties — Fractals — Gaussian noise — Ion transport — Nonlinear dynamics

#### Membrane Electrical Properties Fluctuate

As with many recurring natural events, the resulting shape and duration of biological membrane electrical events *fluctuate* in time. The shape (e.g., height, width, etc.) of each event, as well as each time interval of recurrence, is never an exact replication of any previous event. Measured fluctuations may often reflect experi-

mental *uncertainties* in measured quantities that are usually assumed to be normally distributed and therefore characterized by a mean value and a variance defined for a specific interval of time over which a number of measurements are made. Changes in mean values of these measured quantities under different experimental conditions are often interpreted in terms of physical models. Until recently, a key feature of such models is *linearity*, characterized by two properties: proportionality and independence [39]. Underlying the interpretation of living processes as *linear* phenomena is a powerful and persuasive axiom of 20th-century medical and life sciences — the principle of *homeostasis* — articulated by Walter B. Cannon of Harvard Medical School [6]. Homeostasis means that the normal operation of a physiological system is to reduce fluctuations and to maintain a constant internal function. Homeostasis implies that fluctuations occur about a presumed normal steady state that may be represented (modeled) mathematically as a continuous function of time. The concept that a mathematical function and the geometric representation of a line are related — a seminal idea of the 17th century underlying the method of calculus — has thus promoted development of theories of *linear systems* as mathematical representations (models) of physiological processes. In models of biological membrane function, homeostasis and linearity are served and sustained by a linear network or system with well-defined and identifiable inputs and outputs, attendant governing processes, and often a mechanism or center of control [25].

#### Why Membrane Electrical Properties Fluctuate

Alternatively, fluctuations observed in cell electrical properties such as membrane potential may be inter-

preted as transient responses to a fluctuating environment over a wide range of *scales*. Upon initial inspection, a time sequence of normal fluctuations in magnitude and rate of a measurable quantity appears irregular and completely random. By *random* is meant that one fluctuation is not related to, or *independent* of another, i.e., there is no apparent dependence or correlation among fluctuations. If, however, a sequence of events is considered, the fluctuations may look remarkably like those observed in shorter or longer sequences. That is, fluctuations on different *time scales* may appear to be *self-similar*, like the branches of a geometric *fractal* object [27]. In other words, magnitude and rate of events may fluctuate over many scales, even in the absence of external stimuli that fluctuate, rather than relaxing to a homeostatic steady state. This concept — termed *homeodynamic* by West [39] — arises out of recent applications of nonlinear dynamics to living systems and is based on the premise that there exists a complex of multiple states that determines the behavior of healthy living systems. This may be viewed as a spectrum of small but superimposed fluctuations in internal mechanisms over a wide range of temporal and spatial scales. A characteristic of this new paradigm is flexibility of response and *tolerance of error*. In this paradigm, the single scale steady state of homeostasis is replaced by a multiplicity of nonequilibrium states that are *correlated* over many scales of time and distance.

### Fluctuations in Membrane Electrical Properties are Correlated

Long-term correlation at the microscopic level is observed in a variety of structures and processes ranging from DNA sequences [23, 28] to action potentials [36]. Consider, for example, ion channel proteins. These cell membrane proteins can have different shapes called conformational states. There is sufficient thermal energy in their environment to cause these proteins to switch spontaneously between different conformational states [15, 22]. The switching times between these states have fractal properties. That is, kinetic *rate constants* and related parameters of models that are used to describe the probability per unit time that chemically activated membrane ion channels will change from a closed to an open state are *power law* functions of the time resolution used to determine that probability. A rate constant that describes ion channel switching serves as an example of one of a number of classical linear representations of a cellular process in which a well-defined internal timing mechanism can influence the rate or set the pace. An alternative model is that of a conditional process consisting of a sequence of events extending over a time scale which is long compared with cellular physiological events such as ion channel switching, but which is short compared to

modulating physical or chemical processes. A fractal relationship is therefore the consequence of physical and chemical processes acting over short times and distances at the cellular level, and which are correlated with processes acting simultaneously over long times and distances [25].

Fluctuations in polypeptides, in bilayer lipid cell membrane proteins, in smooth muscle length and actin-myosin interaction kinetics, and in neurotransmitter-excited coherent  $\text{Ca}^{2+}$  waves in cultured glial networks all have spectral features that suggest long-term correlation [8, 14, 20, 30, 34]. Different experimental methods that alter biological membrane electrical activity have quite different physiological effects on events, some of which are quite specific and some that are quite general. Electrical stimulation may have a general effect on many, if not all underlying cellular processes, whereas application of a specific chemical or a specific agonist or antagonist of a chemical receptor site affects, by definition and experimental design, a specific chemoreceptor system and its underlying metabolic pathways [17]. It is *correlation* within and between these and other cell membrane phenomena over a wide range of time and distance scales that underlies the internal regulation of ion transport and which implies that fluctuations in membrane electrical properties are *fractal noise*.

### Fluctuations in Membrane Electrical Properties are Fractal Noise

Fractal sets or series are those series whose characteristic form or degree of irregularity is the same through a succession of *scale* changes [2]. The *measure* of a set may be the values of any physical observable with units of length, area, volume, voltage, etc. Many naturally occurring phenomena, like tree ring widths, water table levels, lightning bolt paths, etc., can be characterized by a fractal (non-integer) dimension rather than by a Euclidean (integer) dimension.

There are fractal sets, series and structures with the same fractal dimension but with very different features. For a fractal structure, the measure of the set increases with an increase in the *resolution* of the measuring instrument. In this instance, the double log plot of measure against resolution is always a straight line, the slope of which is related to the fractal dimension.

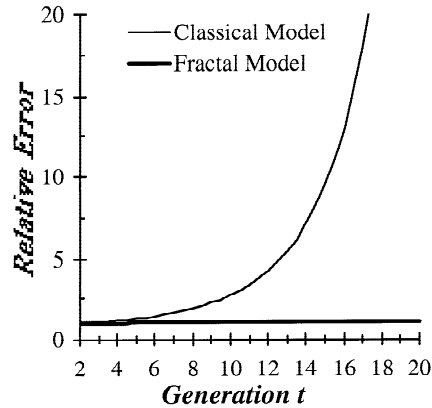
A temporal fractal is a process that does not have a characteristic scale of time, analogous to a geometrical fractal structure that lacks a characteristic scale of length. For example, in the case of neural electrical activity that gives rise to respiration, the time intervals of phrenic nerve bursts have self-similar bursts of activity, power law distributions of the duration of intervals, and a power law form of the Fourier power spectral density. (Note that we use the word *power* here in both its mathematical

and its physical sense.) This neural activity is correlated and a large percentage of spectral power is not harmonic but exhibits a power law relationship. These properties of temporal correlation, self-similarity, power law distributions of intervals and shapes of the power spectra are examples of processes with properties of fractal noise [17, 22].

### Fractal Processes are Error-Tolerant

Why are fractal processes ubiquitous in living phenomena, including the structure and function of membranes? As suggested above, one reason is that fractal processes are more tolerant to error than are classical processes. This possibility has been demonstrated by West and Deering [40]. Briefly, they consider a simple model of error response that introduces a random fluctuation into the parameters of a classical model and of a fractal model and then by averaging (measuring) over an ensemble of these fluctuations. West and Deering consider measurement of a time-dependent phenomenon, (e.g., ion channel switching times) as (1) a classical process represented by an exponential law, and (2) a fractal process represented by a *power law*. Let the variable  $t$  represent the generations of time scales over which measurements are made. Let the scaling factor or *rate constant* for the classical process consist of the sum of two parts: a constant and a *random* part, and that values of measured quantities are distributed according to a Gaussian probability density function with zero mean and variance  $\sigma^2$ . In the case of Gaussian-distributed quantities, carrying out the average demonstrates that the error grows exponentially as the square of  $t$ , [i.e., as  $\exp(\sigma^2 t^2/2)$ ]. In the same way, West and Deering assume that the index for the fractal process consists of the sum of two parts: a constant and a *random* part. Again assuming the same probability density function, the measured fractal quantity is the average over the distribution of time scales, in which the error grows exponentially as the square of the natural logarithm of  $t$ , [i.e., as  $\exp(\sigma^2 (\ln t)^2/2)$ ].

The relative error in both the classical and fractal models for  $\sigma^2 = 0.02$  is plotted in Fig. 1. In Fig. 1, it is clear that as  $t$  increases, relative error in the classical model rises rapidly, compared to the fractal model. For  $t > 20$ , relative error in the classical model is  $>100$ , whereas relative error in the fractal model is only 1.10. This illustration suggests that a fractal process is essentially unresponsive to error and very tolerant of variability in the physiological environment. Therefore, a process such as membrane ion conduction, with a diversity of inputs over a wide range of temporal and spatial scales and with concomitant sensitivity to error incurred by this spectrum of inputs could benefit from the error-tolerant properties of fractals.



**Fig. 1.** Comparison of relative error over generation  $t$  with random noise for classical and for fractal scaling (from West & Deering, 1994 [40], with permission).

### Fractal Noise as a Power Law and a Random Walk

Events that recur with constant frequencies appear as peaks (harmonics) in a power spectrum. On the other hand, *power laws* may dominate the power spectra of *stochastic* processes such as noise [33]. A stochastic process is a process that involves a variate at each moment of *time*, where a variate is a variable that may take on any of the values of a specified set with a specified probability. Time intervals between heart beats, between steps in a walking gait, and between openings and closings of ion channels are all examples of stochastic processes.

Among the many examples of fluctuating natural processes in space and time that the word *noise* may invoke, a familiar concept in biology and physics is that of a *random walk* of a particle undergoing Brownian motion (which we'll call a Brownian particle). A random walk with steps of unit length is often modeled as a Gaussian or normal probability distribution with unit deviation (variance). If each event (step) is independent of another, with unpredictable direction, we refer to the process as *ordinary* [5, 16].

Consider the position of a Brownian particle that is moving in  $D$ -dimensions (where  $D$  is the integer Euclidean dimension 1, 2, or 3) from one position at time  $t_0$  to another position at a later time  $t$ . The position of the Brownian particle is a self-similar stochastic variable with parameter  $\alpha = 1/2$ . To illustrate the concept of self-similarity, consider a simplified computational version of Brownian motion as a  $D$ -dimensional random walk. Let us denote the position of the random walker at time  $t$  by the stochastic variable  $v(t)$  which is a vector denoting the position of the random walker at time  $t$ . Let us consider two simulations of this random walk: In one simulation, the random walker takes a step in random direction of unit length after every unit of time.

In the other simulation, the random walker takes a step in random direction of two unit lengths after every four units of time. If we take pictures of the two random walkers for every time step and play the movie of the two simulations side by side, we will obviously see the difference between them. Now let us take one picture of the two random walks after every four units of time. We will therefore have no information about the position of the random walkers for the times in between. Can we still see the difference between the random walks? What if the time resolution is so poor that we can only record the position of the random walker for every 1,000 time steps? Can we distinguish them now? The fact is, we cannot distinguish between them by any statistical study (up to a certain accuracy). In other words, there is no way to know whether we simulate the position  $v(t)$  of the random walker by one unit step of each unit time or by a two unit step of each four units of time. Expressed in algebraic terms, the stochastic process  $v(4t)$  is statistically indistinguishable from (has the same statistical properties as) the stochastic process  $4^{1/2}v(t)$  [29].

The steps or increments in the position of the Brownian particle are given by the absolute difference in the time increment for the two times  $t$  and  $t_0$  raised to the power  $\alpha$ , and multiplied by a random number. That is, given the position of the Brownian particle at time  $t_0$ , the position at time  $t$  is determined by choosing a random number from a Gaussian distribution. This number is then multiplied by the absolute value of the time difference  $(t - t_0)$  raised to the power  $\alpha$ . The result is then added to the particle's position at time  $t_0$  to obtain its position at time  $t$ . As mentioned above, the exponent  $\alpha = 1/2$  for ordinary Brownian motion. In other words, for ordinary Brownian motion, the increment in position is proportional to the square root of the time difference. A generalization of this to any  $\alpha$  in the range  $0 < \alpha < 1$  is called fractional or *fractal Brownian motion* (fBm). The *derivative* of fractal Brownian motion is called fractal Brownian noise (fBn) or, alternatively, *fractal Gaussian noise* (fGn). The derivative with respect to  $t$  is formally defined as in the differential calculus for continuous functions. For a discrete set of uniformly spaced points, this definition reduces to taking the differences between adjacent positions.

Fractal Gaussian noise has a variance that does not diverge with time and is therefore *stationary*. In common usage, *stationary* means that something is not changing in time. In the present context, stationary means only that the moments (e.g., mean, variance) of the process are defined. Often if the variance in fluctuations of a time series is determined for increasing intervals of time, the value of the variance will increase. That is, the sample variance may not reach a limiting finite value but may increase indefinitely with the length of the time interval used to evaluate it. In the statistical literature, this is known as *heteroscedasticity* [10]. A time

series with such moments is said to be *nonstationary*. For fGn, the average power spectral density or power vs. frequency varies inversely with frequency  $f$  raised to the power  $2\alpha - 1$ , where  $0 < \alpha < 1$ . The power spectrum is thus a power law with exponent  $2\alpha - 1$ . For  $\alpha = 1/2$ , the exponent is zero, which is to say that all frequency components are equally represented, from which the term “white noise” comes, and which is known as ordinary Gaussian noise. For other values of  $\alpha$ , we have what is known as fractal Gaussian noise. For  $0 < \alpha < 0.5$ , this noise is negatively correlated and for  $0.5 < \alpha < 1$ , it is positively correlated.

## Models of Fractal Noise and Methods of Analysis

To determine the fractal dimension of a measured sequence of biological membrane events, we must first be able to simulate noise with *known* fractal dimension and to recover that fractal dimension with analytic methods. Fractal noise may be simulated to an arbitrary resolution using a number of methods [11, 32, 38]. The relationships between  $\alpha$  and the scaling exponents from log-log plots of several different methods of analysis are described in detail by a number of investigators [18, 24, 31]. Time series of biological membrane events lend themselves to analysis with fractal methods characterized by a single parameter: the exponent  $\alpha$ , which is related to the fractal dimension of the time series. The magnitude of the exponent  $\alpha$  is therefore expected to be a sensitive indicator of fractal noise. Fractal methods of analysis include detrended fluctuation analysis [29], power spectral analysis, autocorrelation, relative dispersion analysis, extended range correlation [2], Fano factor, Allen factor [35, 37], and rescaled range analysis.

Rescaled range analysis is one of the earliest fractal methods, first described by Hurst in 1950 [19]. Its importance was recognized at once by Feller [12] and summarized in 1983 by Mandelbrot [27] in his classic treatise on the fractal geometry of nature. In brief, the quantity  $R/S$ , called the rescaled range, is described by the power law,  $R/S \sim t^\alpha$ , where  $t$  is a time interval called the lag, and the exponent  $\alpha$  is called the Hurst exponent. The Hurst exponent (often designated  $H$ ) has the same physical meaning as the scaling exponent  $\alpha$  derived from detrended fluctuation analysis discussed below and will be designated as  $\alpha$  throughout this text. As mentioned above, in the absence of long-term statistical dependence,  $R/S$  becomes asymptotically proportional to the square root of  $t$  ( $t^{1/2}$ , i.e.,  $\alpha = 1/2$ ) for sequences generated by statistically independent processes with finite variances. This expression is an example of a power law that describes a fractal relationship. For positively correlated noise with positive values, the possible slopes of the power law relationship on a log-log plot are bounded by two extreme values. These values are  $\alpha = 0.5$ , for which the data series is indistinguishable from random

uncorrelated noise, and a value of  $\alpha$  near unity, which represents high near-neighbor correlation and uniformity of the signal over all size scales.

In detrended fluctuation analysis (DFA) developed by Peng et al. [29], a linear relationship between a measure of fluctuation and the time scale interval on a double log plot indicates the presence of scaling. That is, the slope of linear regression of root-mean-square fluctuation  $F(n)$  vs. interval length  $n$  yields a scaling exponent  $\alpha$  which characterizes this scaling. For series of events, the cumulative (integrated) departure from the mean is divided into intervals of equal length  $n$ . A least-squares line representing the *trend* in each interval is fitted to the data. The  $y$ -coordinates of the straight-line segments are subtracted from the integrated values in each interval to *detrend* the series. The root-mean-square fluctuation  $F(n)$  is then calculated over all interval sizes. Different values of the exponent  $\alpha$  signify different levels of temporal correlation in fluctuation at different scales. For time series of processes where fluctuations are negatively correlated (“anti-persistent” noise), we have  $0 < \alpha < 0.5$ . For time series with consecutive values generated by statistically independent processes with finite variances,  $\alpha = 0.5$  (uncorrelated or “white” noise), and  $0.5 < \alpha < 1$  corresponds to processes where fluctuations in subsequent values are positively correlated (“persistent” noise), where  $\alpha = 1$  corresponds to power spectral  $1/f$  noise. Values of  $\alpha$  in the range  $1 < \alpha < 1.5$ , correspond to *integrated* negatively correlated (“anti-persistent”) noise, where  $\alpha = 1.5$  correspond to integrated white (“Brown”) noise [29]. Over the range 0 to 1, and in the absence of biases [17, 18, 31] the Hurst exponent and the scaling exponent  $\alpha$  are identical.

As mentioned above, many biological processes consist of a series of discrete recurrent events that fluctuate in time like  $1/f$  noise. In  $1/f$  noise, the power spectral density — the Fourier transform into frequency  $f$  of the autocorrelation function of the time series — behaves as a power law,  $1/f^\beta$ , where  $\beta$  is the power law exponent. For time series in which  $\beta = 1$ , there is no well-defined temporal scale. That is, the current value of the measured signal is temporally correlated not only with its most recent value but also with its long-term history. The time series of a recurrent biological signal that fluctuates as  $1/f$  noise is thus said to be scale-invariant [2, 11]. Schlesinger and West [32] suggest one explanation for this is that the biological process in question has many inputs on different time scales, each of which fluctuate in a random, statistically independent fashion and which superimpose to yield  $1/f$  noise.

### Significance of Fractal Exponent and Comparing Fractal Methods

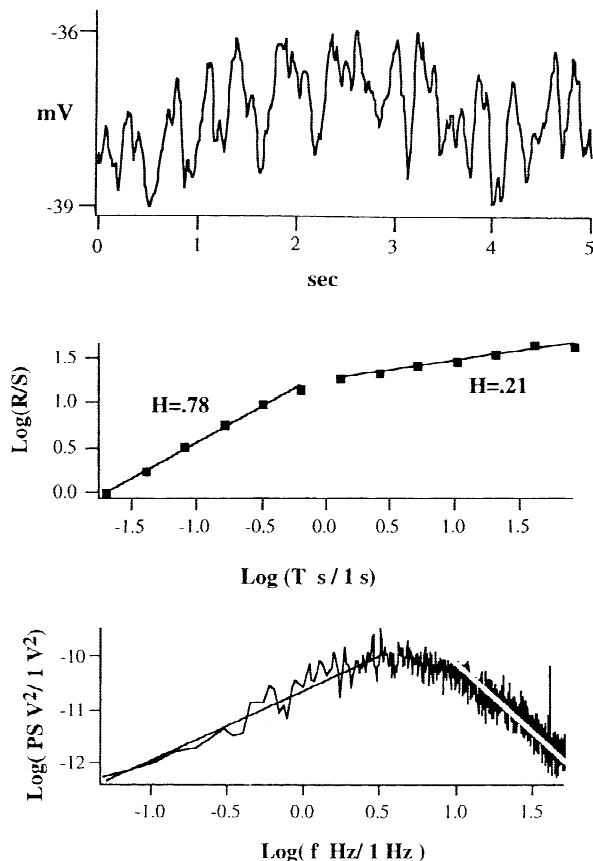
There are several practical methods for determining whether a measured value of  $\alpha$  for a given time series of

events differs significantly from a value of 0.5. One method is to randomly reorder, i.e., shuffle the series  $n$  times and determine the standard deviation in the mean of  $\alpha$  derived from the  $n$  shuffled series. One may then employ a test for the significance of the difference between mean  $\alpha$  determined from the  $n$  shuffled series with the mean  $\alpha$  determined from the original series. Another method is to reduce the sampling rate by one-half by taking every other data point in the series and again determining  $\alpha$  for comparison with  $\alpha$  determined from the original series. Such tests are essential, particularly when one is working with short time series, as has been repeatedly emphasized and demonstrated by a number of investigators [3, 4, 18, 31]. Of equal importance is correction for biases in measured values of  $\alpha$  introduced by different methods of fractal analysis. As first demonstrated by Schepers et al. [31] and stressed by Bassingthwaight and Raymond [3, 4], such corrections to the fractal exponent depend critically not only on the choice of analysis, but on the length of the time series to be analyzed. Lowen and Teich [26] have made comparisons of Fano factor and power spectral density analyses for several different stochastic processes, and Liebovitch and Yang [24] compare different methods of estimating the Hurst exponent.

### Fractal Analysis of Membrane Electrical Properties

Specific neurotransmitters, e.g., acetylcholine (ACh), play an important role in membrane chemoreception, with quantal release from synaptic vesicles taking place via exocytosis. Spontaneous neural activity may often consist of periodic bursts with well-defined frequency and amplitude. However, noise, (i.e., extended bursts and bursts within bursts) occasionally develops during stimulation with neural active agents. For example, Hoop et al. [17] show that during ACh stimulation of a brainstem preparation at concentrations of 200 to 500  $\mu\text{moles/L}$ , noise in respiratory-related neural activity observed at uniform time intervals is not statistically independent and exhibits positive correlation. These investigators caution that results derived from very short time series (64 to 128 events) may not be reliable. Nevertheless, results for even short series merit more extensive investigation, because log-log plots do indeed suggest power law distributions of this noise.

It is worth emphasizing that the type of fractal noise observed in a time series depends on the specific experimental observable and the time regime of the observation. For example, within different time regimes, cell membrane voltage fluctuations appear to be of the form of fractional Brownian motion (fBm), whereas the increments in these fluctuations have characteristics of fractional Gaussian noise (fGn). Churilla et al. [9] were the first to observe these fractal characteristics of voltage fluctuations in the membrane of T-lymphocyte cell lines.



**Fig. 2.** (Top panel): Membrane potential (in mV) vs. time in seconds, recorded under zero current clamp, as a function of time in a murine T-cell line CL1. (Middle panel): Rescaled range analysis of the membrane potential fluctuations shown above. Values of the Hurst exponent determined from the plot are 0.78 and 0.21 for brief time intervals (short lags) and long time intervals (long lags), respectively. (Lower panel): Power spectral analysis of the same data (from Churilla et al., 1996 [9], with permission).

These investigators used Hurst rescaled range and power spectral analyses to find that over short time intervals (lags), correlation in voltage fluctuation is persistent. That is, increases in membrane voltage are more likely to be followed by increases. However, over long time intervals, correlation is anti-persistent. That is, increases in membrane voltage are more likely to be followed by voltage decreases. Representative results obtained by these investigators are reproduced in Fig. 2. The top panel in Fig. 2 shows membrane potential (in mV), recorded under zero current clamp, as a function of time in a murine T-cell line CL1. The plot shows a 5-sec, 500-point series interval sampled at 100 points/sec, taken from a longer record of 8192 points. Fluctuations in membrane potential appear to be self-similar. That is, portions of the record at short time scales resemble portions of the record at long time scales. The middle panel of Fig. 2 shows a rescaled range analysis of the mem-

brane potential fluctuations. Values of the Hurst exponent determined from a plot of the logarithm of rescaled range ( $R/S$ ) vs. logarithm of lag ( $T$ ) are 0.78 and 0.21 for brief time intervals (short lags) and long time intervals (long lags), respectively. The lower panel of Fig. 2 shows a power spectral analysis of the same data. In this panel, the power spectrum of the differences between successive values of the membrane potential sampled at 0.01 sec is shown. Corresponding to what is seen in the rescaled range analysis (middle panel), there are two distinct regimes. In both regions, the power is approximately proportional to  $1/f^\beta$ , where  $f$  is frequency. A fractal process, such as fGn, produces such a power law relationship. The investigators suggest that the existence of regimes that can be fitted by such power law relationships also indicate that the time correlation of membrane potential fluctuations in this cell line have fractal properties. For time series in which the increments are fractional Gaussian noise (fGn), the relationship between the exponent  $\alpha$  determined from rescaled range analysis and the exponent  $\beta$  determined from the power spectrum is  $\beta = 2\alpha - 1$ . The investigators point out that deviation from this relationship may depend on error in determination of  $\alpha$  and  $\beta$  by the two methods, by the magnitude of  $\alpha$ , as well as by the possibility that fluctuations in membrane voltage do not have exactly the form of fGn.

In summary, the exponent  $\alpha$  determines the degree of correlation in time series of fluctuations. For  $0 < \alpha < 0.5$ , such correlations are negative. That is, increases in the values of the time series are more likely to be followed by decreases. When  $\alpha = 0.5$ , there are no correlations. That is, increases in the values of the time series are just as likely to be followed by increases as by decreases. When  $0.5 < \alpha < 1$ , correlations are positive. That is, increases in the values of the time series are more likely to be followed by increases. If we compare rescaled range analysis with power spectral analysis of simulated fractal Gaussian noise generated with known values of  $\alpha$ , we find that the power law dependence of power spectra with exponent  $2\alpha - 1$  applies to simulated noise fluctuations and is satisfied to within the accuracy of determination of the slope of the power spectrum. It must be re-emphasized that the slope  $2\alpha - 1$  of log power vs. log frequency is valid only for fractal Gaussian noise [13]. However, the possibility cannot be ruled out that deviations from this relationship may also be due to the fact that fluctuations in cell membrane electrical properties associated with transport of ions through ion channels may not necessarily be of the form of fractal Gaussian noise.

### Are Biological Membranes Self-organized and/or Highly Tolerant?

This review of fluctuations and fractal noise in biological membranes demonstrates the presence of power law

forms in cellular membrane phenomena. Among them are: membrane ion channel openings and closings in single Ca-activated potassium channel kinetics [21, 22], neurotransmitter-excited coherent  $\text{Ca}^{2+}$  waves in cultured glial networks [20], fluctuations in polypeptides and in protein surfaces [8, 15, 30, 34], actin-myosin interaction kinetics [14], and fluctuations in neurotransmitter-stimulated neural activity [17, 18].

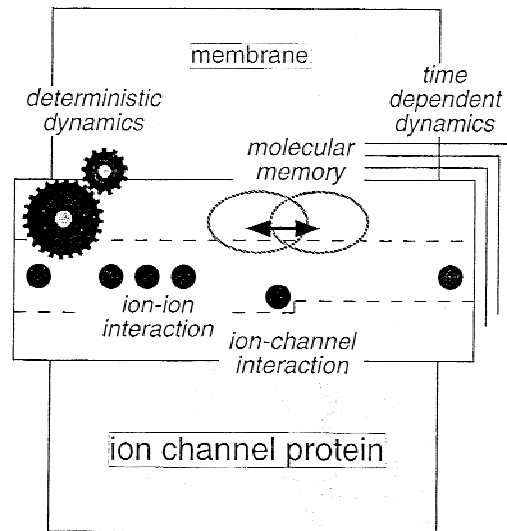
Traditional kinetic and energy level models of ion channels treat ion channel proteins as if they were static structures with non-interacting pieces. As emphasized by Liebovitch [21], dynamic properties of the channel protein and interactions within and between the channel protein and the ions passing through it may play an essential role in the switching of the channel protein between states that are closed and open to the flow of ions. These dynamic properties of ion channel function are illustrated symbolically in Fig. 3. Figure 3 shows that among these properties, there are continuous internal motions and continuous changes of state, the interactions of the ions themselves and with the channel protein, deterministic forces, and time dependent molecular memory. These dynamic properties are important in how the channel protein functions and how the molecular properties of channels at the microscopic level manifest themselves at the macroscopic level.

#### SELF-ORGANIZED CRITICALITY

The complex properties of cell membranes may suggest that cellular systems evolve into and normally function in a *critical* state. The critical state is established solely because of the dynamic interactions among individual elements of the system at all scales of time and distance. That is, the critical state is *self-organized*. Self-organized criticality explains some ubiquitous patterns that exist in nature that we observe as *complex*. Among these observations are fractal structure, correlation of events over long times and distances, and the occurrence of large, sometimes catastrophic events. Two characteristics of a self-organized critical state are a single *universality class* and a common property of *symmetry*.

The concept of *self-organized criticality*, introduced in 1987 by Per Bak and collaborators [1], includes several specific quantitative and measurable properties that reflect the complexity of the self-organized critical state. Among them are: (1) power law forms of spatial and temporal probability density distributions; (2) scale invariance of fluctuations; (3) long-term correlation; (4) system-wide or universal order, i.e., interactions “link up” over many spatial and time scales; and (5) self-similarity of form and function in the critical state.

Complexity observed in cell membranes, as in many other living systems, may indicate that membrane ion transport normally operates in the self-organized critical



**Fig. 3.** Symbolic illustration of dynamic time-dependent properties and interactions within and between channel protein and the ions passing through it. Among these properties are: continuous internal motions and continuous changes of state, the interactions of the ions themselves and with the channel protein, deterministic forces, and time dependent molecular memory (from Liebovitch & Krekora, 2000 [25], with permission).

state, and that diseases and disorders may represent quantifiable departures from this critical state. Self-organized criticality in membrane structure may require the demonstration of specific symmetry properties. By *symmetry* is meant that if a structure (or function) is subjected to a certain operation, it remains exactly the same (invariant) after the operation. One such operation is spatial *scaling*. Invariance with scaling reveals whether or not a structure is *self-similar*.

Another step in demonstrating self-organized criticality in membrane ion transport requires identification of specific *universality classes*. Universality classes are the sets of functions that have the same properties. One particular property of a single universality class is a *power law* form that characterizes fluctuations in membrane potential. That is, fluctuations in cellular function that occur on a time scale most directly associated with ion exchange exhibit long-term correlation governed by a specific power law.

#### HIGHLY OPTIMIZED TOLERANCE

Another mechanism for generating power law distributions is referred to as *highly optimized tolerance*. Functions and structures in biological membrane may be optimized through natural selection to provide robust performance despite variable and uncertain physiological environments. As suggested by Carlson and Doyle [7], power laws may be due to tradeoffs between yield, cost of resources, and tolerance to risks. These tradeoffs lead to highly optimized designs that allow for occasional

large events. The characteristic features of highly optimized tolerance in systems such as ion transport across biological membranes include (1) high efficiency, performance, and robustness to uncertainties designed by natural selection; (2) extreme sensitivity to design errors, flaws, and unanticipated perturbations; (3) nongeneric, specialized, structured configurations, (4) power law distributions of structure and function. Self-organization and optimized tolerance have in common the characteristic of power laws.

We therefore conclude this review with two experimentally testable hypotheses of fluctuations and fractal noise in biological membranes that may help distinguish between self-organized criticality and highly optimized tolerance: First, a single power law form of long-term correlation, that is, having the same temporal scaling exponent, may imply that processes which affect exchange and transport of ions and molecules across biological membranes belong to a single universality class. Secondly, a single exponent of similarity or fractal dimension of spatial heterogeneity in cellular membrane structure representing a spatial range in scale, from the scale of molecular structure to the scale of the whole cell, may imply a single common symmetry property in membrane structure which underlies ion transport.

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