Fractal Modeling of Channel Gating Kinetics, and the Effects on Neural Spike Trains

Beng 260- Neurodynamics Final Report

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Abstract

The project aims to explore two fractal models (by Lowen and Liebovitch) of ion channel kinetics, and how this affects spike train patterns. The project also intends to extend the Liebovitch model and explore how fractal dimension affects potassium ion channel conductance profiles, and the behavior and rate of action potentials.

1 Introduction

Fractal patterns have been used to model many different aspects of our natural world, from coastlines, to mountains, to neuromorphology, all of which deal with fractal behavior as applied to geometry. Fractal behavior can also be imparted to dynamical systems, particularly neural spike train patterns. Experimental evidence has indicated that neurons along the auditory pathway, demonstrate a fractal firing pattern, where the term fractal is used to signify that the fluctuations of spiking rate appear self similar over various integration time periods, as shown in Figure 1 [9].

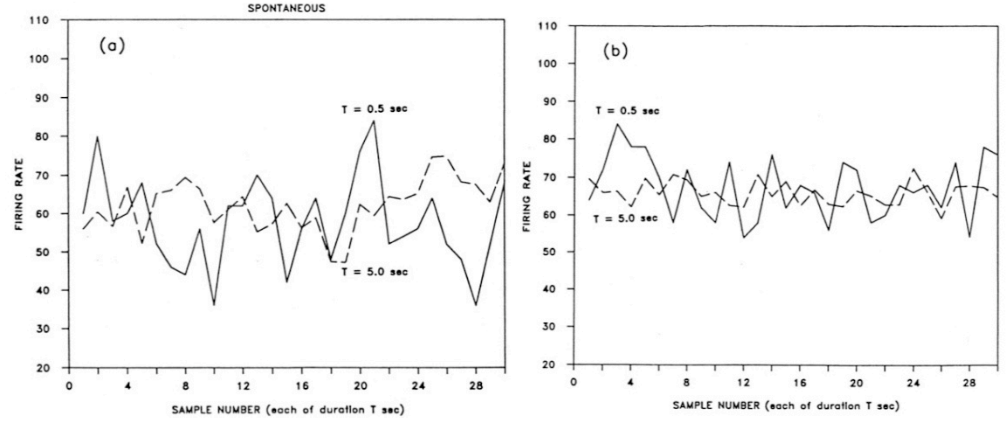


Figure 1: a) A fractal fluctuation rate. Fluctuations don't change in amplitude, even as the rate is taken over longer time periods.

b) Non-fractal fluctuation rate. Fluctuations decline in amplitude and smooth out as the firing rate is taken over longer time periods.

In considering possible biophysical origins of this fractal behavior of auditory nerve spiking trains, one possibility that has been suggested relates to fractal kinetics of neuronal ion channels.

Leibovitch gives the interpretation of fractal kinetics as one way to model memory into ion channels [3]-[5].

Hodgkin and Huxley's original model makes use of constant rate kinetics α and β, that are functions of membrane voltage only. This effectively models the ion channels as a memory-less Poisson processes, where ion channel switching behavior between a few finite states is independent of how long the channel protein has been in a certain state. This fits the understanding of protein dynamics at the time.

However, research has shown us that ion channel proteins, made of hundreds or even thousands of amino acids, are incredibly complicated structures, and have many different conformational states (analogous to microstates in thermodynamics and statistical mechanics). Given our current understanding of ion channel proteins, it seems unlikely that the rates at which an ion channel changes between its thousands of conformational states, don't depend at all on how long the channels have been in those states. If fact, there is already evidence that at least some ion channels exhibit memory [6].

In this project I look at two models of fractal kinetics. My first goal was to be able to understand and implement the first model, a Markov state model developed by Lowen et al., and verify their claim that the resulting spiking behavior demonstrates a characteristic fractal behavior of self-similar fluctuations over time, hence drawing a tentative causal link between ion channel kinetics and resulting spiking patterns [6].

The second goal was to implement a second model of fractal behavior in ion channel kinetics (by Liebovitch, based on a power law self similar function) [3]-[5], and explore how ion channel conductance profiles are affected by a very important model parameter, known as the fractal dimension.

And lastly, my goal was to extend the Liebovitch model of fractal ion channel kinetics, to a full model able to recreate membrane voltage action potential sequences. I wanted to explore whether the spiking pattern demonstrated self-similar fluctuations over time, and also explore the effects of fractal dimension, on the spike train behavior.

2 Fractal Model by Lowen, et al.

2.1 Theory

The first model I looked at, developed by Lowen, Liebovitch, and White, is based on extended state Markov theory. The classical equations of the original Hodgkin Huxley model result from a reduction of multi-state Markov models (Figure 2 a,b) into a single two state model with opening rate α_n, and closing rate β_n [6].

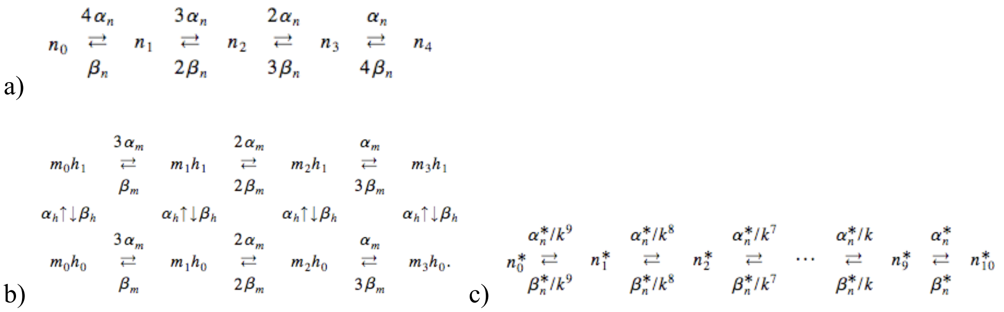


Figure 2: a) Markov model for n, the gating variable for potassium.
b) Markov model for m, and h, the gating variables for sodium.
c) The extended Markov model for potassium, with self similar kinetic rates.

The model by Lowen, et al., imparts fractal behavior onto only the recovery variable, which in this case, is the gating variable for potassium, *n*. In order to better approximate the fact that the potassium channel protein has a large number of conformations (states), Lowen's model consists of an eleven state Markov process, shown in Fig 2, c. The new rates at which the states change are given by $\alpha^*{}_n$ and $\beta^*{}_n$. Each state's rates differ from the previous state's rates by a scaling factor k, which can be treated as some positive constant. This imparts self-similar behavior (with respect to time) into the model. Finding a tractable solution to this model was done by extending and approximating the number of closed states (n_0 to n_9) as infinite, while n_{10} remains the only open state. Renormalization theory and comparison with the average closed and open times calculated for the original Hodgkin and Huxley model, yielded rates $\alpha^*{}_n$, $\beta^*{}_n$, in terms of the original α_n and β_n rates [6].

$$\begin{aligned}\beta^*{}_n(V) &= 4\beta_n(V)\\ \alpha^*{}_n(V) &= \frac{4[\alpha_n(V)+\beta_n(V)]^4\beta_n(V)}{[\alpha_n(V)+\beta_n(V)]^4-[\alpha_n(V)]^4}\end{aligned} \qquad (1)$$

Figure 3 shows the new $\alpha^*{}_n$ and $\beta^*{}_n$ rates, in comparison with the original α_n and β_n rates, for the n gating variable controlling potassium.

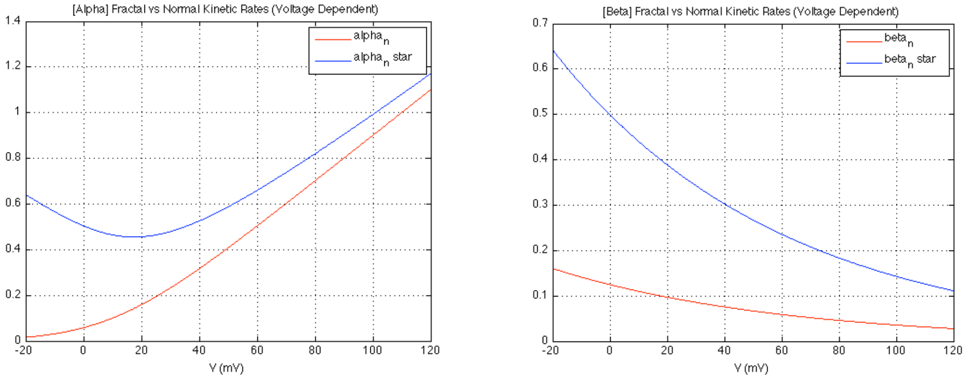


Figure 3: The behavior of $\alpha^*{}_n$, $\beta^*{}_n$, over voltage interval (-20:120 mV), in comparison to the behavior of α_n and β_n.

In order to later study the fractal behavior of fluctuations in spiking rate, I realized that I needed to have a stochastic element in my computational model; instead of using the deterministic modeling method as done during the class homework assignments, I decided to build a stochastic model using a brute force algorithm that stepped through time and used Euler's integration method to calculate potassium gating variable dynamics:

$$n(t+\Delta t) = n(t) + \frac{dn}{dt}\Delta t \qquad (2)$$

In order to implement randomness, this algorithm kept track of the state of every potassium ion channel, and at every time step, a random number was compared to rates of closing and opening, for every single channel. While this is computationally inefficient, and the Gillispie method implements stochastics in a more efficient manner, the Gillispie method also assumes that the ion channels are memory-less [2]. Since this is not true for a memory based fractal model, the brute force algorithm was more accurate way to implement a stochastic fractal model.

2.2 Results

Figure 4 shows the stochastic results of the Lowen et al. model, against the original HH model implemented previously in class.

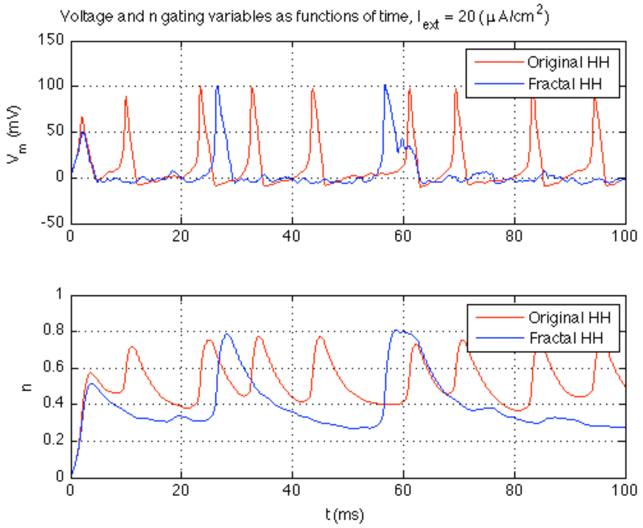


Figure 4: The membrane voltage profile of the fractal model, compared to the original membrane voltage profile given the classical HH set of equations.

Figure 4 shows that while the amplitude and general shape of action potentials remains the same under the new model, the rate of spiking has decreased drastically, for the same input current given to the original model. In addition, the fractal model introduces increased fluctuations in between the action potentials, and also during some of the action potentials.

I had originally intended to verify that the Lowen model resulted in action potentials fluctuation patterns that demonstrated fractal behavior (as in Fig. 1). However, to get enough variation in fluctuations, simulations need to be taken over very long time lengths. Lowen et al. simulated their model over thousands of action potentials. However, since my stochastic model depends on a brute-force algorithm, simulation time for even four thousand milliseconds (only a few hundred action potentials in this case) was too long, and yielded little variation in spike rate. Therefore, it was difficult to show whether the amplitude of fluctuations changed when integrated over different time periods.

3 Liebovitch Model for Fractal Ion Channel Kinetics

3.1 Theory

The model described in Section 2, by Lowen et al., was a good starting off point to demonstrate that action potentials could be modeled with fractal behavior, and gave a better understanding of how a protein's conformation states can be modeled by Markov states. However, Liebovitch, who also worked on the model in Section 2, had written earlier papers about ion channel kinetics where the rate functions were derived directly from a self-similar functional form. Since this model involved a very important parameter in any description of fractals- the dimension- I wanted to implement this model to explore how fractal dimension affected the ion channel kinetics.

Since this model by Liebovitch had only been applied to observe closed time histograms and distribution functions of rate constants, I wanted to expand the model to explore how the dimensional parameter affected the ion channel conductance profiles, and membrane voltage profiles (in essence, the spiking rate patterns).

Liebovitch's model describes the concept of memory in a much more intuitive manner. The model is derived beginning from a statistically self-similar function

$$\begin{aligned} L(x) &= kL(ax) \\ L(x) &= Ax^{1-D} \end{aligned} \qquad (3)$$

where k, a, and A are constants, and D is the fractal dimension. If we model the channel as a two state channel with and opening and closing rate, we can write

$$\begin{aligned} &closed \Leftrightarrow open \\ &k_o = A_{open} t^{1-D_{open}} \\ &k_c = A_{close} t^{1-D_{close}} \\ &P(t) = e^{-[A/(2-D)]t^{2-D}} \end{aligned} \qquad (4)$$

where k_o is the opening rate, k_c is the closing rate, and $P(t)$ is the probability that a channel remains closed over time t [3]-[5].

Here it is easy to see how the rate functions incorporate memory. By plotting the rate functions against time (Fig. 5) we can see that as time increases, rate at which the protein switches states decreases, as well as the probability of leaving the state. This incorporates memory, since the channel protein must remember how long it has been in a certain state (conformation).

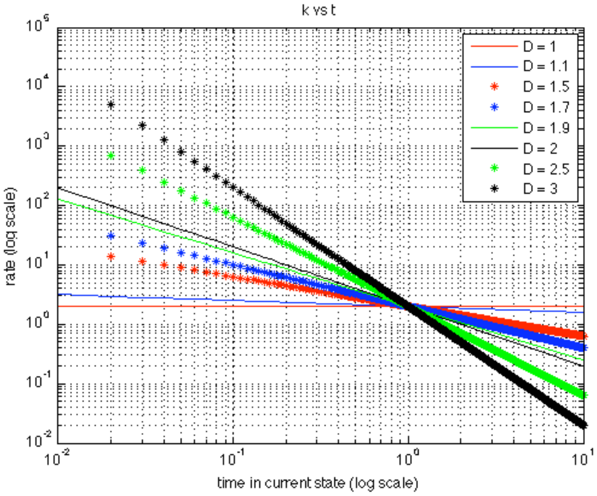


Figure 5: Rate functions (for various values of fractal dimension D) in form of equation (4), plotted against time that a protein has been in its current state.

The plot in Fig. 5 also shows how changing D, the fractal dimension, affects the rate function. The fractal dimension can be intuitively thought of as a measure of self-similarity as we look at an object at finer and finer scales. For example, a classical application of fractals in the past has been to study coastlines. It is easy to imagine that as we zoom in on a coastline, it grows in length, because of all the details in geography that we can now observe. The fractal dimension is a measure of this growth in length (for the west coast of Britain, D = 1.2). If an object were geometrically straight, then it would not increase in length or yield any new information no matter how many times we zoomed in on it. Here the value of D = 1 (no increase in length), and this matches our concept of a straight line being a one-dimensional object [4].

In Fig. 5 as we vary D, we can see that as D approaches 1, the rate function approaches a constant function across all time, which is essentially a memory-less Poisson process that can modeled with a two-state Markov process approximation (such as the original HH model). This demonstrates that Liebovitch's fractal ion channel kinetic model is a generalized model, of which the two-state Markov process is a special case (D = 1) [5].

3.2 Extending the Liebovitch Model

The Liebovitch model has mostly been used to compute closed time histograms, to verify the fractal behavior of self-similarity over various time intervals [3]-[5]. I wanted to look at using this model to observe potassium channel conductances, varying both N, the number of channels, and D, the fractal dimension.

The computation of channel conductances involved building on the stochastic model I used for Part 2. Instead of comparing a random number against the α_n and β_n rates, I compared it against the probability of a channel staying in a state as long as it has (which is dependent on k_o and k_c). If the probability of changing states is high enough, the channel flipped from open conformation to closed, or vice versa. To do this I kept track of which channels were in which state, and how long they had been in that state. At each time step, the total potassium conductance was calculated based on how many of the channels were open at the time, and the individual potassium conductance was normalized such that if all potassium channels were open, the total conductance would be $g_K = 36mS/cm^2$.

Since the Liebovitch model had not been used to generate action potentials, my next goal was to extend the model so as to include oscillating voltage dynamics. In order to apply this model to voltage profiles, I found that I had to change A_{open}, A_{close}, so that instead of being constants, they were functions of voltage, so that the rate constants themselves were functions of both time a channel had been in a certain state, and the membrane voltage at the time of observation.

The functions $A_{open}(V)$, $A_{close}(V)$ were made such that as membrane voltage increases, the probability $P(t,V)$ of staying open is higher, than for lower voltages, since we want potassium current to increase during action potentials, in order to hyperpolarize the membrane potential and bring it back towards the resting potential. At the same time, $k_o(t,V)$, and $k_c(t,V)$ had to follow their original trends where the rate decreased as t increased (for D >1).

$A_{open}(V)$, $A_{close}(V)$ were eventually created to hold the following functional forms:

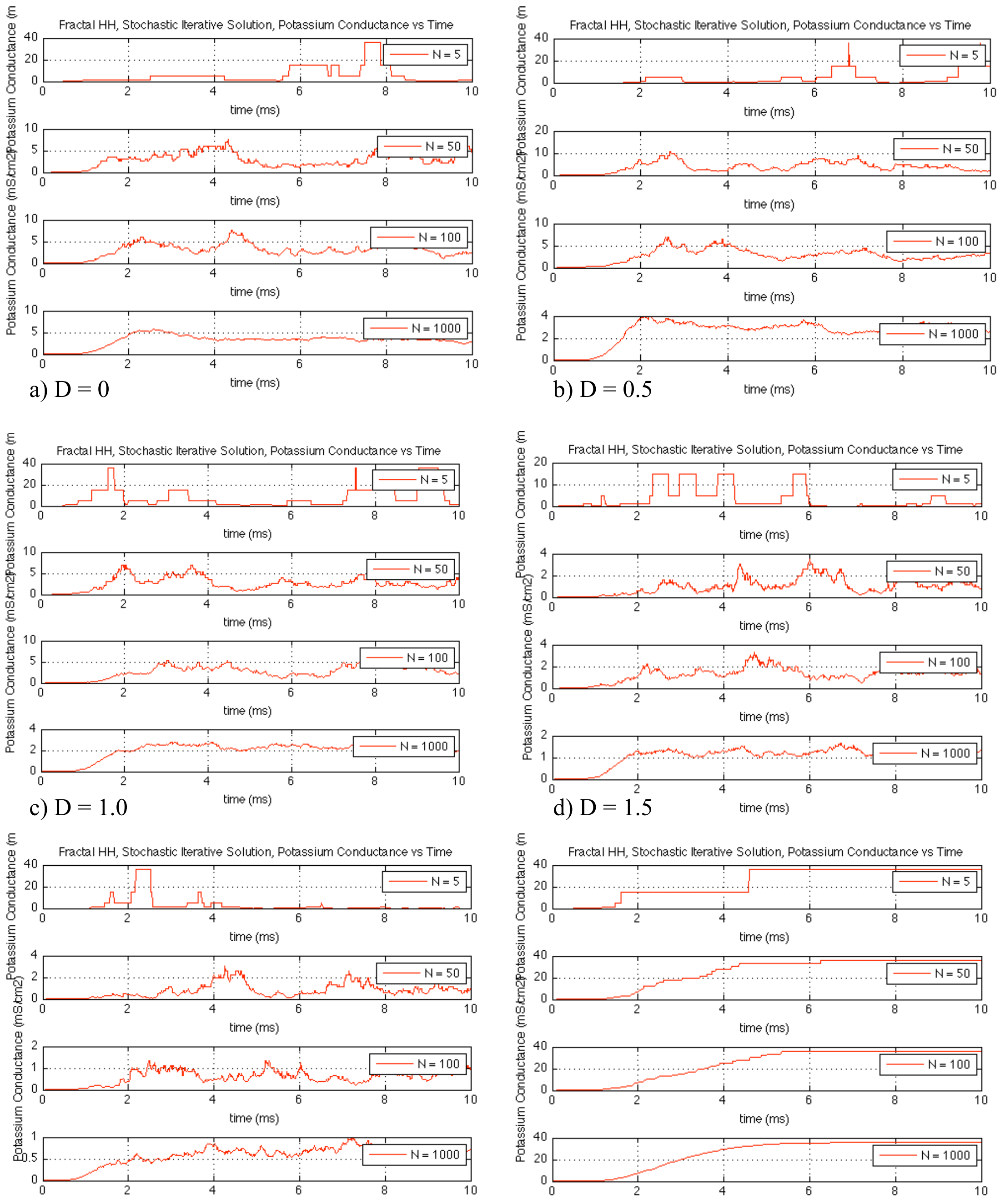
$$\begin{aligned} A_{open}(V) &= \frac{\sigma}{(V-\varsigma)} \qquad (5) \\ A_{close}(V) &= \upsilon * V \end{aligned}$$

where σ, ς, υ are parameter constants than can be adjusted such that the new rates $k_o(t,V)$, and $k_c(t,V)$, yield rates on the same order of magnitude as the original HH rates α_n and β_n. I then incorporated these functions into the stochastic model, by substituting them into the probability function $P(t,V)$. The number of potassium channels that were open or closed was determined stochastically as before. This determined the gating variable for potassium, *n*, at each timestep, and the rest of the gating variables, current equations, and membrane voltage equation, for the HH model were determined as usual.

3.3 Results

3.3.1 Conductance Profiles

Figure 6 shows the calculated potassium conductance profiles, for various values of N, and D, with no external current.



a) D = 0
b) D = 0.5
c) D = 1.0
d) D = 1.5
e) D = 2
f) D = 2.5

Figure 6: Conductance profiles as N and D vary. In all cases, N was increased from N = 5 to N = 1000. D was varied as indicated.

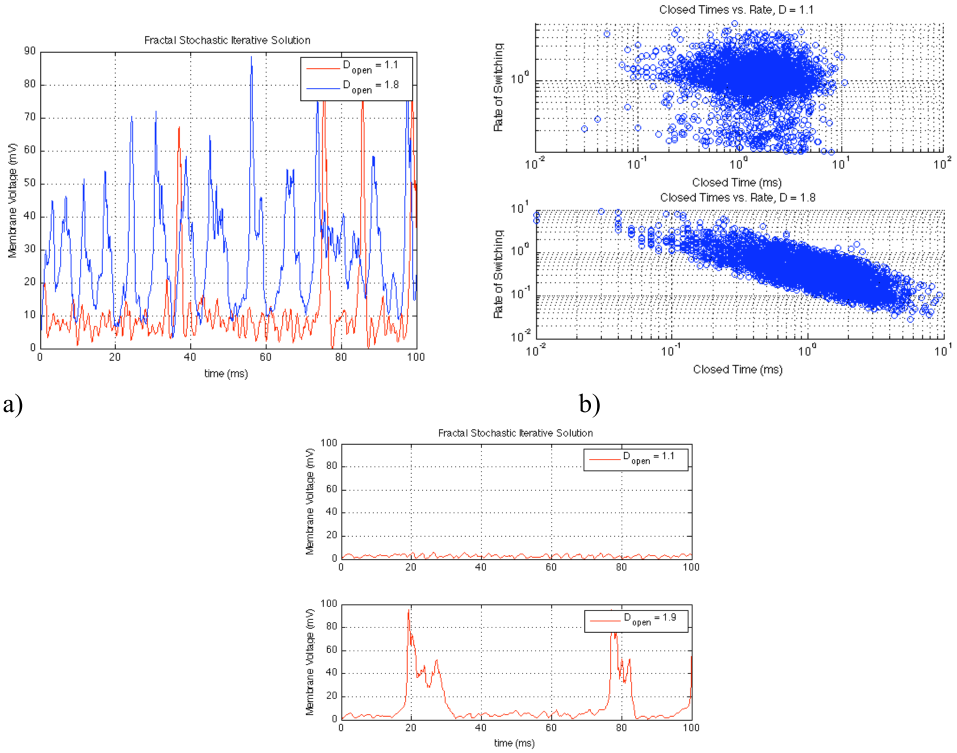
As Figure 6 demonstrates, as N increases, all the conductance profiles approach a continuous, deterministic-type profile. However, changing D doesn't seem to alter much, other than the conductance profile for N = 1000, which shows more minute fluctuations. This seems to suggest that as D increases, there is more small-scale randomization (fluctuations) that become apparent for simulations with large N.

Looking at equations (4), it is easy to see that D should ideally be greater than 1, in order for the rate functions to have a negative slope over time. If the model were to assume that the longer a channel was in a particular configuration, the more likely and faster it leaves that configuration, it would makes sense to lower D below 1. However, looking at the simulation results in Figure 6, D < 1 doesn't seem to yield any irregular behavior in fluctuation patterns.

On the other hand, the results for D = 2.5 are interesting and differ from the other results. Here, the conductance approahes an equilibrium value, with almost no fluctuations. Based on equations (4), D should ideally remain less than 2, in order for the probability function P(t) to have a limit as t approaches 0. While mathematically this constrains D, the results for D = 2.5 also make physiological sense. If we look back at Figure 5, as D grows to higher and higher values, the slope of the rate constant increases so the longer a channel stays in a state, the rate decreases very quicly and to very low values, so that it becomes statistically very improbable that the channel will switch states. In Fig. 6f, potassium channels switched to the open state, and then remained stuck in that state since as time increased, the probability of switching back to the closed state, was very low.

3.3.2 Effects on Spiking Profile and Spiking Rate

Figure 7a demonstrates the effect of varying D_{open}, on the membrane potential profile. Raising D_{open} from 1.1 to 1.8 without changing any other parameters, including external current (kept at $I_{ext} = 60\ \mu A/cm^2$) , drastically raises the rate of spiking. In other words, raising D_{open} makes the model more sensitive to external stimulus. Intuitively we can think of D_{open} as a measure of random fluctuations. Raising this parameter increases the magnitude of random fluctuations between the action potentials high enough so many of these random fluctuations turn into actual action potentials.



a) b)

c)

Figure 7: a) The effect of fractal dimension D_{open}, on action potentials, with $I_{ext} = 60\ \mu A/cm^2$
b) the effect of D_{open}, on the opening rate k_o.
c) The effect of fractal dimension D_{open}, on action potentials, with $I_{ext} = 0\ \mu A/cm^2$

Figure 7b shows the effect of varying D_{open} , on the opening rate k_o . For $D_{open} = 1.1$, the slope is approximately zero, which is the same as a constant rate Poisson process. This makes sense since

D_{open} is so close to 1, which was mentioned before as a special case of the generalized fractal model. Figure 7b is verification that the extended model is yielding the expected ion channel kinetic results.

Figure 7c shows a particular case of varing D_{open}, when there is no external current input into the model. Raising D_{open} to 1.9 has a very strong effect on the amplitude of the random fluctuations, so that spontaneous action potentials are generated. The shape of these action potentials is slightly irregular, due to the fluctuations occurring even during the action potential. However, these spontaneous action potentials simplify demonstrate that at high D_{open} values, the model is extremely sensitive to even the smallest of fluctuations; anything can trigger an action potential.

Figure 8 shows the effect of varying D_{close}, associated with the closing rate function, on voltage profile. As expected, D_{close} has the opposite randomizing effect as D_{open}. Raising D_{close} makes the model much less sensitive to external stimulus, and lowers fluctuations so that action potentials are decreased in amplitude until they become random fluctuations that are too small to reach threshold potential. While Figure 8 shows that the action potentials are suppressed entirely (even for $I_{ext} = 60\ \mu A/cm^2$, this is dependent on many parameters in the model, particularly in equations (5), and also the value that D_{open} is held at. Nevertheless, the general trend that raising D_{close} decreases random fluctuations, holds true.

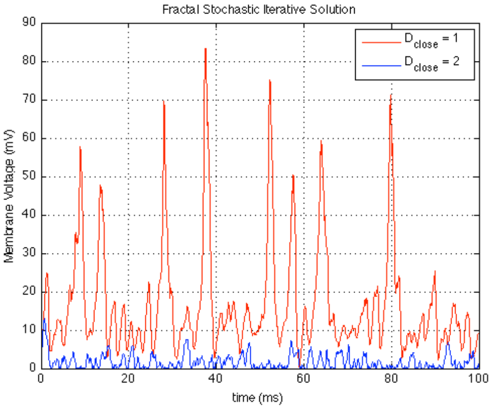


Figure 8: The effect of fractal dimension D_{close}, on action potentials, with $I_{ext} = 60\ \mu A/cm^2$

Figure 9 shows the behavior of the spiking rate fluctuations over time. However, this is not the most convincing evidence that the spiking rate exhibits fractal behavior, because there is very little variation in firing rate to being with. As discussed in Section 2.2, in order to get fluctuations in spiking rate, simulations must be taken for thousands of action potentials, which require extensive computational power and time. The fact that the stochastic aspects of the extended model depend on a time-consuming brute-force algorithm, makes generating action potentials over a long period of time, difficult. Therefore there is not much to be concluded from Fig. 9, which, with more data, should ideally show that between two times (ideally in the thousands of milliseconds range), the amplitude of fluctuations does not change.

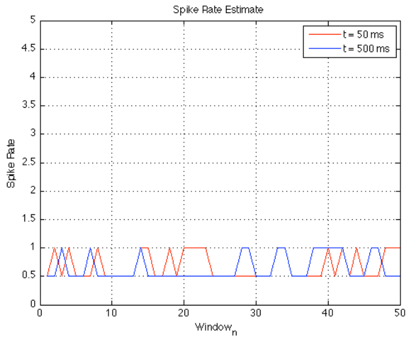


Figure 9: The fluctuations of firing rate, over two different time periods.

4 Conclusion

There are many directions that further work on this project could concentrate on. Firstly, gathering more data to demonstrate the fractal behavior of firing rate fluctuations, would be the first step towards demonstrating a tentative causality between fractal ion channel kinetics, and fractal firing rate behavior, as Lowen et al. tried to show conclusively.

In addition, these fractal models can be compared against experimental data. Liebovitch showed that for mouse hippocampus pyramidal cells, D_{open} ~1.3, D_{close}~2 [3]. The normally occurring values for fractal dimensions can be calculated from the plot of rate functions and probability density functions, which can be created from experimental data. A deviation from the normal values of such parameters could potentially signify pathological behavior. Goldberger's recent article on the connections between fractal dynamics and physiology, also suggests this. This idea of using fractal parameters in physiological models, as a potential way to identify pathological conditions, is another interesting realm of research [1].

In conclusion, the project has successfully implemented a Markov-based fractal model by Lowen et al., using both deterministic and stochastic models. In addition, I have extended the Liebovitch model to explore the effect of fractal dimension on conductance profiles and membrane voltage dynamics. However, there is potentially a lot more research that could be done in conclusively demonstrating causality between fractal ion channel kinetics, and firing rate patterns.

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