1 Introduction

Autosomal dominant nocturnal frontal lobe epilepsy (NFLE) is associated with a defect in the alpha 4 subunit of the nicotinic acetylcholine–gated ion channel (Mann and Mody, 2008). Since the engine for neuronal excitability is the membrane ion channel it is not surprising that there would be a relationship between epilepsy and ion channel abnormalities. The puzzle arises because the ion channel abnormality is a fixed deficit, yet seizures are paroxysmal events.

At the most fundamental level a seizure represents a change in the activity of neurons. Physiological (Abeles et al., 1990) and metabolic (Lennie, 2003) considerations indicate that the cortical interictal state is primarily characterized by low frequency, periodic neuronal spiking. The initial event for seizures is likely associated with a change in the spiking pattern of a sub–population of neurons (Babb et al., 1989; Prince, 1969; Shusterman and Troy, 2008): the spiking frequency becomes higher and the pattern more periodic. Although computational neuroscientists have identified the mechanisms by which changes in neural activity occur, the fact that these concepts are ex-
pressed using mathematical terminologies creates a formidable barrier for clinical epileptologists. Thus discussions between those who have access to clinical data and those who develop models is inhibited and scientific progress impeded.

The purpose of this chapter is to introduce to clinicians the way that scientists who develop mathematical models think about epilepsy, neurons and ion channels. The discussion focuses on the success story of computational neuroscience, namely, the development of the Hodgkin–Huxley model that describes the spiking activities of neurons. Although these equations can be easily derived using the basic principles of electricity taught in introductory physics courses required for admission into medical school, it is surprising that few clinicians appreciate the rich range of dynamical behaviors that single neurons can generate. A fundamental problem is that the mathematical models are sufficiently complex that solutions cannot be obtained analytically, i.e. using paper and pencil. If this point is kept in mind it become easier to appreciate that much of the effort in modeling is directed towards identifying ways to test predictions even though the solutions can only be obtained using computer simulations. This observation motivates a consideration of qualitative techniques that can be used even by non–mathematically oriented epileptologists to propose key experiments that can be tested at the bench top and bedside. This procedure is illustrated in the accompanying chapter (Milton, 2010a).

2 Dynamical systems

Dynamics is concerned with the description of how variables change as a function of time. A variable is anything that can be measured. Examples include the number of neurons, the membrane voltage potential, the number
and types of membrane receptors, and so on. All variables in the nervous system change as a function of time. Figure 1 shows a time series for a hypothetical variable. In the physical sciences the hypothesis that the change in a variable, rather than the magnitude of the variable itself, is important for the development of mathematical models has enjoyed great success. Consequently the starting point for models of the nervous system is based on the same premise.

The change in the variable \( x \) between times \( t_1 \) and \( t_2 \), denoted \( \Delta x / \Delta t \), as

\[
\frac{\Delta x}{\Delta t} = \frac{x(t_2) - x(t_1)}{t_2 - t_1} = \frac{x(t + h) - x(t)}{h} \quad (1)
\]

\[
= \frac{\text{rise}}{\text{run}} \quad (2)
\]

where \( h \) is the time step, i.e. \( h = t_2 - t_1 \). It is natural to ask what happens as the time interval becomes as small as possible, i.e. as \( h \to 0 \). This is the question that Newton posed and leads to the definition of the derivative

\[
\frac{dx}{dt} = \lim_{h \to 0} \frac{x(t + h) - x(t)}{h} \quad (3)
\]

The change in the variable as a function of time, i.e. the predicted time
series, is the solution of the differential equation

\[ \dot{x} \equiv \frac{dx}{dt} = f(x) \]  

(4)

where we have introduced the dot notation for the derivative. The left-hand side of Eq. (4) re-iterates the concept that the change in the variable per unit time is the important variable. The right-hand side states the hypothesis proposed to govern the changes in the variable.

A key point is that the time scale, i.e. the time taken for a significant part of the change to occur, differs markedly for different variables. For example, the binding of a drug to a membrane receptor takes \( \leq 10^{-9} \)s whereas the number of receptors changes on times scales of hours, days and even weeks. Thus what we observe at any instant in time is the consequence of many processes evolving on many time scales. One way to handle this complexity is to introduce the concept of a parameter. A parameter is a variable which changes so slowly, or so quickly, that in comparison to the time scale of variables of interest that it can be regarded as constant. Thus, for example, if we are interested in the dynamics of drug binding to a receptor the number of receptors can be regarded to be a parameter.

The mantra of dynamical systems approaches to the nervous system is that dynamics can qualitatively change as parameters change (Guckenheimer and Holmes, 1990). This observation is closely tied to the concept of stability, i.e. the resistance to change. Historically many experiments were performed on systems that were either at equilibrium or steady state. Mathematically this corresponds to setting \( \dot{x} = 0 \) in Eq. (4): the values of \( x \) for which \( \dot{x} = 0 \) are called the fixed-points, \( \dot{x} \), since if we choose the initial value \( x = \dot{x} \) the system remains there indefinitely. Now suppose we gently perturb a system at steady state and define \( u = x - \dot{x} \). If \( u \) is small enough we can anticipate
that the effects of this perturbation can be described as

\[ \dot{u} = ku \]  

where \( k \) is a parameter. The solution is

\[ u(t) = U_0 e^{kt} \]

where \( U_0 \) represents the initial deviation from the fixed–point due to a perturbation.

Figure 2: Comparison of the dynamics of Eq. (6) for different choices of the parameter \( k \).

Figure 2 shows that the qualitative behavior of this solution depends on the value of \( k \). If \( k < 0 \), then the system returns eventually to its fixed–point value after the perturbation. Thus we say that the fixed–point is stable to the perturbation. On the other hand, if \( k > 0 \), then the system diverges away from the fixed–point and hence the fixed–point is said to be unstable to the perturbation. The value \( k = 0 \) is called a bifurcation point, or stability boundary, since as \( k \) crosses this boundary there is an abrupt, qualitative change in behavior, i.e. following the perturbation the deviation away from the fixed–point either increases or decreases. The advent of the computer led to the remarkable discovery that persistent periodic and aperiodic (quasi–periodic,
chaotic) solutions could arise in situations in which fixed—points were unstable. This observation serves to remind us that discussions of the stability of a fixed—point are local, i.e. the perturbed system must be close enough to the fixed—point so that the approximation given by Eq. (5) holds. Neural systems contain important nonlinearities which operate far from equilibrium that result in stable non—stationary behaviors. This added complexity of nonlinear systems motivated the use of the term attractor for behaviors that are stable to perturbations and repellor for those behaviors that are not. Thus we can have a fixed—point attractor, a limit cycle attractor, a limit cycle repellor, and so on.

3 Neurodynamics

![Image of ion channel and RC circuit](image)

Figure 3: a) Schematic representation of ion channel inserted into lipid bilayer. b) Electrical equivalent RC circuit.

The very same principles used to understand a RC circuit in a physics lab can be used to understand how an action potential is generated by a neuron (Guevara, 2003; Hille, 2001; Hodgkin and Huxley, 1954). The key experimental observation was that the electrical resistance of a neuron is variable ($\leq 10^6 \Omega cm$) and has values that lie intermediate between those obtained for ionic solutions ($\sim 20 \Omega cm$) and those obtained for pure lipid bilayers ($\sim 10^{15}$...
This led to the concept that membrane resistance was determined by the opening and closing of “holes” in the membranes, i.e. the ion channels (Guevara, 2003; Hodgkin and Huxley, 1954): resistance falls when the channels are open and increases when channels close (Fig. 3a). In other words, compared to the RC circuit (Fig. 3b), the resistance of a neuronal membrane, $R$, is not a parameter, but a variable.

Suppose initially that all of the ion channels are closed. Then the capacitance, $C$, across the neuron membrane is

$$Q = CV$$

(7)

where $Q$ is the charge stored across the membrane and $V$ is the potential, or voltage, difference. When an ion channel opens, current ($I$) flows, and $C$ changes according to

$$C \frac{dV}{dt} = \frac{dQ}{dt} \equiv I$$

(8)

They hypothesized that the generation of an action potential is determined by the opening and closing of three types of ion channels: sodium ($Na^+$), potassium ($K^+$) and a “leak” (L) ion channel. Since ion channels function independently, Eq. (8) becomes

$$C \dot{V} = -[I_{Na} + I_K + I_L]$$

(9)

where the negative sign reflects the convention that the inside of the neuron is negative with respect to the outside. Next they assumed that for each channel (“linear membrane hypothesis” (Hille, 2001))

$$I_X = g_X(V - V_X)$$

(10)

where $g_X = R^{-1}$ is the conductance of the ion channel, and hence (9) becomes

$$C \dot{V} = -[g_{Na}(V - E_{Na}) + g_K(V - E_K) + g_L(V - E_L)]$$

(11)
where the terms $E_X$ are the equilibrium potentials determined for each ion from the Nernst equation. However, experimental measurements indicate that the conductances are not constant and hence the $g_X$ are not parameters as assumed in a RC circuit in physics, but are variables. What this means is that we must supplement Eq. (11) with differential equations that describe the changes in the conductances as a function of time.

The differential equations that describe the ion conductances were determined by using the patch clamp technique to isolate single ion channels and then measuring the openings of ion channels when the membrane potential was clamped at values from $-100\text{mV}$ to $+50\text{mV}$. It is observed that each ion channel (even those of the same type) opens after a variable delay and then remains open until the voltage clamp is turned off. An ensemble average is obtained by averaging many such trials for each type of ion channel. Hodgkin and Huxley assumed that the average of multiple trials recorded from the same ion channel is the same as the average for one response measured at the same time for a large number of different K–channels. In other words the time course of activation of the ensemble average which appears in the mathematical model is connected with the variable latencies to first opening of individual ion channels. Thus we see that a differential equation, such as Eq.(4), describes the average behavior of a stochastic dynamical system.

Since changes in membrane resistance are due to the opening and closing of ion channels it was assumed that $g_X(t) = \overline{g}_K n(t)$

where $n$ is a gating variable that controls the opening and closing of the K–channel. Curve fitting techniques combined with simple models describing ion channel dynamics were used to conclude that for the K$^+$–channel $g_K(t) = \overline{g}_K n^4(t)(V - E_K)$
\[ \dot{n} = \alpha_n (1 - n) - \beta_n n \]

where \( \alpha_n \) and \( \beta_n \) are the rate constants for, respectively, the opening and closing of the ion channel.

The same approach was applied to determining the contribution of the Na–current. This current is more complex than the K–current since two gating variables are required to describe its dynamics: an activation gating variable \( m \) and an inactivation gating variable \( h \). The equations that describe the Na–current are

\[
\begin{align*}
g_{Na} &= \bar{g}_{Na} m^3 h (V - E_{Na}) \\
\dot{m} &= \alpha_m (1 - m) - \beta_m m \\
\dot{h} &= \alpha_h (1 - h) - \beta_h h
\end{align*}
\]

The general form of the Hodgkin–Huxley equation is a system of equations: one of the form of Eq. (11) and the others are differential equations that take into account the openings and closings of the various types of ion channels. The specific equations obtained by Hodgkin and Huxley are

\[
\begin{align*}
C \dot{V} &= - \left[ g_{Na} m^3 h (V - E_{Na}) + g_{K} n^4 (V - E_K) + g_{L} (V - E_L) + I_{ext} \right] \\
\dot{m} &= \alpha_m (V) (1 - m) - \beta_m (V) m \\
\dot{h} &= \alpha_h (1 - h) - \beta_h (V) h \\
\dot{n} &= \alpha_n (1 - n) - \beta_n (V) n
\end{align*}
\]

In the context of this model the generation of the action potential arises because the time scales for the sodium and potassium conductances are different: in particular, the sodium conductance changes on time scales shorter than the potassium conductance.

The framework developed by Hodgkin and Huxley has proven to be very robust for the description of the spiking behaviors of neurons and even other
excitable cells including cardiac, pancreatic $\beta$–cells, and muscle cells. As new types of ion currents have been discovered, these have been incorporated into the framework by using the patch clamping and model–based curve fitting techniques to model the gating of these channels. The resulting equations rapidly become exceedingly complex. For example, the Hodgkin–Huxley–type model that describes the leech heartbeat neuronal network includes two different sodium currents, three different potassium currents and two calcium currents resulting in fourteen differential equations that operate on multiple time scales which vary from a few milliseconds through seconds (Hill et al., 2001). In parallel the possible neuronal spiking behaviors become more complex including, for example, bursting and chattering behaviors (Izhikevich, 2004; Wilson, 1999). However, it has become clear that all experimentally observed cortical neuron spiking patterns can be described by mathematical models that are appropriately formulated within the Hodgkin–Huxley framework (Izhikevich, 2004; Wilson, 1999). Thus mathematically–guided computational studies have become a necessary tool for the investigation of neurodynamics.

4 Single neuron dynamics

It is likely that every student who has taken an introductory biology course is familiar with the statement that the action potential of a neuron is described by the Hodgkin–Huxley (HH) equation. However, few realize that this equation successfully predicted that a wide range of dynamical behaviors can be generated by neurons, all of which have been observed experimentally.
Spiking neurons generate action potentials when the membrane potential exceeds a spiking threshold. Figure 4a shows the effect of single excitatory inputs of differing magnitude on the membrane potential of a Hodgkin–Huxley neuron. When the stimulus intensity is less than threshold, the membrane potential following the stimulus (dotted line) decays approximately exponentially back towards its resting membrane potential. However, when the stimulus intensity exceeds the threshold the generation of an action potential produces a very different time course for the return of membrane potential to its resting value (solid line). The term *excitability* refers to the behavior of threshold–type systems in which small perturbations results in a “short path” return to baseline whereas a sufficiently large stimuli results in a disproportionately “longer path” return to baseline.

Excitability is one of the properties of a neuron that can be attributed
to the presence of the so-called cubic nonlinearity (van der Pol and van der Mark, 1928). This terminology is most easily understood by reducing the Hodgkin–Huxley equations to a simpler form. Since the time scale for the relaxation of \( m \) is much faster than \( n \) and \( h \) we can assume that \( \dot{m} = 0 \). If, in addition, we assume that \( h = h_0 \), a constant, then it was found that the resulting reduced system of two differential equation retained many of the features observed experimentally (for an alternate derivation based on a simplified model of the cell membrane see (Keener and Sneyd, 1998)). This system of equations is called the Fitzhugh–Nagumo equation (FitzHugh, 1961; Nagumo et al., 1962)

\[
\begin{align*}
\dot{v} & = f(v) - w + I_{\text{ext}} \\
\dot{w} & = bv - \gamma w
\end{align*}
\]

where

\[
f(v) = v(a - v)(v - 1)
\]

where \( 0 < a < 1, \ b > 0 \) and \( \gamma > 0 \). In the Fitzhugh–Nagumo equation, \( v \) plays the role of the membrane potential and \( w \) plays the role of a recovery variable.

Figure 4b shows the phase plane of the Fitzhugh–Nagumo equation when the parameters are tuned to the excitable regime. The phase plane is a plot of \( v(t) \) versus \( w(t) \), i.e. time does not appear explicitly. The basic principle of phase plane analysis is to use the conditions that \( \dot{v} = 0 \) and \( \dot{w} = 0 \) to divide the phase plane into distinct regions and to identify the fixed points. Following this procedure when \( I_{\text{ext}} = 0 \), we have for \( \dot{v} = 0 \)

\[
w = v(a - v)(v - 1)
\]

This equation is called the \( v \)–nullcline and describes the cubic nonlinearity shown in Figure 4b. Since \( \dot{v} = f(v) - w \) we see that above the \( v \)–nullcline
we have $\dot{v} < 0$ and below the $v$-nullcline we have $\dot{v} > 0$. Similarly the $w$-nullcline is obtained by setting $\dot{w} = 0$ and is

$$w = \frac{b}{\gamma} v$$

Thus it is a straight line through the origin of the phase plane with slope $b/\gamma$. Since $\dot{w} = bv - \gamma v$ we have above the $w$-nullcline $\dot{w} < 0$ and below $\dot{w} > 0$. In other words the $v$ and $w$ nullclines divide the phase plane into four regions in terms of the relative signs of $\dot{v}$ and $\dot{w}$. The points at which the $v$ and $w$ nullclines intersect in the phase plane are the fixed points, in this case there is one fixed-point which corresponds to the resting membrane potential of the neuron. Since the time constant for the changes in $v$ is larger than that for the changes in $w$ by a factor of about 12.5 Haken (2002), the stability of the fixed point is determined by slope of the $v$-nullcline. In particular the fixed point is stable if the $v$-nullcline slopes downwards at the fixed point and unstable if it slopes upwards. Thus in the excitable regime the resting membrane potential is stable; hence it is a fixed-point attractor.

We can see the relationship between excitability and a cubic nonlinearity by picking different starting points, i.e. different initial values of $v(t)$ and $w(t)$, and seeing what happens. Suppose we applied to the neuron in its resting an excitatory input of magnitude $A$ to obtain the initial condition $v(0) = A$ and $w = 0$. Since $\dot{w} > 0$ and $\dot{v} < 0$ we know that $v$ must decrease and $w$ must increase in such a way that the effects on $v$ outweigh the effects on $w$. The next effect is that $v$ (and hence $w$) decays monotonically towards the fixed point (Figure 4b). However, a completely different scenario occurs if we apply an excitatory input large enough to cross the $v$-nullcline, e.g. point $B$ in Figure 4b. Since both $\dot{v} > 0$ and $\dot{w} > 0$ both $v$ and $w$ must increase. However, at some point the $v$-nullcline will be crossed and consequently $\dot{v} < 0$. Consequently $v, w$ are drawn back to the fixed point. These are the
typical time courses that define an excitable system.

The spiking threshold is measured experimentally as the amplitude of a brief current input that produces an action potential 50% of the time (Verveen and DeFelice, 1974). Surprisingly it has only been recently recognized that the spiking threshold of a HH–type neuron has a very complex structure typical of that seen in systems that exhibit chaotic dynamics, namely, a fractal basin boundary (Guckenheimer and Oliva, 2002). Although this observation raises the possibility of chaos in the HH–neuron, it must be kept in mind that these equations are an approximation to a process that should, strictly speaking, be described by a stochastic differential equation. As we have discussed this stochasticity arises because the mathematical expressions for ionic conductances are averages obtained by measuring the variable openings of ion channels. Thus it is possible that this mathematical observation points to a limitation of the ensemble averaging procedure used by Hodgkin and Huxley for describing neural excitability. In any case these observations remind us that there is a degree of unpredictability about the responses of neurons to stimulation.

4.2 Periodic spiking

The question of how neurons change their spiking behavior is of critical importance for understanding the occurrence of an epileptic seizure. Indeed current mechanisms for neural synchronization of large populations of neurons require that individual neurons exhibit some form of periodic spiking behavior (Strogatz, 2003). We can use our phase plane approach to understand why a Fitzhugh–Nagumo neuron generates periodic spiking when an external current is injected (Figure 5). The effect of $I_{\text{ext}} > 0$ is to simply move the position of the $v$–nullcline upwards. Thus there is no longer a fixed
Figure 5: a) Phase plane and b) spiking pattern for the Fitzhugh-Nagumo equation tuned to the periodic regime. See text for discussion.

point at (0, 0). The $v$–nullcline at the new fixed point is positive; however, it is unstable. However, this instability must be only true close to the fixed point. Why? If, for example, $v$ becomes very large positive, $\dot{v} < 0$ and hence both $v$ and $w$ must contract towards the fixed point. The same would be true if we imagined that $v$ became very large negative. In other words the trajectory $(v, w)$ can neither come too close or too far away from the fixed point, but must both be confined to a region, shaped roughly like a doughnut, in which the fixed point lies somewhere inside the hole. Since every solution of a differential equation is determined uniquely by its initial conditions, the trajectory that describes $(v, w)$ can never cross itself. The only possible trajectory which can remain confined within a two–dimensional region and never cross itself is a closed curve such as a circle or ellipse. This means that the solution must be periodic; this periodic solution is called a limit cycle, i.e. a limit cycle attractor. It should be noted that on the limit cycle for the Fitzhugh–Nagumo neuron, trajectory movements in the horizontal direction are typically much faster than those in the vertical direction. This is the property of relaxation–type oscillators.
A change in neuronal activity from a resting, but excitable, state to a periodic spiking behavior is a bifurcation. A great deal of mathematical effort has been expended to show that there are only a few types of bifurcations that produce limit cycles (Guckenheimer and Holmes, 1990). This fact greatly simplifies the task for experimental investigations since it becomes possible to systematically examine each mechanism and decide which are the most likely candidates by directly comparing observation to prediction.

The most common bifurcation that produces periodic activity in single neurons (Guevara, 2003) and neural populations (Wilson and Cowan, 1972) is the sub-critical Hopf bifurcation (Fig. 6a). A bifurcation diagram is constructed by determining the “long time, or steady state behavior” for different choices of the initial conditions as the bifurcation parameter is changed (in this case $\mu$). Our convention is that solid lines correspond to fixed point–attractors (stable), dotted lines to fixed point–repellors (instability), black dots to a stable limit cycle, and so on. Imagine that we slowly increase $\mu$ from $-0.4$. Two interesting phenomena occur. First, oscillation onset occurs abruptly (there is a bifurcation) and once the oscillation occurs its amplitude does not significantly change as $\mu$ increases. Neurons whose oscillation onset behaves in this manner are said to possess Type II excitable membranes. Second, in the region outlined by $abcd$ two stable behaviors co–exist: a fixed–point attractor and a limit cycle attractor. The co-existence of more than one attractor is referred to as multistability: bistability refers to the special case when two attractors co–exist. In the accompanying chapter (Milton, 2010a) we show that the occurrence of bistability in a neuron is intimately associated with the presence of a cubic nonlinearity.

The existence of multistability in a neuron (or neural population) suggests a simple mechanism for starting and stopping neural rhythms. Suppose that
Figure 6: (a) Bifurcation diagram for a generic sub–critical Hopf bifurcation. See text for discussion. b) Simulation using XPPAUT (Ermentrout, 2002) following an exercise described in (Guevara, 2003) that demonstrates that a regular spiking Hodgkin–Huxley neuron can be stopped by applying a single 0.4s, 10 mA pulse (↓).

\( \mu \) is in the range between \( a \) and \( b \). Then a single, carefully honed perturbation would either annihilate an existing oscillation or initiate one. As is shown in Fig. 6b this prediction can be verified using a simulation of the HH equation. In support of this hypothesis, qualitative changes in the dynamics of single neurons (Guttman et al., 1980; Tasaki, 1959) and neural circuits (Foss and Milton, 2000; Kleinfeld et al., 1990) can be induced by applying appropriately timed, brief electrical stimuli. Moreover, single DC pulses terminate seizures in rats (Osorio and Frei, 2009), brief electrical stimuli block after-discharges (Motamedi et al., 2002) and sensory stimuli can abort seizures in humans with epilepsy (Milton, 2000). These observations suggest that, at least for short intervals of time, living neurons and neural populations behave as would be expected for a multistable dynamical system.
5 Discussion

A fundamental postulate of dynamic systems theory is that the dynamics of large populations of neurons can be captured by the dynamics of much simpler systems (Guckenheimer and Holmes, 1990; Lytton, 2008). This is because complex systems with many components exhibit a tendency to self-organize at, or near, stability boundaries in parameter space. The closer the dynamical system is to the stability boundary the better the dynamics can be approximated by a simpler dimensional system. In other words phenomena we have described for single neurons, such as excitability, periodic spiking, multistability and even chaos, all have their counterparts in the dynamics of large neural populations. Of course neural populations exhibit additional properties that arise because they are large (Milton, 2010b) including the effects of energy constraints, the finiteness of dendritic/axonal conduction velocities, anatomical pathways for propagation, and the tendency of a periodically spiking neuron to synchronize with other similarly spiking neurons. However if we believe that the ultimate triggering event for a seizure is a qualitative change in the activity of individual neurons, then these larger scale phenomena shape the resultant seizure, but do not initiate it. An implication of this observation is "little seizures involving just a few neurons" may be as important as important as “large clinically significant seizures” for understanding seizure initiation and the development of methods for seizure prediction. This conclusion is supported by the following observations.

Measurements of the time, $\Delta t$, between successive seizure recurrences indicate the presence of a power law of the form (Osorio et al., 2009)

$$P(\Delta t) \sim \frac{1}{t^\alpha} \quad \text{(14)}$$

where $P(\Delta t)$ is the probability that the time between successive seizures
is $\Delta t$ and $\alpha$ is a constant equal to the power law exponent. This equation indicates that a log–log plot of $P(\Delta t)$ versus $\Delta t$ is linear with slope $\alpha$. Theoretical studies indicate that power laws generically arise in systems of relaxation oscillators, such as neurons, which are tuned very close to stability boundaries, i.e. the “edge of stability” (Sornette, 2004). The fact that a power law is observed is quite disturbing since it implies that there is no characteristic time scale. This means that we would obtain the same power law exponent whether we measured events at an accuracy of milliseconds or years! and hence distinctions between parameters and variables become increasingly blurred. An important observation is that some systems that exhibit power laws may also exhibit long–range correlations (Milton, 2010b; Sornette, 2004); the existence of these correlations raises the possibility of some degree of predictability. Finally, since the size of seizure events also can exhibit a power law (Osorio et al., 2009), there is no characteristic scale for epileptic seizures. In other words, even a single spike–slow wave discharge may be as important for understanding the dynamics of seizure recurrence in patients with epilepsy as the occurrence of clinically significant seizures.

Current mathematical models typically express neural activities in terms of action potentials, either timing or rate, but the clinical methods available to evaluate these models do not directly measure action potentials. There are two types of methods available to test predictions of mathematical models for epilepsy: 1) those that indirectly monitor neuronal metabolism (fMRI,PET); and 2) the electro–encephalogram (EEG), a method that measures the extracellular currents generated by excitatory and inhibitory post-synaptic potentials. Although optical methods have the potential of measuring action potentials these are likely to be of limited clinical usefulness (Haglund et al., 1992). Here lies the barrier that inhibits progress into the application of
computational methods to the study the level of precision required to validate computational models of seizures (Lytton, 2008; Soltesz and Staley, 2008). Thus it is absolutely essential that computational neuroscientists begin to develop models that offer predictions related to the clinically accessible variables. A notable step forward is current attempts to interpret the epileptic spike measured by the surface EEG in terms of depth EEG signals (Cosandier-Rimélé et al., 2007).

The spread of neural activity during a seizure is highly dependent on the topology of the neuronal connectivity. In contrast to the obvious complexity of neural pathways in the brain, mathematical models of populations of neurons consider topologies (random, exponentially distributed, small world) which are obviously overly naive. Consequently issues related to neuro-anatomy and neuro-physiology will always remain of fundamental importance to the study of epilepsy. At the very least this observation emphasizes that progress requires the efforts of inter-disciplinary teams involving clinicians and modelers so that critically important experiments can be designed and conducted.

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