Computer modelling of epilepsy

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Abstract | Epilepsy is a complex set of disorders that can involve many areas of the cortex, as well as underlying deep-brain systems. The myriad manifestations of seizures, which can be as varied as déjà vu and olfactory hallucination, can therefore give researchers insights into regional functions and relations. Epilepsy is also complex genetically and pathophysiologically: it involves microscopic (on the scale of ion channels and synaptic proteins), macroscopic (on the scale of brain trauma and rewiring) and intermediate changes in a complex interplay of causality. It has long been recognized that computer modelling will be required to disentangle causality, to better understand seizure spread and to understand and eventually predict treatment efficacy. Over the past few years, substantial progress has been made in modelling epilepsy at levels ranging from the molecular to the socioeconomic. We review these efforts and connect them to the medical goals of understanding and treating the disorder.

Generalized seizure
A seizure that seems to start simultaneously across cortical sites.

Focal seizure
A seizure that starts at a particular location in the brain.

Secondary generalization
A process whereby an initially focal seizure spreads to involve the entire brain.

Dynamical model
A computer or physical model that reproduces change in an experimentally observable feature. In the case of dynamical models of motion, these changes would be in position and velocity.

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Epilepsy is one of several paroxysmal or episodic disorders of the brain. These disorders, which include multiple sclerosis (MS), transient ischaemic attacks (TIAs) and migraine, are all dynamical disorders — disorders that unfold over time[1]. Whereas MS involves the dynamics of the immune system and TIAs involve haemodynamics, epilepsy is a dynamical disorder of the brain itself. Epilepsy is therefore particularly suited to study from the perspective of computer modelling and dynamical-systems theory.

The signs and symptoms of epilepsy are varied, probably owing to the fact that epilepsy can involve many areas of the cortex as well as underlying deep-brain systems. Epilepsy is therefore a fascinating disorder for both the clinician and those interested in the functioning and interrelations of brain subsystems. Progress in understanding epilepsy has been made in all areas of neuroscience, from neurogenetics and protein crystallography to imaging and behaviour. Modelling can be used to tie together these subfields and enable us to understand one level of organization in terms of others[2]. The concordance between basic science and clinical phenomenology is closer in epilepsy than in most brain disorders. Computer simulation can conceptually link abnormalities at different levels of organization that are identified by experiment.

This Review focuses on two major epilepsy syndromes that are particularly well-studied in modelling and experimental preparations: childhood absence epilepsy and mesial temporal lobe epilepsy (MTLE). Absence seizures are brief episodes of loss of consciousness without convulsions. Absence is considered a primary generalized seizure, although recent findings suggest that an individual absence seizure does have a focal onset[3]. Experimentation and modelling strongly implicate thalamocortical interactions in this disorder[4–6]. By contrast, MTLE seizures produce alterations in consciousness and convulsions. The seizures spread from the temporal lobe in a process termed secondary generalization. MTLE is considered to be the prototypical focal epilepsy disorder[7] and is thought to be largely acquired, presumably through injury and the brain's subsequent reaction to injury[8]. However, familial factors are also important[9–14].

The Review describes several levels and types of models to give the flavour of modelling and to highlight recent progress and the potential for therapeutic application of computer models. I proceed from the macroscopic to the microscopic level, and from modelling the dynamics of seizure occurrence in the pediatric population to a detailed model that takes into account the dynamics of voltage-sensitive ion channels. Throughout, I compare conceptual and dynamical models and indicate how the conceptual model is used as a foundation for a dynamical interpretation of the data. This broad scope has required the omission of many major works in the field in favour of a few studies that illustrate particular approaches. Readers whose curiosity is piqued are referred to REF. 15.

Tonic–clonic
A common pattern of convulsion that involves a phase of contraction of the extensor muscles (the tonic) followed by a phase of alternating flexor–extensor contractions (the clonic phase).

What is epilepsy?

An initial understanding (or model) of something is generally provided by a textbook or dictionary definition, which can provide a root and route to broader taxonomic and classification schemes. The common feature of the epilepsies is the occurrence and recurrence of seizures; epilepsy is thus a seizure disorder. A seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (REF. 16). An additional aspect of the clinical definition of a seizure is the involvement of the cerebral cortex; this allows seizures to be distinguished from excessive or synchronous activity elsewhere in the brain, such as tremors or the pain that arises from a brainstem ganglion (trigeminal neuralgia). In the research literature, the term seizure is also applied to excessive neurological activity in creatures as petite and acortical as zebrafish and fruit flies[17,18]. This is reasonable, as the animal syndromes that are involved do respond to anticonvulsants (as does trigeminal neuralgia). These syndromes thus enable investigators to assess drugs and genetic manipulations that would be impossible to assess in larger animals.

The difficulty in defining epilepsy arises in part from the vast diversity of epilepsy syndromes and seizure manifestations. The current standard clinical classification can be confusing owing to its occasional conflation of aetiology and manifestation[19]. Efforts to amend and replace this classification scheme have led to disagreements and competing suggestions for standards[16,20–25]. Nevertheless, the competing classifications all agree on the use of multidimensional axes to organize our thinking about the disorder (BOX 1). Ideally these schemes will provide a basis for formal (computerized) epilepsy ontologies in the future[26,27].

The difficulty in defining epilepsy also reflects the perennial clinical conflict between splitters and lumpers[22,24]. Splitters want to divide epilepsy into distinct conditions, whereas lumpers suggest that manifestations and causes overlap so greatly that there is little value in splitting. Both views have validity. Several distinct epilepsy syndromes, such as childhood absence and MTLE, can be identified. However, epilepsy generally arises from a confluence of polygenic, proteomic and acquired causes[28]. The metaphor of a river of epilepsy was developed by Lennox to describe this multifactorial causation[164] (FIG. 1). A particular genomic or proteomic makeup provides an interacting substrate of ion channels, synaptic weights and network configurations that make an individual more or less prone to develop epilepsy in response to stroke, head trauma or simple lack of sleep[29–32]. Conversely, a particular ion-channel mutation, even one that is invariably epileptogenic, will produce different disease manifestations in two individuals owing to differences in other channels, network anatomy and acquired brain insults.

The complexity of multifactorial causation highlights the need for a computational approach. Although it is possible to experimentally determine and informally conceptualize how a single mutation could produce a seizure, modelling is required to understand how two, five or ten mutations that would not cause seizures individually do so when they are combined. This complexity extends to the therapeutic domain: many drugs have multiple binding sites and thus produce multiple effects that require modelling to be fully understood.

Multiscale modelling

As epilepsy is characterized by recurrent seizures, one might imagine that we would build an epilepsy model directly out of a seizure model. However, the complexity of such a combined model makes it unattainable for the foreseeable future. More importantly, such a model would violate a central tenet of both mathematical and computer modelling: simplification. A large part of the art of modelling consists of deciding what to leave out. In computer modelling, we use the concept of multiscale modelling. Conceptually, multiscale modelling is familiar in biology: cell biology models depend on molecular biology models and so forth down to quantum mechanics. In biomedical science we build hierarchies of models: models of models of models. A clinical disease is represented by one or more *in vivo* animal models, aspects of which can be further explored *in vitro*. An acute brain slice from an epileptic animal serves as a reduced model system for understanding the seizures in the source animal. Computer models can be explicit models of one of these models or an attempt to translate the results of such models up to a higher model or the clinical level.

Box 1 | **The epilepsy axes**

Of late, much effort and much argument have gone into revising epilepsy taxonomy and classification[19]. The new classification, although it is not officially accepted by the International League Against Epilepsy or even by the committee that designed it, is a step forward from the point of view of computationalists and for neuroscientists in general. Rather than lumping aetiology, semiology and syndromology together, the new classification separates these and other facets of the disorder out into axes, in the manner of the psychiatric classifications promulgated by the various editions of the Diagnosis and Statistical Manuals (DSMs).

- Axis 1 describes 'ictal semiology' — what the patient's seizures look like clinically in terms of signs (observable manifestations) and symptoms (patient complaints). This axis strives for reproducibility by using a standard 'Glossary of Descriptive Terminology'.
- Axis 2 redescribes the seizure types using a somewhat more global and traditional viewpoint, with descriptors that include 'tonic–clonic' and 'typical absence'. These first two axes are therefore not orthogonal.
- Axis 3 provides syndromic diagnosis where possible, including a list of particular symptom complexes that have, in some cases, been shown to have particular chromosomal or even precise genetic linkage.
- Axis 4 provides a descriptor for underlying aetiology (cause). This allows the precise definition of those syndromes that are known at a molecular (channel, neurotransmitter or receptor) level. Again, Axes 3 and 4 are not orthogonal.
- Axis 5 describes the socioeconomic impact of the patient's disorder. An alternative axial framework also provides axes for seizure spread patterns and for seizure frequency[154–156].

Ideally, a multidimensional taxonomic system should permit us to place an individual patient at a particular point in the state space that is defined by the measures on each axis. By analogy with dynamical systems, one could consider the patient's clinical definition moving in this space over years of disease evolution, treatment, remission and relapse.

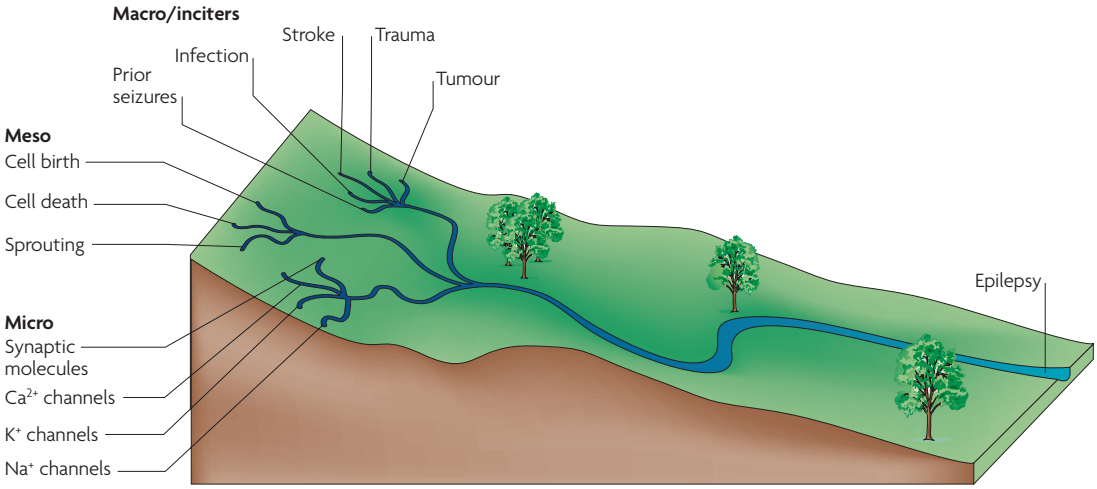

Figure 1 | **The river of epilepsy.** Multiple genetic factors and various acquired insults, here represented as tributaries of a river (a metaphor first proposed by Lennox[164]), feed into epilepsy causation. Factors have been grossly divided into micro-, meso- and macro-levels of change or insult. Many genetic and epigenetic factors come into play in producing combinations of voltage-gated and ligand-sensitive channels that might contribute to an epileptic state. Na^+, K^+ and Ca^{2+} channels, as well as both excitatory and inhibitory synaptic receptors, are implicated. Channel alleles that are not sufficient to cause epilepsy individually might cause epilepsy when they are combined. Alternatively, and remarkably, combinations of alleles might reduce the epilepsy that would be caused by any of the alleles alone[28]. In addition to these factors, life events such as head trauma can incite cell death or wiring changes that will contribute to a greater or lesser extent when they are combined with the genetic factors. This complex, multifactorial causality generally precludes the identification of the root cause of epilepsy in an individual patient or class of patients. Instead, we must think in terms of complex systems, using tools that enable us to manipulate and understand them.

In the case of epilepsy, multiscale modelling can be envisioned across many different dimensions. First, there is spatial scale. Models range from the single ion channel up to the level of brain areas[33,34]. There is also the temporal scale: modelling of interictal spikes (over a millisecond timescale), seizures (over seconds to minutes), drug treatments (over months) and disease evolution (over years). We can also model across and among the clinical axes (BOX 1). For example, modelling seizure semiology would help us to explain seizure spread. Similarly, simulation can evaluate neuronal network dynamics in the context of transitions between tonic and clonic activity[35]. Modelling can also connect seizures to associated signs or underlying causes. Simulation extends to socioeconomic impact: public health models can be used to evaluate trade-offs between various treatments and quality of life or economic impact.

Computer modelling: static and dynamic

Scientific model-building is a set of techniques, ranging from scale models and verbal models to detailed taxonomies (the Linnean system), geometric relations (the periodic table), diagrams and schematics, mathematical models, and animal and *in vitro* models[36]. In order to model seizures and epilepsy on a computer, we need to consider these existing biological and ontological models.

Static models. Computational neuroscience is a branch of computational systems biology[37–40] that combines two interlocking types of study: knowledge discovery and data mining (KDD), and simulation[41]. KDD permits a search for patterns in static data and provides substrate and context for building simulations[42–45]. KDD can be used to explore both biological databases and the taxonomies that have been developed for public health, health insurance and bibliographic purposes[46,47]. As noted above, the complexity of epilepsy has blocked agreement on a taxonomy and classification systems[20,22]. Formal taxonomies and ontologies developed through KDD might help to clarify the aspects and subtypes of epilepsy that are explored through animal research and modelling.

In the context of KDD, a database is a computer model. The structure of complex databases (for example, those for gene networks, cell signalling cascades or metabolic pathways) embodies the data, incorporating relations such as hierarchies, inheritance and lateral associations. KDD extracts information that would not be apparent through unmediated human reading of these models[48,49]. Similarly, a formal ontology organizes data within a taxonomy, with rules for linking, embedding or transforming concepts[47]. Various qualitative models can be built from a database or ontology. Such models coarsely define phenomenology in terms of classes, types or gross sizes.

Another type of static computer model, the graph model, generates and examines connectivity diagrams. Directed graphs, in which A to B differs from B to A, are used to define patterns of neuronal connectivity. A major distinction is made between random graphs (with uniform connectivity probabilities) and small-world graphs with low average distances from any node to any other[50]. Small-world graphs often contain hubs (similar

Seizure semiology
The detailed study of the progress of a seizure.

Scale model
A small physical model of an object, with correct proportions.

Verbal model
An informal descriptive explanation of an object or phenomenon.

Systems biology
The analysis of element interactions in biological systems. Owing to the complexity of these systems, the computer is often used as a tool for analysis and simulation. Objects of study include metabolic and expression pathways but extend up to the study of macroscopic systems. The goal is to insert the results of reductionist study back into the systems from which they were extracted.

to the airline hub system). Graph theory has been used at the level of brain areas as well as at the level of neuronal networks and is further discussed below.

Dynamic models. Dynamical modelling involves loading equations that describe change into a computer. These equations are numerically solved to provide precise predictions of how a complex system will evolve. Although computer modelling is a direct extension of mathematical modelling, it differs by being in itself an experimental pursuit that yields unexpected insights during exploration[51]. Simulation produces a large quantity of virtual data that complement experimental data. The virtual data can then be mined[52] to provide comparison with the original system, to allow the exploration of missing parameters and to contribute to the development of new hypotheses[44,53]. In this way, simulation and KDD are partnered in mutual support[54,55].

Dynamical models include stochastic (random) models, such as Poisson models, Monte Carlo models, Markov models and others. In these models, intervals or instances are drawn randomly from a distribution. Markov models have been used to model seizure-occurrence times[56] and are also widely used to model ion-channel transitions[57]. Monte Carlo models are used to follow trajectories of individual molecules and ions at a synapse[33].

The workhorse of dynamical modelling is the deterministic model, which generally is described by differential equations. For computerization, these equations are discretized in space and time (using finite-difference approximations). Neurobiological examples of dynamical models include compartmental models and the Hodgkin–Huxley equations[58,59]. Another form of deterministic model is the event-driven model, which manages time discontinuously by direct modelling of chains of event dependence. Such models can be used to model spike cascades[60–65]. In the following sections, I describe some specific dynamical seizure and epilepsy models.

Stochastic models

Most scientists are quite familiar with a basic type of mathematical modelling — that of fitting data to a distribution. It is easy to turn the data-fitting process around to create synthetic data from statistical model parameters — for example, the two parameters (μ and σ) of a Gaussian distribution — and in turn create a simple stochastic model. Stochastic models might be used when a system is too complex to consider modelling the underlying details. They are also used when a system is subject to vagaries that cannot reasonably be modelled. For example, seizures are more likely to occur after a night's sleep has been missed. It is not feasible to model the behavioural or employment patterns that might lead to this. Stochastic modelling can be used to understand the clinical course of epilepsy and to investigate whether we can predict seizure onset times.

Predicting seizures. Initial stochastic models of seizure-occurrence times suggested that they follow a Poisson distribution[66]. Subsequent clinical studies indicated that some patients will show deviations from this pattern through cyclicity (periodic seizure recurrence, such as is sometimes seen with menses) or seizure clustering[67–69]. Further modelling research then suggested that the brains of some patients exhibit two states that have different seizure-occurrence probabilities (high and low, corresponding respectively to seizure-prone and seizure-resistant periods)[70–72]. A two-state Markov model was also able to fit an animal seizure model: a long period in the seizure-prone state was associated with a subsequent long period in the seizure-resistant state[73].

Markov modelling has also been used to determine the adequacy of seizure-prediction algorithms[74]. A model for this purpose used three Markov brain states: 'normal', 'pre-seizure' and 'seizure', with bidirectional transitions possible between any two states. The only state that was directly observable was the seizure state. This was therefore a hidden Markov model: the other two states could not be directly observed from the data but were inferred through the model. In addition to the probabilistic transitions between states, the model included emission probabilities: the probability that a given state would be observed. For example, detection of the pre-seizure state was associated with a specific emission probability. The model could therefore suggest where false positives (the algorithm indicating pre-seizure when the brain was normal) and false negatives (the algorithm not being triggered even though the brain was pre-seizure) occurred.

From a neurobiological point of view, this model is interesting because it makes explicit the notion of a pre-seizure state and makes specific predictions about transitions into and out of this state. Meaningful seizure prediction (minutes ahead) will be possible only if such a state exists. The existence of this state in some patients is suggested by their ability to predict their seizures up to a day before they occur[75]. Without a pre-seizure state, the most that can be accomplished is an improvement in detecting seizure onset. The model demonstrated frequent bidirectional transitions between the pre-seizure and seizure states, a possible cause of seizure clustering[68,76]. Similarly, it demonstrated the pre-seizure-to-normal transitions that would have to be made more likely to occur by any prediction-triggered therapy.

Modelling clinical course. Another study used modelling to follow clinical course (remission and relapse)[77]. A three-state Markov model fitted the course of epilepsy in 602 children (FIG. 2). The model predicted that a subset (approximately 20%) of patients would never undergo remission. The proportion of patients expected to be in remission after 4–5 years was predicted to be approximately 70%. These groups could then be analysed to diagnose their underlying disorders and connect these disorder's dynamics with their definition (taxonomy). This model has prognostic value: we can give a parent some idea of the chance of remission once the child reaches school-age. Additionally, the model showed that the probability of remaining in remission differed little with the length of time from the onset of epilepsy to remission during the initial 3-year period following

Parameter
In a computer model, parameters are the constant values in the set of equations that describe the model. These values are set by the user and determine the behaviour of the model.

Stochastic model
A computer model that attempts to replicate phenomenology by drawing exemplars (which might be locations or time intervals) from a probability distribution. The prototypical example is the model of Brownian motion.

Poisson model
A stochastic model that generates time intervals that are independently drawn from a Poisson distribution. The Poisson distribution is the limiting case of the binomial distribution for large 'n' (number of events) and small 'p' (probability of event occurrence).

Monte Carlo model
A stochastic model that uses repeated random sampling from one or more distributions.

Markov model
A stochastic model that uses a series of connected states with transition probabilities between them.

Discretization
A process whereby continuous time is divided into timesteps, or whereby continuous space is divided into segments or compartments, in order to simulate continuous reality in the discontinuous words of computer memory.

Finite-difference approximation
A process whereby the infinitesimal changes of continuous curves (in time or space) are approximated with a finite change that is based on the curve's values at a discrete timestep or spatial interval.

State variable
In a dynamical model, state variables are the values that change with time.

Trajectory
In a dynamical model, the trajectory is the path that is followed by the n state variables through the n-dimensional state space. This is a higher-dimensional generalization of the notion of trajectory as a term that is commonly used to describe motion. However, trajectories in models of motion include velocities as well as locations.

Attractor
The set of stable trajectories of a dynamical system in state-space. If a trajectory is perturbed away from an attractor it will tend to move back to it.

Mean-field approximation
An approximation that is used when large numbers of elements (for example, neurons) make it impracticable to model the influence of each element individually. Instead, the effect of a large ensemble of elements is estimated as a field, the influence of which is widely felt.

diagnosis. The probability was slightly reduced if the child took 4 years to undergo remission. This result might have neurobiological implications. Clearly epilepsy in the child's brain is a highly non-stationary process — the brain is continuously changing owing both to the effects of seizures and to normal or abnormal developmental processes. One can imagine that there are vulnerable (critical) periods in brain development or epilepsy development, during which therapeutic interventions would be particularly efficacious[78].

Lumped deterministic models

By contrast to stochastic models, deterministic models do not evolve randomly: they are precisely determined by their initial conditions and can therefore offer precise predictions rather than probabilities. This precision is exemplified in a moon shot (a voyage from the earth to the moon), which is controlled through computer models that predict trajectories with an error on the order of metres over a distance of ~384 million metres. Unfortunately, complex nonlinear systems such as the brain do not lend themselves to such precision. Nonlinearity implies that a small change can produce a big effect: for example, in the neuron a small current near the dynamic spike threshold will produce a spike. In a nonlinear dynamical system, this might lead to such sensitivity to initial conditions that tiny, unobservable alterations in the initial state of the system will lead to vastly different outcomes. Thus, a deterministic system can produce apparently random behaviour, called chaos[79,80]. This is how a computer produces random (actually, pseudo-random) numbers. A moon shot, by contrast, is a nonlinear dynamical system that is neither complex (in the technical sense) nor chaotic.

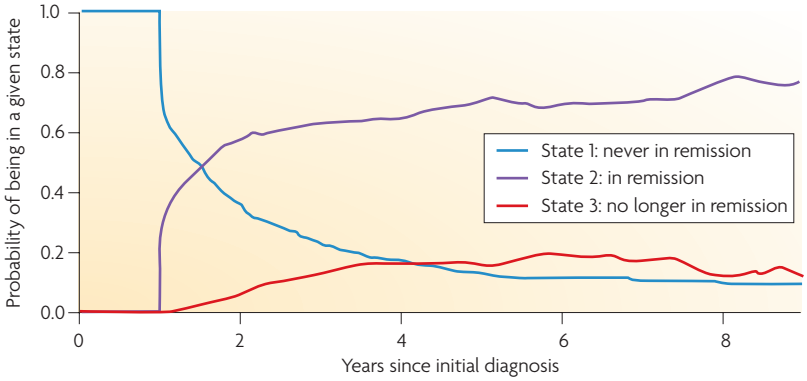

Figure 2 | **Markov model of childhood-epilepsy outcome in 602 children.** The model consists of three states: initial disease (State 1, a starting state to which there is no return), remission (State 2) and relapse (State 3). A time period of 1 year seizure-free was used to define remission. The model indicated that the probability for being in each of the three states plateaued over a 5-year period. Most patients go into remission (stop having seizures), although some of these will relapse. Note that these results could not have been readily obtained using standard statistical measures. This is partially due to the nature of the sample: patients are enrolled over time and so only a few, if any, are followed for the full 8 years of the study — there is no single time-point at which all patients can be assessed. It is also due to the difficulty of extrapolating probabilities out across multiple cycles of remission and relapse. Figure modified, with permission, from REF. 77 © (2004) Elsevier Science.

A dynamical system is defined by equations (in the case of the moon shot, these are Newton's equations), parameters (the strength of gravity, the mass of the rocket) and initial conditions (a location in Florida and zero velocity in the earth frame) and is described by the evolution of its state variables (position and velocity) along a trajectory. In some cases a trajectory might lie on an attractor, making it resistant to perturbation. In neurobiology, the exemplary dynamical system is the four-dimensional Hodgkin–Huxley system for action-potential generation. Here, the state variables are membrane voltage and levels of channel activation and inactivation, and a given current injection (a parameter) results in the evolution of these variables along a stable trajectory that lies on an attractor.

The four-dimensional Hodgkin–Huxley equation is a low-dimensional dynamical system. By contrast, hundreds of state variables are required to describe a neuron, even if we only evaluate membrane voltage generation, and millions more are required if we consider ion and peptide concentrations and proteomic cascades. A brain area would be described by the dynamics of very many neurons and glia and by the dynamics of the connections among them. Fortunately, system trajectories in such a high-dimensional system will not fill the high-dimensional space but will be confined to the lower-dimensional subspaces of attractors, just as water flows along low-lying paths rather than spreading across an entire landscape. Indeed, the enormous dynamical complexity of the brain, like its structural complexity, would be unmanageable if it was not organized into subsystems. The existence of widespread distinct oscillatory frequencies in the electroencephalogram (EEG) suggests that dynamical subsystems are detectable. Hence, it has been proposed that the enormous dimensionality of the brain produces trajectories that lie in much lower-dimensional subspaces that can then be modelled by equivalent low-dimensional dynamical systems.

Following this hypothesis, low-dimensional mean-field or lumped models have been developed to simulate the dynamics of a large ensemble of neurons (the lump). Depending on the model, this neural lump is interpreted to be a minicolumn, a column, a Brodmann area, a thalamic nucleus, *et cetera*[81]. Most such models are based explicitly or loosely on Wilson and Cowan's 1972 model[82–85]. The neural lump of the Wilson–Cowan model has two state variables: excitable population firing and inhibitory population firing. Within a single lump of the model, excitatory and inhibitory populations interact to produce an oscillator — mathematically comparable to a mass bouncing on a spring — for which the two state variables are position and velocity. These state variables trade-off sinusoidally: the extreme position (fully stretched spring) is associated with zero velocity. Similarly, in the Wilson–Cowan model, excitation and inhibition trade off and so periods of high inhibition are associated with minimal excitation. Connecting Wilson–Cowan oscillators through their excitatory outputs leads to a system of coupled oscillators[58,82,86–91].

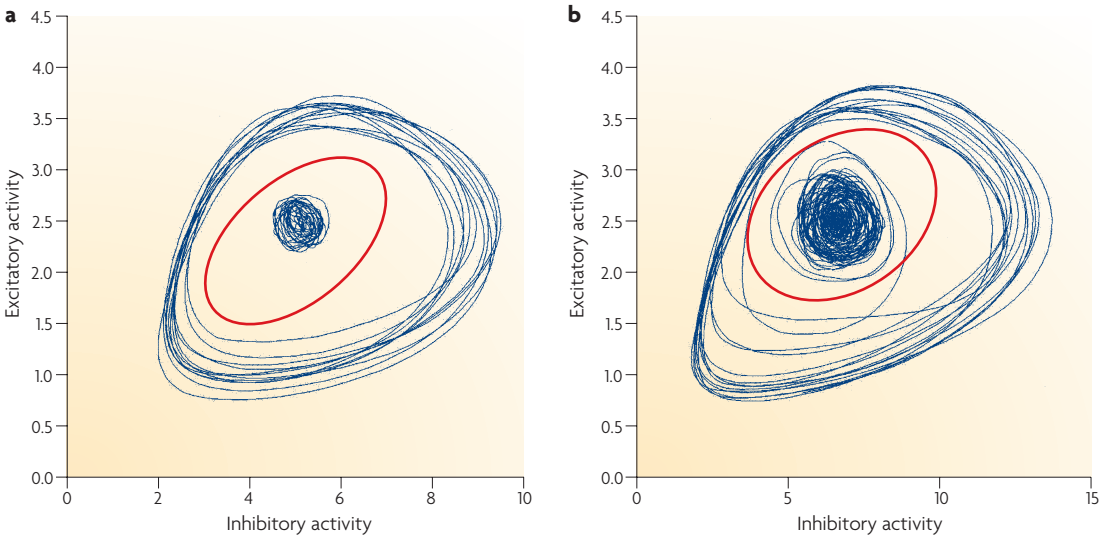

Figure 3 | **A lumped model of absence epilepsy.** Sample trajectories (blue lines) from normal (**a**) and epileptic (**b**) models projected onto a two-dimensional slice of state space. The axes are values of two state variables: cortical excitatory activity and cortical inhibitory activity. The red line is a separatrix separating two attractors. The attractors are not explicitly represented but can be inferred from the trajectories. In both cases normal activity is the inner trajectory and a seizure is the outer trajectory (with higher-amplitude activity). Note that the seizure attractor exists even for the normal model, corresponding to the fact that anyone can have a seizure under stress conditions (such as fever, ischaemia, hypoglycaemia or insomnia). However, the attractors are well separated in the normal model, and so random perturbations do not result in transitions. In the epileptic model, the attractors are closer and perturbations produce transitions to seizure. Figure modified, with permission, from REF. 97 © (2003) IEEE.

A lumped model of absence. Over the years, a series of epilepsy and seizure models have been based on variations of the Wilson–Cowan approach[92–96]. Because these models are low-dimensional, they are amenable to graphical explorations of their trajectories. FIGURE 3 shows a slice of state-variable space (called state space or phase space) in a model of absence epilepsy. An analogy would be looking down at a ball rolling in a broad-rimmed bowl. The ball can roll around on the rim (outer trajectories) as well as inside the bowl (central trajectories): the centre and rim of the bowl represent attractors. An outer trajectory is a seizure. In the normal model, in which the attractors are well-separated, it would take a lot of random activity (noise) to shift the system out of its normal attractor and into the pathological attractor. In the epileptic model, a parameter change (such as an increase in external drive or an alteration in intrinsic time constants) has deformed the attractors, expanding and lowering the 'energy barrier' between them. Thus, in this model, random transitions between attractors will occur more frequently, leading to seizures[97,98].

This deterministic model of absence epilepsy produces dynamics that suggest stochastic seizure causation: the attractors in the vulnerable individual lie so close together that minor perturbations can trigger a seizure. As they are randomly triggered, these seizures would not be predictable from the EEG — there is no pre-seizure state. The model suggests that some kinds of epilepsy will not be amenable to seizure prediction. However, triggering factors could still be identified and avoided[99,100].

A lumped model of MTLE. A different class of seizure transitions has been identified using a similar low-dimensional model applied to MTLE[101]. This model uses an archicortical rather than a thalamocortical organization and can successfully reproduce a variety of the patterns that are seen in patients (FIG. 4). FIGURE 4a compares patterns of activity from this lumped cortical model to patterns recorded from hippocampal depth electrodes in an epilepsy patient who was undergoing evaluation for surgery. The activity patterns in FIG. 4a were produced by the parameter sets illustrated in the two-dimensional slice of parameter space shown in FIG. 4b. Changes in activity patterns can be produced by changes in parameters that will deform existing attractors or produce new ones. A sequence of parameter transitions like those indicated by the arrow in FIG. 4b would cause passage from normal activity, through a pre-seizure state, into a seizure. In contrast to the case modelled in FIG. 3, such a seizure would be predictable: there is a defined pre-seizure state that could be detected.

Although I have emphasized the difference between state variables and parameters, it is important to note that the hypothetical movement in parameter space discussed above is itself a dynamic. In order to model these dynamics, it would be necessary to promote this inhibitory parameter to a state variable, one with far slower time constants than those of the existing state variables. In fact, the fast dynamics of brain activity are continually altered by the slower dynamics of synaptic and cellular plasticity[102]. Similarly, as I discuss in the next section, these dynamics are in turn altered by the still-slower

Lumped model
A model that approximates the activity of a large ensemble of neurons using a single-state variable that typically represents the proportion of neurons that are active at a given time.

Cortical minicolumn
A group of cortical cells that interact with each other more than they interact with neurons in neighbouring columns. Although columnar structure was originally identified physiologically as groups of neurons with shared properties, it has since been sought anatomically and variously identified as groups of 100–200 neurons (~30 μm across).

State space
The dimensionality of a dynamic system. The current state of the system can be described as a point in state-space. Also called phase space.

Parameter space
The m-dimensional space in which the parameters of a system can be defined as a single point.

dynamics of development, of cell growth and death, and of synaptic sprouting and pruning.

Detailed deterministic models: neuronal networks

Detailed neuronal modelling has been one of the most productive areas of neural modelling and of neural modelling applied to epilepsy. Unlike the lumped models described above, detailed neural models incorporate particulars of the nervous system; this should permit greater verisimilitude. However, this goal is limited by three factors. First, we do not know enough (particularly discouraging is the lack of a wiring diagram). Second, we do not have enough computer power. Third, a model generally needs to perform some simplification to be useful (see above). Detailed modelling is performed across a wide range of spatial scales, from single synapse to cortical column to whole brain[33,103]. The best-defined epilepsies (neurobiologically) are those associated with specific ion-channel abnormalities. Many anticonvulsants function in part by altering channel conductances or kinetics. Modelling has shown how alterations in channel dynamics (that is, alterations at the molecular level) can change neural firing patterns (at the cellular level)[104,105].

Much effort in detailed modelling has taken place at the network level, following pioneering studies of network activity in MTLE models[106–109]. Similarly, there has been considerable progress in modelling the thalamocortical interactions that give rise to absence seizures[110]. One notable success involved the computational prediction of activity entrainment into pathologic hypersynchronized oscillations at approximately 3 Hz[111–113]. Computational load generally limits the use of detailed models to depictions of seizures or of interictal events, rather than to the longer timescales that are required to directly model epilepsy. However, just as with the lumped MTLE model described above, detailed models can assume that slower dynamics have taken place without explicitly modelling them.

Connectivity predicts dynamics in the dentate gyrus. Owing to the prevalence of MTLE, the hippocampus has been a focus of basic investigation. The dentate gyrus (DG), and the hilus in particular, demonstrates a

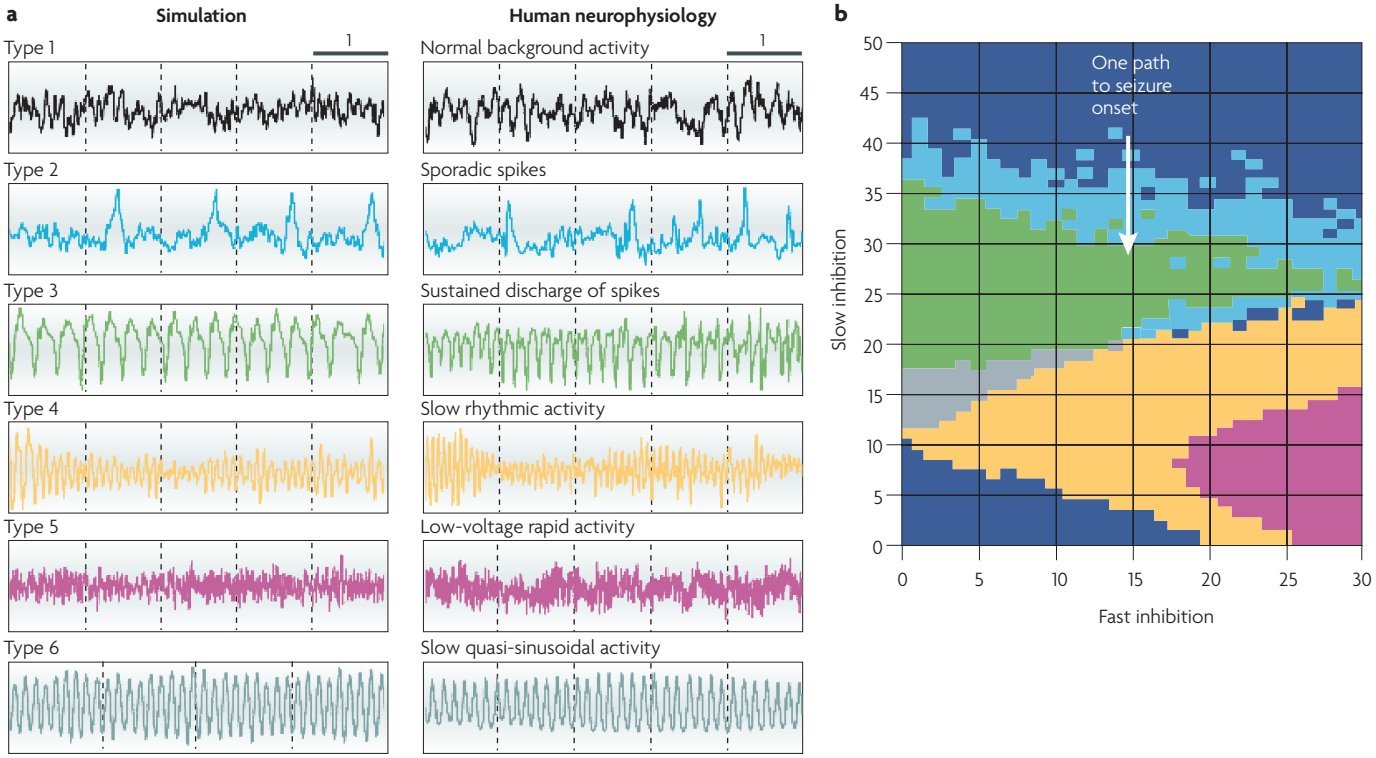

Figure 4 | **A lumped model of MTLE. a** | A simulated cortical electroencephalogram from a lumped model of excitatory and inhibitory interactions produced various activity patterns (left-hand series of plots) that are comparable to those that are seen in depth recordings from human patients (right-hand series of plots). Each of the colour-coded patterns is the result of a different location in a two-dimensional slice of parameter space (**b**). In the simulated traces, we are only seeing a single state variable (the excitatory activity); this variable is comparable to the *y* axis of the two-dimensional portrait in FIG. 3. Note that this single state variable is only the dimensional tip of the ten-dimensional state space that is used in this model: most of the interactions and transitions are hidden from view. **b** | Parameter space. The slow inhibitory parameter is shown on the *y* axis and the fast inhibitory parameter is shown on the *x* axis. One route from normal activity to a seizure is shown by the arrow: downward movement in parameter space from the top-most blue area (normal activity) to the green area (seizure). This movement represents a decrease in the parameter for slow (largely dendritic) inhibition. Hence, the model makes a specific prediction that a reduction in these inhibitory inputs could be responsible for transitions to the seizure. Figure adapted, with permission, from REF. 101 © (2002) Blackwell Science.

wide variety of alterations during epileptogenesis in both patients and animals[114–119]. The various effects include cell death with attendant synaptic pruning, and cell birth or axonal sprouting with addition of synapses. Excitatory sprouting might be on to excitatory cells, on to inhibitory cells, or on to both[120].

Several studies have focused on the consequences of axonal sprouting and cell death for hyperactivity in the dentate gyrus[121,122]. In a recent series of models, dynamic simulation was coupled with a database model and a formal graph model[123,124]. These interlocking static and dynamic models were used not only to understand and predict physiology, but also to highlight gaps in the anatomical record and make predictions about wiring[53,125,126]. The simulation showed that sprouting that led to the formation of additional excitatory–excitatory synapses led to long-duration activation in models that would otherwise show minimal activity beyond the initial stimulation period. However, maximum activation was seen at an intermediate level of pathology, involving both sprouting and hilar cell loss. Furthermore, although activity propagation was dependent on the presence of long-range excitatory mossy cells in the hilus, only relatively few mossy cells had to be present to sustain activity. These simulation results are in agreement with histological results that indicate that some mossy cells frequently survive in the sclerotic hippocampus of patients with MTLE.

Further analysis of the directed graph model suggested that an effect of the pathogenic process might be to make the network more 'small world'. Small-world networks could provide hubs to distribute seizure activity extensively, owing to their characteristic short path lengths between nodes[50,88,127]. The study suggested that sprouting might lead to a preponderance of such neuronal hubs owing to rewiring. These hubs could be produced by projections onto granule cells that have hilar basal dendrites[124].

A model of disexcitatory ictogenesis. Computer modelling is perhaps most useful, and certainly most provocative, when the emergent properties of a system are contrary to expectations[128]. For example, a long-held general model of epilepsy is that normal activity represents a homeostatic balance between excitation and inhibition, and that seizures represent a shift towards excessive excitation[129]. This general picture undoubtedly has some validity: many proconvulsants block inhibition or augment excitation. However, the notion of an excitation–inhibition balance is not always applicable. Absence seizures, for example, are dependent on inhibitory (hyperpolarizing) influences that are effectively excitatory in thalamocortical cells owing to this cell-type's burst rebound from hyperpolarization[130–134]. Inhibition has been shown to have various roles in other systems as well[135–137].

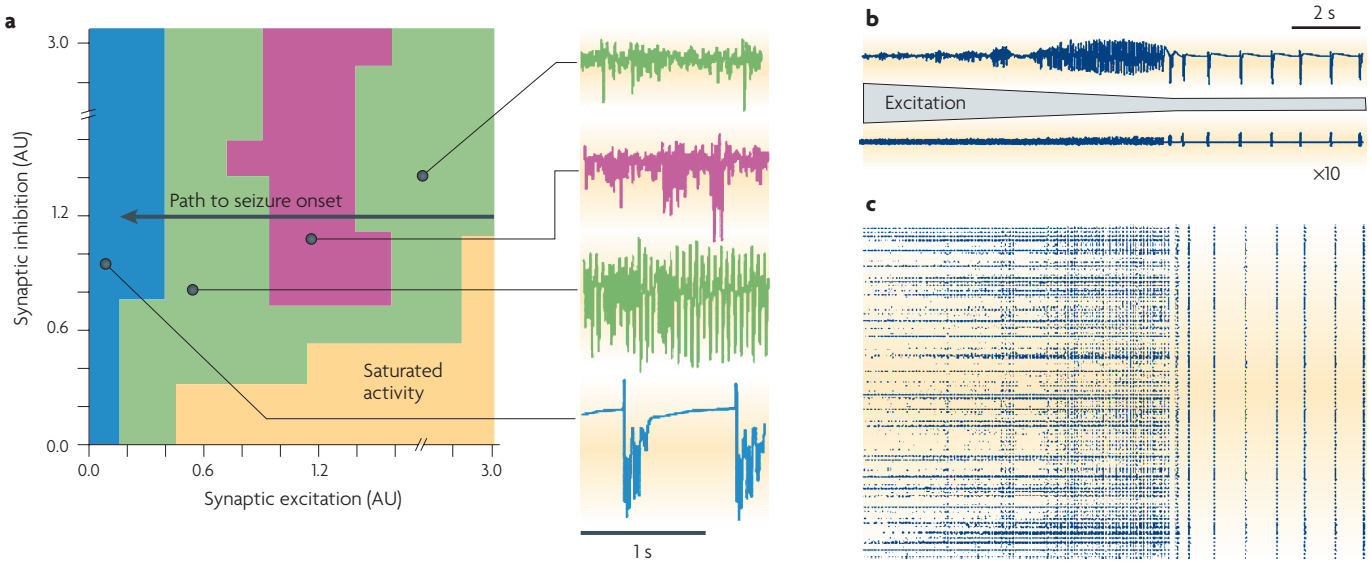

Figure 5 | **Reduction of excitatory strength leads to seizure in a detailed neocortical model.** Unlike in the lumped models in FIGS 2,3, individual neurons in this detailed neocortical model are represented by compartmental models: sections of dendrite and the soma are represented as separate resistor–capacitor circuits in parallel with active channels that are represented by Hodgkin–Huxley-type channel models set within the Hodgkin–Huxley parallel-conductance model. These individual compartments are then linked together with resistors that represent the axial resistance. Single neurons are simulated by performing numerical integration of the associated differential equations. Synaptic dynamics are also represented by differential equations. The model simulates 656 neurons of 4 types: regular-firing pyramidal cells, bursting pyramidal cells, basket cells and chandelier cells. **a** | Movement in parameter space from high to low excitation (represented by the arrow moving from right to left) leads from normal activity (top trace) to high-amplitude seizure-like bursting (bottom trace). Note that this result is different from that in FIG. 4. **b** | Bursting gradually develops as excitatory connectivity strength is gradually reduced. The top trace shows the field that is generated by excitatory cells and the bottom trace shows the field that is generated by inhibitory cell. The bottom trace has been magnified (×10) in the *y* direction. **c** | Raster plot of firing for individual superficial pyramidal cells in the network. Figure modified, with permission, from REF. 143 © (2005) IEEE.

Ictogenesis
The generation of a seizure (the ictus) by dynamical, cellular and synaptic processes.

With advances in computing, it is now possible to use supercomputers to run massive simulations, again with the hope of providing greater verisimilitude by more closely approximating the large numbers of cells in brain areas[103,106,138–142]. A recent series of studies used such models to explore coupling both between cortical layers and among neighbouring cortical columns or areas[143,144]. FIGURE 5 shows a path from normal activity to seizure in a format that is comparable to that of FIG. 4. However, the direction of change, and hence the conclusion, are entirely different. According to this detailed model, a reduction in excitation, rather than a reduction in inhibition, causes the transition to seizure. Spurred on by these paradoxical findings, the investigators subsequently demonstrated disexcitatory ictogenesis in mouse neocortical slices[143].

What at first seems to be contradiction between the detailed and the lumped models — one showing disinhibitory and the other showing disexcitatory ictogenesis — does not in fact represent a disagreement between models but instead again illustrates the complexity of seizure causality. A particular model, or a particular parameter range, is likely to be relevant to a particular seizure type or even to a particular patient. Referring back to FIG. 1, it is to be expected that the vast number of possible contributors to seizures and epilepsy allows for a number of surprising dynamical mechanisms. For example, it has been shown experimentally that combining two 'epilepsy genes' can produce an animal with reduced seizure propensity[28]. Multiple mechanisms will similarly coexist in patients. This explains, for example, how a particular pharmacotherapeutic treatment could treat one of the patient's seizure patterns while either not affecting or even exacerbating another seizure pattern[35,145,146].

A disadvantage of detailed modelling is that it is difficult to understand the dynamics in terms of specific attractors; we cannot visualize the high-dimensional space in which these attractors exist. This lack of detailed dynamical understanding reduces the explanatory power of the models by making attractor transitions opaque to our current visualization tools. A compensatory advantage of the detailed models is that one can look directly at single-cell firing (FIG. 5c) and compare it with intra- or extracellular recordings *in vivo* or in slice. An additional advantage is that one can test specific drug effects in the simulation by including explicit models of ion channels or synaptic mechanisms.

Future directions

This Review has shown that epilepsy and seizure modelling can be used at various levels to further our understanding of the various clinical aspects of the disorder: prognostication, prediction, classification, therapeutics and diagnosis. I have shown how a model of pediatric disease progression can be used to provide prognostic information for patient subgroups. It would be particularly valuable to directly connect models of this sort with taxonomic databases and ontologies, as well as with genetic databases, in order to correlate these various clinical sources with patient outcome. In this way, ontologic modelling and KDD can help us to develop new classifications and define syndromes and subsyndromes[37,38,43,147,148].

Successful seizure prediction will require a combination of further modelling and experimental work. Seizure prediction will not only permit the development of implantable seizure-termination devices, but also the development of devices that simply alert patients to periods of high seizure probability. However, as suggested by the absence-epilepsy model of FIG. 3, some seizure types are likely to have no pre-seizure state and be therefore unpredictable. We have seen how models can interface with seizure-prediction algorithms. Similarly, we could develop computer models that interact directly with ongoing clinical seizure monitoring; this would enable us to gradually form a model of a particular patient's seizures.

I have suggested that the multifactorial causation of epilepsy (exemplified in the river metaphor (FIG. 1)) can best be approached by computer models that can encapsulate the many conspiring and counteracting causes and mitigating or exacerbating influences. This complexity also extends to the therapeutic domain, as many drugs are noted to have multiple binding sites and multiple effects. This complexity of drug action has sometimes been downplayed by calling the drugs 'dirty', in the presumption that the additional binding is likely to be a cause of undesirable side effects whereas a single primary binding site is responsible for the therapeutic effect. However, in many cases dirtiness might be a critical aspect of drug efficacy[149–151]. The development of new anticonvulsant drugs will benefit from the modelling of such synergistic effects. Currently, rational pharmacotherapeutics is carried out by

Box 2 | **How modelling is done**

Compared with most subspecialty areas of neuroscience, computational modelling is notable for its accessibility, particularly given today's computer-literate scientific community. Whereas a neuroscientist or epileptologist would hardly expect to be able to casually pick up the technique of electron microscopy, he or she could spend a weekend learning and exploring a computer model. Most computational researchers are quite happy to share their computer code. Hundreds of models, including some of those discussed here, are available for immediate download at ModelDB[157]. This database provides runnable models producing one or more of the figures in a published modelling paper. It is a good starting point for further explorations. Several software packages are commonly used to run simulations. Most of the stochastic and low-dimensional models are done in Matlab, a commercial general-purpose engineering and simulation environment, or Octave, Matlab's free counterpart[158]. Low-dimensional deterministic models can also be run using XPPAuT, a freely available general-dynamical-system simulator[159]. Detailed computer models are generally run using specialized software, such as Neuron (a freely available general-neural-simulation system) and Genesis[160,161]. A variety of other neural simulators, that operate at various levels, are also available[162]. For a recent review, see REF. 163.

designing ligands for specific receptors. Rational pharmacotherapeutics will also be able to use detailed computer modelling to determine which receptors should be targeted together.

A major area of computational systems biology has not been discussed here: the dynamical simulation of genomics, proteomics and cellular physiomics (signal-transduction pathways) that permits the study of alterations at the cell-biology level[26,152]. This research has enormous importance for the synaptic and cellular plasticity that probably underlies many kinds of epilepsy. It has not been discussed here because little work in this area has thus far been applied to epilepsy[153].

An exciting aspect of computational neuroscience is its accessibility to researchers with widely differing backgrounds (BOX 2). It has recently been suggested that, "The application of systems biology to medical practice is the future of medicine." (REF. 41). With wide participation, advances in computer modelling, and clinical application of results, this prediction might be fulfilled early for epilepsy.

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DATABASES

ModelDB: http://senselab.med.yale.edu/modelDB
Hodgkin–Huxley equations | model applied to MTLE | model of absence epilepsy | Wilson and Cowan's 1972 model

FURTHER INFORMATION

William W. Lytton's homepage: http://it.neurosim.downstate.edu/
From Computer to Brain: http://www.springer.com/biomed/neuroscience/book/978-0-387-95528-5
Genesis: http://www.genesis-sim.org/GENESIS/
Matlab: http://www.mathworks.com
Neuron: http://www.neuron.yale.edu
Octave: http://www.gnu.org/software/octave
Task force on epilepsy classification and terminology: http://www.ilae-epilepsy.org/Visitors/Centre/ctf
XPPAuT: http://www.math.pitt.edu/~bard/xpp/xpp.html

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