Understanding and predicting epilepsy

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EPILEPSY

Epilepsy is the second most prevalent neurological disorder after migraine. It affects 1-2% of the world population. Epilepsy is a spectrum of disorders defined by the occurrence of epileptic seizures, which are characterized by the abnormal firing of large populations of neurons. Epilepsies can have a genetic component (as a direct cause or as risk factor) or can be triggered by a brain insult (including stroke, meningitis and brain trauma). After the initial insult, complex reorganizations occur in neuronal networks (epileptogenesis), ultimately favoring the emergence of spontaneous seizures [1]. Epilepsy is a dynamic process as the reorganization continues during one's life. Other brain regions may get involved, possibly invoking different mechanisms, requiring changes in medication. Seizures can be very difficult to control, and 30% of patients are drug-resistant. Epilepsy research thus faces two major challenges:

i) Understanding the basic mechanisms underlying seizure genesis. This is a key issue if one wants to design new therapeutic solutions to prevent the occurrence of seizures (in particular to treat drug-resistant patients) and if one wants to identify which brain regions produce seizures in a given patient (in particular to plan neurosurgery).

ii) Predicting seizures. If seizure control cannot be achieved, it is equally crucial to warn patients of incoming seizures. They could inform people around them and place themselves in safe conditions.

Despite decades of research, we do not really know how seizures start, propagate and terminate, and we still do not understand how a "normal" brain becomes "epileptic". Using

human tissue and experimental animal models, we learned that the molecular architecture of epileptogenic networks is considerably modified. Hundreds to thousands of proteins are up or down regulated in epilepsy. But this reorganization is so complex that we don't know how to interpret such amount of data, i.e. it is difficult to determine which of these modifications are causally related to seizure genesis and propagation. One way to make sense of it is to use a computational approach to identify key parameters. As will be developed below, such computational approach is not straightforward, and some guiding principles should be proposed.

Considerable efforts have been made to address the second challenge, predicting seizures. Numerous approaches/algorithms have been developed, but so far, none is successful enough for clinical use.

Why are breakthroughs so difficult to obtain in epilepsy research? Two main challenges need to be considered: 1) There are multiple possible mechanisms underlying seizure genesis and propagation; and 2) we over rely on one type of observation (electrophysiological recordings) to build our conceptual frameworks or theories. Historically, we have used electrophysiological signals as a gold standard, i.e. as objective markers of seizures. Electrophysiological signals are time-dependent fluctuations in field potential due to the movement of charged particles in the neuronal tissue. These fluctuations are a highly integrated signal as compared to the biological processes that gave rise to them. Arguably, the answers to our questions need to be investigated at the molecular scale, since brain activity is molecular by nature. To understand the nature of the problem, let's consider the classical example of the fluttering of a butterfly's wings that unleashes a storm. If weather scientists only have access to air temperature and pressure data, they may never be able to identify the cause of the storm. The analogy holds for seizures. The brain is a highly interconnected complex molecular system. Electrophysiological signals may hold some clue (i.e. key

molecular events may have an electrophysiological trace), but, so far, we don't really know what to look for.

Future progress may require accepting the multiplicity of solutions and focusing on molecular events. Theoretical studies clearly showed the complexity of the problem, and already provided important insights.

MODELING SEIZURES

Two broad types of modeling approaches are commonly used: detailed and lumped models [2]. Microscopic detailed models try to be as realistic as possible, including a maximum of biophysical details. Neurons can be modeled as multi-compartment structures, including a large variety of ionic and ionotropic channels with specific spatial distributions along the somato-dendritic tree. Roger Traub pioneered this approach, and as computational power increased, it has been possible to include an increasing number of neurons and parameters. The group of Ivan Soltesz is able to model a whole part of the hippocampus with 100,000s of neurons, using exquisite detailed network architecture. The caveat of this approach is the size of the parameter space. Many parameters have never been measured (e.g. the deactivation curve of ion channel X in the distal dendrite of interneuron type Y). They must be guessed from other values measured in other types of cells. Even if a given parameter has been determined, we must choose from a distribution of values measured experimentally, characterized by a mean and a standard deviation (measures of the same parameter in different experiments invariably lead to different results). Which value should be use, the mean, the median, or the extremes? When trying to understand how the simple rhythms could emerge in the stomatogastric ganglion network, Eve Marder faced the same challenge. The approach she took was to explore the whole parameter space. Each parameter could take a finite number of values, and she extracted all sets of parameters, which could produce the

same rhythm in silico as was observed in vivo. She demonstrated that there exist a huge number of parameter configurations, all giving rise to in vivo-like network activity [3]. The same concept can be extended to seizures in the temporal lobe. Although extremely time consuming, it would be particularly interesting to use "à-la-Marder" strategy, and determine which sets of parameters can give rise to seizure-like events (e.g. in a detailed model of the hippocampal network), and compare these sets to those giving rise to physiological rhythms (e.g. theta or gamma oscillations) in the same model. Perhaps certain parameters are functional "hubs", i.e. their modification would consistently lead to seizure genesis/propagation regardless of alterations in other parameters. Such predictions could then be tested experimentally. There is however a major difficulty to solve. In Eve Marder's work, the activity in the stomatogastric network can easily be described and quantified (she used a some well-established metrics: interburst frequency, intraburst frequency, refractory period etc.). Except for absence seizures, seizures with focal onset do not appear to follow general rules of organization. Hence, how can we accept as a seizure-like event, the activity generated in silico? Pure mathematical approaches may give us some clues.

Lumped (e.g. neural mass/field) models are based on the assumption that temporal and spatial averages are sufficient to characterize the dynamics of neuronal networks. They are more focused on general rules than on biophysical details. Hence, their predictive value is limited to general principles, since by nature they manage to reduce the size of the parameter space. However, the general rules thus obtained can be used as guiding principles for detailed models, as developed hereafter.

Most modeling approaches tried to reproduce seizure genesis/propagation by appropriate modifications of model parameters. Few attempted to understand the nature of seizure genesis/propagation. Clinicians have described many forms of epilepsies, and they have

underlined the difficulty that they may encounter to achieve seizure control in patients. Hence, it is generally assumed that seizures are very complex phenomena. But are they?

Two important clinical observations can give us some hint about the way we should phrase the problem:

i) Seizures are found in numerous neurological disorders, e.g. Alzheimer's disease, Huntington's disease, and autism. Why are seizures so common in other diseases?

ii) Any normal brain can be forced to have a seizure, for example, after an electroconvulsive shock. Hence, a seizure is a type of physiological activity; it is hardwired in neuronal networks.

SEIZURES ARE HARWIRED PHYSIOLOGICAL ACTIVITIES

Epileptic seizures can be triggered and recorded across species (from flies to Humans) and brain regions. Interestingly, seizures with focal onset share similar properties: the presence of fast oscillations and the occurrence of slower spike-and-wave discharges (Figure 1). Each type of activity occurs with a different time scale (frequency), fast and slow, respectively. The activity of neuronal networks can be represented by a time series expansion of the electrophysiological signals and described by state variables. Two state variables are sufficient to describe fast oscillations, and two other state variables are sufficient to describe slower spike-and-wave discharges. Since, by definition, seizures are a recurring phenomenon in epilepsy, it is possible to introduce a fifth state variable evolving on a very slow time scale, driving neuronal networks to seizure onset, controlling the seizure dynamics, and its offset. Such fifth variable allows the system to switch autonomously from control to seizure activity and from seizure activity back to control activity. Five state variables are thus sufficient to account for the properties of seizures with partial onset (i.e. dynamics and constituents in terms of fast oscillations and spike and wave discharges). The resulting model is called The

Epileptor [4], and its equations are shown on Figure 1. In the model, seizure onset and offset occur via bifurcations. When looking at the mechanisms of bursting, Eugene Izhikevich identified four possible bifurcations at bursting onset and four at bursting offset. There are thus 16 possible types of bursts. Generalizing this concept to seizures, The Epileptor equations correspond to one class of these 16, with saddle-node and homoclinic bifurcations at seizure onset and offset, respectively. These bifurcations were found across brain regions and non-human species, and in 83% of drug-resistant patients [4]. Interestingly, seizures triggered in "healthy" brains were characterized by the same bifurcations, supporting the universal nature of the model and the fact that seizures are endogenous brain activities. Topologically, when projected in three dimensions (i.e. using the first state variable describing fast oscillations, the first state variable describing the spike and wave discharge and the fifth very slow variable), a seizure with partial onset is a spiral on a cone (Figure 1), a very simple geometrical object.

Based on the work of Izhikevich, we predict that there are at least 16 types of seizures. Although 83% of seizures recorded in drug-resistant patients belong to the saddle node-homoclinic class, it will be important to identify which other classes are also represented. This is particularly essential to consider in terms of mechanistic insight. The Epileptor is a phenomenological model, i.e. it does not claim any biophysical relevance. However, it imposes strong constraints on the behavior of the network at seizure onset and offset. As mentioned above, there is no consensual definition of what a seizure should look like (in contrast to basic brain rhythms such as theta and gamma oscillations). In the absence of a well-defined metric, it is difficult to assess whether seizures obtained in silico bear any physiological relevance. The Epileptor shows that a "dynamic" metric in terms of bifurcations can be considered. When using a very detailed model (or even a lumped model) to study a specific type of seizure, the set of parameters must satisfy the properties of the bifurcations

(e.g. logarithmic slowing down of the activity for a homoclinic bifurcation at seizure offset for the main class of seizures measured in patients). This should greatly limit the size of the parameter space.

The Epileptor also provides a different approach to tackle seizure mechanisms. Since seizure onset occurs via a bifurcation, it means that the trajectories of brain activities need to cross a certain threshold (or barrier of energy). It can be argued that in order to understand how seizures start it is sufficient to identify the forces that drive the network over the threshold. It is equally important to determine the forces that drive the network back to a "normal" state at seizure offset. If such forces can be identified, specific interventions may be designed to prevent reaching seizure onset. Likewise, protocols could be designed to abort seizures as soon as they start, as successfully demonstrated with optogenetic approaches by the groups of John Huguenard, Dimitri Kullmann, and Ivan Solstesz. Finally, the other key concept is that of the threshold. It is important to assess the threshold of a given's individual (to assess their susceptibility to seizures). It is also essential to measure at which distance the brain trajectories are from the threshold when trying to devise ways to predict seizures. Such knowledge regarding driving forces and thresholds is proving very challenging to obtain. The difficulty stems from the multiplicity of possible forces and thresholds, which may be constitute the core reason why seizures may be so difficult to treat.

ALL ROADS LEAD TO SEIZURES

The key concept is that there are multiple different ways to cross multiple thresholds, always ending up with the same type of seizure (Figure 2). For example, overdoses or electroconvulsive shocks are external forces that can trigger similar forms of seizures in humans, yet their underlying biophysical mechanisms are totally different. In addition, the

sensitivity to these forces vary from one individual to the next, meaning that the thresholds related to these forces are specific to a given individual. We provided direct experimental evidence of the existence of multiple thresholds in a neuronal network [4]. Using the same hippocampus, we first triggered a seizure-like event by increasing the level of synaptic noise in the preparation. When the noise reached a critical value (stochastic resonance) a seizure-like event occurred. Returning to baseline conditions, we then increased the osmolarity, thereby triggering a second seizure-like event similar to the first one. In that case, there was no change in synaptic noise, as a different mechanism was involved in seizure crossing. Finally, when we combined individual subthreshold conditions for noise and osmolarity, we triggered a seizure-like event via a third pathway. These results demonstrate that multiple conditions (hence multiple mechanisms) can lead to the same seizures in the same preparation [4]. Despite the multiplicity of possibilities, the dynamics of seizures remains invariant. Therefore, there are multiple entry points to the seizure state; each characterized by its own threshold, hence its own underlying biophysical mechanisms. In a given patient, it is possible that different thresholds are weakened thus providing as many different seizure entry points. We can make the reasonable assumption that the modus operandi of antiepileptic drugs is to increase the threshold and/or to act negatively on the forces that drive the networks close to a threshold. Since current antiepileptic drugs cannot control all entry points, we can speculate that drug-resistance is due to the fact that there are too many possible entry points in some patients.

Theoretical models could play a determinant role here. Instead of using hypothesis-driven approaches (an imbalance between excitation and inhibition, a downregulation of a given ion channel, etc.), it would be important to run a systematic search for seizure thresholds (their nature, their location) in the network. Since we are dealing with a complex interacting system at the molecular level, such thresholds may be looked for in the main pathways that can have

major and widespread influence on network activity, such as metabolism, inflammatory response, ion homeostasis, and hormones. Such predictions may then be tested in experimental models (the data may already exist in the literature) or even in patients, which could lead to new therapeutical approaches. Taking a step in this direction complements the traditional electrophysiological approach with a molecular one. Yet, electrophysiology provides invaluable information. Many methods have been designed to extract the maximum of information from it.

ANALYZING ELECTROPHYSIOLOGICAL SIGNALS

In the clinic, electroencephalography is central for the diagnosis of epilepsy. It is essential when neurosurgery is the last remaining hope for patients with drug-resistant epilepsy. Neurosurgery is considered successful if patients become seizure-free or at least controlled with anti-epileptic drugs. Before attempting neurosurgery, it is necessary to precisely delineate the epileptogenic zone (EZ), i.e. the set of brain regions that are responsible for seizure genesis. Seizures are a network phenomenon, and the EZ is often made of multiple different brain regions. Seizures can thus originate from various regions in a given patient, and then propagate to another set of regions (the propagation network). The difficulty is to determine the exact extent of the EZ. In such a clinical context, this means unraveling seizure mechanisms in a patient-specific manner. If the EZ is not properly assessed, neurosurgery may fail, which happens in 30% of the cases on average. Since neurosurgery consists of removing parts of the brain, it is essential to remove only what is necessary, and thus limit possible subsequent functional deficits. Many patients cannot be operated on because their epileptogenic zone includes eloquent cortex (like motor and language cortex). Mapping the EZ can be a very difficult endeavor (as assessed by the failure rate). Clinicians use a number of modalities, including imaging methods, but the gold standard remains intracranial

electrophysiological (iEEG) recordings. This technique is the only one providing direct access to human brain activity in situ. Since it is not possible to place electrodes in every possible region, a number of sites are chosen before electrode implantation based on a first clinical assessment using non-invasive modalities (surface EEG, imaging). Patients are recorded during several days/weeks in order to measure a maximum of spontaneous seizures. Visual inspection of electrophysiological signals can give some hints of the possible size of the EZ. However, in many instances, it is difficult to determine whether a region belongs to the EZ or to the propagation zone (it is assumed that the propagation zone does not include regions from where the spontaneous seizures can emerge – seizures just pass through these regions).

Many computer-based analysis techniques have been developed to identify the EZ based on multisite iEEG recordings [5]. These techniques make use of various methods developed in the field of information processing. Usually, these methods try to unravel the relationships between the different signals (i.e. between the different recorded regions). For example, cross-correlation measures the similarity of two time series as a function of a time-lag. Coherence identifies significant frequency-domain correlation between the two time-series. Mutual information quantities show the shared information between two time series. The h2 method calculates nonlinear correlation coefficients. Transfer entropy measures the connectivity if the information of one time series can reduce the degree of uncertainty about future values of another.

However, there is no ideal method. Using computer-generated signals, for which the interdependency between the signals was known, a systematic test of 42 different methods demonstrated that all methods failed to correctly identify the relationships between signals [6]. In addition, all methods need the setting of some parameters (time lag, frequency band, etc.), which values cannot be known a priori [6]. This may explain why four different analysis

algorithms developed by four independent groups gave very different results regarding the evaluation of EZ when using the same clinical dataset [5].

Hence, despite the amount of efforts put in designing complex signal processing methods, there is no good solution available to clinicians to evaluate the EZ. Perhaps the main difficulty lies in the fact that there is no available ground truth to validate any of these methods. The validation either comes from the visual inspection by the clinicians and/or indirectly, because the removal of brain areas made the patient seizure-free. There is no known objective procedure to characterize the EZ. So far, the most reliable readout would be a decrease in surgery failure rate based on the predictions obtained from computer models.

Despite its caveats, signal processing can bring some deep insight into seizure mechanisms. However, the traditional spatio-temporal approach is favorable to start with. Here we define spatial as making use of all recording sites (including those performed in assumed "healthy" regions) and temporal as taking into account the dynamics of signals far from, close to, during, and after a seizure. Since we don't know where and when the markers of the EZ are to be found, it is important to consider all possible options. The same principles apply to seizure prediction.

SEIZURE PREDICTION, WHICH SIGNAL TO PROCESS?

Since seizure control cannot be achieved in 30% of patients, it would be very important to be able to predict incoming seizures, if only to provide patients with a warning signal. Seizures can be life threatening, and a warning signal would enable patients to inform people around them or give them enough time to insure their own safety. It is assumed that EEG signals contain some type of hidden information about incoming seizures. That is to say, with appropriate signal processing, one would be able to extract from the EEG the necessary predictive markers. After two decades of extensive work, and multiple forms of signal

processing applied to EEGs, the results are rather negative [7]. Computer models can be trained on specific datasets, but they fail when applied to different sets of patients [7]. One alternative solution is to train the algorithm on a specific patient during a certain time, and use this information to predict the incoming seizures in the same patient (personalized medicine). This strategy was used on a set of patients equipped with electrocorticography grids for long-term recordings and a wireless system to transfer EEG signals to a data processing unit [8]. After training the system during several weeks, the incoming seizures could be reasonably reliably detected provided that the detection threshold was maintained at a low value. But the major caveat was a high rate of false alarms [8]. Reliable seizure detection would open the way to closed loop system to stop seizures, e.g. with neurostimulation [9].

Perhaps the analysis of electrophysiological signals is not the best way to predict seizures and to understand the mechanisms underlying their genesis. The fact that clinicians and basic researchers focus on EEG signals has a historical origin, with the discovery that brain activity could be characterized by electrical signals. As mentioned above, EEG signals reflect a highly integrated flux of charged particles, mostly due to synaptic activity. Since a seizure can be objectively characterized at the EEG level, it was assumed that some changes in network activity would occur before the seizure. As developed above, it is possible to postulate the existence of a "force" driving neuronal networks toward seizure threshold [4]. The main characteristic of this force is to evolve on a very slow time scale (the fifth state variable in The Epileptor), which naturally points at slow molecular processes. The biophysical correlates of this slow variable remain unknown. But some have already been identified during seizures, including extracellular K+ and O2 concentrations and molecules linked to energy metabolism, like adenosine triphosphate (ATP) production [4]. It would be particularly interesting to monitor such molecular activities in vivo before, during and after seizures.

Since seizure crossing can occur at multiple locations, the "force", and hence its biophysical mechanisms, may vary from one seizure to the other, evolve in time as a function of environmental factors, or as the nature of the epilepsy changes during the patient's lifetime. These arguments may also explain why seizure prediction based on EEG signals has mostly failed, as its hidden assumption is that preictal states follow rules that are universal across patients and seizure types. Experimental evidence demonstrates the multiplicity of solutions, supporting the notion that the way networks approach seizure thresholds is not universal [4].

CONCLUSION

Epilepsy research has been conducted with the firm belief that magic bullets may be found to treat patients (with the ultimate drug), predict seizures (the key EEG biomarker) and identify the epileptogenic zone (the key algorithm). Perhaps, it is time to accept the complexity and multiplicity of solutions. The work of Eve Marder is instrumental in that respect. Her laboratory demonstrated rigorously that there exists a huge number of network configurations (or detailed molecular architectures) giving rise to exactly the same type of network activity [3]. Seizures being an activity endogenous to most neuronal networks, they are multiple ways to produce them. If the paths leading to seizures are very diverse in a given patient, their fingerprints may also be different. Perhaps the solution lies in the use of multimodal approaches, monitoring different paths/mechanisms simultaneously. This would require the development of new technological tools [10, 11], and conceptual approaches.

Figure 1: Principles of dynamics of seizures with focal onset. The bottom trace is the recording of a seizure in the hippocampus of a mouse. Two patterns are clearly apparent: fast discharges (or oscillations), and spike and wave discharges. The top left panel shows the equations of The Epileptor. The two state variables x1 and y1 describe the fast oscillations,

and x2 and y2 the spike and wave discharges. The z state variable leads the system to seizure onset, drives the seizure dynamics until its offset. As written, the equations predict a saddle node bifurcation at seizure onset, and a homoclinic bifurcation at seizure offset. These predictions were verified in various species, and brain regions, including in patients with different types of seizures with focal onset. Geometrically, seizures are spirals travelling on a cone (when projected in 3D).

Figure 2: Different paths/mechanisms can lead to the same type of seizure. Seizures are part of the landscape of possible brain activities; they are hardwired in neuronal networks from flies to humans. Multiple roads can lead to the same endpoint (the seizure). In humans, seizures can be triggered by alcohol abuse, meningitis, fever, light (a reflex epilepsy), stroke, overdosis, food poisoning and electroconvulsive shocks. Each path is characterized by a specific threshold. In the case of an established cause, e.g. food poisoning with domoic acid in mussels, domoic acid would act as a "force" driving the network above seizure threshold. Each path is also characterized by specific underlying mechanisms, e.g. domoic acic and fever are likely to act via very distinct mechanisms. When there is no obvious causal event, which is usually the case when seizures occur spontaneously, the trajectory may be very complex (orange line). From one seizure to the next, the trajectory is not necessarily the same. In that case, the underlying mechanisms would be different. Perhaps the complexity to treat epilepsy stems from such multiplicity of entry points and mechanisms.

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$$\dot{x}_1 = y_1 - f_1(x_1, x_2) - z + I_{rest1}$$

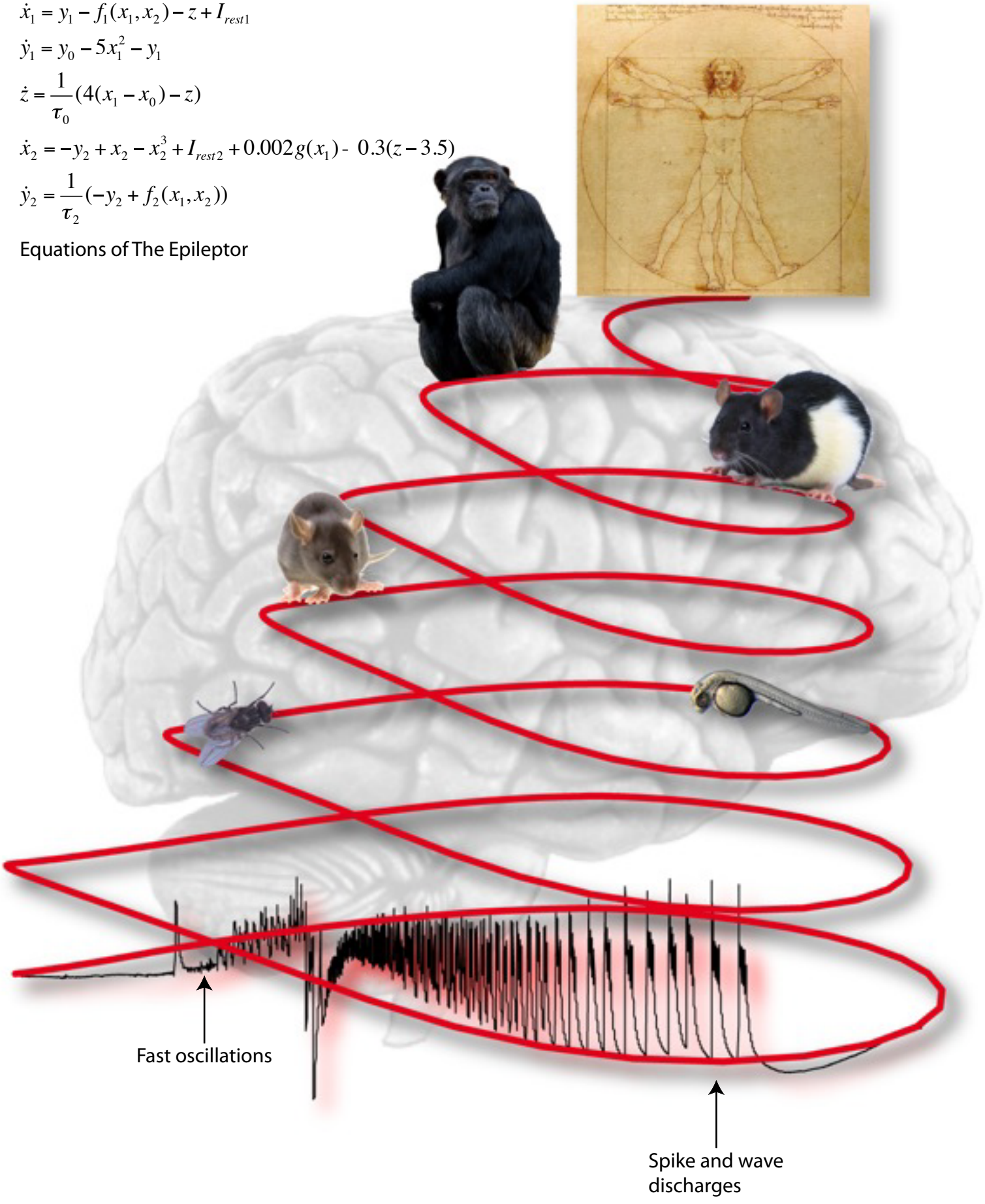
$$\dot{y}_1 = y_0 - 5x_1^2 - y_1$$

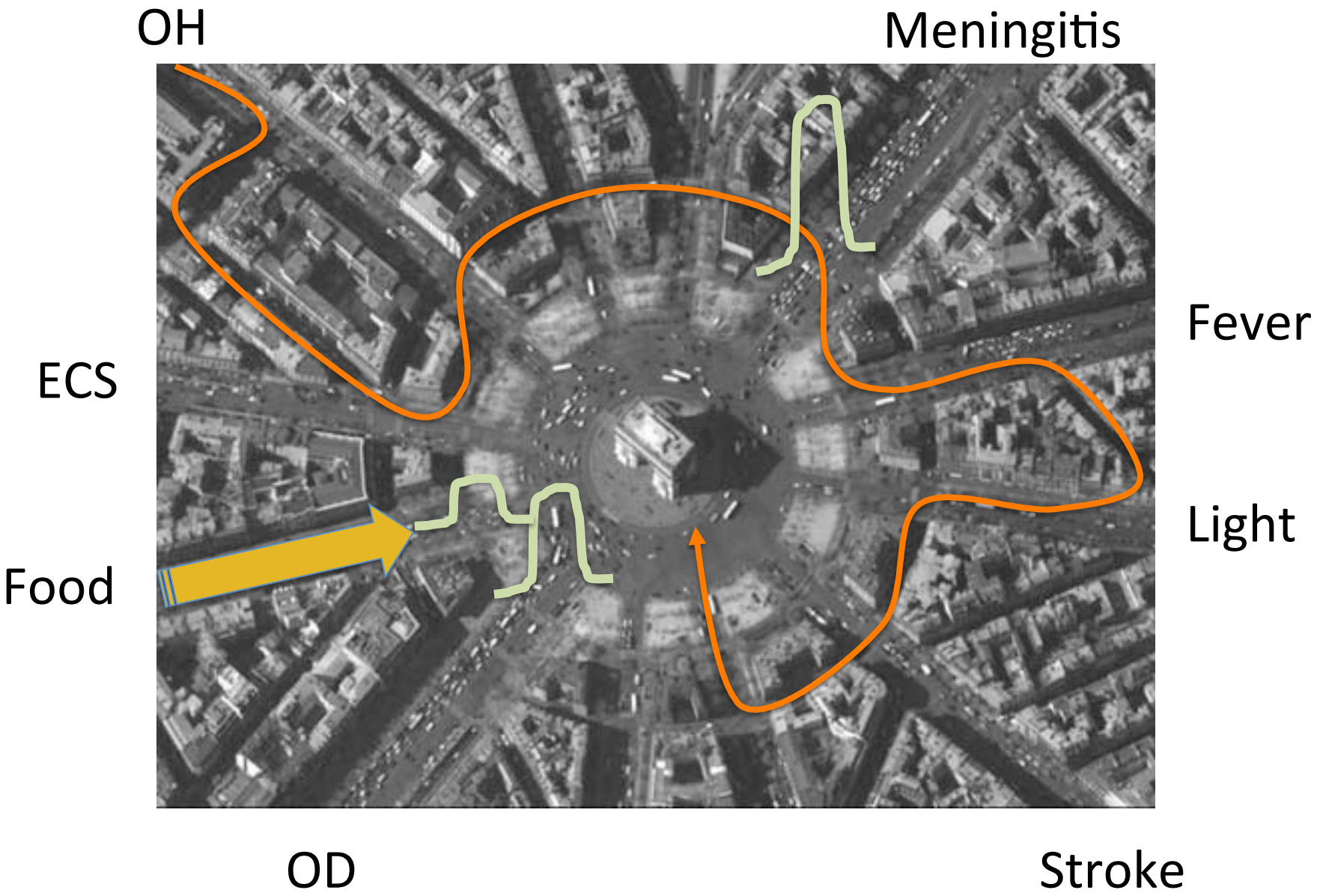
$$\dot{z} = \frac{1}{\tau_0}(4(x_1 - x_0) - z)$$

$$\dot{x}_2 = -y_2 + x_2 - x_2^3 + I_{rest2} + 0.002g(x_1) - 0.3(z - 3.5)$$

$$\dot{y}_2 = \frac{1}{\tau_2}(-y_2 + f_2(x_1, x_2))$$

Equations of The Epileptor




OH
Meningitis
ECS
Fever
Food
Light
OD
Stroke