Welcome to Novela’s series on Neurostimulation. We explore applications to pathologies like epilepsy, Parkinson’s disease and neuropsychiatric disorders. Our educational articles use simpler constructs when possible, rather than the precise scientific terminology.
A BRIEF OVERVIEW OF DEEP BRAIN STIMULATION

The placement of electrodes in very specific brain regions allows for a localized stimuli to be delivered. The greatest success of Deep Brain Stimulation has been at ameliorating Parkinsonian symptoms.
Non-invasive and invasive methods

The story of electrical stimulation of the nervous system has a long history that goes back to the times of the emperors Tiberius, Caligula and Claudius. Around 46 CE, Roman physician Scribonius Largus apparently used stingrays for the treatment of headaches, by touching the affected area with the animal.

Later, in the 11th century, the Indian physician Ibn-Sidah is said to have used torpedo fish applied on the forehead of epileptic patients to relieve their seizures.

Today these primitive interventions would be called non-invasive i.e. they are treatments that do not break the skin, as opposed to the invasive Deep Brain Stimulation (DBS), where electrodes have to be inserted into the tissue.

Non-invasive methods have the obvious advantage that surgery is not needed. However, the technology is currently immature. We seek non-invasive brain stimulation that has similar beneficial effects to those of Deep Brain Stimulation (DBS).

The modern history of electrical brain stimulation is considered to have started in the second half of the 1880’s by the pioneers E. Sciamanna, G.B. Duchenne de Boulogne and a few others.

Altering the activity of nerve cells

In brief, the main idea of brain cell networks is that cells in the nervous system activate one another in chains.

In primitive nervous systems like those of insects, one neuron activates another cell, and the chain from cell to cell can be mapped.

However, in advanced nervous systems, like our brains, it is more like a mass action. Many neuronal action potentials converge simultaneously on one neuron and many of its neighbors. This set of neurons then becomes synchronously active, generating action potentials that activate another set of many neurons downstream.

The neuronal activity is, mainly due to electrical fields, ions, moving in and out of the cell. This is what generates action potentials and synaptic transmission from one neuron to another. Information is then passed from one cell network to another.

Neurotransmitters carrying information

Neurotransmitter information is carried any time one cell network is bombarding another network with neurotransmitters,
propagating the activity to others.

This spread of potential differences gives rise to patterns of organized activity. They are recorded as a variety of oscillations which represent the activity of very large numbers of brain cells.

The characteristic pattern of nervous systems is that highly synchronous cellular activity effectively drives downstream cells, coordinating the activity in large cell ensembles. Therefore, any direct electrical field applied to the brain tissue will affect the mutual activation of cells.

In some cases, the activity will be significantly perturbed. For example, events like epileptic seizures, that require large synchronization of cellular activity, can be averted.

From these basic neurophysiological considerations, one can foresee that direct electrical stimulation can be used to prevent pathological brain activity, to control the brain.

**The most effective means to apply electric currents**

The placement of electrodes in very specific brain regions allows for a more localized stimuli to be delivered. The method is invasive, as surgery is needed to have electrodes inserted into the brain. Normally those wires will remain inside for the duration of the treatment, sometimes throughout the life of the patient.

Certainly, there are non-invasive methods to apply stimuli, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). The former uses a coil to deliver magnetic fields that generate electrical potentials in the brain tissue, and the latter uses constant low direct current delivered via electrodes on the head.

However, for the time being these operations lack enough specificity to be used in some pathologies. Additionally, the device that sends the magnetic fields cannot be carried easily on the head. On the other hand, the DBS devices (electrodes and accessories) are fully portable and can be inserted deep into the tissue.

A current area of great interest in neuroscience is the possibility that DBS offers to change those collective cellular activity patterns. That enables altering cellular behavior and stopping pathological manifestations of the brain activity in incidences like epileptic seizures or Parkinsonian tremors.

Perhaps the greatest success of DBS has been at ameliorating Parkinsonian symptoms. Interested readers can review
several videos available on the Internet
the almost immediate reduction of tremor
after the DBS device is turned on.
DBS has been applied to a variety of
pathologies, even though some applications
are still in their infancy. Examples include
the treatment of psychiatric disorders like
depression, addiction, obsessive-compulsive
disorder, anorexia nervosa, and Tourette’s.
To those interested in the non-invasive
methods (TMS and tDCS) in the treatment
of addiction, the review by Feil and Zangen
(2010) is recommended.

The future of neurostimulation
in psychiatry

While some reasonable progress has been
made with DBS in epilepsy and Parkinson’s
disease, it is the neurostimulation meth-
ods in psychiatry that will probably revo-
lutionize the field.

The history of medical treatments imposed
on neuropsychiatric patients starts with
staggeringly cruel — at least by our
current standards— therapies, like
castration, ablative neurosurgery and its
old predecessor of trepanation (pictorially
represented in the 16th century painting
by H. Bosch “The cure of folly”), cerebral
diathermia (electrically induced heat), and
treatments using compounds like insulin
or other hormones, and lobotomy.

There is still today some psychosurgery
being performed, but the advances in
neuromodulation is paving the way
towards non-invasive, and thus gentler,
treatments which are based on the general
idea of changing the electrical activity
in the nervous system.

Nevertheless, as aforementioned, we are
still in a time where non-invasive
neuromodulation is at its infancy. Today
most of these therapies still rely on the
implantation of electrodes in brain tissue.
For a recent and short perspective on
electrical stimulation of the psychopathic
brain, one can read Canavero (2014).

However, most of the present
perturbations of brain dynamics use a
rather brute-force approach, as the
current deep brain stimulation techniques
are mostly blind to the intrinsic brain
dynamics. Because we lack deep
understanding of brain dynamics, it is
relatively unknown what the effects may
be after disrupting one neural activity
pattern that becomes another.

We seek an alternative method to this
trial-and-error approach. A manner that
considers neuronal dynamics in order
to obtain the DBS protocol for a specific
pathological condition in a way that a
more efficient treatment is achieved.
There are some problematic aspects of DBS such as a succession of on and off episodes which results in having the device stimulating the brain almost all the time. This reduces battery life and can cause side-effects of the stimuli, such as anxiety, mania or a decline in word fluency. It should be noted, however, that the DBS side effects are few and much more tolerable than those caused by medications.

**Brain stimulation on-demand**

To circumvent the DBS side effects, protocols that trigger the stimulation on-demand are being developed.

The name On-Demand Stimulation refers to the general idea is that aberrant brain activity patterns can be perturbed — abolished, or “normalized”— by the application of precisely timed intracerebral and localized current stimulation.

The stimulation on-demand, also known by other names like closed-loop, feedback or responsive stimulation, has certain advantages over continuous stimulation of brain tissue. Among the benefits are longer battery life of the device (since it is used only when needed) and fewer side effects.

Great advances in detecting abnormal patterns of brain cellular collective activity associated with neurological and psychiatric disorders have been achieved. This encourages to use these discoveries to trigger the feedback stimulation.

**How can deep brain stimulation help?**

Whether it is closed-loop or continuous/intermittent stimulation protocols, all DBS procedures seem to work to some extent. However, a complex system like the nervous system precludes the finding of one technique of wide, general application.

This should not be a problem though. There is no reason why specific methods could not be tailored for each patient in the rapidly emerging field of personalized medicine.

And indeed, there is a patient-individual approach using electrodes manufactured by Novela Neurotech. The method has shown to be very efficient at arresting seizure generation in a rodent model of epilepsy.

Several years of research was needed to unravel some features of the neural dynamics of epileptiform activity, before the DBS protocol was designed and applied to the rats experiencing seizures.

The use of this informed approach to stimulate the brain still needs some careful
study of the neural dynamics, though. The combination of the DBS hardware and software with the **deep knowledge of brain dynamics** could allow very efficient treatment of neuropsychiatric syndromes. This field of **Dynamiceuticals** is an extension of the old field of **Pharma-ceuticals** and the more modern field of **Electroceuticals**.

**Dynamiceuticals: The next stage in personalized medicine**

The name Dynamiceuticals indicates the importance of knowing the intrinsic dynamics of the organ and pathology in question. It does not need to be the brain, it can be applied to almost any other system.

The miniaturization trend of electronic materials has fostered a vast interest in DBS coupled with **microdevices** that are able to record and analyze on-line brain activity. The current developments are starting to sound fantastic – even beyond science-fiction!

Large-Area Electronics is an example of new ways of manufacturing electronics. Their **flexible, printable and organic electronic materials** could support distributed intelligence based on printable logic circuits.

Not too far in the future, these advances, added to the novel organic electronics that can almost “fuse” with cell membranes, herald what can be considered a revolution in the brain-computer interface.

The emerging field of neurostimulation is growing so rapidly that soon the fiction will become the science.

We began with a broad overview of the field. Our next installments will present more specific applications to different syndromes and the approaches to design DBS protocols.
Epilepsy I

Part one of the article on epilepsy reminds us that in spite of antiepileptic drugs, about 30% of patients still have pharmaco-resistant seizures.
Reducing or halting seizures by brief direct electrical stimulation

In spite of the efforts of combinatorial chemistry and high throughput screening in the design of new antiepileptic drugs, about 30% of patients still have pharmaco-resistant seizures.

These patients are candidates for Deep Brain Stimulation (DBS), or other alternative treatments like Electroconvulsive Therapy (ECT)—which, paradoxically, promoting hyperexcitability of the brain using ECT reduces seizure frequency. We will explain why in one of our following blogs—vagal nerve stimulation (VNS), ketogenic diet and others...

Therefore, the somewhat limited success in the pharmacological treatment of epileptic syndromes has aroused an increasing interest in the possibility of stopping seizures by brief direct electrical stimulation of specific brain areas using DBS.

The idea substantiating the possible success of electrical perturbations at preventing seizures—or, if not stopping them at least shortening the ictal events—is based on the assumption that if the dynamics of the presumed abnormal synchrony that characterizes these paroxysms is perturbed by stimulations, then the ictus may not occur at all, or is forced to stop if already initiated.

We should note that one thing is to stop seizures, another to cure epilepsy.

Reducing or halting seizures may not resolve the underlying neurophysiological abnormality that results in the syndrome of epilepsy, of which seizures represent just one manifestation.

Having said this, however, stopping seizure occurrence will be undoubtedly beneficial because these events represent a most disabling manifestation of the epileptic condition.

So, using electrical means to stop ictal events may not cure the syndrome but it will make the patient’s life easier.

Experimental efforts to alter epileptiform activity by direct electrical stimulation date back to the mid 1950s, when it was shown that cerebellum stimulation shortened electroshock-induced seizures.

This led to the implantation of cerebellar stimulators in epilepsy patients, and some promising results were reported. (Readers are encouraged to consult chapter 3 of ‘The Brain-Behaviour Continuum’ / World Scientific.)

In the late 1960s, headsets with earphones were used to monitor electrical activity...
of the brain (EEG). These headsets, that triggered a loud noise in the contralateral ear, were tried on patients, reporting success in just a number of them.

Thus, we can see that a variety of non-specific perturbations seem to halt, transiently, paroxysmal activity. And perhaps at the summit of non-specificity, we find the report by Penfield and Jasper in 1954, where a spike-and-wave discharge (a type of seizure) was suppressed both by electrical stimulation of the neocortex and by a cognitive task.

In the task the patient was forced to concentrate on a problem; resulting in the ictus stopping for a while until the patient found the solution to the problem (FIGURE 1, from Penfield and Jasper, 1954).

Animal models of epilepsy

The fact that very non-specific stimuli can arrest seizures can be seen in animal models of epilepsy too.

As a comparison to the above results in patients, the next figure shows the arrest of a seizure in two rats (rat 1 and rat 2), that occurs when the experimenter (yours truly) claps his hands. The recording of rat 3 does not show any seizure but is presented because the artefact associated with hand clasping is clearly visible.

Notice too that the seizure resumes after ~1 second.

These figures demonstrate that one does not need much to stop seizures. Indeed, some patients know when they are about to have a seizure and have learned a response (like touching a part of their body) to stop it.

Some seizures are difficult or impossible to stop once they start. This is why it is important to stop the generation of the ictus. These methods that attempt to halt
seizure generation by stimulating the brain just ahead of an impending ictus are known generally as closed-loop, or on-demand, DBS. They will be commented in a future blog, as these techniques are currently the main interest.

**Vagus nerve stimulation (VNS)**

A diversity of brain areas (or the nervous system) have been the targets for neurostimulation. The following list shows some of these brain (or others outside the brain) regions where electrodes have been placed.

![Regions of the brain](image)

Apparentely, it all started based on the observations that vagal stimulation desynchronized the EEG of the cat. VNS cannot be called DBS because the electrodes are not implanted into the brain, rather it is the vagus nerve, outside the brain, that stimulated.

But the vagus nerve is connected to many brain areas. Hence the neuroanatomical bases for possible VNS effects have been proposed to be a direct effect via nucleus tractus solitarii projections to the medulla, cerebellum, locus coeruleus, hypothalamus, thalamus, amygdala, hippocampus, cingulate gyrus and somatosensory cortex (see figure *Regions of the brain*).

As one can see, stimulating the vagus stimulates almost half of the brain! There could be other indirect effects acting via the reticular activating system... so now the brain stimulation would be almost complete!

It was also studied in dogs with refractory epilepsy, but the results were unclear, although some decrease in seizures experienced by the animals was found during the last 4 weeks of the treatment (Muñana et al., 2002).

More than 18,000 patients have been treated worldwide with this method of Vagus Nerve Stimulation (VNS).
In fact, after battery depletion (and thus the device would not operate), some patients continued to experience very few seizures. Does this mean we are witnessing a placebo effect?

The concept of neuroplasticity is globally accepted, and DBS, VNS, and neurostimulation in general act by changing this neuroplasticity.

However, nobody said that the stimuli to cause this plasticity have to come from the outside. It could come from the inside, from the brain itself. The celebrated placebo effect is a most interesting phenomenon. The internal brain dynamics may be at work here self-altering its activity.

We have already seen above in the figure the result of the Penfield’s “cognitive-based” trick to stop seizures: the brain itself is perturbing its own dynamics, arresting the paroxysmal discharge while occupied in solving a problem. There are other psychological methods (Schmid-Schönbein, 1998) that can be considered as cognitive-based approaches.
As in the case of VNS, some controversies have appeared in the intracerebral stimulation using DBS. But the fact is that, one way or another, direct current stimulation of nervous tissue works at stopping seizures.

**What can we learn from these results?**

Considering the wide variety of neurostimulation targets and protocols for the electrical stimulation that have been used, and as well the efficacy of pharmacological medications with such a variety of actions, putting all together seems to suggest that being too specific may not be the best strategy to treat epilepsy.

It is conceivable that the aforementioned drugs or electrical therapies are efficacious due to their wide-spectrum actions (recall the aforementioned wide action brain arousal after the vagus nerve is stimulated), rather than operating via one specific action.

A possible answer to the question of why there is such a success in a majority of patients (~70%) with pharmacological therapy rests in the many actions of the drugs, which, as a result, alter significantly the brain state space dynamics.

The more parameters are perturbed, the more likely the neural dynamics is to change.

To understand the neurophysiological basis of DBS and related methods, we need some knowledge of how the nervous system functions.

Our previous article already presented some basic notions. The next will present a few more ideas that will help understand the reasons for the possible success of DBS in epilepsy, Parkinson’s disease, and other neuropsychiatric syndromes.
Part two of the article on epilepsy states that seizure anticipation would stop seizures – but then asks: “Are ictal events really predictable?”
A THERAPY BUT NOT A CURE

The previous article was devoted to present general approaches to neurostimulation to treat epilepsy (epileptiform activity).

Now we will focus on Deep Brain Stimulation (DBS) to stop seizures.

As mentioned in the last blog, it is important to realize, that DBS is a therapy to decrease seizures, but not to cure epilepsy.

Epilepsy is the name given to the condition characterized by recurrent seizures. Seizures are just one manifestation of the abnormal epileptic brain, although the most noticeable.

For a description of the diverse epilepsies, see Perez Velazquez and Wennberg, 2004.

The advantages of high level phenomena: neural synchronization

Let us recall another very basic aspect of nervous system function which was explained in the first blog: the functioning of brain cell networks relies on mutual activations of the constituent cells.

(See paragraph ALTERING THE ACTIVITY OF NERVE CELLS).

The principal feature of the cellular activity in the nervous system is that of collective activity that results from cells activating one another in chains. These are mainly neurons but, to some extent, glial cells too regulate neuronal activity.

It is like mass action. Many neurons in one network fire action potentials with high degree of synchrony. That activates a connected set of neurons in a downstream network. Thus we see that synchronization of action potential firing is fundamental for proper brain function.

Basic notions of brains activity and the importance of synchrony are expounded in some chapters in Perez Velazquez & Frantseva (2011).

The fact that synchrony of cellular activity is crucial gives us a chance to alter it by direct electrical stimulation of brain tissue. This is the basis of DBS.

The fact that seizures represent a network phenomenon implies that it may not be
crucial to place the stimulating electrodes in the focus (the brain region where seizures start is known as the focus). Instead, it may be enough to place them in another area that is active during the ictus i.e. seizure.

Here the electrical stimuli can break the chain and make the ictus halt. Nevertheless, normally it is the focus the brain region that is targeted by the neurosurgeon implanting the electrodes or removing tissue.

It is also an advantage that disparate microscopic events will lead to similar macroscopic patterns. In this case the “patterns” are the seizures.

This may be a disadvantage for pharmacological treatments because the distinct microscopic events (molecules) that cause seizures in different patients will have to be treated with the adequate pharmacological therapy. However, for DBS this is irrelevant. Regardless of the molecular/genetic abnormalities, the important thing is, that there are highly synchronous events which underlie the ictus, and that the electrical pulses can suppress such abnormal high synchrony.

(Those highly synchronous events are mainly firing of neuronal action potentials but, concomitant with this, there are also other related neurophysiological phenomena that display synchronicity.)

The dynamical dream in epilepsy therapy

The most widely used DBS protocol is the basically continuous intermittent stimulation. This was explained in the first article “Brief overview of deep brain stimulation” (paragraph HOW CAN DEEP BRAIN STIMULATION HELP?).

In the article it was mentioned that this is a rather brute-force, trial-and-error approach that is blind to the intrinsic brain dynamics.

This ignorance is a bit dangerous because lacking a deep understanding of brain dynamics, and how it changes after DBS, may result in pernicious side-effects.

These DBS methods, that operate almost continuously, are generally termed open-loop protocols.

On the other hand, the “dynamical dream” in this field is the implementation of minimal perturbations. This means that a precisely timed brief stimulation with low frequencies and intensities would be used to stop the transition to the ictal event (Perez Velazquez and Wennberg, 2004).

Some understanding of the neural dynamics leading to seizures is needed to achieve that dynamical dream. Applying a short duration stimulus (say, a current pulse of a few seconds instead of minutes
or hours) requires knowing somewhat accurately, when an ictal event will appear.

The reason that a stimulation is more efficient, if given just before the ictus, is because ictal events are considered dynamical bifurcations.

As physics teaches us, systems are very sensitive to perturbations just at the moment ahead of the bifurcation. Therefore, if you want to alter brain activity with minimal effort, you should try to apply the perturbation – DBS, or any other means at hand – just ahead of the bifurcation point.

In the article Epilepsy 1 it was mentioned that some patients know when they are about to have a seizure and have learnt an action that will stop it.

Dynamical system theory

Allow me a brief digression into dynamical system theory.

In simple words, a dynamical bifurcation is a qualitative change in dynamics of a phenomenon.

Some research indicate that, in the nervous system, fluctuations in synchrony occur via dynamical bifurcations.

Indeed, the existence of bifurcations in brain activity during epilepsy has been obtained in vivo (Perez Velazquez et al., 2003).

“In vivo”
Latin for “within the living”

“In vitro”
Latin for “within the glass”

These dynamical bifurcations create patterns of organised neuronal activity. It is this organised activity that is the fundamental for a proper, healthy brain information processing.

In seizures you find high cellular synchrony with little variability in the configurations of connections among diverse brain regions. Hence it is not good for sensorimotor processing, and therefore, loss of awareness is common during seizures.

There is an extensive literature suggesting that variability in brain activity is associated with good health—not only in neurophysiology, but also in cardiac activity, hormonal concentrations etc... Variability makes you healthy!
Now, armed with the knowledge that the best moment to perturb the brain dynamics leading to the seizure is just before the impending ictus, then, to apply the DBS at that moment we have to know with certain accuracy, when the ictus will materialise.

This is the realm of a very popular field, and some scientists prefer to use one term rather than the other: seizure prediction, or anticipation, or forecast. However, for our purposes—we need to know when the seizure will appear—let’s assume all these words mean the same.

On seizure prediction

Implementing the aforementioned dynamical dream (closed-loop DBS) starts with anticipating an impending ictus. It is the basis of a personalized approach to seizure control.

I have termed it dynamicceptual approach (Perez Velazquez, 2017).

Later on, I will describe our own studies. In those studies, we used electrodes manufactured by Novela, on a feedback— or closed-loop—DBS protocol. The “predictor” of seizures was synchronization (Salam et al., 2015).

Trends in synchronization among neuronal networks have been investigated for quite some time as a possible indicator of approaching ictal periods. Particularly, differences in the phase of the recorded brain signals have been scrutinised.

However, a variable number of results can be found in the literature. Some studies have described a decrease in phase synchronization during the pre-ictal period, just before the seizure (Mormann et al., 2000, 2003; Le van Quyen et al., 2001, Perez Velazquez et al., 2011).

Meanwhile, other studies reported an enhancement in local synchrony (van Putten, 2003), and still others found no clear trend in synchrony patterns.

More importantly, some studies found trends in the spatio-temporal characteristics of synchrony, that were unique for each patient (Schevon et al., 2007). This emphasises that a personalised approach is needed.

But the field of seizure prediction has had a long history, and recently, it has been investigated with an unparalleled enthusiasm, within the field of the dynamics of epilepsy.
Nevertheless, already in the 1970s, McDonnell Douglas Astronautics Co. funded projects on seizure predictability from EEG recordings. These projects were abandoned, due to variable outcomes across patients—a first indication of what was to come.

The end result of many studies is that, presently, a host of seizure prediction algorithms exist. The number of such algorithms is probably even more than 30 (see figure 1 in Le van Quyen et al., 2001, for the state of affairs at the turn of the century).

Some of these algorithms have been reviewed in many publications, e.g. Litt and Lehnertz, (2002), Ebersole (2005), Alotaiby et al. (2014). These methods all seem to work to some extent. The prediction time windows range from a few minutes to hours.

As aforementioned, the variables used in the creation of these algorithms are quite a few: from variation in synchrony patterns to complexity measures and correlation integrals (Lerner, 1996).

Failed attempts to anticipate seizures have been reported in Aschenbrenner-Scheibe et al. (2003) and Harrison et al. (2005), to cite a few. Such negative results are almost always related to the generality of the validity of the different methods for all epileptic patients.

However, whereas there is no one general algorithm applicable to all patients, the vast majority of algorithms work in specific cases. Therefore, we can say that nearly all seizure-prediction algorithms succeed, at least to some extent – but only in certain cases.

The question is whether a general seizure-prediction rule, that would anticipate seizure occurrence in the immense majority of epileptic cases, can be found. Our contention is that, most likely, not.

As an illustration, let’s look at one variable that was thought could be of value for seizure prediction. That is, possible changes in synchronization before the ictal events.

In fact, synchrony does seem to change as the ictus approaches, but it is patient-specific, as reported by Aarabi et al. (2008). The synchrony increases in 63% of seizures during a presumed “pre-ictal” state, and decreases in 31% of the cases studied.
Perez Velazquez et al. (2007) described, based on MEG recordings, phase synchrony decreases before (and after) seizures in restricted cortical areas.

In other words, depending on what MEG sensors were taken to be analysed, a change would be appreciable or not. Finally, Schevon et al. (2007) found that the variation in synchrony was unique to each patient, and Winterhalder et al. (2006) reported that 50% of the patients showed a trend, either increase or decrease in synchrony.

These authors judiciously recommend that “the prediction methods [...] have to be determined for each patient individually”.

In all these discussions on seizure prediction something seems to be taken for granted: the predictability of ictal events. But, are seizures really predictable? (Bahar, 2006). Within the framework of brain multistable/metastable phenomena, a fundamental role of noise can be expected.

The result of noise-induced transitions in brain activity may lead to unpredictability of brain states.

**Multistable Perception**

perceptual phenomena with unpredictable sequences of spontaneous changes.

In addition, the presence of bifurcations and critical states in brain dynamics furnishes another reservation regarding the possible predictability.

Nevertheless, to end this section on seizure anticipation, let us say that it is very probable that for each patient there is an algorithm that will predict upcoming seizures. It is all a matter of investigating each patient’s brain dynamics. That is, a personalised approach.
Part three of the article on epilepsy focuses on the control of seizures. When to stimulate? For how long to stimulate? Where to stimulate—is the epileptic focus known?
From predicting seizures to controlling them

The aberrant neural synchronization results in epileptic seizures. The previous article discussed the necessary steps to achieve the “dynamical dream” of controlling these seizures: firstly, anticipating when the ictal event will occur, and secondly, sending a precisely timed, short electrical stimulation (Deep Brain Stimulation, DBS) to stop the abnormal synchrony pattern.

In this article, we will focus on the control of seizures. The attempt at stopping seizures is in reality an introduction, a precursor if you will, to the control of brain activity using electrical signals.

The relative success in Parkinson disease (will be a topic of a future blog) and epilepsy heralds a future—a future when brain control by electrical methods can be employed in a variety of scenarios.

Some of these scenarios still belong to science fiction, but fiction is becoming reality in a number of applications.

Thus, neurostimulation is used today not only in neurological pathologies but also to potentiate memory (Titiz, et al. 2017; Meisenhelter and Jobst, 2018).

In fact, there is an International Neuromodulation Society INS (www.neuromodulation.com), a non-profit group dedicated to the scientific development and awareness of neuromodulation. Only time will tell what may occur in the future. Now, let’s concentrate on the control of epileptic activity.

“The richness of out-of-equilibrium systems lies in the multiplicity of mechanisms generating similar behaviors.”


When to stimulate?

The start of seizures represent dynamical bifurcations i.e. qualitative change in dynamics. (A bifurcation occurs when a small change in the parameters of a system causes a sudden qualitative change in its behavior.)

Therefore, the start of seizures offers the best opportunity to use minimal stimulation currents to change the abnormal neural synchrony leading to the full ictus.
Stimuli (DBS, or any other that can be used for this purpose) are more efficient if given just at the critical point that occurs before the ictus. The reason for that is that systems are very sensitive to perturbations just at this precise moment.

Yes, these are somewhat abstract concepts (bifurcation, critical points...) but have been useful in some practical applications.

An additional advantage in this business of the control of brain activity is what Sornette’s sentence above says: we don’t need to care about the specific molecular/cellular mechanism that triggers the abnormal synchrony resulting in the seizure. This is because it all ends up in higher than normal neuronal synchronization that can be altered by delivering current pulses.

The activity of nervous systems has unstable/metastable states. The transient stabilization of these states manifests as synchronous oscillations in normal or abnormal brain rhythms. Therefore, it is a matter of favoring the normal, physiological brain rhythms.

In case of DBS, current stimulation is used, but medicines can be used too. However, chemical intervention is more difficult because of the reason aforementioned: the molecular events leading to high cellular synchronization may be very different from patient to patient, which has to be taken into account for molecular interventions.

But what kind of current pulses can be efficient at stopping an incoming seizure?

For how long do the DBS electrodes need to stimulate the brain areas where those electrodes are inserted?

To answer these questions needs research, basic research, so that a personalised DBS protocol can be created for each specific patient.

Many patients have very similar epileptic syndromes, and what is good for one will probably be good for the other. But an evaluation of the dynamics of epileptiform activity in each case is greatly advised before DBS is implemented.

**Where to stimulate?**

If the epileptic focus is known, then inserting the DBS electrodes there will be adequate. But even if the focus has not been found, there is hope.

A fundamental point has to be considered: seizures are a network phenomenon. One cell network over-stimulates another
network, and that, in turn, stimulates others connected. In principle, the chain can be stopped at any stage.

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Latin for “within the living”

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In vitro and in vivo studies indicate that this is a possibility. Some cell networks (stages) will be better targets than others, but, again, the opportunity to stop the chain of abnormal high synchrony at any place remains. Hence, the issue of the focus may not be that crucial after all.

**How to stimulate?**

This depends on the dynamics leading to the epileptiform activity.

Our own 10-year research project ended up in an in vivo study. A closed-loop DBS was used to stop the generation of seizures in the rat models (Salam et al., 2015, 2016).

Specific signs of certain dynamical regimes were found leading to seizures. This led to the basic idea of stabilising the normal synchronization states using electrical stimuli (Deep Brain Stimulation / DBS).

The whole procedure can be summarised like this: we recorded signals from the brain areas known as hippocampus. Our algorithm detected a change (decrease) in synchrony between two signals. That heralded a possible incoming seizure. At this moment a DBS of about 5–10 seconds was applied to those same brain areas at certain frequency (between 5 and 20 Hz) and low current amplitude (otherwise the tissue could be damaged).

Low frequencies of stimulation, 5 Hz specially, resulted in the rats becoming basically seizure-free. Higher frequencies (20 Hz) diminished seizures too but to a lesser degree than the low frequency. And too high frequencies (>50 Hz) could trigger seizures.

We chose low frequencies because both our own and other groups’ research showed that low frequency stimuli promoted interictal activity and avoided the route to the ictus. Interictal activity is what epileptologists call some brain activity that appears between seizures in the neurophysiological recordings.
As well, we tried an open-loop protocol. Stimuli that operate almost continuously, intermittently, are termed open-loop. An open-loop system is really a blind device. It does not have any “intelligent” mechanism built-in to monitor brain states and tune the stimulation schedule accordingly to improve seizure control.

In our work, the open loop paradigm that stimulated the brain at random, reduced seizures in the rats by 17%. In another research, the closed-loop (or on-demand, or feedback) paradigm that stimulated the brain when the change was detected, reduced seizures in the rats by ~90% (Salam et al., 2016).

The immense majority of clinical DBS protocols are of the open-loop variety. To my knowledge, there is only one closed-loop responsive DBS protocol approved for use in patients, the RNS system (Sun and Morrell, 2014).

Those interested in the full story can read chapters 2 and 3 of ‘The Brain-Behaviour Continuum’ [World Scientific] and some papers like Perez Velazquez et al., 2003, Khosravani et al., 2003.

A common approach to control pathophysiology, or how to circumvent molecular complexity

It is not without interest to note that the approach we used to study brain dynamics and stop seizures is very similar to the approach used to control cardiac arrhythmias (Christini et al., 2001).

I mentioned before the general applicability to many fields of the methods of study we conducted in epilepsy. I accentuated this fact using Sornette’s words: “The richness of out-of-equilibrium systems lies in the multiplicity of mechanisms generating similar behaviors”.

Let me emphasise it again: different causes, same results. This is very true in seizures. It is known that there are several molecular dysfunctions that will lead to the same result, higher than normal neuronal synchrony, and a subsequent ictus.

Some of these molecular events may sound even contradictory – to wit, promoting inhibition in some brain areas (thalamus mainly) favours seizures.
But how can this be, if seizures represent abnormal hyper-excitability of brain cells?

And, in addition, inhibitors of neuronal activity are normally used to stop seizures?

“Hyperexcitability normally leads to hypersynchrony that normally leads to neuropathology.” This admittedly very general scheme was proposed in my monograph *The Brain-Behaviour Continuum*.

Why sometimes inhibitory neurotransmission promotes ictal events? Suffice to say, that sometimes the action of an inhibitory neurotransmitter leads to overexcitation of *thalamic neurons*. That will translate to hyperexcitability of cortical neurons, and the loop will be closed by the cortical cells exciting in turn those same thalamic cells already overexcited.

This is just an illustration of the complicated cellular/molecular machinery that, depending on the time and place, may go all wrong.

Nevertheless, the point I was trying to make is that a similar approach to finding dynamical regimes has been used in disparate systems: biochemical (Decroly and Goldbeter, 1987), physical (Bergé, et al., 1984), chemical (Roux, 1983), and cardiac (Christini and Glass, 2002; Christini et al., 2001) systems, plus our own study on epilepsy.

The methods are part of dynamical systems theory, popularly known as chaos theory, and they are quite technical. Chapter 2 of my aforementioned monograph contains a basic introduction to the theme.

The application of the knowledge gained by using these methods can be put to some very good use, like stopping Parkinsonian tremor, halting seizures or mending cardiac arrhythmias.

**An extremely brief micro-survey of seizure control techniques**

In addition to our own efforts, there have been many others that have used a wide variety of paradigms to stop the hypersynchrony in epilepsy.
The interest to control epileptiform activity has been among us for a long time. It was already in the 1960s that headsets with earphones that monitored EEG were used to trigger loud noises – in the hope that this could substantially perturb the brain activity before it goes into a seizure.

This may be seen as very non-specific, but a variety of non-specific perturbations seem to halt, transiently, paroxysmal activity. For instance, psychological interventions reduce seizure frequency in some patients (Schmid-Schönbein, 1998). The ketogenic diet (mainly used for children) help reduce seizure too, and so does deep brain stimulation (DBS) in the centromedian thalamic nucleus, plus many other brain areas (see the article Epilepsy I).

Among the electrical protocols, we find proportional feedback, chaos control techniques, vagal nerve continuous stimulation, and many others. One review of the field is Lockman and Fisher 2009, but there is a very extensive literature on the topic that interested readers can find with any search.

I would like to point out that being non-specific may be good here. The reason is that we do not know what exact parameters are determining the state space where brain dynamics unfolds (the state space is used in dynamical systems theory to visualise and characterise the system’s dynamics).

Hence, to alter the “epileptic state space” and revert it to the “normal state space” with normal dynamics, one could change at the same time many parameters.

So, rather than being specific about one variable, just do something that will affect many parameters. Like vagal nerve stimulation that causes a global alteration of brain activity. Or the ketogenic diet aforementioned that results in many molecular events that reduce seizures in some patients.

And this non-specificity is, by the way, a feature of many medications. They promote inhibition, and thereby reduce propensity to ictal events by acting on several molecular mechanisms. Drugs are rarely very specific. It has been said that we know two things with certainty about a drug: the molecular mechanism by which it acts, and that there is another mechanism that it surely acts on, but remains unknown.

On the other hand, what looks like very specific methods, are on the way. They are presaged by new technologies that are emerging and can be of great potential in this business. For example, optogenetics; some advances have been made recently in rodent models of epilepsy using this
relatively novel technique, the method involving a closed-loop “optogenetic” stimulation. Details in Krook-Magnuson et al., 2013.

**Technical addendum**

**Neurostimulation devices for treating epilepsy and other neurological disorders**

In our epilepsy research, abovementioned chronically implanted electrodes were used to record and stimulate brain areas in rats. **Novela electrodes**, among others, were utilized. These have very good sensitivity and can capture individual neuronal spikes (action potentials).

In the end, **local field potentials (LFPs)** were used both for the analysis of the seizure precursor (commented in article II) and to evaluate the results of the stimulation.

**The local field potential**

LFP is the electric potential recorded in the extracellular space in the brain tissue, typically using micro-electrodes.

The reason that LFPs are so useful is that they represent the collective neuronal firing of many neurons.

One neuronal network activates another down the chain because many cells fire spikes in synchrony, but not all cells need to fire.

To understand the progression of excitability in brain tissue we would need to record from thousands of individual neurons, which is unfeasible with current methods. But the LFP offers us the solution: it already represents that collective firing. Hence, all these studies focus on LFPs.

The following figure from one of our papers (Salam et al., 2016), depicts an envisaged therapeutic neurostimulation system.

![Figure 1.](image-url)

The neurostimulator could be a microchip with capabilities to **analyze** brain signals and to **stimulate** when needed. The device
interfaces with the electrode arrays and wirelessly communicates with a computer.

Commercial neurostimulation systems for medically refractory epilepsy treatment are available from several companies, like Cyberonics, Medtronic or Neuropace.

Medtronic offered a programmable, open-loop DBS system, using about eight electrodes. The system delivers stimuli to the anterior nucleus of the thalamus at scheduled intervals.

As exemplified in the Figure 1, the main idea is to employ advanced electronic microchips. The devices need to perform the computations needed for early seizure detection, and to stimulate in a responsive, or closed-loop, fashion.

The advances in integrated circuit technologies enable miniaturization (less than 1cm³) to design single-chip implementations of neuroprostheses*

*neuroprosthesis, plural neuroprostheses = a replacement used to improve the function of an impaired nervous system.

Figure 2 shows one of our microchips we were developing while I worked in Toronto. It is compared in size with a Canadian coin. The small size would make it feasible to be implanted in a patient’s head (perhaps under the skin of the skull, as in Figure 1).

Regarding on-chip neural signal processing, ours is not the only chip that can perform online computations to detect seizures. Other integrated circuits that target seizure detection (but not early detection) have been reported (e.g. Verma, et. al., 2010).

Several neurostimulation systems with multiple recording and stimulation channels on the same chip have been reported in the very abundant engineering literature on this topic. For instance, a system with 128 biocompatible electrodes for recording and stimulation interface (Heer et al., 2006).
However, univariate algorithms* generally used in these devices/algorithms have been shown inferior for early detection of seizures. Detecting a seizure early significantly increases the chances of success in controlling the seizure by early electrical stimulation.

Bivariate algorithms** (such as neural synchrony computation on many channels) are effective but very expensive, and they cannot easily be implemented on a chip in real time.

A general survey on closed-loop neurostimulators where many technical details are expounded can be found in one of our recent papers (Kassiri et al., 2017).

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*Univariate data consists of only one variable. The information deals with only one quantity that changes.

**Bivariate data involves two different variables. The analysis of this type of data deals with causes and relationships.

Univariate Data consists of only one variable. Bivariate Data involves two variables.

Univariate and bivariate data.

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