

New insights offered by a computational model of deep brain stimulation

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Abstract

Deep brain stimulation (DBS) is a standard neurosurgical procedure used to treat motor symptoms in about 5% of patients with Parkinson's disease (PD). Despite the indisputable success of this procedure, the biological mechanisms underlying the clinical benefits of DBS have not yet been fully elucidated. The paper starts with a brief review on the use of DBS to treat PD symptoms. The second section introduces a computational model based on the population density approach and the Izhikevich neuron model. We explain why this model is appropriate for investigating macroscopic network effects and exploring the physiological mechanisms which respond to this treatment strategy (i.e., DBS). Finally, we present new insights into the ways this computational model may help to elucidate the dynamic network effects produced in a cerebral structure when DBS is applied.

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1. Introduction

Today, our ability to treat symptoms frequently exceeds our ability to understand the underlying diseases. One example is Parkinson's disease (PD), in which the physiological mechanisms underlying the symptoms respond to dopamine (L-DOPA) or chronic intracerebral stimulation. In some cases, however, complex interactions among cerebral structures may be modelled by simulating the healthy or diseased brain state (with or without treatment). The recent development of Systems Biology and Computational Neuroscience has led to an increase in the number of models published in the literature. Although computational models are frequently still unrealistic and cumbersome to use, a number of scientists are now convinced that the development of more realistic, dynamic, multiscale

models of neural activity will lead to the discovery of new therapeutic strategies for regulating brain rhythms.

The success of computational models depends on many factors. One key issue is the ability of a model to build meaningful bridges between successive levels of description (i.e., scales or orders of magnitude), each integrating neurophysiological and neuroanatomical information. Of course, this does not mean that every spatial and temporal scale must be fully represented in these models, but rather that complexity can be reduced by restricting the model to relevant temporal and spatial scales without losing its dynamics. The obvious difficulty is to identify the relevant elements to be included in the model.

One particularly interesting situation concerns chronic electrical stimulation of the brain. While this is now a standard therapeutic procedure, generally used in neurosurgery to treat motor symptoms, the underlying causes of clinical improvement observed have not yet been completely elucidated. A number of research teams are investigating why the motor symptoms of PD decrease drastically within a few seconds when stimulation is applied, but have not yet fully explained the action mechanisms involved.

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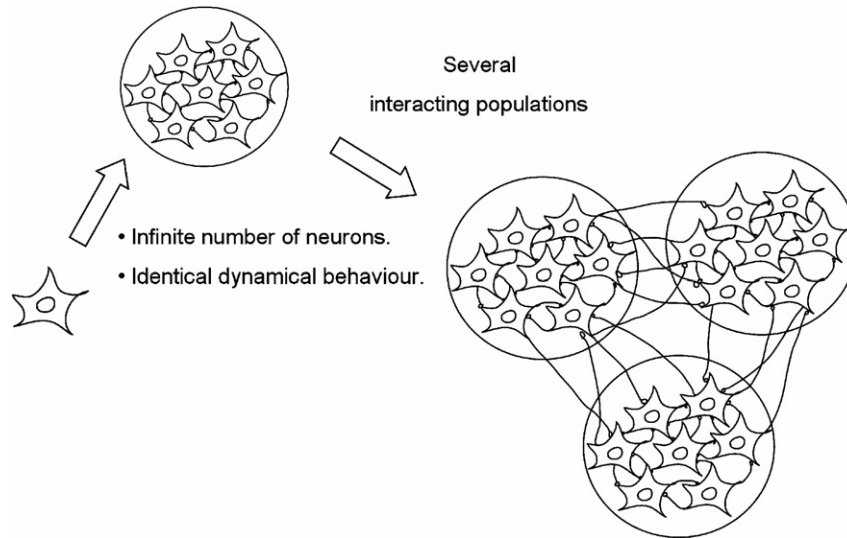


Fig. 1. Illustration of the multiscale aspect of the population density approach, linking individual neuronal properties with the behaviour of a multiple-population network.

We propose a new computational model for exploring the effects of deep brain stimulation (DBS) on motor symptoms in PD. The aim of this model is to link the microscopic-local level (neurons) with the macroscopic-global level (interacting populations of neurons) as illustrated in Fig. 1. This model was built using the methodology pioneered by Knight et al. (1996) and extended by Omurtag et al. (2000) and Nykamp and Tranchina (2000). The main advantage of this approach is that it provides a global description of a large number of neurons (virtually an infinite number) with only a single equation (a conservation law) in a significantly shorter computing time than the usual discrete simulations. This is due to the fact that, in population dynamics, only the state distribution (independent of the number of neurons simulated) is computed. By contrast, in discrete simulations (referred to below as “direct simulation”) the computing time increases rapidly with the number of neurons and synapses simulated. Therefore, this paper proposes a computational model which, in our opinion, is appropriate for exploring the network effects responsible for the improvement of motor symptoms in patients with PD following DBS.

2. Deep brain stimulation: an overview

Before presenting the details of the model, it is important to understand the neurological and pathological context of its development. DBS is a therapeutic procedure proposed to patients with movement disorders such as PD, essential tremor, and multiple sclerosis. There are a number of patient selection criteria for receiving DBS and the final decision is taken jointly by the clinical team. In PD, DBS targets include the subthalamic nucleus (STN) – currently the preferred target – and the internal part of the Globus Pallidus (GPi). The Vim nucleus of the thalamus is stimulated in essential tremor and in multi-

ple sclerosis. Previously, these structures were lesioned rather than stimulated and, curiously, the clinical improvements following pallidotomy, subthalamotomy, and thalamotomy were similar to those produced by DBS. Another surprising observation was that the targets for DBS are located in a network of structures (the cortex-basal ganglia–thalamus–cortex loop) and stimulation of different neural structures in this network results in varying degrees of improvement in the symptoms. Fig. 2 illustrates the position of these brain structures in a coronal view.

Precision positioning of a permanent stimulation electrode in a brain target is quite difficult due to the highly variable geometry of the brain and the lack of reliable reference points. Clinicians are assisted by various imaging techniques, such as computed tomography or magnetic resonance imaging scans, often complemented by recordings of cerebral activity in the vicinity of the target using micro- or macroelectrodes.

During the surgical procedure, an electrode is implanted on each side of the brain and connected to a stimulator implanted in the chest wall of the patient. This electrode is tipped with four possible active contacts. Once the electrode is connected to the stimulator, electrical pulses are sent continuously to the target zone. The active contact(s) positioned in the “best” spots are used for DBS. The stimulator is programmed using radio signals and the therapeutic effect is obtained with stimulation parameters adjusted around typical values (Garcia et al., 2005), such as polarity (cathode), as well as pulse amplitude (≈ 3 V), duration (≈ 0.1 ms), and frequency (≈ 150 Hz). In some cases, polarity is reversed during an individual pulse to avoid excessive charge accumulation. The patient may also turn the stimulator “off” at night. The optimum adjustment of the stimulating parameters is a trade-off between minimizing side effects and medication, and maximizing battery longevity and clinical improvement. DBS may generate adverse side

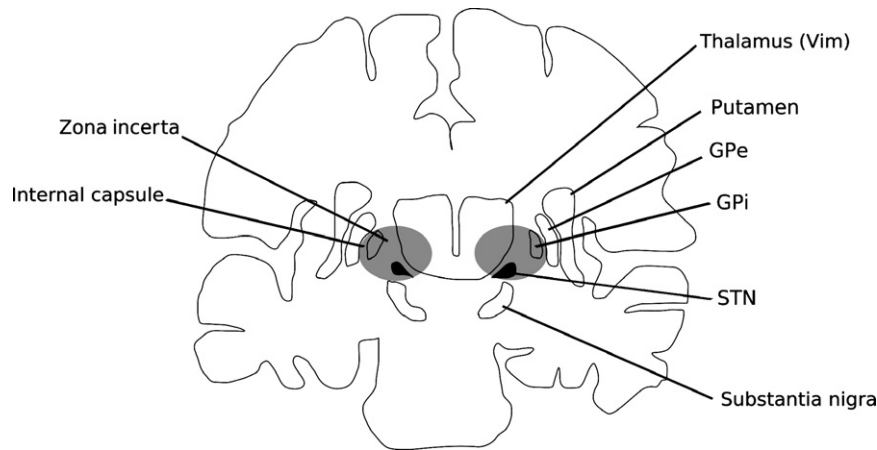


Fig. 2. Position of the optimum stimulation sites (indicated by two grey ellipses) in the brain for PD. These sites include the GPi, Vim (thalamus) and STN.

effects, such as speech difficulties, weight gain, or postural instability (Guehl et al., 2007). Typically clinical improvement affects most motor symptoms, thus significantly reducing the level of medication required. Over the years, the parameters are adjusted regularly as the disease develops. The stimulator must be replaced every few years.

In addition to the paradoxical observations mentioned above, other surprising phenomena have been reported. For example, motor symptoms in PD disappear during sleep and some reports indicate that motor control in patients with PD is “normal” during short episodes of somnambulism or in emergency situations (Cohen de Cock et al., 2007), suggesting that the effects of DBS are also more complex than initially expected. Several hypotheses have been proposed, including inhibition of the stimulated structure by neurotransmitters (e.g., GABA), depolarization blockade, resynchronization of erratic neuron activity, and change of activity in the beta band (Boraud et al., 2005). However, none of these has yet been considered satisfactory by the scientific community (Garcia et al., 2005).

Electrophysiological recordings in the STN of patients with PD show synchronous neuronal activity throughout the nucleus, which is not the case in healthy subjects (Farmer, 2002). It has also been suggested that the STN-GPe (external Globus Pallidus, another basal ganglia structure) network acts as a “pacemaker” in the basal ganglia, driving the motor loop in a synchronous oscillatory regime. Does DBS work by desynchronizing the network? This interesting hypothesis has not yet been confirmed. However, several computational studies (Tass, 2003; Hauptmann et al., 2005), describing decoupling neuronal bursting by shifting the relative phases of different cellular subgroups, indicate that this may be the case. There is also some controversy concerning the structures stimulated: one hypothesis concerns the stimulation of fibres of passage (Miocinovic et al., 2006), i.e., it is important to stimulate the surrounding fibres rather than the structure itself. More complex network effects, rather than simple excitation/inhibition, are also thought to play a role in DBS effectiveness, e.g., by antidromic/orthodromic stimulation.

Recent results (Beuter et al., 2007) showed that, even if DBS (of the GPi or STN) and L-DOPA medication provide similar benefits for patients, the effect on tremor is different, i.e., tremor characteristics in the frequency domain remain more “Parkinsonian” with DBS than L-DOPA. This suggests that different mechanisms may underlie the effects of DBS and L-DOPA. However, this contradicts results reported by Asanuma et al. (2006), suggesting that both treatments shared a common mechanism. Finally, the recent discovery of interneurons in the STN opens up interesting prospects (Levesque and Parent, 2005), as interneurons can play an important role in regulating neuronal activity and synchrony.

3. Model

3.1. Population-based model

Our model is based on the population density approach (Omurtag et al., 2000; Nykamp and Tranchina, 2000), which makes it possible to perform large-scale simulations of neural networks in a reasonable computing time, using the *Izhikevich model* (Izhikevich, 2003). This model consists of two non-linear and coupled differential equations and a reset mechanism, similar to the one in the “Leaky integrate and fire” (LIF) model (Lapicque, 1907). The model uses two variables to describe the state of a neuron: *membrane potential* v [mV] and a *recovery variable* u [mV]. Despite its simplicity, this model is capable of reproducing most of the spiking patterns observed experimentally, as shown in Fig. 3, by using the appropriate set of parameters a , b , c , d

$$\begin{cases} v' = 0.04v^2 + 5v + 140 - u + I(t) \\ u' = a(bv - u) \end{cases}$$

v' denotes the time derivative of v , the numerical parameters have been adjusted according to the state variable units, and time is measured in [ms]. The Izhikevich model also includes a reset mechanism: when $v \geq 30$ mV (referred

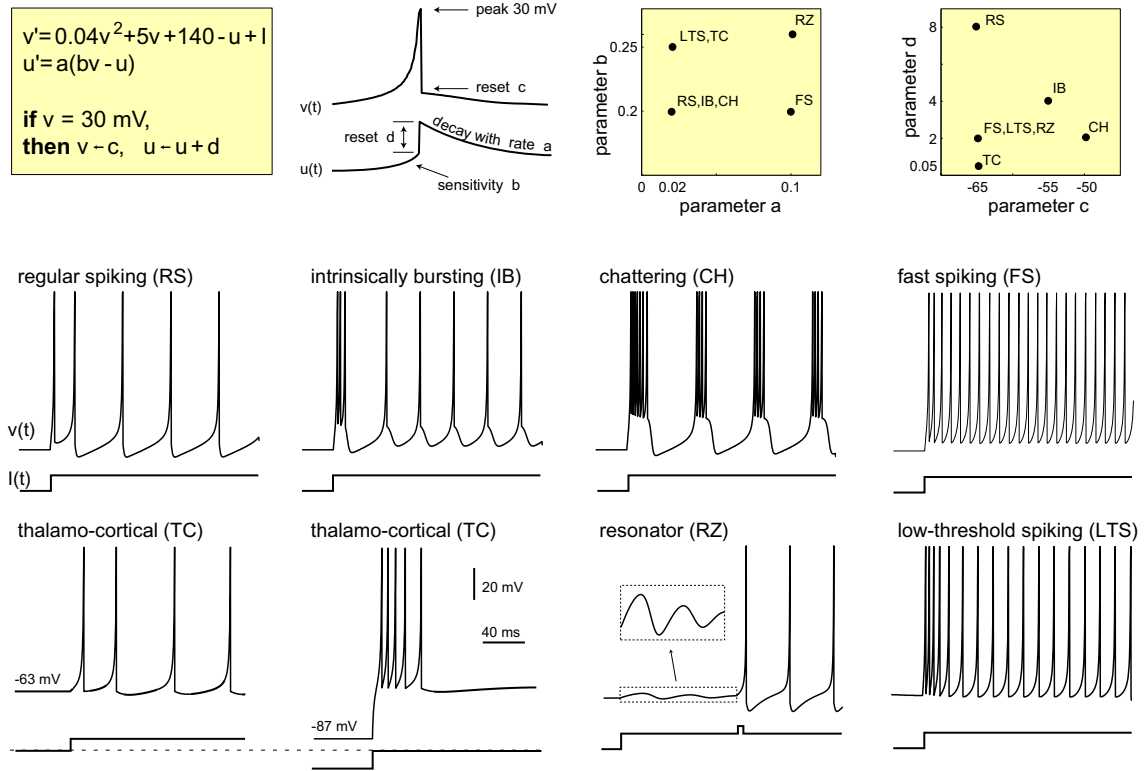


Fig. 3. Spiking patterns of the Izhikevich model with their associated sets of parameters (*Electronic version of the figure and reproduction permissions are freely available at www.izhikevich.com*). The parameters c and d are expressed in mV.

to as s throughout the paper), then $v = c$ and $u = u + d$. Fig. 3 presents the spiking patterns reproduced by the Izhikevich model.

Let $\vec{w} = (v, u)$ be the state of a neuron. The variation of the neuronal population density $p(v, u, t)$ [neurons \times mV $^{-2}$] is given by the following conservation law on the state space $\Omega = \Omega(v, u)$:

$$\frac{\partial}{\partial t} p(\vec{w}, t) = -\vec{\nabla} \cdot \vec{J}(\vec{w}, t) \quad (1)$$

where the *neural flux* $\vec{J}(\vec{w}, t)$ flowing through state \vec{w} at time t may be split into two terms (Omurtag et al., 2000): a *streaming flux* \vec{J}_s , dependent on the internal dynamic properties of the neuron, and an *interaction flux* \vec{J}_i , which accounts for the neuron's interaction with its environment (e.g., the other neurons in the network). For an excitatory neuronal population, this gives (Modolo et al., 2007, in press)

$$\begin{cases} \frac{\partial}{\partial t} p(\vec{w}, t) = -\vec{\nabla} \cdot \vec{J}(\vec{w}, t) \\ \vec{J}(\vec{w}, t) = \vec{J}_s(\vec{w}, t) + \vec{J}_i(\vec{w}, t) \\ \vec{J}_s(\vec{w}, t) = \vec{F}(\vec{w})p(\vec{w}, t) \\ \vec{J}_i(\vec{w}, t) = \hat{e}_v \sigma(t) \int_{v-c}^v p(\tilde{v}, u, t) d\tilde{v} \\ \sigma(t) = \frac{W}{N} \int_{\tau_0}^{\infty} r(t - \tau) \alpha(\tau) d\tau \\ J_v(c^+, u + d, t) = J_v(c^-, u + d, t) + J_v(s, u, t)(BC) \end{cases}$$

where \hat{e}_v is a unitary vector in the v direction and $J_v = \vec{J}(\vec{w}, t) \cdot \hat{e}_v$ is the v -component of neuronal flux $\vec{J}(\vec{w}, t)$. The parameters are as follows:

- $\vec{F}(\vec{w}) = \frac{d\vec{w}}{dt}$ given by the Izhikevich model.
- $\sigma(t)$ [spikes \times ms $^{-1}$] is the average individual neuron spike reception rate. This *mean-field variable* (accounting for the average interaction between neurons) is a function of: the mean number of afferences per neuron, the number of neurons in the population, past population activity, and the distribution of conduction delays within the population.
- τ_∞ and τ_0 [ms] are *extreme values* of spike conduction delays. Their distribution is given by $\alpha(\tau)$, using arbitrarily chosen values. A convenient choice is $\alpha(\tau) = 1$ for a constant delay and $\alpha(\tau) = 0$ else $\bar{\tau}$, as this simplifies the expression of $\sigma(t)$.
- W is the *mean connectivity degree* (i.e., the mean number of synaptic afferences per neuron).
- ϵ [mV] is the amplitude of the *membrane potential variation* when an action potential occurs on a neuron. This potential variation is assumed to be instantaneous.
- The factor (BC) represents the boundary condition. This factor ensures the conservation of population density in the state space: an additional flux depending on the number of neurons that cross the threshold $s = 30$ mV at time t^n is injected at the discontinuity $v = c$ at the same time step, I^n (for a demonstration; see Modolo et al., in press).

The complete form of the conservation law including the Izhikevich model as a description of individual neuronal dynamics is

$$\frac{\partial}{\partial t} p(\vec{w}, t) = -\vec{\nabla} \cdot \left(\begin{bmatrix} 0.04v^2 + 5v + 140 - u + I(t) \\ a(bv - u) \end{bmatrix} \right) \times p(\vec{w}, t) + \hat{e}_v \sigma(t) \int_{v-\epsilon}^v p(\tilde{v}, u, t) d\tilde{v} = 0 \quad (2)$$

A key point is that the expression of the firing rate, $r(t)$, computed as the total neuronal flux through $v = s$, is a function of population density $p(\vec{w}, t)$

$$r(t) = \int_{u_-}^{u_+} v'(t)|_s p(s, u, t) du + \sigma(t) \int_{u_-}^{u_+} \int_{s-\epsilon}^s p(\tilde{v}, u, t) dv du \quad (3)$$

where $\vec{w}_s = (s, u)$ and u_-, u_+ ; the extreme values of the u variable, are determined on an empirical basis to avoid a population density “leak” into the state space. Population density is used to compute observable variables: the *neuronal activity* of the population (number of action potentials per unit of time) and *synchronization* with other neuronal populations. Under these circumstances, the population density of two neuronal assemblies with synchronous activity will vary in a synchronous manner.

3.2. Validation of the model

The philosophies behind the population-based and direct-simulation models are drastically different. Consequently, we compared the results from the population-based model with simulation results from direct simulations, following the methodology used by Omurtag et al. (2000) and Nykamp and Tranchina (2000). Indeed, the population density function does not describe individual neuronal dynamics but only the *distribution* of states. This approach constitutes a *mean-field model*, where the complex N -body problem (in which each element interacts with many others) is transformed into a tractable mathematical form, where each element is assumed to be under the influence of a “mean-field”, i.e., an average interaction. Even if this hypothesis seems crude, this approach has produced accurate descriptions of many problems in statistical physics.

The validation of our population-based model is presented in Modolo et al. (in press). In brief, we compared simulation results with those generated by direct-simulation software developed by Garenne and Chauvet (2004) to model temporal learning in the cerebellum. Several conditions were tested in the study: a synaptically uncoupled neuronal population with constant or high-frequency applied current, a neuronal population with a given connectivity pattern receiving a constant or high-frequency applied current, and, finally, various time delays for spike conduction. Individual neuronal dynamics were described by the *tonic spiking* regime of the Izhikevich model (Izhikevich, 2003). The agreement noted between the two

approaches, under the conditions examined, suggests that our population-based model provides a reliable, valid description of the behaviour of large neuronal populations. The computing time required to simulate a network of 10^4 neurons with sparse connectivity (15 synapses/neuron) was equivalent in both approaches (≈ 28 min on a 3 GHz dual core CPU with 2 Go RAM), so it would not be reasonable to carry out a direct simulation of, for example, the population of projection neurons in the subthalamic nucleus (about 2×10^5 neurons) with a massive intraconnectivity (several hundred synapses per neuron).

3.3. Application example

In order to illustrate the model’s capabilities, we applied it to the problem of synchronization modulation in a simple 2-population network. Both populations contained 10^4 neurons but population 1 was excitatory, while 2 was inhibitory. Synaptic wiring was such that $W_{ij} = 30 \forall i, j = 1, 2$, where W_{ij} denotes the number of synaptic afferences that a neuron in population j receives from population i . The amplitude of excitatory/inhibitory post-synaptic potentials (resp. EPSP/IPSP) was 3 mV and -3 mV, respectively, with an identical absolute value, noted ϵ . The spike conduction delay in each population was 1 ms and the inter-population delay was 3 ms. The system of hyperbolic partial differential equations (PDE) describing the 2-population network in simplified form is as follows:

$$\frac{\partial}{\partial t} p_E(\vec{w}, t) = -\vec{\nabla} \cdot \{ \vec{F}_E(\vec{w}) p_E(\vec{w}, t) + \vec{G}_{EE}(t) - \vec{H}_{IE}(t) \} \quad (4)$$

$$\frac{\partial}{\partial t} p_I(\vec{w}, t) = -\vec{\nabla} \cdot \{ \vec{F}_I(\vec{w}) p_I(\vec{w}, t) - \vec{H}_{II}(t) + \vec{G}_{EI}(t) \} \quad (5)$$

where the subscripts ‘E’ and ‘I’ denote excitatory and inhibitory neurons, respectively and \vec{G}_{ij} and \vec{H}_{ij} denote the excitatory/inhibitory interaction¹ from population i to population j , respectively. Both \vec{G}_{ij} and \vec{H}_{ij} depend on the mean-field variable, $\sigma(t)$, presented above. \vec{F}_E and \vec{F}_I represent the Izhikevich model for the *tonic spiking* and *low-threshold spiking* modes (the latter describes the dynamics of inhibitory neurons; Izhikevich, 2003). We assumed that neurons in population 1 received an input current $I = 50$ pA. The system of PDE was solved using the finite volume-based numerical scheme presented in Modolo et al. (in press), except that, in this case, it dealt with inhibitory neurons. The firing rate and mean membrane potential for both populations are presented in Fig. 4.

We observed an in-phase synchrony between the firing rate and mean membrane potential (MMP) of the two populations, as the excitatory population, 1, drove the inhibitory neurons. A DBS-like current with therapeutic values: $I_{DBS} = 250$ pA, $f_{DBS} = 130$ Hz, pulse width 150 μ s, was

¹ The complete expression of these terms is similar to the general one given in Section 3.

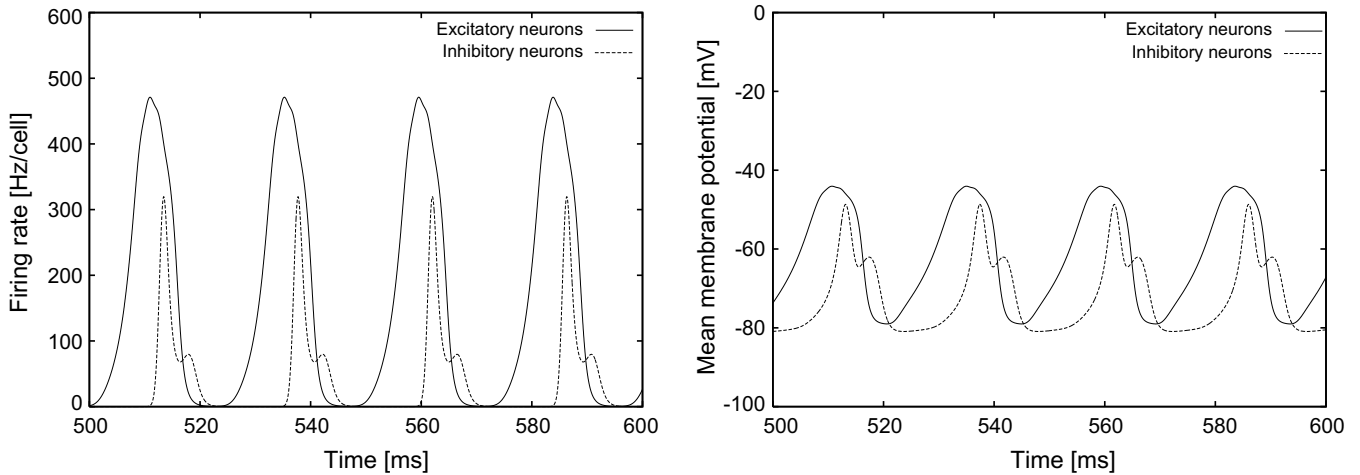


Fig. 4. Synchronization of a simple 2-population network (one excitatory, population 1 and one inhibitory, population 2), each consisting of 10^4 neurons. Both the firing rates and mean membrane potential were synchronized, as population 1, which received the input current, “drives” population 2.

applied to population 1 to test the impact of DBS on this simple synchronized network. N.B.: Even if we used therapeutic values, this simple 2-population network was not intended to simulate the activity of a precise brain network. The neuronal activity and mean membrane potential of the populations during 100 ms simulated time are shown in Fig. 5.

The DBS-like current changed the synchronization regime in the 2-population network, as both variables studied (firing rate and mean membrane potential) reached a state of anti-phase dynamics. These results show that our population-based model is useful for studying the modulation of synchronization phenomena. This is of particular relevance in understanding the effects of DBS in PD: in the pathological state, the external segment of the globus pallidus (GPe), together with the STN, is assumed to play the role of a “pacemaker”. It is hypothesized that the sub-thalamopallidal network (globally viewed as a 2-population

excitatory/inhibitory system) drives the cortex-basal ganglia–thalamus–cortex loop into synchronized oscillations, leading to pathophysiological manifestations, such as tremor. Consequently, this model is likely to be appropriate for investigating the activity of motor loop structures, which synchronize/desynchronize depending on connectivity, activity patterns, and stimulation currents.

4. Future prospects and concluding remarks

We have proposed a new strategy for investigating the mechanisms underlying the effects of deep brain stimulation in Parkinson’s disease. One of the advantages of this model is that it does not depend on the number of neurons simulated. This approach is appropriate, as we are exploring macroscopic phenomena, such as changes in symptoms or behaviours. Furthermore, the limited number of parameters required to describe a neural population makes it

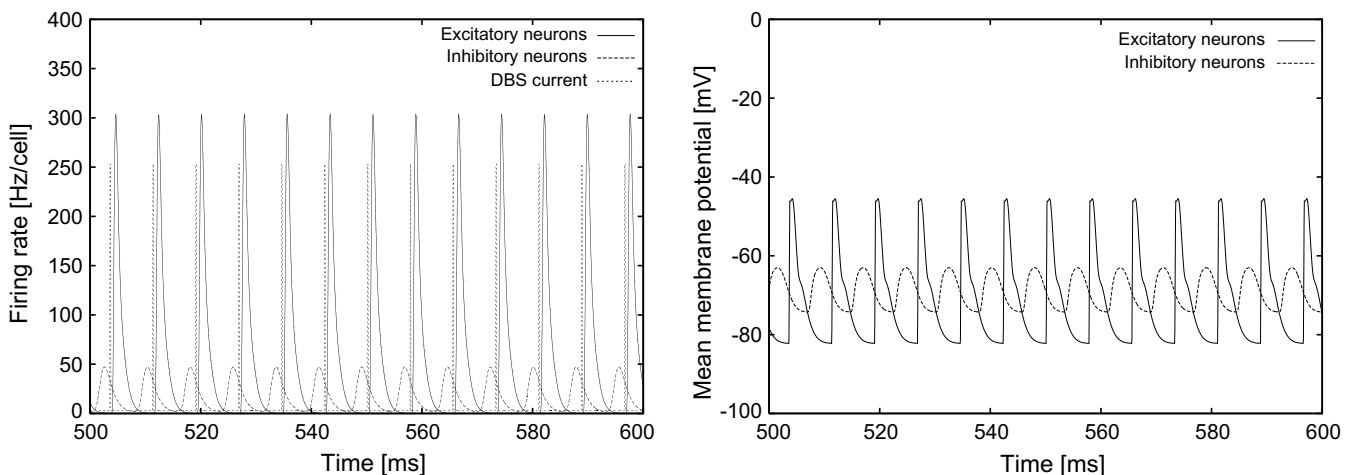


Fig. 5. Switching from an in- to an anti-phase synchrony regime when a DBS current ($I_{DBS} = 250$ pA, $f_{DBS} = 130$ Hz, pulse width 150 μ s) was applied to population 1.

possible to simulate a network of structures, such as the cortex-basal ganglia–thalamus–cortex loop, and integrate neurophysiological properties of neurons in the various structures, thanks to the Izhikevich neuron model, as well as neuroanatomical data, such as neuronal connectivity, time delays, etc. This relatively simple model is capable of complex dynamics, such as bursting or resonating (Izhikevich, 2003). In this context, various hypotheses concerning DBS mechanisms may be tested by including the appropriate structures and corresponding time delays in the model, e.g., orthodromic/antidromic stimulation of structures via the fibres of passage surrounding the STN (Miocinovic et al., 2006).

However, it should be borne in mind that our modelling approach has several limitations. Firstly, this approach assumes an “infinite” number of neurons, which, of course, is not the case in biological neural networks. However, Nykamp and Tranchina (2000) showed that simulations using a population-based model converged in a convincing manner with direct simulations including fewer than 10^4 neurons. Secondly, population equations are derived by simplifying an “average” wiring pattern, which does not account for local variations in connectivity, potentially capable of modulating the network’s functional and dynamic properties. Furthermore, the synaptic model is highly simplified for two reasons: (1) the time course of the EPSP/IPSP is not taken into account, as the variation in membrane potential is instantaneous, and (2) the amplitude of this jump in membrane potential does not depend on the membrane potential of the neuron, whereas a highly depolarized neuron is much less responsive than a neuron at its rest potential. Haskell et al. (2001) proposed a sophisticated technique for including synaptic kinetics in the population-density approach, using dimensional reduction. Finally, the model presented here does not describe a spatially-extended network (although it is possible to include a spatial variable in the population-density function).

One possible application of the model would be to extend work by Titcombe et al. (2001) on tremor dynamics in PD during DBS. A simple three-unit network was studied, with excitatory and inhibitory connections, showing that a supercritical Hopf bifurcation occurred between the DBS “off” and “on” conditions, switching the network from oscillating to stable state. The bifurcation was defined by a parameter, μ , purely related to the system dynamics, as this study did not focus on neurophysiological data. Our model is likely to provide a physiological interpretation of the μ parameter. This bifurcation parameter may be related to the potential role of GABAergic interneurons in the STN (Levesque and Parent, 2005) in modulating the activity of this nucleus, which, to our knowledge, has not yet been investigated. This lack of interest may be explained by the low proportion of these interneurons (7.5%) in this nucleus, which consists mainly of glutamatergic projection neurons. However, the study reported by Tsodyks et al. (1997) showed that inhibitory interneurons

may affect a neuronal network in a counter-intuitive way. Consequently, the simple 2-population network presented above could be used to test this hypothesis by modelling the two neuronal assemblies of the STN (glutamatergic projection neurons and GABAergic interneurons) and systematically explore a variety of connectivity configurations. Indeed the low number of STN GABAergic interneurons may have a drastic effect on its dynamic behaviour, depending on connectivity parameters with STN projection neurons. If STN interneurons play an important role in regulating STN activity, then the dopaminergic depletion in PD may disrupt this regulation, radically modifying the STN activity pattern and resulting in abnormal basal ganglia responses. Our computational model offers innovative prospects for exploring the details of this regulation under the effects of DBS.

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Appendix

The main conservation law of the model is solved using a numerical scheme based on the finite volumes method (for a complete review, see Leveque, 2002). Briefly, the main steps of this numerical method are

- The states space Ω is discretized in $N_i \times N_j$ identical cells of volume $\Delta u \times \Delta v \times \Delta t$.
- The Green–Ostrogrady theorem is applied to the conservation law on each cell: $\int \int \int_V \vec{\nabla} \cdot \vec{F} \, dv = \int \int_S \vec{F} \, d\vec{s}$.
- Finally, this leads to a balance equation of incoming/outgoing flux at the interface of each cell

$$p_{ij}^{n+1} = p_{ij}^n - \frac{\Delta t}{\Delta v} (j_v^+ - j_v^-) - \frac{\Delta t}{\Delta u} (j_u^+ - j_u^-) \quad (6)$$

where $j_{v/u}^{+/-}$ are the incoming/outgoing flux at the interface of each cell. We used $\Delta t = 4 \mu\text{s}$, $\Delta v = 0.5 \text{ mV}$ and $\Delta u = 1 \text{ mV}$ in all the simulations to satisfy the CFL condition (Courant et al., 1928). In opposition, the principle of the direct simulation is as follows:

- At the initial time, a distribution of states for all the neurons is loaded into the software.
- The direct-simulation software builds the network using a bootstrap-based method.
- At the current time step: the state of each neuron is determined by the Izhikevich model and the equations are solved using a fourth-order Runge–Kutta method.
- The state of each neuron at each time step is stored in a datafile.
- Skip to the next time step.

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