Coupled effects of channels and synaptic dynamics in stochastic modelling of healthy and PD-affected brains

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Abstract:
Our brain is a complex information processing network in which the nervous system receives information from the environment to quickly react to incoming events or learns from experience to sharp our memory. In the nervous system, the brain states translate collective activities of neurons interconnected via synaptic connections. In this paper, we study a model of coupled effects of channels and synaptic dynamics in stochastic modelling of healthy brain cells with applications to Parkinson’s disease (PD). In particular, we consider a cell membrane potential model in the thalamus part of the human brain. This model allows us to deal with an array of coupled small-scale neural subsystems. The subthalamic nucleus (STN) bursting phenomena and parkinsonian hypokinetic motor symptoms are closely connected, as electrical and chemical maneuvers modulating STN bursts are sufficient to ameliorate or mimic parkinsonian motor deficits. One of the main factors that causes the burst discharges in STN is adequately available calcium (Ca\textsuperscript{2+}) currents. Our numerical results show that controlling the dynamics of sodium (Na\textsuperscript{+}), potassium (K\textsuperscript{+}) and calcium (Ca\textsuperscript{2+}) channels together with the presences of additive and multiplicative noises in the cell membrane potential model decreases the burst discharges in STN. These burst discharges in STN contribute to slow the progressive loss of dopaminergic neurons and improve motor symptoms in PD. Furthermore, we show that the presence of noise with suitable choices of parameters in the system could delay the burst discharges in STN.

Keywords: Neurodegenerative disorders; coupled synaptic connections; hyperpolarization; damaged cells; burst discharges; systems with random fluctuations; deep brain stimulation; parkinsonian symptoms; neuronal feedback; plateau action potential
1. Introduction

One of the most common age-associated human neurodegenerative disorders is Parkinson’s disease (PD). PD is characterized by cardinal motor symptoms such as static tremor, bradykinesia, and muscle rigidity. Many different treatments focus on STN to improve such motor symptoms, for instance, ablation surgery of STN or its fiber connections. Recently STN has become an effective target for deep brain stimulation (DBS) [22]. The DBS is a very impressive method [10] due to the fact that PD characterized by the inadequacy of a chemical substance in the brain can also be successfully treated with passage of only electrical currents without concomitant supply of biological or chemical reactions/factors. In general, all brain functioning is represented by networks of neurons, which are connected by synapses that process and store information. To better understand the brain activities, we, therefore, need to know how synapses work [18]. Many models have been proposed to analyze the dynamics of synaptic coupling of human brains in neurodegenerative disorders and therapeutic targets for such diseases (e.g., [9] and references therein). In particular, a model of T-type Ca2+ channels as a new therapeutic target for Parkinson’s disease has been proposed in [22]. The authors in [5] have shown that subthalamic burst discharges play an imperative role in cortico-subcortical information relay, and they critically contribute to the pathogenesis of both hypokinetic and hyperkinetic parkinsonian symptoms. The role of the CaV1.3 channels in calcium and iron uptake in the context of pharmacological targeting for improving the PD pathology has been discussed in [16].

A review on the evaluation of the therapeutic potential of LTCC, RTCC, and TTCC inhibition in light of novel preclinical and clinical data and the feasibility of available Ca2+ channel blockers to modify PD disease progression has been reported in [17]. The authors in [2] have considered an engineering selectivity into RGK GTPase inhibition of voltage-dependent calcium channels that is in connection with treatment strategies for diseases including chronic pain and Parkinson’s disease. Beside the effects of calcium channels on PD, the potassium (K+) channels also play an important role in managing and controlling the PD. There are several results available along this line. In particular, the authors in [5] have shown that subthalamic burst discharges are dependent on input from the motor cortex, causing erroneous re-entrant information relays from corticosubthalamic to pallido-thalamocortical loops and thus parkinsonian tremors. In [21], the authors have summarized the physiological and pharmacological effects of three K+ channels as a potential therapeutic target for PD. The effects of pharmacological blockade or activation of K+ channels in the progression and treatment of PD have been discussed in [13].

To get closer to the real scenarios in the application of neuronal models for PD, we should account for the existence of random fluctuations in the system. In particular, the stochastic inputs arise through sensory fluctuations, brainstem discharges and thermal energy (random fluctuations at a microscopic level, such as Brownian motion of ions). The stochasticity can arise even from the devices which are used for medical treatments, e.g., devices for injection currents in DBS. The noises in the neuronal system are not only a problem for neurons, they can also be a solution in information processing [1]. The authors in [3] have shown that brain rhythm bursts are enhanced by multiplicative noise. The presence of noise in gamma oscillations in a model of neuronal networks with different reversal potentials has been reported in [20].

Taking the inspiration from the fields of PD studies as well as from therapeutic targets to improve motor symptoms in PD, we develop and investigate a model of coupled effects of channels and synaptic...
dynamics in stochastic modelling of healthy brain cells with applications in PD. In particular, we focus on a cell membrane potential model in the thalamus part of the human brain. We define the local neural dynamics in terms of voltage- and ligand-gated ion channels and feedback between densely interconnected excitatory and inhibitory neurons. The STN bursting phenomenon is one of the main factors that cause parkinsonian hypokinetic motor symptoms. The occurrence of burst discharges in STN is caused by an increase in the potassium (K+) and the calcium (Ca2+) currents in the system. We aim at investigating the interplay between sodium (Na+), potassium (K+) and calcium (Ca2+) channels in a cell membrane potential model for the thalamus part. We show that controlling the dynamics of such channels affects therapeutic targets for PD that slow the progressive loss of dopaminergic neurons and attenuate motor and non-motor symptoms. Furthermore, the presence of the noises in the system could delay the burst discharges in STN.

2. Model description

The second most common neurodegenerative disease after Alzheimer’s disease is PD. PD is caused by naturally occurring proteins that fold into the wrong shape and stick together with other proteins, eventually forming thin filament-like structures called amyloid fibrils. Researchers in [11] have found that calcium influences the way alpha-synuclein proteins interact with synaptic vesicles. In fact, alpha-synuclein is almost like a calcium sensor. In the presence of calcium, alpha-synuclein changes its structure and how it interacts with its environment, which is likely very important for its normal function. In nervous systems, calcium channels play an important role in the release of neurotransmitters (Fig. 1). In particular, when the level of calcium in the nerve cell increases, the alpha-synuclein binds to synaptic vesicles at multiple points causing the vesicles to come together. The normal role of alpha-synuclein is to help the chemical transmission of information across nerve cells. Moreover, releasing of dopamine (DA) midbrain neurons is essential for multiple brain activities, e.g. voluntary movement, working memory, emotion and cognition. Losing DA midbrain neurons within the substantia nigra (SN) can cause prevalent movement disorder. One of the most prevalent disorders is PD. In a cell membrane potential model, there are not only calcium channels, but also sodium, potassium channels and so on (Fig. 2). The potassium (K+) channel also plays an important role in modulating cellular excitability, synaptic transmission, and neurotransmitter release. In particular, delayed rectifier K+ channels are a group of slow opening and closing voltage-gated K+ channels [21]. The increase in K+ channels may cause an increase in intracellular Ca2+ or promote Ca2+ influx into the cell, thereby exacerbating cell damage and linking K+ following out with the calcium signalling that underlies neurodegenerative diseases.

In general, a significant increase of the calcium currents in the neuronal system could cause burst discharges in STN. This phenomenon of burst discharges is linked to the loss of dopaminergic neurons in the midbrain STN. A suitable model to understand the mechanisms of such sodium, potassium and calcium channels in PD would need to be investigated.

Taking the inspiration from the field of cell membrane potential studies and motivated by [22, 21, 13, 12], we consider a cell membrane potential model in the thalamus part of human brain. In particular, we choose first a healthy cell in the thalamus part and study behavior of the membrane potential under the interplay between ion channels (sodium (Na+), potassium (K+) and calcium (Ca2+)). We consider the following stochastic dynamics of the membrane potential ($V_m$) described by the model (based on
Figure 1. [Color online] Schematic representation for the general structure of voltage-gated calcium channels. Voltage-gated calcium channels consist of several different subunits $\alpha_1, \alpha_2/\delta, \beta, \gamma$.

Figure 2. [Color online] Schematic representation of neurotransmitter receptor ion channels in a nervous system.

\[ \frac{C_m}{m} \frac{dV_m}{dt} = - \sum I_i + I_{app}, \]  

(2.1)
where \( C_m \) is the membrane capacitance, \( I_i \) is the \( i \)-th current due to ionic channels, \( I_{app} \) is an external applied current. In this model, the applied current density \( I_{app} \) is set initially to 0 \( \mu \text{A/cm}^2 \). We consider two cases of noise in the system. In the additive noise case, the applied current is set to \( I_{app} = I_0 + \sigma_1 \eta(t) \), where \( \eta \) is the zero-mean Gaussian white noise with unit variance. Here, \( \sigma_1 \) denotes the standard deviation of this random component to the input. For the multiplicative noise case, the applied current is set to \( I_{app} = I_0 + \sigma_2 V_m(t) \eta(t) \). Ionic currents are voltage-dependent that are defined as follows

\[
I_i = \tilde{g}_i m_i^p(V_m) h_i^p(V_m)(V_m - E_i),
\]

(2.2)

where \( \tilde{g}_i \) is the maximal conductance, \( m_i \) is the activation variable, \( p_i \) is an integer between 1 and 4, \( q_i \) is either 0 or 1, and \( E_i \) is the reversal potential of the channel. Here, \( i \in \{ \text{Na; K; K,D; Ca,T; H; leak} \} \).

Following [8, 12], we define the activation and inactivation variables as \( m_i \) and \( h_i \), respectively, and consider their evolution based on the following equations:

\[
\frac{dm_i}{dt} = \frac{1}{\tau_{m_i}(V_m)} (m_{i,\text{\scriptsize{steady}}} - m_i)
\]

(2.3)

\[
\frac{dh_i}{dt} = \frac{1}{\tau_{h_i}(V_m)} (h_{i,\text{\scriptsize{steady}}} - h_i),
\]

(2.4)

where \( m_{i,\text{\scriptsize{steady}}} \) and \( h_{i,\text{\scriptsize{steady}}} \) are the steady-state values of the activation and inactivation variables.

The model (2.1)-(2.4) is composed of a leak current \( I_{\text{leak}} = \tilde{g}_{\text{leak}}(V - E_{\text{leak}}) \), a transition sodium current \( I_{\text{Na}} = \tilde{g}_{\text{Na}} m_{\text{Na}}^3 h_{\text{Na}}(V - E_{\text{Na}}) \), a delayed-rectifier potassium current \( I_{K,D} = \tilde{g}_{K,D} m_{K,D}^4 h_{K,D}(V - E_K) \), a T-type of calcium current \( I_{Ca,T} = \tilde{g}_{Ca,T} m_{Ca,T}^3 h_{Ca,T}(V - E_{Ca}) \) and a calcium-activated potassium current \( I_{K,Ca} = \tilde{g}_{K,Ca} m_{K,Ca}(V - E_{Ca}) \). The hyperpolarization-activated cation current \( I_H = \tilde{g}_H m_H(V - E_H) \), where \( m_i \) represents activation variables and \( h_i \) represents inactivation variables. These parameters have been used in [8, 12].

\[
\begin{array}{|c|c|}
\hline
m_{\text{Na,\scriptsize{steady}}} & \tau_{m_{\text{Na}}} = 1.32 - \frac{1.26}{1 + \exp(V + 120)(-25)} \\
\hline
h_{\text{Na,\scriptsize{steady}}} & \tau_{h_{\text{Na}}} = 0.67 - \frac{1.5}{1 + \exp(V + 34.9)(3.6)} \\
\hline
m_{K,D,\scriptsize{steady}} & \tau_{m_{K,D}} = 7.2 - \frac{6.4}{1 + \exp(V + 28.3)(-19.2)} \\
\hline
m_{Ca,T,\scriptsize{steady}} & \tau_{m_{Ca,T}} = 21.7 - \frac{21.3}{1 + \exp(V + 68.3)(-20.5)} \\
\hline
h_{Ca,T,\scriptsize{steady}} & \tau_{h_{Ca,T}} = 410 - \frac{179.6}{1 + \exp(V + 55)(-16.9)} \\
\hline
m_{K,Ca,\scriptsize{steady}} & \tau_{m_{K,Ca}} = 9.9 + \frac{1}{\exp(V - 81)(25.6) + \exp(V + 132)(-18)} \\
\hline
m_{H,\scriptsize{steady}} & \tau_{m_{H}} = 120 + \frac{1}{\exp(V - 3.329)(200) + \exp(V + 130)(-7.1)} \\
\hline
\end{array}
\]

Table 1. Steady-state functions for channel gating variables and time constants for the different ion channels.

The calcium-dependent activation of the calcium-activated potassium current is modelled as follows

\[
\frac{d}{dt}[\text{Ca}] = -k_1 I_{Ca,T} - k_2 [\text{Ca}],
\]

(2.5)
All of the steady-state functions for channel gating variables and time constants for the different ion channels that we use in our model follow [12] and are presented in Table 1.

Mathematically, the developed model (2.1)-(2.5) is a SDE-ODEs evolution system, where the stochastic membrane potential equation is coupled to the activation and inactivation ion channels equations, as well as to the calcium-activated potassium current equation. Note that there is no explicit coupling between equations (2.3)-(2.5).

Models proposed in [8, 12] represented different firing patterns observed in a thalamic neuron, for instance, depolarized tonic modes, hyperpolarization modes, bursting discharges, etc and the switch between them. However, in their models, they studied the robustness of conductance-based models with a special focus on the dynamics of voltage-gated T-type calcium channel activation in a deterministic case. In real-world applications, the stochastic factors are also important to capture the effects of ion channels. Taking the inspiration from the studies in [15, 19], we are interested in coupled effects of channels and synaptic dynamics in stochastic modelling of healthy brain cells. In general, the external current controls the firing mode. The presence of a hyperpolarizing current could switch the neuron from a regular spiking mode to a burst mode. In our model, motivated by [8, 12, 15, 19], we focus on analyzing the bursting phenomenon not only under the presence of hyperpolarizing current, but also in activation and inactivation of sodium, potassium and calcium channels, and in the presence of noises. At this moment, we do not consider the neuron connections via AMPA, GABA synapses for simplicity, while keeping the time scale akin to the time scale in the earlier studies [19, 14, 4].

3. Numerical results

The numerical results reported in this section are obtained by using a variable order method for stiff differential equations and DAEs (based on ode15) together with an integration scheme for SDEs [19] (by using the stochastic analogue of Heun’s algorithm). In particular, we consider a coupled SDEs-ODEs system (2.1)-(2.5), modelling the dynamics of the membrane potential model in the thalamus part of the human brain. As we have mentioned in the previous section, we consider two cases of noise in the system. In the model with noises, we use the stochastic Heun integration scheme for SDEs [19]. Moreover, to compare such stochastic cases to their deterministic counterpart, we also provide the numerical results on the deterministic case. In our numerical results, we plot the time evolution of the membrane potential model and the corresponding phase portrait. From the dynamical system perspectives, phase portrait representations assist us in capturing the qualitative physiological behavior of Hodgkin-Huxley models. These phase portrait representations have revealed the power of simple dynamical models to unfold complex firing patterns and can be seen as graphical (or geometric) representations of the dynamics of neuronal excitability [6, 7].

The main numerical results of our analysis are shown in Fig. 3-8, where we plot the time series for the membrane potential $V_m$, the phase portraits in the membrane potential for $(m_{Ca,T}, V_m)$, as well as the injection currents $I_0$.

We modify the original model from [12] by adding the noises in the applied current $I_{app}$. We know that a significant increase of burst discharges in the STN has been observed in dopamine-deprived conditions such as PD [22]. Such dopamine-deprived factors have a direct relationship with parkinsonian symptoms. One of the main factors causing the burst discharges in the STN is a significant increase of the T-type Ca2+ currents. Moreover, we know that T-type Ca2+ currents are effected also by others.
ion channels dynamics (e.g. sodium (Na+), potassium (K+) and calcium (Ca2+) channels) in a cell membrane potential model. Therefore, managing such T-type Ca2+ channels in the cell membrane potential model would lead to a better control of the bursting discharges.

In the simulations, we fix the parameters for $E_{\text{leak}} = -59$ (mV), $g_{\text{leak}} = 0.055$ (mS/cm$^2$), $E_{Na} = 50$ (mV), $g_{Na} = 170$ (mS/cm$^2$), $g_{KD} = 40$ (mS/cm$^2$), $g_{Ca} = 0.55$ (mS/cm$^2$), $g_{K,Ca} = 4$ (mS/cm$^2$), $g_{H} = 0.01$ (mS/cm$^2$), $g_{L} = 0.055$ (mS/cm$^2$), $E_{Ca,T} = 120$ (mV), $E_{K} = -85$ (mV), $g_{K} = 10$ (mS/cm$^2$), $V_0 = -65$ (mV), $E_{H} = -20$ (mV), $k_0 = 170, k_1 = 0.1, k_2 = 0.01$. These parameters have been used in [8, 12], where the authors considered conductance-based models of thalamic neurons.

3.1. Case 1: inactivating T-type calcium channels, while controlling sodium (Na+) and potassium (K+) channels

In Fig. 3, we consider the system with a transient sodium current, a T-type calcium current, a calcium activated potassium current, a hyperpolarization-activation cation current and a leak current (see, e.g. in [12]). The goal is to control the current of sodium by the quantity $I_{Na} = g_{Na}m_{Na}^2h_{Na}(V - E_{Na})$ , and control the current of potassium current by the quantity $I_{K} = g_{K}m_{K}^3h_{K}(V - E_{K})$, while we fully activated the T-type calcium channel by $I_{Ca,T} = g_{Ca,T}m_{Ca,T}^2(V - E_{Ca})$. In the first row of Fig. 3, we plot the time evolution of the membrane potential $V_m$. We see that the cell is getting damaged dramatically in Fig. 3. This is visible in the first row of Fig. 3, after occurring burst discharges, the membrane potential increases significantly in the three cases with no noise, additive and multiplicative noises. This burst discharge phenomenon is due to the fact that the T-type calcium channel is fully opened. We note that the presence of multiplicative noise with amplitude $\sigma_2 = 0.2$ enhanced the bursting phenomenon in the system. In particular, if there are fluctuations in the membrane potential (from $t = 0$ (ms) to $t = 9$ (ms)), then the bursting occurs (with value of 50 (mV)). After reaching the value of 50 (mV), the membrane potential increases dramatically to a maximum value of approximately 215 (mV) then decreases slowly with fluctuations. Similarly, as it is the case in Fig. 3, when the stimulus pulse ends, the membrane potential does not return to rest but simply remains in the depolarized state of approximately 50 (mV). We observe a T-type calcium plateau action potential since we let the T-type calcium current be activated in the deterministic case and in the case in presence of additive noise. Looking at the corresponding phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$ in the second row of Fig. 3, we note that there exist attractors of the spiking neuronal model in the cases of additive and multiplicative noises. The attractors are unstable due to the fact that there are bifurcations in the attractors [6, 7]. In general, the molecular basis of burst discharges is popular in quite a few brain areas including the thalamus part of the brain. The increased thalamus burst discharges and parkinsonian symptoms are closely connected. A significant increase of burst discharges could lead to wrong handling of the input information and inappropriate signal output of the STN or in the thalamus in general. Moreover, loss of dopaminergic neurons in the midbrain (substantia nigra pars compacta) is one of the main factors that cause PD symptoms. The increased thalamus burst discharges can influence the dopamine deprivation for the discharges of STN neurons. Sufficiently available T-type Ca2+ currents, e.g. $I_0 = 10$ (mV) in this case, contribute to the occurrence of burst discharges in STN. To manage such burst discharges in STN, we carry out further analyses presented in Fig. 4-8.
Figure 3. [Color online] Cell membrane potential model in the case of inactivating T-type calcium channels, while controlling sodium (Na+) and potassium (K+) channels. Parameters: $C_m = 1 \mu F/cm^2$, $\sigma_1 = 10$, $\sigma_2 = 0.2$. First row: Time series for the membrane potential $V_m$ with no noise (green line), additive noise (red line) and multiplicative noise (blue line). Second row: Phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. Third row: the injection currents $I_0$. 
3.2. **Case 2: considering a delayed-rectifier potassium (K+) current, while controlling T-type calcium and sodium (Na+) channels**

![Graph showing cell membrane potential model](image)

**Figure 4.** [Color online] Cell membrane potential model in the case of considering a delayed-rectifier potassium (K+) current, while controlling T-type calcium and sodium (Na+) channels. Parameters: $C_m = 1 \, \mu F/cm^2, \sigma_1 = 10, \sigma_2 = 0.2$. First row: Time series for the membrane potential $V_m$ with no noise (green line), additive noise (red line) and multiplicative noise (blue line). Second row: Phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. Third row: the injection currents $I_0$. 
In Fig. 4, we consider the same quantities as in the case of Fig. 3. However, instead of controlling the potassium channel as in the case of Fig. 3, we add a delayed-rectifier potassium current. In this case, the injection currents $I_0$ are presented in the third row of Fig. 4. The numerical results presented in Fig. 4 show that controlling the sodium and T-type calcium channels in the presence of an activation potassium channel could reduce the bursting phenomena in the membrane potential of the thalamus. Furthermore, the presence of the noises in the system strongly affects the membrane potential. In particular, looking at Fig. 4, first row, we see that in the dynamics with additive noise, from $t = 0$ (ms) to $t = 5$ (ms) and with $I_0 = 0$ (mV), there is a fluctuation in membrane potential. Then, at $t = 5$ (ms), the burst discharge occurs with its maximum equals to 13 (mV). After reaching the maximum value, the membrane potential depolarizes and remains in a depolarized state with a slow repolarizing droop. This state is a potassium plateau action potential since we let the potassium current be activated. The potassium plateau action potential has fluctuations with amplitude $\sigma_1 = 10$ due to additive noise representation. It is clear that when the stimulus pulse ends, the membrane potential does not return to rest, but simply remains in the depolarized state (with a value equals to 13 (mV)). This slow depolarization phenomenon is probably due to the fact that $K^+$ accumulates during the prolonged stimulus and to the effect of the calcium activated potassium current, but not to the conductance $\tilde{g}_K$ [4]. Moreover, the presence of additive noise in the system lets the burst mode occur earlier even with the initial injection value $I_0 = 0$ (mV). In the deterministic case, we still have similar effects as in the case of additive noise. The difference is that, the membrane potential keeps silent from $t = 0$ (ms) to $t = 10$ (ms) with $I_0 = 0$ (mV), there is a slight increase of the membrane potential from $t = 10$ (ms) to $t = 11$ (ms) and then bursting occurs immediately after that. When the bursting attains a maximum value of approximately 15 (mV), soon after we have similar effects as in the case with additive noise. In particular, we also observe a potassium plateau action potential (without fluctuations) and the membrane potential does not return to rest, but simply remains in the depolarized state of approximately 13 (mV). In the case with multiplicative noise, from $t = 0$ (ms) to $t = 13$ (ms), we note that there are strong fluctuations of the membrane potential. Those fluctuations let the membrane potential goes down hyperpolarization to approximately -110 (mV). Then, at $t = 13$ (ms), the burst discharges occur with maximum value of approximately 10 (mV). After reaching its maximum, we observe similar effects, both in the deterministic and additive noise cases, in which the potassium plateau action potential (with fluctuations where amplitude is $\sigma_2 = 0.2$) and the membrane potential does not return to rest, but simply remains in the depolarized state of approximately 13 (mV). Furthermore, we look at the second row of Fig. 3 where we show the corresponding phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. It is clear that the spiking limit cycle for all three cases (deterministic, additive noise and multiplicative noise) in the second row of Fig. 3 explains the presence of plateau oscillations [7]. As the stimulation is turned off, the spiking limit cycle disappears in a saddle-homoclinic bifurcation (see, e.g. in [6]), although the resting states are not covered. In the case presented in Fig. 4, we observe an improvement of the burst mode compared to the case in Fig. 3. This is due to the fact that we have controlled the T-type Ca$^{2+}$ channels. Furthermore, the presence of a delayed rectifier potassium current together with the help of a hyperpolarization-activation cation current also contribute to managing such T-type Ca$^{2+}$ channels.
Figure 5. [Online color] Cell membrane potential model in the case of controlling T-type calcium channel, sodium (Na+) and potassium (K+) channels. Parameters: $C_m = 1 \mu F/cm^2, \sigma_1 = 10, \sigma_2 = 0.2$. First row: Time evolution for the membrane potential $V_m$ with no noise (green line), additive noise (red line) and multiplicative noise (blue line). Second row: Phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. Third row: the injection currents $I_0$. 
3.3. Case 3: controlling T-type calcium channel, sodium (Na\textsuperscript{+}) and potassium (K\textsuperscript{+}) channels

In Fig. 5, we consider the case where we control sodium, potassium and calcium channels. Looking at the first row of Fig. 5, we plot the time evolution of the membrane potential $V_m$. It is clear that the burst discharges decrease more than in the case of Fig. 4 since we control the entire set of three channels, that is sodium, potassium and calcium. In particular, in the case of multiplicative noise, there are fluctuations from $t = 0$ (ms) to $t = 10$ (ms), then the bursting occurs at $t = 10$ (ms). After reaching a maximum value of the bursting phenomenon, the membrane potential is slightly depolarized and remains in a depolarized state with a slow repolarizing droop for a long time. This is a plateau action potential similar to the case of Fig. 4. However, instead of remaining in the depolarized state, when we inject a negative current $I_0 = -20$ (mV), the membrane potential does not return to rest but simply undergoes a small voltage drop caused by the negative injection. We also observe a plateau action potential when we control the three channels of sodium, potassium and T-type calcium in the deterministic case and the presence of additive noise similar to cases in Fig. 4. The only difference with the cases in Fig. 4 is that the position and the size of the maximum values in such plateau action potential changes. Looking at the corresponding phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$, similar to the case in Fig. 5, there exist attractors of the spiking neuronal model in the cases of additive and multiplicative noise. The attractors are unstable due to the fact that there are bifurcations in the attractors (see, e.g. in [7]).

3.4. Case 4: inactivating T-type calcium channels, while controlling potassium (K\textsuperscript{+}) and sodium (Na\textsuperscript{+}) channels

In Fig. 6, we consider the case where we inactivated the calcium channel, activated the potassium channel, while the sodium channel has been kept under control. We obtain similar results as in the case of Fig. 5. However, in contrast to the case of Fig. 5, the position and the size of the maximum values in such plateau action potential changes. In particular, in the case of multiplicative noise, the bursting discharge still occurs earlier (at $t = 10$ (ms)), while such bursting phenomena occur nearly the same in the deterministic case and in the case of additive noise (at $t = 32$ (ms)). We also obtain similar results for the corresponding phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. However, the position and the size of the maximum values in such unstable attractors changes. In general, the phase portrait pictures are affected by the presence of calcium channels in firing mechanisms. In this case, when we inactivated the T-type calcium channels, we still observe the plateau oscillations, then such plateau state converges to a limit cycle. This is due to the presence of slow activating sodium and potassium currents (see, e.g. in [7]). In this case, the bursting discharges are delayed in the deterministic and additive noise cases.

3.5. Case 5: activating potassium (K\textsuperscript{+}) channels, while controlling T-type calcium and sodium (Na\textsuperscript{+}) channels

In Fig. 7, we plot the case of controlling the T-type calcium and sodium channels while the potassium channel is activated with $C_m = 1 \mu F/cm^2$. In this case, instead of considering delayed-rectifier potassium (K\textsuperscript{+}) current as in Fig. 4, we add the activated and inactivated potassium channel in our system. We obtain similar results as in the case of Fig. 6. However, the position and the size of the maximum values in such unstable attractors changes. In particular, the occurrences of burst discharges
Figure 6. [Color online] Cell membrane potential model in the case of inactivating T-type calcium channels, while controlling potassium (K+) and sodium (Na+) channels. Parameters: $C_m = 1 \mu F/cm^2$, $\sigma_1 = 5$, $\sigma_2 = 0.2$. First row: Time evolution for the membrane potential $V_m$ with no noise (green line), additive noise (red line) and multiplicative noise (blue line). Second row: Phase portraits in the membrane potential model for $(m_{\text{Ca,T}}, V_m)$. Third row: the injection currents $I_0$. \\

happen earlier then in the case of additive (at $t = 33$ (ms)) and multiplicative noises (at $t = 10$ (ms)), while the burst discharges occur at $t = 41$ (ms) in the deterministic case. Looking at the corresponding
Figure 7. [Color online] Cell membrane potential model in the case of activating potassium (K+) channels, while controlling T-type calcium and sodium (Na+) channels. Parameters: \( C_m = 1 \, \mu F/cm^2, \sigma_1 = 5, \sigma_2 = 0.2 \). First row: Time evolution for the membrane potential \( V_m \) with no noise (green line), additive noise (red line) and multiplicative noise (blue line).

Second row: Phase portraits in the membrane potential model for \((m_{Ca,T}, V_m)\). Third row: the injection currents \( I_0 \).
phase portrait pictures, we still observe the plateau oscillations, then such oscillations converge to a limit cycle, as in Fig. 6. This case confirms that not only the calcium channels affect the phase portrait, but also the potassium channels act on maintaining the plateau oscillations.

### 3.6. Case 6: activating potassium (K+) channels, while controlling T-type calcium and sodium (Na+) channels

In Fig. 8, we plot the case of controlling the T-type calcium and sodium channels while the potassium channel is activated with $C_m = 2 \mu F/cm^2$. There is a strong delay in the whole three cases (without noise, additive noise, multiplicative noise). This effect is caused by the changes in the membrane capacitance per unit area $C_m$. When we increase the membrane capacitance quantity, the burst discharges of all three cases (without noise, additive noise, multiplicative noise) occur later than in the cases shown in Fig. 7. In particular, in the presence of multiplicative noise, the membrane potential starts bursting at $t = 37$ (ms), while the burst discharges occur at $t = 45$ (ms) and $t = 55$ (ms) in the case of additive noise and in the case without noise. Moreover, before the burst discharges occur, the membrane potential is slightly hyperpolarized compared to the cases in Fig. 7. In the second row of Fig. 8, we obtain similar results as in the case of Fig. 7 but the position and the size of the maximum values in such unstable attractors change.

For all analyzed cases, presented in Figs. 4-8, for both deterministic and stochastic cases, we observe that by controlling the T-type Ca$^{2+}$ and the potassium channels under suitable choices of parameters, we could decrease the burst discharges in STN or in the thalamus in general. Furthermore, the presence of the additive and multiplicative noises with suitable choices of parameters in the system could delay the burst discharges in STN. The interplay between sodium, potassium and calcium channels together with the presence of the noise in the membrane potential model can contribute to various treatments and bioengineering technique modalities for PD including the DBS procedures. In general, the DBS treatment is characterized by delivering electrical impulses to a targeted area of the brain that is responsible for the movement symptoms (i.e. motor symptoms) caused by PD. The electrical targets are to disrupt the abnormal activity that occurs in the brain’s circuitry, which is causing the symptoms. A better understanding of cell membrane potential models at the targeted area of the brain that is responsible for the movement symptoms caused by PD would allow for supporting and improving the DBS therapy.

### 4. Conclusions

We have proposed and described a model of coupled effects of channels and synaptic dynamics in stochastic modelling of healthy brain cells with applications to PD. Specifically, our numerical results have shown that the interplay between sodium (Na$^+$), potassium (K$^+$) and T-type calcium channels together with the presence of noises in the system decrease the burst discharges in STN that can lead to improvements in the motor symptoms of PD. Furthermore, we have found that the presence of the noises in our cell membrane potential model could delay the burst discharges in STN. A delay of the burst discharges in STN could also contribute to the DBS treatments to improve the motor symptoms in PD. As a continuation of this work, it would be instructive to further investigate the developed cell membrane potential model in the presence of random fluctuations in the activation and inactivation variables. Finally, we note that the ideas presented in this contribution may be extended to a mean field
Figure 8. [Color online] Cell membrane potential model in the case of activating potassium (K+) channels, while controlling T-type calcium and sodium (Na+) channels. Parameters: $C_m = 2 \, \mu F/cm^2$, $\sigma_1 = 5$, $\sigma_2 = 0.05$. First row: Time evolution for the membrane potential $V_m$ with no noise (green line), additive noise (red line) and multiplicative noise (blue line). Second row: Phase portraits in the membrane potential model for $(m_{Ca,T}, V_m)$. Third row: the injection currents $I_0$. 
limit model where the averaging over many cells is carried out.

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Conflict of interest

Authors declare no conflict of interest.

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Supplementary (if necessary)