Multi-scale modeling of complex neuronal networks: a view towards striatal cholinergic pattern formations

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Abstract The phenomena related to brain function occur as the interplay of various modules at different spatial and temporal scales. Particularly, the integration of the dynamical behavior of cells within the complex brain topology reveals a heterogeneous multi-scale problem, which has, to date, mainly been addressed by methods of statistical physics such as mean-field approximations. In contrast, the present study introduces an abstract mathematical model of a deterministic nature that provides a robust integral transformation of the microscopic activities into macroscopic spatiotemporal patterns. The existence of the transformation operator is guaranteed by the convergence of a repetitive patching of the network domain with its fundamental domains that express the local topologies of the tissue. Depending on the choice of the local connectivity function, this framework represents a computationally efficient generalization of the classical Kirchhoff's, Hebbian, and Hopfield's approaches. The capabilities of this multi-scale method have been evaluated within the structure of the dorsal striatum of rats, a brain region with major involvement in motor and cognitive information processing. Numerical simulations suggest the formation of characteristic spatiotemporal patterns due to the activation of cholinergic interneurons.

Keywords Multi-scale transformations • Mathematical modeling • Dorsal striatum • Rat

1 Introduction

The interplay of neuronal processes at different spatial and temporal scales is a heterogeneous multi-scale problem that has seriously attracted the attention of scientists in recent years. In particular, the functional integration of synaptic processes (nm scale) within

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neuronal network processing (mm-cm scale) defines such a multi-scale problem. Understanding the transition between these scales is a key to gaining insight into the correlations between neuronal topology and information processing within deep brain structures. To date, the most common approach is to connect microscopic single-cell behavior to the global macrostate of the central nervous system analogously to the procedures applied in statistical mechanics [1–5]. Deterministic, field-theoretic [6–8], and more statistical approaches [9, 10] have been vigorously developed. Particularly, structure-based bottom-up models such as multi-compartmental simulations and simulations of networks comprising physiologically simple elements provide powerful strategies to address multi-scale transition problems. In brief, multi-compartmental simulations rely on experimental parameters obtained from cell morphology and kinetics of voltage- and calcium-dependent ion channels and describe the electrogenesis and spatiotemporal propagation of action potentials in single cells and in small and moderately sized networks, whereas, more computationally efficient models for larger neuronal networks rely on less biological properties and consider neural populations of homogeneously distributed identical neurons that have similar properties and receive excitatory and inhibitory synaptic inputs with the same average rate.

The present approach shares common components with both strategies by capturing the essential morphological and physiological traits of a brain region within the model, while intentionally overlooking the computationally expensive geometric properties of cells such as their shape and orientation. Based on experimental studies, the topological and chemical architecture of the network of a neuronal tissue is determined. This network is represented as a triple $T = (\Omega, \Delta, \Psi)$, where $\Omega \subset \mathbf{R}^3$ is a finite set, while Δ and Ψ denote the probability distribution function of specific neuronal types and the connectivity weights between them, respectively. For each brain region, a unique set, $T_n = (\Omega_n, \Delta_n, \Psi_n)$ of N with $1 \leq n \in \mathbf{N}$ is defined, which extends to N in a repetitive manner. In other words, we identify a covering of the space Ω with copies of discrete fundamental domains consisting in minimal generating neuronal assemblies. Starting with the fundamental domain or n -cell, symmetric linear functionals $F_i \in L(C(\Omega_i \times \mathbf{R}^+))$ exist, which converge to a polynomial operator describing the averaging transformations of the activity of single neurons into the activity of a brain region.

By using the strengths of previous approaches, the proposed model becomes an efficient and realistic multi-compartmental model for the transition of the cellular processes up to the system level of neuronal tissues. In contrast to previous strategies, this method does not rely on the integration of large systems of coupled differential equations. By capturing the local topology into the present mathematical formalism, this model enables us to dramatically reduce (a reduction factor of ≈ 1000 for neuronal networks) the dimension of the dynamical system into a small number representing the different neuronal types in a tissue, while simultaneously providing the possibility to increase the size of considered networks. Consequently, it provides an appropriate framework to investigate the dynamical behavior of physiologically accurate models of neuronal activity such as the Hodgkin-Huxley equations on large heterogeneous populations. In addition, this method enables us to verify the significance of microscopic parameters for macroscopic processes, which is a major issue in *in silico* pharmacological studies. Furthermore, the abstract mathematical structure of the model provides a suitable framework for further multi-scale applications, especially in material sciences and statistical physics with explicit information on the constituent molecular compounds leading to the identification of n -cells.

In order to evaluate the capabilities of our mathematical model, we examine the formation of spatial patterns due to cortical cholinergic activations within the dorsal striatum

of rats. The dorsal striatum is a heterogeneous structure within the basal ganglia [11–14] with an average volume of $50.1 \pm 3.7 \text{ mm}^3$ [15] and a neuronal (medium spiny neurons) density of 84900 per mm^3 [16] (a scale difference of 10^6 orders of magnitude).

Previous studies [17, 18] have already suggested that the striatum possesses the topology and intrinsic mechanisms necessary to orchestrate specific pattern formations. Particularly, Carrillo-Reid and colleagues [17] showed that striatal pattern formations are produced at the microcircuit level by the activity of cell assemblies by using Ca^{+} imaging techniques on transverse corticostriatal slices of Wistar rats. This experimental observation supports our idea of n-cells as pattern-generating fundamental domains within neuronal tissues, especially the dorsal striatum. Although these studies focused on the activity patterns induced by the *N*-methyl-D-aspartate (NMDA) receptor activations, recent studies on cholinergic interneurons [19] further suggest that these minority populations should be considered in analyses of striatal pattern formations.

Numerical simulations of the model based on this information suggest the formation of characteristic spatial patterns in a frequency range of $\approx 50 \text{ Hz}$ comparable with local-field potential (LFP) observations in human subjects.

2 Methods

The cytoarchitecture of the dorsal striatum of rats has already been described in several studies. In general, the heterogeneity of the neuronal populations of the dorsal striatum in rats (similar to most mammals) is based on the appearance of morphological and neurochemically distinct neuronal subtypes: About 95% of the whole neural population comprises γ -aminobutyric acid (GABA) releasing medium spiny neurons [20], which express different receptor subtypes, particularly the dopaminergic D_1 and D_2 receptors [21] and have been shown to be projection neurons by retrograde axonal transport methods [22]. The remaining striatal neurons are interneurons (i.e., without projection axons out of the striatum) [23, 24]. Among these are large aspiny cholinergic neurons [25–27] and medium aspiny neurons, which use GABA as a transmitter [27, 28]. In contrast to these well-characterized interneuron subtypes, the striatum contains a group of cells immunoreactive for tyrosine hydroxylase (aspiny dopaminergic neurons), which have been described by Tashiro et al. [29] and Betarbet et al. [30] in rats. The projection neurons receive significant inputs from cortical structures [20], thalamus [31], and mid-brain dopamine neurons [32, 33], which have been identified at the ultra-structural level with immunohistochemical localizations of glutamate and dopamine or their synthesizing enzymes. In addition, the medium spiny neurons appear to be the target of GABAergic feedback from the lateral globus pallidus [34] and sparse glutamatergic responses from the subthalamic nucleus [35]. Furthermore, the projection neurons receive inputs from the large aspiny cholinergic neurons, which in turn receive inhibitory symmetric inputs from the axon collaterals of medium spiny neurons containing substance P and excitatory asymmetric inputs, which resemble those from the cortex and thalamus to the projection neurons [36]. In addition, the medium spiny neurons are interconnected with the aspiny, parvalbumin- and somatostatin/NPY-coexpressing GABAergic interneurons, which also make symmetrical synapses with the somata and dendrites of other interneurons. The dopaminergic aspiny interneurons have also been shown to provide inputs to the medium spiny neurons, while simultaneously receiving cholinergic inputs from the large aspiny interneurons. The output of the medium spiny neurons divides their population into two approximately equal groups,

which selectively express dopaminergic D_1 and D_2 receptors. The D_1 -expressing neurons use the direct pathway and send a sparsely arborized axon to the lateral globus pallidus while extending further collaterals into either medial globus pallidus or the substantia nigra. The D_2 -expressing neurons on the other hand represent the indirect pathway of the basal ganglia and project exclusively to the lateral globus pallidus. The composition of all this anatomical and chemical information suggests a network representing the complete topology of the striatum (Fig. 1).

2.1 Mathematical model

In the following, we will introduce a general mathematical model to describe the pattern formations within the dorsal striatum as a multi-scale process. Although an abstract formalism is used to describe the model, we use the biological terminologies in parallel to show its appropriateness for the purposed problem. Furthermore, we skip the proofs of the lemmas and propositions, which are indeed straight consequences of the model construction.

Let us, without the loss of generality, assume that the considered material (neuronal tissue) is composed by $k \in \mathbf{N}$ distinct microscopic elements (cell types) and let $M^l = (V^l, E^l)$ with $(l \leq k)$ denote its comprising sub-networks based on the type of microscopic elements l , which are represented as nodes in V^l and their connections or edges E^l within the whole tissue. The structure of the neuronal tissue can now be described as a network $M = (\cup_l V^l, \cup_l E^l)$. For a given spatial distribution function of the nodes in the material (experimental boundary conditions), there exists an up to affine transformation unique

Fig. 1 Schematic representation of the cytoarchitectural network of the dorsal striatum. The medium spiny neurons (MSN) denoted by D_1 and D_2 coexpressing the respective types of dopamine receptors receive inputs (pink) from the striatal interneurons (GABA: GABAergic interneurons; ACh: cholinergic interneurons; DA: dopaminergic interneurons), while reciprocally connecting within their population and with the cholinergic neurons. They also receive extra-striatal inputs (black) from the cerebral cortex and thalamus (glutamatergic) as well as dopaminergic inputs from the midbrain areas such as the substantia nigra pars compacta. In turn, the MSNs project to the lateral globus pallidus (LGP) and globus pallidus (GP: medial and lateral parts) as well as substantia nigra (SN) depending on the activation of the corresponding dopamine receptors

metric embedding of $M^l \hookrightarrow \mathbf{R}^3$, which implies a realistic representation of the sub-networks in the three-dimensional Euclidean space. Indeed, the existence of such an embedding is guaranteed by Bourgain's theorem [37], which states that for every n -point metric space there exists an embedding into Euclidean space with distortion $O(\log n)$. The representation provides a triple $T^l = (\Omega^l, \Delta^l, \Psi^l)$, where $\Omega^l \subset \mathbf{R}^3$ is a finite set with a canonical metric, while Δ^l and Ψ^l denote the probability distribution function of the distinct microscopic element and the connectivity function within its population, respectively. The association function $\chi : T^l \rightarrow T^j (\forall l \neq j, j < k)$ patches the network representations of the distinct populations by identification of the common nodes and fixing the connectivity functions. For $\Omega = \bigcup_l (\Omega^l \setminus \chi(\Omega^l)^c)$ with c denoting the multiplicity of the common nodes in the union of $\chi(\Omega)$ -cosets, a global distribution function with $\Delta|_l := \Delta^l$, and a global connectivity Ω function with $\Psi|_{\Omega^l \cup \Omega^j} := \Psi^l \Psi^j$ if $\chi(\Omega^l) \subset \chi(\Omega^j)$ or $\chi(\Omega^j) \subset \chi(\Omega^l)$, there is now a representation of the whole material $T^\chi = (\Omega, \Delta, \Psi)$.

Definition 1 Let $\Omega_n \subset \Omega$ be the minimal non-empty subset including at least one of each microscopic subtype, such that $\#A = n < \infty$ for $A = \{x \in \Omega_n | \Delta_n(x) = 0\}$ and $\Psi_n(A \times A) \neq \emptyset$, where $\Delta_n := \Delta|_{\Omega_n}$ and $\Psi_n := \Psi|_{\Omega_n}$ are the restrictions of the distribution function Δ and the connectivity function Ψ , respectively, on Ω_n . Then we call the triple $T_n = (\Omega_n, \Delta_n, \Psi_n)$ an n -cell of the network or its fundamental domain. In other words, the n -cells, in case of existence, capture the complete topological properties of Ω as a minimal generating set.

The appropriateness of the framework of n -cells for striatal pattern formation analysis is implicated by Ca^{2+} imaging methods, which show that the activation of striatal NMDA receptors induces a sequential activity of assemblies of striatal neurons. These assemblies are generated by pattern-formation mechanisms intrinsic to the striatal activity [17, 38].

Lemma 1 (Repetitive covering) *If an n -cell T_n exists, then there is a continuous χ operator G so that for some finite $m \in \mathbf{N}$*

$$\bigcup_i G^m(T_n^\chi) = T^\chi. \quad (1)$$

Now, Let $u^x \in C(\Omega \times \mathbf{R}^+)$ be the continuous solution of a differential equation (for example the integrate-and-fire equations) in time $t \in [0, T] \subset \mathbf{R}^+$ in $x \in \Omega$ describing the dynamical state of the microscopic element depending on its position within the tissue, which in turn characterizes its morphological type.

Definition 2 For any n -cell T_n , there is a symmetric linear functional $F_n \in L(C(\Omega_n \times \mathbf{R}^+))$ defined by the scalar product

$$F_n[u^x(t)] := (\Psi_n, \Delta_n)[u^x(t)] = \int_{\Omega_n} \Psi_n(x) \Delta_n(x) u^x(t) dx, \quad (2)$$

defining the local average of the dynamical states of all nodes within Ω_n .

Remark 1 The Ψ_n functions define the weights of the connections between neurons.

Thus, the functionals F_n represent appropriate choices of the connectivity functions Ψ_n , local generalizations of Kirchhoff's law ($\Psi_n \in \{0, 1\}$), Hebbian network theory ($\Psi_n|_{ij} = x_i x_j$), as well as Hopfield network theory [39]. In particular, Hebbian formalism defines the weight functions as the product of synaptic inputs from a neuron i to neuron j . By defining the Ψ_n functions as multiple products of synaptic inputs from the surrounding neurons, the

functionals F_n represent a natural generalization of the Hebbian theory. An exclusion of reflexive connections in Ψ_n will then consequently lead to Hopfield network structures.

Proposition 1 *The successive sequence of functionals $(F_i) \in L(C(\Omega_i \times \mathbf{R}^+))$ for $i \geq n$ defined as $F_i[u^x(t)] := \sum_{l=0}^i \chi^l(F_n[u^x(t)])$ with $x \in \Omega_i$ and $\Omega_{i+1} = G(\Omega_i)$, converges in $m < \infty$ steps to a polynomial operator describing the structural average of the dynamical behavior within a material*

$$G^i(F_n)[u^x(t)] = (\Psi, \Delta)[u^x(t)], \quad (3)$$

$$= \sum_{l=0}^m \chi^l(F_n[u^x(t)]). \quad (4)$$

The proof of this proposition is straightforward by using the construction of n-cells and a direct consequence of Lemma 1.

2.2 Numerical simulation

MATLAB was used as the numerical simulation platform of the model. The neurons have been realized as homogeneously distributed diamond-shaped nodes on a plane in the shape of the -0.8 mm Bregma level of the caudate putamen of the rat. In order to achieve high computational efficacy, we have rescaled the overall number of striatal neurons to 6,000 nodes while keeping the observed proportions of the neuronal populations, i.e., 95% projection neurons, 2% cholinergic interneurons, 2% GABAergic interneurons, and about 1% dopaminergic interneurons of the total number. The neuronal specification of the nodes was based on their local topology provided by experiments (Fig. 1). Since these neurons are homogeneously distributed, a striatal n-cell is defined as a small network of 100 cells (95 projection nodes, two with cholinergic topology, two with GABA interneuron topology, and one dopaminergic node). Based on the small size of the neurons in comparison to the size of the dorsal striatum and the decreasing amplitudes of the traveling waves descending exponential functions (weights) were assumed for the local connectivity functions Ψ_n within the n-cell. The activity of each neuron was modeled with integrate-and-fire equations. For the investigation of activity patterns, the cholinergic nodes were modified with an initial normalized (in length and level) single-pulse activation function with a duration of 5 ms. The duration of a whole pattern formation cycle, i.e., from the initiation to the overall spreading of the activity finalized by the inactivation of all nodes, provides in turn a measure for the frequency of pattern formations that have been qualitatively compared with local field potential estimates in the same area. For a progressive visualization of the pattern formation process, the simulation was discretized in time with a step size of $1/4$ of the frequency.

3 Results and conclusions

Numerical simulations of the described mathematical model on the topological structure of the dorsal striatum of rats have revealed spatiotemporal patterns that correspond directly to the averaging stage of the respective functionals F_i (Fig. 2).

The results show that the induced activity of the sparsely distributed cholinergic neurons within the dorsal striatum (Fig. 2a) leads to the identification of surrounding n-cells (Fig. 2b) in terms of their activity functionals F_n and a subsequent convergence of the functionals into an overall integration of the activity (Fig. 2c), which reflects the convergence of the functional F_i in finite steps. The single-pulse activation induces abrupt spreading and declining of spikes. Furthermore, considering the temporal step-size of 5 ms (giving a total cycle duration of 20 ms), we could observe the velocity of the pattern formation, which provides a cycle from initiation of the activity to the total inactivation (ongoing inactivation process: Fig. 2d) of the network. This observation suggests a frequency of the formation of characteristic spatial patterns in a range of ≈ 50 Hz, which is comparable with LFP observations in human subjects [40].

Using only two integration steps (first: solution of the integrate-and-fire equation for single cells; second: integration of the solution using the topological weights) our model reveals characteristic pattern formations respective to the morphological structure of the activated cells. Most of the active cells show correlated activity (80%) at any time, which suggests that the network activity is caused by spatiotemporal dynamics of the cell

Fig. 2 The spatial pattern formation with the dorsal striatum of rats (2D-projection at -0.8 Bregma level) due to the cortical activation of cholinergic neurons. The cycle of pattern formation has a frequency of ≈ 50 Hz (20 ms duration) and shows at each step (a–d) the distribution of active (pink) and inactive (grey) neurons. In particular, a) shows the initial activation (pink coloring) of the sparsely distributed cholinergic neurons followed by b) the activation of a few n-cells containing the activated ACh-neurons based on the predefined local topologies. c) reveals the induced “overall” activation of the neuronal populations within the dorsal striatum as the n-cell functionals converge and d) represents the ongoing inactivation (grey coloring) process throughout the structure. The temporal step-size of the snapshots is 5 ms

population and not by chance correlation of neuronal pairings. By unifying the conditions for stimuli, this result is validated by electrophysiological measurements of the striatal activity pattern measured on corticostriatal slices of the brain of Wistar rats caused by stimuli of 0.1-Hz frequency [17], observing an average correlated activity among active cells at any given moment of $77 \pm 4\%$. In addition, our simulations of the spatiotemporal patterns generated by single-pulse activations of other neuronal populations (medium spiny neurons) of the striatum (data not shown) showed similar convergence behavior (with different convergence speeds), while varying the pattern formation frequencies and forming characteristic spatial patterns.

Our model suggests the existence of different activity patterns within the striatum, depending on the local connectivities of the cells. The activation of the few sparsely distributed cholinergic interneurons leads to fast and robust activation of the majority of striatal cell populations. The fast propagation of the cholinergic signals throughout the striatum might also reveal an insight into the pathophysiology of the sedative effects of muscle relaxants. In addition, the results (the transition from Fig. 2a to b) show a direct relationship between the morphological structure of the acetylcholine-expressing neurons and the activation patterns. These large aspiny neurons tend to non-radially activate the more distant cells rather than those in more proximate distances.

In agreement with previous studies [41, 42], we have been able to observe the sensitivity of the striatal activity with respect to the local connectivities and the initial activity of the different types of neurons, which has been hypothesized to play a role in the choreiform movements in Huntington's disease [42] in the case of asymmetric synaptic connectivities. However, the present model appears to capture more morphological information, while being computationally more efficient in its capability of simulating the activity of a large amount of cells in the model and providing robust results. Furthermore, our results, in agreement with previous studies [17, 18], suggest that the dorsal striatum is a central pattern generator, which transforms afferent inputs into detailed spatiotemporal outputs.

Based on the simulation results, the mathematical model appears to provide an appropriate framework for *in silico* investigations of the cholinergic system within the dorsal striatum. In particular, it enables us to compare the microscopic effects of specific drugs acting on acetylcholine receptors (e.g., nicotine receptors) with their global effect on the activity of the dorsal striatum. Furthermore, the propagation of small parameter fluctuations within the network structure might be used to investigate viral propagations along neuronal arborizations, which is a crucial issue of recent optogenetic tracing studies [43]. In addition, the generality of the model suggests its appropriateness for further applications in biomechanics, signaling networks, and material sciences.

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