Journal of Theoretical Biology 386 (2015) 34–43

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Inferring pathological states in cortical neuron microcircuits

Jakub Rydzewski [a], Wieslaw Nowak [a,*], Giuseppe Nicosia [b]

[a] Institute of Physics, Faculty of Physics, Astronomy and Informatics, Nicolaus Copernicus University, Grudziadzka 5, 87-100 Torun, Poland
[b] Department of Mathematics and Computer Science, University of Catania, Viale A. Doria, 6-95125 Catania, Italy

HIGHLIGHTS

- We develop a methodology for classifying states in a model biased by uncertainties.
- We test this protocol on a cortical neuron microcircuit.
- We delimit domains of parameters that cause a pathological neuron state in the model.

ARTICLE INFO

Article history:
Received 27 April 2015
Received in revised form
3 September 2015
Accepted 6 September 2015
Available online 12 September 2015

Keywords:
Ordinary differential equations model
Sensitivity analysis
Cortical neuron microcircuit
Clustering
Neuroinformatics

ABSTRACT

The brain activity is to a large extent determined by states of neural cortex microcircuits. Unfortunately, accuracy of results from neural circuits' mathematical models is often biased by the presence of uncertainties in underlying experimental data. Moreover, due to problems with uncertainties identification in a multidimensional parameters space, it is almost impossible to classify states of the neural cortex, which correspond to a particular set of the parameters. Here, we develop a complete methodology for determining uncertainties and the novel protocol for classifying all states in any neuroinformatic model. Further, we test this protocol on the mathematical, nonlinear model of such a microcircuit developed by Giugliano et al. (2008) and applied in the experimental data analysis of Huntington's disease. Up to now, the link between parameter domains in the mathematical model of Huntington's disease and the pathological states in cortical microcircuits has remained unclear. In this paper we precisely identify all the uncertainties, the most crucial input parameters and domains that drive the system into an unhealthy state. The scheme proposed here is general and can be easily applied to other mathematical models of biological phenomena.

1. Introduction

A wide variety of natural phenomena such as the locust swarming behavior (Buhl et al., 2006), features of the escape panic in humans (Li et al., 2014), the apoptosis process (Janes et al., 2005) and the optimal triggering level in economics (Lee and Lee, 2010) are well described by mathematical models. Using ordinary differential equation (ODE) modeling, computer simulations and statistical analysis are desirable for contrasting empirical observations of any dynamical phenomena or evolution. Therefore, developing a complete methodology for an analysis of such complex processes is of crucial importance, particularly in biology. Typically, patterns in behaviors of studied phenomena are revealed after a complexity reduction by, i.e. sensitivity analysis. After that step, a holistic puzzle may become a simple sum of its components, which can be further cluster in sets in such a way that objects in the same group are more similar to each other than to those in other groups. Particularly, a need for such a protocol is very appealing not only in systems biology (Marino et al., 2008), but also in neurology.

The human brain poses a great challenge to all branches of science, including systems biology, neuroinformatics and applied mathematics. The computer simulations of neuronal activities are an indispensable source of new information and understanding (Markram, 2007). Cognitive processes take place in the brain cortex. Thus, the concept of a neuronal microcircuit, a group of connected neurons performing a specified function (Opris and Casanova, 2014), is very popular in the studies of both the normal (N) and pathological (P) activities of the brain. Numerous diseases, such as autism (Markram and Markram, 2010; Duch et al., 2012), schizophrenia (Konstantoudaki et al., 2014), Parkinson's disease (Lopez-Huerta et al., 2013), are subject of intensive computational studies. The mechanisms underlying cortical dysfunctions are of high significance, because the cognitive changes in the Huntington's disease (HD) can

* Corresponding author.
E-mail addresses: jr@fizyka.umk.pl (J. Rydzewski), wiesiek@fizyka.umk.pl (W. Nowak), nicosia@dmi.unict.it (G. Nicosia).

http://dx.doi.org/10.1016/j.jtbi.2015.09.004
0022-5193/

be explained by pathological intracortical circuits. Recently, the promising model of the neuronal microcircuit has been proposed by Giugliano et al. (2008) and La Camera et al. (2008). Later, in the paper by Gambazzi et al. (2010), it has been successfully used in the studies of HD – an autosomal dominantly inherited neurodegenerative disorder. Specific clinical manifestations of HD involve motor and cognitive impairments, i.e. chorea, depression and problem with decision-making (Vonsattel and DiFiglia, 1998).

In the paper by Gambazzi et al. (2010) experimental recordings on the electrical activity of the in vitro neuron colonies have been collected. The electrophysiological activity measurements of a group of neurons led to the data, expressed in terms of rate functions R, for both healthy (or normal N) and pathological (P) states. A relatively simple mathematical model has been applied to interpret data from Giugliano et al. (2008). One may expect that such a model might be used for identifying of malfunctioning neuron activities in further studies of the other brain pathologies, i.e. autism spectrum disorders or schizophrenia. The model involves a set of the parameterized nonlinear differential equations. Unfortunately, up to now, it has been impossible to discriminate what parameters should be used for modeling normal activities of the microcircuit and what are suitable for the description of HD (or other) pathological states.

In this paper the outlined methodological problem is tackled with an emphasis on revealing the experimental data uncertainties and labeling a multidimensional space of the input parameters that are crucial for inferring pathological states in the HD disorder model. Thus, our findings may contribute to the identification of "glitches" in the behavior of any cortical circuit, for instance inconsistencies in neuronal spike-bursts that forbids the system from providing "healthy", unbiased responses. This would be important in achieving a better mechanistic understanding of a disease etiology. Furthermore, the developed protocol is suitable in any kind of a biology-based mathematical model that inherits uncertainties from experimental measurements.

Our intermediate goal was to use the sensitivity analysis (SA) approach (Saltelli et al., 2000, 2004) to check possible couplings between the parameters in the model from Giugliano et al. (2008). We have selected this model as an illustrative example of our general methodology. A set of distinct methods were used: Morris (Morris, 1991), Sobol' (Saltelli and Sobol, 1995), Fourier amplitude sensitivity testing (FAST) (McRae et al., 1982) and stochastic sampling (Rubinstein and Shapiro, 1993). Then, the rate function data from our own extensive simulations of the microcircuit model activity has been collected. The analysis of inter-burst interval data histograms, based on Poisson distributions, allowed us to select the subspaces of parameters leading to the N and P states.

Following protocol for discovery of mathematical models states, which are biased with uncertainties from an experimental work, is proposed and tested:

1. Constructing a mathematical model.
2. Deriving sampling distributions for all input parameters in the model.
3. Identifying uncertainties of the input parameters inferred from experimental studies by several sensitivity analysis methods (i.e. Morris, FAST, and Sobol').
4. Analysis of sensitivity analysis results; the model complexity reduction.
5. Performing the constraint sampling simulations.
6. Unrevealing hidden patterns of the model.
7. Classifying the models' states.

2. Cortical neuron circuit model

In general, models can be divided into two categories, deterministic and stochastic. In the first category, the output of the model is entirely determined by the input factors and its topology. Therefore, the same input factor will result in the accurately identical output. The replicas of the model will not vary in any detail. Consequently, only uncertainty affecting the result of the model is associated with an input factors variation. This type of so-called reducible uncertainty, derives from a lack of knowledge in determining the nominal values and sampling domains. On the other hand, stochastic models will not result in the same output for identical sets of the input factors. In such models, random variables are introduced, which leads to the stochastic behavior of the whole system. In contrast to the reducible, this type of uncertainty is termed irreducible.

2.1. Mathematical model of neuron microcircuit

In the brain cortical neurons are organized within microcircuits. The activity of a microcircuit may be characterized by the instantaneous firing rate $R(t)$ function, related to an action potential. Neurons transmit information by a train of action potentials. Such a quantity is referred to as *spike trains*. An activity can be represented as a sequence of spike timings. Let us define $\rho(t)$, the neural response function, to be a set of impulses modeled by $\delta(t)$ Dirac's function, one for each action potential

$$\rho(t) = \sum_{i=1}^{k} \delta(t - t_i) \tag{1}$$

where k is the total number of spikes and t_i are instants when each spike occurred.

The instantaneous firing rate $R(t)$ is defined as

$$R(t) = \frac{1}{M} \sum_{j=1}^{M} \rho_j(t) \tag{2}$$

where M is the number of measurements and $\rho_j(t)$ is the neural response function for each trial.

We define a neuronal *burst* as the sum of firing intervals within the burst. An inter-spike interval (ISI) is defined as the time interval between consecutive spikes. The duration of a burst is the sum of the ISIs within that burst (see Fig. 1).

To test the outlined methodology, minimalistic firing rate-based model of the microcircuit has been chosen to simulate firing of a homogeneous population of cortical neurons (Wilson and Cowan, 1972). The recursive aspects of the model are assembled in two ways: (i) positive feedback determines the potential of a network to burst within a group of neurons and (ii) negative feedback terminates these bursts, which results in irregular stochastic behavior of cortical circuit. The model was implemented to

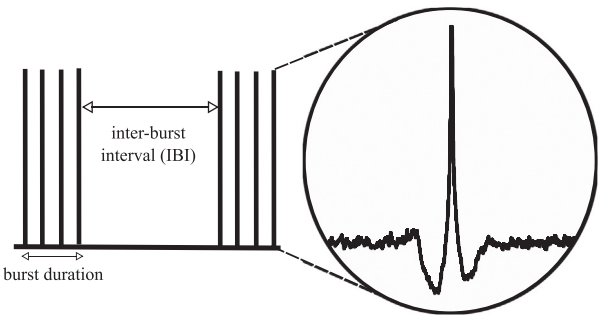

Fig. 1. A schematic definition of a burst duration and an inter-burst interval.