

RESEARCH ARTICLE



Mathematical Modelling of Basal Ganglia for Parkinson's Disease: A System Biology Approach

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Abstract

Objectives: To mathematically model the oscillatory behaviour of Basal Ganglia for Parkinson's disease as well as to simulate the model by using Cell designer and Scilab. **Method:** The pathway of Parkinson's disease was downloaded from the KEGG database and oscillatory behaviour was studied using scilab programming and cell designer tool. In this work, the pathway of Parkinson's disease was loaded to cell designer, that is working on the basis of systems biology mark-up language, and analysed the entire pathway. **Findings:** The oscillatory behaviour of basal ganglia is due to the absence or lack of dopamine and it can be verified with the aid of Scilab, programming. **Novelty:** Through this study, the computational tool cell designer and scilab programming, was newly introduced for analysis and modelling of oscillatory behaviour of neurons. It is concluded that the pathway and simulation of all disease can be analyzed in an accurate way using this software with in a short time period.

Keywords: Scilab; Cell designer; Basal ganglia; Parkinson's disease

1 Introduction

Parkinson's disease is one of the high-risk neurodegenerative diseases with symptoms of involuntary tremor of the hand and head, muscle rigidity, slow movement, and imbalance of posture⁽¹⁾. The main pathological causes of Parkinson's disease ascribe to the loss of dopamine neurons in the basal ganglia⁽²⁾, which consists of the striatum, globus pallidus (GP), subthalamic nucleus (STN), compacta (SNc), and reticular (SNr) structure of the substantia nigra⁽²⁾. The loss of dopamine neurons causes beta oscillations with frequencies ranging from 13 Hz to 30 Hz in the basal ganglia^(2,3). So, it is very important for understanding the mechanism of Parkinson's disease to analyze the oscillations in the basal ganglia.

Furthermore, a model with two STN and one GP populations are considered to get the stability boundary of oscillations⁽²⁾. However, GP population has not been divided into the external and internal segment (GPe and GPi) in the above models, where GPi is the main output structure of the basal ganglia and also used to treat dystonia by deep brain electrical stimulation in medicine⁽¹⁾. Actually, GPi and GPe are affected by different intensities from striatum to result in Parkinson's disease. Therefore, it is necessary to add both GPe and GPi into the basal ganglia network. Researchers studied the mathematical modelling and oscillatory behaviour studies using several differential equations and almost all mathematical modelling is done by using, firing rate equations, Terman model and Gillies and Willshaw model. In all the above-mentioned methods complicated differential equations were used to find the neural simulations. All of them are very complicated and time consuming. Based on the above considerations, we introduce a new mechanism of finding oscillatory behavior with the help of system biology software cell designer and with the help of scilab programming.

2 Material and methods

Mathematical modelling and simulation of basal ganglia for Parkinson's disease is done by using cell designer and verified using Scilab. The following tools and programmes used to carry out this work.

2.1 KEGG

Pathway of Parkinson's disease collected from KEGG. Kyoto Encyclopedia of Genes and Genomes or KEGG is a collection of databases dealing with genomes, enzymatic pathways, and biological chemicals.

2.2 Cell Designer

Modelling and simulation done by using Cell designer. Cell designer is software mainly used for drawing biological pathways and also represent them in a graphical mode.

2.3 SBML

The Systems Biology Markup Language (SBML) is a representation format, based on XML, for communicating and storing computational models of biological processes⁽⁴⁾. It is a free and the open standard software support a community of users and developers. SBML can represent many different classes of biological phenomena, including metabolic networks, cell signalling pathways, regulatory networks, infectious diseases, and many others^(5,6). It is the best way for representing computational models in systems biology today.

2.4 Scilab

Scilab is an open source, cross-platform numerical computational package and a high-level, numerically oriented programming language. Scilab is an interpreted language. This generally allows getting faster development processes. It can be used for signal processing, statistical analysis, image enhancement, fluid dynamics simulations, numerical optimization, and modelling, simulation of explicit and implicit dynamical systems and symbolic manipulations.

3 Methodology

In early used methods they are using complex equations to find out the oscillation, for that spike interval, coefficient variation and fano factor many things are required. But this scilab programming makes these process very simple by assigning parameters, in this study the mathematical modelling of basal ganglia was done by using cell designer and Scilab. It follows Two Population Models. A localized neural population composed of an excitatory sub population and an inhibitory sub population⁽³⁾. The evolution of the activity of the neural population is described by the nonlinear differential equations. Population models are useful method of looking at the nonlinear dynamics involved in neuronal activity and allow the global effect of the manipulation of connections to be observed. The model consists of two neuronal populations: the glutamatergic neurons of the subthalamic nucleus (STN) and the GABAergic neurons of the external segment of the globus pallidus (GPe)⁽²⁾. Each population connects both to itself and the other population. The following parameters were used to write programs in scilab. The oscillatory behaviour can be analysed with the help of scilab by using the parameters given below.

Scales the weights in the system between healthy and Parkinsonian values, where = 0 corresponds to the healthy state and = 1 corresponds to the Parkinsonian state.

The strength of self-excitation in the STN.

The size of the constant input to the STN from the cortex.

In scilab by considering the above parameters it will produce the output as graphs and it can be verified with the help of cell designer. Then the pathway of Parkinson's disease was loaded which is available in the KEGG database. While loading these pathways it will check the presence of dopamine. If dopamine present, it shows normal behaviour and oscillatory behaviour indicates the absence of dopamine and it can be analysed with the help of graphical visualization.

4 Results

The results suggest that parkinsonian brain oscillations can only rise under particular cortical conditions, since the cortical pathway is prokinetic, which mean that oscillations can only be seen during initiation of movement. Getting closer to the system parameter found in Parkinson conditions, oscillations become possible. Dopamine and Parkinson's disease is characterized by two main symptoms, tremors and losing the ability to move. This results from malfunctioning of Dopamine. The dopamine produced by the SNc is used as a signal in two pathways in the basal ganglia. Dopamine acts as an excitatory impulse for the direct pathway and an inhibitory impulse for the indirect pathway. A small amount of dopamine in Parkinson's disease leads to more inhibition and less excitations of the thalamus. This will result in an abnormal behaviour. The lack of inhibition to the indirect pathway combined with the interaction between the neurons STN and GPe will results an oscillatory behaviour.

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If the dopamine is present, it means the neurons will exhibit normal behaviour when the amount of dopamine decrease it will start to show the oscillatory behaviour. In scilab by including these parameters we can do programming, output obtained as graphs, where the presence of dopamine results linear graph, otherwise shows oscillations. The same can be verified with the help of cell designer for that we have to load the pathway of Parkinson's disease which is available in the KEGG database. While loading these pathways they will check the presence of dopamine if it is present, they will show normal behaviour otherwise shows oscillatory behaviour and can be analysed with the help of graphical visualization.

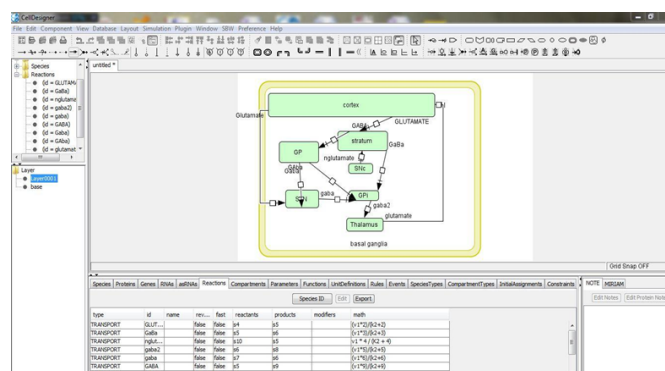


Fig 1. Pathway of Parkinson's diseases loaded in Cell Designer

5 Discussion

Parkinson's disease is one of the major neurological disorders and is found to be increasing day by day. The disease is characterized by resting tremor, slowness of movement, poverty of movement and rigidity. The degeneration or death of dopamine producing neuronal cell is the major cause of this disorder. In this study the oscillatory behaviour of dopamine was analyzed with the help of scilab and cell designer. Many researchers studied the mathematical modeling and oscillatory behavior using several differential equations and almost all mathematical modelling was done by using, firing rate equations, Terman model and Gillies and Willshaw model. In all the above-mentioned methods complicated differential equations were used to find the neural simulations.

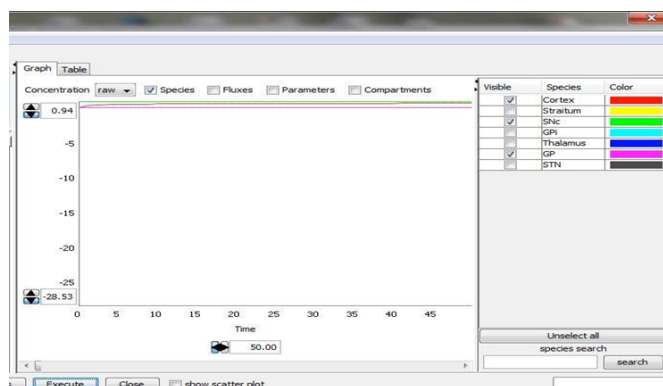


Fig 2. Normal behaviour of the neuron due to the presence of dopamine.

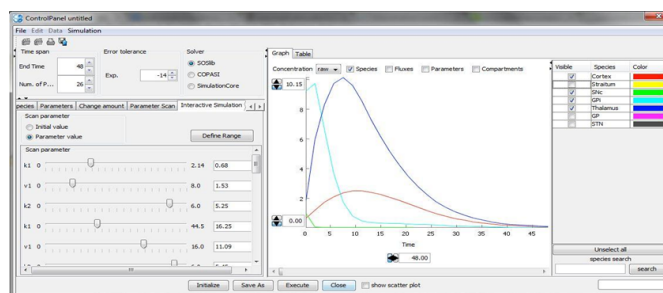


Fig 3. The loss of dopamine results Parkinson's disease. In this diagram the dopamine is absent as well as the transport of glutamate doesn't take place from the thalamus to the cortex, as a result an oscillatory behaviour occurs in the basal ganglia. This will generate the Parkinson's disease

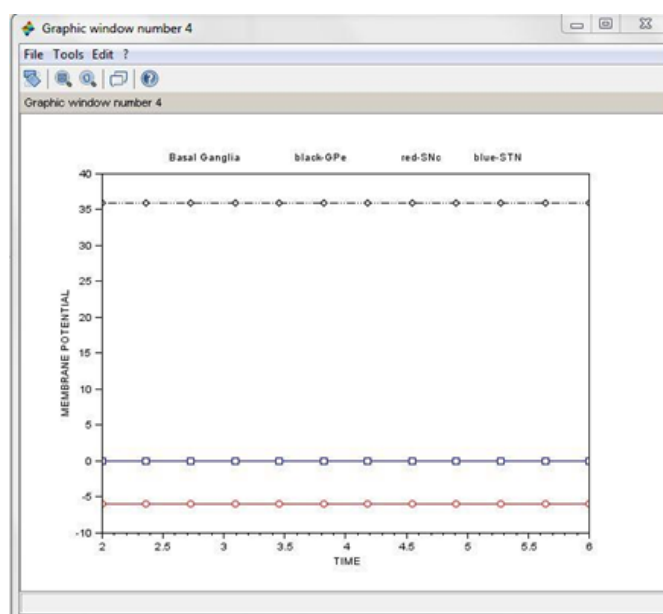


Fig 4. Scilab Graph showing the overall neuron behaviour

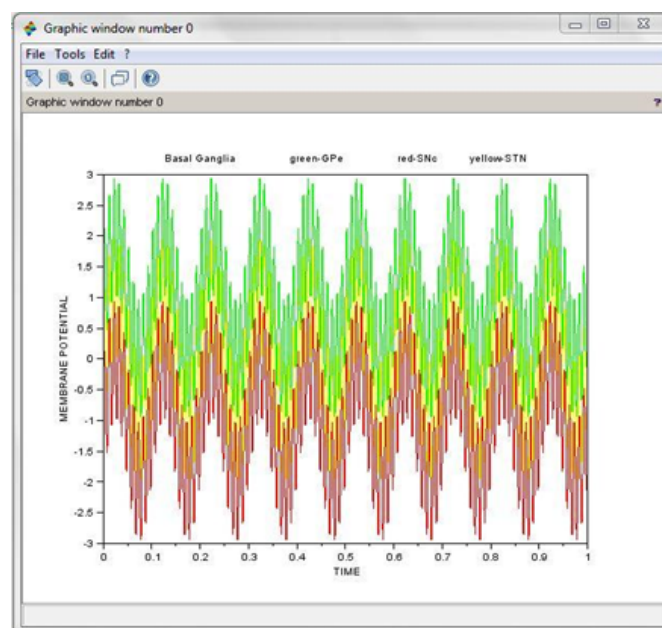


Fig 5. Neurons showing oscillatory behaviour.

Bi et al in 2020 analyzed the conditions of beta oscillation in the basal ganglia to understand the mechanism of Parkinson's disease by STN-GPe-GPi model for different cases⁽²⁾. Correspondingly, Lopez et al in 2021 proposed a novel dynamical model for the BGthalamo-cortical network which reproduces the fine-tuning of the oscillatory activity of the BG with changing DA levels and explained how different frequency-band oscillations can emerge due to the BG activity based on dopaminergic regulation⁽⁷⁾. Similarly, Maith et al in 2020 discussed the implications of spiking neuro-computational model of the basal ganglia and compare its results also with the popular “rate model” of the basal ganglia and the result suggested that a model-based analysis of imaging data from healthy and Parkinsonian subjects is a promising approach to better understand Parkinson-related changes in the basal ganglia and corresponding treatments when compared to “rate model” of the basal ganglia⁽⁸⁾.

Cohen & Frank in 2009 focused on two classes of models: those that incorporate aspects of biological realism and constrained by functional principles, and more abstract mathematical models focusing on the higher-level computational goals of the BG and suggested that empirical studies ranging from those in transgenic mice to dopaminergic manipulation, deep brain stimulation, and genetics in humans largely support model predictions and provide the basis for further refinement⁽⁹⁾. Similarly, Badr et al in 2018 introduced a novel system-level mathematical model of the Basal Ganglia (BG) for kinematic planning and this model is simulated to generate the commands of a redundant manipulator and some symptoms of Parkinson's disease such as bradykinesia and akinesia are simulated by modifying the model parameters, inspired by the dopamine depletion⁽¹⁰⁾. The above-mentioned methods are difficult to understand and take much time for the pathway analysis and also it is very difficult to apply in entire pathways

In the present study the mathematical modeling of basal ganglia was done by using cell designer and Scilab. The scilab programming makes these processes very simple by assigning parameters. By using the scilab and cell designer the result obtained was same as that of studies related to the oscillatory behaviour by using firing rate and other differential equations. The main advantages of using this system biological software are, they are easy and the result can be obtained within a short moment compared to early used methods and also, we can load entire pathway or complete pathway of a disease very easily. So, the pathway of all other diseases can be attained by analyzing the pathway of corresponding disease with the aid of scilab programming and system biological tool cell designer.

6 Conclusion

The mechanism behind the Parkinson's disease can be obtained through the Analysis of conditions of beta oscillation in the basal ganglia. The present study aimed to determine the pathway of PD through scilab programming and system biological tool cell designer. The main advantage of using this system biological software is that the result can be obtained within a short

moment when compared to early used methods and also, we can load entire pathway or complete pathway of a disease very easily. Through this study we have newly introduced a mathematical model for pathway analysis and simulations using of scilab and system biological tools.

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