MODELING THE EFFECTS OF SCHIZOPHRENIA ON WORKING MEMORY IN A MATLAB GRAHPICAL USER INTERFACE

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Summary

Enormous recent advances in easily accessible computational power have increased the significance and usage of mathematical models in biology. The GUI proposed in this paper utilizes one such model created by Qi *et al.* (2016) to model the effects of schizophrenia, a devastating psychiatric disorder, on working memory. Working memory is a type of short term memory concerned with the planning and execution of immediate behavior and actions. The model by Qi et al. utilizes the format of a neurotransmitter interaction matrix, combined with a balancing scheme among these neurotransmitters. It permits the characterization not only of neurochemical details of schizophrenia, but also of various perturbations on working memory, and accurately predicts qualitative changes in the system, due to disease or pharmaceutical interventions. The GUI provides a useful simulation tool for researchers, clinicians, psychiatrists, medical students, and caregivers, and can be used to visualize the consequences of schizophrenia, as well as other diseases or drugs that affect working memory. The mobile matrix output is a visual appealing description of these effects and may be used to explain disease perturbations to patients and families.

CHAPTER 1.   INTRODUCTION

The role of computation in biological research has increased immensely in the past twenty years, and advances in neurobiology and mental diseases coincide with the increased power of easily accessible computation. This increase of computational power has been utilized effectively to provide quantitative models of complex biological systems, such as the simulation models created in the Human Brain Project and the Human Connectome Project. These models not only allow researchers to explain previously measured data and observed interactions, but to also find and/or predict patterns that were unknown before the creation of these models. (Kitano, 2002).

Schizophrenia, a mental disease characterized by a variety of so-called "positive" and "negative" symptoms and cognitive dysfunction, occurs in approximately 1% of the world's population (Bakhshi *et al.*, 2015). Positive symptoms include hallucinations and delusions, while negative symptoms include lack of emotion and reduced social behavior. Modeling the full interactions of neurological diseases, such as schizophrenia, in varying brain regions is a formidable challenge. While individual pathways can be described more or less in their entirety by ordinary differential equations, modeling larger neurological systems often requires much more complicated approaches (Bender *et al.*, 2006). Additionally, a comprehensive understanding of the pathology and effects of mental diseases requires data on both the macro level, which represents the brain's regions, anatomy, density and volume, as well as the micro level, which focuses on neuro-electrical activity and neurotransmitter signaling.

Previous computational research has attempted to model both macro and micro effects in schizophrenia, based on numerous clinical and experimental observations. One intriguing study (Bakhshi *et al.*, 2015) showed that patients diagnosed with schizophrenia tend to have less grey matter and smaller brain volume compared to healthy individuals. In addition, important regions, such as the thalamus and the anterior cingulate cortex, which are involved in processing sensory information, attention and motivation respectively, actually change shape in schizophrenia patients. Both the cause and the exact consequences of the shape change are unknown, but schizophrenia patients generally exhibit negative symptoms associated with the functions of these regions. A study conducted by Arvid Carlsson (2006), which is of special importance here, aimed to describe how the activation and inhibition of the most important neurotransmitters, dopamine, serotonin, glutamate, gamma-Aminobutyric acid (GABA), acetylcholine, and norepinephrine, are altered in schizophrenics. Interestingly, the results showed that schizophrenic symptoms can occur when either too little or too much of a neurotransmitter is present in specific brain regions. In the striatum, for example, a region involved in information processing, too little glutamate or too much dopamine may lead to poor processing. One reason for this imbalance was explored by both Carlsson (2006) and Pogarell *et al.* (2012). It was suspected that certain regions experience an increase in dopamine as a compensation for poor synaptic transmission. The poor transmission causes neural activity to increase, with the consequence that more dopamine is released into associated regions. A computational study conducted by Qi *et al.* (2016) modeled the interactions among neurotransmitters in working memory, or the memory associated with planning, organizing, and completing specific and current tasks, of schizophrenia patients. The prefrontal cortex, which is the main brain region involved in executive function, has been identified as a key area of deficit and malfunction in schizophrenics. Qi's model, while developed to shed light on schizophrenia and how working memory is affected, can also be used to represent other drug abuse and clinical interventions.

While plenty of computation and modeling has been conducted on both the causes and effects of schizophrenia, most of these models are quite complex and require advanced modeling expertise. Therefore they are foreign and inaccessible to researchers and clinicians, who are not trained in computational modeling, and deprive them of the opportunity to utilize these models and their simulation power in order to gain a better quantitative understanding of the perturbed neurotransmitter systems.

The Graphical User Interface (GUI) proposed here, developed in MATLAB, is based on the most recent Qi model of working memory; it expands the usability of the model to all researchers looking for an accessible simulation platform. Specifically, the aim of the project is to enable researchers, clinicians, and students to easily simulate the effects of any perturbation on working memory by giving them the power to change parameters on their own, while also providing a set of pre-defined perturbations. The GUI includes menus with parameters categorized by brain region, so that users can change the values of any parameter to any value within an acceptable range. This option enables them to explore numerous features of the model, which has proven to describe neurotransmitter function in working memory quite accurately, and to adapt it to other neurological diseases. The GUI is able to achieve this feat because of the model's general format, which combines a neurotransmitter interaction matrix with a mobile representing the balances among them. While made with the effects of schizophrenia on working memory in mind, the model is created with the ability to describe any effects on working memory by any outside perturbation. Therefore, researchers will be able to use this GUI for any perturbation in working memory which they desire to simulate.

Literature Review

The intersection of computation and biology has opened the door for the creation of quantitative descriptions of biological systems and the effects of disease on these systems. Neurological diseases have especially seen a huge increase in knowledge in recent years, as more computational scientists have taken an interest in diseases such as Parkinson's, Alzheimer's, depression, and schizophrenia, among others. With respect to schizophrenia, especially, efforts to characterize the full effects have become more and more effective. Researchers have accurately described the positive and negative symptoms of the disease, as well as its effects on brain density and volume, neurotransmitters, and synaptic activity.

As described by Kitano (2002), knowledge is gained in computational biology through two means: data mining and simulation-based analysis. The main goals to be achieved with data mining include finding patterns within large datasets, which are then used to create novel hypotheses based on such patterns. By contrast, in simulation-based analysis, a computational model is created to elucidate the mechanisms and processes within a system. The goal is to explain system features or to predict outcomes of scenarios that had not been experimentally or clinically assessed yet. If the model is proven to be an effective predictor of the system, it can be used extensively in multiple applications. Since computational power is seldom a limiting factor today, simulation-based analysis has gained popularity because complex models that accurately describe the system can generally be analyzed with greater ease than one can perform actual experiments. As Kitano also notes, being able to create models that can be shared across labs and research centers is imperative. As models are shared, fewer data need to be collected, and the entire process of model creation, validation, and application is accelerated.

In regards to schizophrenia, a disease which affects approximately 1% of the world population, computational models have advanced our understanding greatly. Before systems science gained popularity, the symptoms of schizophrenia were already fairly well understood.

There was evidence to support both the existence of positive symptoms, such as hallucinations and delusions, as well as negative symptoms, such as, reduced social behavior and a lack of emotion. However, a true mechanistic understanding of how schizophrenia caused these outward symptoms and cognitive effects was elusive due to both a lack of reliable data and the inability to model such a complex system as the brain. As mentioned by Bender *et al.* (2006), a full systemic model could be achieved through a variety of means, including describing whole brain activity, neuronal and synaptic activity, and even biochemical activity, but all of these models require some manner of dynamic nonlinear description. It wasn't until recently that such types of models could be created.

Bakashi and Chance's research (2015) focused on creating a model which relates neuroplasticity to the effects of schizophrenia. The results of the study showed that schizophrenics generally have less grey matter and less brain volume overall compared to others. Moreover, specific brain regions were affected in different ways. For example, the thalamus and anterior cingulate cortex both change shape when the effects of schizophrenia are present. Additionally, the study was able to show that overall neuronal size is decreased in schizophrenia patients, and that while total neuron density is increased, that of inhibitory neurons is actually decreased. While the study's findings give some insights into the disease, the model itself cannot really be used in any expanded manner.

Carlsson was one of the first to qualitatively describe the interactions between neurotransmitters, such as dopamine, serotonin, GABA, acetylcholine, and norepinephrine in the brain, and to show how their activation and/or inhibition are changed in schizophrenia patients (Carlsson, 2006). His results indicate that an imbalance between typical activating neurotransmitters, such as glutamate, and typical inhibiting neurotransmitters, like GABA, is likely to cause the onset of schizophrenia. His results are corroborated by study conducted by Pogarell *et al.* (2012), which determined that poor synaptic transmission is a likely cause of the imbalances,

especially those concerning dopamine. Carlsson, while modeling multiple neurotransmitters, did not account for most of the brain regions. Pogarell's study focused only on dopamine, and thus the importance of the other neurotransmitters was not quantified.

In a study conducted by Qi *et al.* (2016), a heuristic model was created in relation to working memory in schizophrenia. The results of the model output are consistent with all previously collected data and, in addition, the model accurately describes drug perturbations in working memory. This feature is significant because it allows other researchers to use the same model and predict the results of other, not yet tested interventions in working memory. This type of model is ideal for creating a user-friendly interface, which researchers can then easily apply to their own studies, although a certain amount of programming and modeling skill is still required.
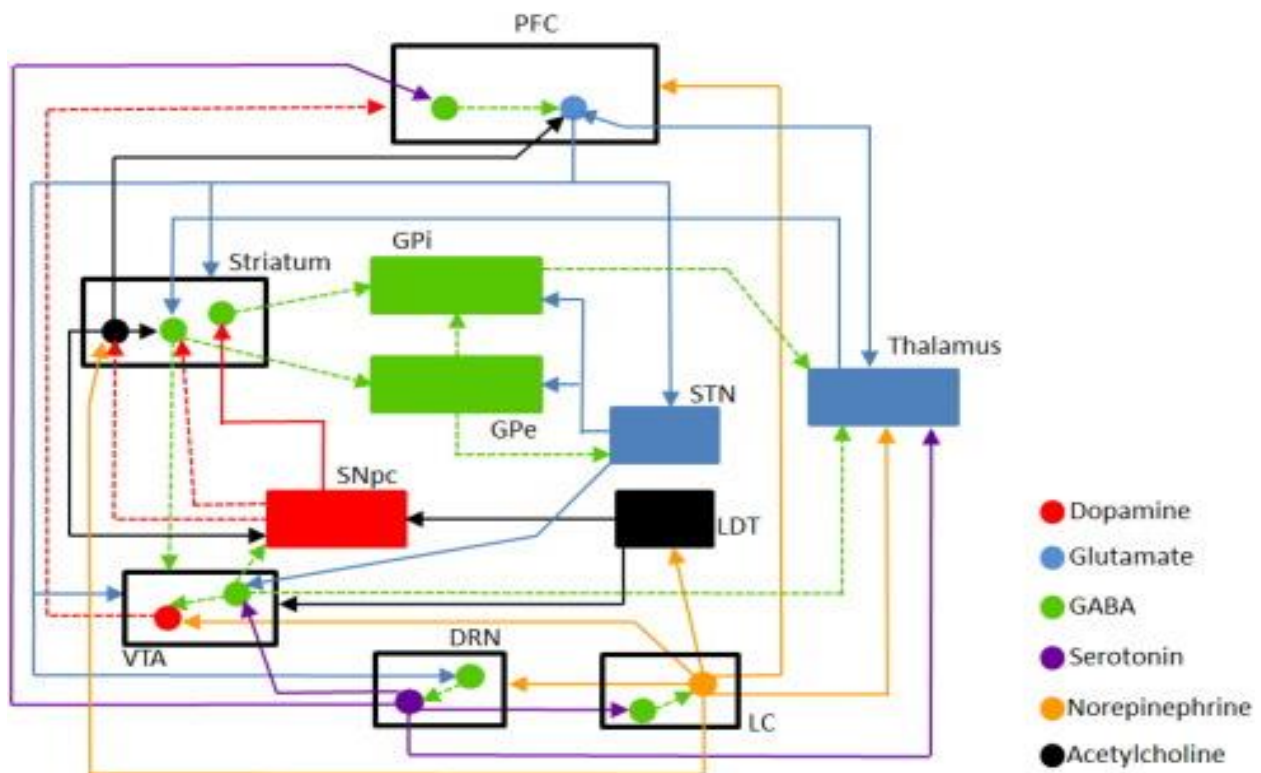

Figure 1: The interactions of the six neurotransmitters among brain regions associated with working memory is shown here. Each arrow pointing to circles indicates a projection onto that specific neurotransmitter, whereas arrows pointing to a box project onto all neurotransmitters in

the box. The brain regions include: prefrontal cortex (PFC), striatum, global pallidus internal (GPi), global pallidus external (GPe), subthalamic nucleus (STN), thalamus, substantia nigra pars compacta (SNpc), laterodorsal tegmental nucleus (LDT), ventral tegmental area (VTA), dorsal raphe nucleus (DRN), and locus coerulus (LC). Solid lines represent excitation, while dashed lines represent inhibition.

The GUI works in conjunction with Qi's model and ideally expand its functionality with respect to exploring working memory. As earlier mentioned by Kitano, the ability of researchers to share models will rapidly increase the speed at which simulations for all types of interactions in working memory can be run. Additionally, this GUI can serve as a competent teaching tool for medical students and patients wanting to learn more about the effects of schizophrenia.

CHAPTER 2.   METHODOLOGY

GUI Functions

The GUI runs in MATLAB and requires the .m files associated with the interface, the file associated with the mathematical model and other background processes, and the file corresponding to the mobile matrix. No other significant software or hardware is needed for the user to run simulations.

Prioritizing what functions the GUI must be capable of performing is an important aspect of GUI creation. The GUI should strike a critical balance between complexity and ease of use. Each function should serve an important purpose, while ideally not bombarding the user with an overload of buttons and options. Figure 1, below, displays the user flowchart which was created to serve as a basis for deciding the most critical needs of the user.
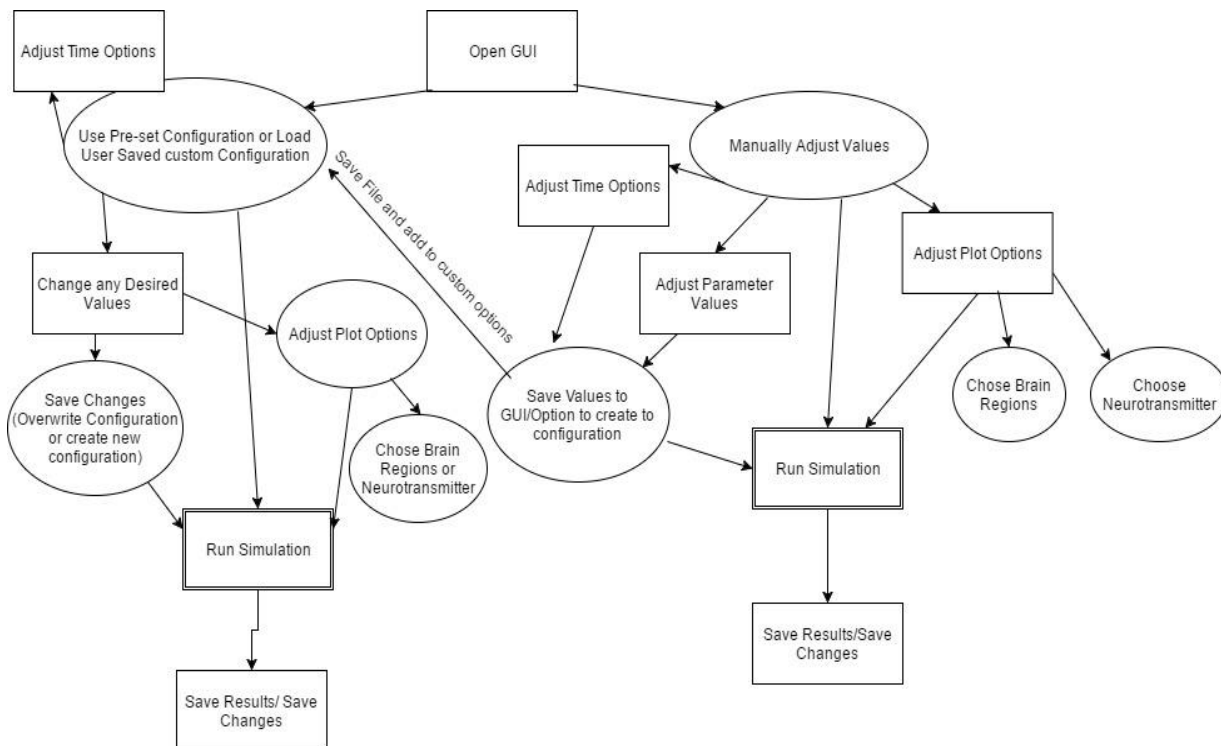
Figure 2: The flowchart exhibits the different abilities of the GUI. Options include running pre-set or custom-made simulations, adjusting parameter values, saving and loading configurations, saving results, and plotting neurotransmitter imbalances in different brain regions.

Pre-set Options

The GUI comes packaged with 15 pre-set options which have already been checked for accuracy. Each of these options adjusts parameter values to those which precisely result in the output determined from literature and previous simulations.

Time Options

The user has the ability to change four different time parameters; these parameters are the perturbation point, the adaptation point, the final time point, and the time step of the model.

Parameter	Description
Perturbation Point	Time point where parameters change via introduction of a disease/drug state
Adaptation Point	Time point where parameters change via the brain's adaptation to the disease/drug state
Final Time Point	Time point where simulation stops
Time Step	Period of time between points in which the model runs/evaluates

Table 1: The four different time options and their respective meanings within the model and GUI.

Selection of Brain Region

The user has the option of selecting to output the mobile matrix as well as the neurotransmitter dynamics over the entirety of the brain regions associated with working memory, or only for one of these nine regions, namely: Prefrontal Cortex (PFC), Striatum, Inner Globus Pallidus (GPi), External Globus Pallidus (GPe), Subthalamic Nucleus (STN), Thalamus, Substantia Nigra Pars Compacta (SNpc), Ventral Tegmental Area (VTA), and Dorsal Raphe Nucleus (DRN).

Changing Parameters

Each brain region has a certain number of parameters associated with the different neurotransmitters located within the region. Users may change these parameters within a certain range specified by the model. In general, parameters associated with excitatory effects can be changed to values within the range of zero to 5, while parameters associated with inhibitory effects can be changed to values within the range of negative 5 to zero.

Neurotransmitters Plotting

If desired, the user may set the GUI to output a plot of any one of seven neurotransmitters within the model. This plot depicts the change in the dynamics of the neurotransmitter over time within the entire brain. The seven neurotransmitters are: Dopamine (DA), Glutamate (Glu), GABA, Serotonin (HT), Norepinephrine (NE), and Acetylcholine (ACh).

Run Simulation

Running a simulation outputs the mobile matrix for the brain region(s) chosen by the user as well as any neurotransmitter plot the user has chosen to output.

Load/Save Configurations

Users may save customized parameter settings to a MAT file and load this file back into the GUI at a later time.

Restore Parameters

Parameters can be restored to the values originally set by the default GUI configuration.

GUI Interface

The layout of the GUI should be organized logically so that the user's learning curve is a steep as possible. Figure 2 shows the main layout of the GUI.

Figure 3: Main interface of the GUI

The interface is organized as follows:

Left (Top): Preset perturbations which the user may simulate and observe results.

Left (Bottom): Restore button which returns all parameters to their default values

Middle (Top): Area for output plot as well as a plot legend and simulate button.

Middle (Bottom): Buttons which open interfaces with parameters for each brain region.

Right (Top): Time options which include time step and perturbation and adaptation points.

Right (Middle): Brain region plotting options; Users choose what region to plot

Right (Bottom) : Load and save current configurations and parameter values.

This interface plainly defines borders and regions of options which are related to each other, while clearly displaying the important functions. Different regions are color-coded, which serves to further distinguish features from one another.

CHAPTER 3.   Results

Qualitative Comparison

In accordance with Qi *et al.* (2016), simulations were run in the GUI using the heuristic model and the qualitative results were compared to data collected from literature (Table 2). The simulations effectively show the same qualitative changes as those witnessed in other studies.

Table 1
Clinical data of chronic pharmacological perturbations and comparisons with simulation results.

Pharmacological agent	Pharmacological action[a]	Targeted regions	Chronic effects[b]	Sim[c]
Ethanol (5 weeks)	Increased GABA binding (positive allosteric modulator)	Brain-wide	No change in DA or ACh release to PFC; decrease release of Glu and NE to PFC	√
PCP (7 days, daily)	Glu (NMDA receptor antagonist)	Brain-wide	Enhanced activation of DA neurons in VTA	√
Ketamine (7 or 10 days, daily)	Glu (NMDA receptor antagonist)	Brain-wide	Increased DA release to striatum and mPFC; increased 5-HT release to mPFC; increased Glu release to mPFC	√
Nicotine (7 or 13 weeks)	ACh (nAChR agonist)	Brain-wide	Increased DA release to striatum; increased Glu release to PFC; decreased ACh release to striatum	√
5,7-DHT	5-HT (lesion)	Intracerebro-ventricular	Increased firing of DA neurons in VTA	√
Tph2 (heterozygote)	5-HT (reduced 5-HT synthesis)	Brain-wide	Decreased GABA in PFC	√
Fluoxetine (2 or 3 weeks, daily)	5-HT (reuptake inhibitor)	Brain-wide	No change in DA release to PFC; increased 5-HT release to PFC; decreased firing of NE neurons in LC; decreased firing of pyramidal PFC cells	√
HT2c (null mutant)	5-HT (5-HT_{2c} receptor elimination)	Brain-wide	Increased DA release from SNpc to striatum	√
Olanzapine (21 days)	5-HT (5-HT_2 antagonist) & DA (D_2 antagonist)	Brain-wide	Increased firing of NE neurons in LC	√
Clozapine (21 days)	5-HT (5-HT_2 antagonist) & DA (D_2 antagonist)	Brain-wide	Increased DA release to mPFC; no change in DA release to striatum	√
Venlafaxine (3 weeks, daily)	5-HT & NE (reuptake inhibitor)	Brain-wide	Increased NE, DA, and 5-HT release to PFC	√
Desipramine (2 weeks, daily)	NE (reuptake inhibitor)	Brain-wide	No change in DA release to striatum; increased DA and NE release to PFC	√
Nomifensine (22 days, daily)	NE & DA (reuptake inhibitor)	Brain-wide	Increased DA release to striatum; no change in DA release to PFC; increased ACh release to PFC and striatum; no change in Glu release to PFC and striatum; no change in GABA release to PFC	√
Mirtazpine (21 days)	NE ($alpha_2$ antagonist)	Brain-wide	Increased firing of 5-HT and NE neurons	√
6-OHDA	DA (lesion)	SNpc	Increased firing rate of pyramidal neurons in PFC; increased firing rate of neurons in STN	√
6-OHDA	DA (lesion)	VTA	Increased firing of NE neurons	√
6-OHDA	DA (lesion)	Intracerebro-ventricular	Decreased spontaneous firing of 5-HT neurons	√

Table 2: List of pharmaceutical perturbations tested and validated by the heuristic model by Qi *et al.* (2016).

GUI Output

Mobile Matrix

Visualization of the simulations were displayed via a mobile, which weighs the various neurotransmitters in the brain region based on amount. Larger imbalances lead to larger mobile angles.
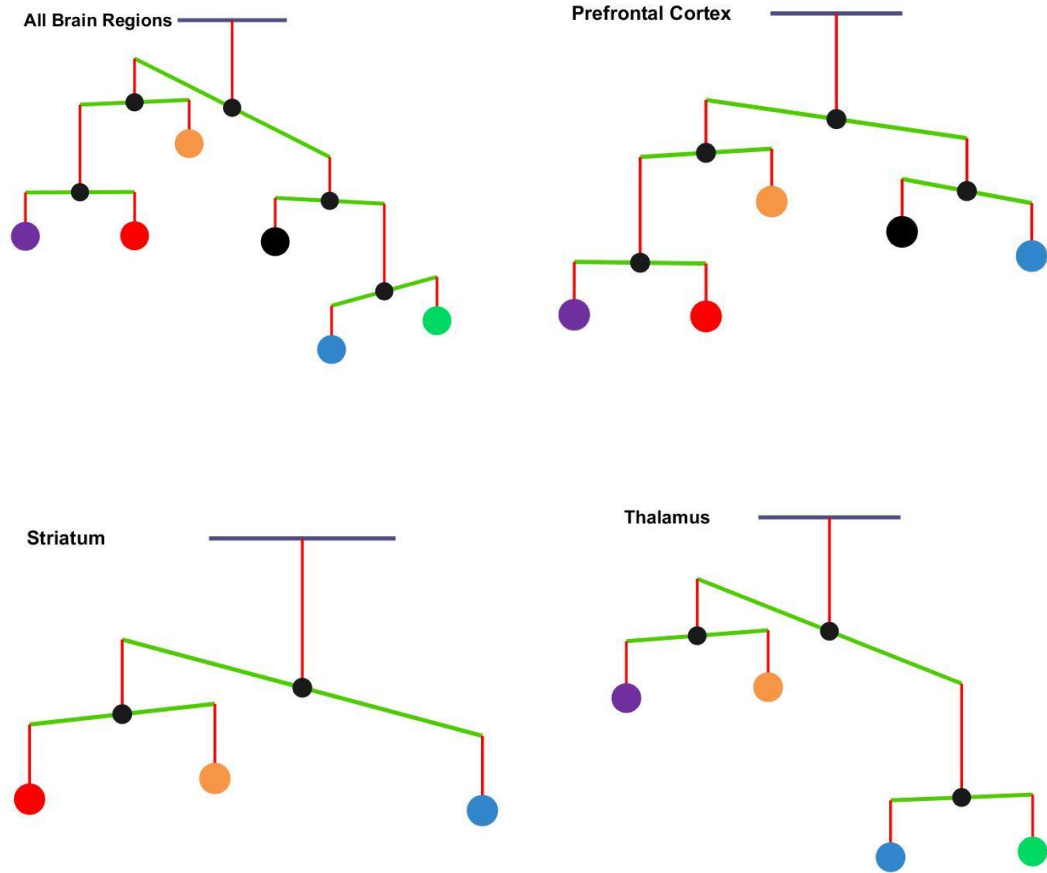

Figure 4: Mobile outputs of various regions perturbed by ethanol. From top left clockwise: 1. All Brain Regions; 2. Prefrontal Cortex; 3. Striatum; 4. Thalamus

Neurotransmitter Plots

The dynamics of each neurotransmitter can be plotted and outputted by the GUI as well. The region in which the dynamics are plotted are indicated by the user in the same manner as the mobile matrix.
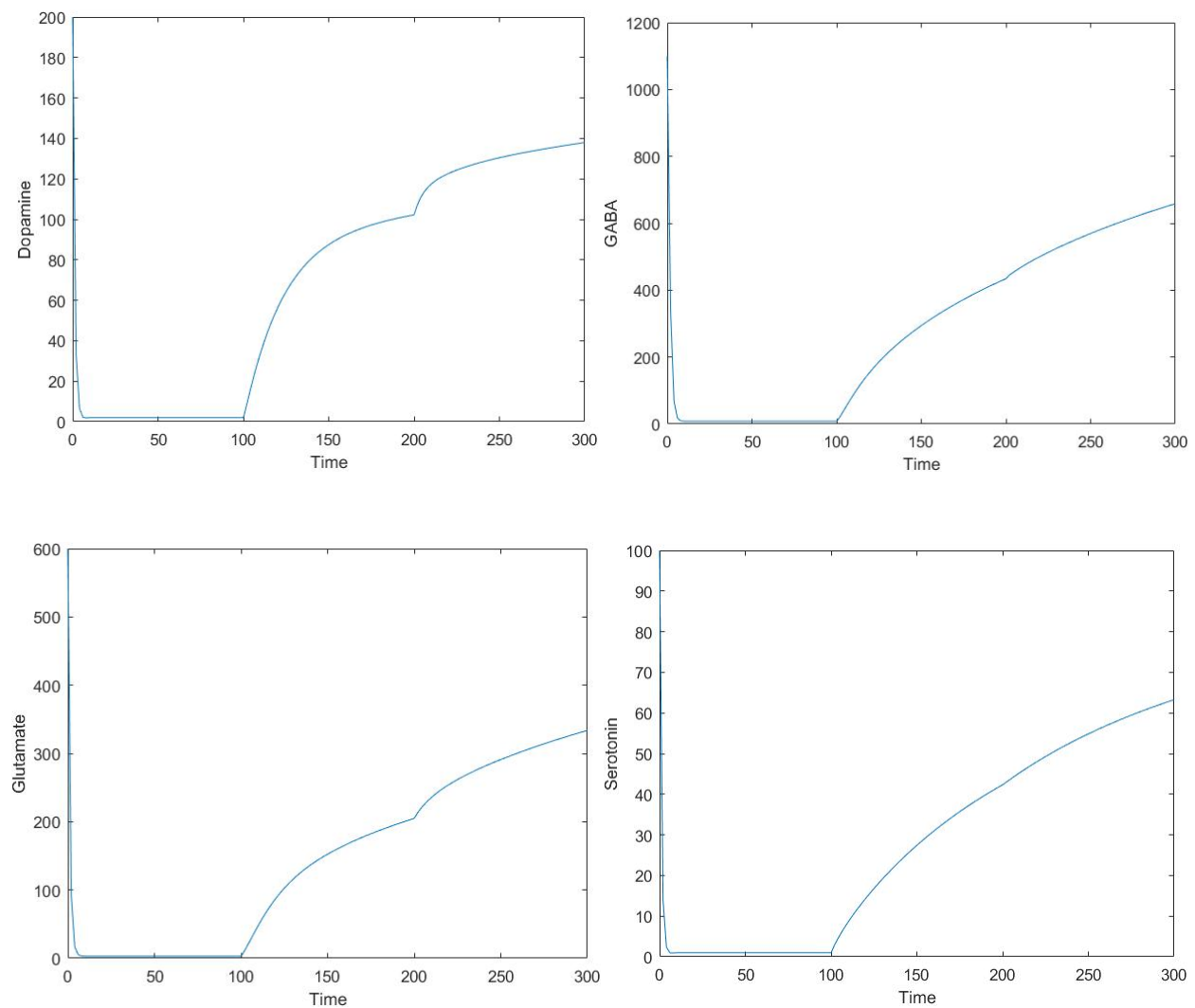

Figure 5: From top left clockwise: Plots of Dopamine, GABA, Serotonin, and Glutamate over time when perturbed by ethanol. Time parameters (unit less) were set as follows: Perturbation Point: 100; Adaptation Point: 200; Final Time: 300; Time Step: 2.

Discussion

The GUI created here is effectively able to utilize and view Qi's model. It should support future research, including better quantitative insight on both schizophrenia and working memory. Understanding the underlying mechanisms and effects of perturbations on working memory will help the development treatments for these perturbations. The GUI should also help educate medical students as well as patients and families on the effects of these diseases. Of course, the GUI can always be altered based on user feedback and needs. Since a relatively comprehensive understanding of mathematical modeling and neurotransmitters is necessary to run custom simulations, simplifying parameter names may lead to expanded use throughout various communities. Additionally, the GUI's current mobile output only shows the final form. An effective change to the simulation could show and keep multiple outputs of the mobile, specifically at the perturbation and adaptation points as well as the final result. Finally, minor changes to the GUI's appearance, including more appropriate parameter menus, may help alleviate any confusion for the user.

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