The Neurochemical Mobile: Analysis of Dynamic Interactions between Six Neurotransmitters

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The Neurochemical Mobile: Analysis of Dynamic Interactions between Six Neurotransmitters

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Abstract

A mobile, typically seen in an infant's crib, is an eloquent representation of the balance between multiple items. The neurochemical mobile is a tool used to visualize the balance between six major neurotransmitters in the human brain. Neurotransmitters are chemical compounds that govern the behavior of the brain. Here, this somewhat abstract model has been converted into a more applicable form. This was done using nonlinear computational systems modeling within the framework of biochemical systems theory, which allows even ill-characterized systems to be mapped into a mathematical representation. The interactions between the individual neurotransmitters and the system are described by the "neurochemical interaction matrix". This matrix explicitly records whether the reaction between two neurotransmitters is excitatory or inhibitory. These interactions have an effect on the concentrations of the six compounds, which in turn make up the symbolic weight. The various weights are then incorporated into a model of a spring-mass system in order to quantitatively represent overall shifts in balance upon alterations in weights. Simulations show how short- and long-term perturbations in any of the neurotransmitters migrate through the entire system, thereby affecting the balances within the mobile. In cases of short-term alterations, transients are of particular interest, whereas long-term changes shed light on persistently altered, allostatic states, which in mental diseases and sleep disorders could be due to a combination of unfavorable factors, resulting from a specific genetic predisposition, epigenetic effects, disease, or the repeated use of drugs, such as opioids and amphetamines. Based on the research done here, the Voit lab continued this line of investigation and published the paper, "The Neurochemical Mobile with Non-Linear Interaction Matrix: An Exploratory Computational Model" [19].

Introduction

Neurotransmitters are the basis for many bodily functions and processes. It is these chemical compounds that allow for communication between different parts of the brain, as well as between the brain and the body. In addition to the very prevalent excitatory and inhibitory neurotransmitters glutamate and GABA, there are four other neurotransmitters that have a large impact. These are acetylcholine, norepinephrine, dopamine, and serotonin. It is essential to have these six chemicals in the correct balance to ensure healthy function. Any significant perturbations to this balance tend to cause a number of pathologies. A complicated network governs the interactions of these modulators [1].

Substance abuse is defined as a syndrome characterized by symptoms such as withdrawal, tolerance, persistent desire, unsuccessful attempts to quit, and the use of larger than intended amounts of the substance. Many times drug abuse and substance dependence are used interchangeably. However, it is important to note that drug abuse refers to any maladaptive pattern of drug use resulting in occupational, social, or recreational problems for the user, whereas addiction causes neural plastic changes such as withdrawal, tolerance, and sensitization. A main factor of drug abuse is the reinforcement or reward provided by the central nervous system, which leads to the long lasting effects created by addiction. The rewards are caused by the physiological effect that drugs have on the nervous system. Drugs of abuse typically act on proteins at specific synapses. This will typically lead to an imbalance in the functional levels of neurotransmitters [2] [3]. The purpose of this project is to develop a model capable of quantifying these interactions and the consequences of their alterations. The goal is to both provide a useful

model for a healthy system, while providing the opportunity to investigate problems such as drug abuse. In particular, this paper will address the neurological effects of opioids. This will be achieved using a systems biology approach.

Computational biology has exploded over the last two decades due the increasing level of information available through molecular biology and vastly expanded computing power. The discipline addresses two main goals. The first is to discover new organizing principles that govern biological phenomena such as metabolic processes. The second goal is to create effective disease simulators that will function in predicative health and personalized medicine. These must be simple yet accurate enough to be used in a clinical setting. It is clear that these goals call for a move in opposite directions in the size and complexity of desired models. In the last decade, most models have not yet been able to accomplish either goal. One partial solution to the challenge is a framework known as mesoscopic modeling. This approach allows for the potential to achieve both goals when they are expanded further or used as part of a larger model. It has the future potential for clinical applications and yet can serve as a template capable of supporting small detailed "anchor" models that allow studies of design and function [4][5].

The neurochemical mobile will be designed as such a mesoscopic model with the modeling framework of Biochemical Systems Theory (BST) [4]. It represents the functional weight of the six neurotransmitters on a dynamic balance or scale. The balance will be governed by interactions among the six highlighted molecules. The mobile will have educational, clinical and research applications. It will be capable of aiding in the treatment of certain pathologies by suggesting a necessary change in the concentrations of neurotransmitters. Furthermore, as any good mesoscopic model can do, it will have room for more specific anchor models which will allow for further exploration of the system [6].

Materials

The six neurotransmitters were represented as follows: X_1 Norepinephrine, X_2 Acetylcholine, X_3 Dopamine, X_4 Glutamate, X_5 Serotonin, X_6 GABA. Initial values were set as: $X_1(0) \sim .0035\mu M$[7][8], $X_2(0) \sim .003\ \mu M$, $X_3(0) \sim 1.14e\text{-}4\ \mu M$[9], $X_4(0) \sim 2\ \mu M$[10][11][12], $X_5(0) \sim 1.14\ \mu M$[13], $X_6(0) \sim .25\ \mu M$[14][15]. These initial values of each neurotransmitter were subsequently scaled to a relative value. The highest concentration, $X_4(0)$, was set at 10,000. The remaining concentrations were adjusted proportionately. The value for the kinetic orders and rate constants, which are the prominent parameter values in BST, were set based on previous experience. The kinetic orders were set at .5 for activation and -.3 for inhibition. The rate constants, defined as $alpha_i$, were all set to 5.

Methods

The model was created under the paradigm of Biochemical Systems Theory (BST) [4]. BST uses two main components. The ability to describe biochemical systems using ODE's and the representation of all processes that govern these systems through products of power law functions. One class of BST model is an S-system model [4], which is applied here. It constitutes of equations that represent the dynamic change of variables X_i. in particular, the format consists of the difference between one influx term and one efflux term, as shown below.

S-system:

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n} X_j^{h_{ij}}, \qquad i = 1,\ldots,n.$$

Each flux is described as a power-law term. The first term represents synthesis of the variable being described and the second represents degradation. Kinetic orders are represented by doubly indexed *g* and *h*, respectively. A positive kinetic order signifies activation, a negative one signifies inhibition [16]. The parameters alpha and beta denote the rate constants of synthesis and degradation, respectively. Not only does the power law provide an accurate representation of rate laws, many features of S-system models are consistent with features of biochemical systems (see [4] for details).

The neurochemical mobile assigns a functional weight to each neurotransmitter. Each weight is in dynamic balance with the rest of the system (Fig. 1). The dynamic interactions between the weights can be quantified by the change in overall balance. An equation for each balance was generated using the neurochemical mobile schematic. Each region of the brain is interconnected through a mesh of axons and synapses. This mesh results in constant interaction between neurotransmitters. The activation of one neurotransmitter often leads to the activation or inhibition of another. Therefore, the ability to quantify the balance between concentrations of neurotransmitter could prove to be very valuable.

A system of ODE's was created that describes the change in each neurotransmitter with an S-system model. Using the neurochemical interaction matrix (Fig. 2), activation and inhibition effects were included into the degradation term in the form of power-law terms. Simulations were then run in Power Law Analysis Software (PLAS), in order to test the robustness of the system and search for critical parameter values. For a preliminary diagnosis, the initial values were both increased and decreased 10 fold. A local sensitivity analysis was performed on the kinetic orders, as well as a global sensitivity analysis. These simulations shed light on which variables are the most critical. The ones that have larger effects on the system when changed are said to be the most critical. Sensitivity analysis was also performed for kinetic orders with initial values of .3 for activation and -.1 for inhibition. The global sensitivities of kinetic orders 3_5 and 4_6 turned out to be high, and these kinetic orders were therefore tested over the range of values .3 to -1 and .45 to .75, respectively. A dynamic perturbation or permanent change was evaluated at t=5000 seconds. This was done by increasing and decreasing the neurotransmitter concentration by 50% and setting the variable representing dynamic change for that neurotransmitter to zero at the indicated time. The eigenvalues were assessed to assure stability of the steady state. Finally, opiate was introduced, and its effect on each neurotransmitter evaluated. The details of this effect were modeled according to findings in the literature [17][18].

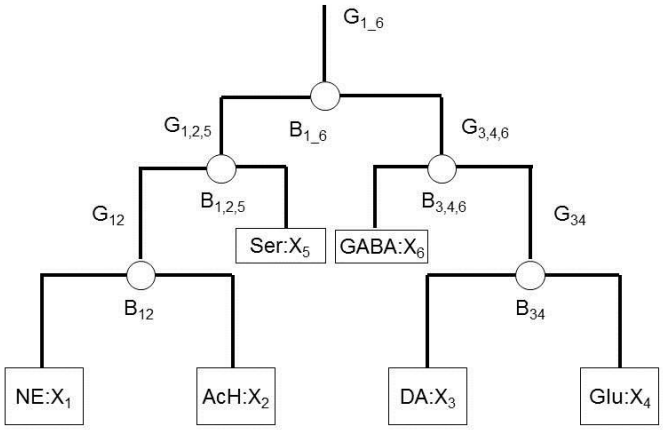

Fig. 1 - "The Neurochemical Mobile" This is a schematic representation of the model. Each box represents the functional weight of a neurotransmitter. The six boxes are in dynamic balance with one another.

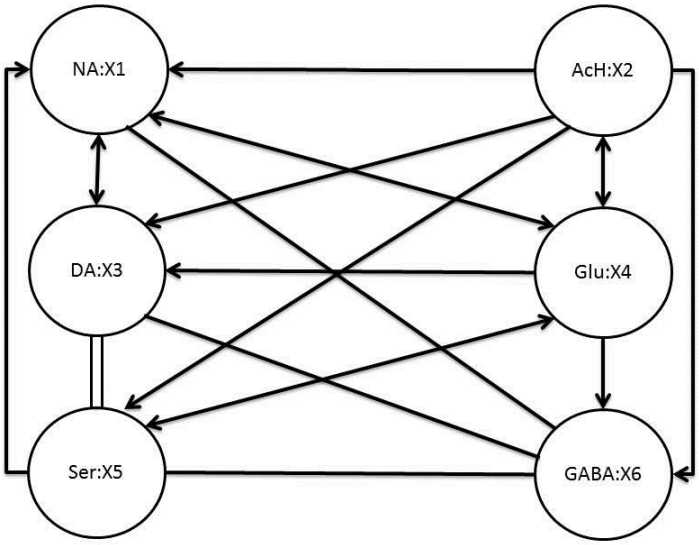

Fig. 2 - "Neurochemical Interaction Matrix" A network map of the connections between the six neurotransmitters. An arrow represents activation, a thin line with no arrow denotes inhibition, and a thick line signifies both activation and inhibition

Results

We assessed the global stability of the system by increasing and decreasing the initial values individually by a factor of 10. The results confirmed a robust steady state. For all temporary changes, that is, changes to the initial values, the system returned quickly to its original steady state. The global sensitivities were also assessed by changing the kinetic orders by 25%. The system harbors several large sensitivities. These could indicate the more critical parameters. ACh proved to have the largest effects. To analyze the situation further, we permanently changed the concentration of individual neurotransmitters and assessed the effect on the system. In each simulation where a structural change was applied, the system never became unstable. Rather, a monotonic shift from the original steady state was observed. The value that caused the largest shift in the system was X_2 (acetylcholine). The added opiate concentration caused a similar monotonic shift. The largest effect due to the opioid was observed on X_1 (Norepinephrine), and X_3 (Dopamine). Both showed more than a 20 fold increase.

Perturbation	Opio (1.5μM)	Change
% X1	20927.65	Up
% X2	38.78	Down
% X3	21158.56	Up
% X4	1752.34	Up
% X5	605.93	Up
% X6	1.03	Down

It should be noted that the work done here was continued by the Voit laboratory, leading to a peer-reviewed publication [19]. Also, a poster was presented based on this continued work at the international conference Frontiers in Systems and Synthetic Biology in 2013.

Conclusion

The goal of the neurochemical mobile is three fold: academic, educational and clinical. The results address all three goals. The fact that the model showed a robust steady state is in line with most natural systems. The human brain is quite resistant to most changes in neurotransmitter concentrations. It is difficult to cause the system to become unstable. Further research allows additive diagnostic evaluations. The possibility to create a detailed system model of the interactions of neurotransmitters could lead to the discovery of underlying design and operating principles. Finally, each structural perturbation, as well the addition of opiates showed a different monotonic shift in steady state. This set of results can be very useful in clinical applications because it allows for the prediction of neurotransmitter levels based on certain perturbations that could be due to disease or substance abuse. The monotonic shift could be countered by making the correct changes in either neurotransmitter concentrations or the re-uptake of certain neurotransmitters. This possibility suggests a future direction for the project that would make it useful for training physicians and the public. A direct, quantitative connection

between the resulting values of the neurotransmitters after a shift and the altered balance of the mobile has been made by Mojdeh Faraji. She utilized a functional weight and modeled each beam as a cantilever free body system. For example, healthy levels of neurotransmitters will show a certain balance. By quantifying changes to this balance, Faraji's model will make it possible to go from a shift in the mobile to the correct change in neurotransmitter level. This would open new possibilities when prescribing drugs for neurological diseases such as depression, sleep disorder, and anxiety.

References

1) Purves, D. "Neurotransmitters and Their Receptors." *Neuroscience*. 5th ed. Sunderland, MA: Sinauer, 2008. 109-12.
2) Koob, G. F., Nestler, E. J. "Neurobiology of Drug Addiction." *Journal of Neurophyschiatry* 9.3 (1997): 482-97.
3) Koob, G. F. "The Role of the Striatopallidal and Extended Amygdala Systems in Drug Addiction." *Annals of the New York Academy of Sciences* 877.1 ADVANCING FRO (1999): 445-60.
4) Voit, E. O. *Computational Analysis of Biochemical Systems: A Practical Guide for Biochemists and Molecular Biologists*. New York: Cambridge University Press, 2000.
5) Voit, E. O., Qi, Z., Kikuchi, S. "Mesoscopic Models of Neurotransmission as Intermediates between Disease Simulators and Tools for Discovering Design Principles."*Pharmacopsychiatry* 45 (2012): 22-30.
6) Tretter, F. "Mental Illness, Synapses and the Brain – Behavioral Disorders by a System of Molecules within a System of Neurons?" *Pharmacopsychiatry* 43 (Suppl. 1) (2010): S9-S20.
7) Taylor, M.J. "The Normal Levels of Norepinephrine in the Body." *EHow*. Demand Media, 22 July 2010. Web. 05 Dec. 2012.
8) Goldstein, D. S. Eisenhofer, G. Kopin, I. J. "Sources and Significance of Plasma Levels of Catechols and Their Metabolites in Humans." *The Journal of Pharmacology and Experimental Therapies* 305 (2003): 800-11.
9) "What Are Abnormal Dopamine Levels?" *LIVESTRONG.COM*. N.p., n.d. Web. 05 Dec. 2012.
10) "Amyotrophic Lateral Sclerosis, Glutamate, and Oxidative Stress." *Amyotrophic Lateral Sclerosis, Glutamate, and Oxidative Stress*. N.p., n.d. Web. 05 Dec. 2012.
11) Danbolt, N. "Glutamate as a Neurotransmitter - An Overview." *Glutamate*. Center for Molecular Biology and Neuroscience, n.d. Web. 05 Dec. 2012.
12) Divino Filho, J. C., Hazel, S. J., Furst, P., Bergstrom, J., Hall, K."Glutamate Concentration in Plasma, Erythrocyte and Muscle in Relation to Plasma Levels of Insulin-like Growth Factor (IGF)-I, IGF Binding Protein-1 and Insulin in Patients on Haemodialysis." *Journal of Endocrinology* 156.3 (1998): 519-27.
13) "Serum Serotonin Level: MedlinePlus Medical Encyclopedia." *U.S National Library of Medicine*. U.S. National Library of Medicine, n.d. Web. 05 Dec. 2012.

14) Minuk, G. Y., Winder, A., Burgess, E. D., Sarjeant, E. J. "Serum Gamma-aminobutyric Acid (GABA) Levels in Patients with Hepatic Encephalopathy." *Hepatogastroenterology* 32.4 (1985): 171-74.
15) Schulz, P., K. G., Lloyd, C., Voltz, S., Lustenberger, and R. Degli Agosti. "The Plasma Concentration of GABA Shows No Evidence of a Circadian Rhythm and Is Stable over Weeks in Normal Males." *Biological Rhythm Research* 25.3 (1994): 291-300.
16) Voit, E. O., and I-C. Chou. "Parameter Estimation in Canonical Biological Systems Models." *International Journal of Systems and Synthetic Biology* 1.1 (2010): 1-19.
17) Dermitzaki, E., Gravanis, A., Venihaki, M., Stournaras, C., Margioris, A. N. "Opioids Suppress Basal and Nicotine-Induced Catecholamine Secretion Via a Stabilizing Effect on Actin Filaments." *Endocrinology* 142.5 (2001): 2022-031.
18) Tongjaroenbungam, W., Jongkamonwiwat, N., Cunningham, J., Phansuwan-Pujito, P., Dodson, H. C., Forge, A., Govitrapong, P., Casalotti, S. O. "Opioid Modulation of GABA Release in the Rat Inferior Colliculus." *BMC Neuroscience* 5:31 (2004).
19) Qi, Z., David F., Tretter, F. and E. O. Voit. "The Neurochemical Mobile with Non-Linear Interaction Matrix: An Exploratory Computational Model." Pharmacopsychiatry 46 (2013): S1-S11.