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Information dynamics in dopaminergic networks

Amir Assadi*[1], Hesam Dashti-Torabi[2], Mary Kloc, Gregory Michelotti[3] and Tong H Lee[4]

Address: [1]Department of Mathematics, University of Wisconsin-Madison, Madison, WI 53706, USA, [2]Department of Computer Science, Tehran University, Tehran, Iran, [3]Department of Anesthesiology, Duke University and Medical Center, Durham, NC 27710, USA and [4]Department of Psychiatry, Duke University and Medical Center, Durham, NC 27710, USA

Email: Amir Assadi* - assadi@math.wisc.edu

* Corresponding author

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Deficits in dopamine (DA) release and uptake kinetics due to neurodegeneration of the nigral DA neurons are key features of Parkinson's Disease (PD). A deficit in dopamine (DA) reuptake kinetics in brain is known to be a hallmark of Parkinson's Disease (PD). Our long-term research program in this direction has led us to study healthy and pathological dopamine reuptake kinetics at the level of *collective dynamics of networks of brain modules*. A quantitative objective of this research is to describe a model that will allow analysis of DA uptake in a behaviorally more realistic framework; e.g., to determine specific structural parameters of the network kinetics in "*Parkinsonian*" rats from real-time voltammetric measurements of DA clearance (uptake) from the extracellular space. Common models of dopamine (DA) uptake kinetics are based on variations of the Michaelis-Menten equations (MM) in a single site of the brain. However, utilization of DA uptake measurements for more practical purposes (e.g., measurements under pathological conditions for diagnostic or therapeutic applications) requires a model which could also provide for more robust descriptions of healthy and pathological kinetics at the level of *collective dynamics of networks of brain modules*. Such models will allow analysis of DA uptake in a behaviorally more realistic framework; e.g., specific structural parameters of the network kinetics in "*Parkinsonian*" rats could be determined from voltammetric measurements of DA uptake. These more realistic models, such as our earlier Network Eigen Kinetic Analysis (NEKA) model, require addition of nonlinearities to the MM and controlled adaptation of nonlinearities to match desired forms of normal and "*diseased*" kinetics. Once the basic topology of a NEKA model is established, the natural question of the dynamics of information flow in the network must be answered in order to make neurologically significant inferences regarding PD, such as the clinical and pathological progression or improvement over the course of time due to specific clinical interventions, comparisons of various therapies and other clinically significant results. Our mathematical model introduces new mathematical tools and computation techniques to provide: (1) a general model of information flow independent of the choice of sample animals; and (2) a robust method to adapt the model to an explicit approximation of DA uptake without ignoring spurious fluctuations, noise and nonlinear dynamical events. As in the case of NEKA, we assume that sufficiently large data sets from DA uptake at multiple sites of the animal brain *implicitly* contain all the information regarding: (a) model-complexity; (b) the range of parameter values for signals; and (c) the probability distribution functions for system noise and other variables irrelevant to the particular behavior. The extraction of dynamics in the network uses the method of diffusion in graphs based on Brownian processes generated from the Laplace operator. The results are expected to allow explicit derivation of either deterministic or stochastic models from data sets, which will provide *a priori*, biologically more realistic descriptors of experimental groups. We explore the biological strengths and limitations of this method by providing a more general volume transmission kinetic theory for the

specific case of altered dopamine release/uptake in a rat PD model (unilateral 6-hydroxydopamine lesion). We also provide quantitative measures for nonlinearities in the dynamic flow through comparison of the suitable functions of the eigenvalues of the Laplace operator associated with the NEKA in control and "Parkinsonian" animals in animal models versus models of dyskensia of early PD.