# Hybrid Modeling of Dopamine Signal Transduction

Jialiang Wu[1] and Eberhard Voit[2]

***Short Abstract* —Dopamine signal transduction occurs across the synaptic cleft, initiating in the presynaptic neuron of the striatum, where dopamine is synthesized, compartmentalized, released, recycled, and degraded, and acting upon processes in the postsynapse. The processes governing this dynamics consist of interacting discrete and continuous components, which operate at different time scales and in a crowded environment. The hybrid nature of the system requires special means of modeling, simulation and analysis. We show here how hybrid functional Petri-nets (HFPNs) and Agent Based Modeling (ABM) facilitate computational analyses of systems that simultaneously contain deterministic, stochastic, delay and spatial effects.**

***Keywords* — Agent based modeling, Biochemical System Theory, crowding, delay, dopamine signaling, hybrid modeling, HFPN, Parkinson's disease, Petri net, stochasticity.**

## I. Purpose

DOPAMINE is a critical neurotransmitter for the normal functioning of the central nervous system. Abnormal dopamine signal transmission in the brain has been implicated in diseases such as Parkinson's disease (PD) and schizophrenia, as well as in various types of drug addition. It is therefore important to understand the dopamine signaling dynamics in the presynaptic neuron of the striatum and the synaptic cleft, where dopamine synthesis, degradation, compartmentalization, release, reuptake, and numerous regulatory processes occur. The biochemical and biological processes governing this dynamics consist of interacting discrete and continuous components, operate at different time scales and in a crowded environment, and must function effectively in spite of intrinsic stochasticity and external perturbations. Not fitting into the realm of purely deterministic phenomena, the hybrid nature of the system requires special means of modeling, simulation and analysis. We show here how hybrid functional Petri-nets (HFPNs) and Agent Based Modeling (ABM) can facilitate computational analyses of systems that simultaneously contain deterministic, stochastic, delay and spatial effects.

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[1]School of Mathematics, Bioinformatics Ph.D program, Georgia Institute of Technology, Atlanta, Georgia, USA. E-mail: wjl@gatech.edu

[2]Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia, USA. E-mail: eberhard.voit@bme.gatech.edu

## II. HFPN hybrid model

Based originally on an ODE model, the first hybrid model was formulated as a Hybrid Functional Petri Net (HFPN), which allowed explorations of combined effects of delays and noise on dopamine signal transduction [1]. Simulations showed that noise and delays can affect the signaling function of the dopamine system in a significant manner. For instance, in situations of low-frequency noise and large delays at the order of hundreds of milliseconds, the dopamine responses to signal trains may degrade into one abnormally long response, thus impairing the normal functioning of the dopamine signaling system.

While the simulations show that noise and delays can corrupt a true signal, our results also show that the signaling system is surprisingly robust. Most processes involved in the dopamine dynamics are fast events, such as biochemical reactions and ion fluxes, which occur at the order of a few or tens of milliseconds, while the important transport and release of dopamine into the cleft is somewhat slower. Much of the noise associated with small numbers of molecules contributing to the governing reactions can be expected to be at the order of tens to one hundred Hertz. The dopamine signaling system can successfully tolerate noise of such frequencies even if the noise amplitude is as large as 50% of the baseline.

## III. ABM hybrid model

The second hybrid model uses ABM to capture the vesicle trafficking dynamics in a complicated intracellular environment where crowding effects cannot be ignored, while applying ODE based Biochemical System Theory to model biochemical reactions in the signal transduction process. The sensitivity of important biological parameters is analyzed to answer the following questions: How does the spatial distribution of calcium influx affect the neurotransmitter release of a single vesicle? How does the quantal size of dopamine release affect the evoked postsynaptic current response? What are the effects of the distribution among different recycling pathways on the dopamine signaling dynamics? How does the recovery time between exocytosis events affect the efficiency of postsynaptic responses?

## References

[1] Wu, J., Z. Qi, E.O.Voit (2010). "Impacts of Delays and Noise on Dopamine Signal Transduction." In Silico Biology 10(0005).