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3 Neuron attribution

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4 Script

1/9 I'm Jai Jeffryes and I'm an analyst and programmer at the Sulzer Neuroscience Laboratory at Columbia University.

2/9 I'm waving to you from the lab (while getting photobombed). On the left of the screen is Dr. David Sulzer, the principal investigator of the lab and my boss. The lab researches the dopamine system, which figures prominently in Parkinson's Disease, schizophrenia, and drugs of abuse. On the right of the screen is Dr. Mahalakshmi Somayaji. Since I joined the lab in March, my main responsibility has been supporting Maha's research into the effects of amphetamine on the neurotransmitter, dopamine.

3/9 Signal propagates in a neuron from dendrites, seen on the left, to the axon terminals, detailed on the right. The bubbles in the axon terminal represent synaptic vesicles, tiny sacks containing molecules of dopamine. They transmit dopamine by fusing with the plasma membrane and discharging their cargo into the synaptic cleft. A few such molecules are depicted here. Some of those will bind with neurotransmitter receptors in the dendritic spines of the adjacent neuron. The rest will be pumped back up into the axon terminal. Keep in mind these dual processes of release and reuptake.

4/9 We can model the kinetics of dopamine in a one-dimensional random walk of its diffusion. The release locations are modeled here from left to right. Here I release 2.75 micromolar of dopamine. Time slices proceed downwards on the matrix. In the next time slice, half of the molecules will diffuse to the left neighbor and half to the right. Then reuptake reduces the concentration. Now, the next site will diffuse to the left and right in the time slice after that. I cut out a lot of the matrix. It propogates like this to a column representing a measuring electrode, where you see the concentration of dopamine over time.

5/9 The reduction in dopamine from reuptake is given by the Michaelis-Menten equation. Note the quantity, km, which expresses the affinity between dopamine and its target transporter. If km is lowered, the reuptake increases.

6/9 Thus, I can plot a simulation of dopamine concentration. We see release followed by reuptake. If I reduce km from 2 to .8, the decay of the concentration of dopamine is more rapid in the model.

7/9 This is a plot of the data I receive from Maha. She stimulates a mouse brain every two minutes and it evokes dopamine release. Animal research can be a sensitive subject. I can tell you that it is highly regulated, the animals are anesthetized and they feel nothing.

Note the change in height of the peaks. Here, in the fourth stimulation, is where Maha administers amphetamine. Amphetamine both raises dopamine release and reduces its reuptake, but how much of each? You can't tell from this plot, for the concentration is the net of the two.

Maha believes she has learned something novel about the mechanism of

amphetamine's influence on dopamine release. To demonstrate it, she needs to isolate and quantify dopamine's release and reuptake.

8/9 We do this by superimposing the model on the data from a single stimulus. The model is the green line, Maha's data is red. My first estimate isn't very good. I've underestimated the release, so the peak height is too low, and I've underestimated the reuptake so the curve is spread too widely. I adjust the two until I find a good fit. The correlation is quantified by the statistic r-squared.

9/9 I've inferred measures of release and reuptake based on the model, and hopefully these estimates are sufficiently reliable for Maha to draw conclusions about the mechanism of dopamine kinetics. Her hypothesis involves a particular protein playing a role in vesicular fusion. Her control for the experiment is so-called knock out mice, animals genetically engineered to lack the protein of interest.

Whatever Maha learns, she'll publish, and I will join the byline as one of the co-authors. My contribution is an R package hosted on GitHub and my analysis.

That concludes my presentation, Dr. Catlin.