Potential Collaborations on Modeling Neurotransmission

Bing Liu

Bahar Lab
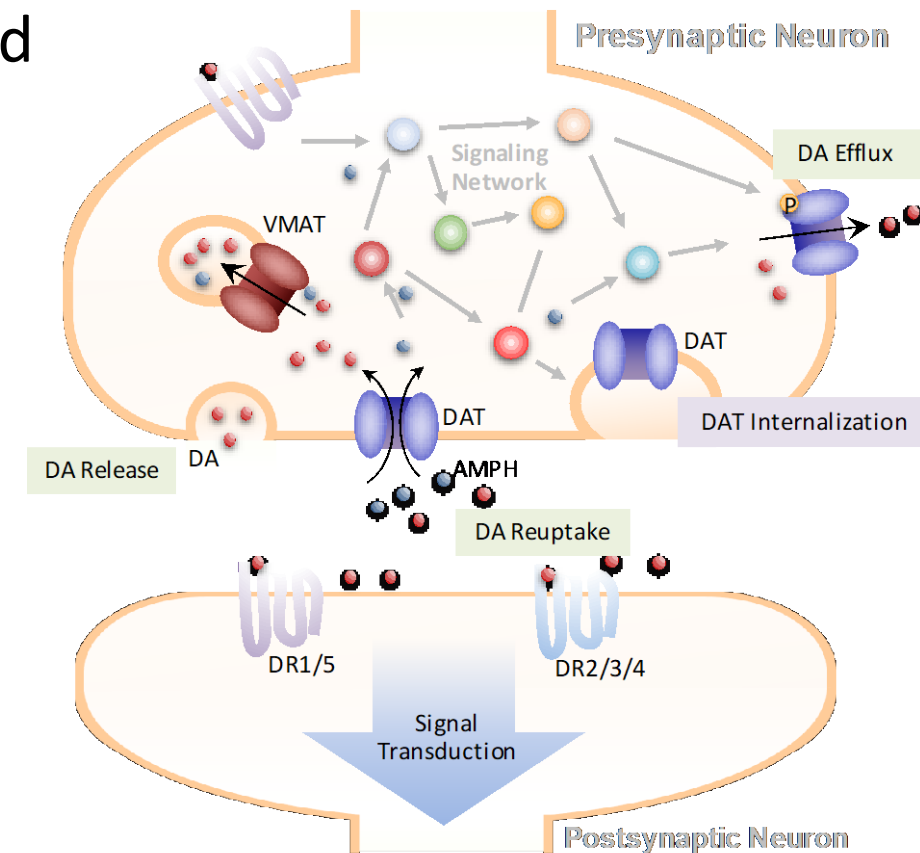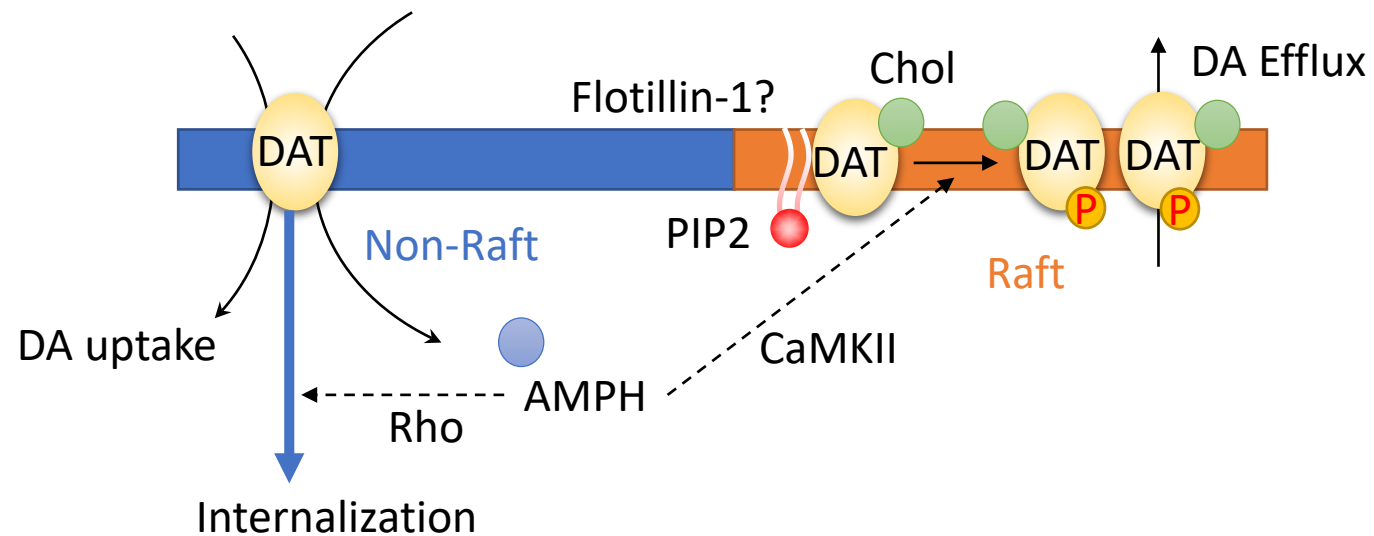
TR&D1 **TR&D3**

Lipid Rafts (Nanodomains)

Sezgin, et al. *Nat Rev Mol Cell Biol*, 2017

What is the role of lipid rafts in DA uptake?

- Hypothesis: Raft DATs can be phosphorylated and induce DA efflux, while non-raft DATs tend to undergo internalization.

Adkins et al. *Biochemistry* 2007, Galli et al, *Nat Neurosci*, 2011, Sorkin et al, *Traffic* 2013, Galli et al, *Nat Chem Biol*, 2014
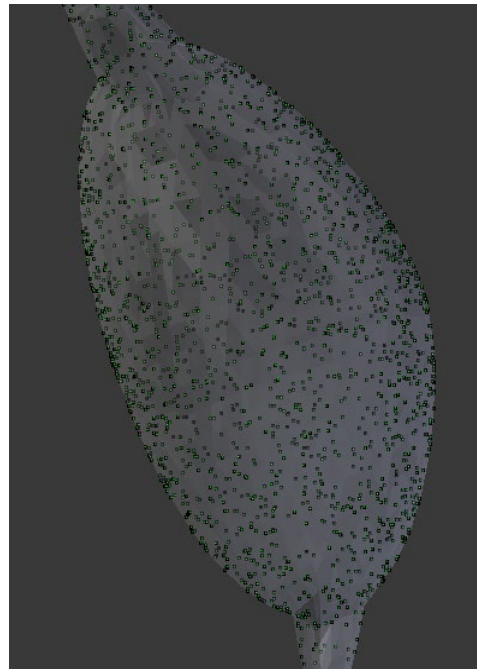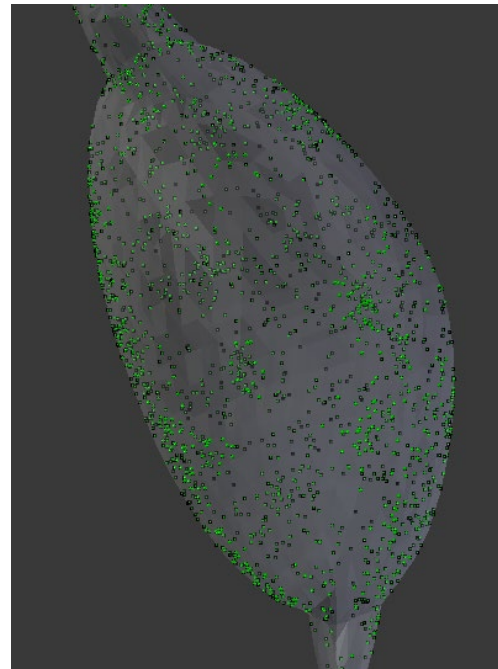
Preliminary Results

- MCell Simulation of DAT clustering in varicosity and extension

varicosity

t = 0

t = 500

With Quinn Butcher (CoBRA Academy Student)
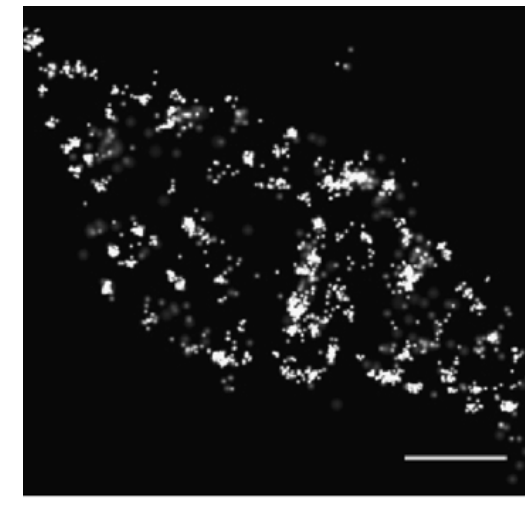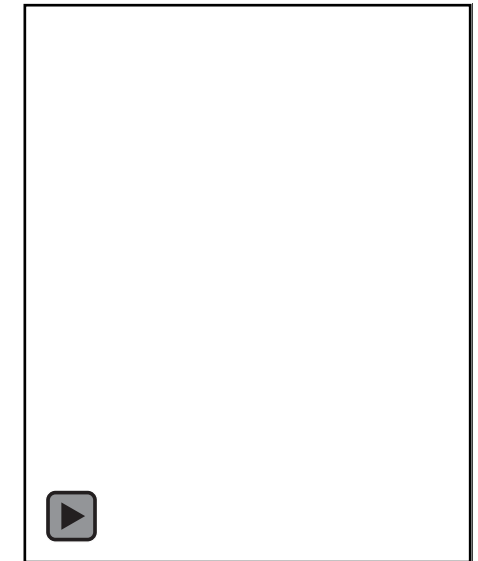
Troels Rahbek-Clemmensen,
…, Freja H. Hansen & Ulrik Gether
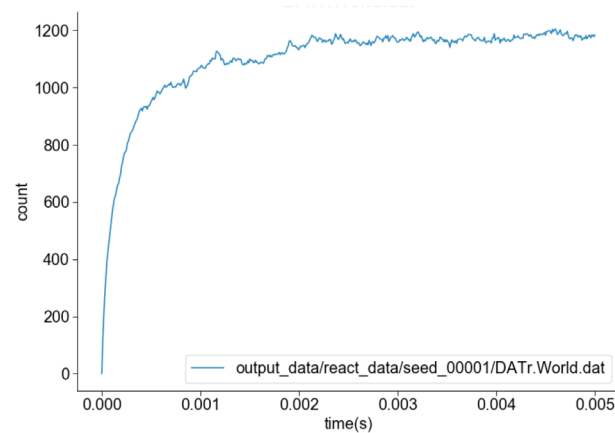, et al. *Nat Comm*. 2017

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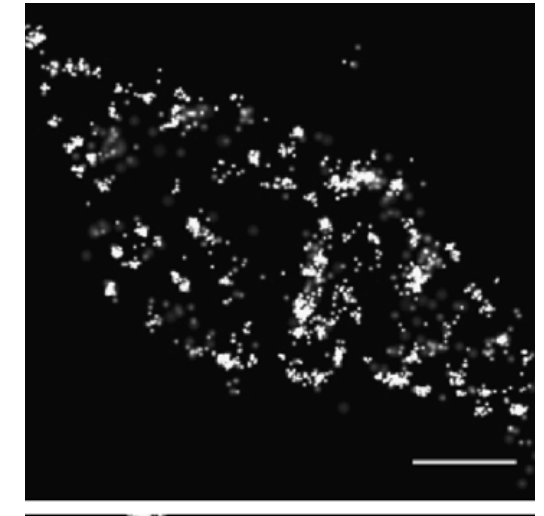
Preliminary Results

- Model simulation vs. Experimental data
  - Varicosity (WT): 1147/2000 = 57.4%

Model

Experiment

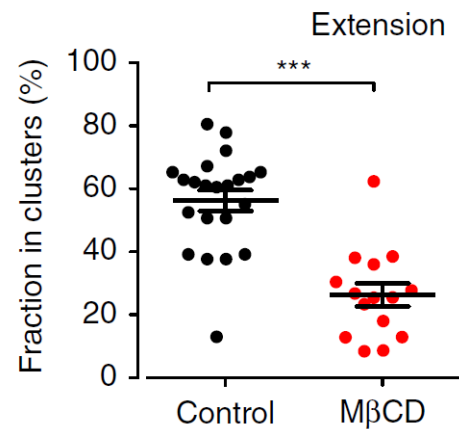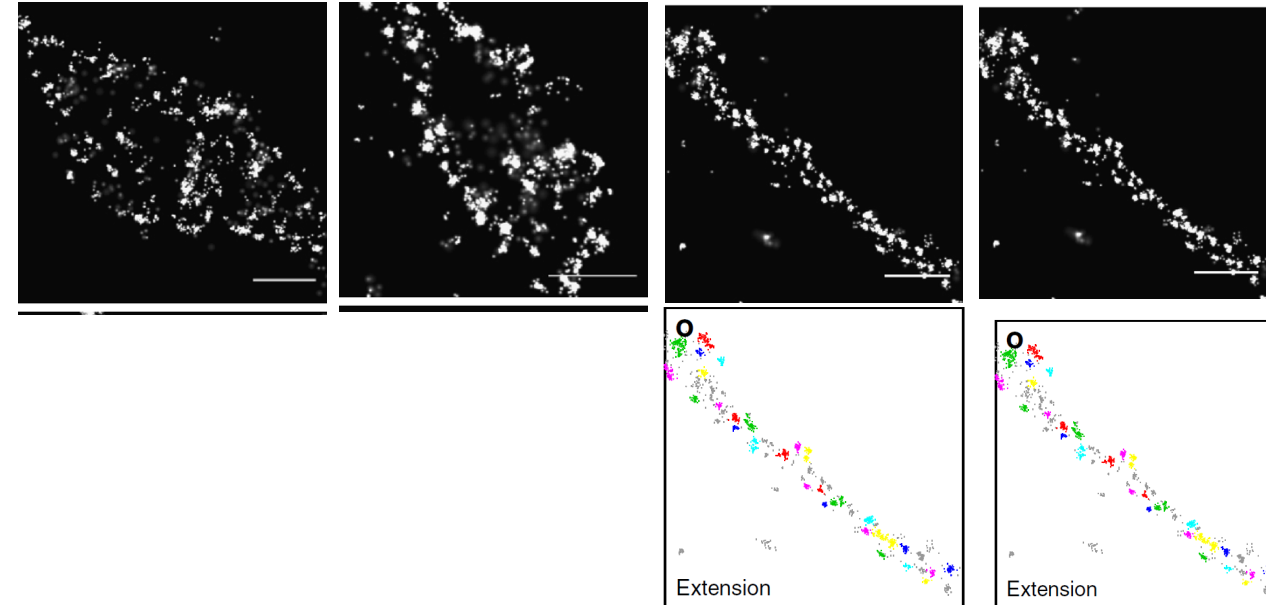Rahbek-Clemmensen, et al. *Nat Comm*. 2017
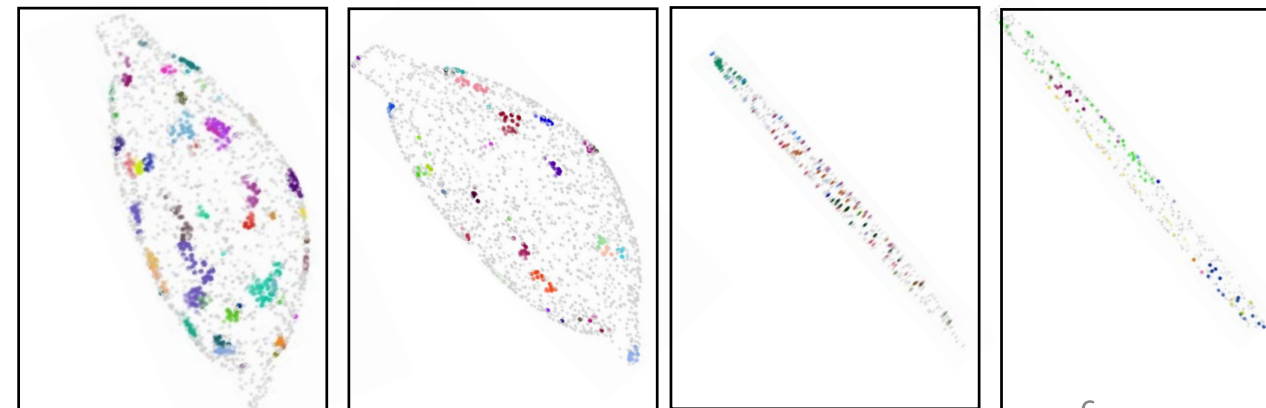
Preliminary Results

Experiment

- Model simulation vs. Experimental data
  - Varicosity (WT): 1147/2000 = 57.4%
  - Varicosity (Chol KD): 574/2000 = 28.7%
  - Extensions (WT): 316/500 = 63.2%
  - Extensions (WT): 209/500 = 41.8%

Model

Rahbek-Clemmensen, et al. *Nat Comm*. 2017
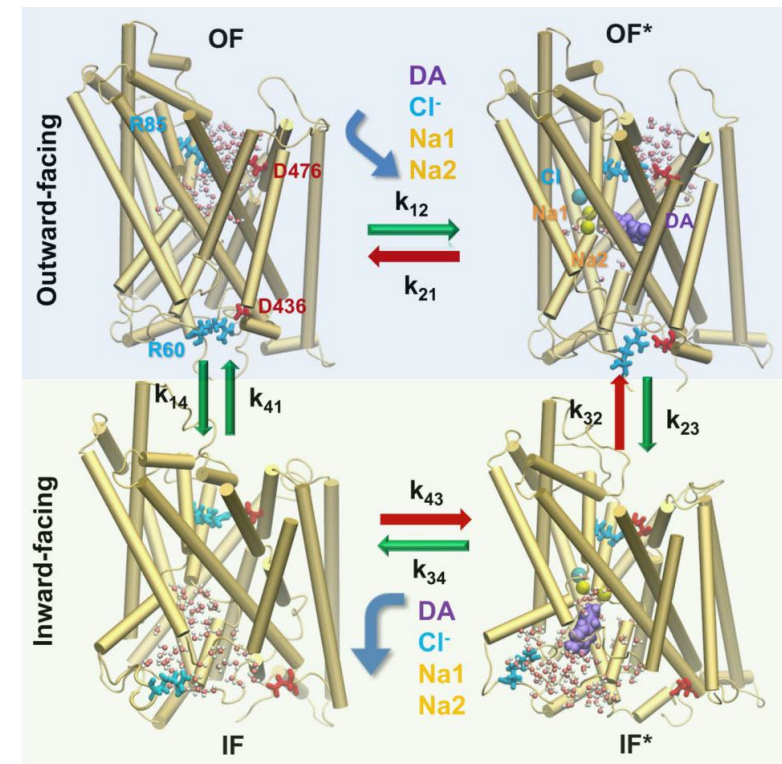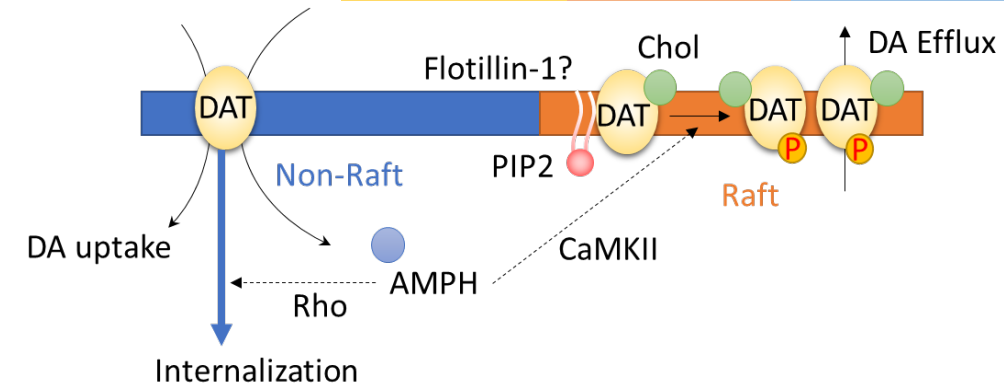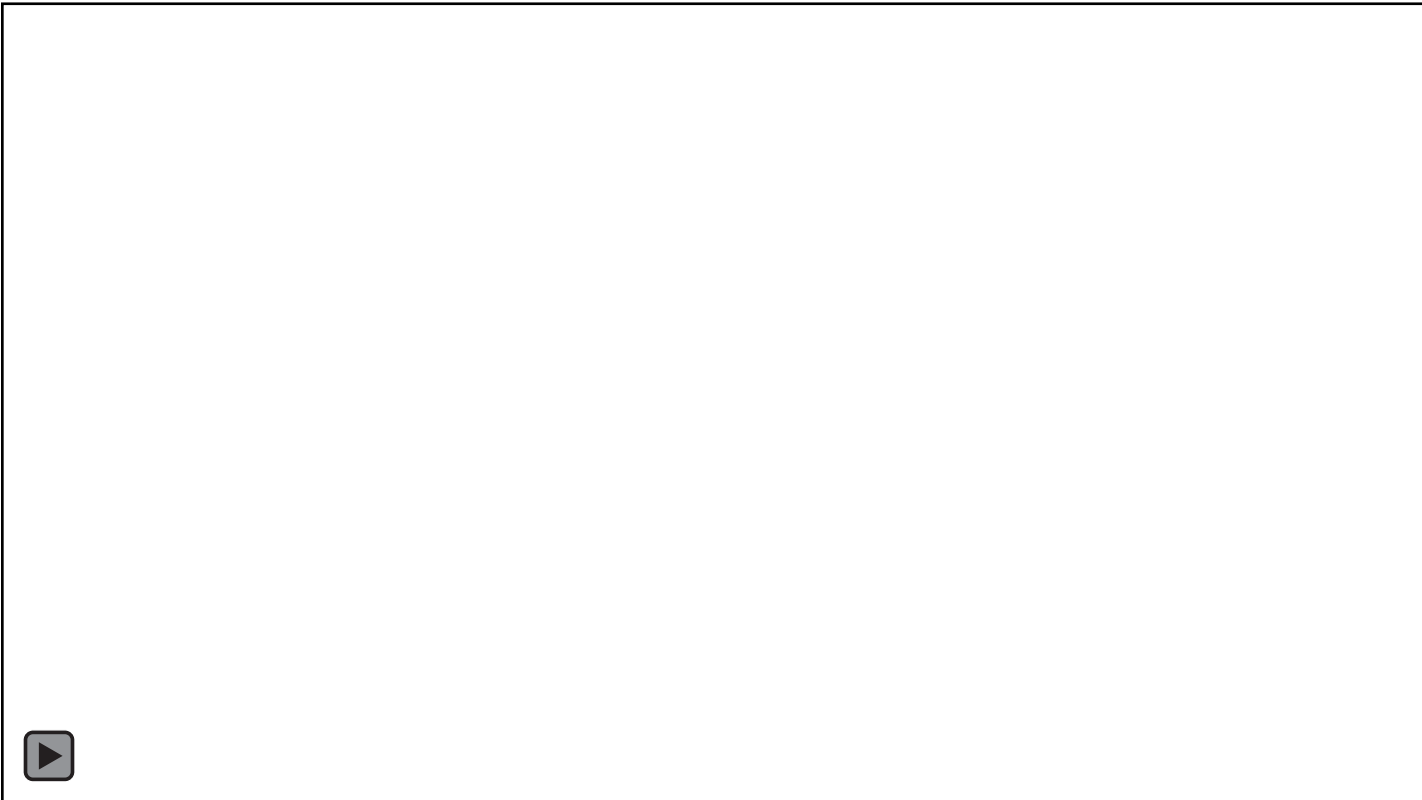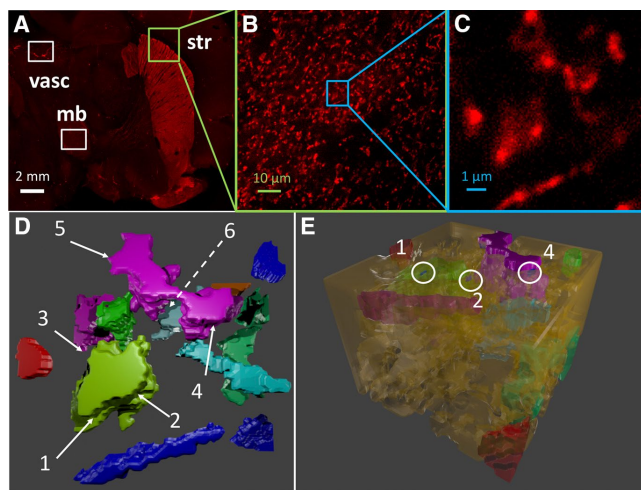
One Step Further

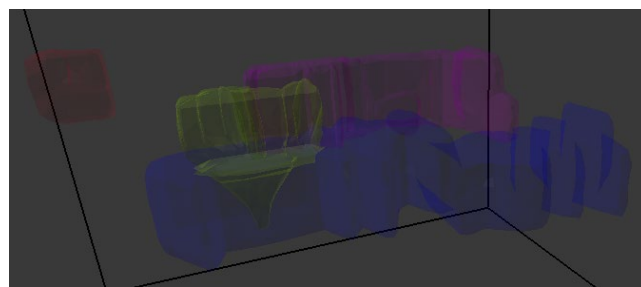- Including DA, and the four states of DAT
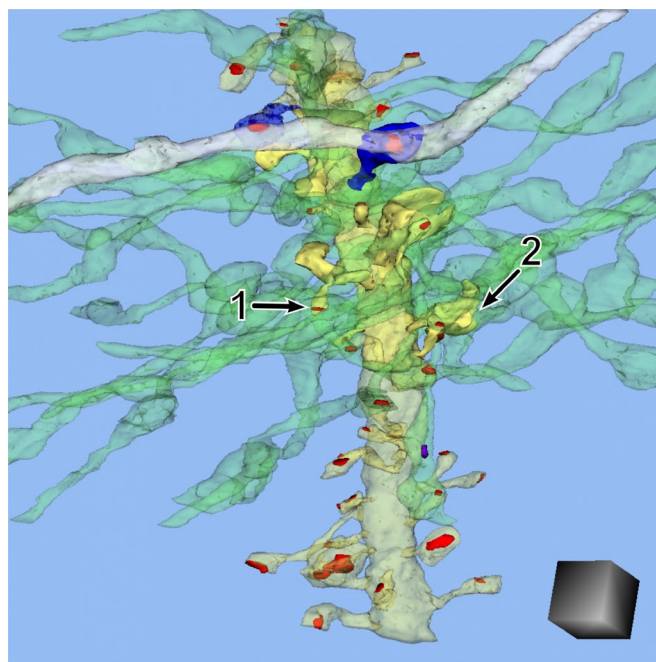

Kaya et al, *eNeuron* 2017

What's Next

- Realistic geometry + more reactions
- What are the effects cocaine and amphetamine in the presence of different lipid raft sizes/distributions
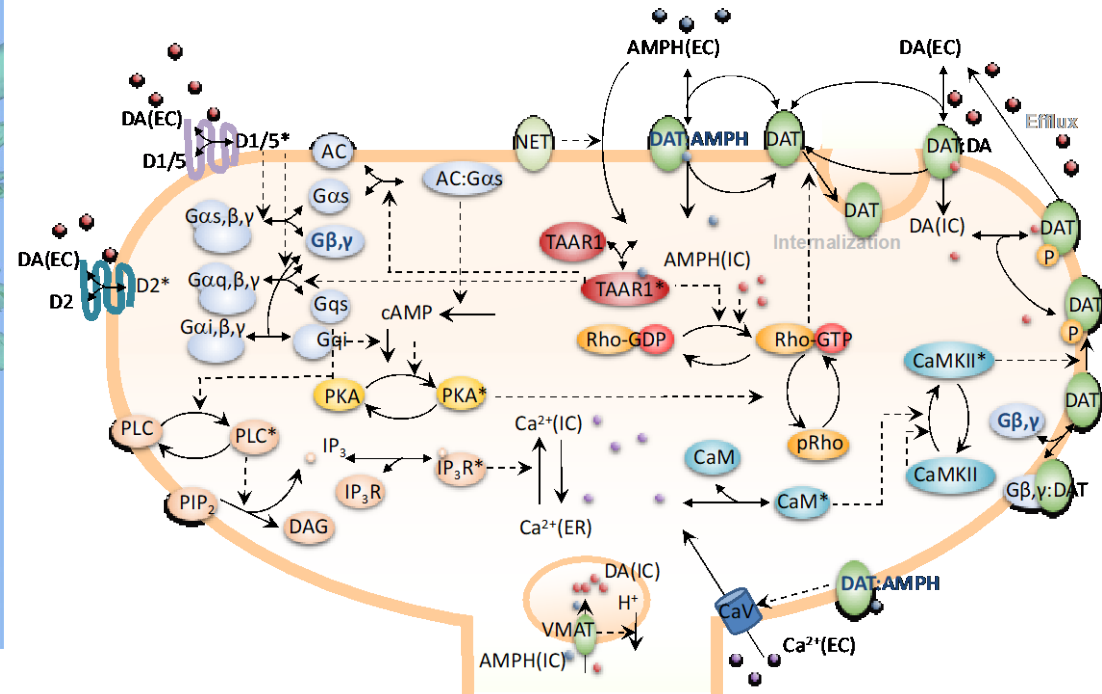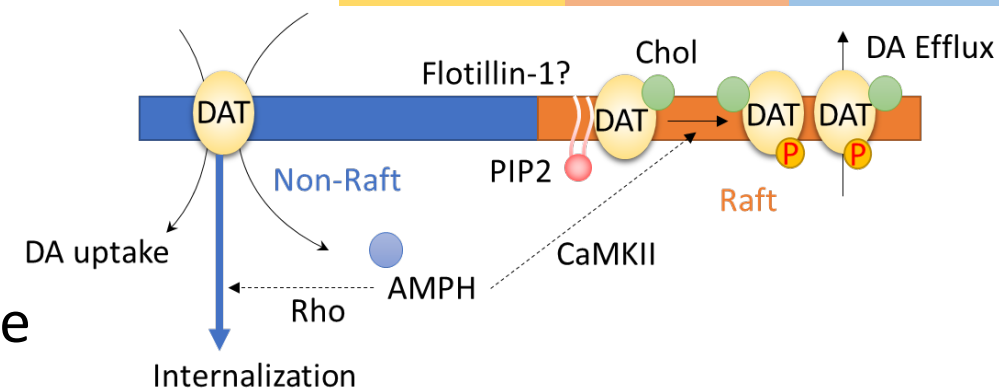

Kaya et al, *eNeuron* 2017

A simplified geometry
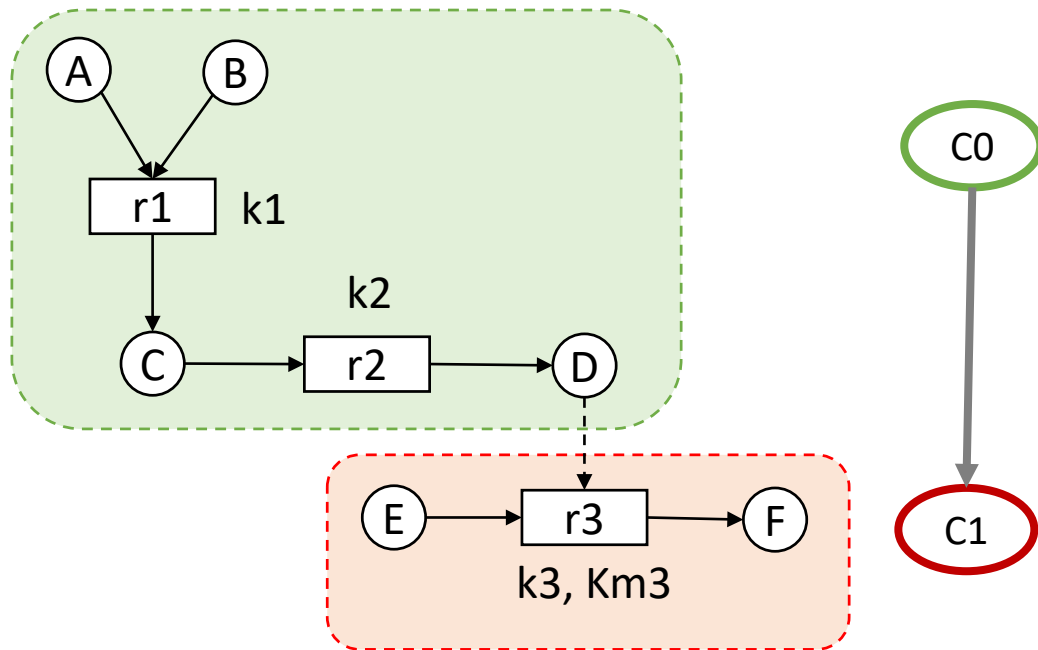

Bromer et al, *PNAS* 2018

Systems-level modeling of amphetamine induced DA dynamics -- **TR&D1** and **DBP1** (Amara)
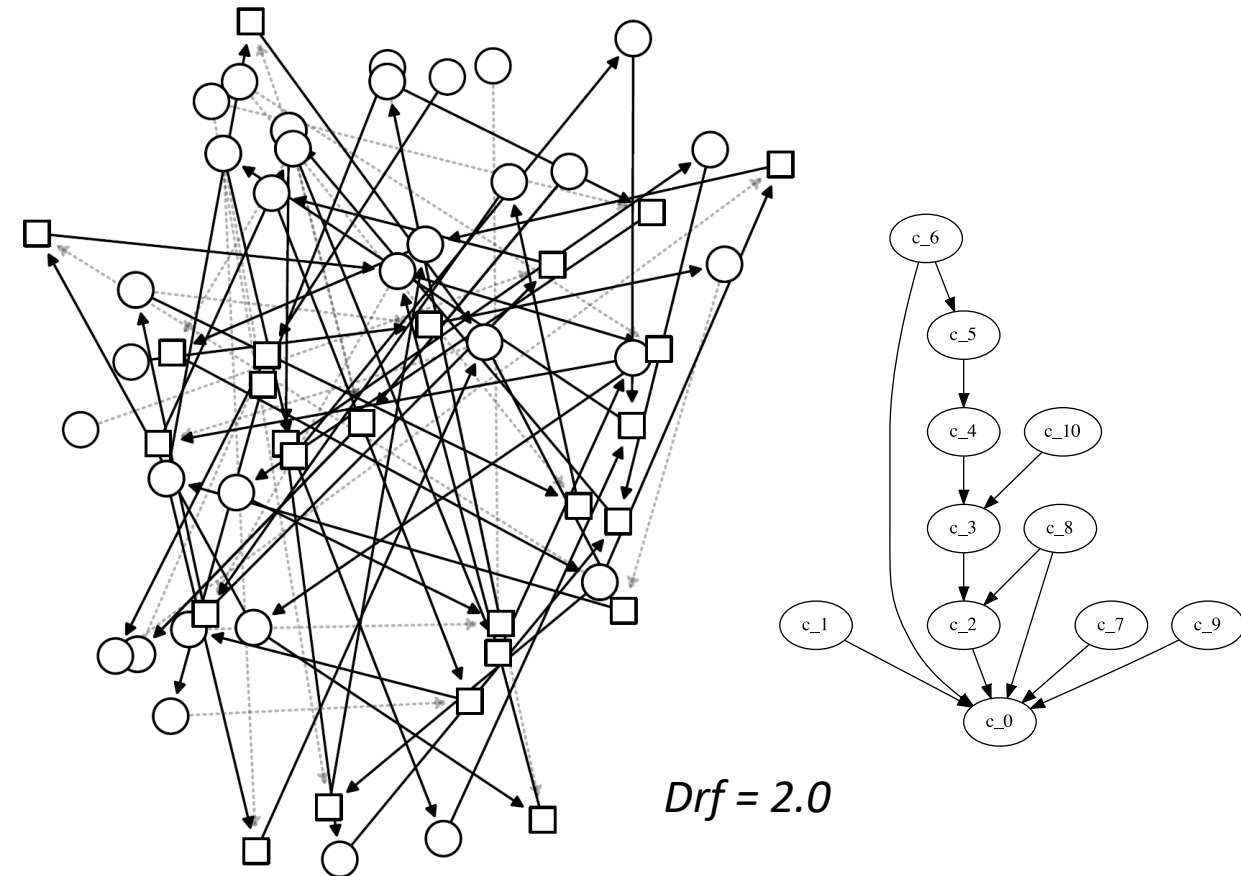
Modular Design in the Biological Network

A toy example:

Dimension reduction factor:

drf = total parameter / # parameters in biggest component
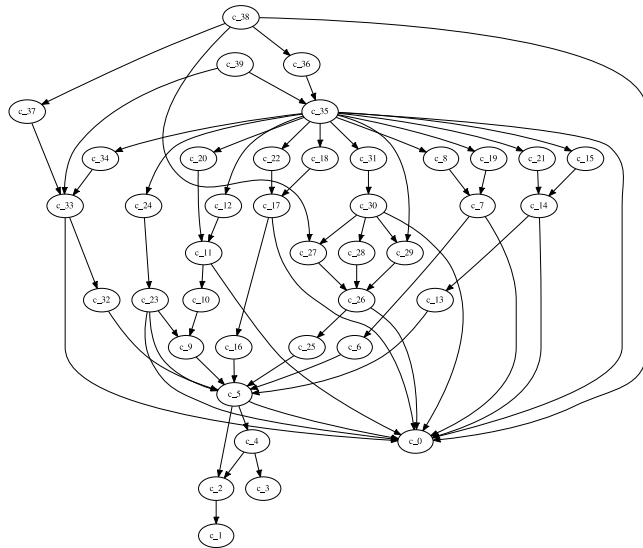
= 4 / 2 = 2.0

With Thiagu (TR&D3)

EGF-NGF pathway (BioModels ID: 033)

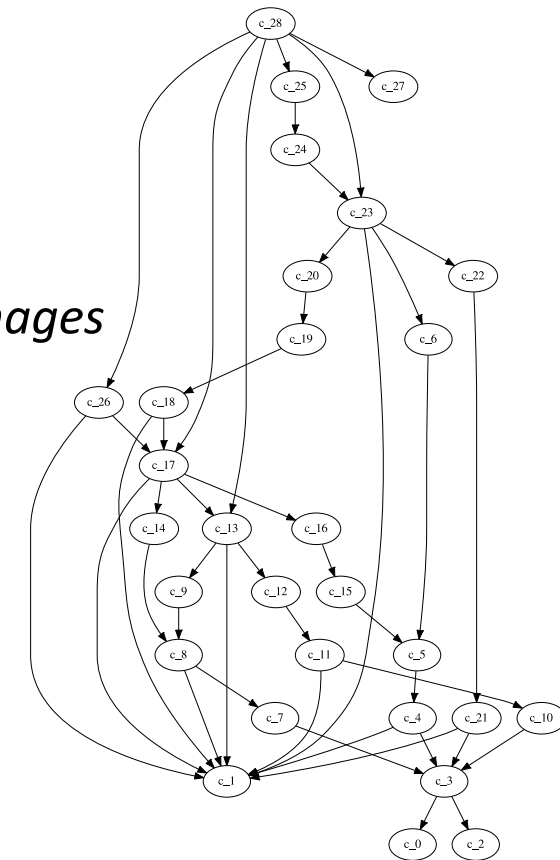*Drf = 2.0*

Decomposition based Dimension Reduction

- Scan all (640) models in BioModels database:
  - 149 models with drf >= 2.0
- May accelerate MCell simulations   **TR&D2**
- May help   **TR&D3**   and   **TR&D4**   with **DBP8** (Sorger)
  - *Scalable approaches to modeling using large set of rules and images*

BioModels ID: 503 (Messiha2013)
glycolysis and pentose phosphate pathway model

BioModels ID: 559 (Ouzounoglou2014)
alpha-synuclein effects on neuronal homeostasis