

# Proposal: MCell/Simulations of Amphetamine Reversal of escalated cocaine intake

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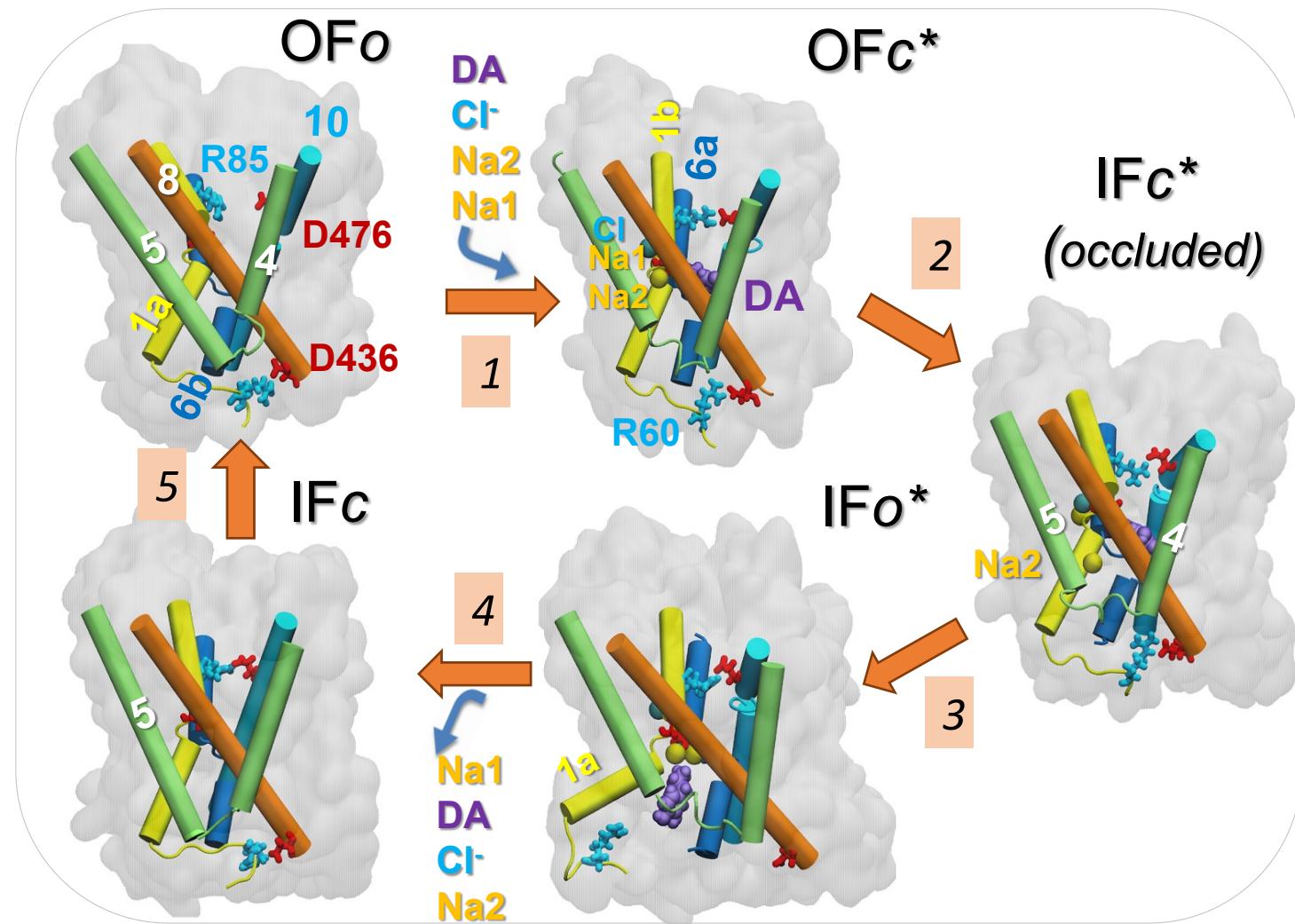
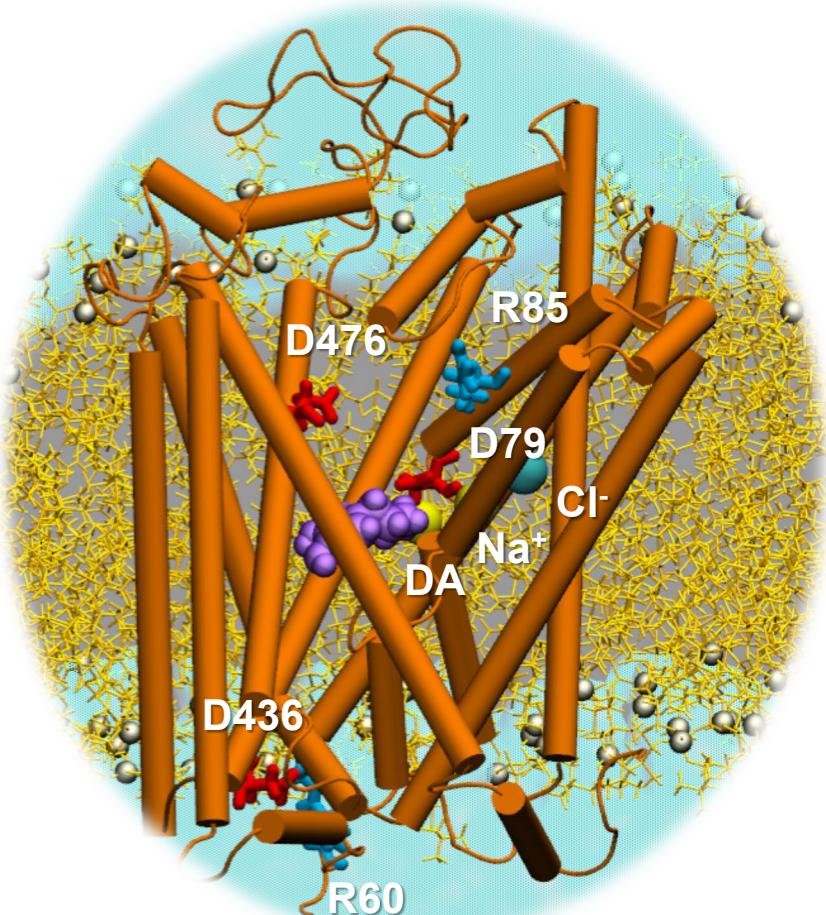
# Amphetamine reverses escalated cocaine intake via restoration of dopamine transporter (DAT) conformation

- Tolerance is a hallmark of cocaine addiction.
- Low dose, continuous amphetamine treatment, during self-administration or abstinence, completely reverse cocaine tolerance (i.e. **escalated cocaine intake**)
- FRET imaging analysis found that cocaine tolerance is associated with the formation of DAT-DAT complexes
- Amphetamine disperses DAT-DAT complexes

Compounds that disperse DAT-DAT complexes may have potential for cocaine addiction treatment

Proposal: combination of molecular- and cellular-level modeling in collaboration with Amy Newman (NIDA) and Habibeh Khoshbouei (U of Florida)

# Neurotransmitter transport cycle of hDAT



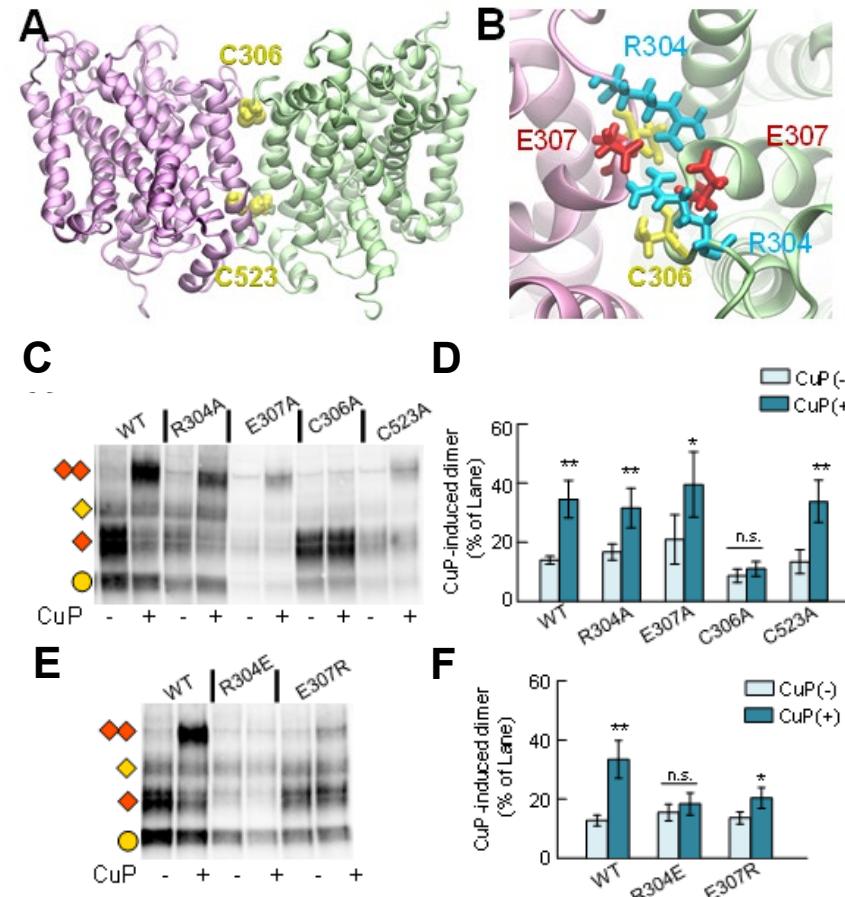
Cheng MH, Bahar I. *Nat Struct Mol Biol*; **2019**;26, 545–556; *Structure* **2015**; 23:2171.

Cheng MH, Kaya C, and Bahar I. *J. Chem Phys B* **2018**; 122:5336

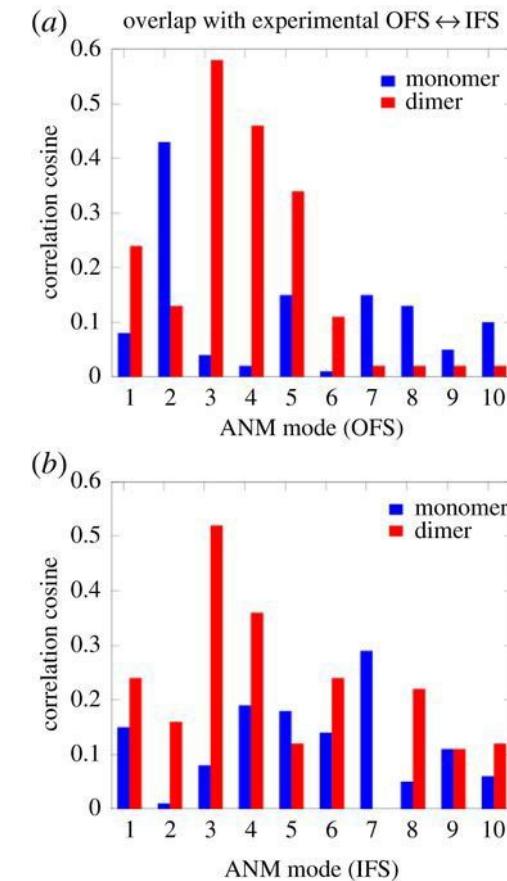
Cheng MH, Block E, Hu F, Cobanoglu MC, Sorkin A, Bahar I (2015) [Insights into the modulation of dopamine transporter function by amphetamine, orphenadrine, and cocaine binding](#) *Front Neurol* **6**: 134.

# Allosteric modulation of dopamine transporter function upon dimerization

## The hDAT dimer interface may differ from LeuT



## Dimerization may facilitate transport

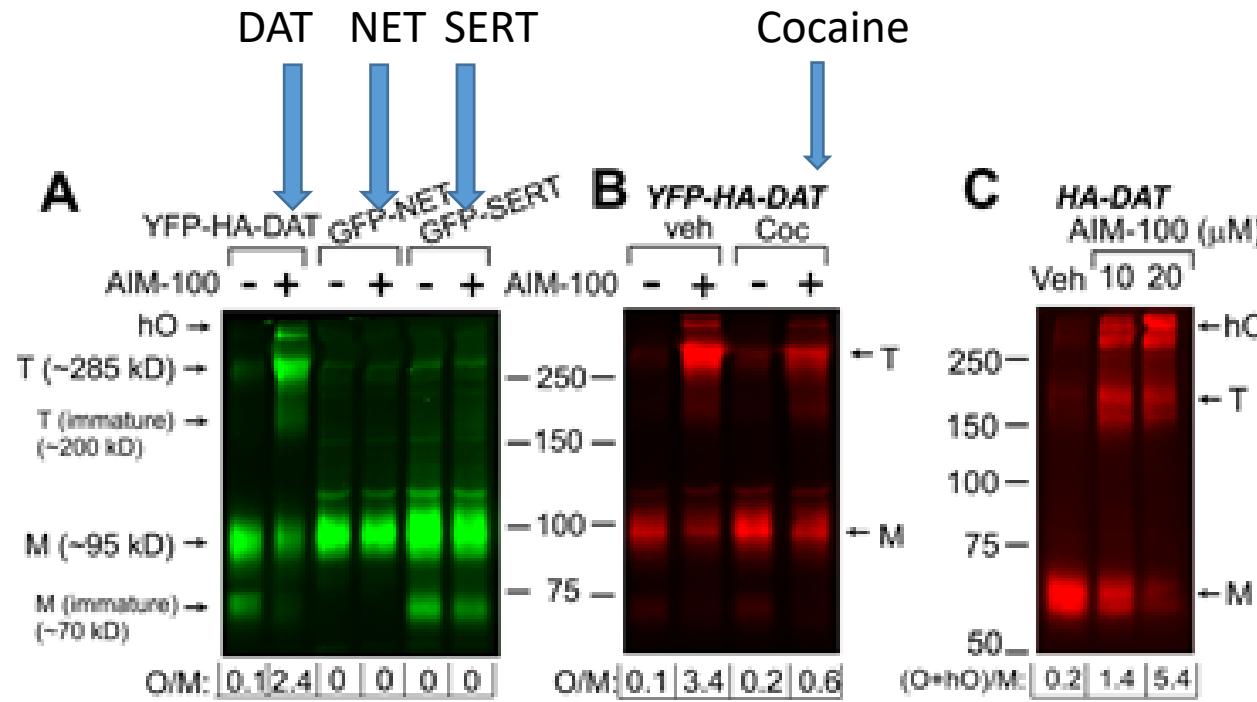


Cheng MH\*, Garcia-Olivares J\*, Wasserman S, DiPietro J, Bahar I.  
*J. Biol. Chem.* 2017; 292:12471

Ponzoni L\*, Zhang S\*, Cheng MH\*, Bahar I. *Philos Trans R Soc Lond B Biol Sci* 2018;  
373: 1749.  
Gur M, Cheng MH, Zomot E, Bahar I. (2017) *J Phys Chem B* 2017 121:3657.

# Motivations

## *AIM-100 enhances the formation of trimers and higher oligomers of DAT but not NET or SERT*



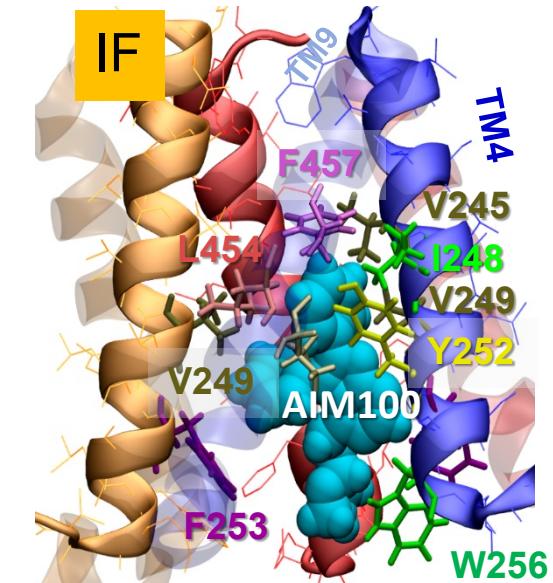
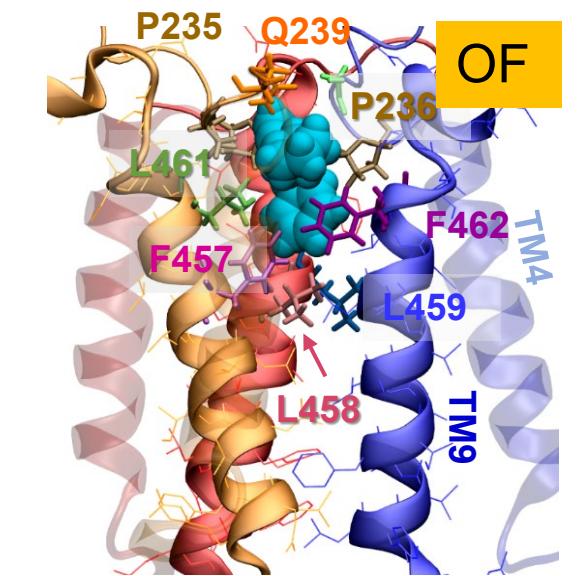
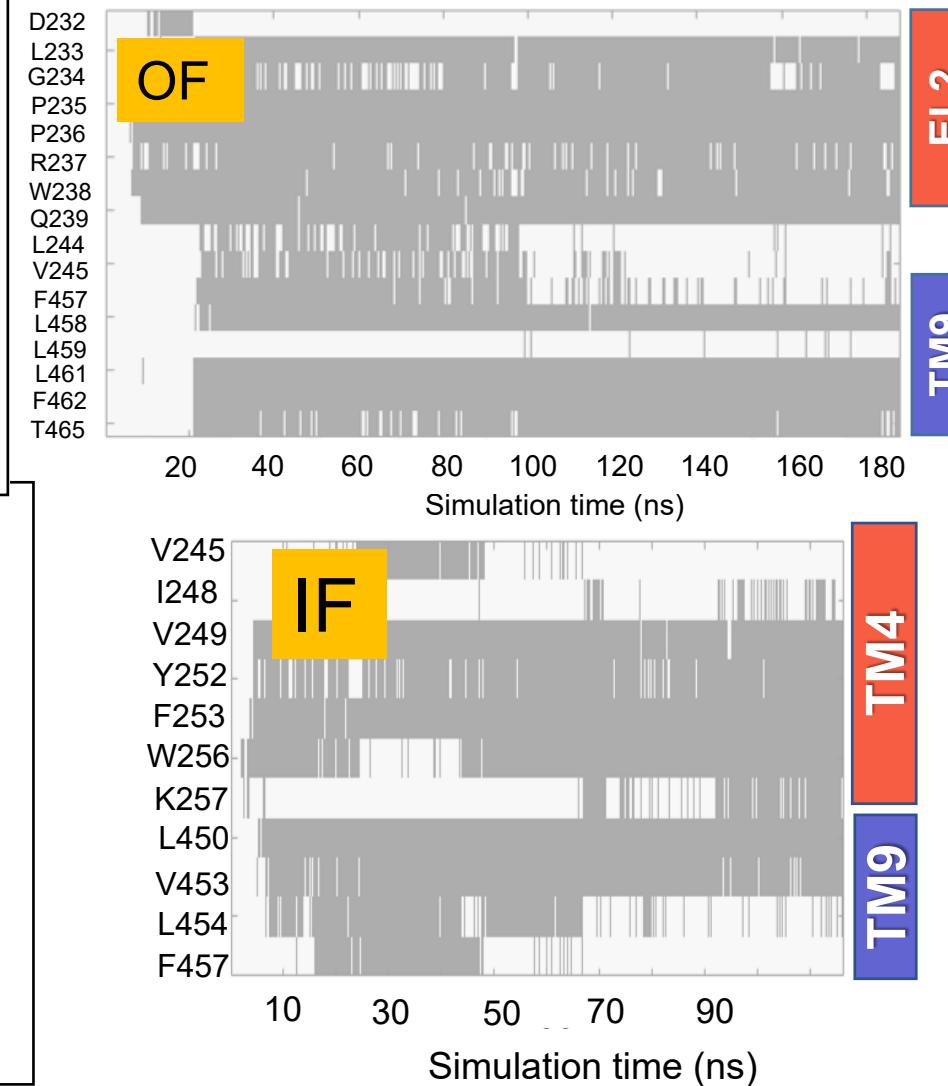
- ◆ AIM-100 promotes dramatic oligomerization or clustering of hDAT and mDAT; but not of their close homologues, NET and SERT.
- ◆ AIM-100 may act by binding to DAT.
- ◆ DAT inhibitors and substrates diminish the effects of AIM-100 on DAT.

Sorkina, T., Ma, S., Larsen, M. B., Watkins, S. C. & Sorkin, A. (2018) Small molecule induced oligomerization, clustering and clathrin-independent endocytosis of the dopamine transporter. *eLife* 7, e32293.

# AIM-100 binding to DAT trimer-W238 in OF or IF state highlight the involvement of EL2b, TM4 and TM9 in stabilizing the trimer and coordinating the drug



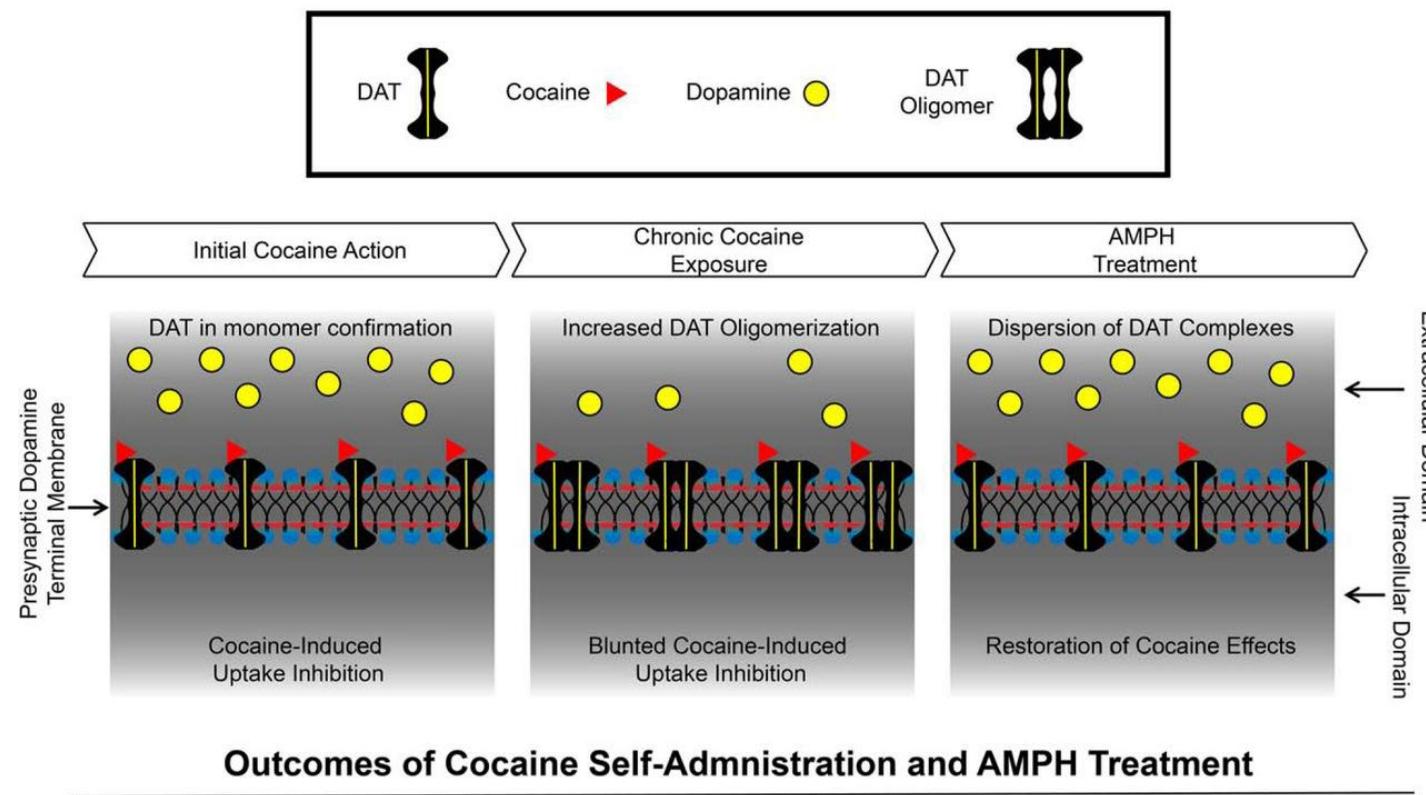
Time evolution of hDAT-AIM-100 interaction



# Rational and hypothesis: application to cellular-level simulations

- Cocaine binds to outward-facing (OF) hDAT and stabilizes the OF conformation.
- Cocaine enables molecular adaptations and promotes formation of DAT-DAT complexes.
- Amphetamine binds hDAT and stabilizes hDAT in the inward-facing (IF) conformation.
- Like dopamine, amphetamine serves as hDAT substrate (i.e. it is transported through hDAT; cocaine is not)
- Amphetamine facilitates reverse transport of dopamine from the intracellular to extracellular region.
- Amphetamine disperses DAT-DAT complexes
- Cocaine, amphetamine and dopamine compete for binding the same site, S1, on hDAT OF conformation, when binding from the EC region

# Mechanism of cocaine tolerance and AMPH rescue



Siciliano, et al, *J Neuroscience* 2018; 38. 484