

The Future of MD

Prof. Vijay S. Pande, PhD

Departments of Chemistry, Computer Science, and Structural Biology

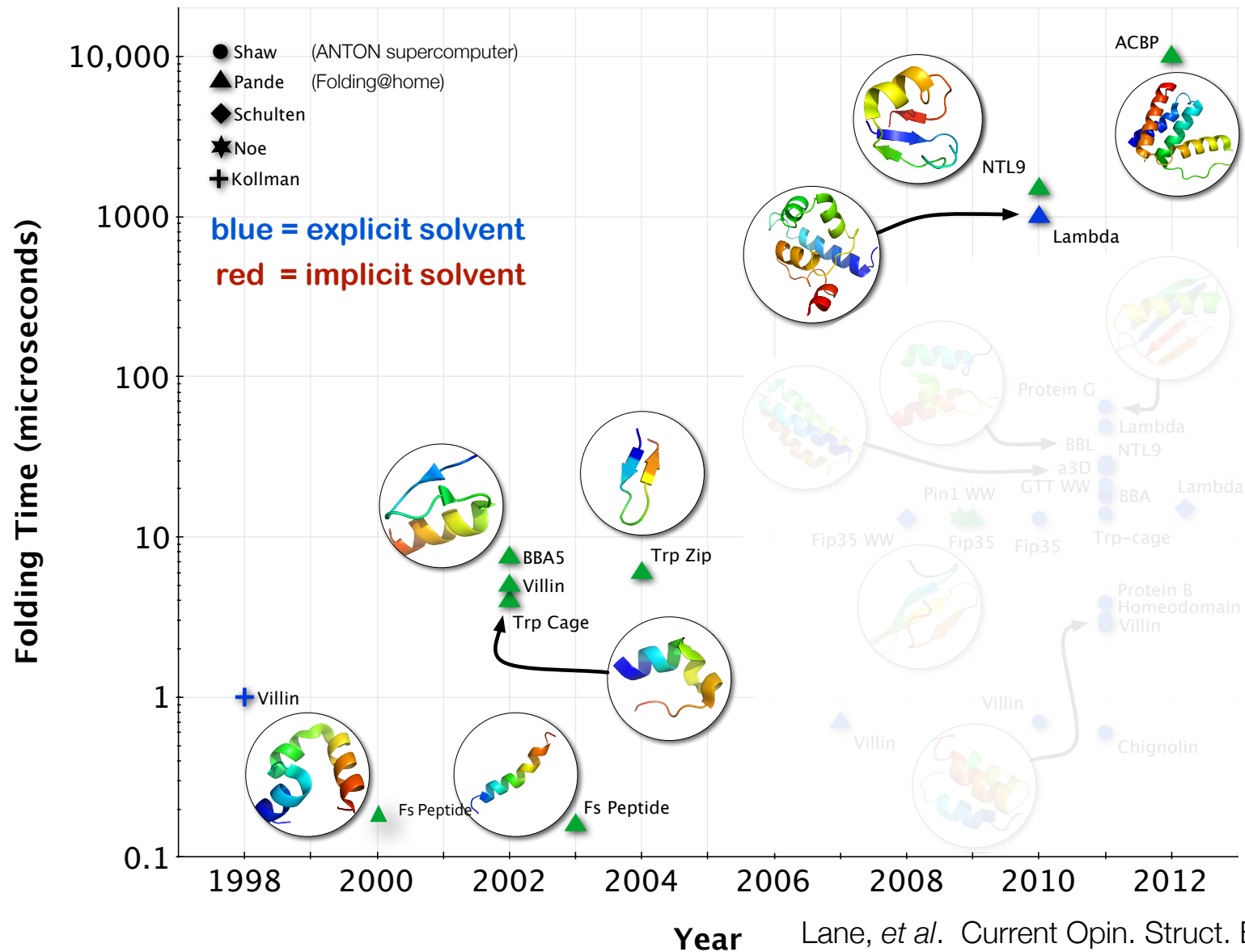
Director, Biophysics Program

Director, Folding@home Distributed Computing Project

Stanford University

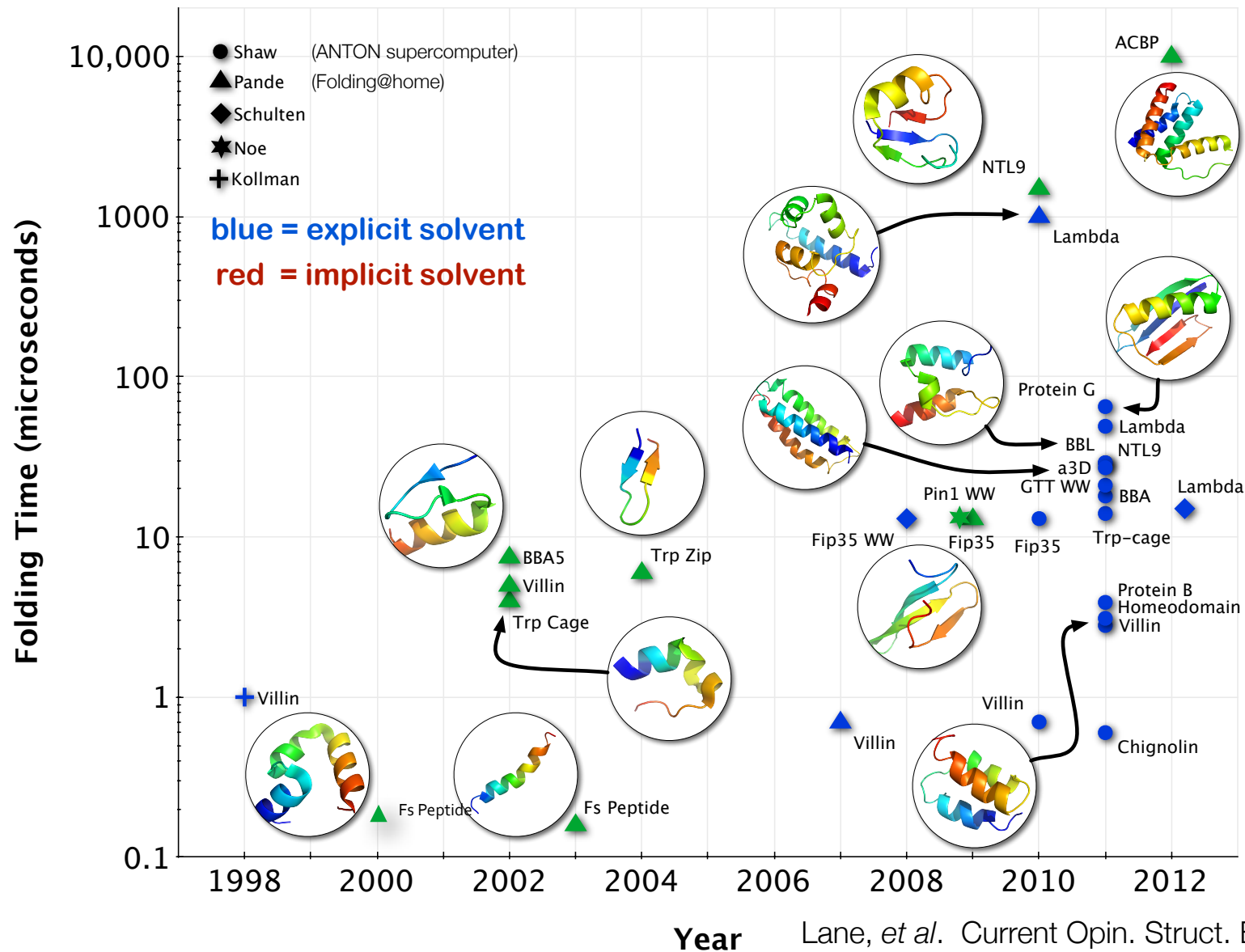


MD simulation has come a long way



Lane, *et al.* Current Opin. Struct. Bio. (2013)

MD simulation has come a long way



**What do these methods teach
us about protein folding?**

(1) We see non-native interactions

snapshots from a NTL9 folding trajectory:

(1) We see non-native interactions

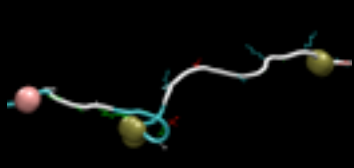
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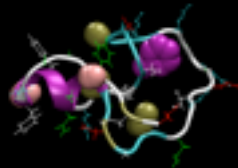
starts in
unfolded
state

(1) We see non-native interactions

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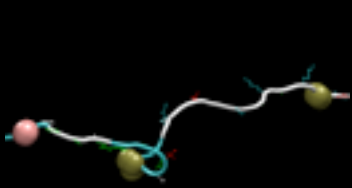
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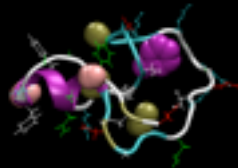
helix
forms
early

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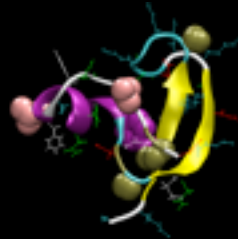
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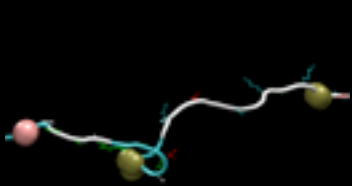
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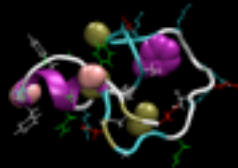
collapse,
then beta
sheet forms

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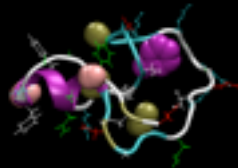
final part of
beta ready
to align

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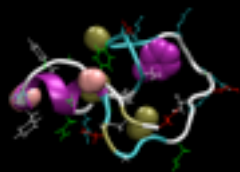
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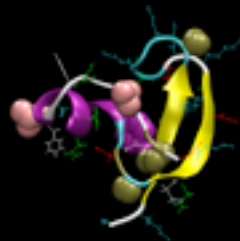
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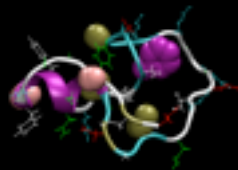
correspond to states from our Markov State Model:

(1) We see non-native interactions

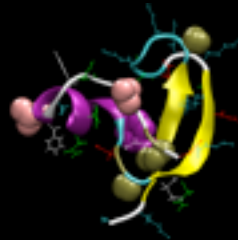
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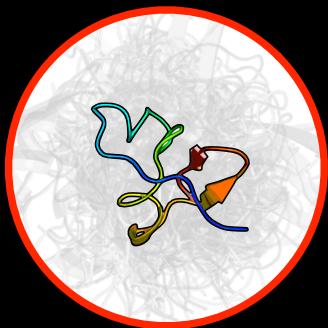


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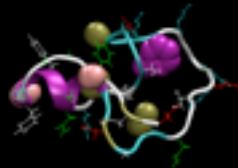


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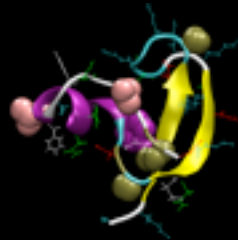
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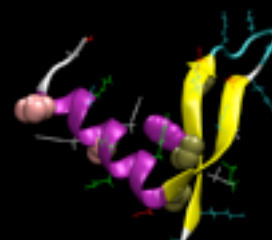
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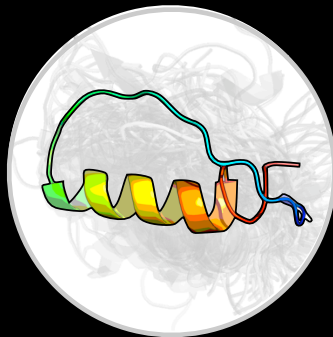
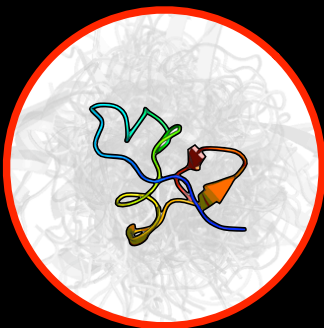


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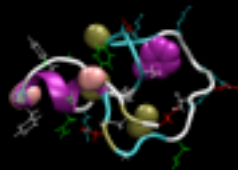


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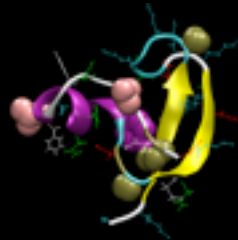
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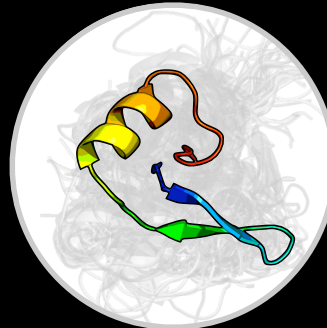
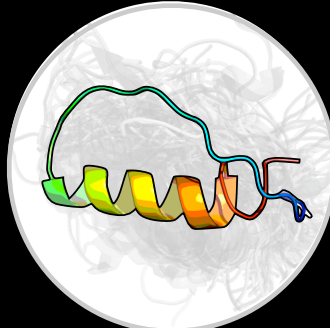
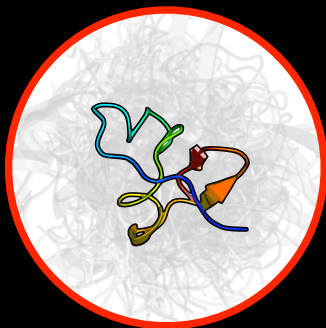


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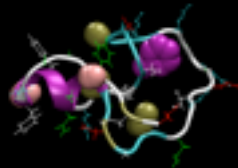


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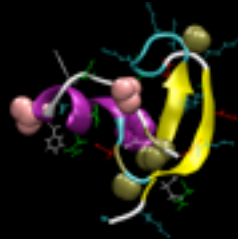
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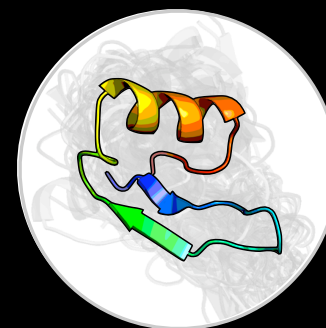
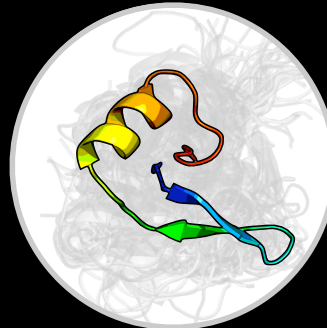
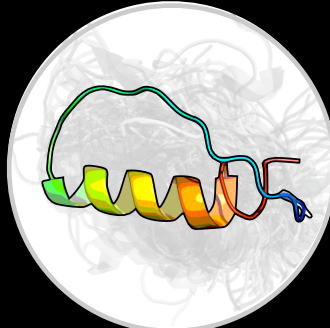
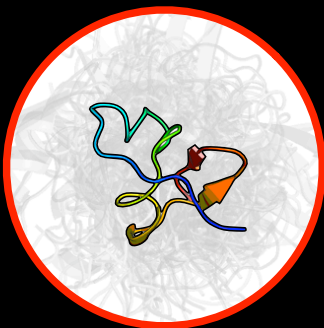


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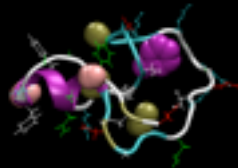


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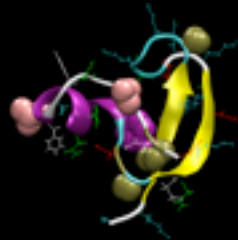
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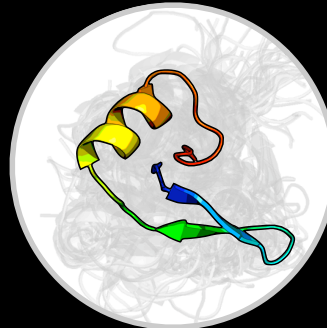
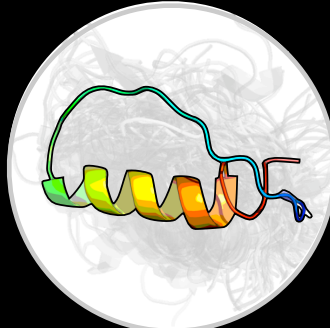
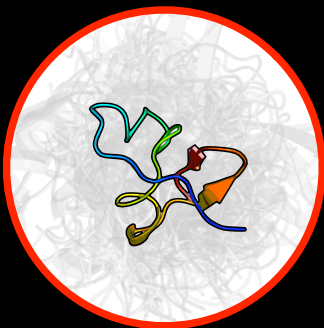


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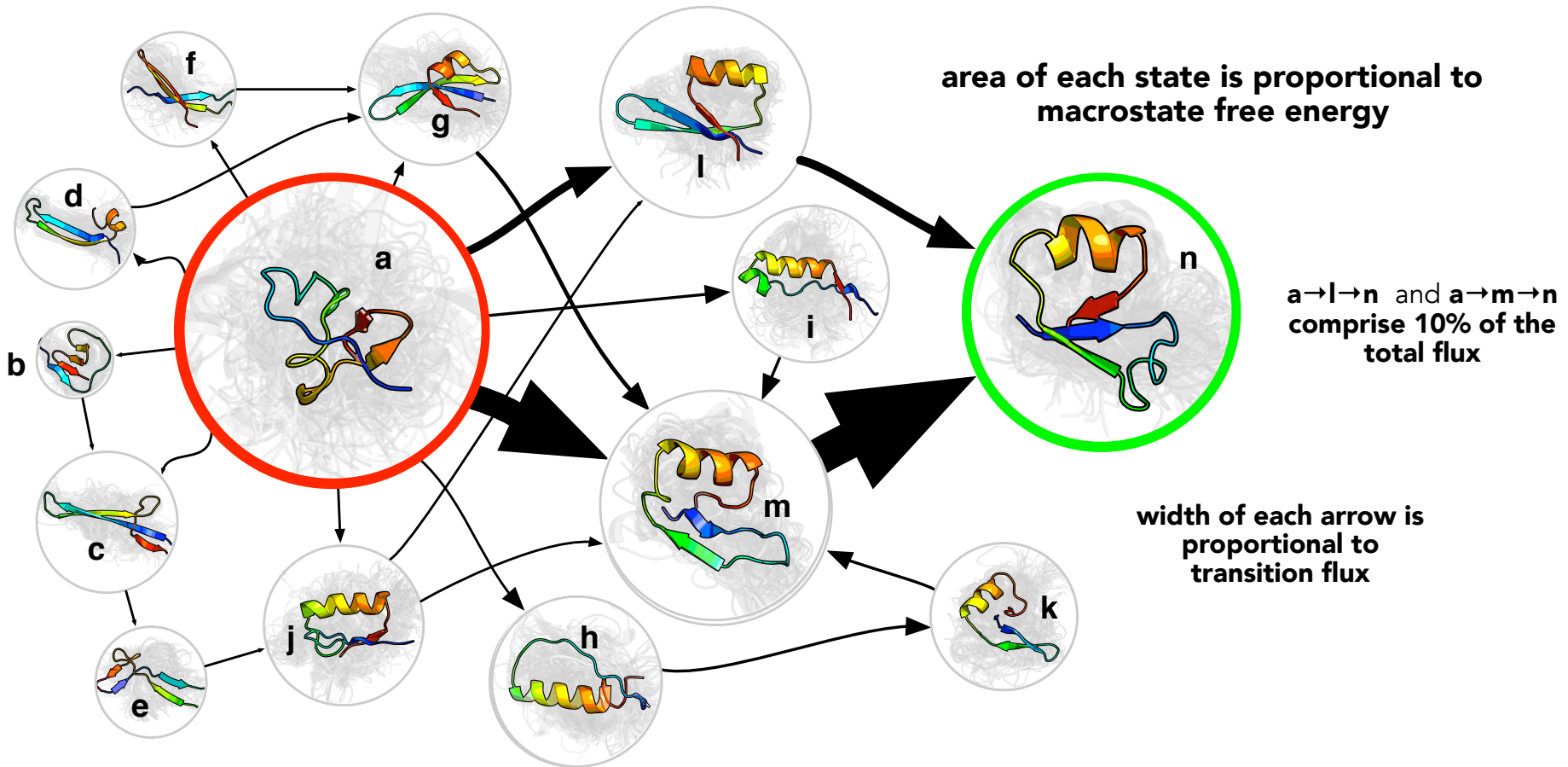


folded
structure
forms

correspond to states from our Markov State Model:



(2) We find many paths & states

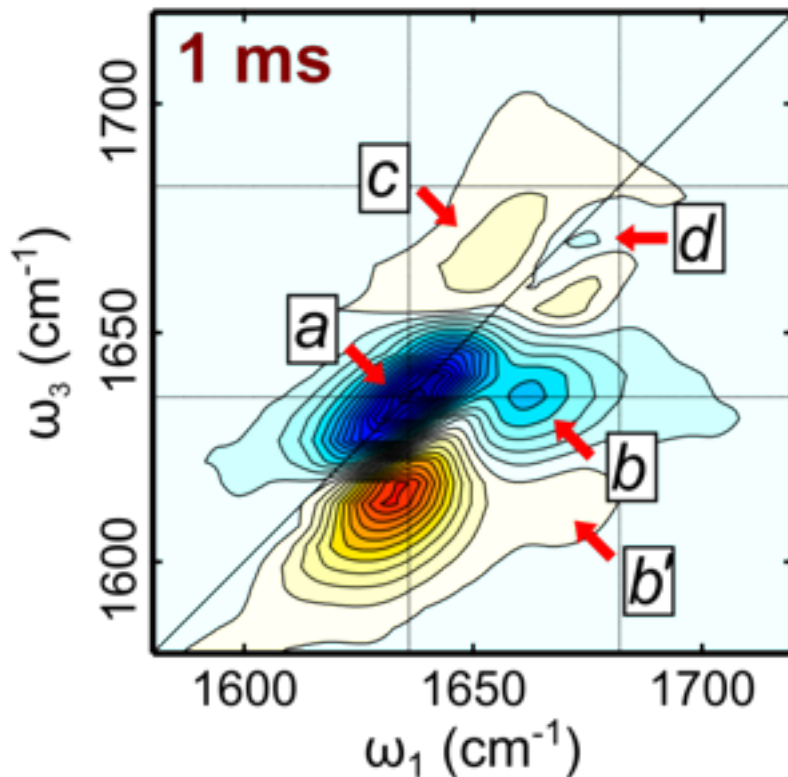


Flux calculation method: TPT: Vanden-Eijnden, et al (2006); Berezhkovskii, Hummer, Szabo (2009) 35

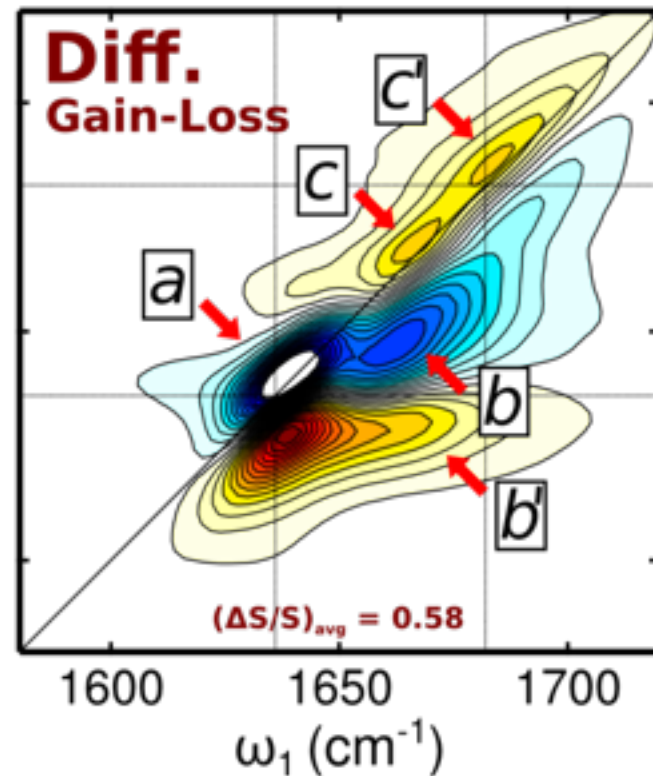
NTL9: Detailed connections to experiment

NTL9

Experiment

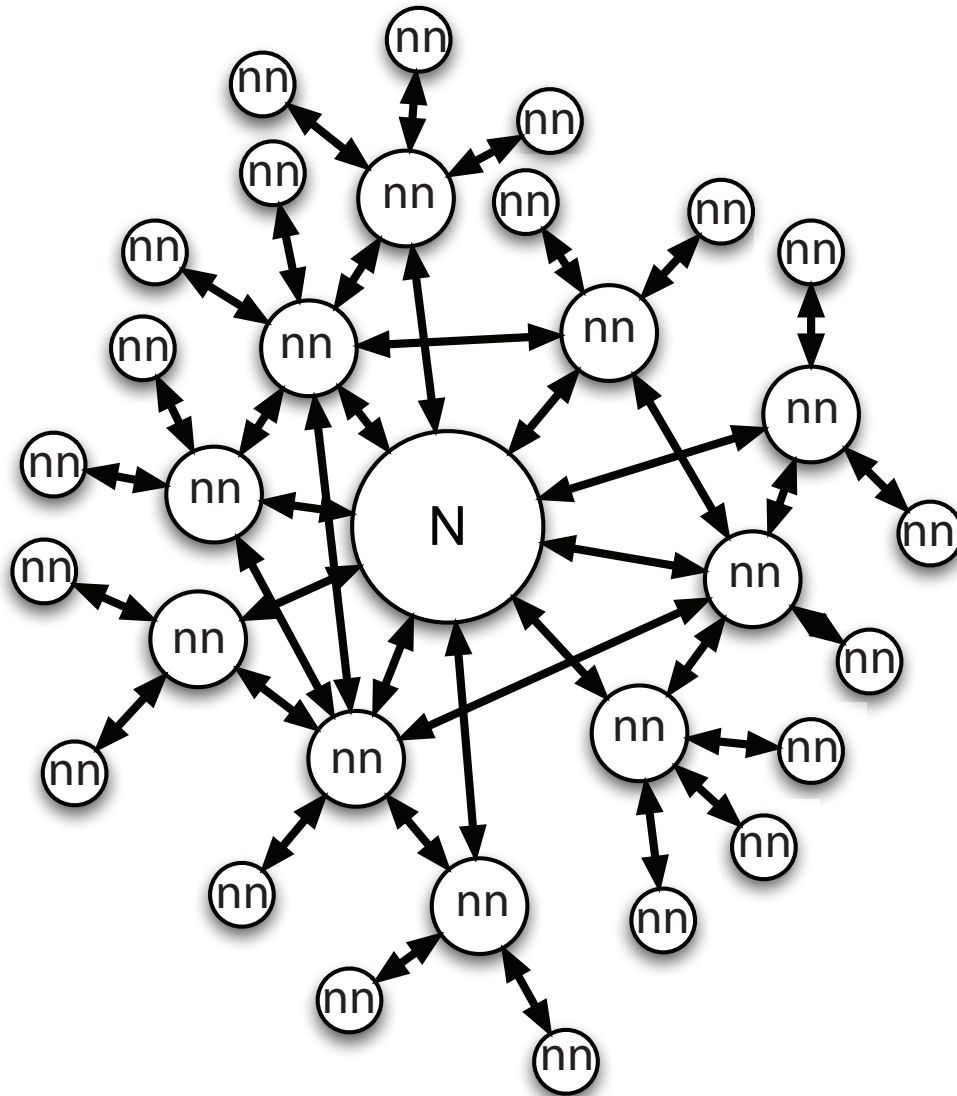


Simulation



Collaboration with Andrei Tokmakoff's lab

(3) Native state is a kinetic hub



**hub = highly
connected state**

See the work from
the labs of Brooks,
Caflisch, and
Pande.

Simulating kinase activation dynamics

In collaboration with Benoit Roux's lab

Kinase drugs are not selective enough

Staurosporine



Sunitinib



Sorafenib



Imatinib



Dasatinib



Erlotinib



Gefitinib



Lapatinib



CP-690550

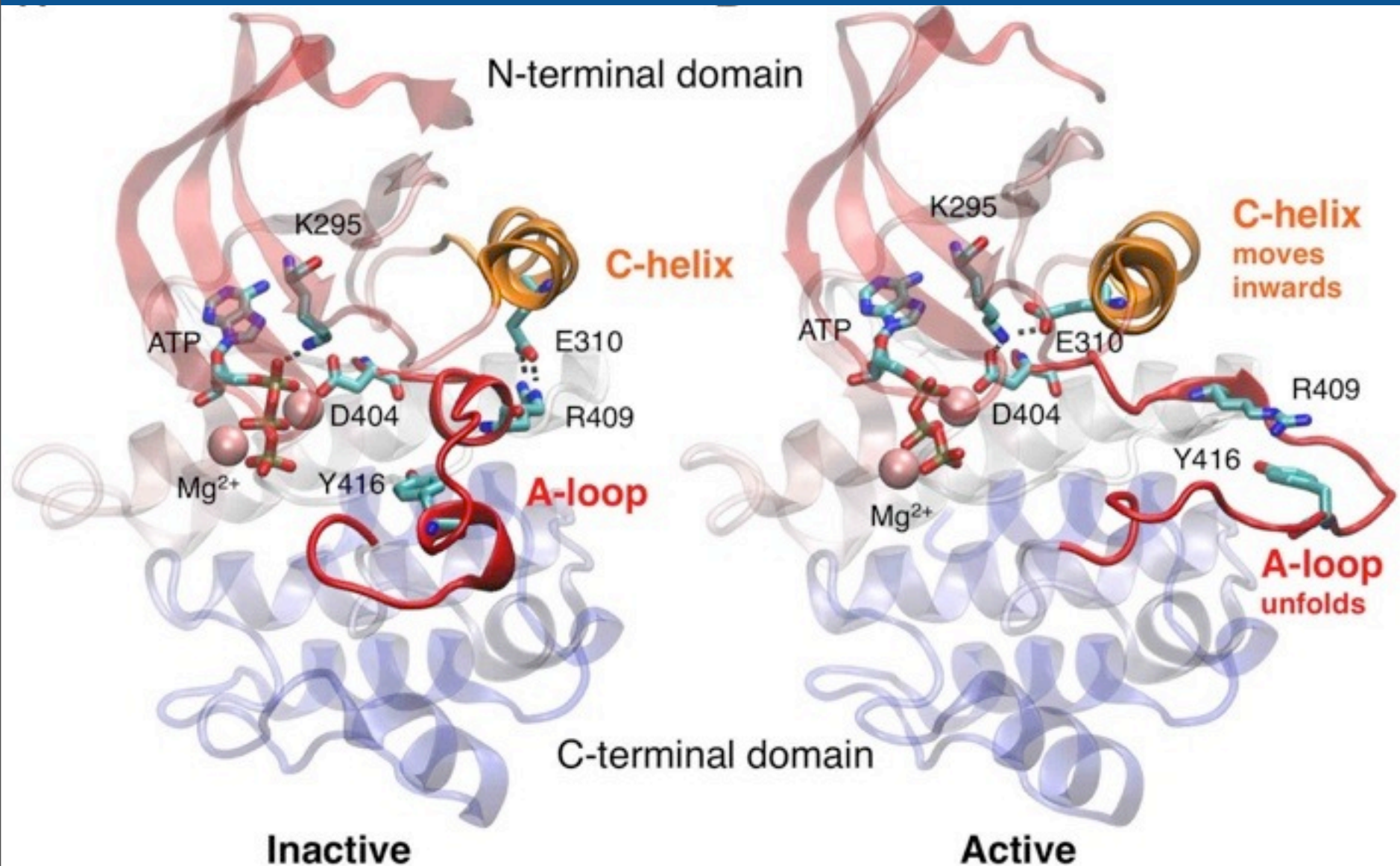


VX-680

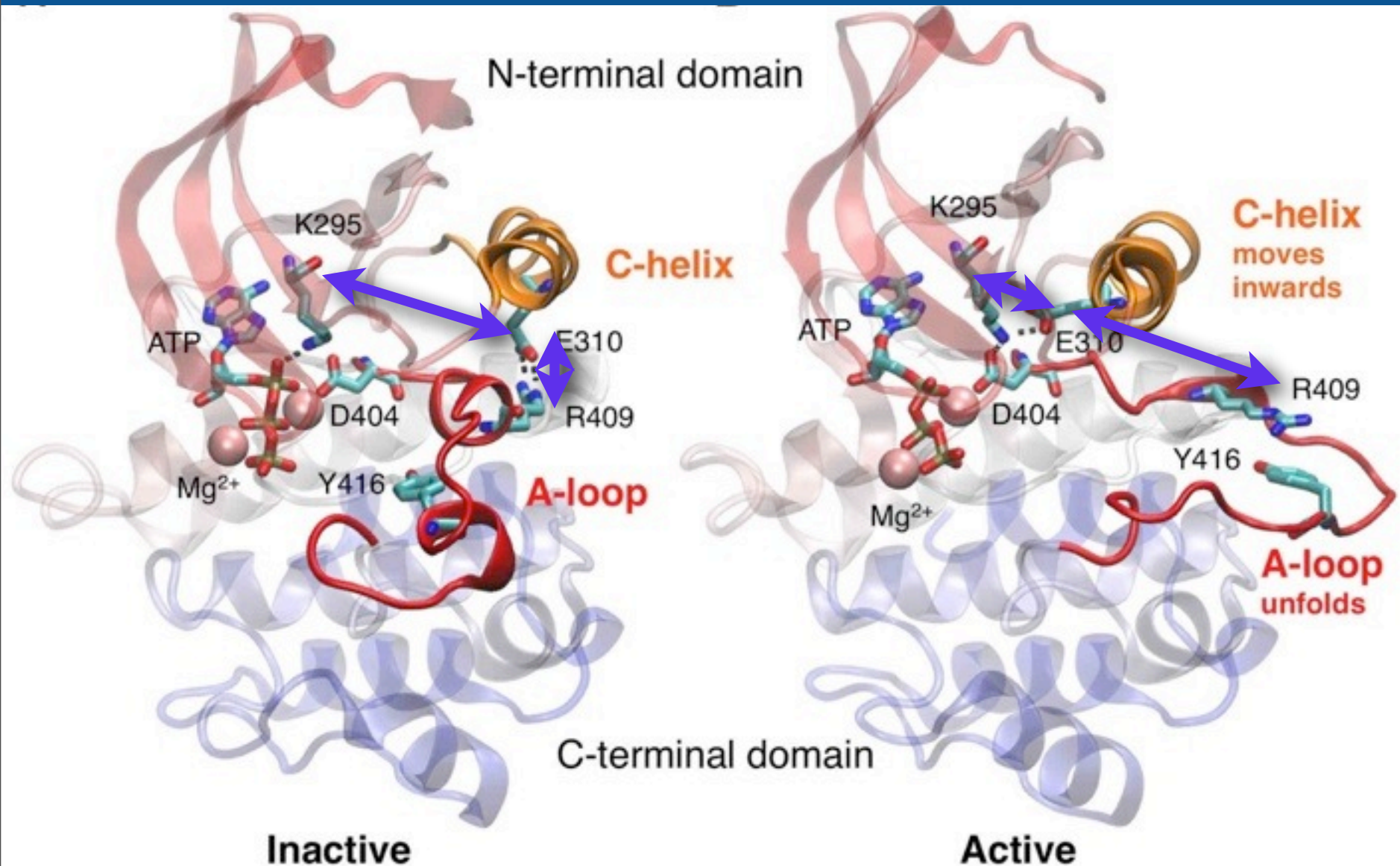


Ghoreschi et al, Nature Immunology **10**, 356 - 360 (2009)

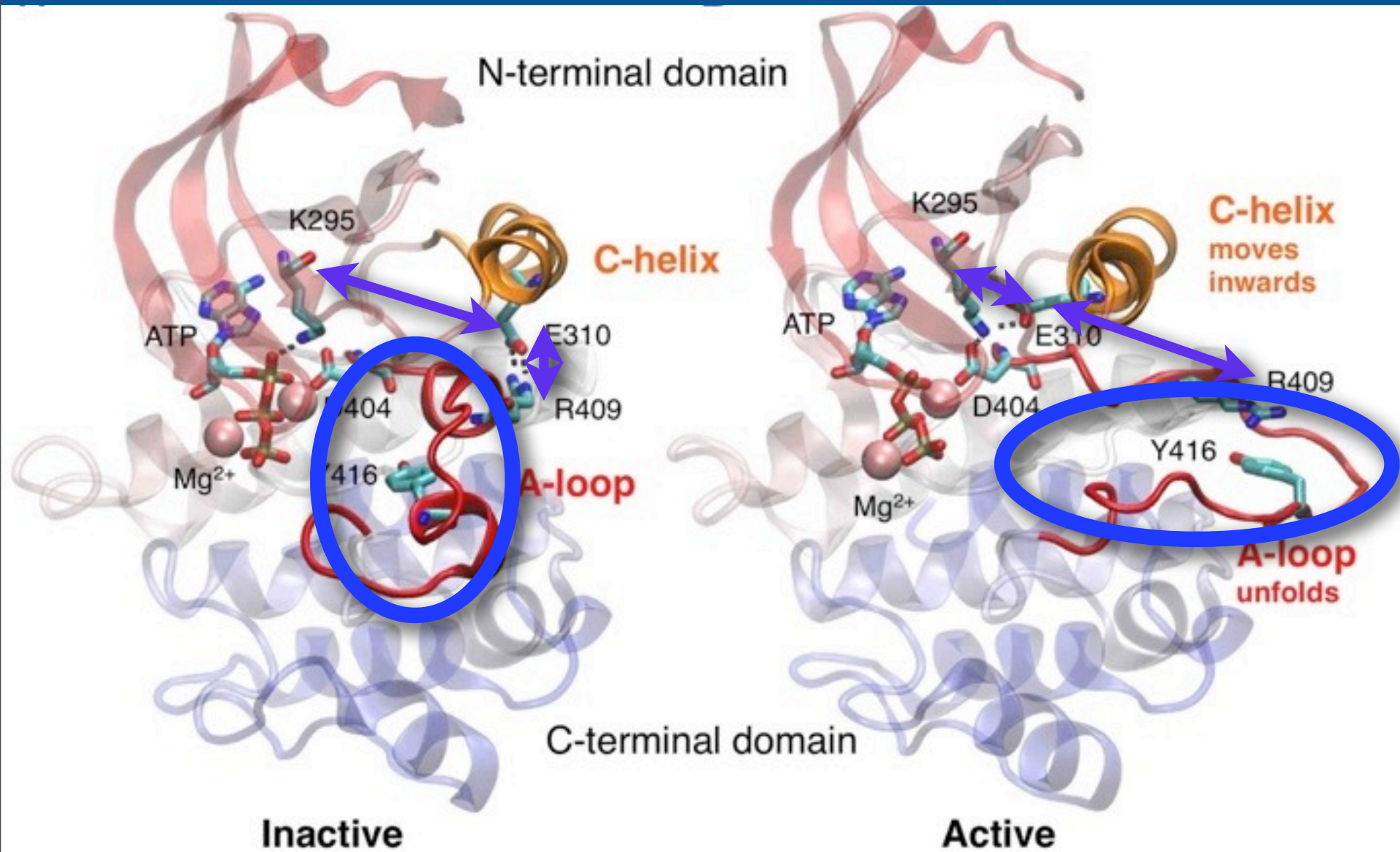
Conformational change in src kinase



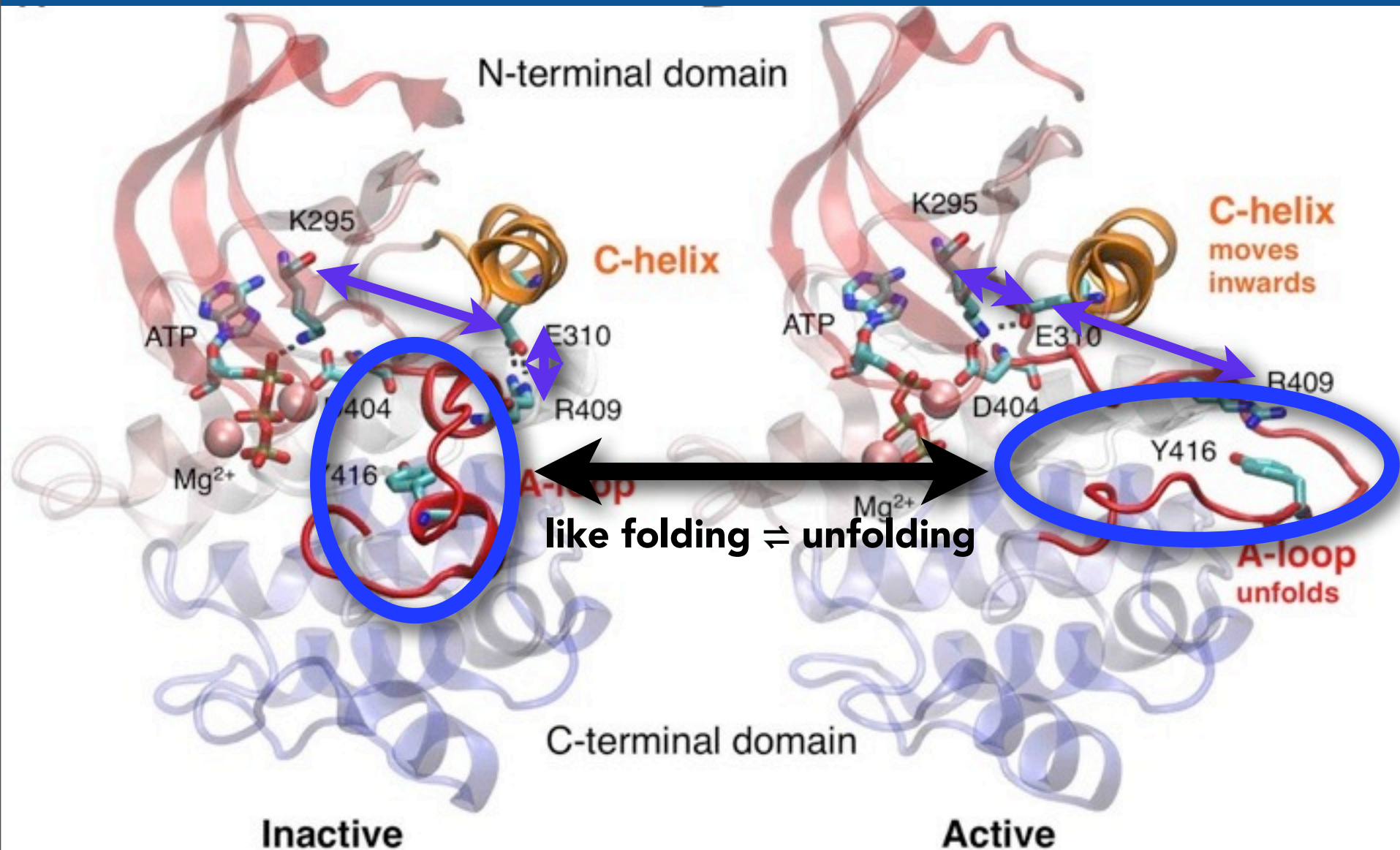
Conformational change in src kinase



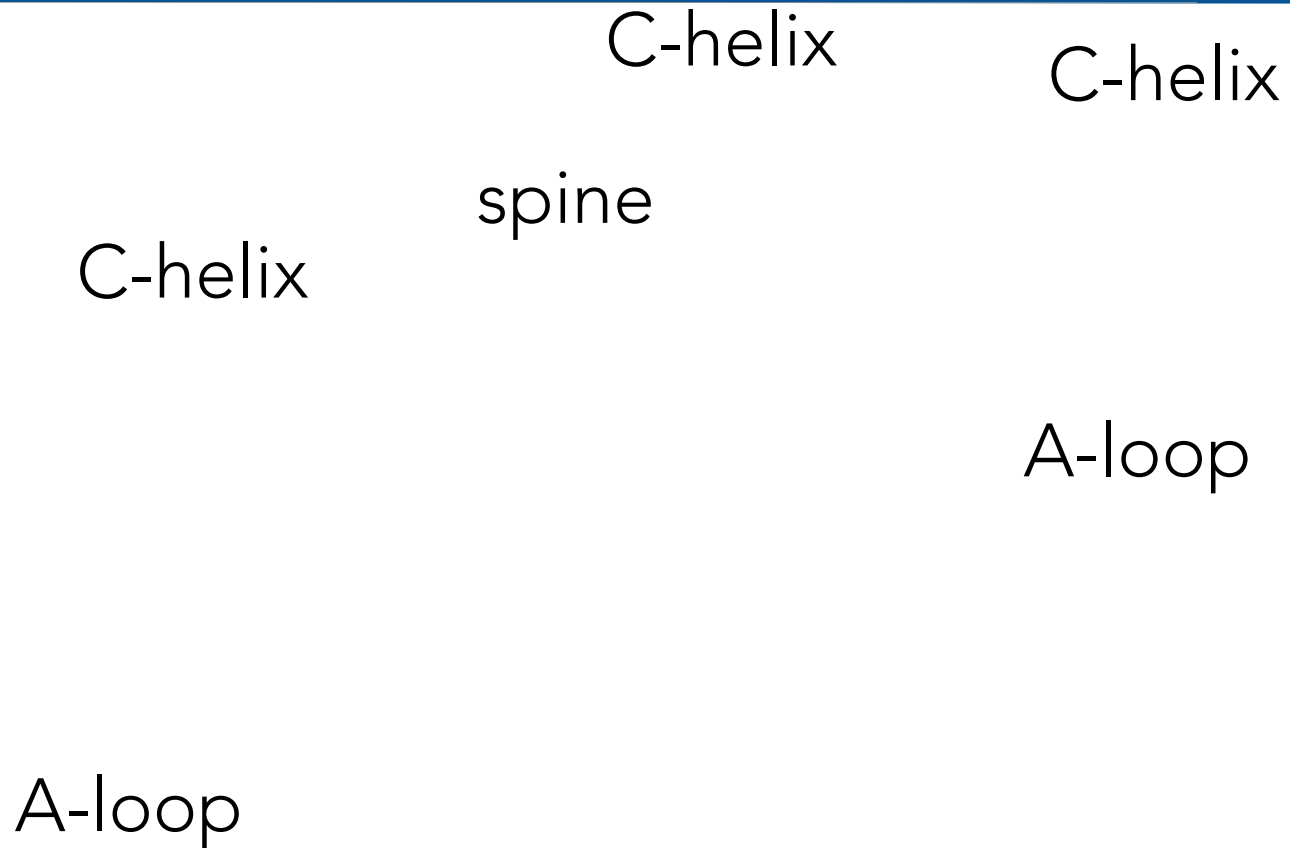
Conformational change in src kinase



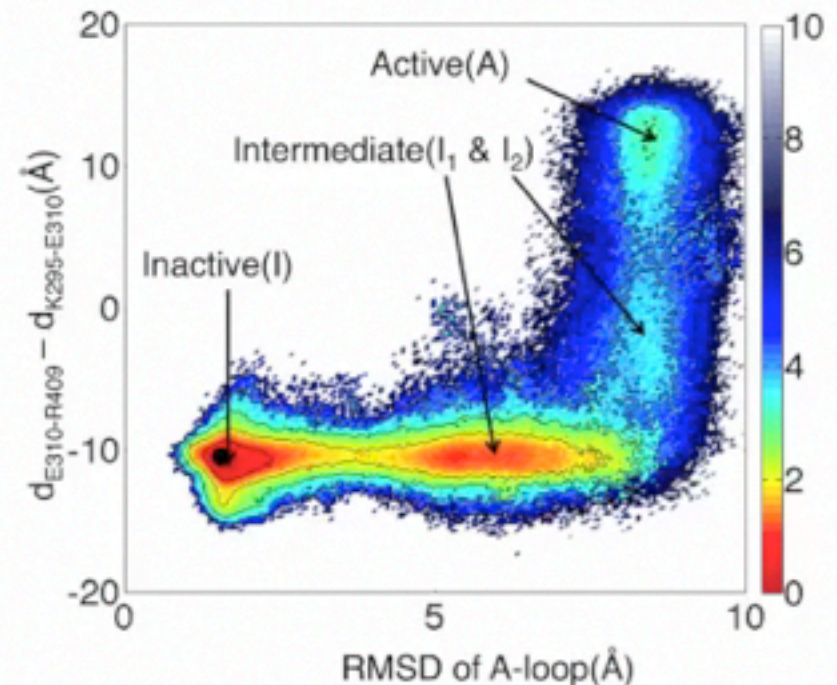
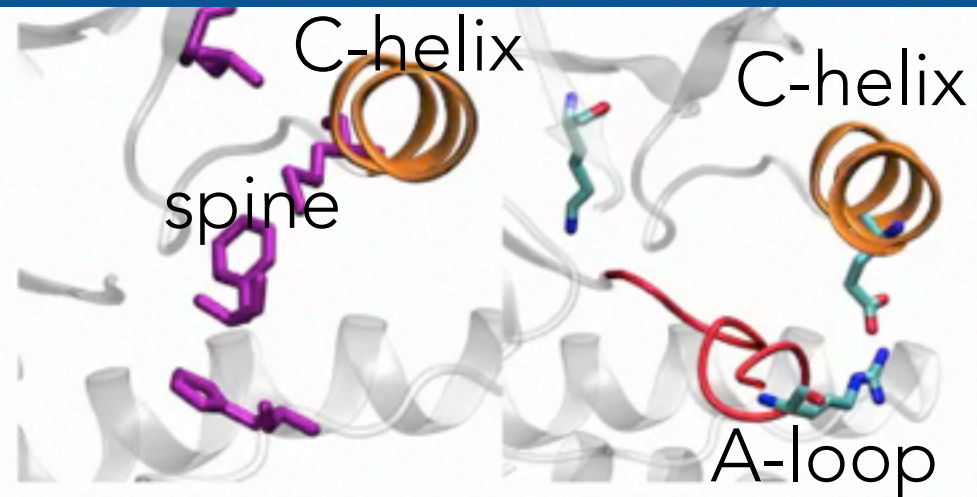
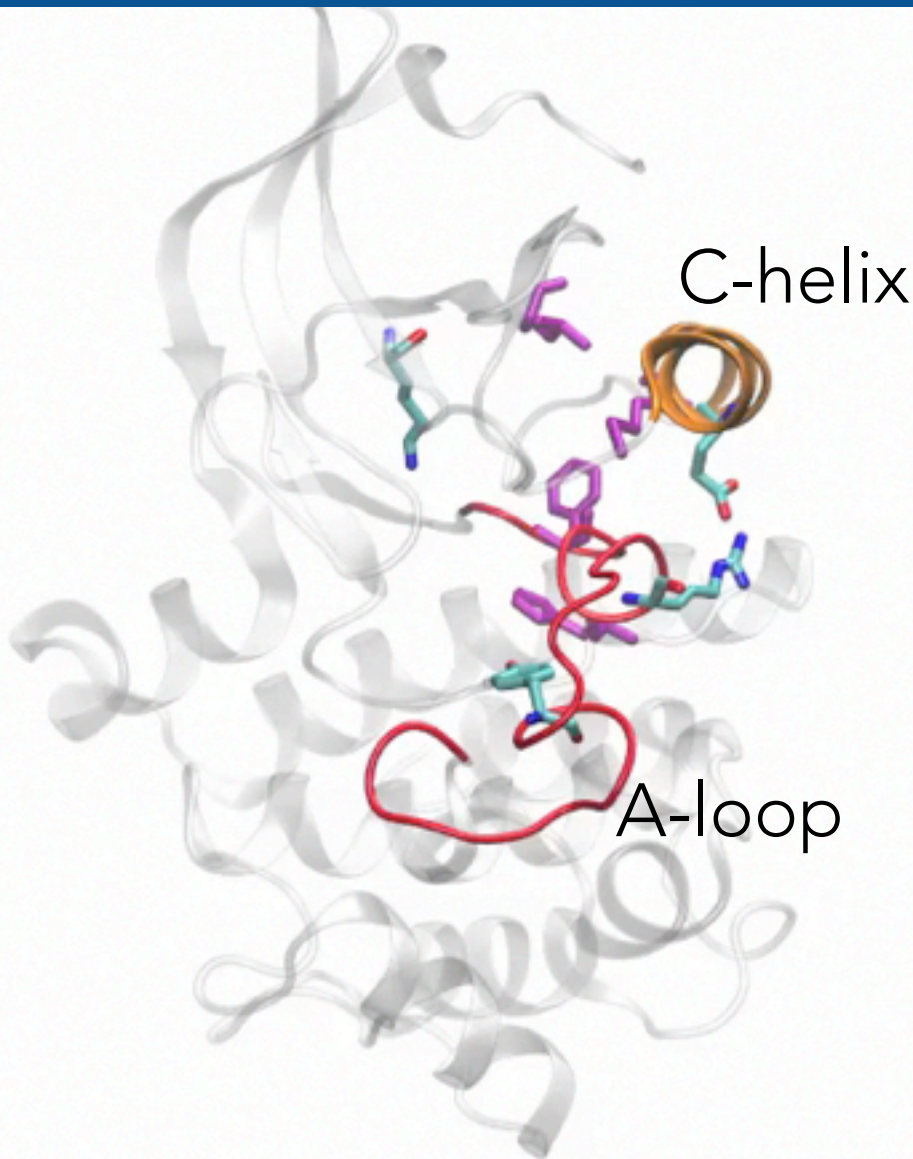
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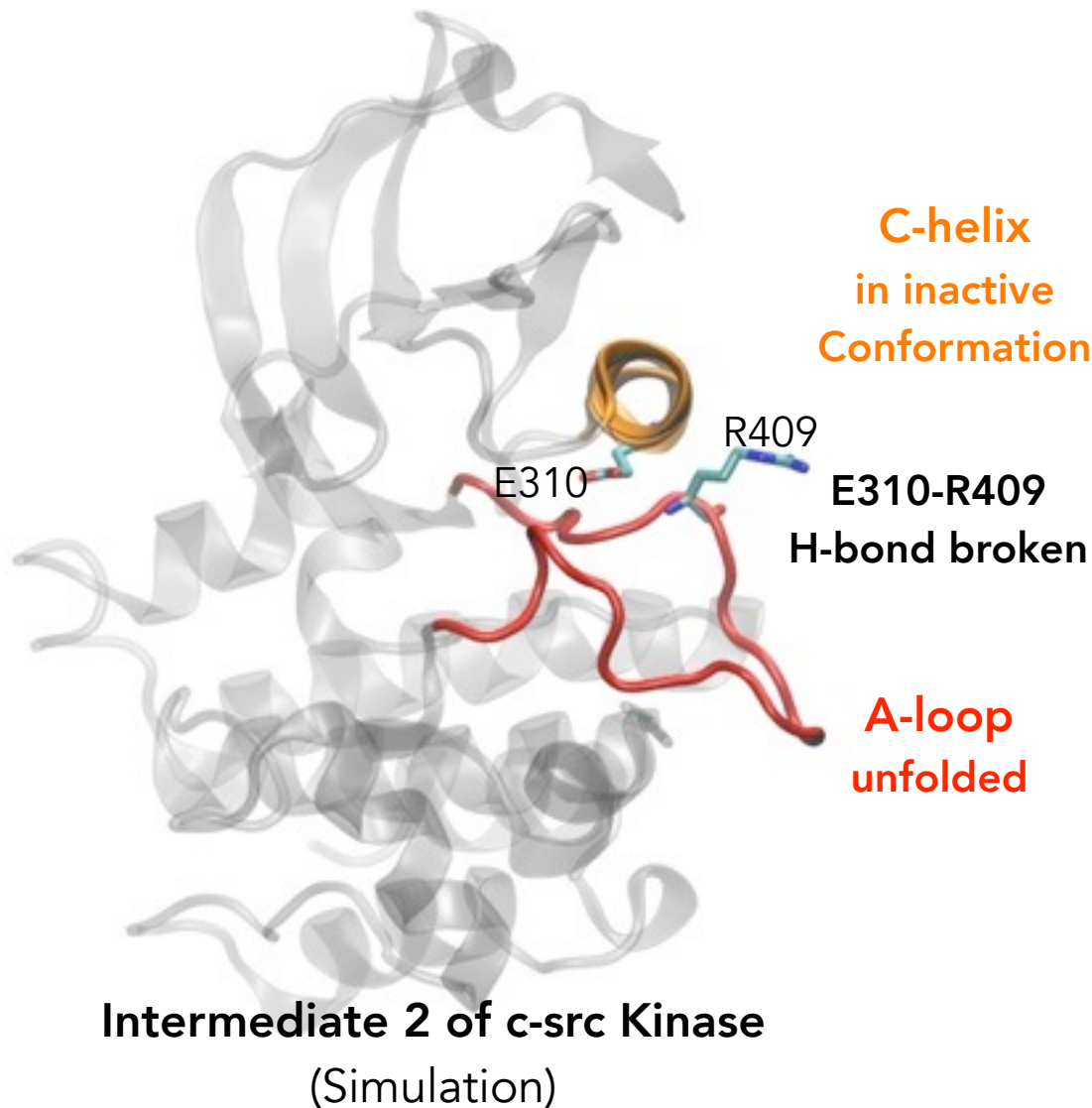
Mechanism of activation dynamics



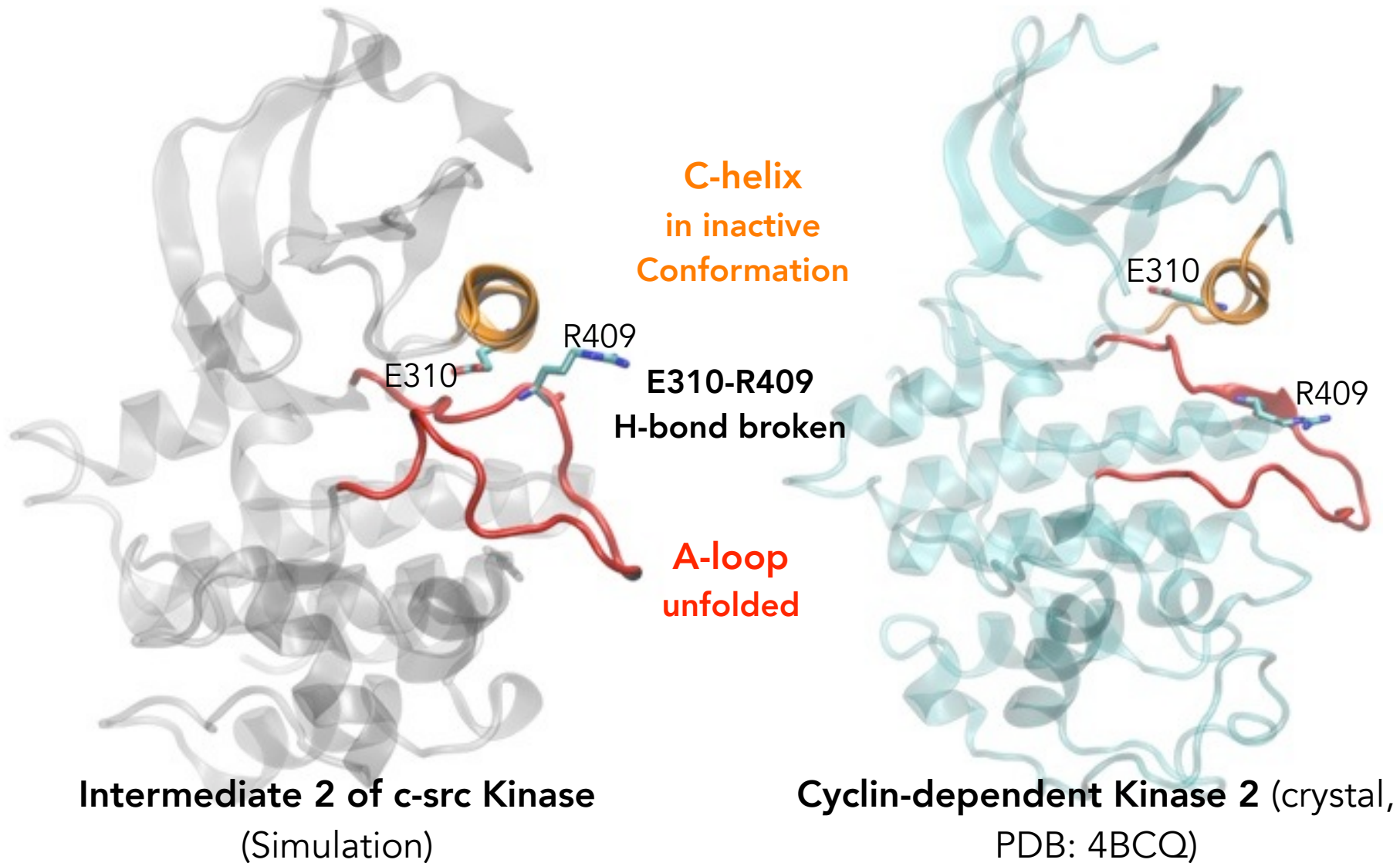
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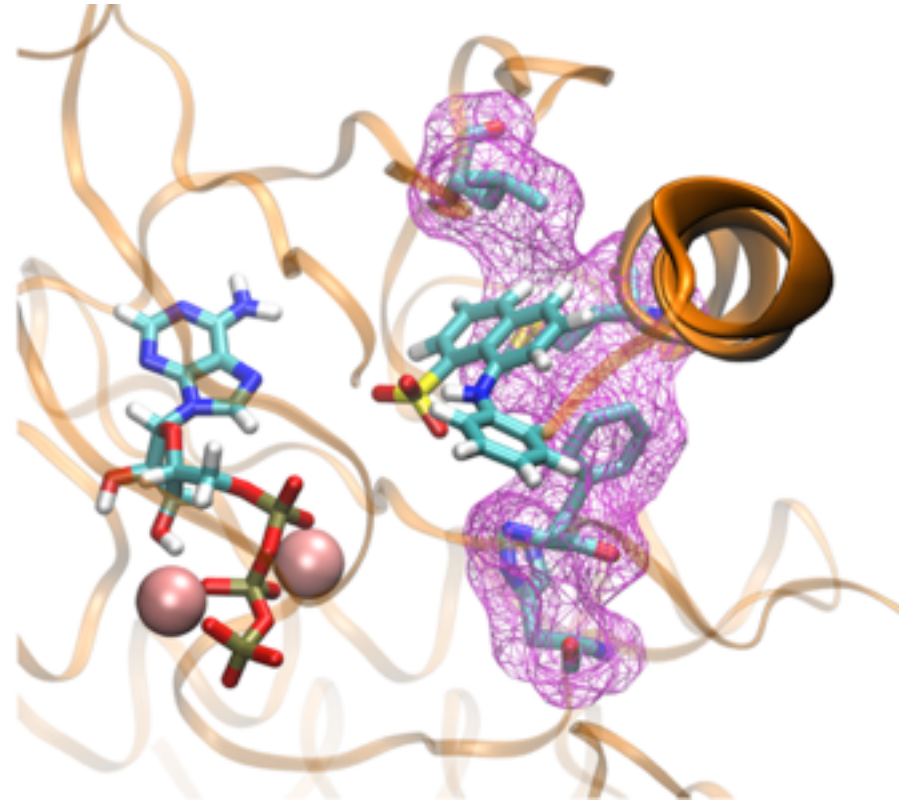
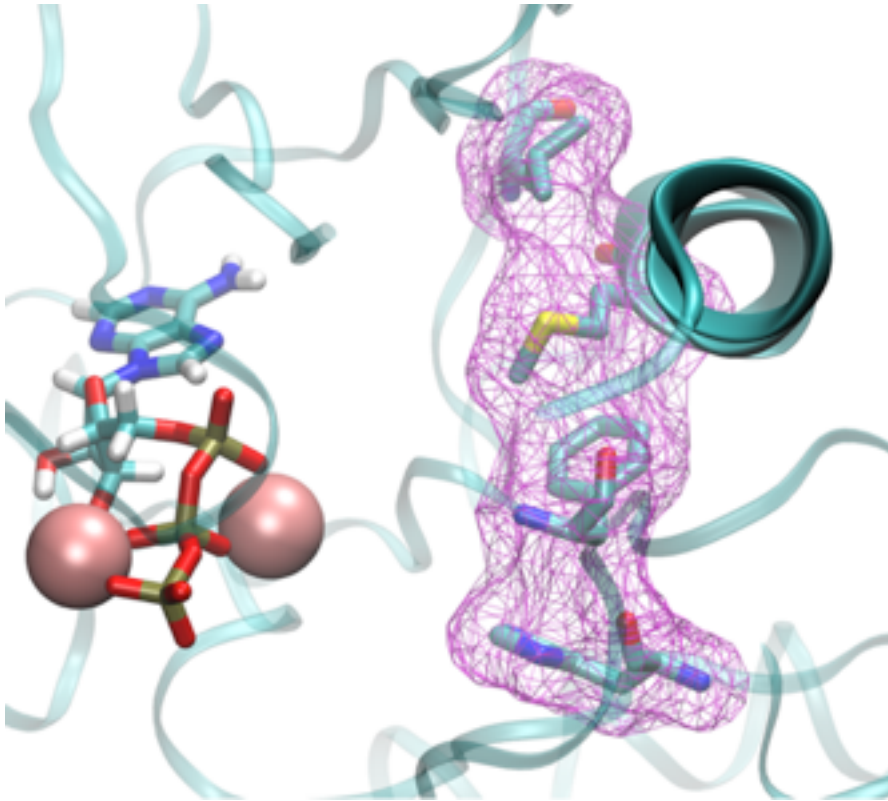
Characterizing intermediate 2



Characterizing intermediate 2



ANS binding disrupts the hydrophobic spine



Seeing correlated motion is useful

Seeing correlated motion is useful



Can you tell what this is?

Seeing correlated motion is useful

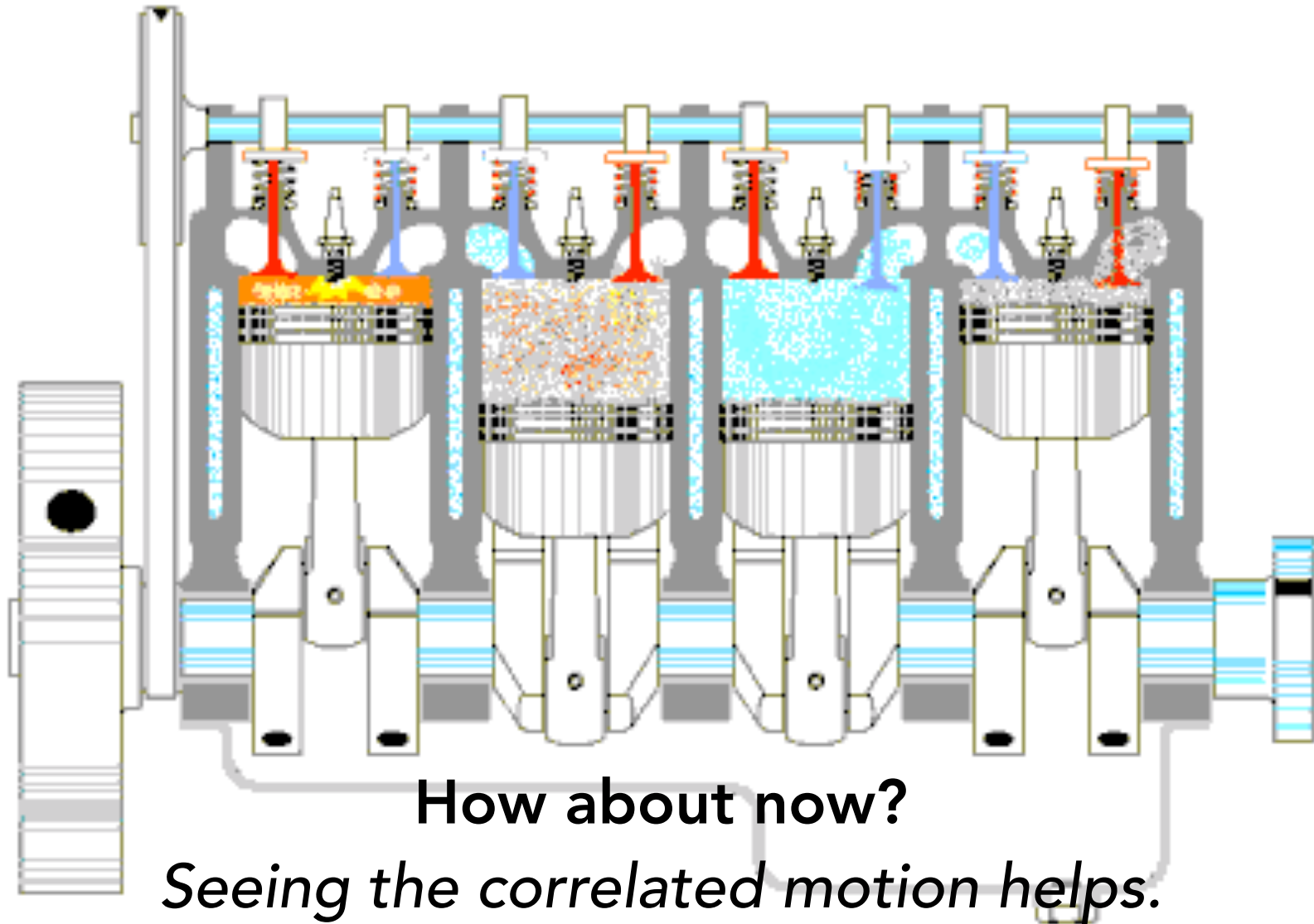


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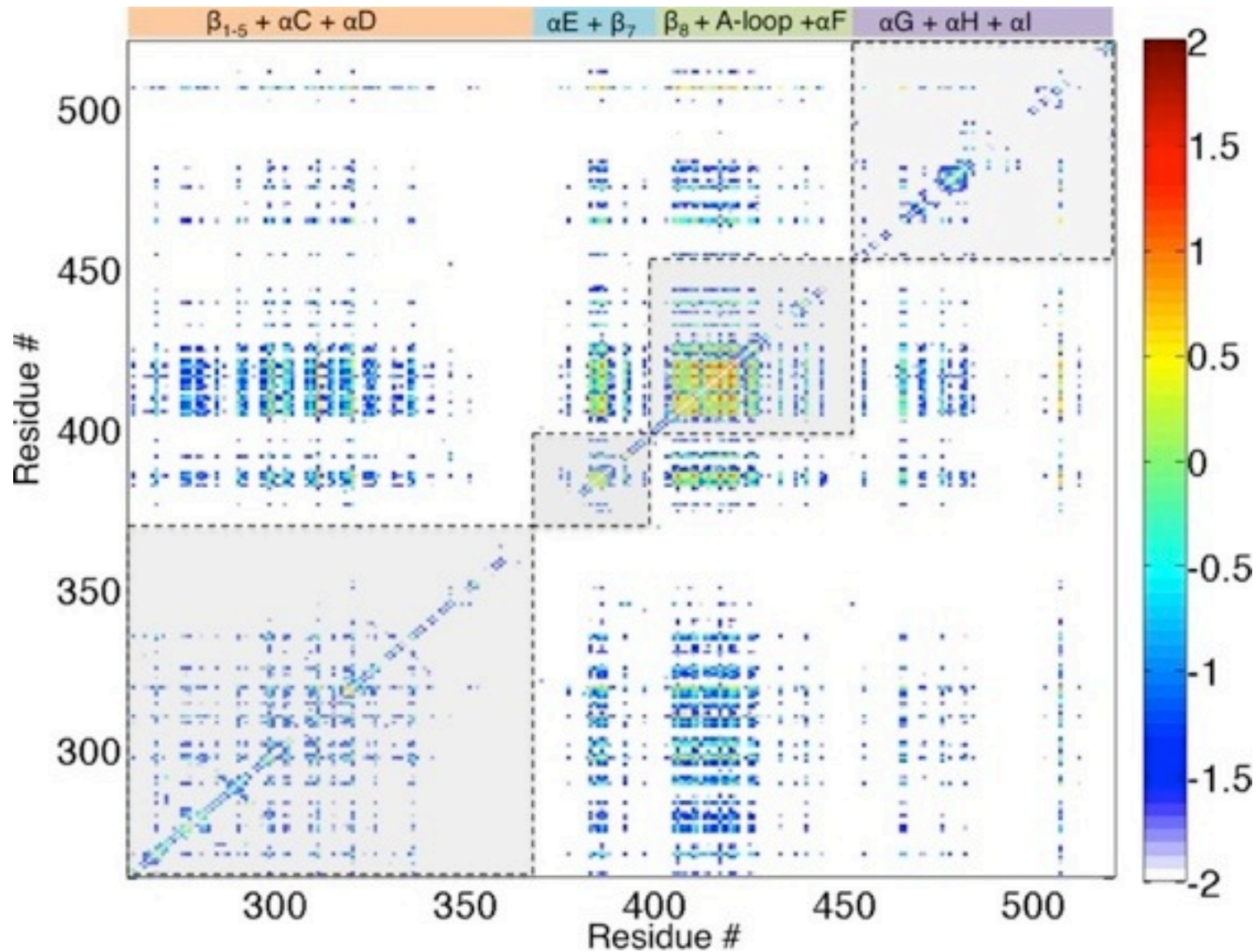
How about now?

Seeing the correlated motion helps.

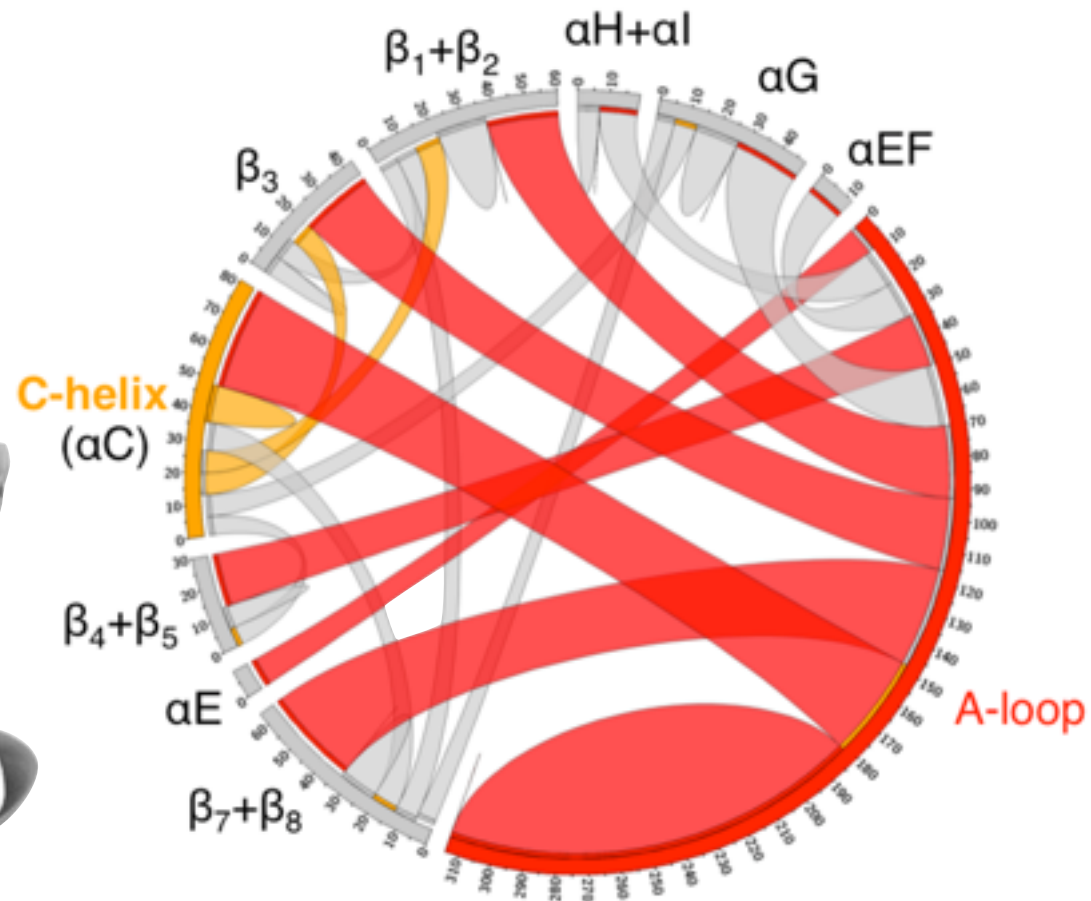
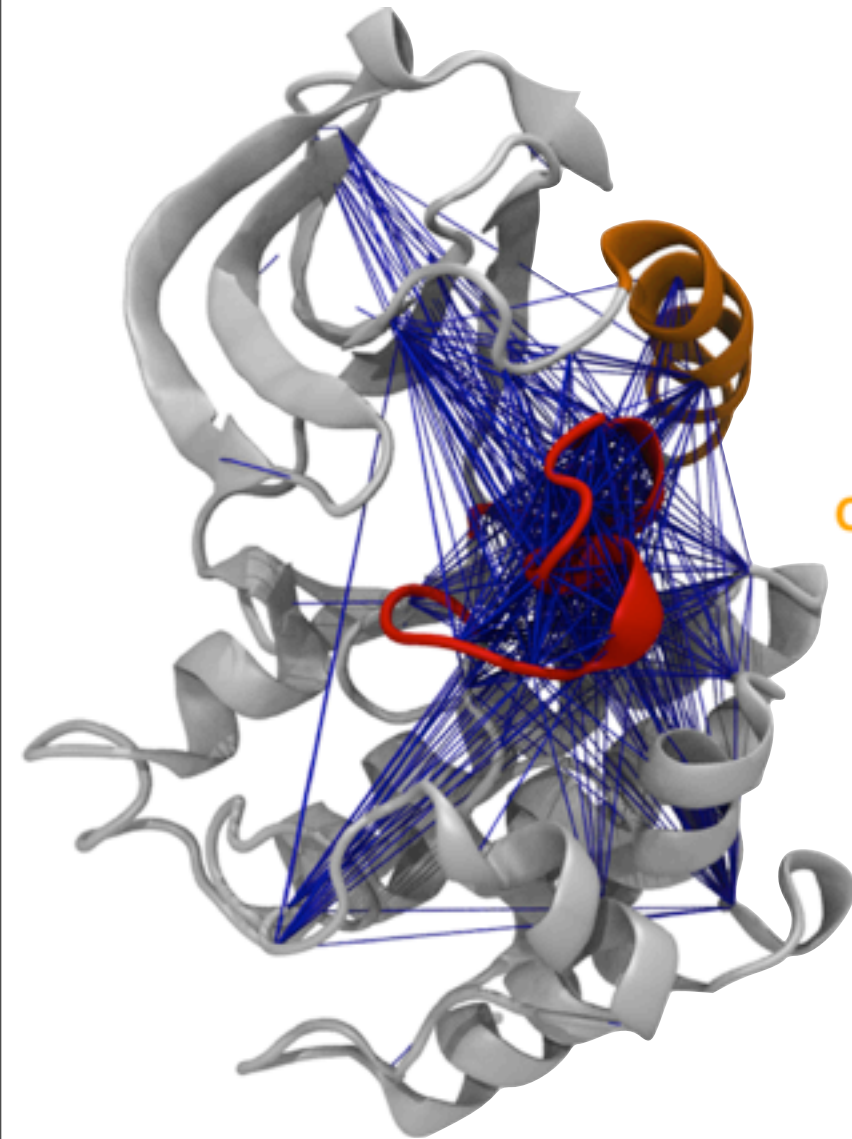
Seeing correlated motion is useful



Mutual information finds coupled dynamics



Mutual information: non-local correlation



Do crystal structures tell the whole story in ligand binding?

MSMs improve protein-ligand predictions in GPCRs

Kohlhoff, et al, *Nature Chemistry* (2014)

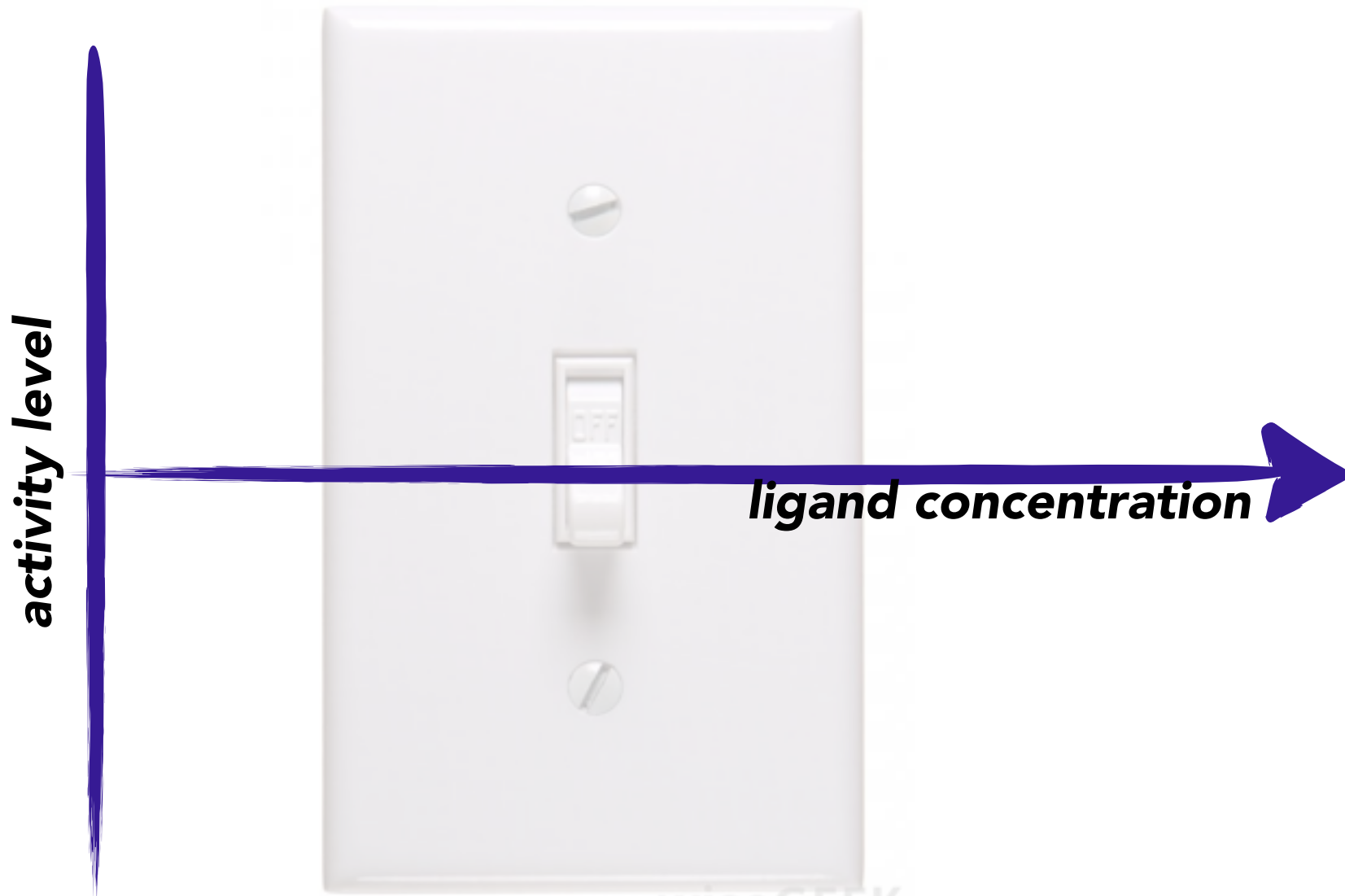
Collaboration with Google Exacycle

Are GPCRs just simple switches?



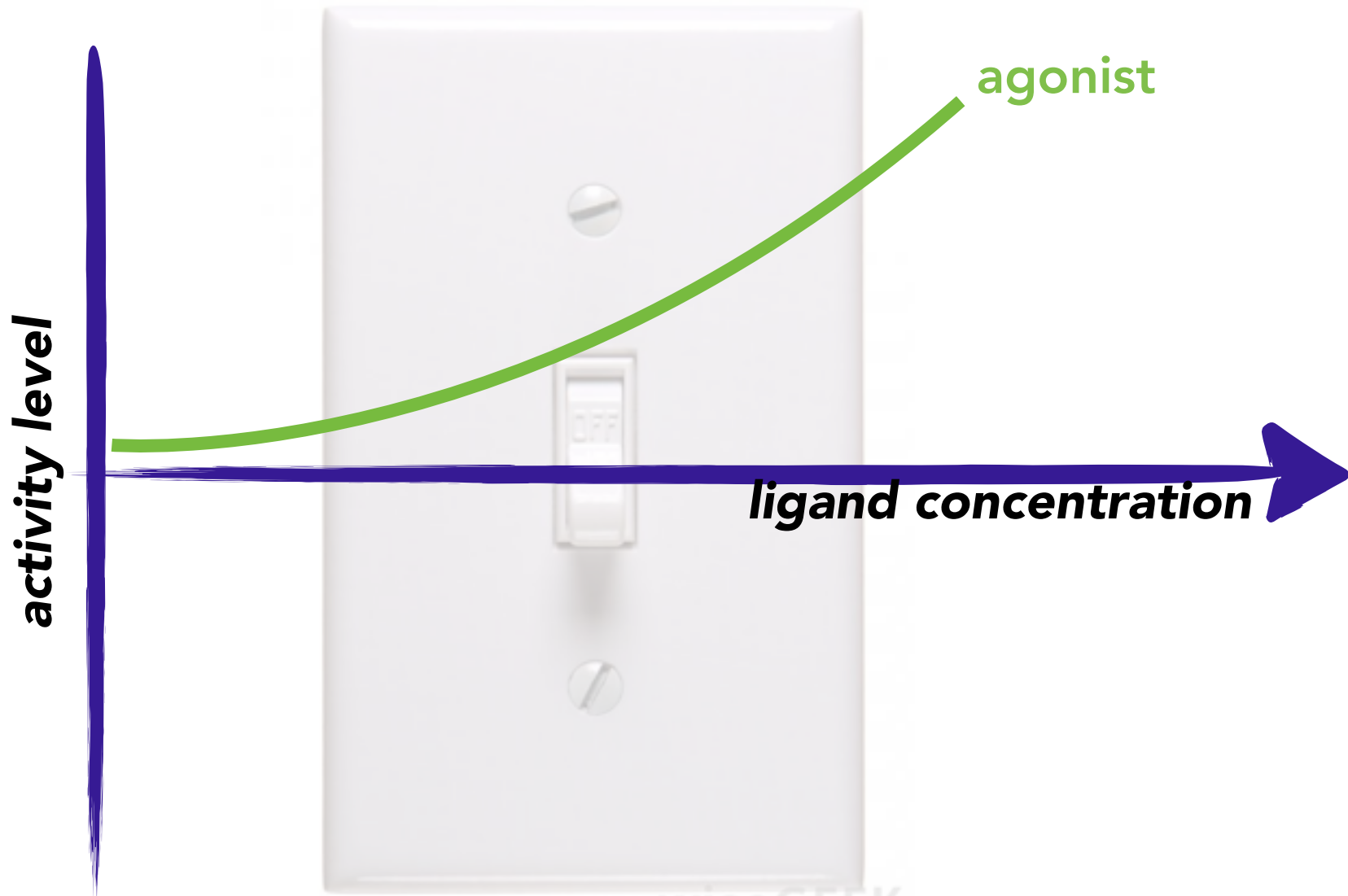
wiseGEEK

Are GPCRs just simple switches?



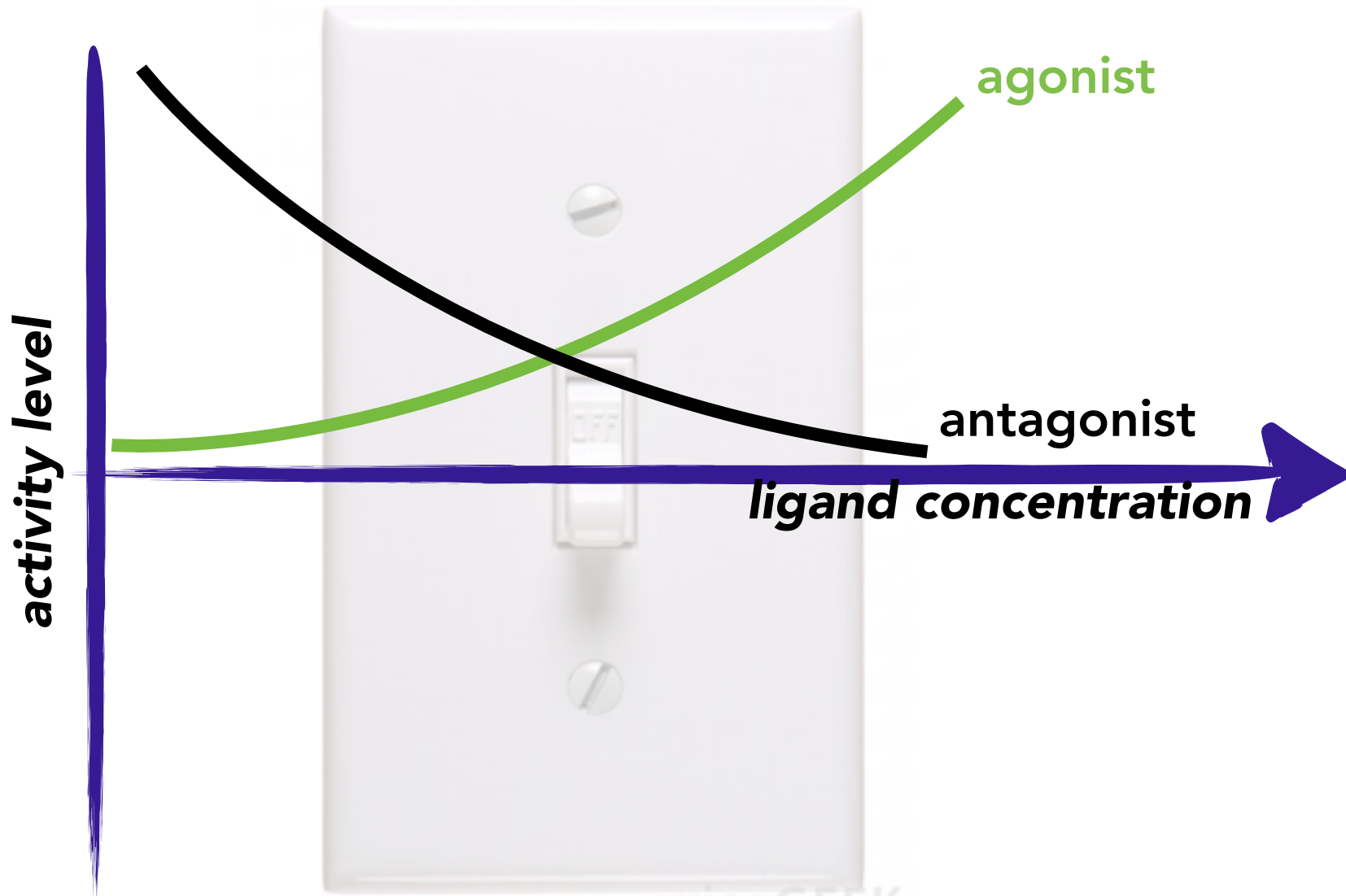
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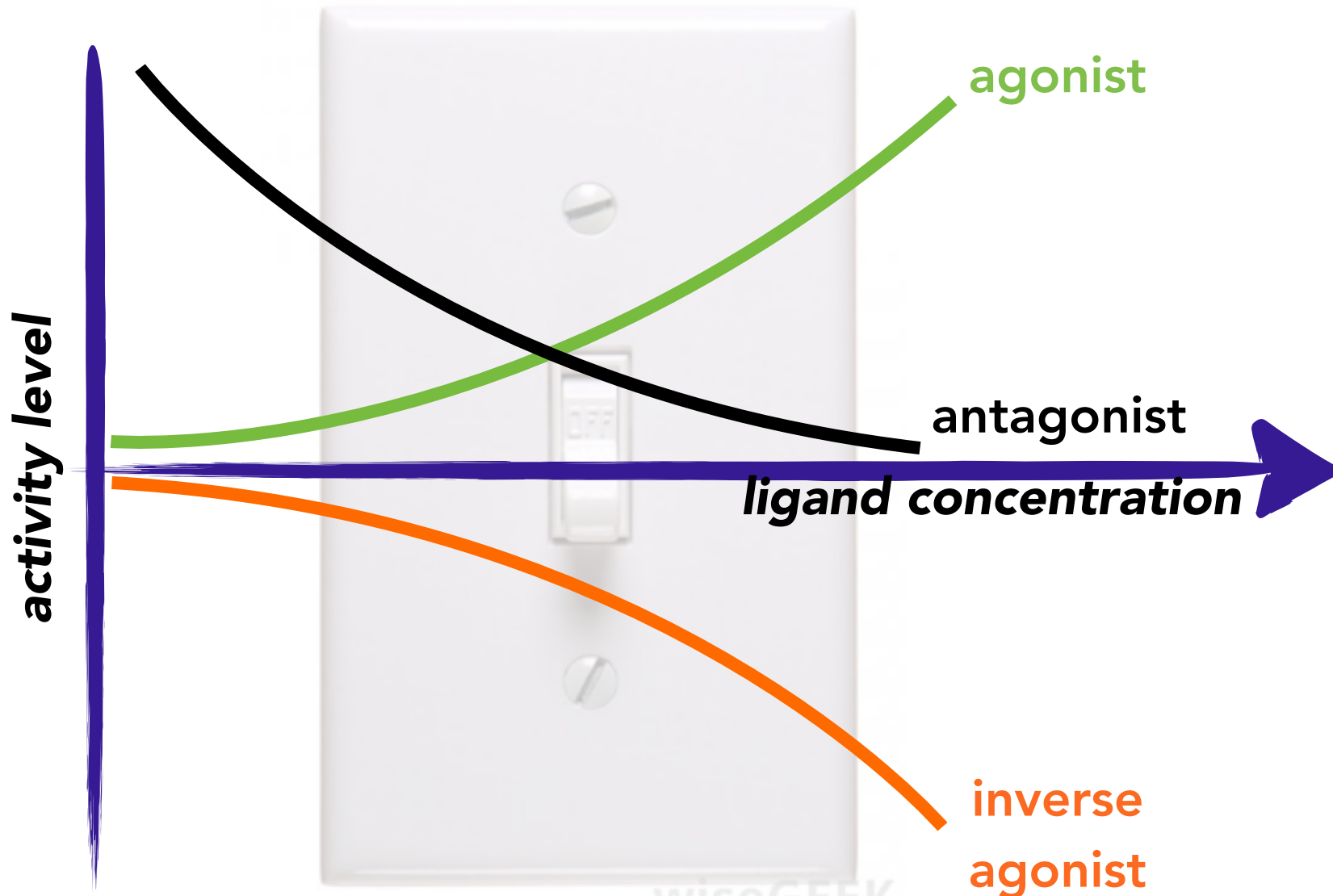
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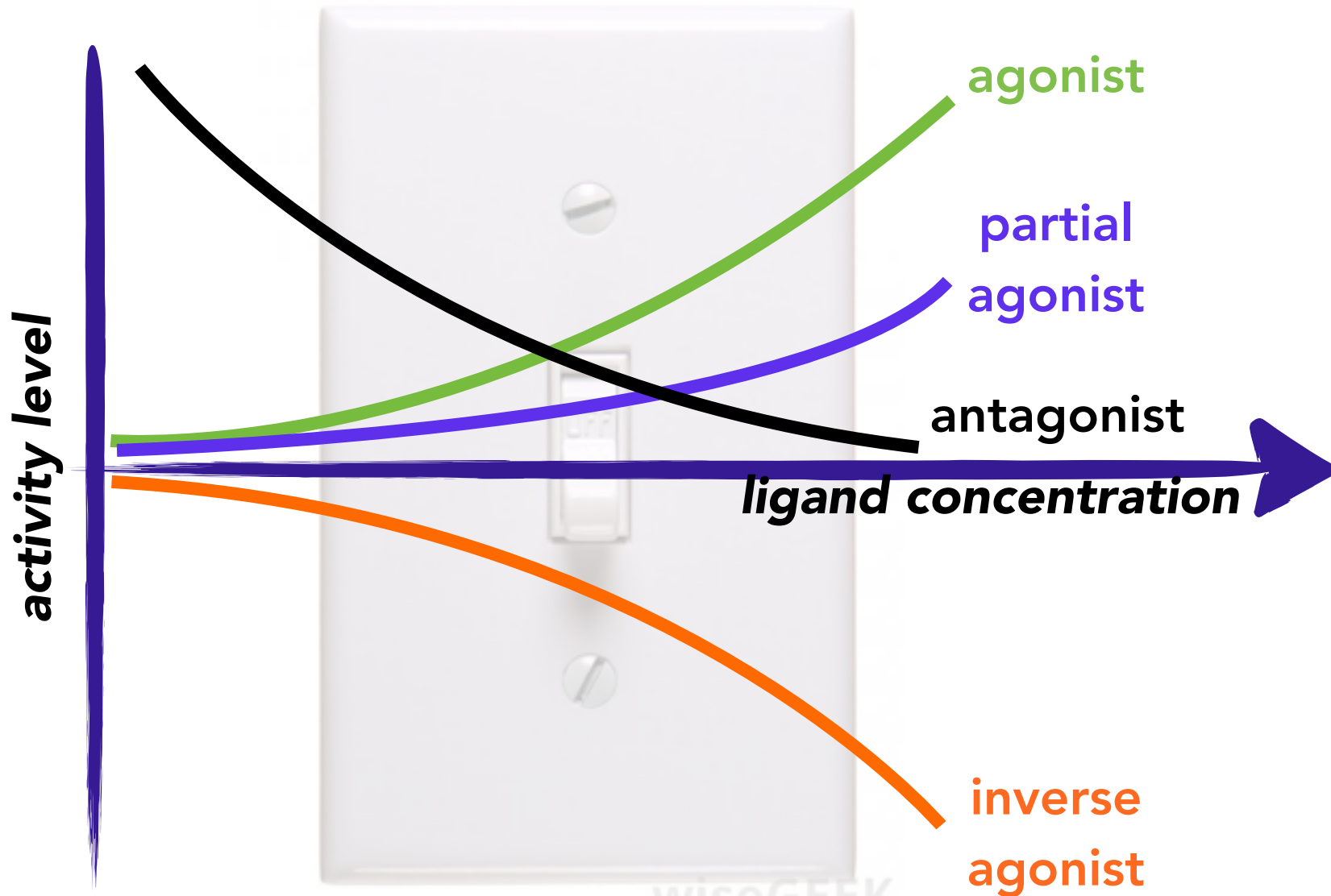
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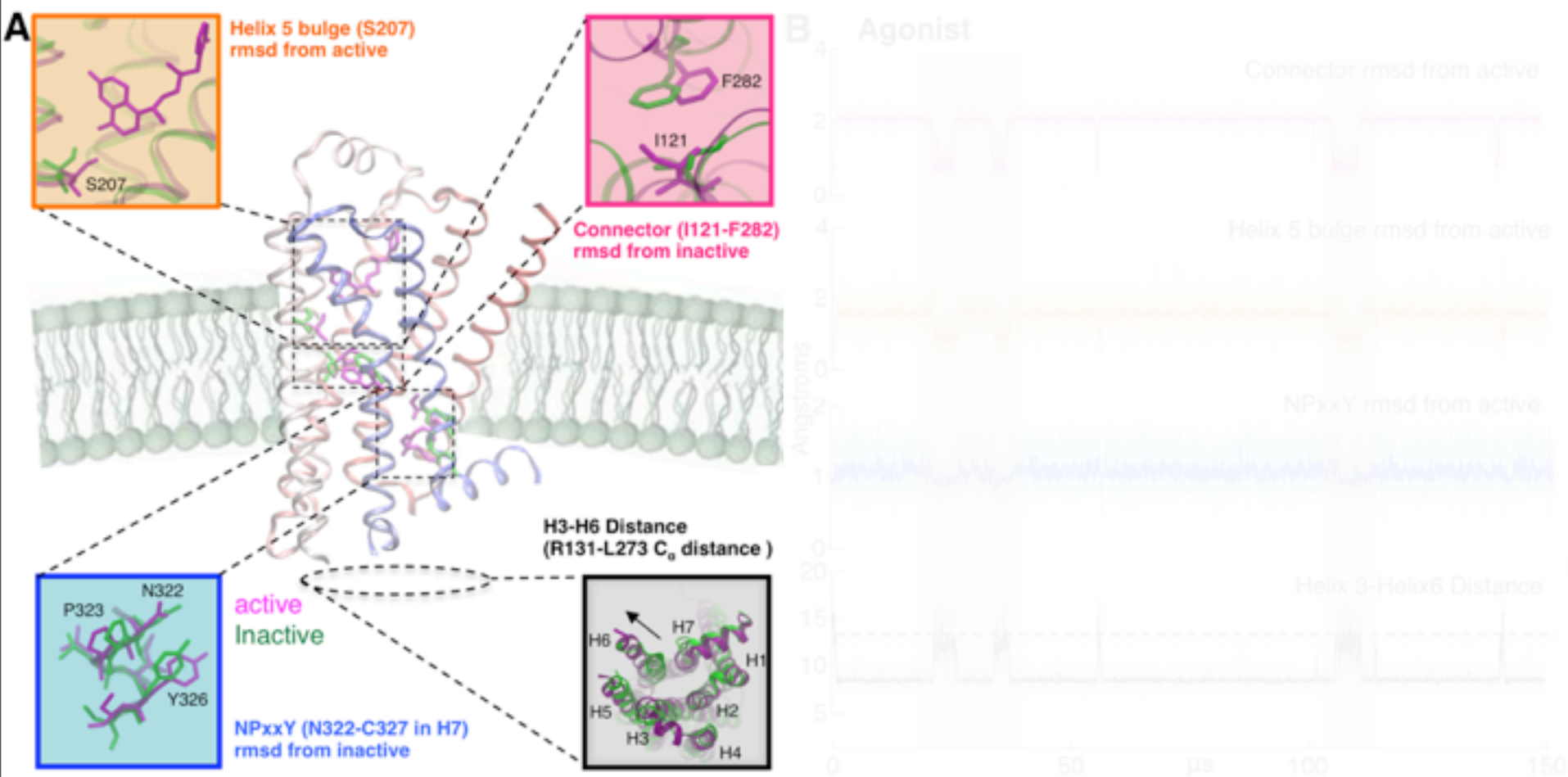
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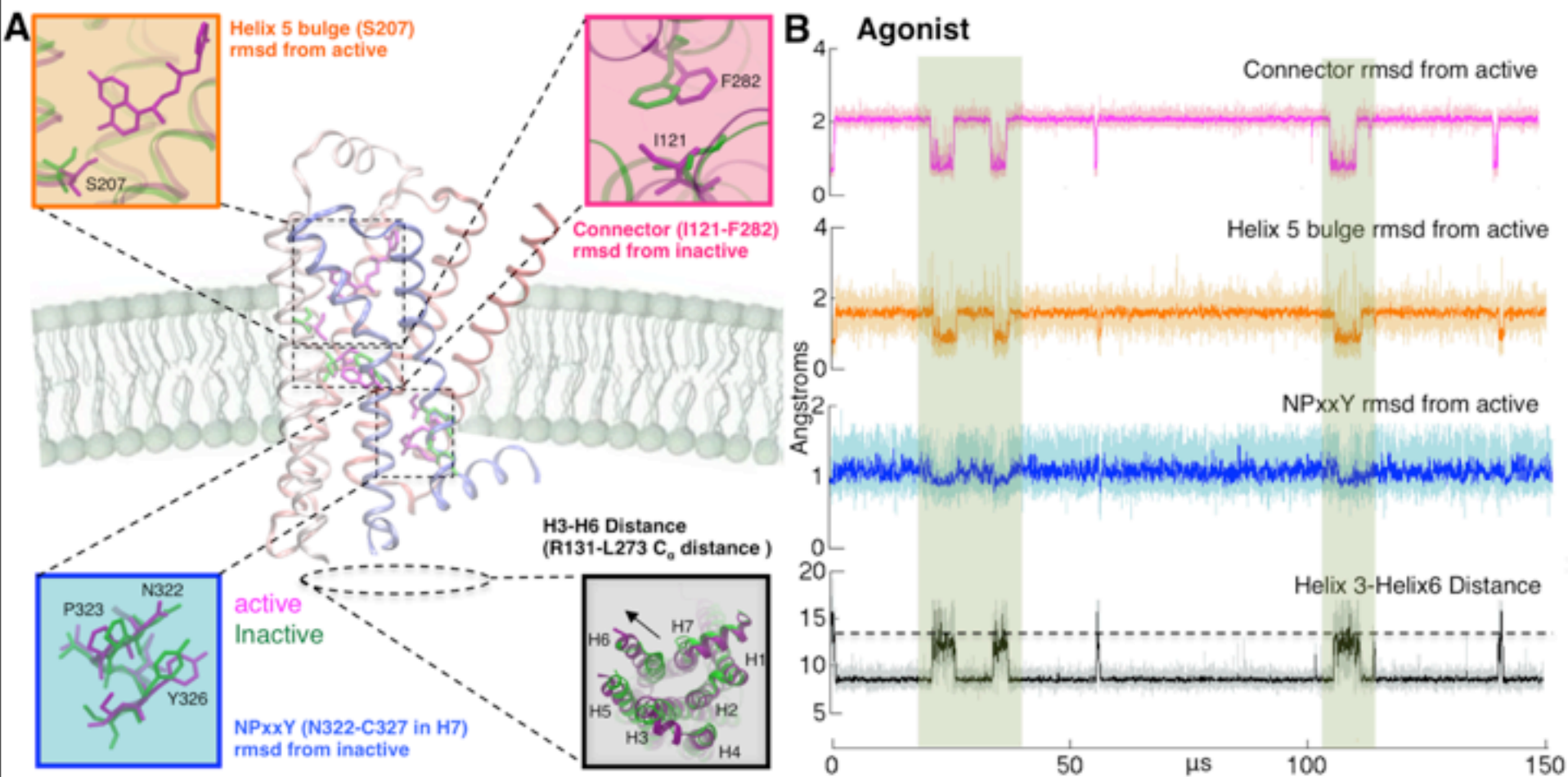


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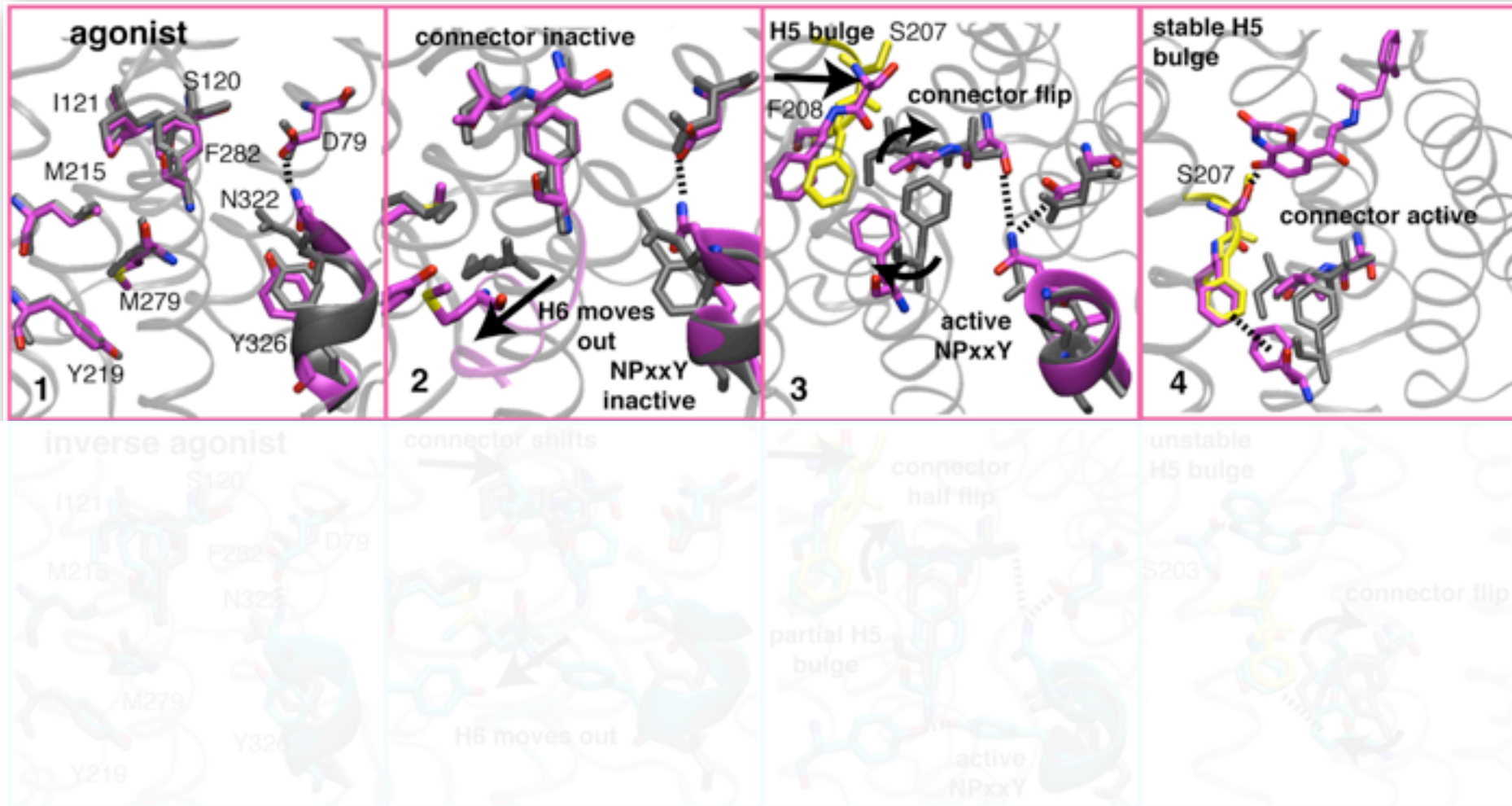
Simulating B2AR GPCR function



Simulating B2AR GPCR function

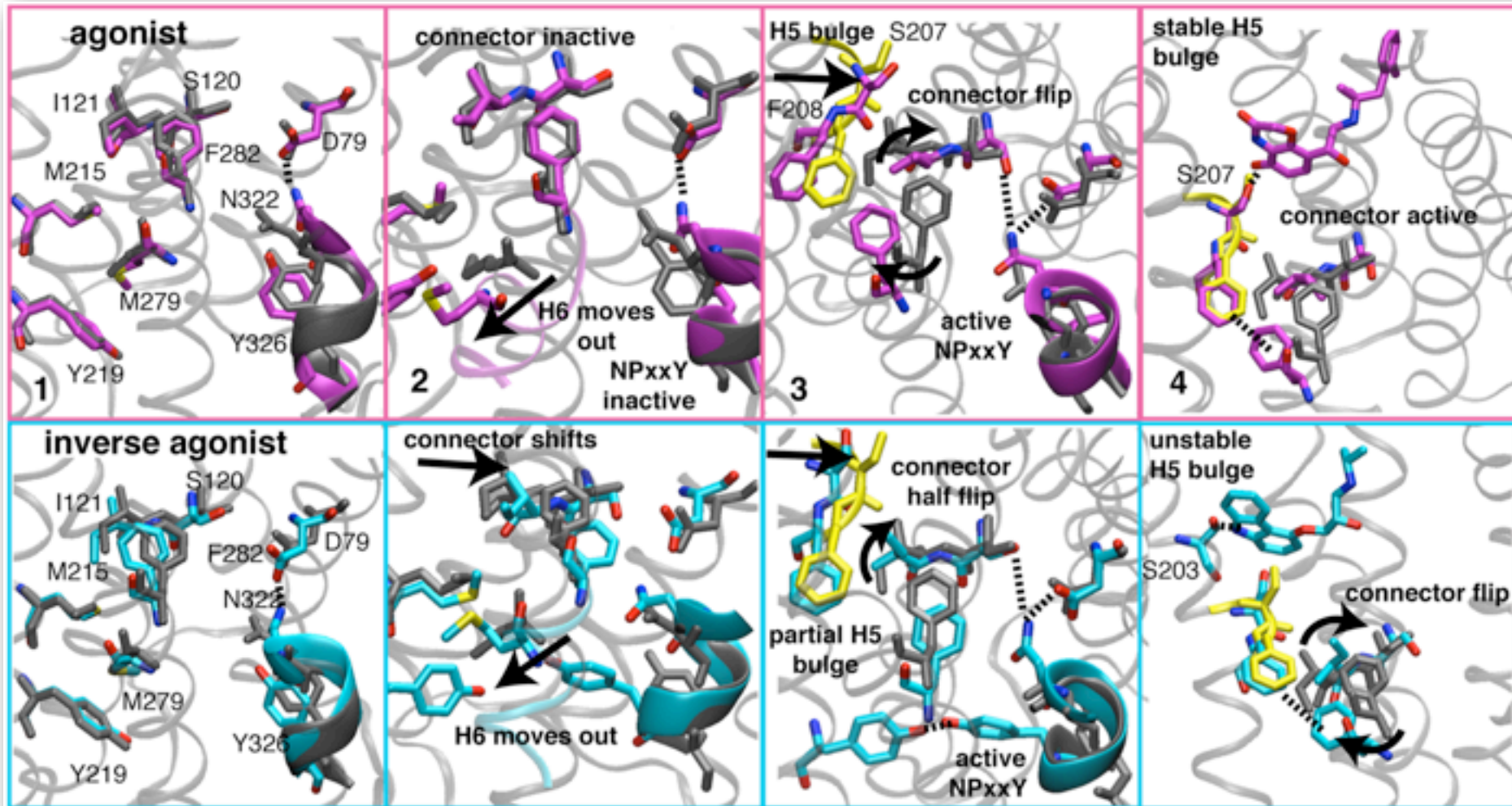


Key steps in activation



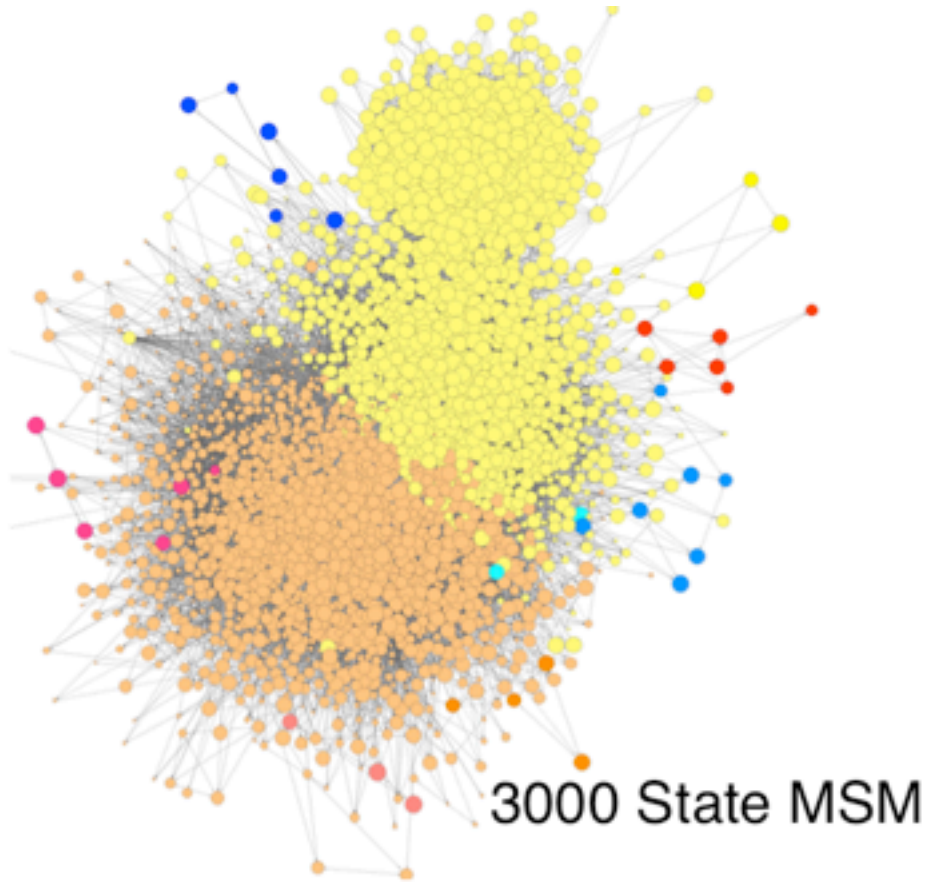
Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

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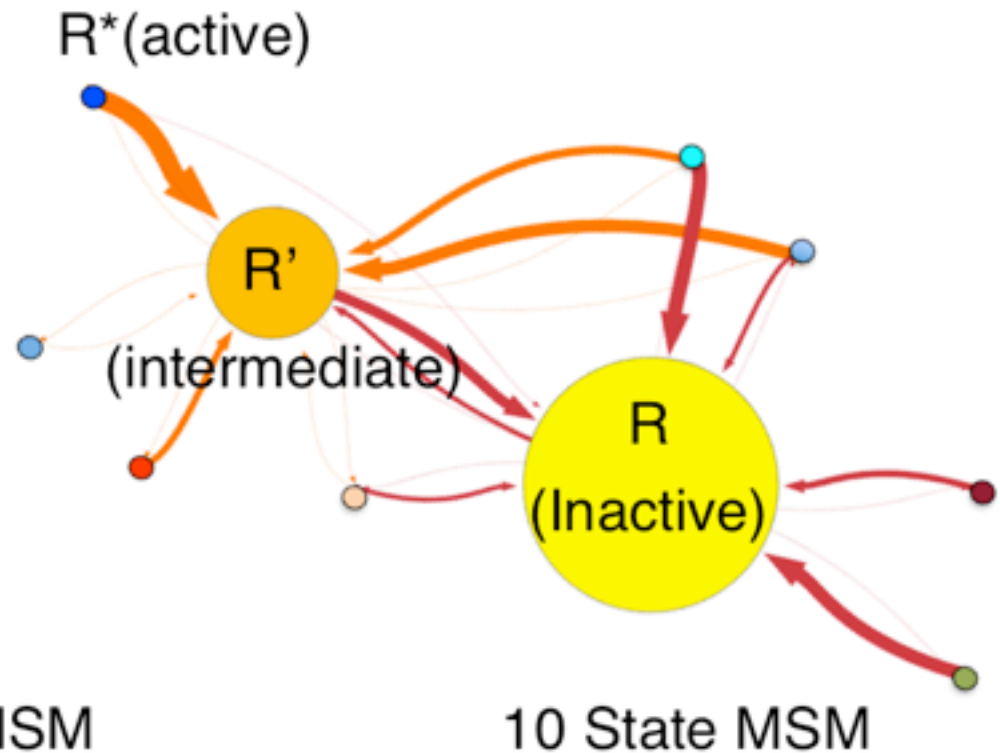
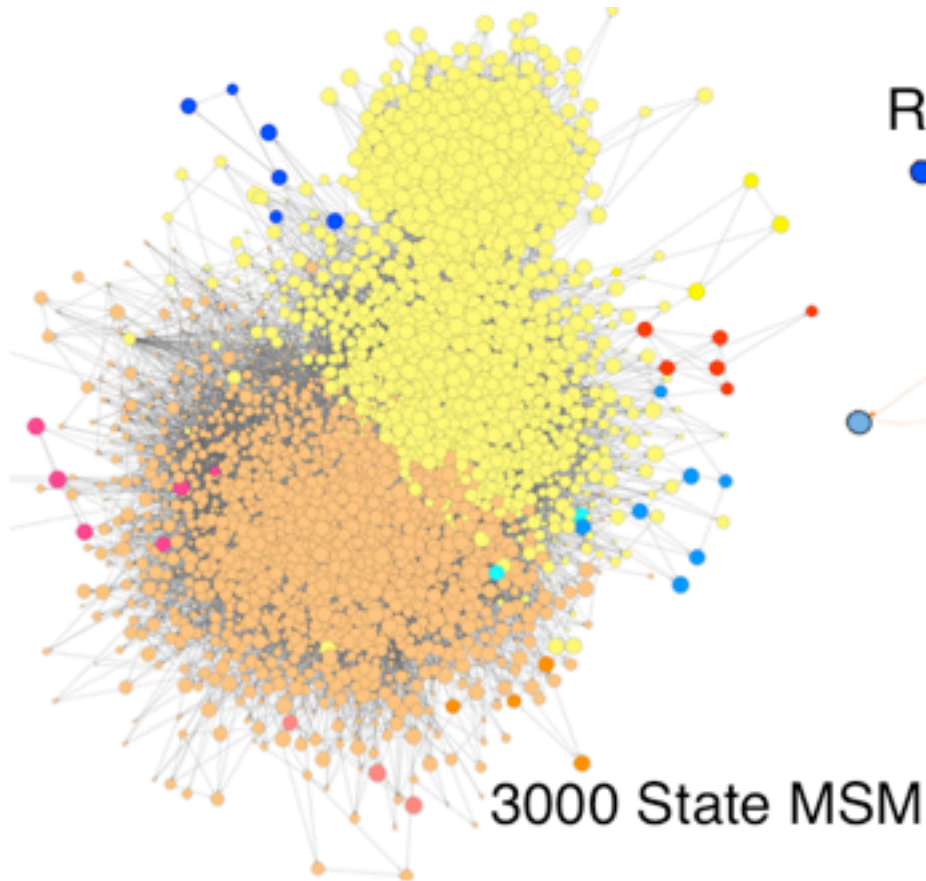
Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

MSM finds intermediate state



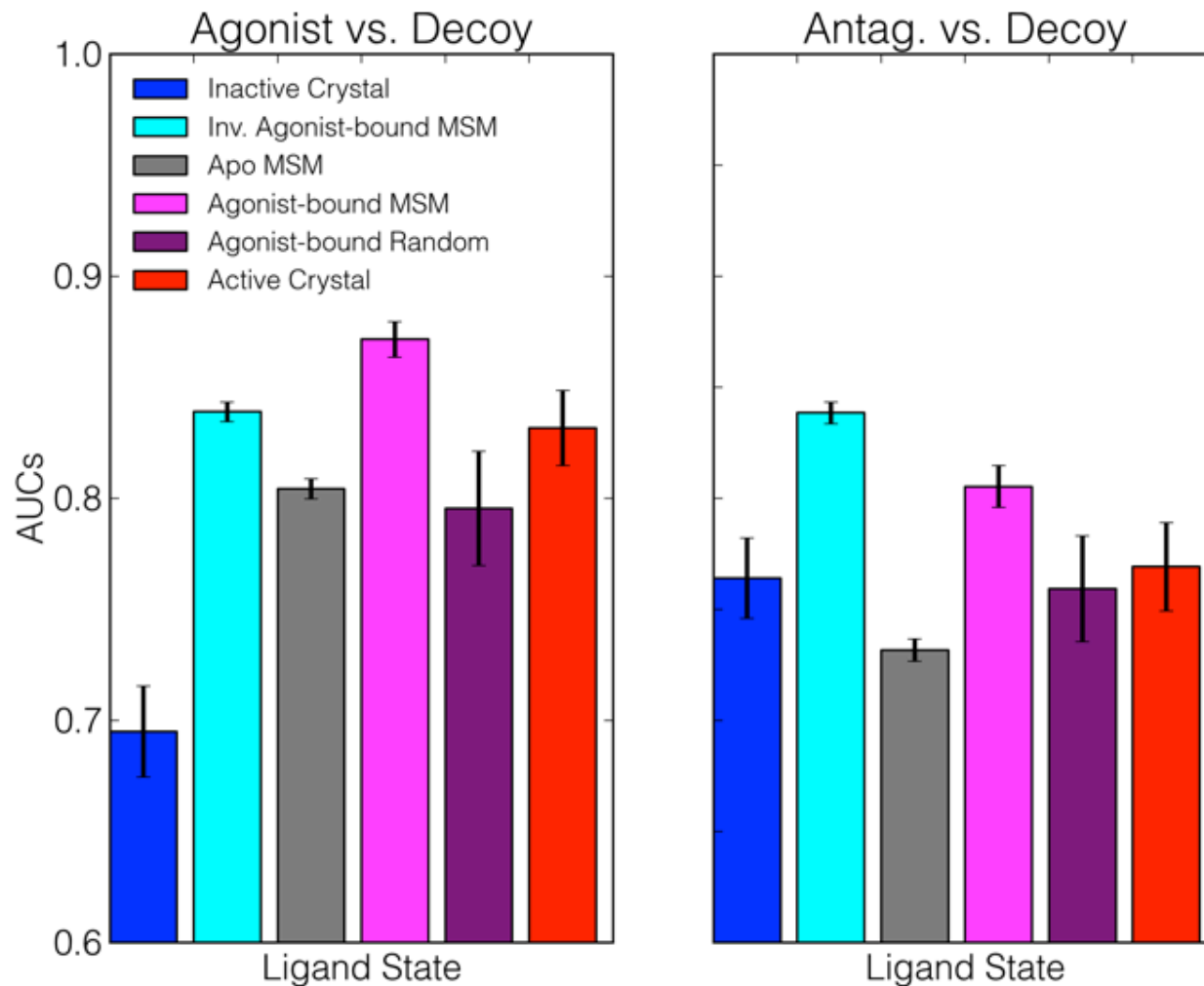
Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

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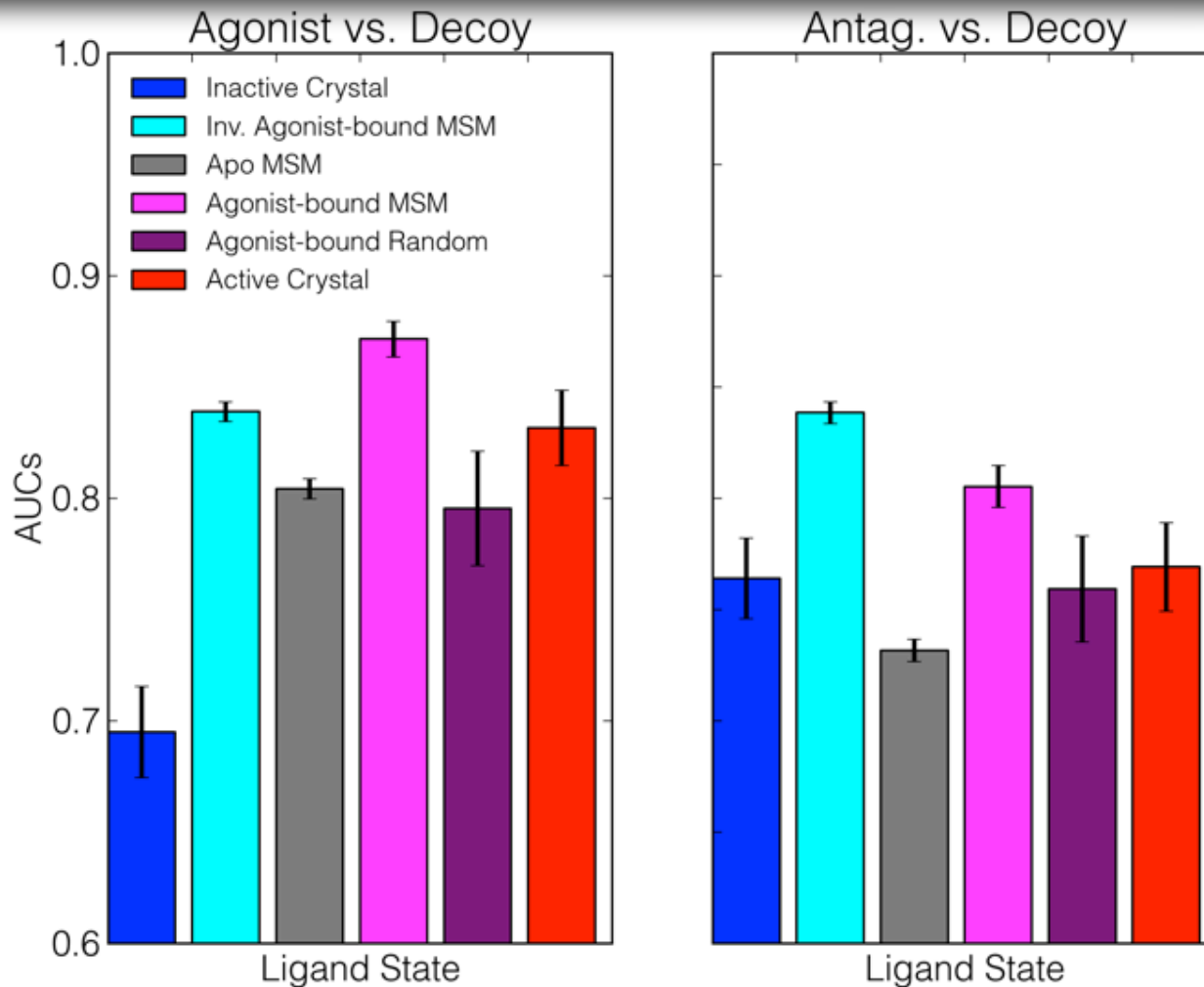
Protein flexibility important in binding



Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

Protein flexibility important in binding

MSM states improves Docking accuracy (AUC)

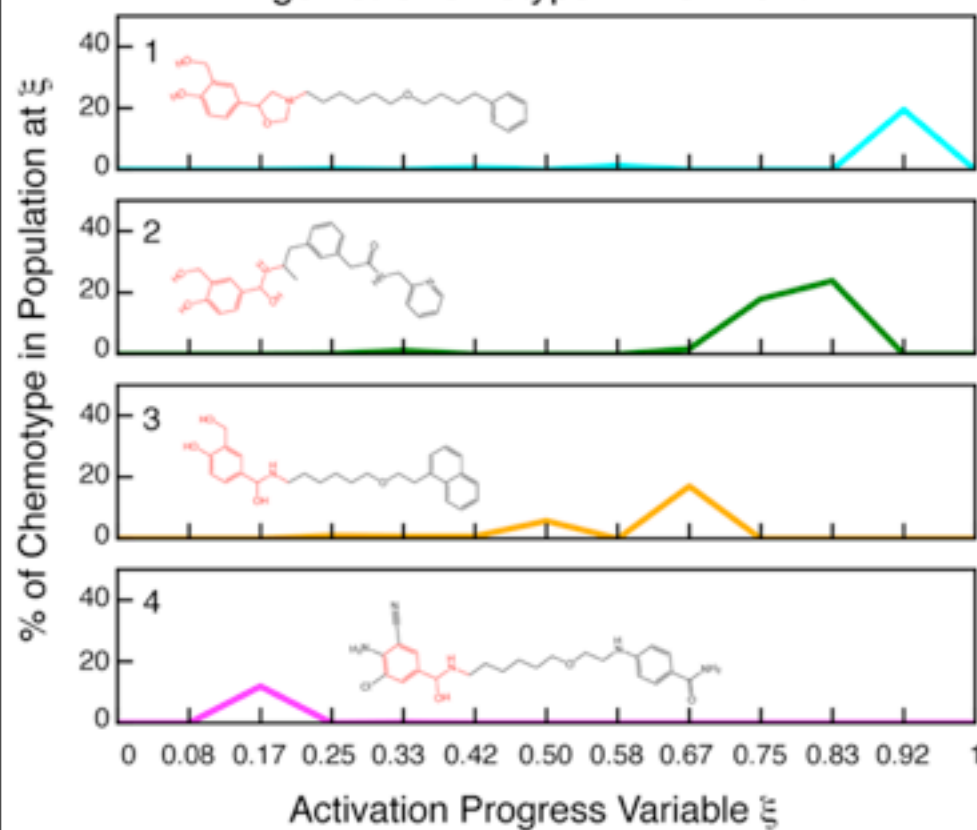


Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

Intermediates are functionally relevant

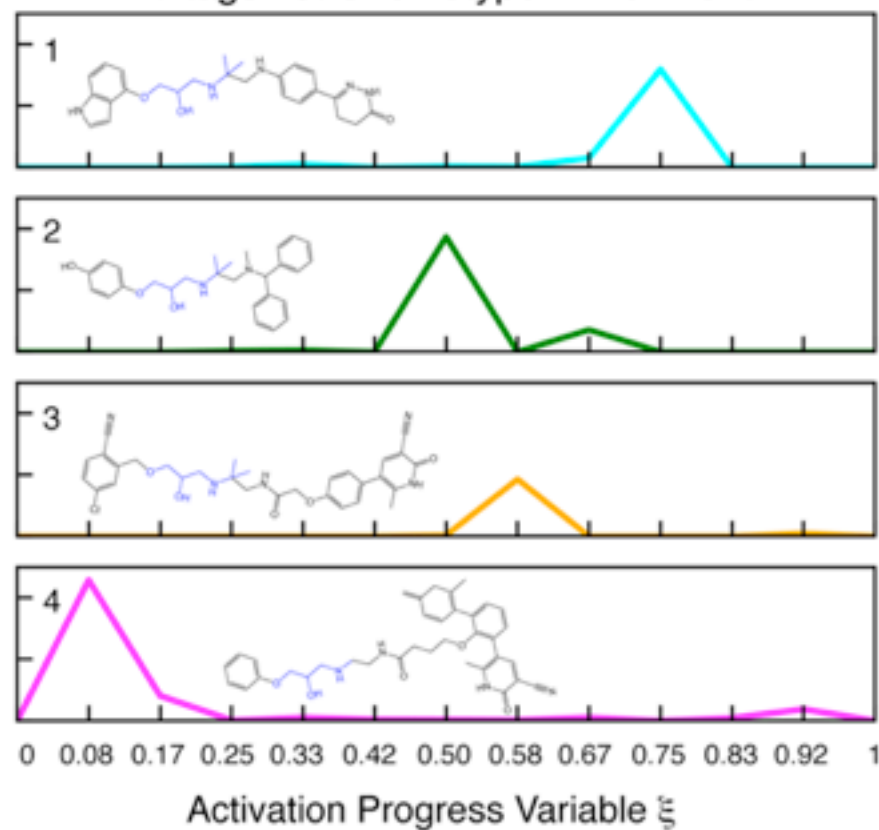
A

Agonist Chemotype Enrichment



B

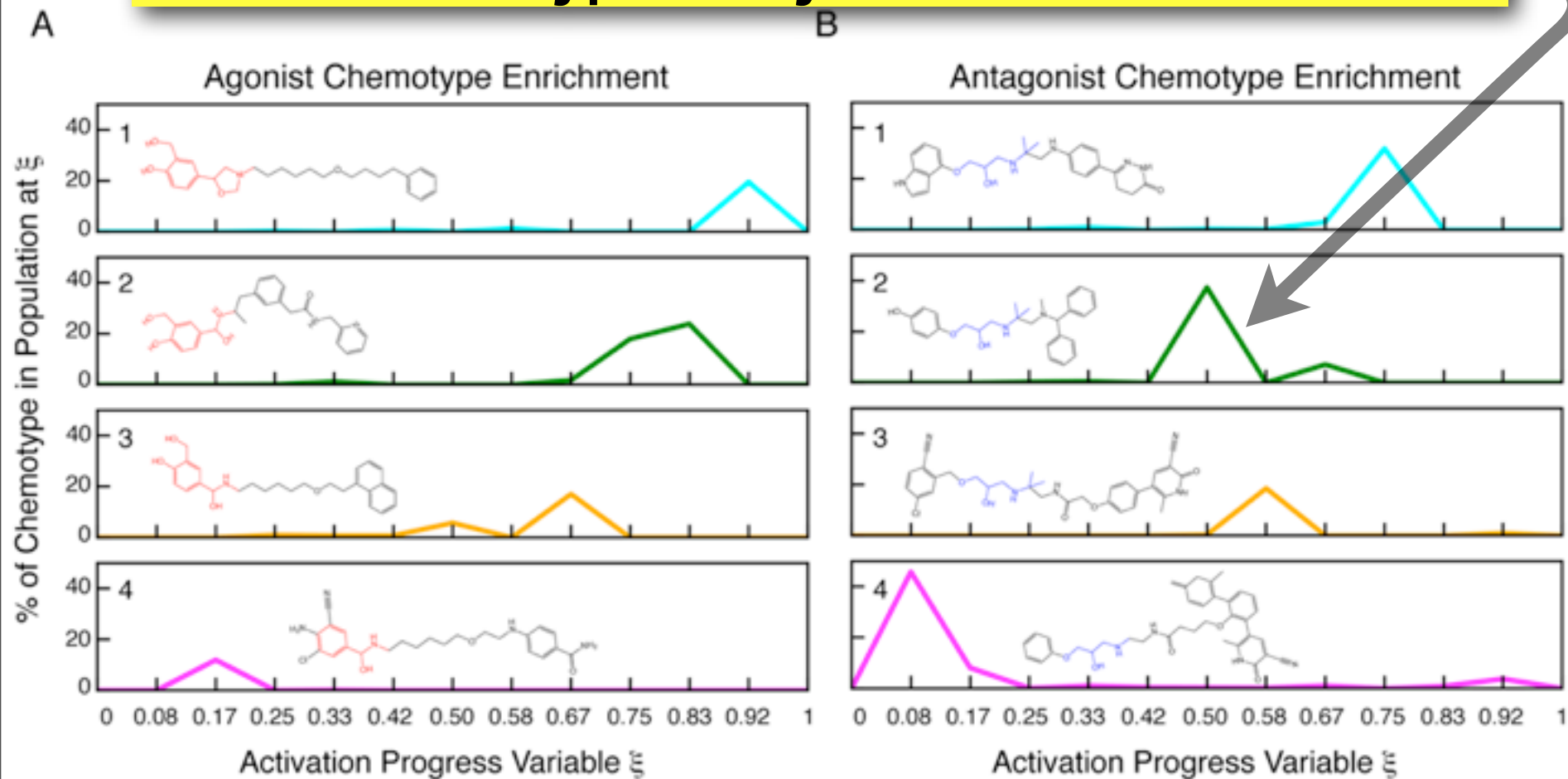
Antagonist Chemotype Enrichment



Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

Intermediates are functionally relevant

Some chemotypes only dock to intermediates



Kohlhoff*, Shukla*, Lawrenz*, ..., Altman, Pande, *Nature Chemistry* (2014)

Concluding remarks

Many of the features of pathways in folding also appear in the functional dynamics of cell-signaling proteins

Common elements in protein dynamics

Common elements in protein dynamics

Parallel pathways



GPCR:
*parallel paths,
intermediates*

Common elements in protein dynamics

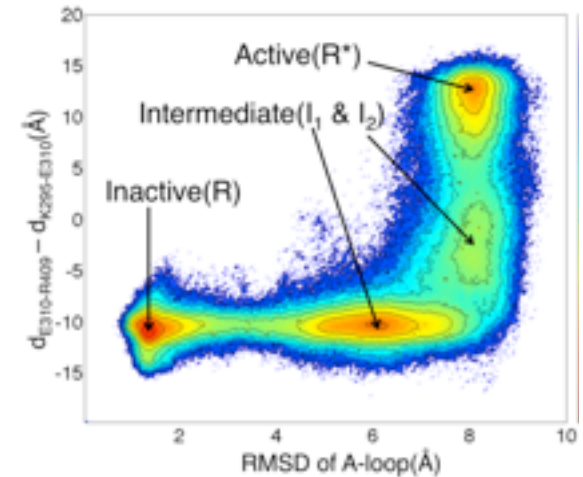
Parallel pathways

Intermediates — the
1% can be important
(conformational
selection)



GPCR:
*parallel paths,
intermediates*

kinase:
*key on-pathway
intermediates*



Common elements in protein dynamics

Parallel pathways

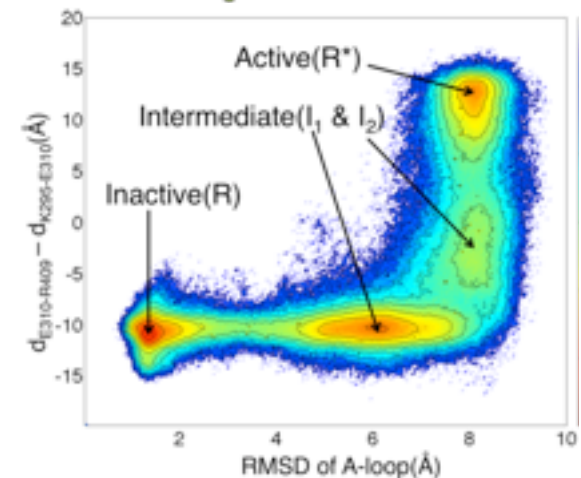
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selection)

Non-native interactions



GPCR:
*parallel paths,
intermediates*

kinase:
*key on-pathway
intermediates*



Switch	Active	Transition	Inactive
Y ₁₀₁ T ₈₂ Coupling	Yes	No	No
K ₆₇ Q ₉₆ h-bond	Yes	No	No
Y ₁₀₁ Q ₉₆ h-bond	No	Yes	No
S ₈₅ D ₈₆ h-bond	No	Yes	No
Y ₁₀₁ F ₉₉ Y ₉₄ Packing	No	Yes	Yes
K ₆₇ Q ₉₅ h-bond	No	No	Yes
H ₈₄ D ₈₆ h-bond	No	No	Yes

NtrC:
*non-native
interactions along
the path between
active & inactive*

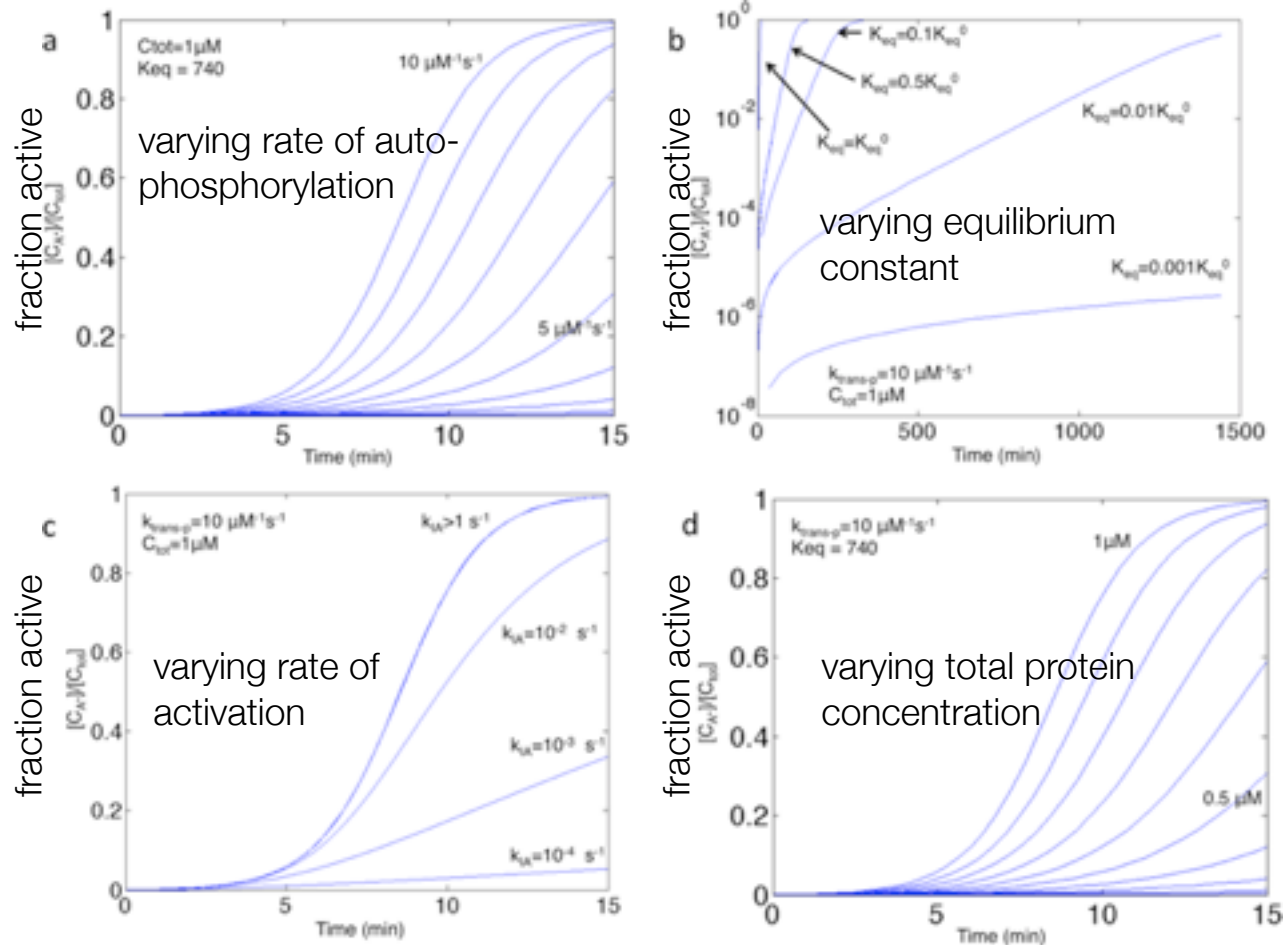
MSMs of simple pathway

Autophosphorylation



MSMs of simple pathway

Autophosphorylation

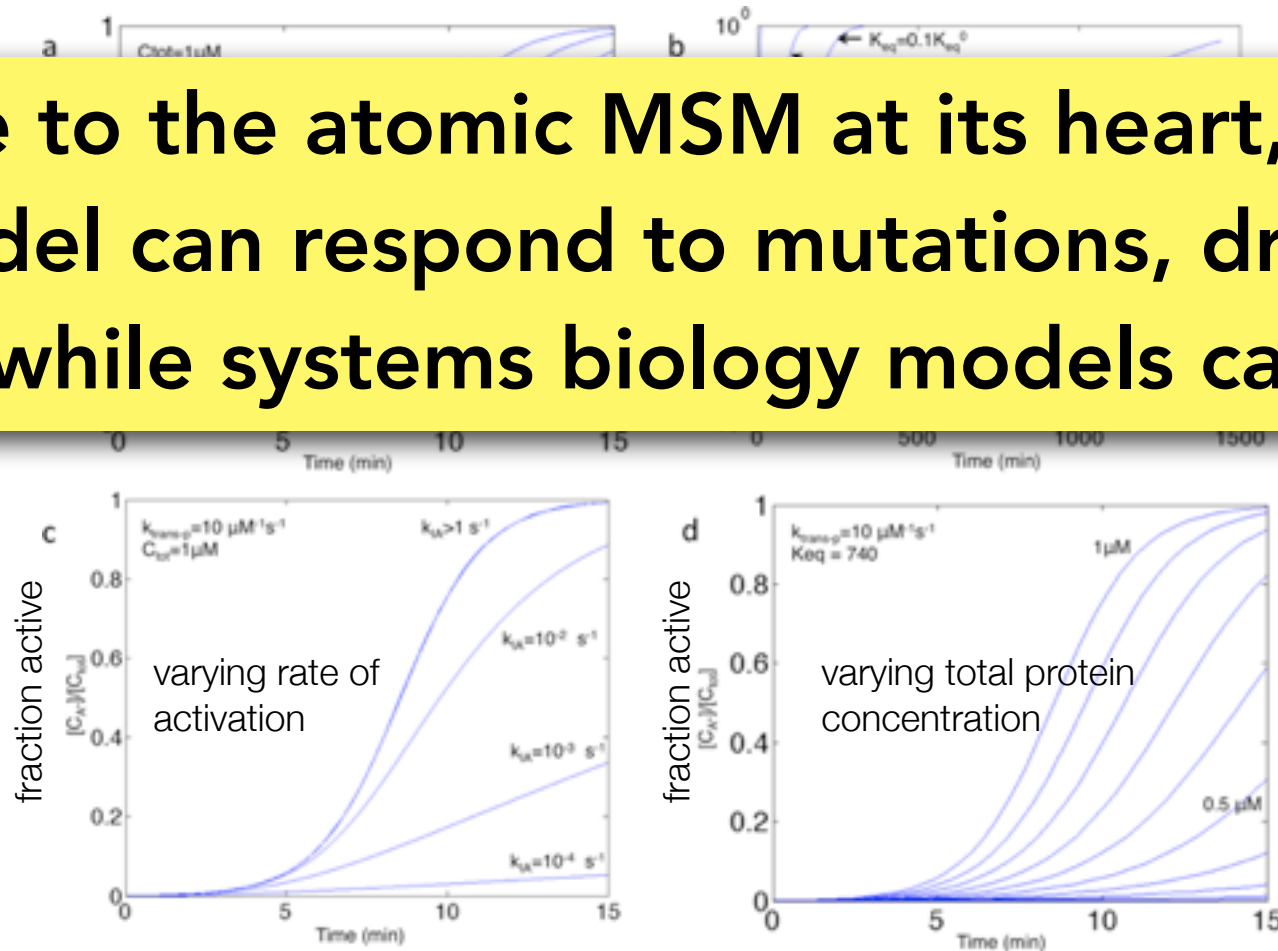


MSMs of simple pathway

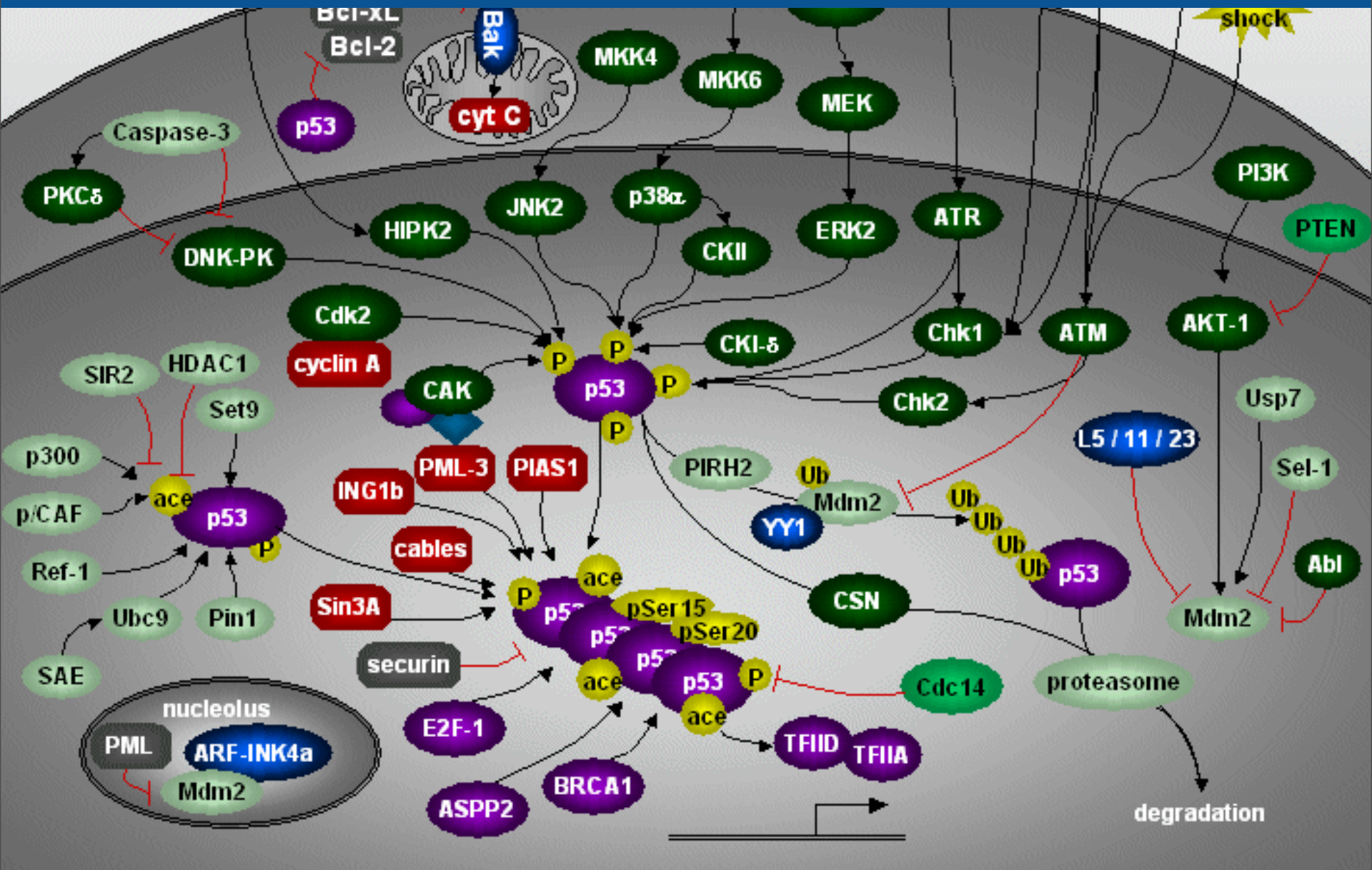
Autophosphorylation



Due to the atomic MSM at its heart, this model can respond to mutations, drugs, etc (while systems biology models cannot)



P53 is a hub in protein-protein networks



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Greg
Bowman

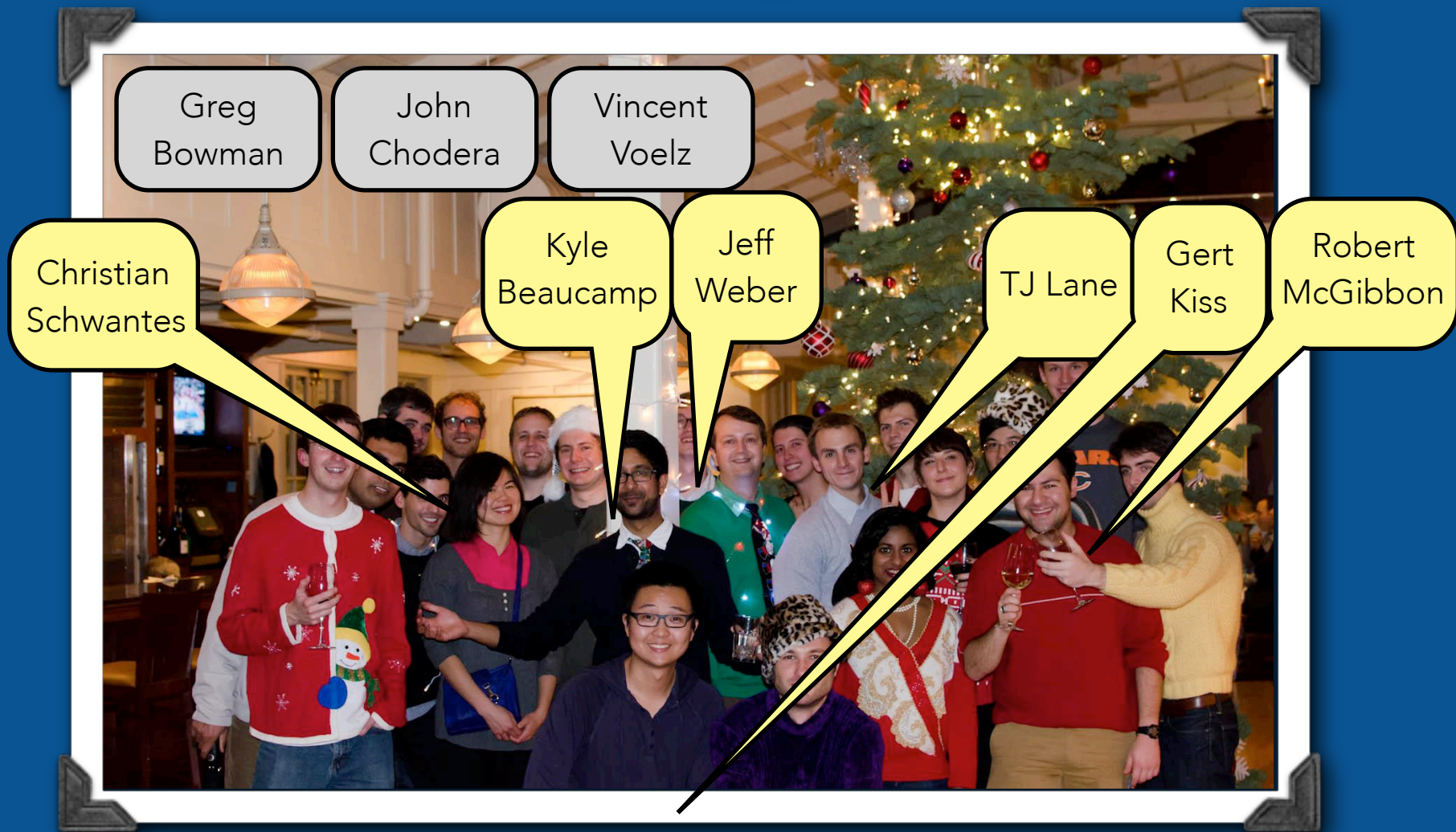
John
Chodera

Vincent
Voelz



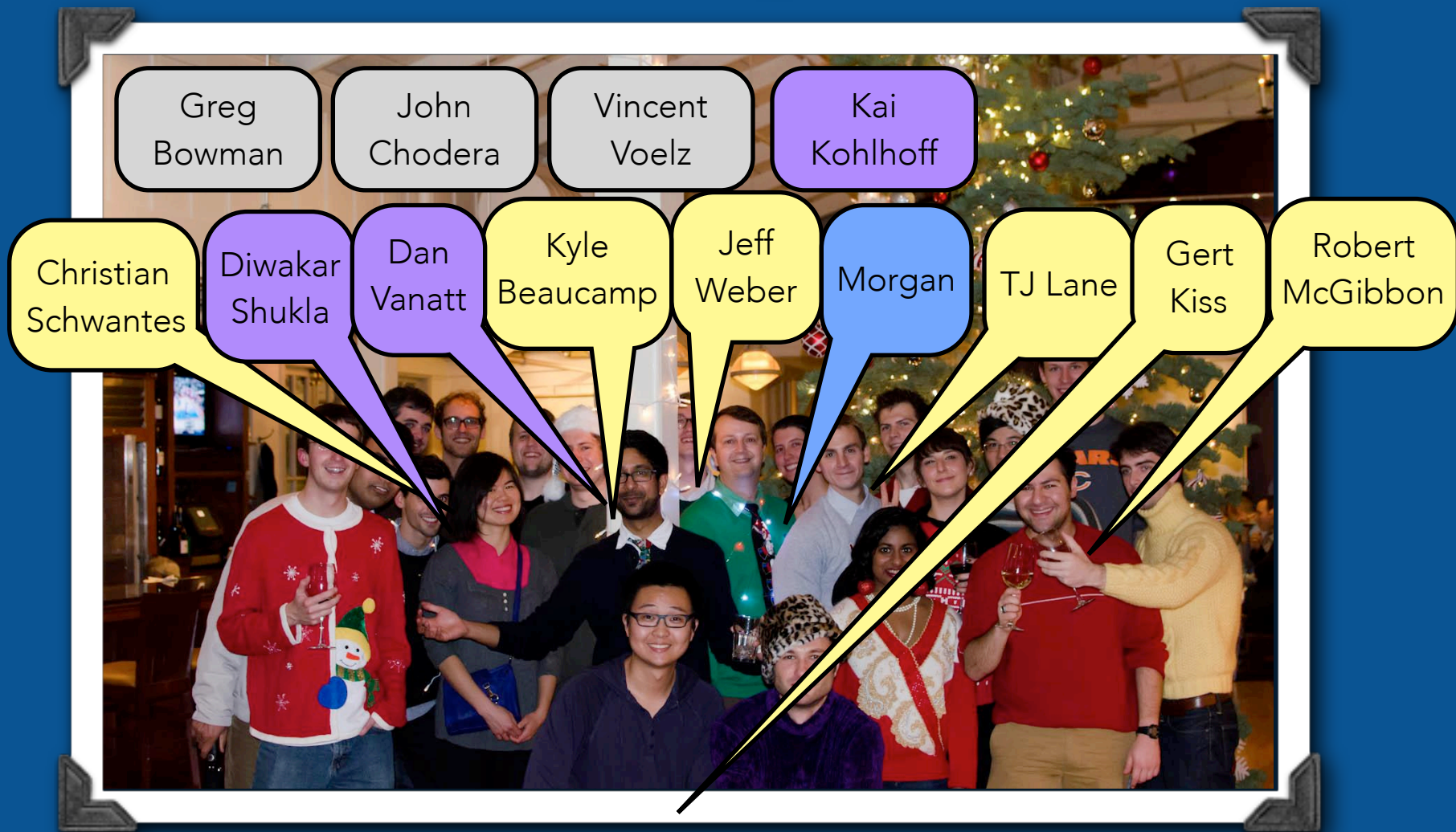
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Summary

- OpenMM is very flexible as both an application and a library
- OpenMM + MSM Builder allows one to efficiently use many GPUs to simulate long timescale dynamics
- These methods have already been used to study many challenging systems
