Rule-based modeling of CaMKII dynamics: Subunit exchange and beyond

Cihan Kaya

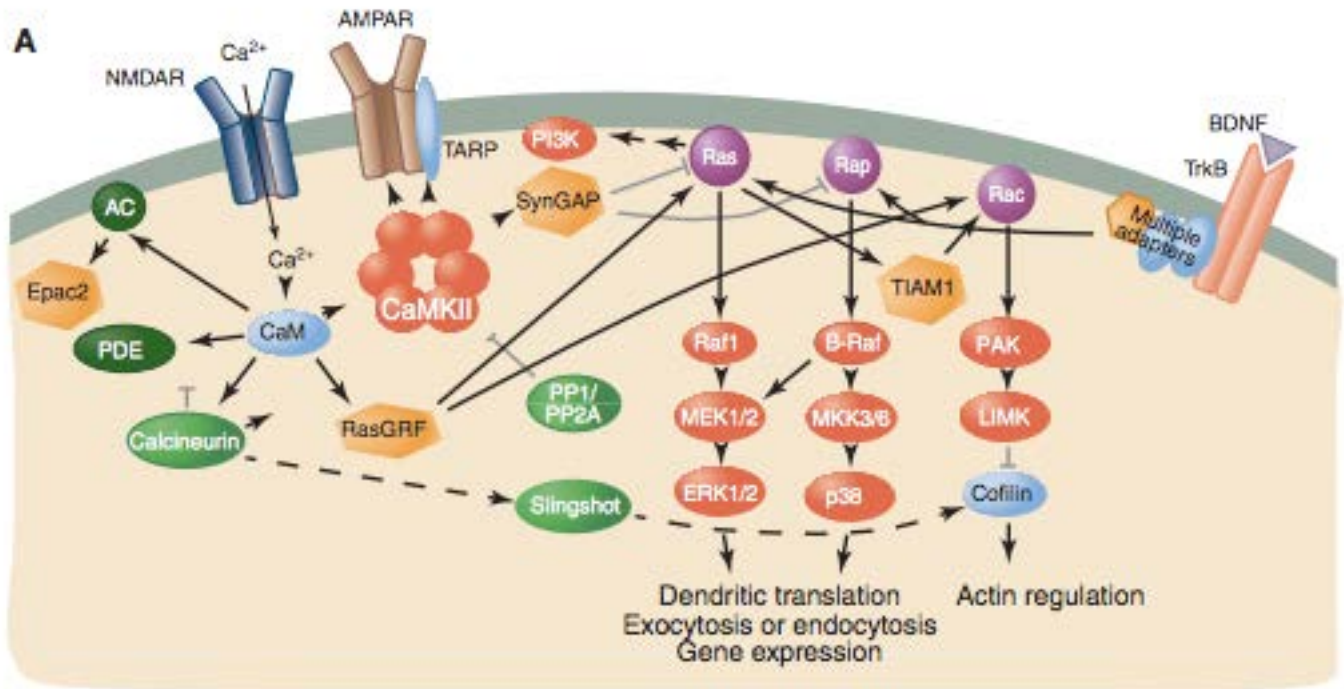
Why CaMKII?

- One of the main drivers of NMDA-dependent synaptic plasticity

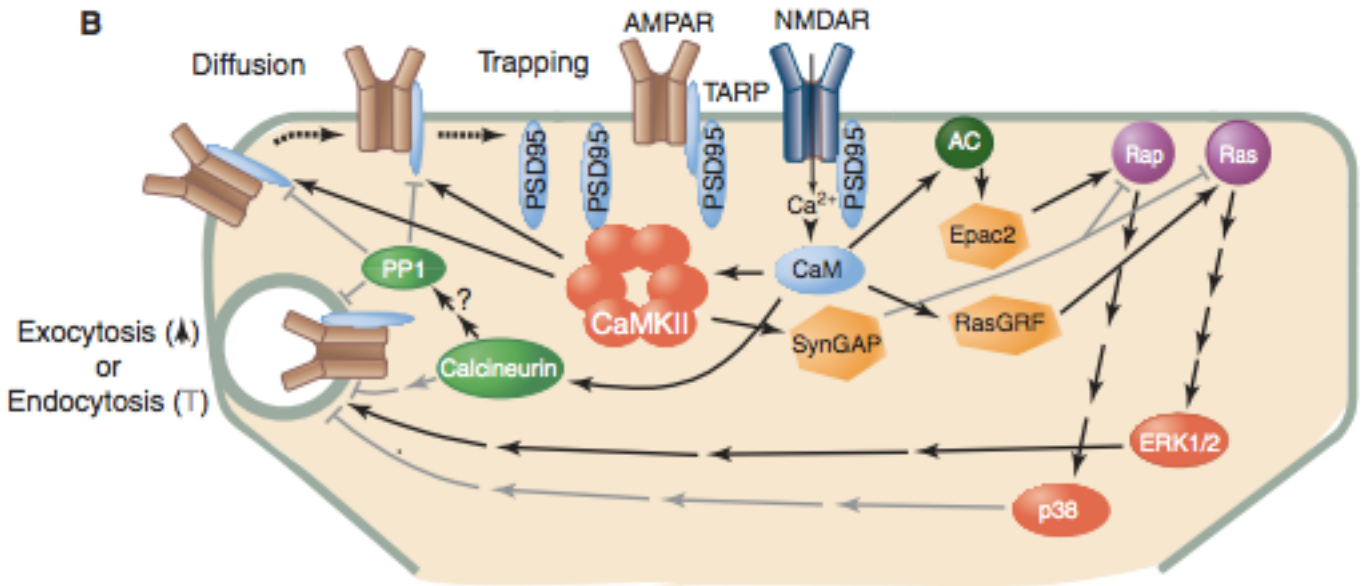
Why CaMKII?

- One of the main drivers of NMDA-dependent synaptic plasticity
- Highly expressed compared to other kinases (at least 10 times) and connected to many signaling molecules.

Kennedy, MB., 2015, CSHL Perspectives



Kennedy, MB., 2015, CSHL Perspectives

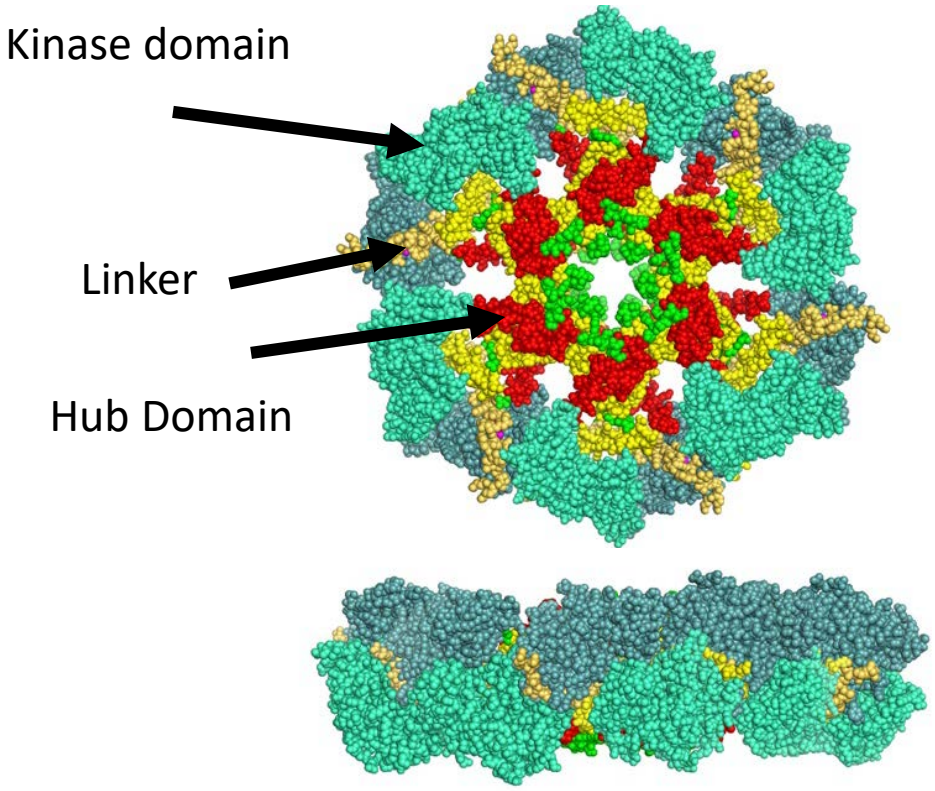


Kennedy, MB., 2015, CSHL Perspectives

Why CaMKII is important?

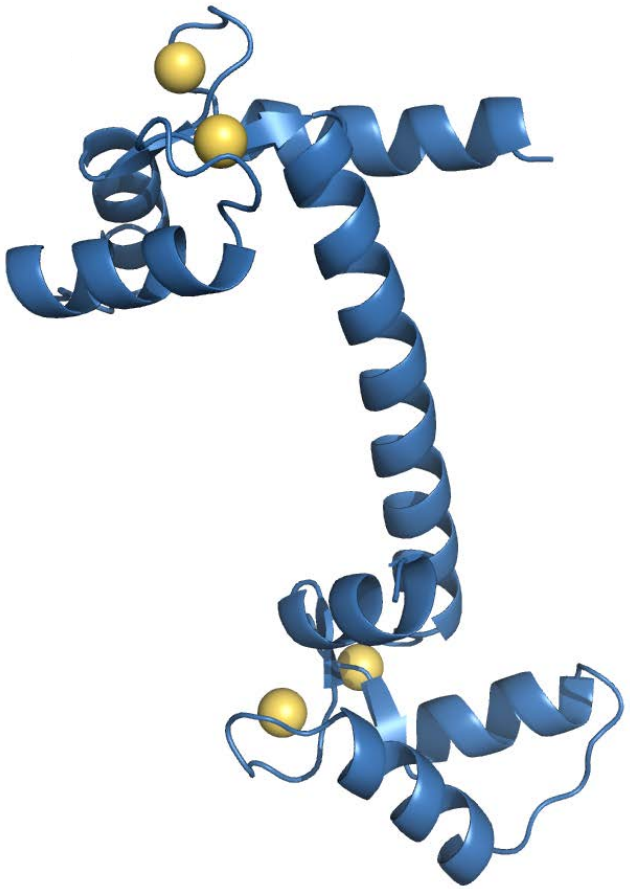
- One of the main drivers of NMDA-dependent synaptic plasticity
- Highly expressed compared to other kinases (at least 10 times)[1] and connected to many signaling molecules.
- Structurally complex dodecamer with multiple phosphorylation and binding sites in addition to complexity from CaM.

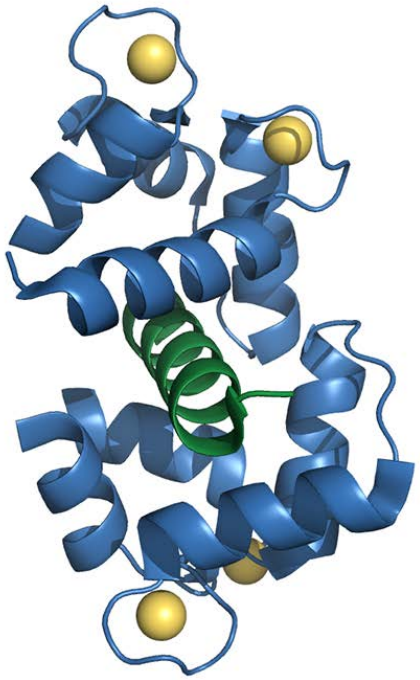
CaMKII Structure

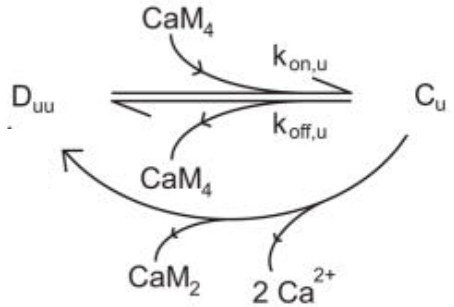


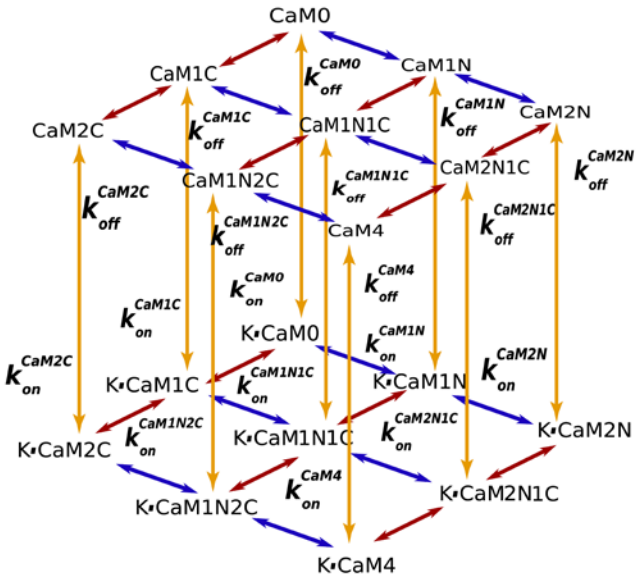
Activation

Mechanism of Action





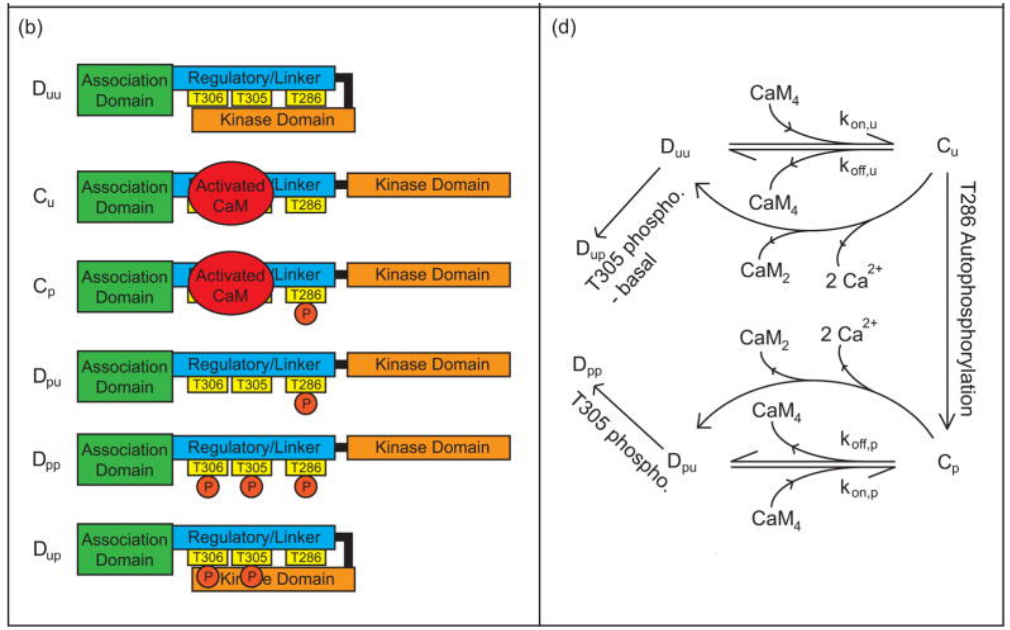




Pepke et al. , 2010, PLOS Comp Bio

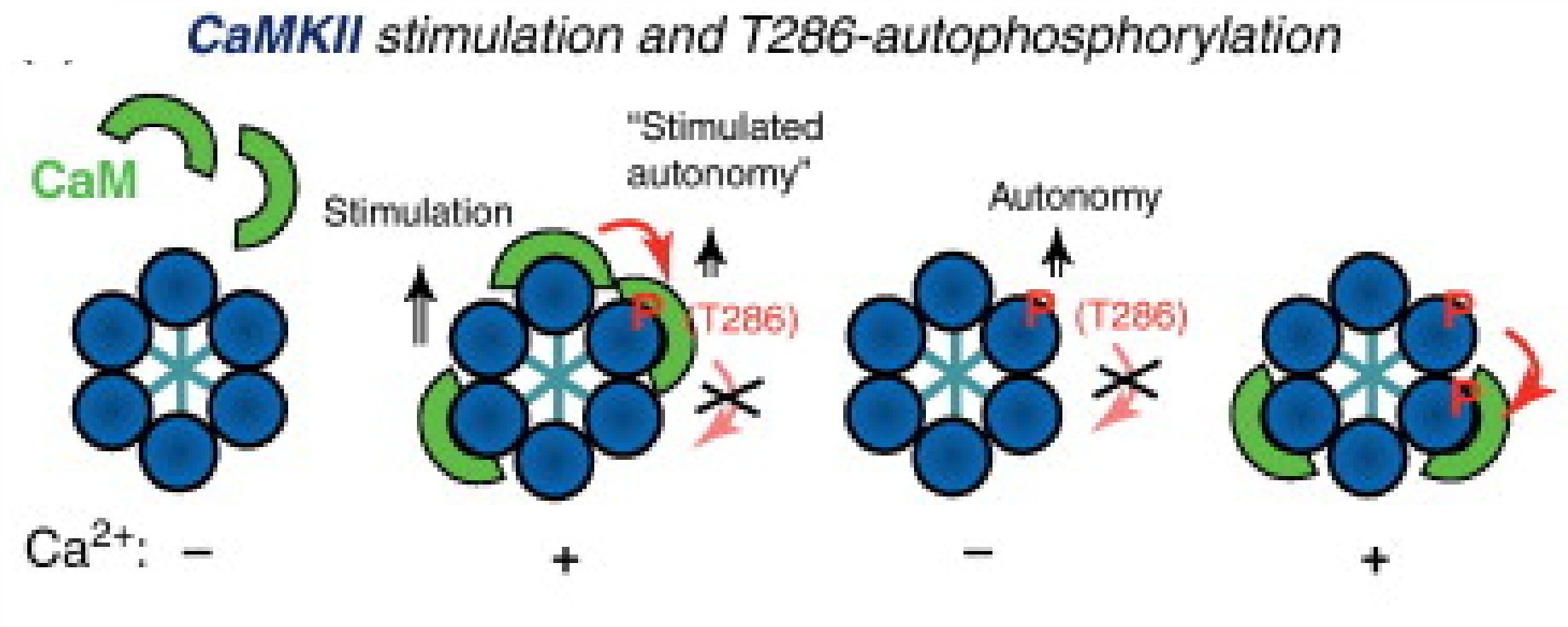
Michalski and Loew, 2012, Phys Biol

Mechanism of Action



Michalski and Loew, 2012, Phys Biol

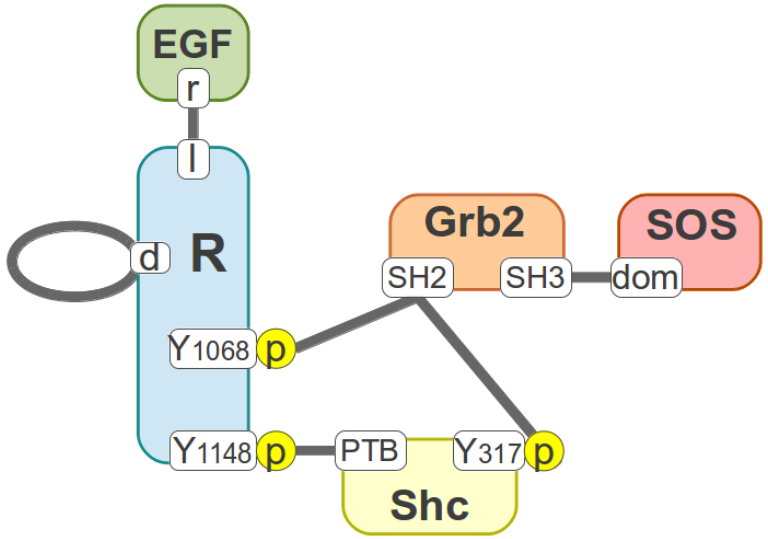
Autophosphorylation



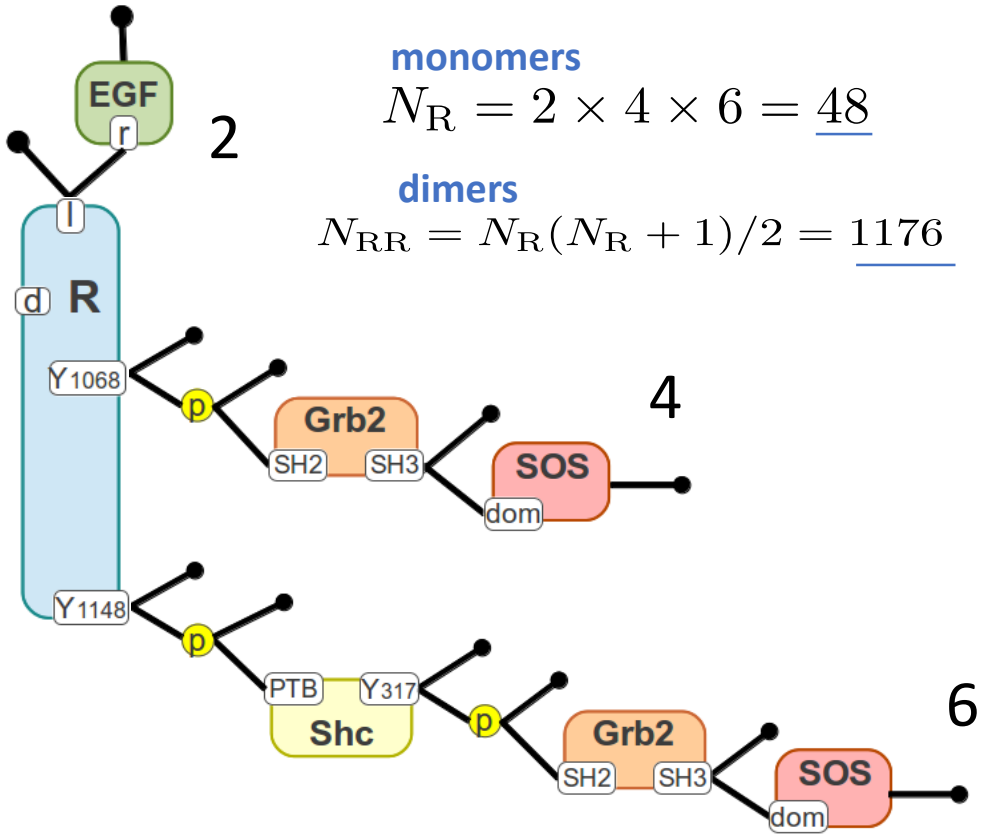
Coultrap and Mayer, 2012, Trends in Neuro.

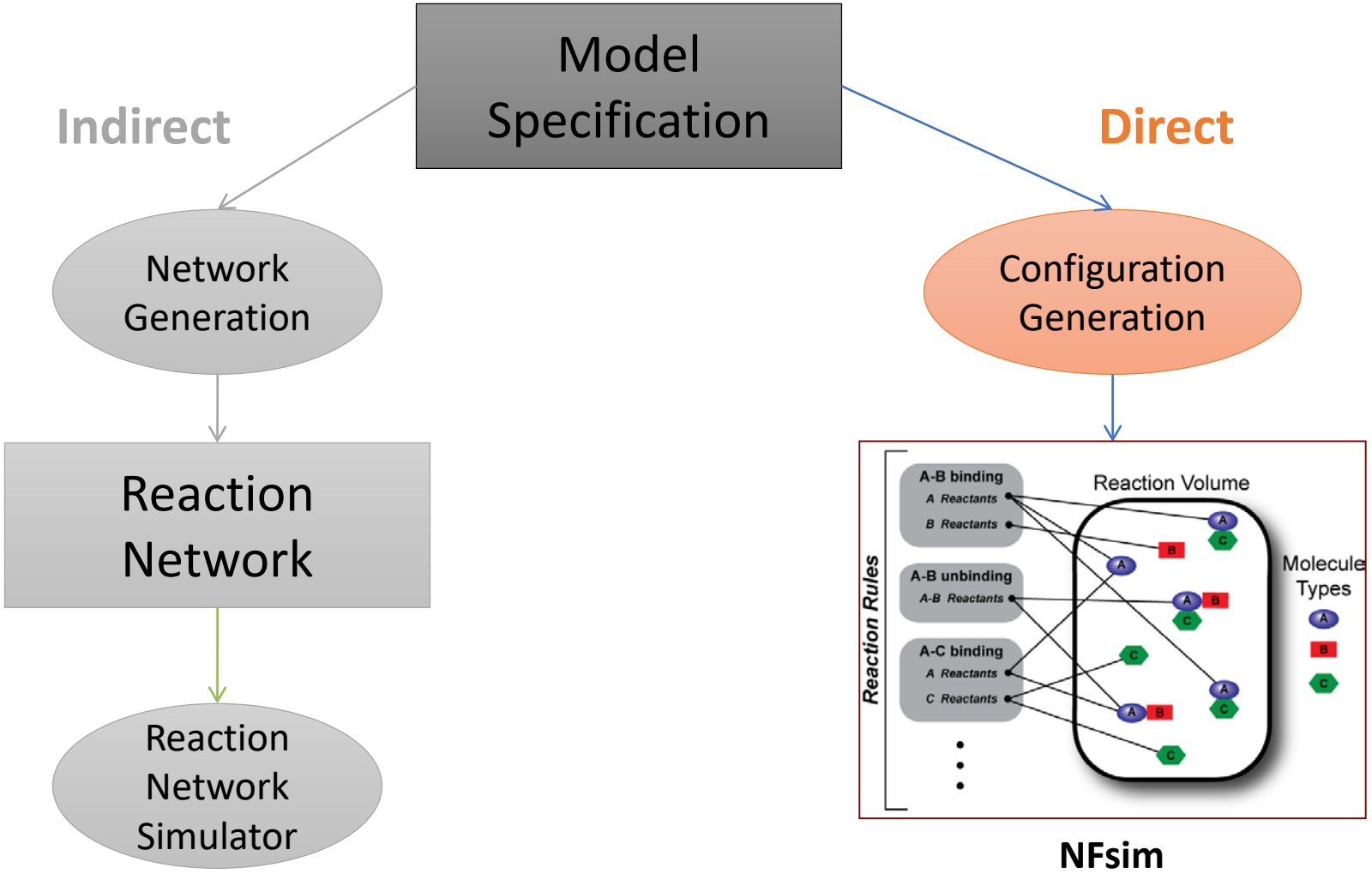
Combinatorial Complexity in Biochemical Interactions

Contact Map for molecules involved in EGFR signaling

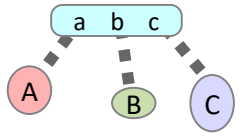


Enumeration of receptor-containing species



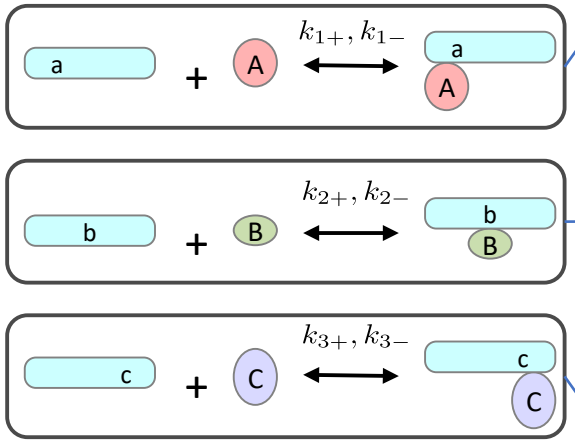

Model Specification
Indirect
Direct
Network Generation
Reaction Network
Reaction Network Simulator
Configuration Generation
A-B binding
A Reactants
B Reactants
A-B unbinding
A-B Reactants
A-C binding
A Reactants
C Reactants
Reaction Rules
Reaction Volume
Molecule Types
NFsim

Indirect Methods – Network Generation



contact map

reaction rules



$$\begin{aligned}
\mathtt{S} + \mathtt{A} &\overset{k_{1+},k_{1-}}{\rightleftharpoons} \mathtt{SA} \\
\mathtt{SB} + \mathtt{A} &\overset{k_{1+},k_{1-}}{\rightleftharpoons} \mathtt{SAB} \\
\mathtt{SC} + \mathtt{A} &\overset{k_{1+},k_{1-}}{\rightleftharpoons} \mathtt{SAC} \\
\mathtt{SBC} + \mathtt{A} &\overset{k_{1+},k_{1-}}{\rightleftharpoons} \mathtt{SABC}
\end{aligned}$$

$$\begin{aligned}
\mathtt{S} + \mathtt{B} &\overset{k_{2+},k_{2-}}{\rightleftharpoons} \mathtt{SB} \\
\mathtt{SA} + \mathtt{B} &\overset{k_{2+},k_{2-}}{\rightleftharpoons} \mathtt{SAB} \\
\mathtt{SC} + \mathtt{B} &\overset{k_{2+},k_{2-}}{\rightleftharpoons} \mathtt{SBC} \\
\mathtt{SAC} + \mathtt{B} &\overset{k_{2+},k_{2-}}{\rightleftharpoons} \mathtt{SABC}
\end{aligned}$$

$$\begin{aligned}
\mathtt{S} + \mathtt{C} &\overset{k_{3+},k_{3-}}{\rightleftharpoons} \mathtt{SC} \\
\mathtt{SA} + \mathtt{C} &\overset{k_{3+},k_{3-}}{\rightleftharpoons} \mathtt{SAC} \\
\mathtt{SB} + \mathtt{C} &\overset{k_{3+},k_{3-}}{\rightleftharpoons} \mathtt{SBC} \\
\mathtt{SAB} + \mathtt{C} &\overset{k_{3+},k_{3-}}{\rightleftharpoons} \mathtt{SABC}
\end{aligned}$$

reactions

S, A, B, C,
SA, SB, SC,
SAB, SAC, SBC,
SABC

species

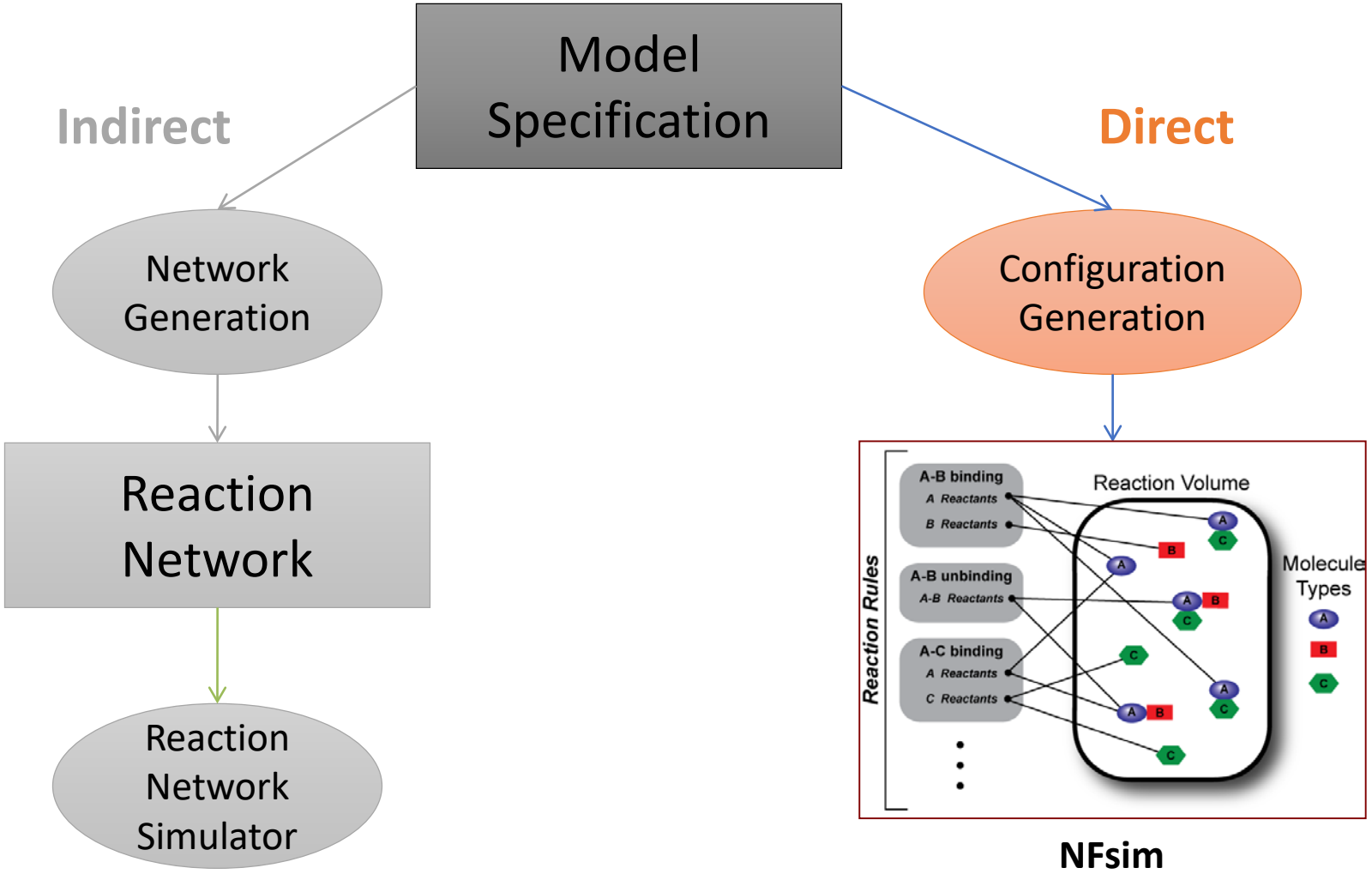
4 molecule types
3 rules

11 species
12 reactions

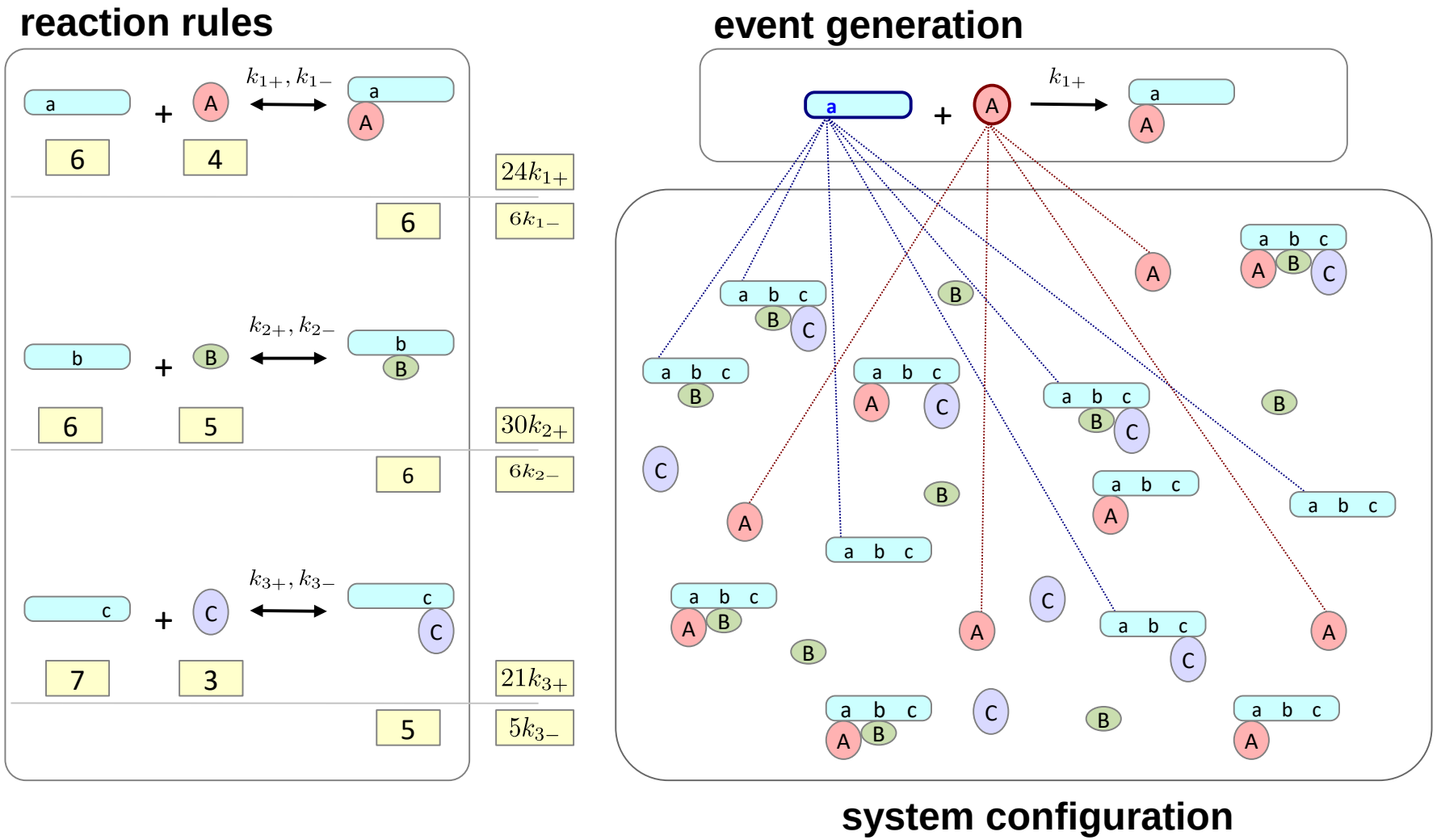
Graph enumeration

“For the CaMKII system, the size of the reaction network increases non-linearly (approximately exponentially) with holoenzyme size(...) A 2.53 GHz Intel Xeon processor took 6 hours to generate the network for a six-state pentamer model, and an exponential fit suggests it would take over 290 years to generate the network for a six-state, 10-subunit-holoenzyme model.”

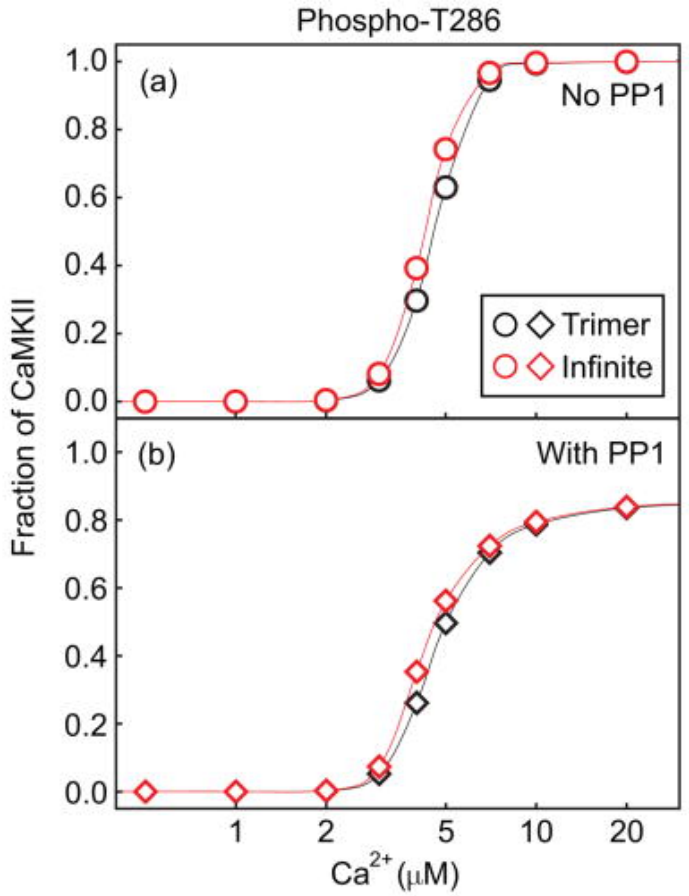
Michalski and Loew, 2012, Phys Biol


Model Specification
Indirect
Direct
Network Generation
Reaction Network
Reaction Network Simulator
Configuration Generation
A-B binding
A Reactants
B Reactants
A-B unbinding
A-B Reactants
A-C binding
A Reactants
C Reactants
Reaction Rules
Reaction Volume
Molecule Types
NFsim

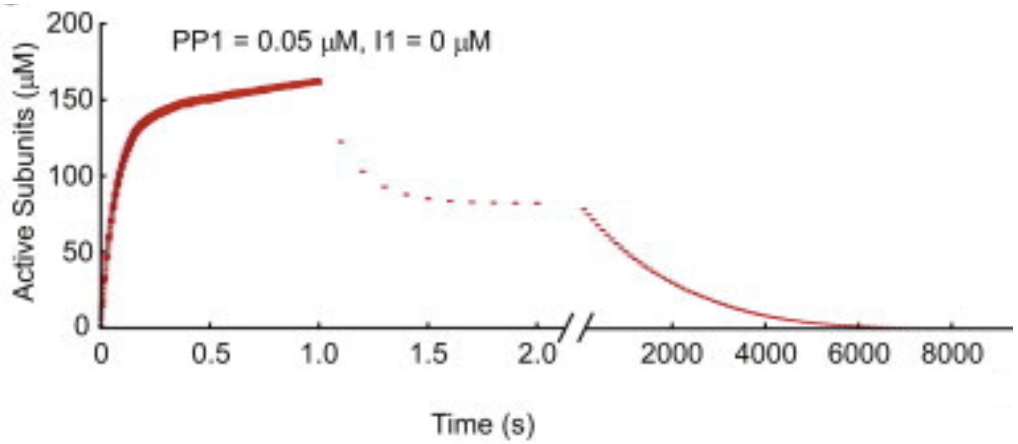
NFsim


reaction rules
event generation
k_{1+}, k_{1-}
k_{2+}, k_{2-}
k_{3+}, k_{3-}
k_{1+}
6
4
$24k_{1+}$
6
$6k_{1-}$
6
5
$30k_{2+}$
6
$6k_{2-}$
7
3
$21k_{3+}$
5
$5k_{3-}$
system configuration

Bistability of CaMKII

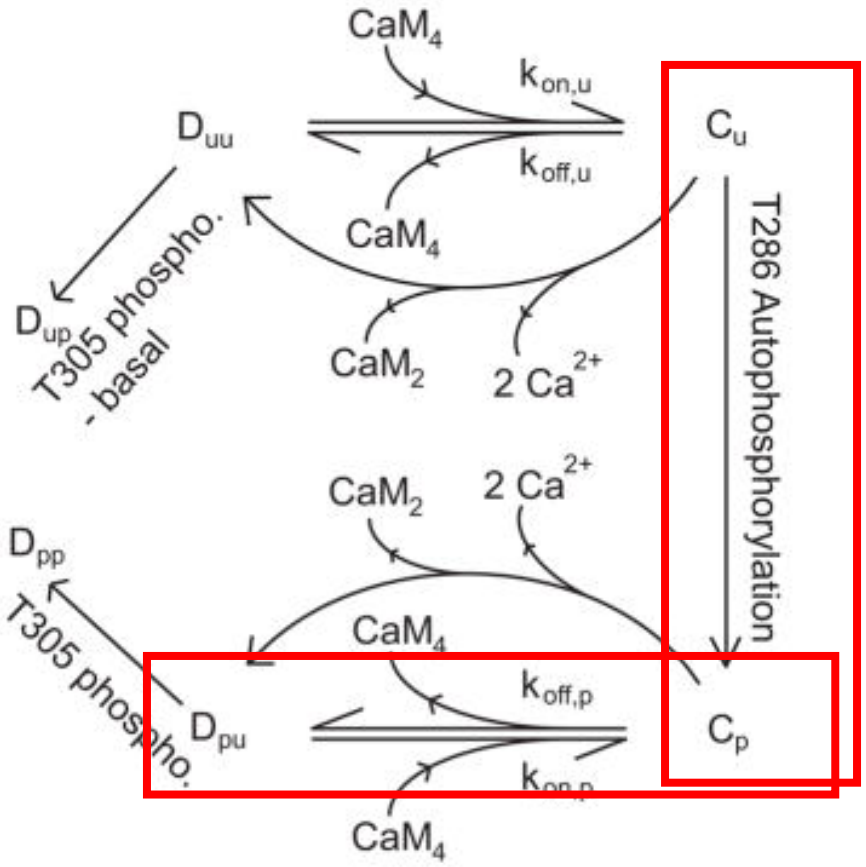


Michalski and Loew, 2012, Phys Biol



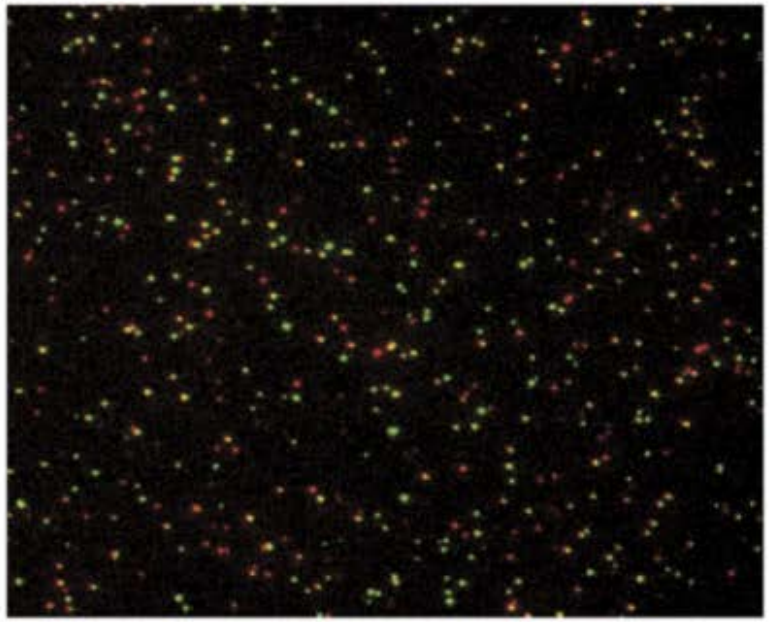
Michalski and Loew, 2012, Phys Biol
Michalski, 2013, Biophys J

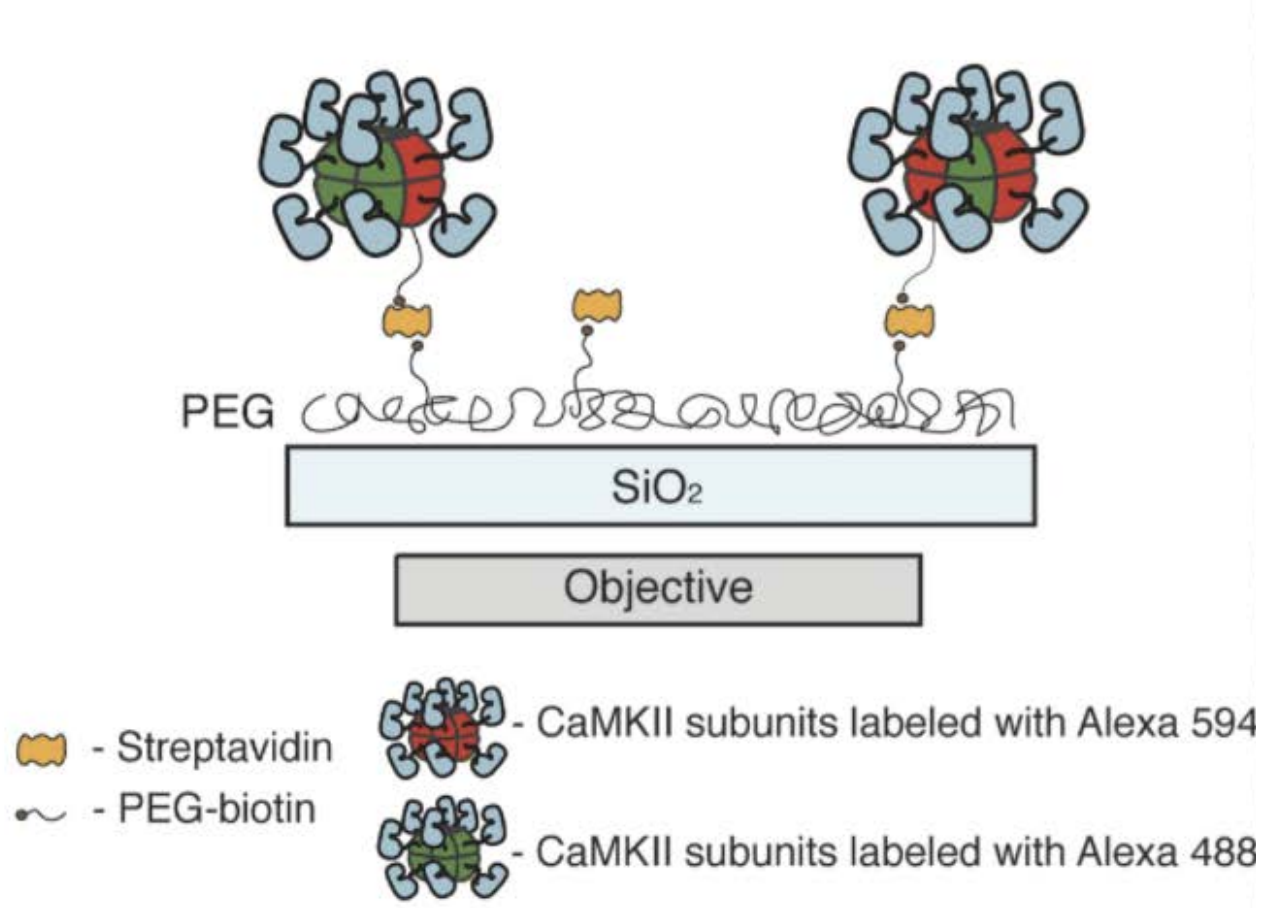
Calmodulin Trapping



Michalski and Loew, 2012, Phys Biol

Another mechanism to sustain activity

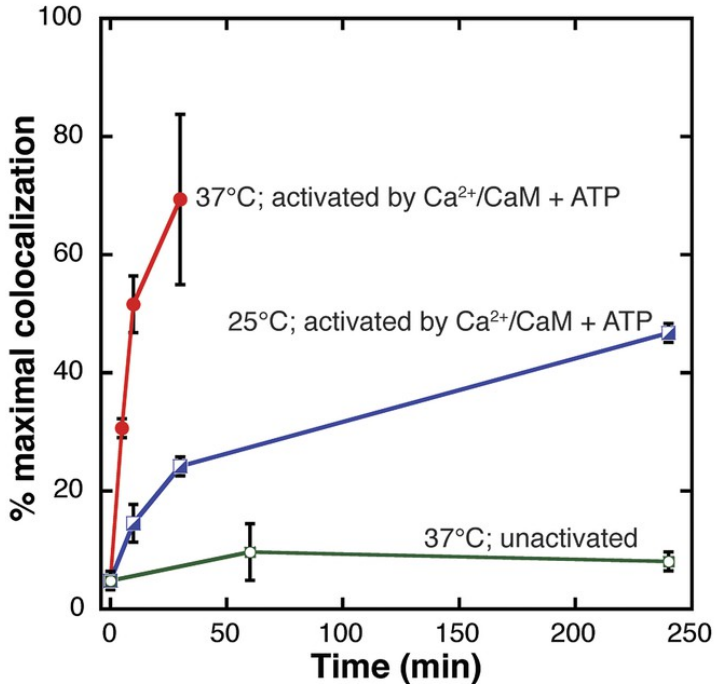




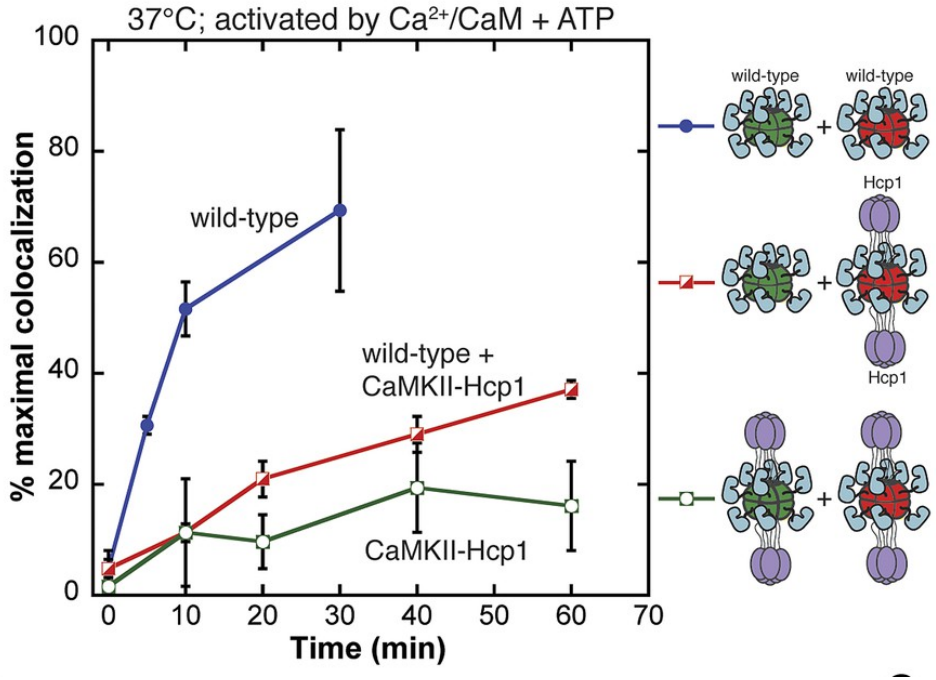
Stratton et al, 2014, eLife

Mechanism

Activation dependent subunit exchange



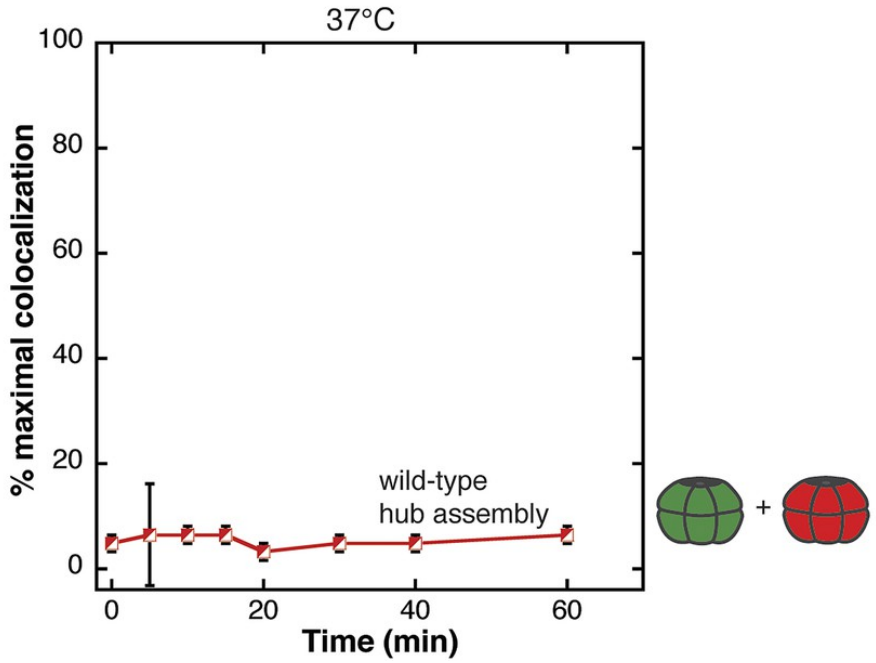
Hcp1 blocks subunit exchange



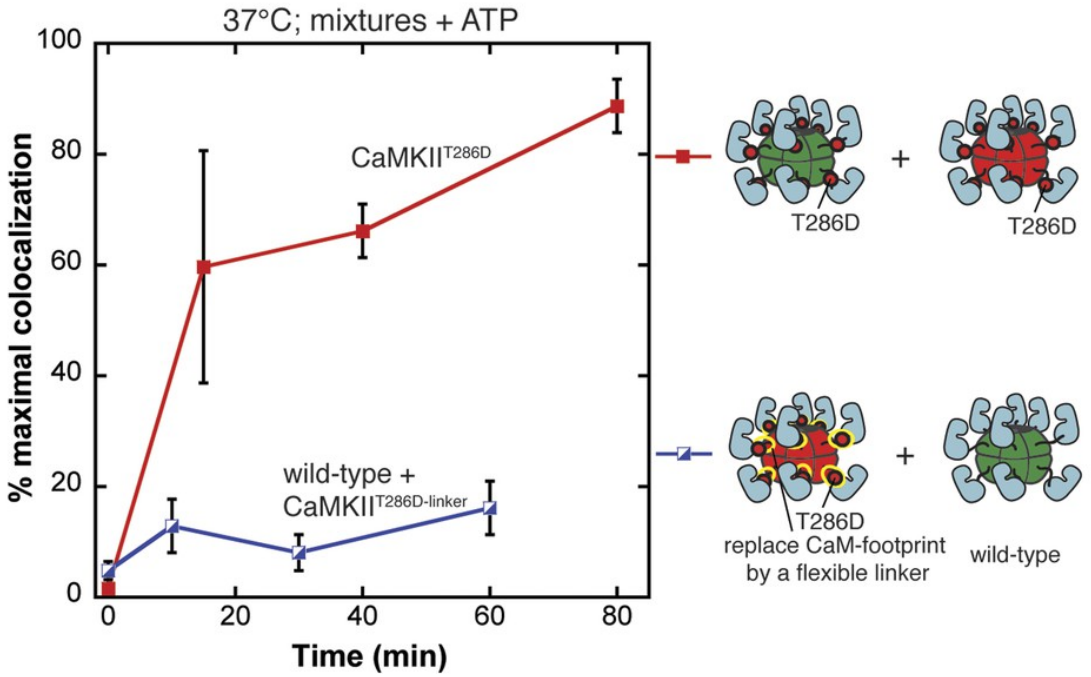
Stratton et al, 2014, eLife

Mechanism

Kinase domain is required for subunit exchange



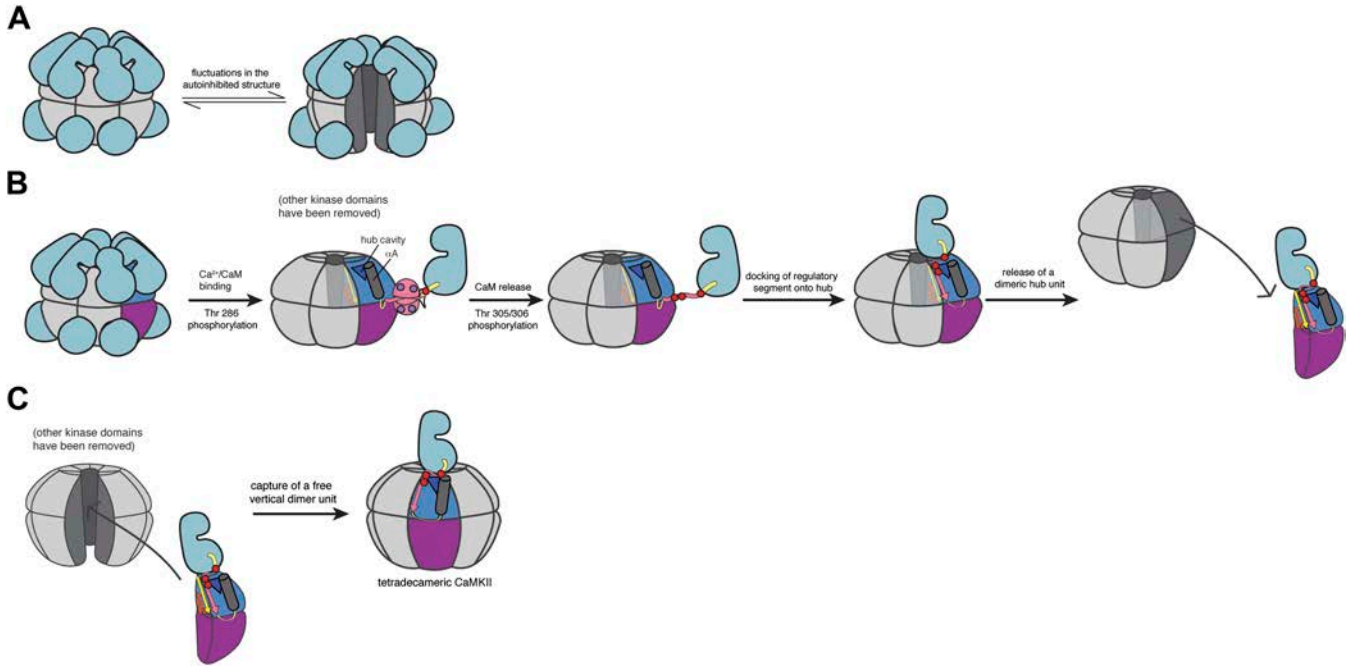
Active CaMKII exchange subunits regardless of Ca++/CaM



Stratton et al, 2014, eLife

Suggested mechanism

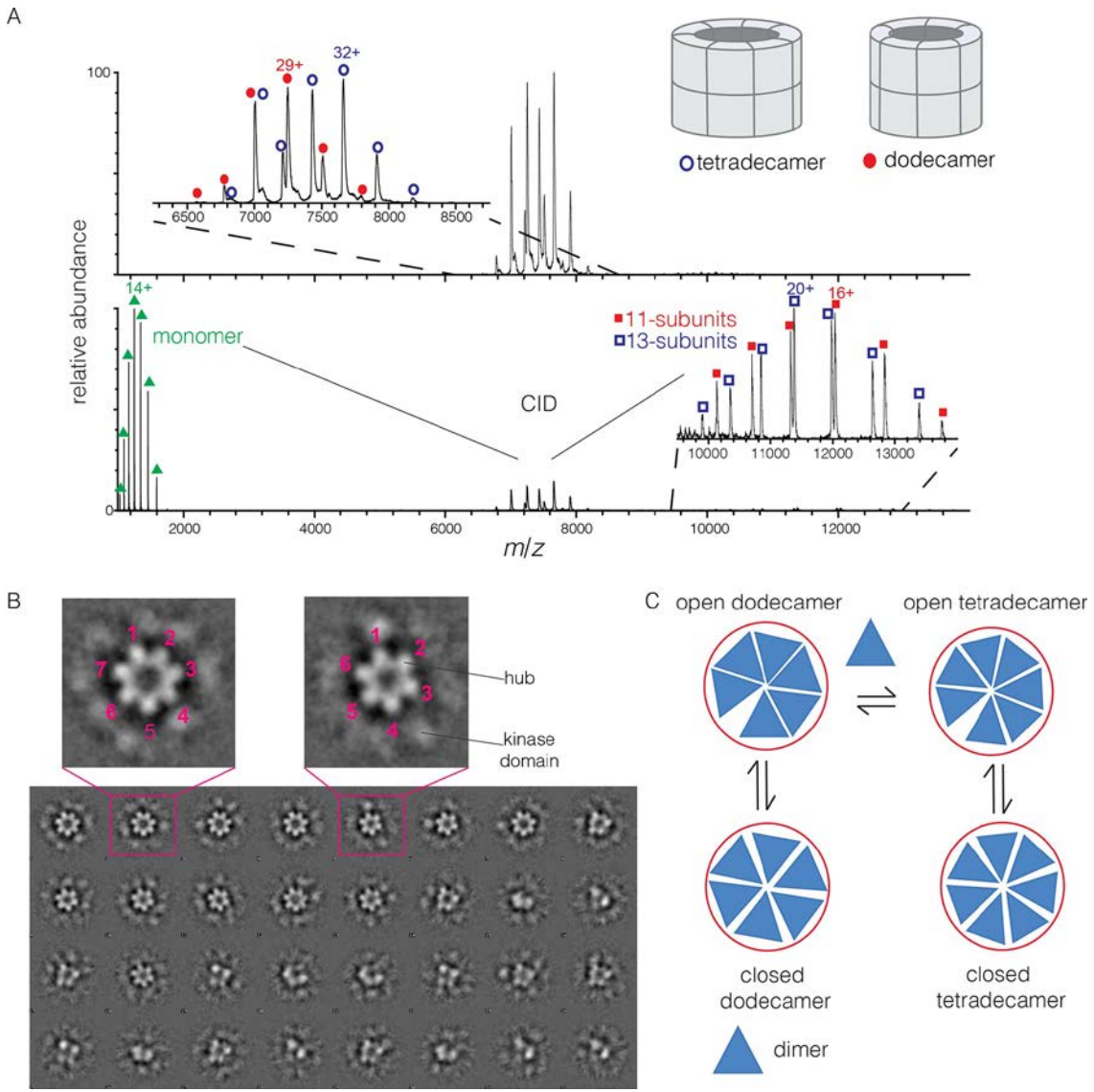
- Subunit exchange mechanism



Stratton et al, 2014, eLife

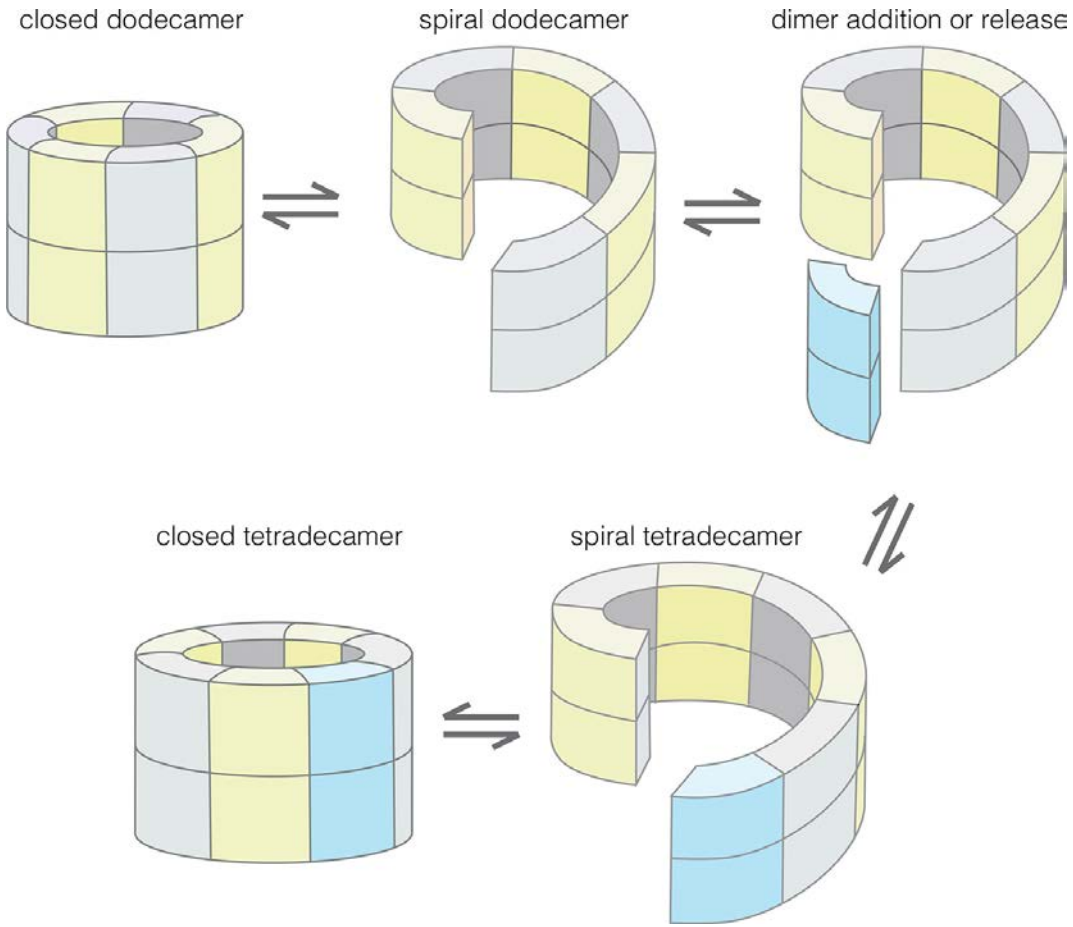
Mechanism

- No decamer.
- Dodecamer and tetradecamer are equally distributed.
- Opening and closing are individual motions.

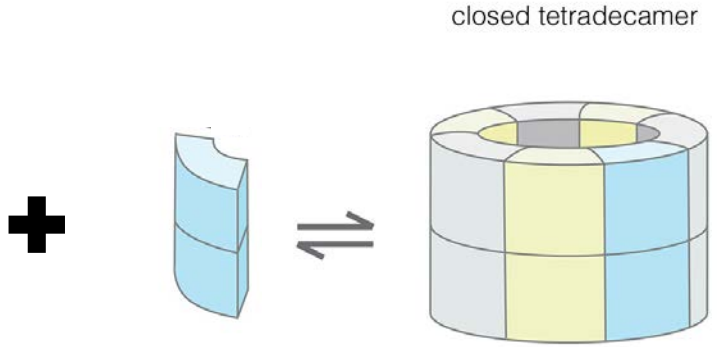


Stratton et al, 2014, eLife

Suggested mechanism

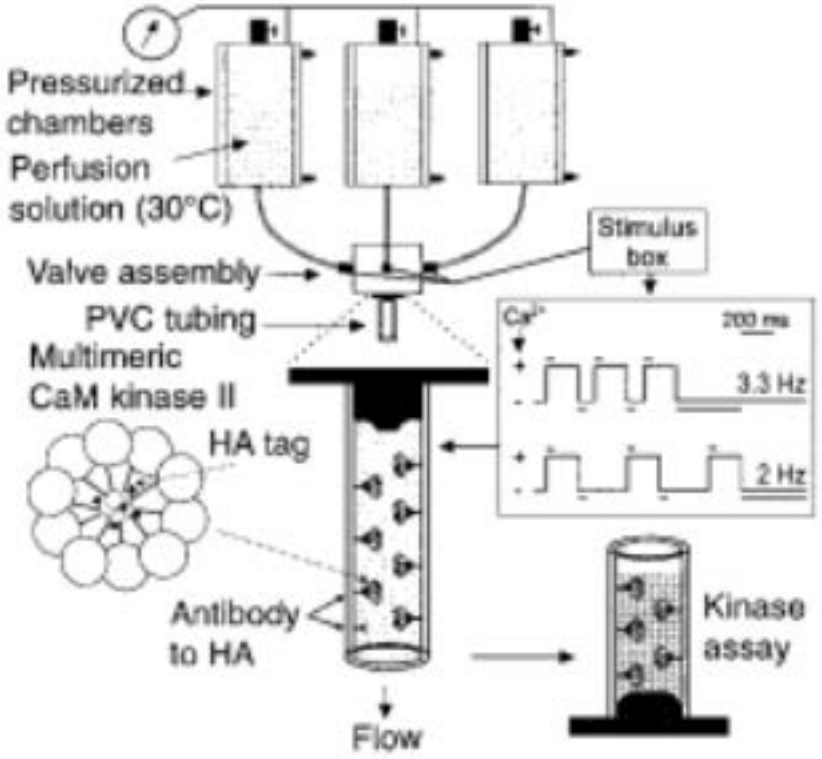


Diffusion limited subunit exchange



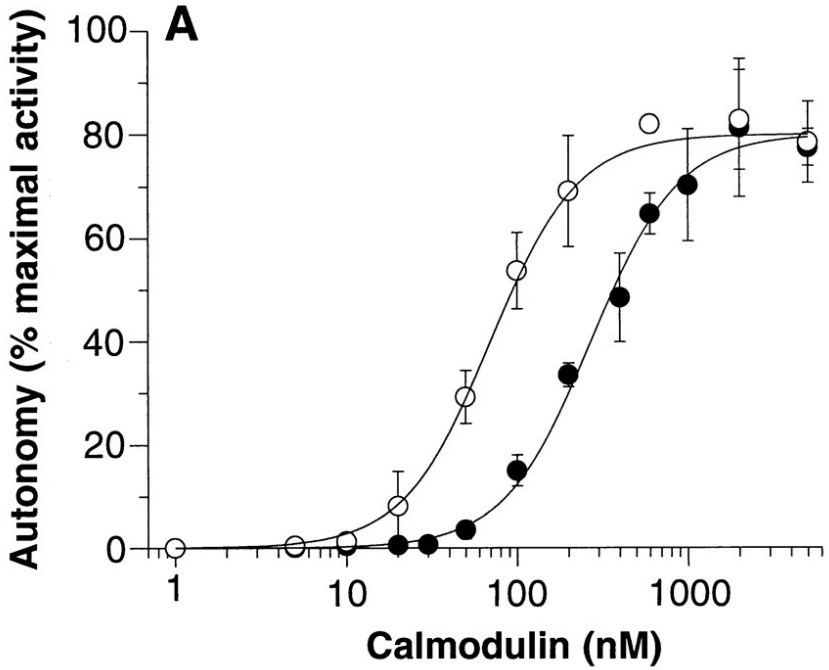
Bhattacharya et al, 2016, eLife

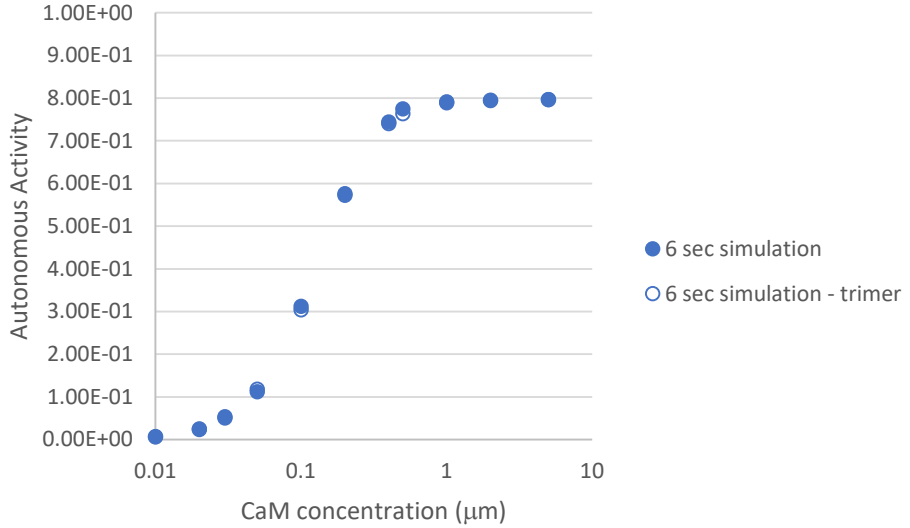
Baseline experiment



De Konnick and Schulman, 1998, Science

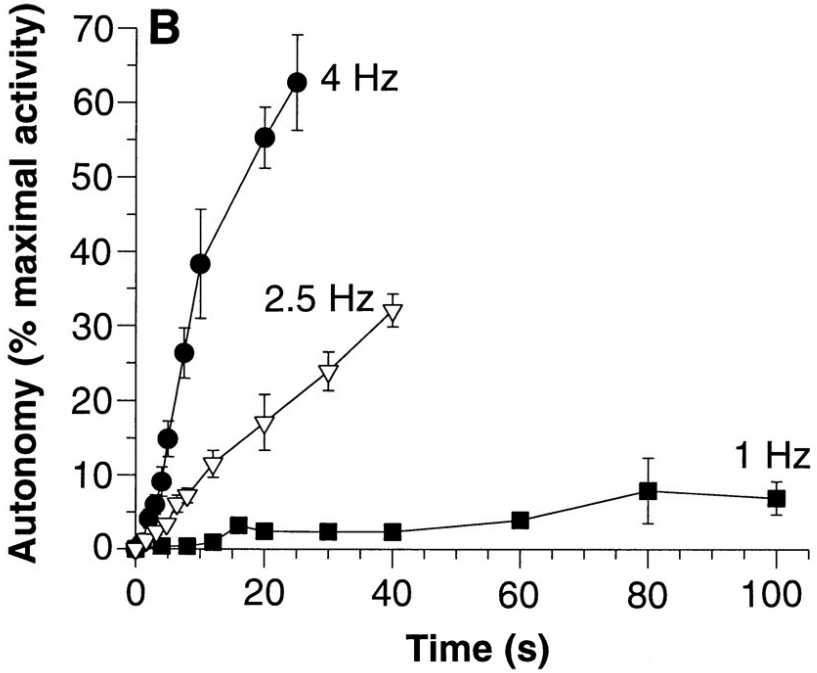
6 seconds pulse

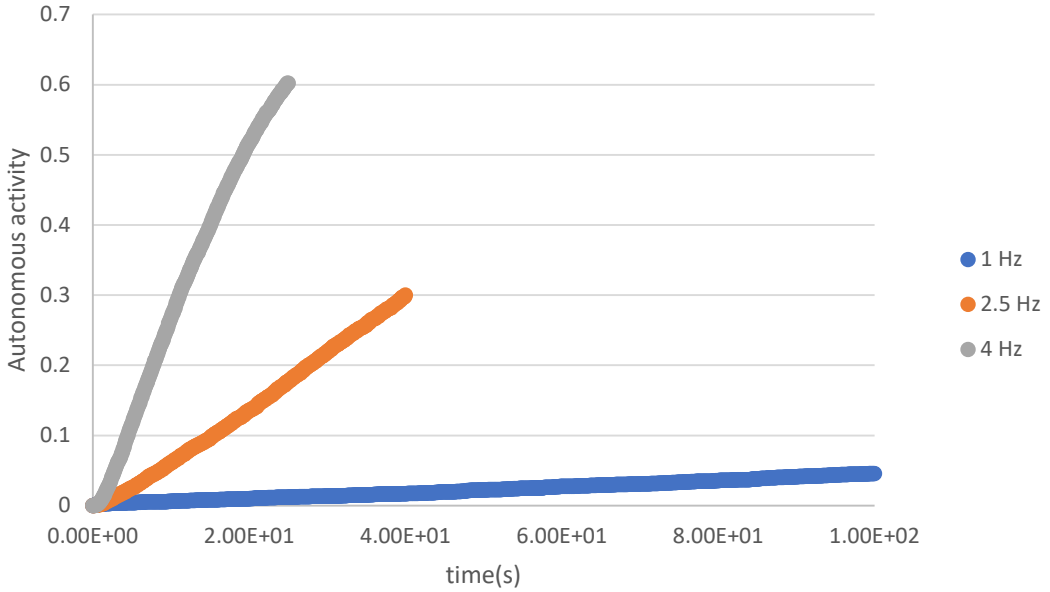




Baseline experiment

200 ms pulses with total of 6 seconds

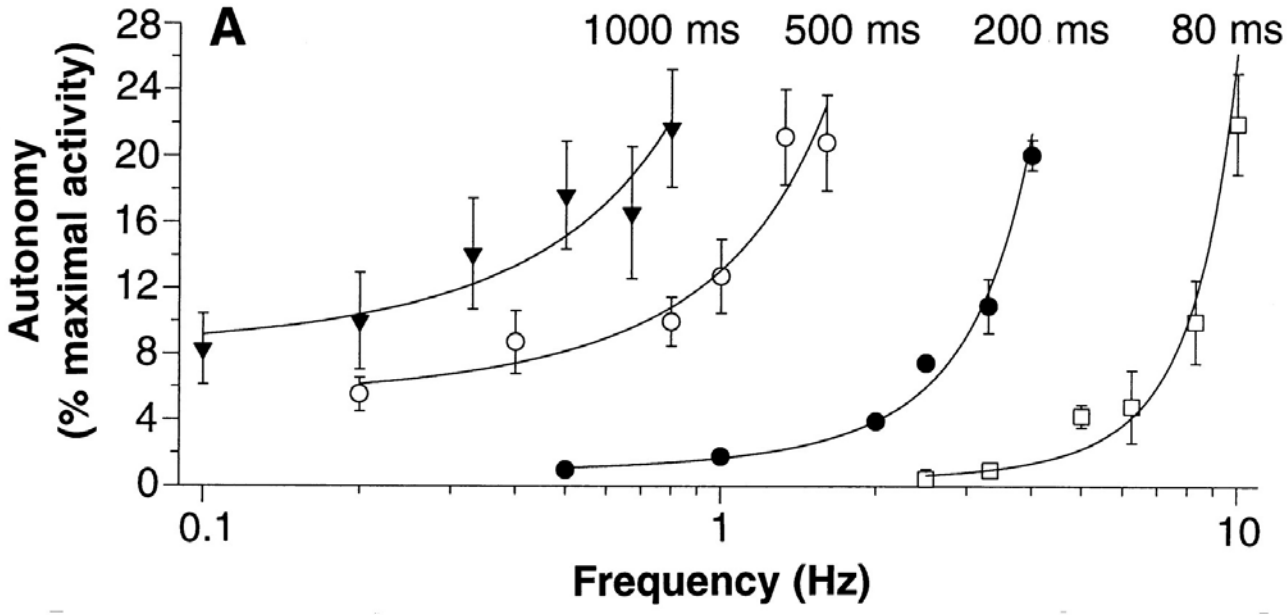


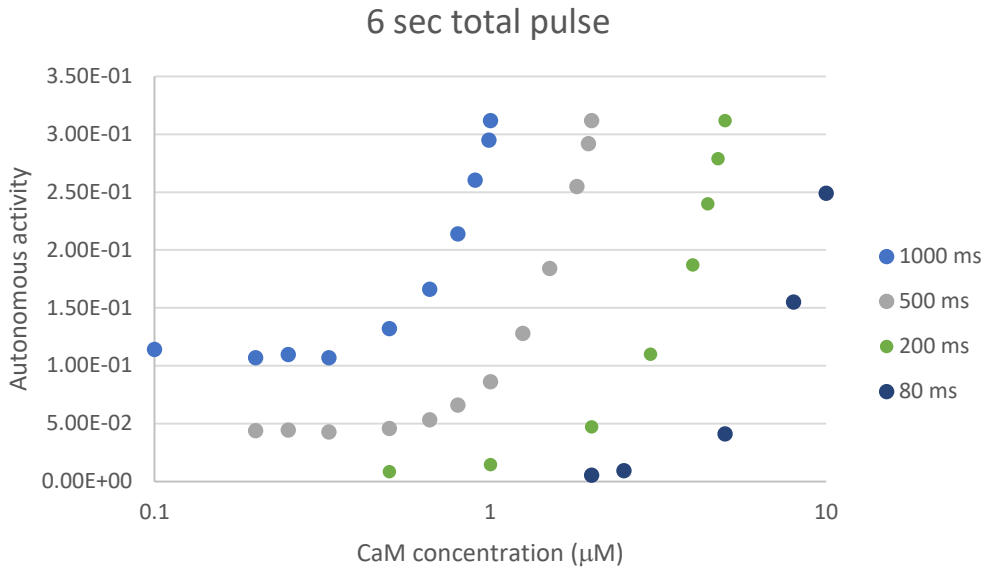


De Konnick and Schulman, 1998, Science

Baseline experiment

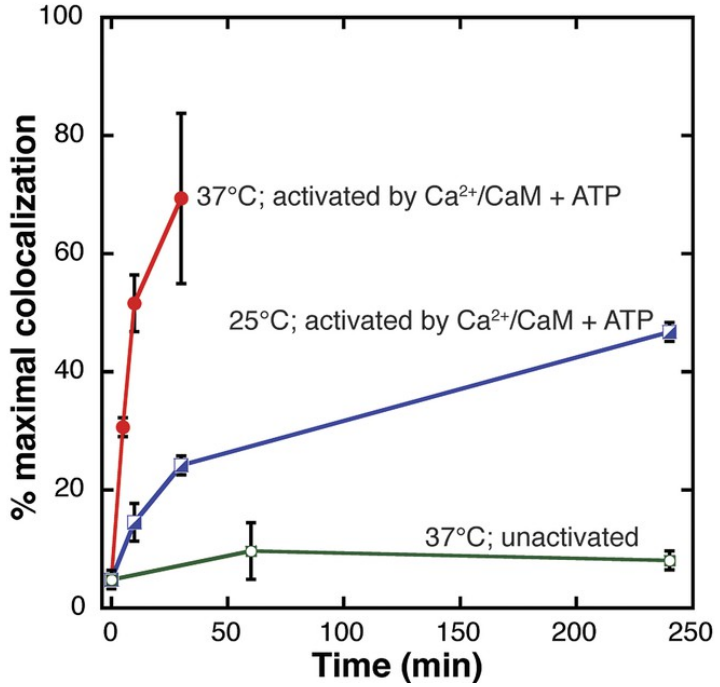
Variable pulse lengths and frequencies with total of 6 seconds

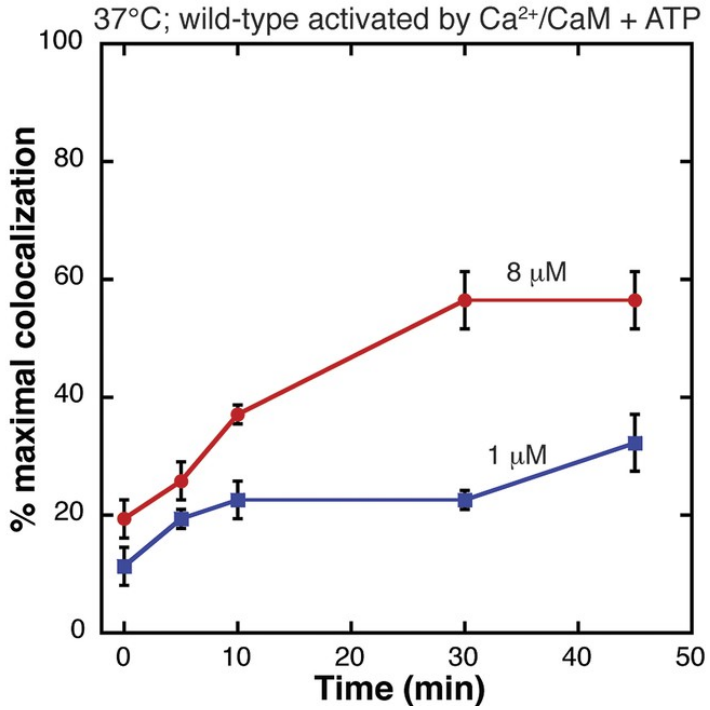


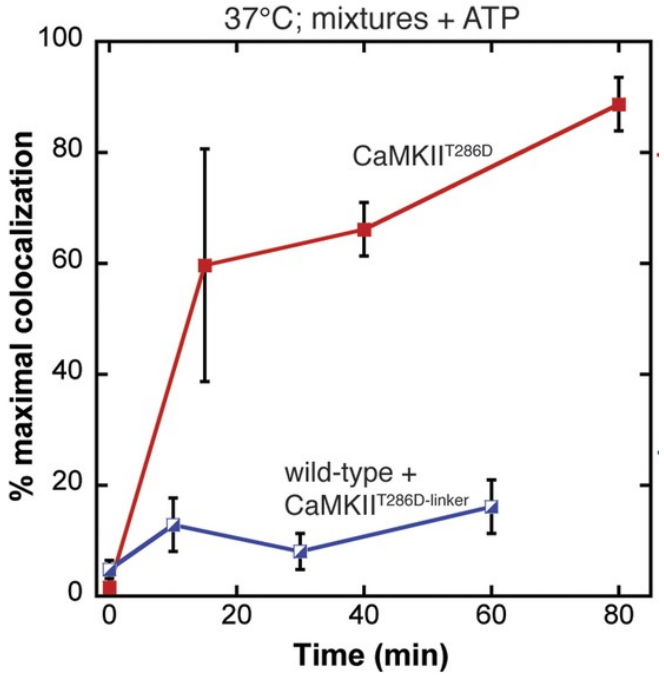


De Konnick and Schulman, 1998, Science

Fitting based on TIRF microscopy data





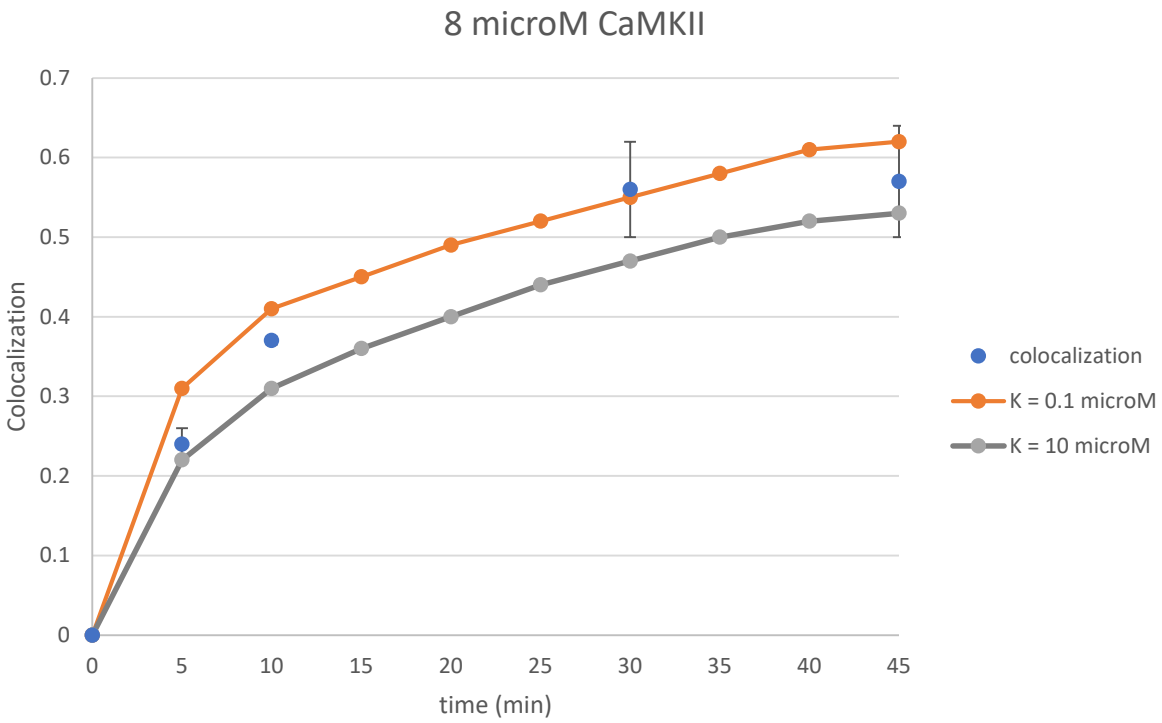


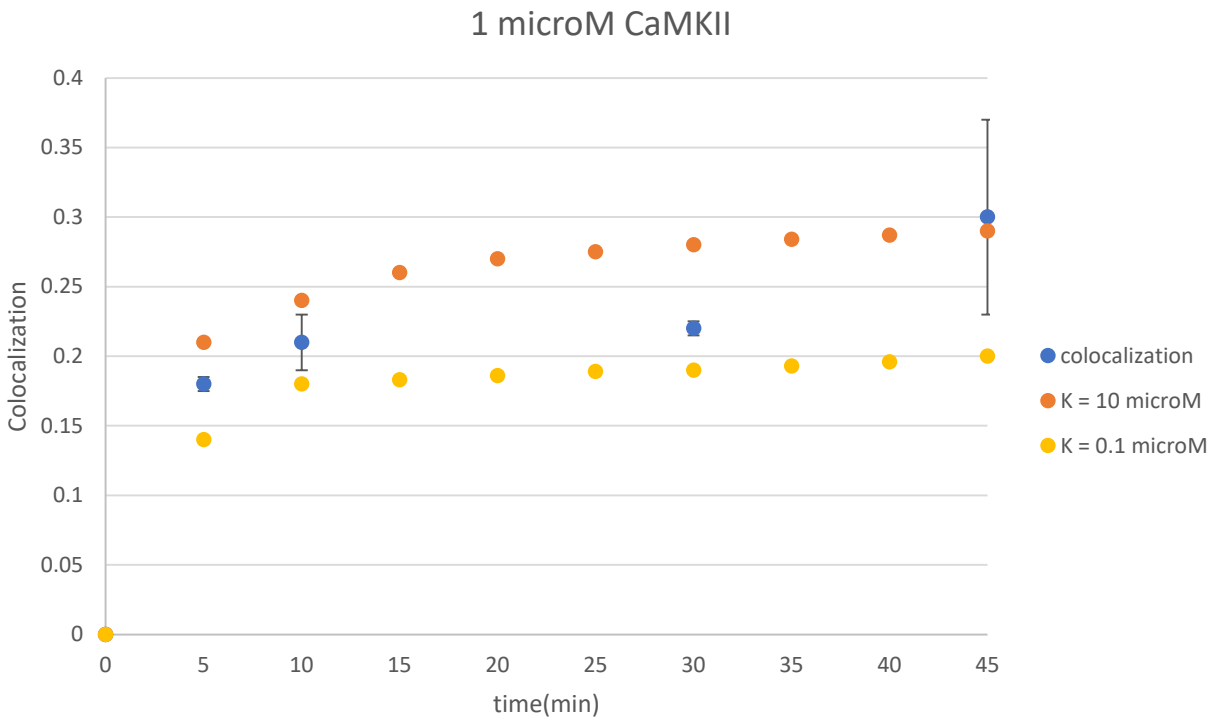
Two different fitting strategy

- Manual fitting
  - Slow
  - Non-analytic
  - Qualitative
  - Good for detecting parameter ranges

- BioNetFit
  - Genetic algorithms
  - Good for parallelization
  - Data quality?

Manual Fitting



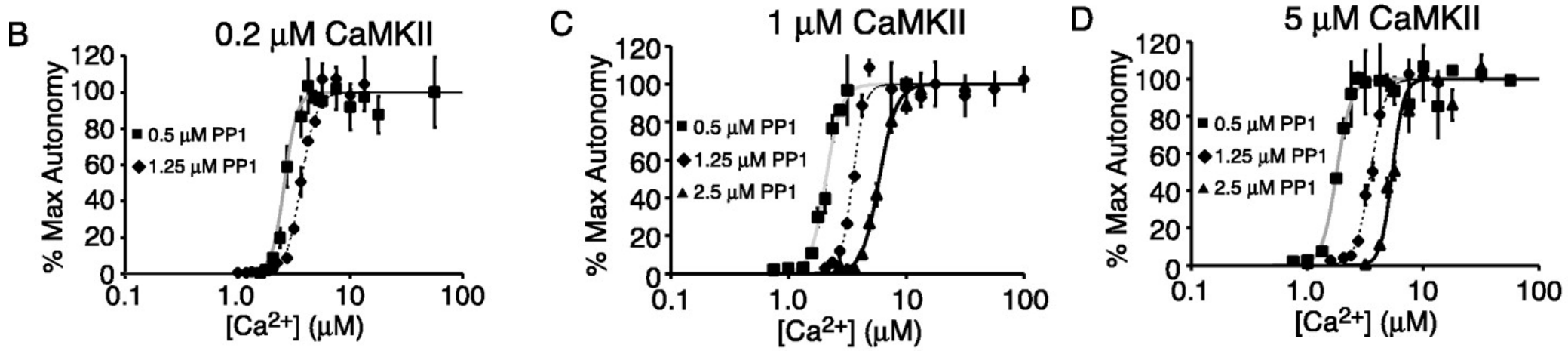


Work in progress

- Fitting with dodecamer and trimer model (2 generations per day / Bridges).

What is next?

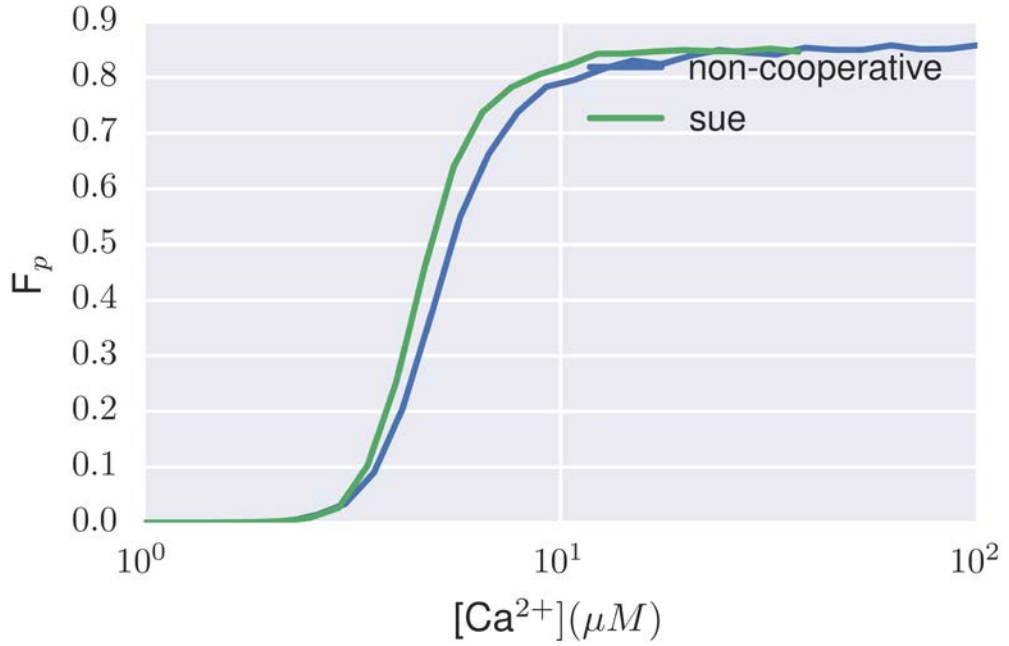
- Fitting to steady state properties based on Bradshaw et. al., 2003, PNAS.



What is next?

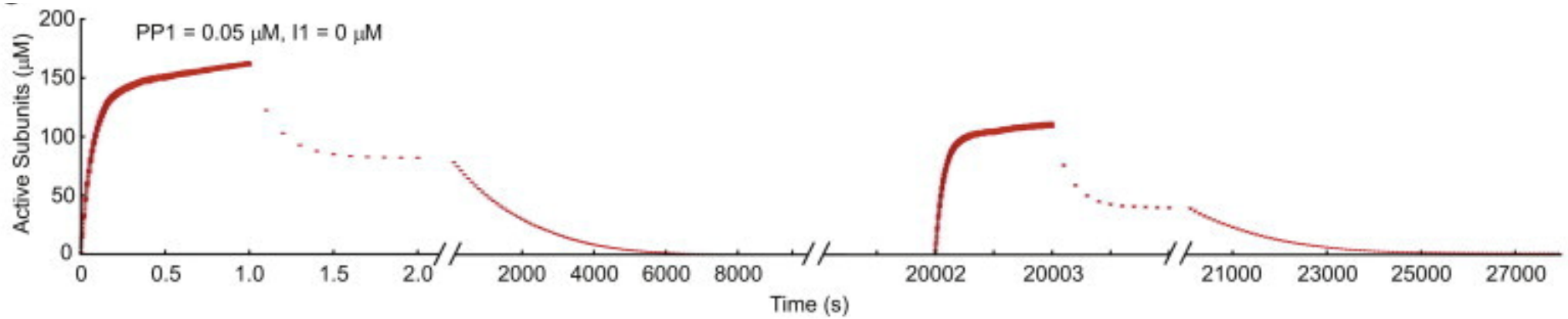
- LTP protocol with 5 ms Ca^{++} pulses with 100 Hz for 1 seconds with varying Ca^{++} pulse amplitudes.

10 seconds simulation



What is next?

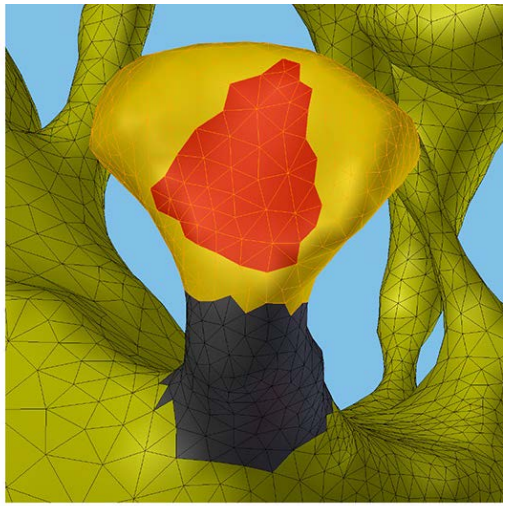
- Bi-exponential behaviour can be fixed with subunit exchange

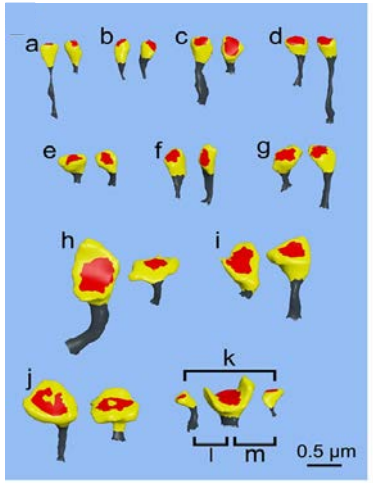


Future Direction

Volume Effects

- CaMKII is highly concentrated in PSD area.
- Diffusion of CaMKII is slow due to bulky nature of protein (~750 kDa)
- A strong variability in spine shapes may have an effect on activation.





Bartol et. al, 2015, eLife