A Rule-based Model of the Complete CaMKII Holoenzyme

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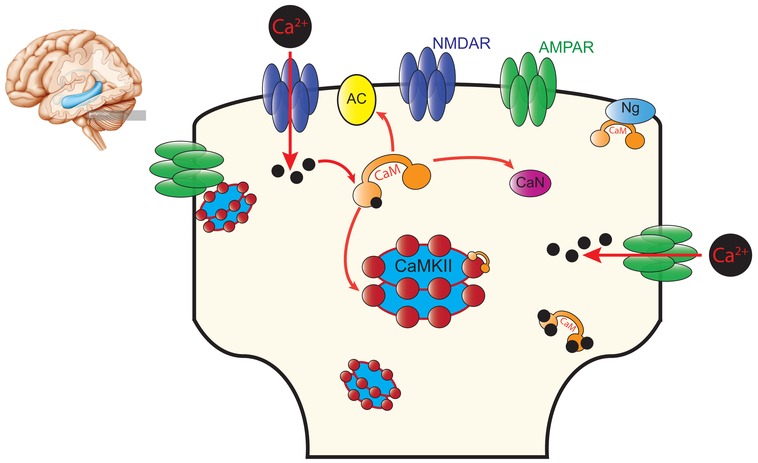
Motivation

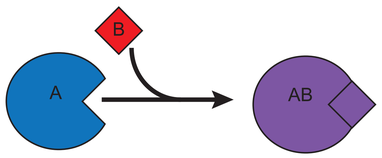
Neurons are connected by specialized structures called synapses, which are thought to facilitate memory formation by a process called synaptic plasticity. During synaptic plasticity, synapses dynamically shift in size and conductivity. These shifts are controlled within the synapse by calcium-dependent proteins, and essential among these is the 12-subunit enzyme CaMKII. When protein signaling pathways involving CaMKII become dysregulated, they can lead to neurological disorders such as Alzheimer's Disease.

A CaMKII subunit can exist in variety states: these include open or closed, active or inactive, ligand-bound or ligand-unbound. Critically, a subunit's states can depend on its neighboring subunits.

Modeling CaMKII states for all twelve subunits over time and space by typical systems of differential equations is computationally intractable. Without rule-based methods, our model would require 10^{20} lines of code.

Signaling in the Dendritic Spine





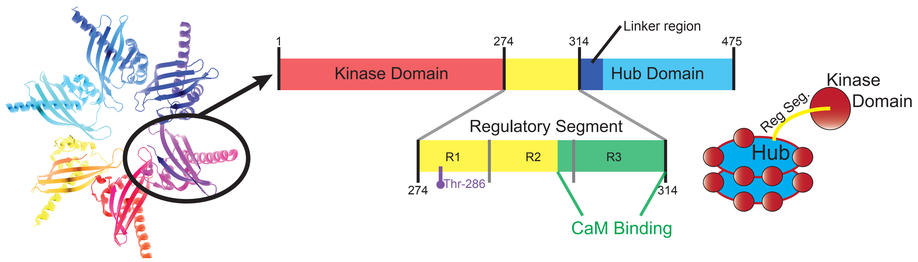
$$A + B \xrightarrow{k} AB$$

$$\frac{d[A]}{dt} = -k[A][B] \qquad \frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[AB]}{dt} = k[A][B]$$

For CaMKII, we'd need $\mathbf{10^{20}}$ equations like these!

How to Model Each CaMKII Subunit?



Reactions Only Occur if Rules Allow

Rule:	Event:	Allowable IF:	
Subunit Docking	Undock	Subunit is Docked	Undock ⇄ Dock
	Dock	Subunit is Closed	
Subunit Opening	Open	Subunit is Undocked	Open ⇄ Close
Open = "Active"	Close	Subunit is Unbound OR Non-Phosphorylated	
CaM Binding	Bind	Subunit is Open	Bind ⇄ Un-Bind
	Un-Bind	Subunit is Bound	
Auto-Phosphorylation	Phosphorylate	Subunit is Active AND Neighbor Subunit is Active	Phos. →
	De-Phosphorylate	Subunit is Phosphorylated AND PP1-bound	
Phosphatase Access	PP1-Bind	Subunit is Phosphorylated AND Unbound	

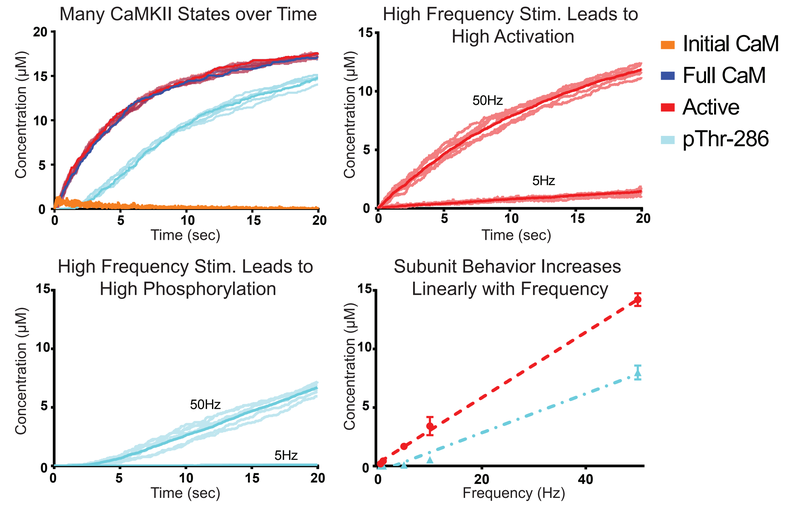
Conclusions

-Rules allow models of CaMKII as a complete, multi-state holoenzyme.

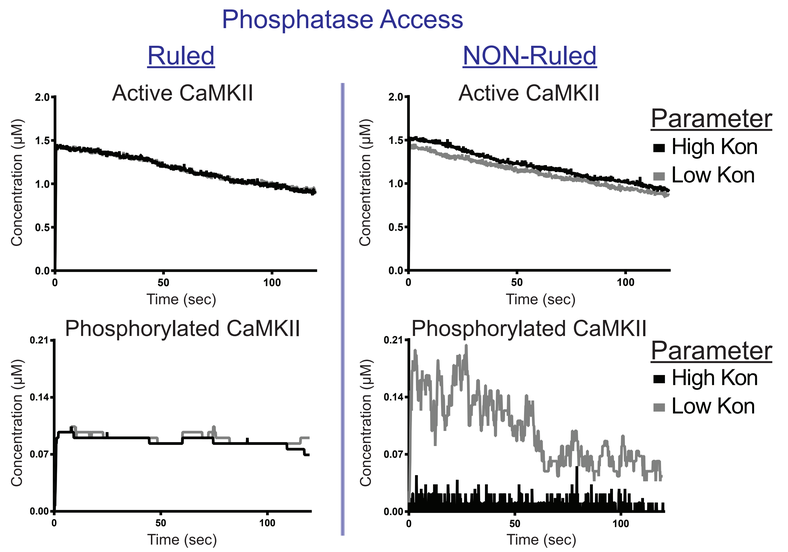
-Incorporating rule-based CaMKII into larger models of protein networks will increase their accuracy at little added computational expense.

-Future models with rule-based CaMKII will help characterize the molecular mechanisms of learning and memory formation and identify potential therapeutics for neurological diseases.

Rule-based Results Match Expectation



Rules Make Parameters Robust



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