# CaMKII as a molecular switch: from digital to analog

Mariam Ordyan, postdoc, Sejnowski lab

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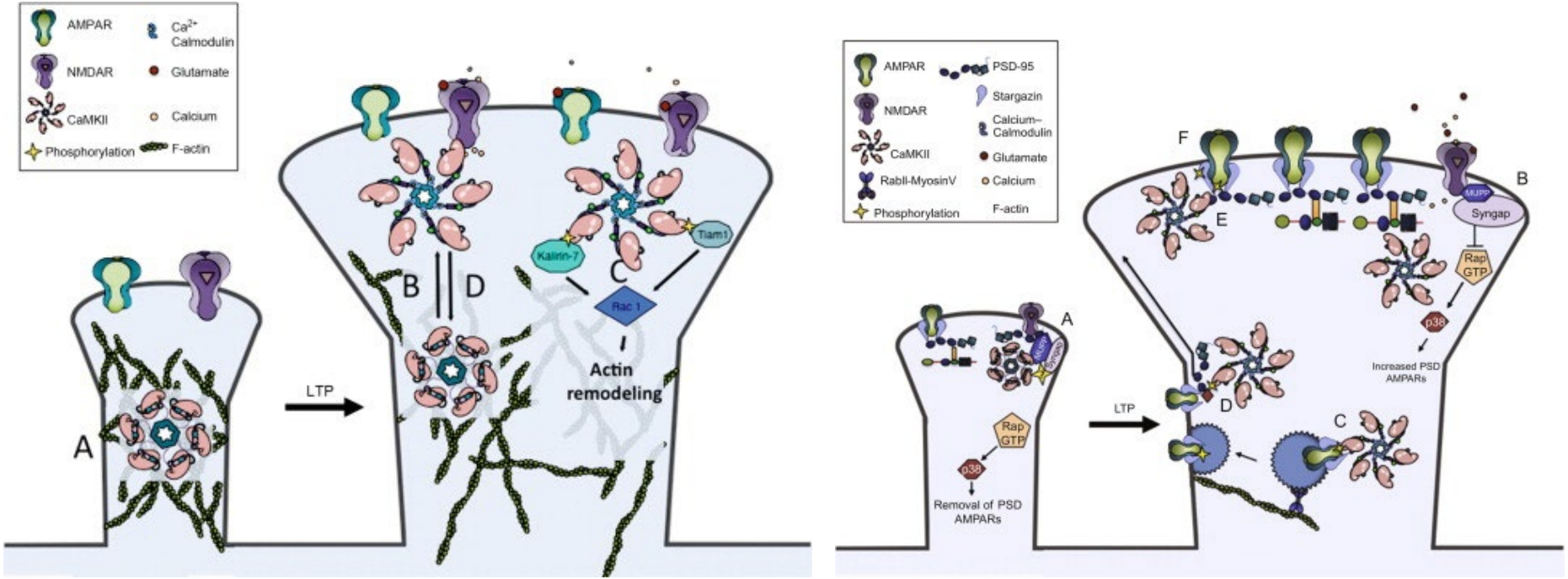
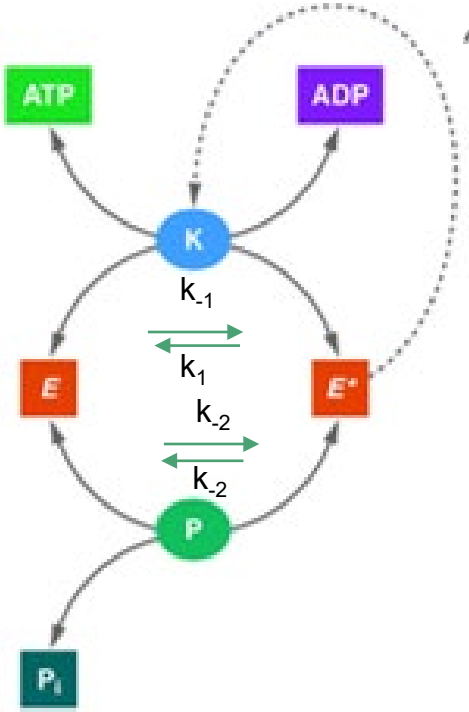
# Why CaMKII?




Shonesy, Brian C., et al. "CaMKII: a molecular substrate for synaptic plasticity and memory." *Progress in molecular biology and translational science*. Vol. 122. Academic Press, 2014. 61-87.

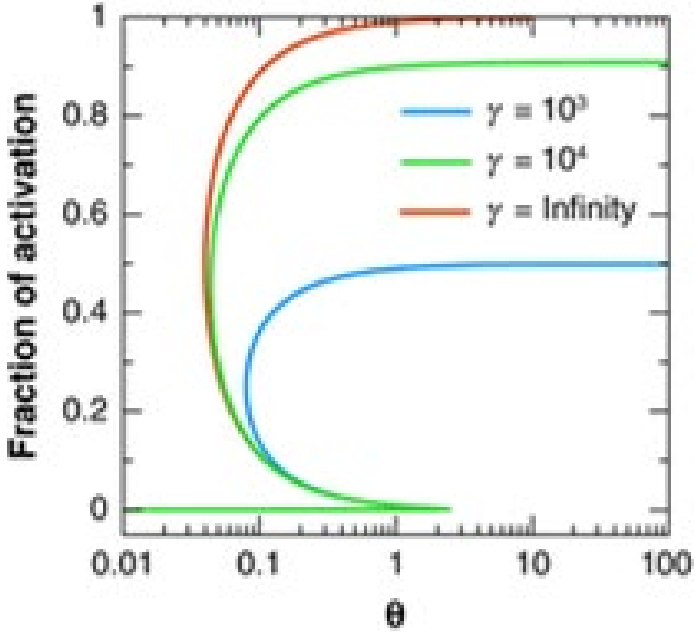
# Phosphorylation, free energy and switchlike behaviour




$$\gamma = \frac{k_{-1}k_{-2}[ATP][ADP]}{k_1 k_2 [ATP]}; \quad \Delta G = k_B T \ln \gamma;$$

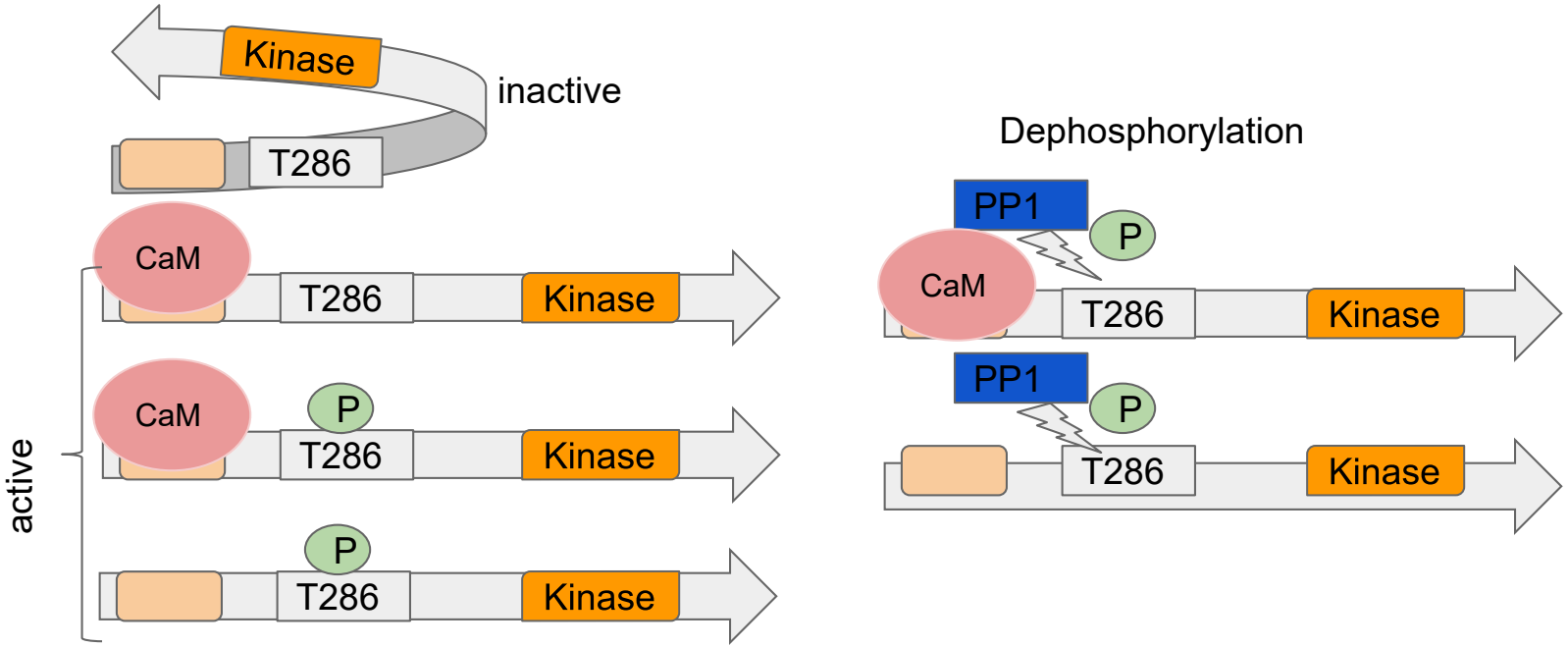
$$\theta = \frac{k_1[K]}{k_2[P]}$$

Inside the cell there is no equilibrium, **γ** >> 1 => ΔG >>0, and the fraction of activation shows hysteresis, there are multiple steady states for a range of $\theta$

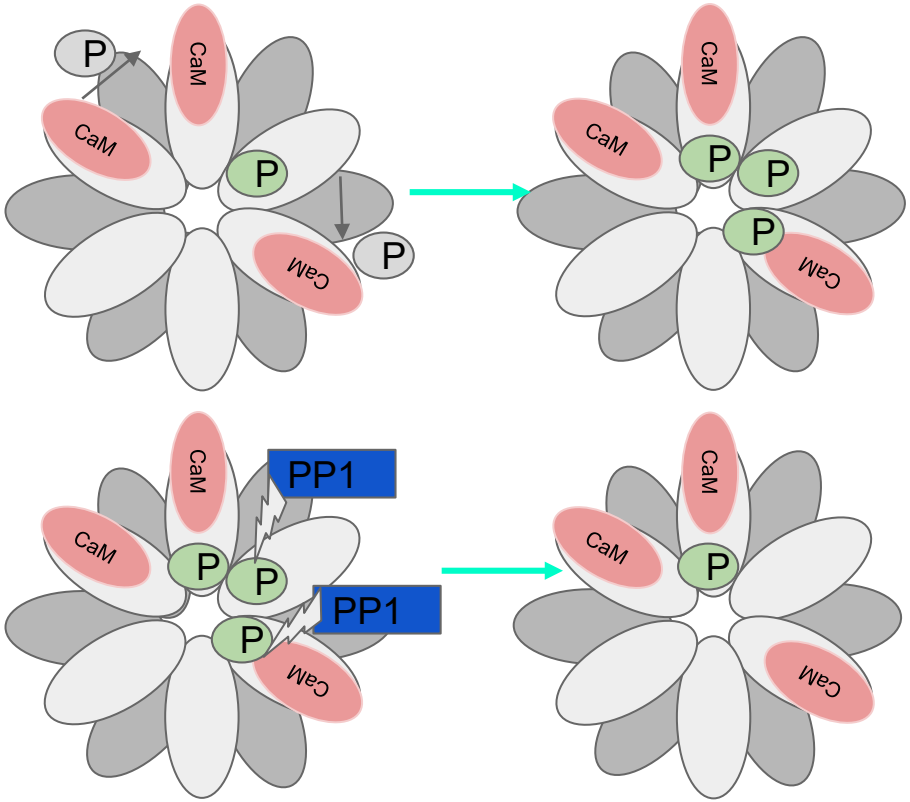



Hong Qian "Phosphorylation energy hypothesis: open chemical systems and their biological functions" *Annual Review of Physical Chemistry*. Vol. 58. Academic Press, 2007.

# CaMKII: a closer look (monomers)



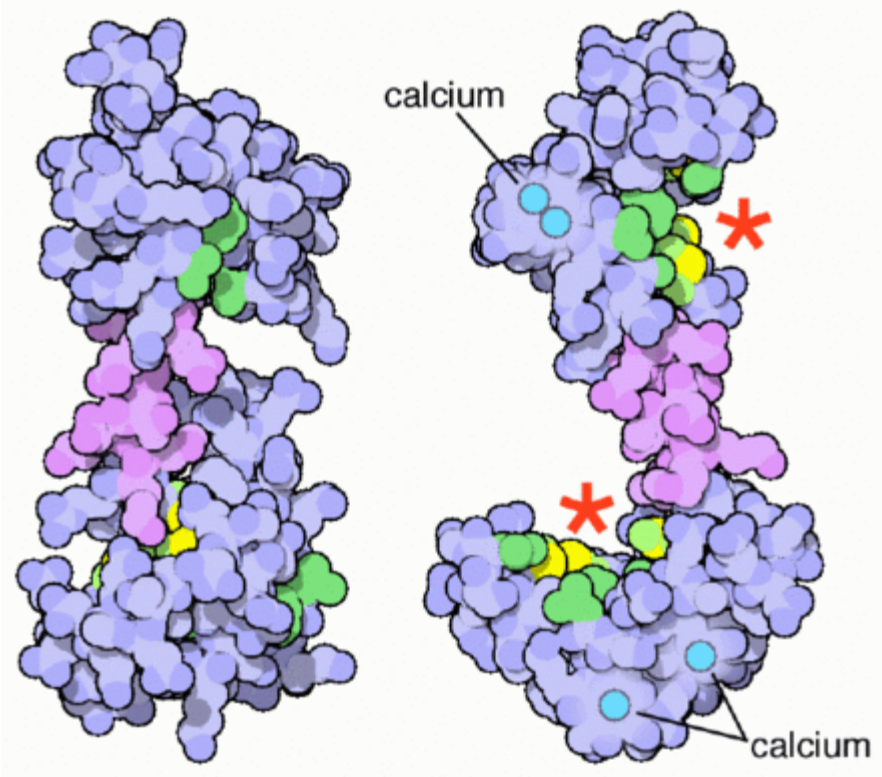
# CaMKII: a closer look (holoenzyme)




Questions worth exploring:

1. How does the behaviour of a mix of individual CaMKII monomers differ from that of the holoenzymes?
2. What can we learn about the holoenzyme by studying the monomers?
3. What attributes of the holoenzyme cannot be explained by our understanding of the monomers and need a more holistic approach?

# Calmodulin




From Wikipedia

1. CaMKII monomers are activated by Calmodulin (CaM) which has 4 Ca binding sites. Depending on how many Ca ions are bound to CaM, it's binding constant to CaMKII as well as CaMKII (substrate, but not kinase) phosphorylation rate change. This makes Ca concentration a crucial variable.
2. Ng is a CaM binding protein, which dramatically decreases its affinity for Ca. In this model we assume that Ca and Ng are binding CaM mutually exclusively

# Rule Based modeling with BioNetGen

Set of rules for you model

Generate network (population based)

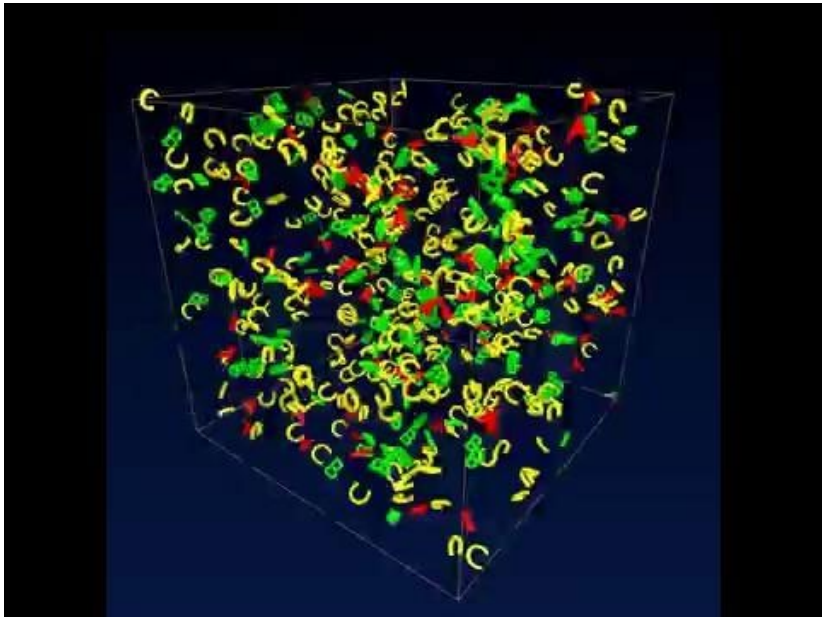
ODE's

Network Free Simulation (agent based)

Monte Carlo method

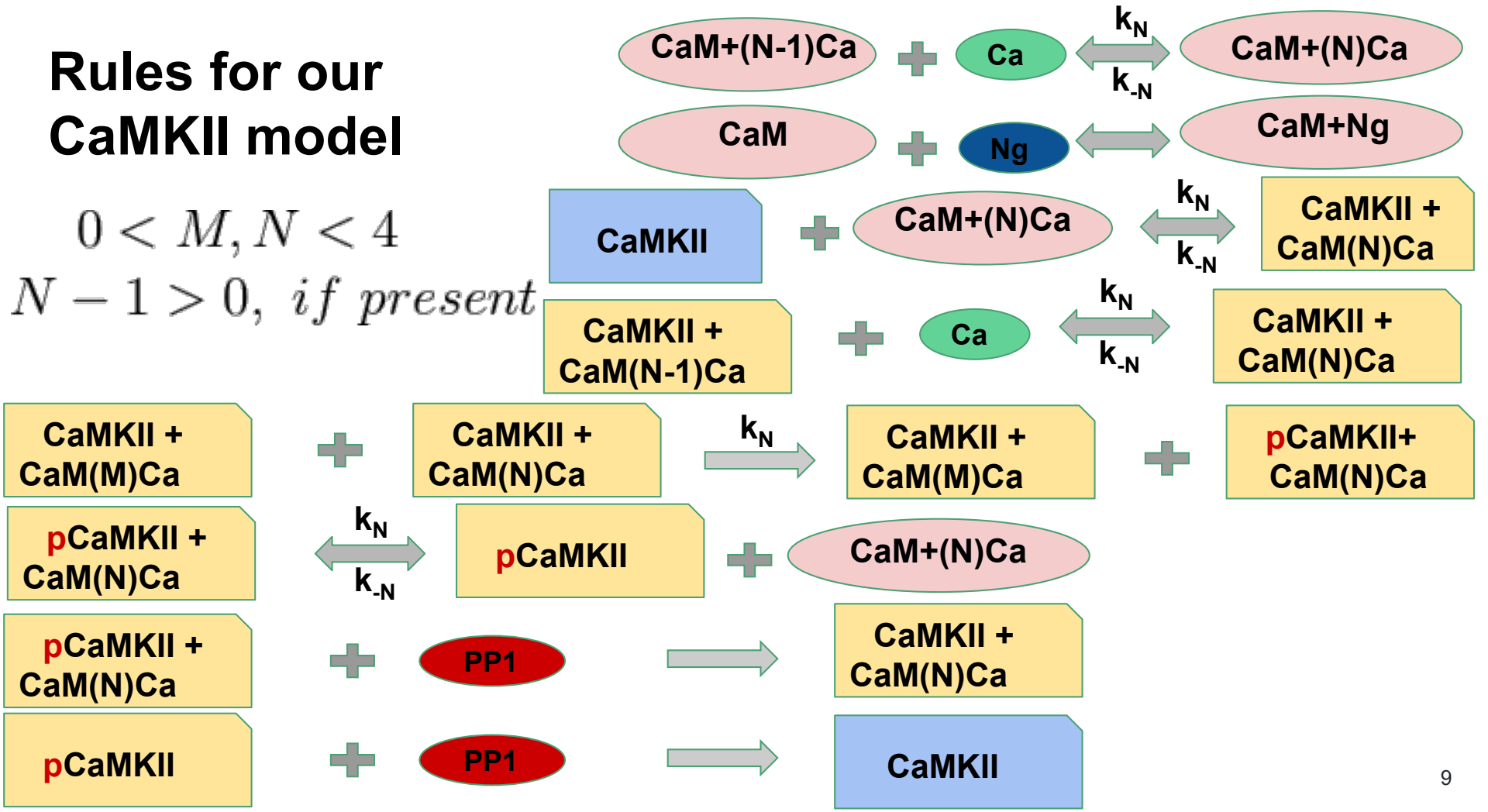
$$A + B \xrightarrow{k} C,\ k = 10^9\ M^{-1}s^{-1}$$

$$C \xrightarrow{k_1} 0, k_1 = 1000\ s^{-1}$$



# Rules for our CaMKII model

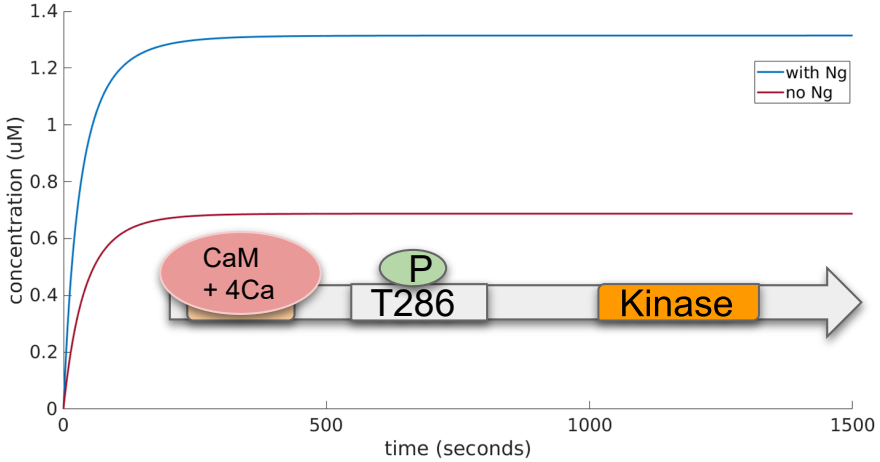
$$0 < M, N < 4$$
$$N - 1 > 0, \; if \; present$$

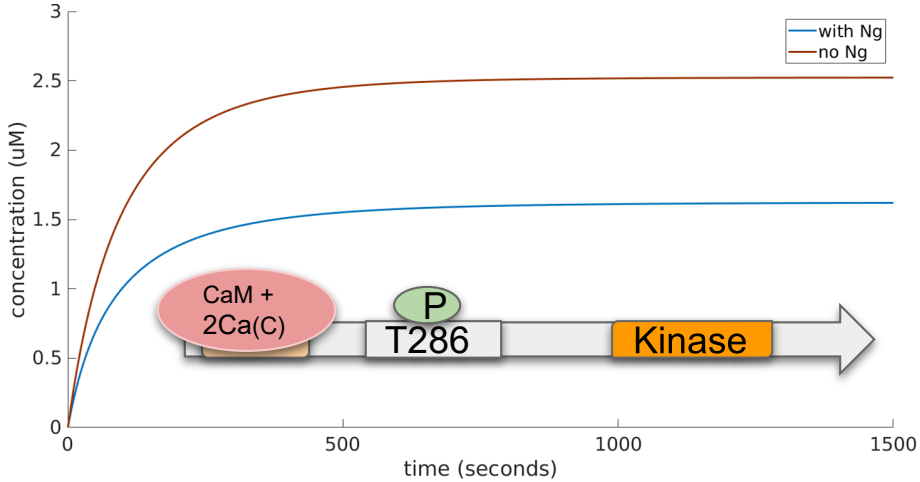


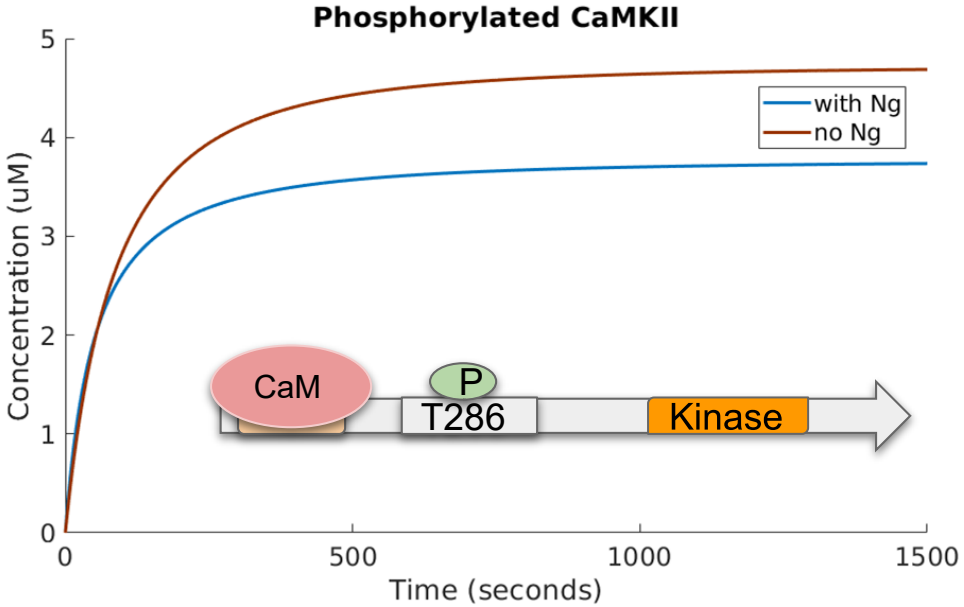
# Background information and variables of interest

1. PP1 is the phosphatase that dephosphorylates CaMKII, making the cycle complete.
2. We care not only about the final or peak concentrations of phosphorylated CaMKII, but the dynamics of the reactions.
3. Pepke et al did thorough research on CaMKII monomers, and found all the relevant reaction rates. (Pepke et al. *PLoS computational Biology,* 2010)
4. However this model included only CaM, CaMKII and Ca, disregarding the effects of the scaffolding molecule Ng, and dephosphorylation. This is a good place to start...

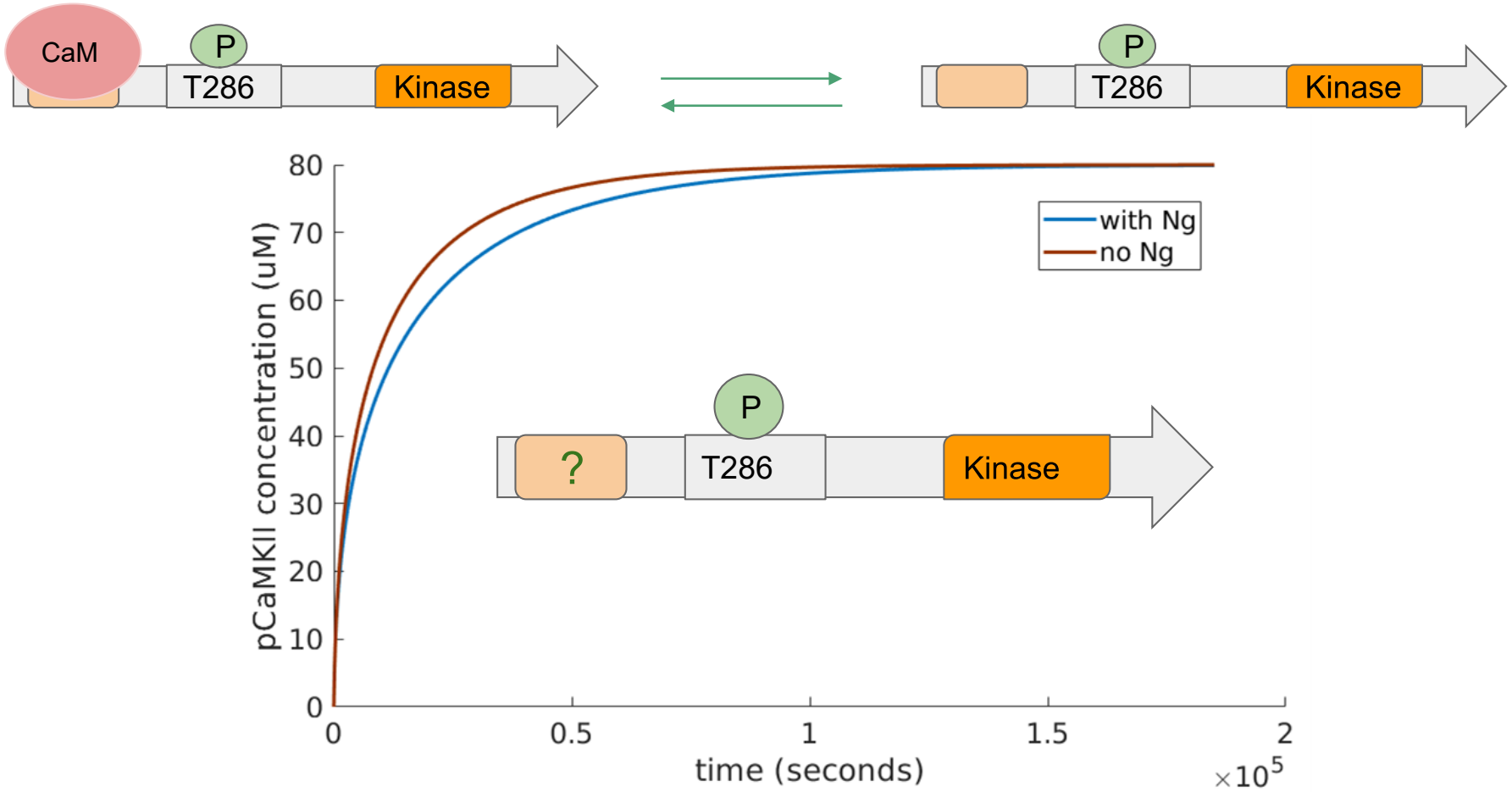
# Adding only Ng dramatically affects the dynamics



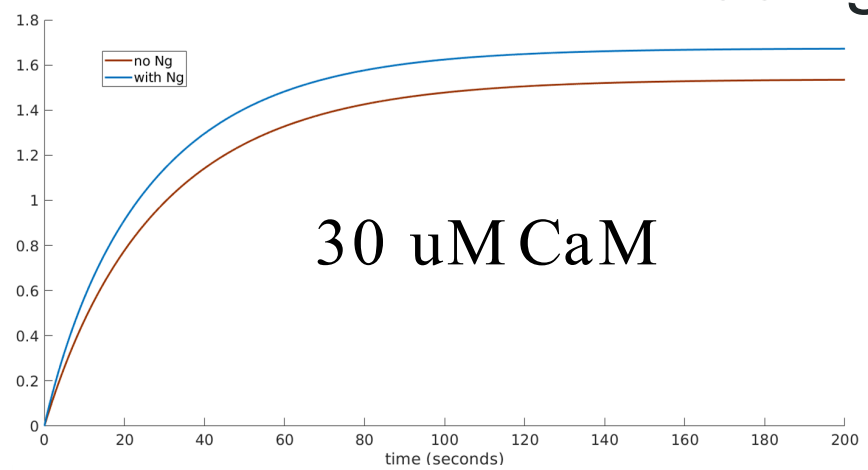



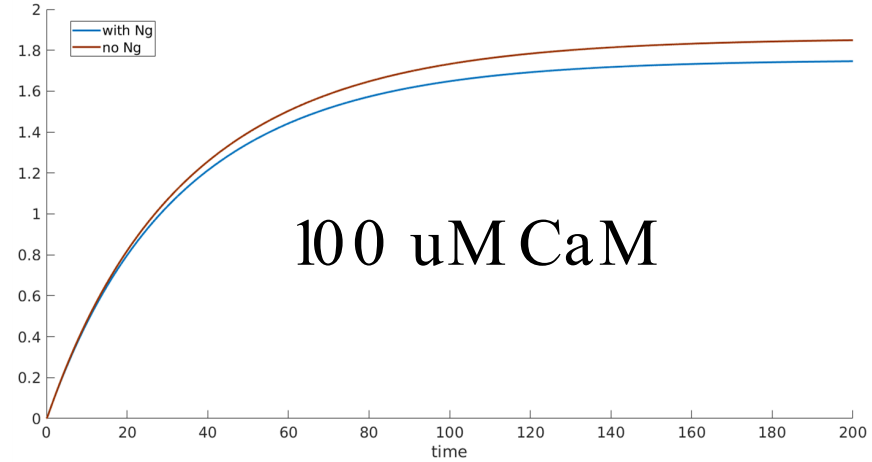



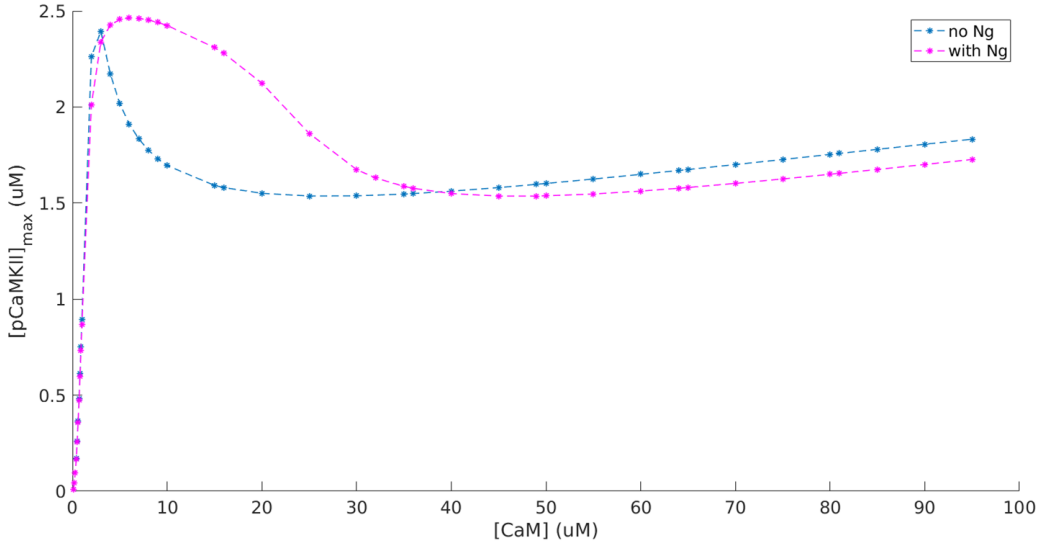
# A missing step: relevant for our timescales



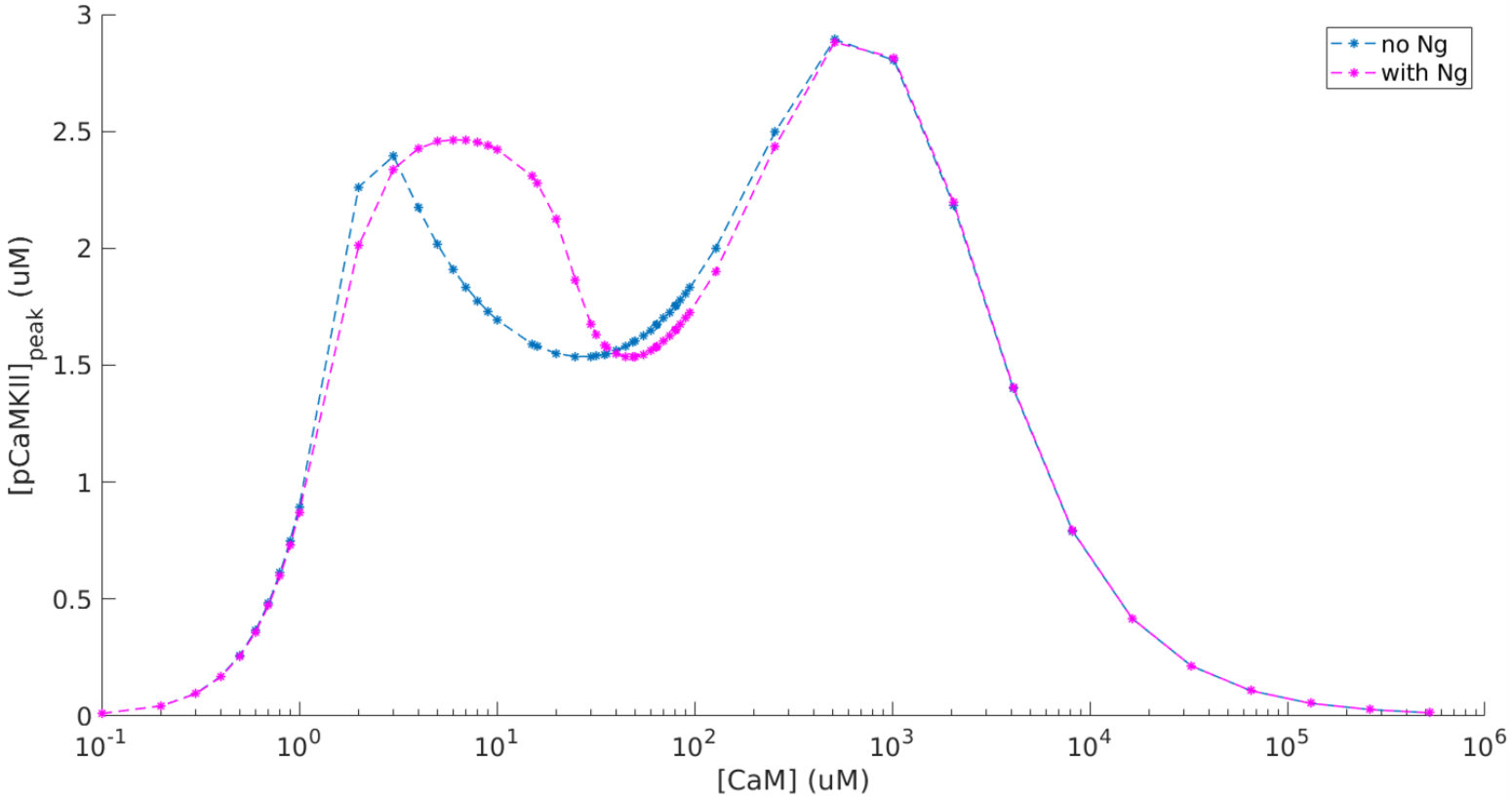
# Adding the dephosphorylation step



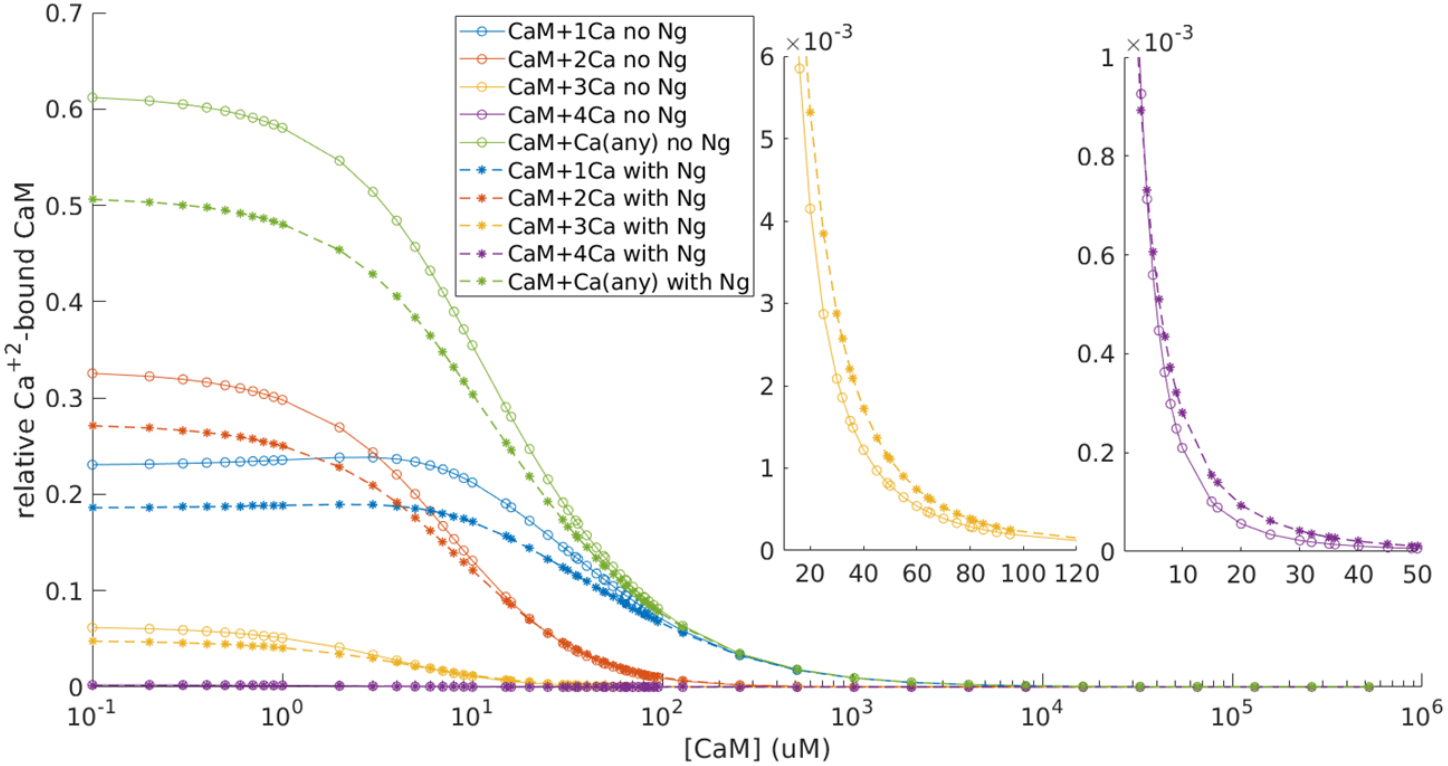



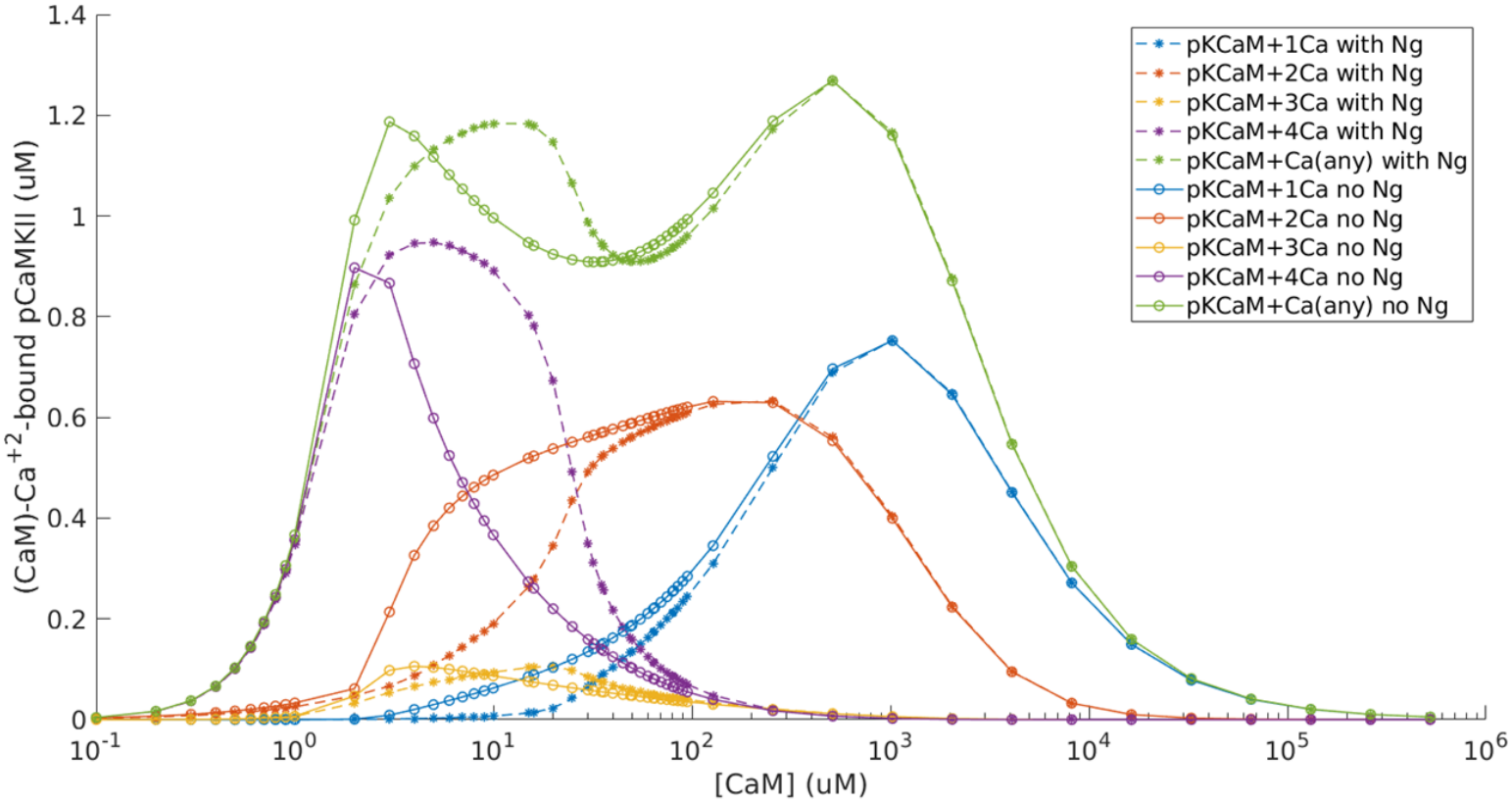
# Dose response over a large range



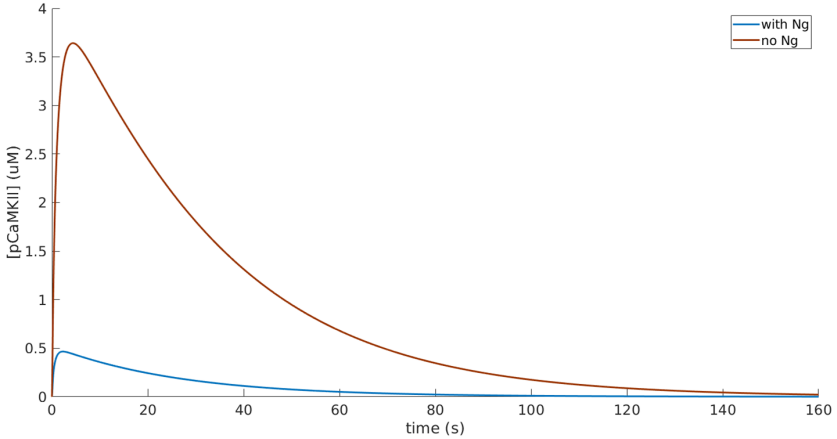
# Ca-bound CaM dependence on [CaM]

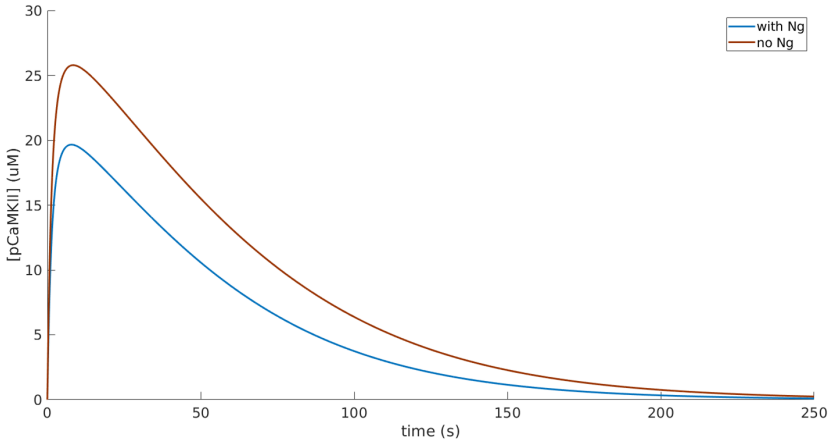


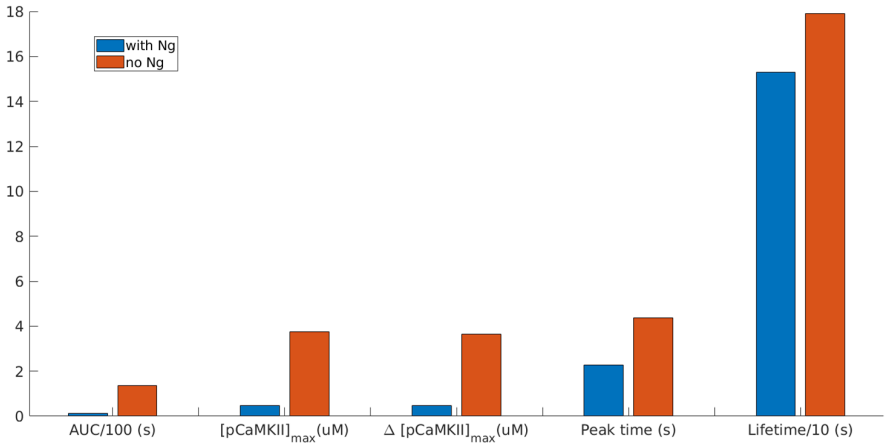
# Ca-bound pCaMKII dependence on [CaM]

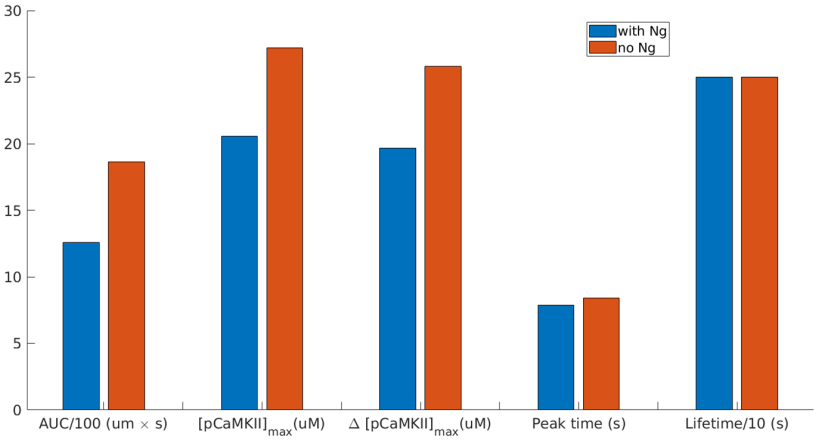


# Response to 10uM (‘measured’) spike

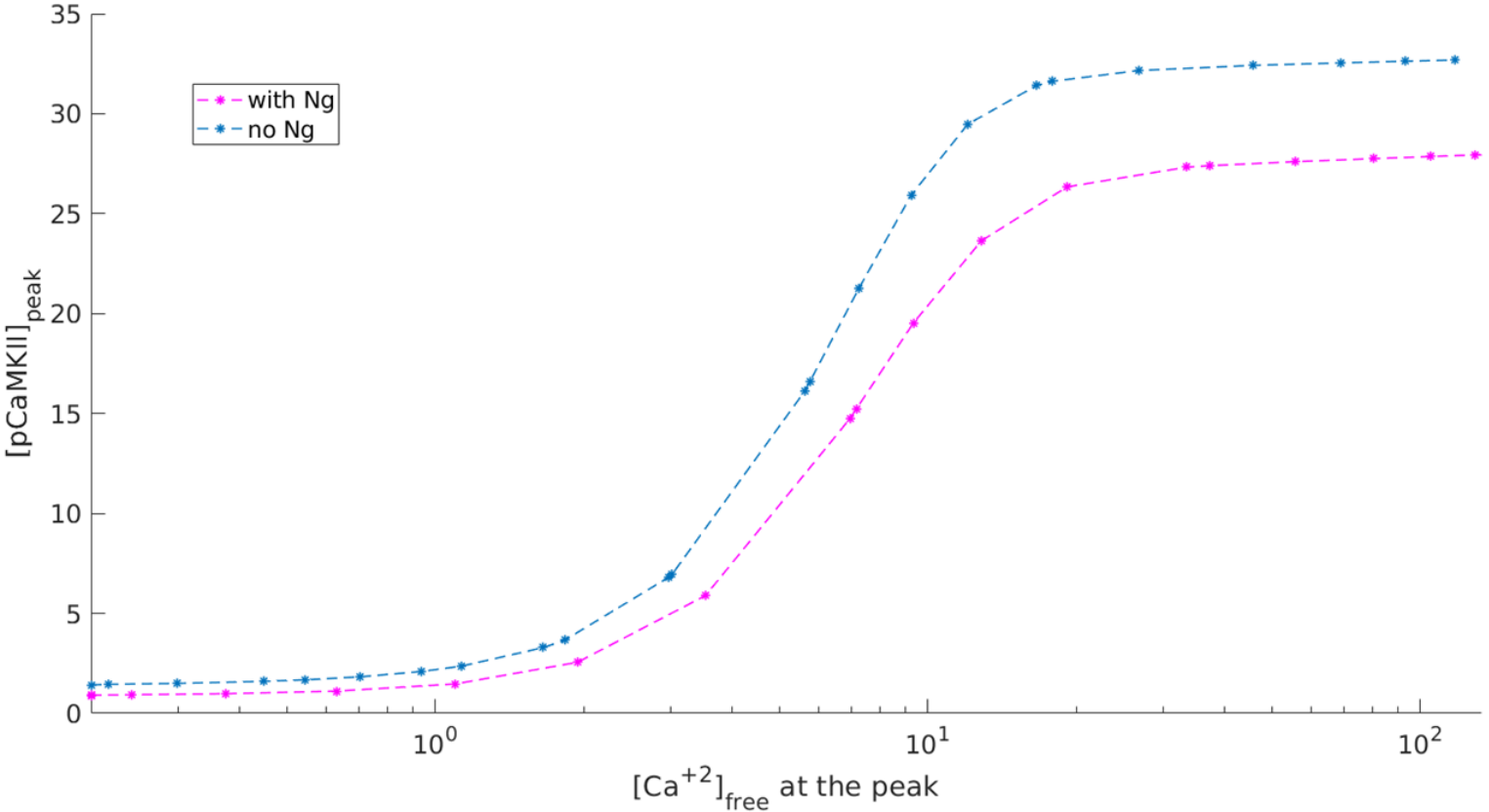


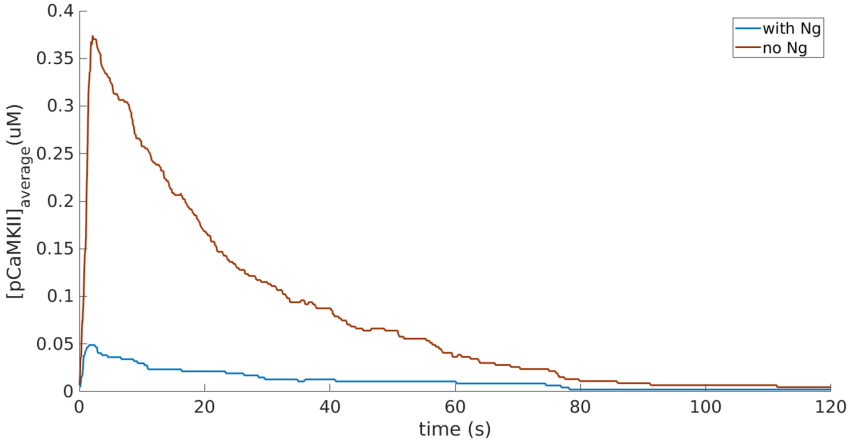



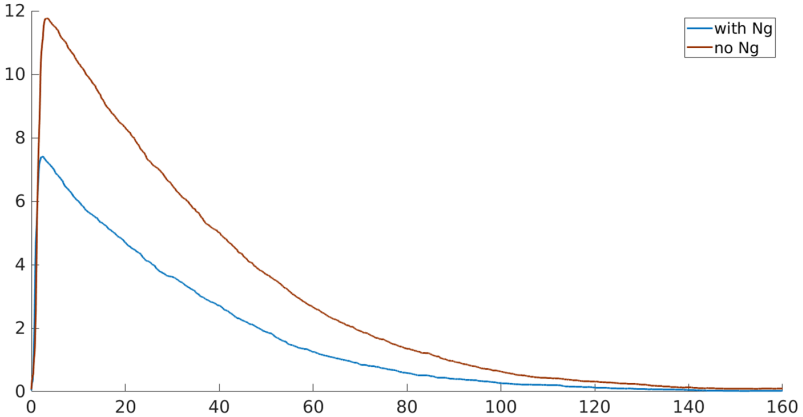



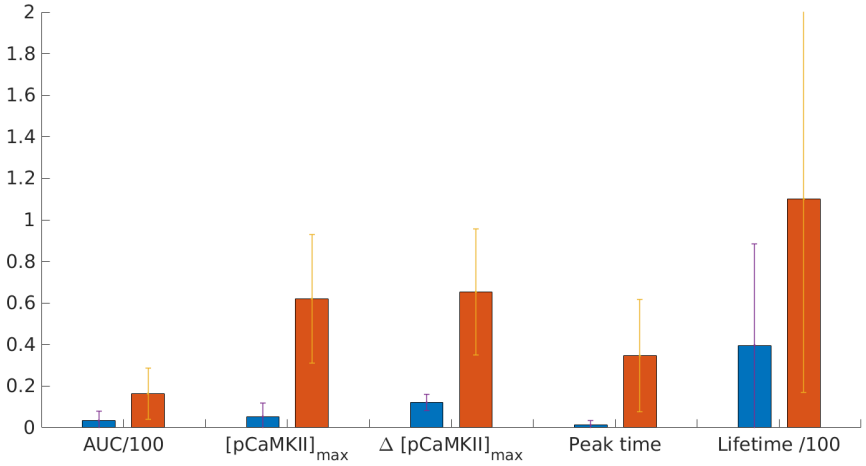
# Dose response with a Ca Spike

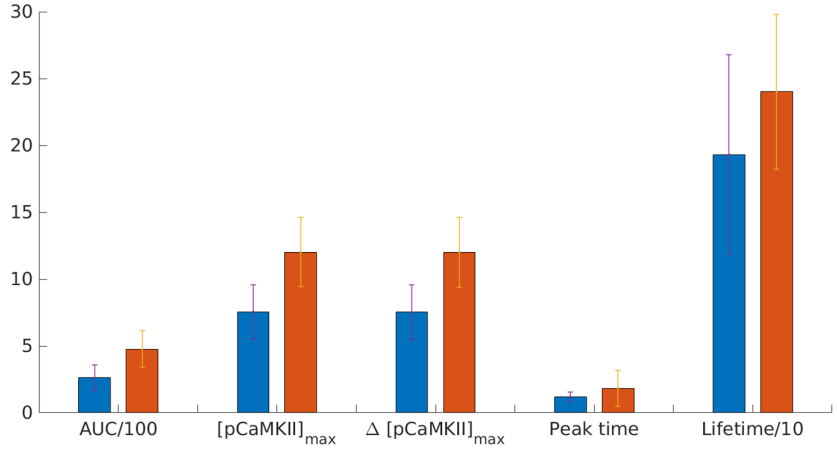


# What about the holoenzyme?

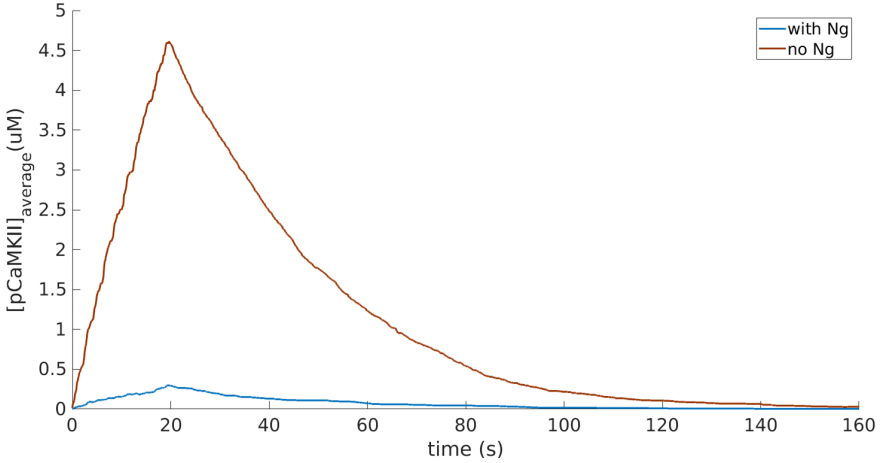


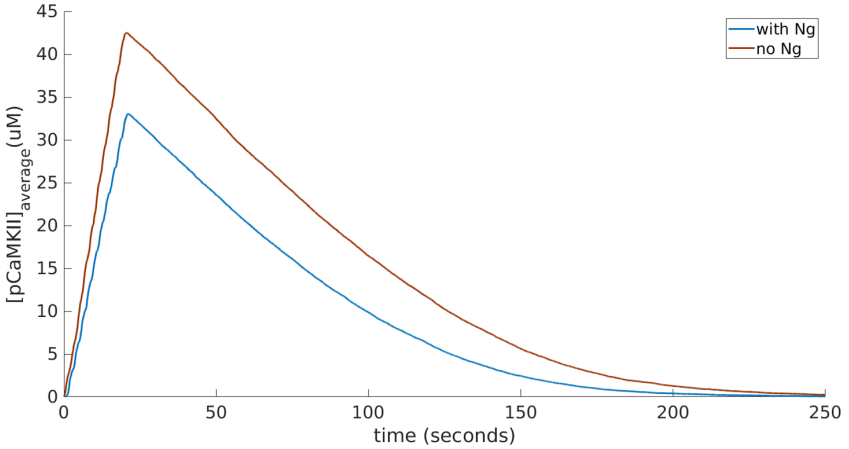



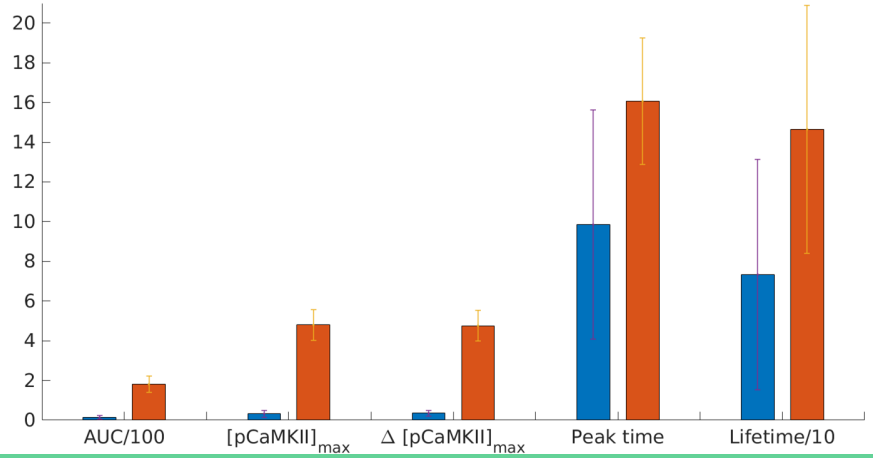



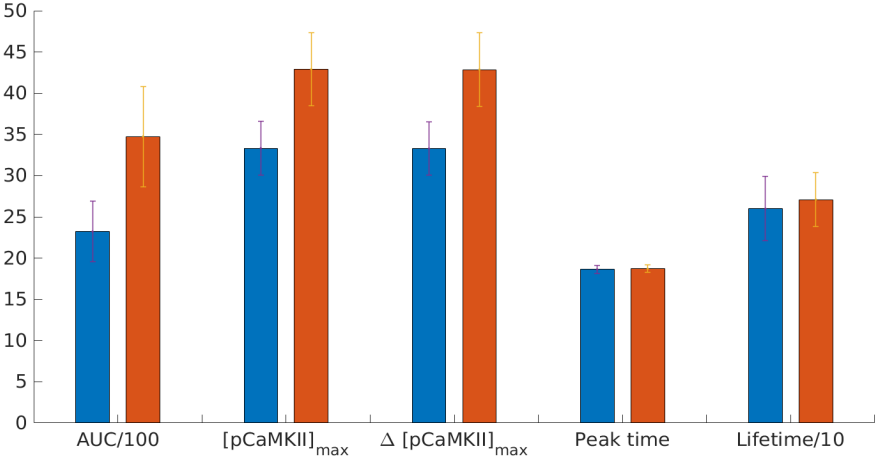



# 10 Ca pulses (at 0.5 Hz)

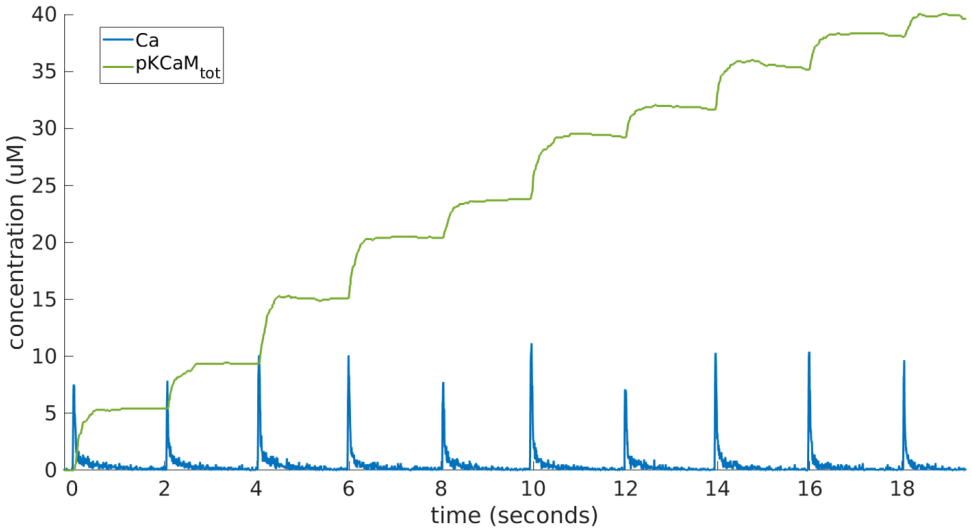


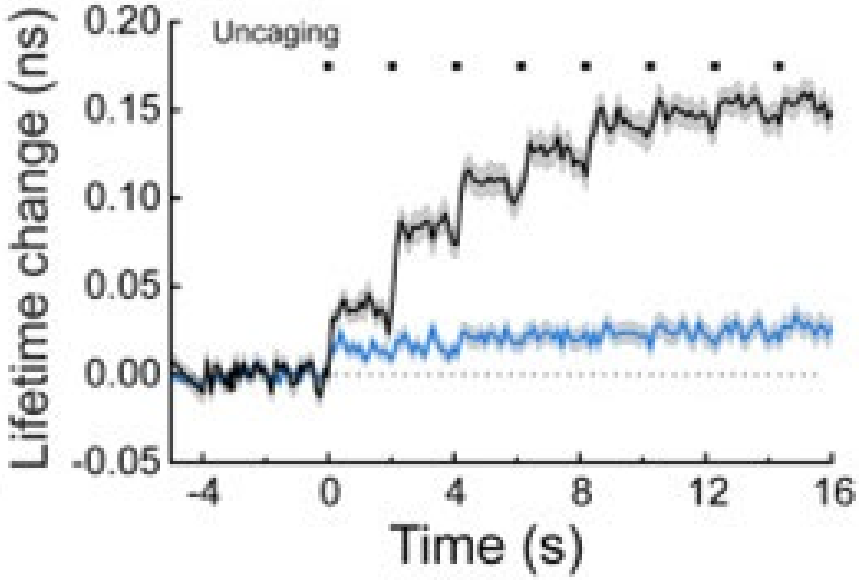



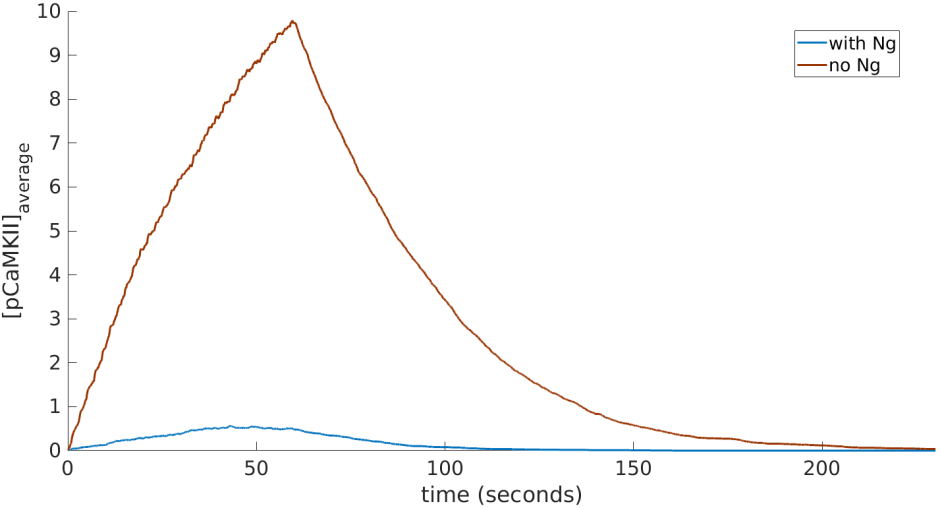
# CaMKII as a leaky integrator

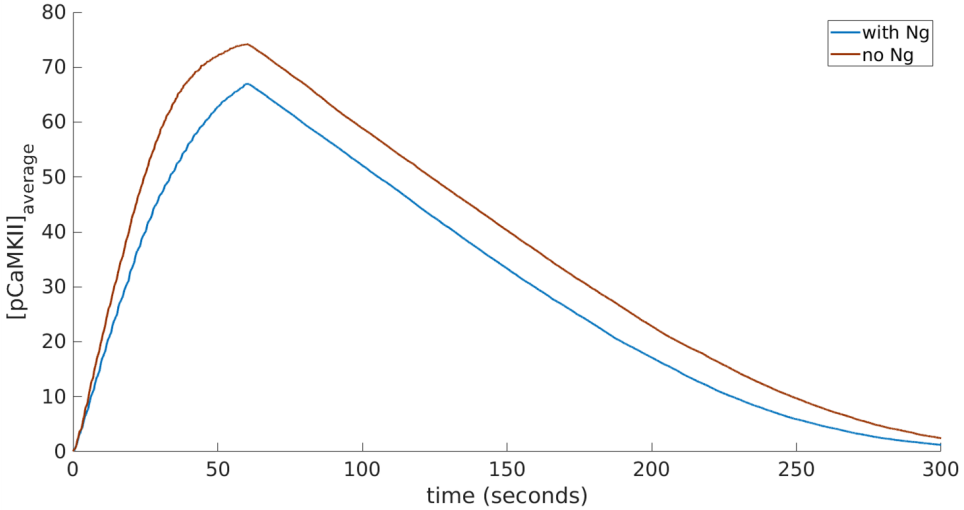



J. Chang et al “CaMKII Autophosphorylation is Necessary for Optimal Integration of $Ca^{2+}$ Signals During LTP Induction, but not Maintenance” *Neuron,* 2017

# 30 Ca pulses (at 0.5 Hz)



# So long and thanks for all the fish...

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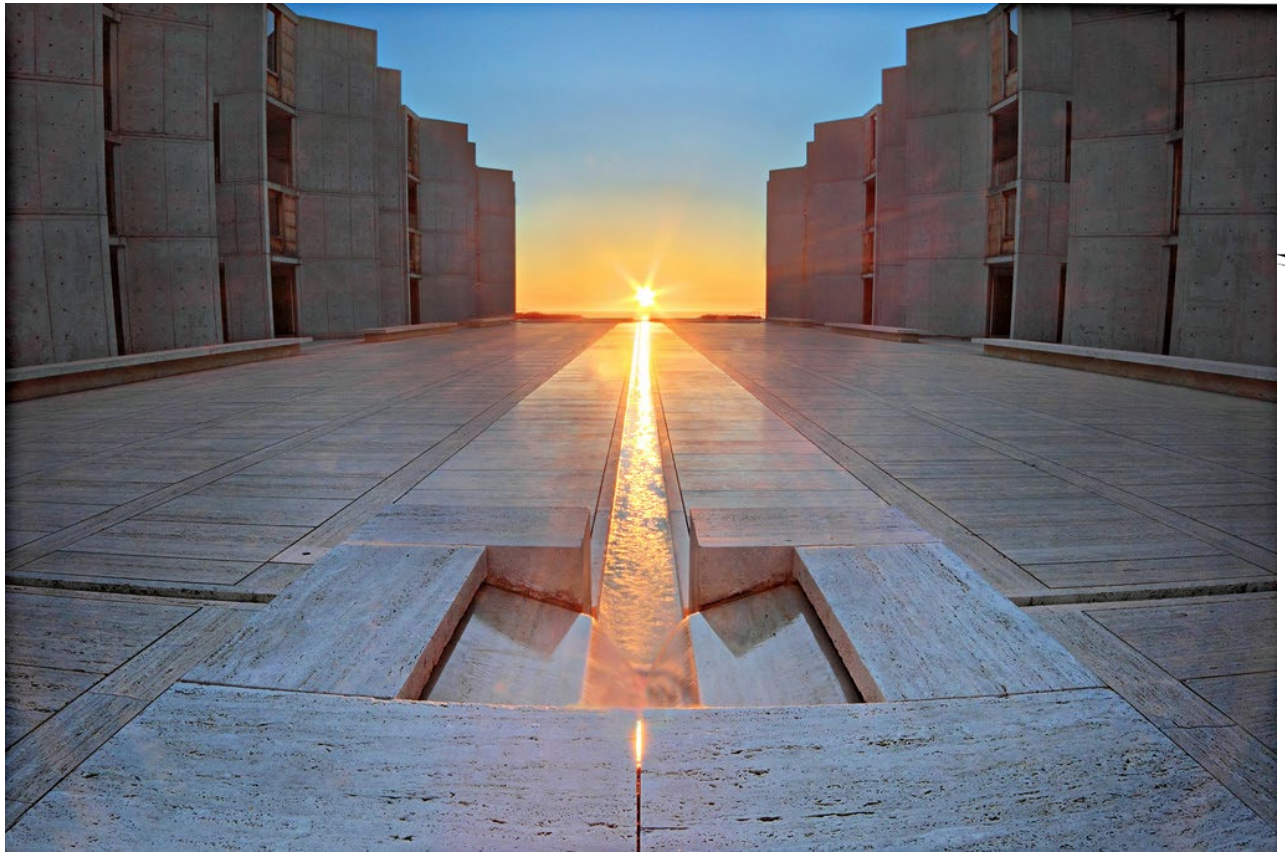

Tom Bartol

Terry Sejnowski

UCSD

Miriam Bell

Padmini Rangamani

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