

The diagram illustrates the Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release (CICR) pathway. At the top, Ca<sup>2+</sup> (represented by a yellow circle) and CaM (represented by a yellow rectangle) bind to a blue square, which then activates CaM\* (yellow rectangle). CaM\* activates three CaMKII molecules (yellow rectangles). The first CaMKII molecule is activated by a blue square with a white triangle (inhibition) and a blue square with a white circle (activation). The second CaMKII molecule is activated by a blue square with a white triangle (inhibition) and a blue square with a white circle (activation). The third CaMKII molecule is activated by a blue square with a white triangle (inhibition) and a blue square with a white circle (activation). The second CaMKII molecule is phosphorylated to CaMKII(2P) (yellow rectangle with a white circle containing '2P'). The third CaMKII molecule is phosphorylated to CaMKII(6P) (yellow rectangle with a white circle containing '6P'). CaMKII(6P) is dephosphorylated by PP1 (yellow rectangle) to CaMKII(2P). PP1 is also regulated by PKA (yellow rectangle) and I1 (yellow rectangle). PKA activates I1 (yellow rectangle) via a blue square with a white circle (activation). I1 activates PP1 via a blue square with a white triangle (inhibition). I1 is also regulated by a blue square with a white triangle (inhibition) and a blue square with a white circle (activation). The diagram shows a positive feedback loop where CaMKII(2P) activates CaMKII(6P), which in turn activates PP1, leading to the dephosphorylation of CaMKII(6P) to CaMKII(2P). The diagram also shows that CaMKII(6P) activates PP1, which dephosphorylates CaMKII(6P) to CaMKII(2P). The diagram also shows that PKA activates I1, which inhibits PP1. The diagram also shows that I1 is regulated by a blue square with a white triangle (inhibition) and a blue square with a white circle (activation). The diagram is labeled 'Cytosol' at the bottom.

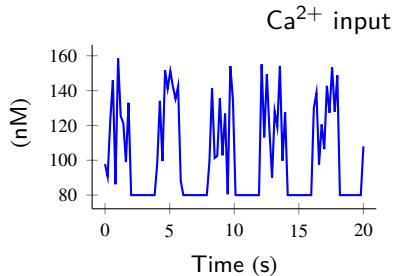
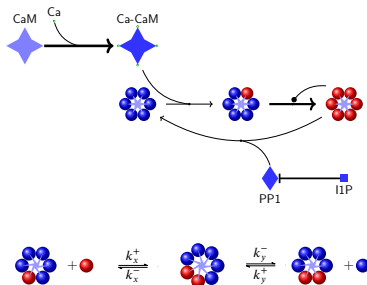


Figure 1 consists of two vertically stacked line plots. The top plot shows the time evolution of  $\text{CaMKII}^*$  concentration over time in days for  $N_{\text{CaMKII}} = 15$ . The y-axis is labeled  $\text{CaMKII}^*$  and ranges from 0 to 1. The x-axis is labeled 'Time (day)' and ranges from 0 to 1.5. The signal is highly fluctuating, with peaks reaching 1 and troughs near 0. The bottom plot shows the time evolution of  $\text{CaMKII}^*$  concentration over time in months for  $N_{\text{CaMKII}} = 35$ . The y-axis is labeled  $\text{CaMKII}^*$  and ranges from 0 to 1. The x-axis is labeled 'Time (month)' and ranges from 0 to 120. The signal is a step function, switching between 0 and 1 at discrete intervals.

