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# Cytoplasmic polyadenylation switching mechanism A comparison between deterministic and stochastic approaches

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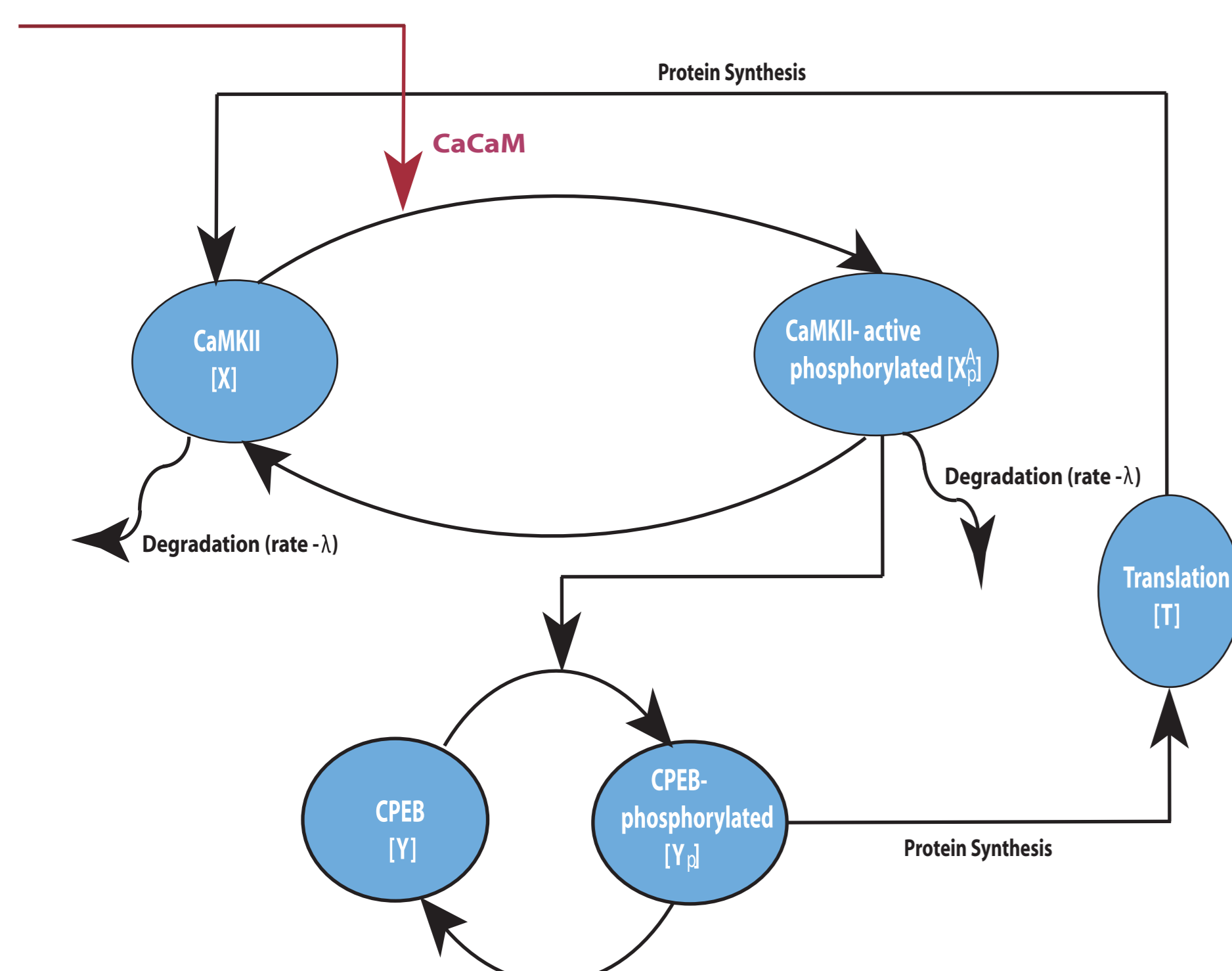
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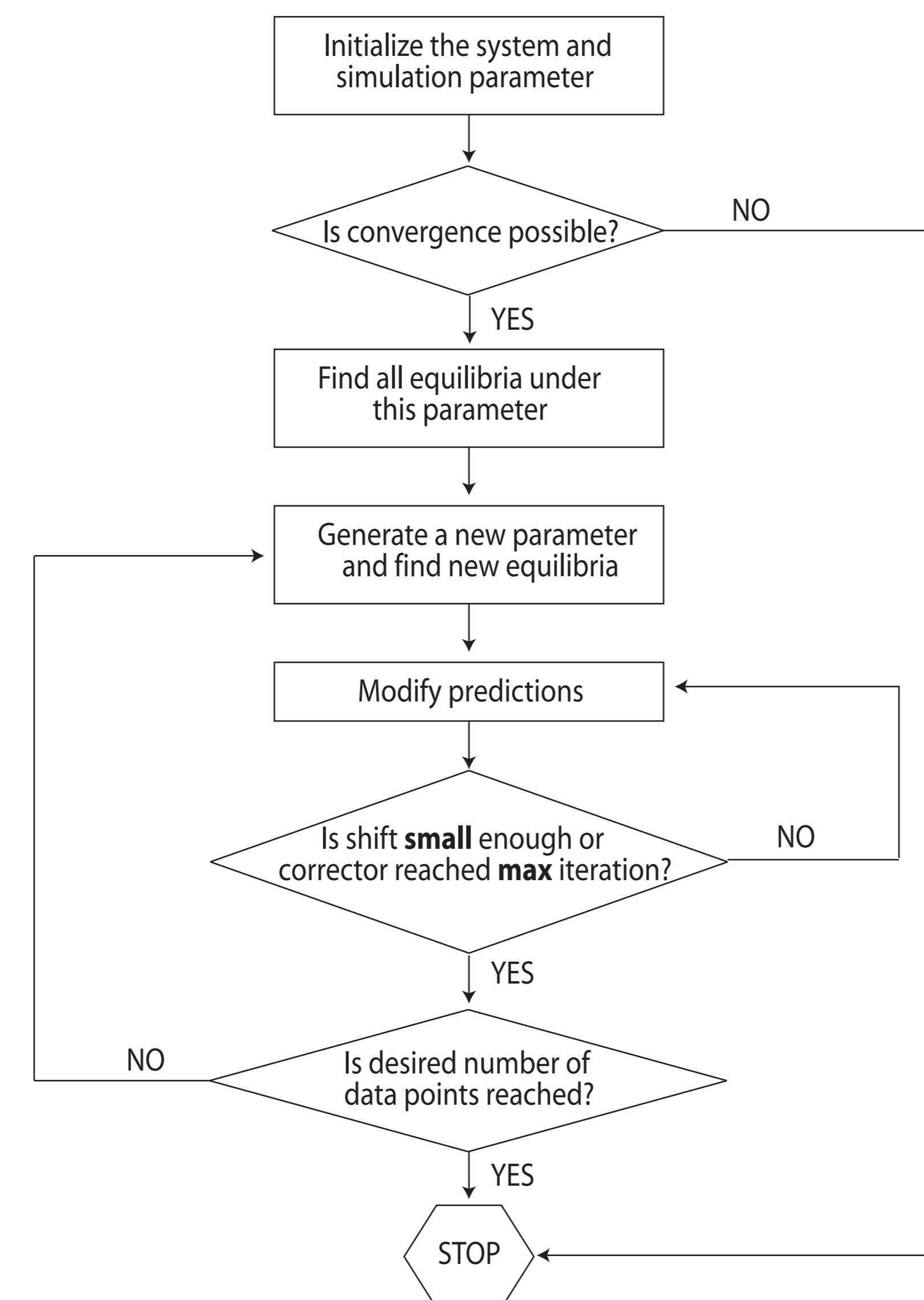
## Abstract

Translation efficiency of certain mRNAs is regulated through a cytoplasmic polyadenylation process at pre-initiation phase. A translation factor regulates the polyadenylation process through its posttranscriptional modification e.g., phosphorylation. The cytoplasmic polyadenylation binding protein (CPEB1) is one such translation factor which regulates the translation of mRNAs through cytoplasmic polyadenylation element (CPE). The cytoplasmic polyadenylation process can be turned on or off by the phosphorylation or dephosphorylation state of CPEB1. The phosphorylated form of CPEB1 increases the translational activity of an otherwise dormant mRNA. A physiological instantiation could be the regulation of  $\alpha$ CaMKII mRNA stability through the phosphorylation - dephosphorylation cycle of CPEB1. Here, we show that CPEB1 mediated translation of  $\alpha$ CaMKII mRNA through polyadenylation is regulated through a bistable switching mechanism. The simple translation switch for regulating the polyadenylation is based on two state model  $\alpha$ CaMKII-CPEB1 molecular pair. Here, the de-novo synthesis of  $\alpha$ CaMKII is modeled through an active/inactive form of  $\alpha$ CaMKII mRNA. Based on elementary biochemical kinetics a high dimensional system of non-linear ordinary differential equations can describe the dynamic characteristics of the polyadenylation loop. We used deterministic and stochastic approaches to analyze the feasibility of CaMKII translation switching mechanism. We also developed the one parameter bifurcation diagram to show the numerical robustness of proposed switching mechanism.

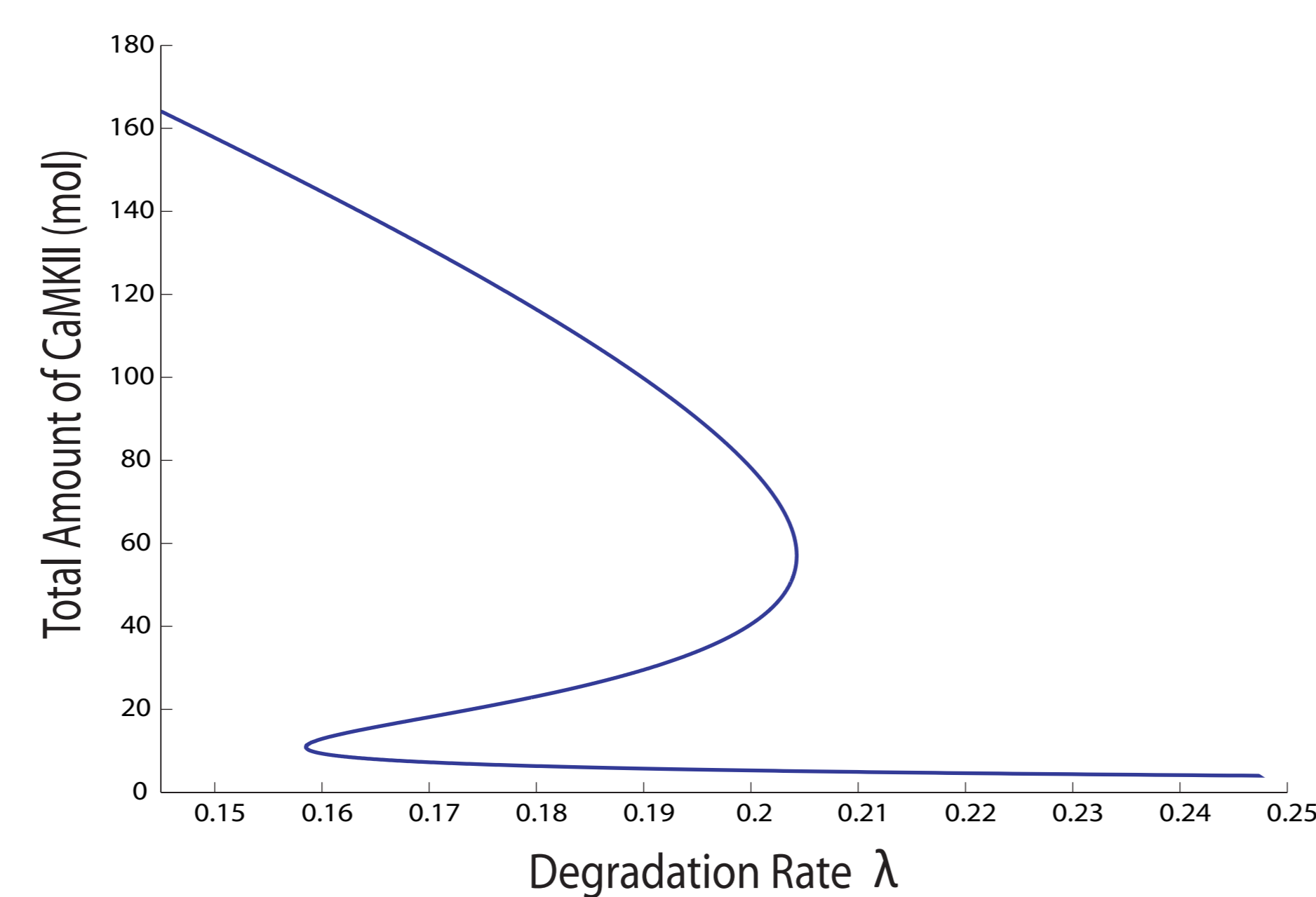
## Molecular Model of $\alpha$ CaMKII-CPEB Interaction Loop



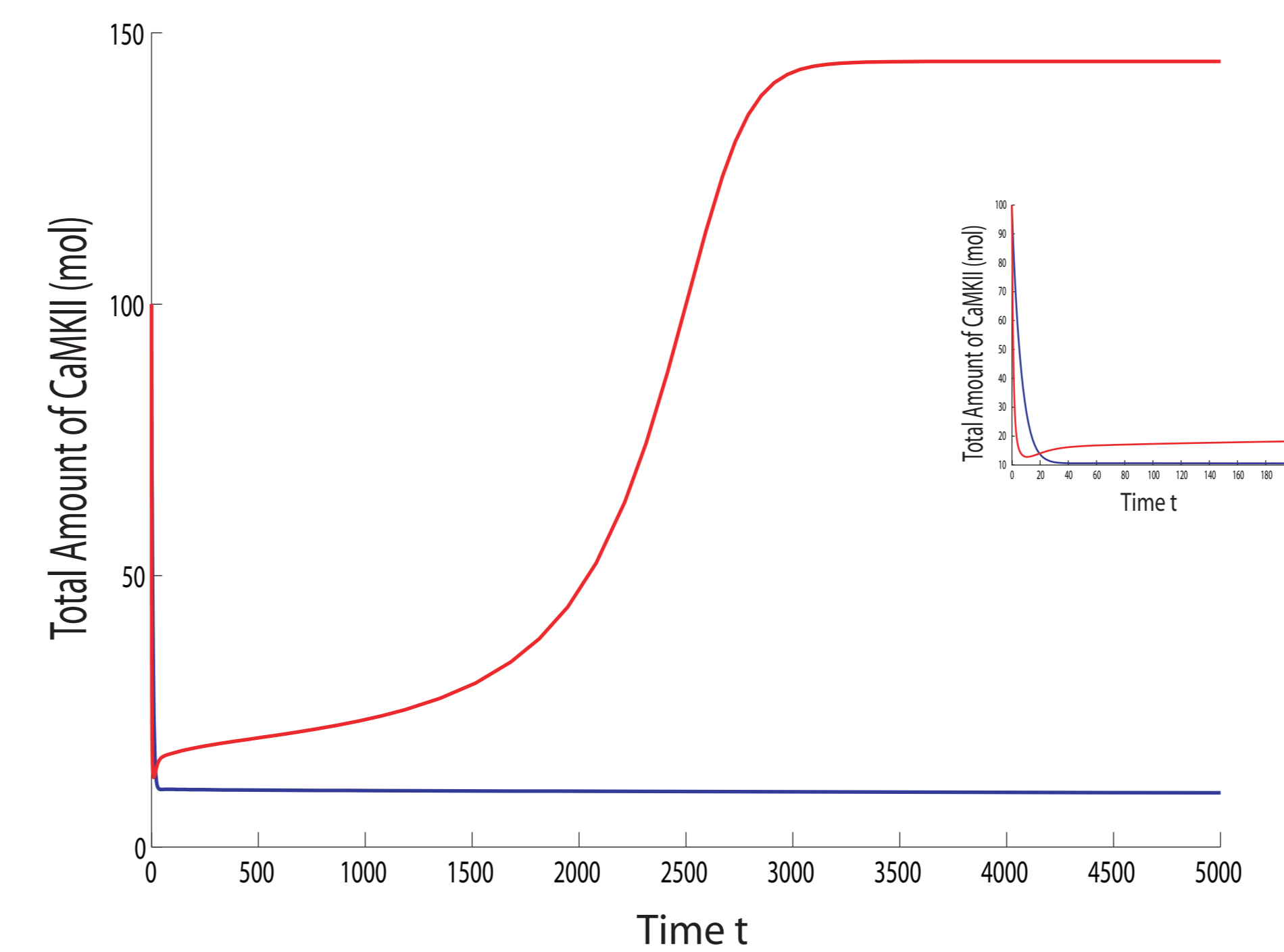
## Bifurcation Algorithm



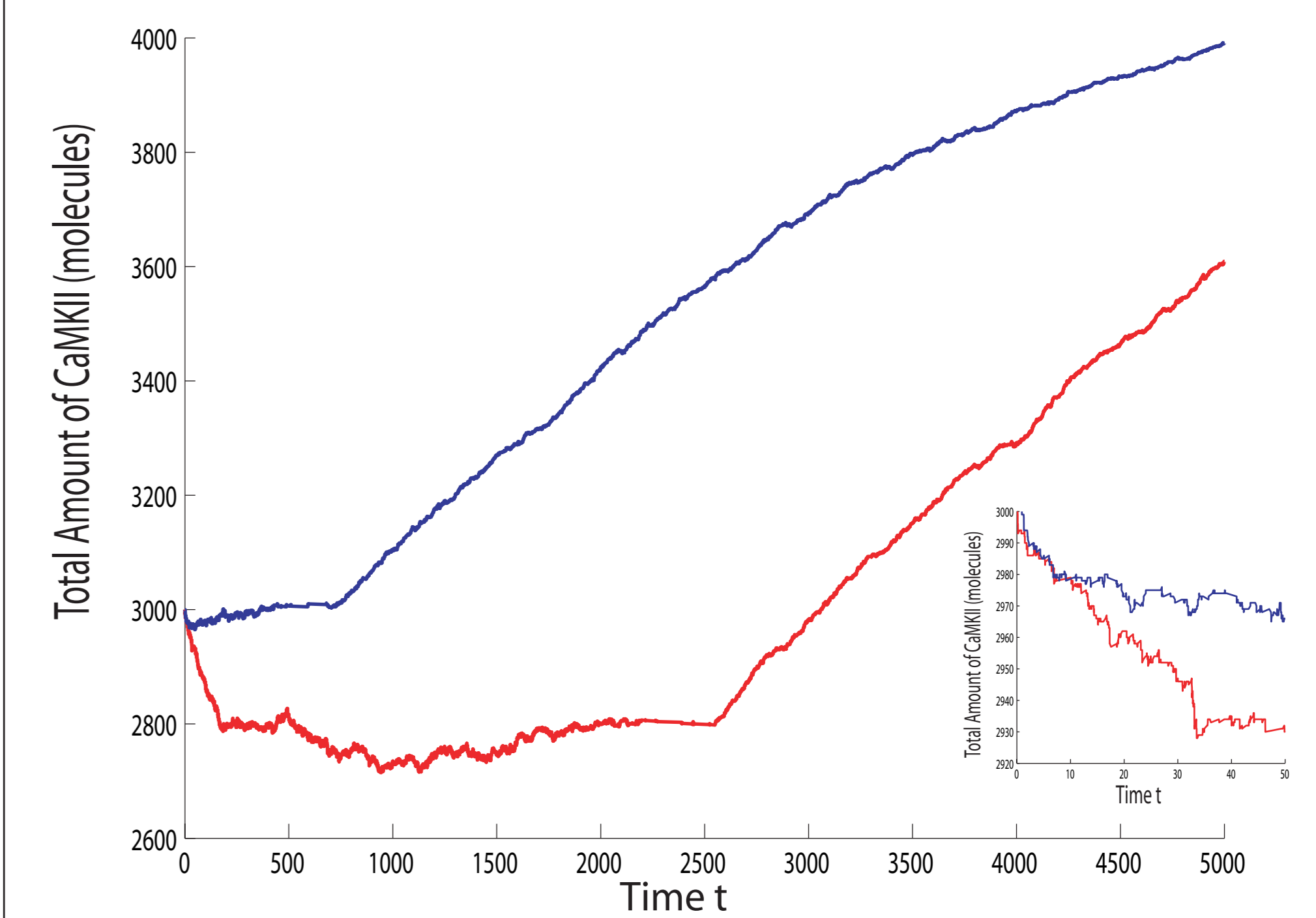
## CPEB Deterministic Bifurcation Curve



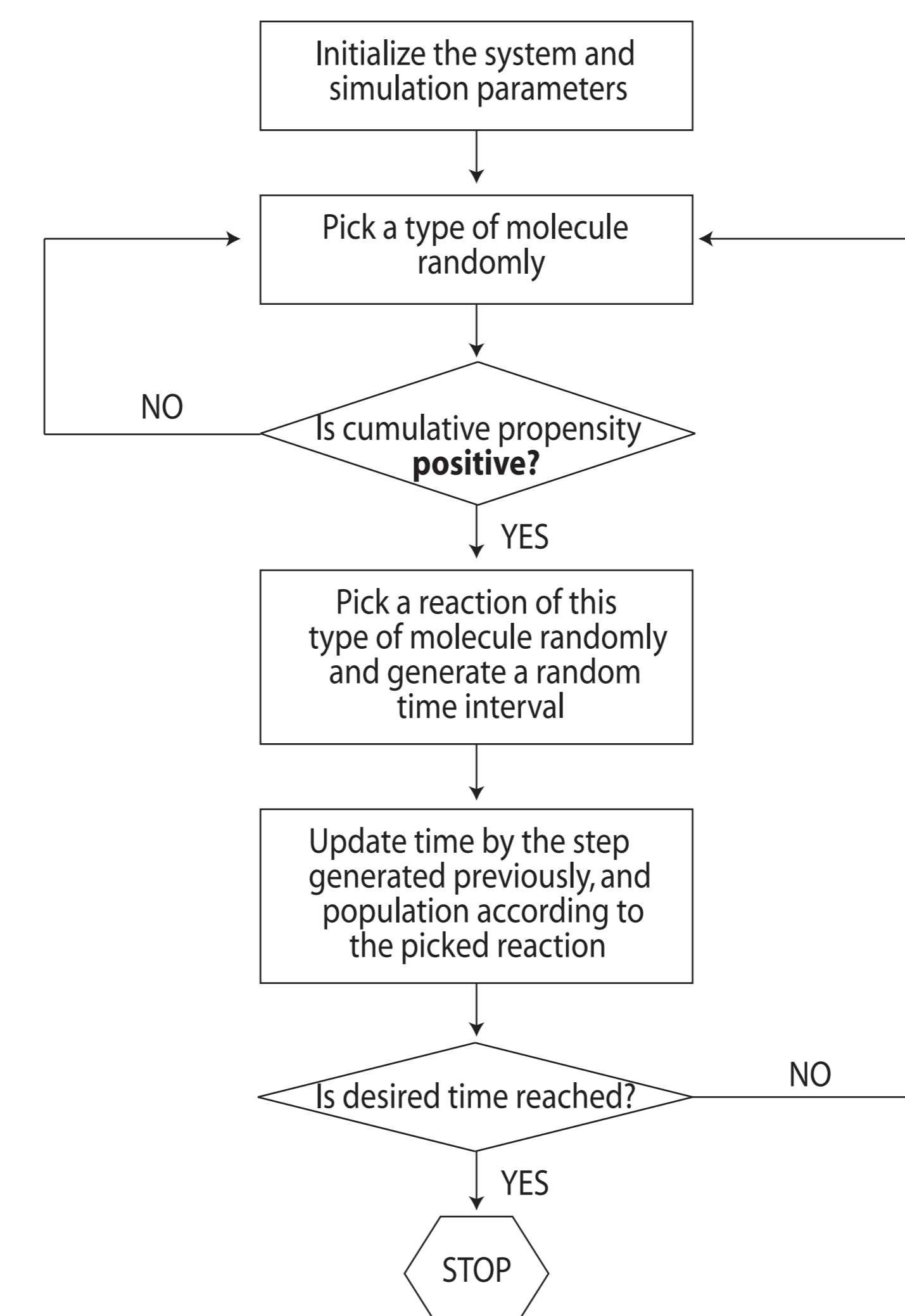
## CPEB Deterministic Dynamics Curves ( $\lambda = .16$ )



## CPEB Stochastic Dynamics Curves ( $\lambda = .16$ )



## Gillespie Algorithm



## Discussion

This work proposes the general hypothesis that a feedback loop between a plasticity related kinase and its translation factor can act as a bistable switch that stabilizes long term memory. The one parameter bifurcation diagram proves the existence of such a bistable switching system. In the deterministic dynamics graph, with a set of appropriate parameter, we also see two clearly separated steady states. However, because the concentration of translation machinery is extremely low in necks of spines and spines, it is more reasonable to assume that the translation process happens stochastically. Here, we observed differences between results from deterministic and stochastic approaches. The initial condition that merged to the lower steady state in deterministic approach seems to rise to the upper steady state in stochastic approach, and does so faster than the other condition that rose to the upper steady state in deterministic approach. This discrepancy happened either because there was an error in the implementation of Gillespie Algorithm or because stochasticity disturbs the system to an extent that bistability is impossible and so do the systems in nature behave. Further investigations are needed to arrive at a more detailed conclusion.

## Acknowledgements and References

1. Allgower, E.L., Georg, K. (1990). *Numerical Continuation Methods: An Introduction*. Springer-Verlag, New York
2. Ullah, M., Schmidt, H., Cho, K.H. and Wolkenhauer, O. (2006). Deterministic modelling and stochastic simulation of biochemical pathways using MATLAB. *IEE Proceedings-Systems Biology* 153, 53-60

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