Stochastic sequestration dynamics can act as intrinsic noise filter in signaling network motifs

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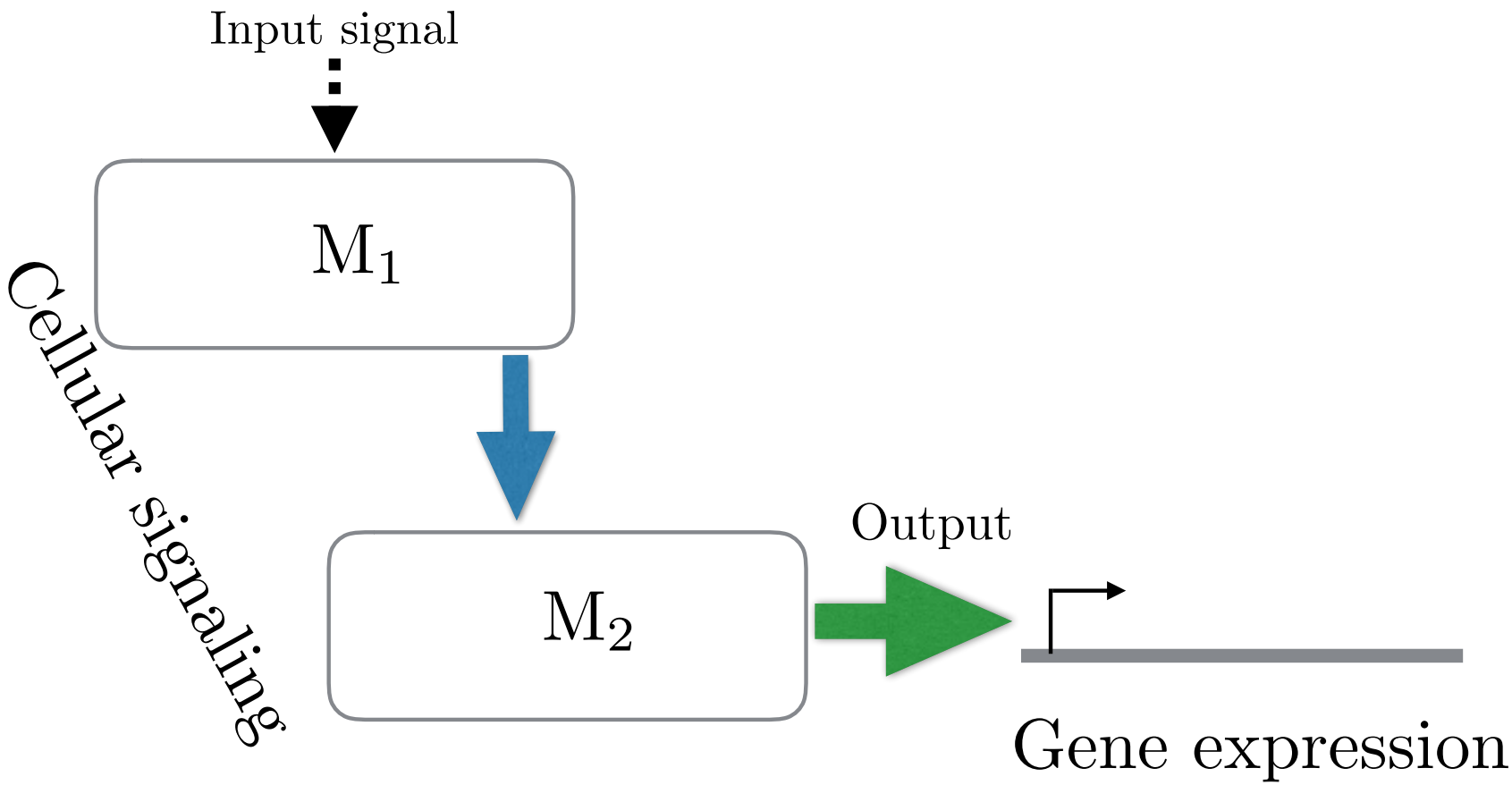
INRIA, Saclay 15.05.2018

Biological design at cellular & molecular level



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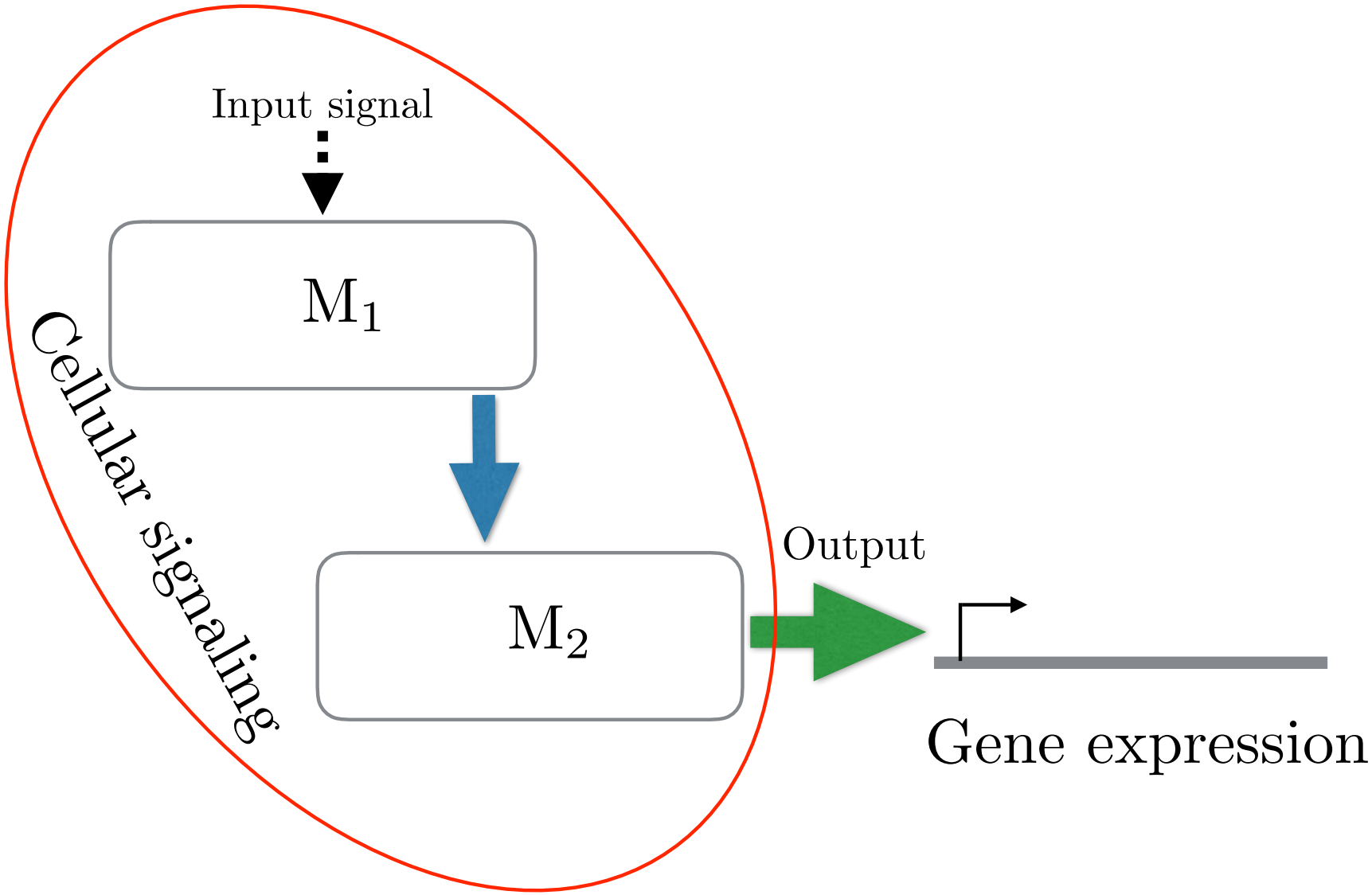
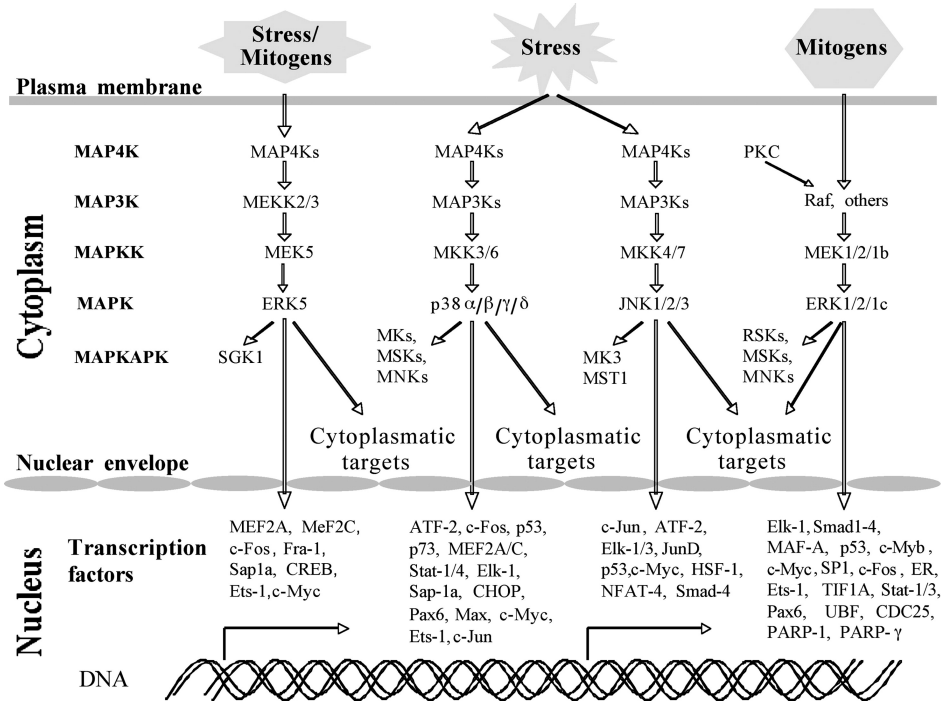


Modular architecture of signaling networks

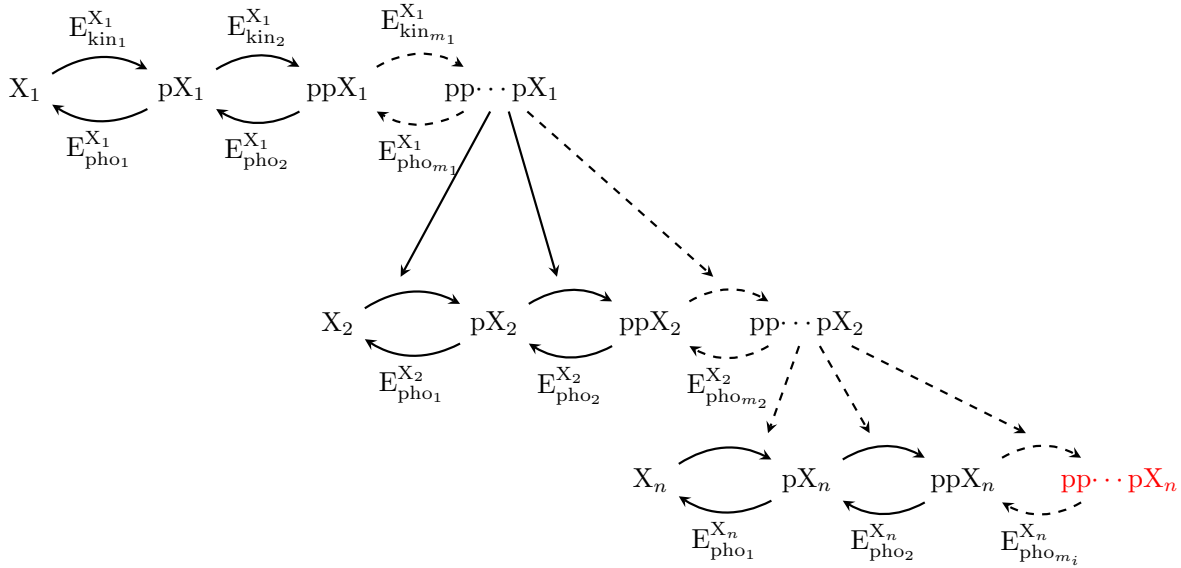
MAPK - Mitogen Activated Protein Kinase



- signal is propagated by sequential phosphorylation and activations of the sequential kinases (MAP3K, MAPKK, and MAPK).
- Responsible for cellular processes including growth, proliferation, stress response,and apoptosis.

[Source: Plotnikov et al., *Biochimica et Biophysica Acta*, 1813(9), 2011]

Modular architecture of signaling networks



- $\{X_i\}_{i=1}^{n}$: Proteins
- $\underbrace{pp\cdots p}_{m_i}X_i$: ($m_i \geq 0$ times) Phosphorylated forms of X_i
- $\{E^{X_i}_{kin(pho)_j}\}_{i=1\ldots n, j=1\ldots m_i}$: Kinases (phosphatases) for $\underbrace{pp\cdots p}_{j-1}X_i \rightarrow \underbrace{pp\cdots p}_{j}X_i$ ($\underbrace{pp\cdots p}_{j}X_i \rightarrow \underbrace{pp\cdots p}_{j-1}X_i$)
- $pp\cdots pX_n$: Final output of the (multi-tier) signaling cascade
- Example: MAPK pathway

Does modularity bring any advantage?

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Robustness and filtering properties of ubiquitous signaling network motifs ⋆

Debdas Paul * **Nicole Radde** *

* *Institute for Systems Theory and Automatic Control, University of Stuttgart, Pfaffenwaldring 9, 70569 Stuttgart, Germany(e-mails: debdas.paul@ ist.uni-stuttgart.de, nicole.radde@ist.uni-stuttgart.de).*

Abstract: Biological systems are intrinsically robust. The system, being an open one, is permanently exposed to perturbations due to external noise from the surrounding environment. In this context, the architecture and information processing capabilities of a signaling network play an important role in attenuating the noise. Multi-layered phosphorylation cascades are architectures prevalent in some of our major signaling pathways. In this work, we investigate the robustness of such signaling cascades with respect to external input variations. We employ local sensitivity and output-variance based sensitivity as measures of robustness for such cascades and observe that the efficiency of high frequency signal attenuation increases with the number of in the cascades. Filtering properties of cascades have been observed previously but not under a very rigorous theoretical framework and not in comparison with other models. This work provides an example of optimality versus robustness tradeoff in the design principles of biological systems.

Keywords: Systems biology, Sensitivity analysis, Robustness, Signaling cascades, Monte Carlo

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- Modeling approach: deterministic
- Findings:
  1. Cascades are less *sensitive* to the input variation

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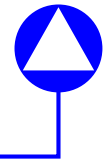
Keywords: Systems biology, Sensitivity analysis, Robustness, Signaling cascades, Monte Carlo

- Modeling approach: deterministic
- Findings:
  1. Cascades are less *sensitive* to the input variation
  2. Cascading prolongs the duration of signal propagation and hence acts as a low-pass filter

Any disadvantage (of modularity)?

Retroactivity - bi-directional flow of signal



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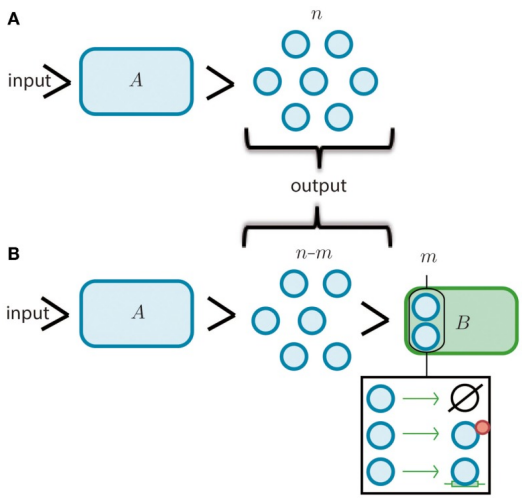
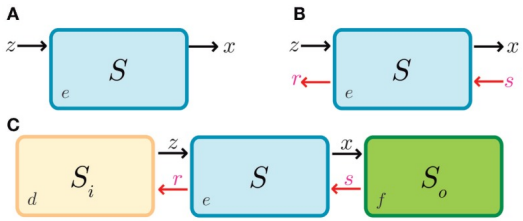


modules and retroactivity



symbolic representation

downstream module *influencing* the upstream module through:

- degradation
- covalent modification
- simple sequestration by binding

[Adapted from: Pantoja-Hernández, L. and Martónez-García, J.C., *Front. in bioeng. & biotech.*, 3, 2015]

How modularity contributes to the robustness in a stochastic environment?

New Results

The role of stochastic sequestration dynamics for intrinsic noise filtering in signaling network motifs

Debdas Paul, Nicole Radde

doi: https://doi.org/10.1101/278929

This article is a preprint and has not been peer-reviewed [what does this mean?].

Abstract

The relation between design principles of signaling network motifs and their robustness against intrinsic noise still remains illusive. In this work we investigate the role of cascading for coping with intrinsic noise due to stochasticity in molecular reactions. We use stochastic approaches to quantify fluctuations in the terminal kinase of phosphorylation-dephosphorylation cascade motifs and demonstrate that cascading highly affects these fluctuations. We show that this purely stochastic effect can be explained by time-varying sequestration of upstream kinase molecules. In particular, we discuss conditions on time scales and parameter regimes which lead to a reduction of output fluctuations. Our results are put into biological context by adapting rate parameters of our modeling approach to biologically feasible ranges for general binding-unbinding and phosphorylation-dephosphorylation mechanisms. Overall, this study reveals a novel role of stochastic sequestration for dynamic noise filtering in signaling cascade motifs.

[under review]

Outline

1. Models of phosphorylation-dephosphorylation (PD)
2. Coefficient of output variation and sequestration dynamics
3. Real biological example
4. Conclusion

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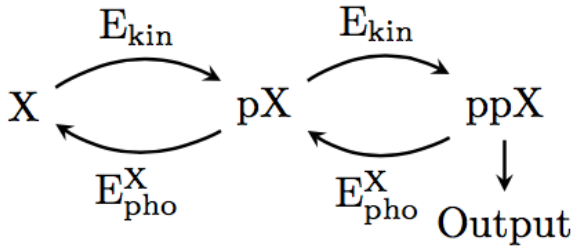
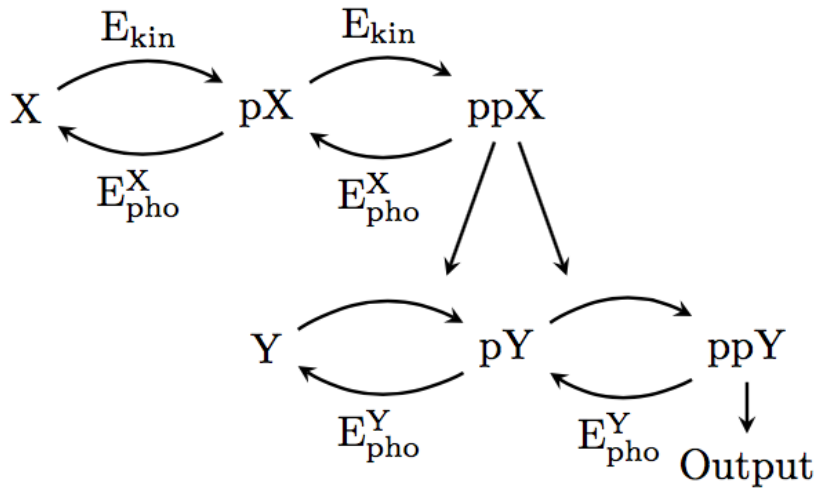
Comparison between two models



Model A



Model B

- Reactions are modeled according to the two-step enzyme kinetics:

$$S + E \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftarrows}} ES \xrightarrow{k_{\text{cat}}} P + E$$

- Subsequent results correspeond to an ensemble average of 1000 SSA realizations.

Initial number of molecules	X_{init}	Y_{init}	E^X_{pho}	E^Y_{pho}
	100	100	20	20
Stochastic rate constants	k^X_{on}	k^X_{off}	k^X_{cat}	
	0.01	0.02	0.08	

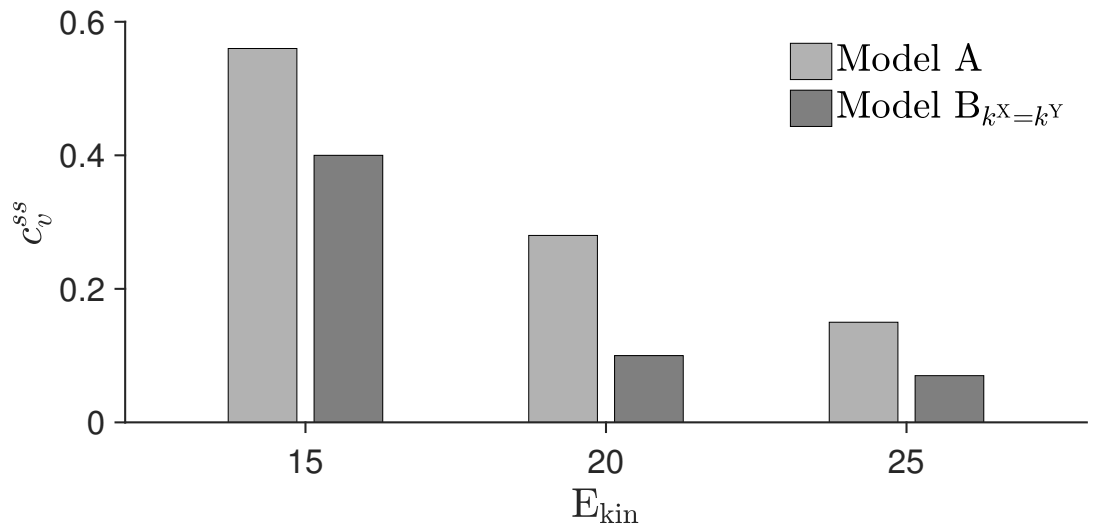
1 Models of phosphorylation-dephosphorylation (PD)

2 Coefficient of output variation and sequestration dynamics

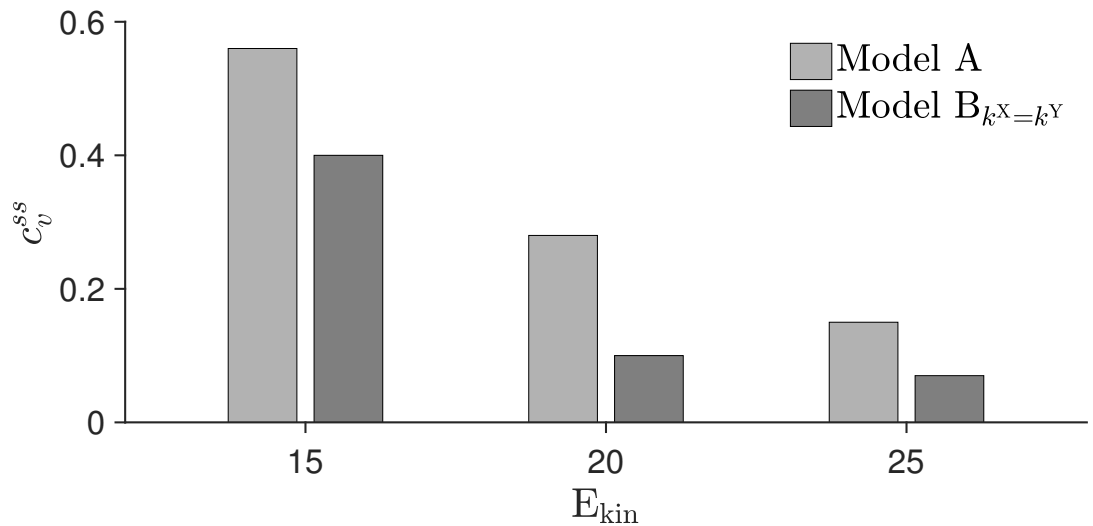
3 Real biological example

4 Conclusion

Coefficient of output variation in model B

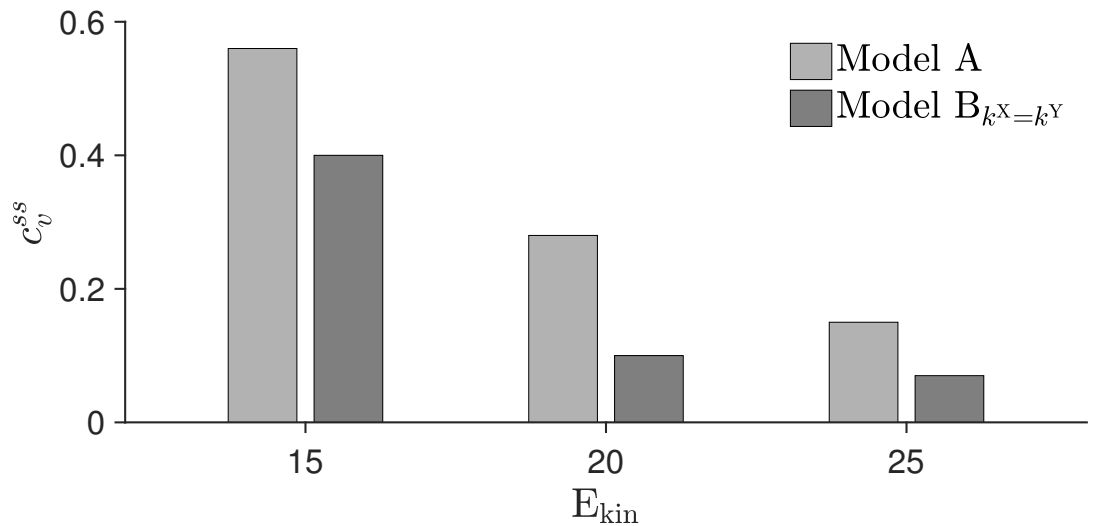


Coefficient of output variation in model B



- $B_{k^Y=k^X}$: Corresponding rates of the X and the Y protein modules are same.

Coefficient of output variation in model B



- $B_{k^Y=k^X}$: Corresponding rates of the X and the Y protein modules are same.
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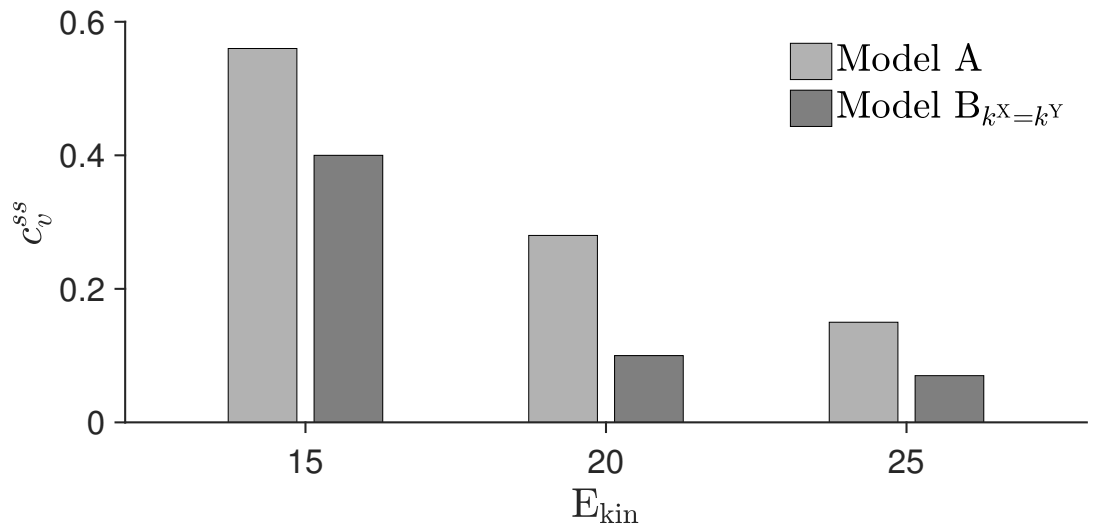
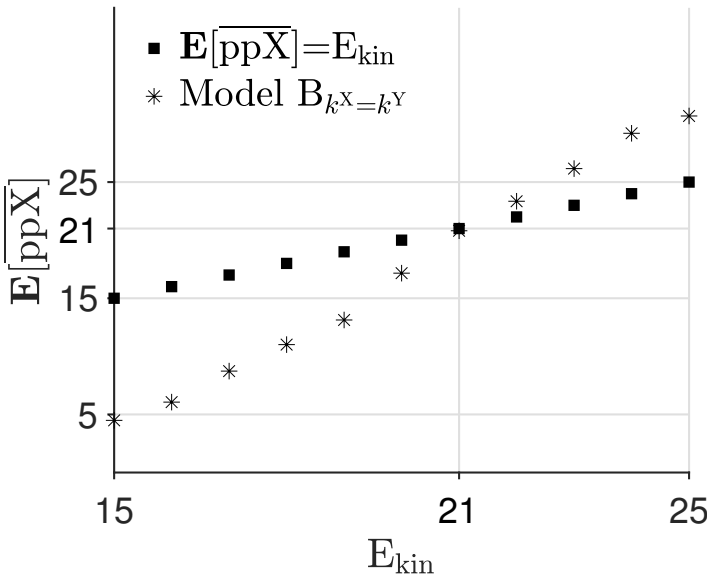
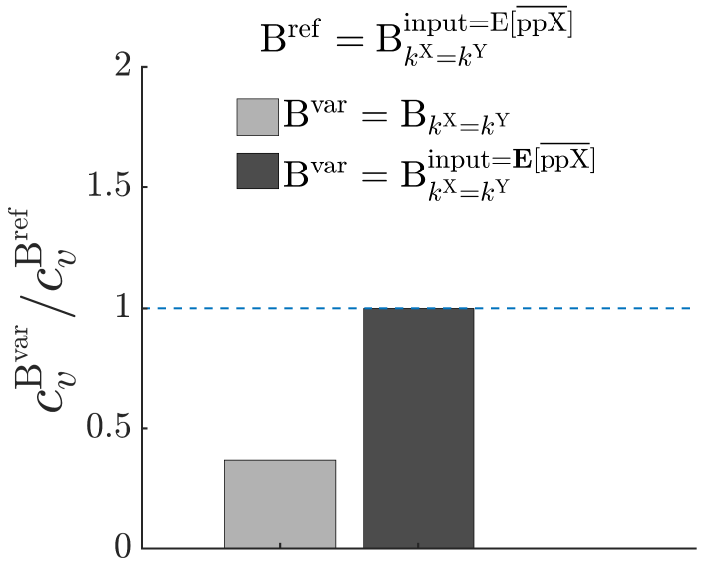
Coefficient of output variation in model B



- $B_{k^Y=k^X}$: Corresponding rates of the X and the Y protein modules are same.
- Coefficient of output variation (c_v^{ss}) decreases for cascade.
- The reduction in the CV could either be caused by differences in E_{kin} and $\mathbf{E}[\overline{ppX}]$, or by the fact that ppX is a time-dependent variable.

Constant input to the Y protein module





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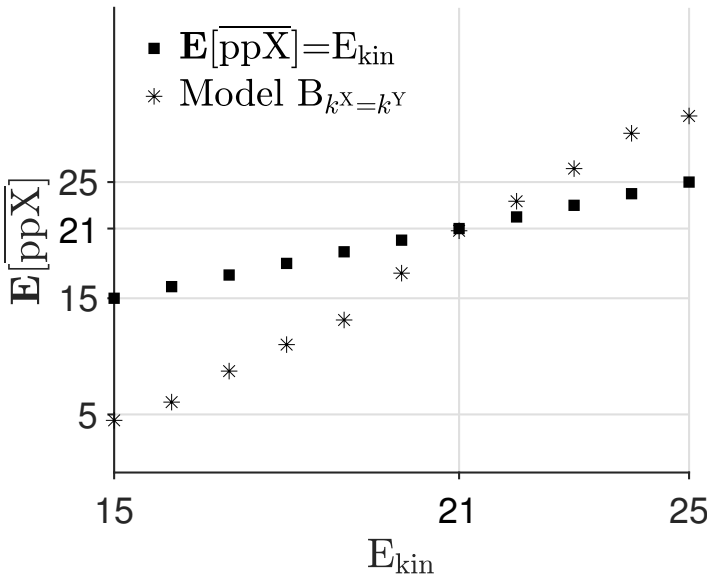
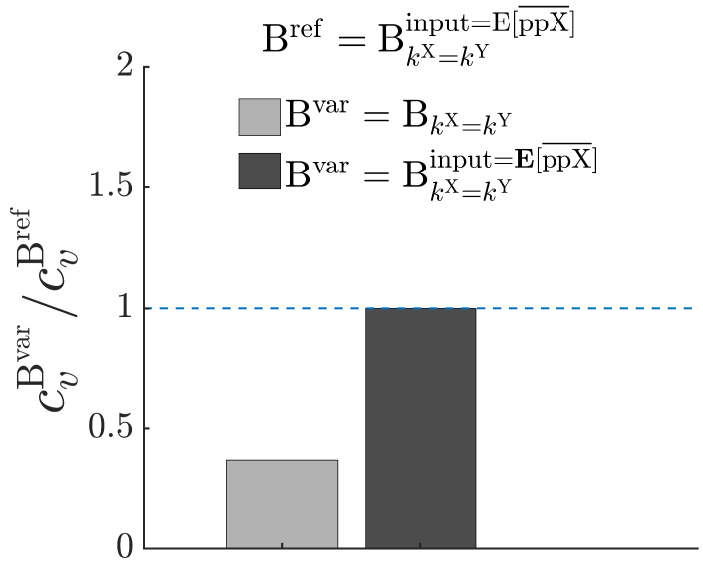
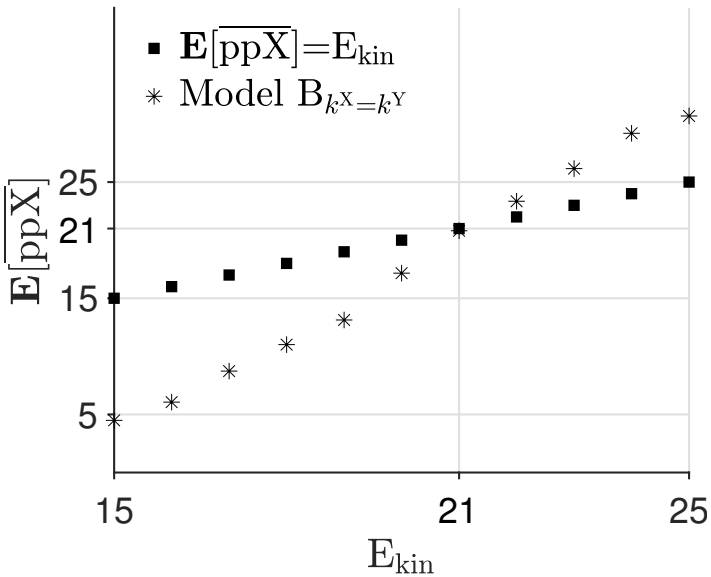
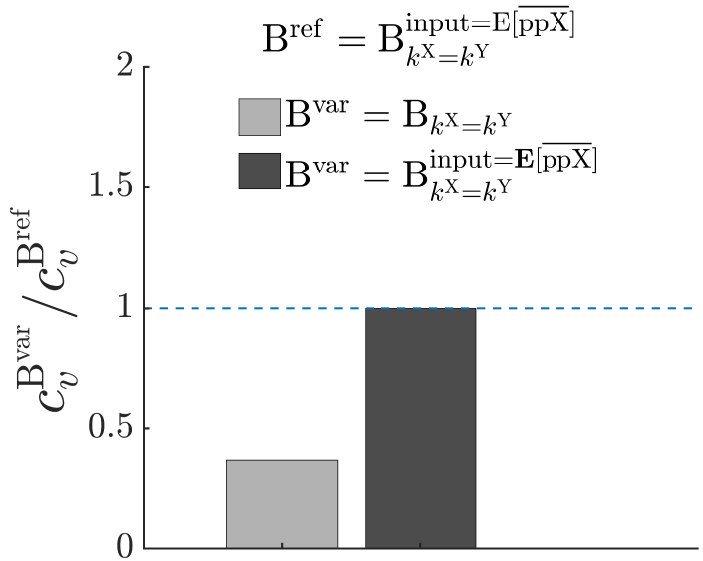




- The stochastic dynamics in ppX is responsible for the reduction in the CV of model B.

Constant input to the Y protein module





- The stochastic dynamics in ppX is responsible for the reduction in the CV of model B.
- What if we increase the sequestration of ppX?

Increased sequestration

- Reducing the unbinding (k_{off}) and the catalytic (k_{cat}) rates for the Y module (100 times to that of X).
- Accumulating ppX-Y and ppX-pY complexes.

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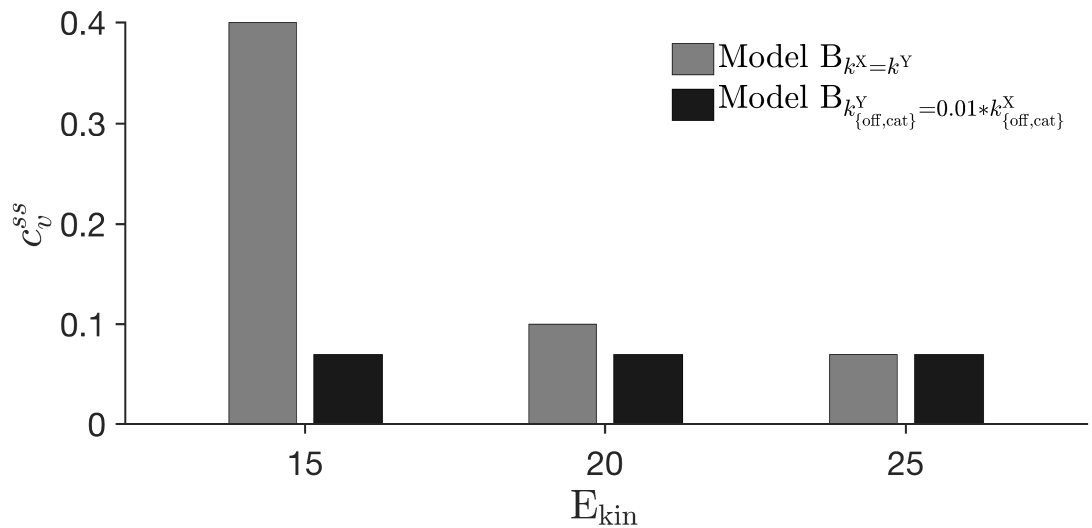

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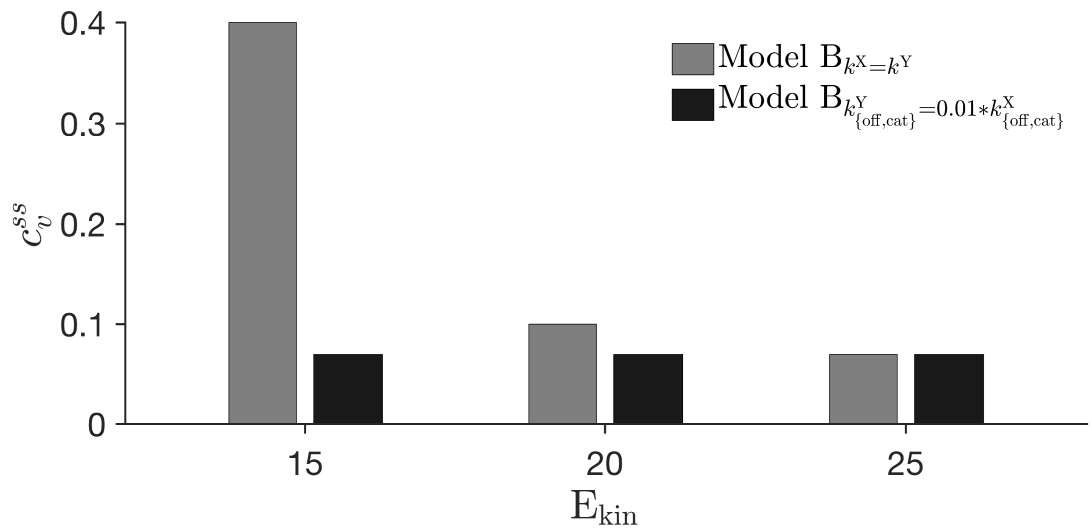
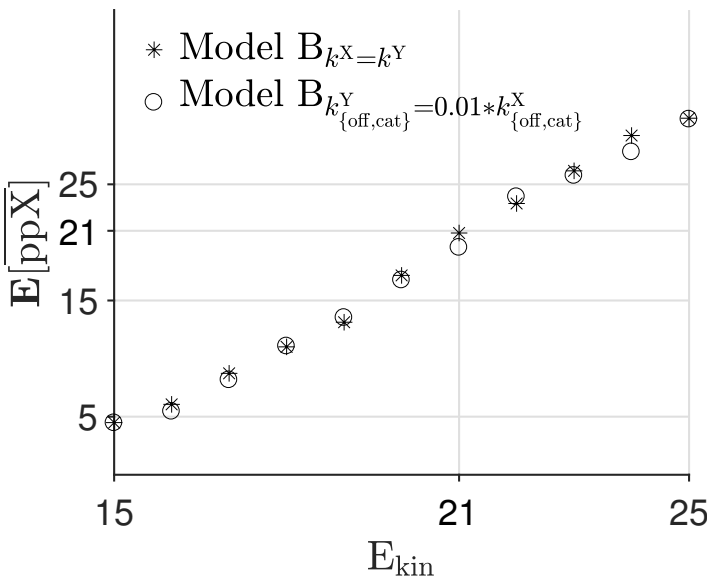
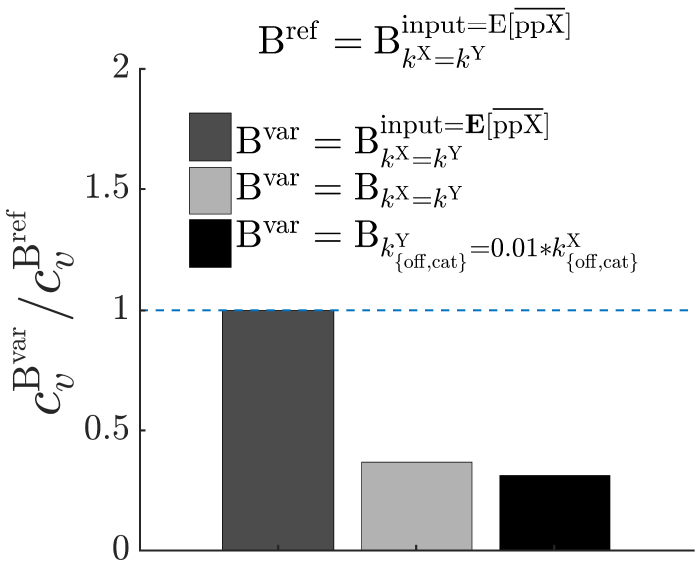


- Increased sequestration of ppX further reduces the CV.

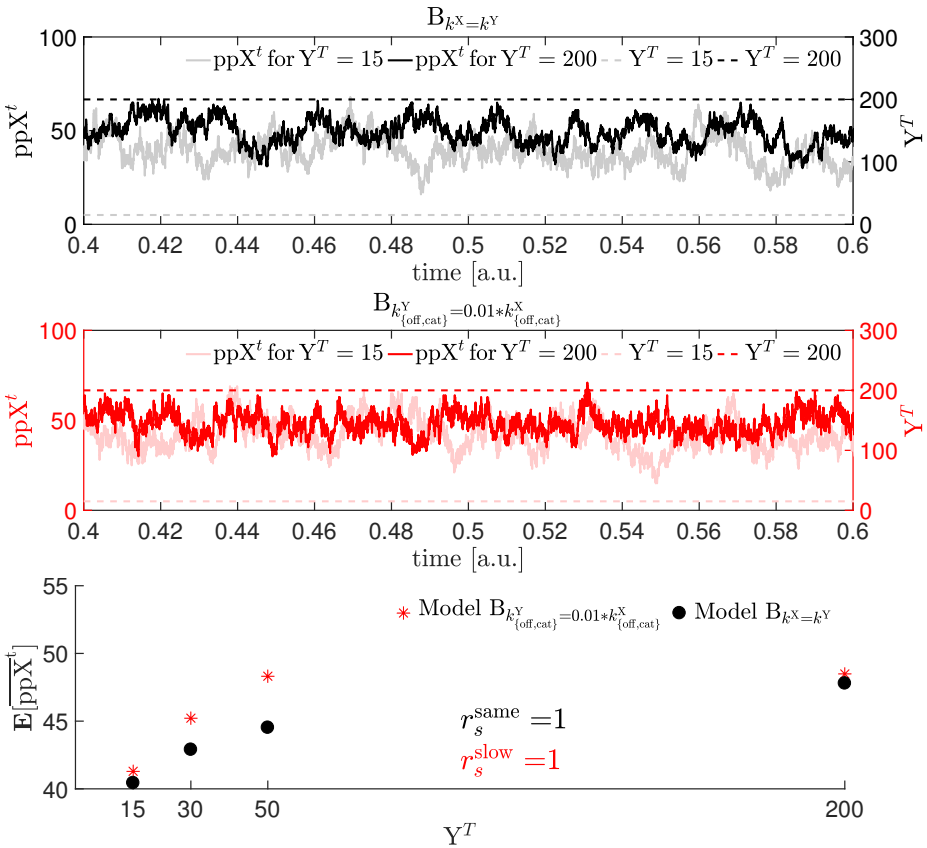
Constant input to the Y protein module





How X and Y *talk* to each other?

Static correlation



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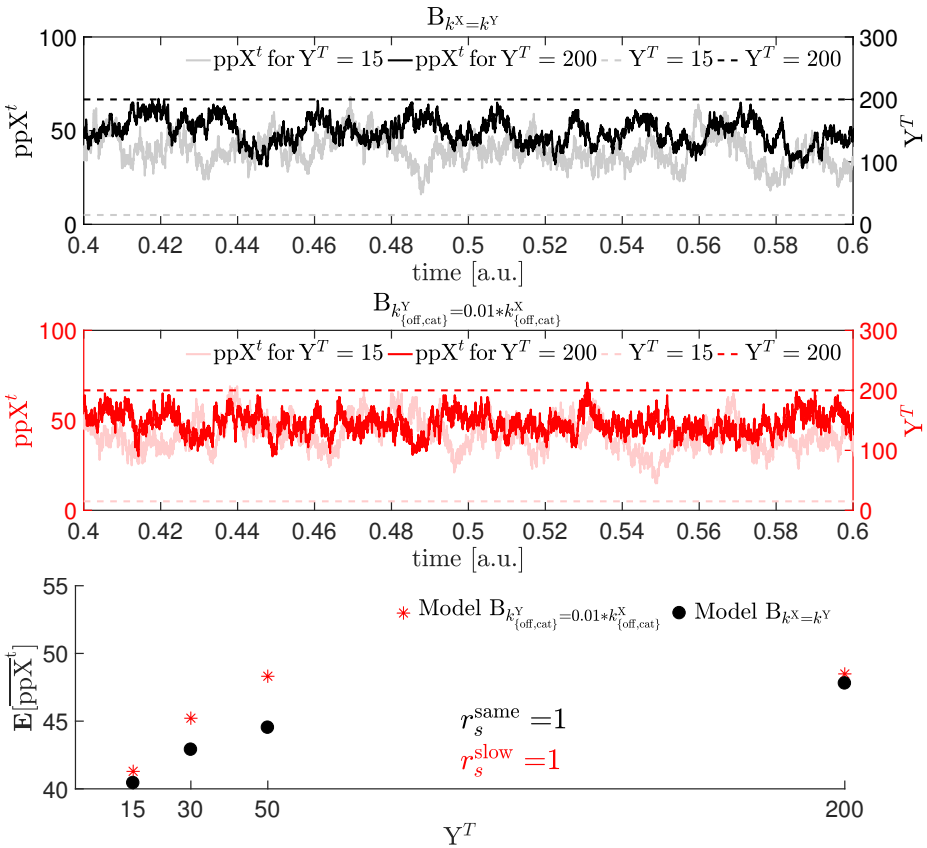
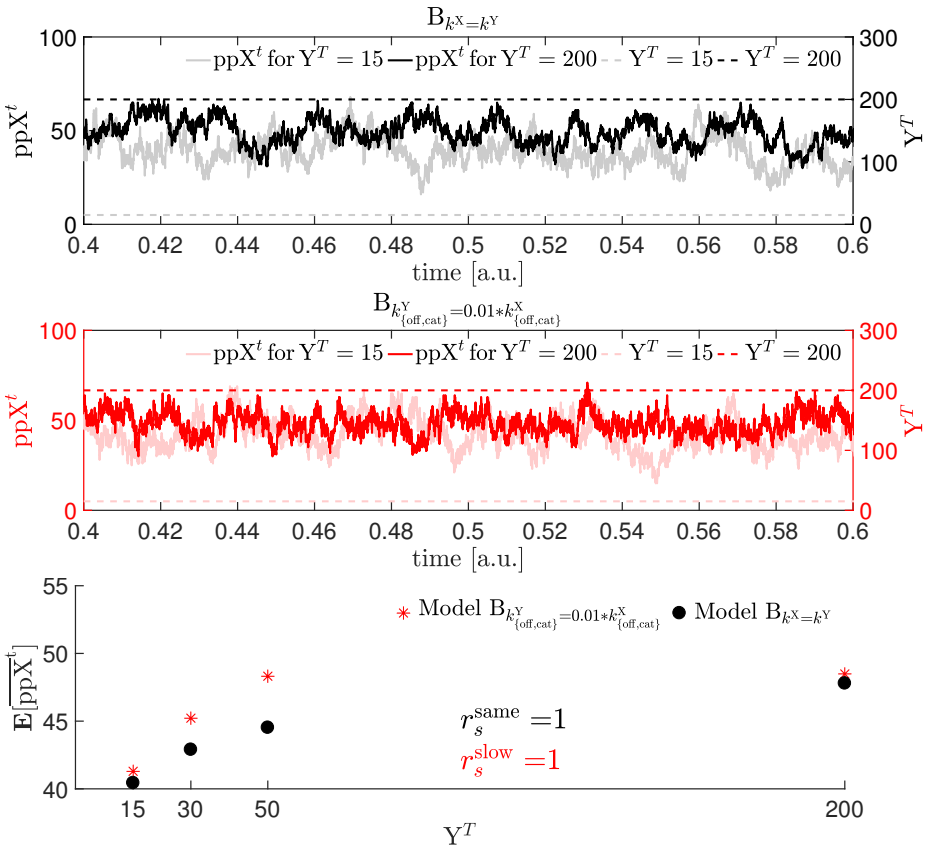


- X molecules *senses the need* of the Y molecules via sequestration and adapts the state of the Y system

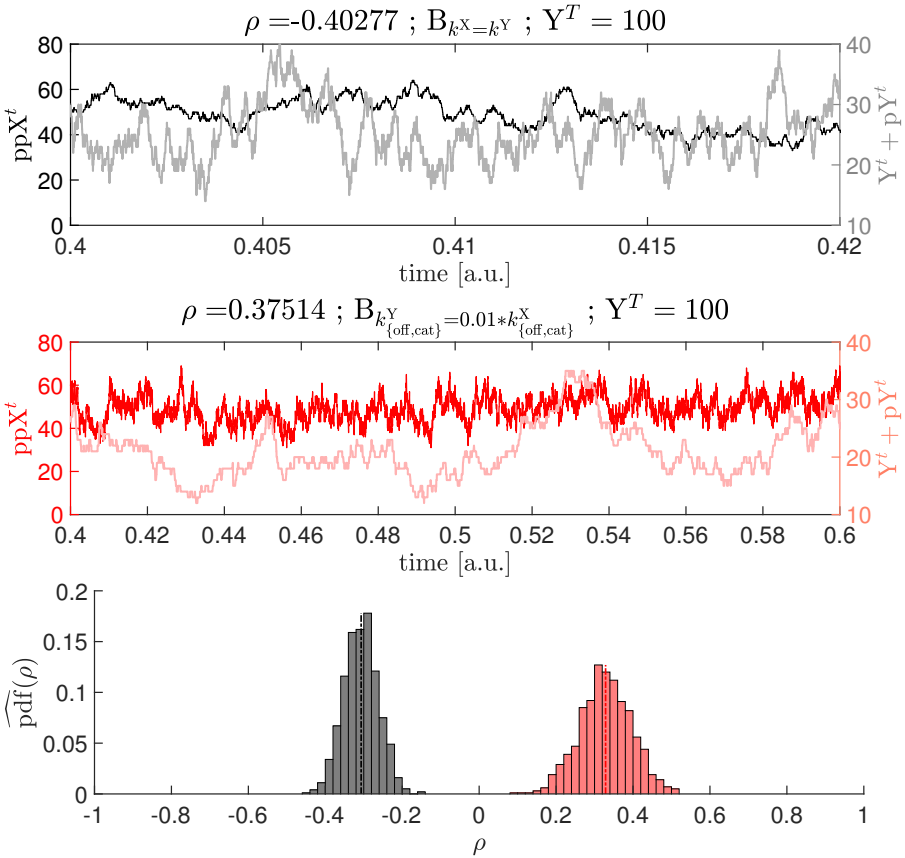
Static correlation



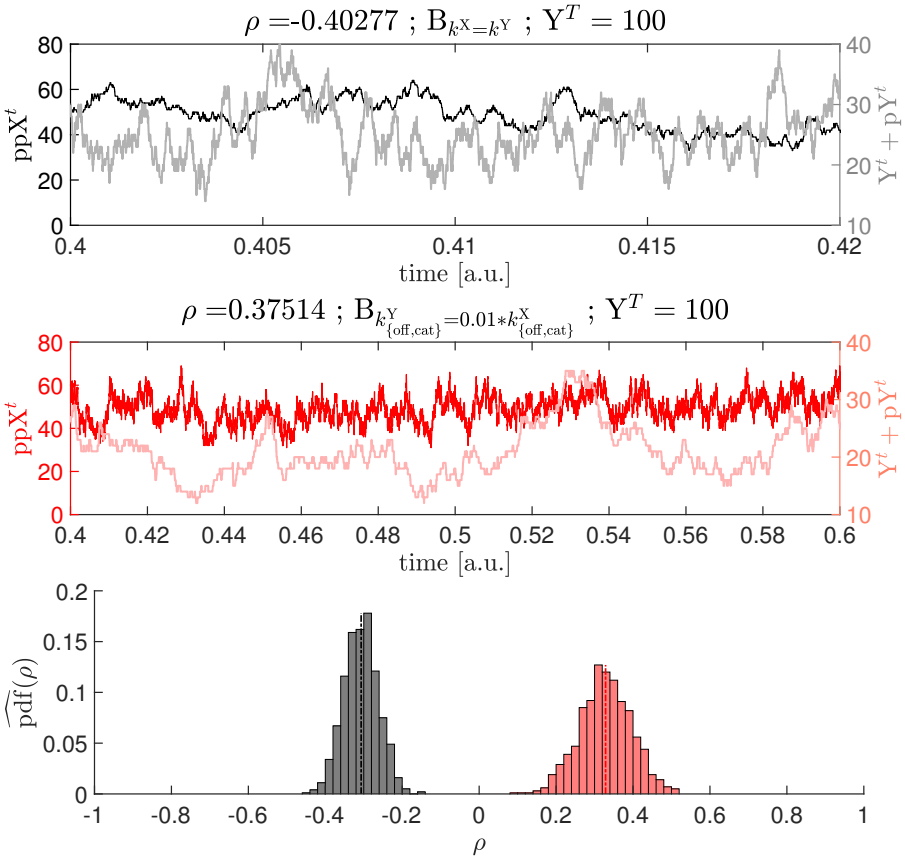
- X molecules *senses the need* of the Y molecules via sequestration and adapts the state of the Y system

But Y^T is a conserved quantity!

Dynamic correlation

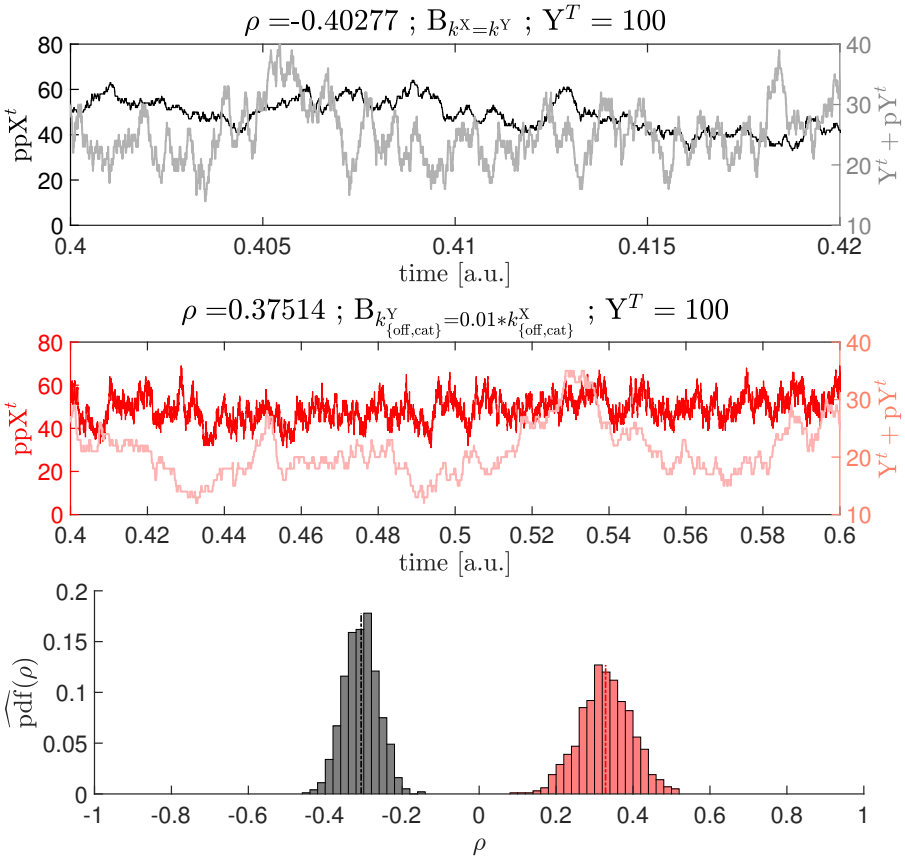


Dynamic correlation



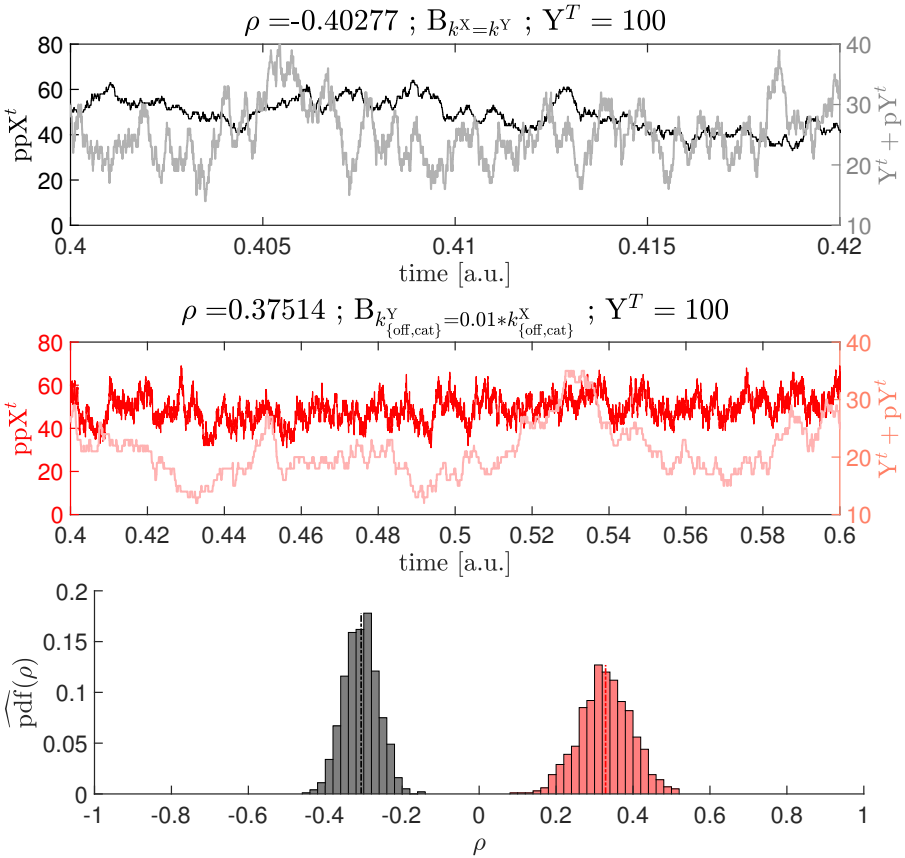
- Correlations are significantly different from zero

Dynamic correlation



- Correlations are significantly different from zero
- Negative correlation due to *time delay* for comparable time scales.

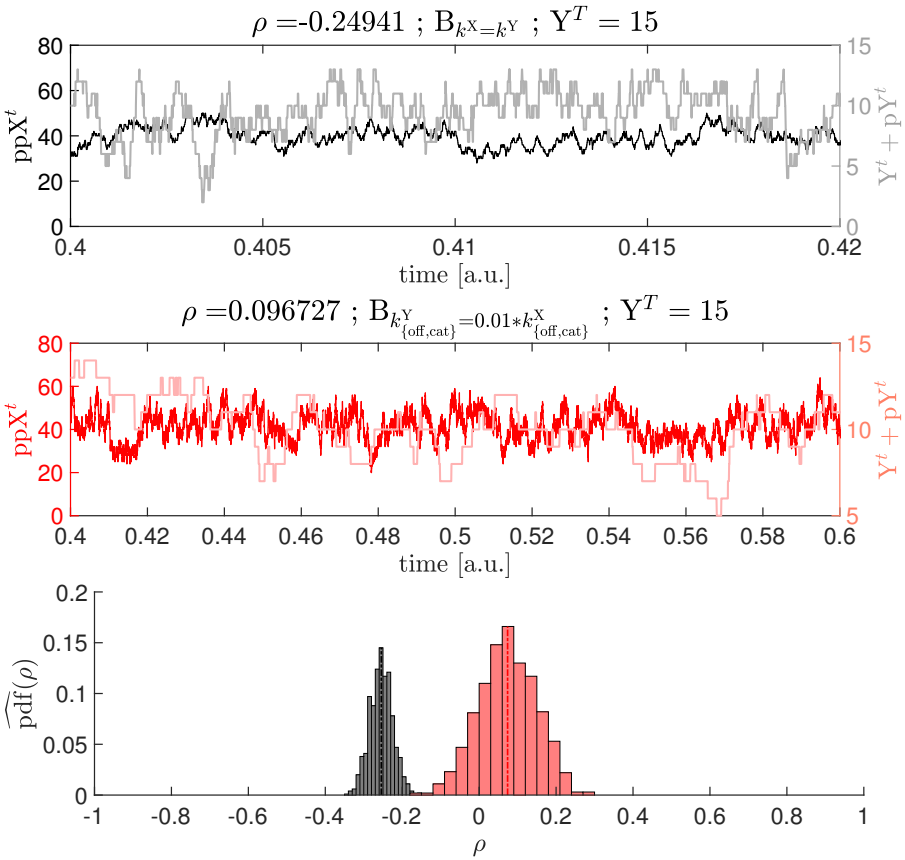
Dynamic correlation



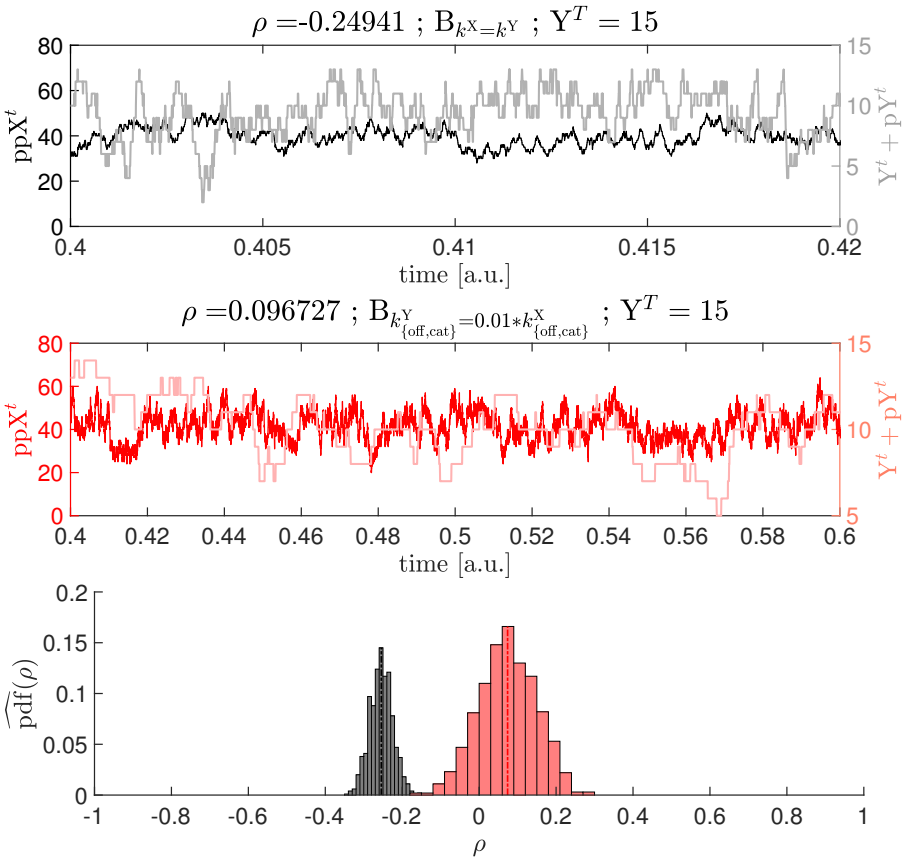
- Correlations are significantly different from zero
- Negative correlation due to *time delay* for comparable time scales.
- Slower dynamics of the Y module leads to positive correlation as X module has enough time to follow the changes

Dynamic correlation when Y^T is small

Dynamic correlation when Y^T is small



Dynamic correlation when Y^T is small



- Correlations become smaller.

1 Models of phosphorylation-dephosphorylation (PD)

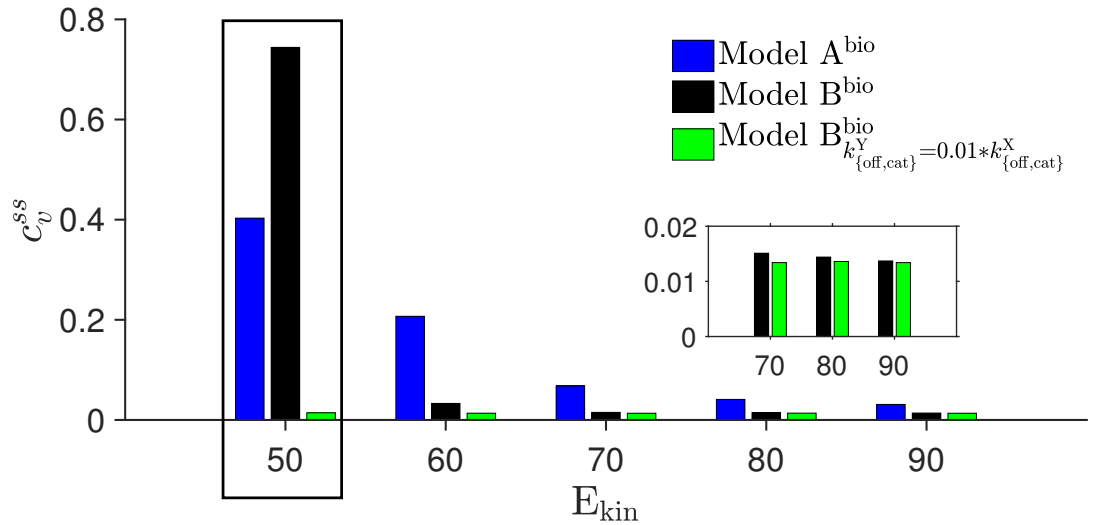
2 Coefficient of output variation and sequestration dynamics

3 Real biological example

4 Conclusion

Does this phenomenon have a biological context?

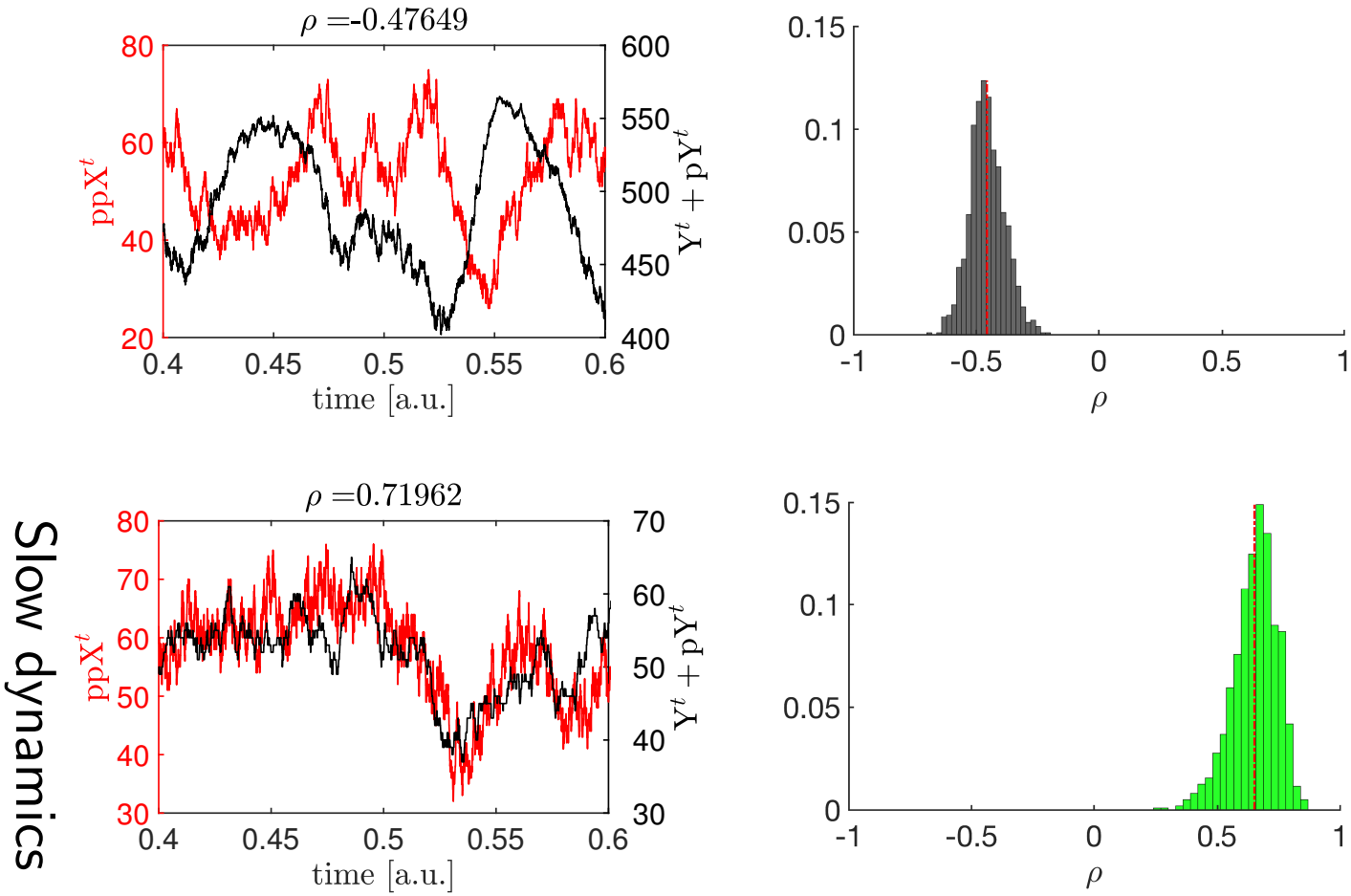
Dynamic correlation in biological context



Initial number of molecules	X_{init}	Y_{init}	E^X_{pho}	E^Y_{pho}
	757	567	32	32
Stochastic rate constants	k^X_{on}	k^X_{off}	k^Y_{on}	k^Y_{off}
phosphorylation	0.0016	0.01	0.0021	0.01
dephosphorylation	0.0141	0.01	0.0141	0.01

[Parameters are taken (& calculated) from: Dhananjaneyulu V et al., *PloS One*, 7(5), 2012]

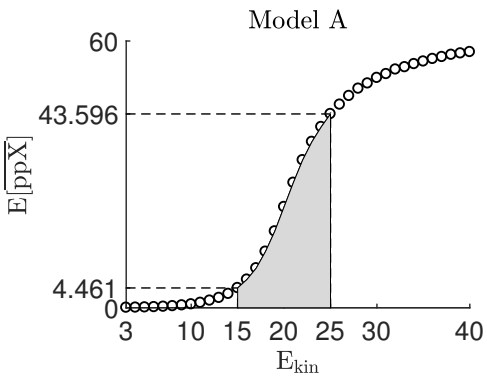
Dynamic correlation in biological context

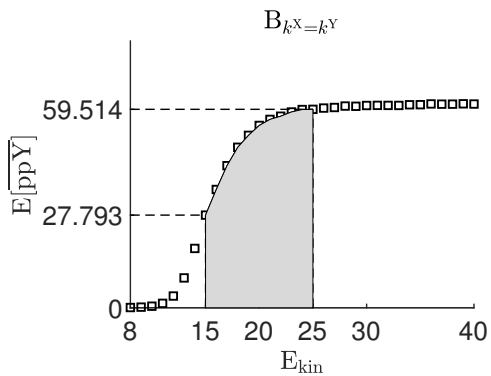


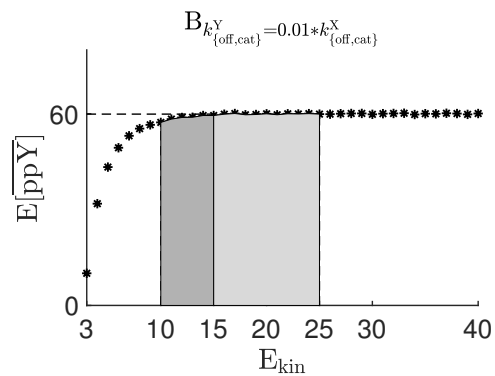
- Negative or positive correlation can not explain the increase of CV at kinase molecule 50.

Operating regimes of the models

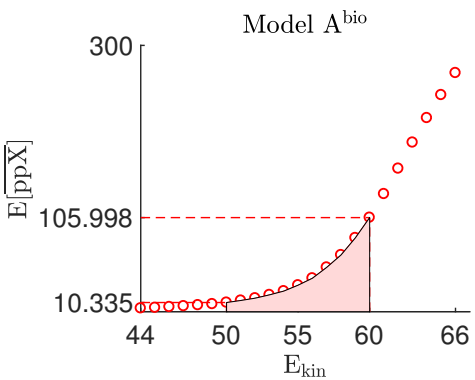
Non-biological

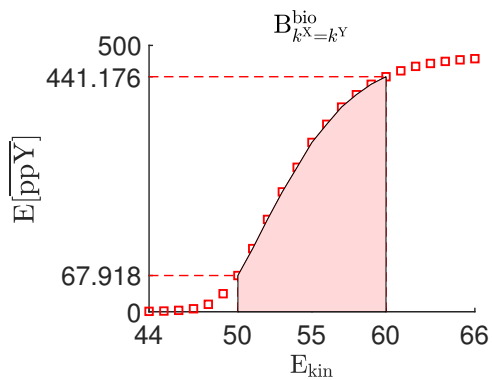


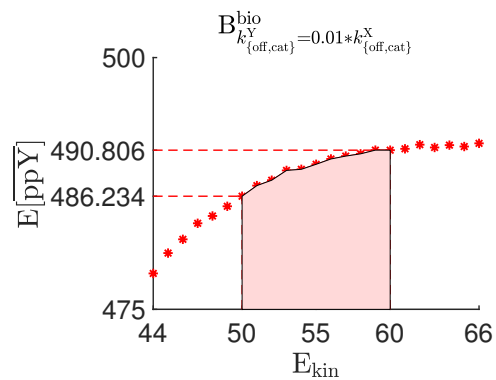




Biological







- The reduction depends not only on correlations but also in which operating regime the network is.

1. Models of phosphorylation-dephosphorylation (PD)
2. Coefficient of output variation and sequestration dynamics
3. Real biological example
4. Conclusion

Conclusion

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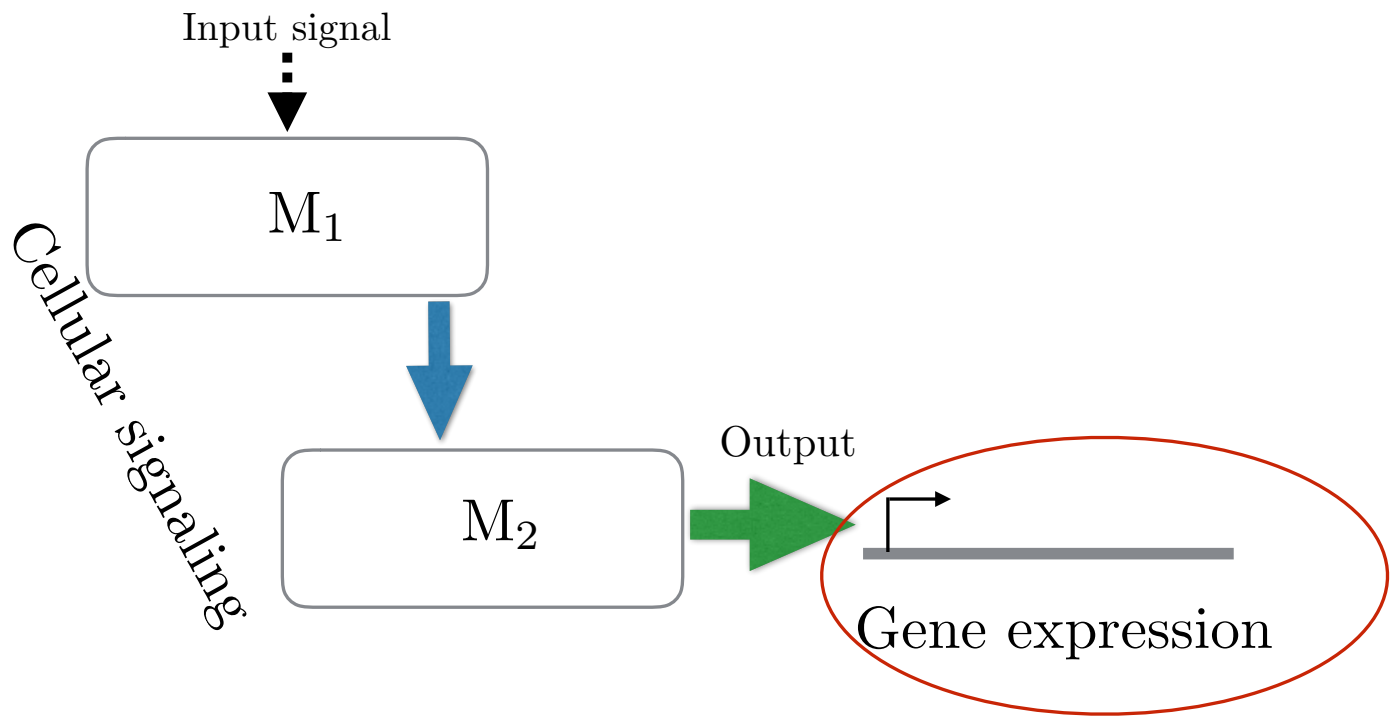
- Outlook
  - Effect of multisite phosphorylation and different enzyme kinectics on dynamic sequestration

Acknowledgements

- Prof. Dr. rer. nat. Nicole Radde, IST, University of Stuttgart, Germany.
- German Research Foundation (DFG) as part of the Transregional Collaborative Research Centre (SFB/Transregio) 141 'Biological Design and Integrative Structures'/project B05.
- Cluster of Excellence in Simulation Technology (EXC 310/2) at the University of Stuttgart.

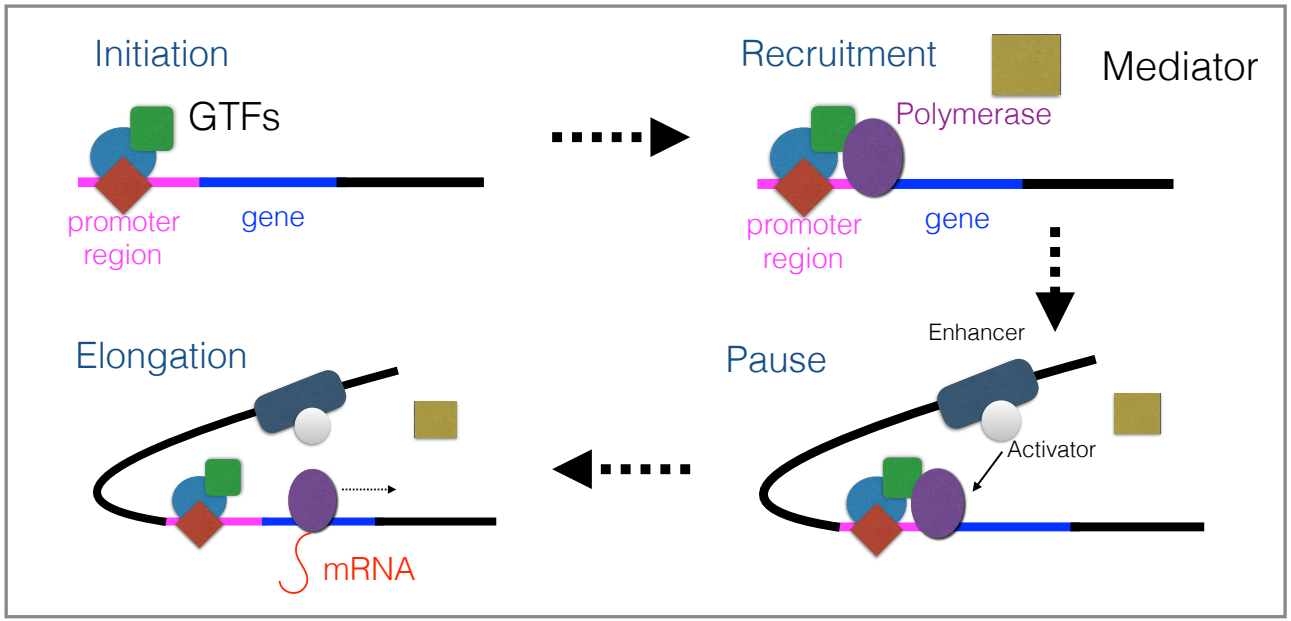
Merci!

Robustness in gene expression



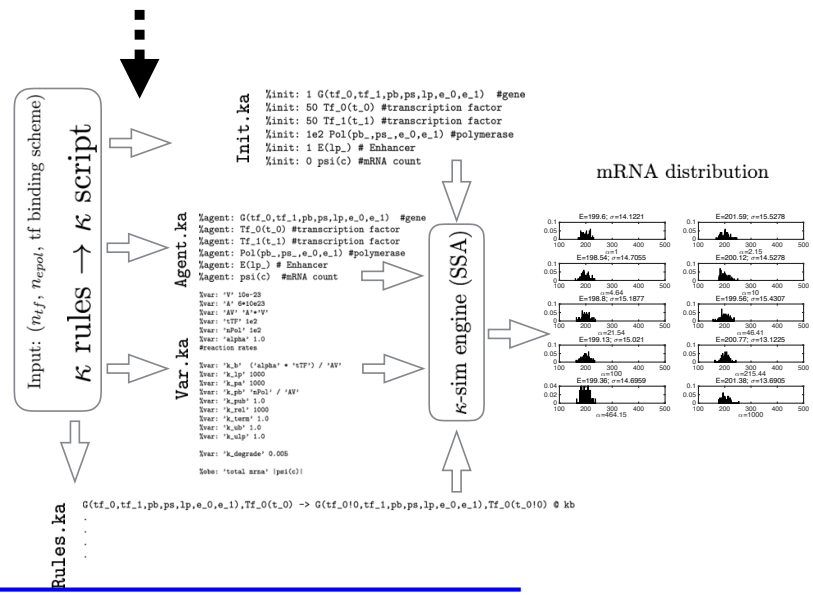
[Ongoing collaboration with Gunawardena lab at the Harvard Medical School]

Rule-based modeling approach



Kappa- a rule based framework

[Danos V, et al. Methods Syst. Biol. 2008]



Eigenvector-based identification of bipartite subgraphs

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Abstract

We report our experiments in identifying large bipartite subgraphs of simple connected graphs which are based on the sign pattern of eigenvectors belonging to the extremal eigenvalues of different graph matrices: adjacency, signless Laplacian, Laplacian and normalized Laplacian matrix. We compare performance of these methods to a combinatorial method based on the Erdös' bound that each graph contains a bipartite subgraph with at least half of its edges. Experiments with one scale-free and three random graph models, which cover a wide range of real-world networks, show that the methods based on the eigenvectors of the normalized Laplacian and the adjacency matrix yield slightly better, but comparable results to the combinatorial method. We also formulate two edge bipartivity indices based on the former eigenvectors, and observe that the method of iterative removal of edges with maximum bipartivity index until one obtains a bipartite subgraph, yields significantly better results than the combinatorial method, and an analogous method that employs the edge bipartivity index of Estrada and Rodríguez-Velázquez.

Keywords: Bipartite subgraphs, Eigenvectors, Complex networks

[Manuscript in preparation]