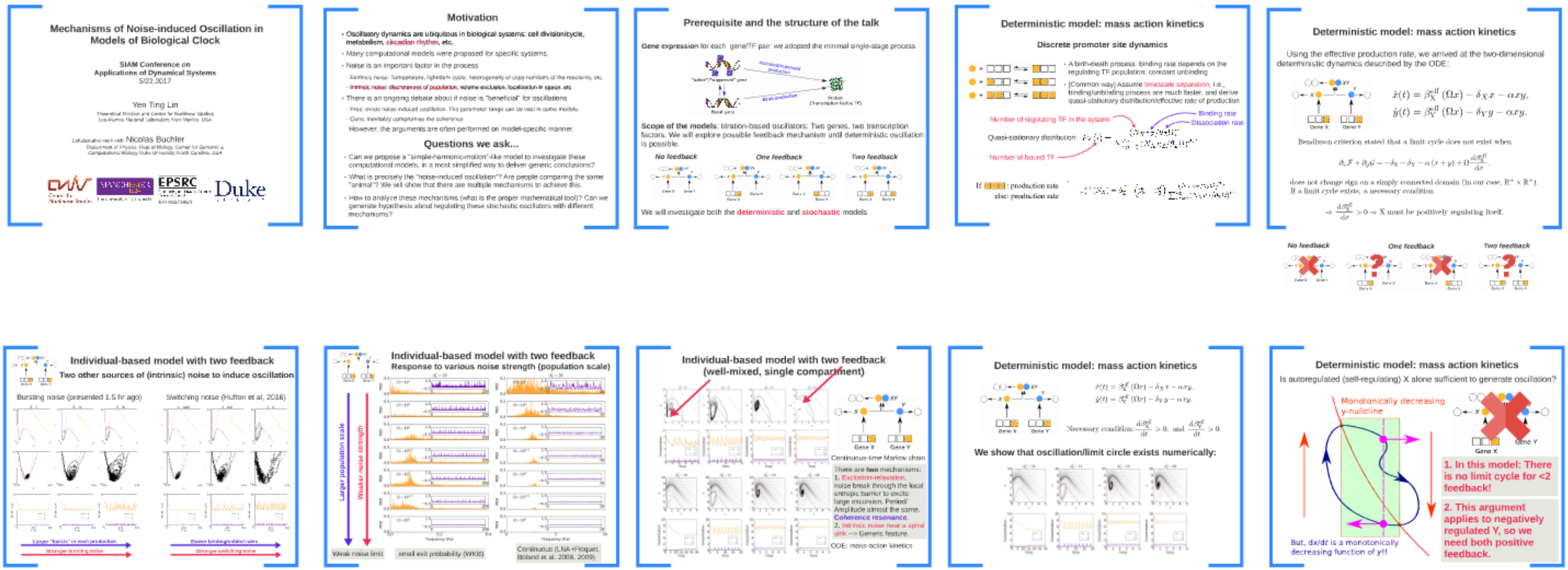

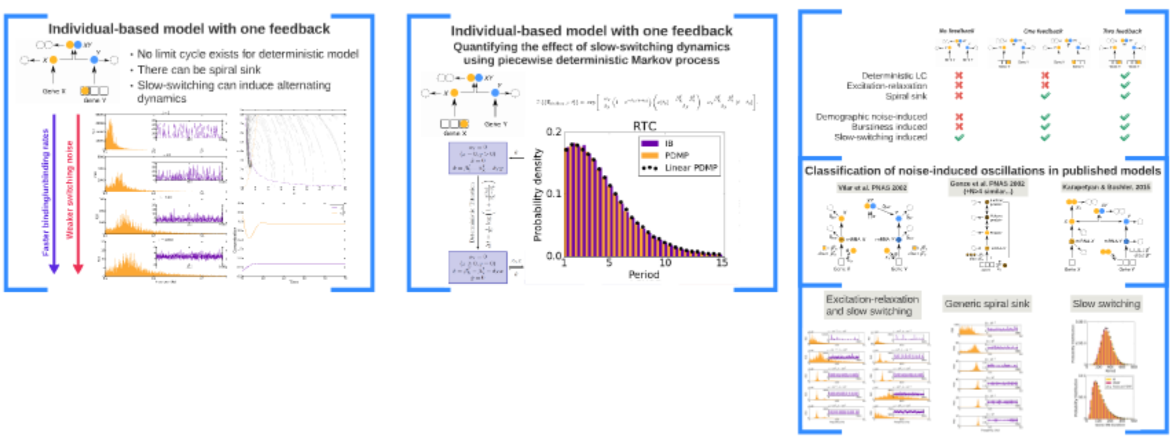

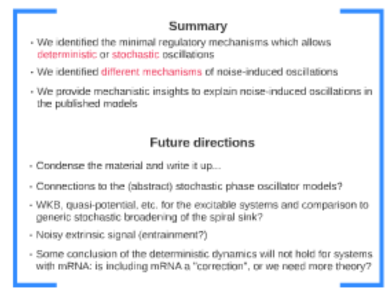

Very rough draft available; if you are interested: yentingl@lanl.gov

Thank you for your attention!

Mechanisms of Noise-induced Oscillation in Models of Biological Clock

SIAM Conference on
Applications of Dynamical Systems
5/22,2017

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Collaborative work with: Nicolas Buchler

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Center for Nonlinear Studies
MANCHESTER 1824 The University of Manchester
EPSRC Engineering and Physical Sciences Research Council
EP/ K037145/1
Duke UNIVERSITY

Motivation

- Oscillatory dynamics are ubiquitous in biological systems: cell division/cycle, metabolism, circadian rhythm, etc.
- Many computational models were proposed for specific systems.
- Noise is an important factor in the process

  - Extrinsic noise: Temperature, light/dark cycle, heterogeneity of copy numbers of the reactants, etc.

  - Intrinsic noise: discreteness of population, volume exclusion, localization in space, etc
- There is an ongoing debate about if noise is "beneficial" for oscillations

  - Pros: exists noise-induced oscillation. The parameter range can be vast in some models.

  - Cons: inevitably compromise the coherence

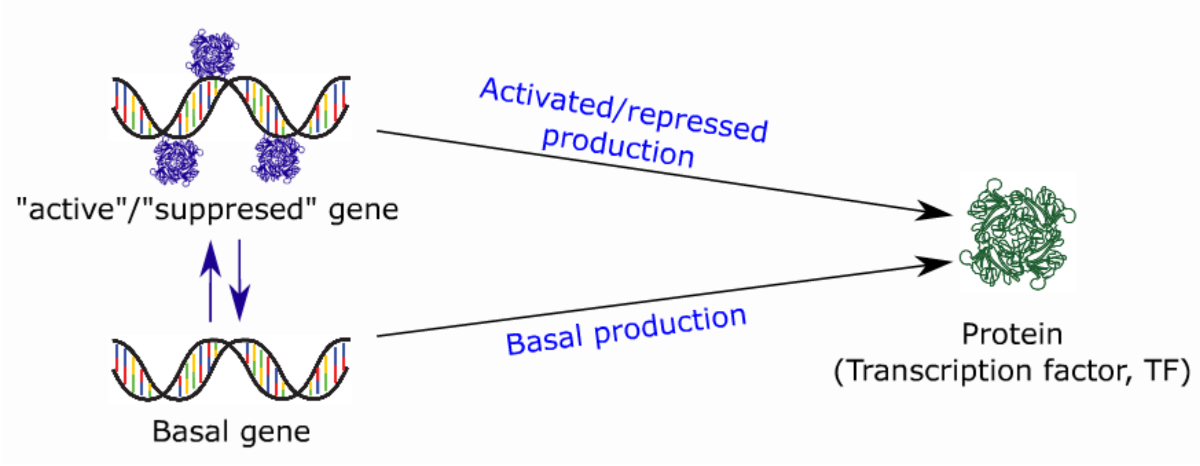
  However, the arguments are often performed on model-specific manner.

Questions we ask...

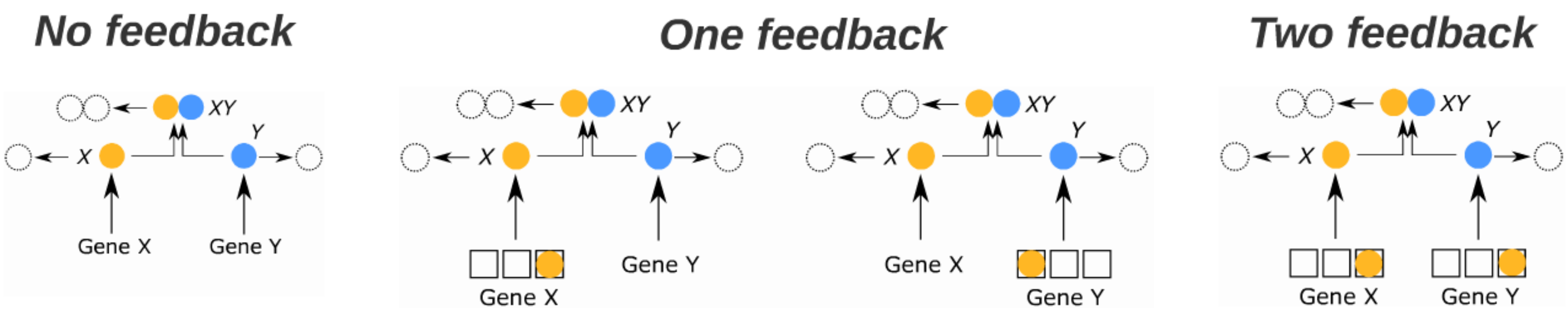
- Can we propose a "simple-harmonic-motion"-like model to investigate these computational models, in a most simplified way to deliver generic conclusions?
- What is precisely the "noise-induced oscillation"? Are people comparing the same "animal"? We will show that there are multiple mechanisms to achieve this.
- How to analyze these mechanisms (what is the proper mathematical tool)? Can we generate hypothesis about regulating these stochastic oscillators with different mechanisms?

Prerequisite and the structure of the talk

Gene expression for each gene/TF pair: we adopted the minimal single-stage process

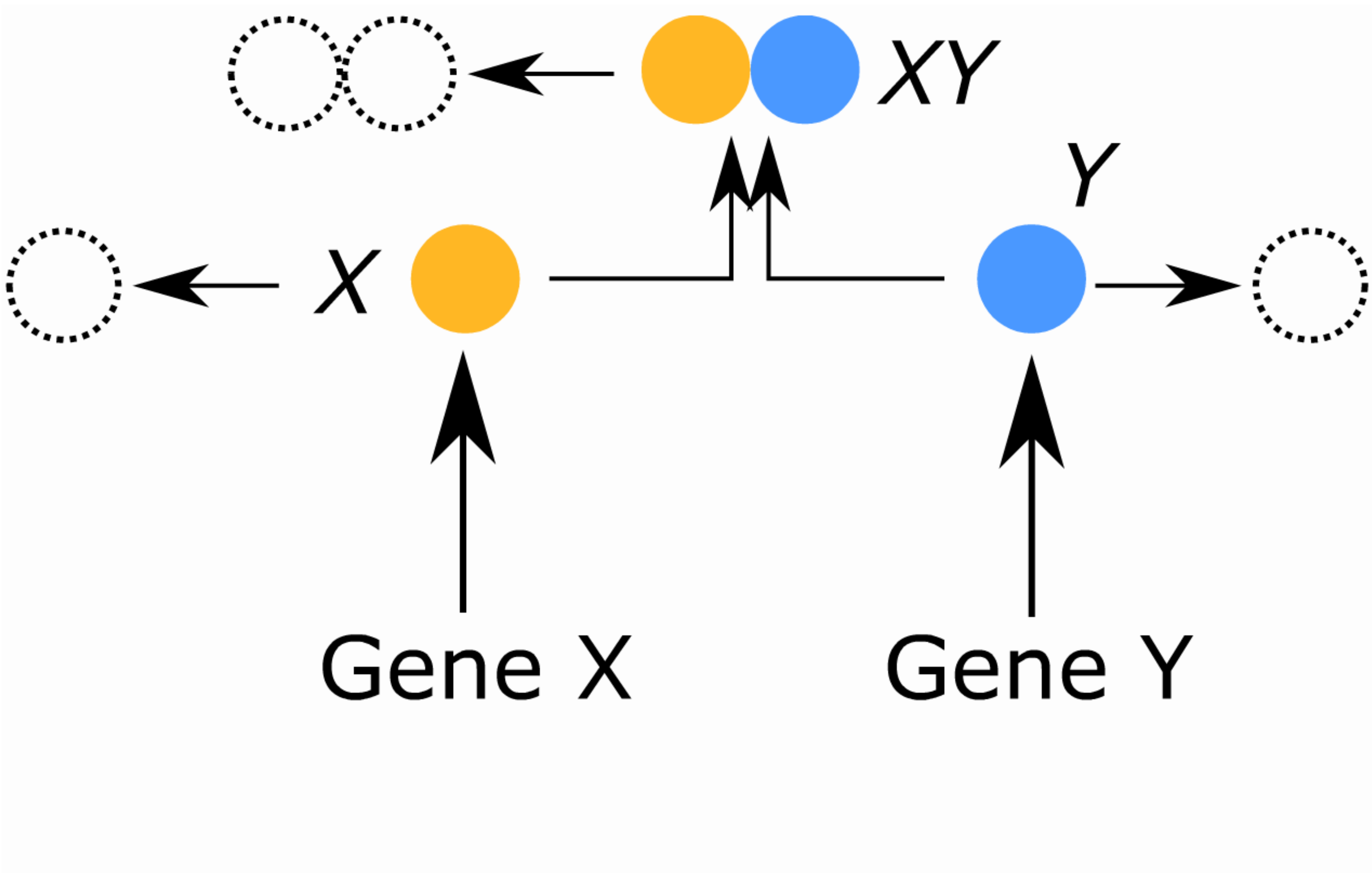


Scope of the models: titration-based oscillators: Two genes, two transcription factors. We will explore possible feedback mechanism until deterministic oscillation is possible.



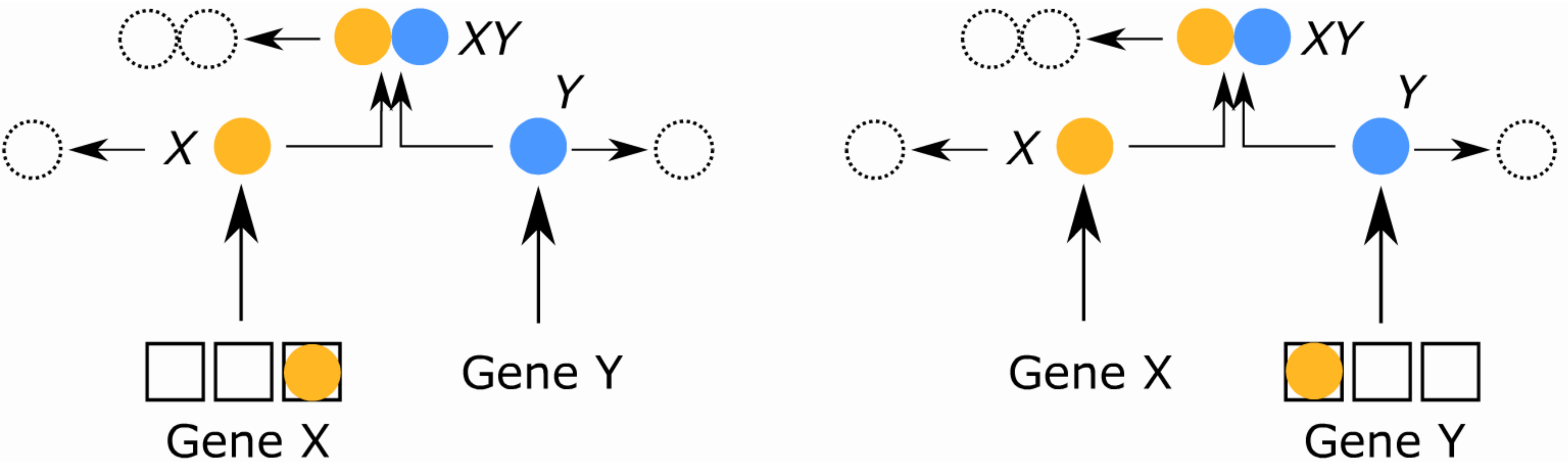
We will investigate both the **deterministic** and **stochastic** models

No feedback



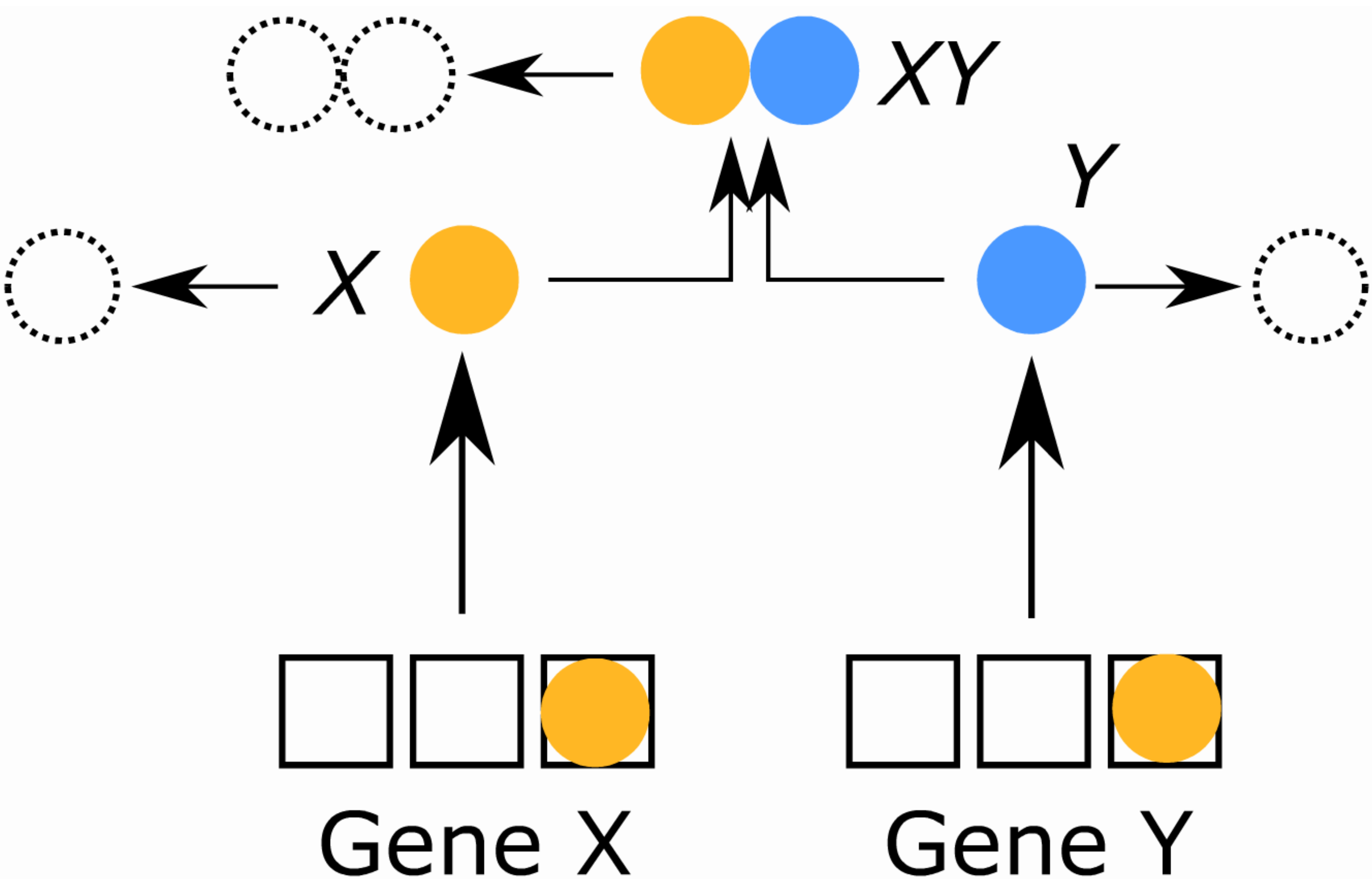
re possible feedback mechanism un

One feedback



oth the **deterministic** and **stochasti**

Two feedback



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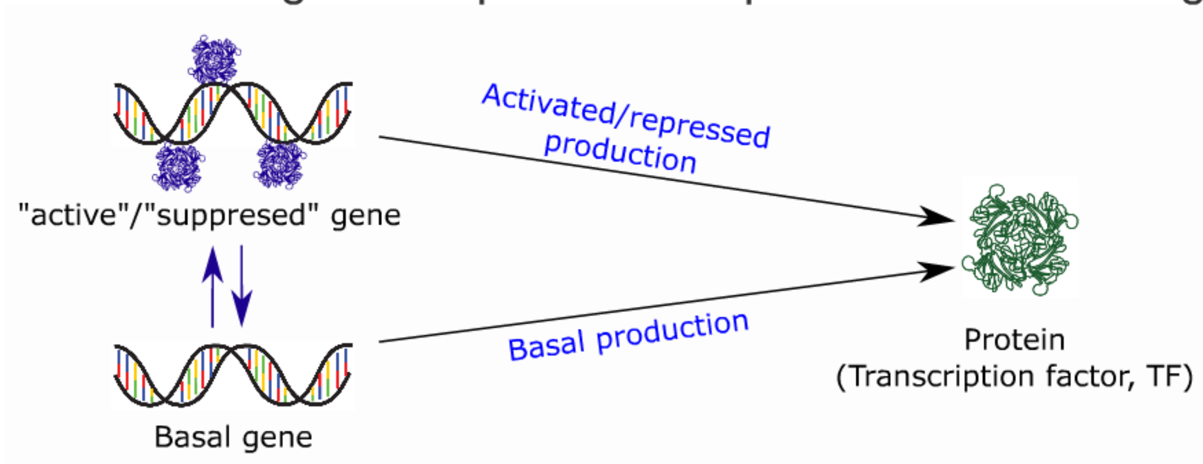

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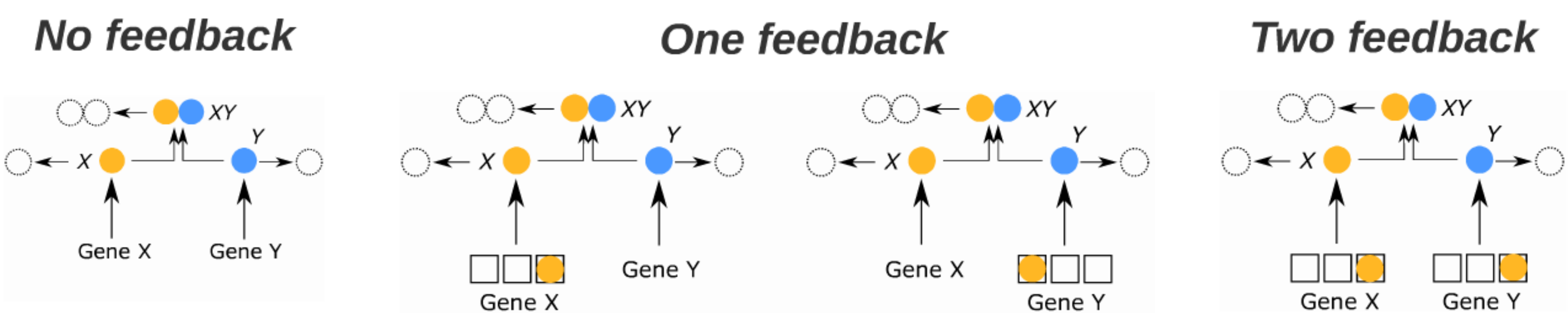
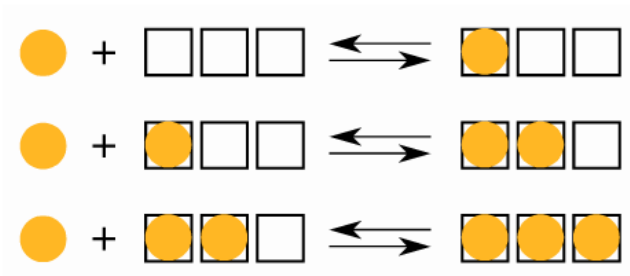


We will investigate both the **deterministic** and **stochastic** models

Deterministic model: mass action kinetics

Discrete promoter site dynamics



- A birth-death process: binding rate depends on the regulating TF population; constant unbinding
- [Common way] Assume timescale separation, i.e., binding/unbinding process are much faster, and derive quasi-stationary distribution/effective rate of production

Number of regulating TF in the system

Binding rate

Dissociation rate

Quasi-stationary distribution: $$P_{\mathrm{Z}}(i) = \frac{\left(N_X \kappa_{\mathrm{Z}} / \theta_{\mathrm{Z}} \Omega\right)^i}{\sum_{m=0}^{n_{\mathrm{Z}}} \left(N_X \kappa_{\mathrm{Z}} / \theta_{\mathrm{Z}} \Omega\right)^m}.$$

Number of bound TF

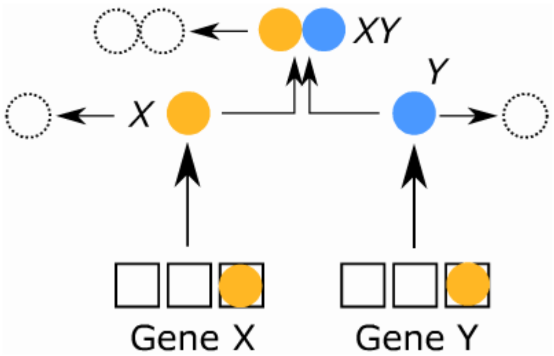
If  : production rate β_{Z}^{b}

else: production rate β_{Z}^{f}

$$\beta_{\mathrm{Z}}^{\mathrm{eff}}(N_X) = \beta_{\mathrm{Z}}^{f} + \left(\beta_{\mathrm{Z}}^{b} - \beta_{\mathrm{Z}}^{f}\right) \frac{\left(N_X \kappa_{\mathrm{Z}} / \theta_{\mathrm{Z}} \Omega\right)^{n_{\mathrm{Z}}}}{\sum_{m=0}^{n_{\mathrm{Z}}} \left(N_X \kappa_{\mathrm{Z}} / \theta_{\mathrm{Z}} \Omega\right)^m}.$$

Deterministic model: mass action kinetics

Using the effective production rate, we arrived at the two-dimensional deterministic dynamics described by the ODE:



$$\dot{x}(t) = \beta_{\mathrm{X}}^{\mathrm{eff}}\left(\Omega x\right) - \delta_X x - \alpha x y,$$
$$\dot{y}(t) = \beta_{\mathrm{Y}}^{\mathrm{eff}}\left(\Omega x\right) - \delta_Y y - \alpha x y.$$

Bendixson criterion stated that a limit cycle does not exist when

$$\partial_x \mathcal{F} + \partial_y \mathcal{G} = -\delta_{\mathrm{X}} - \delta_{\mathrm{Y}} - \alpha\left(x + y\right) + \Omega \frac{\mathrm{d}\beta_{\mathrm{X}}^{\mathrm{eff}}}{\mathrm{d}x}.$$

does not change sign on a simply connected domain (in our case, $\mathbb{R}^+ \times \mathbb{R}^+$). If a limit cycle exists, a necessary condition

$$\Rightarrow \frac{\mathrm{d}\beta_{\mathrm{X}}^{\mathrm{eff}}}{\mathrm{d}x} > 0 \Rightarrow \text{X must be positively regulating itself.}$$

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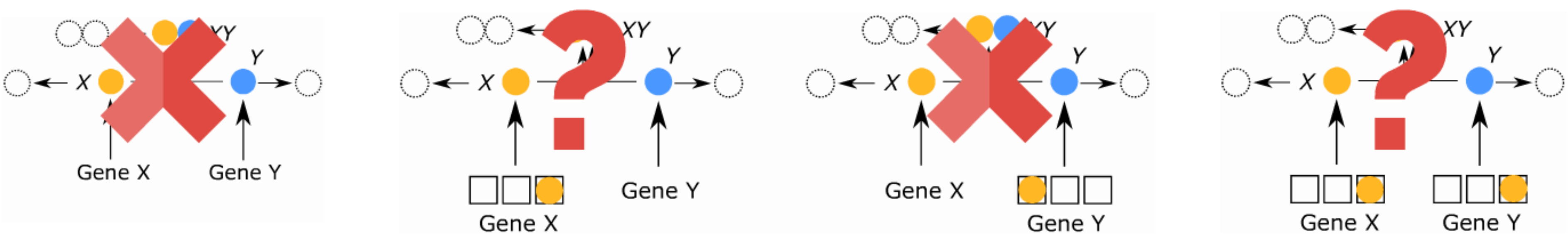
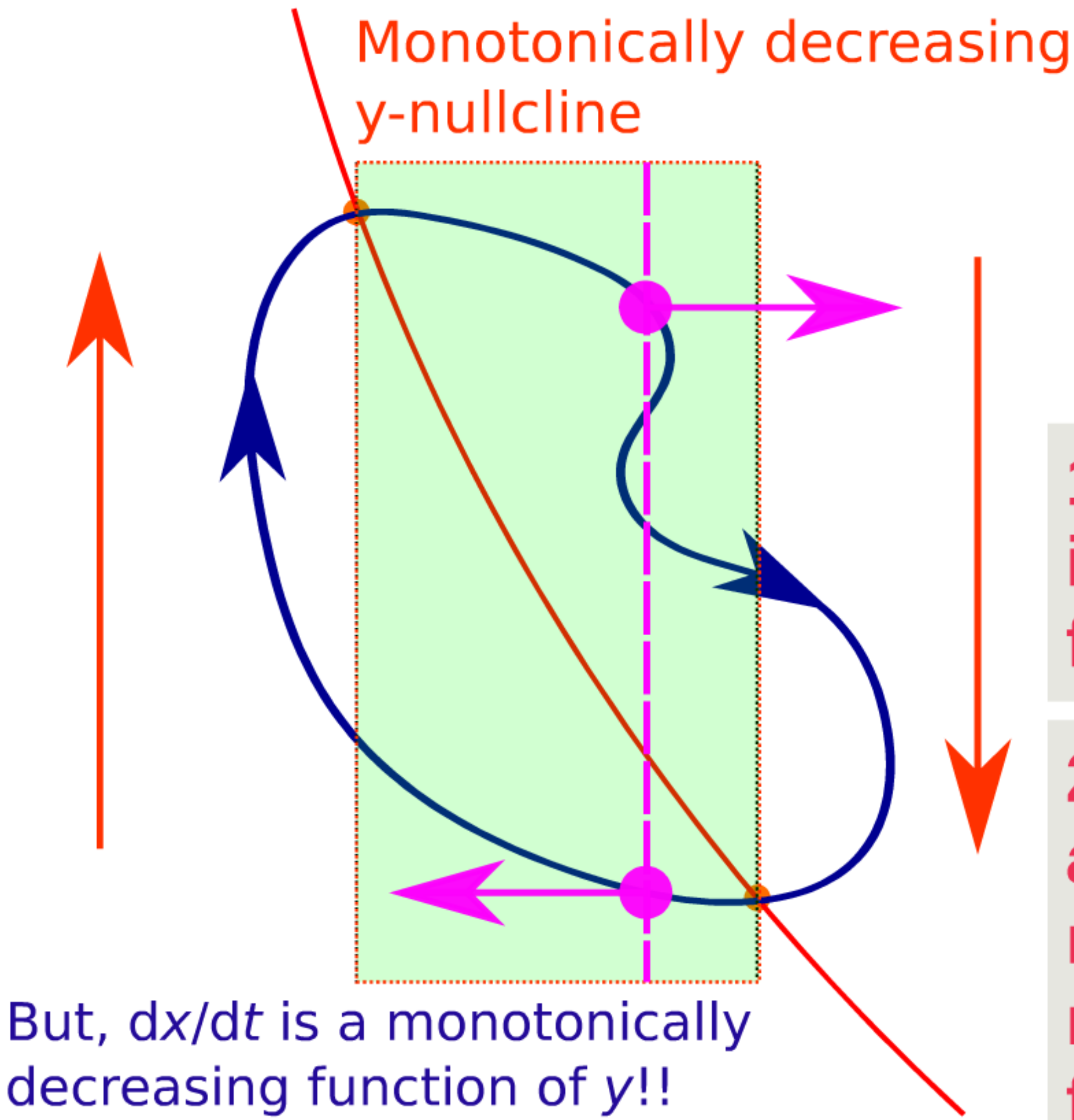
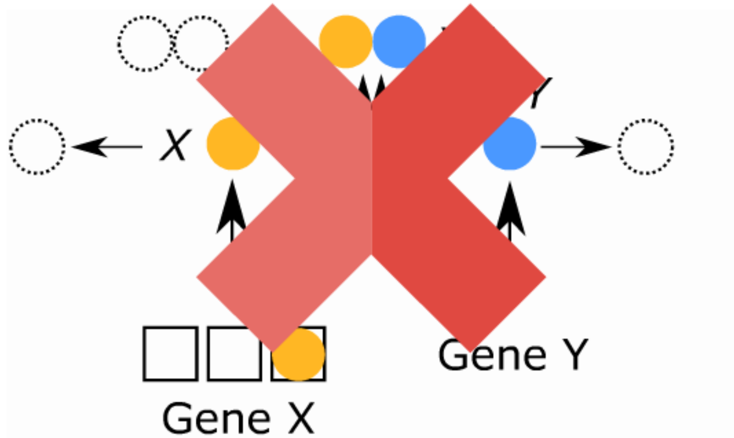
No feedback ***One feedback*** ***Two feedback***



Deterministic model: mass action kinetics

Is autoregulated (self-regulating) X alone sufficient to generate oscillation?

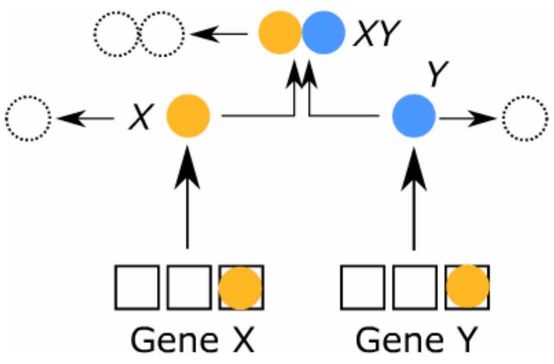




1. In this model: There is no limit cycle for <2 feedback!

2. This argument applies to negatively regulated Y, so we need both positive feedback.

Deterministic model: mass action kinetics



$$\dot{x}(t) = \beta_X^{\text{eff}}(\Omega x) - \delta_X x - \alpha x y,$$
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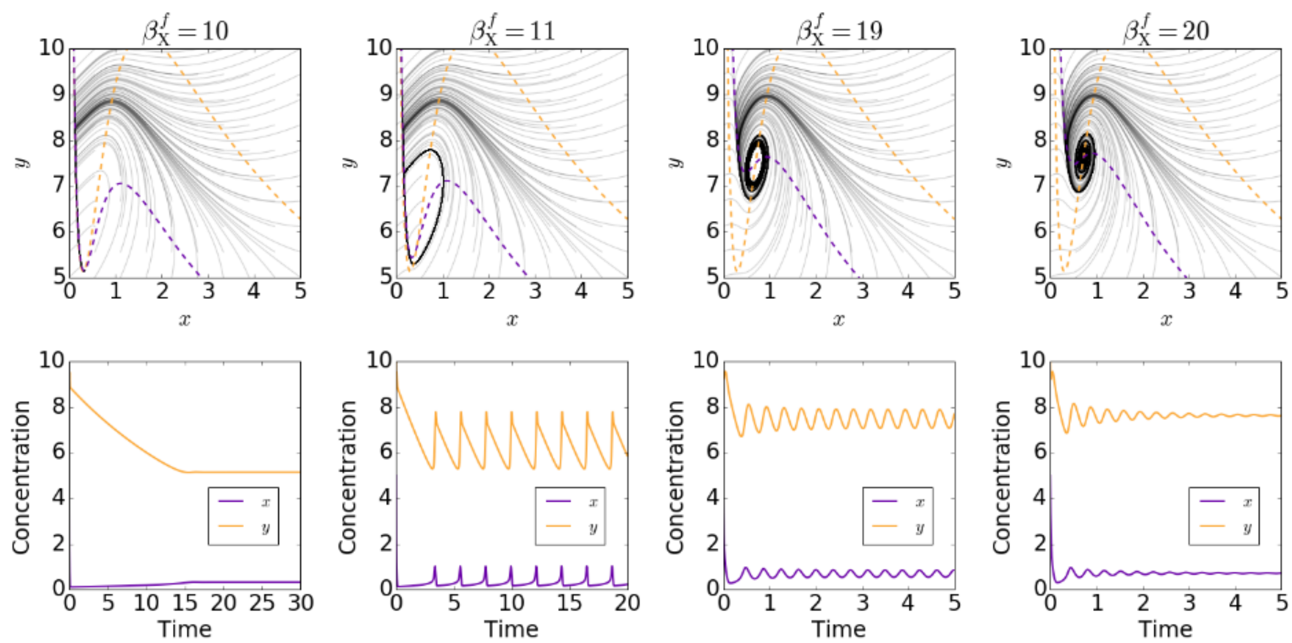
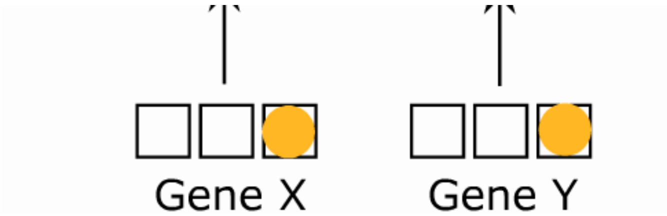
$$\text{Necessary condition:} \frac{\mathrm{d}\beta_X^{\text{eff}}}{\mathrm{d}t} > 0, \text{ and } \frac{\mathrm{d}\beta_Y^{\text{eff}}}{\mathrm{d}t} > 0.$$

We show that oscillation/limit circle exists numerically:





Necessary condition: $\frac{d\beta_X^{eff}}{dt} > 0$, and $\frac{d\beta_Y^{eff}}{dt} > 0$.

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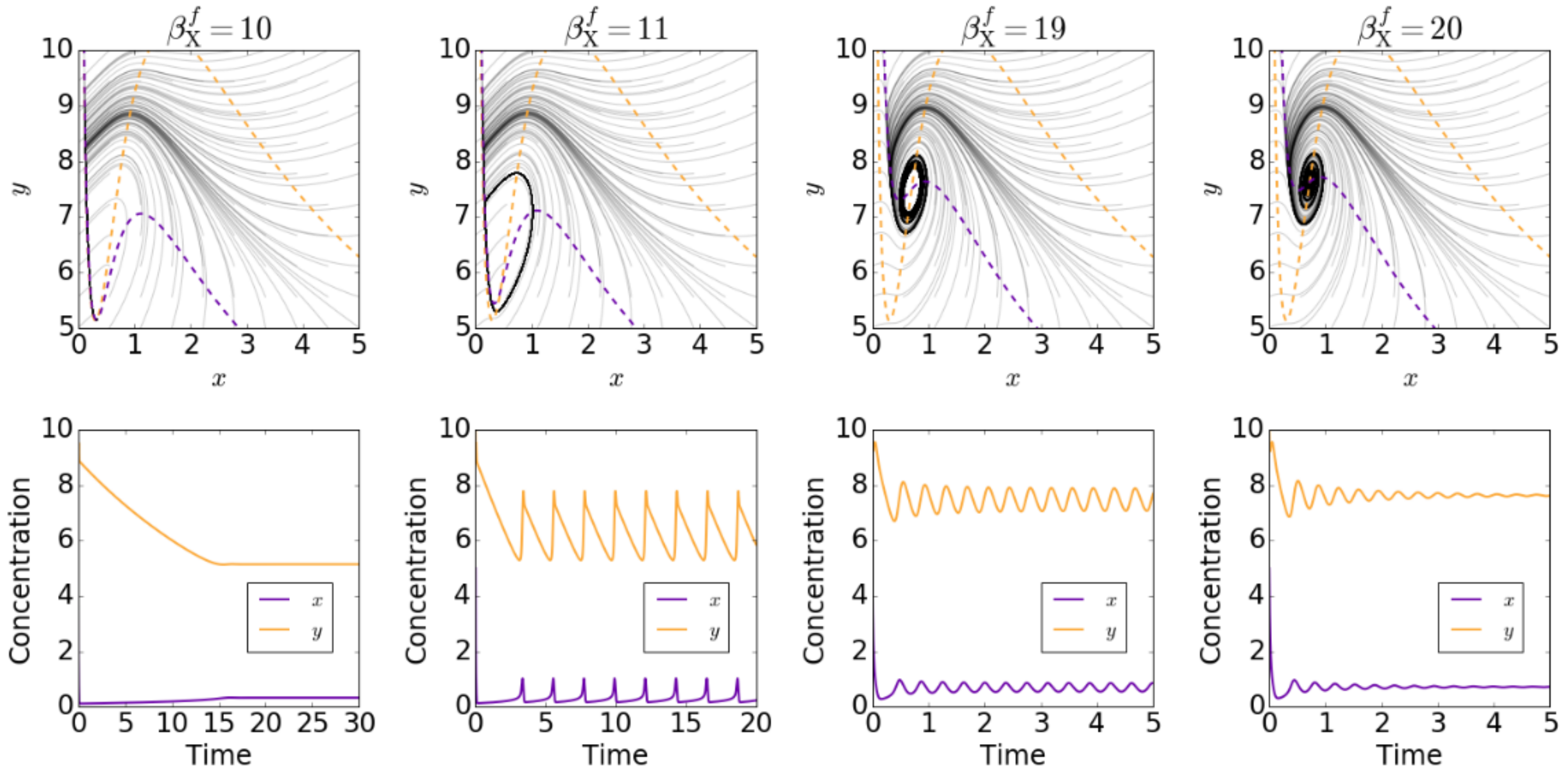
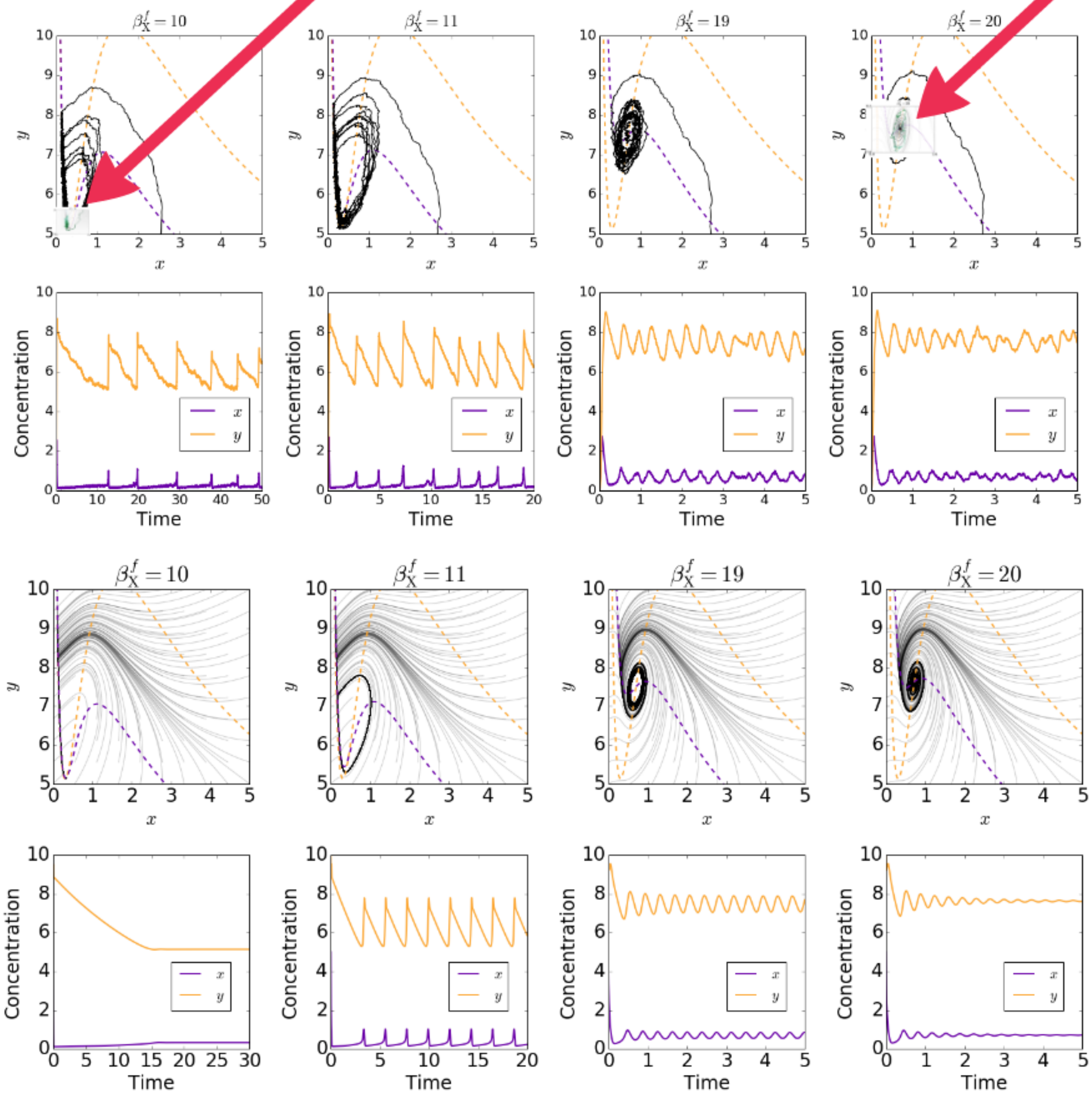
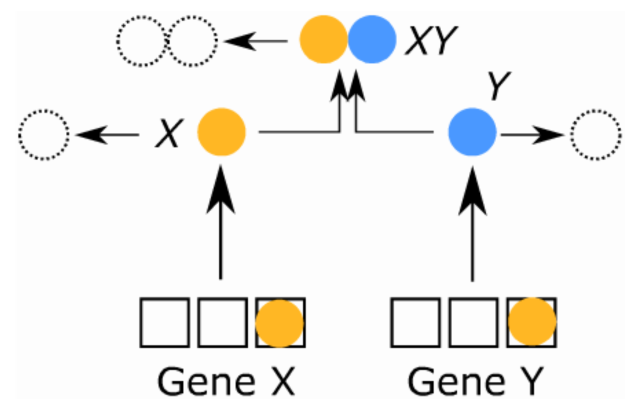


Individual-based model with two feedback (well-mixed, single compartment)



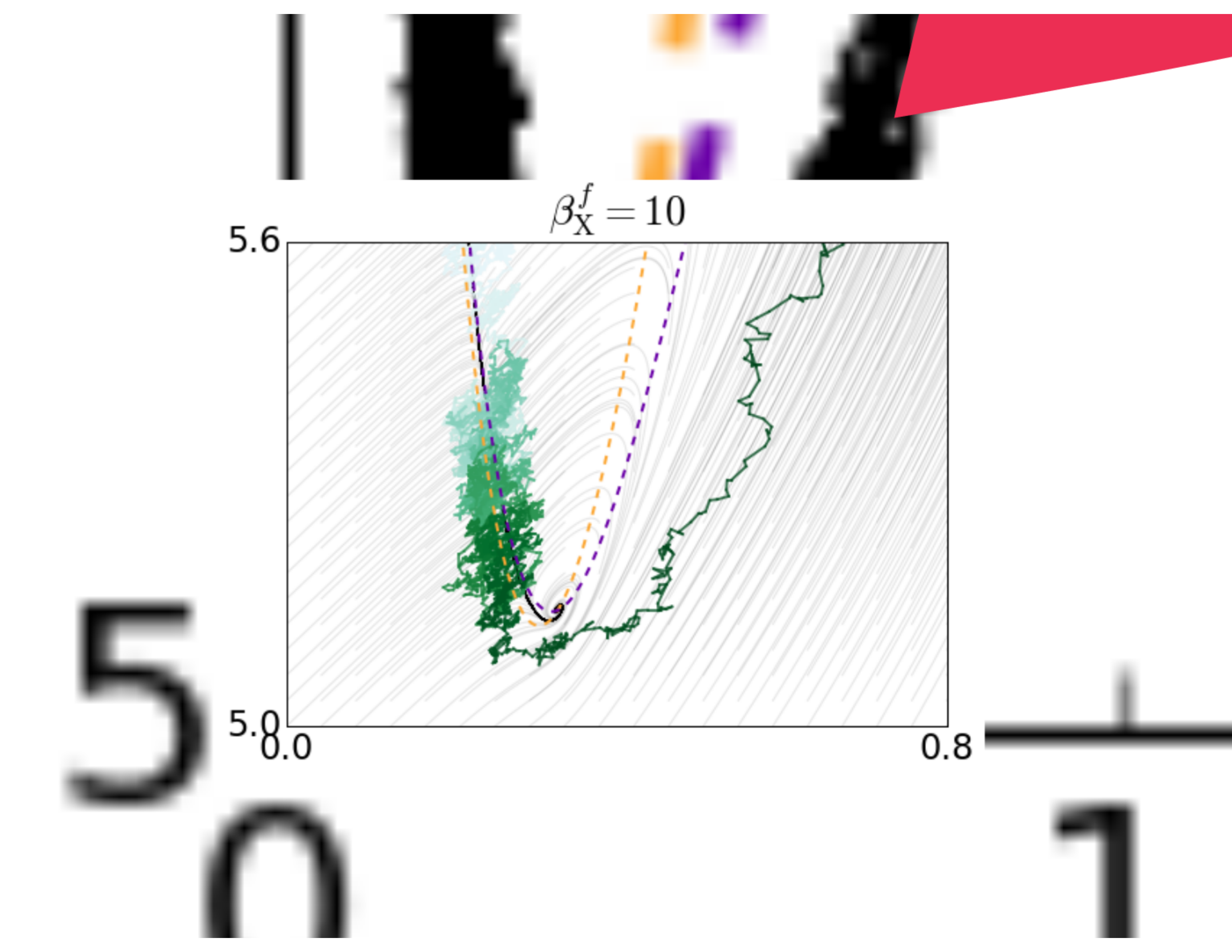


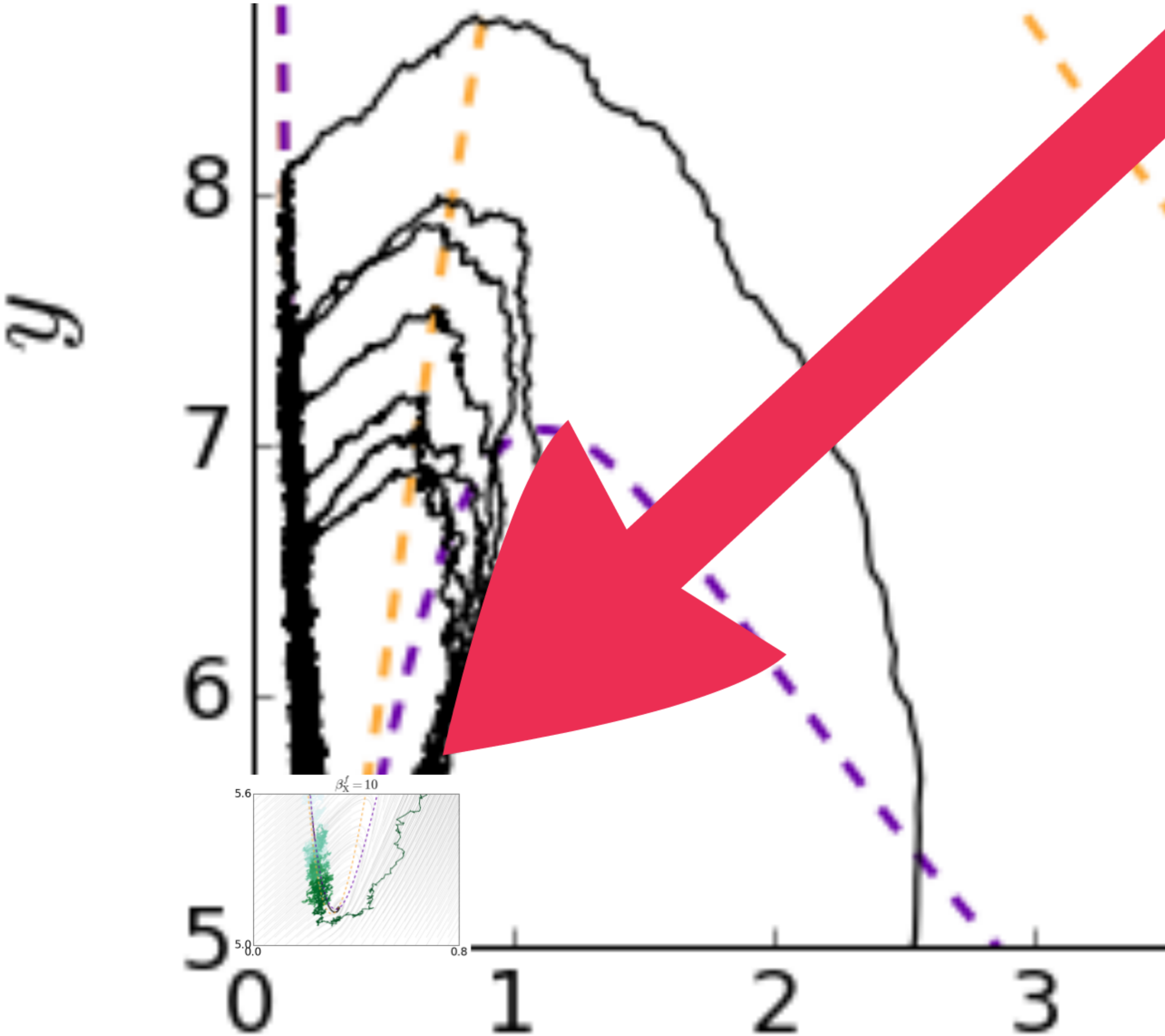
Continuous-time Markov chain

There are **two** mechanisms:

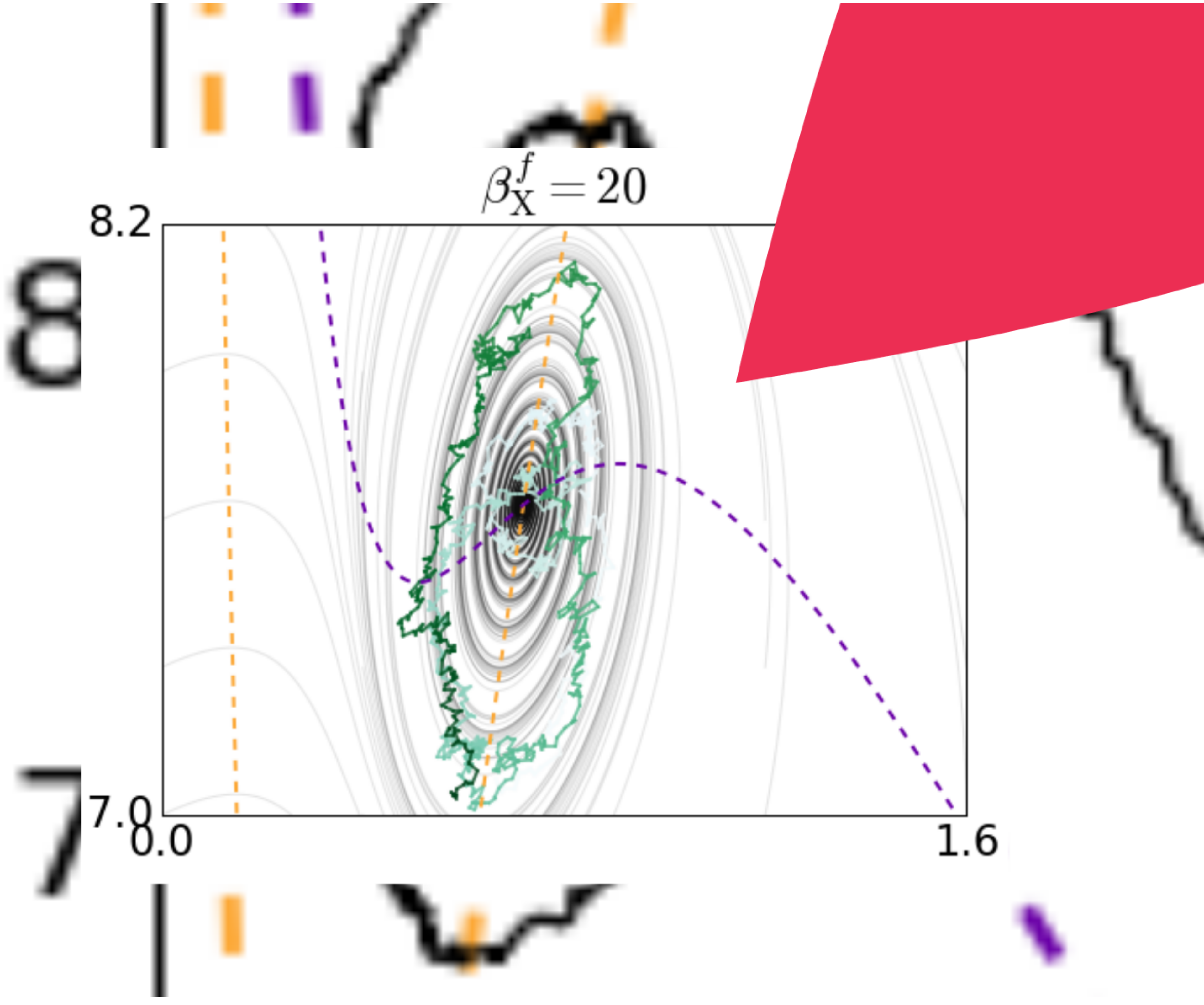
1. Excitation-relaxation, noise break through the local entropic barrier to excite large excursion. Period/ Amplitude almost the same. **Coherence resonance**.
2. Intrinsic noise near a spiral sink --> Generic feature.

ODE: mass-action kinetics


$\beta_X^f = 10$
5.6
5.0
0.0
0.8

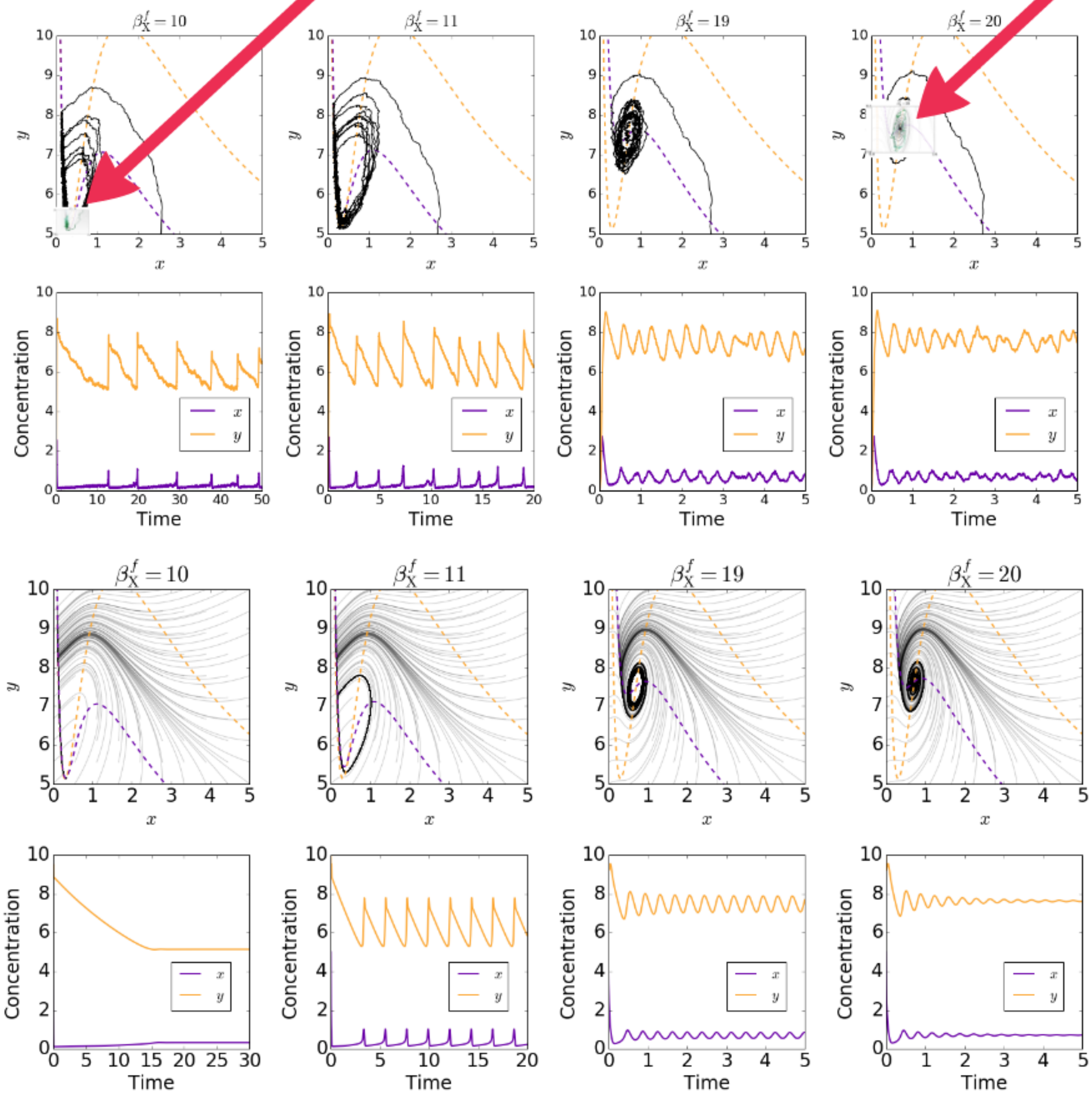


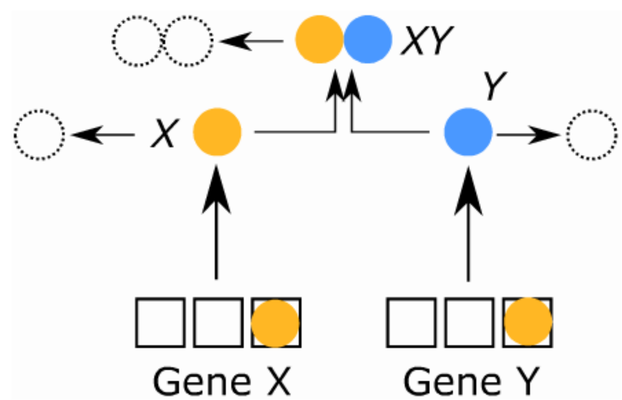
y
8
7
6
5
0
1
2
3
$\beta_X^f = 10$
5.6
5.0
0.0
0.8



$\beta_X^f = 20$
8.2
7.0
0.0
1.6

Individual-based model with two feedback (well-mixed, single compartment)





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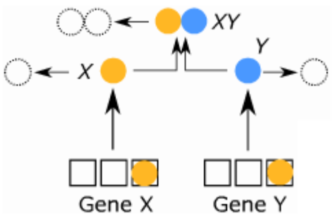
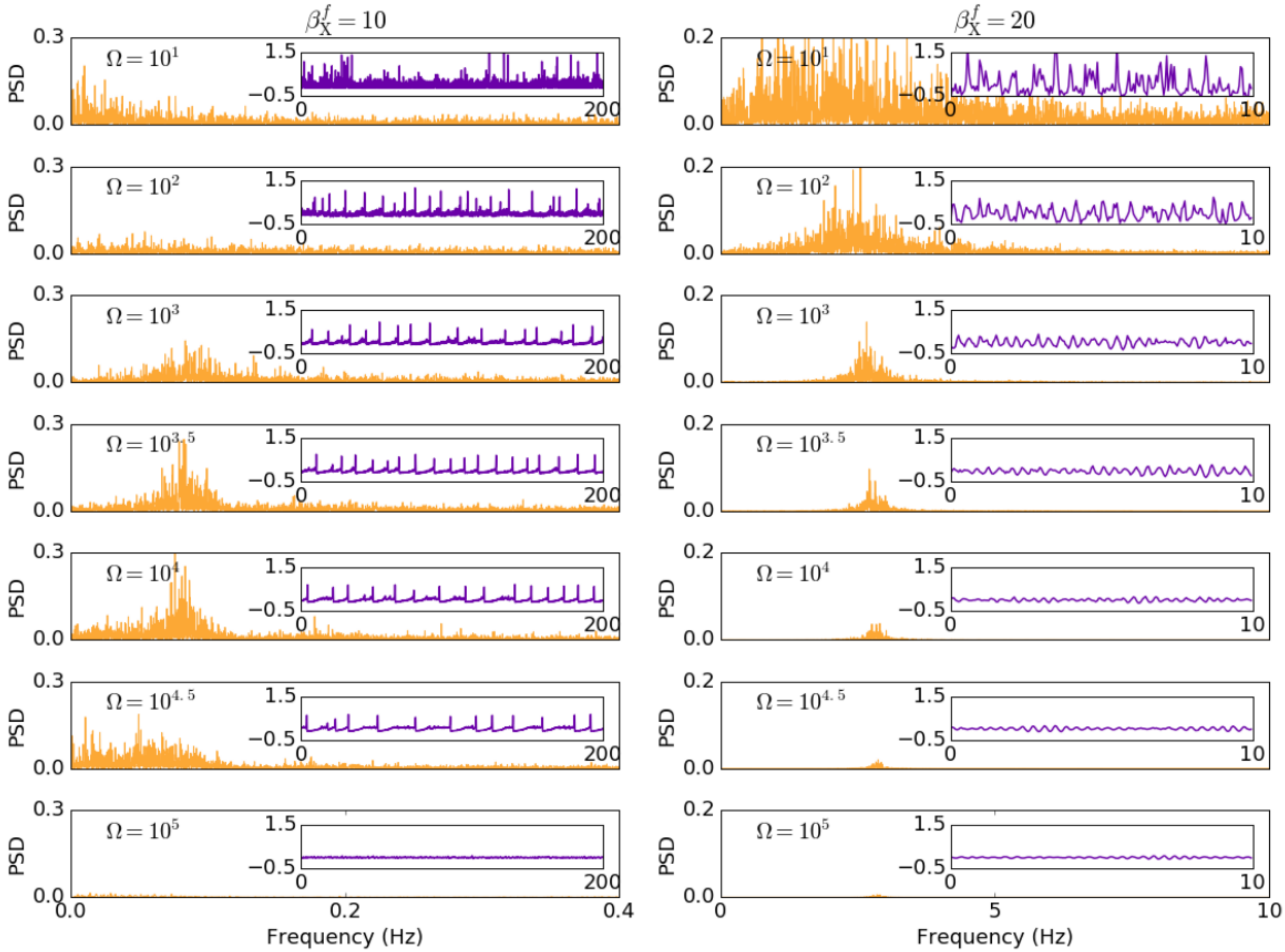


Individual-based model with two feedback

Response to various noise strength (population scale)



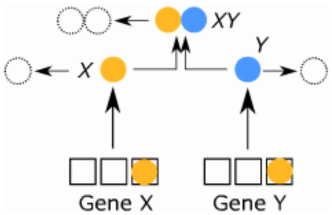
Larger population scale

Weaker noise strength

Weak noise limit

small exit probability (WKB)

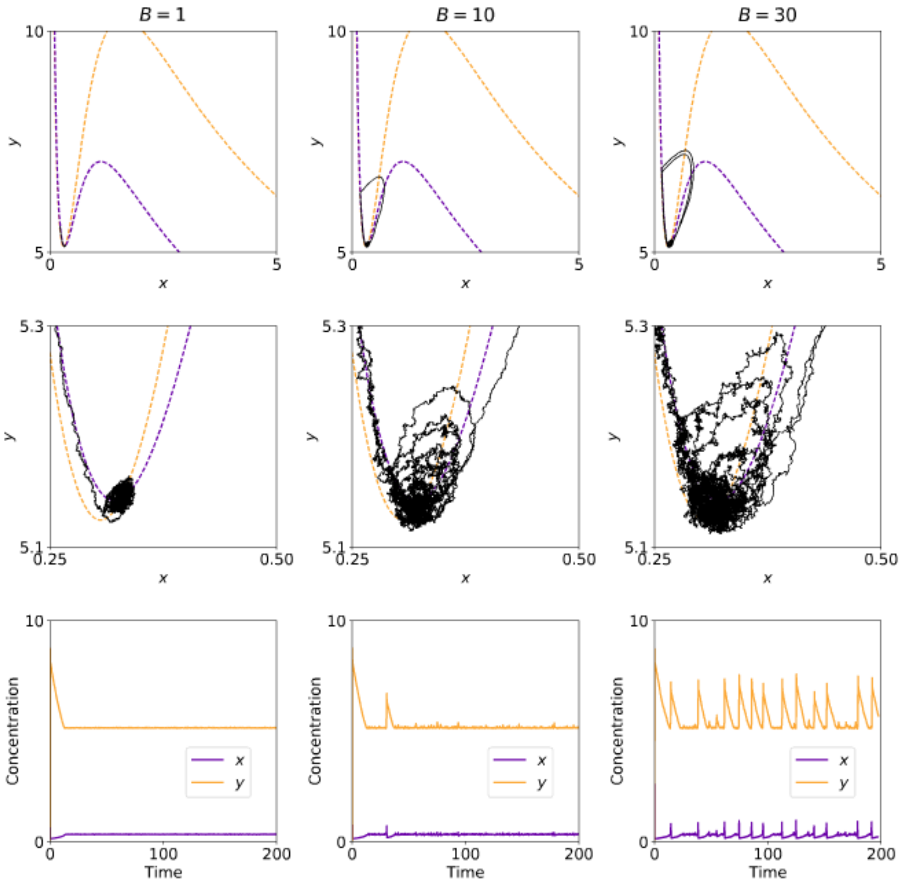
Continuous (LNA+Floquet, Boland et al. 2008, 2009)



Individual-based model with two feedback

Two other sources of (intrinsic) noise to induce oscillation

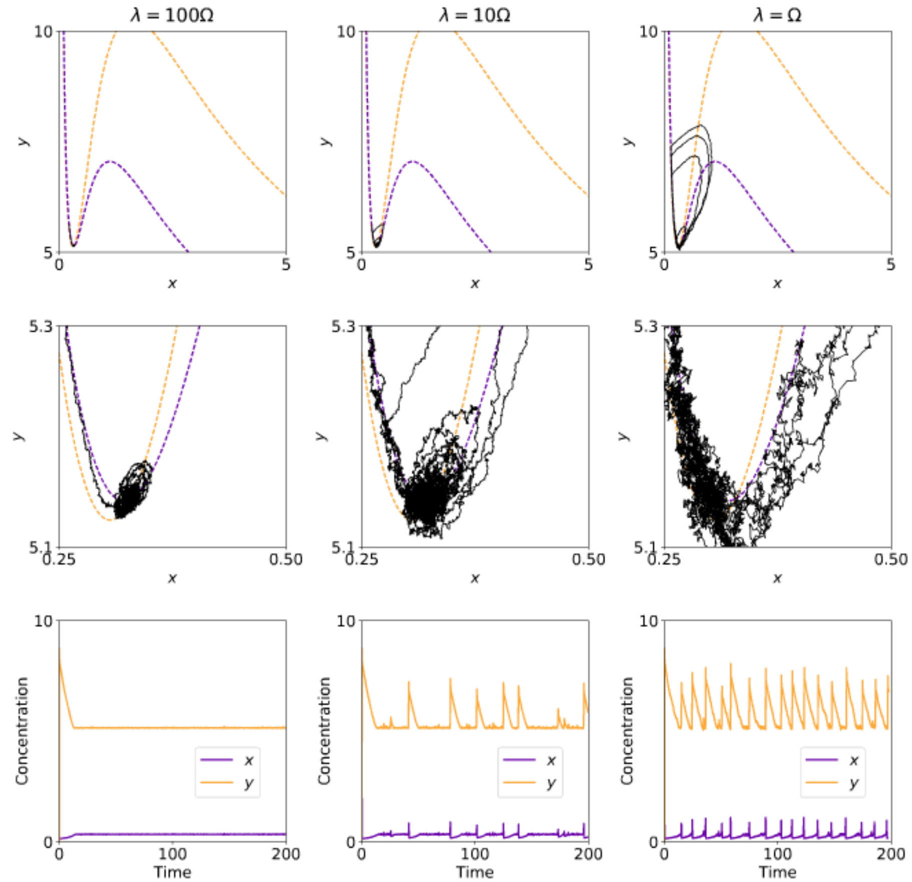
Bursting noise (presented 1.5 hr ago)



Larger "bursts" in each production

Stronger bursting noise

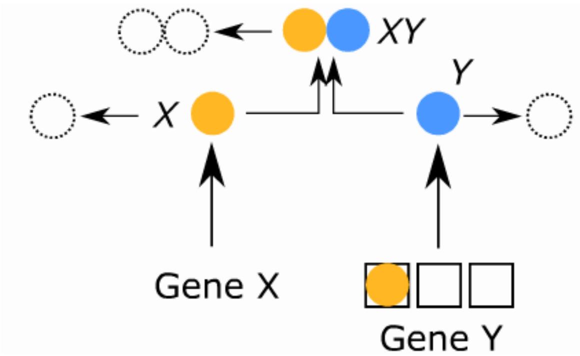
Switching noise (Hufton et al, 2016)



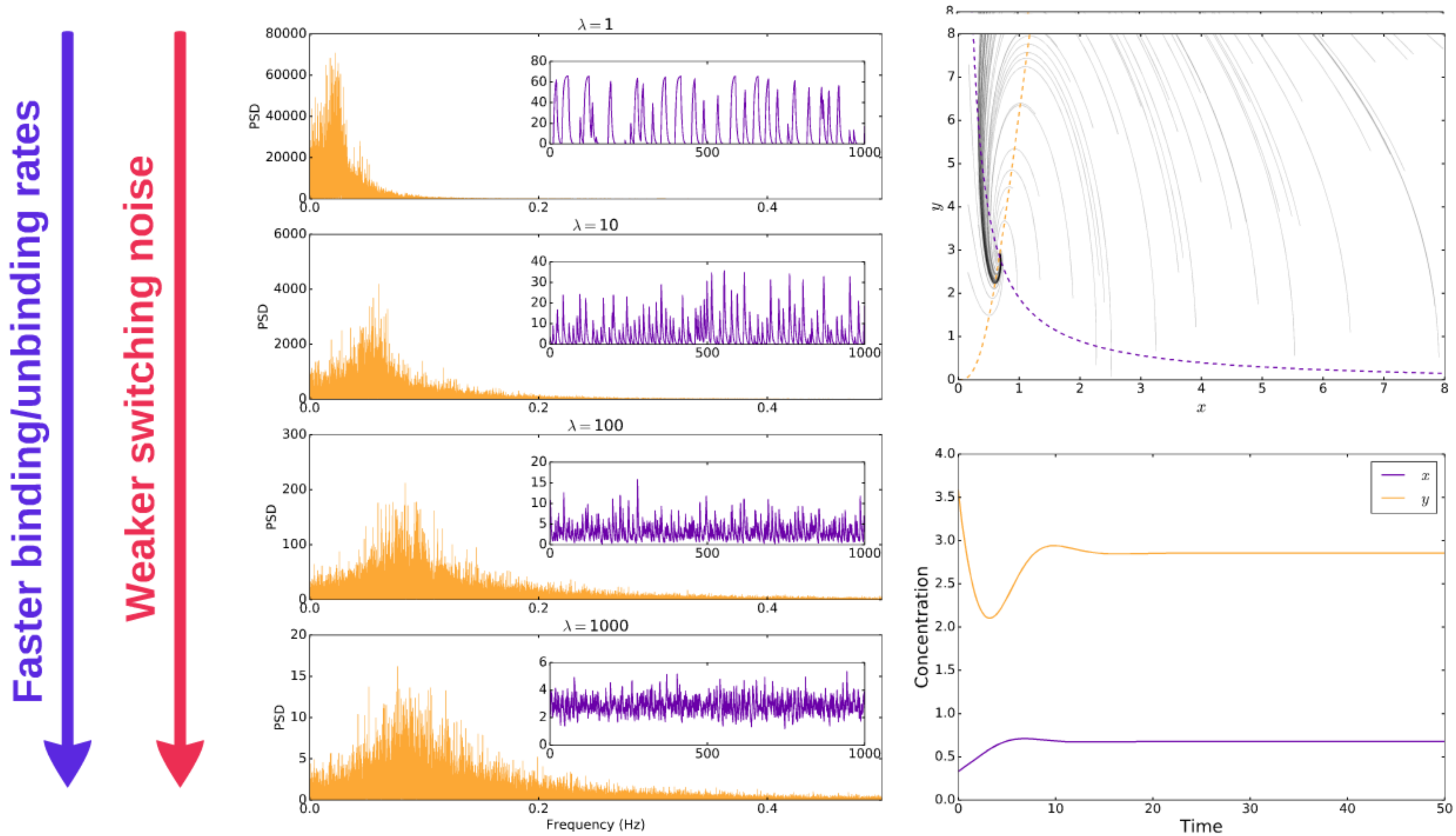
Slower binding/unbind rates

Stronger switching noise

Individual-based model with one feedback

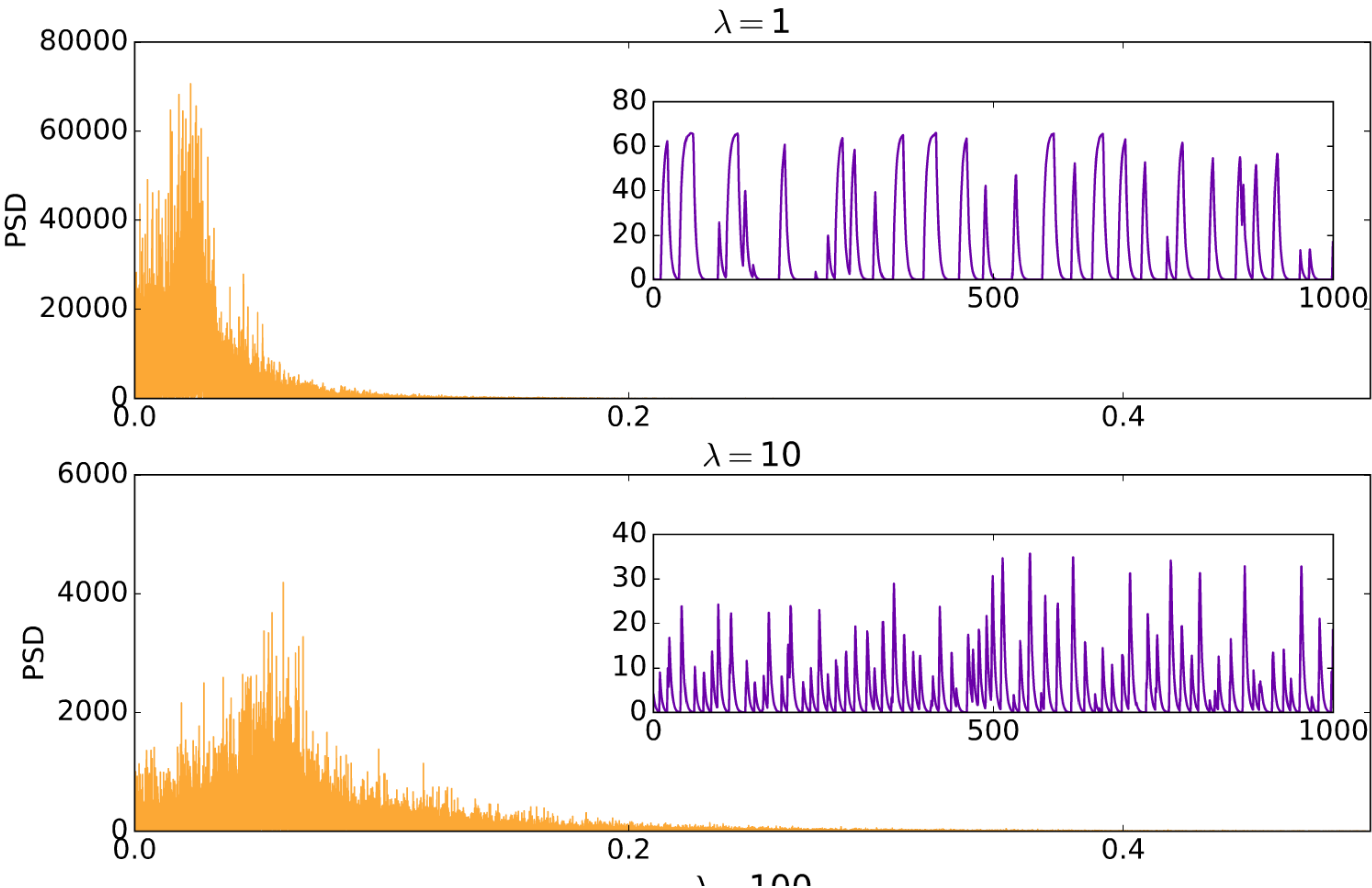


- No limit cycle exists for deterministic model
- There can be spiral sink
- Slow-switching can induce alternating dynamics



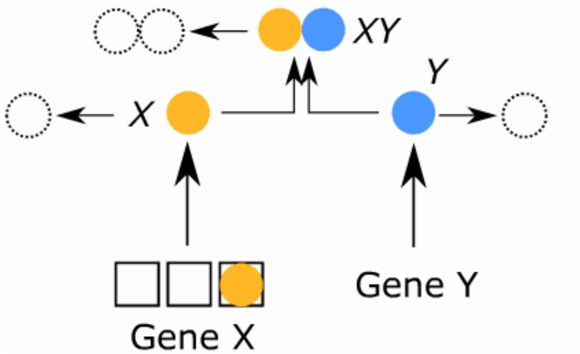
ene Y

dynamics

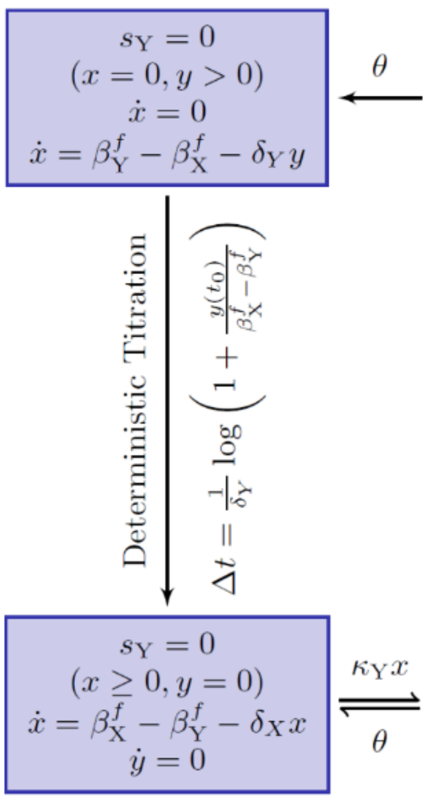


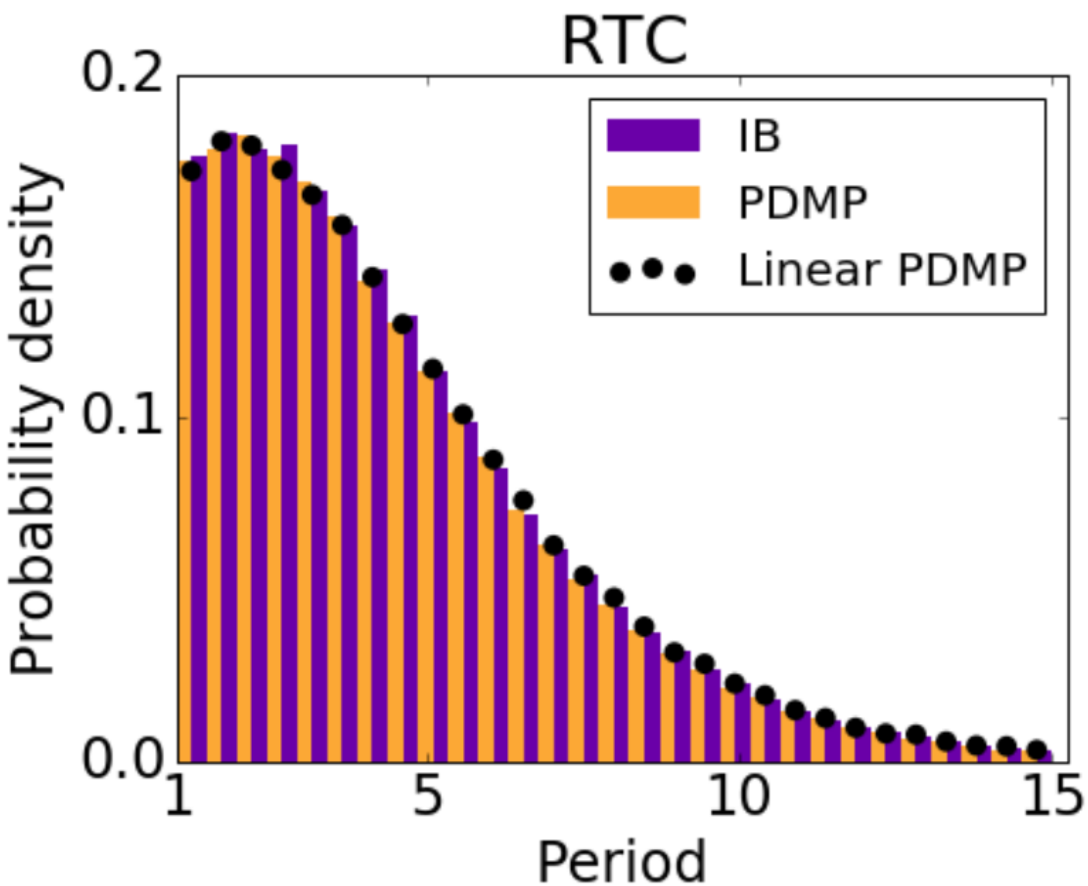
Individual-based model with one feedback

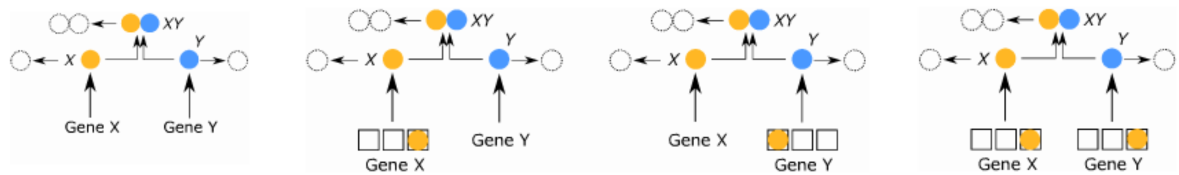
Quantifying the effect of slow-switching dynamics using piecewise deterministic Markov process



$$\mathbb{P}\left\{\{T_{\text{binding}} > t\}\right\} = \exp\left[-\frac{\kappa_{\mathrm{Y}}}{\delta_X}\left(1 - e^{-\delta_X (t-t_0)}\right)\left(x(t_0) - \frac{\beta^f_{\mathrm{X}} - \beta^f_{\mathrm{Y}}}{\delta_X}\right) - \kappa_{\mathrm{Y}}\frac{\beta^f_{\mathrm{X}} - \beta^f_{\mathrm{Y}}}{\delta_X}(t - t_0)\right].$$



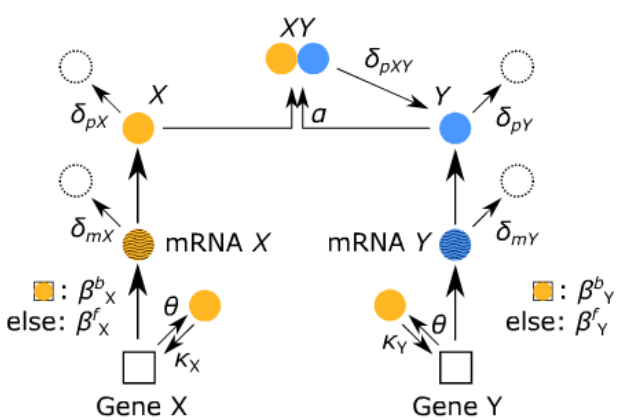




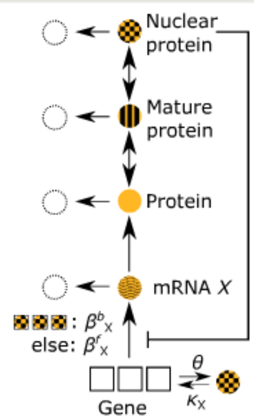
	No feedback	One feedback	Two feedback
Deterministic LC	✗	✗	✓
Excitation-relaxation	✗	✗	✓
Spiral sink	✗	✓	✓
Demographic noise-induced	✗	✓	✓
Burstiness induced	✗	✓	✓
Slow-switching induced	✓	✓	✓

Classification of noise-induced oscillations in published models

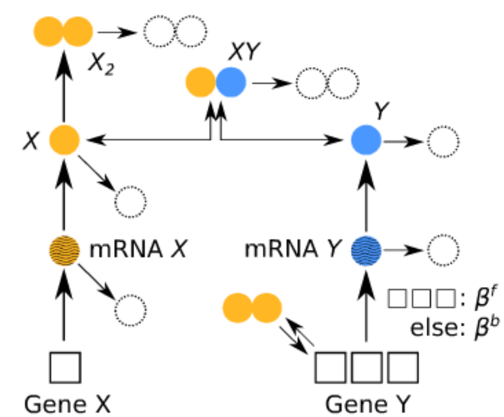
Vilar et al. PNAS 2002



Gonze et al. PNAS 2002 (+N>4 similar...)



Karapetyan & Buchler, 2015



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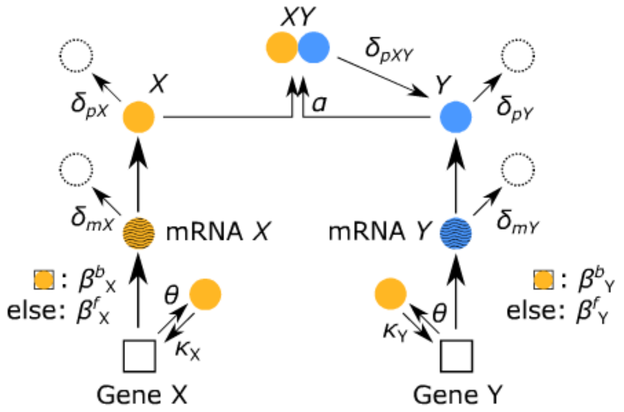

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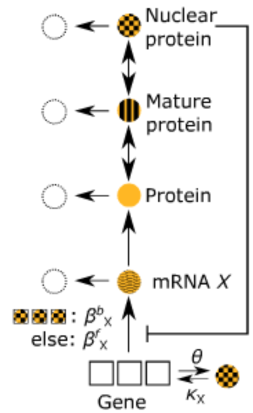

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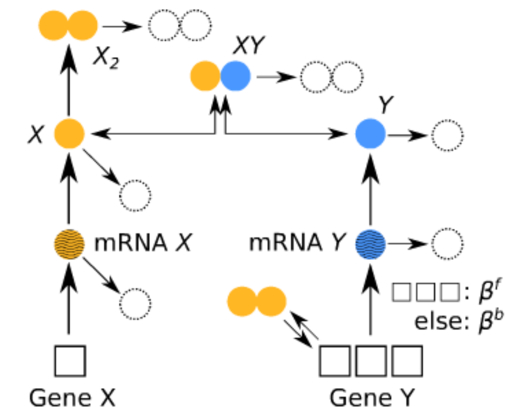
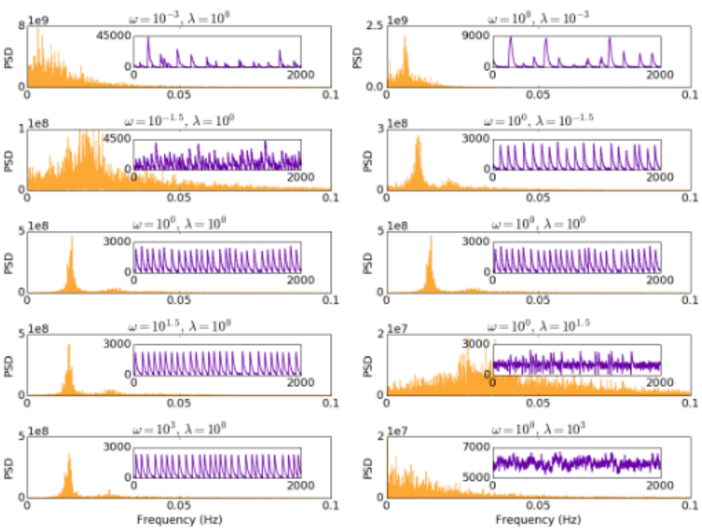
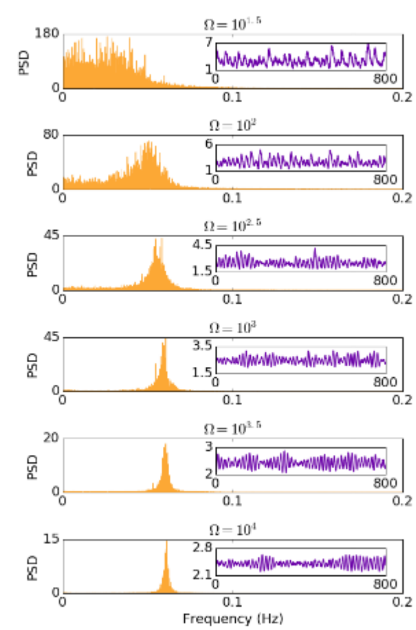


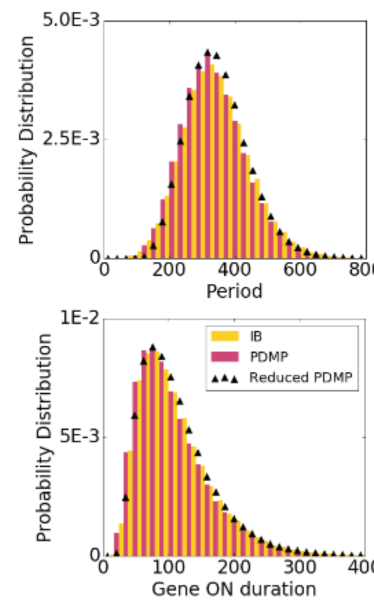
Excitation-relaxation and slow switching



Generic spiral sink



Slow switching

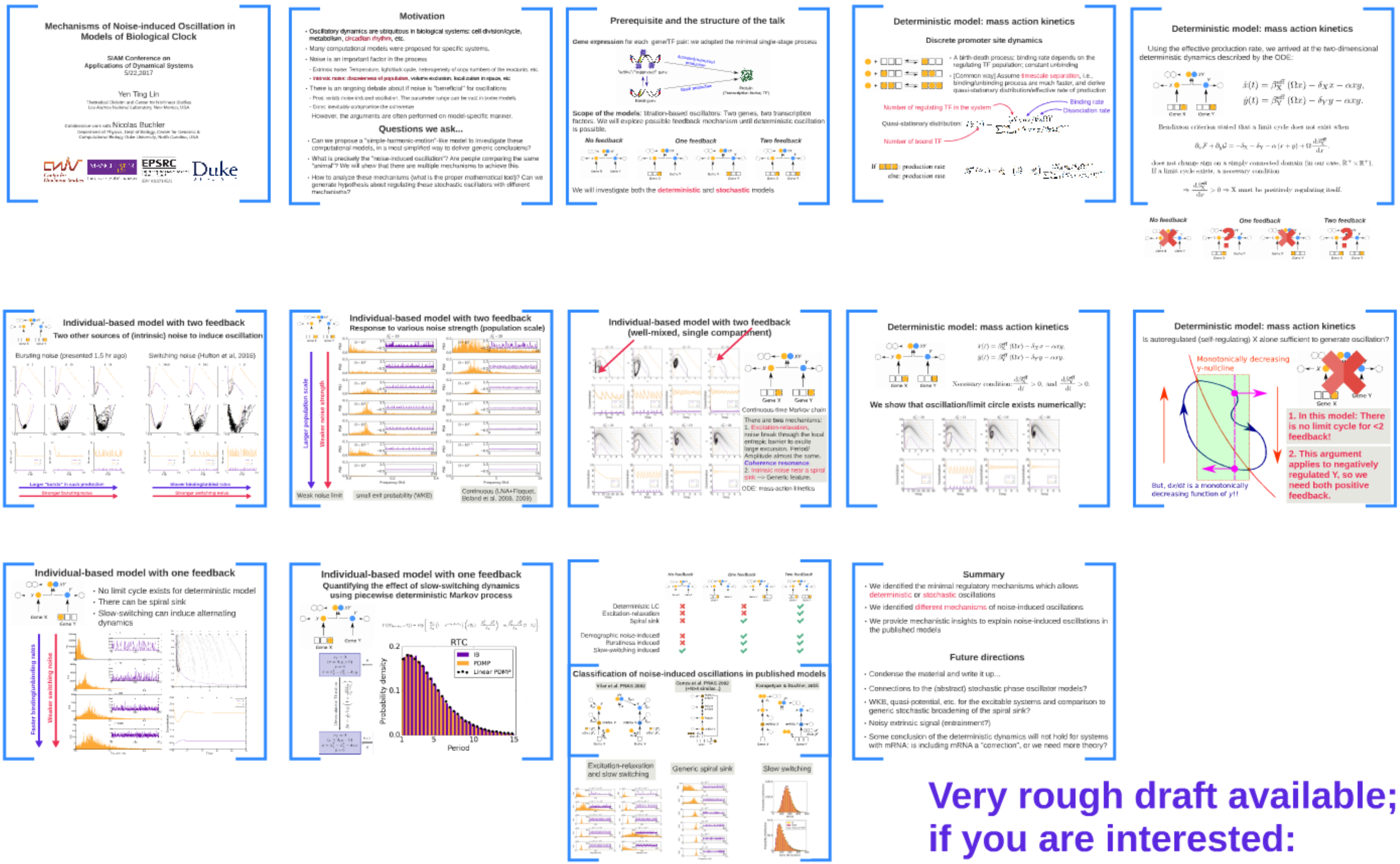


Summary

- We identified the minimal regulatory mechanisms which allows deterministic or stochastic oscillations
- We identified different mechanisms of noise-induced oscillations
- We provide mechanistic insights to explain noise-induced oscillations in the published models

Future directions

- Condense the material and write it up...
- Connections to the (abstract) stochastic phase oscillator models?
- WKB, quasi-potential, etc. for the excitable systems and comparison to generic stochastic broadening of the spiral sink?
- Noisy extrinsic signal (entrainment?)
- Some conclusion of the deterministic dynamics will not hold for systems with mRNA: is including mRNA a "correction", or we need more theory?



Very rough draft available; if you are interested: yentingl@lanl.gov

Thank you for your attention!