

Mechanisms of Noise-induced Oscillation in Models of Biological Clock

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Applications of Dynamical Systems
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Motivation

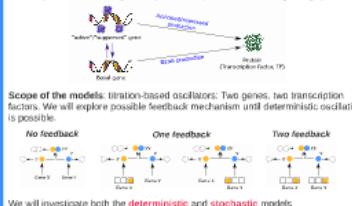
- Oscillatory dynamics are ubiquitous in biological systems: cell division/cycle, metabolism, circadian rhythms, etc.
- Many computational models were proposed for specific systems.
- Noise is an important factor in the process:
 - Intrinsic noise: Temperature, light/dark cycle, heterogeneity of copy numbers of the reactions, etc.
 - Intrinsic noise: differences of population, volume exclusion, localization in space, etc.
- There is an ongoing debate about if noise is "beneficial" for oscillations:
 - Pros: noise induced oscillations. The parameter range can be vast in some models.
 - Cons: instability compromises 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 oscillations with different mechanisms?

Prerequisite and the structure of the talk

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



Deterministic model: mass action kinetics

- \bullet Birth-death process: binding rate depends on the regulating TF population, constant unbinding
- \bullet Common way: Assume **infinite separation**, i.e., binding/unbinding process are much faster, and derive quasi-stationary distribution/effective rate of production

$$\text{Number of regulating TF in the system} \quad \frac{\partial}{\partial t} X(t) = \beta_{XY}^{eff} (\Omega x) - \delta_X x - \alpha xy,$$

$$\text{Quasi-stationary distribution} \quad \frac{\partial}{\partial t} Y(t) = \beta_Y^{eff} (\Omega x) - \delta_Y y - \alpha xy.$$

If $\beta_{XY}^{eff} > \beta_Y^{eff}$: production rate
else: production rate

$$\frac{dx}{dt} = \beta_{XY}^{eff} (\Omega x) - \delta_X x - \alpha xy, \quad \frac{dy}{dt} = \beta_Y^{eff} (\Omega x) - \delta_Y y - \alpha xy.$$

Deterministic model: mass action kinetics

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

$$\begin{aligned} \dot{x}(t) &= \beta_{XY}^{eff} (\Omega x) - \delta_X x - \alpha xy, \\ \dot{y}(t) &= \beta_Y^{eff} (\Omega x) - \delta_Y y - \alpha xy. \end{aligned}$$

Bendixon criterion stated that a limit cycle does not exist when

$$\partial_x F + \partial_y G = -\delta_X - \delta_Y - \alpha(x+y) + \frac{\partial \beta_{XY}^{eff}}{\partial x}.$$

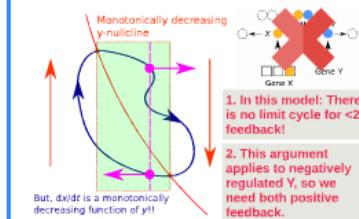
does not change sign on a simply connected domain (in our case, $\mathbb{R}^+ \times \mathbb{R}^+$). If it limit cycle exists, a necessary condition:

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

No feedback One feedback Two feedback

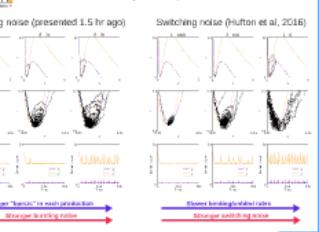
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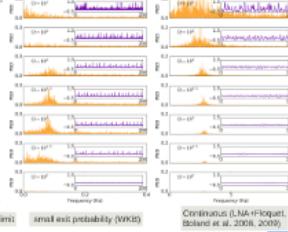
Individual-based model with two feedback

Two other sources of (intrinsic) noise to induce oscillation



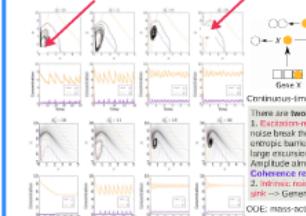
Individual-based model with two feedback

Response to various noise strength (population scale)



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

Continuous-time Markov chain



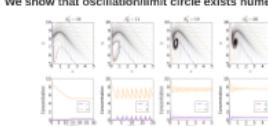
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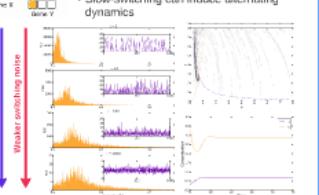
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We show that oscillation/limit circle exists numerically:



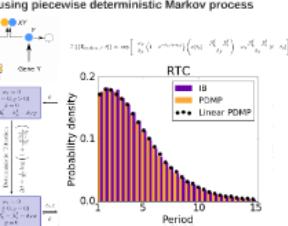
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- No limit cycle exists for deterministic model
- There can be spiral sink
- Slow-switching can induce alternating dynamics



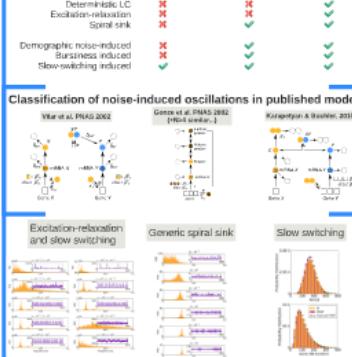
Individual-based model with one feedback

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



Classification of noise-induced oscillations in published models

No feedback One feedback Two feedback



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!

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Collaborative work with: Nicolas Buchler

Department of Physics, Dept of Biology, Center for Genomic &
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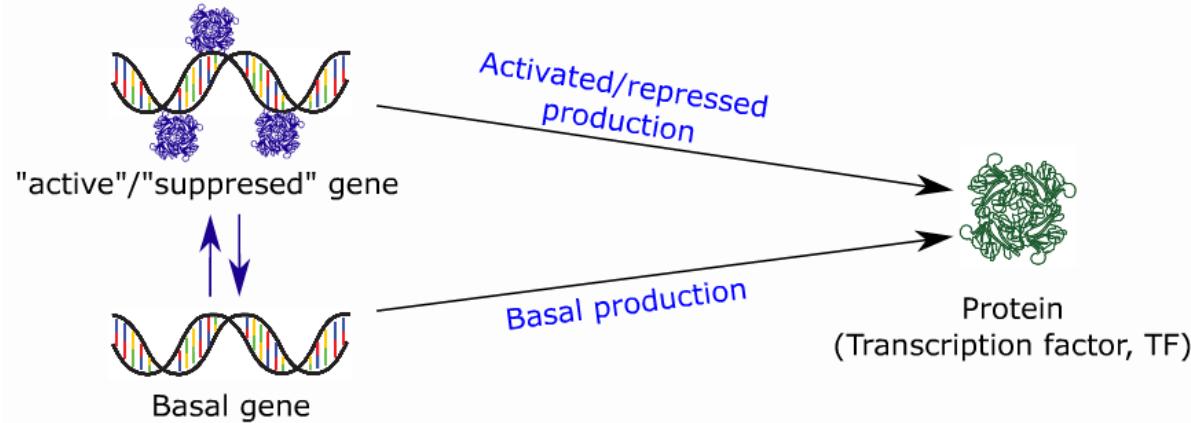
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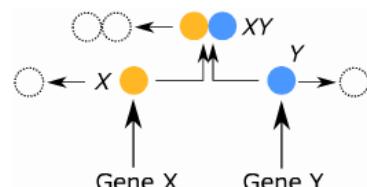
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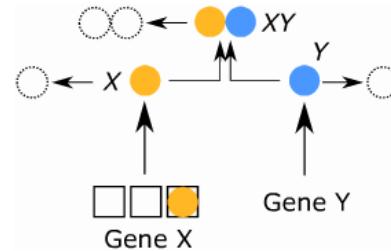


Scope of the models: titration-based oscillators: Two genes, two transcription factors. We will explore possible feedback mechanism until deterministic oscillation is possible.

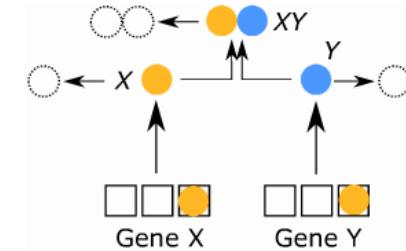
No feedback



One feedback

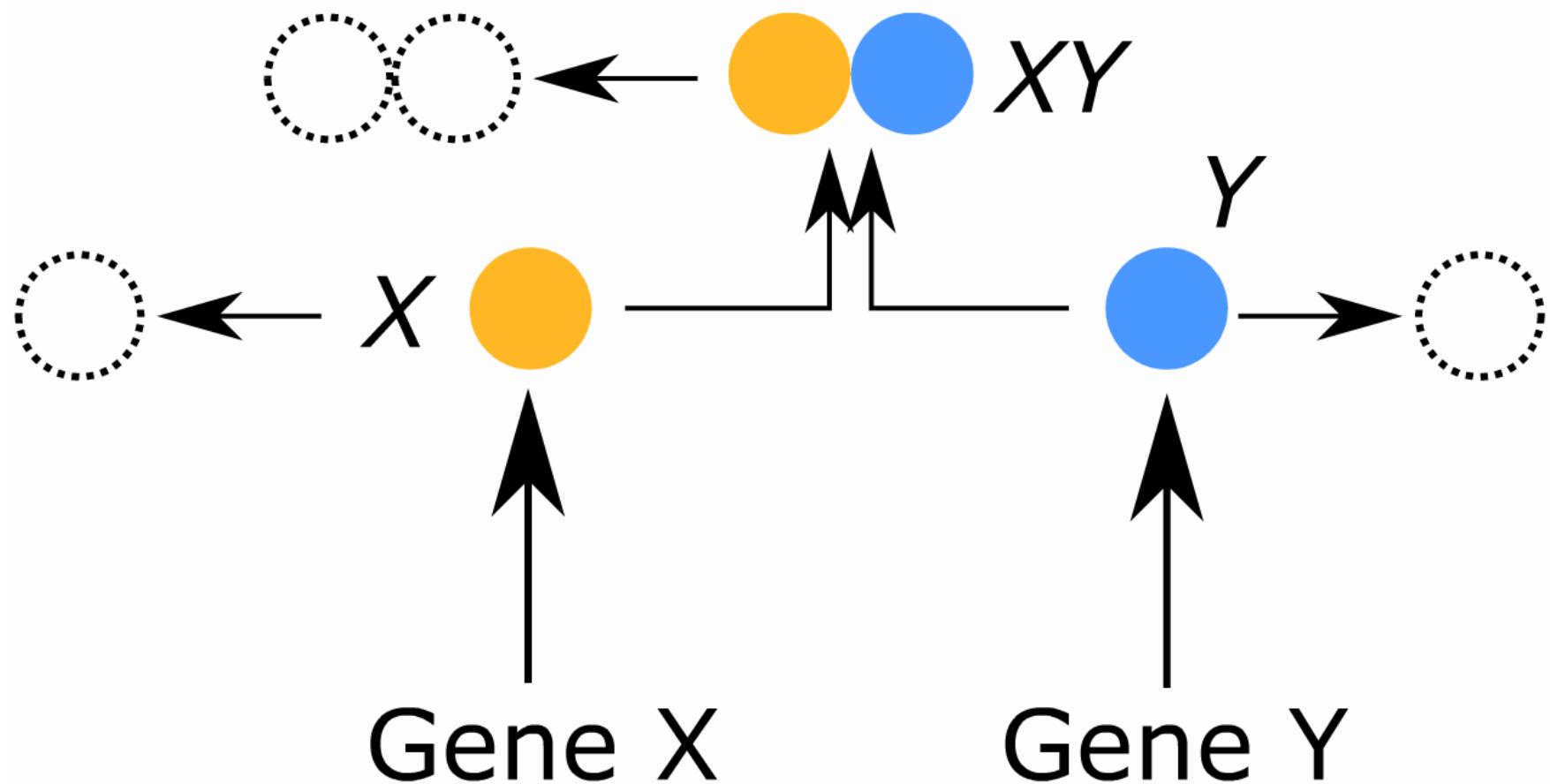


Two feedback



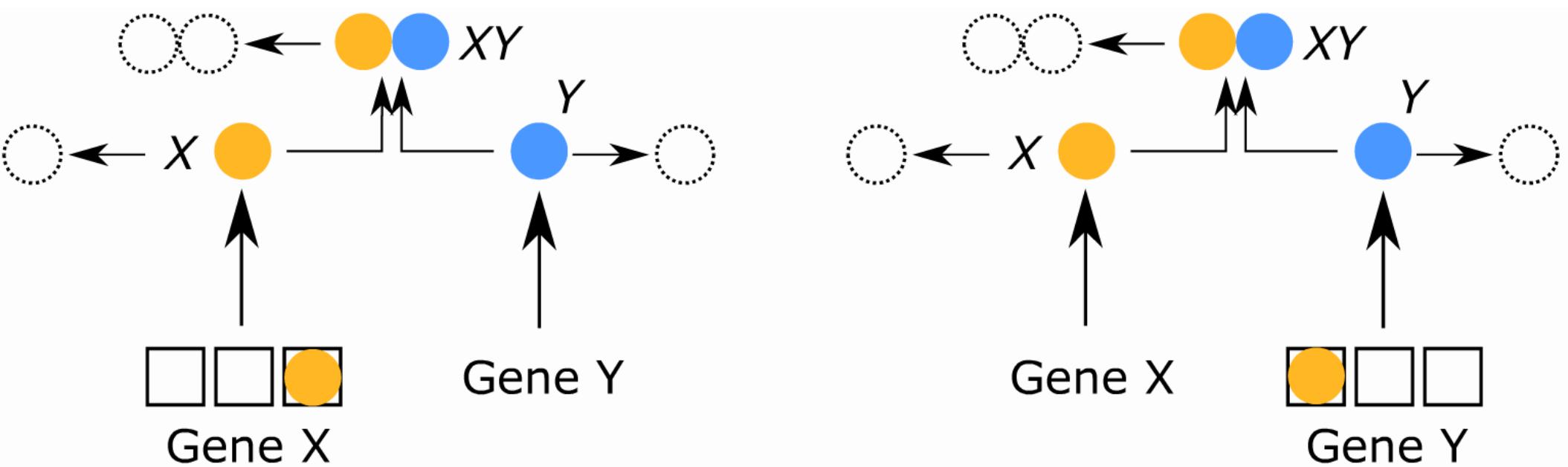
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No feedback



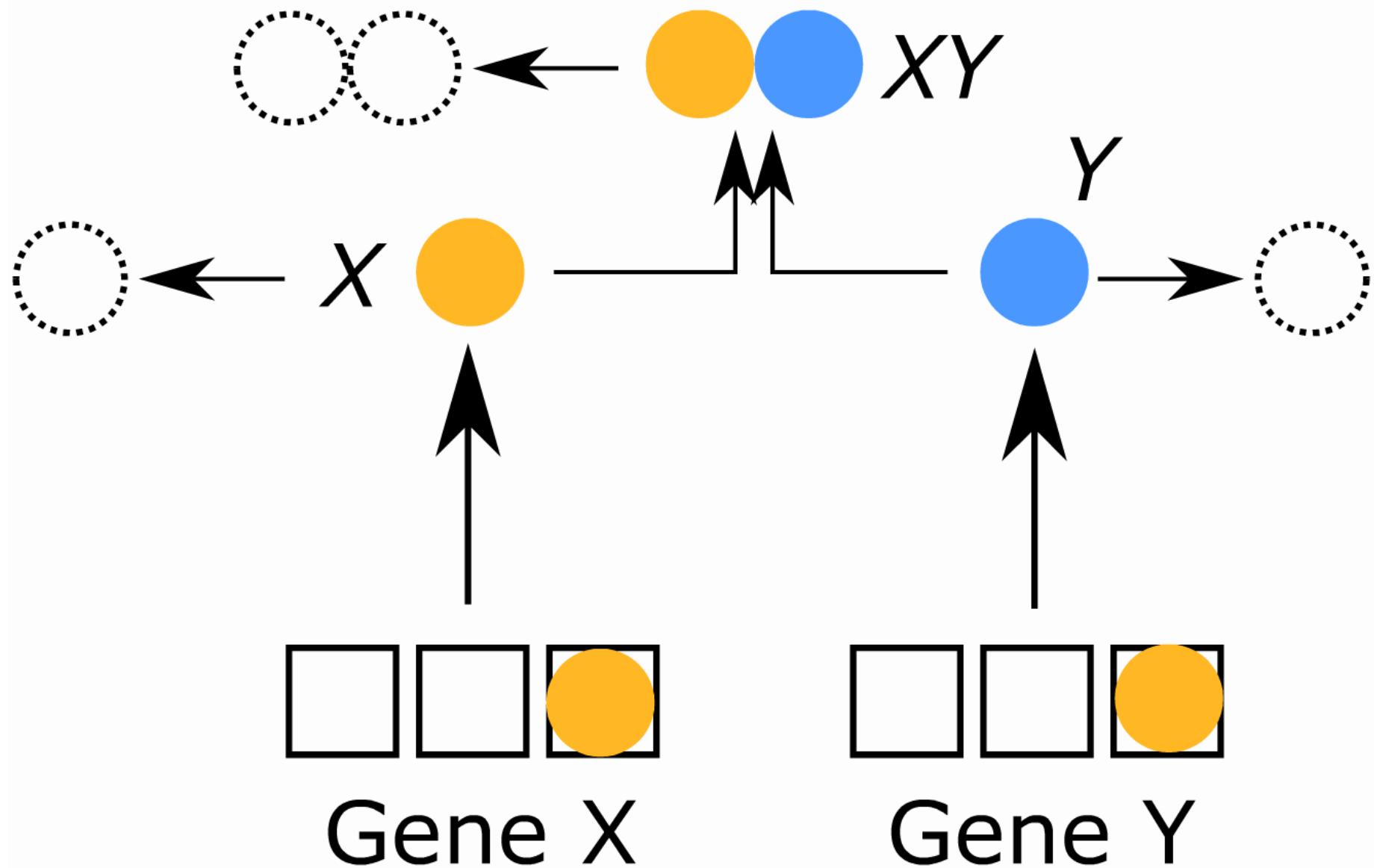
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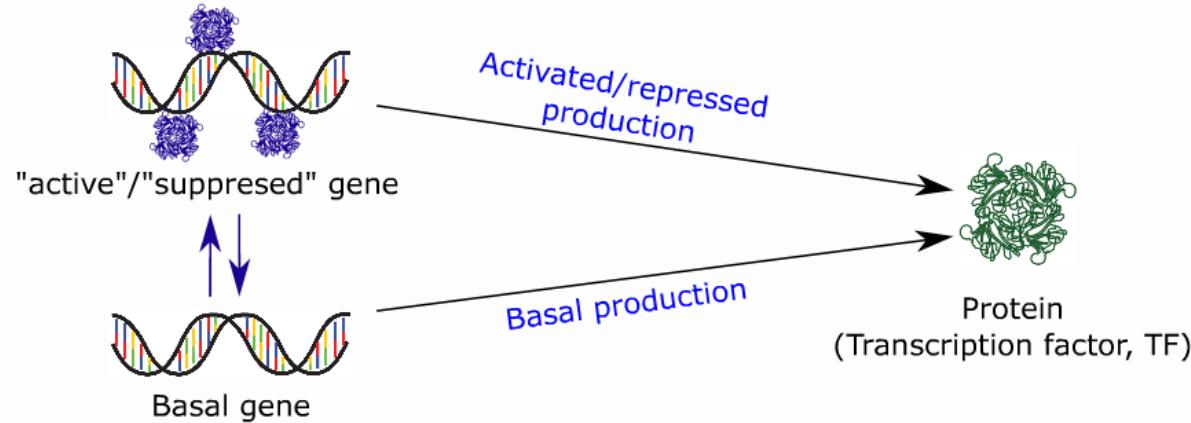
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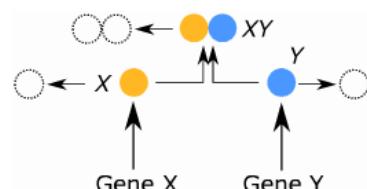
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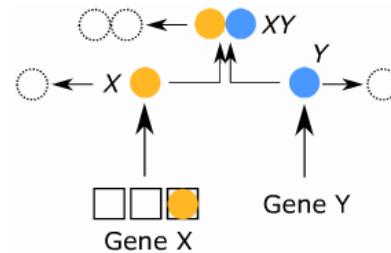


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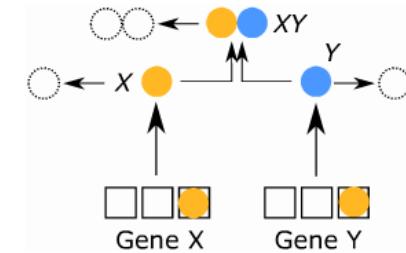
No feedback



One feedback



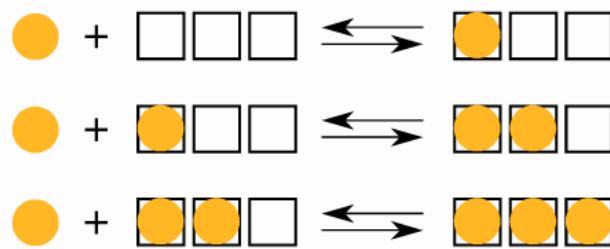
Two feedback



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

Quasi-stationary distribution: $P_Z(i) = \frac{(N_X \kappa_Z / \theta_Z \Omega)^i}{\sum_{m=0}^{n_Z} (N_X \kappa_Z / \theta_Z \Omega)^m}.$

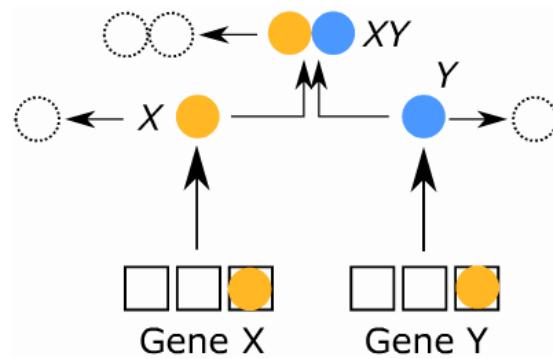
Number of bound TF

If $\text{Doubly Bound Promoter}$: production rate β_Z^b
else: production rate β_Z^f

$$\beta_Z^{\text{eff}}(N_X) = \beta_Z^f + (\beta_Z^b - \beta_Z^f) \frac{(N_X \kappa_Z / \theta_Z \Omega)^{n_Z}}{\sum_{m=0}^{n_Z} (N_X \kappa_Z / \theta_Z \Omega)^m}.$$

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



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Bendixson criterion stated that a limit cycle does not exist when

$$\partial_x \mathcal{F} + \partial_y \mathcal{G} = -\delta_X - \delta_Y - \alpha(x + y) + \Omega \frac{d\beta_X^{\text{eff}}}{dx}.$$

does not change sign on a simply connected domain (in our case, $\mathbb{R}^+ \times \mathbb{R}^+$).
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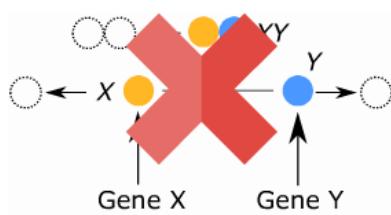
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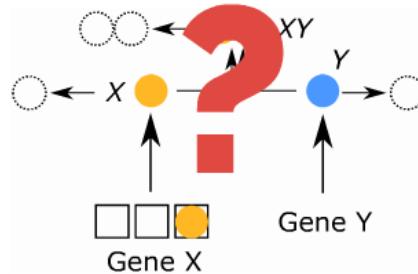
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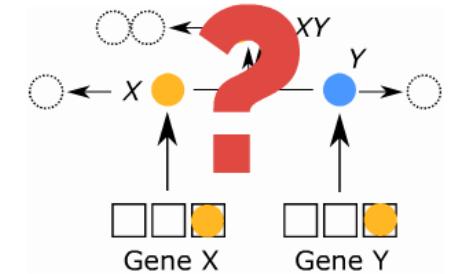
No feedback



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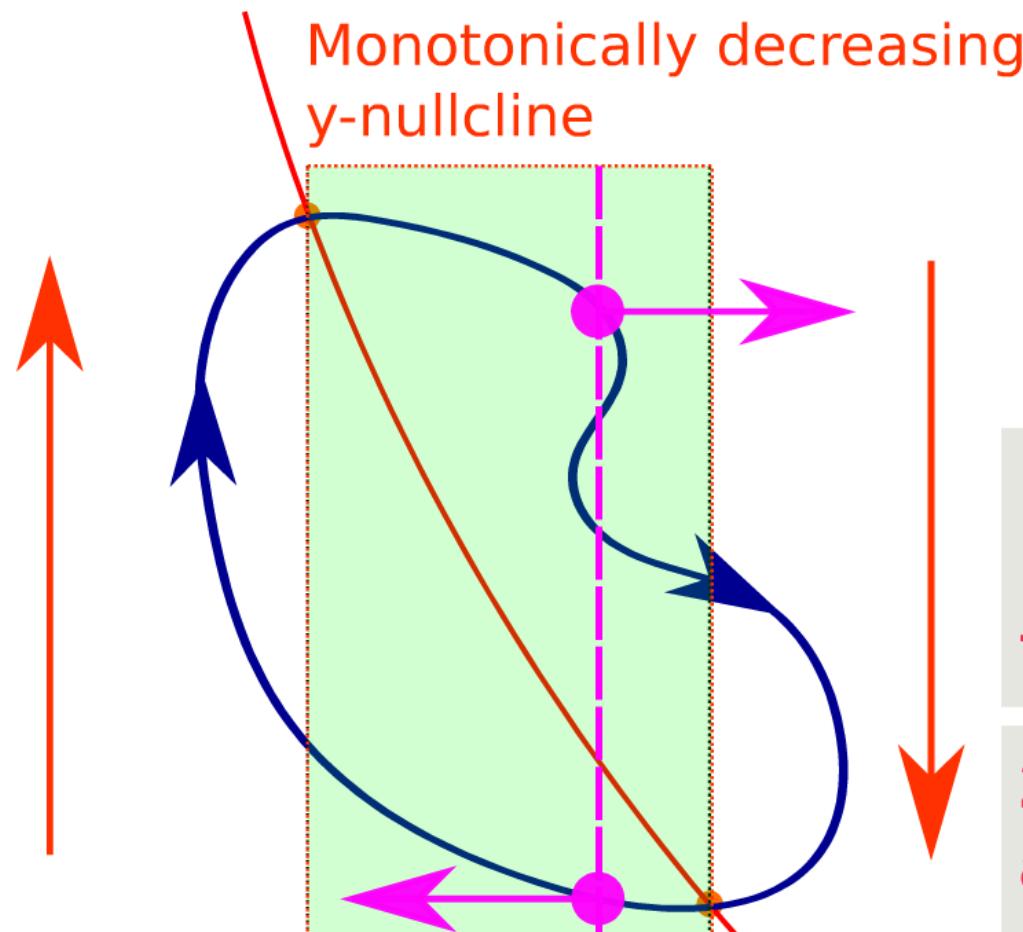


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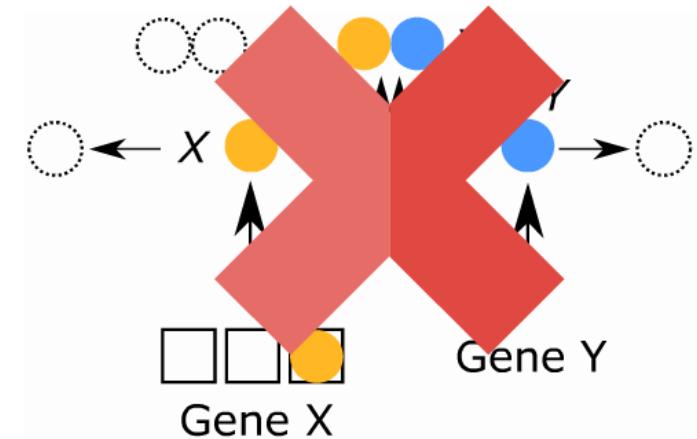


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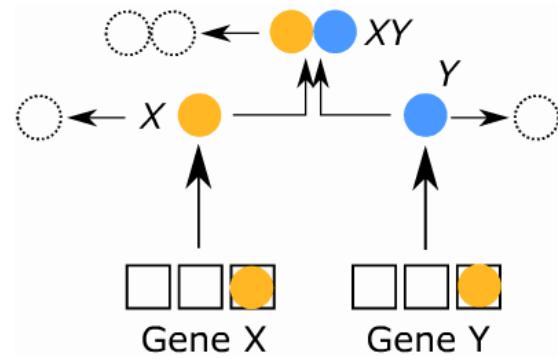
But, dx/dt is a monotonically
decreasing function of y !!



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.

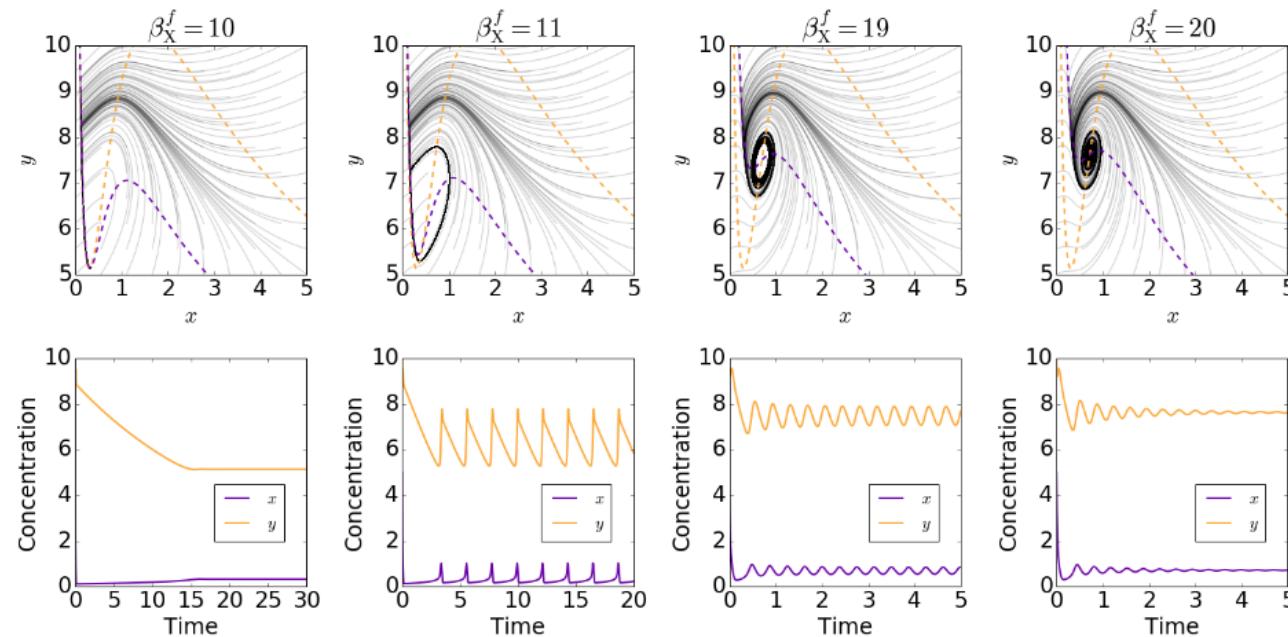
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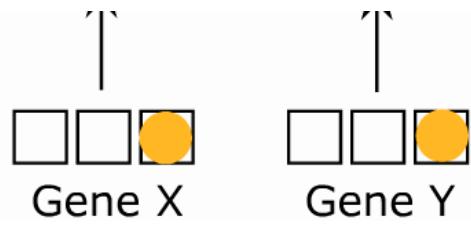


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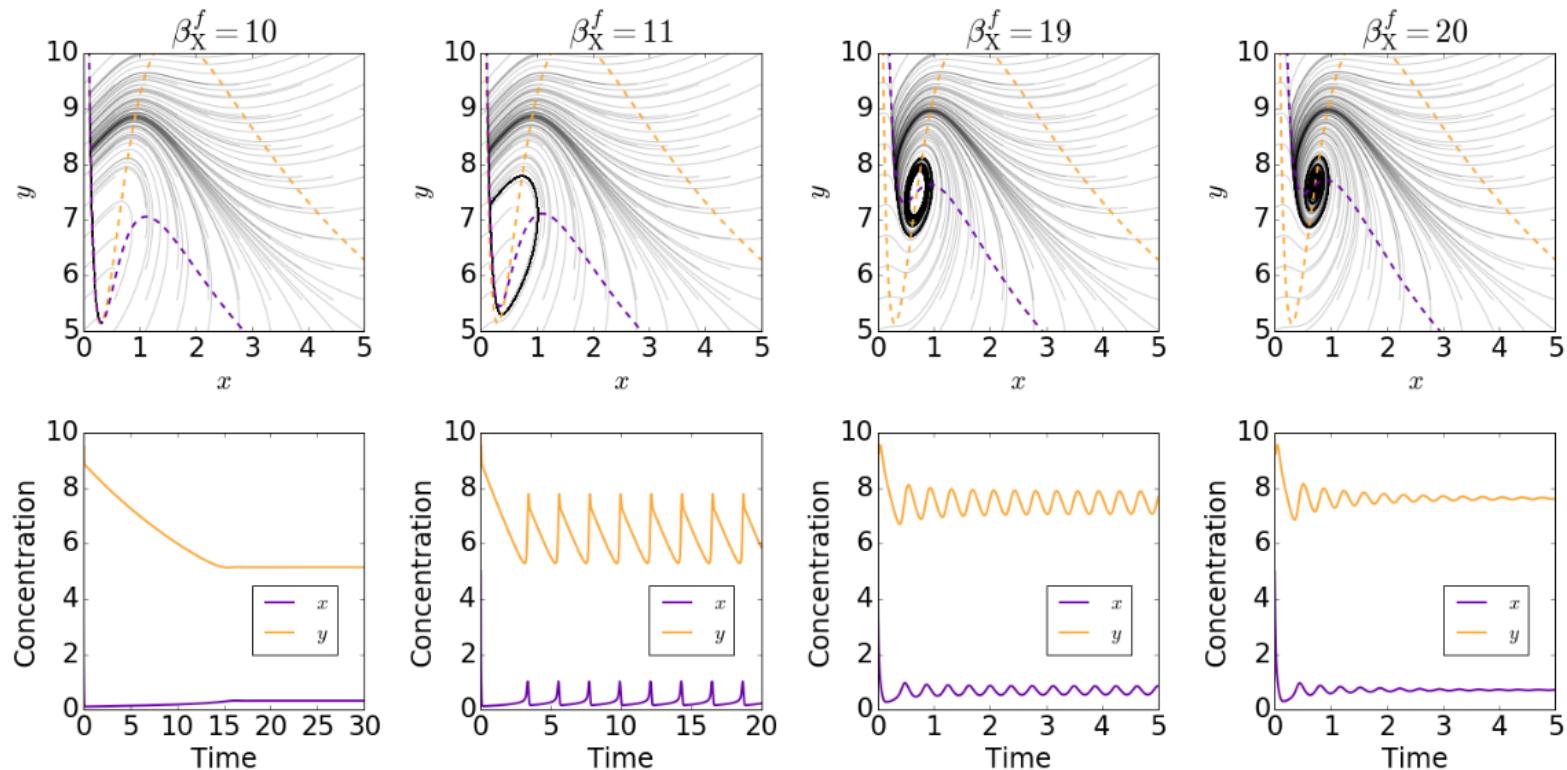
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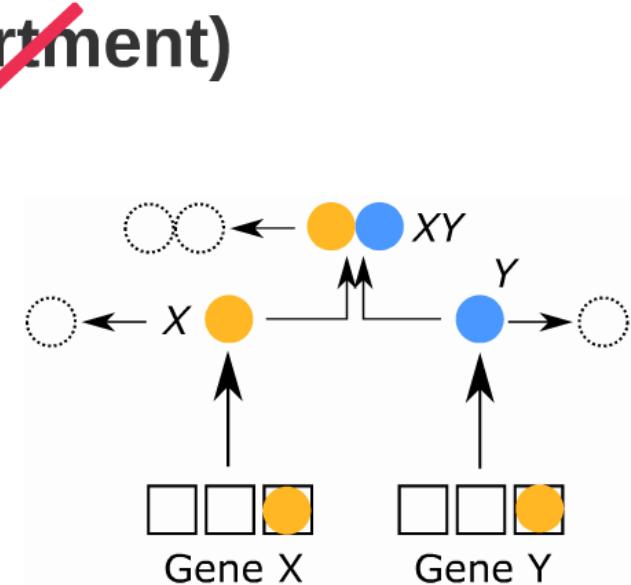
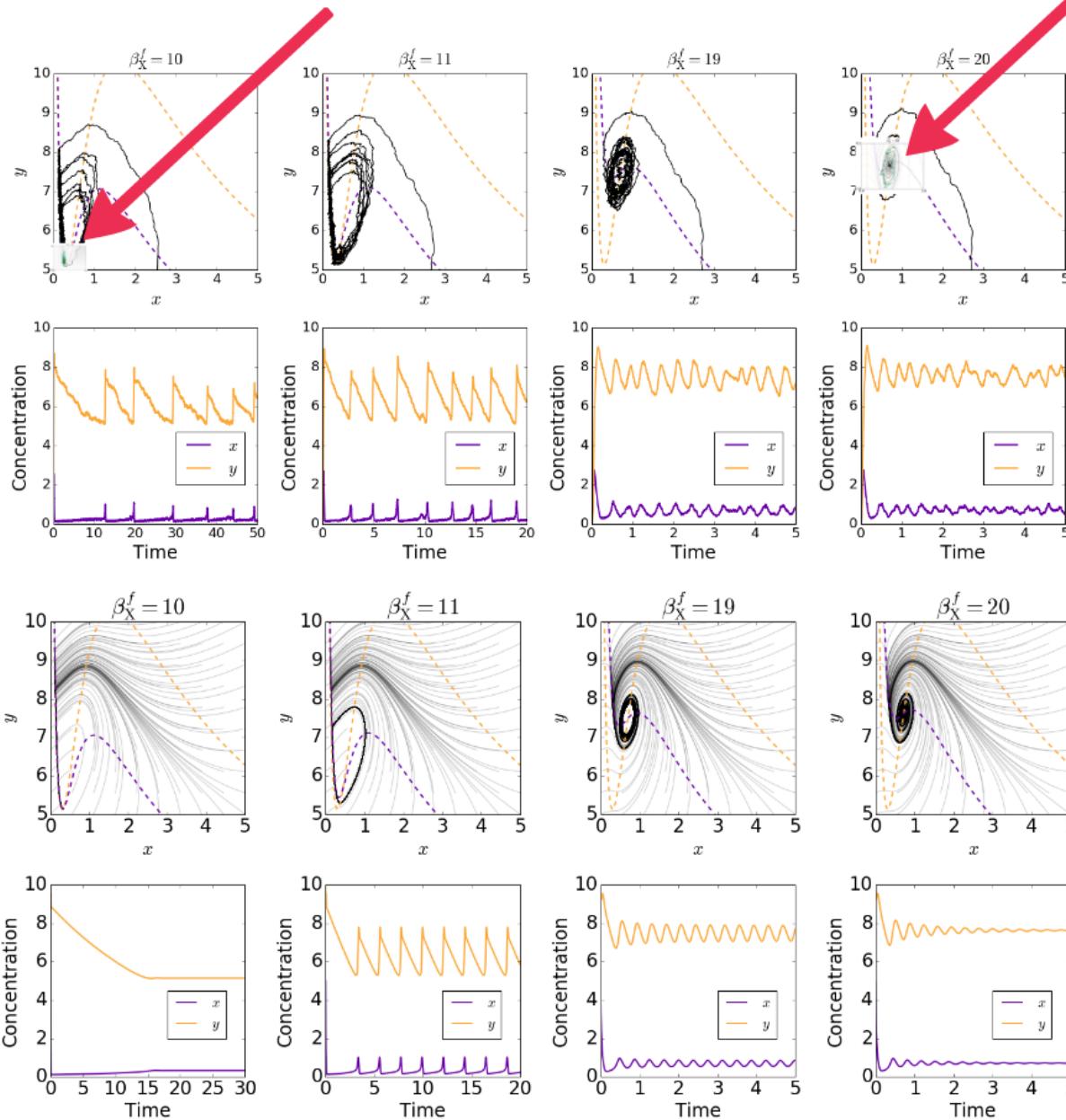


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Individual-based model with two feedback (well-mixed, single compartment)

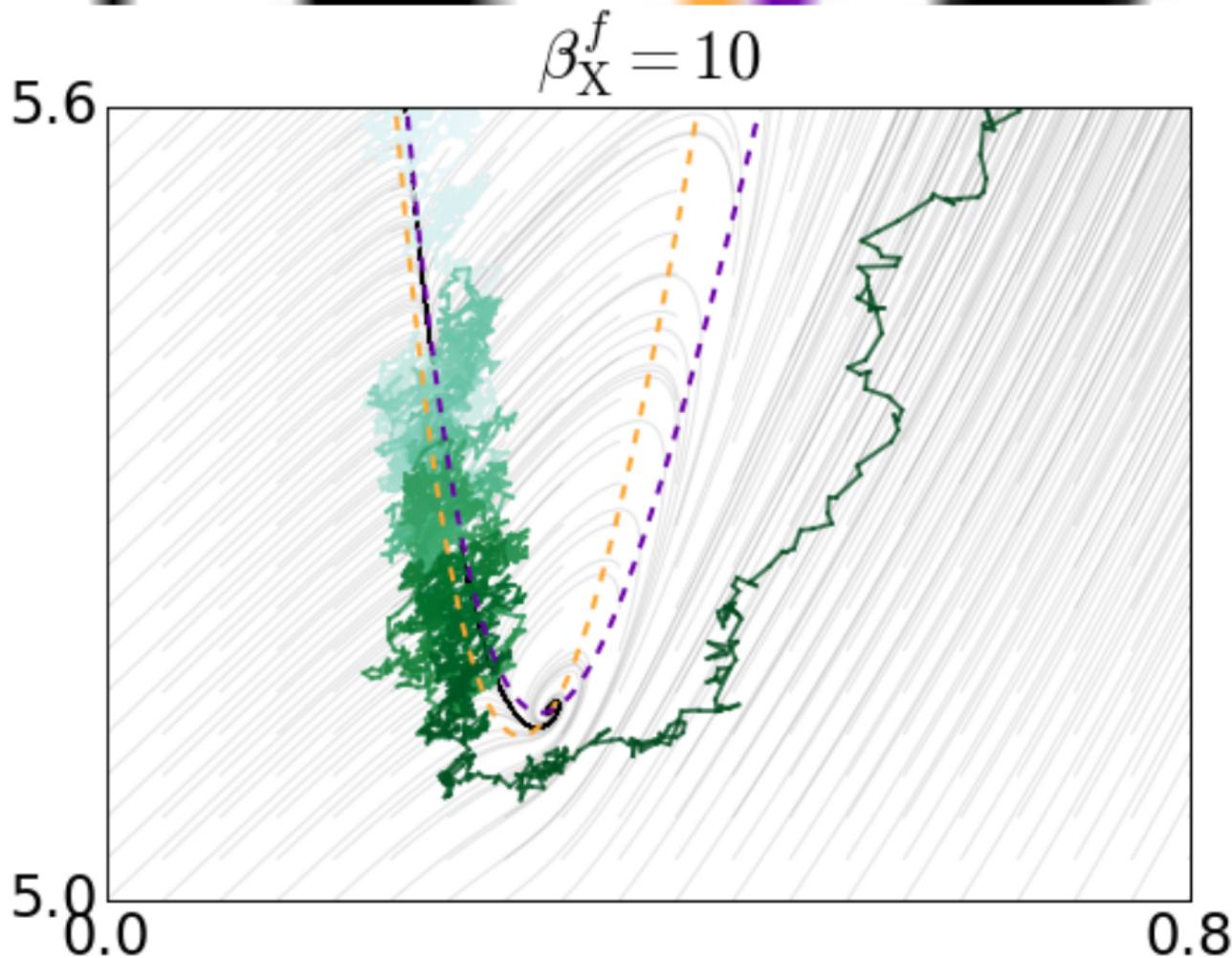


Continuous-time Markov chain

There are **two** mechanisms:

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

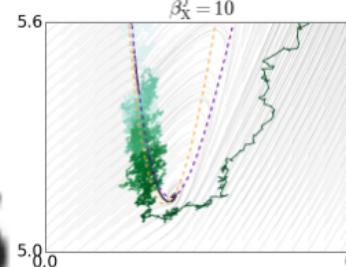
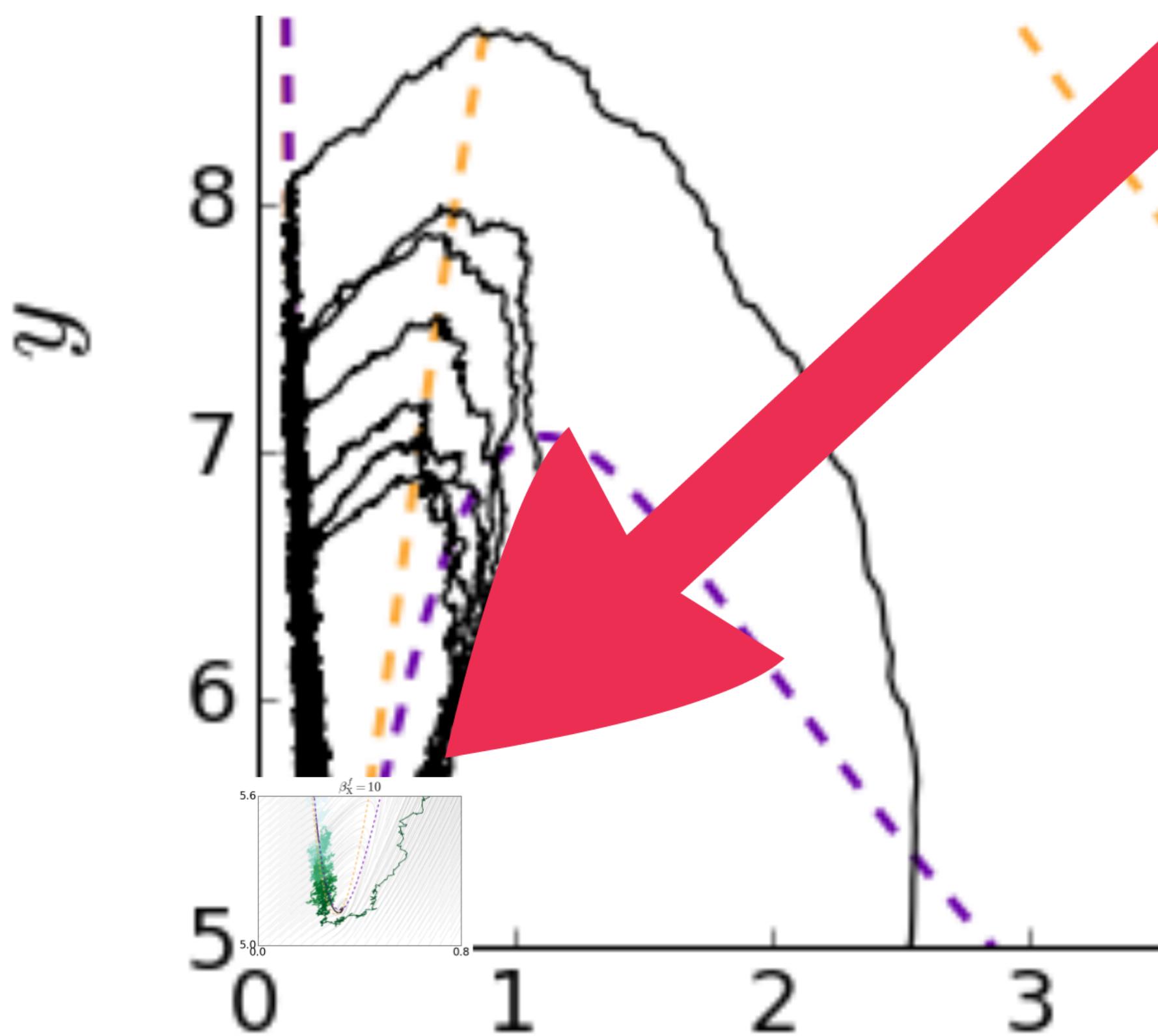
ODE: mass-action kinetics



5.0

0.8

5.6



8

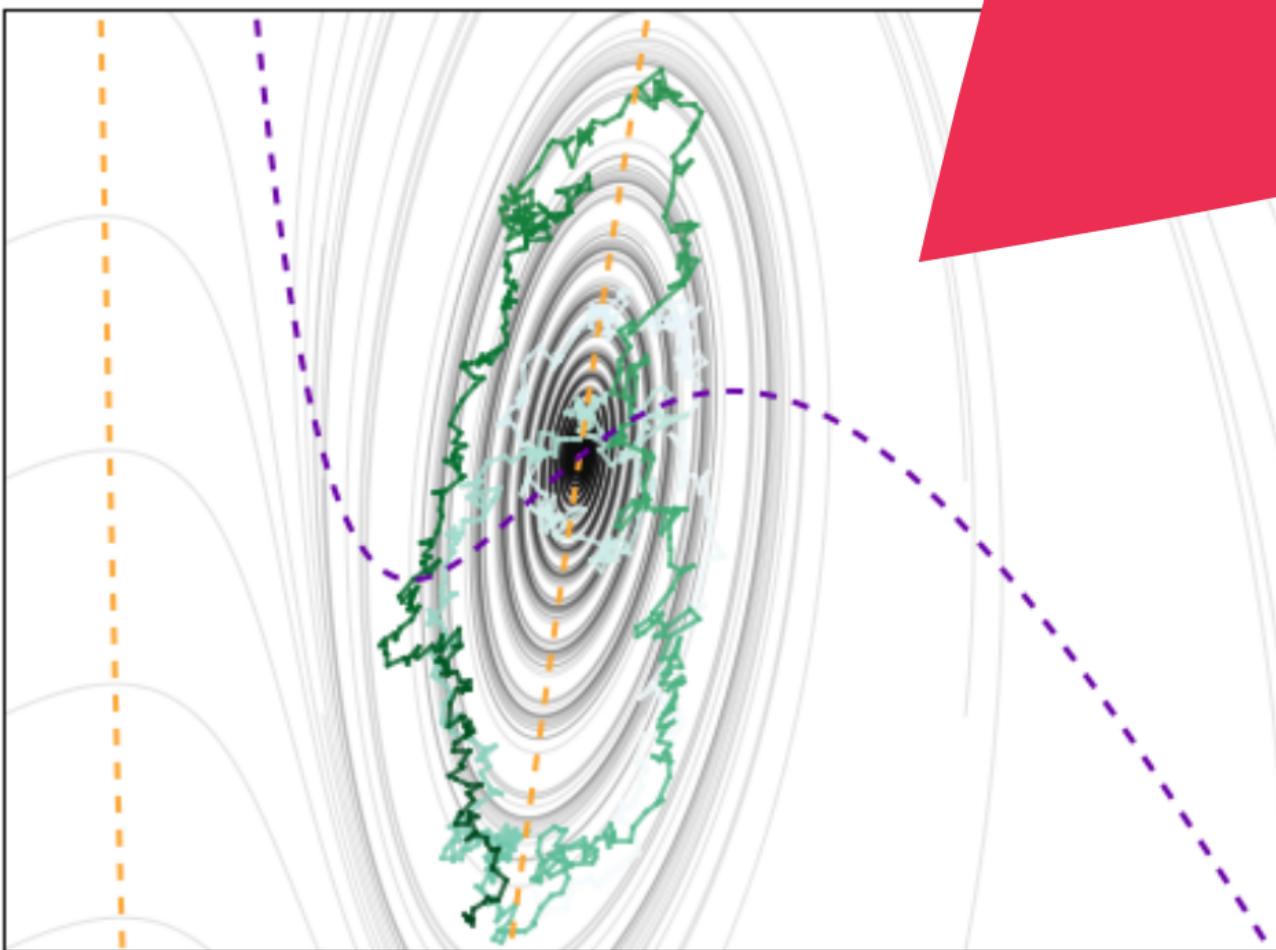
8.2

7

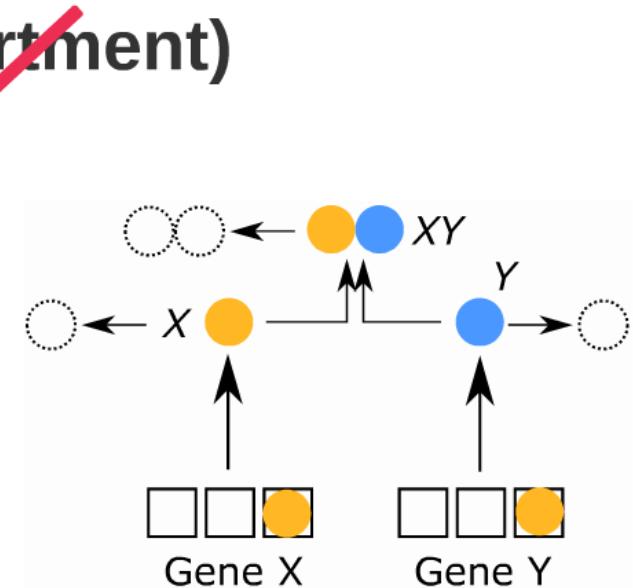
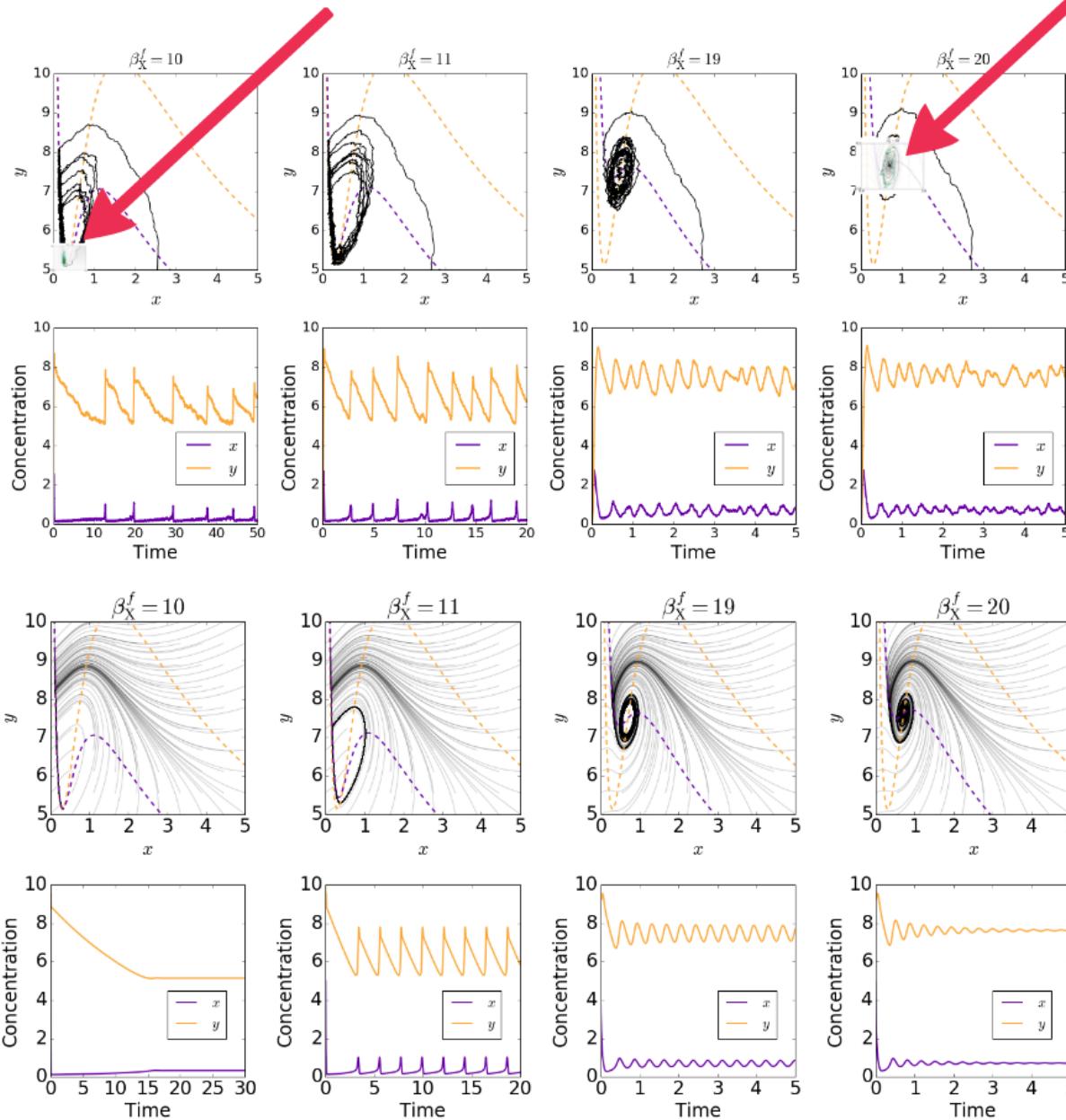
7.0

1.6

$$\beta_X^f = 20$$



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

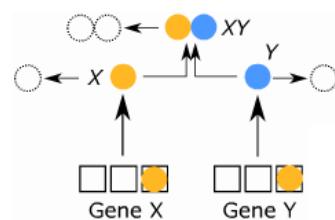


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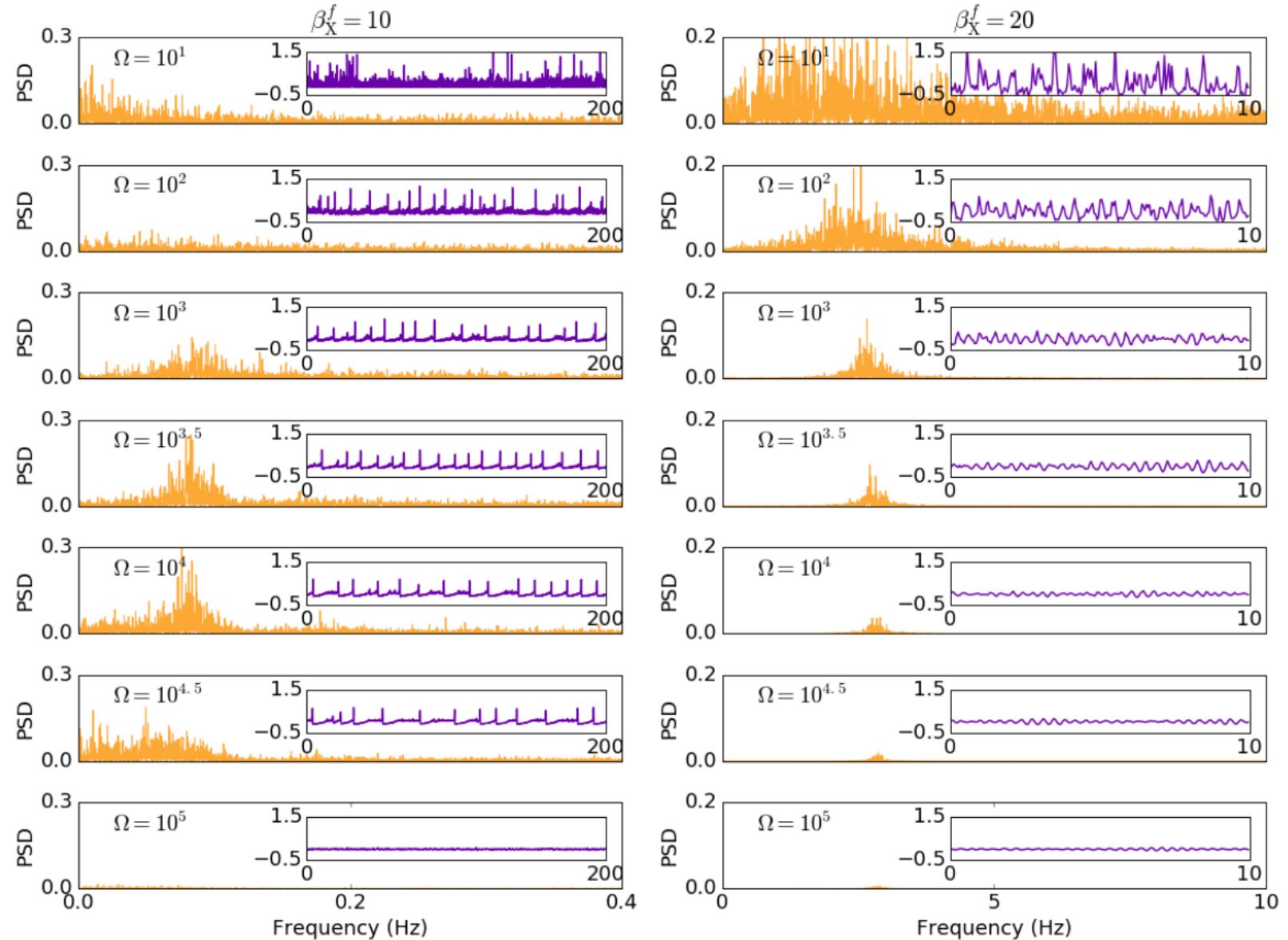


Larger population scale

Weaker noise strength

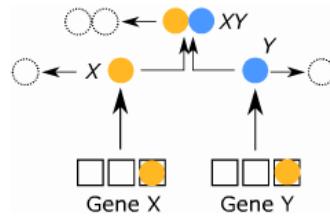
Weak noise limit

Individual-based model with two feedback Response to various noise strength (population scale)



small exit probability (WKB)

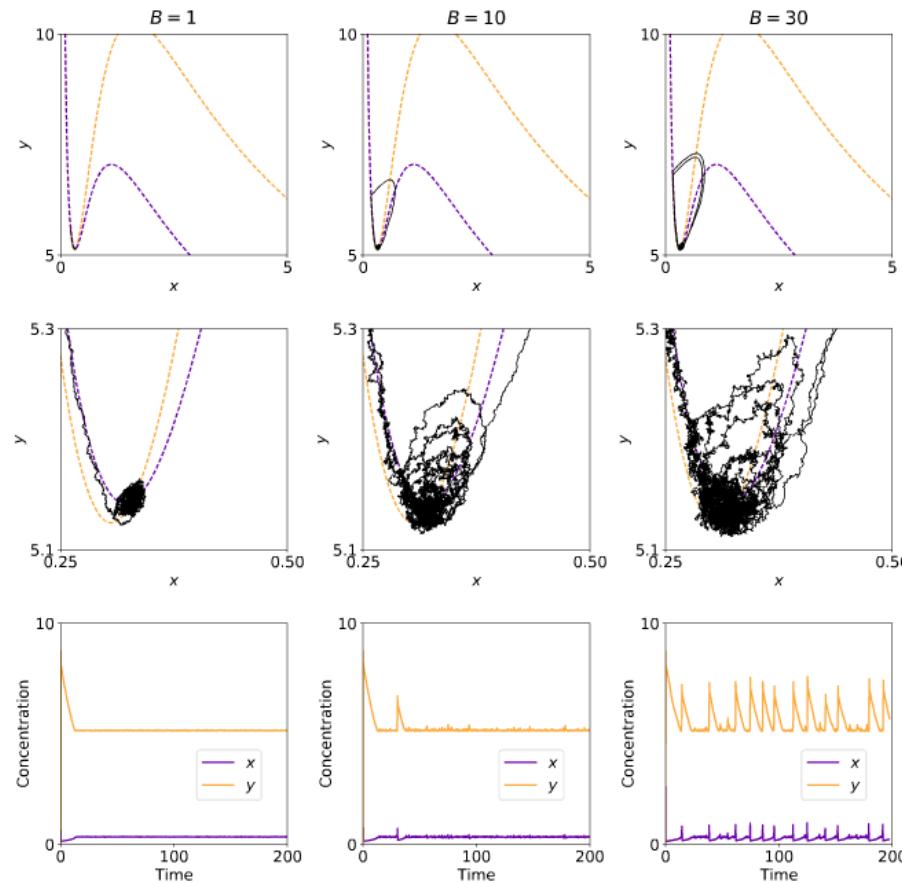
Continuous (LNA+Floquet,
Boland et al. 2008, 2009)



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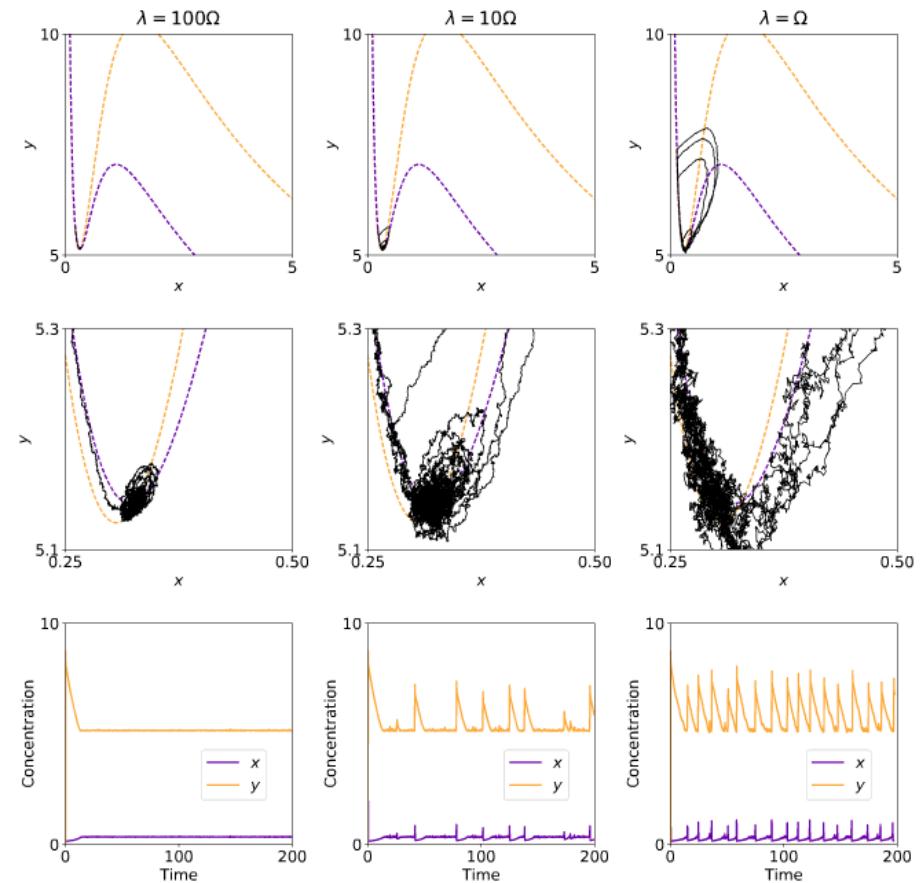
Bursting noise (presented 1.5 hr ago)



Larger "bursts" in each production

Stronger bursting noise

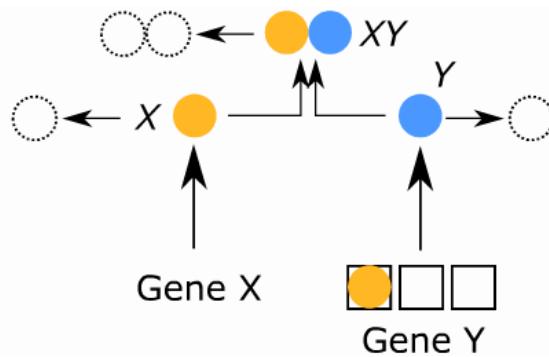
Switching noise (Hufton et al, 2016)



Slower binding/unbind rates

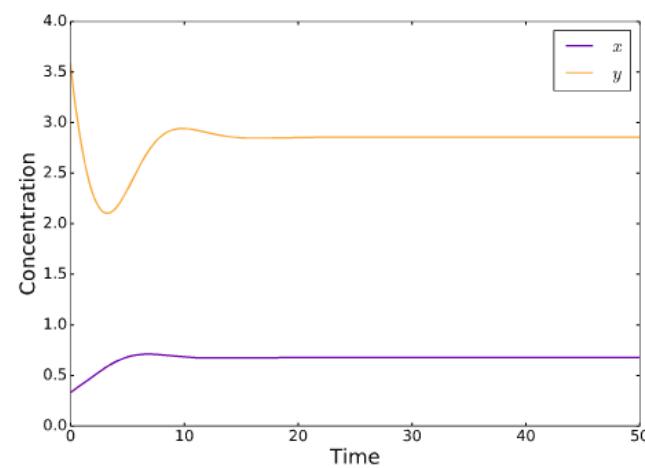
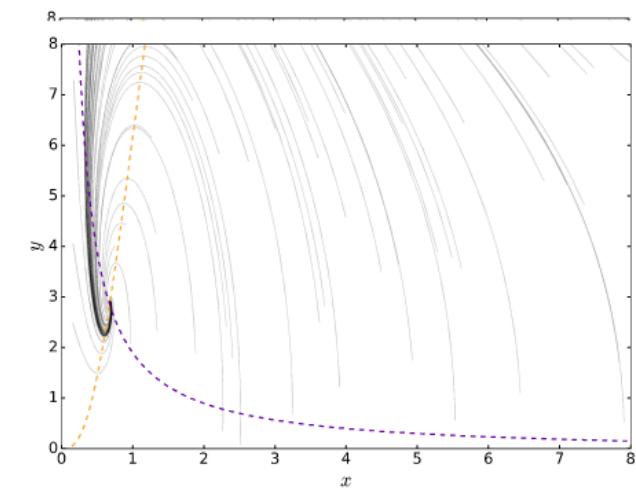
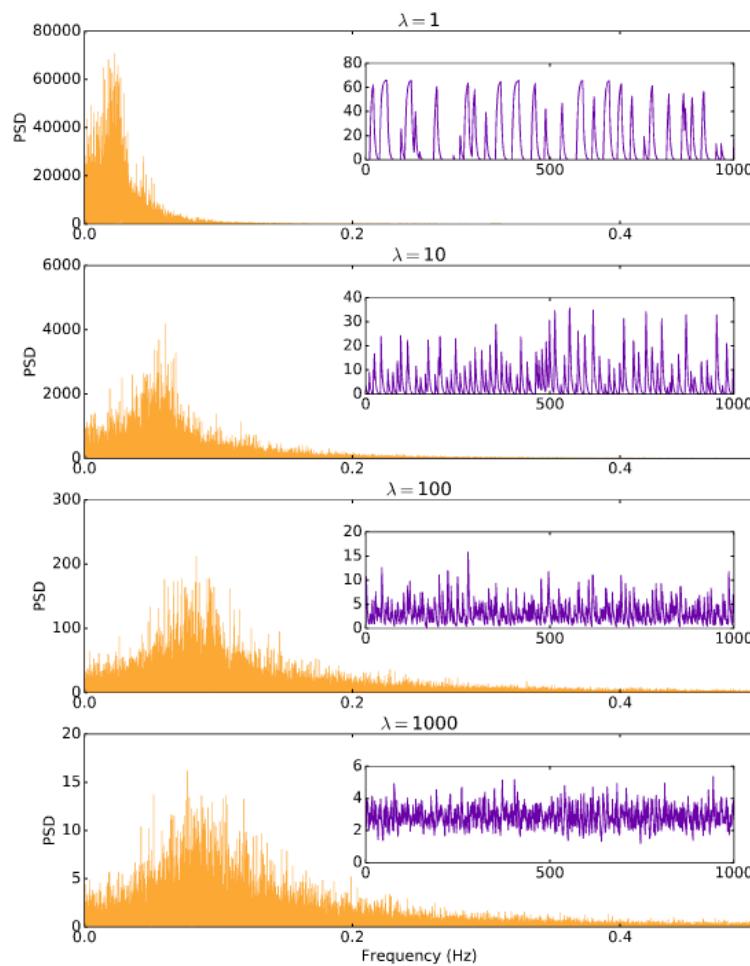
Stronger switching noise

Individual-based model with one feedback



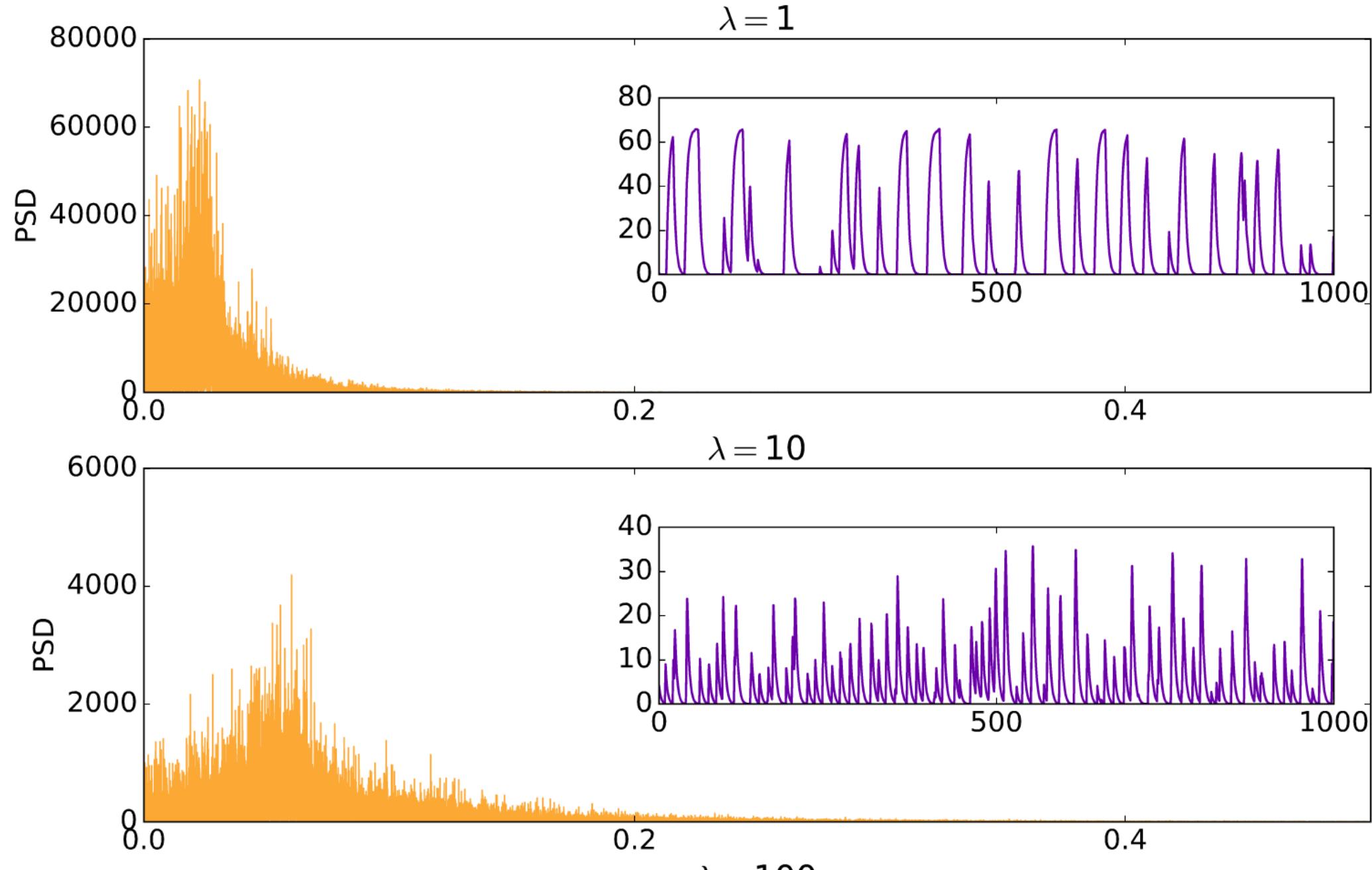
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Faster binding/unbinding rates
↓
Weaker switching noise
↓



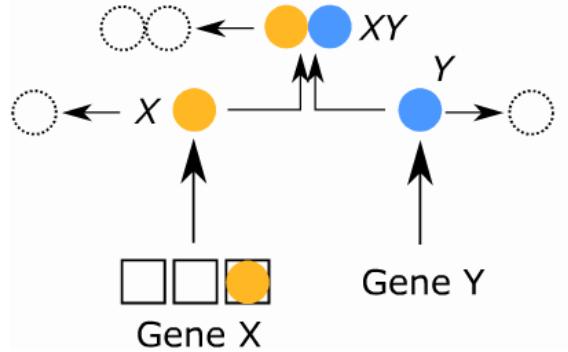
ene Y

dynamics



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

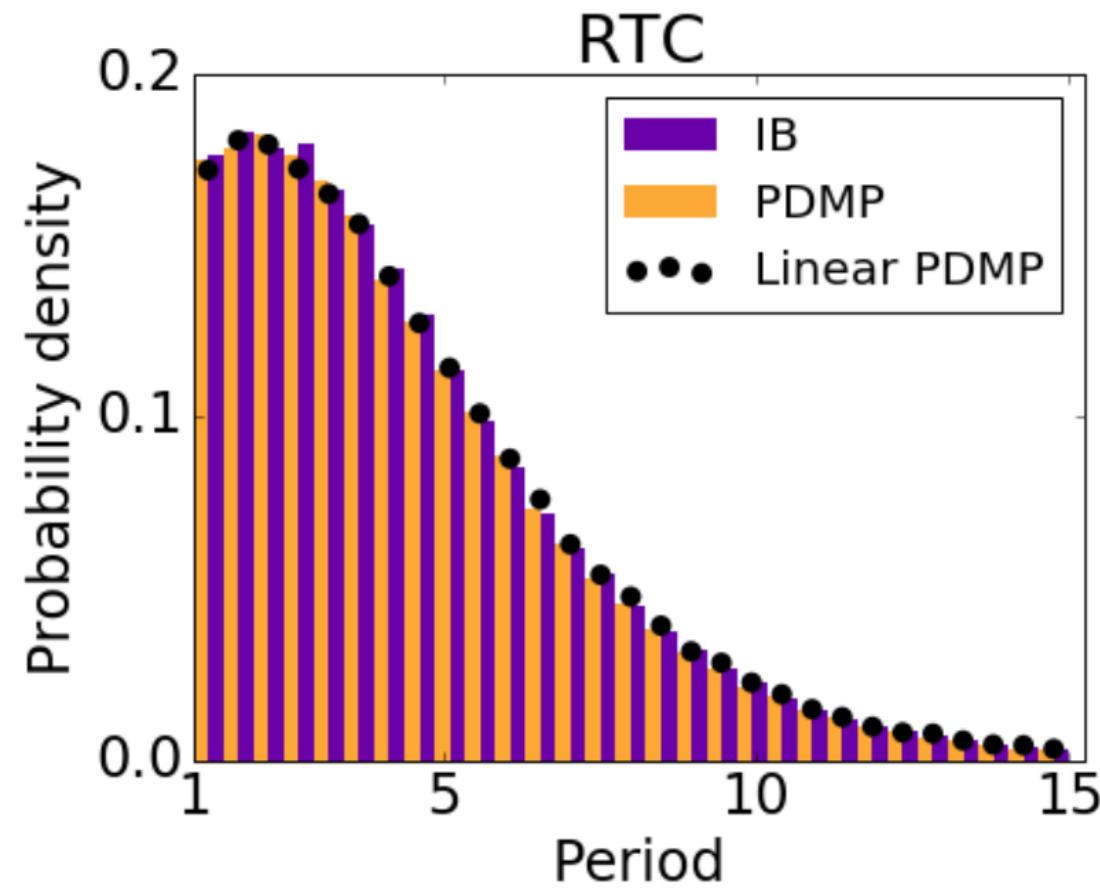


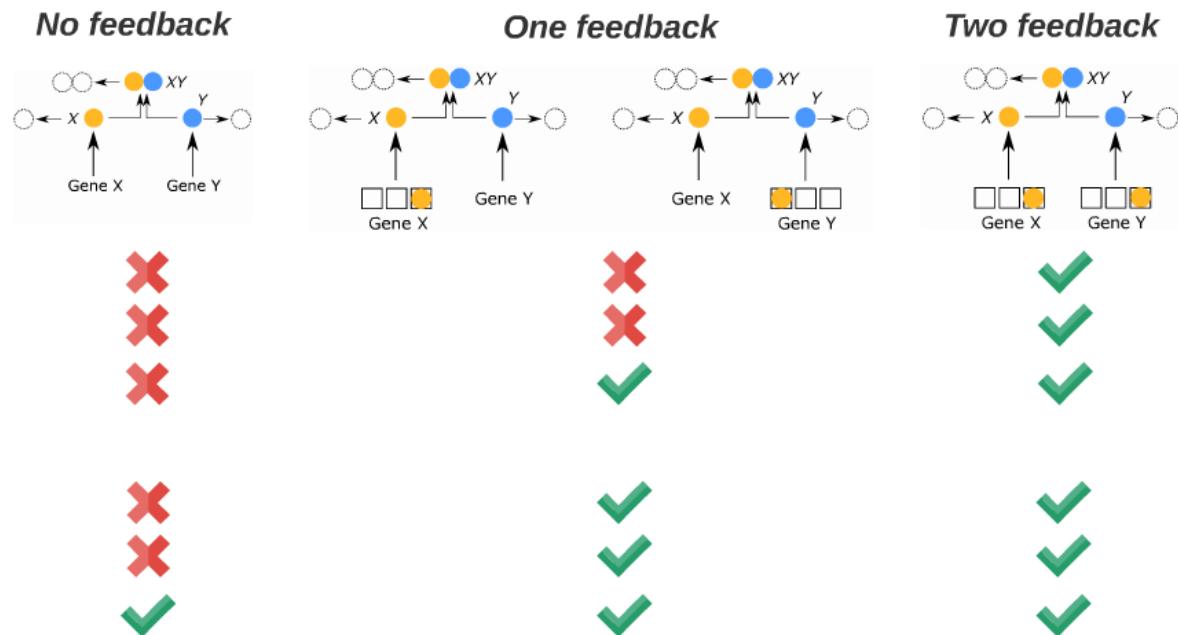
$$\begin{aligned} s_Y &= 0 \\ (x &= 0, y > 0) \\ \dot{x} &= 0 \\ \dot{x} &= \beta_Y^f - \beta_X^f - \delta_Y y \end{aligned}$$

$$\frac{\text{Deterministic Titration}}{\Delta t = \frac{1}{\delta_Y} \log \left(1 + \frac{y(t_0)}{\beta_X^f - \beta_Y^f} \right)}$$

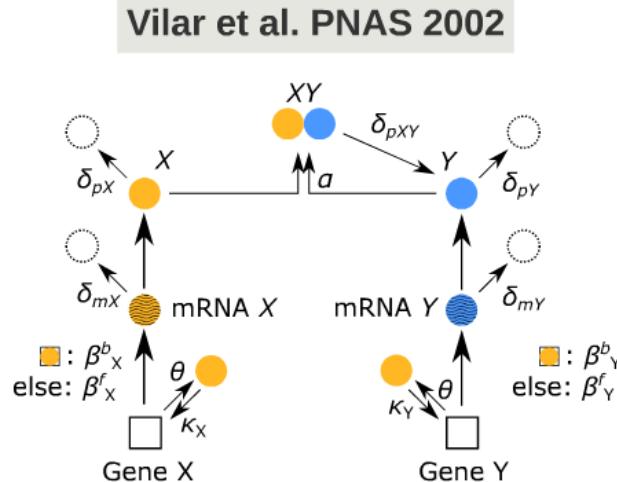
$$\begin{aligned} s_Y &= 0 \\ (x &\geq 0, y = 0) \\ \dot{x} &= \beta_X^f - \beta_Y^f - \delta_X x \\ \dot{y} &= 0 \end{aligned}$$

$$\mathbb{P}\{\{T_{\text{binding}} > t\}\} = \exp \left[-\frac{\kappa_Y}{\delta_X} \left(1 - e^{-\delta_X(t-t_0)} \right) \left(x(t_0) - \frac{\beta_X^f - \beta_Y^f}{\delta_X} \right) - \kappa_Y \frac{\beta_X^f - \beta_Y^f}{\delta_X} (t - t_0) \right].$$

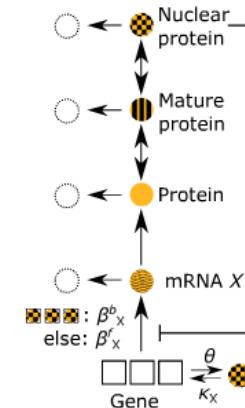




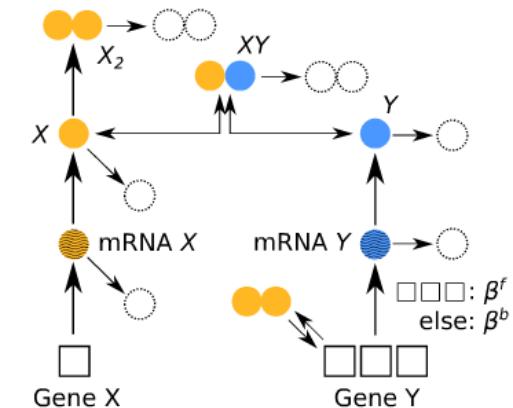
Classification of noise-induced oscillations in published models



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

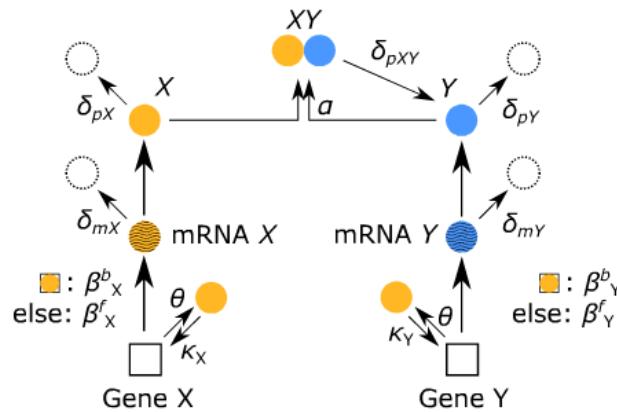


Karapetyan & Buchler, 2015

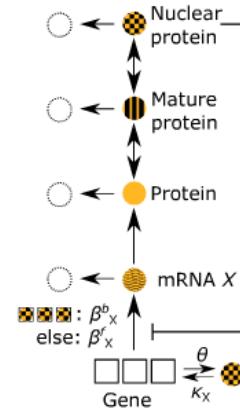


Classification of noise-induced oscillations in published models

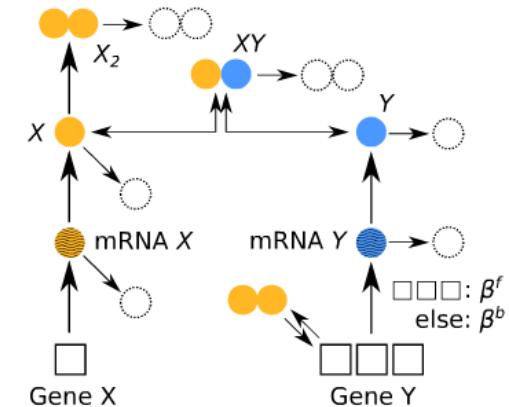
Vilar et al. PNAS 2002



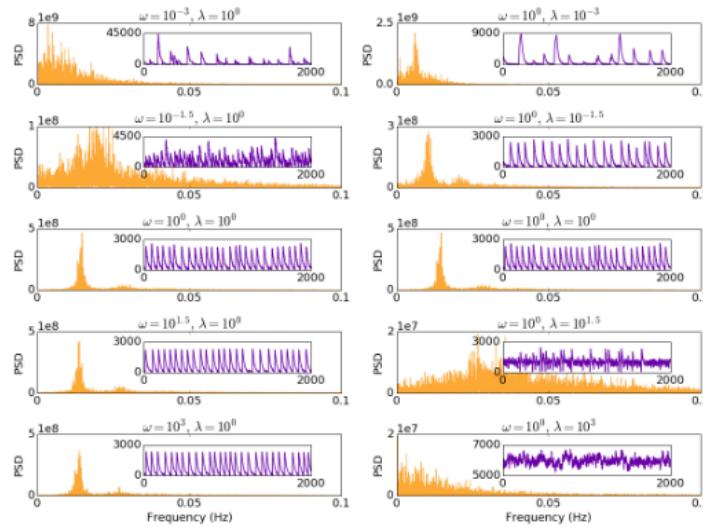
Gonze et al. PNAS 2002
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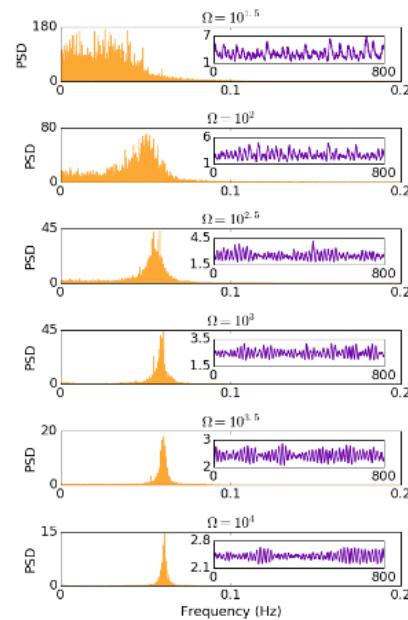
Karapetyan & Buchler, 2015



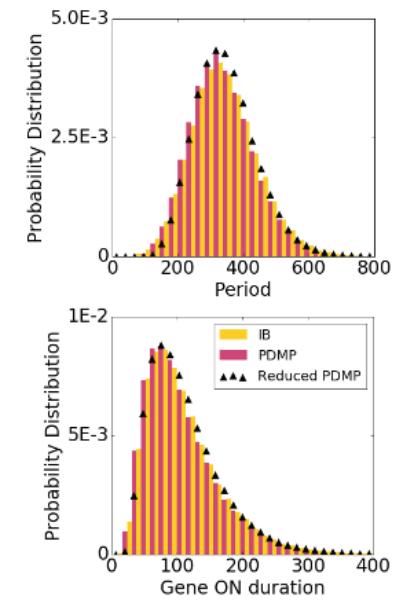
Excitation-relaxation and slow switching



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?

Mechanisms of Noise-induced Oscillation in Models of Biological Clock

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

Yen Ting Lin
Theoretical Biology and Computation Group,
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Collaborative work with: Nicolas Buceler
Department of Mathematics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA



EPSRC
Duke

Motivation

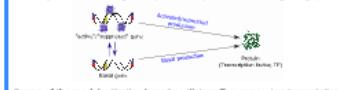
- Oscillatory dynamics are ubiquitous in biological systems: cell division/cycle, metabolism, circadian rhythms, etc.
- Many computational models were proposed for specific systems.
- Noise is an important factor in the processes:
 - Genetic noise: Temperature, light/dark cycle, heterogeneity of donor numbers of the reactants, etc.
 - Enviro noise: displacement of population, volume exclusion, localization in space, etc.
- There is an ongoing debate about if noise is “benign/neutral” for oscillations:
 - Prev: noise introd oscillations! The parameter range can be vast in linear models.
 - Conc: eventually 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 oscillations”? Are people comparing the same “noise”? 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 hypotheses 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: traitor-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

Deterministic model: mass action kinetics

Discrete promoter site dynamics

$$\begin{array}{l} \text{+ } \square \square \xleftarrow{\beta} \square \square \\ \text{+ } \square \square \xrightarrow{\alpha} \square \square \end{array} \quad \begin{array}{l} \text{+ } \square \square \xleftarrow{\gamma} \square \square \\ \text{+ } \square \square \xrightarrow{\delta} \square \square \end{array}$$

As birth-death process: binding rate depends on the regulating TF separation; constant unbinding

$$\begin{array}{l} \text{+ } \square \square \xleftarrow{\gamma} \square \square \\ \text{+ } \square \square \xrightarrow{\delta} \square \square \end{array} \quad \begin{array}{l} \text{(Common way) Assume **timescale separation**, i.e.,} \\ \text{binding/unbinding process are much faster, and derive quasi-stationary distribution/ineffective rate of production} \end{array}$$

$$\text{Number of regulating TF in the system} \quad \frac{dx}{dt} = \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} - \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} \frac{dx_i}{dt}$$

$$\text{Quasi-stationary distribution: } \frac{dx}{dt} = \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} - \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} \frac{dx_i}{dt}$$

$$\text{If } \square \square \text{ production rate} \quad \frac{dx}{dt} = \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} - \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} \frac{dx_i}{dt}$$

$$\text{else: production rate} \quad \frac{dx}{dt} = \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} - \sum_{i=1}^n \frac{N_i}{\Omega} x_i \frac{\partial f}{\partial x_i} \frac{dx_i}{dt}$$

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

$$\begin{array}{l} \square \square \xrightarrow{\beta} \square \square \\ \square \square \xrightarrow{\alpha} \square \square \end{array} \quad \begin{array}{l} \dot{x}(t) = \beta \bar{x}^{\text{eff}}(\Omega t) - \delta x \bar{x} - \alpha xy, \\ \dot{y}(t) = \alpha \bar{x}^{\text{eff}}(\Omega t) - \delta y \bar{x} - \alpha xy. \end{array}$$

Denudum criterion stated that a limit cycle does not exist when $\partial_x \mathcal{F} + \partial_y \mathcal{G} = -\delta x - \delta y - \alpha(x+y) + \Omega + \frac{d\bar{x}^{\text{eff}}}{dt}$.

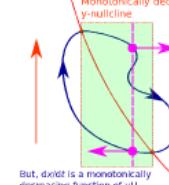
does not change sign on a single connected domain (in our case, $\mathbb{R}^+ \times \mathbb{R}^+$). If a limit cycle exists, a necessary condition

$$\Rightarrow \frac{d\bar{x}^{\text{eff}}}{dt} > 0 \Rightarrow x \text{ must be positively regulating itself.}$$



Deterministic model: mass action kinetics

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



- In this model: There is no limit cycle for <2 feedback!
- This argument applies to negatively regulated Y, so we need both positive feedback.

But, dx/dt is a monotonically decreasing function of y !!

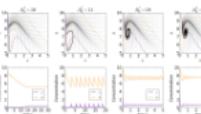
Deterministic model: mass action kinetics

$$x(t) = \beta \bar{x}^{\text{eff}}(\Omega t) - \delta x \bar{x} - \alpha xy,$$

$$y(t) = \alpha \bar{x}^{\text{eff}}(\Omega t) - \delta y \bar{x} - \alpha xy,$$

$$\text{Necessary condition: } \frac{d\bar{x}^{\text{eff}}}{dt} > 0, \text{ and } \frac{d\bar{y}^{\text{eff}}}{dt} > 0.$$

We show that oscillation/limit circle exists numerically:



Summary

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

Thank you for your attention!