Distributed delay constructively impacts the dynamics of genetic regulatory networks

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ICERM
Workshop: Uncertainty Quantification for Mathematical Biology

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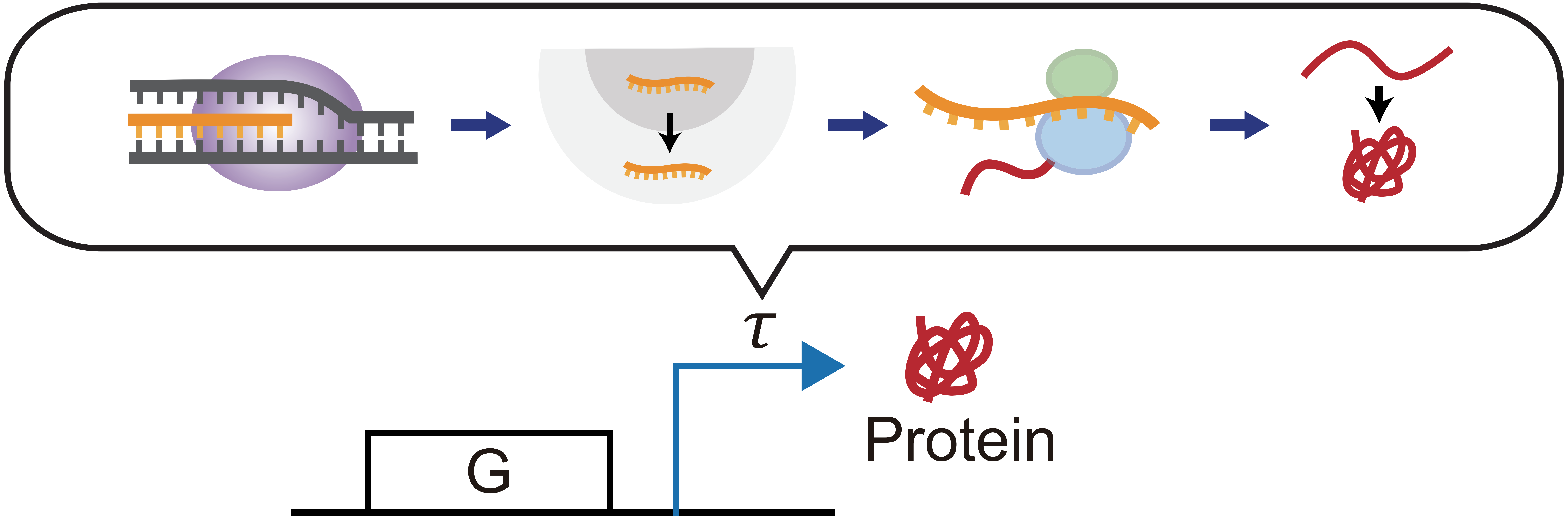
Part 1: Setting

How does distributed delay impact the dynamics of genetic regulatory networks?

Origins of distributed delay



The modeling hierarchy

small system sizes: delay stochastic simulation algorithm (dSSA), stochastic process of Schlicht and Winkler

moderate system sizes: delay chemical Langevin equation (dCLE)

system size $\rightarrow \infty$: delay reaction rate equation (dRRE)

[Gupta et alli, Modeling delay in genetic networks: From delay birth-death processes to delay stochastic differential equations, J. Chem. Phys., 2014]

Part 2: Delayed negative feedback

How does distributed delay impact biochemical oscillators?

[Song et alli, Noisy delay denoises biochemical oscillators, PRL, 2024]

Mather oscillator

$$\dot{r} = \alpha \frac{C_0^2}{[C_0 + r(t)]^2} - \frac{\gamma r(t)}{R_0 + r(t)} - \beta r(t)$$ ← No delay, does not oscillate

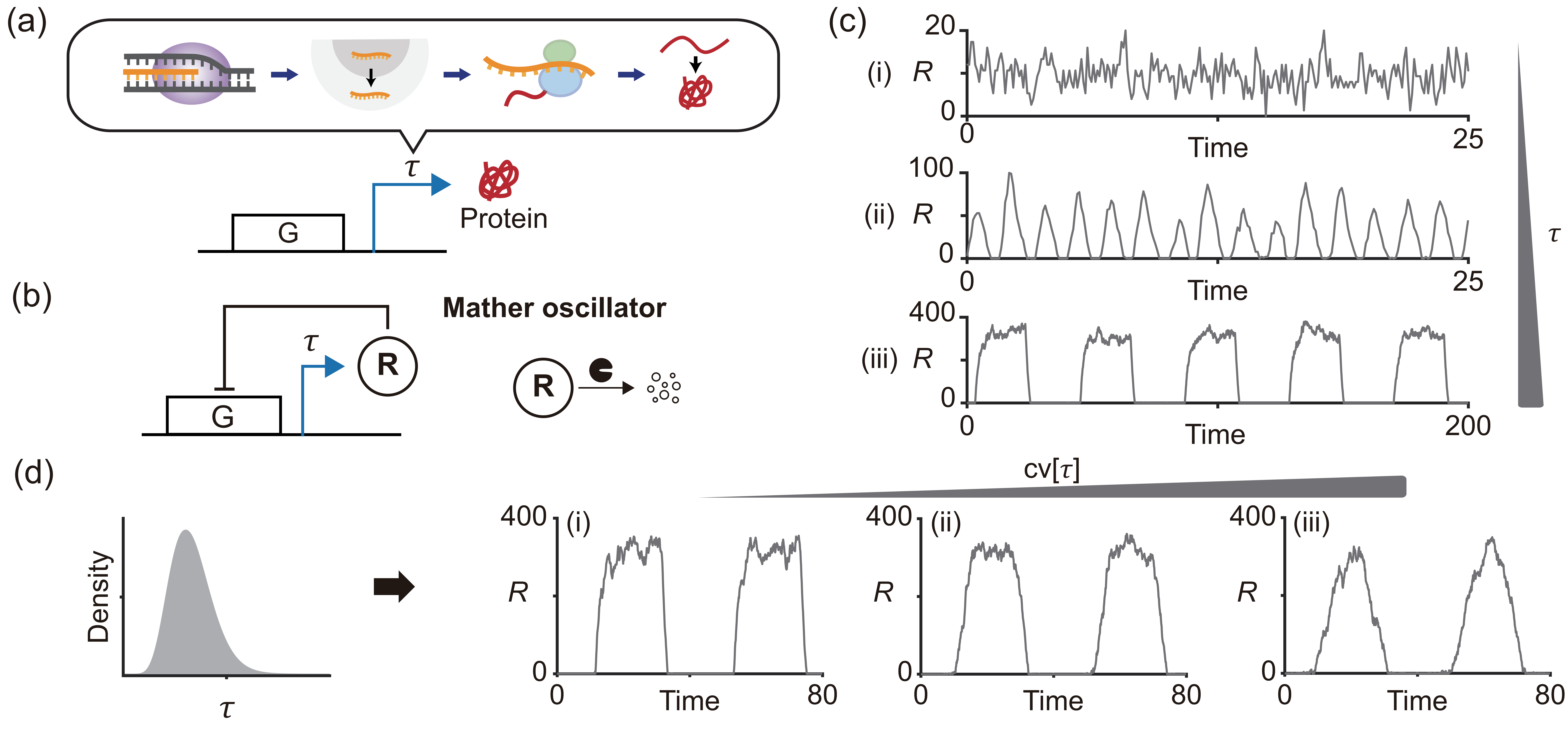
$$\dot{r} = \alpha \frac{C_0^2}{[C_0 + r(t - \tau)]^2} - \frac{\gamma r(t)}{R_0 + r(t)} - \beta r(t)$$ ← Degrade and fire oscillations

fixed delay

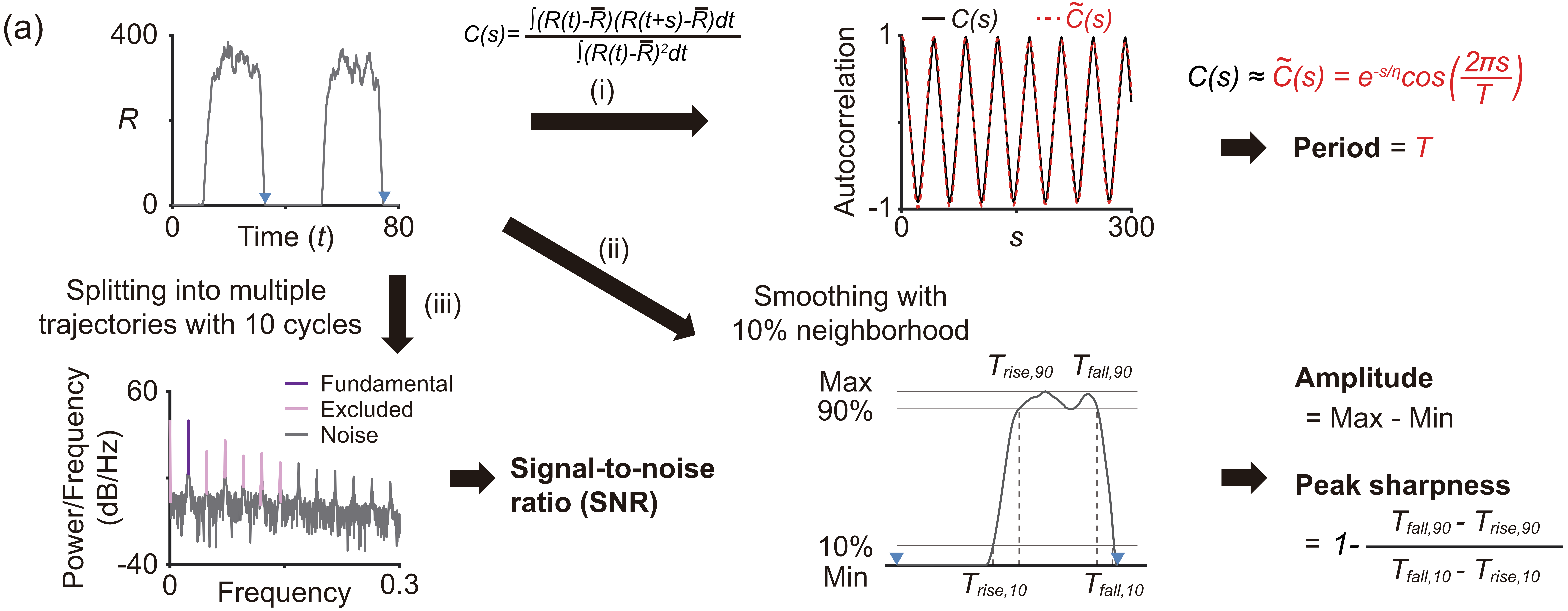
What does distributed delay induce?

$$\dot{r} = \alpha \left[\int_0^\infty \frac{C_0^2}{[C_0 + r(t - \tau)]^2} \mathrm{d}\mu(\tau) \right] - \frac{\gamma r(t)}{R_0 + r(t)} - \beta r(t)$$

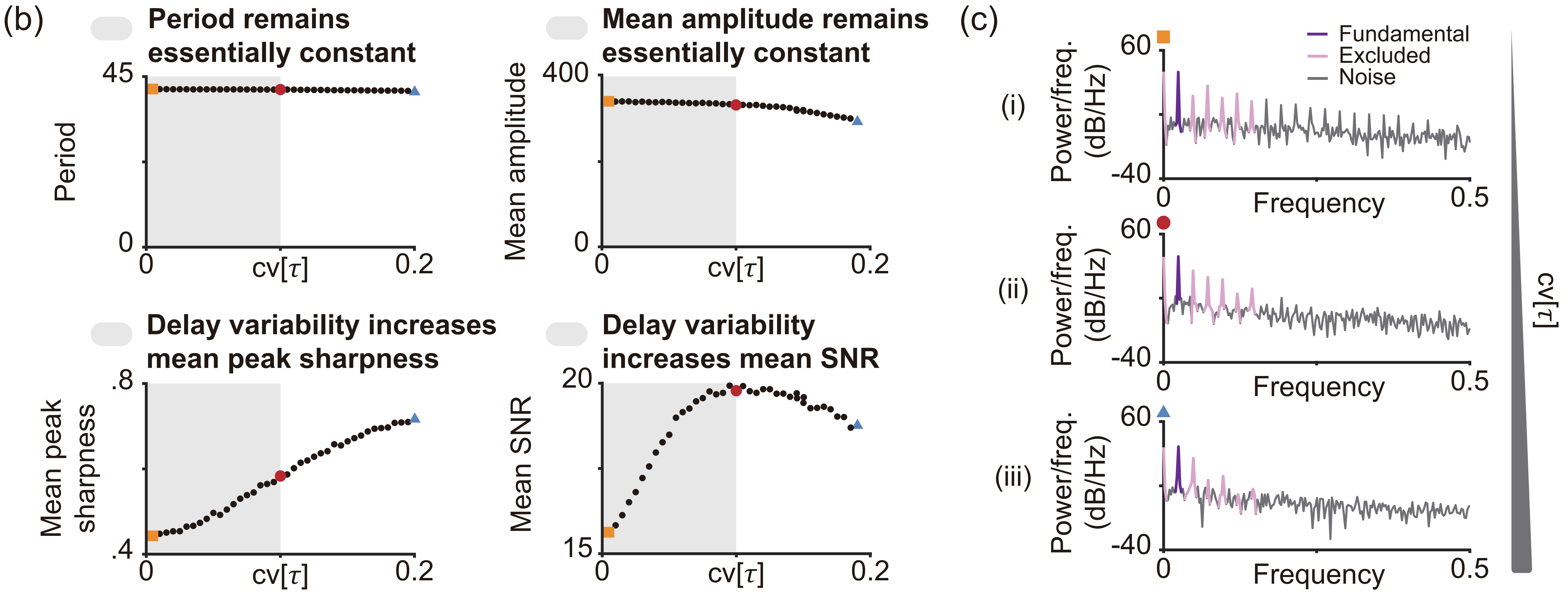
Philosophy: Fix delay mean, tune delay CV



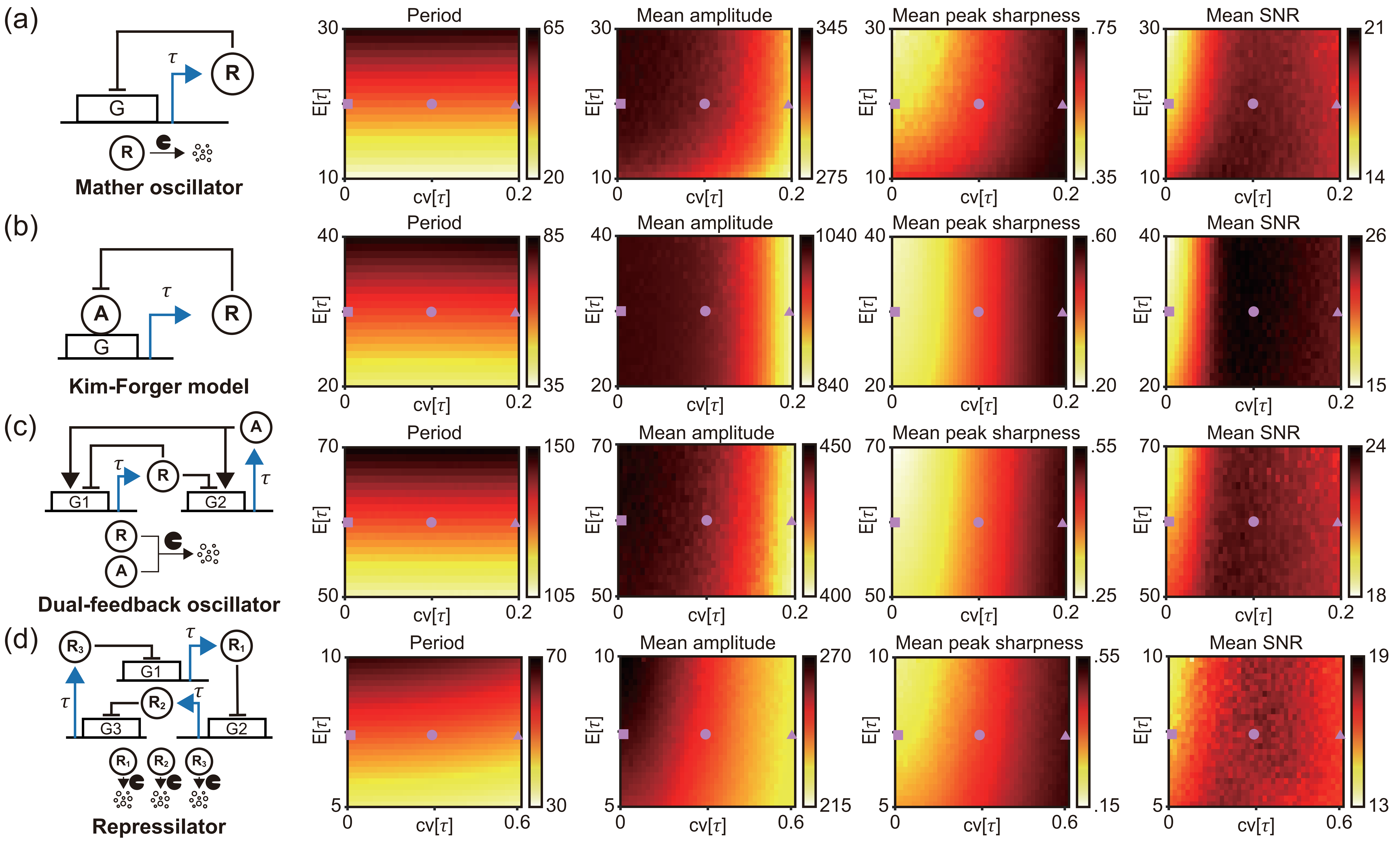
Quantifying the stochastic oscillation



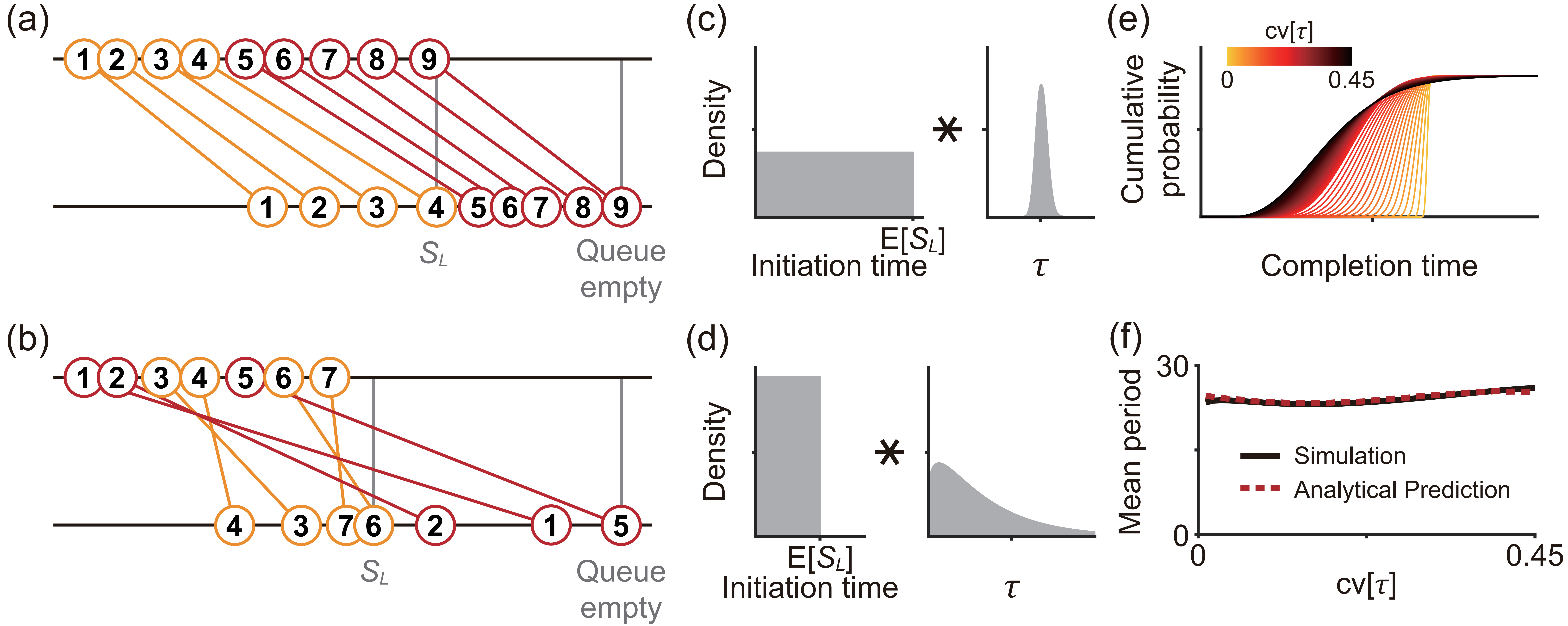
Distributed delay acts constructively: Denoising



Denoising occurs for a variety of models



Queueing theory explains why period remains stable



Part 3: Delayed positive feedback, fixed delay

How does fixed delay impact bistable switches?

[Gupta et alli, Transcriptional delay stabilizes bistable gene networks, PRL, 2013]

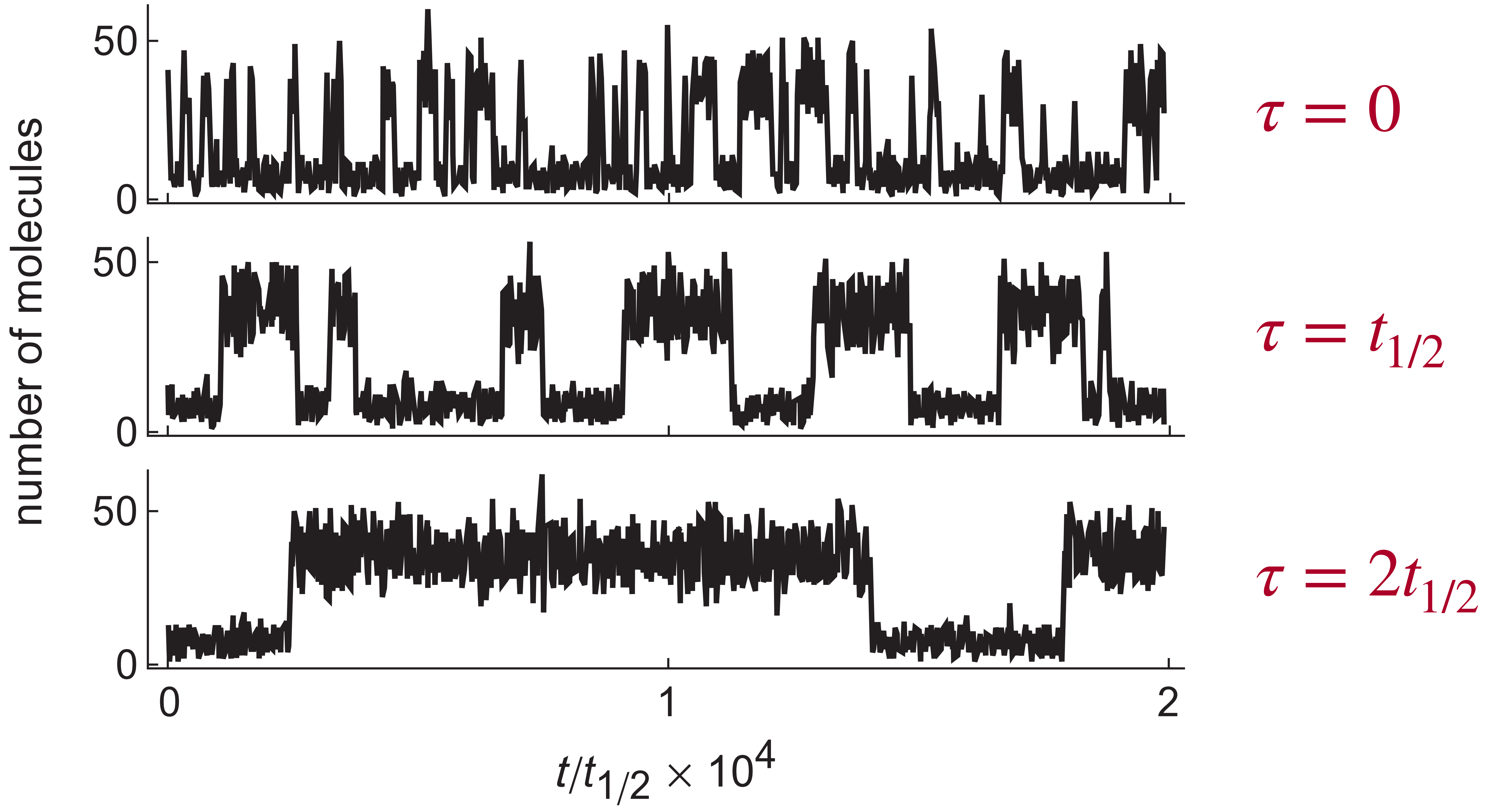
A single-gene positive feedback loop: Intriguing data

$$\dot{x} = \underbrace{\alpha + \beta\frac{x(t-\tau)^b}{c^b + x(t-\tau)^b}}_{\text{birth}} - \underbrace{\gamma x}_{\text{death}}$$

tune for bistability

dSSA simulations

$t_{1/2}$ = protein half-life



Mean residence time: A metric for metastability

Let R_τ denote mean residence time in the metastable states.

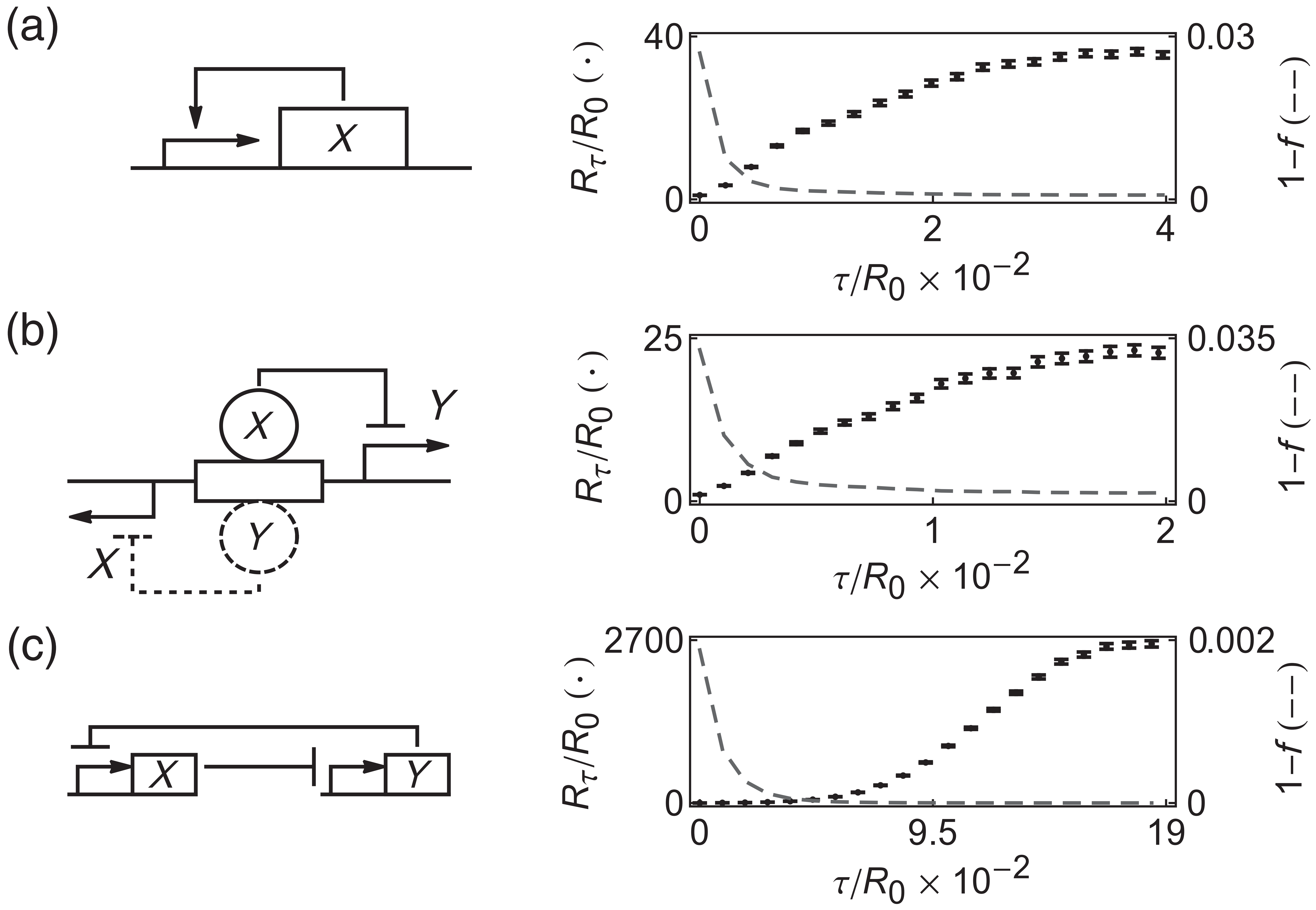
QUESTION. How does R_τ vary with fixed delay τ?

Significant stabilization of metastable states is prevalent!

single-gene positive feedback loop

bacteriophage-λ switch

co-repressive toggle switch



In search of an explanation for the dramatic stabilization

QUESTION 1. Is there a local explanation for the stabilization?

QUESTION 2. Do the fixed points become more stable as τ increases?

In search of an explanation for the dramatic stabilization

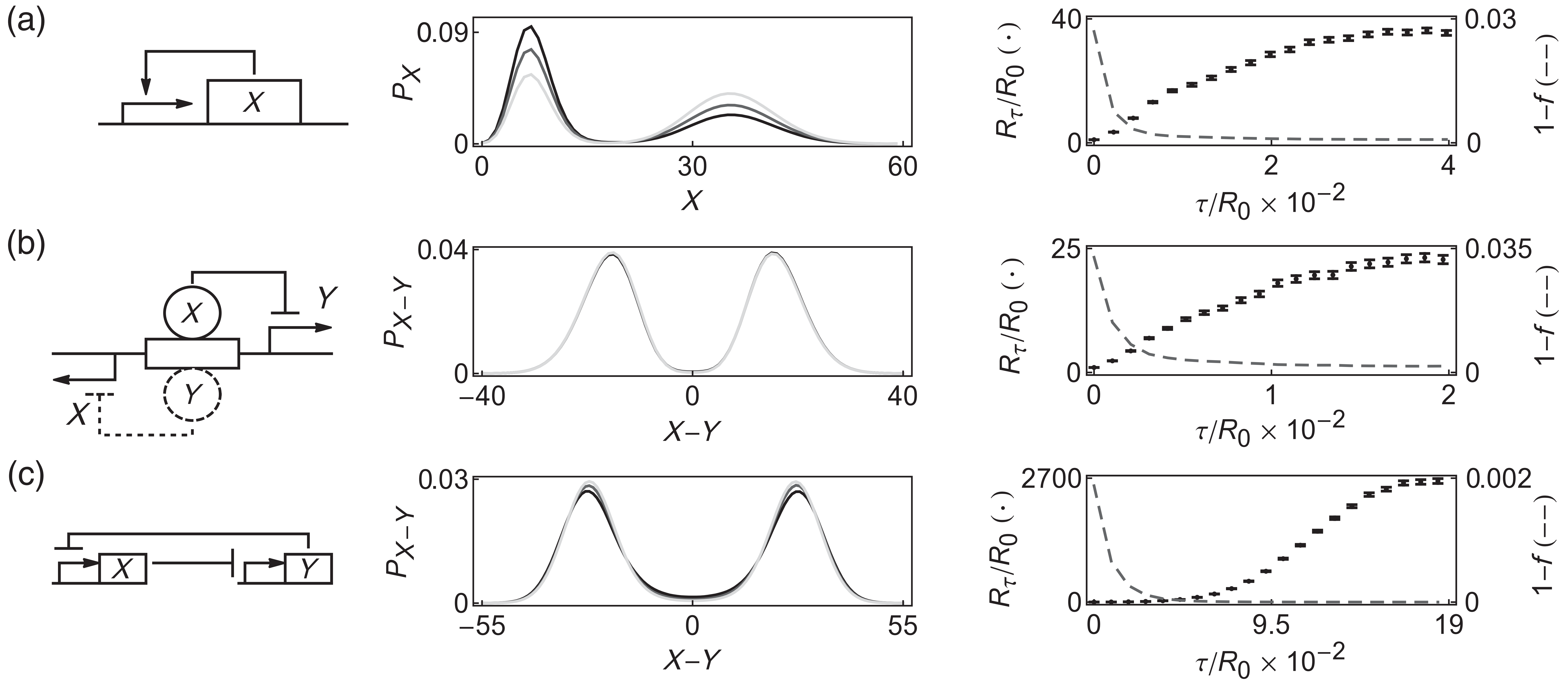
QUESTION 1. Is there a local explanation for the stabilization?

QUESTION 2. Do the fixed points become more stable as τ increases?

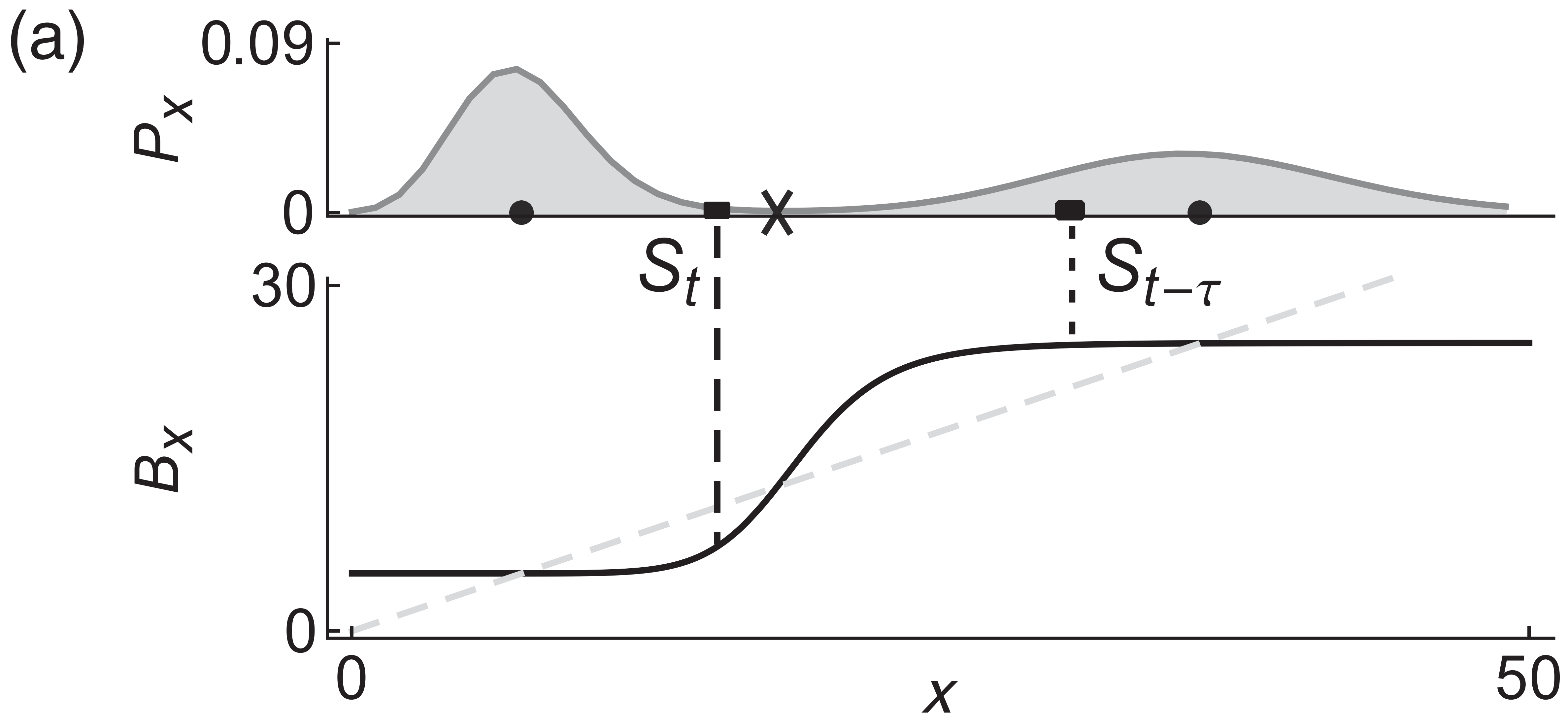
Answer to Q2: No. In fact, the fixed points can become less stable as τ increases!

The mystery deepens: Stationary distributions

lighter shade indicates larger delay

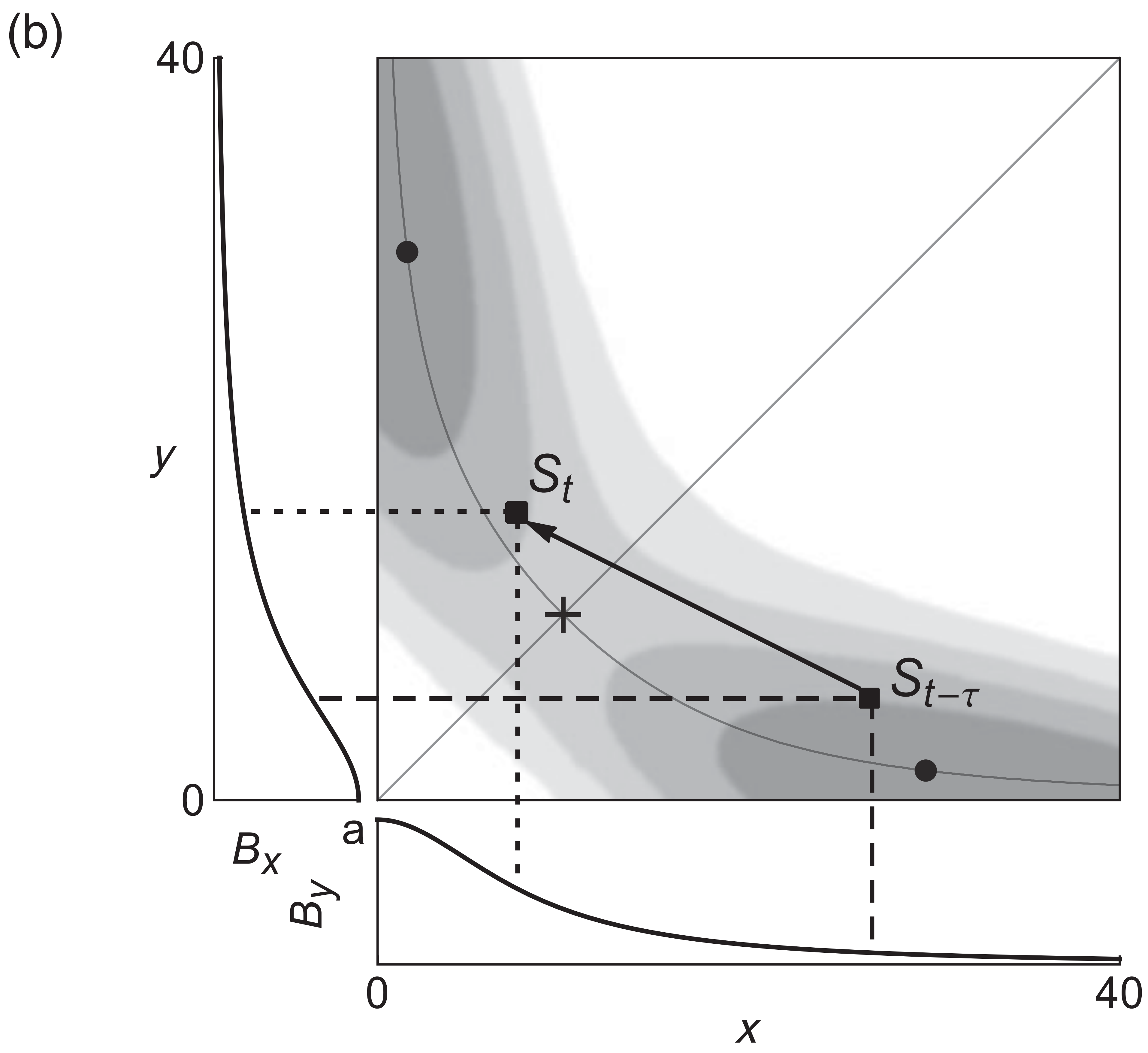


Resolution: A rubber-band effect



single-gene positive feedback loop

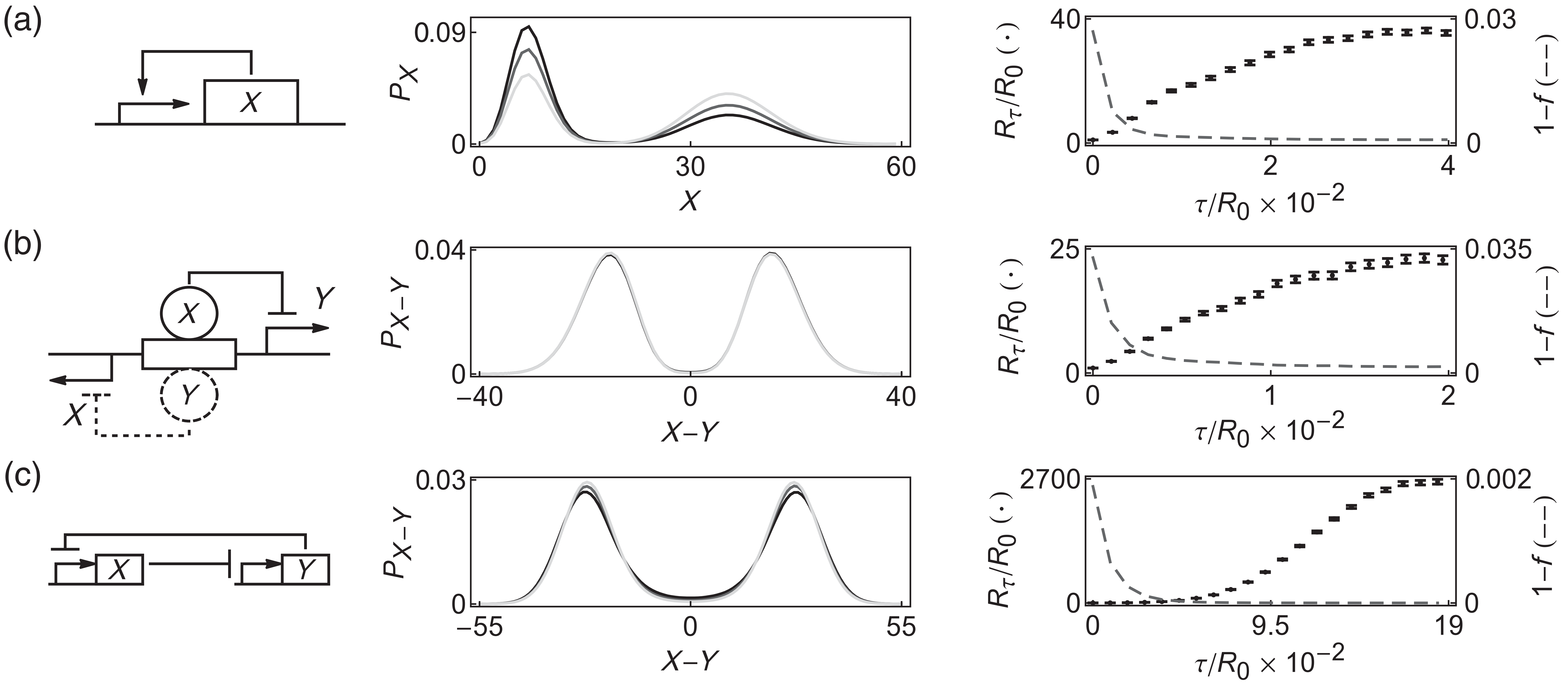
co-repressive toggle switch



Transition attempts are increasingly likely to fail as τ increases!

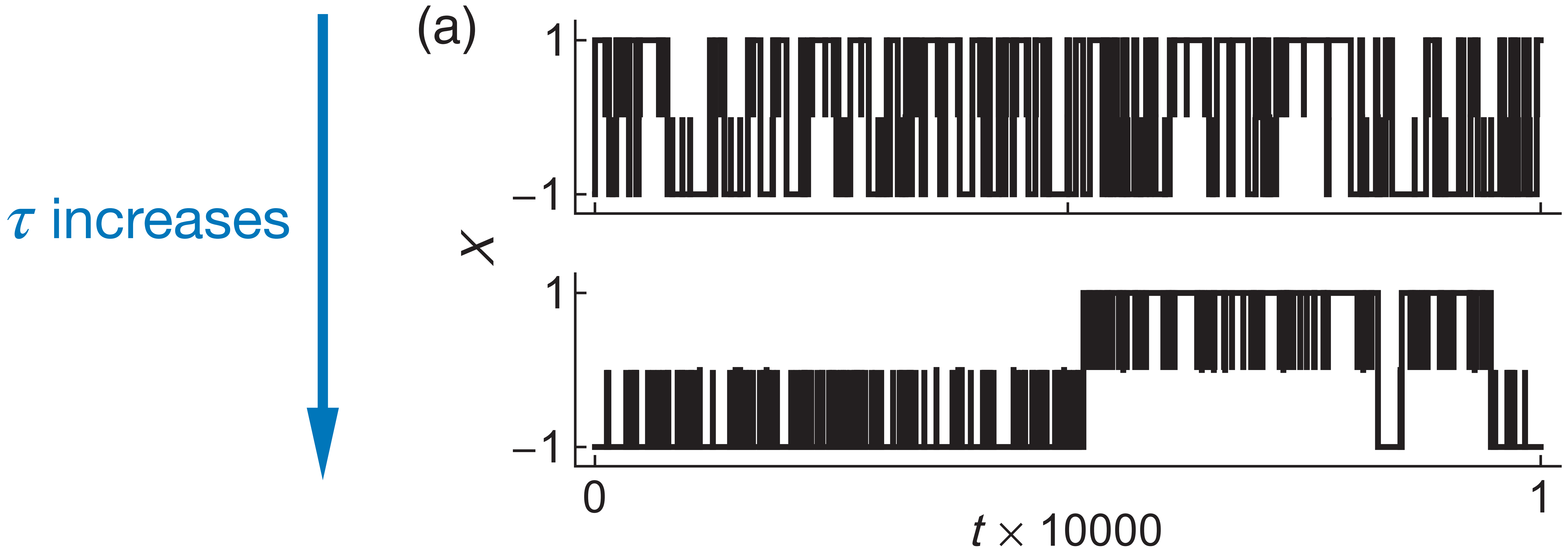
Data supports the rubber-band theory

dashed line indicates the probability of a successful transition



A 3-states model captures the rubber-band effect

- non-Markovian symbolic model
- state space: $\{L, I, H\}$
- transition rates: $\lambda^{i}_{j,k}$ (rate of transition from state j to state k, given that τ units of time in the past, the system was in state i)



Part 4: Delayed positive feedback, distributed delay

This is work in progress! Chat with Amanda Alexander.

Thank you!