Does delay constructively influence the dynamics of genetic networks?

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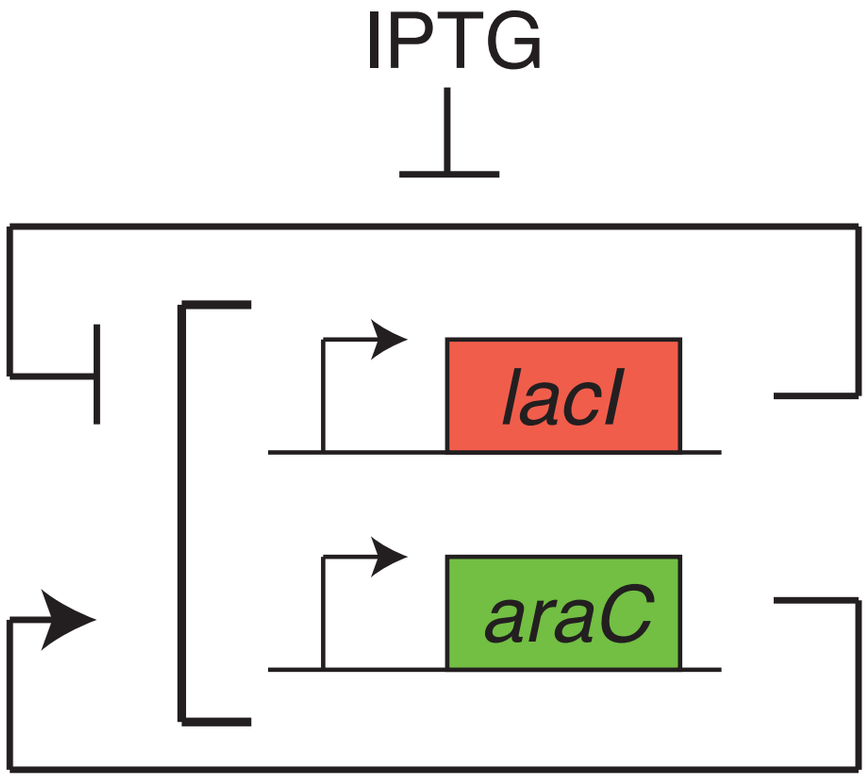
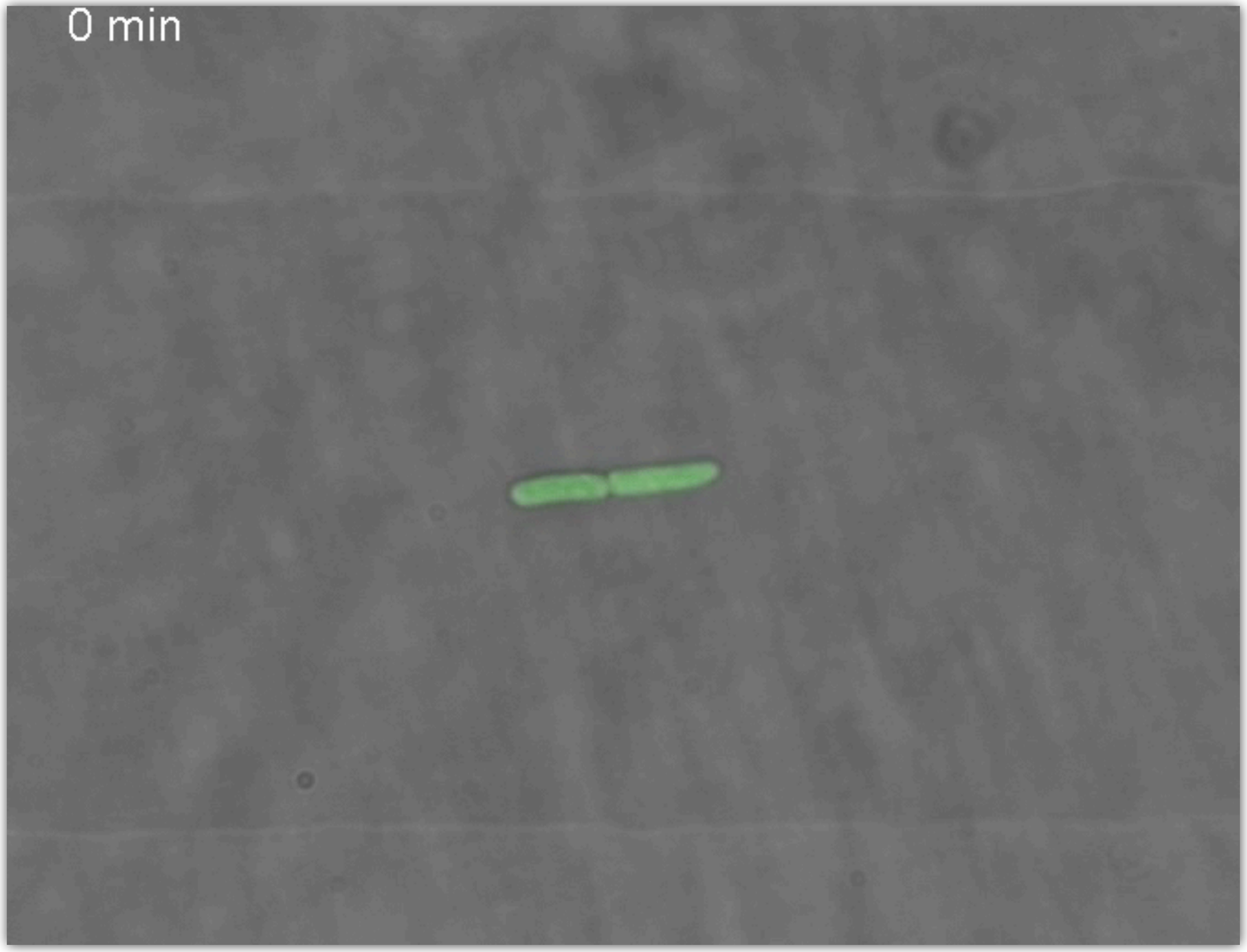
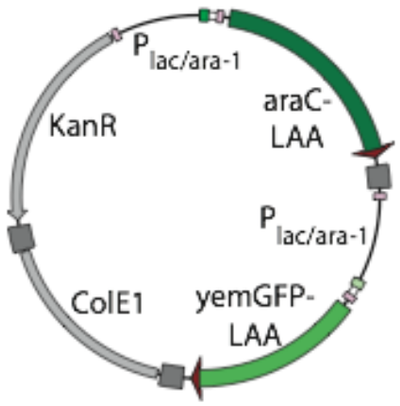
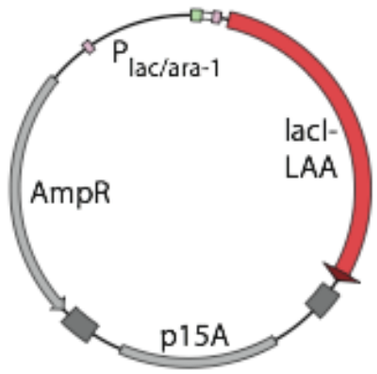
Inspiration: synthetic biology







activator/reporter plasmid (pJS167)

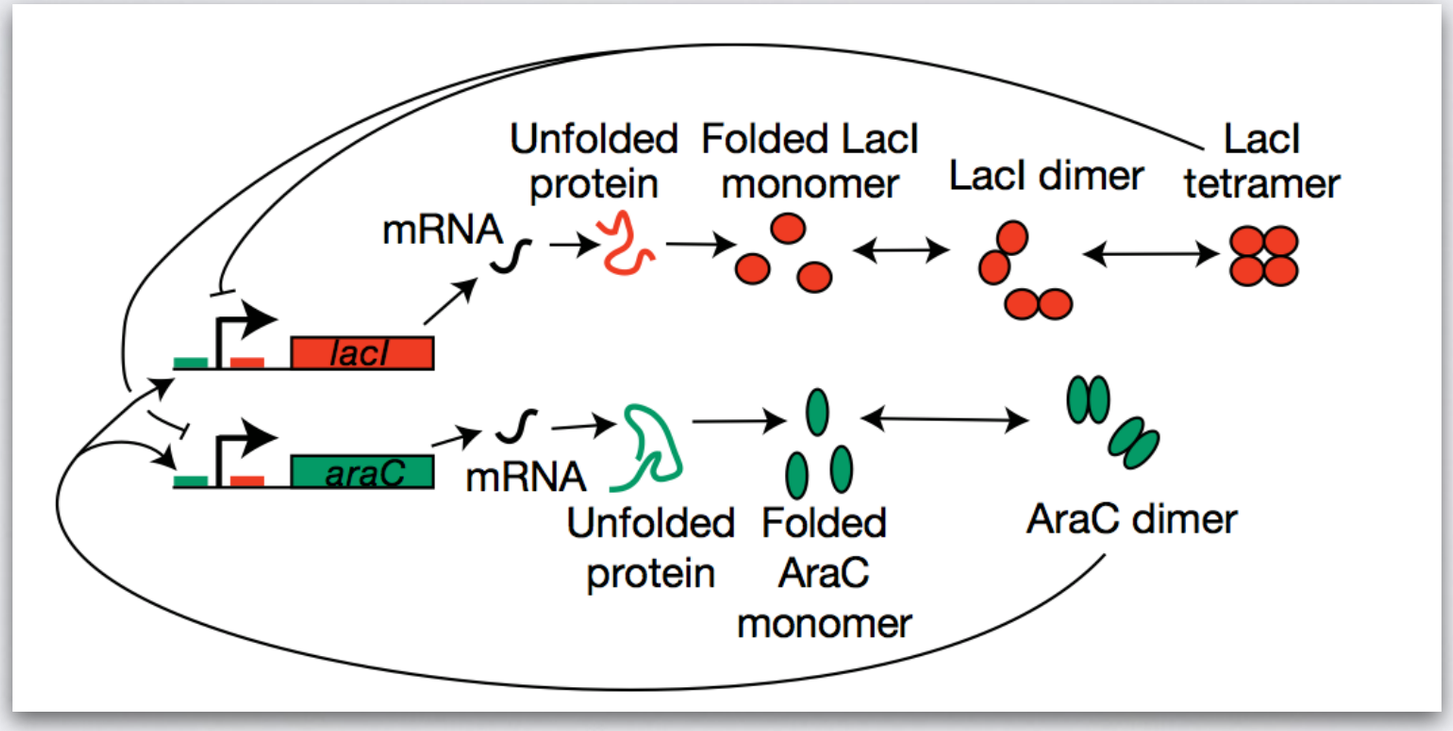


repressor plasmid (pJS169)

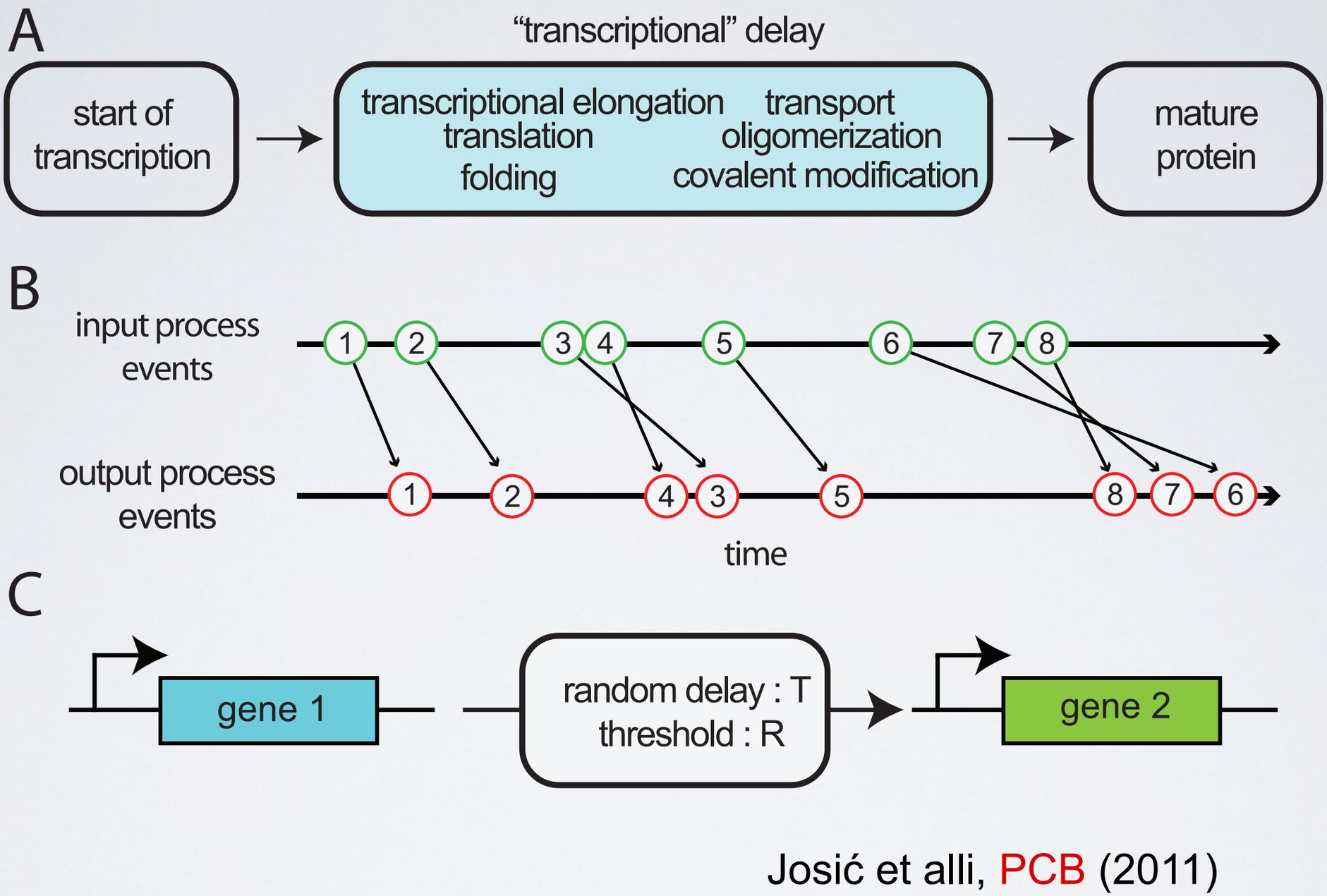
Stricker et alli, Nature **456**, 516 (2008)

Delay and stochasticity in metastable systems

- Origins
- Modeling hierarchies
- Delay stabilizes metastable states
  - Numerical results
  - Symbolic stochastic modeling
- Impact of the cell cycle



Protein production as a queueing system



Josić et alli, PCB (2011)

Modeling hierarchies

Stochastic simulation algorithm (SSA)

↓

Tau leaping

↓

Langevin approximations (SDEs)

↓

Ordinary differential equations

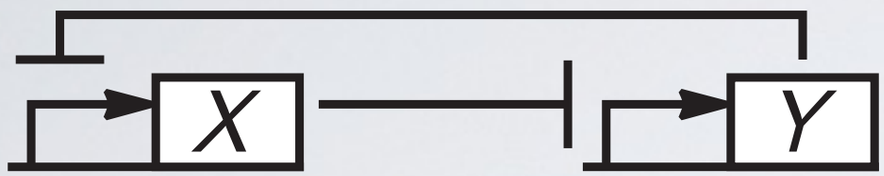
⇒

(1) Delay analogs?

(2) Delay chemical Langevin equations?

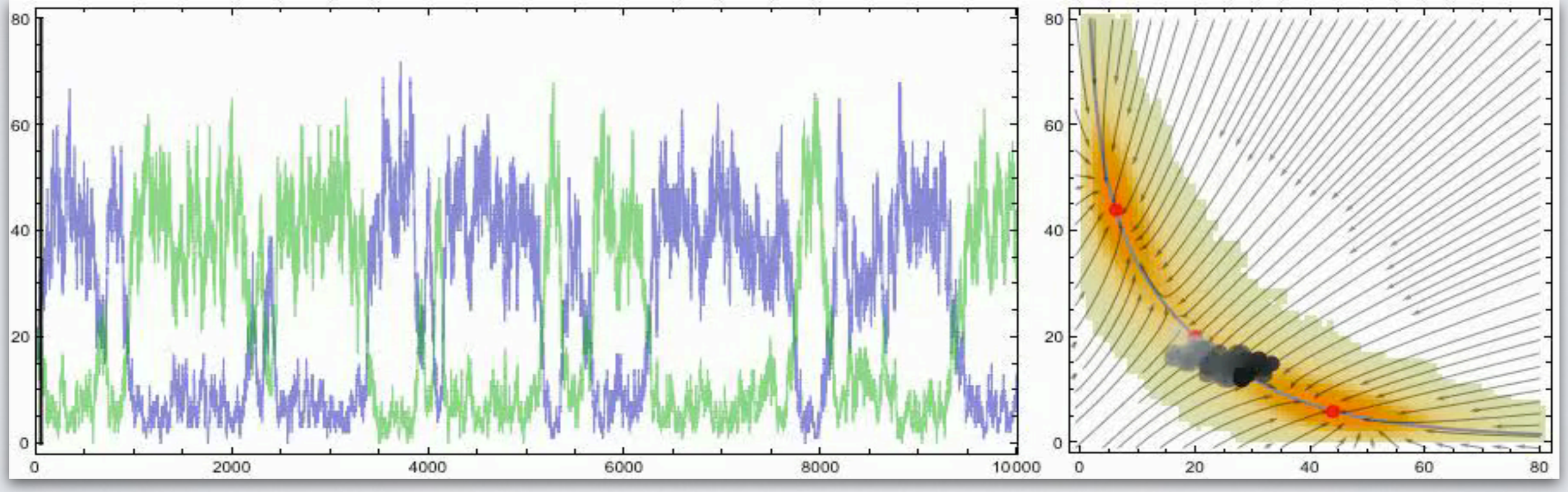
- Schlicht-Winkler: theoretical foundation for delay SSA
- Delay chemical Langevin equations
  - Brett-Galla: derivation via generating functionals
  - Ott et alli: quantitative results

Genetic switch: Co-repressive toggle



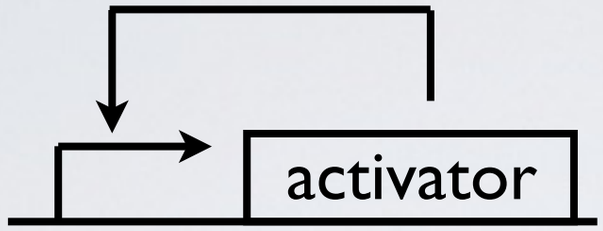
$$\frac{dx}{dt} = \frac{\alpha}{c^b + y(t-\tau)^b} - \gamma x$$

$$\frac{dy}{dt} = \frac{\alpha}{c^b + x(t-\tau)^b} - \gamma y$$

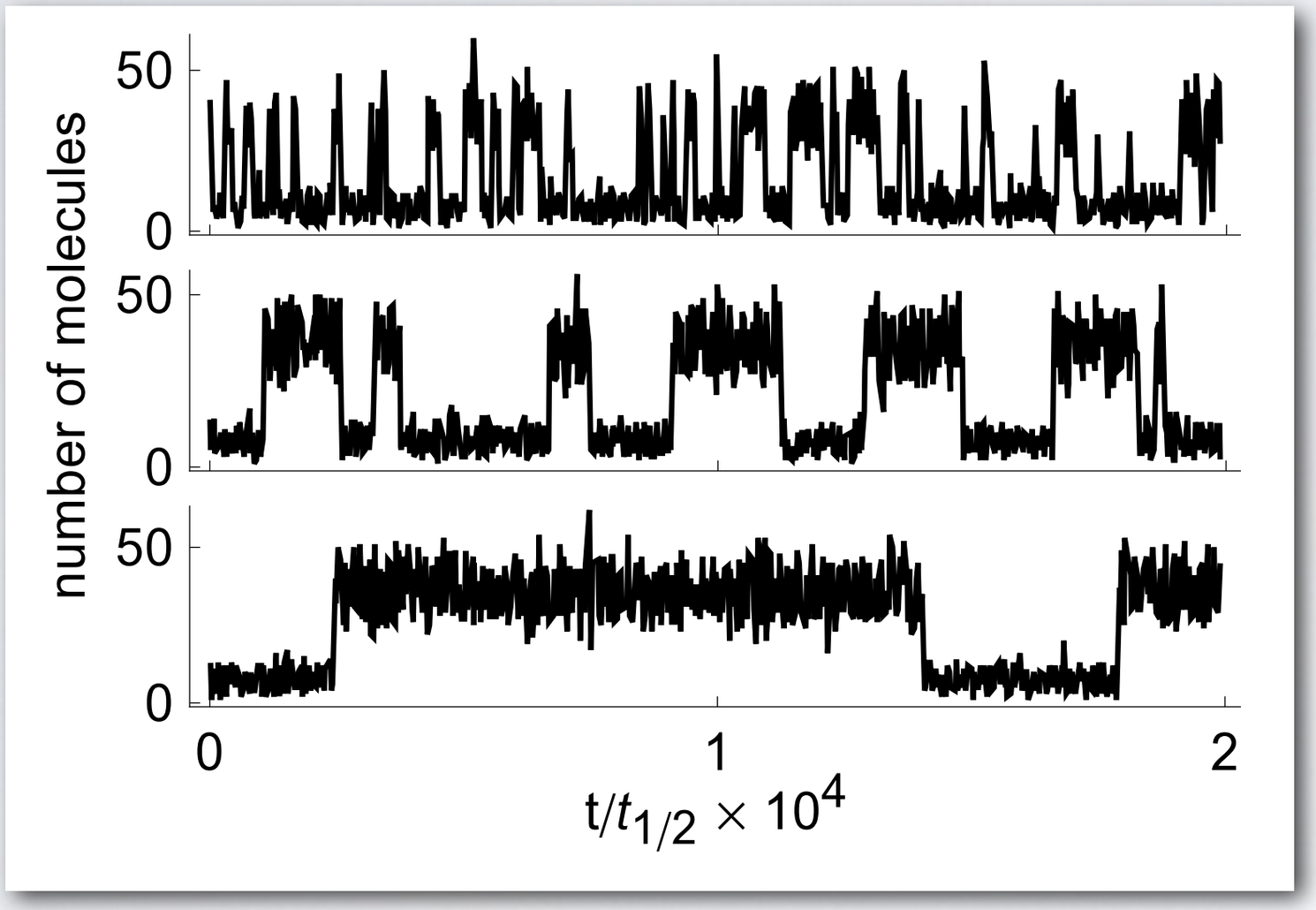


Gupta and Ott et alli, PRL **111**:058104 (2013)

Transcriptional delay stabilizes bistable gene networks



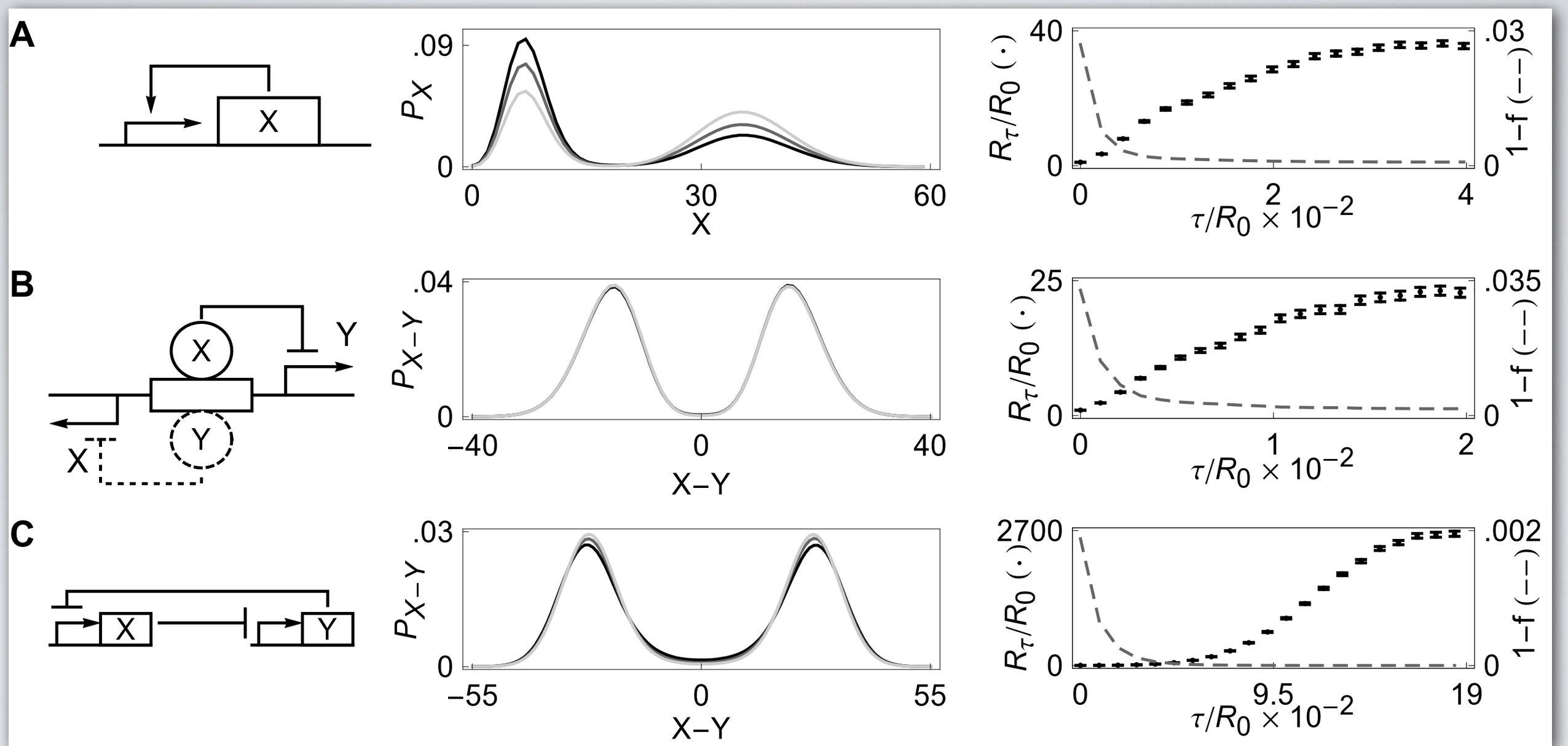
single-gene
positive feedback



increasing
delay

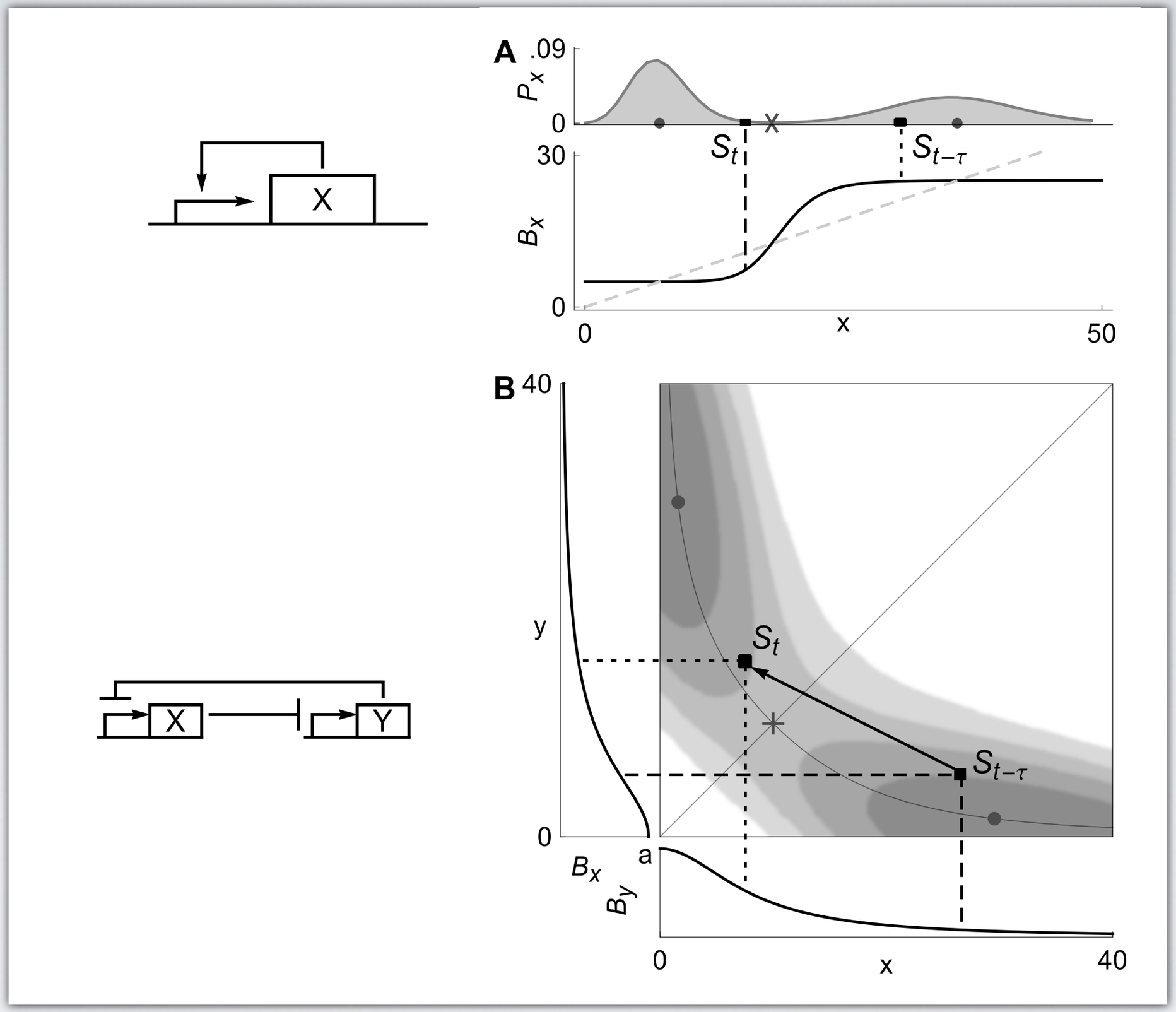
Gupta and Ott et alli, PRL **111**:058104 (2013)

Transcriptional delay stabilizes bistable gene networks



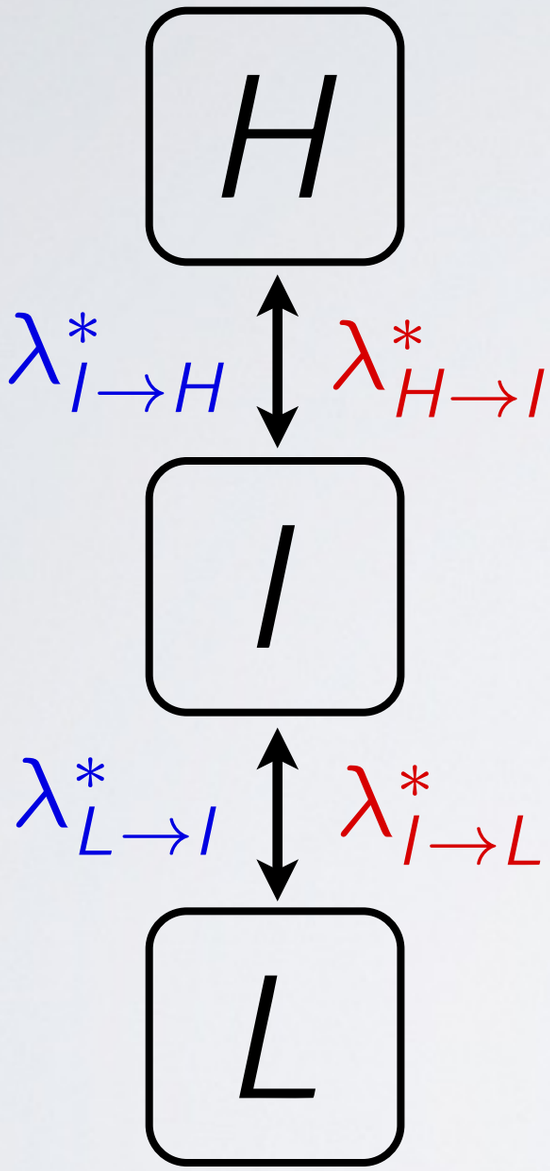
Gupta and Ott et alli, PRL **111**:058104 (2013)

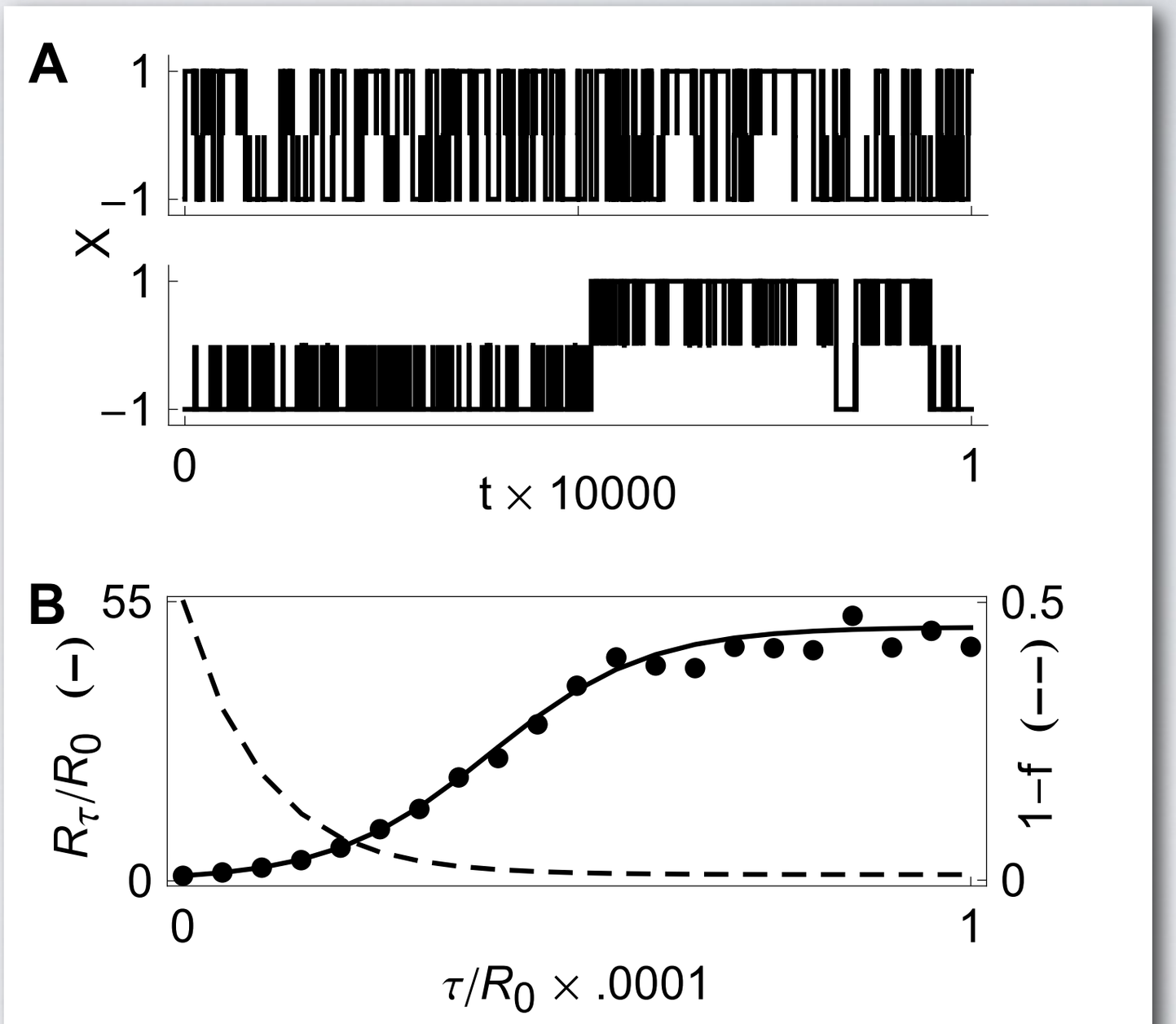
Delay-induced rubber band effect



Gupta and Ott et alli, PRL **111**:058104 (2013)

3-states model

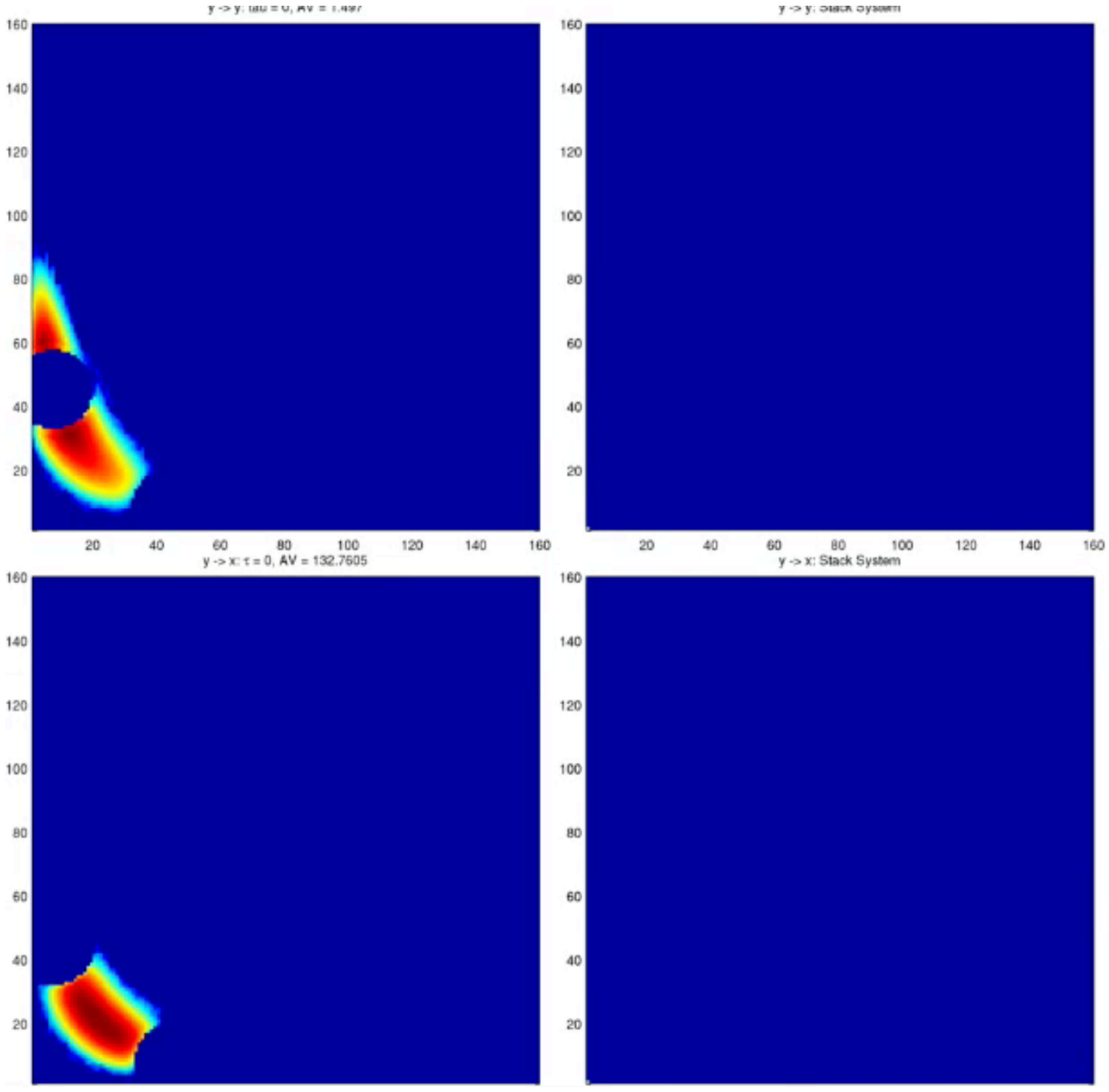




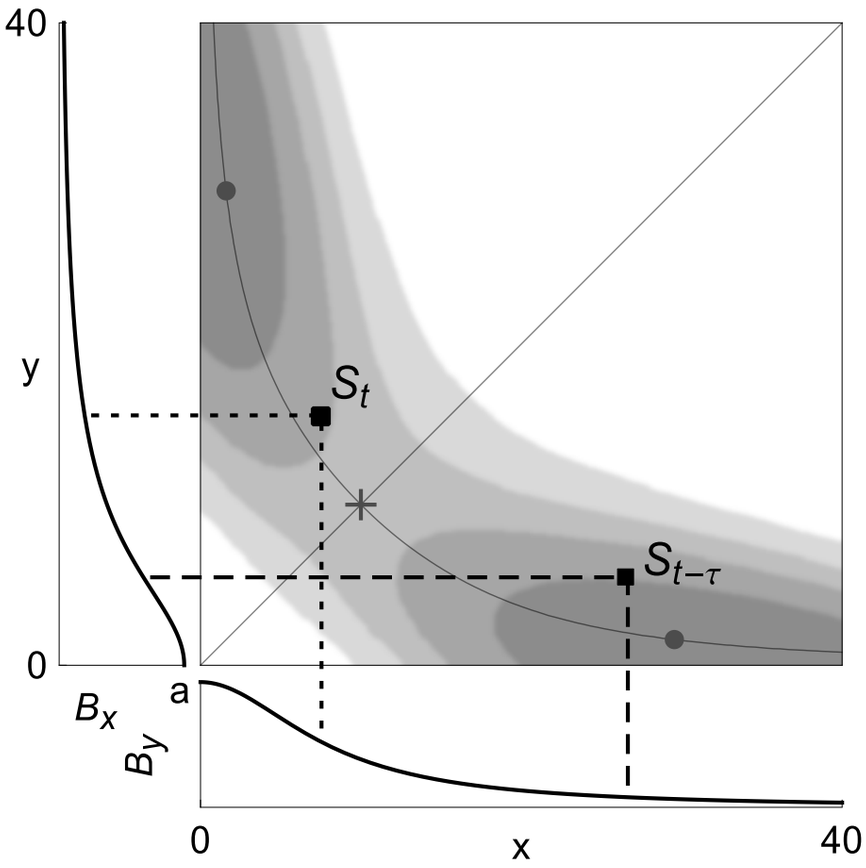
Gupta and Ott et alli, PRL **111**:058104 (2013)

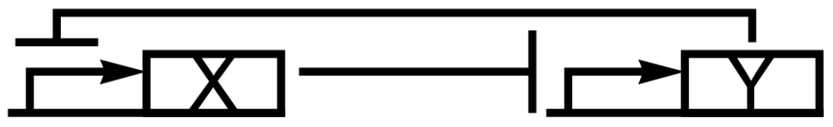
Spatial transition mechanics change with delay

Y → Y



Production Queue

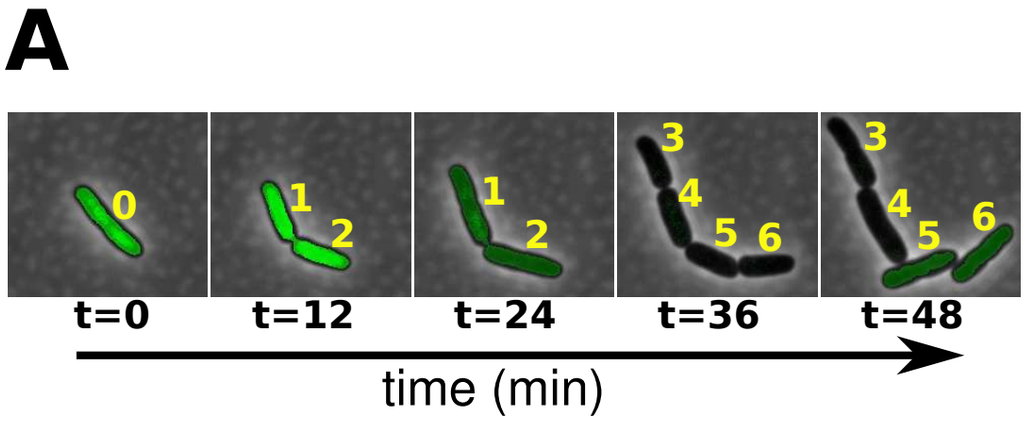


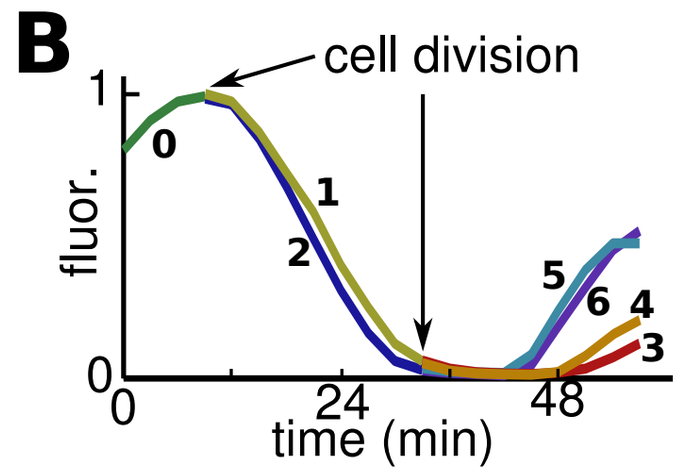


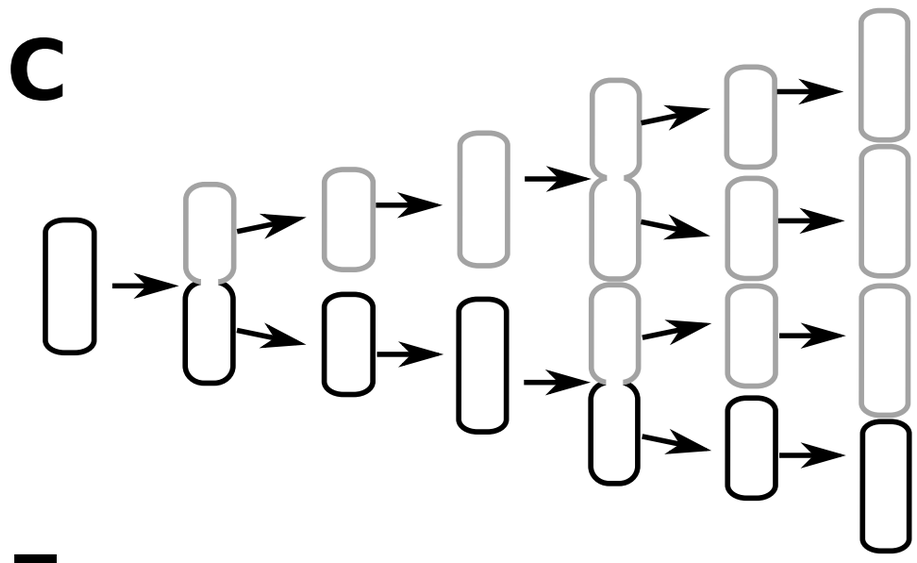
Y → X

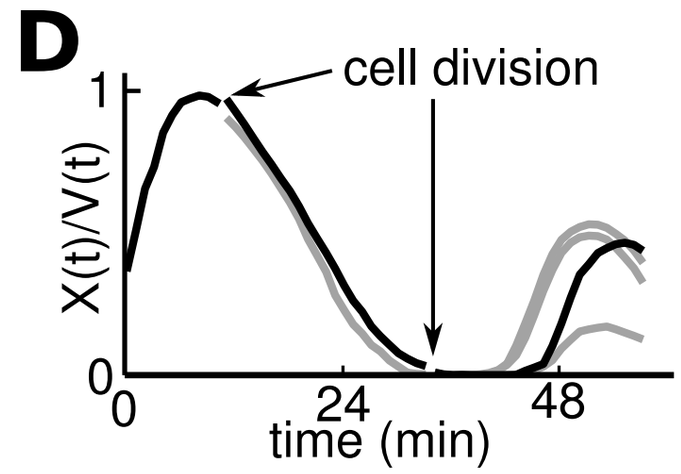
Production Queue

Modeling frameworks

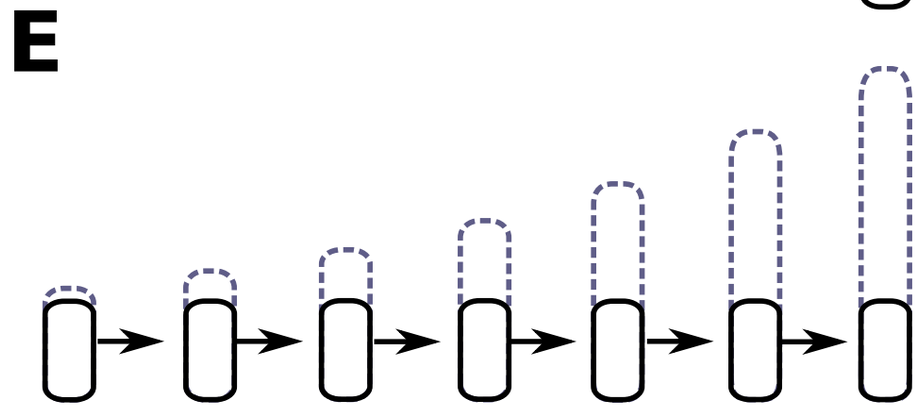


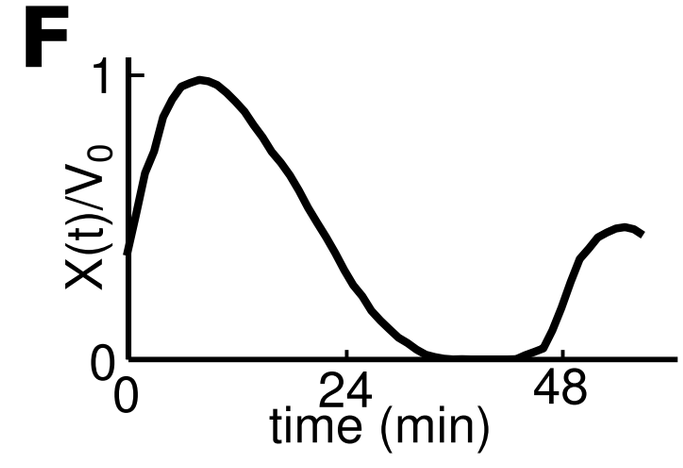






cell growth/division framework



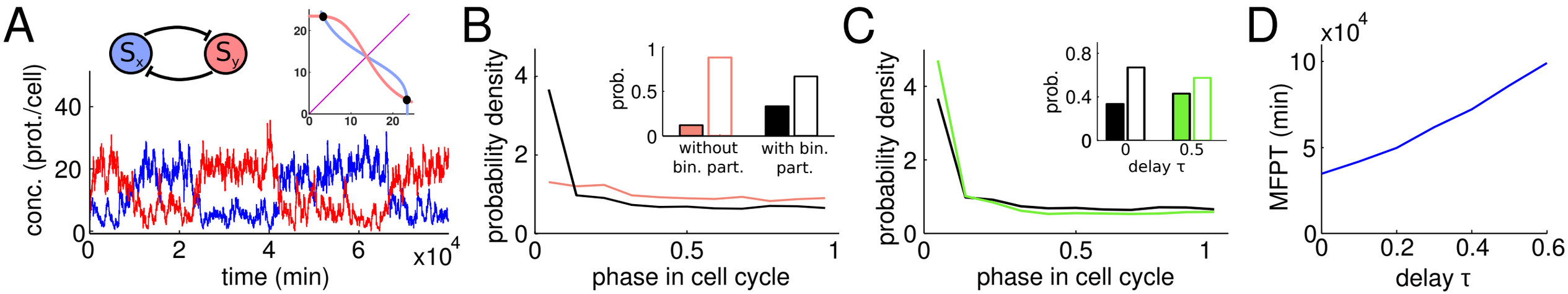


dilution framework

Veliz-Cuba et alli (2016)

Concentration effect for metastable systems

- Transitions most likely occur just after cell division
- Transcriptional delay intensifies this concentration effect
- Binomial partitioning - primary cause

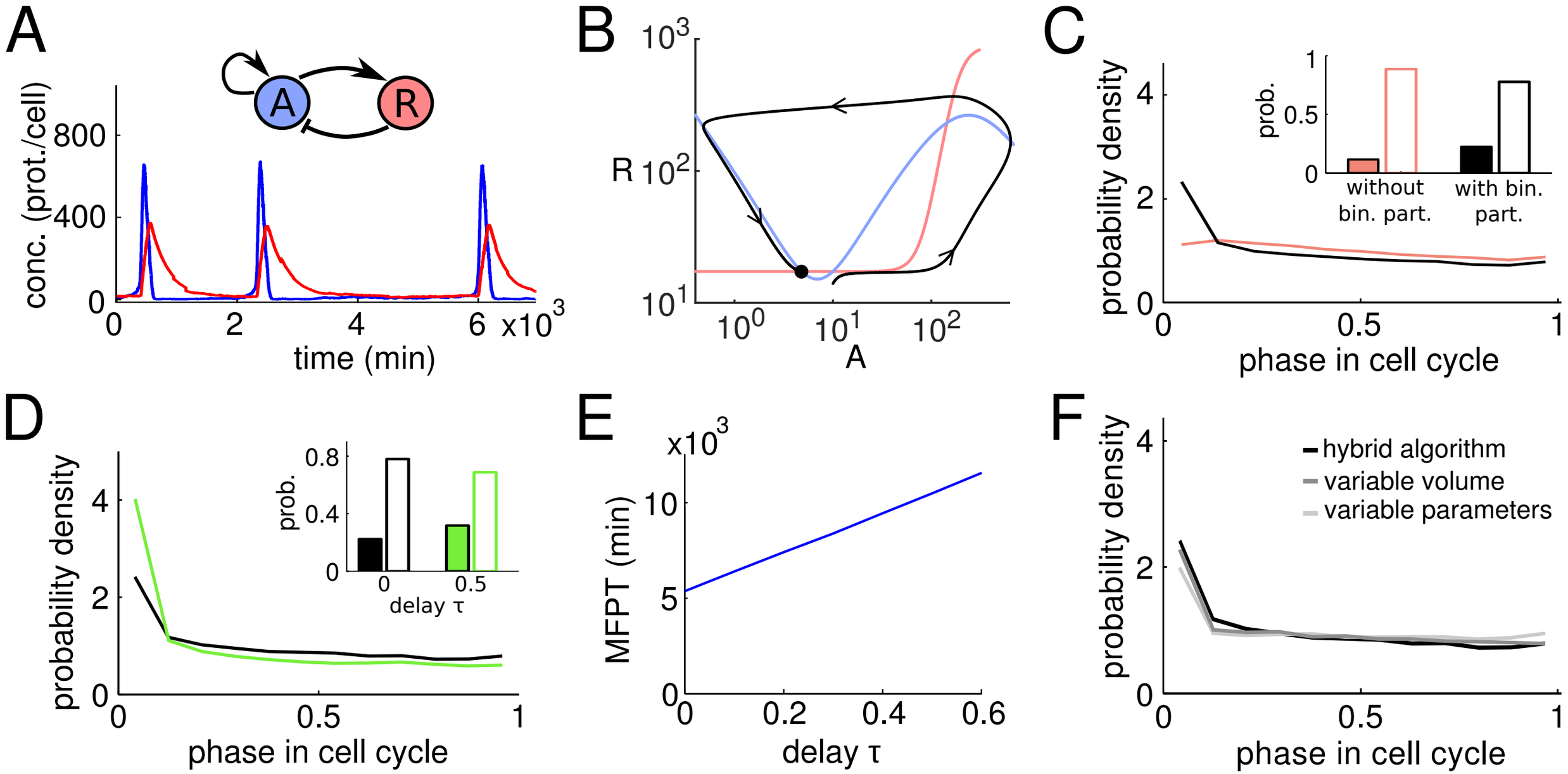


system:
co-repressive toggle

conditional PDFs

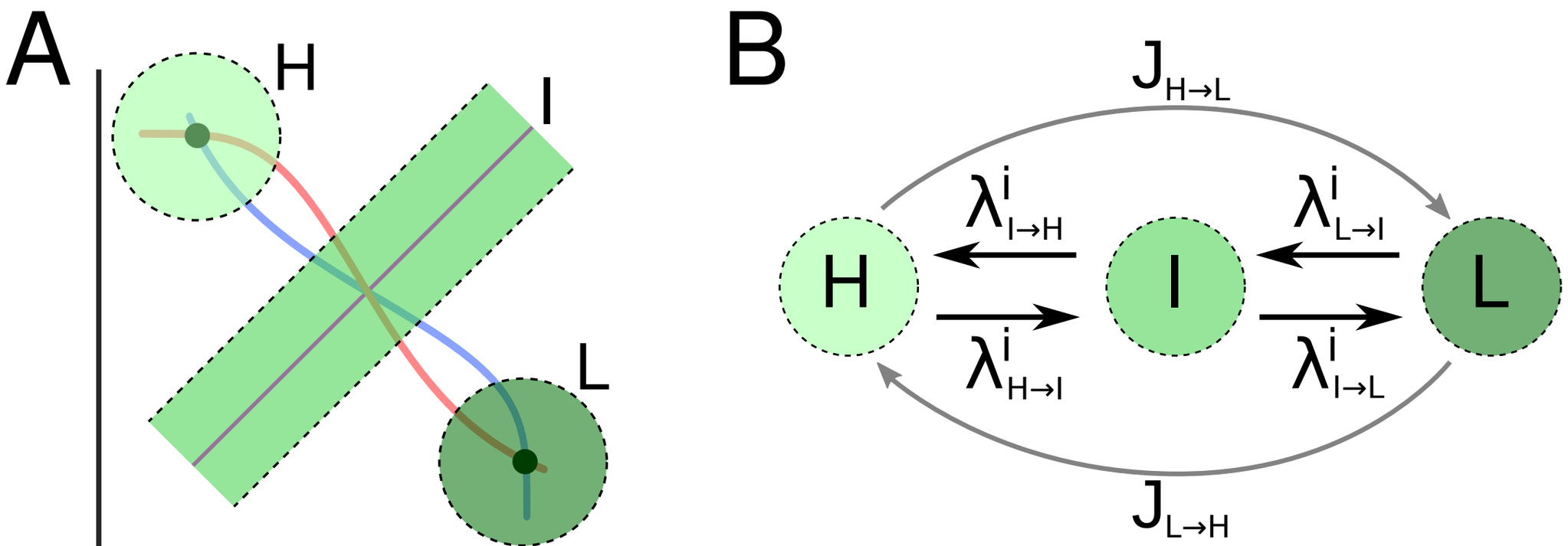
Veliz-Cuba et alli (2016)

Robustness: an excitable system



Veliz-Cuba et alli (2016)

3-states model with teleportation



Veliz-Cuba et alli (2016)

Next steps

- Large deviations for processes with delay
  - Optimal transition pathways
  - Importance sampling
  - Transition rates
  - Work underway (e.g. Schwartz, Billings et alli, PRE (2015))

Acknowledgments

- Houston: Robert Azencott, Chinmaya Gupta, Kreso Josić, Manuel Lopez
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- Dayton: Alan Veliz-Cuba

NIGMS

NSF