Design principles of biochemical oscillators

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Overview

- Cellular rhythms from complex/dynamic interactions of genes
- Control cell physiology
- General requirements for oscillations
- Oscillators classified by topology of feedback loops in regulatory mechanism

Dynamics of Oscillators

- Systems-level characteristics
  - Periodicity, robustness, entrainment
  - Topology of network
- Theoretical perspective and quantitative mathematical modeling of processes
- Demonstrate design principles by rate plots, signal-response curves, constraint diagrams

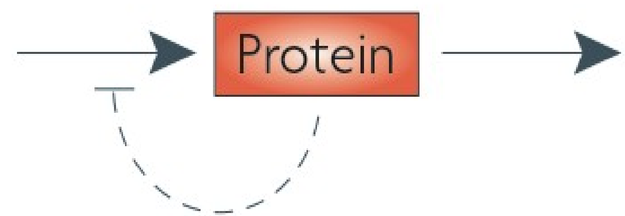
General Requirements for Oscillation

- Negative feedback
  - Carries reaction back to starting point
- Time delay
  - Feedback signal delayed
  - Prevents settling at steady state
- Sufficient nonlinearity
  - Kinetic rates destabilize steady state
- Appropriate timescales
  - Balance of production and decay rates

Self-Repressing Gene

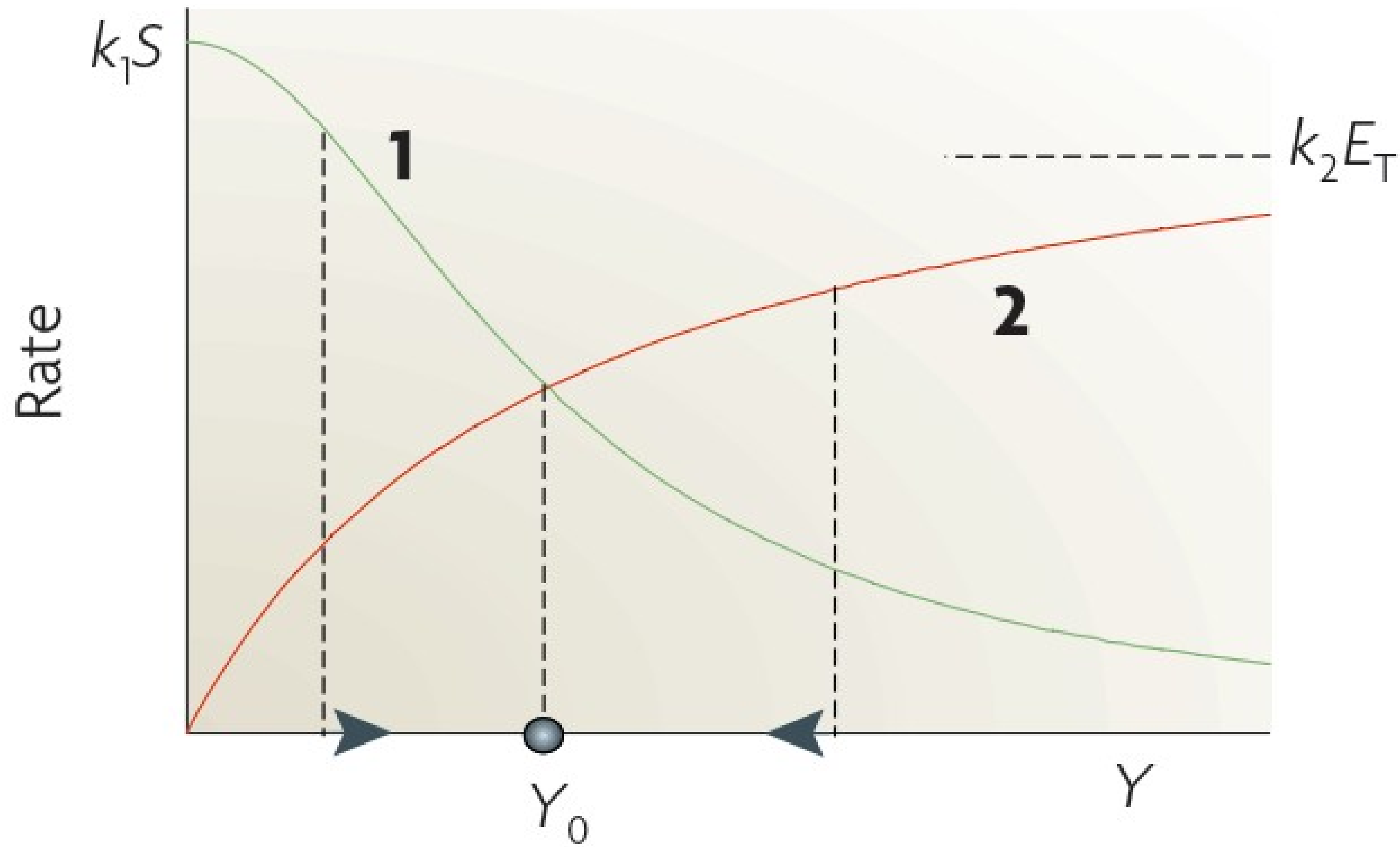
$$\frac{dY}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_2 E_T \frac{Y}{K_m + Y}$$

- *S:* transcription factor
- *Y*: protein concentration
- K_d: dissociation constant
- *p*: monomer, dimer, etc.
- E_T: total protease, degrades Y
- k_2: turnover rate
- K_m: Michelis-Menton constant



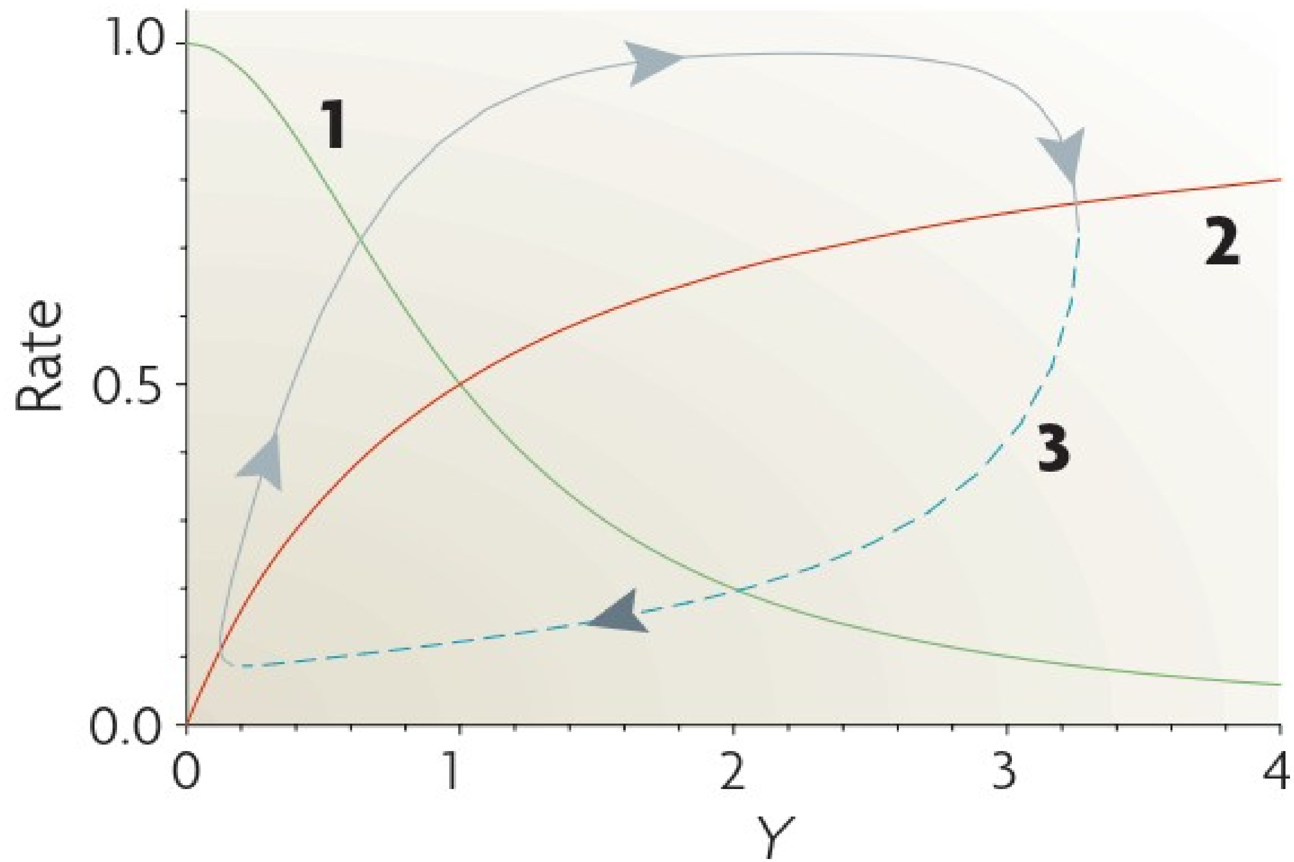
Self-Repressing Gene

$$\frac{dY}{dt} = \boxed{k_1 S \frac{K_d^p}{K_d^p + Y^p}} - \boxed{k_2 E_T \frac{Y}{K_m + Y}}$$



Self-Repressing Gene with Explicit Time Delay

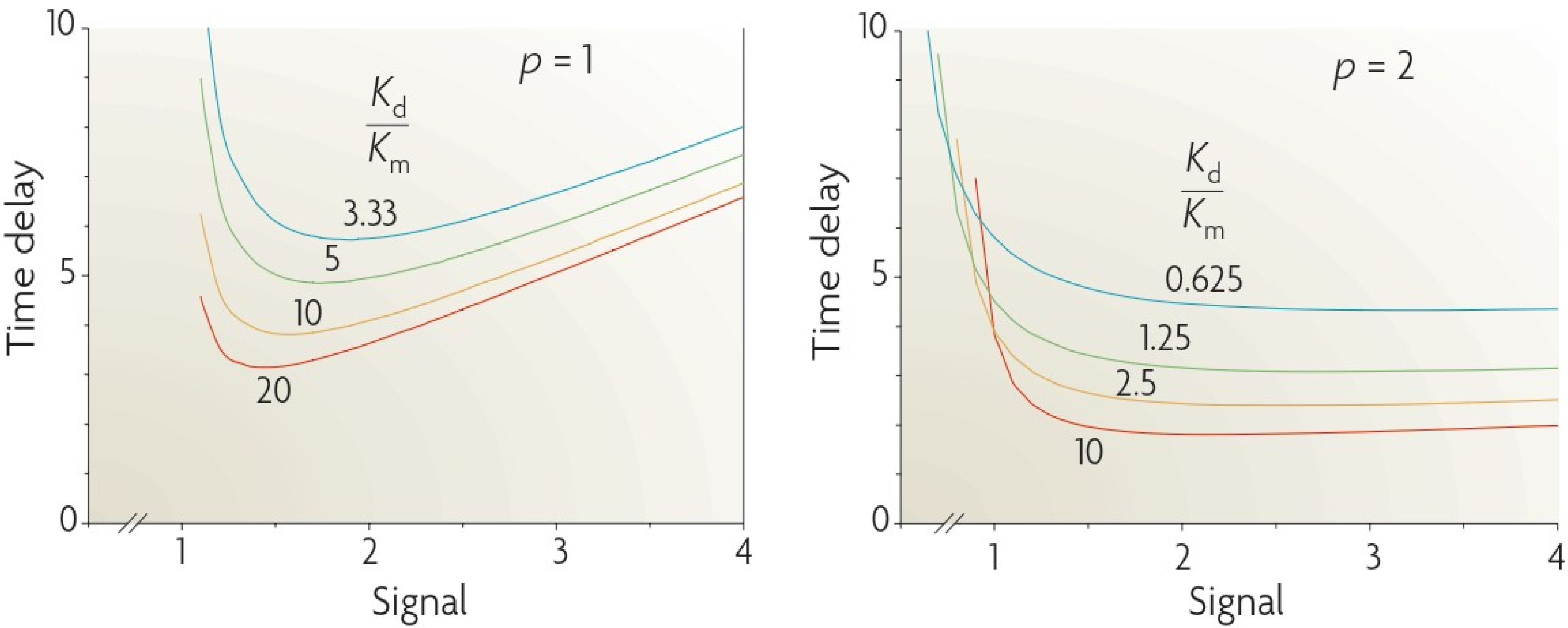
$$\frac{dY}{dt} = \boxed{k_1 S \frac{K_d^p}{K_d^p + Y(t-\tau)^p}} - \boxed{k_2 E_T \frac{Y(t)}{K_m Y(t)}}$$



Attributes of Rate Constants

- τ sufficiently long
- p or (K_d / K_m) increases → smaller τ_{min}
- τ vs. signal strength: $(\tau/T_{deg},\ T_{deg}/T_{syn})$
- Constraint curves depend on p and K_d / K_m
- Oscillation period 2–4x time delay

Attributes of Rate Constants

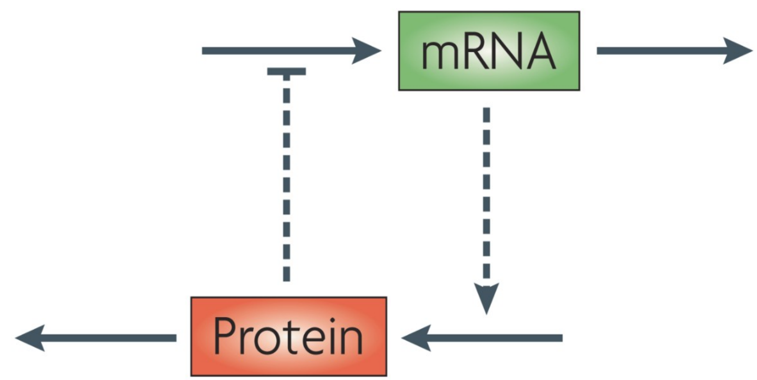


Time Delay by Intermediates

- Negative feedback with mRNA
- X [mRNA], Y [protein]

$$\frac{dX}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_{dx} X$$

$$\frac{dY}{dt} = k_{sy} X - k_2 E_T \frac{Y}{K_m + Y}$$

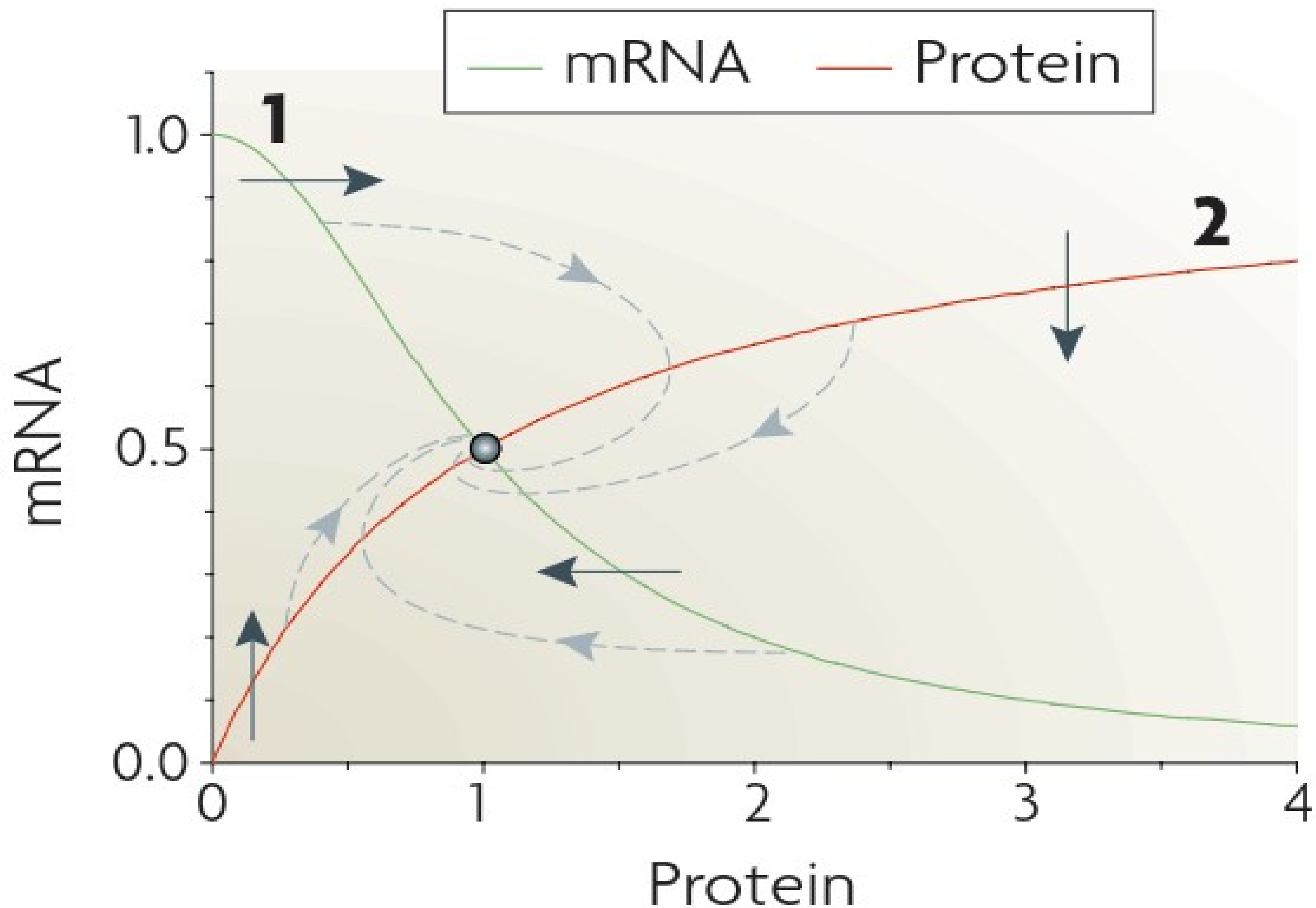


- Alone only damped oscillations

Time Delay by Intermediates

$$\frac{dX}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_{dx} X$$

$$\frac{dY}{dt} = k_{sy} X - k_2 E_T \frac{Y}{K_m + Y}$$

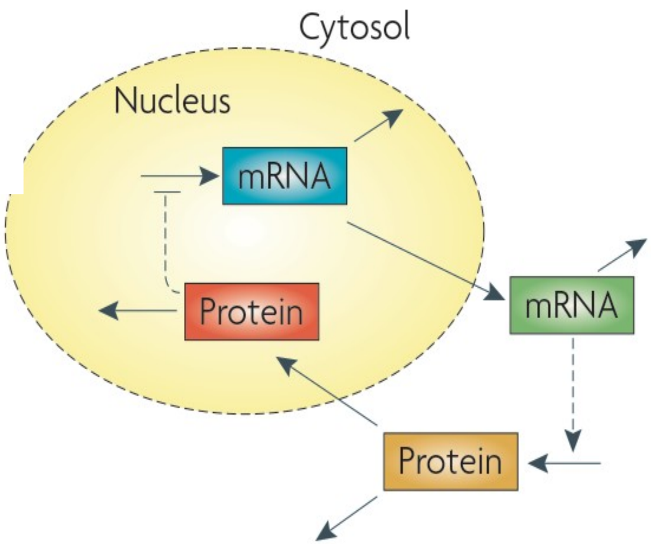


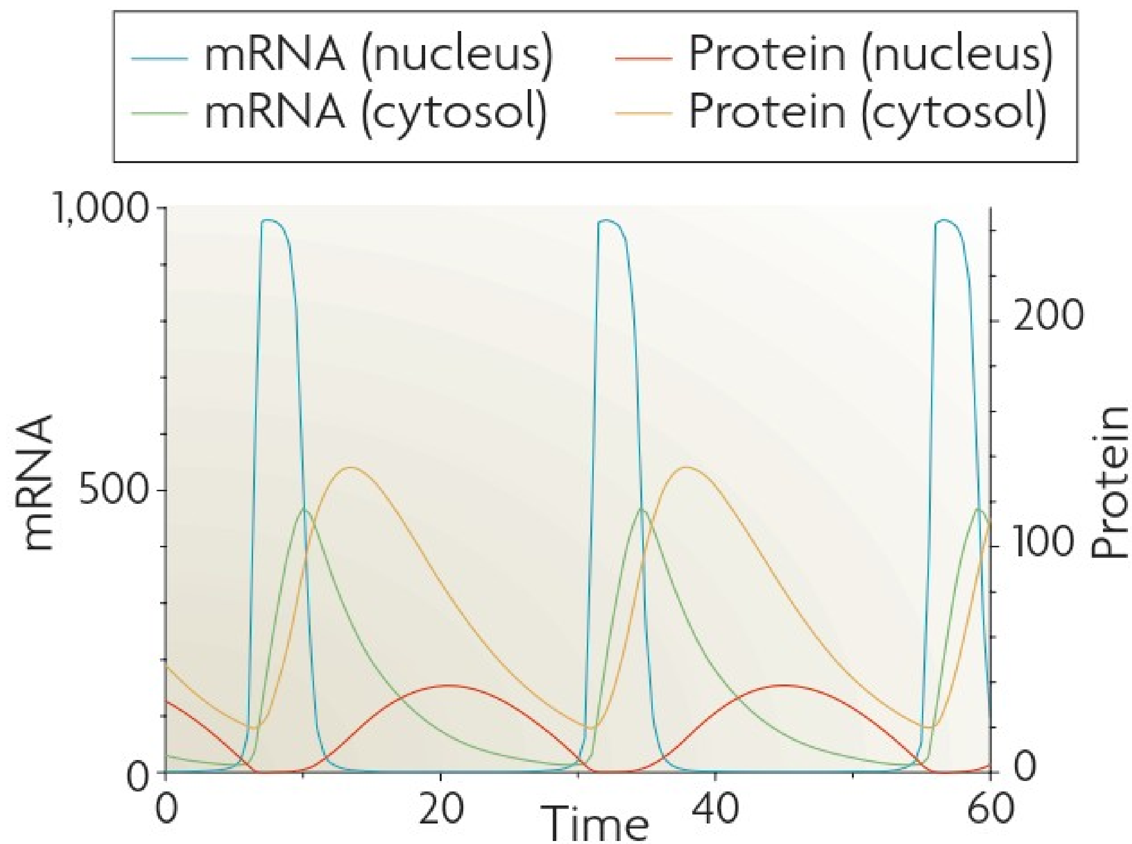
Time Delay by Intermediates

- mRNA alone not enough
  - Still need time delay

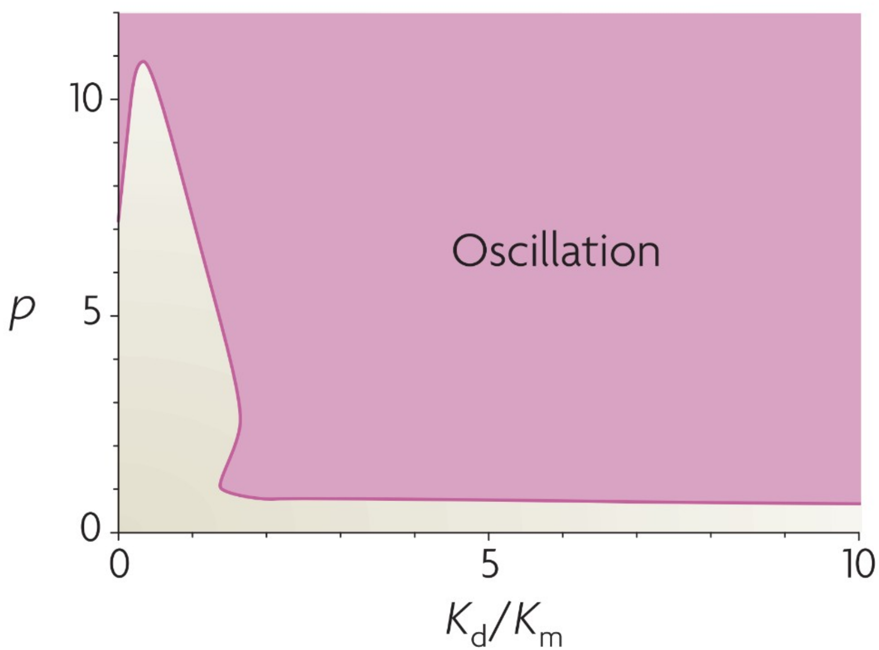
- Transport of mRNA and protein
  - Expand equations to 4 variables
  - Nucleus (X_n, Y_n)
  - Cytoplasm (X_c, Y_c)

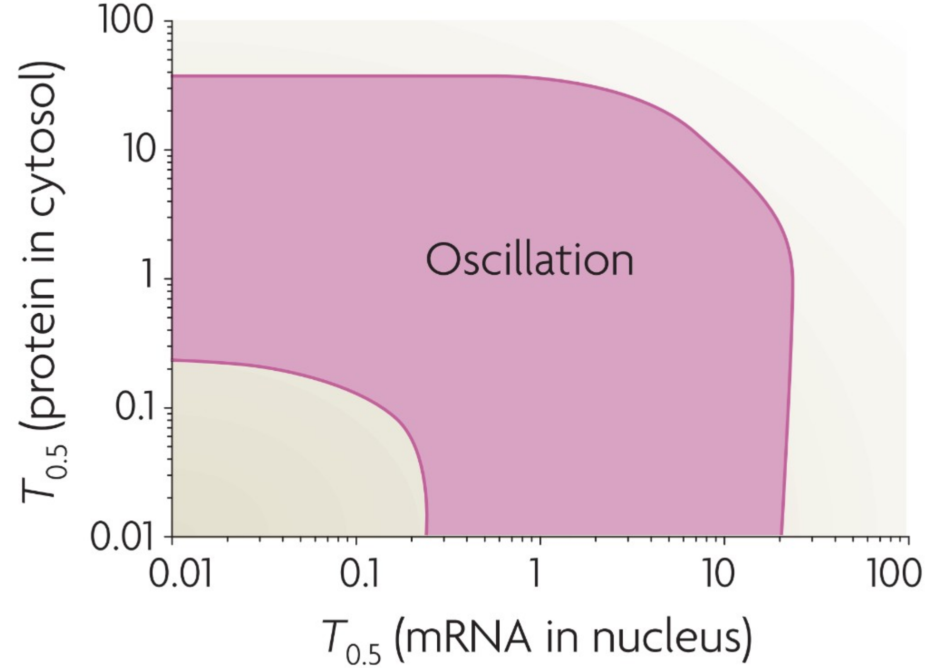
Time Delay by Intermediates





Time Delay by Intermediates





Time Delay by Intermediates

- Only 3 components for oscillations
  - Half-life affects number of components
- Goodwin modeled enzyme synthesis
- Circadian rhythm, PER protein
  - Slow post-translational modifications
- Elowitz and Leibler engineered repressilator

Time Delay by Positive-Feedback

- Time delay pseudo-memory
  - Current rate depends on past concentration
  - Property of systems with bistability
- Y both inhibits itself and activity of X

$$\frac{dX}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_{dx} X$$

$$\frac{dY}{dt} = k_{sy} X - k_{dy} Y - k_2 E_T \frac{Y}{K_m + Y + K_1 Y^2}$$

Time Delay by Positive Feedback

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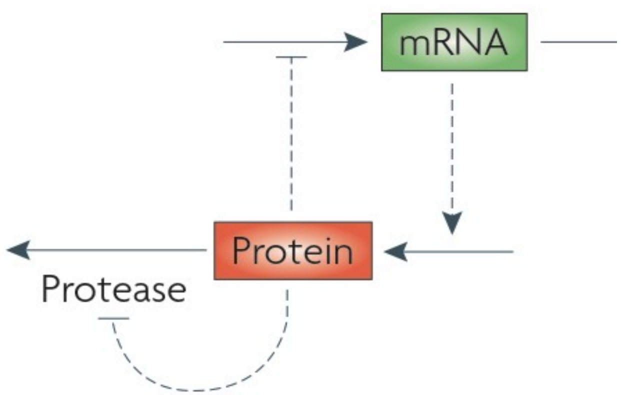
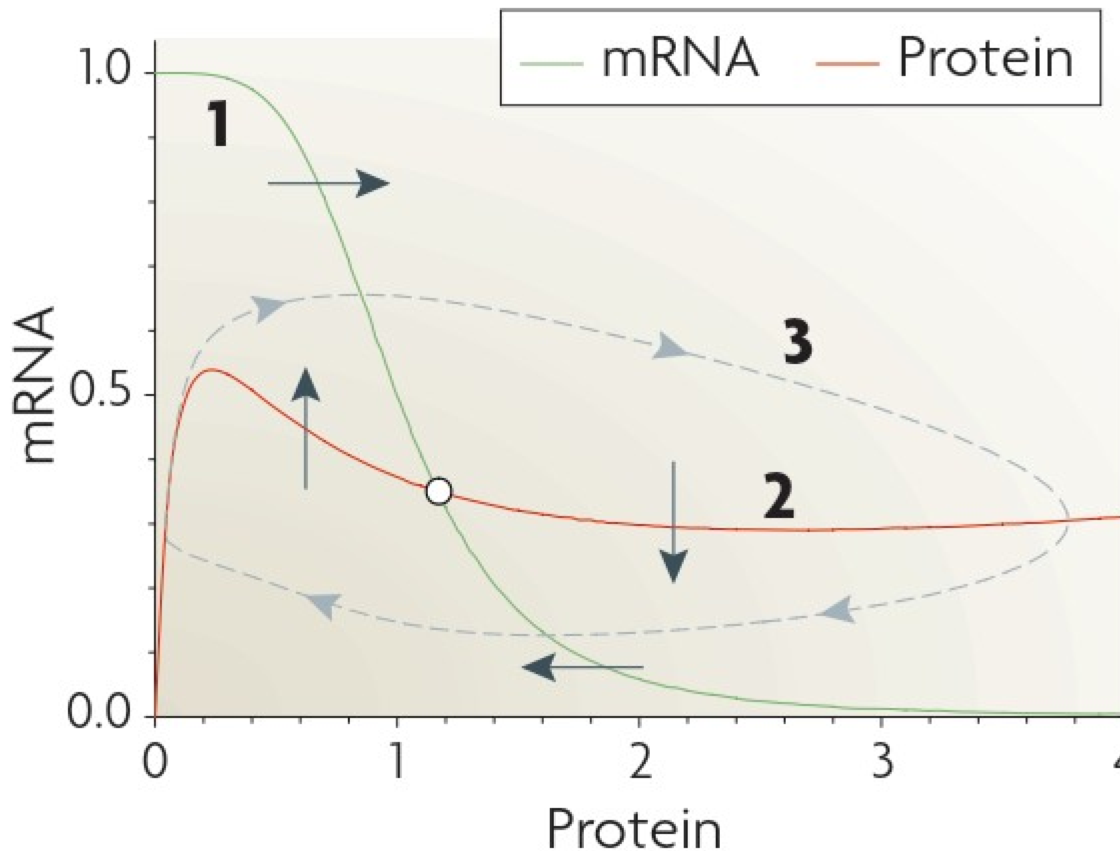
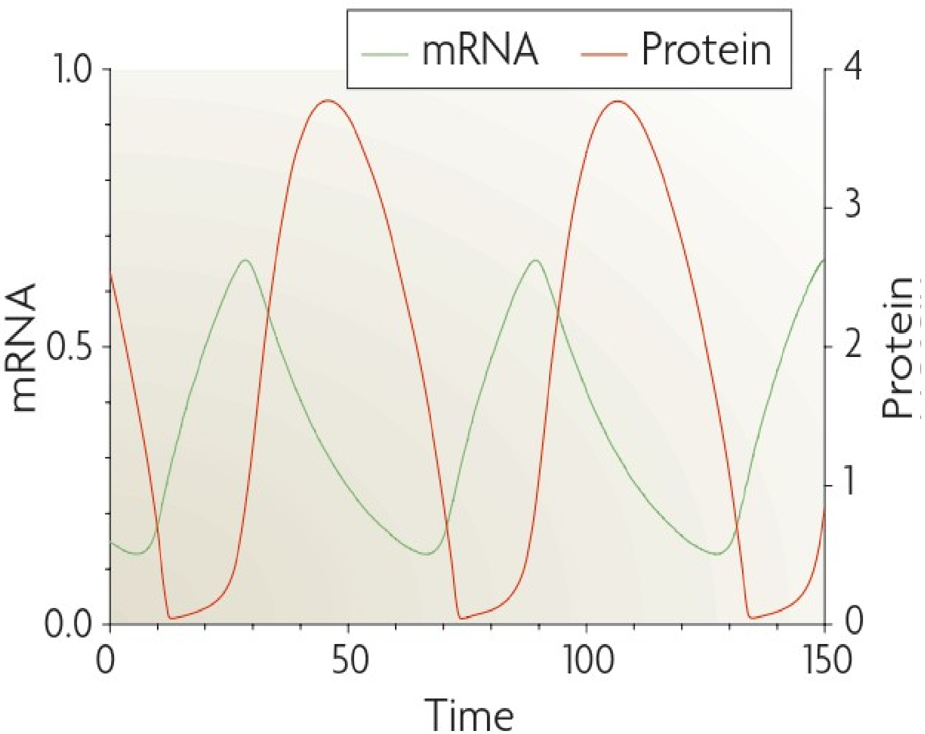
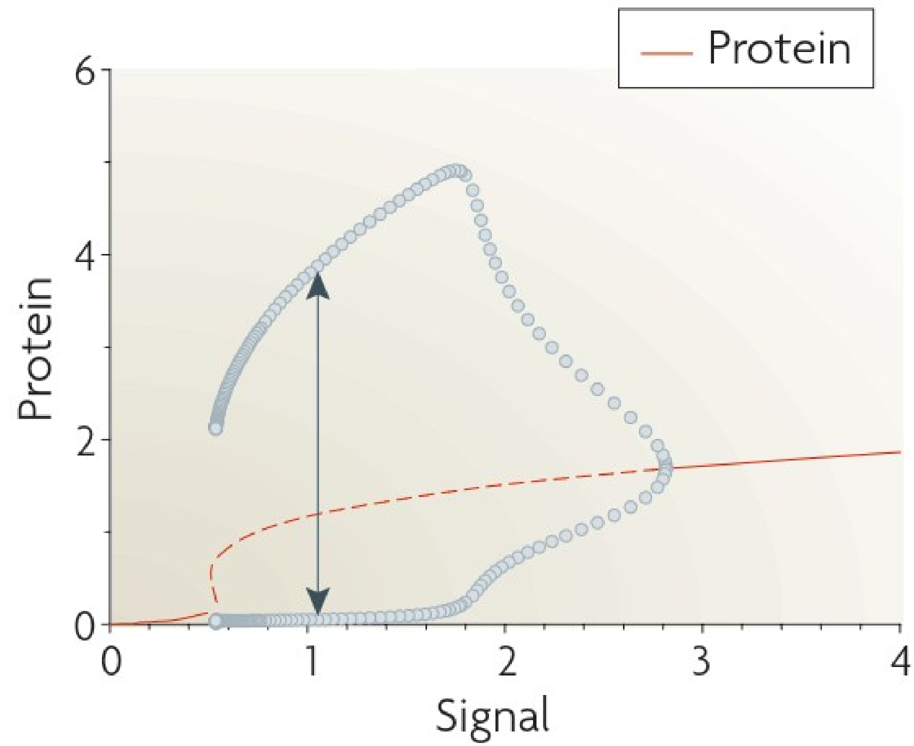


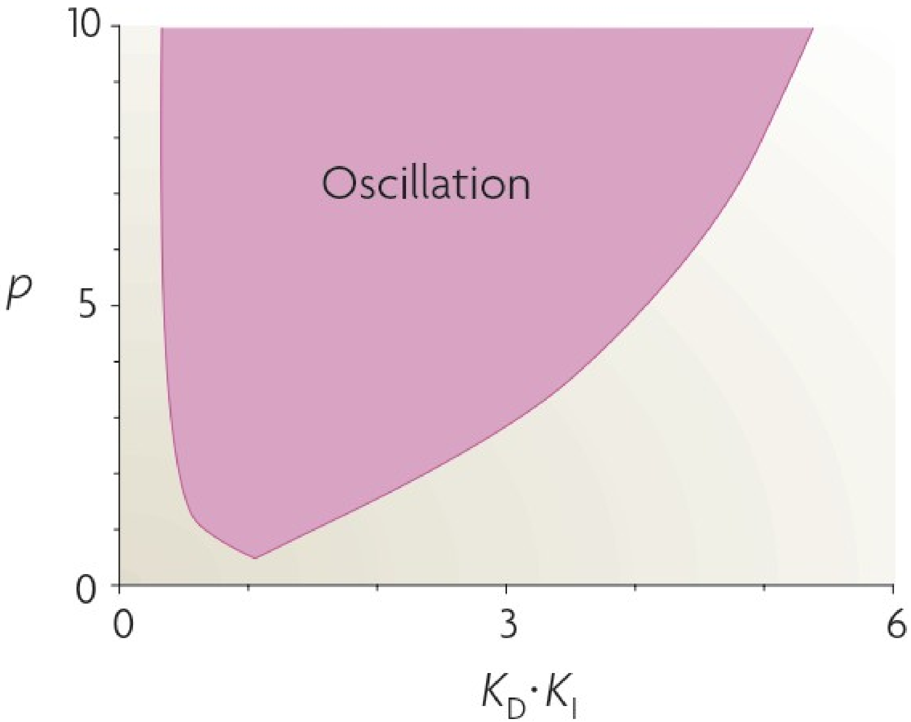


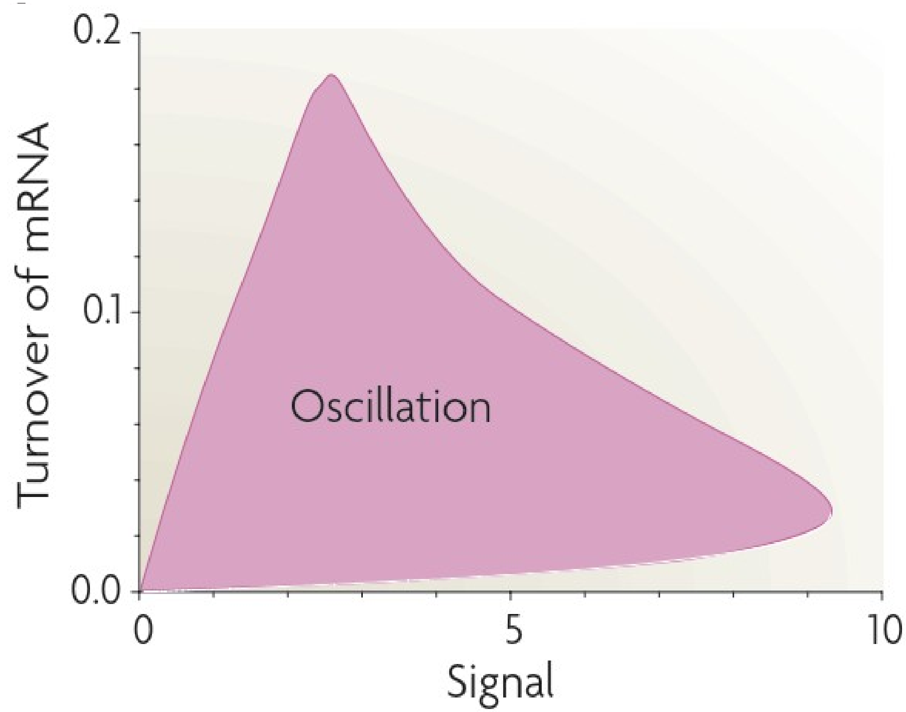
Time Delay by Positive Feedback





Time Delay by Positive Feedback



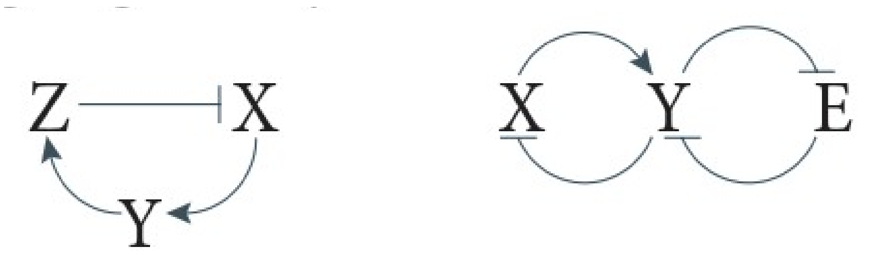


Effects of Positive Feedback

- Kink in nullcline curve for protein
  - Over/undershooting of steady state
- Sustained oscillations
  - Provided S and K_1 within certain bounds
- Possible source of circadian rhythms for PER gene in fruit flies
  - Tyson *et al.* believe PER forms dimers
  - Less prone to degradation

Biochemical Interaction Networks

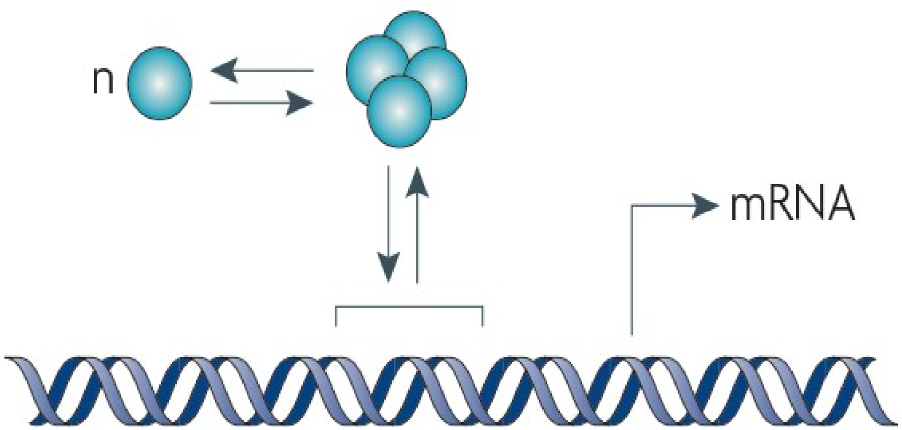
- Two distinct oscillation mechanisms
  - Three component negative feedback loop
  - Combination of short positive and negative feedback loops
- X = activator, Y = inhibitor
  - Direct or indirect
- No auto-catalysis

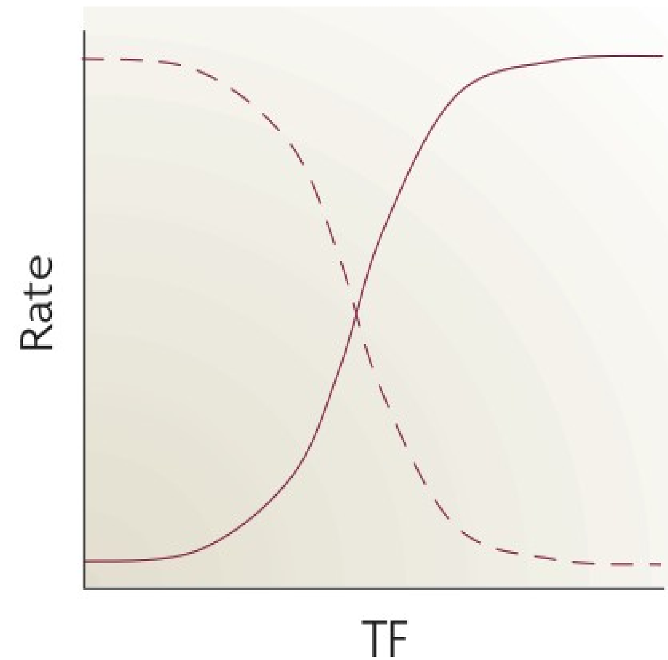


(A) (B)

Biochemical Sources of Nonlinearity

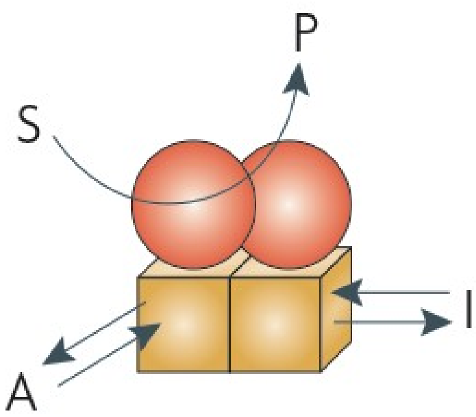
- Oligomer binding

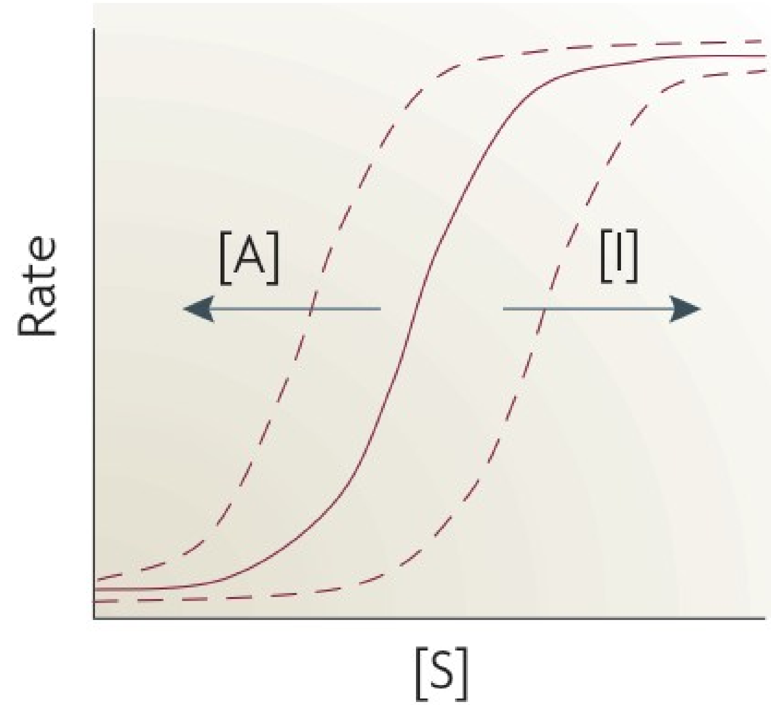




Biochemical Sources of Nonlinearity

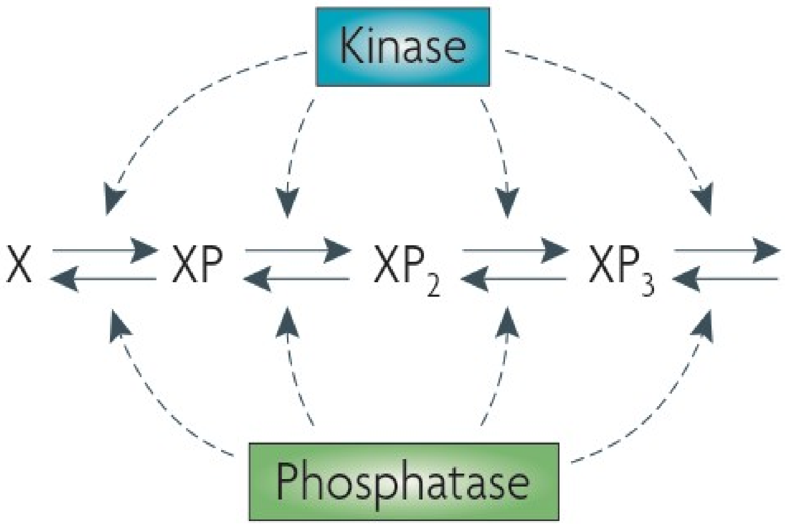
- Cooperativity and allostery

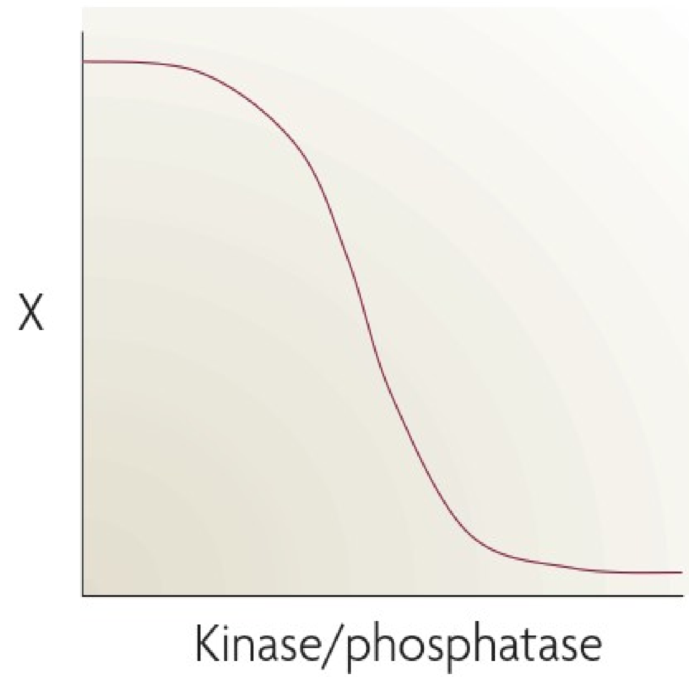




Biochemical Sources of Nonlinearity

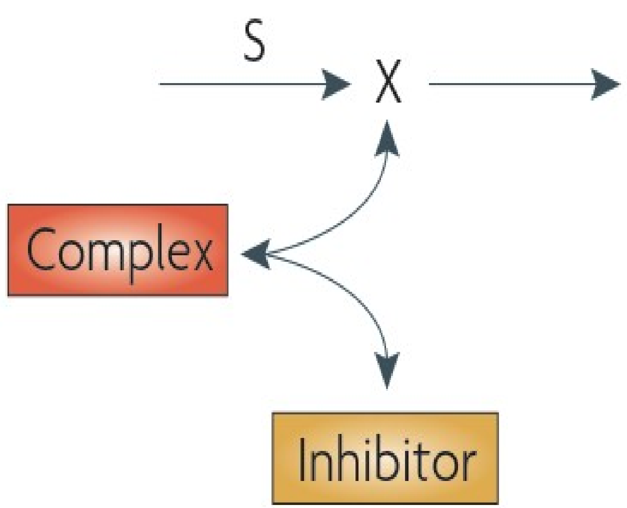
- Multisite phosphorylation

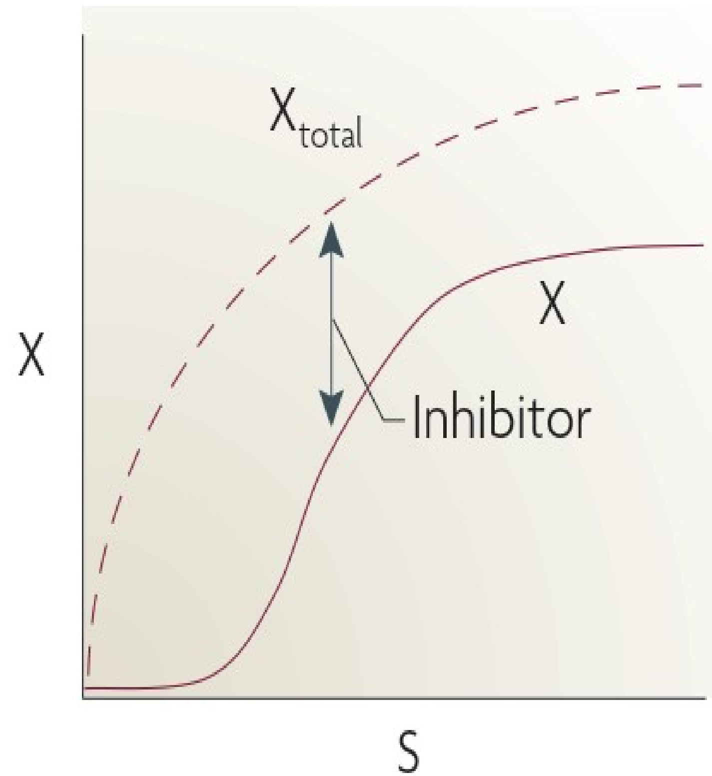




Biochemical Sources of Nonlinearity

- Stoichiometric inhibition

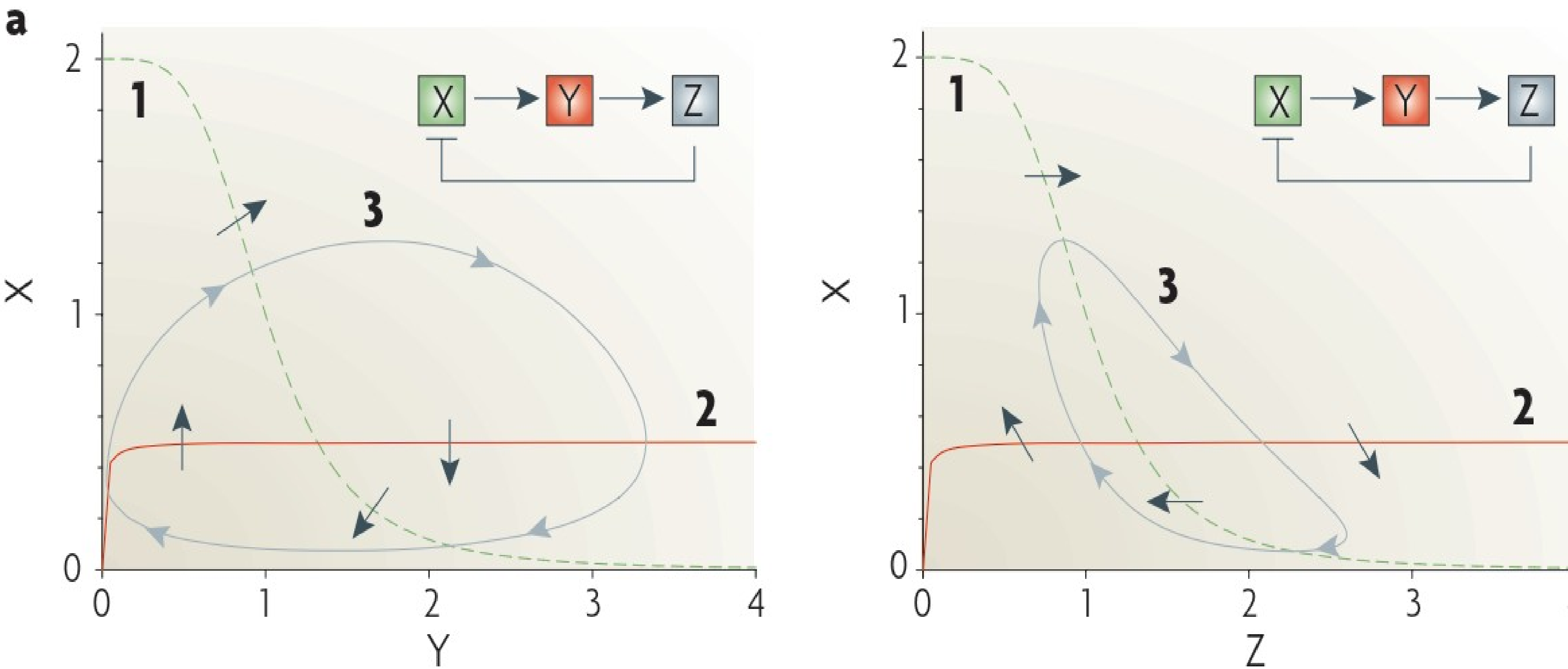




Delayed Negative Feedback Loops

- 3 components, odd number of inhibitory links
- Biological examples:
  - PER in fruit flies
  - p53 response to ionizing radiation
  - NF-κB response to tumor necrosis factor
- Needs three variables
  - Trajectories in XY and XZ planes
- Flow through nullclines not strictly vertical/horizontal

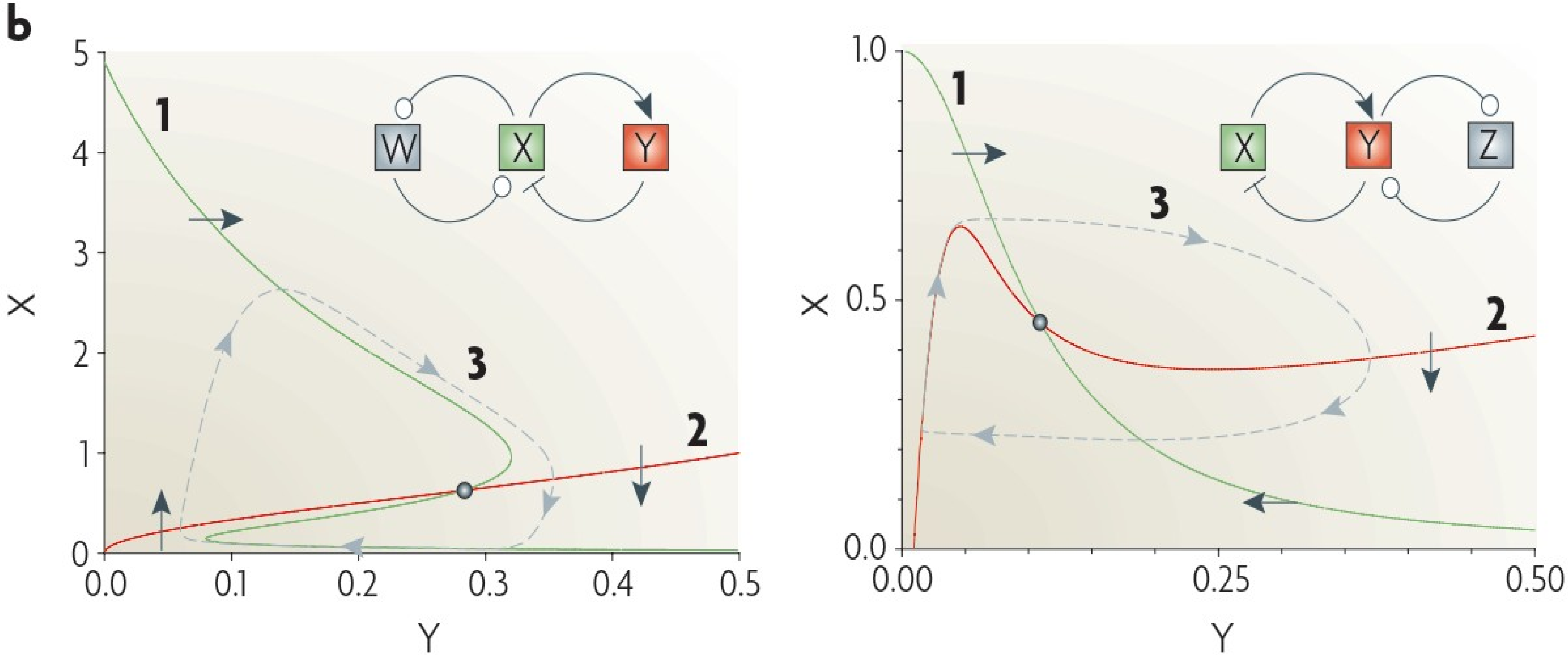
Delayed Negative Feedback Loops



Amplified Negative-Feedback Loops

- Activator amplification by positive feedback
  - Kink in X-nullcline
  - Bistability of X with respect to Y
- Inhibitor amplification
  - Kink in Y-nullcine
  - Bistability of Y with respect to X
- Negative feedback causes rotation around SS
- Positive feedback prevents spiraling into SS
- Models
  - Mitosis-promoting factor in frog eggs
  - Endoreplication in mutant fission yeast cells

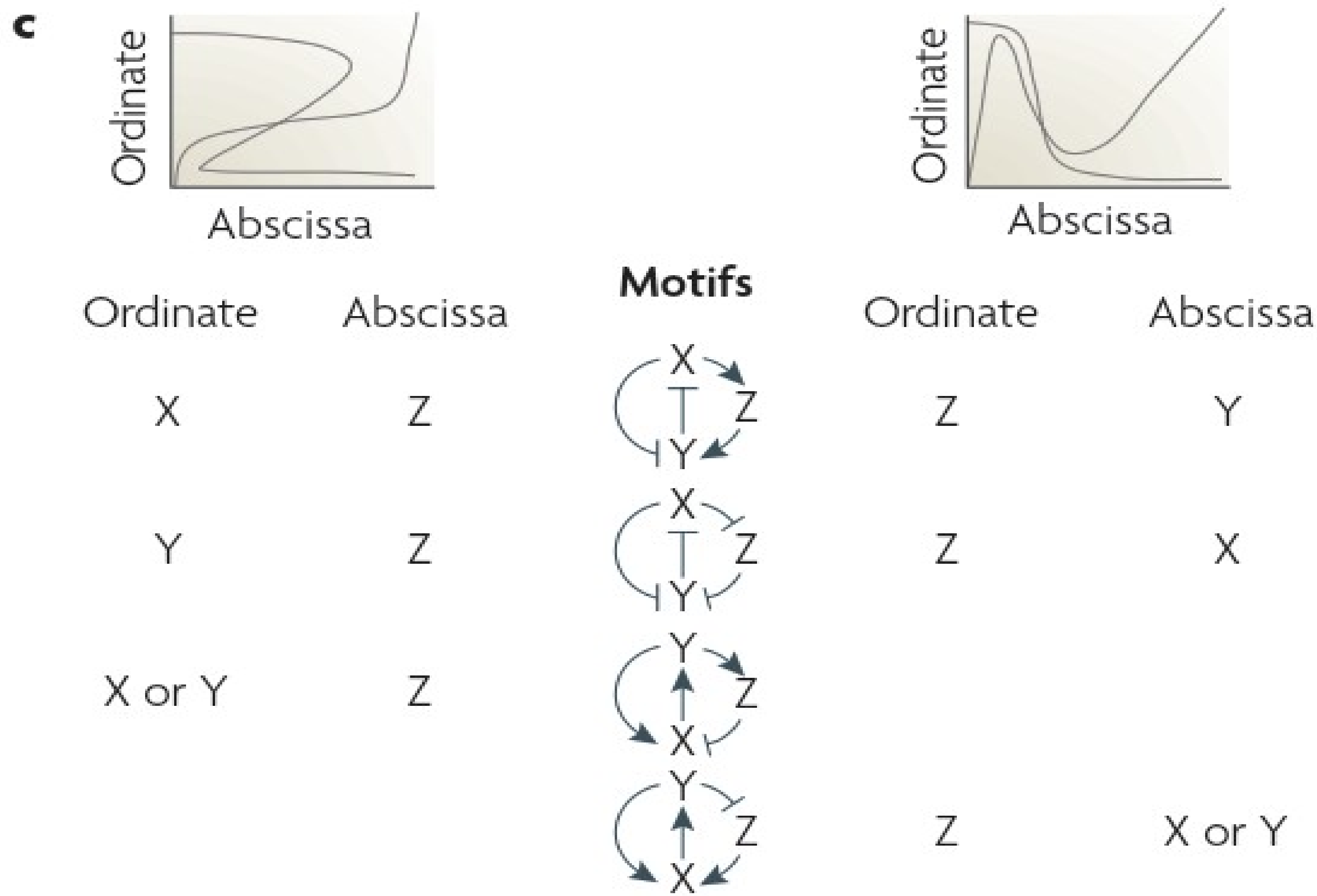
Amplified Negative-Feedback Loops



Incoherently Amplified Negative-Feedback Loops

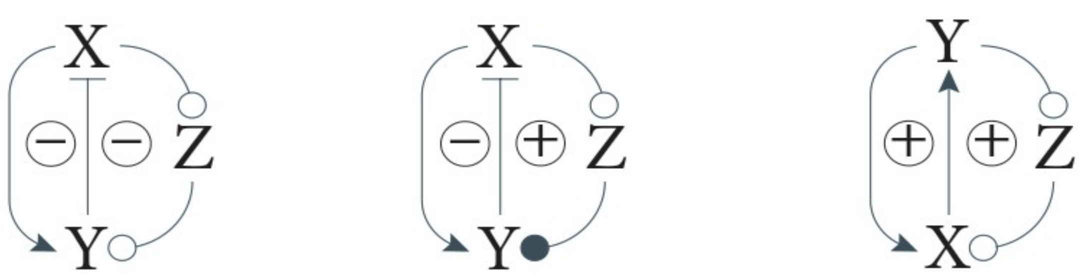
- Rewire activator-amplified feedback loop
  - Positive feedback has 2 components
  - Negative feedback has 3 components
- Negative loop can oscillate on its own
  - Positive loop adds bistability and robustness
- Models of glycolytic , cAMP, p53 oscillations, cell cycle transitions

Incoherently Amplified Negative-Feedback Loops



Other Possibilities

- Coherently repressed loops
  - Two negative loops
- Another incoherently amplified negative loop
  - Positive has three components, negative has 2
- Two positive loops
  - Expect bistability, but no oscillations

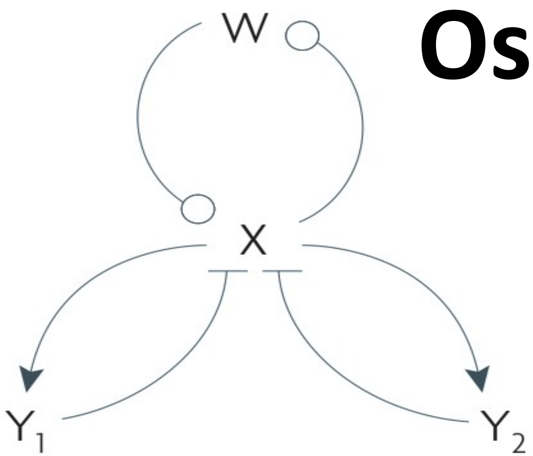


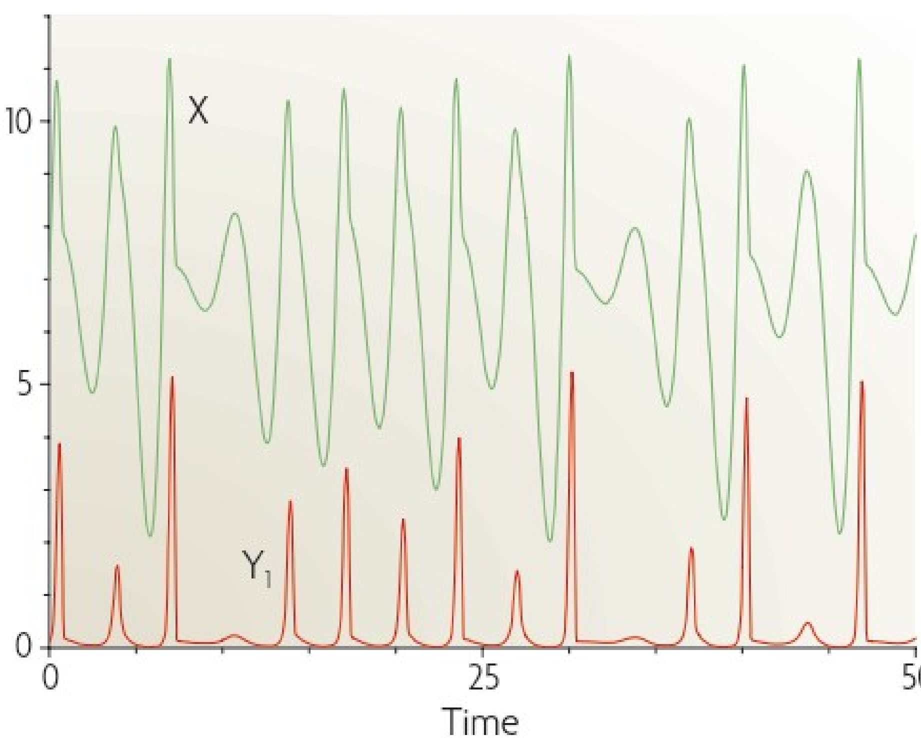
(F) (G) (H)

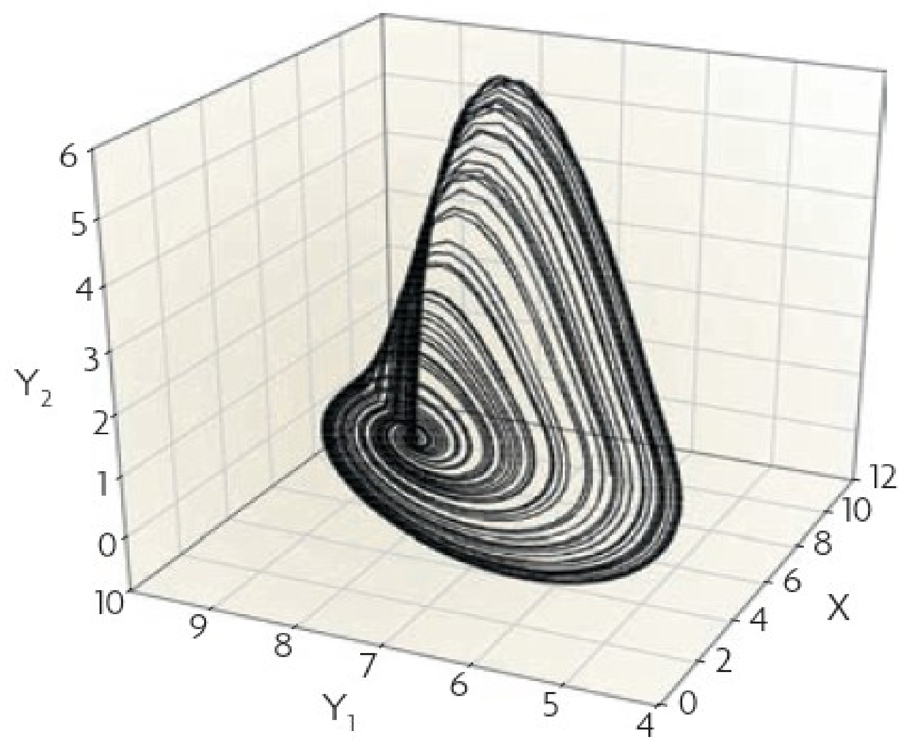
More Complex Topologies and Oscillatory Behaviors

- Examined all motifs with 3 components and at most 4 links
- Combine motifs that oscillate individually
  - Deterministic chaos possible
  - However, not seen much experimentally
  - Canceled out by white noise
- Model circadian oscillations in phosphorylation state of KaiC protein in cyanobacteria

More Complex Topologies and Oscillatory Behaviors







Review – Requirements for Oscillation

- Negative-feedback loop
  - Bring reaction back to start
- Time delay or memory in negative loop
  - Positive feedback or long negative loops
- Sufficient nonlinearity
  - Reaction kinetics
- Timescale balance of components in loop

Review – Classes of Oscillators

- Delayed negative-feedback loops
- Amplified negative-feedback
- Incoherently amplified negative-feedback

Review – Biochemical Connections

- Oscillators can evolve
  - Mutations affect rate constants
  - Dynamical diseases can occur
- Circadian rhythm
  - Likely evolved multiple times
- Cell cycle
  - Likely from one common ancestor
  - Highly constrained and universal