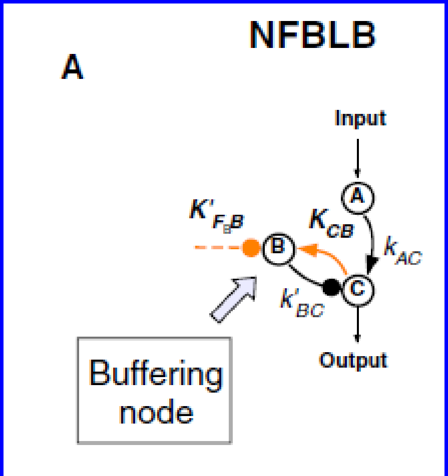
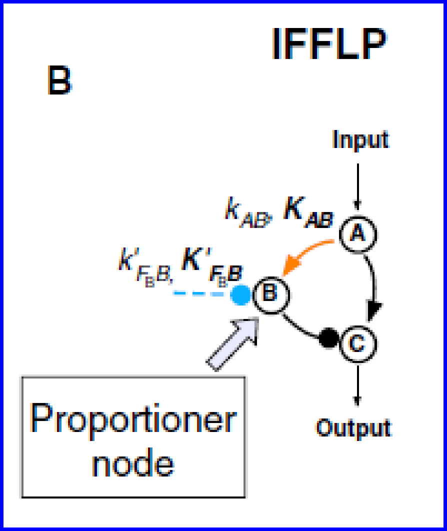
Review

Only two major core topologies emerge as robust solutions: a negative feedback loop with a buffering node and an incoherent feedforward loop with a proportioner node.

Minimal circuits containing these topologies are, within proper regions of parameter space, sufficient to achieve adaptation.

More complex circuits that robustly perform adaptation all contain at least one of these topologies at their core.

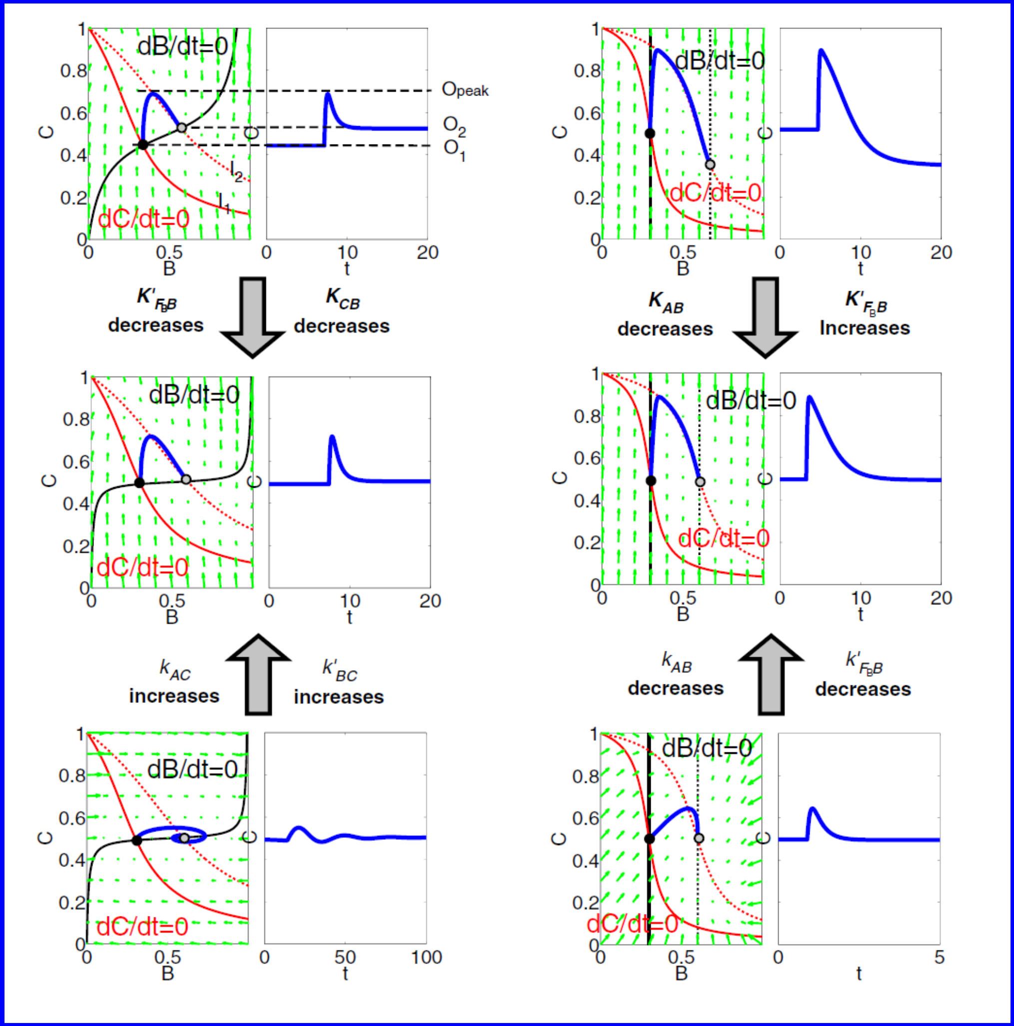




Assignment 6

Reproducing Fig.3 in the following literature:

Ma, W., A. Trusina, et al. (2009). "Defining Network Topologies that Can Achieve Biochemical Adaptation." ***138****(4): 760-773.*



Pointing out:

Sensitivity and Precision

2.5 Design principles in interlinked positive and negative feedback loops

Outline

- Interlinked positive and negative feedback loops produces robust, tunable oscillations.
- Interlinking positive and negative feedback loops creates a tunable motif in gene regulatory networks.
- Modulation of dynamic modes by interplay between positive and negative feedback loops

Interlinked positive and negative feedback loops produces robust, tunable oscillations.

A simple negative feedback loop of interacting genes or proteins has the potential to generate sustained oscillations. However, many biological oscillators also have a positive feedback loop, raising the question of what advantages the extra loop imparts.

Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

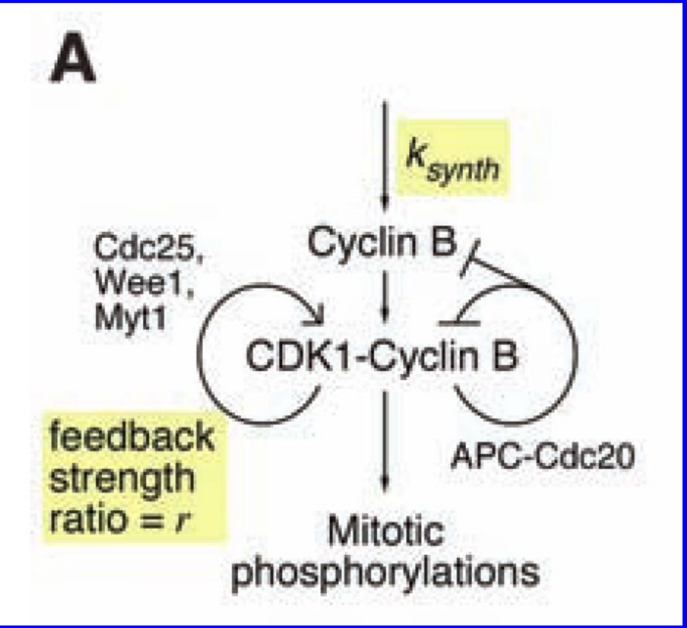
Positive feedback loops in biological oscillators

Oscillator	Period	Positive feedback	Refs.
Sino-atrial pacemaker	~1 s	Depolarization → Na$^+$ channel activation → depolarization	*(29)*
Calcium spikes	~100 s	Cytoplasmic Ca^{2+} → PLC → IP$_3$ → cytoplasmic Ca^{2+} Cytoplasmic Ca^{2+} → IP$_3$R → cytoplasmic Ca^{2+} Cytoplasmic Ca^{2+} → IP$_3$R -| ER Ca^{2+} -| SOC → cytoplasmic Ca^{2+}	*(25, 30, 31)*
Myxobacterial gliding	~10 min	None known	*(22)*
Animal cell cycle (*Xenopus laevis* embryos)	~30 min	Cdk1 → Cdc25 → Cdk1 Cdk1 -| Wee1 -| Cdk1 Cdk1 -| Myt1 -| Cdk1	*(32, 33)*
Somitogenesis	~30 min	DeltaC → Notch → DeltaC	*(34)*
Yeast cell cycle (*S. cerevisiae*)	~2 hours	CLN1,2 transcription → CDK1 → CLN1,2 transcription CDK1 -| Sic1 -| CDK1 CDK1 -| Cdh1 -| CDK1	*(6, 35–39)*
NF-κB responses	~100 min	None known	*(40, 41)*
p53 responses	~100 min	p53 → PTEN -| Akt → Mdm2 -| p53 p53 → p21 -| Cdk2 -| Rb -| Mdm2 -| p53	*(42, 43)*
Animal cell cycle (somatic cells)	~24 hours	CDK2 -| Rb -| E2F → CDK2 Cdk1 → Cdc25 → Cdk1 Cdk1 -| Wee1 -| Cdk1 Cdk1 -| Myt1 -| Cdk1	*(44)*
Circadian rhythm (mammals)	~24 hours	BMAL1 → Rora → BMAL1	*(45)*
Circadian rhythm (*Drosophila*)	~24 hours	CLK → PDP1 → CLK	*(45)*
Circadian rhythm (fungi)	~24 hours	FRQ → WC-1 → FRQ	*(46)*
Circadian rhythm (cyanobacteria)	~24 hours	KaiC-SP -| KaiA -| KaiC-SP	*(26)*

Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

Positive feedback provides an oscillator with a tunable frequency and nearly constant amplitude

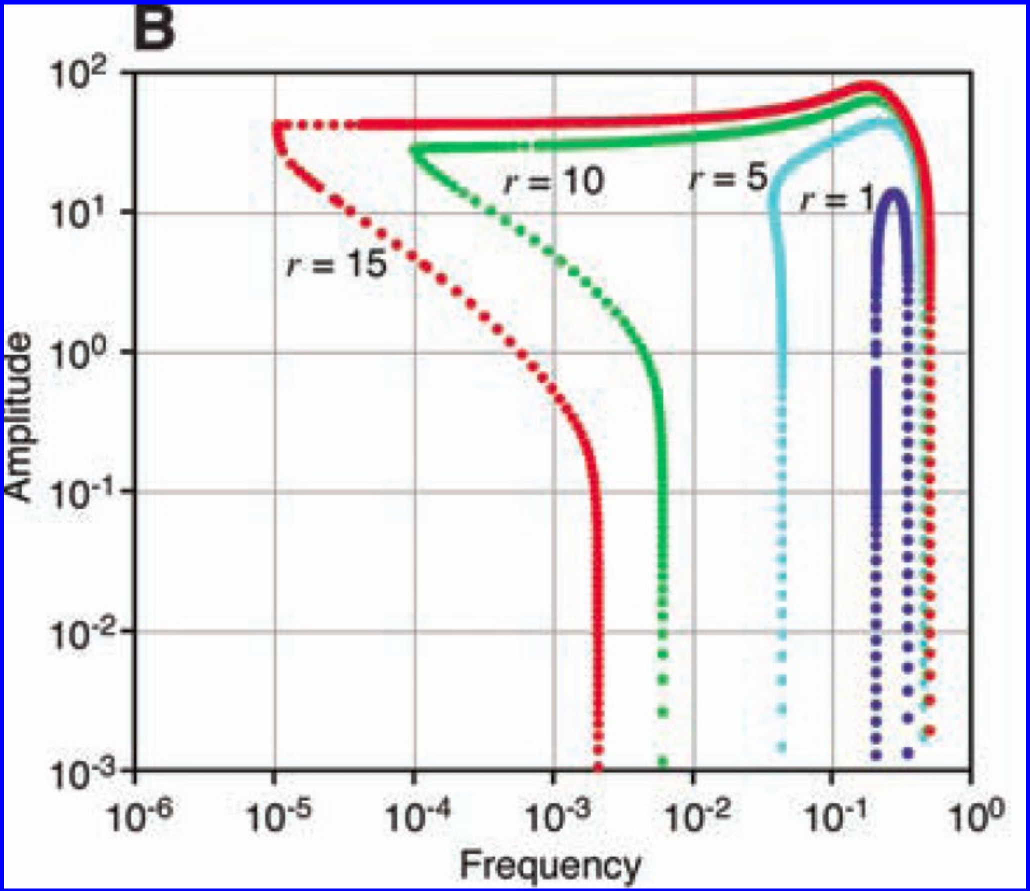
Schematic view of the Xenopus embryonic cell cycle



Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

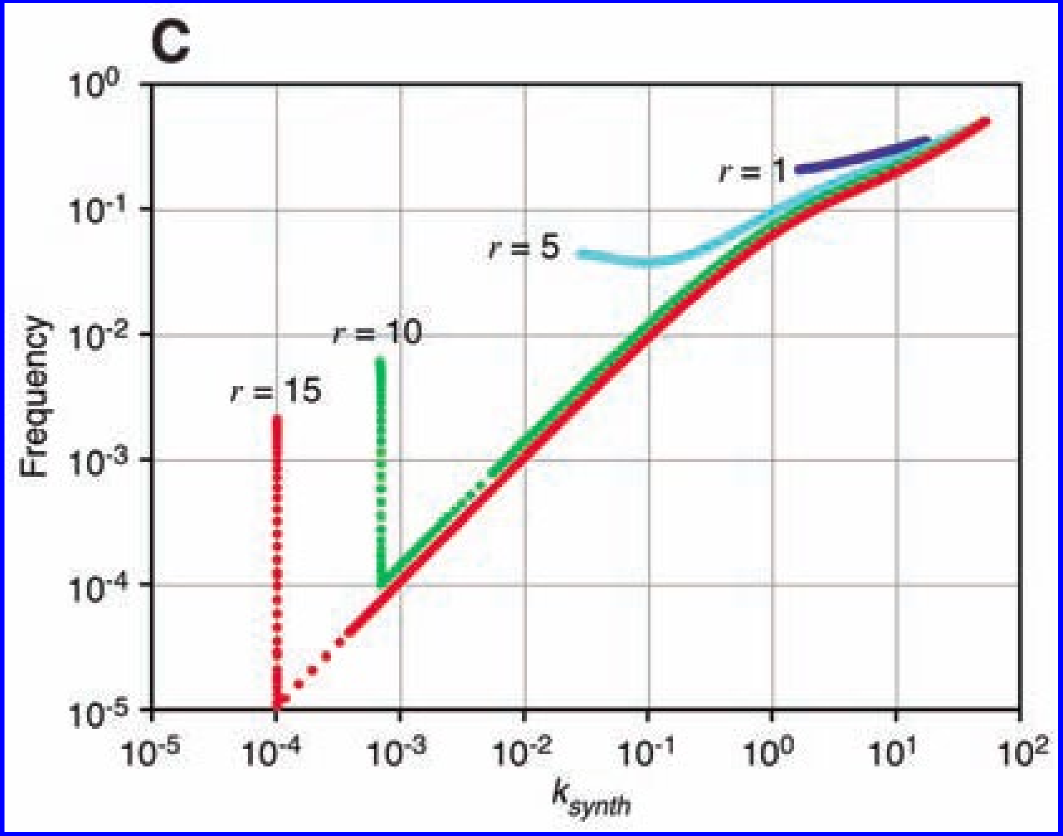
Amplitude/frequency curves for various strengths of positive feedback (r)

The frequency of the oscillator was changed by varying the rate constant for cyclin B synthesis, k_{synth}.



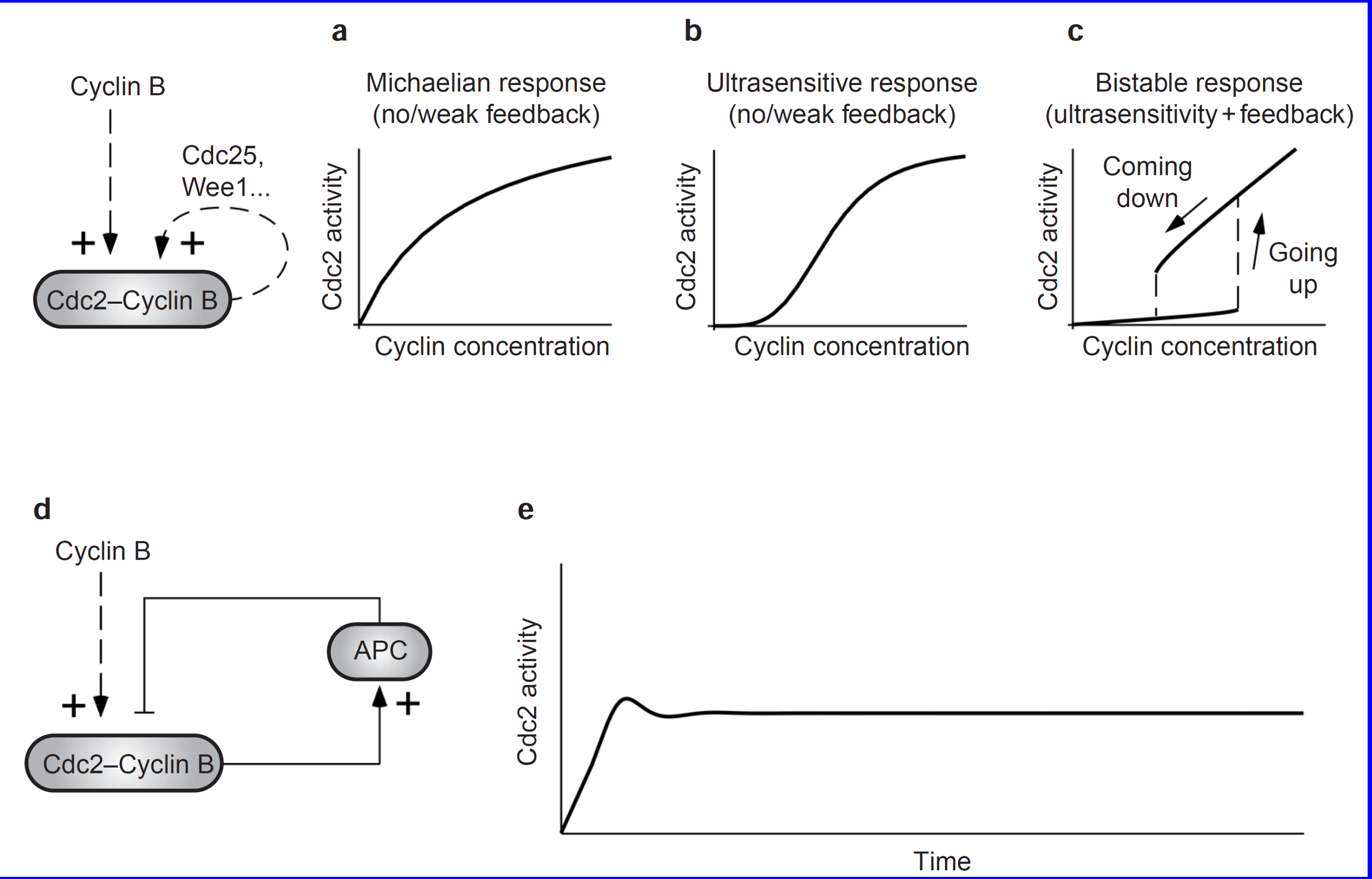
Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

Frequency as a function of *k*synth for various strengths of positive feedback



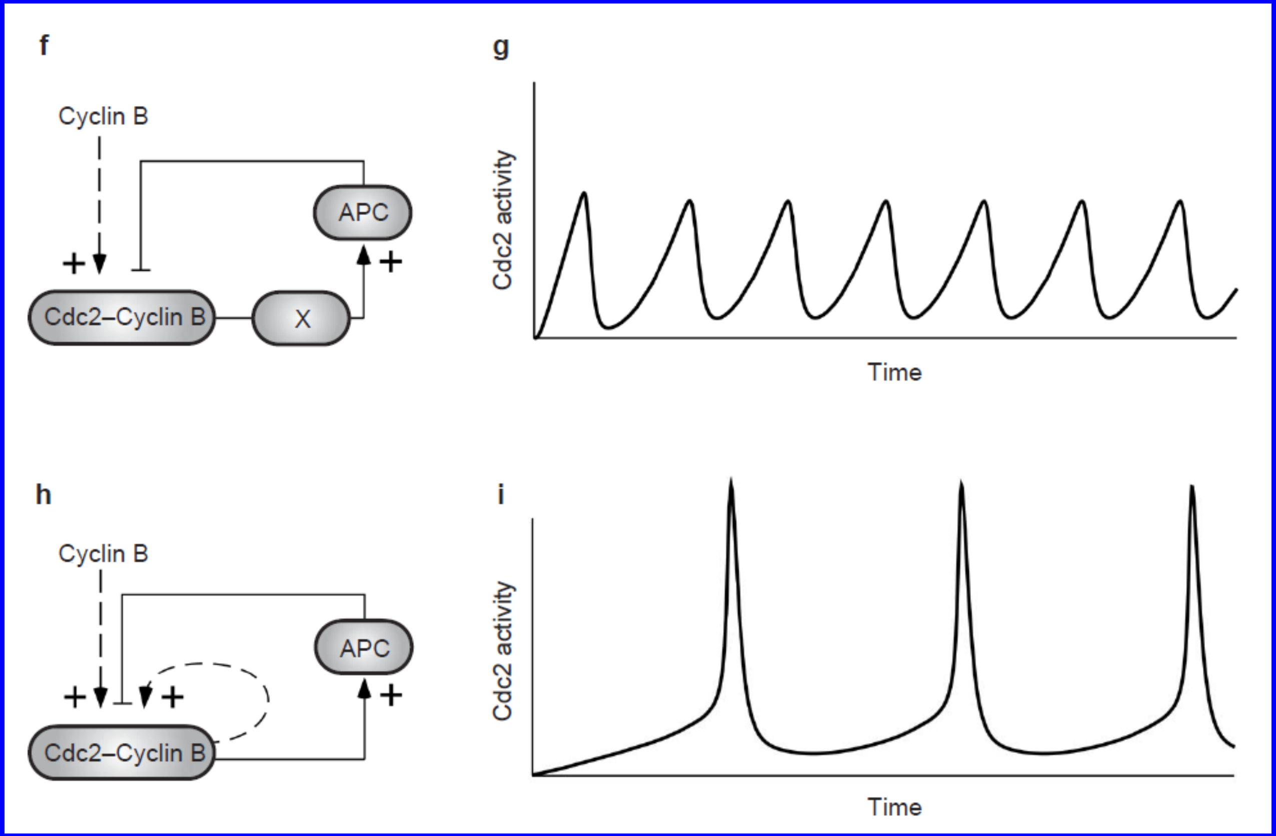
Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

Positive feedback and oscillation



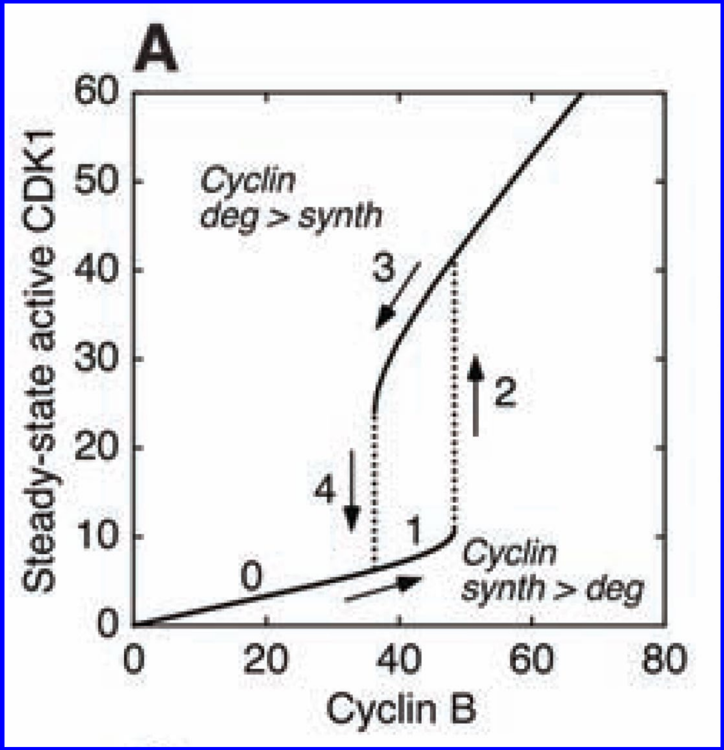
Tsai TY-C, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell JE, Jr. Science. 2008; **321**(5885): 126-9.

Relaxation oscillator

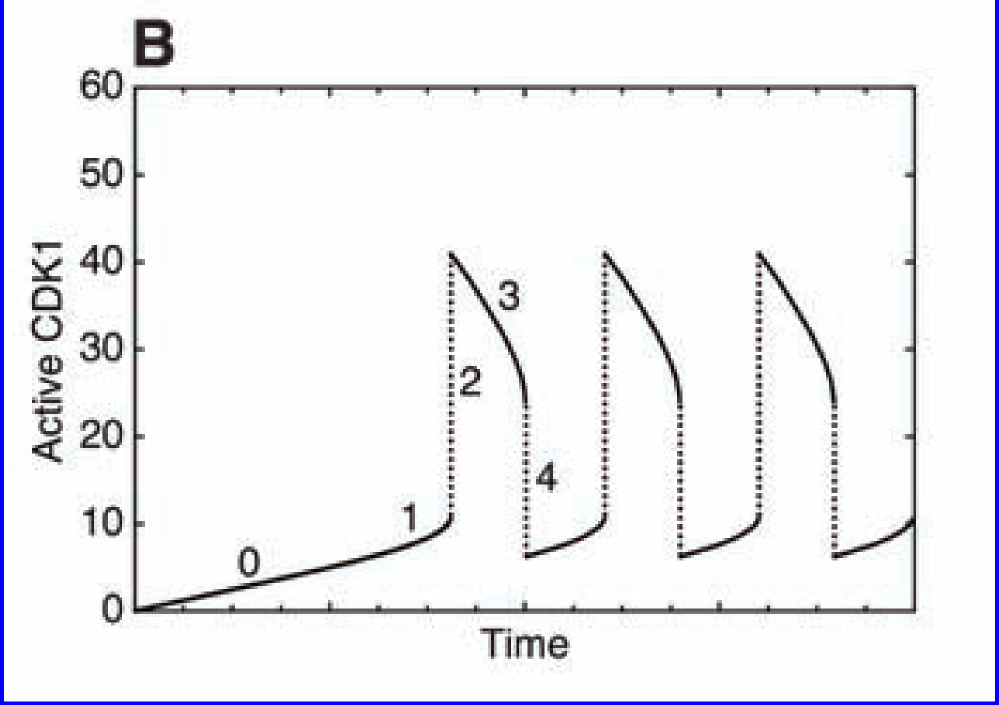


Pomerening, J. R., E. D. Sontag, et al. (2003). Nat Cell Biol **5**(4): 346-351.

From a hysteretic switch to a relaxation oscillator

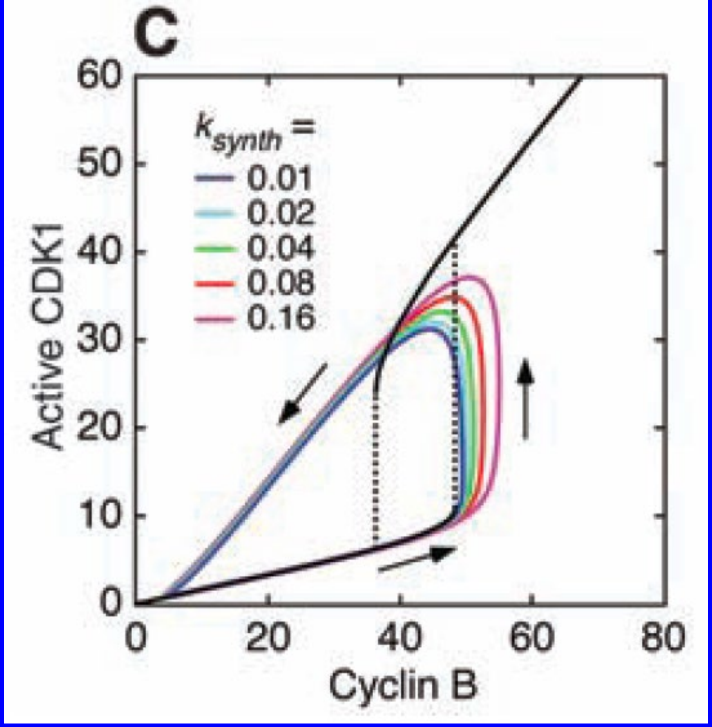


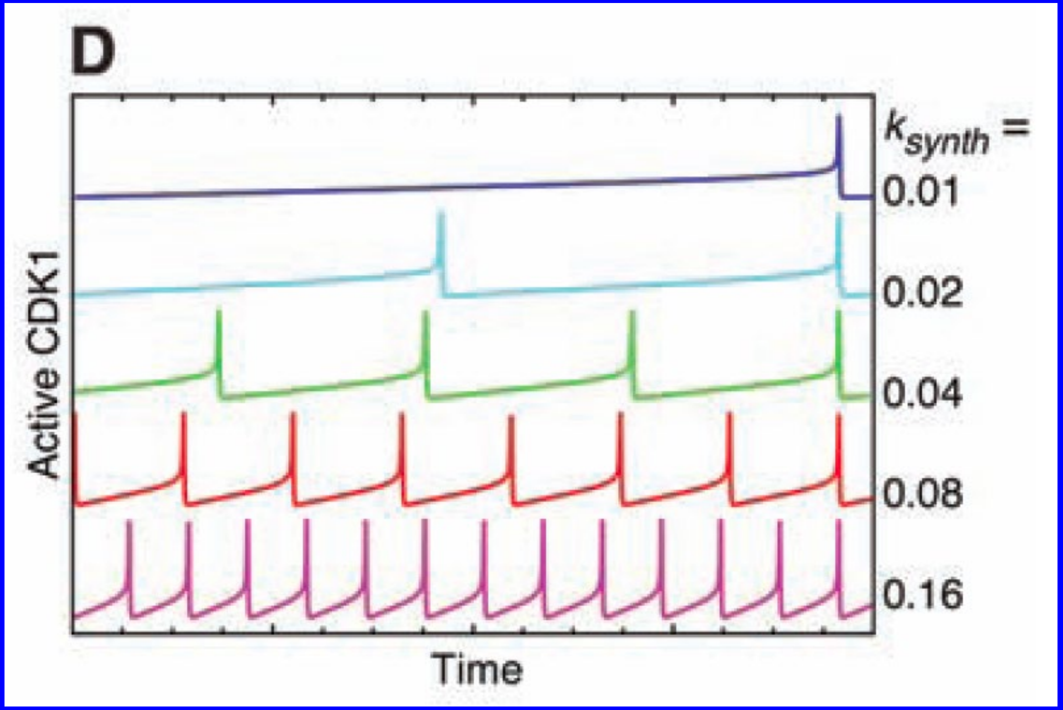
Hysteretic steady-state response of CDK1 to Cyclin B



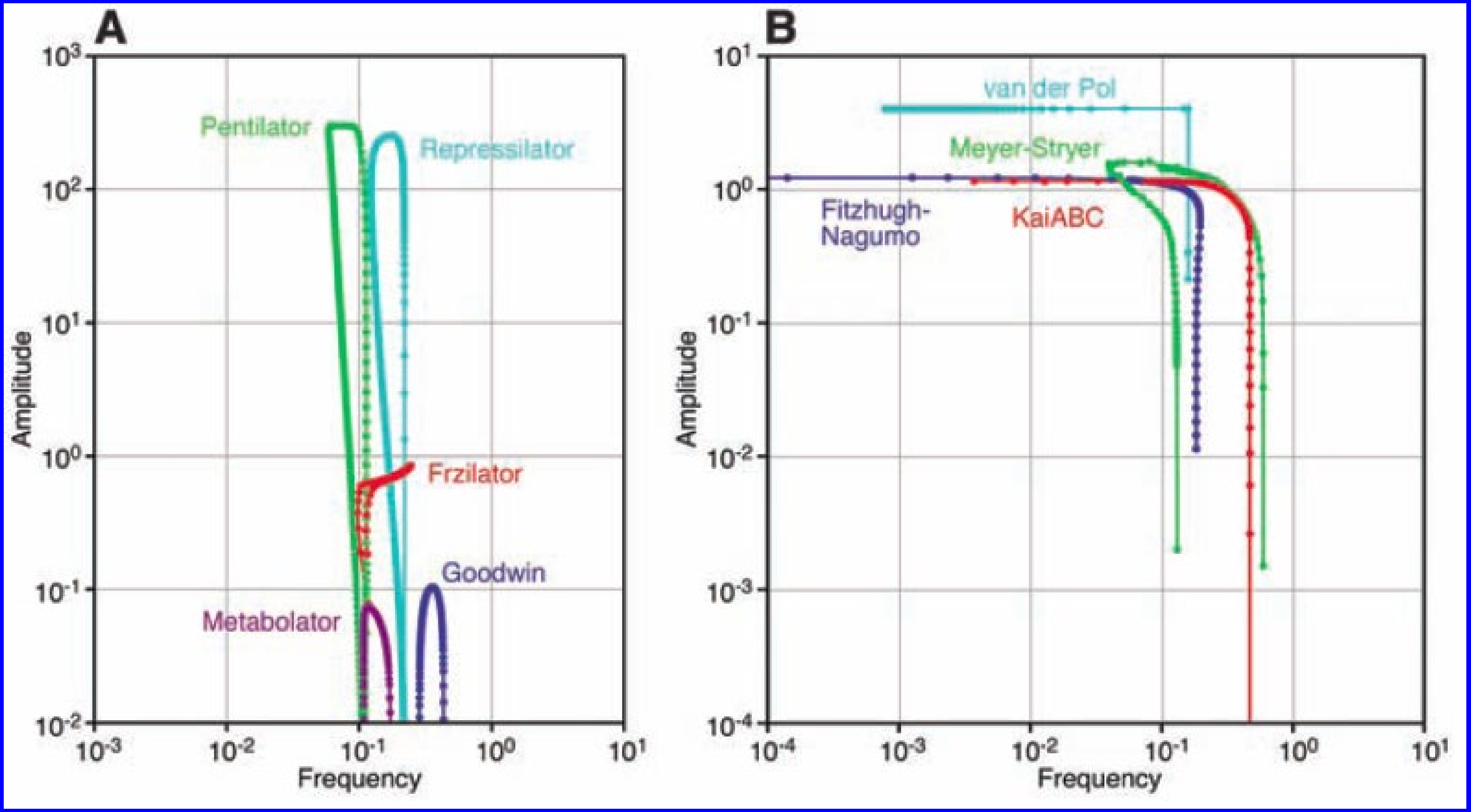
Oscillations due to CDK1 activation and inactivation in the limit of slow cyclin B synthesis and degradation

A looser relation between the oscillations and the hysteretic steady-state response





Amplitude/frequency curves for various legacy oscillators

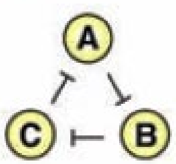


(A) Negative feedback–only models.

(B) Positive-plus-negative feedback models.

Randomly parameterized oscillator models

A

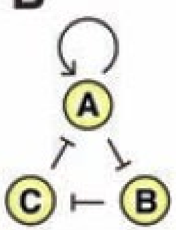


$$\frac{dA}{dt} = k_1(1-A) - \frac{k_2 C^{n1}}{K_1^{n1} + C^{n1}} A$$

$$\frac{dB}{dt} = k_3(1-B) - \frac{k_4 A^{n2}}{K_2^{n2} + A^{n2}} B$$

$$\frac{dC}{dt} = k_5(1-C) - \frac{k_6 B^{n3}}{K_3^{n3} + B^{n3}} C$$

B

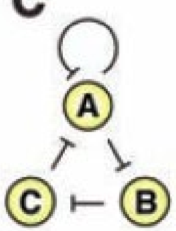


$$\frac{dA}{dt} = k_1(1-A) - \frac{k_2 C^{n1}}{K_1^{n1} + C^{n1}} A + k_7(1-A)\frac{A^{n4}}{K_4^{n4} + A^{n4}}$$

$$\frac{dB}{dt} = k_3(1-B) - \frac{k_4 A^{n2}}{K_2^{n2} + A^{n2}} B$$

$$\frac{dC}{dt} = k_5(1-C) - \frac{k_6 B^{n3}}{K_3^{n3} + B^{n3}} C$$

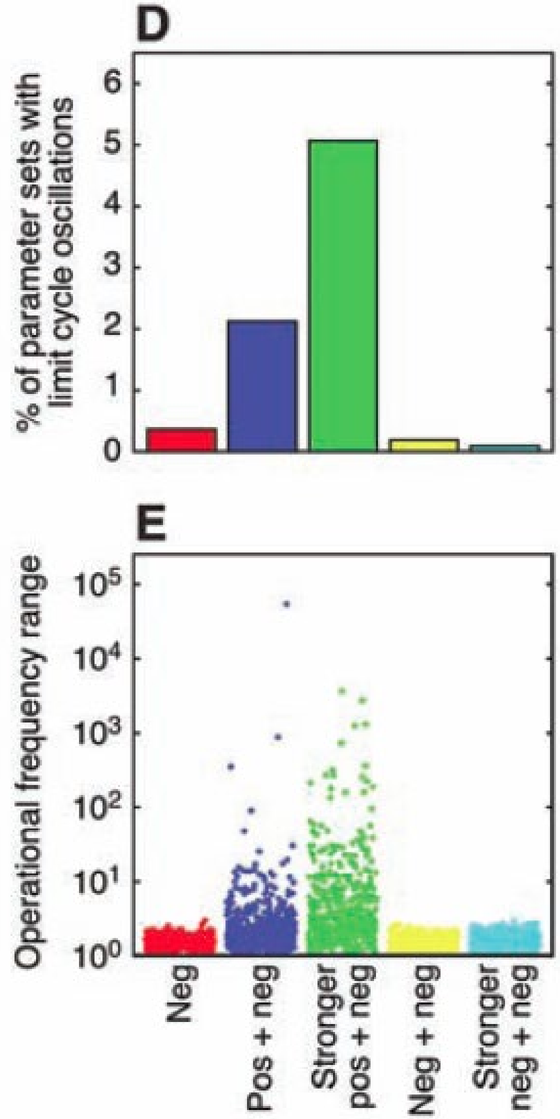
C



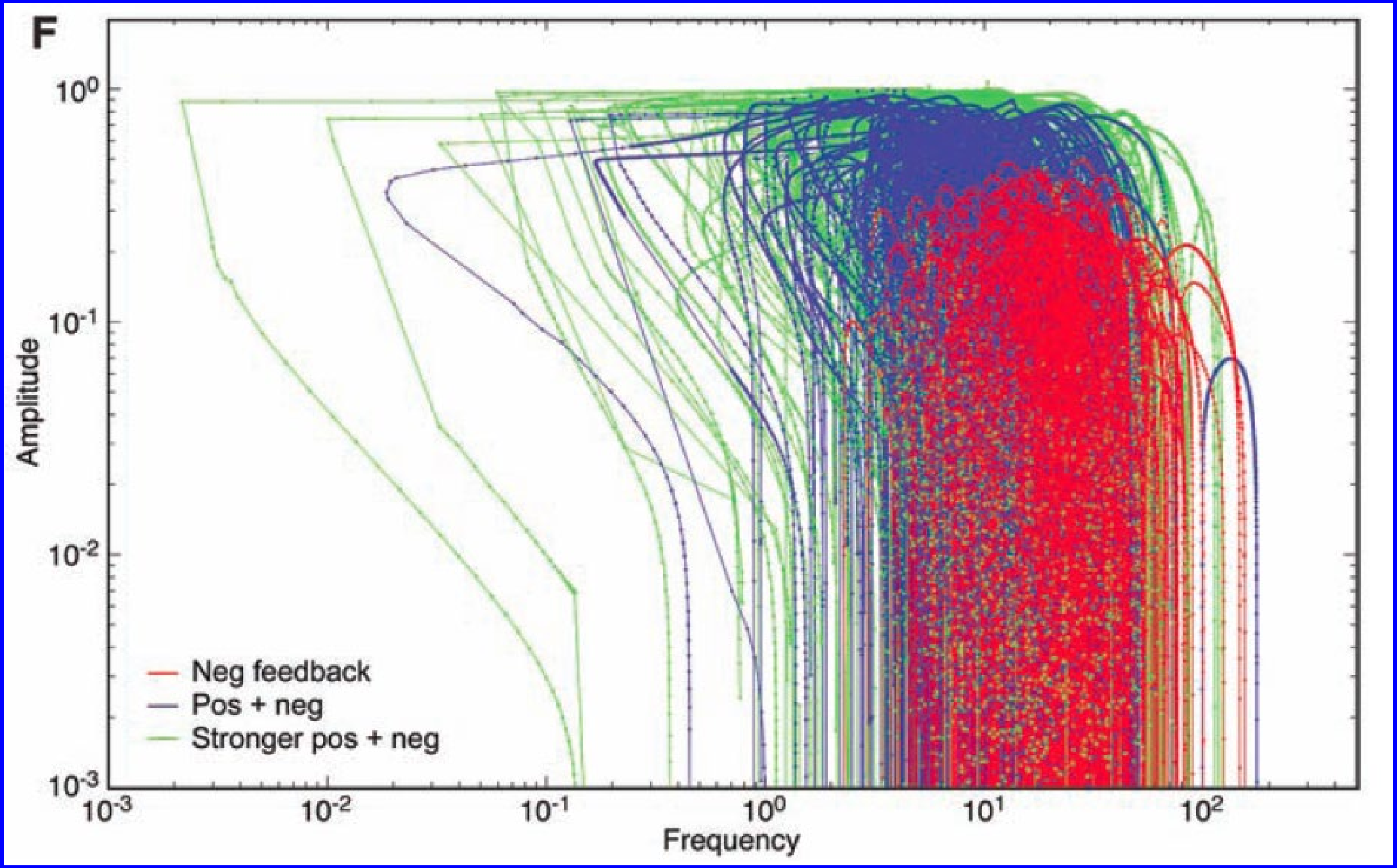
$$\frac{dA}{dt} = k_1(1-A) - \frac{k_2 C^{n1}}{K_1^{n1} + C^{n1}} A - k_7 A\frac{A^{n4}}{K_4^{n4} + A^{n4}}$$

$$\frac{dB}{dt} = k_3(1-B) - \frac{k_4 A^{n2}}{K_2^{n2} + A^{n2}} B$$

$$\frac{dC}{dt} = k_5(1-C) - \frac{k_6 B^{n3}}{K_3^{n3} + B^{n3}} C$$



Amplitude/frequency curves for the randomly parameterized models



Summary I

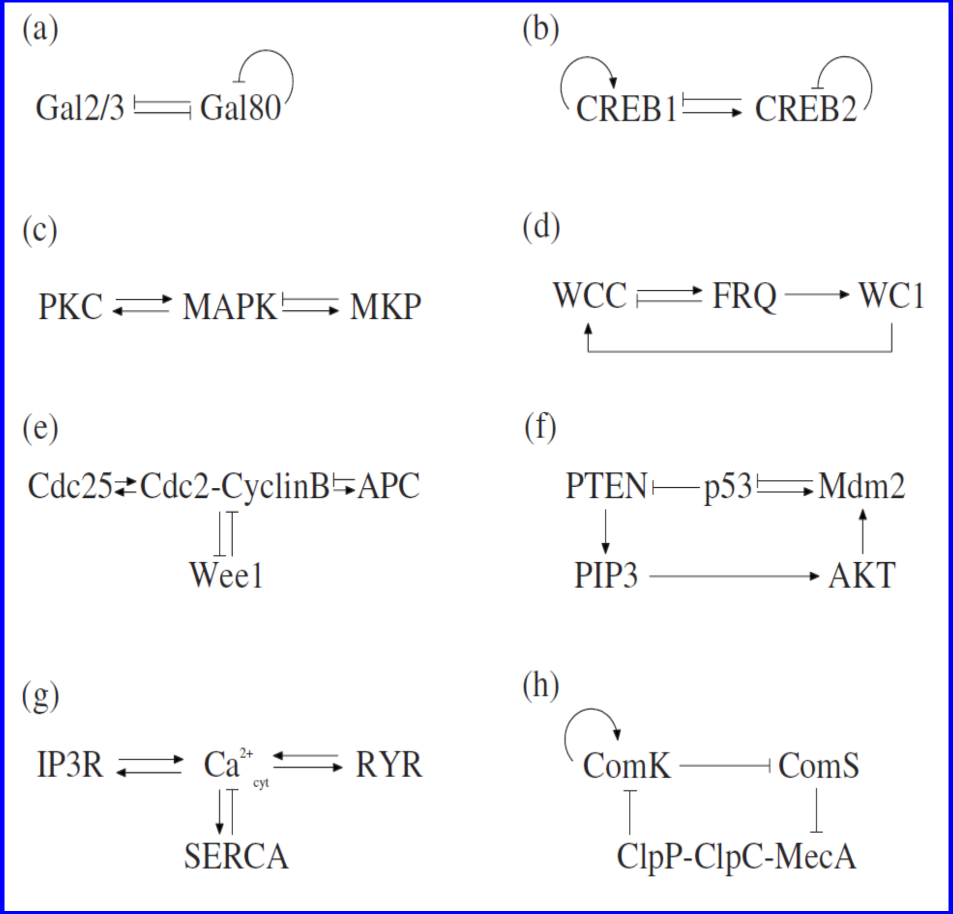
The positive feedback loops in natural biological oscillators possesses two performance advantages over simple negative feedback loops:

(i) the ability to tune the oscillator's frequency without changing its amplitude;

(ii) a greater robustness and reliability.

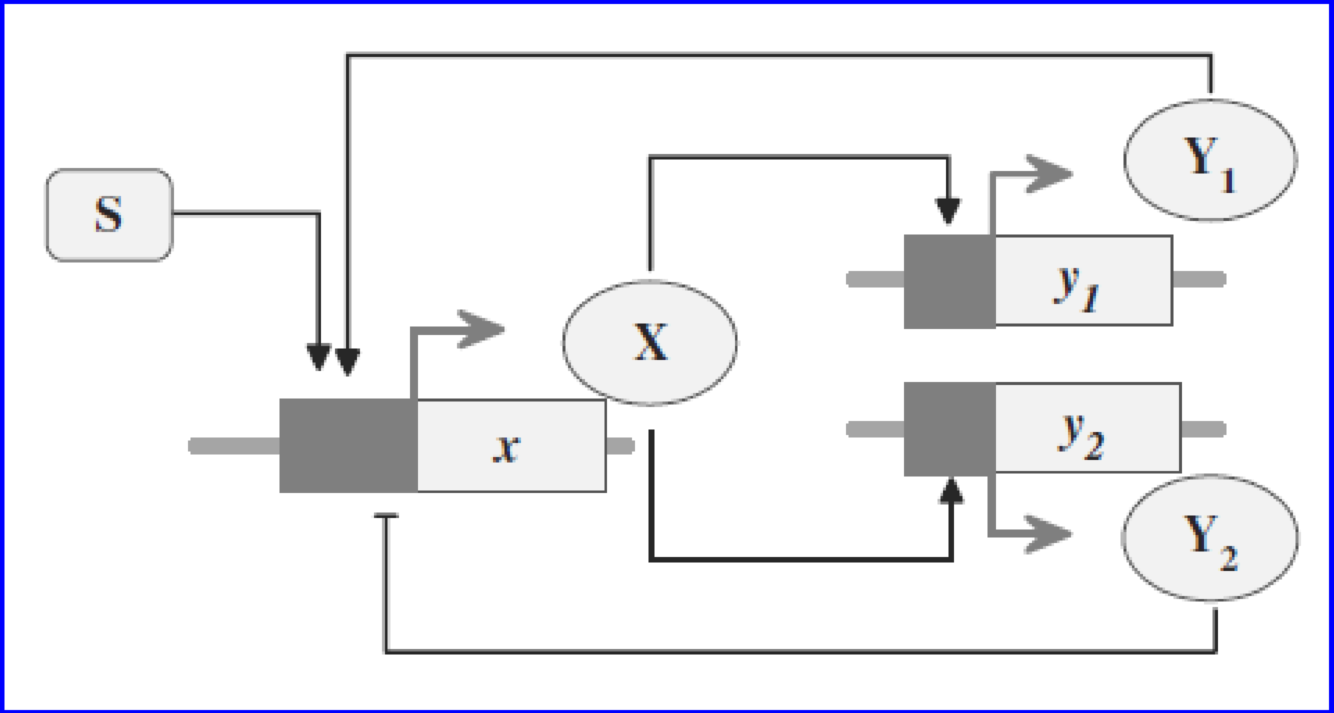
Interlinking positive and negative feedback loops creates a tunable motif in gene regulatory networks

Examples of biological systems with interlinked positive and negative feedback loops



Tian, X.-J., X.-P. Zhang, et al. (2009). Physical Review E **80**(1): 011926-011928.

Schematic depiction of the model



The transcription factor X induces expression of genes y_1 and y_2. The activation of X by Y_1 encloses a positive feedback while the repression of X by Y_2 yields a negative feedback.

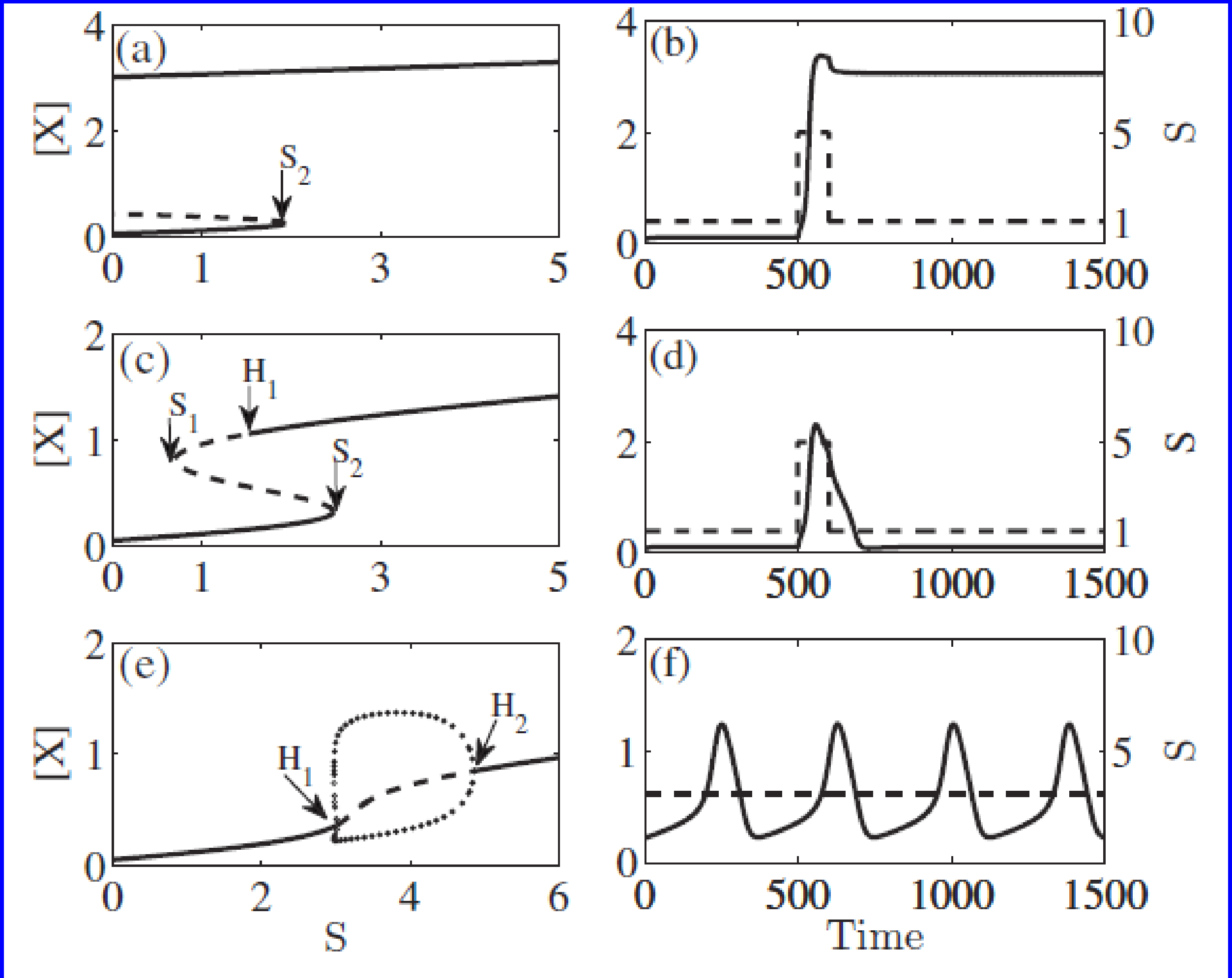
Model

$$\frac{d[X]}{dt} = V_x \frac{\left(\frac{[Y_1]}{K_{y_1x}}\right)^n}{1 + \left(\frac{[Y_1]}{K_{y_1x}}\right)^n + \left(\frac{[Y_2]}{K_{y_2x}}\right)^n} - d_x[X] + b_xS, \qquad (1)$$

$$\frac{d[Y_1]}{dt} = V_{y_1} \frac{\left(\frac{[X]}{K_{xy_1}}\right)^n}{1 + \left(\frac{[X]}{K_{xy_1}}\right)^n} - d_{y_1}[Y_1] + b_{y_1}, \qquad (2)$$

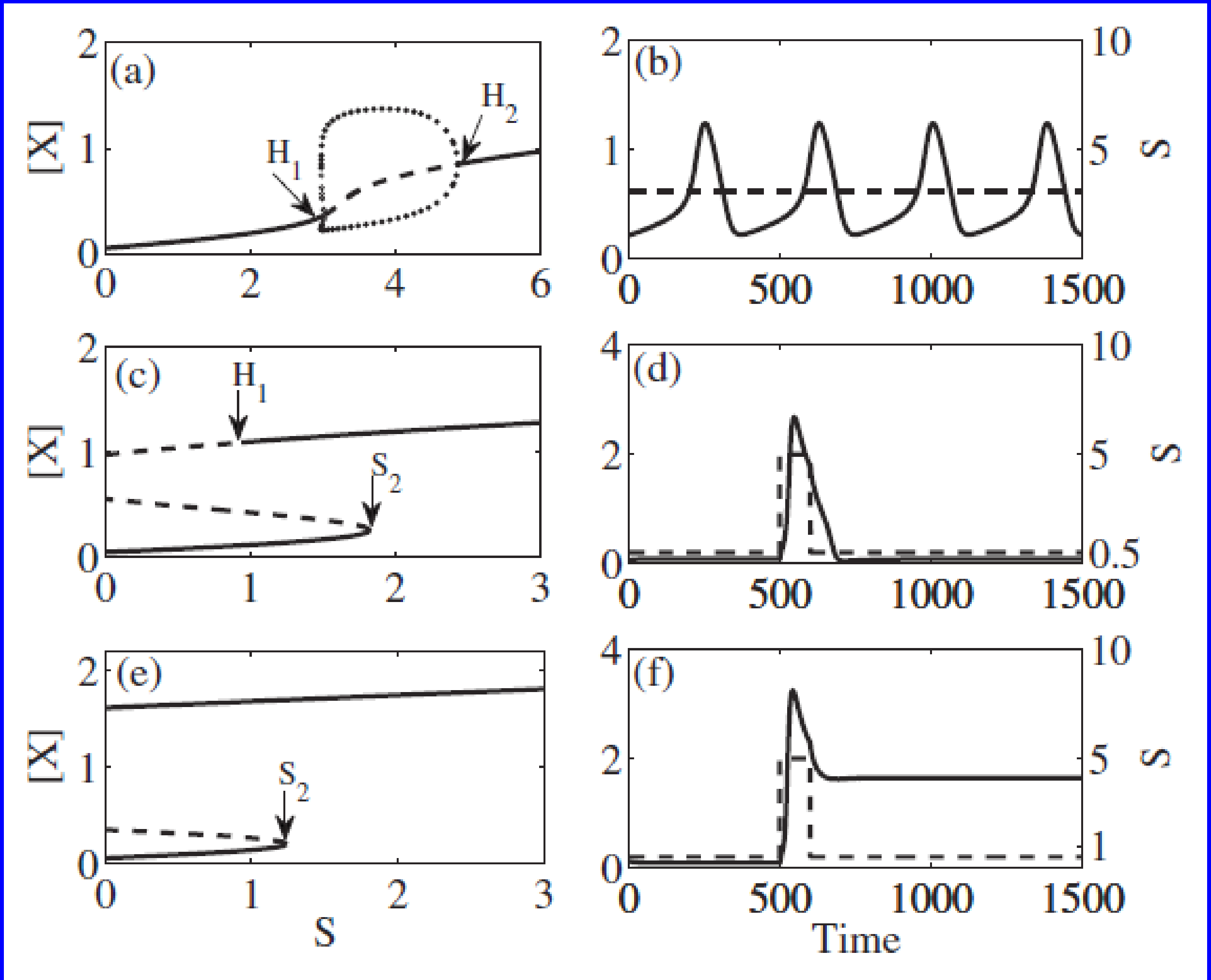
$$\frac{d[Y_2]}{dt} = V_{y_2} \frac{\left(\frac{[X]}{K_{xy_2}}\right)^n}{1 + \left(\frac{[X]}{K_{xy_2}}\right)^n} - d_{y_2}[Y_2] + b_{y_2}. \qquad (3)$$

Transition from bistability to oscillation



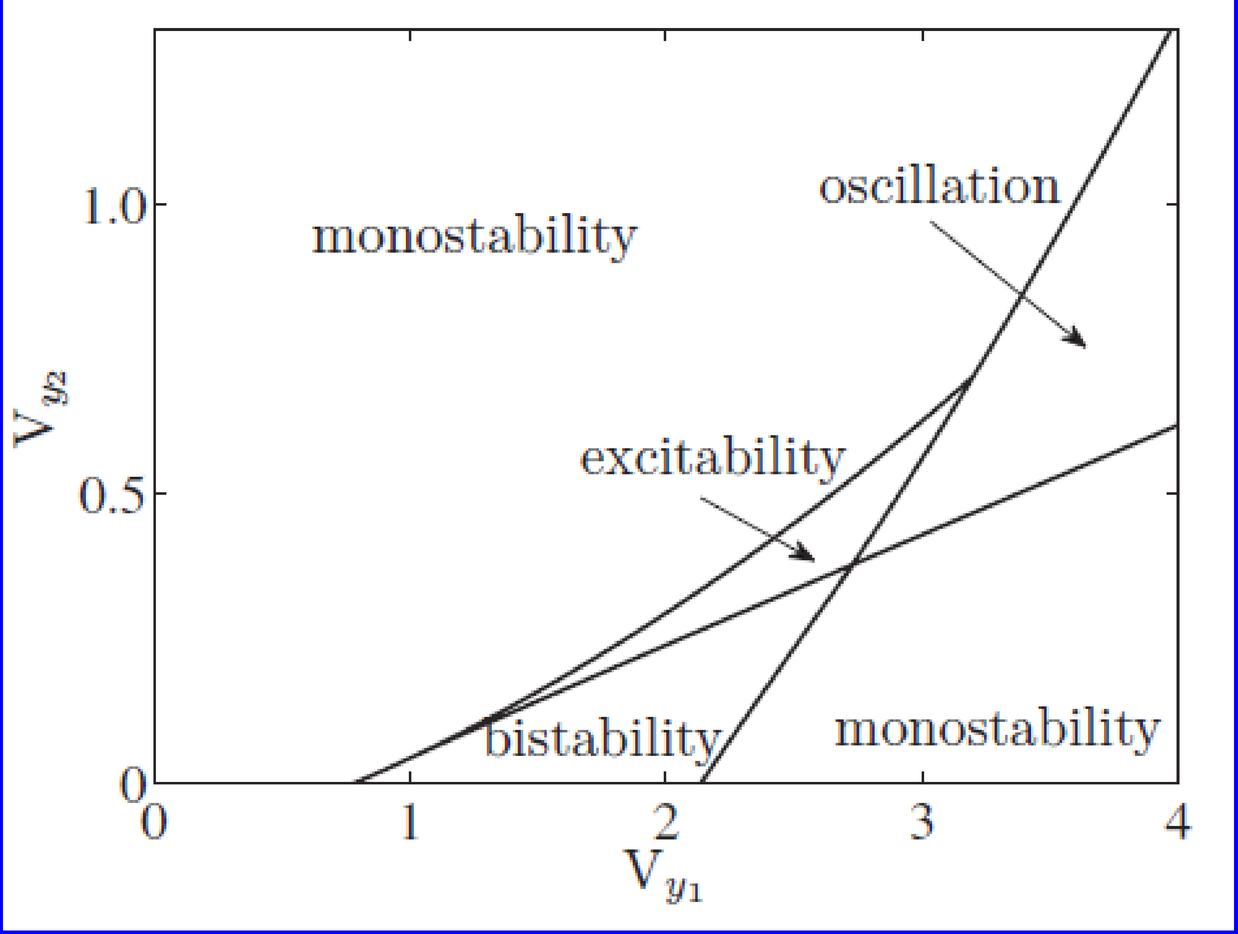
Enhancing the PFL

Reversion from oscillation to bistability



Enhancing the NFL

Two-parameter bifurcation diagram with S=1



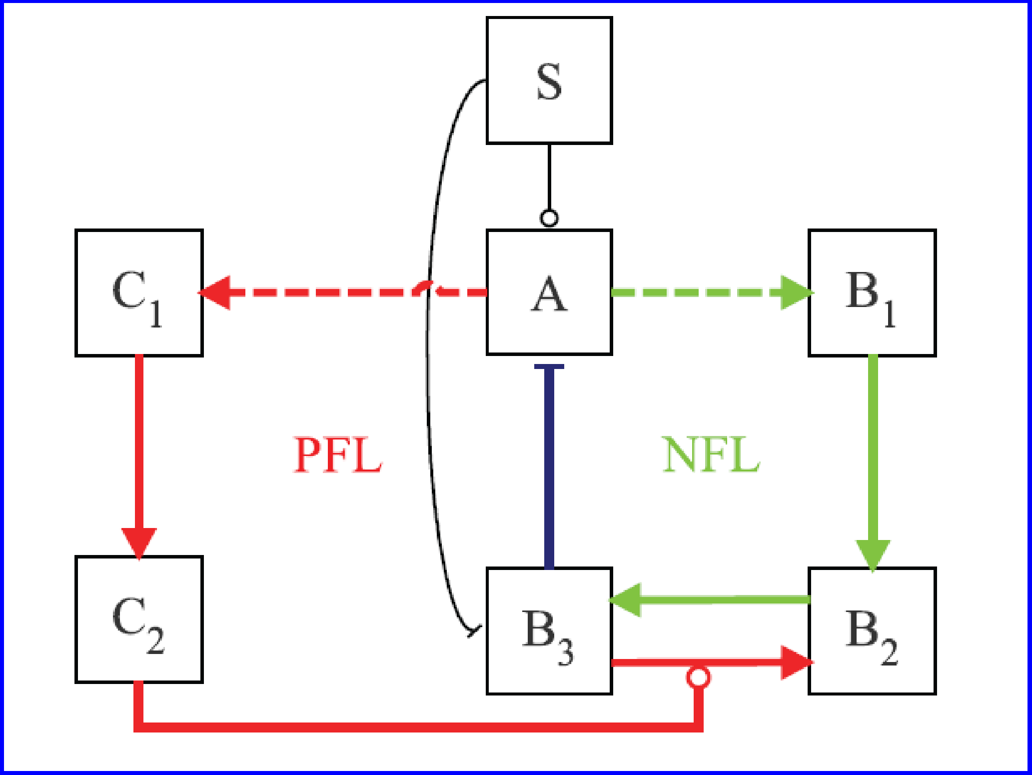
Summary II

Our results suggests the performance advantages of positive and negative feedback loops:

It is unnecessary to change the topology of such systems in order to perform distinct functions.

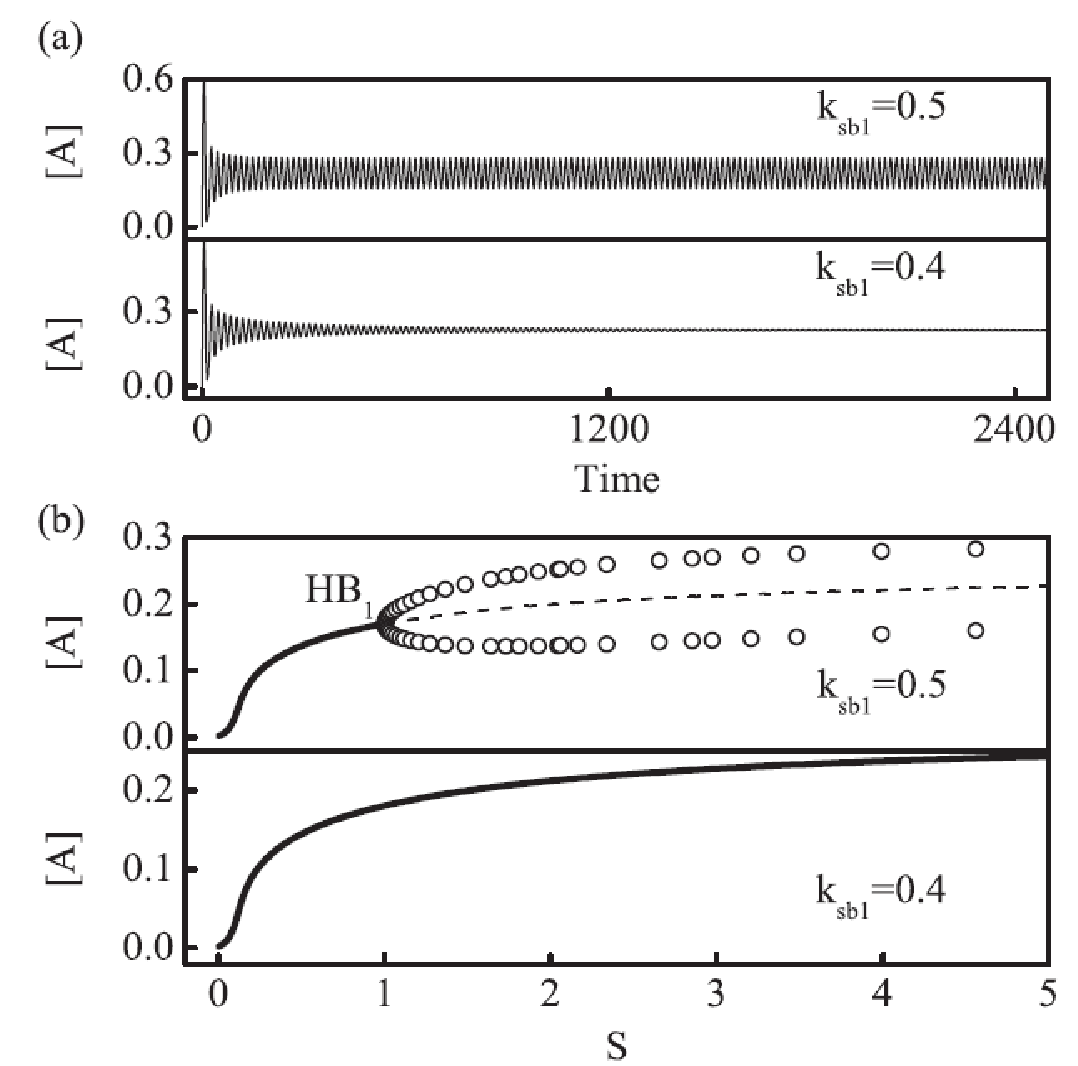
Modulation of dynamic modes by interplay between positive and negative feedback loops

Abstract model



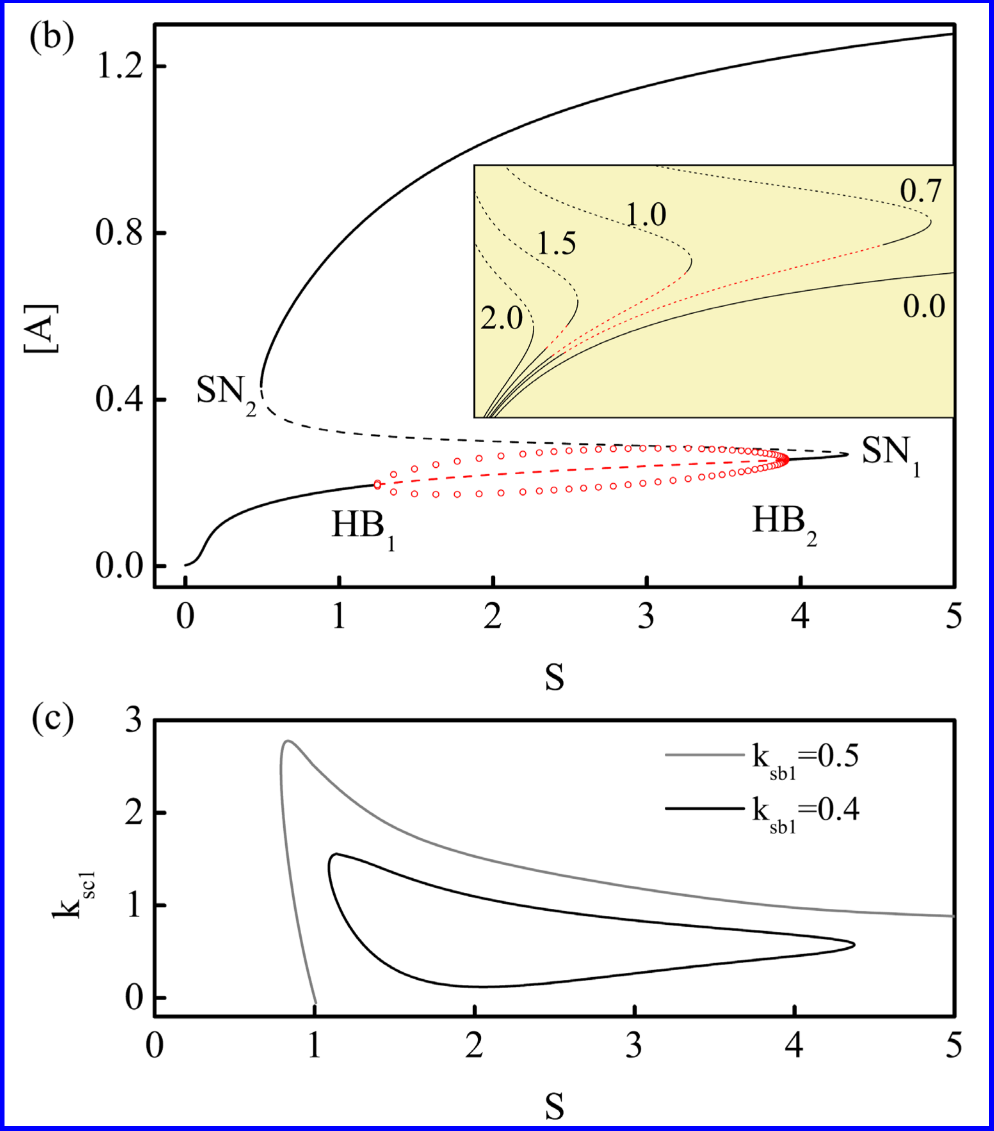
Wang LS, Li NX, Chen JJ, Zhang, XP, Liu F and Wang W. Phys. Rev. E, 97: 042412 (2018).

Negative feedback is required but not sufficient for oscillation

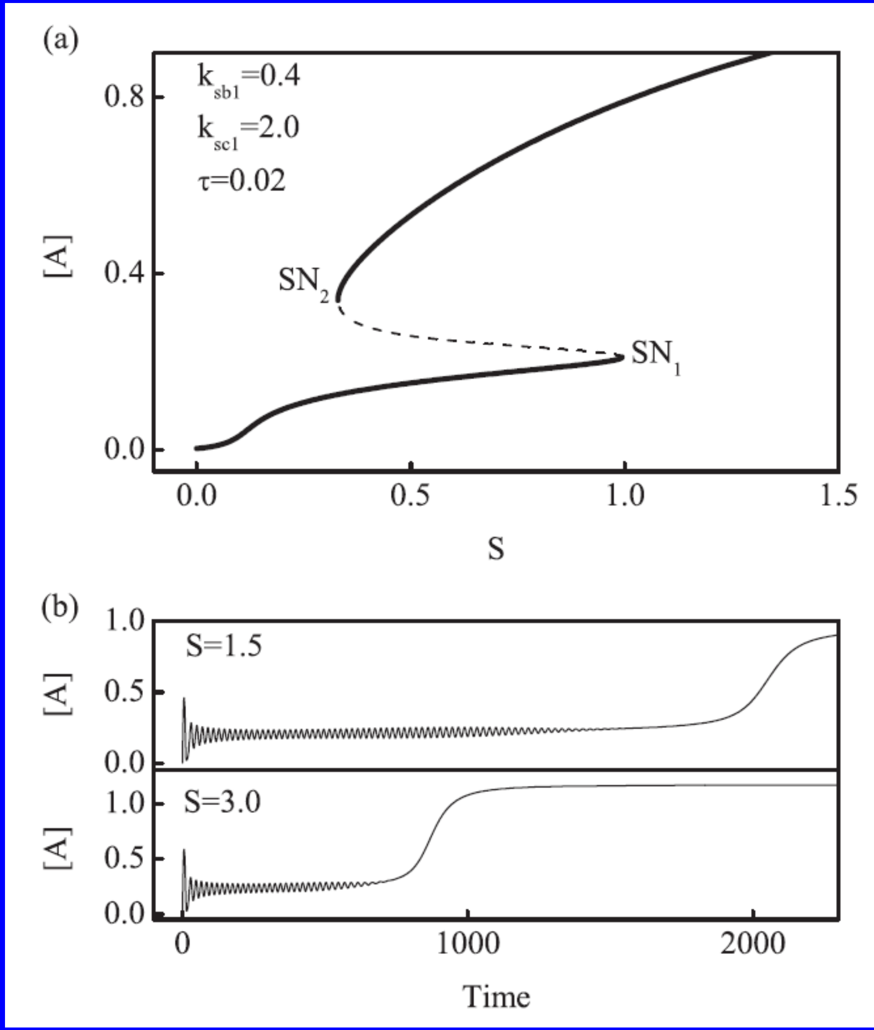


$k_{sc1} = 0$

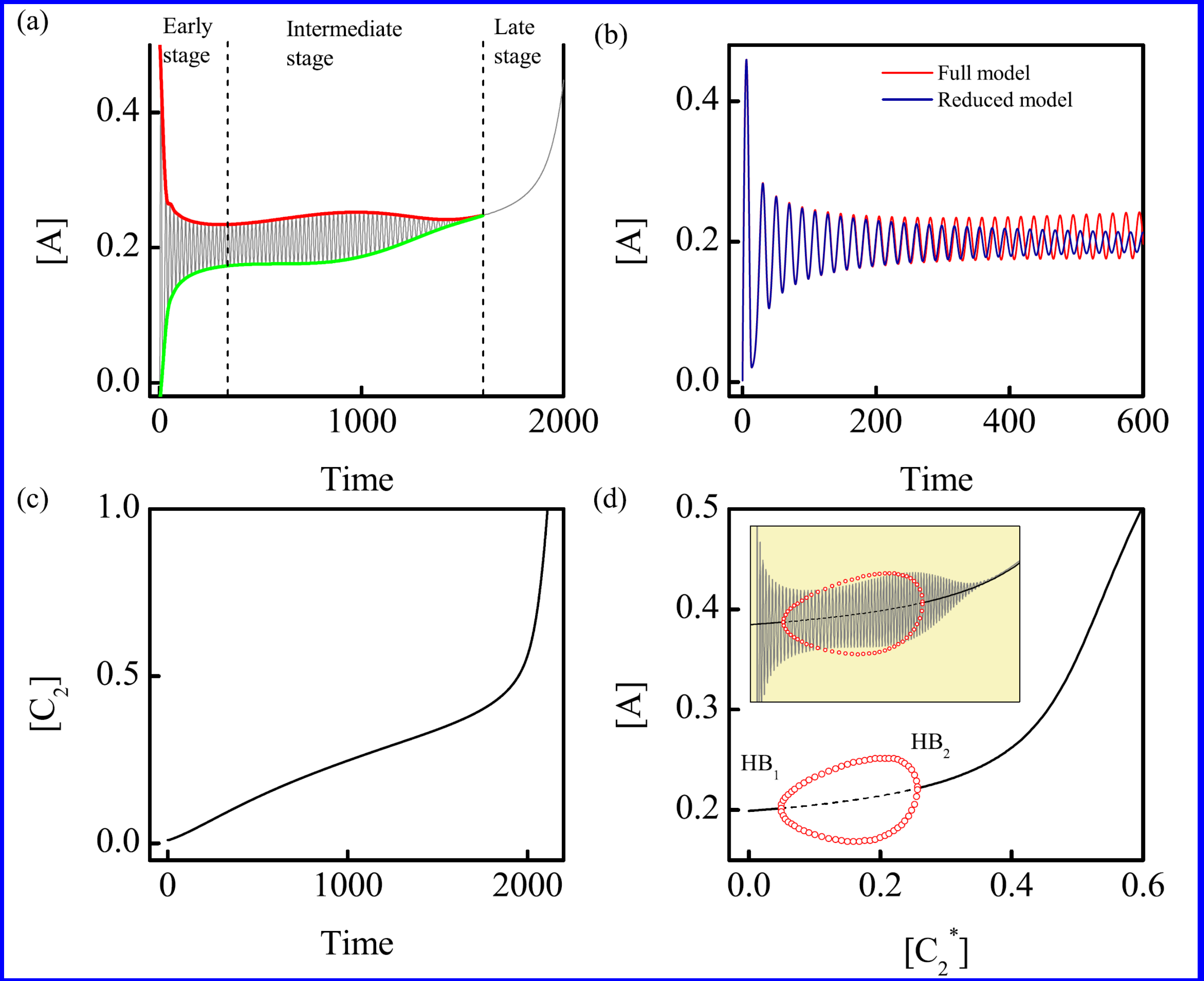
Dual Role of PFL in producing oscillation



Spontaneous transition between dynamic modes



Transition in domination of feedback loops leads to variation in the dynamic modes



Summary III

PFL plays a dual role in NFL-mediated oscillations depending on the strength of the NFL .

Alternation in the predomination of feedback loops results in the transition from oscillation to bistability.

Assignment 7

Reproducing Figures 5 in the literature:

Tian, X.-J., X.-P. Zhang, et al. (2009). Physical Review E **80**(1): 011926-011928.