Oscillatory Circuits

Systems and Synthetic Biology
Class

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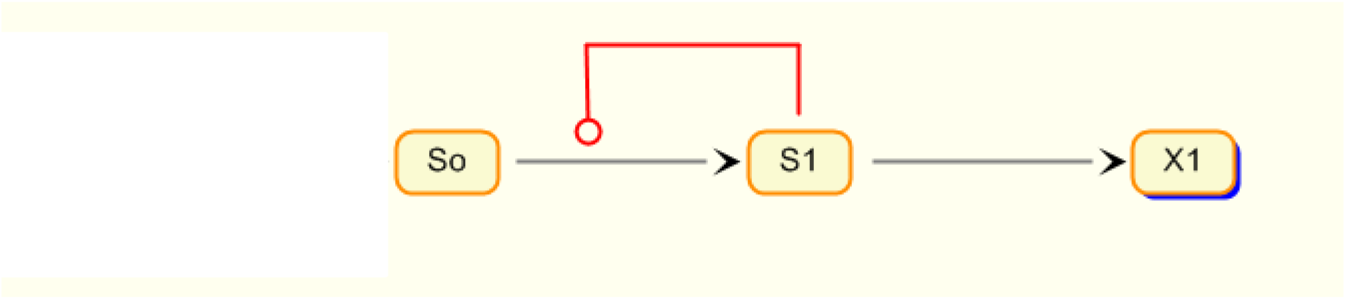
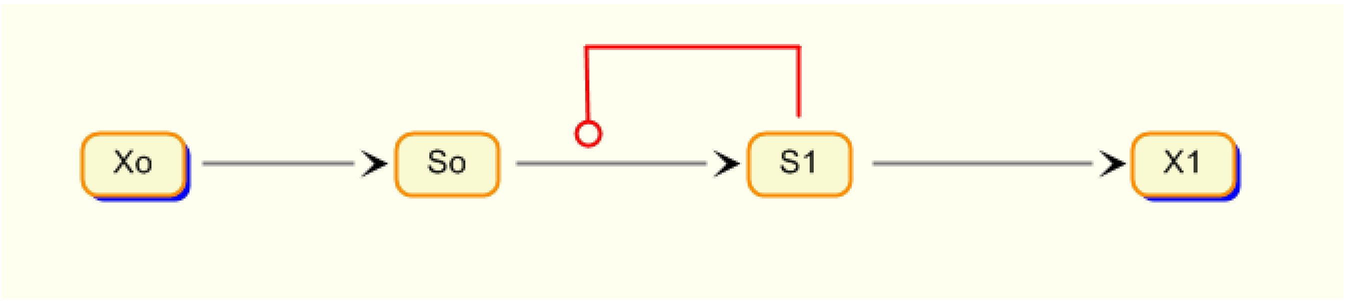
Modifying a Bistable System



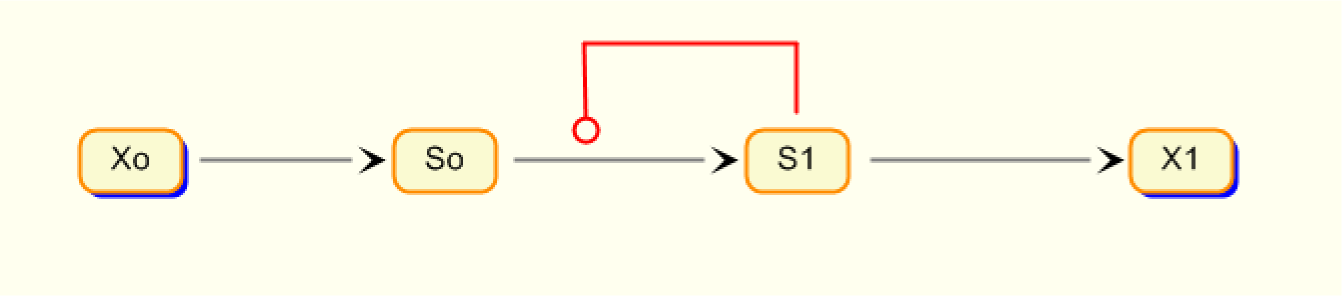
This small network shows bistable behavior

Modifying a Bistable System



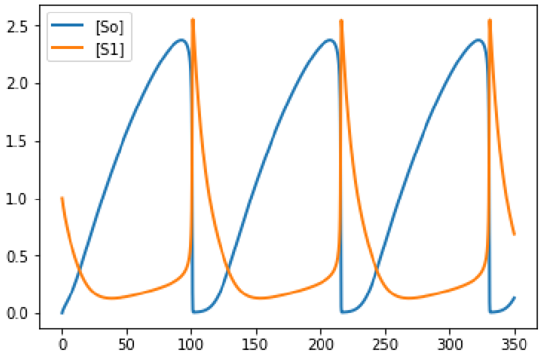
With only the addition of a single reaction, this network will oscillate.

Modifying a Bistable System to form a Relaxtion Oscillator

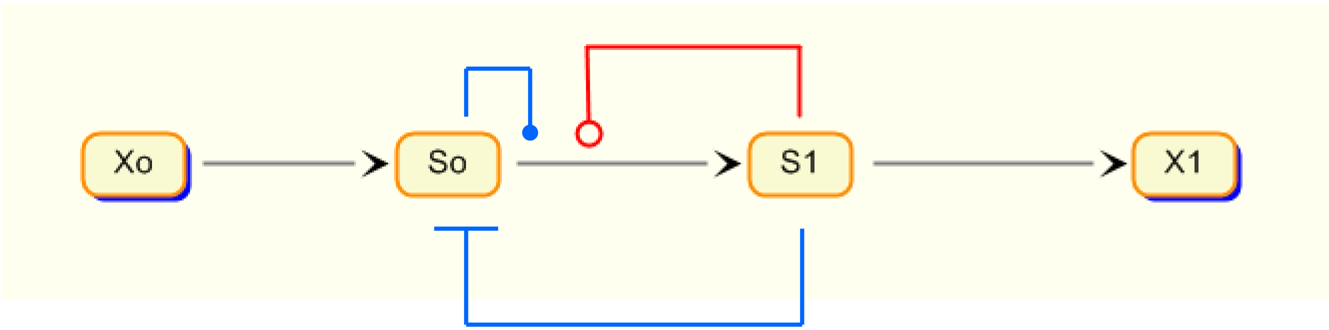


Using the Tellurium Python package at: tellurium.analogmachine.org

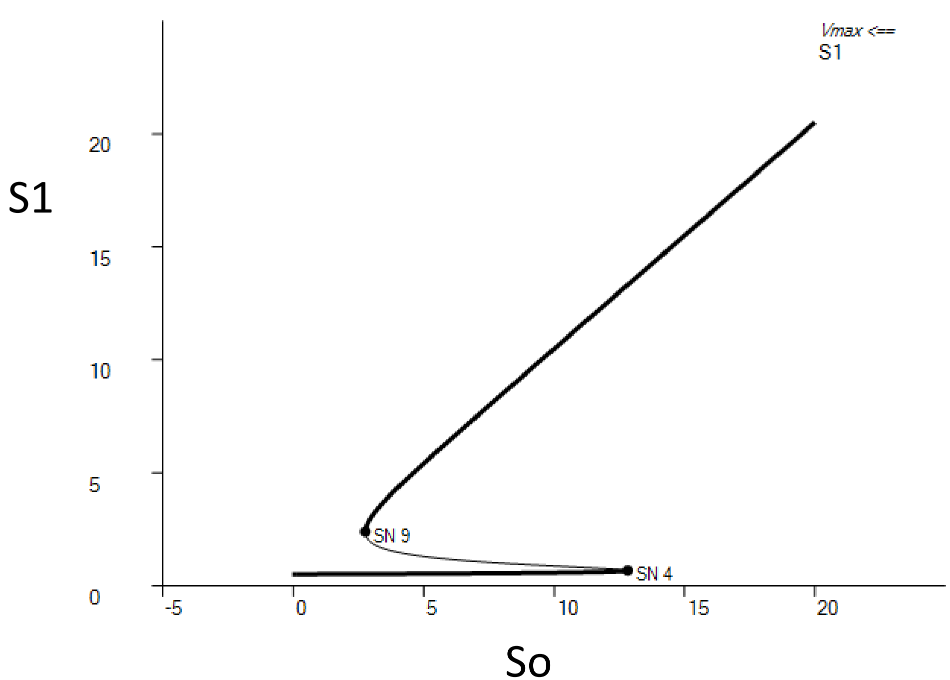
```
import tellurium as te

r = te.loada("""
  $Xo -> So;  k0*Xo;
   So -> S1;   k1*So + Vmax*So*S1^n/(15 + S1^n);
   S1 -> $X1;  k2*S1;

  Xo = 1; X1 = 0; S1 = 1; n = 4;
  Vmax = 12; k0 = 0.044;
  k1 = 0.01; k2 = 0.1;

""")

m = r.simulate (0, 300, 1600)
r.plot()
```

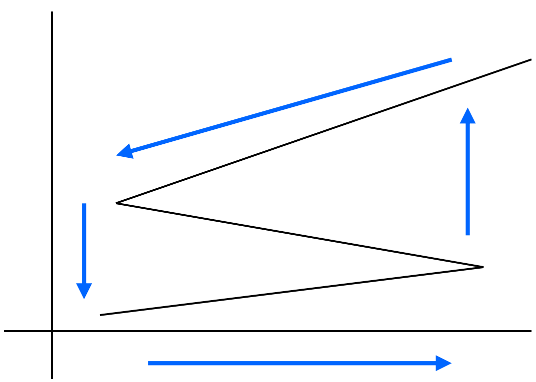


Relaxation Oscillator

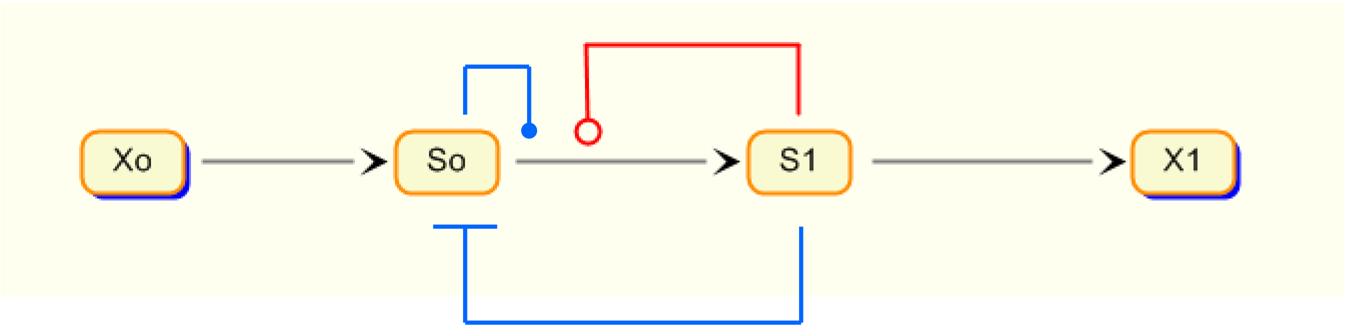


One Parameter Bifurcation Data [1/1]: Vmax

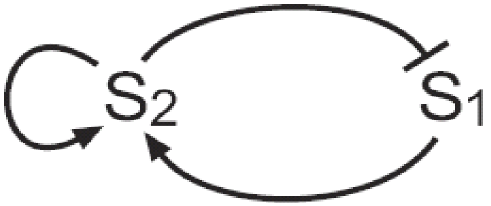




Relaxation Oscillator



A relaxation oscillator has two parts, a threshold device, for example a bistable system, and a negative feedback loop.



Relaxation Oscillator

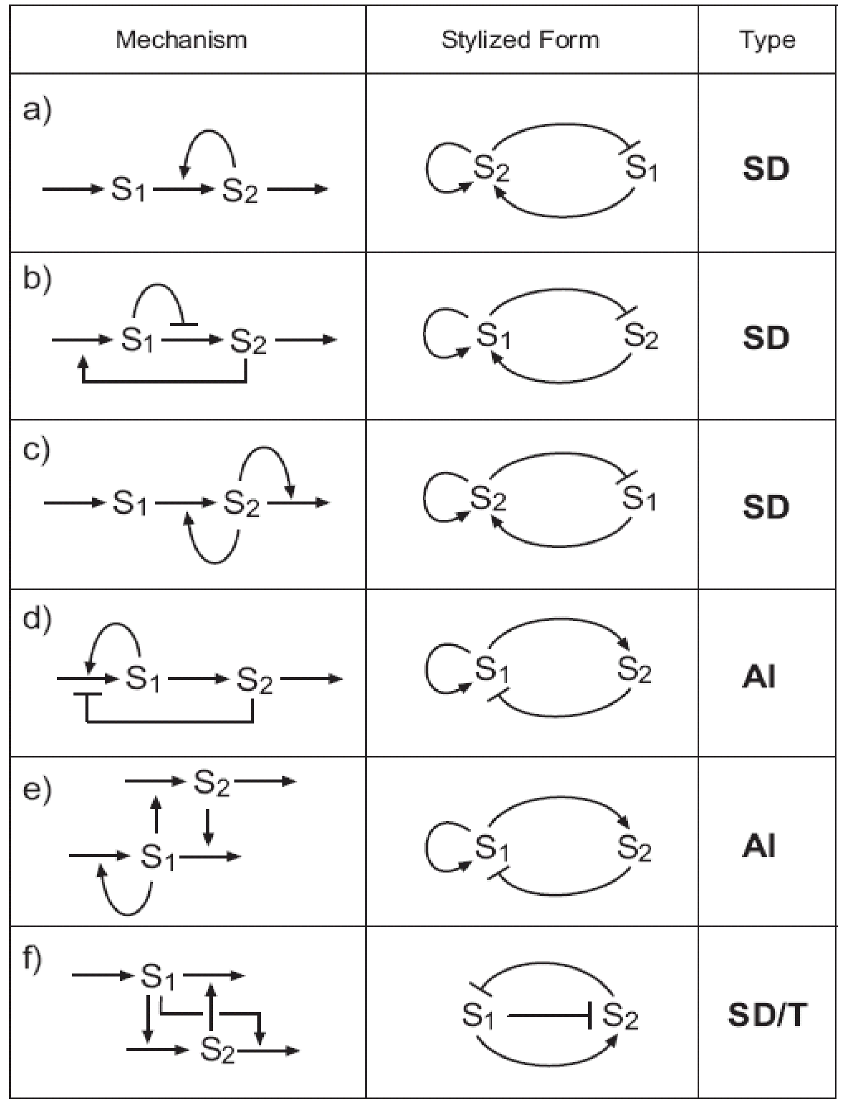
SD = Substrate Depletion

AI = Activator-Inhibitor

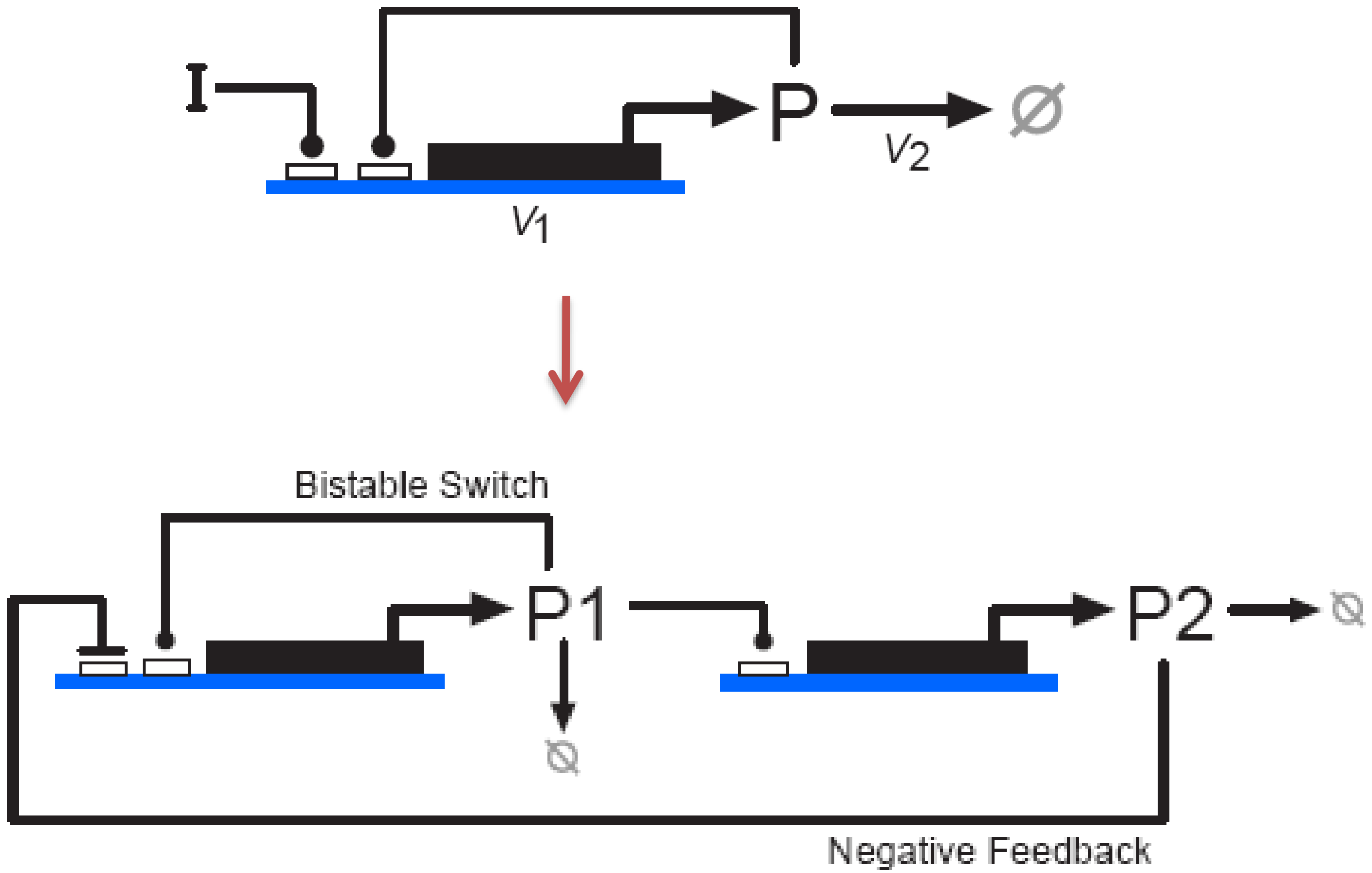
SD/T = Substrate Depletion/
Toggle.

Classifications
according to Tyson

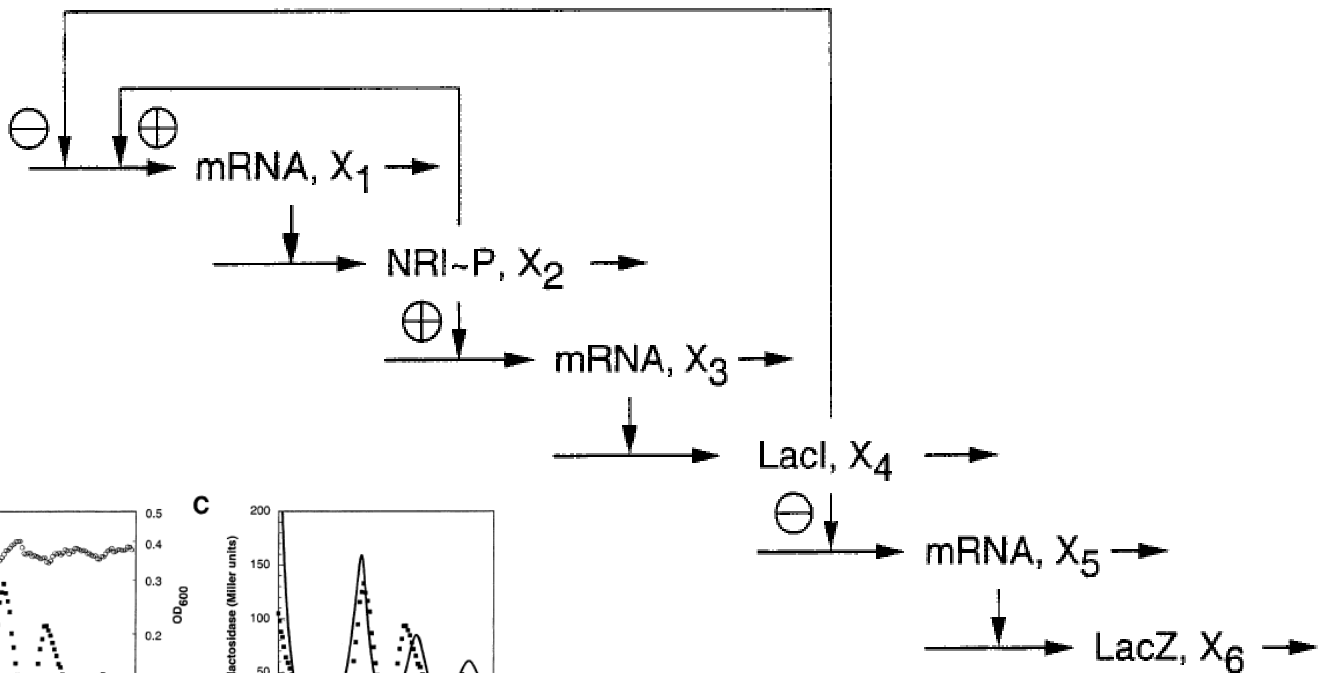
Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell John J Tysony, Katherine C Chenz and Bela Novak
Current Opinion in Cel Biology, vol 15, 221-231 (2003)

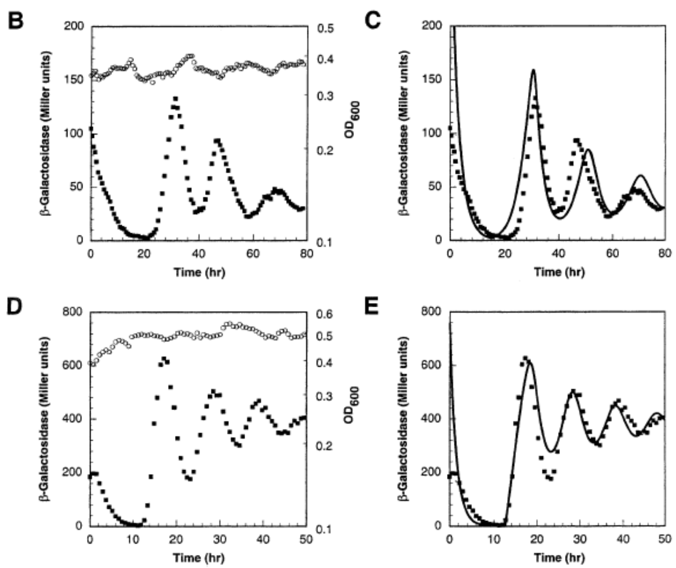


Relaxation Oscillator



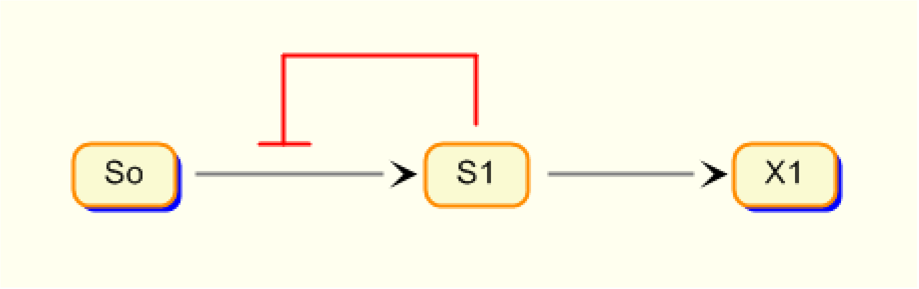
Synthetic Relaxation Oscillator



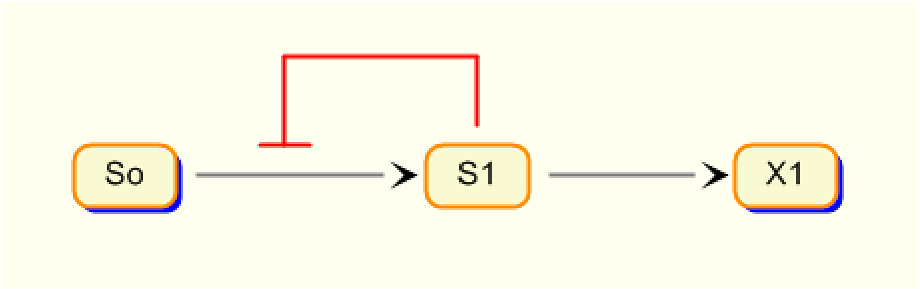


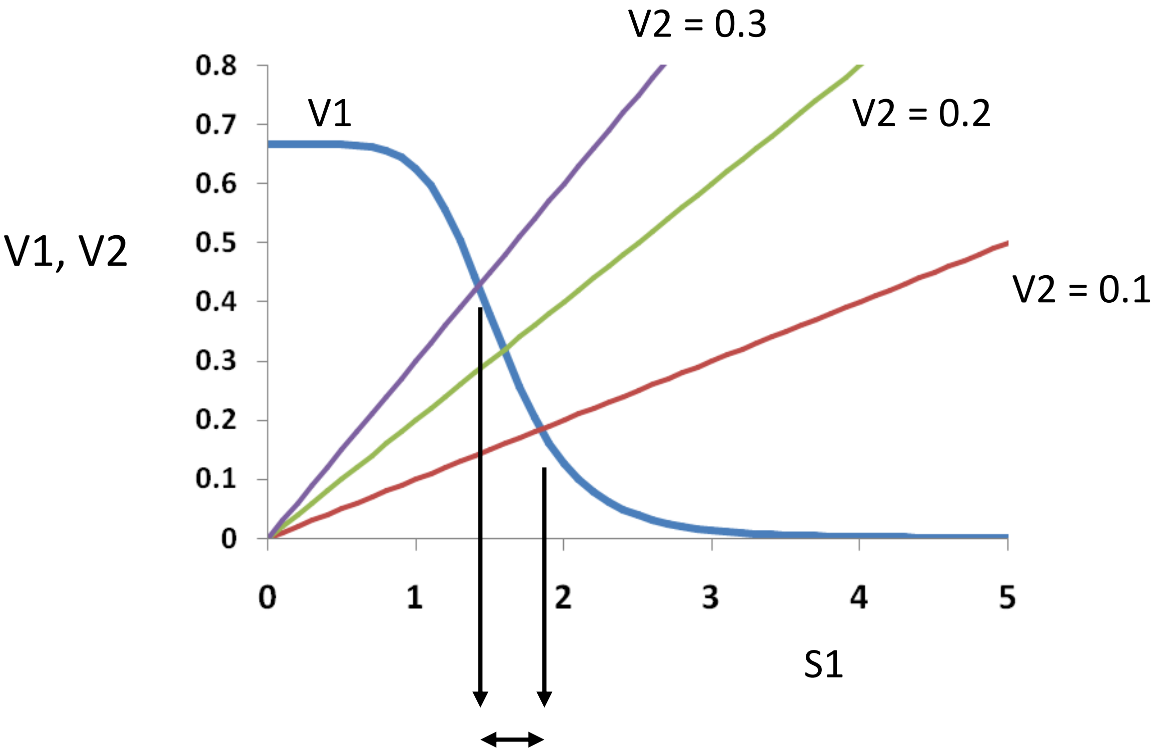
Cell, Vol. 113, 597–607, May 30, 2003, Development of Genetic Circuitry Exhibiting Toggle Switch or Oscillatory Behavior in *Escherichia coli,* **Mariette R. Atkinson Michael A. Savageau Jesse T. Myers and Alexander J. Ninfa**

Negative Feedback

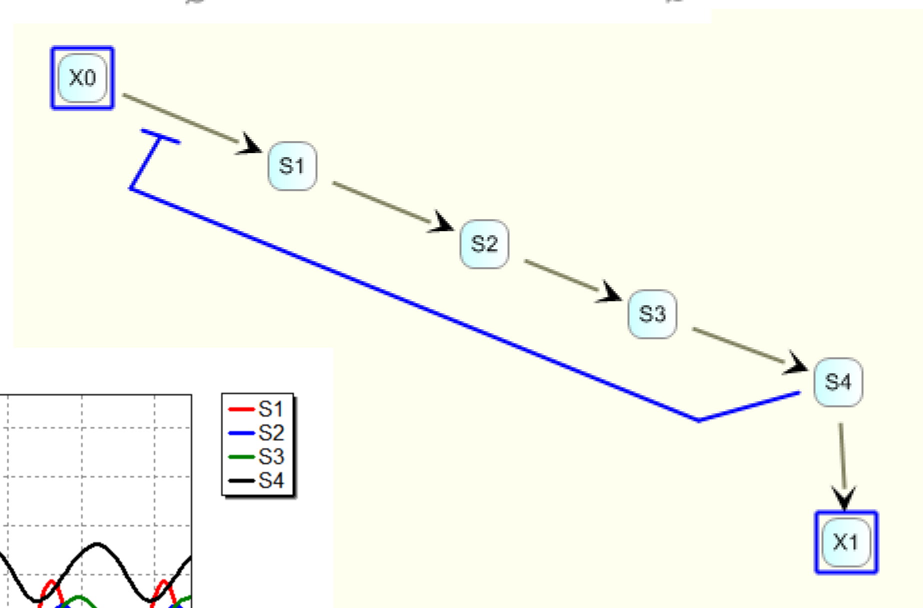


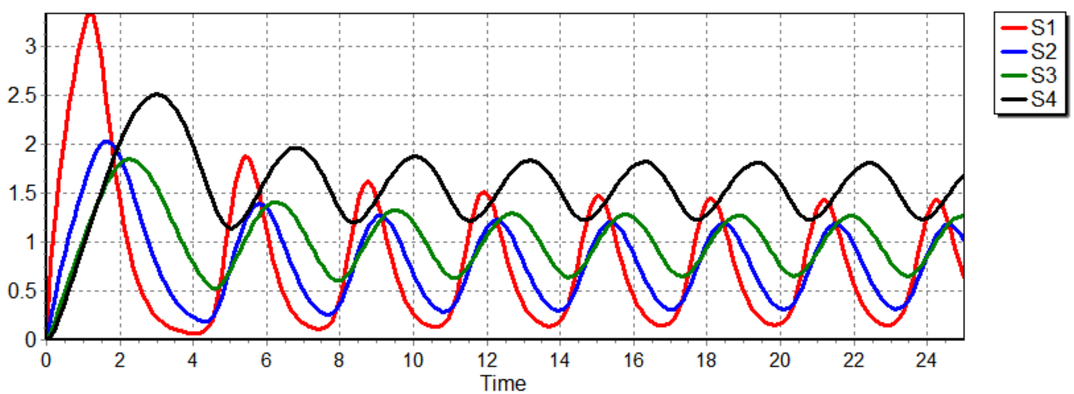
Negative Feedback





Negative Feedback: Phase Shift Oscillator

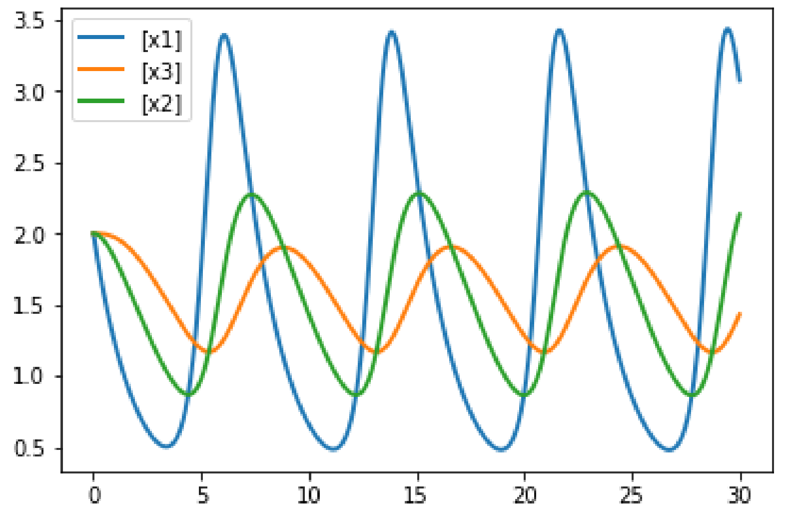




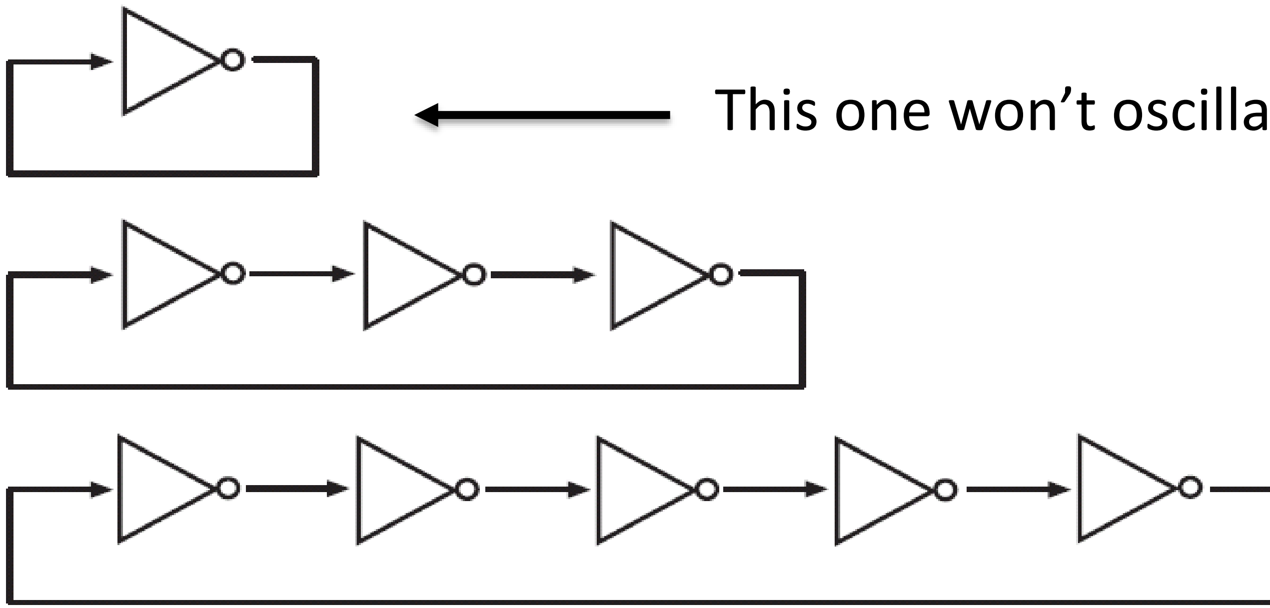
If the signal takes too long to make the appropriate adjustment, the system can go out of phase and begin to spontaneously oscillate.

Negative Feedback Phase Shift Oscillator

```
import tellurium as te

r = te.loada("""
   J1: -> x1; vm/(km + x3^n);
    x1 -> x2; k1*x1
    x2 -> x3; k2*x2
    x3 ->;    k3*x3;

    k1 = 0.5; k2 = 0.5; k3 = 0.5;
    n = 10;
    x1 = 2; x2 = 2; x3 = 2
    vm = 18; km = 0.5;
""")

m = r.simulate (0, 30, 1000)
r.plot()
```

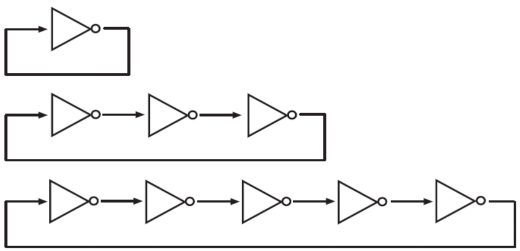


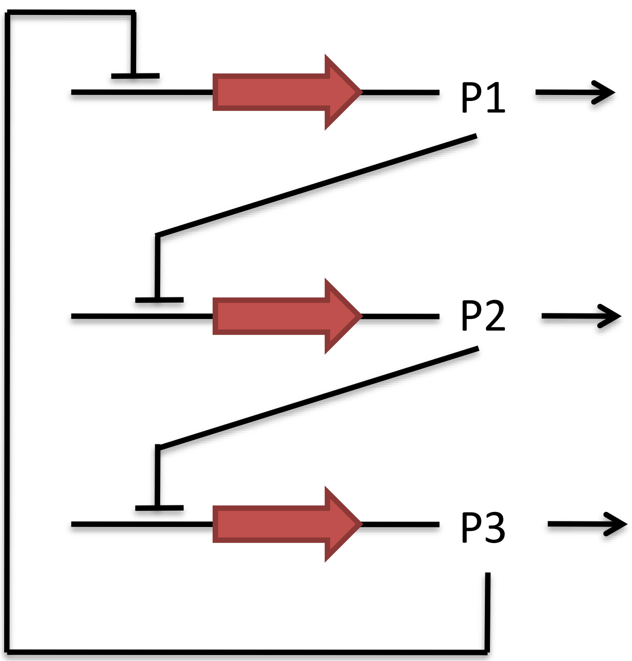
Ring Oscillator



This one won't oscillate

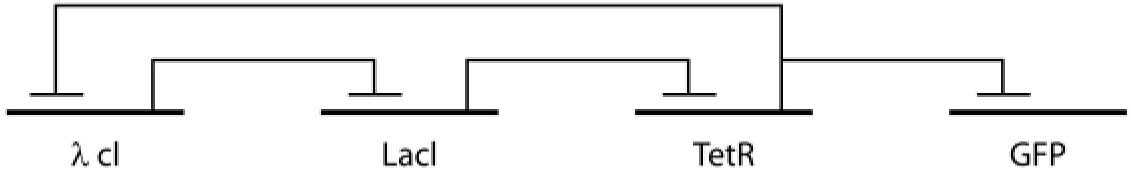
Ring Oscillator – Jarnac Model

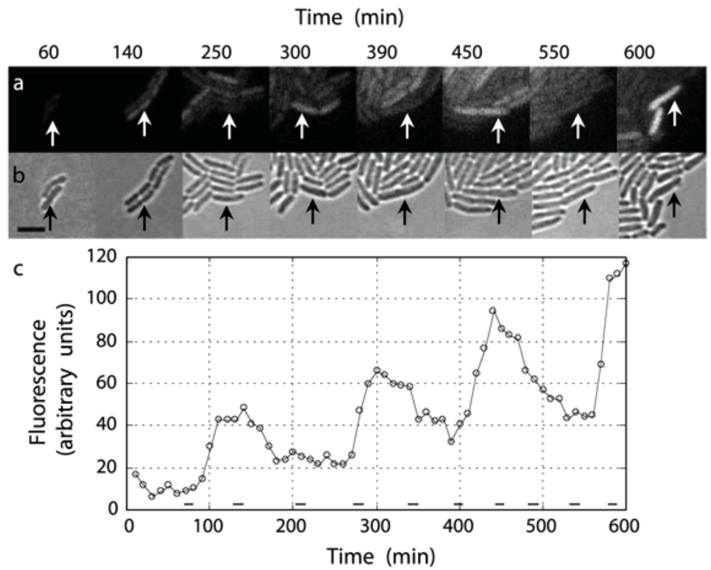


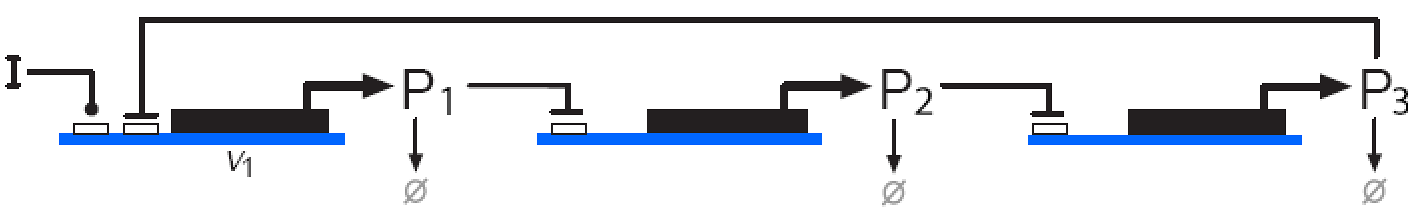



```
import tellurium as te

r = te.loada("""
  J1:  -> x1; vm1/(km1 + x3^n);
    x1 -> ; k1*x1;

  J3:  -> x2; vm2/(km2 + x1^n);
    x2 -> ; k2*x2;

  J4:  -> x3; vm3/(km3 + x2^n);
    x3 -> ; k3*x3;

   k1 = 0.5; k2 = 0.5; k3 = 0.5;
   n = 4; vm1 = 5; vm2 = 5; vm3 = 5;
   km1 = 0.5; km2 = 0.5; km3 = 0.5;
   s1 = 0.6; x1 = 1; x2 = 1; x3 = 2
""")

m = r.simulate (0, 40, 100)
r.plot()
```

Ring Oscillator: Repressilator

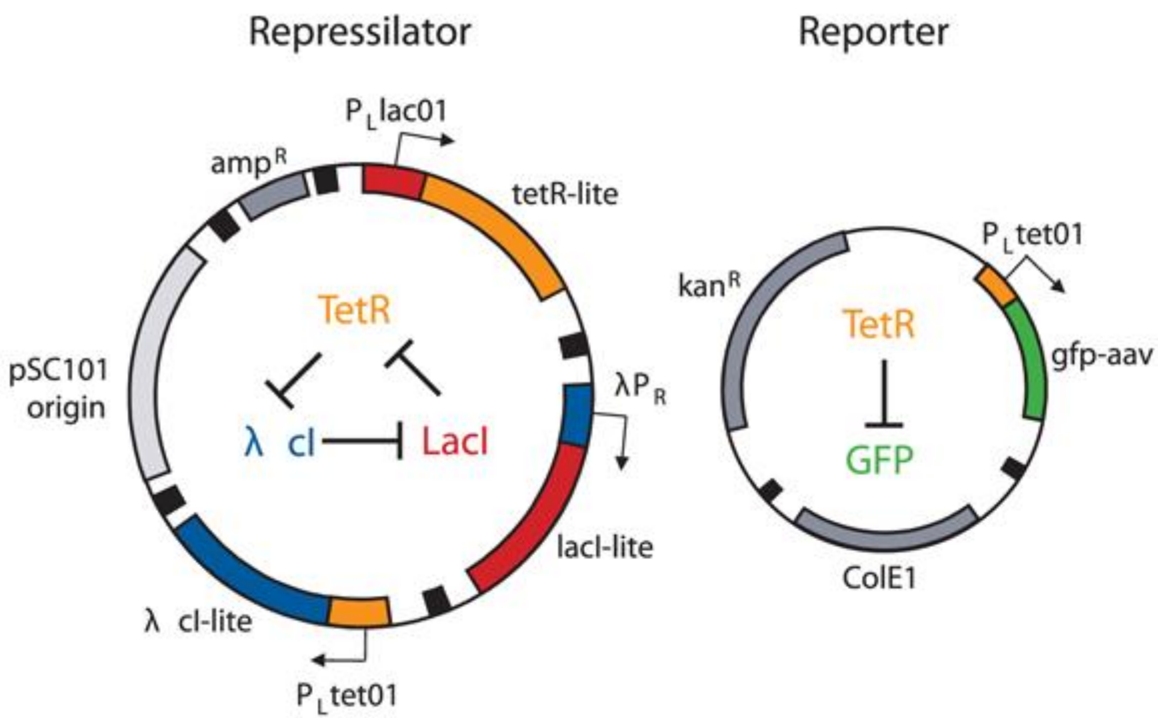


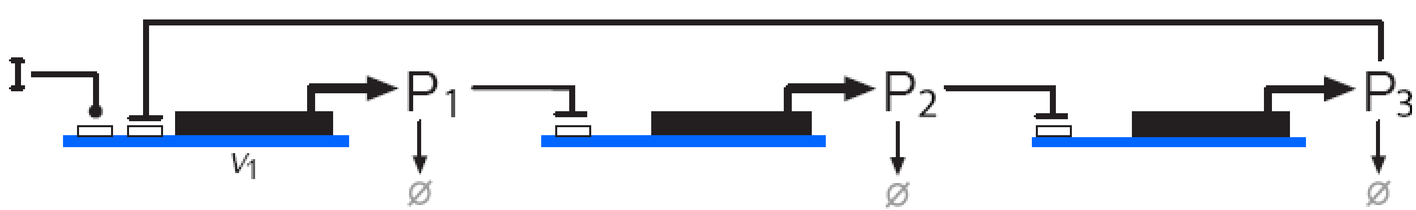




A synthetic oscillatory network of transcriptional regulators Michael B. Elowitz and Stanislas Leibler Nature 403, 335-338(20 January 2000)

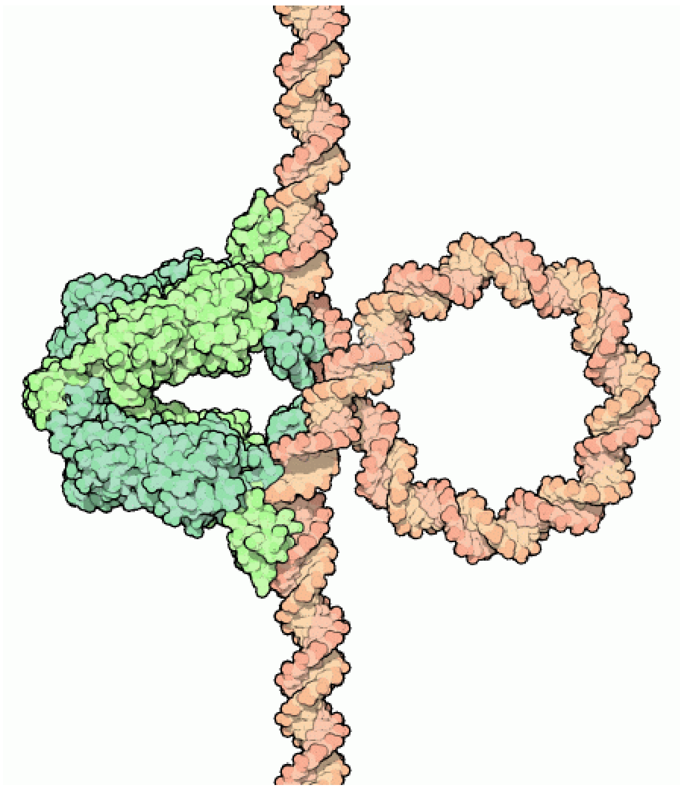
Ring Oscillator: Repressilator



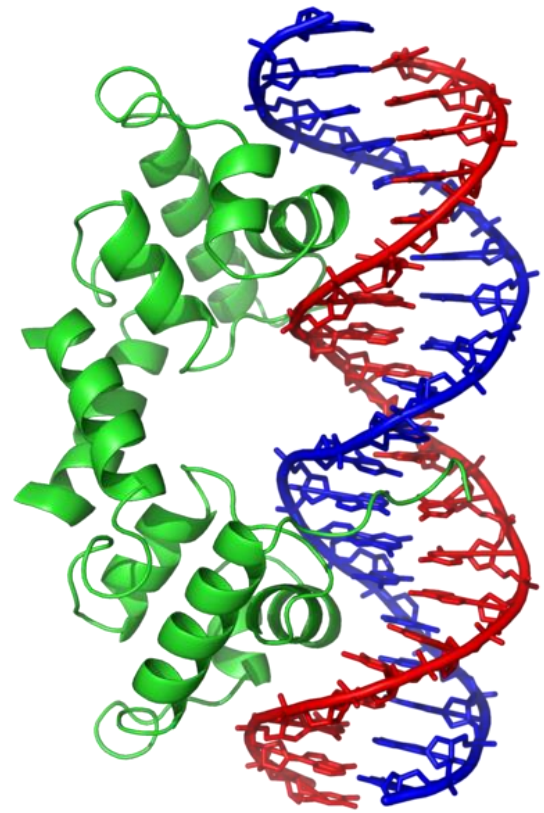


[A synthetic oscillatory network of transcriptional regulators] Michael B. Elowitz and Stanislas Leibler Nature 403, 335-338(20 January 2000)

We'll Talk About Parts in the Next Class



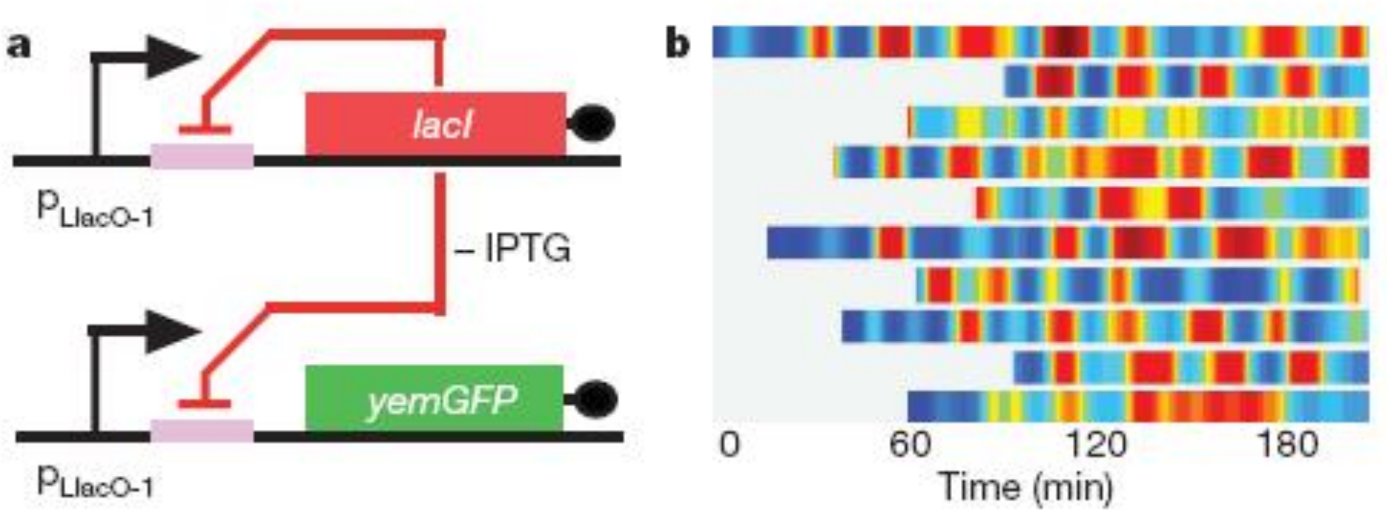
LacI Repressor



Lambda cI Repressor

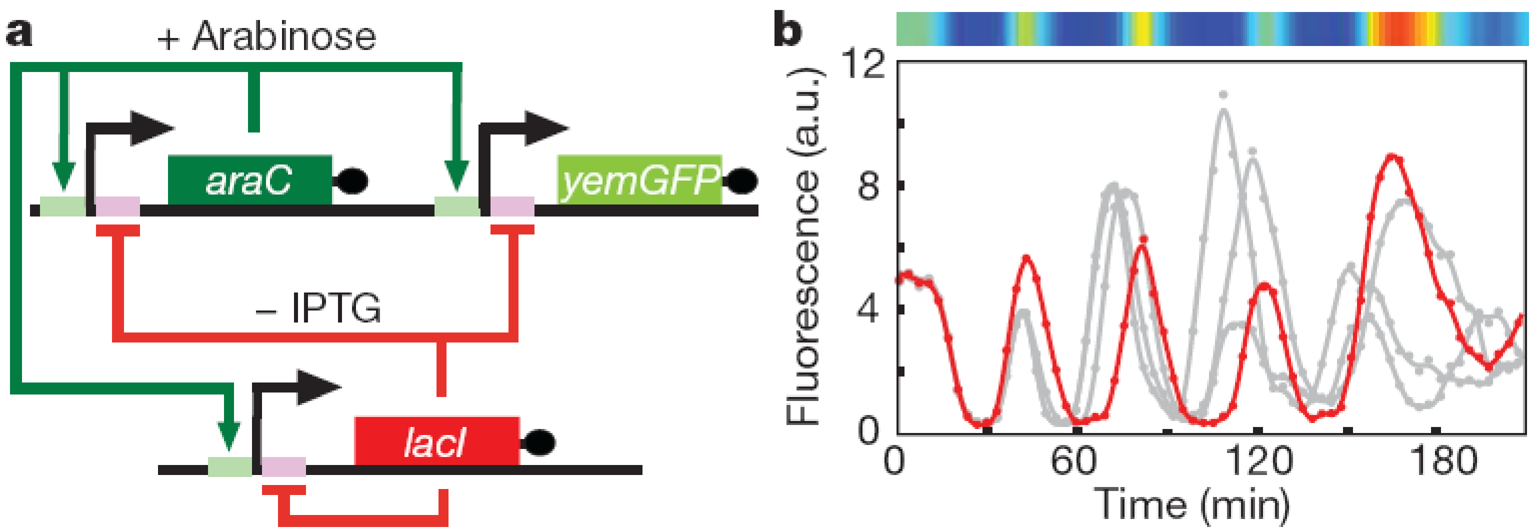
Synthetic Oscillators: Feedback Oscillator

Ideally Oscillators should be studied in single cells.



A fast, robust and tunable synthetic gene oscillator. Jesse Stricker, Scott Cookson, Matthew R. Bennett, William H. Mather, Lev S. Tsimring & Jeff Hasty. *Nature* advance online publication 29 October 2008

Synthetic Oscillators: Relaxation Oscillator



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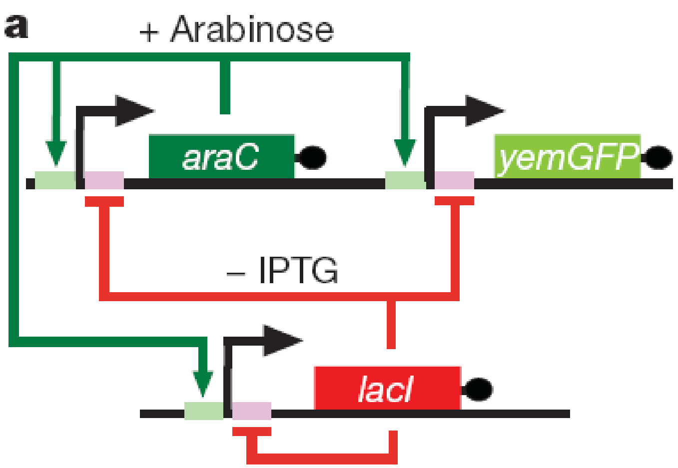
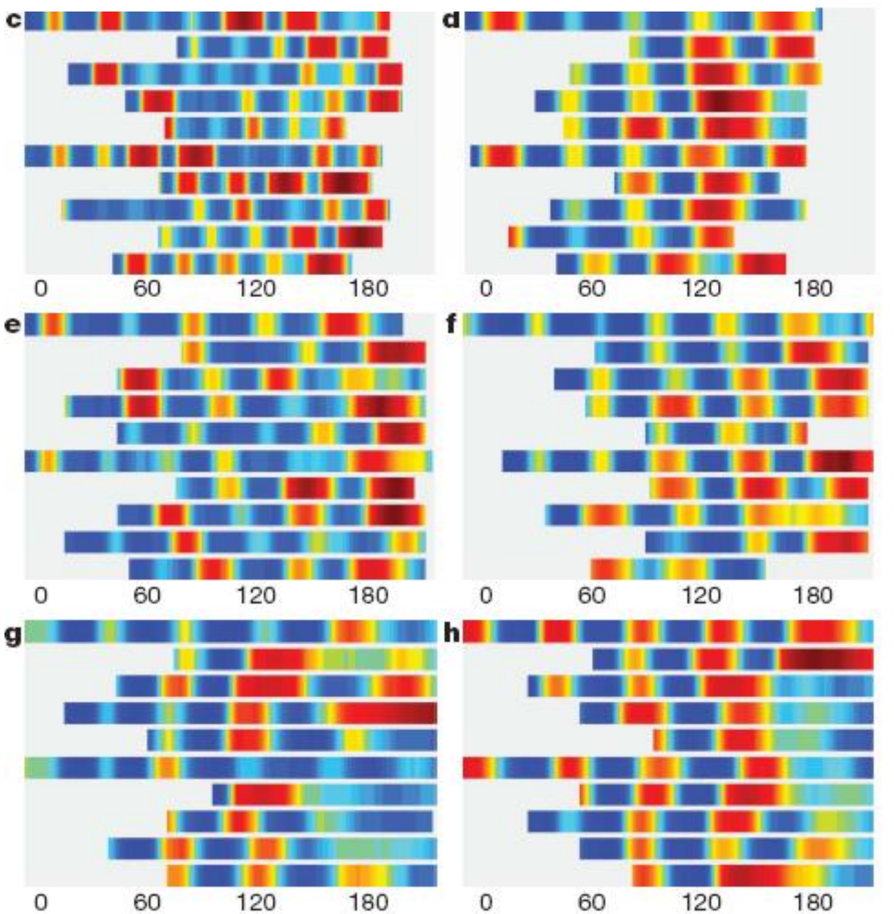
Synthetic Oscillators: Relaxation Oscillator

arbitrary units. **c–h**, Single-cell density map trajectories for various IPTG conditions (**c**, 0 mM IPTG; **d**, 0.25 mM; **e**, 0.5 mM; **f**, 1 mM; **g**, 2 mM; **h**, 5 mM).





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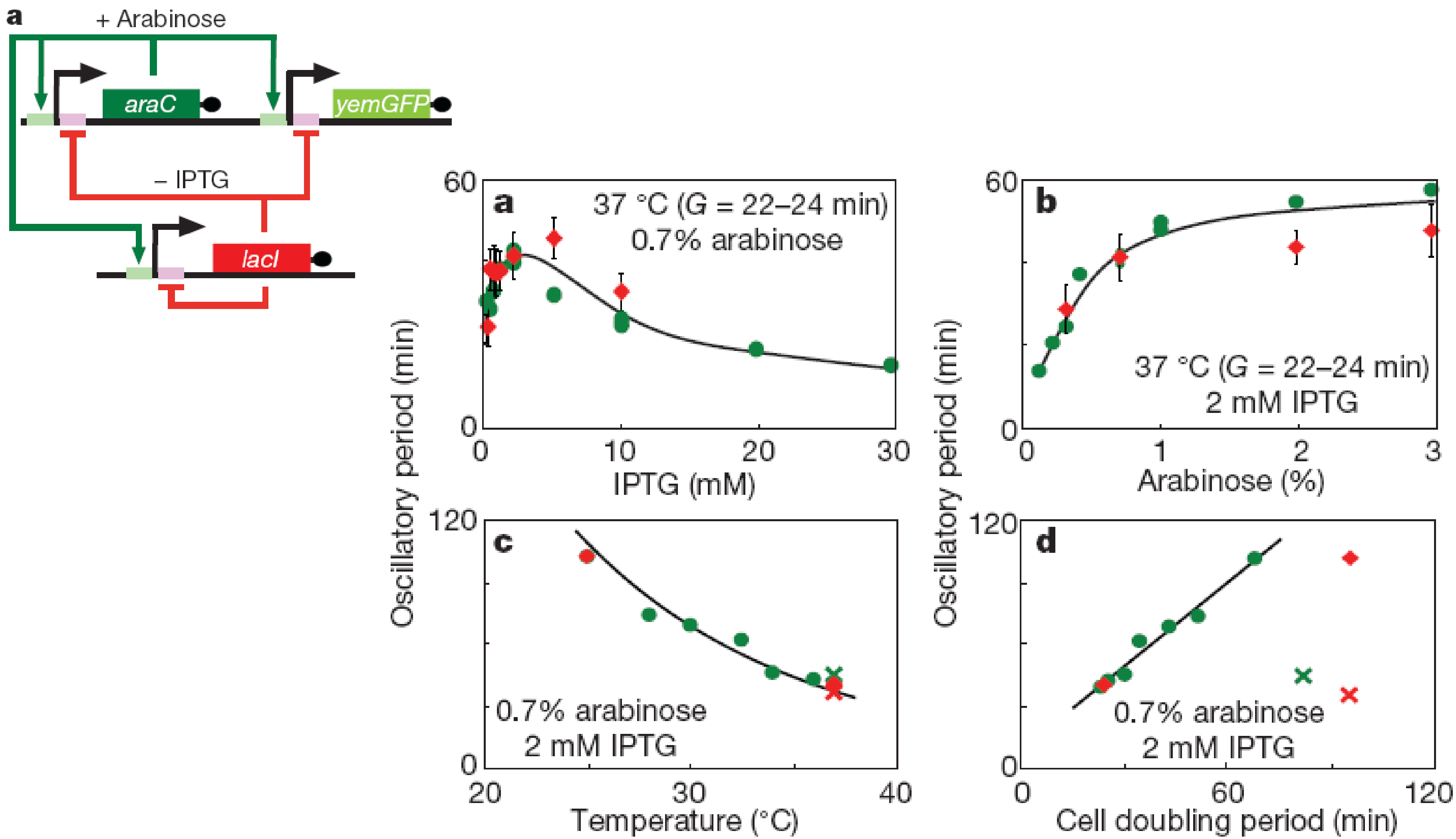
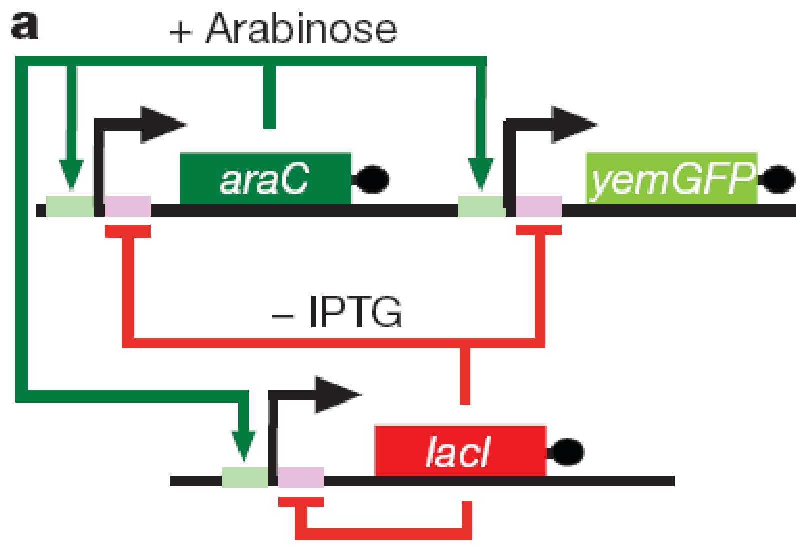


Figure 2 | Robust oscillations. a–c, Oscillatory periods on transects with

Synthetic Oscillators: Movies

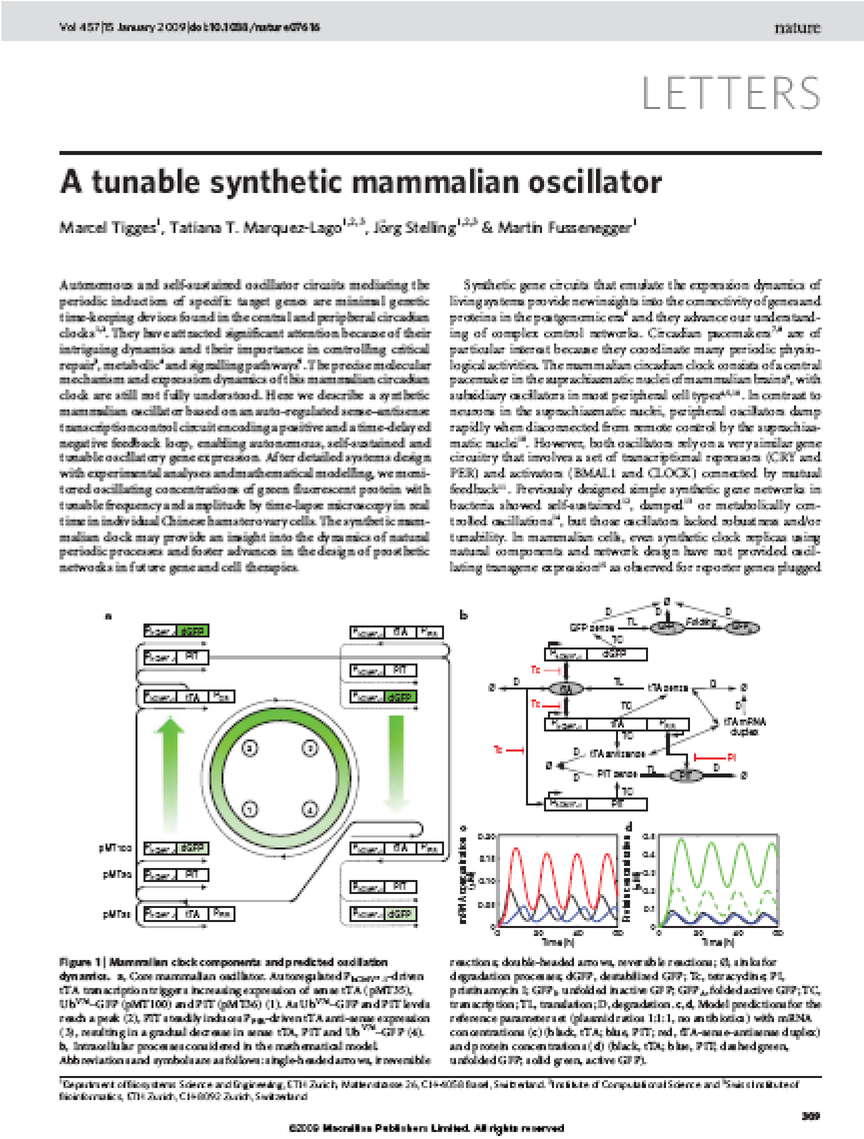


http://www.nature.com/nature/journal/vaop/ncurrent/suppinfo/nature07389.html

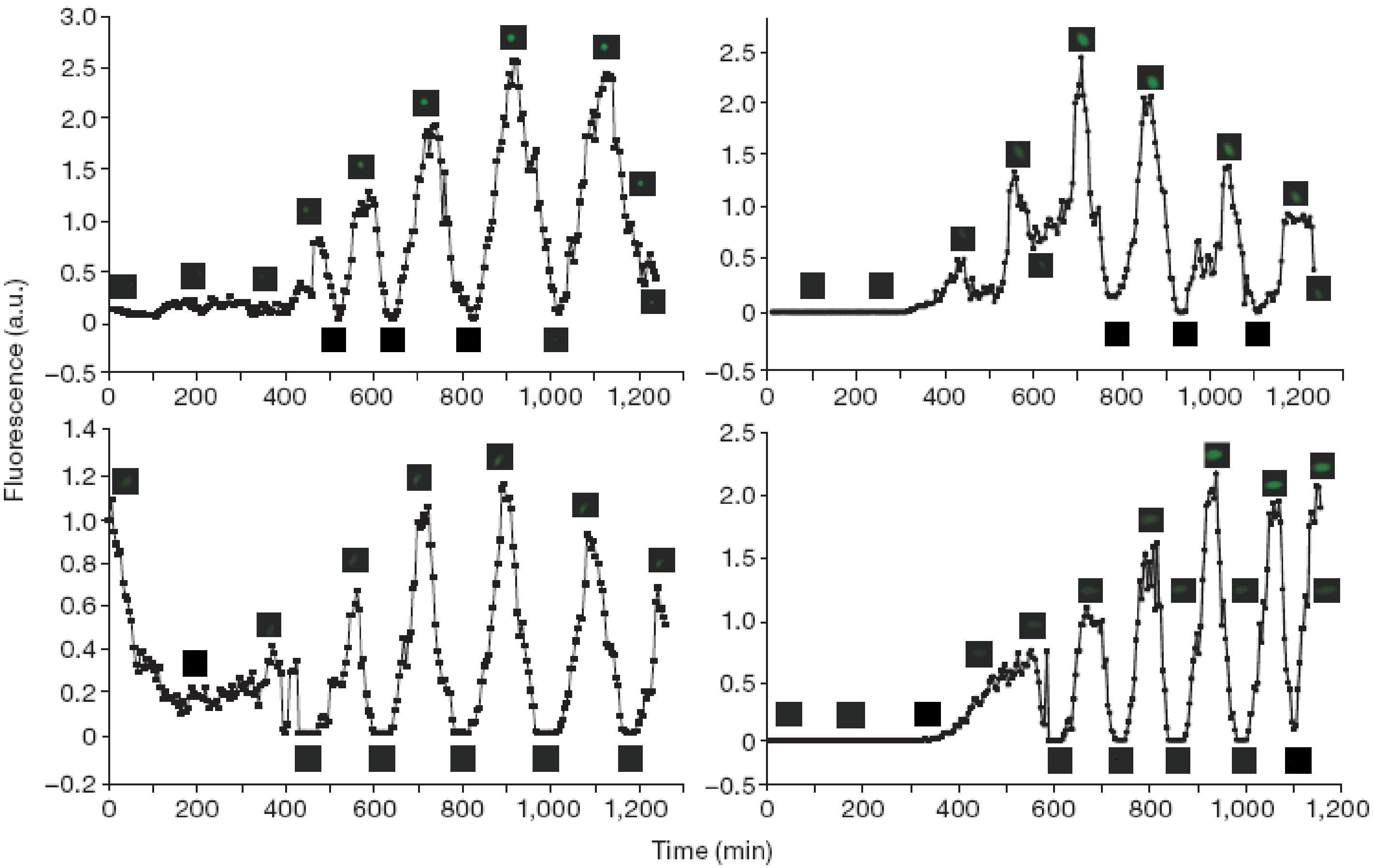
Synthetic Oscillators: Mammalian

Nature **457**, 309-312 (15 January 2009) doi:10.1038/nature07616; Received 26 July 2008; Accepted 4 November 2008

A tunable synthetic mammalian oscillator Marcel Tigges, Tatiana T. Marquez-Lago, Jörg Stelling & Martin Fussenegger



Synthetic Oscillators: Mammalian



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Natural Oscillators

1. Circadian rhythms (eg Drosophila, 24 hour period, feedback oscillator)
2. Ca++ Oscillations
3. Glycolytic Oscillations* (relaxation oscillator)
4. Signaling Pathway Oscillations (P53, ERK, NF-kB)
5. Cell Cycle (relaxation oscillator)
6. Synchronous Rhythmic Flashing Of Fireflies
7. Segmentation during development
8. Many examples of chemical oscillators (mostly relaxation oscillators)
9. ….

* During growth phase on glucose and ethanol, starve yeast of glucose, add cyanide and glucose, the glycolytic pathway will oscillate (NAD/NADH, ATP/ADP)

Buck, John; "Synchronous Rhythmic Flashing of Fireflies. II," *Quarterly Review of Biology*, 63:265, 1988

Oscillatory Systems

Natural Oscillatory Networks

Resilient circadian oscillator revealed in individual cyanobacteria Irina Mihalcescu, Weihong Hsing & Stanislas Leibler, *Nature* **430**, 81-85 (1 July 2004)

Hoffmann, A., Levchenko, A., Scott, M.L. and Baltimore, D. (2002) Science 298, 1241–1245 The IkappaB-NF-kappaB signaling module: temporal control and selective gene activation.

Oscillations and variability in the p53 system. Naama Geva-Zatorsky et al, Molecular Systems Biology **2** Article number: 006.0033 doi:10.1038/msb4100068

Shih YL, Le T, Rothfield L: Division site selection in Escherichia coli involves dynamic redistribution of Min proteins within coiled structures that extend between the two cell poles. Proc Natl Acad Sci USA 2003, 100:7865-7870.

Transduction of Intracellular and Intercellular Dynamics in Yeast Glycolytic Oscillations, Wolf et al, Biophys J, 78, 1145-1153 (2000)

Review: Oscillations in cell biology Karsten Kruse and Frank Julicher, Current Opinion in Cell Biology 2005, 17:20–26

Oscillatory Systems

Synthetic Oscillatory Networks

Elowitz, M. B. & Leibler, S. A synthetic oscillatory network of transcriptional regulators. Nature 403, 335–338 (2000).

Atkinson, M. R., Savageau, M. A., Myers, J. T. & Ninfa, A. J. Development of genetic circuitry exhibiting toggle switch or oscillatory behavior in Escherichia coli. Cell 113, 597–607 (2003).

A synthetic gene–metabolic oscillator Eileen Fun et al, Nature, 435, 118-122 (2005)

An excitable gene regulatory circuit induces transient cellular differentiation, *Nature* **440**, 545-550 (23 March 2006) , Gürol M. Süel et al

Elowitz, M. B. & Leibler, S. A synthetic oscillatory network of transcriptional regulators. Nature 403, 335–338 (2000).

Nature **457**, 309-312 (15 January 2009) doi:10. 1038/nature07616; Received 26 July 2008; Accepted 4 November 2008 **A tunable synthetic mammalian oscillator** Marcel Tigges, Tatiana T. Marquez-Lago, Jörg Stelling & Martin Fussenegger

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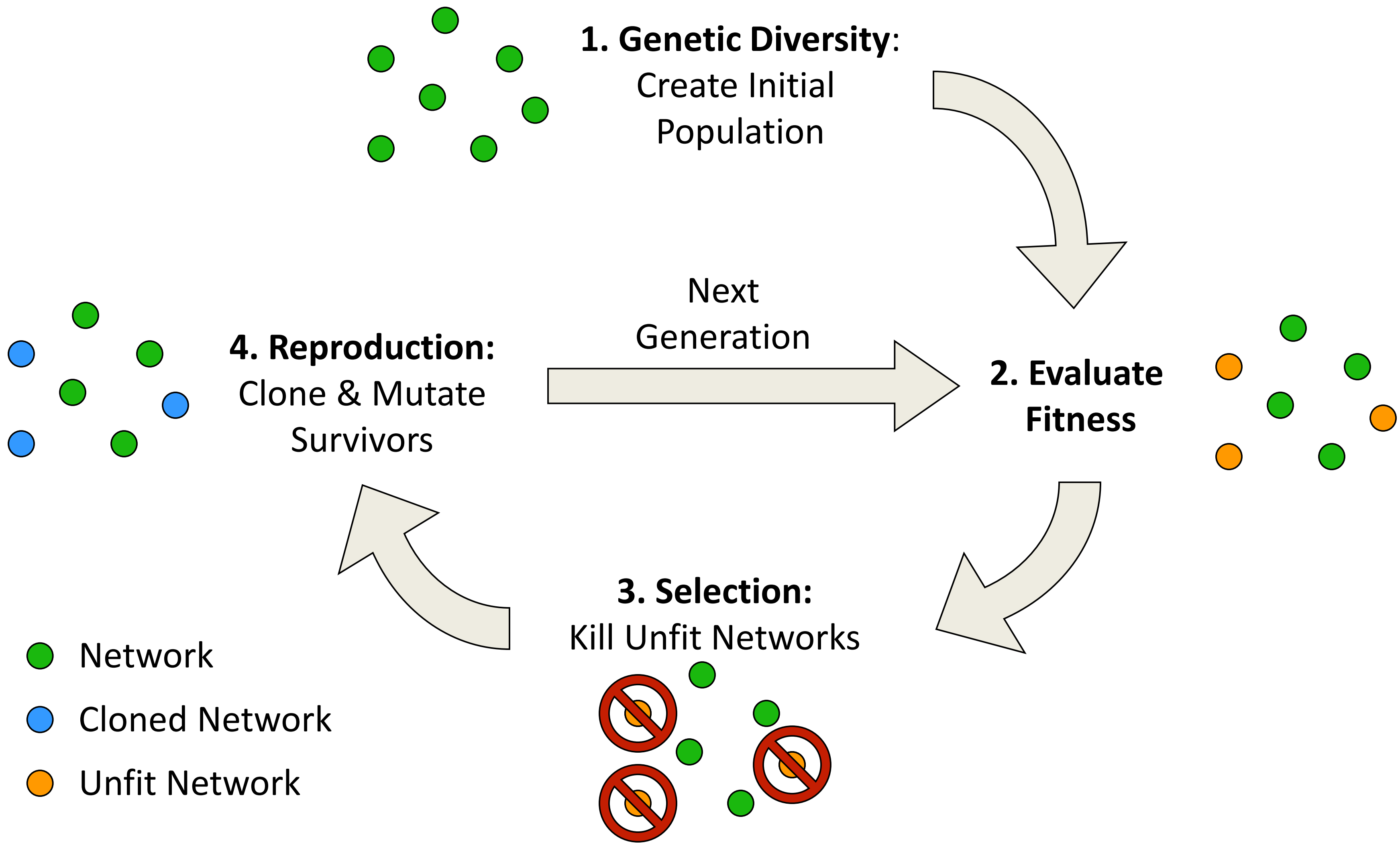
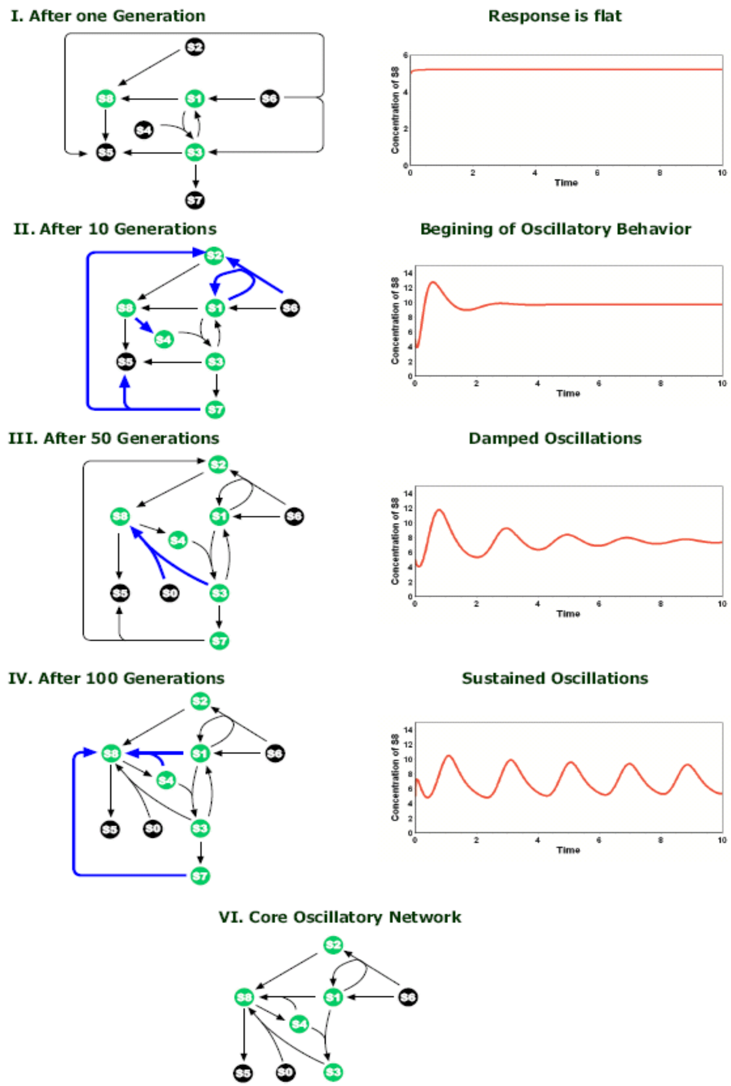
Review: Oscillations in cell biology Karsten Kruse and Frank Julicher, Current Opinion in Cell Biology 2005, 17:20–26

Evolving Oscillators in silico

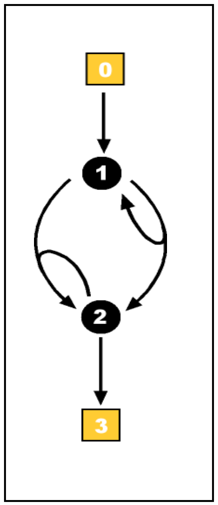


Evolution of an Oscillator

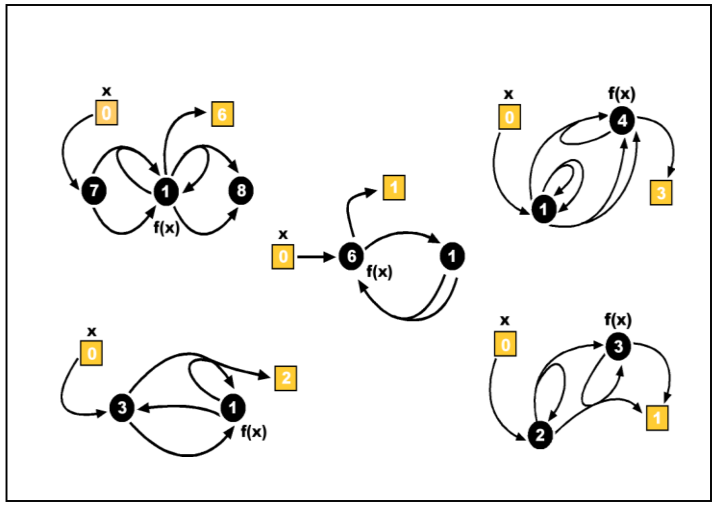


Selection of Evolved Networks

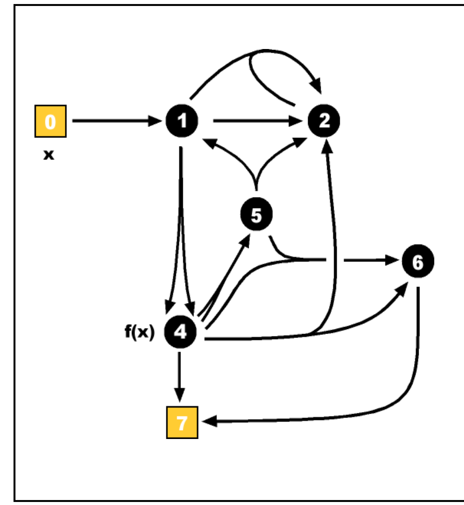
Mathematical Functions



Quadratic



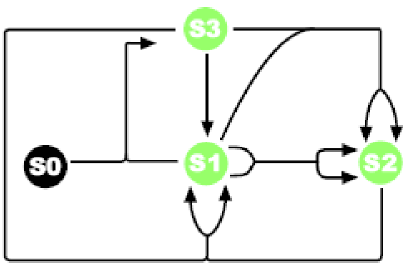
Square Root

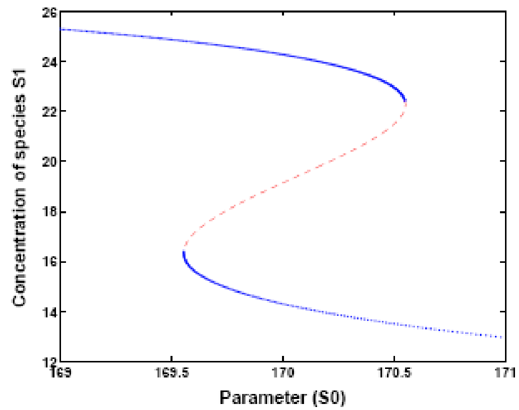


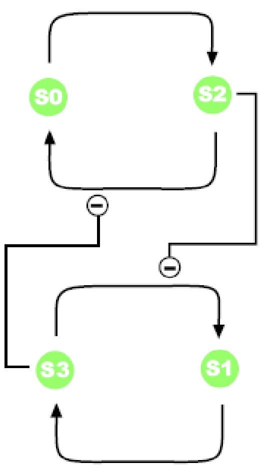
Cubic

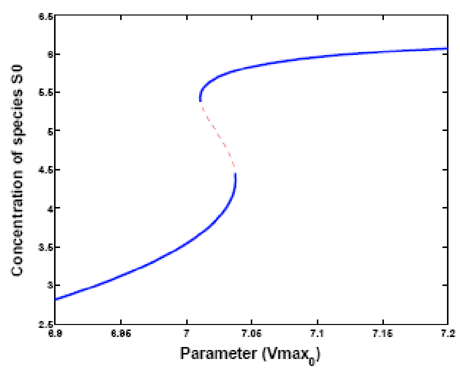
Selection of Evolved Networks

Bistable Networks



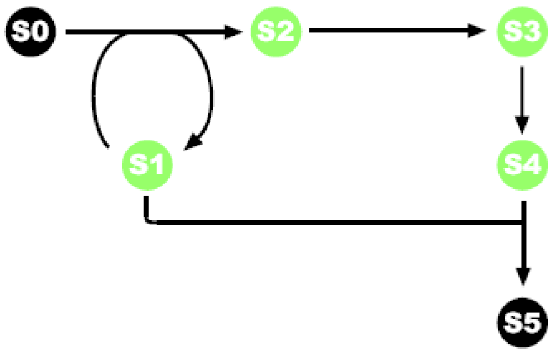


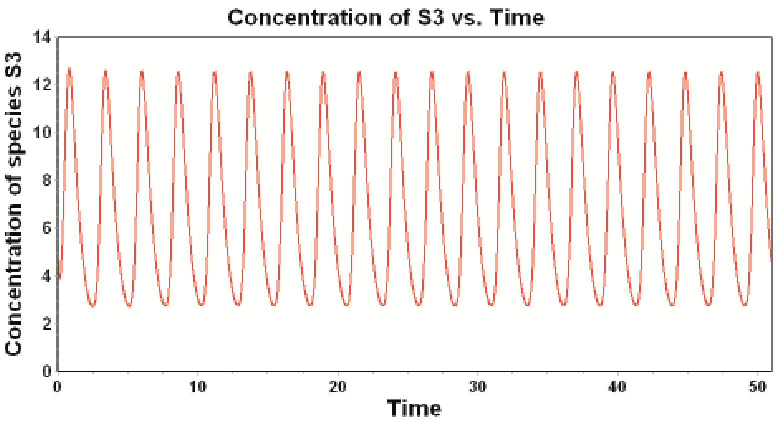




Selection of Evolved Networks

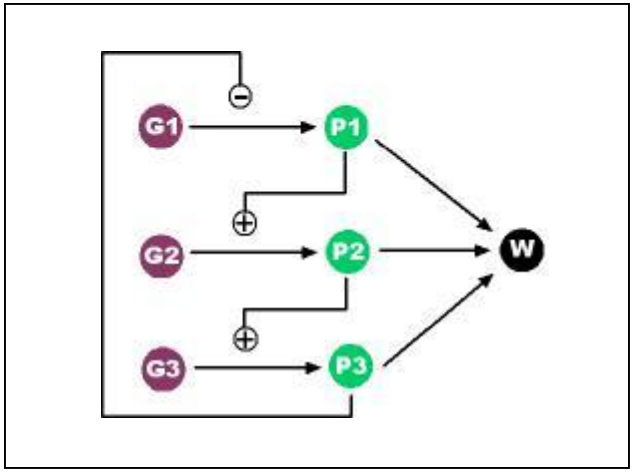
Oscillators

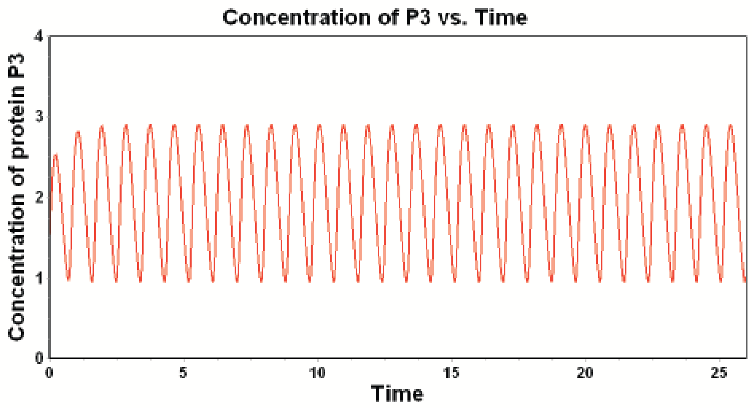


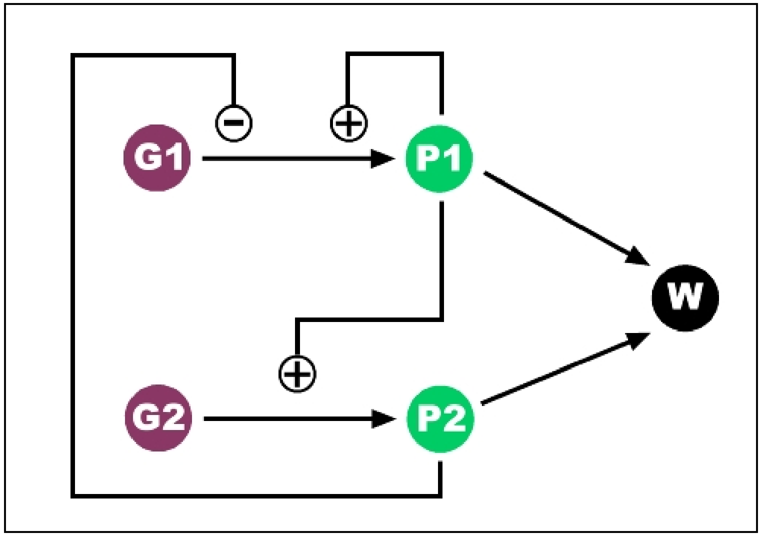


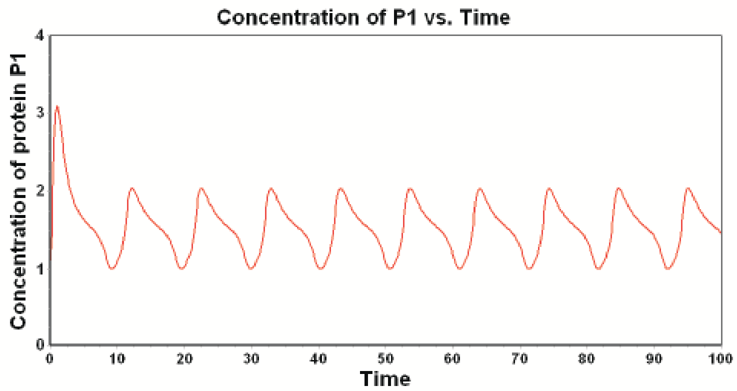
Selection of Evolved Networks

Oscillators



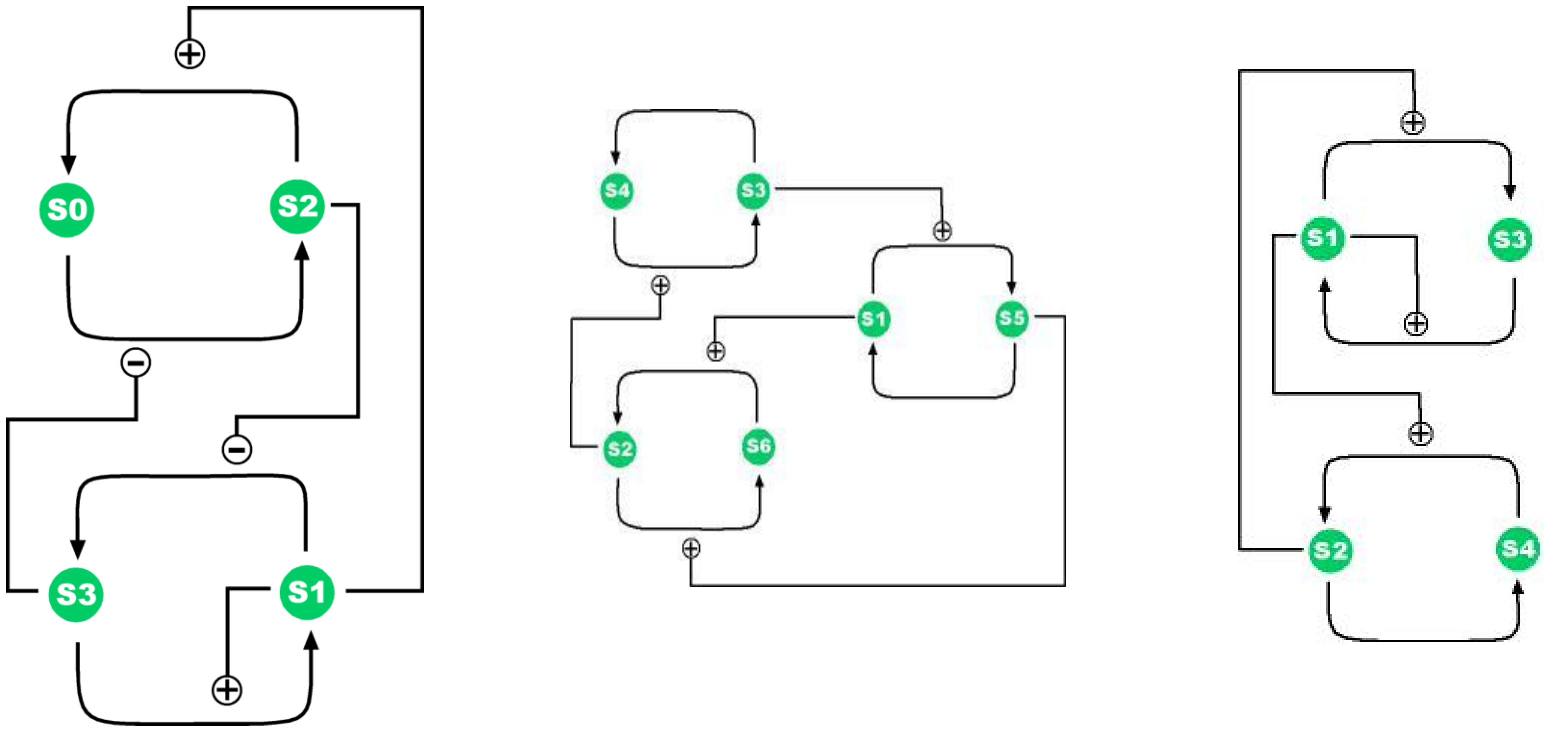






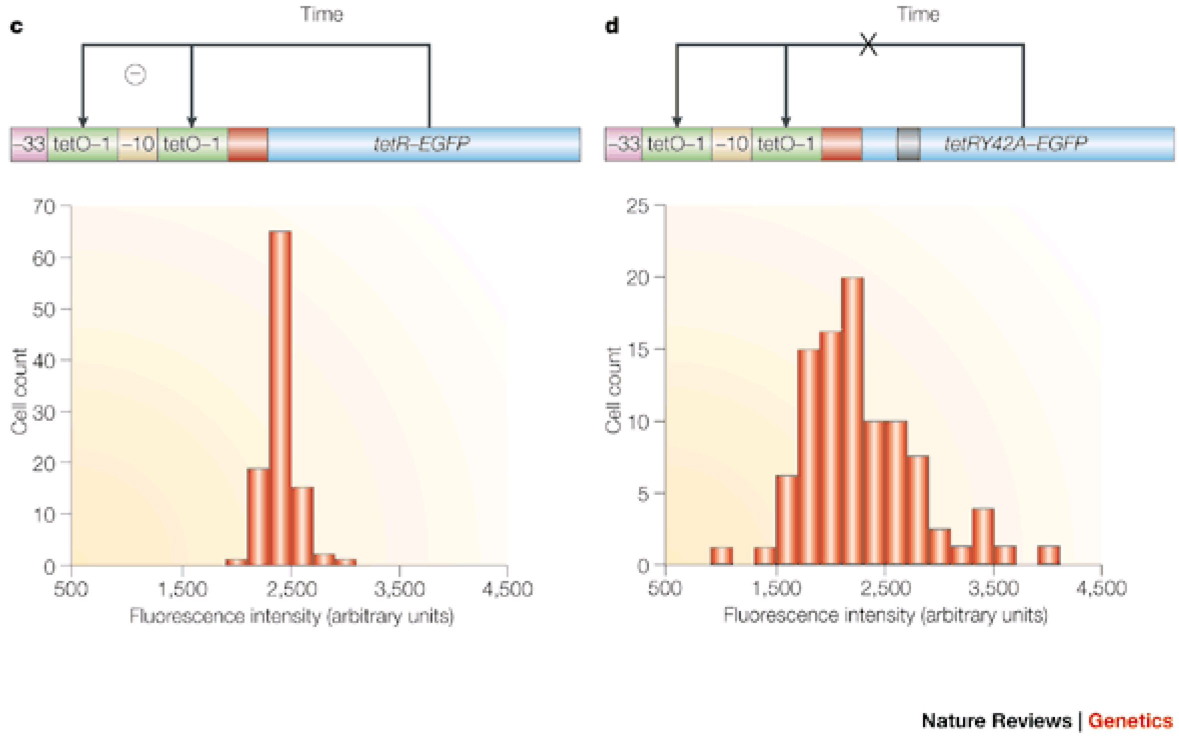
Selection of Evolved Networks

Oscillators



Negative Feedback

Reduction in noise due to negative feedback.



Review: Computational studies of gene regulatory networks: in numero molecular biology Jeff Hasty, David McMillen, Farren Isaacs & James J. Collins
Nature Reviews Genetics 2, 268-279 (April 2001)

Original Paper: Becskei, A. & Serrano, L. Engineering stability in gene networks by autoregulation. Nature 405, 590– 593 (2000).