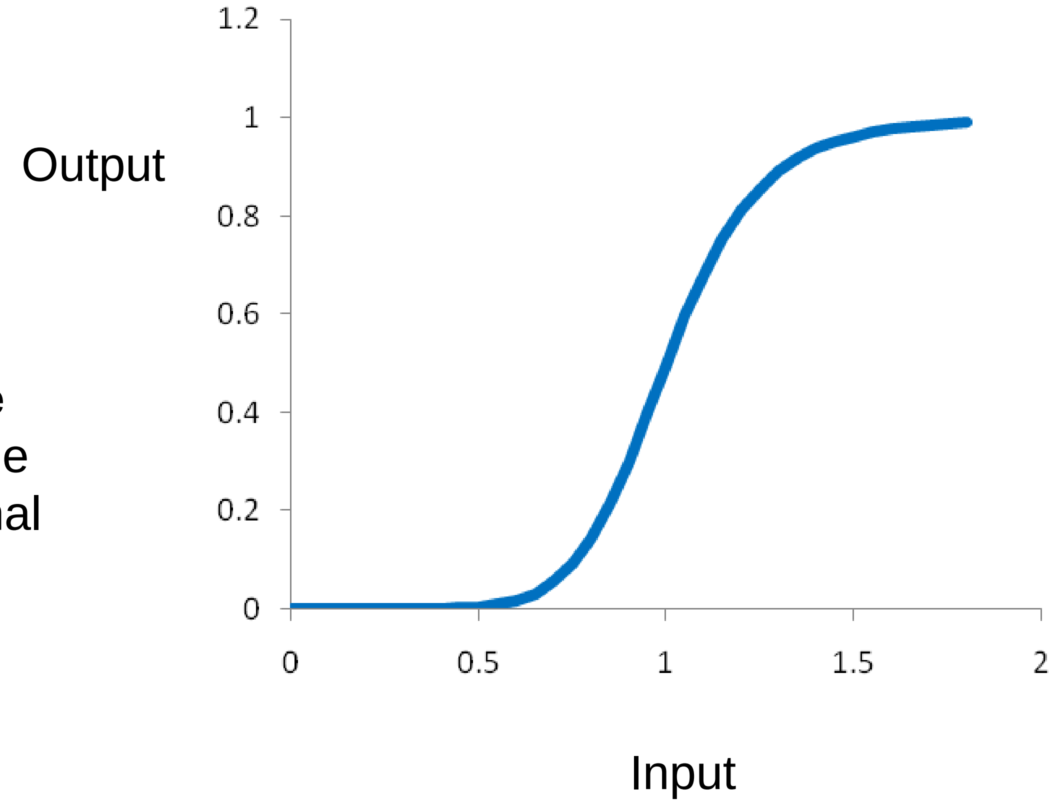
Positive Feedback and Bistable Systems

Non-Hysteretic Switches; Ultrasensitivity; Memoryless Switches



These systems have no ‘memory’, that is, once the input signal is removed, the system returns to its original state.

Hysteretic Switches
Bistability

Bistable systems, in contrast, have memory. That is, when switched to one state or another, these systems remain in that state unless forced to change back.

The light switch is a common example of a bistable system from everyday life.

Hysteretic Switches
Bistability

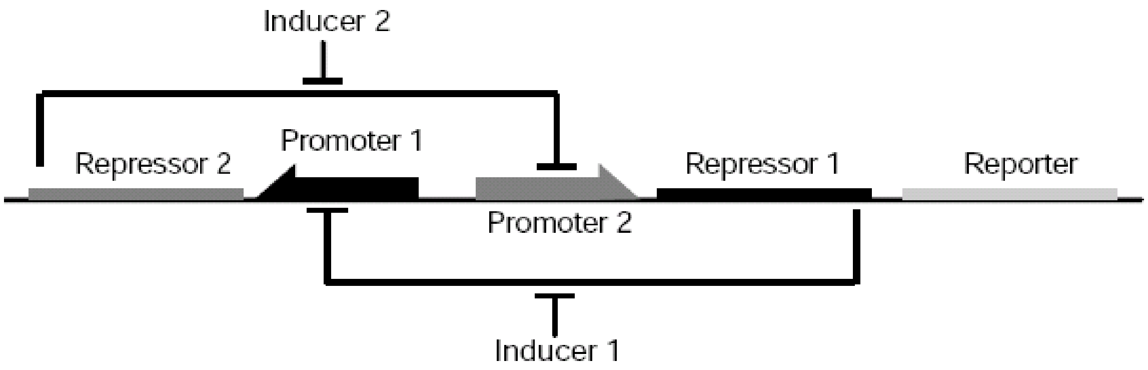
All bistable systems are based around some form of positive feedback loop.

Very common in electronic circuits.

Synthetic Bistable Systems

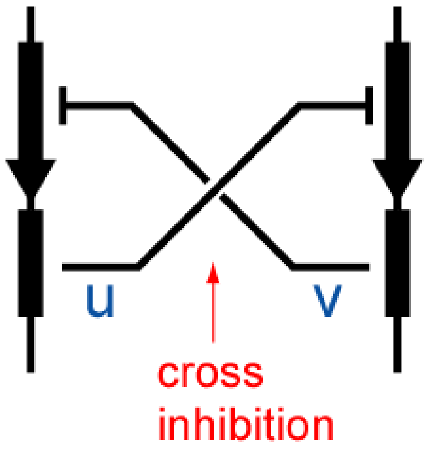
T. S. Gardner, C. R. Cantor, and J. J. Collins. Construction of a genetic toggle switch in Escherichia coli. Nature, 403:339-342, (2000).

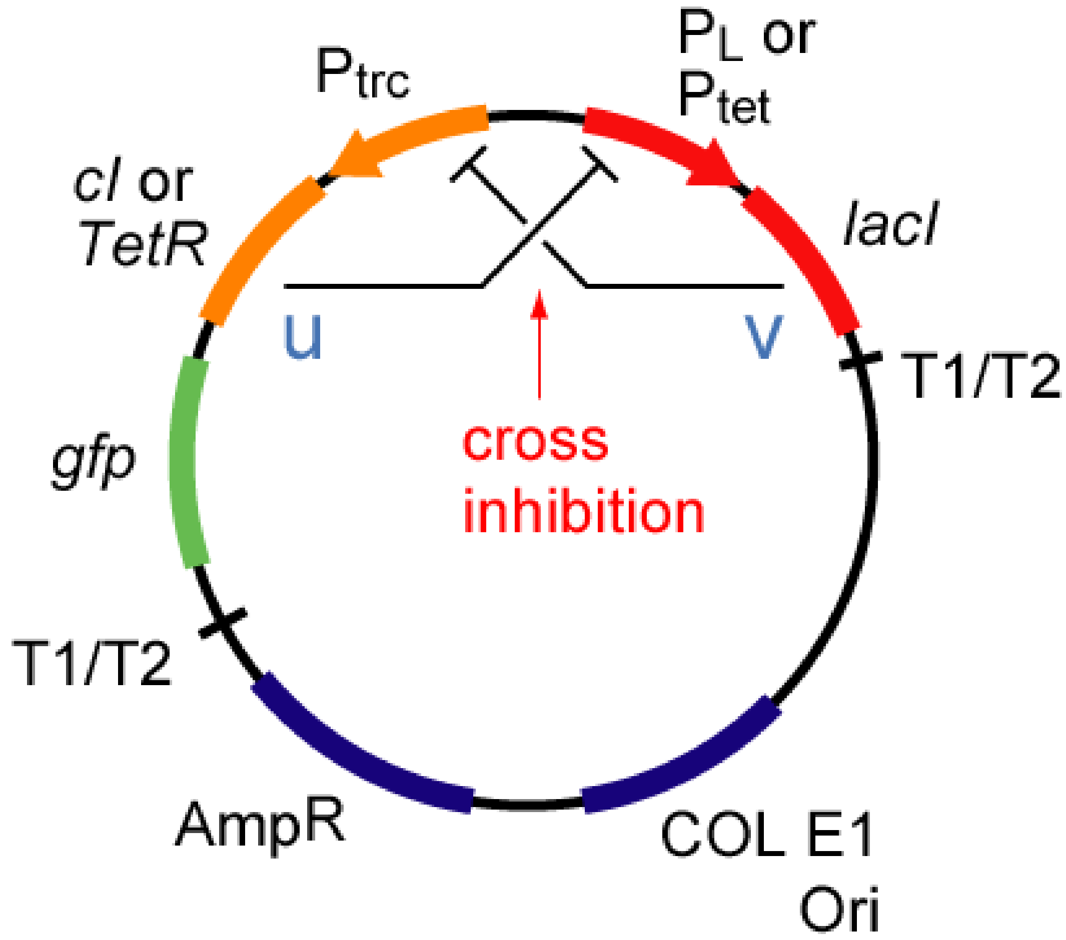
Toggle Switch



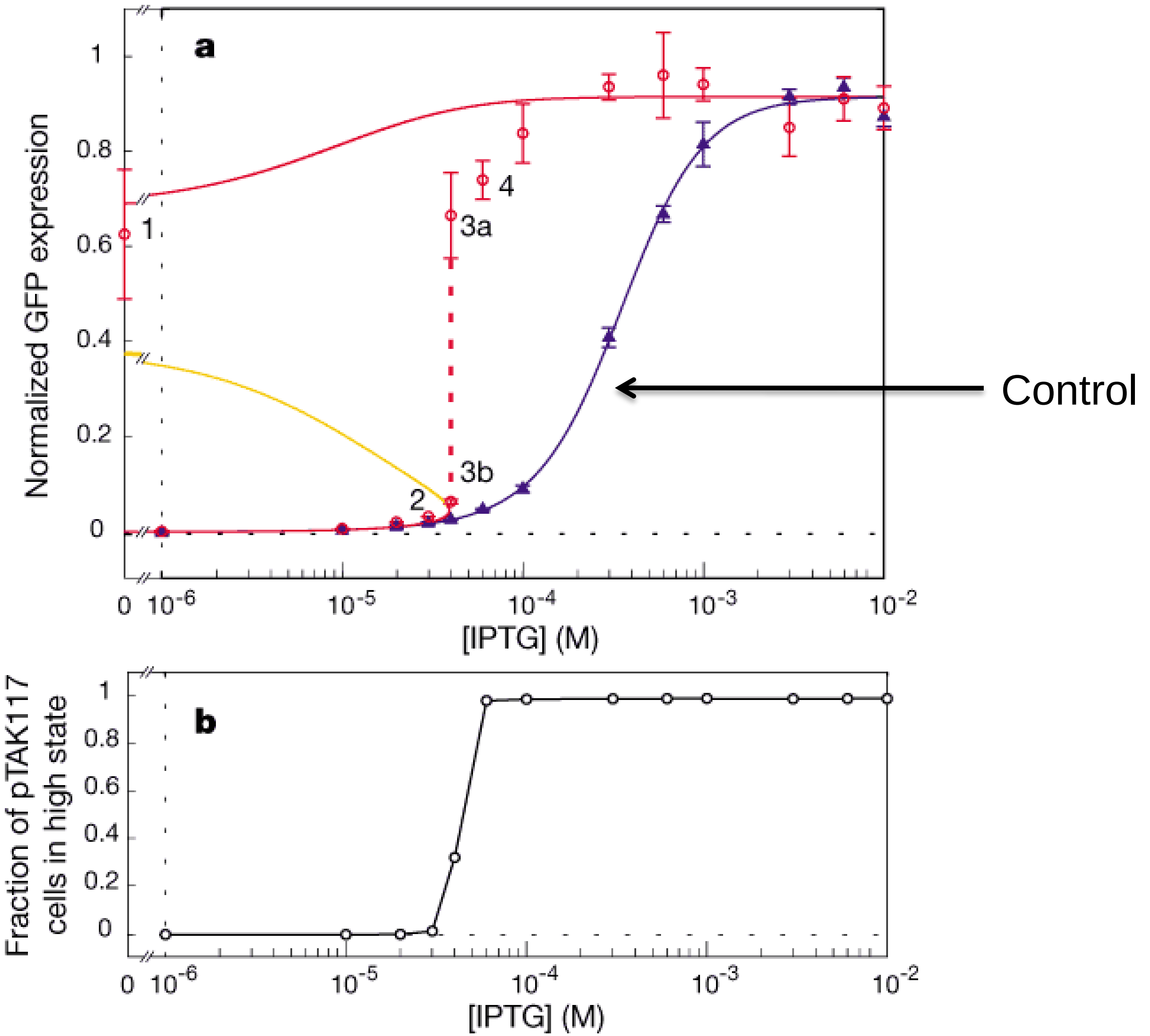
A number of variants were made but a group of successful constructs were made from LacI and CI lambda phage repressor. The toggle switch only requires two genes.

Toggle Bistable Systems

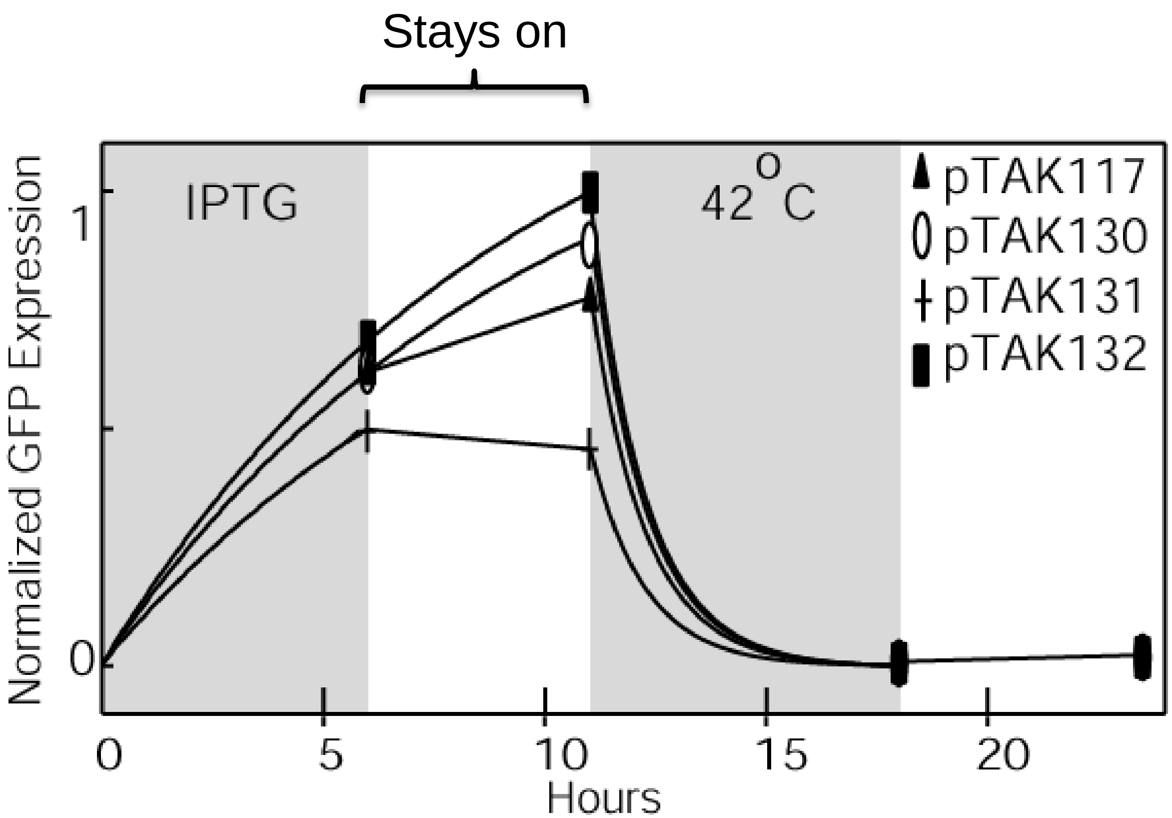




Bistable Systems



Bistable Systems

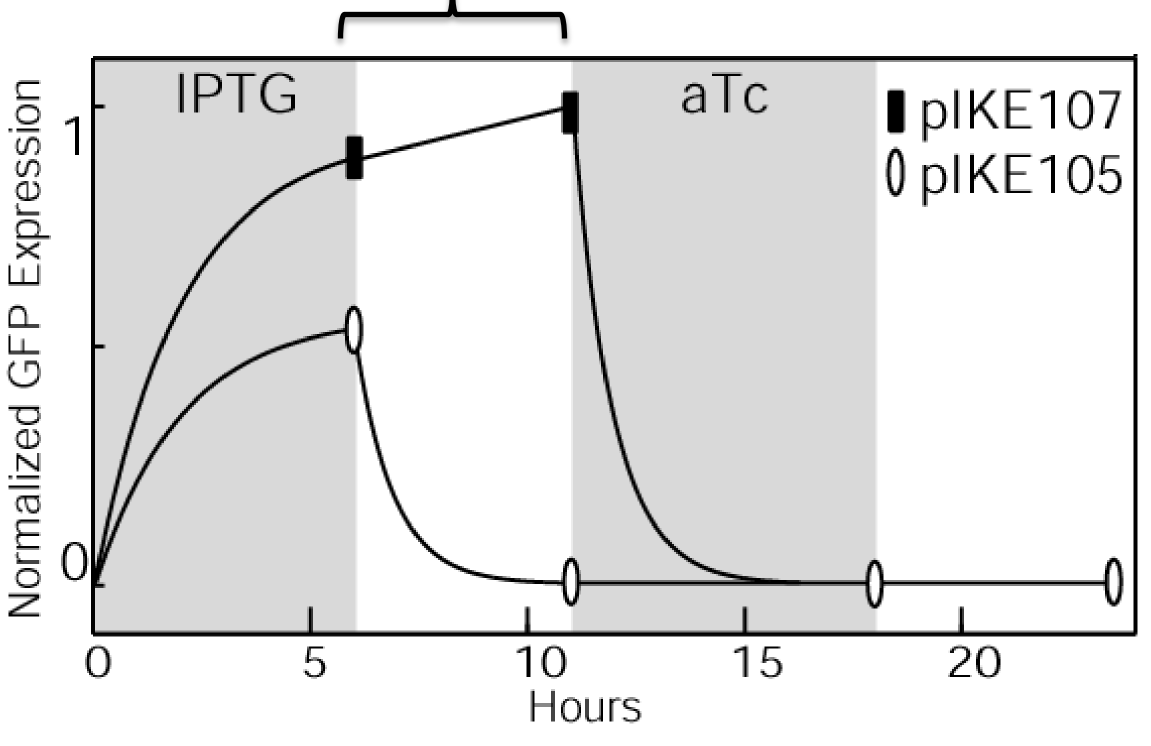


IPTG was used to switch the circuit on.

They used a temperature sensitive repressor (cI) to knock the switch back down (42C).

Bistable Systems

Empty Circle Line Goes Off



One that didn't work – repression too weak on one arm of the switch.

Bistable Systems – Alternative Design

Rational design of memory in eukaryotic cells

Caroline M. Ajo-Franklin,[1,3,4] David A. Drubin,[1,3] Julian A. Eskin,[1] Elaine P.S. Gee,[2] Dirk Landgraf,[1] Ira Phillips,[1,5] and Pamela A. Silver[1,6]

[1]Department of Systems Biology, Harvard Medical School, Boston, Massachusetts 02115, USA; [2]Harvard University Program in Biophysics, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

GENES & DEVELOPMENT 21:2271–2276

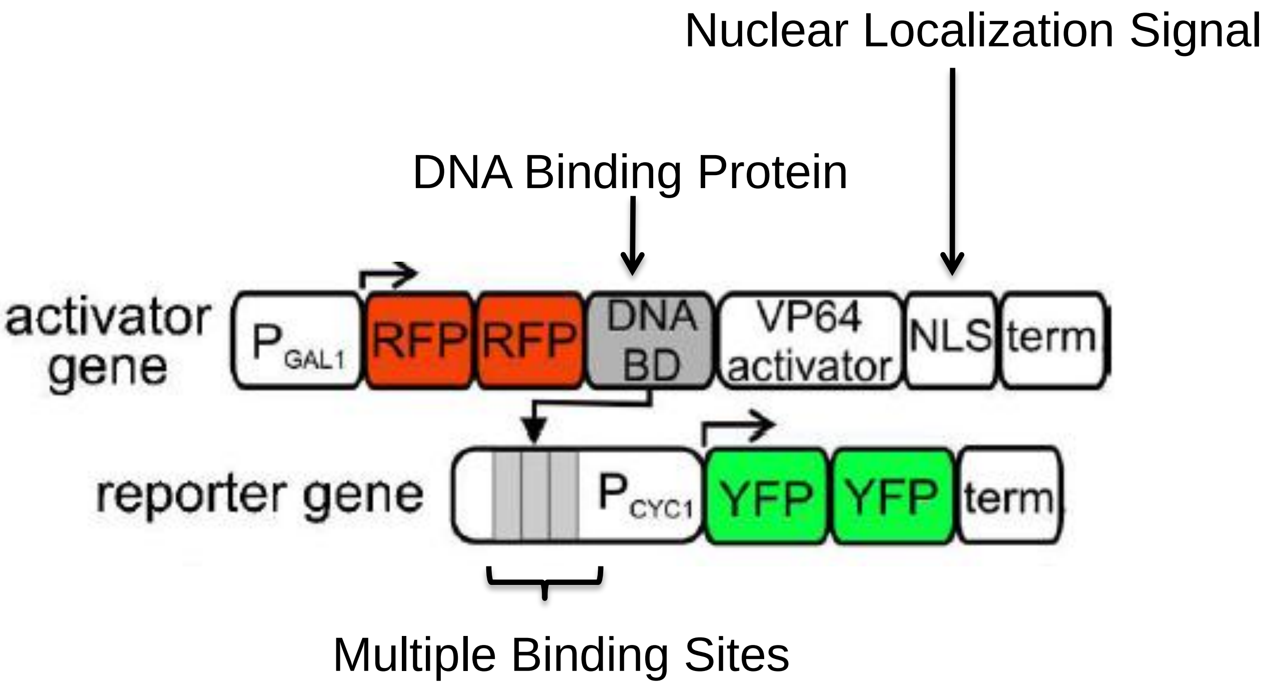
(2007)

The ability to logically engineer novel cellular functions promises a deeper understanding of biological systems. Here we demonstrate the rational design of cellular memory in yeast that employs autoregulatory transcriptional positive feedback. We built a set of transcriptional activators and quantitatively characterized their effects on gene expression in living cells. Modeling in conjunction with the quantitative characterization of the activator-promoter pairs accurately predicts the behavior of the memory network. This study demonstrates the power of taking advantage of components with measured quantitative parameters to specify eukaryotic regulatory networks with desired properties.

Supplemental material is available at http://www.genesdev.org.

Received June 22, 2007; revised version accepted July 27, 2007.

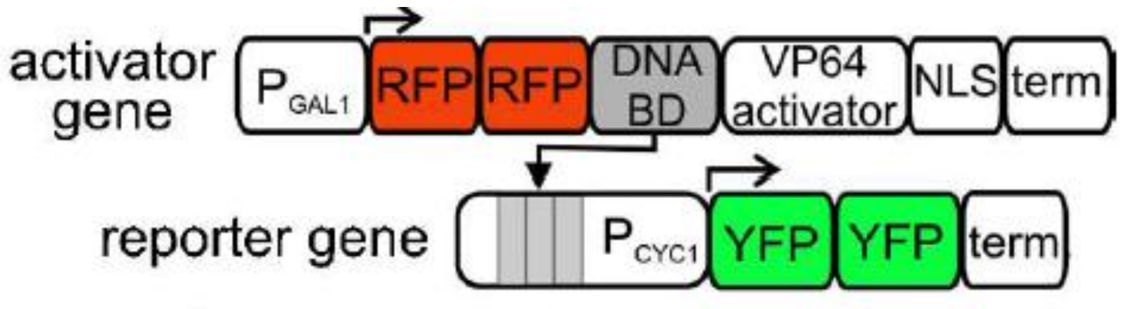
Bistable Systems – Alternative Design

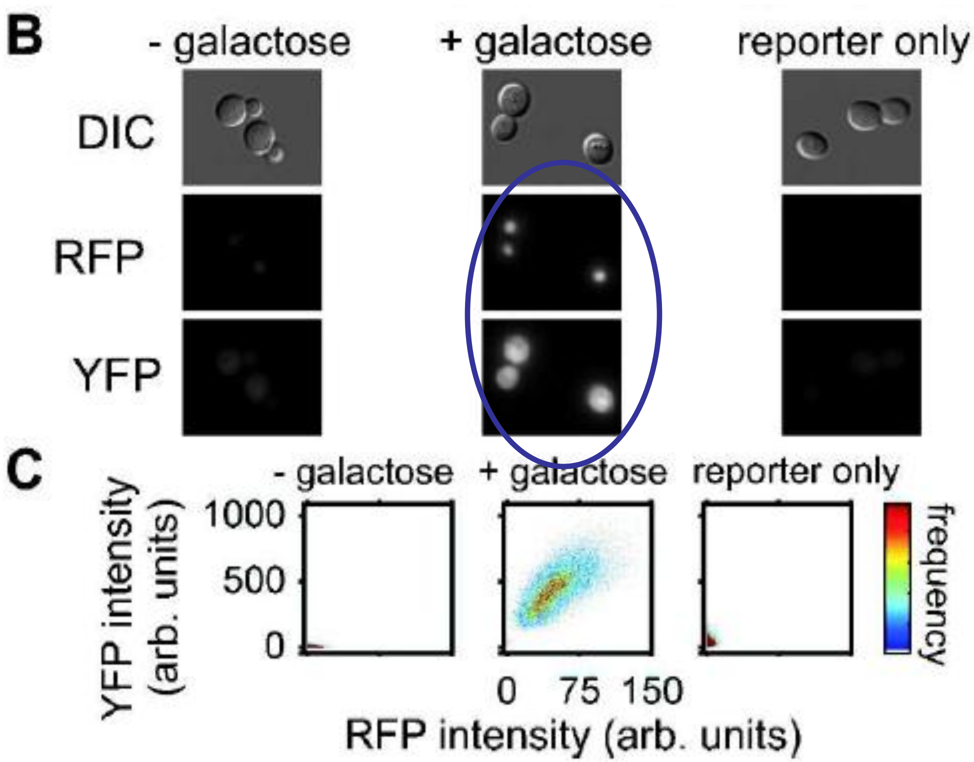


VP64 is a virus derived protein domain that is used to enhance the binding efficiency of the DNA binding protein.

Bistable Systems – Alternative Design

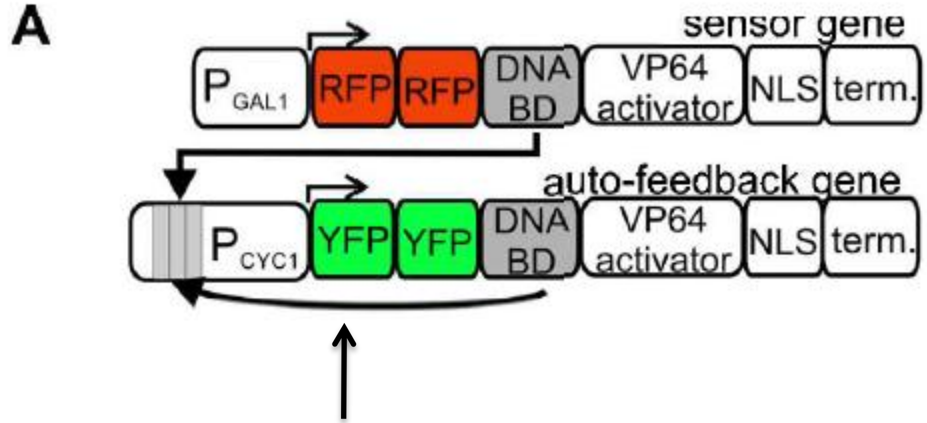
Controls



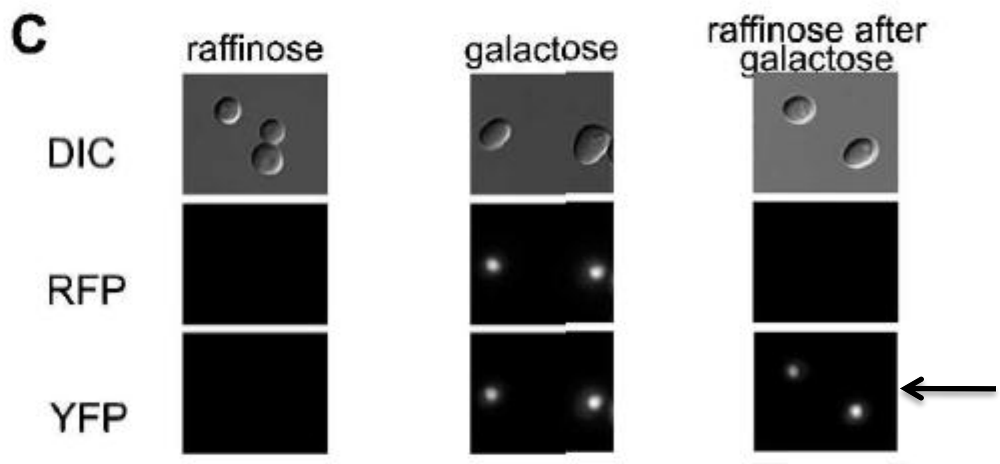


Bistable Systems – Alternative Design

With Positive Feedback



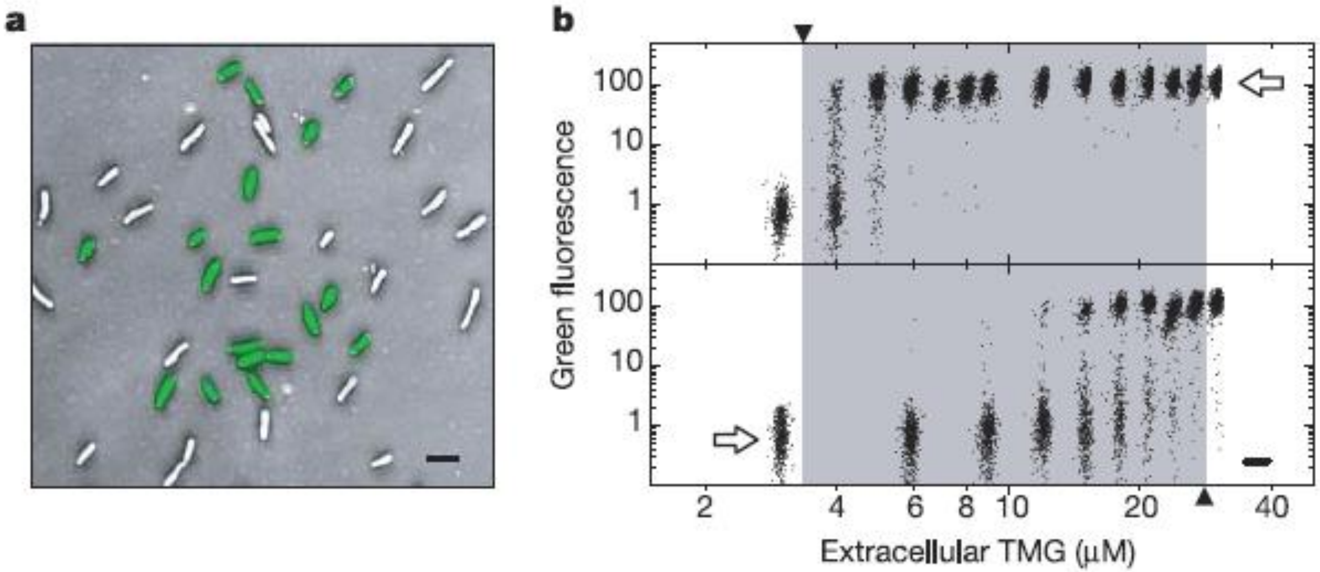
Positive Feedback



Remains on

Natural Examples

Lac Operon



Green fluorescence measures the level of TMG in the cytoplasm and therefore indirectly the lac operon expression level in the Lac operon.
TMG is a lactose analog that can be transported by the permease but isn't metabolized.

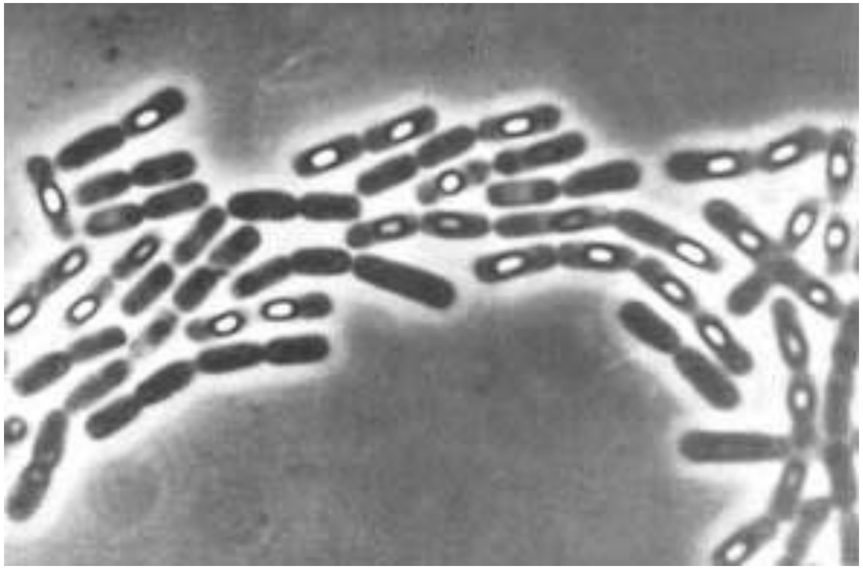
Multistability in the lactose utilization network of Escherichia coli, Ertugrul M. Ozbudak et al, Nature, vol 247, (2004), 737-740

Natural Examples

Sin (**S**porlation **In**hibition) Operon

Sporulation is an expensive and dramatic response to stress.

The sin operon is central to the timing and early dynamics of sporulation. The circuit that makes the final decision is bistable.

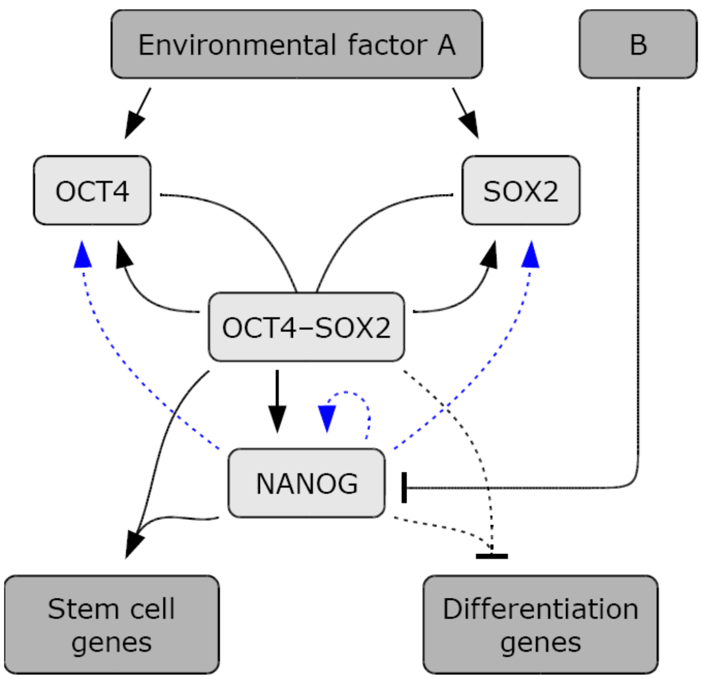


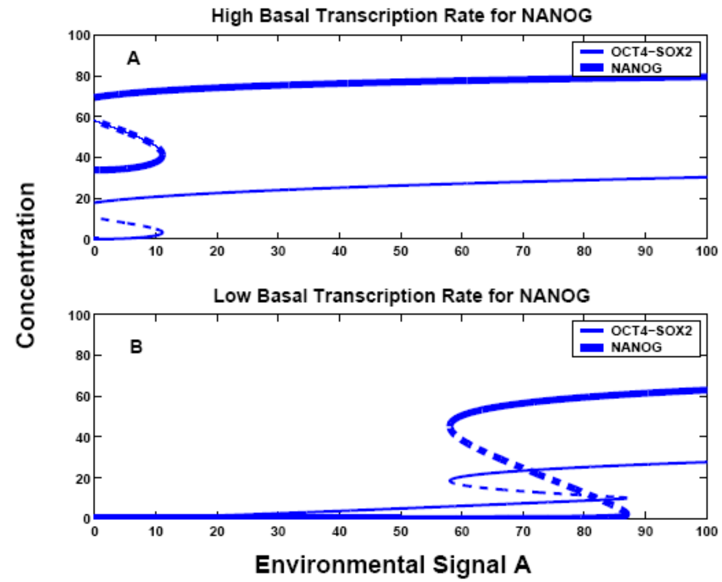
http://www2.kenyon.edu

The *Bacillus subtilis sin* Operon
Christopher A. Voigt, Denise M. Wolf and Adam P. Arkin
Genetics, Vol. 169, 1187-1202, March 2005

Natural Examples

Stem Cell Fate Decision Circuit





Over-expression of NANOG due to “leaky transcription”. NANOG latches onto the OCT4/SOX2 genes and keeps the switch in the **ON** state.

Transcriptional Dynamics of the Embryonic Stem Cell Switch
Chickarmane et al. (2006), PLoS Comp Bio, 2(9): e123
doi:10.1371/journal.pcbi.0020123

Natural Examples

Cell Cycle

A bistable circuit is also at the core of the cell cycle. Part of its function is to prevent the cycle from slipping back to interphase.

Network dynamics and cell physiology
John J. Tyson, Kathy Chen and Bela Novak
Nature Reviews Molecular Cell Biology, 2, 908-916 (2001)

Hysteresis meets the cell cycle Mark J. Solomon, Proc Natl Acad Sci U S A. 2003 February 4; 100(3): 771–772.

Bistable Systems

Natural Bistable Networks

E. M. Ozbudak, M. Thattai, H. N. Lim, B. I. Shraiman, and A. Van Oudenaar-den. Multistability in the lactose utilization network of Escherichia coli. Nature, 427:737-740, (2004).

W. Xiong and J. E. Ferrell. A positive-feedback-based bistable `memory module' that governs a cell fate decision. Nature, 426:460-465, 2003.

Multistability in the lactose utilization network of Escherichia coli, Ertugrul M. Ozbudak et al, Nature, vol 247, (2004), 737-740

Review: Phenotypic variation in bacteria: the role of feedback regulation Nature Reviews Microbiology 4, 259-271 (April 2006) , Wiep Klaas Smits et al.

Synthetic Bistable Networks

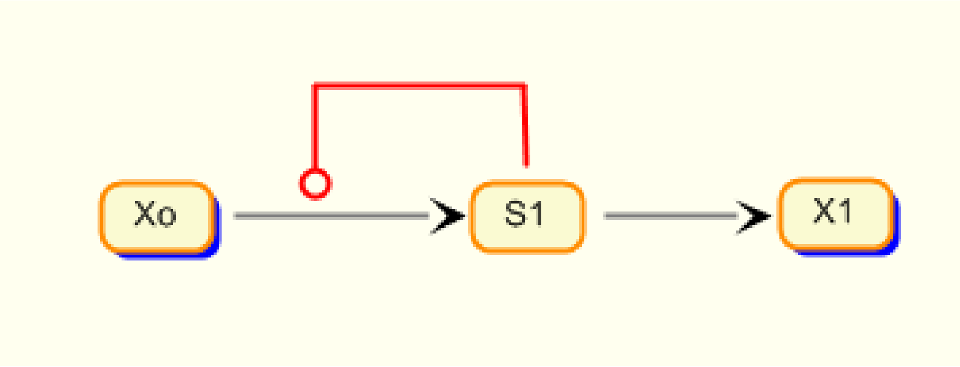
T. S. Gardner, C. R. Cantor, and J. J. Collins. Construction of a genetic toggle switch in Escherichia coli. Nature, 403:339-342, (2000).

Prediction and measurement of an autoregulatory genetic module Farren J. Isaacs, Jeff Hasty, Charles R. Cantor, and J. J. Collins, PNAS, 100:7714 (2003)

Ajo-Franklin et al. Rational design of memory in eukaryotic cells. Genes and Dev. 21:2271-2276 (2007)

An engineered epigenetic transgene switch in mammalian cells. *Nature Biotechnology* **22**, 867 - 870 (2004) , Beat P Kramer et al.

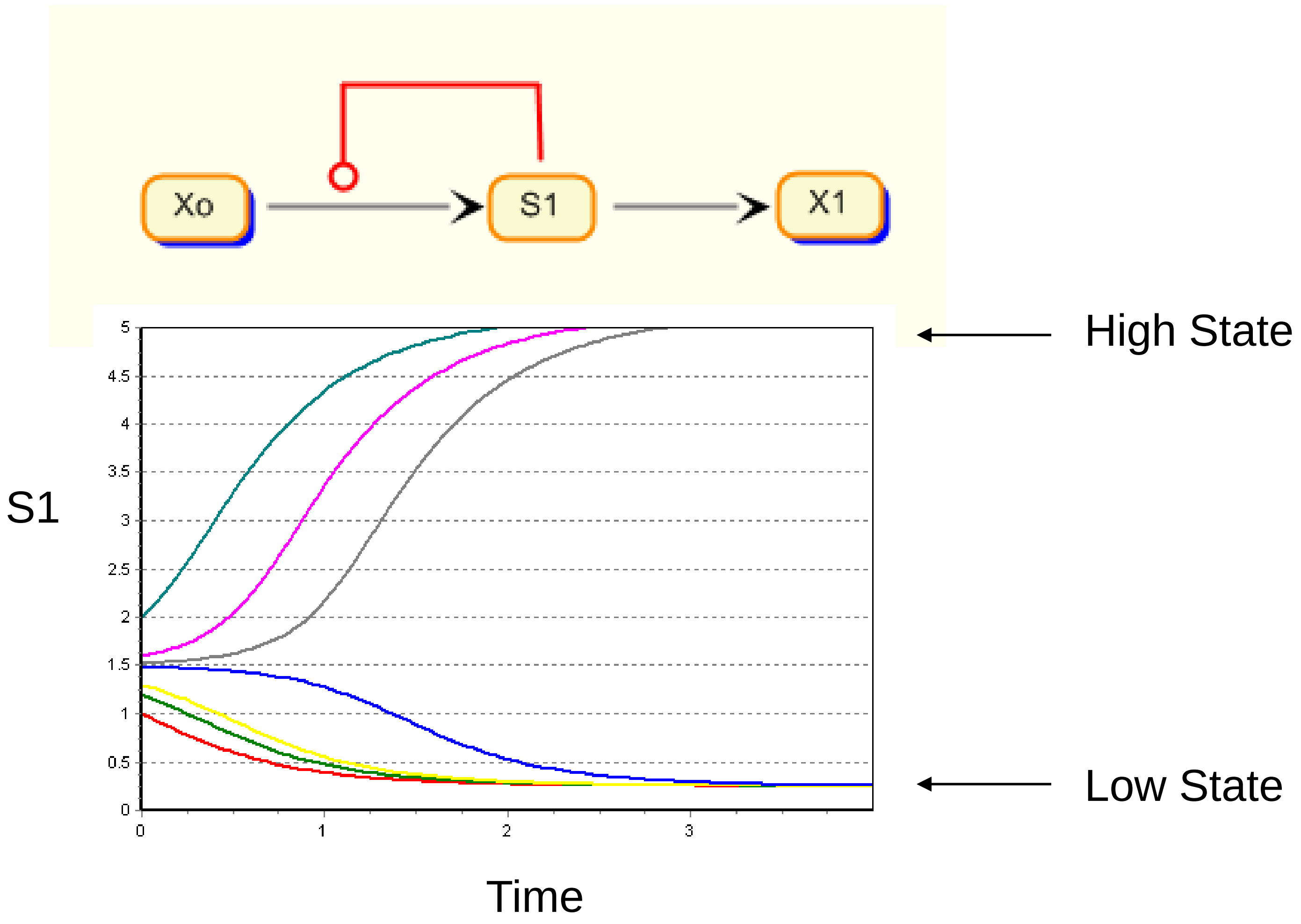
Bistable Systems



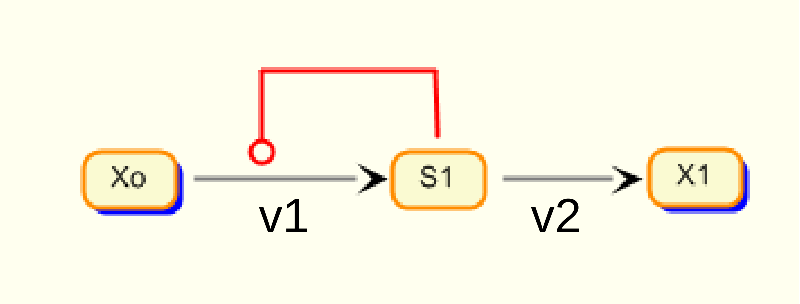

```
p = defn cell
     $Xo -> S1;   0.5 + Vmax*S1^n/(15 + S1^n);
      S1 -> $X1;  k1*S1;
end;
```

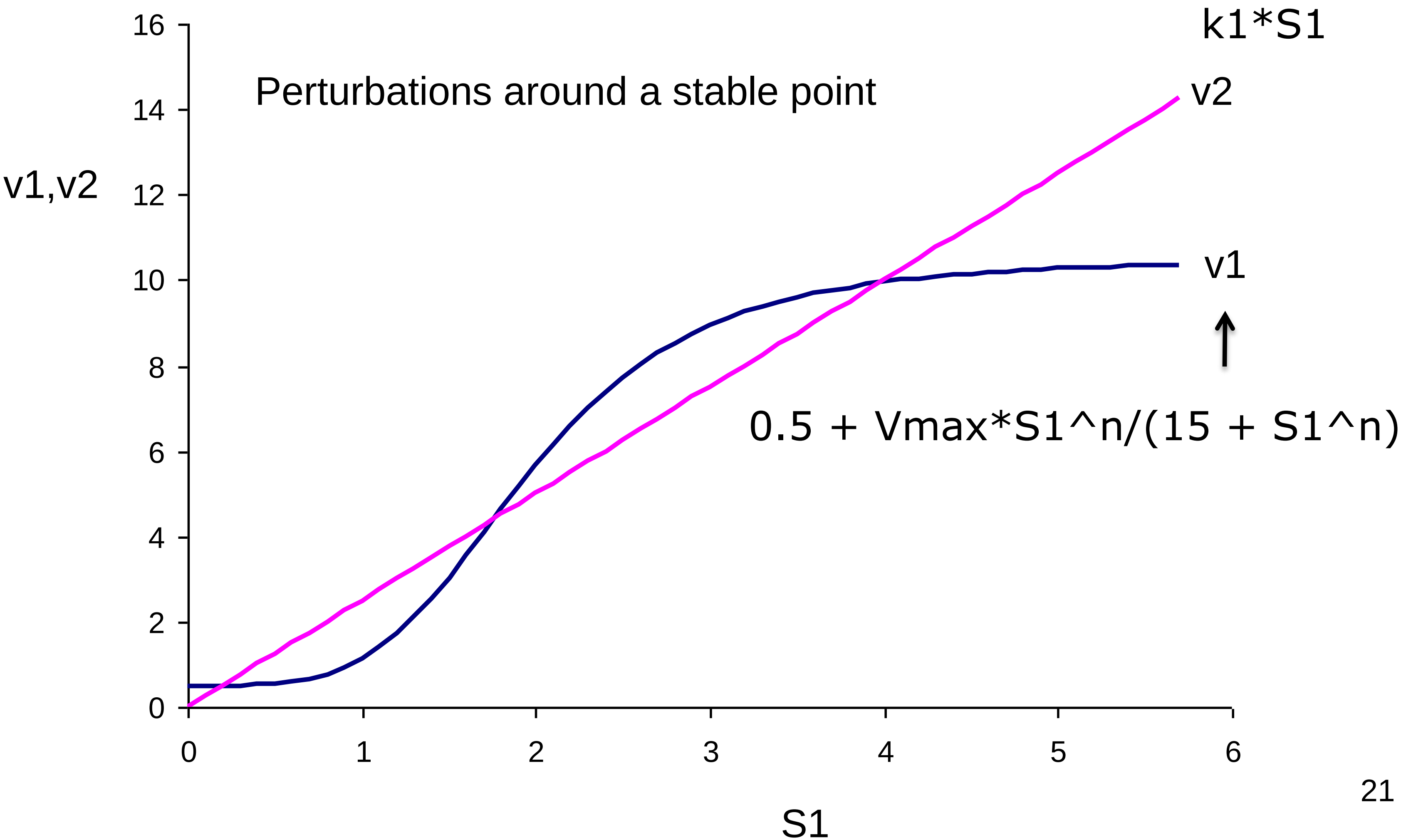
```
p.Xo = 1;
p.X1 = 0;
p.S1 = 1;
p.n = 4;
p.Vmax = 10;
p.k1 = 2;
```

Bistable Systems

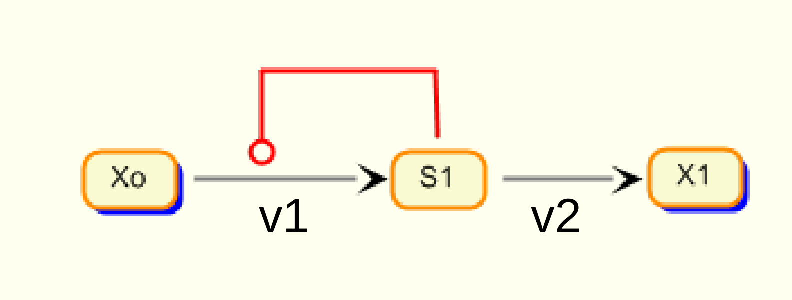


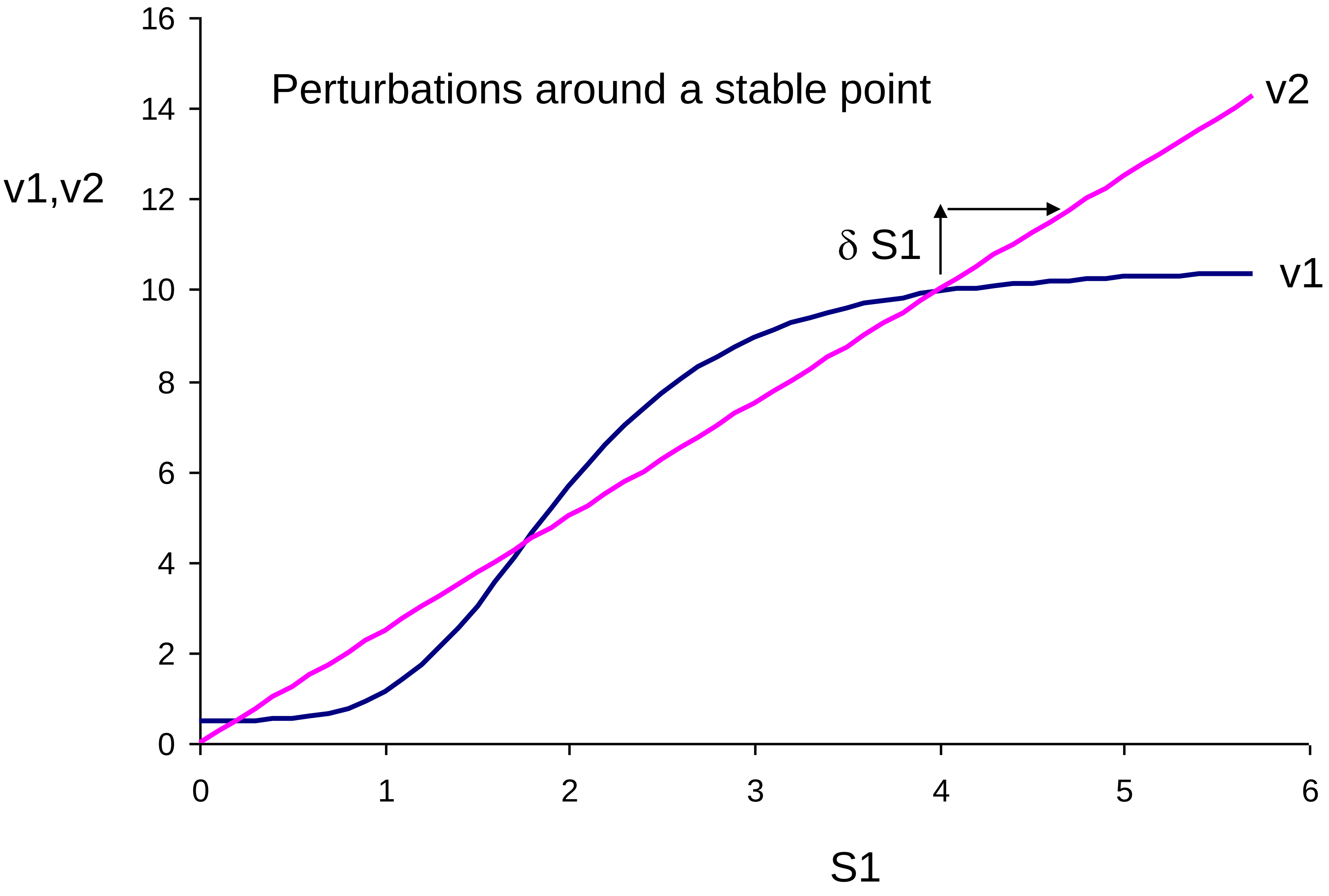
Bistable Systems



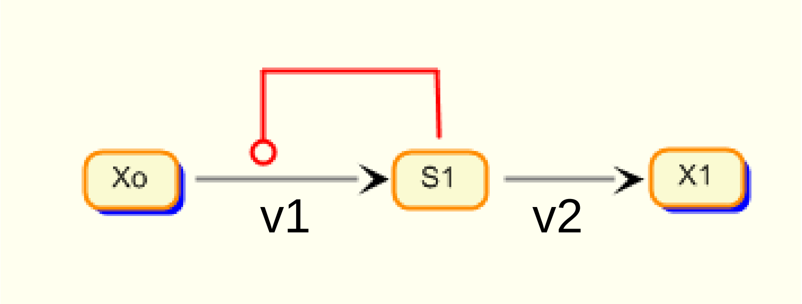


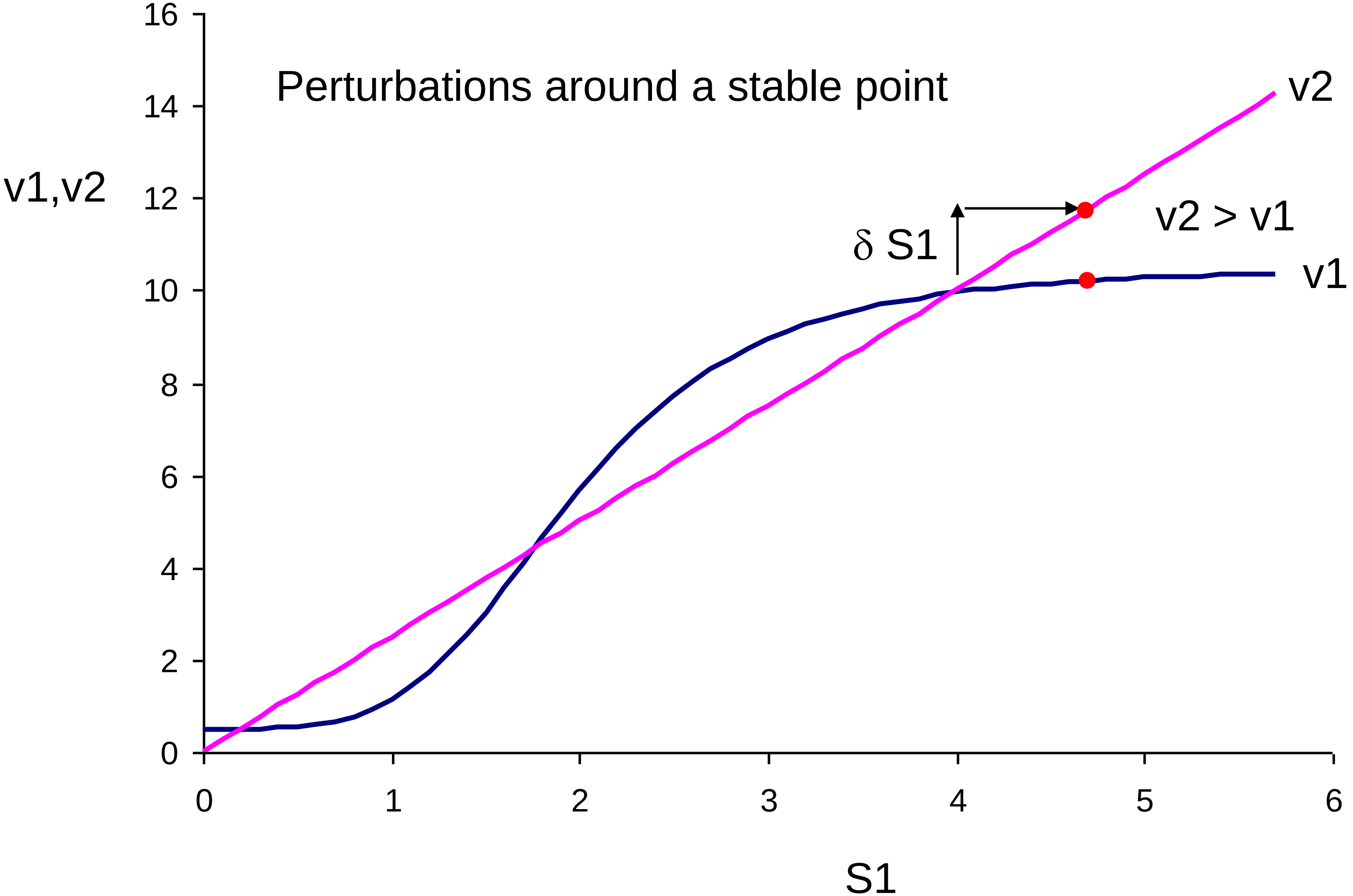
Bistable Systems



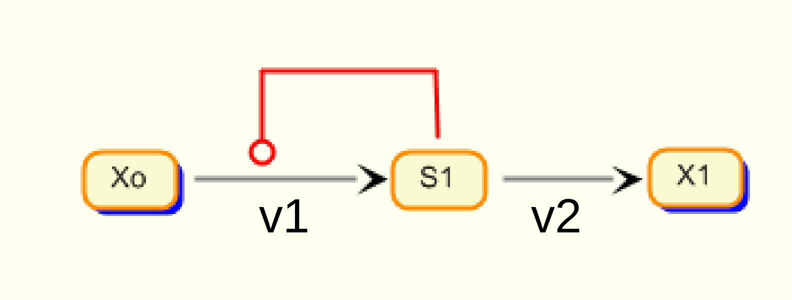


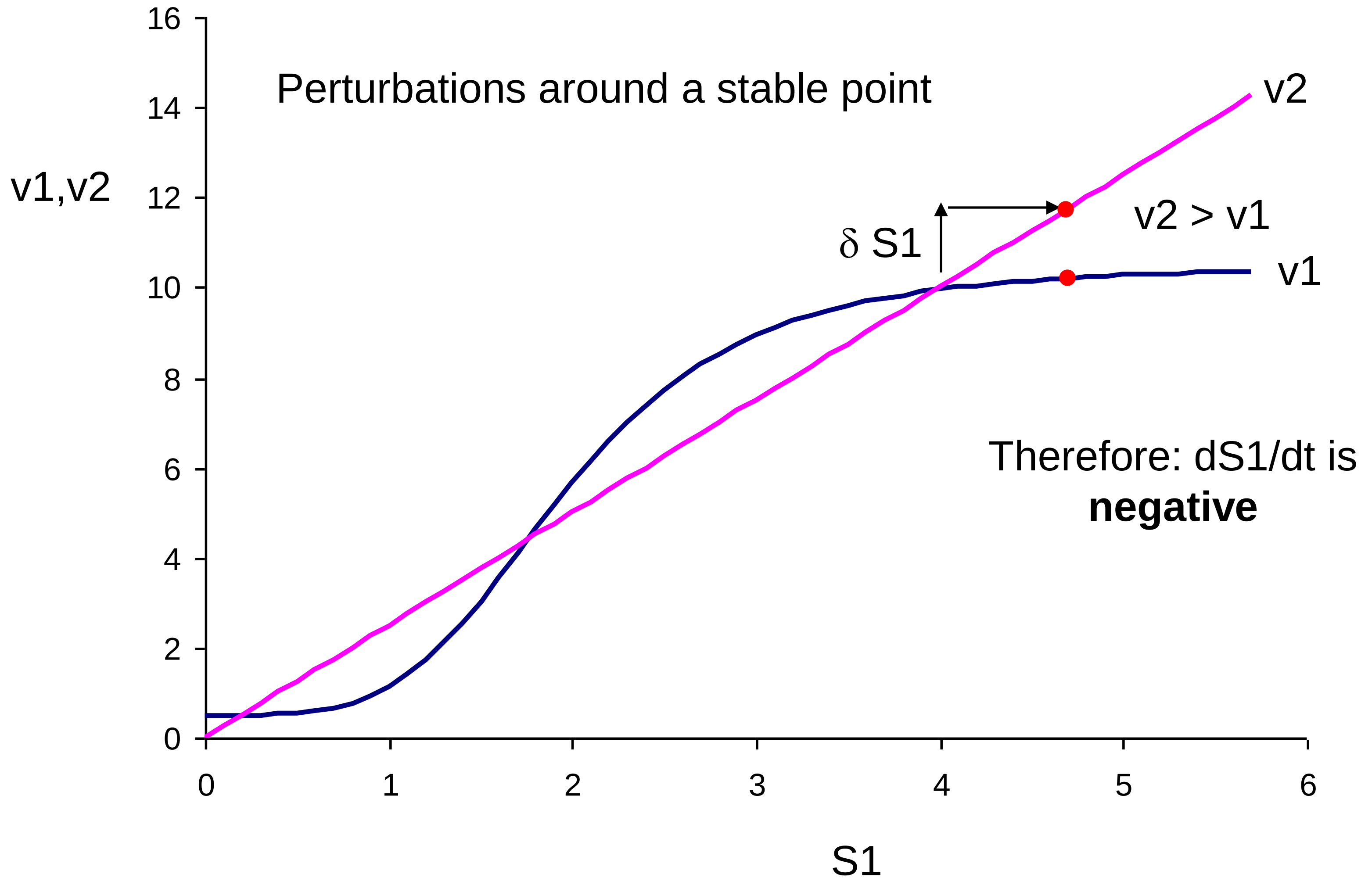
Bistable Systems



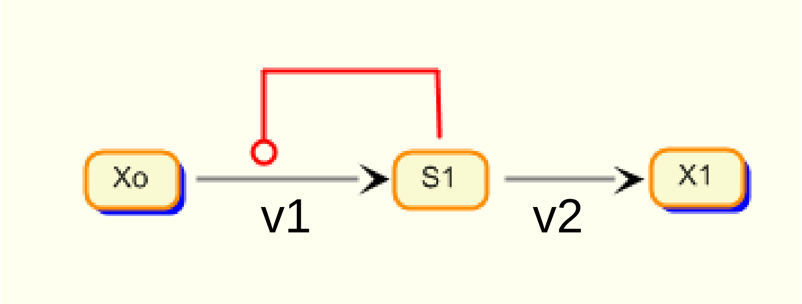


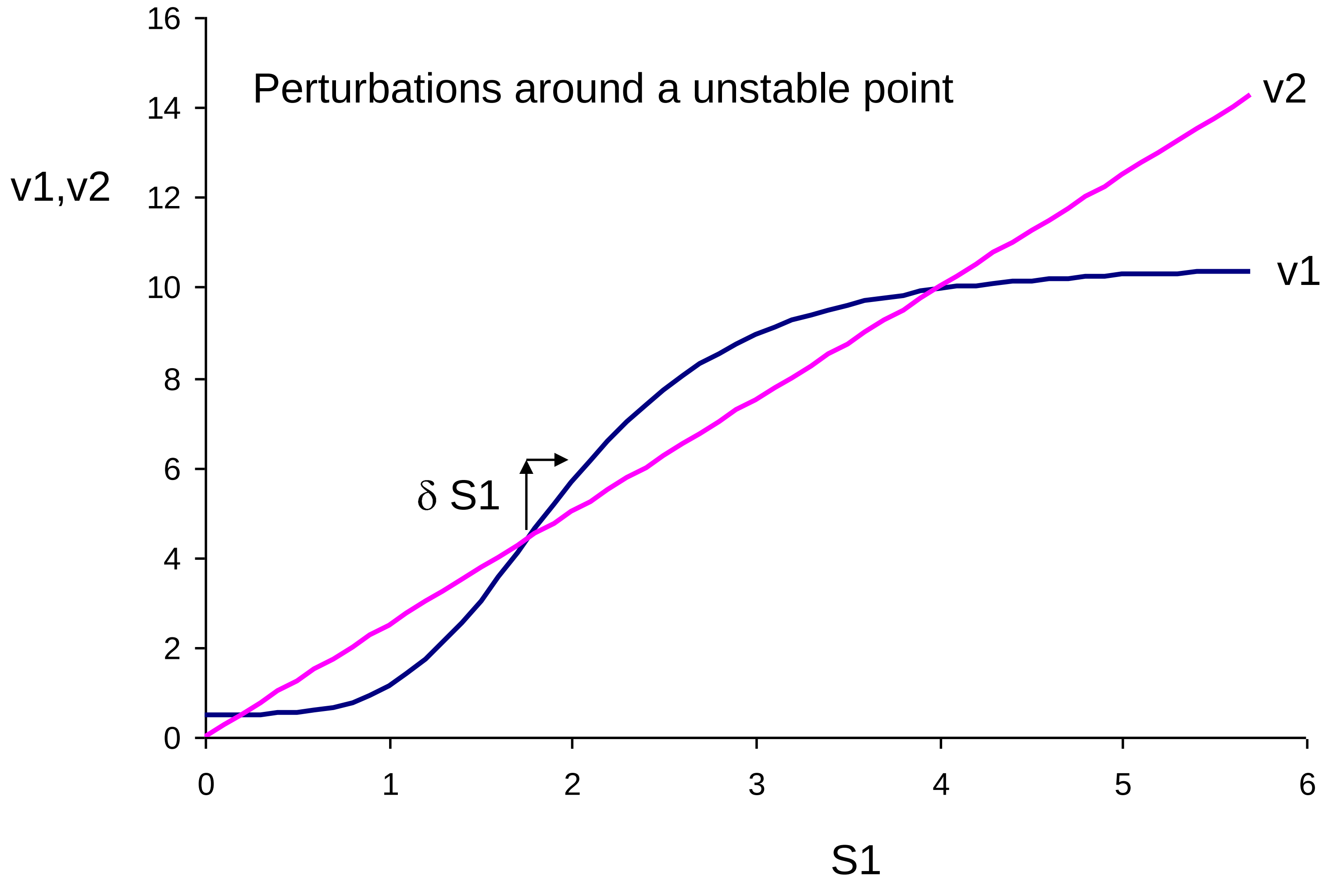
Bistable Systems



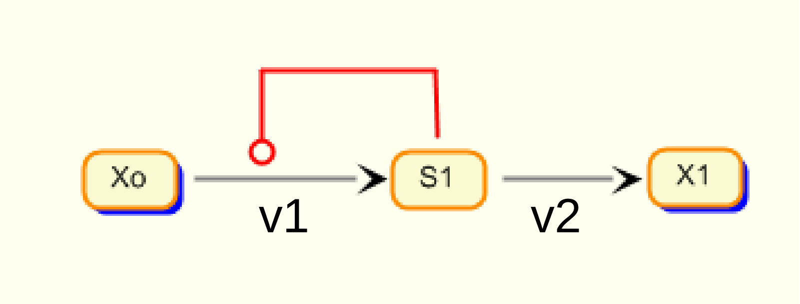


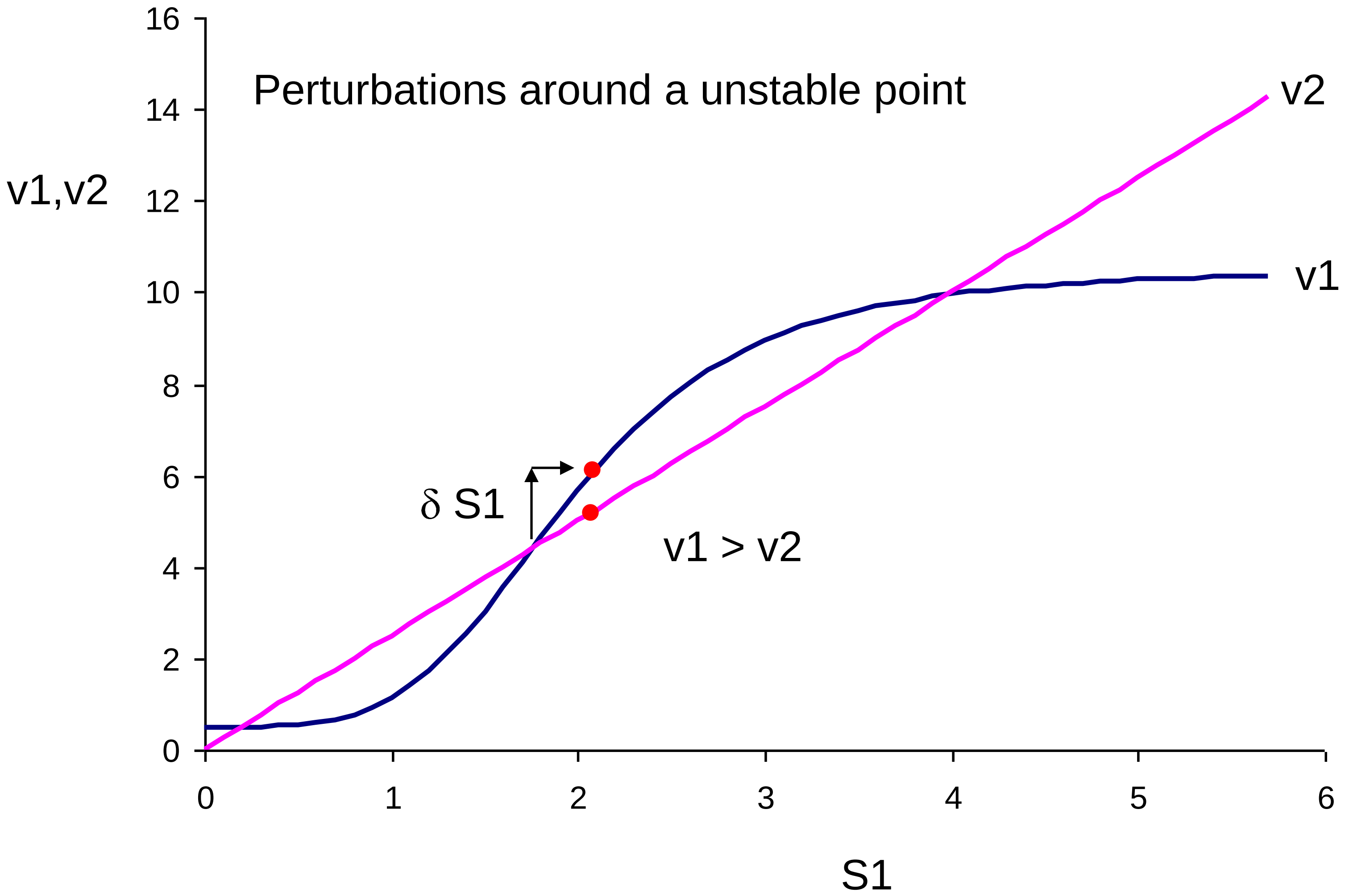
Bistable Systems



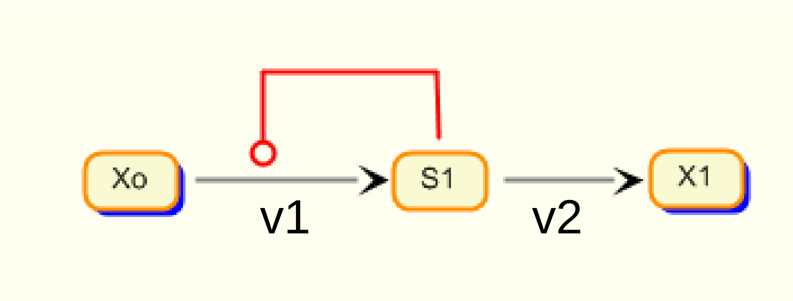


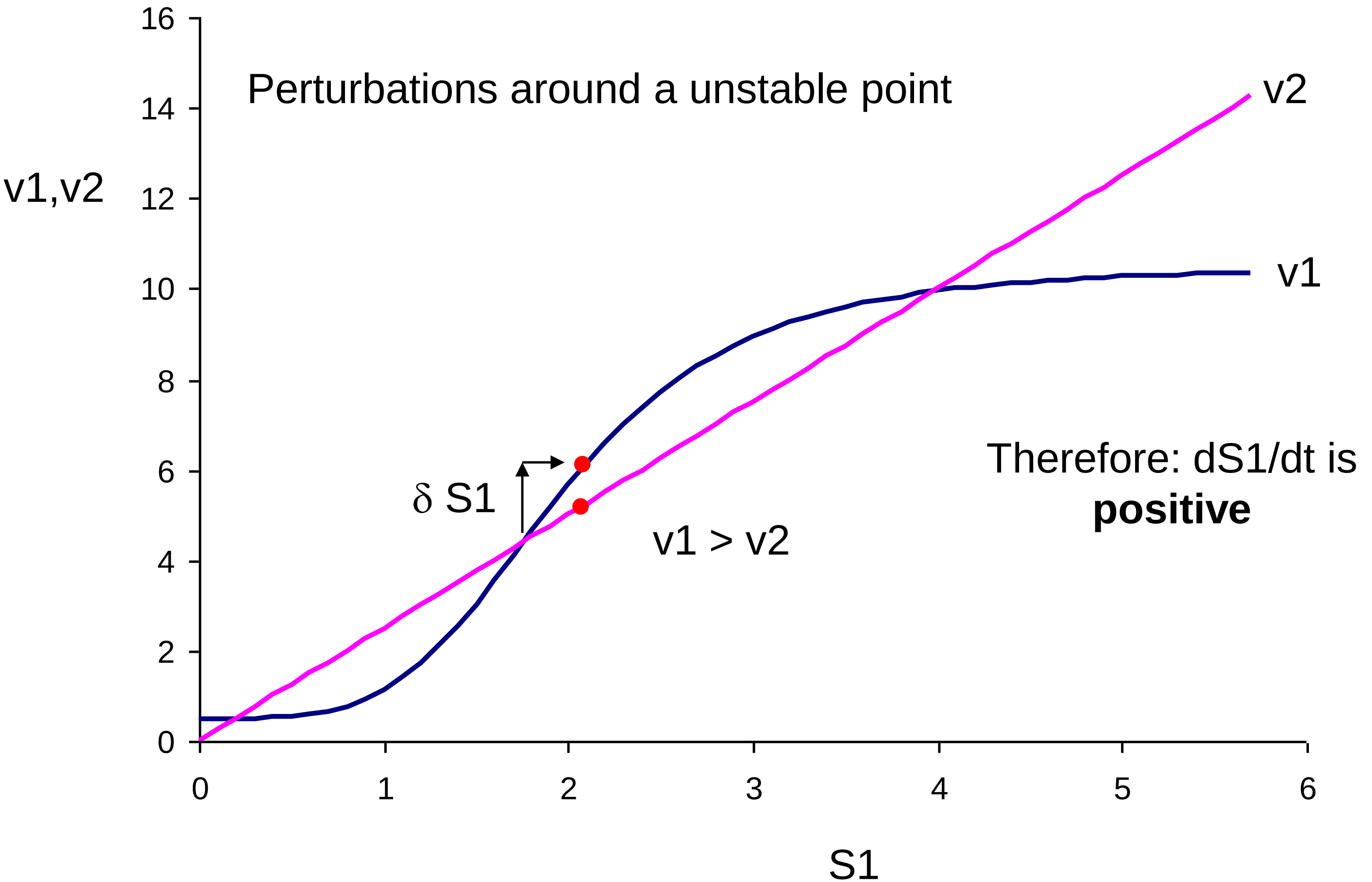
Bistable Systems

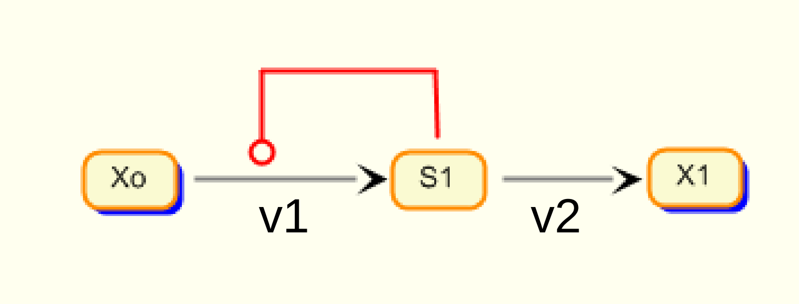




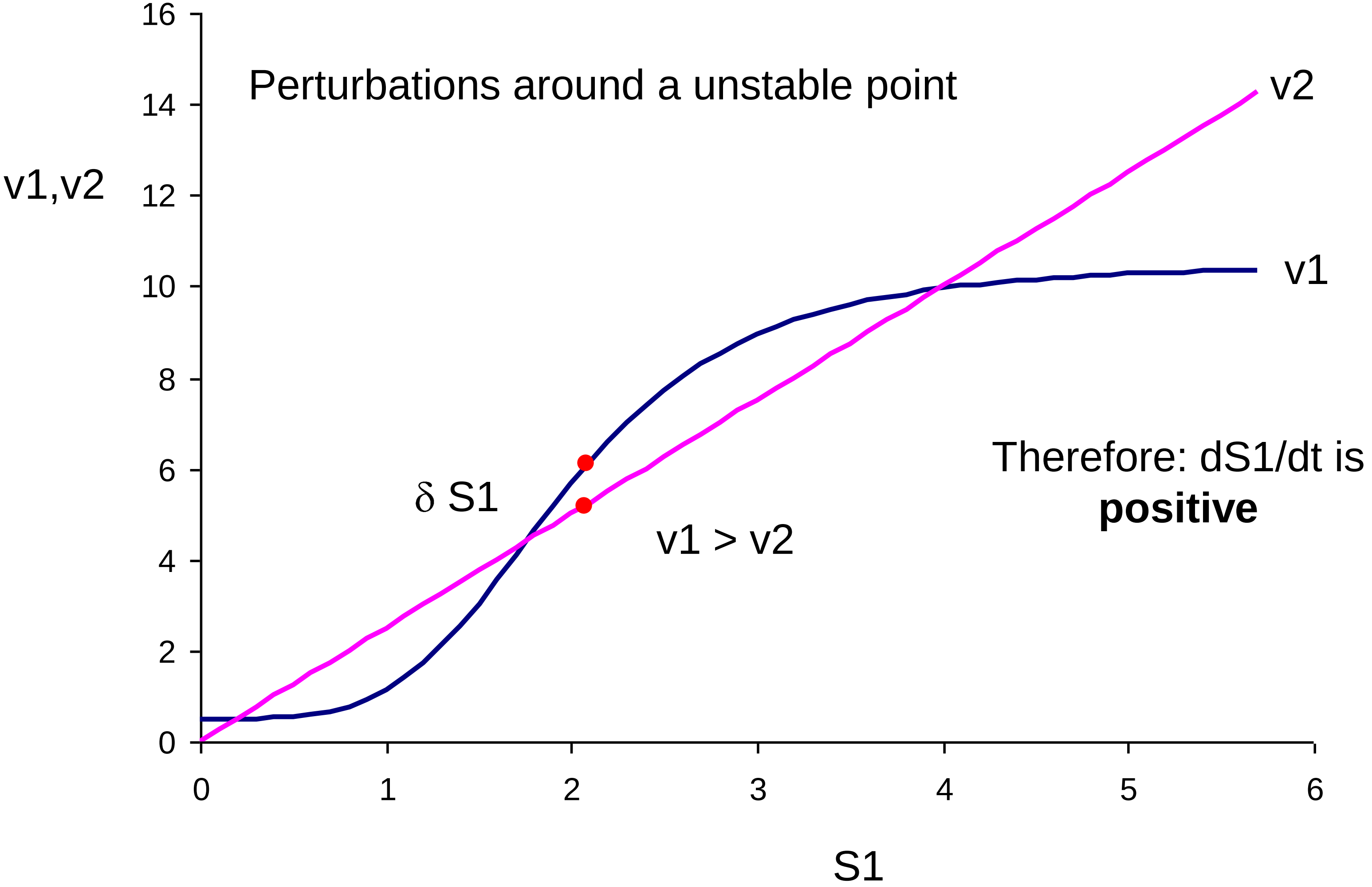
Bistable Systems



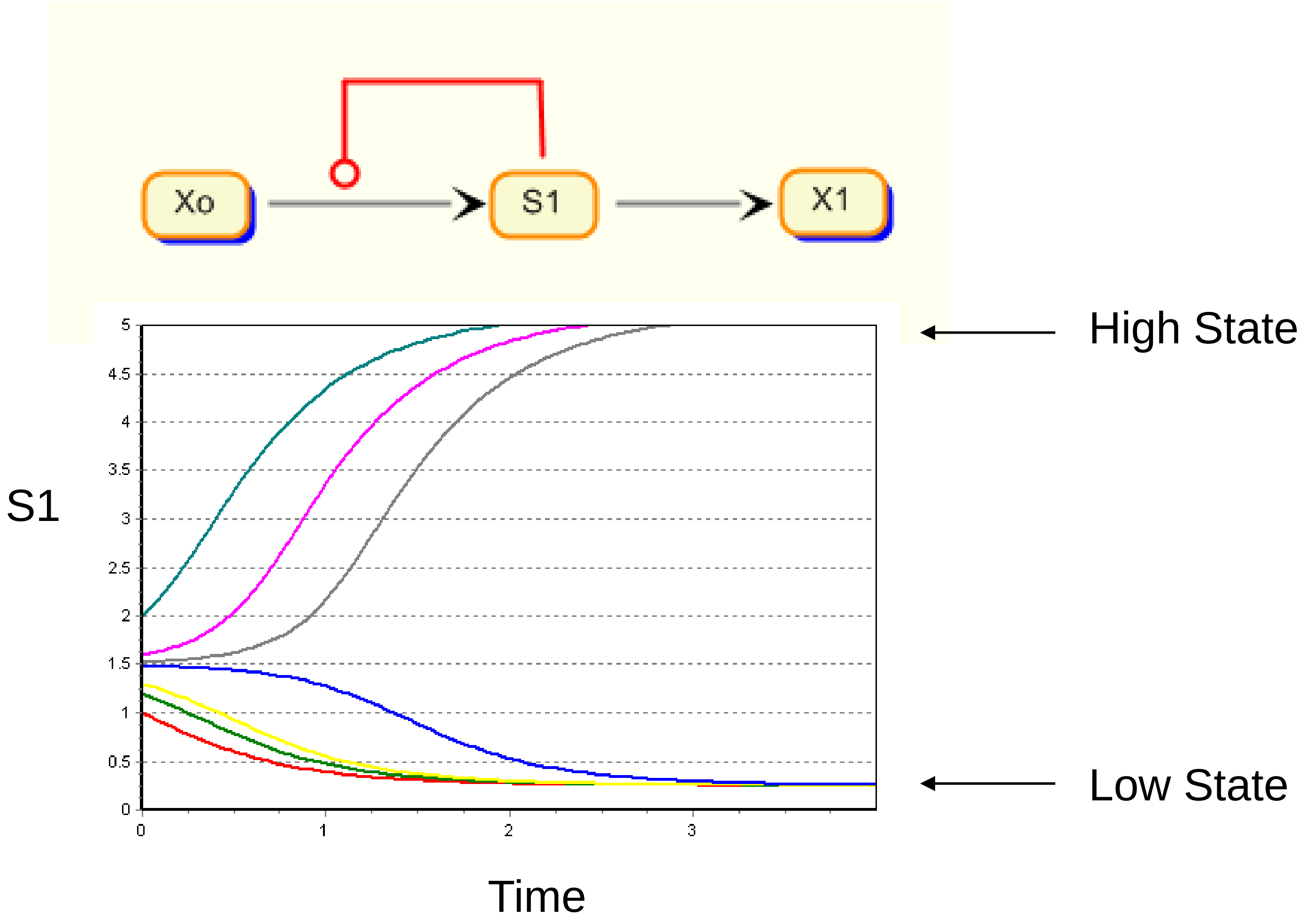




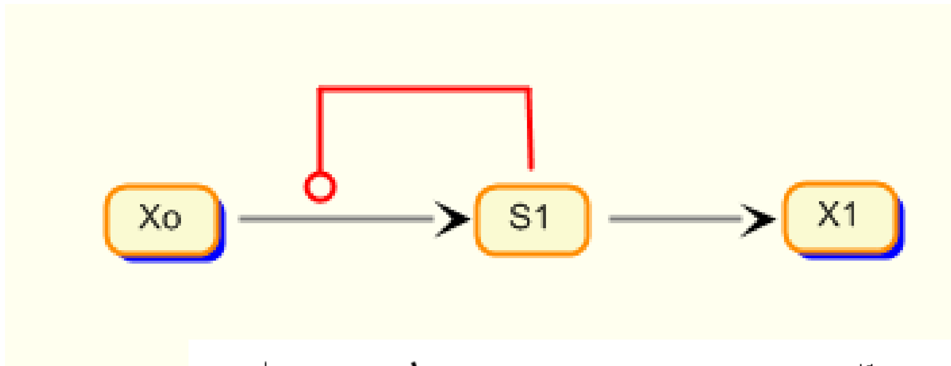
Bistable Systems



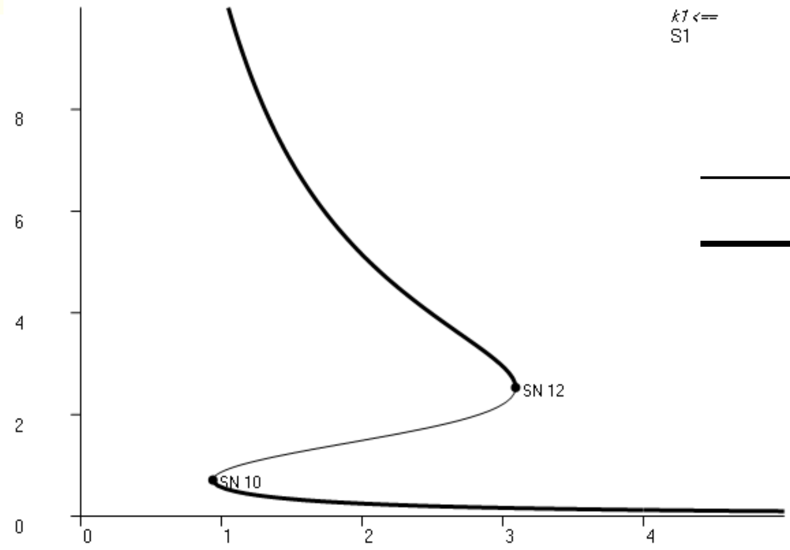
Bistable Systems



Bifurcation Plots



Steady State: S1

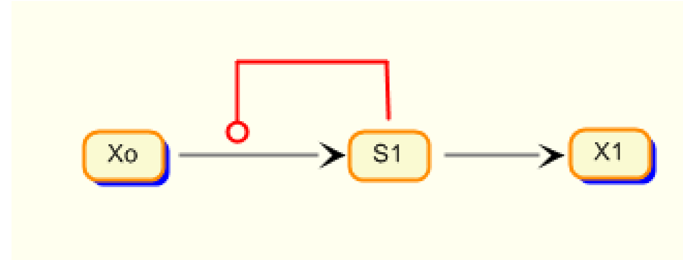


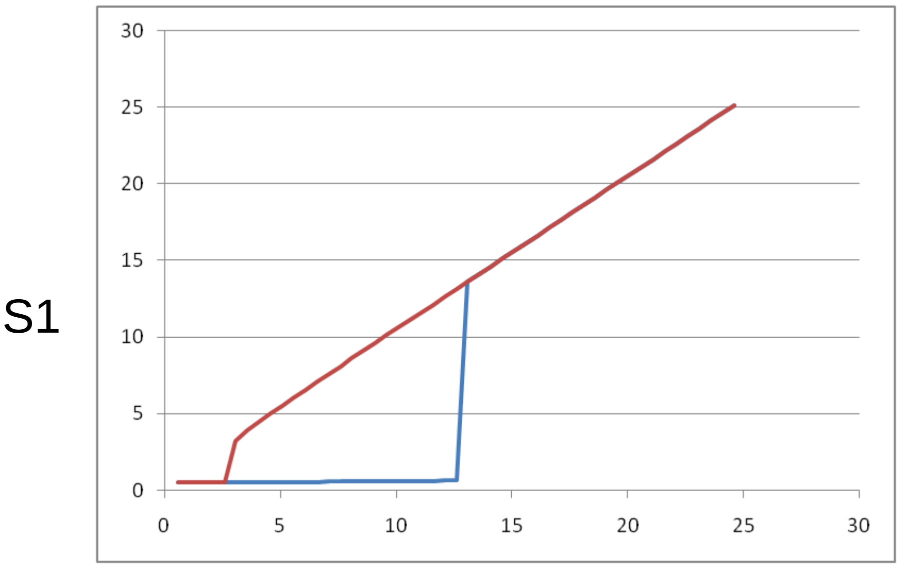
Unstable branch

Stable branch

Parameter: k1

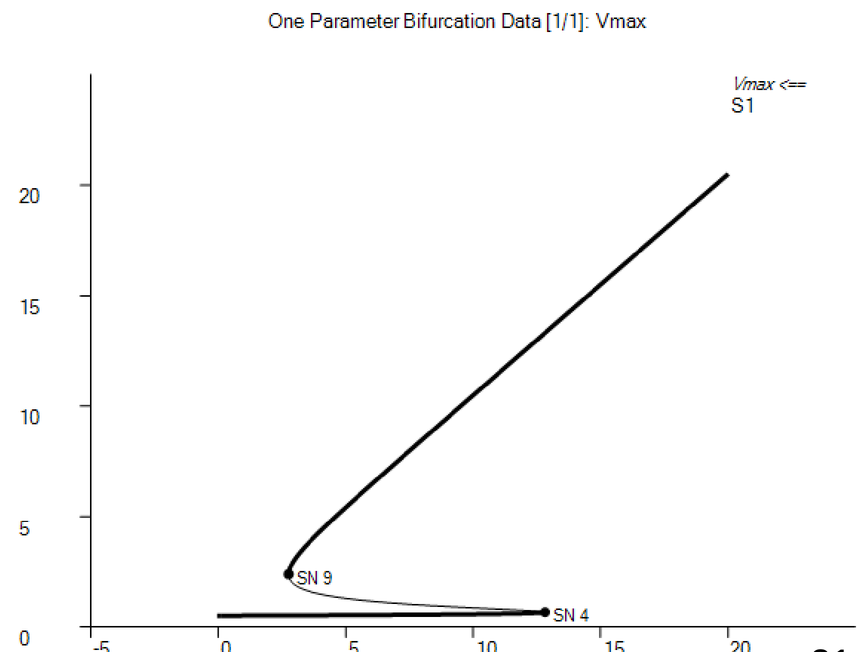
Bifurcation Plots





Upward scan
Downward scan

Parameter: Vmax on v1
Generated using Jarnac/Excel

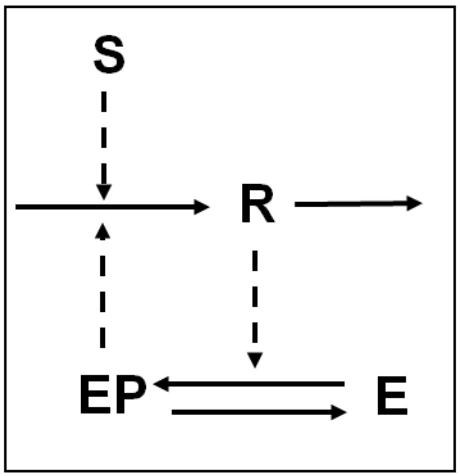


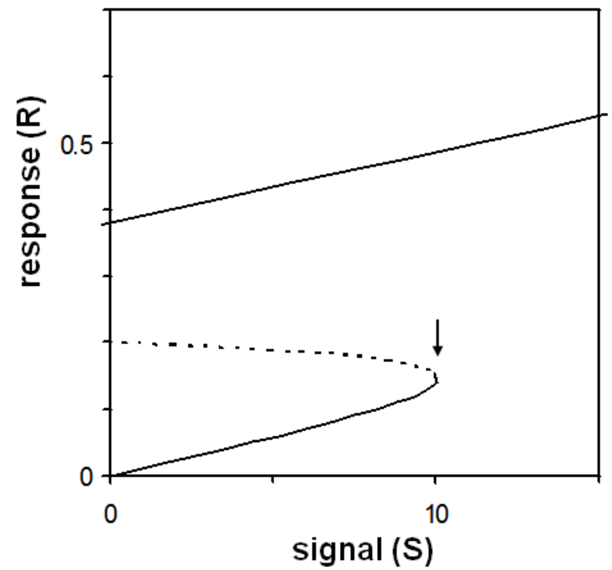
Jacnac Script to Generate Previous Plot

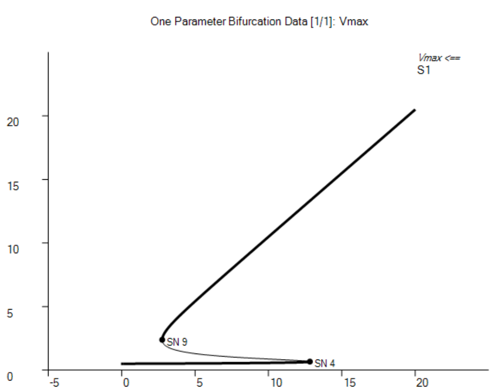
```
p = defn cell
      $Xo -> S1;   0.5 + Vmax*S1^n/(15 + S1^n);
       S1 -> $X1;  k1*S1;
end;

p.Xo = 0.1;
p.X1 = 0;
p.S1 = 1;
p.n = 4;
p.Vmax = 0.1;
p.k1 = 1;

// Upward scan
m1 = matrix (50, 2);
p.sim.eval (0, 100, 100, []);
p.ss.eval;
for i = 1 to 50 do
    begin
    p.Vmax = p.Vmax + 0.5;
    p.sim.eval (0, 100, 100, []);
    p.ss.eval;
    m1[i] = {p.Vmax, p.S1};
    end;
graph (m1);
```

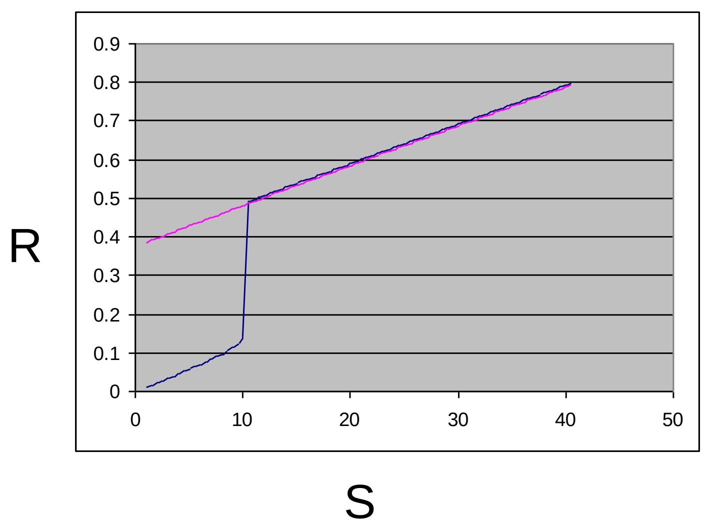
```
// downward scan
m2 = matrix (50, 2);
p.sim.eval (0, 100, 100, []);
p.ss.eval;
for i = 1 to 50 do
    begin
    p.Vmax = p.Vmax - 0.5;
    p.sim.eval (0, 100, 100, []);
    p.ss.eval;
    m2[i] = {p.Vmax, p.S1};
    end;
graph (m2);
```

Irreversible Bistable System









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)

Toggle System

$$\overset{0}{\cancel{\dot{u}}} = \frac{\alpha_1}{1 + v^{\beta}} - u$$

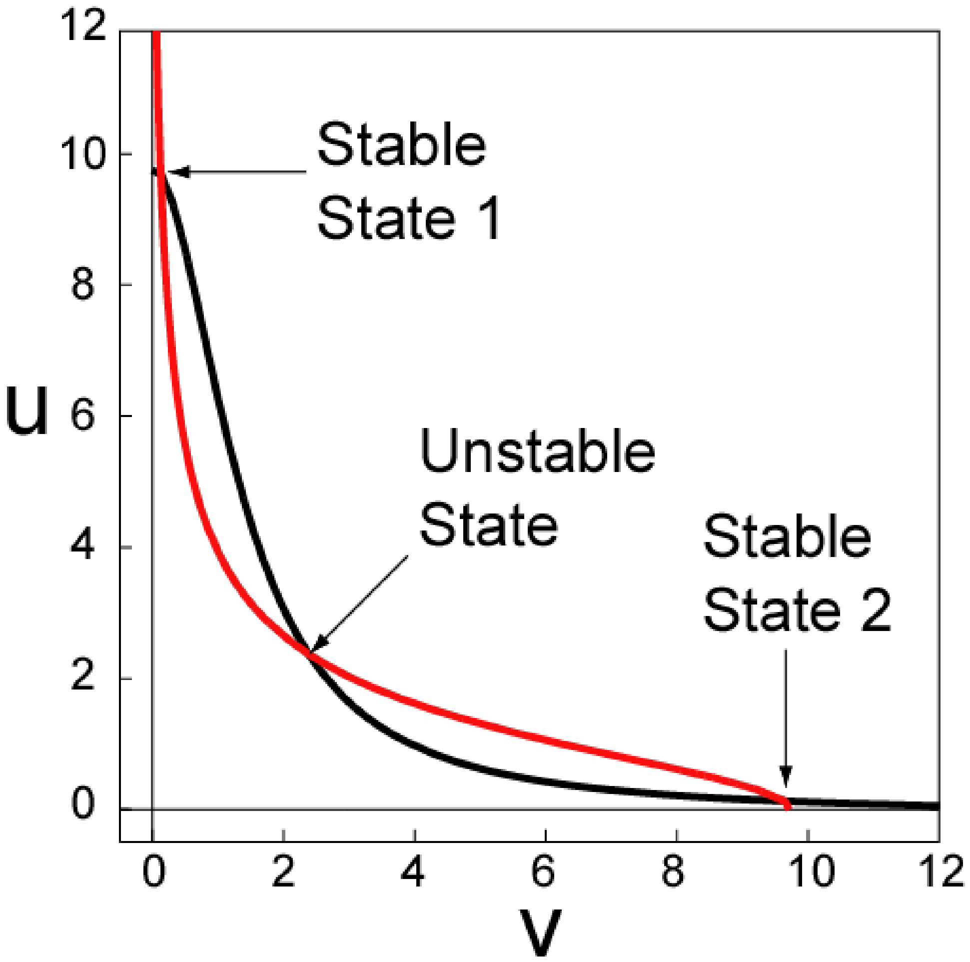
$$\overset{0}{\cancel{\dot{v}}} = \frac{\alpha_2}{1 + u^{\gamma}} - v$$

⇓

$$u = \frac{\alpha_1}{1 + v^{\beta}}$$

$$v = \frac{\alpha_2}{1 + u^{\gamma}}$$

These are called Nullclines



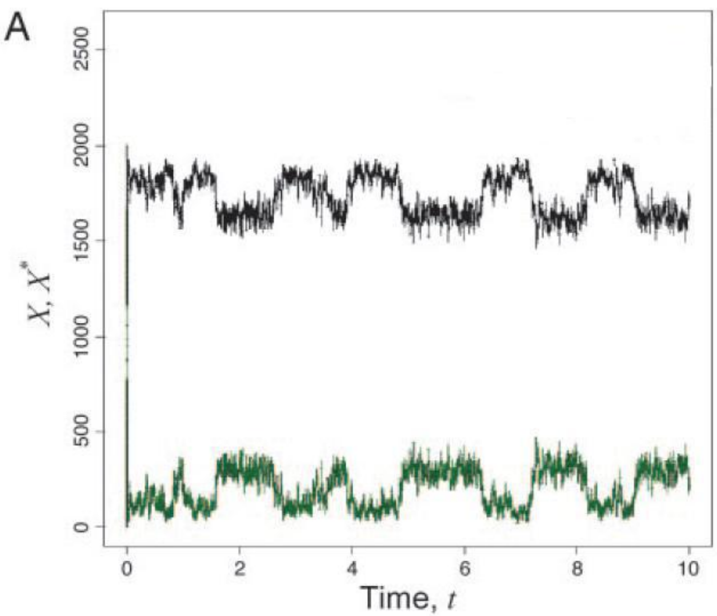
Toggle System – Jarnac Model

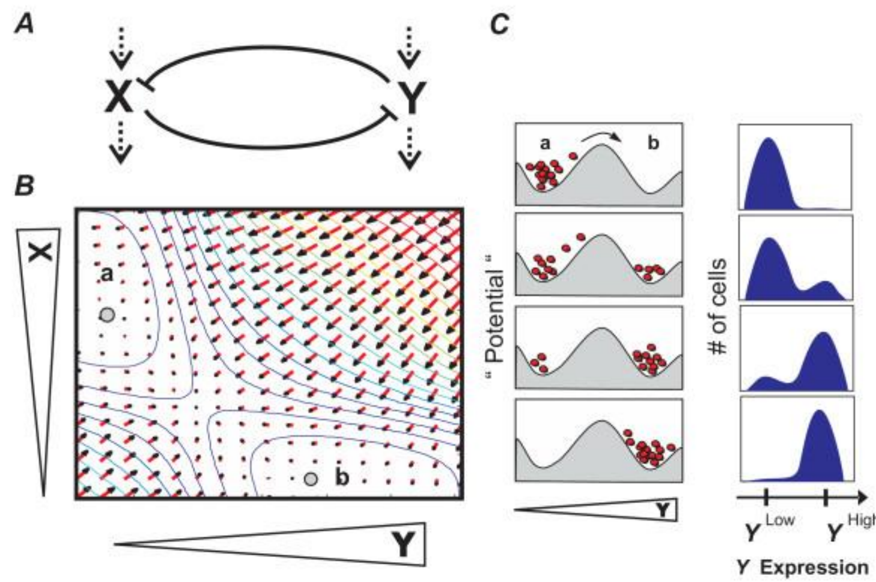
```
p = defn cell
      $x -> u; a1/(1 + v^g);
       u -> $w; u;
       v -> $w; v;
      $x -> v; a2/(1 + u^b);

end;

p.u = 0;
p.v = 0;
p.x = 0;
p.g = 3;
p.b = 3;
p.a1 = 10;
p.a2 = 10;
```

```
p.sim.eval (0, 100, 100, []);
p.ss.eval;
// Unstable point
println "Eigenvalues:";
println eigenvalues (p.jac);
println "Unstable: u = ", p.u, " v = ",
p.v;

// The first stable point
p.u = 0.1;
p.v = 1;
m = p.sim.eval (0, 100, 100, [<p.time>,
<p.u>, <p.v>]);
p.ss.eval;
println "Stable A: u = ", p.u, " v = ",
p.v;


// The second stable point
p.u = 1;
p.v = 1;
m = p.sim.eval (0, 100, 100, [<p.time>,
<p.u>, <p.v>]);
p.ss.eval;
println "Stable B: u = ", p.u, " v = ",
p.v;
```

Noise and Bistable Systems

If the jump distance between the two states is small compared to the level of noise, then bistable switches can spontaneously switch between the two states.





Chang *et al. BMC Cell Biology* 2006
7:11 doi:10.1186/1471-2121-7-11