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.
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


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

cross inhibition

cross inhibition
Bistable Systems

Diagram:

- **a**
  - Normalized GFP expression vs. [IPTG] (M)
  - Data points with error bars

- **b**
  - Fraction of pTAK117 cells in high state vs. [IPTG] (M)
  - Step function indicating bistability
They used a temperature sensitive repressor (cl) to knock the switch back down (42C).

IPTG was used to switch the circuit on.
Bistable Systems

One that didn’t work – repression too weak on one arm of the switch.
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. Silver1,6

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

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.
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

[Diagram showing genetic circuitry and fluorescent protein expression under different conditions]
Bistable Systems – Alternative Design

With Positive Feedback

Positive Feedback

remains on
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.

Natural Examples

Sin (Sporlation Inhibition) 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.

The *Bacillus subtilis* sin Operon
Christopher A. Voigt, Denise M. Wolf and Adam P. Arkin
Genetics, Vol. 169, 1187-1202, March 2005
Over-expression of NANOG due to “leaky transcription”. NANOG latches onto the OCT4/SOX2 genes and keeps the switch in the ON state.
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)

Bistable Systems

Natural Bistable Networks


Synthetic Bistable Networks


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

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

[Diagram showing bistable system with states X0, S1, and X1.]

High State

Low State

Time
Bistable Systems

Perturbations around a stable point

\[ v_1, v_2 = 0.5 + V_{\text{max}} S_1^n / (15 + S_1^n) \]
Bistable Systems

Perturbations around a stable point

$\delta S1$
Bistable Systems

Perturbations around a stable point

v₁, v₂
Perturbations around a stable point

Therefore: $\frac{dS_1}{dt}$ is negative
Bistable Systems

Perturbations around a unstable point

$v_1, v_2$

$\delta S_1$
Bistable Systems

Perturbations around a unstable point

$\delta S_1$  

$v_1 > v_2$
Therefore: $\frac{dS_1}{dt}$ is positive.

Perturbations around a unstable point

$v_1 > v_2$
Bistable Systems

Therefore: \( \frac{dS1}{dt} \) is positive

Perturbations around a unstable point

\[ v1 > v2 \]
Bistable Systems

![Diagram of bistable system]

The system transitions between High and Low states over time. The diagram illustrates the state transitions and the time course for each state.
Bifurcation Plots

Steady State: S1

Parameter: k1

Unstable branch

Stable branch
Bifurcation Plots

Parameter: Vmax on v1
Generated using Jarnac/Excel

Upward scan
Downward scan
Jacnac Script to Generate Previous Plot

```jacnac
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
ml = 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;
        ml[i] = {p.Vmax, p.S1};
    end;
graph (ml);

// 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);
```
Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell John J Tyson, Katherine C Chenz and Bela Novak
These are called Nullclines
Toggle System – Jarnac Model

\[ p = \text{defn cell} \]
\[ x \rightarrow u; \ a_1/(1 + v^g); \]
\[ u \rightarrow w; \ u; \]
\[ v \rightarrow w; \ v; \]
\[ x \rightarrow v; \ a_2/(1 + u^b); \]
\end{equation}

\[ p.\text{sim}.\text{eval} \ (0, 100, 100, \ []); \]
\[ p.\text{ss}.\text{eval}; \]

// 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.\text{sim}.\text{eval} \ (0, 100, 100, [<p.time>,
<p.u>, <p.v>]);
p.\text{ss}.\text{eval};
println "Stable A: u = ", p.u, " v = ", p.v;

// The second stable point
p.u = 1;
p.v = 1;
m = p.\text{sim}.\text{eval} \ (0, 100, 100, [<p.time>,
<p.u>, <p.v>]);
p.\text{ss}.\text{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