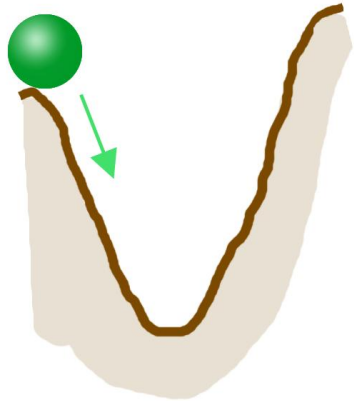


Positive Feedback and Bistability

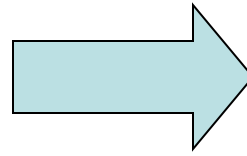
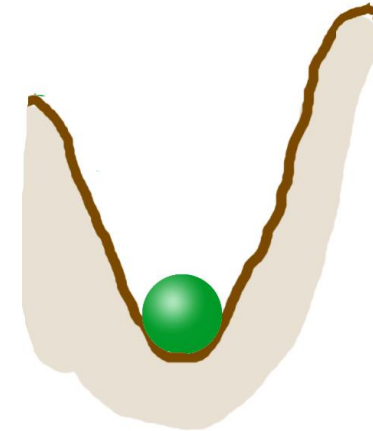
Systems and Synthetic Biology
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Stable state

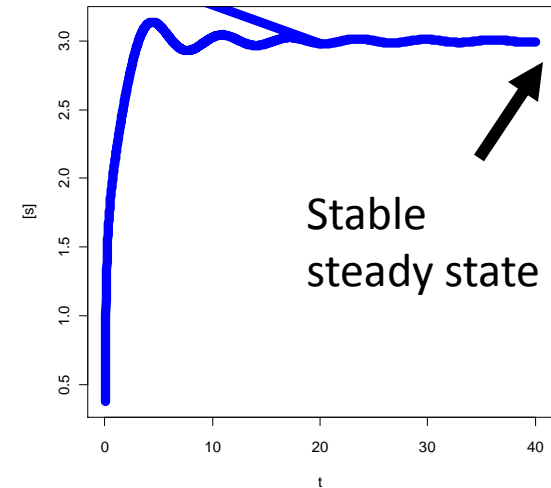
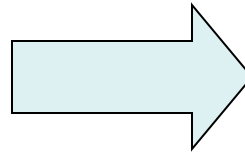
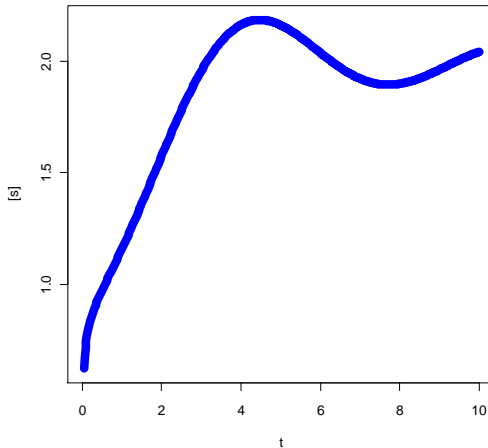
Transient state



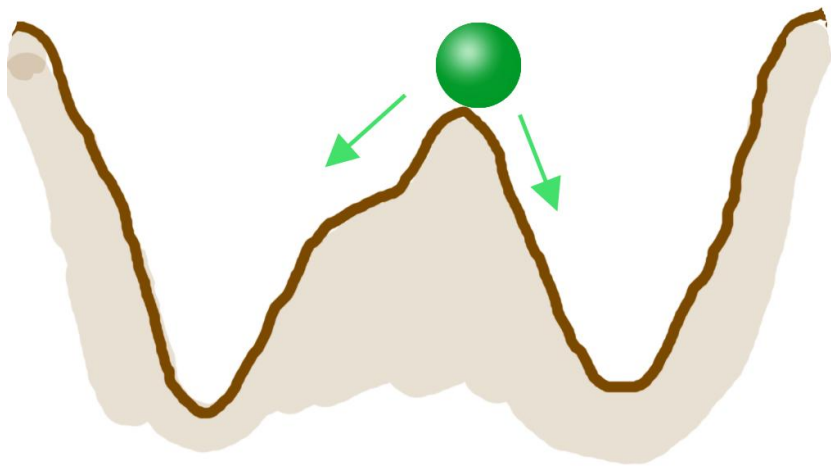
Stable state



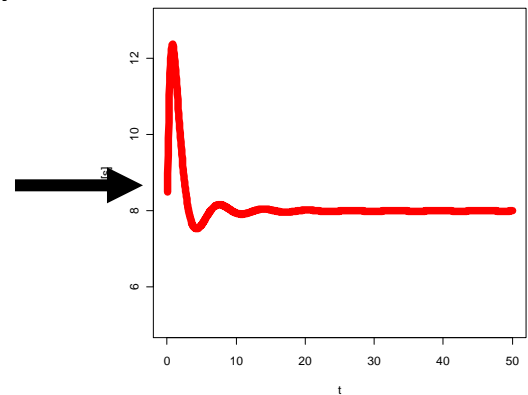
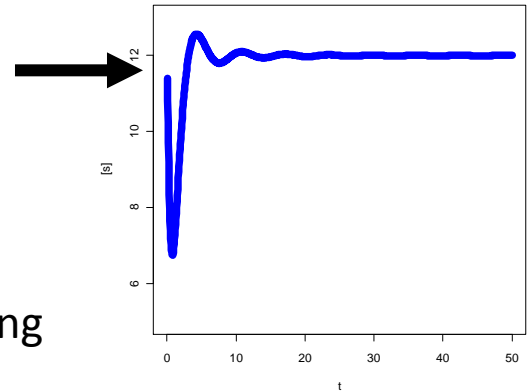
Simulation of biochemical network



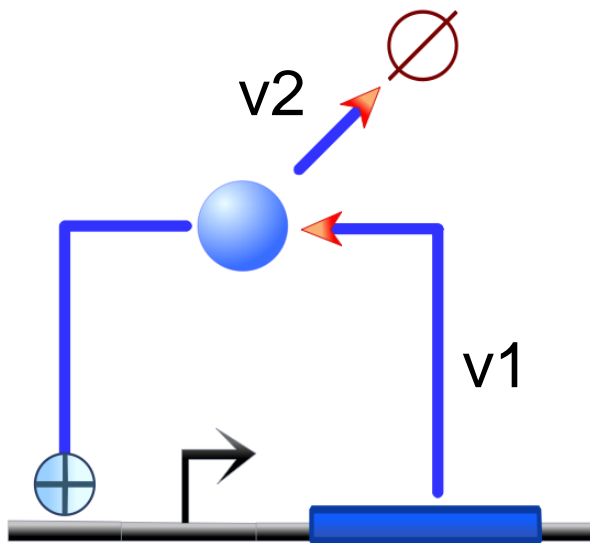
Multiple stable states



Different starting points lead to different steady states



Positive Feedback



$$v_1 = ?$$

$$v_2 = ?$$

$$dS/dt = ?$$

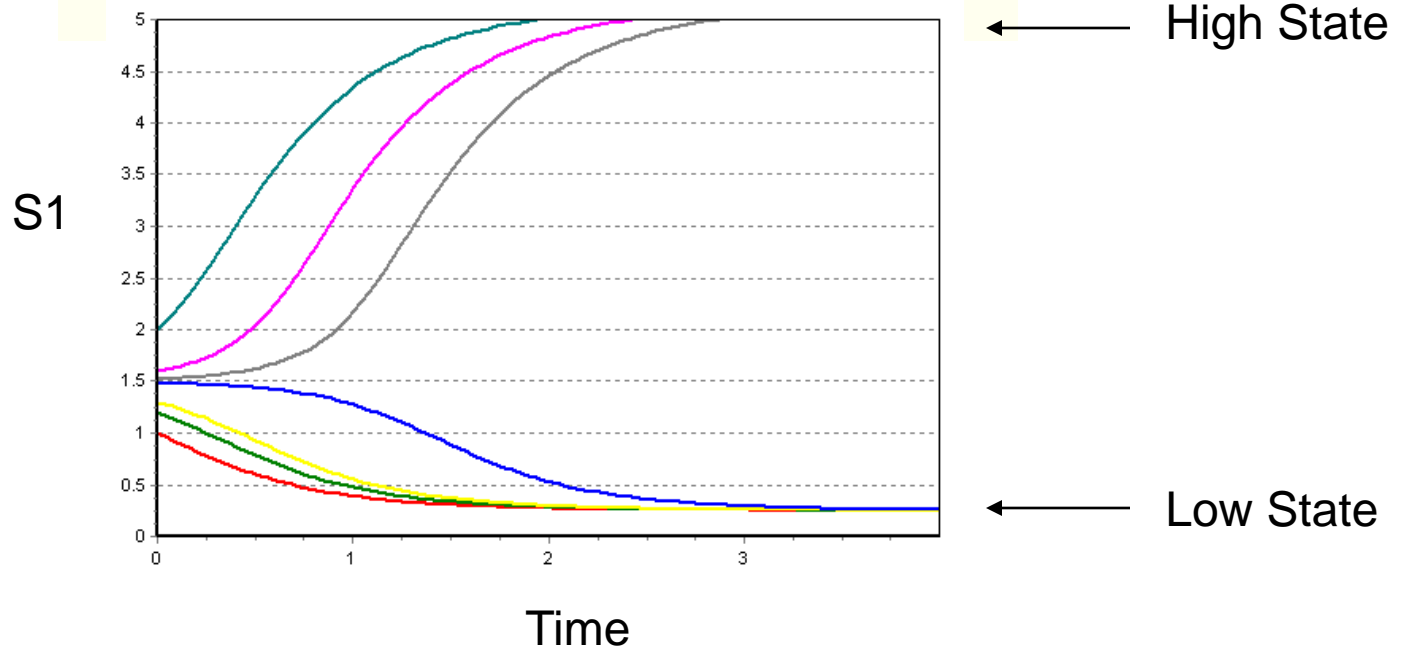
Positive Feedback



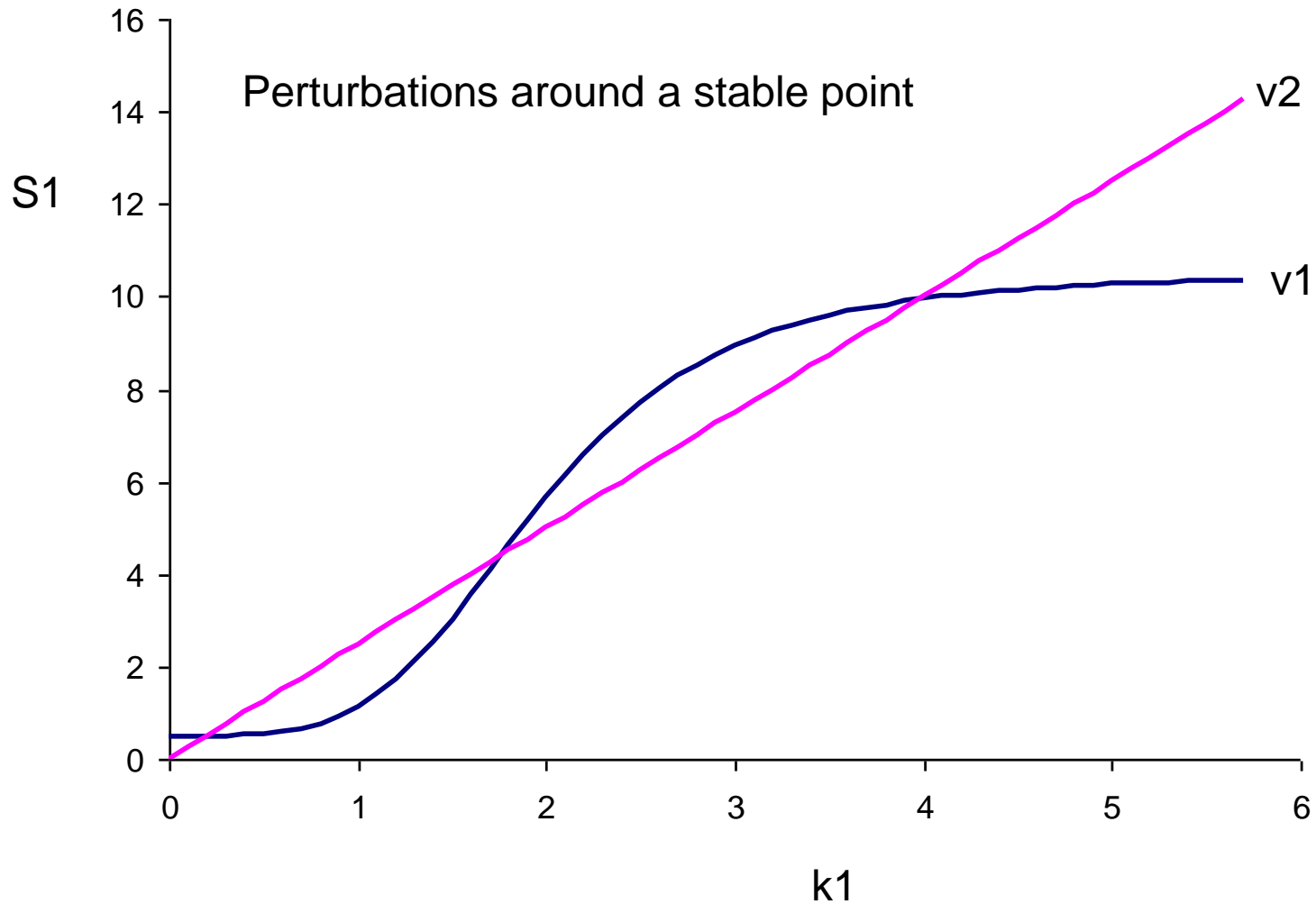
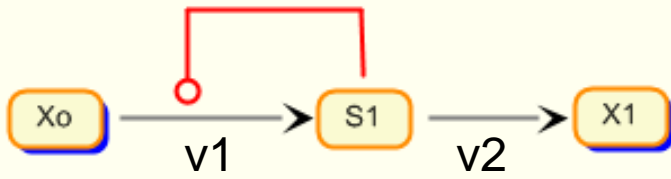
```
p = defn cell
  $Xo -> S1; 0.5 + Vmax*S1^n/(15 + S1^n);
  S1 -> $X1; k1*S1;
end;
```

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

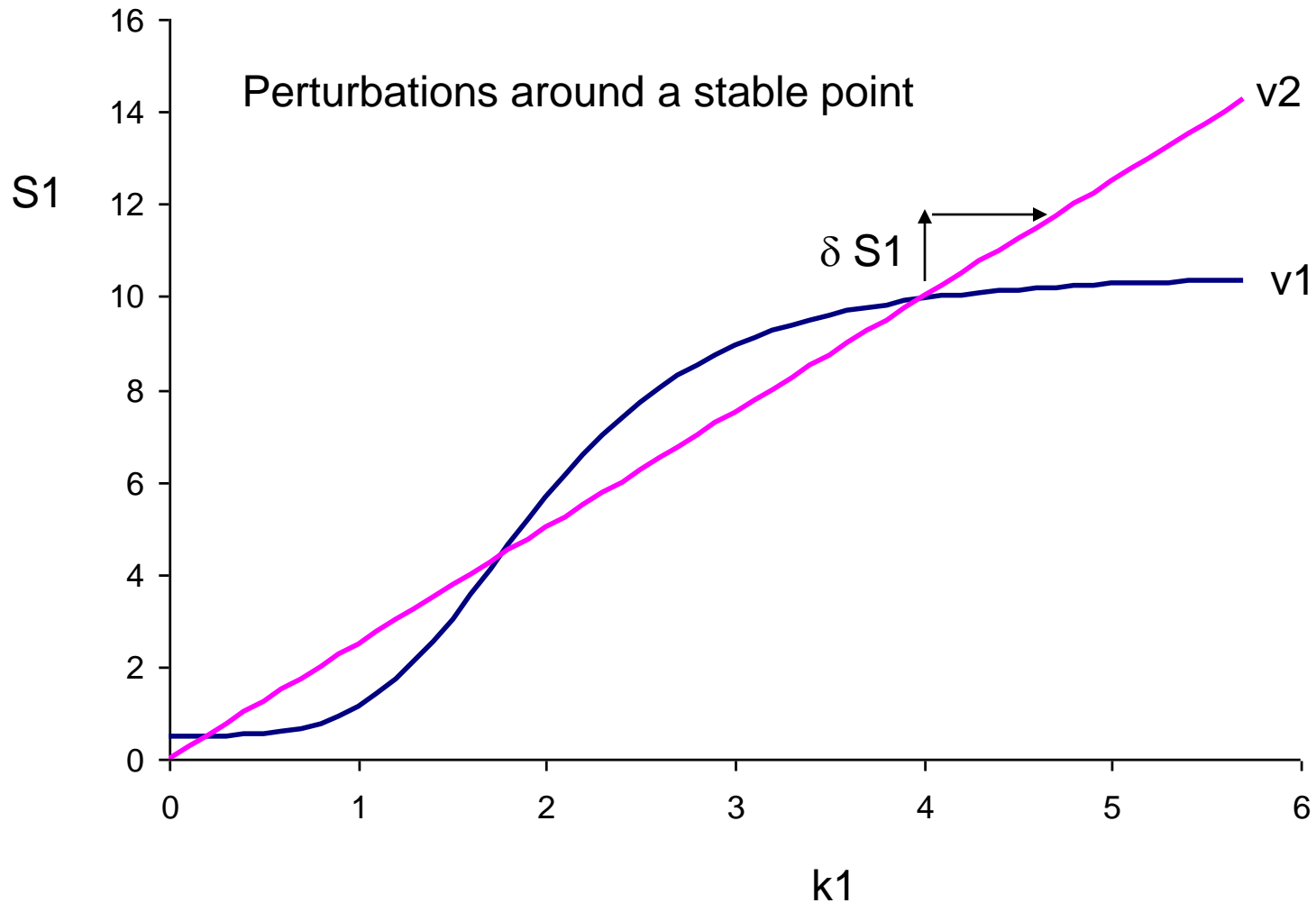
Positive Feedback



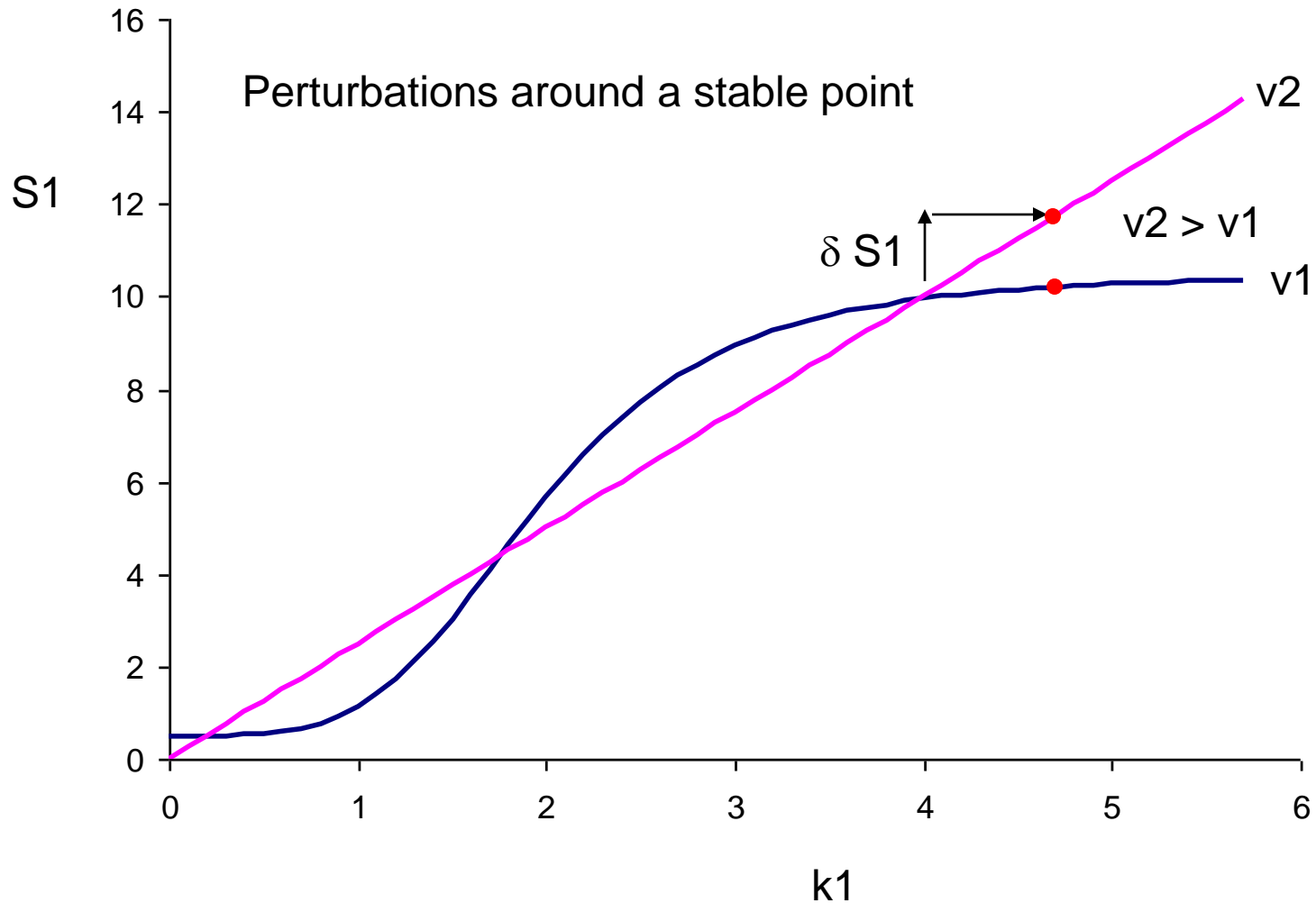
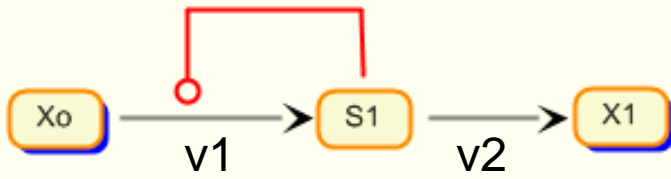
Positive Feedback



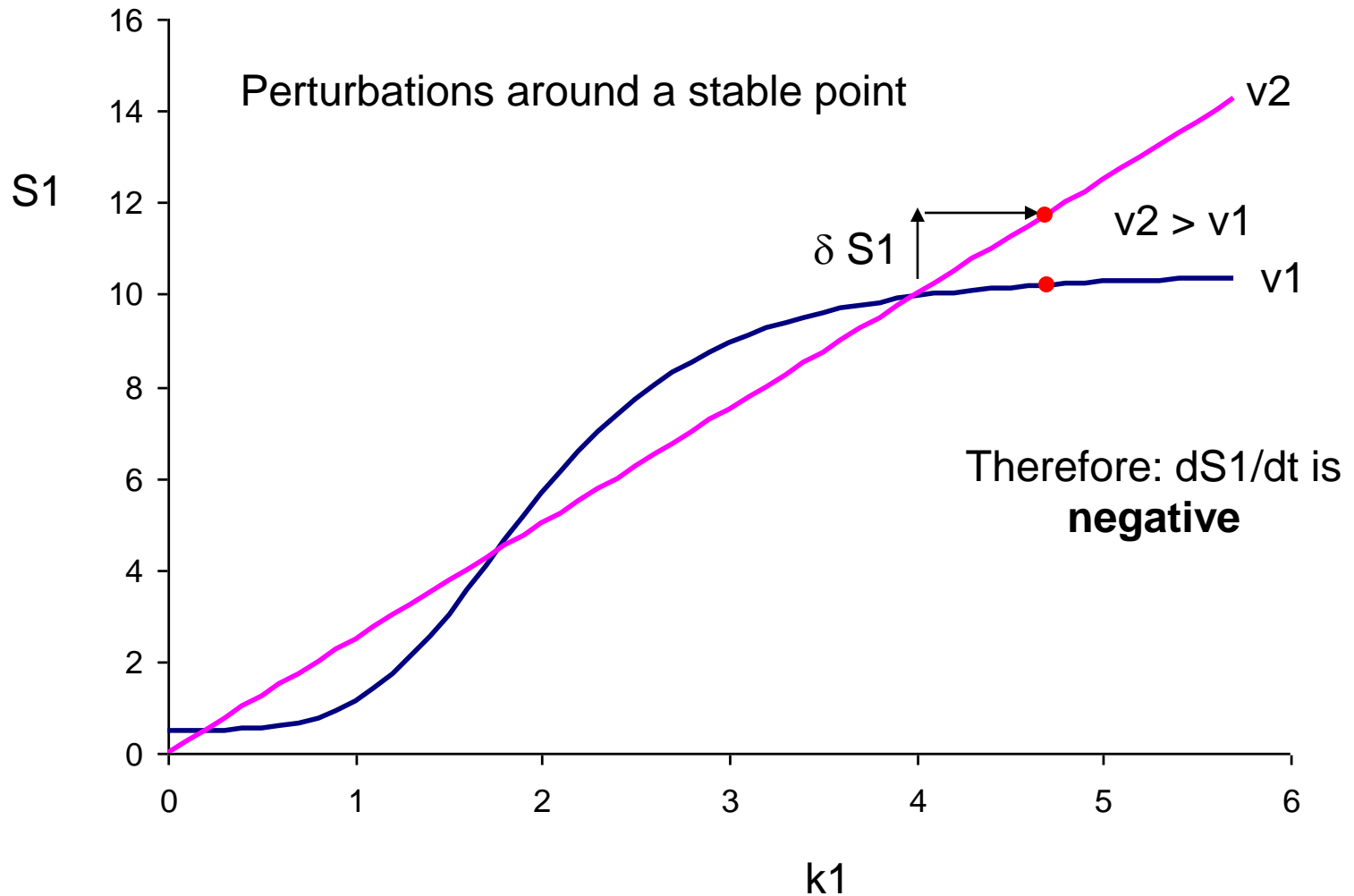
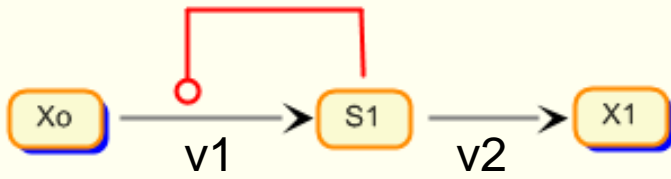
Positive Feedback



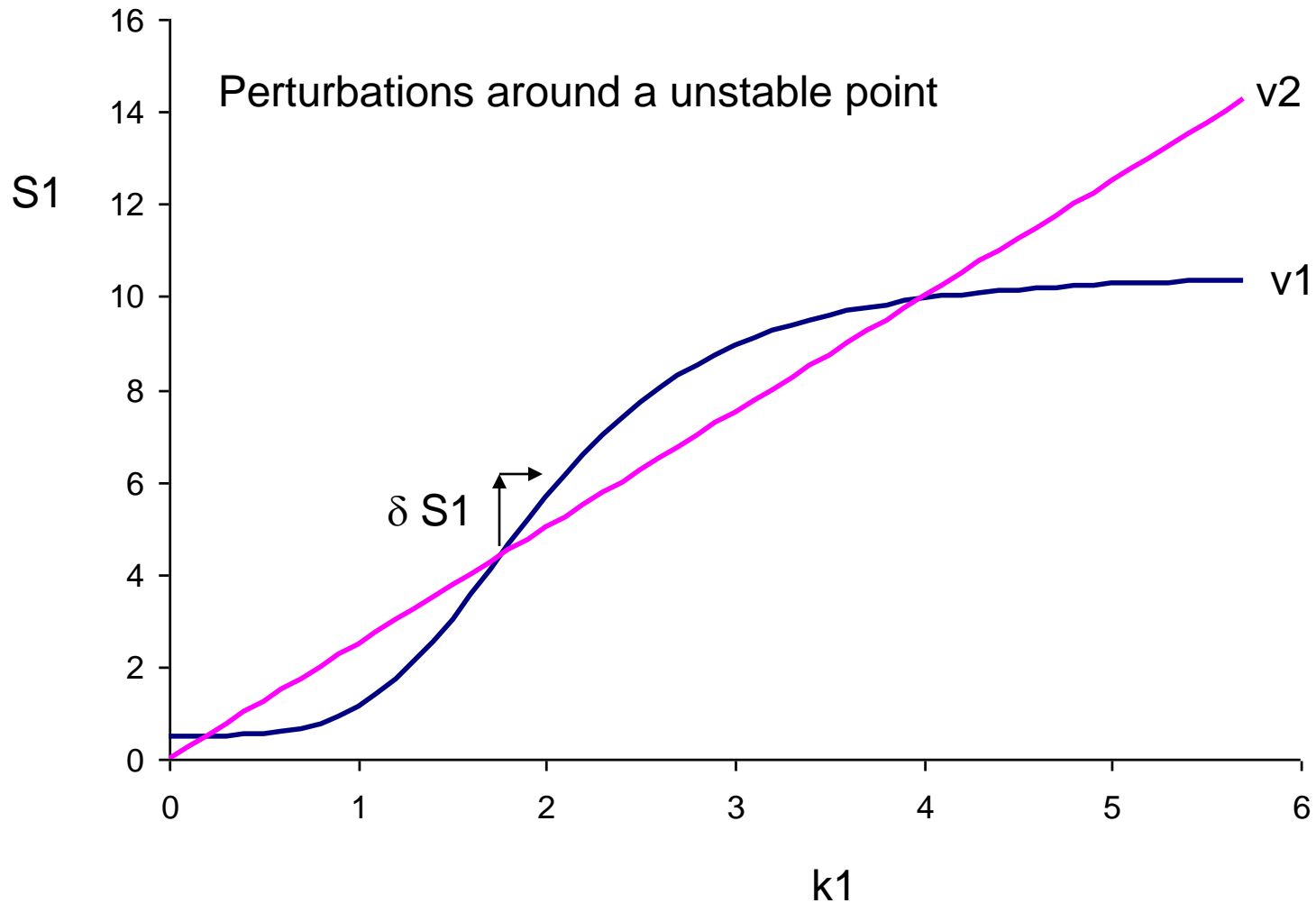
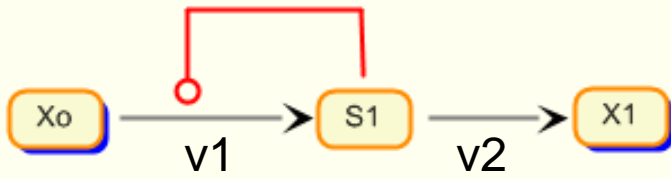
Positive Feedback



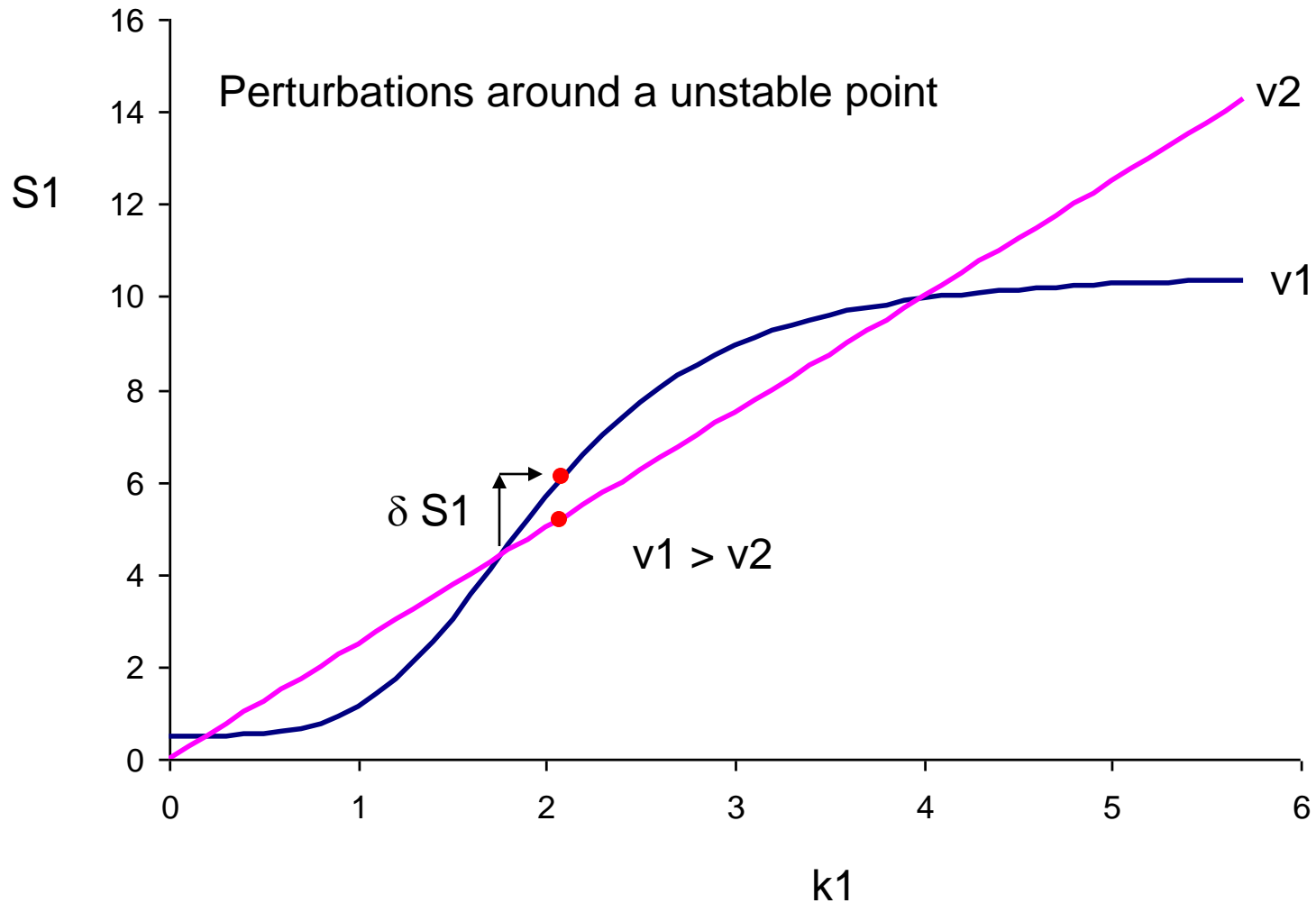
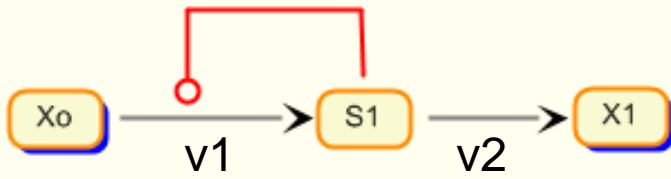
Positive Feedback



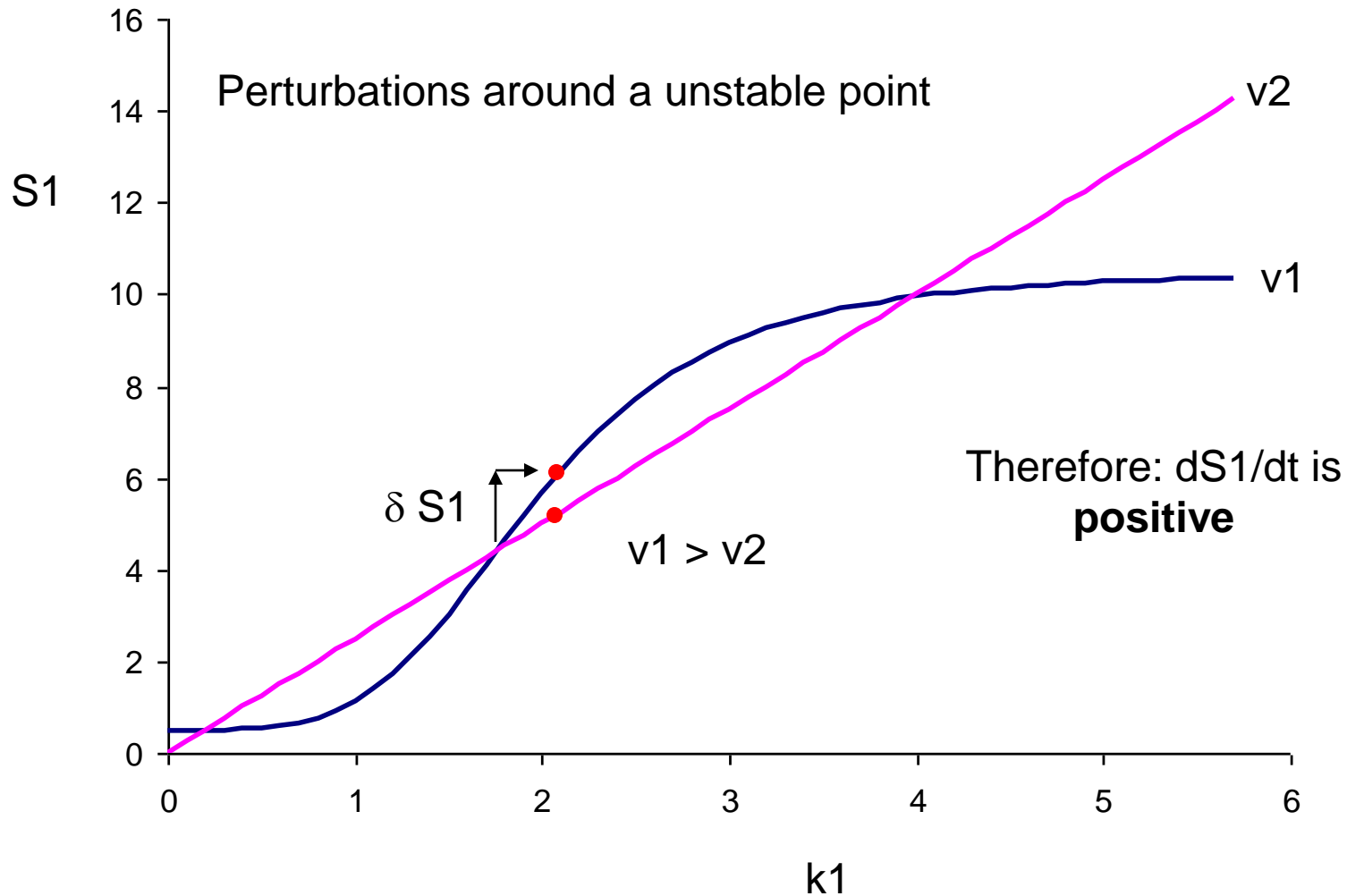
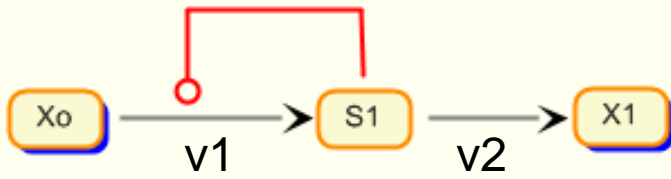
Positive Feedback



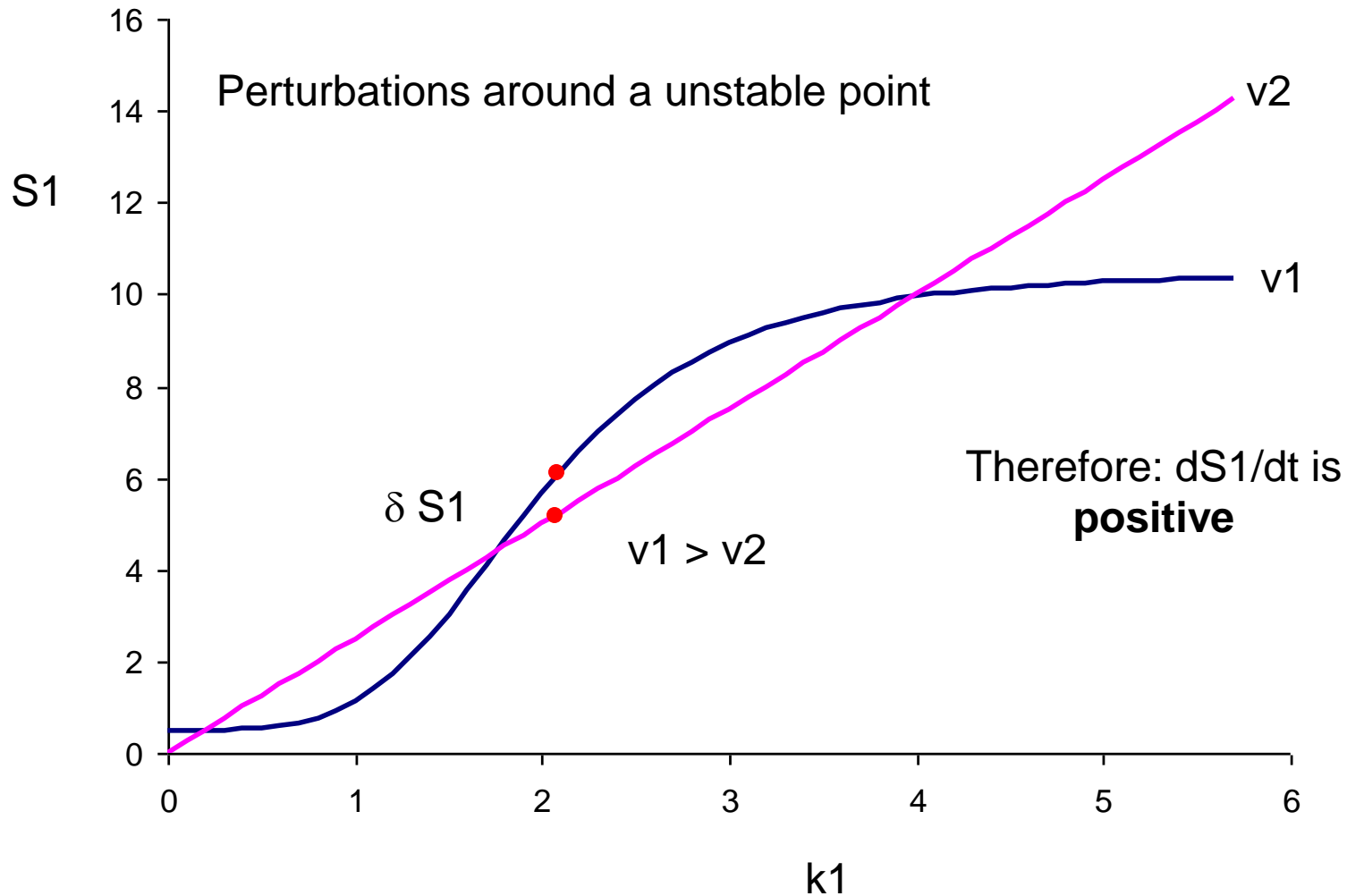
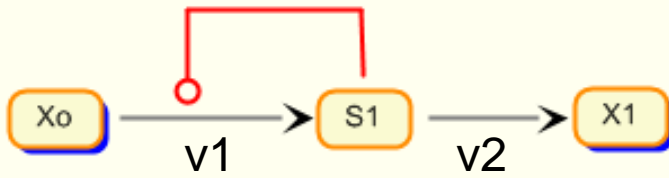
Positive Feedback



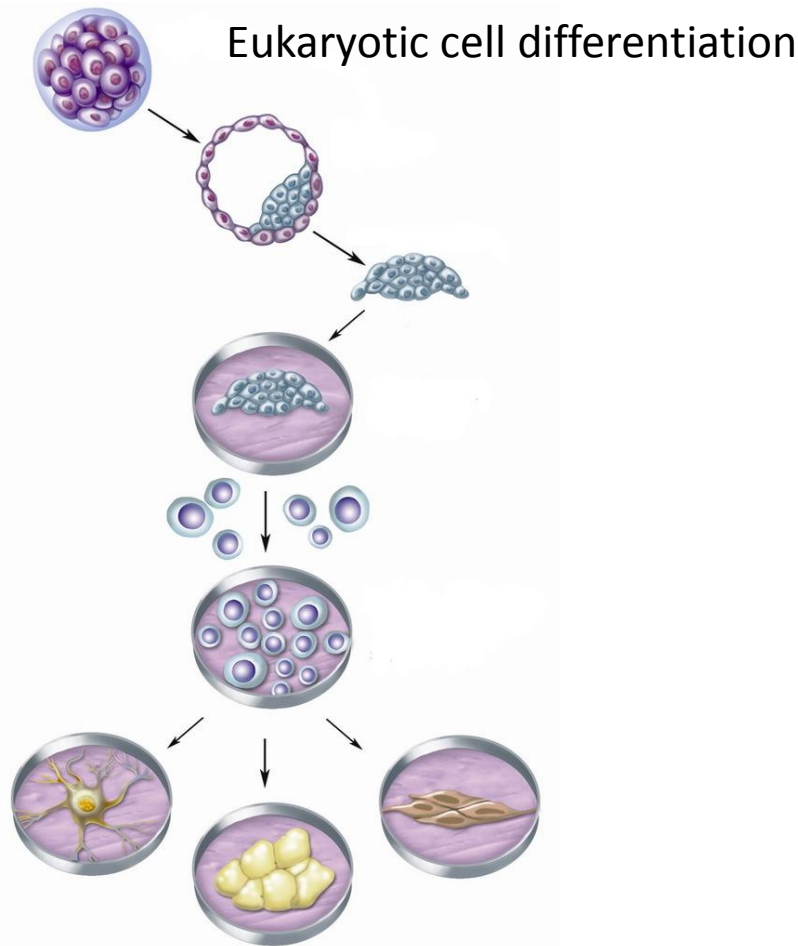
Positive Feedback



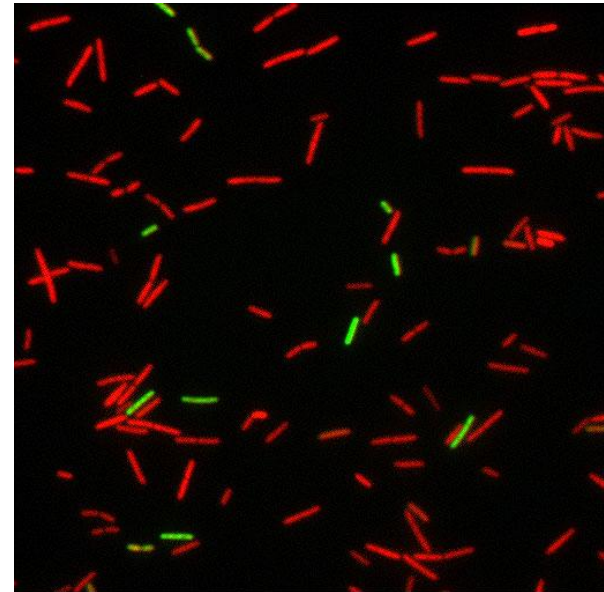
Positive Feedback



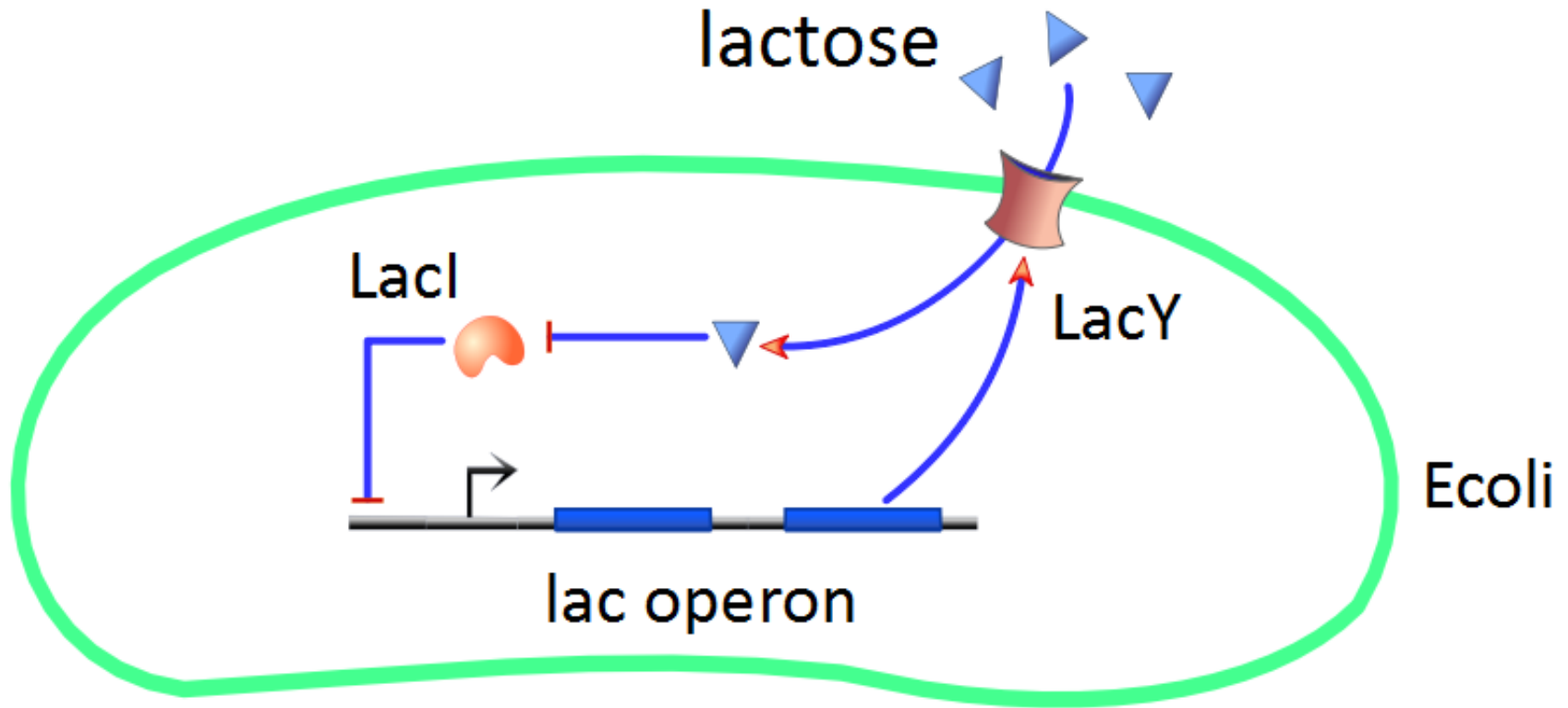
Where in nature do we find multiple steady states?



Bacterial differentiation and adaptation

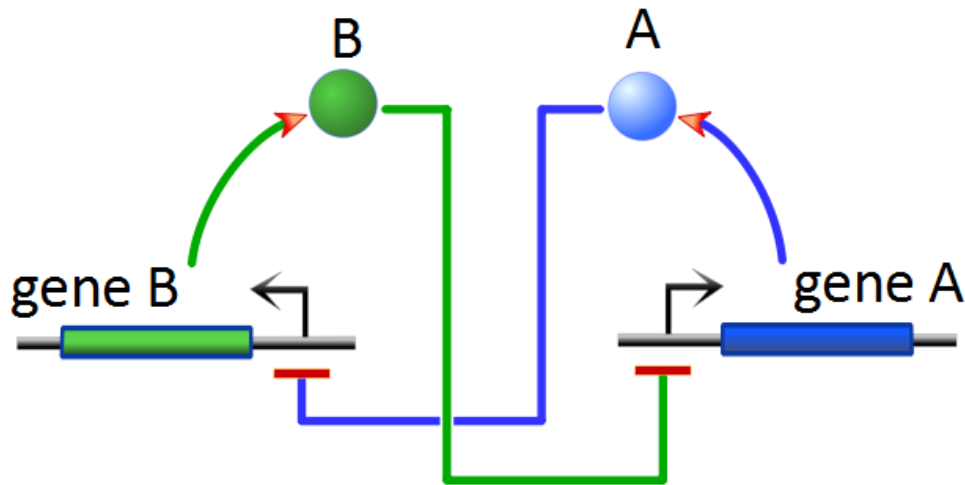


Bistability of the lac operon



Where is the positive feedback?

Genetic Toggle Switch



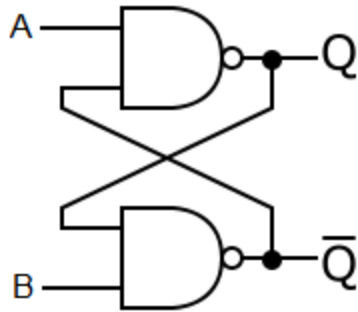
$$dA/dt = ?$$

$$dB/dt = ?$$

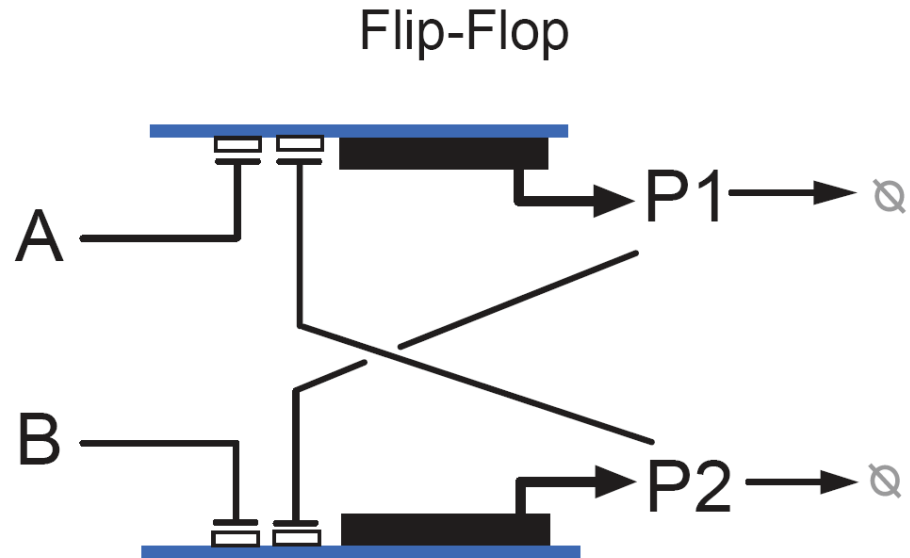
Where is the positive feedback?

Synthetic toggle switch has been built using *lacI* and *tetR* repressors.

Flip-Flop (Latch)



A	B	Q	\bar{Q}
1	0	1	0
0	0	1	0
0	1	0	1
0	0	0	1
1	1	?	?

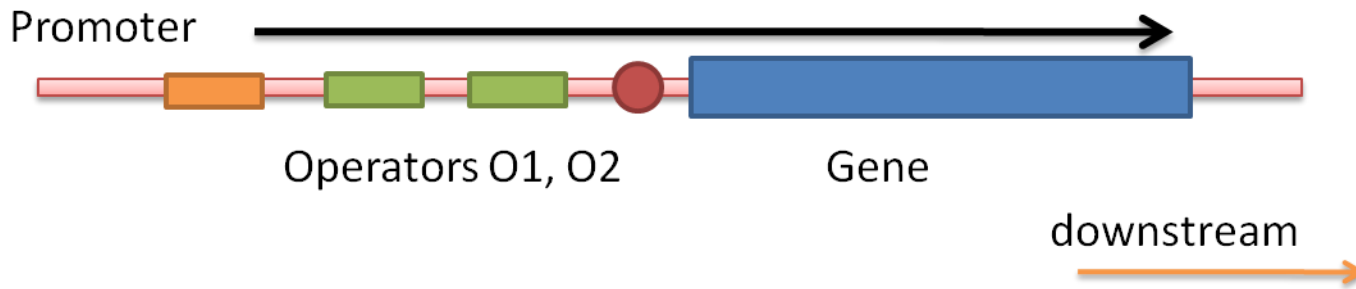
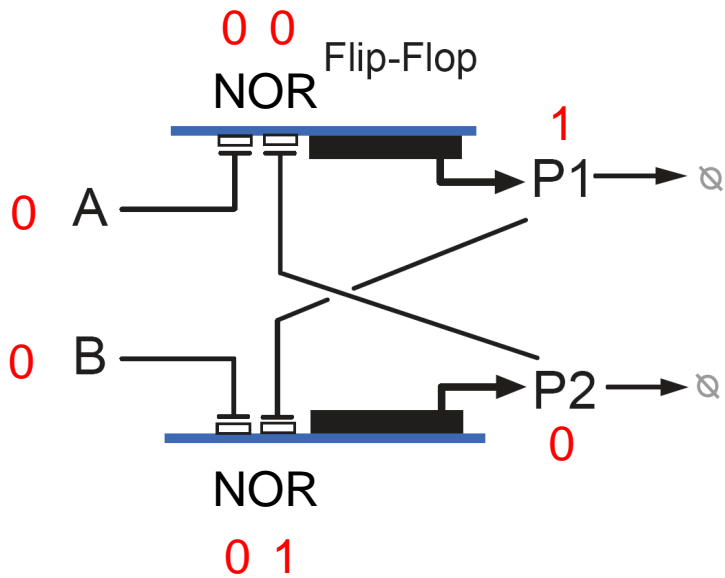


Flip-flops can be made either from NAND or NOR gates. In synthetic biology it is probably easier to construct OR like gates than AND gates.

In addition an OR based flip-flop is quiescent when both inputs are low, meaning low protein levels. Latching occurs when one or other of the inputs is brought to a high state.¹⁸

Flip-Flop

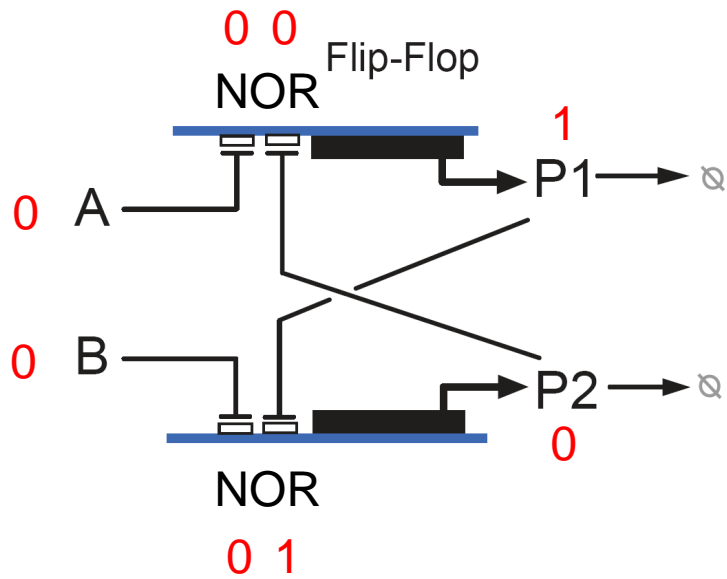
A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



Making NOR gates is 'relatively' easy and requires only two operator sites downstream of the RNA polymerase binding site (promoter).

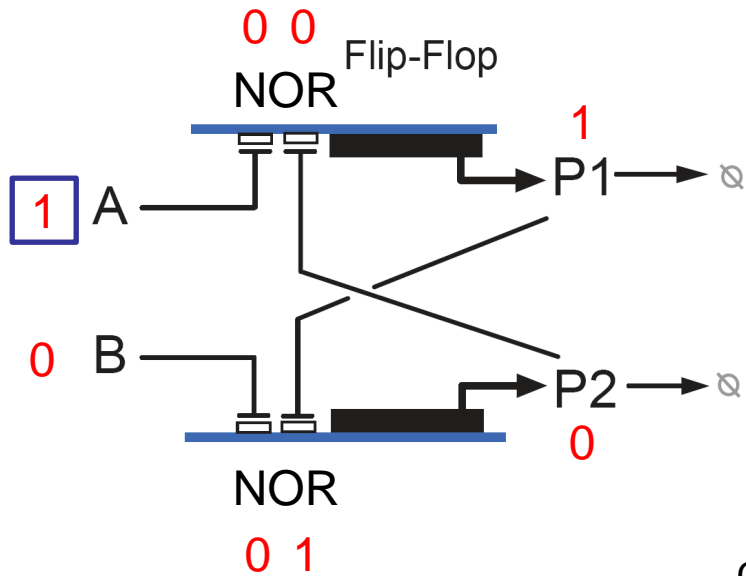
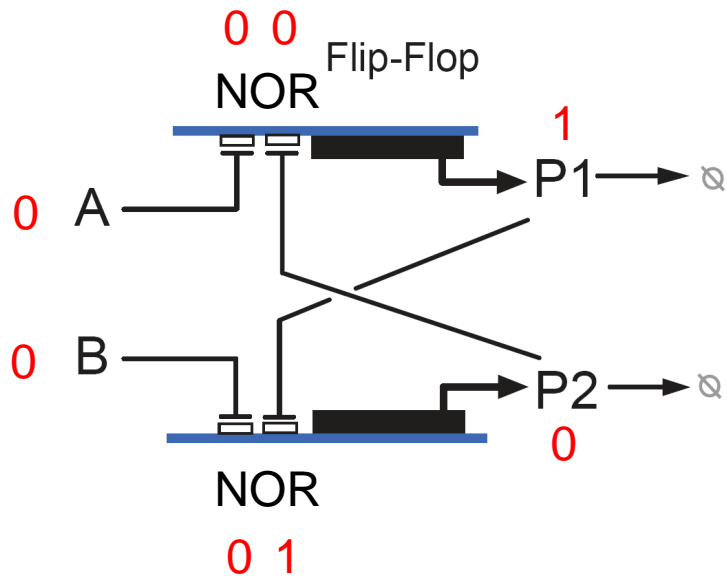
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



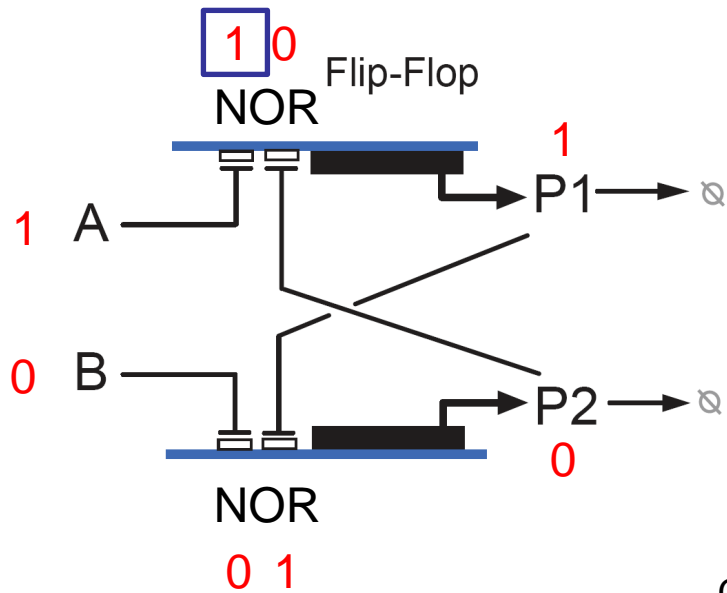
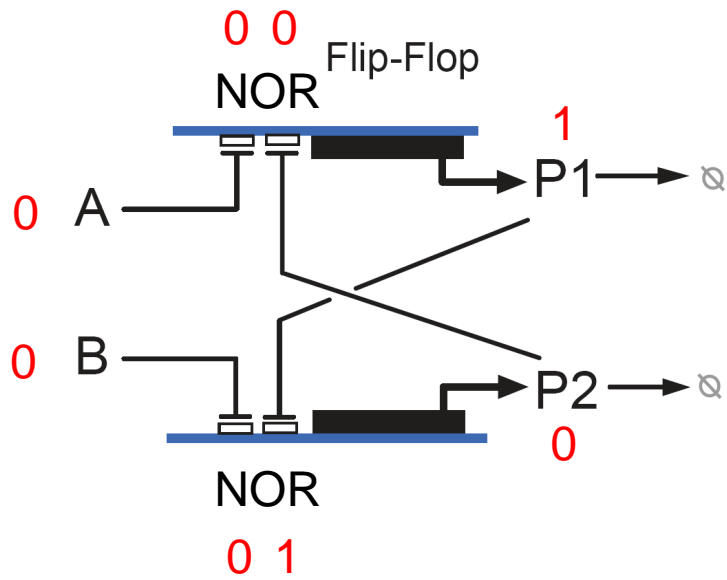
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



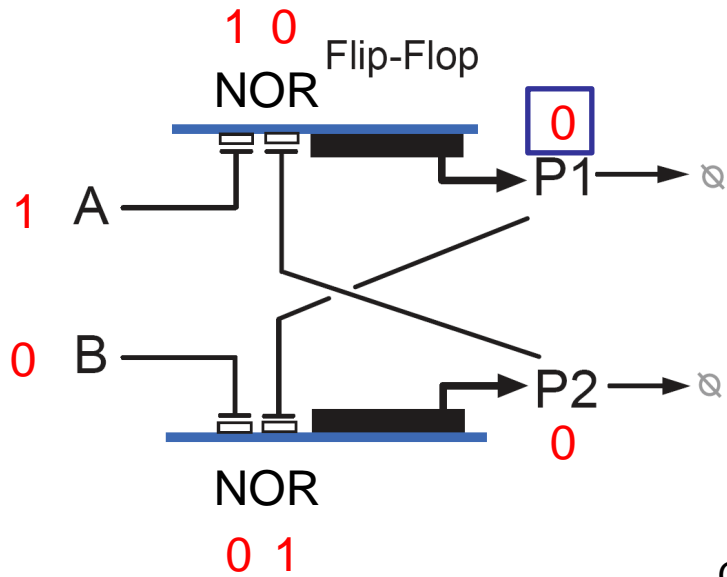
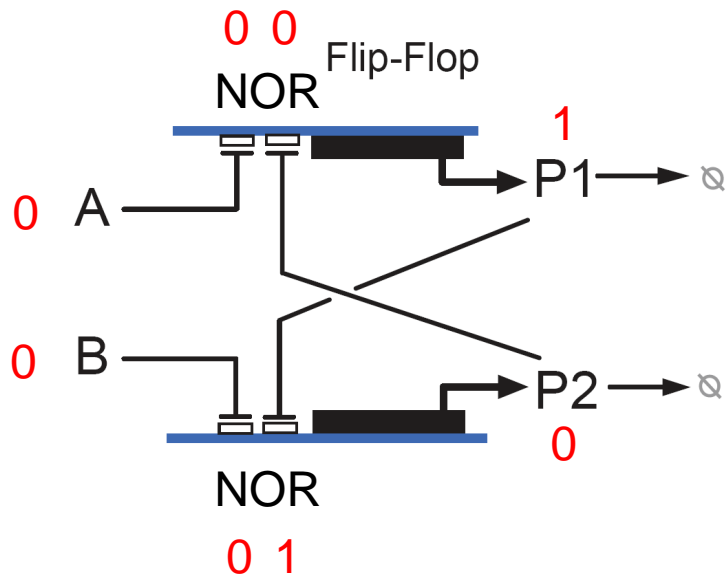
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



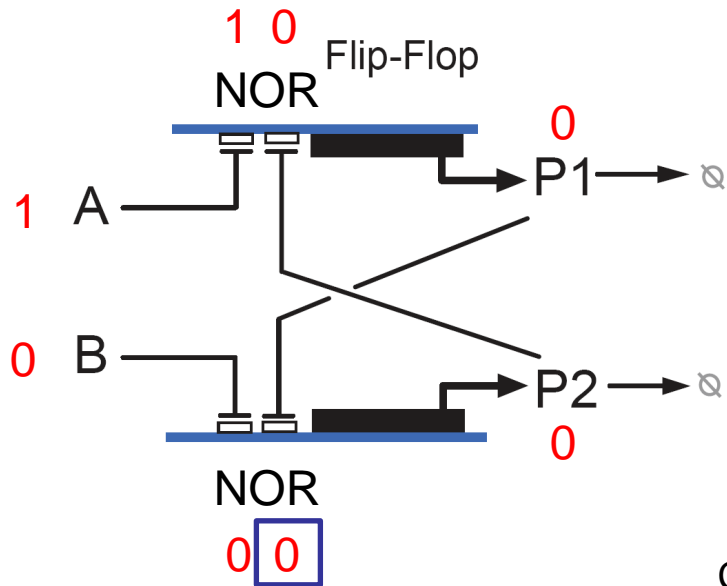
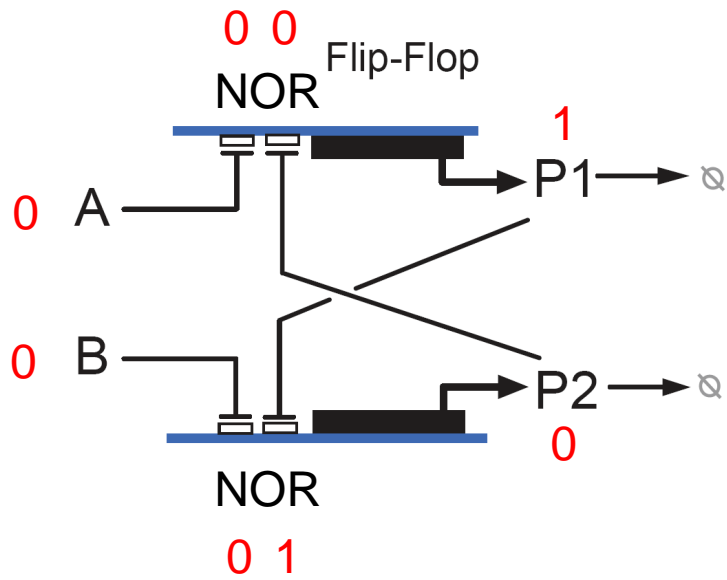
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



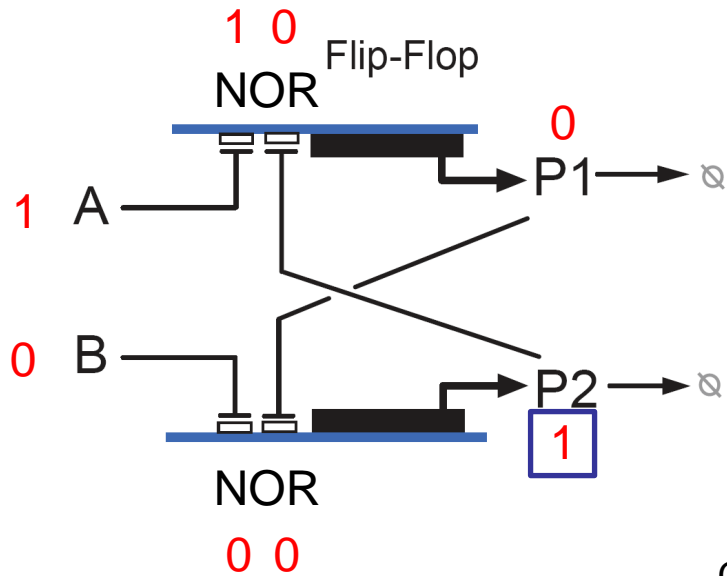
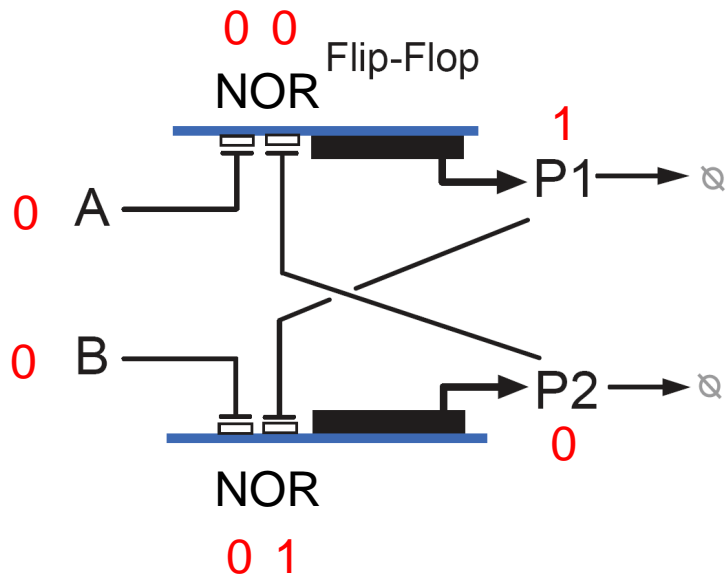
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



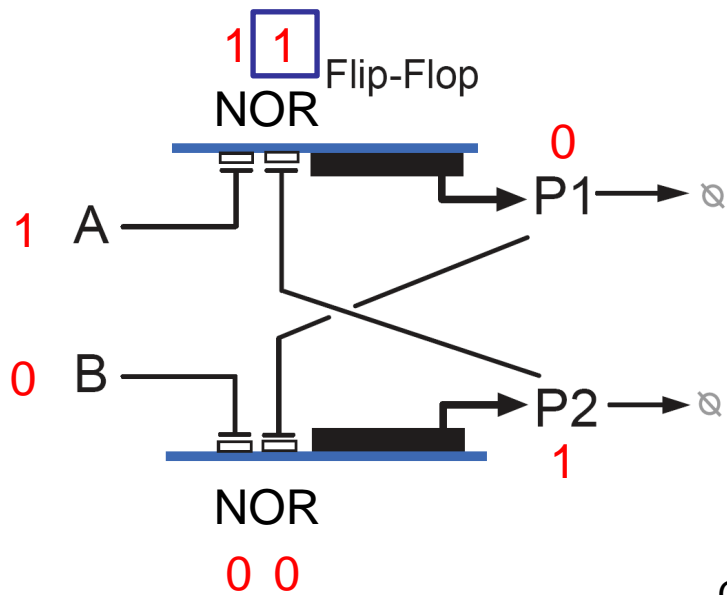
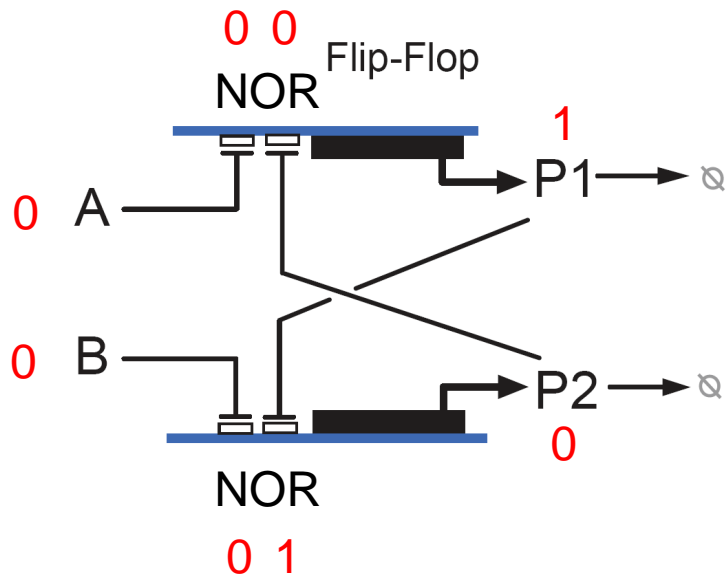
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



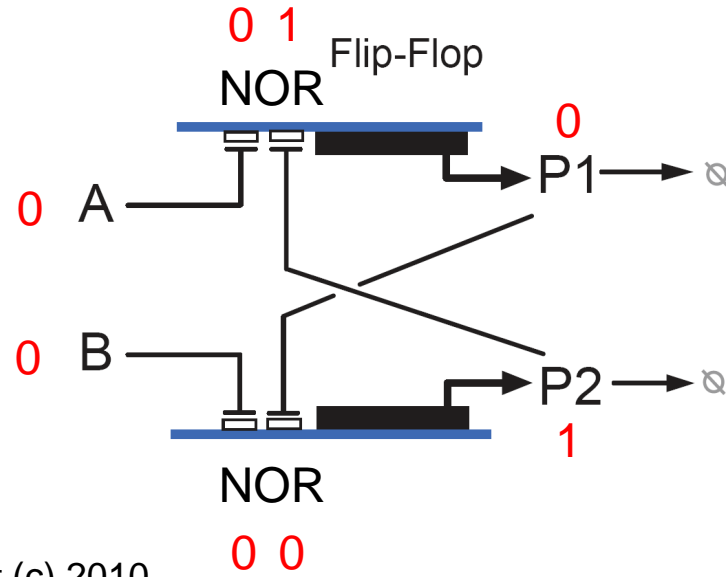
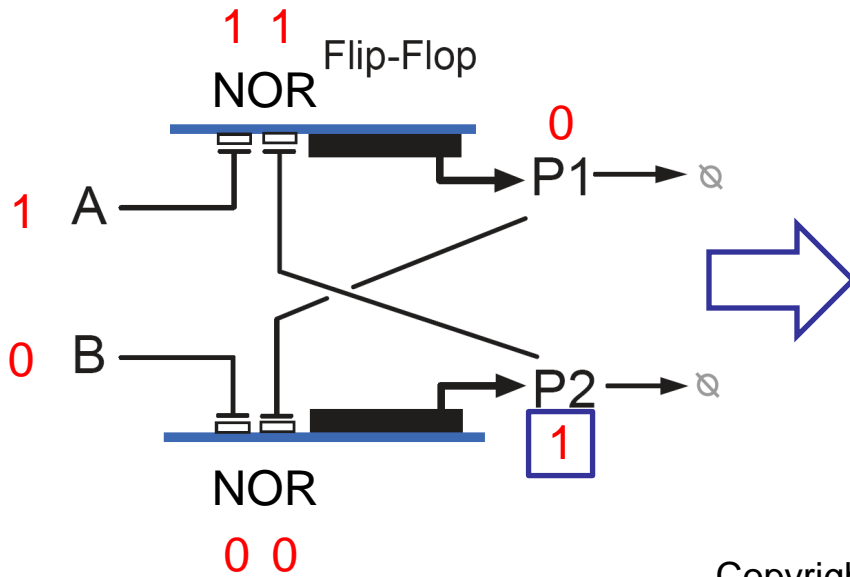
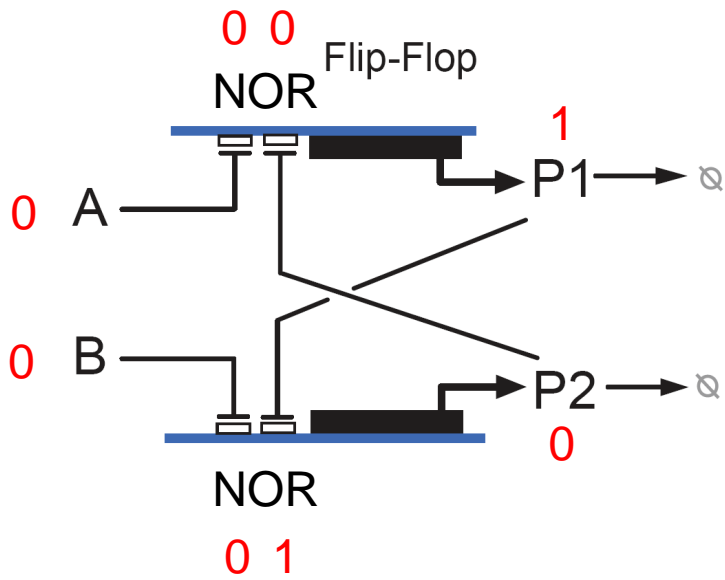
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



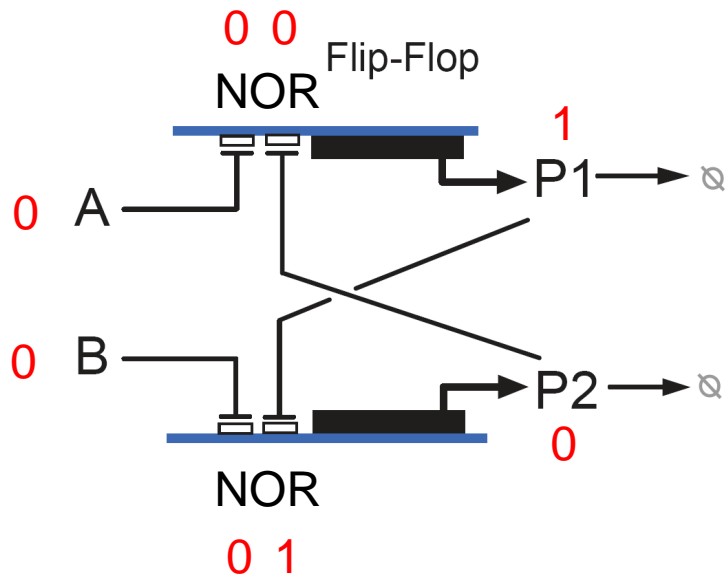
Flip-Flop

A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1

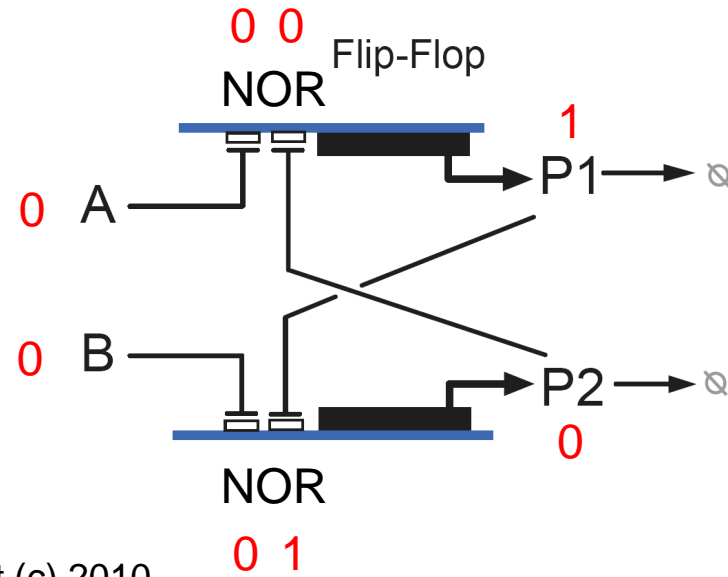
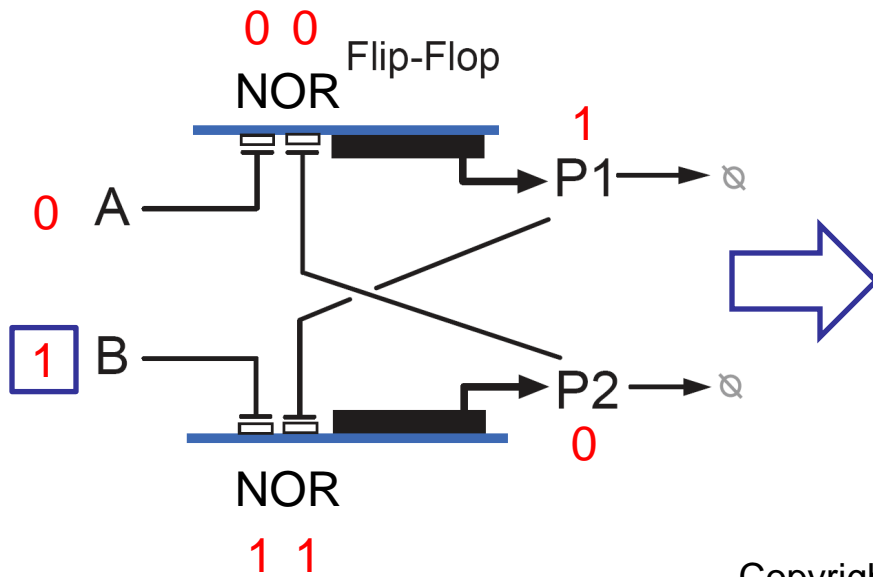


Flip-Flop

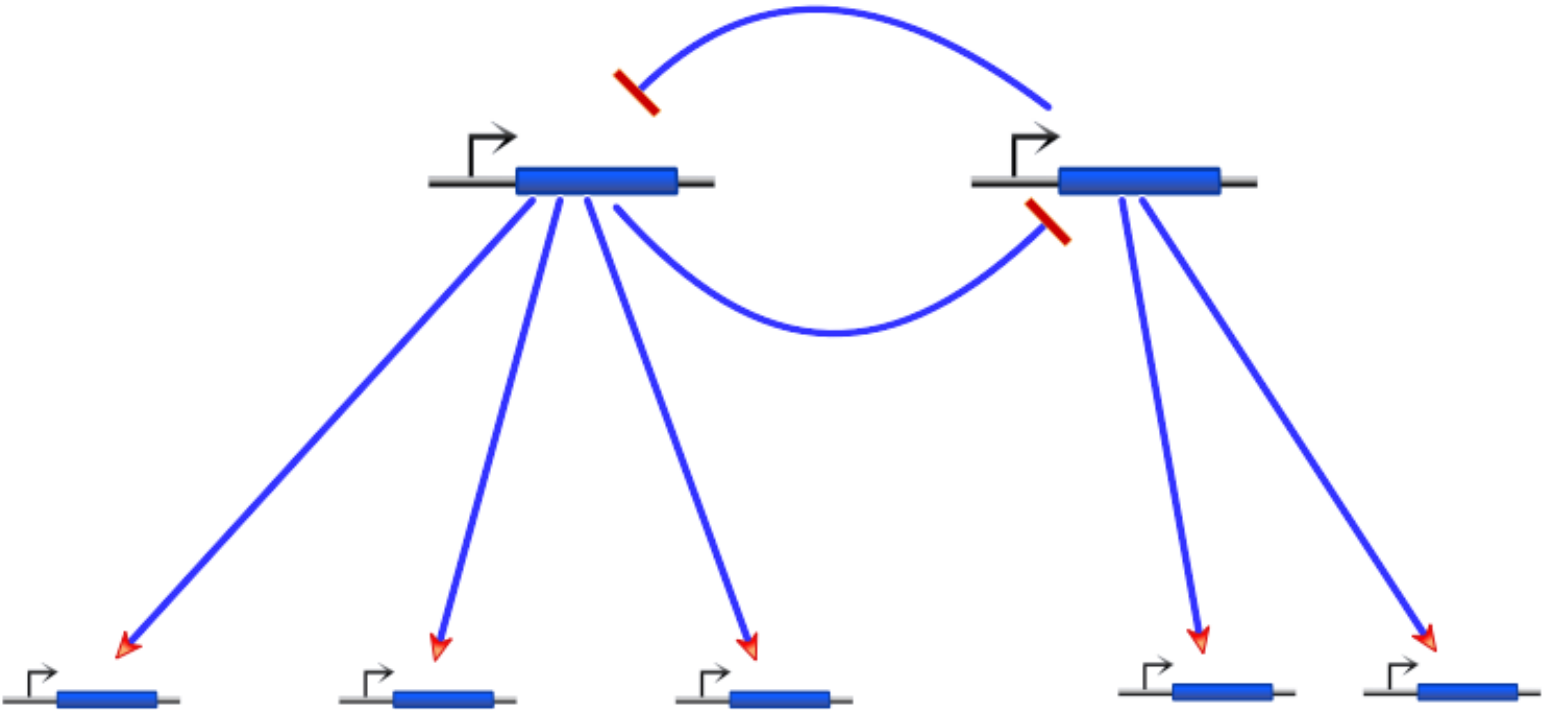
A	B	NOR
1	1	0
0	1	0
1	0	0
0	0	1



Toggle A to reset P1
Toggle B to set P1

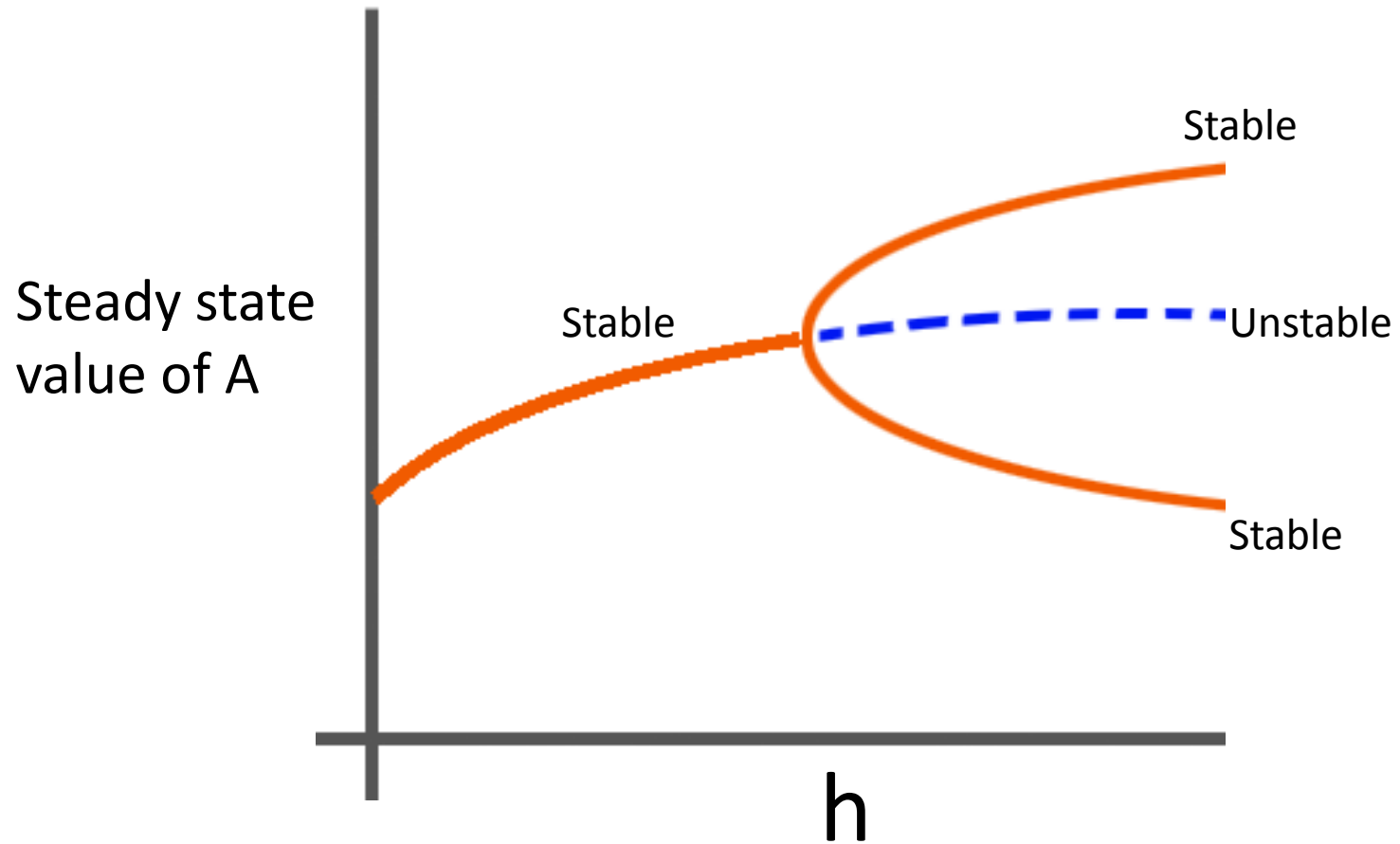


Network structures involving toggle switches

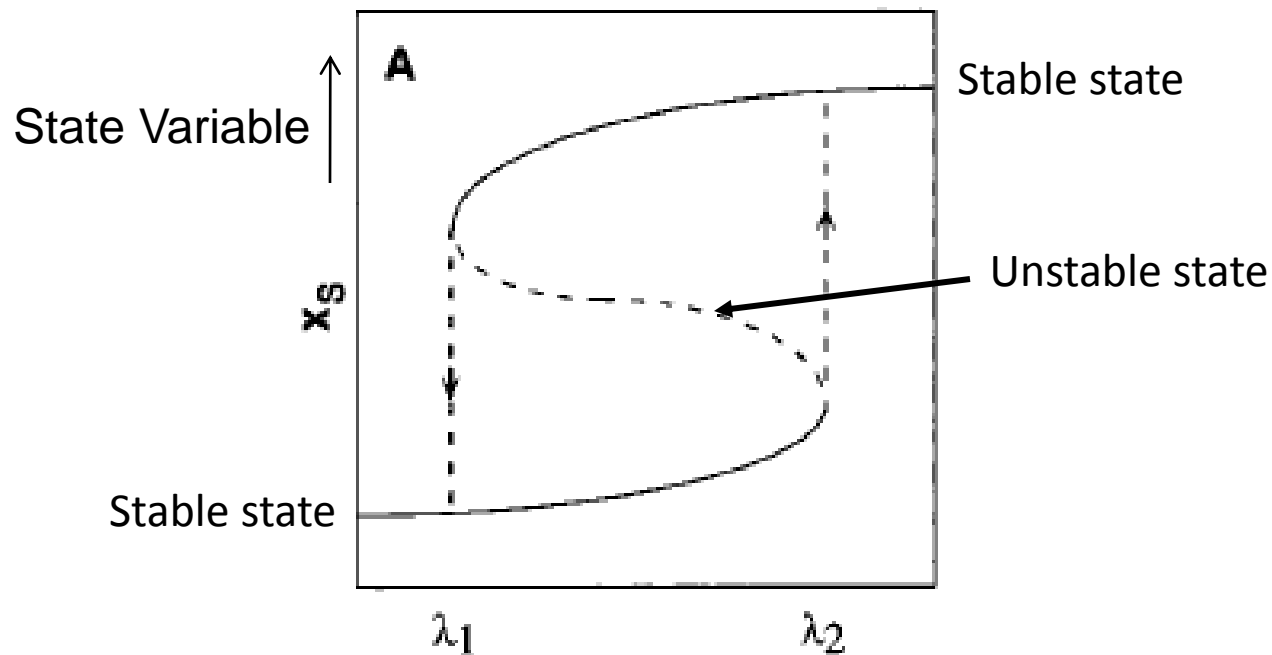


Developmental Switch

Bifurcation Diagram



Bistability with Hysteresis



One of the parameters in the model

Bistability with Irreversibility

