Designing multistability with AND gates

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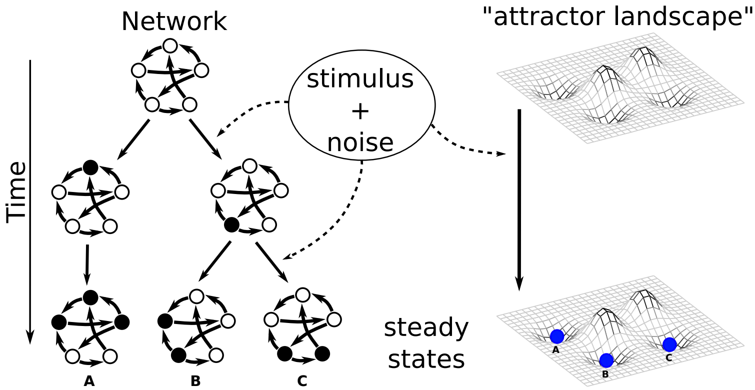
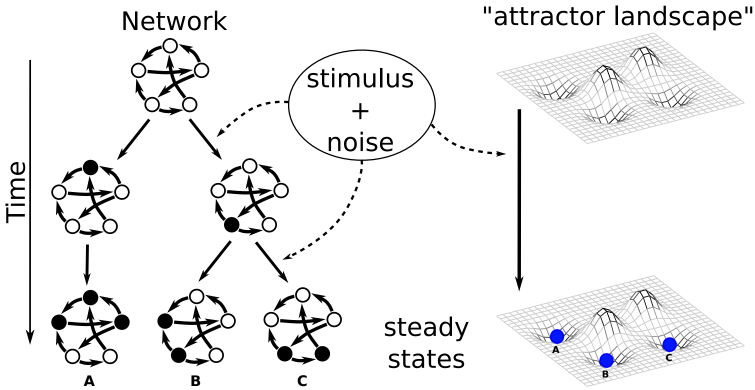
Outline

Problem


Network
"attractor landscape"
Time
stimulus
+
noise
steady
states
A
B
C
A
B
C

Problem



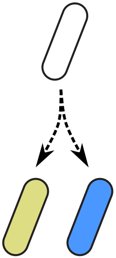
How can we control the attractor landscape?

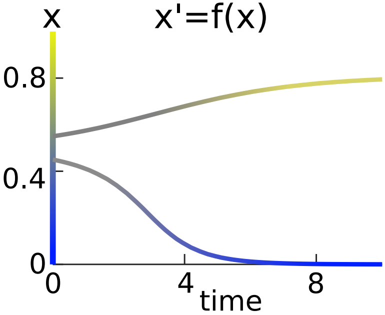
Outline

1. Introduction/Motivation
   - Bistability
2. Preliminaries
   - Approach
   - Conjunctive networks
3. Results
   - Designing multistability
   - Minimal networks

Bistability

Two coexisting stable patterns:





How to design bistability?

Minimal network must have a positive feedback loop.

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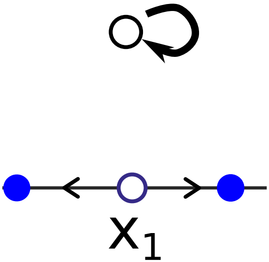
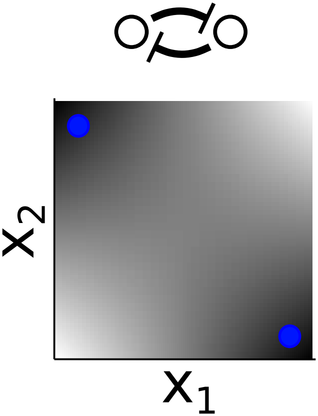
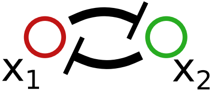
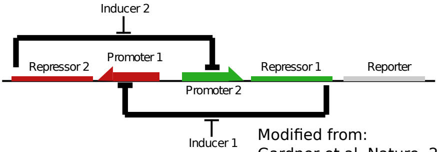




Example of designed bistability: Genetic toggle switch





Modified from:
Gardner et al. Nature, 2000.

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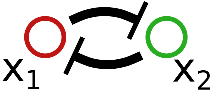

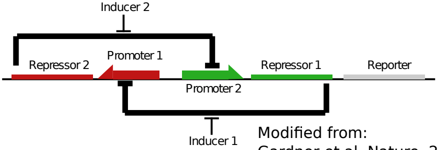

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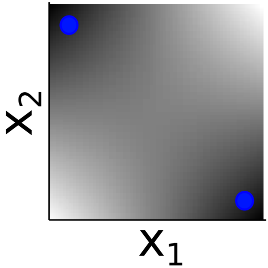
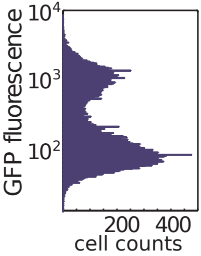
Gardner et al. Nature, 2000.

Synthetic gene network is bistable!

$$\frac{dx_1}{dt} = \frac{1}{1+(x_2/\theta)^n} - x_1$$

$$\frac{dx_2}{dt} = \frac{1}{1+(x_1/\theta)^n} - x_2$$





Gardner et al.
Nature, 2000.

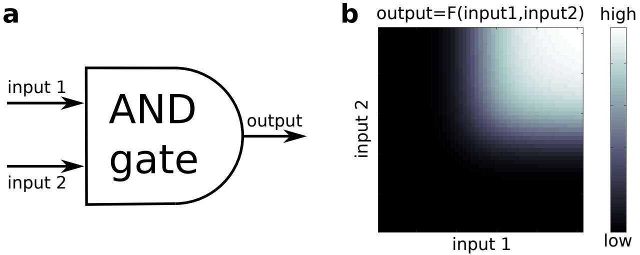
Main questions

- How to design multistability? How to construct a network that has a given number of stable steady states?

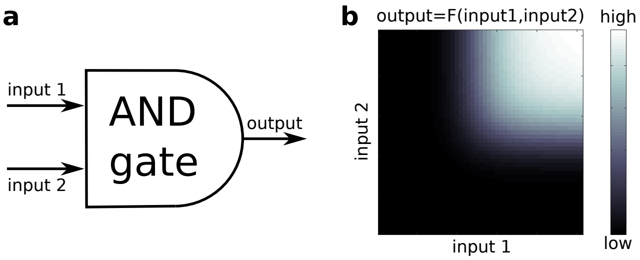
- How to make the size of the network (number of variables) minimal?

Outline

AND gates


a
input 1
input 2
AND
gate
output
b
output=F(input1,input2)
high
low
input 1
input 2

AND gates



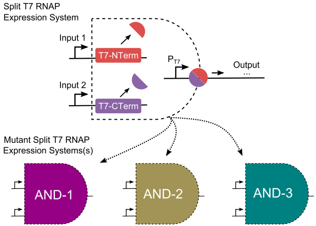
AND gates can be modeled as a product of Hill functions

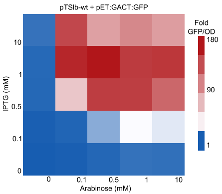
$$\text{output} = H(x_1)H(x_2)\cdots H(x_N)$$

$$\text{where } H(z) = \frac{z^n}{\theta^n + z^n}, \quad \theta = 0.5 \text{ (threshold)}, \quad n = \text{large}$$

Why AND gates?

- AND gates have already been constructed in the lab





Shis et al, 2013, PNAS

- Positive interaction can be replaced by two negative interactions

$$\text{input} \rightarrow \text{output}$$

$$\text{input} \dashv \text{inter.} \dashv \text{output}$$

Differential equations with AND gates

A system of differential equations of the form $\dfrac{dx_i}{dt} = \displaystyle\prod_{k \in I_i} \frac{x_k^n}{\theta^n + x_k^n} - x_i$ is called a *conjunctive network*.

Differential equations with AND gates

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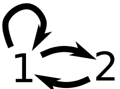
Example.

$$\frac{dx_1}{dt} = \frac{x_1^n}{\theta^n + x_1^n} \frac{x_2^n}{\theta^n + x_2^n} - x_1,$$
$$\frac{dx_2}{dt} = \frac{x_1^n}{\theta^n + x_1^n} - x_2$$



wiring diagram

Outline

Main questions

1. How to design a network that has a given number of stable steady states?

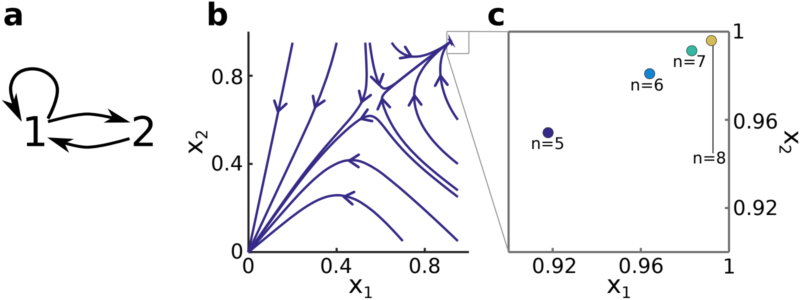
2. How to make the number of variables minimal?

Main results

1. There exists an algorithmic way to design a network with a given number of stable steady states.

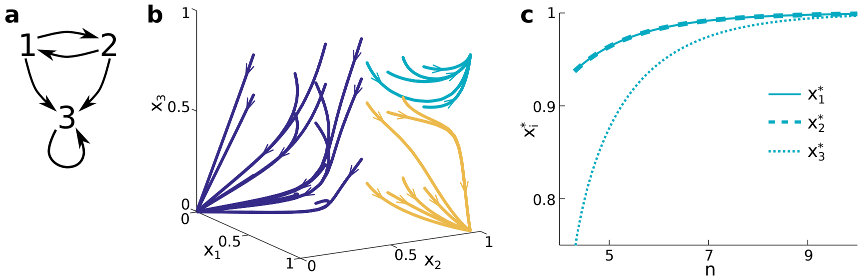
Number of stable steady states

Lemma. (For large n) A conjunctive network with strongly connected wiring diagram has exactly 2 stable steady states; the zero steady state and a *positive* steady state that converges to $\mathbf{1} = (1, \ldots, 1)$.



Number of stable steady states

What about the general case?



Number of stable steady states

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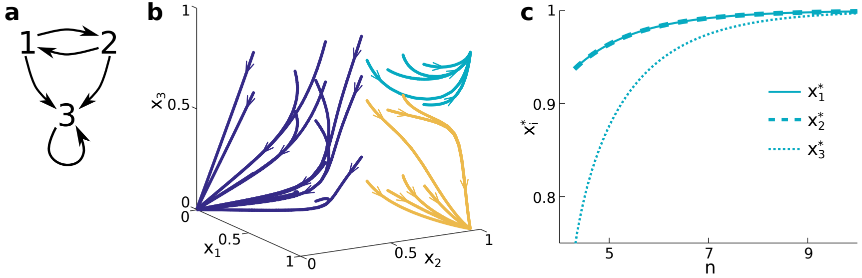

More than 2 stable steady states!

Number of stable steady states

Consider a conjunctive network with **strongly connected components** (scc) $G_1, \ldots, G_r$.

Number of stable steady states

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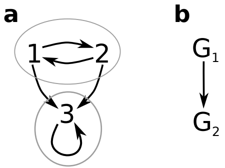

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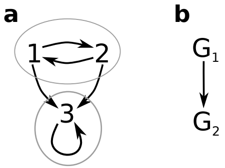
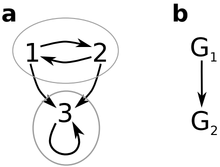


Theorem. (For large n) For any antichain $\{G_{k_1}, \ldots, G_{k_l}\}$ (collection of scc that have **no path between them**), there is a stable steady state x such that $x_i = 0$ if there is a path from some G_{k_j} to i. Also, all stable steady states have that form.

Number of stable steady states

Example.



There are 3 antichains: $\{\ \}, \{G_1\}, \{G_2\}$,
corresponding to: (“1”,“1”,“1”), (0,0,0), (“1”,“1”,0),

The conjunctive network has 3 steady states.

Number of stable steady states: Large example

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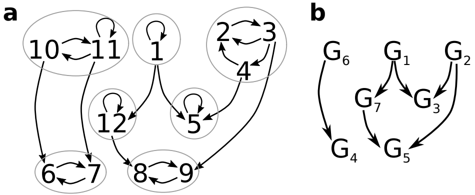

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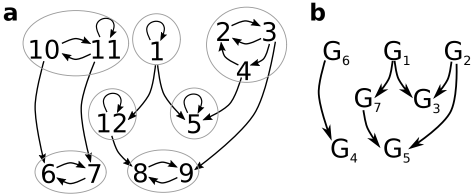
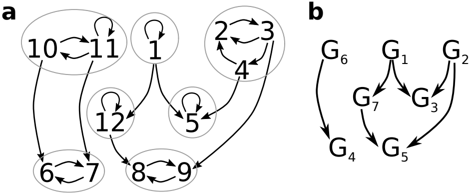


Theorem. (For large n) If $\{G_{k_1}, \ldots, G_{k_l}\}$ is an antichain, then there is a stable steady state x such that $x_i = 0$ if there is an path from some G_{k_j} to i. Furthermore, all stable steady states have that form.

Number of stable steady states: Large example

Example.



Number of stable steady states: Large example

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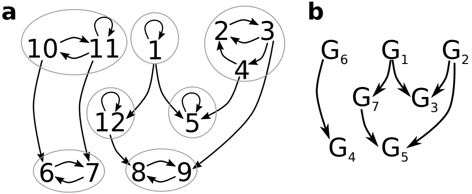

There are 30 antichains: $\emptyset$, $\{G_1\}$, $\{G_2\}$, $\{G_3\}$, $\{G_4\}$, $\{G_5\}$, $\{G_6\}$, $\{G_7\}$, $\{G_1, G_2\}$, $\{G_1, G_4\}$, $\{G_1, G_6\}$, $\{G_2, G_4\}$, $\{G_2, G_6\}$, $\{G_2, G_7\}$, $\{G_3, G_4\}$, $\{G_3, G_5\}$, $\{G_3, G_6\}$, $\{G_3, G_7\}$, $\{G_4, G_5\}$, $\{G_4, G_7\}$, $\{G_5, G_6\}$, $\{G_6, G_7\}$, $\{G_1, G_2, G_4\}$, $\{G_1, G_2, G_6\}$, $\{G_2, G_4, G_7\}$, $\{G_2, G_6, G_7\}$, $\{G_3, G_4, G_5\}$, $\{G_3, G_4, G_7\}$, $\{G_3, G_5, G_6\}$, $\{G_3, G_6, G_7\}$

The conjunctive network has 30 steady states.

Outline

Designing networks with arbitrary stable steady states

How can we design a network with s steady states?

ANS: Construct a wiring diagram with s antichains.

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For $s = 5$:

$$\frac{dx_1}{dt} = \frac{x_1^n}{\theta^n + x_1^n} - x_1$$

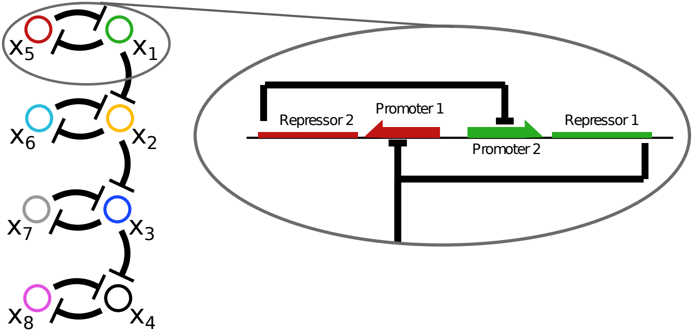
$$\frac{dx_2}{dt} = \frac{x_2^n}{\theta^n + x_2^n}\frac{x_1^n}{\theta^n + x_1^n} - x_2$$

$$\frac{dx_3}{dt} = \frac{x_3^n}{\theta^n + x_3^n}\frac{x_2^n}{\theta^n + x_2^n} - x_3$$

$$\frac{dx_4}{dt} = \frac{x_4^n}{\theta^n + x_4^n}\frac{x_3^n}{\theta^n + x_3^n} - x_4$$

Designing networks with arbitrary stable steady states

Biological example for $s = 5$:
Network topology of a gene network using repression only:



Outline

What about a network with 100 stable steady states?

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ANS: 99 variables

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How can we make the number of variables minimal?

What about a network with 100 stable steady states?

ANS: 99 variables

How can we make the number of variables minimal?

ANS: Smallest wiring diagram with s antichains (previous theorem)
$\mathcal{N}(s)$:= size of smallest wiring diagram with s antichains

Minimal networks: Preliminary remarks

Two cases for s = number of stable steady states:

Case 1. $s = 2^N$ for some N:

Minimal networks: Preliminary remarks

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Case 1. $s = 2^N$ for some N: Must use N uncoupled variables.

$$\frac{dx_i}{dt} = \frac{x_i^n}{\theta^n + x_i^n} - x_i \ , \quad i = 1, \ldots, N$$

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Idea: Start with N uncoupled variables (2^N stable steady states) and add connectivity.

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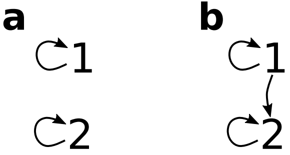
Example. For $s = 3$. Use $N = 2$ variables and add an edge from x_1 to x_2.



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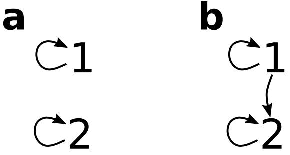
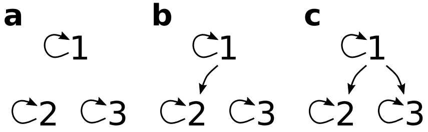


stable steady states: $2^2 = 4$ 3

Minimal networks: Preliminary remarks

Case 2. $2^{N-1} < s < 2^N$: Must use **at least** N variables.
Example. For $s = 5, 6, 7$. Use $N = 3$ variables and add connectivity.



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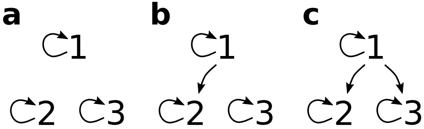

stable steady states: $2^3 = 8$ 6 5

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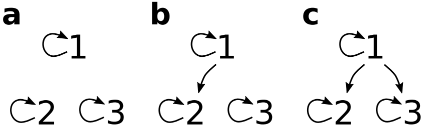

stable steady states: $2^3 = 8$ 6 5

No way to get 7 stable steady states this way!

Minimal networks with s stable steady states: Final remarks

If $2^{N-1} < s < 2^N$, then N is **not** always the minimal number of variables, but it is a lower bound.

Minimal networks with s stable steady states: Final remarks

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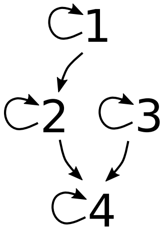
For $s = 7$ stable steady states, the minimal network has 4 variables.



$$
\begin{aligned}
\frac{dx_1}{dt} &= \frac{x_1^n}{\theta^n + x_1^n} - x_1 \\
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\end{aligned}
$$

Minimal networks with s stable steady states: Final remarks

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Minimal networks with s stable steady states: Final remarks

If $2^{N-1} < s < 2^N$, then N is **not** always the minimal number of variables.

If $\mathcal{N}(s)$:= size of smallest network with s steady states, then:

$\mathcal{N}(s)$ = size of smallest wiring diagram with s antichains

$\lceil \log_2(s) \rceil \leq \mathcal{N}(s)$

Minimal networks with s stable steady states: Final remarks

$\mathcal{N}(s_1 s_2) = \mathcal{N}(s_1) + \mathcal{N}(s_2)$?

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$\mathcal{N}(s_1 s_2) = \mathcal{N}(s_1) + \mathcal{N}(s_2)$?   No

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Minimal networks with s stable steady states: Final remarks

$\mathcal{N}(s_1 s_2) = \mathcal{N}(s_1) + \mathcal{N}(s_2)$?   No

$\mathcal{N}(s_1 s_2) \leq \mathcal{N}(s_1) + \mathcal{N}(s_2)$

It turns out that

$\mathcal{N}(s)$ = size of smallest topology with s open sets (OEIS A137813)

Future work

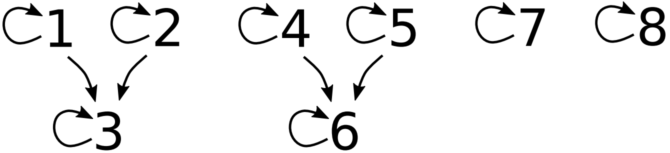
- Other gates (eg. OR, NAND)
- Achieve not only a given number but also a ”steady state signature”. Eg. What is the minimal size (N) of a network ($x_i' = f_i(x), i = 1, \ldots, N$) that has exactly 3 steady states such that $(x_1, x_2, x_3) = (1, 1, 0)$, $(0, 1, 1)$, $(1, 0, 1)$?

References/Funding

References

- A. Veliz-Cuba and R. Laubenbacher. Dynamics of semilattice networks with strongly connected dependency graph. Automatica, 2019.
- A. Veliz-Cuba et al. On the Relationship of Steady States of Continuous and Discrete Models Arising from Biology. Bulletin of Mathematical Biology, 2012.

Minimal network with 100 stable steady states



$5 \times 5 \times 2 \times 2 = 100$ stable steady states