The computational power of execution bounded chemical reaction networks

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UCDAVIS
COMPUTER SCIENCE

Acknowledgments

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Matthias Köppe
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UC Davis

For teaching us about
"*Theorems of the Alternative*"

Chemical reaction networks

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reactant(s) $R \rightarrow P_1 + P_2$ *product(s)*

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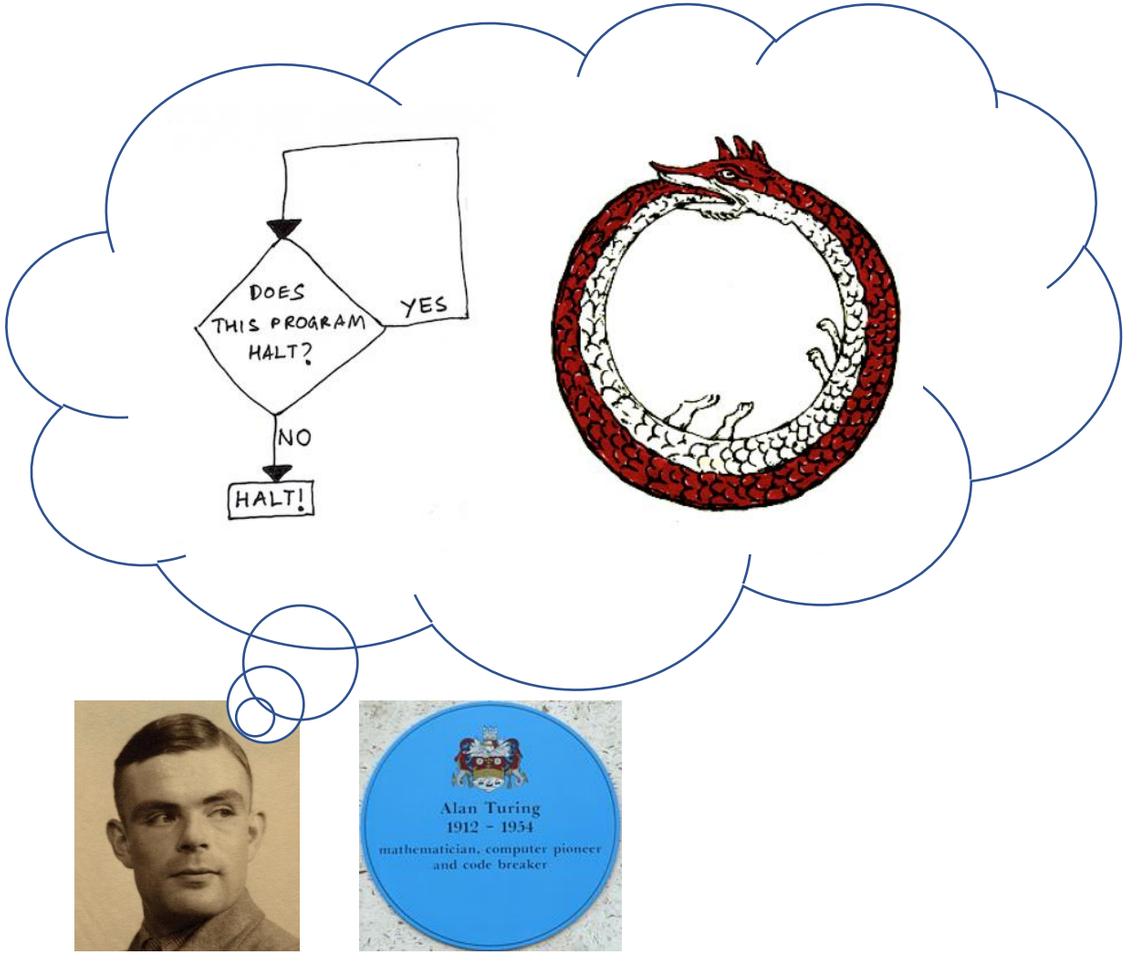
Traditionally a descriptive modeling language…
Let's instead use it as a prescriptive programming language

Theoretical Computer Science Approach



What computation is possible and what is not?
(Computability theory)

NP

NP-complete

protein folding

Boolean satisfiability

Hamiltonian path

integer factoring

P

DNA sequence alignment

polynomial factoring

integer multiplication

shortest path

What computations necessarily take a long time and what can be done quickly?
(Computational complexity theory)

Outline

- **Formal definition of chemical reaction networks**
- Execution bounded chemical reaction networks and linear potential functions
- What is “computation” with chemical reactions?
- Limitations of computation with execution bounded chemical reaction networks
- Possibilities of computation with execution bounded chemical reaction networks

Chemical Reaction Network (CRN)

- finite set of *d* species $\Lambda = \{ A, B, C, D, \ldots \}$
- finite set of reactions: *e.g.*

$$A+B \rightarrow A+C$$

$$C \rightarrow A+A$$

$$C+B \rightarrow C$$

- state $\mathbf{x} \in \mathbb{N}^d$: molecular counts of each species

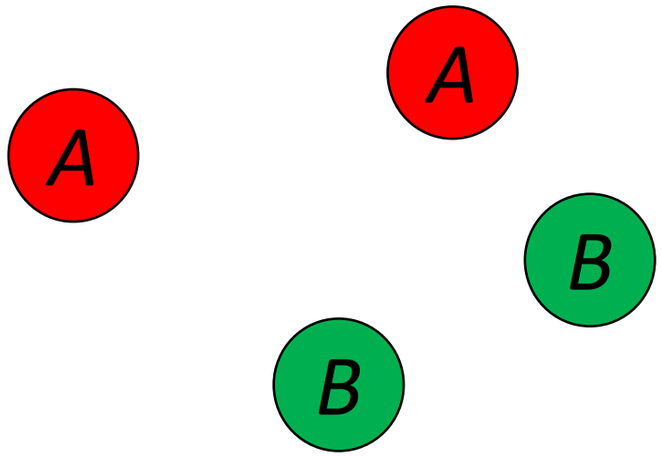
What is **possible**:

Example execution (reaction sequence)

α: $A + B \rightarrow A + C$

β: $C \rightarrow A + A$

A	*B*	*C*
x =	**(2,**	**2,**	**0)**



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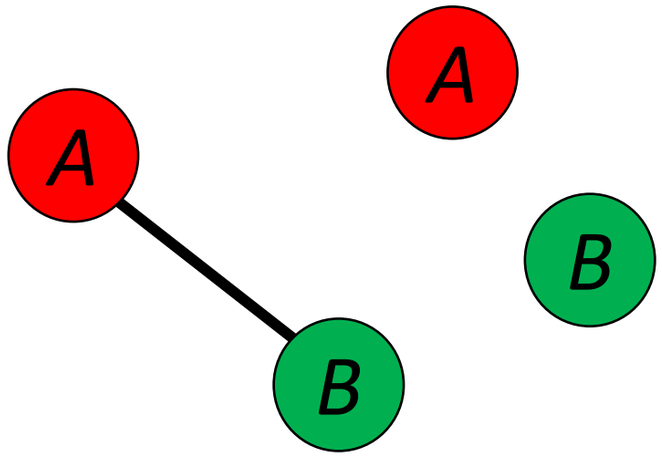

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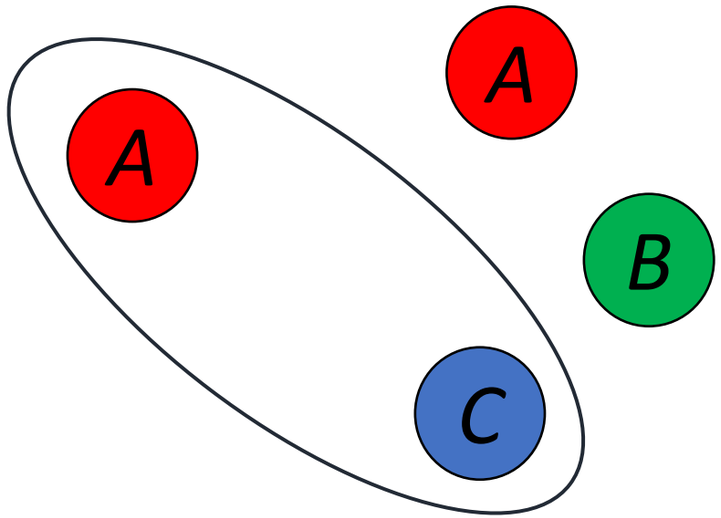

	A	*B*	*C*
x =	2,	2,	0)
	α ⇓		
	2,	1,	1)

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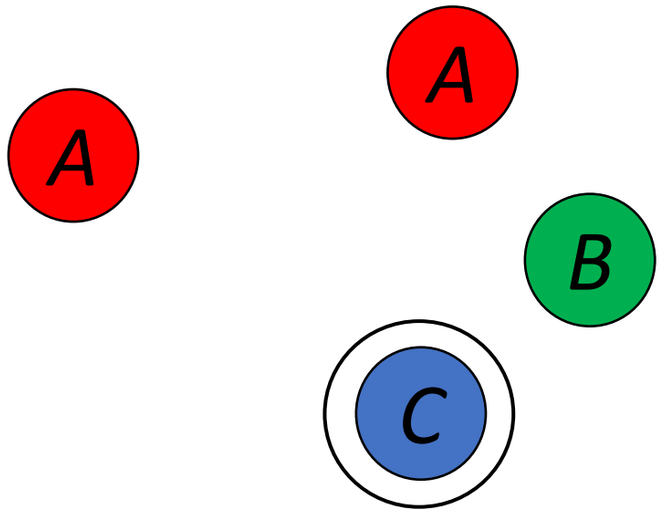

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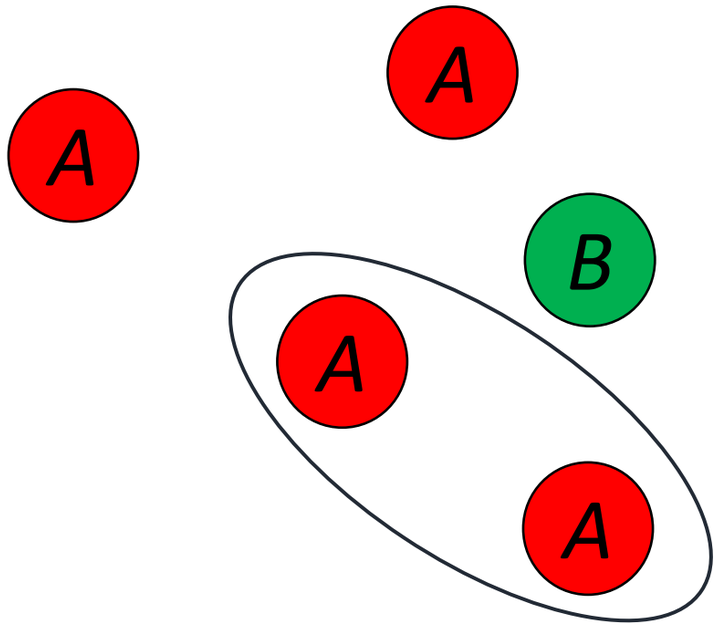

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	β ⇓		⇘α
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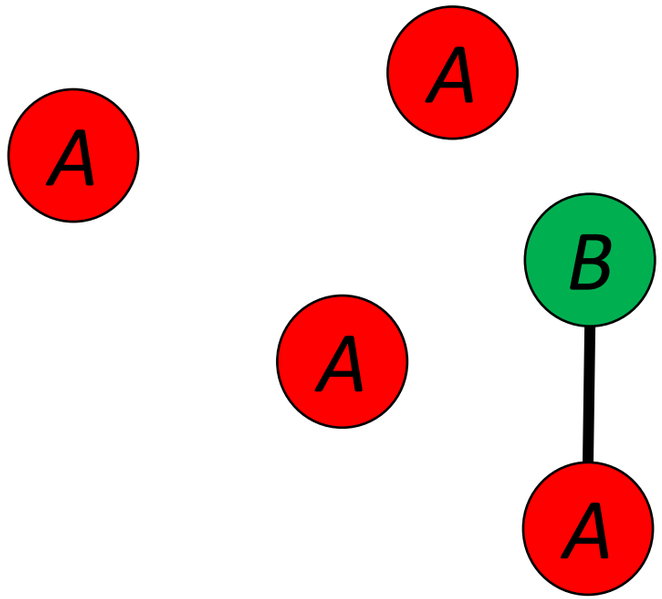

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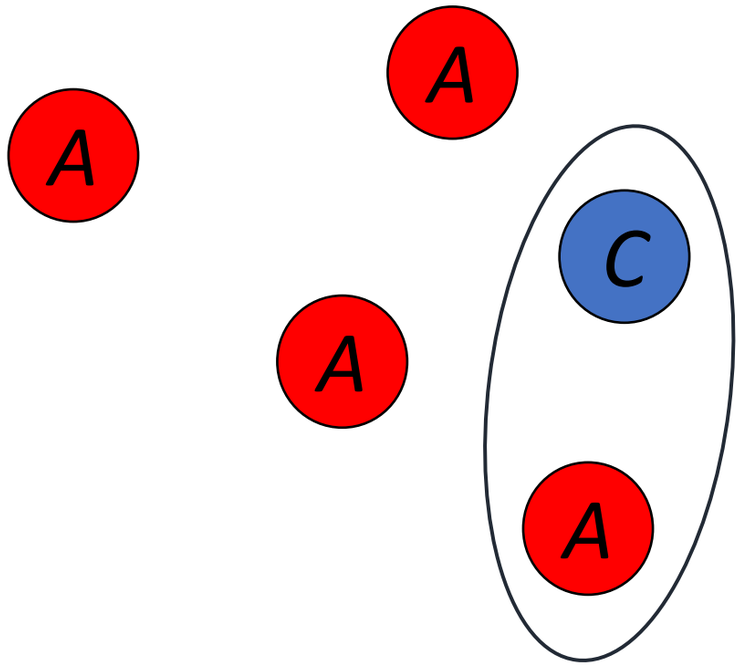

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	...		

Key property of reachability: additivity

If we can reach from state **x** to **y**, written **x** $\Rightarrow$ **y**, then for all **c** $\in \mathbb{N}^d$, **x**+**c** $\Rightarrow$ **y**+**c**

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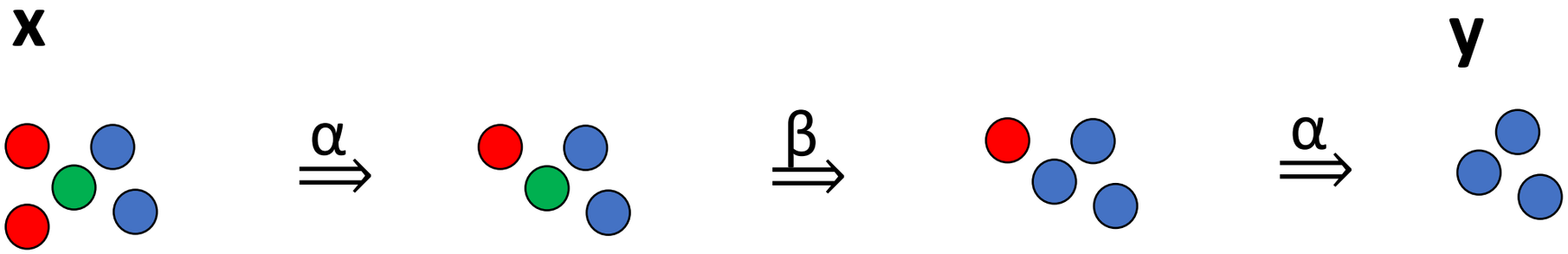

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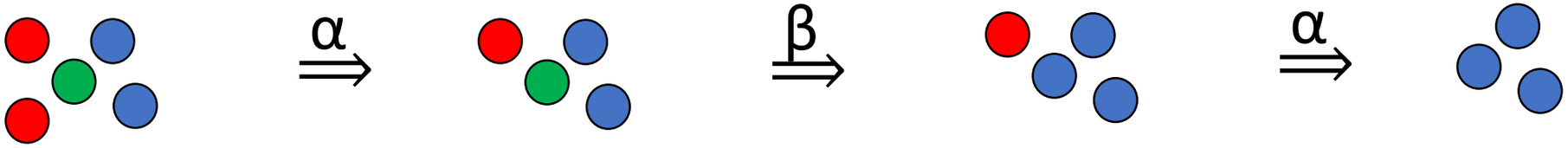

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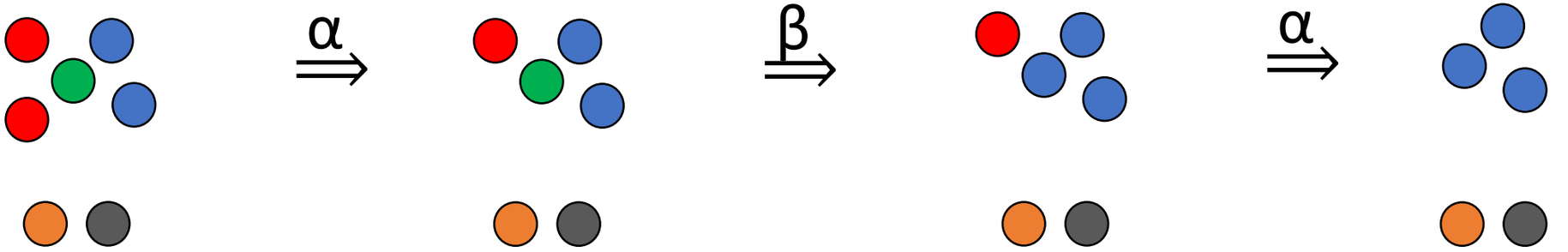

y + c

Notation

- For vectors $\mathbf{x},\mathbf{y} \in \mathbb{N}^d$
  - $\mathbf{x} \leqq \mathbf{y}$: $\mathbf{x}(i) \leq \mathbf{y}(i)$ for $1 \leq i \leq d$ $(1,2) \leqq (1,2)$
  - $\mathbf{x} \leq \mathbf{y}$: $\mathbf{x} \leqq \mathbf{y}$ and $\mathbf{x} \neq \mathbf{y}$ $(1,2) \leq (1,4)$
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  - $\mathbf{x} < \mathbf{y}$: $\mathbf{x}(i) < \mathbf{y}(i)$ for $1 \leq i \leq d$ $(1,2) < (3,4)$
  - If $\mathbf{x} \geqq \mathbf{0}$, $\mathbf{x}$ is **nonnegative**. $(0,0)$
  - If $\mathbf{x} \geq \mathbf{0}$, $\mathbf{x}$ is **semipositive**. $(0,1)$
  - If $\mathbf{x} > \mathbf{0}$, $\mathbf{x}$ is **positive**. $(1,1)$

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Execution bounded CRNs

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- Why prefer execution bounded CRNs?
  - Wet lab implementations of CRNs use up “fuel” to execute reactions; execution bounded CRNs limit the amount of fuel needed
  - Easier to reason about: as long as reactions keep happening, they make “progress” towards reaching a final state.

Self-covering executions

Easy Lemma: CRN *C* is not execution bounded from $\mathbf{x}_0$ if and only if there is an execution ($\mathbf{x}_0$, $\mathbf{x}_1$, $\mathbf{x}_2$, …) that is **self-covering**: $\mathbf{x}_i \leqq \mathbf{x}_k$ for some $i < k$.

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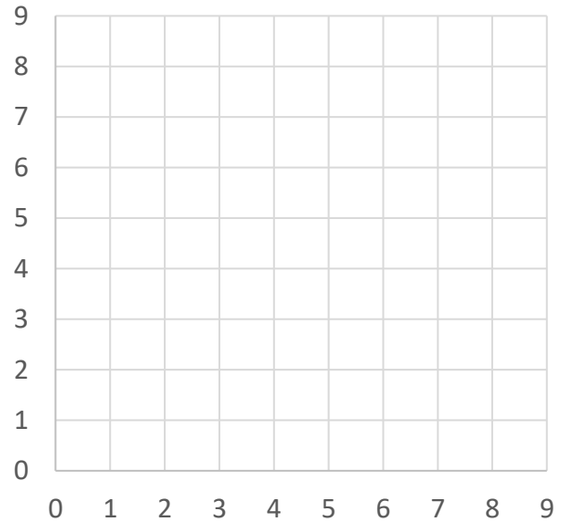

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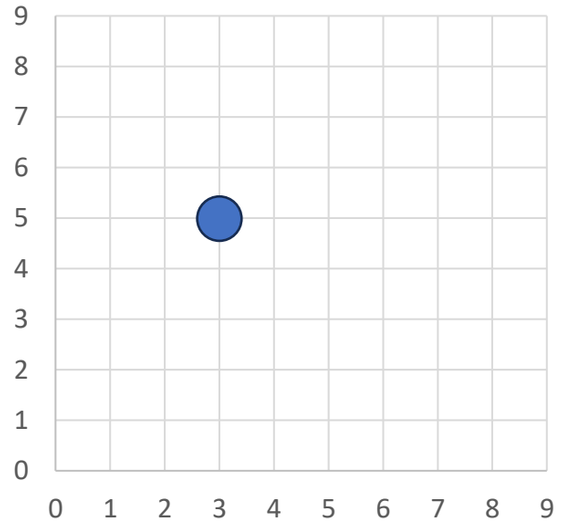

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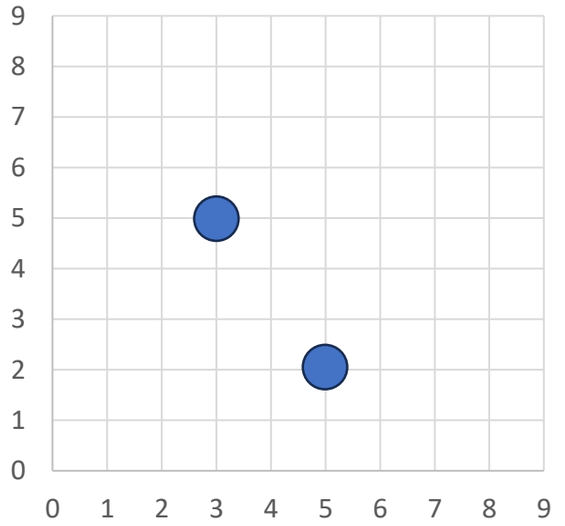

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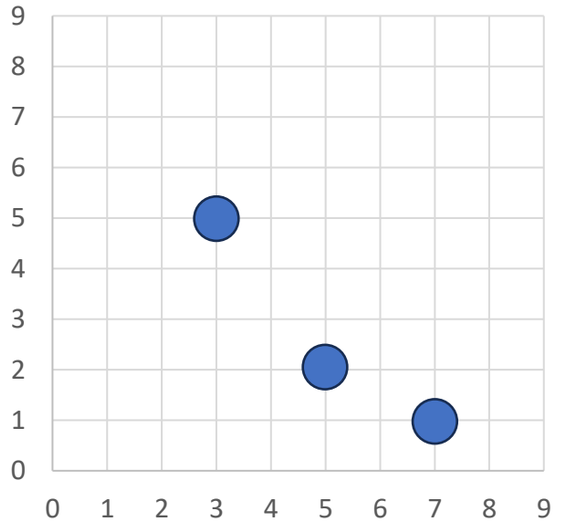

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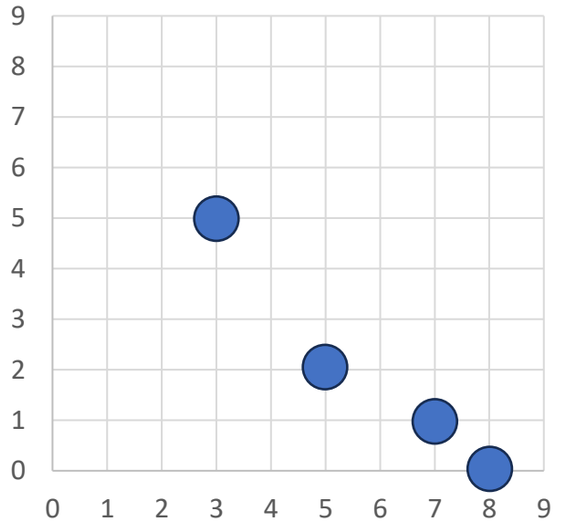

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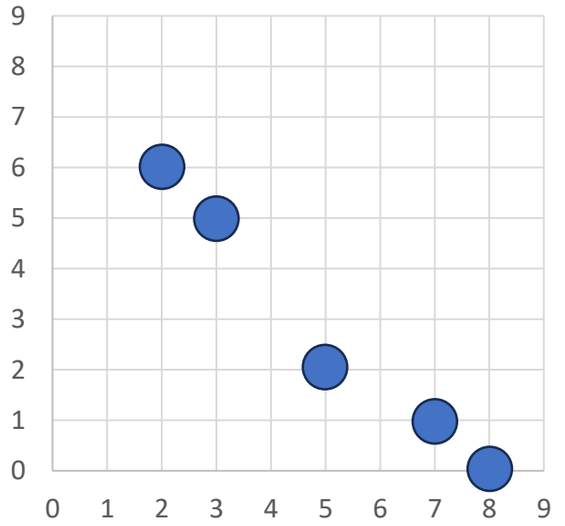

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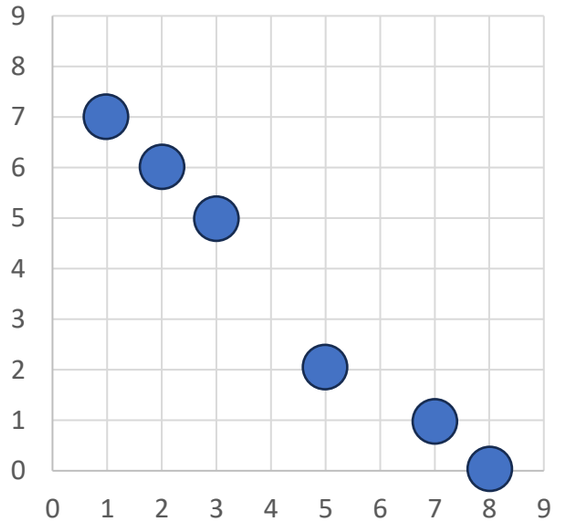

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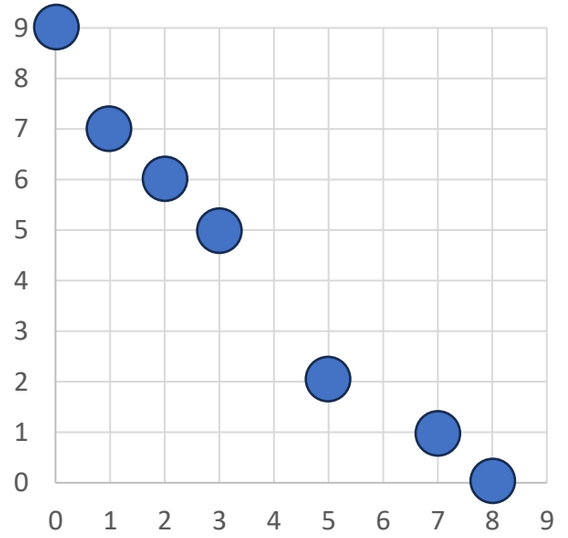

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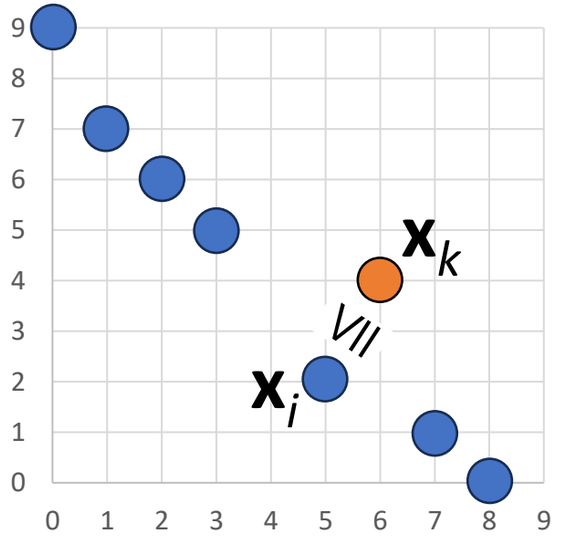

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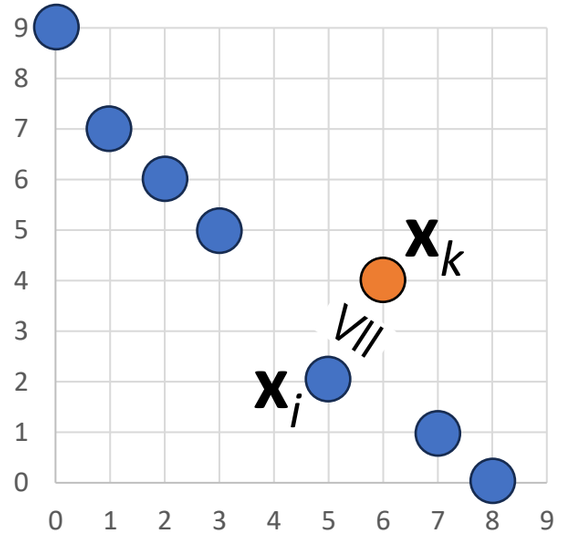
$\Leftarrow$: If an execution is self-covering, by additivity we can repeat indefinitely the reactions leading from $\mathbf{x}_i$ to $\mathbf{x}_k$, so C is not execution bounded from $\mathbf{x}_0$.



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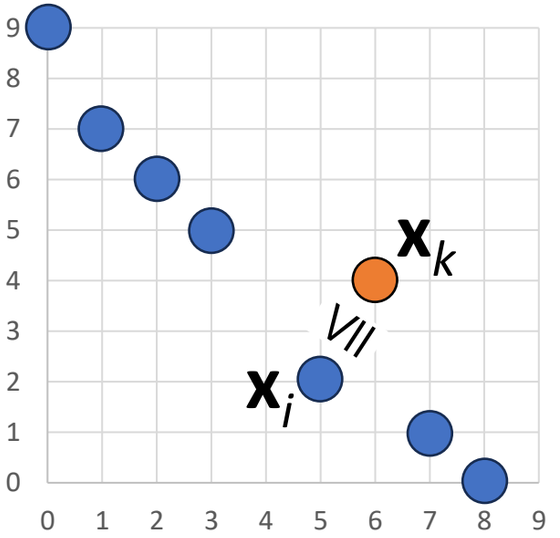

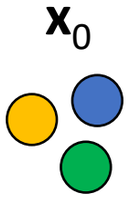

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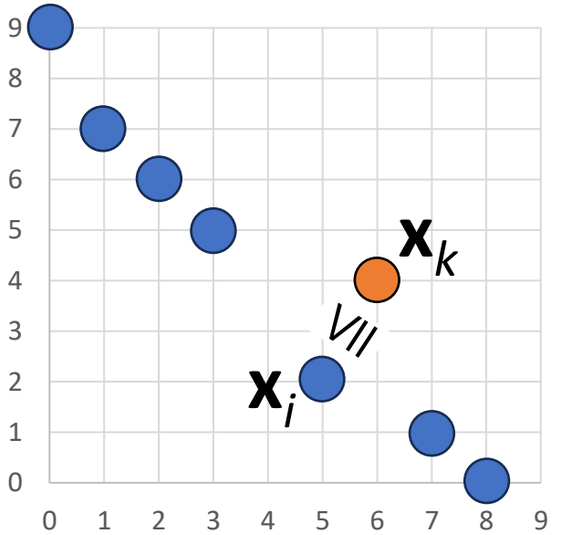

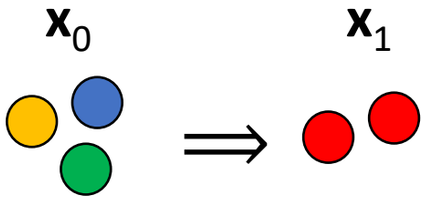

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Easy Lemma: CRN *C* is not execution bounded from $\mathbf{x}_0$ if and only if there is an execution $(\mathbf{x}_0, \mathbf{x}_1, \mathbf{x}_2, \ldots)$ that is **self-covering**: $\mathbf{x}_i \leqq \mathbf{x}_k$ for some $i < k$.

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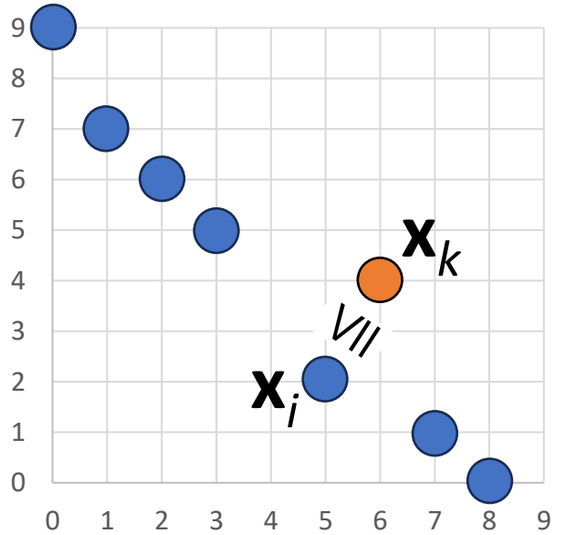

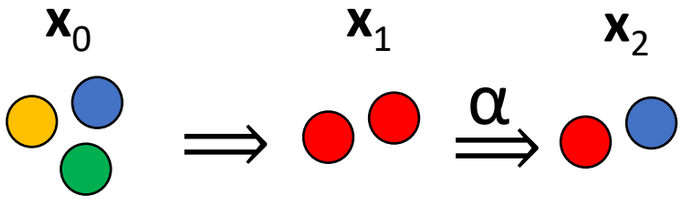

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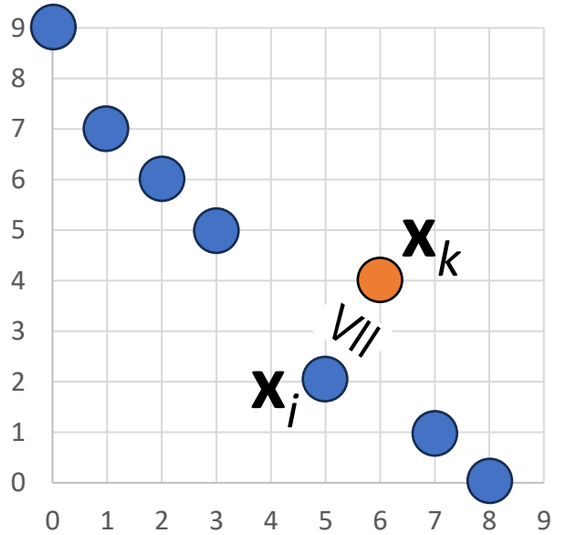

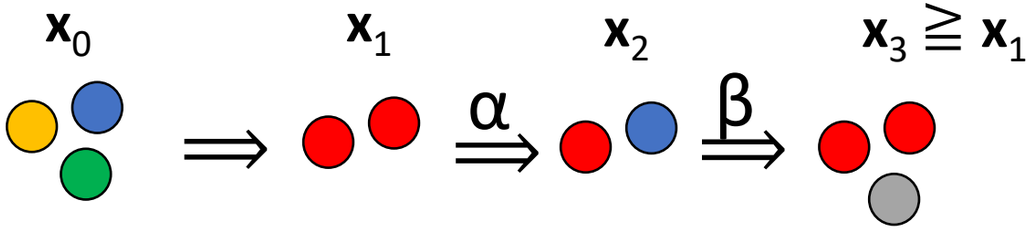

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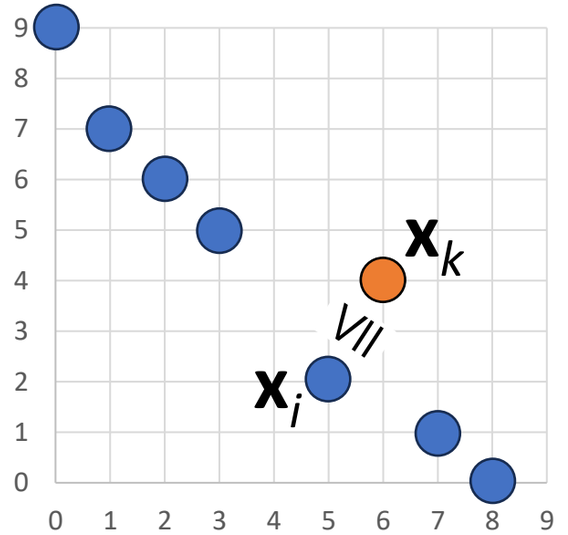

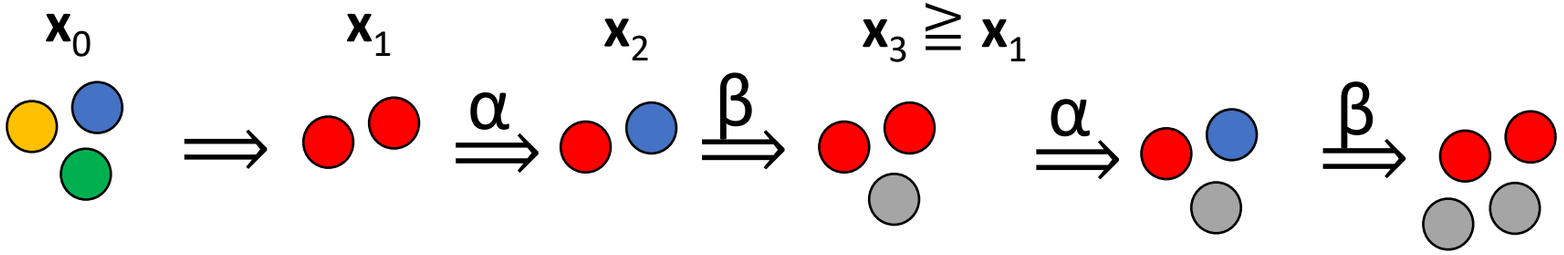

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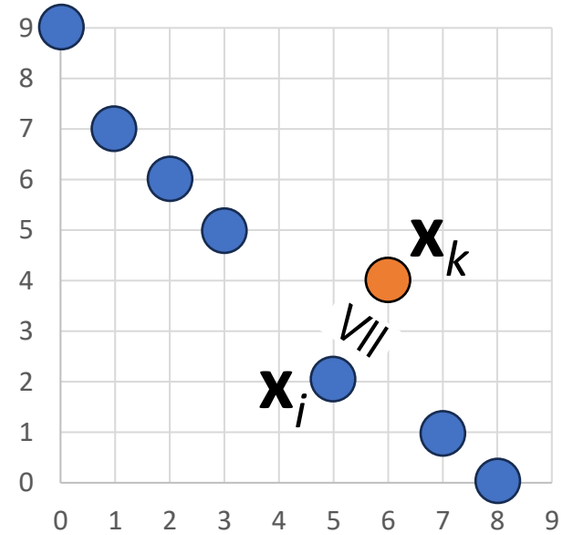

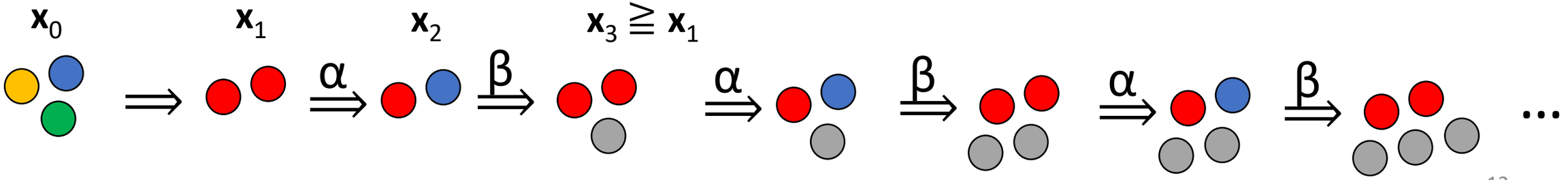

Linear potential function

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- By clearing denominators, we can assume each v_S is an integer, so each reaction decreases Φ by at least 1.

Linear potential functions characterize execution bounded CRNs

Theorem: A CRN has a linear potential function if and only if it is execution bounded from every state.

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Forward direction is easy: Since each reaction reduces Φ by at least 1, from any state $\mathbf{x}$, at most $\Phi(\mathbf{x})$ reactions are possible.

Key technical tool for reverse direction

Theorem: (Gale 1960) "*Theorem of the Alternative*" (similar to Farkas' Lemma): Let **M** be a matrix. Then exactly one of the following statements is true:

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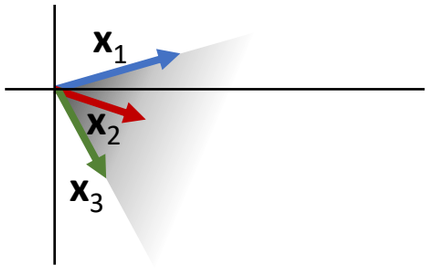

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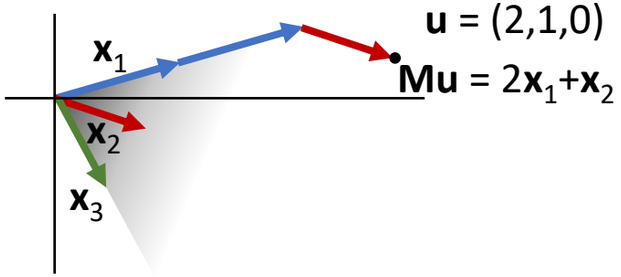

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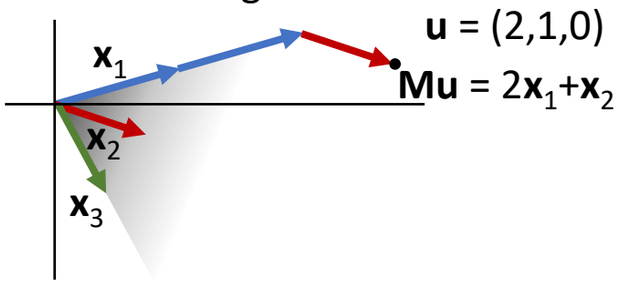

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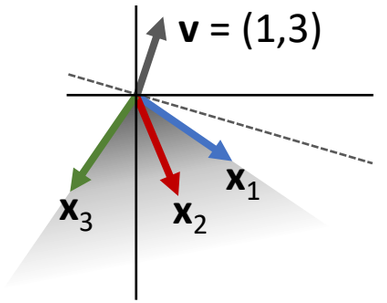
2. Or it doesn't, and then some hyperplane (dashed line) separates that cone from the nonnegative orthant:



$\mathbf{vM} < \mathbf{0} \Rightarrow$
$(\forall i)\ \mathbf{v}\cdot\mathbf{x}_i < 0$

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Then there is a vector **v** ≥ **0** such that **vM** < **0**. Let **v** be the coefficients of a linear function Φ(**x**) = **v**·**x**. Then **vM** < **0** means each reaction decreases Φ: it is a linear potential function. QED

Outline

- Formal definition of chemical reaction networks
- Execution bounded chemical reaction networks and linear potential functions
- **What is “computation” with chemical reactions?**
- Limitations of computation with execution bounded chemical reaction networks
- Possibilities of computation with execution bounded chemical reaction networks

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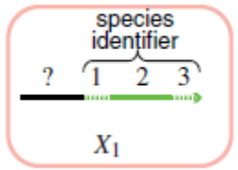

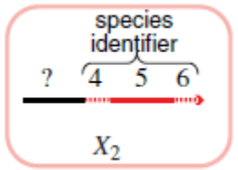

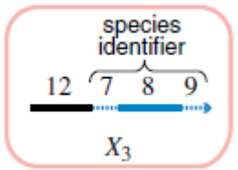

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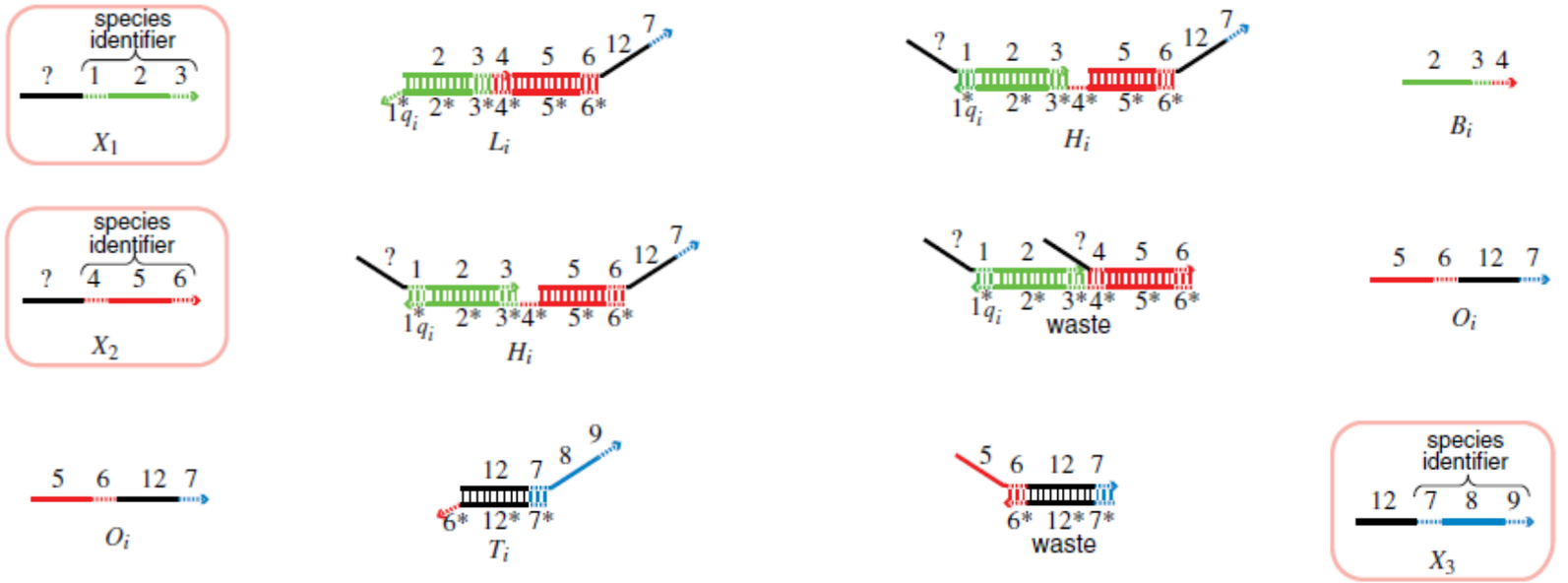

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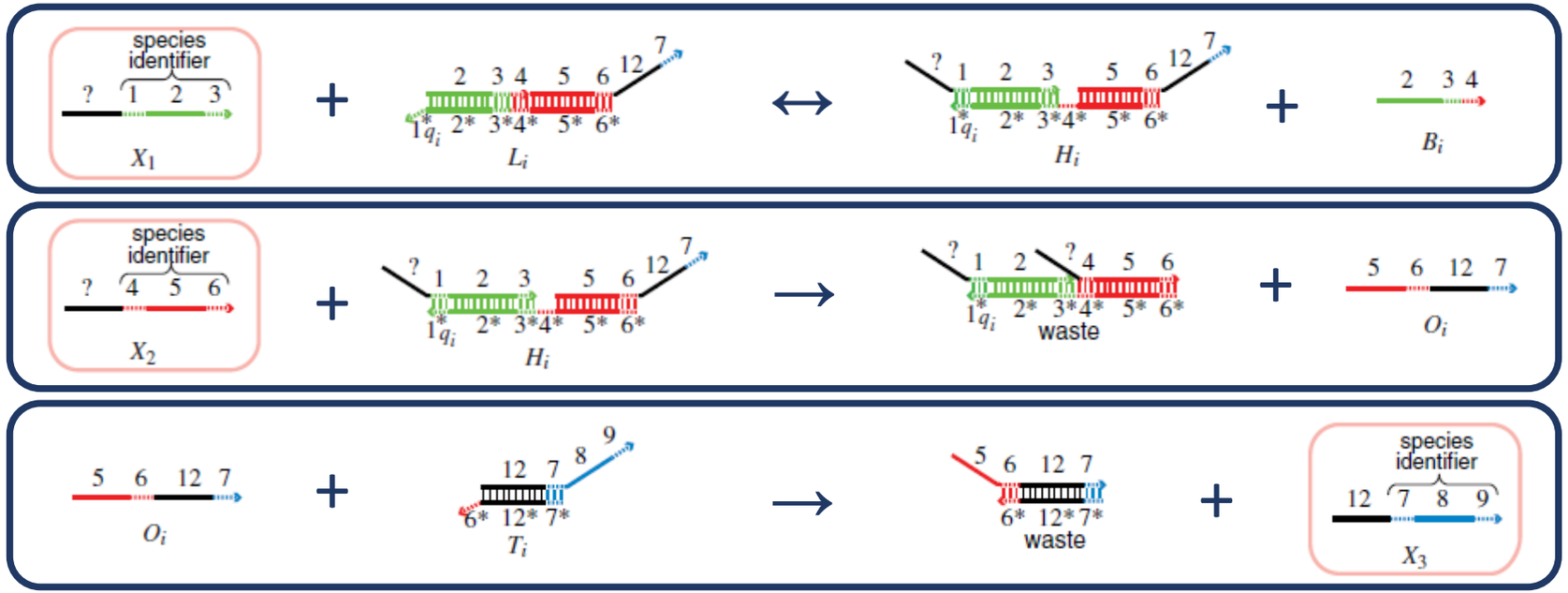

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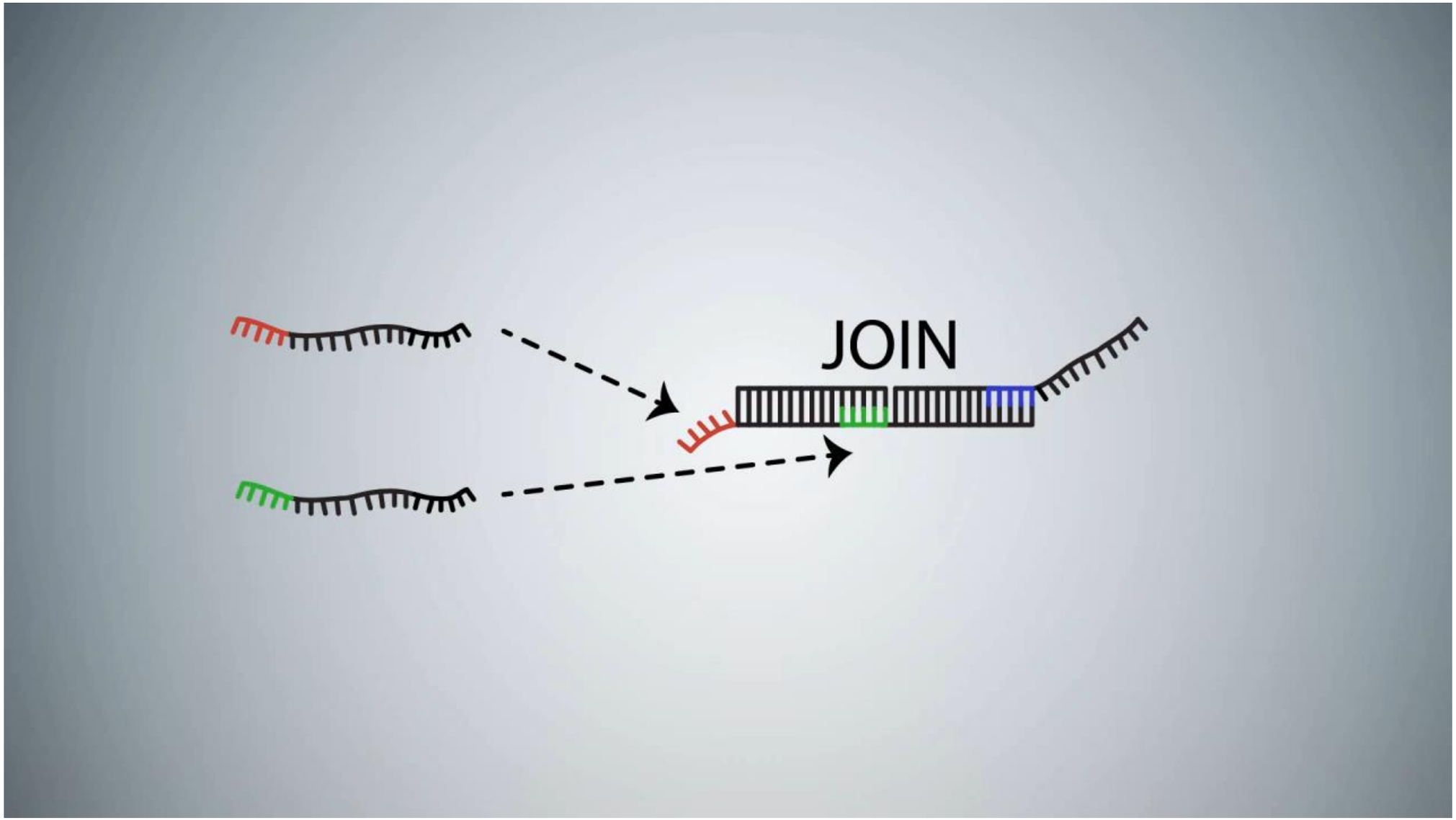
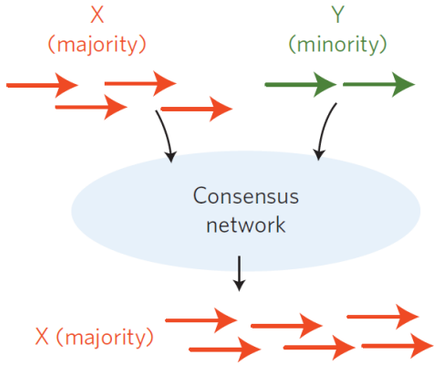
DNA strand displacement implementing A+B → C



video: Microsoft Research Cambridge

Experimental implementations of synthetic chemical reaction networks with DNA

Analog majority computation



$X+Y \rightarrow B+B$

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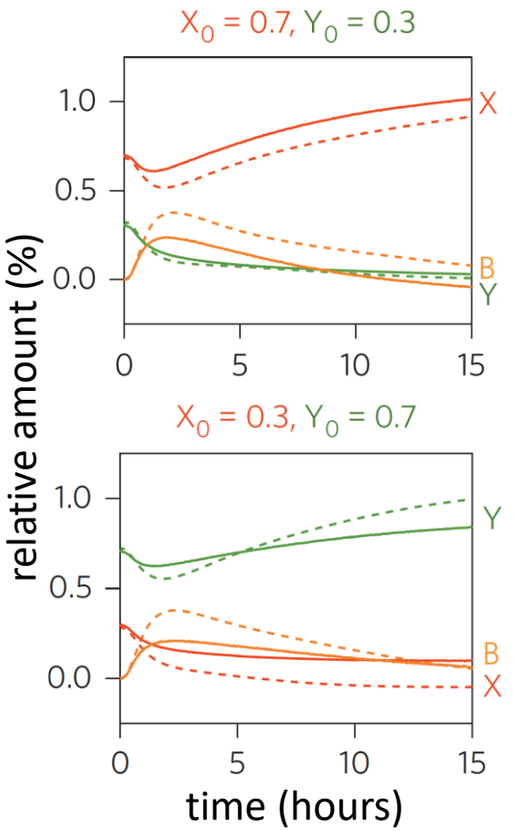
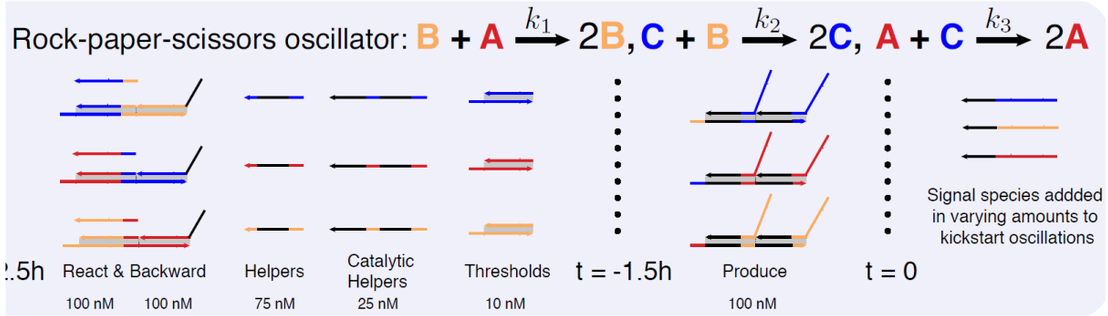


[*Programmable chemical controllers made from DNA.* Chen, Dalchau, Srinivas, Phillips, Cardelli, Soloveichik, Seelig, Nature Nanotechnology 2013.]

Chemical oscillator



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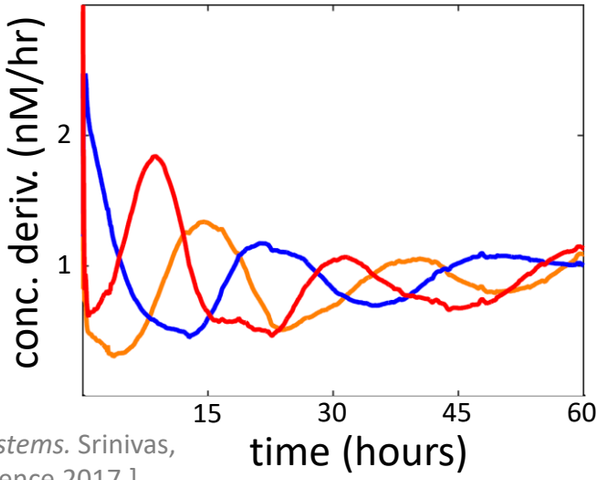
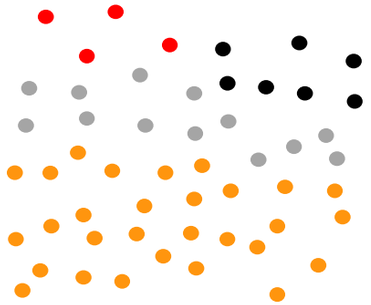


[*Enzyme-free nucleic acid dynamical systems.* Srinivas, Parkin, Seelig, Winfree, Soloveichik, Science 2017.]

Defining **stable** computation

i

initial
state



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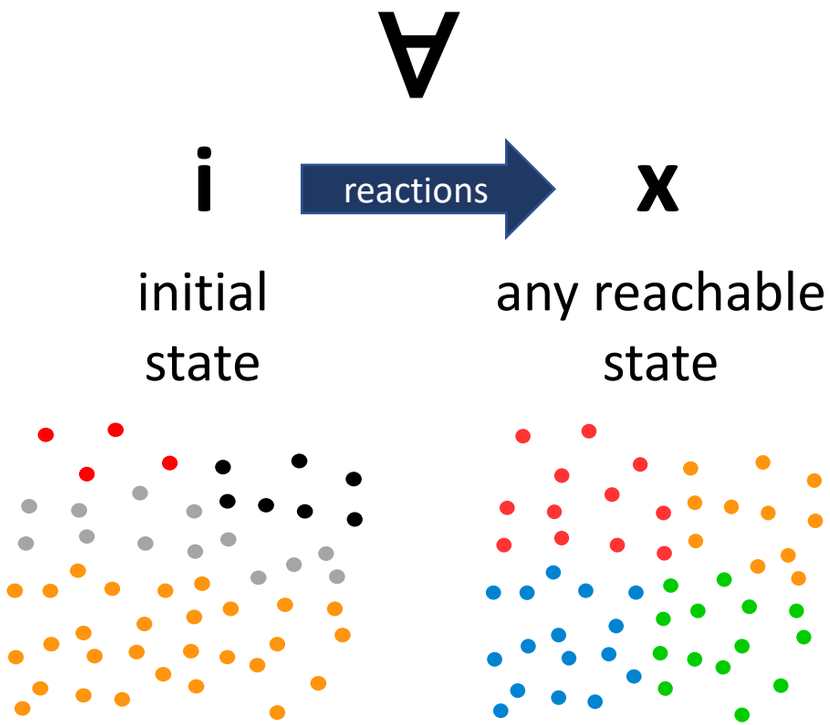

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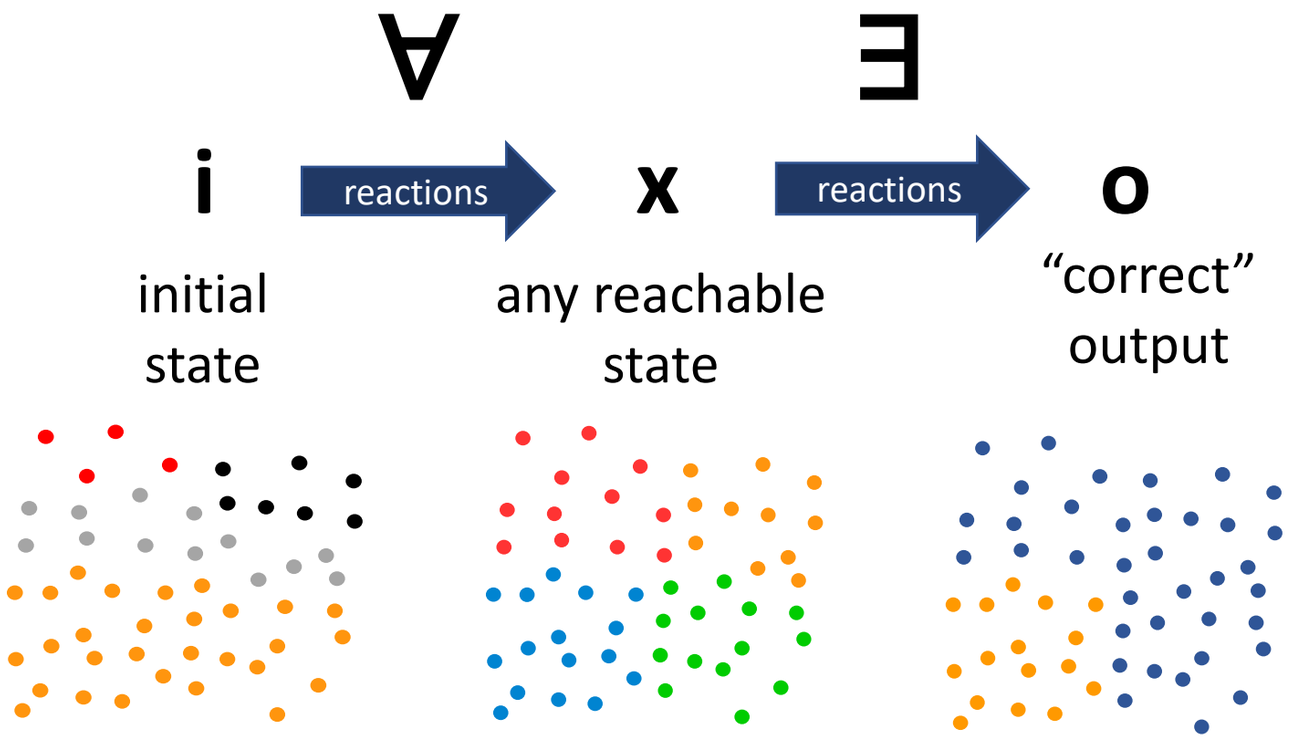

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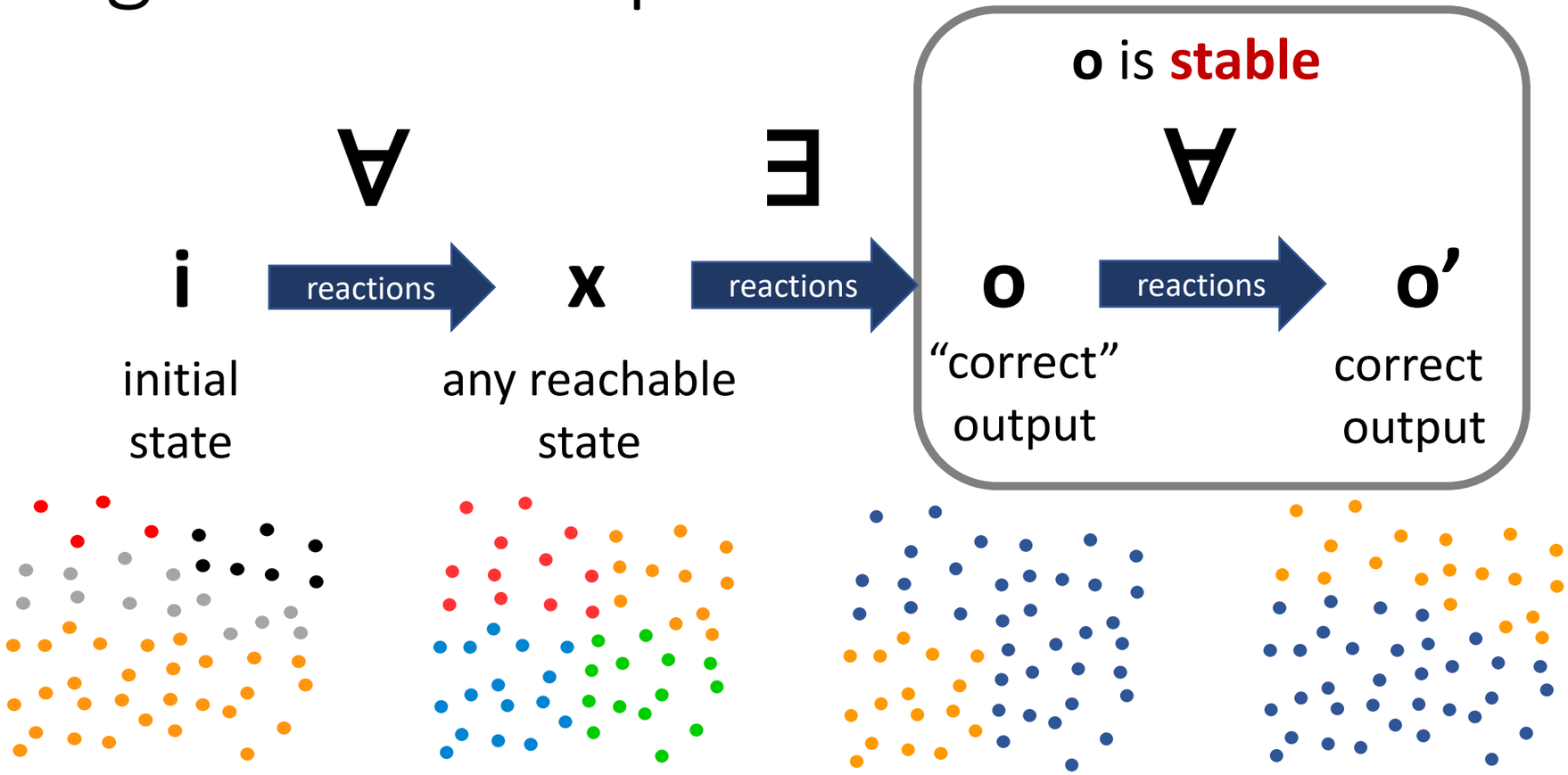

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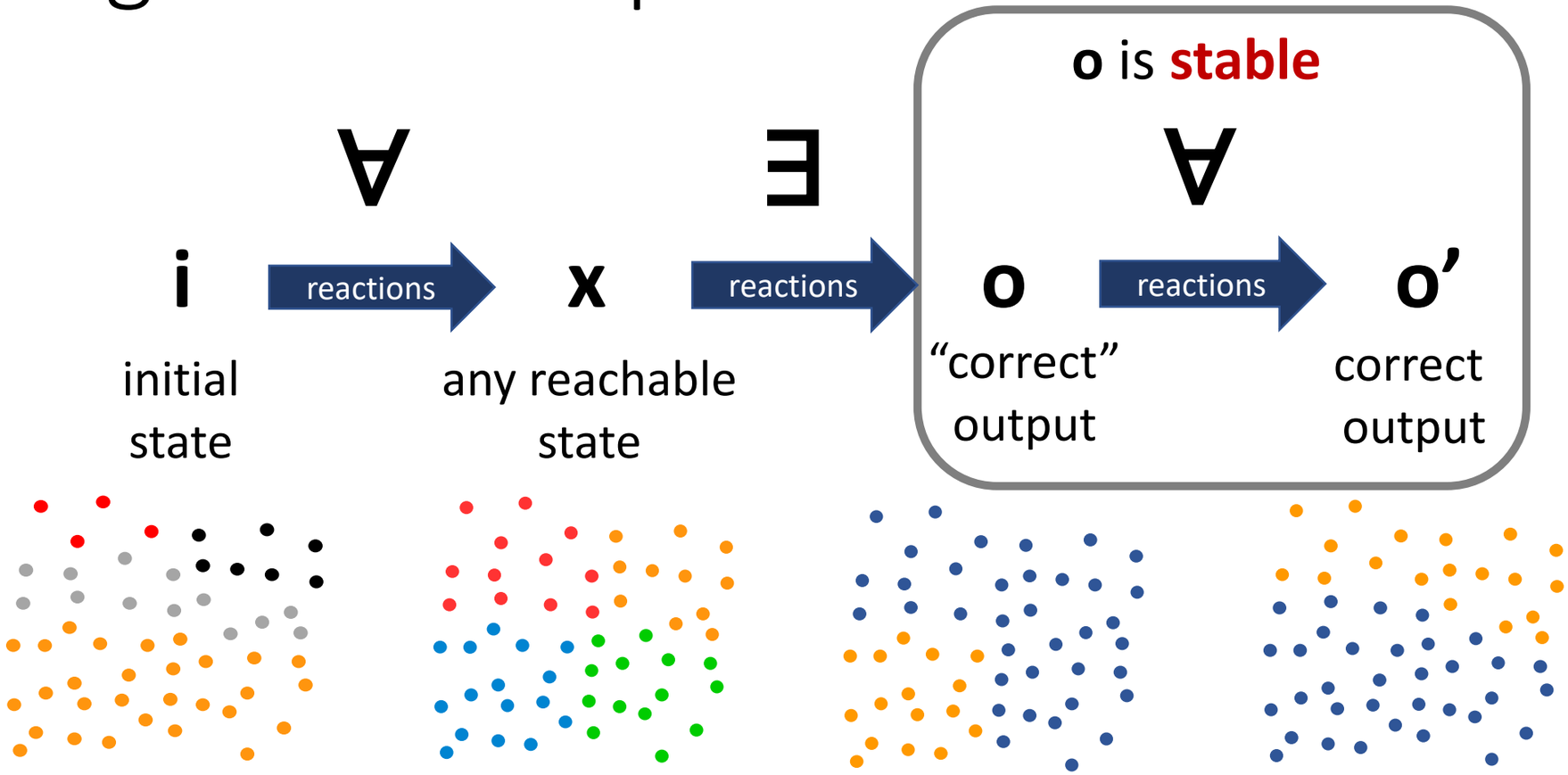

(assuming finite set of reachable states) equivalent to:
The system will reach the correct output with probability 1.

Definition of *predicate* (decision problem) computation

- goal: compute predicate φ: $\mathbb{N}^k \to \{Y,N\}$, e.g., $\varphi(a,b)=Y \iff a \geq b$

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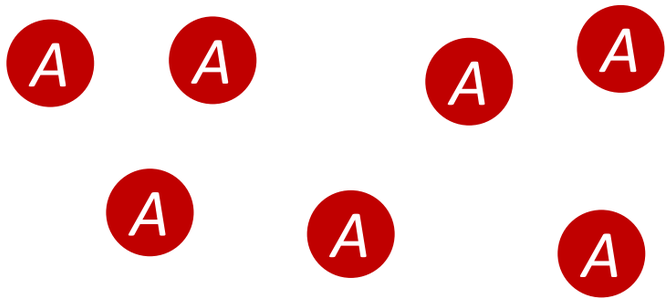
Examples of predicate computation

Detection: $\varphi(a,b) = \text{Y} \Leftrightarrow b > 0$



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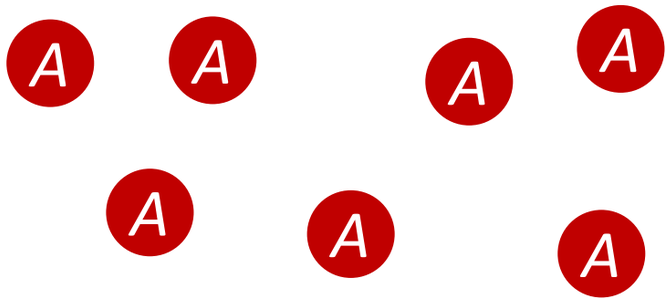

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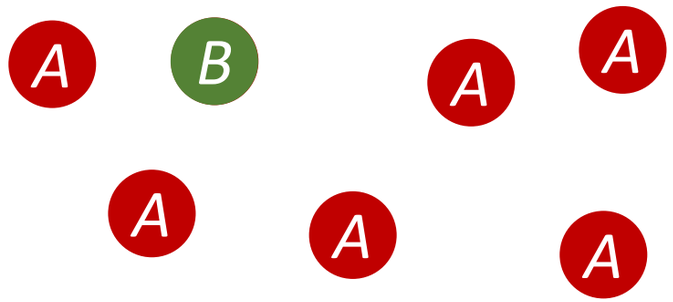

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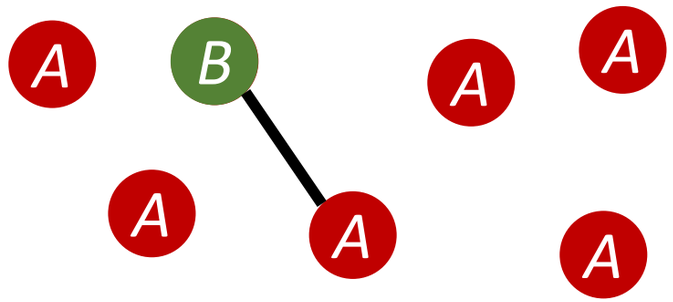

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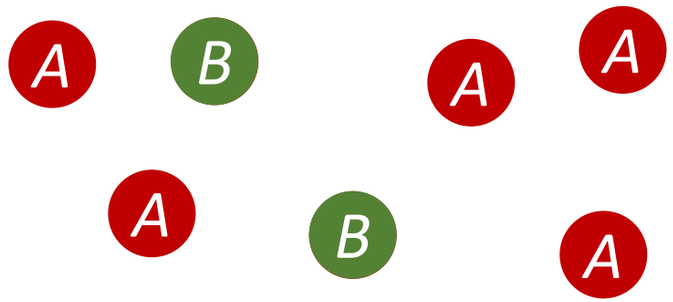

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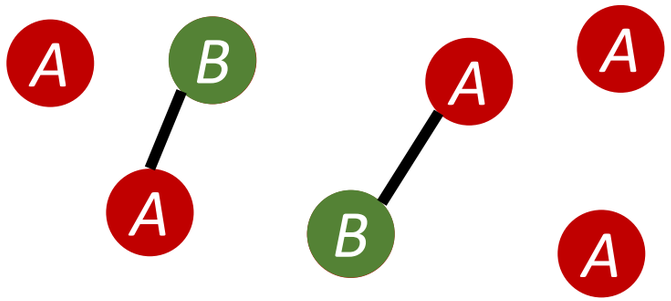

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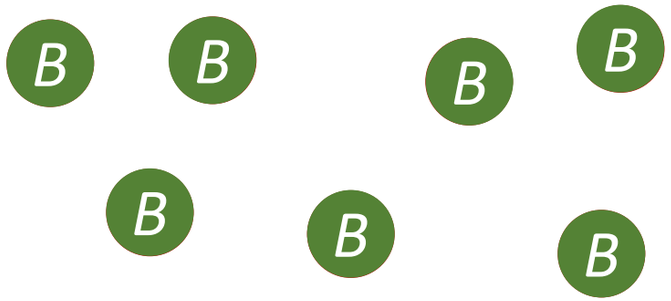

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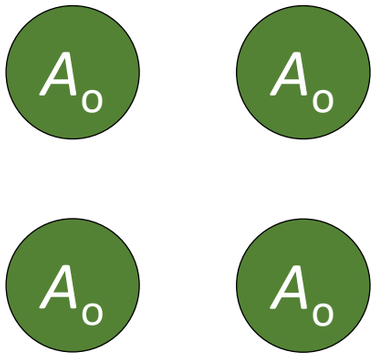

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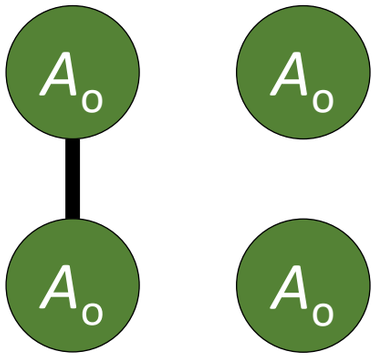

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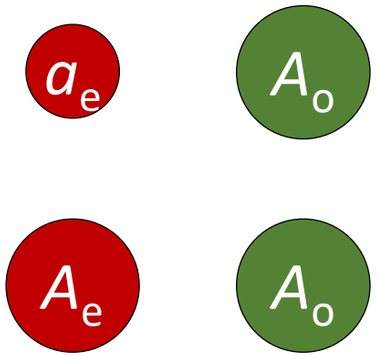

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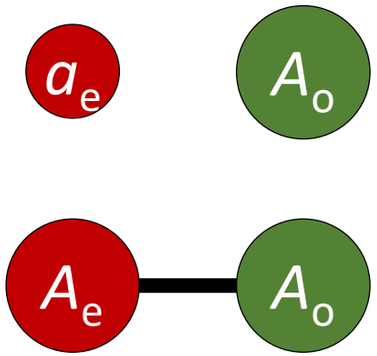

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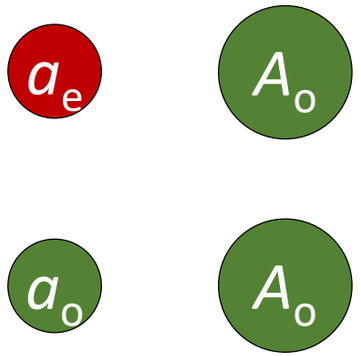

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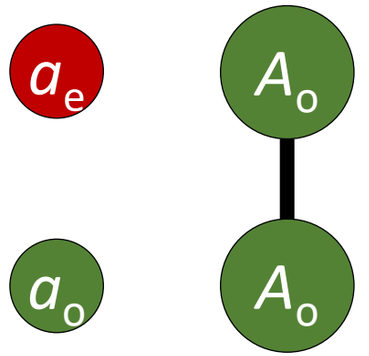

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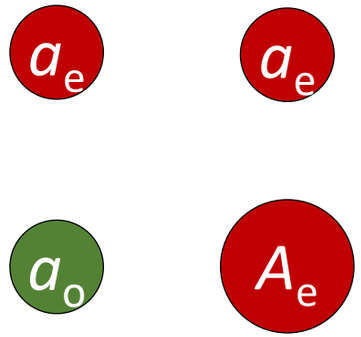

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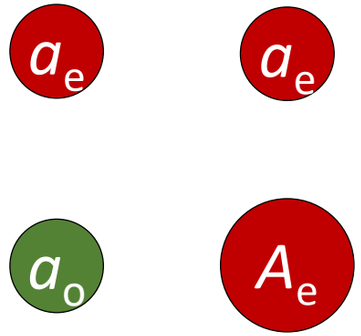

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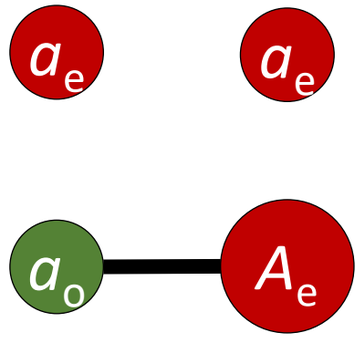

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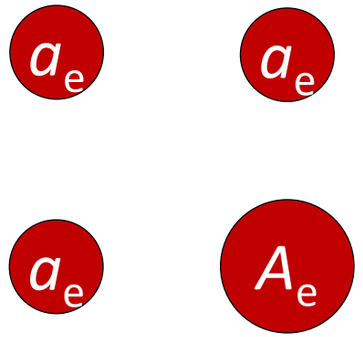

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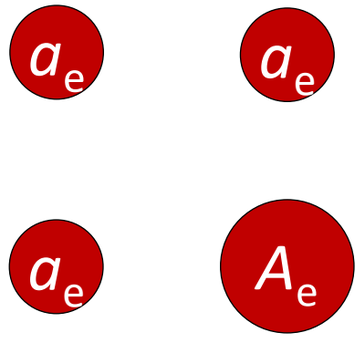

Not execution bounded!

Examples of predicate computation

Majority: $\varphi(a,b) = \mathrm{Y} \Leftrightarrow a \geq b$

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[Draief, Vojnovic. Convergence speed of binary interval consensus. *SIAM Journal on Control and Optimization*, 50(3):1087–1109, 2012]
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Limits of stable computation

Theorem: φ: $\mathbb{N}^k \to$ {Y,N} is stably computable by a CRN if and only if φ is *semilinear*.

semilinear = Boolean combination of threshold and mod predicates:

take weighted sum $s = w_1 \cdot x_1 + \ldots w_k \cdot x_k$ of inputs $x_1 \ldots x_k$ and ask if

$s \leq$ constant c?

$s \equiv c \bmod m$ for constants c,m?

$a>b$? $a=b$? a is odd? $a>1$? $a>1$ and b is odd?

NOT $a=b^2$? a is a power of 2? a is prime?

[Angluin, Aspnes, Diamadi, Fischer, Peralta, Computation in networks of passively mobile finite-state sensors, *PODC* 2004]
[Angluin, Aspnes, Eisenstat, Stably computable predicates are semilinear, *PODC* 2006]

Outline

- Formal definition of chemical reaction networks
- Execution bounded chemical reaction networks and linear potential functions
- What is “computation” with chemical reactions?
- **Limitations of computation with execution bounded chemical reaction networks**
- Possibilities of computation with execution bounded chemical reaction networks

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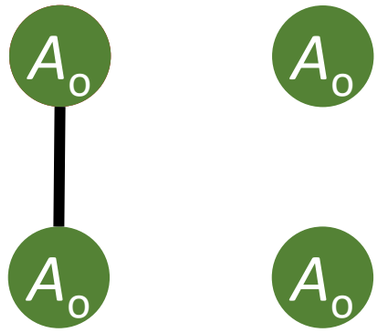

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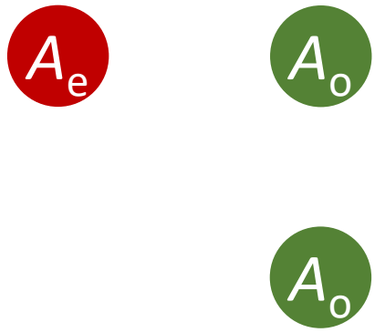

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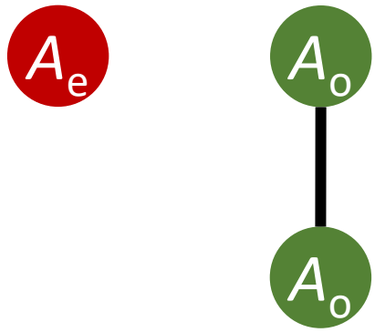

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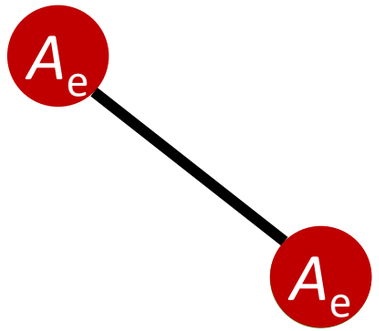

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which computes parity but always ends up with a single voter.

Eventually constant predicates

Definition: A predicate $\varphi: \mathbb{N}^k \to \{Y,N\}$ is **eventually constant** if, for some $c \in \mathbb{N}$, $\varphi(\mathbf{x})$ is constant on all inputs $\mathbf{x} \geqq (c,c,\ldots,c)$.

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Non-eventually constant predicates:

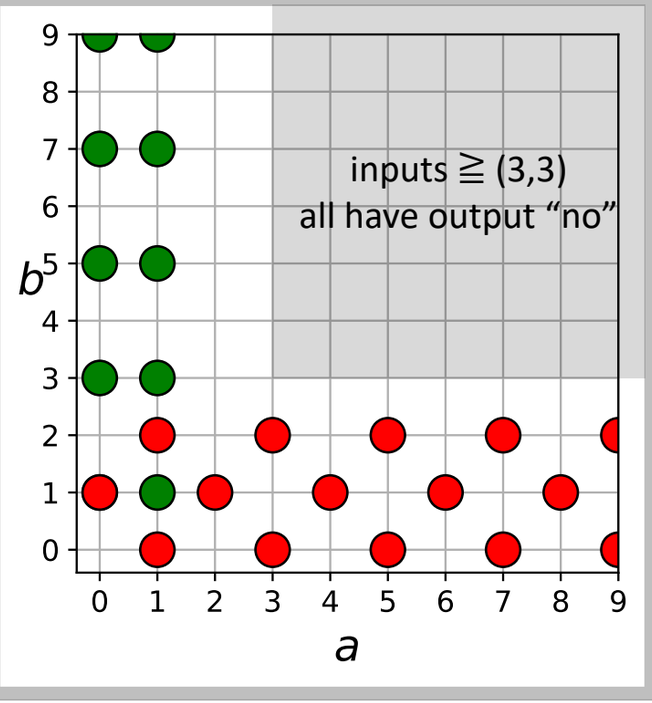
majority ($a \geq b$?)

parity (a is odd?)

equality ($a=b$?)

and most anything interesting.

Example of eventually constant predicate:
$a < 2$ and b is odd, or $b < 3$ and $a+b$ is odd



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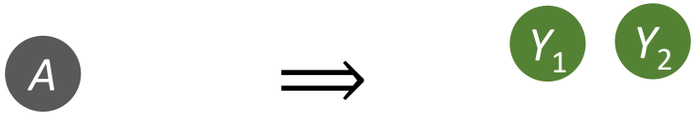

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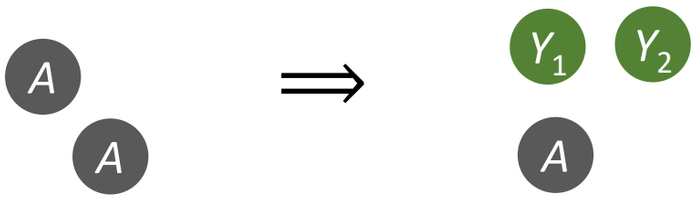

$\Longrightarrow$

$\{A\} + \{A\}$ $\quad\quad$ $\mathbf{s}_1 + \{A\}$

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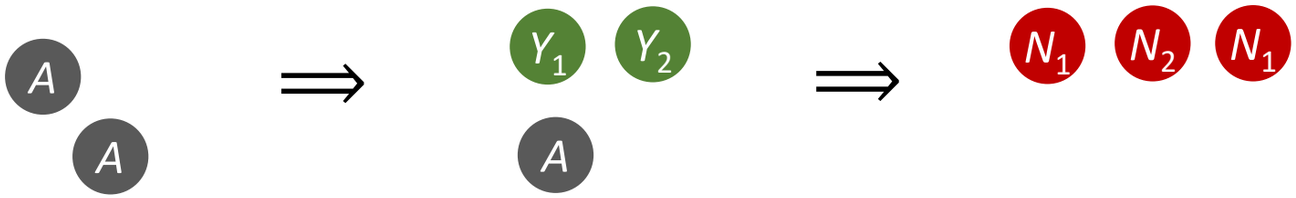

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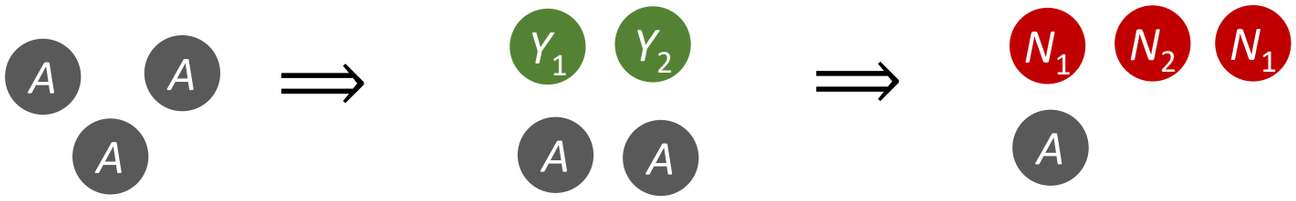

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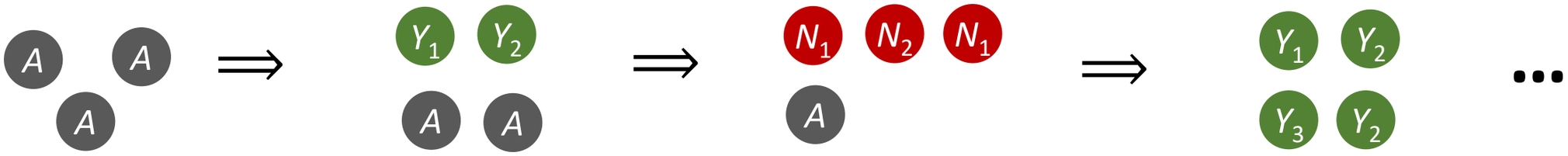

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- Since Φ is nonnegative, at some point we cannot continue. QED

Outline

- Formal definition of chemical reaction networks
- Execution bounded chemical reaction networks and linear potential functions
- What is “computation” with chemical reactions?
- Limitations of computation with execution bounded chemical reaction networks
- **Possibilities of computation with execution bounded chemical reaction networks**

Are execution bounded CRNs good for any computation?

Yes! Execution bounded CRNs *can* stably compute all semilinear predicates if the CRN is *leader-driven*: it starts with an "initial leader", e.g., to compute majority ($a \geq b$?), start in initial state {1 *L*, *a A*, *b B*}… these are execution bounded from such states, but not from states with multiple leaders.

We also relax the voting requirement and allow only the leader to vote. (though this requirement can be relaxed; not shown in slides)

Single-voting CRNs

Definition: A CRN computing a predicate $\varphi: \mathbb{N}^k \to \{Y,N\}$ is **single-voting** if all states reachable from the input have a single voter.

Such CRNs are leader-driven: valid initial configurations have a single leader/voter molecule, and only the leader votes.

Semilinear predicates are Boolean combinations of threshold and mod predicates

Recall: Theorem: φ: $\mathbb{N}^k \to$ {Y,N} is stably computable by a CRN if and only if φ is *semilinear*. (= Boolean combination of threshold and mod predicates)

To show execution bounded CRNs can compute all semilinear predicates, it suffices to show:

- They can compute all threshold predicates.
- They can compute all mod predicates.
- They can be composed to compute AND, OR, and NOT of other CRNs.

Execution bounded CRNs can compute threshold predicates

Theorem: Every threshold predicate [$w_1x_1 + \ldots + w_kx_k \leq c$?] can be stably computed by a single-voting execution bounded CRN.

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P will have count = weighted sum of inputs with positive weights

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Now we compute majority [$P \leq N$?]

$$L_Y + P \to L_N$$
$$L_N + N \to L_Y$$

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Proof by example: To compute [$2x_1 + 3x_2 \equiv 4 \mod 5$?], in addition to inputs X_1, X_2, start with 1 L_0, and have reactions:

$$L_i + X_1 \rightarrow L_{i+2 \bmod 5} \qquad \text{for } i = 0,1,2,3,4$$
$$L_i + X_2 \rightarrow L_{i+3 \bmod 5}$$

L_4 votes **yes**, L_0, L_1, L_2, L_3 vote **no**

Composing CRNs to compute Boolean combinations of predicates

Theorem: If single-voting, execution bounded CRNs C_1 and C_2 stably compute predicates $\varphi_1: \mathbb{N}^k \to \{Y,N\}$ and $\varphi_2: \mathbb{N}^k \to \{Y,N\}$, then there are single-voting, execution bounded CRNs stably computing [φ_1 and φ_2], [φ_1 or φ_2], and [not φ_1].

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"global" voters of composed CRN:
V_{NN}, V_{NY}, V_{YN}, V_{YY}; start with 1 V_{NN}

Let S_Y, S_N be yes and no voters of C_1
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Let S_Y, S_N be yes and no voters of C_1
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C_1 is execution bounded, so can only switch between S_Y and S_N a finite number of times, limiting how many times we can flip between $V_{N?}$ and $V_{Y?}$, so full CRN is execution bounded.

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Open question

- Using standard stochastic model of chemical kinetics (not shown), the execution bounded CRNs stably computing semilinear predicates can be shown to take expected time $O(n \log n)$ to converge.

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- Without the execution bounded constraint, it is known they can be computed exponentially faster: polylog(n). [Angluin, Aspnes, Eisenstat, Fast computation by population protocols with a leader, *DISC* 2006]
- Conjecture: Execution bounded CRNs require $\Omega(n)$ time to stably compute any non-eventually constant predicate (e.g., majority or parity).

Thank you!

Questions?