The limits of chemical computing

Computation with chemical reaction networks

David Doty

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Acknowledgments

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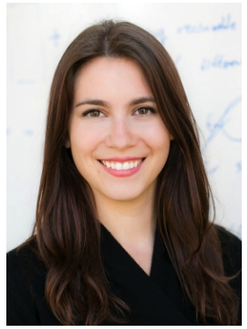

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Chemical reaction networks

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

Chemical caucusing

$X + Y \rightarrow U + U$

[Angluin, Aspnes, Eisenstat, A simple population protocol for fast robust approximate majority, *DISC* 2007]

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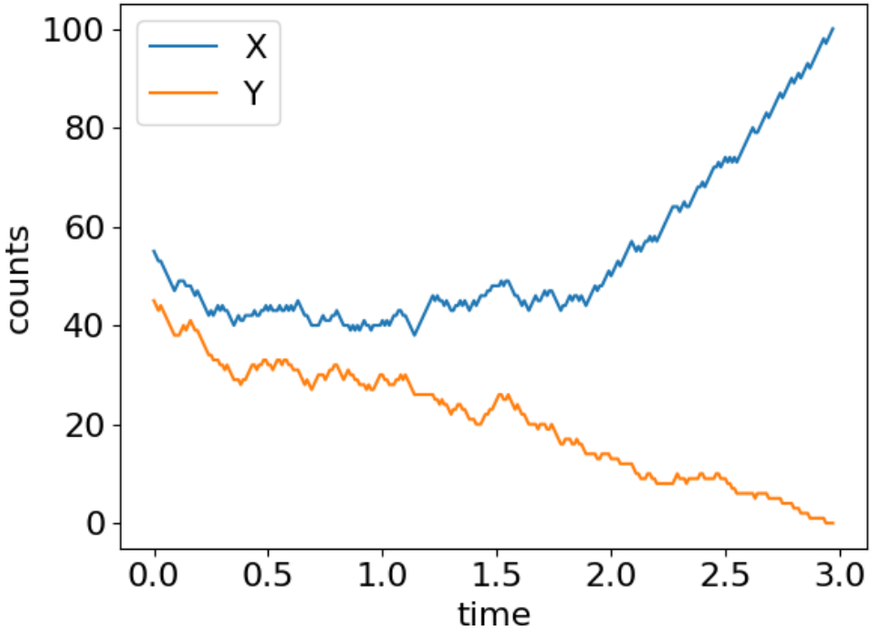

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initial majority (X or Y) quickly overtakes whole population

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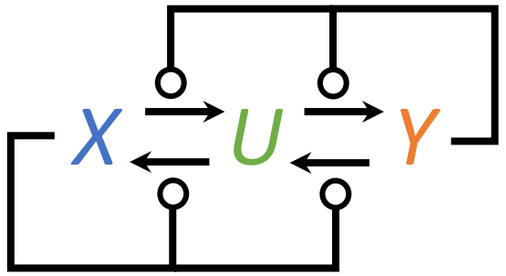

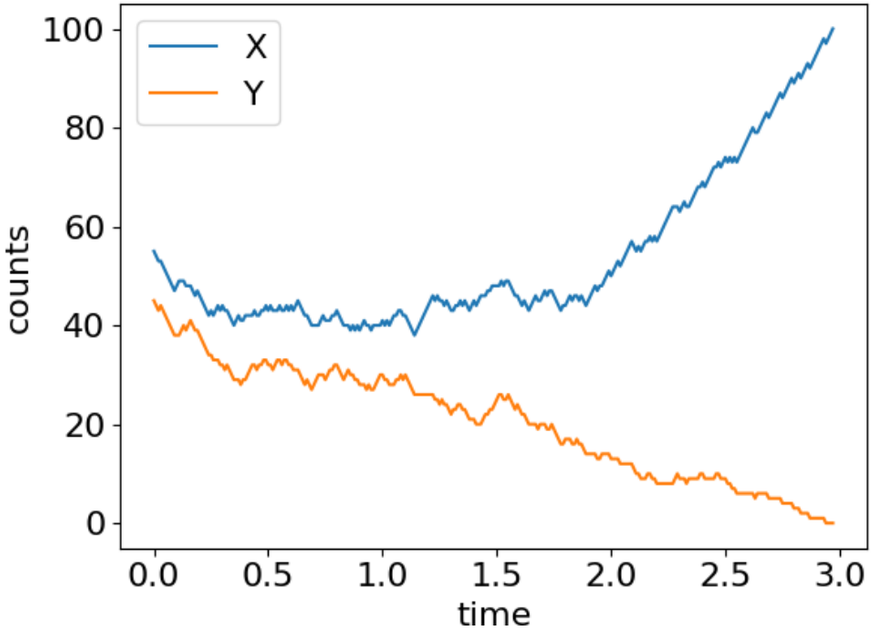

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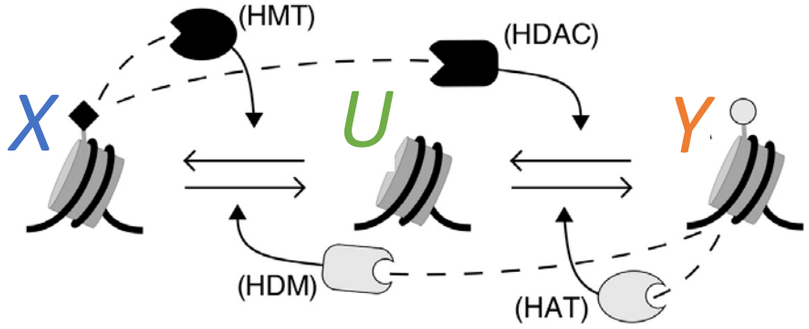

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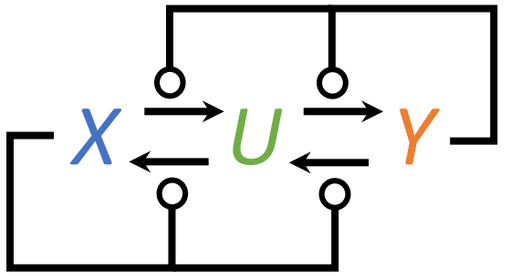

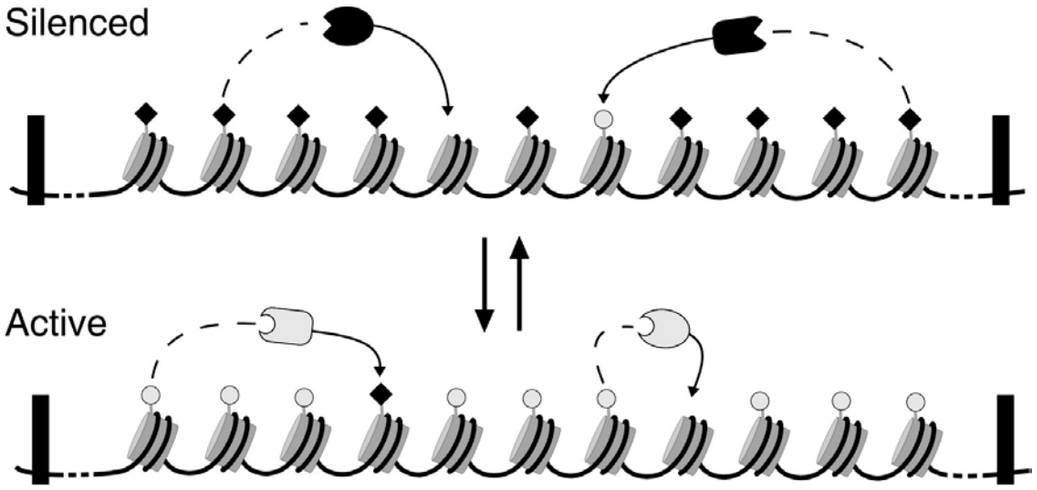

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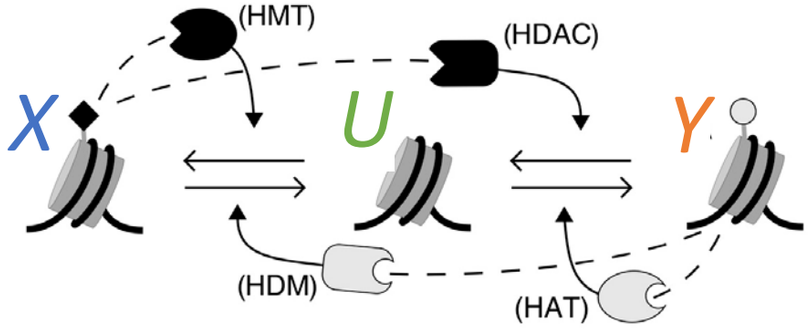

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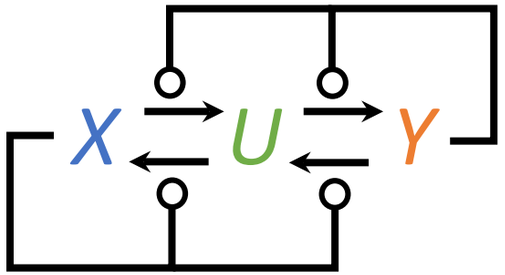

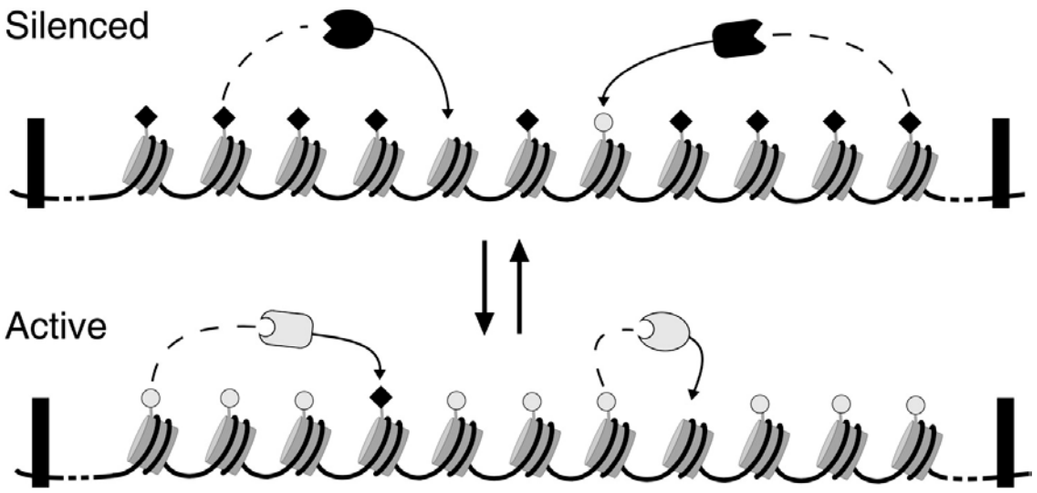

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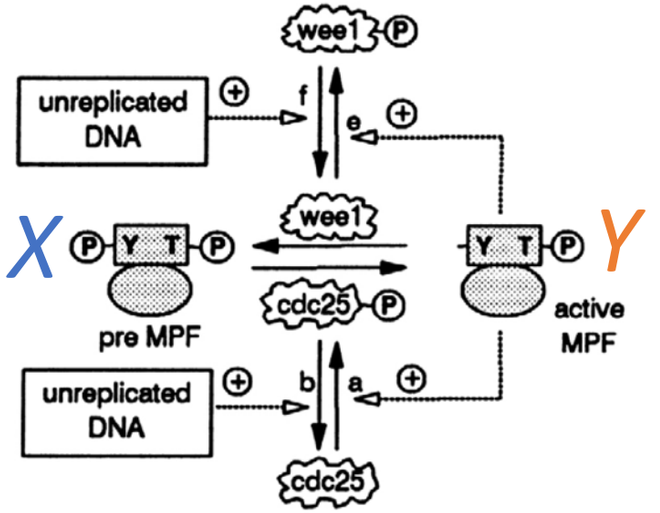

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[Cardelli, Csikász-Nagy. The cell cycle switch computes approximate majority. *Nature Scientific Reports* 2012]

[Cardelli, Morphisms of reaction networks that couple structure to function, *BMC Systems Biology* 2014]

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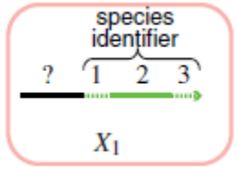

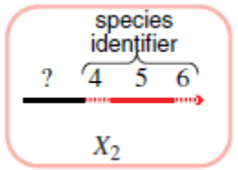

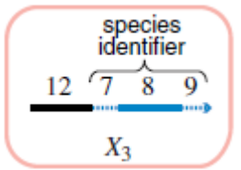

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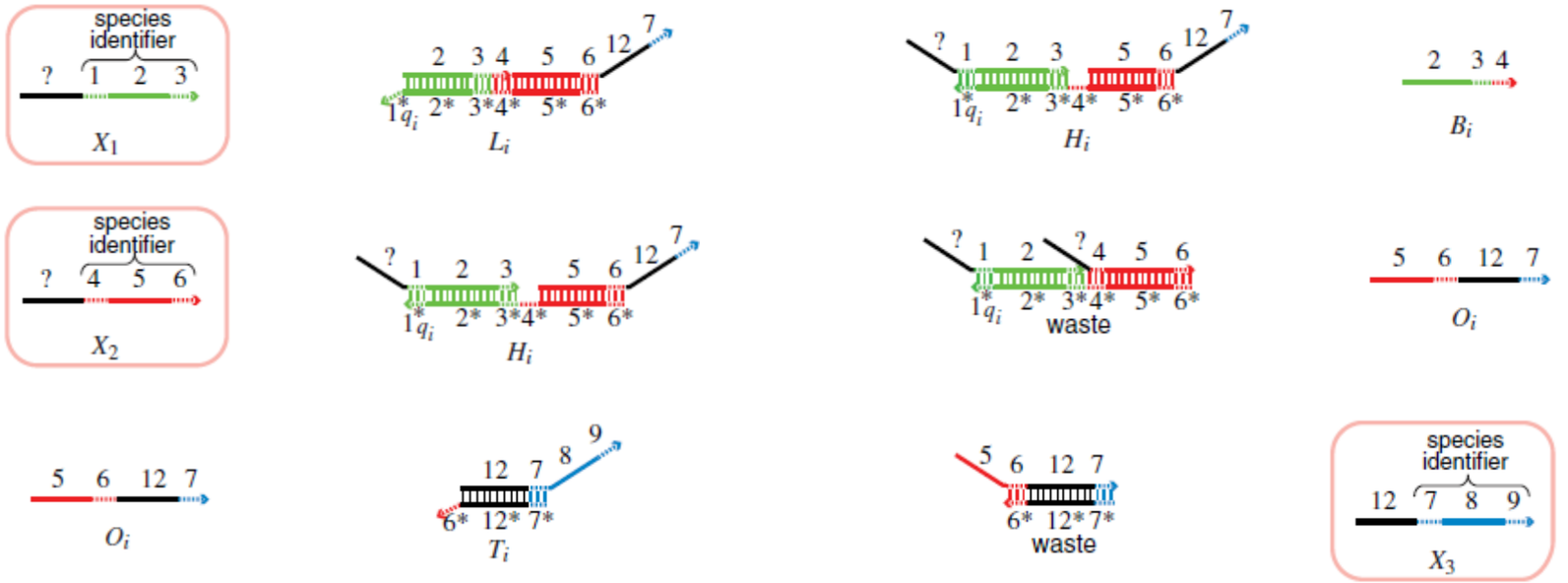

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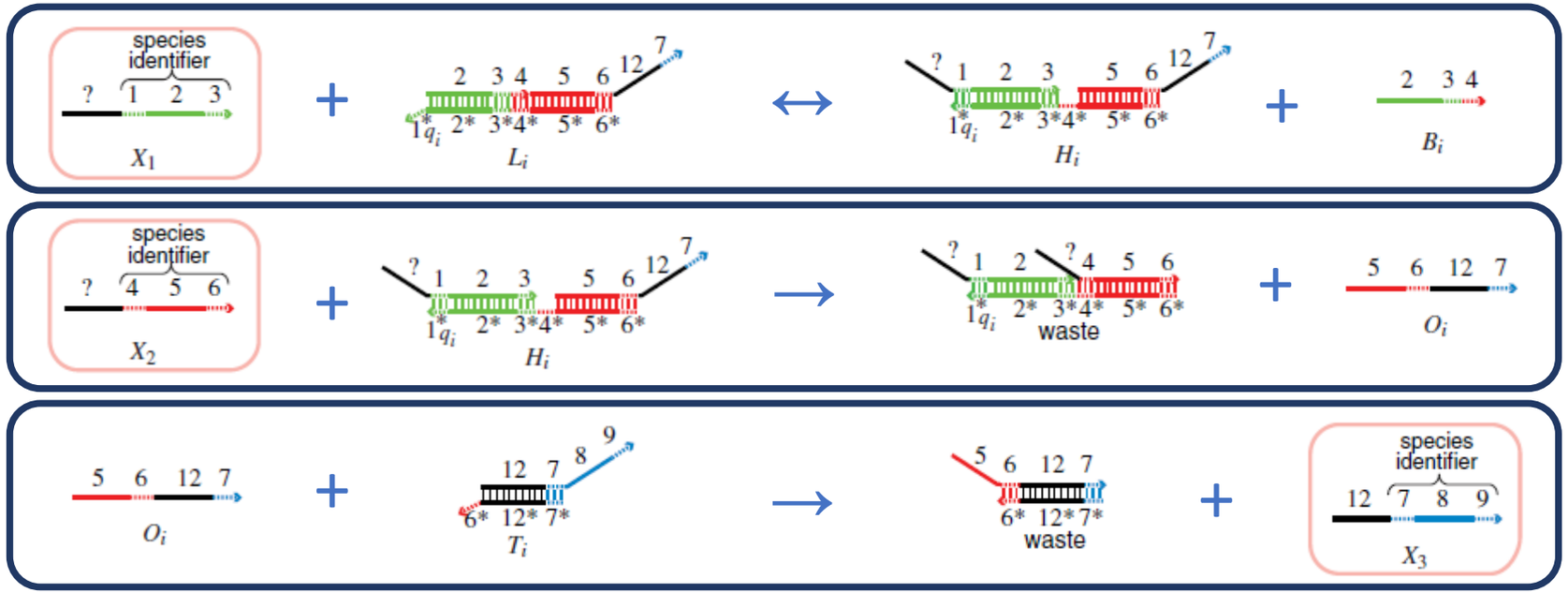
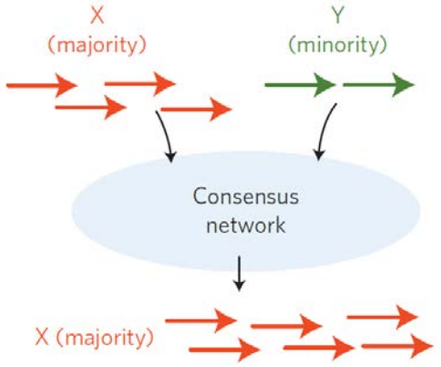


DNA strand displacement implementing A+B → C

video: Microsoft Research Cambridge

Experimental implementations of synthetic chemical reaction networks with DNA

Analog majority computation



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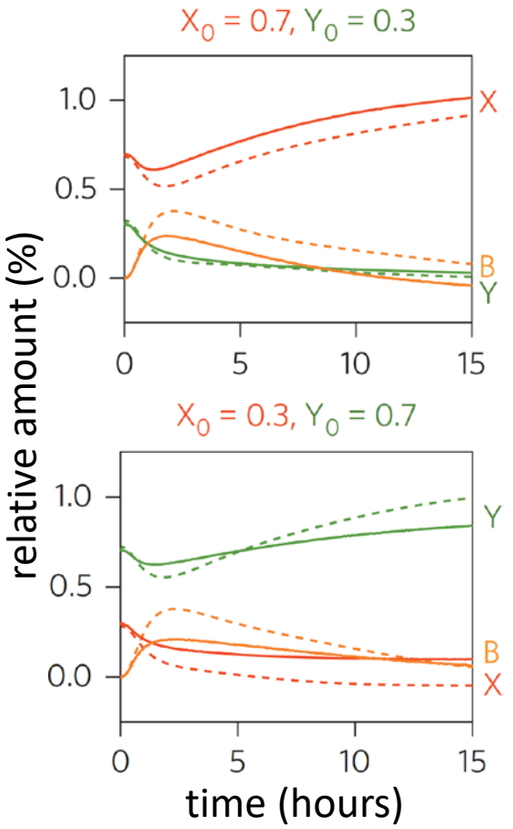
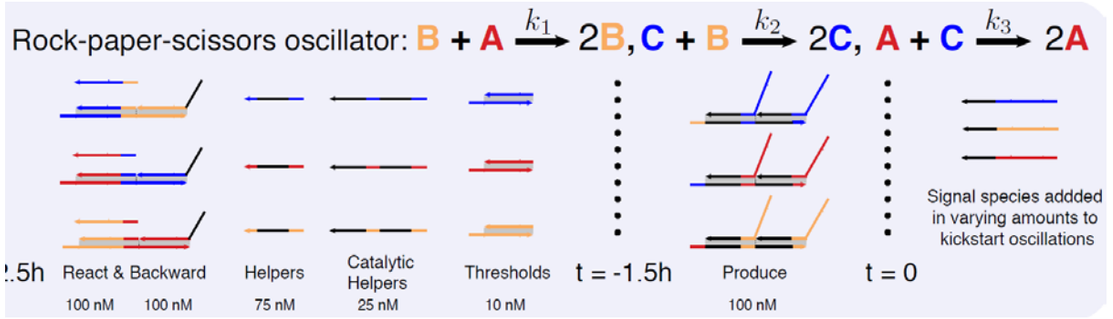


[*Programmable chemical controllers made from DNA.* Chen, Dalchau, Srinivas, Phillips, Cardelli, Soloveichik, Seelig, Nature Nanotechnology 2013.]

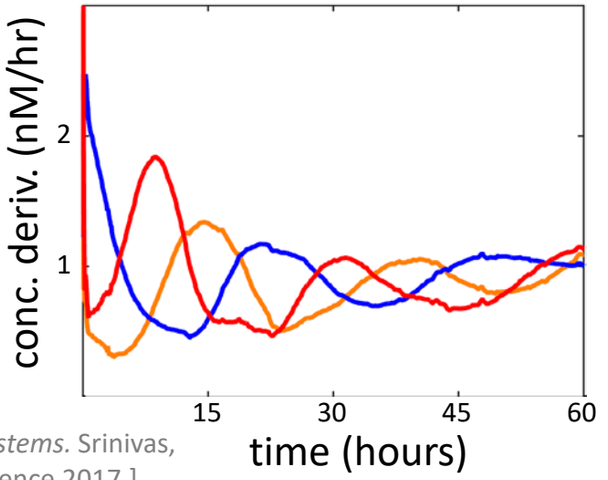
Chemical oscillator



$A+B \rightarrow B+B$

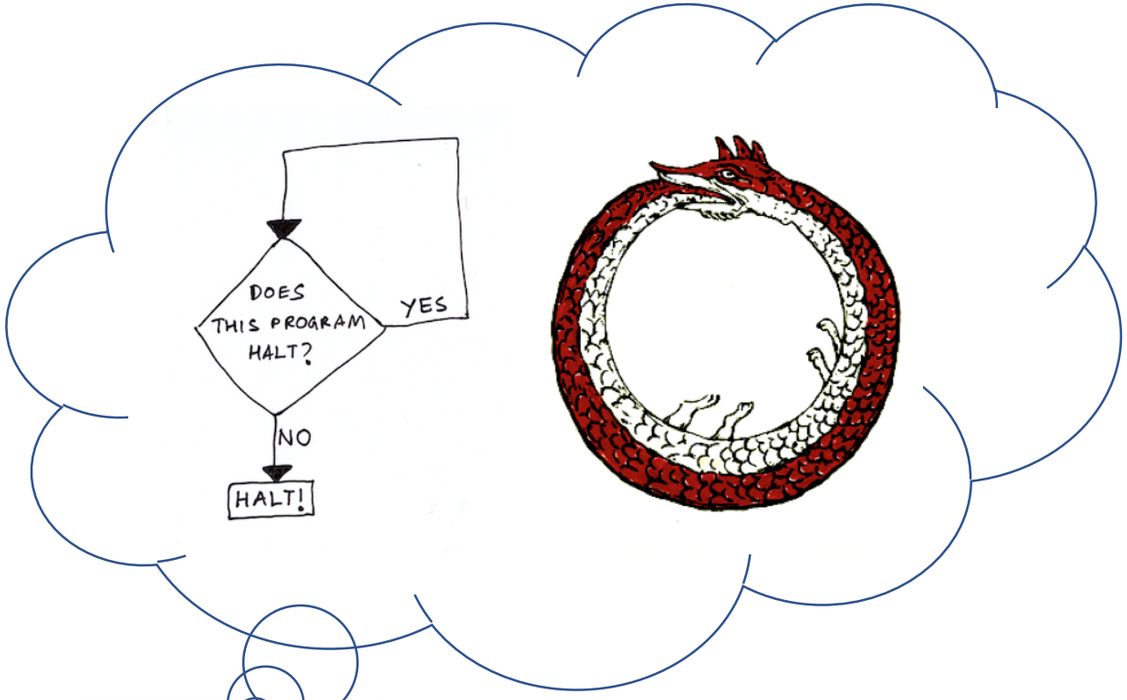
$B+C \rightarrow C+C$

$C+A \rightarrow A+A$



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

Theoretical Computer Science Approach



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

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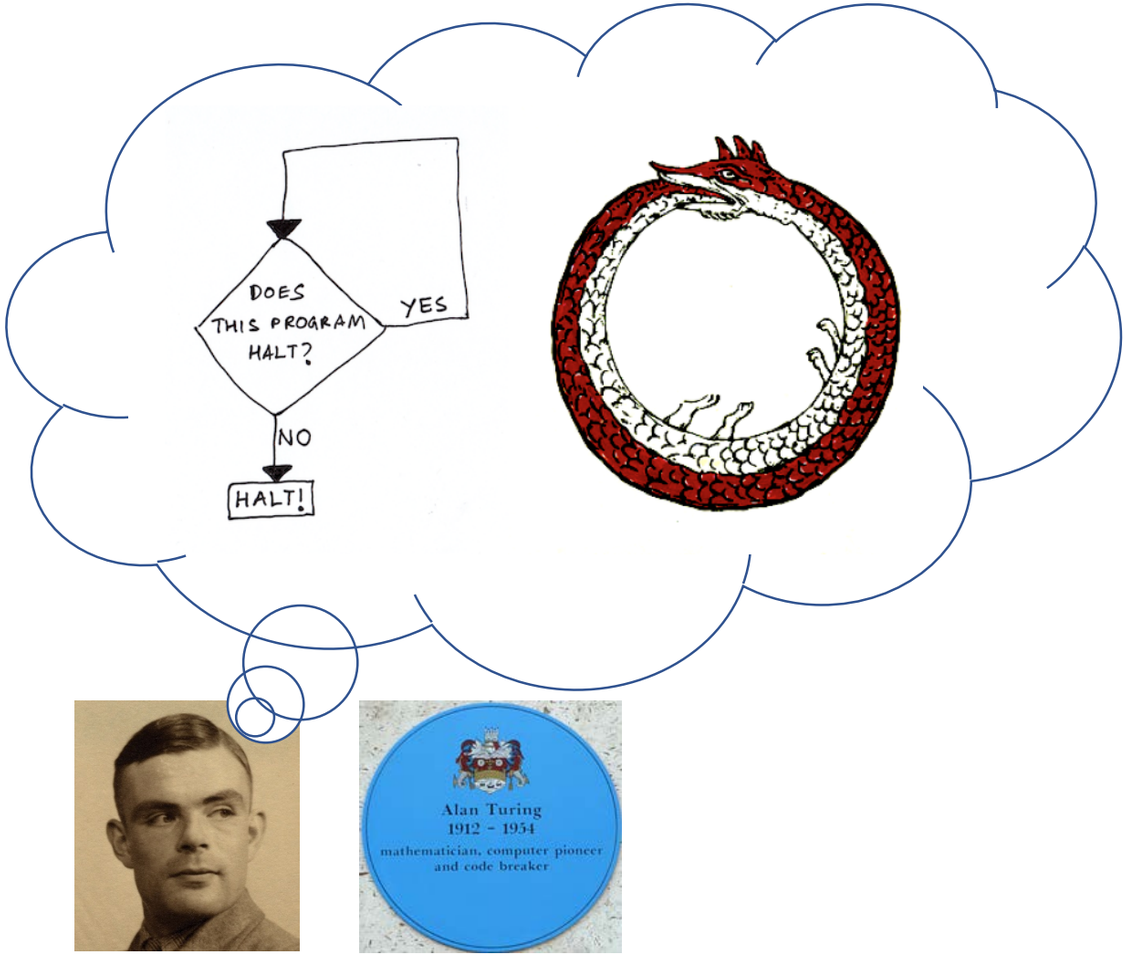


What computation is possible and what is not?
(Computability theory)

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
- What do we mean by “computation” with chemical reactions?
- What do we mean by “efficient computation” with chemical reactions?
- What is known
- What is not yet known

Chemical Reaction Networks (formal definition)

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

$$A+B \xrightarrow{k_1} A+C$$

$$C \xrightarrow{k_2} A+A$$

$$C+B \xrightarrow{k_3} C$$

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

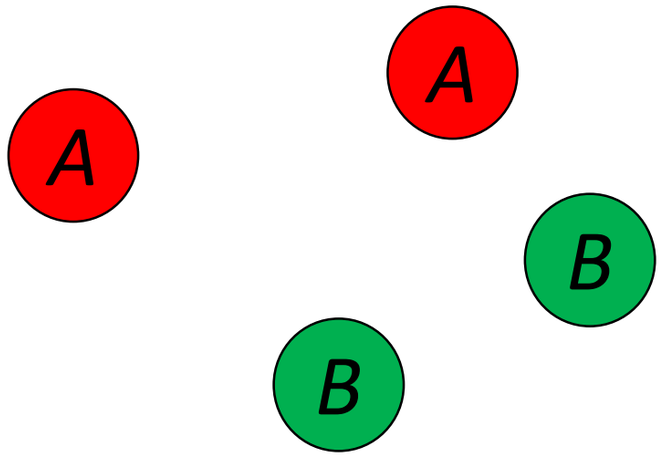
What is **possible**:
Example reaction sequence

α: $A + B \rightarrow A + C$

β: $C \rightarrow A + A$

$A \quad B \quad C$

$\mathbf{x} = (2,\ 2,\ 0)$



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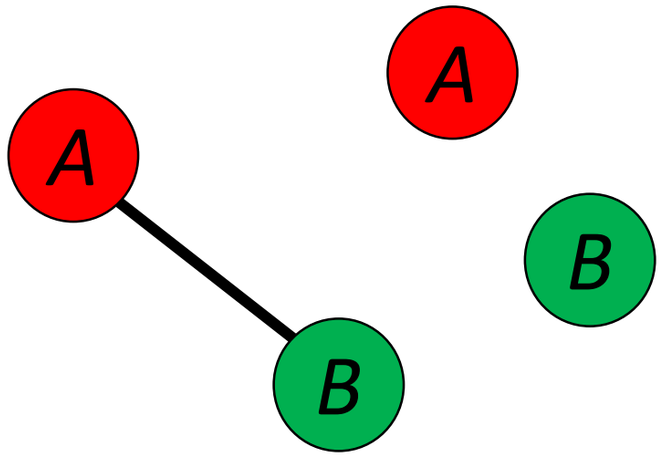

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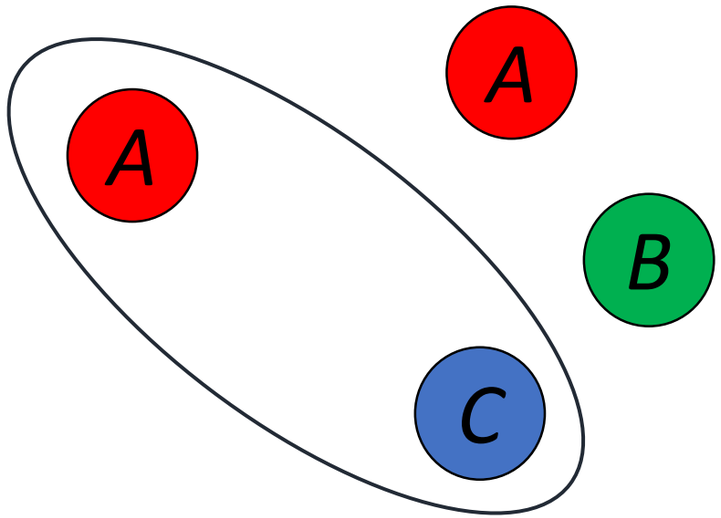

	A	*B*	*C*
x =	**(2,**	**2,**	**0)**
	α ⇓		
	(2,	**1,**	**1)**

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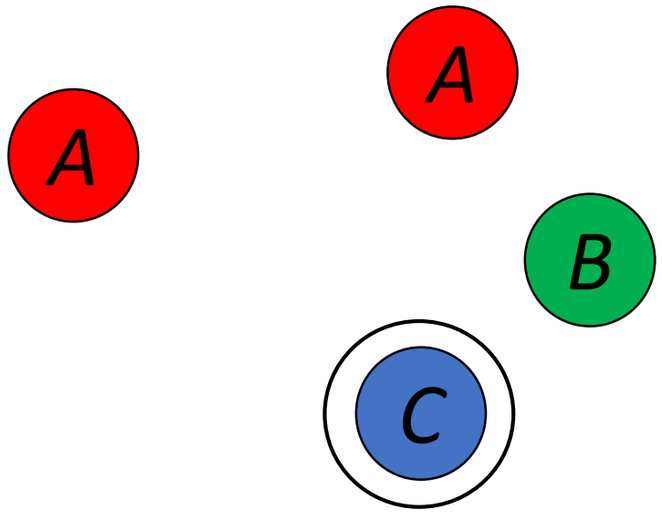

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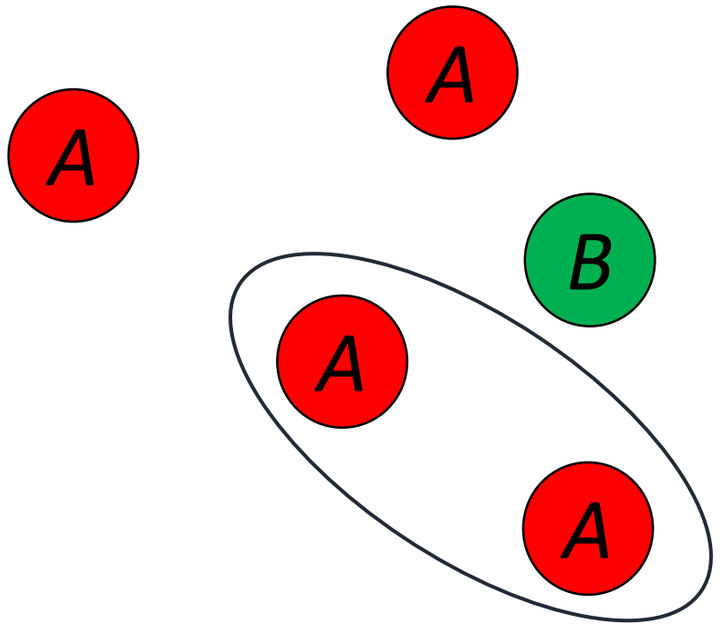

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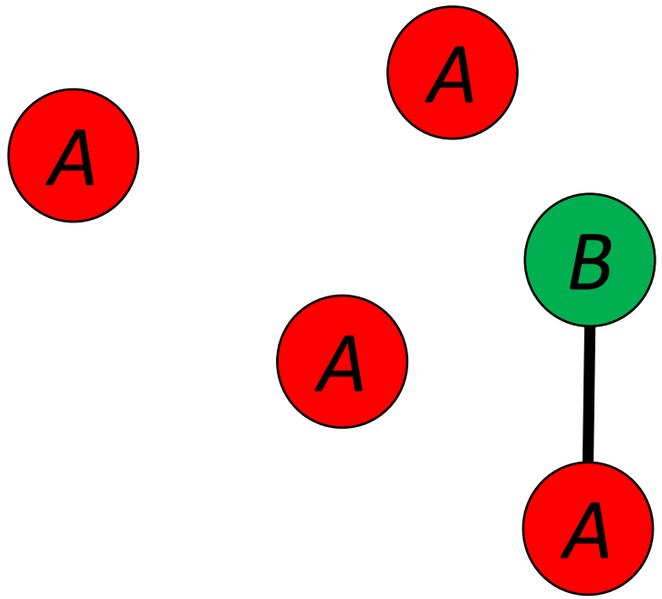

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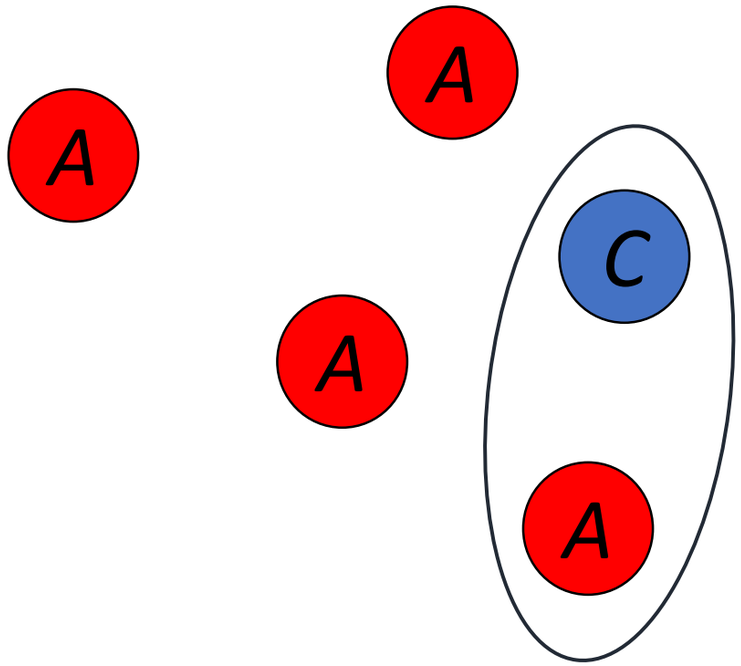

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	···		

What is probable:
Stochastic kinetic model of chemical reaction networks

Solution volume v

reaction type	*rate*
$A \xrightarrow{k} \ldots$	$k \cdot \#A$
$A+B \xrightarrow{k} \ldots$	$k \cdot \#A \cdot \#B \,/\, v$

[McQuarrie 1967, van Kampen, Gillespie 1977]

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expected time until next reaction is 1 / (*sum of all reaction rates*)

[McQuarrie 1967, van Kampen, Gillespie 1977]

Relationship to distributed computing

population protocol = list of *transitions* such as

$x,y \to x,x$ $\quad$ $a,b \to c,d$ $\quad$ $a,a \to a,a$ (*null* transition)

- Repeatedly, two *agents* (molecules) are picked at random to *interact* (react) and change *state* (species).

[Angluin, Aspnes, Diamadi, Fischer, Peralta, Computation in networks of passively mobile finite-state sensors, *PODC* 2004]

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population protocols $\subsetneq$ chemical reactions, but "most" ideas that apply to one model also apply to the other

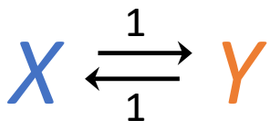
[Angluin, Aspnes, Diamadi, Fischer, Peralta, Computation in networks of passively mobile finite-state sensors, *PODC* 2004]

Time complexity in population protocols

- pair of agents picked uniformly at random to interact (possibly null interaction)
- *parallel time* = number of interactions / *n*

  i.e., each agent has $O(1)$ interactions per “unit time”

Some simple reactions



start with *n* copies of molecule *X*

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$$X \underset{1}{\overset{1}{\rightleftharpoons}} Y$$

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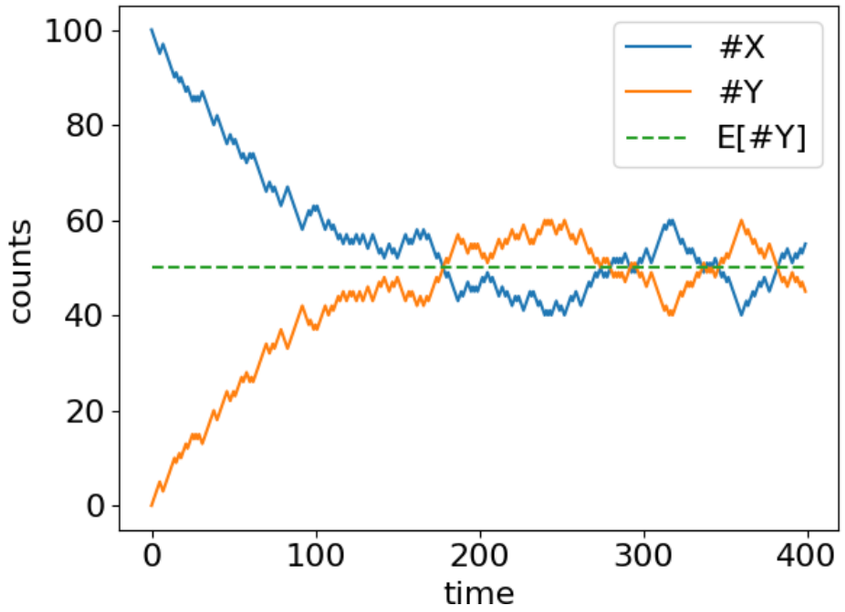
$\#Y = n/2$ expected at equilibrium



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$$X \xrightarrow{1} Y$$

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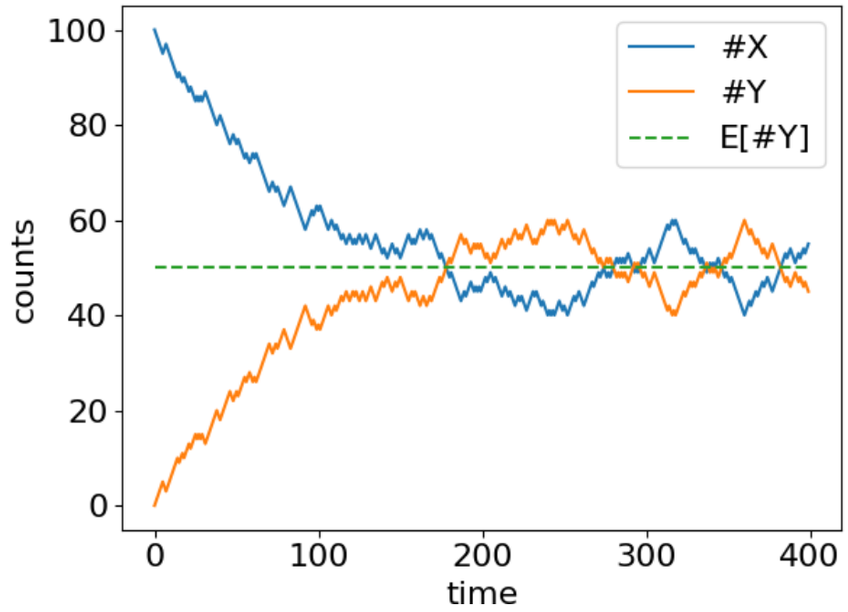

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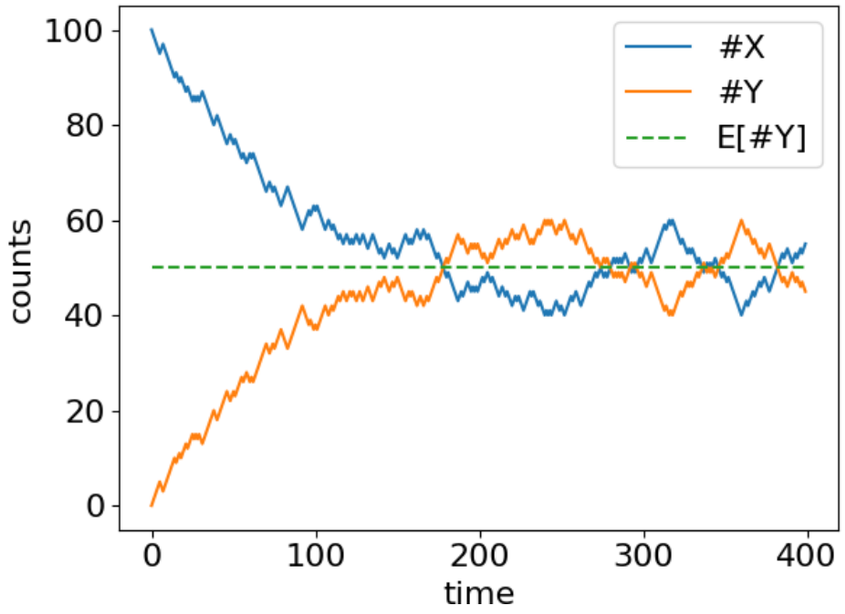
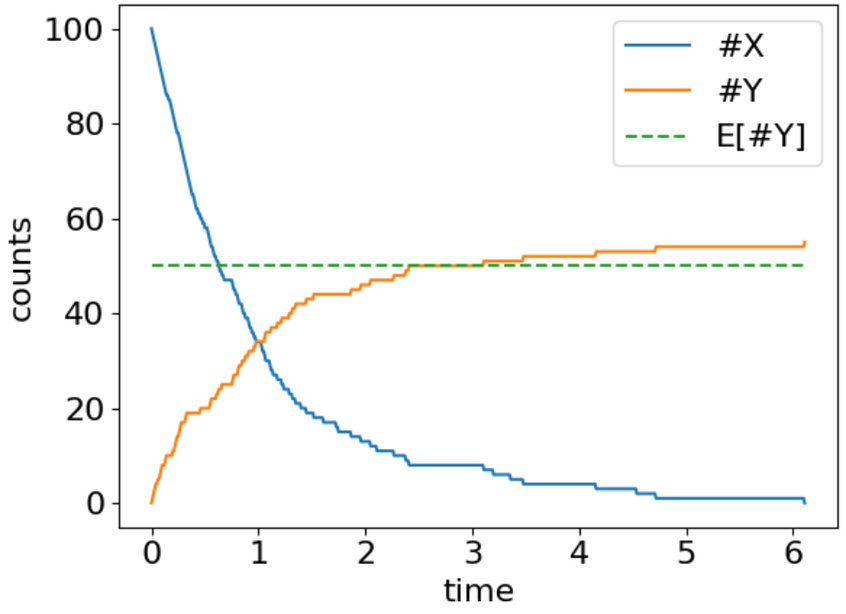
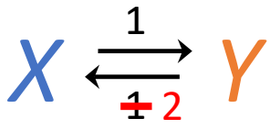
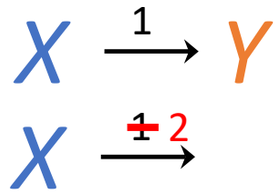


$\#Y$ stabilizes, with expected value $n/2$



Some simple reactions





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#Y = ~~*n/2*~~ *n/3* expected at equilibrium

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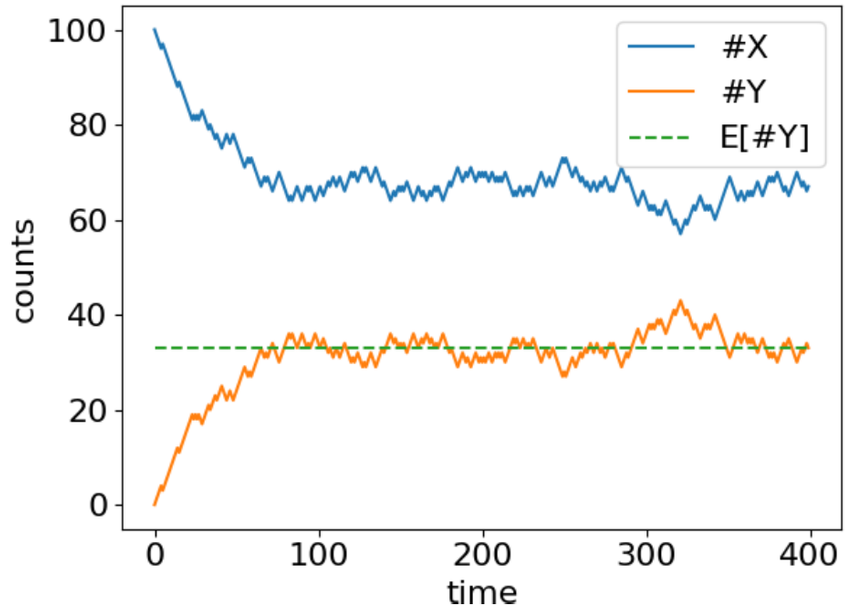

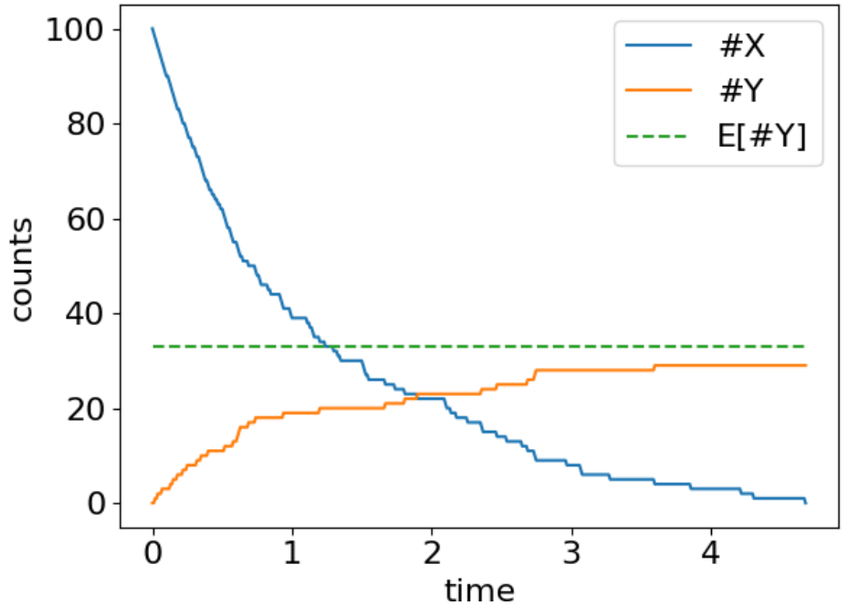

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Defining **stable** computation

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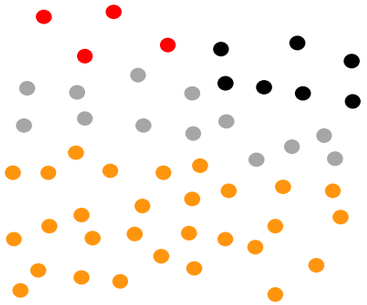
i

initial
configuration



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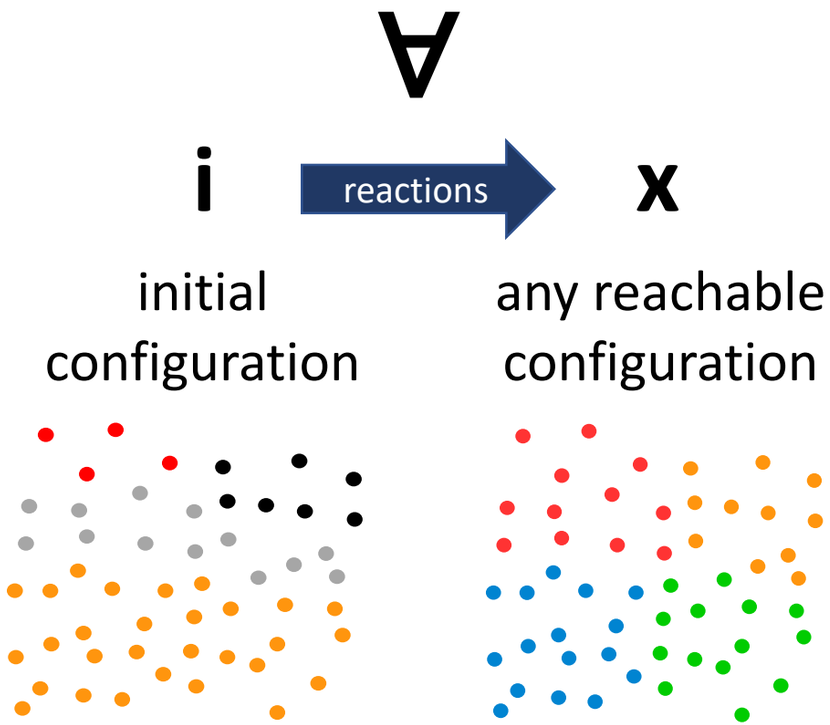

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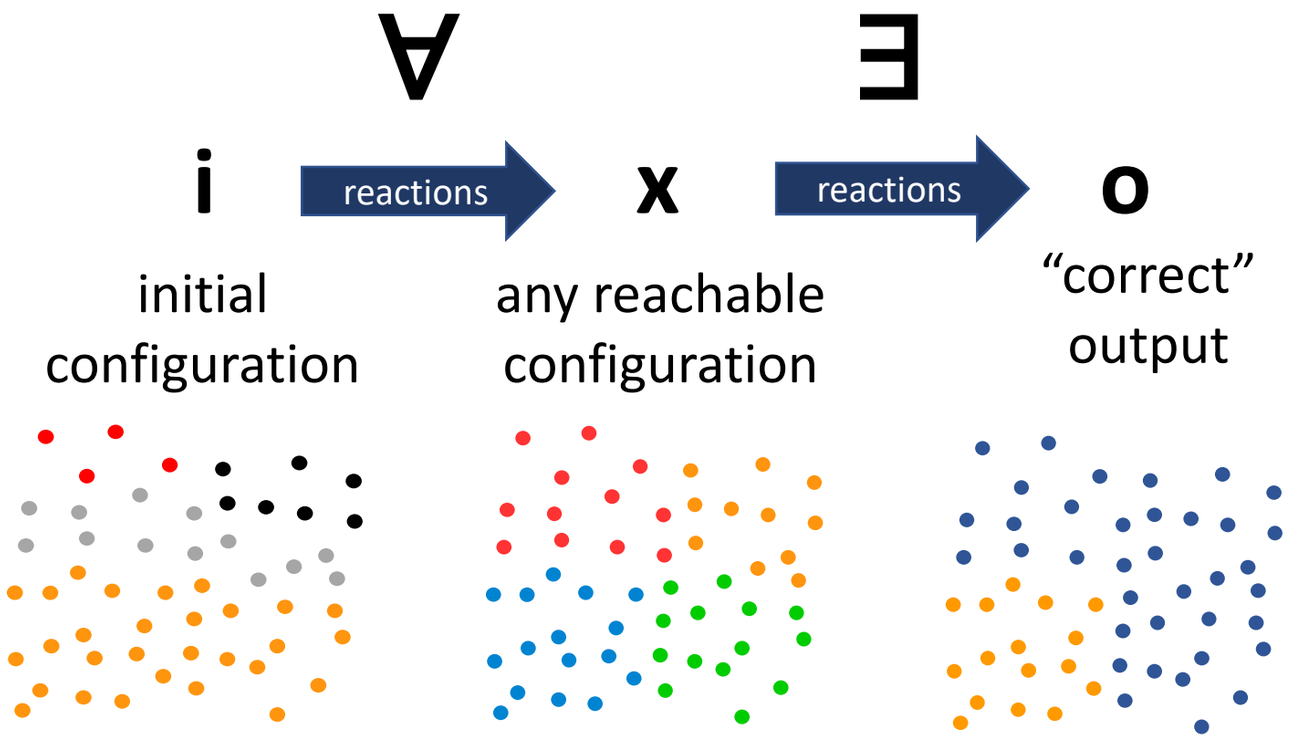

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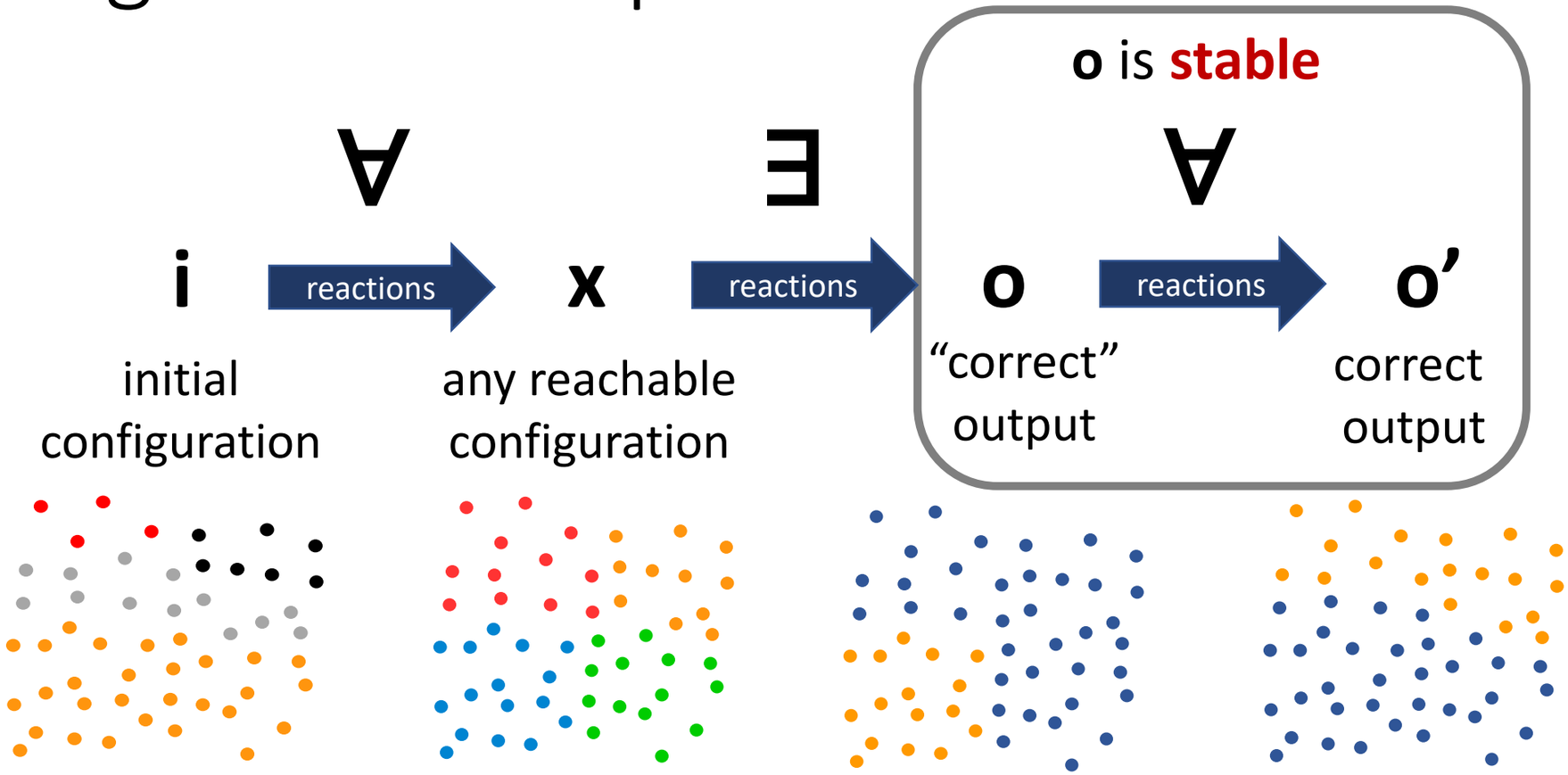

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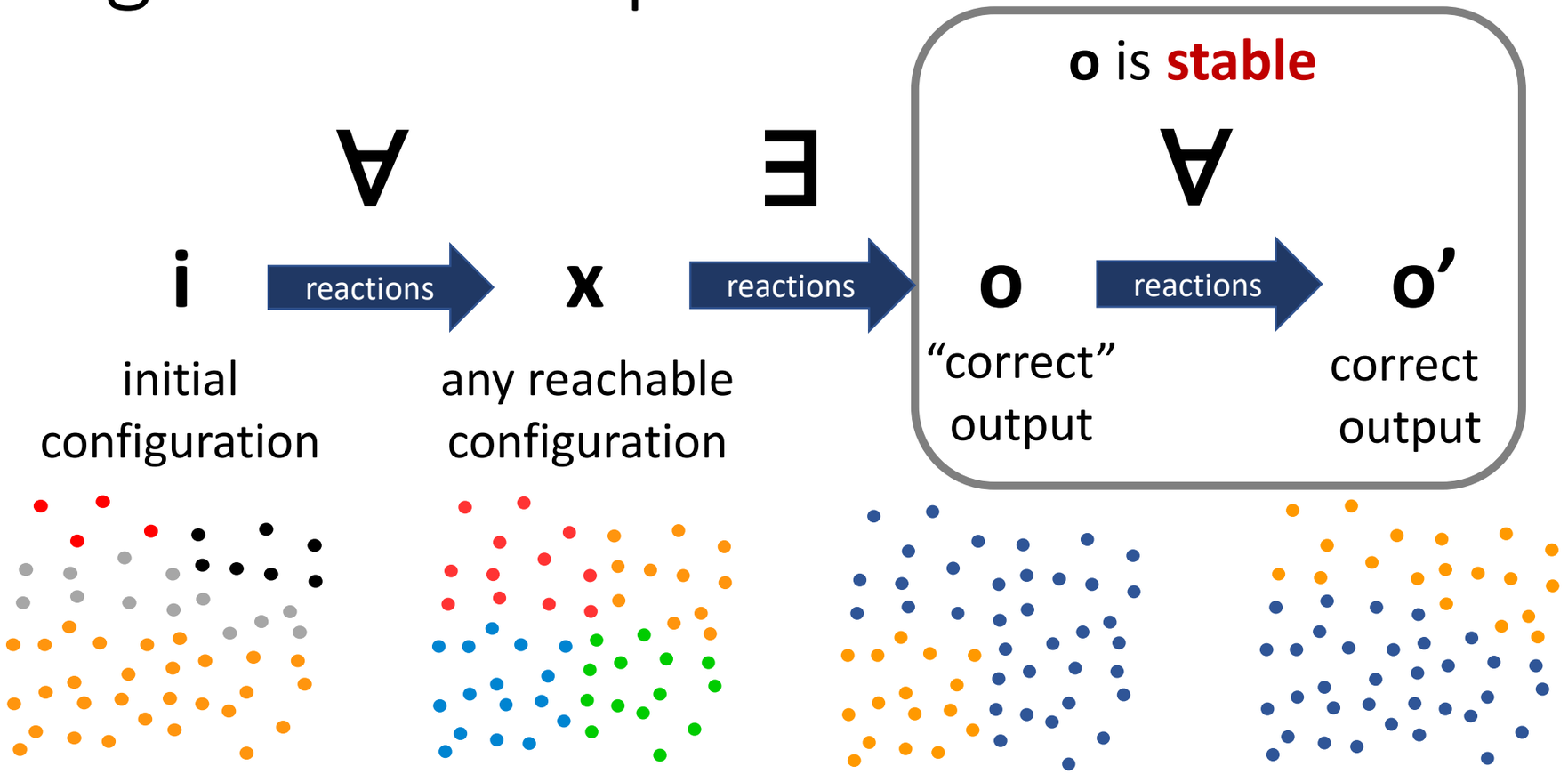

(assuming finite set of reachable configurations) equivalent to:
The system will reach a correct stable configuration with probability 1.

Speed of computation

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How to fairly assess speed?

Like any respectable computer scientist…

1) as a function of input size *n* (how required time grows with *n*)
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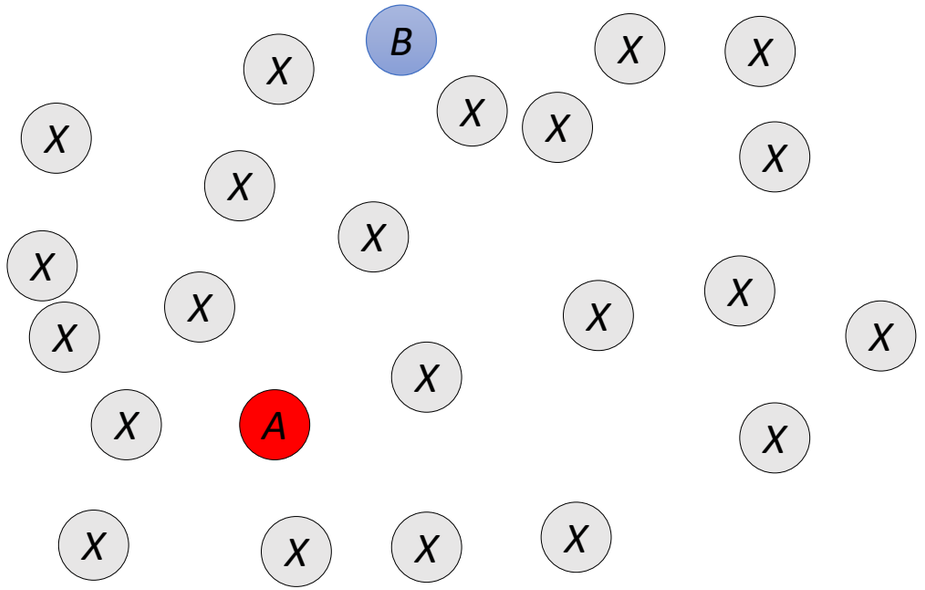
n = total molecular count
volume $v = O(n)$
i.e., require bounded concentration (finite density constraint)

An exponential time difference

n molecules
volume $v = O(n)$



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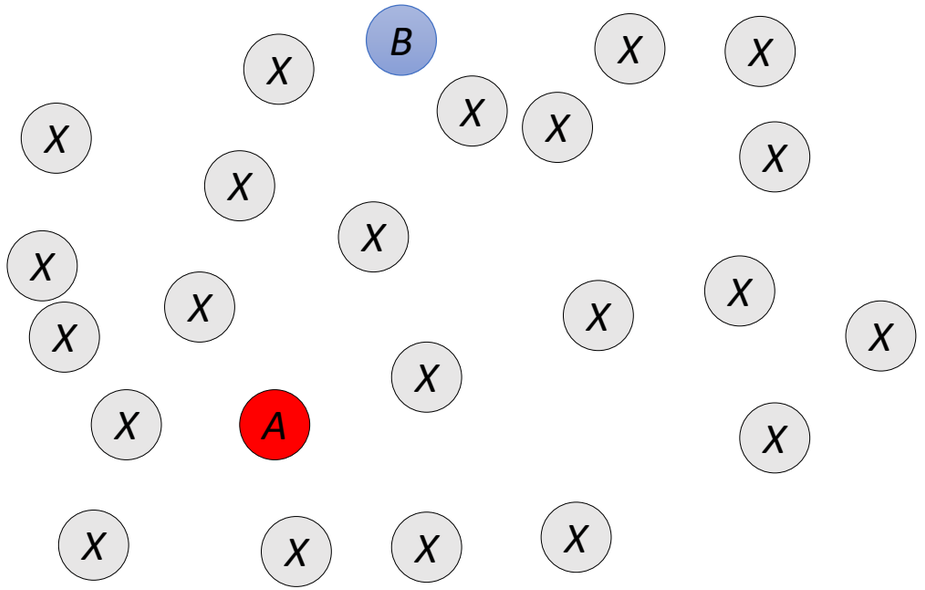

$$A + B \rightarrow Y + B$$

propensity: $\#A \cdot \#B \,/\, v = O(1/n)$

expected time to produce *Y*:

$O(n)$

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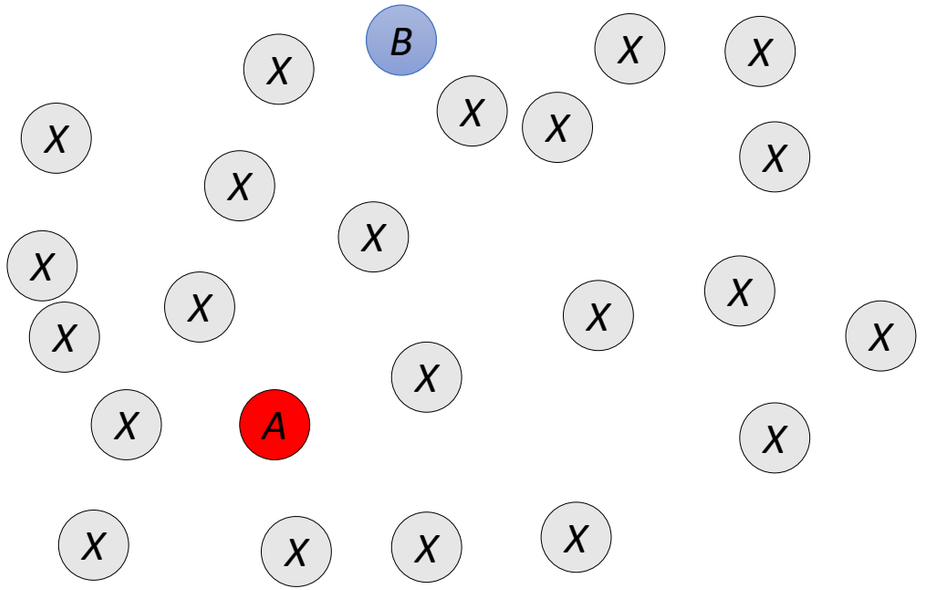

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distributed computing terms:
- *epidemic*
- *rumor/gossip spreading*

chemical term:
- *autocatalysis*

expected time to produce Y:

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$O(\log n)$

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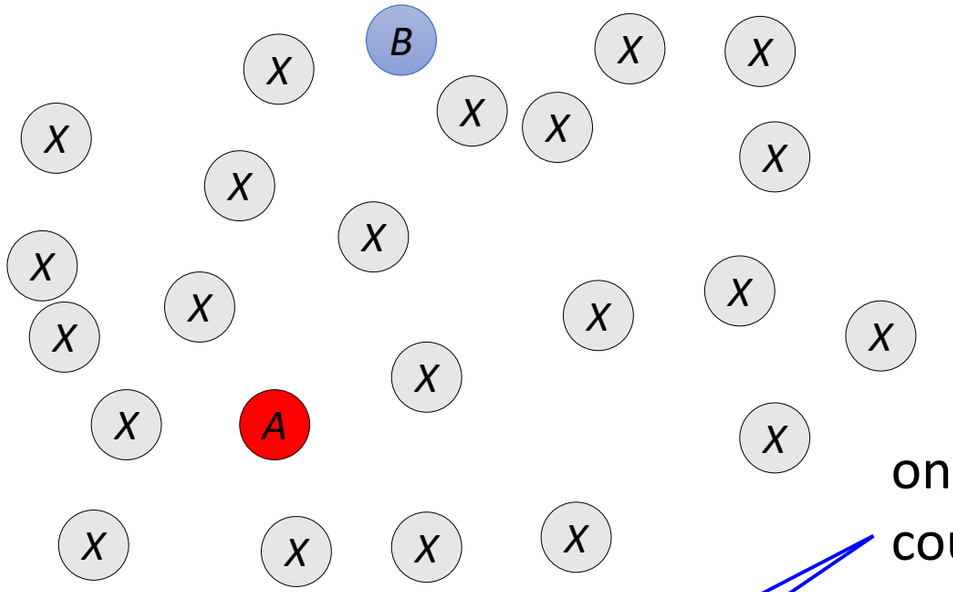

one of these is always
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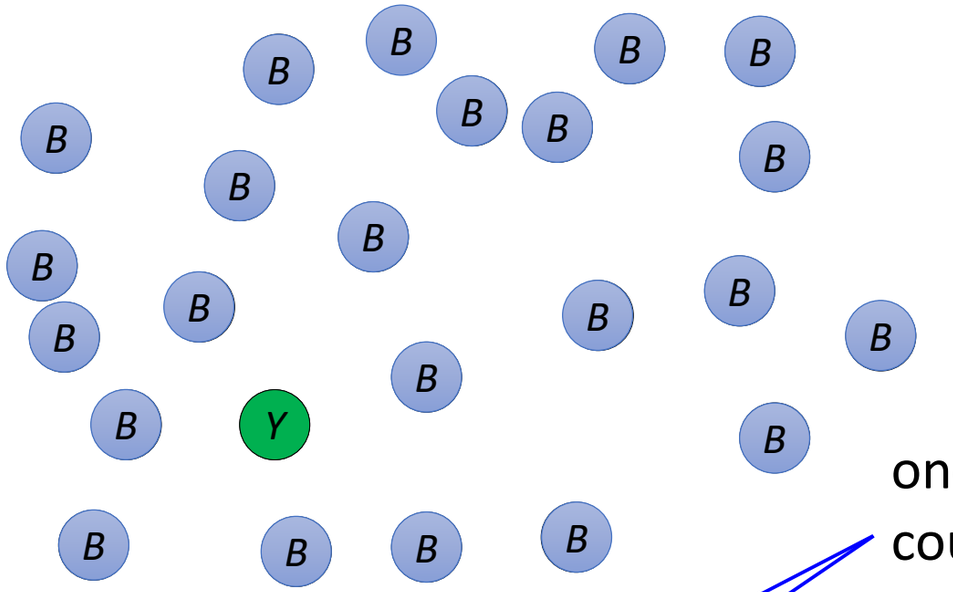

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Definition of *predicate* (decision problem) computation

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

[Angluin, Aspnes, Diamadi, Fischer, Peralta, Computation in networks of passively mobile finite-state sensors, *PODC* 2004]

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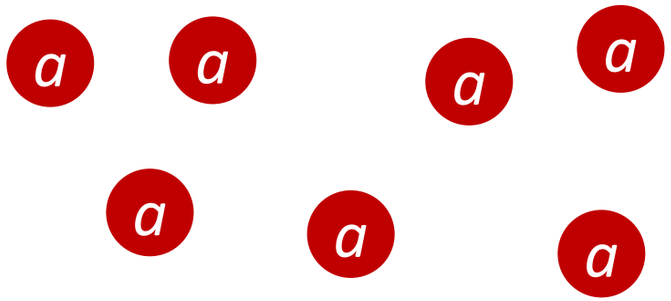
Examples of predicate computation

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



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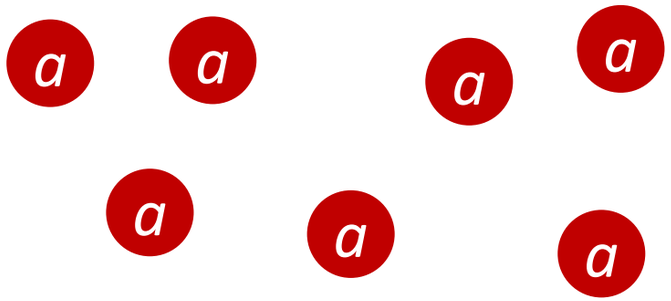
$$b+a \rightarrow b+b$$

a votes no; b votes yes
E[time] = O(log n)



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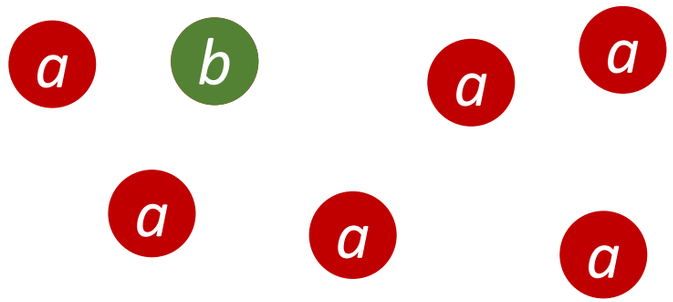

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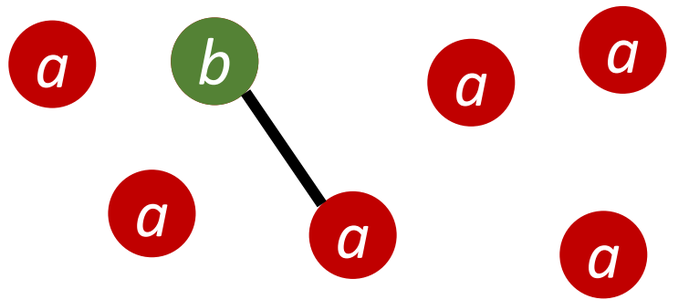

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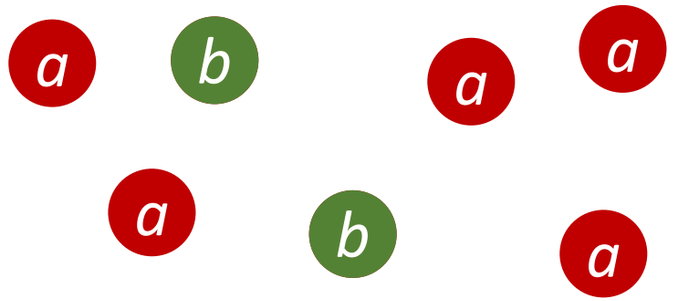

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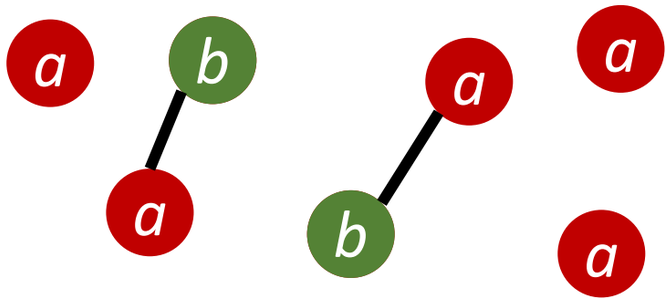

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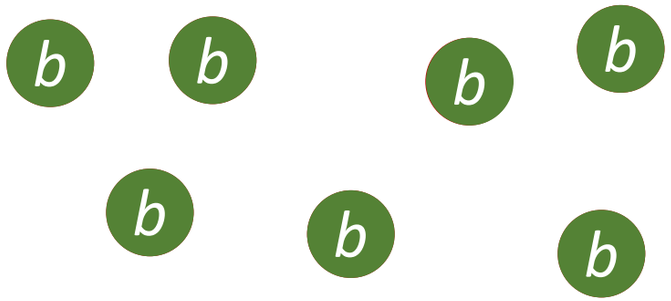

Examples of predicate computation

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Counting: $\varphi(a,b) = Y \Leftrightarrow b > 1$

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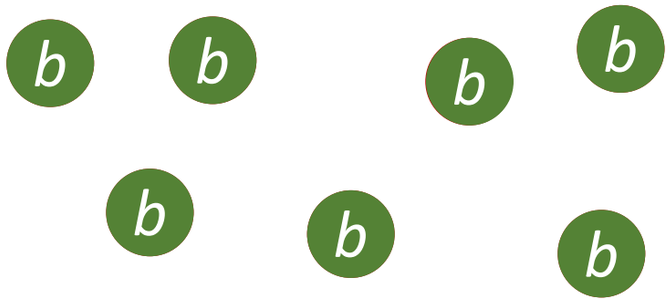

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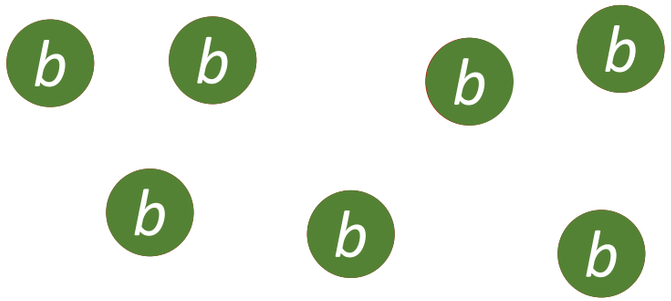

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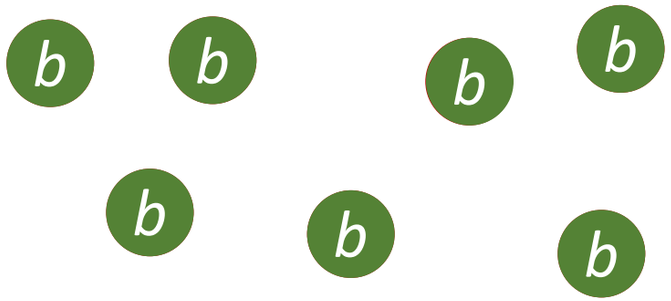
exponential time difference!



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

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$A+B \rightarrow a+b$ (both become "followers" but preserve difference between *A*'s and *B*'s)

[Draief, Vojnovic. Convergence speed of binary interval consensus. *SIAM Journal on Control and Optimization*, 50(3):1087–1109, 2012]
[Mertzios, Nikoletseas, Raptopoulos, Spirakis, Determining Majority in Networks with Local Interactions and very Small Local Memory, *Distributed Computing* 2015]

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$A+b \rightarrow A+a$ (leader changes vote of follower)

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$O(n)$ time if $a - b = O(1)$

$O(\log n)$ time if $a - b > 0.01n$

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$O(n \log n)$ time

$O(n)$ bottleneck transition before leader reaches count 1, then $O(n \log n)$ coupon collector for leader to encounter each follower

possible to optimize to $O(n)$
[Angluin, Aspnes, Eisenstat, DISC 2006]

Definition of function computation

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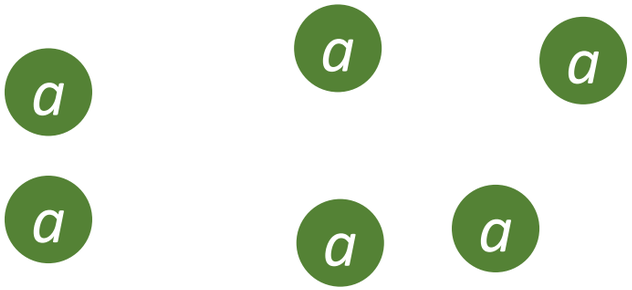
- recall: **o** is stable if **o**(y) = **o'**(y) for all **o'** reachable from **o**

Examples of function computation

division by 2: $f(a) = a/2$



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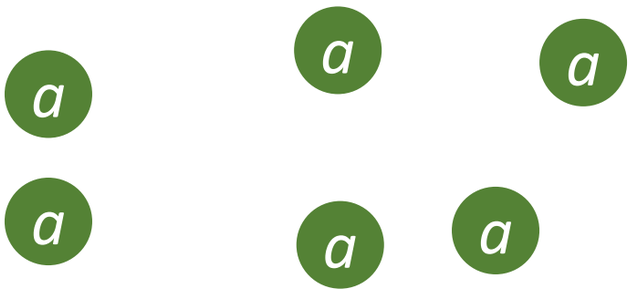
E[time] = $O(n)$
(last transition is bottleneck: has count ≤ 3 of a)



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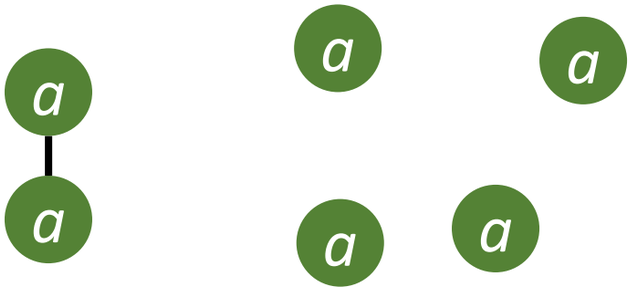

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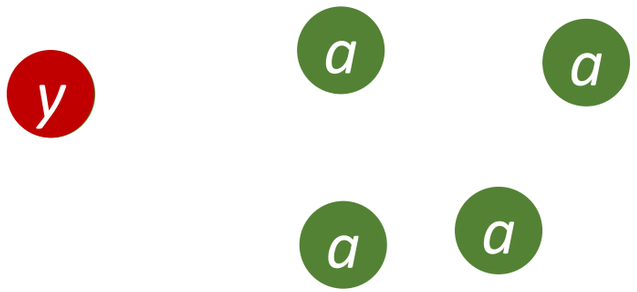

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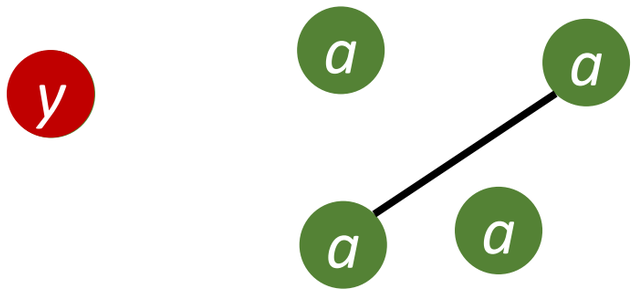

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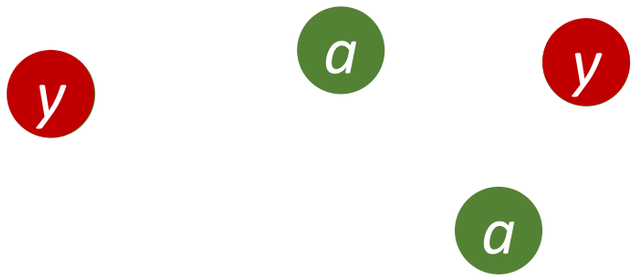

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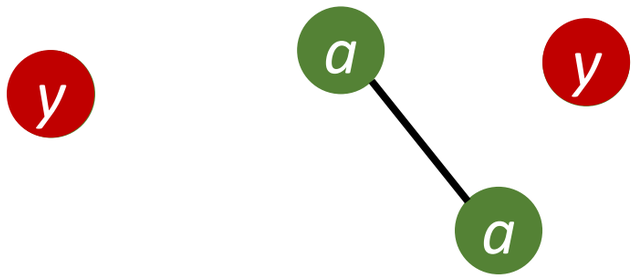

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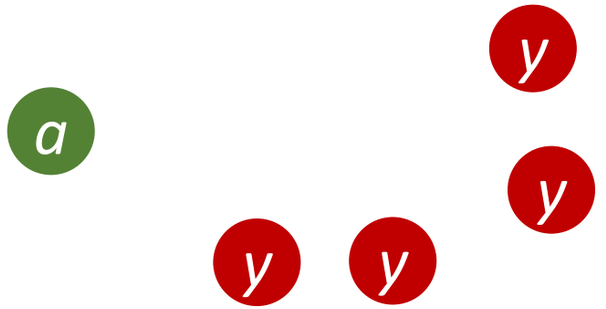

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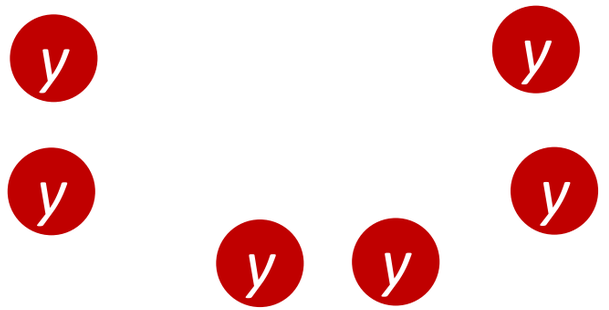

Examples of function computation

division by 2: $f(a) = a/2$

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exponential time difference!

multiplication by 2: $f(a) = 2a$

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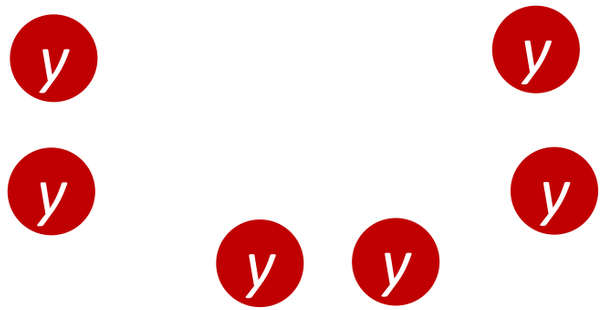

Examples of function computation

addition: $f(a,b) = a+b$

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$a \rightarrow y$

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subtraction: $f(a,b) = a-b$

$a \rightarrow y$

$b+y \rightarrow$

E[time] = $O(n)$ if $a - b = O(1)$ initially
(last transition is bottleneck)

Examples of function computation

subtract constant: $f(a) = a - 1$

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addition

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$a_2+b_2 \rightarrow k$ minimum

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$b \rightarrow y+b_2$ addition

$a_2+b_2 \rightarrow k$ minimum

$k+y \rightarrow$ subtraction

E[time] = $O(n)$ (uses minimum and subtraction as "subroutines")

Examples of function computation

constant: $f(a) = 1$

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$$a \rightarrow y$$
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constant: $f(a) = 1$

$a \to y$

$y+y \to y$

E[time] = O(n)

a.k.a. “leader election”

Limits of stable computation (unbounded time)

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Predicates

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  $s >$ constant c?

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

$a>b$?	$a=b$?	a is odd?	$a>0$?	$a>1$?

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

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- piecewise linear, with semilinear predicate to determine which piece.

$a+b$	$a-b$	$2a$	$a/2$	$\min(a,b)$	$a+1$	$a-1$

$f(a) = 2a-b/3$ if $a+b$ is odd, else $f(a) = a/4+5b$

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All semilinear predicates/functions are known to be computable in $O(n)$ time.

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Functions

$\mathbb{N}$-linear functions (coefficients are nonnegative integers)

e.g., $f(a,b) = 2a + 3b$

$a \to y+y$

$b \to y+y+y$

[Angluin, Aspnes, Eisenstat, Fast computation by population protocols with a leader, *DISC* 2006]
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Known time lower bounds: “most” predicates/functions

- Informal: “most” semilinear predicates and functions not known to be computable in $o(n)$ time, actually require at least $O(n)$ time to compute

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- Definition: $\varphi: \mathbb{N}^k \to \{Y,N\}$ is eventually constant if there is $m \in \mathbb{N}$ so that $\varphi(\boldsymbol{a}) = \varphi(\boldsymbol{b})$ for all $\boldsymbol{a},\boldsymbol{b}$ with all components $\geq m$

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  - Both definitions allow exceptions "near a face of $\mathbb{N}^k$"
- Formal theorem: Every predicate that is not eventually constant, and every function that is not eventually $\mathbb{N}$-linear, requires at least time $O(n)$ to compute.
  - They're all computable in at most $O(n)$ time, so this settles their time complexity.

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What is currently known/unknown

	Predicates	Functions
computable in $O(\log n)$ time	detection $a>0$ **AND** ($b>0$ **OR** $c=0$)	$\mathbb{N}$-linear $3a + b + 2c$
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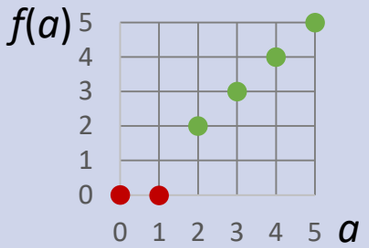
unknown (best known protocol is $O(n)$ time)	eventually constant but not constant on positive values $a>1$?	eventually $\mathbb{N}$-linear but not $\mathbb{N}$-linear $f(a) = \begin{cases} a \text{ if } a>1, \\ 0 \text{ otherwise} \end{cases}$ 

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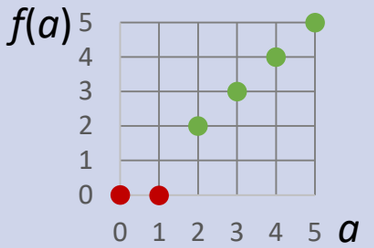
unknown (best known protocol is $O(n)$ time)	eventually constant but not constant on positive values $a>1$?	eventually $\mathbb{N}$-linear but not $\mathbb{N}$-linear $f(a) = \begin{cases} a \text{ if } a>1, \\ 0 \text{ otherwise} \end{cases}$ 

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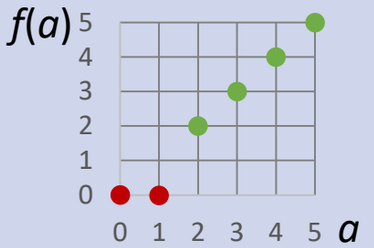
unknown (best known protocol is $O(n)$ time)	eventually constant but not constant on positive values $a>1$?	eventually $\mathbb{N}$-linear but not $\mathbb{N}$-linear $f(a) = \begin{cases} a \text{ if } a>1, \\ 0 \text{ otherwise} \end{cases}$ 

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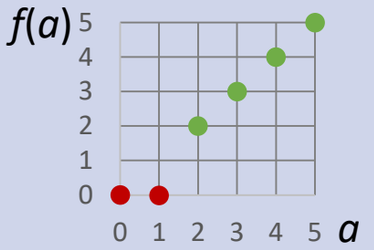
unknown (best known protocol is $O(n)$ time)	eventually constant but not constant on positive values $a>1$?	eventually $\mathbb{N}$-linear but not $\mathbb{N}$-linear $f(a) = \begin{cases} a \text{ if } a>1, \\ 0 \text{ otherwise} \end{cases}$ 

Other modeling choices?

Modeling choices in formalizing *"Computing with chemistry"*

- integer counts ("stochastic") or real concentrations ("mass-action")?
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  - yes/no decision problem? *"number of A's > number of B's?"*
  - numerical function? *"make Y become double the amount of X"*
- guaranteed to get correct answer? or allow small probability of error?
  - if Pr[error] = 0, system works *no matter the reaction rates*
- to represent an input $n_1,\ldots,n_k$, what is the initial configuration?
  - only input species present?
  - auxiliary species can be present?
- when is the computation finished? when…
  - the output stops changing? (convergence)
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first part of talk

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summarized in next few slides

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But *fundamental computability* doesn't change: exactly the semilinear predicates/functions can be computed (same as without a leader).

[Angluin, Aspnes, Diamadi, Fischer, Peralta, *PODC* 2004] [Angluin, Aspnes, Eisenstat, *PODC* 2006] [Chen, Doty, Soloveichik, *DNA* 2012] [Doty, Hajiaghayi, *DNA* 2013]

Convergence vs stabilization and leader vs anarchy

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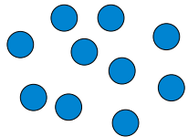

initial

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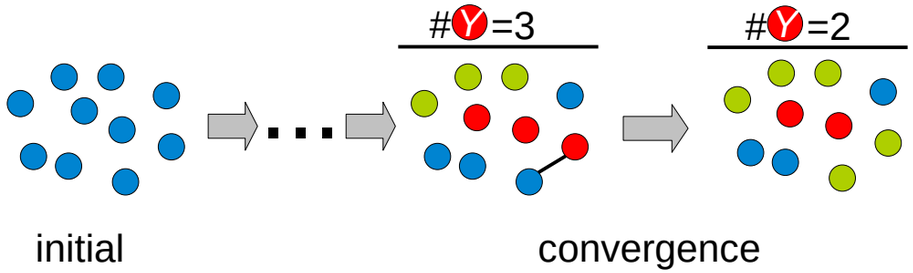

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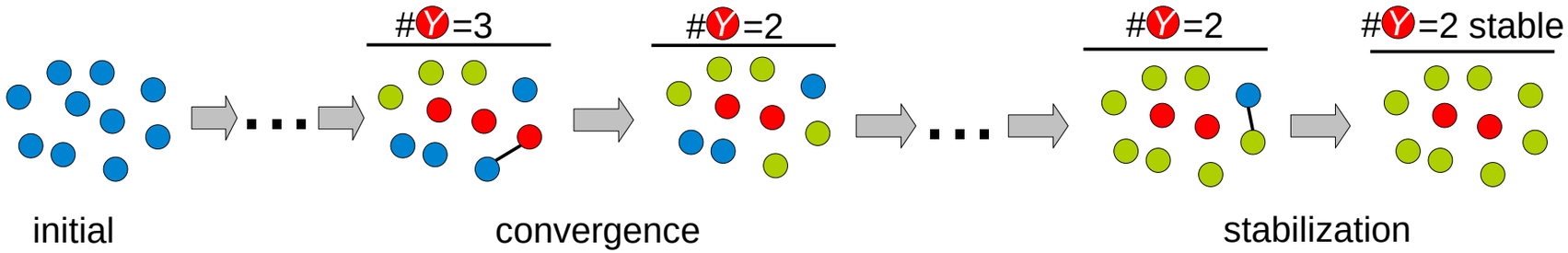

Theorem: Without a leader, all non-eventually constant predicates and non-eventually-$\mathbb{N}$-linear functions require at least $O(n)$ stabilization time. [Belleville, Doty, Soloveichik, *ICALP* 2017]

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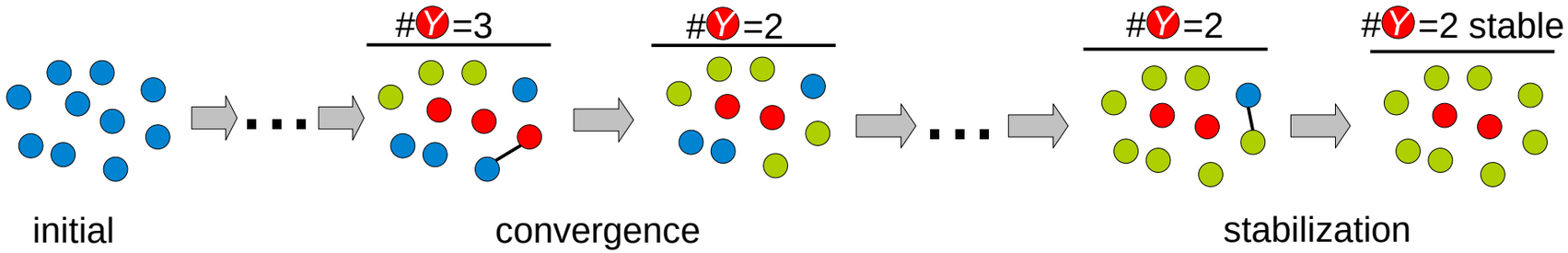

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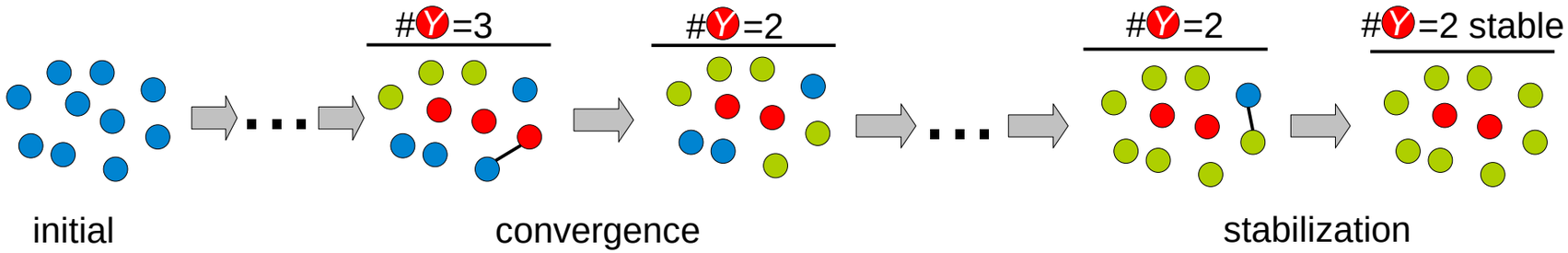

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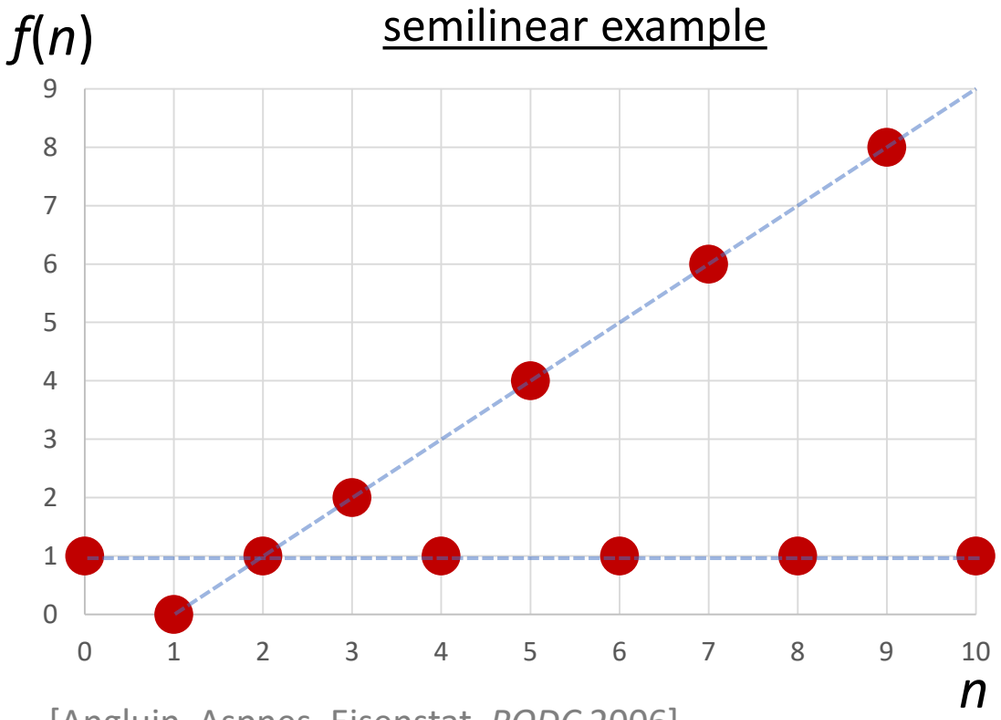

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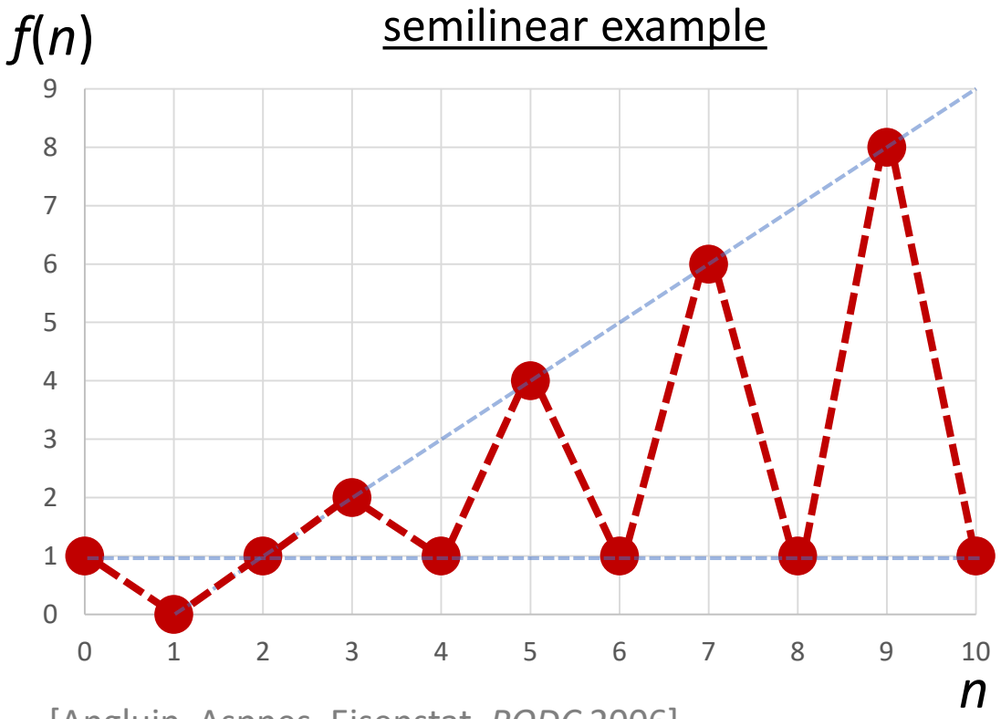

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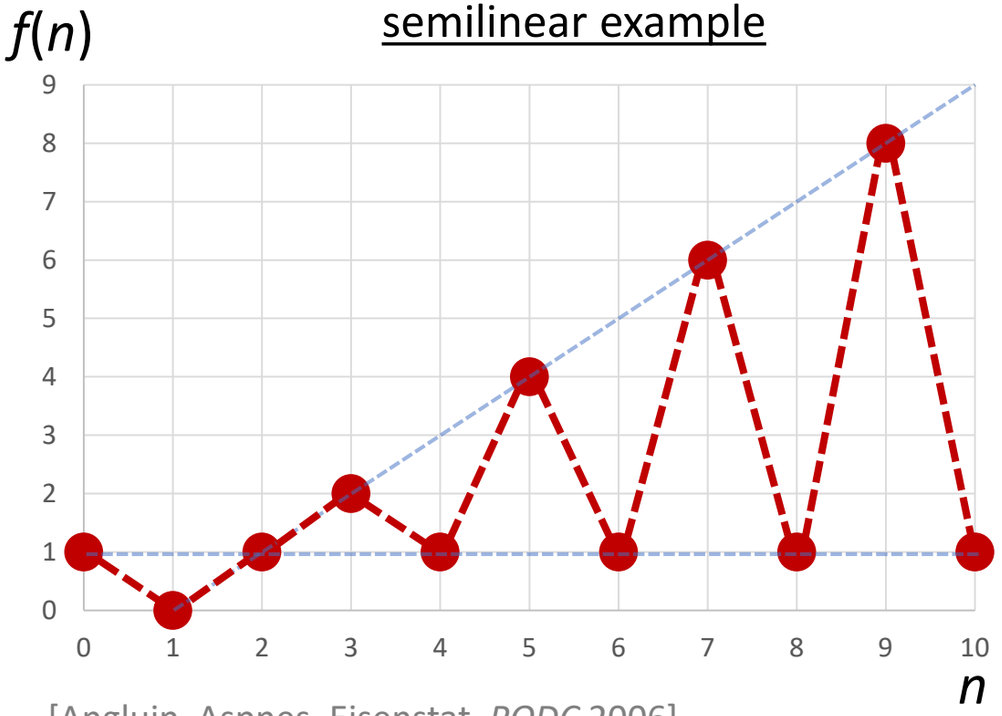

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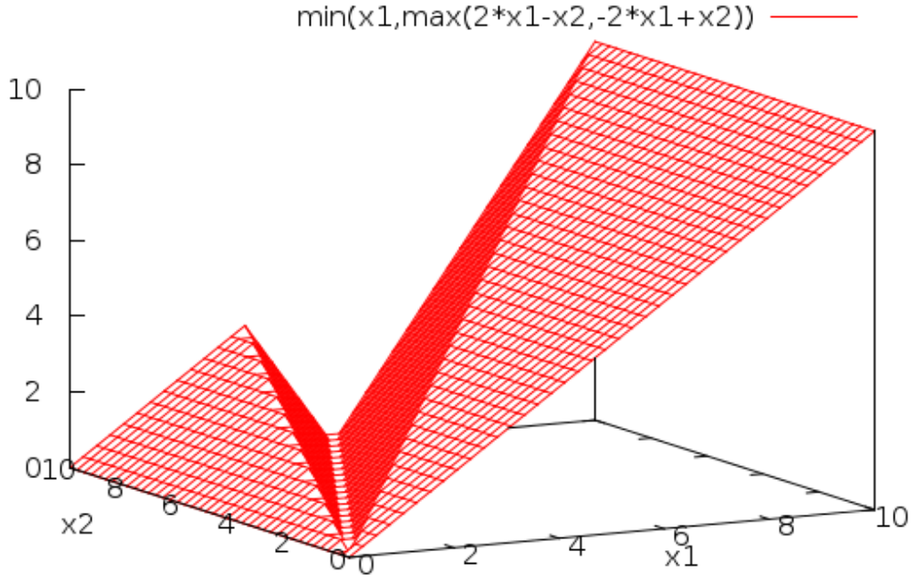
Theorem: A function is stably computable by a real-valued chemical reaction network if and only if it is *continuous* and piecewise linear.

continuous piecewise linear example



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Theorem: A function is computable with probability of error < 1% by an integer-valued chemical reaction network if and only if it is computable by any algorithm whatsoever…

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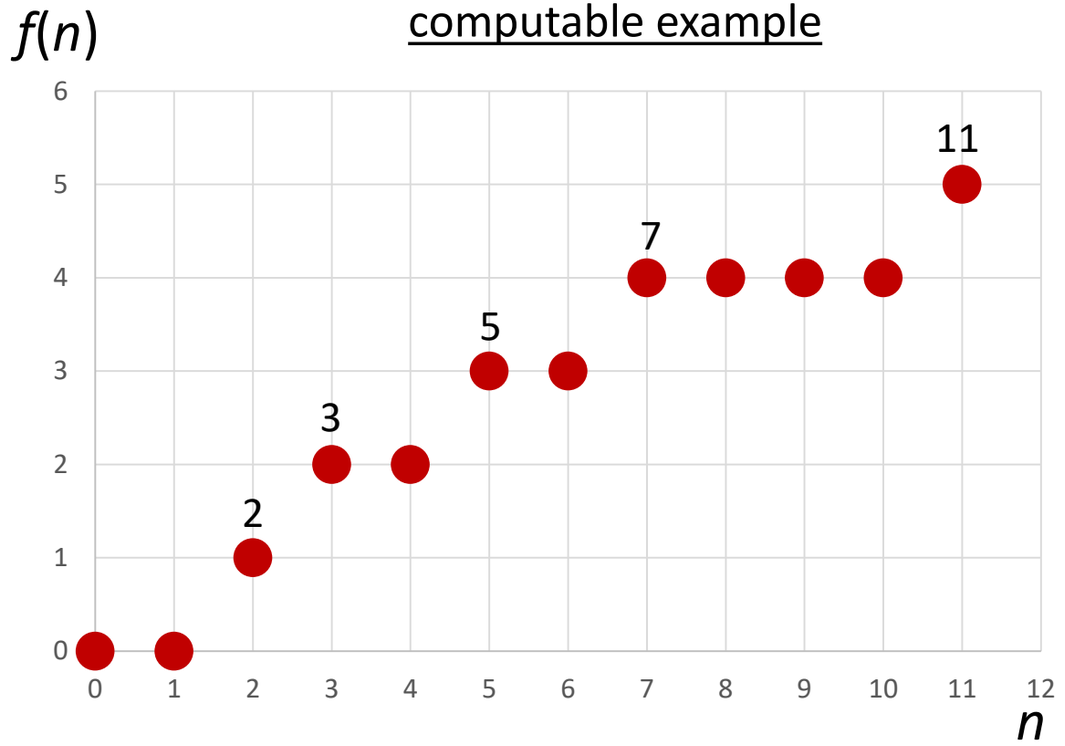

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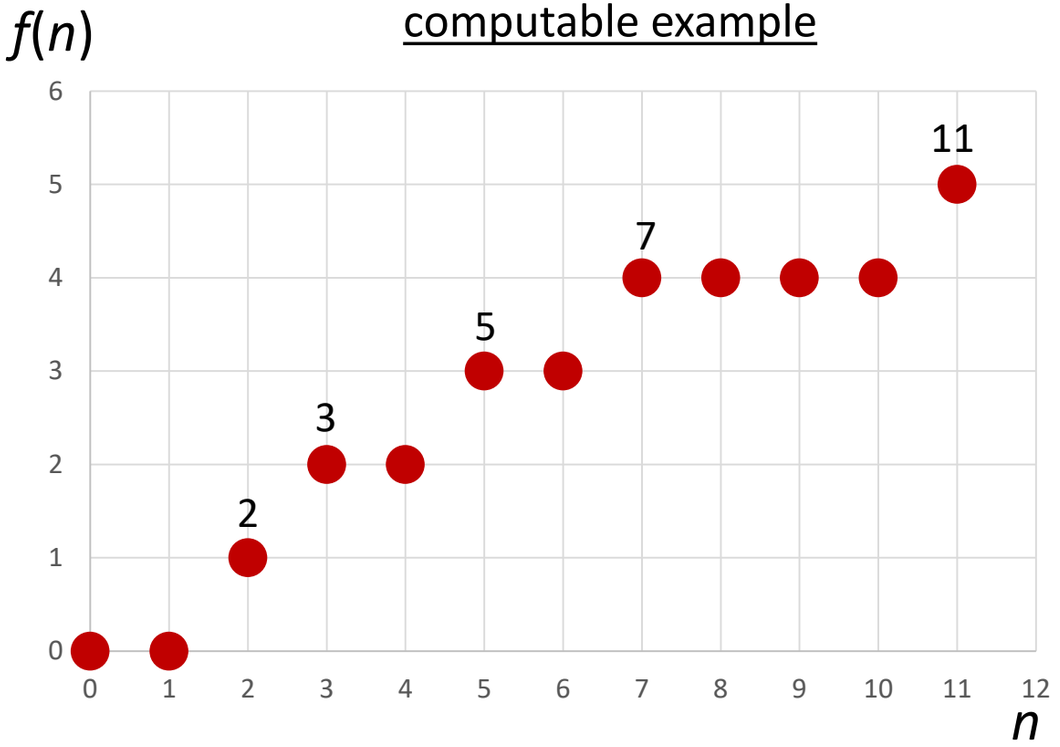

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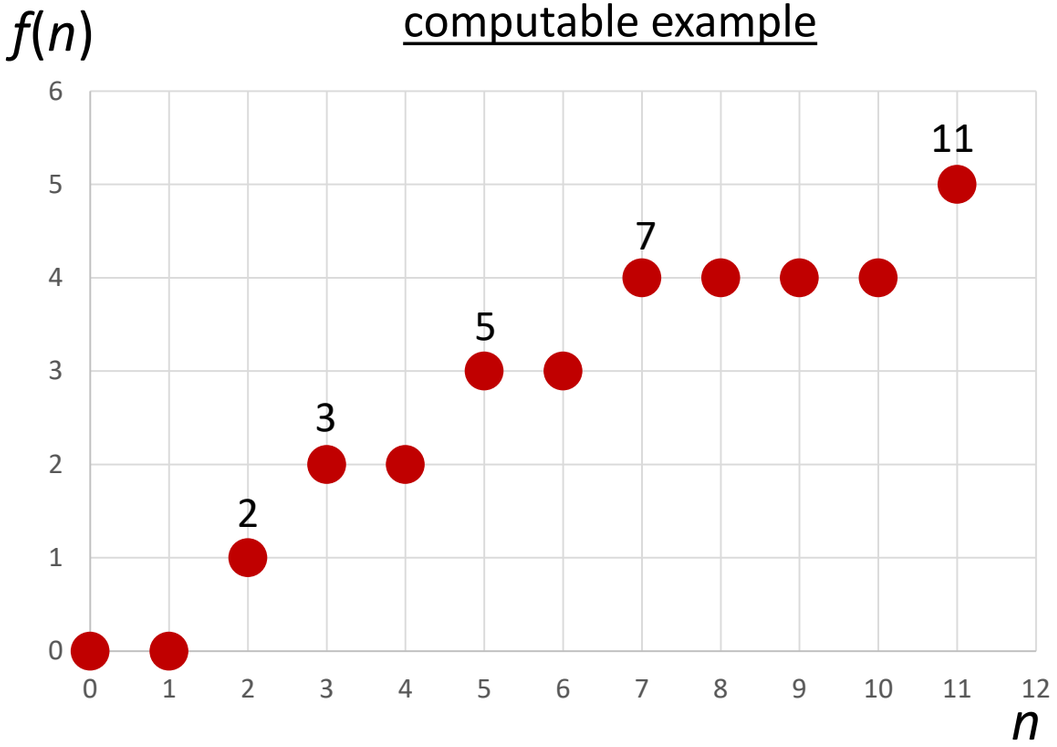

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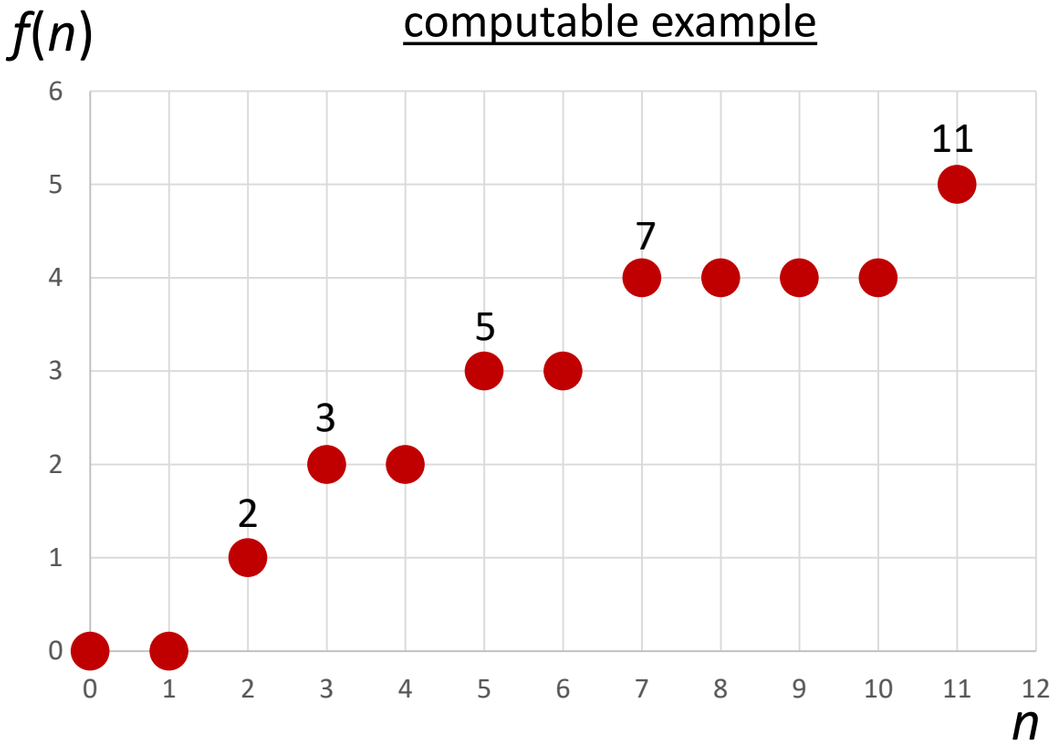

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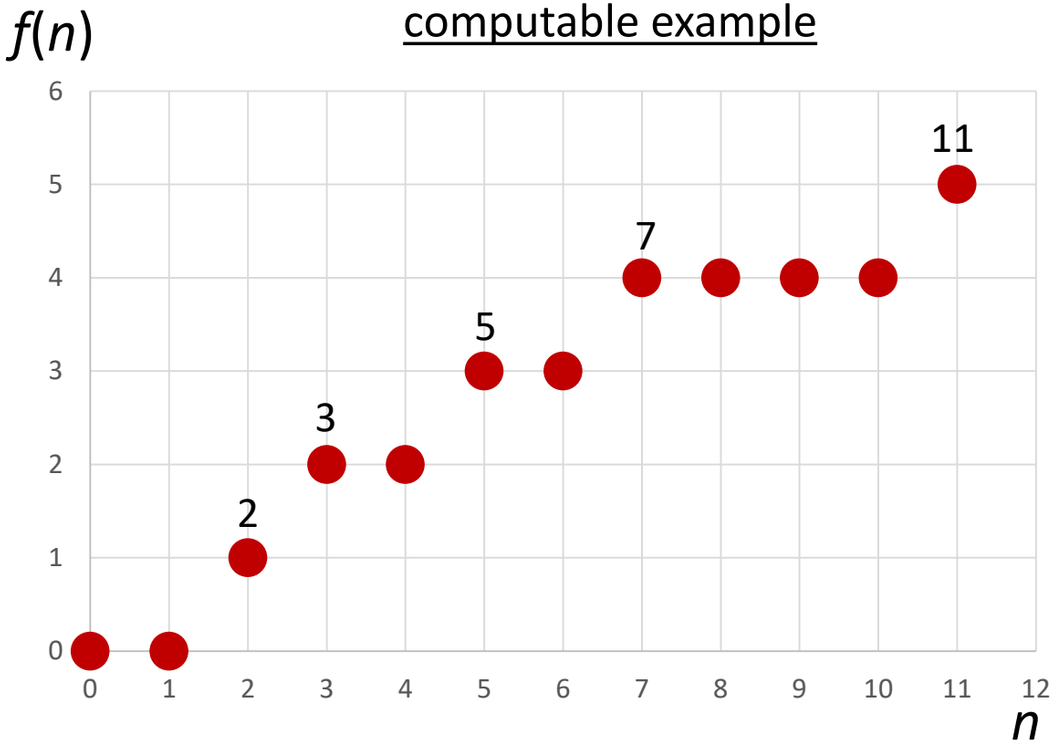

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Conjecture: *Even without a leader*, any computable function can be efficiently computed with high probability.

What if we use real-valued concentrations… **and** allow reaction rates to influence outcome??

Theorem: A function is computable by a real-valued chemical reaction network using mass-action kinetics if and only if it is computable by any algorithm whatsoever.

[Fages, Le Guludec, Bournez, Pouly. Strong Turing completeness of continuous chemical reaction networks and compilation of mixed analog-digital programs. *Computational Methods in Systems Biology – CMSB* 2017]

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… with only a polynomial-time slowdown.

[Bournez, Graça, Pouly. Polynomial time corresponds to solutions of polynomial ordinary differential equations of polynomial length. *Journal of the ACM* 2017]

Fast approximate division by 2

initial configuration:
{ $n\,X$, $\varepsilon n\,A$, $\varepsilon n\,B$ }

$$X + A \to B + Y$$
$$X + B \to A$$

guaranteed to get
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E[time] = O(log n) / ε

[Belleville, Doty, Soloveichik, Hardness of computing and approximating predicates and functions with leaderless population protocols, *ICALP* 2017]

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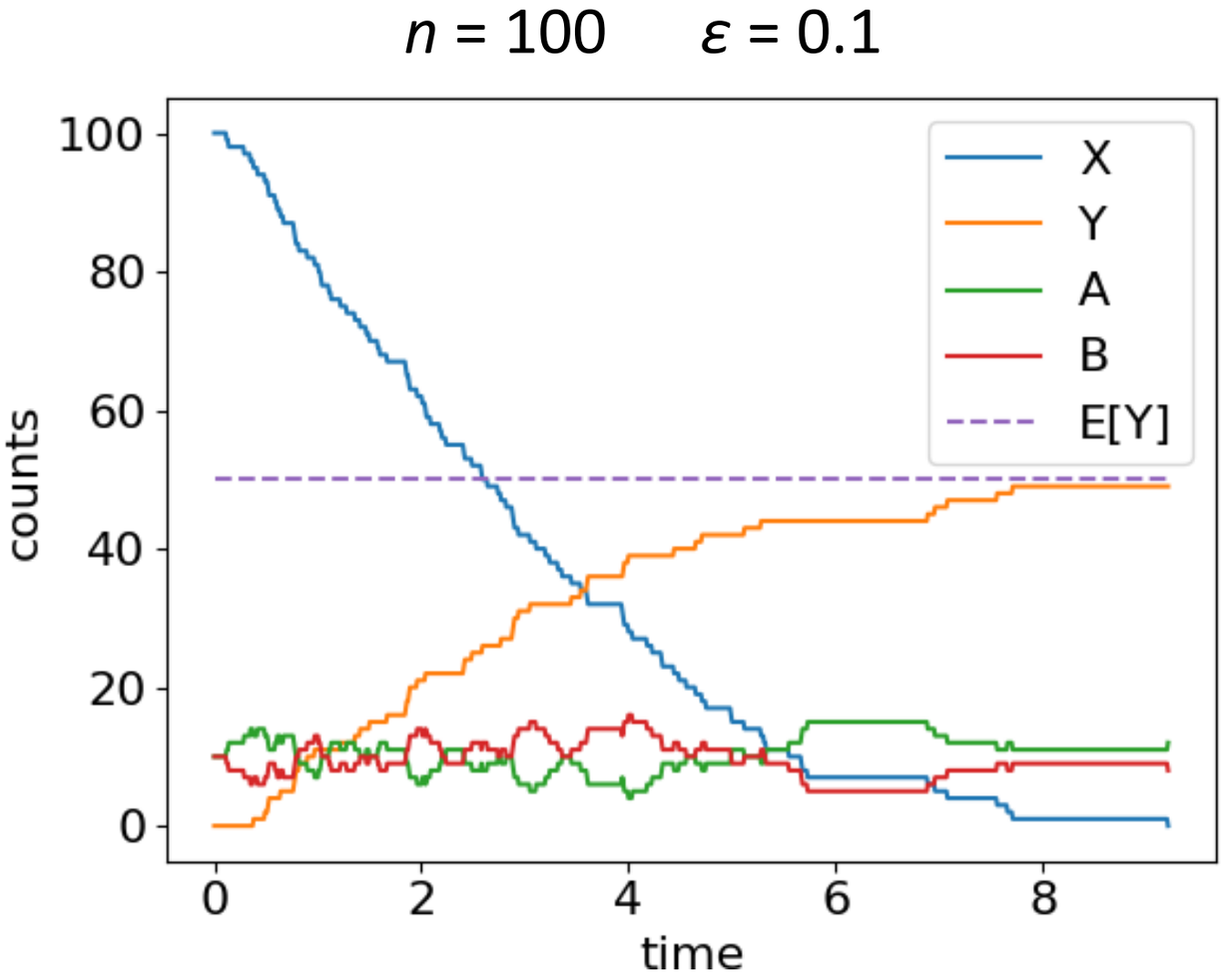

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Thank you!

Questions?

Proofs of conjectures?

Criticism of model?

suggestions: 1) lack of reverse reactions (energy dissipated = ∞), 2) assumption of single initial copy of leader, 3) reactions aren't mass-conserving, 4) what about leak reactions?, 5) no discussion of diffusion rates, 6) this has nothing to do with how biological cells compute