Computation by (not about) chemistry

Workshop on mathematical trends in reaction network theory
University of Copenhagen, July 2015

David Doty

The software of life

How does the cell compute?

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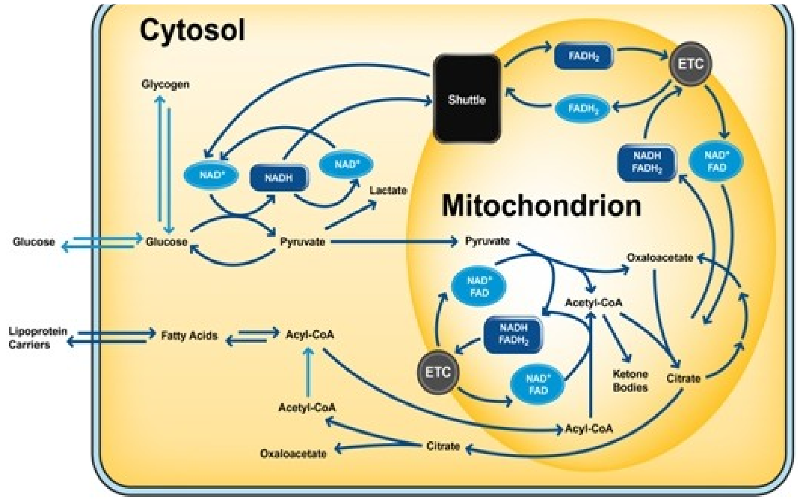
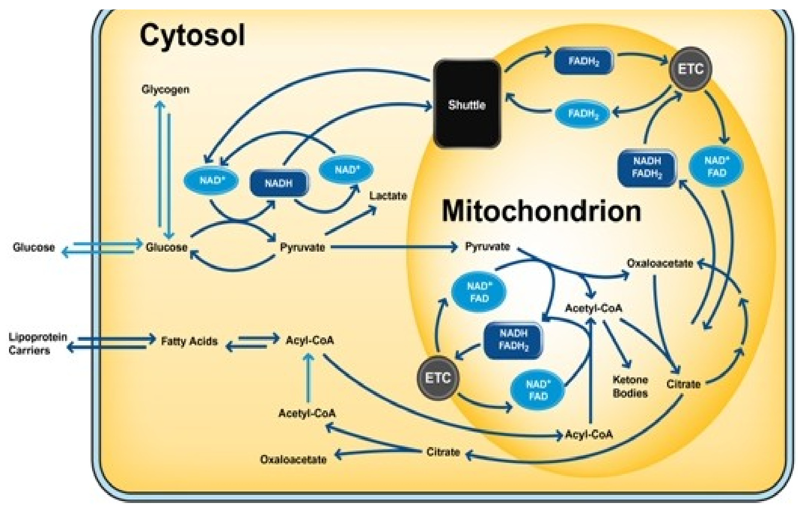


chemistry / geometry

The software of life

~~How does the cell compute?~~

What is possible to compute with chemistry?/ ~~geometry~~



Chemical reaction networks (CRN)

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(anonymous
waste product)

$$X \rightarrow 2X$$

(anonymous
fuel source)

Chemical reaction networks (CRN)

$$R \xrightarrow{2.5} P_1 + P_2$$

$$A + B \xrightarrow{1} C$$

$$X + Y \xrightarrow{5} X + Z$$

$$A + Z \xrightarrow{0.1}$$

(anonymous
waste product)

$$X \xrightarrow{0.1} 2X$$

(anonymous
fuel source)

What behavior is possible for chemistry in principle?

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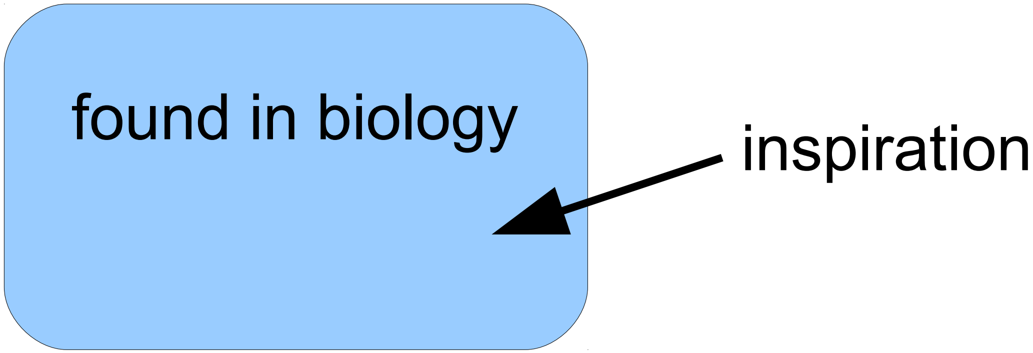

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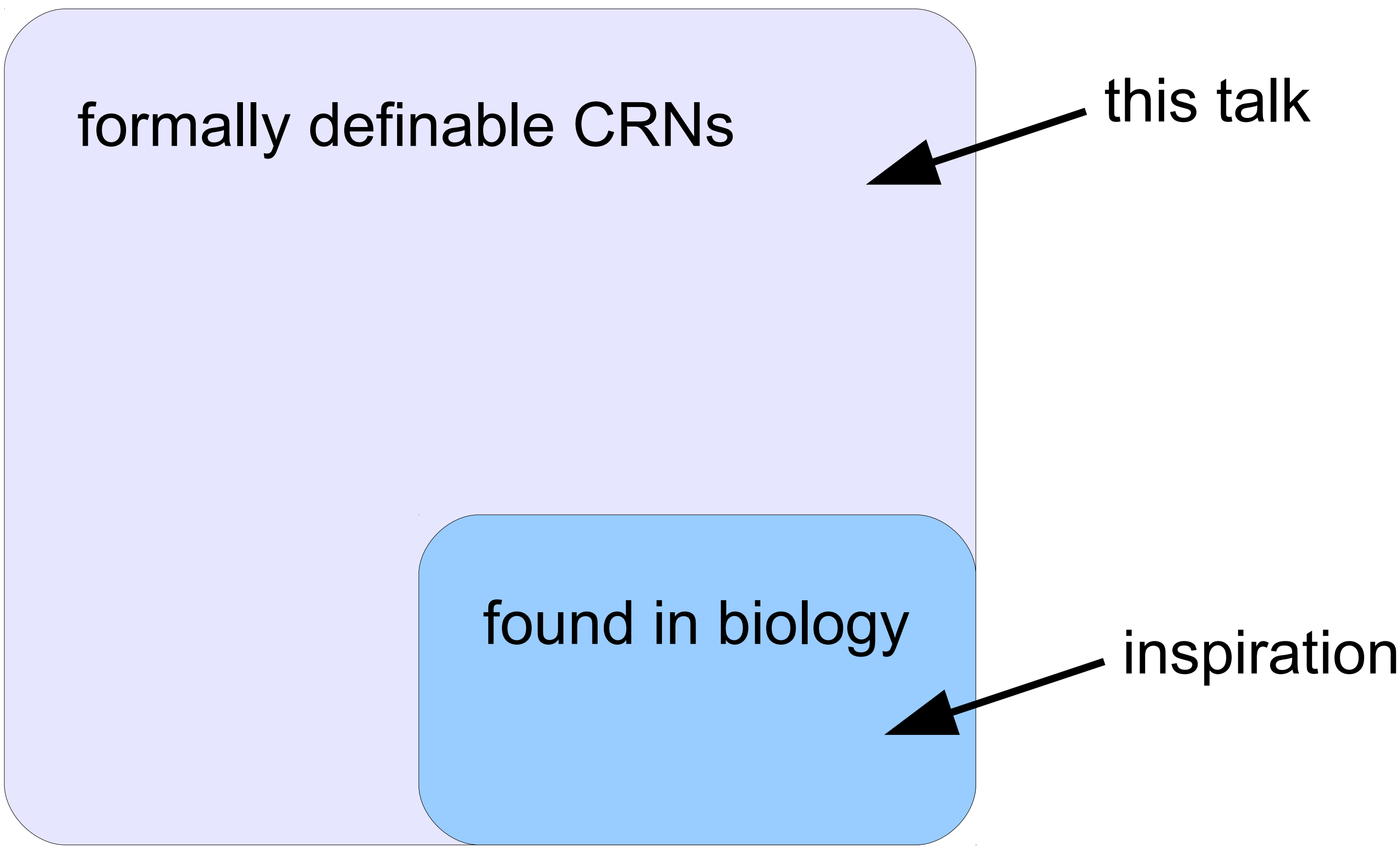

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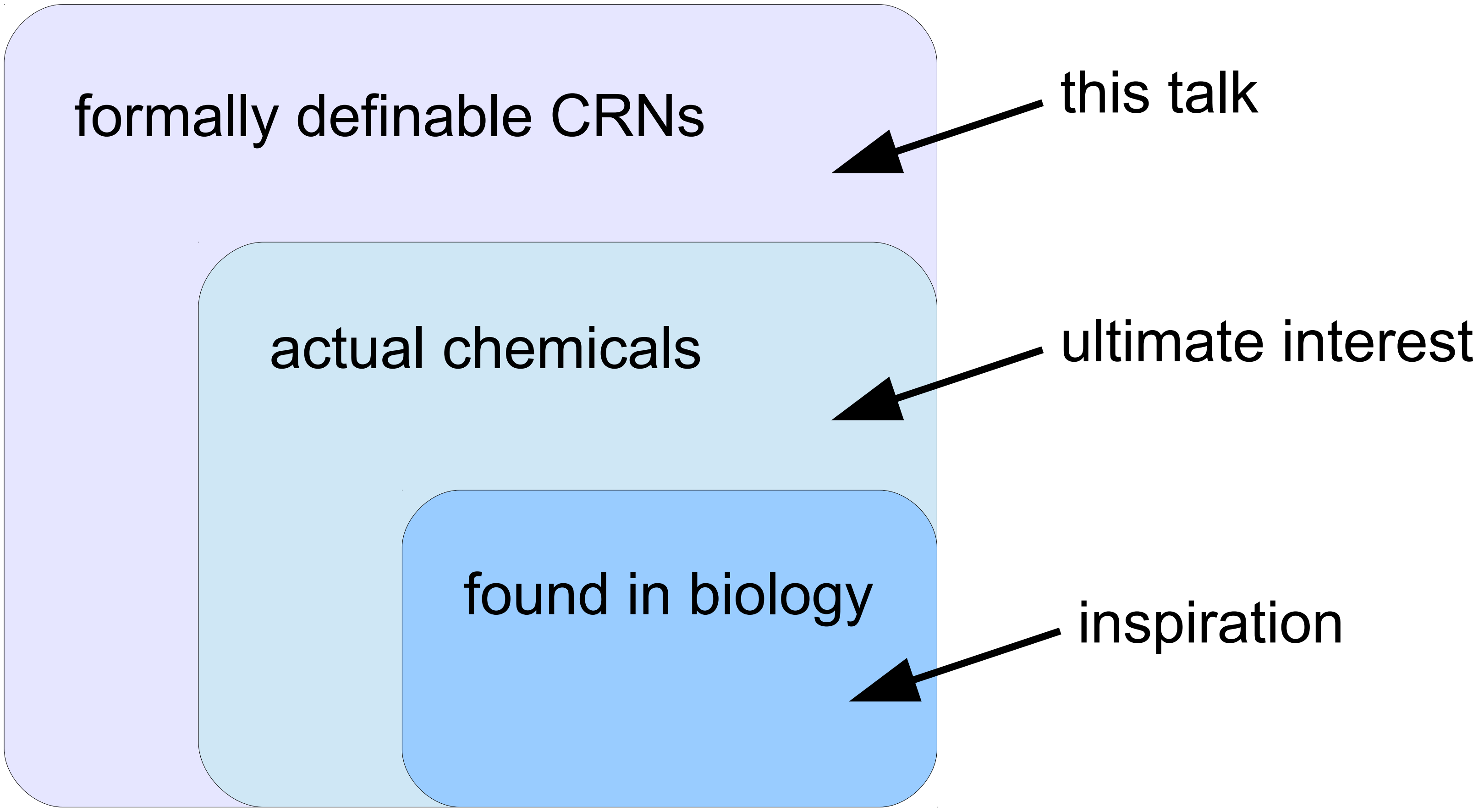

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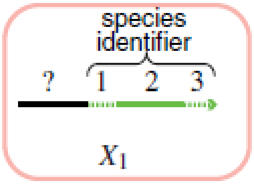

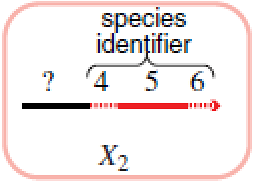

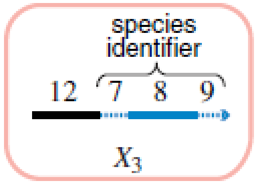

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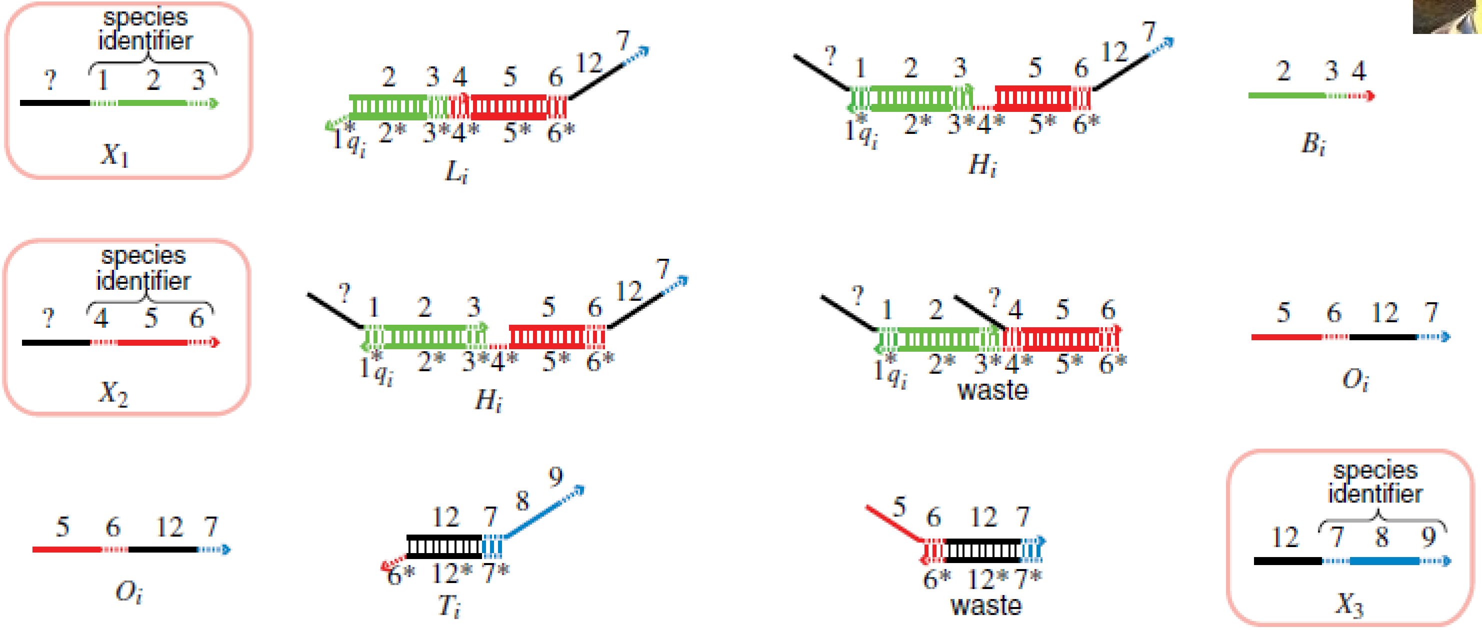

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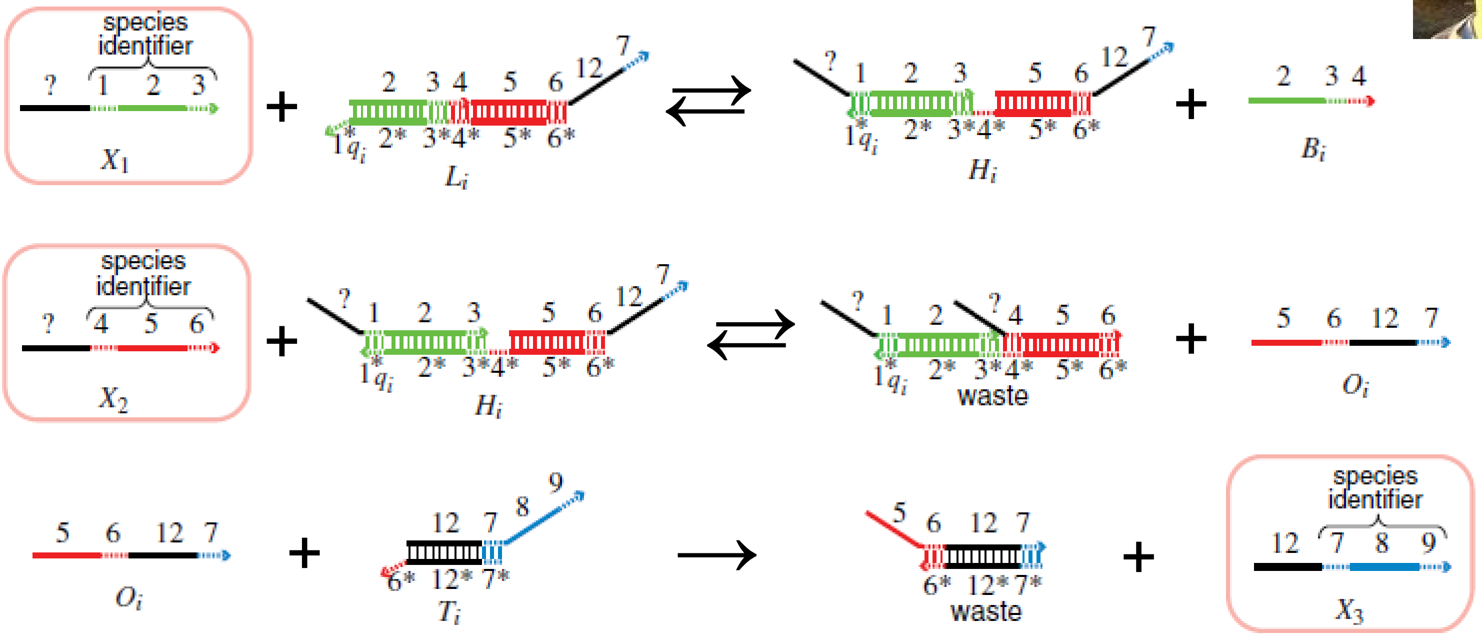

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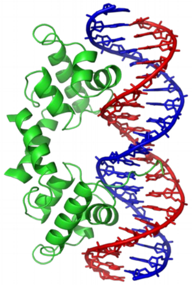

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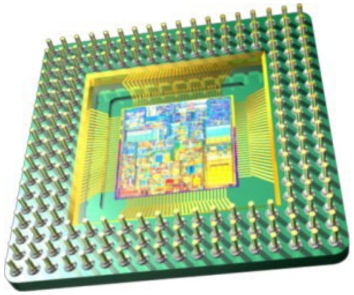

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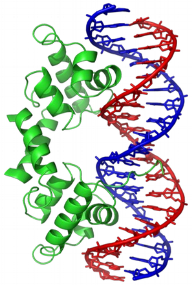

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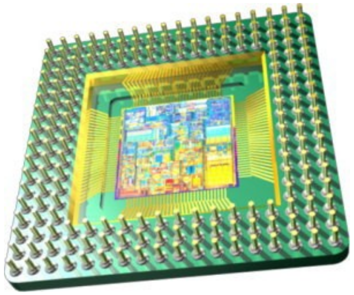

speed?

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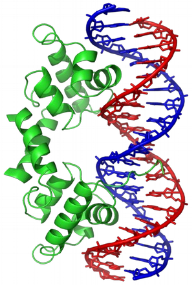

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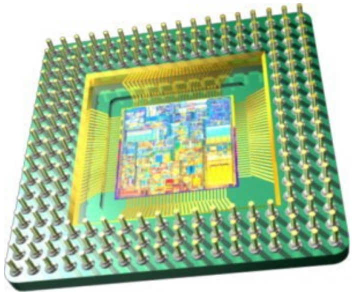

slower

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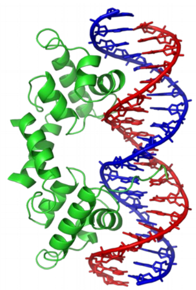

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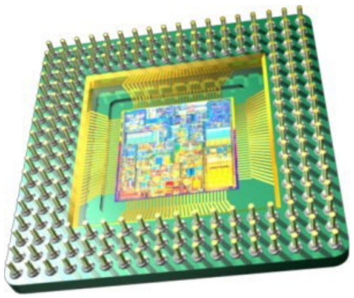

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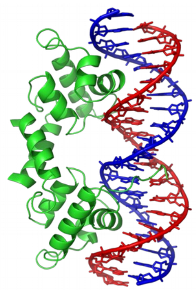

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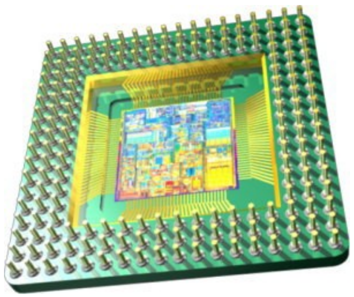

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component size?

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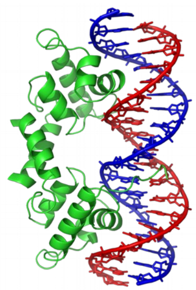

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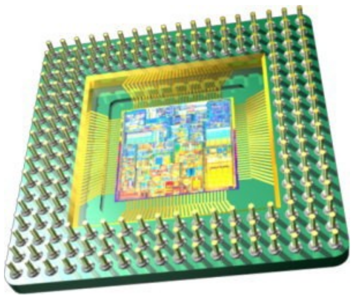

slower

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faster

≈ 10-100 nm

component size?

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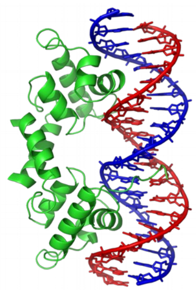

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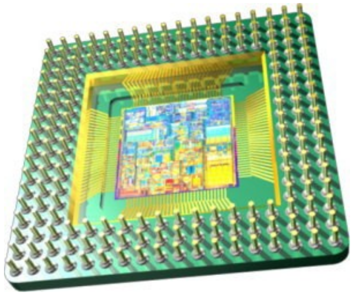

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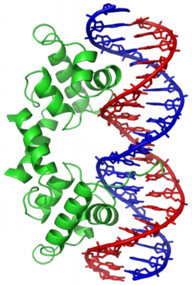

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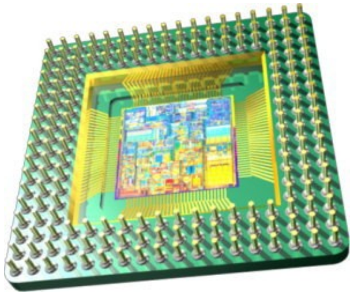

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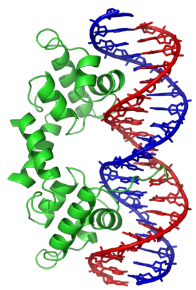

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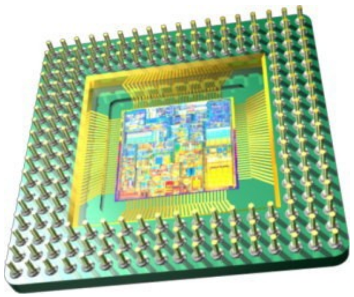
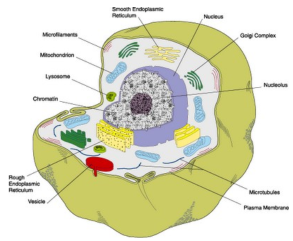


slower	~~speed?~~	faster
≈ 10-100 nm	~~component size?~~	≈ 10-100 nm
yes	✓ Compatible with biological or other “wet environments”?	not easily

cells



“smart drug” released only in certain cellular conditions

bioreactors

“chemical controller” to optimize yield of metabolically produced biofuels/drugs/etc.

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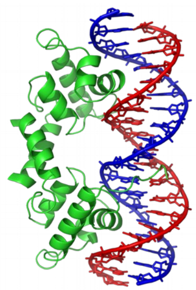

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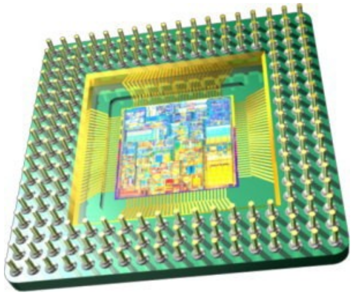

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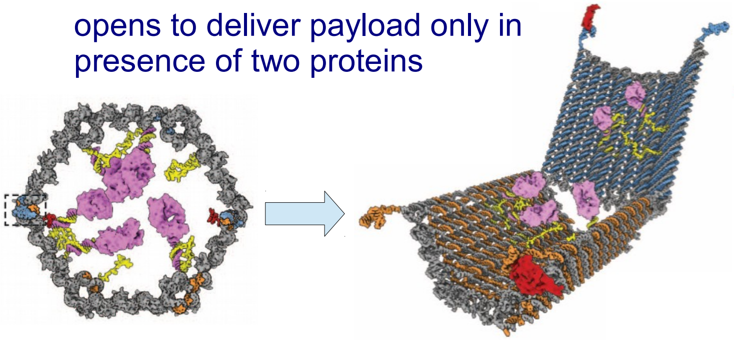
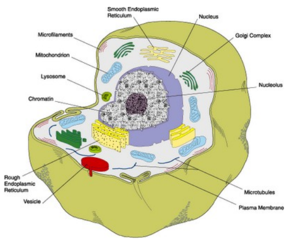
opens to deliver payload only in presence of two proteins



Douglas et al, *Science* 2012

cells



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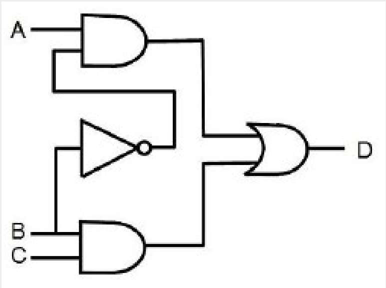

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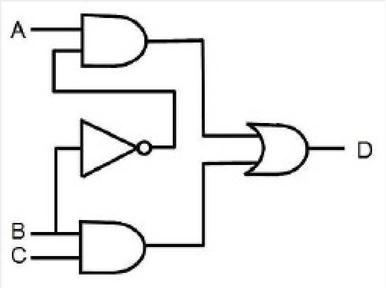
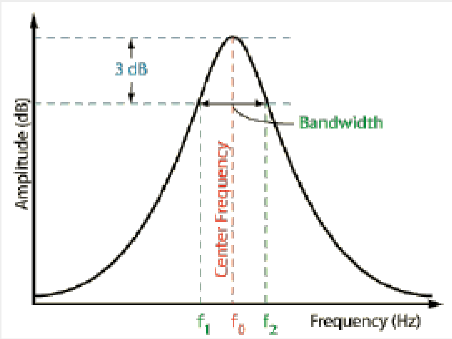


signal processing



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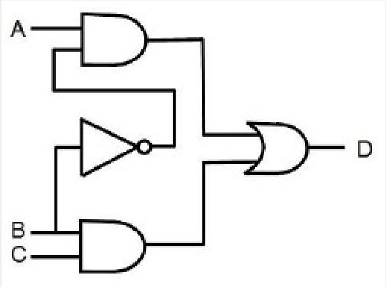
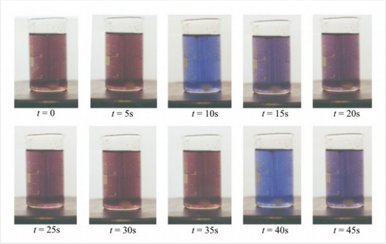


oscillation



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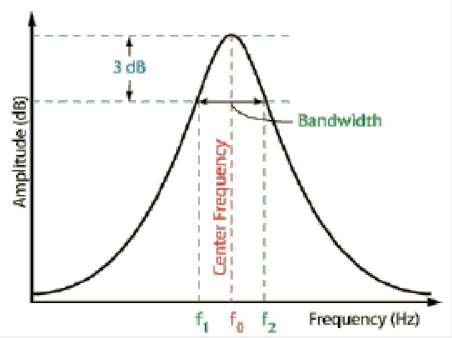

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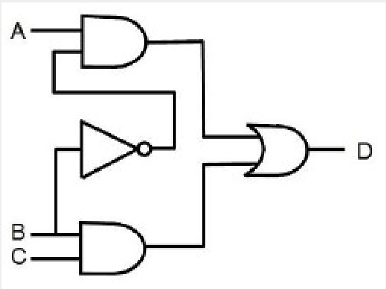
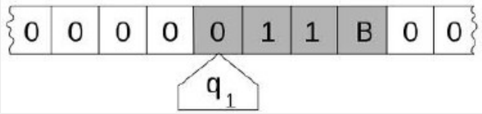
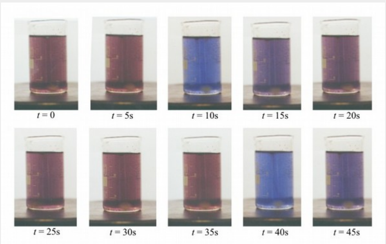


discrete algorithms



analog computing

oscillation



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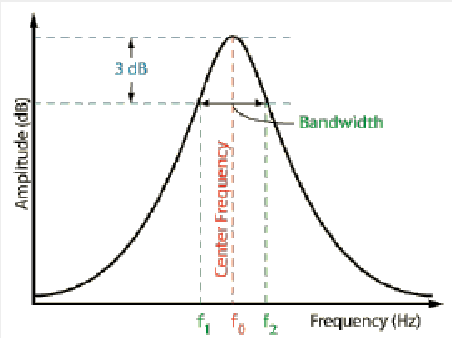

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E[time until next reaction] = 1 / rate

CRN function computation (example)

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$X \xrightarrow{1}$

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Rate-independent CRN computation

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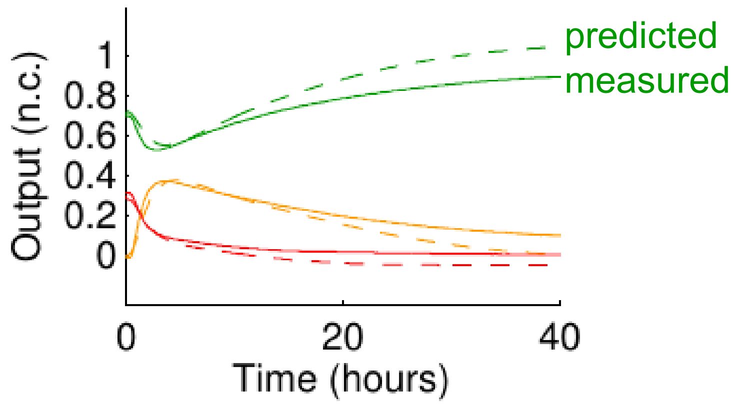

Rate-independent CRN computation (a.k.a. “stable”, “deterministic”)

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not the mass-action model!!

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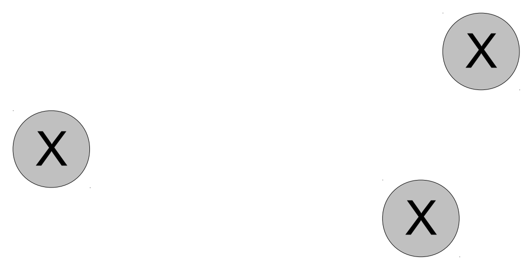
reactions: ??



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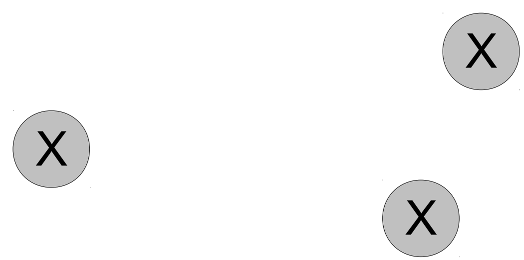
reactions: $X \to 2Y$



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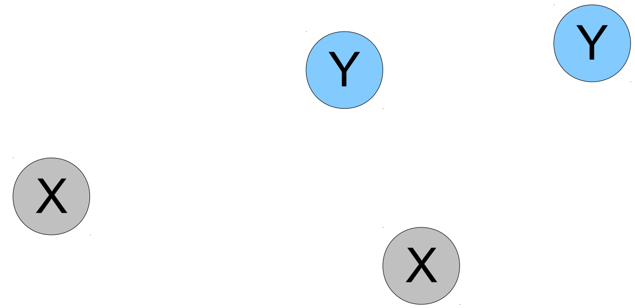

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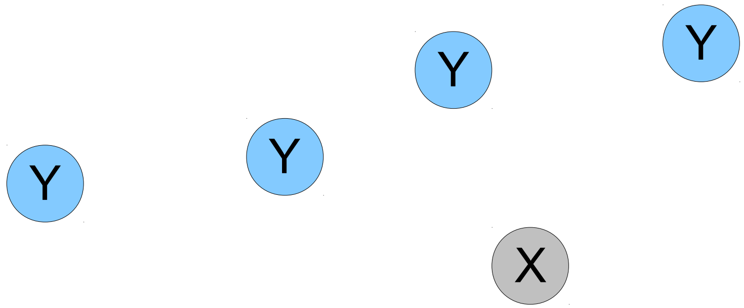

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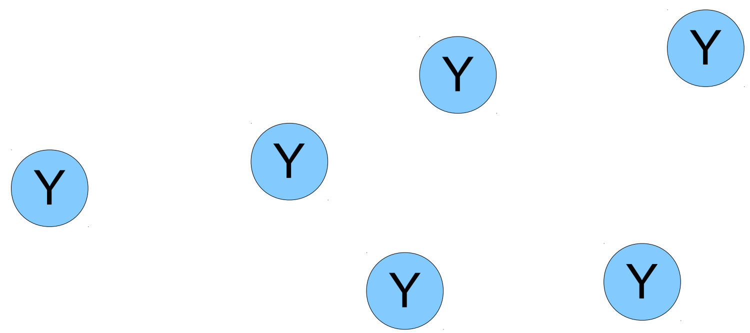

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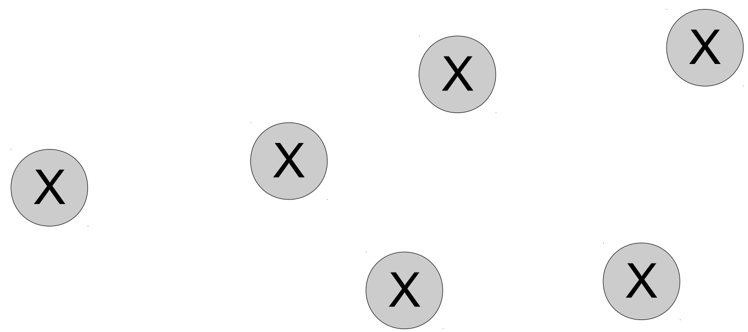
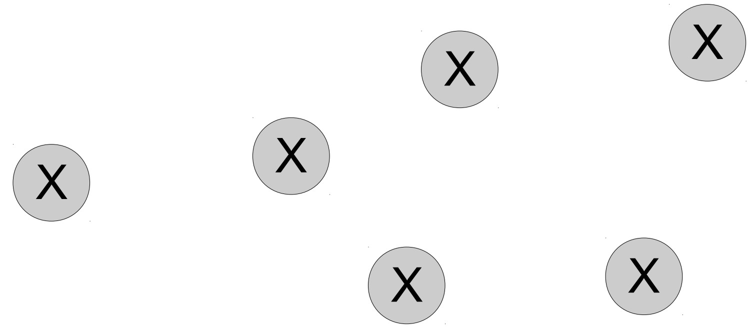
function: $f(x) = x/2$



CRN function computation (example)

function: $f(x) = x/2$

reactions: $2X \rightarrow Y$



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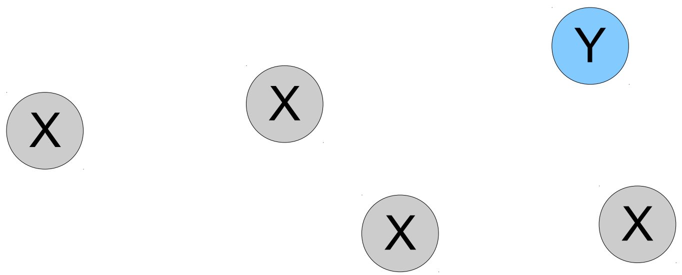

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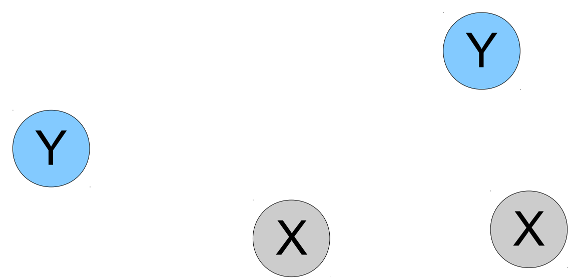

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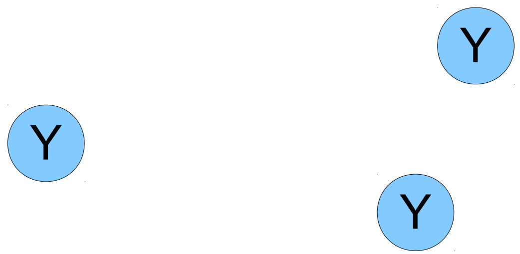
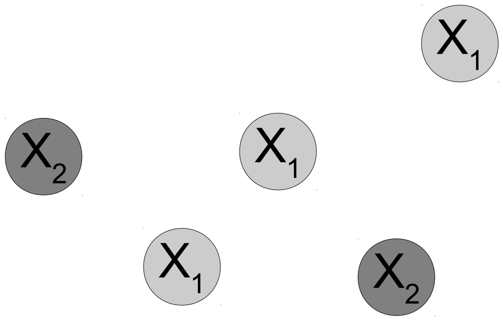


CRN function computation (example)

function: $f(x_1,x_2) = x_1 + x_2$

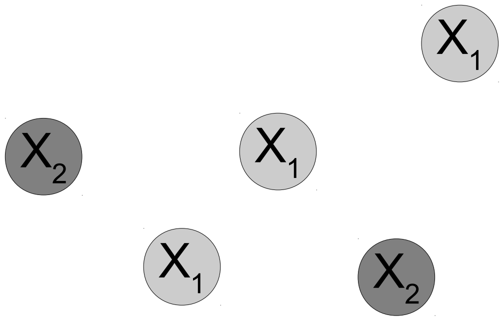


CRN function computation (example)

function: $f(x_1,x_2) = x_1 + x_2$

reactions: $X_1 \rightarrow Y$

$X_2 \rightarrow Y$



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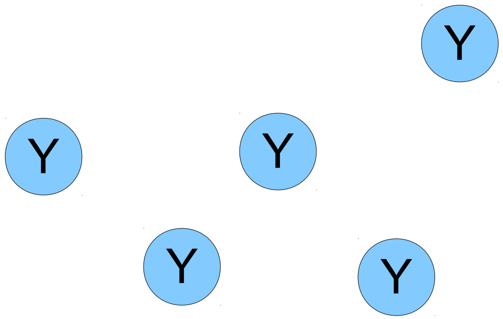
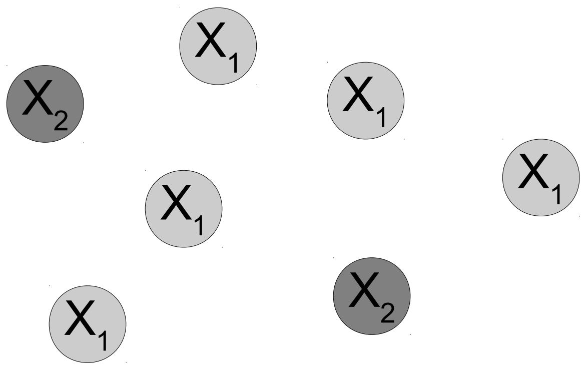


CRN function computation (example)

function: $f(x_1,x_2) = x_1 - x_2$

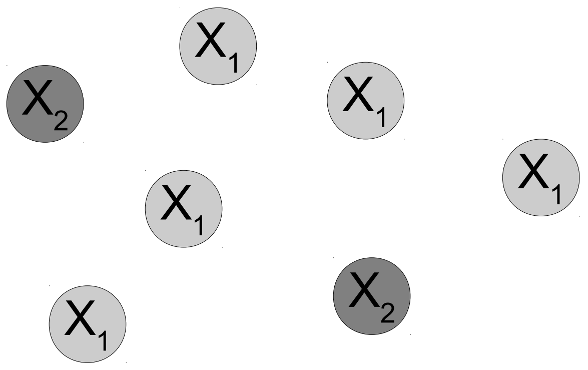


CRN function computation (example)

function: $f(x_1,x_2) = x_1 - x_2$

reactions: $X_1 \rightarrow Y$

$X_2 + Y \rightarrow$

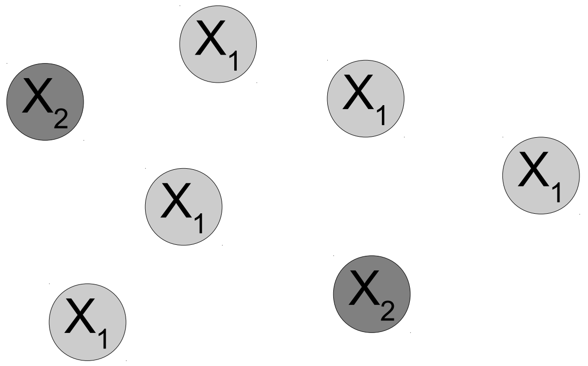


CRN function computation (example)

function: $f(x_1,x_2) = x_1 - x_2$

reactions: $\boxed{X_1 \to Y}$

$X_2 + Y \to$



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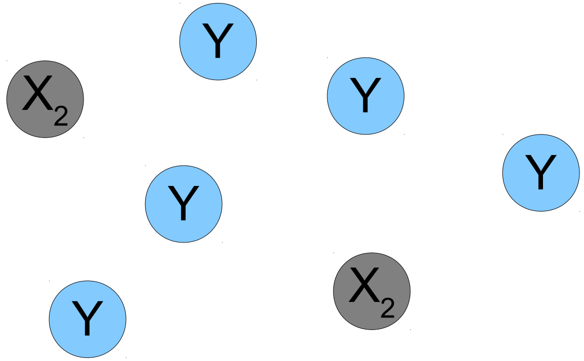

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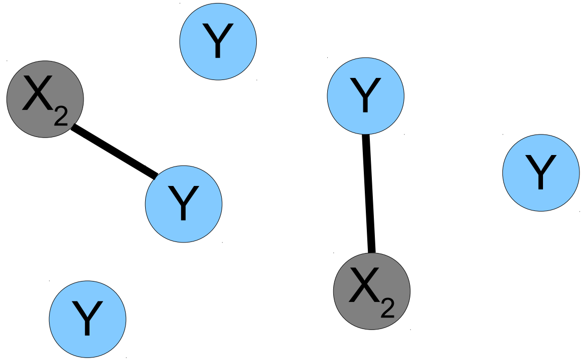

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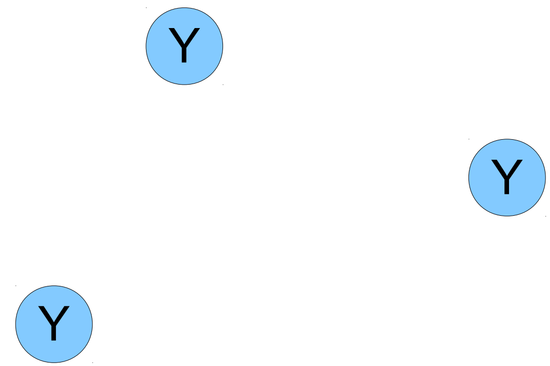
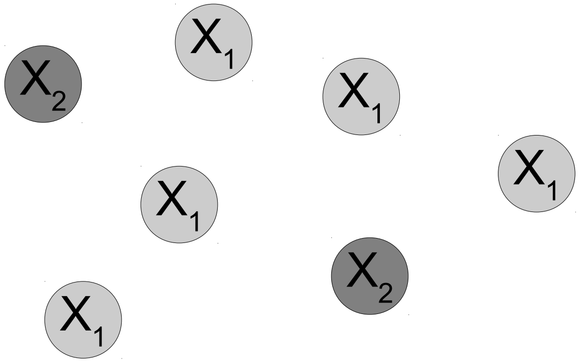


CRN function computation (example)

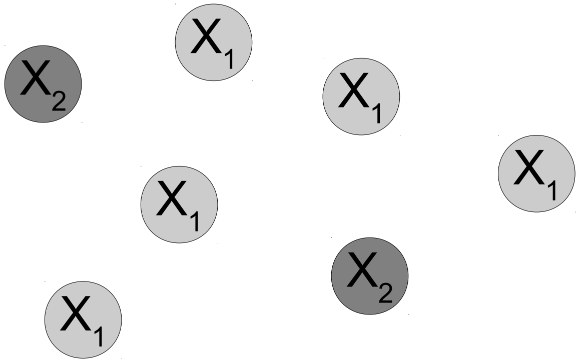
function: $f(x_1,x_2) = \min\{x_1,x_2\}$



CRN function computation (example)

function: $f(x_1,x_2) = \min\{x_1,x_2\}$

reactions: $X_1 + X_2 \rightarrow Y$



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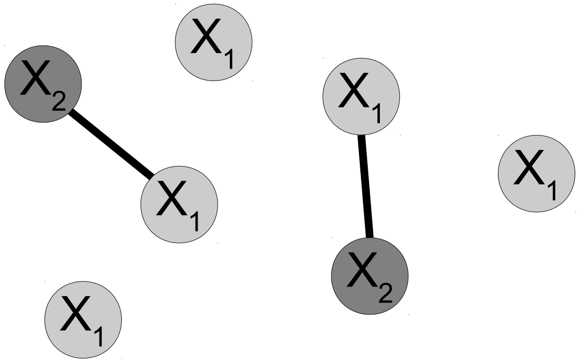

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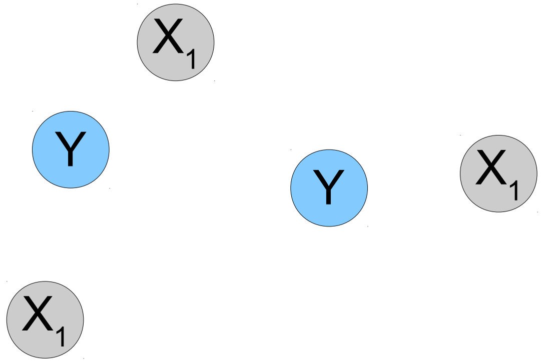

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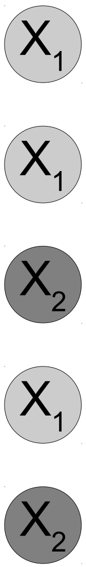
CRN function computation (example)

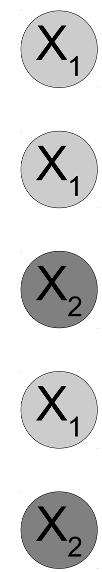
function: $f(x_1,x_2) = \max\{x_1,x_2\} = x_1 + x_2 - \min\{x_1,x_2\}$



CRN function computation (example)

function: $f(x_1,x_2) = \max\{x_1,x_2\} = \boxed{x_1 + x_2} - \min\{x_1,x_2\}$

reactions: $\boxed{\begin{array}{l} X_1 \to Y + X_1' \\ X_2 \to Y + X_2' \end{array}}$



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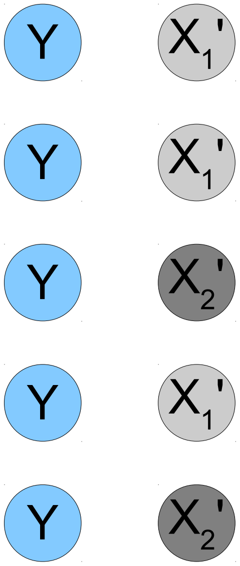

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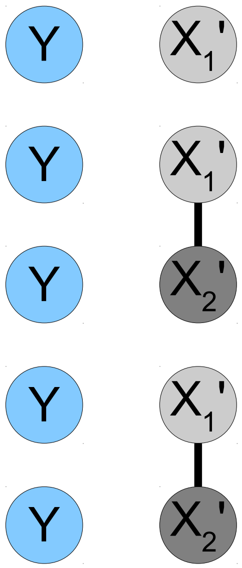
reactions: $X_1 \to Y + X_1'$

$X_2 \to Y + X_2'$

$\boxed{X_1' + X_2' \to K}$



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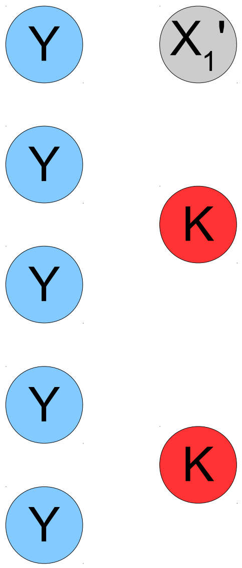


CRN function computation (example)

function: $f(x_1,x_2) = \max\{x_1,x_2\} = x_1 + x_2 \boxed{-} \min\{x_1,x_2\}$

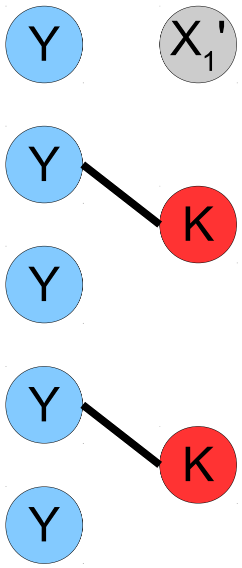
reactions:

$$X_1 \to Y + X_1'$$

$$X_2 \to Y + X_2'$$

$$X_1' + X_2' \to K$$

$$\boxed{K + Y \to }$$



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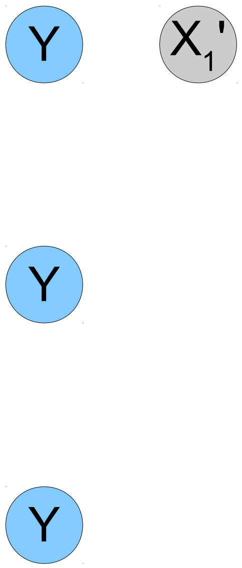
$$K + Y \rightarrow$$



CRN predicate computation (example)

predicate: $p(x)$: parity of x ("yes" $\Leftrightarrow x$ is odd)

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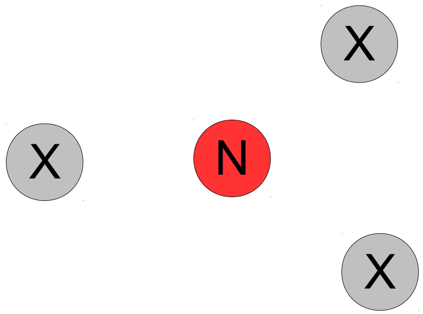

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initial state: $\{\, x\,X\,,\ 1\,N\,,\ 0\,Y \,\}$

reactions: $N + X \rightarrow Y$
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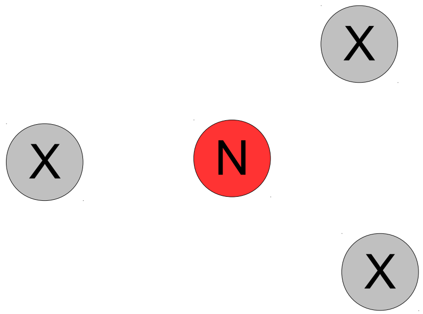

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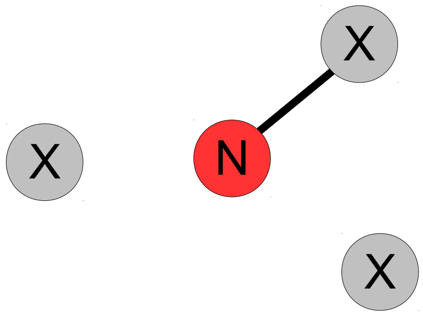

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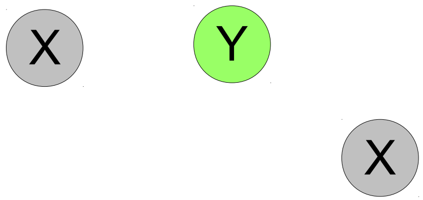

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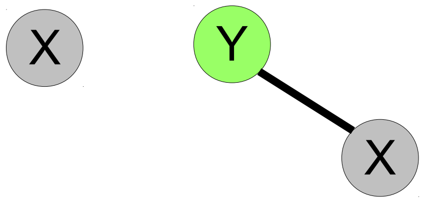

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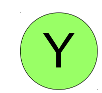

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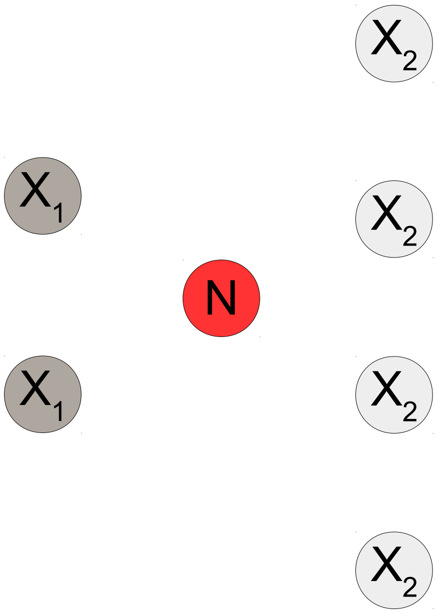

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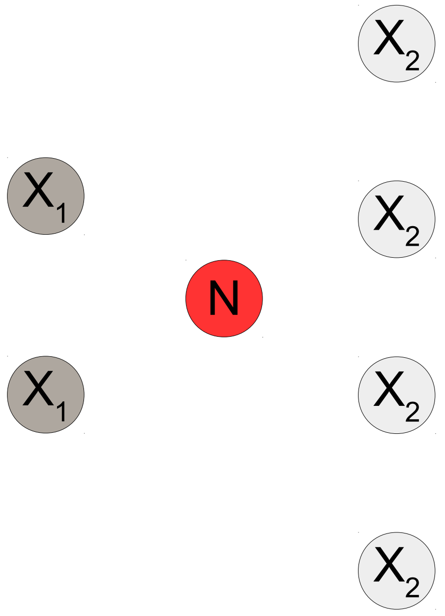

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initial state: $\{\, x_1\, X_1\,,\; x_2\, X_2\,,\; 1\, N \,\}$

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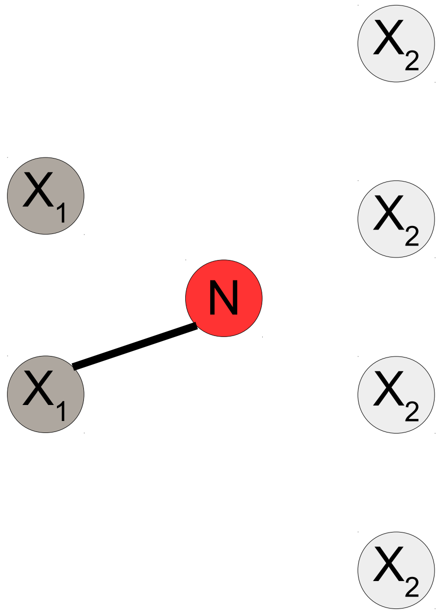

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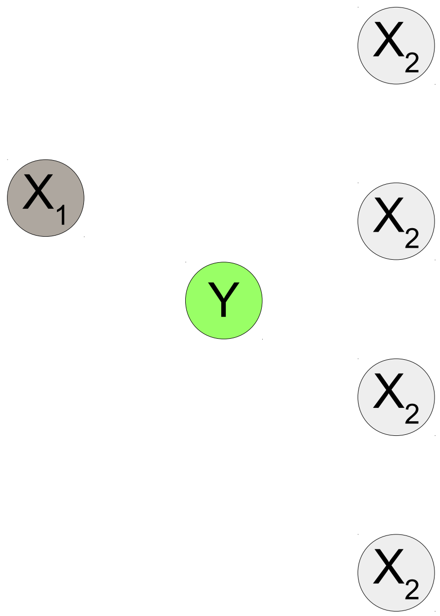

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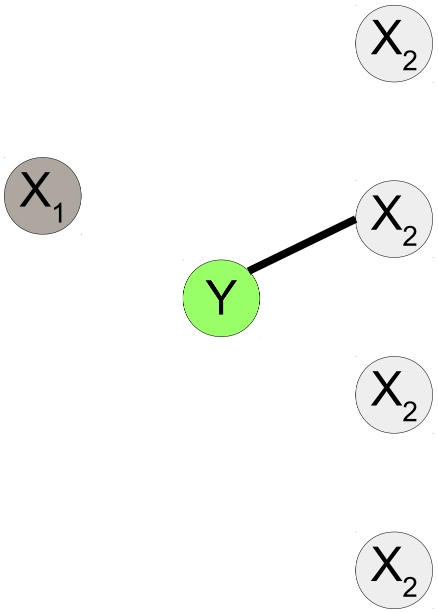

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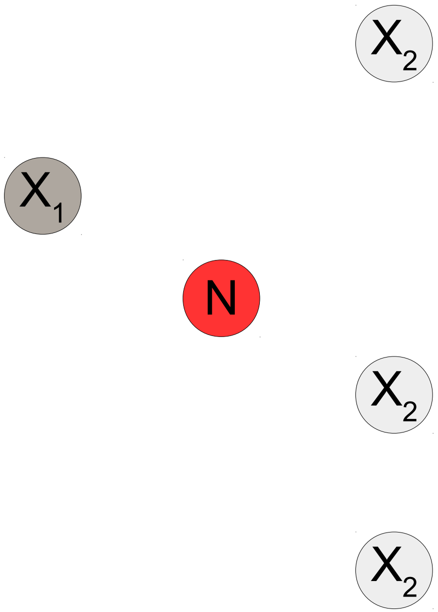

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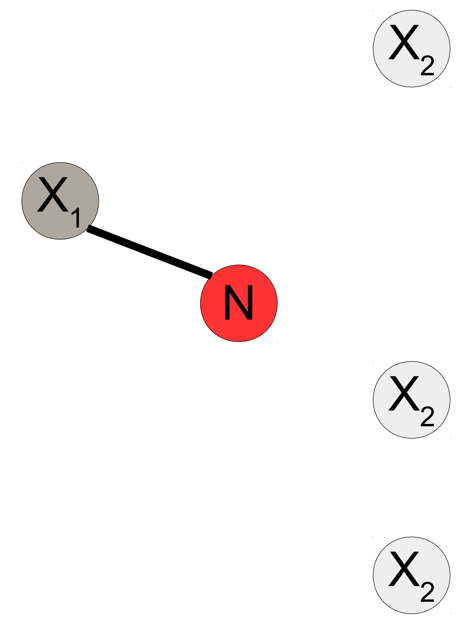

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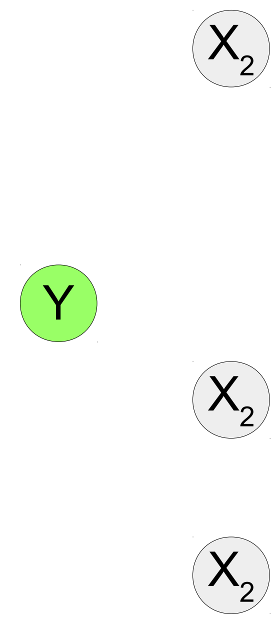

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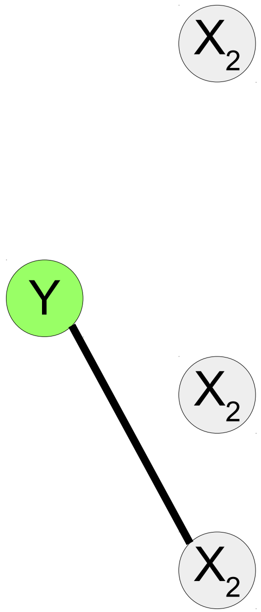

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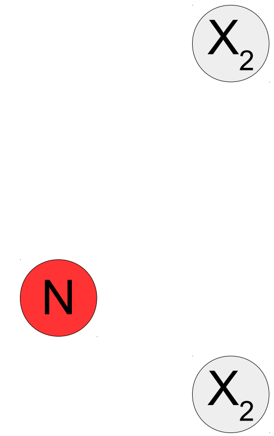

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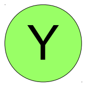

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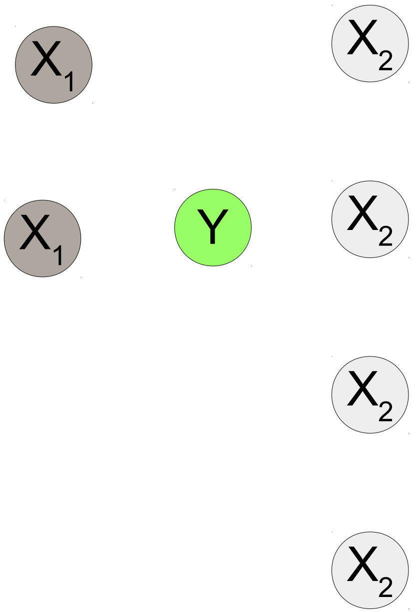
initial state: $\{\, x_1\, X_1 \,,\, x_2\, X_2 \,,\, 1\ Y \,\}$



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initial state: $\{\, x_1\, X_1\, ,\, x_2\, X_2\, ,\, 1\ Y \,\}$

reactions:

$$X_1 + X_2 \rightarrow Y$$
$$Y + N \rightarrow Y$$
$$X_1 + Y \rightarrow X_1 + N$$
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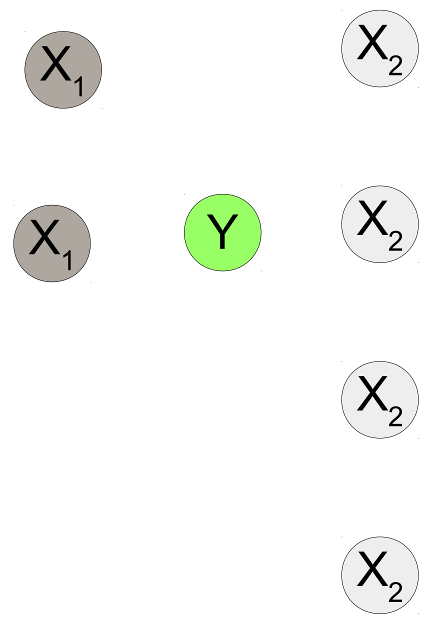

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initial state: $\{\, x_1\, X_1\,,\ x_2\, X_2\,,\ 1\ Y \,\}$

reactions: $\boxed{X_1 + X_2 \rightarrow Y}$

$Y + N \rightarrow Y$

$X_1 + Y \rightarrow X_1 + N$

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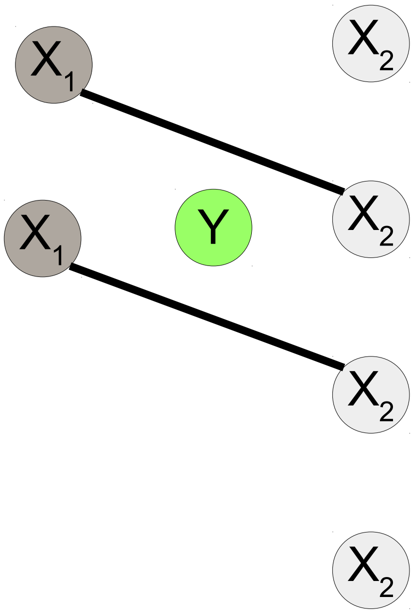

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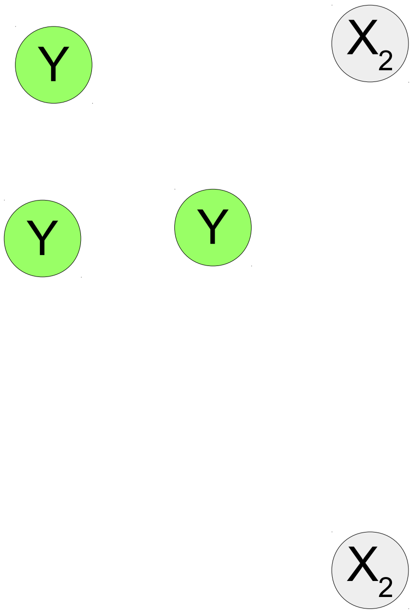

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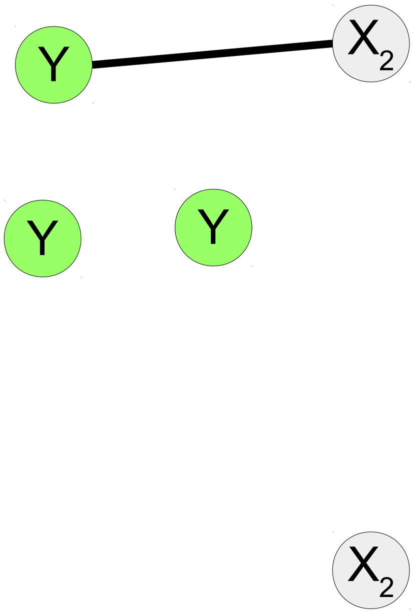

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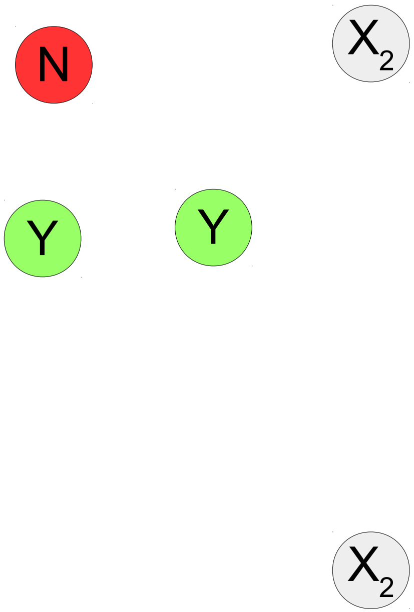

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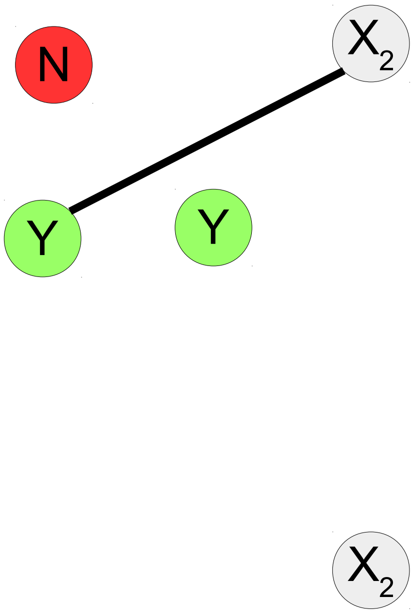

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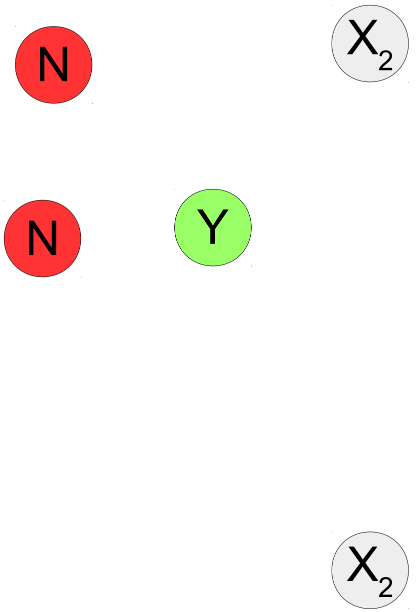

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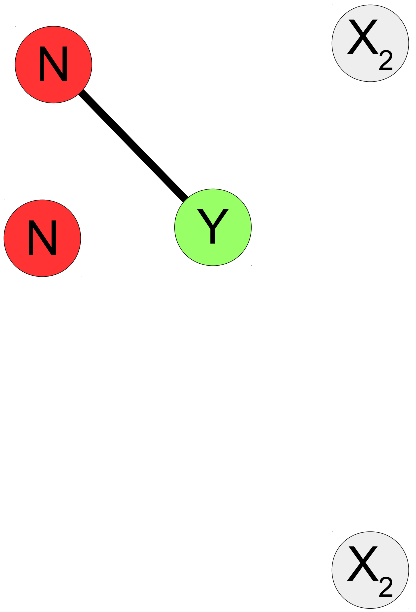

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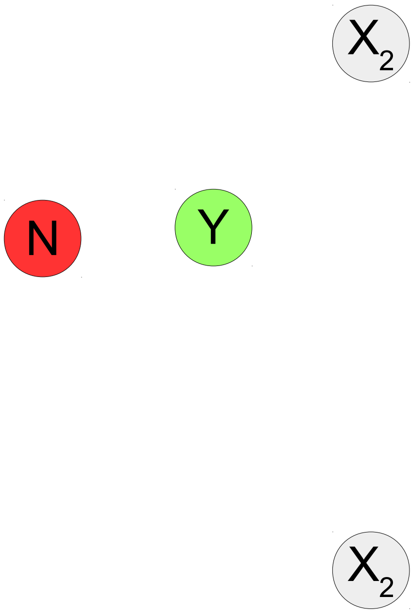

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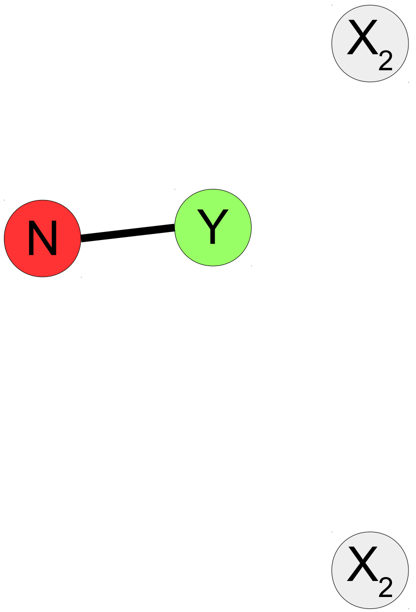

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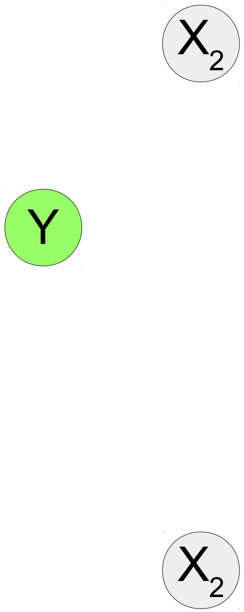

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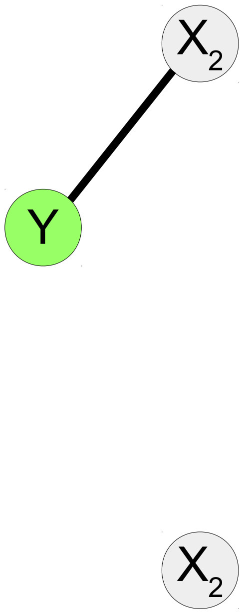

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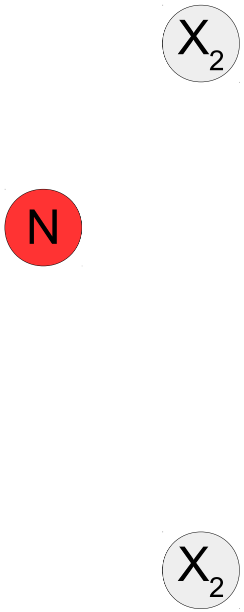

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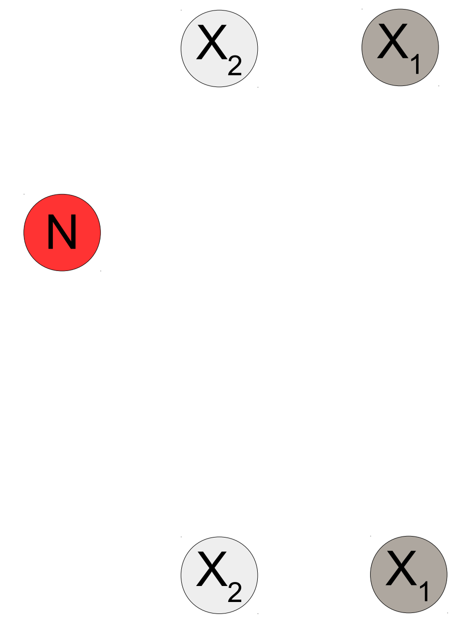

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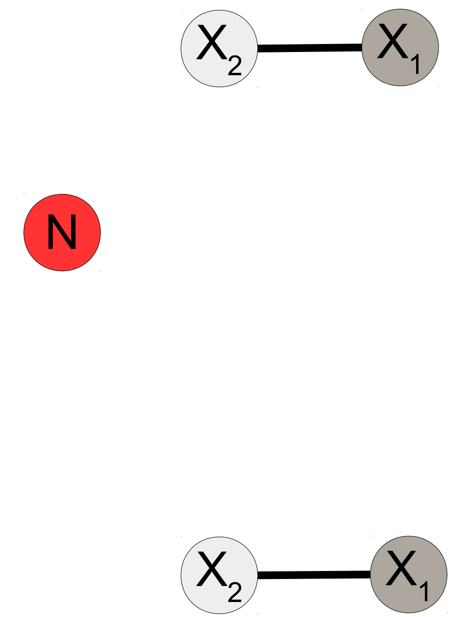

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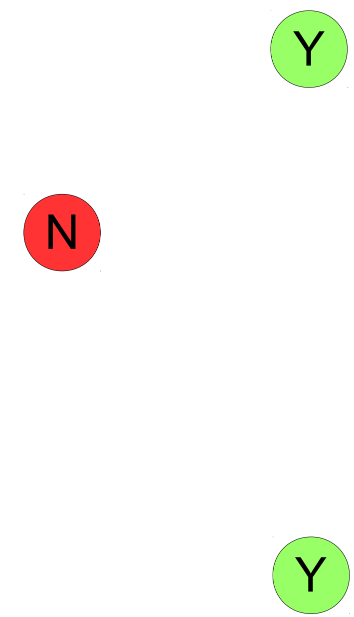

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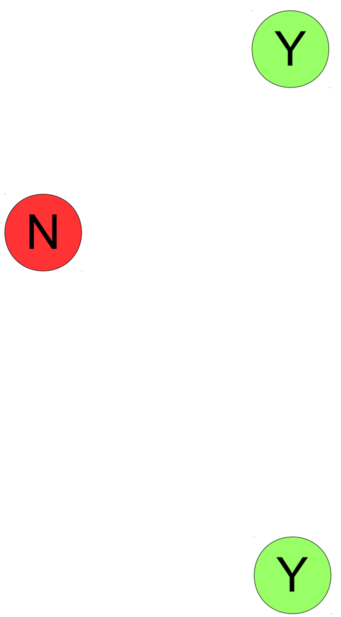

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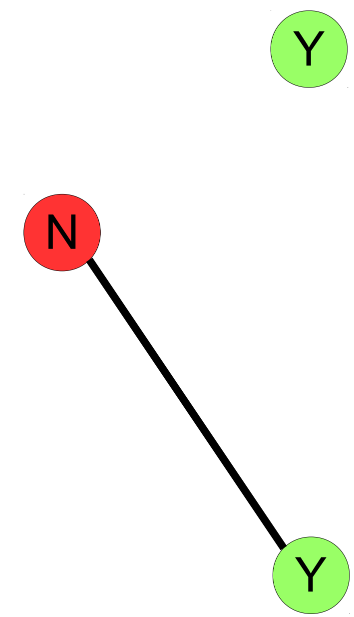

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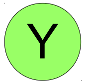

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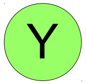

CRN predicate computation (example)

predicate: $p(x_1,x_2)$: "$3x_1 > x_2/2$"?

initial state: $\{\ x_1\ X_1\ ,\ x_2\ X_2\ ,\ 1\ N\ \}$

CRN predicate computation (example)

predicate: $p(x_1,x_2)$: "$\boxed{3x_1} > x_2/2$"?

initial state: $\{\, x_1 X_1 \,,\, x_2 X_2 \,,\, 1\, N \,\}$

reactions: $\boxed{X_1 \to 3Z_1}$

CRN predicate computation (example)

predicate: $p(x_1,x_2)$: "$3x_1 > \boxed{x_2/2}$"?

initial state: $\{\ x_1\ X_1\ ,\ x_2\ X_2\ ,\ 1\ N\ \}$

reactions: $X_1 \rightarrow 3Z_1$

$\boxed{2X_2 \rightarrow Z_2}$

CRN predicate computation (example)

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initial state: $\{\, x_1\, X_1\, ,\ x_2\, X_2\, ,\ 1\ N \,\}$

reactions:

$$X_1 \to 3Z_1$$

$$2X_2 \to Z_2$$

$$\boxed{\begin{array}{l} N + Z_1 \to Y \\ Y + Z_2 \to N \end{array}}$$

Stable predicate computation (definition)

task: compute $p(x_1,...,x_k) \in \{\text{yes},\text{no}\}$, $\quad x_1,...,x_k \in \mathbb{N}$

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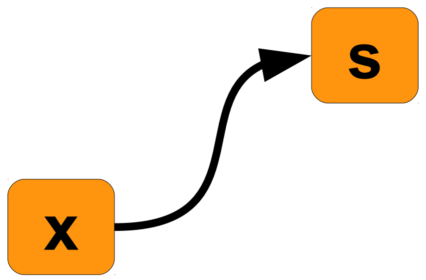

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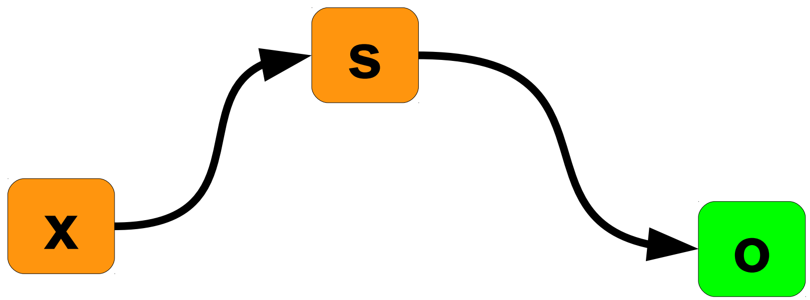

$\varphi(\boldsymbol{o}) = p(x_1,\ldots,x_k)$

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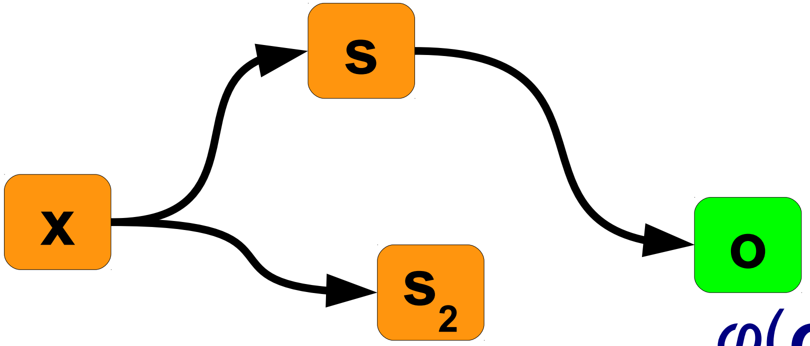

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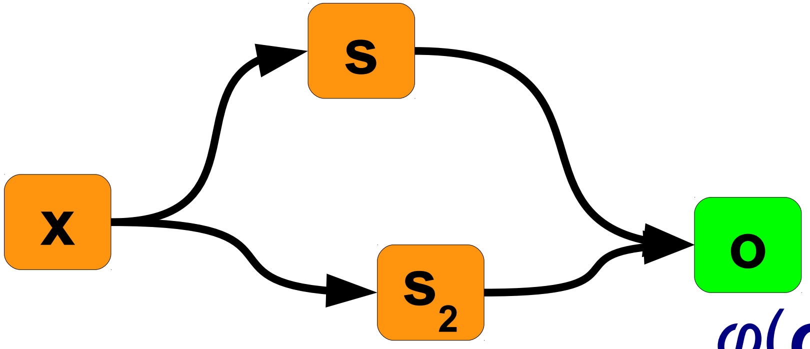

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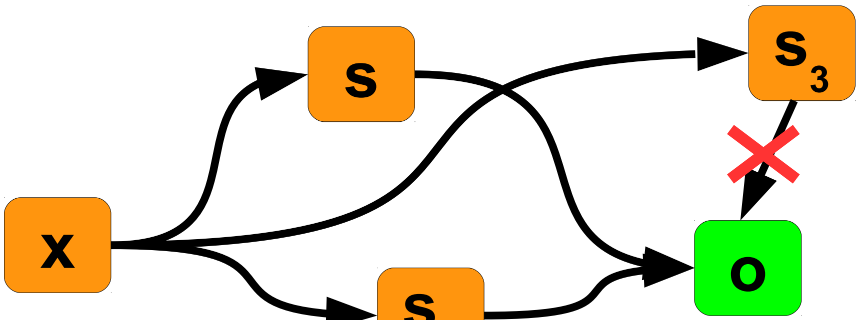

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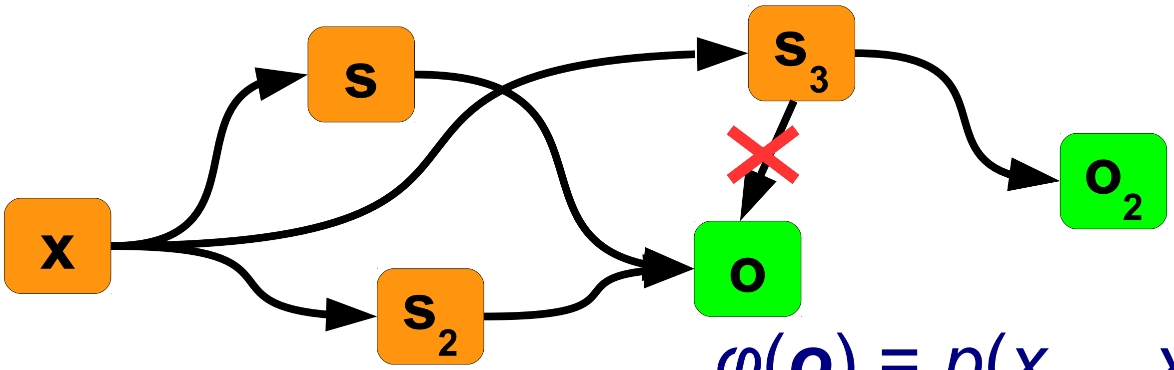

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Stable ~~predicate~~ computation (definition)
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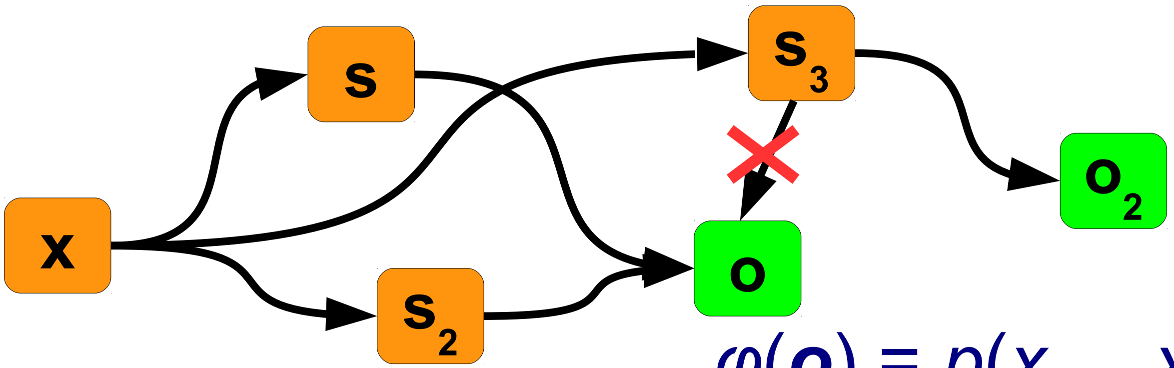

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Stable ~~predicate~~ computation (definition)

function

$\mathbb{N}$

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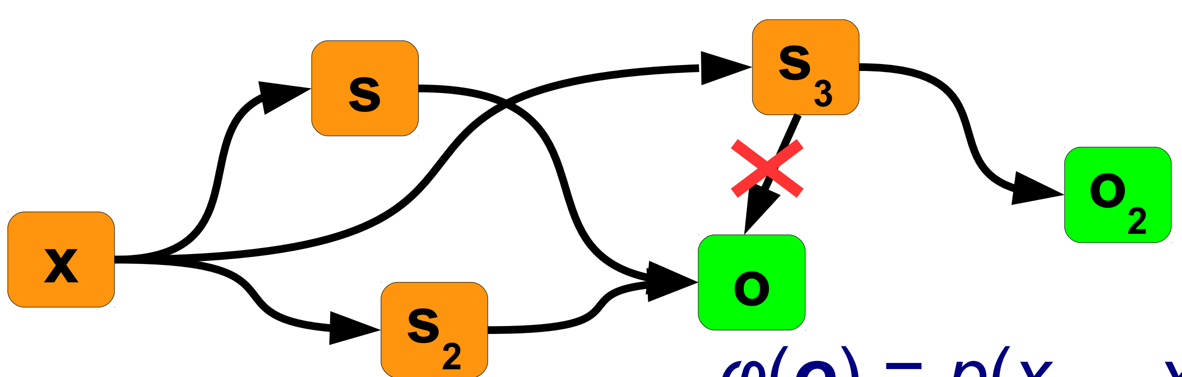

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Stable ~~predicate~~ computation (definition)

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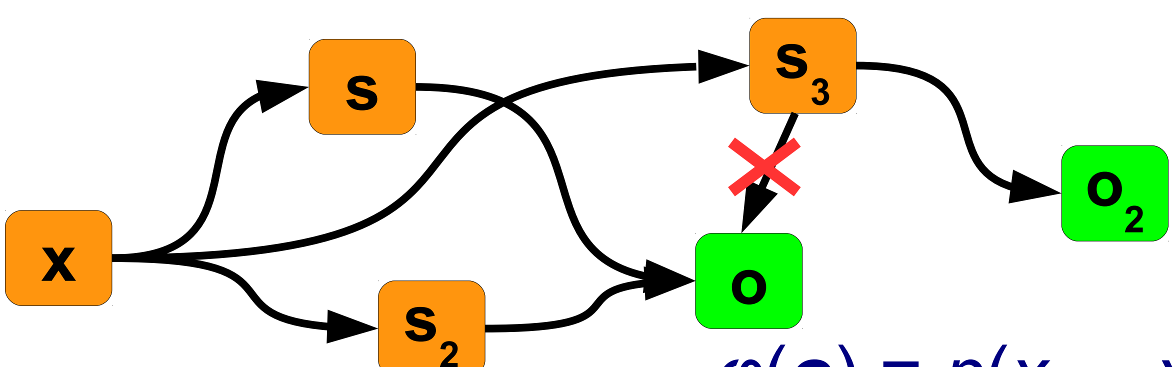
output-stable state: all states reachable from it have same output

stable computation: for all states **s** reachable from the initial state **x**, a correct output-stable state **o** is reachable from **s**



$\varphi(\mathbf{o}) = p(x_1,\ldots,x_k) = \varphi(\mathbf{o}_2)$

Stable ~~predicate~~ function computation (definition)

task: compute $p(x_1,\ldots,x_k) \in \cancel{\{\text{yes},\text{no}\}}\ \mathbb{N}$, $\quad x_1,\ldots,x_k \in \mathbb{N}$

initial state: $\#X_1 = x_1,\ldots,\#X_k = x_k$, constant counts of other species

~~**votes**: two disjoint subsets of species: "yes" and "no" voters~~

output φ(s) of state s: ~~consensus vote (if voters unanimous)~~ #Y

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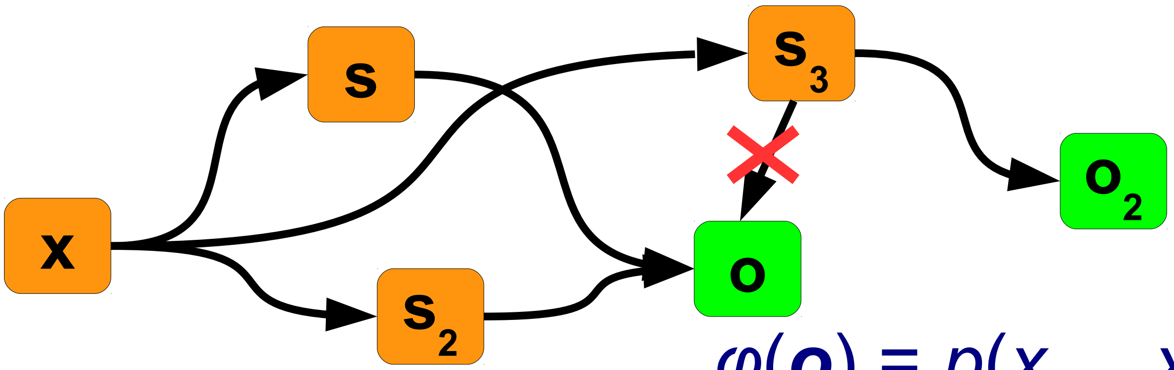

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Stable computation characterization

Theorem: A predicate/function is stably computed by a CRN if and only if it is *semilinear*.

[Angluin, Aspnes, Diamadi, Fisher, Peralta, Principles of Distributed Computing 2004]

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predicates

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semilinear function ≈ piecewise linear

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Real-valued CRNs

Theorem from previous slide: A function is stably computed by a integer-valued CRN if and only if it is *semilinear*.

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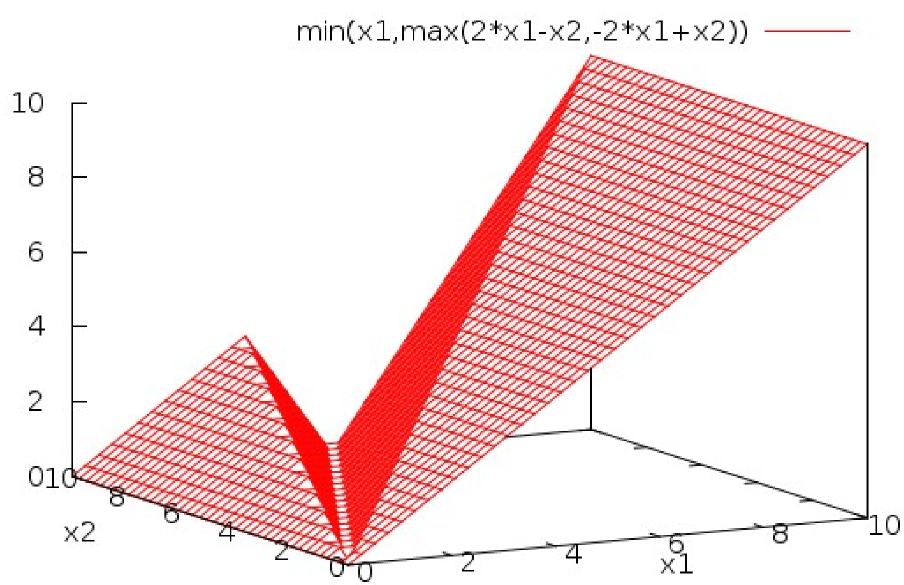
Real-valued version: A function is stably computed by a real-valued CRN if and only if it is *continuous* and *piecewise linear*.

[Chen, D, Soloveichik, Innovations in Theoretical Computer Science 2014]



Real-valued CRNs

Theorem from previous slide: A function is stably computed by a integer-valued CRN if and only if it is *semilinear*.

≈ piecewise linear functions with "discontinuous" pieces

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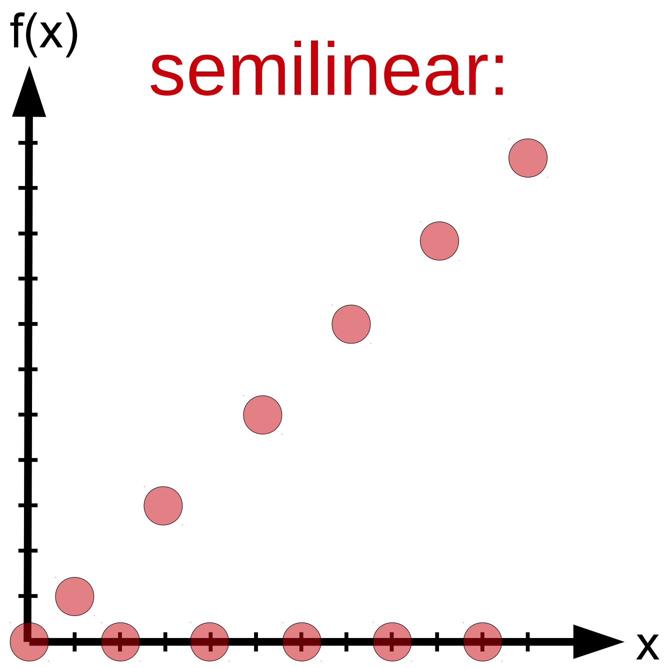

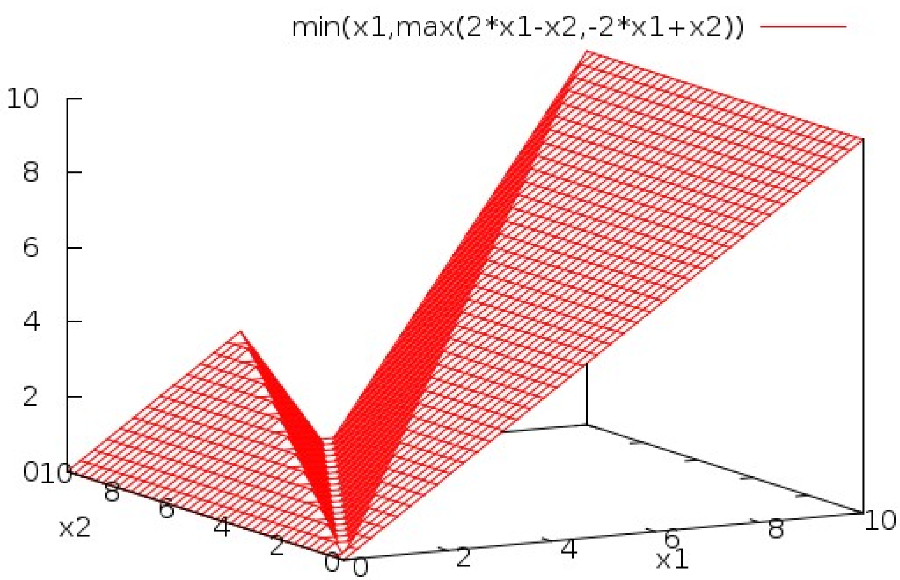

Time complexity of stable computation

n = # molecules in initial state ≈ volume

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polylogarithmic time = "fast" = polynomial in binary expansion of n

linear time = "slow" = exponential in binary expansion of n

Time complexity in CRNs

time until next reaction = exponential random variable

<u>reaction</u>	<u>expected time</u>
$X \rightarrow W + 2Y + Z$	$1 / \#X$
$A + B \rightarrow X$	volume / $(\#A \bullet \#B)$

Time complexity (example)

$$\{n\ X\}$$
$$X \rightarrow Y + Y$$

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$$\{n\,X\}$$
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E[time to consume all *X*] = E[time to consume 1st X]
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+ ...
+ E[time to consume final X]

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$$\{n\ X\}$$
$$X \to Y + Y$$

E[time to consume all X] =	E[time to consume 1st X]	1/n
	+ E[time to consume 2nd X]	1/(n-1)
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≈ log n

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$\{n\ X\}$, volume n

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volume

$\#X^2$

E[time to consume all X] = $n/n^2 + n/(n-2)^2 + n/(n-4)^2 + \ldots + n$

Time complexity (example)

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#X²

$$\text{E[time to consume all } X] = \overbrace{n}^{\text{volume}}/n^2 + n/(n-2)^2 + n/(n-4)^2 + \ldots + n$$

$$< n(1/2^2 + 1/4^2 + 1/6^2 + 1/8^2 + \ldots)$$

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volume $\#X^2$

$$
\begin{aligned}
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&< n(1/2^2 + 1/4^2 + 1/6^2 + 1/8^2 + \ldots) \\
&= O(n)
\end{aligned}
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$$< n(1/2^2 + 1/4^2 + 1/6^2 + 1/8^2 + \ldots)$$

$$= O(n) = \Theta(n)$$

Is there a faster CRN for dividing by 2 from initial state $\{n\ X\}$?

(Open problem)

Time complexity (leader election)

$\{n\ L\}$, volume n

$L + L \to L$

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  - if we require 0 probability of error, no [*D and Soloveichik, <u>in submission</u>*]

What if we allow a small probability of error?
(rate-dependent CRN computation)

CRNs with small probability of error are Turing universal

[Angluin, Aspnes, Eisenstat, Symposium on Distributed Computing 2006]
[Soloveichik, Cook, Winfree, Bruck, Natural Computing 2008]

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(Informally) A CRN can simulate any algorithm, with a small chance of error.

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Implication: *General CRN long-term behavior cannot be predicted faster than by simulating.*

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Counter (register) machine

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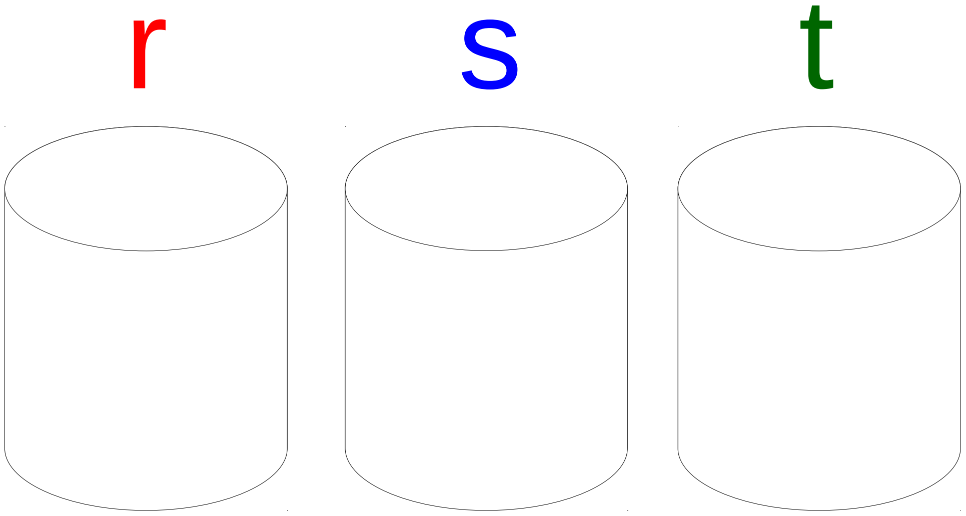

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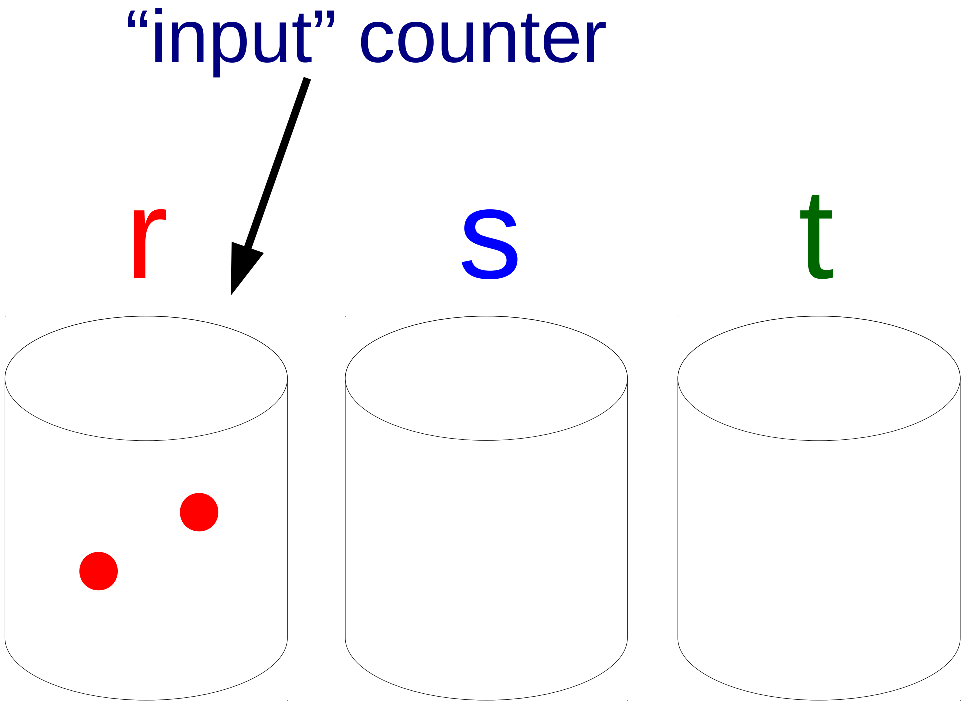

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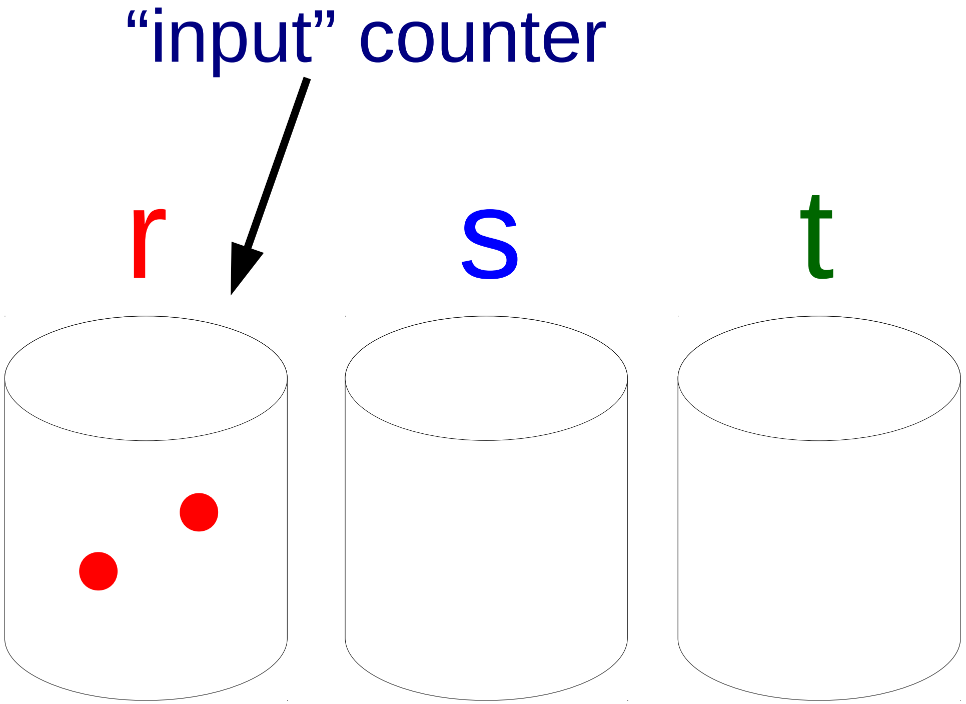

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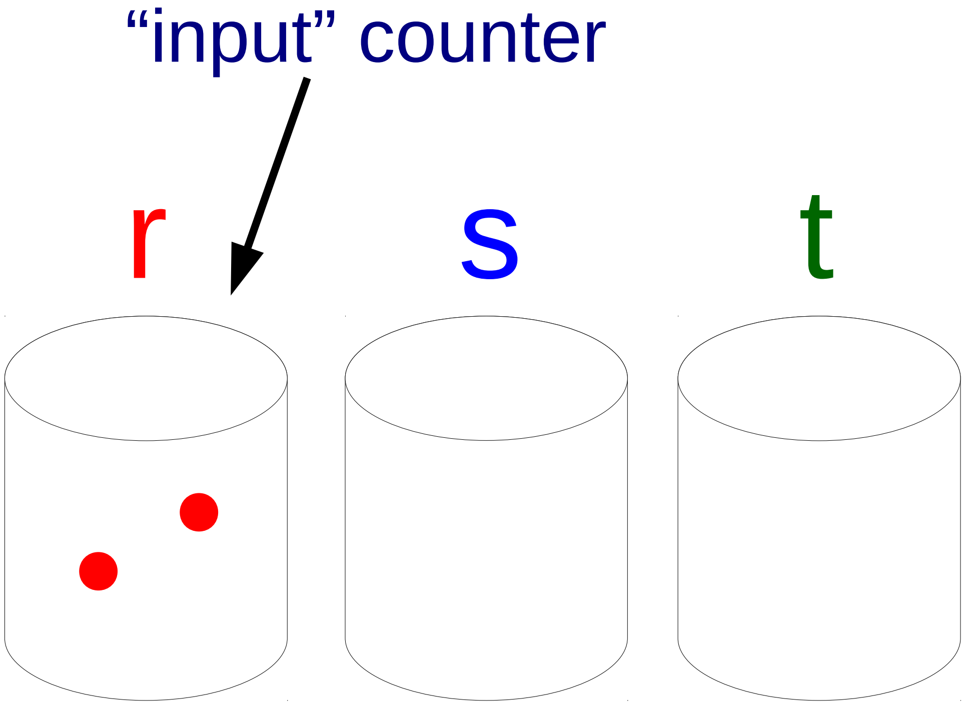

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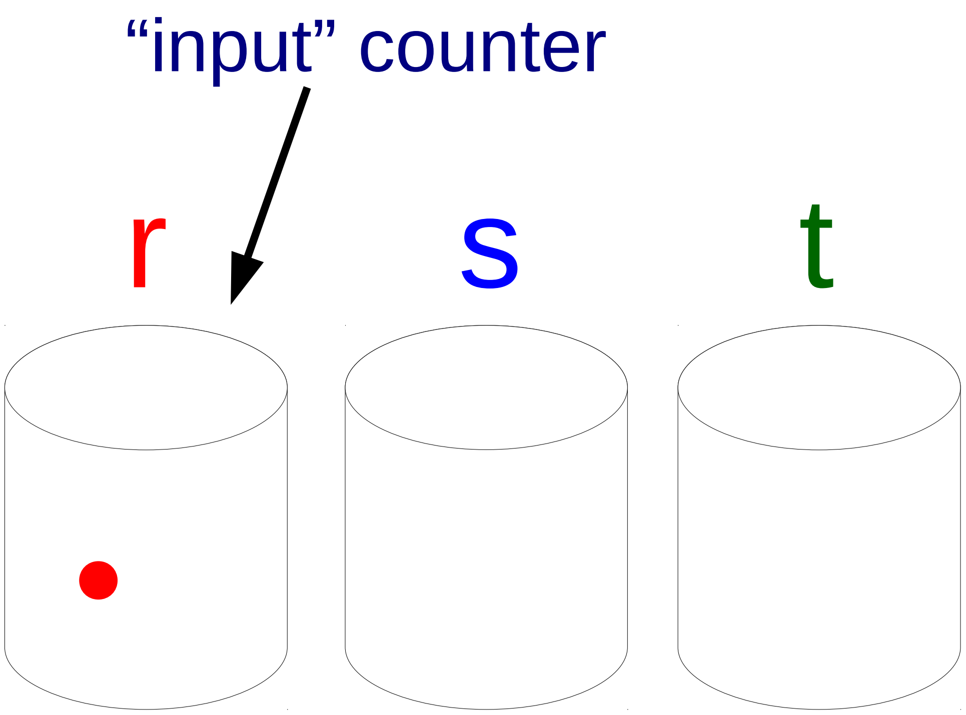

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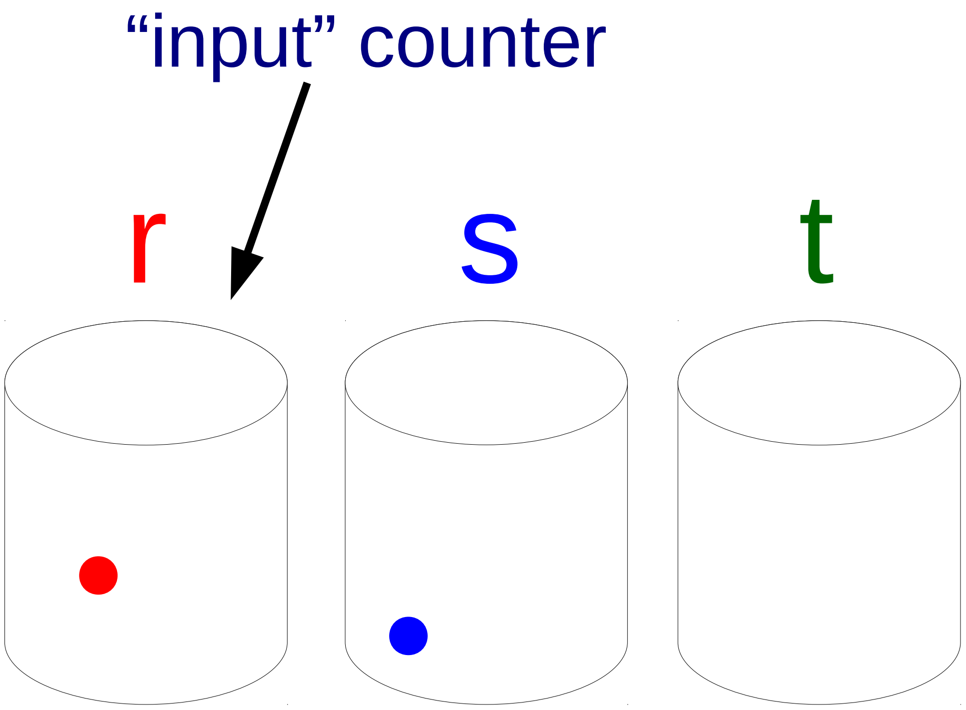

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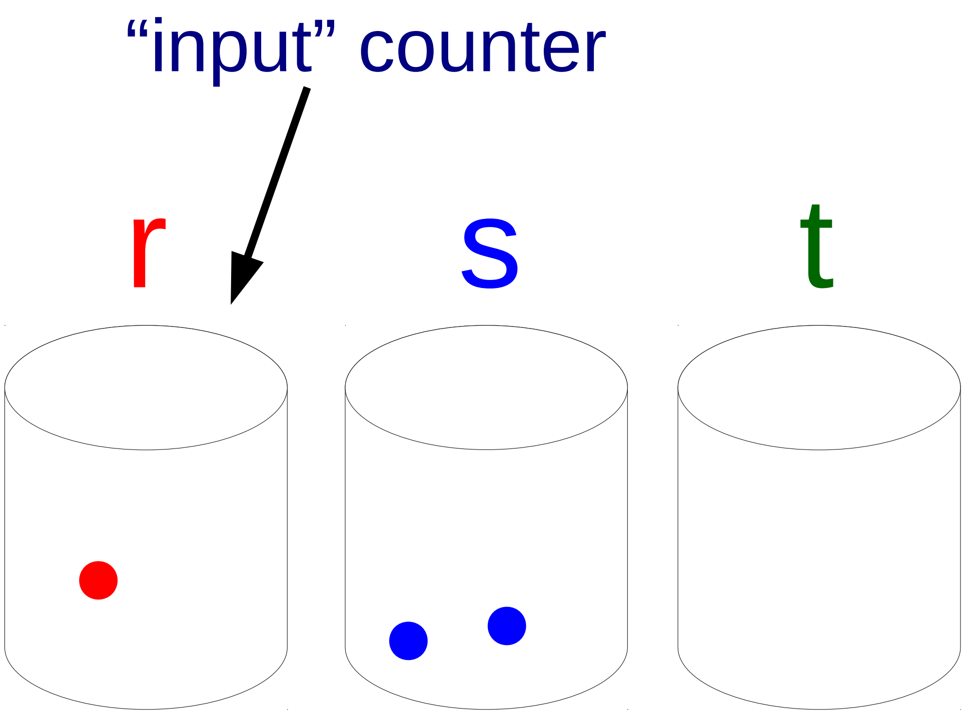

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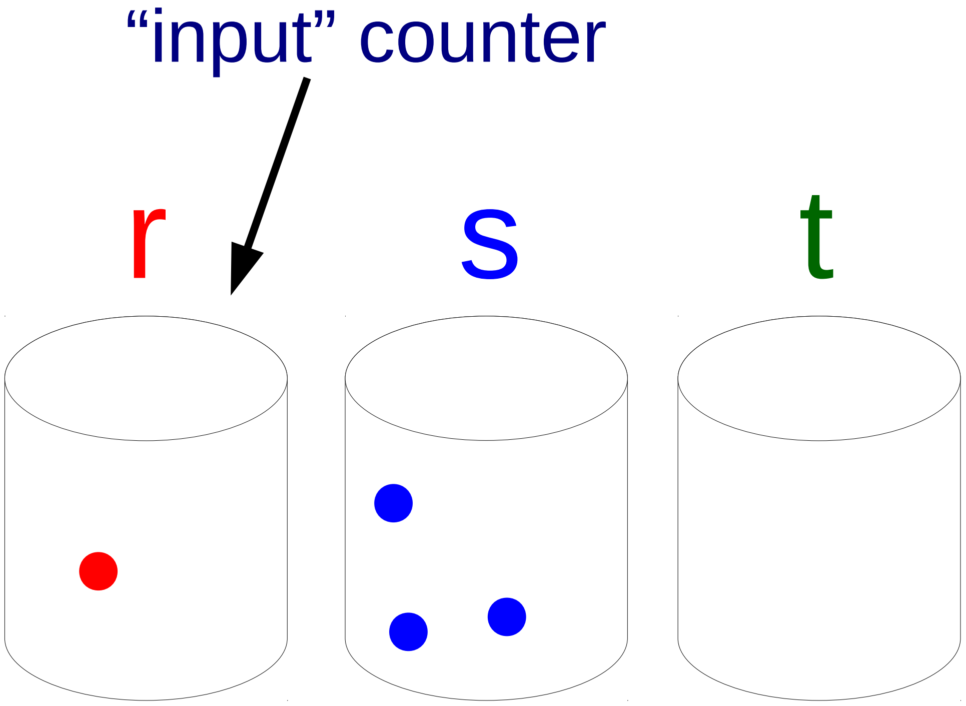

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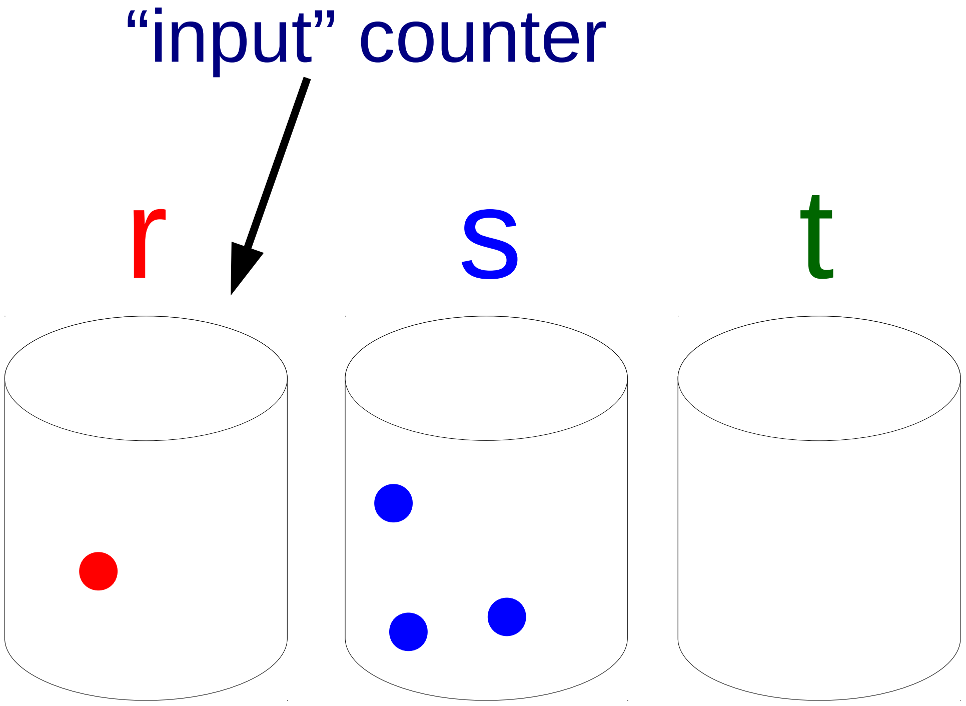

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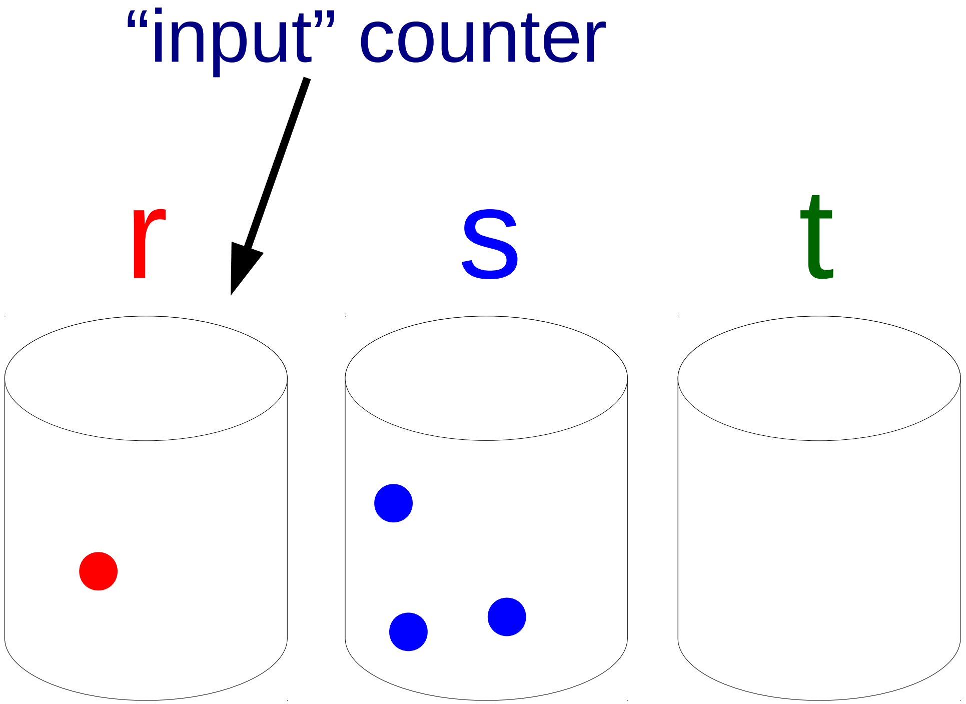

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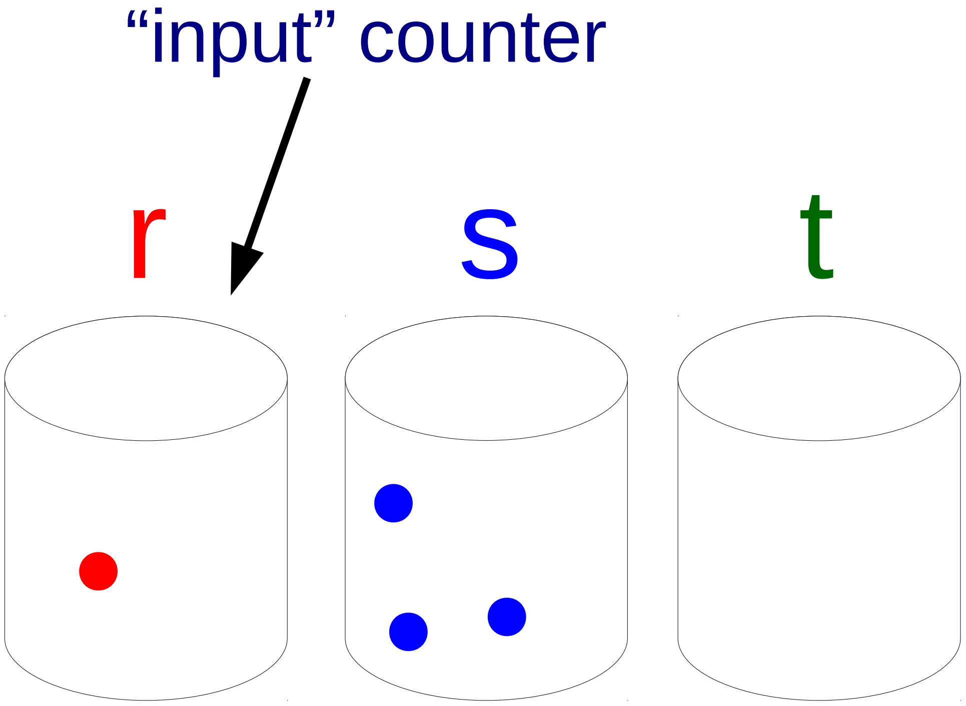

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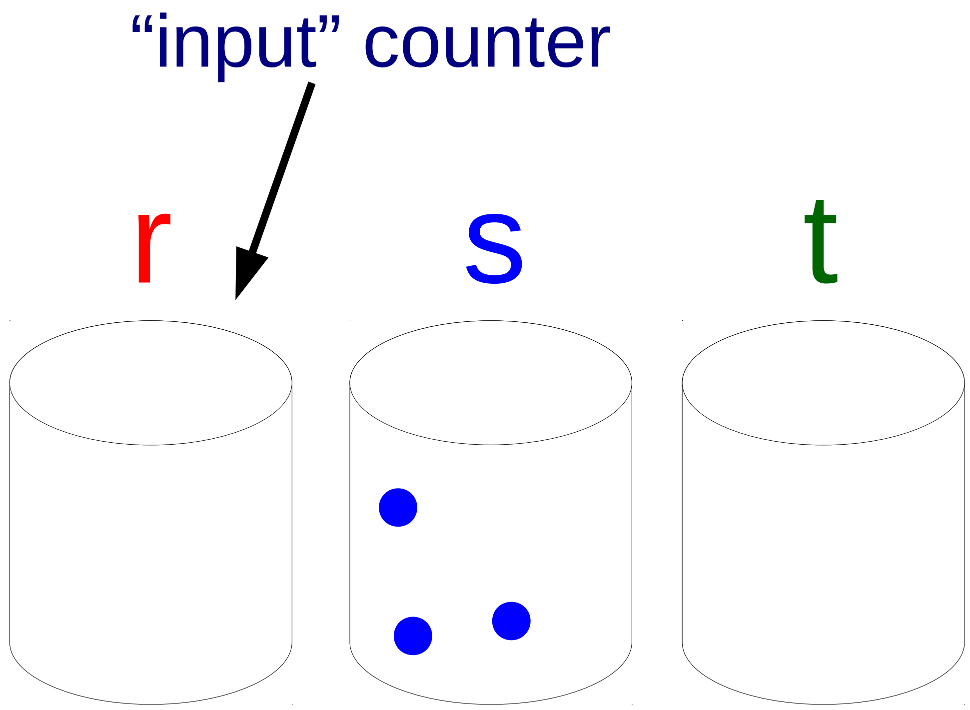

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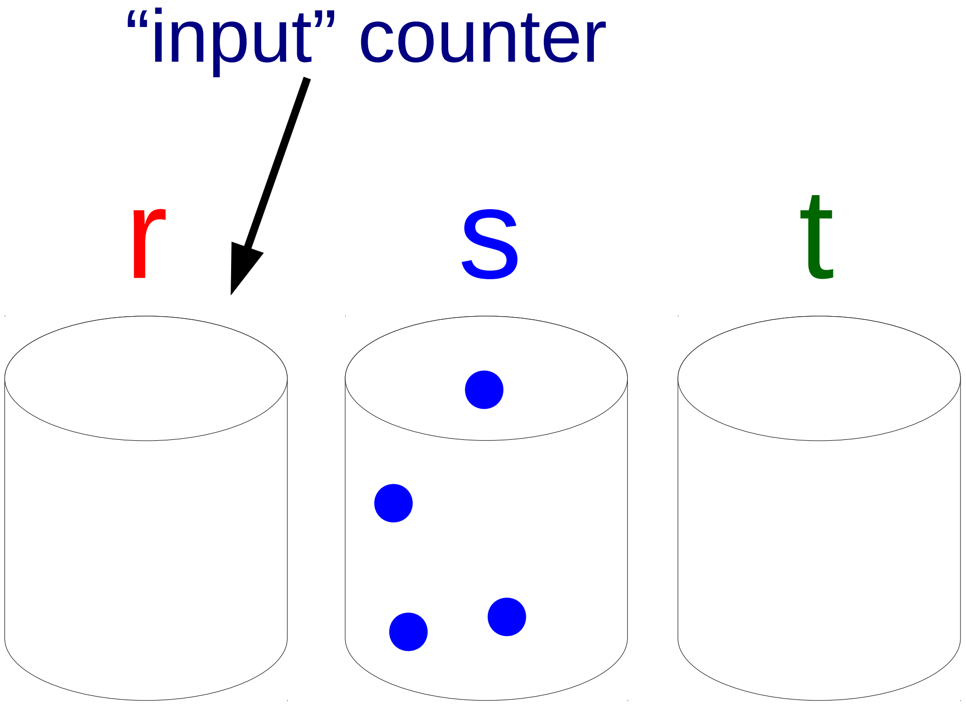

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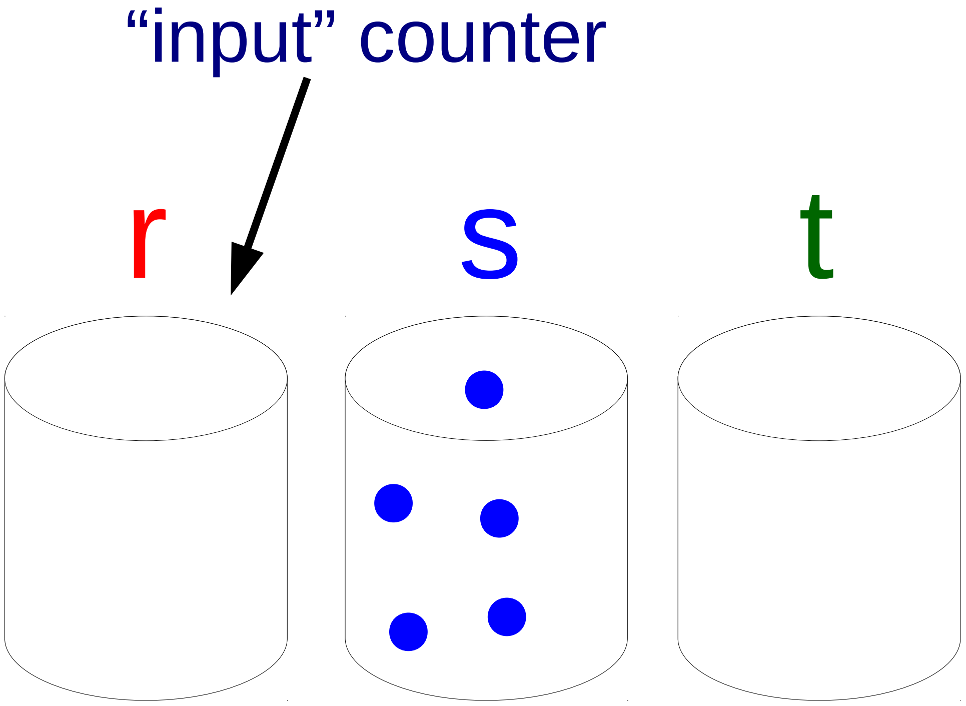

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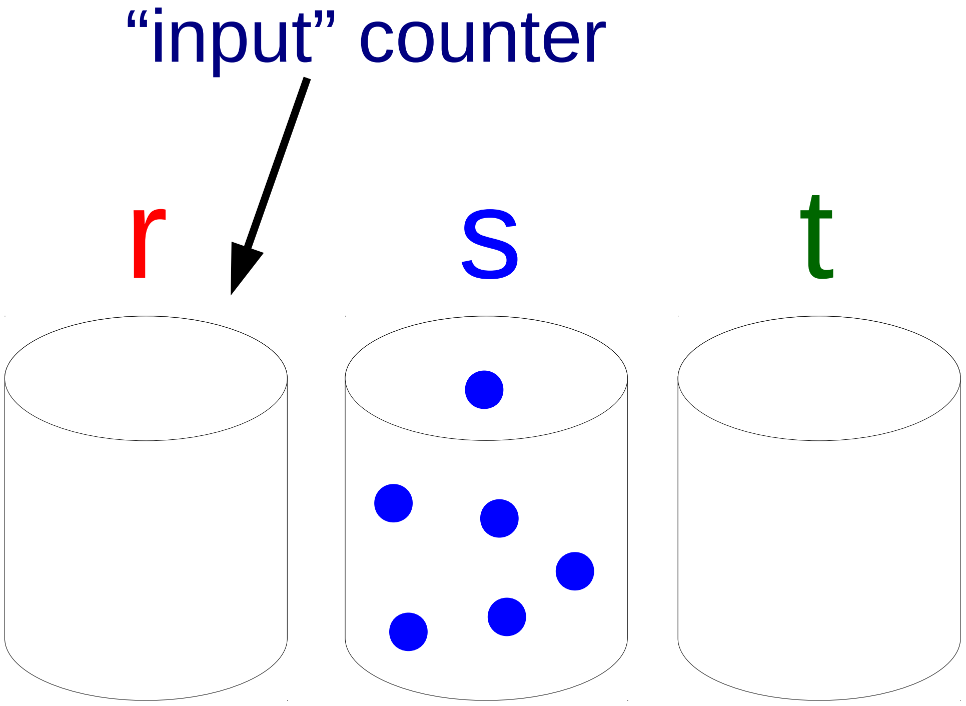

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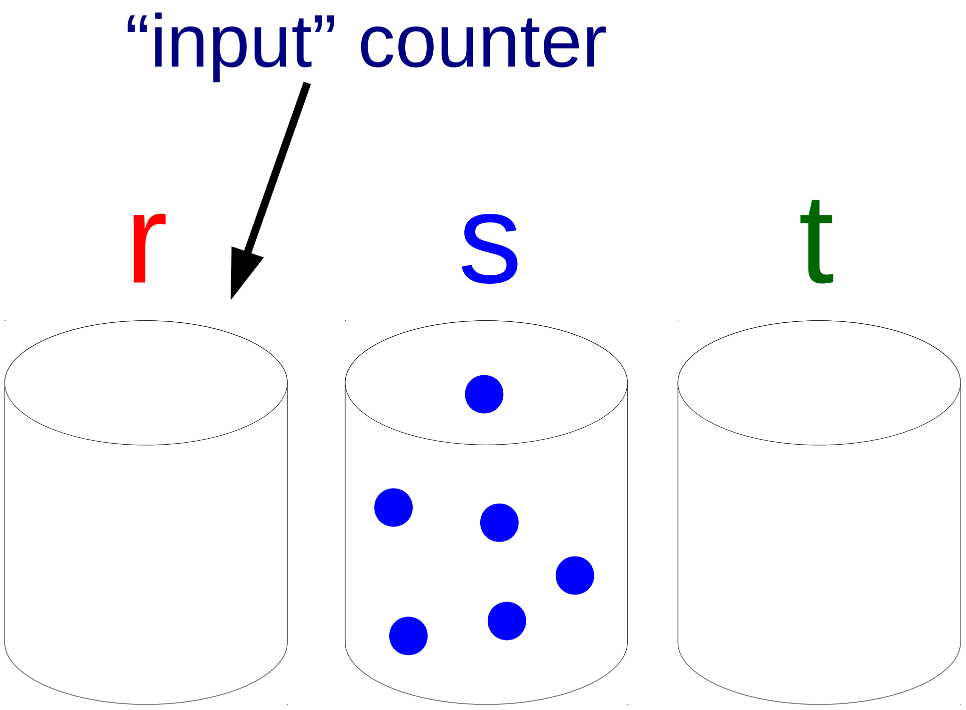

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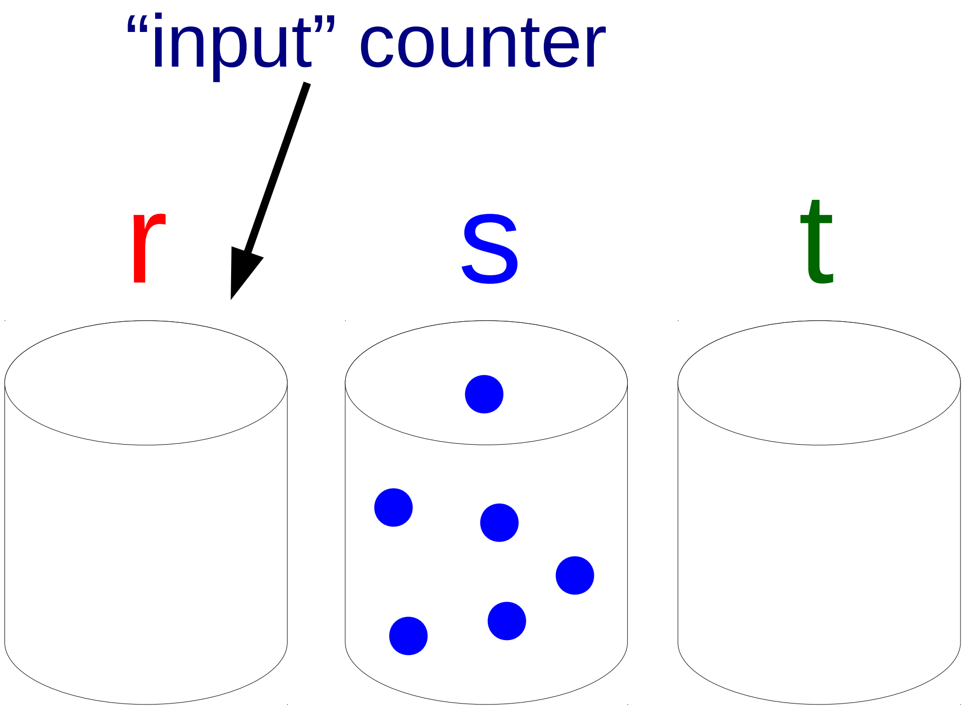

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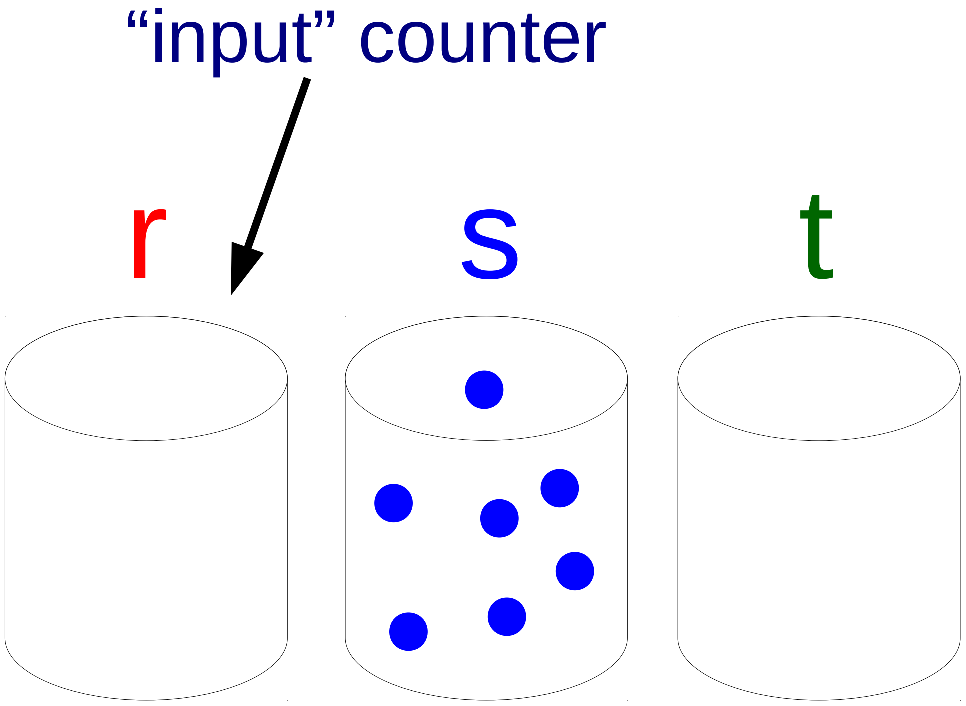

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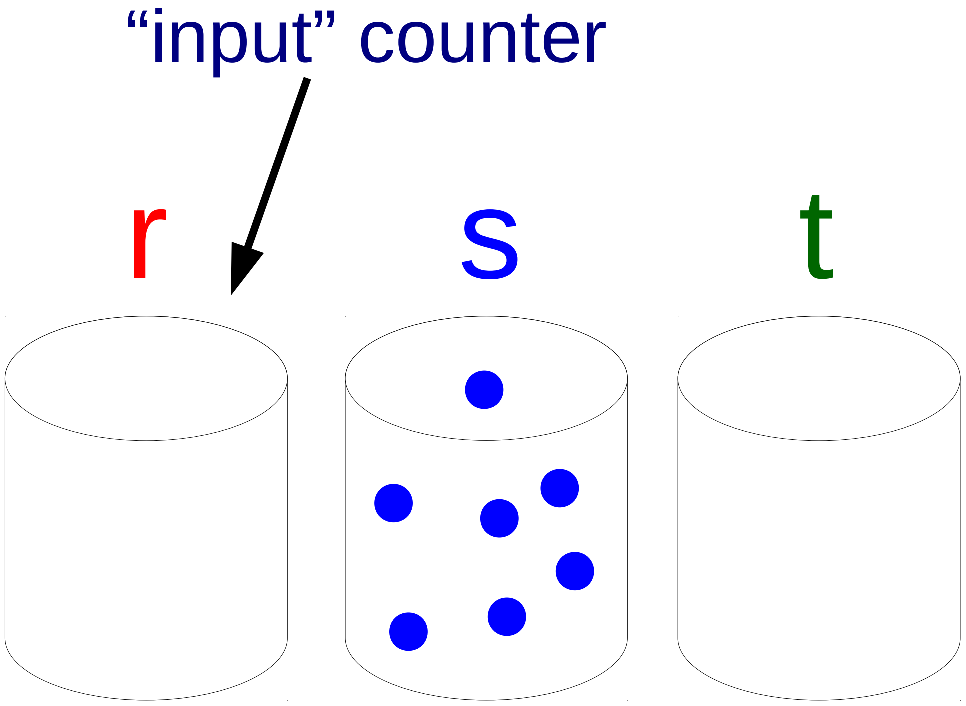
HALT



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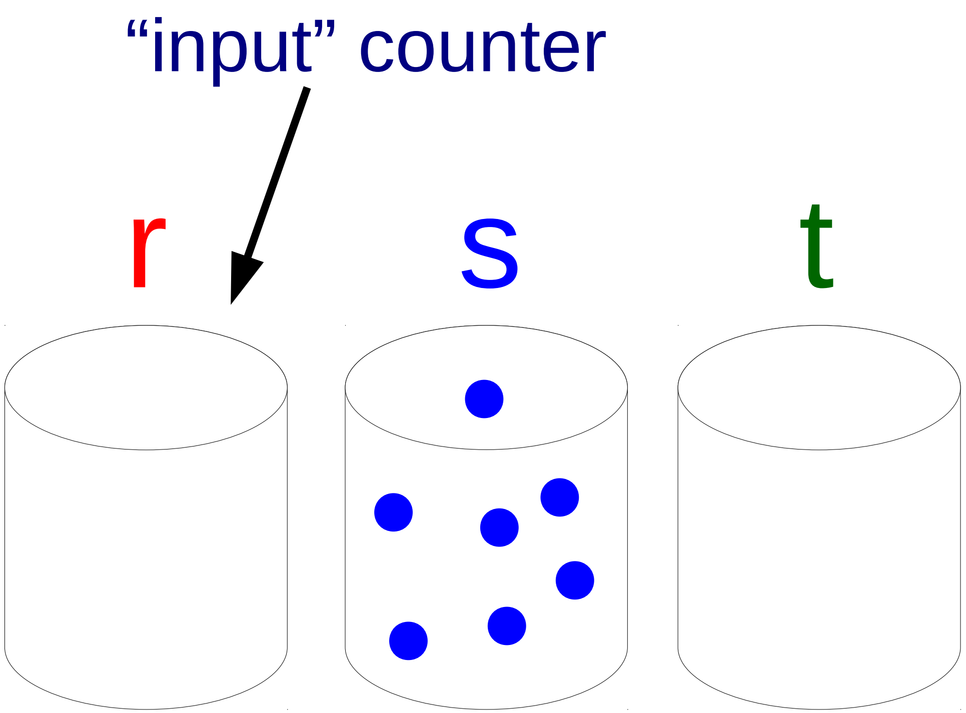

computes $f(n) = 3n+1$

CRNs can simulate counter machines

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Counter machine:

r = input *n*, start line 1

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CRN:

initial state $\{n\ R, 1\ L_1\}$

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$$L_1 \rightarrow L_2 + R$$

$$L_2 + R \rightarrow L_3$$

CRNs can simulate counter machines

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r = input *n*, start line 1

1) *inc*(r)

2) *dec*(r) if zero goto 1

3) *inc*(s)

4) *dec*(s) if zero goto 2

CRN:

initial state $\{n\ R, 1\ L_1\}$

$L_1 \rightarrow L_2 + R$

$L_2 + R \rightarrow L_3$

CRNs can simulate counter machines

Counter machine:

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CRN:

initial state $\{n\,R, 1\,L_1\}$

$L_1 \rightarrow L_2 + R$

$L_2 + R \rightarrow L_3$; $L_2 \rightarrow L_1$

$L_3 \rightarrow L_4 + S$

$L_4 + S \rightarrow L_5$; $L_4 \rightarrow L_2$

CRNs can simulate counter machines with probability < 1

Counter machine:

r = input *n*, start line 1

1) *inc*(r)

2) *dec*(r) if zero goto 1

3) *inc*(s)

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CRN:

initial state $\{n\,R, 1\,L_1\}$

$L_1 \to L_2 + R$

$L_2 + R \to L_3$; $L_2 \to L_1$

$L_3 \to L_4 + S$

$L_4 + S \to L_5$; $L_4 \to L_2$

Need to be **very** slow!

How to slow down reaction $L_2 \to L_1$?

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Use a clock:

1 C_1, 1 F

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$$F + C_1 \to F + C_2$$

$$F + C_2 \to F + C_3$$

How to slow down reaction $L_2 \rightarrow L_1$?

Use a clock:

$1\ C_1$, $1\ F$, $n\ B$

$$F + C_1 \rightarrow F + C_2 \qquad B + C_2 \rightarrow B + C_1$$

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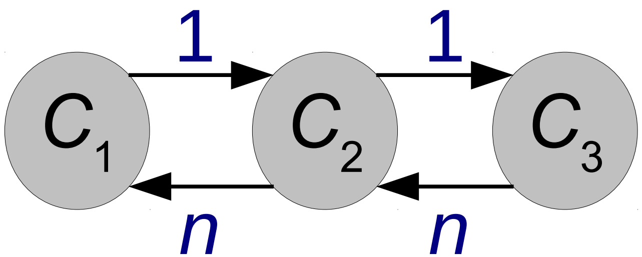

reverse-biased random walk

How to slow down reaction $L_2 \to L_1$?

Use a clock:

$1\ C_1$, $1\ F$, $n\ B$

$$F + C_1 \to F + C_2 \qquad B + C_2 \to B + C_1$$

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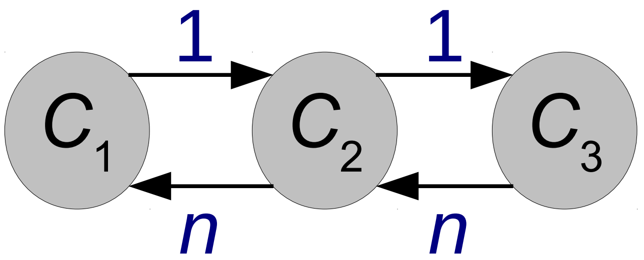


reverse-biased random walk

C_3 appears after expected time $\approx n^2$

How to $\boxed{\text{slow down reaction } L_2 \to L_1}$?

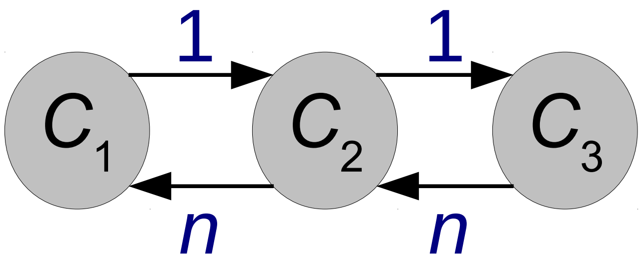
Use a clock:

$$\boxed{C_3 +} L_2 \to \boxed{C_1 +} L_1$$

1 C_1, 1 F , n B

$$F + C_1 \to F + C_2 \qquad B + C_2 \to B + C_1$$

$$F + C_2 \to F + C_3 \qquad B + C_3 \to B + C_2$$



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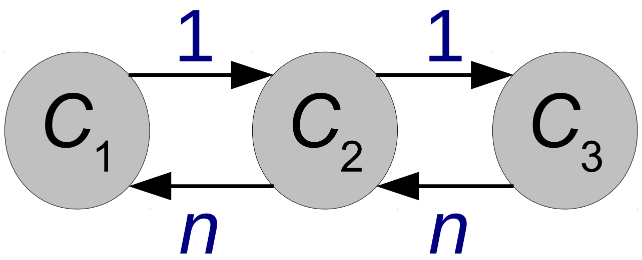
$F + C_1 \to F + C_2$ $\quad$ $B + C_2 \to B + C_1$

$F + C_2 \to F + C_3$ $\quad$ $B + C_3 \to B + C_2$



reverse-biased random walk

C_3 appears after expected time $\approx n^2$

E[time for $L_2 + R \to L_3$] $\leq n$

Probability 1 computation

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Consider...

$$Y \xrightarrow{2} 2Y$$

$$Y \xrightarrow{1}$$

stably computes φ = no (prob < 1)

initial state {1Y,1N}

Probability 1 computation

- Errr... isn't that stable computation?
- With finite state space, yes.

Consider...

$$Y \xrightarrow{2} 2Y$$
$$Y \xrightarrow{1}$$
$$\xrightarrow{1} Y$$

computes φ = yes with prob 1 (not stably)

Probability 1 computation

- Errr... isn't that stable computation?
- With finite state space, yes.

Consider...

$$Y \xrightarrow{2} 2Y$$

$$Y \xrightarrow{1}$$

$$\xrightarrow{1} Y$$

computes φ = yes with prob 1 (not stably)

Theorem: All (Turing) computable predicates/functions can be computed by a CRN with probability 1.

[Cummings, D, Soloveichik, DNA Computing 2014]

Acknowledgments

Ho-Lin Chen

Rachel Cummings

David Soloveichik

American Institute of Mathematics

UCSF center for systems & synthetic biology
an NIGMS national systems biology center