Graphical Conditions for Rate Independence in Chemical Reaction Networks



Elisabeth Degrand, François Fages, Sylvain Soliman

INRIA Saclay – Ile de France

LIFEWARE group: *Computational Systems Biology and Optimization*

http://lifeware.inria.fr/

Analog Computations with Chemical Reaction Networks (CRN)

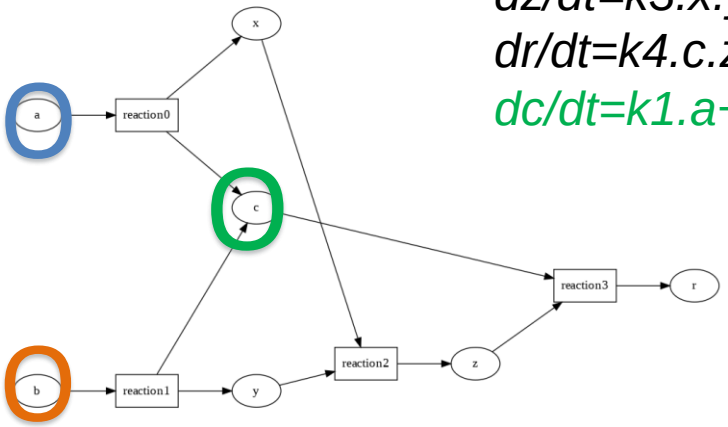
CRN:

*k1*a for* a => x+c

*k2*b for* b => y+c

*k3*x*y for* x+y => z

*k4*c*z for* c+z => r



ODE

da/dt=-k1.a

db/dt=-k2.b

dx/dt=k1.a-k3.x.y

dy/dt=k2.b-k3.x.y

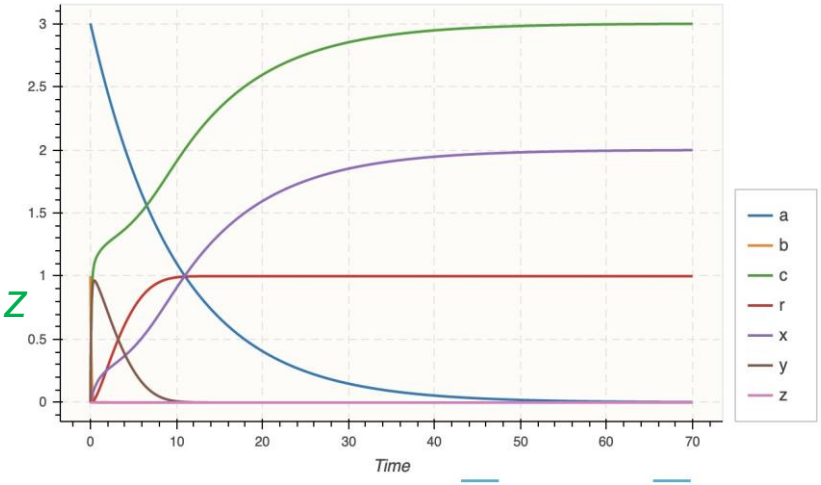
dz/dt=k3.x.y-k4.c.z

dr/dt=k4.c.z

dc/dt=k1.a+k2.b-k4.c.z

Input: a, b Initialization: x=y=z=r=c=0

Output: c



Computed function at steady state:

c(∞)= max(a(0),b(0))

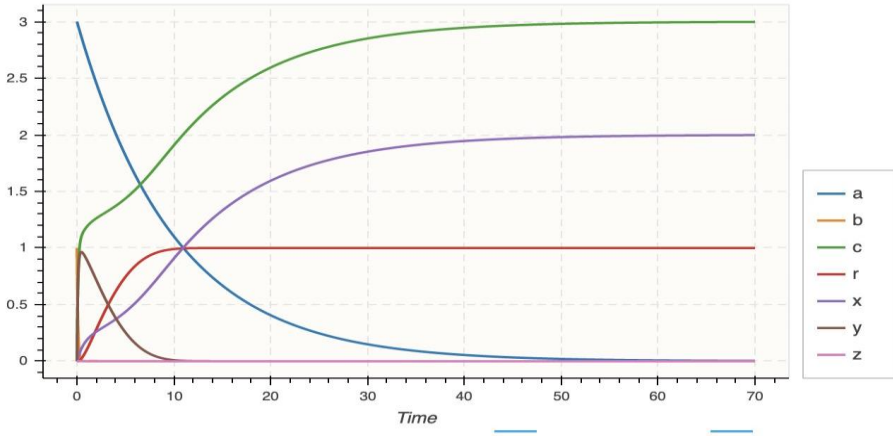
Theorem [F, Le Guludec, Bournez, Pouly CMSB 2017]

A real function is Turing-computable (in Ptime) if and only if it can be computed by a CRN over a finite set of molecular species (with polynomial length trajectories)

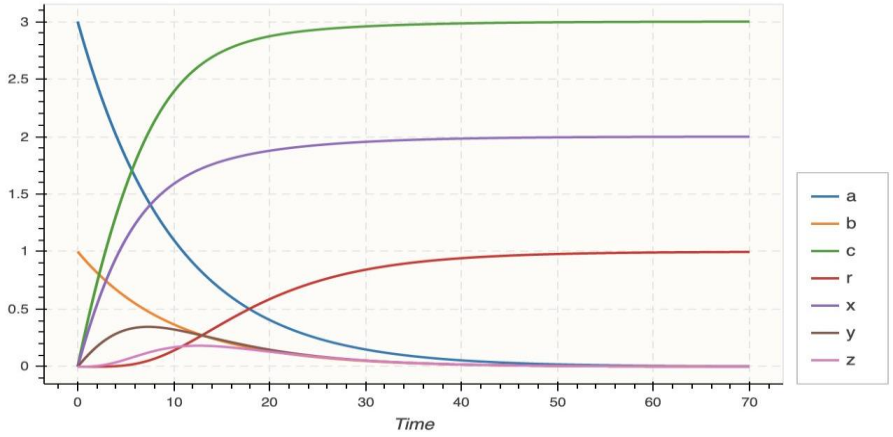
Rate-Independent CRN Computation

Input: a(0)=3 b(0)=1 **Result** c*=3 **independently of the reaction rates**

k1=0.1, k2=10.0, k3=1, k4=100.0:



k1=0.1, k2=0.1, k3=0.1, k4=0.1:



The I/O function computed by that CRN structure is independent of the kinetics

a => x+c

b => y+c

x+y => z

c+z => r

$c^* = \max(a(0),b(0)) = a(0)+b(0)-\min(a(0),b(0))$

$x^* = \max(0,a(0)-b(0))$

$y^* = \max(0,b(0)-a(0))$

$r^* = \min(a(0),b(0))$

$z^* = 0$, $a^* = 0$, $b^* = 0$

Absolute robustness
Ideal circuit designs
for synthetic biology

Mathematical Characterization of the Functions Computed by Rate-Independent CRNs

Theorem [Chen-Doty-Soloveichik 2014 ITCS]

A real function is computable by a rate-independent CRN if and only if it is positive-continuous piecewise linear with rational coefficient.

Theorem [Chalk Kornerup Reeves Soloveichik 2018 CMSB]

A real function is computable by a composable CRN if and only if it is superadditive positive-continuous piecewise rational linear.

Does not help to show that a given CRN is rate-independent nor to design a rate-independent CRN

Graphical conditions on the CRN ensuring rate-independence ?

Simple Rate-Independent CRN Structures

A => B

output B: computes the *identity function* B(∞)=A(0)+B(0) rate-independent !

output A: computes the *zero function* A(∞)=0 rate-independent !

A => C

B => C

Harmless join

output C: computes the *sum* C(∞)=A(0)+B(0)+C(0) rate-independent

output A: computes the *zero function* A(∞)=0 rate-independent !

C => A

C => B

Harmfull fork

output A: computes A(∞)=$\frac{\alpha}{\beta}$C(0)+A(0) not rate-independent !

C => A

C => B

B => C

Harmless fork with a circuit

output A: computes the *sum* A(∞)=C(0)+B(0)+A(0) rate-independent !

Rate-Independent CRN Structures

A+B => C

output C: computes C(∞)=*minimum*(A(0),B(0))+C(0) rate-independent !

output B: computes B(∞)=max(0,B(0)-A(0)) rate-independent !

C => A+B

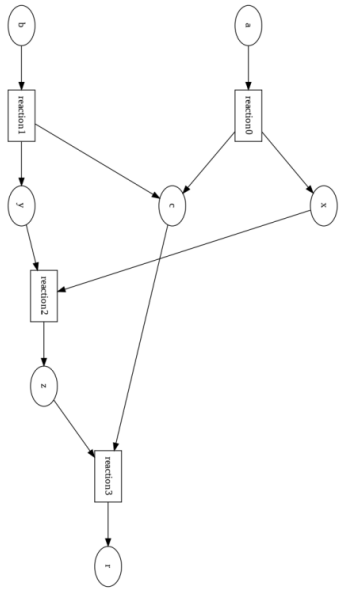
output A: makes copies A(∞)=C(0)+A(0) rate-independent !

A => X+C

B => Y+C Rate-independent on all species, why ?

X+Y => Z

C+Z => R



Definition *A* funnel *CRN is a CRN that is:*

- *fork-free on species nodes*
- *circuit-free*
- *synthesis-free*

Theorem A funnel CRN is rate-independent for any output species.

Sufficient condition, not a necessary condition (e.g. harmless fork with circuit)

Global Rate-Independence Condition

Lemma *The structure of a funnel CRN* C *is a DAG with no reaction source node*

Lemma *All steady fluxes of a funnel CRN* C *are equal to* 0*.*

Proof: by induction on the topological order of the graph.

Definition *We shall denote* x^+_i *the total amount of species* x_i *available in an execution of the corresponding ODE system.*

$$x_i^+ = x_i^0 + \int_0^{+\infty} \frac{dx_i^+}{dt} = x_i^0 + \int_0^{+\infty} \sum_{P_j(x_i) > R_j(x_i)} (P_j(x_i) - R_j(x_i)) f_j$$

Theorem *The ODE system associated to* a funnel CRN *has a single steady state* x^* *that does not depend on the kinetic functions* f_i *of* C*.*

Corollary *A funnel CRN is globally rate-independent for all species.*

Theorem Any function computable by a rate-independent CRN is computable by a funnel CRN.

Proof: by Chen-Doty-Soloveichik's characterization and Ovchinnikov's max-min representation of piecewise linear functions

Rate-Independence for « Persistent » Outputs

The harmless-fork-with-circuit CRN is rate-independent on outputs A, B, C

C => A C => B B => C

Def. A species x

- is a product of a CRN if it can only increase: $\forall i\ R_i(x) \leq P_i(x)$
- is structurally persistent if it is covered by a P-invariant $S, \forall i\ S.R_i = S.P_i$, and does not belong to a critical (gets empty) siphon (when empty remains empty)

Theorem. Any CRN is rate-independent on its structurally persistent products.

Proof: P-invariant covering ensures boundedness and convergence for products.

The species reaching 0 are localized in siphons and exclude persistent outputs.

Implemented in BIOCHAM using Constraint Logic Programming for computing P-invariants and siphons [Nabli, Martinez, F, Soliman 2016 *Constraints*]

Evaluation on BioModels

590 CRNs from SBML models
(many not well-formed CRNs)

[F Gay Soliman 2011 *TCS*]

94 with rate-independent products

29 with non trivial rate-ind. products

2 globally rate-ind. CRNs

Size of those 29 models:

- 4-136 species
- 2-316 reactions

Constraint solving time:

- between 0.07 and 151 seconds
- except 2 timeouts >240s

Biomodel#	#species	#reactions	#products	#RI	#NTRI	NTRI-product species	Time (s)
037	12	12	2	2	2	Yi, Pi	0.950
104	6	2	3	3	1	species_4	0.074
105	39	94	11	3	1	AggP_Proteasome	63.366
143	20	20	4	1	1	MLTH_c	3.333
178	6	4	1	1	1	lytic	0.139
227	60	57	2	1	1	s194	17.299
259	17	29	1	1	1	s10	2.308
260	17	29	1	1	1	s10	2.310
261	17	29	1	1	1	s10	2.297
267	4	3	1	1	1	lytic	0.086
283	4	3	1	1	1	Q	0.053
293	136	316	14	4	3	aggE3, aggParkin, AggP_Proteasome	>240
313	16	16	4	2	1	IL13_DecoyR	2.071
336	18	26	1	1	1	IIa	4.148
344	54	80	7	2	1	AggP_Proteasome	>240
357	9	12	1	1	1	T	0.561
358	12	9	4	2	1	Xa_ATIII	0.892
363	4	4	1	1	1	IIa	0.067
366	12	9	4	2	1	Xa_ATIII	0.901
415	10	5	7	7	7	s10, s11, s12, s13, s14, s9, s15	0.894
437	61	40	22	8	1	T	16.109
464	14	10	6	3	1	s12	2.282
465	16	14	5	5	1	s23	59.554
525	18	19	8	3	1	p18inactive	33.479
526	18	19	8	3	1	p18inactive	33.858
540	22	11	12	11	8	s14, s15, s16, s17, s18, s19, s20, s21	56.134
541	37	32	13	9	7	s14, s15, s16, s17, s18, s19, s21	31.573
559	90	136	18	2	2	s493, s502	150.954
575	76	58	9	1	1	DA_GSH	66.806

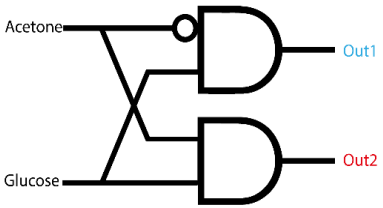
Conclusion

- Graphical conditions to ensure rate-independence of a CRN on all species
  - « funnel » CRN structure: fork-free, circuit-free, synthesis-free
- Graphical condition to ensure rate-independence on CRN product species
  - Non-standard use of Petri Net notions of P-invariant and siphon
  - NP-hard problems implemented in BIOCHAM by Constraint Logic Programming
- Scales-up to models in BioModels
  - Few timeouts for models with a hundred of species or reactions
  - Possible improvements using SAT solvers
- Theory of analog computational complexity beyond Ptime characterization?
  - Computational complexity class of rate-independent CRNs?
  - Low time complexity class of funnel CRNs?

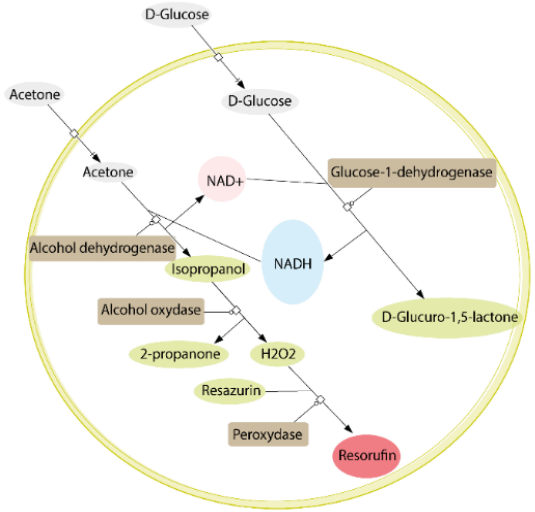
Perspectives

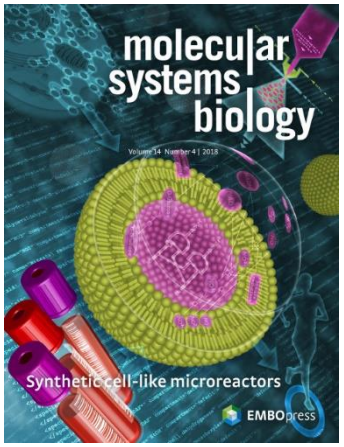
- Rate-independence by design for Synthetic Biology
  - Graphical constraints for CRN design
  - Constraint-based synthesis method

- « Morally » rate-independent CRNs
  - Rate-independent CRN kernel
  - Plus reverse reactions breaking formal rate-independence (limited robustness)
  - Boolean function CRNs for diagnosis [Courbet Amar F Renard Molina 2018 MSB]



Glucose	Acetone	Out2	Out1
0	0	0	0
1	0	0	1
0	1	0	0
1	1	1	0





Lifeware team at INRIA Saclay

François Fages (Research Scientist, Prof X)
Mathieu Hemery (Engineer)
Anna Niaraki (Assoc. Prof. Univ. Evry)
Sylvain Soliman (Research Scientist)
Éléonore Bellot (PhD Inria)
Elisabeth Degrand (PhD Inria)
Eléa Greugny (PhD Johnson&Johnson)
Jeremy Grignard (PhD Servier)
Julien Martinelli (PhD INSERM-Inria)

<u>Current collaborations</u>:

- O. Bournez, Ecole Polytechnique, Palaiseau, A. Pouly, CNRS Univ. Paris
  - ANR δifference project: Computing with Discrete Differential Equations
- F. Molina CNRS Sys2diag, Montpellier, J.H. Jiang, NTU, Taiwan
  - ANR-MOST BIOPSY project: Biochemical Programming Systems
- A. Weber, Univ. Bonn, T. Sturm, Inria Nancy, O. Radulescu, Montpellier, S. Walcher
  - ANR-DFG SYMBIONT project: Symbolic Methods for Biological Networks
- A. Ballesta, INSERM Villejuif