Modeling with SQUAD

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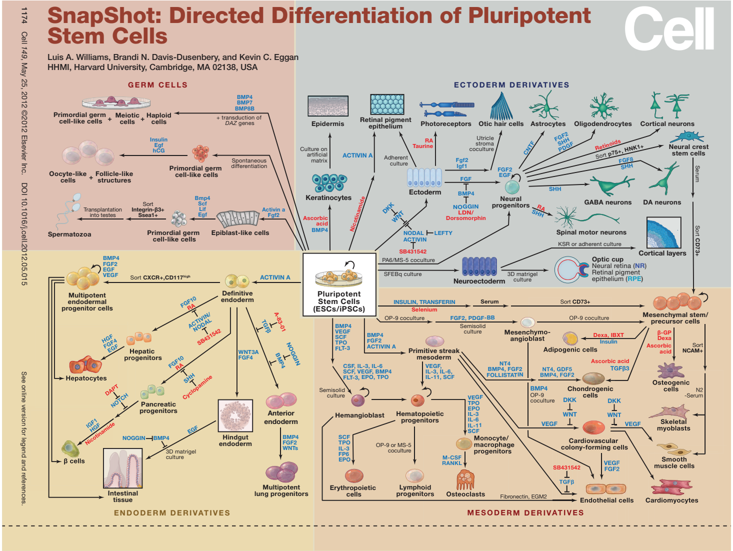
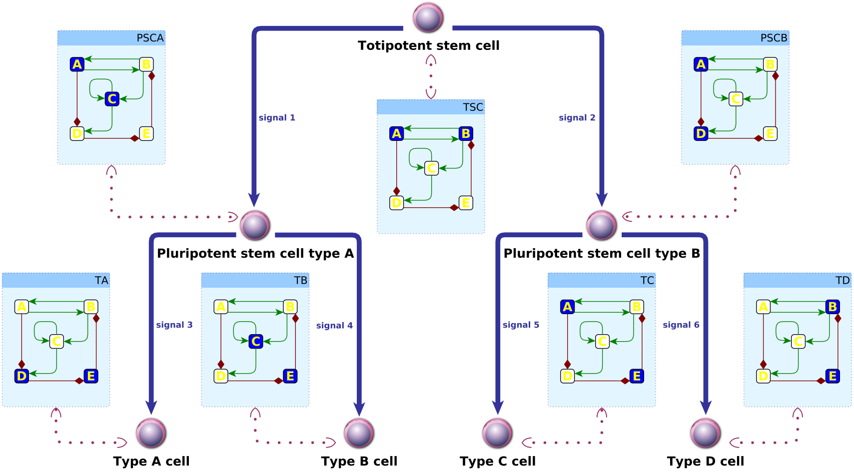
Differentiation of human cells

Williams *et al.* (2012) *Cell* **149**. DOI: 10.1016/j.cell.2012.05.015



The big picture

Cell differentiation as transitions among attractors



What is SQUAD?

- Stands for *S*tandardized *Qu*alitative *D*ynamical systems.
- Approximates a Boolean network with the use of a set of ordinary differential equations.
- Variables representing the state of activation are normalized: they are constrained in the range [0,1].
- Enables a direct comparison of the attractors obtained with a continuous model against the attractors of a purely binary model.

Why?

- There are many biological systems where there are gradients, and concentration-dependent effects.
- There is not enough quantitative data available for such systems.

SQUAD

Mendoza and Xenarios (2006). *Theor. Biol. Med. Model.* **3**: 13

Theoretical Biology and Medical Modelling

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Research

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A method for the generation of standardized qualitative dynamical systems of regulatory networks

Luis Mendoza* and Ioannis Xenarios

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Discrete equations

Equation 1.

$$x_i(t+1) = \begin{cases} \left(x_1^a(t) \vee x_2^a(t) \ldots \vee x_n^a(t) \right) \wedge \neg\left(x_1^i(t) \vee x_2^i(t) \ldots \vee x_m^i(t)\right) & \S \\ x_1^a(t) \vee x_2^a(t) \ldots \vee x_n^a(t) & \S\S \\ \neg\left(x_1^i(t) \vee x_2^i(t) \ldots \vee x_m^i(t)\right) & \S\S\S \end{cases}$$

$\vee, \wedge,$ and $\neg$ are the logical operators OR, AND, and NOT

$x_i \in \{0, 1\}$

$\{x_n^a\}$ is the set of activators of x_i

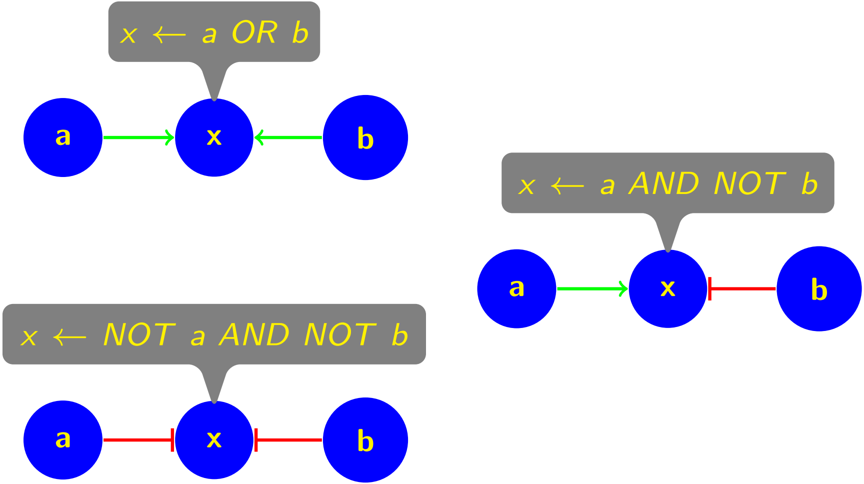
$\{x_m^i\}$ is the set of inhibitors of x_i

$\S$ is used if x_i has activators and inhibitors

$\S\S$ is used if x_i has only activators

$\S\S\S$ is used if x_i has only inhibitors

Discrete equations



Finding attractors analyzing regulatory circuits

The logical formalism developed by René Thomas enables us to dissociate a complex network into a well-defined set of feedback circuits and check their dynamical roles individually, yet keeping complete control of the ways in which these circuits are interconnected.

Continuous equations

Equation 3.

$$\frac{dx_i}{dt} = \frac{-e^{0.5h} + e^{-h(\omega_i - 0.5)}}{(1-e^{0.5h})(1+e^{-h(\omega_i-0.5)})} - \gamma_i x_i$$

$$\omega_i = \begin{cases} \left(\frac{1+\sum\alpha_n}{\sum\alpha_n}\right)\left(\frac{\sum\alpha_n x_n^a}{1+\sum\alpha_n x_n^a}\right)\left(1-\left(\frac{1+\sum\beta_m}{\sum\beta_m}\right)\left(\frac{\sum\beta_m x_m^i}{1+\sum\beta_m x_m^i}\right)\right) & \S \\ \left(\frac{1+\sum\alpha_n}{\sum\alpha_n}\right)\left(\frac{\sum\alpha_n x_n^a}{1+\sum\alpha_n x_n^a}\right) & \S\S \\ \left(1-\left(\frac{1+\sum\beta_m}{\sum\beta_m}\right)\left(\frac{\sum\beta_m x_m^i}{1+\sum\beta_m x_m^i}\right)\right) & \S\S\S \end{cases}$$

$$0 \le x_i \le 1$$

$$0 \le \omega_i \le 1$$

$$h, \alpha_n, \beta_m, \gamma_i > 0$$

$\{x_n^a\}$ is the set of activators of x_i

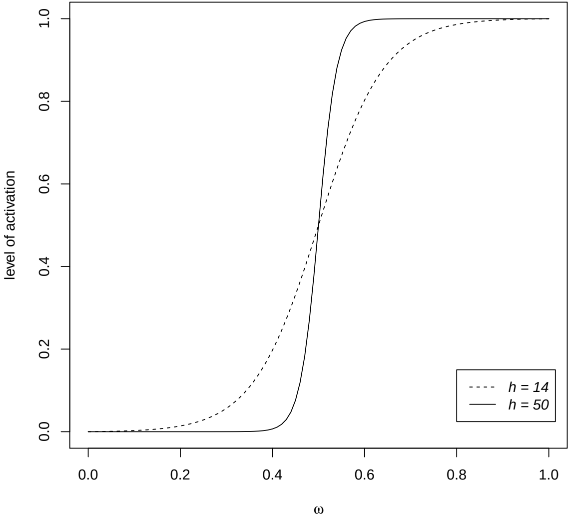
$\{x_n^i\}$ is the set of inhibitors of x_i

§ is used if x_i has activators and inhibitors

§§ is used if x_i has only activators

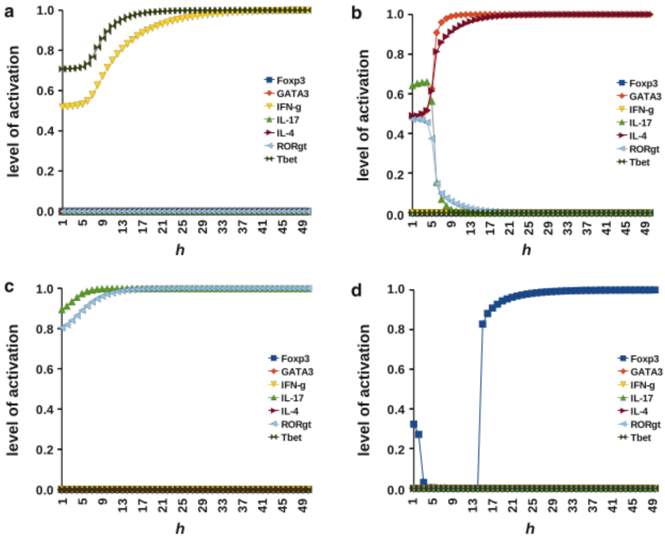
§§§ is used if x_i has only inhibitors

The parameter h



Relative insensitivity to parameter h

Mendoza and Pardo (2010). *Theor. Biosci.* **129**: 283



Continuous equations

Equation 3.

$$\frac{dx_i}{dt} = \frac{-e^{0.5h} + e^{-h(\omega_i - 0.5)}}{(1 - e^{0.5h})(1 + e^{-h(\omega_i - 0.5)})} - \gamma_i x_i$$

$$\omega_i = \begin{cases} \left(\frac{1+\sum \alpha_n}{\sum \alpha_n}\right)\left(\frac{\sum \alpha_n x_n^a}{1+\sum \alpha_n x_n^a}\right)\left(1 - \left(\frac{1+\sum \beta_m}{\sum \beta_m}\right)\left(\frac{\sum \beta_m x_m^i}{1+\sum \beta_m x_m^i}\right)\right) & \S \\ \left(\frac{1+\sum \alpha_n}{\sum \alpha_n}\right)\left(\frac{\sum \alpha_n x_n^a}{1+\sum \alpha_n x_n^a}\right) & \S\S \\ \left(1 - \left(\frac{1+\sum \beta_m}{\sum \beta_m}\right)\left(\frac{\sum \beta_m x_m^i}{1+\sum \beta_m x_m^i}\right)\right) & \S\S\S \end{cases}$$

$$0 \le x_i \le 1$$

$$0 \le \omega_i \le 1$$

$$h, \alpha_n, \beta_m, \gamma_i > 0$$

$\{x_n^a\}$ is the set of activators of x_i

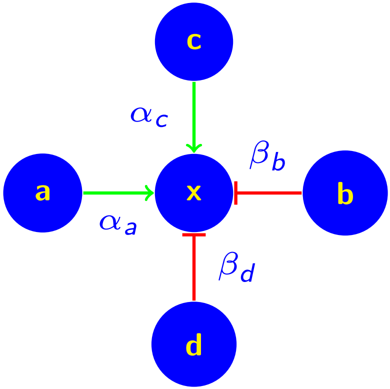
$\{x_n^i\}$ is the set of inhibitors of x_i

§ is used if x_i has activators and inhibitors

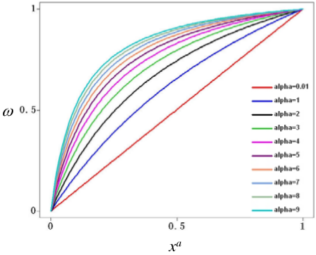
§§ is used if x_i has only activators

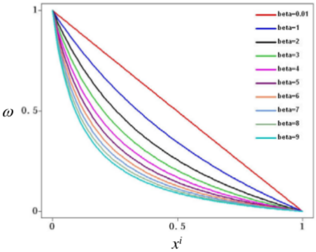
§§§ is used if x_i has only inhibitors

Parameters α and β

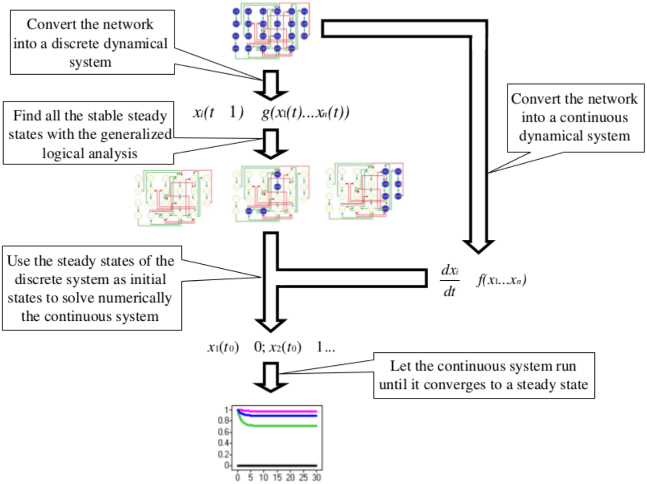


Strength of interactions





SQUAD workflow



SQUAD

Di Cara *et al.* (2007). *BMC Bioinformatics* **8**: 462

BMC Bioinformatics

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Dynamic simulation of regulatory networks using SQUAD

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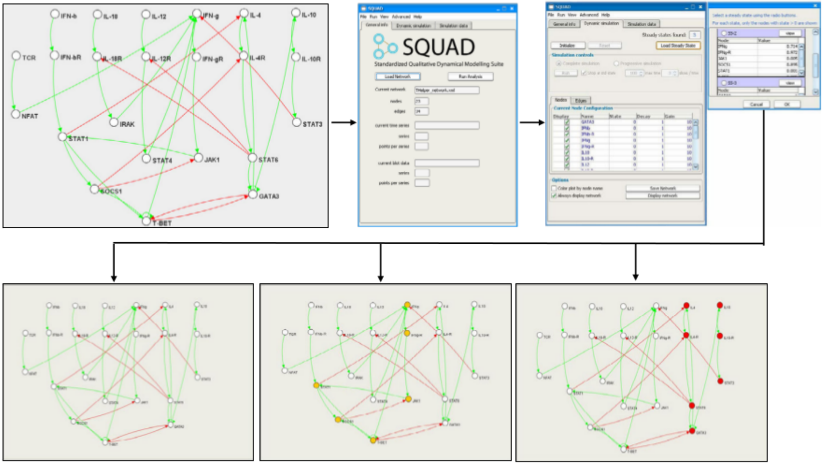
Workflow



State1: Th_0 State2: Th_1 State3: Th_2

Finding the steady states of a network with BDDs

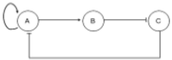


Fig. 2. An example of Gene Regulatory Network

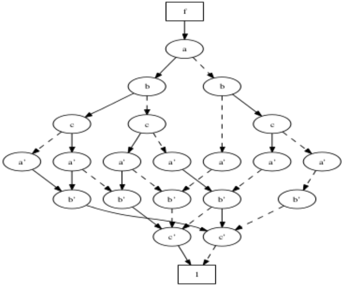
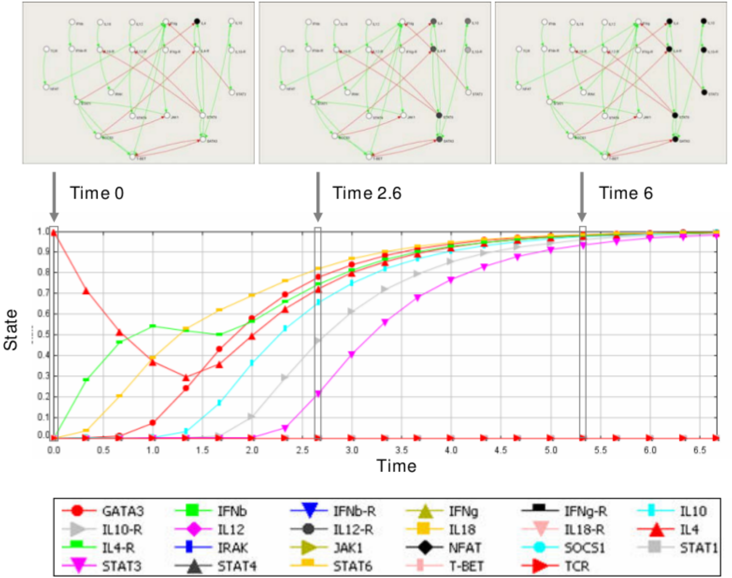


Fig. 3. BDD representing the state space of example in figure 2. The dashed edges represent **0** evaluation of the variables and the solid edges represent the **1** evaluation. For clarity, edges going to **0**-terminal are not shown in this figure.

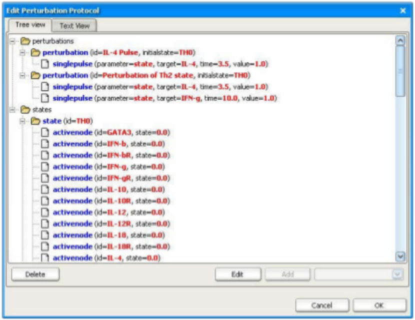
Dynamics



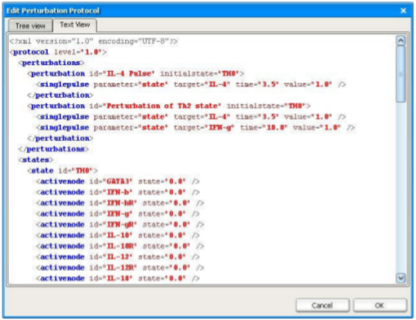
Time 0
Time 2.6
Time 6
State
Time
GATA3
IFNb
IFNb-R
IFNg
IFNg-R
IL10
IL10-R
IL12
IL12-R
IL18
IL18-R
IL4
IL4-R
IRAK
JAK1
NFAT
SOCS1
STAT1
STAT3
STAT4
STAT6
T-BET
TCR

Perturbations

A

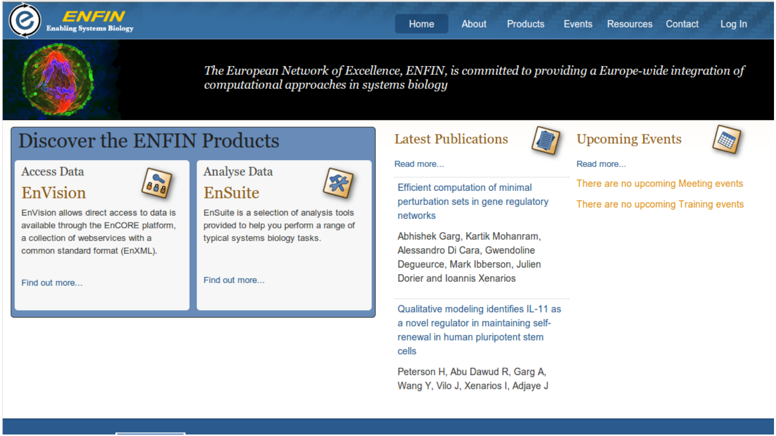


B



SQUAD is part of ENFIN

http://www.enfin.org



SQUADD

Sankar *et al.* (2011). *Bioinformatics* **27**: 1404

BIOINFORMATICS **ORIGINAL PAPER**

Vol. 27 no. 10 2011, pages 1404–1412
doi:10.1093/bioinformatics/btr158

Systems biology

Advance Access publication March 30, 2011

A qualitative continuous model of cellular auxin and brassinosteroid signaling and their crosstalk

Martial Sankar[1,*], Karen S. Osmont[1], Jakub Rolcik[2], Bojan Gujas[1], Danuse Tarkowska[2], Miroslav Strnad[2], Ioannis Xenarios[3] and Christian S. Hardtke[1,*]

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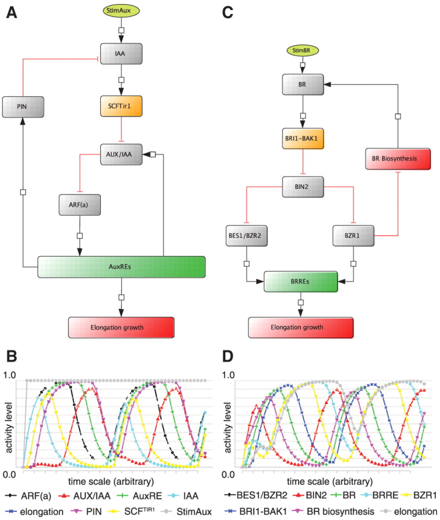
Associate Editor: Alfonso Valencia

SQUADD

Used to model cyclic behavior



SQUADD is part of Bioconductor

http://www.bioconductor.org/packages/release/bioc/html/SQUADD.html

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SQUADD

Add-on of the SQUAD Software

Bioconductor version: Release (2.13)

This package SQUADD is a SQUAD add-on. It permits to generate SQUAD simulation matrix, prediction Heat-Map and Correlation Circle from PCA analysis.

Author: Martial Sankar, supervised by Christian Hardtke and Ioannis Xenarios

Maintainer: Martial Sankar <martial.sankar at unil.ch>

To install this package, start R and enter:

```
source("http://bioconductor.org/biocLite.R")
biocLite("SQUADD")
```

To cite this package in a publication, start R and enter:

```
citation("SQUADD")
```

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- Annotating Variants
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- Flow Cytometry and other assays
- Candidate Binding Sites for Known Transcription Factors
- Cloud-enabled cis-eQTL search and annotation

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Modification of SQUAD

Sánchez-Corrales *et al.* (2010). *J. Theor. Biol.* **264**: 971

Journal of Theoretical Biology 264 (2010) 971–983

Contents lists available at ScienceDirect

Journal of Theoretical Biology

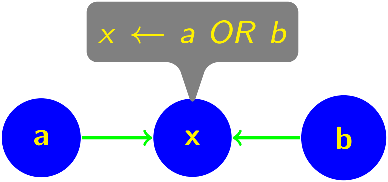
journal homepage: www.elsevier.com/locate/yjtbi

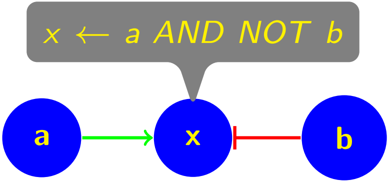
The *Arabidopsis thaliana* flower organ specification gene regulatory network determines a robust differentiation process

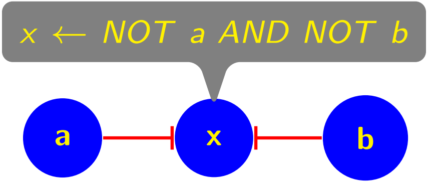
Yara-Elena Sánchez-Corrales[a,1], Elena R. Álvarez-Buylla[a,b], Luis Mendoza[b,c,*]

[a] Instituto de Ecología, Universidad Nacional Autónoma de México, Ciudad Universitaria, D.F. CP04510, México
[b] Centro de Ciencias de la Complejidad, Universidad Nacional Autónoma de México, Ciudad Universitaria, D.F. CP04510, México
[c] Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, D.F. CP04510, México

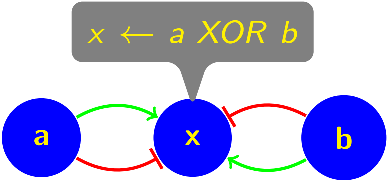
In the original version of SQUAD ...

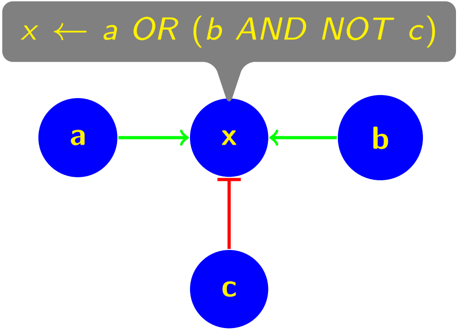


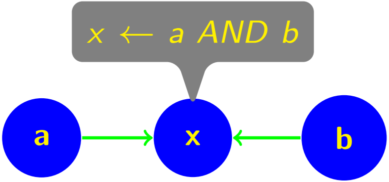




... this is not possible

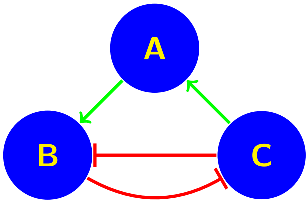






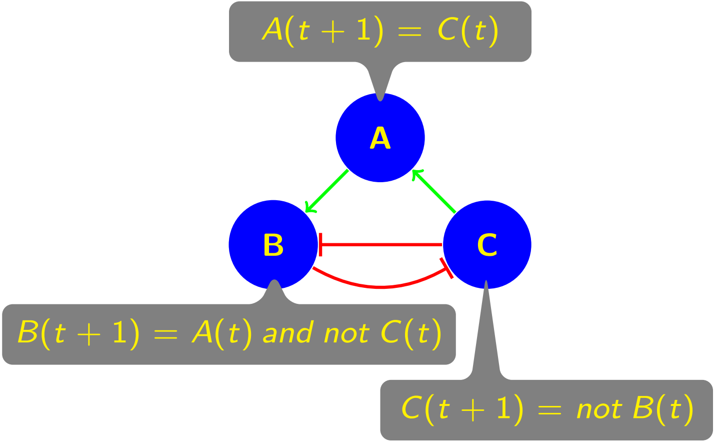
A Boolean Network

Its topology



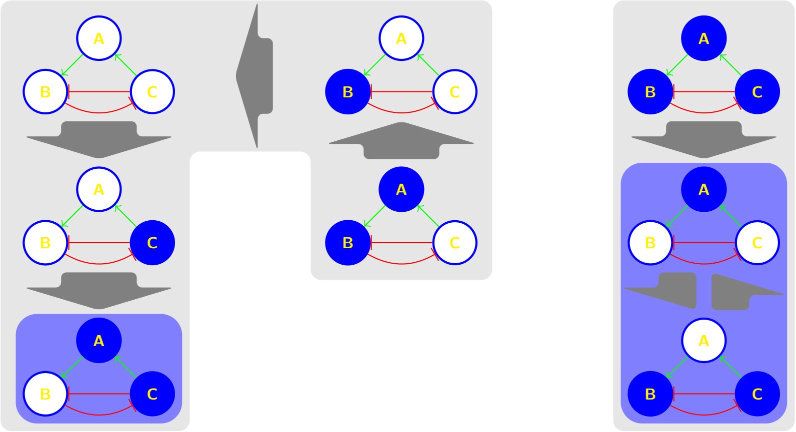
A Boolean Network

Its associated functions



A Boolean Network

Attractors and basins of attraction



The continuous equations

$$\frac{dx_i}{dt} = \frac{-e^{0.5h_i} + e^{-h_i(\omega_i - 0.5)}}{(1-e^{0.5h_i})(1+e^{-h_i(\omega_i-0.5)})} - \gamma_i x_i$$

x_i is the activation level of node *i*.
ω_i is the continuous form of the logical rule describing the response of the node.
h_i is the gain of the input.
γ_i is the decay rate.

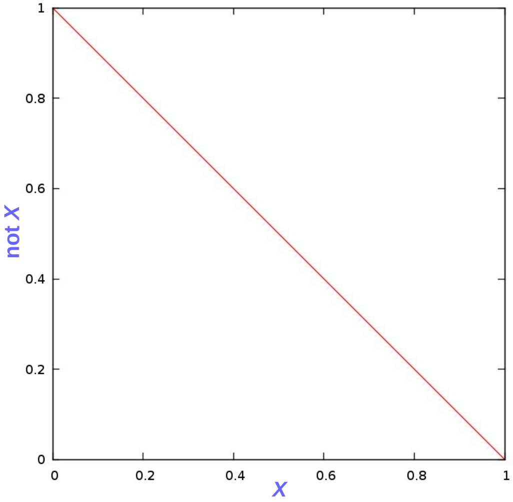
From classic to fuzzy logic

$$NOT\,x \rightarrow 1 - x$$

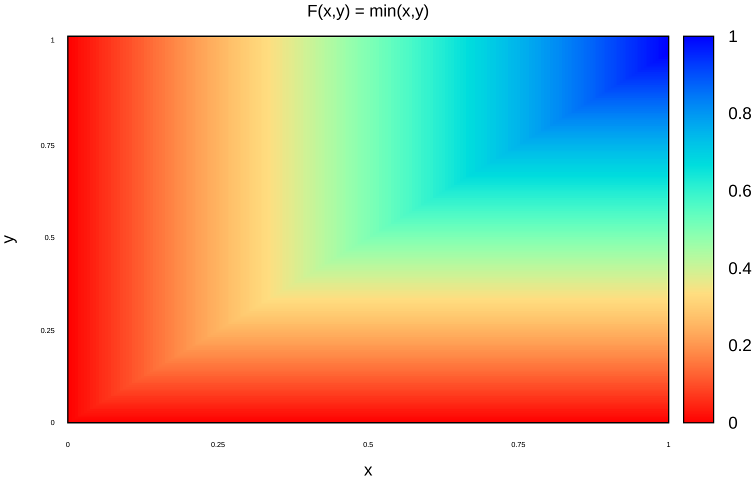
$$x\,AND\,y \rightarrow min(x, y)$$

$$x\,OR\,y \rightarrow max(x, y)$$

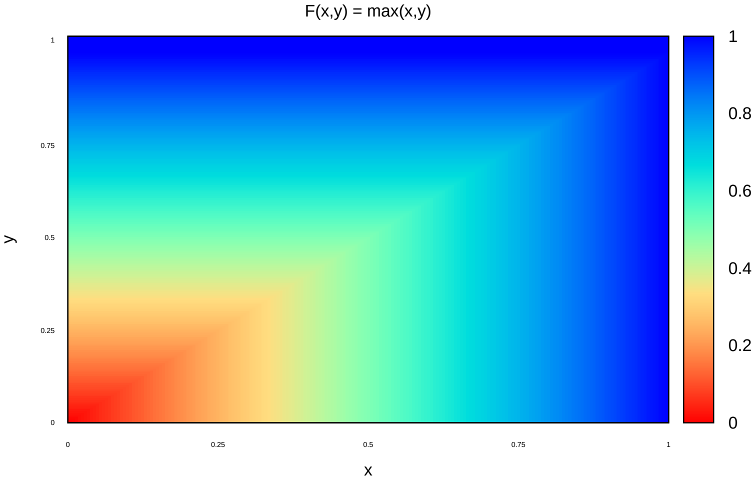
The fuzzy logic version of the NOT function



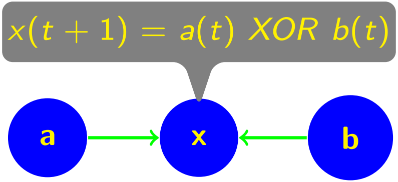
The fuzzy logic version of the AND function



The fuzzy logic version of the OR function



From a discrete to a continuous function



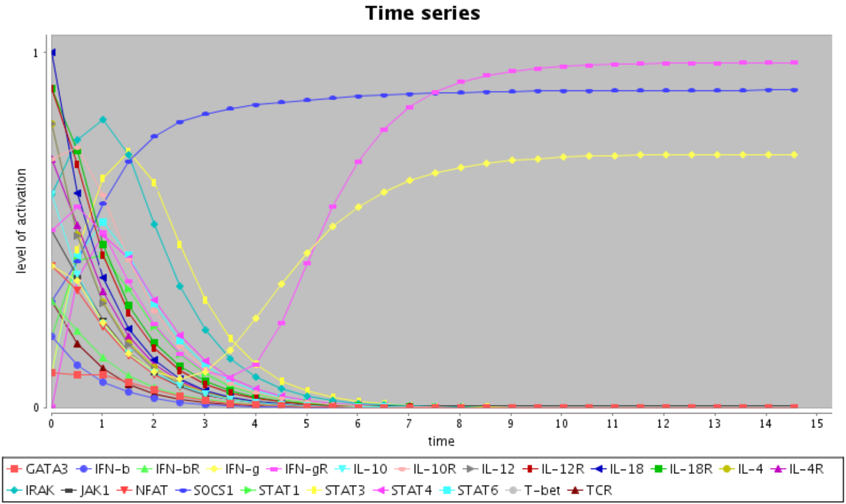
$$x \leftarrow a\, XOR\, b$$

$$x \leftarrow (a\, AND\, NOT\ b)\, OR\, (NOT\ a\, AND\, b)$$

$$x \leftarrow max(min(a, 1-b), min(1-a, b))$$

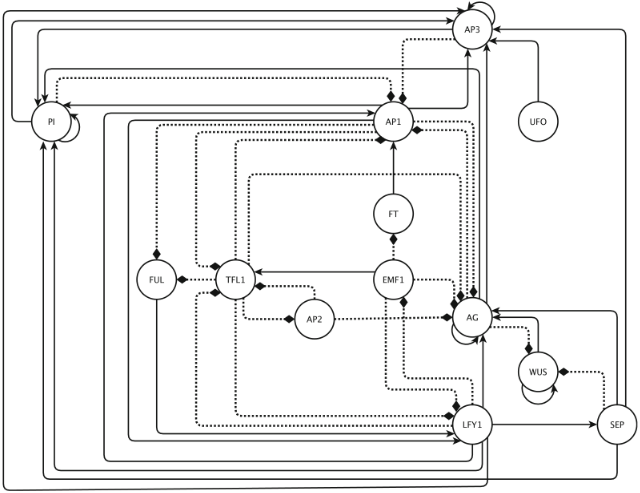
$$\frac{dx_i}{dt} = \frac{-e^{0.5h_i} + e^{-h_i(max(min(a,1-b),min(1-a,b))-0.5)}}{(1-e^{0.5h_i})(1+e^{-h_i(max(min(a,1-b),min(1-a,b))-0.5)})} - \gamma_i x_i$$

Finding attractors



Using SQUAD in Arabidopsis

Sánchez-Corrales *et al.* (2010). *J. Theor. Biol.* **264**: 971



Attractors of the discrete model

	INF1	INF2	INF3	INF4	SEP	PET1	PET2	STM1	STM2	CAR
AG	0	0	0	0	0	0	0	1	1	1
AP1	0	0	0	0	1	1	1	0	0	0
AP2	0	0	0	0	1	1	1	1	1	1
AP3	0	0	0	0	0	1	1	1	1	0
EMF1	1	1	1	1	0	0	0	0	0	0
FT	0	0	0	0	1	1	1	1	1	1
FUL	0	0	0	0	0	0	0	1	1	1
LFY	0	0	0	0	1	1	1	1	1	1
PI	0	0	0	0	0	1	1	1	1	1
SEP	0	0	0	0	1	1	1	1	1	1
TFL1	1	1	1	1	0	0	0	0	0	0
UFO	0	1	0	1	0	1	0	1	0	0
WUS	0	0	1	1	0	0	0	0	0	0

Attractors of the continuous model (part 1)

	INF1	INF2	INF3	INF4	SEP	PET1	PET2	STM1	STM2	CAR
AG	1.3E−9	1.3E−9	1.2E−9	1.2E−9	1.1E−9	1.1E−9	9.6E−10	1.0E+0	1.0E+0	1.0E+0
AP1	1.0E−9	1.0E−9	1.1E−9	1.1E−9	1.0E+0	1.0E+0	1.0E+0	3.1E−9	2.0E−9	3.4E−9
AP2	1.2E−9	1.2E−9	1.2E−9	1.2E−9	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0
AP3	1.2E−9	1.3E−9	1.1E−9	1.2E−9	9.5E−10	1.0E+0	1.0E+0	1.0E+0	1.0E+0	8.6E−10
EMF1	1.0E+0	1.0E+0	1.0E+0	1.0E+0	2.1E−9	2.0E−9	1.5E−9	1.3E−9	9.9E−10	1.4E−9
FT	1.1E−9	1.1E−9	1.1E−9	1.1E−9	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0
FUL	1.2E−9	1.2E−9	1.2E−9	1.2E−9	1.81E−9	1.8E−9	1.5E−9	1.0E+0	1.0E+0	1.0E+0
LFY	8.6E−10	8.7E−10	8.4E−10	8.3E−10	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0
PI	1.2E−9	1.2E−9	1.2E−9	1.2E−9	1.3E−9	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0
SEP	1.2E−9	1.2E−9	1.1E−9	1.0E−9	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0	1.0E+0
TFL1	1.0E+0	1.0E+0	1.0E+0	1.0E+0	9.4E−10	9.2E−10	7.8E−10	1.0E−9	1.0E−9	1.1E−9
UFO	5.4E−10	1.0E+0	5.2E−10	1.0E+0	5.2E−10	1.0E+0	5.2E−10	1.0E+0	5.3E−10	5.2E−10
WUS	5.8E−10	5.9E−10	1.0E+0	1.0E+0	5.5E−10	5.5E−10	5.5E−10	3.5E−9	2.2E−9	3.9E−9

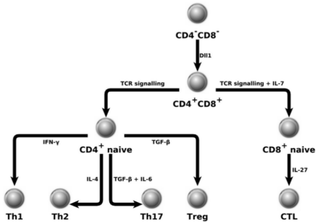
[a] Values are averages of 50,000 runs (see Section 4). In all cases the associated standard deviations are smaller than 1.00E−9.

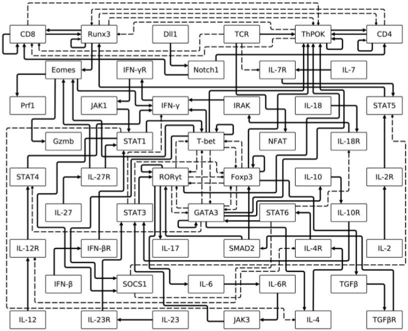
Attractors of the continuous model (part 2)

	NEW1	NEW2	NEW3	NEW4	NEW5	NEW6	NEW7	NEW8	NEW9	NEW10	NEW11	NEW12	NEW13	NEW14
AG	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0
AP1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0	1
AP2	0.5	0.5	0.5	0.5	1	0.5	1	1	0.5	1	1	1	1	1
AP3	0	0.5	0	0.5	0	0.5	1	0	0.5	1	0.5	0.5	0.5	0.5
EMF1	0.5	0.5	0.5	0.5	0	0.5	0	0	0.5	0	0	0	0	0
FT	0.5	0.5	0.5	0.5	1	0.5	1	1	0.5	1	1	1	1	1
FUL	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0
LFY	0.5	0.5	0.5	0.5	1	0.5	1	1	0.5	1	1	1	1	1
PI	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	1	0.5	0.5	1	0.5
SEP	0.5	0.5	0.5	0.5	1	0.5	1	1	0.5	1	1	1	1	1
TFL1	0.5	0.5	0.5	0.5	0	0.5	0	0	0.5	0	0	0	0	0
UFO	0	1	0	1	0	0	1	0	0	1	0	0	0	0
WUS	0	0	1	0.5	0	0	0	0.5	0.5	0.5	0	0.5	0	0

SQUAD in the modeling of T cells

Martínez-Sosa and Mendoza (2013). *BioSystems* **113**: 96





Conclusion

SQUAD:

- It is a flexible modeling tool.
- It has been extensive tested in systems with fixed point attractors.
- It still needs to be fine-tuned to study cyclic attractors.

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