

Mathematical modeling of cancer-related molecular mechanisms:

cell fate decisions, cancer biology, discrete modeling and BiNoM software

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Curie-Servier alliance on basal breast cancer

Cancer bioinformatics

Institut national de la santé et de la recherche médicale

Scientific coordinator of the Systems Biology team

Systems Biology of Cancer, Complexity and Model reduction



Plan of the presentation

- Recent developments using (BINOM)
 - NaviCell
 - Atlas of Cancer Signaling Networks
 - Creating CellDesigner files
- What can be done for cancer biology, using discrete modeling
 - Cell fate decision model
 - OCSANA (minimal cut sets)
 - Computing phenotype probabilities
 - Model reduction
 - Dosage response curves
 - Sensitivity analysis
 - MaBOSS: discrete states, continuous time

Biological Network Manager

Part of Curie platform for network systems biology of cancer

Java library + Cytoscape 2.* plugin



Manipulating standards (SBML, BioPAX, CellDesigner, and others)

- importing/exporting/creating
- conversion between formats
- BioPAX 3.0 editor
- merging/decomposing/transforming
- annotating

Network analysis (graph theory, semantics-based)

Analysis of data using biological networks

http://binom.curie.fr/

Bonnet E., Calzone L., Rovera D., Stoll G., Barillot E. and Zinovyev A..

BiNoM 2.0, a Cytoscape plugin for accessing and analyzing pathways using standard systems biology formats. 2013, BMC Systems Biology, 7:18.

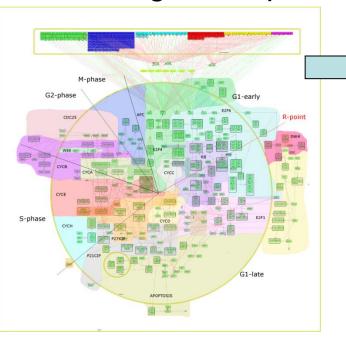
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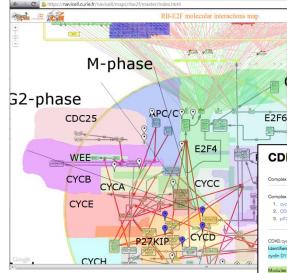
BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. 2008. Bioinformatics 24(6):876-877



factory tool

CellDesigner map





Google Maps+ WordPress blog

http://navicell.curie.fr



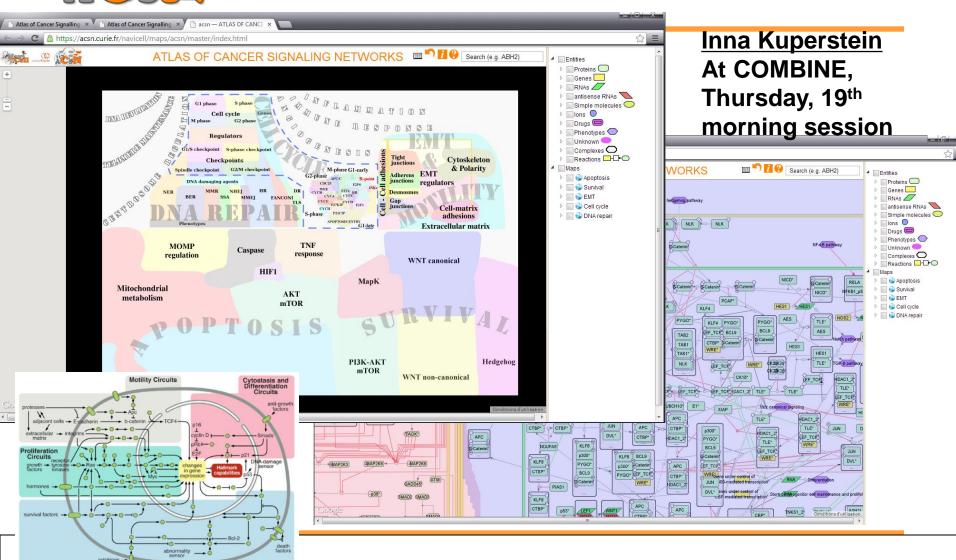


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 NPP-EPR-FANCH SINGE BUYGRH In \$100 finations ⊕ → ⊕ DPP-EPR-FAHDACH SINGE BUYGRH In \$100 find Sinders ⊕ DPH-EPR-IHADCH SINGEN pRB find Sinders ⊕ → ⊕ HDACH Gradeus ⊕ + DP EPR-IHADCH SINGEN pRB find plot for finations ⊕ DPP-EPR-FATOP finations ⊕ → DPP-EPR-FAT p107 finded finations ⊕ This entry was posted in complex by binom. Bookmark the permattink. Leave a Reply	MODULE:I Reference: Modification In compart 1. CDK 2. CDK Participate As Reactar 1. CDK p271 2. p271	ons: Participates in ment: nucleus B:cyclin D1*:p27/6/8 B[Thr_pho:cyclin D1 s in reactions: nt or Product: B:cyclin D1*:p27/6/8 ftp1*@nucleus @ 4p1*@nucleus @	complexes: p1*@nucleus © 1*:p27Kip1*@n p1*@nucleus ©	ucleus ©) → © CDK6[1		
SNBBS.N98Ht p1010/bc8hudas @ 2. DP1-ESP14ACS19MSNP-SPB/bc8hudas @ — @ HDAC1Gnudes @ + DE ESP1.9MSNP-pRPjr-bolhodinudes @ 3. DP2-ESF4.p107-Gnudes @ — @ DP2-ESF4.p107-jbc6hudas @ This entry was posted in complex by bhom. Bookmark the permatikik. Leave a Reply	MODULE:I Reference: Modification In compart 1. CDK 2. CDK Participate As Reactar 1. CDK p271 2. p271	ons: Participates in ment: nucleus B:cyclin D1*:p27/6/8 B[Thr_pho:cyclin D1 s in reactions: nt or Product: B:cyclin D1*:p27/6/8 ftp1*@nucleus @ 4p1*@nucleus @	complexes: p1*@nucleus © 1*:p27Kip1*@n p1*@nucleus ©	ucleus ©) → © CDK6[1		
2. DPI+ESPI+BAC1:SMSNP-PRBI]holdmucles @ → @ HDAC1@nucleus @ + DF ESPI:SMSNP-pRBI]holphore@nucleus @ @ B DPI+ESPI+pt (D7*Bnucleus @ W B DPI+ESPI+pt (D7*Bnucleus & W B DPI+ESPI+PT (D7*Bn	MODULE: Reference: Modification in compart 1. CDK 2. CDK Participate As Reactar 1. CDK p27i 2. p27i 2. p27i	sines: Participates in ment: nucleus B:cyclin D1*:p27kg B[[hr.pho:cyclin D1 s in reactions: nt or Product: B:cyclin D1*:p27kg kip1*@nucleus @ kp1*@nucleus @	complexes: p1*@nucleus © 1*:p27Kip1*@n p1*@nucleus ©	ucleus ©) → © CDK6[1		
2. DPH-ESPH-BACH SMRNP - pRB*jhol@nucleus @ → @ HDACH@nucleus @ + DF ESPH-SMRNN*-pBR*jholphol@nucleus @ 3. DPH-ESPH-pt-07*@nucleus @ - DPH-ESPH-pt-07*jhol@nucleus @ This entry was posted in complex by binom. Bookmark the permatick. Leave a Reply	MODULE: Reference: Modification in compart 1. CDK 2. CDK Participate As Reactar 1. CDK p271 2. p271 p271 As Catalys	s participates in ment: nucleus Bioyalin D1*:p27kg BE[Thr_pho:oyalin D1 si reactions: the revolution of the revolution o	complexes: p1*@nucleus © 1*;p27Kp1*@n p1*@nucleus © CDK6:cyclin D	udeus © → © CDK6[] 1*@nudeus ©	→ © CDK6	oyolin D1*:
DP2*E2F4:p107*@rudeus ♥ → ♥ DP2* E2F4:p107*[sho@rudeus ♥ This entry was posted in complex by binom. Bookmark the permatinik. Leave a Reply	MODULE:f Reference: Modificatic In compart 1. CDK 2. CDK Participate As Reactar 1. CDK p27i 2. p27i p27i As Catalys 1. DP2	sines: Participates in ment: nucleus 8:cyclin D1*:p276g 8:cyclin D1*:p276g 8:tyclin D1*:p276g 8:tyclin D1*:p276g 6p1*@nucleus @ 4p1*@nucleus	complexes: p1*@nucleus @ 1*:p27Kp1*@n p1*@nucleus @ CDK8:oydin D	udeus © → © CDK6[] 1*@nucleus ©	→ © CDK6	oyolin D1*:
DP2*E2F4:p107*@rudeus ♥ → ♥ DP2* E2F4:p107*[sho@rudeus ♥ This entry was posted in complex by binom. Bookmark the permatinik. Leave a Reply	MODULE: Reference Modificatic In compart 1. CDK 2. CDK Participate As Reacta 1. CDK p27/1 2. p27/1 2. p27/1 As Catalys 1. DP2 SIN3	ons: Participates in ment rudeus Bioydin D11:p27Kg Bioydin D11:p27Kg Bioydin D11:p27Kg Biother	complexes: p1*@nucleus @ 1*:p27Kp1*@n p1*@nucleus @ CDK8:cyclin D	udeus © → © CDK6[1 1*@nucleus © 0130*@nucleu	→ © CDK6	:oyolin D1*: *2*:E2F4:HDAC1:
Leave a Reply	MODULE: References Modification In compart 1. CDK 2. CDK Participate As Reactar 1. CDK p271 2. p271 As Catalys 1. DP3 2. DP1	ons: Participates in ment: ruufeus Bicyclin D1*:p27Kg BlThr_pho:oyclin D1 s in reactions: nt or Product: Bicyclin D1*:p27Kg Kgp1*@nucleus © 4 fgp1*@nucleus © 4 fgp1*@nucleus © 4 fgp1*@nucleus © 4 fgp1*@nucleus © 5 fg1*@nucleus © 6 fg1*@nucleus	complexes: p1*@nucleus @ 1*:p27Kp1*@n p1*@nucleus @ CDK8:cyclin D	udeus © → © CDK6[1 11*@nucleus © 1130*@nucleus 1100*@nucleus	→ © CDK6	:oyolin D1*: *2*:E2F4:HDAC1:
· ·	MODULE: References Modification In compart 1. CDK 2. CDK Participate As Reactar 1. CDK p271 2. p271 p271 As Catalys 1. DP2 SIN3 2. DP11 E2F:	ons: Participates in ment: nucleus inment: nucleus inment: nucleus illusional in 11-12-1746 illusional illusiona illus	complexes: p1*@nucleus @ i*:p27Kp1*@n p1*@nucleus @ .*CDK8:cydin D .*GDK8:cydin D	udeus ♥ → ♥ CDK6[1 1*@nudeus ♥ p130*@nudeus wo@nudeus ♥ s ♥	D → © CDK6 D → © DF D → © HDAC1	:oydin D1*: *2*:E2F4:HDAC1: 1@nucleus • + DP
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You must be looped in to post a comment.	MODULE: References Modification of the compart of	ons: Participates in ment includes all size of the Transport of the Transp	complexes: p1*@nucleus @ p1*@n	udeus ©	D → © CDK6 S © → © DF → © HDAC1 7* pho@nucle	:oydin D1*: *2*:E2F4:HDAC1: 1@nucleus • + DP
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P21CIP



Atlas of Cancer Signaling Networks

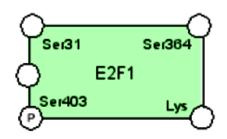


http://acsn.curie.fr

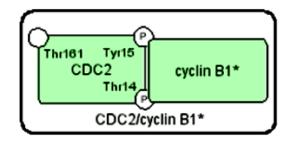
Viability Circuits

Naming conventions in BiNoM

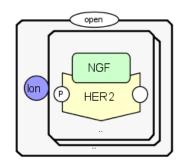
Entity1_name|Modification1|Modification2|...: Entity2_name|Modifications...[_active|_hmN]@compartment







CDC2|Tyr15_pho|Thr14_pho:cyclinB1*@cytoplasm



(Ion:(HER2|pho|:NGF)|hm2)|open@plasma_membrane

Creating CellDesigner files from simple textual description (BiNoM reaction format)

Reactions Regulators CATALYSIS STATE_TRANSITION UNKNOWN_CATALYSIS --> KNOWN_TRANSITION_OMMITED -| INHIBITION -?> UNNKNOWN_TRANSITION -.| UNKNOWN_INHIBITION -+> POSITIVE_INFLUENCE -* MODULATION -|> NEGATIVE_INFLUENCE -) PHYSICAL_STIMULATION -/> TRANSPORT **Entities** TRANSCRIPTION TRANSLATION gMDM2 gene of MDM2 HETERODIMER ASSOCIATION rTP53 RNA of TP53 -=> DISSOCIATION arMIR200 antisense RNA of MIR200

P14ARF+Mdm2 -:> Mdm2:P14ARF rP14ARF - > P14ARF gCDKN2A@nucleus-E2F1|Ser31_pho|Ser20_pho|ace -.. > rP14ARF gMIR34A@nucleus-P53|Ser15_pho|Ser20_pho|ace|active-..>arMIR34A E2F1|Ser31 pho|Ser20 pho|ace-P14ARF-|Mdm2->null Mdm2|pho->null

rCHK1/2-.>CHK1/2

gCHK1/2@nucleus-E2F1|Ser31_pho|Ser20_pho|ace-..>rCHK1/2

rATM-.>ATM

gATM@nucleus-E2F1|Ser31 pho|Ser20 pho|ace-..>rATM

DNA_damage-?>PCAF

P53-.|E2F1|Ser31_pho|Ser20_pho|ace-Mdm2 -> P53|ubi|active

CHK1/2 -ATM -> CHK1/2|pho|active

rP53 -. > P53

gP53@nucleus -..> rP53

P53|ubi|active -> null

rMdm2 -. > Mdm2

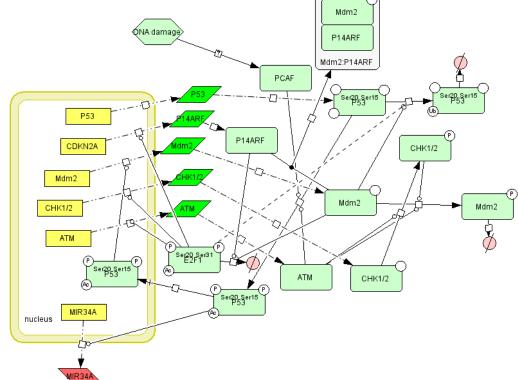
gMdm2@nucleus -P53|Ser15_pho|Ser20_pho|ace|active@nucleus -..> rMdm2

P53|Ser15_pho|Ser20_pho|ace|active -/>

P53|Ser15 pho|Ser20 pho|ace|active@nucleus

P53 -PCAF -ATM -> P53|Ser15_pho|Ser20_pho|ace|active

Mdm2-CHK1/2|pho|active-ATM -> Mdm2|pho



Cell fate decisions in cell death machinery

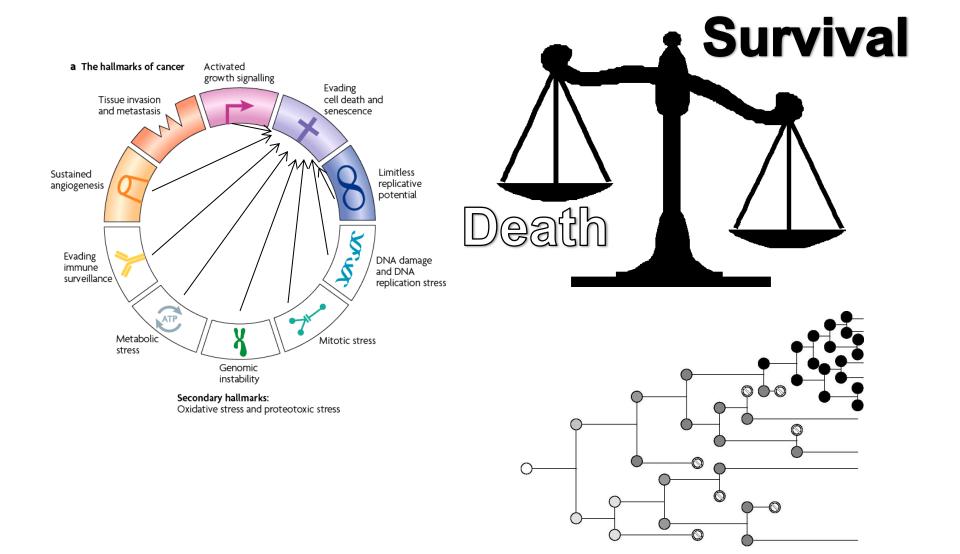
Illustrating discrete modeling toolbox



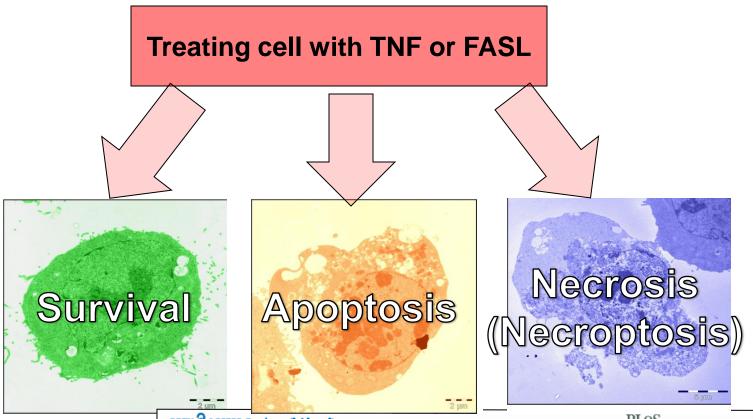




Cell life/death decisions in cancer



"Nature integrates empirically": Apoptosis vs Necrosis vs Survival





PLOS COMPUTATIONAL BIOLOGY

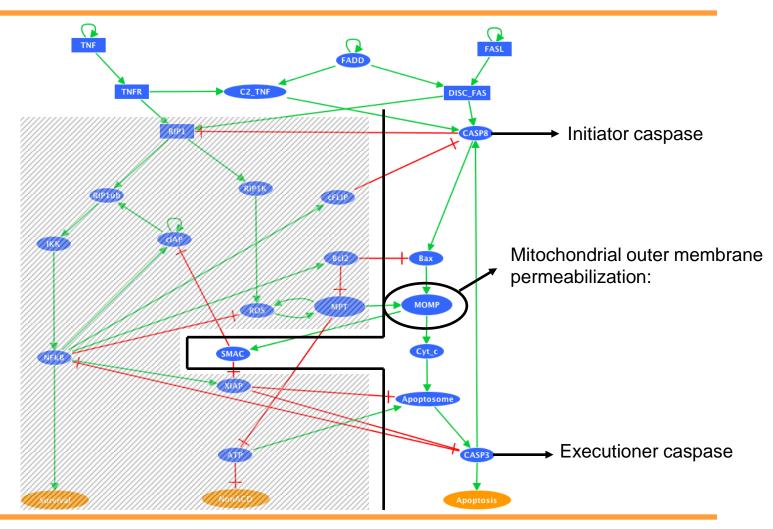
Mathematical Modelling of Cell-Fate Decision in Response to Death Receptor Engagement

Laurence Calzone^{1,2,3*}, Laurent Tournier^{1,2,3}, Simon Fourquet^{1,2,3}, Denis Thieffry^{4,5}, Boris Zhivotovsky⁶, Emmanuel Barillot^{1,2,3†}, Andrei Zinovyev^{1,2,3†}

1 Institut Curie, Paris, France, 2 Ecole des Mines ParisTech, Paris, France, 3 INSERM U900, Paris, France, 4 TAGC – INSERM U928 & Université de la Méditerranée, Marseille, France, 5 CONTRAINTES Project, INRIA Paris-Rocquencourt, France, 6 Karolinska Institutet, Stockholm, Sweden



APOPTOSIS

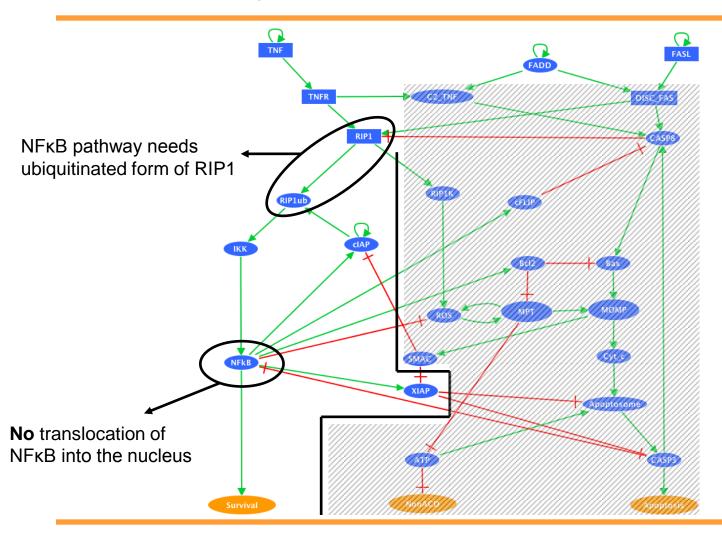








NFkB pathway

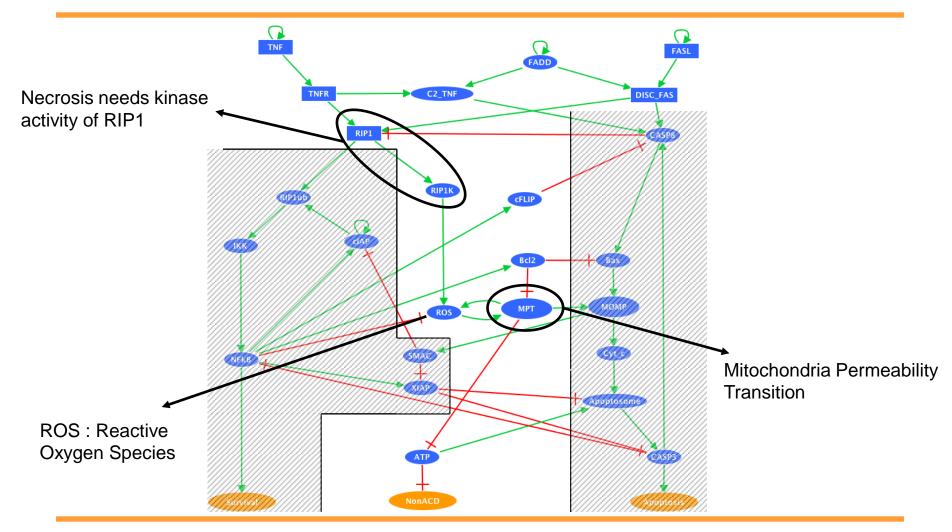








NECROSIS

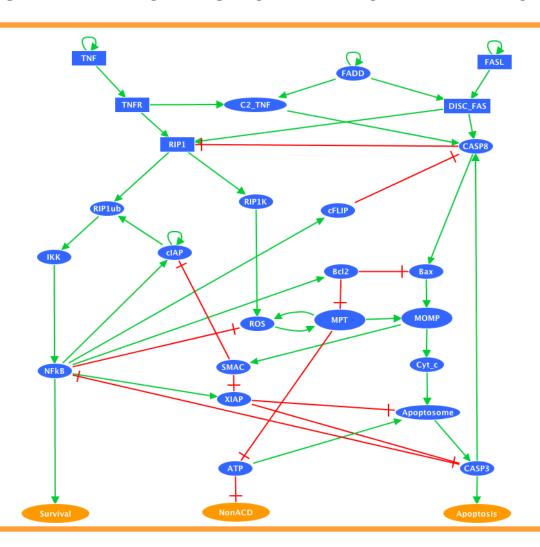








ASSEMBLED MECHANISM OF THREE CELL FATE DECISION

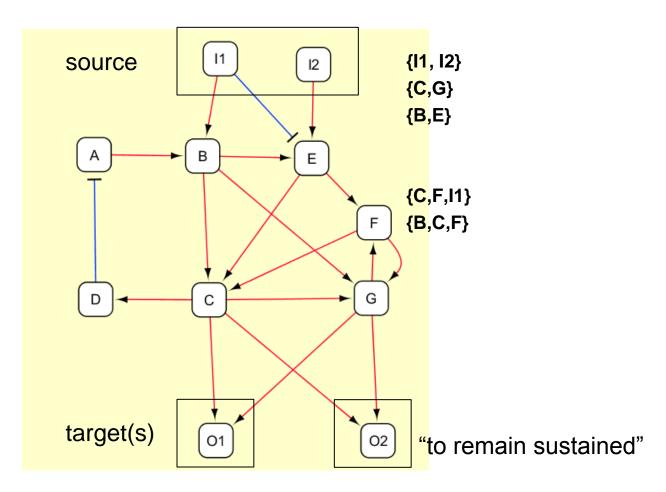








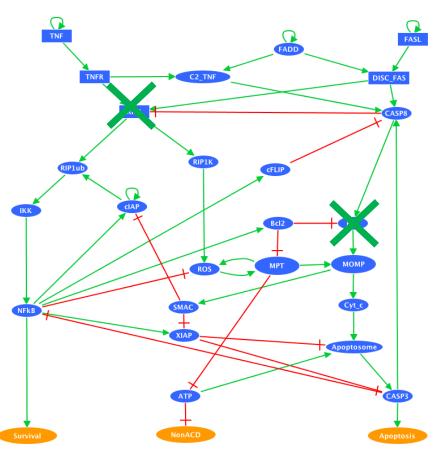
OCSANA: solving the minimal cut set problem



Vera-Licona, P., et al. OCSANA: optimal combinations of interventions from network analysis. (2013). *Bioinformatics* **15**:29(12).

http://bioinfo-out.curie.fr/projects/ocsana

Cell fate decision in cancer (survival vs apoptosis/necrosis)



Problem #1 (how): (cancer treatment strategy)

Minimal intervention disabling

survival with least effect on

surviv	'AL W	ith ic	12C	ΔΪΤΔΛ	t on		
cell de	Path	Number of Elementary Paths Nodes	Number and Sizes of CIs	Smallest CIs	Highest Scored CIs (according to OCSANA's score)	Top 5 Most Frequently Press Nodes in all IS and Number o Occurrences	
Probl (canc		6 elementary paths 20 elementary nodes	Total 130 CIs: 9 CIs of size 2 92 CIs of size 3 24 CIs of size 4	[CASP ₃ , ATP] [CASP ₃ , MPT] [CASP ₃ , ROS] [CASP ₃ , RIP ₁ K]	[CASP3, ATP]	ROS RIPiK MPT ATP	30 29 26 29 29
Minim cell de surviv	optimal Shortest Paths	14 elementary paths 22 elementary nodes	Total 140 CIs: 10 CIs of size 2 59 CIs of size 3 69 CIs of size 4 2 CIs of size 5	[CASP ₃ , ATP] [CASP ₃ , RIP ₁] [CASP ₈ , RIP ₁] [BAX, RIP ₁]	[CASP8, ATP, RIPrub]	ROS XIAP NFkB IKK RIPrub	38 35 34 34 34
nserm	All Non Self- intersecting Paths	124 elementary paths 24 elementary nodes	Total 134 CIs: 9 CIs of size 2 53 CIs of size 3 68 CIs of size 4	[CASP ₃ , ATP] [CASP ₃ , MPT] [MOMP, RIPt] [CASP ₈ , RIPt]	[ATP, NFkB, MOMP]	ROS XIAP NFkB IKK	38 37 33

4 CIs of size 6





Boolean modeling

C2 TNF

Assign logic to nodes

Example of CASP8

CASP8 = 0 when

DISC-Fas=0 and DISC-TNF=0 and CASP3=0 (equivalent to no external signals from death receptors

and no intracellular problems)

cFLIP=1

(equivalent to inhibition by the NFkB pathway)

CASP8 = 1 when

DISC-Fas=1 or/and DISC-TNF=1

(equivalent to signal from death receptors)

CASP3=1

(amplification signal, feedback activation)

AND no cFLIP



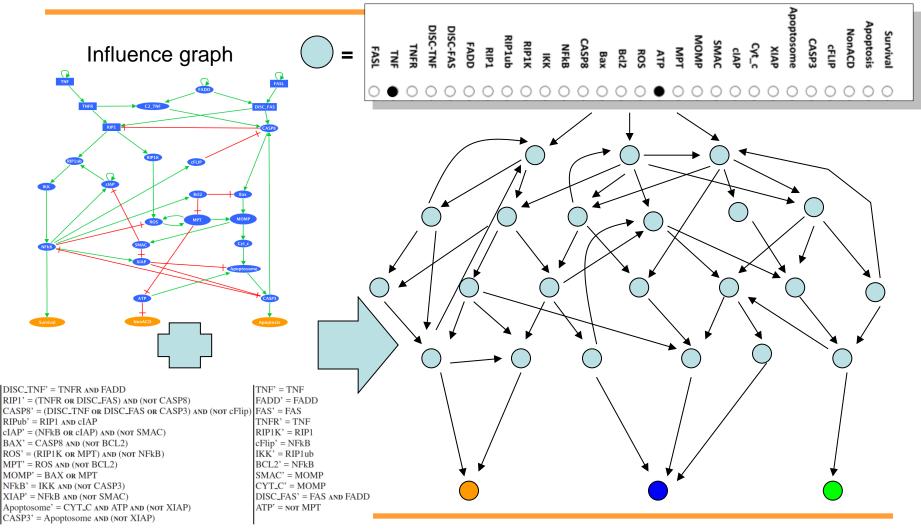




DISC FAS

CASP

Asynchronous state transition graph

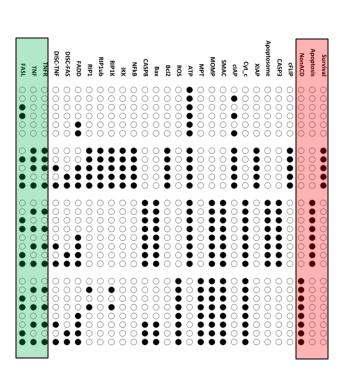


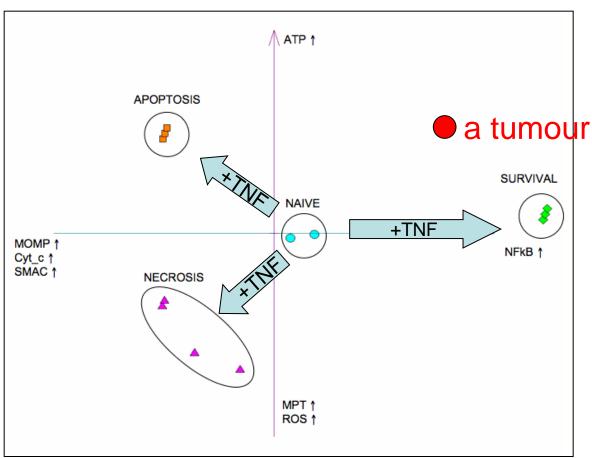






Structure of attractors: distribution of logical stable states



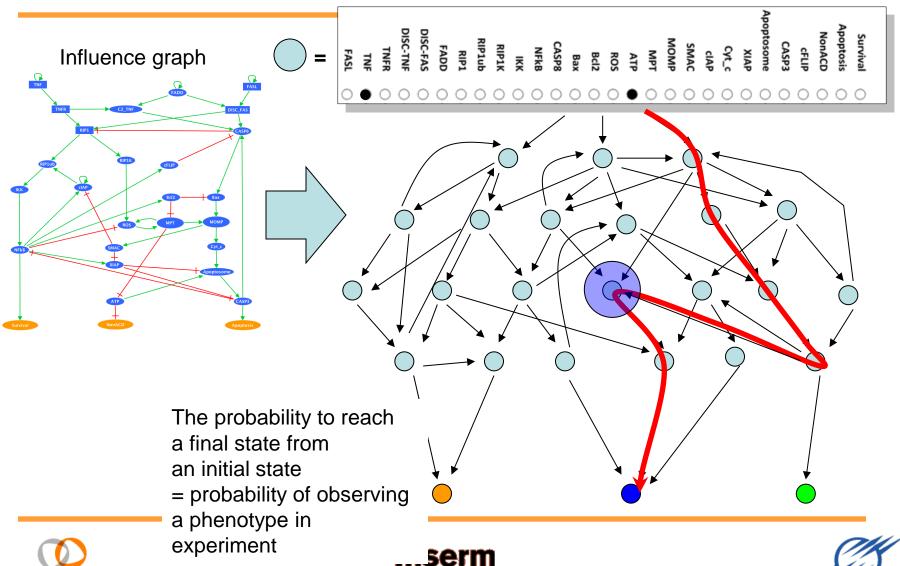








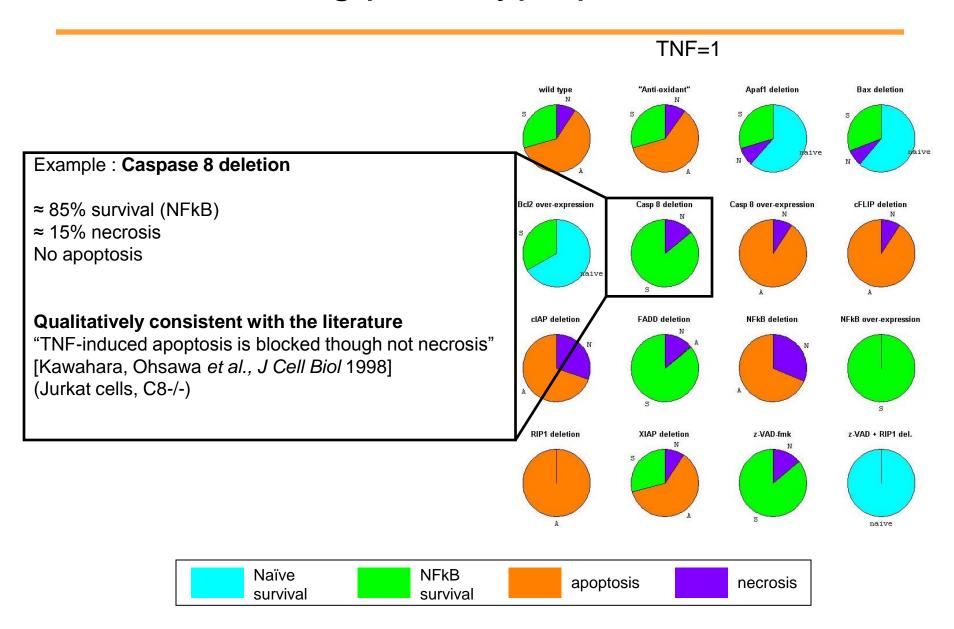
Asynchronous state transition graph



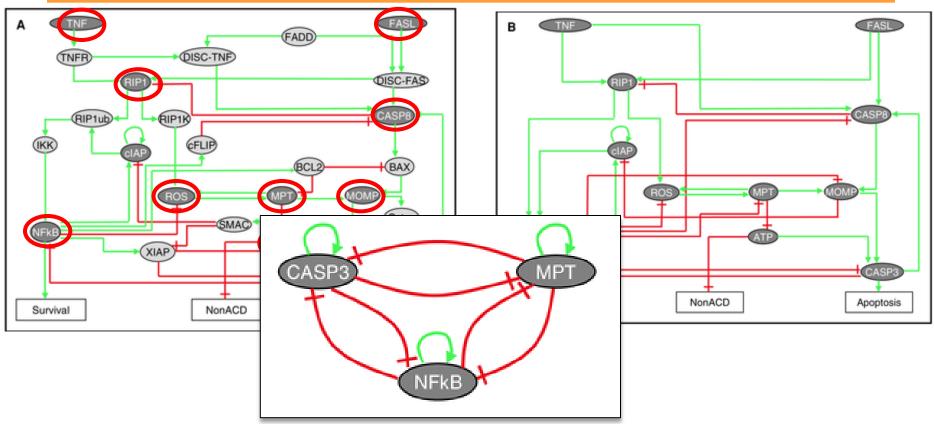




Predicting phenotype probabilities



Model reduction of logical models



Naldi A, Remy E, Thieffry D, Chaouiya C. A reduction of logical regulatory graphs preserving essential dynamical properties. *Computational Methods in Systems Biology, Lect. Notes in Bioinformatics* 5688:266-80, 2009.







"Ligand dosage" experiments

What if the signal was removed...

at which point would the cell commit to one or the other phenotype?

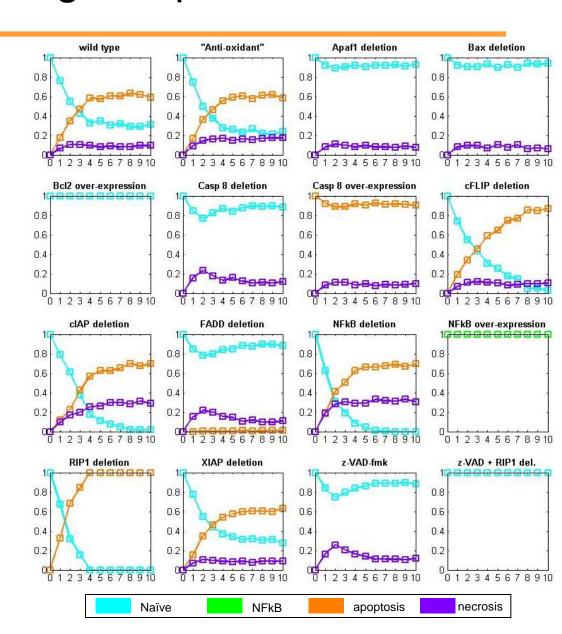
Introduction of "pulse" of TNF instead of constant induction

t: integer

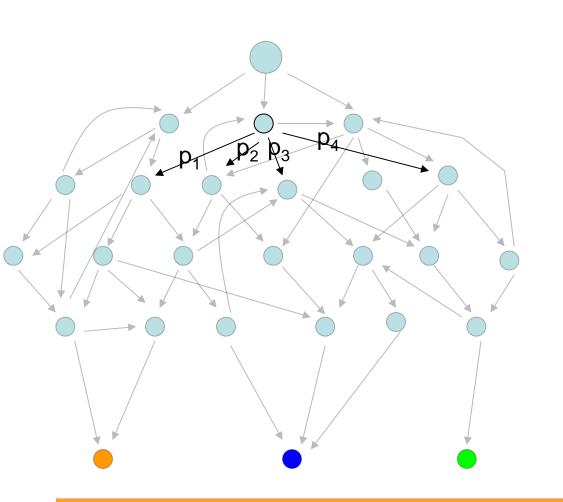
During *t* steps, the system evolves with TNF=1

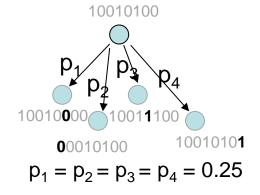
At step *t*+1, TNF is switched to 0 (until the end)

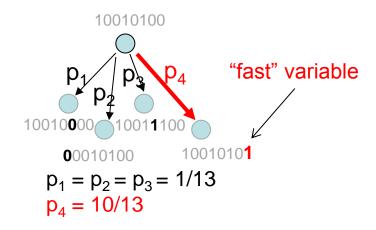
(x-axis → duration of TNF "pulse")



Sensitivity analysis: testing "rates" of variables





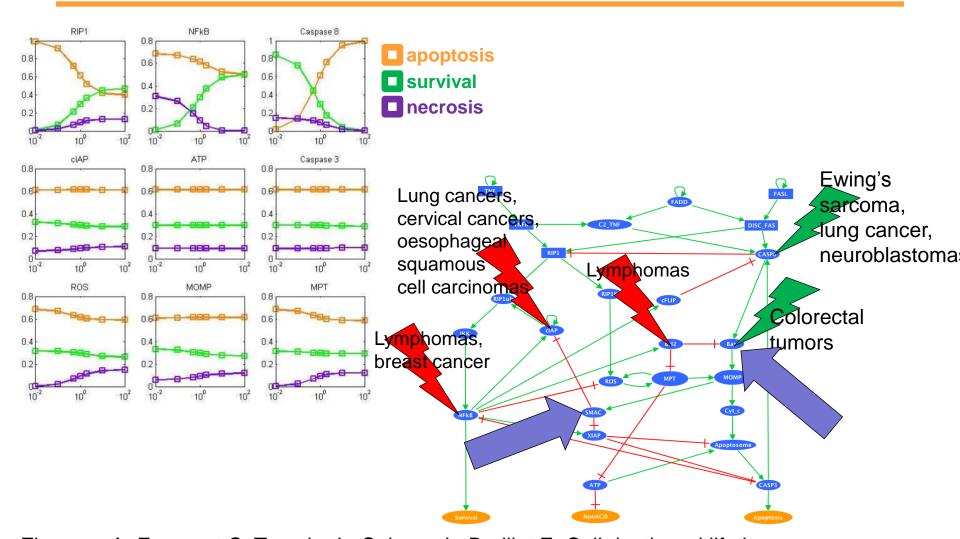






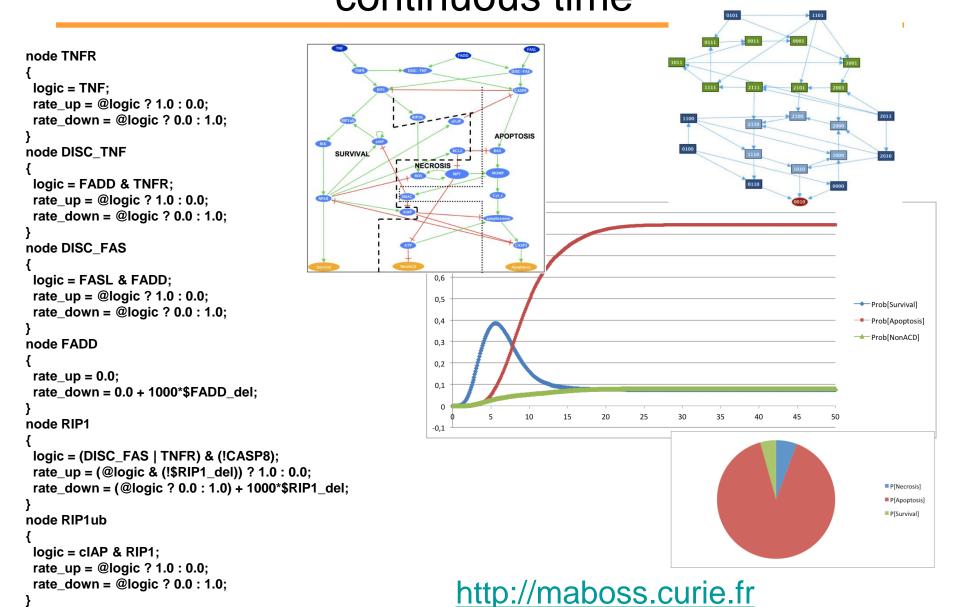


"Sensitivity" analysis: testing the effect of "rates" of variables



Zinovyev A, Fourquet S, Tournier L, Calzone L, Barillot E. Cell death and life in cancer: mathematical modeling of cell fate decisions. *Adv Exp Med Biol.* 2012;736:261-74.

MaBOSS: introducing rates and continuous time



Acknowledgements

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Stuart Pook







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