Mathematical modeling of cancer-related molecular mechanisms:

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

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Emmanuel Barillot, PhD
Director of the U900 Institut Curie/INSERM/Ecole de Mines ParisTech
Data integration, Systems Biology of Cancer, Dynamics of network motifs

Laurence Calzone, PhD
INVADE and PIC SysBio projects
Mathematical modeling of cell signalling in cancer

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Atlas of Cancer Cell Signalling
Network building and analysis

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ACSN, INVADE and PIC SysBio projects
Systems biology of cancer

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BiNoM project
Integrative computational biology

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Cancer bioinformatics

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Next-generation sequencing
Genome sequence analysis

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Retinoblastoma project
Cancer bioinformatics

Luca [illegible], PhD
ACSN project, meta-analysis of cancer omics data
Modelling and data analysis for signalling networks

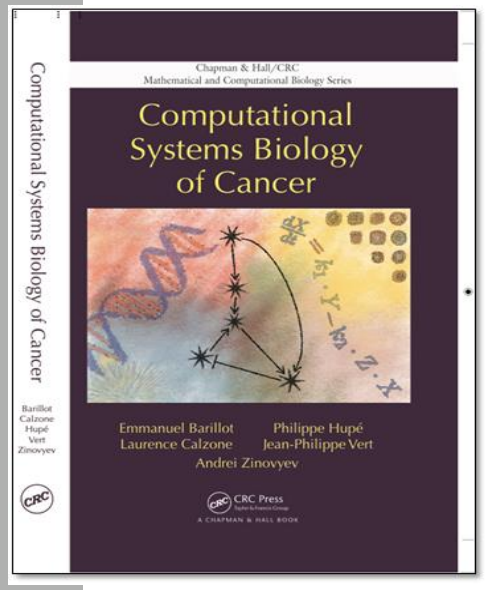
Antonio Coppuccio, PhD
'Brain in TSLP' project
Systems Immunology

Paola Vera-Licona, PhD
Curie-Servier alliance on basal breast cancer
Mathematical modeling of biological networks

Daniel Rovera, volunteer
BiNoM project
Methods for network analysis

Andrei Zinovyev, PhD
Scientific coordinator of the Systems Biology team
Systems Biology of Cancer, Complexity and Model reduction

Hiring post-docs and PhD data analysis mathematical modeling for cancer biology



http://www.cancer-systems-biology.net/

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Plan of the presentation

- Recent developments using (BiNoM)^n
  - 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)

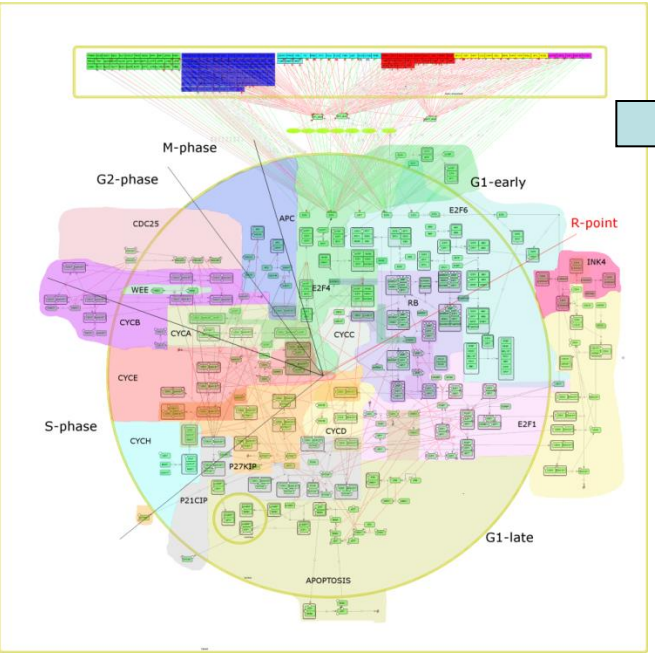
Analysis of data using biological networks

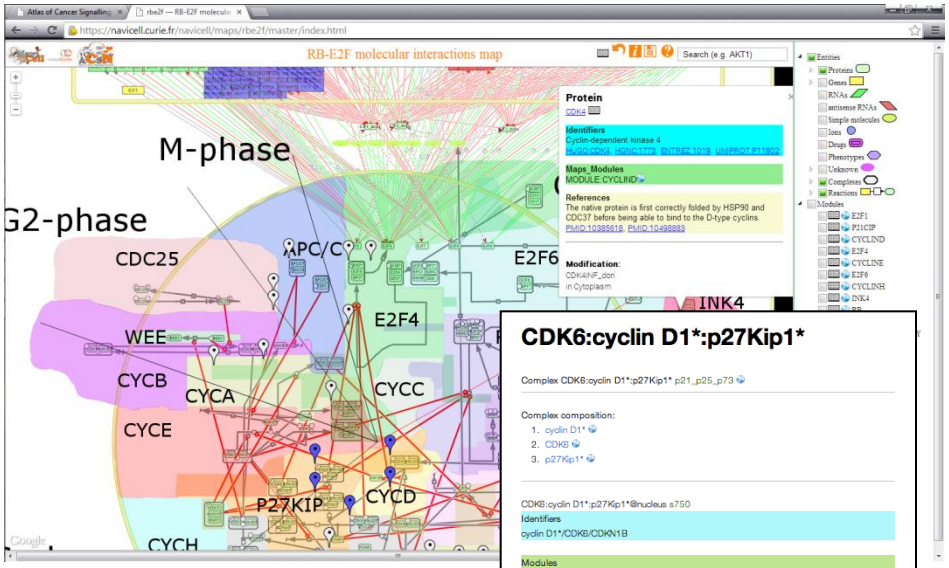
http://binom.curie.fr/

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.
Zinovyev A., Viara E., Calzone L., Barillot E.
BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. 2008. *Bioinformatics* **24**(6):876-877

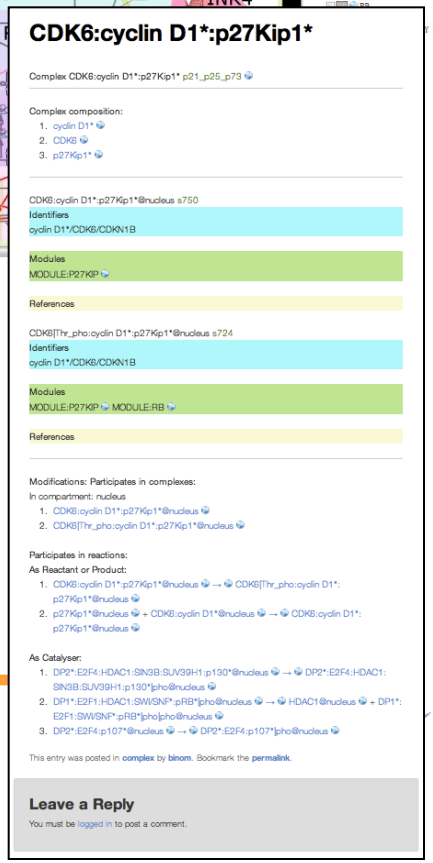
NaviCell factory tool

CellDesigner map





Google Maps+
WordPress blog



http://navicell.curie.fr

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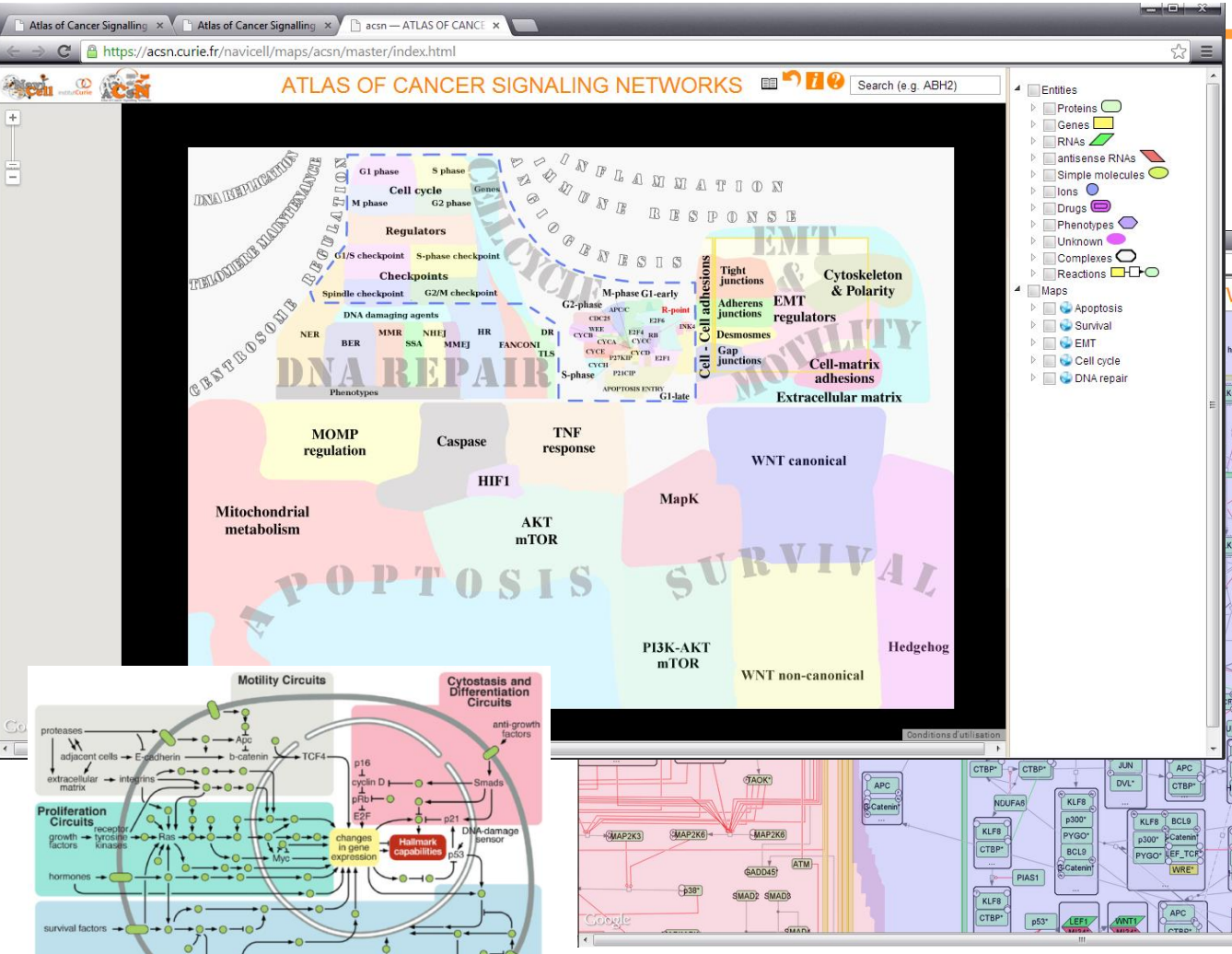
Atlas of Cancer Signaling Networks



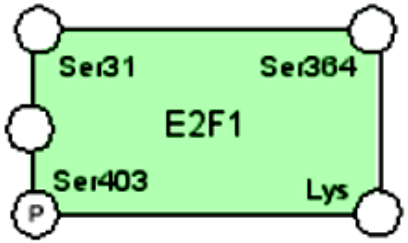
Inna Kuperstein

At COMBINE, Thursday, 19th morning session

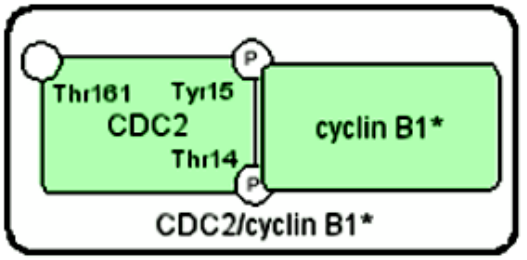
http://acsn.curie.fr

Naming conventions in BiNoM

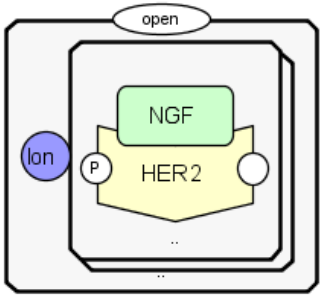
Entity1_name|Modification1|Modification2|…: Entity2_name|Modifications...[_active|_hmN]@compartment



E2F1|Ser403_pho@nucleus



CDC2|Tyr15_pho|Thr14_pho:cyclinB1*@cytoplasm



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

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

Reactions

- -> STATE_TRANSITION
- --> KNOWN_TRANSITION_OMMITED
- -?> UNNKNOWN_TRANSITION
- -+> POSITIVE_INFLUENCE
- -|> NEGATIVE_INFLUENCE
- -/> TRANSPORT
- -..> TRANSCRIPTION
- -.> TRANSLATION
- -:> HETERODIMER_ASSOCIATION
- -=> DISSOCIATION

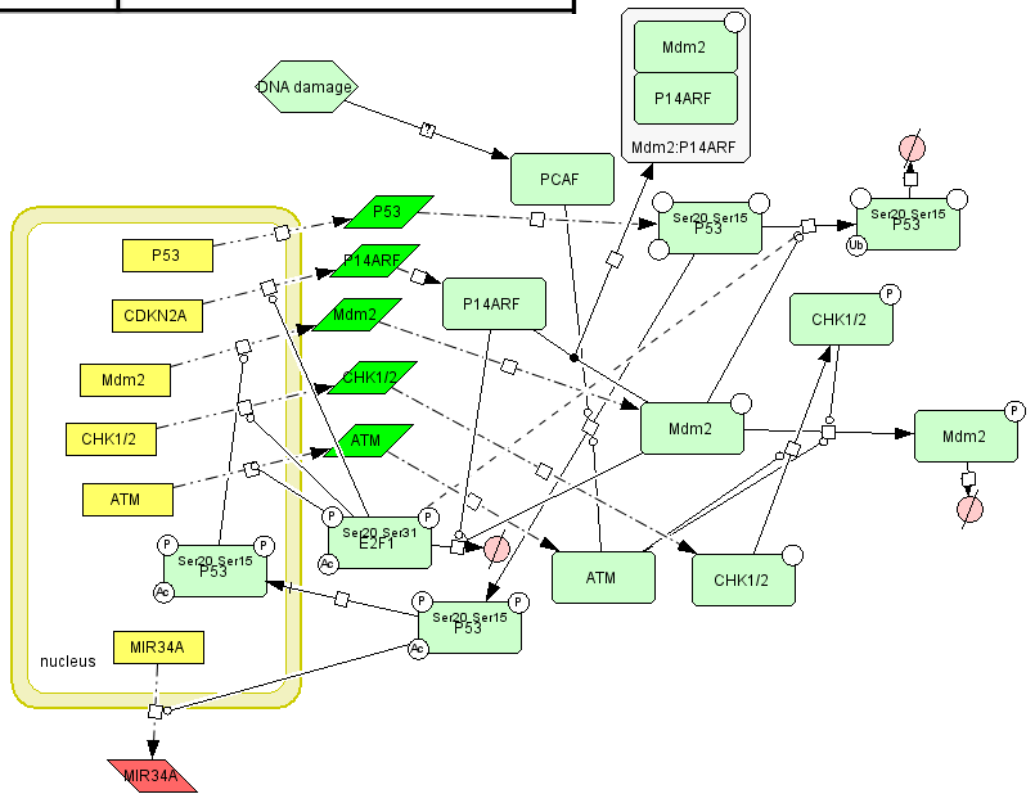
Regulators

- - CATALYSIS
- -. UNKNOWN_CATALYSIS
- -| INHIBITION
- -.| UNKNOWN_INHIBITION
- -* MODULATION
- -) PHYSICAL_STIMULATION

Entities

gMDM2 gene of MDM2
rTP53 RNA of TP53
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

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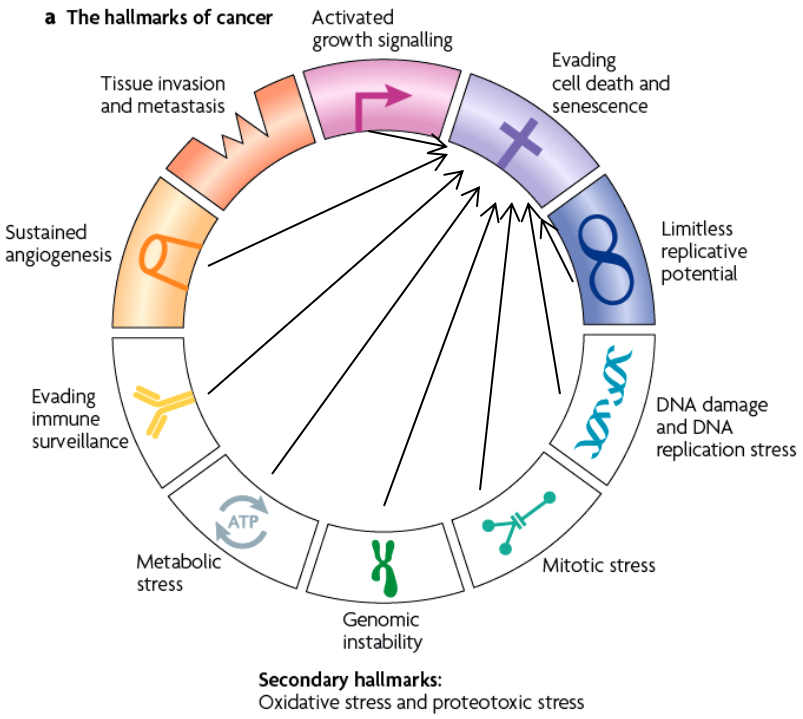
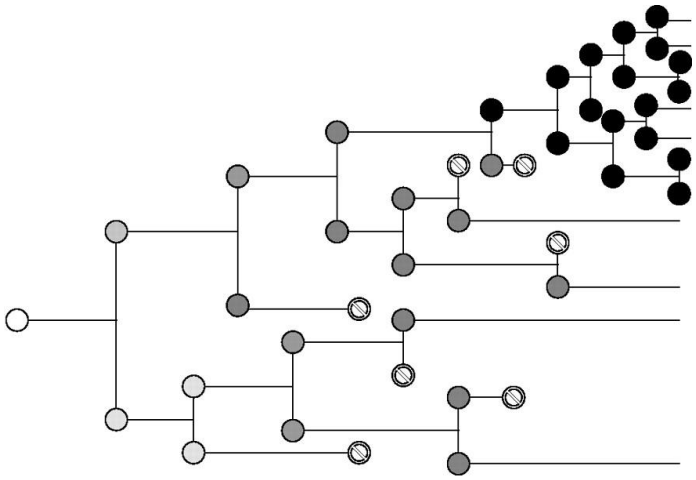
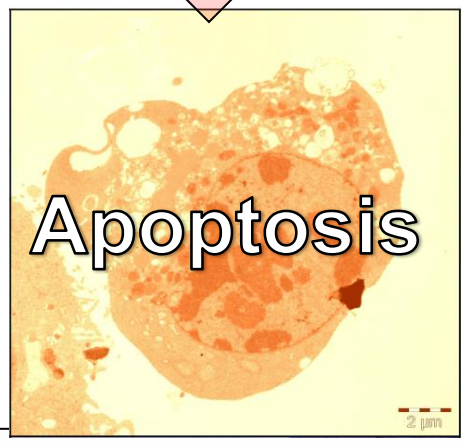
Cell life/death decisions in cancer

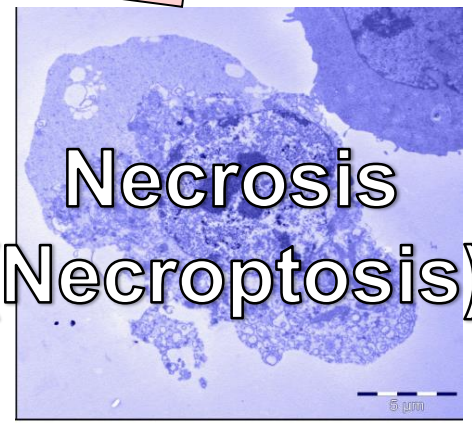




“Nature integrates empirically”: Apoptosis vs Necrosis vs Survival

Treating cell with TNF or FASL





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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 Zhivotovsky[6], 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

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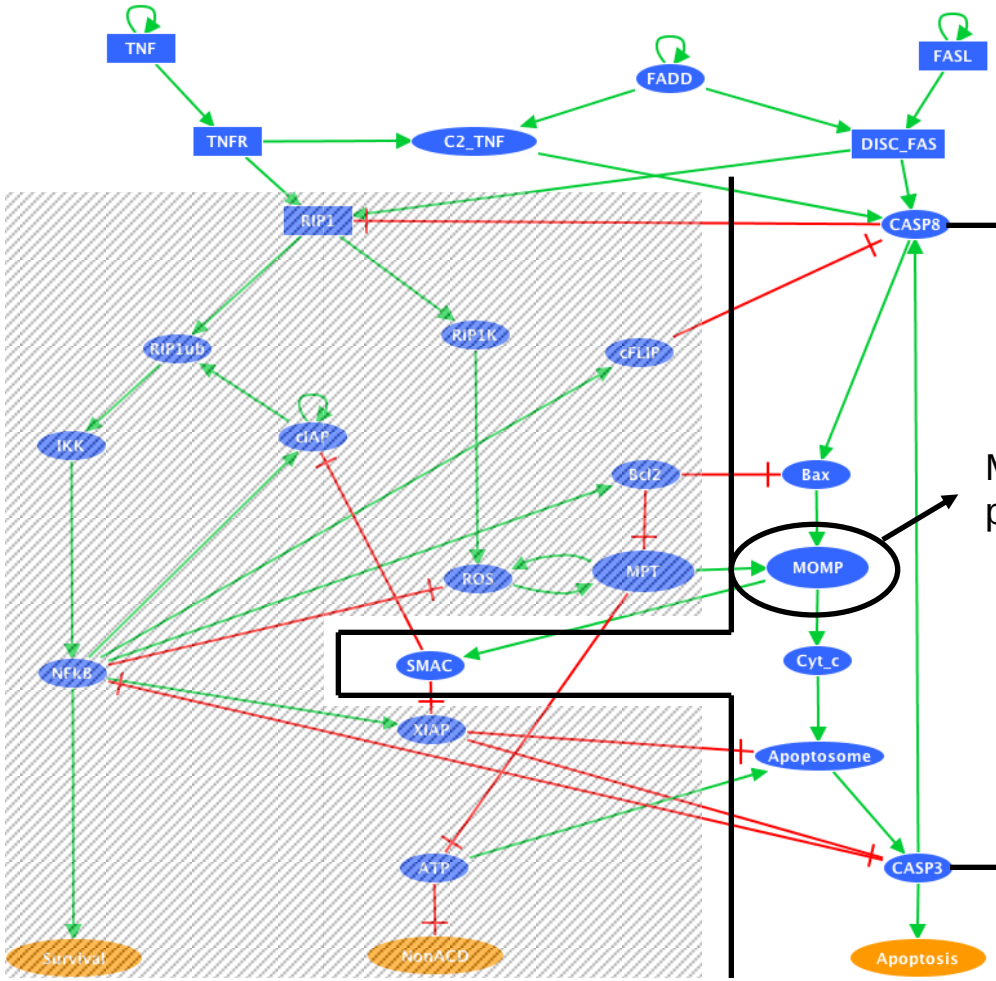
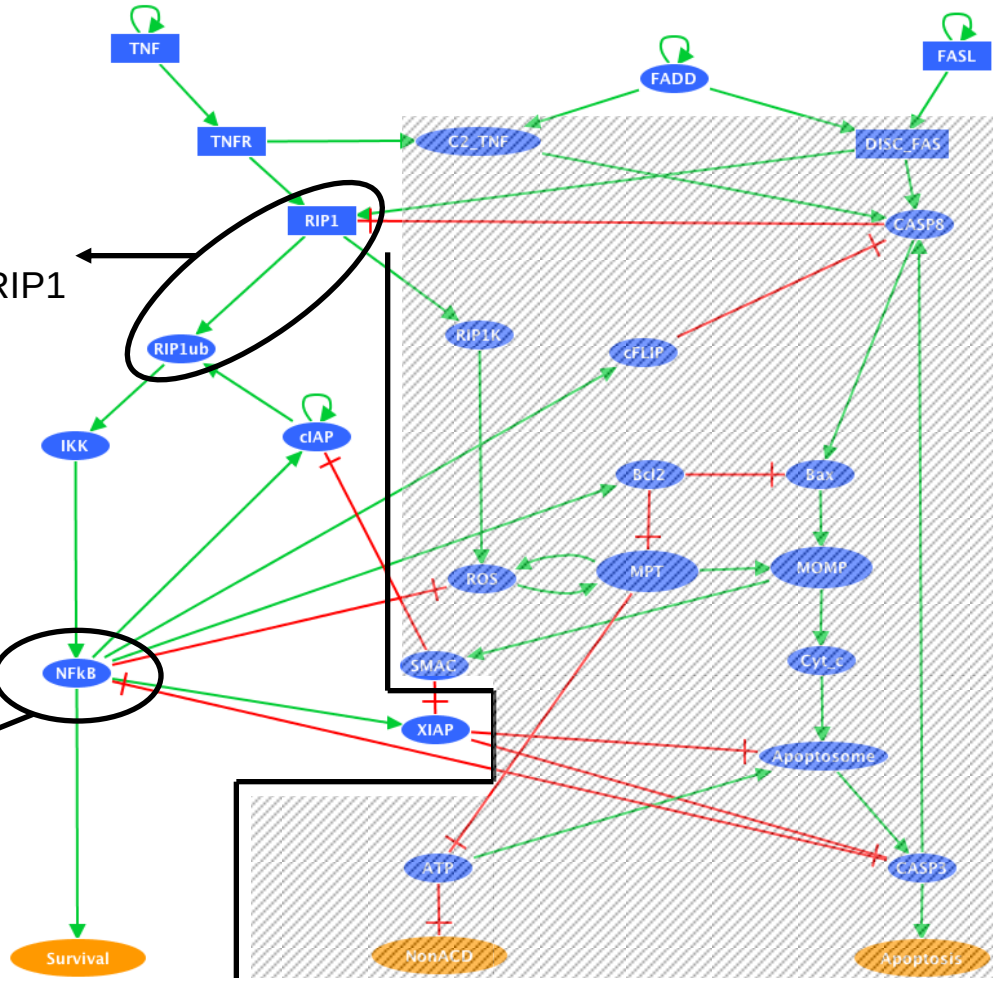
APOPTOSIS


TNF
FADD
FASL
TNFR
C2_TNF
DISC_FAS
RIP1
CASP8
Initiator caspase
RIP1ub
RIP1K
cFLIP
IKK
cIAP
Bcl2
Bax
Mitochondrial outer membrane permeabilization:
ROS
MPT
MOMP
SMAC
Cyt_c
NFkB
XIAP
Apoptosome
ATP
CASP3
Executioner caspase
Survival
NonACD
Apoptosis

NFκB pathway

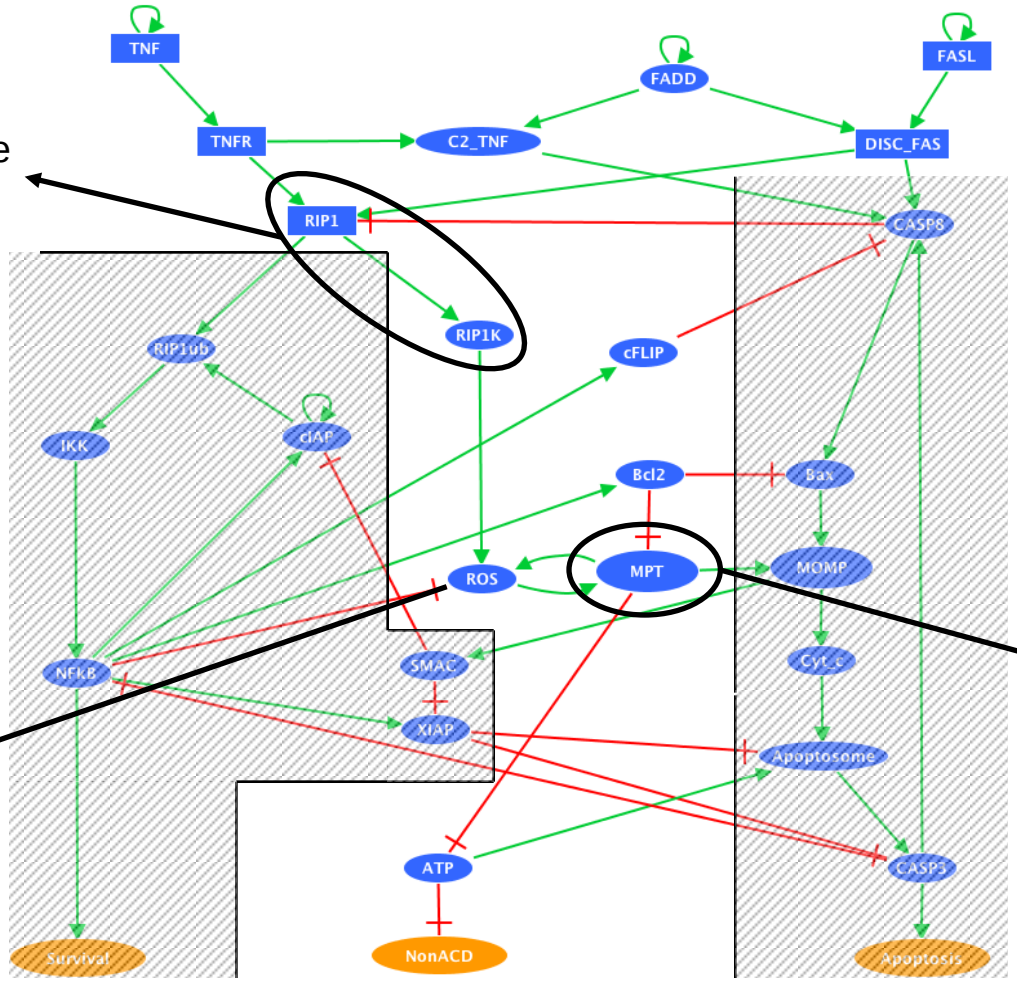
NFκB pathway needs ubiquitinated form of RIP1

No translocation of NFκB into the nucleus



NECROSIS

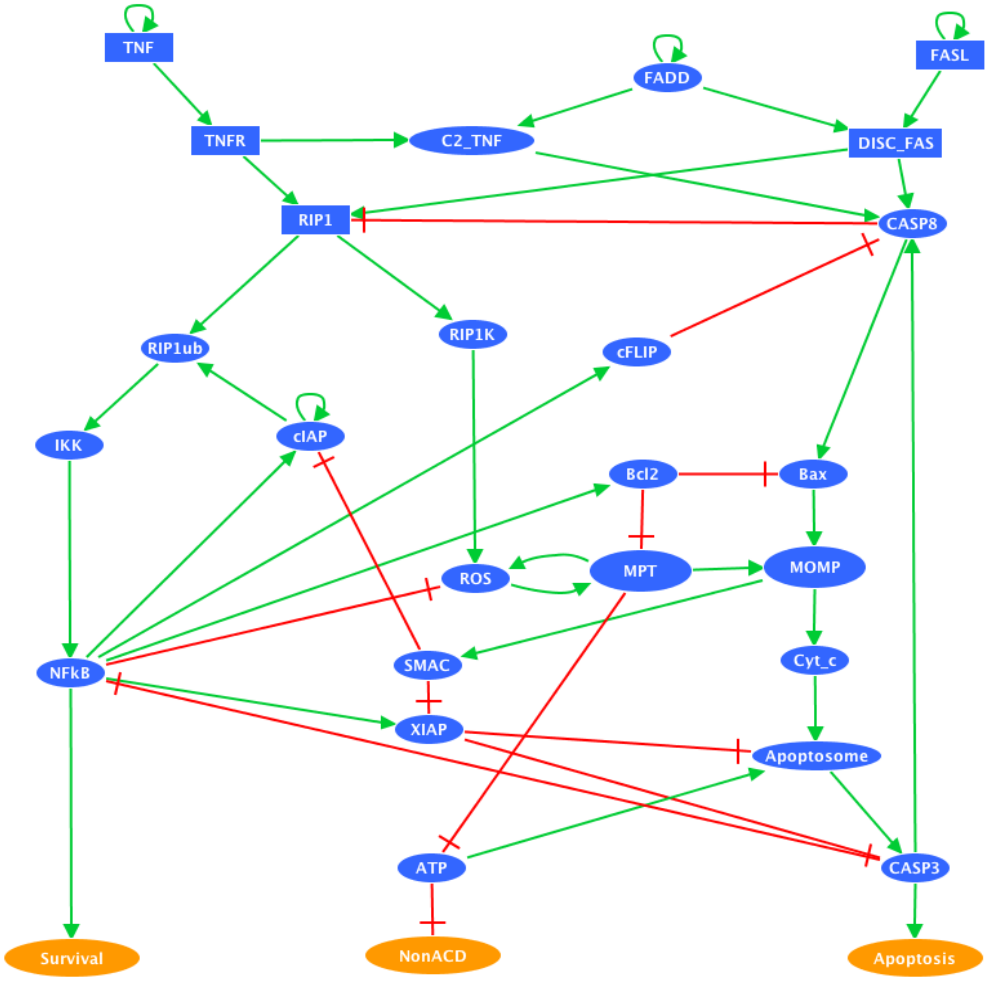
Necrosis needs kinase activity of RIP1



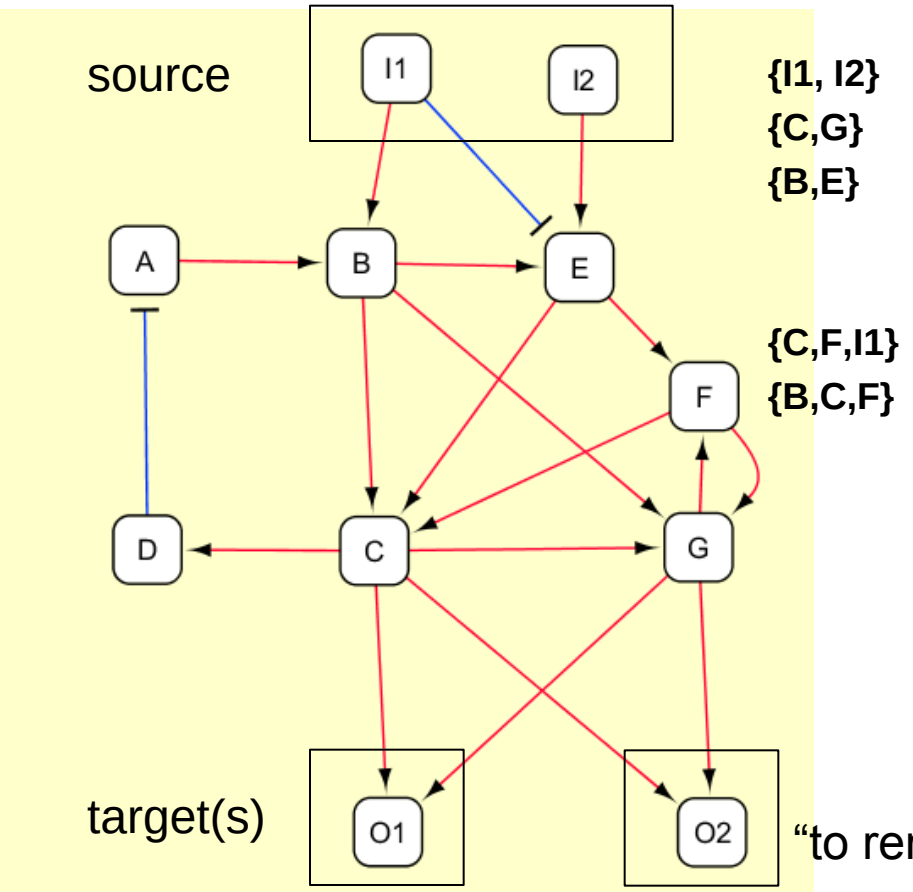
Mitochondria Permeability Transition

ROS : Reactive Oxygen Species

ASSEMBLED MECHANISM OF THREE CELL FATE DECISION



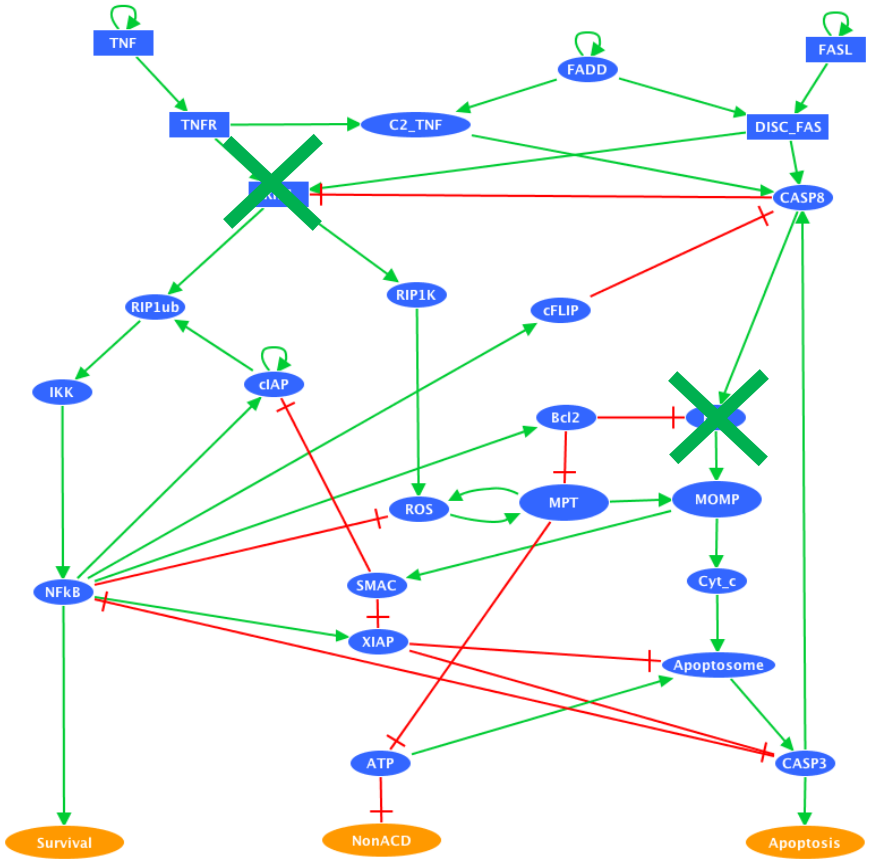
OCSANA: solving the minimal cut set problem



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 cell de

Probl
(canc
Minim
cell de
surviv

Type of Path Analysis	Number of Elementary Paths Nodes	Number and Sizes of CIs	Smallest CIs	Highest Scored CIs (according to OCSANA's score)	Top 5 Most Frequently Present Nodes in all ISs and Number of Occurrences
Shortest Paths	6 elementary paths 20 elementary nodes	Total 130 CIs: 9 CIs of size 2 92 CIs of size 3 24 CIs of size 4	[CASP3 , ATP] [CASP3 , MPT] [CASP3 , ROS] [CASP3 , RIPrK]	[CASP3 , ATP]	XIAP 30 ROS 29 RIPrK 26 MPT 29 ATP 29
Optimal and Sub-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	[CASP3 , ATP] [CASP3 , RIPt] [CASP8 , RIPt] [BAX , RIPt]	[CASP8 , ATP , RIPrub]	ROS 38 XIAP 35 NFkB 34 IKK 34 RIPrub 34
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 4 CIs of size 6	[CASP3 , ATP] [CASP3 , MPT] [MOMP , RIPt] [CASP8 , RIPt]	[ATP , NFkB , MOMP]	ROS 38 XIAP 37 NFkB 33 IKK 33 RIPrub 33

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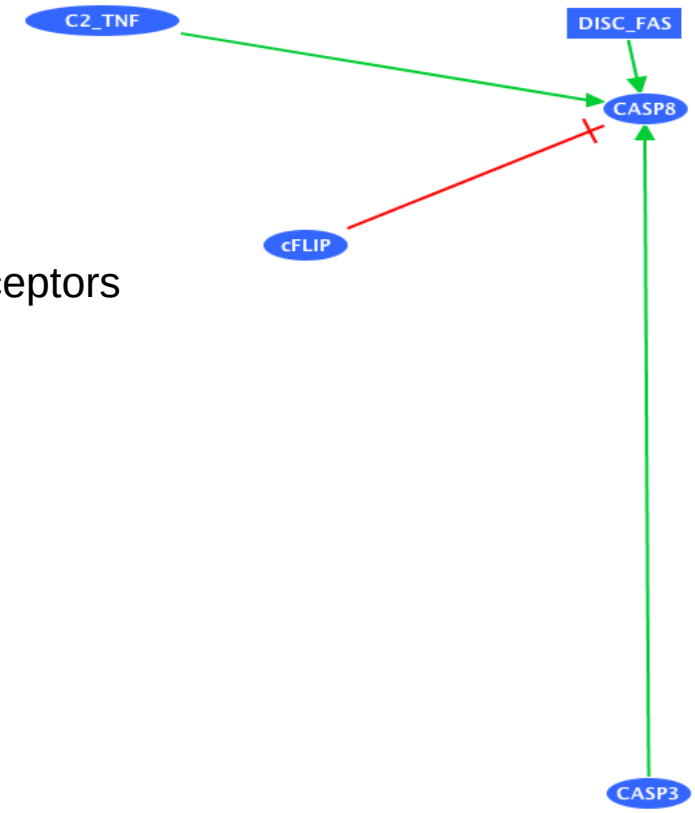
Boolean modeling

Assign logic to nodes

Example of CASP8

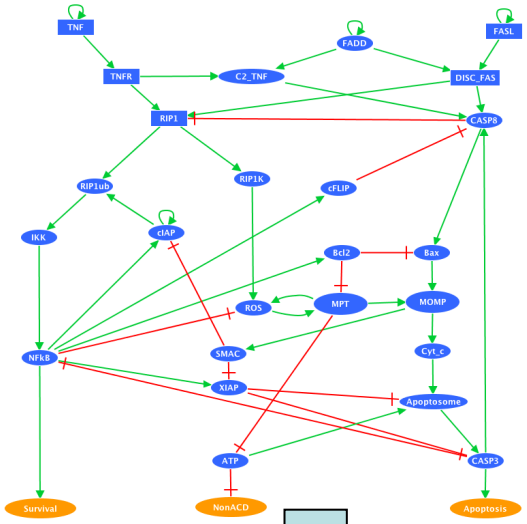


CASP8 = 0 when
DISC-Fas=0 and DISC-TNF=0 and CASP3=0
(equivalent to no external signals from death receptors and no intracellular problems)
cFLIP=1
(equivalent to inhibition by the NFkB pathway)

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

Asynchronous state transition graph

Influence graph



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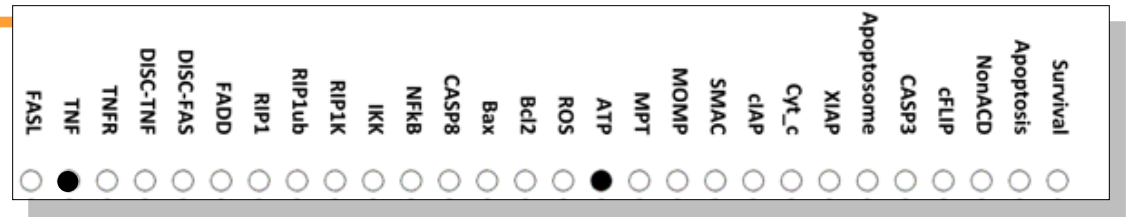

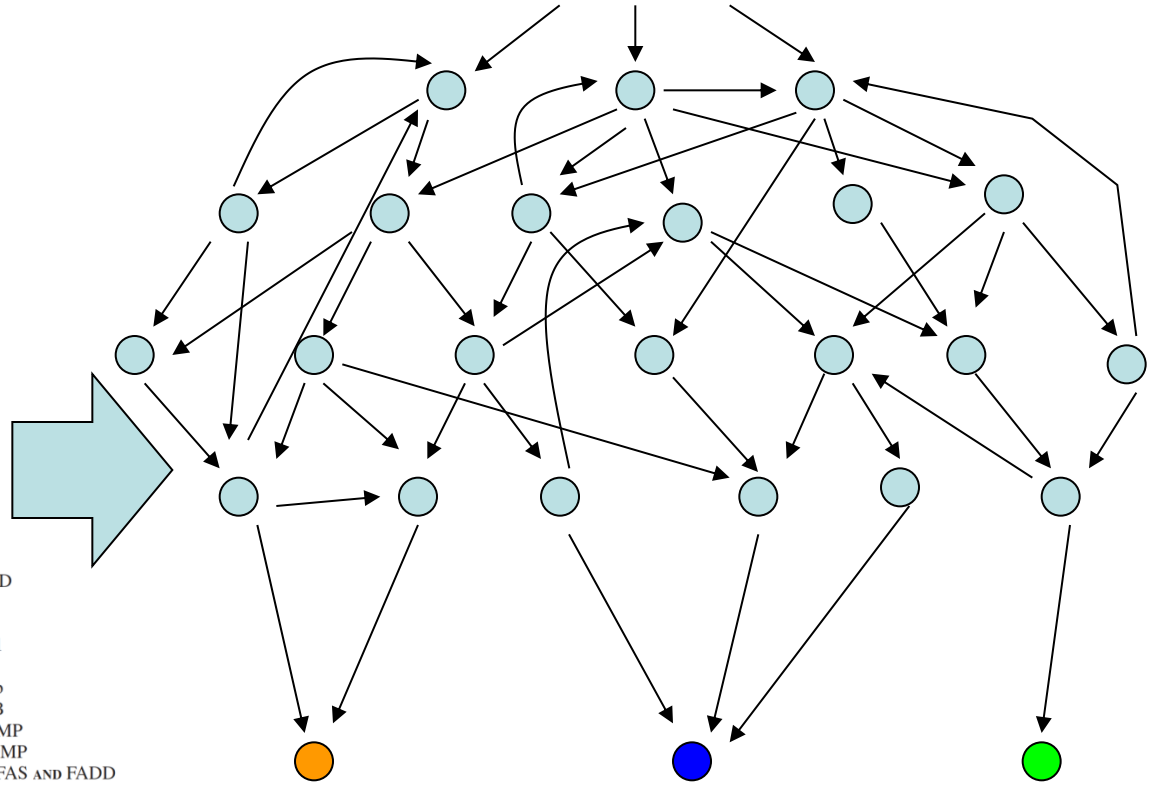

DISC_TNF' = TNFR AND FADD
RIP1' = (TNFR OR DISC_FAS) AND (NOT CASP8)
CASP8' = (DISC_TNF OR DISC_FAS OR CASP3) AND (NOT cFlip)
RIPub' = RIP1 AND cIAP
cIAP' = (NFkB OR cIAP) AND (NOT SMAC)
BAX' = CASP8 AND (NOT BCL2)
ROS' = (RIP1K OR MPT) AND (NOT NFkB)
MPT' = ROS AND (NOT BCL2)
MOMP' = BAX OR MPT
NFkB' = IKK AND (NOT CASP3)
XIAP' = NFkB AND (NOT SMAC)
Apoptosome' = CYT_C AND ATP AND (NOT XIAP)
CASP3' = Apoptosome AND (NOT XIAP)

TNF' = TNF
FADD' = FADD
FAS' = FAS
TNFR' = TNF
RIP1K' = RIP1
cFlip' = NFkB
IKK' = RIP1ub
BCL2' = NFkB
SMAC' = MOMP
CYT_C' = MOMP
DISC_FAS' = FAS AND FADD
ATP' = NOT MPT

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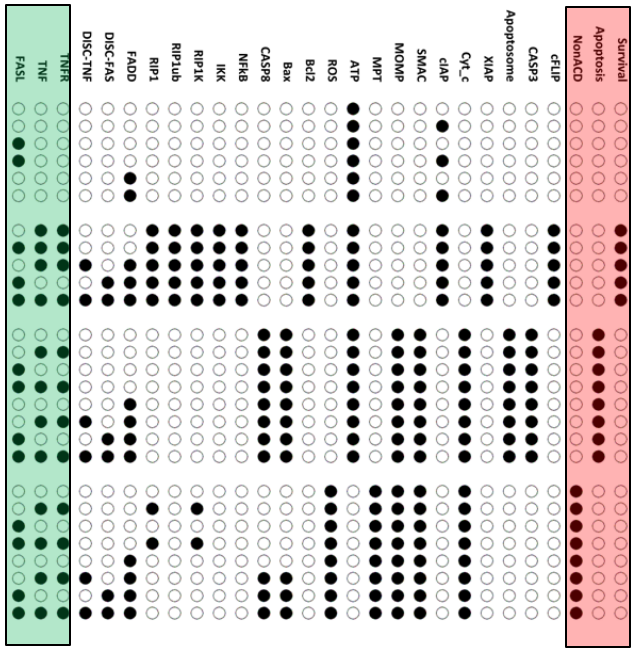
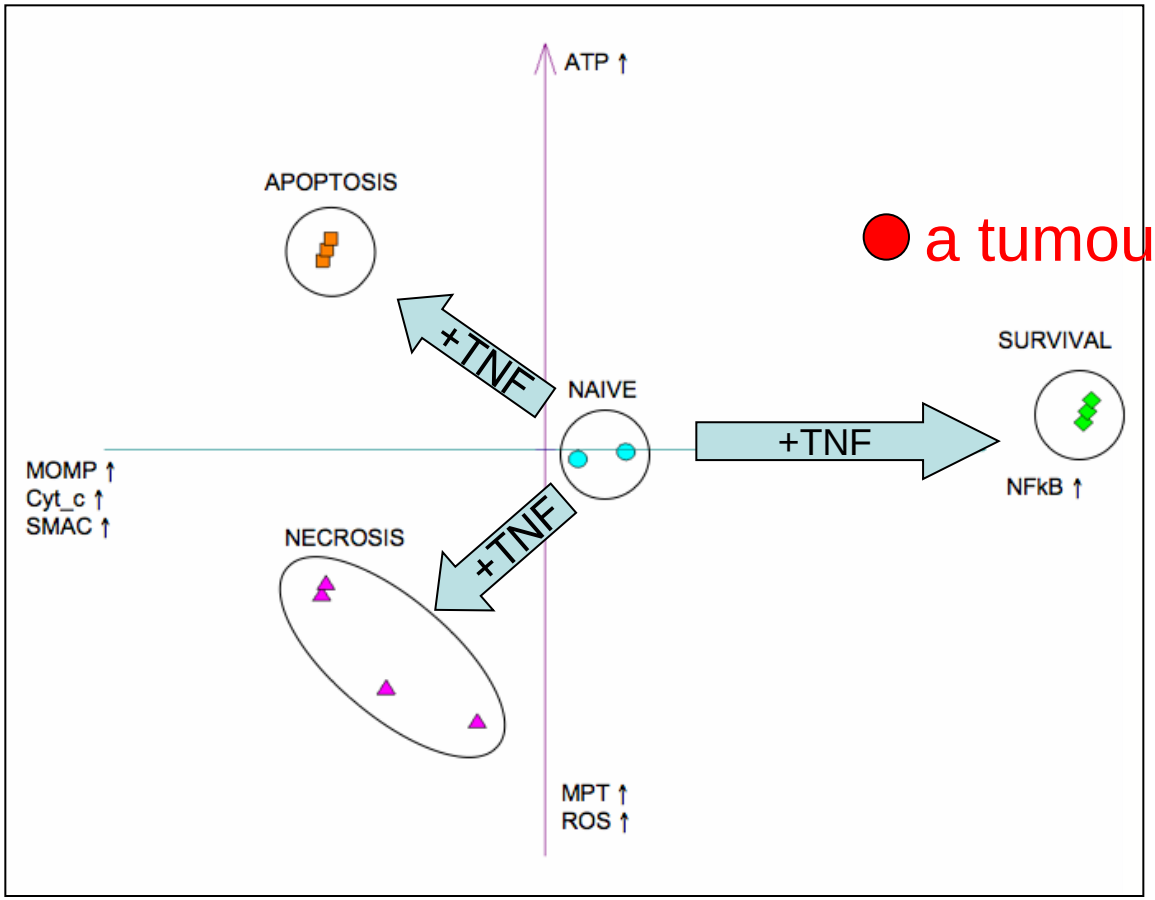
Structure of attractors: distribution of logical stable states





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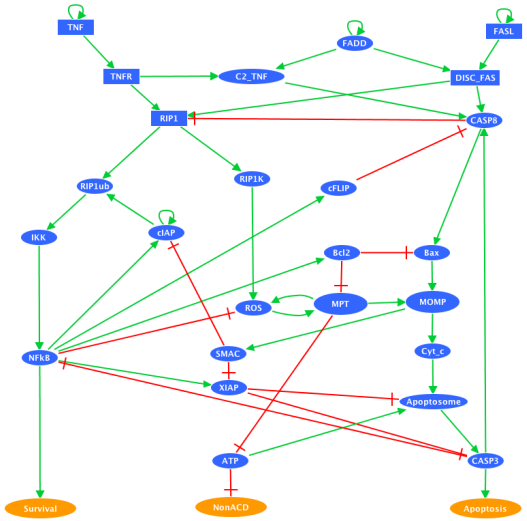
Asynchronous state transition graph

Influence graph



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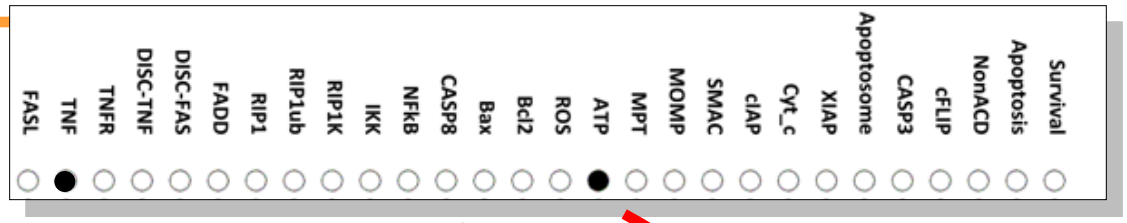

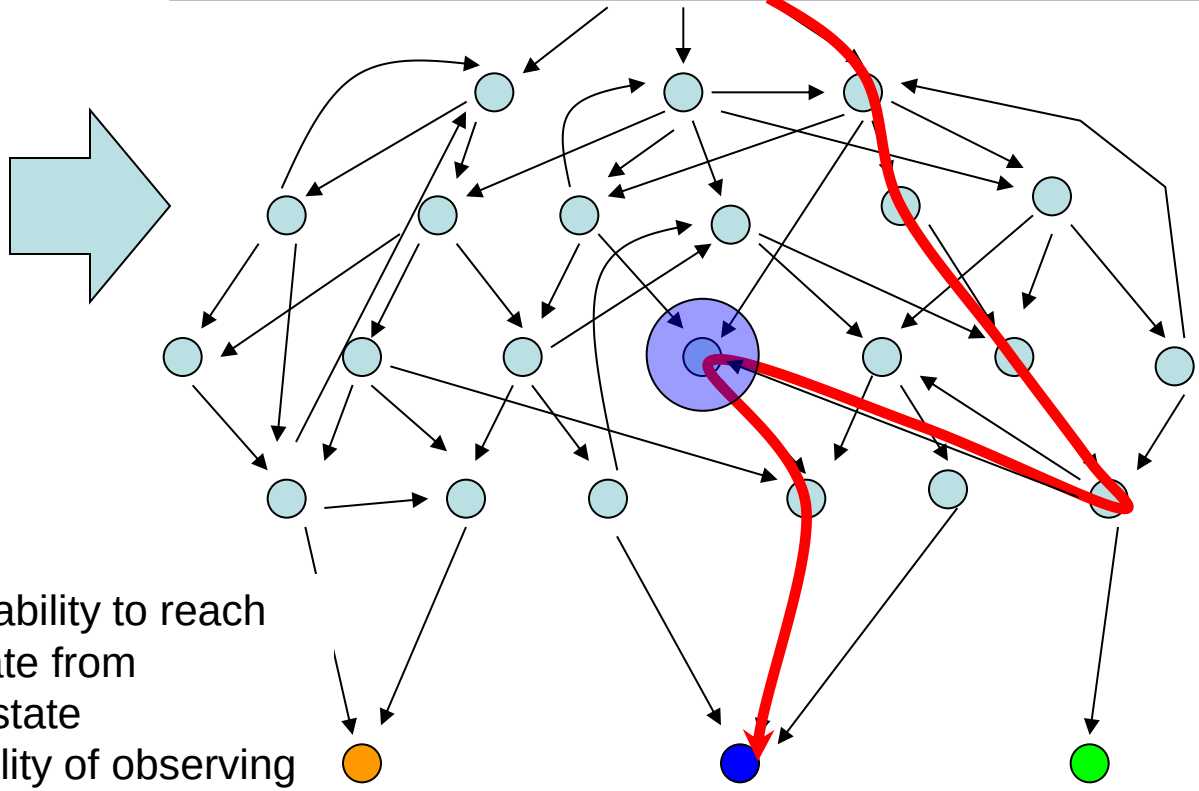

The probability to reach
a final state from
an initial state
= probability of observing
a phenotype in
experiment

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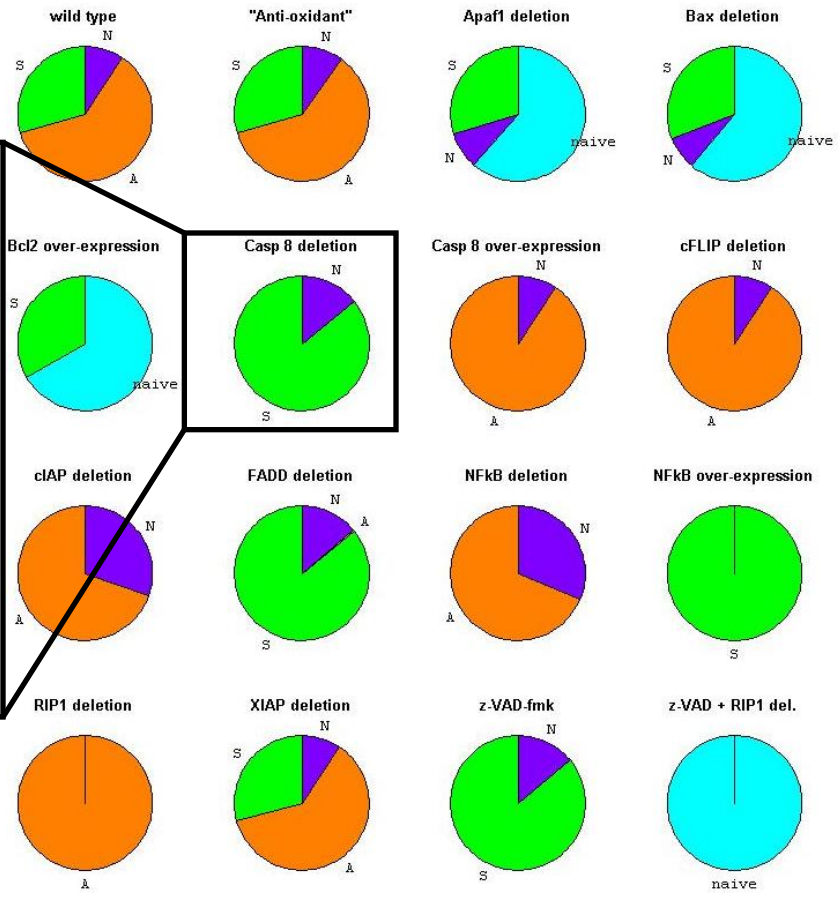
Predicting phenotype probabilities

TNF=1



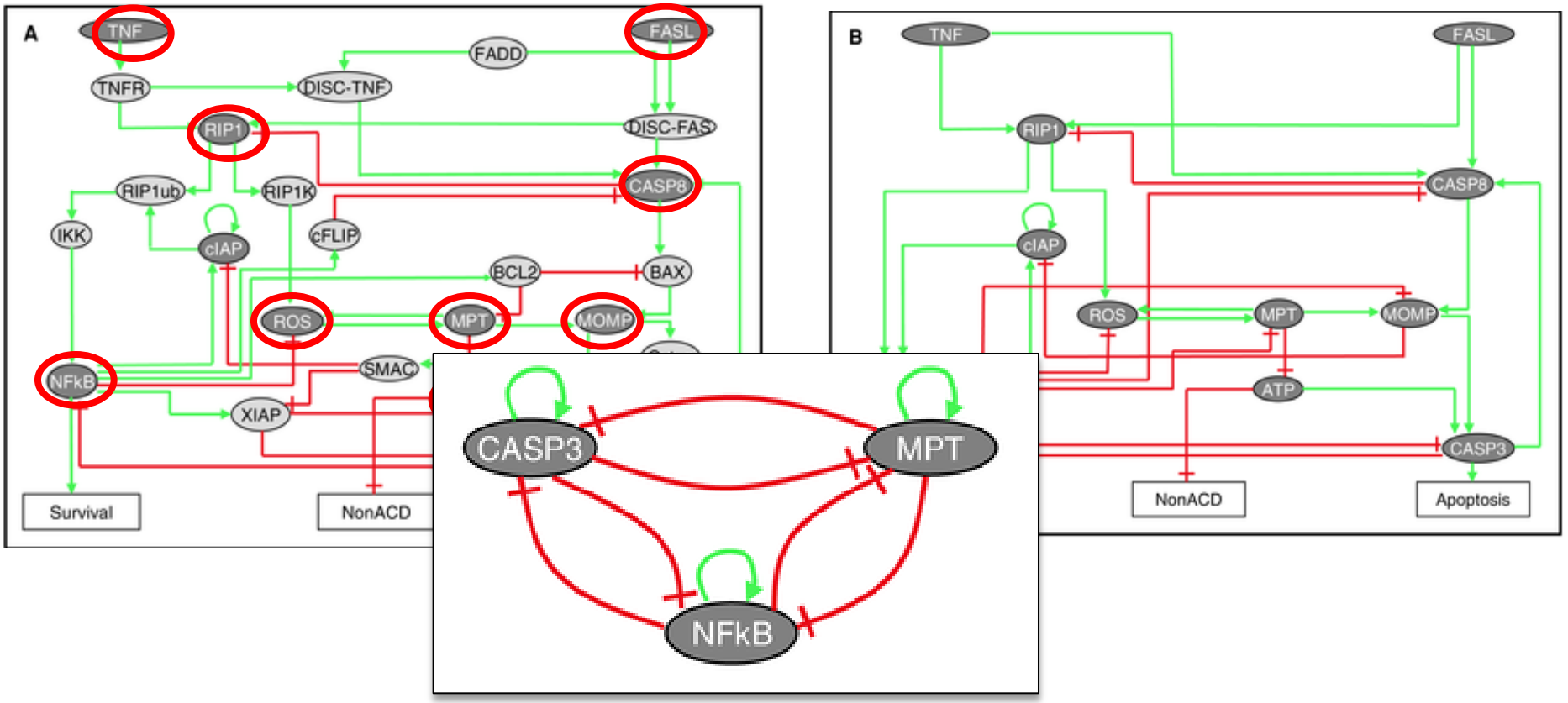
Example : **Caspase 8 deletion**

≈ 85% survival (NFkB)
≈ 15% necrosis
No apoptosis

Qualitatively consistent with the literature
"TNF-induced apoptosis is blocked though not necrosis"
[Kawahara, Ohsawa *et al., J Cell Biol* 1998]
(Jurkat cells, C8-/-)

Naïve survival | NFkB survival | apoptosis | necrosis

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.

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“Ligand dosage” experiments

What if the signal was removed…

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

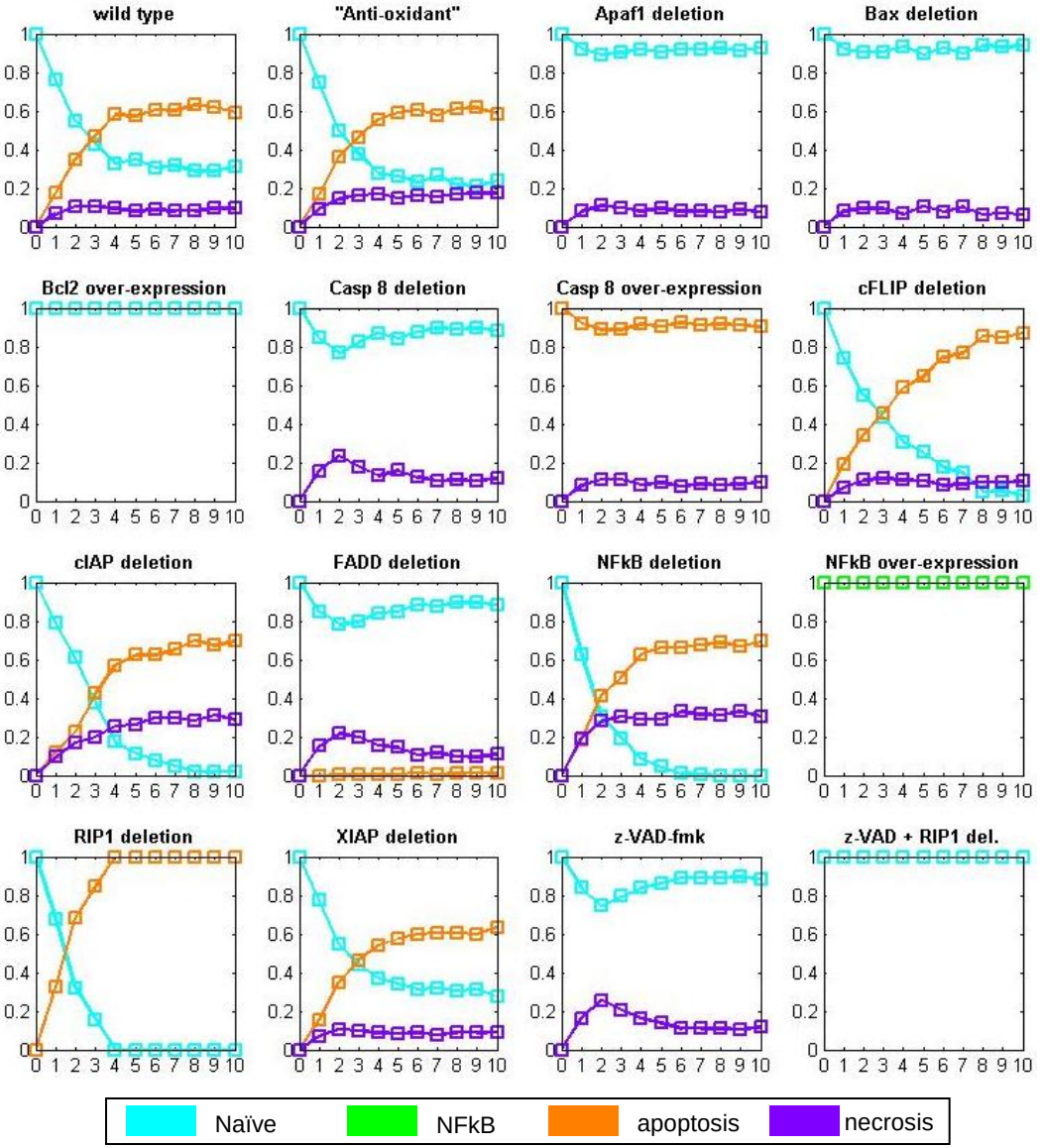
Introduction of “pulse” of TNF instead of constant induction

t : integer

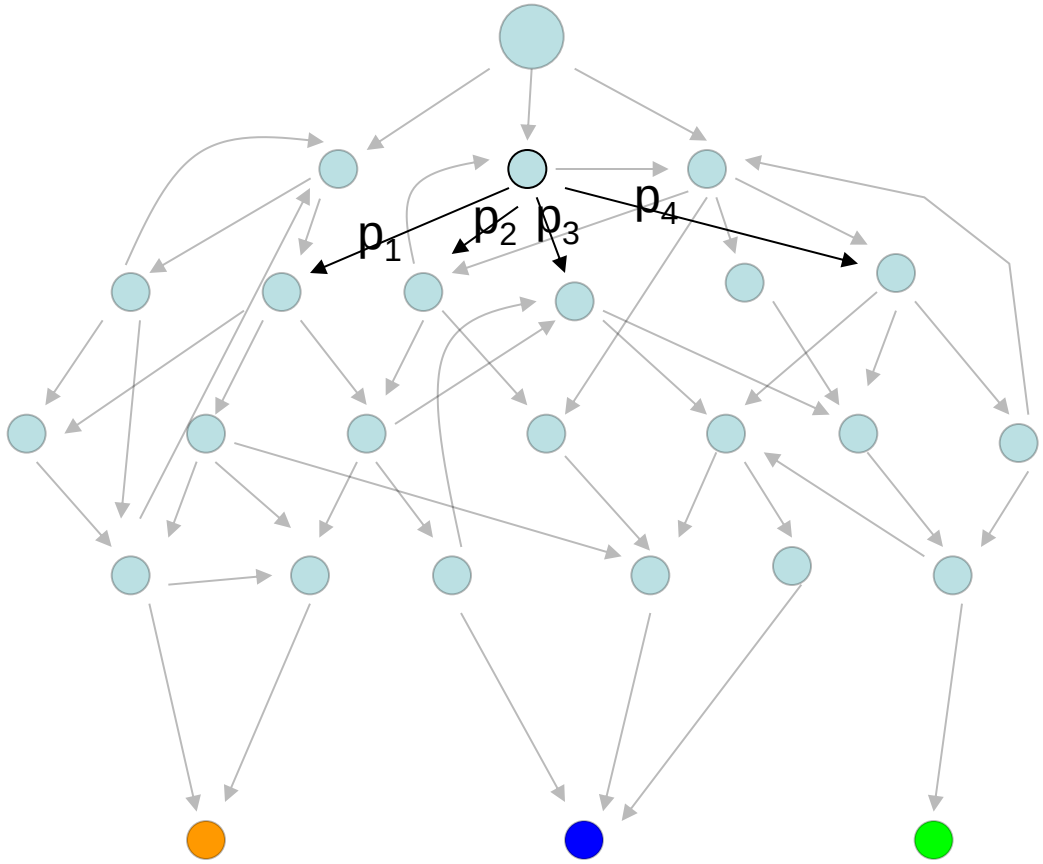
During *t* steps, the system evolves with TNF=1

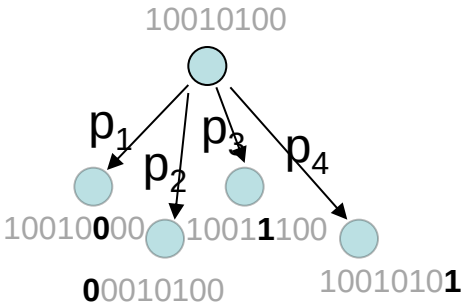
At step *t*+1, TNF is switched to 0 (until the end)

(x-axis → duration of TNF “pulse”)

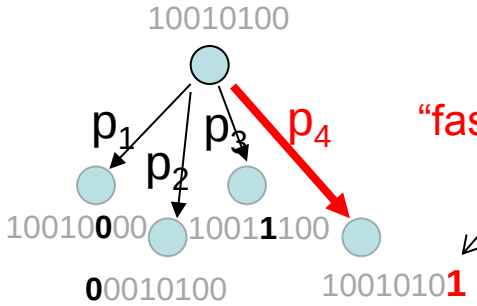


Sensitivity analysis: testing “rates” of variables





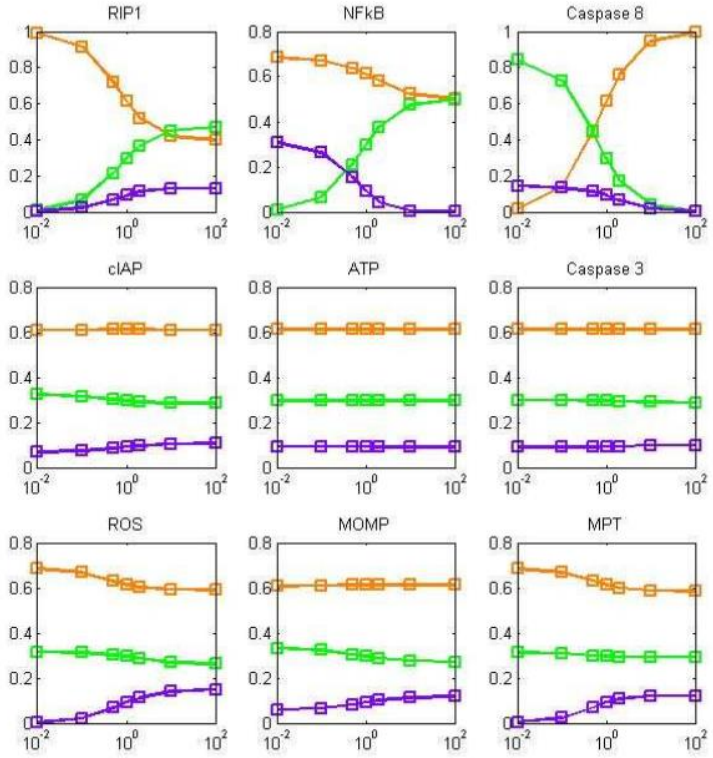
$p_1 = p_2 = p_3 = p_4 = 0.25$



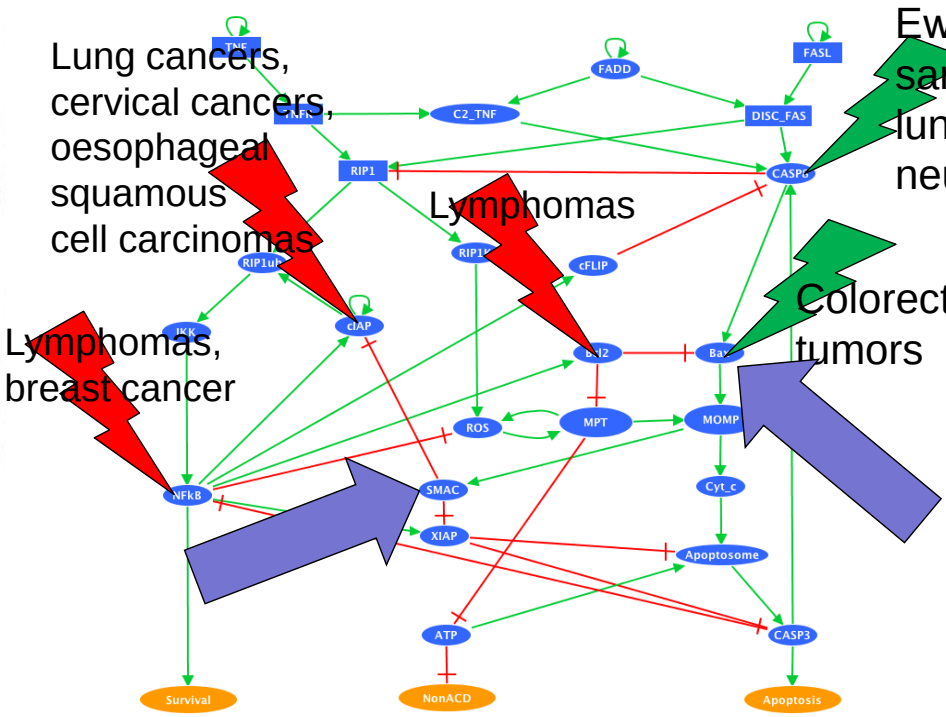
$p_1 = p_2 = p_3 = 1/13$

$p_4 = 10/13$

“Sensitivity” analysis: testing the effect of “rates” of variables



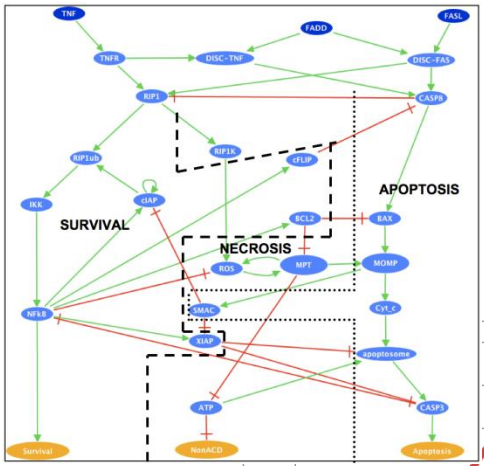
apoptosis
survival
necrosis

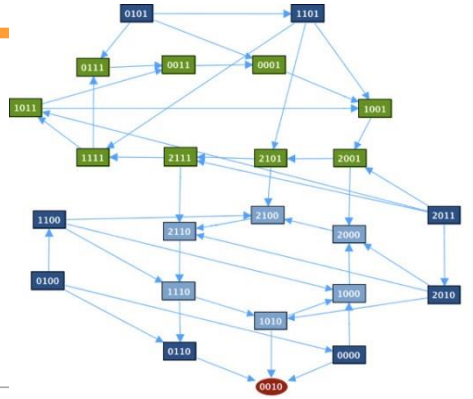


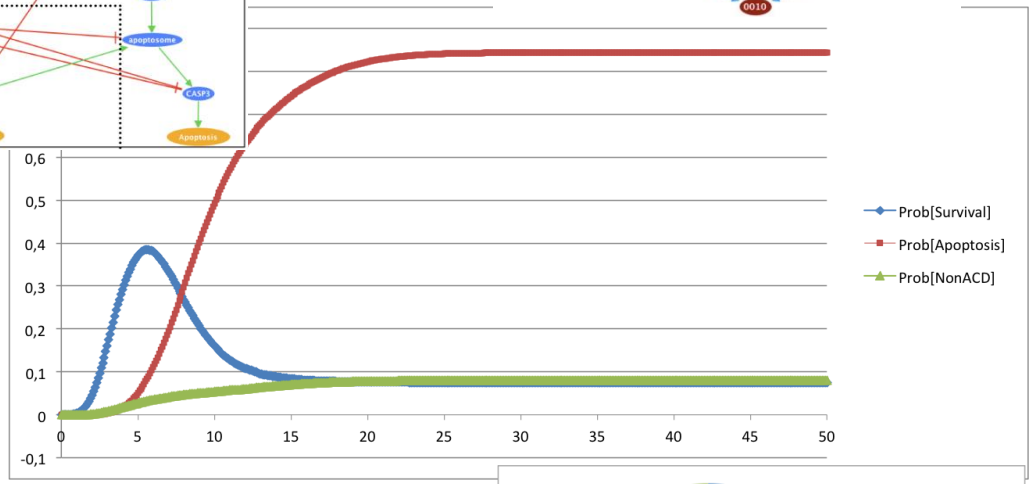
Zinovyev A, Fourquet S, Tournier L, Calzone L, Barillot E. Cell death and life in cancer: mathematical modeling of cell fate decisions. *Adv Exp Med Biol.* 2012;736:261-74.

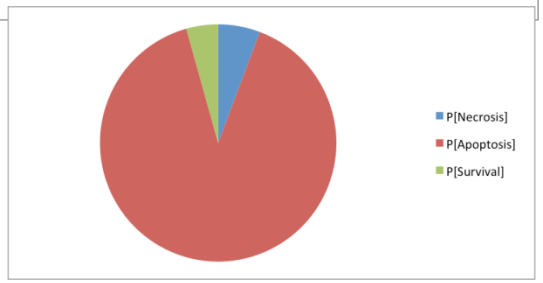
MaBOSS: introducing rates and continuous time

```
node TNFR
{
  logic = TNF;
  rate_up = @logic ? 1.0 : 0.0;
  rate_down = @logic ? 0.0 : 1.0;
}
node DISC_TNF
{
  logic = FADD & TNFR;
  rate_up = @logic ? 1.0 : 0.0;
  rate_down = @logic ? 0.0 : 1.0;
}
node DISC_FAS
{
  logic = FASL & FADD;
  rate_up = @logic ? 1.0 : 0.0;
  rate_down = @logic ? 0.0 : 1.0;
}
node FADD
{
  rate_up = 0.0;
  rate_down = 0.0 + 1000*$FADD_del;
}
node RIP1
{
  logic = (DISC_FAS | TNFR) & (!CASP8);
  rate_up = (@logic & (!$RIP1_del)) ? 1.0 : 0.0;
  rate_down = (@logic ? 0.0 : 1.0) + 1000*$RIP1_del;
}
node RIP1ub
{
  logic = cIAP & RIP1;
  rate_up = @logic ? 1.0 : 0.0;
  rate_down = @logic ? 0.0 : 1.0;
}
```









http://maboss.curie.fr

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