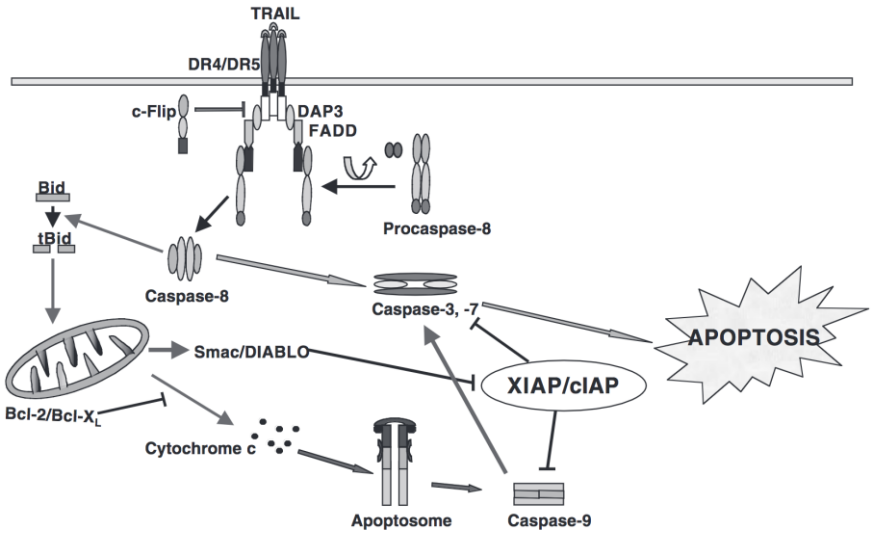
What we have done in ANR STOCH-MC

Apoptosis

TRAIL

- TNF-related apoptosis-inducing ligand
- Induces apoptosis
- More effective on some cancer cells
- Binds to the cell's death receptors
- Fractional killing: resistance

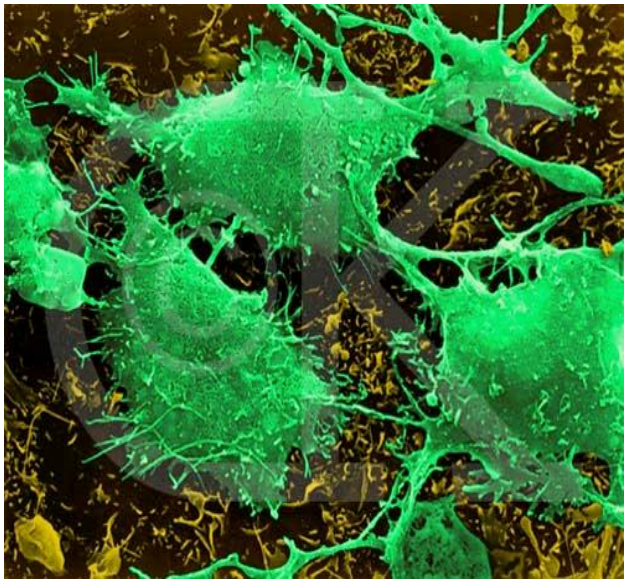


Biological Problem

- Design efficient cancerous tumor treatments.

- Efficient protocol = Optimize drug quantity :
  - frequency of treatment
  - choice of concentration

- Testing many treatments *in vivo* is long/costly.

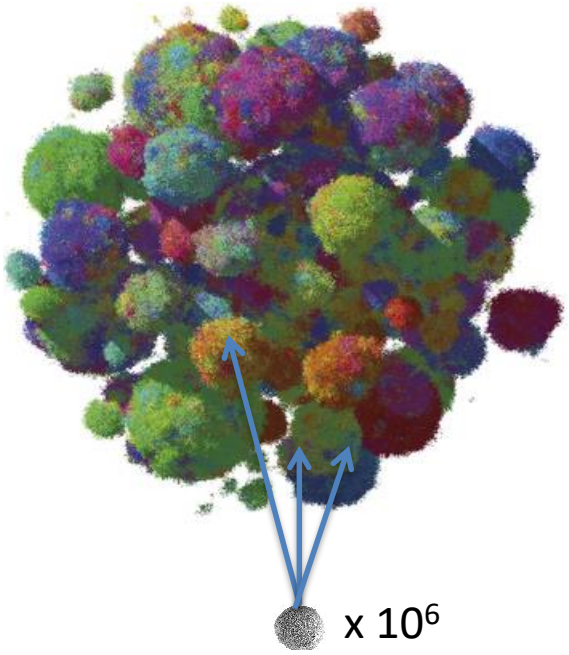


Goal : Propose *in silico* method to sort candidate protocols

Study case : HeLa cells (cervical cancer). TRAIL protein triggering the apoptosis (programmed cell death) process.

Challenge

- Modeling treatment of non-vascularized tumor (Tumor up to 10^6 cell).
- TRAIL diffusion
- Survival after each treatment
- Temporary resistance
- Temporary holes: Need topology



Consider two scales:

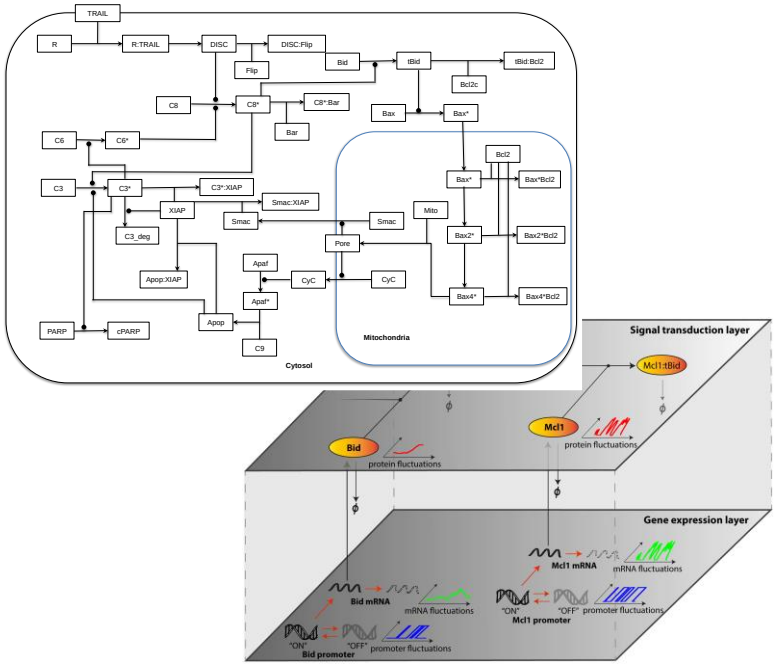
- Tissue : Tumor evolution, treatment diffusion
- Cell : Effect of the treatment, Transient treatment resistance

Issue: High complexity model (combinatory explosion) => Abstractions

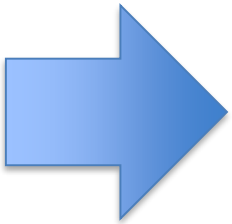
What we have done in ANR STOCH-MC

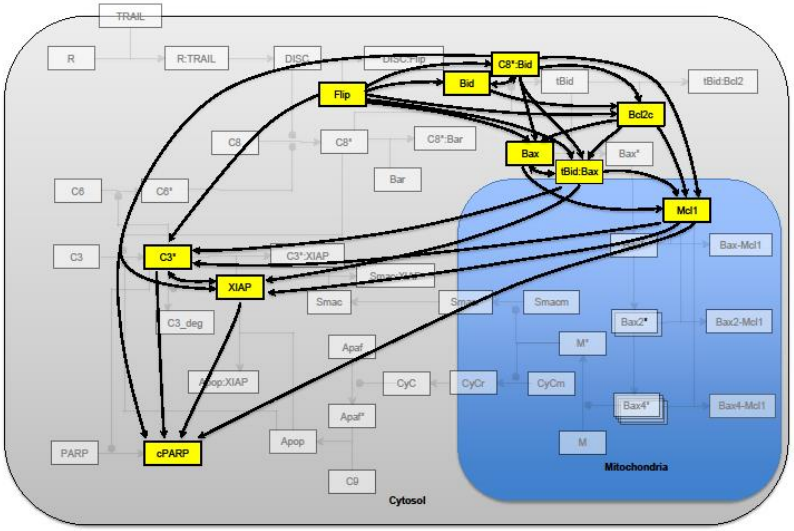
Cellular level

Abstracting the model for TRAIL-induced apoptosis



52 ODE species, 96 reactions
+ 40 stochastic variables
1 simulation step represents 1 second
(fine grain)





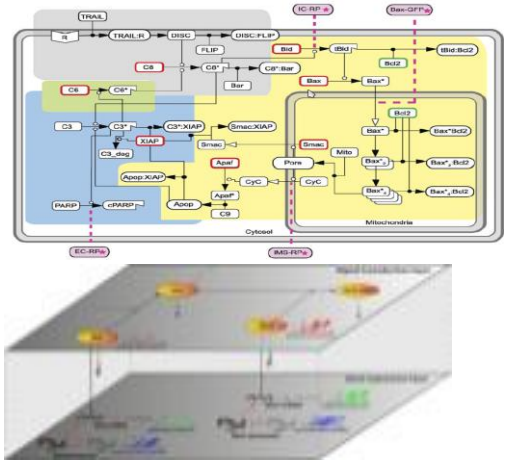
Around 10 variables (=species concentration)

1 time step corresponds to 15 min
(coarse grain)

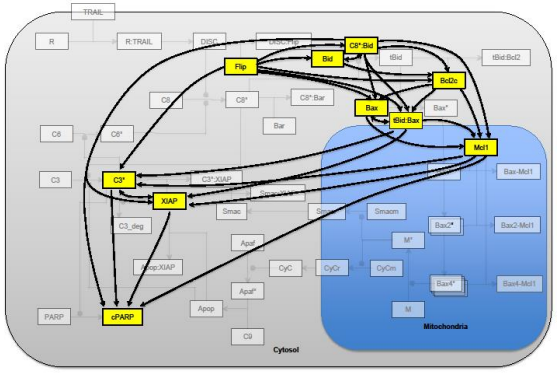
Sucheendra Palaniappan, François Bertaux, Matthieu Pichené, Eric Fabre, Gregory Batt, Blaise Genest. Discrete Stochastic Abstraction of Biological Pathway Dynamics: A case study of the Apoptosis Pathway. *Bioinformatics*, 33 (13): 1980–1986, Oxford University Press.

How good is the Abstraction?

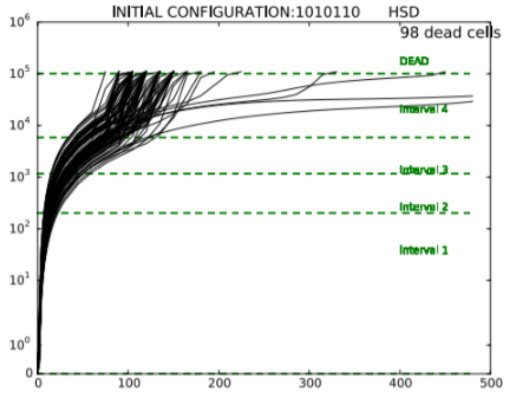
HSD model

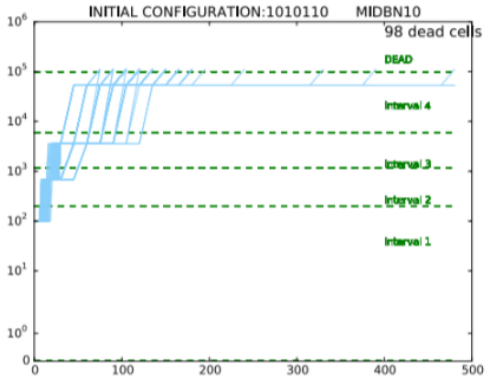


DBN abstraction



100 runs: 98% dead

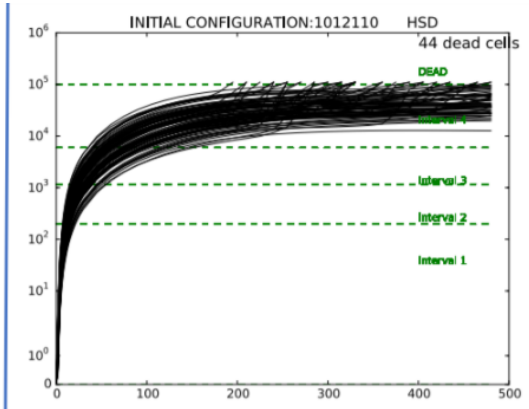


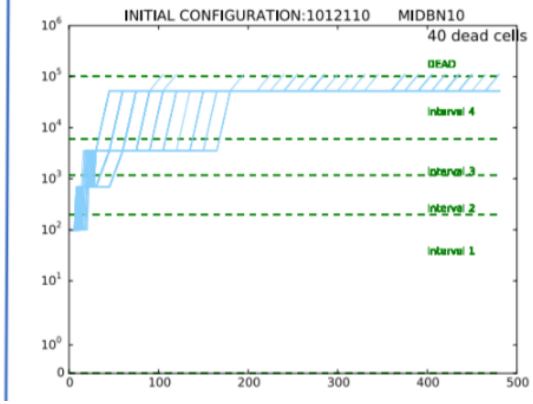


100 runs: 98% dead

Less antiapop. molecules

100 runs: 44% dead



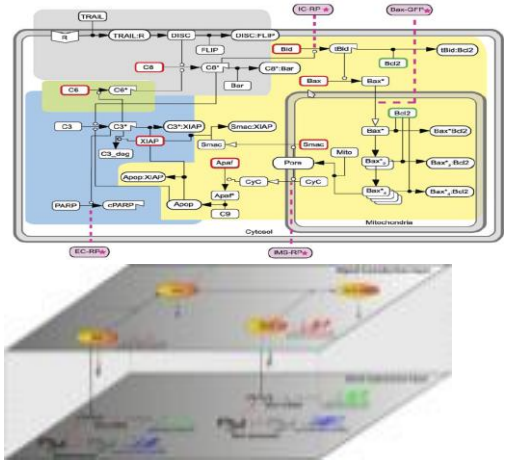


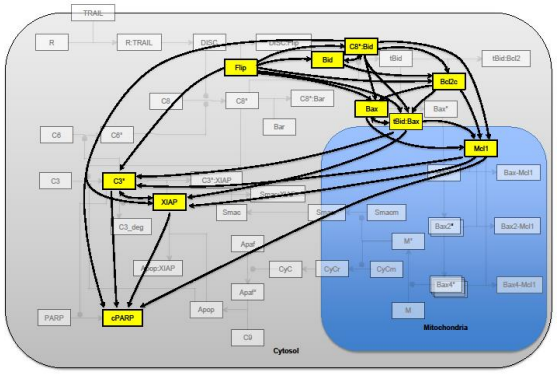
100 runs: 40% dead

More antiapop. molecules

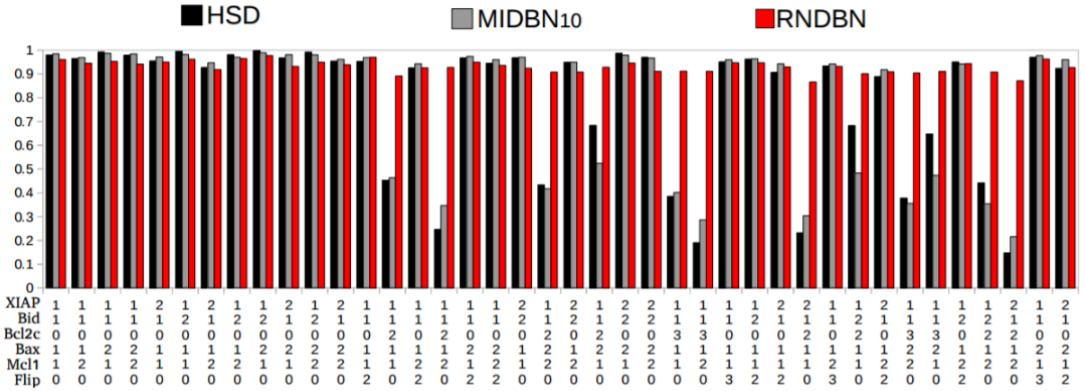
How good is the Abstraction?

HSD model





DBN abstraction



Model	cell death (**HSD: 69.9%**)	discerning power (**HSD: 100%**)	Time / 1000 simulations (**HSD: 56s**)
MIDBN$_7$	70.43%	96.14%	**2.13**s (**26.3**X)
MIDBN$_8$	**69.57**%	96.31%	2.64s (21.21X)
MIDBN$_9$	69.33%	96.37%	2.98s (18.8X)
MIDBN$_{10}$	69.03%	**96.84**%	3.30s (17X)
MIDBN$_{58}$	66.85%	94.12%	73.05s
RNDBN	92.29%	85.53%	299s

Time efficient:

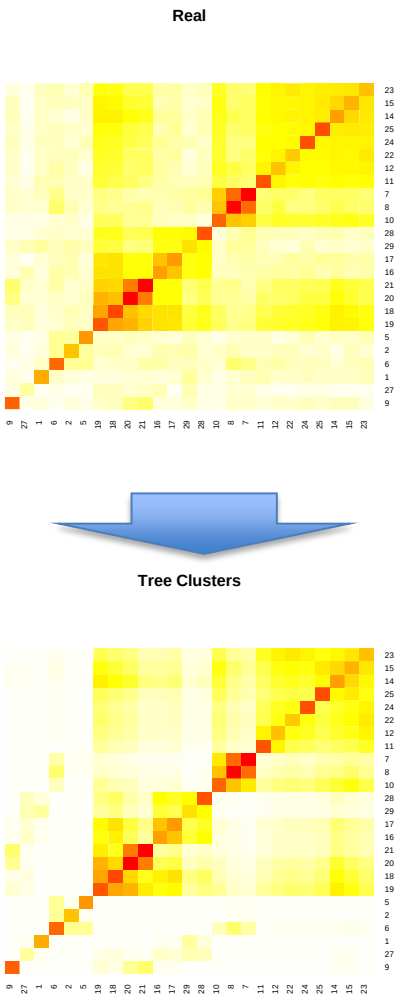
1 simu CMC 20x faster than 1 simu HSD

Approx. Distribution Representation

non disjoint clusters

P(X1=1,X2=1),
P(X1=S,X2=1)…
P(Xn=S,Xk=S)
c S^d values

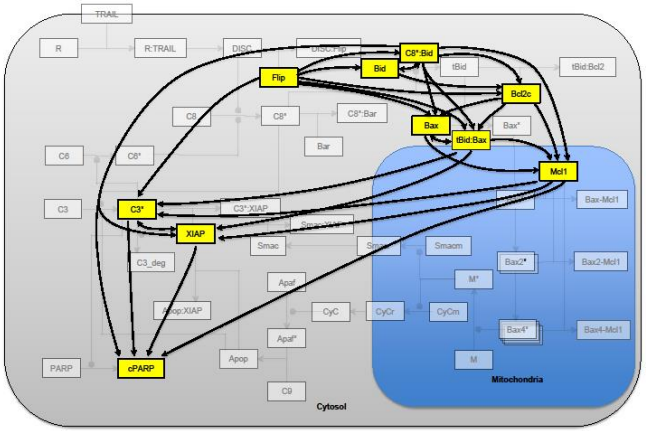
$$P_{NDC}(X_1 = x_1, \cdots, X_n = x_n) = \prod_{j \leq c} \frac{P(X_i = x_i, i \in K_j)}{P(X_i = x_i, i \in \bigcup_{\ell<j} K_\ell \cap K_j)}$$

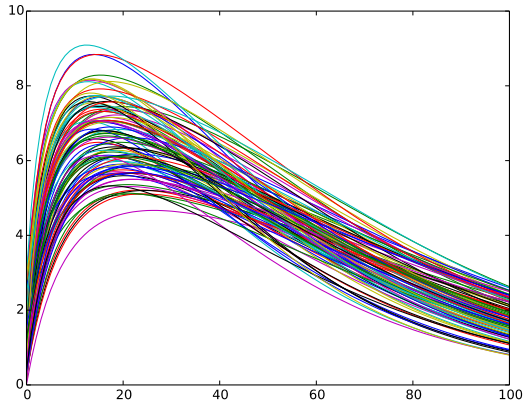


Correlations are quite preserved

Analysing the evolution

To obtain the probability distribution produced by the DBN





Lots of simulations
[HSB'16]

$$P^t(\boldsymbol{X} = \boldsymbol{x}) = \sum_{\boldsymbol{u} \in V^X} P^{t-1}(\boldsymbol{X} = \boldsymbol{u}) \prod_{i=1}^{n} CPT_{t,i}(\boldsymbol{x}_i \mid \boldsymbol{u}_{\hat{i}})$$

Inference (1 computation). ~10sec.
[submitted]

Inference: Comparison

Test of different approximate distributions for inference in compact Markov chains.
Program : Inferno (based on different distribution approximations)

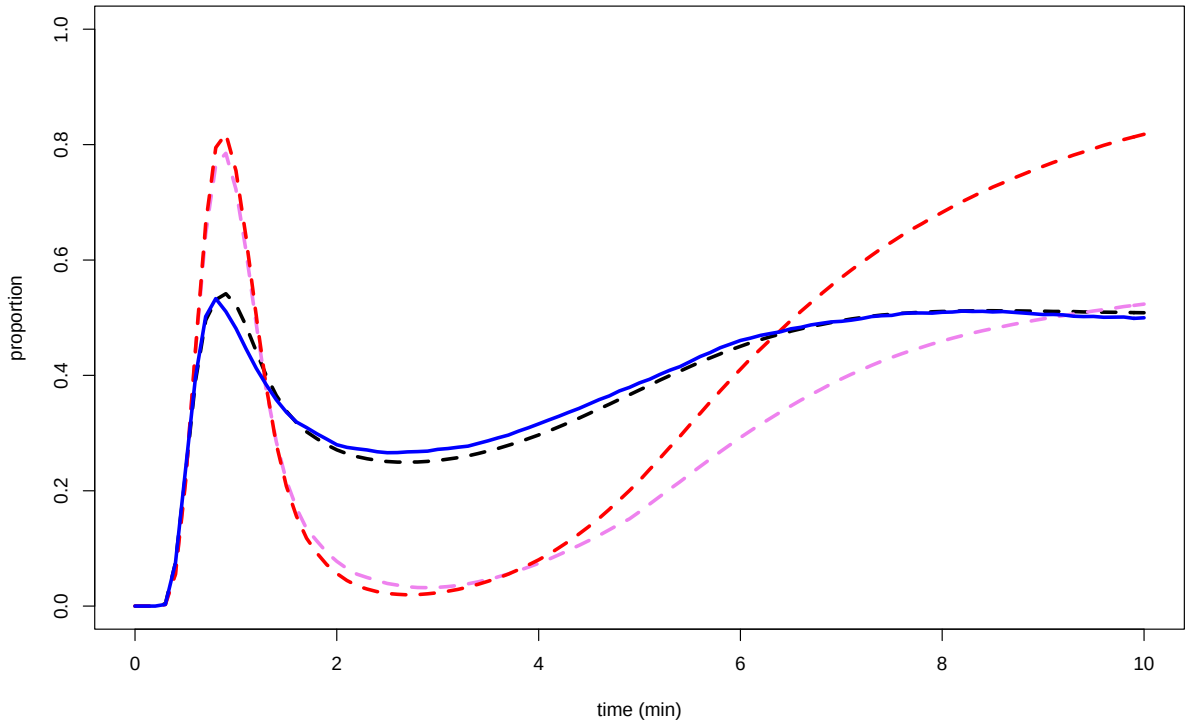
Apoptosis pathway:

Method	Max. Error	Mean Error (normalized)	Nb. Error > 0.1	Comput. Time
FF	0.44	100%	124	2.2s
Disj. Cluster	0.12	24%	2	9.8s
Inferno	0.06	14%	0	13.8s

EGF-NGF pathway (normalized wrt FF for comparison with HFF):

Method	Max. Error	Mean Error	Nb. Error > 0.1	Comput. Time
FF	100%	100%	100%	1x
HFF (3k)	62%	60%	50%	10x
HFF (32k)	49%	38%	35%	1100x
Disjoint Cluster	84%	79%	84%	1.9x
Inferno	32%	14%	16%	4.2x

Inference with approximate distribution



EGF-NGF pathway Proba(ErkAct = 2)

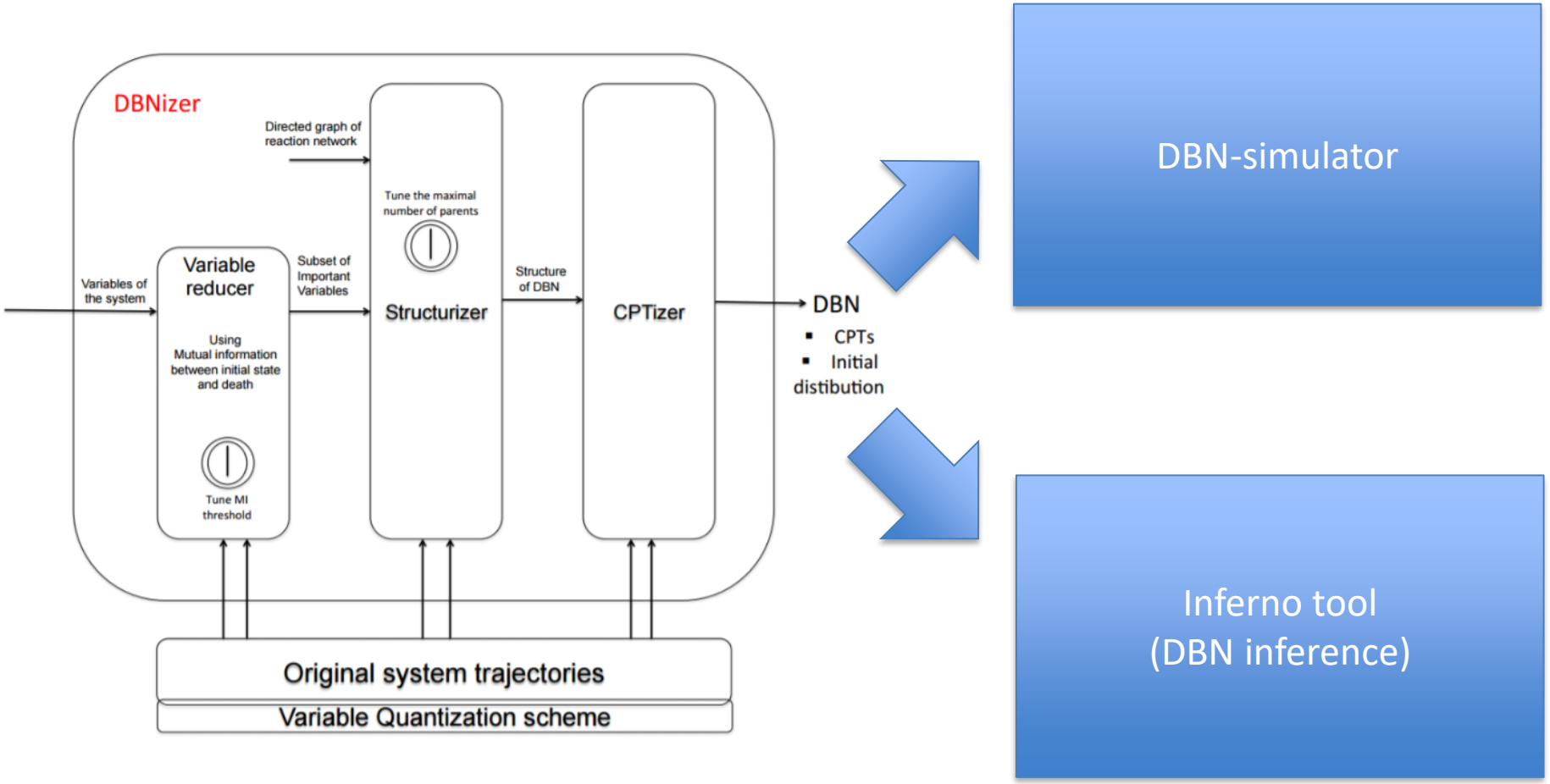
FF (factored Frontier) :
No correlations between var.

Disjoint clusters

Inferno

Simulations

Software developped



available freely at
https://suchee.bitbucket.io/DBNizer/

Cellular level:
Full success!

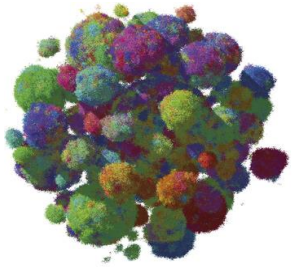
Work in progress:

Tissular level

(not planned in STOCH MC)

Tissular level : Abstraction

- Obtaining tumor simulations using (modified) *TumorSimulator* (agent-based) [Waclaw et al. 2015]

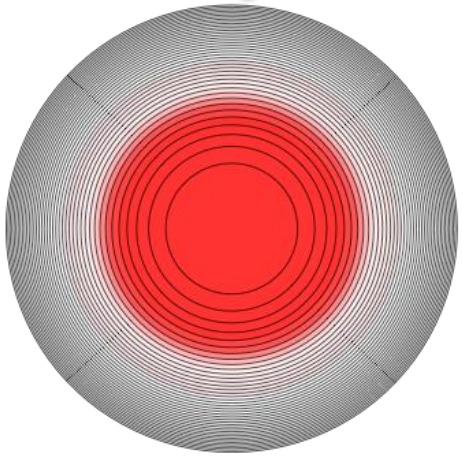


Simulations of TumourSimulator

LayPopGenerator

- Abstraction : Compact Markov chain

Several layers, each representing subpopulation with similar conditions (same depth).

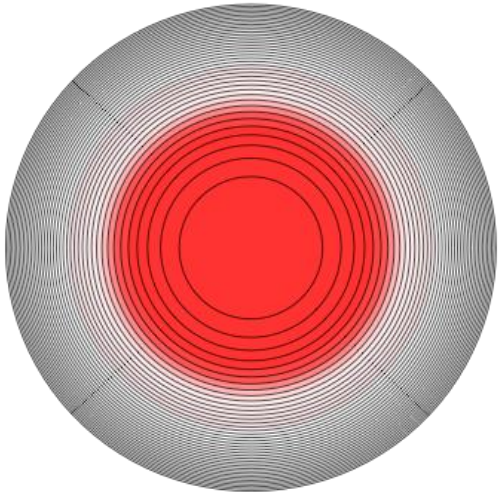


Waclaw, B., Bozic, I., Pittman, M., Hruban, M., Vogelstein, B., Nowak, M. (2015).
A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity. **Nature** 525, 261-264.

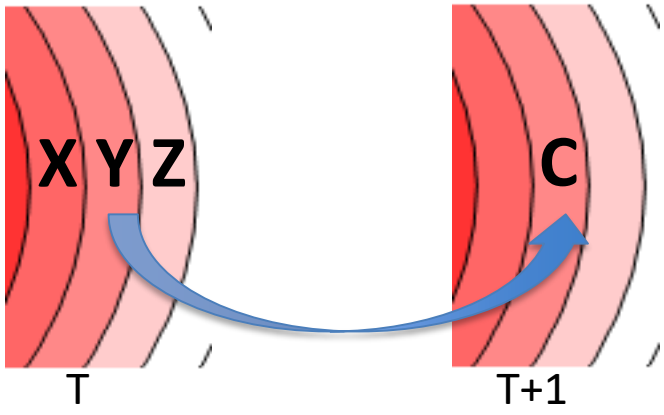
Using DBN idea

Work in progress.

- Variables : concentrations of cells in layers

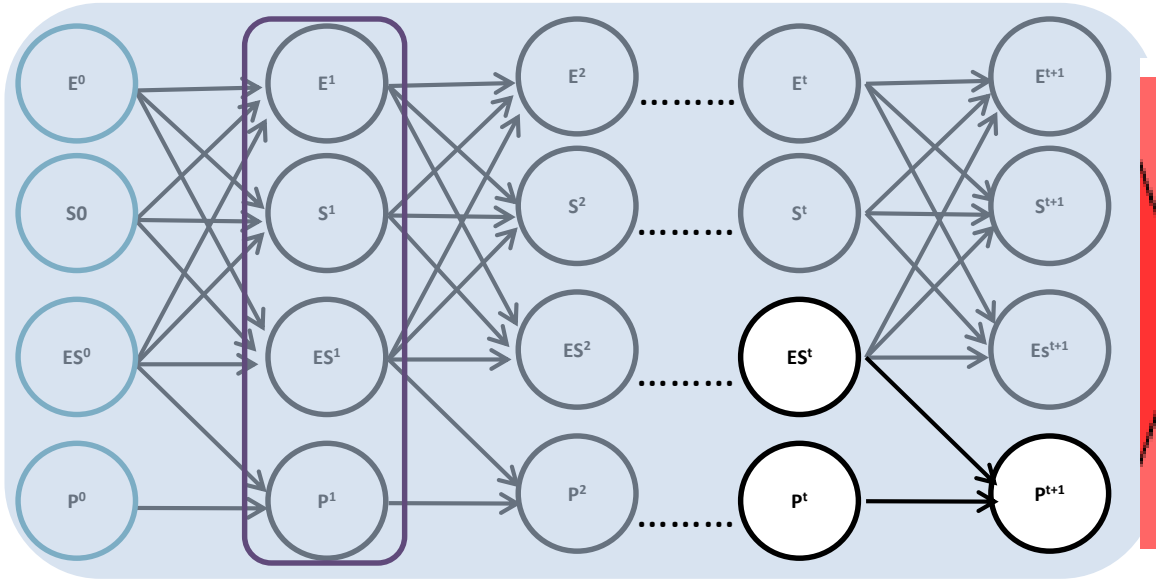


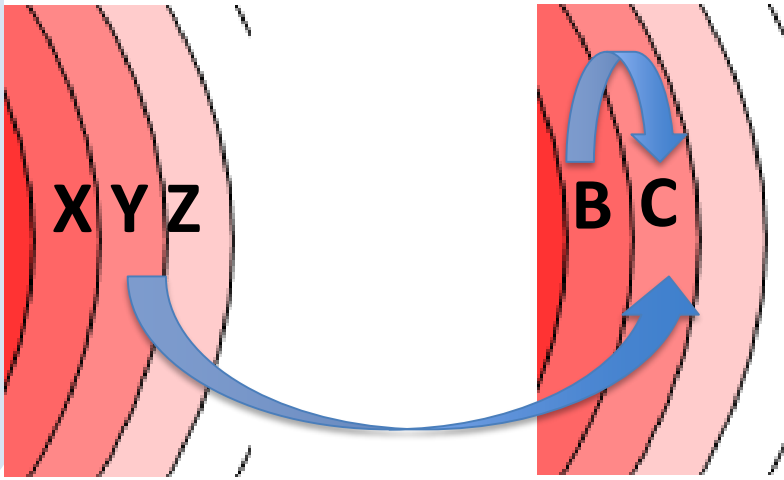
How concentration C relates to concentrations X, Y, Z ?



~5.000 simulations to learn the « rules »

Towards a Predictive model?





0 1 2 t t+1

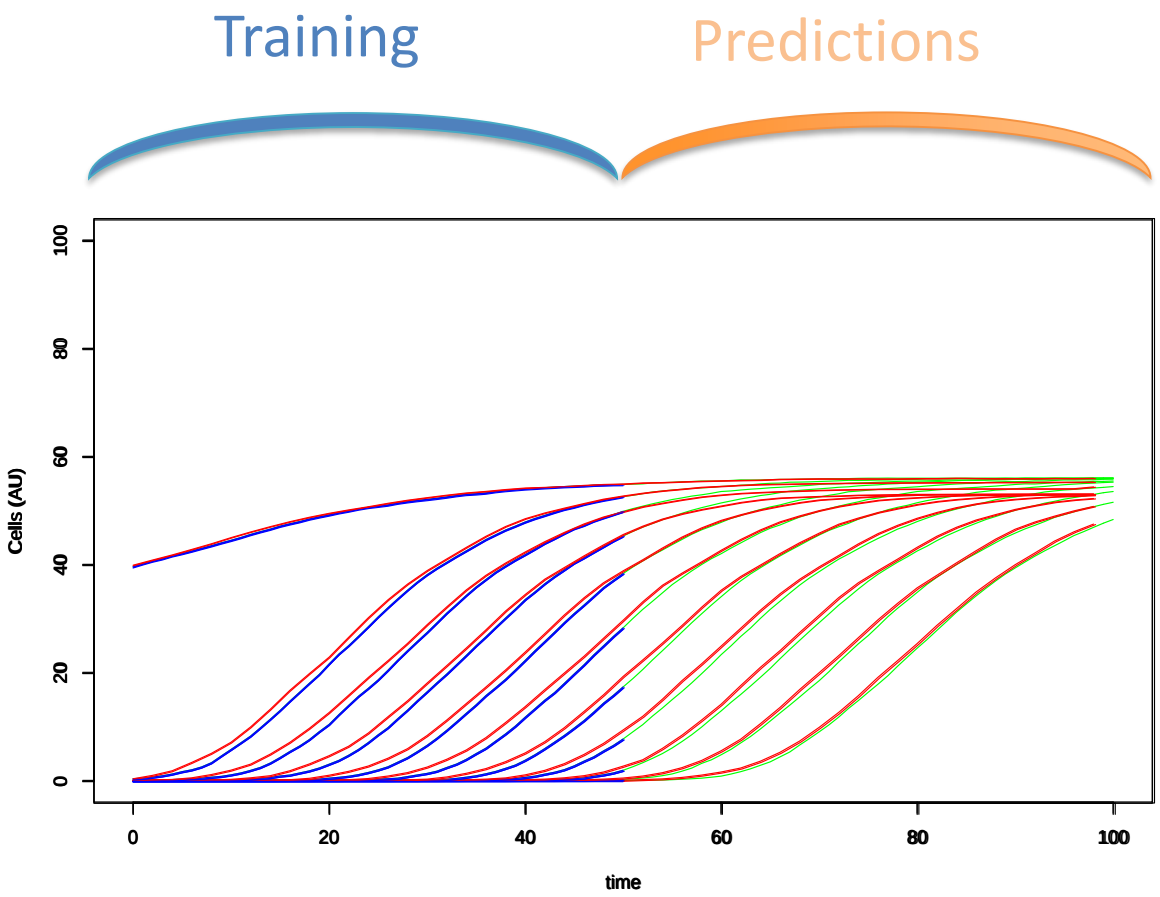
Usual DBN:

1 different probability table per time point.
Very precise, few discrete states (5/variable)
Cant handle too many time points (becomes imprecise)
No prediction capabilities,
can only « replay » time points learnt

Predictive DBNlike model

Same proba table for all time points.
Need many discrete states
(>=81/variable),
New ideas: same level relation (B->C),
reduced precision for some variables
Reparations of CPTs

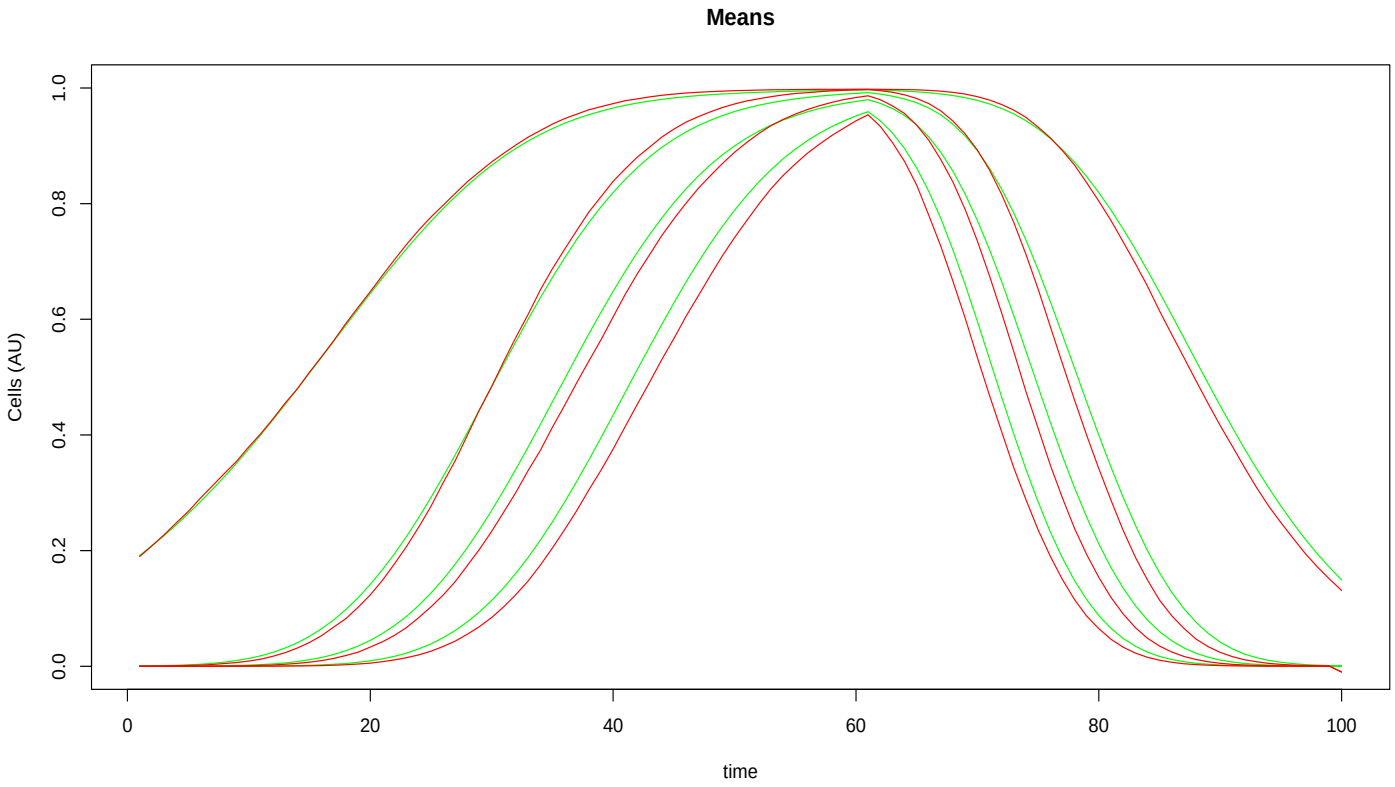
Results so far



Blue/Green : Initial model
Blue : Used for training
Red : Model prediction

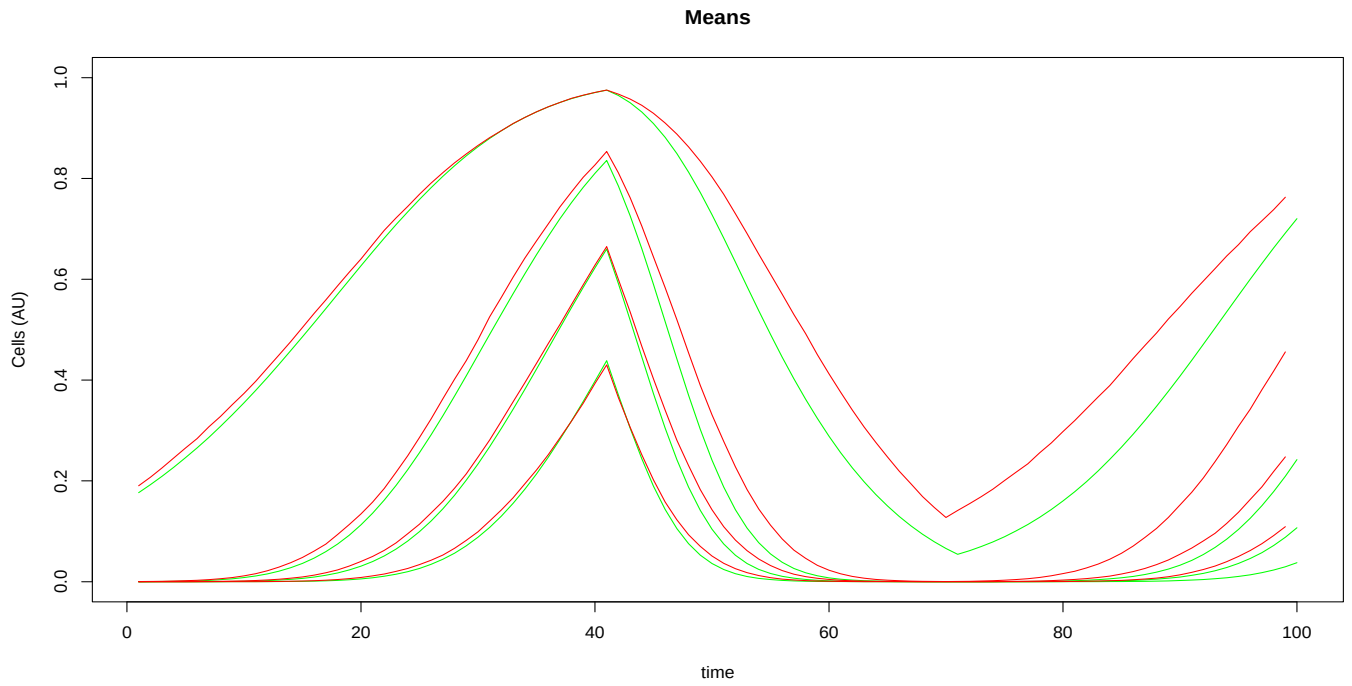
Leant from ~5000 cases.

Results so far



With treatmant where it was learnt.
(60 days)

Results so far



With treatmant at time (40d) different than learnt (60d) then
and new increase (stopping treatment)
(main problems there). => new Learning method?