Multiscale model to recapitulate breast cancer invasion phenotypes

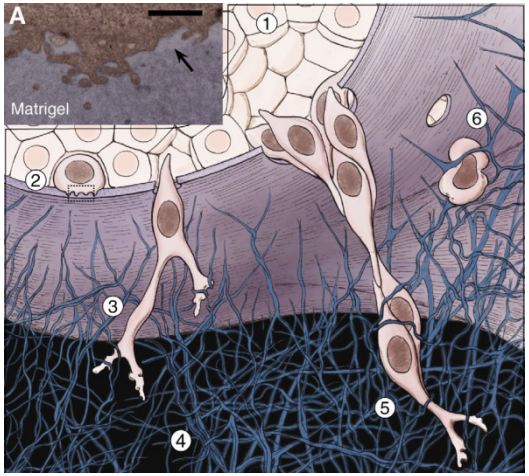
Arnau Montagud

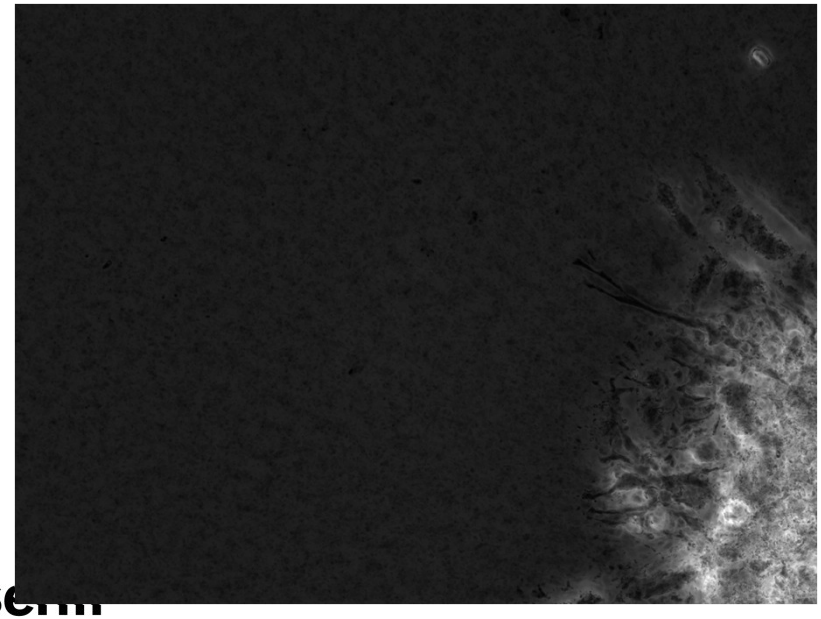
U900 – Institut Curie

Tumour invasion is diverse

- Tumour is a mix of cells with potentially different
  - Genome
  - Transcriptome
  - Neighbours
  - Local microenvironment
    - Density
    - Architecture

- Diversity of invasion modes
  - Tissue-specific
  - Epithelial to mesenchymal transition (EMT)





Video from P. Chavrier, Institut Curie

Tumour invasion is diverse

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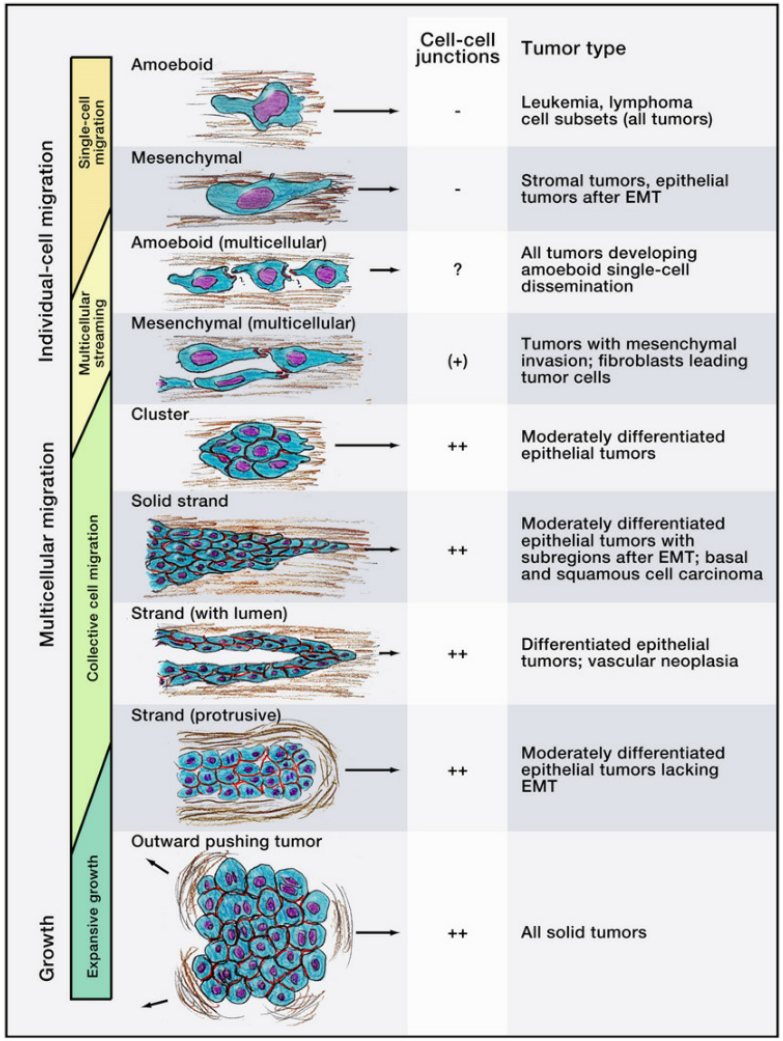


Cell fates and invasion modes

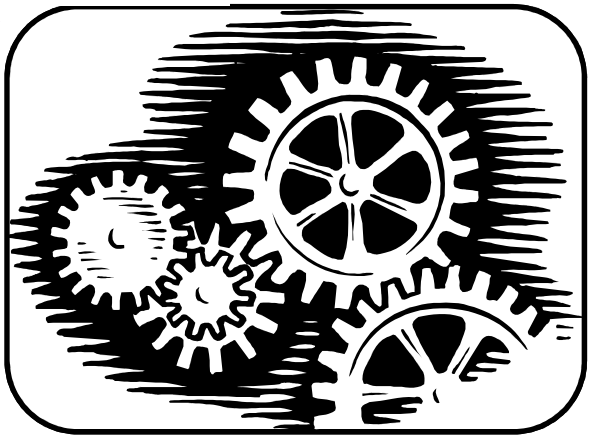
Hormones

ECM density

Mutations

Cell-cell adhesion

Cell-ECM adhesion



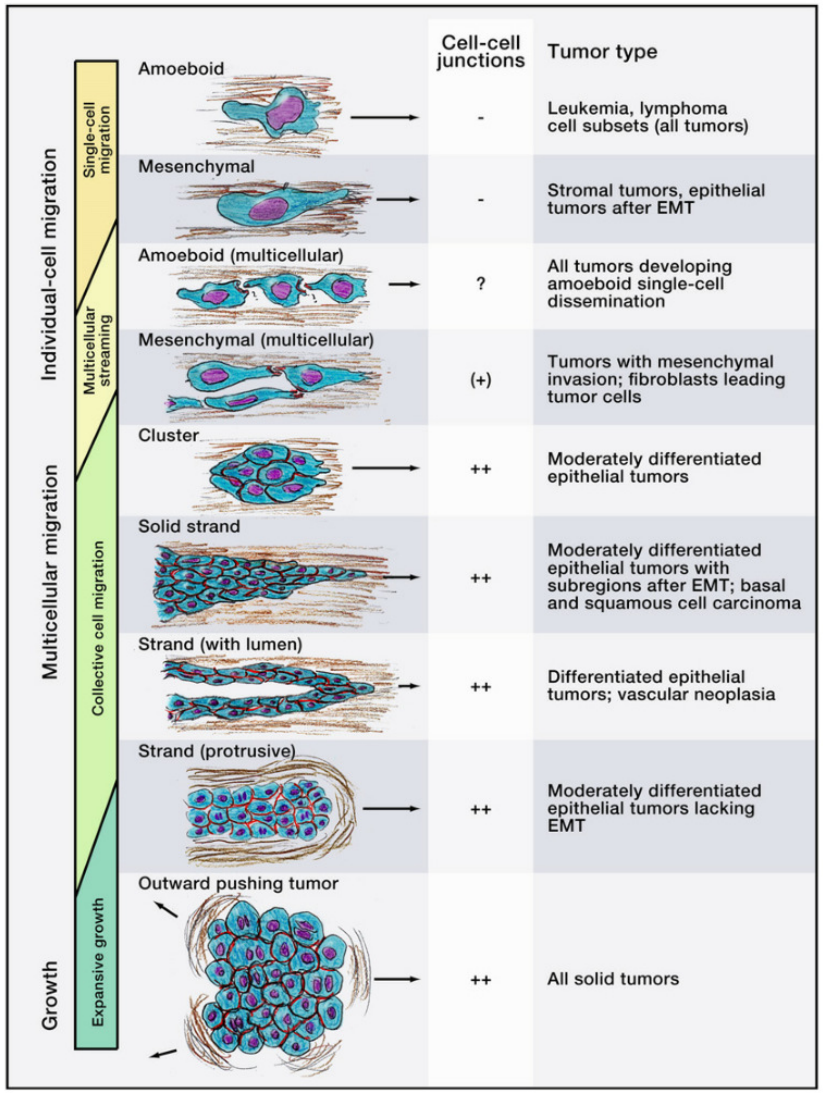
Multiscale modelling

Gene mutations

Signalling pathways

Cell - environment

ECM modification



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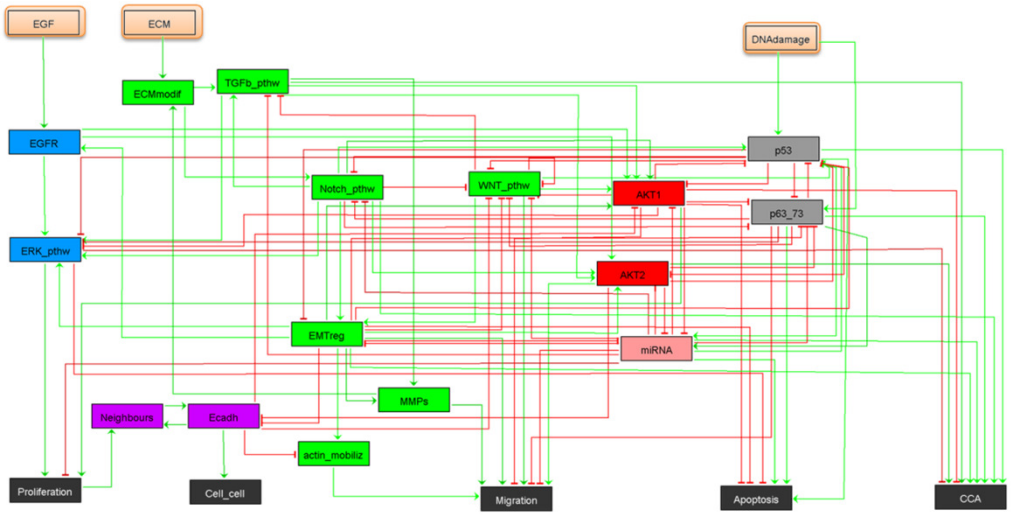
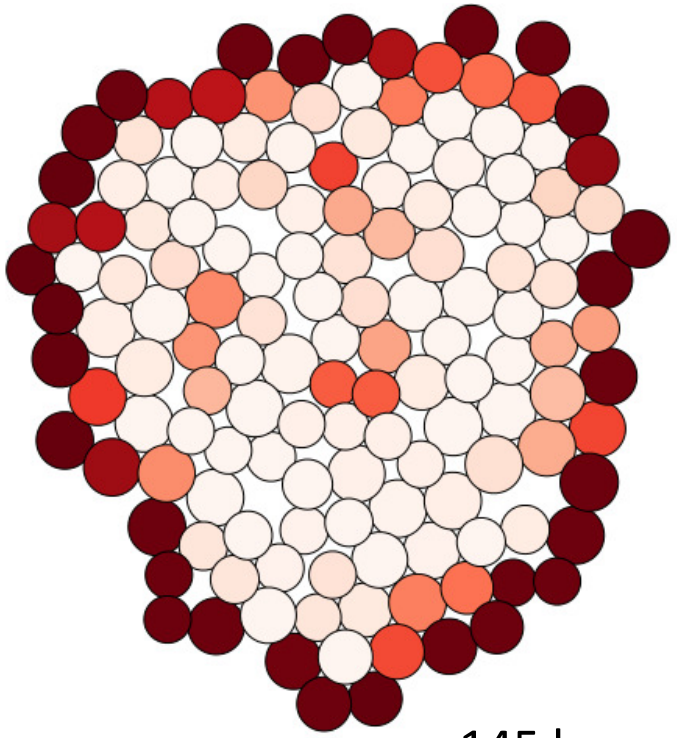
Towards multiscale modelling





145 hours

Intracellular cell fate decision modeling using discrete formalisms

Agent-based cell population modeling using physical laws and rules

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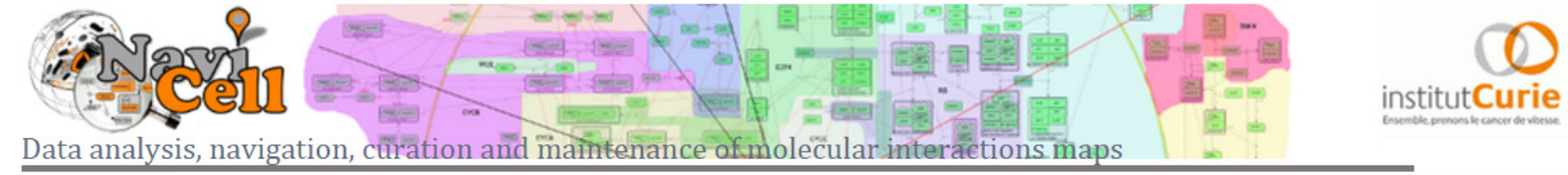
Building the network

navicell.curie.fr



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Collection of Maps

Institut Curie Collection

Cell Cycle (RB-E2F) molecular interaction map

Signalling network of EMT regulation

Ewing's sarcoma signalling network

For other maps, please have a look at the following web site: acsn.curie.fr

External Collection

In mammals

mTOR signalling network

Toll-like receptor signalling network

Resources

ACSN ATLAS OF CANCER SIGNALING NETWORKS

CELLDESIGNER

SBGN SYSTEMS BIOLOGY GRAPHICAL NOTATION

CYTOSCAPE

BINOM

LITERATURE

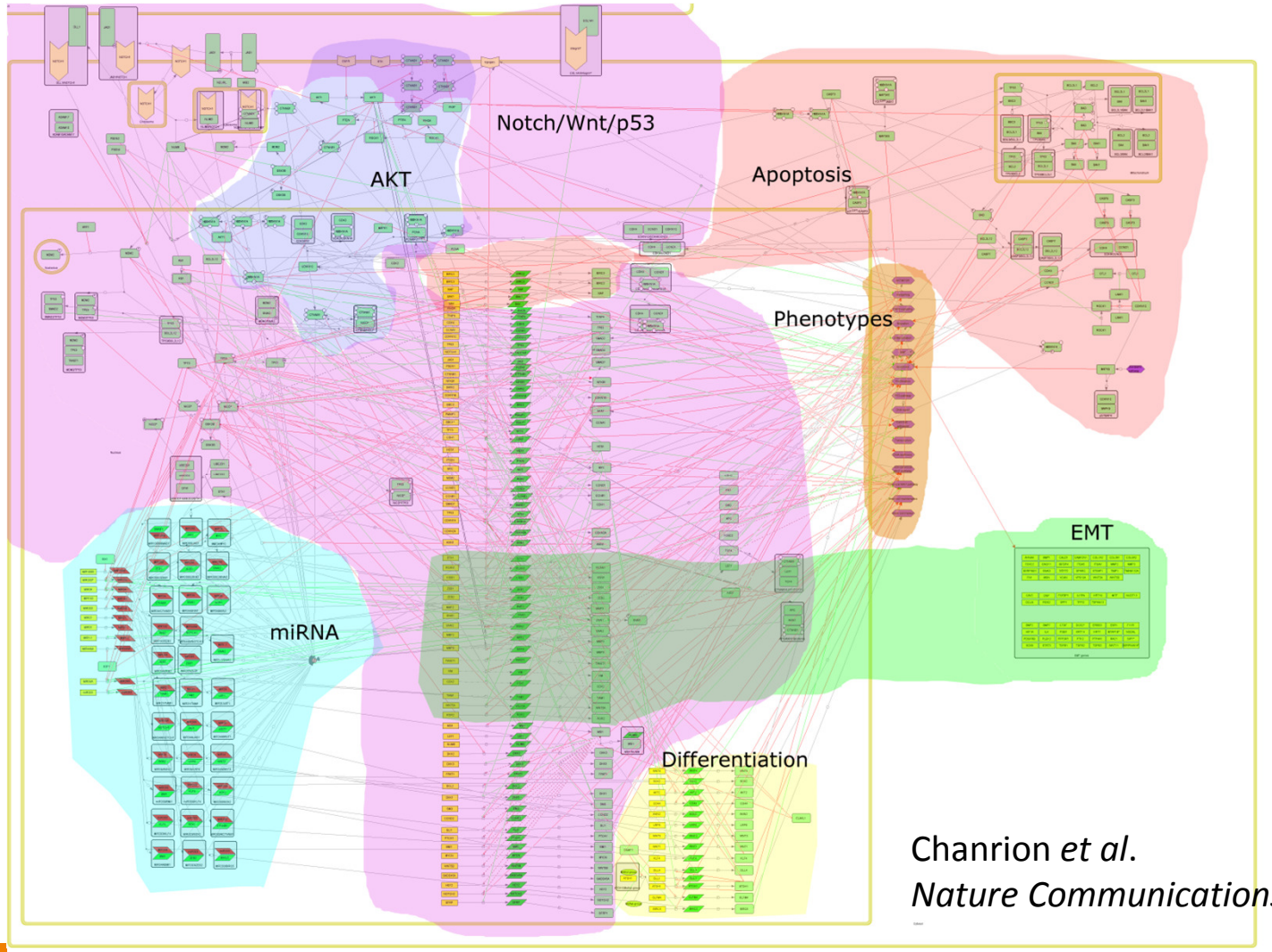
Databases

CELL SIGNALING

KEGG

PANTHER

Building the network



Chanrion *et al*.
Nature Communications 2014

From network to model

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Mathematical Modelling of Molecular Pathways Enabling Tumour Cell Invasion and Migration

David P. A. Cohen, Loredana Martignetti, Sylvie Robine, Emmanuel Barillot, Andrei Zinovyev *, Laurence Calzone * ✉

Published: November 3, 2015 • DOI: 10.1371/journal.pcbi.1004571

S4 Text. From the master model to the reduced model.

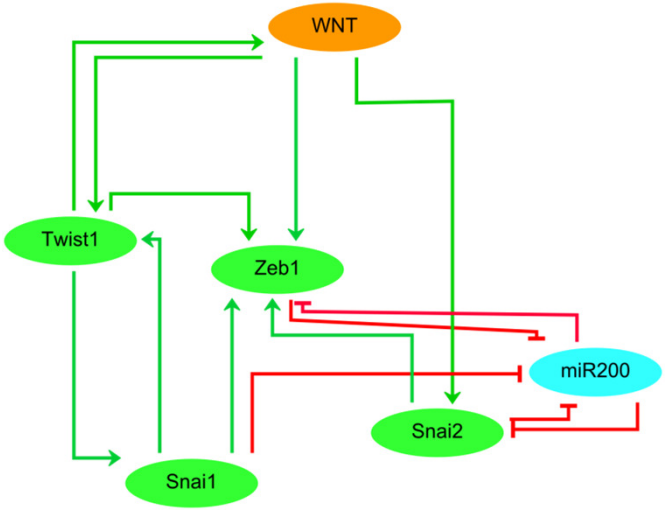
doi:10.1371/journal.pcbi.1004571.s004
(DOCX)

S1 Table. Annotations of the logical model.

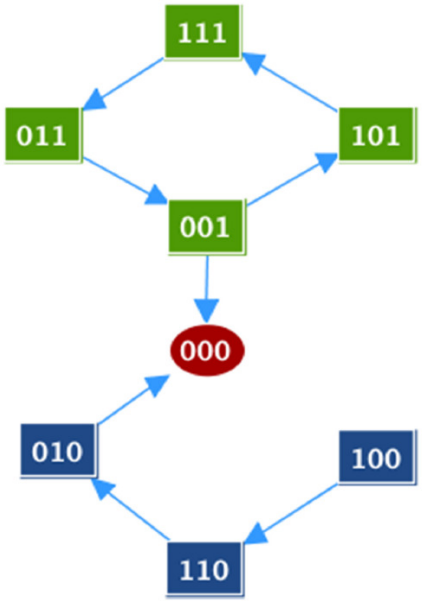
doi:10.1371/journal.pcbi.1004571.s011
(DOCX)

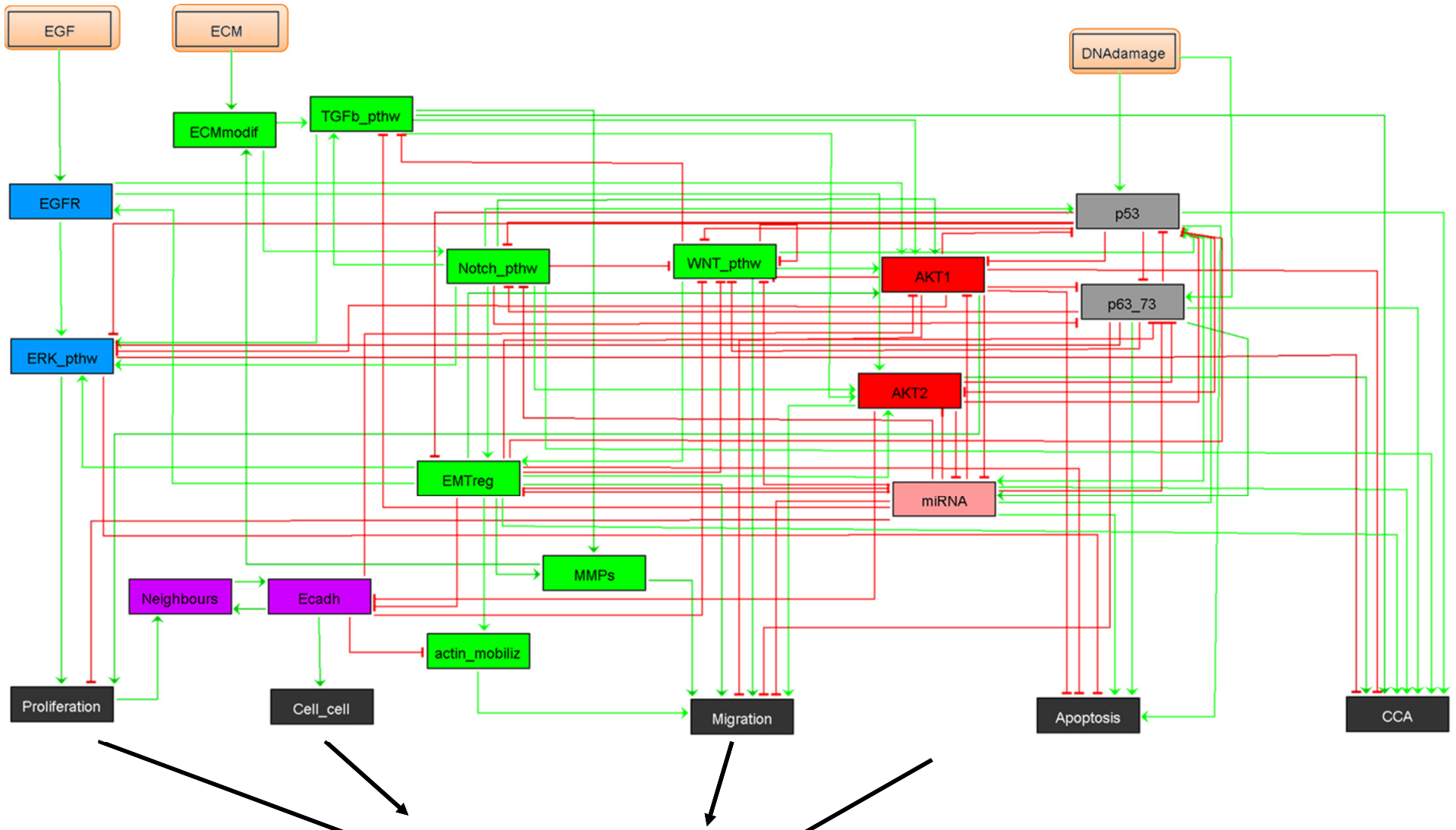
Intracellular model

- Logical model
  - Network with Boolean rules
    - NOT, AND, OR
    - Node activity is either ON or OFF
  - Stable states, limit cycle study
  - Transition state space



- Stable states = cell fates = phenotypes
  - Known mechanisms
  - Perturbations study





To cell population model's inputs

Adapted from model by Cohen et al, PLoS Comp Biol, 2015
DOI: 10.1371/journal.pcbi.1004571

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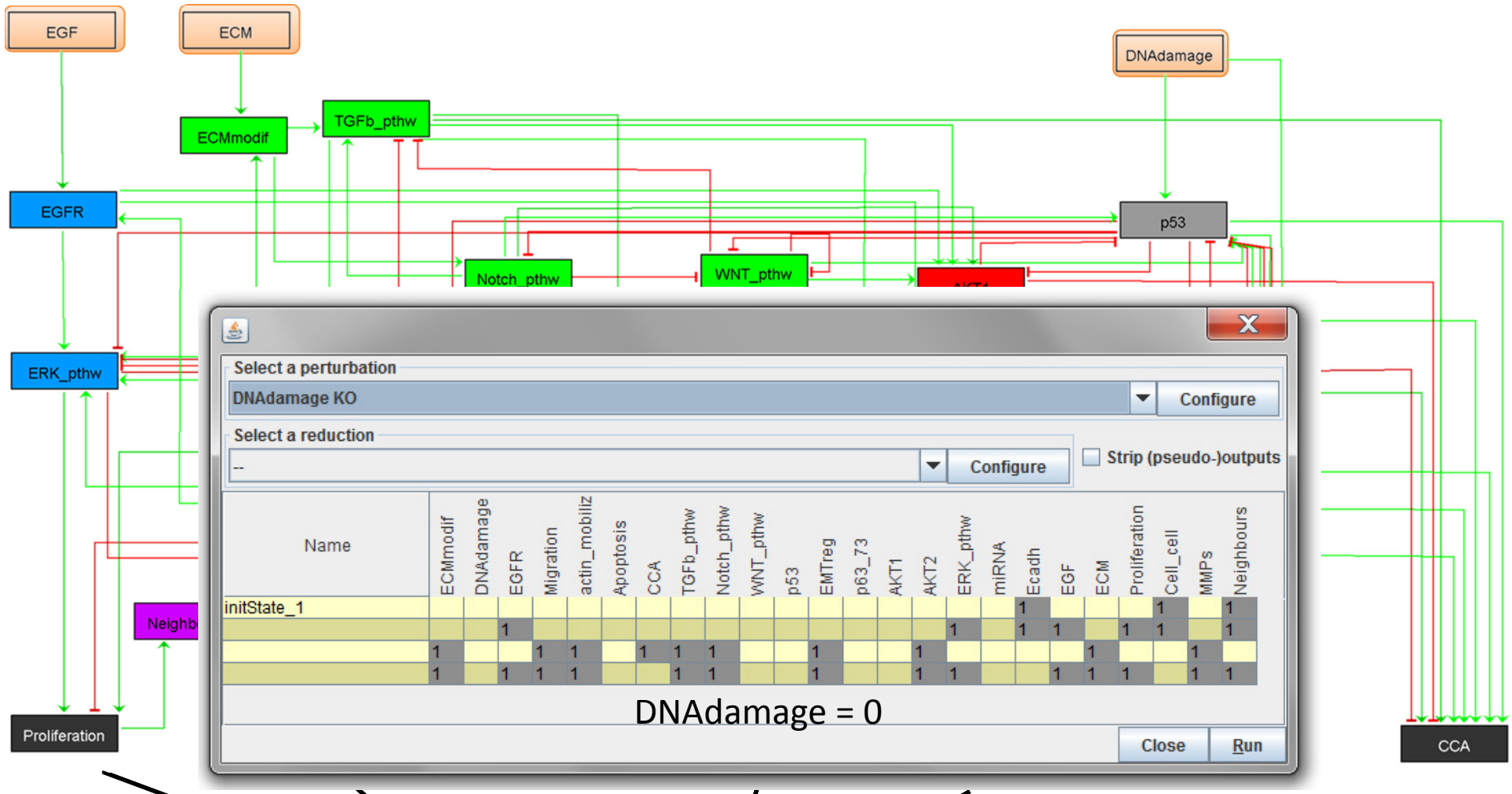

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Model outputs

- Cells resting
  - Ecadh
- Cells proliferating
  - Ecadh, EGF
- Single cell migration
  - ECM, CCA
- Proliferative cell migration
  - ECM, EGF

DNAdamage = 0

Name	ECMmodif	DNAdamage	EGFR	Migration	actin_mobiliz	Apoptosis	CCA	TGFb_pthw	Notch_pthw	WNT_pthw	p53	EMTreg	p63_73	AKT1	AKT2	ERK_pthw	miRNA	Ecadh	EGF	ECM	Proliferation	Cell_cell	MMPs	Neighbours
Cells resting																		1				1		1
Cells prolif			1													1		1	1		1	1		1
Single cell migration	1			1	1		1	1	1			1			1					1			1	
Prolif cell migration	1		1	1	1			1	1			1			1	1			1	1	1		1	1

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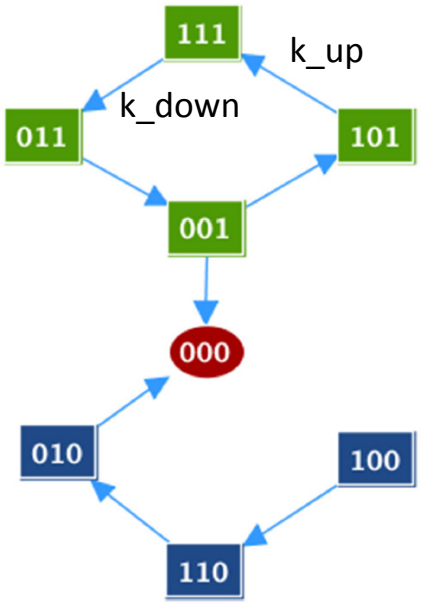
MaBoSS simulation

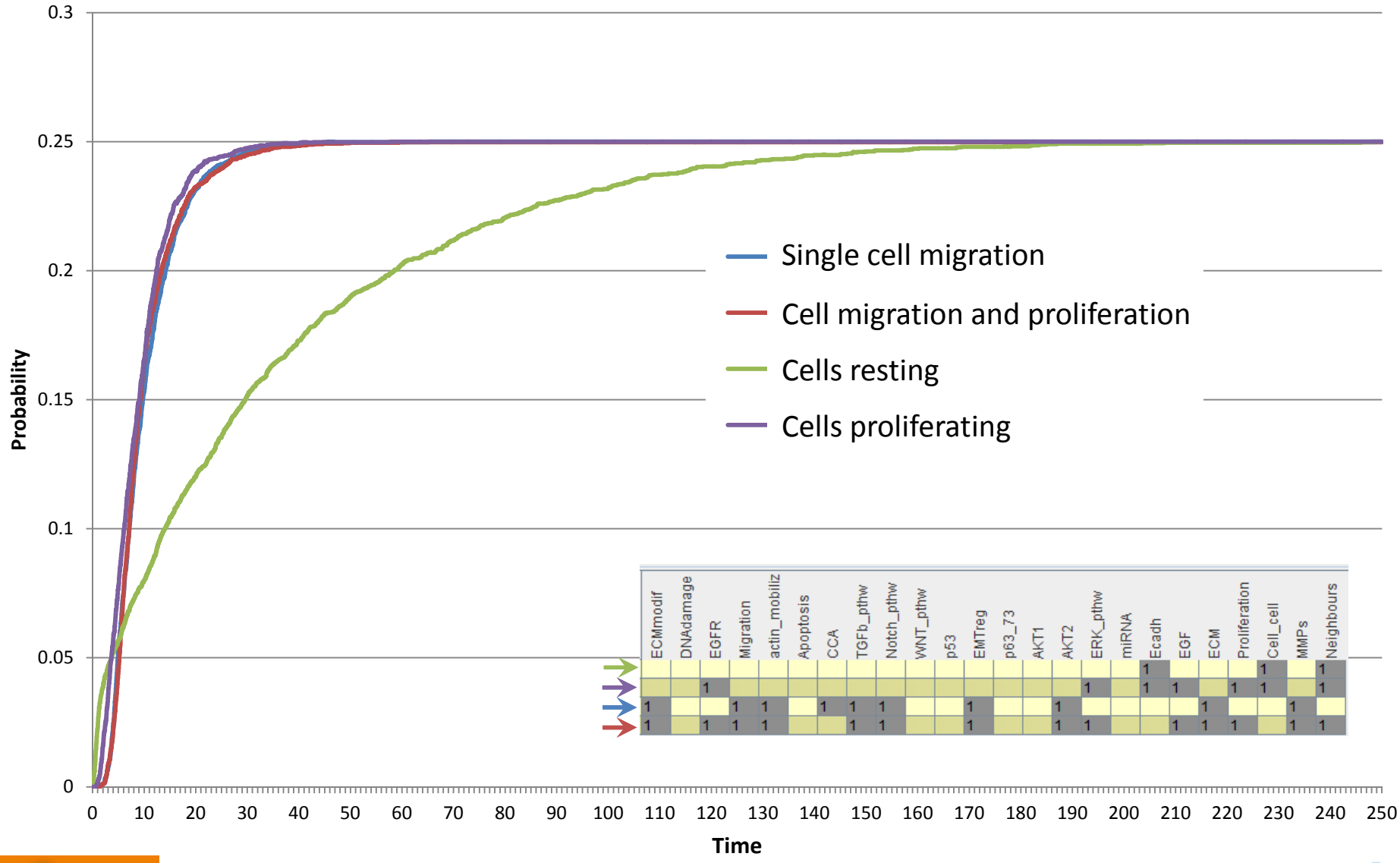
- Software developed by Stoll *et al*, *BMC Systems Biology* 2012
  - DOI: 10.1186/1752-0509-6-116

- Gillespie algorithm on the Boolean transition state space
  - Study probabilities of the possible solutions in a population of cells
  - Parameters for 0 → 1 and 1 → 0

- Perturbations can be studied in a probabilistic manner



Evaluating the model without DNA damage



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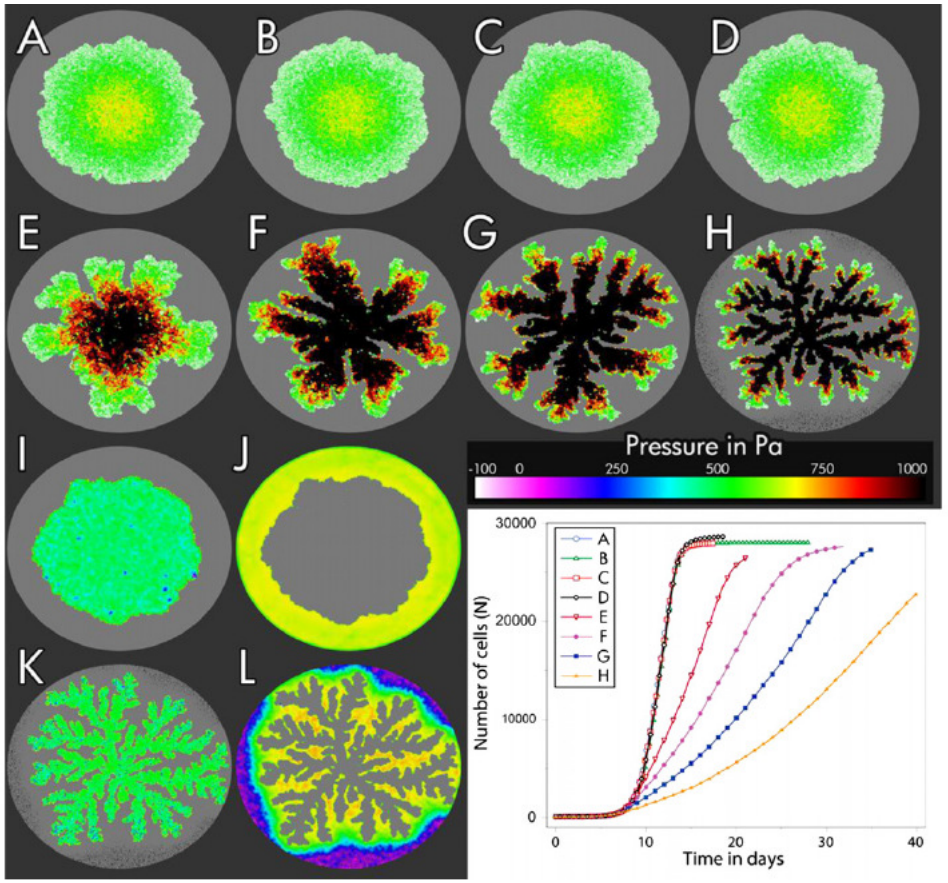
Intercellular model

- Centre-based model
- Langevin equation
  - used to model macroscopic events
  - Migration, Division, Adhesion
    - tensors are defined for each effect



$$\underbrace{\underline{\underline{\Gamma}}^{\mathrm{f}}_{\mathrm{is}}\underline{v}_{\mathrm{i}}}_{\text{s-friction}} + \sum_{\mathrm{j\,nn\,i}} \underbrace{\underline{\underline{\Gamma}}^{\mathrm{f}}_{\mathrm{ij}}(\underline{v}_{\mathrm{i}} - \underline{v}_{\mathrm{j}})}_{\text{cell-cell friction}} = \underbrace{\sum_{\mathrm{i\,nn\,j}} \underline{F}_{\mathrm{ij}}}_{\text{forces}} + \underbrace{\underline{f}_{\mathrm{i}}(t)}_{\text{noise}} + \underbrace{\chi \underline{\nabla} Q(t)}_{\text{chemotaxis}}$$

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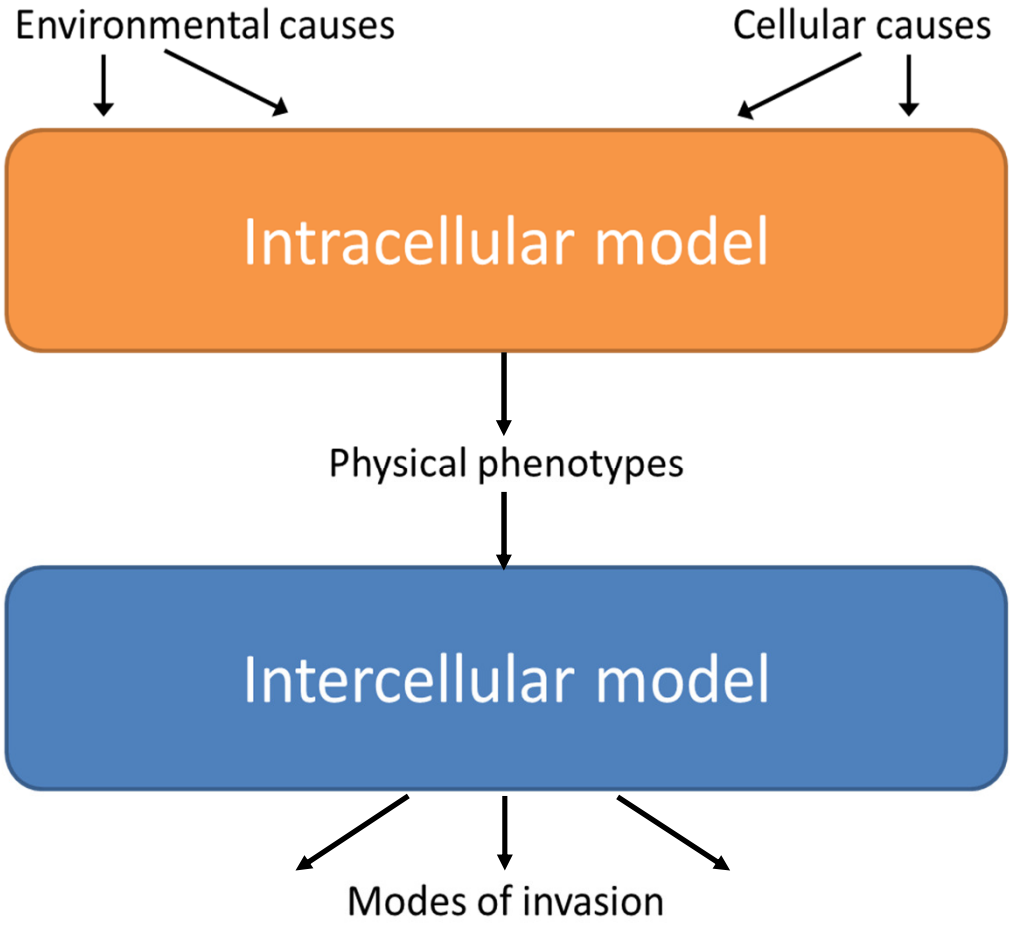
Integrate both models



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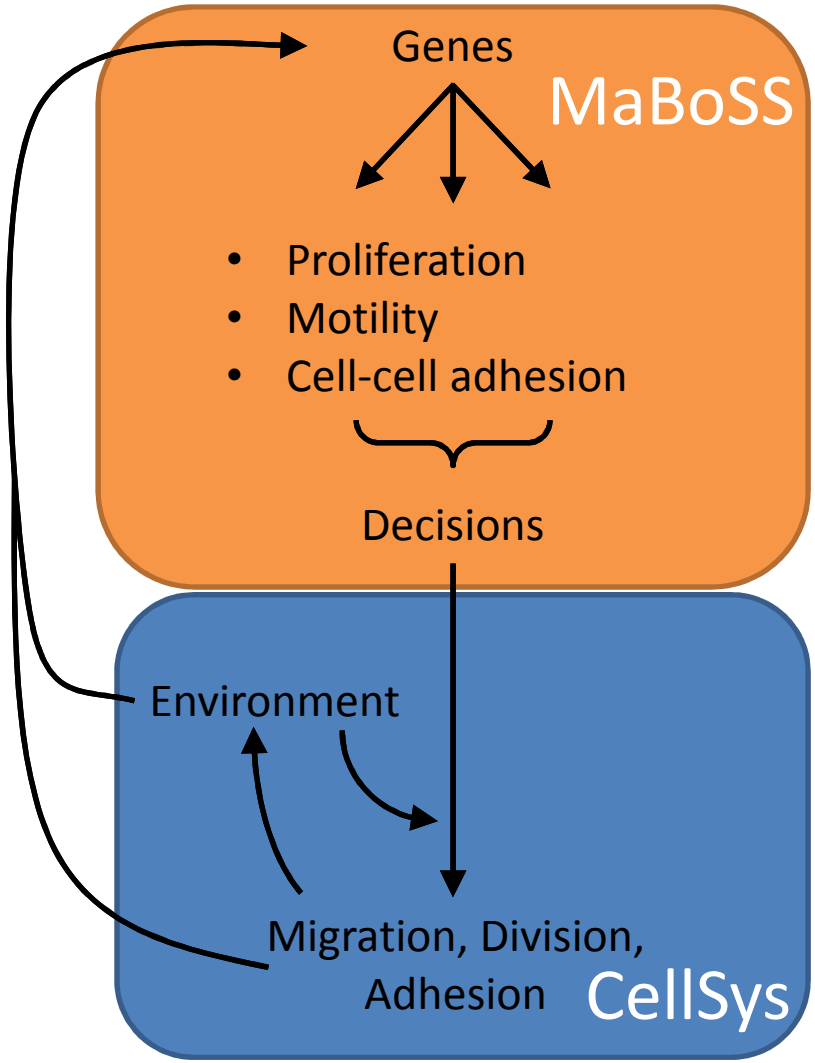
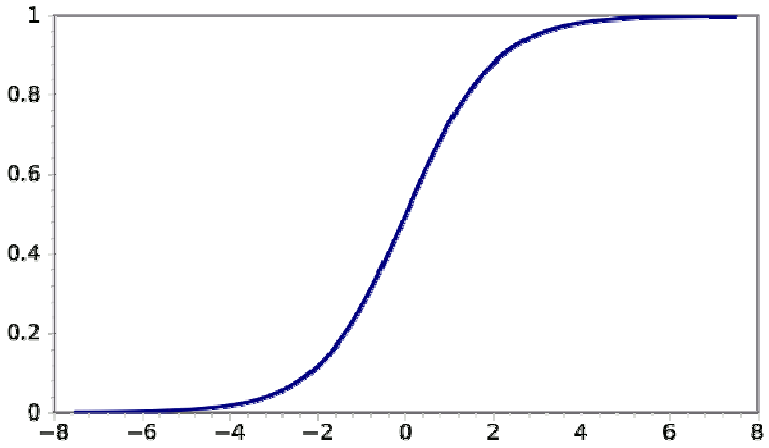


CellSys-MaBoSS feedback



- Sigmoid shape
  - Max, min and slope

Feedback MaBoSS → CellSys

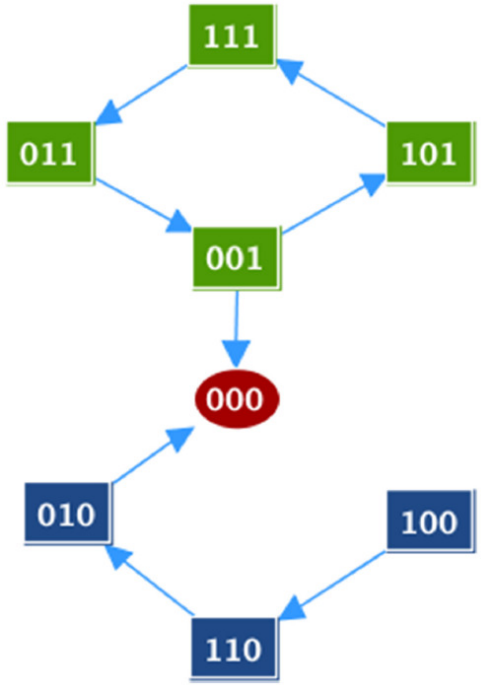
- State “1” causes CS parameter to have “greater” values
- State “0” causes CS parameter to have “lower” values

CellSys-MaBoSS feedback

Feedback CellSys → MaBoSS

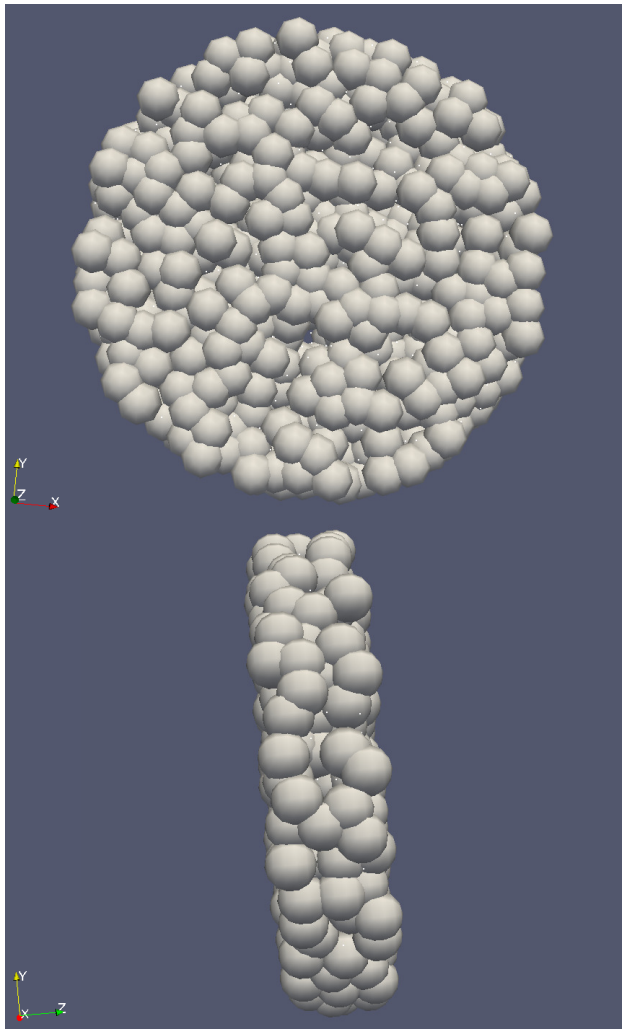
- Parameter (from CS) above given threshold forces state transition from 0 to 1

- Specifically,
  - ECM sensing
  - Neighbours presence



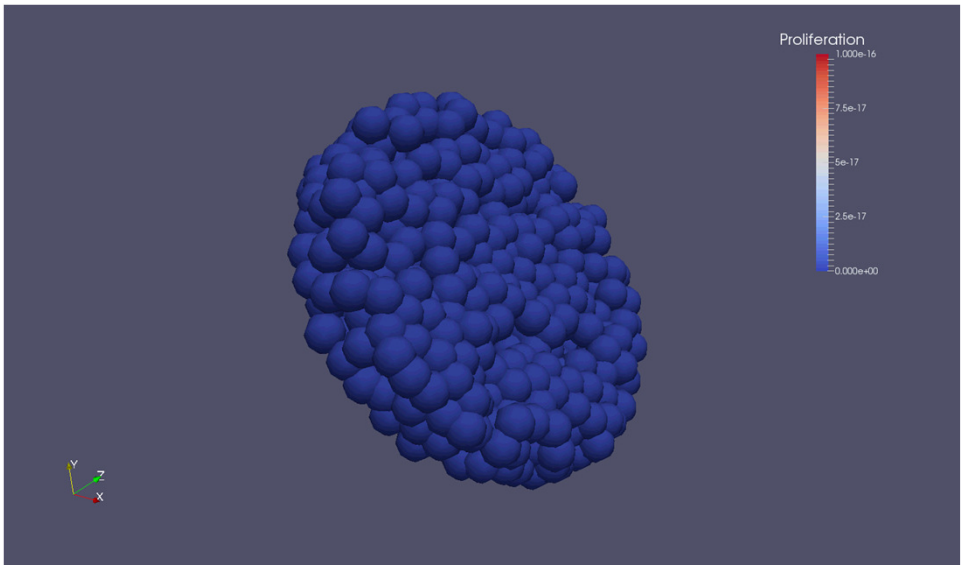
Experimental setup

- It's alive !
  - 3D simulation
  - "Organic" Petri dish
- Multi-scale modelling of
  - Physics-oriented cellular population
  - Biology-oriented intracellular cell fates



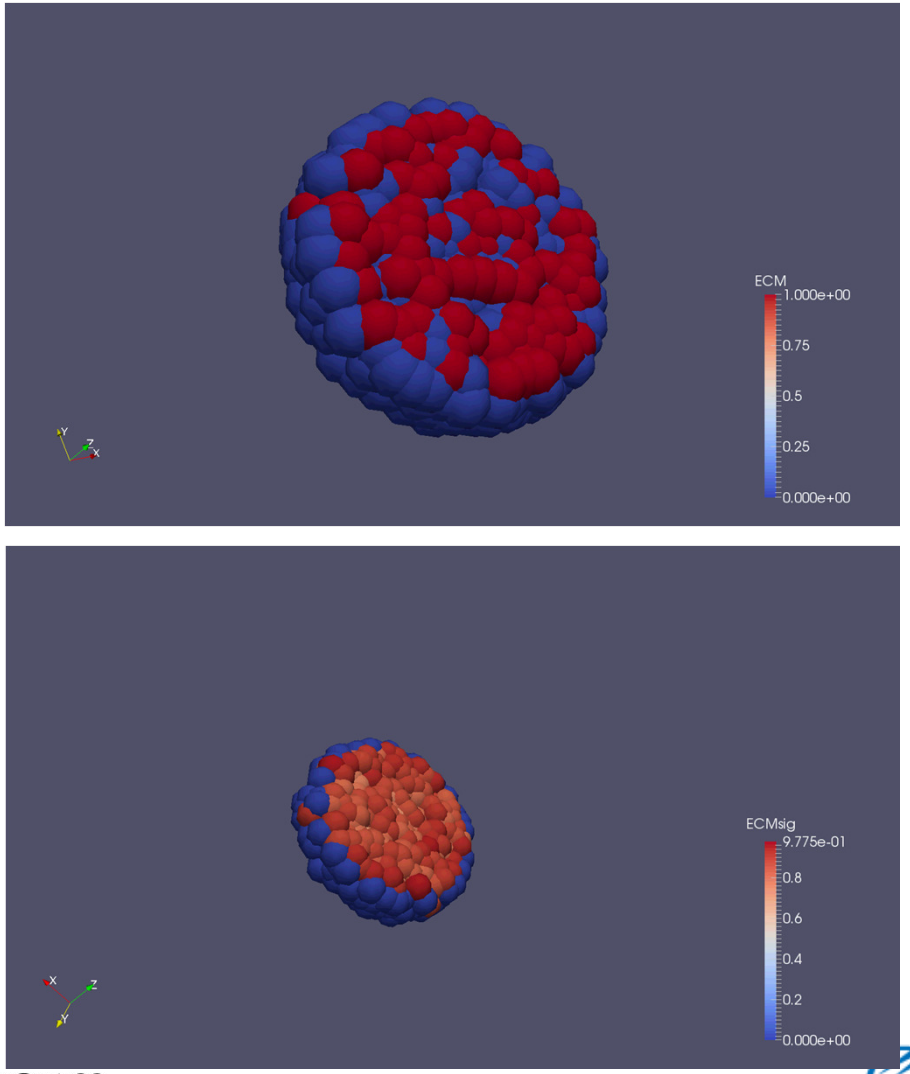
Resting cells state

- It's alive !
  - 3D simulation
  - "Organic" Petri dish
- Multi-scale modelling of
  - Physics-oriented cellular population
  - Biology-oriented intracellular cell fates
- Stable state
  - Cells resting
- Colour
  - Red is Proliferation



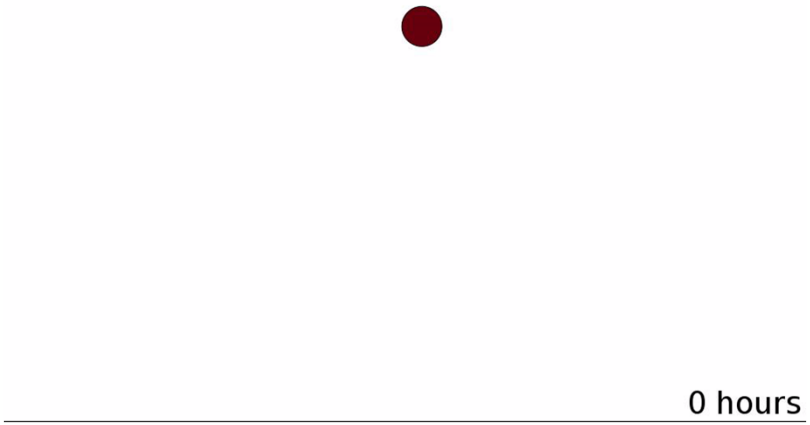
Cancer growth

- It's alive !
  - 3D simulation
  - "Organic" Petri dish
- Multi-scale modelling of
  - Physics-oriented cellular population
  - Biology-oriented intracellular cell fates
- Stable state
  - Cells proliferating
- Colour
  - (Up) Red is ECM node status
  - (Down) Red is ECM signal

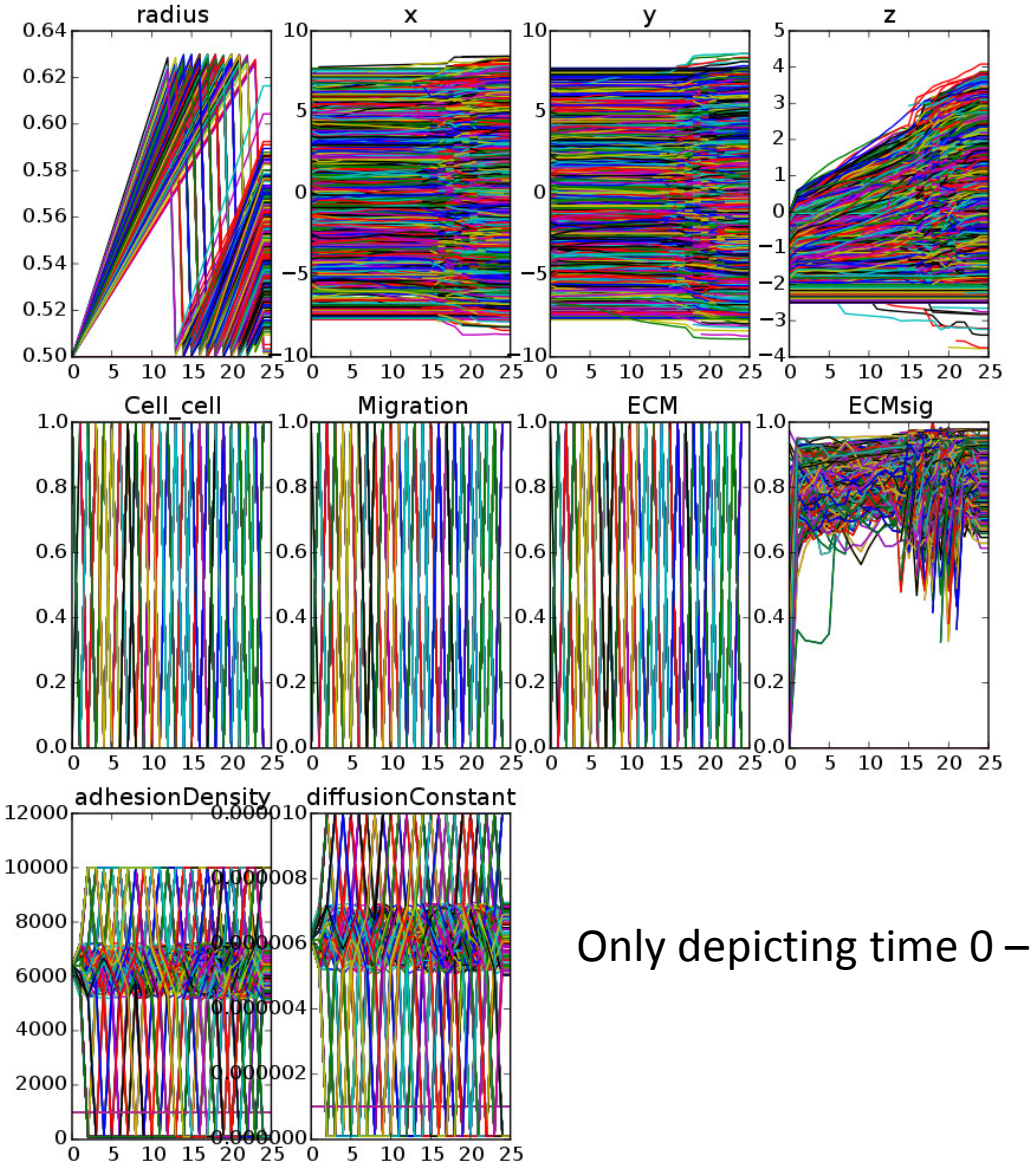


2D slice of cancer growth

- It's alive !
  - 2D representation of a 3D simulation
- Multi-scale modelling of
  - Physics-oriented cellular population
  - Biology-oriented intracellular cell fates
- Stable state
  - Cells proliferating
- Shades of red
  - Potential cell motility



Data underlies video



Only depicting time 0 – 24 h

Acknowledgments

Computational Systems Biology group

Barillot team

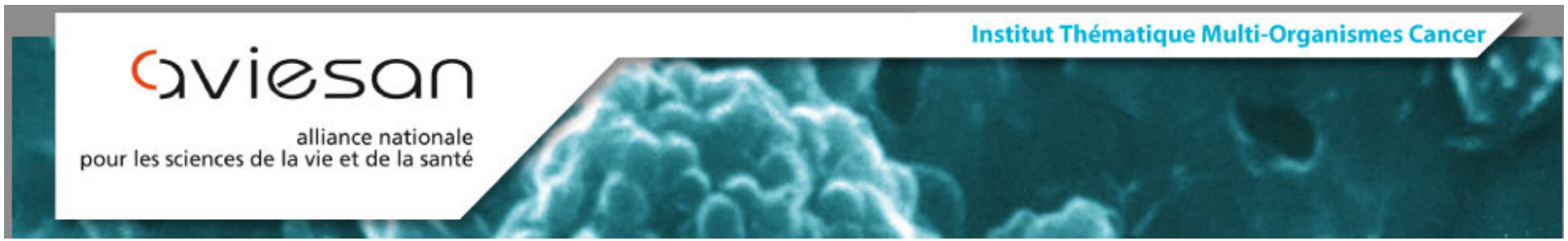
Laurence Calzone
David Cohen
Andrei Zinovyev
Luca Grieco

Valentina Boeva
Eric Bonnet
Urszula Czerwinska
Paul Deveau
Maria Kondratova
Inna Kuperstein
Christine Lonjou
Loredana Martignetti
Victorin Martin
Daniel Rovera
Christophe Russo

ITMO Cancer's INVADE project

Chavrier team
Soumelis team
Mechta-Grigoriou team
Vincent-Salomon team
Radvanyi team

Drasdo team



Computational Systems Biology of Cancer

group at Institut Curie http://sysbio.curie.fr

Directions:

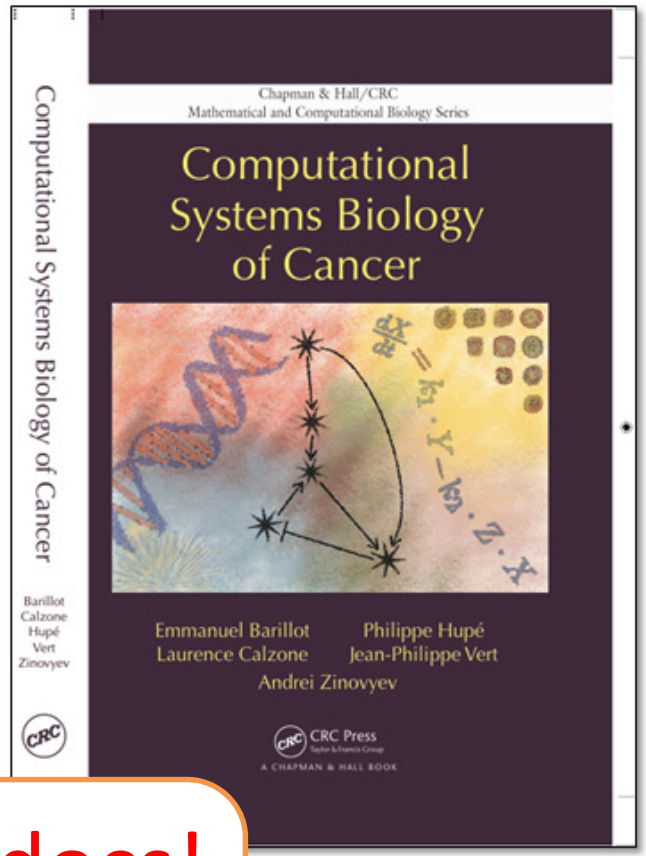
1) Omics data analysis using **biological networks**

2) Statistical **analysis of multi-level omics data**

3) **Mathematical modeling** of networks involved in tumor growth, interaction with microenvironment, metastases

4) Methods and **software development** for systems biology

Dynamic international and multidisciplinary environment
Numerous collaborative projects on concrete questions cancer biology and cancer treatment
Access to original large-scale data from application of latest technologies



We are HIRING postdocs!

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