Artificial Intelligence for multimodal data integration and multiscale modeling in oncology: toward a digital twin for the cancer patient

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Institut Curie - INSERM U900 / Mines ParisTech - PSL University

Paris Artificial Intelligence Research Institute (PRAIRIE)

RIKEN-AIP & PRAIRIE Joint Workshop
on Machine Learning and Artificial Intelligence

Tokyo, 20-21 March 2023

institutCurie

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

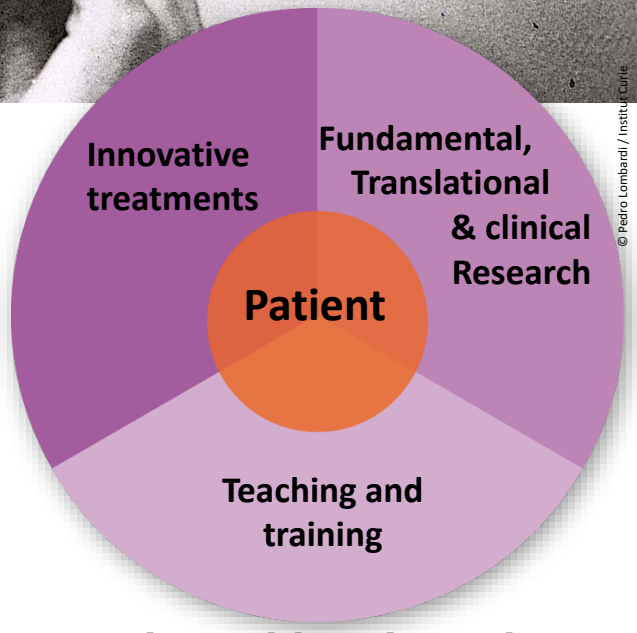
PR[AI]RIE
PaRis Artificial Intelligence Research InstitutE

MINES ParisTech

PSL RESEARCH UNIVERSITY

Institut Curie

- **A Comprehensive Cancer Center**
- Private **Fundation**, state-approved, established 1909.
- Collecting **charity donations**
- **3200 collaborators, 100 000 m²**
- **18 core facilities**
- **High Performance Computing**

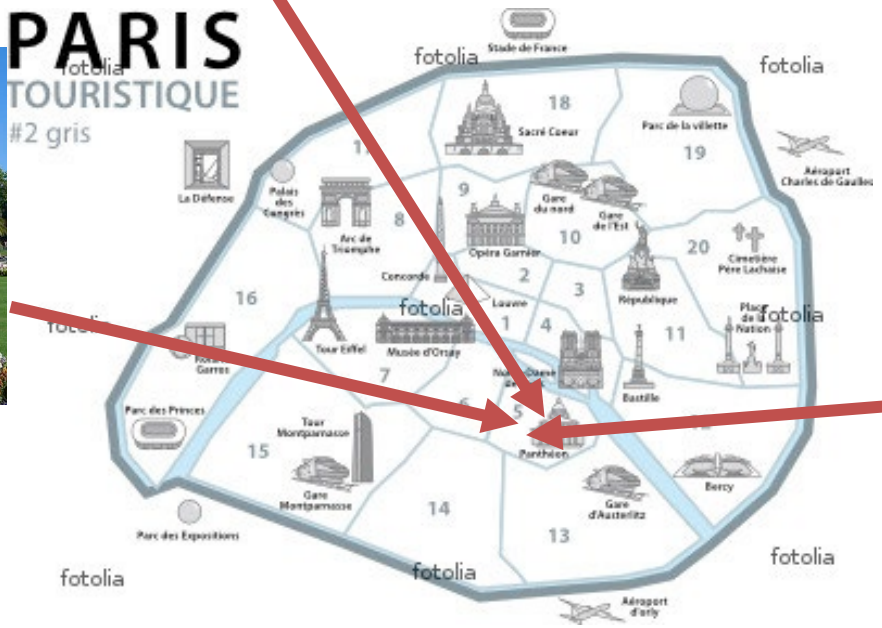


A reference and a continuum of expertise on cancer research and treatment

Focus on pediatric tumors, uveal melanoma, lung, breast carcinomas…

Interdisciplinary research : biology, physics, medicine, chemistry, comput.

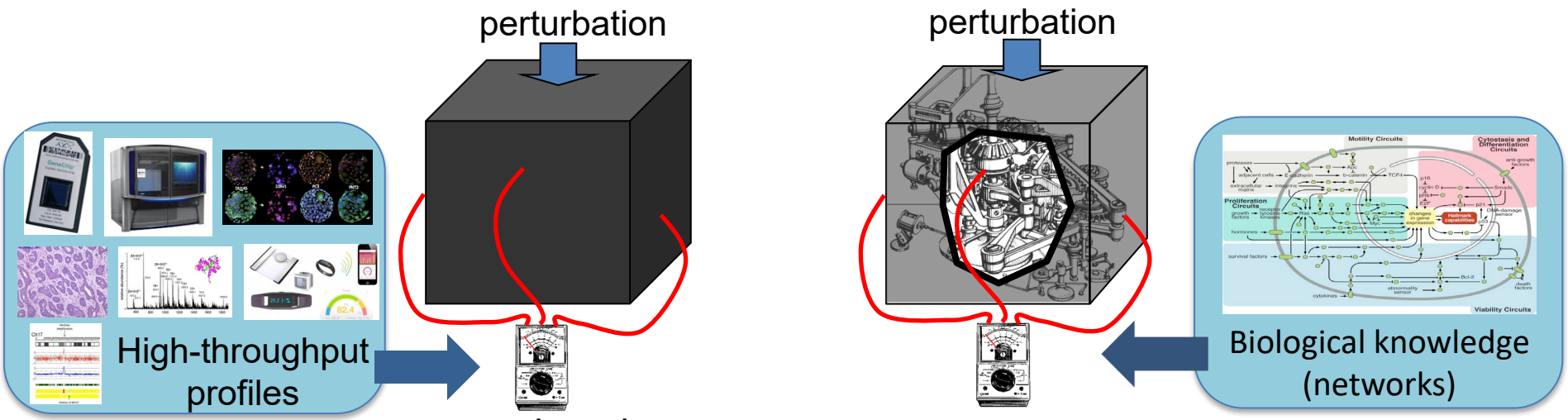
Department of Computational Oncology at Institut Curie



- ***Seeking students and postdocs in computational (systems) biology: contact us!***

Emmanuel.Barillot@curie.fr

Computational Systems Biology of Cancer



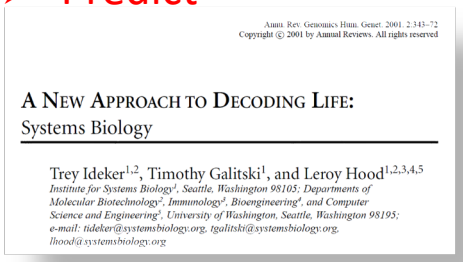
Data-driven
Phenomenology?

➢ Predict

Curie approach

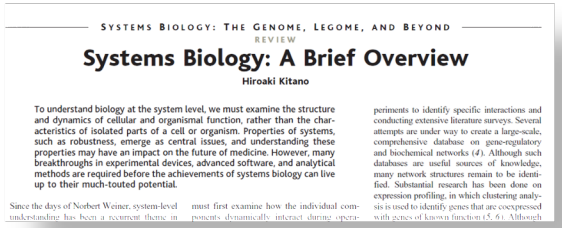
Model-driven
Abstraction?

➢ Explain



A NEW APPROACH TO DECODING LIFE:
Systems Biology

Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]



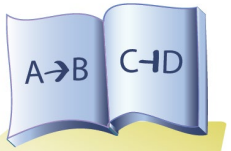
SYSTEMS BIOLOGY: THE GENOME, LEGOME, AND BEYOND

Systems Biology: A Brief Overview

Hiroaki Kitano

Computational Systems Biology of Cancer lab

http://sysbio.curie.fr (U900 INSERM)



KNOWLEDGE MAPS

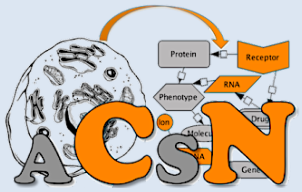
MECANISTIC MATH MODELING

Part 2 of this talk

PhysiCell

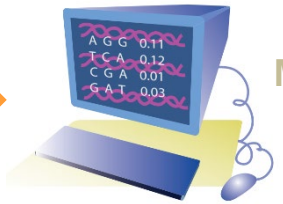
MaBoSS

acsn.curie.fr



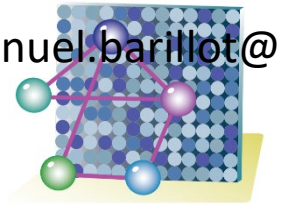
Atlas of Cancer Signaling Networks

CANCER BIOLOGY & CLINICS



DEVELOPING METHODOLOGY & SOFTWARE FOR SYSBIO

MULTI-MODAL DATA ANALYSIS



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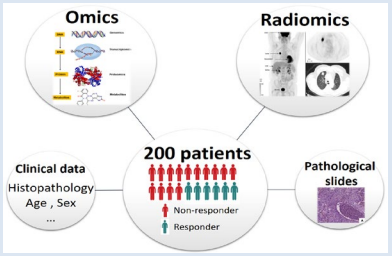
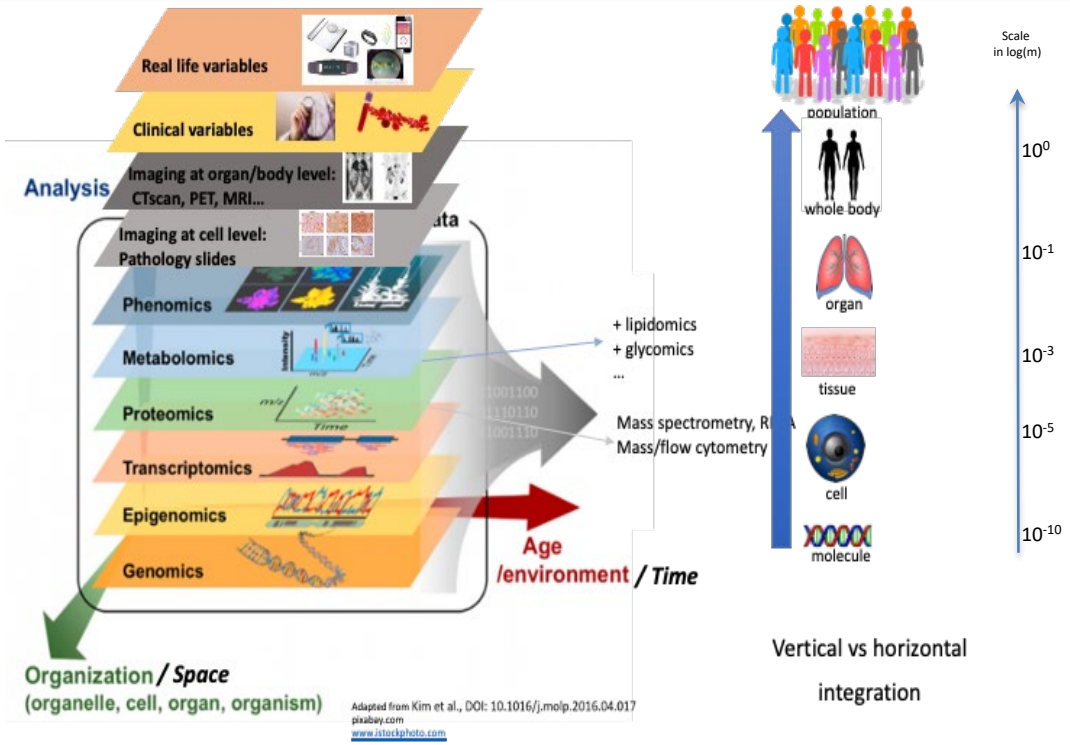
Part 1 of this talk



Main axes of research

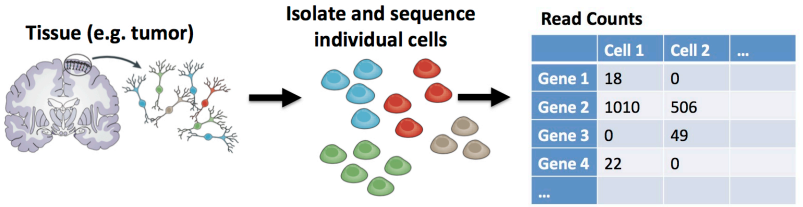
1 Multimodality:
Integrative analysis



Multiple data modalities: other dimensions

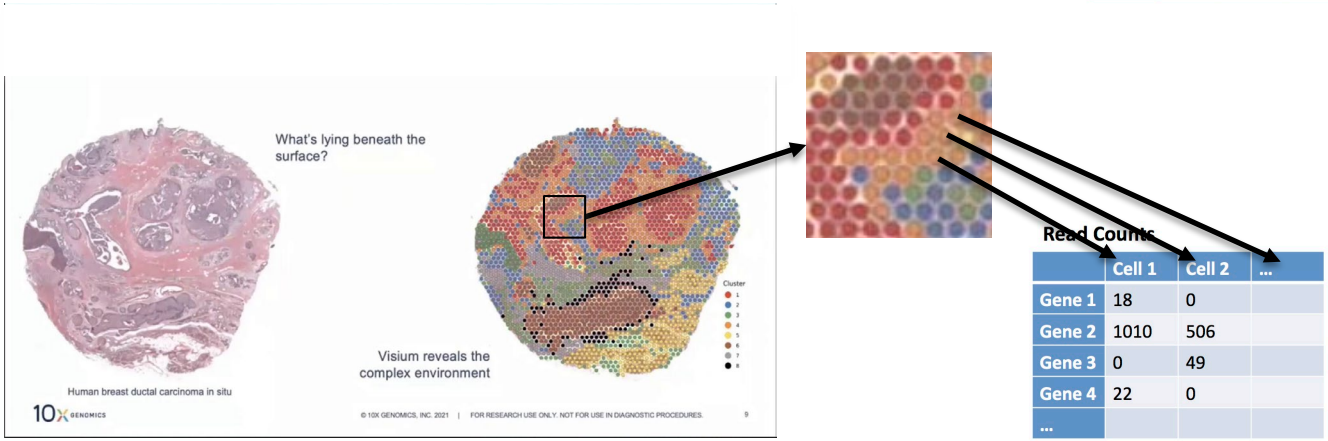
- Vertical (more data modalities) vs horizontal (more samples) vs diagonal (other samples with new modality) integration

- Single cell omics (genome, transcriptome, epigenome, proteome…)



	Cell 1	Cell 2	…
Gene 1	18	0	
Gene 2	1010	506	
Gene 3	0	49	
Gene 4	22	0	
…			

- Spatial omics



	Cell 1	Cell 2	…
Gene 1	18	0	
Gene 2	1010	506	
Gene 3	0	49	
Gene 4	22	0	
…			

- Time series (imaging, ctDNA…)
- …

Main axes of research

1 Multimodality:
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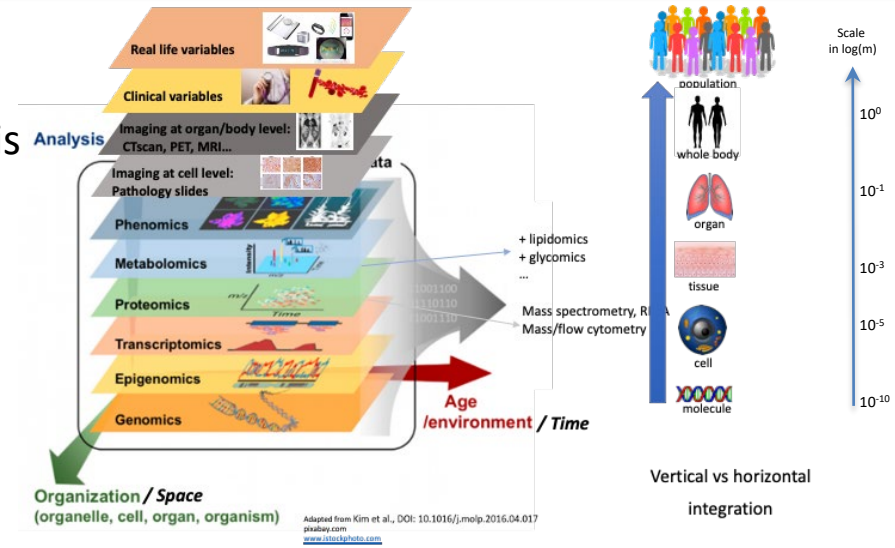
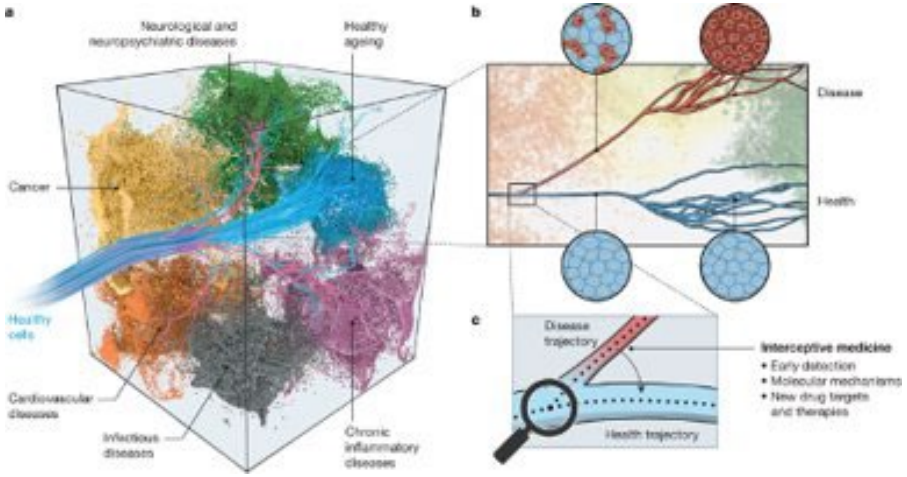
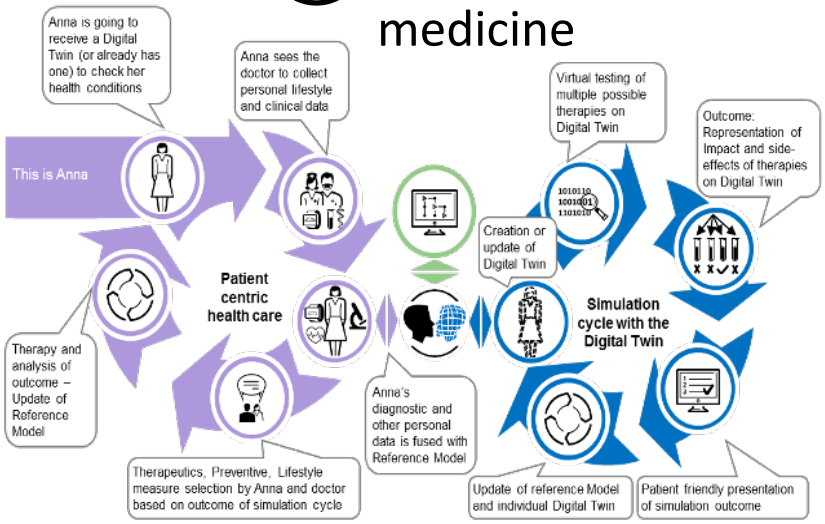


2 Trajectories: interceptive medicine



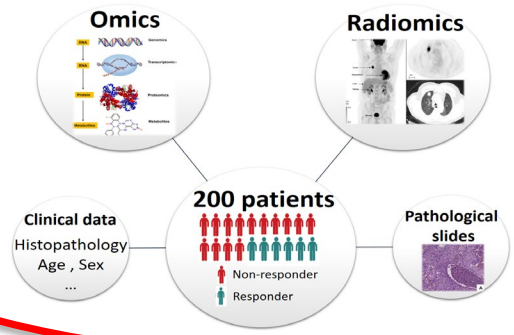
3 Digital twins : precision medicine



Two typical projects

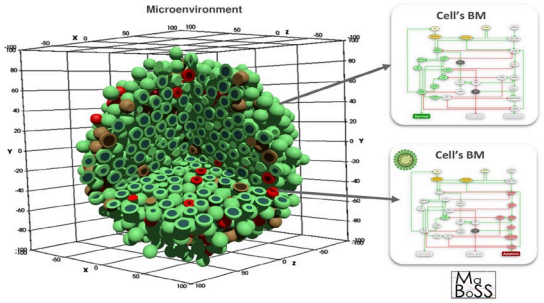
PROJECT 1

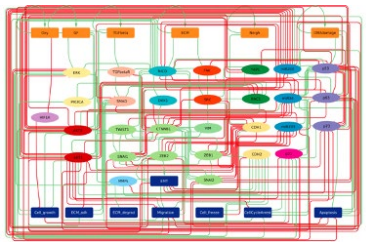
TIPIT: Signature of Immunotherapy response in Non Small Cell Lung Cancer



PROJECT 2

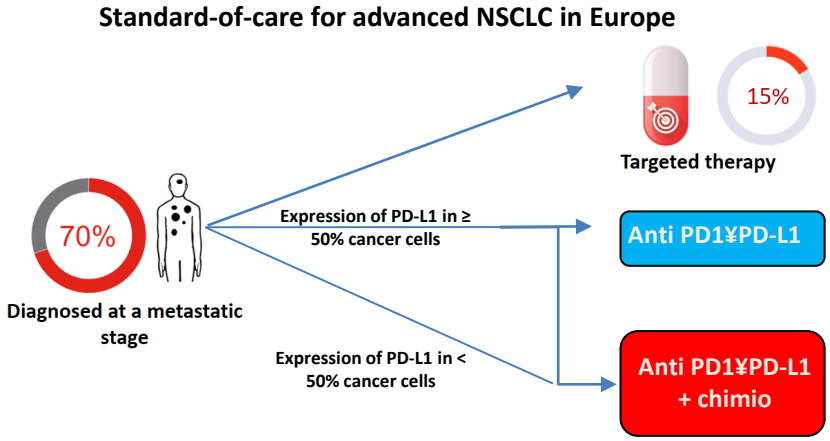
Spatial modelling of a tumour growth

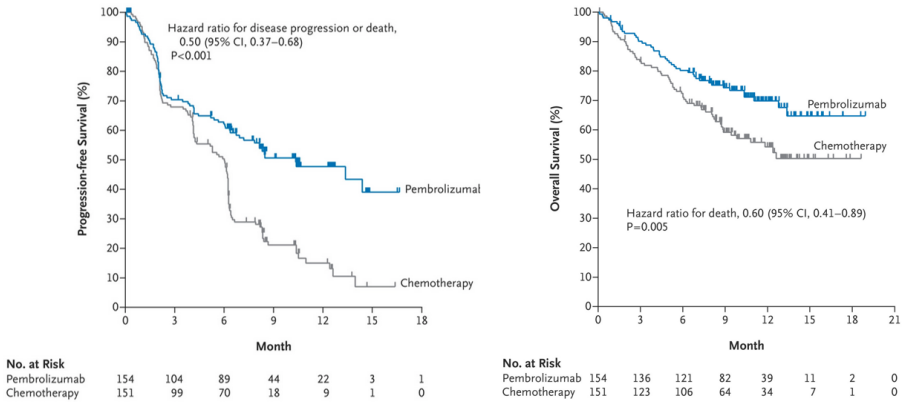




TIPIT: Signature of Immunotherapy response in Non Small Cell Lung Cancer

- Lung cancer is the leading cause of cancer-related death worldwide
- The most frequent type, non-small cell lung cancer (NSCLC) is diagnosed at a metastatic stage in about 70% of the patients
- Checkpoint inhibitor-based immunotherapies have transformed the standard of care for NSCLC patients.



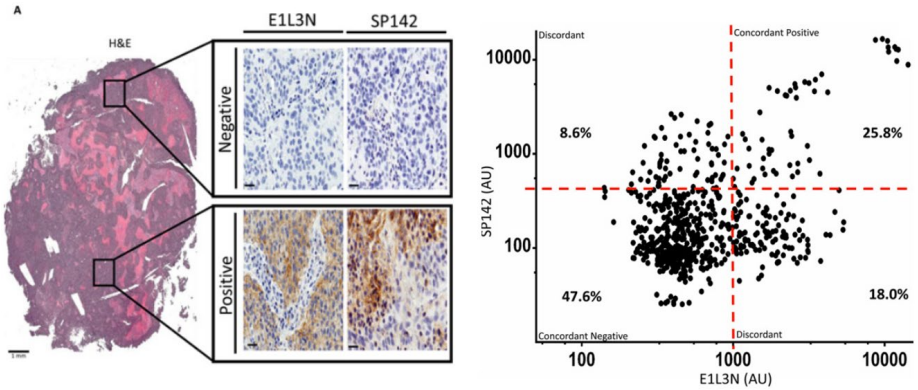


KEYNOTE-024 trial, chemotherapy vs pembrolizumab for ≥ 50% PD-L1 advanced NSCLC patients (Reck et al. 2016)

Standard-of-care still needs to be optimized

- **Only 45-50% of patients present an objective response** to anti PD-1/L1 immunotherapy
- The duration of response remains highly variable and **only 40% of the patients are alive at 2 years**
- Some straightforward predictors have been proposed for the response to immunotherapy (e.g Tumor Mutation Burden, PD-L1 expression, lymphocytic infiltrates…)
- **They are highly suboptimal** and not always reliable.

➢ **Therapeutic decision is thus suboptimal, and there is a critical need for good biomarkers for response prediction.**

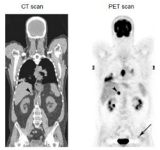


Heterogeneity of expression of PD-L1 and variation with antibody use (Maclaughlin et al. 2016).

Cancer patient journey and data

Prevention Detection Diagnosis Prognosis Treatment Monitoring

Clinical data, EHR



Radiomics:
CTscan, MRI, PETscan…

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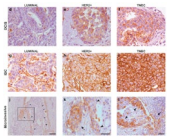
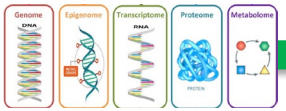
CTscan, MRI, PETscan…



Pathological slides



Omics (DNA, RNA, proteins, metabolites…)

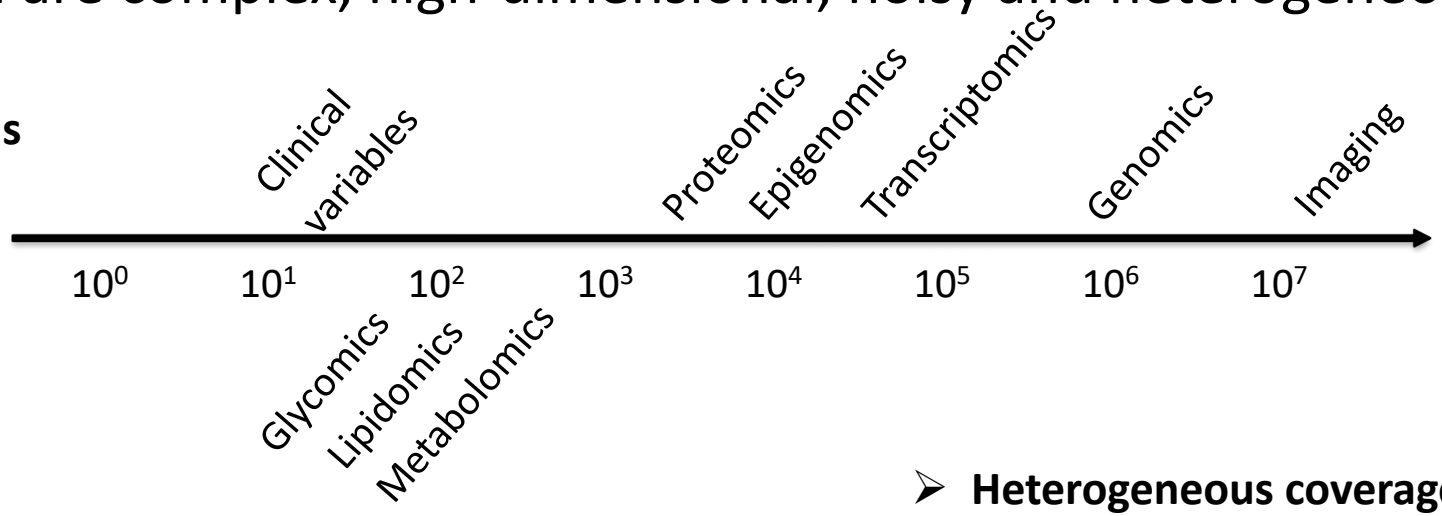
Omics

Real life variables

Challenges with multi-omics and multimodality

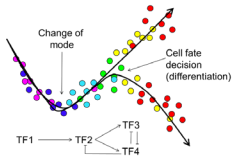
Omics data are complex, high-dimensional, noisy and heterogeneous…

Heterogeneous dimensions:

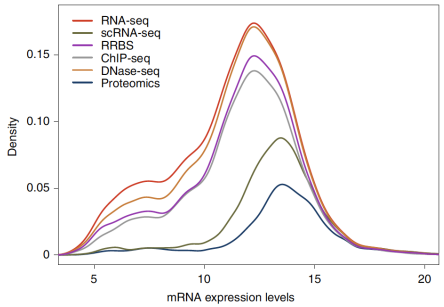


Heterogeneous types :
continuous, discrete, categorical…

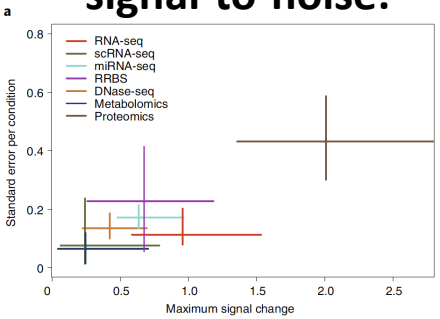
- **Heterogeneous coverage**
- **Sparsity**
- **Non linearity**



Heterogeneous distribution:



Heterogeneous signal-to-noise:

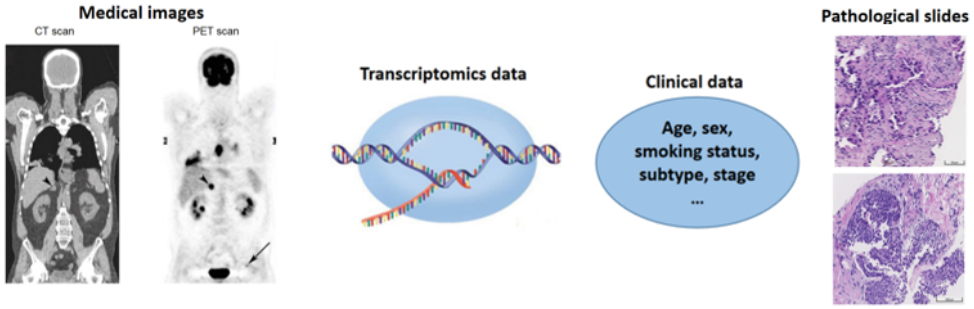


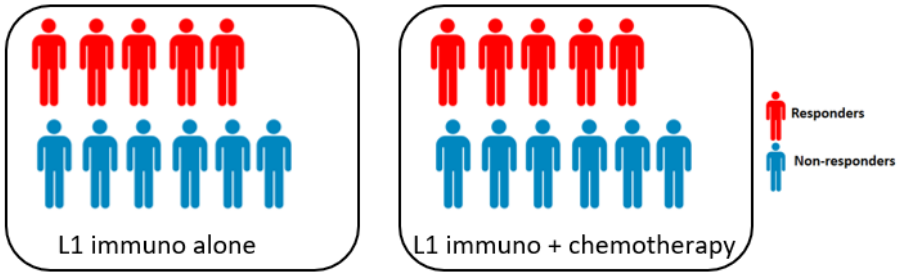
Multimodal integration is delicate!

Tarazona et al, Nat comp sci 2021

TIPIT: seeking for new multimodal biomarkers

Leverage Curie cohorts to explore the benefit of combining several data modalities to predict the patient's outcome





- Curie Patients with metastatic NSCLC who received immunotherapy as first line treatment
- Gathering of multimodal baseline data
- Monitoring of their outcome/response to treatment (overall survival, Progression-Free survival)

TIPIT: Signature of Immunotherapy response in Non Small Cell Lung Cancer

Fondation ARC pour la recherche sur le cancer

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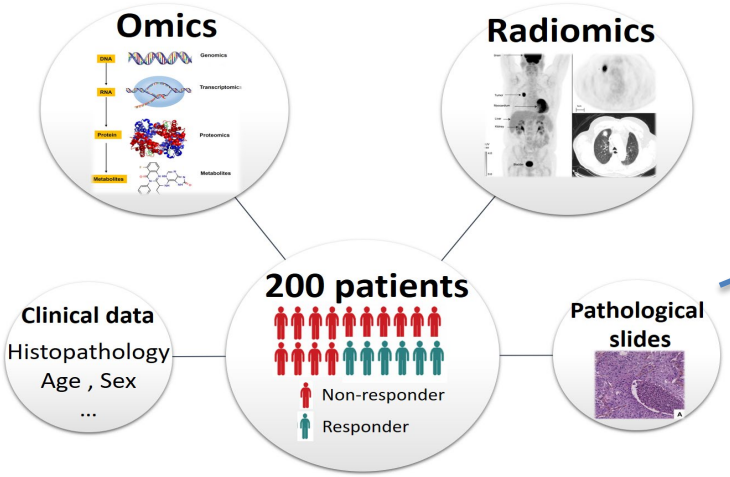
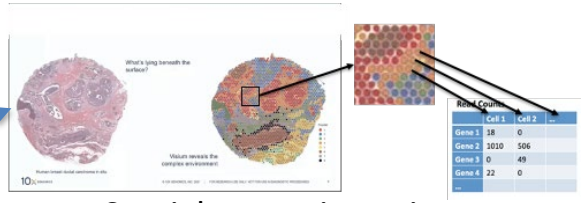
PaRis Artificial Intelligence Research InstitutE

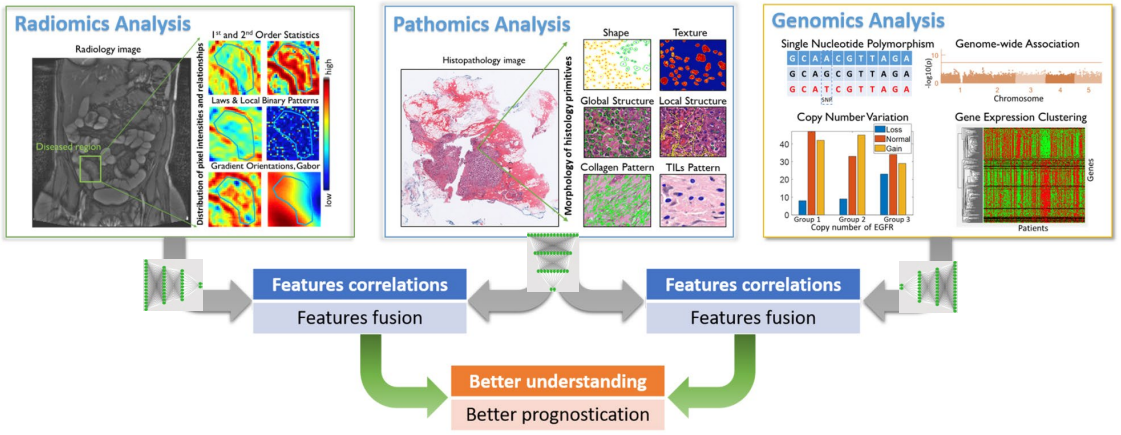


Multi-modal multi-scale integration with Machine Learning to predict response to immunotherapy in the most deadly cancer



Spatial transcriptomics

increases predictive power, explanatory insights and open the road to spatial modeling



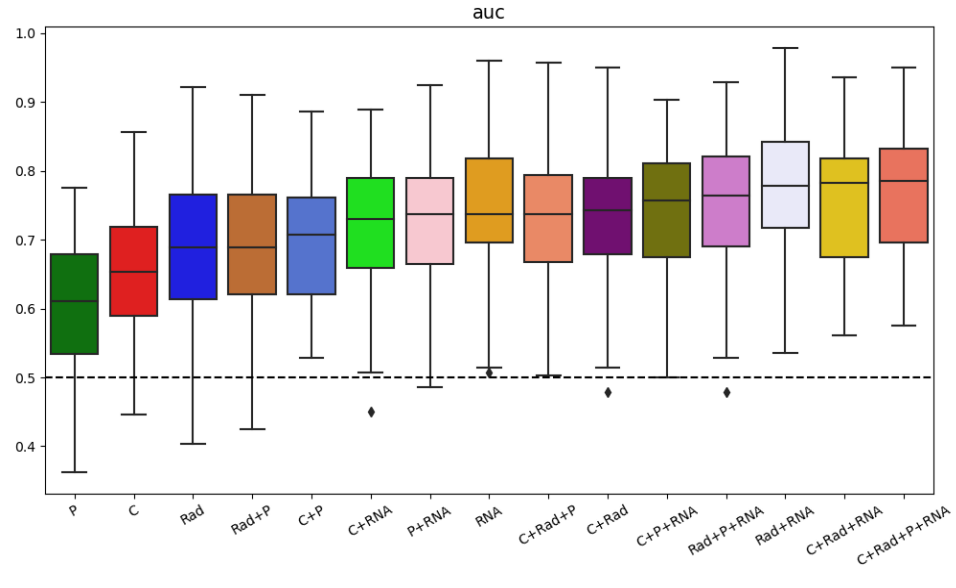
Emmanuel Barillot , Thomas Walter, Andrei Zinovyev
(U900 Inserm-Curie/CBIO Mines, PRAIRIE)
Irène Buvat (U1288 Inserm-Curie)
Nicolas Girard (IMM/Hal Curie)

Nicolas Captier / Marvin Lerousseau (U900)

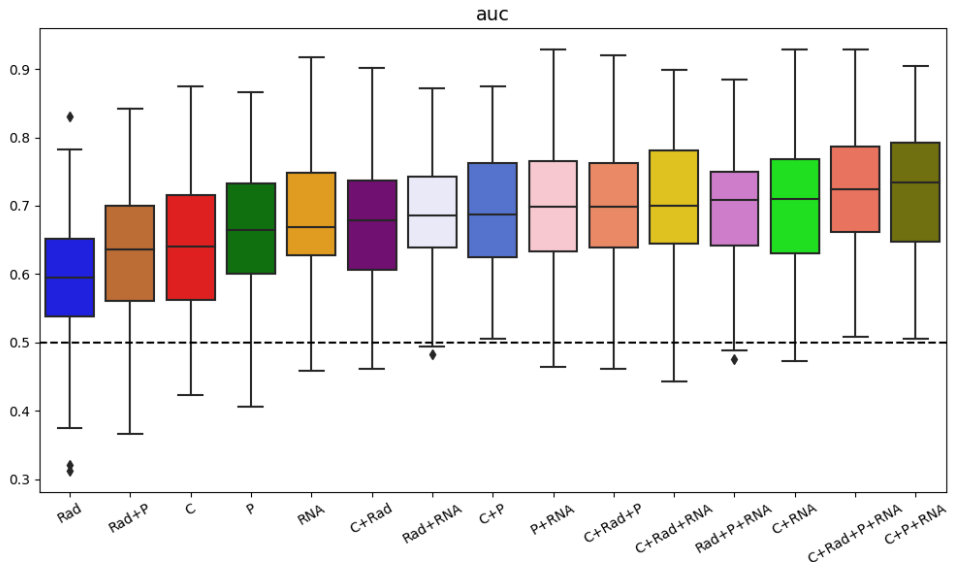
TIPIT preliminary results – AUCs

Naive late fusion scheme: average of the probability scores predicted by the different models

Death at 12 months



Progression at 6 months

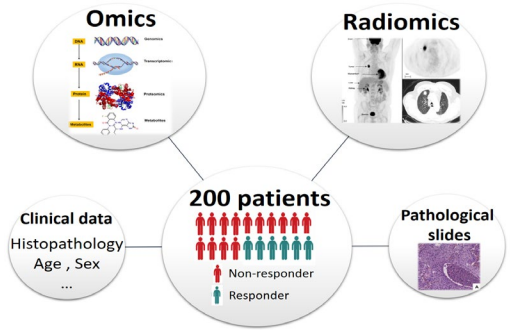


- Combining different multimodalities improves the performances of unimodal approaches.
- More complex late fusion schemes (weighted average) did not outperform the naïve average
- The recruitment is still limited (57 patients with all modalities so far), more samples are needed and will follow soon

Two typical projects

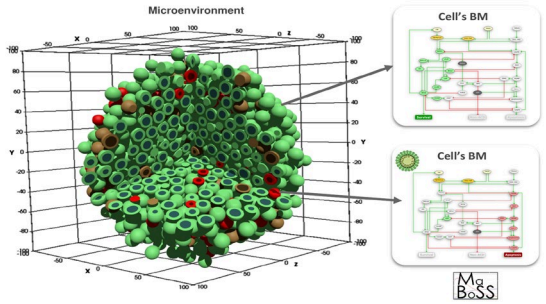
PROJECT 1

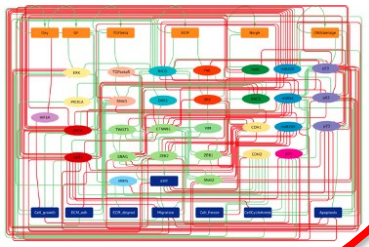
TIPIT: Signature of Immunotherapy response in Non Small Cell Lung Cancer



PROJECT 2

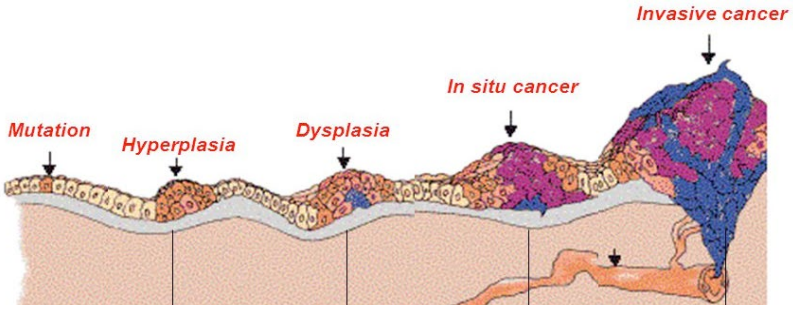
Spatial modelling of a tumour growth



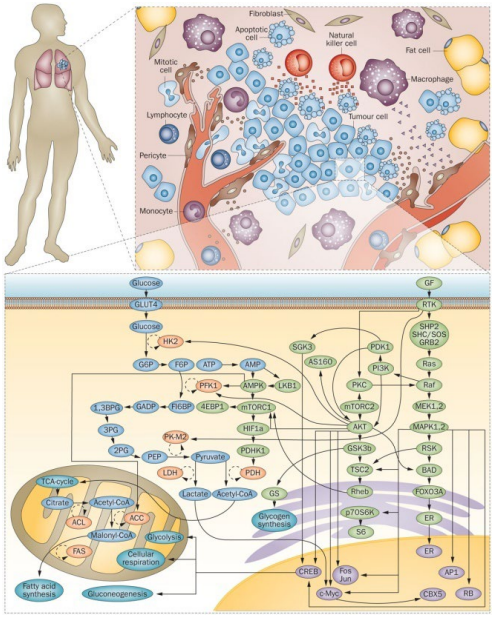


Biology of Cancer

Cancer is a disease in which abnormal cells divide without control and invade the nearby tissues



https://www.cancer.gov/publications/dictionaries/
https://slideplayer.com/



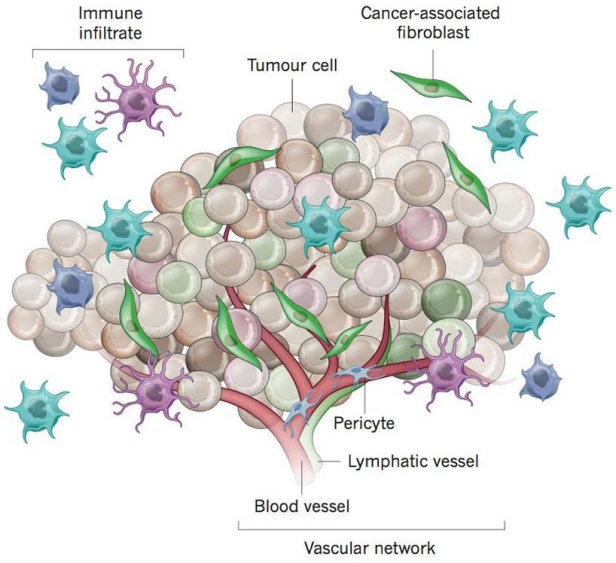
Werner *et al.*, 2014, *Nat. Rev. Clin. Oncol.*
Visual Art © 2013 The Univ. of Texas MD Anderson Cancer Center

Cancer is a **DNA disease**: tumors harbor **mutations**, and a tumor is genetically heterogeneous

Cancer is a **biological network disease**, and altered biological pathways are common to many tumor types

Cancer is a **microenvironment and immunity** disease

Cancer is a **tissue** disease

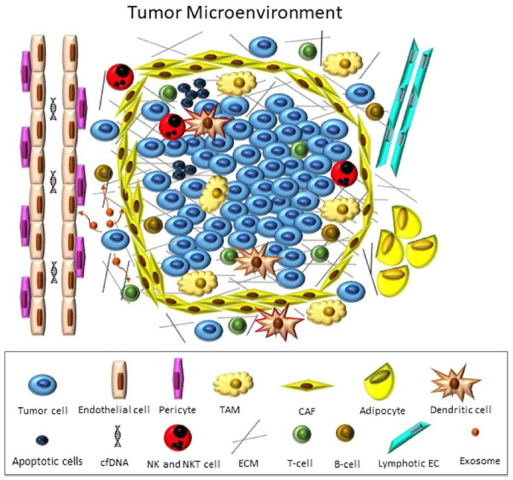


How to bring this knowledge together with patient omics profiles into mathematical modeling for predicting tumor evolution?

Space is key to understand cancer

- Spatial organisation of the tumour :
  - Heterogeneity: clones and subclones
  - Micro-environment and Internal structure : immune infiltrates, fibroblasts, signaling molecules, vascularization …
  - Physical barriers: epithelium, extracellular matrix …
  - Physical interactions: adhesion, polarity …

  From a molecular disease to a tissue disease



- Space is essential in understanding tumor biology, treatment response, and proposing new therapeutic strategies

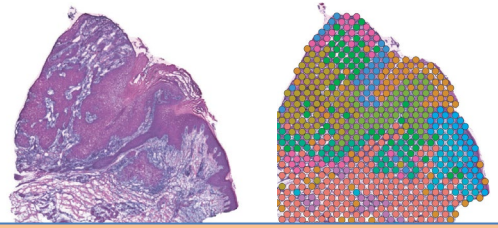
Signaling networks with non-linear behaviour govern this organisation

- **Multiomics multiscale spatial modelling is needed!**

How to achieve space modeling?

- How to account for space in statistical analysis?
- Eg with spatial transcriptomics: many works just consider distances between cells from different types (eg distance between tumor cells and CD8+ or CD4+ T cells)

  besides it is 2D and not 3D



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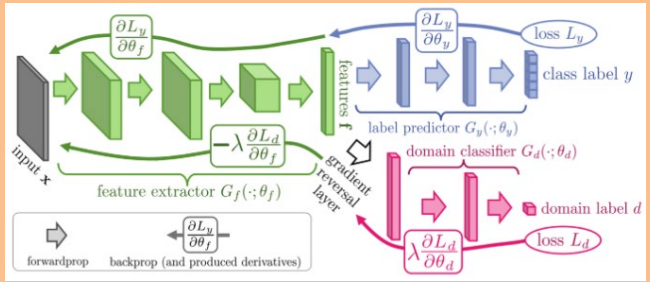
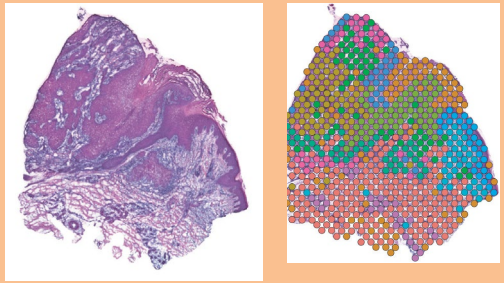
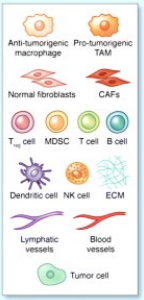


spatial transcriptomics



Loïc Chadoutaud thesis

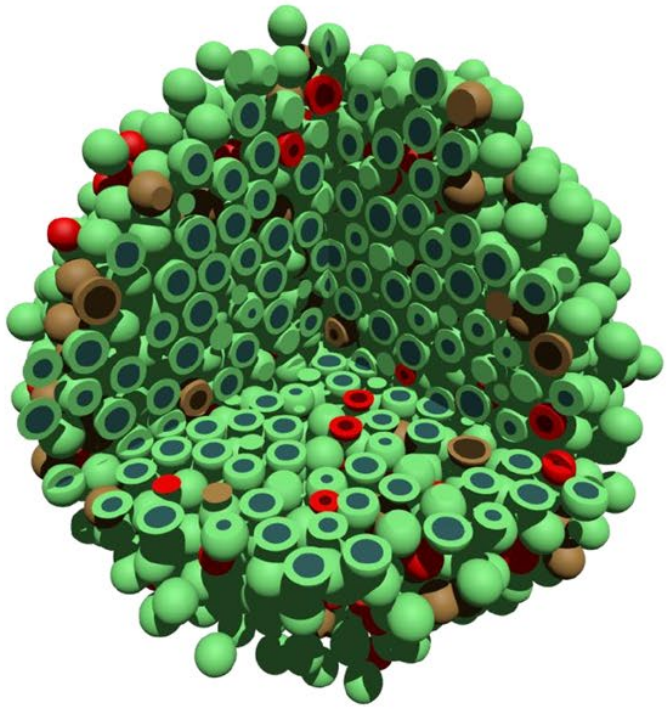
PR[AI]RIE
PaRis Artificial Intelligence Research InstituteE



PhysiCell: physics-oriented agent-based cell simulator

Paul Macklin

Randy Heiland

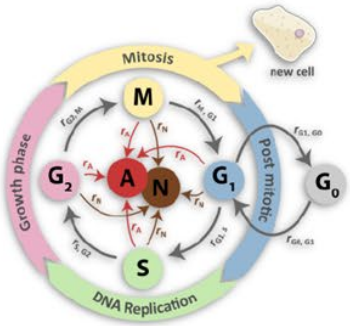


http://physicell.org
https://github.com/MathCancer/PhysiCell

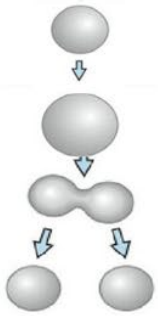
Cell agent properties

- Size (cell volume)
- Position (x, y, z)
- Phenotype
  - Cell cycle Model (G_0, *M, etc*)
  - Death Models
  - Rates
  - Custom Variables
  - Molecular models

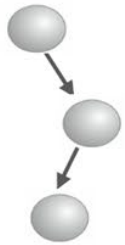
Cell Cycle



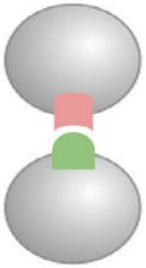
Growth



Migration



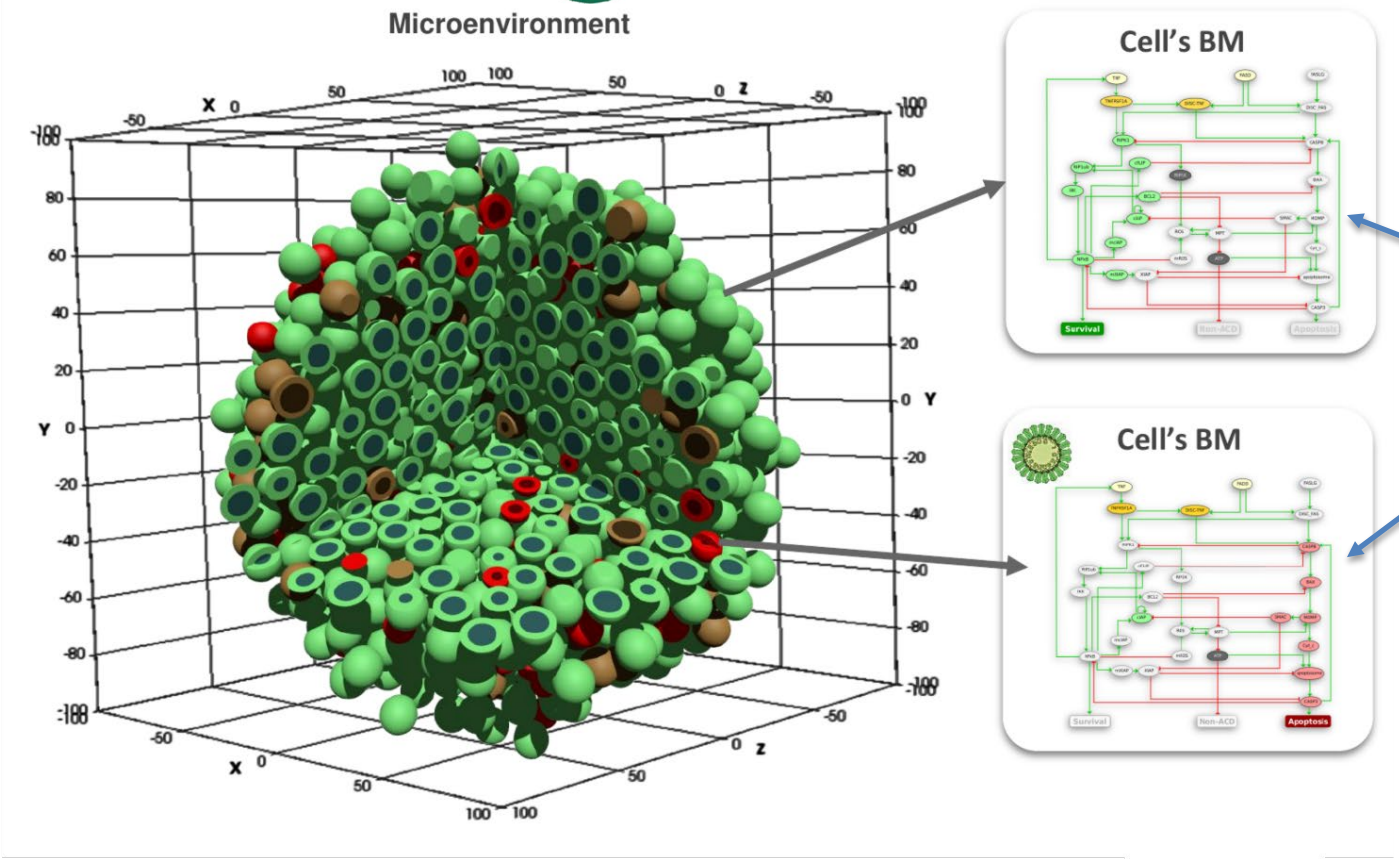
Cell-Cell interactions



PhysiBoSS, a multi-scale modeling framework:
Agent-based biophysics and Boolean network-based biochemistry

PhysiBoSS = PhysiCell + MaBoSS*

*MaBoSS: Markovian Boolean Stochastic Simulator (Stoll et al 201,2022; Noël 2021)




Arnau Montagud

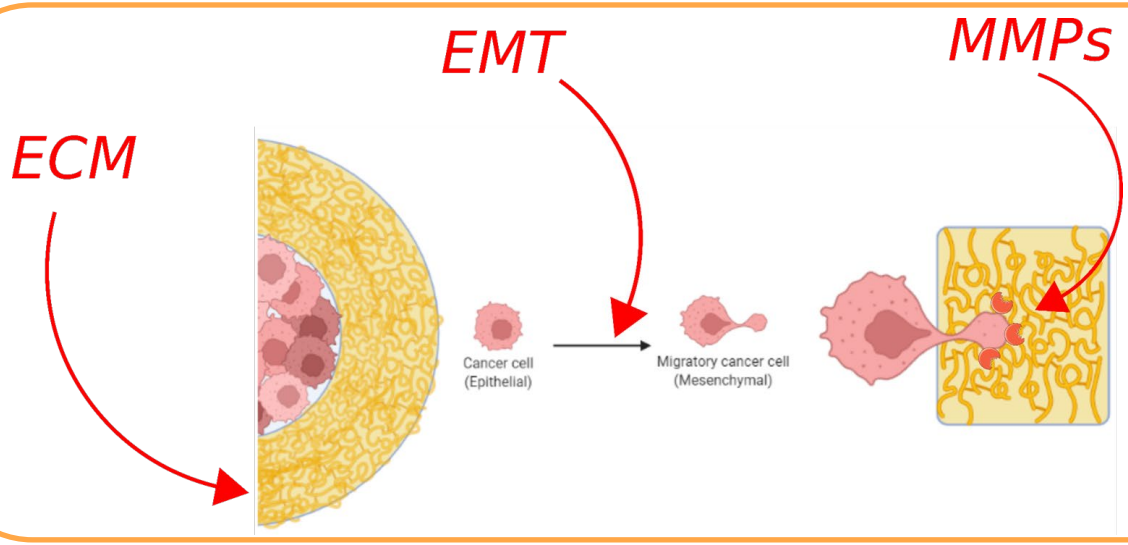

Gaëlle Letort


Vincent Noël


Laurence Calzone

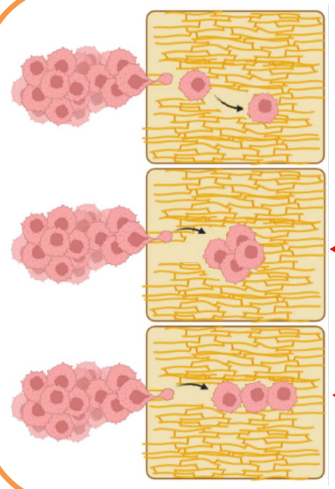
In collaboration with Alfonso Valencia at Barcelona Supercomuting Center

Modeling cell invasion process upon Epithelio-Mesenchymal Transition



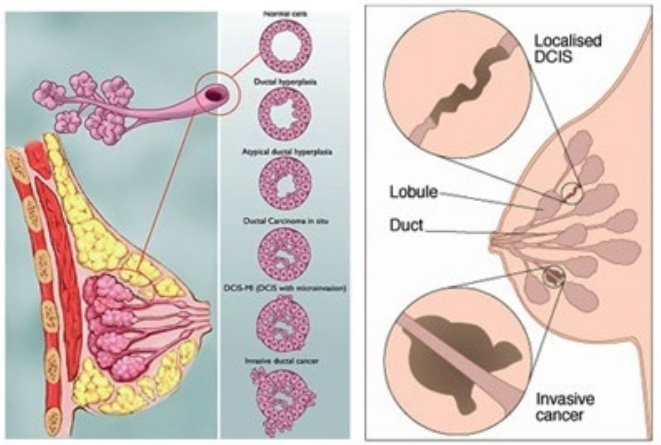
Scheme of EMT process and invasion through ECM

- Collective Migration is more aggressive
- To reproduce the different modes and mechanisms of invasion
- Comparison and validation with in vitro experiments
- Learn biological insights



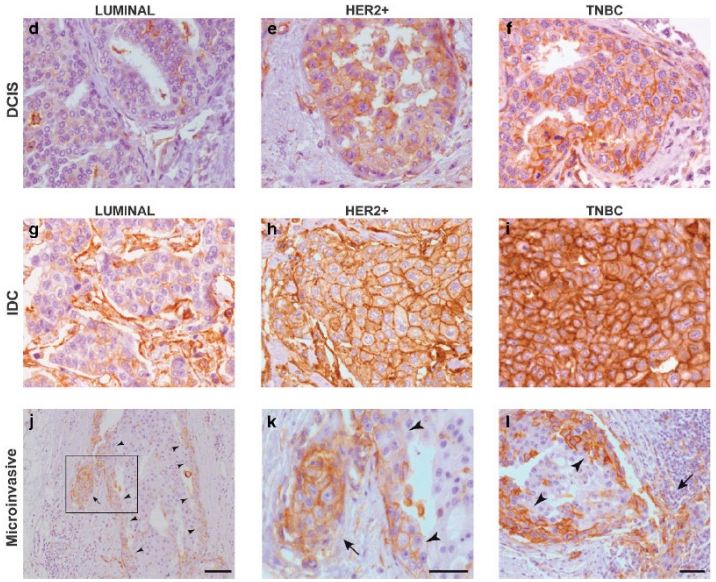
Different modes of invasion

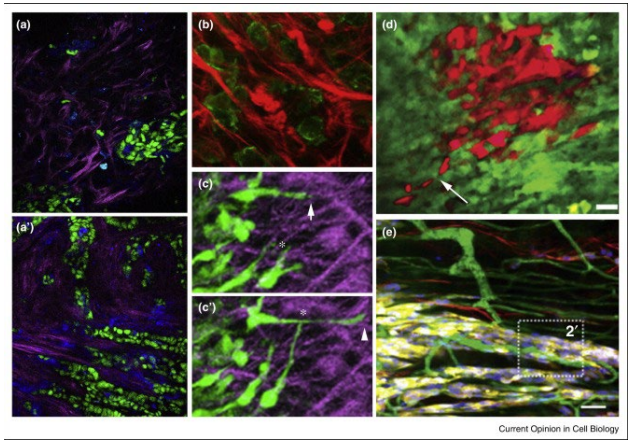
Breast cancer different invasion status and migration modes in situ, microinvasive or invasive (collab. Anne Salomon, Philippe Chavrier)



http://www.melbournebreastcancersurgery.com.au

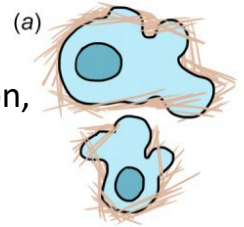
Lodillinsky et al, 2016



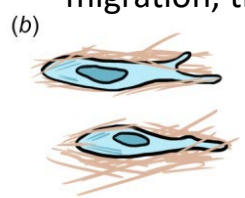


Clark et al, 2015

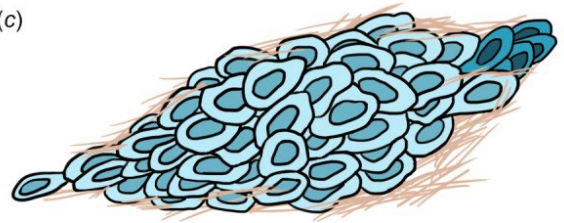
Amoeboid migration, isolated cell



Mesenchymal migration, trailing



Lintz et al, 2017



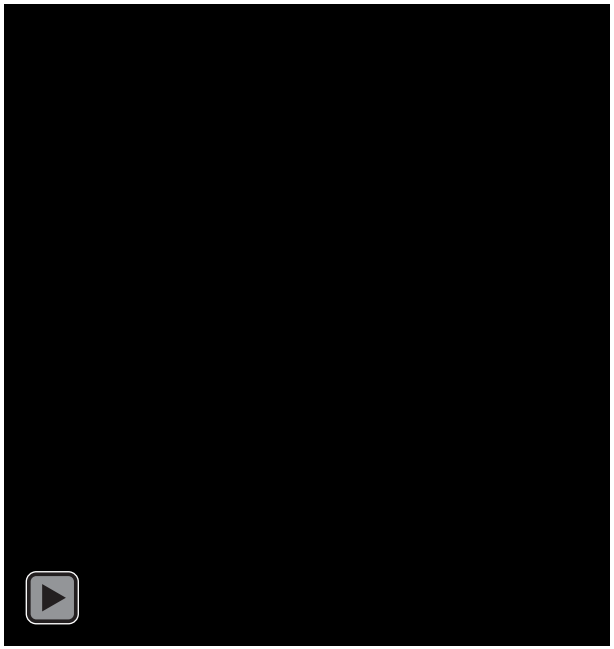
Collective, cluster migration

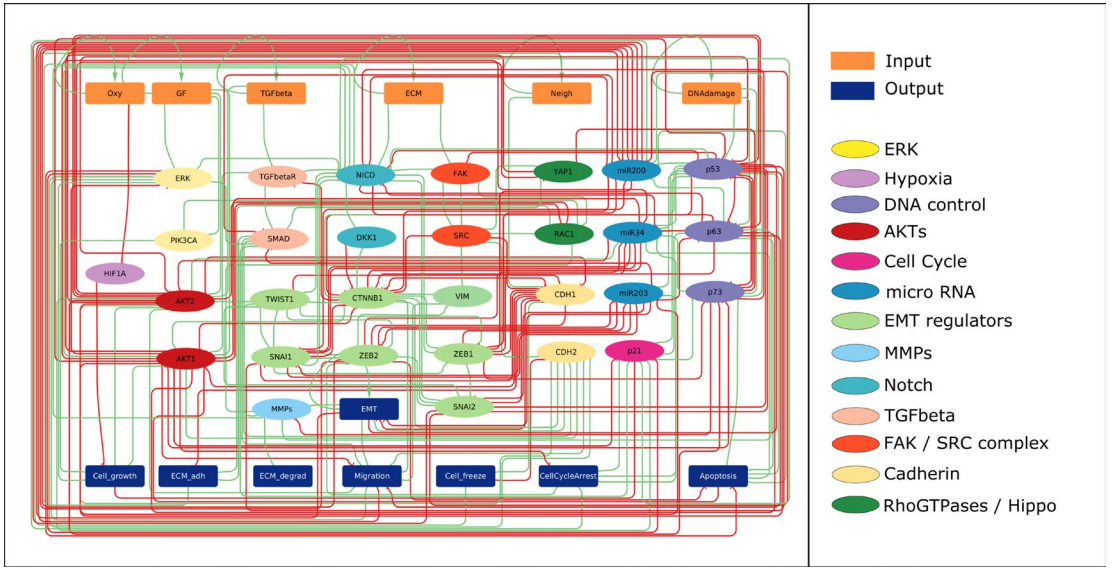
Modeling the cell invasion process


Marco Ruscone


Vincent Noël


Laurence Calzone





Intracellular signaling network of the model

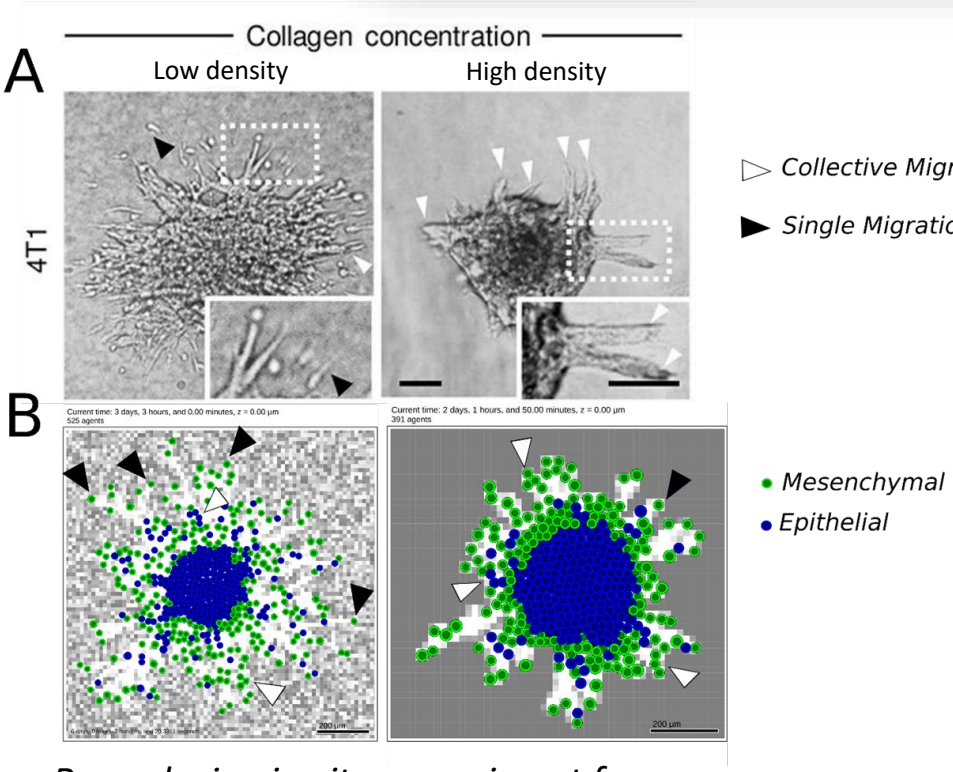
Ruscone et al. submitted to Bioinformatics

institut Curie

Cell adhesion and density changes in the ECM regulate modes of invasion

Cell–cell adhesion and 3D matrix confinement determine jamming transitions in breast cancer invasion

Olga Ilina[1], Pavlo G. Gritsenko[1], Simon Syga[2], Jürgen Lippoldt[3], Caterina A. M. La Porta[4,5,6], Oleksandr Chepizhko[7], Steffen Grosser[3], Manon Vullings[1], Gert-Jan Bakker[1], Jörn Starruß[2], Peter Bult[8], Stefano Zapperi[4,9,10], Josef A. Käs[3], Andreas Deutsch[2], Peter Friedl[1,11,12]



- Changes in ECM density will affect different modes of invasion
- Low non-uniform density induces more single cell migrations
- High uniform density induces more collective cell migrations

Reproducing in vitro experiment from Ilina et al.

Ruscone et al. paper submitted to Bioinformatics, under review

Multiscale model of the different modes of invasion:

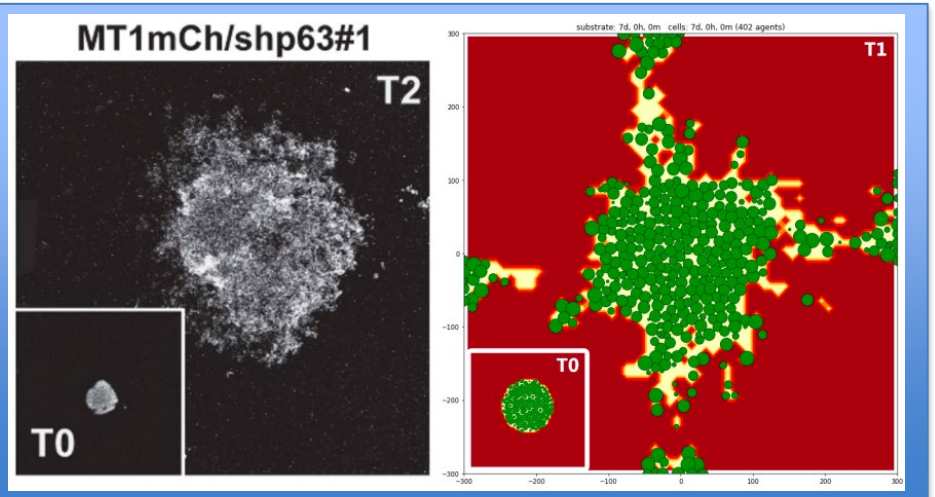
Comparison of experimental culture in Matrigel (left) with simulation (right)

p63/MT1-MMP axis is required for in situ to invasive transition in basal-like breast cancer

C Lodillinsky [1], E Infante [1], A Guichard [1], R Chaligné [2], L Fuhrmann [1], J Cyrta [1], M Irondelle [1], E Lagoutte [1], S Vacher [3], H Bonsang-Kitzis [4], M Glukhova [5], F Reyal [4], I Bièche [3], A Vincent-Salomon [2 6], P Chavrier [1]

Comparison with invasive cell line

Green cells have MMPs node ON



Comparison with non-invasive cell line

Red cells have MMPs node OFF

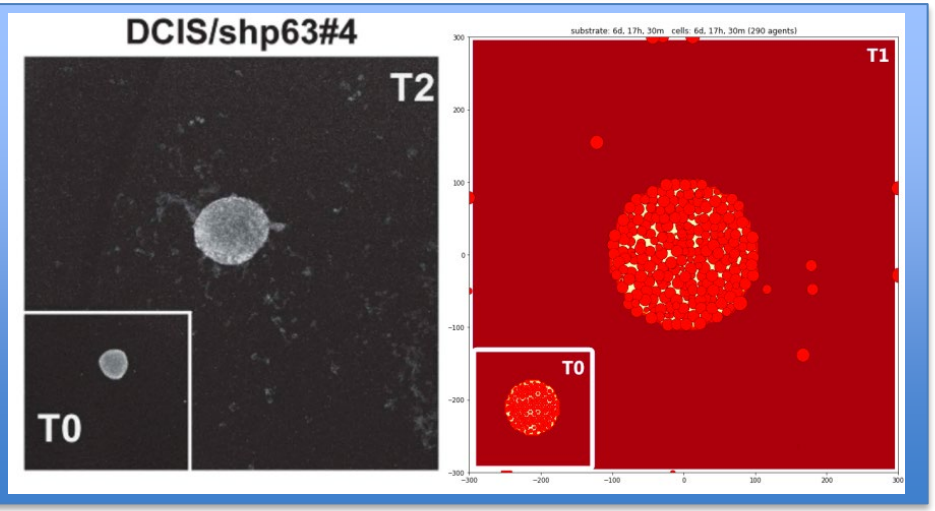
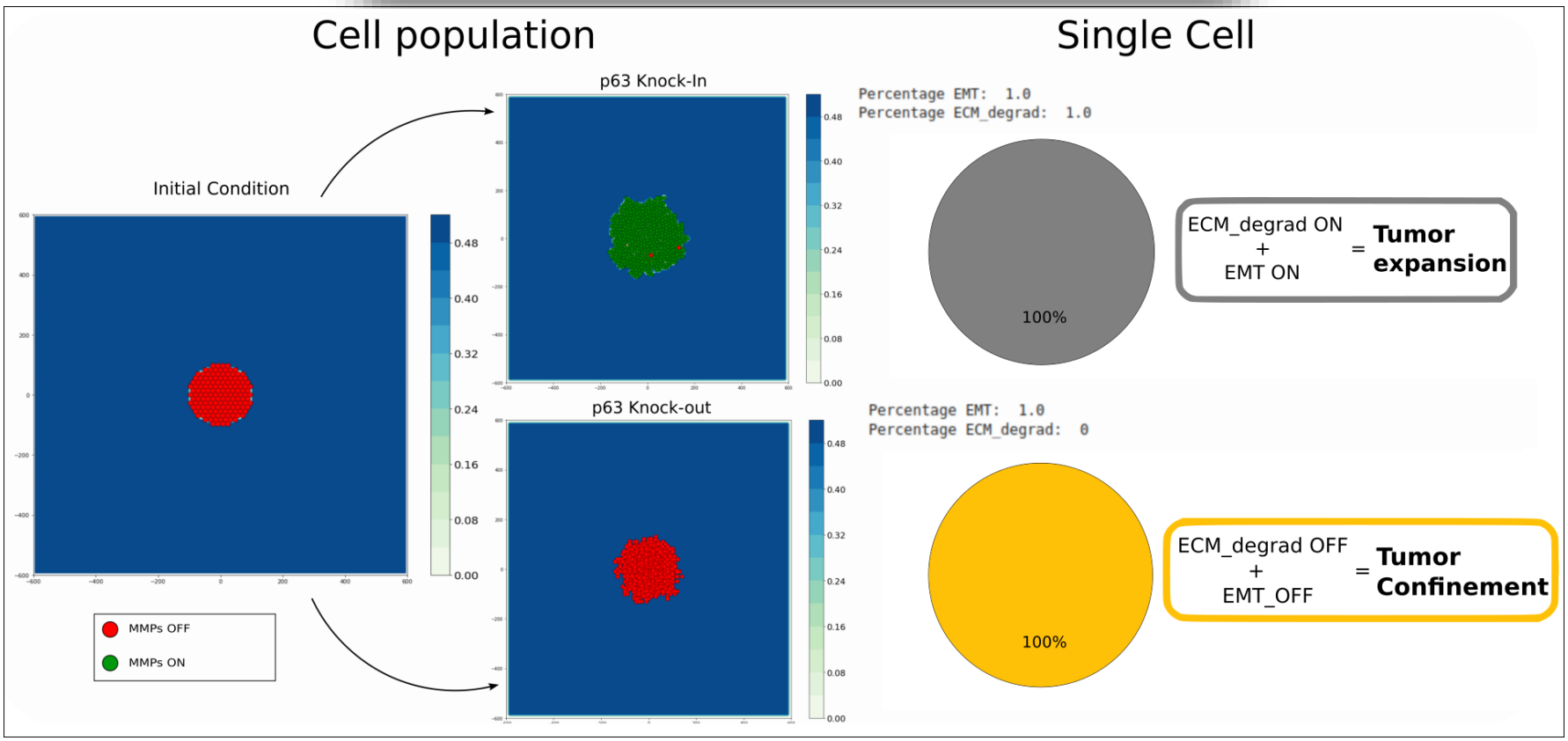


Figure 6.a, C. Lodillinsky et al, 2016

Simulation of p63/MT1-MMP axis is required for in situ to invasive transition

p63/MT1-MMP axis is required for in situ to invasive transition in basal-like breast cancer

C Lodillinsky [1], E Infante [1], A Guichard [1], R Chaligné [2], L Fuhrmann [1], J Cyrta [1], M Irondelle [1], E Lagoutte [1], S Vacher [3], H Bonsang-Kitzis [4], M Glukhova [5], F Reyal [4], I Bièche [3], A Vincent-Salomon [2 6], P Chavrier [1]



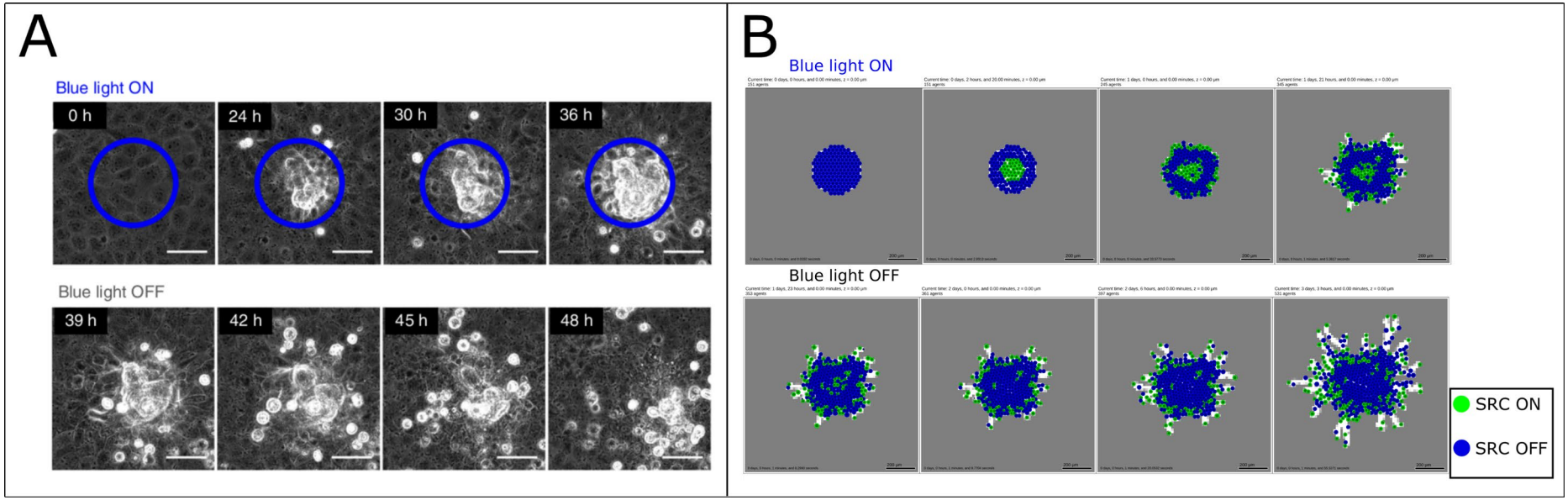
Ruscone et al. paper submitted to Bioinformatics, under review

Reproducing in vitro experiment from Lodillinsky et al.

Local light-activation of SRC in epithelial monolayer promotes collective extrusion

Local light-activation of the Src oncoprotein in an epithelial monolayer promotes collective extrusion

Sarah Moitrier[1], Nastassia Pricoupenko[1,3], Adèle Kerjouan[2,3], Christiane Oddou[2,3], Olivier Destaing[2,3], Aude Battistella[1], Pascal Silberzan [1] & Isabelle Bonnet [1]

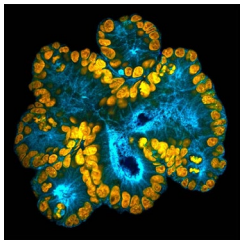


Ruscone et al. paper submitted to Bioinformatics, under review

Reproducing in vitro experiment from Moitrier et al.

Take-home messages

- Multi-modal biological and clinical using machine learning improves immunotherapy response prediction in lung cancer
- Multi-scale agent-based modelling coupled with stochastic Boolean network modelling recapitulates the mechanisms of tumor progression at biophysical and biochemical levels; it can be used for virtual screening of drug combination in different genetic contexts (digital twin)



www.corning.com

- How to decipher the spatial organization principles of the tumor and use this information to defeat it?

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Alfonso Valencia
Miguel Leon de Ponce
Arnau Montagud

Fundings

http://sysbio.curie.fr,
https://github.com/sysbio-curie/
https://hub.docker.com/u/sysbiocurie/

POSTDOC / PhD positions open
Contact Emmanuel.Barillot@curie.fr