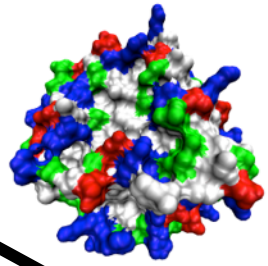
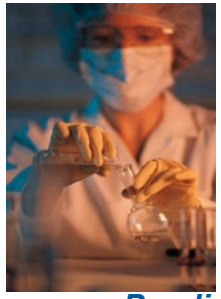

MOFFITT
CANCER CENTER
IMO
Integrated
Mathematical
Oncology
Mathematical modeling
in support of drug discovery
Kasia Rejniak
H. Lee Moffitt Cancer Center & Research Institute
Integrated Mathematical Oncology
Moffitt—IMO, 15th June 2016
Integrative Cancer
Biology Program
NATIONAL CANCER INSTITUTE
PHYSICAL SCIENCES
in ONCOLOGY
American
Cancer
Society
PNC BANK
MILES FOR MOFFITT
at the University of South Florida

Drug development process

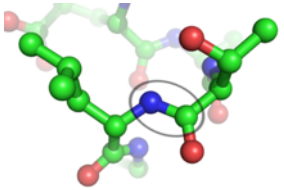
Identify disease

Identify therapeutic target (2-5 years)





Preclinical testing (1-3 years)



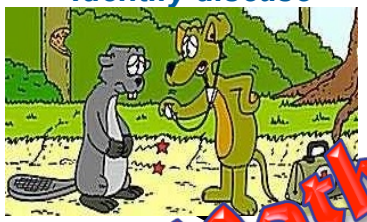
Find compound effective against target (2-5 years)

Human clinical testing (2-10 years)

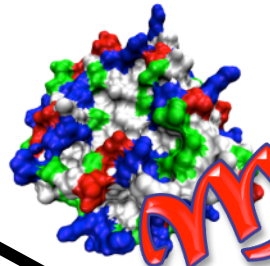
FDA approval

Drug development process

Identify disease

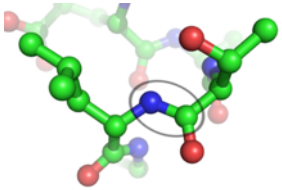


Identify therapeutic target (2-5 years)



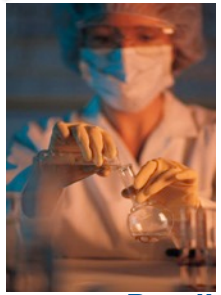
Math

Math



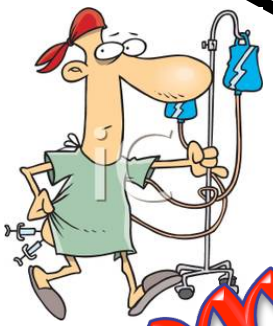
Find compound effective against target (2-5 years)

Math



Preclinical testing (1-3 years)

Math

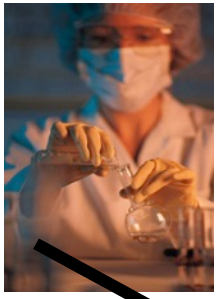


Human clinical testing (2-15 years)

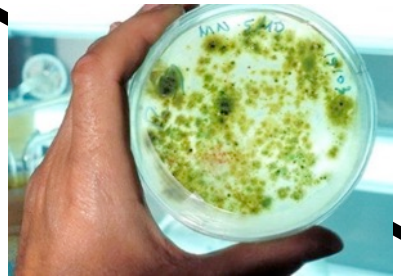
Math

FDA approval

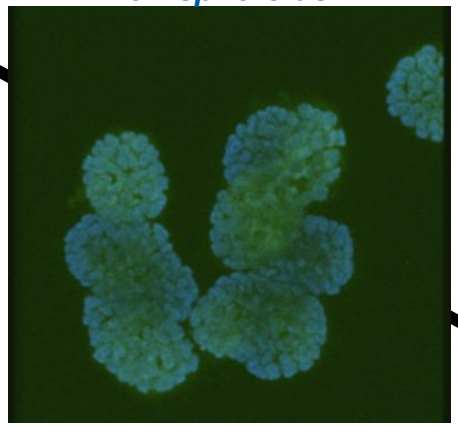
Pre-clinical tests



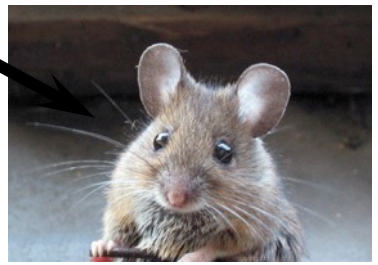
Petri dish



3D spheroids

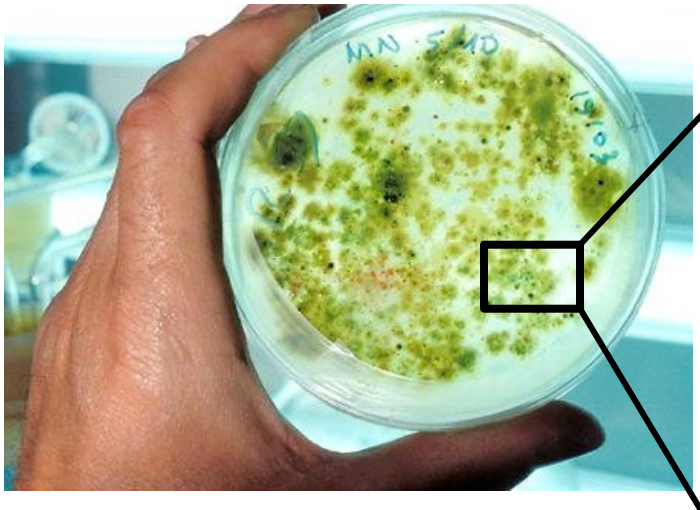


mouse

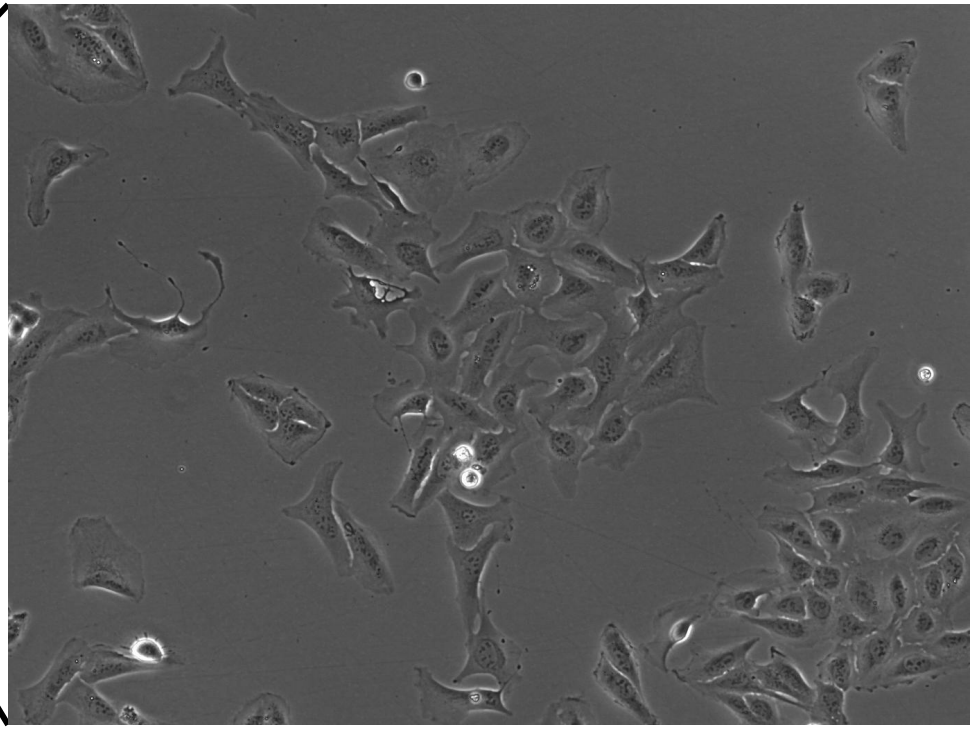


Cell colony experiments

In cancer biology new anticancer treatments are first tested in the cell culture.



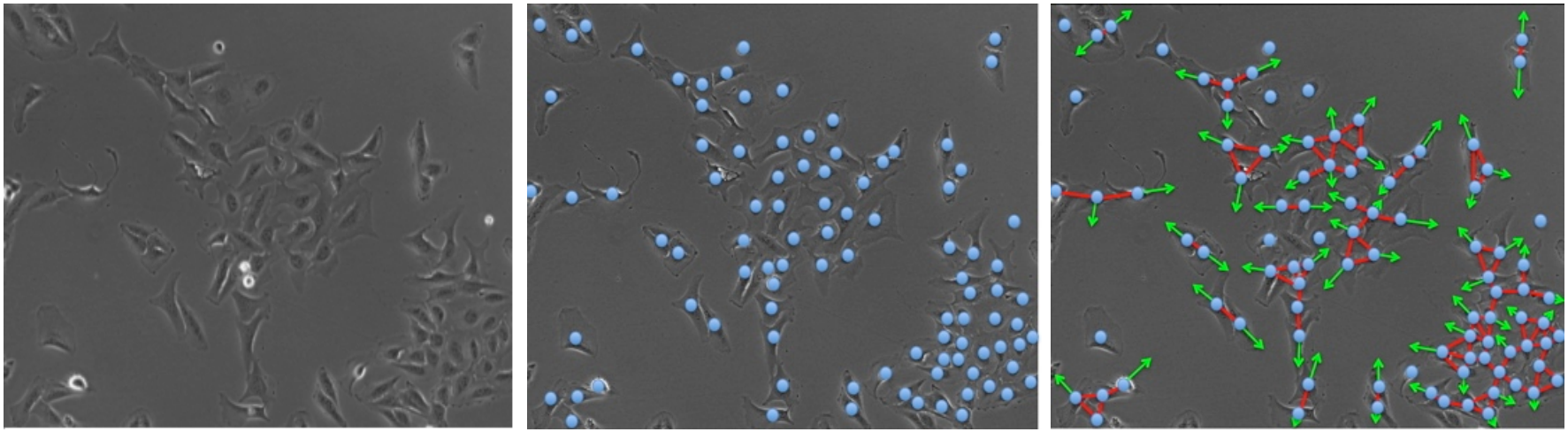
Petri dish



Part of the Petri dish seen under the microscope

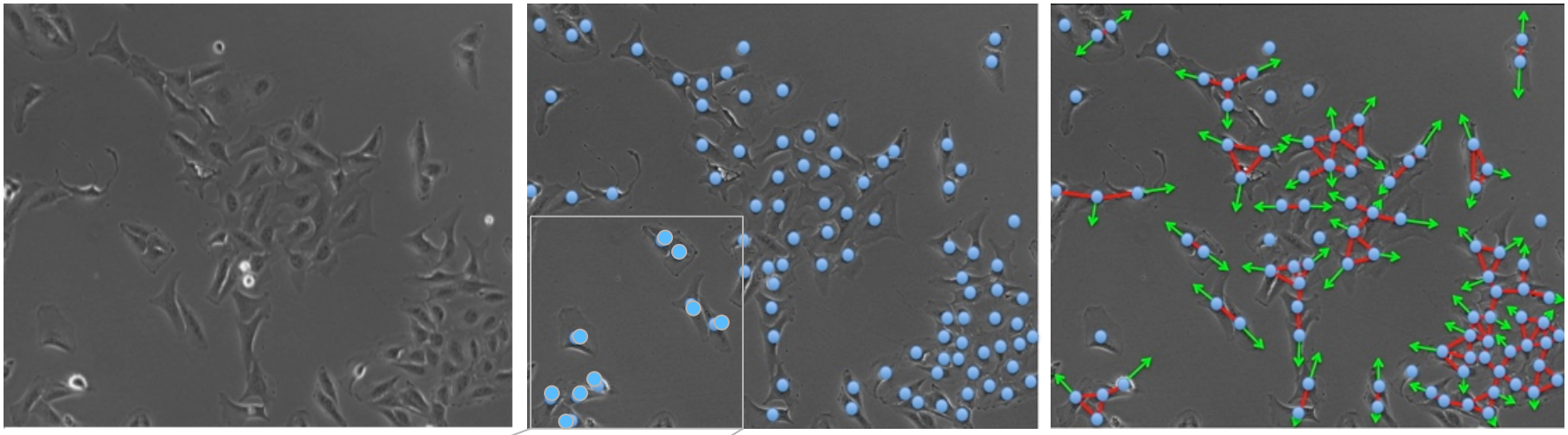
The cells grow in a two-dimensional dish in a medium that contains nutrients. Initially, the cells are seeded sparsely, but due to their divisions and movement the cell colony grows and spreads in the available space. Chemotherapeutic drugs are added to the medium in known concentrations. The total toxicity in the medium has to be controlled. The number of viable cells can be counted.

How to model these cells?

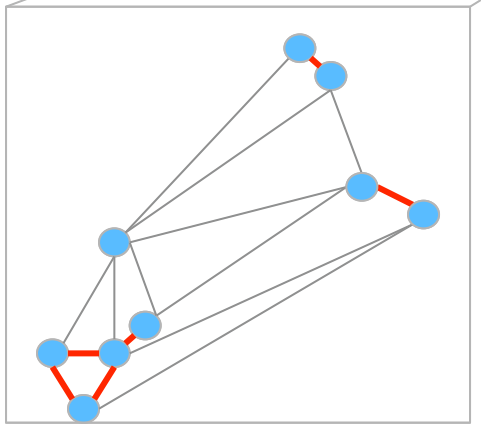


Cell nuclei
Spring connections
Repulsive forces

Find cells that are near-by



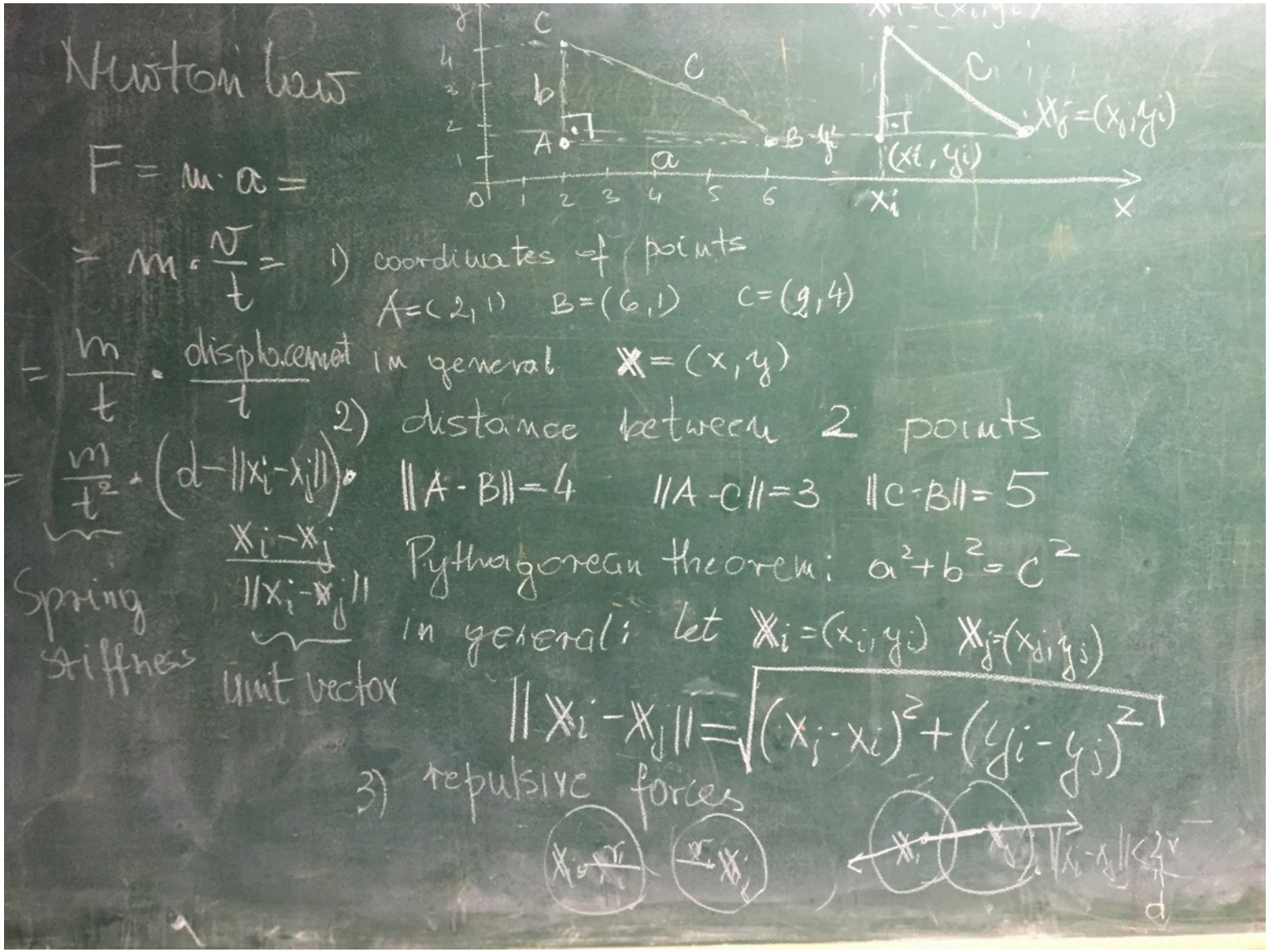
Cell nuclei
Spring connections
Repulsive forces



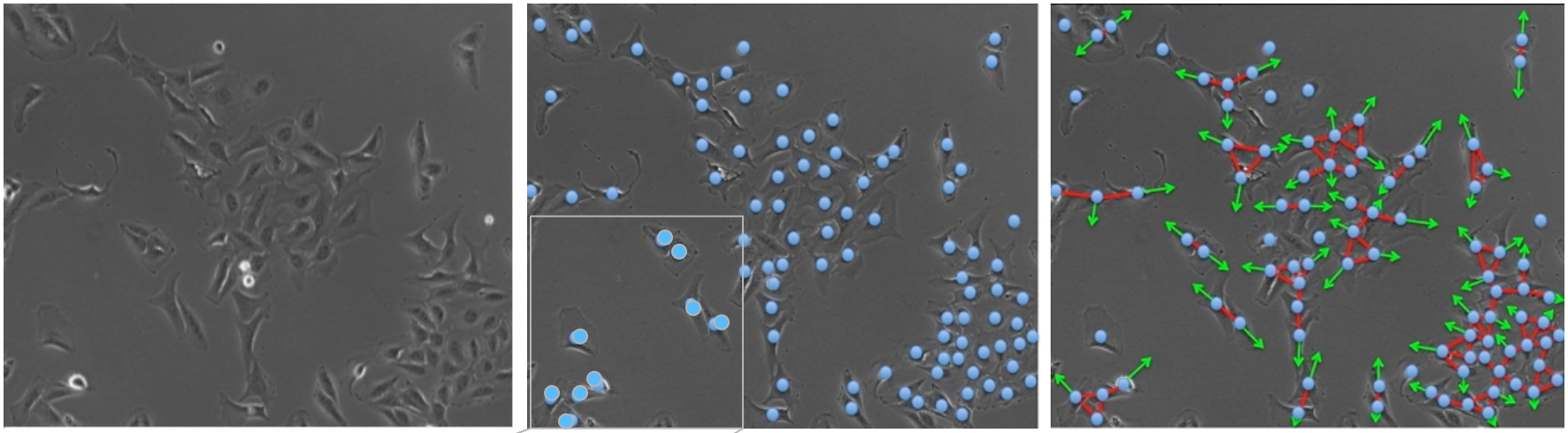
Neighborhood relation

Goal: the cells that are too close to one another should be pushed away on a distance equal to cell diameter.

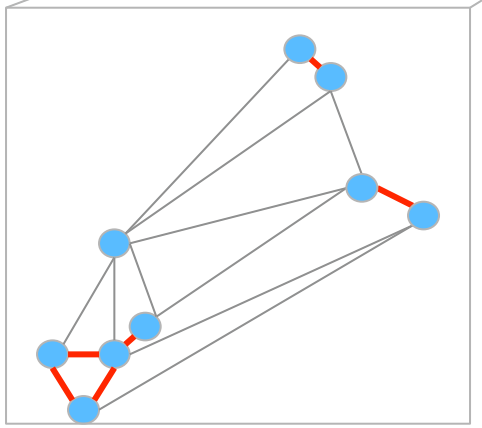
Let's do some math!



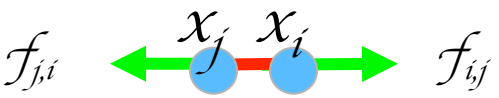
Exert force for too-close cells



Cell nuclei
Spring connections
Repulsive forces



Neighborhood relation



$$f_{i,j} = \begin{cases} \mathcal{S}\left(d - \|\mathbf{x}_i - \mathbf{x}_j\|\right)\frac{\mathbf{x}_i - \mathbf{x}_j}{\|\mathbf{x}_i - \mathbf{x}_j\|}, & \text{if } \|\mathbf{x}_i - \mathbf{x}_j\| < d, \\ 0, & \text{otherwise.} \end{cases}$$

Forces from several neighboring cells:

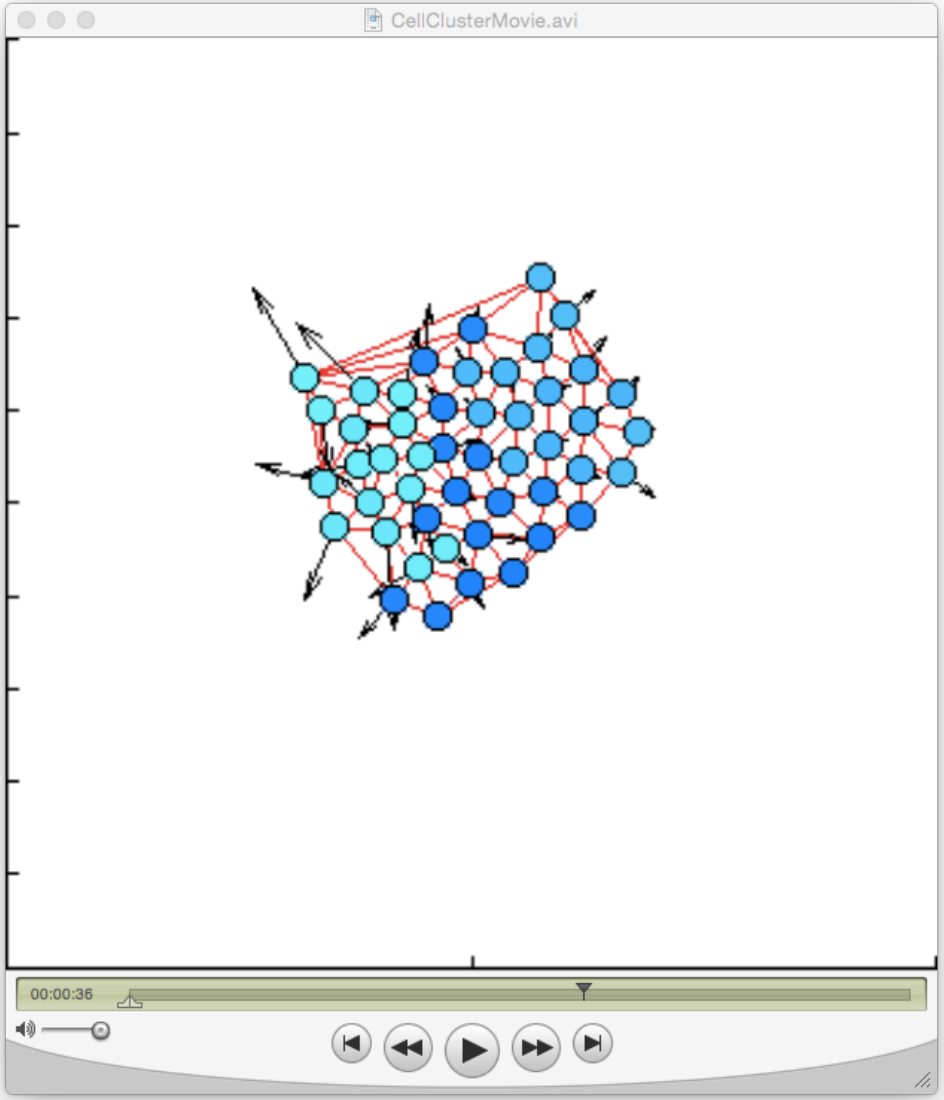
$$\begin{aligned} F_i &= f_{i,j_1} + \ldots + f_{i,j_M} = \\ &= \mathcal{S}\left(d - \|\mathbf{x}_i - \mathbf{x}_{j_1}\|\right)\frac{\mathbf{x}_i - \mathbf{x}_{j_1}}{\|\mathbf{x}_i - \mathbf{x}_{j_1}\|} + \ldots + \mathcal{S}\left(d - \|\mathbf{x}_i - \mathbf{x}_{j_M}\|\right)\frac{\mathbf{x}_i - \mathbf{x}_{j_M}}{\|\mathbf{x}_i - \mathbf{x}_{j_M}\|}. \end{aligned}$$

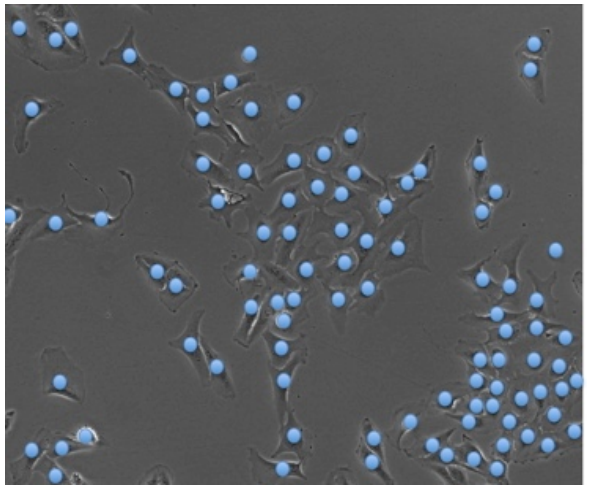
Change in cell position:

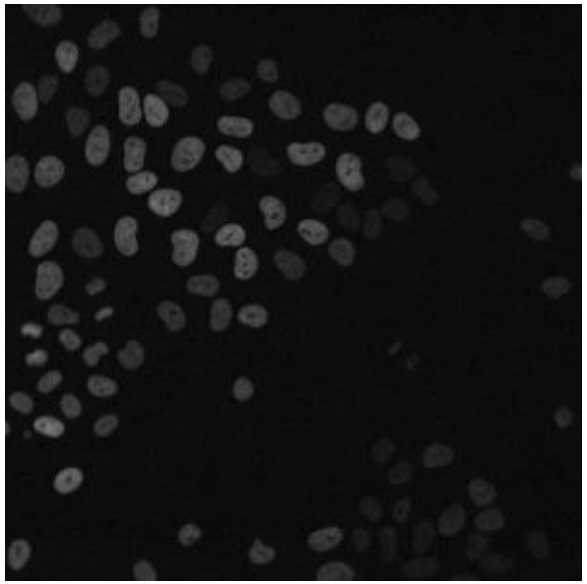
$$\mathbf{x}_i(t + \Delta t) = \mathbf{x}_i(t) - \frac{1}{\nu}\Delta t F_i$$

d-resting length (cell diameter),
S-spring stiffness
ν-media viscosity

How this model works?

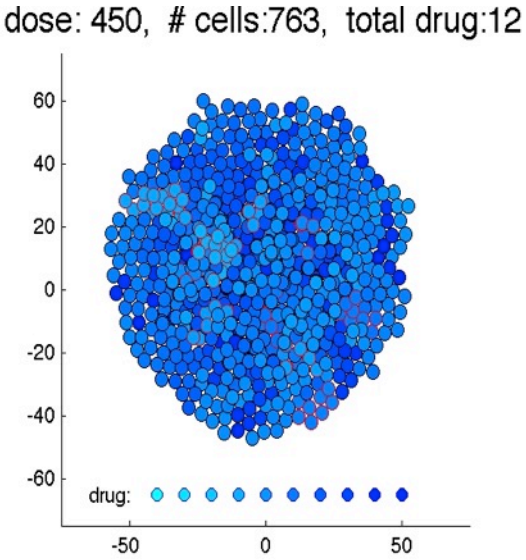


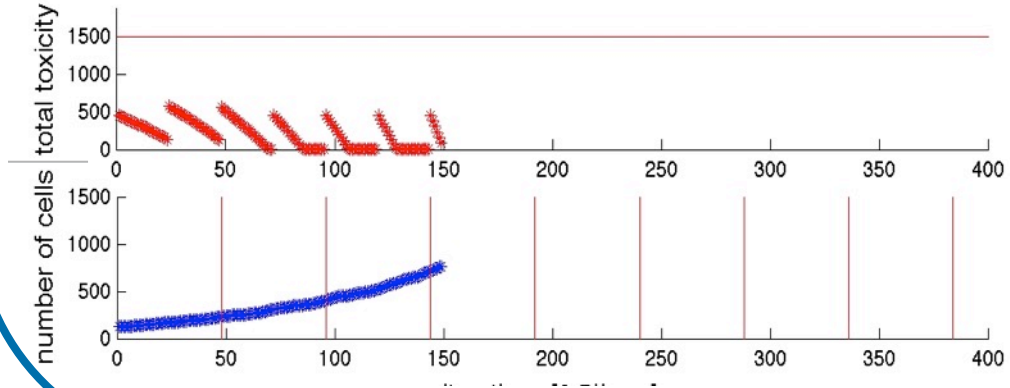




Let's do some experiments

Question:
What is the best drug schedule that will allow us to suppress growth of the whole tumor colony, but will use the smallest drug concentration (minimal toxicity)?





Model of a discrete colony of cells

Level of absorbed drug – color coded
Mutated cells have red perimeter

Drug schedule can be chosen:

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*******************************
 possible treatment schedule:
     1. daily
     2. twice daily
     3. hourly
     4. continuous
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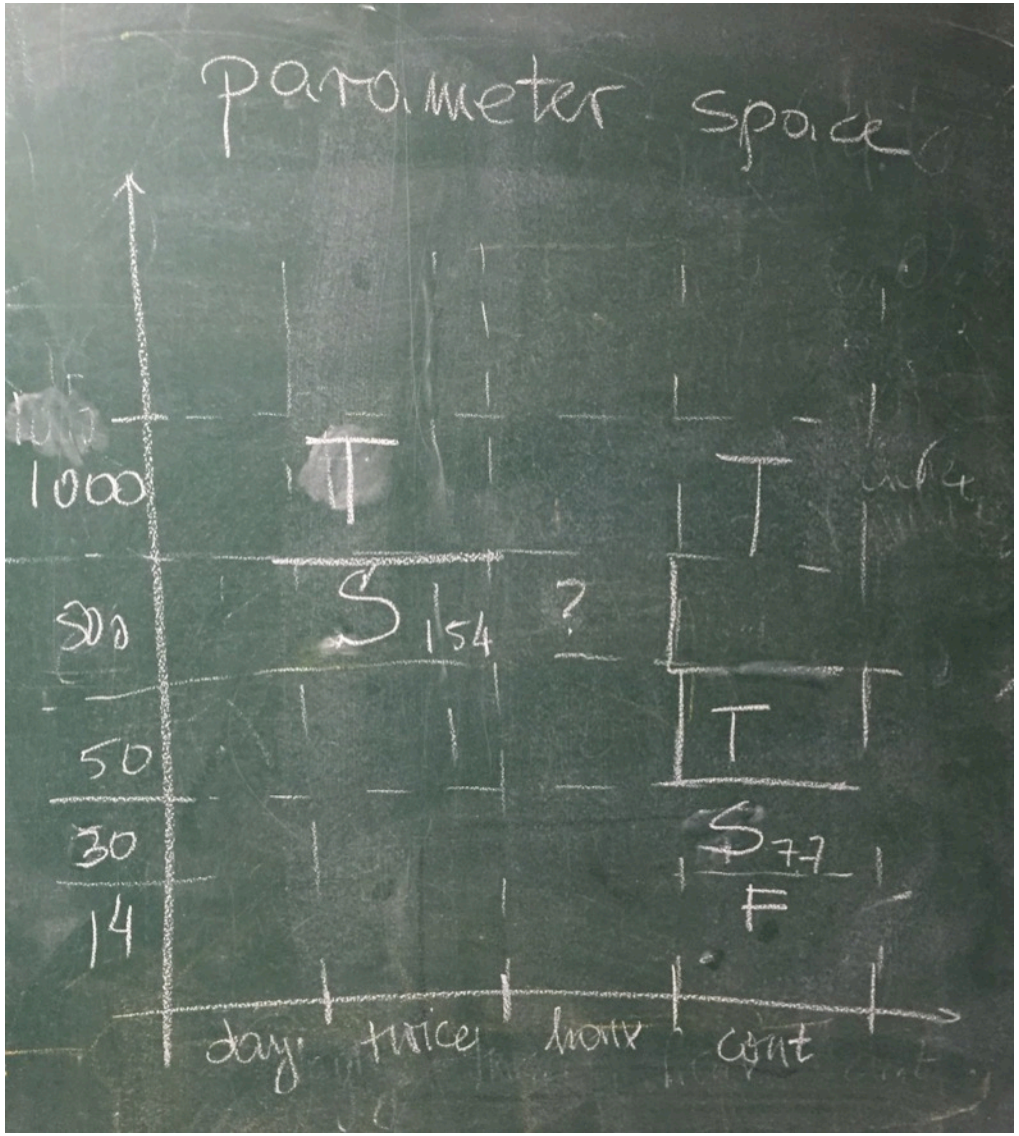
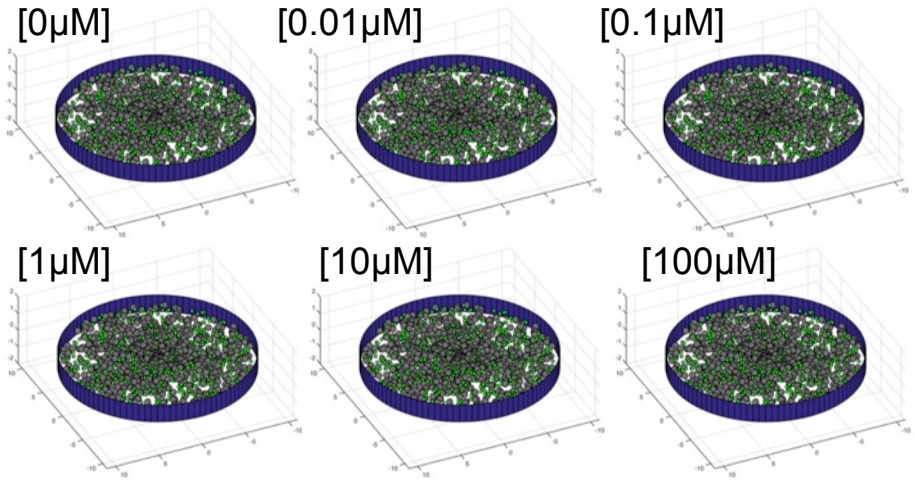
Control total toxicity

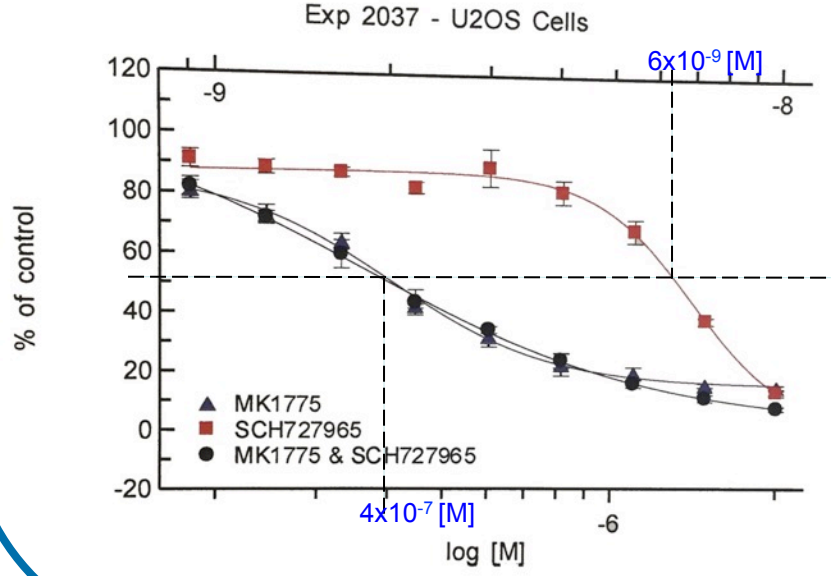
Control the number of cells

Let's do some experiments!



Drug response curves (IC_{50})

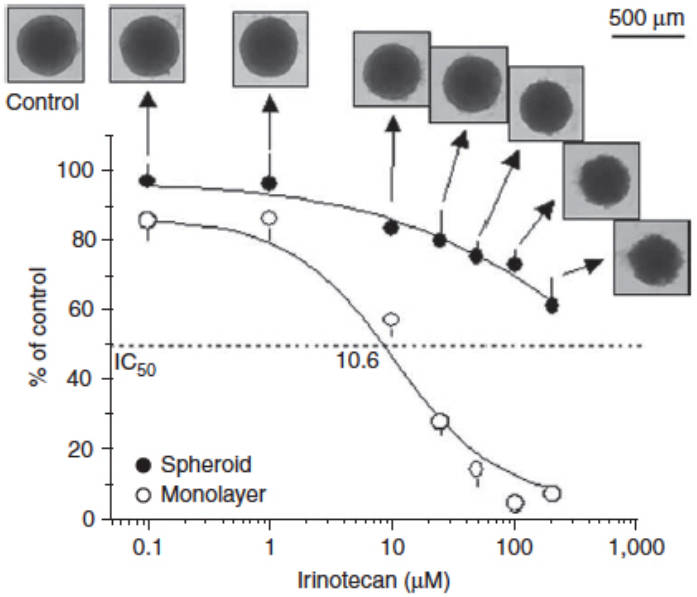




IC_{50} curve

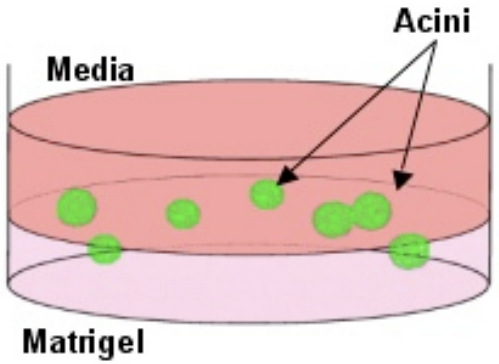
This quantitative measure indicates how much of a particular drug is needed to inhibit a given biological process by half.

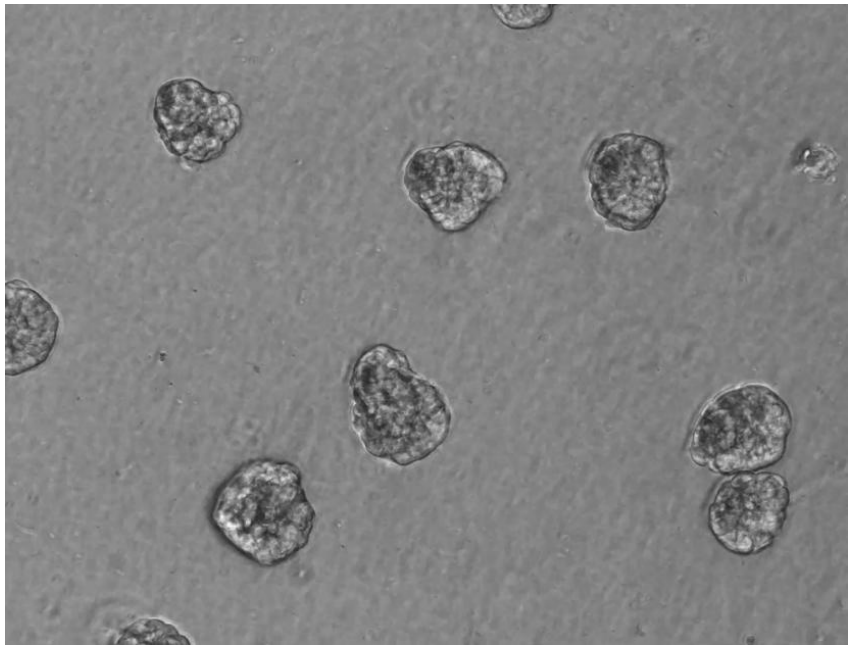
The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function.



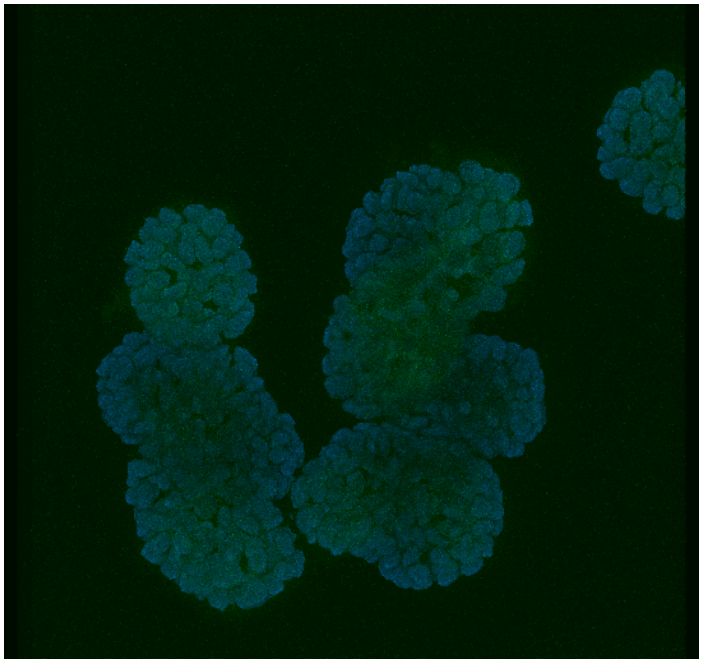
Friedrich et al. Nature Protocols, 2009

3D tumor spheroids

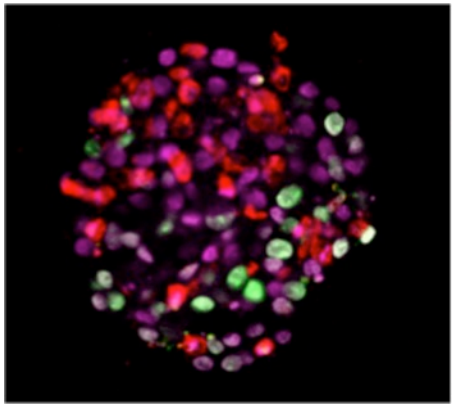




Tumor cells in 3D culture (top view)



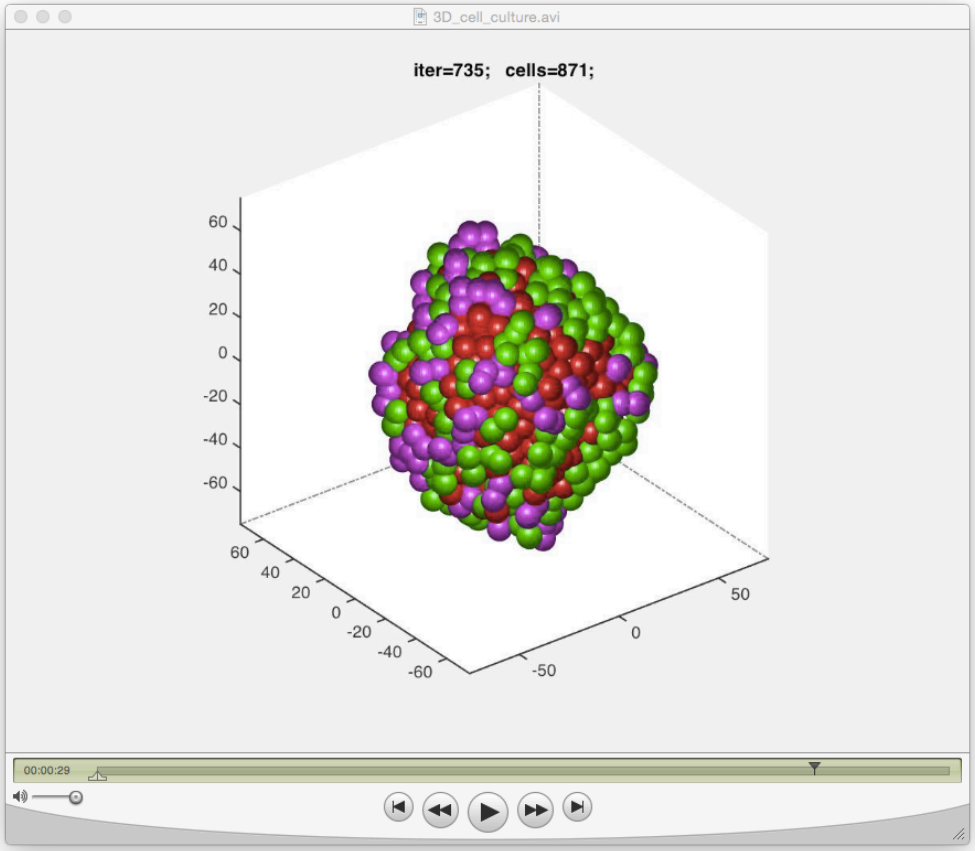
Tumor cells in 3D culture (side view)

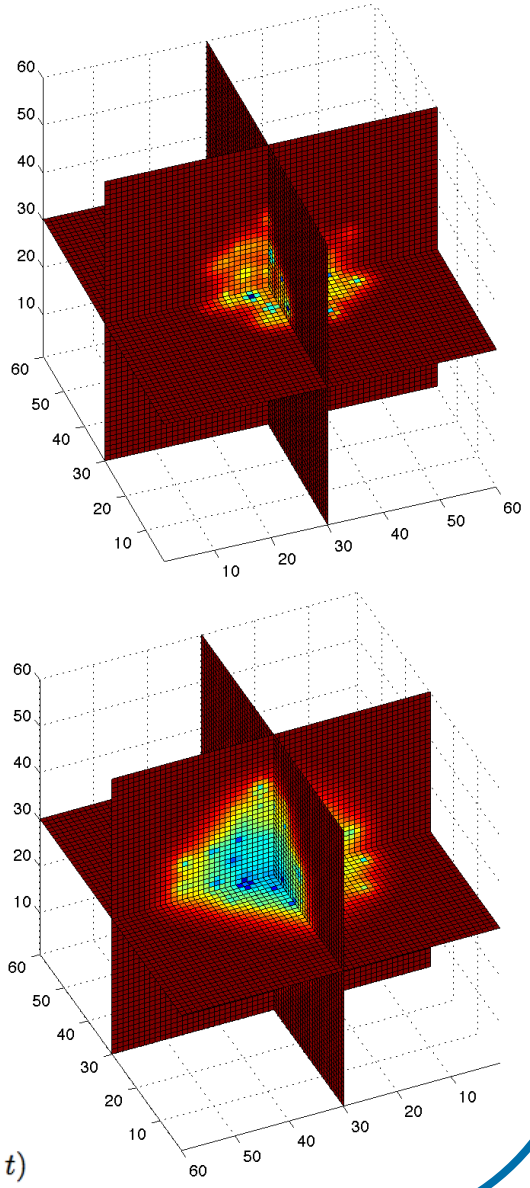


Central cross section

3D model of tumor spheroids

Branton Huffstutler (USF)

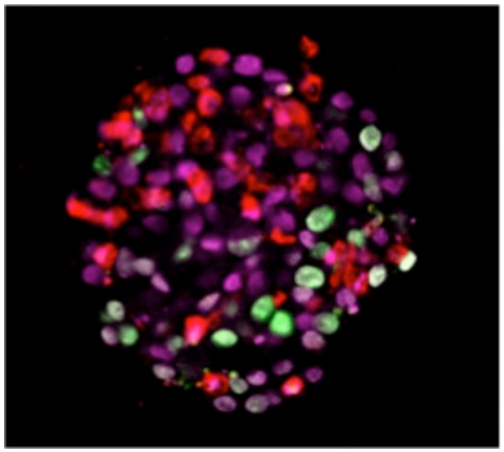




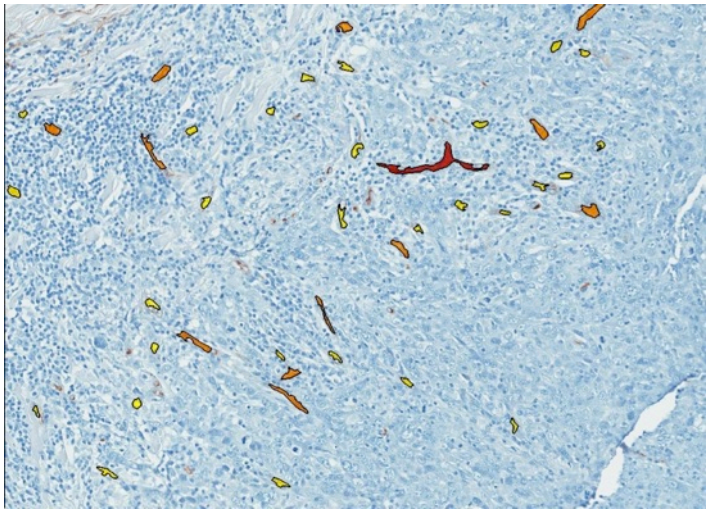
Diffusion equation with cellular uptake

$$\frac{\partial \gamma(x,y,z,t)}{\partial t} = \frac{\partial^2 \gamma(x,y,z,t)}{\partial x^2} + \frac{\partial^2 \gamma(x,y,z,t)}{\partial y^2} + \frac{\partial^2 \gamma(x,y,z,t)}{\partial z^2} - \alpha\gamma(X_{cell}, Y_{cell}, Z_{cell}, t)$$

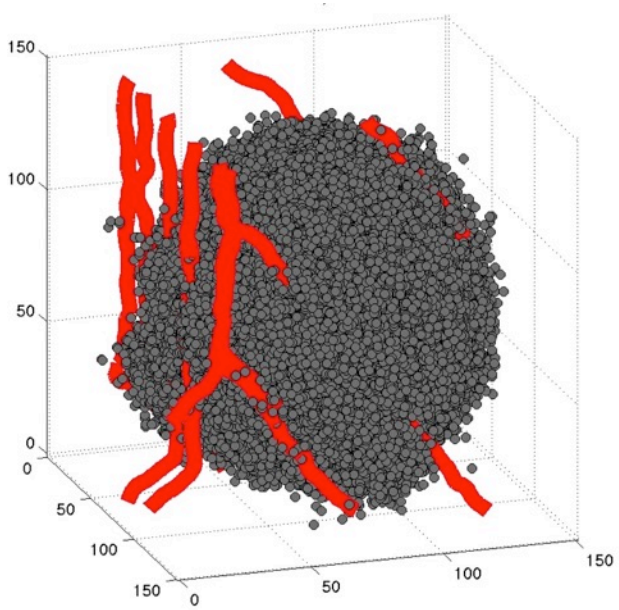
Models of tumor tissue

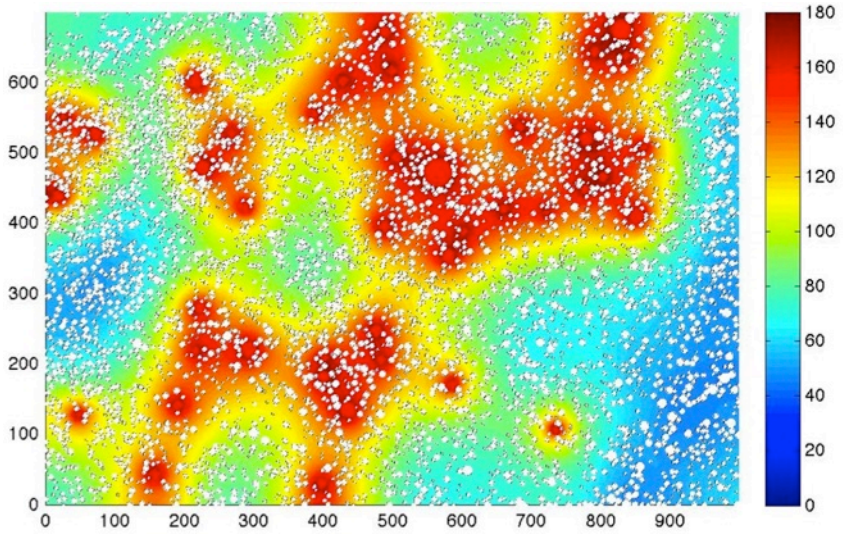


Cross section
through 3D spheroid



Cross section
through the tumor tissue

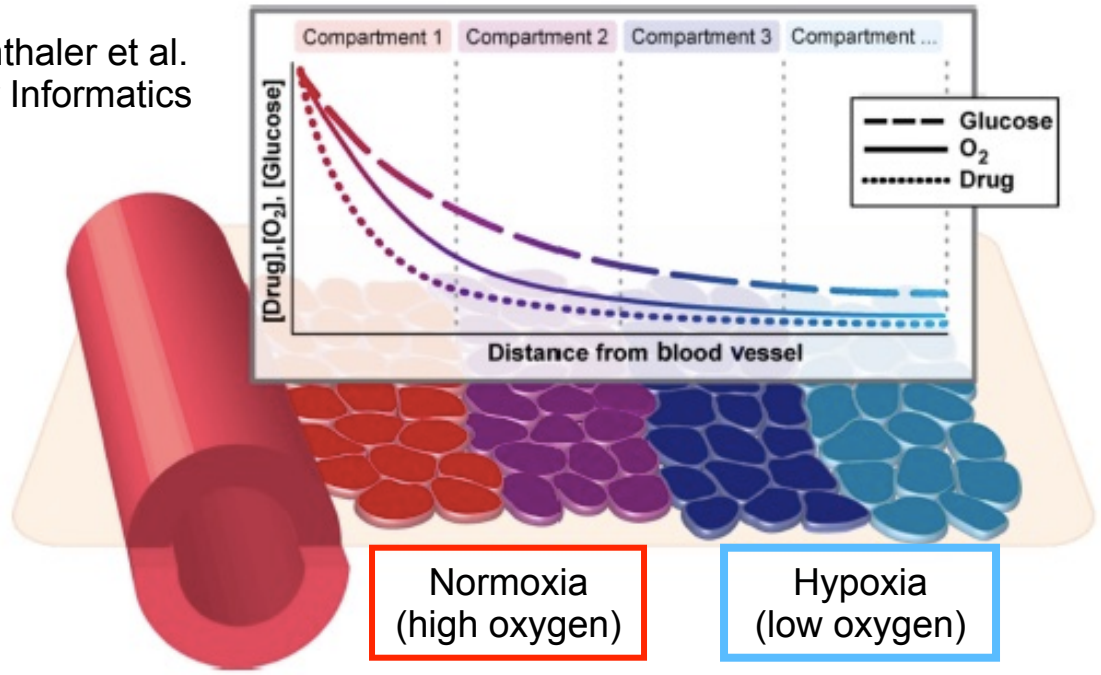


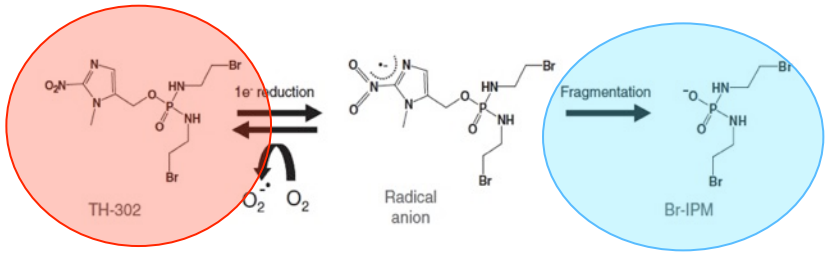


Mathematical models

Hypoxia-activated drugs

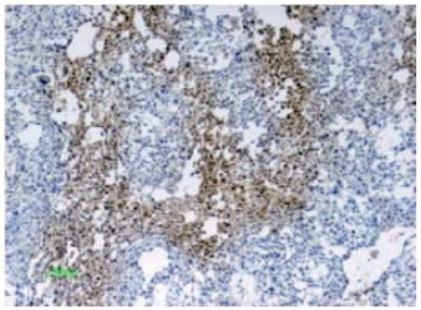
Mumenthaler et al.
Cancer Informatics
2015



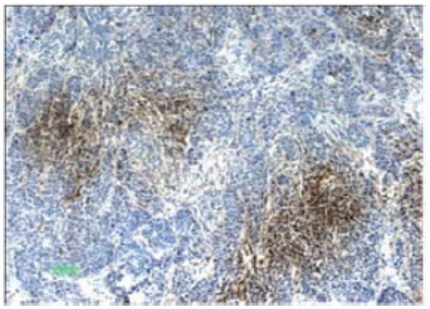


Meng et al. Mol Cancer Ther, 2012

Hs766t

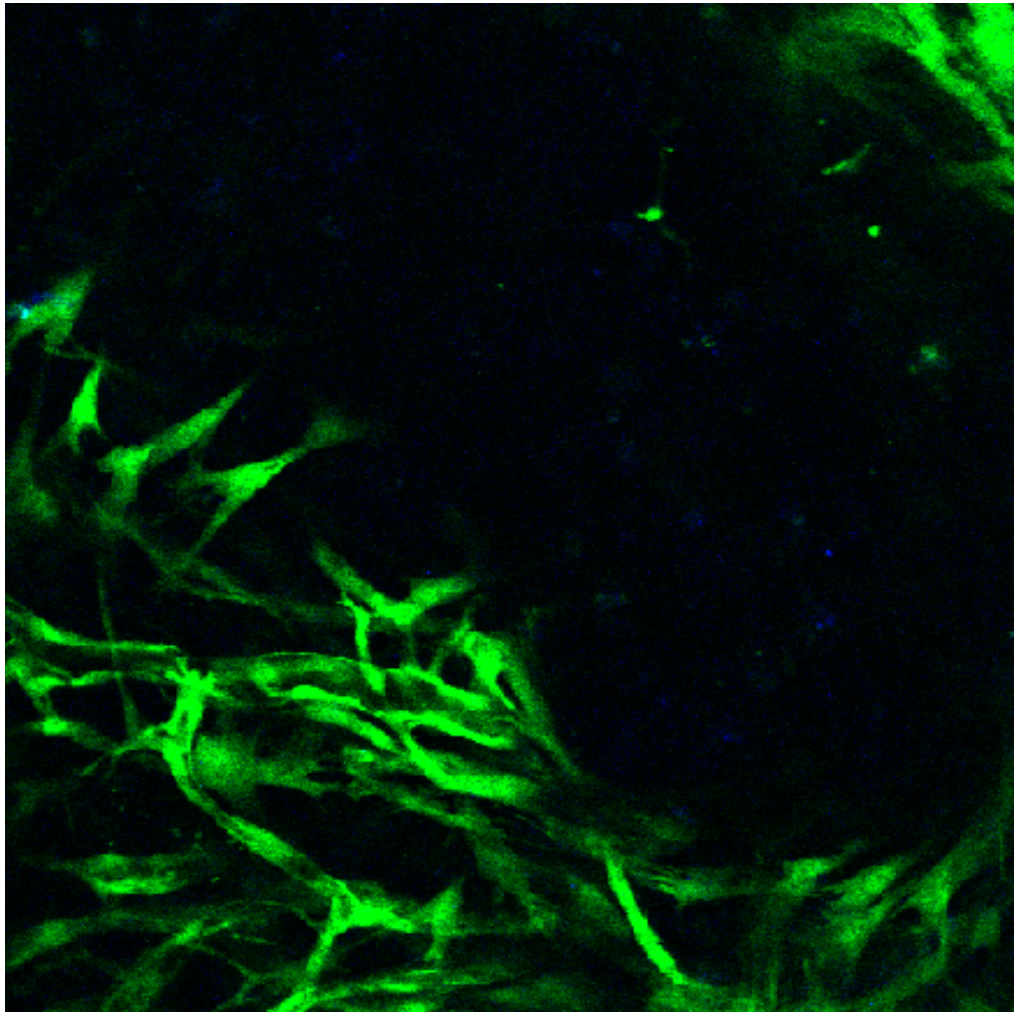


BxPC-3

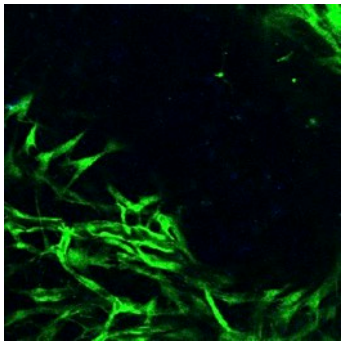


Pimonidazole (PIMO) staining for hypoxia
Sun et al. 2012

Intravital microscopy model (mice)



Green – blood vessels
Blue - dextran



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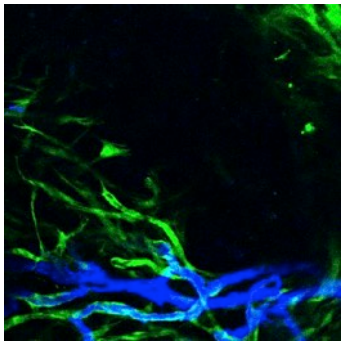

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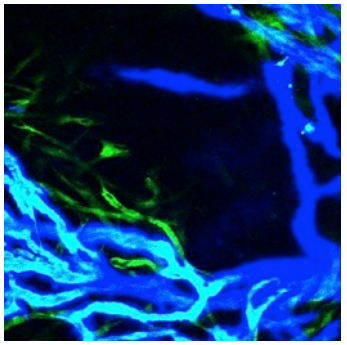

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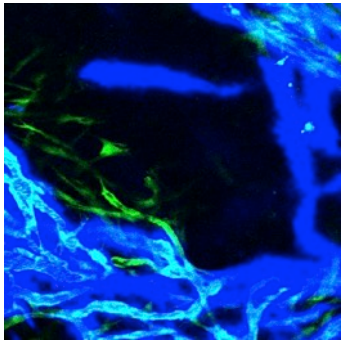

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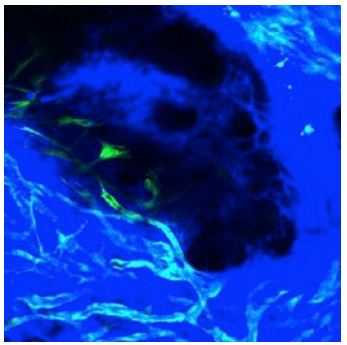
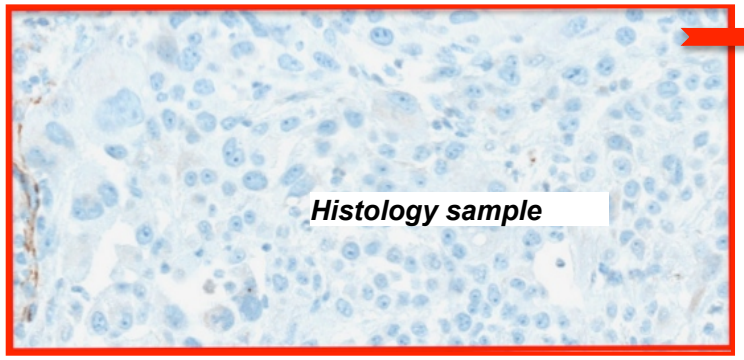
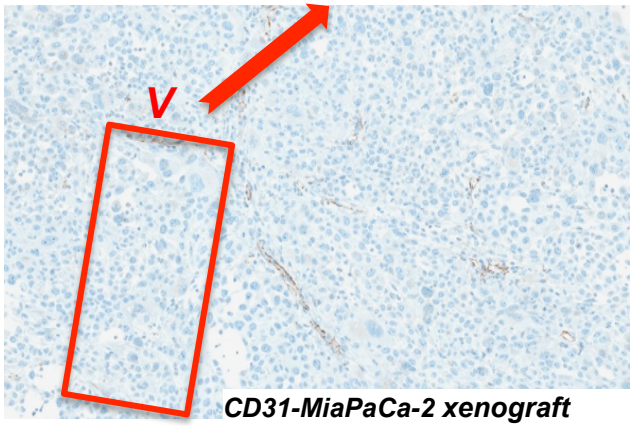


25

In silico tissue morphology & tissue oxygenation

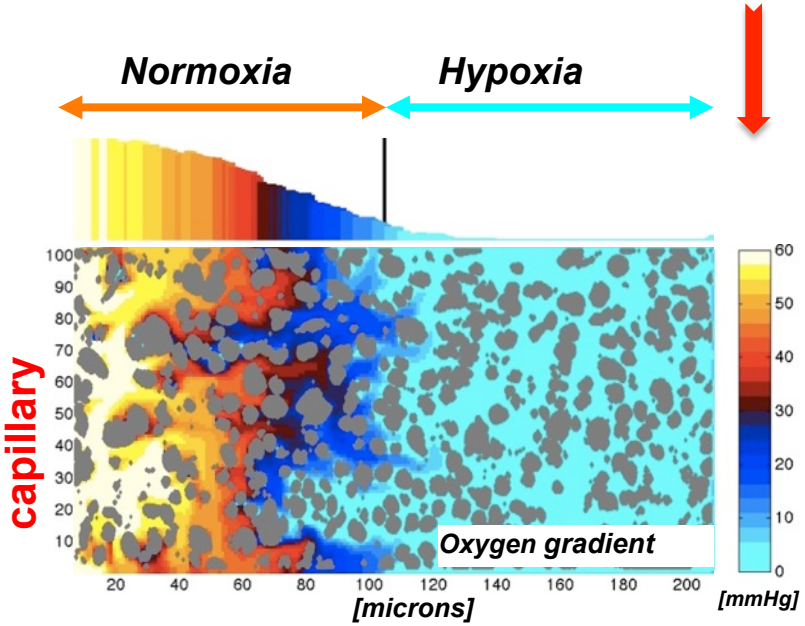
MiaPaCa-2
Human pancreatic carcinoma cell line





CD31-MiaPaCa-2 xenograft

J. Wojtkowiak,
R. Gillies Lab



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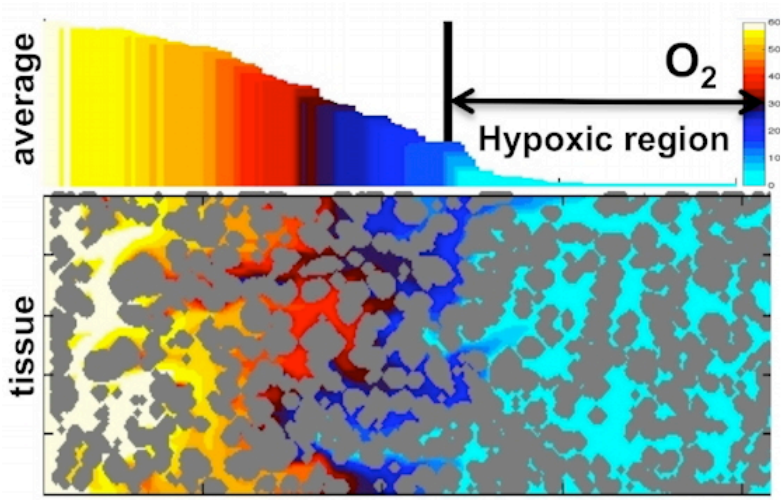
HAPs action – microPD model

Normoxia/Hypoxia border



$$\mu\Delta\mathbf{u}(\mathbf{x}) = \nabla p(\mathbf{x}) - \mathbf{f}(\mathbf{x}) \quad \text{and} \quad \nabla\cdot\mathbf{u}(\mathbf{x}) = 0 \tag{1}$$

$$\text{where} \quad \mathbf{f}(\mathbf{x}) = \mathbf{f}_0\,\phi_\varepsilon(\mathbf{x}-\mathbf{x}_0), \quad \text{and} \quad \phi_\varepsilon(\mathbf{x}) = \frac{2\varepsilon^4}{\pi(\|\mathbf{x}\|^2+\varepsilon^2)} \tag{2}$$

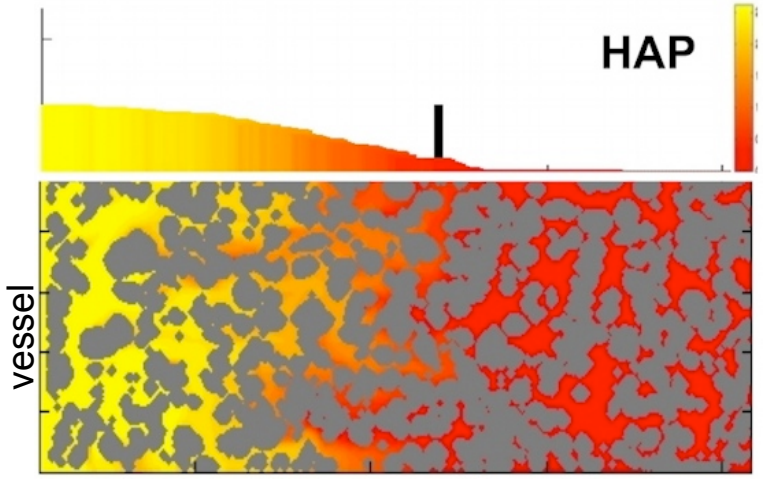
$$\frac{\partial c(\mathbf{x},t)}{\partial t} = \underbrace{\mathcal{D}_c\Delta c(\mathbf{x},t)}_{diffusion} - \underbrace{\mathbf{u}(\mathbf{x},t)\cdot\nabla c(\mathbf{x},c)}_{advection} - \underbrace{\frac{\kappa_m c(\mathbf{x},t)}{\kappa_n + c(\mathbf{x},t)}\chi(\Omega_\Gamma)}_{cellular\ \ uptake} \tag{3}$$

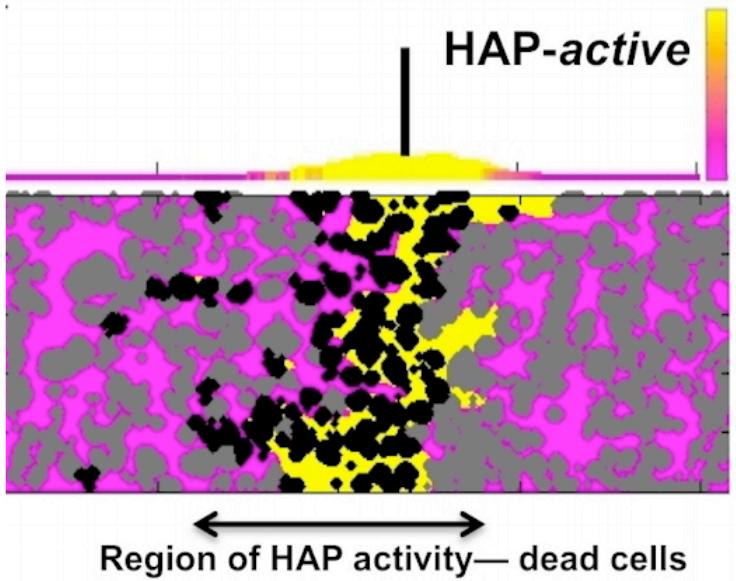
$$\frac{\partial \eta_i(\mathbf{x},t)}{\partial t} = \underbrace{\mathcal{D}_{\eta_i}\Delta\eta_i(\mathbf{x},t)}_{diffusion} - \underbrace{\mathbf{u}(\mathbf{x},t)\cdot\nabla\eta_i(\mathbf{x},c)}_{advection} - \underbrace{\xi(c(\mathbf{x},t))\eta_i(\mathbf{x},t)}_{activation} - \underbrace{\omega_i\eta_i(\mathbf{x},t)}_{decay} \tag{4}$$

$$\frac{\partial \eta_a(\mathbf{x},t)}{\partial t} = \underbrace{\mathcal{D}_{\eta_a}\Delta\eta_a(\mathbf{x},t)}_{diffusion} - \underbrace{\mathbf{u}(\mathbf{x},t)\cdot\nabla\eta_a(\mathbf{x},c)}_{advection} + \underbrace{\xi(c(\mathbf{x},t))\eta_i(\mathbf{x},t)}_{activation} - \underbrace{\alpha\eta_a(\mathbf{x},t)\chi(\Omega_\Gamma)}_{cellular\ \ uptake} \tag{5}$$

initial conditions: $\mathbf{u}(\mathbf{x},t_0) = \mathbf{u_0}(\mathbf{x}),\ \ c(\mathbf{x},t_0) = c_0(\mathbf{x}),$

vessel boundary conditions: $\mathbf{u}(\mathbf{x_0},t) = \mathbf{u^0},\ c(\mathbf{x_0},t) = c^0,\ \eta_i(\mathbf{x_0},t) = \eta_i^0$)





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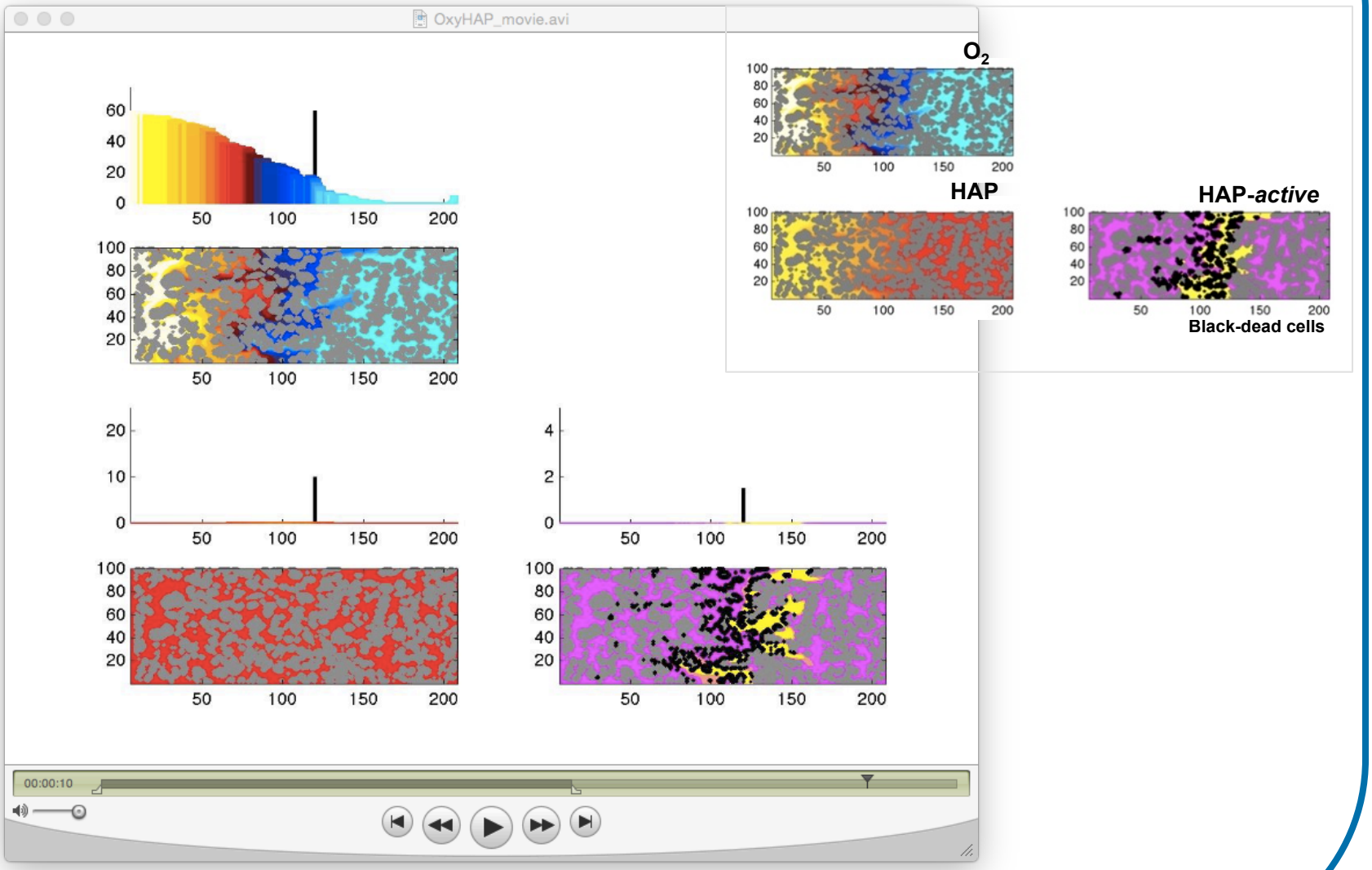
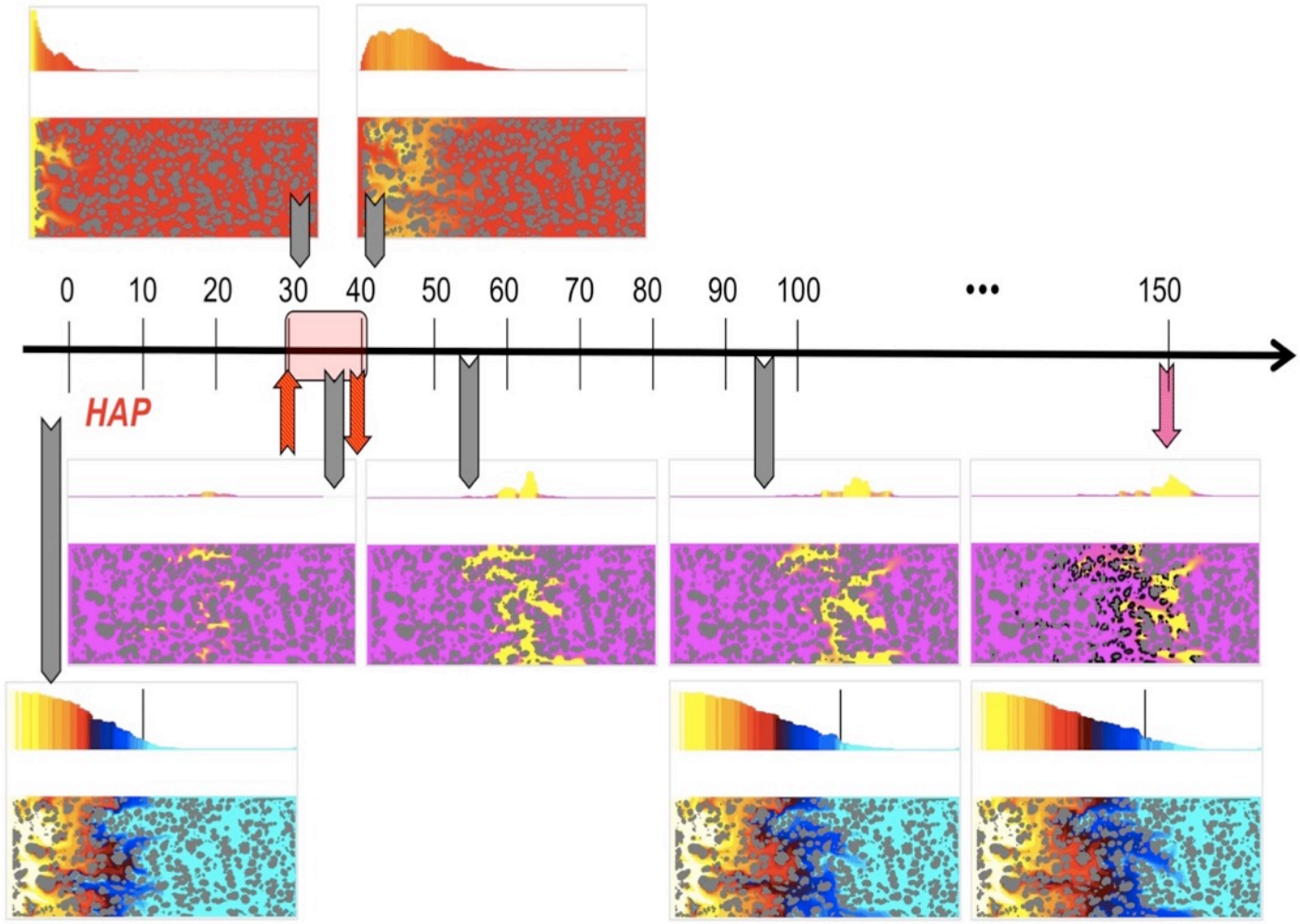
Tissue metabolic landscape under HAP



Inactive drug

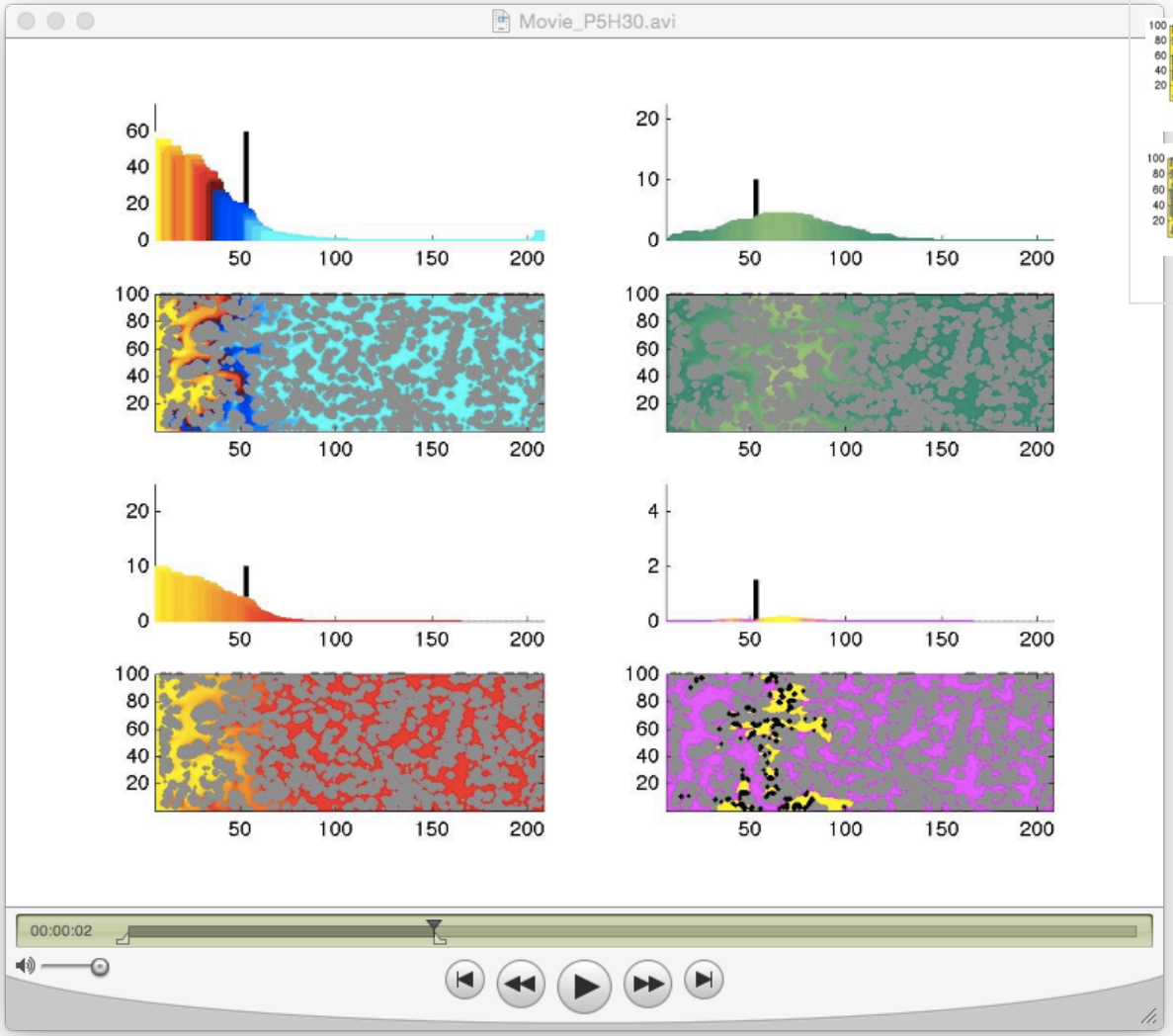
activated drug

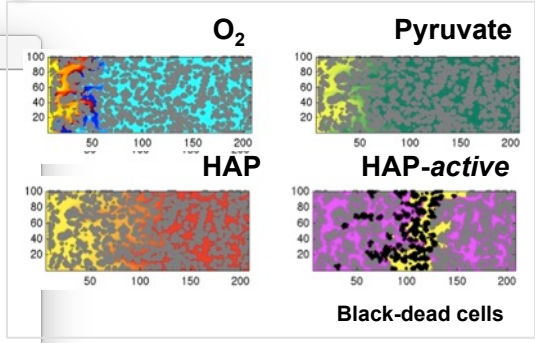
HAPs-O_2 interplay



HAP injection can perturb the metabolic landscape of a tissue and increase the O_2 levels due to diminished oxygen uptake as a result of cell death. The steady gradient of O_2 (control case) can be shifted after HAP application.

HAP+Pyruvate simulation
Combination therapy

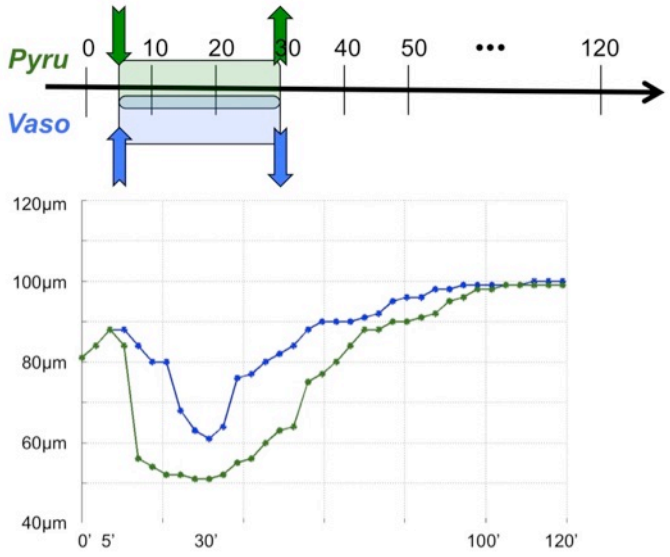


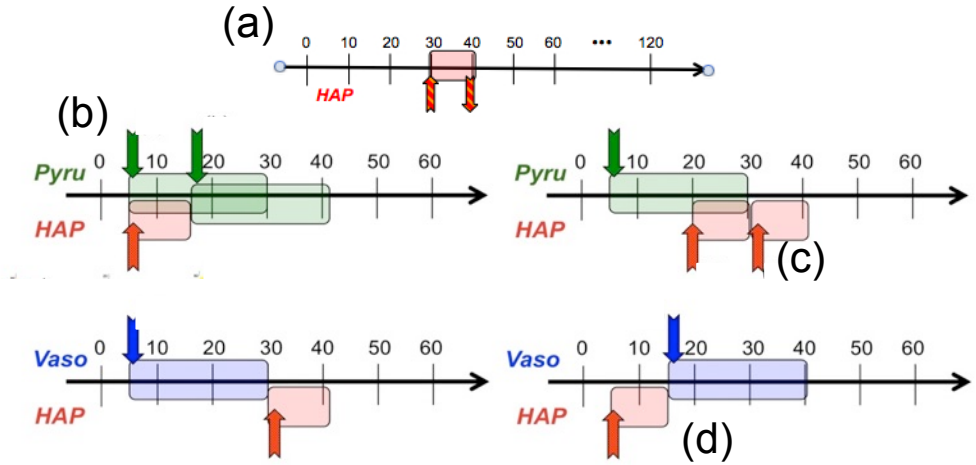


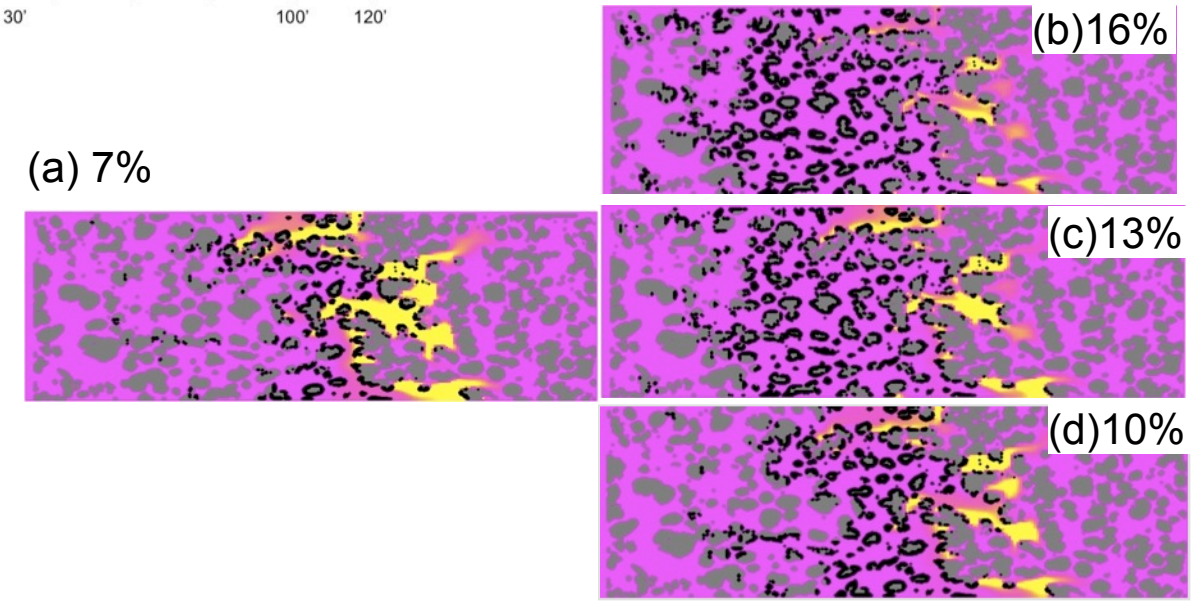
Inactive drug

activated drug

Enhancing HAPs efficacy by combination therapy scheduling

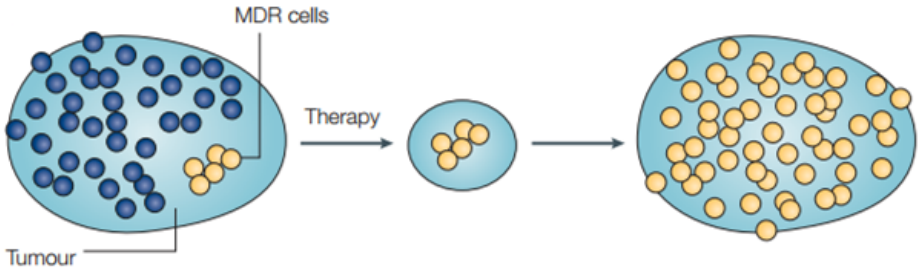




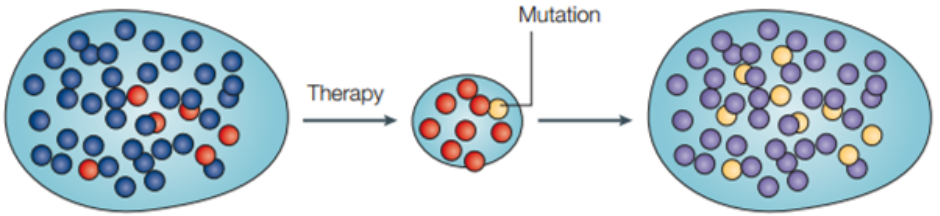


Drug resistance

- ***Pre-existing resistance***



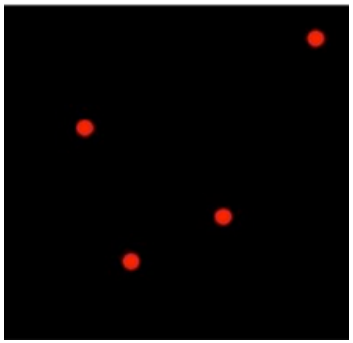
- ***Acquired resistance***



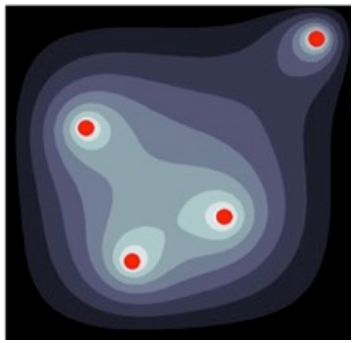
Clinically, drug resistance is defined as a reduced effectiveness of treatment during or after the course of therapy.

As a result, a cancer can progress even months or years after treatment, leading to tumor recurrence.

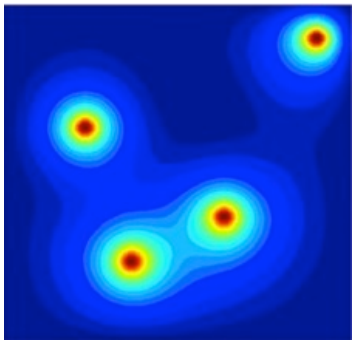
Model of drug resistance



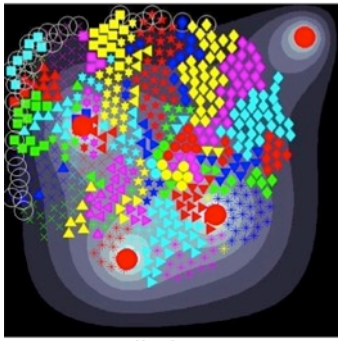
vessels



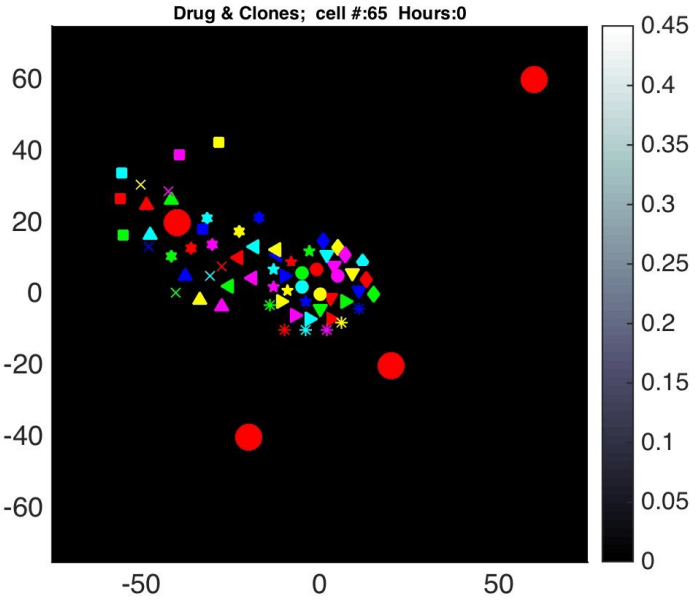
oxygen gradient

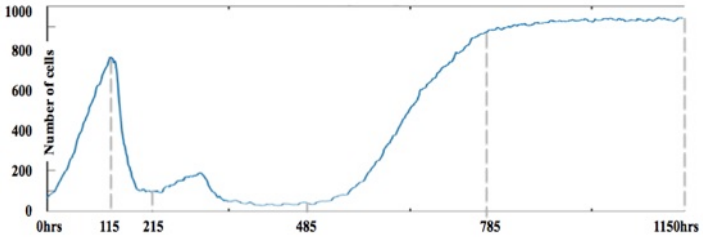


drug gradient

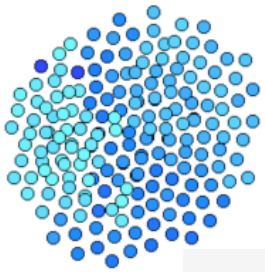


cell clones

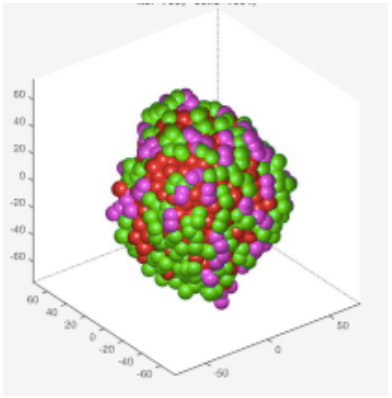




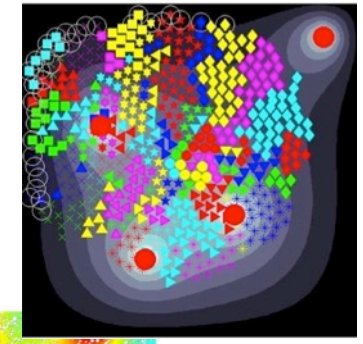
Drug delivery modeling



1. Initial experiments are don in 2D cell cultures to determine whether the drug can kill the cells or suppress their growth.

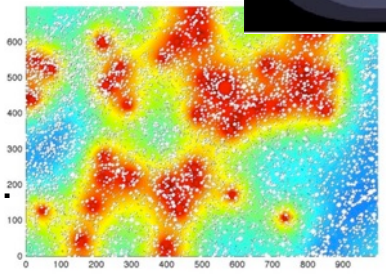


2. All cell in the 2D culture are exposed to the drug, but in 3D environments (in the tissue or in spheroids) only cells close to the source od drug (vasculature or medium) are exposed to the drug.



3. Combinations of drugs (or other therapeutic treatments) often work better than mono-therapy, however, it is difficult to know what the right order, timing and dosing of the drugs is.

4. Cells exposed to drugs may stop responding to the drug, and become resistant; It is not known how avoid drug resistance.



Math models are helping to address these problems via simulations and analysis, and can help to solve them.

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