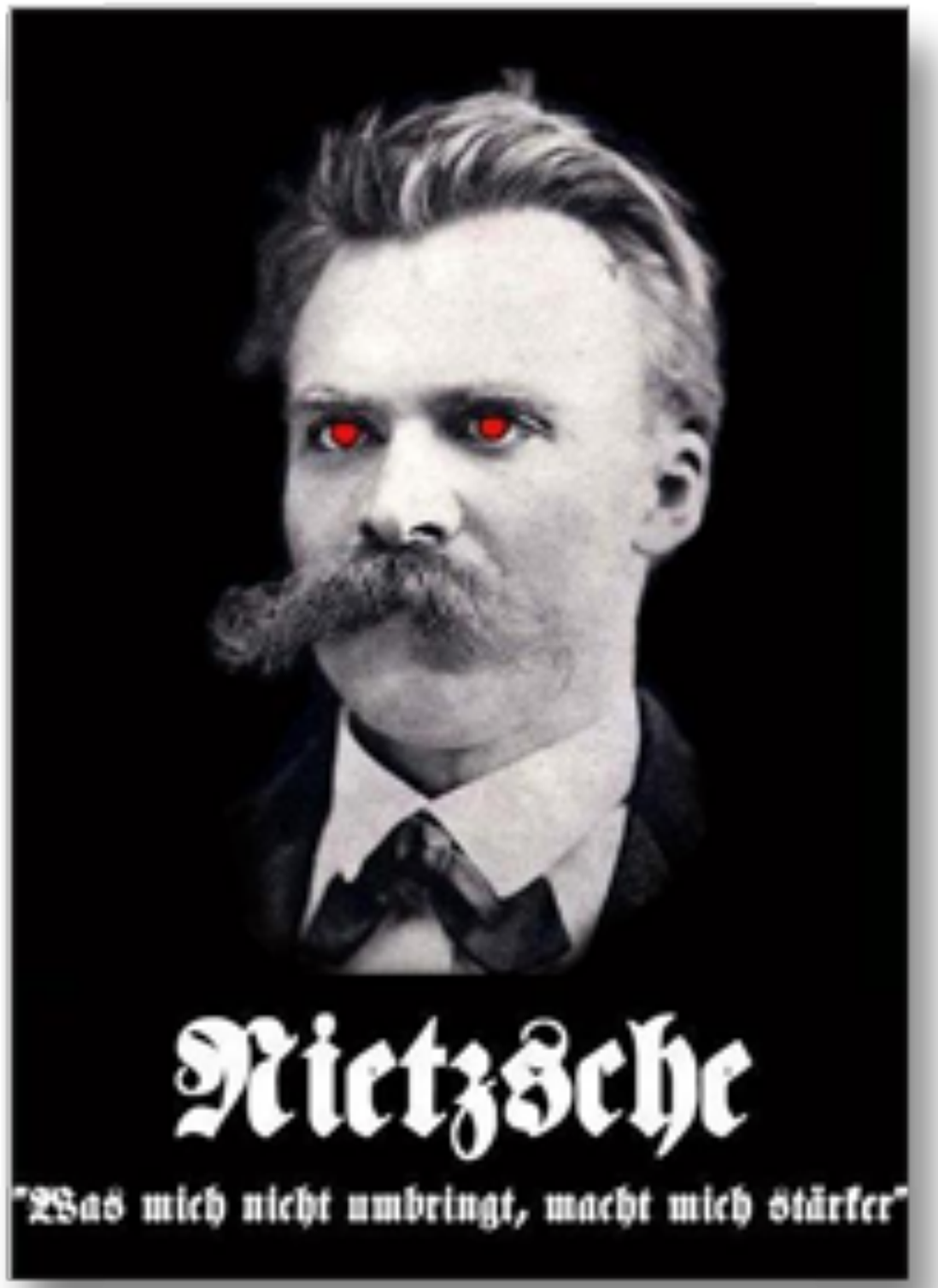
Game Theory and Cancer

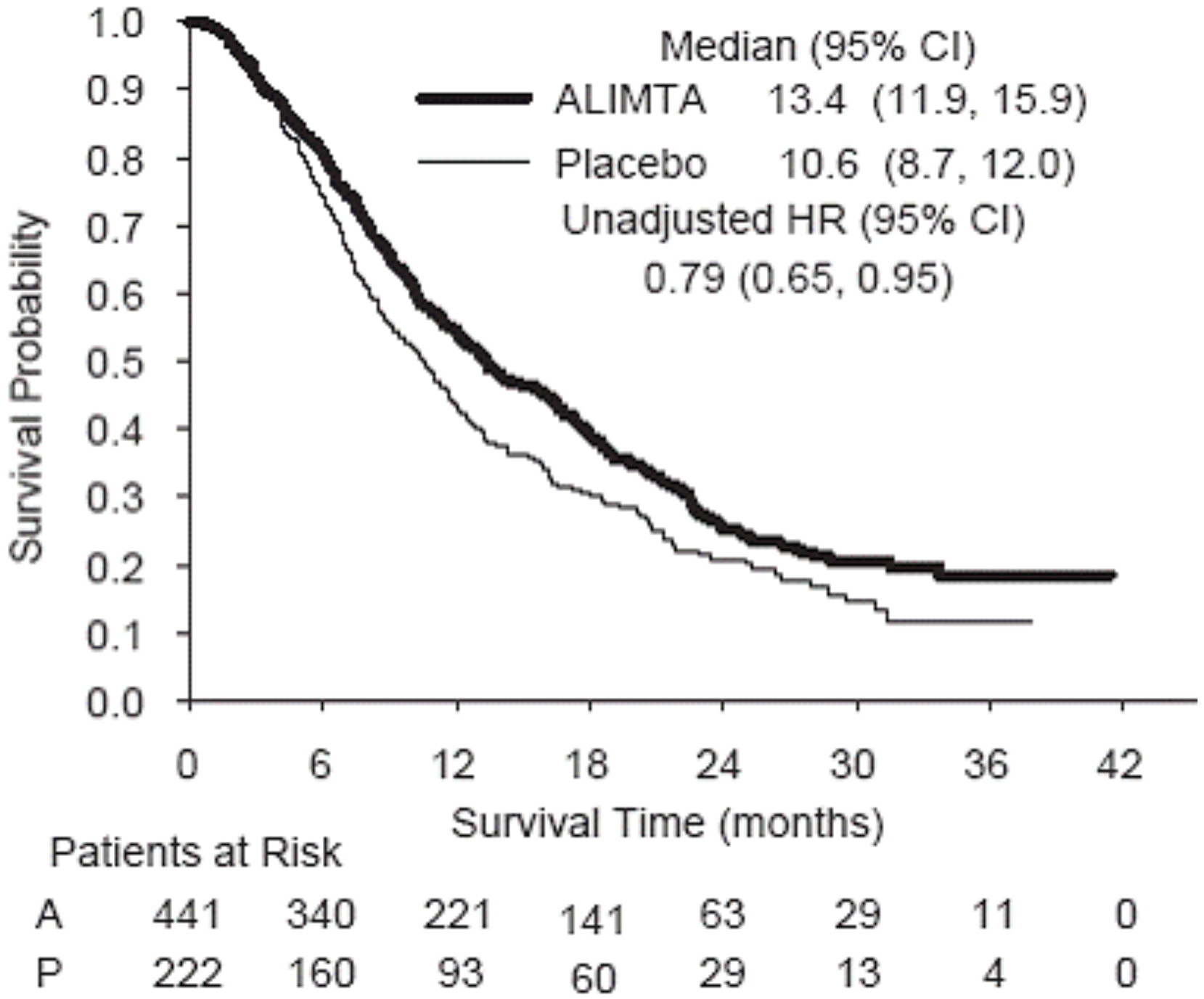
or

What Doesn't Kill Me Makes Me Stronger

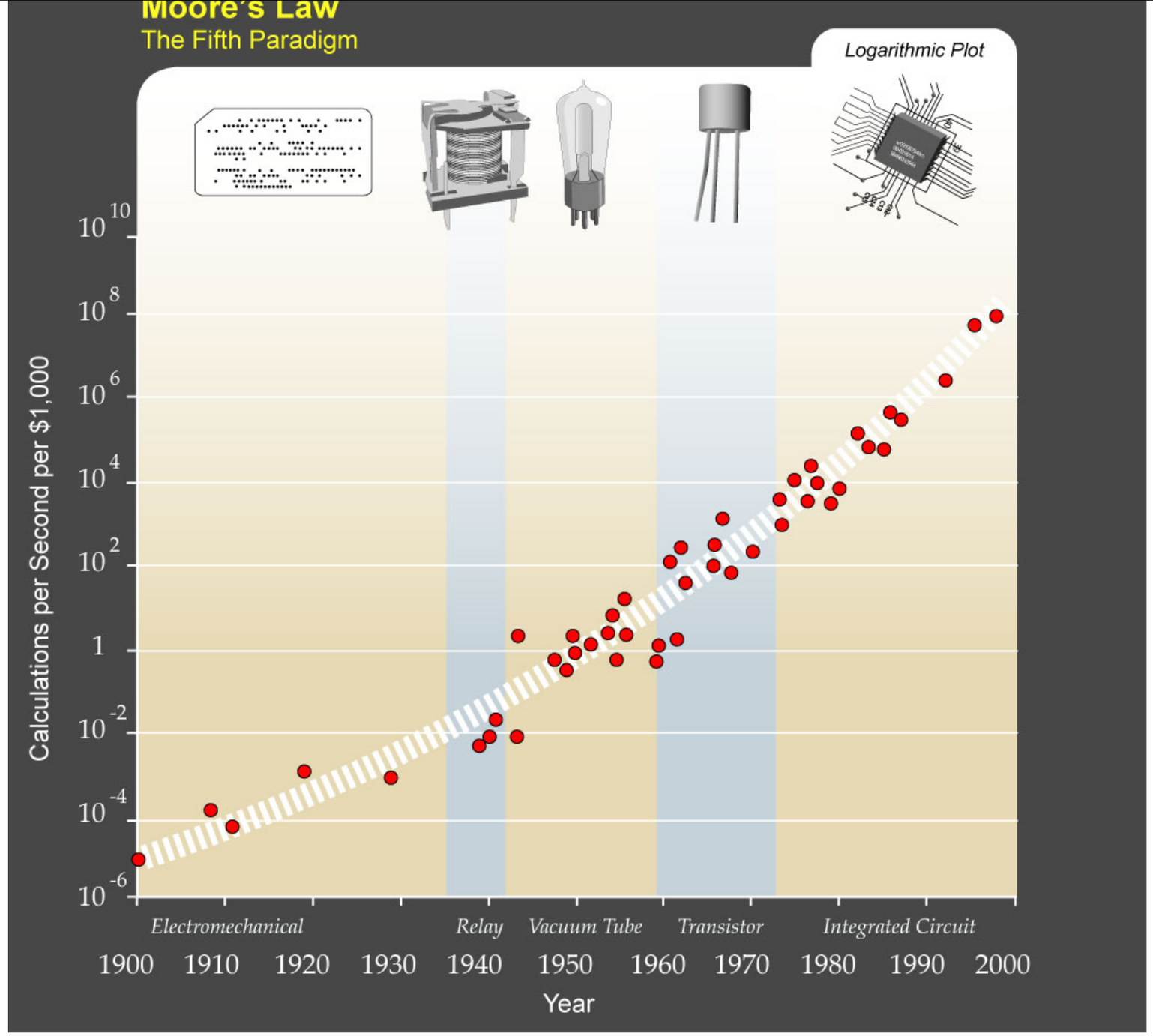
Bob Austin
Princeton University


Nietzsche
"Was mich nicht umbringt, macht mich stärker"

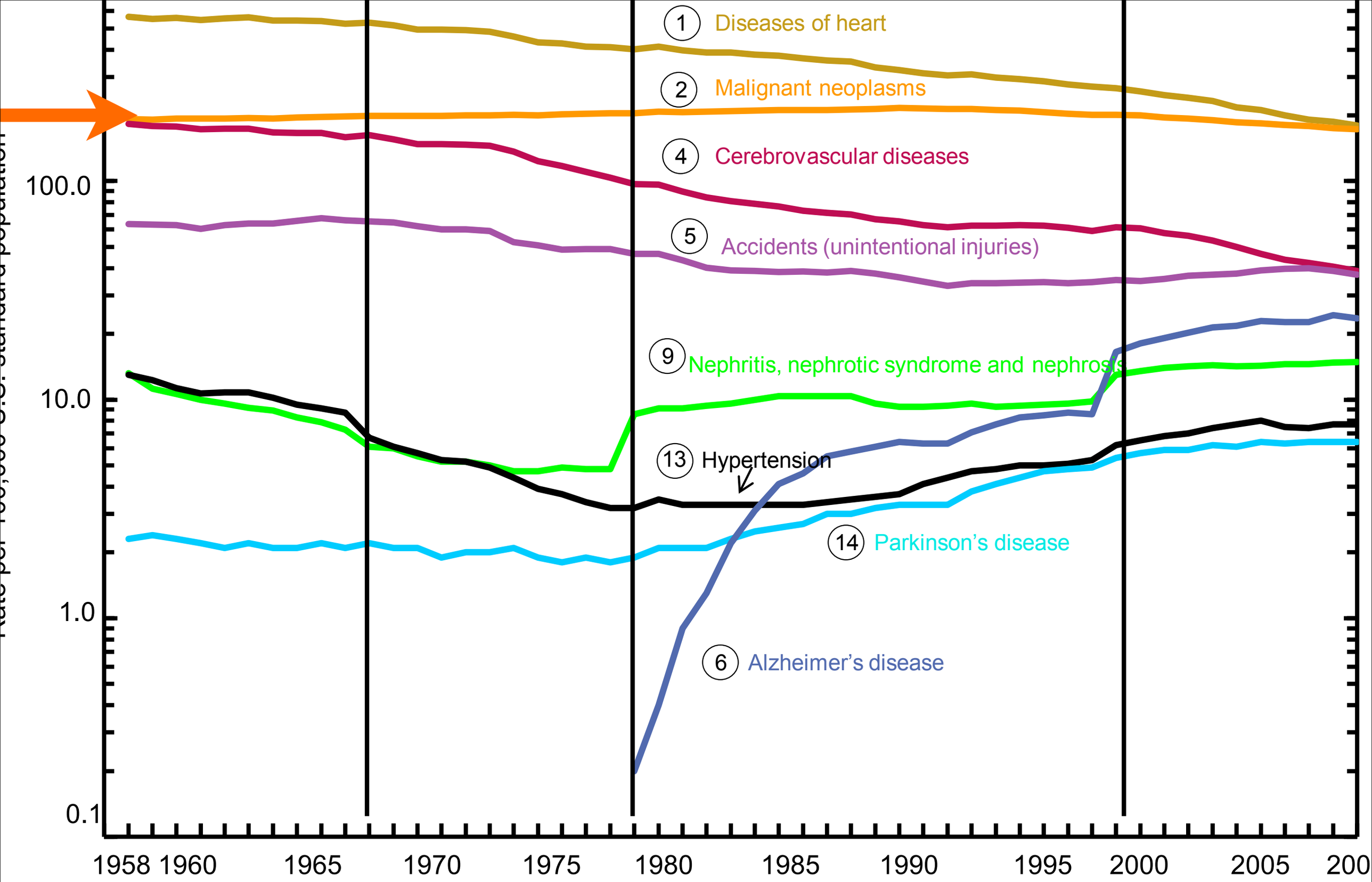
I. Why Cancer?



Two Major problem: evolution of drug resistance, and failure to predict metastasis (90% of deaths?).



16 orders of magnitude improvement in 100 years!
And it was on the shoulders of those great paradigm shifts which we learn as physicists.
(PS: Microsoft has been a negative influence)



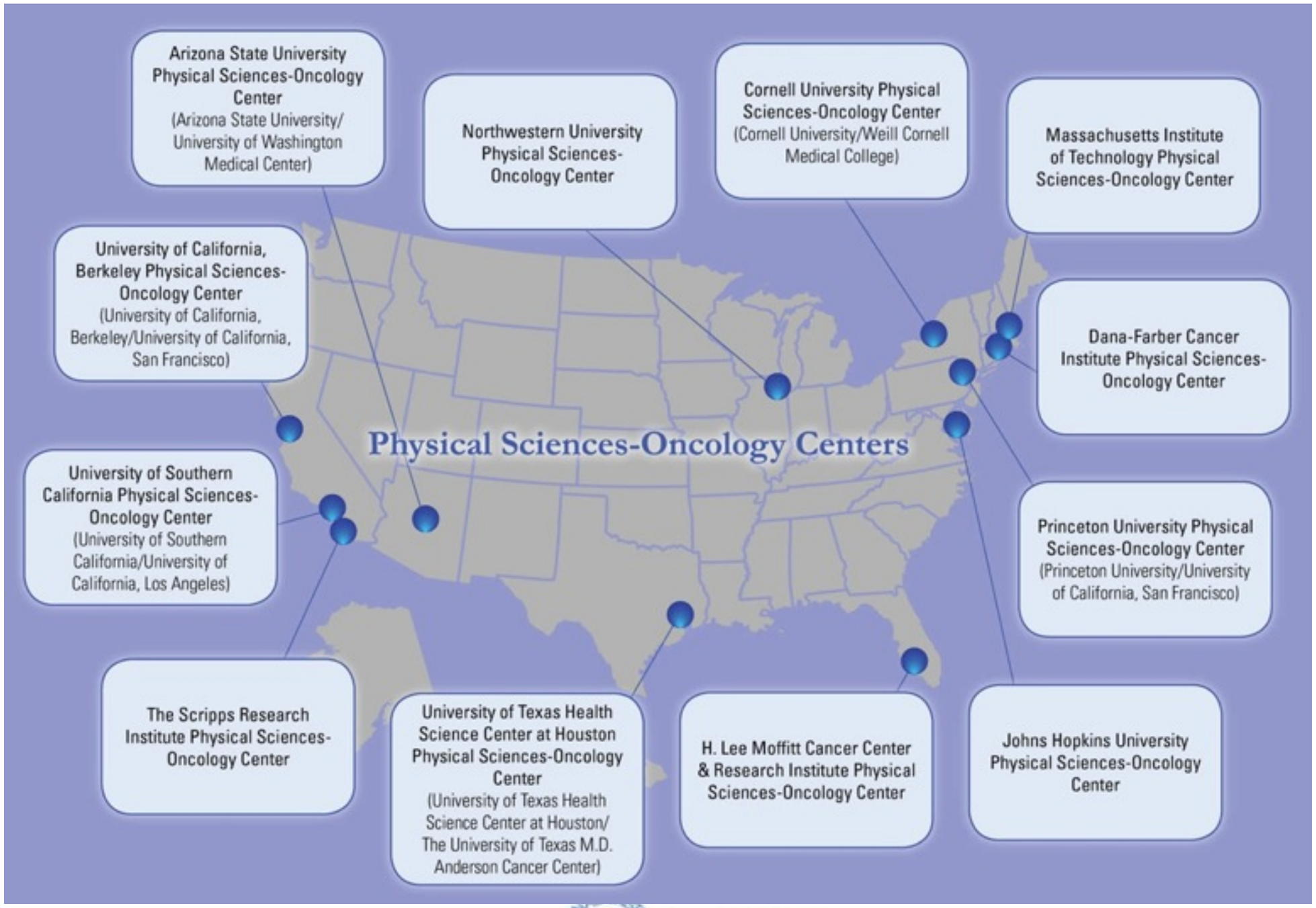
NOTE: ICD is the *International Classification of Diseases.* Circled numbers indicate ranking of conditions as leading causes of death in 2009.
Age-adjusted death rates per 100,000 U.S. standard population; see "Technical Notes."
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

There has been NO paradigm shift in cancer!

So I say that our basic regime of surgery chemotherapy has on average only bought time, not a cure, and at a terrible cost which is getting worse and worse.

So where is the paradigm shift? Where are the disruptive ideas to break this disaster?

What exactly do we not understand?


Arizona State University Physical Sciences-Oncology Center (Arizona State University/ University of Washington Medical Center)
Northwestern University Physical Sciences-Oncology Center
Cornell University Physical Sciences-Oncology Center (Cornell University/Weill Cornell Medical College)
Massachusetts Institute of Technology Physical Sciences-Oncology Center
University of California, Berkeley Physical Sciences-Oncology Center (University of California, Berkeley/University of California, San Francisco)
Dana-Farber Cancer Institute Physical Sciences-Oncology Center
Physical Sciences-Oncology Centers
University of Southern California Physical Sciences-Oncology Center (University of Southern California/University of California, Los Angeles)
Princeton University Physical Sciences-Oncology Center (Princeton University/University of California, San Francisco)
The Scripps Research Institute Physical Sciences-Oncology Center
University of Texas Health Science Center at Houston Physical Sciences-Oncology Center (University of Texas Health Science Center at Houston/ The University of Texas M.D. Anderson Cancer Center)
H. Lee Moffitt Cancer Center & Research Institute Physical Sciences-Oncology Center
Johns Hopkins University Physical Sciences-Oncology Center

II. What is Game Theory (in 10 minutes)?

Excellent review article:

"Game theory in evolutionary biology"- Zachary Ernst

in: The Cambridge Companion to the Philosophy of Biology

PRINCETON PHYSICAL SCIENCES-ONCOLOGY CENTER (PPS-OC)

WORKSHOP ON

GAME THEORY AND CANCER

You are cordially invited to participate in a workshop on **Game Theory and Cancer** to be held in Baltimore, MD. The workshop will begin on Monday, August 12 and will conclude on Tuesday, August 13. The specific goal of this workshop is to bring together a diverse group of researchers studying various aspects of the physics of cancer.

August 12-13, 2013

Mt. Washington Conference Center
5801 Smith Avenue
Baltimore, MD 21209
http://www.acc-mtwashingtonconferencecenter.com

SPEAKERS:

Erol Akcay, Princeton University
Robert Austin, Princeton University, Organizer
Charles Cowden, University of Georgia
Ruchira Datta, University of California-San Francisco
Guillaume Lambert, University of Chicago
Jorge Pacheco, Kavli Institute for Theoretical Physics, University of California-Santa Barbara
Ken Pienta, Johns Hopkins University
Thea Tlsty, University of California-San Francisco
Amy Wu, Princeton University

Hosted by Princeton Physical Sciences-Oncology Center (PPS-OC) and co-sponsored by Johns Hopkins University

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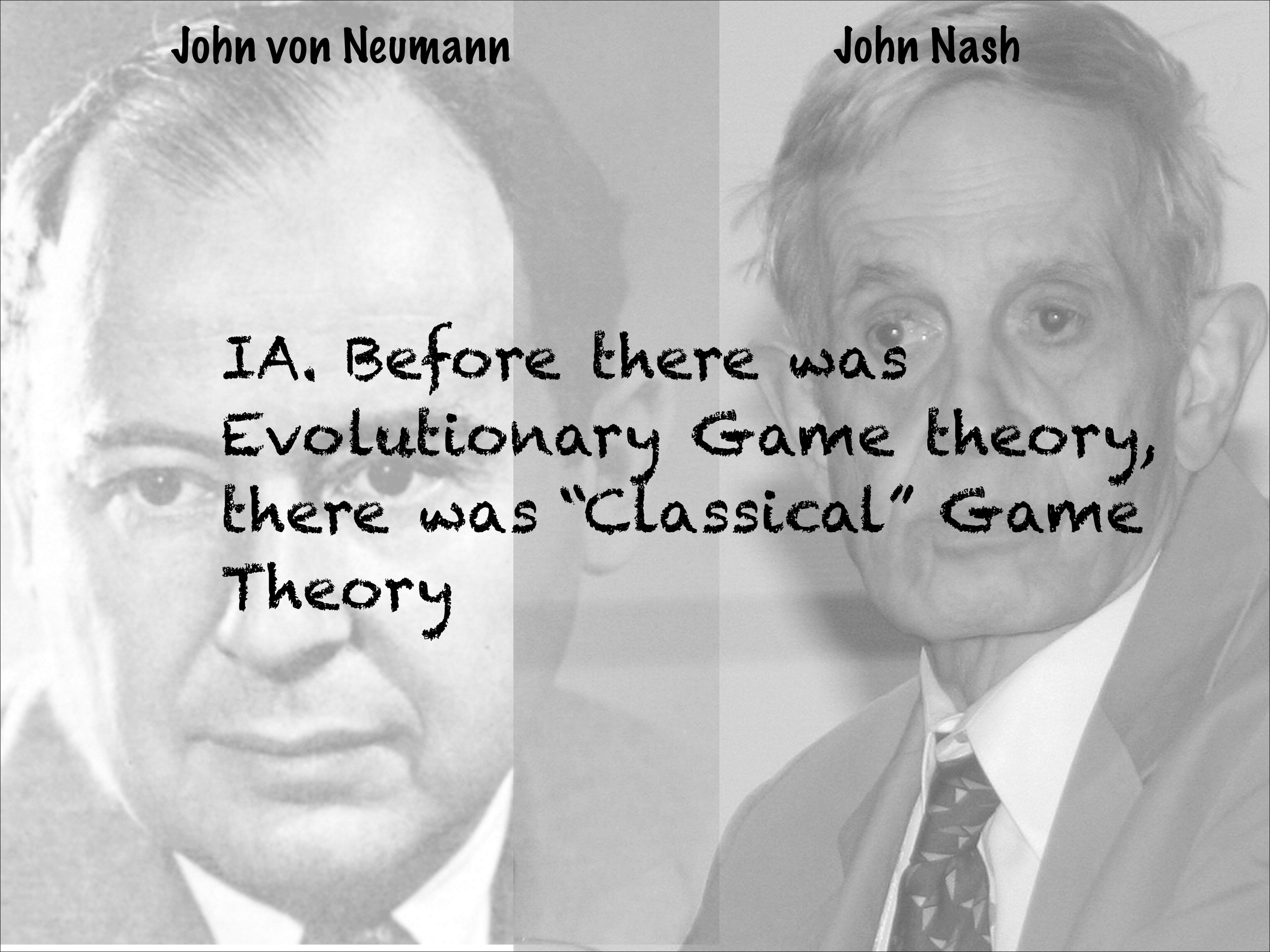
To register and for more information,
please visit **http://www.princeton.edu/psoc/training/**



IA. Before there was Evolutionary Game theory, there was "Classical" Game Theory

There are many classical games, the standard one is the Prisoner's Dilemma.

Just-so Story: Science mag accuses 2 collaborators of falsifying an oncology paper, but doesn't know enough to convict. They offer a deal for future submissions:

0) You defect, your colleague is silent: you get 0 year wait (Temptation, T), he gets -10 years (Sucker, S)

1) Both remain silent (Cooperate): both no submissions for -2 years (Reward, R)

3) Both defect: both get -3 years (Punishment, P)

What is your strategy?

Player 1 / Player 2	Cooperation	Defection
Cooperation	win,win	win++, lose--
Defection	lose--, win ++	lose,lose

Temptation (win++) > Reward (win) > Punishment (lose) >Sucker (lose--)

(0 > -2 > -3 > -10)

(this order defines a particular game)

The RATIONAL thing is cooperation: both remain silent, -2 year block.

However, your reasoning will be: if I defect and she doesnt, I get 0 years, if we both defect we get -3 years, if I cooperate and he defects I get -10:

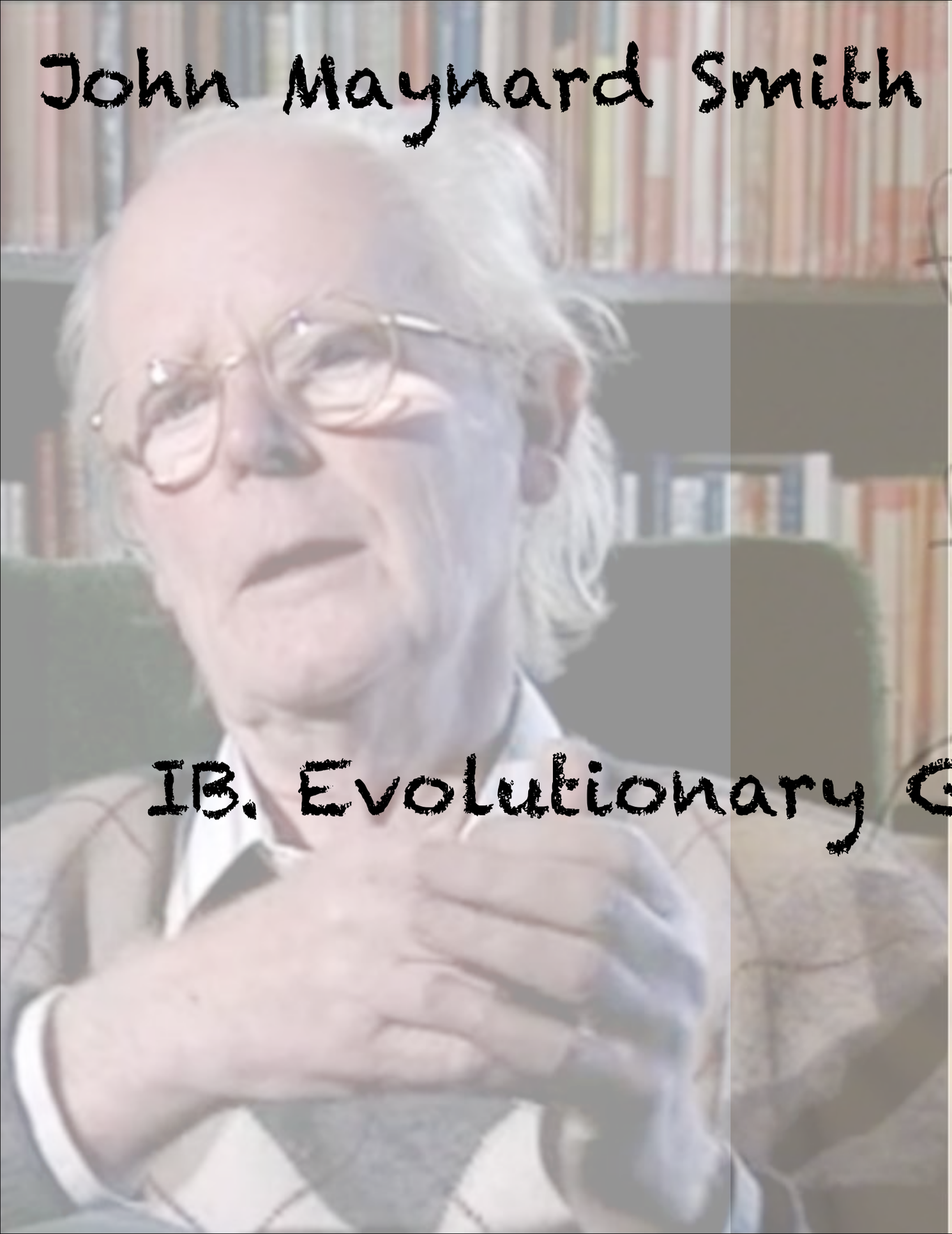
I will defect, because cooperation screws me. Nash Equilibrium: both defect. Cold War games. Nietzsche.

"Classical" game theory implies rational agents with strategies that can change based on their perception of what the competitor will do.

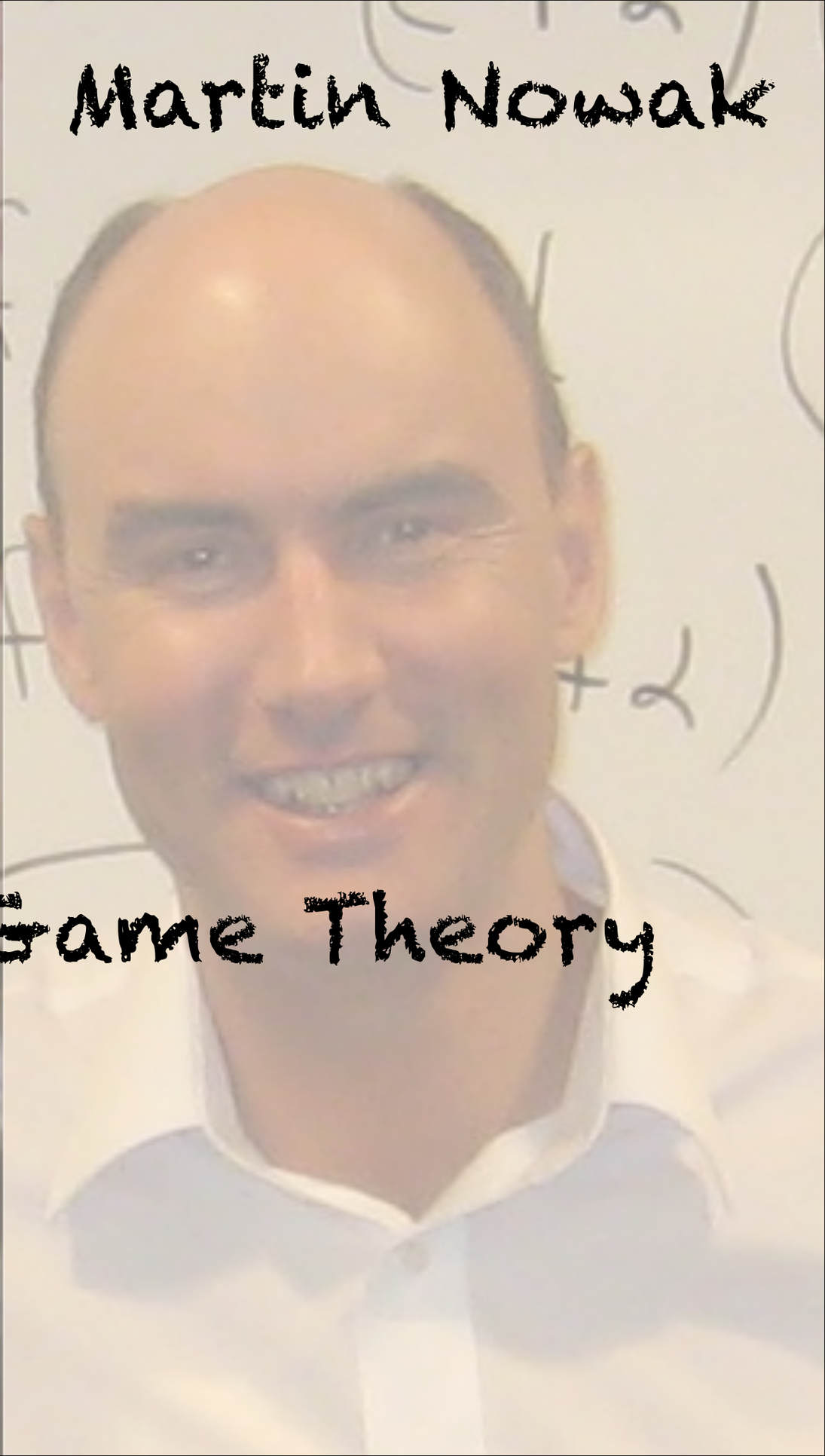
Evolutionary game theory is based at its simplest level on rates of growth (fitness) and how other populations can change that rate.

One need not have sentient beings.

John Maynard Smith



Martin Nowak



1B. Evolutionary Game Theory

Allen and Nowak (Science 23 August 2013)

"Evolutionary Game Theory applies whenever fitness depends on the phenotype or actions of others: the fitness landscape changes as the population explores it."

That's pretty general!

Evolutionary game theory is a bit different, and actually quite a bit more quantitive, than classical GT.

Good place to look: Web site of David Liao (former student):

http://qbio.lookatphysics.com/tour.egt.php#videospatiality

Tour: Evolutionary game theory for the biologist

(not actually for biologists)

Here is a slide from David's website that explains his evolutionary game theory deals with cell densities.

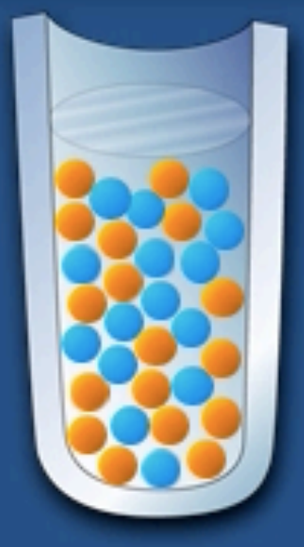
Collisional population events

$$C \xrightarrow[f_0]{R_C} 2C \qquad 2C \xrightarrow[R/[N]]{R_R} 3C \qquad C + D \xrightarrow[S/[N]]{R_S} 2C + D$$

$$D \xrightarrow[f_0]{R_D} 2D \qquad C + D \xrightarrow[T/[N]]{R_T} C + 2D \qquad 2D \xrightarrow[P/[N]]{R_P} 3D$$

This gets turned into a set of Ordinary Differential Equations:

Collisional population events



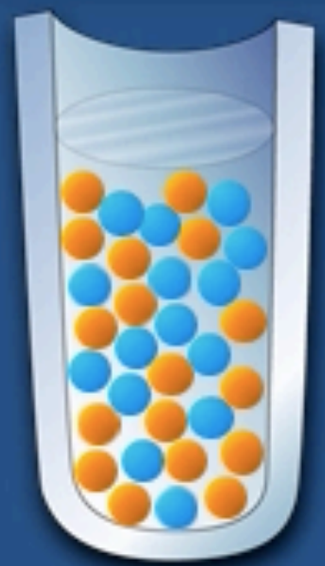
$$C \xrightarrow[f_0]{R_C} 2C \qquad 2C \xrightarrow[R/[N]]{R_R} 3C \qquad C + D \xrightarrow[S/[N]]{R_S} 2C + D$$

$$D \xrightarrow[f_0]{R_D} 2D \qquad C + D \xrightarrow[T/[N]]{R_T} C + 2D \qquad 2D \xrightarrow[P/[N]]{R_P} 3D$$

$$\frac{dC}{dt} = \frac{\partial C}{\partial R_C}\frac{dR_C}{dt} + \frac{\partial C}{\partial R_R}\frac{dR_R}{dt} + \frac{\partial C}{\partial R_S}\frac{dR_S}{dt}$$

And we finally have a set of coupled non-linear equations to solve.

Collisional population events



$$C \xrightarrow[f_0]{R_C} 2C \qquad 2C \xrightarrow[R/[N]]{R_R} 3C \qquad C + D \xrightarrow[S/[N]]{R_S} 2C + D$$

$$D \xrightarrow[f_0]{R_D} 2D \qquad C + D \xrightarrow[T/[N]]{R_T} C + 2D \qquad 2D \xrightarrow[P/[N]]{R_P} 3D$$

$$\frac{dC}{dt} = \textbf{+1}\ f_0 C + \textbf{+1}\ \frac{R}{[N]}[C]C + \textbf{+1}\ \frac{S}{[N]}[D]C$$

$$\frac{dC}{dt} = (f_0 + Rp_C + Sp_D)C$$

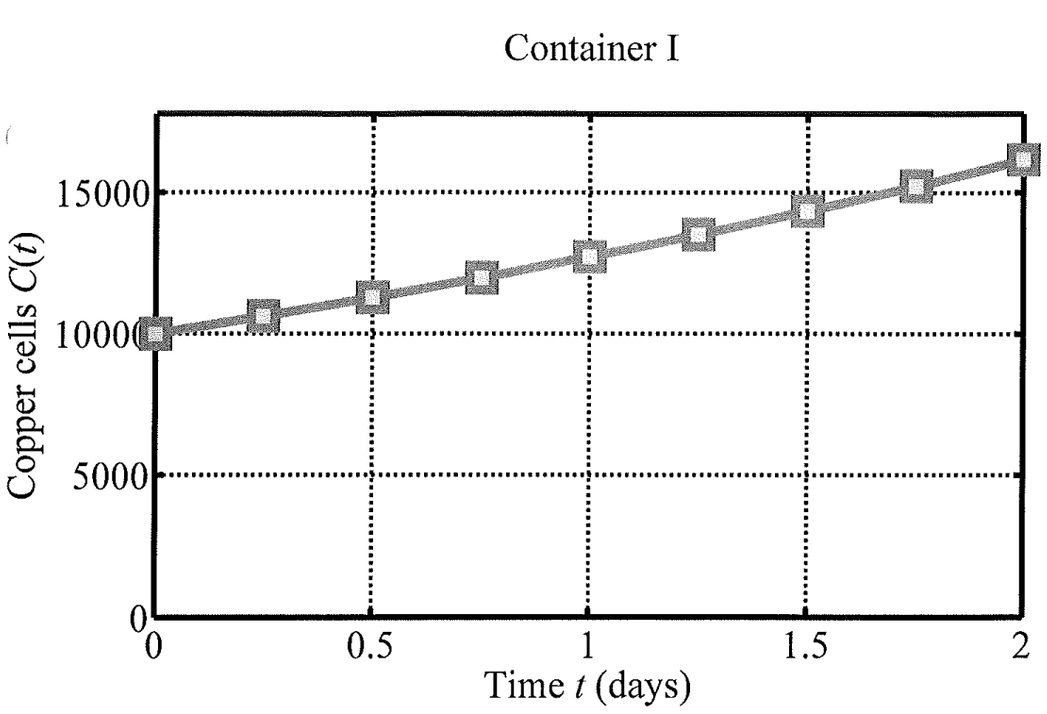
$$\frac{dD}{dt} = \textbf{+1}\ f_0 D + \textbf{+1}\ \frac{T}{[N]}[C]D + \textbf{+1}\ \frac{P}{[N]}[D]D$$

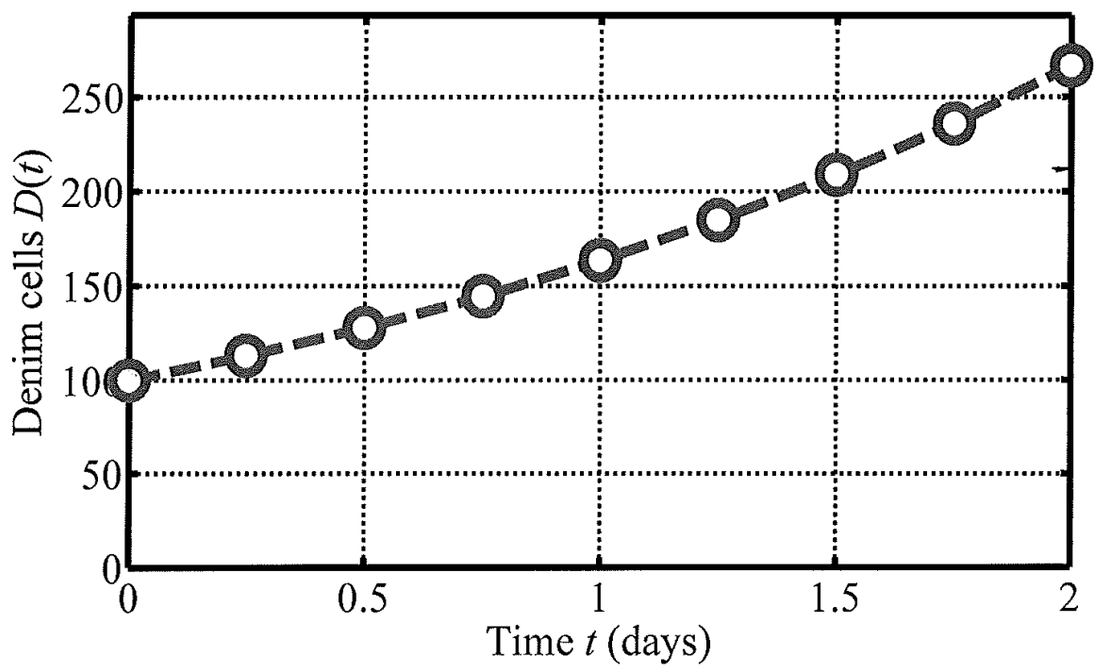
It is possible to construct a phase map of this game (David Liao+ Amy Wu), using Evolutionary Game Theory, but averaged over space right now.

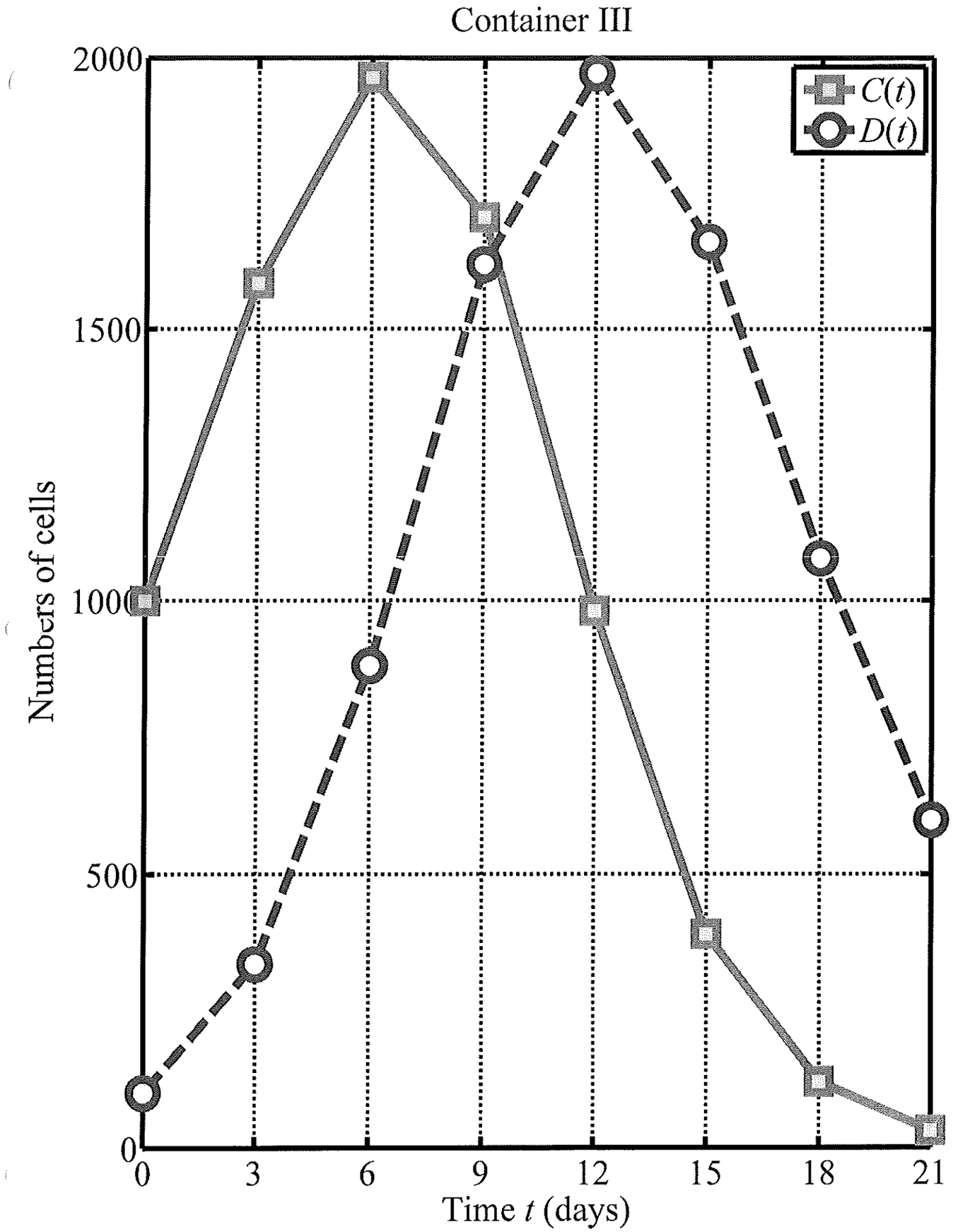
$$\frac{dC}{dt} = (Rp_C + Sp_D)C \qquad \frac{dD}{dt} = (Tp_C + Pp_D)D$$

This is written in the terminology again of the Prisoner's Dilemma, but that's really of no meaning.

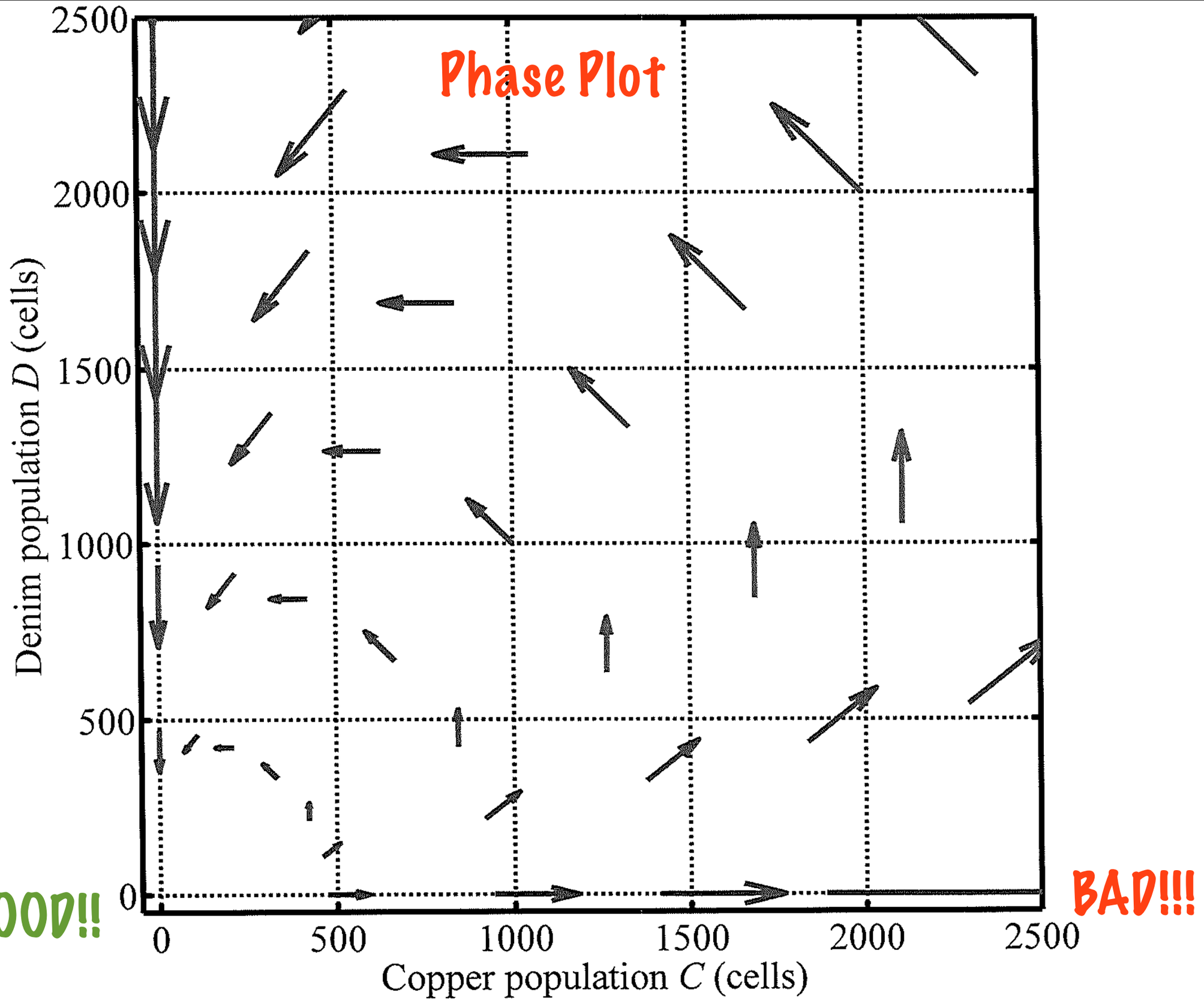
You have to do experiments with individual cells "competing" with each themselves get the on-diagonal terms, then compete them against one another to get the off-diagonal terms. This is called "training" the model.






Container III
2000
1500
1000
500
0
Numbers of cells
C(t)
D(t)
0
3
6
9
12
15
18
21
Time t (days)

Phase Plot



GOOD!!

BAD!!!

There are mathematical tricks to numerically solving these equations.

Smith:

"(1) Evolutionary version of Game Theory not really a requirement that players be rational – it is only required that they have a strategy. The results of the game will test how good that strategy is.

(2) That is what Evolution does – it tests alternative strategies for the ability to survive and reproduce.

(3) Strategies are algorithmic – just like computer programs. (Yes, mathematics and physics).

(4) The key point in the Evolutionary Game Theory model is that the success of a strategy is not just determined by how good the strategy is in itself, it is a question of how good the strategy is in the presence of other alternative strategies."

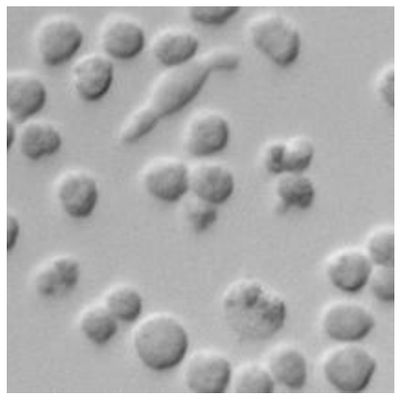
End of Evolutionary Game Theory Introduction and why cancer cells must have a strategy in dealing with competition (or help).

This does NOT mean they are sentient! Remember that EGT is not like Classical Game Theory where the players are "(ir)-rational".

III. Games cancer cells play

(Amy Wu, Qiucen Zhang, Jim Sturm, David Liao, and Moffitt Cancer Center)

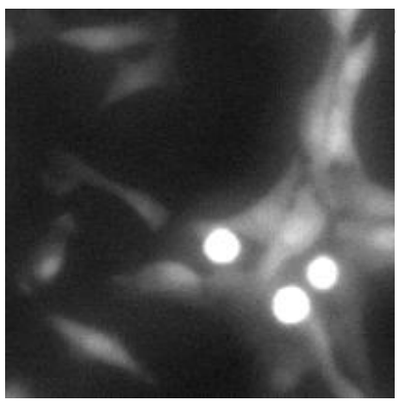
Who are the players in our game?



100µm

Myeloma (8226/RFP)

- Bone marrow cancer, incurable
- Malignant B lymphocytes

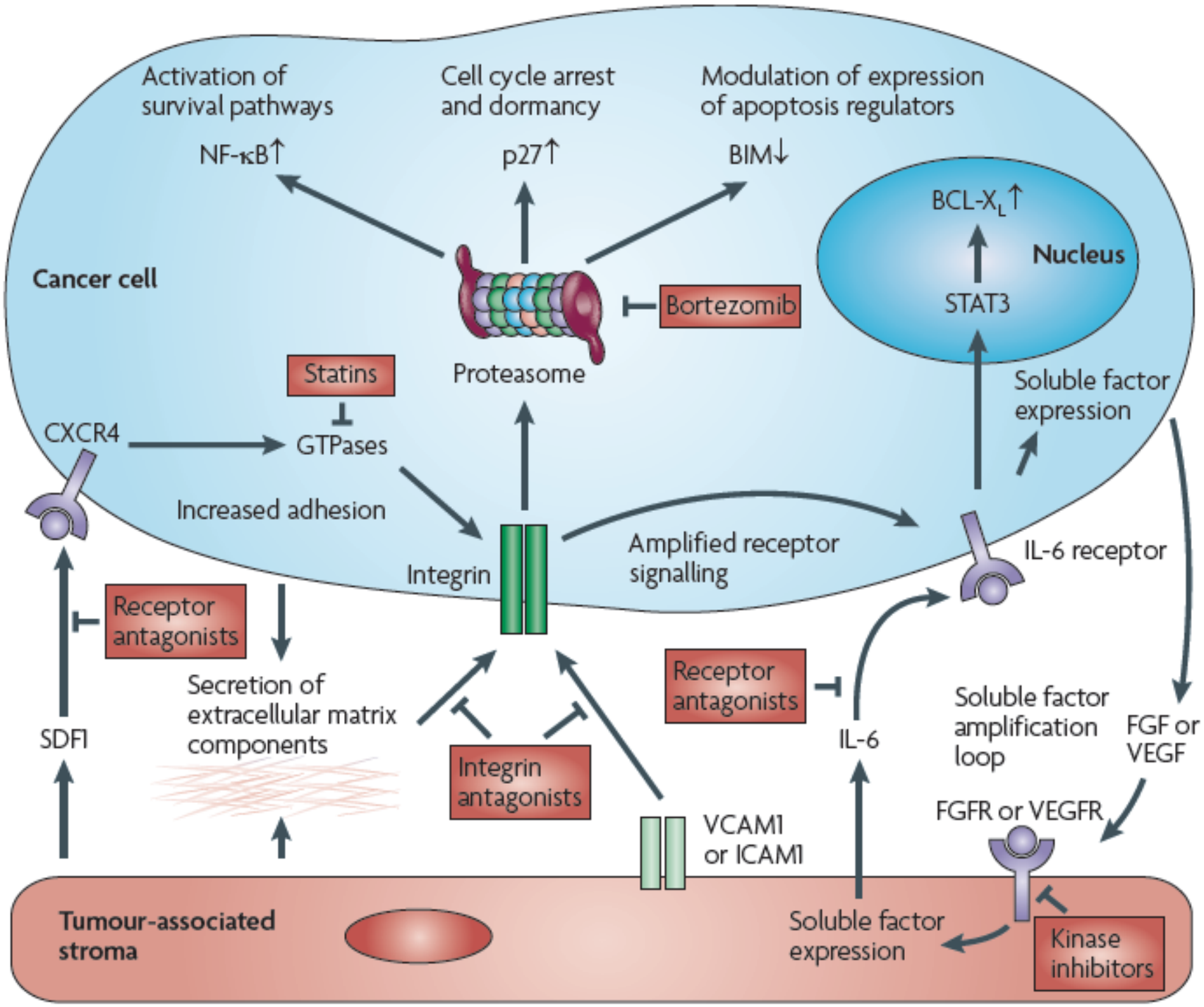


100µm

Stroma (HS-5/GFP)

- Bone marrow stromal cells, fibroblasts

Tumor-stroma communication is the basis of environmental-mediated drug resistance

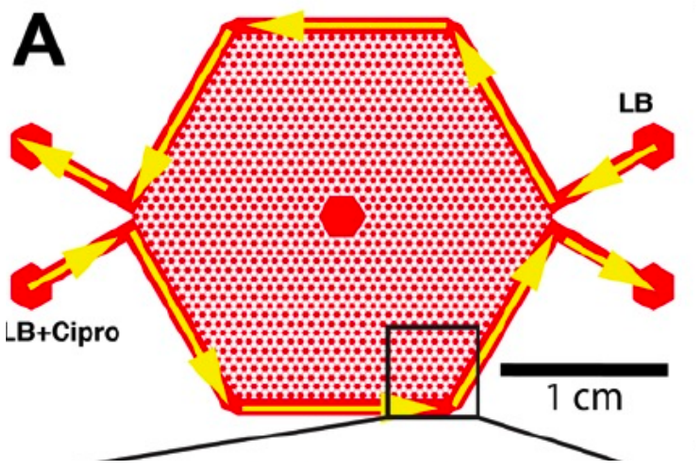


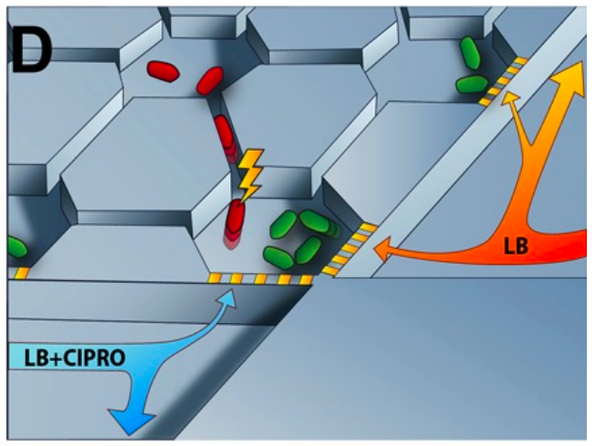
Meads et al, Nat Rev Cancer 2009

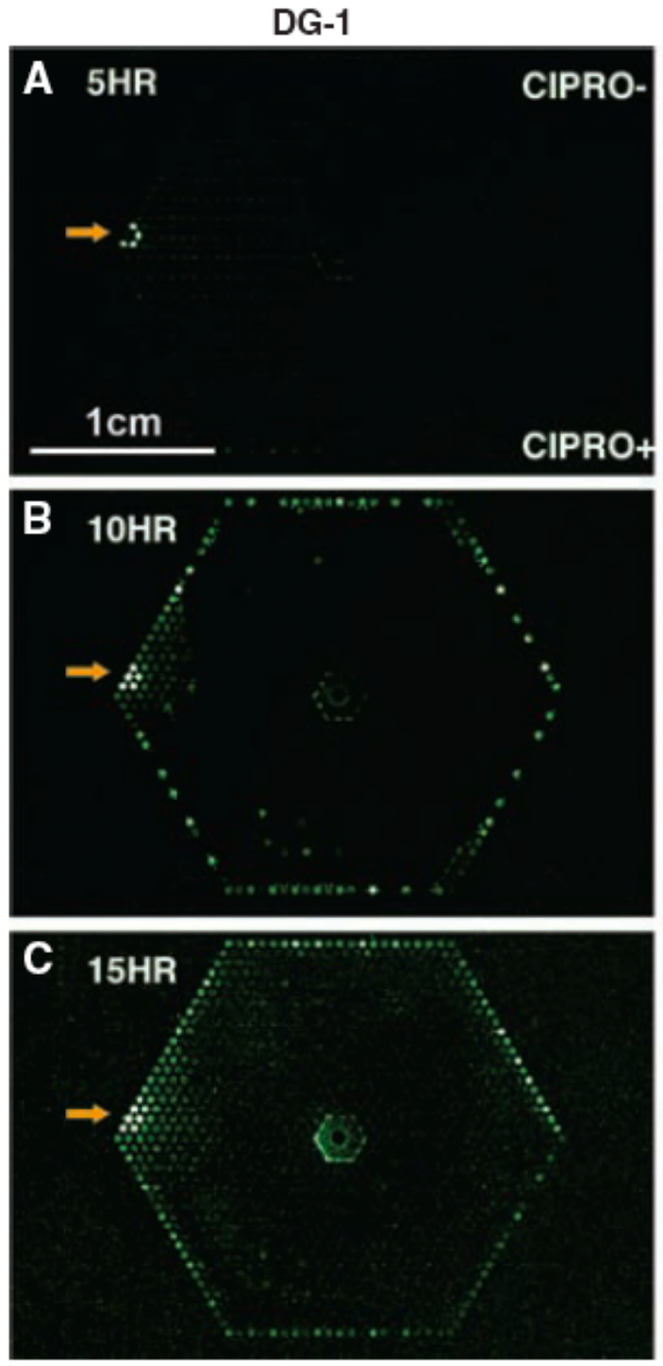
The Death Galaxy for E coli

Acceleration of Emergence of Bacterial Antibiotic Resistance in Connected Microenvironments

Qiucen Zhang,[1] Guillaume Lambert,[1] David Liao,[2] Hyunsung Kim,[3] Kristelle Robin,[4] Chih-kuan Tung,[5] Nader Pourmand,[3] Robert H. Austin[1,4]*

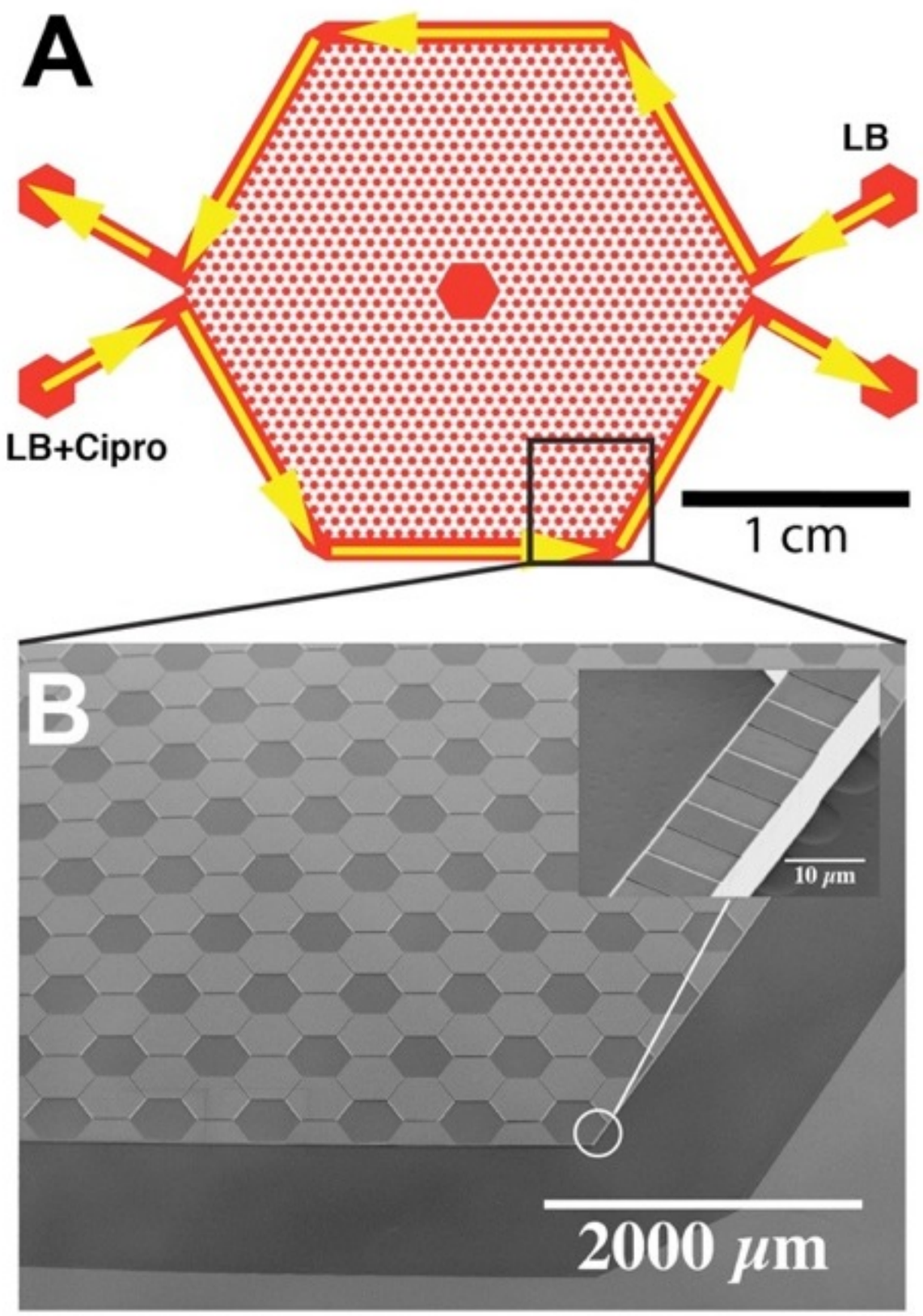


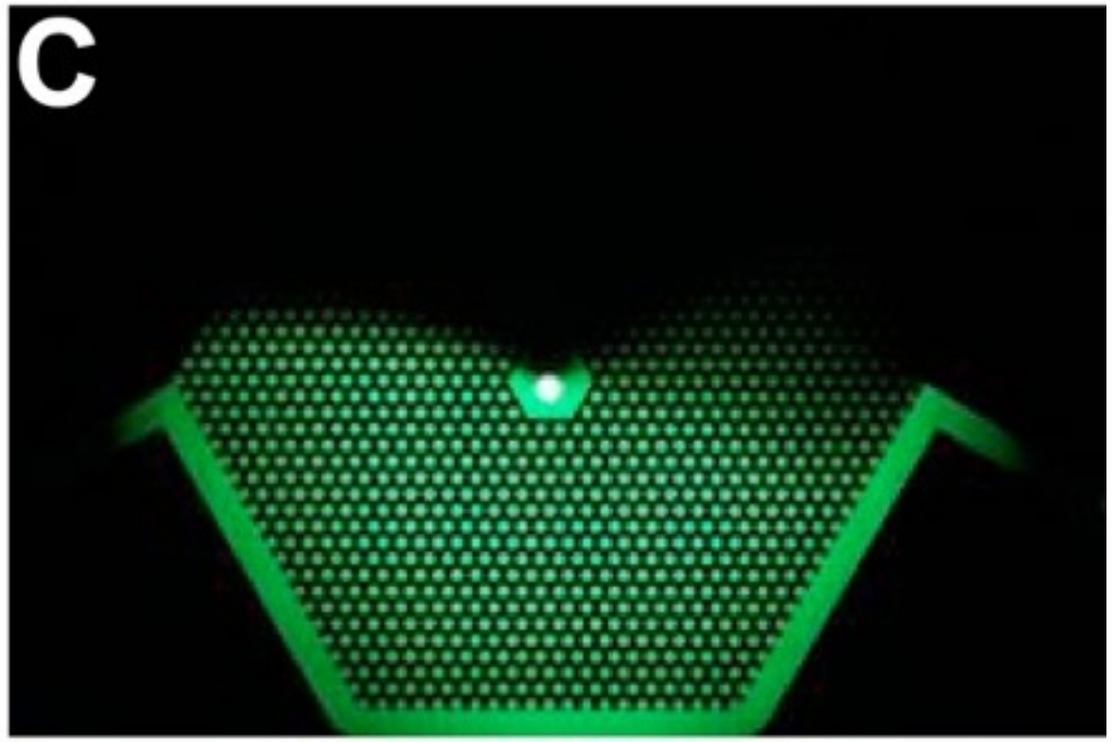


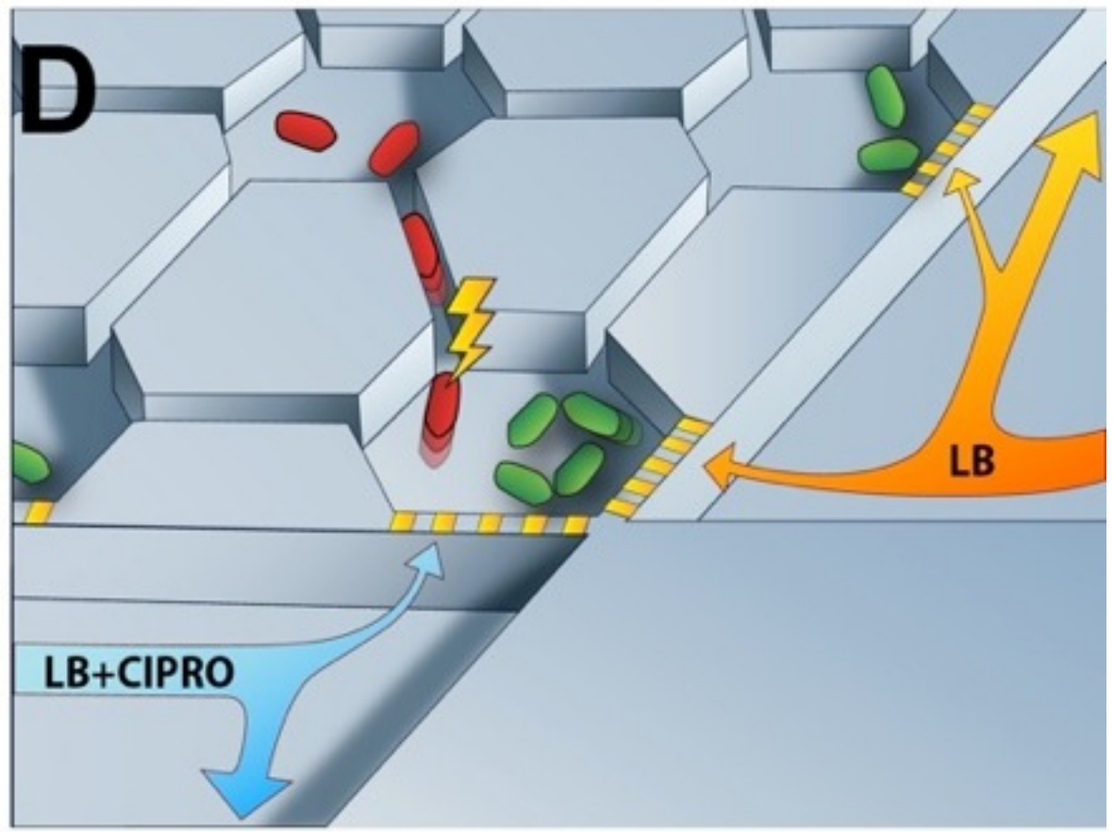


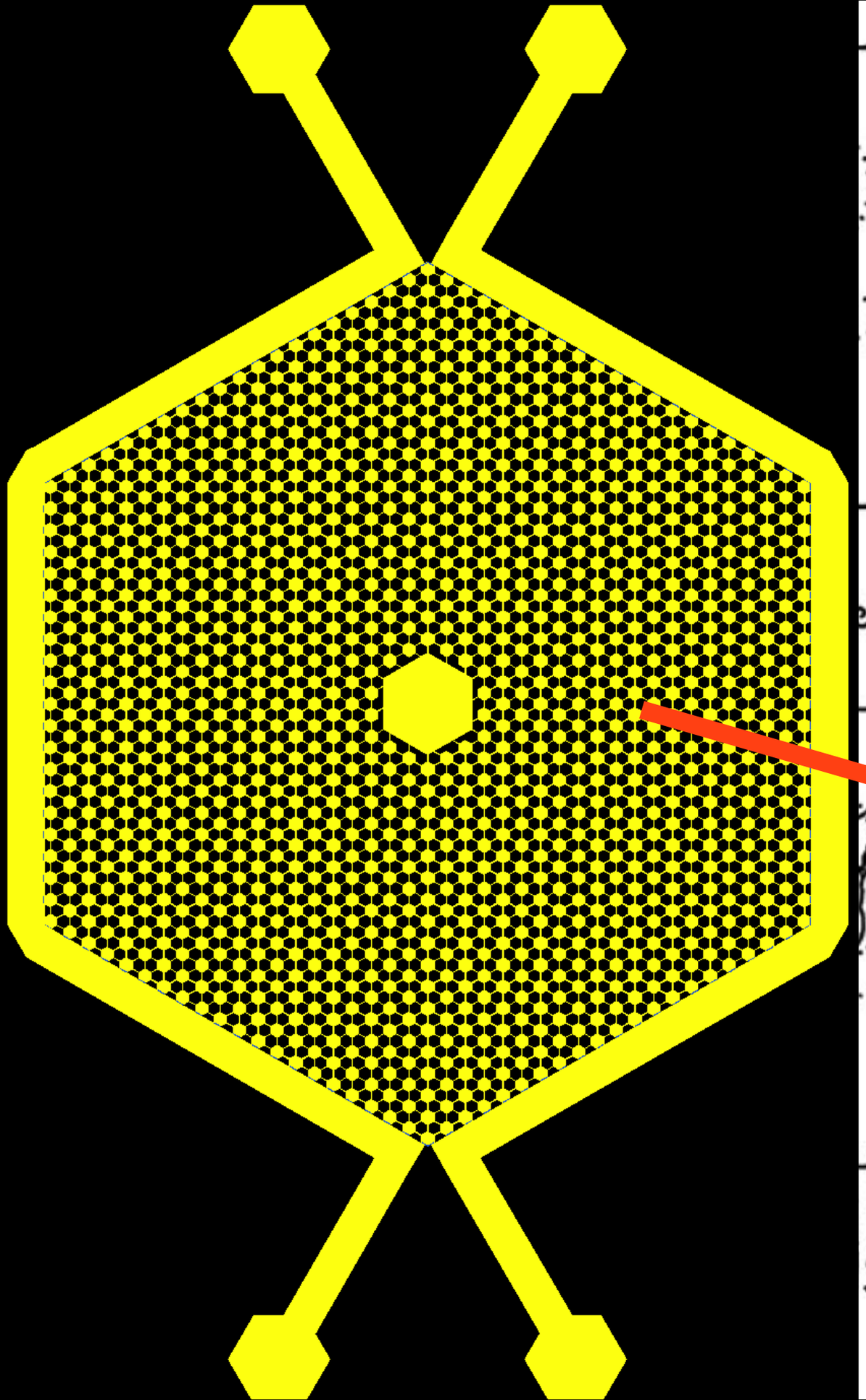
Q Zhang et al, Science 2012

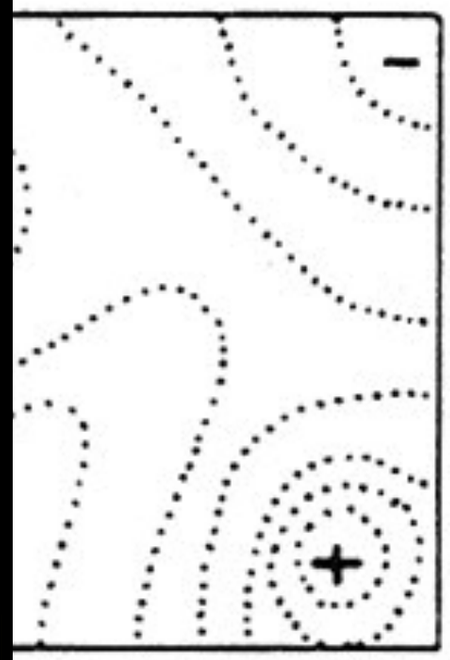
Evolution for the 21st Century



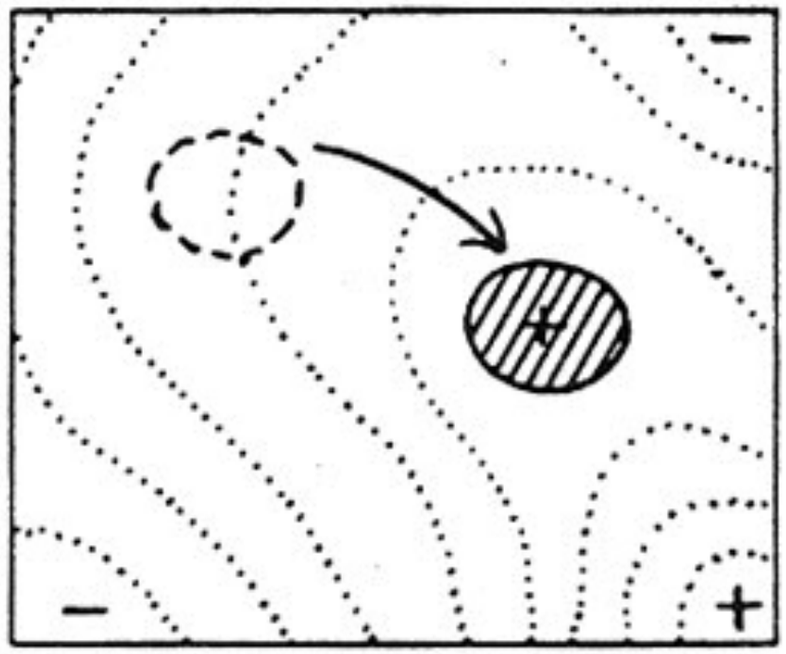




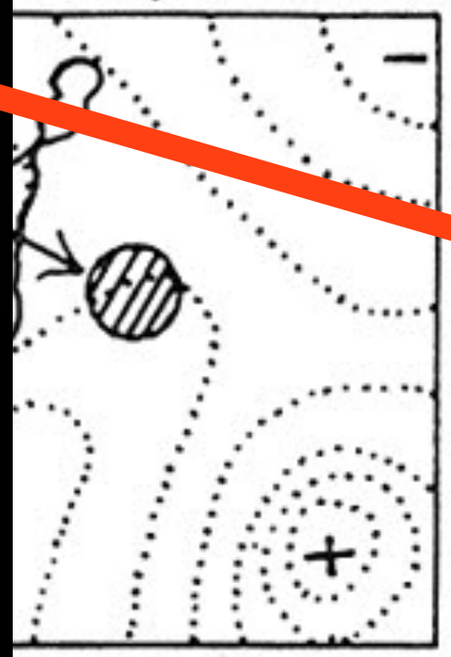




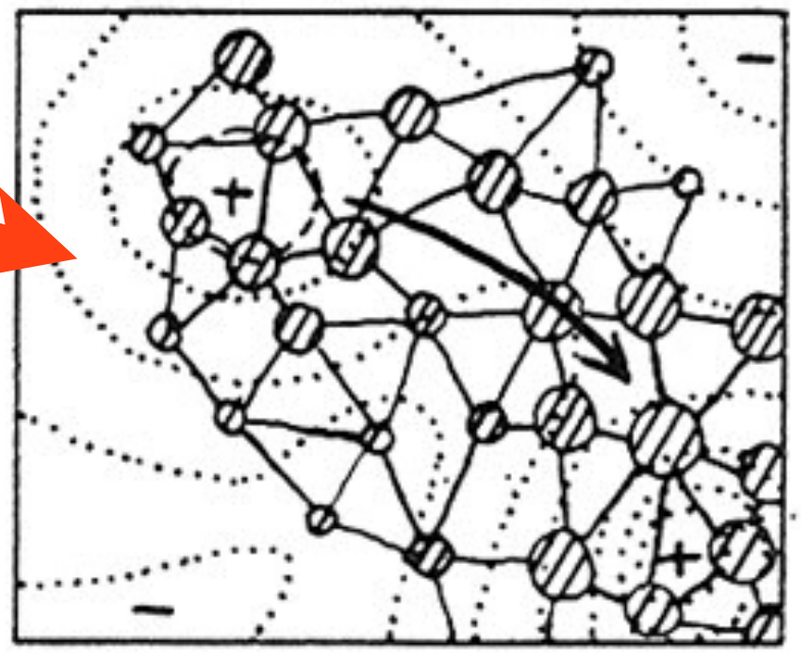
Selection
ed Mutation
very large



Qualitative Change
of Environment
4NU, 4NS very large

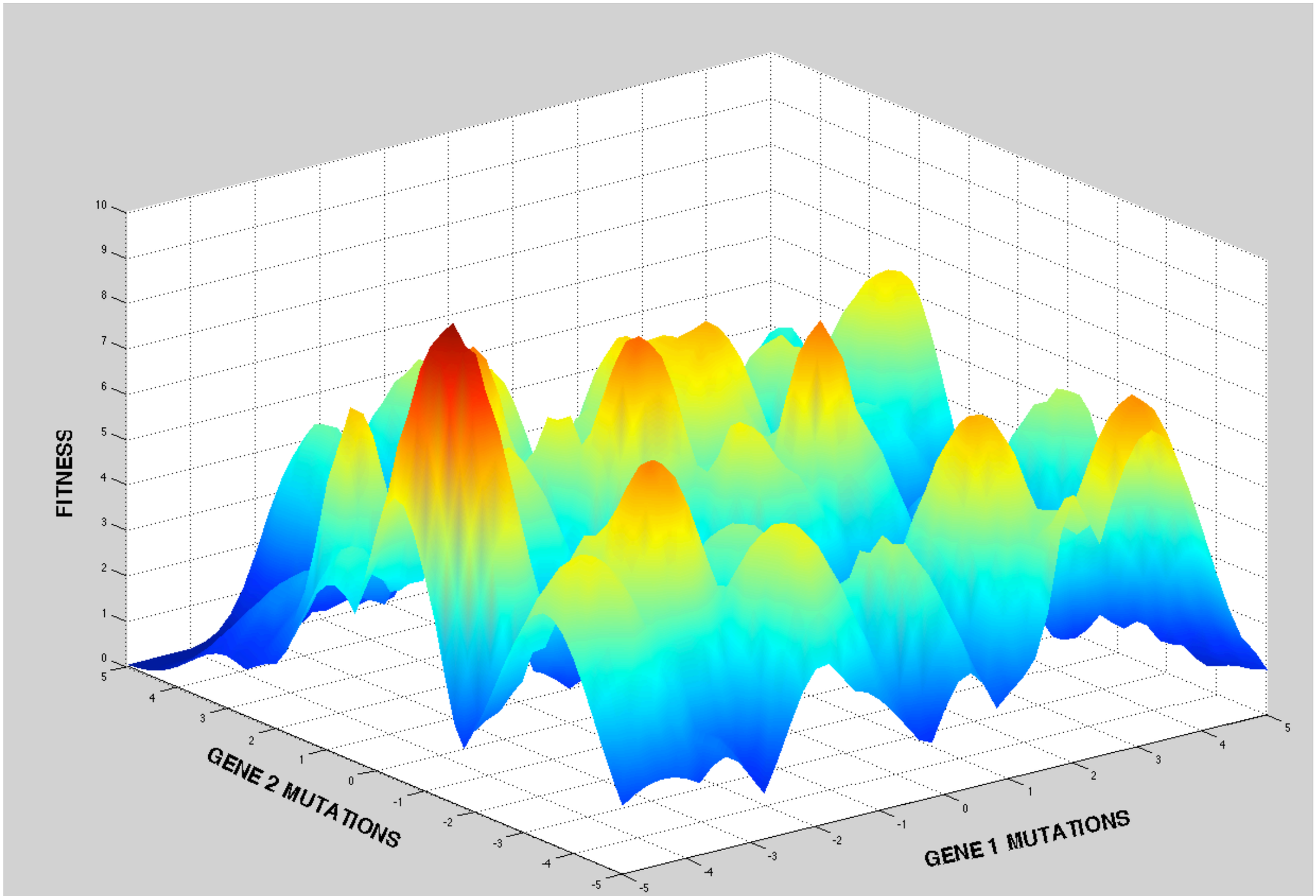


nbreeding
S medium

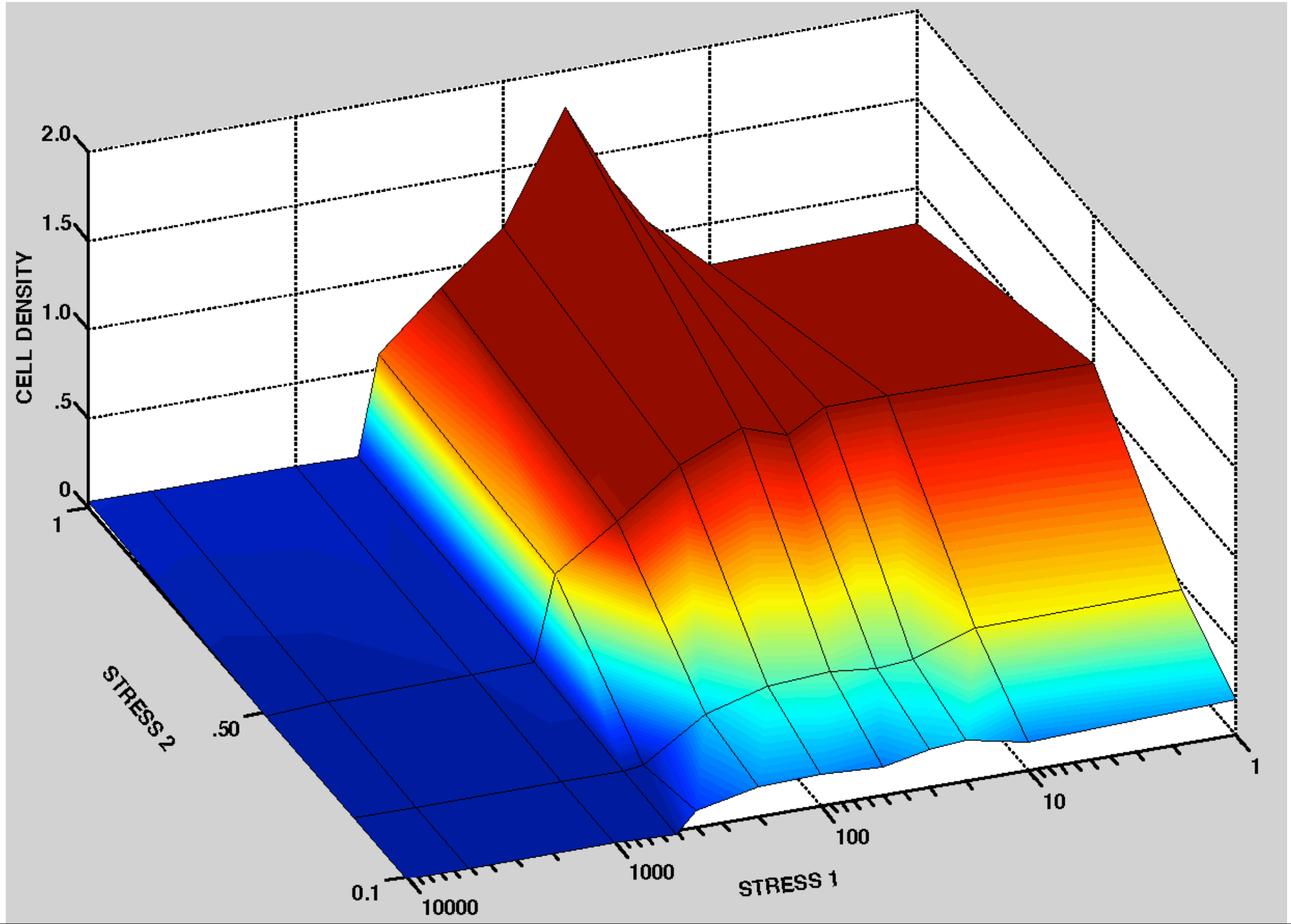


Division into local Races
4nm medium

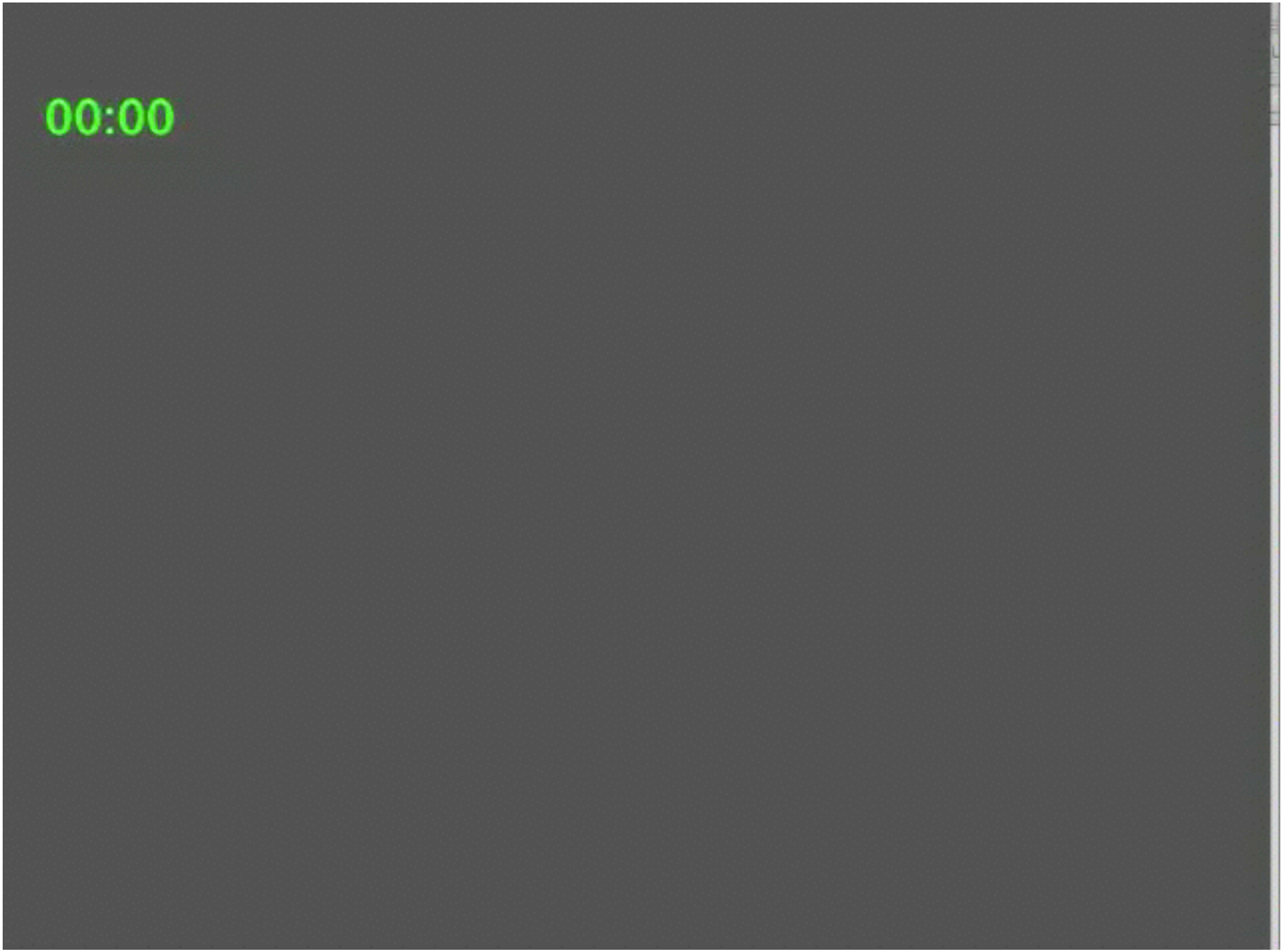
Genomic Fitness Landscape (fixed ecology)



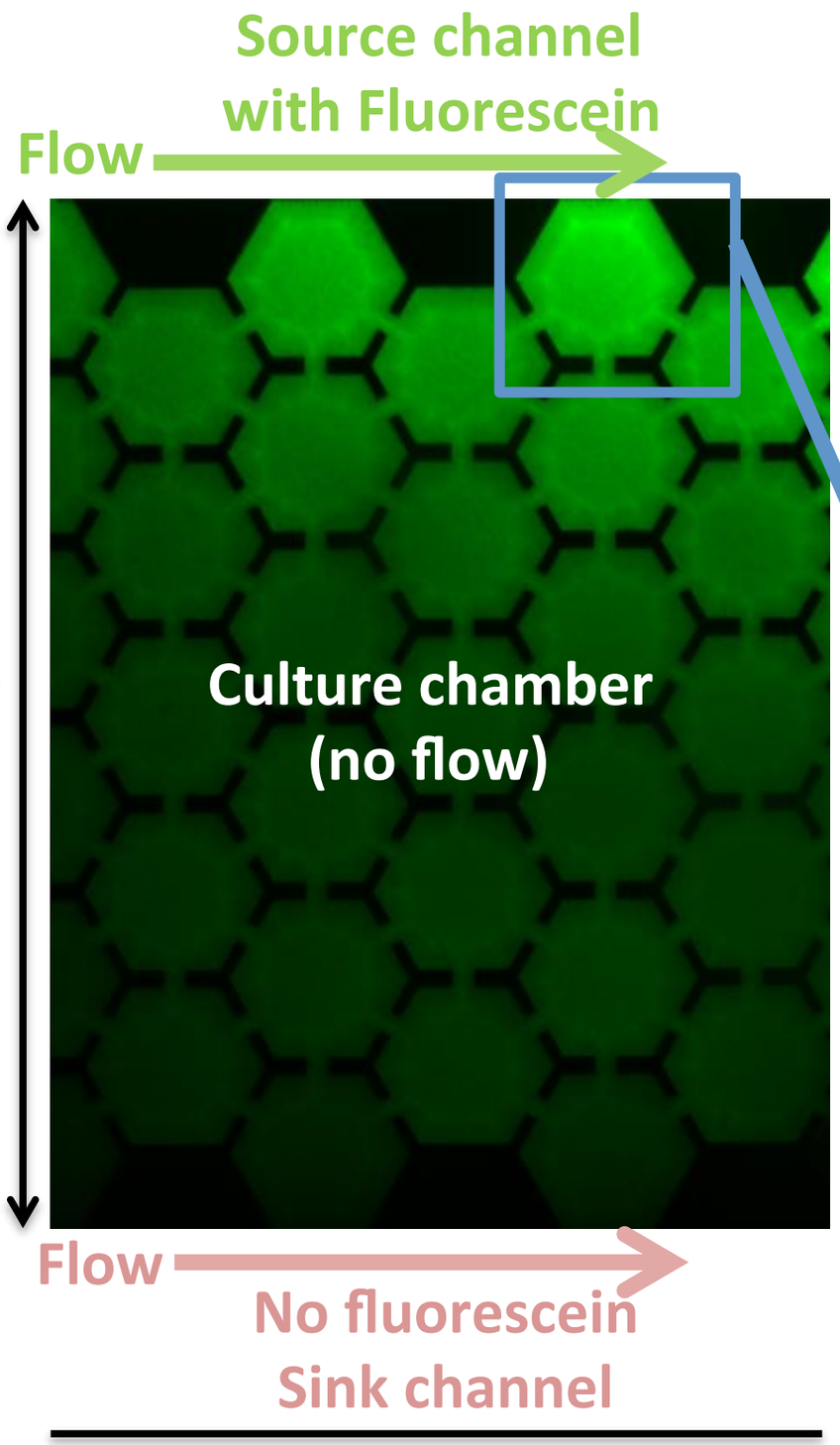
Ecological Fitness Landscape (fixed genome)

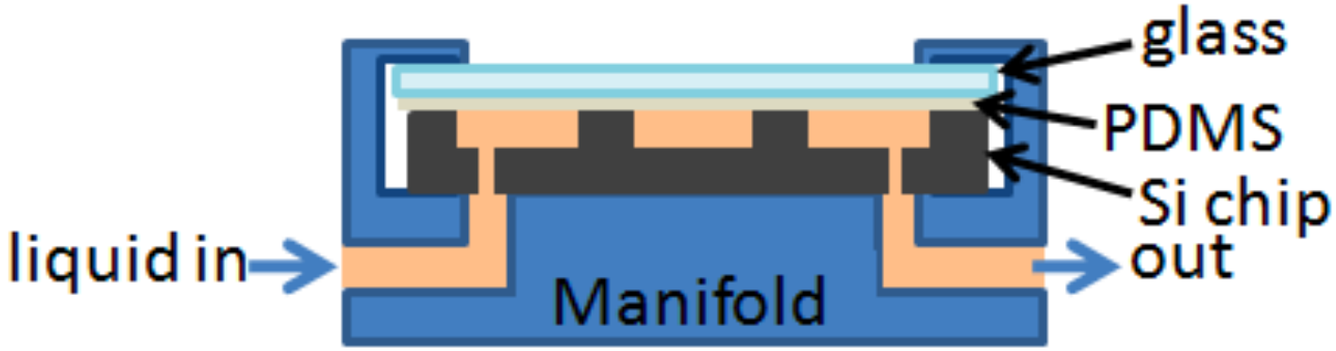


100 E.coli inoculation: de-novo evolution.

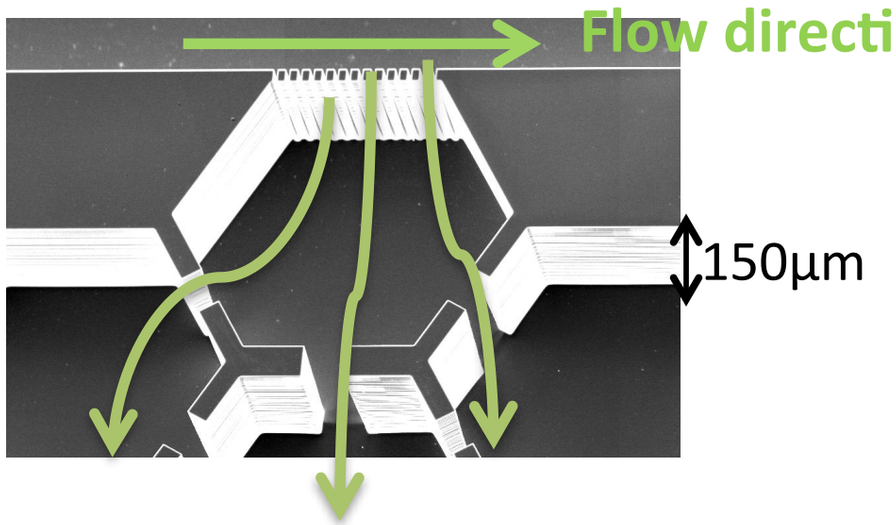


The Death Galaxy for Cancer Cells

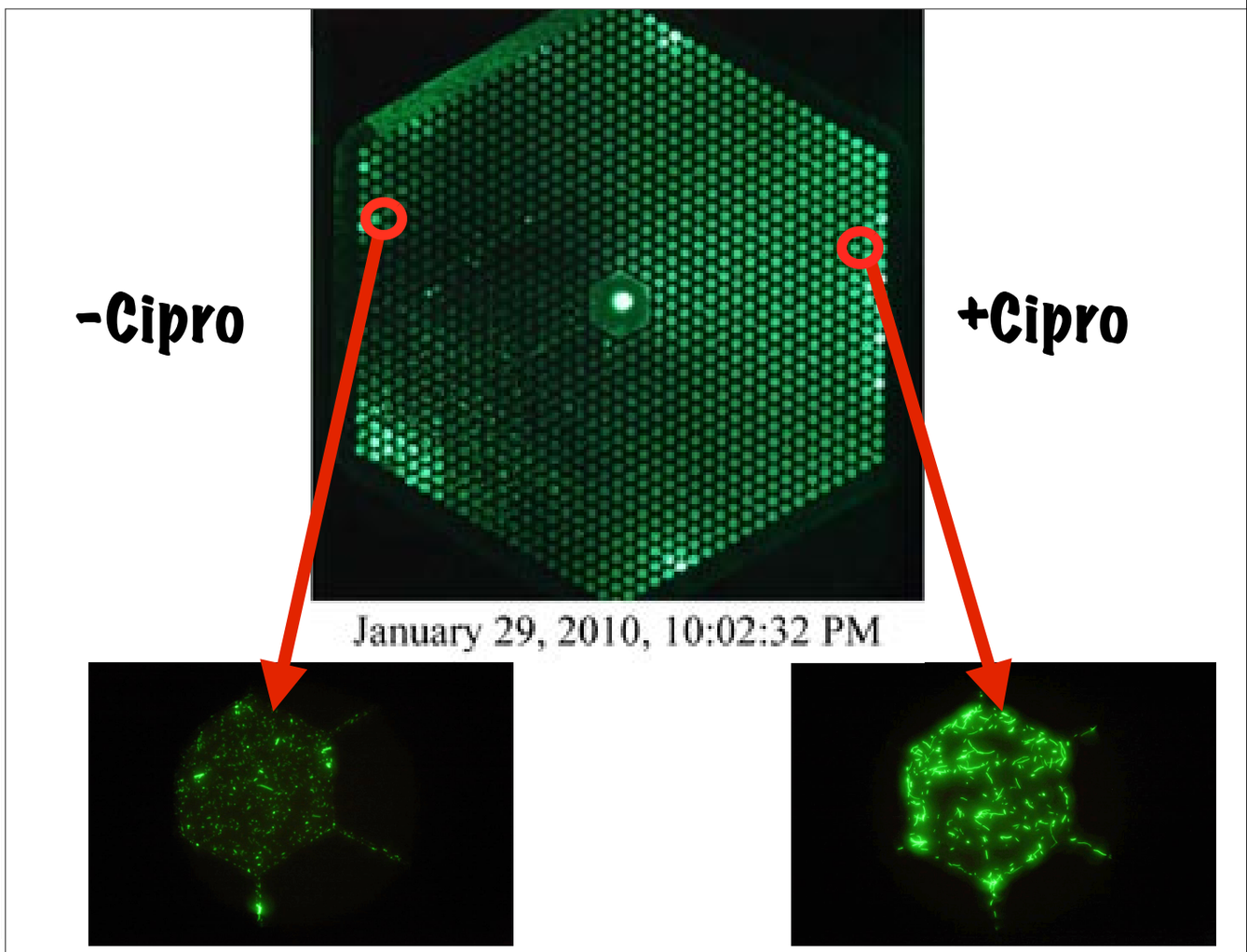




Microposts allow diffusion of biomolecules



- Reconstruct tumor microenvironment
  - Stable drug gradient
  - Connected microhabitats
  - Extracellular matrix (matrigel)



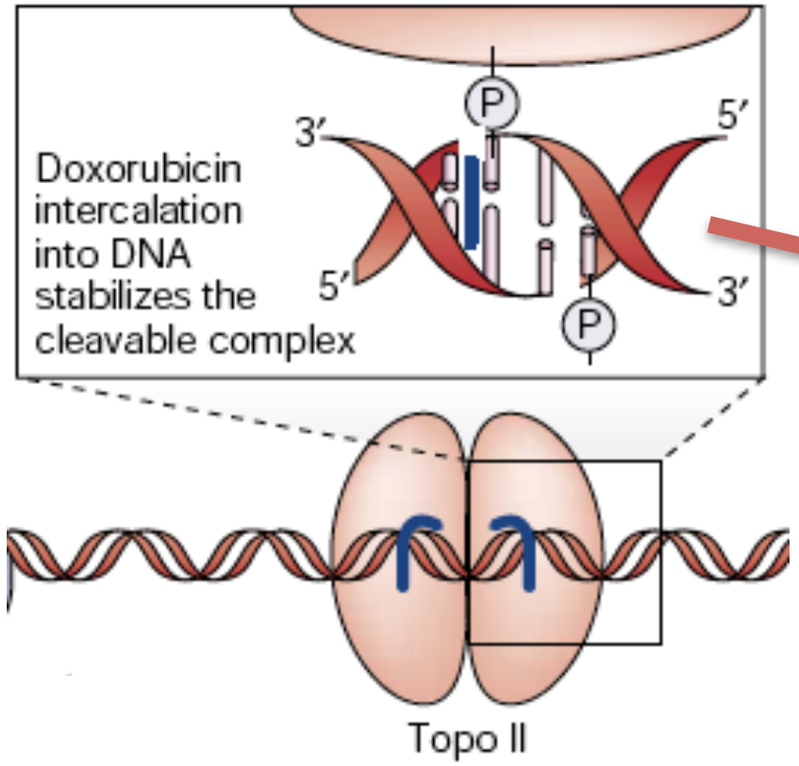
You can't recapitulate the evolution of cancer in a homogeneous environment.

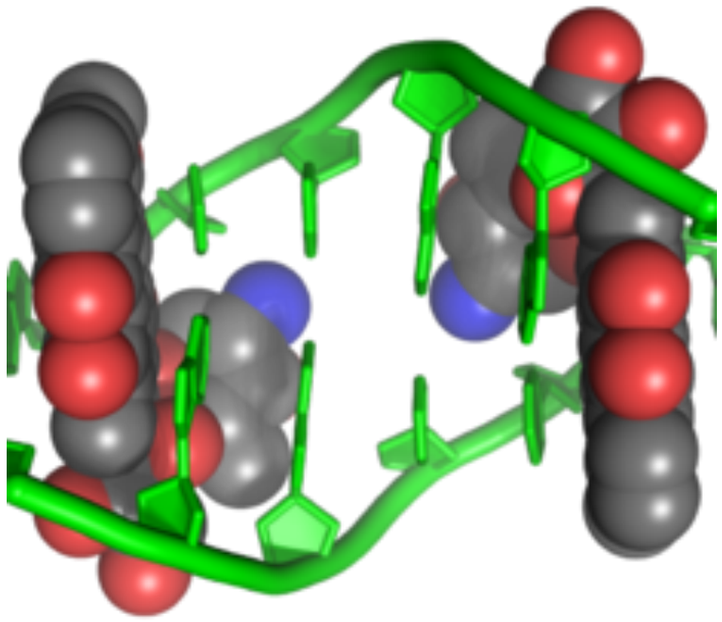
The Bottom Line:

If you want to understand how drug resistance evolves!

What is the stress we applied?

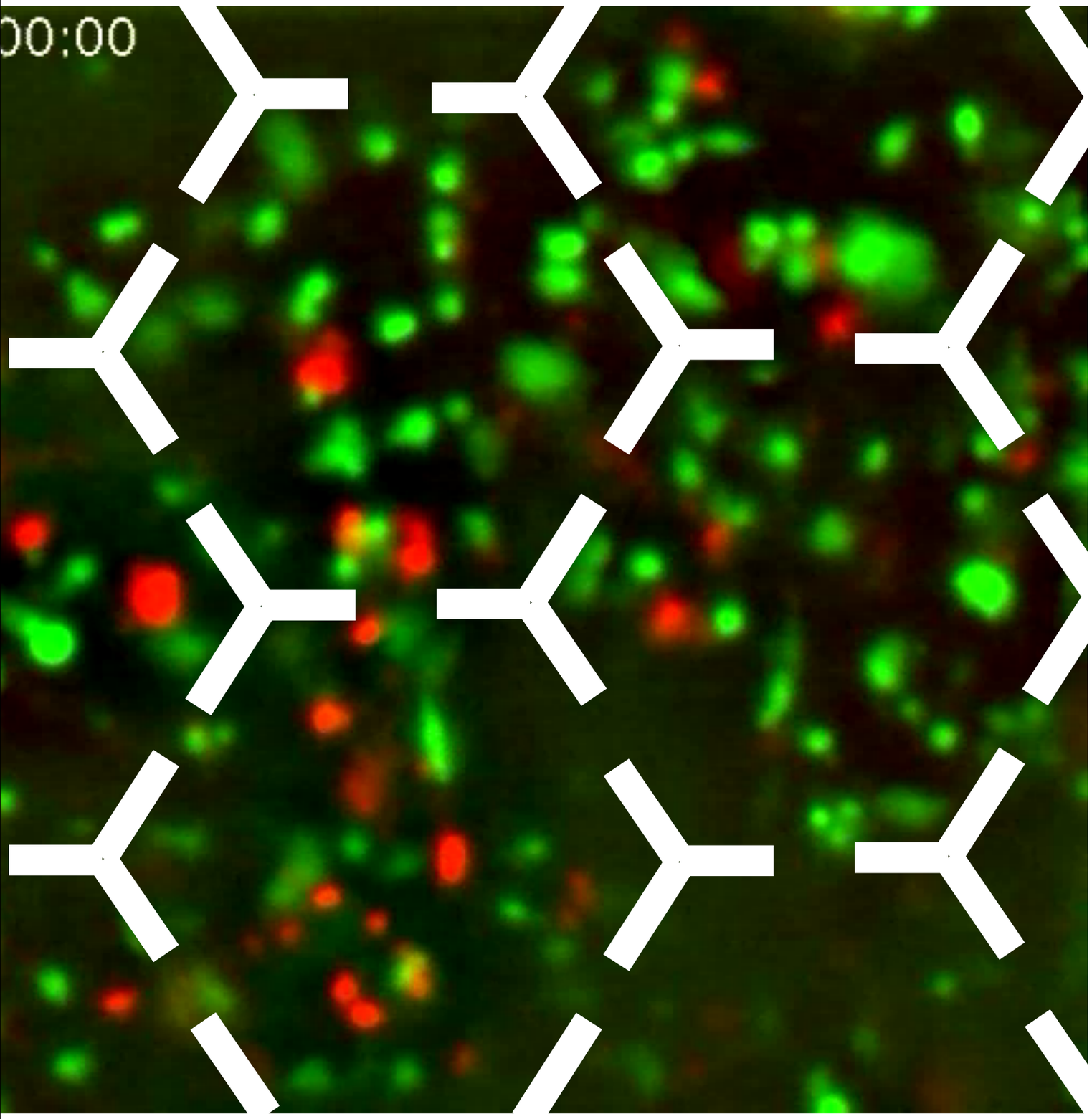
- Doxorubicin
  - Chemotherapeutic drug
  - Genotoxic, blocks DNA replication
  - 20 nM Kills 100% myeloma cells within 144 hours





Protein Data Bank

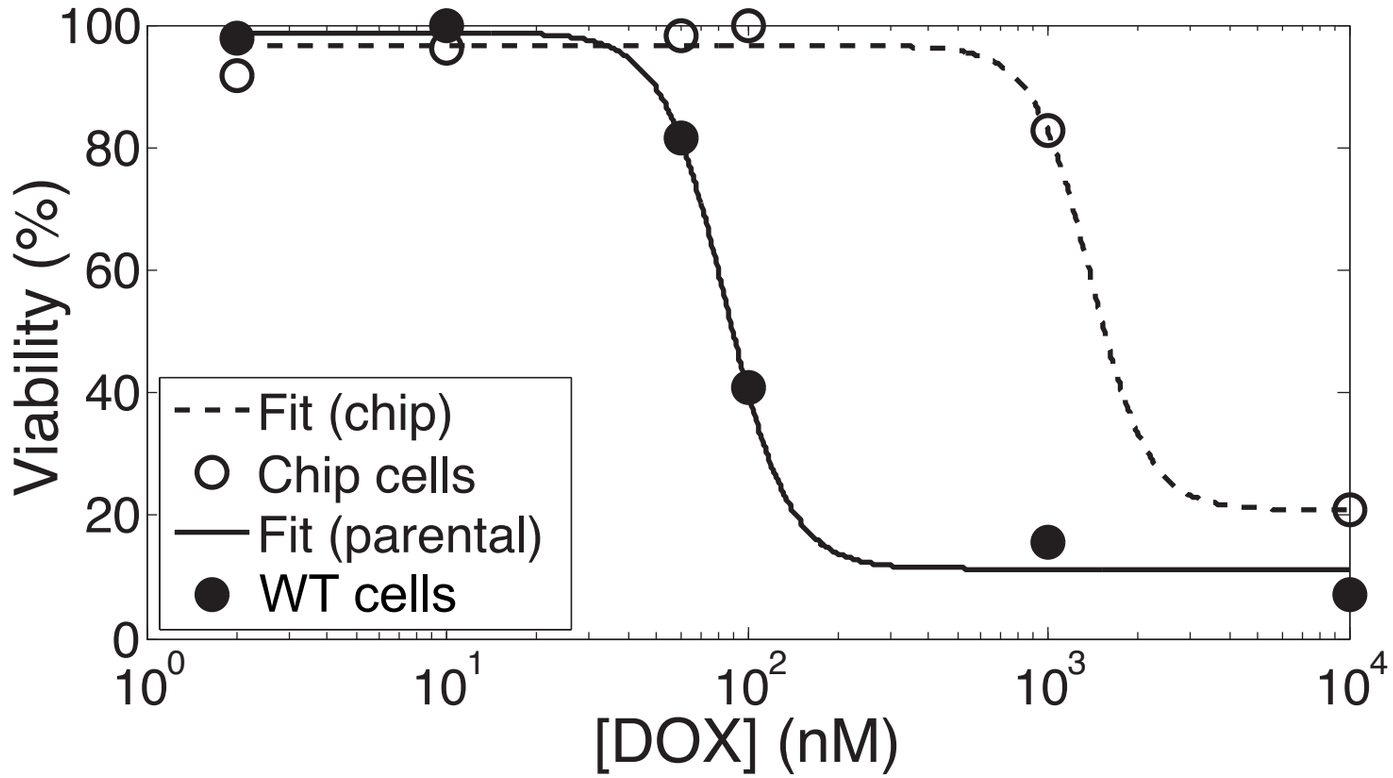
Hurley, Nat Rev Cancer 2002



Red: myeloma (8226/RFP)
Green: stroma (HS-5/GFP)

How resistant the cells have become? How fast?

Take cells out of chip (Chip cells) after 288 hours and compare the dose response with that of the parental cells (WT cells)



- Degree of cross-resistance (48-hour exposure) $= \frac{IC_{50}(Chip)}{IC_{50}(WT)} = \frac{1390}{85} = 16.3$
- Using the traditional protocol, it takes several months in tissue culture flasks to develop resistant cell lines (Dalton et al, Cancer Research 1986)

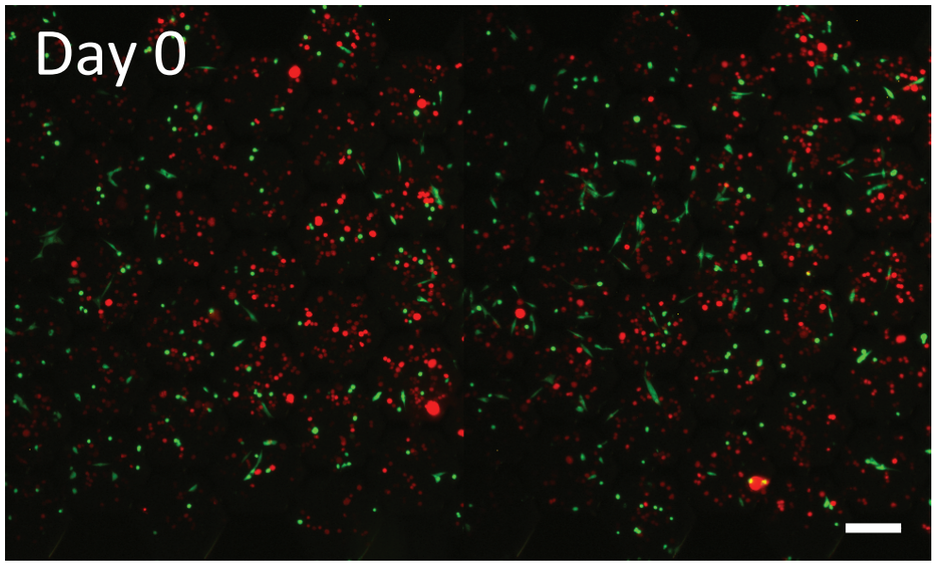
We are the PSOC that built a cancer time machine.

VI. Real Game Theory:

David Liao (former student)

2012: DOX gradient (0-200nM/2mm)

DOX 200nM

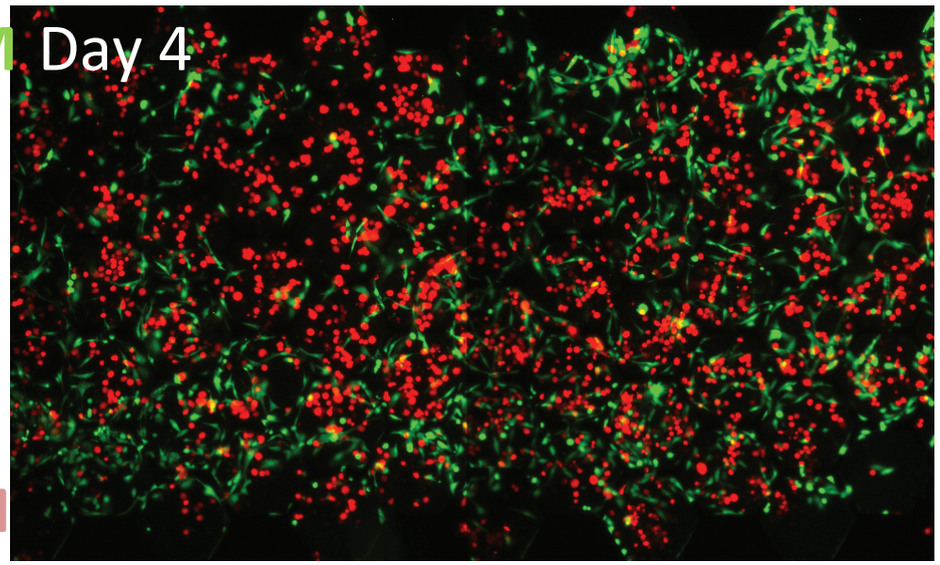


DOX 0nM

Myeloma
Stroma

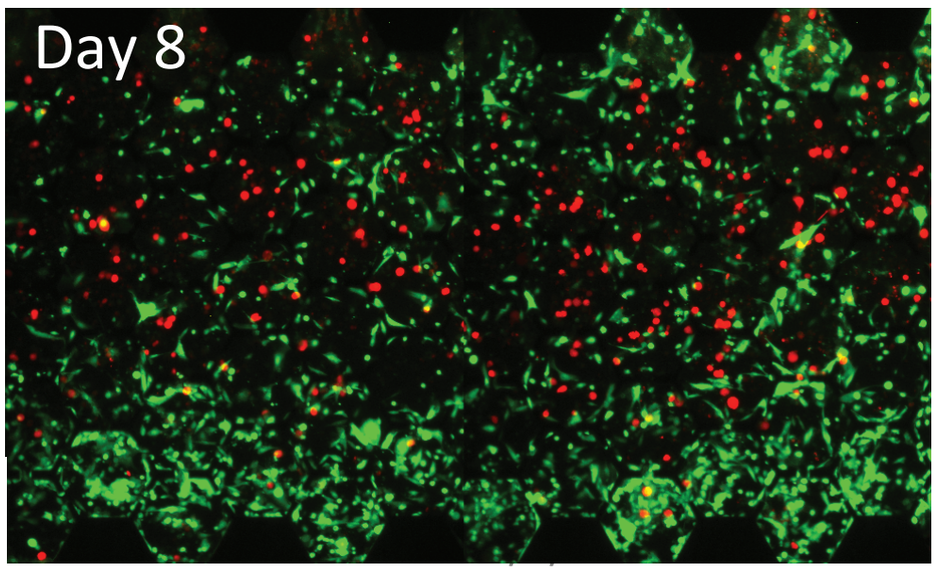
White line: 200µm

DOX 200nM



DOX 0nM

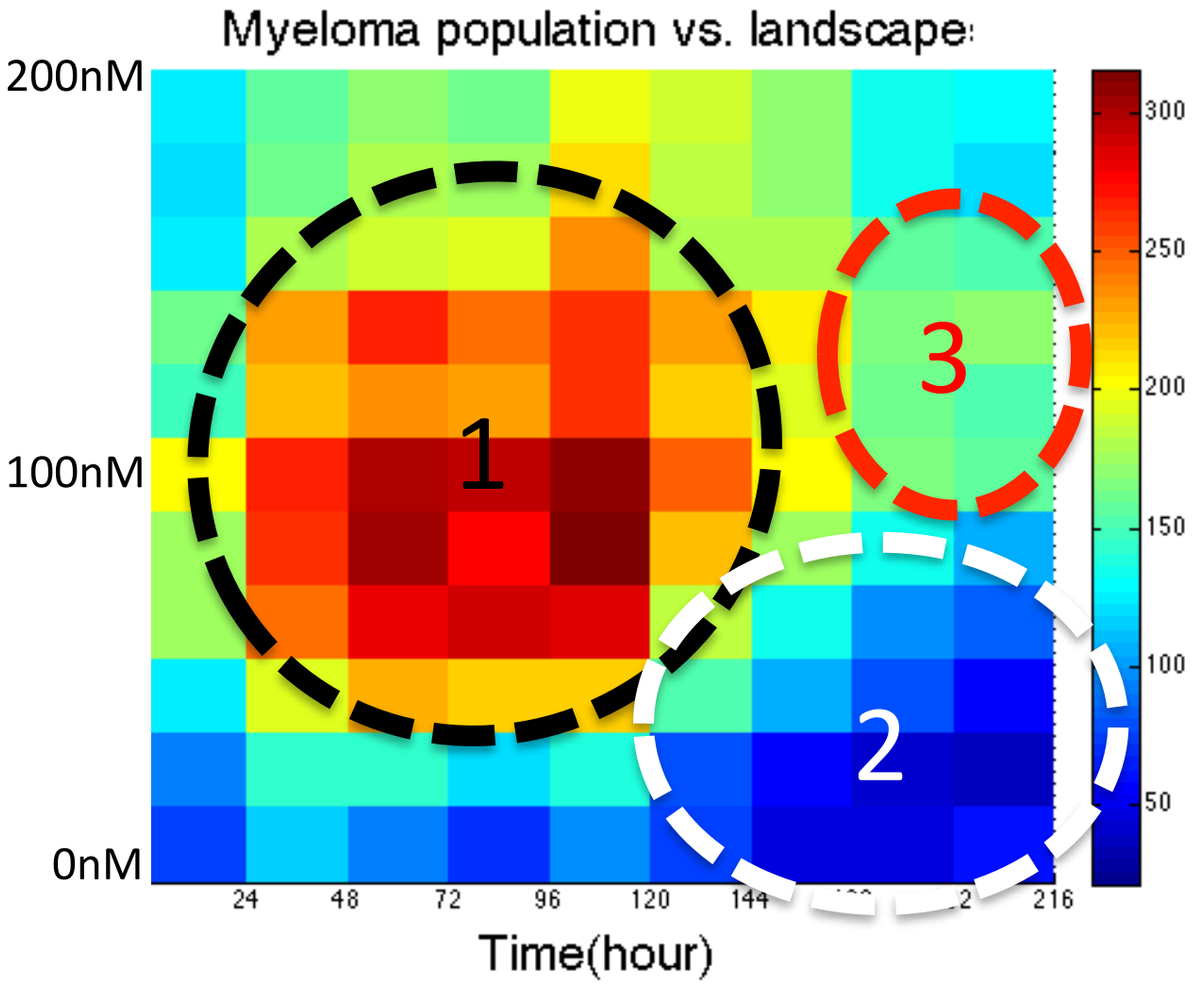
DOX 200nM

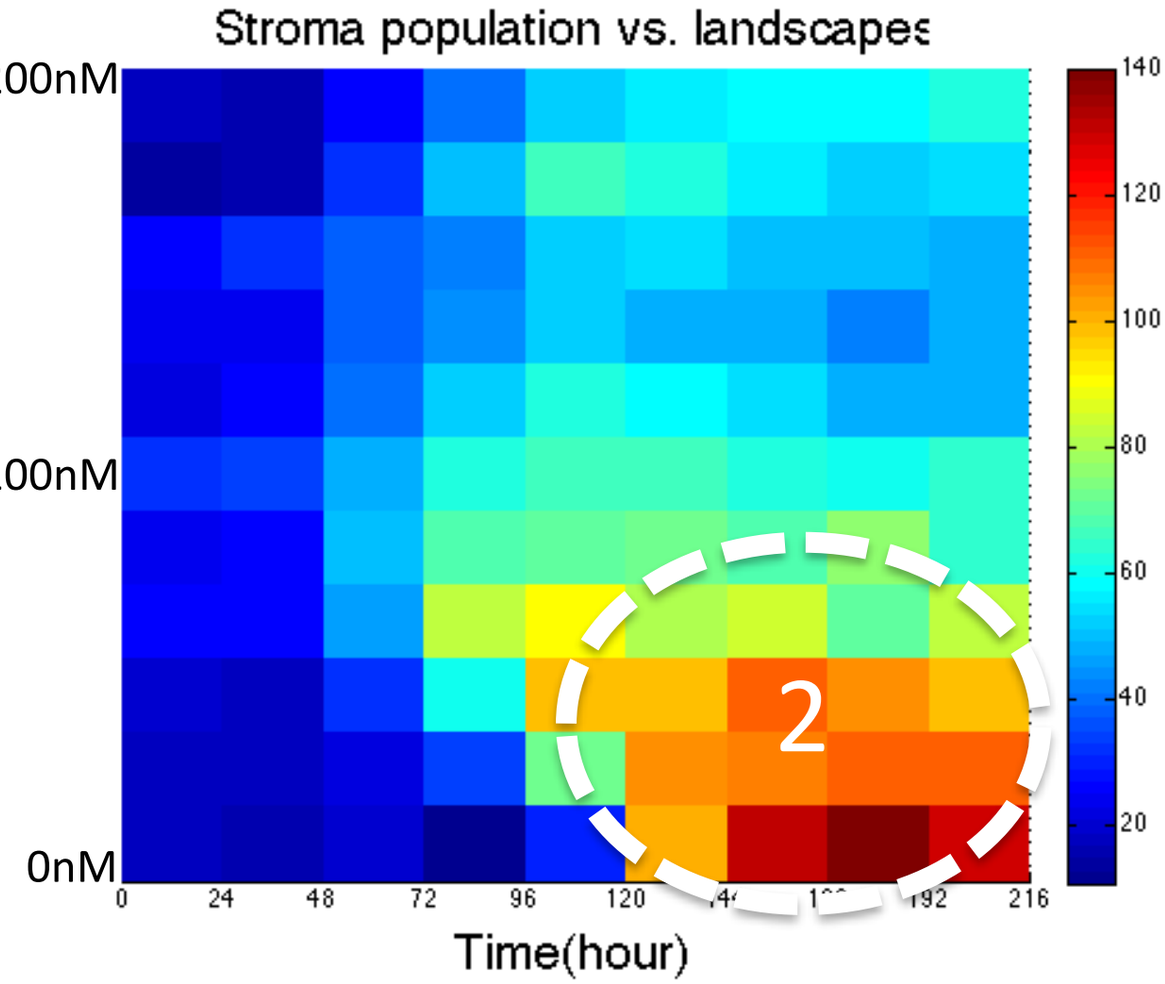


DOX 0nM

Lots of myeloma can bare >100nM drug for > 1 week

DOX gradient (0-200nM/2mm)





1) Myeloma first grew
->stroma "pain-killer" transient effect
Stroma adhesion inhibits apoptosis signals in myeloma
Ref: Hazlehurst et al, Oncogene 2003

2) Stroma crowds out the myeloma

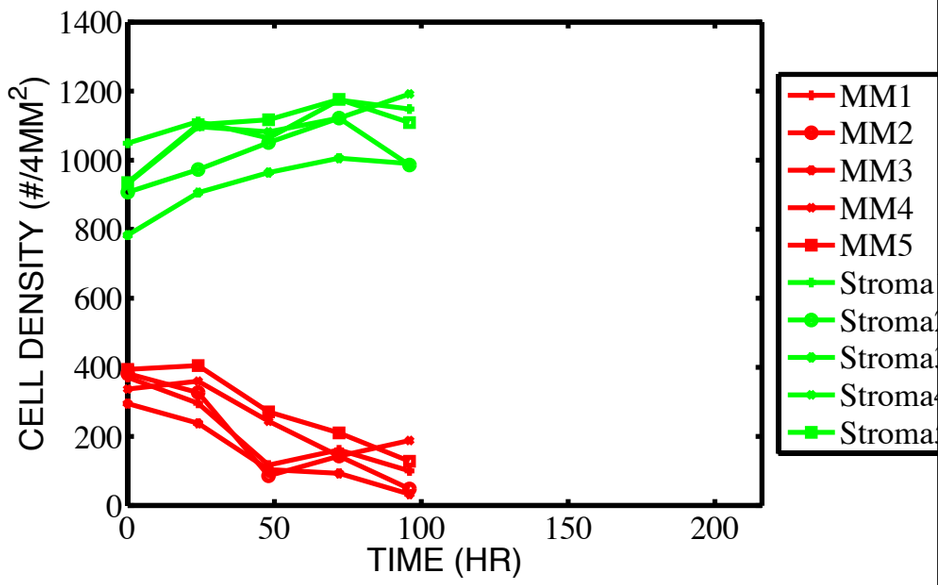
3) Myeloma is more resistant than the case without stroma

2013: quantitative analysis

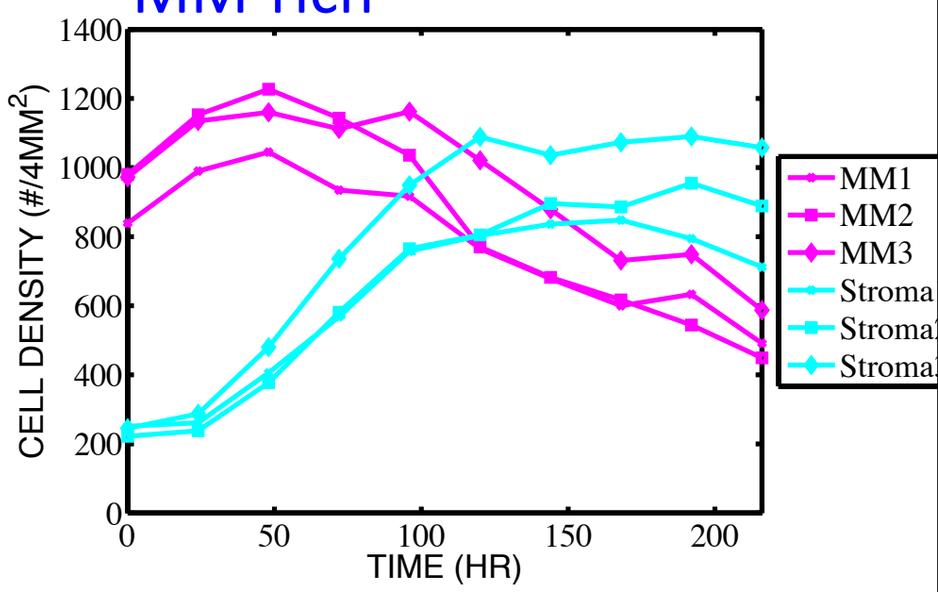
- How to model the complex dynamics?
- First, we start with temporal dynamics (total population of each cell types in the gradient chip vs. time)

DOX gradient (0-200nM/2mm)

Stroma-rich



MM-rich



$$\frac{dMM}{dt} = (Ap_{MM} + Bp_{ST})MM$$

$$\frac{dST}{dt} = (Cp_{MM} + Dp_{ST})ST$$

where $p_{MM} = \frac{MM}{MM + ST}, p_{ST} = \frac{ST}{MM + ST}$

If ST>>MM, p_{MM}~0 Stroma-rich

$$\frac{dMM}{dt} \approx (Bp_{ST})MM \Rightarrow \frac{1}{p_{ST}MM}\frac{dMM}{dt} \approx B \Rightarrow \frac{1}{p_{ST}}\frac{\Delta}{\Delta t}(\ln MM) \approx B$$

$$\frac{dST}{dt} \approx (Dp_{ST})ST \Rightarrow \frac{1}{p_{ST}ST}\frac{dST}{dt} \approx D \Rightarrow \frac{1}{p_{ST}}\frac{\Delta}{\Delta t}(\ln ST) \approx D$$

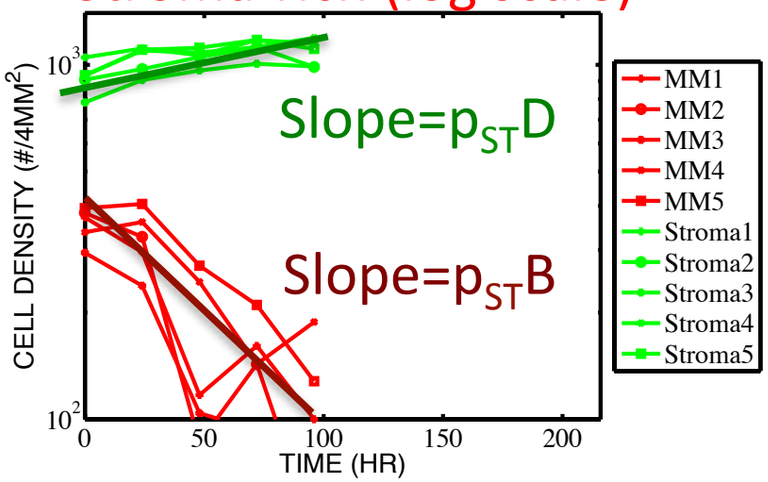
If MM>>ST, p_{ST}~0 MM-rich

$$\frac{dMM}{dt} \approx (Ap_{MM})MM \Rightarrow \frac{1}{p_{MM}MM}\frac{dMM}{dt} \approx A \Rightarrow \frac{1}{p_{MM}}\frac{\Delta}{\Delta t}(\ln MM) \approx A$$

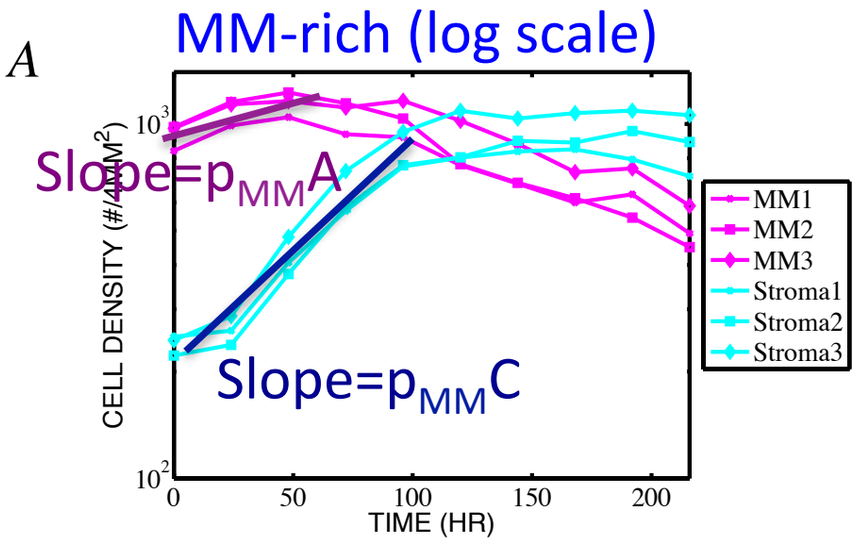
$$\frac{dST}{dt} \approx (Cp_{MM})ST \Rightarrow \frac{1}{p_{MM}ST}\frac{dST}{dt} \approx C \Rightarrow \frac{1}{p_{MM}}\frac{\Delta}{\Delta t}(\ln ST) \approx C$$

- A=0.0032; B=-0.0089;C=0.01; D=0.0022 (unit: hour^{-1})
- Then draw the quivers and phase portrait.

Stroma-rich (log scale)

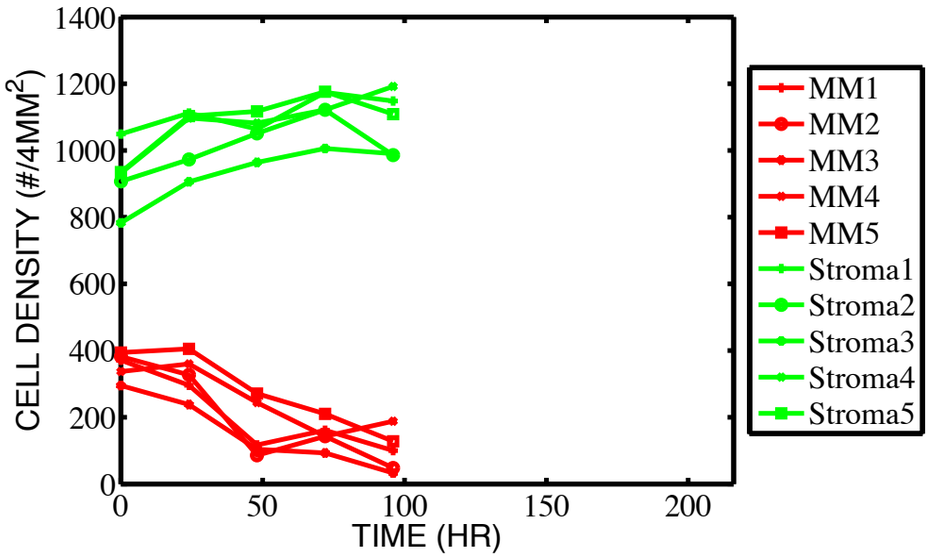


MM-rich (log scale)

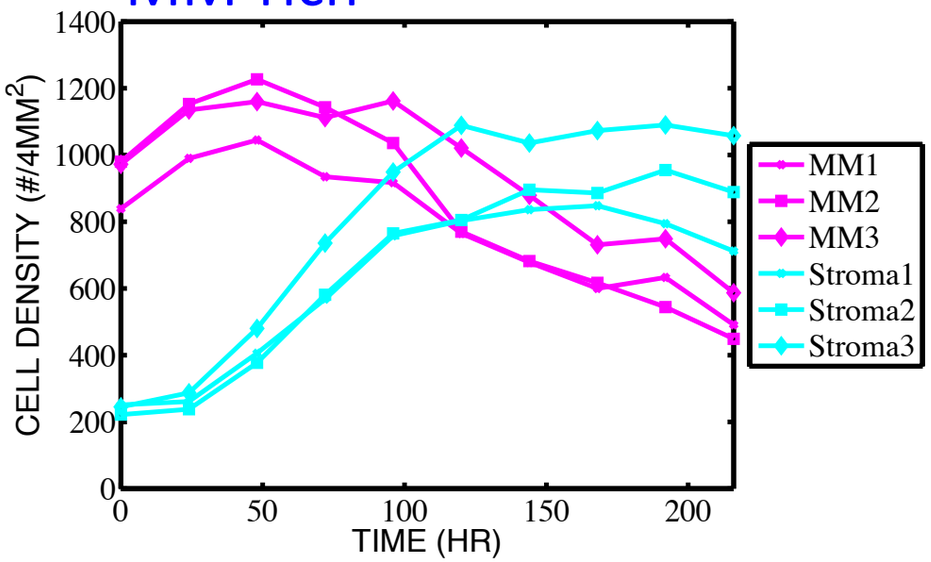


DOX gradient (0-200nM/2mm)

Stroma-rich

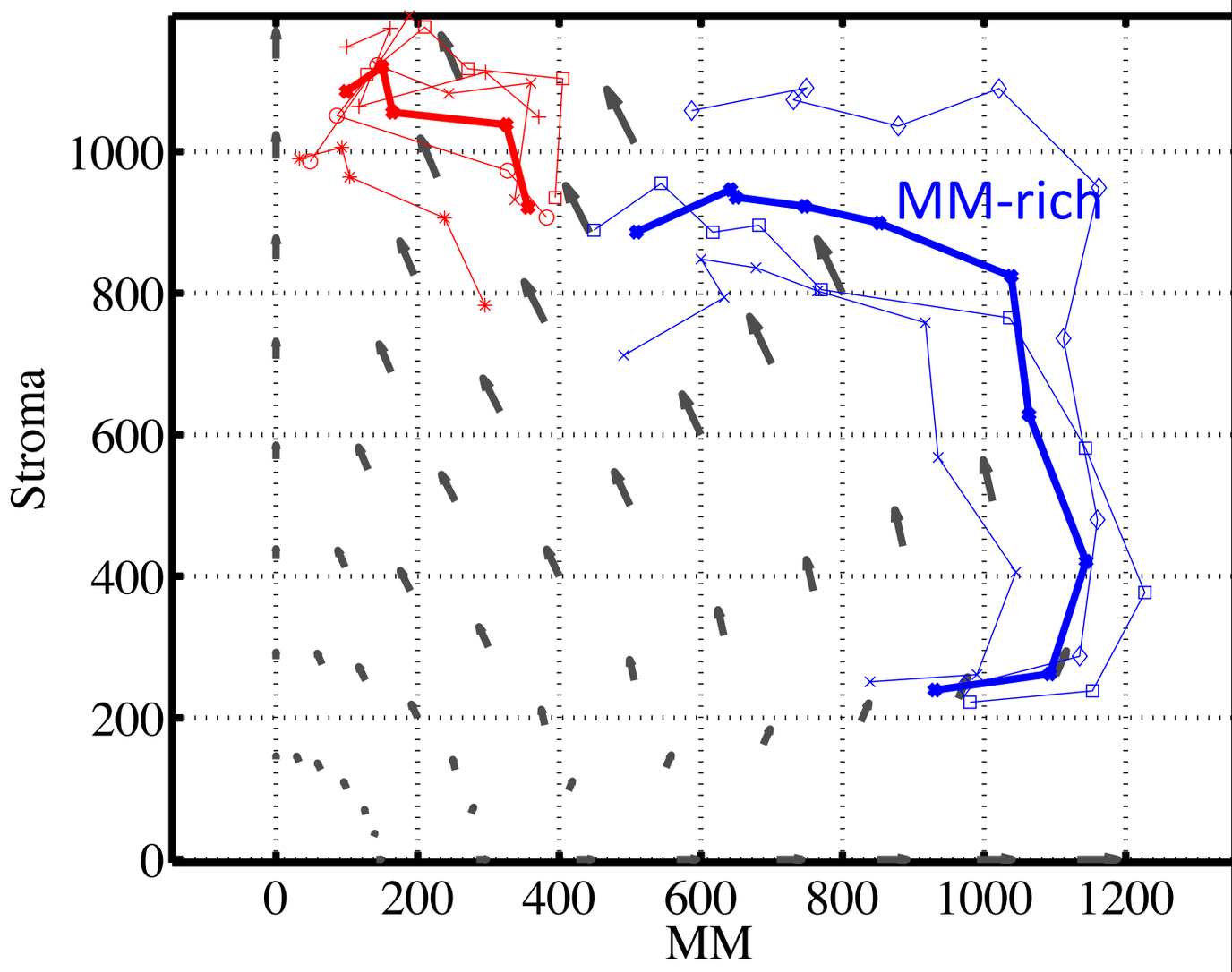


MM-rich

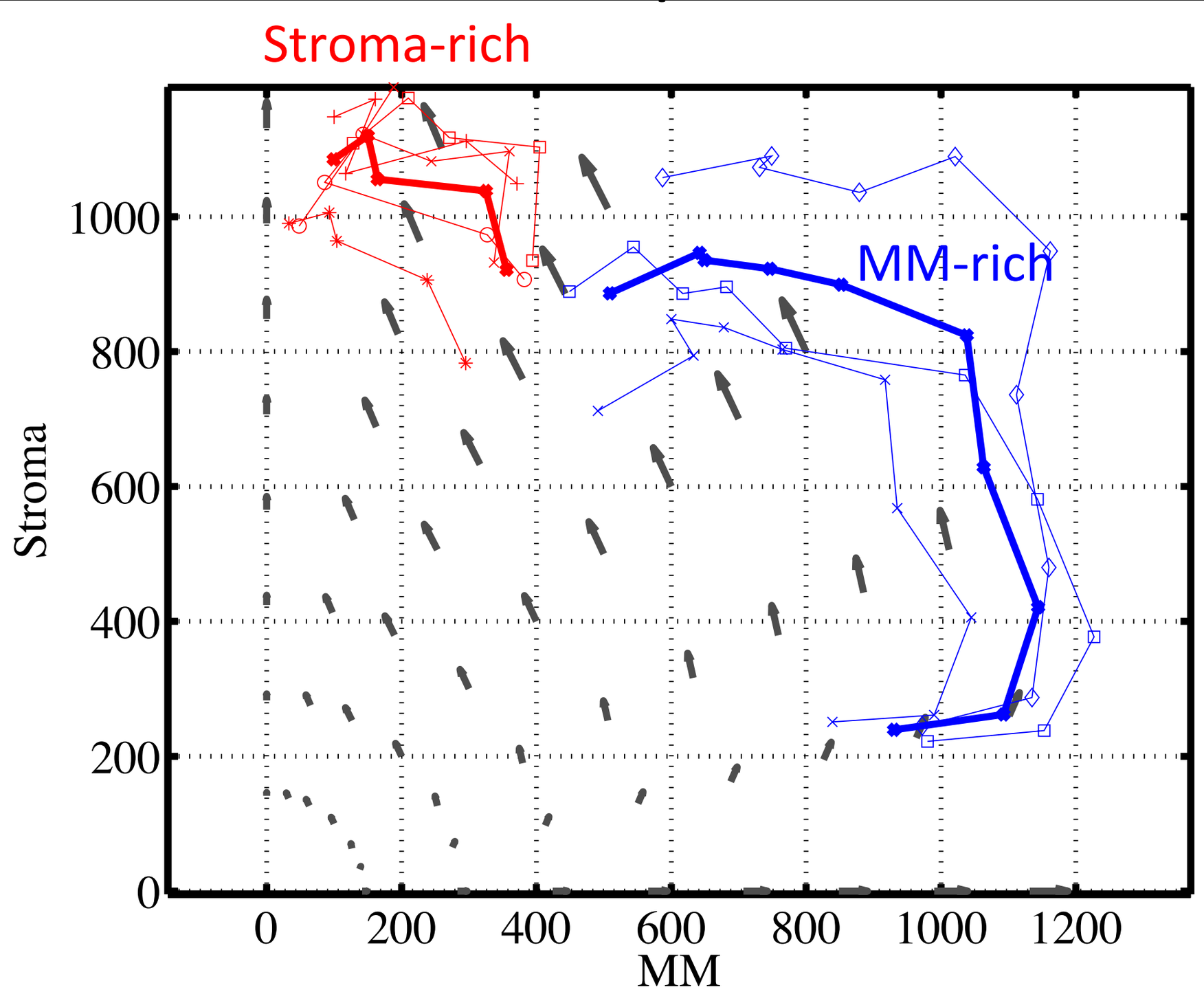


Phase portrait

Stroma-rich



The vector field of arrows is the prediction of the game theory model, the solid lines are the data.



Note that prediction here is that the stroma cells ("bystanders") win and the cancer cells lose.

VIII. Future Games.

1. Our message has been negative up to this point:

(a) Evolution (mutations) followed by natural selection in landscapes with steep fitness gradients and small sub-populations inevitably leads to drug resistance: What does not kill me makes me stronger.

(b) There is no way out if Darwin is right! Stop talking about a "cure" and be more realistic.

2. It's naive to examine cancer cells alone without including their interactions with other cells on the fitness landscape that drives evolution.

3. The interplay of cells on a fitness landscape can be re-cast into an evolutionary game-theoretic model ("all models are wrong but some are useful" - George Box) which allows prediction of the future of the games.

4. Can we learn the control points of the game and move the system over the fitness landscape to a (strange attractor?) where the cancer+stromal cells are either stationary or shrinking?

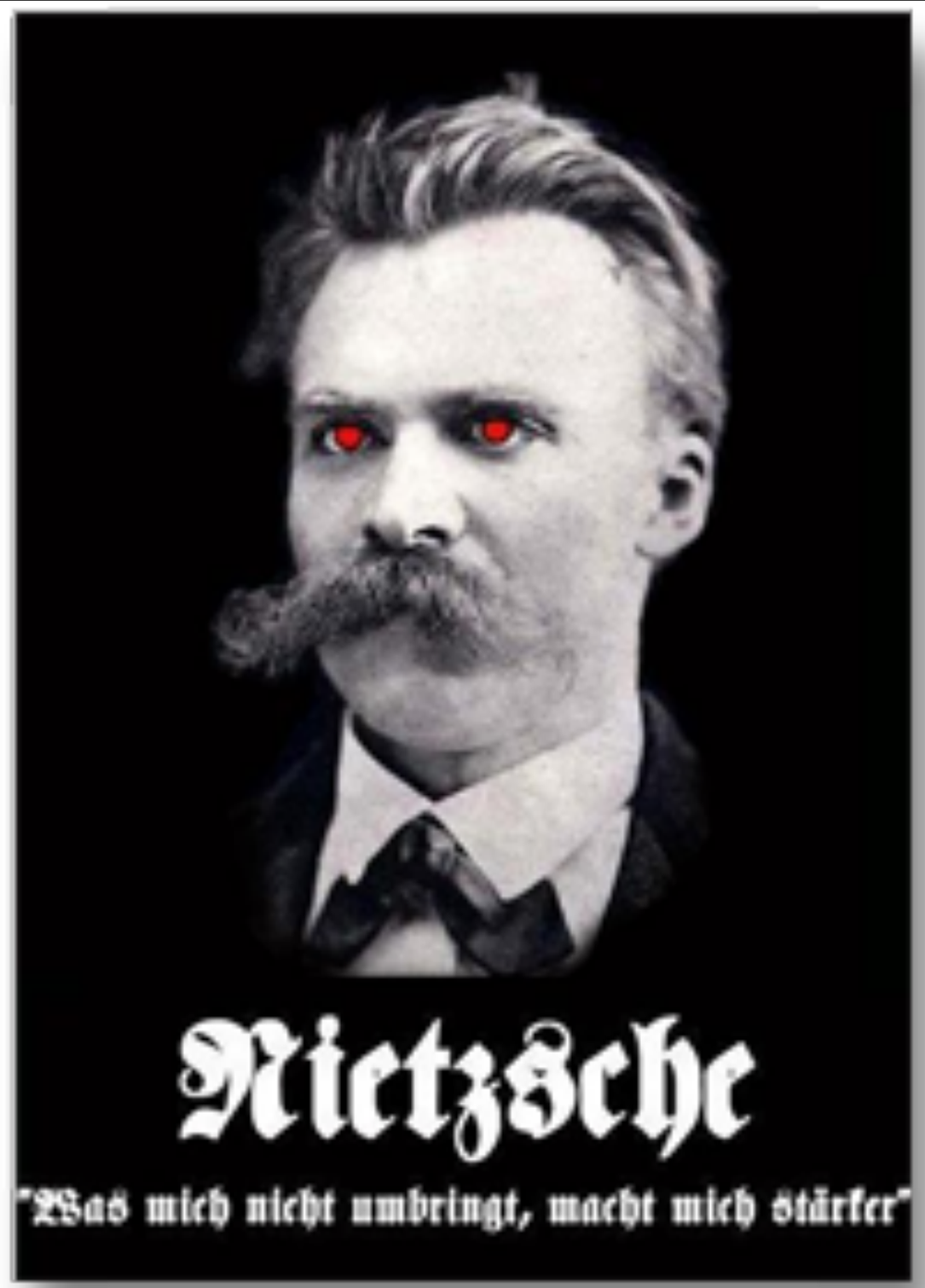
Is that even possible? Up to now, we only see the cancer winning.

1) 5 years ago the NCI took a chance on putting physicists into oncology at a non-widget building level. Crazy!

2) I think a vigorous and robust cancer cell evolution effort in complex ecologies has emerged.

3) New physics (I think so) , certainly new physical/ biological tools.

4) I hope we will see potentially transformative ways to view cancer emergence, from "blue-sky" research.



THANKS!!!