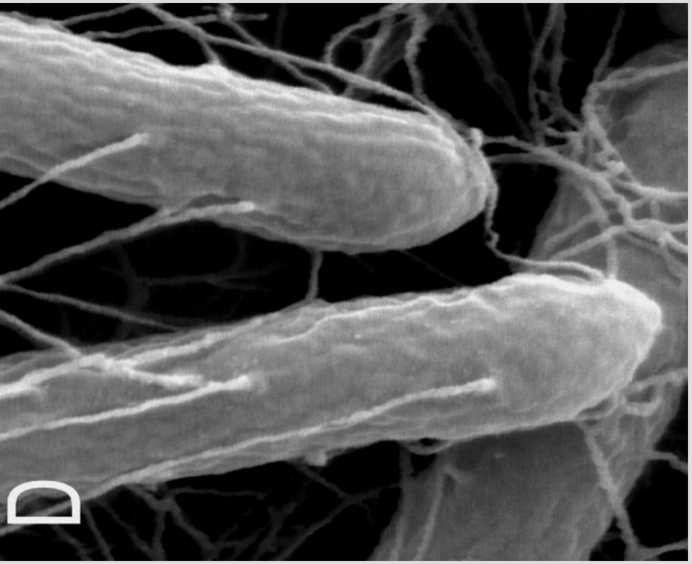
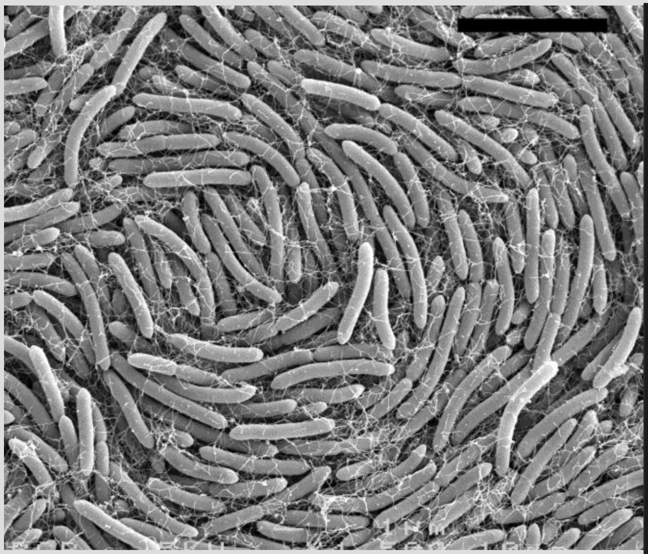
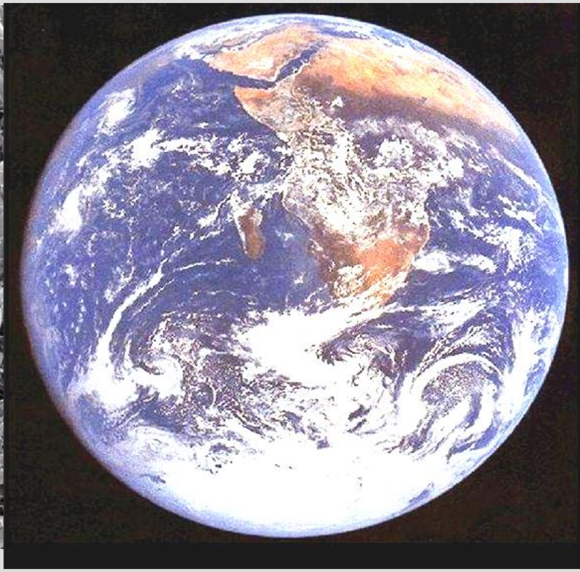
From Bacteria Thou Art

First organisms, ~4 billion years ago







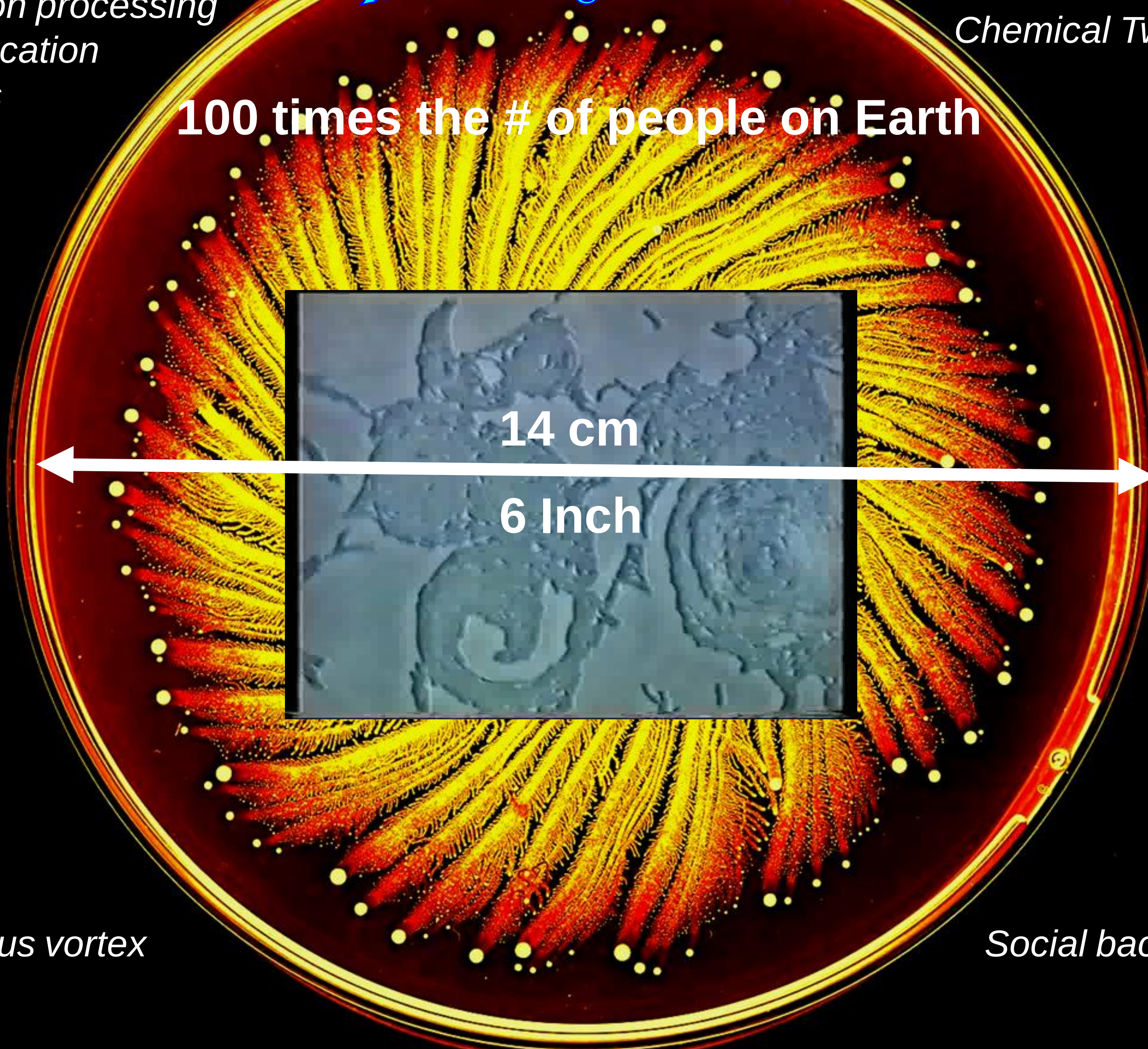
Paved the way for all life

Our best friends and worst enemies

Rethinking Bacteria

Sensing
Information processing
Communication
Decisions

Bacterial Global Village
Chemical Twittering



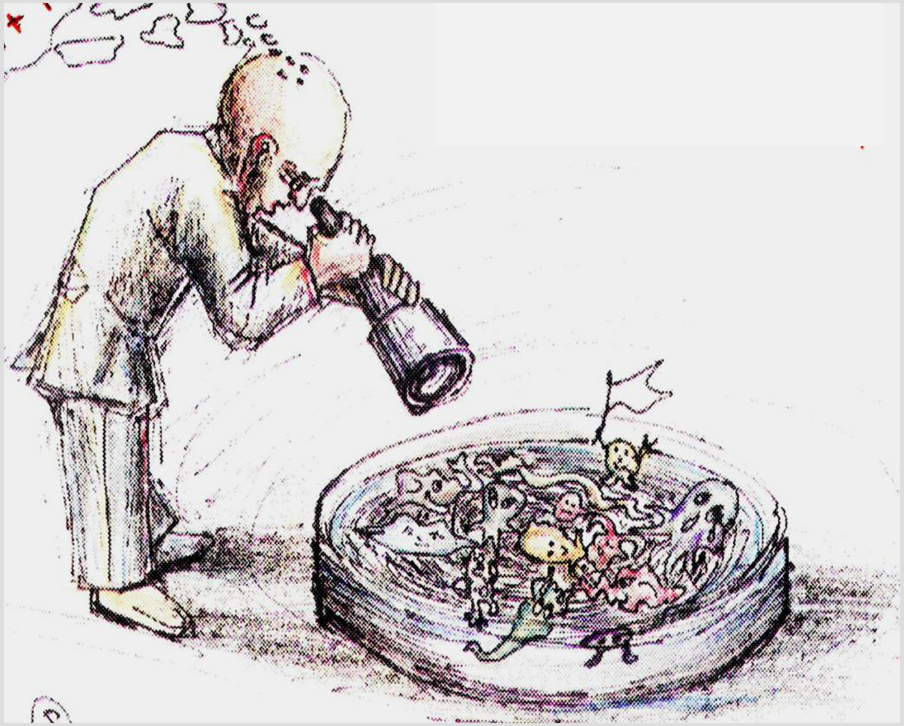
Paenibacillus vortex

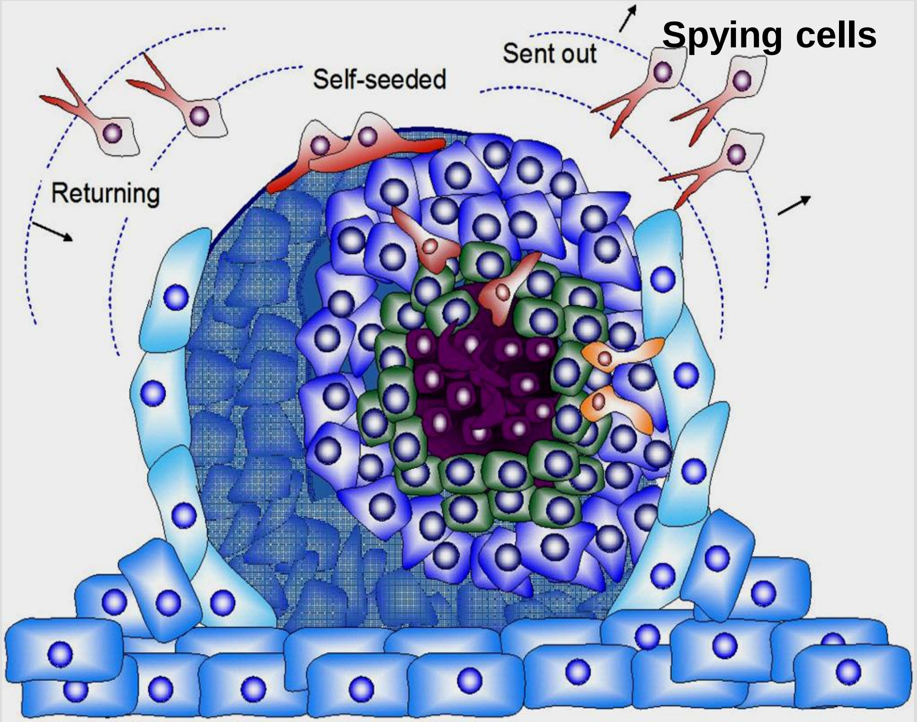
Social bacteria

Bacteria, and Cancer Metacommunity

Eshel Ben-Jacob

School of Physics Tel Aviv University and CTBP Rice University





Physics and Mathematics of Cancer, KITP July 5, 2012

The Big Challenges

Multiple Drug Resistance

Dormancy and Relapse

Metastasis Colonization

These most alarming aspects of cancer are little understood and clinically insuperable

A Need for a Paradigm Shift ?

Looking at bacterial sociality as a source of inspiration and suggestion

Ben-Jacob, Coffey, Levine Opinion in *Trends in Microbiology* (2012)

Bacterial Survival Strategies Suggest Rethinking Cancer Cooperativity

Why Bacteria and Cancer?

Rapid development of drug resistance

Rapid proliferation and Advanced motility

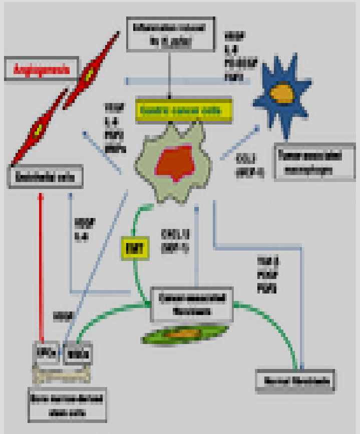
Advanced communication and Collective behaviors

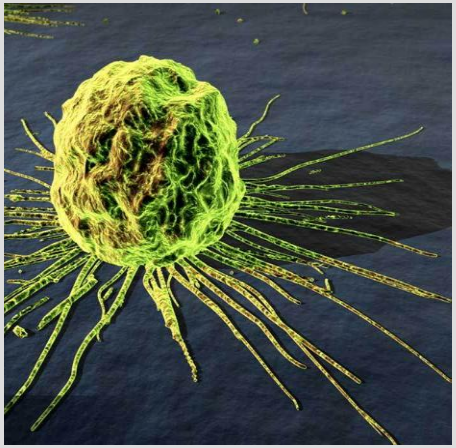
Changing the environment

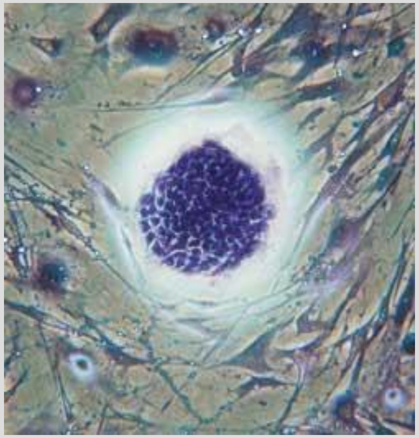
"Learned" to avoid and manipulate the immune system

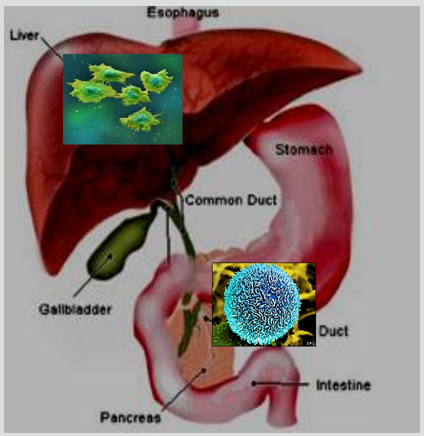
Why Physicists?

Intracellular ⟺ Cellular ⟺ Multicellular & Environment ⟺ Metacommunity









Bacteria and Cancer

Hickson, Bassler et al *Clin. Exp. Metstasis* (2009)

Societal interactions in ovarian cancer metastasis: a quorum-sensing hypothesis

Deisboeck and Couzin *BioEssays* (2009)

Collective behavior in cancer cell populations

Dawson et al *PLoS Phatogens* (2011)

"Persisters": Survival at the Cellular Level

Austin et al Perspective in *Nature Reviews Cancer* (2011)

An Analogy Between the Evolution of Drug Resistance in Bacterial Communities and Malignant Tissues

Glickman and Sawyers *Perspective in Cell* (2012)

Converting Cancer Therapies into Cures: Lessons from Infectious Diseases

Today

The Wisdom of the Colony

The Cancer Metacommunity Hypothesis
The Tumor Community and the Cancer Metacommunity)

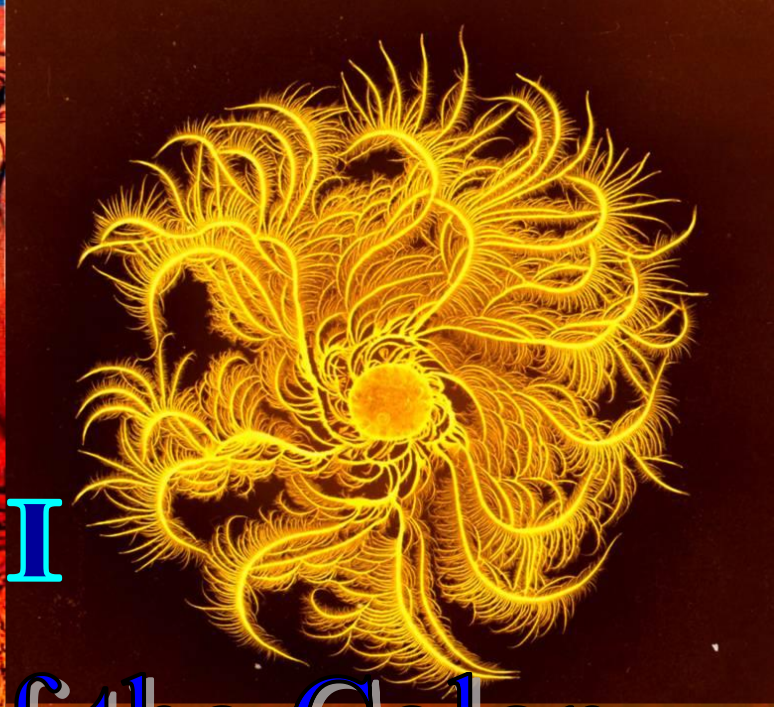
Bacterial Collective Decisions

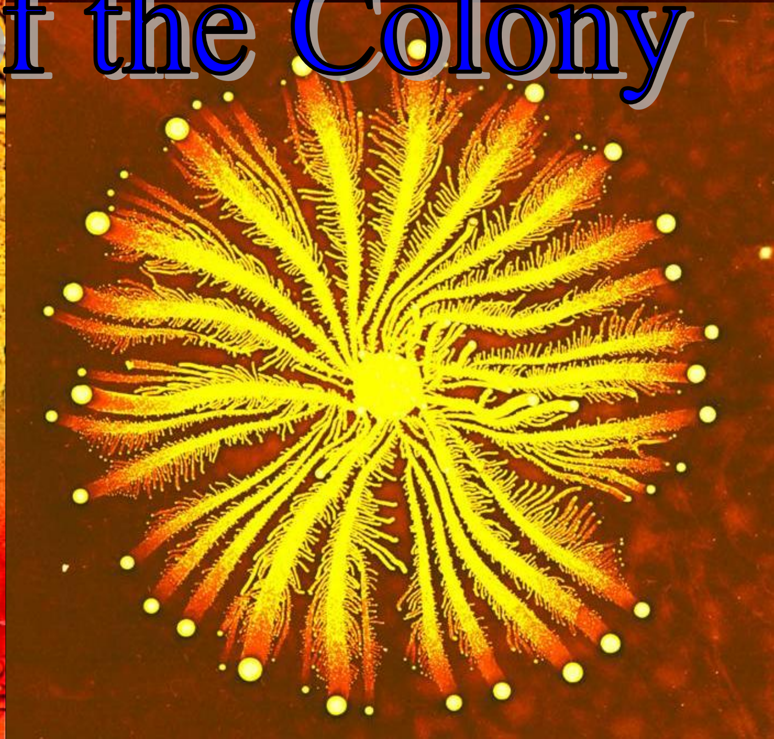
Cancer Navigation – Proliferation vs. Invasion

Implications and Possible Applications
(New Research Directions and Strategies to Fight Cancer)

Part I

The Wisdom of the Colony





The Wisdom of the Colony

Communication and Social Behaviors

Task Distribution and Cell Differentiation

Sharing Resources and Risks

Learning from Experience

Collective Decisions

Changing the Environment

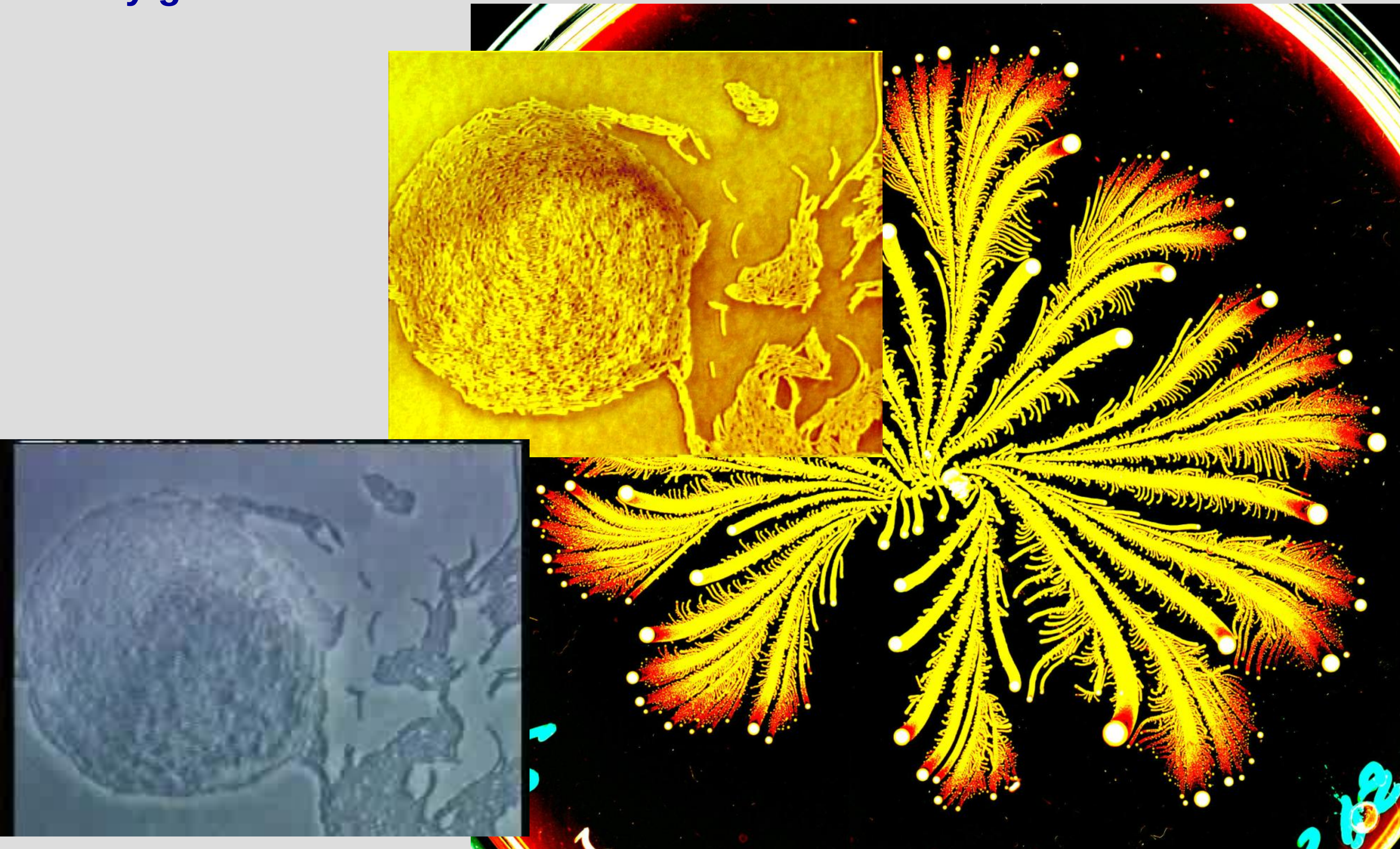
Planning for the Future

Ben-Jacob Roy. Soci. 2003 ;
Ben-Jacob, Becker, Shapira, Levine Trends in Microbiology 2004

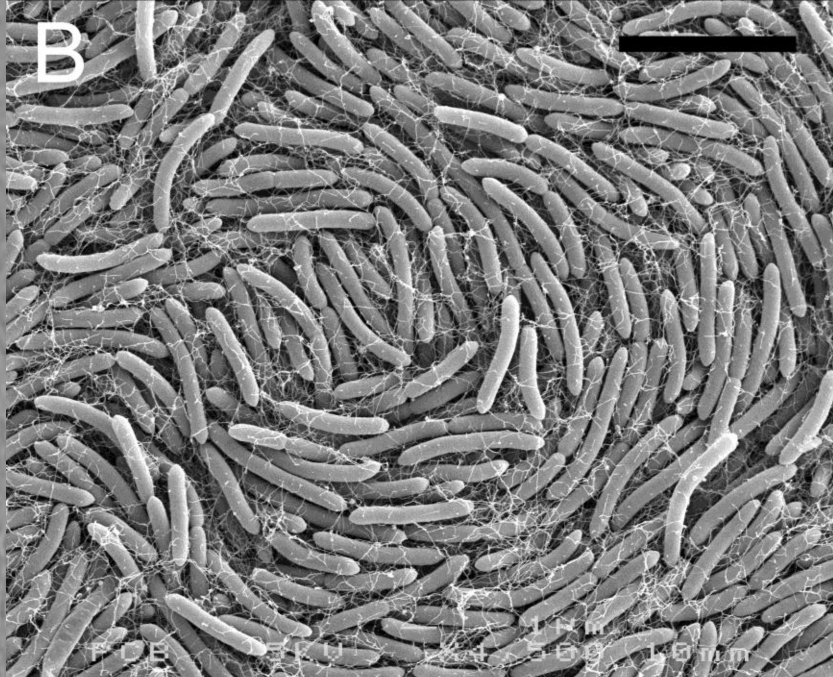
Complex Organization

Colony growth: Ina Brainis

Paenibacillus vortex



Ben-Jacob, Nobel Symposium, 2002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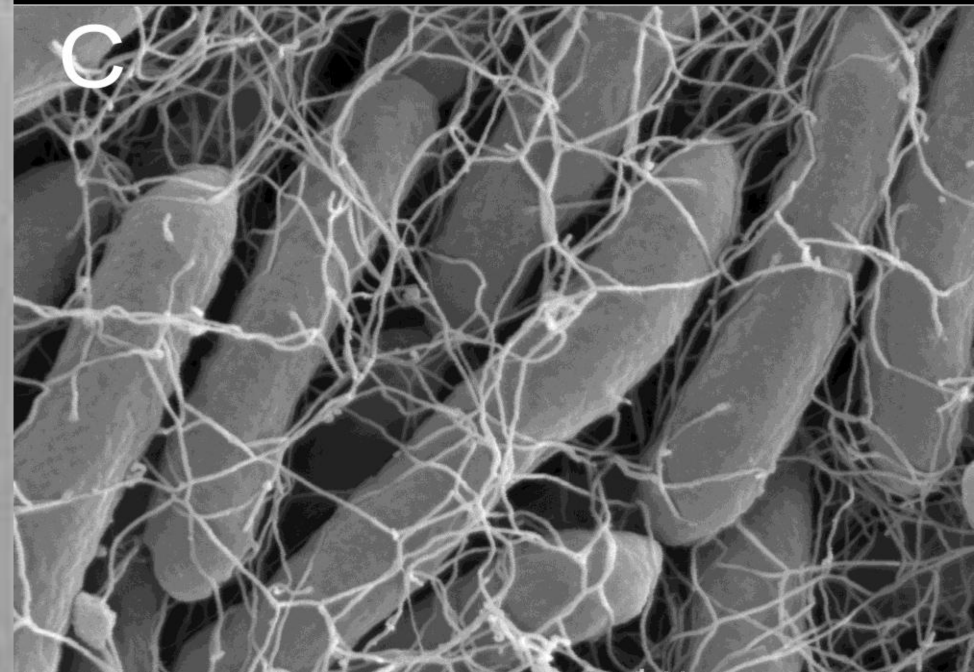
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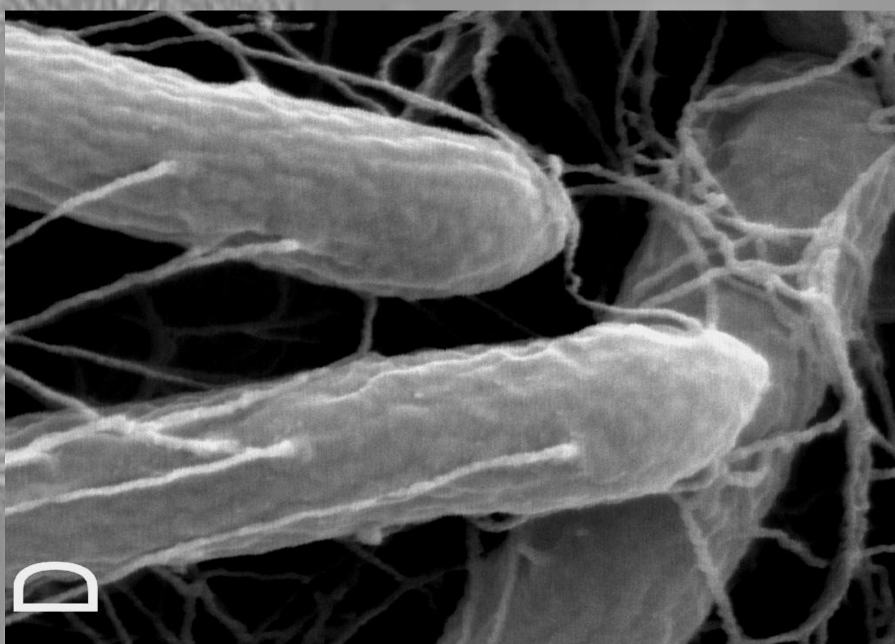
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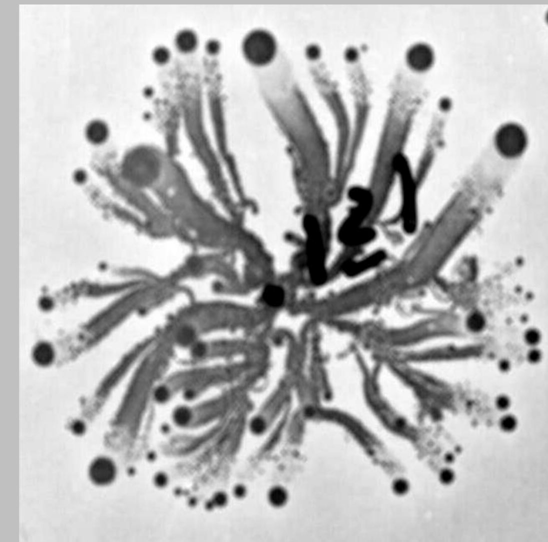
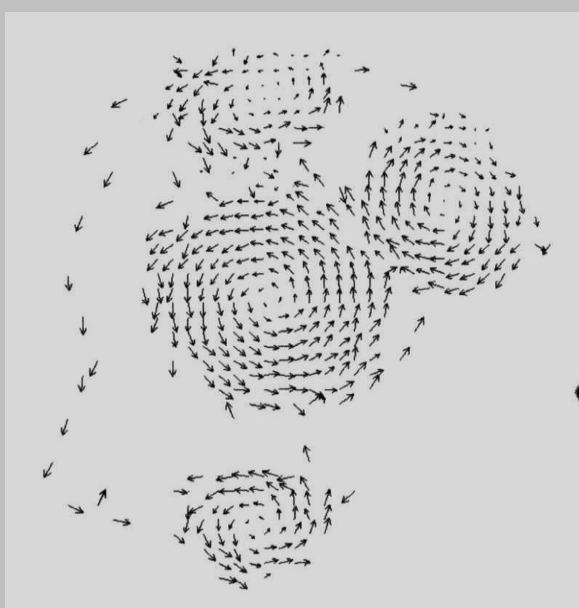
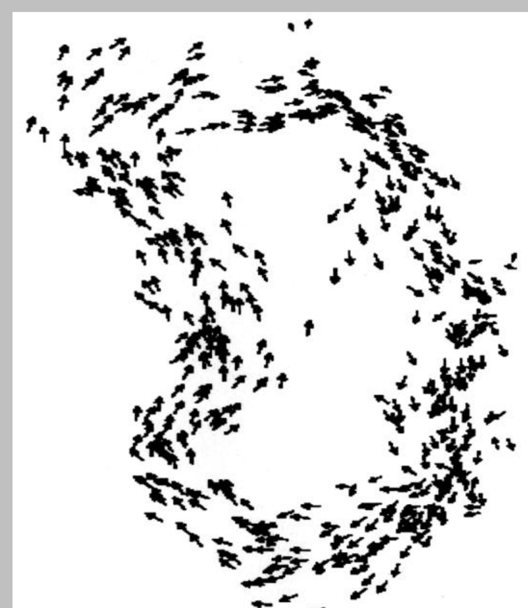
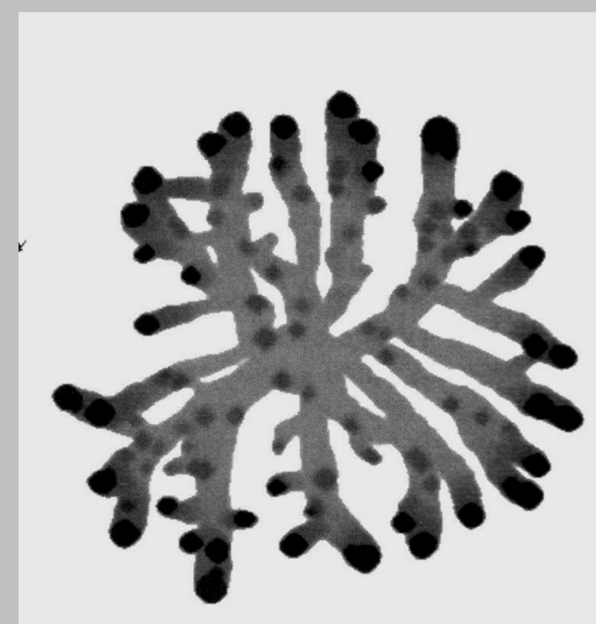
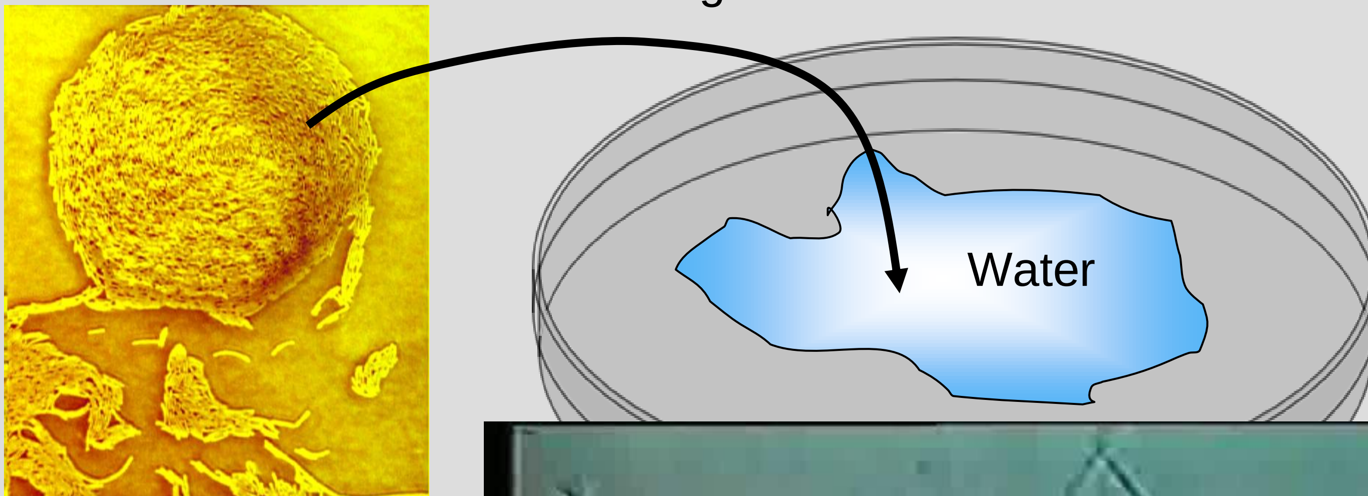


Modeling

Variability of cells composing a vortex

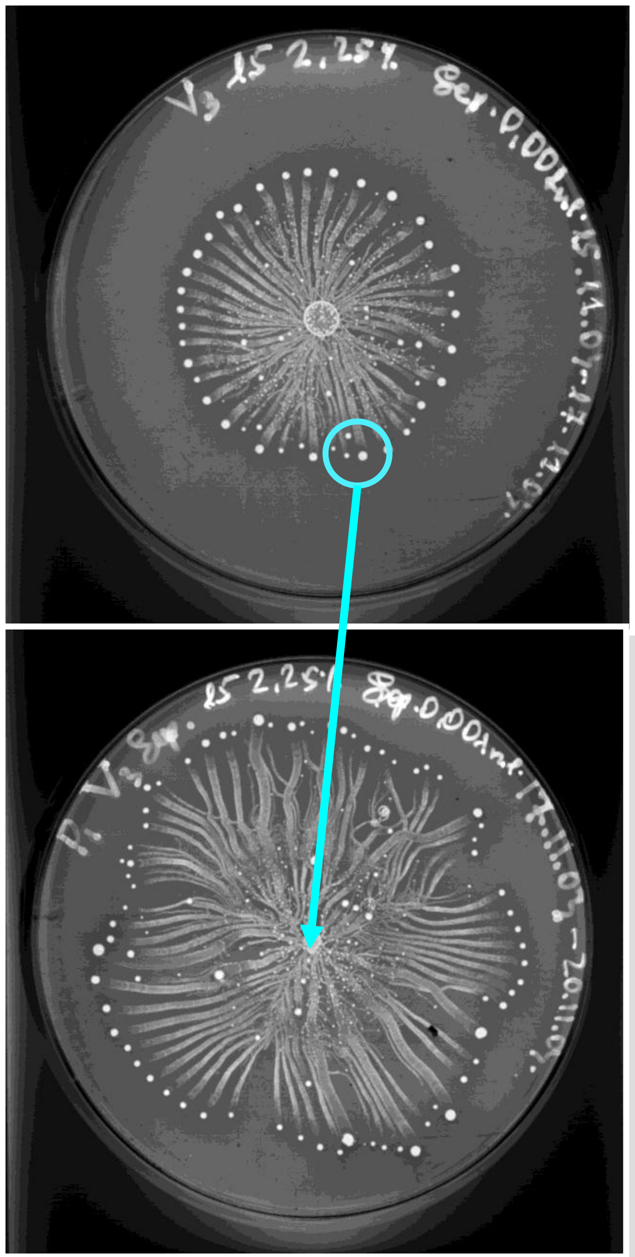
Breaking a vortex and let the cells move



"Learning from Experience"

Exposure to antibiotics

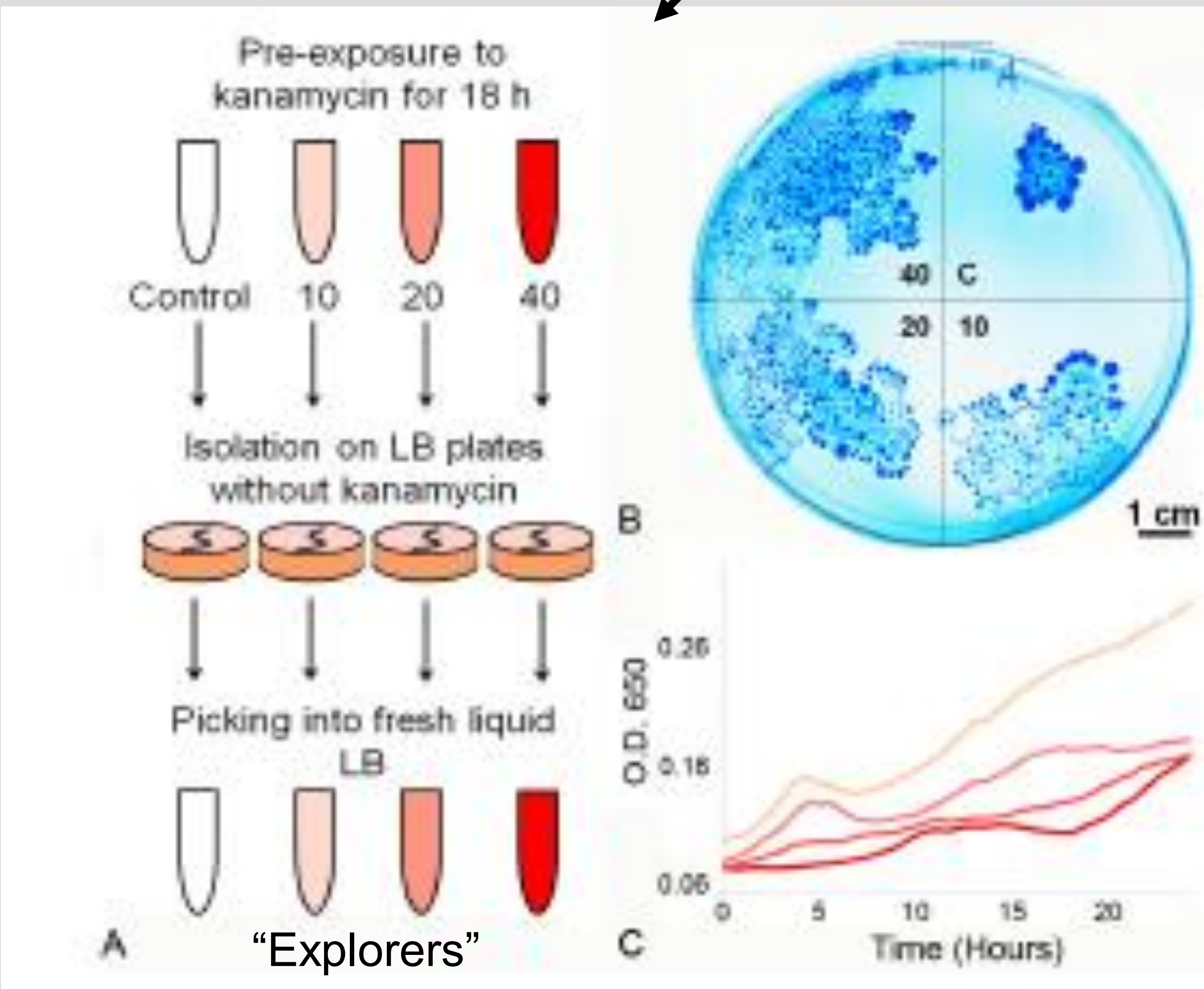
Normal growth

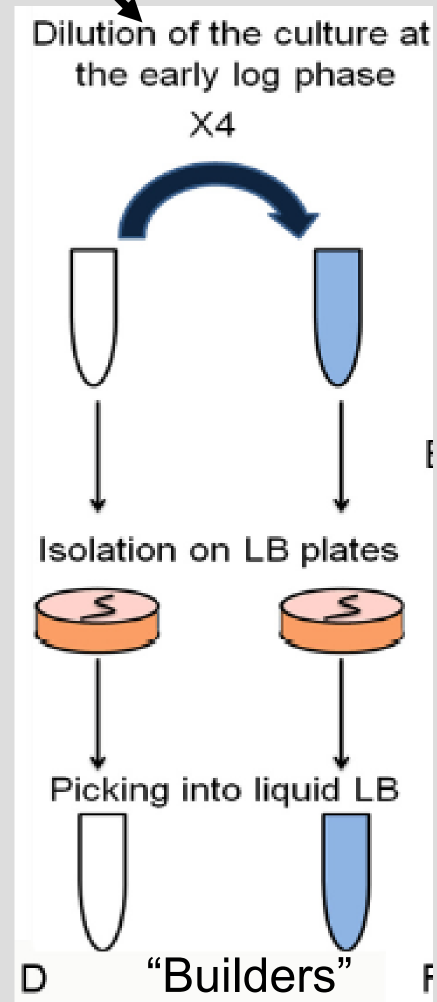


Second exposure

Identification and isolation of two sub-populations

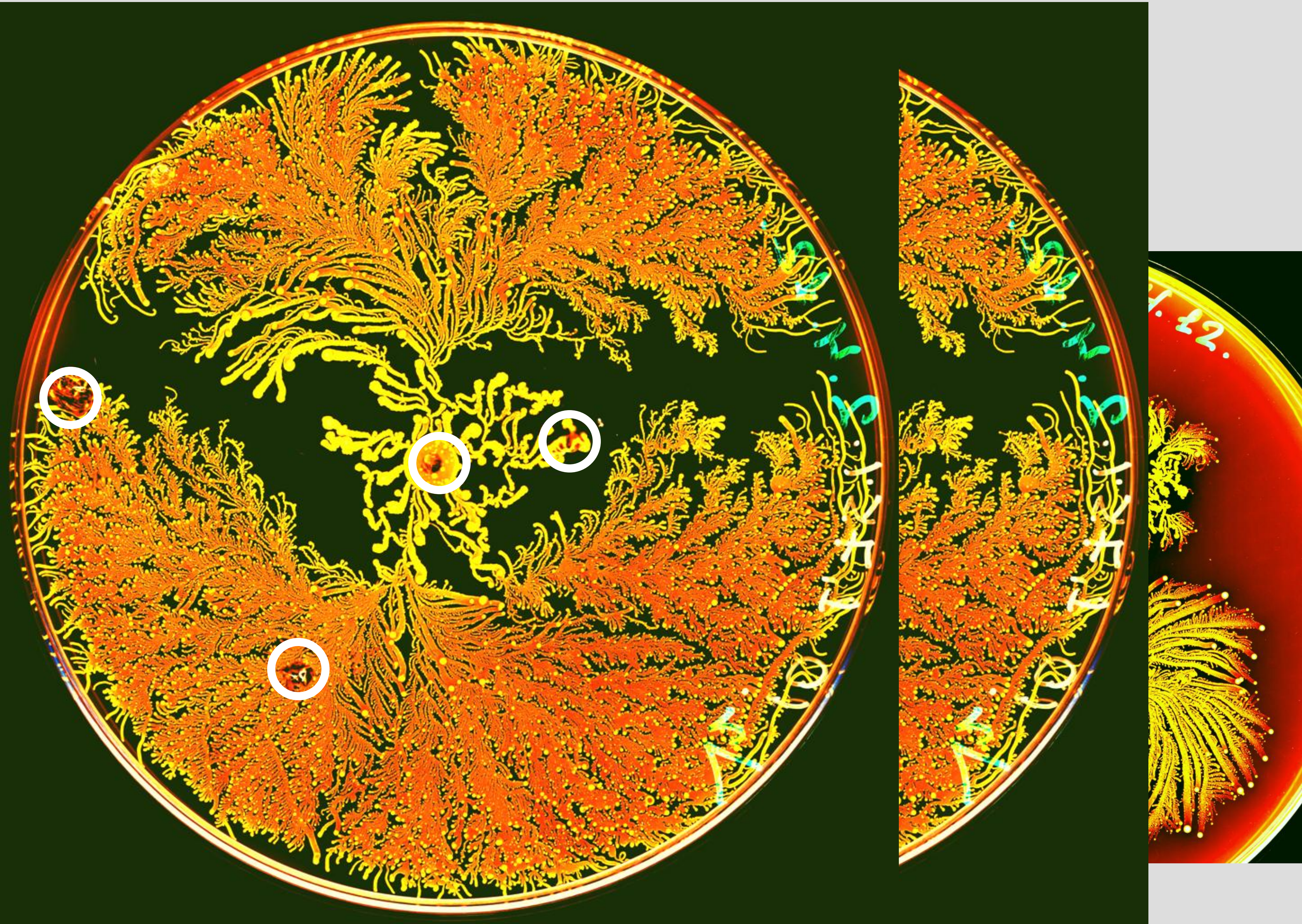
Low proliferation, hyper flagellated resistant vs. higher proliferation, slow, sensitive





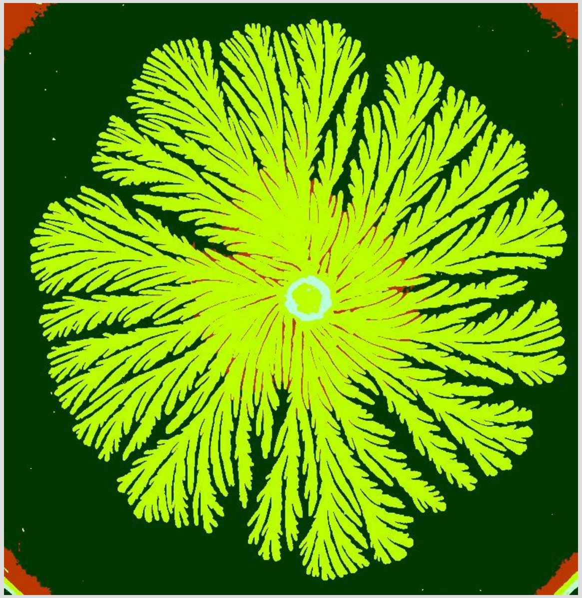
With Roth, Finkelstein, Ingham, Helman unpublished

Task Distribution and Cell Differentiation

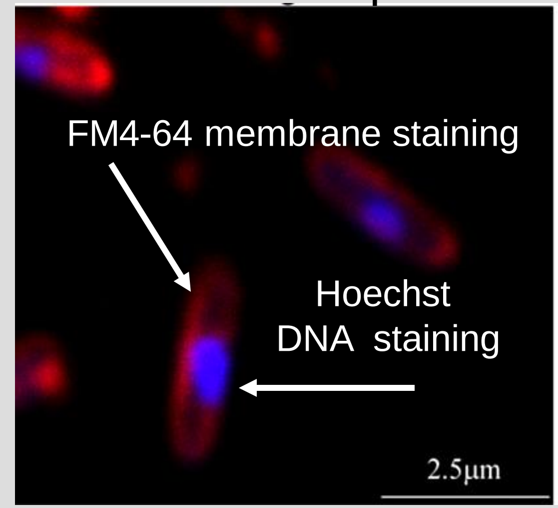


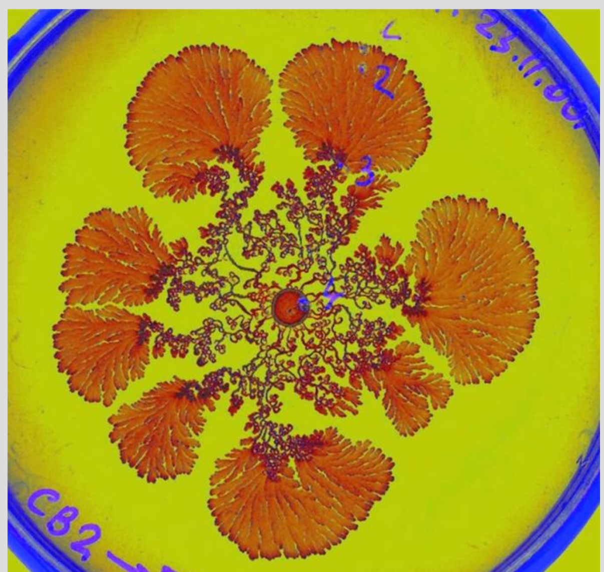
Epigenetic transitions - "Social Revolutions"

Proliferation vs. Invasion and Drug Resistance

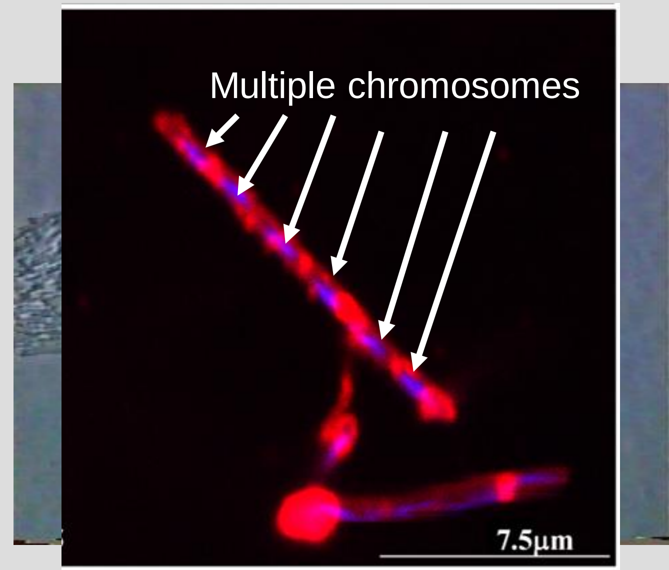


Finkelstein et al unpublished



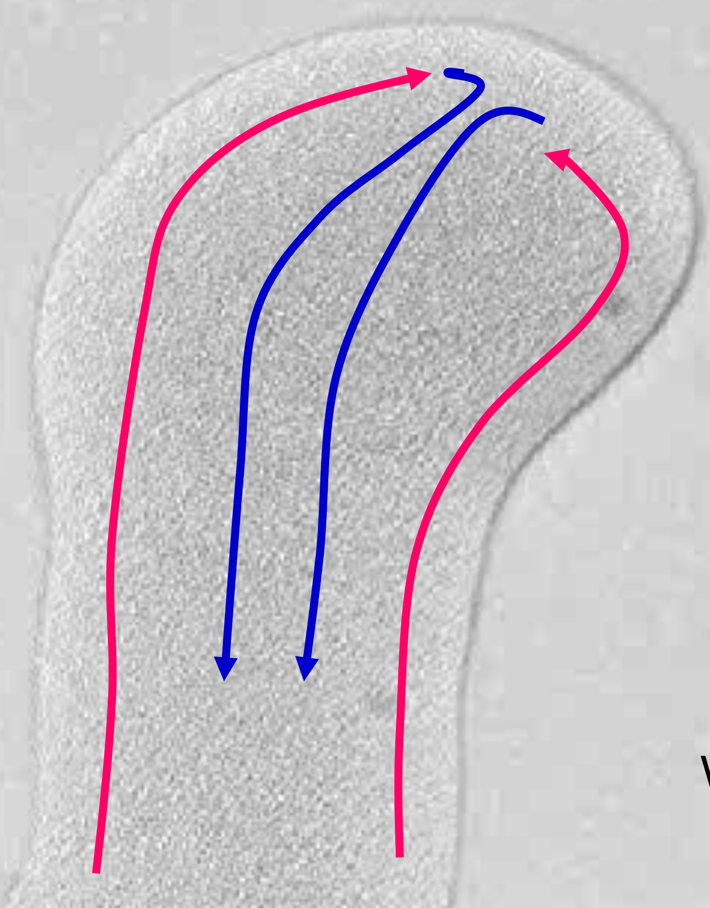


Paenibacillus dendritiformis



Searching for New Territories

Collective Navigation

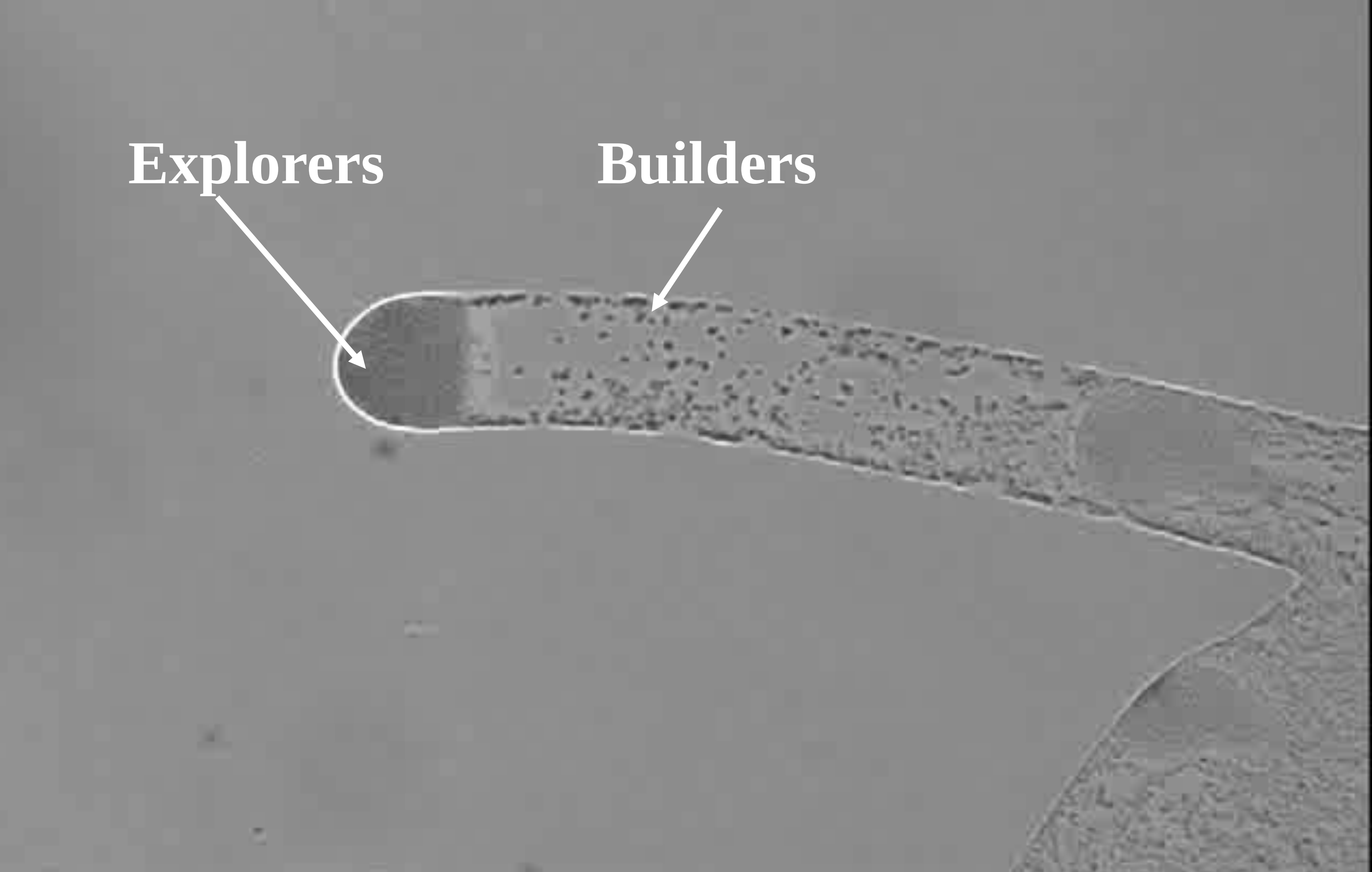


Paenibacillus vortex

With Ingham, BMC Microbiology 2009

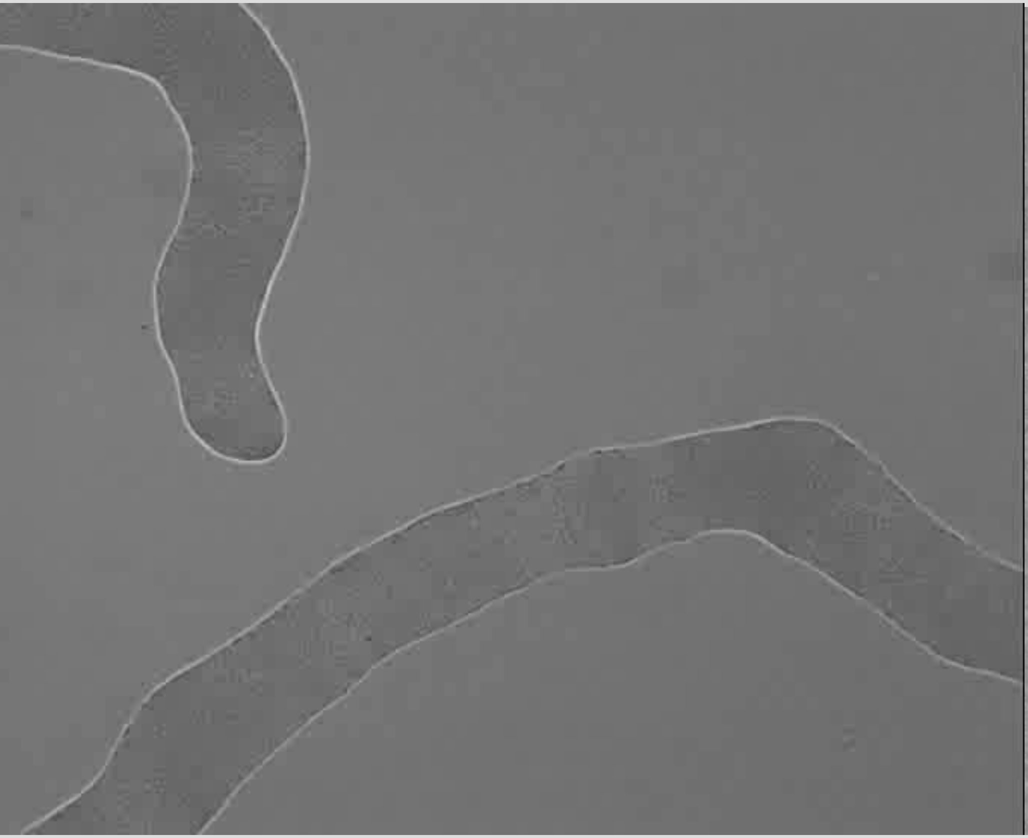
With Ingham, Kalishman and Finkelstein, PNAS 2011

Task Distribution and Cell Differentiation

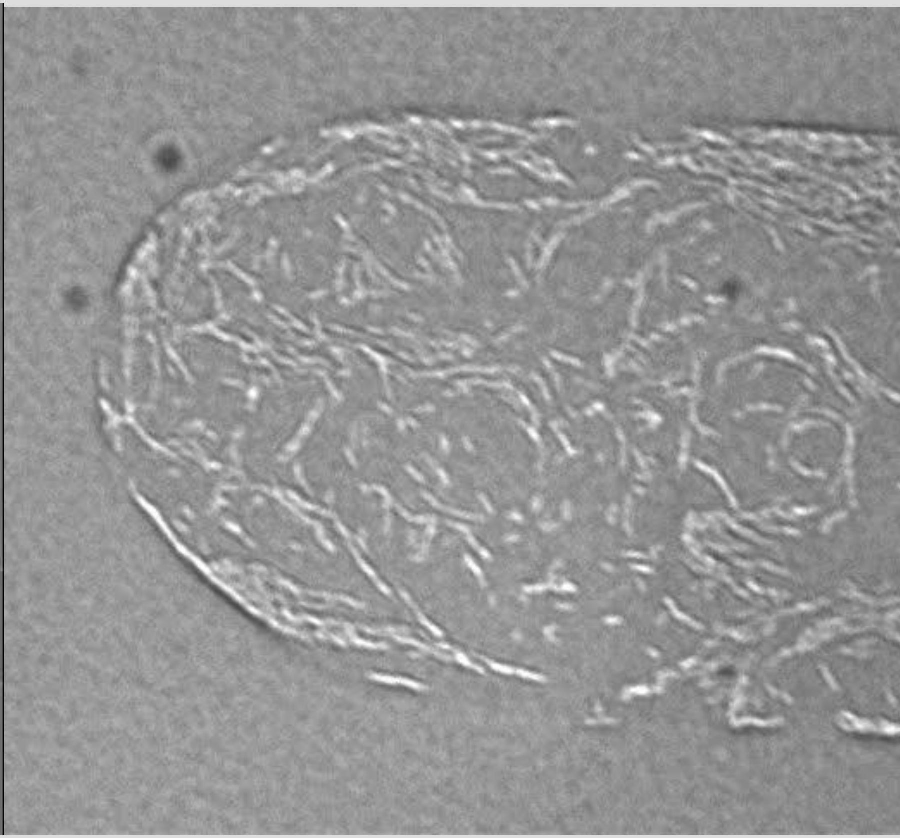


Additional Features

Swarm-Swarm Repellent



Marking the trail



Colin Ingham and Ben-Jacob BMC Microbiology 2009

Collective Navigation in Search for Food

Collective (Distributed) Information Processing

Social Networking by Chemical Twitting

Collective Navigation in Search for Food

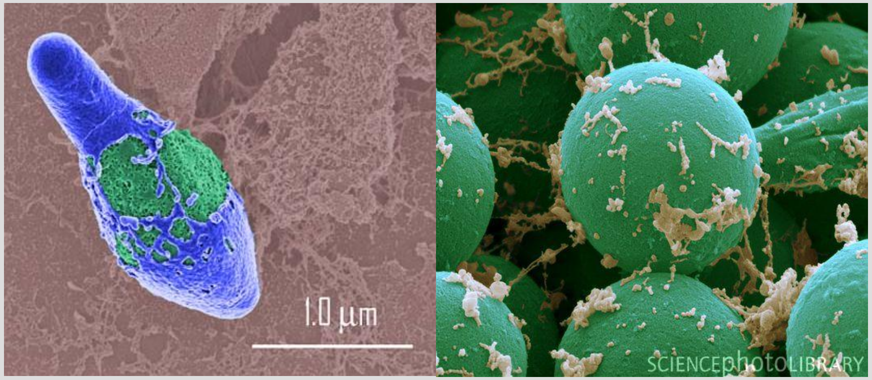
Deciding Fate at Adverse Times

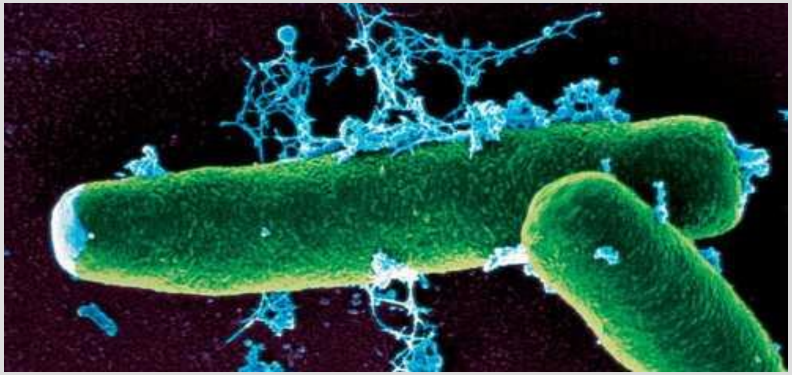
Example I

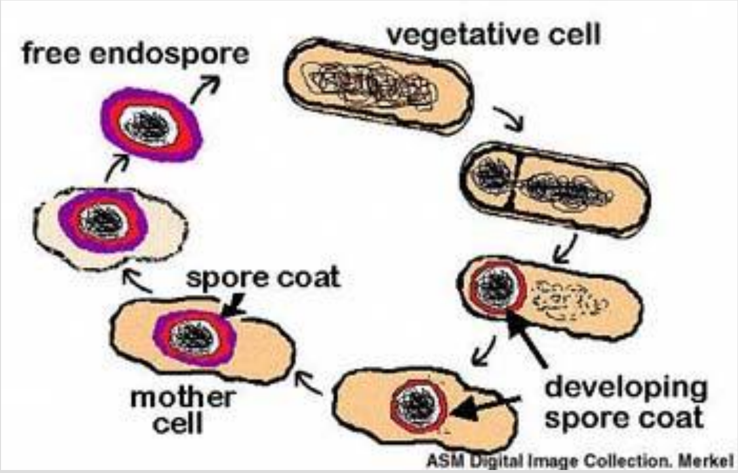
Sporulation Vs. Competence

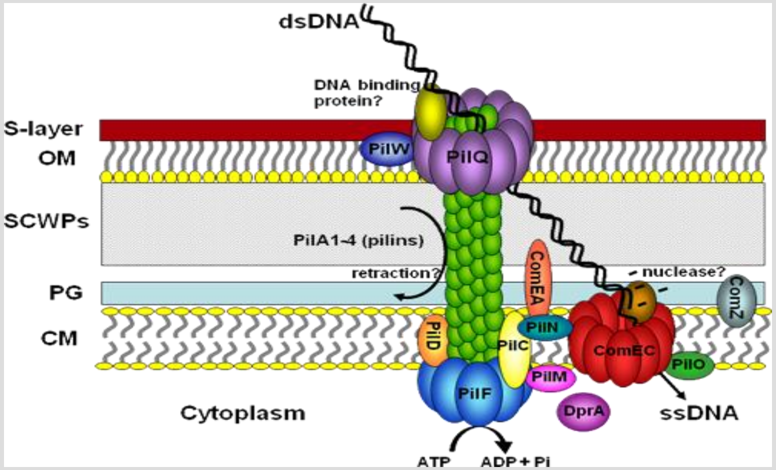
Bet on better future

Bet on the present









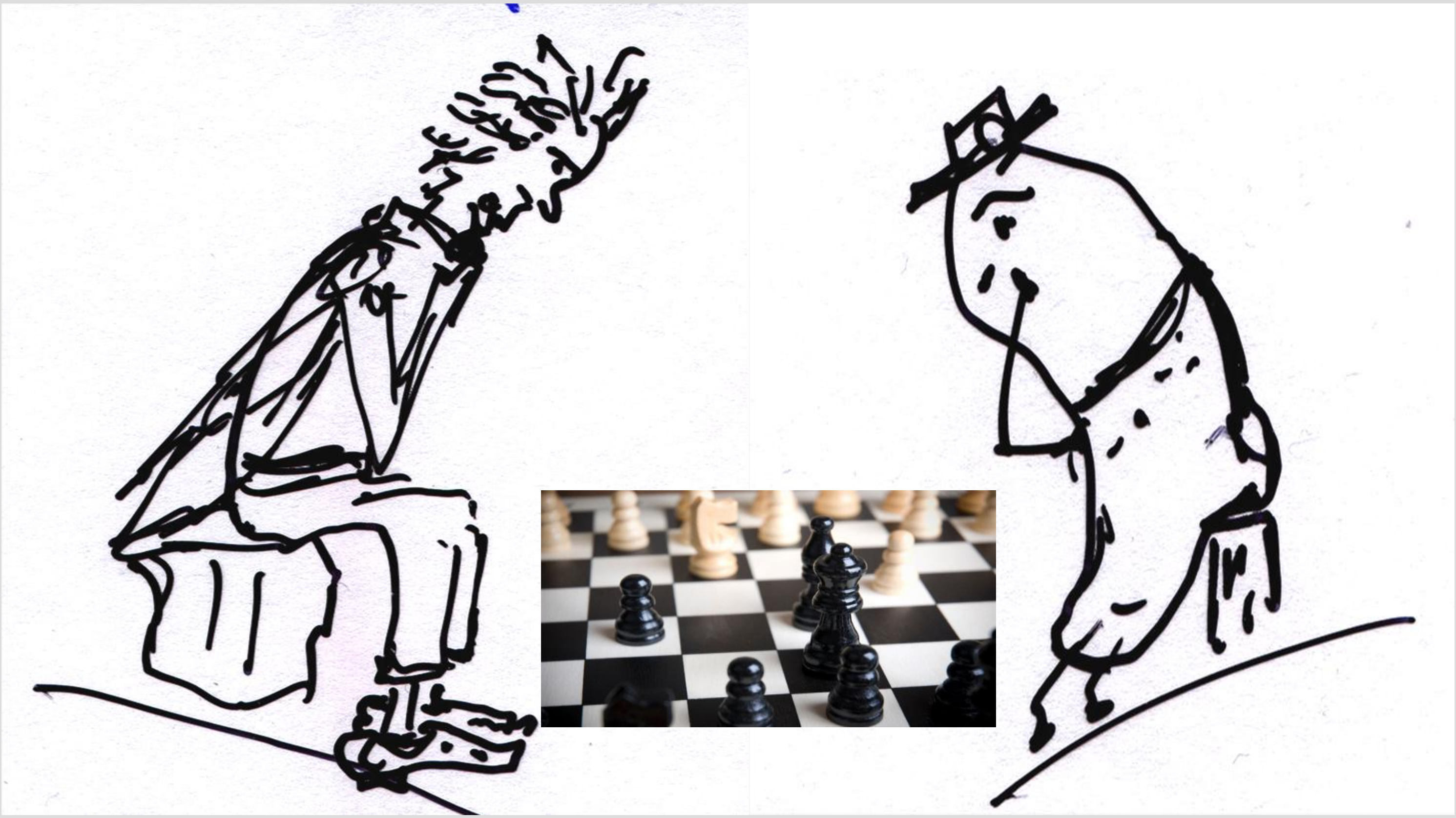
Deciding Fate at Adverse Times

Altruism, Cannibalism and Fratricide

Gonzalez-Pstor et al Science 2003

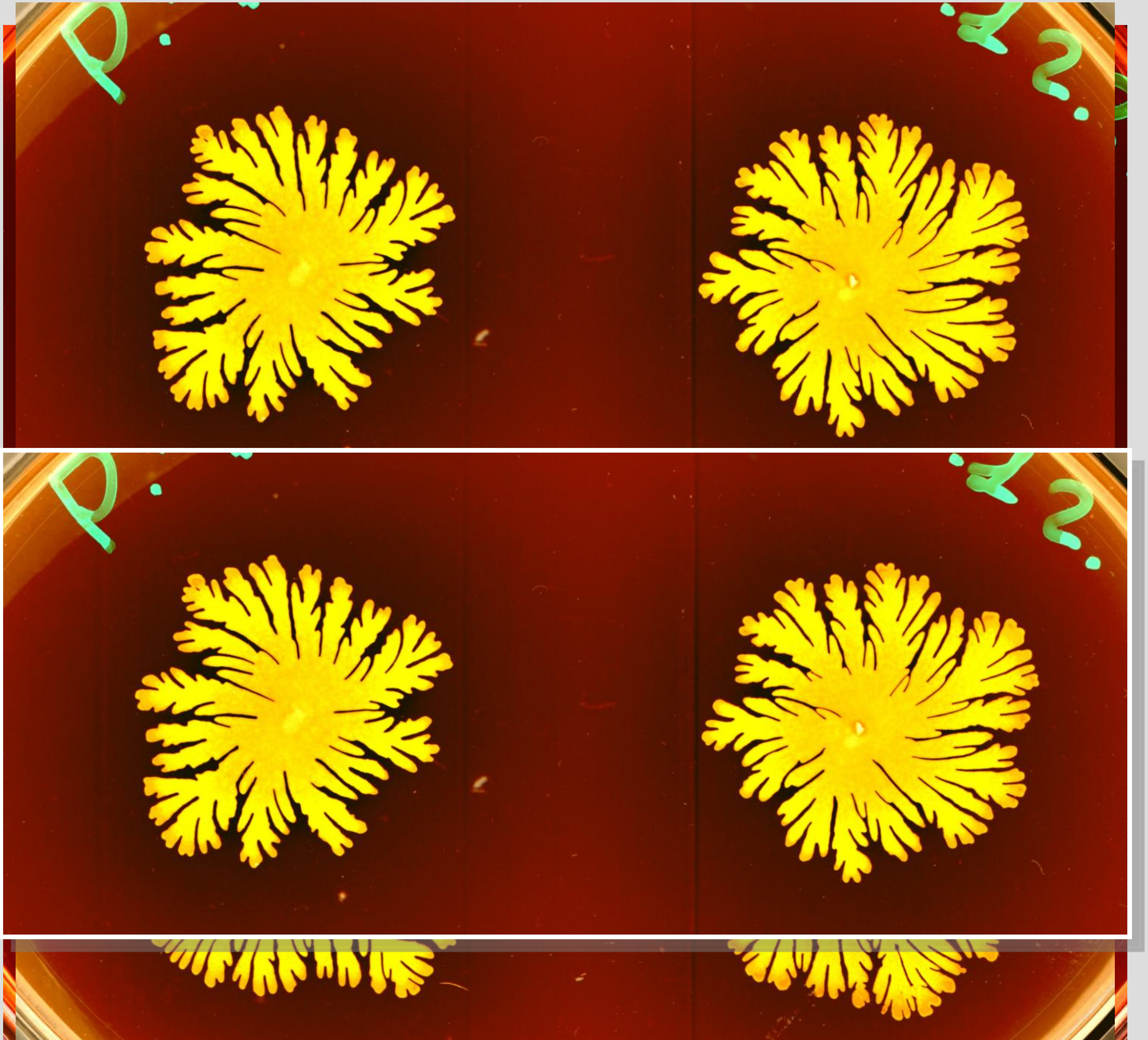
G
o

Harnessing Fratricide to Outsmart Bacteria



With Be’er, *et al., PNAS 2009,* Be’er, Ariel *et al., PNAS 2010*

Bacteria Societies (Metacommunities)

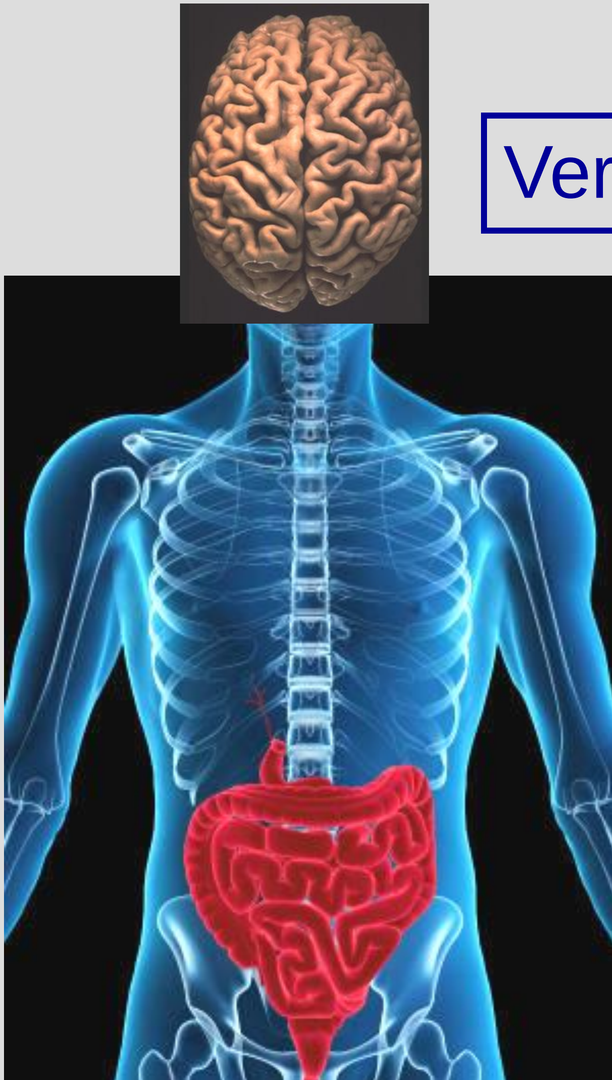


Microbota - A Metacommunity of Bacteria in the digestive tracta

10 trillion bacteria of more than 40,000 different strains

Affect digestion, the immune system, the endocrine system and the brain

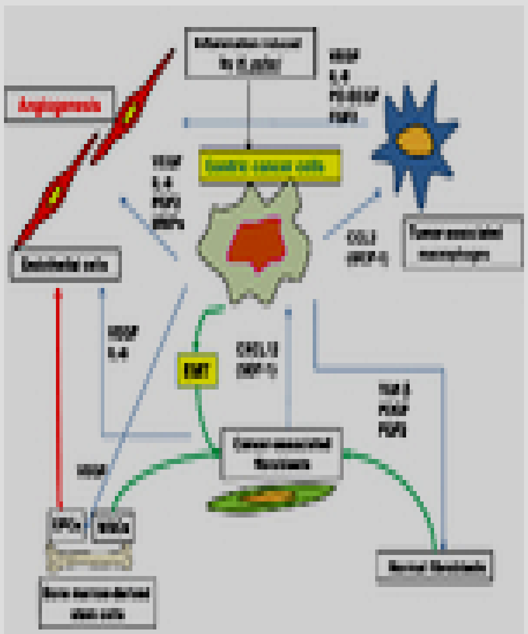
Very relevant for cancer but not today

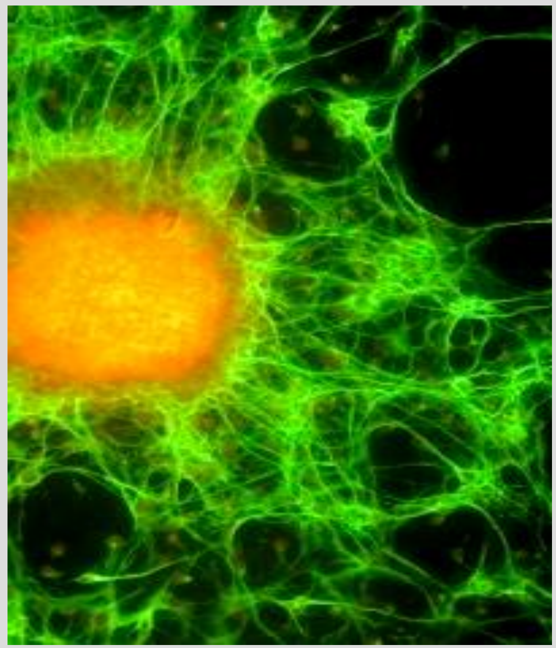


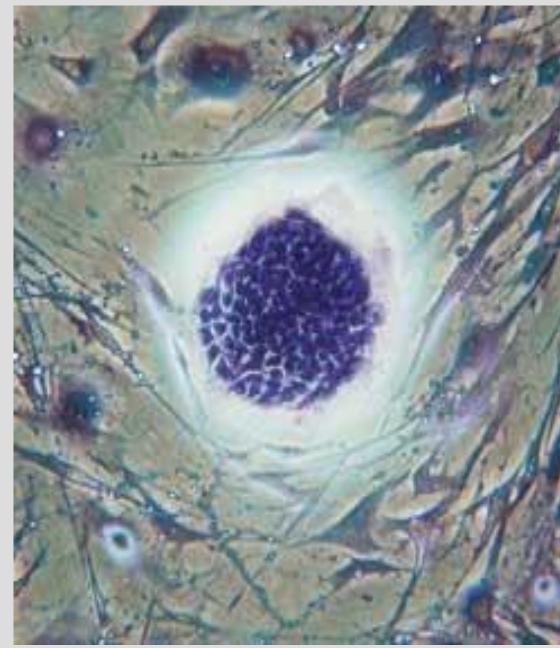
Part II

The Metacommunity Hypothesis

I. The Tumor Community





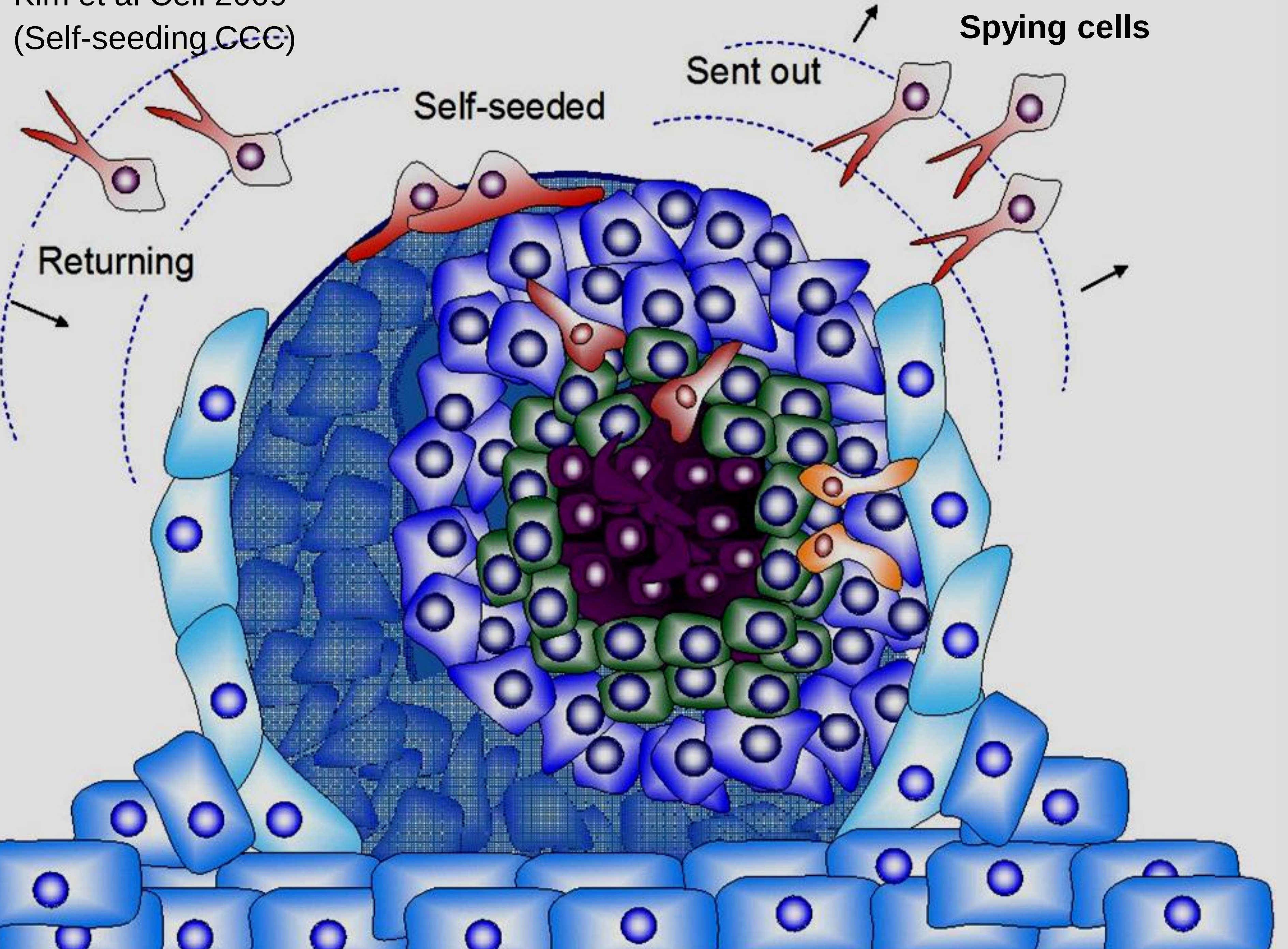


Eshel Ben-Jacob, Donald Coffey, Herbert Levine

Trends in Microbiology Online June 29, 2012

Kim et al Cell 2009
(Self-seeding CCC)

Spying cells



Advanced Communication

Physical interactions

Chemical signaling

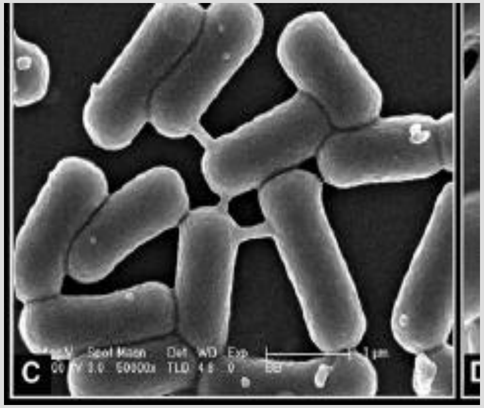
Exchange of genetic information

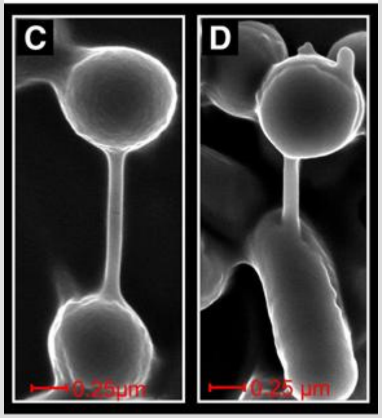
Exosomes

Gap junctions and Nanotubes

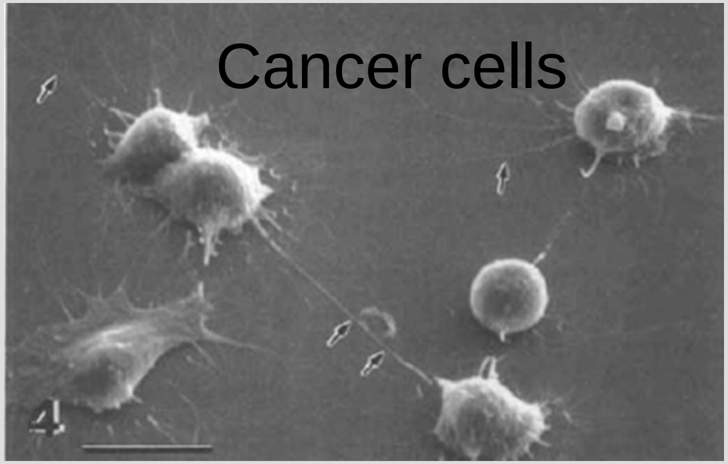
(calcium waves? ; electrical signals?)

Bacteria





Dubey and Ben-Yehuda Cell 2011

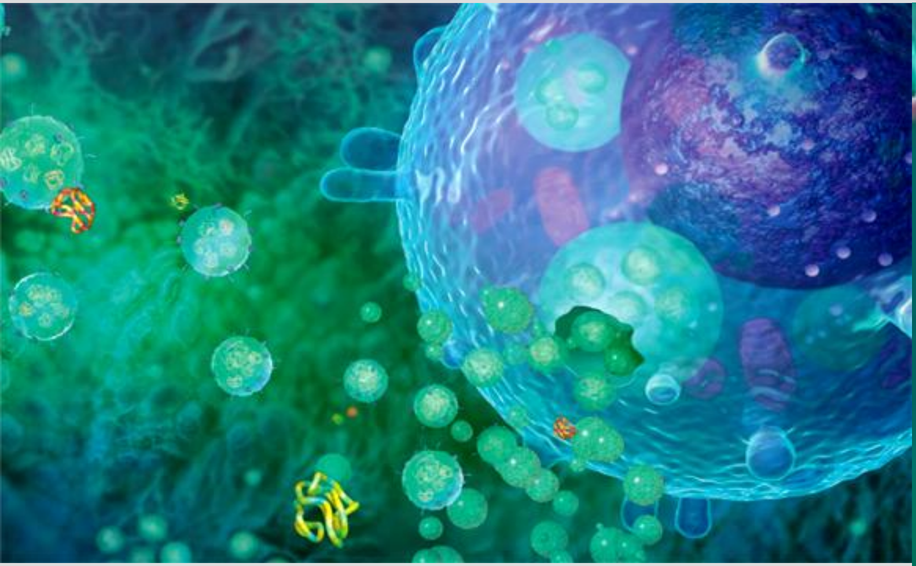


Gilloteaux et al *SCANNING* (1998)

Exosomes: A new dimension in cell-cell communication

These small membrane vesicles do much more than clean up a cell's trash they also carry signals to distant parts of the body, where they can impact multiple dimensions of cellular life.

Clotilde Théry TheScientist July 1, 2011

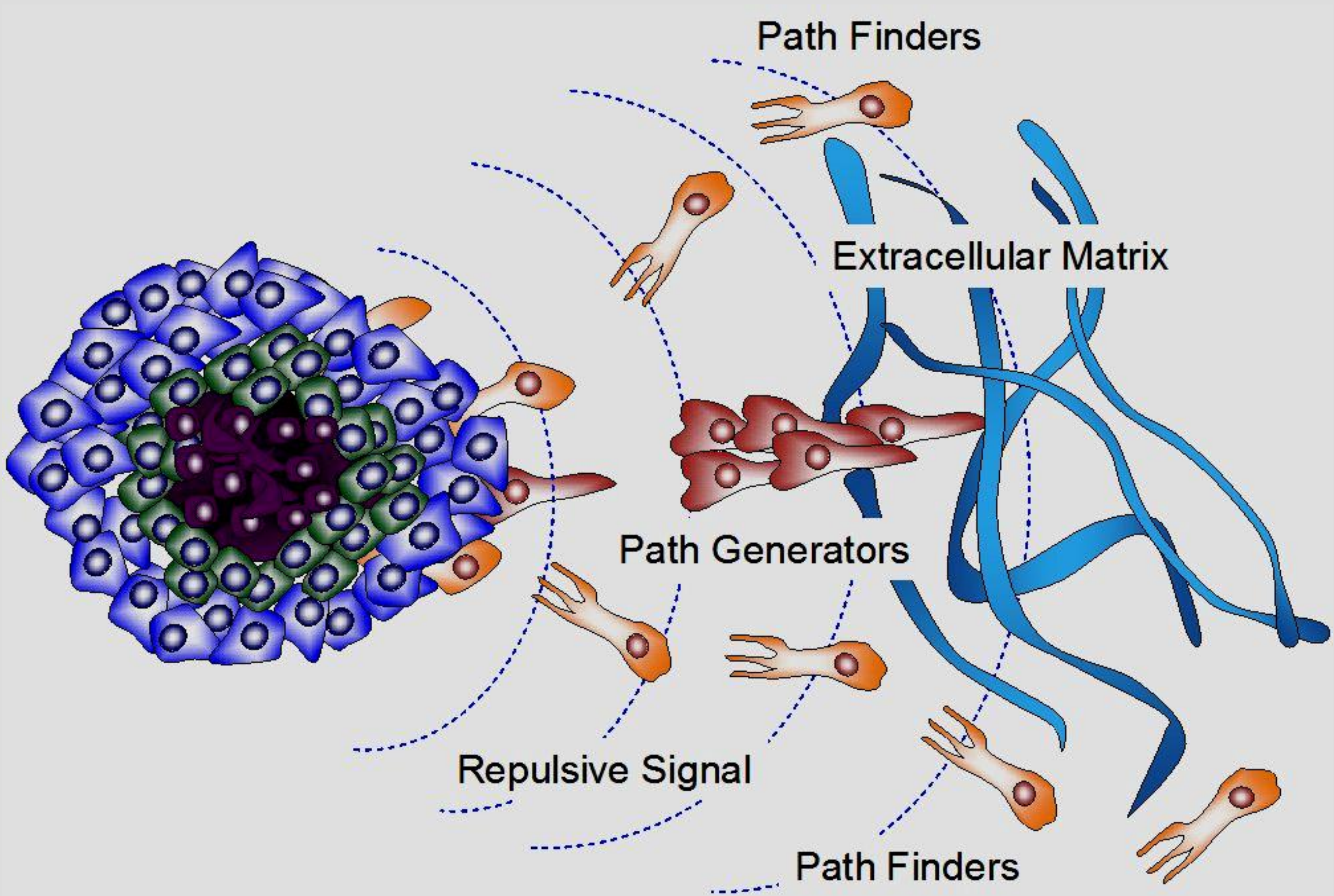


Zhang and William "Exosomes and Cancer: A Newly Described Pathway of Immune Suppression" *Clinical Cancer Research* 2011

Camussi et al "Exosome/microvesicle-mediated epigenetic reprogramming of cells" *J. Am. Cancer Research* 2011

Metacommunity

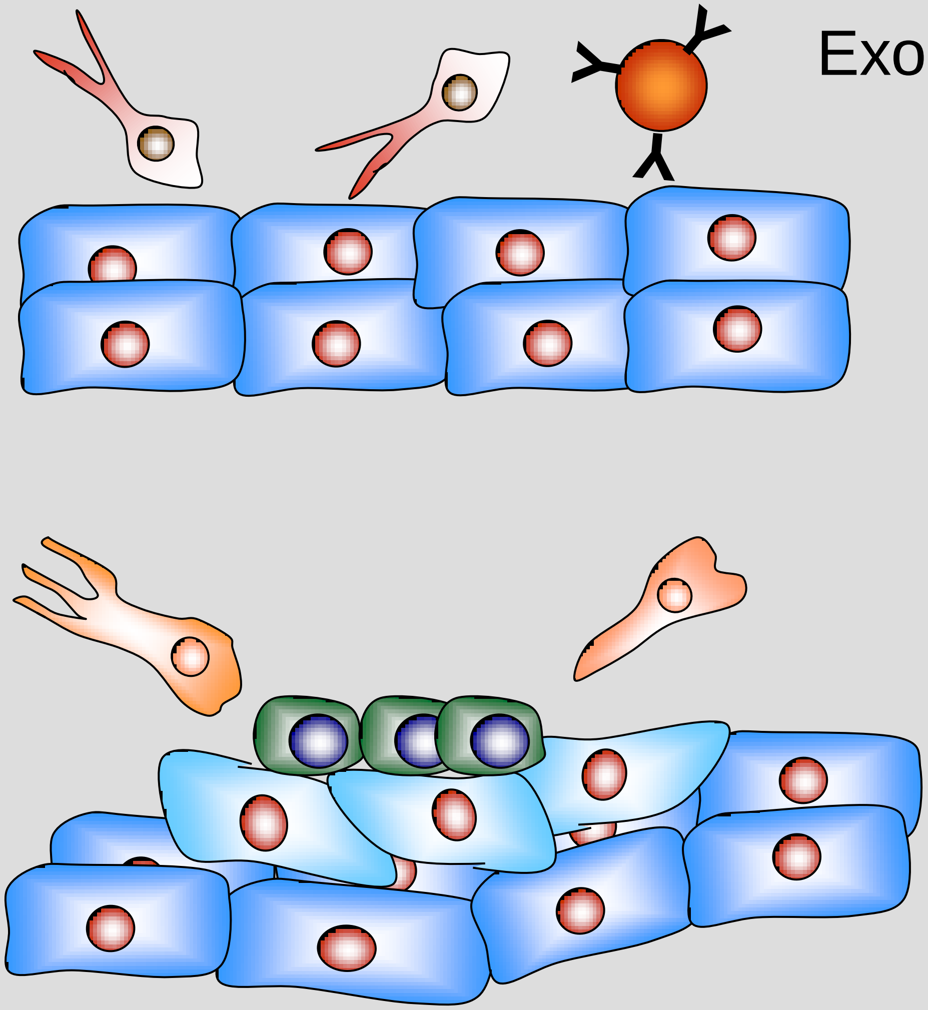
Collective Decisions and Collective Colonization



Selecting and Preparing the Niche

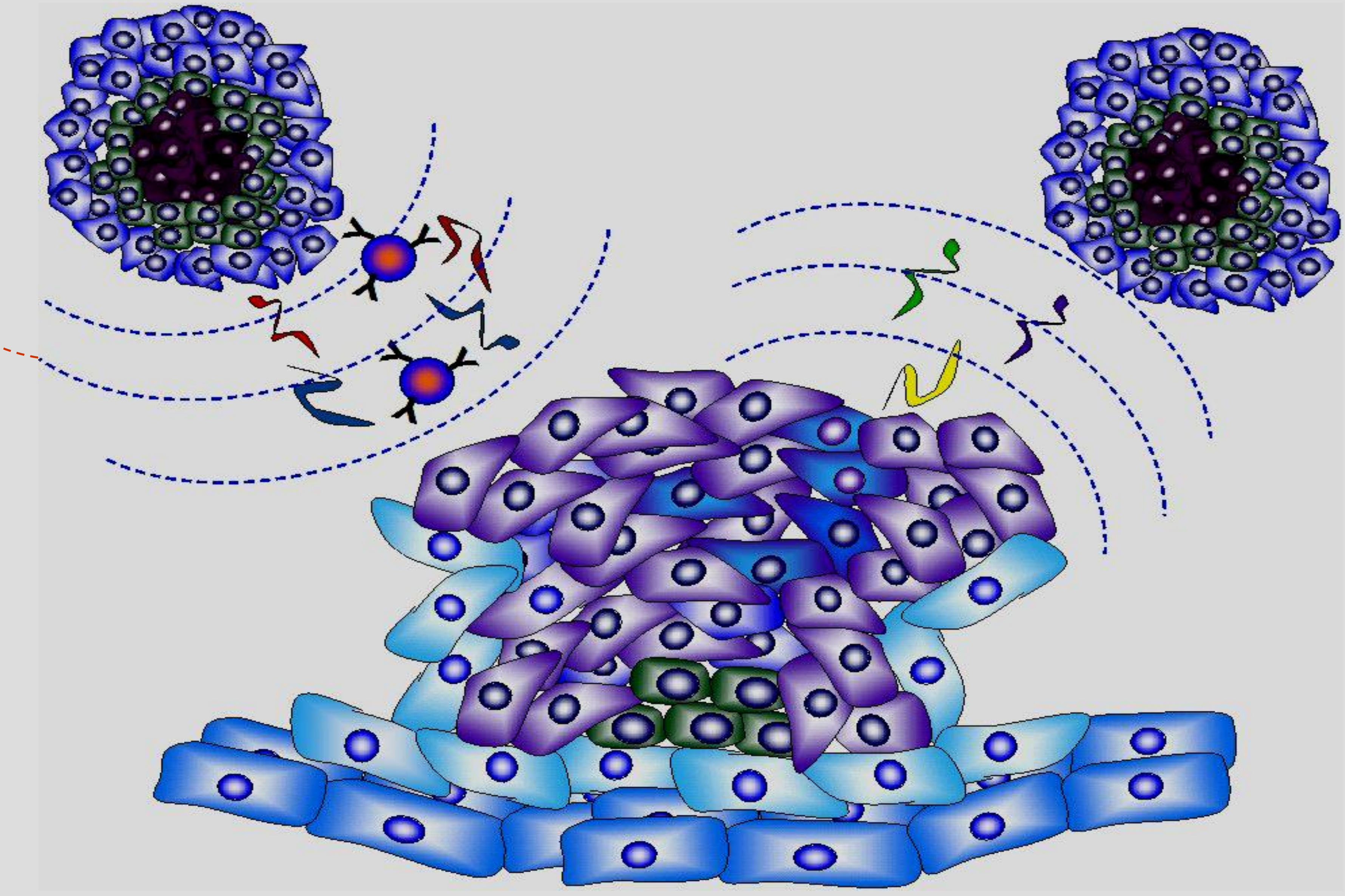
Spying Cells

Exosomes

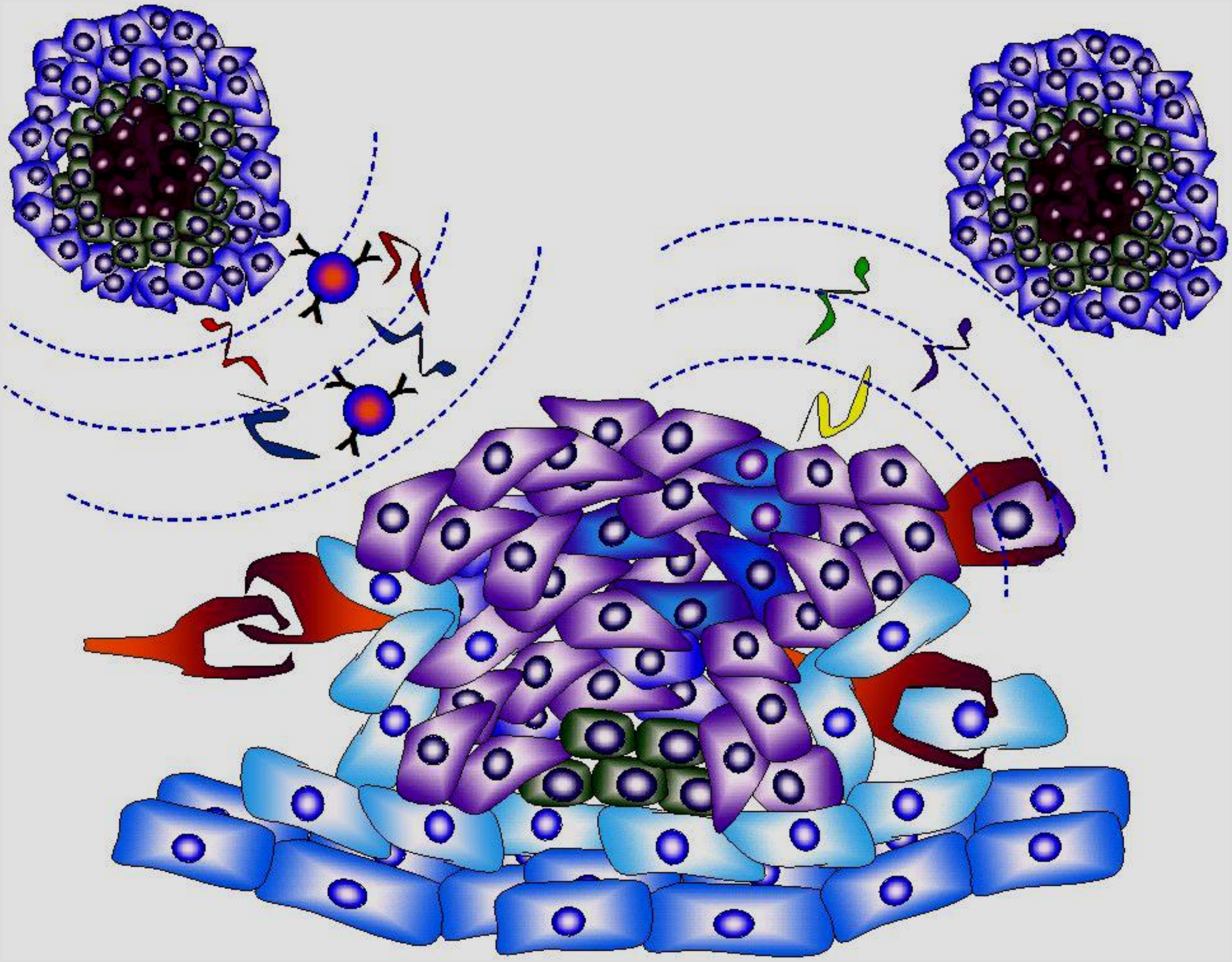


Kaplan et al Nature 2005

Germination of Micrometastases



Cancer Cannibalism



Fais et al Cancer Lett. 2007

A New Challenge: Deciding or Playing Dice

Looking for hints at the way bacteria decide fate

Gamblers should take a hint from bacteria

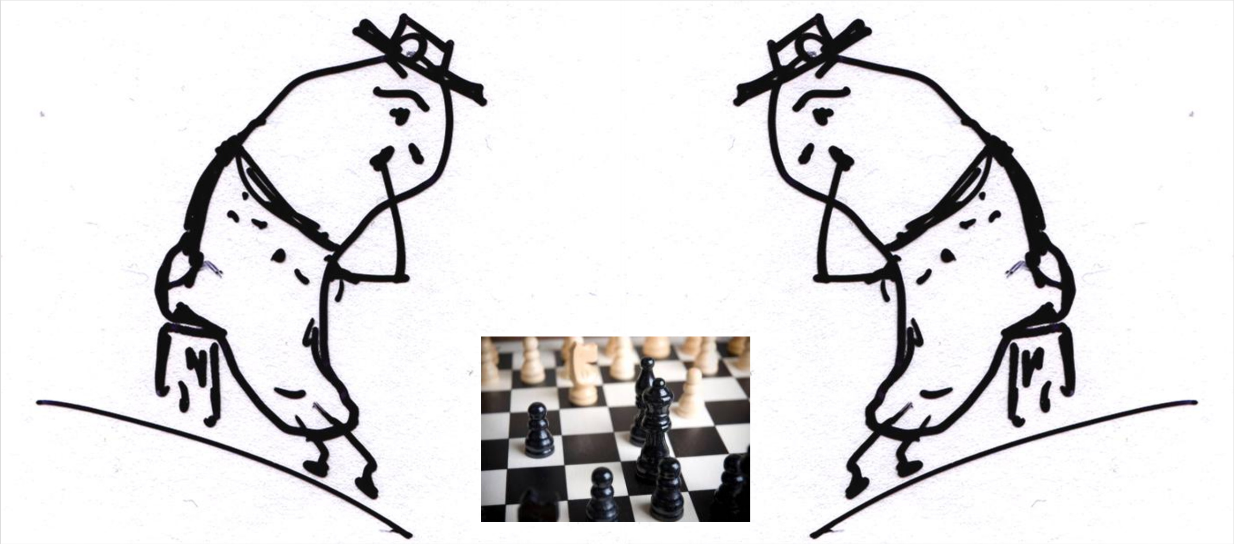
Forget that lucky charm

12 Oct 2010 17:11 | by Andrea Petrou | posted in Science

Part III

Bacterial Collective Decisions

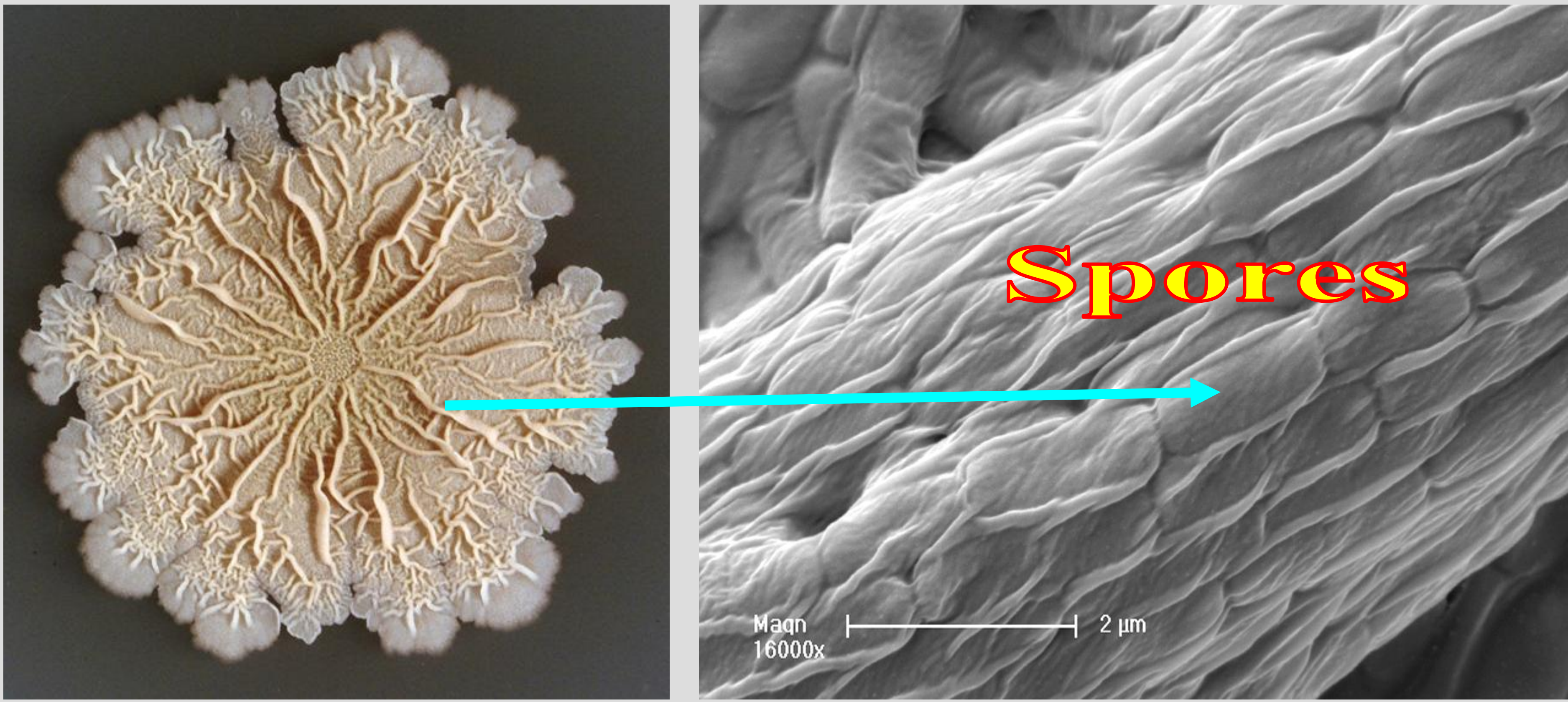
Bacterial Game Theory
During Phenotypic Transitions



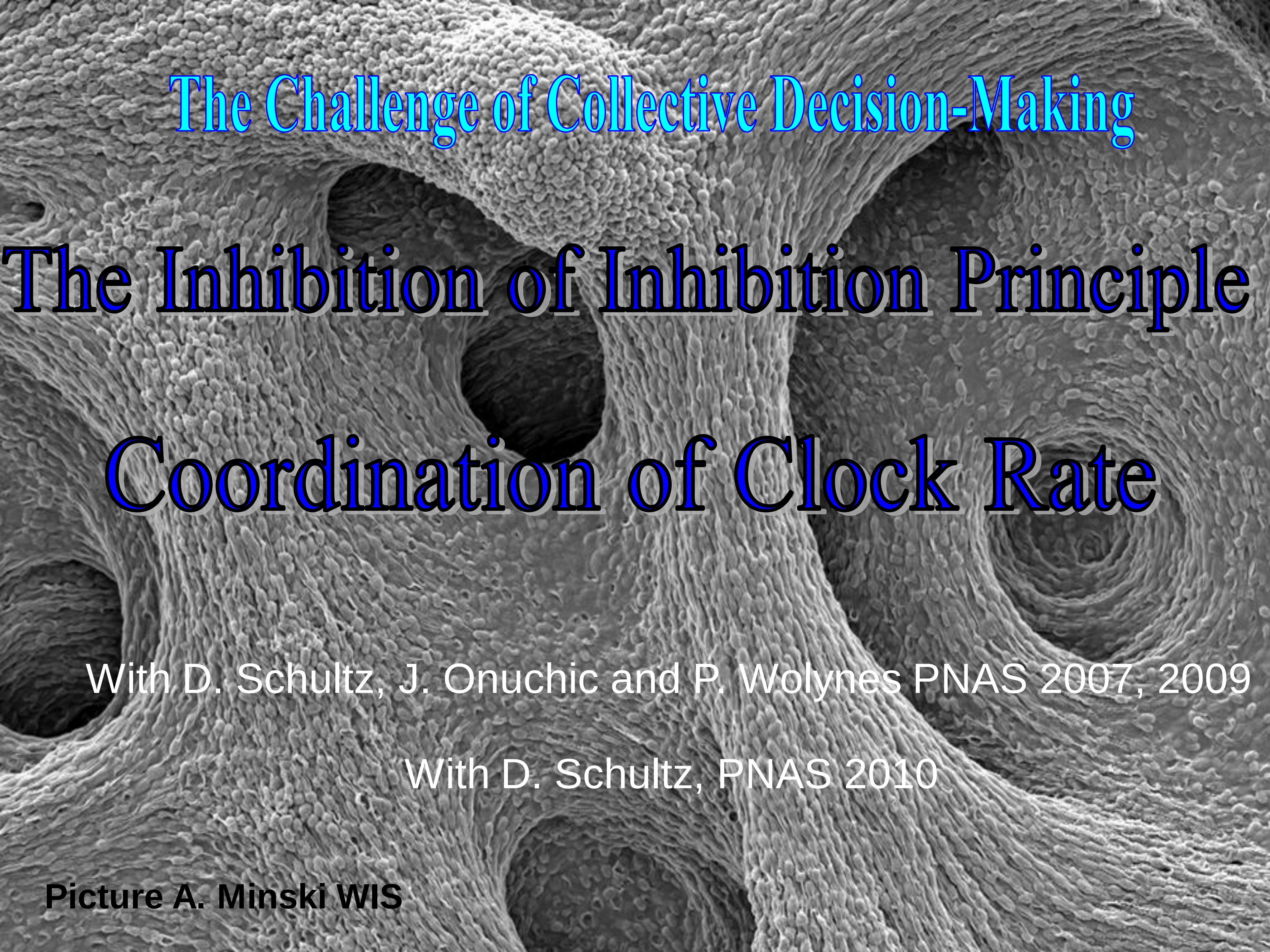
Schultz et al PNAS 2007, 2009, Ben-Jacob and Schultz PNAS 2010

To Be or Not To Be

Sporulation vs. Competence under starvation



Pictures Avi Minski Weizmann



The Challenge of Collective Decision-Making

The Inhibition of Inhibition Principle

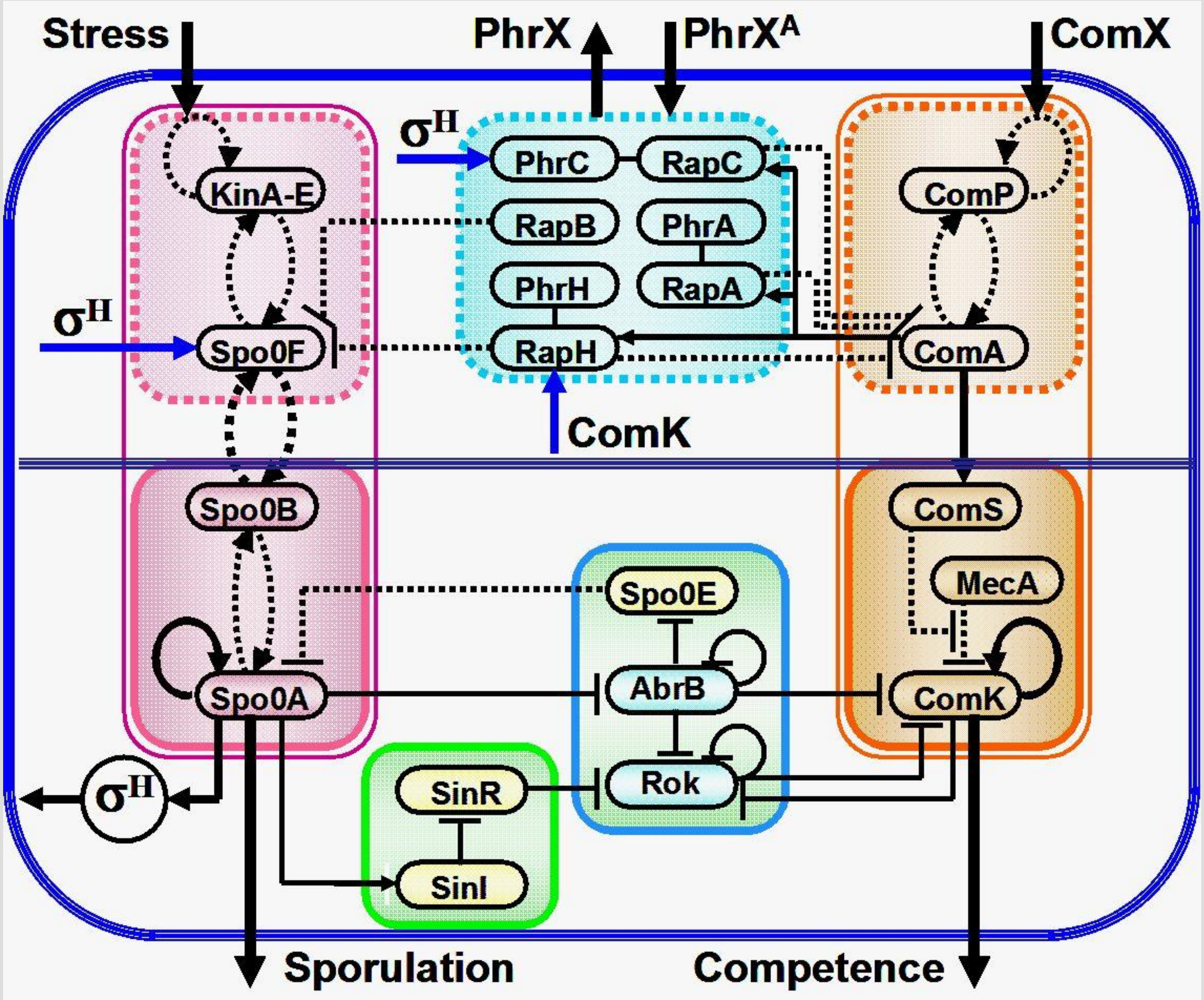
Coordination of Clock Rate

With D. Schultz, J. Onuchic and P. Wolynes PNAS 2007, 2009

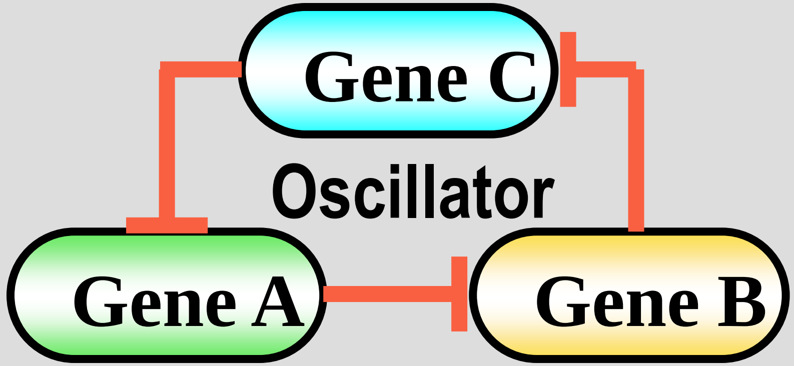
With D. Schultz, PNAS 2010

Picture A. Minski WIS

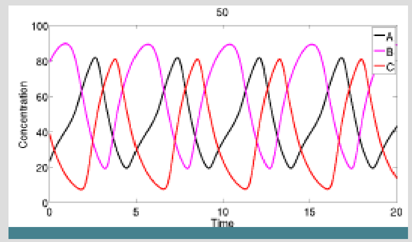
The Decision Network

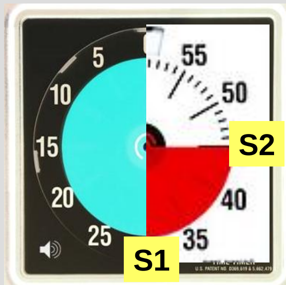


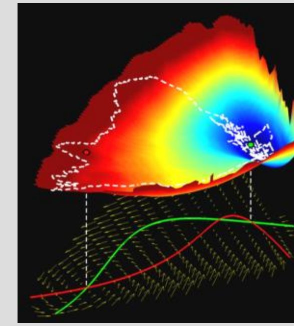
Let the complex be simple – looking for key elements



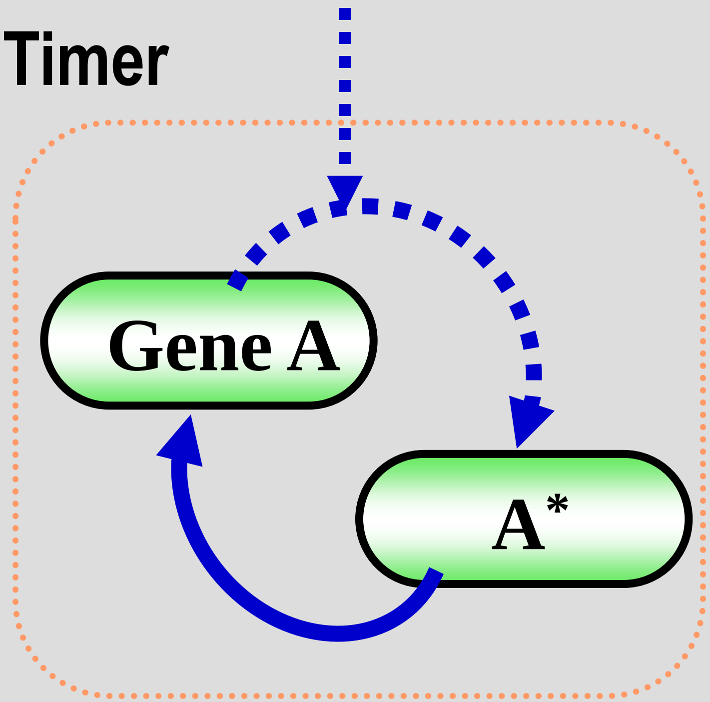
Oscillator



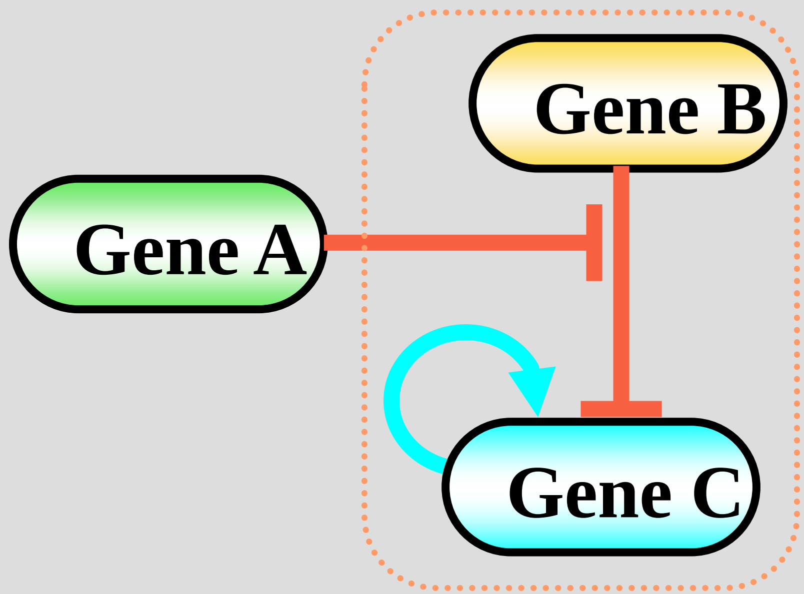




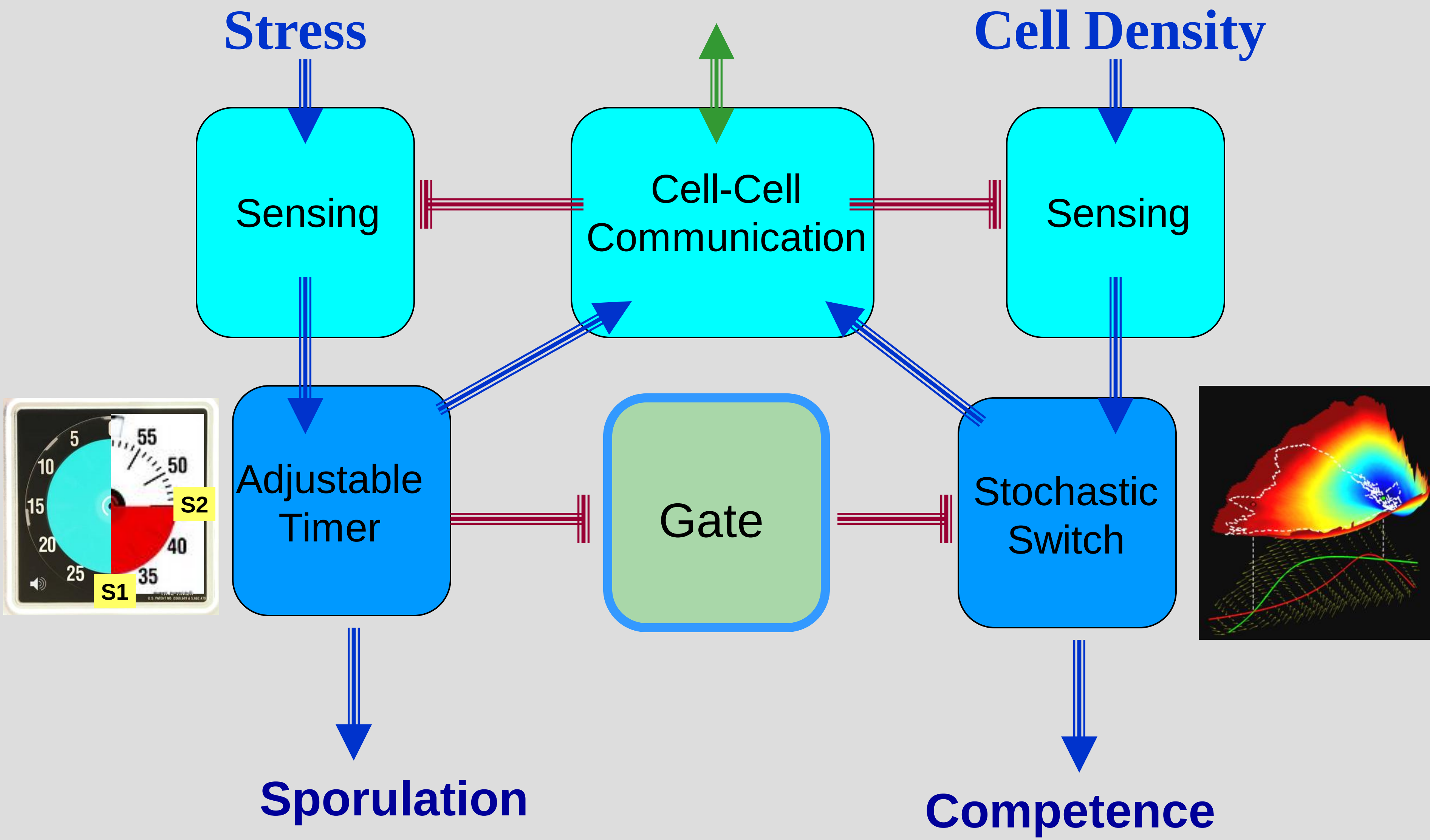
Timer



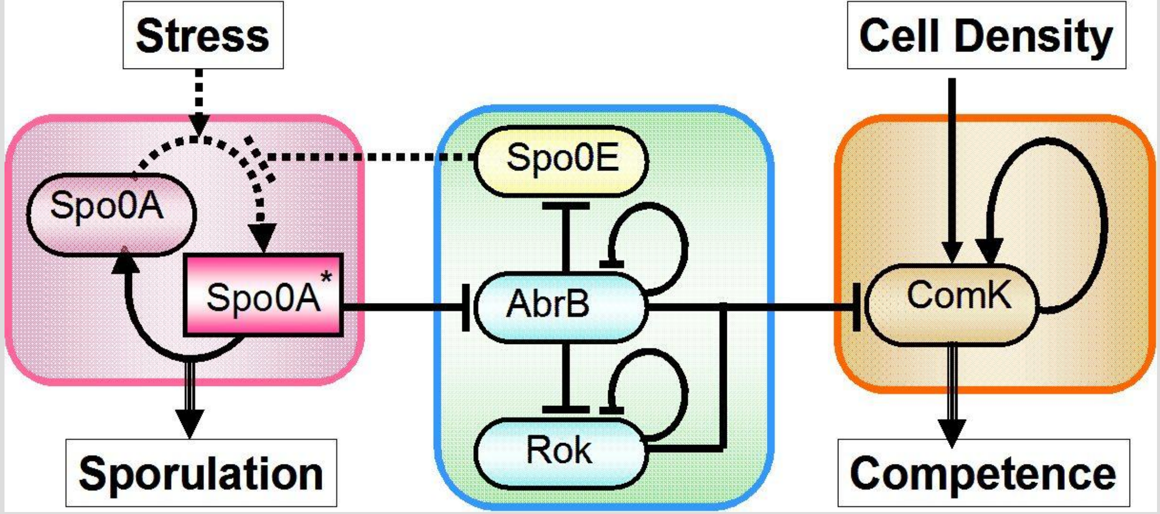
Stochastic Switch



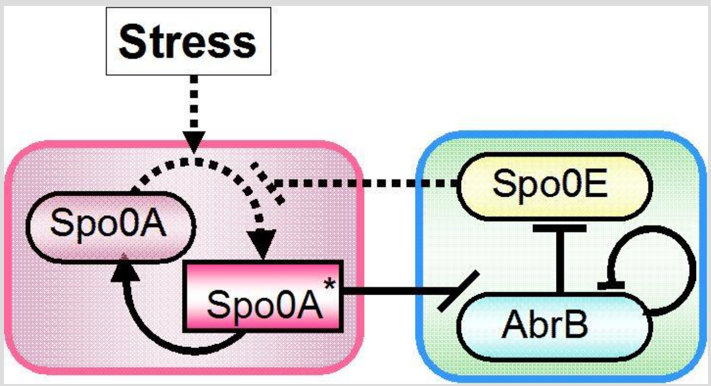
The Inhibition of Inhibition Principle

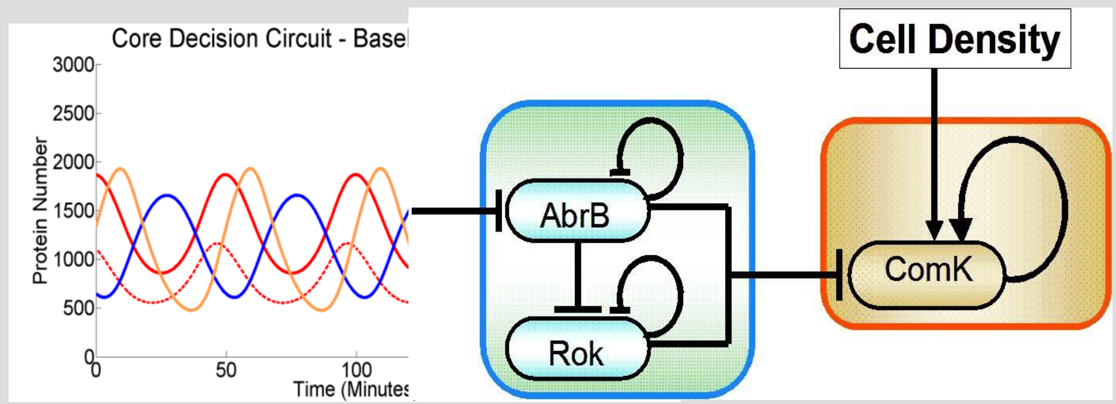


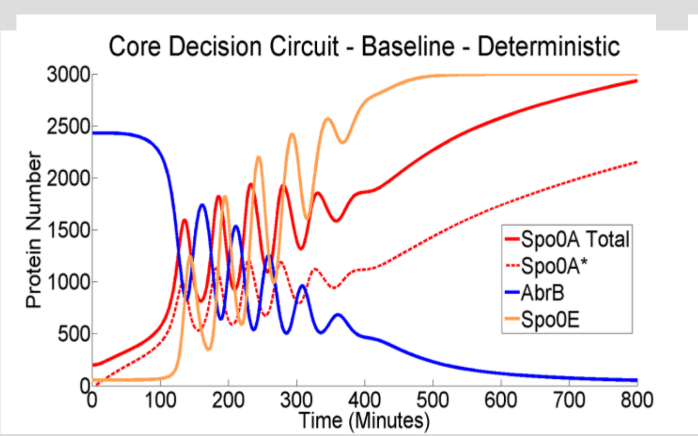
With
Trevor
Schultz
Onuchic
(unpublished)

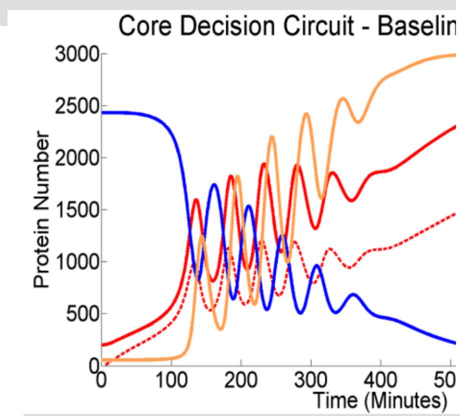


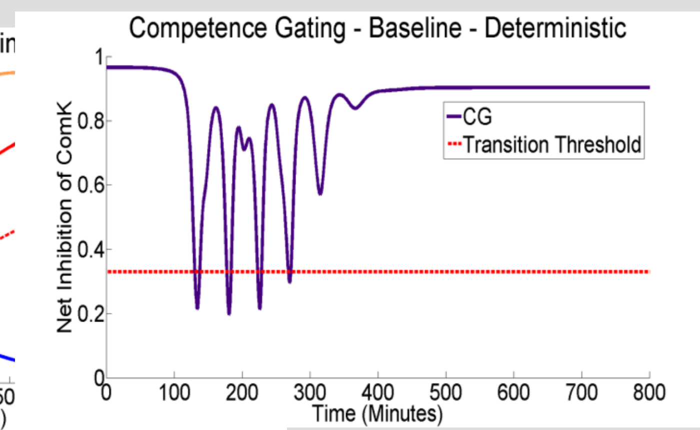
With
Trevor
Schultz
Onuchic
Süel
(RMP unpublished)

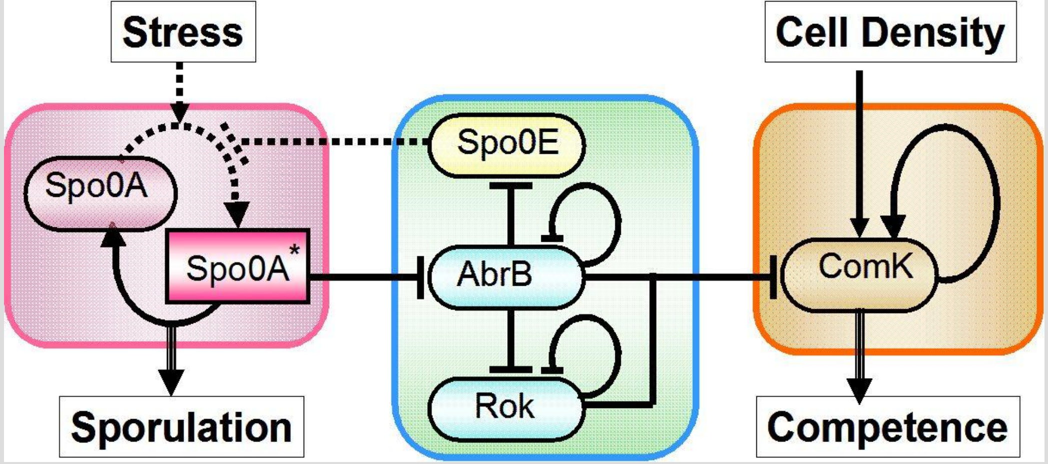


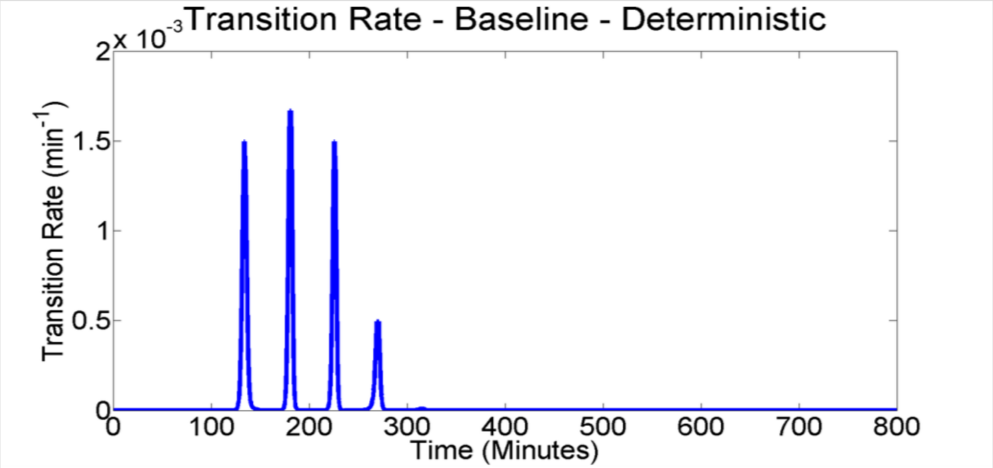


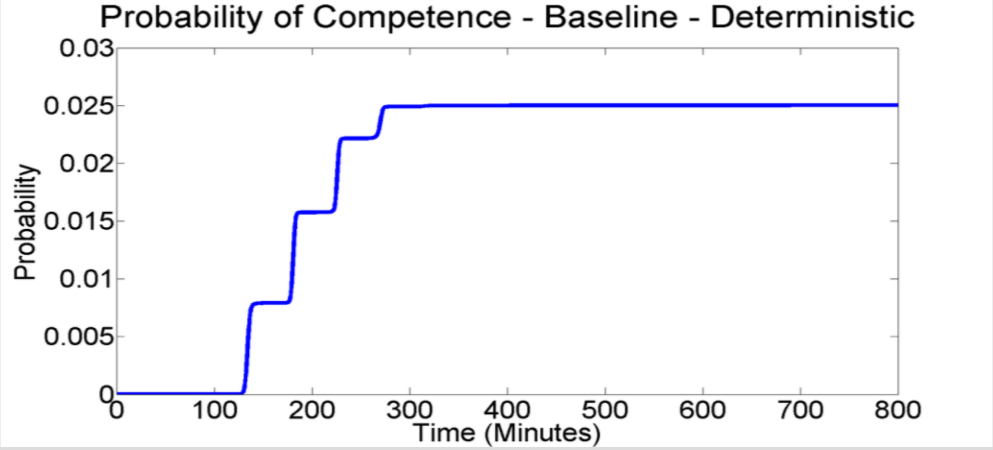




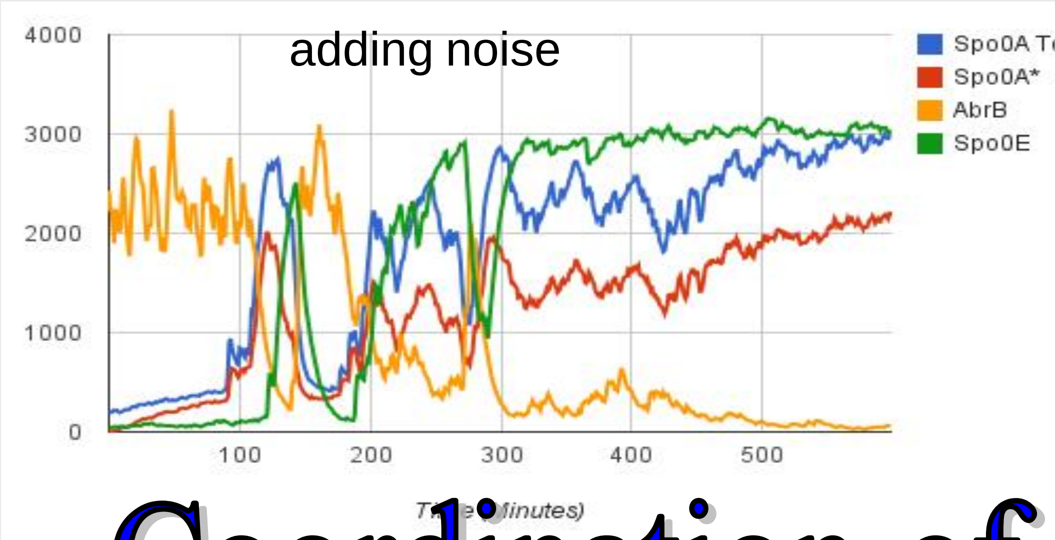


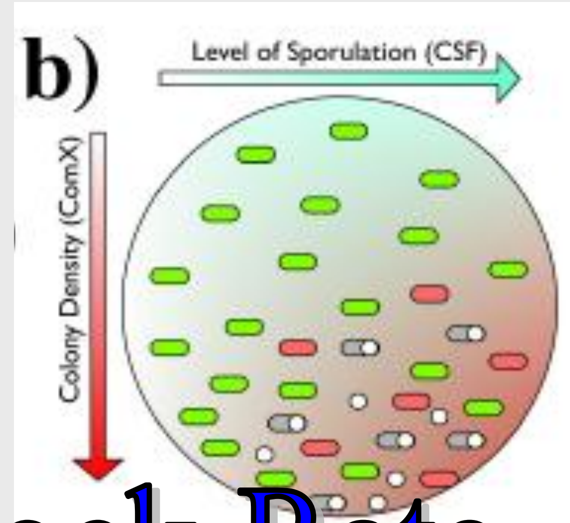

Stress
Cell Density
Spo0E
Spo0A
Spo0A*
AbrB
ComK
Rok
Sporulation
Competence


Transition Rate - Baseline - Deterministic
x 10-3
Transition Rate (min-1)
2
1.5
1
0.5
0
0
100
200
300
400
500
600
700
800
Time (Minutes)

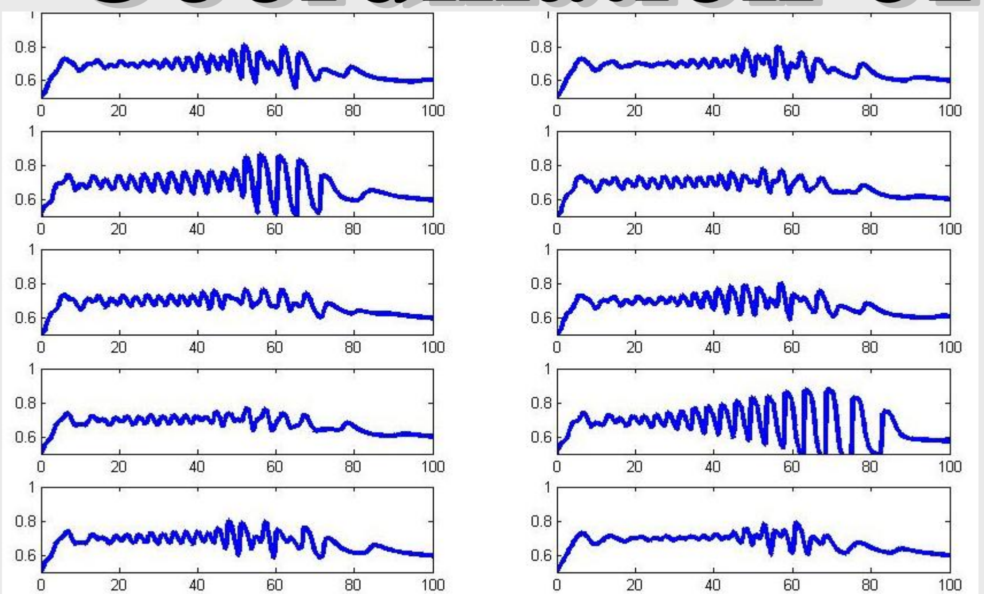

Probability of Competence - Baseline - Deterministic
Probability
0.03
0.025
0.02
0.015
0.01
0.005
0
0
100
200
300
400
500
600
700
800
Time (Minutes)

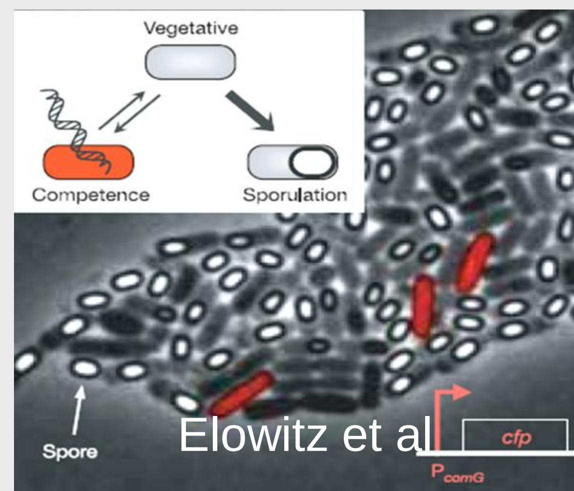
Comparison with experiments



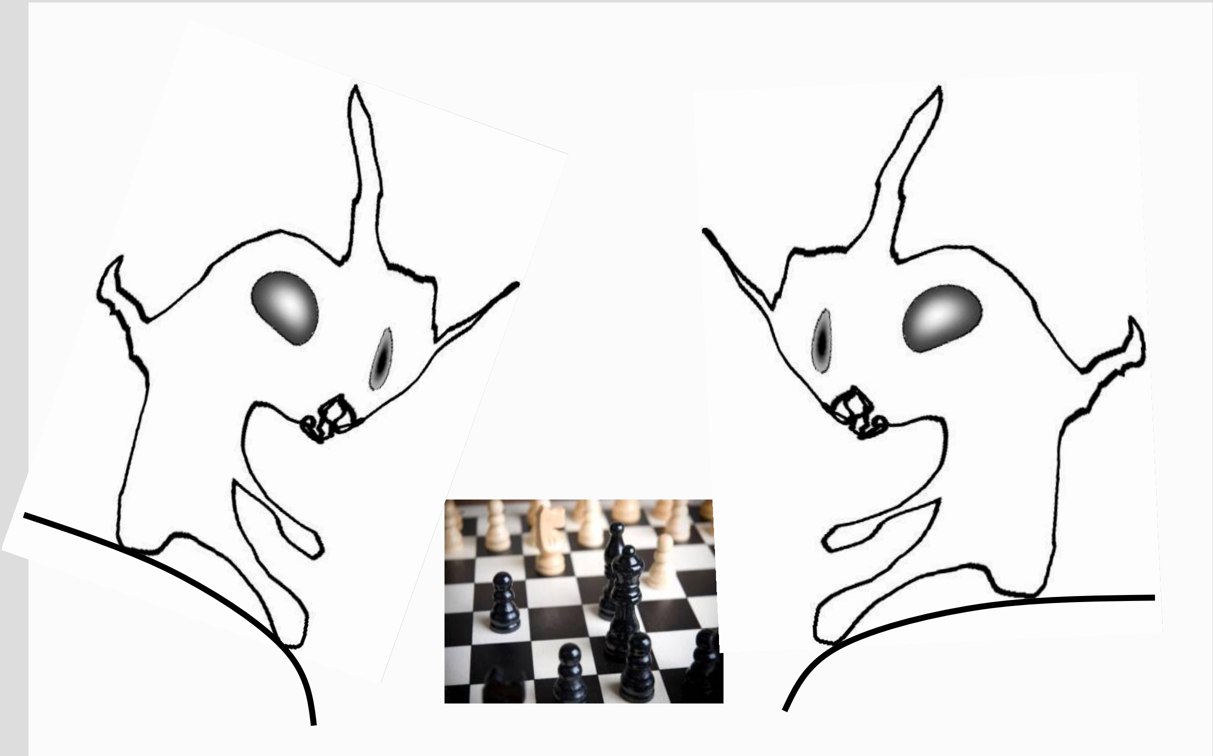


Coordination of Clock Rate





Back to cancer decisions during colonization



Part IV

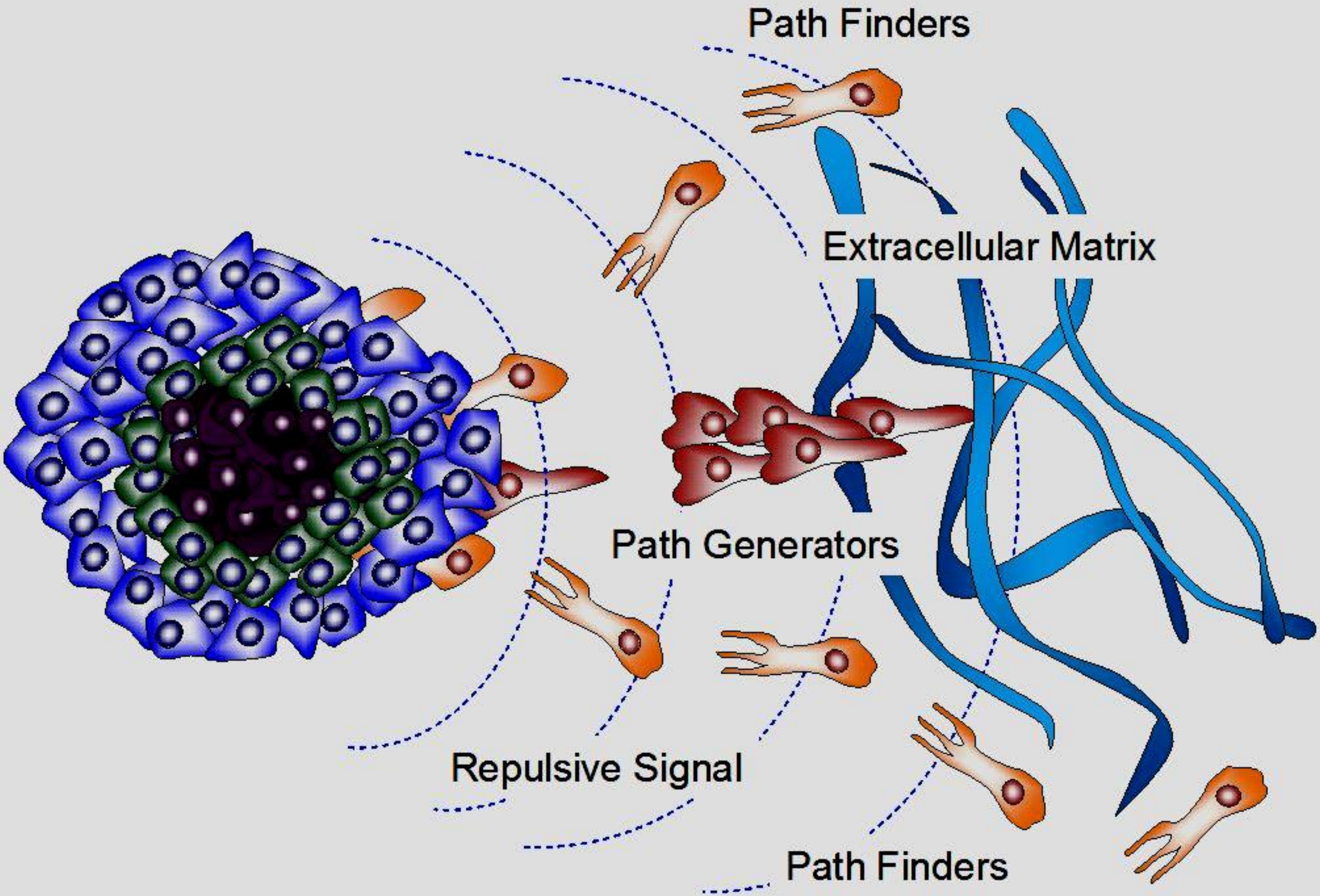
From Single Cell Motility

Last week
Sander – ECM assisted motility ; Wirtz – 3D vs 2D ;
Levine –Dicty and Amoeboid motility + Chemotaxis

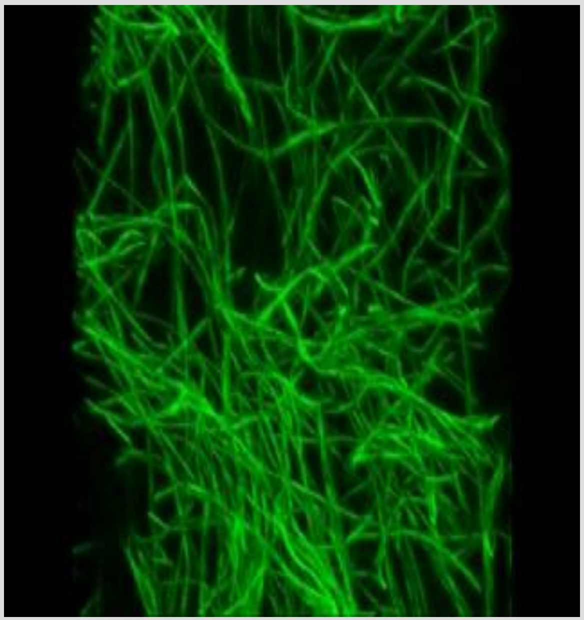
To Navigation
Proliferation vs. Invasion
Collective Navigation

With, Inbal Hecht, Assaf Zaritsky, Ilan Tsarfaty
Noam Cayron, Lior Wolf, Herbert Levine

Cancer Navigation Strategies

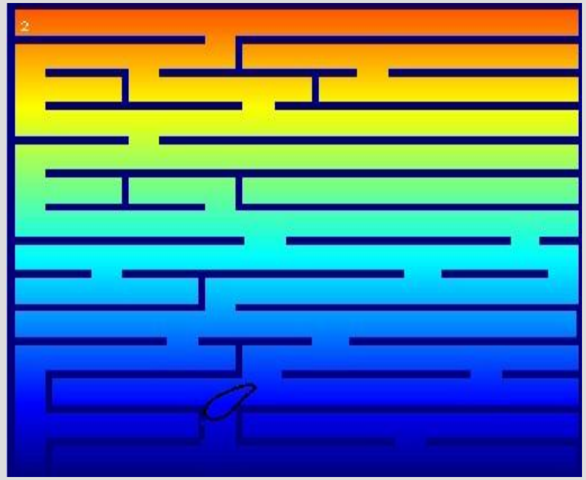


The ECM as a Maze

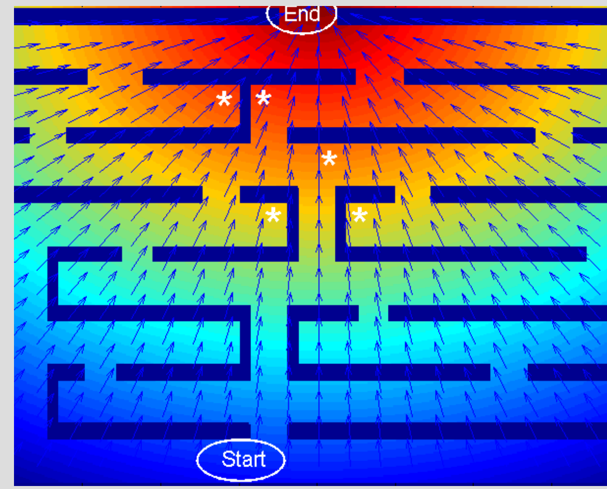


Collagen Mesh
(Len sander Lecture)

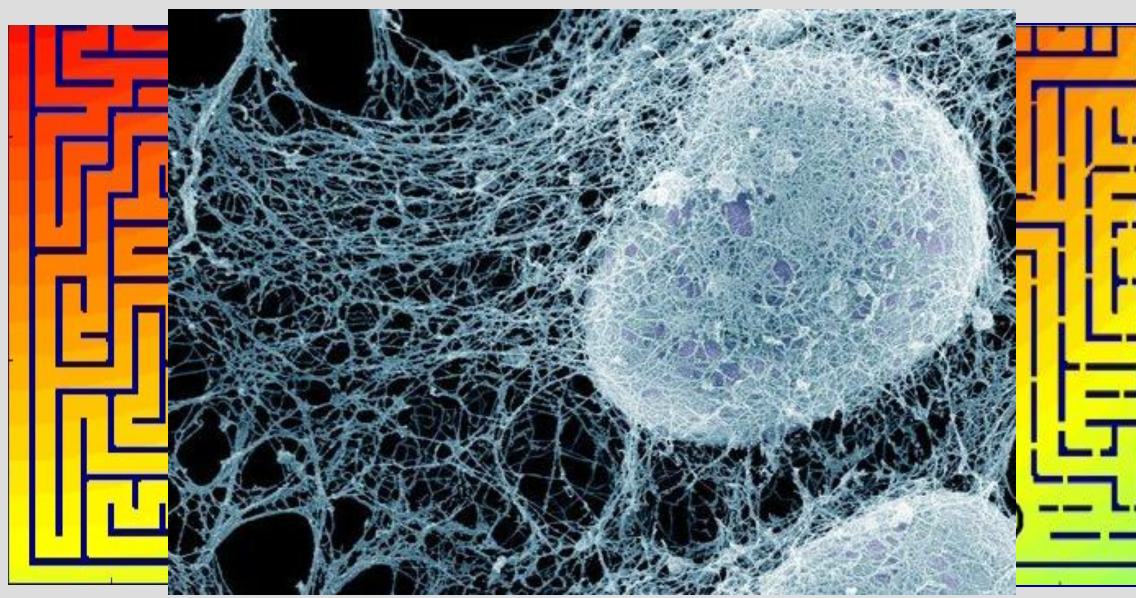
Chemical signaling



Attractive – from blood vessels

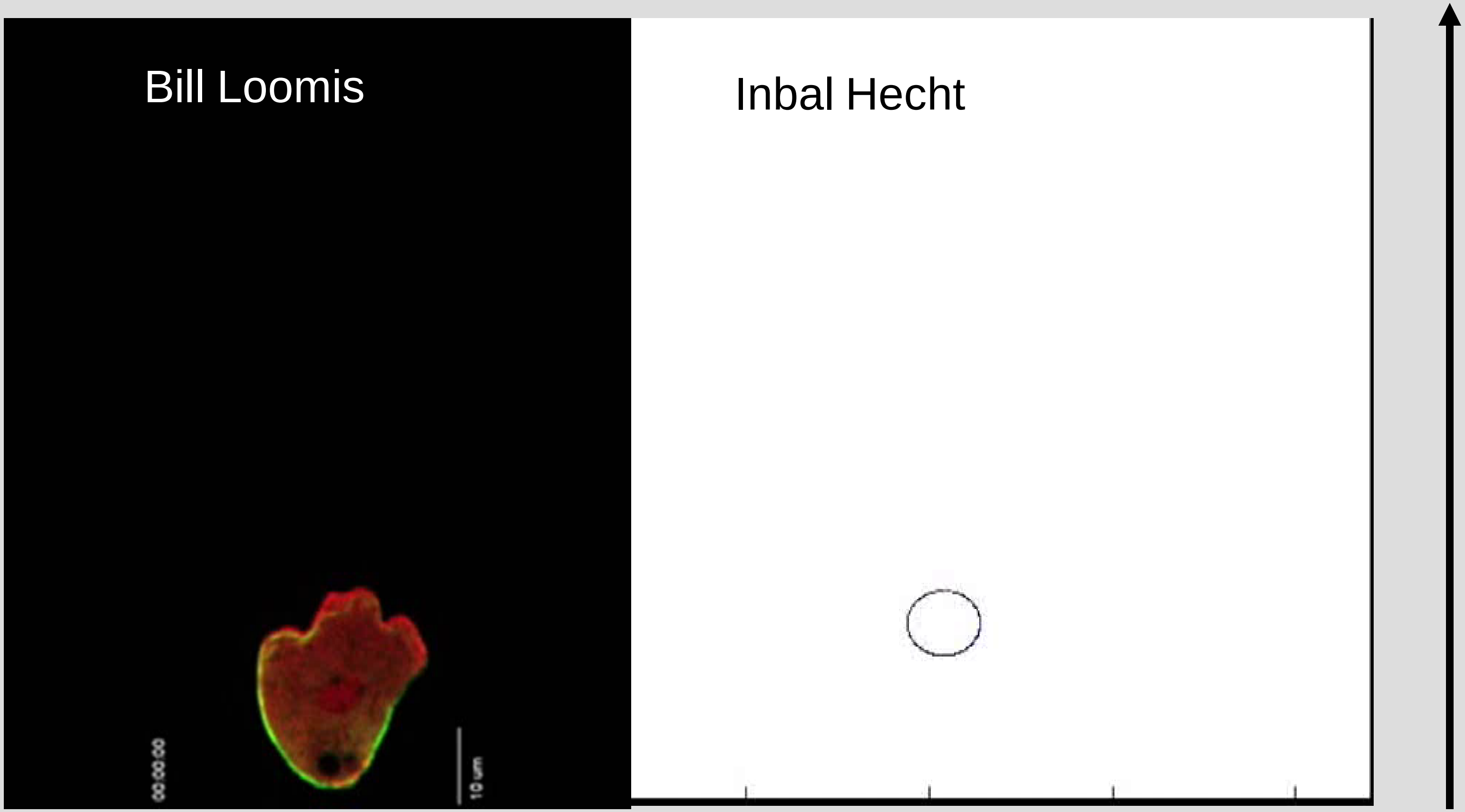


Repulsive – from the Tumor



Single Cell Motility - Amoeboid

(Dicty as a model for amoeboid motility)

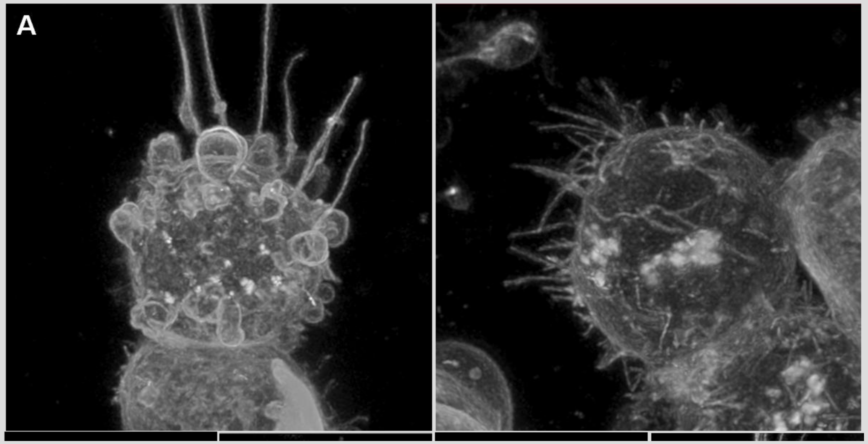


(Details - Levine lecture last week)

Chemical Gradient

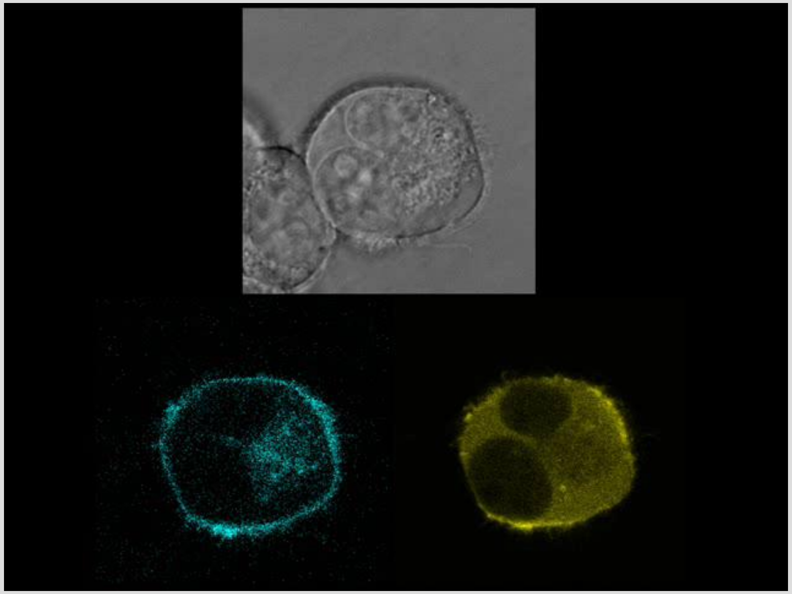
Hecht et al PLoS Comp Bio (2011)

Single Cell Motility – Blebbing



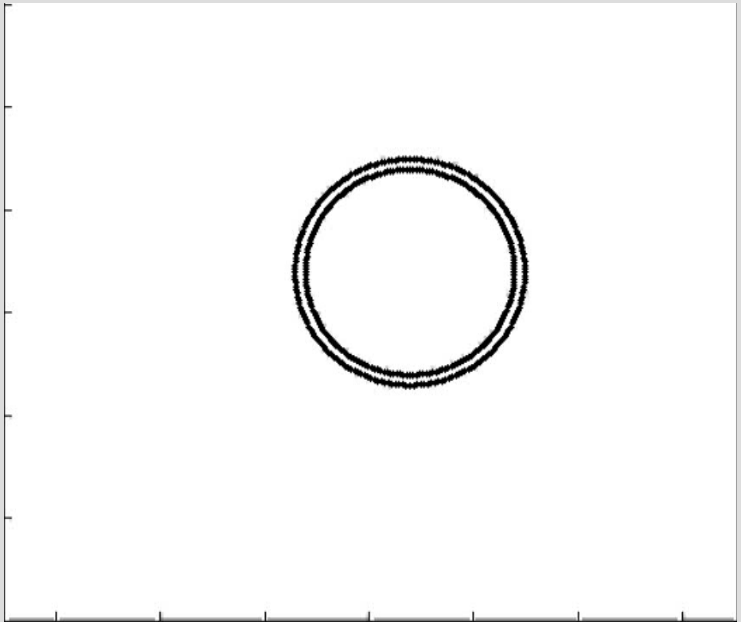
Met induced blebbing

Tsarfaty Group Unpublished



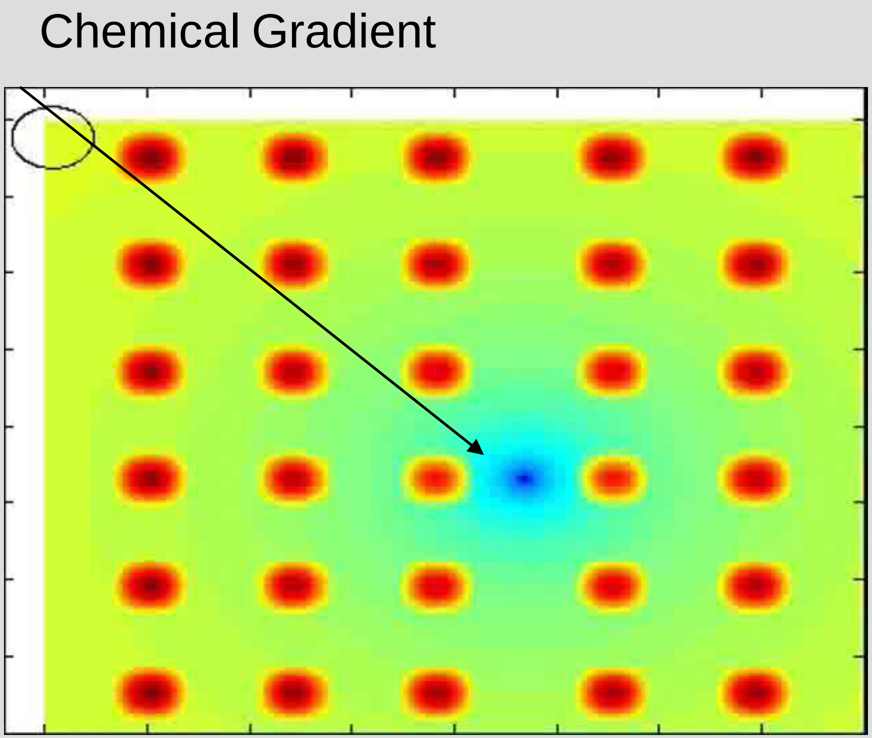
CFP - Met YFP - actin

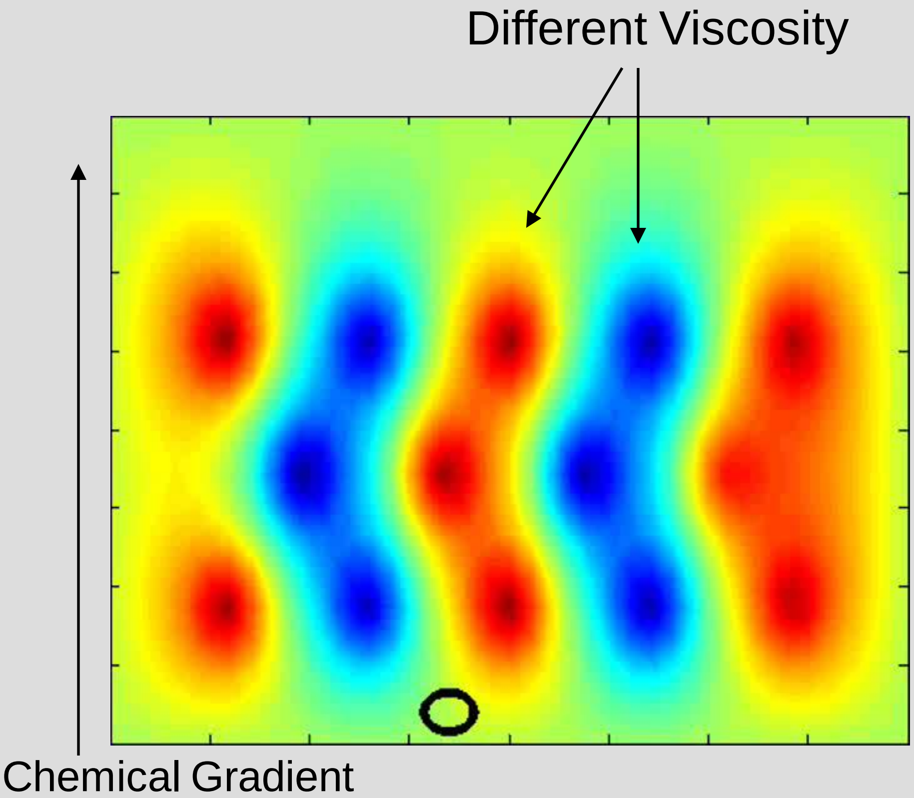
Reconnecting the cortex and membrane by stochastic dynamics
Membrane wrinkles are formed during retraction



With Inbal Hecht and Ilan Tsarfaty

Navigation in Complex Terrains





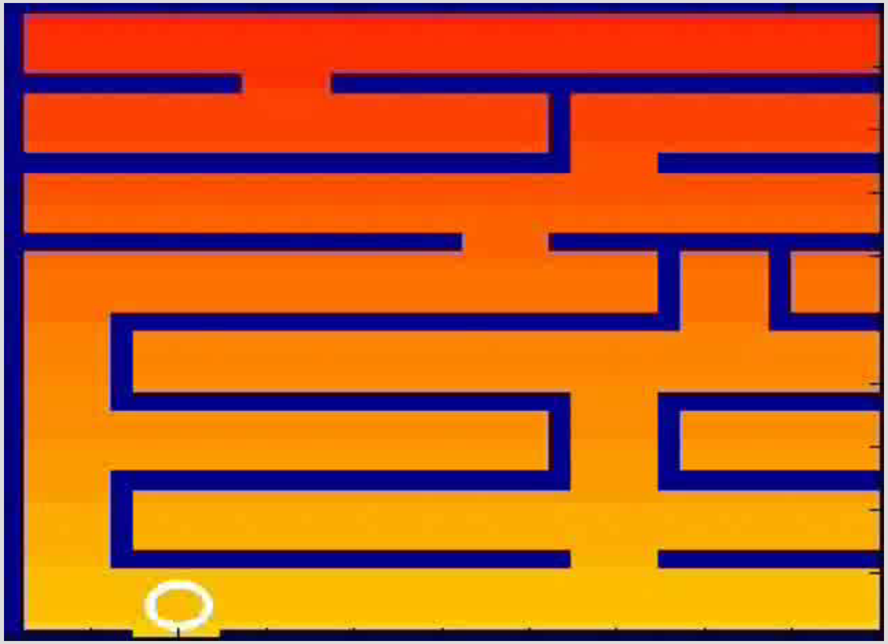
Possible implications to breast cancer

With Hecht and Tsarfaty

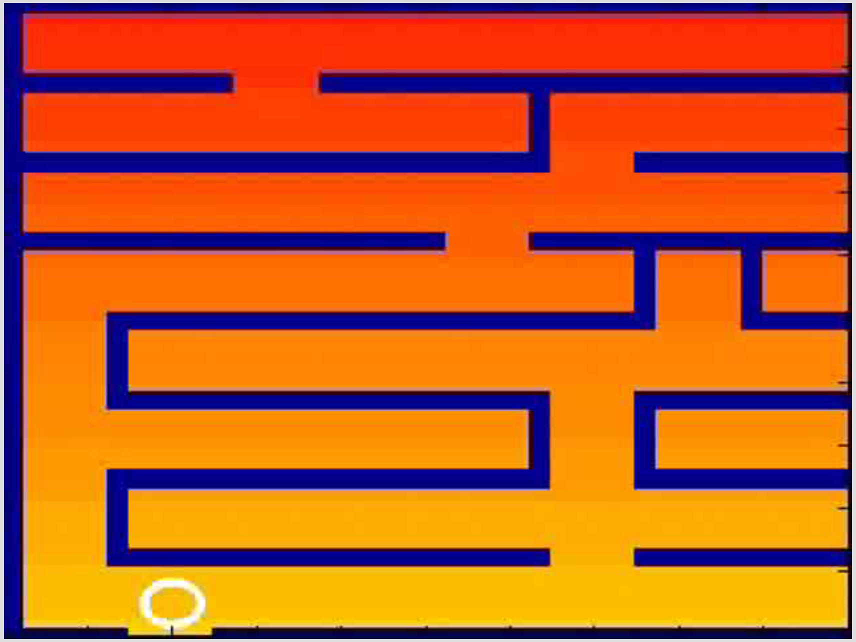
Self-Assisted Navigation

Prediction to be Tested

Escaping traps by secretion of repulsive agent



Trapped

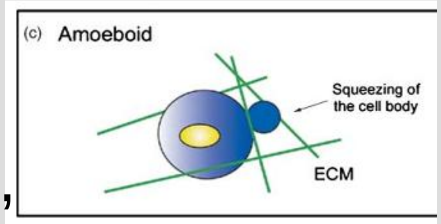


Escaping

With Inbal Hecht, Herbert Levine, Wouter-Jan Rappel, PLoS ONE 2011

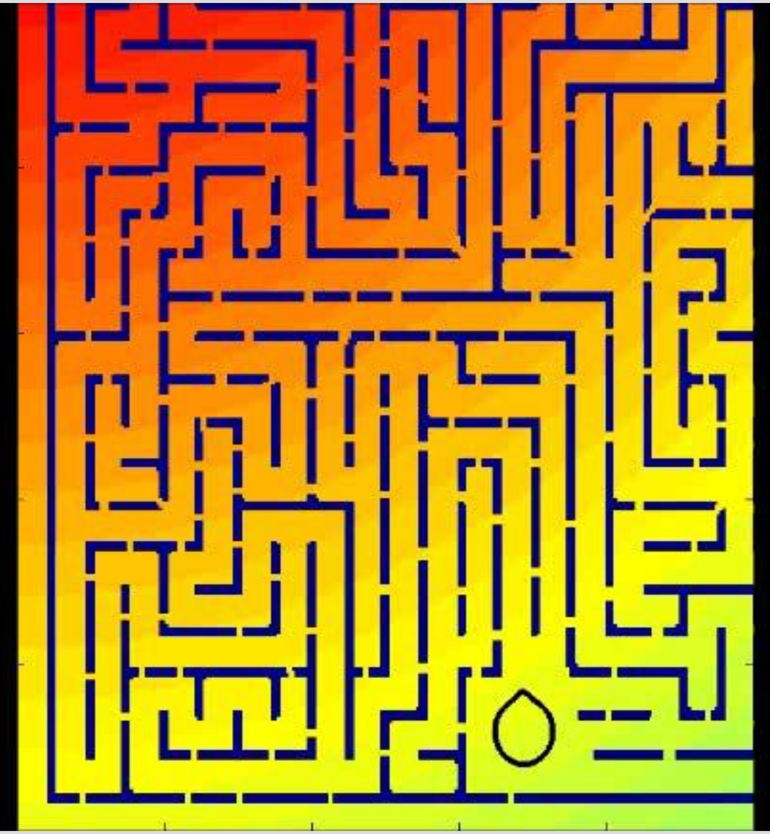
Amoeboid -Path finder

Fast, flexible,

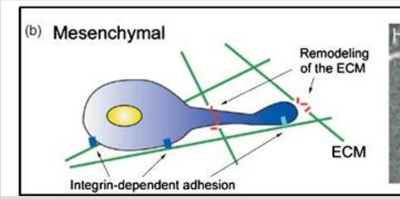


squeezes through small gaps

Mesenchymal - Path generator

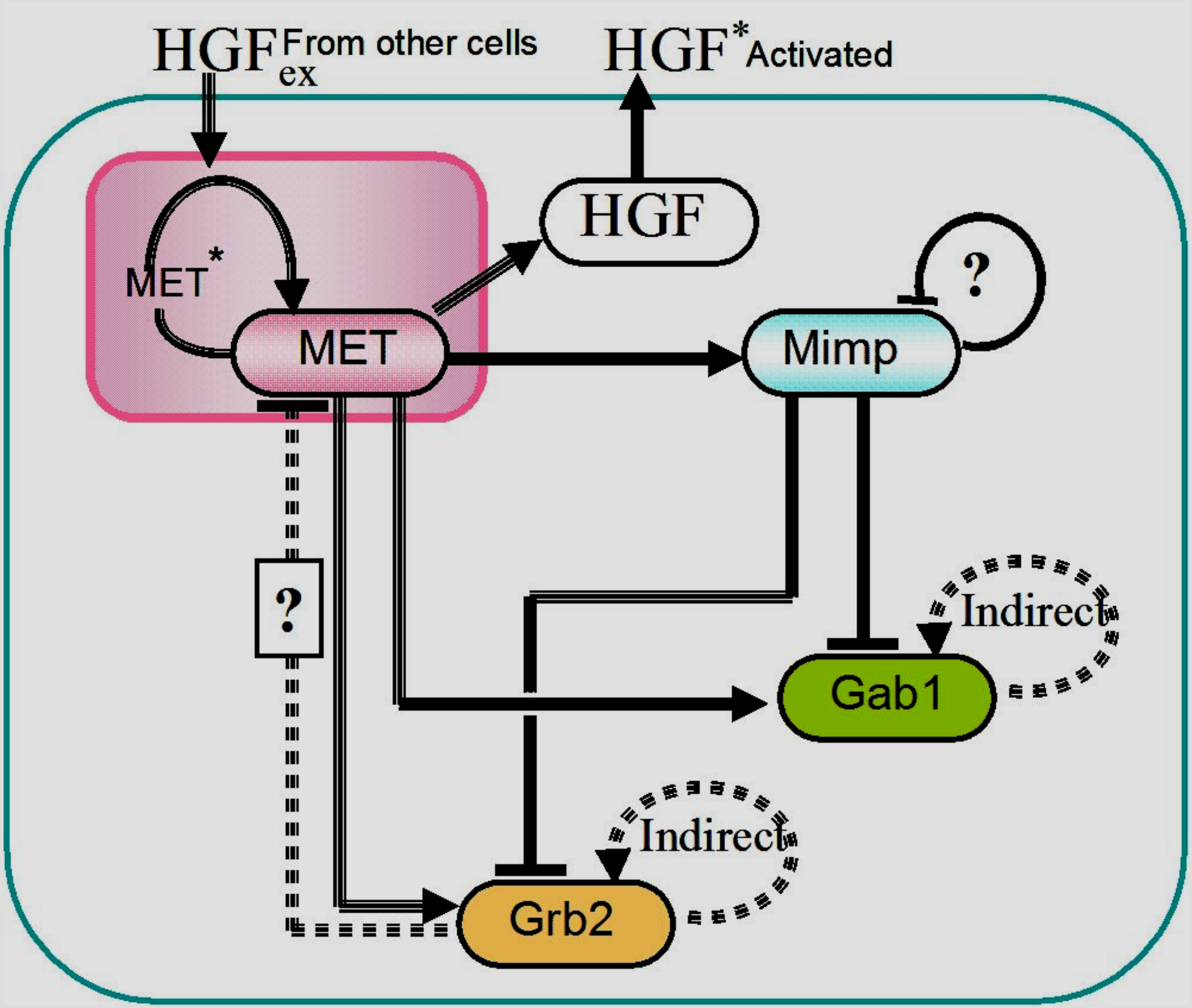


Slow, rigid,

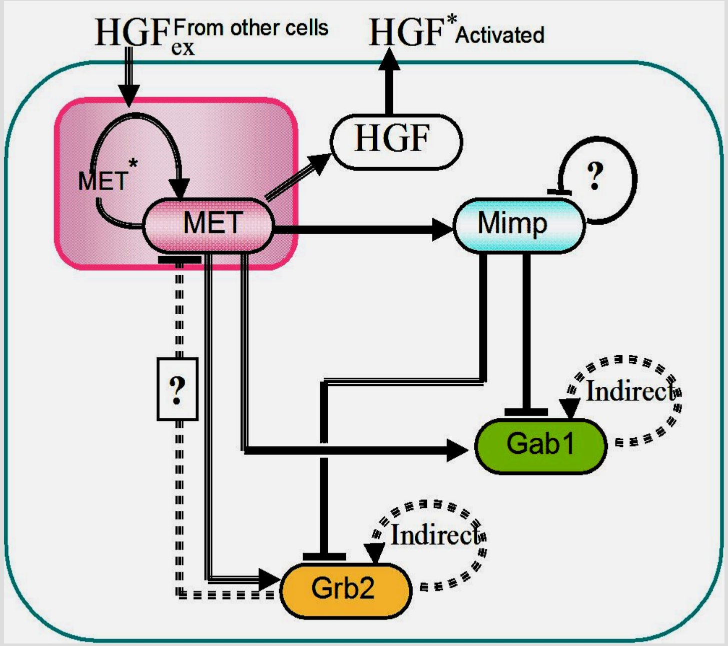


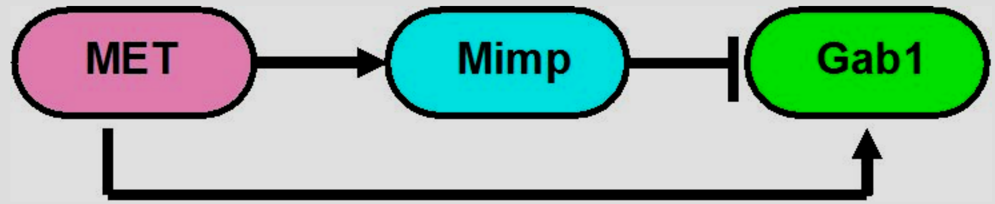
degrades the wall

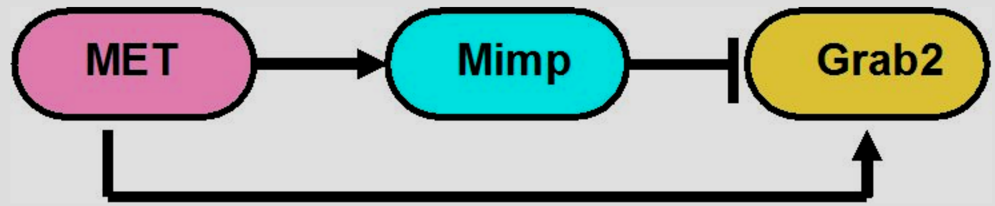
Example of a Cancer Decision Circuit

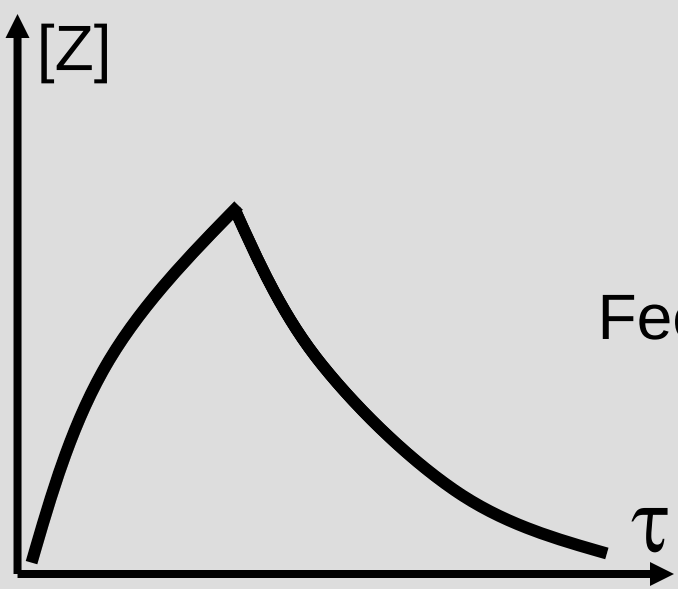


With Ilan Tsarfati (TAU), Jose’ Onuchic and Herbert Levine (Rice)

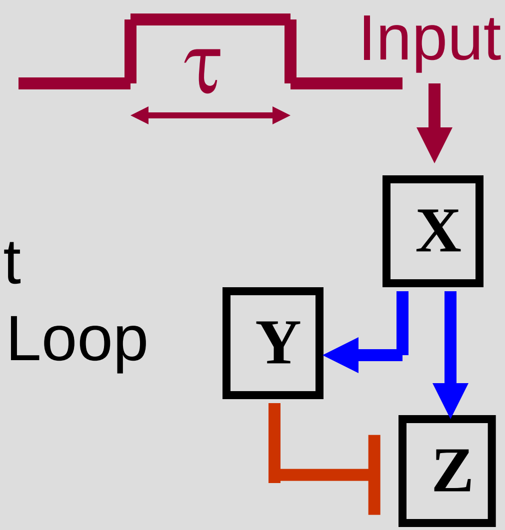






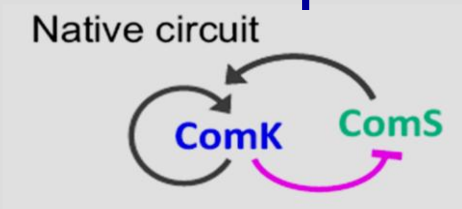


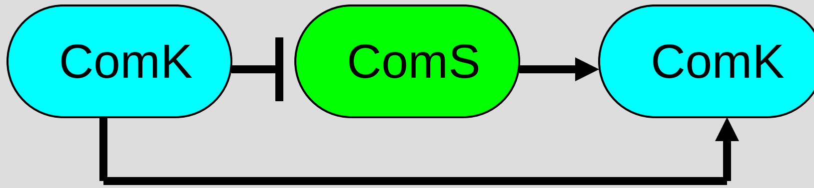
Incoherent
Feed Forward Loop



Learning from Bacteria Decisions

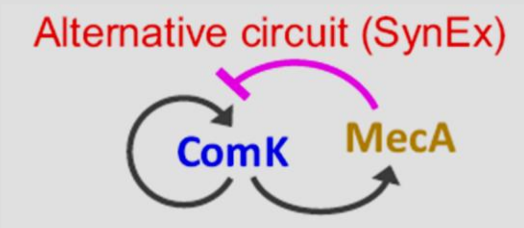
Competence switch as an Incoherent Feed Forward Loop

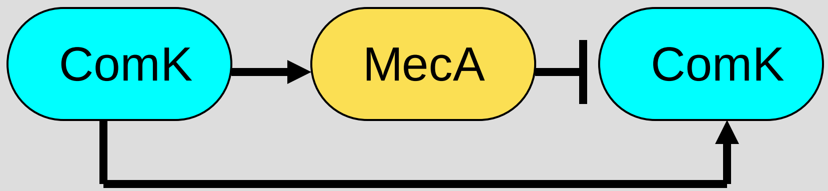




Rare transitions

Süel et al *Cell* 2009

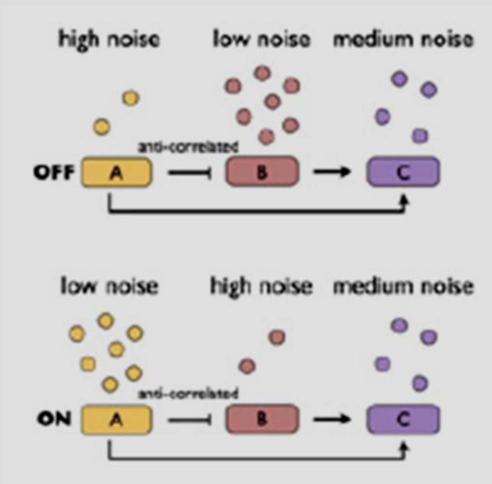




Frequent transitions

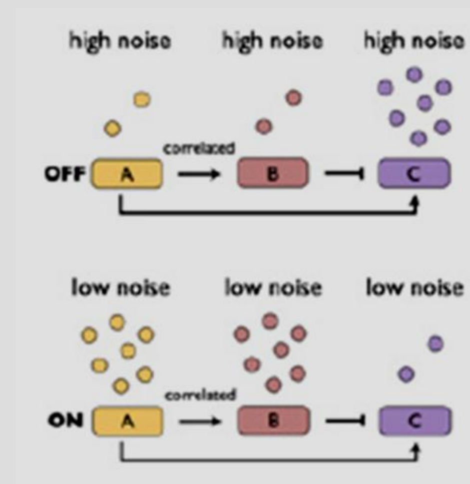
Circuit architecture and noise effect

Süel et al *PNAS* 2010



Used for rare events

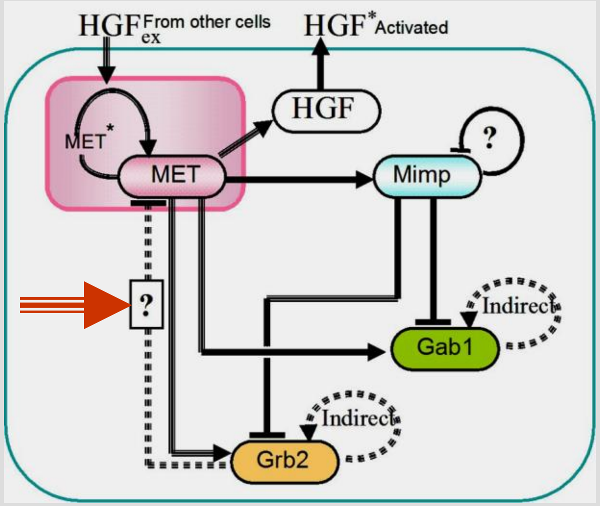
Used for frequent events



“Bacteria play dice with controlled odds”

Ben-Jacob and Schultz *PNAS* 2010

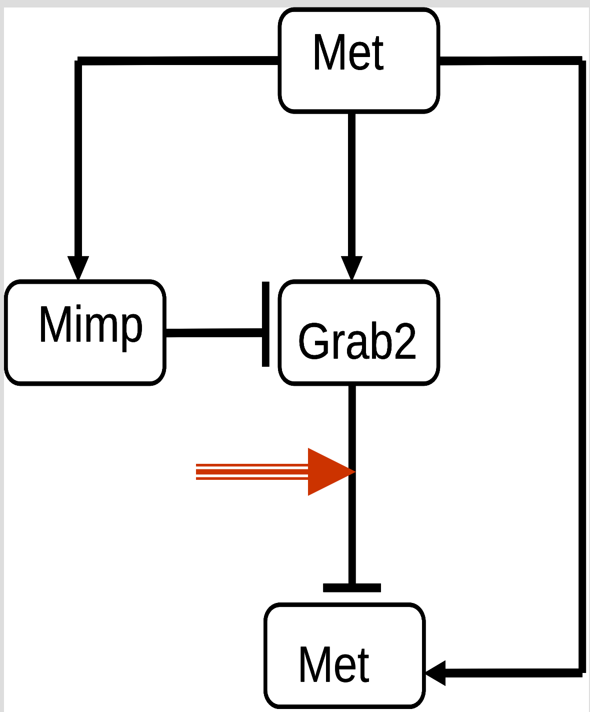
”Games” of Incoherent FFL

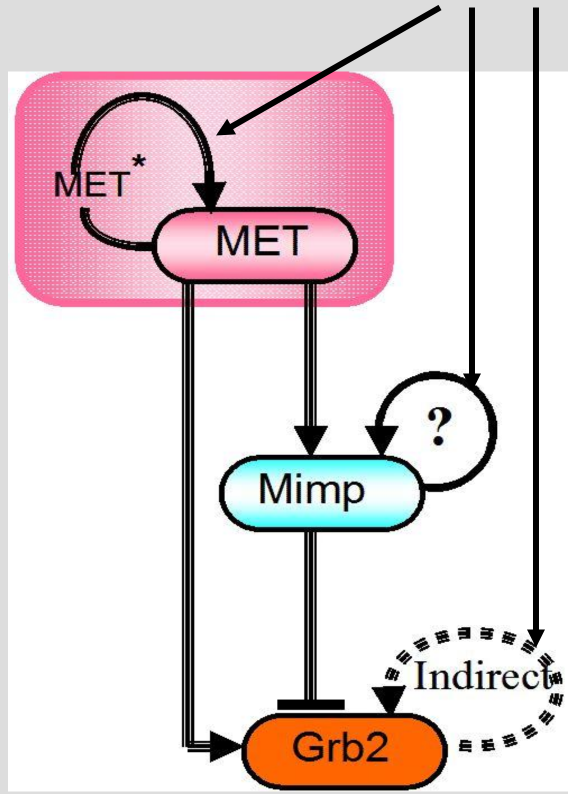


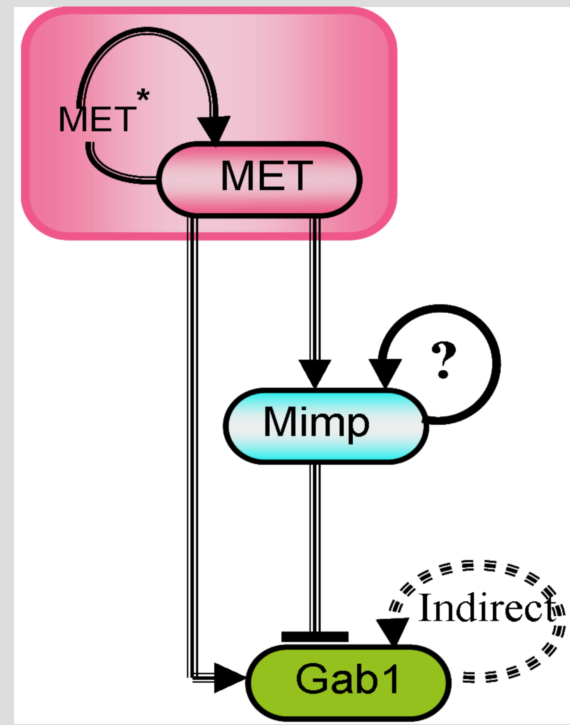
Work in progress

With Ilan Tsarfati (TAU), Jose’ Onuchic and Herbert Levine (Rice)

The additional elements control the noise effect





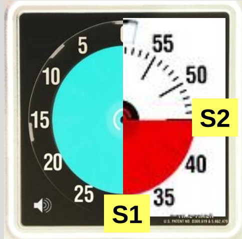


A Step Towards Multicellularity

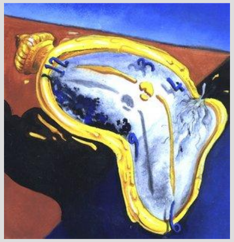
Invasion vs. Proliferation

Inclusion of metabolism:

Internal Energy E_{int} and Internal Clock Ω_{int}



Ω_{int} Depends on E_{int}



dE_{int}/dt - Depends on energy absorbed, motility rate and secretion of degrading enzymes

Proliferation requires E_{thr} and cost ΔE_{int}

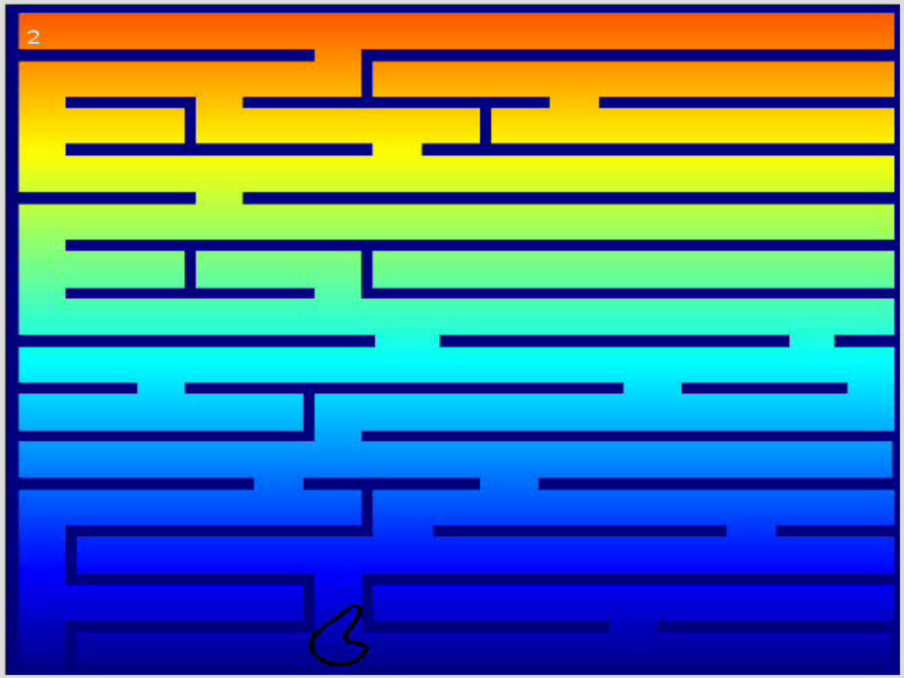
Probability of cell death depends on E_{int}

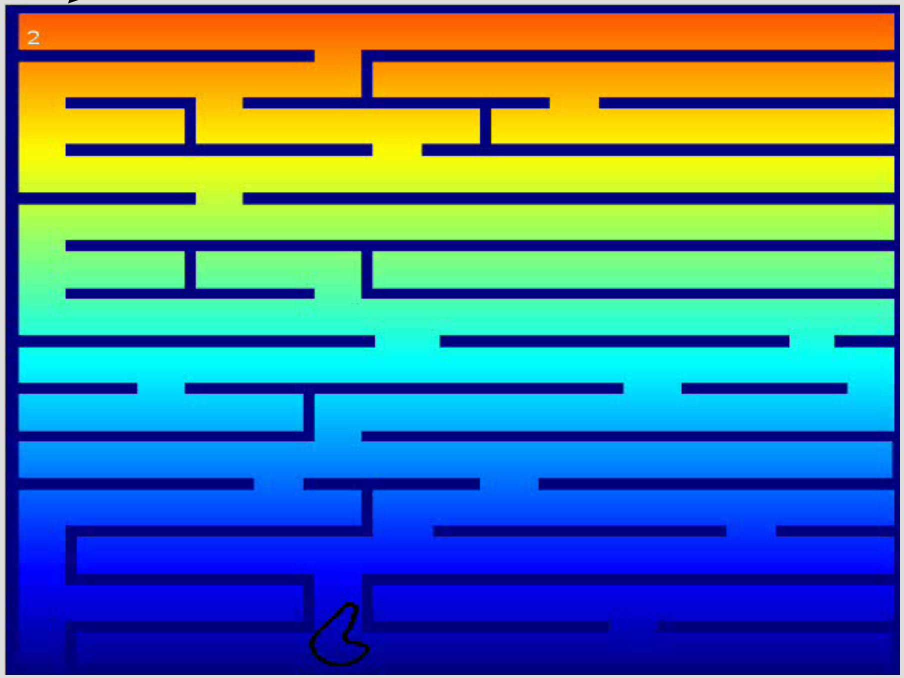
Work in progress

With Inbal Hecht, Assaf Zaritsky and Ilan Tsarfati

Invasion vs. Proliferation

Counter of cell divisions



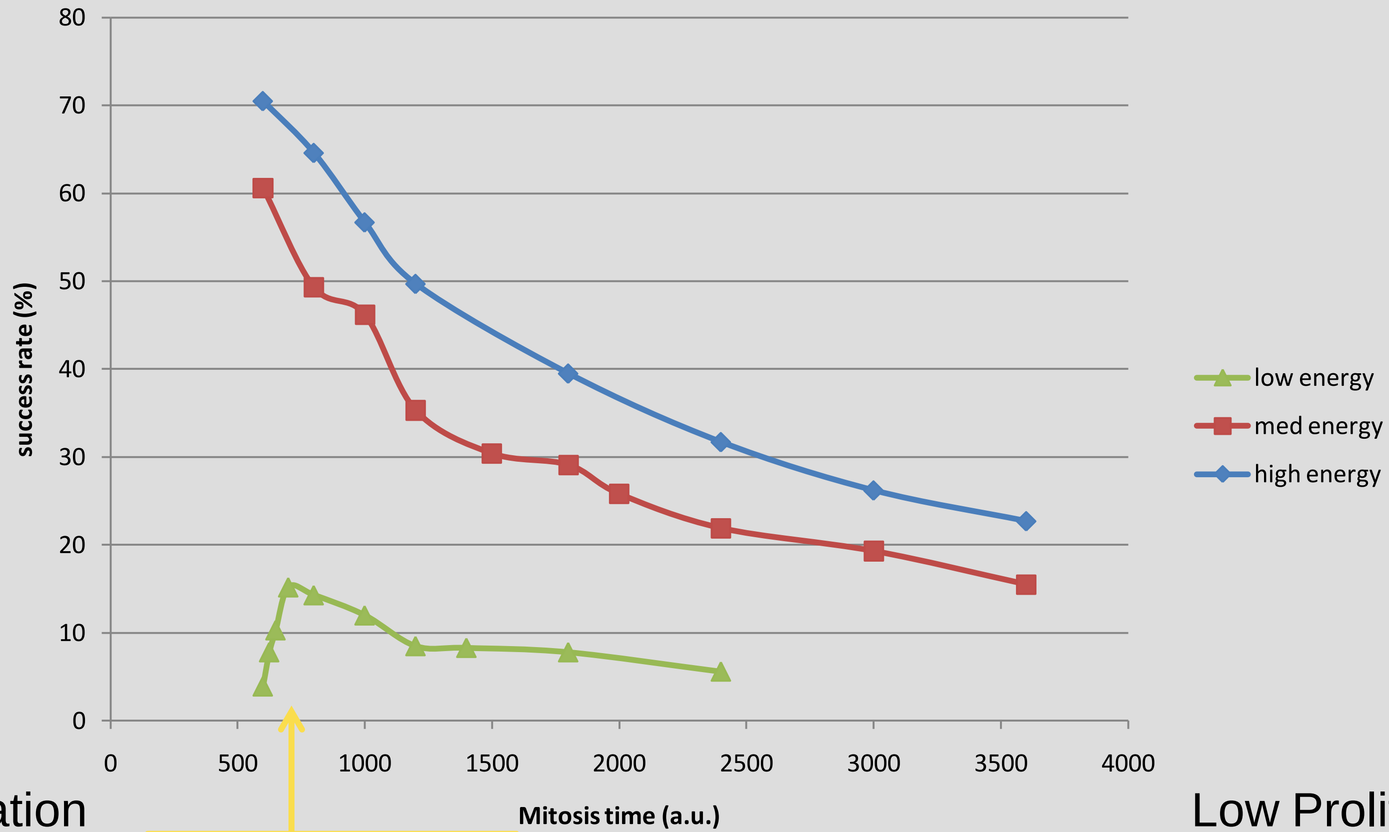


Invasion only

Invasion and Proliferation

With Inbal Hecht and Ilan Tsarfaty

Success rate



High Proliferation

Low Proliferation

Equiv. to ~36 h.

With very low energy, high proliferation results in no invasion and therefore very low success rate.

Model-based Predictions I: Cell-Cell Competition

Unlimited resources (no competition)

1. Behavior depends on the internal clocks
2. Success rate mostly depends on proteolysis rate
3. Mitosis slows down motion and invasion

Limited resources (competition)

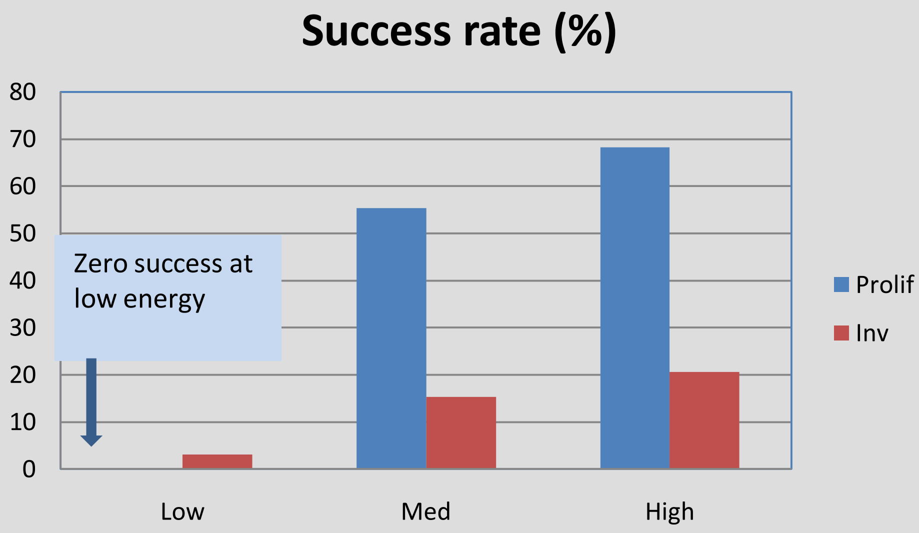
Elevated Mitosis

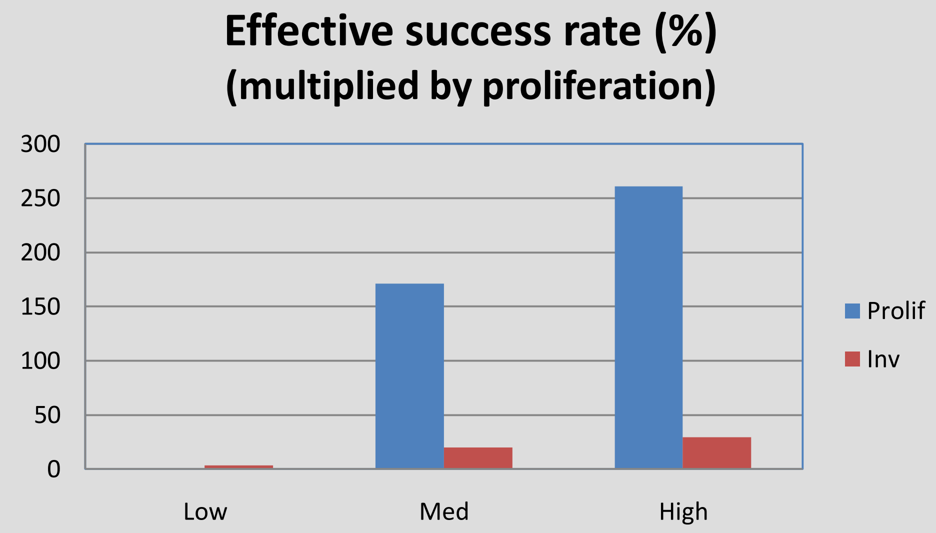
Higher survival,
Higher success rate
Longer time to goal

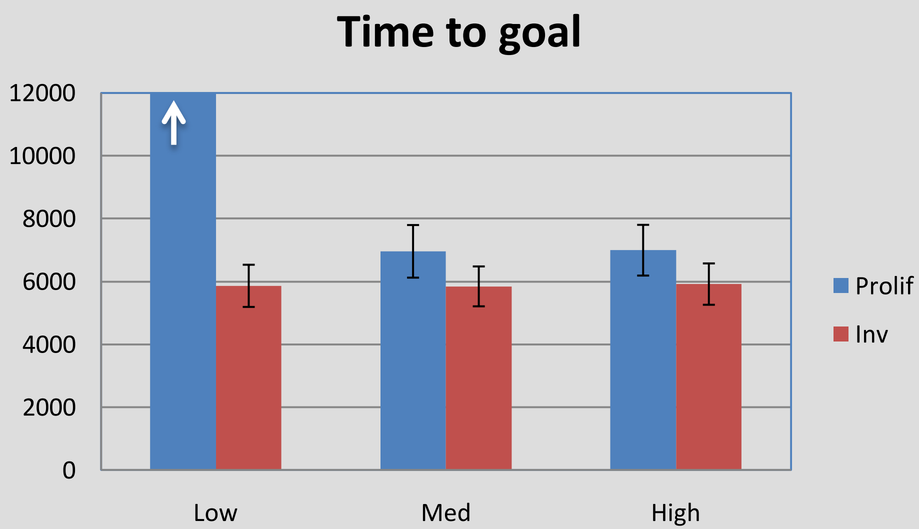
Elevated Proteolysis

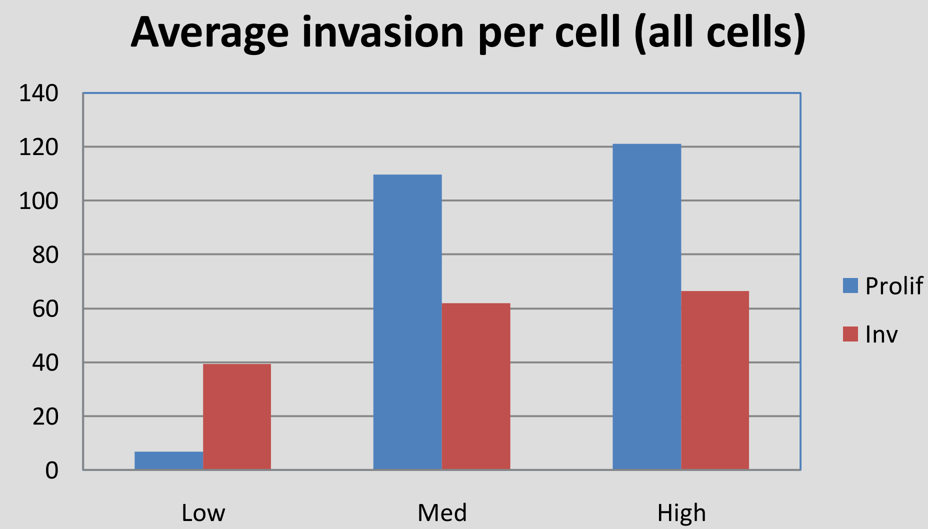
Lower success rate
Shorter time to goal

Proliferative vs. Invasive : Trade-off between success rate and time to goal









Model-based Predictions II: HGF Effect

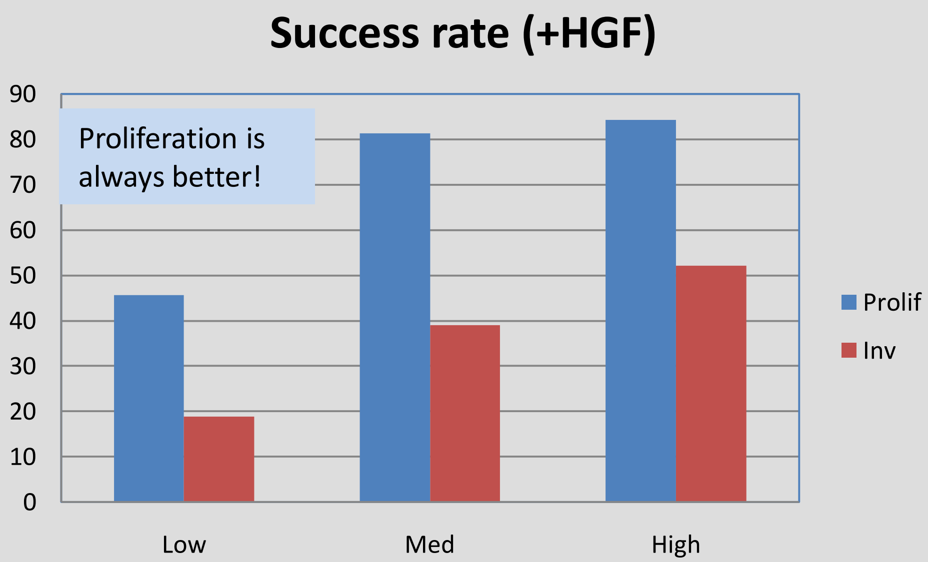
Inclusion of experimental information:

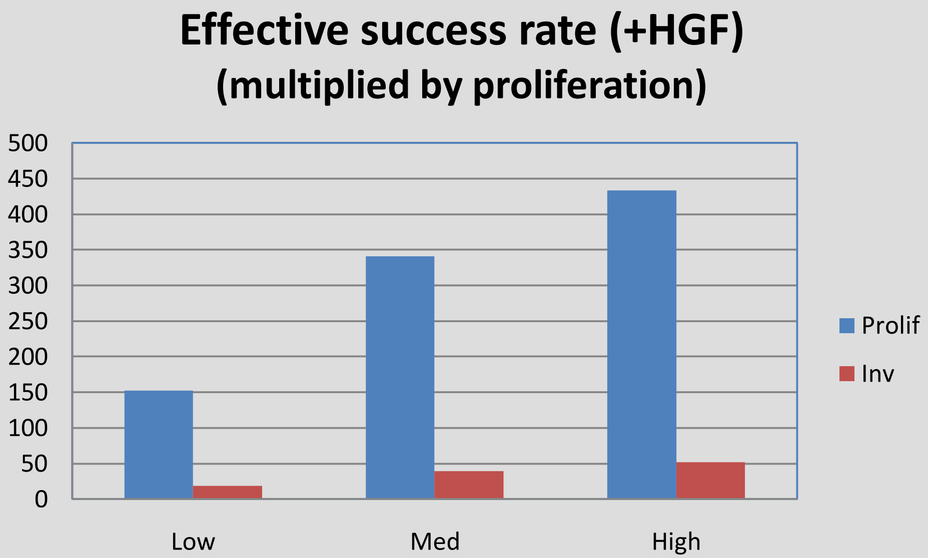
Increases glucose consumption by 50%
Increases metabolism and glycolysis by 20-30%
Increases MMP production two-fold
Increases cell speed two-fold
Decreases generation time (mitosis time) from 36 to 24 hours

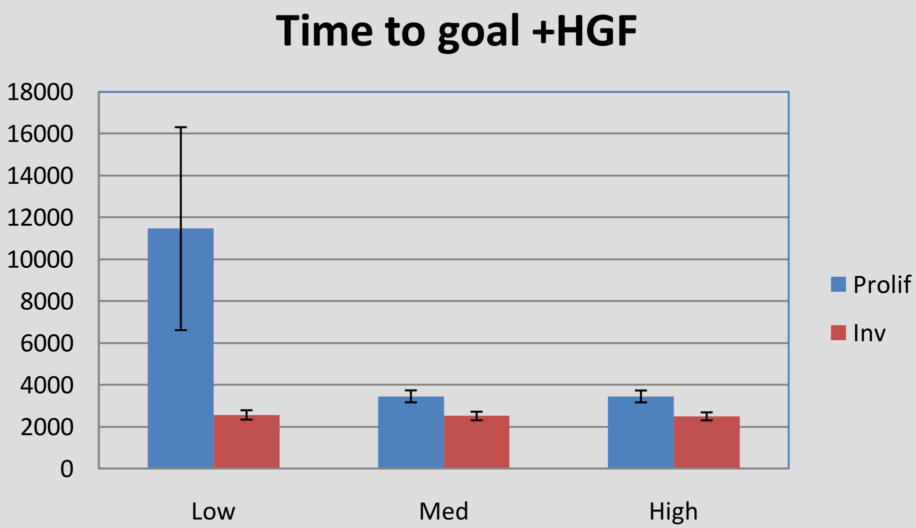
Model Predictions:

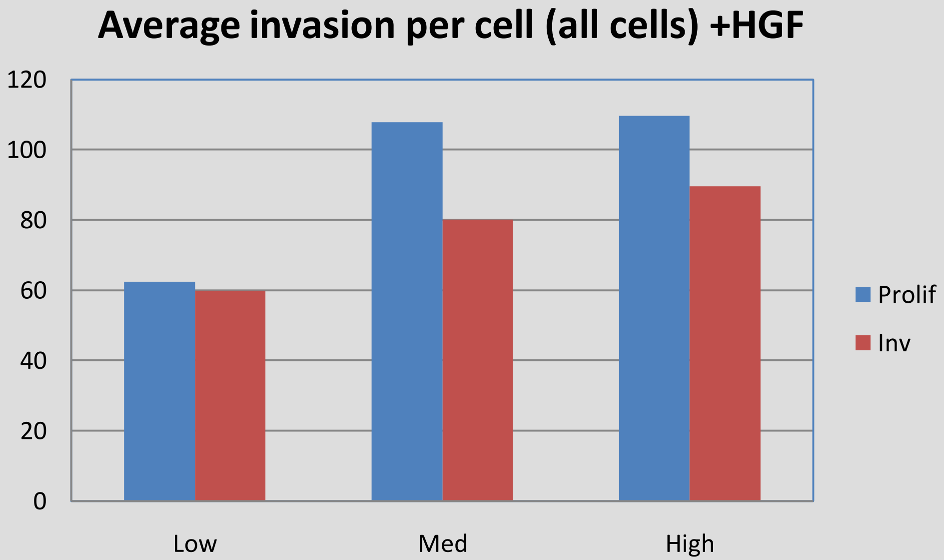
1. Cells can cope with low-energy environment
2. Proliferation is always beneficiary
3. But invading cells have much higher success rate relative to invasion in the absence of HGF!

HGF effect


Success rate (+HGF)
90
80
70
60
50
40
30
20
10
0
Proliferation is always better!
Low
Med
High
Prolif
Inv


Effective success rate (+HGF)
(multiplied by proliferation)
500
450
400
350
300
250
200
150
100
50
0
Low
Med
High
Prolif
Inv


Time to goal +HGF
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Low
Med
High
Prolif
Inv


Average invasion per cell (all cells) +HGF
120
100
80
60
40
20
0
Low
Med
High
Prolif
Inv

Conclusions from the "Tumor Perspective"

1. At "good times" (no stress),
A combined strategy of proliferation and invasion is preferred.

2. At "bad times" (e.g. hypoglycemia and hypoxia conditions),
Proliferation should be limited, to allow enough resources for invasion.

3. Tumors growth induces repeating cycles of hypoxia and angiogenesis.
Therefore, the population of colonizing cells should always include
a fraction of invading cells

Therapeutic implications if correct!

Like the bacteria do

Future Experiments:

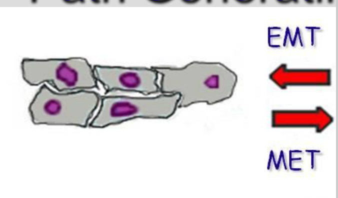
- Cells grown under starvation and with increasing glucose levels
- Mitosis measurements
- Motility and invasion assays

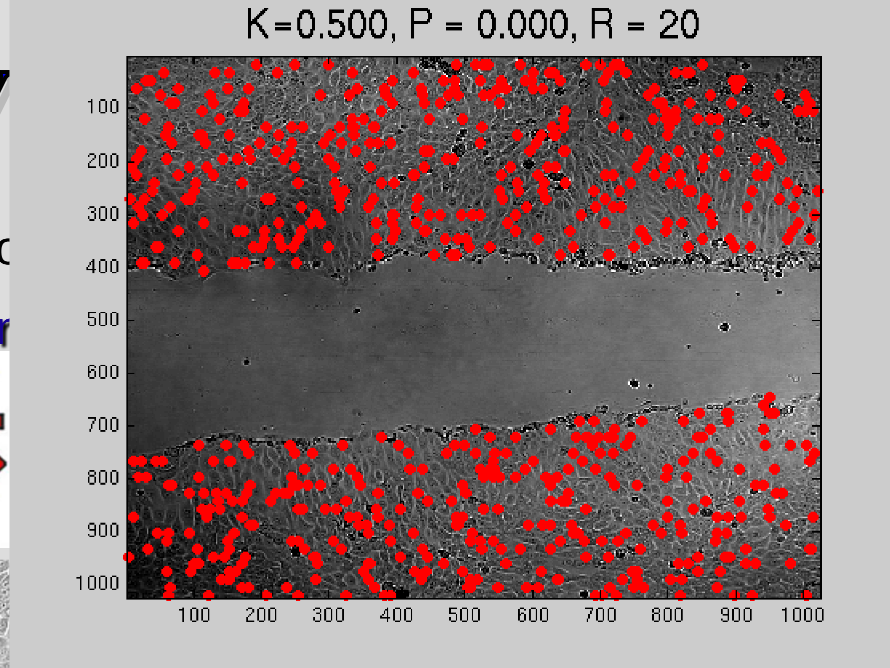
Tow… gration

…ility

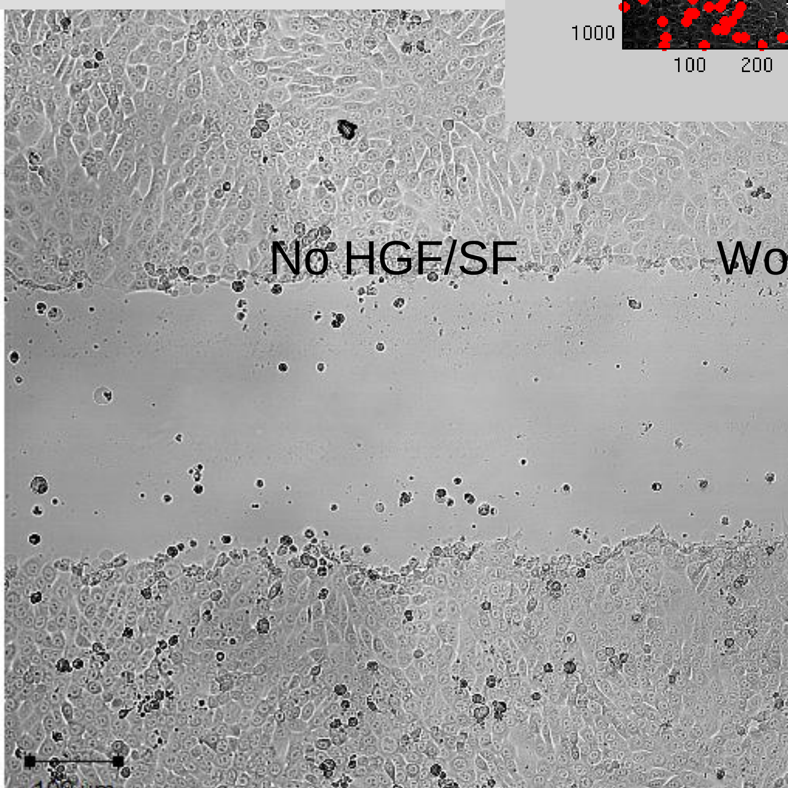
Wo… Tsarfaty

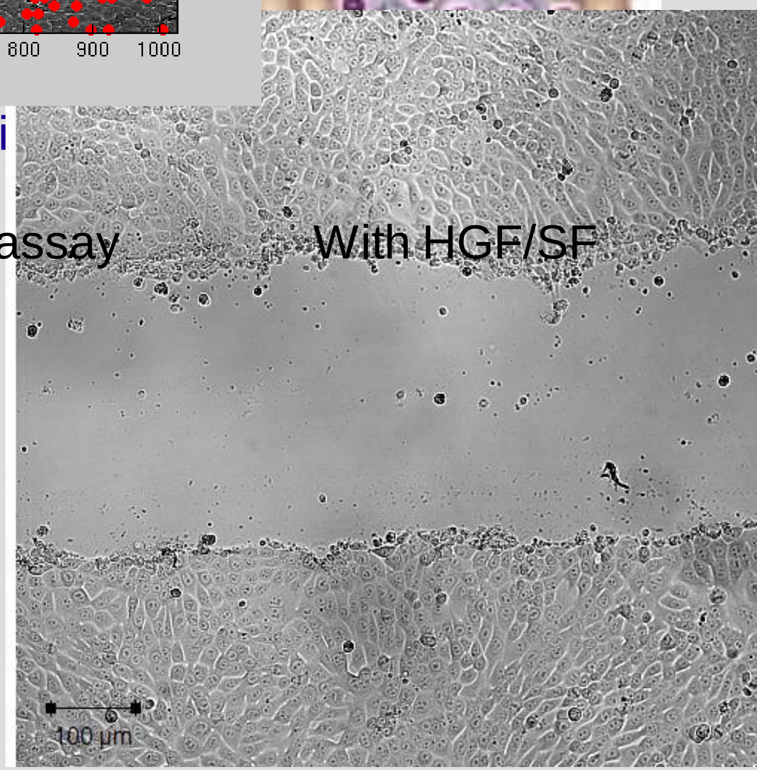
Path Generatin… | **…Collective Motility**





…boidal cell Transi…





No HGF/SF   Wound healing like assay   With HGF/SF

Zaritsky et al PLoS ONE in press 2012

Part V

Possible Implications and Applications

New Research Directions?

New Strategies to Fight Cancer?

Drugs to imitate and confuse communication

Fighting cancer with cancer – cancer cannibalism

Using bacteria to fight cancer

Fighting cancer with Dnase and Rnase

Using Bacteria to Fight Cancer

TUMOR IMMUNOLOGY

Bacteria-Induced Gap Junctions in Tumors Favor Antigen Cross-Presentation and Antitumor Immunity

Fabiana Saccheri,[1] Chiara Pozzi,[1] Francesca Avogadri,[2] Sara Barozzi,[1] Mario Faretta,[1] Paola Fusi,[3] Maria Rescigno[1]*

(Published 11 August 2010; Volume 2 Issue 44 44ra57)

Injected *Salmonella* can cause melanoma cells to form gap junctions with adjunct immune dendritic cells. Consequently, the dendritic cells use peptides transferred from the cancer cells to 'teach' T cells to recognize and kill the tumor cells at the primary site and prevent metastasis formation.

Fighting Cancer with Dnase and Rnase

Nature **214**, 100-102 (1 April 1967) | doi:10.1038/214100a0; Received 26 January 1967

Effect of Deoxyribonuclease on the Course of Lymphatic Leukaemia in *AKR* Mice

Proc. Nat. Acad. Sci. USA
Vol 73, No. 2, pp. 573–576, February 1976
Cell Biology

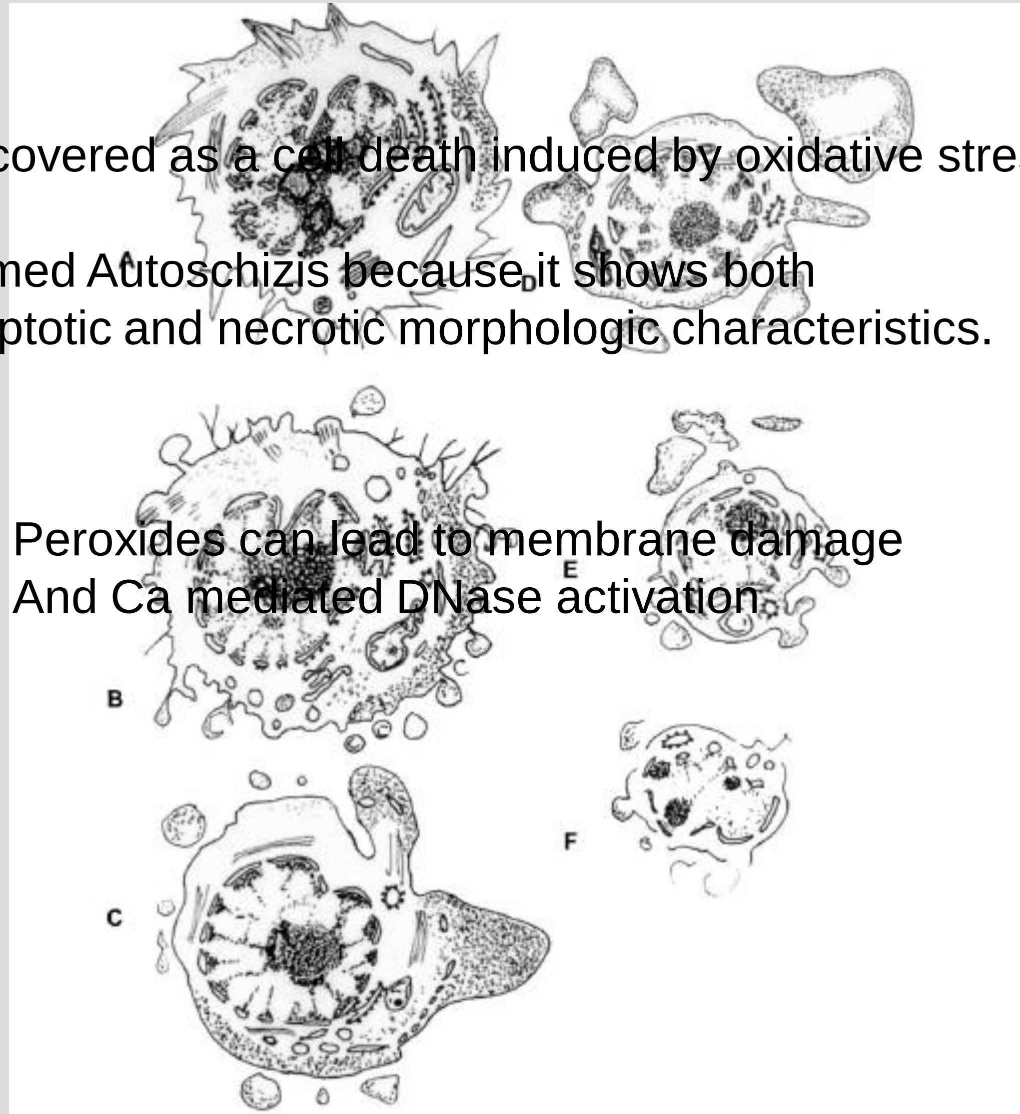
Inhibition of tumor cell proliferation by dimerized ribonuclease

(antimitotic effect/cytotoxicity/endocytosis/lysosomes/cancer)

Rnase triggers Apoptosis

Dnase triggers Autoschizis

Autoschizis Cancer Cell Death



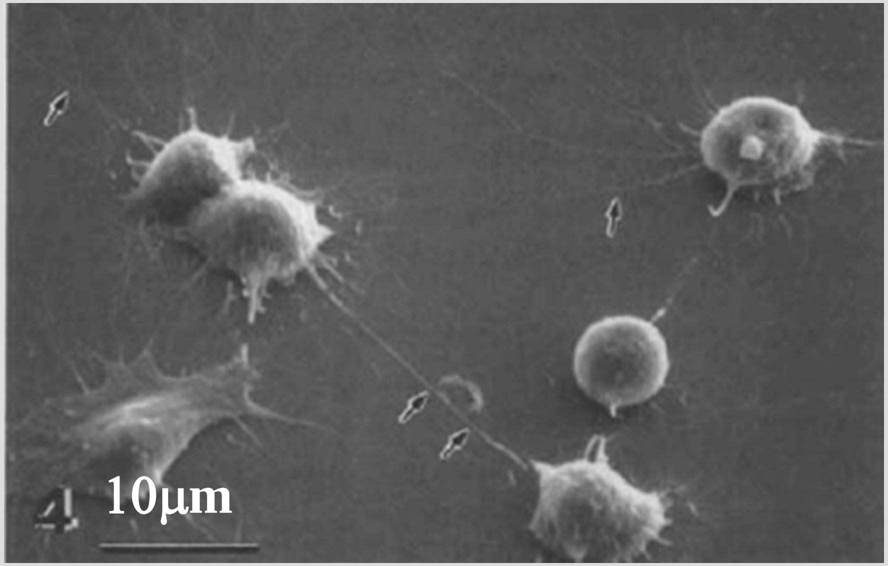
Discovered as a cell death induced by oxidative stress.

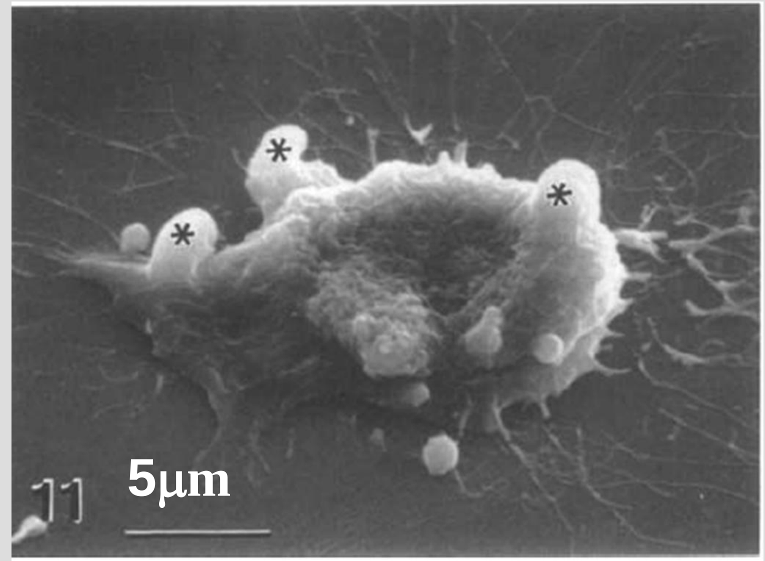
Termed Autoschizis because it shows both apoptotic and necrotic morphologic characteristics.

Peroxides can lead to membrane damage
And Ca mediated DNase activation.

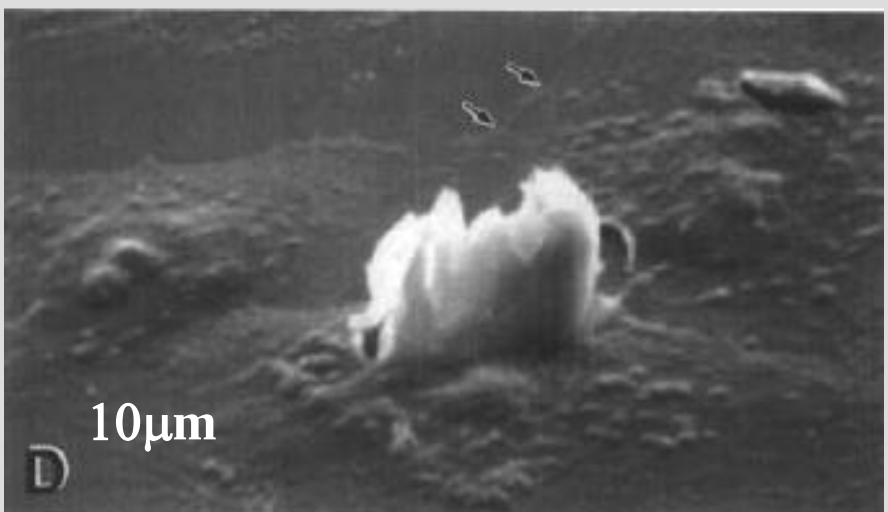
Jamison et al *Biochemical Pharmacology* (2002)

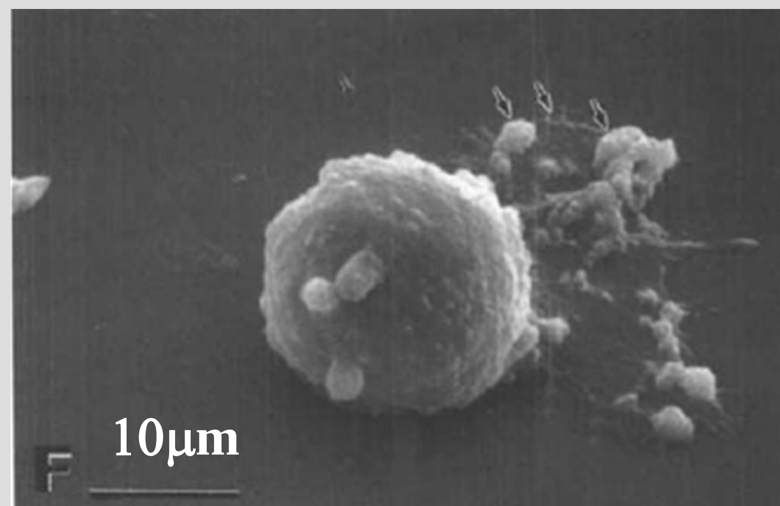
Autoschizis Cancer Cell Death





Gilloteaux et al *SCANNING* (1998)



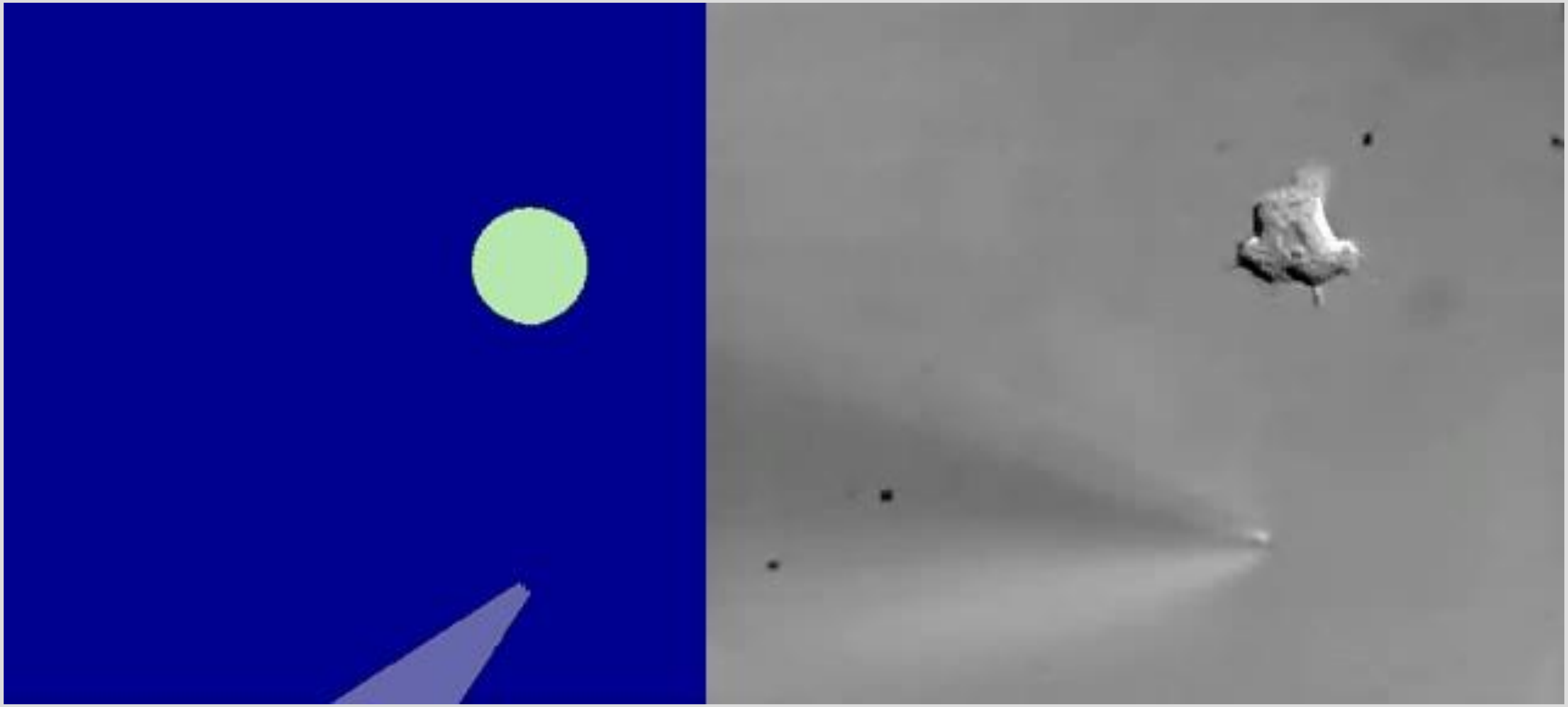


Conclusions & Reflections


The End

Shaped to Survive

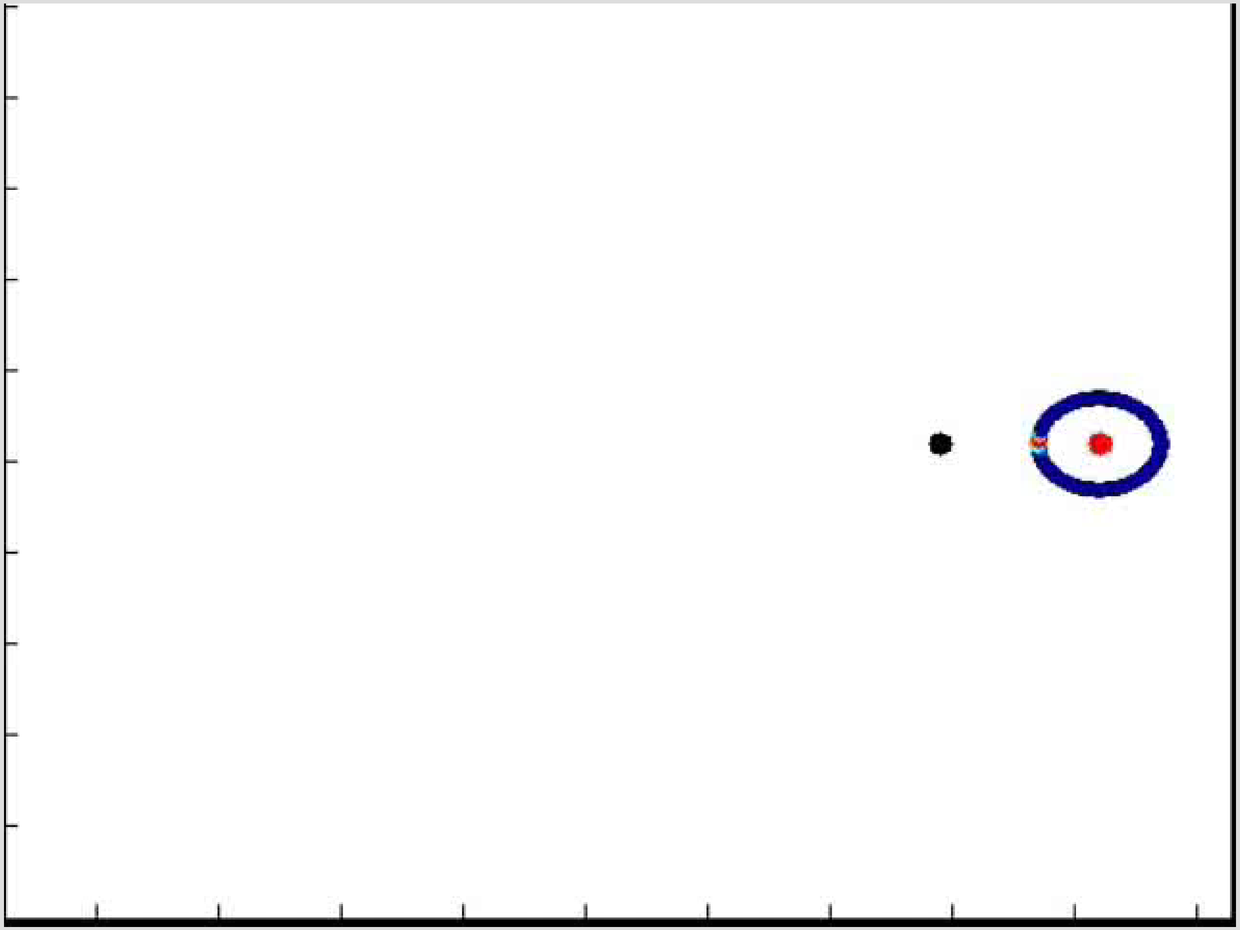
Fun "games" with the model I



(Details – Levine lecture last week)

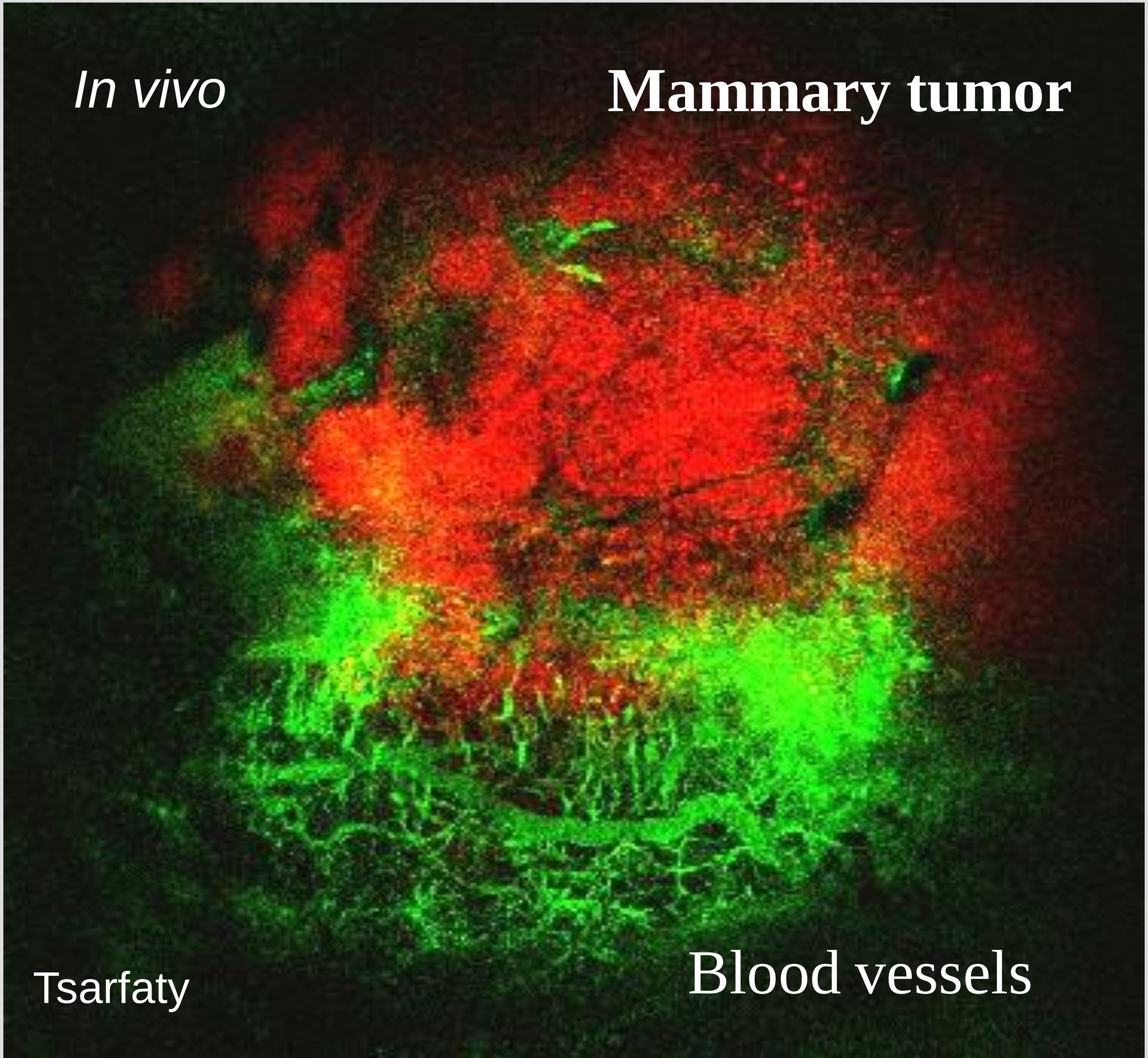
Fun "games" with the model II

Sensing, Information-processing, Decisions

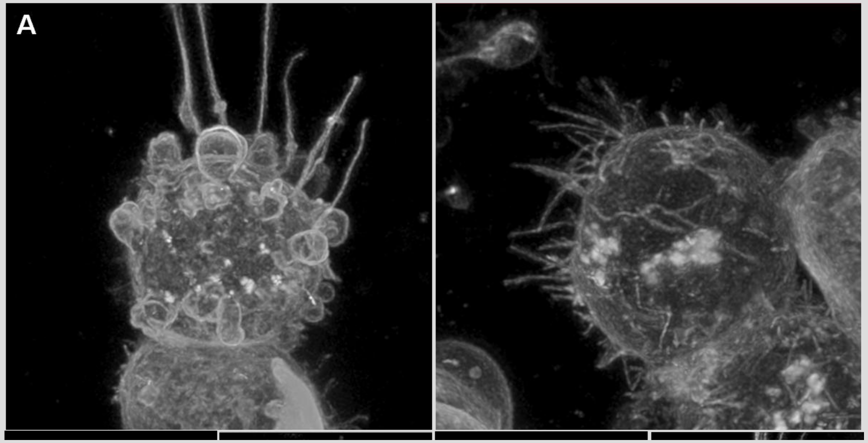


With Inbal Hecht, Herbert Levine, David Kessler (Unpublished)

Single Cell Motility - Blebbing

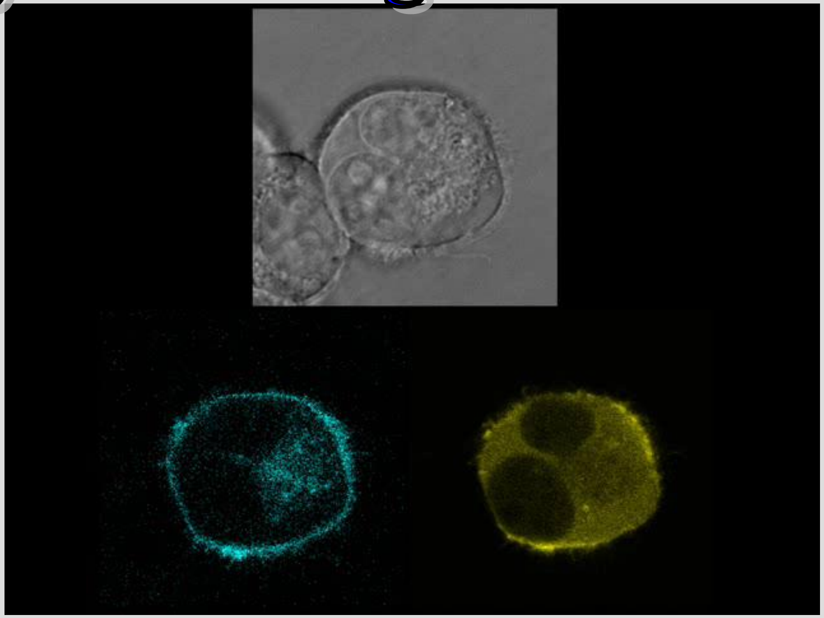


Single Cell Motility - Blebbing

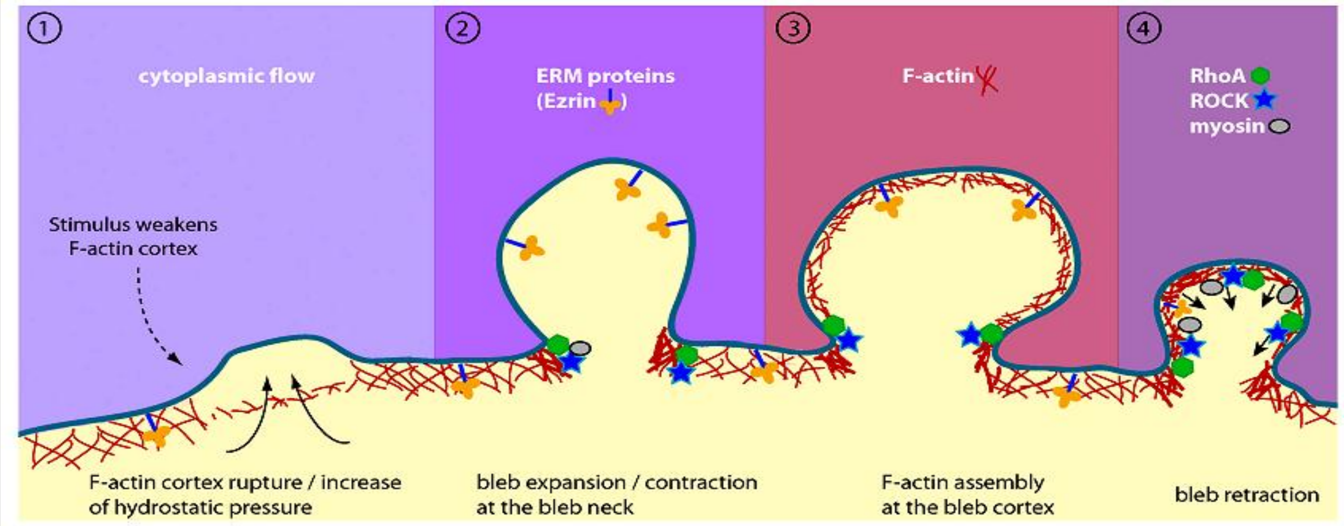


Met induced blebbing

Tsarfaty Group Unpublished

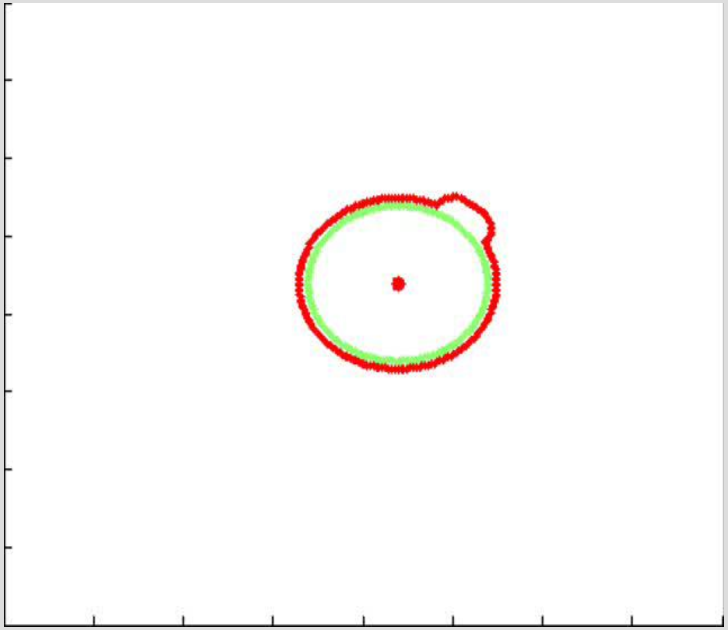


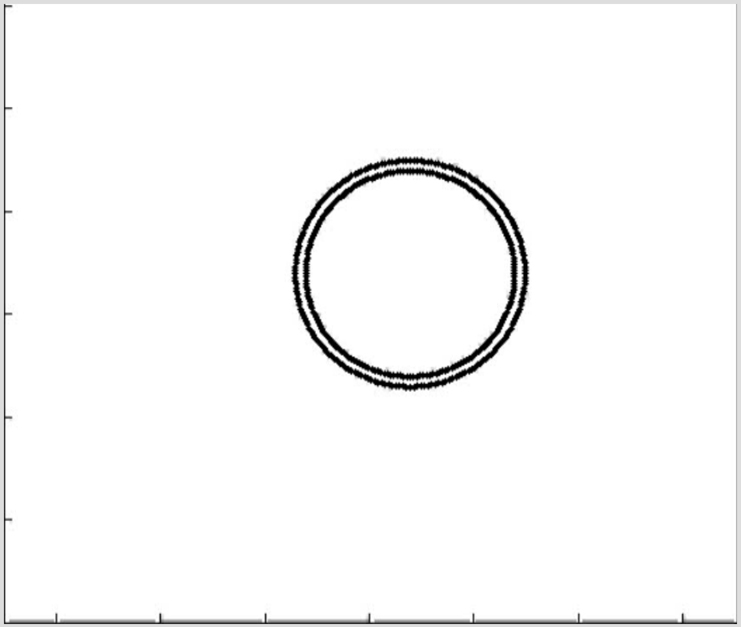
CFP - Met YFP - actin



Fackler & Grosse *Cell Biol* (2008) ; Charras & Paluch *Nat Rev Mol Cell Biol* (2008)

Model Testing of the Proposed Mechanisms

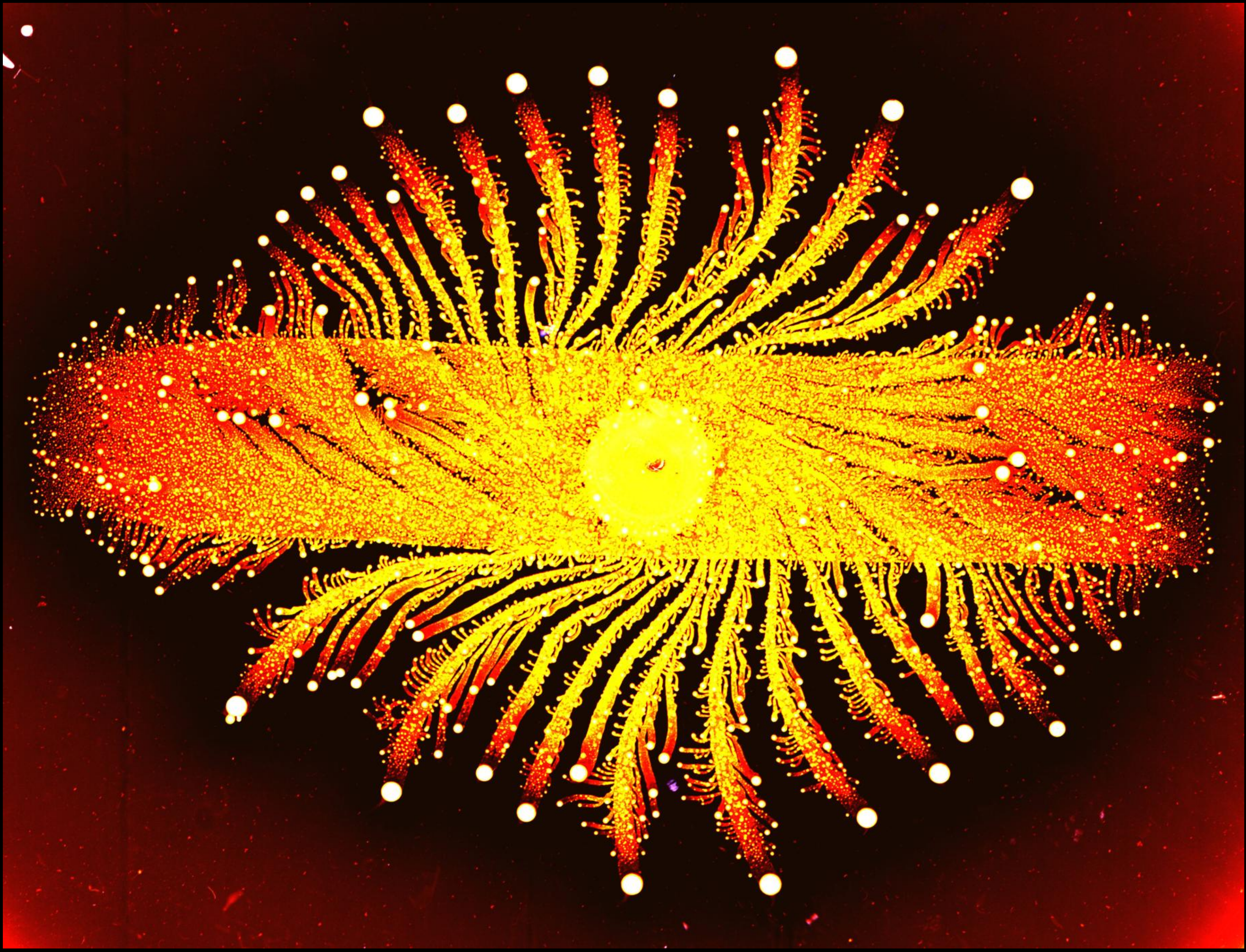




Cortex rebuilding from the sides
No membrane wrinkles are formed

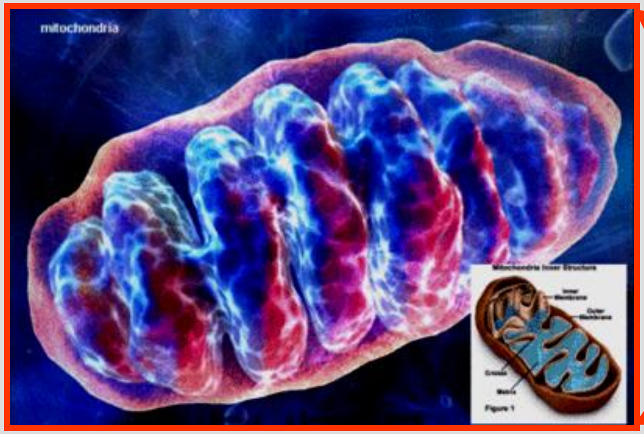
Reconnecting the cortex and membrane by stochastic dynamics
Membrane wrinkles are formed during retraction

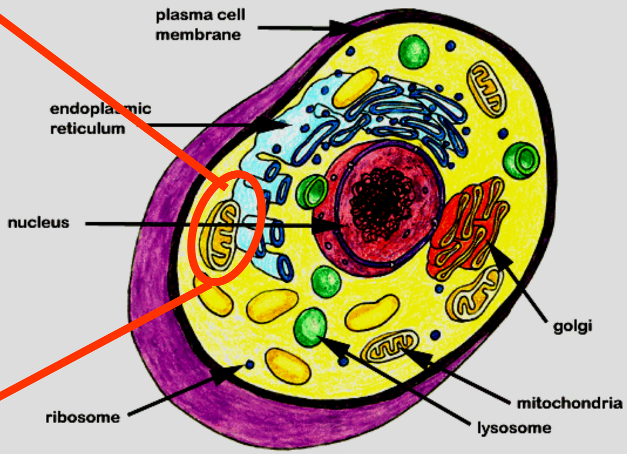
Yoshida K, Soldati T (2006) Dissection of amoeboid movement into two mechanically distinct modes. J Cell Sci 119: 3833-3844.



From Bacteria Thou art

Mitochondria - former bacterial colony in each cell



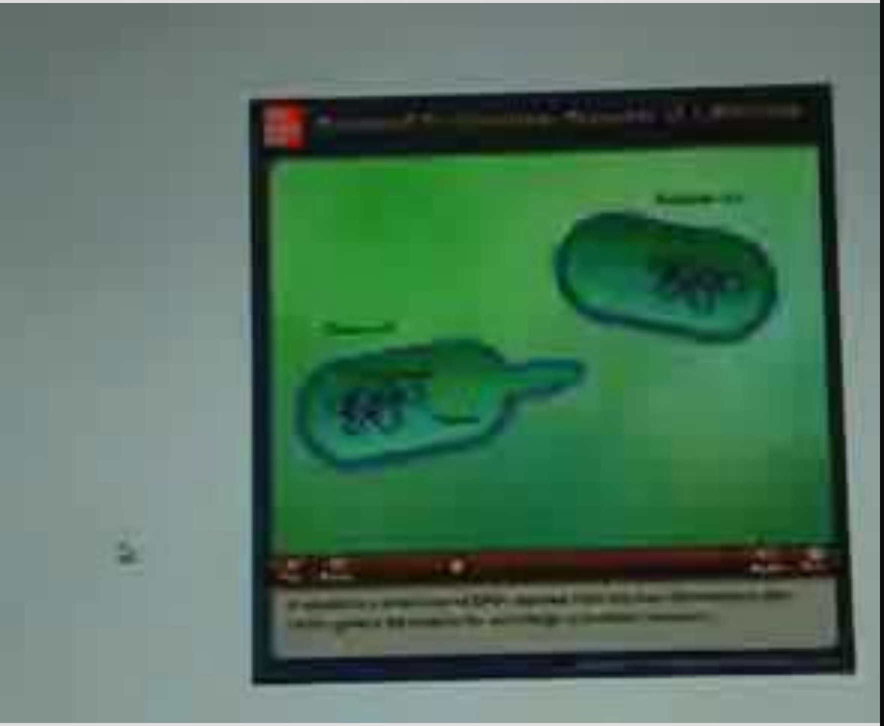


Cell power plants

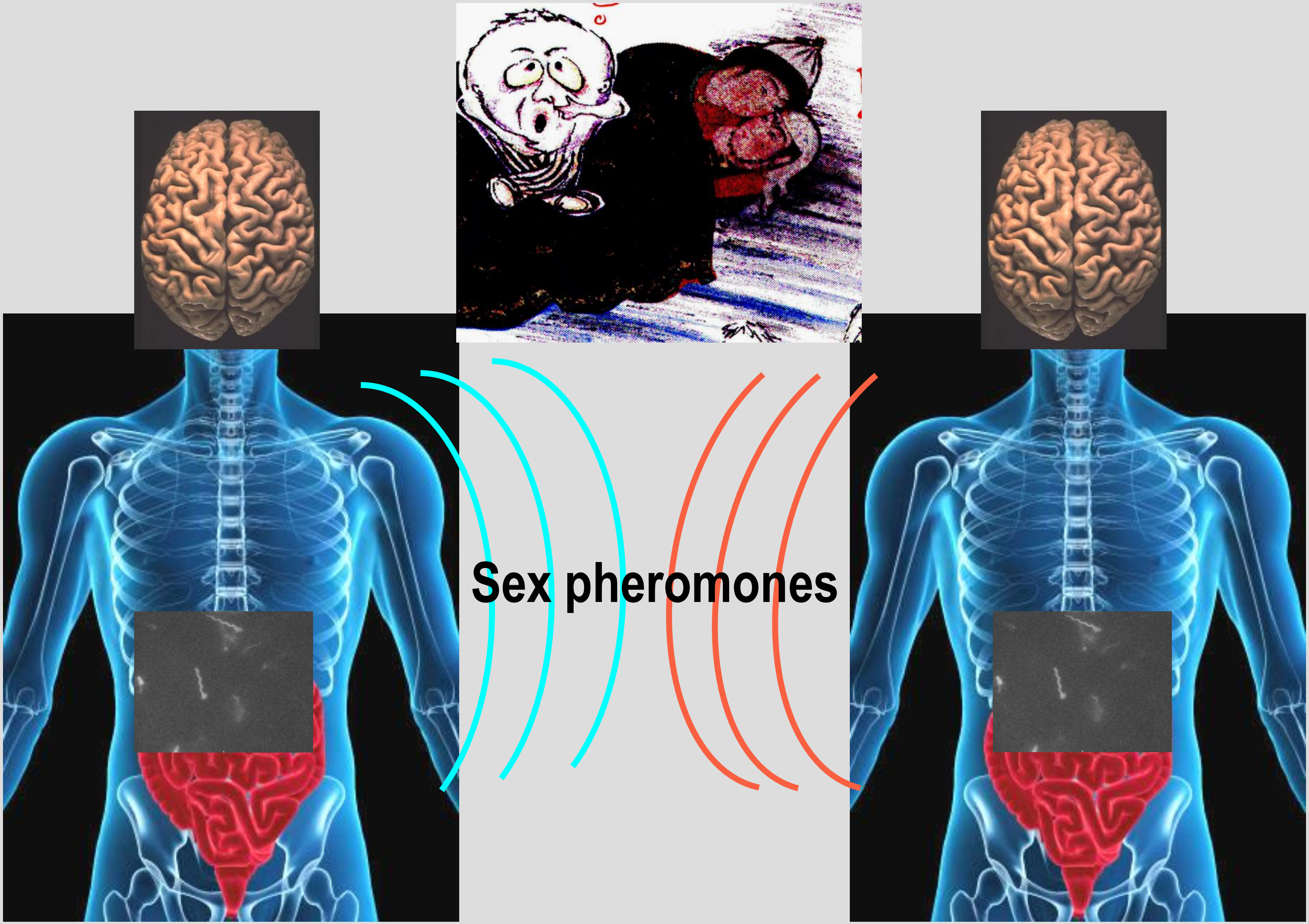
Production and control of sex hormones

Production and control of neurotransmitters

Bacteria Mating

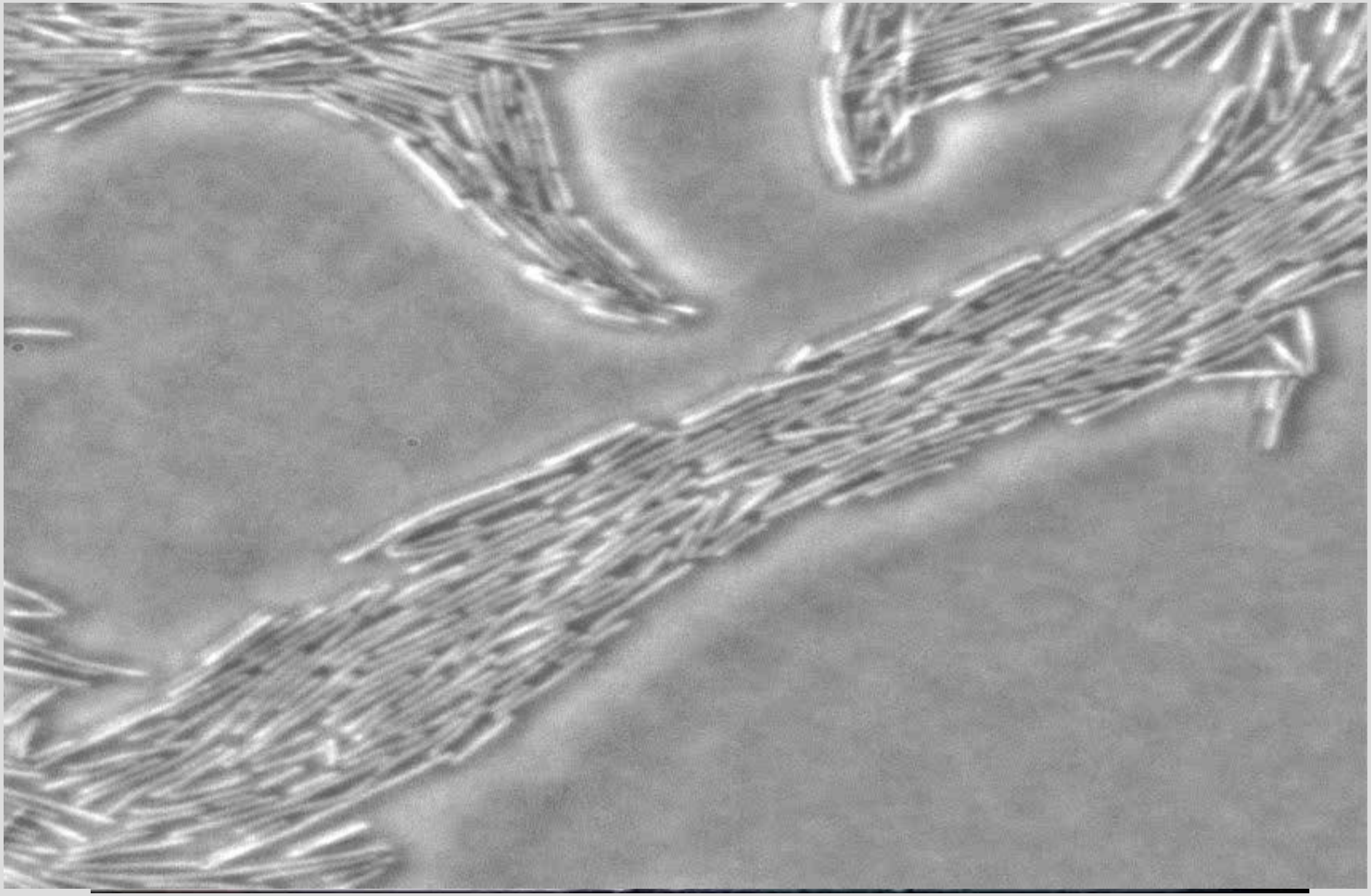


Gut Bacteria and Human Mating - Choice of Partners



How Bacteria Move

Swimming by Flagella, Gliding by Pili and more



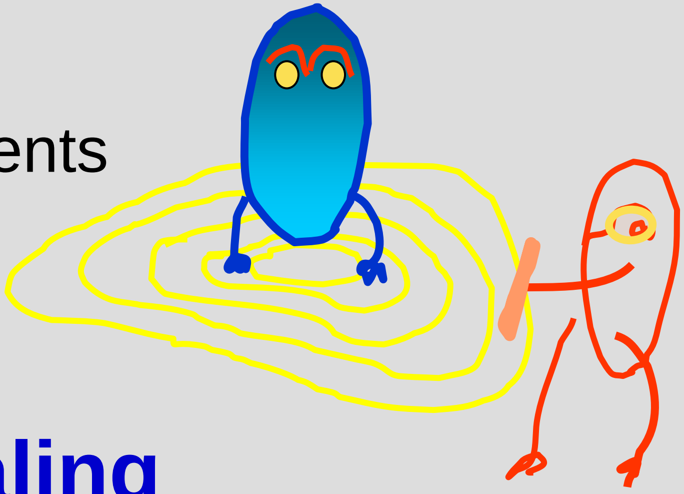
Flagella swimming (- Howard Berg

Movie: Thanks to Avraham (Memi) Be'er, Sde Boker

Chemical Navigation - Chemotaxis

Sensing, Memory, Information Processing

Chemotaxis –
Movement according to chemical gradients

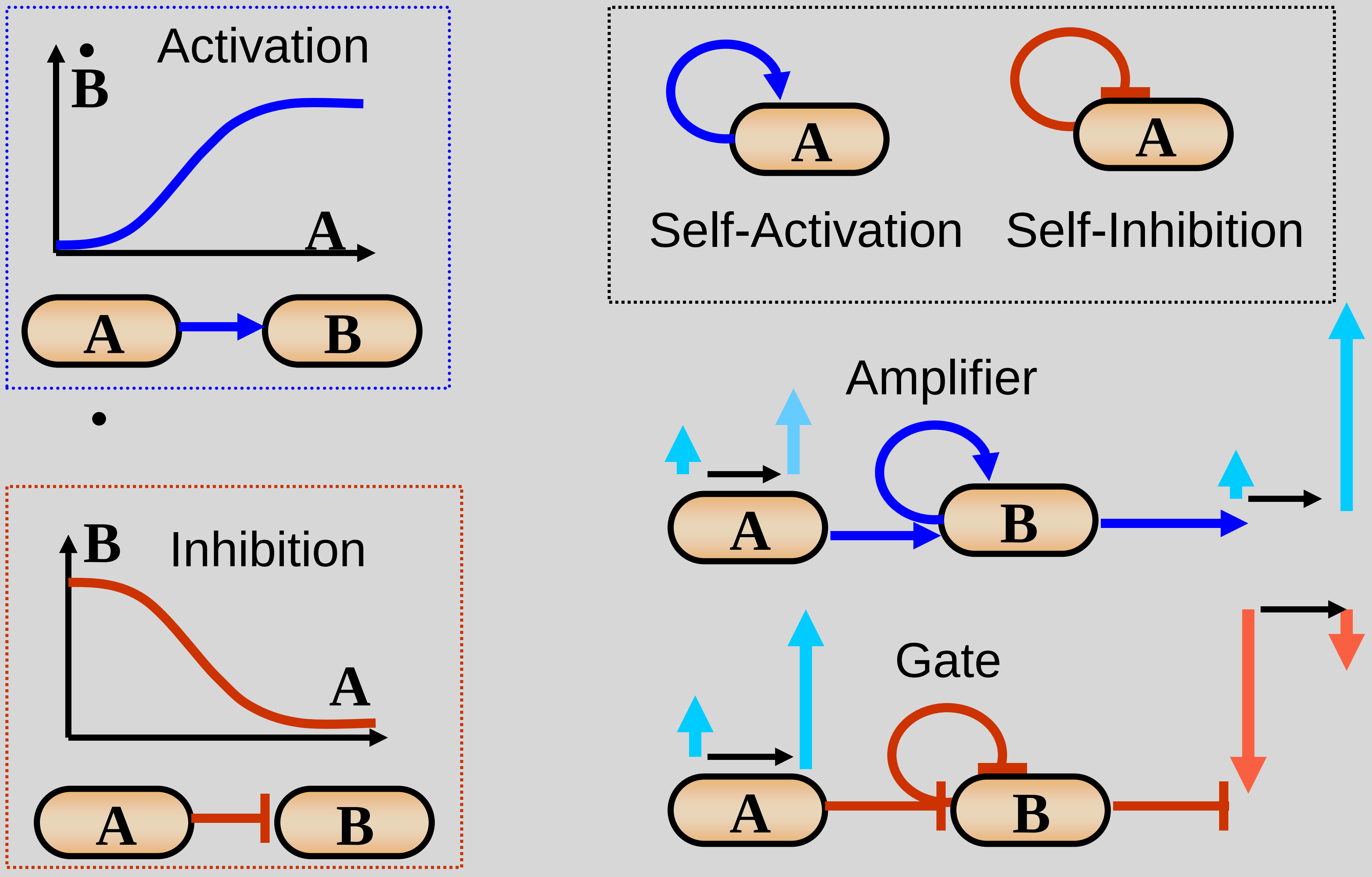


Chemotactic Signaling

Chemotactic Signaling–
Chemotaxis in response to chemicals secreted by the cells

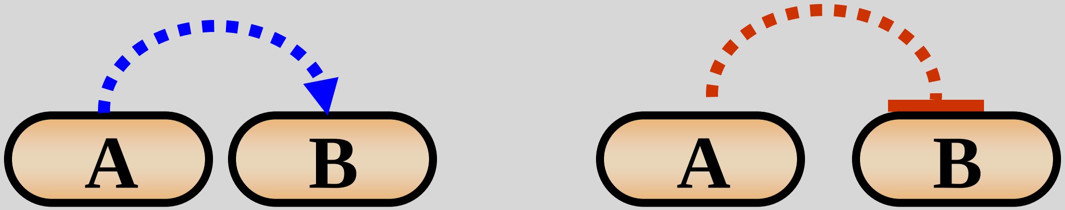
Ben-Jacob *et al*., Nature 1994,1995,2001,2005,
Royal Society 2003, Trends in Microbiology 2004

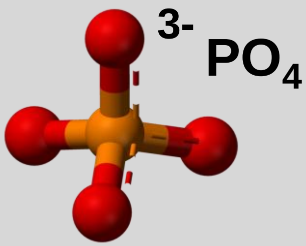
Elements of Intra-cellular Information processing I

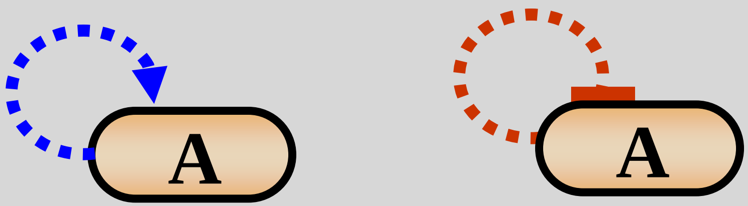


Elements of Intra-cellular Information processing II

Phosphorylation and Dephosphorylation

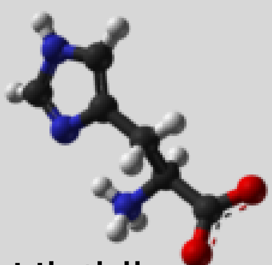




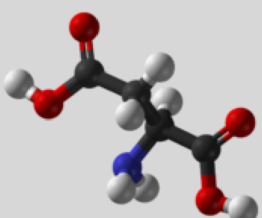


Self-Activation   Self-Inhibition

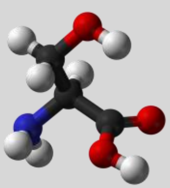
Time scale control by using different Amino Acids



Histidine



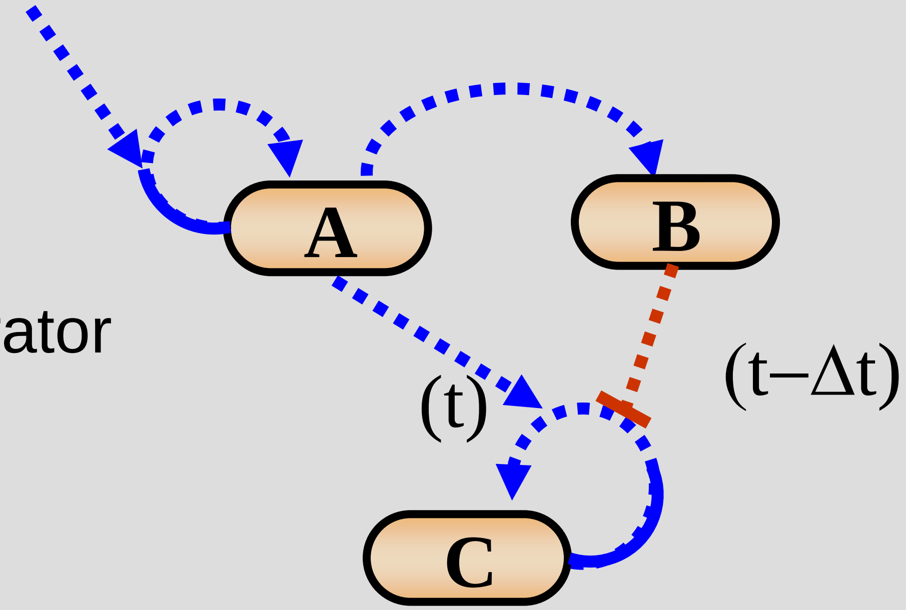
Aspartic acid



Serine

Example of Phosphorylation-Based Calculations

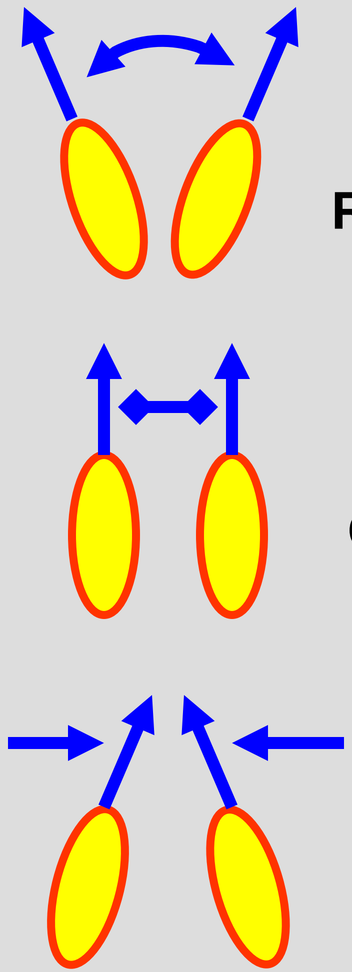
The measured concentration



An hypothetical comparator
for chemotaxis

Collective Navigation of Interacting Agents

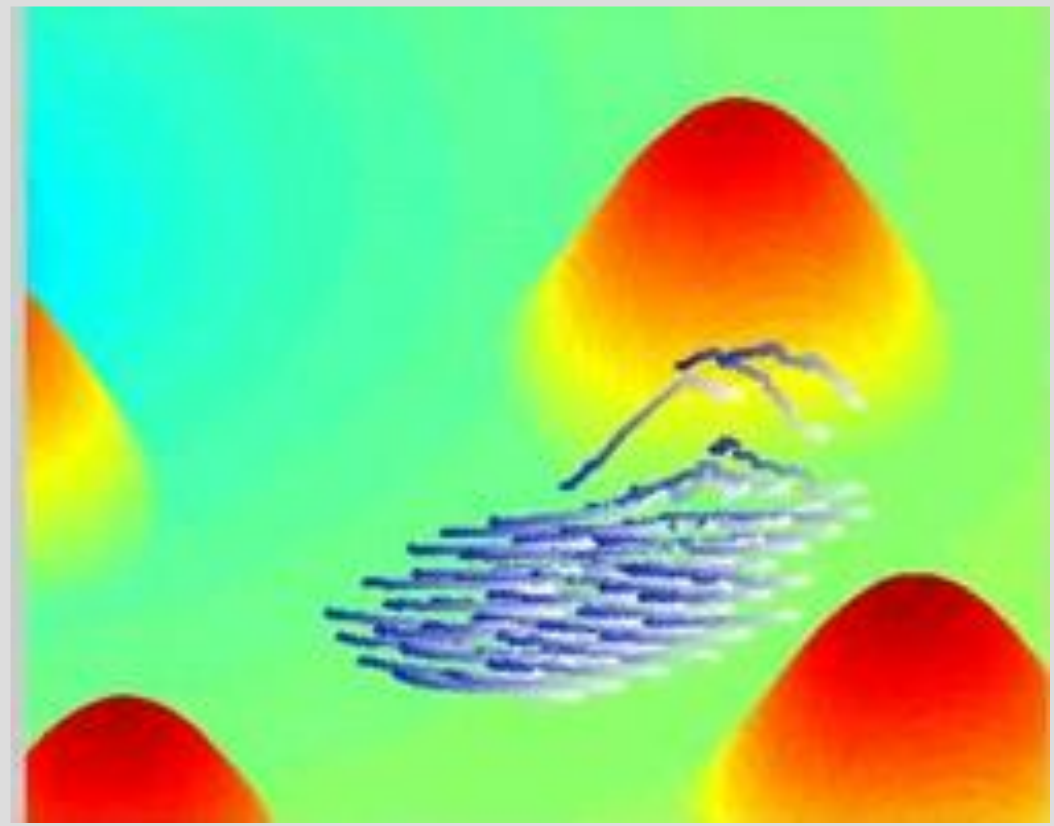
With A. Shklarsh, E. Schneidman. G. Ariel, PLos Comp. Bio 2011



Repulsion

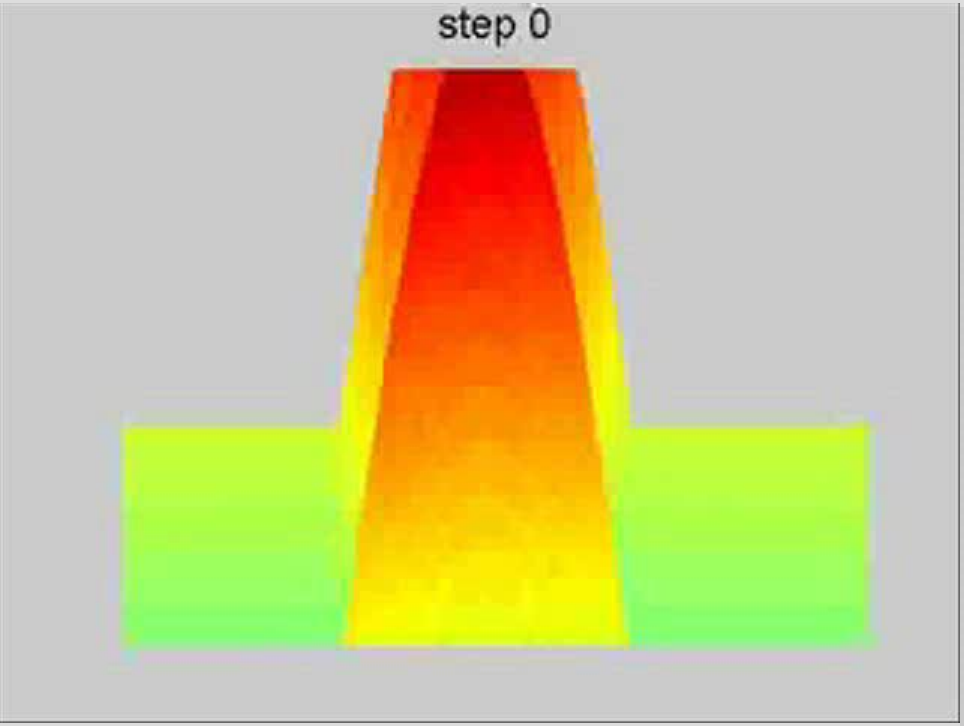
Orientation

Attraction

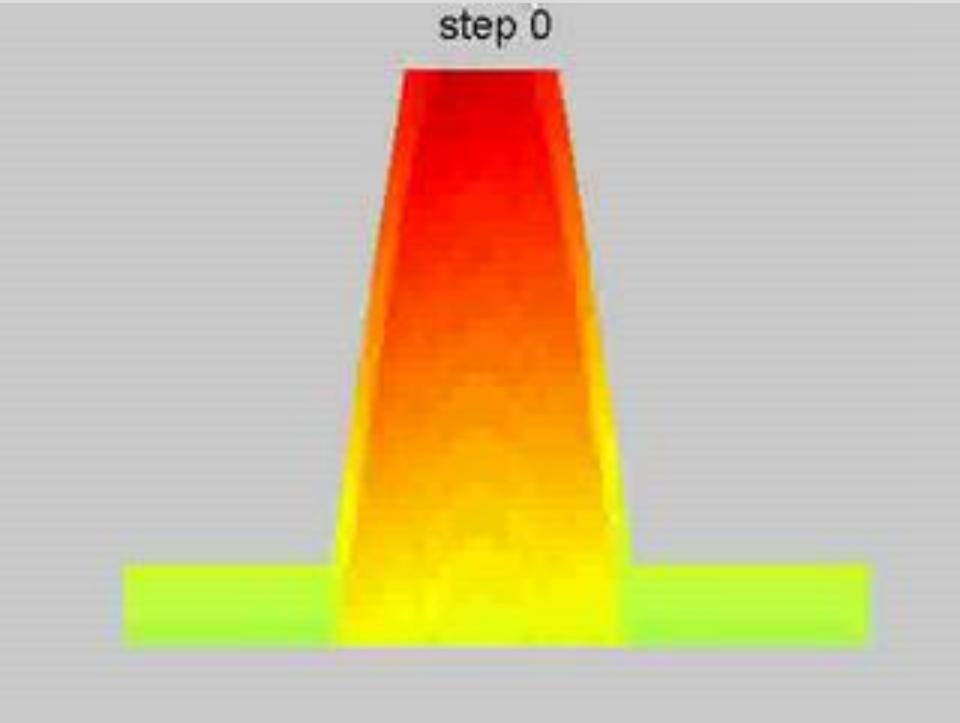


Extension of Vicsek, Ben Jacob et al., PRL 1995 + Couzin et al., Nature 2005

Independent agents



Interacting agents

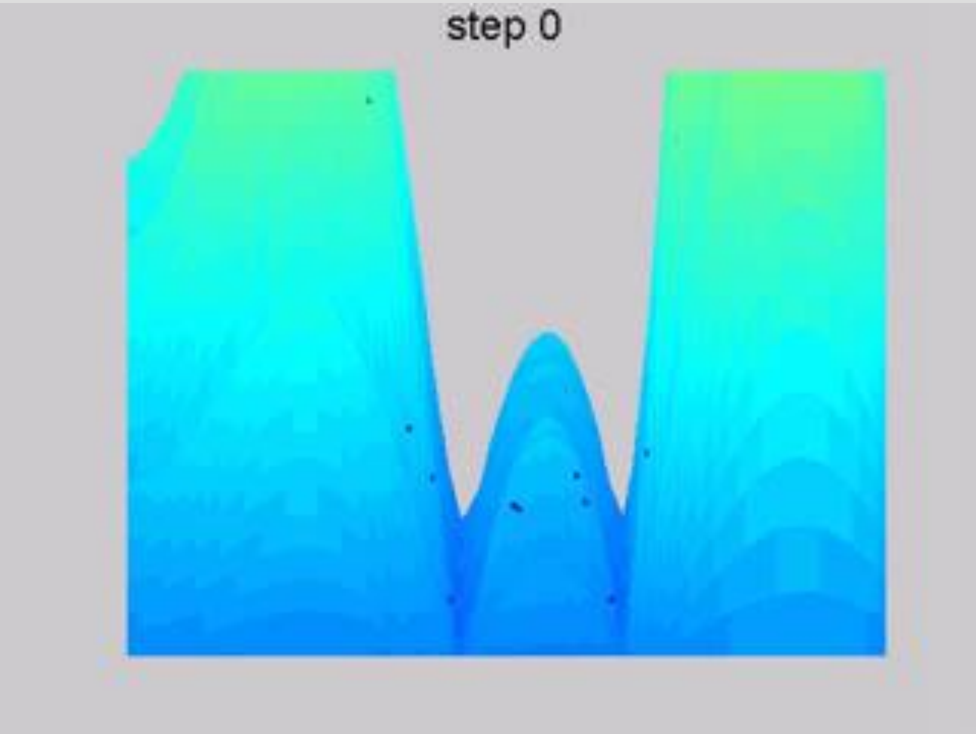


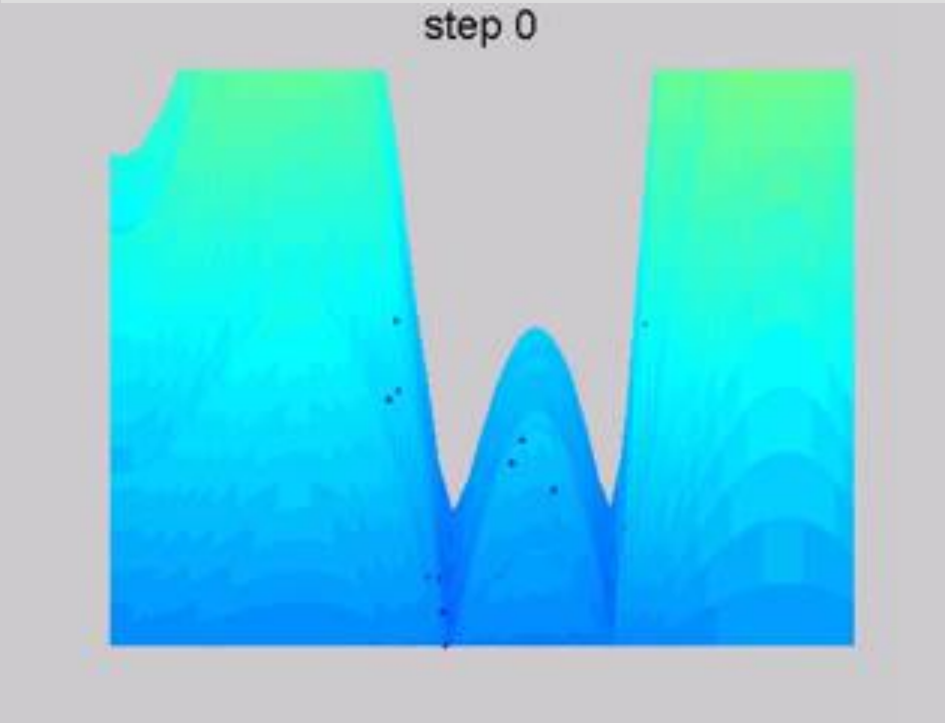
Collective sensing and
Distributed information processing

Navigation in highly complex terrains

Fixed interactions

Adaptable interactions

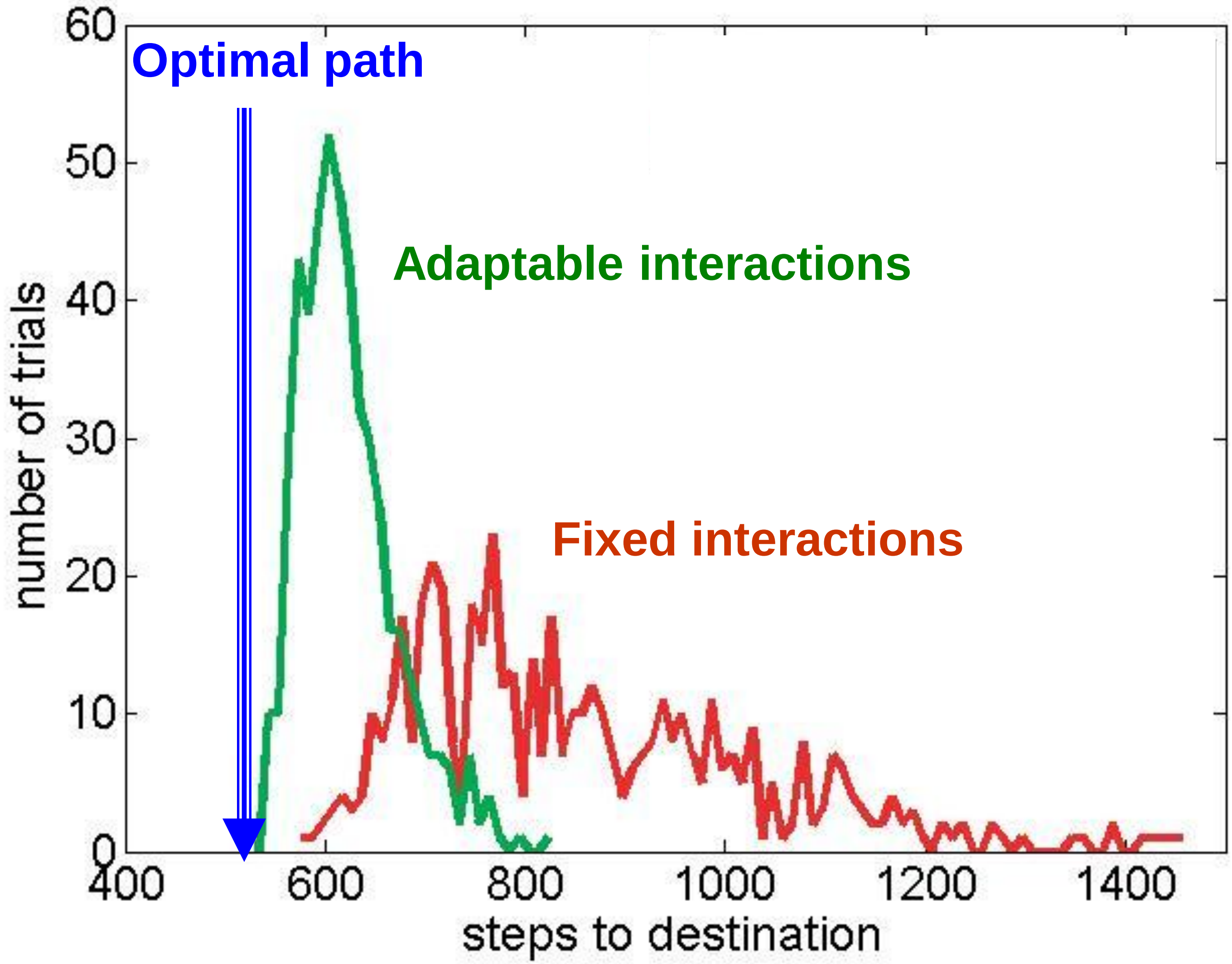




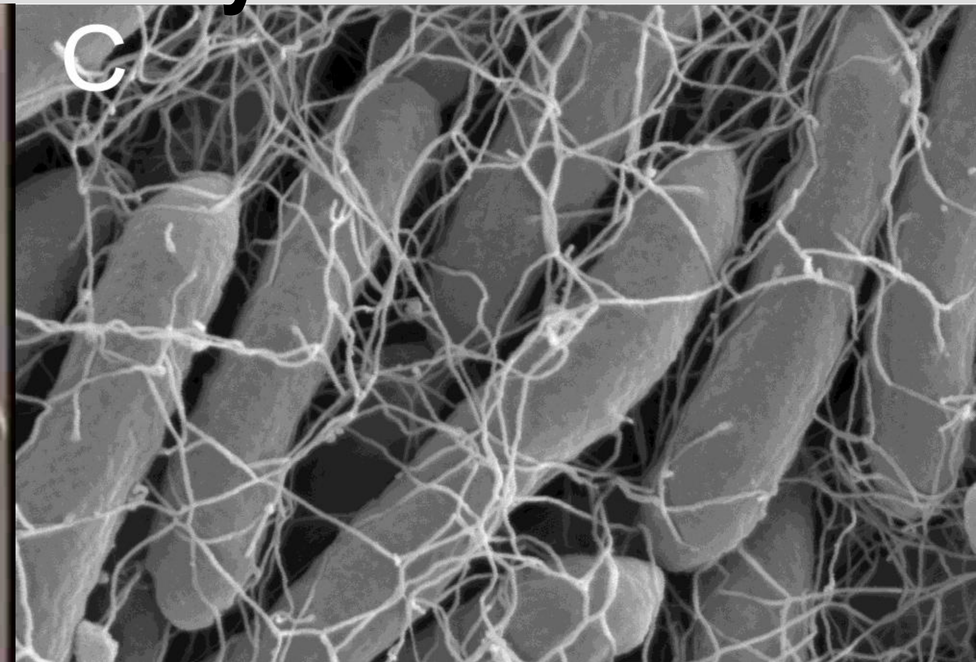
What is the advantage?

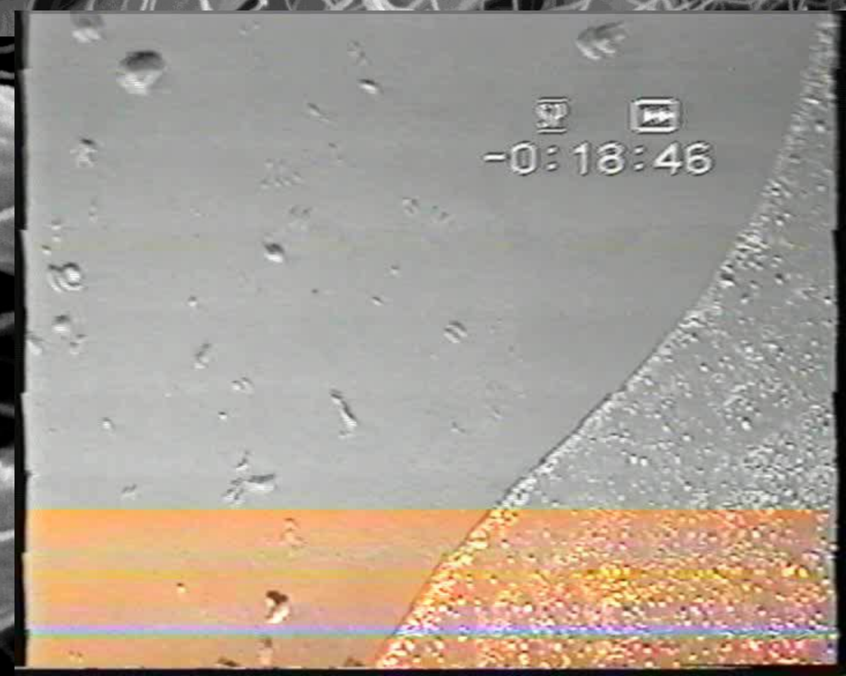
With A. Shklarsh, E. Schneidman. G. Ariel, PLos Comp. Bio 2011

Quantification of the results



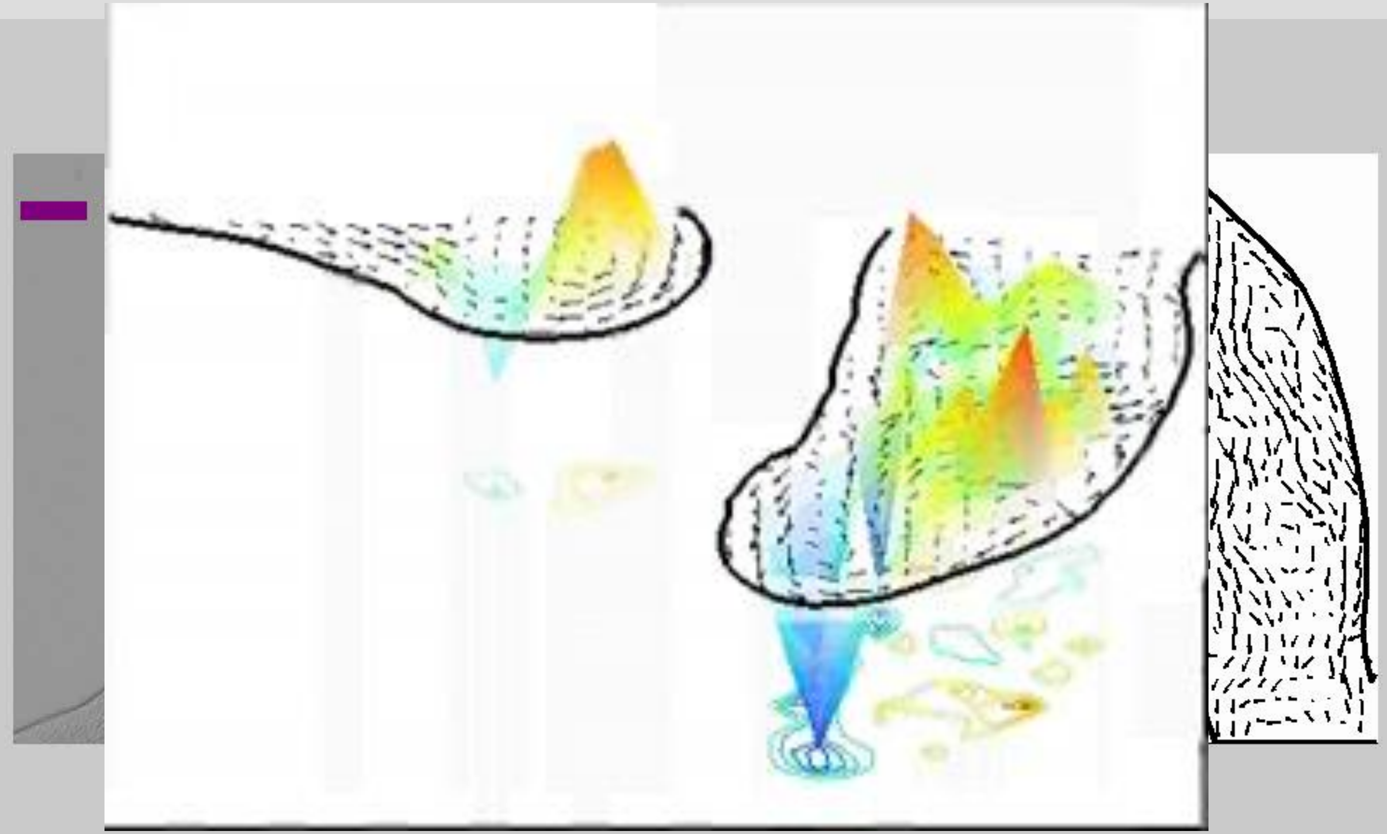
Pile Motility





Physics Based Understanding

Investigating the Vorticity



Velocity alignment with curl chemotaxis

Self-Propulsion — Velocity alignment — Bacterial density — Noise

$$\frac{d\mathbf{v}_i}{dt} = \Gamma \frac{\mathbf{v}_i}{|\mathbf{v}_i|} - \nu \mathbf{v}_i$$

Friction — Averaged velocity — Hard-core repulsion

Curl Chemotaxis

$$-\chi_A \frac{1}{v_i} \mathbf{v}_i \times (\mathbf{v}_i \times \nabla C_A),$$

Moving in an envelope

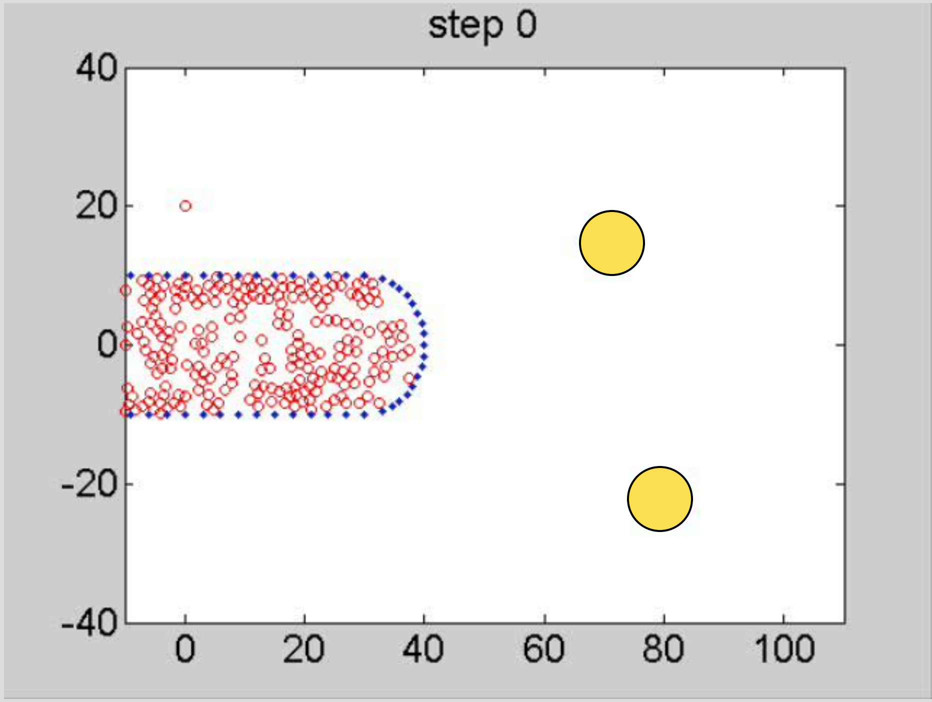
Ben-Jacob Royal Soci. 2003

With Ariel, Kalishman, Shklarsh, Ingham (Royal Soci. Interface in press)

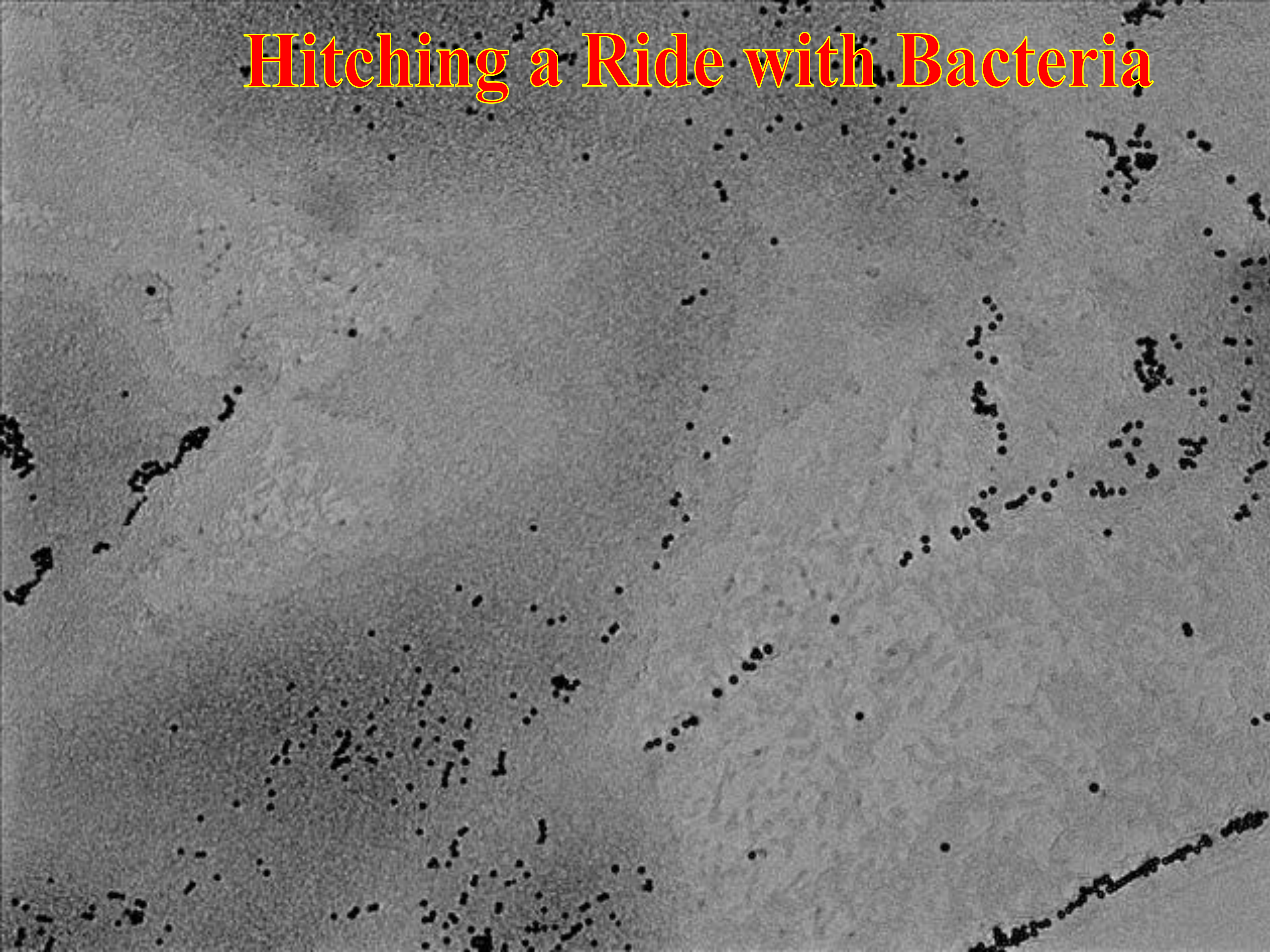
Simulations

Repulsion

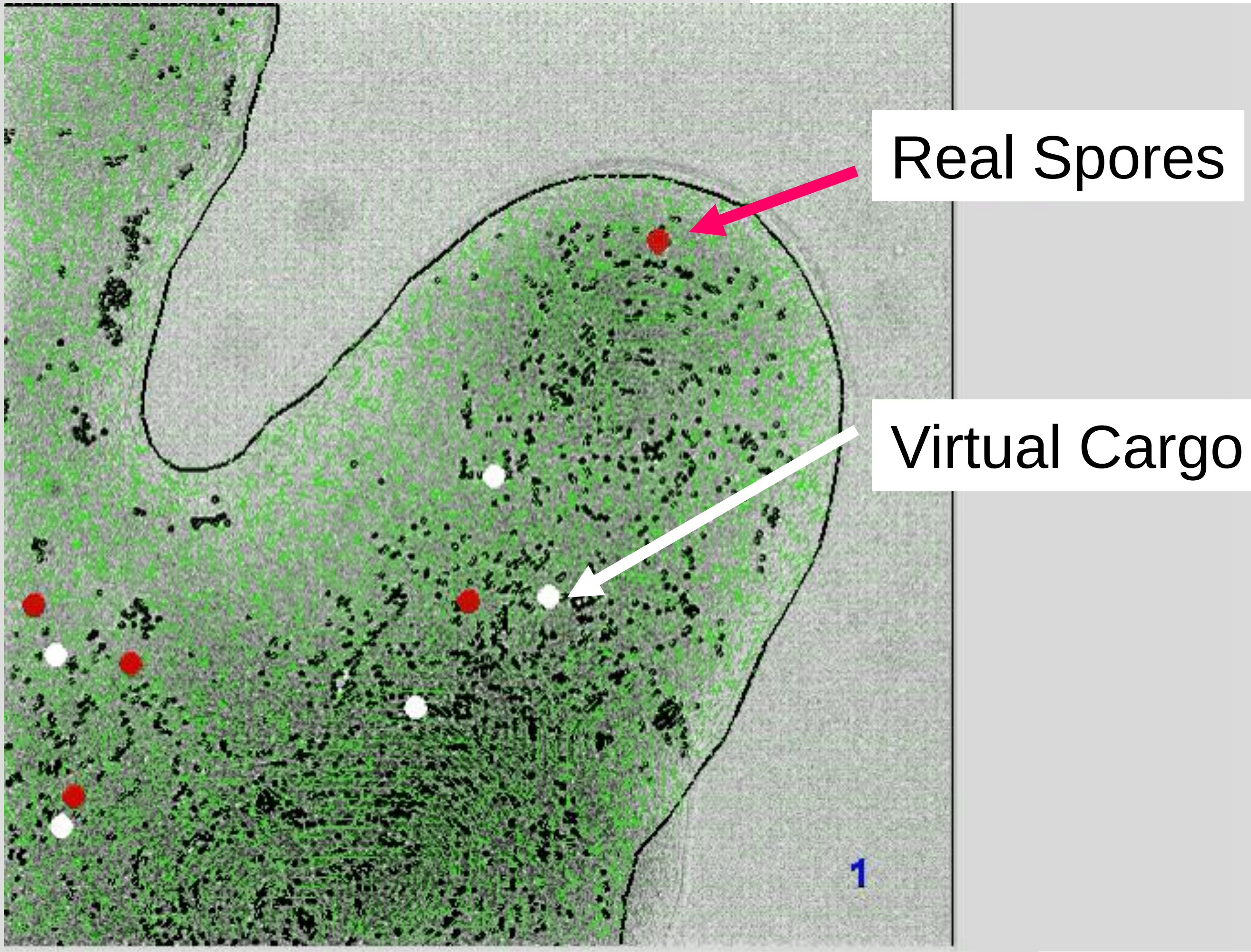
Attraction

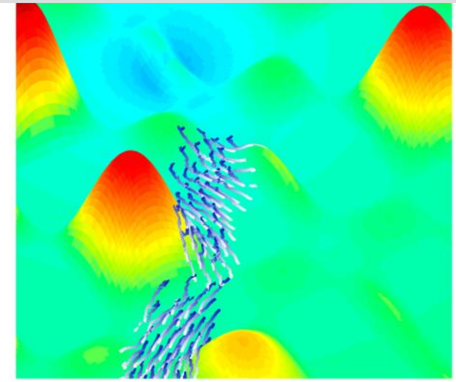


Hitching a Ride with Bacteria

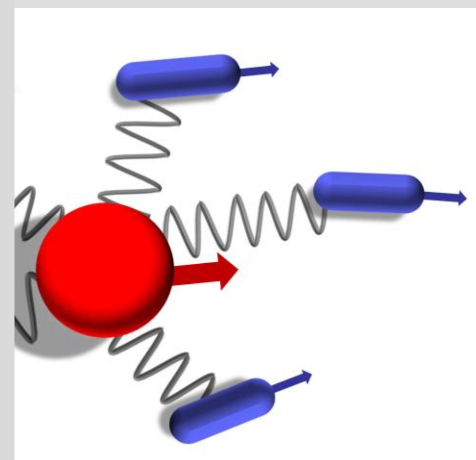


Physics Based Understanding





Comp Bio 2011



With Adi Shklarsh, Alin Finkelstein, Gil Ariel, Oren Kalisman Colin Ingham Roy Soci INTERFACE (2012 to be published)

The Bacteria Benefit