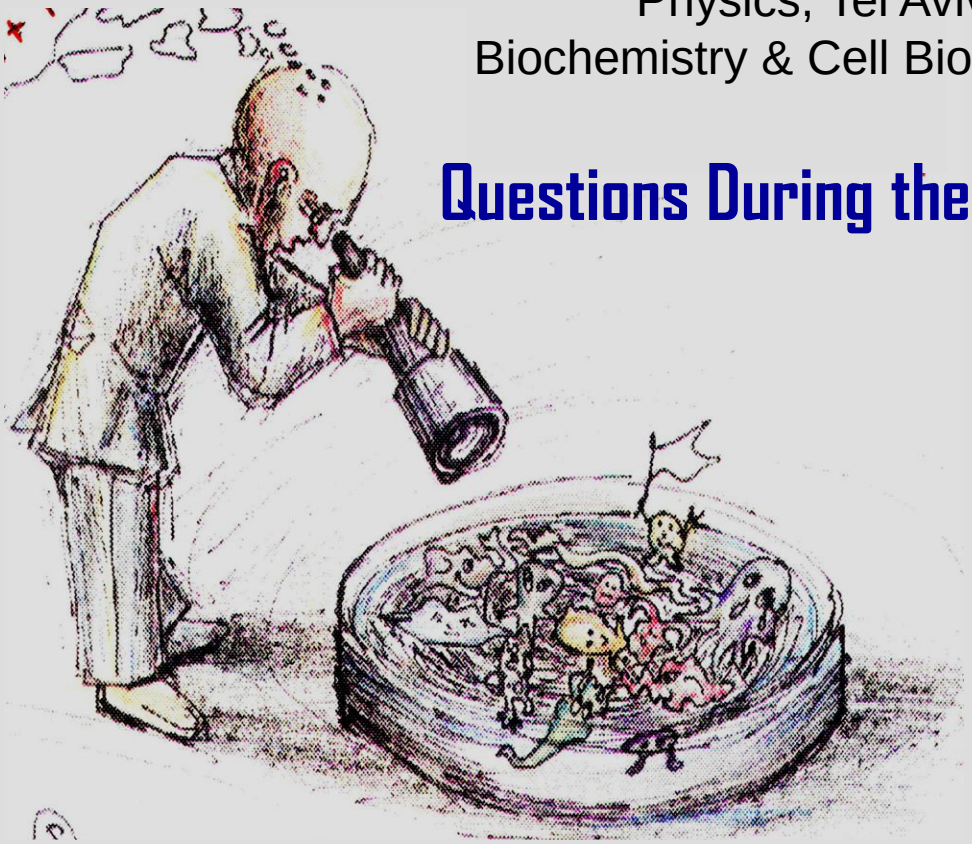
From Bacterial Swarming Logistics to Cancer Metastatic Migration

Eshel Ben-Jacob

Physics, Tel Aviv University
Biochemistry & Cell Biology, Rice University



Questions During the Lecture are Encouraged

KI-Net CSCAMM Workshop , Univ. Maryland, November 5-9, 2012

The Big Challenges

Metastasis Colonization
Dormancy and Relapse
Multiple Drug Resistance

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

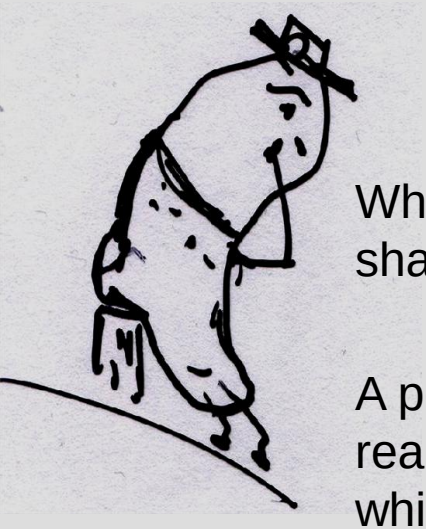
Looking at bacterial sociality as a source of inspiration and suggestion

Bacterial Survival Strategies Suggest Rethinking Cancer Cooperativity

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

Parallels Between Bacteria and Cancer

Why?



Why is it that cancer, a disease of eukaryotic organisms, shares so many features with a colony of prokaryotes?

A possible resolution to this conundrum comes from the realization that cancer represents an atavistic form of life, which ensues following a breakdown of the regulatory processes that underlie multicellular organization of eukaryotic cells.

This breakdown unlocks 'ancient toolkits' of pre-existing adaptations.

Thus, the cancer cells resort to more fundamental (primitive) survival strategies that have been perfected by bacteria.

Davis and Lineweaver *Phys. Biol.* (2011)
Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors

Ben-Jacob et al *Trends in Microbiology* (2012)

Collaborations & Acknowledgments

Tel Aviv University	Adi Shklarsh, Ilan Tsarfaty, Inbal Hecht, Assaf Zaritsky
Tel Aviv University	Gil Ariel
Rice University	Herbert Levine, Jose' Onuchic
Johns Hopkins	Donald Coffey
University of Michigan	Leonard Sander
Asaf Harofeh Medical Center	Shai Efrati

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The Tauber Family Foundation, Tel Aviv University

Today

Why Bacteria and Cancer?

Bacterial Swarming Logistics & Cancer Cell Migration

Reflections on Cancer Selection of navigation Strategy

Reflections on "Cyber Warfare" against cancer

Today

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Bacterial Drug Resistance
#1 World Health Problem
Why?
The Wisdom of the Crowd
The Bacteria Strike Back

Cooperative Behavior

Task Distribution and Cell Differentiation

Sharing Resources and Risks

Learning from Experience

Collective Decisions

Changing the Environment

Planning for the Future

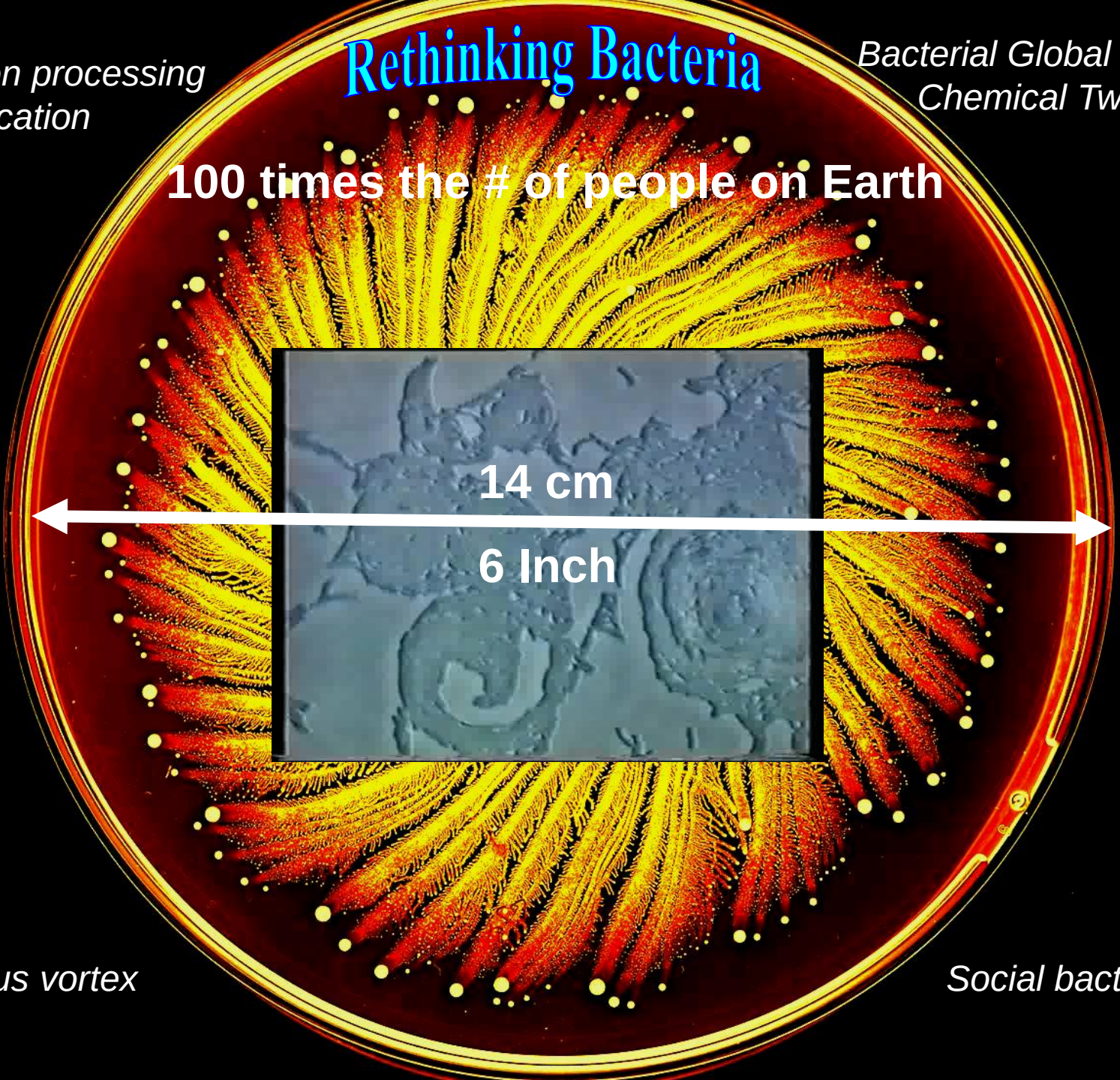
Ben-Jacob, *Roy. Soci*. 2003 ;
Ben-Jacob, et al Trends in Microbiology 2004 , 2012

Sensing
Information processing
Communication
Decisions

Rethinking Bacteria

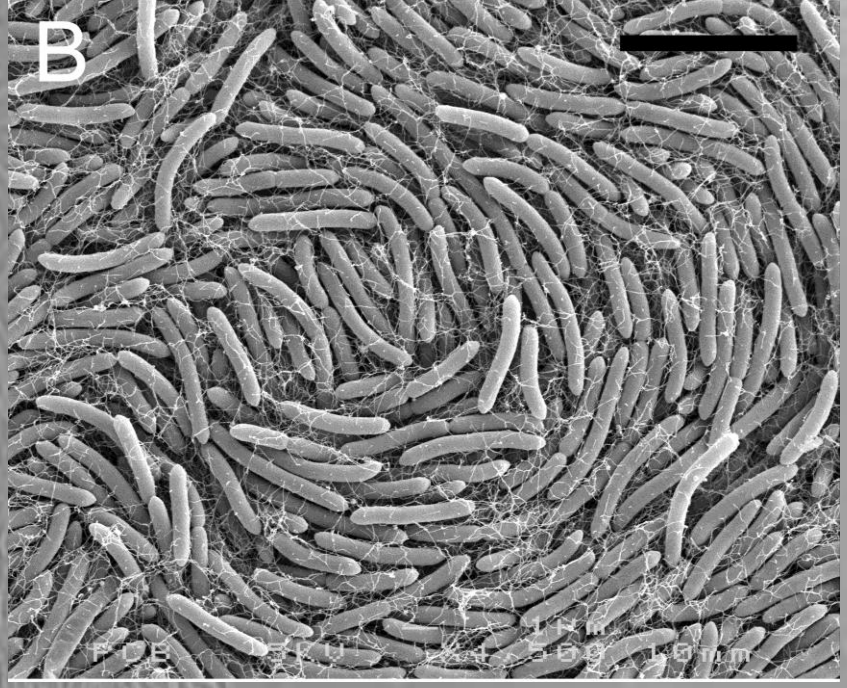
Bacterial Global Village
Chemical Twittering

100 times the # of people on Earth



Paenibacillus vortex

Social bacteria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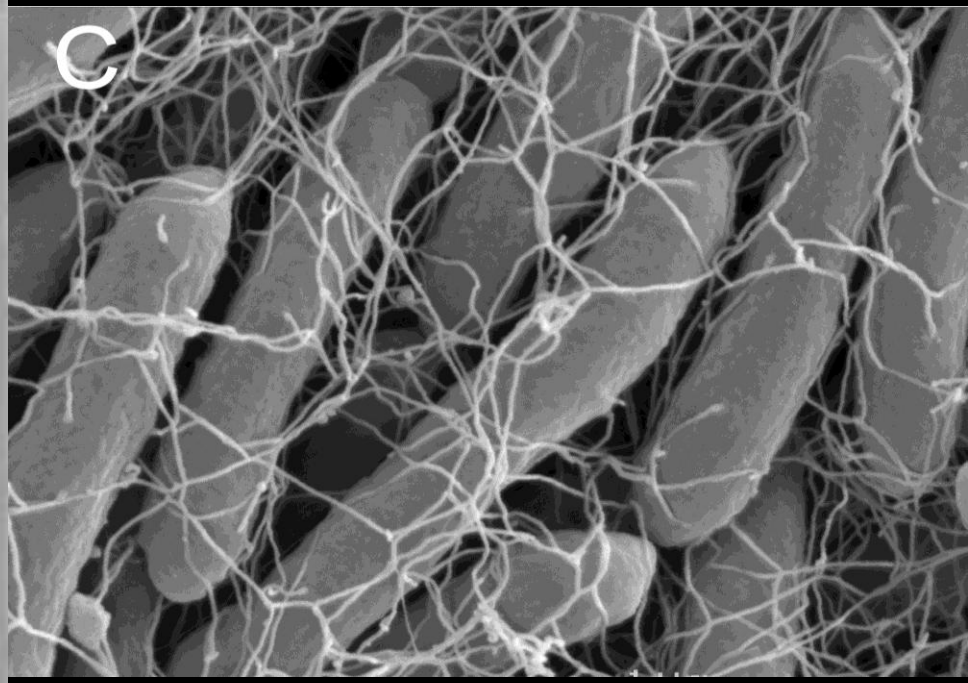
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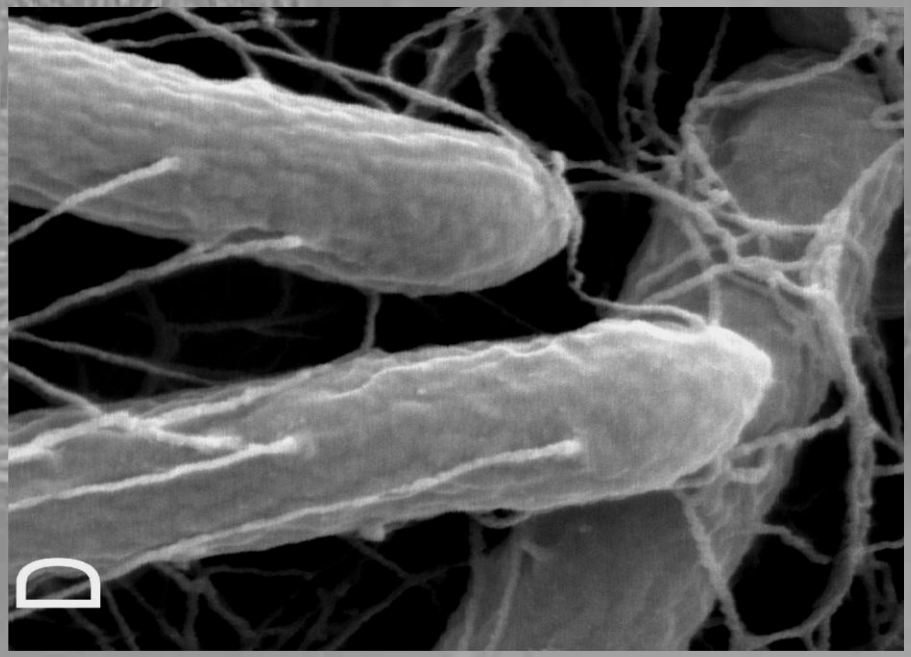
D


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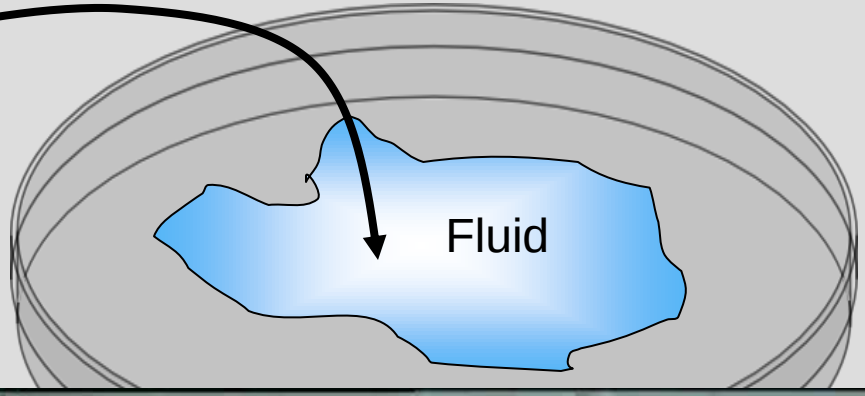
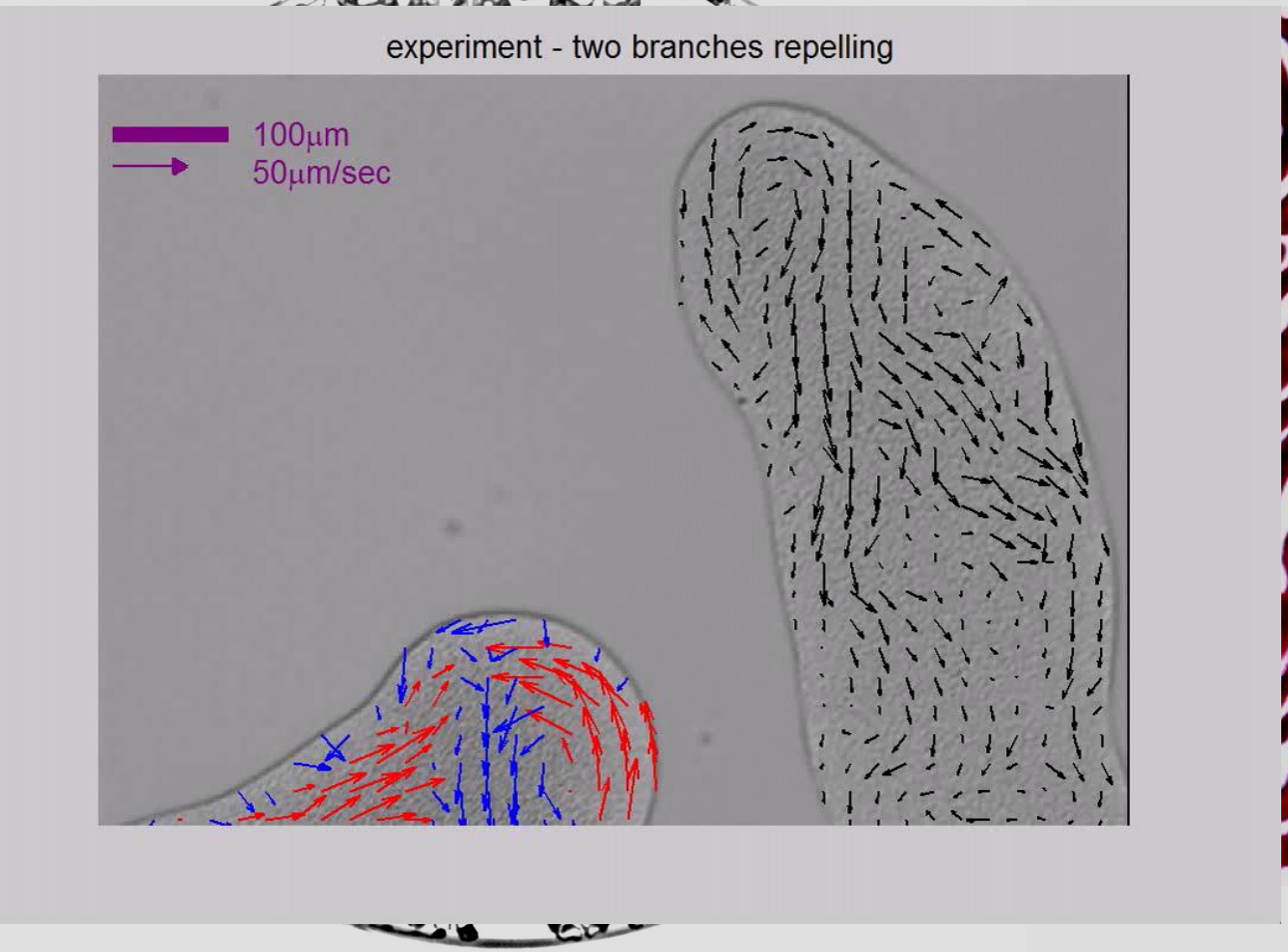
Variability of cells composing a vortex

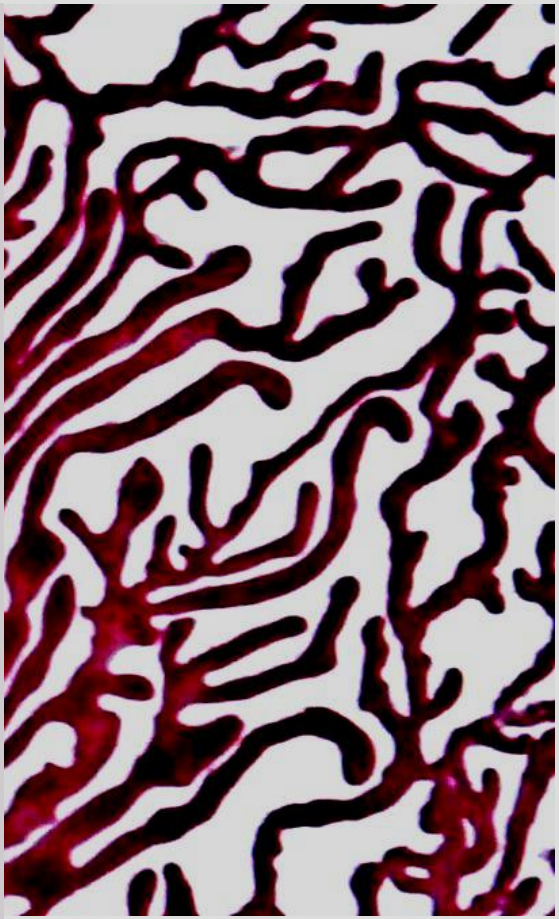
Breaking a vortex and let the cells move



Searching for New Territories

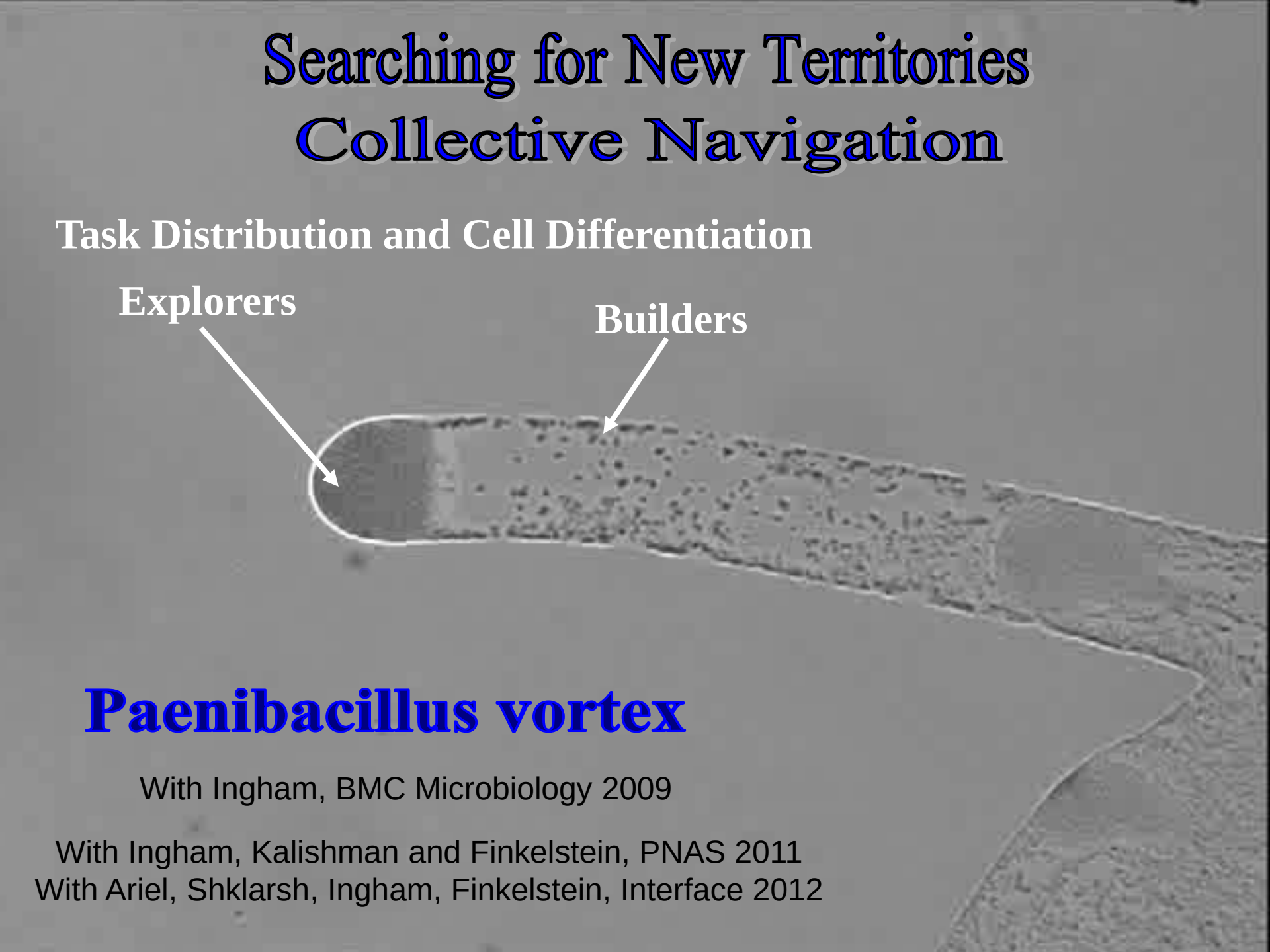
With Ingham, Kalishman and Finkelstein, PNAS 2011
With Ariel, Shklarsh, Ingham, Finkelstein, Interface 2012





Searching for New Territories
Collective Navigation

Task Distribution and Cell Differentiation

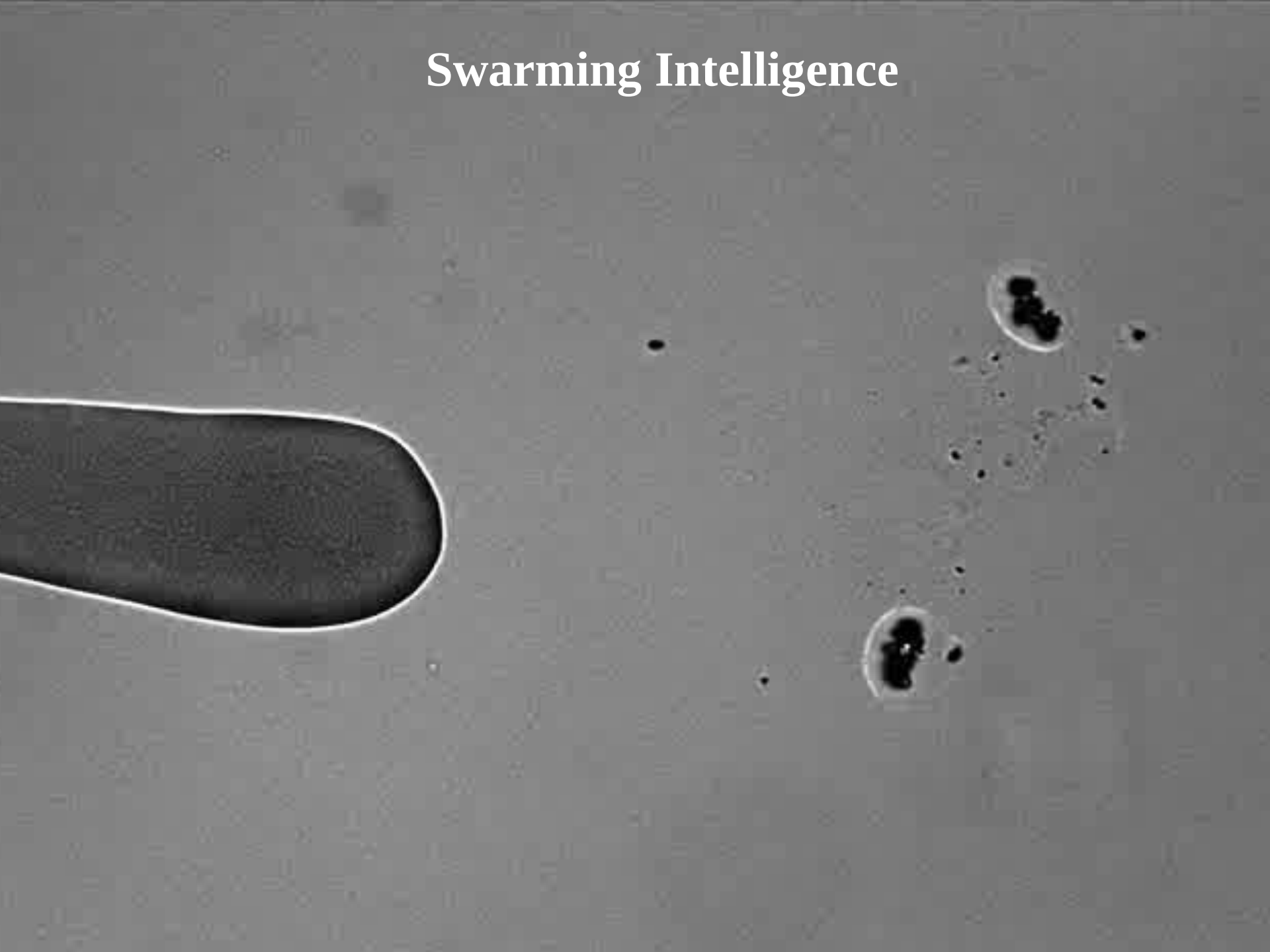


Paenibacillus vortex

With Ingham, BMC Microbiology 2009

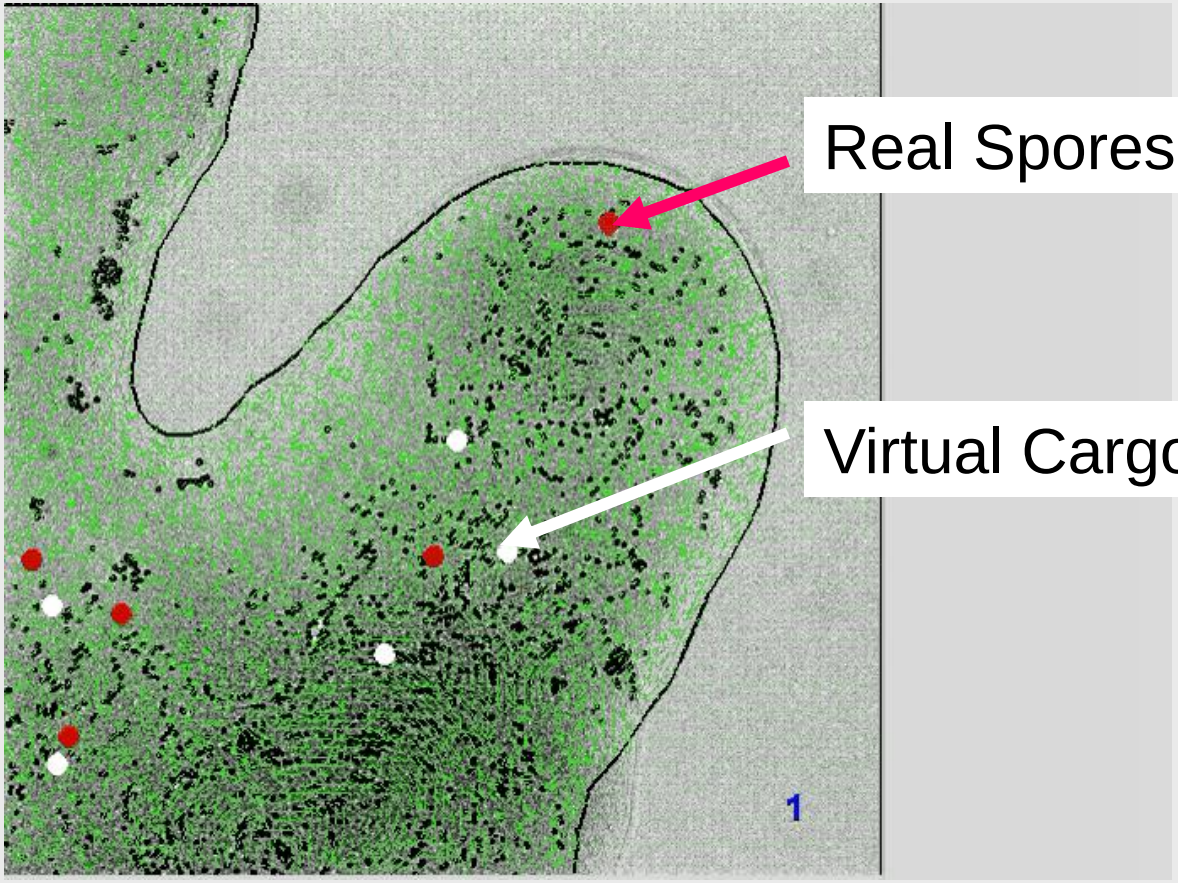
With Ingham, Kalishman and Finkelstein, PNAS 2011
With Ariel, Shklarsh, Ingham, Finkelstein, Interface 2012

Swarming Intelligence

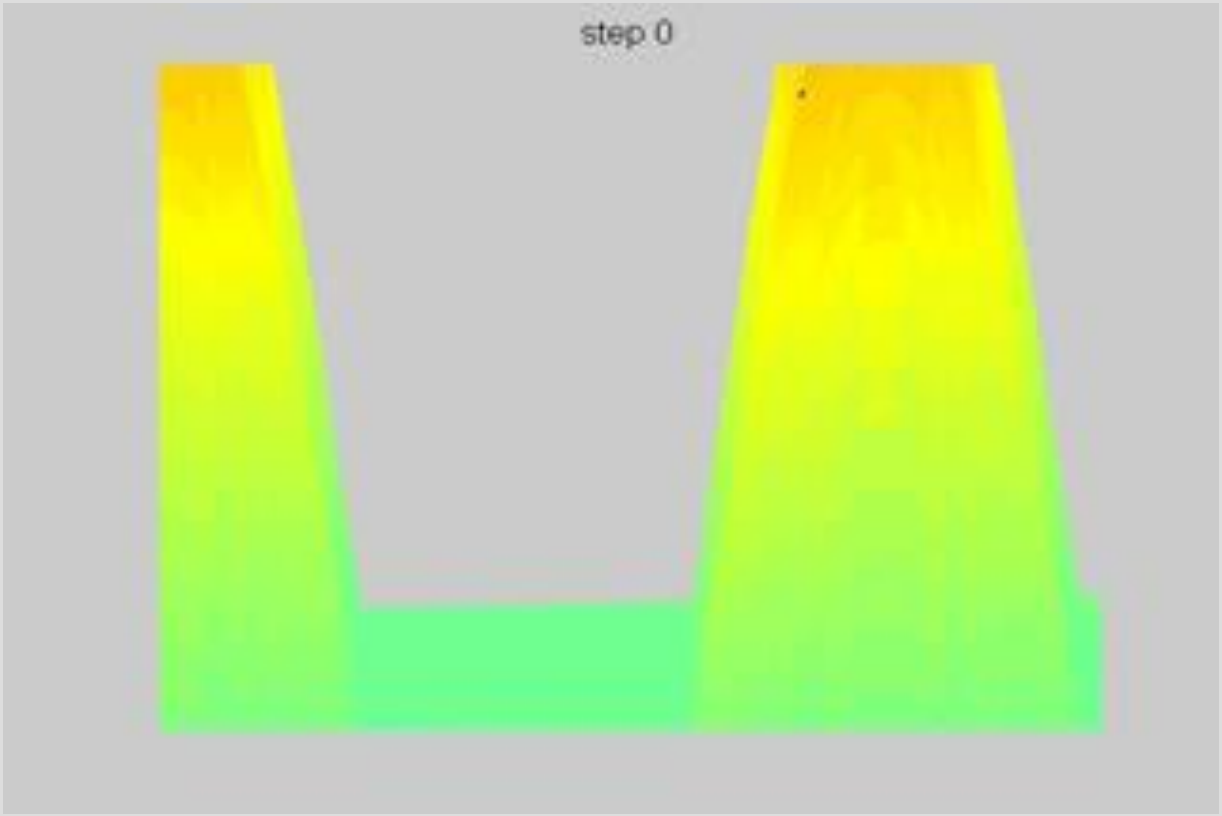


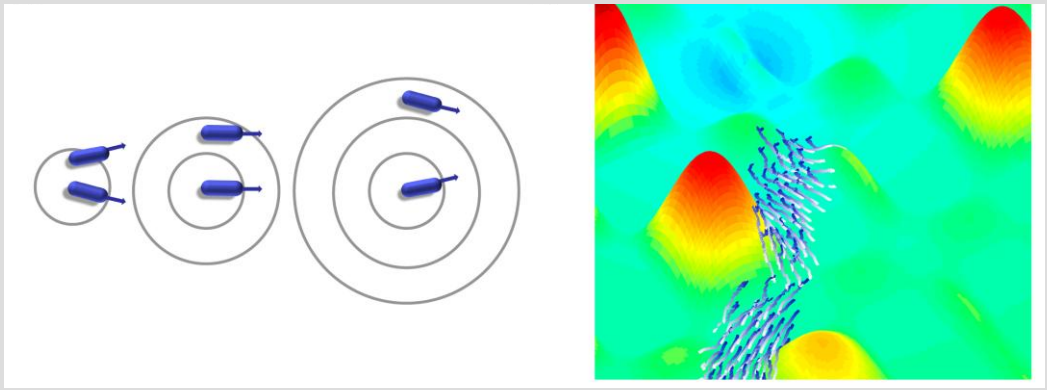
Hitching a Ride with Bacteria

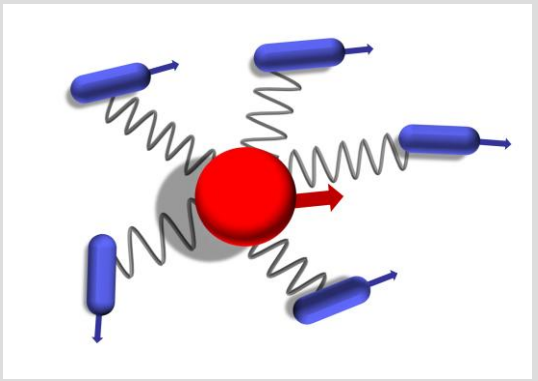
Fungal spores hitching a ride on bacterial swarms
Bacteria use the fungal mycelia as natural bridges



With Ingham, Kalishman and Finkelstein, PNAS 2011
With Ariel, Shklarsh, Ingham, Finkelstein, Interface 2012

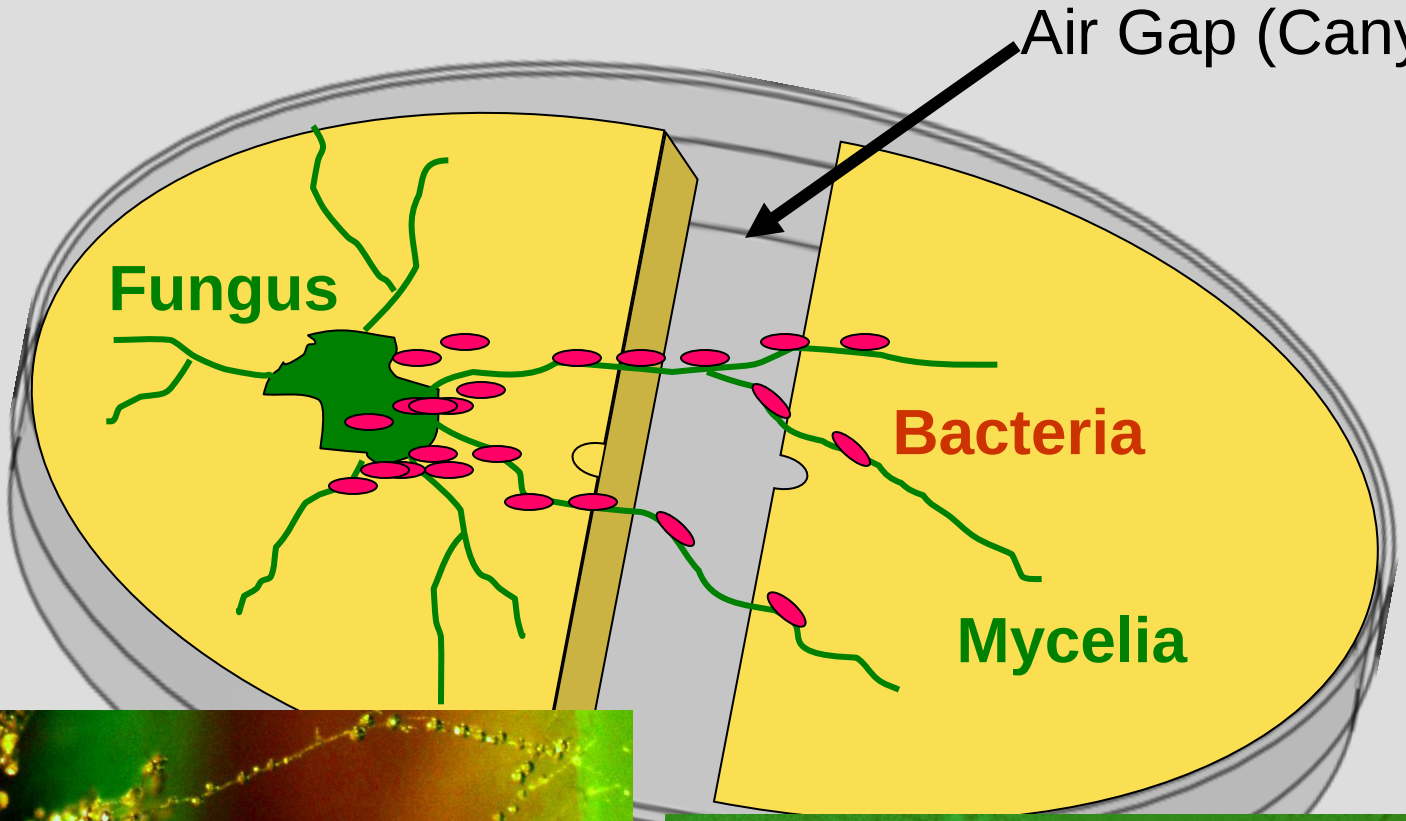


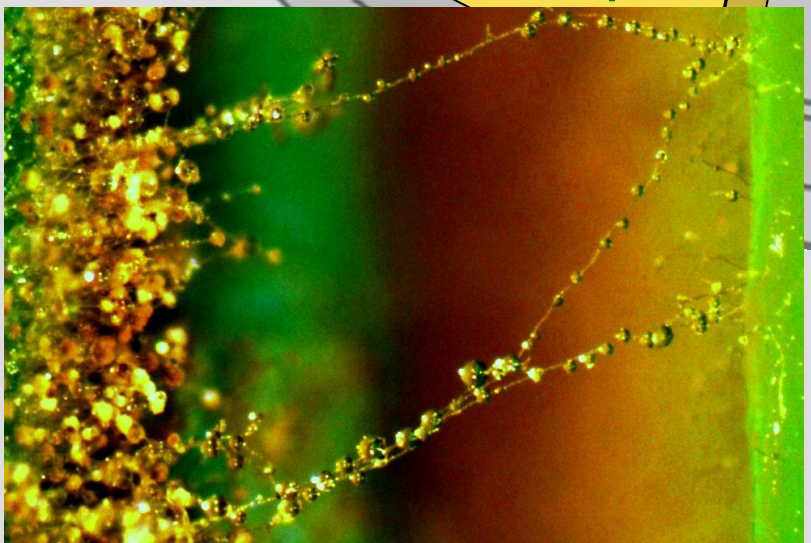


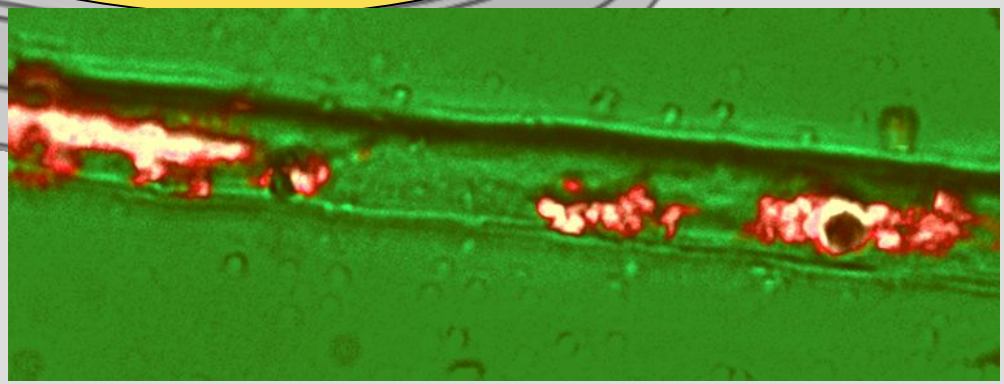


With Adi Shklarsh, Alin Finkelstein, Gil Ariel, Oren Kalisman Colin Ingham
Roy Soci INTERFACE (2012 to be published)

The Bacteria Benefit







Today

Why Bacteria and Cancer?

Bacterial Swarming Logistics **& Cancer Cell Migration**

Reflections on Cancer Selection of navigation Strategy

Reflections on "Cyber Warfare" against cancer

Parallels Between Bacteria and Cancer

Rapid proliferation

High Phenotypic Variability
(Genetic&Epigenetic Plasticity)

Advanced Motility and Navigation

Rapid development of drug resistance

Dormancy (sporulation) and relapse (germination)

Capacity to Decoy the immune system

Cooperative behaviors

Deisboeck and Couzin *BioEssays* (2009)

Collective behavior in cancer cell populations

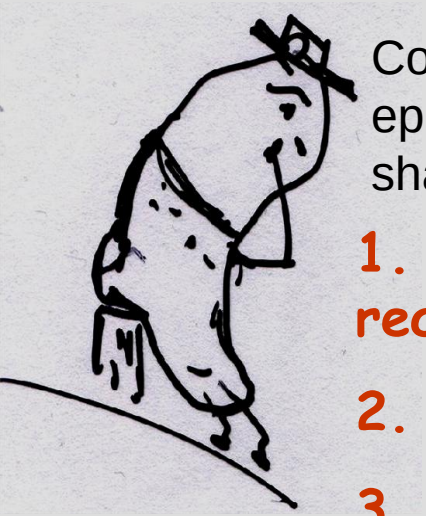
Austin et al Perspective in *Nature Reviews Cancer* (2011)

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

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

Bacterial Survival Strategies Suggest Rethinking Cancer Cooperativity

Why Advanced Communication?

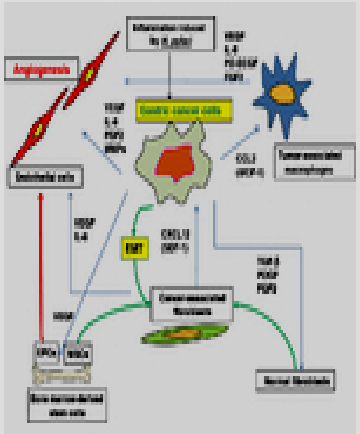


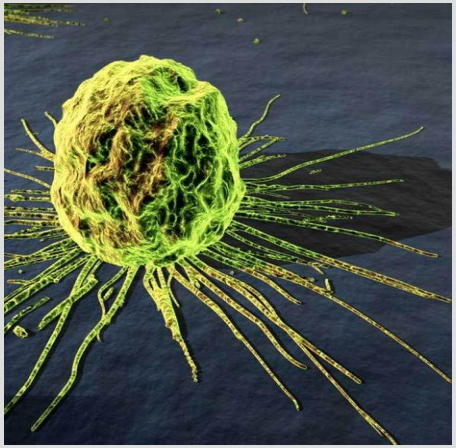
Collectively regulated innate plasticity (phenotypic, epigenetic and genetic diversification) is a key strategy shared by bacteria and cancer cells.

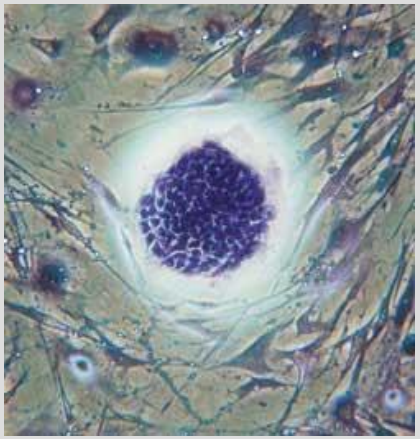
1. Coordination of heterogenic population requires linguistic plasticity
2. Decoy of the immune system
3. Enslaving stromal cells

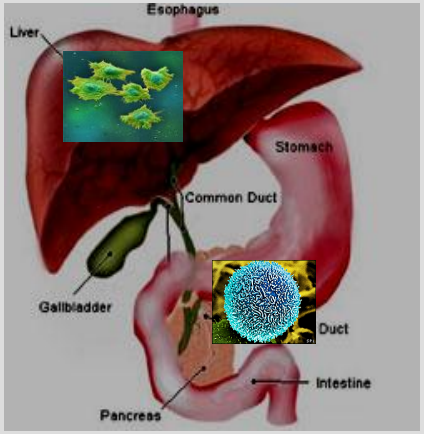
Bridging the Gap and Closing the Loop

Intracellular ⟺ Cellular ⟺ Multicellular ⟺ Metacommunity









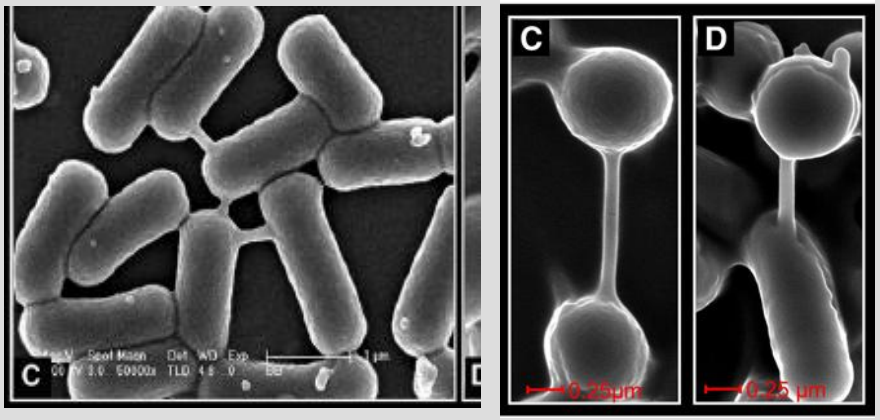
Advanced Communication

Physical interactions
Chemical signaling

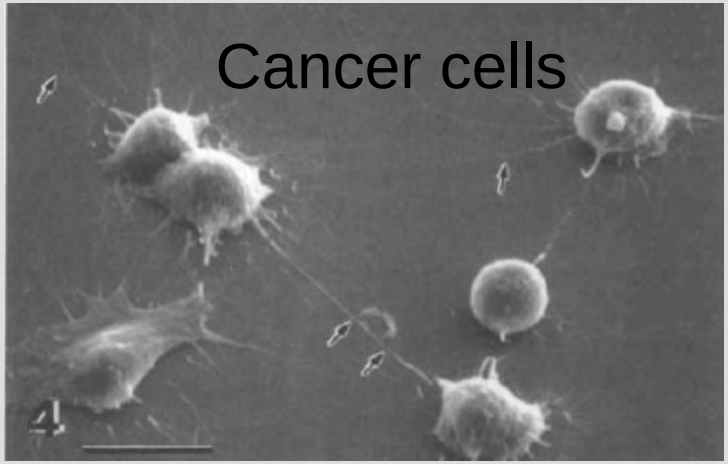
Exchange of genetic information -Exosomes

Gap junctions and Nanotubes
(calcium waves? electrical signals?)

Bacteria

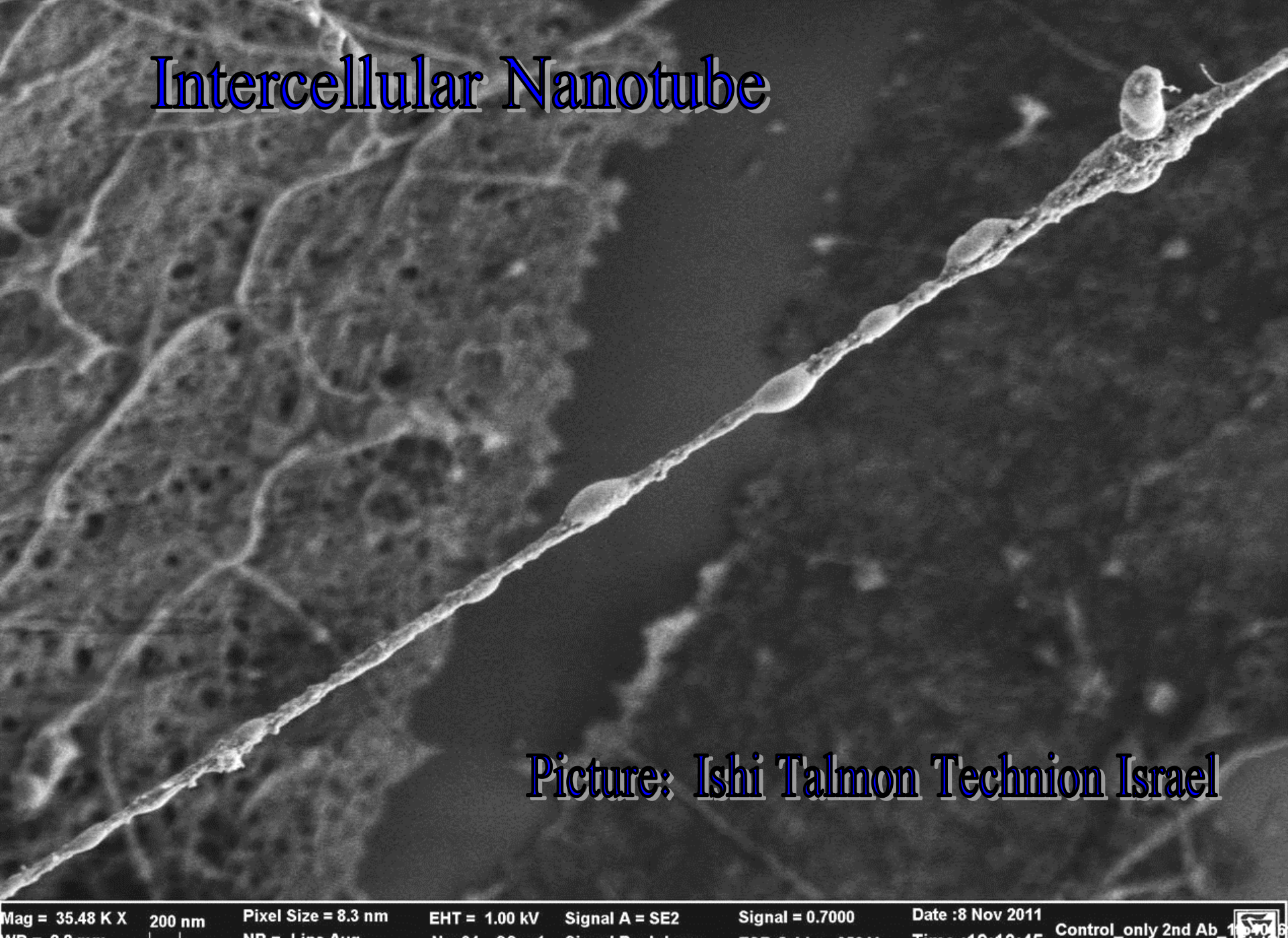


Dubey and Ben-Yehuda Cell 2011

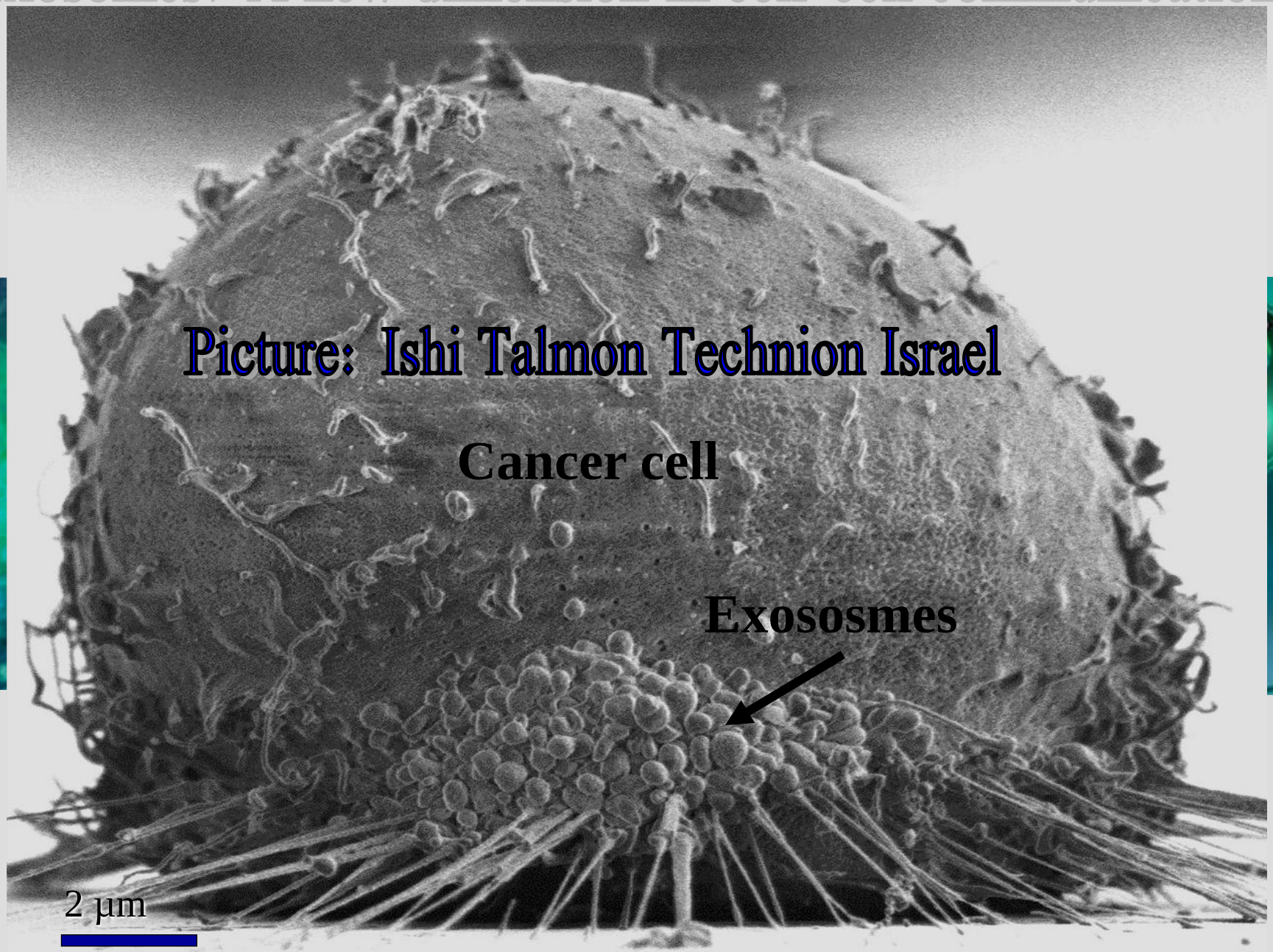


Gilloteaux et al *SCANNING* (1998)

Intercellular Nanotube



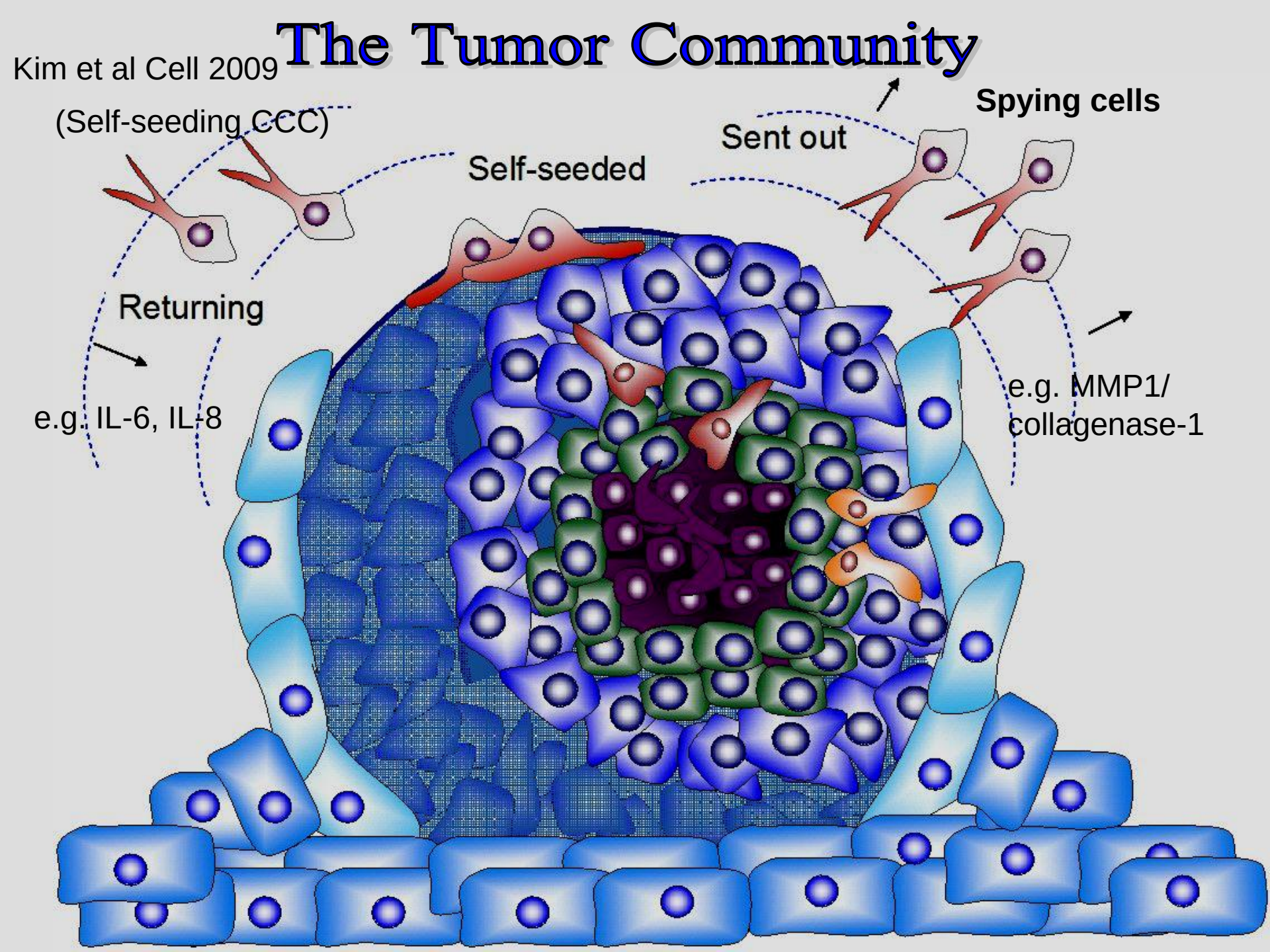
Exosomes: A new dimension in cell-cell communication



The Tumor Community

Kim et al Cell 2009

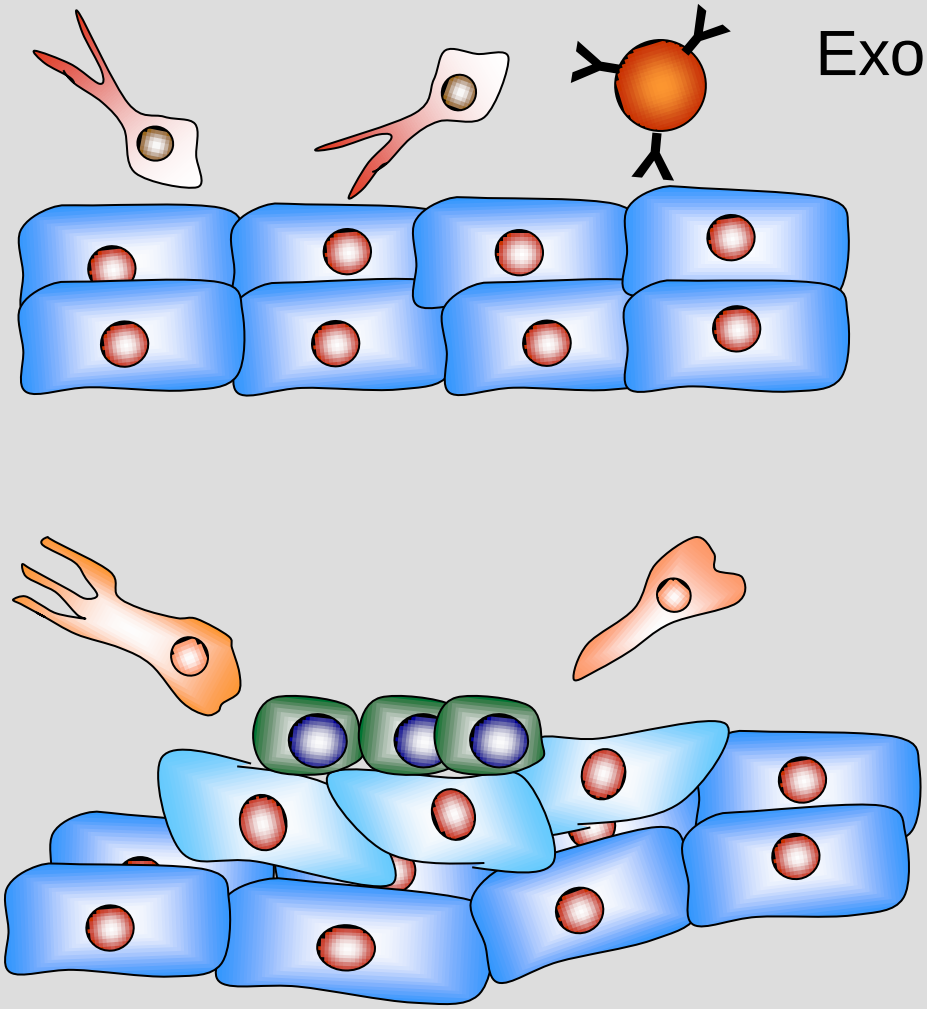
(Self-seeding CCC)



Selecting and Preparing the Niche

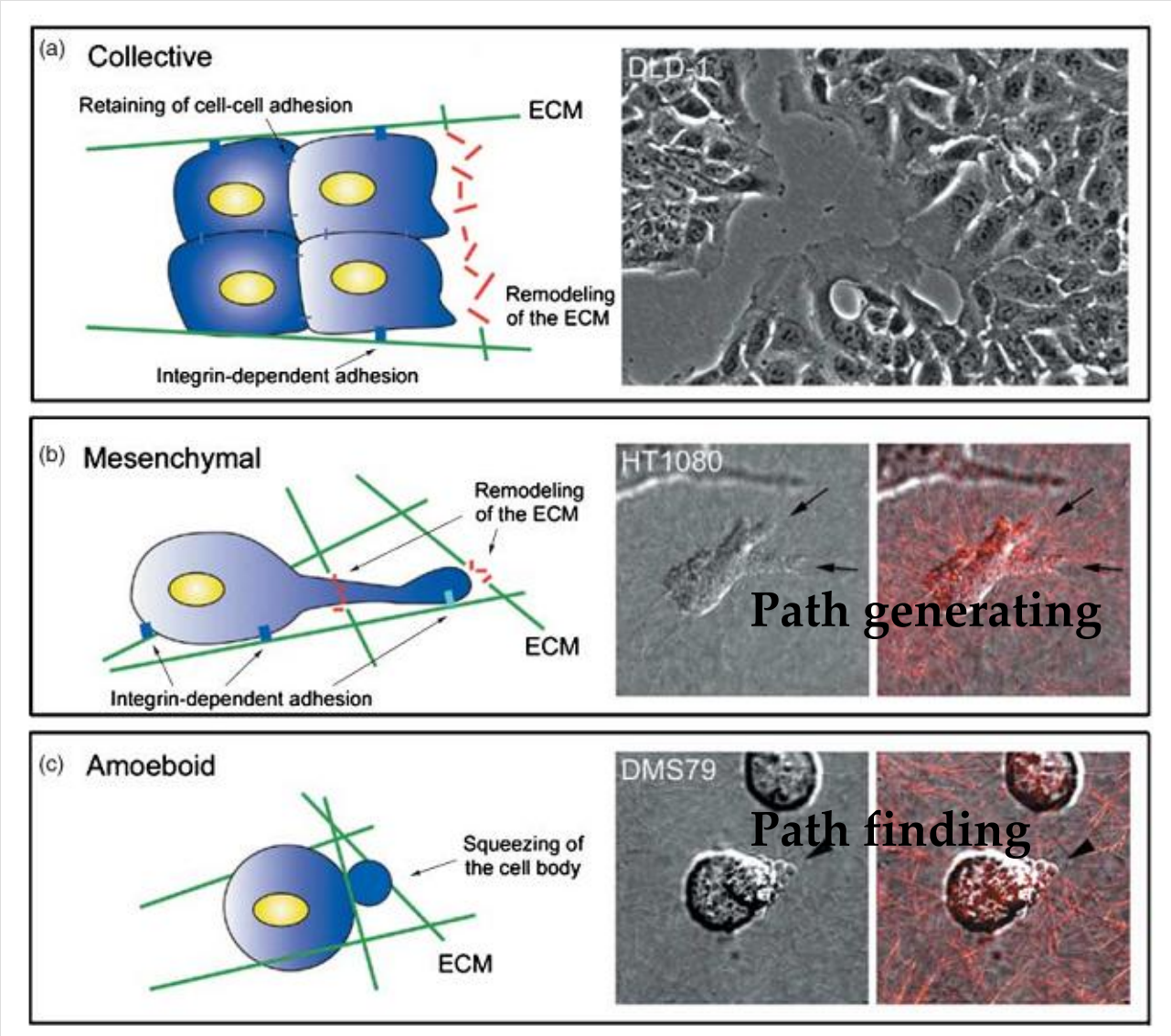
Spying Cells

Exosomes



Kaplan et al Nature 2005

Cancer Navigation Strategies



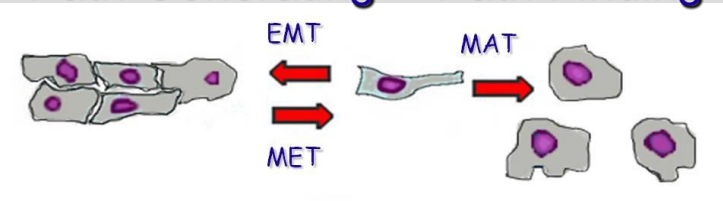
Yamazaki, Kurisu & Takenawa, Cancer Sci 96, 379 (2005)

Collective Migration

HGF/SF Induced collective motility

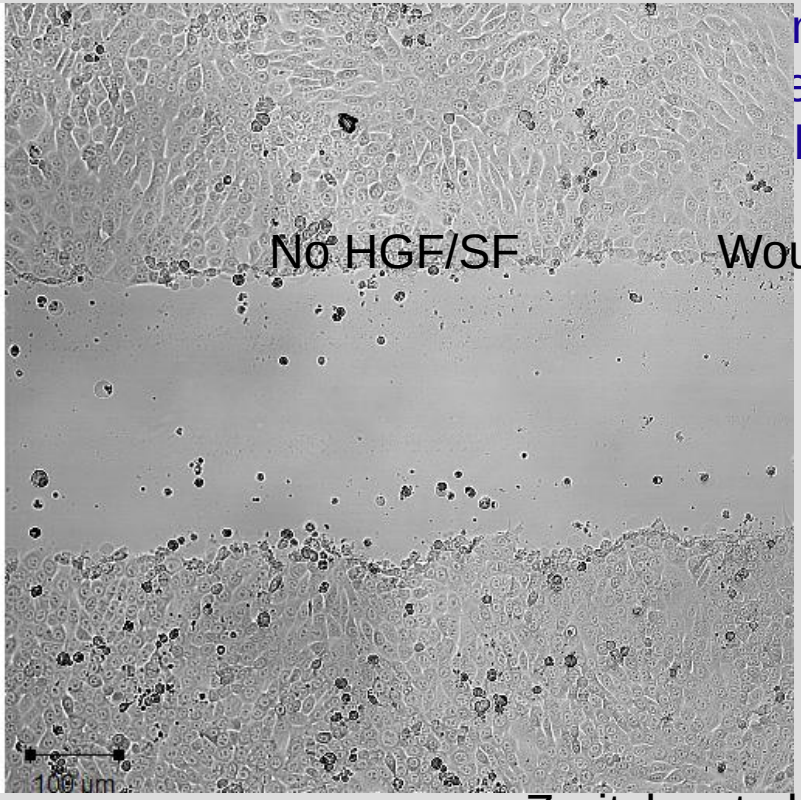
Work in progress with Assaf Zaritsky and Ilan Tsarfaty

Path Generating **Path Finding**

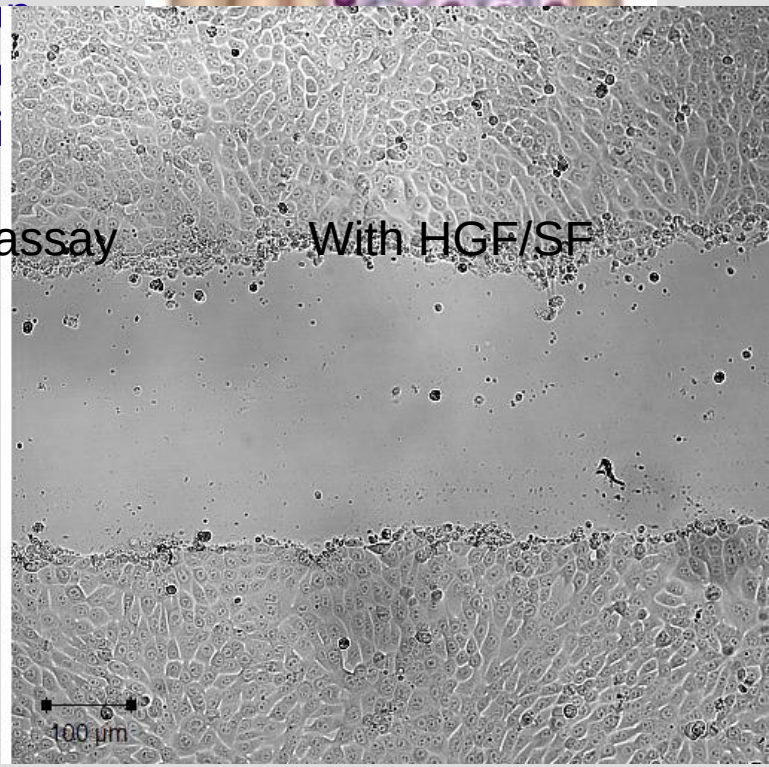


Collective Motility

mal cell Transitio
elial cell Transitio
boidal cell Transi

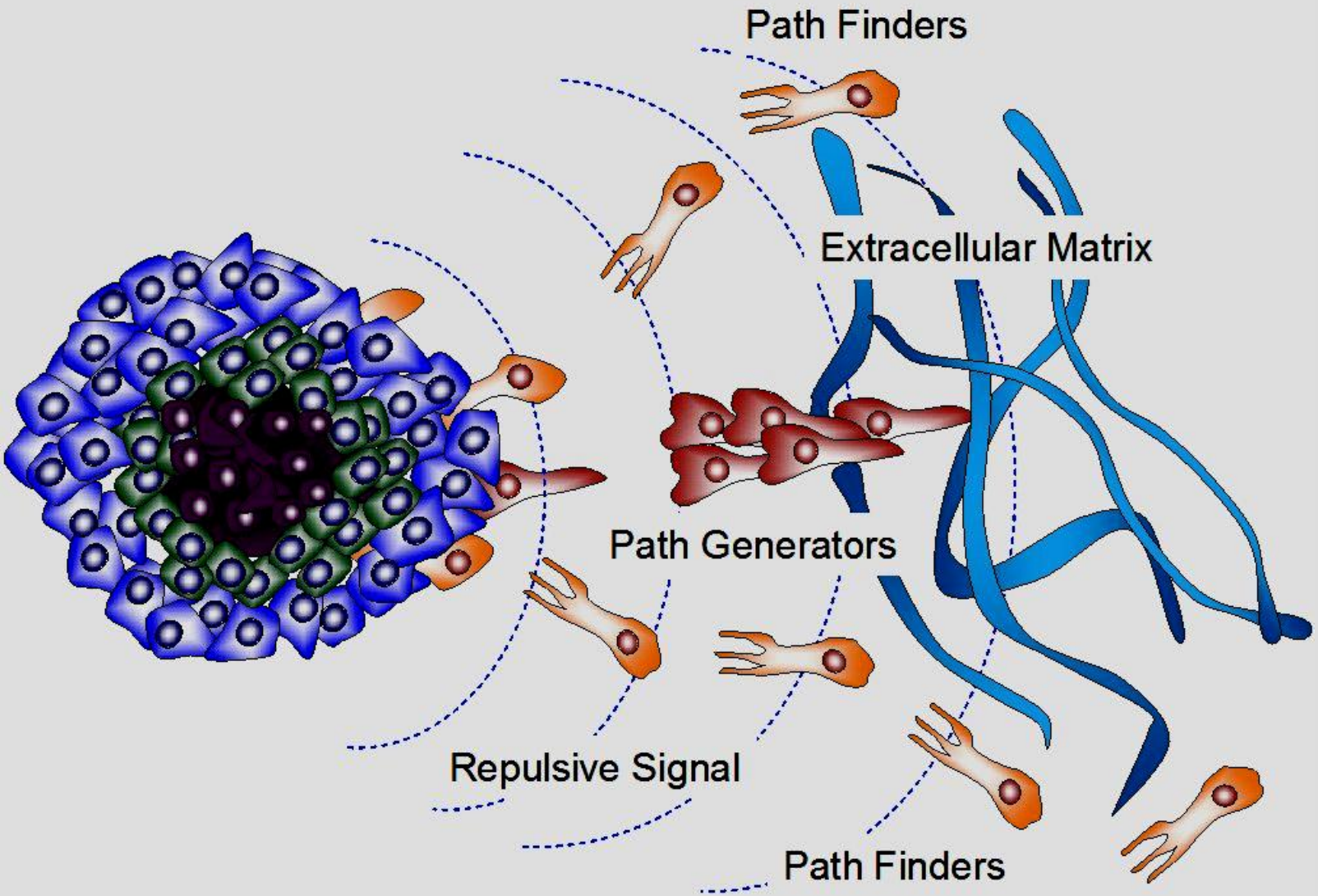


Wound healing-like assay



Zaritsky et al PLoS ONE in press 2012

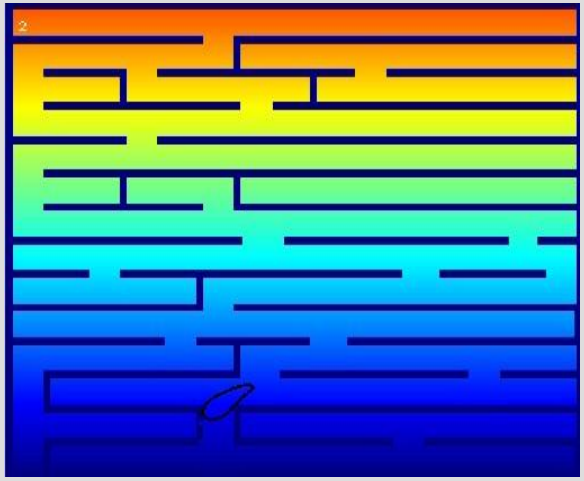
Cancer Navigation Strategies



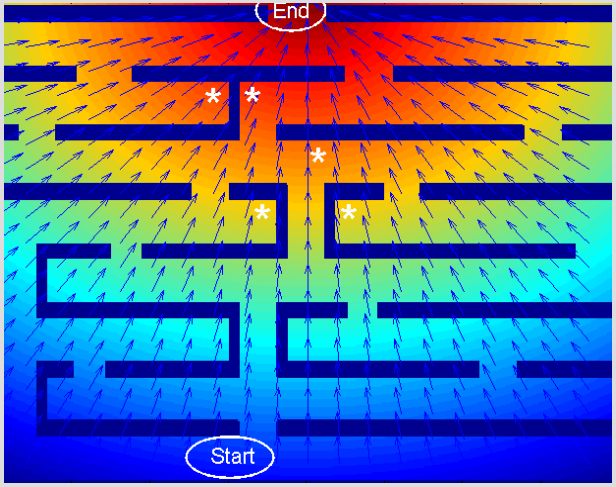
Ben-Jacob et al 2012

The ECM as a Maze

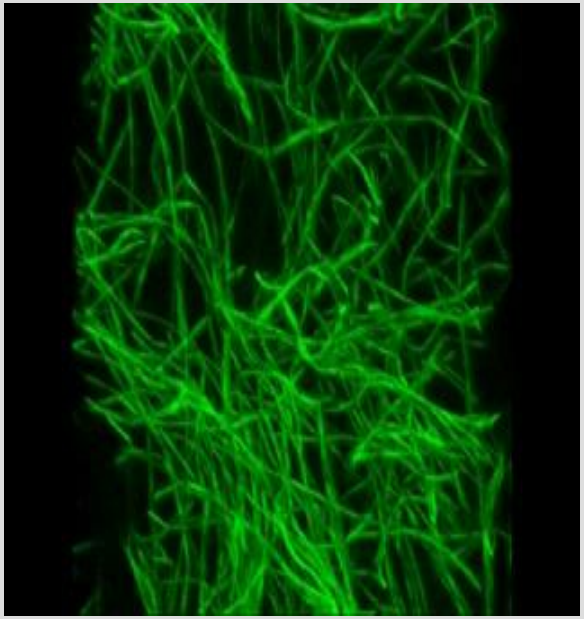
Chemical signaling



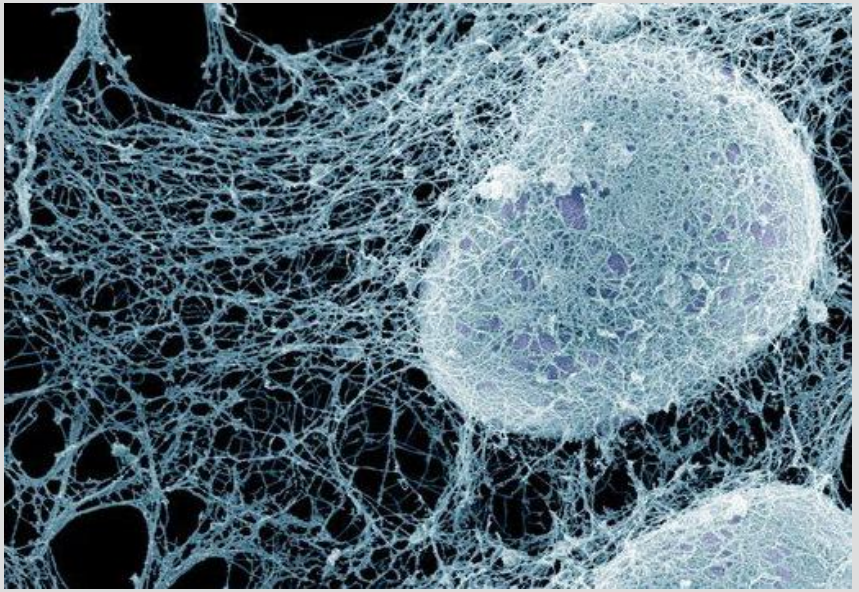
Attractive – from blood vessels



Repulsive – from the Tumor

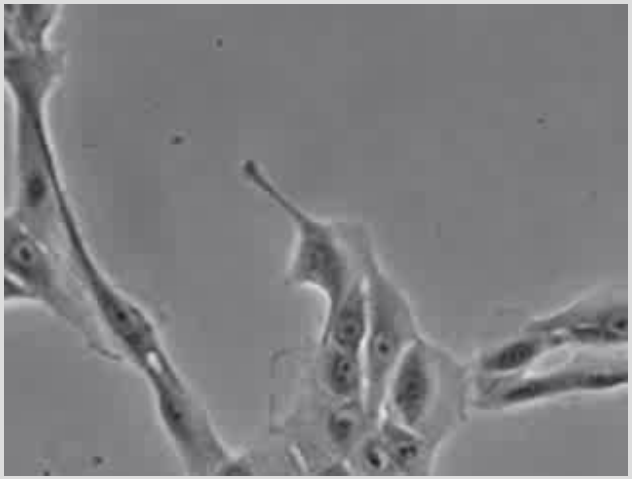


Collagen Mesh



Single Cell Motility - Amoeboid

(Dicty as a model for amoeboid motility)



Exp Cancer

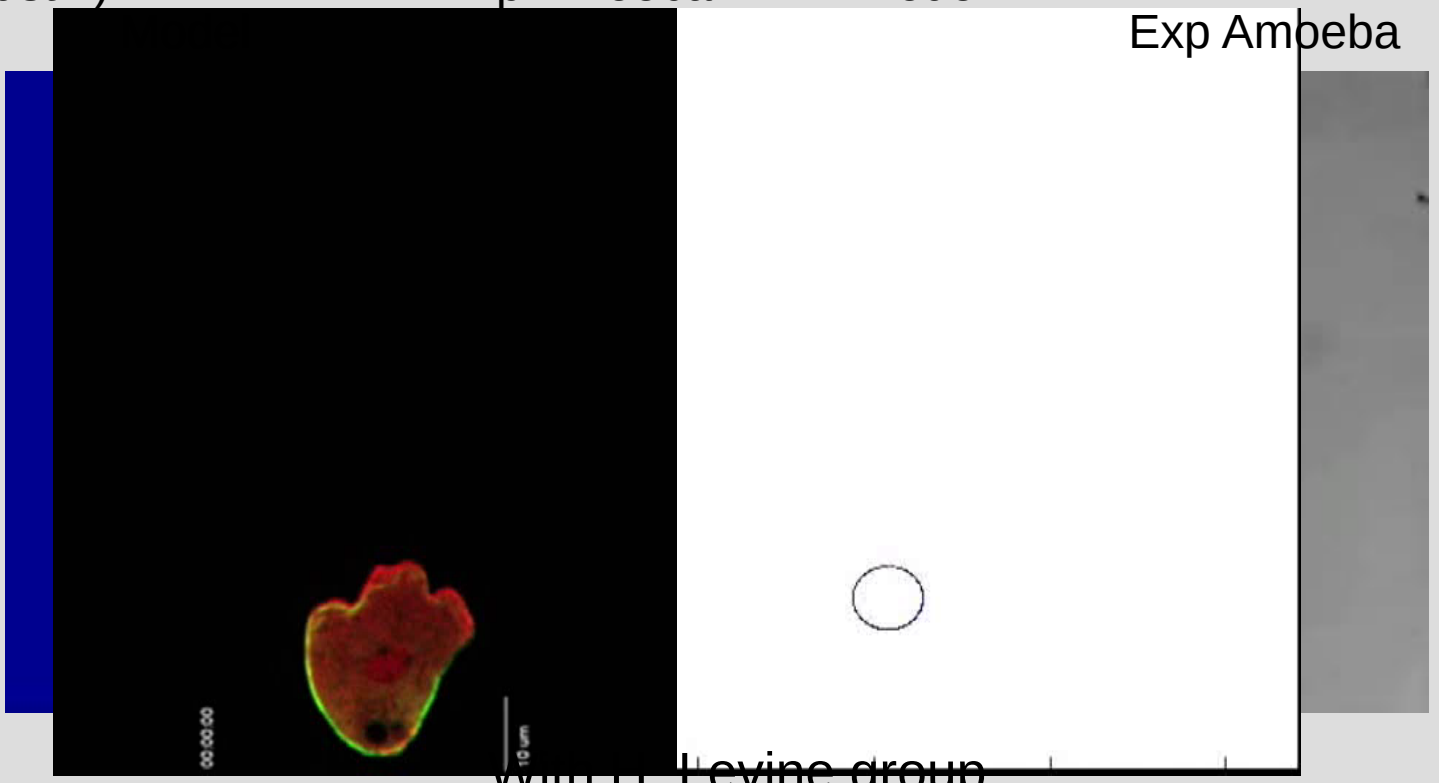
(Bob Austin)

Exp Amoeba

Model

Chemical gradient

Exp Amoeba

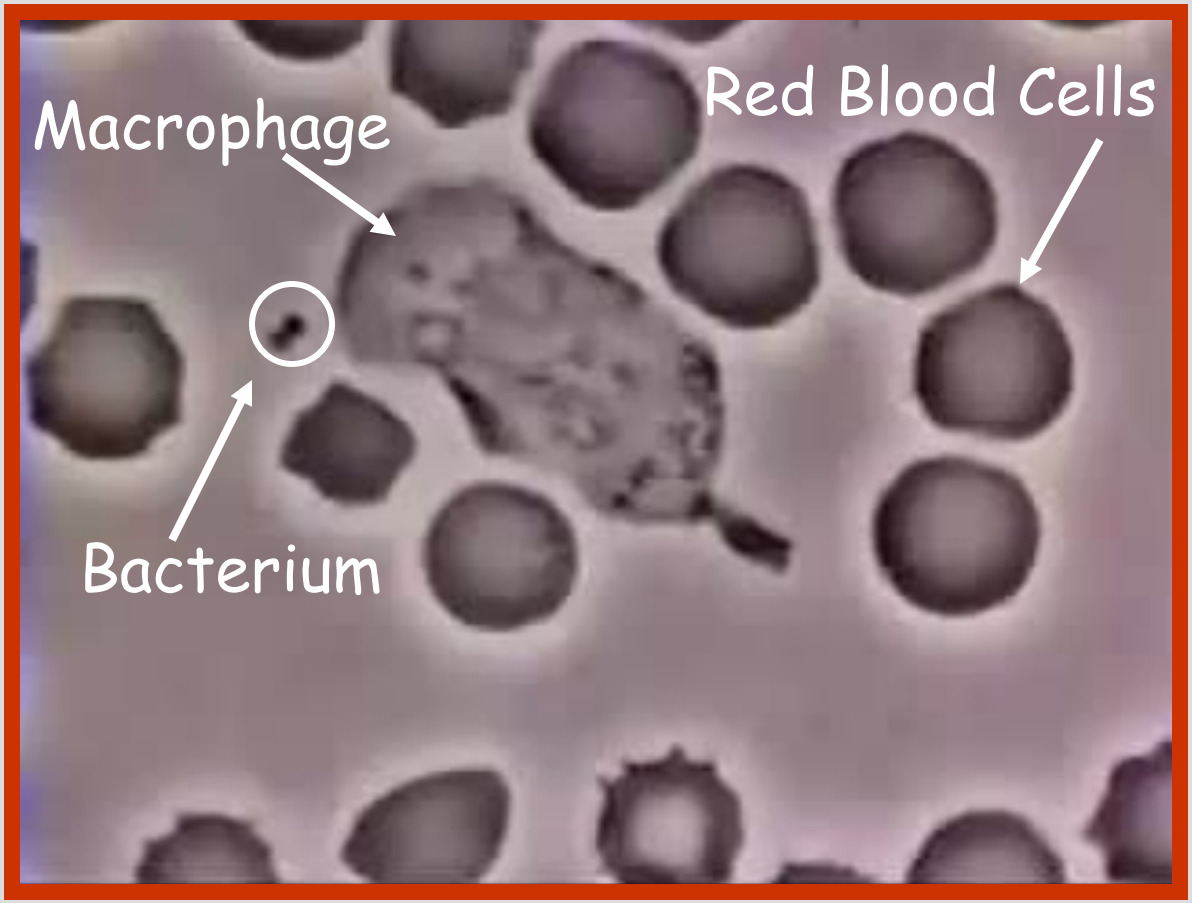


with H. Levine group

Hecht et al PLoS Comp Bio (2011)

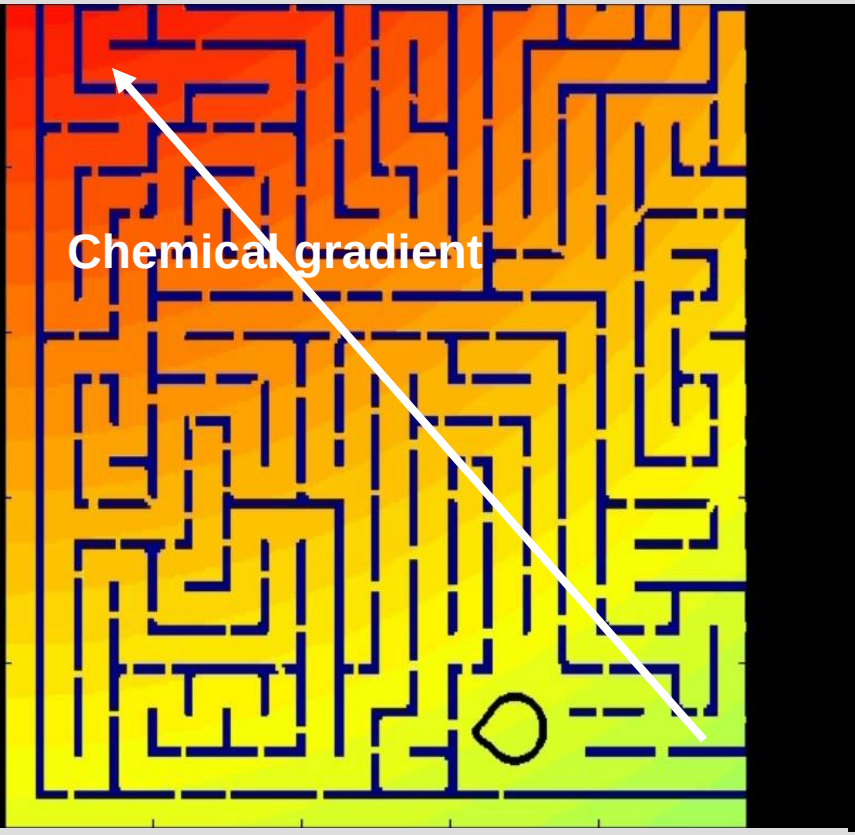
Energy – Risk Considerations

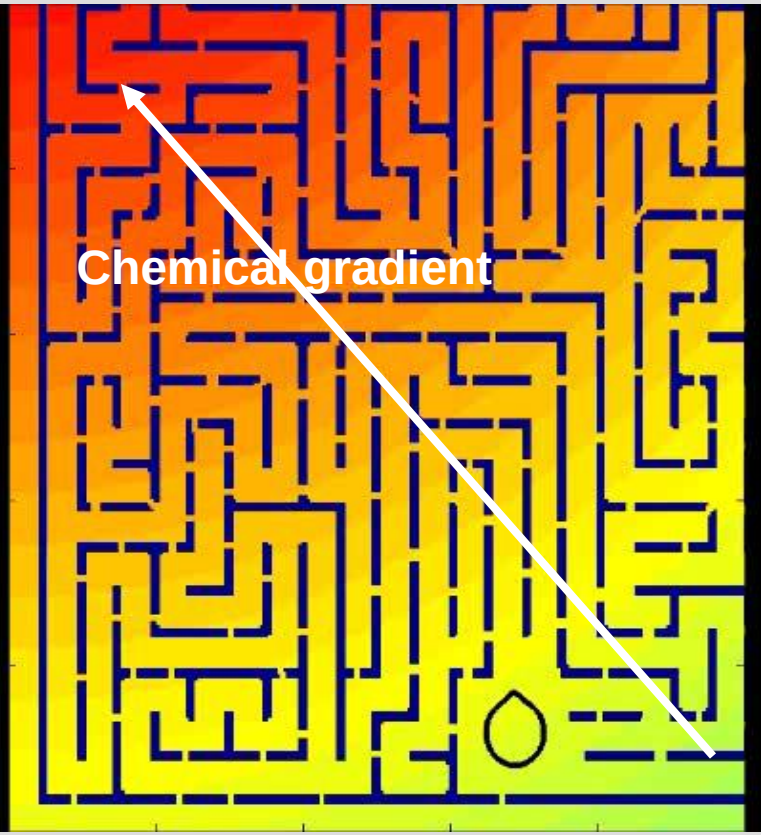
Let see how bacteria make-decisions



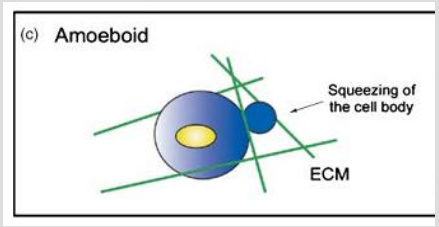
Path finder - Amoeboid

Path generator - Mesenchymal

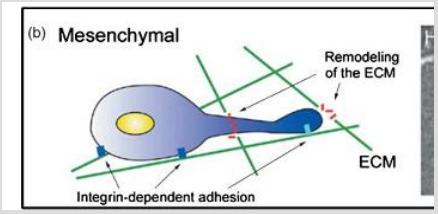




Flexible,
squeezes through small gaps



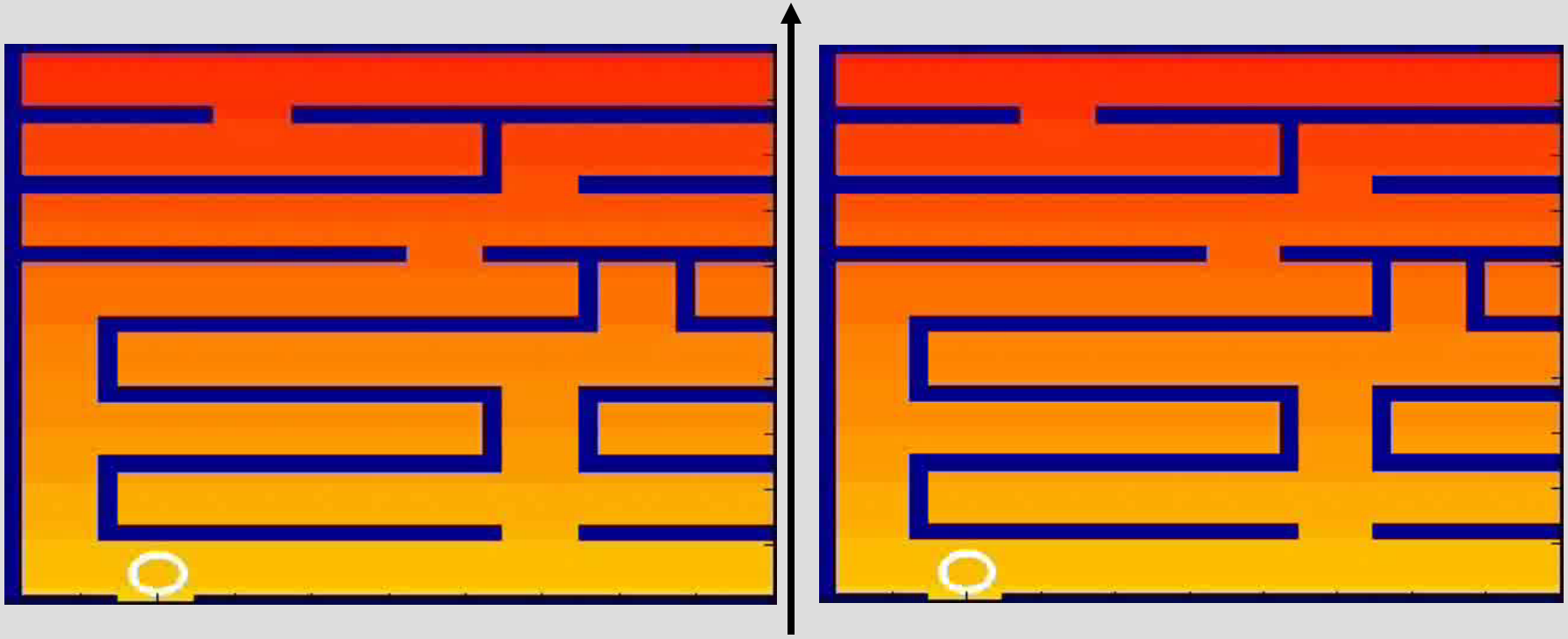
Rigid,
degrades the wall



Self-Assisted Navigation

Escaping traps by secretion of repulsive agent

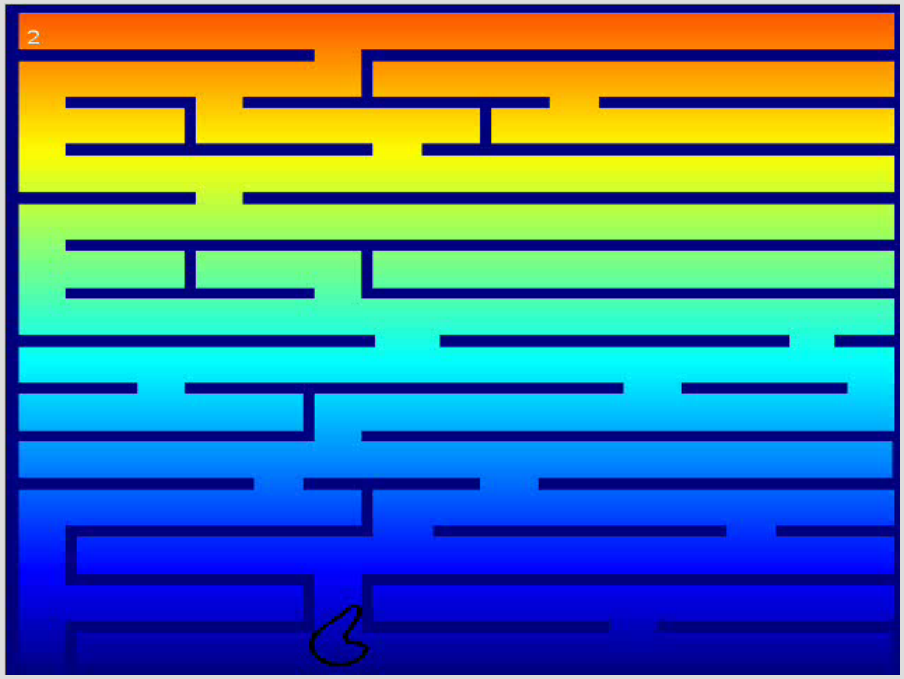
Predictions to be Tested



Trapped **Chemical gradient** Escaping

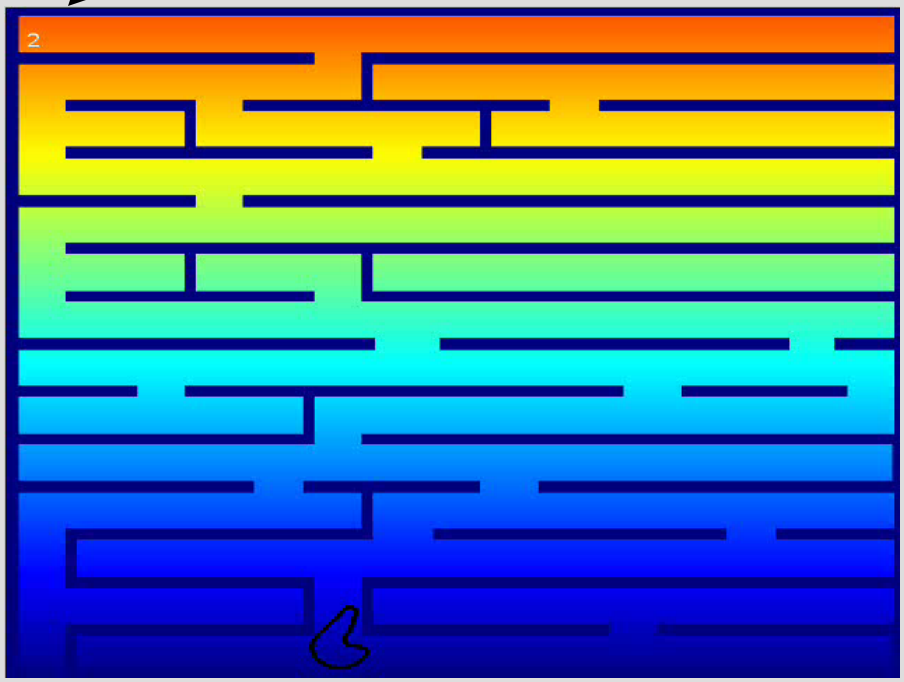
With Inbal Hecht, Herbert Levine, Wouter-Jan Rappel, PLoS ONE 2011

Invasion vs. Proliferation



Invasion only

Counter of cell divisions



Invasion and Proliferation

With Inbal Hecht and Ilan Tsarfaty

Model-based Predictions

Theoretical models can bridge the gap between intracellular processes, cell dynamics and population behavior

1. Proliferation is always beneficiary
2. But invading cells have much higher success rate relative to invasion in the absence of HGF!

3. At “bad times” (e.g. hypoglycemia and hypoxia conditions) proliferation should be limited, to allow enough resources for invasion.

4. Tumor growth induces repeating cycles of hypoxia and angiogenesis. Therefore, the population of colonizing cells is expected to always include a fraction of invading cells.

Therapeutic Implications?

Today

Why Bacteria and Cancer?

Bacterial Swarming Logistics & Cancer Cell Migration

Reflections on Cancer Selection of navigation Strategy

Reflections on "Cyber Warfare" against cancer

A New Challenge:
Deciding or Playing Dice

Looking for hints at the way bacteria decide fate

Gamblers should take a hint from bacteria

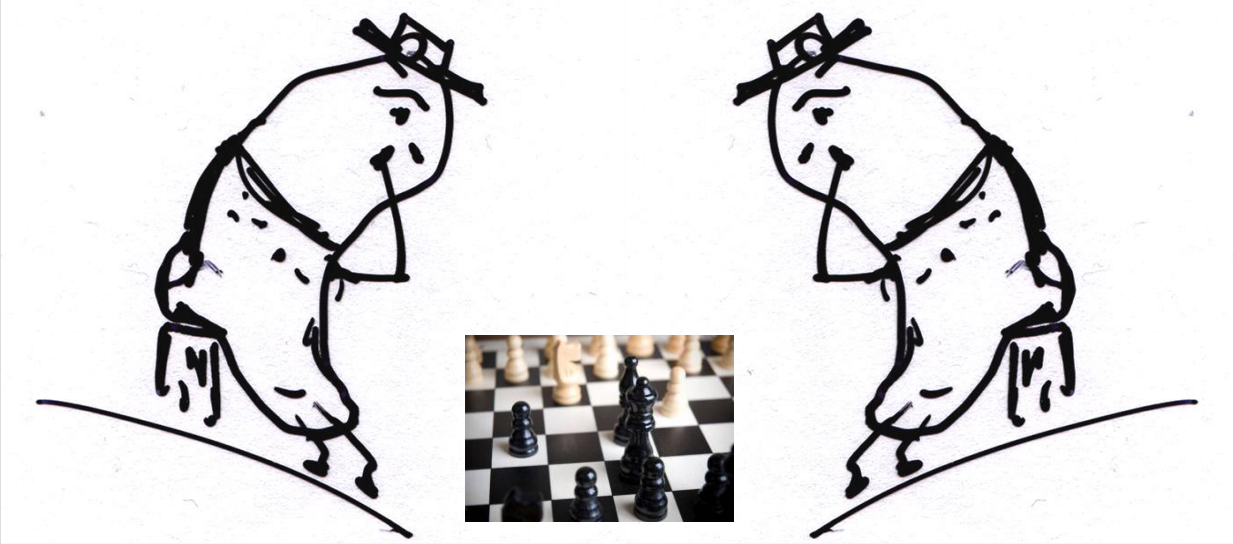
Forget that lucky charm

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

Schultz and Ben-Jacob *PNAS*, 2011

Bacterial Collective Decisions

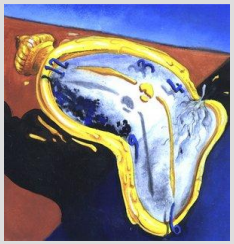
Bacterial Game Theory
During Phenotypic Transitions



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


Can we learn from the ways
Bacteria Determine Fate Under Stress
Gene Circuit Principles
Operational Principles
Inhibition of Inhibition
Coordination of Clock Rate

The Elements of Bacterial Collective Decision-Making



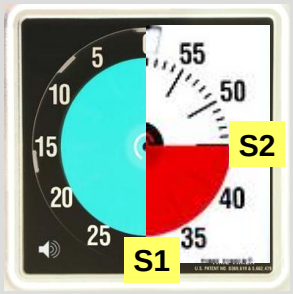
Stress

Sensing

Cell-Cell Communication

Cell Density

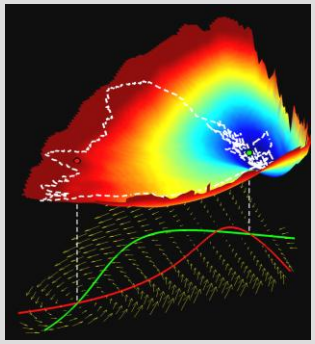
Sensing



Adjustable Timer

Gate

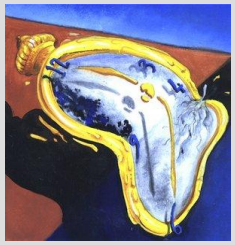
Stochastic Switch

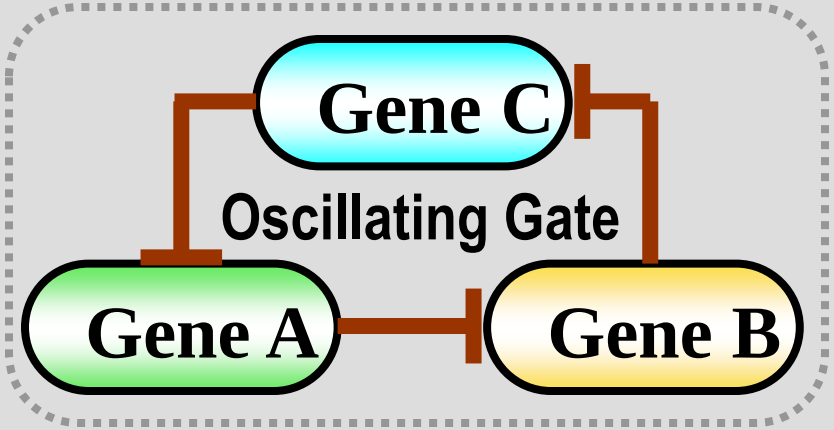


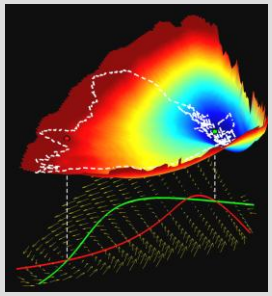
Sporulation

Competence

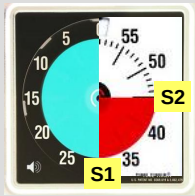
Let the complex be simple – looking for key elements

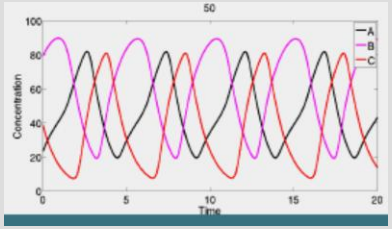




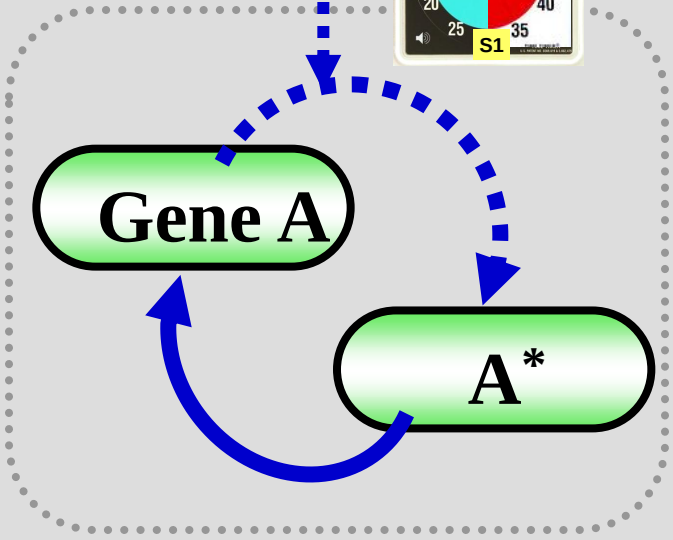


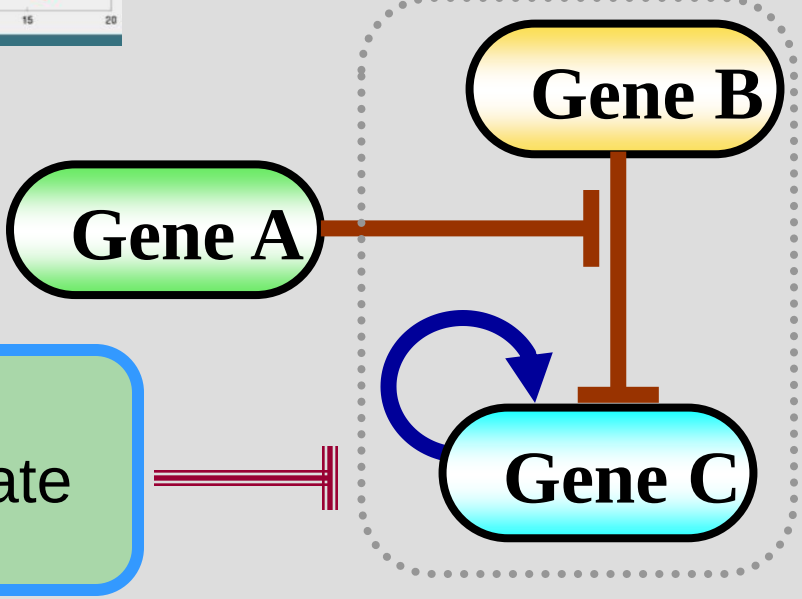
Timer with adaptable
Clock rate

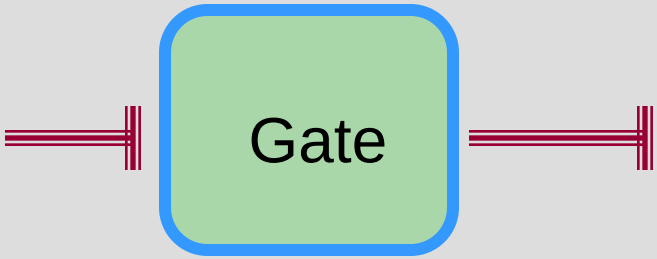




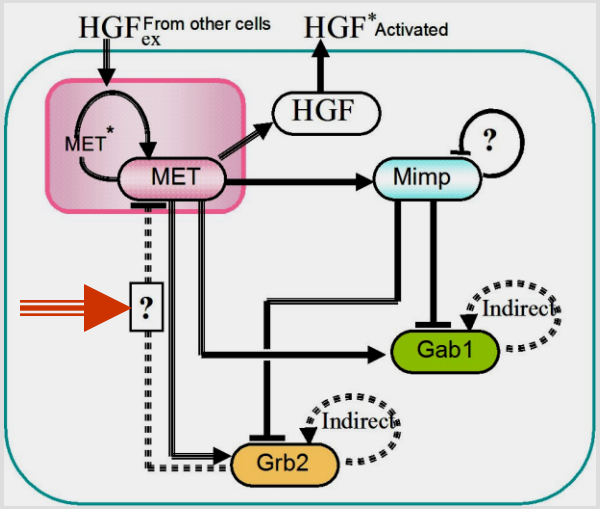
Stochastic Switch







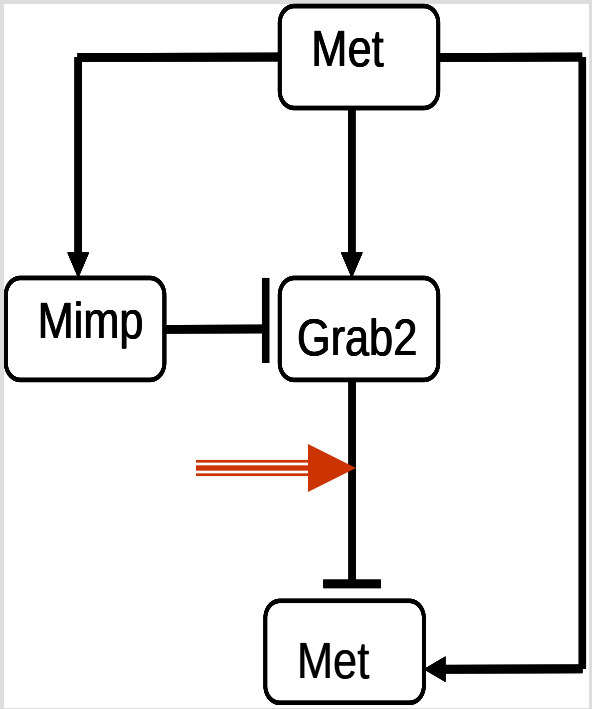
"Games" of Incoherent FFL

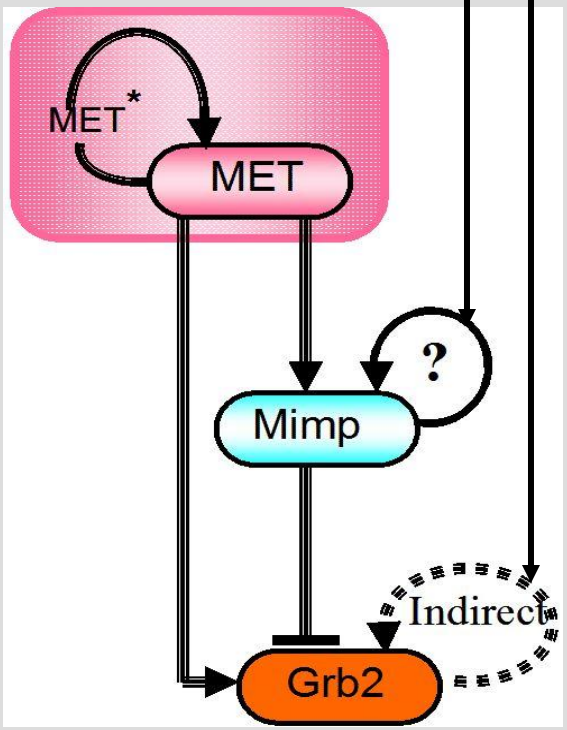


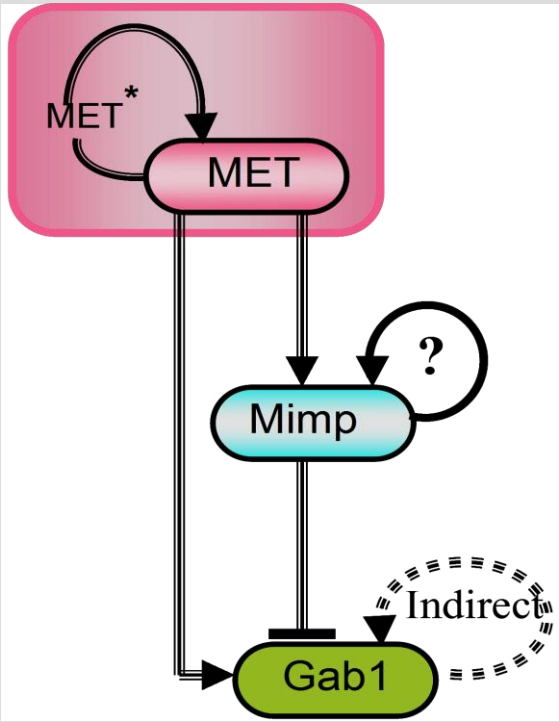
Work in progress

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

The additional elements control the noise effect







Today

Why Bacteria and Cancer?

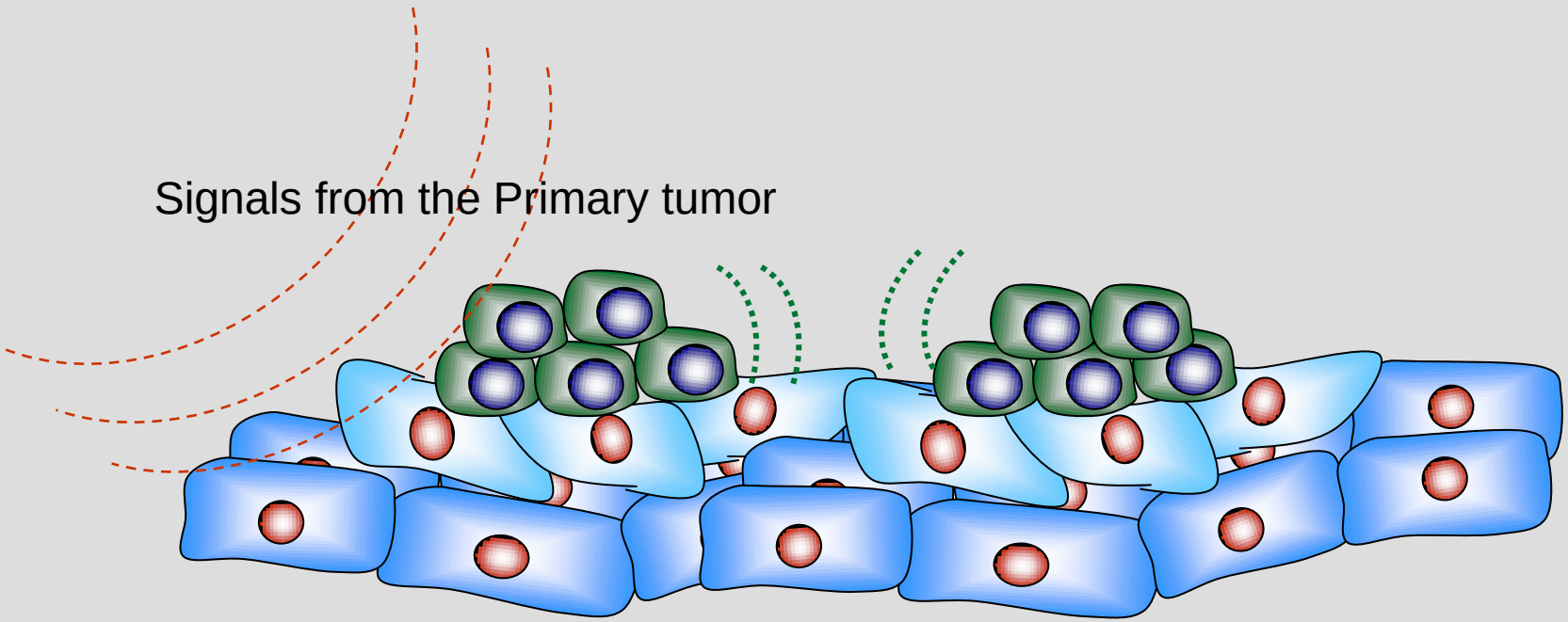
Bacterial Swarming Logistics & Cancer Cell Migration

Reflections on Cancer Selection of navigation Strategy

Reflections on "Cyber Warfare" against cancer

Ben-Jacob, Coffey, Levine *Trends in Microbiology* 2012

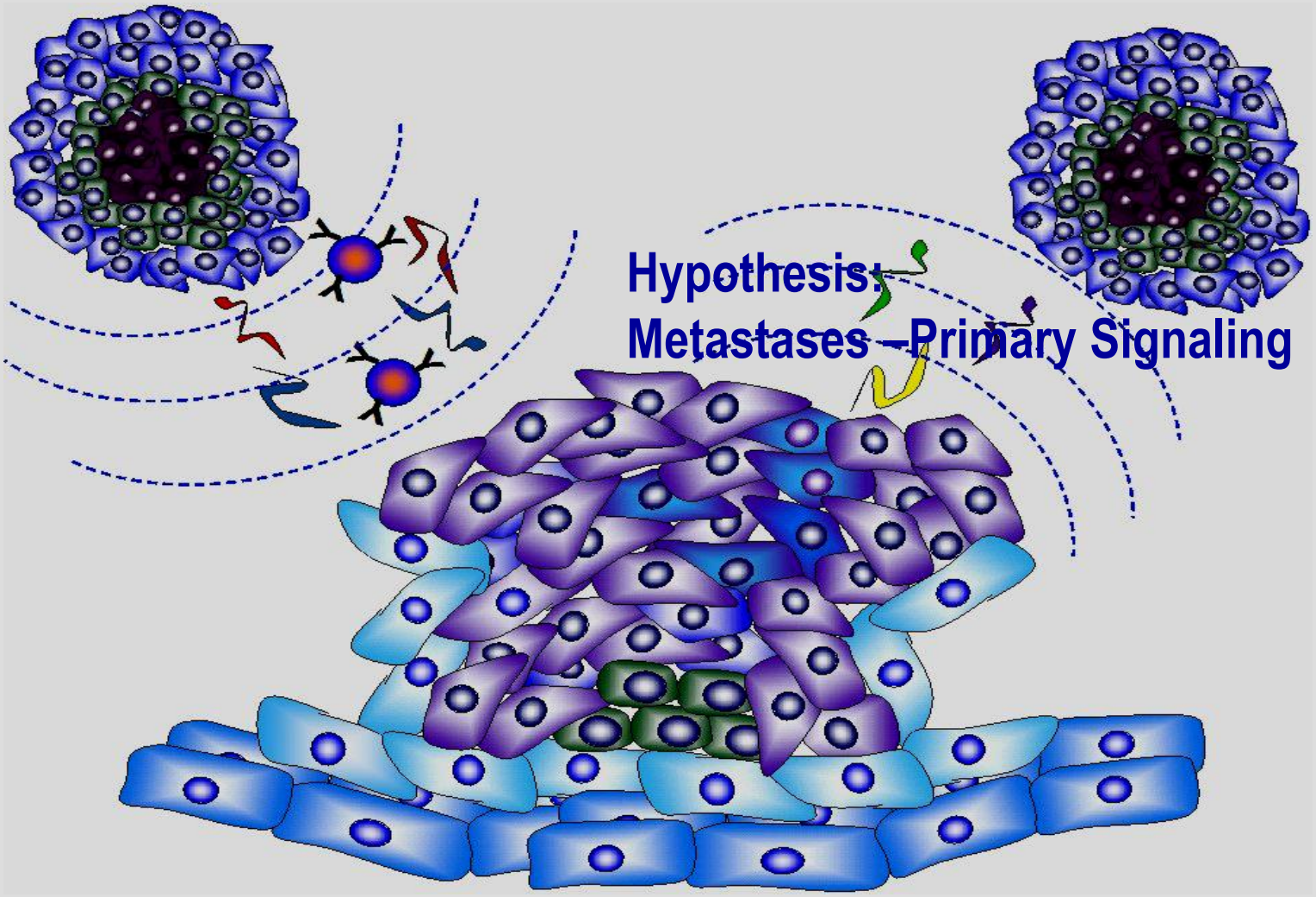
Germination of Micrometastases



Kaplan et al Nature 2005

Maturation of Micrometastases

Can Metastasis be Controlled by Breaking the Code?



For by wise counsel thou shalt make thy war

בתחבולות תעשה לך מלחמה

To decipher the secrets of cancer communication.

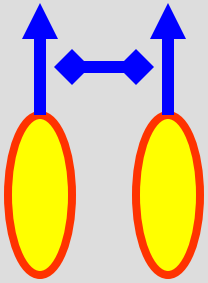
To develop drugs targeting cancer communication, cooperation and control.

The End

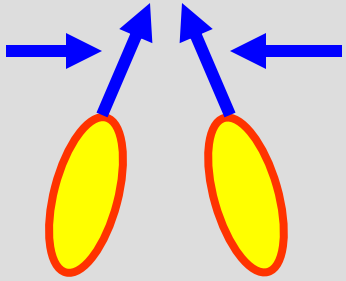
Collective Navigation of Interacting Agents

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

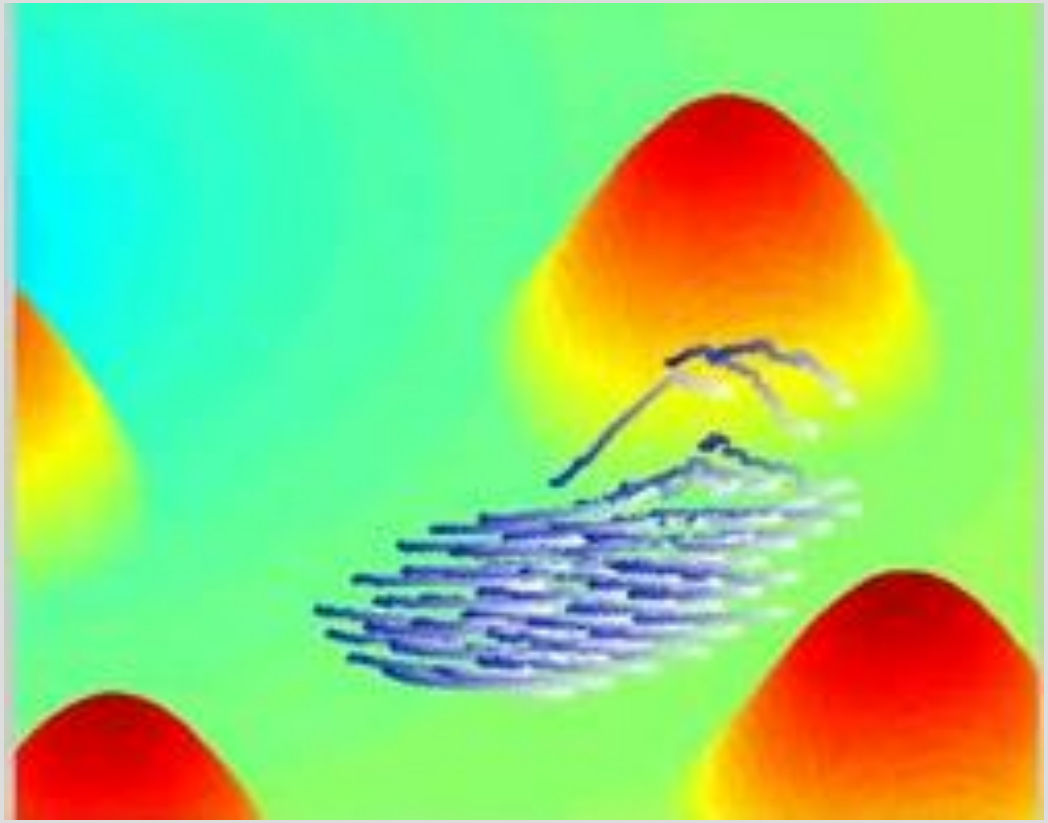
Repulsion



Orientation

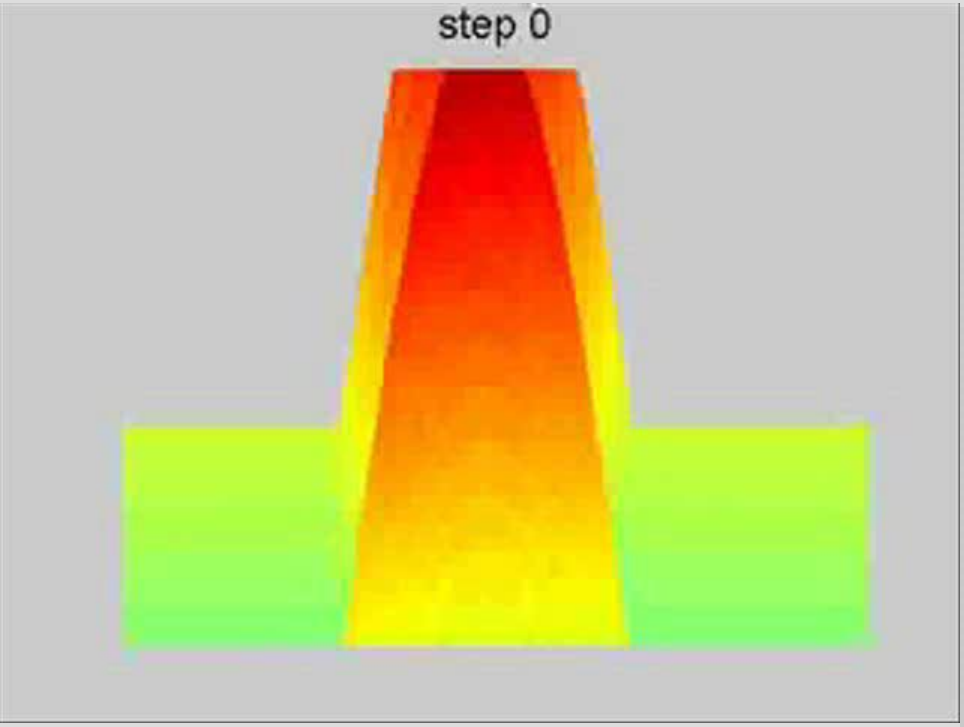


Attraction

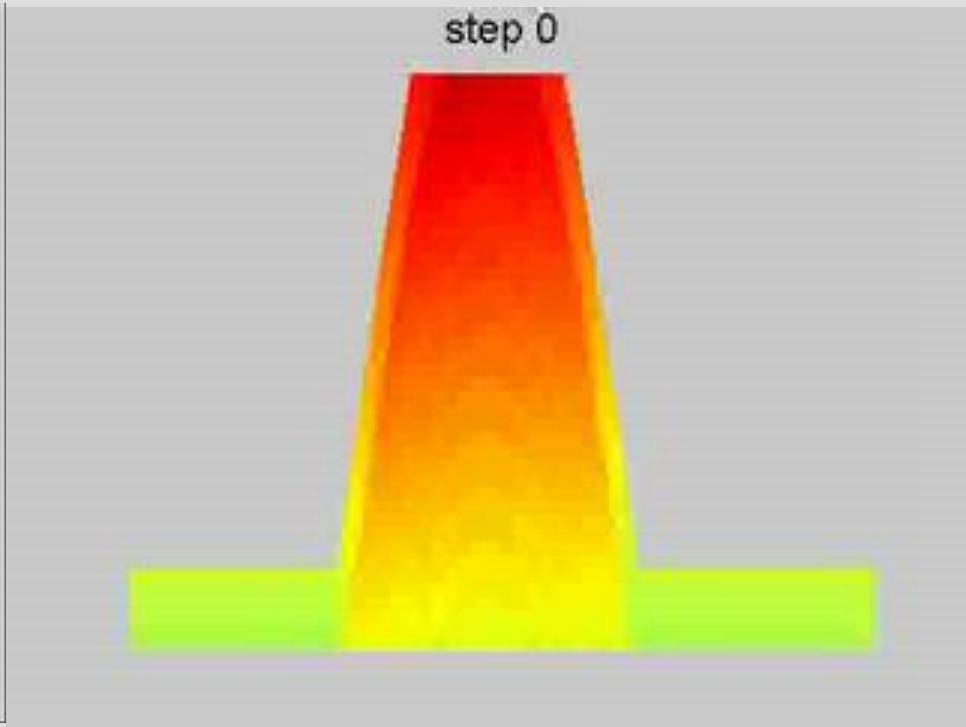


Extension of Vicsek, Ben Jacob et al., PRL 1995 + Couzin et al., Nature 2005

Independent agents



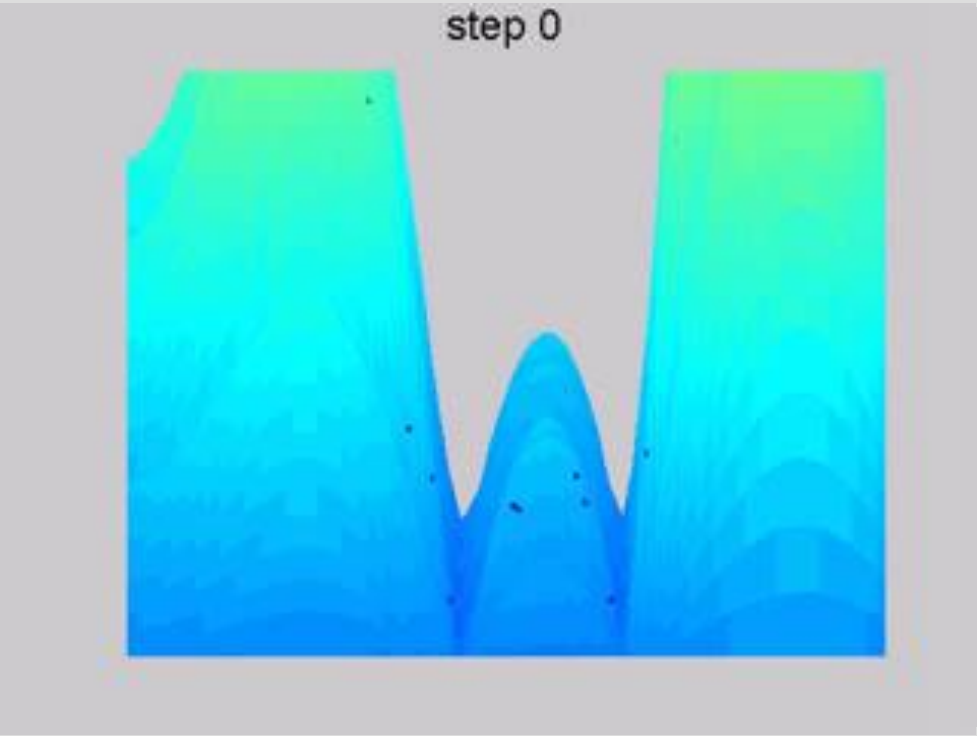
Interacting agents



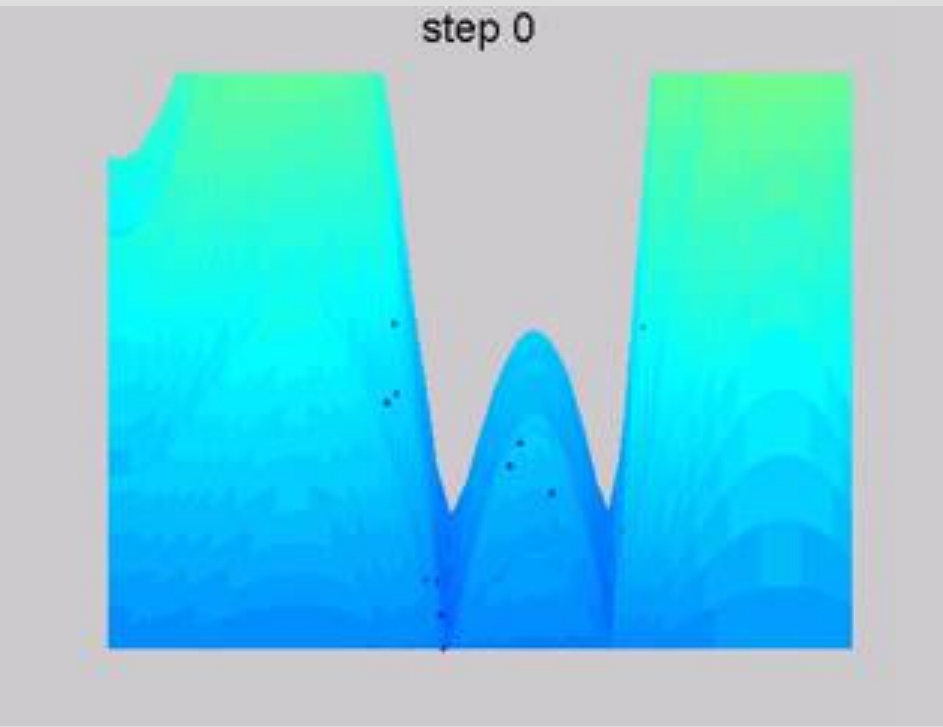
Collective sensing and
Distributed information processing

Navigation in Complex Terrains

Fixed interactions



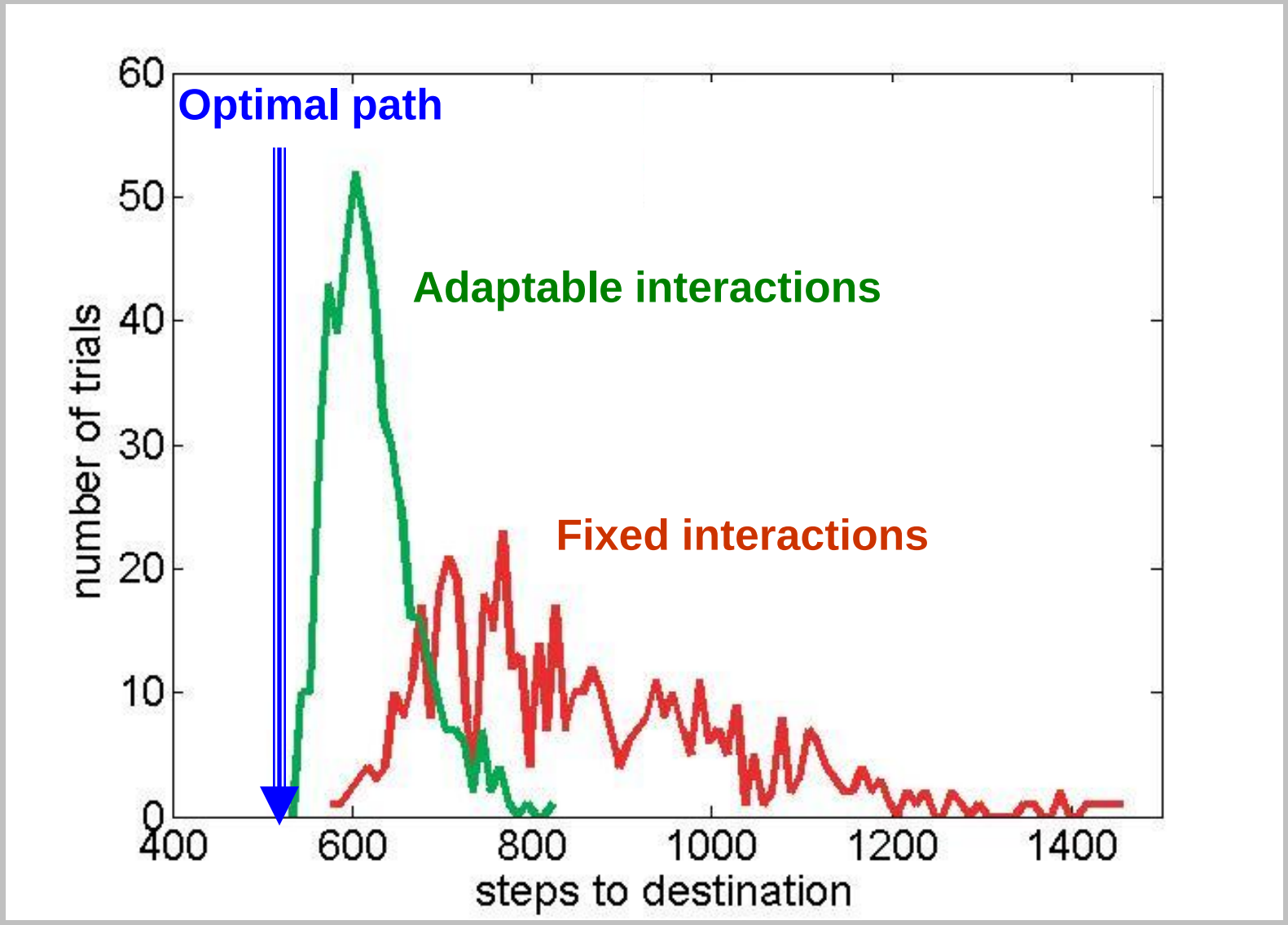
Adaptable interactions

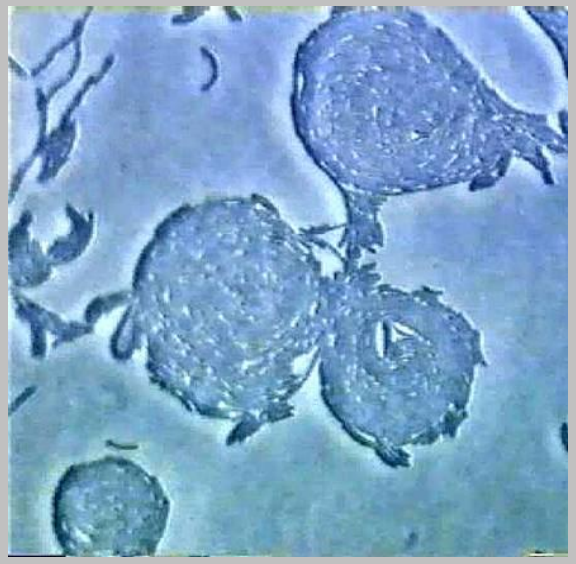


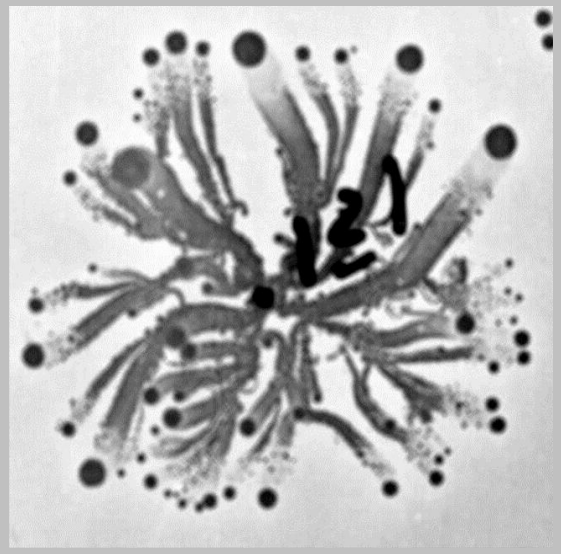
What is the Advantage?

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

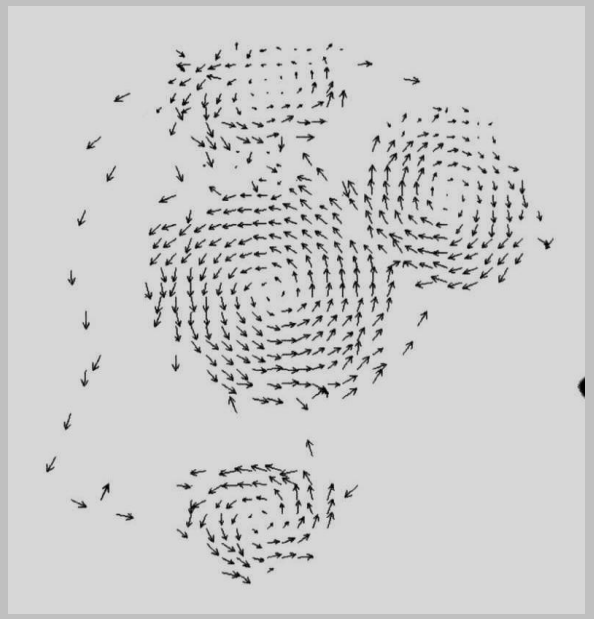
Quantification of the results

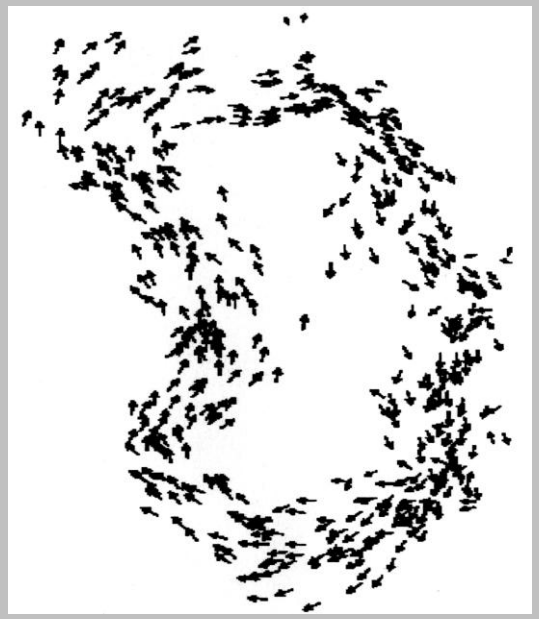


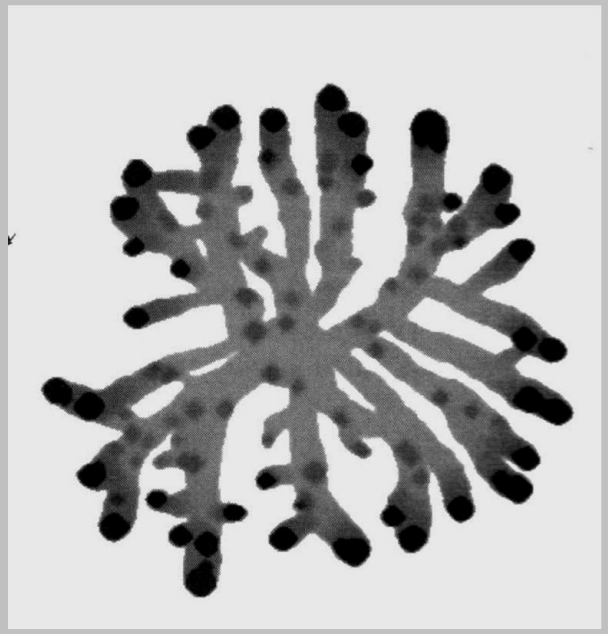




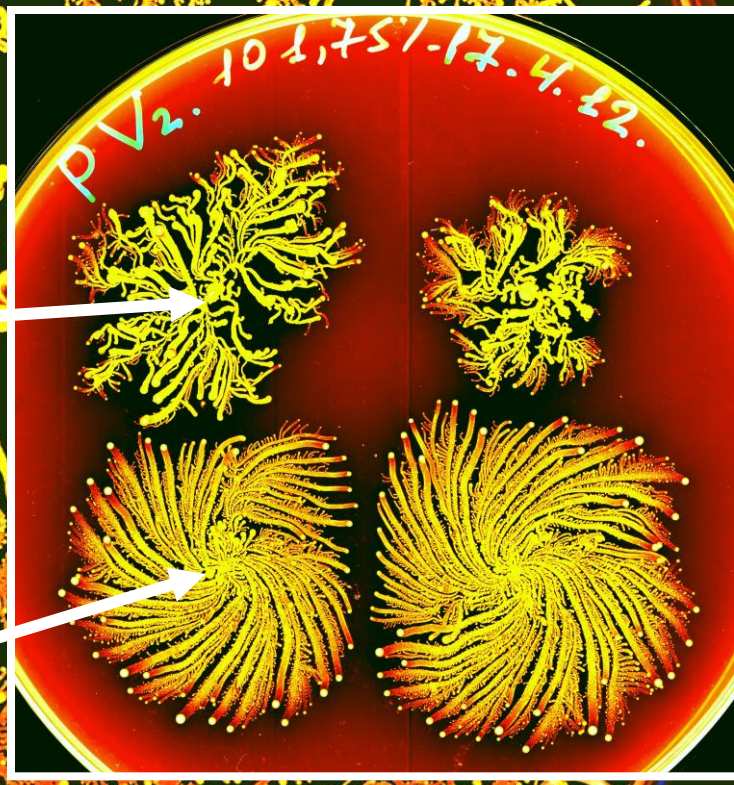
Modeling





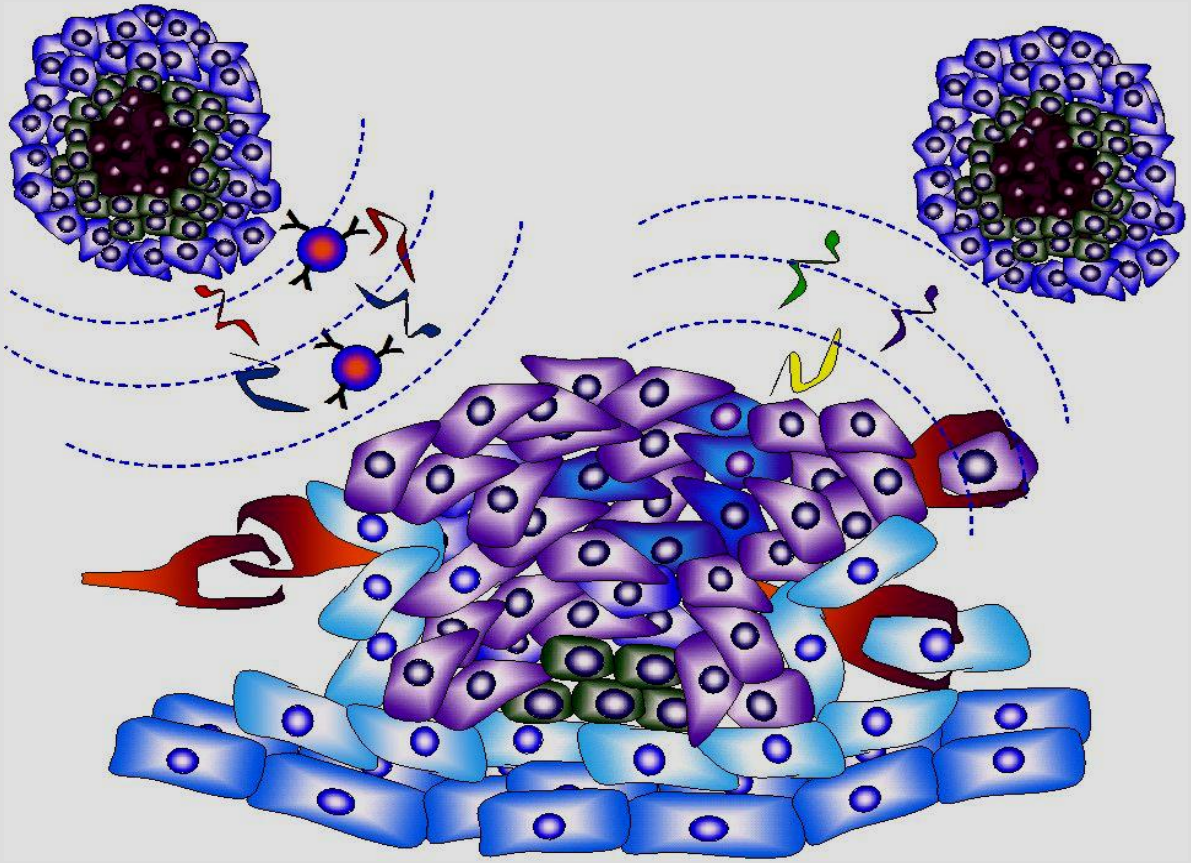


Task Distribution & Cell Differentiation



Cancer Cannibalism

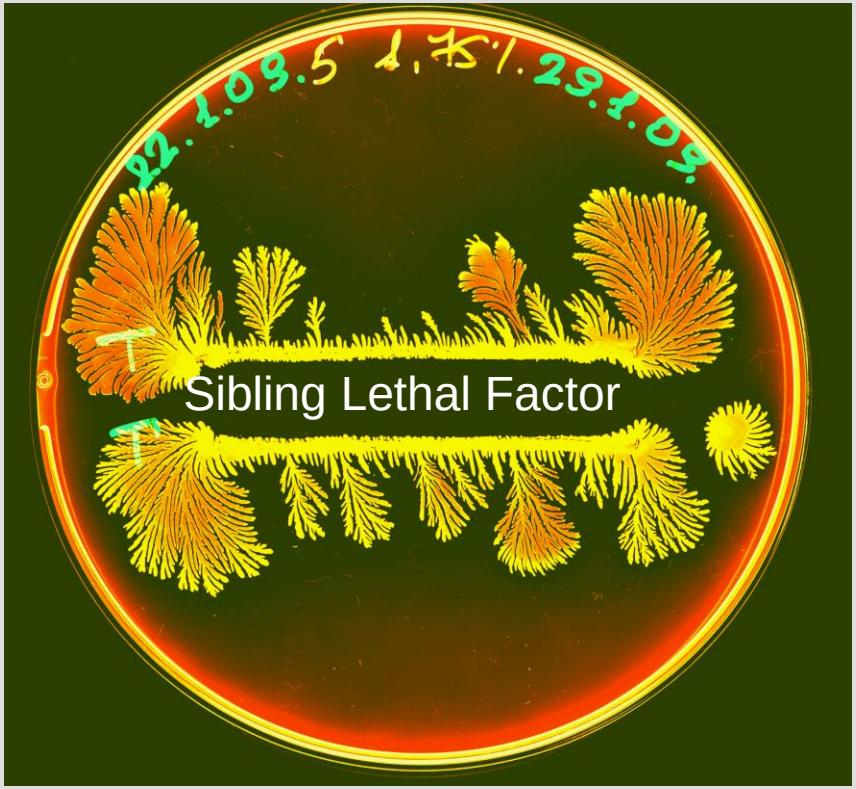
Can Breaking the Code Help Fighting Cancer?



Fais et al Cancer Lett. 2007

Deadly Competition Between Sibling Colonies

Discovery of a New Toxin



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

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)

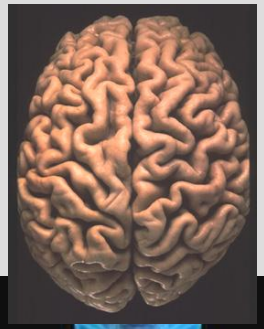
Injected *Salmonella* can cause melanoma cells to form gap junctions with adjunct immune dendritic cells. Consequently, the dendritic cells use peptides transferred from the cancer cells to 'teach' T cells to recognize and kill the tumor cells at the primary site and prevent metastasis formation.

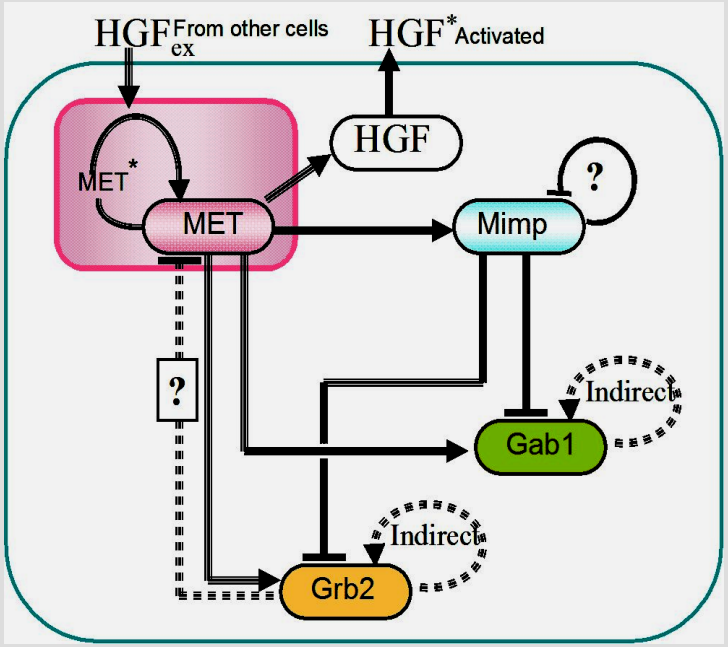
The digestive tracta

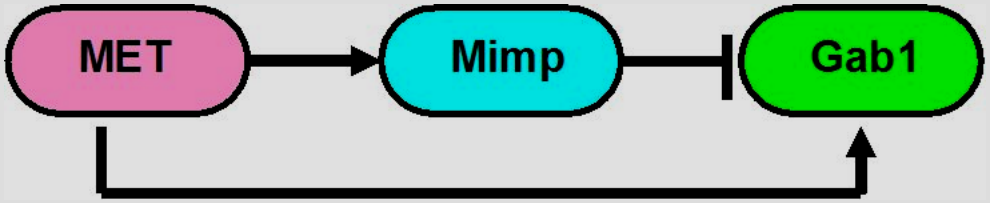
10 trillion bacteria of more than 40,000 different strains

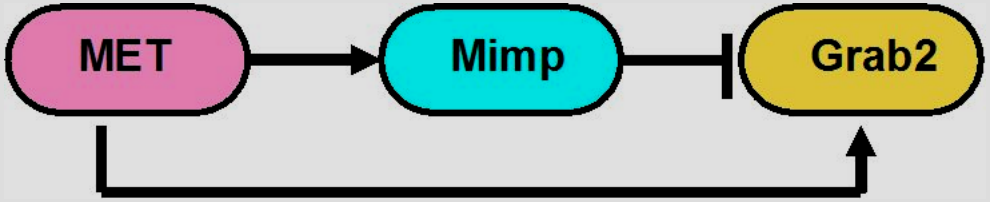
Affect digestion, the immune system, the endocrine system and the brain

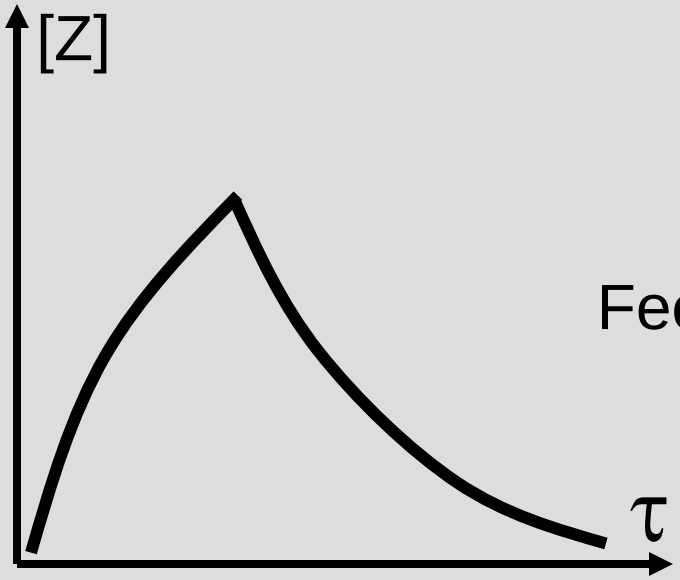
Very relevant for cancer but not today



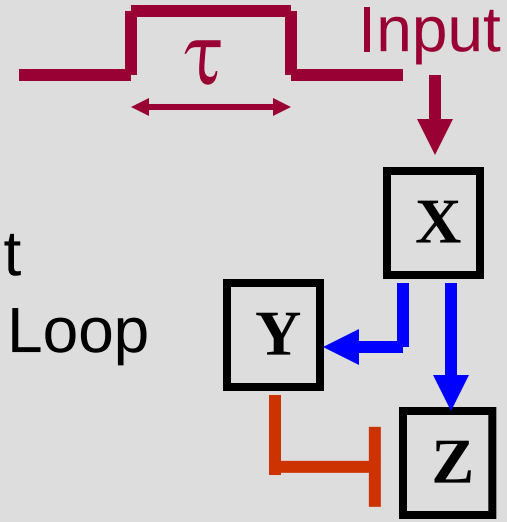






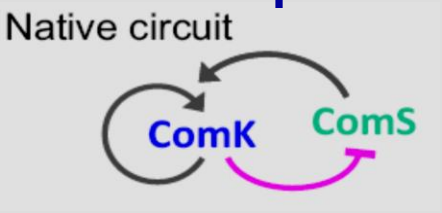


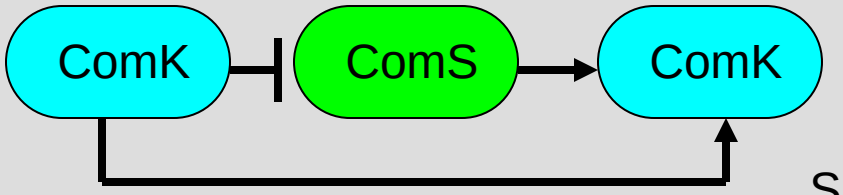
Incoherent
Feed Forward Loop



Learning from Bacteria Decisions

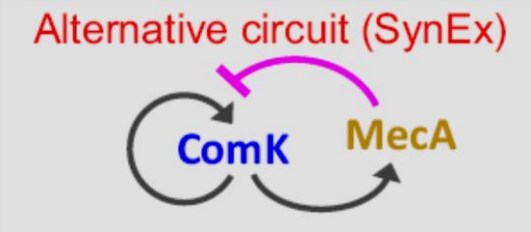
Competence switch as an Incoherent Feed Forward Loop

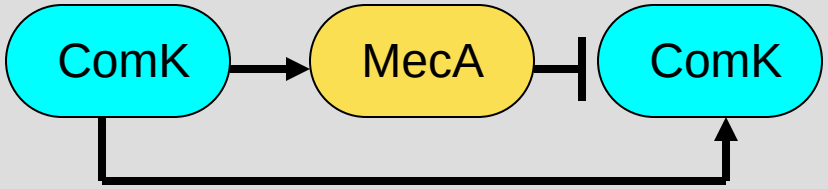




Rare transitions

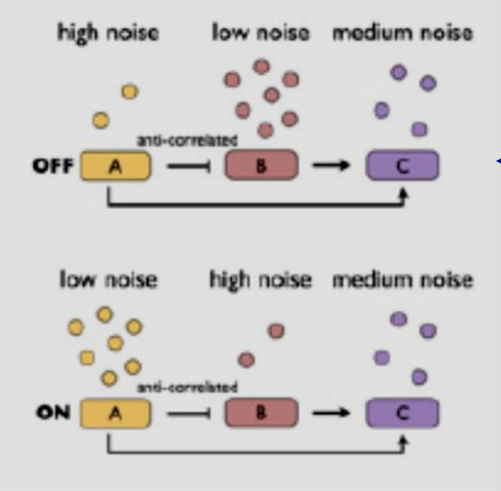
Süel et al *Cell* 2009





Frequent transitions

Circuit architecture and noise effect



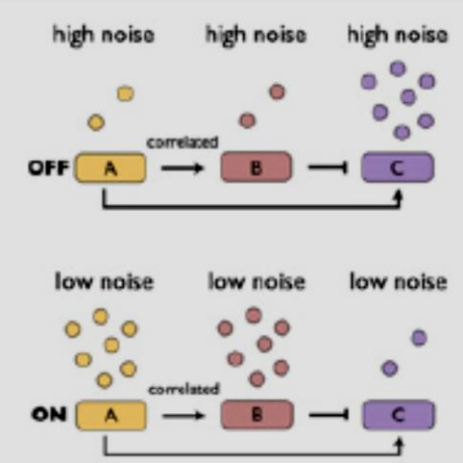
Süel et al *PNAS* 2010

Used for rare events

Used for frequent events

"Bacteria play dice with controlled odds"

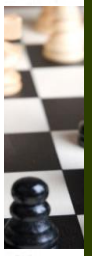
Ben-Jacob and Schultz *PNAS* 2010

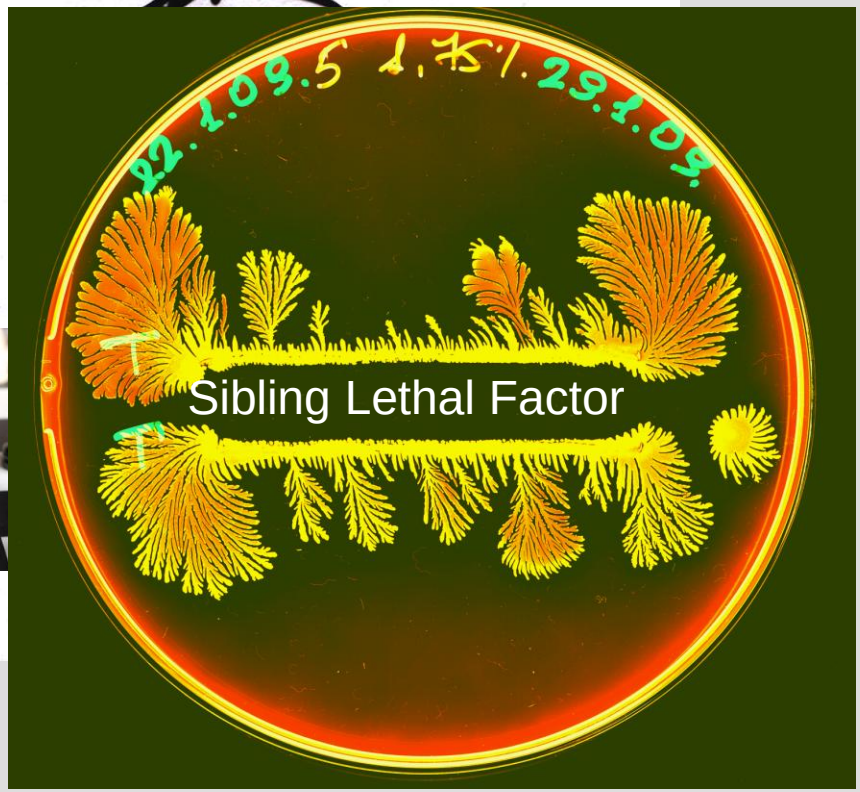


Harnessing Cannibalism to Fight Bacteria

Deadly Competition Between Sibling Colonies

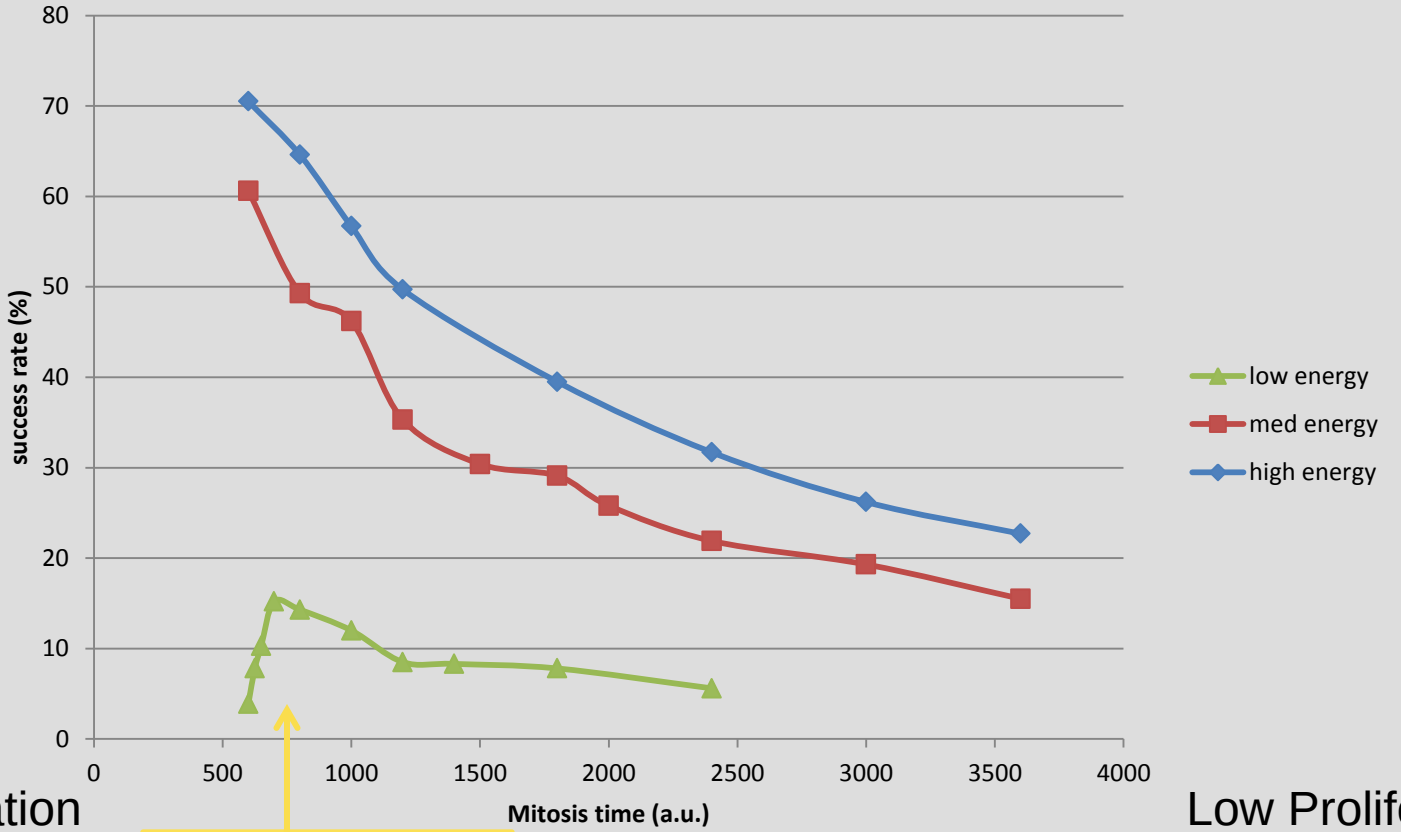
Discovery of a New Toxin





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

Success rate



High Proliferation

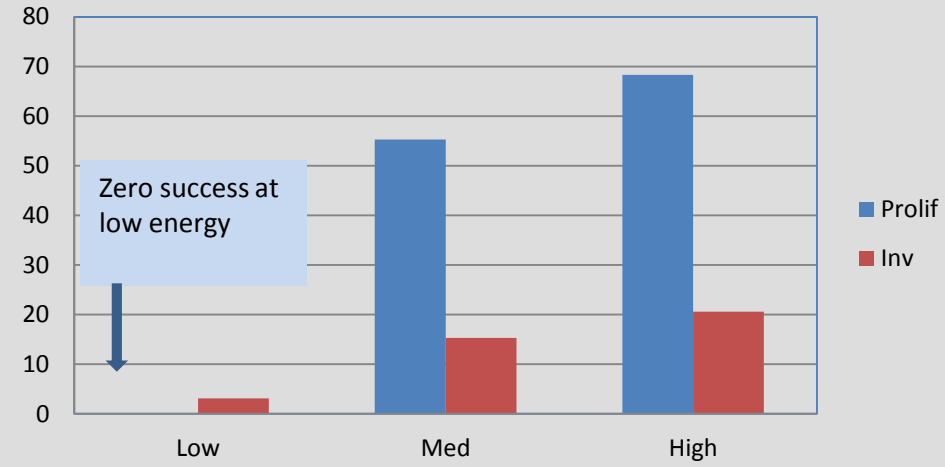
Low Proliferation

Equiv. to ~36 h.

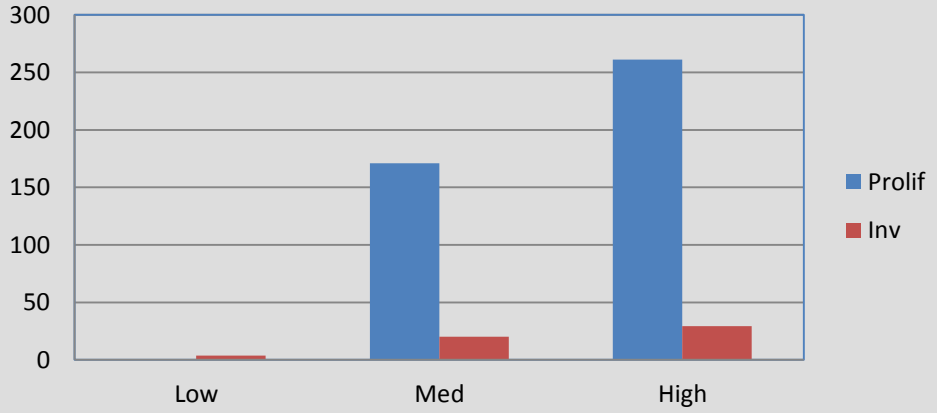
With very low energy, high proliferation results in no invasion and therefore very low success rate.

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

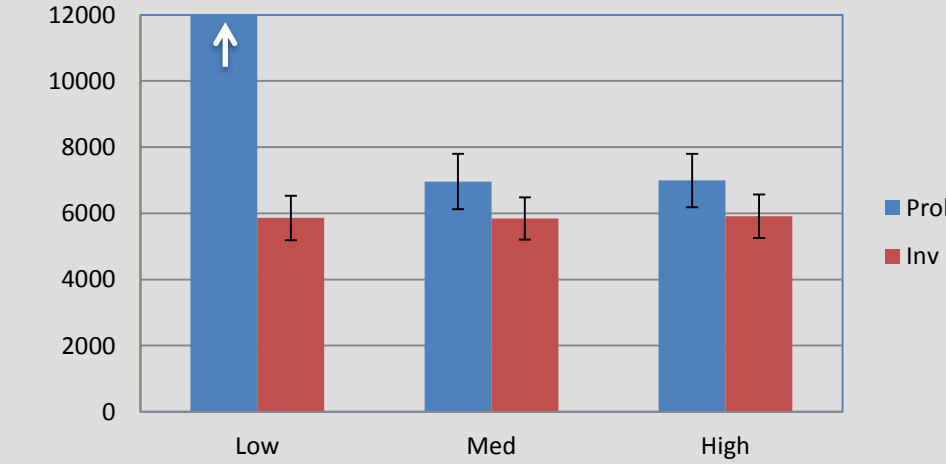
Success rate (%)



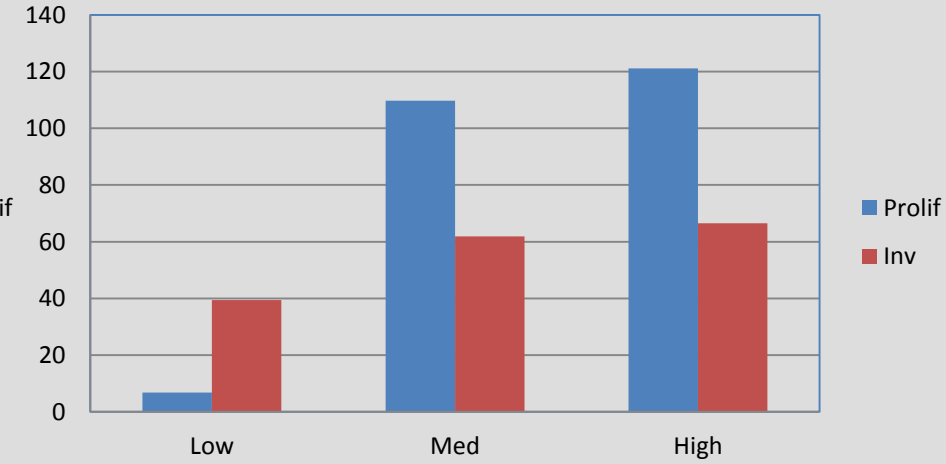
Effective success rate (%) (multiplied by proliferation)



Time to goal

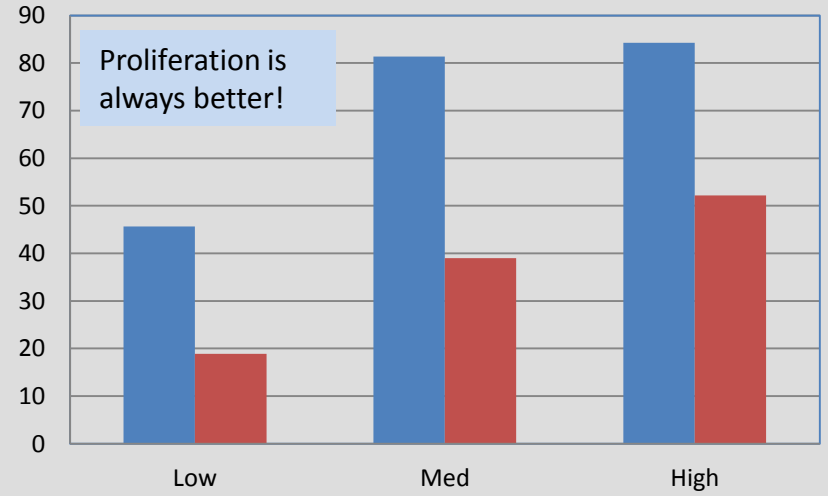


Average invasion per cell (all cells)

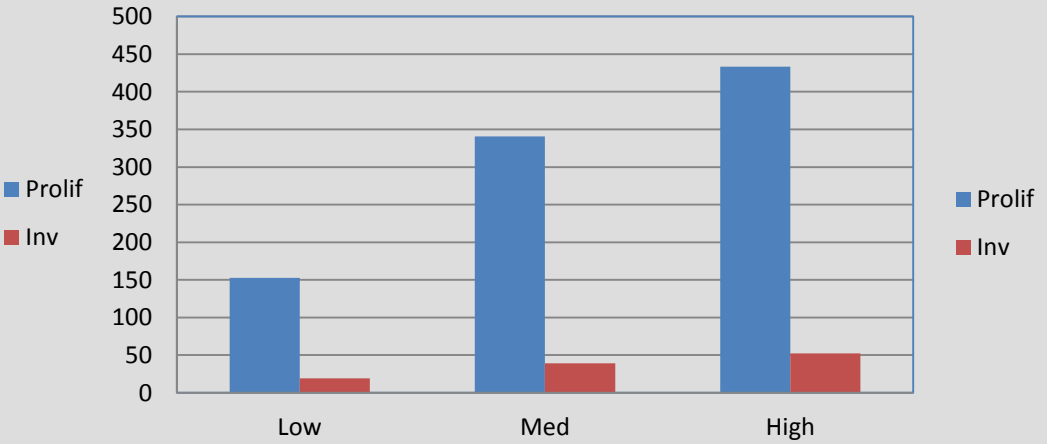


HGF effect

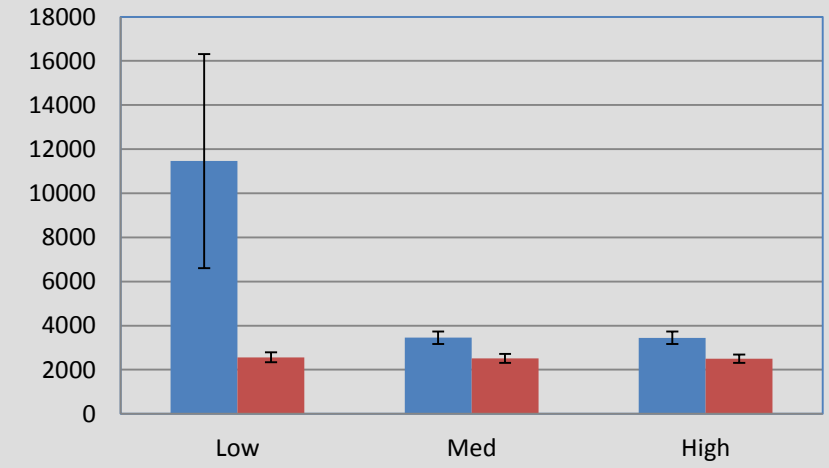
Success rate (+HGF)



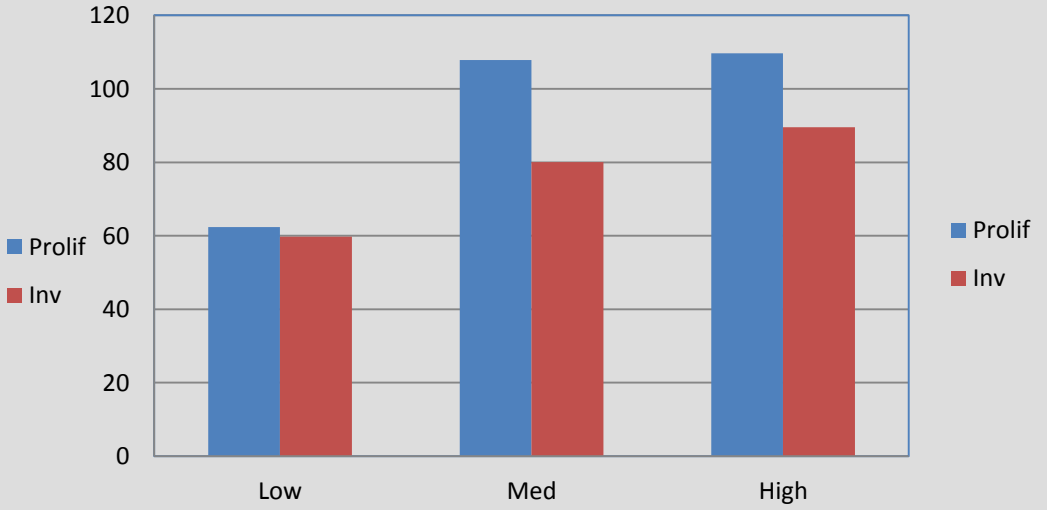
Effective success rate (+HGF) (multiplied by proliferation)

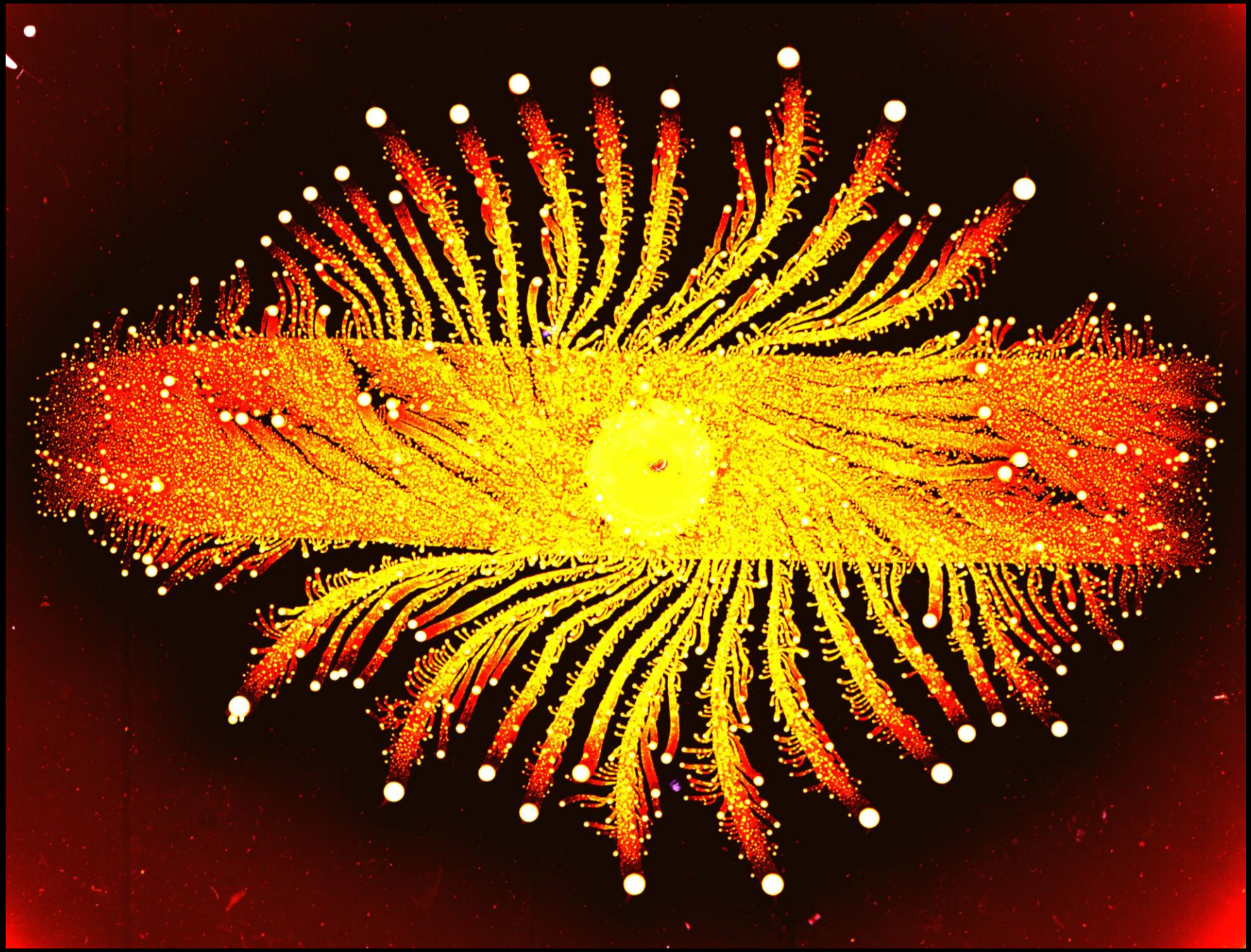


Time to goal +HGF

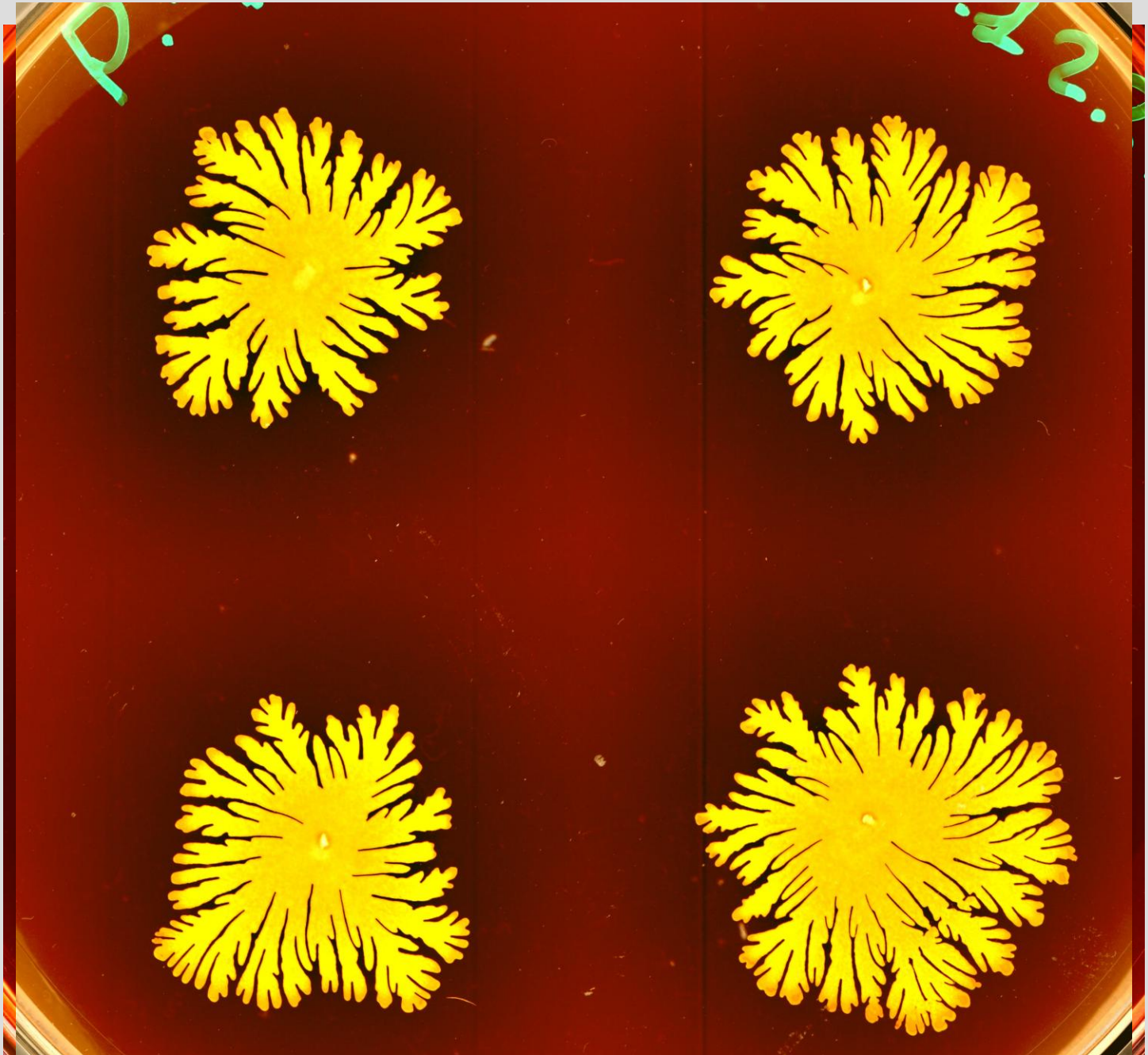


Average invasion per cell (all cells) +HGF





Bacteria Societies (Metacommunities)



Deciding Fate at Adverse Times

Altruism, Cannibalism and Fratricide

Gonzalez-Pstor et al Science 2003

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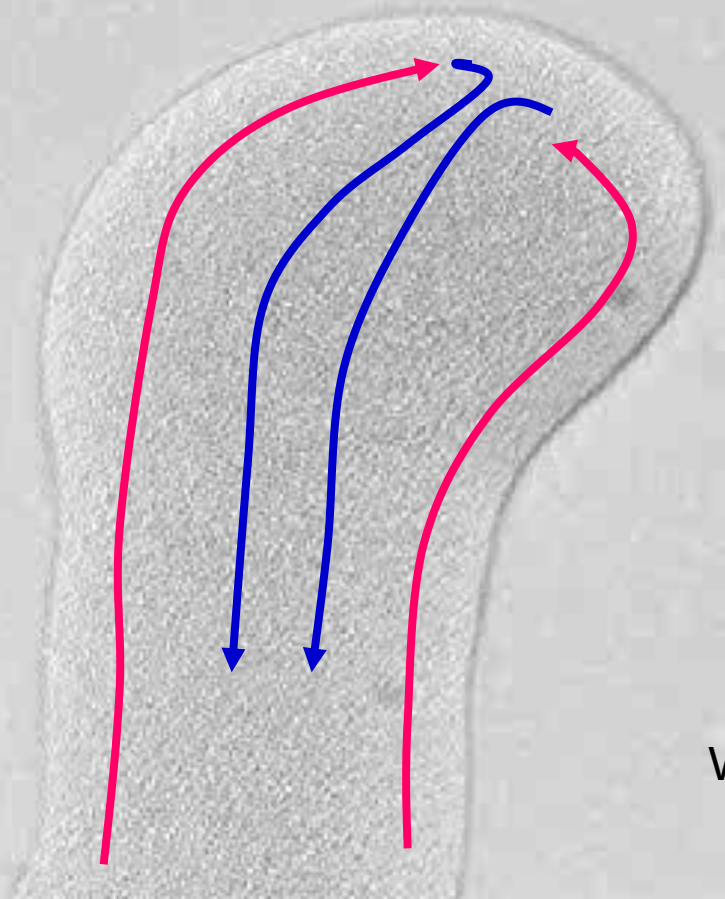
Searching for New Territories

Collective Navigation



Paenibacillus vortex

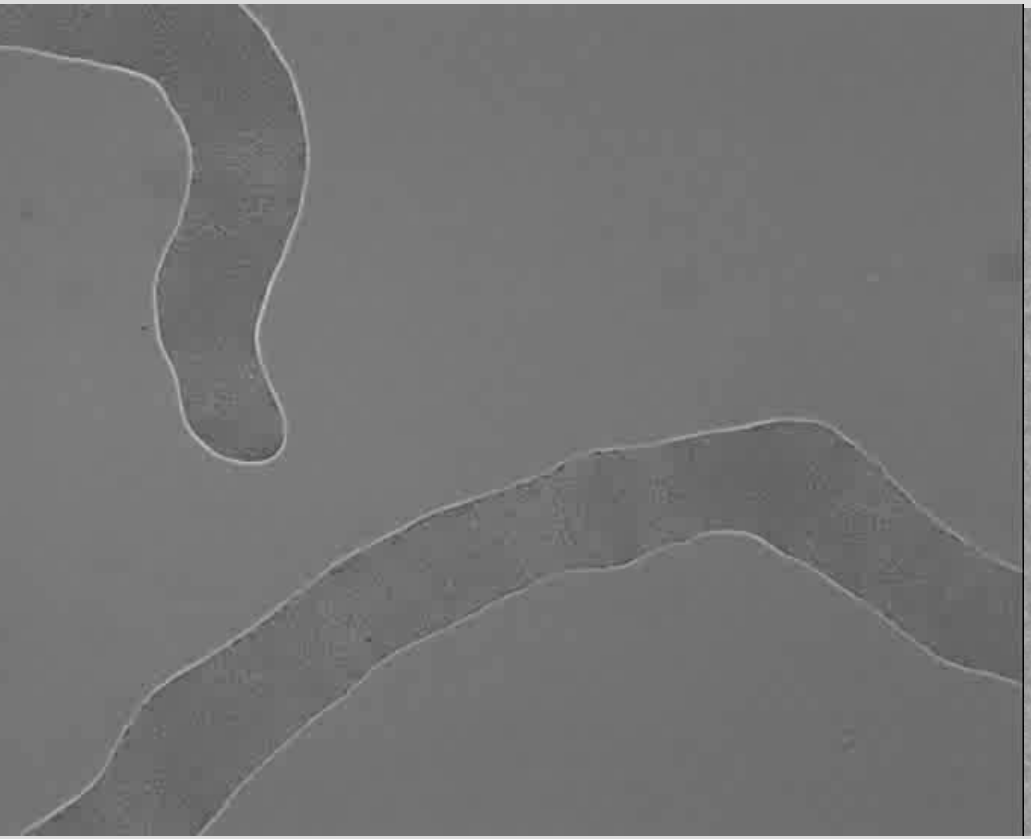
With Ingham, BMC Microbiology 2009

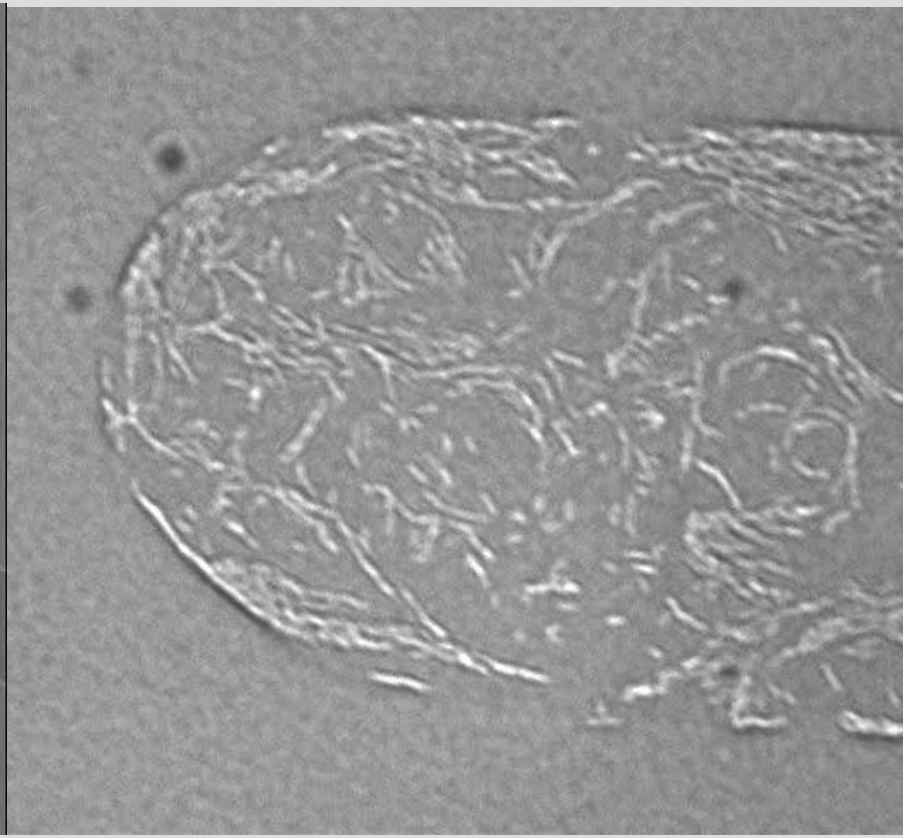
With Ingham, Kalishman and Finkelstein, PNAS 2011

Additional Features

Swarm-Swarm Repellent

Marking the trail





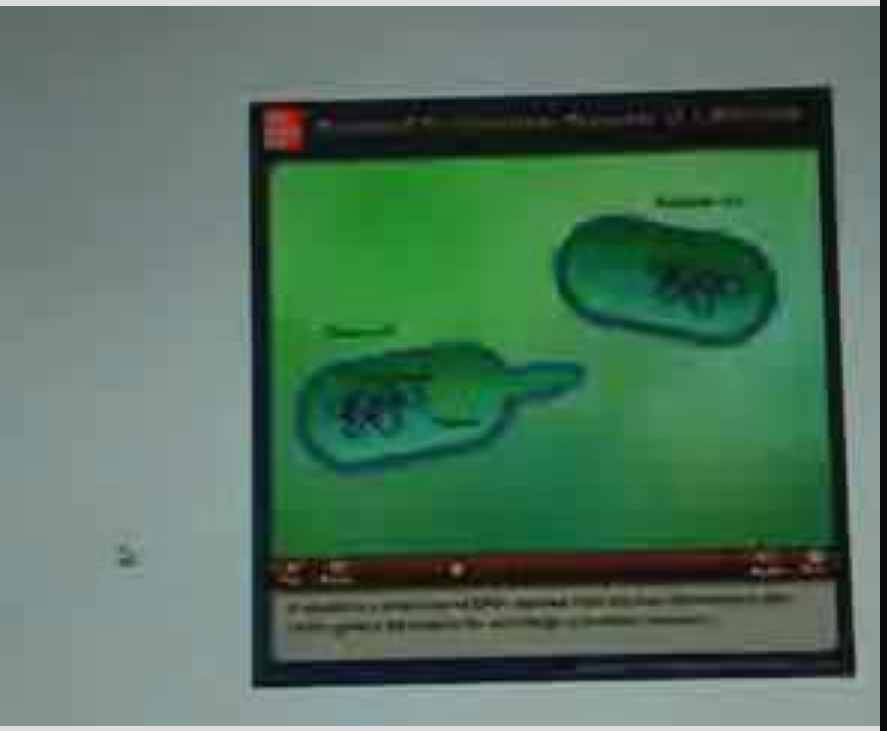
Colin Ingham and Ben-Jacob BMC Microbiology 2009

Collective Navigation in Search for Food

Collective (Distributed) Information Processing

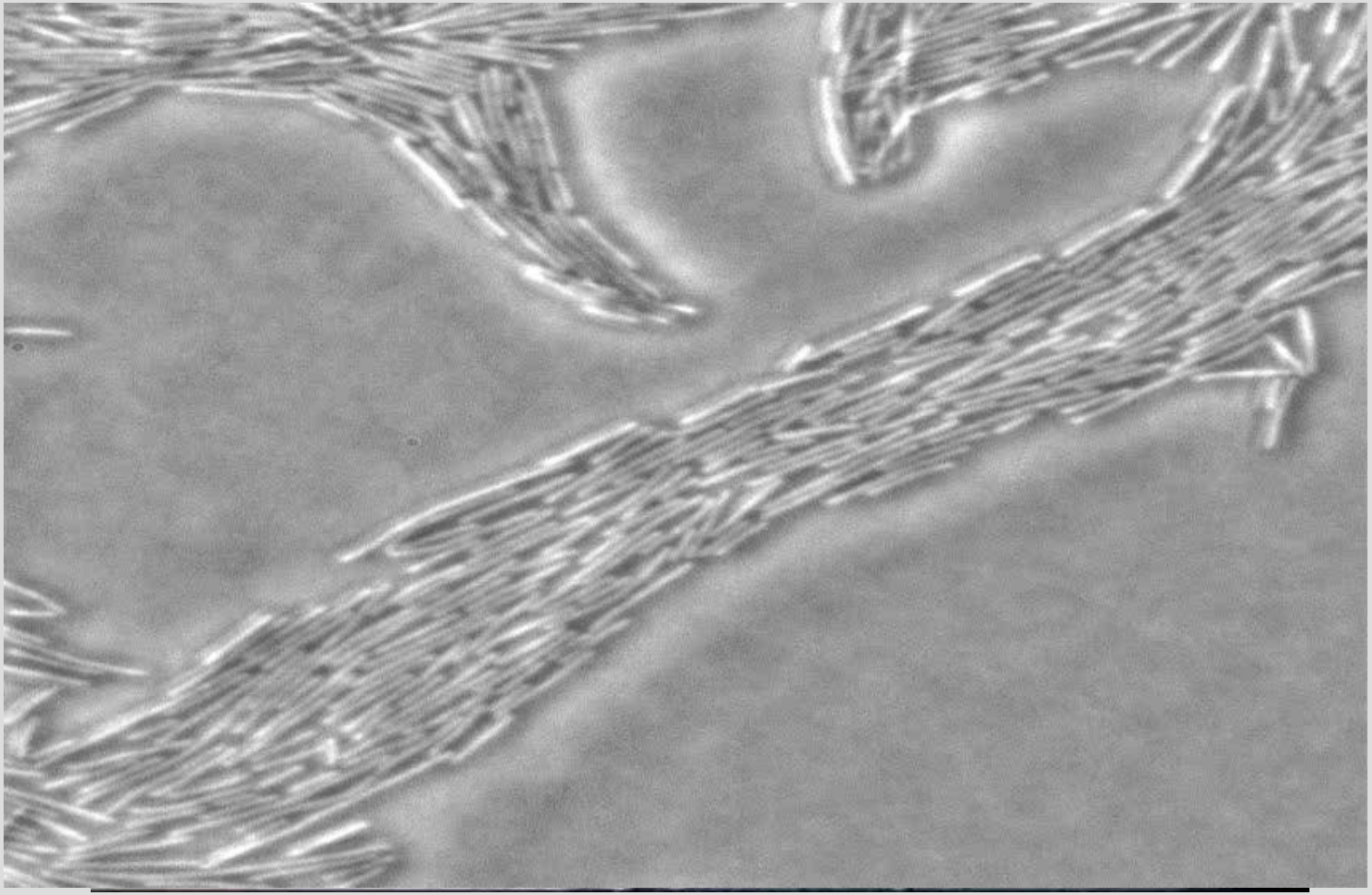
Social Networking by Chemical Twitting

Bacteria Mating



How Bacteria Move

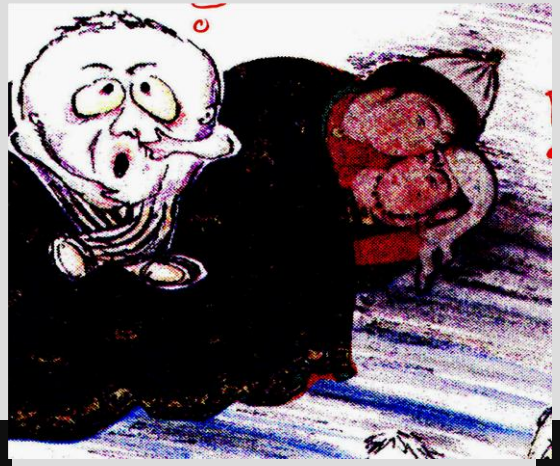
Swimming by Flagella, Gliding by Pili and more

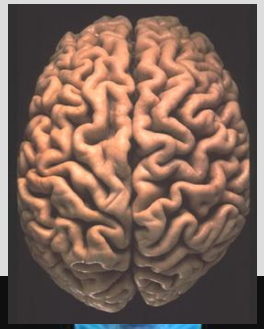


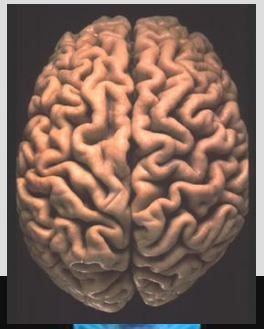
Flagella swimming (Howard Berg)

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

Gut Bacteria and Human Mating - Choice of Partners





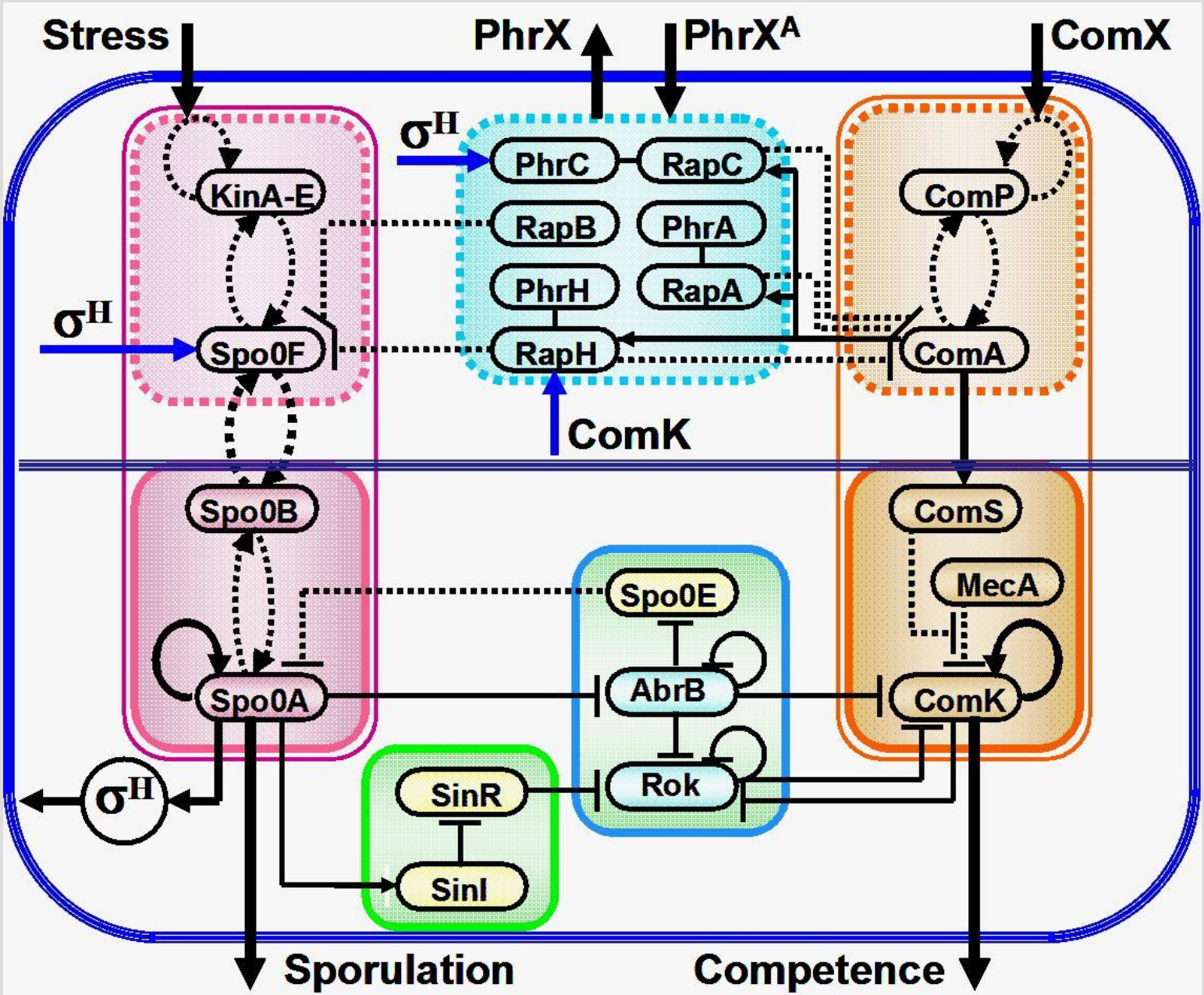


Sex pheromones

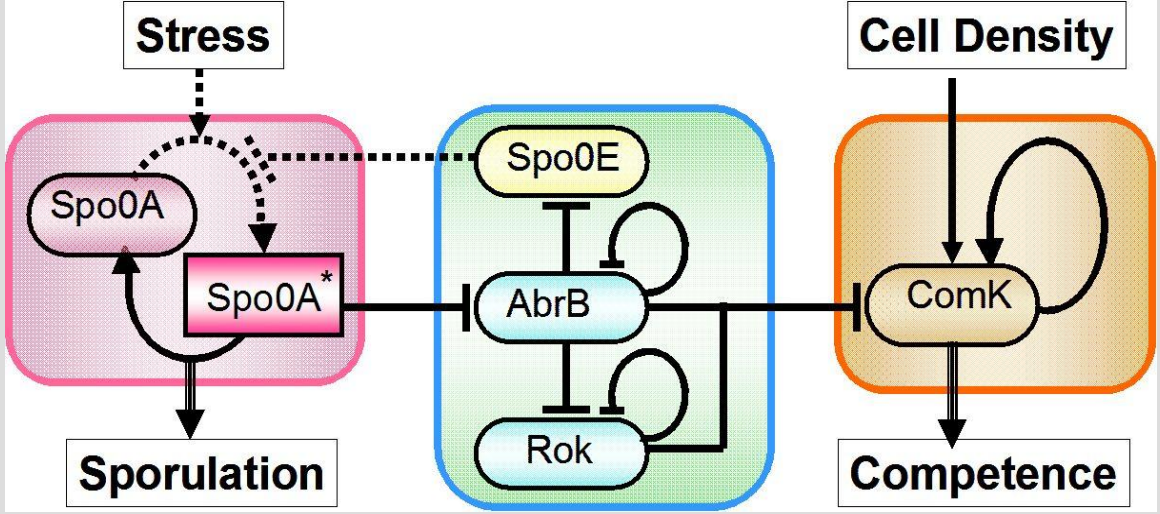

Conclusions & Reflections


THE END

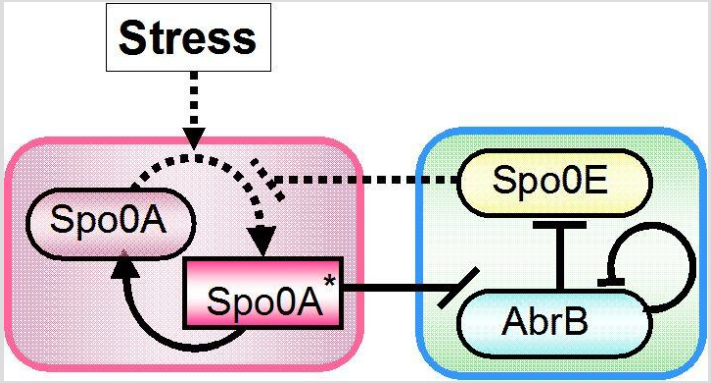
The Decision Network

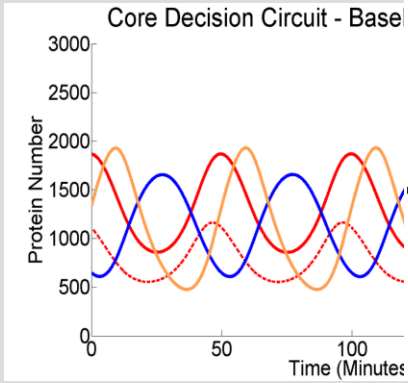


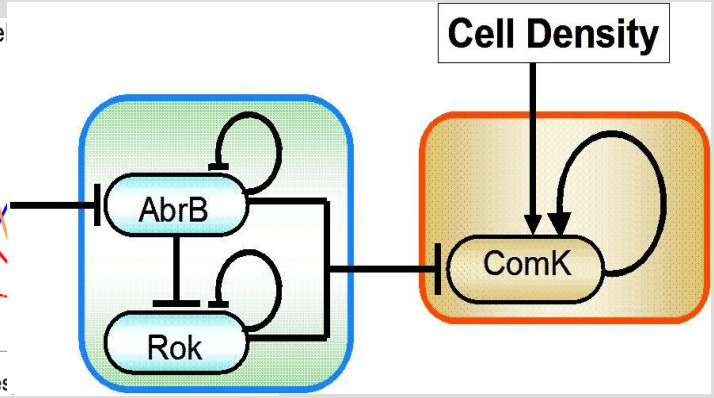
With Trevor Schultz Onuchic (unpublished)

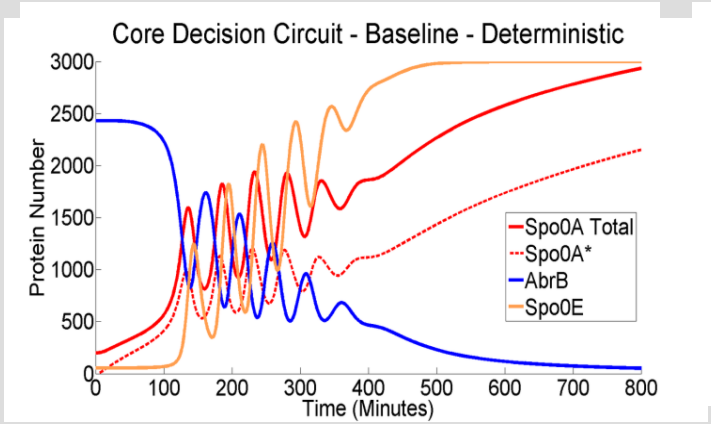


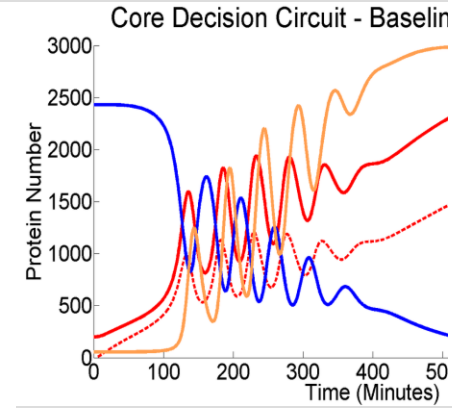
With Trevor Schultz Onuchic Süel (RMP unpublished)

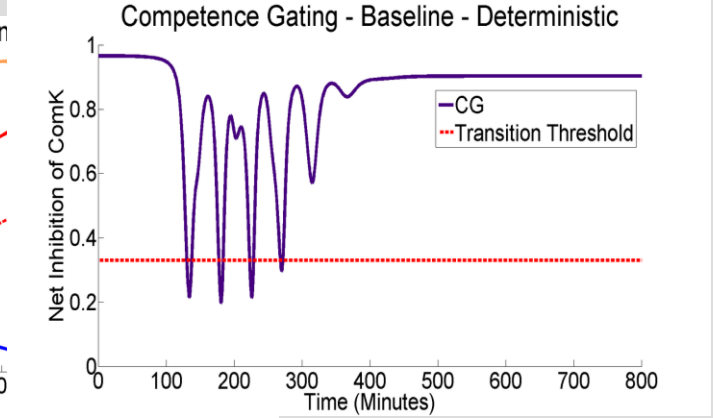


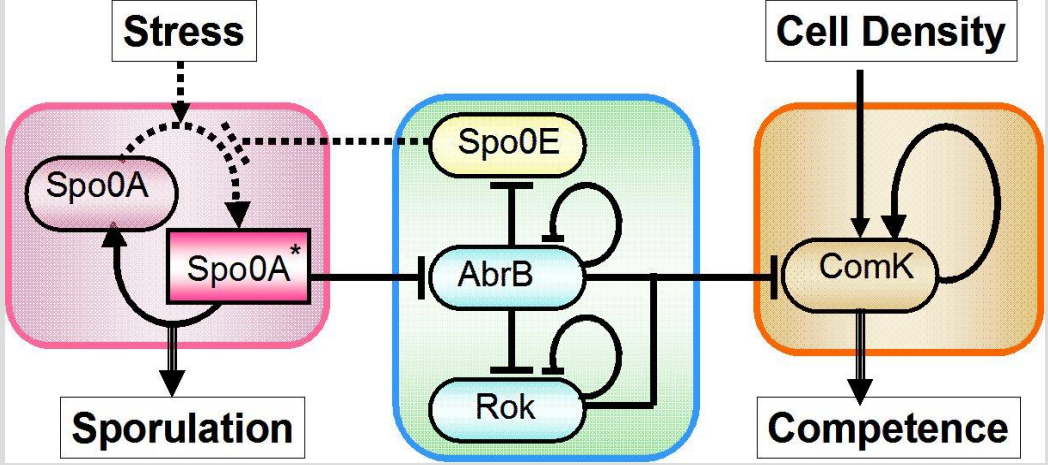


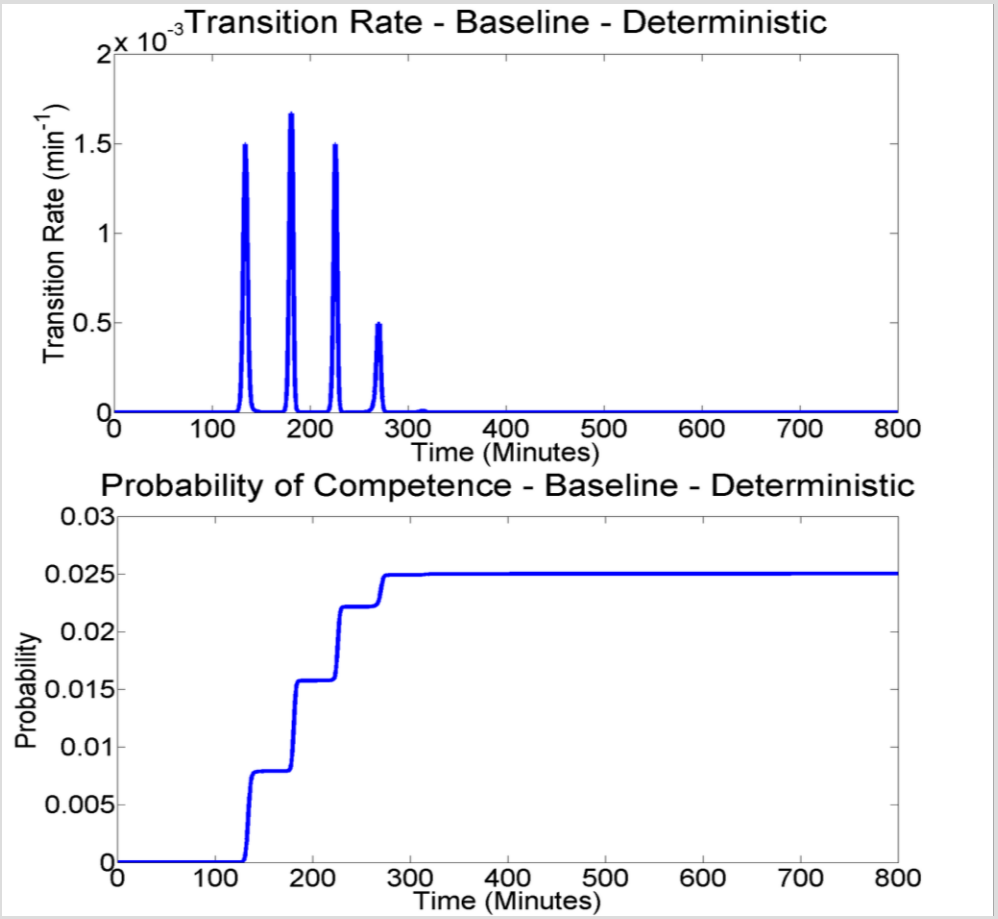




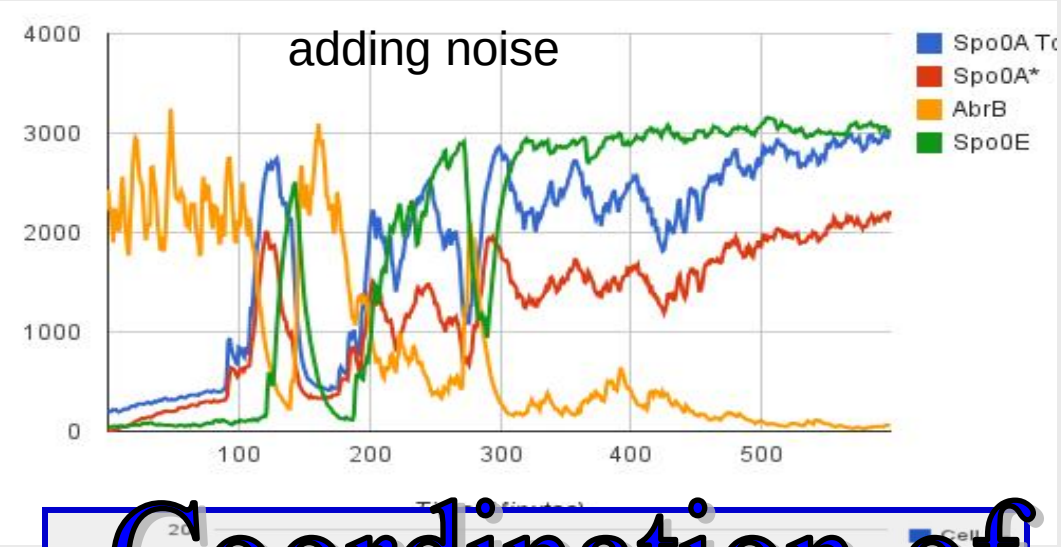


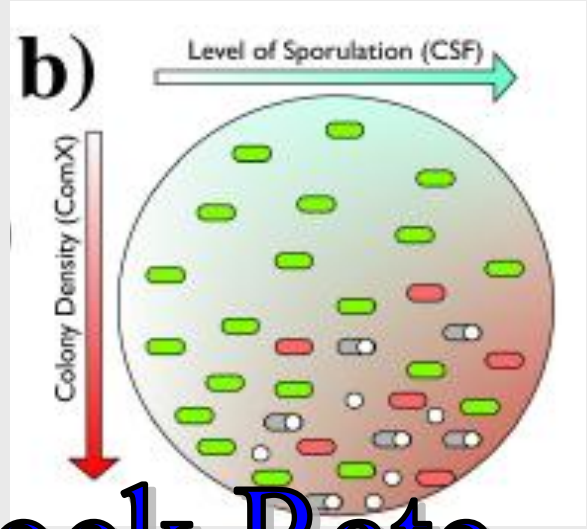



Stress
Cell Density
Spo0A
Spo0A*
Spo0E
AbrB
Rok
ComK
Sporulation
Competence


Transition Rate - Baseline - Deterministic
x 10^-3
Transition Rate (min^-1)
Time (Minutes)
Probability of Competence - Baseline - Deterministic
Probability
Time (Minutes)

Comparison with experiments





Coordination of Clock Rate