

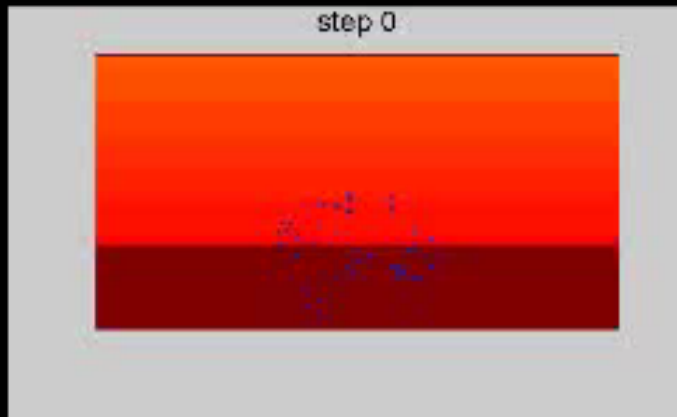
The Social Life of Bacteria

Eshel Ben-Jacob

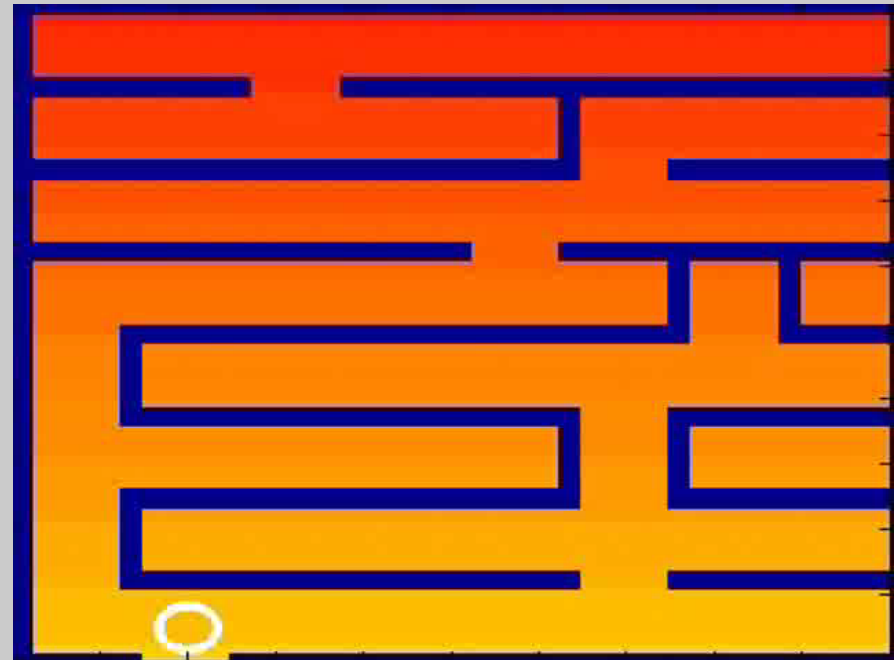
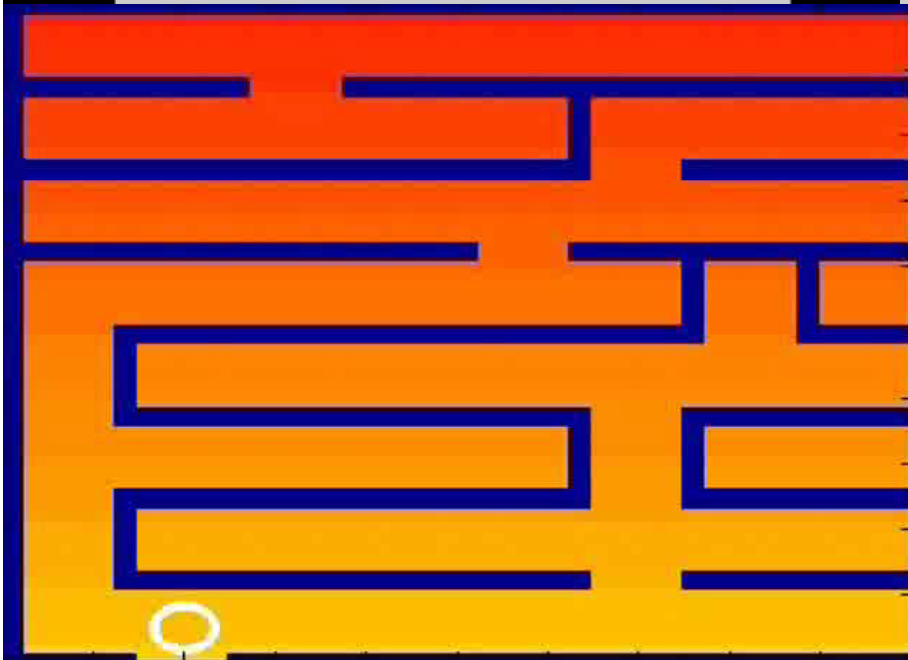


Genspace NY May, 28, 2011

Implications on cells in a maze



A bootstrapping mechanism



Prologue - Classses of Rudimentary Intelligence

Elementary Cognition –
Sensing, Information-processing, Decisions

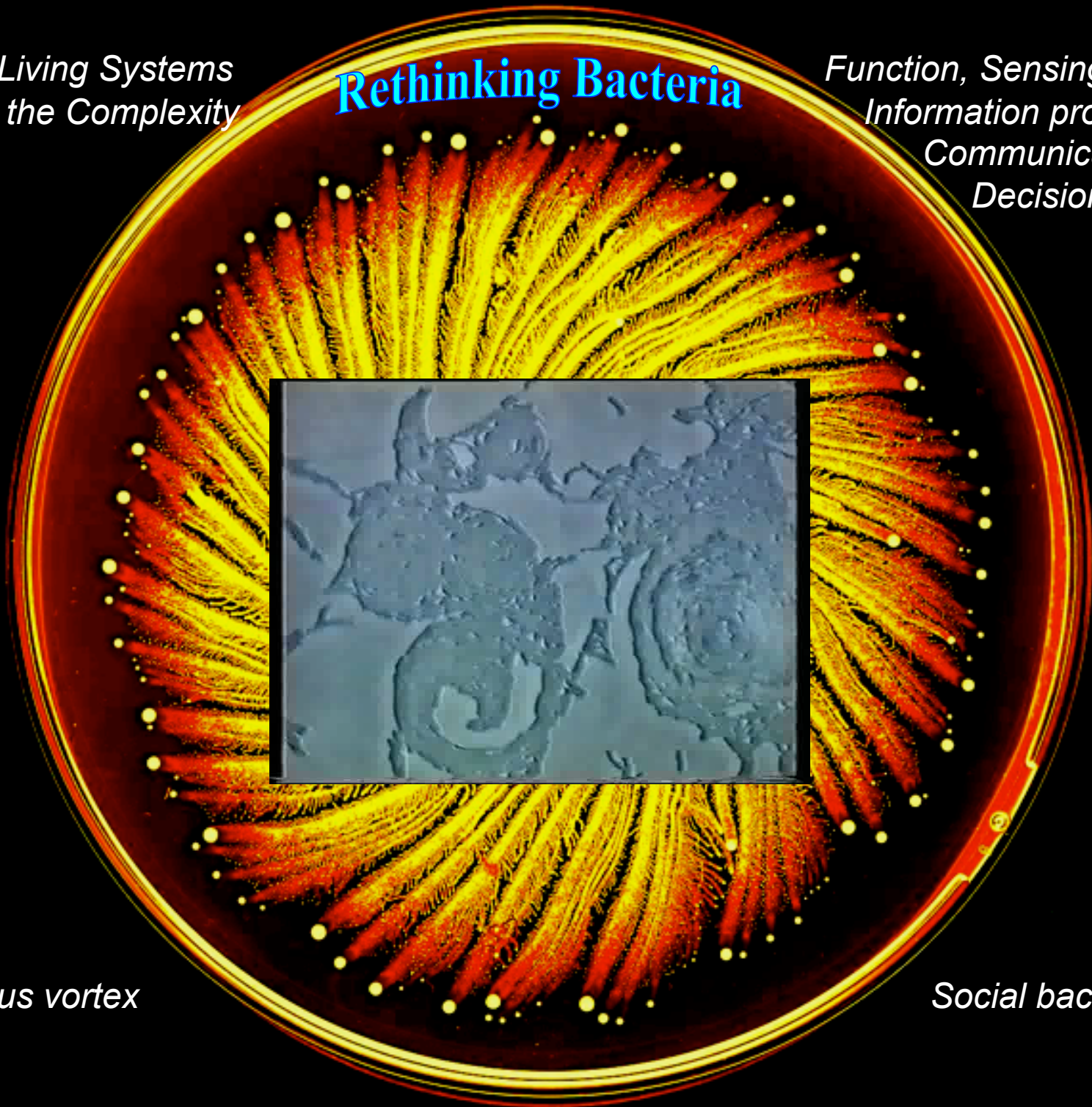




*Physics of Living Systems
Simplifying the Complexity*

Rethinking Bacteria

*Function, Sensing,
Information processing
Communication,
Decisions*



Paenibacillus vortex

Social bacteria

THE MISSING ANTIMATTER • WHAT THE MILKY WAY HIDES • THE SLIME EEL

SCIENTIFIC AMERICAN

OCTOBER 1998 \$4.95

SPECIAL REPORT:

How Hackers Break In

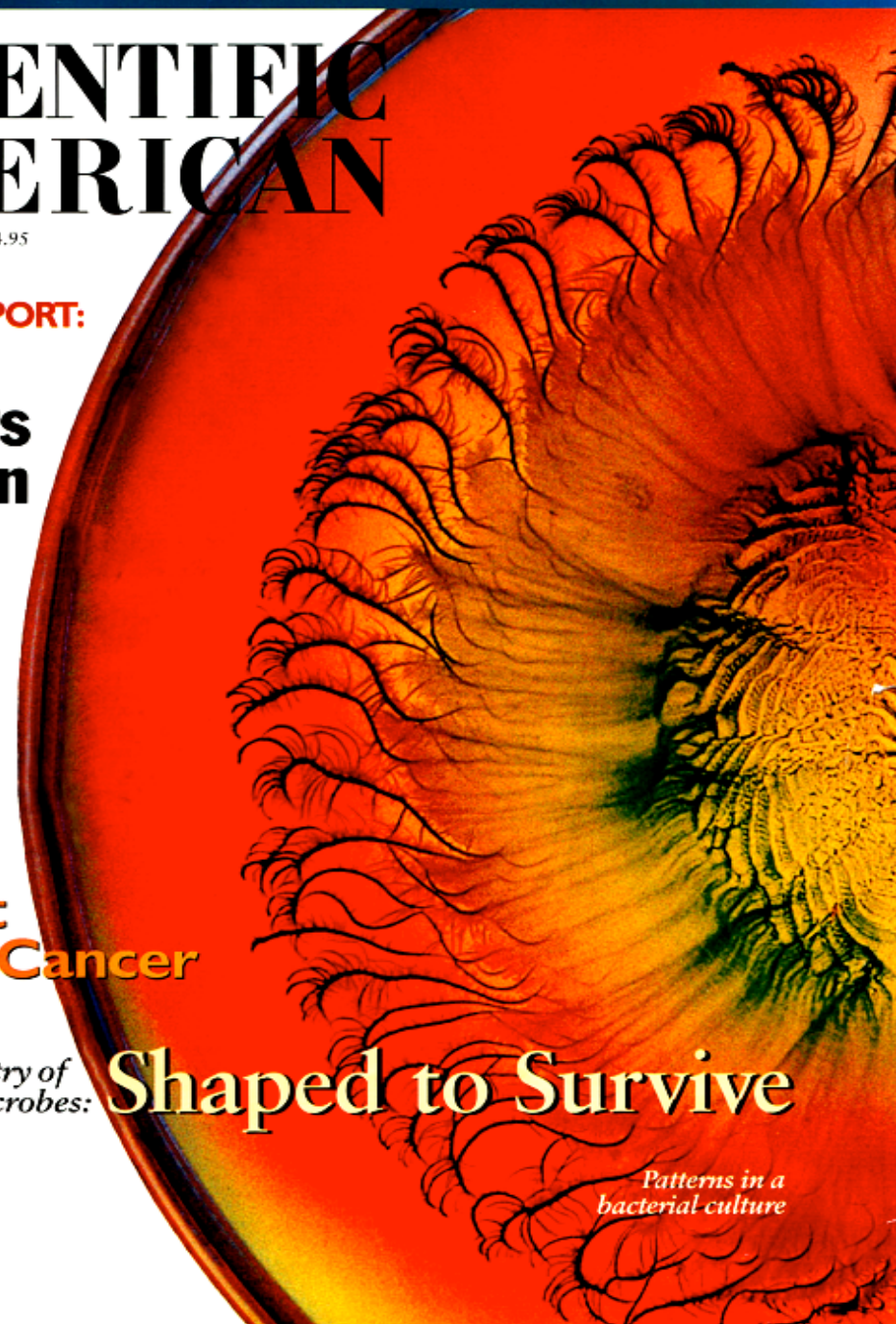
Keep
networks
and data
safe from
Internet
spies

Drugs that Prevent Breast Cancer

*The Artistry of
Microbes:*

Shaped to Survive

*Patterns in a
bacterial culture*



MICROBIOLOGY

The Smartest Bacteria on Earth

One species of soil microbe makes unusually wise communal decisions

By Anna Kuchment, staff editor

ESHI BEN-JACOB IS INTERESTED NOT ONLY IN THE genomes of the bacteria he studies but also in their personalities. He compares many to Hollywood celebrities. "On the one hand, we admire them, but on the other hand, we think that they are stupid," says Ben-Jacob, a professor of physics at Tel Aviv University in Israel. In December, though, he and his colleagues published a paper in the journal *PNAS* reporting that a species of soil bacteria he discovered in the mid-1990s, *Bacillus subtilis*, is surprisingly smart by microbial standards.

The team identified this relative intelligence by comparing the *B. subtilis* genome with that of six different bacterial species whose genomes were known well, based on that comparison, calculating what Ben-Jacob calls the bugs' "social IQ score." The researchers counted genes associated with social functions, such as those allowing bacteria to communicate and process environmental information and to synthesize chemicals that are useful when competing with other organisms. *B. subtilis* and two other *Bacillus* species have more of those genes than any of the other 400 bacteria Ben-Jacob studied, including pathogenic bacteria

such as *Escherichia coli*, indicating a capacity for "exceptionally brilliant social skills."

This social sophistication is manifested in the elaborate colonies that *B. subtilis* can form, such as the ones in the accompanying micrograph, which grow over several days in a petri dish. The colony, about eight centimeters in diameter, contains 100 times more bacteria than the number of people on earth. The blue dots are dense groups of bacteria, called vortices, that swirl collectively around a common center to better pave the way on hard surfaces and protect themselves from hazards. As the cells replicate, each vortex expands in size and moves outward as a unit, leaving behind a trail of older, more complicated cells, which form branches that maintain communication across the colony.

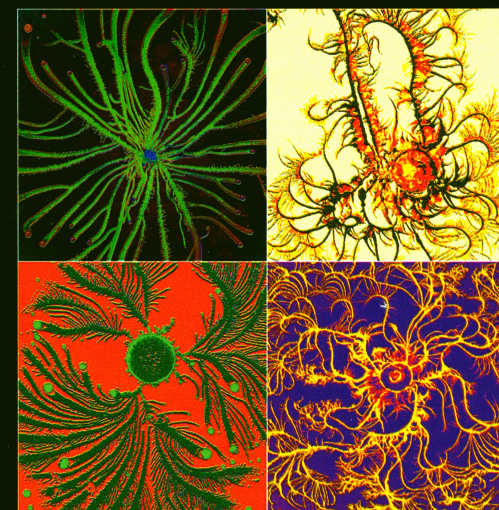
"Acting jointly, these tiny organisms can sense the environment, process information, solve problems and make decisions so as to thrive in harsh environments," Ben-Jacob says. "Never in development a single-celled unit."

SCIENCE ILLUSTRATION BY JIM HAN

More images and readings: www.sciencemag.com/june2011/bacteria

COURTESY OF THE JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

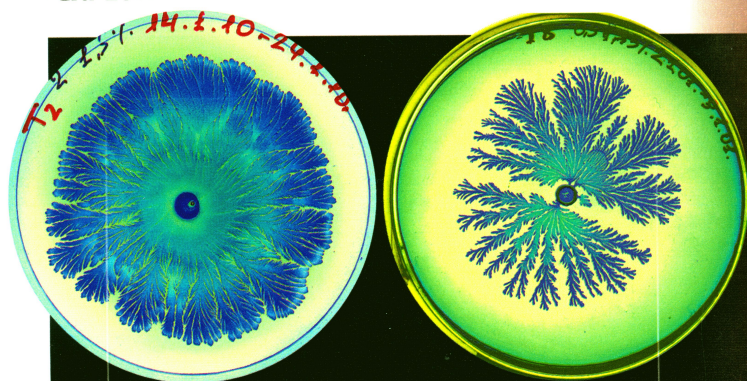
FONDAMENTAL
EXPLOIT



BACTÉRIES LEUR Q.I. A PU ÊTRE MESURÉ

*L'idée même de quotient intellectuel, chez ces êtres unicellulaires, peut surprendre.
Et pourtant : rassemblées en colonies de milliards d'individus, les bactéries sont
capables de communiquer, de prendre des décisions et de s'adapter à leur milieu.
Les preuves d'un potentiel génétique... qu'il est désormais possible de quantifier !*

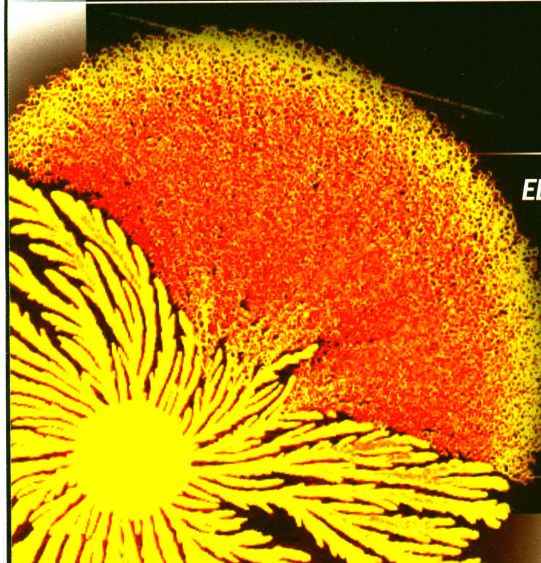
PAR ÉMILIE RAUSCHER



LES COLONIES DE BACTÉRIES ADAPTENT LEUR ARBORESCENCE À LA DURETÉ DU MILIEU

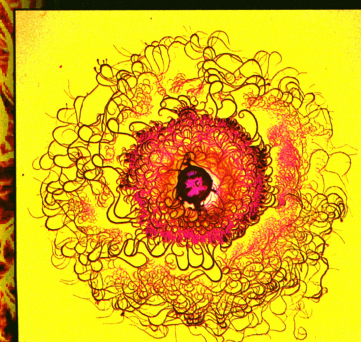
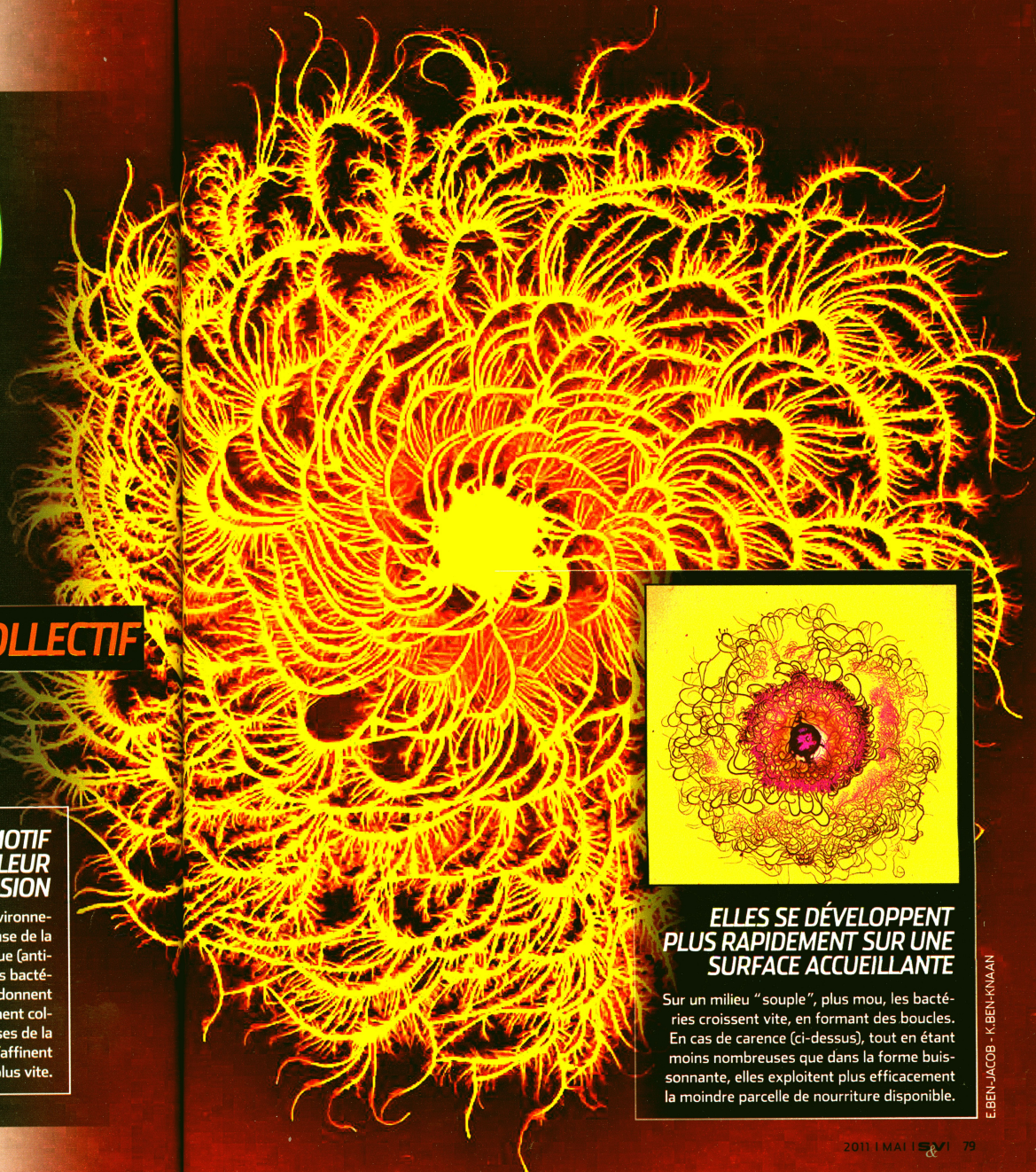
Les colonies ont du mal à grandir sur des surfaces dures et fermes. Dans ce cas, *P. dendritiformis* adopte une forme buissonnante (à g.) : les bactéries, regroupées en branches épaisses, sécrètent ensemble un lubrifiant "cirant" le sol sous elles. Si la nourriture manque, l'arborescence se fait alors moins dense pour limiter les besoins (à dr.).

DES COLONIES DOUÉES DE GÉNIE... COLLECTIF



ELLES CHANGENT DE MOTIF POUR OPTIMISER LEUR TAUX D'EXPANSION

Ci-contre, parce que l'environnement s'est ramolli ou à cause de la présence d'un agent toxique (antibiotique ou champignon), les bactéries *P. dendritiformis* coordonnent différemment leur mouvement collectif : les branches épaisses de la colonie s'allongent et s'affinent pour aller plus loin et plus vite.



ELLES SE DÉVELOPPENT PLUS RAPIDEMENT SUR UNE SURFACE ACCUEILLANTE

Sur un milieu "souple", plus mou, les bactéries croissent vite, en formant des boucles. En cas de carence (ci-dessus), tout en étant moins nombreuses que dans la forme buissonnante, elles exploitent plus efficacement la moindre parcelle de nourriture disponible.

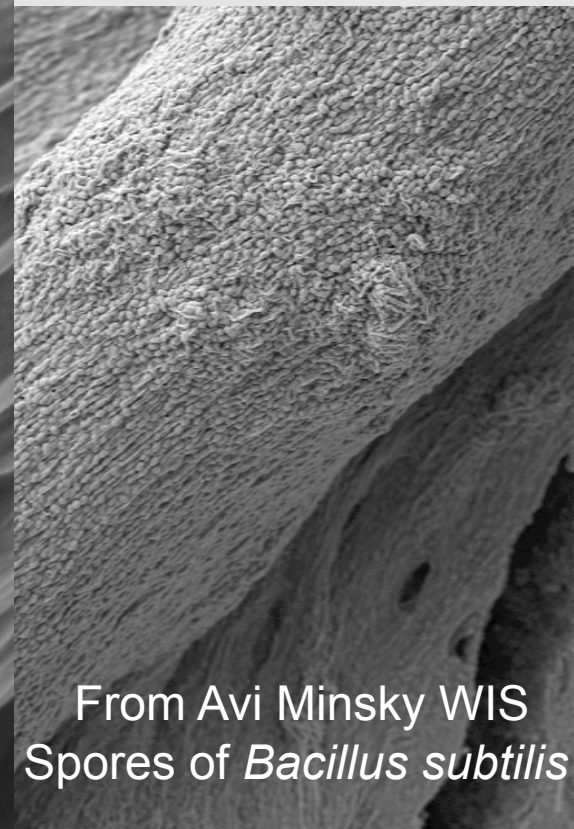
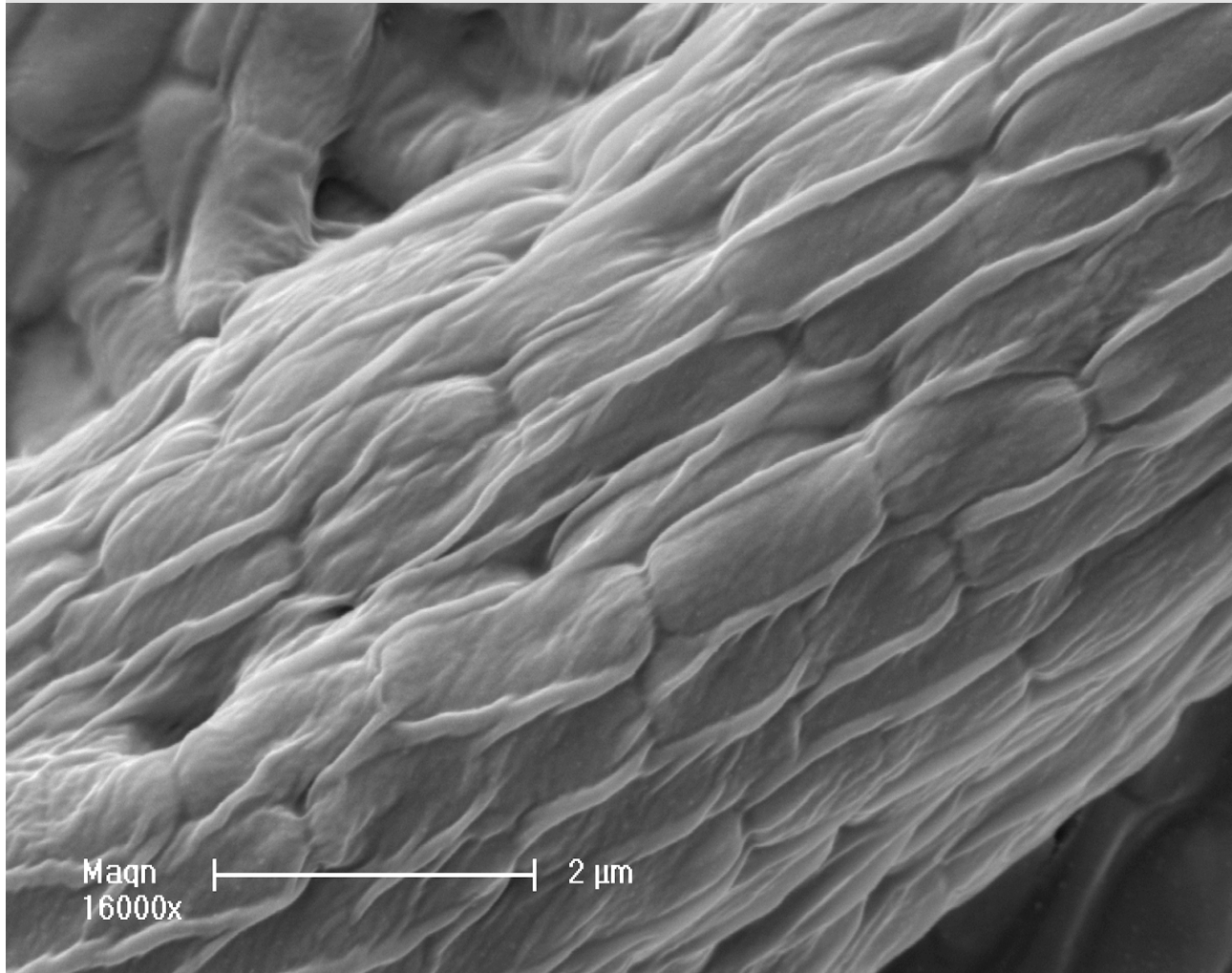
Part 1: In vs. Competence

Part 2: Utilism to Fight Bacteria

Part Organization

Part 4ing Intelligence

Sporulation, Competence, Cannibalism

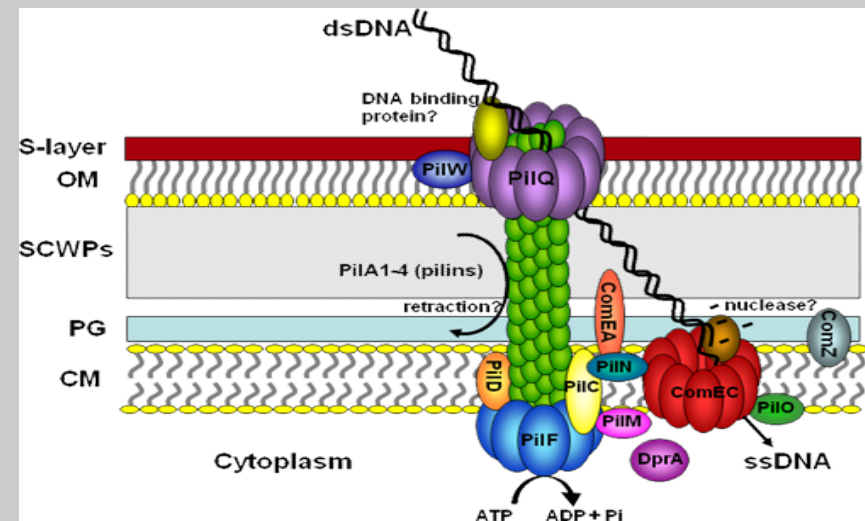
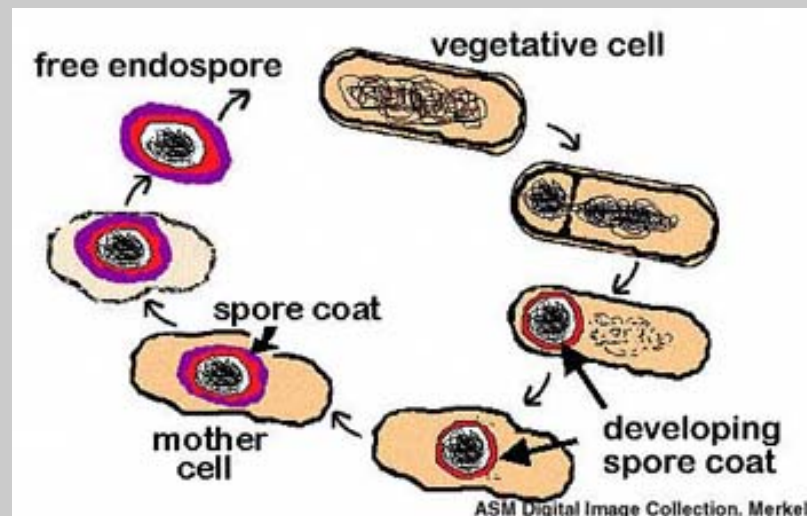
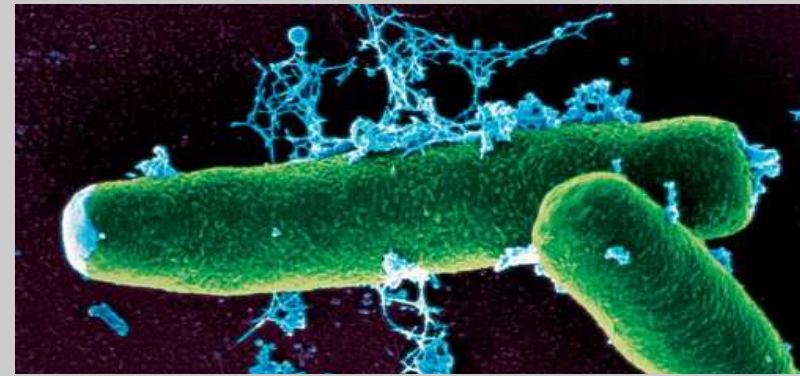
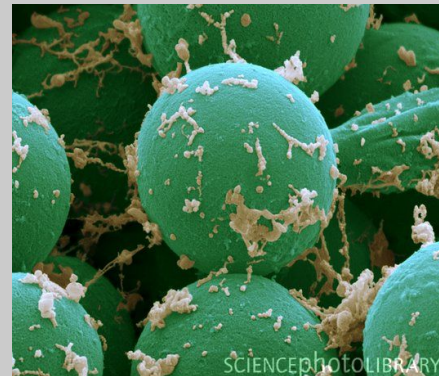
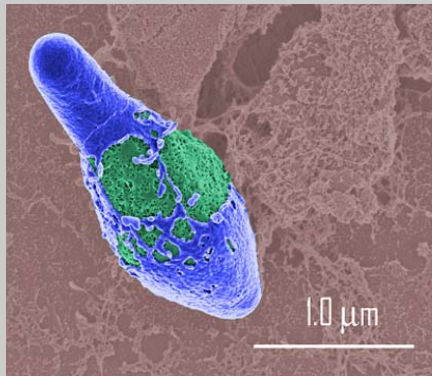


From Avi Minsky WIS
Spores of *Bacillus subtilis*

Sporulation

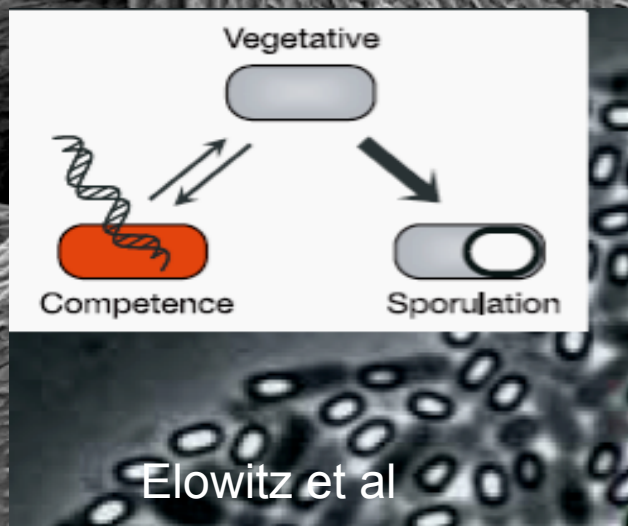


Competence



With Schultz, Wolynes, Onuchic, *PNAS*, 2007,2009,2010

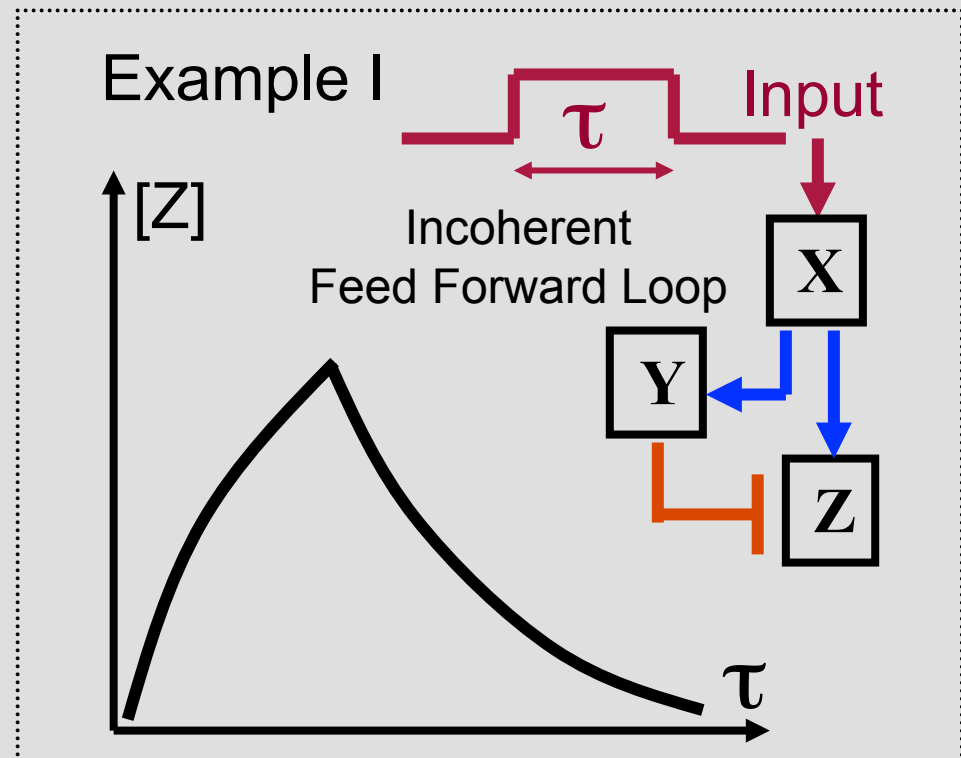
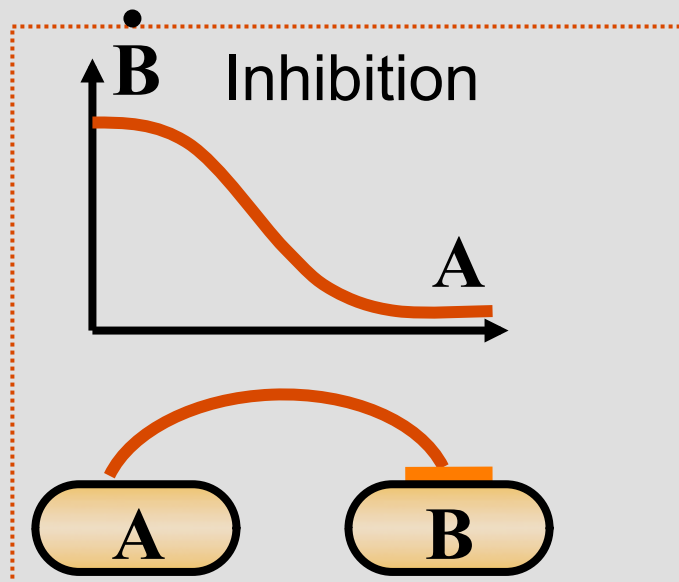
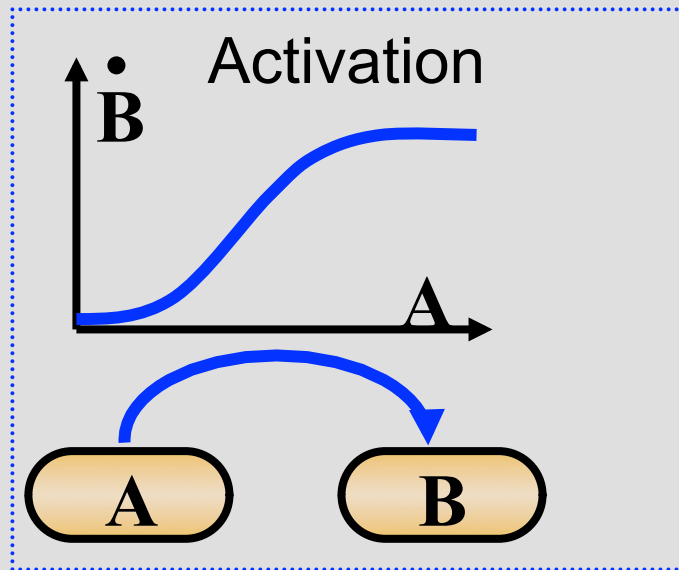
The Challenge of Collective Decisions

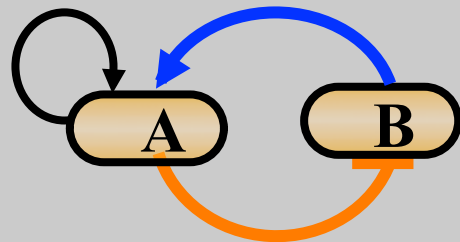


Identification of the logical functions

Stress

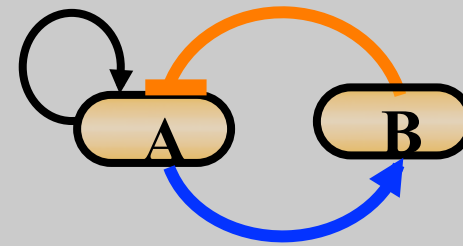






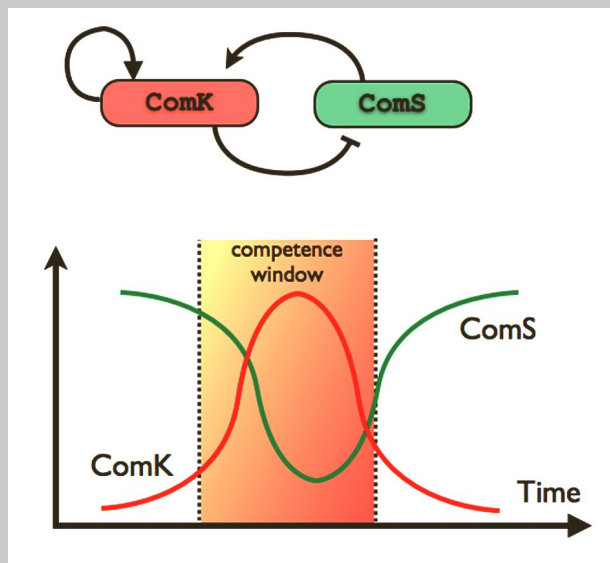
Low noise

For rare events



High noise

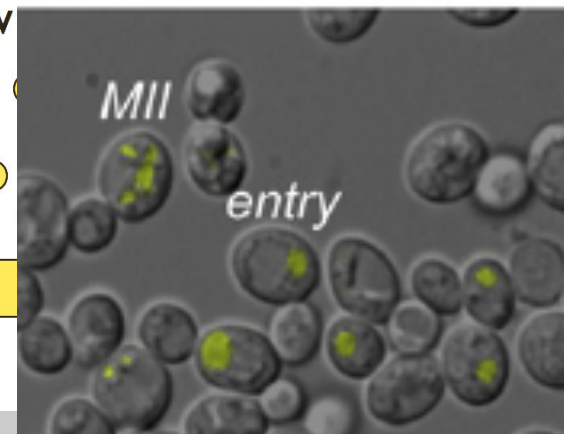
For frequent events



dium noise

low

ON



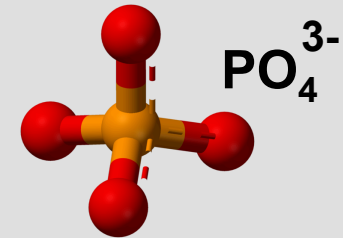
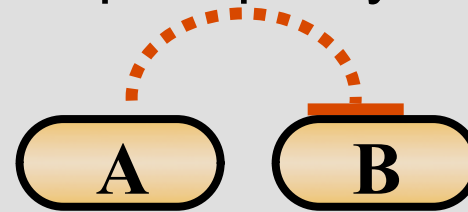
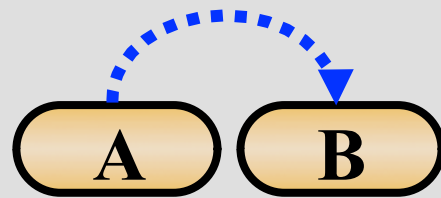
"Bacteria determine fate by playing dice with controlled odds"

Suel et al., *Science* 2007 and *PNAS* 2010

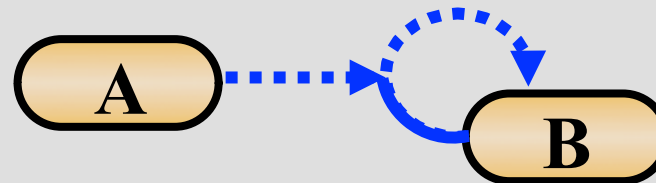
Ben-Jacob & Schultz, *PNAS* 2010

Nachman et al., *Cell* 2007

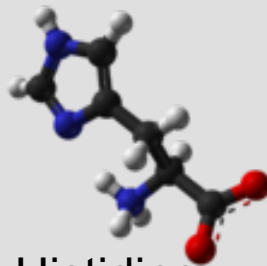
Phosphorylation and Dephosphorylation



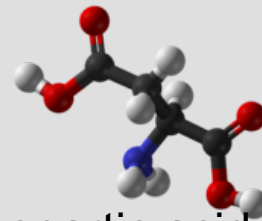
Example



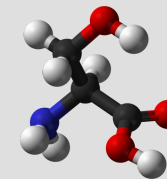
Time scale control by using different Amino Acids



Histidine

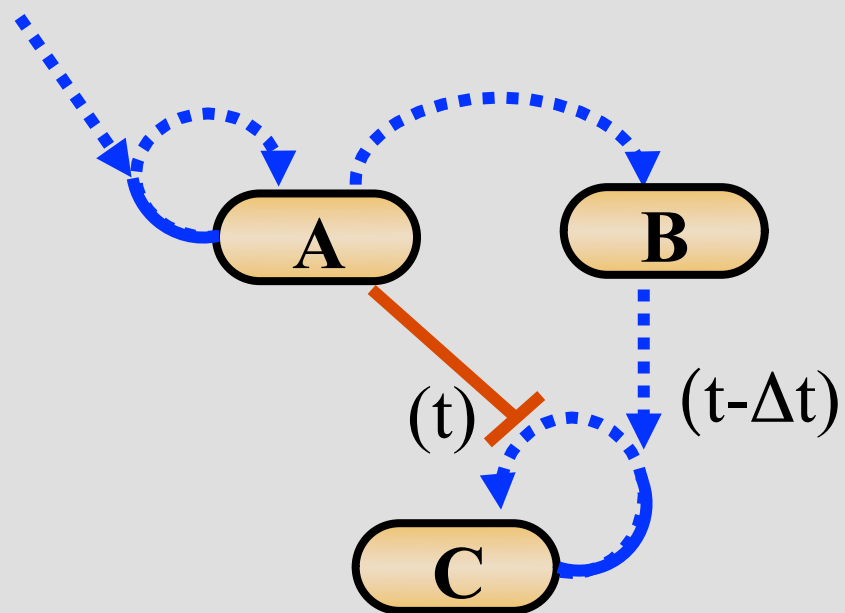


Aspartic acid



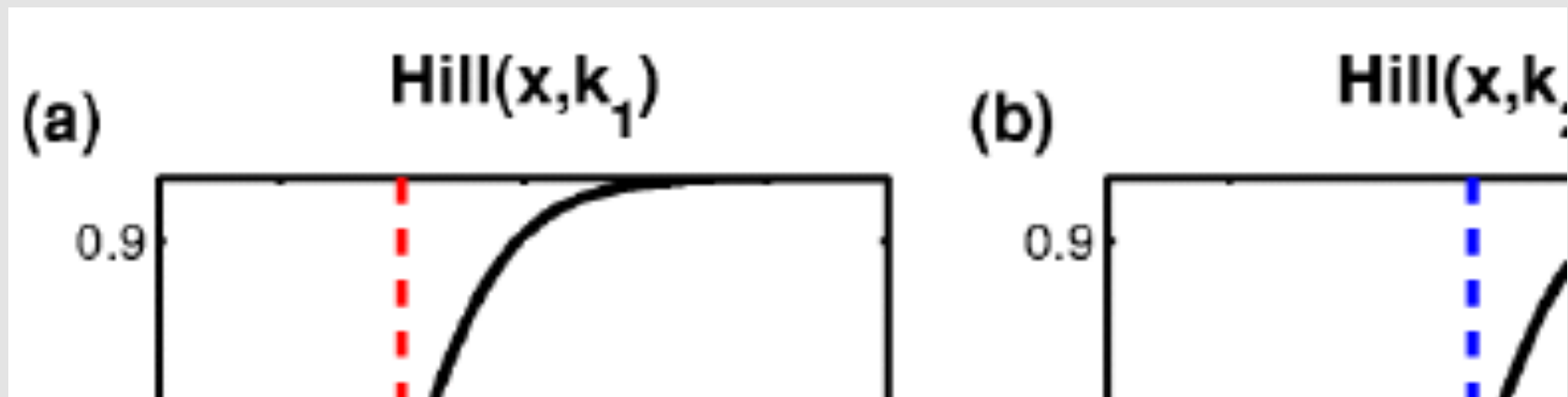
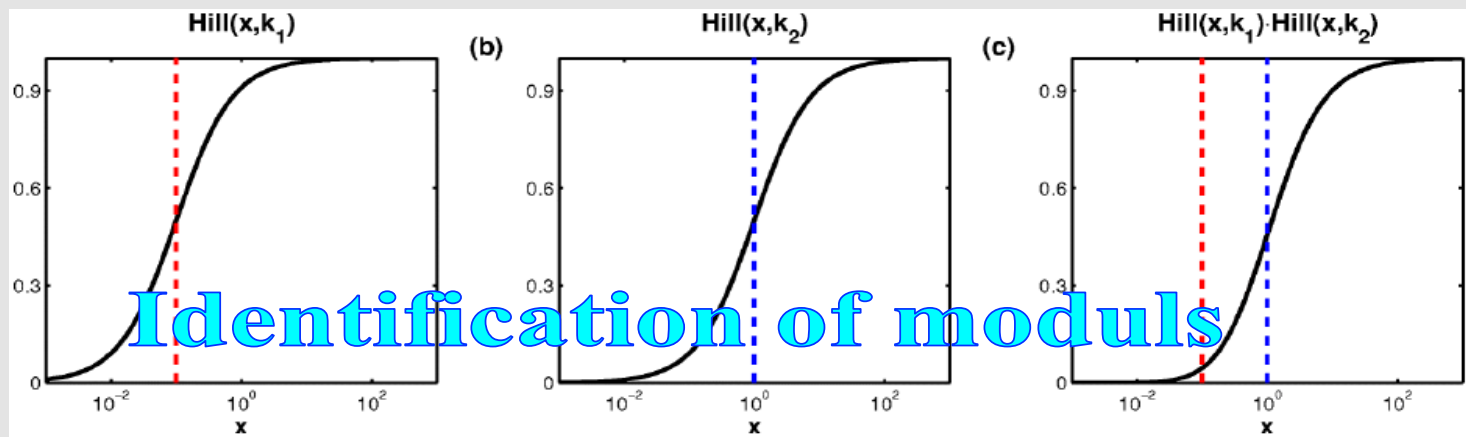
Serine

The measured concentration



Using the Properties of Hill Functions

$$\text{Hill}(x^n, K) \equiv \frac{x^n}{x^n + K^n}$$

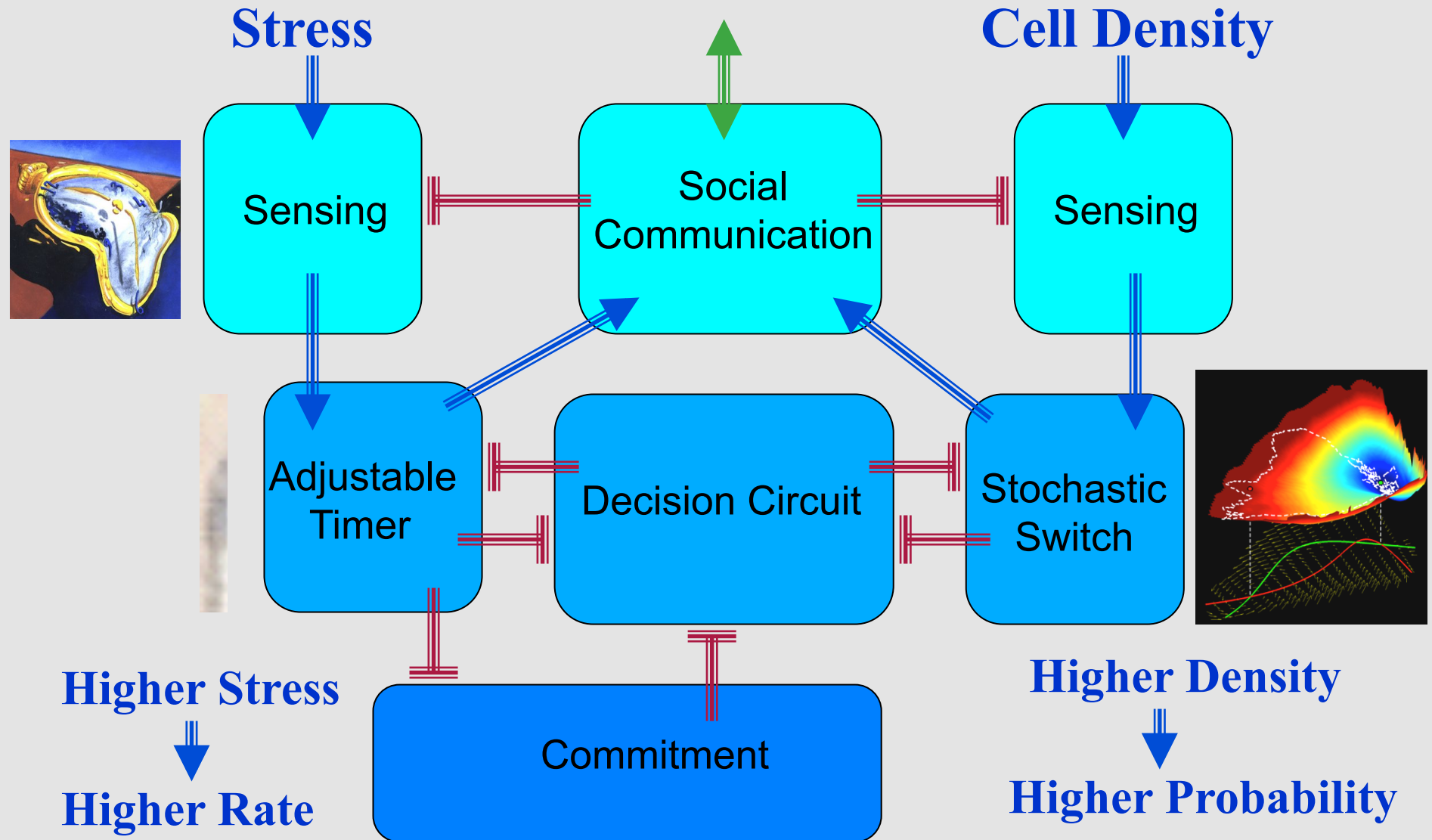


Identification of moduls

Stres



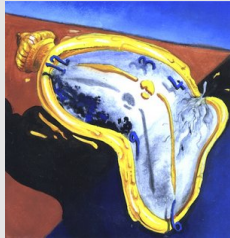
System Level Perspective - The Decision System



Stress

Spo0A* = Internal time or Proper time

Sensing



Timer

Spo0A*

Social
Communication

Memory (Kernel)

“Social Coordination”

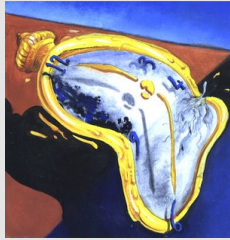
“Social Normalization”
of the clock rate



Example of “Social Coordination”

Stress

Sensing



Timer

Spo0A*



“Proper time” $\uparrow$ Spo0A*

ComA*

Cell Density

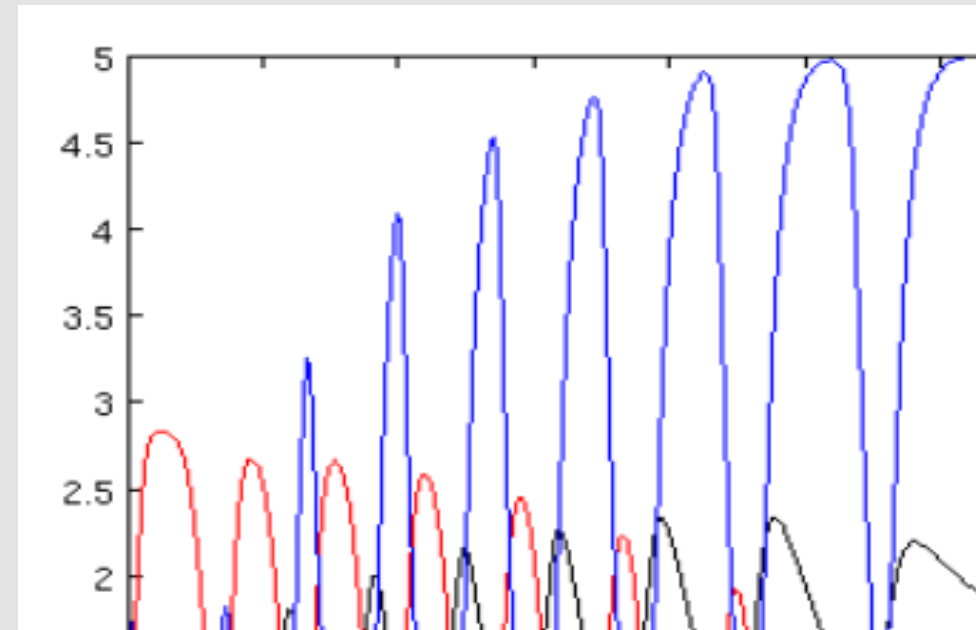
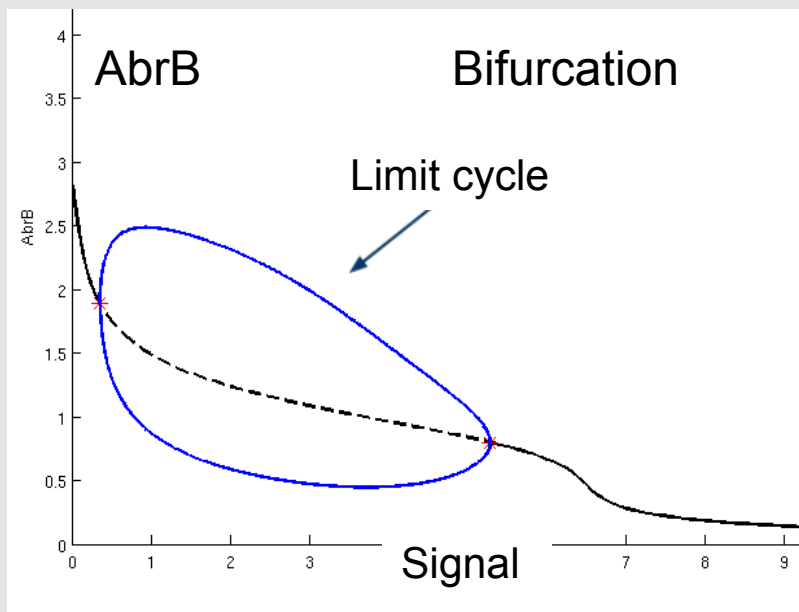
“Proper time” Synchronization

Increasing the clock rate if the “proper time” of the other cells is more advanced, and vice versa

Signal



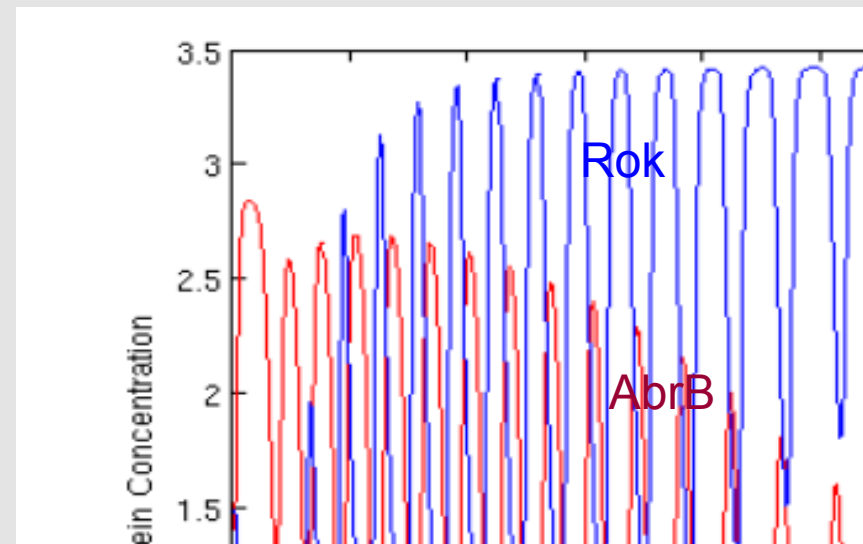
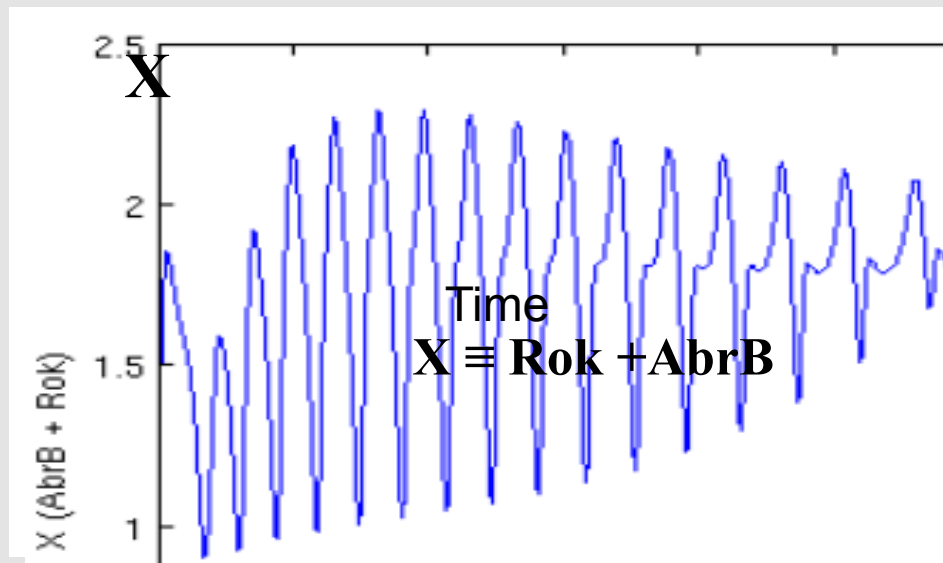
Adjustable Timer

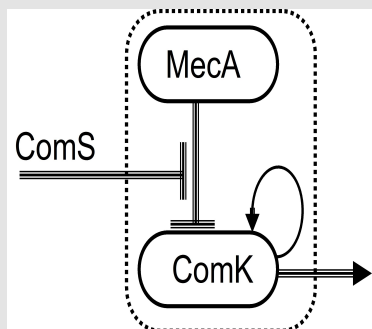


Interplay between the two master regulators

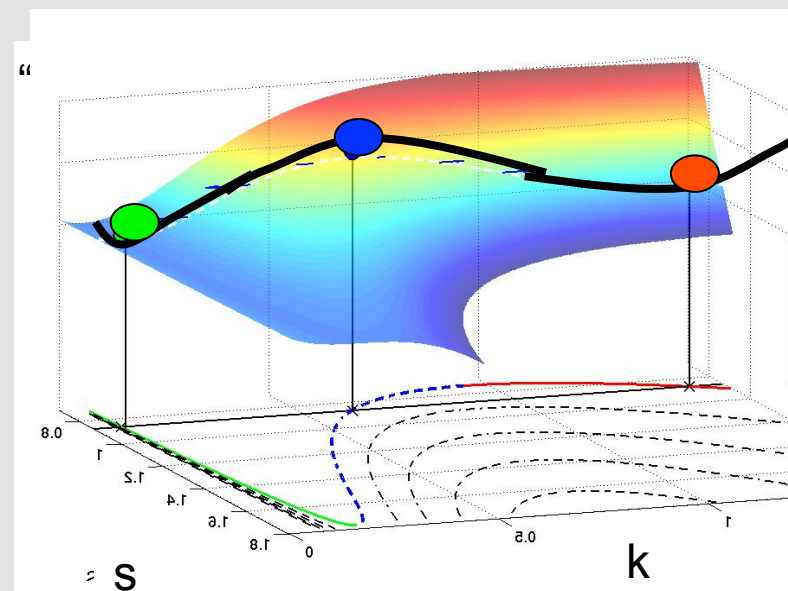
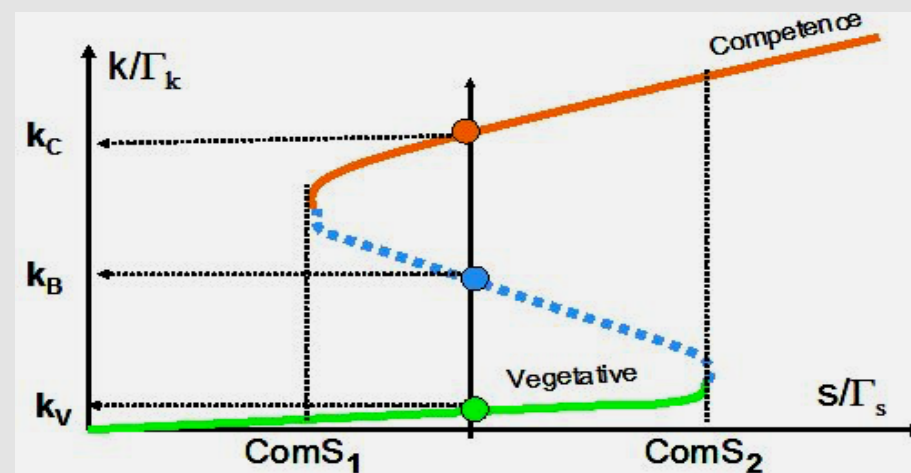
Adjustable Timer

Stochastic Switch





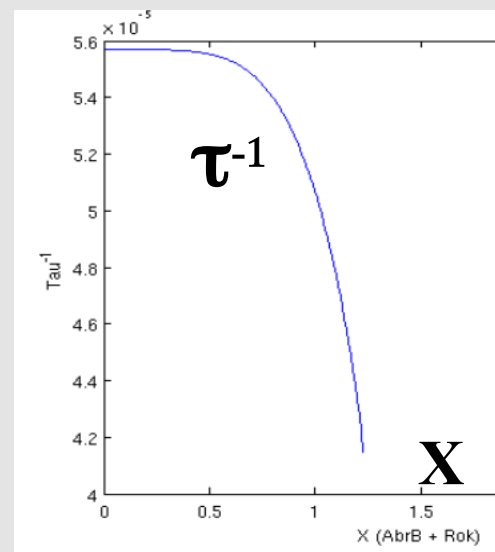
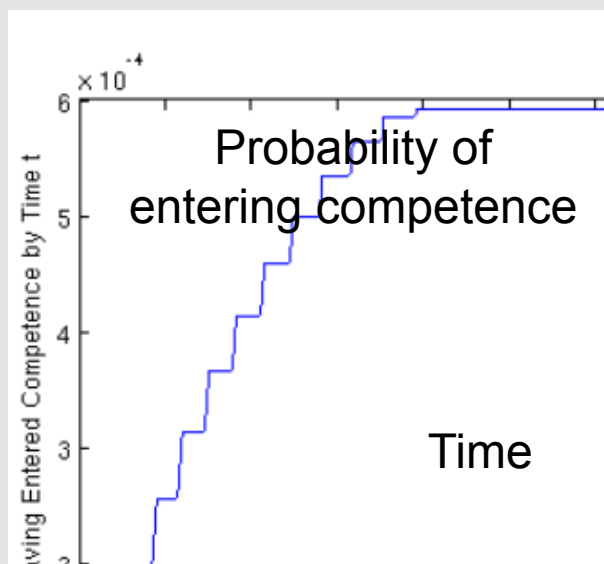
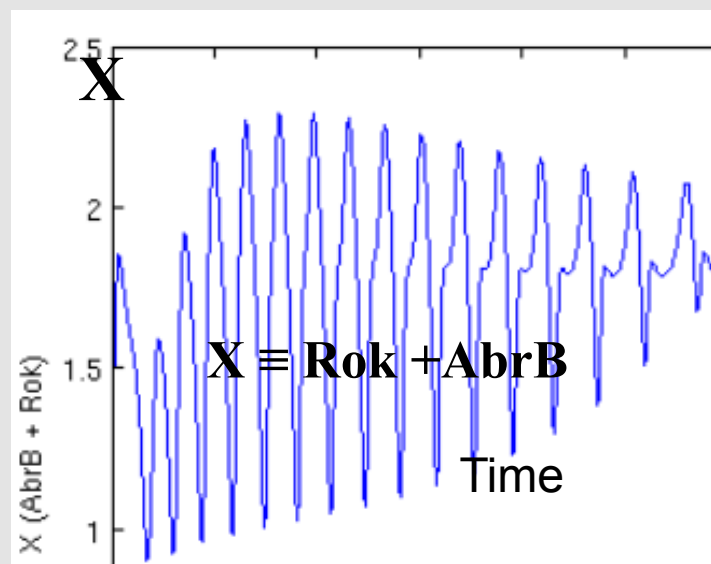
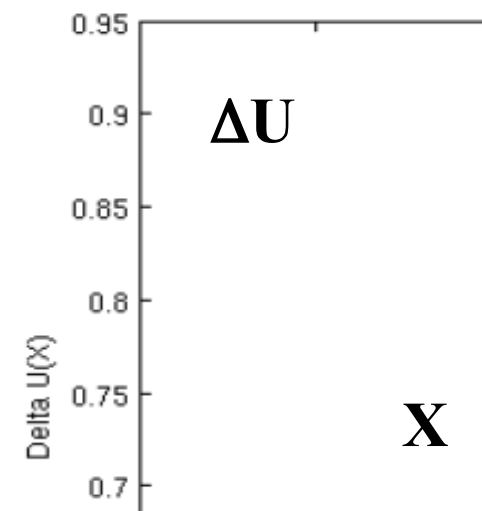
$$dk(t)$$



$$dk(t)$$

$$\left(\frac{X_0^m}{X_0^m + X^m} \right)$$

$$\pi - 1 \approx$$



Stress
Sensing



Timer



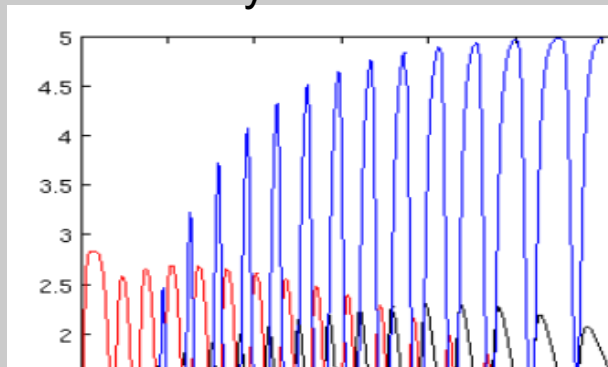
Social
Communication

Cell Density

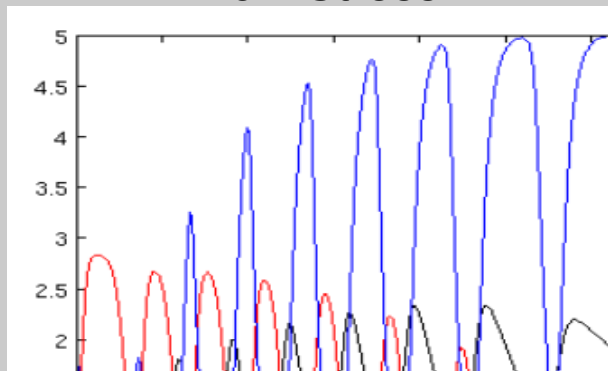
Stochastic Switch

“Social Synchronization”
of the clock rate

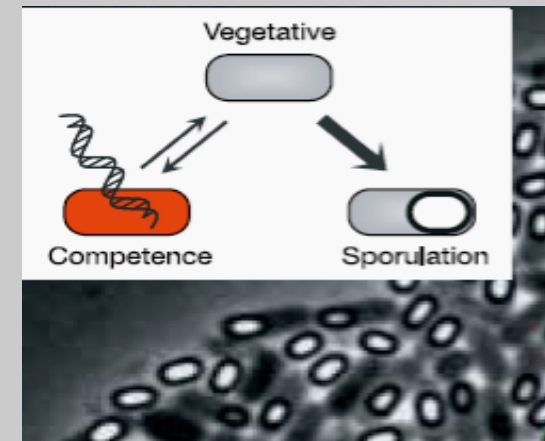
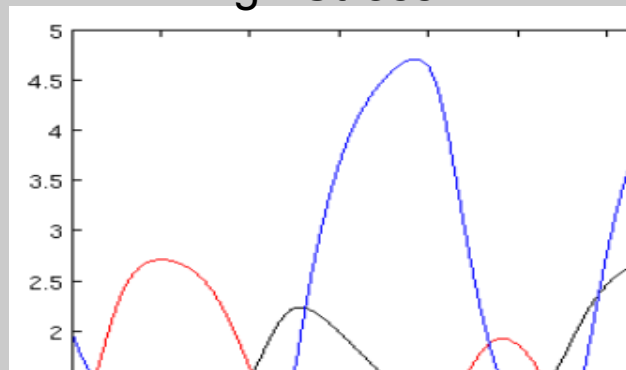
Very Low Stress



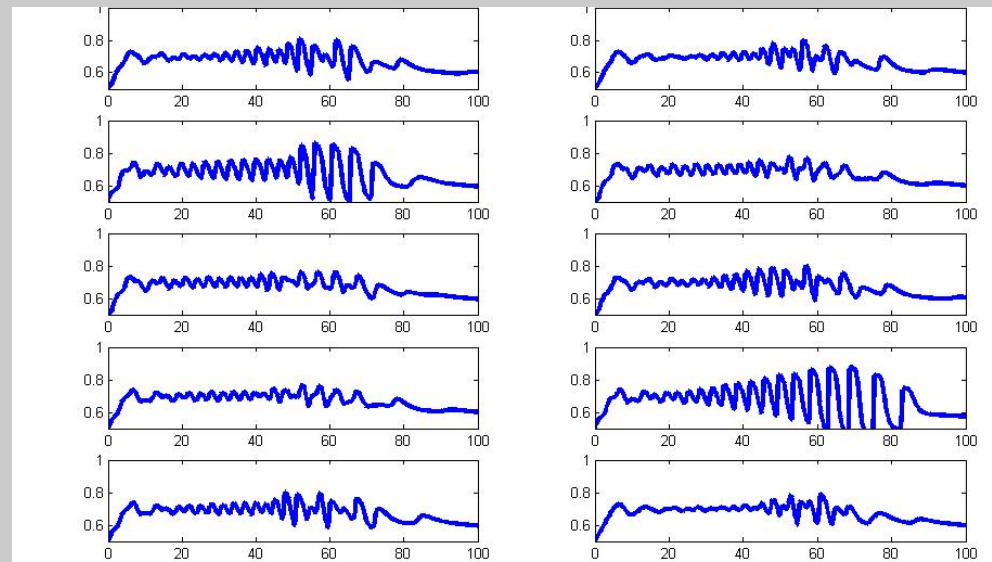
Low Stress



High Stress



AbrB in Different Cells



Individual Flexibility and Expected Group Decision

Physics perspective: new universality class

EE perspective: new synchronization class

Biology perspective: decision by other cells (e.g. cancer)

Mathematics perspective: game theory

Neuroscience perspective:
The role of inhibition in human decision

THE JERUSALEM POST - FRONT

Can bacteria teach us how to make life decisions?

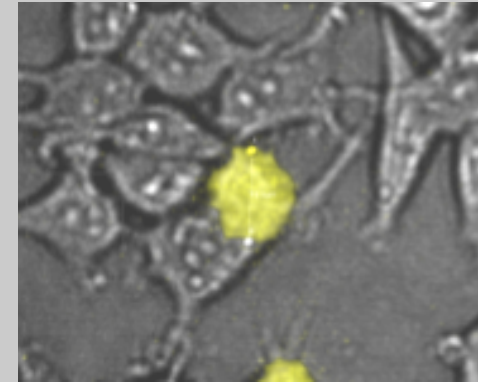
TAU physicist says single-cell organisms can show humans how to cope with stress

Navigatils in cancer cells

Mesenchymal vs. Amoeboid

“Path generating”

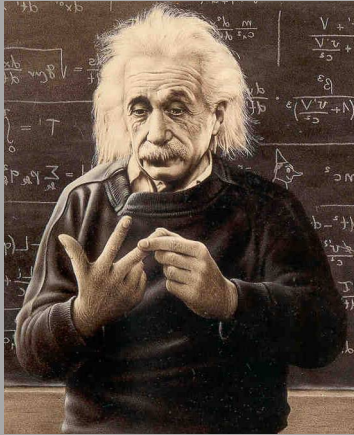
Rely on proteolytic degradation
of the surrounding matrix



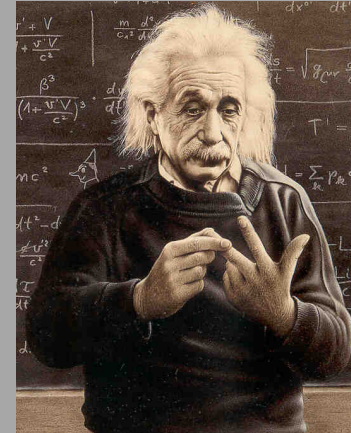
“Path finding”

Amoeboid motility that is accompanied
by membrane blebbing

With Inbal Hecht, Assaf Zaritsky, Ilan Tzarfati, Herbert Levine



\$2 - \$100



\$100

\$97

\$96

\$99

\$101

\$98

\$100

Minimization of Maximum Regret



From Science News March 24

Knowing It in Your Gut: Cross-Talk Between Human Gut Bacteria and Brain

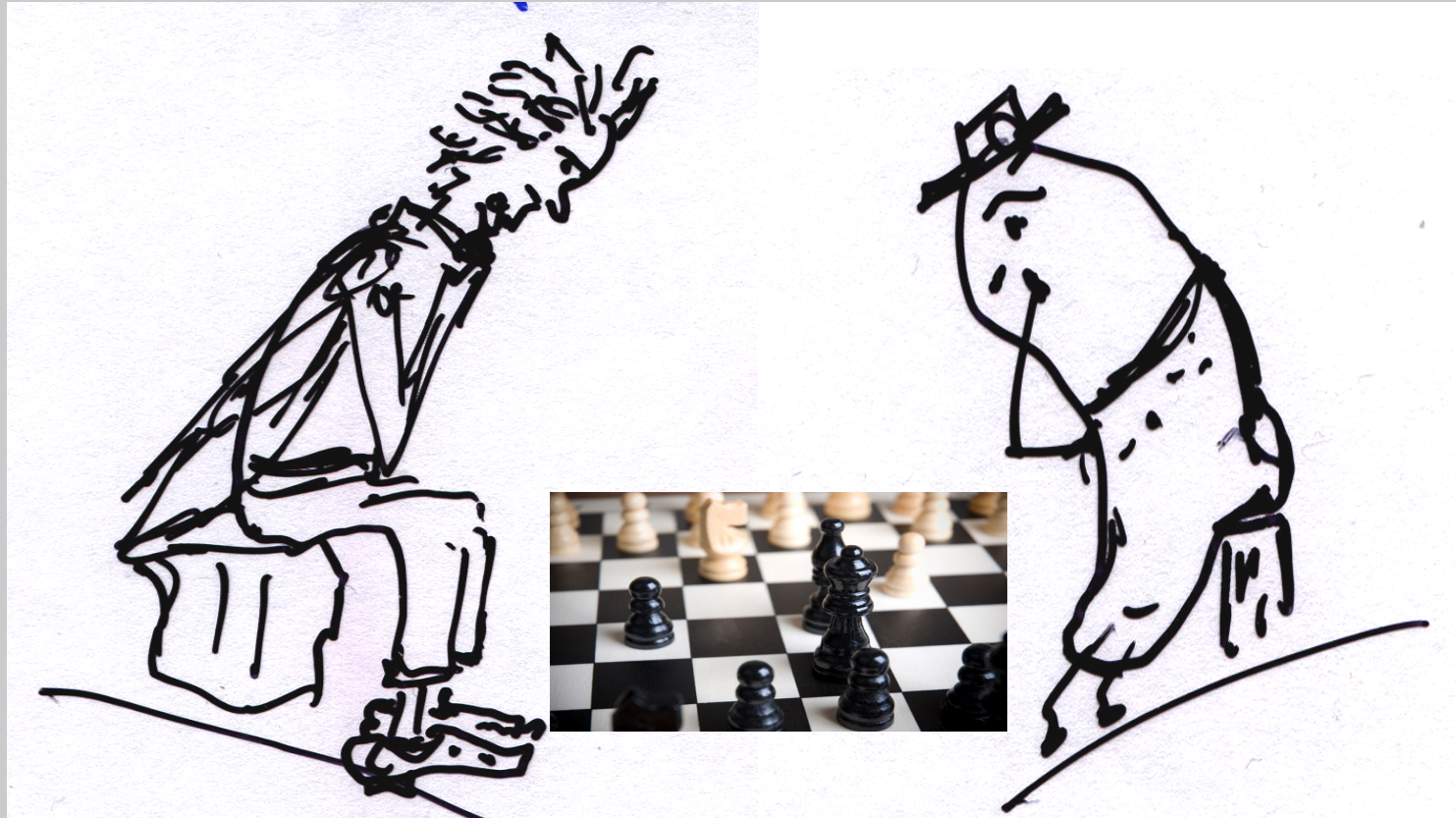




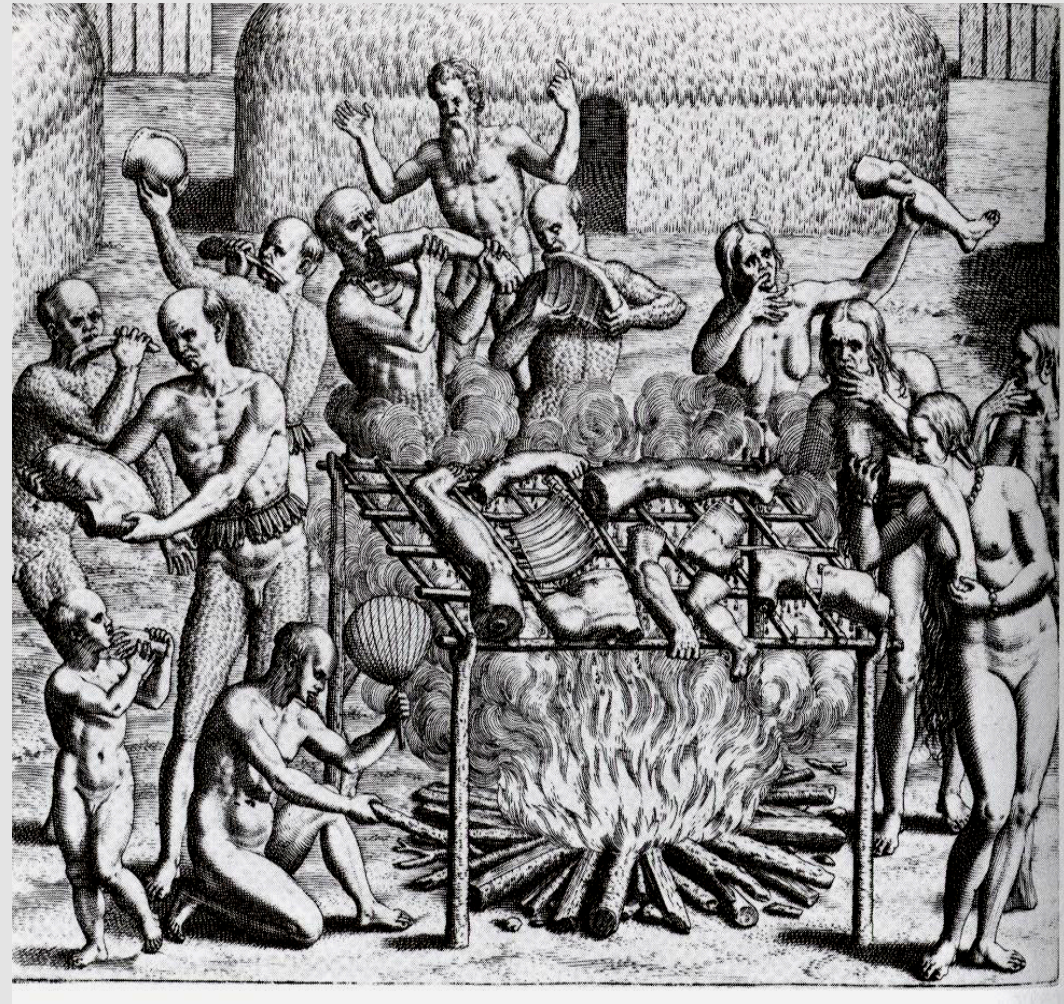
Bacterial "Blue Movies"



Harnessing Cannibalism to Outsmart Bacteria



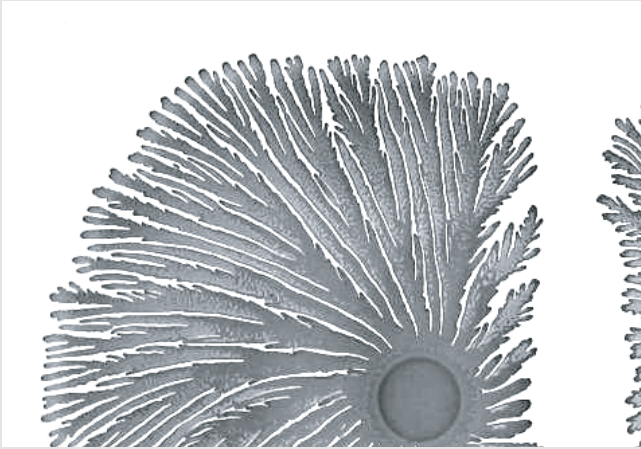
With Be'er, *et al.*, *PNAS* 2009, Be'er, Ariel *et al.*, *PNAS* 2010



Beyond a single colony

Colony-colony competition

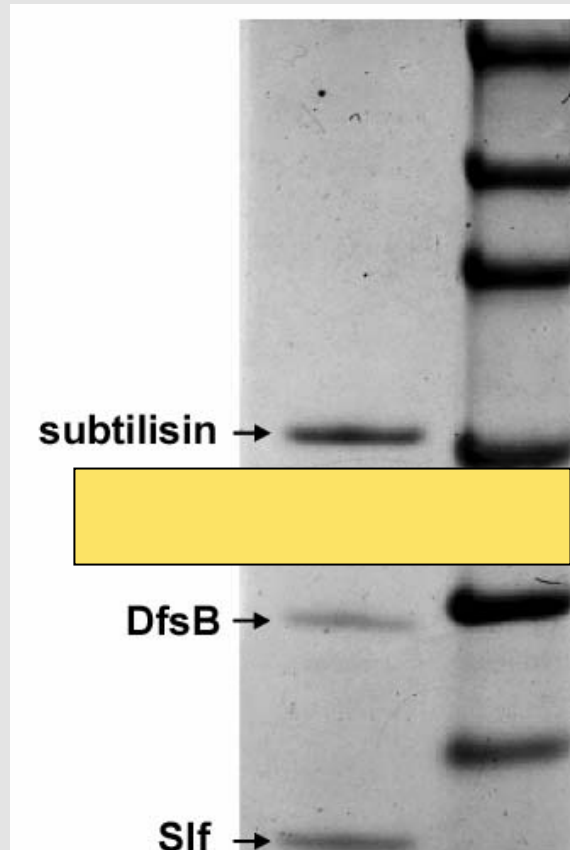




With A. Sirota, O. Kalishman, Y. Helman

MASY

*EYTSKEELKKTIHAAYLLLDGEFEGIDDSQKDNRVPE
VDRTPAEIIYQLGWLHLVMGWDRDELAK_
PVIMPAPGYKWNQLGGLYQSFYAAYADLSLTELR
RLFRDTMARWIHINERQWLDWIDTLSEEDLFTQ
SVRKWTGDKPNWP SAAPFKTFRAKIRKWKK
HQRQA*



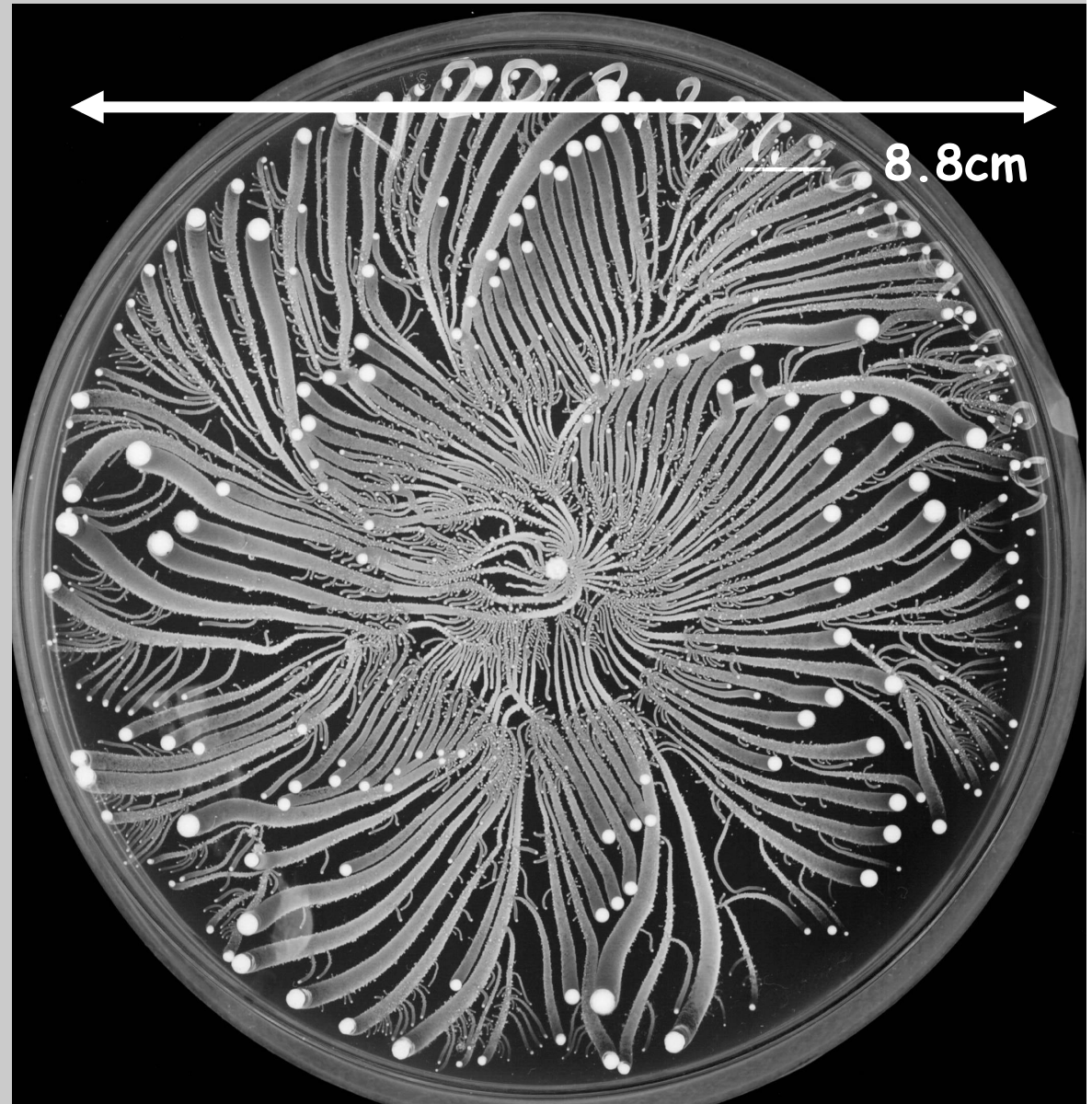
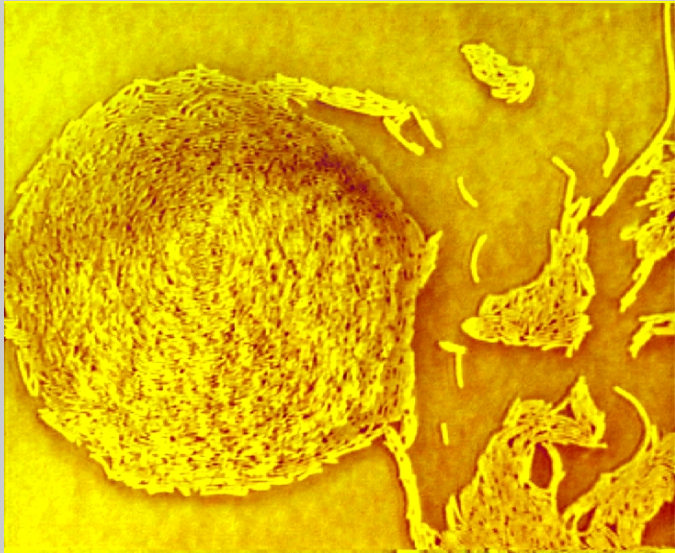
**DfsB – Dendritiformis sibling bacteriocin
(Siblicidin)**

DfsB + Subtilisin → Slf

Slf – Sibling Lethal Factor

Example of Self-Organization: Modular Organization

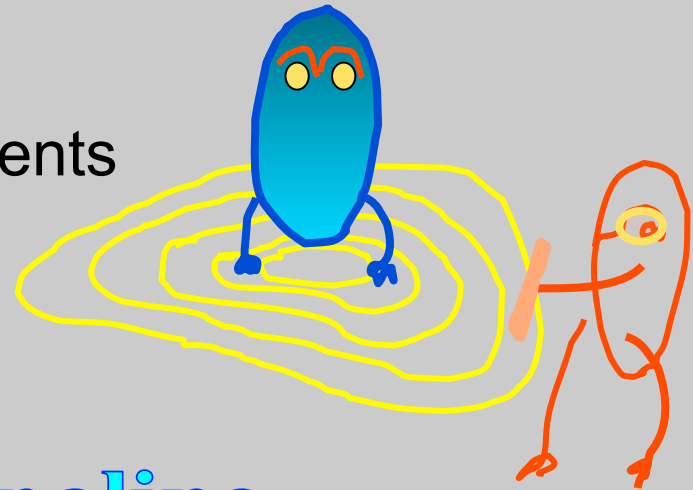
Ben-Jacob, Nobel Symposium on *self-organization*, 2002



Chemotaxis

Sensing, memory, information processing

Chemotaxis –
Movement according to chemical gradients

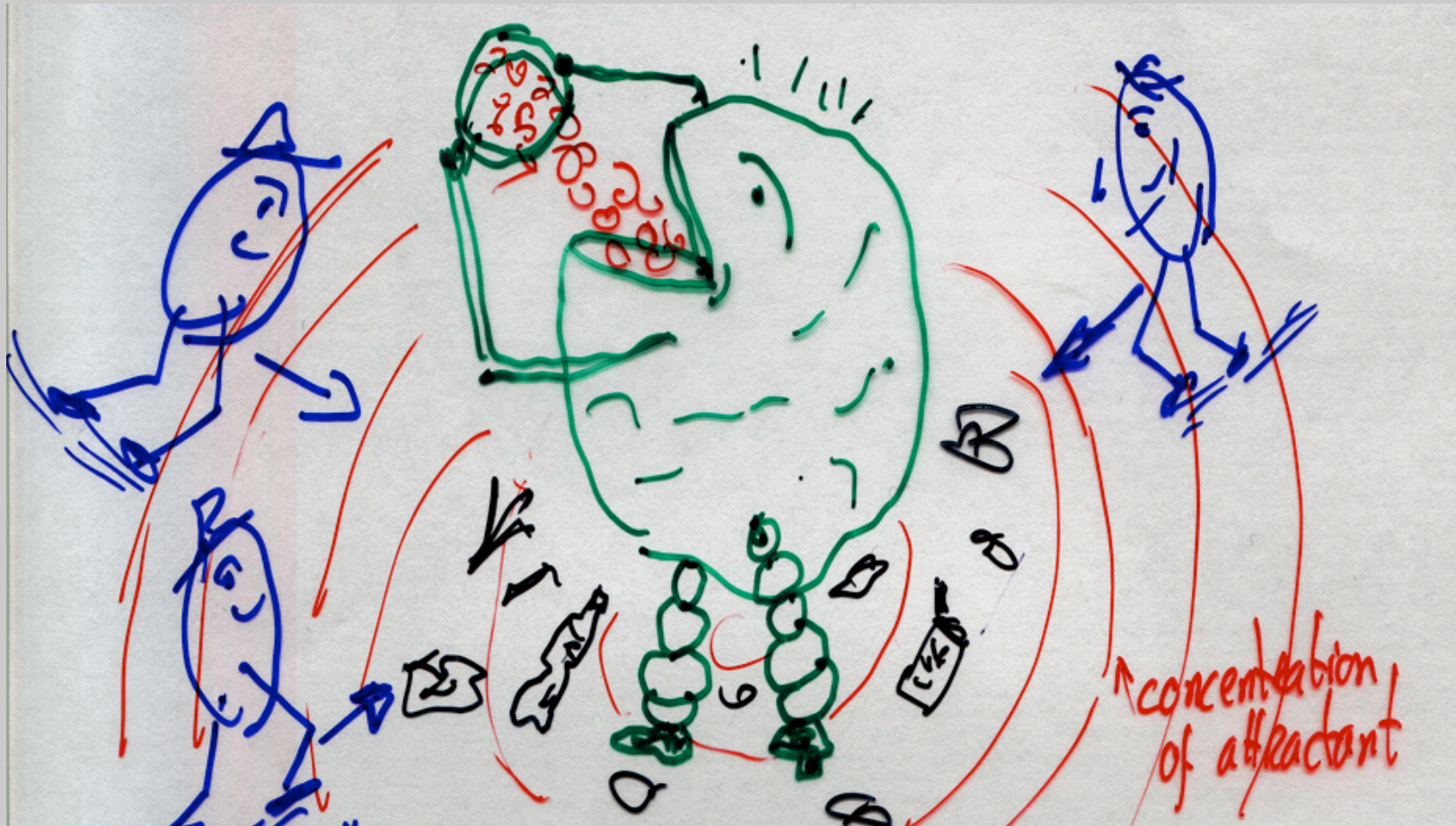


Chemotactic Signaling

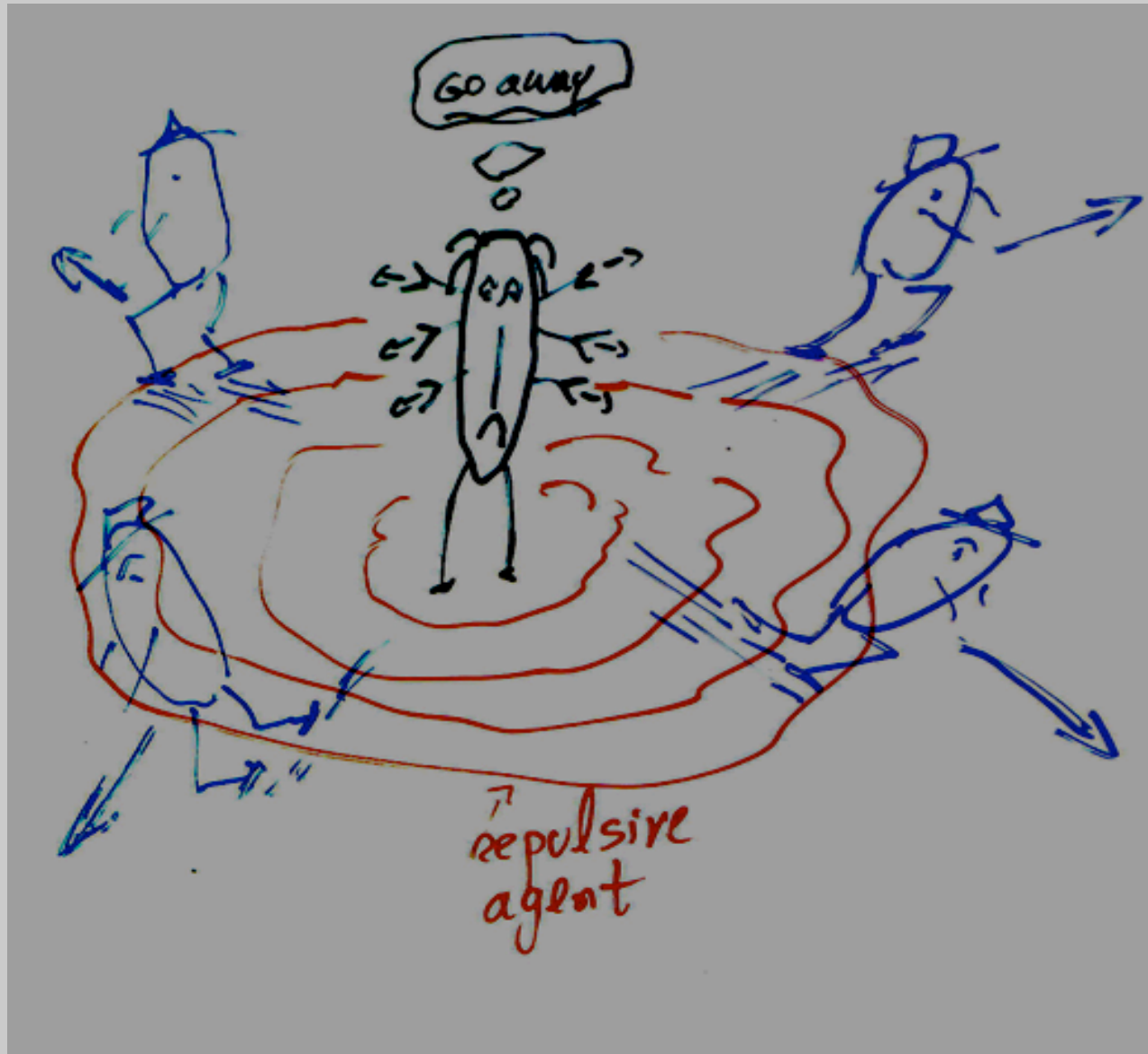
Chemotactic Signaling–
Chemotaxis in response to chemicals secreted by the cells

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

Attractive chemotaxis



Repulsive chemotaxis



Velocity alignment with curl chemotaxis

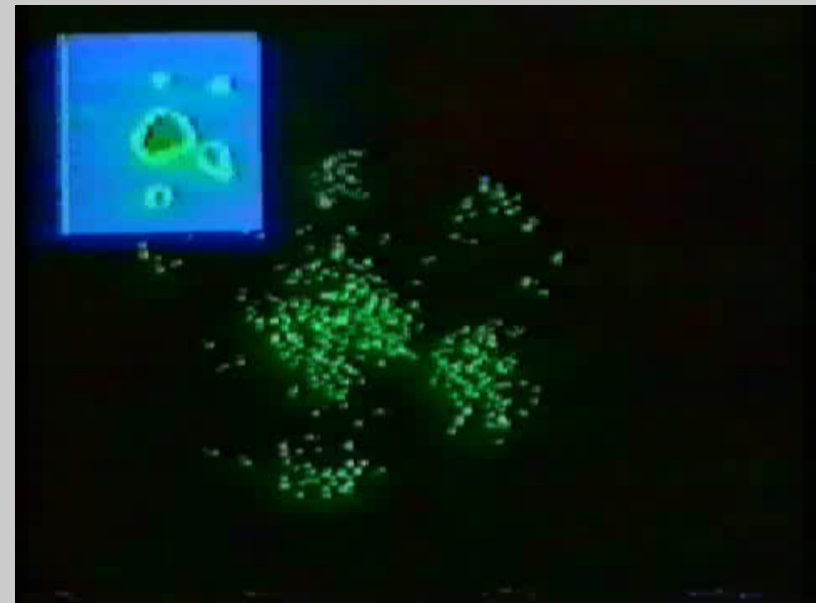
$$\frac{d\mathbf{v}_i}{dt} = \Gamma \frac{\mathbf{v}_i}{|\mathbf{v}_i|} - \nu \mathbf{v}_i$$

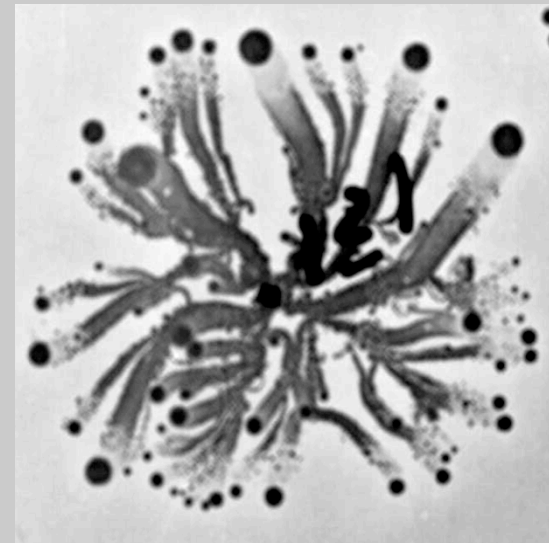
Diagram illustrating the forces acting on a bacterium's velocity vector $\mathbf{v}_i$:

- Self-Propulsion**: Indicated by a downward arrow pointing to the term $\Gamma \frac{\mathbf{v}_i}{|\mathbf{v}_i|}$.
- Friction**: Indicated by an upward arrow pointing to the term $-\nu \mathbf{v}_i$.
- Velocity alignment**: Indicated by a vertical line pointing to the term $\Gamma \frac{\mathbf{v}_i}{|\mathbf{v}_i|}$.
- Averaged velocity**: Indicated by a vertical line pointing to the term $\Gamma \frac{\mathbf{v}_i}{|\mathbf{v}_i|}$.
- Hard-core repulsion**: Indicated by a vertical line pointing to the term $-\nu \mathbf{v}_i$.
- Bacterial density**: Indicated by a vertical line pointing to the term $-\nu \mathbf{v}_i$.
- Noise**: Indicated by a vertical line pointing to the term $-\nu \mathbf{v}_i$.

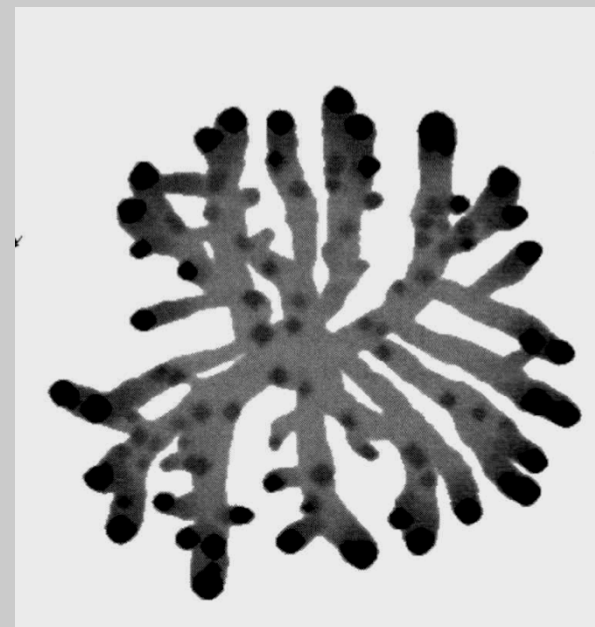
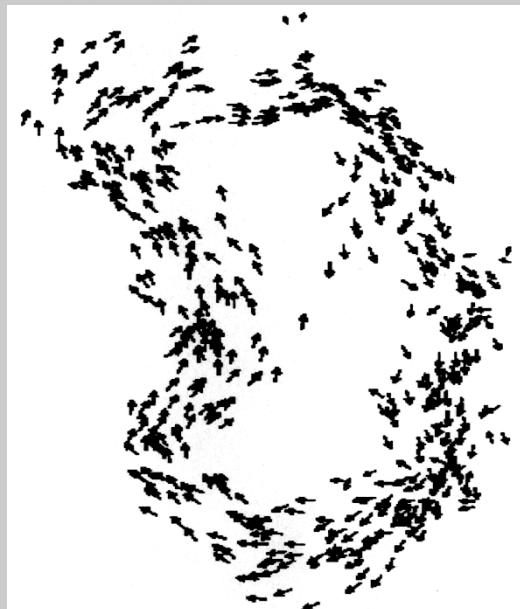
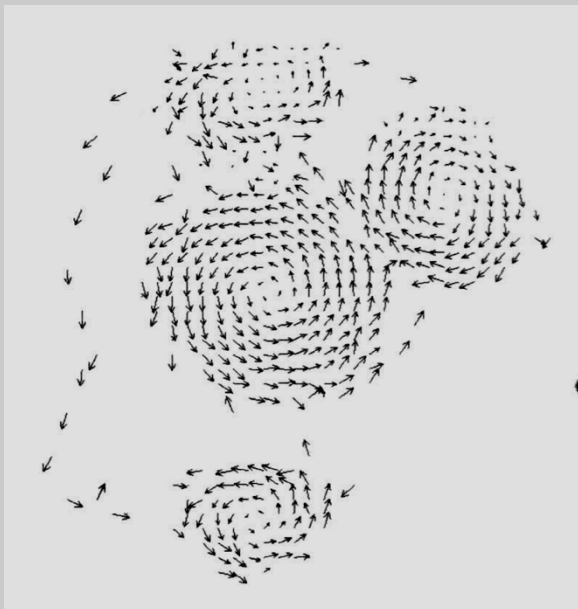
Curl Chemotaxis

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





Modeling



Bacterial Mathematics I

Adjusting the viscosity and the rate of production
of the lubricating fluid

Mathematical corner

From diffusion to non-linear diffusion
(singular perturbation)

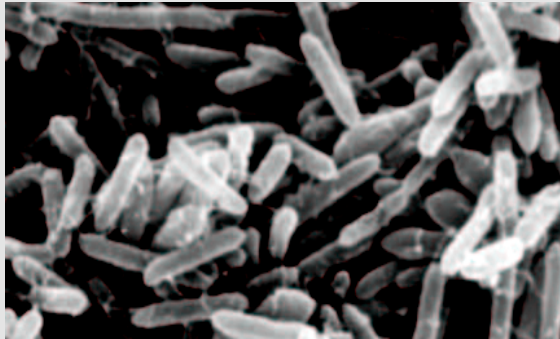
Clues about a new mathematics: Functional Solvability

Adjustment of the value of **K** as needed

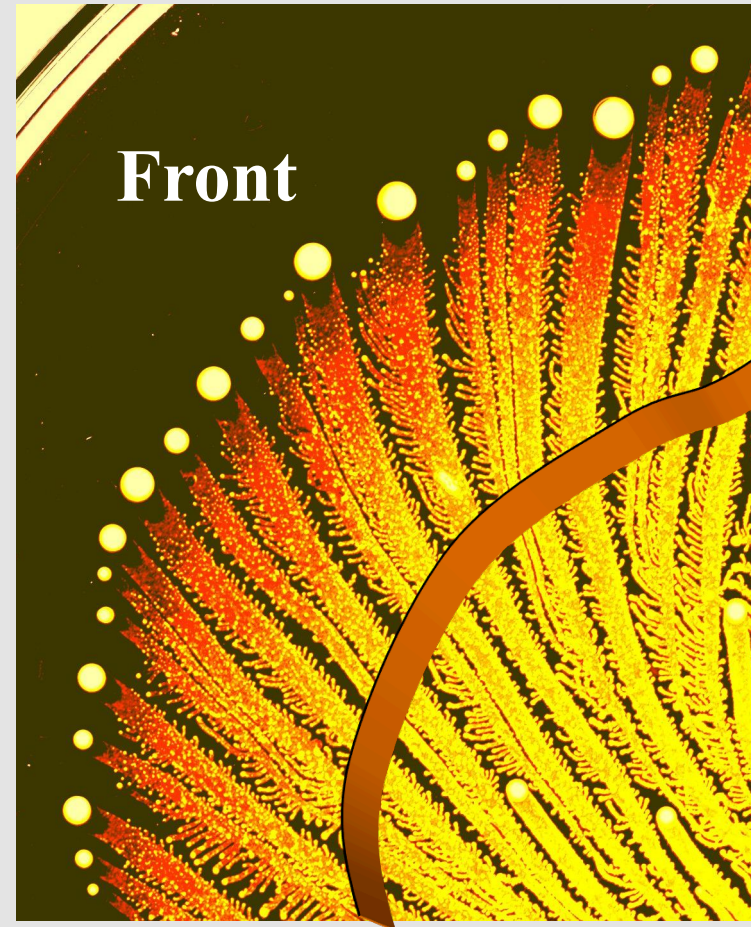
Bacterial Mathematics II

Nonlinear Stability of the Branches

Active bacteria



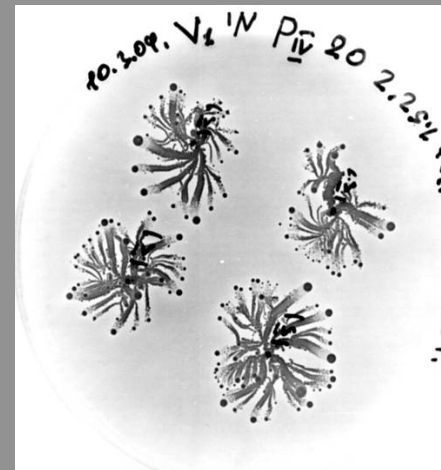
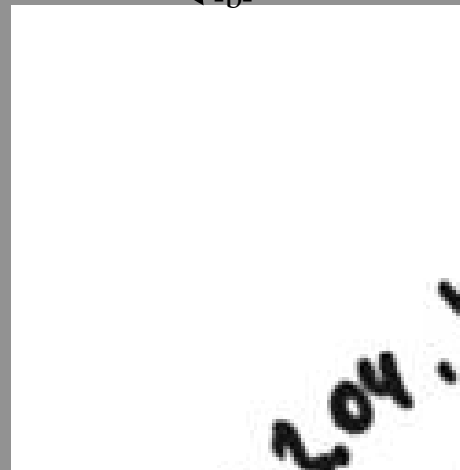
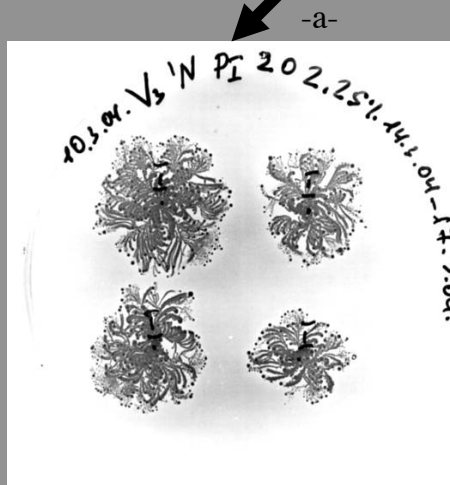
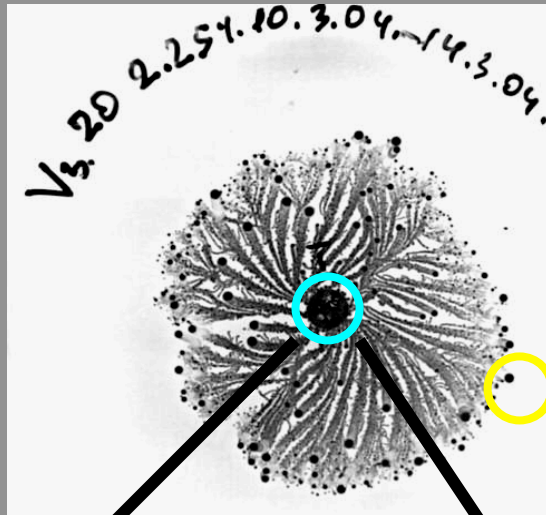
Stationary (pre-spore) bacteria



Back

Epigenetic memory?

Distribution of tasks
and Cell differentiation



-c-

-d-

Part VI: Swarming Intelligence

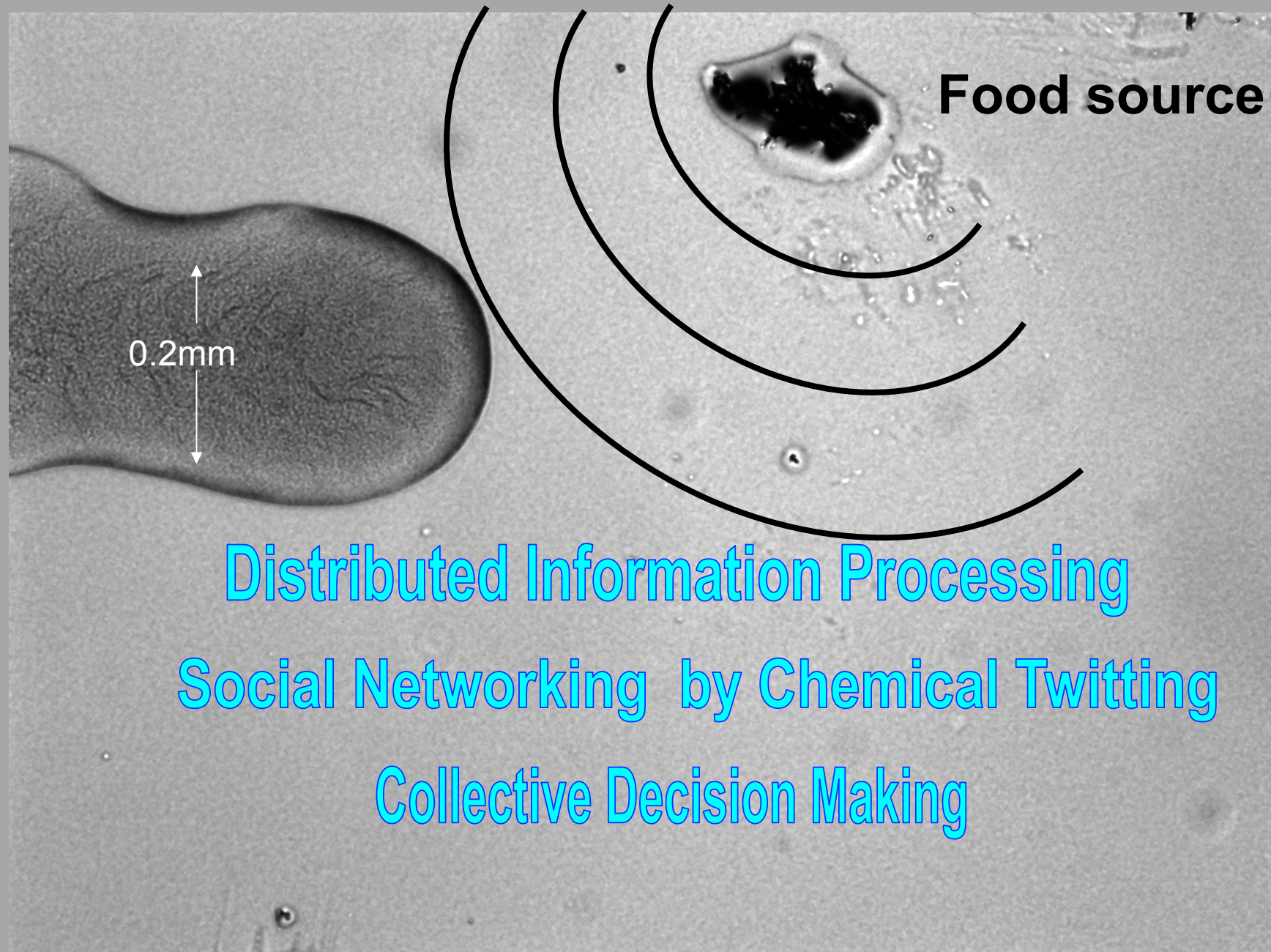
Collective (Distributed) Information Processing

Ingham and Ben-Jacob, BMC Microbiology 2009

With Oren Kalishman and Colin Ingham



Collective Navigation



Distributed Information Processing
Social Networking by Chemical Twitting
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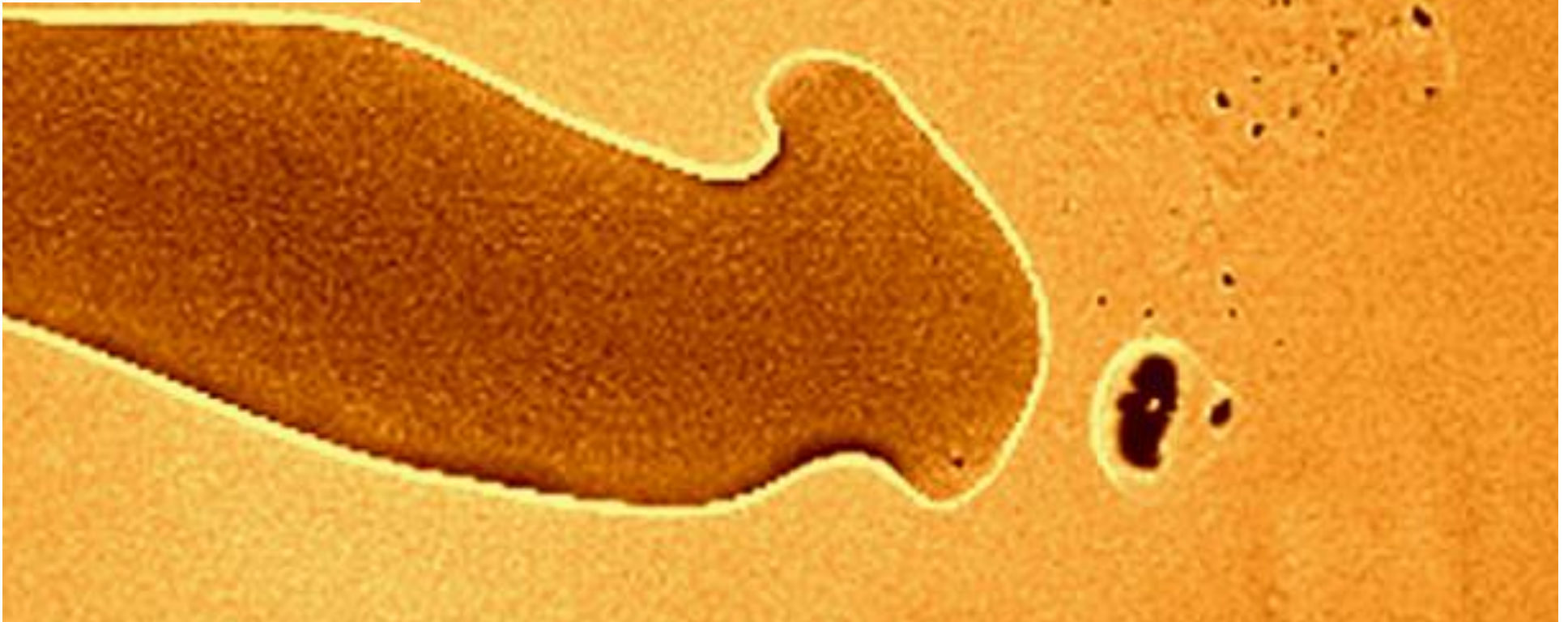
Buridan's Ass

The Dilemma of choice



Collective Sensing & Decision making

The Puzzle

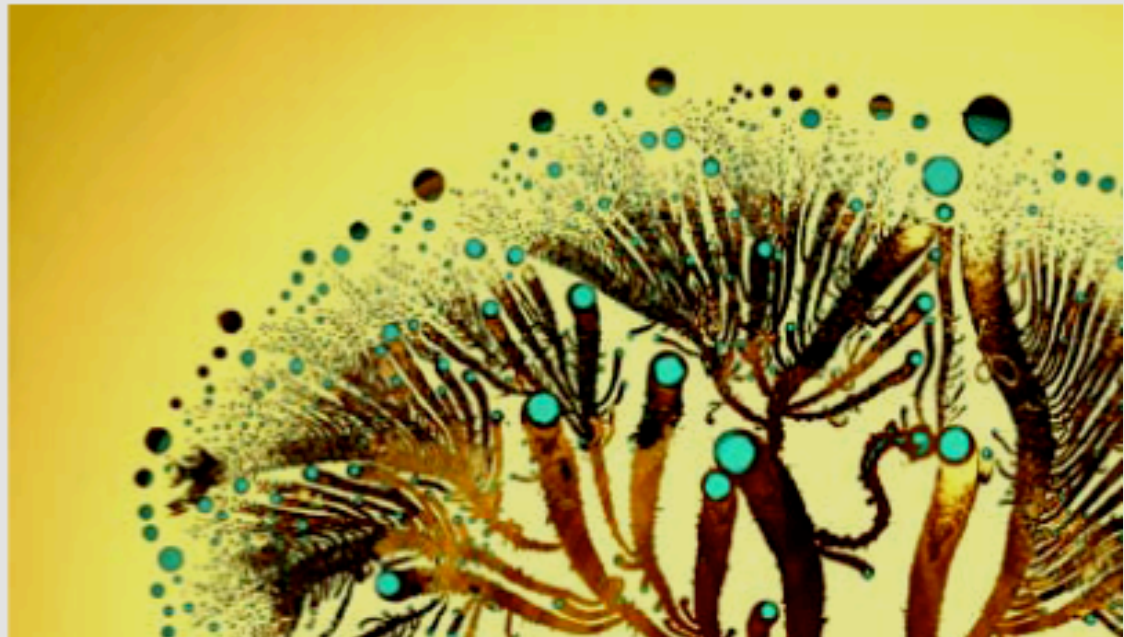


The Genius of Bacteria

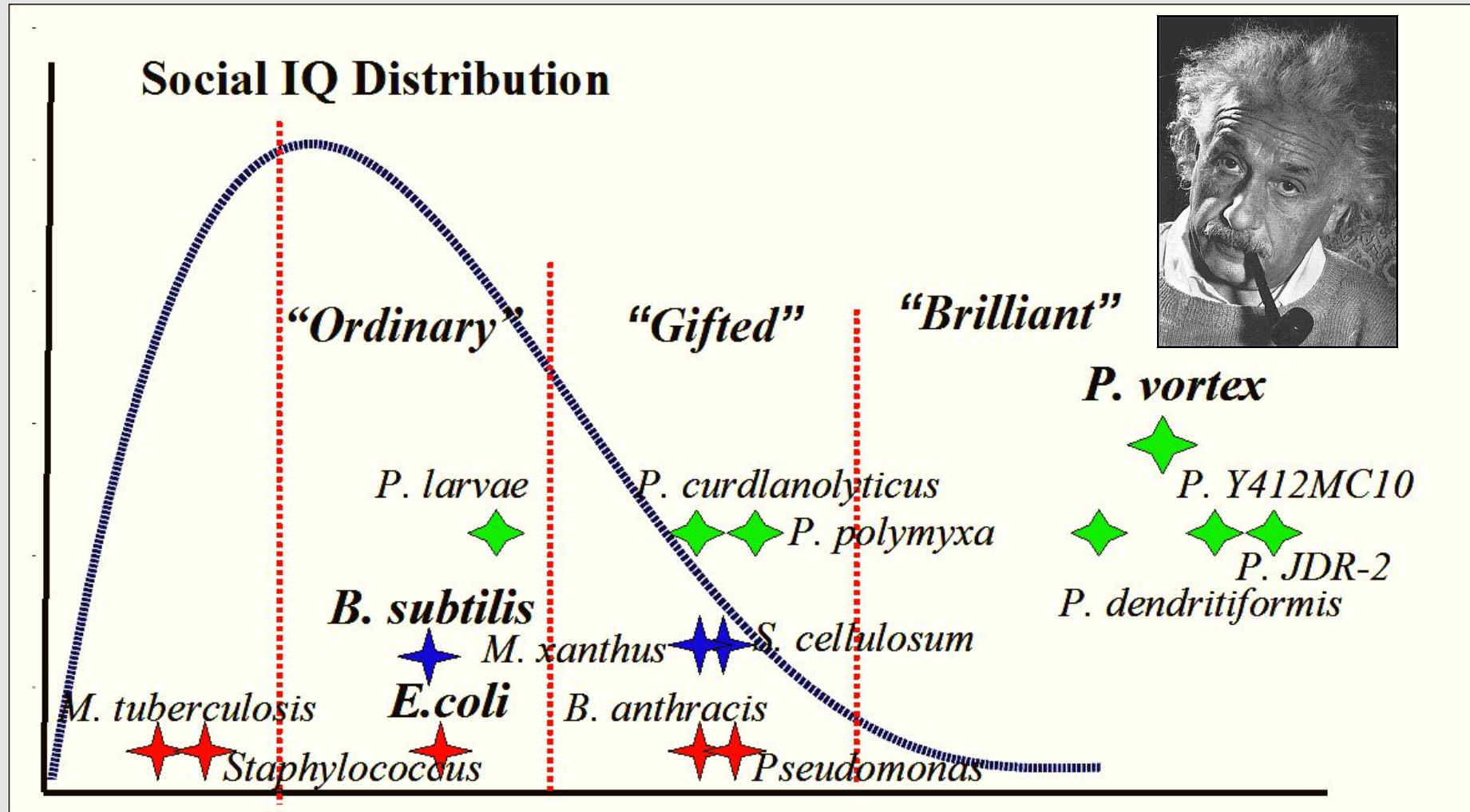
Monday, January 24, 2011

TAU develops an IQ test to assess and outsmart bacteria

IQ scores are used to assess the intelligence of human beings. TAU has developed a "Social-IQ score" for bacteria — and is developing powerful bacteria-based "green" pesticides for the agricultural industry.

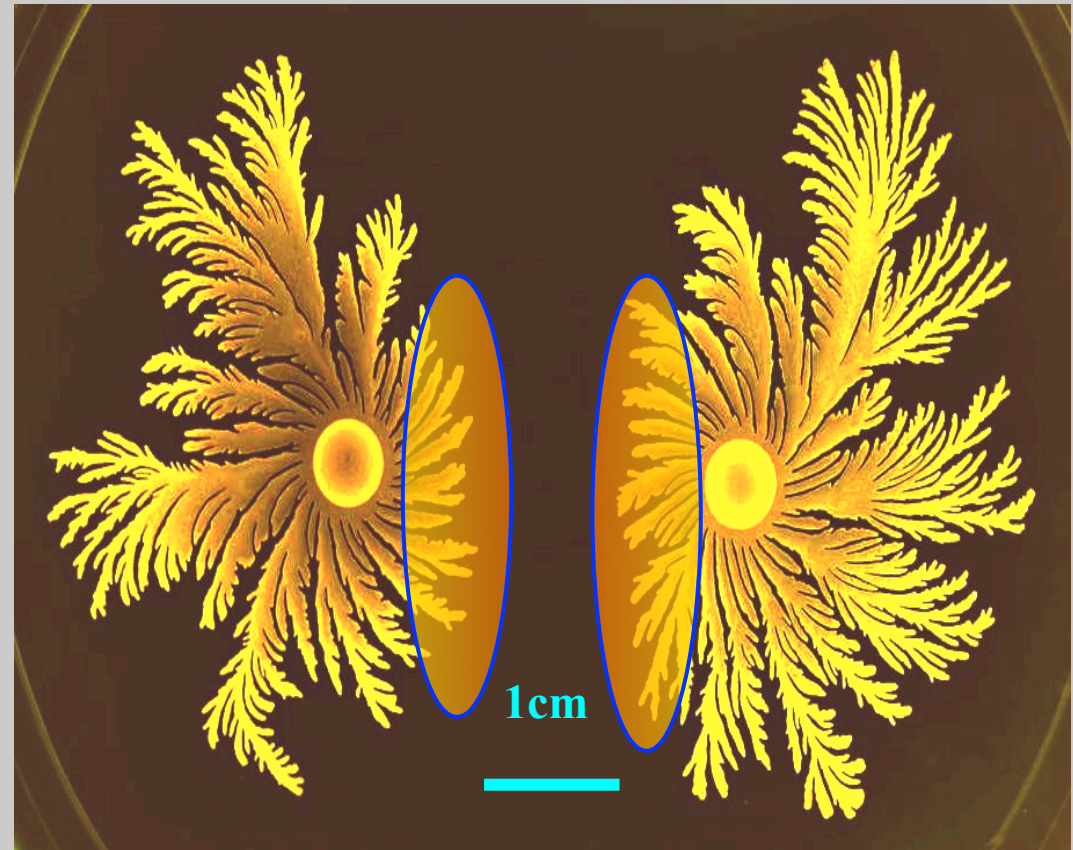
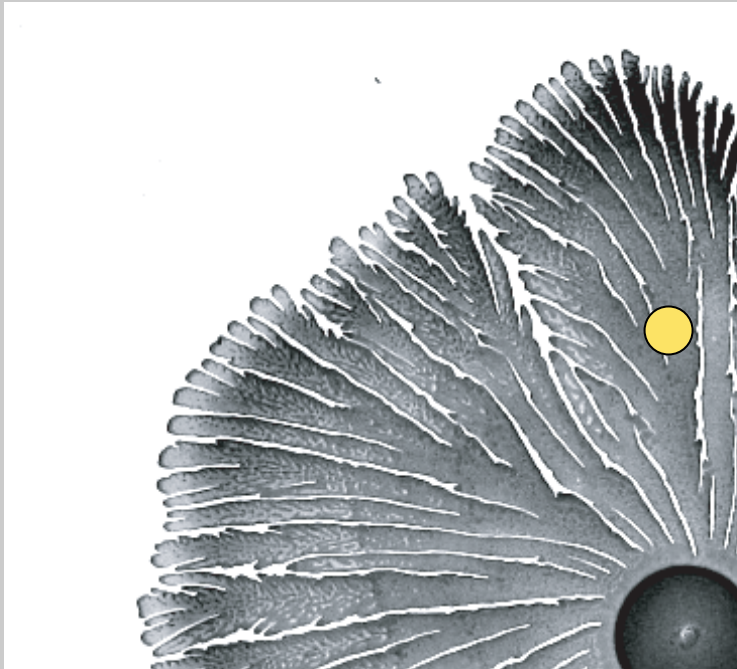


Social IQ of Bacteria





Deadly Competition Between Sibling Colonies



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

Part VI: Swarming Intelligence

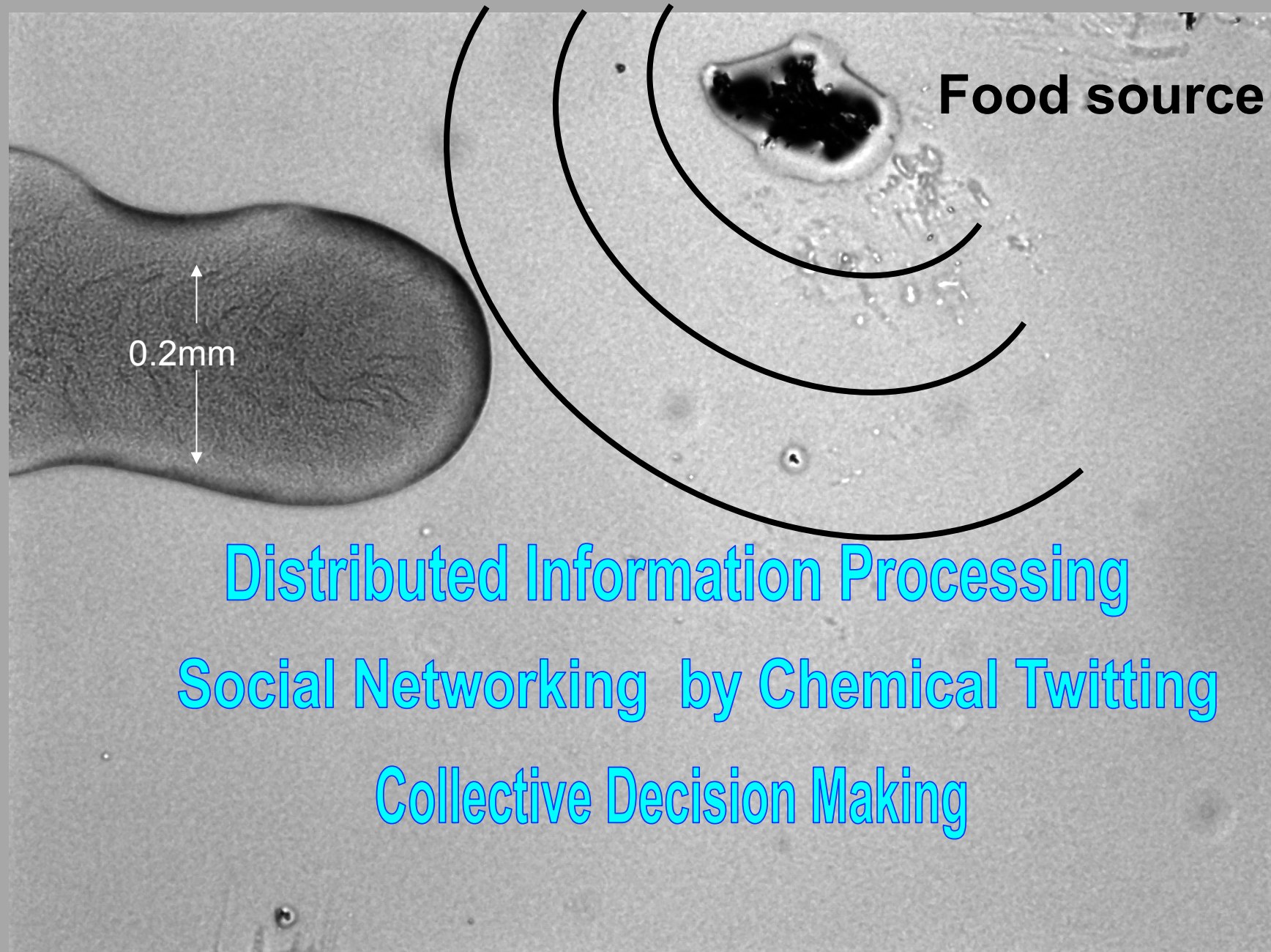
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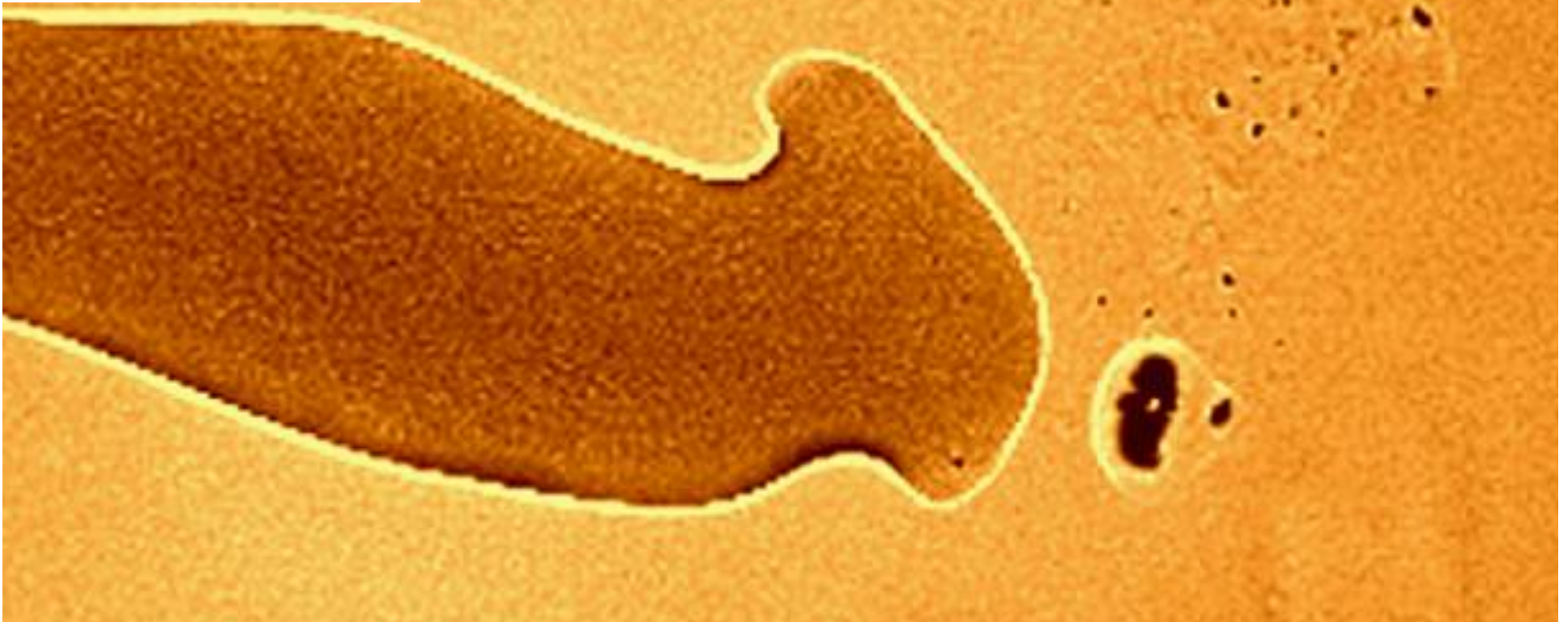
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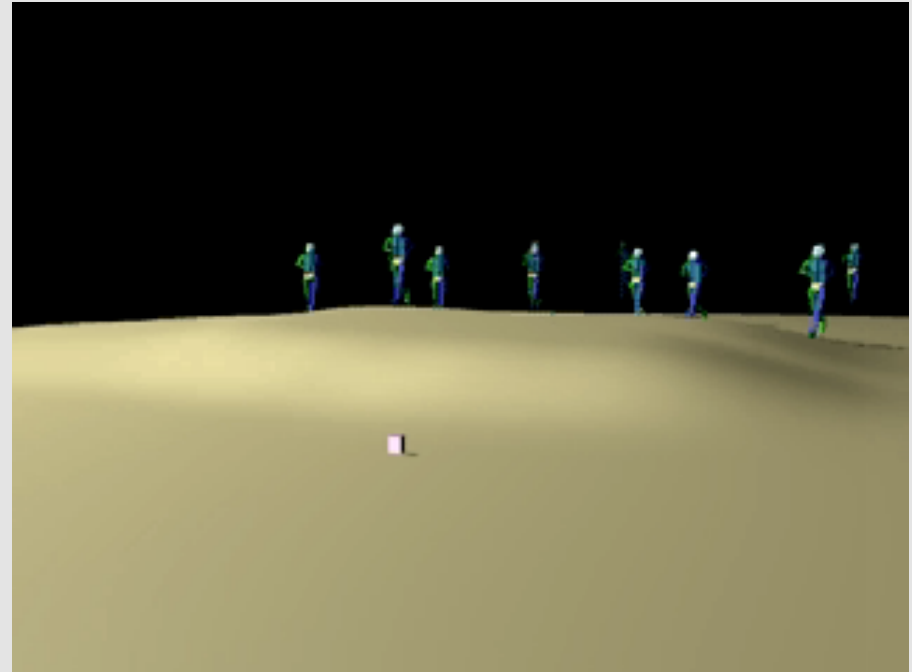
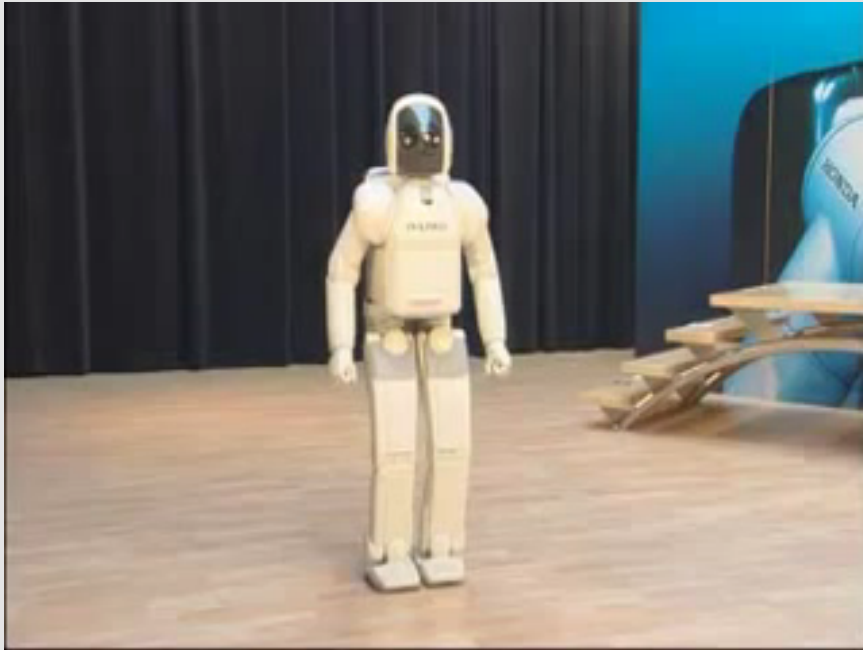


Collective Sensing & Decision making

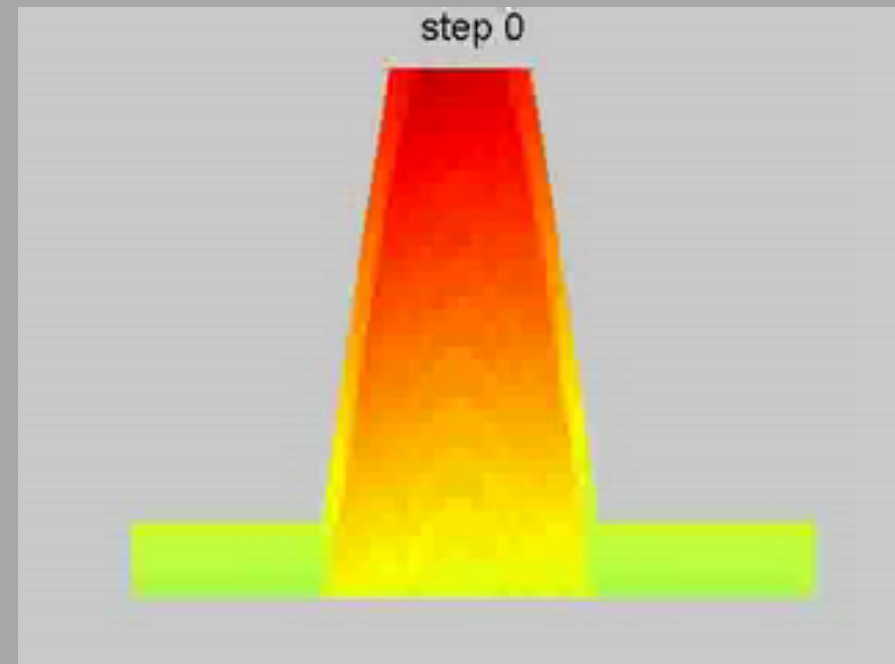
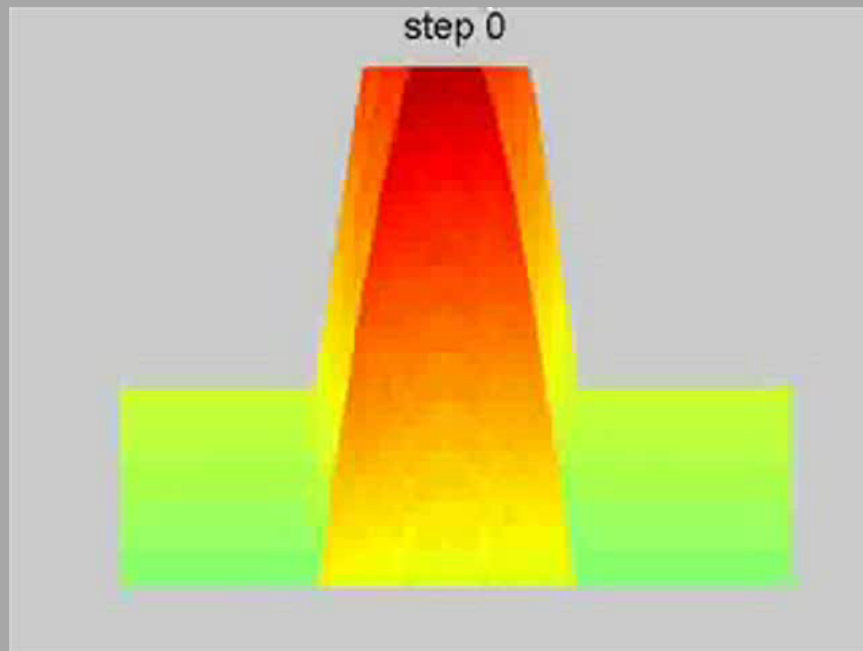
The Puzzle



Swarms of Bacteria-like Smart Robots



Collective agent navigation

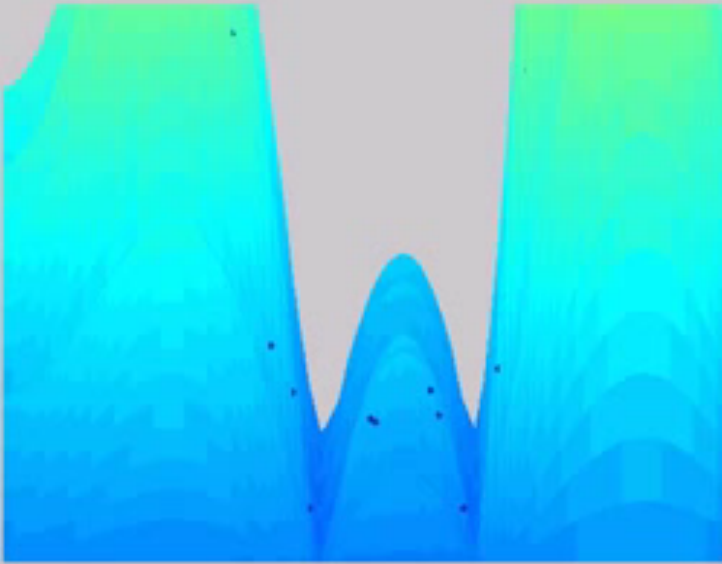


Collective sensing and
Distributed information processing

Highly complex terrain

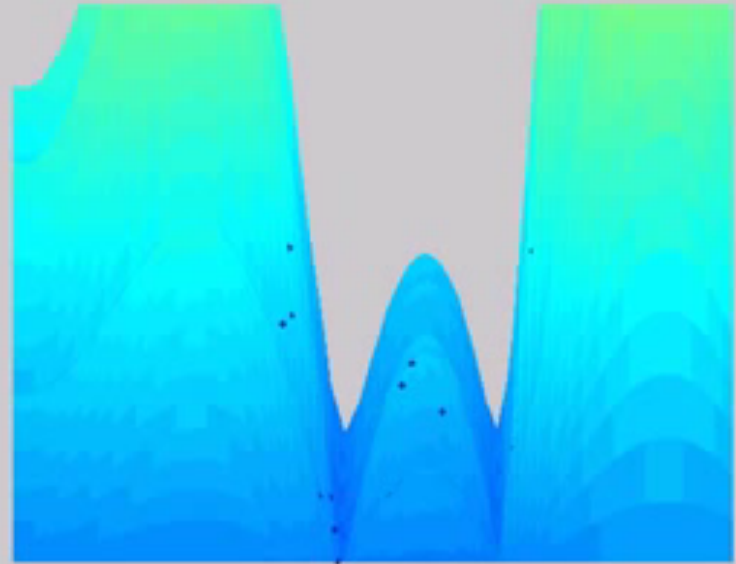
Fixed interactions

step 0



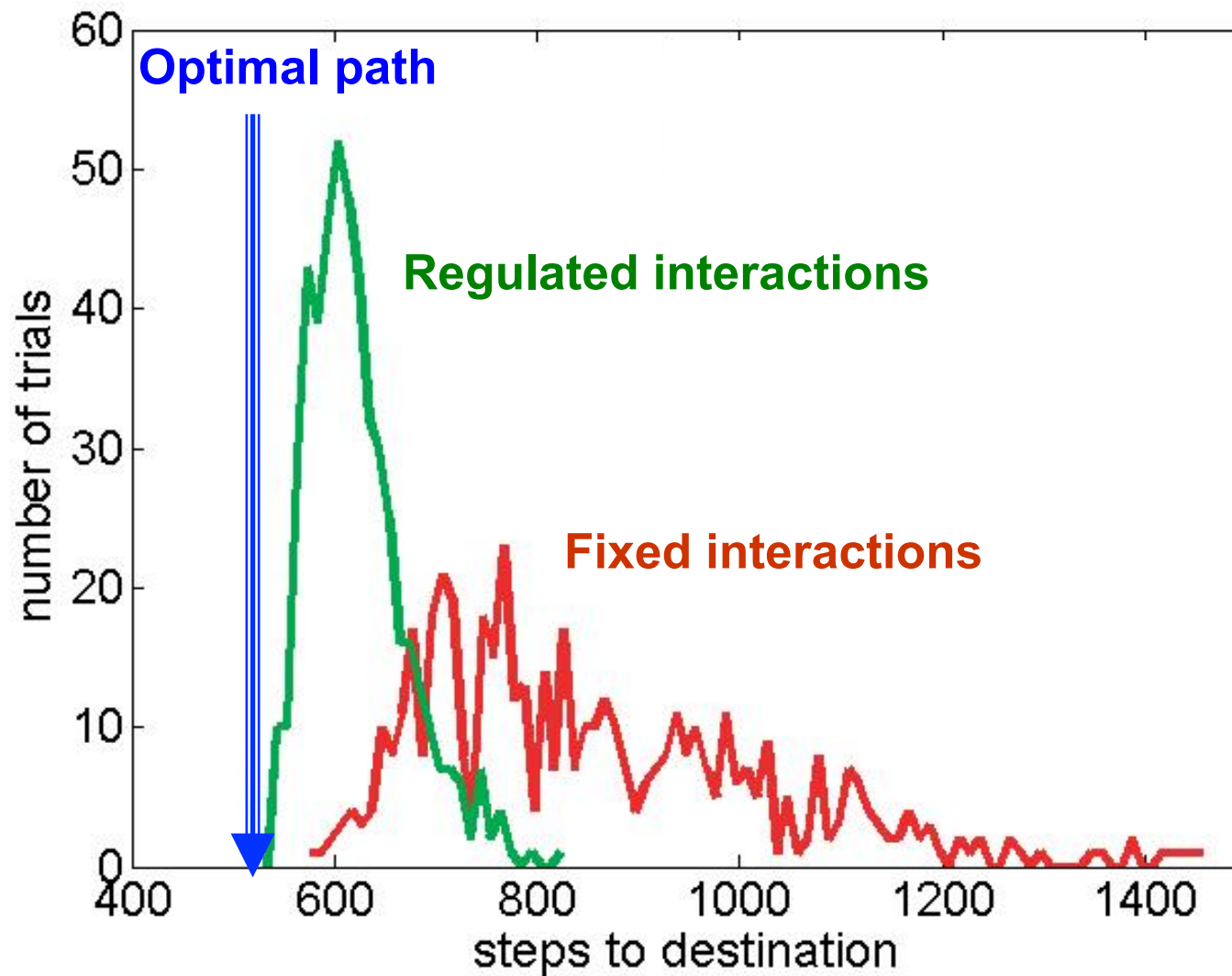
Regulated interactions

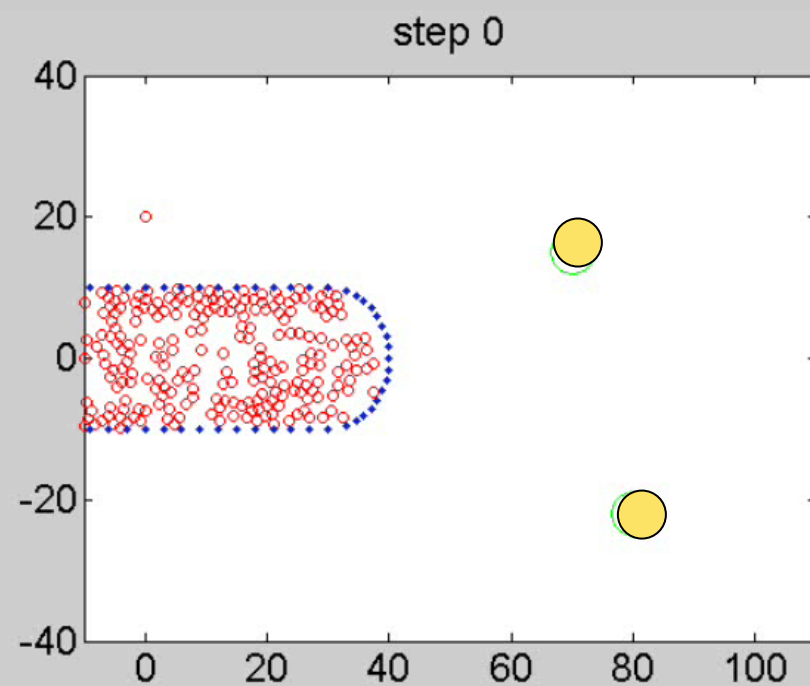
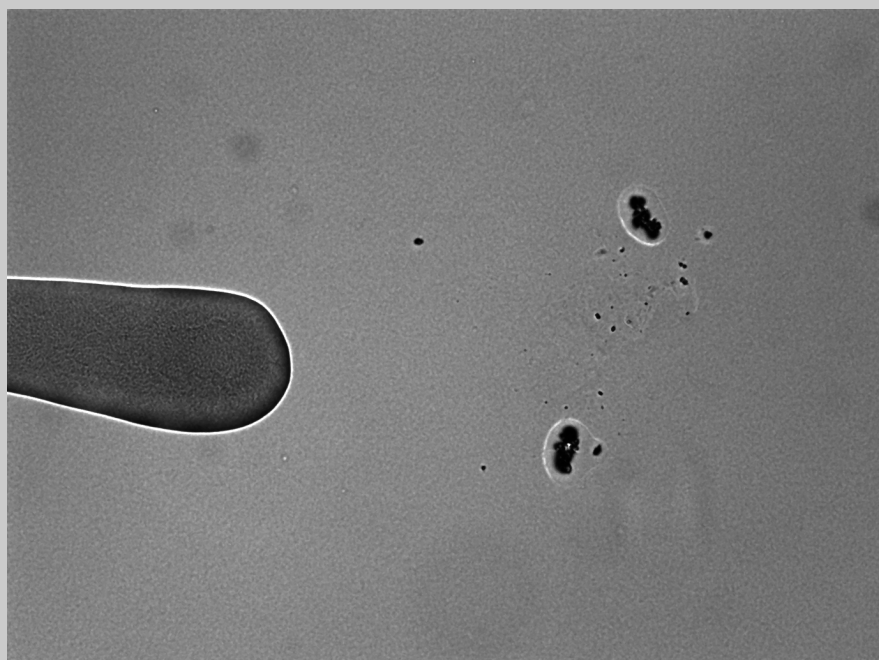
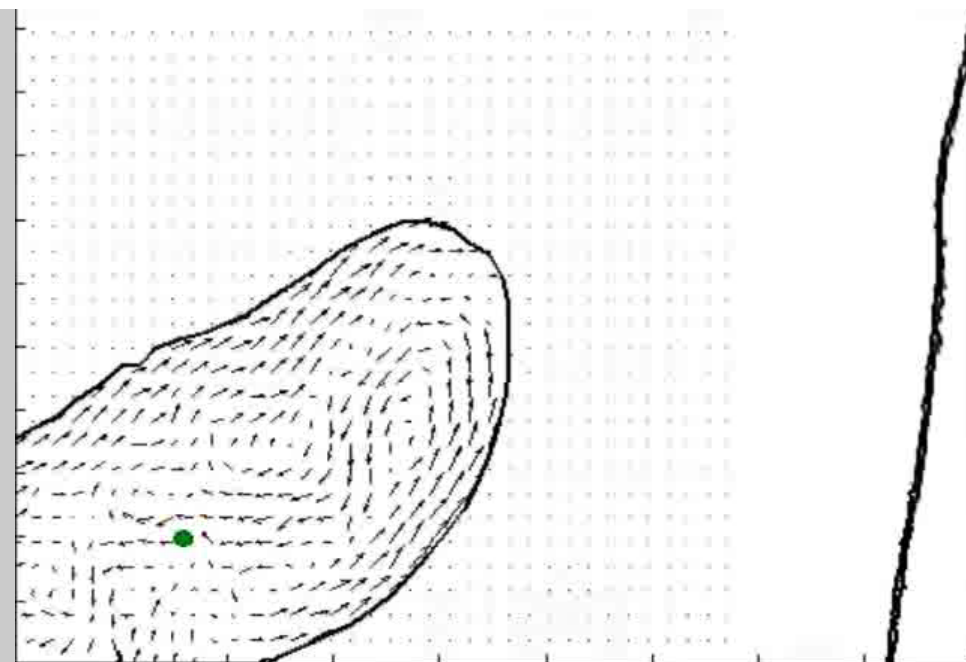
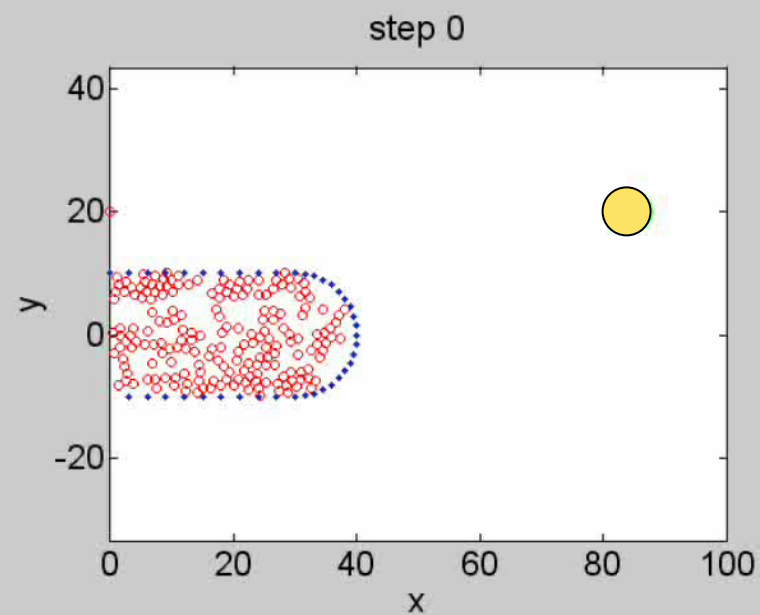
step 0



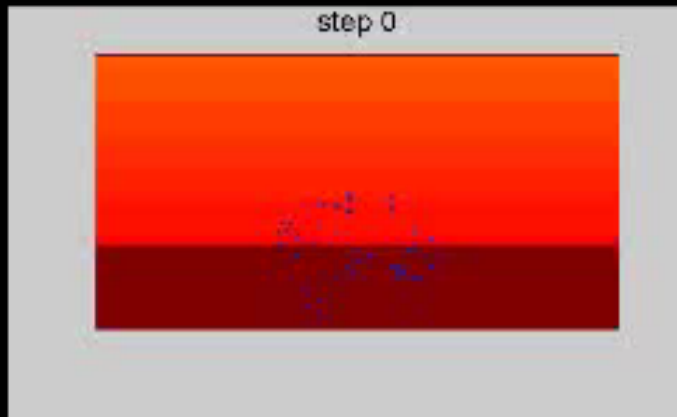
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Quantification of the results

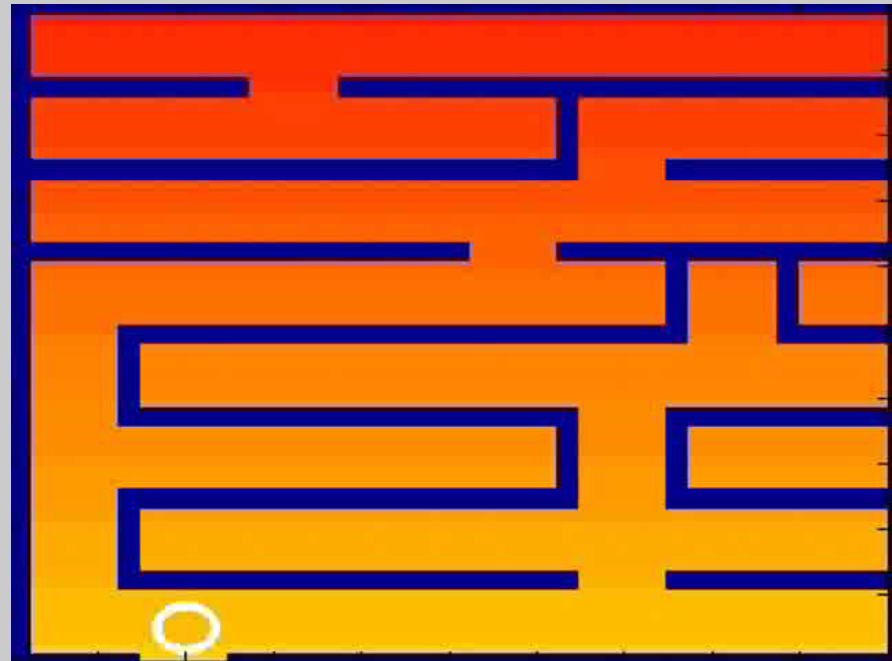
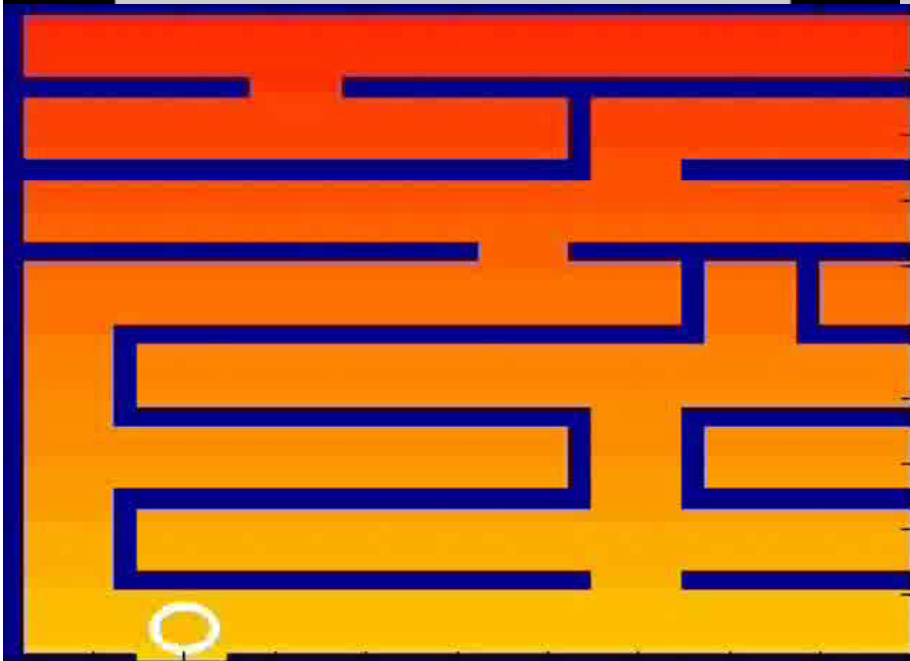




Implications for cells in a maze



A bootstrapping mechanism



Long Range Communication



10 Cm

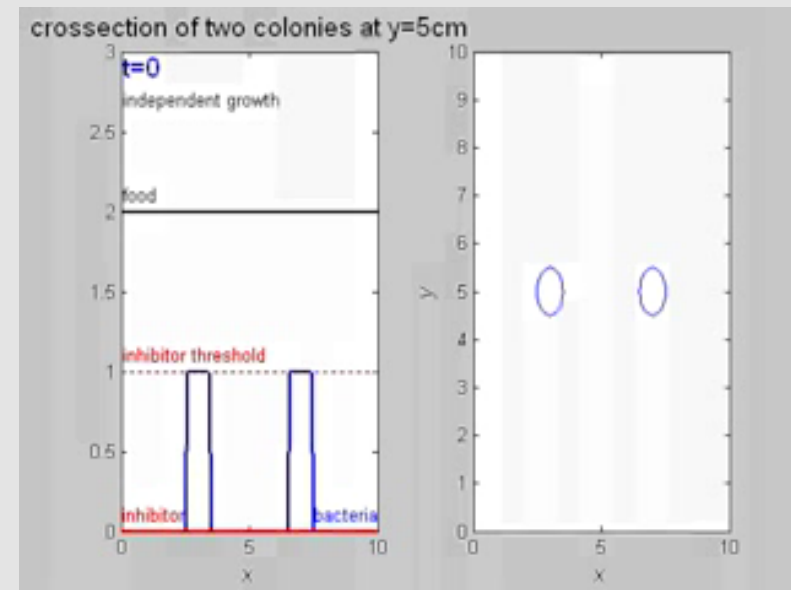
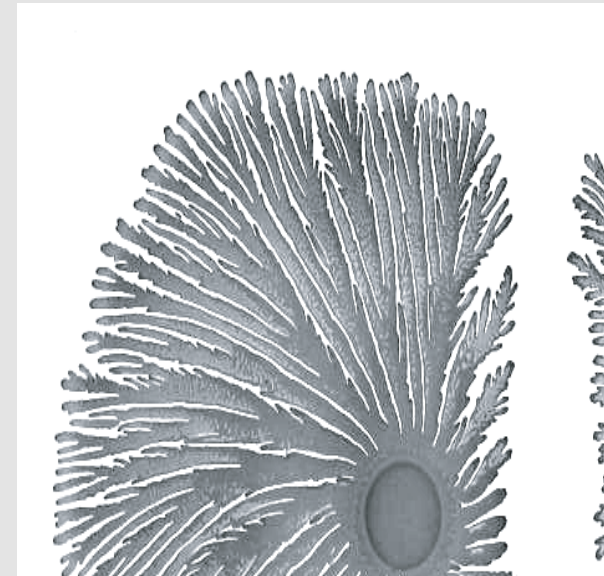
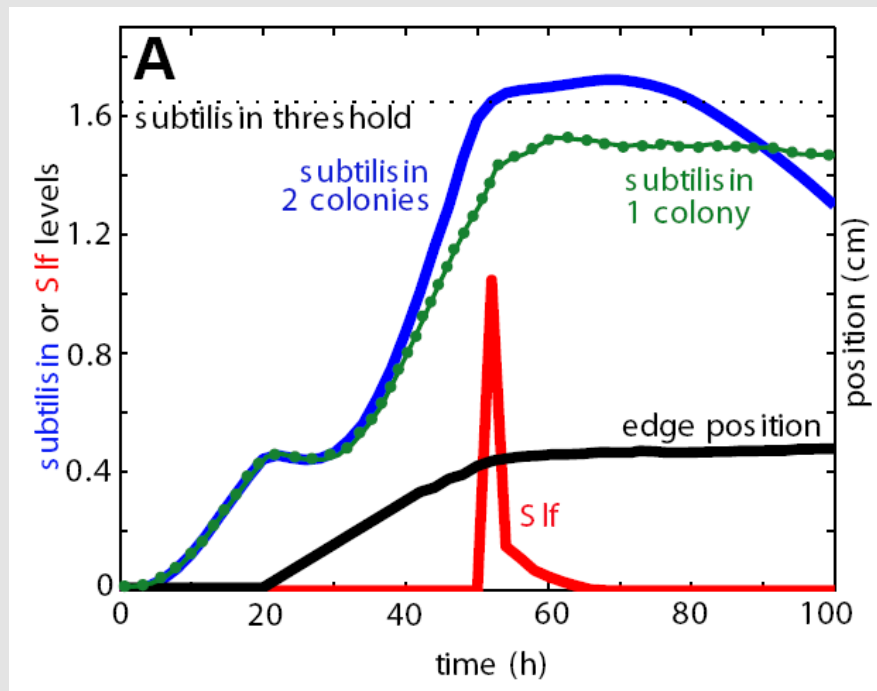


With Be'er et. al., PNAS, 2009

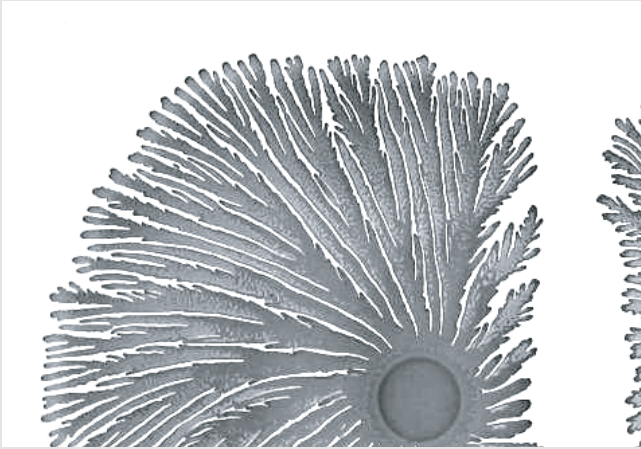


100 Km

Theoretical Investigations – Hybrid Model



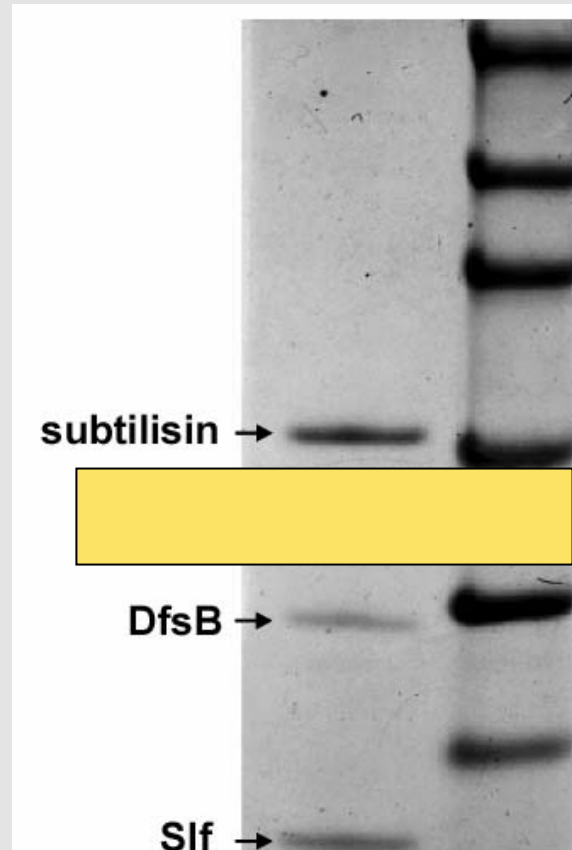
With Avraham Be'er, Gil Ariel et al., PNAS 2010



With A. Sirota, O. Kalishman, Y. Helman

MASY

*EYTSKEELKKTIHAAYLLLDGEFEGIDDSQKDNRVPE
VDRTPAEIIYQLGWLHLVMGWDRDELAK_
PVIMPAPGYKWNQLGGLYQSFYAAYADLSLTELR
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HQRQA*

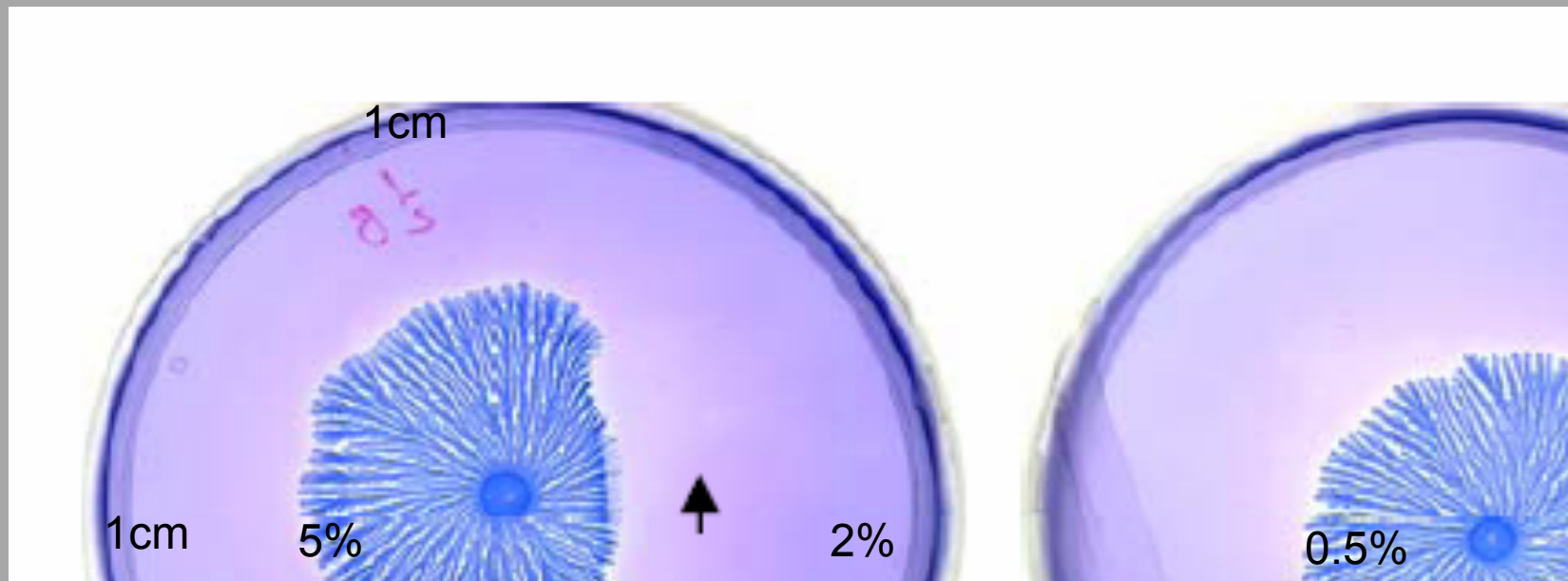
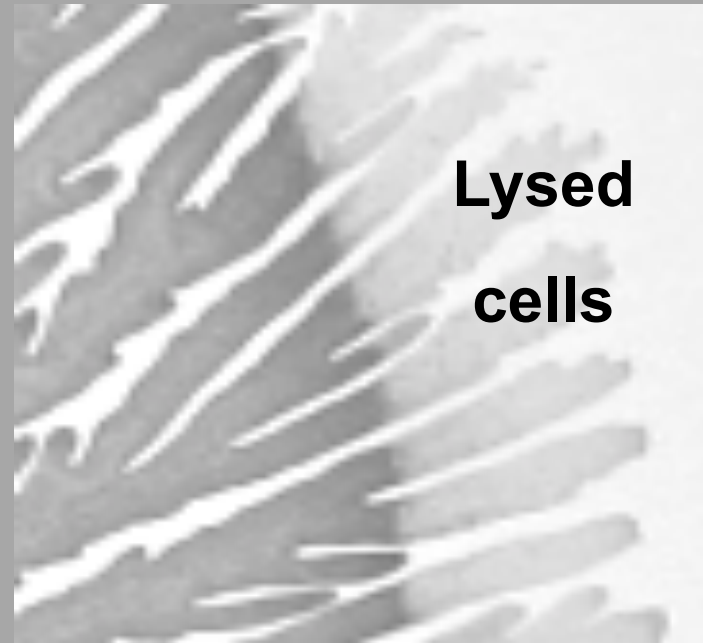
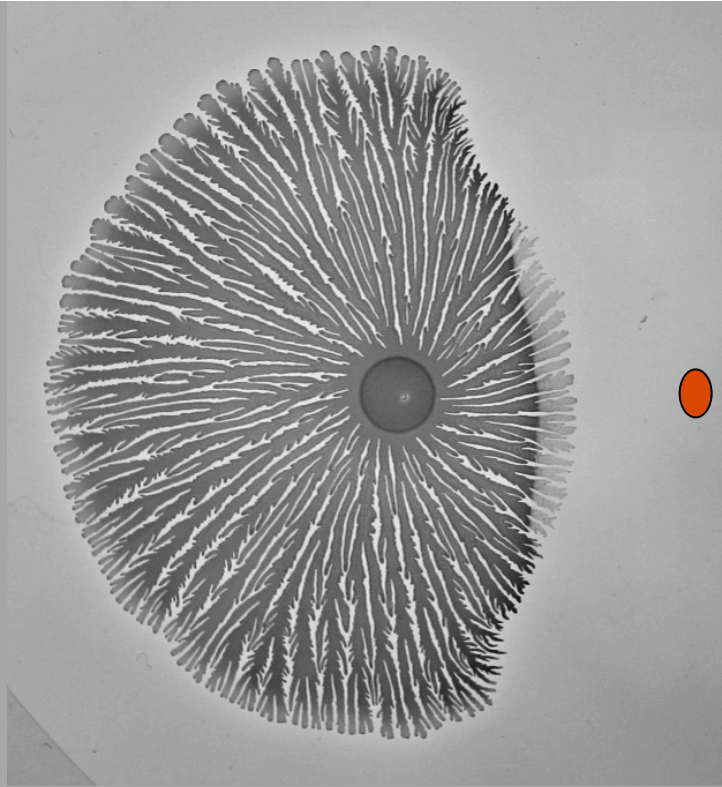


**DfsB – Dendritiformis sibling bacteriocin
(Siblicidin)**

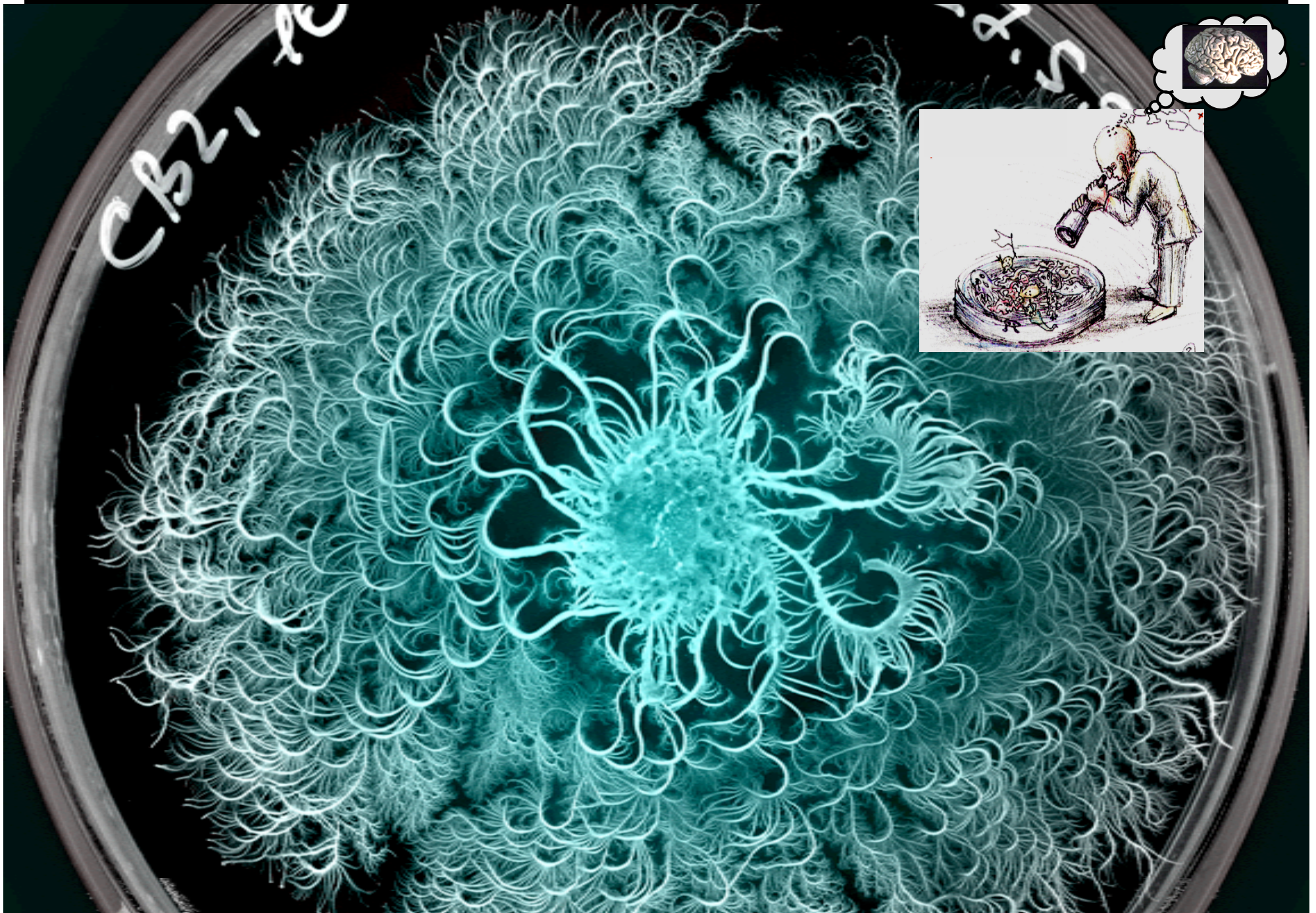
DfsB + Subtilisin → Slf

Slf – Sibling Lethal Factor

The Slf Effect



Bacteria Art



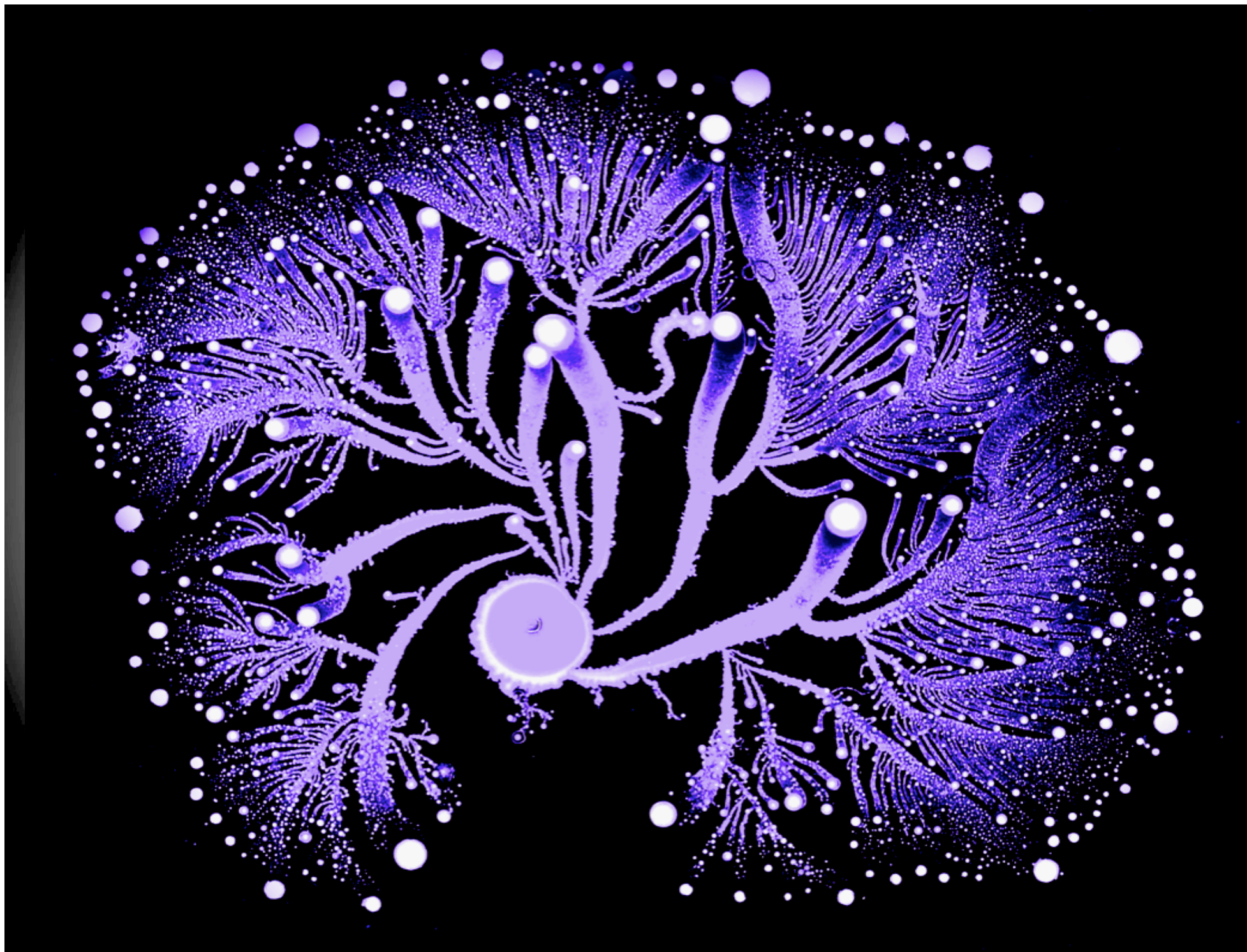
Why are the Patterns so Appealing?







Broken Symmetry

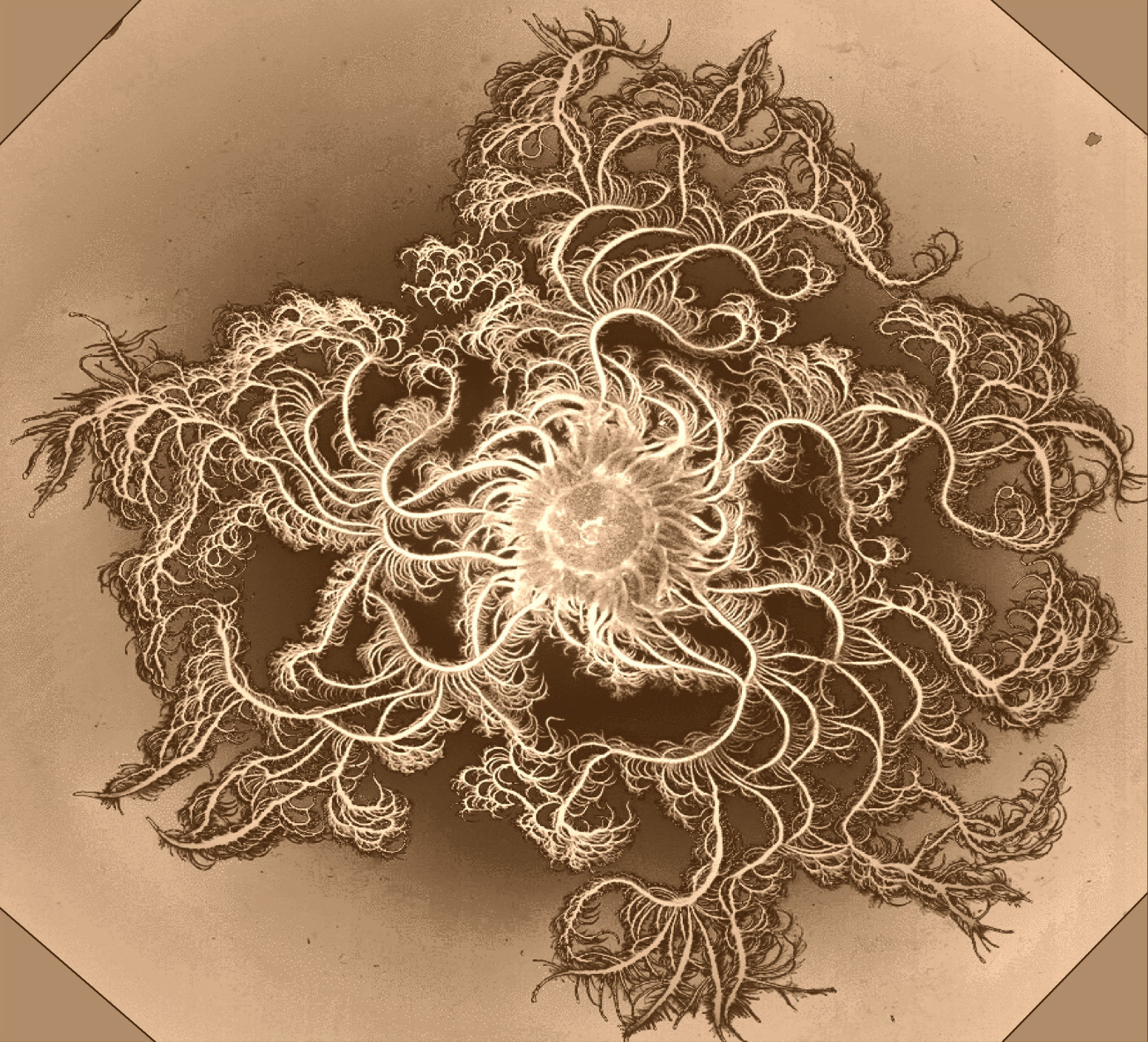


The Bacteria and I - Full Disclosure

How did I Persuade the Bacteria
to
Generate the Patterns

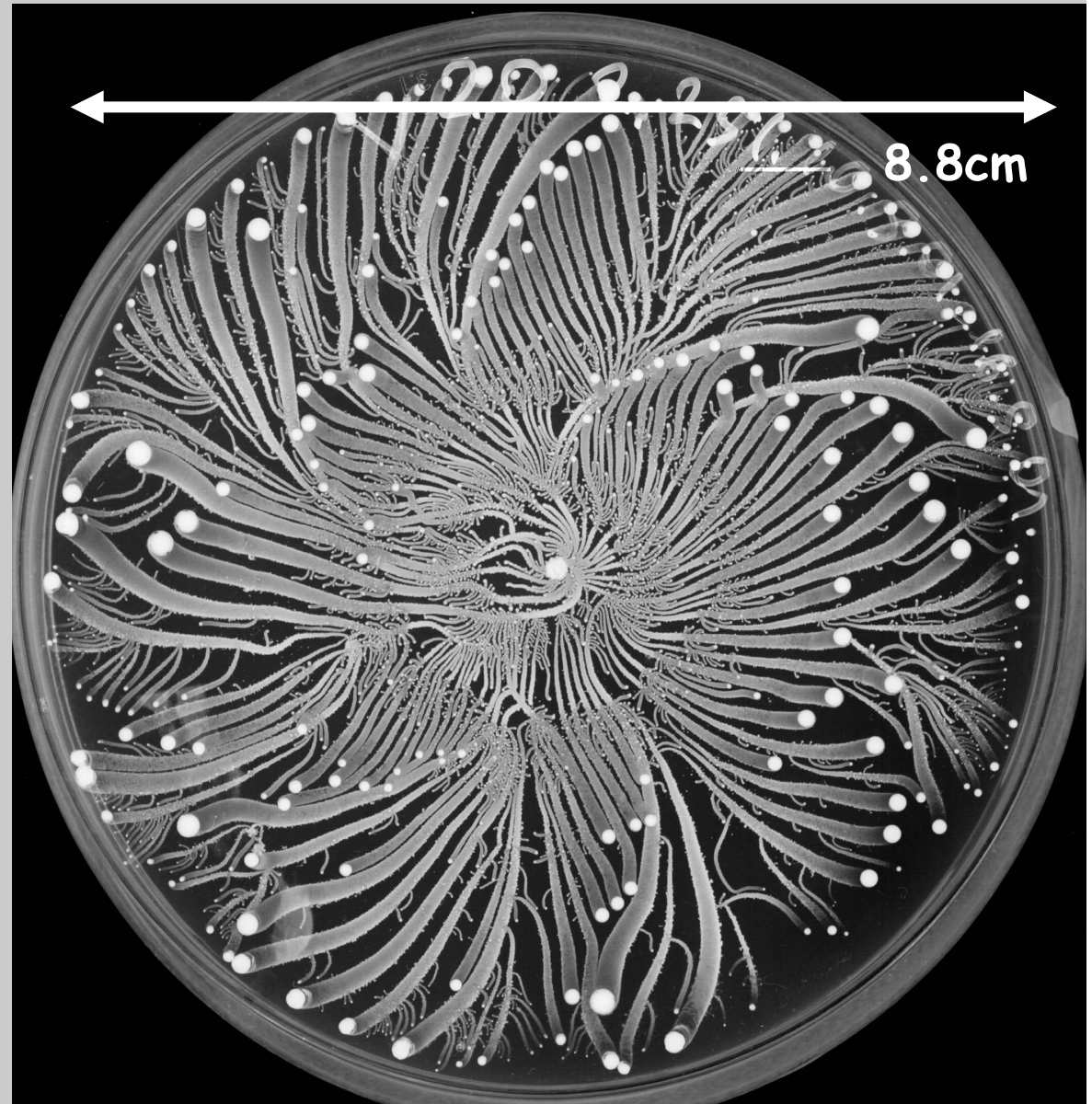
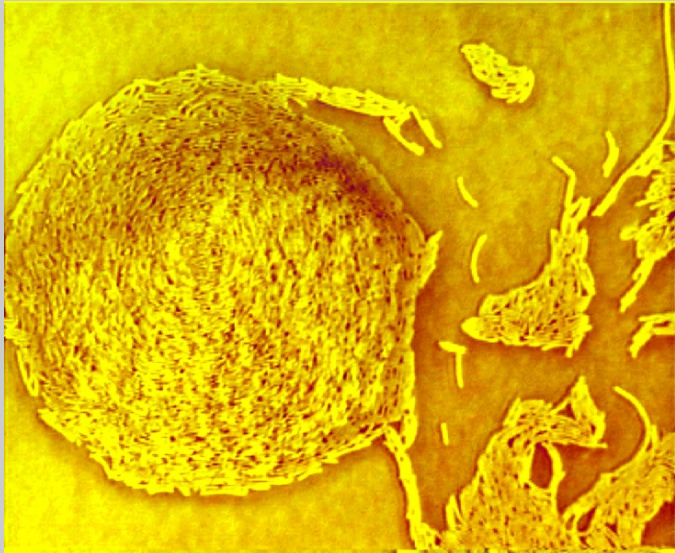


A New Kind of Art ?



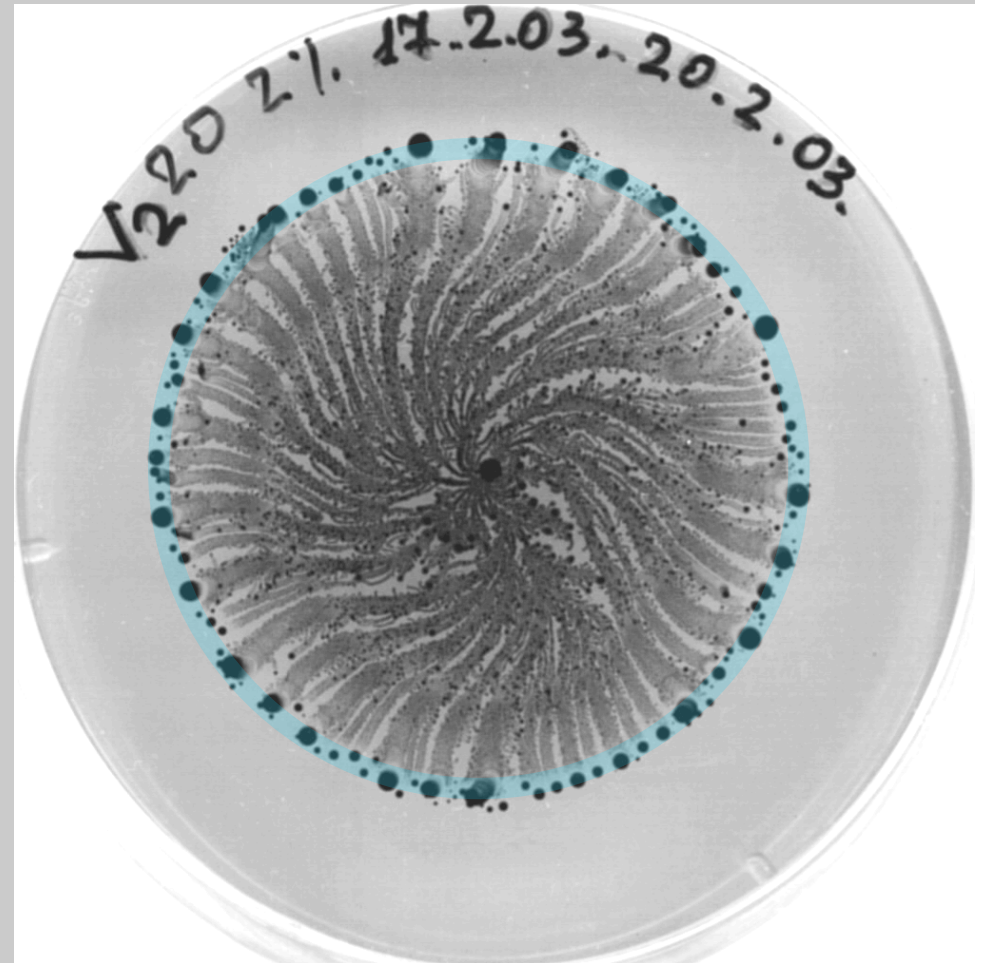
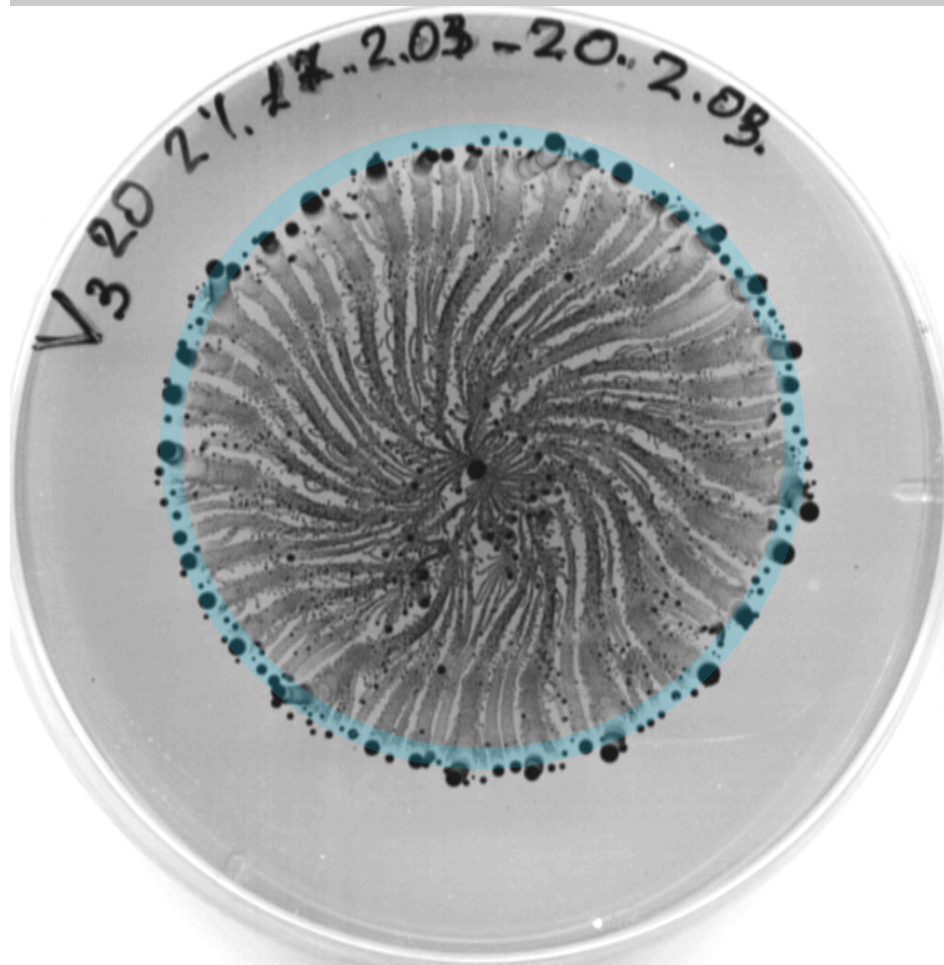
Additional Example: Modular Organization

Ben-Jacob, Nobel Symposium on *self-organization*, 2002

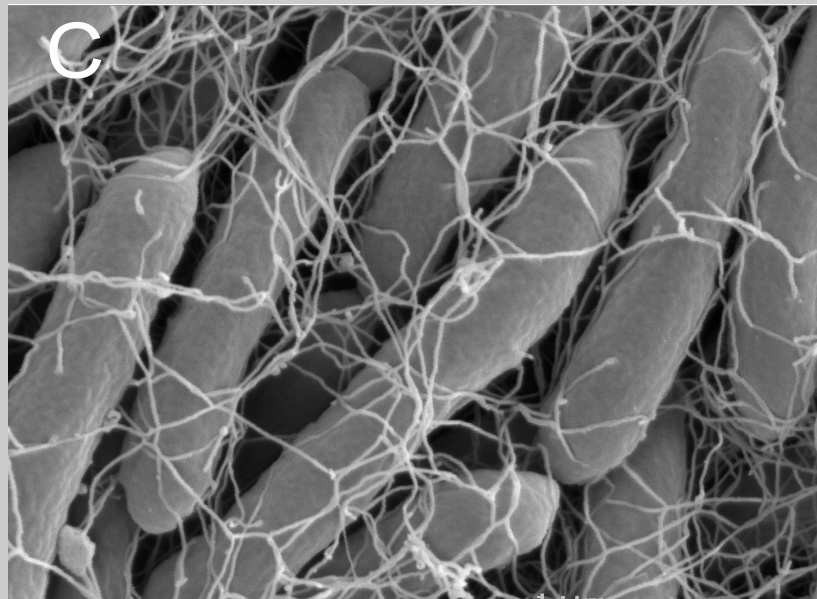


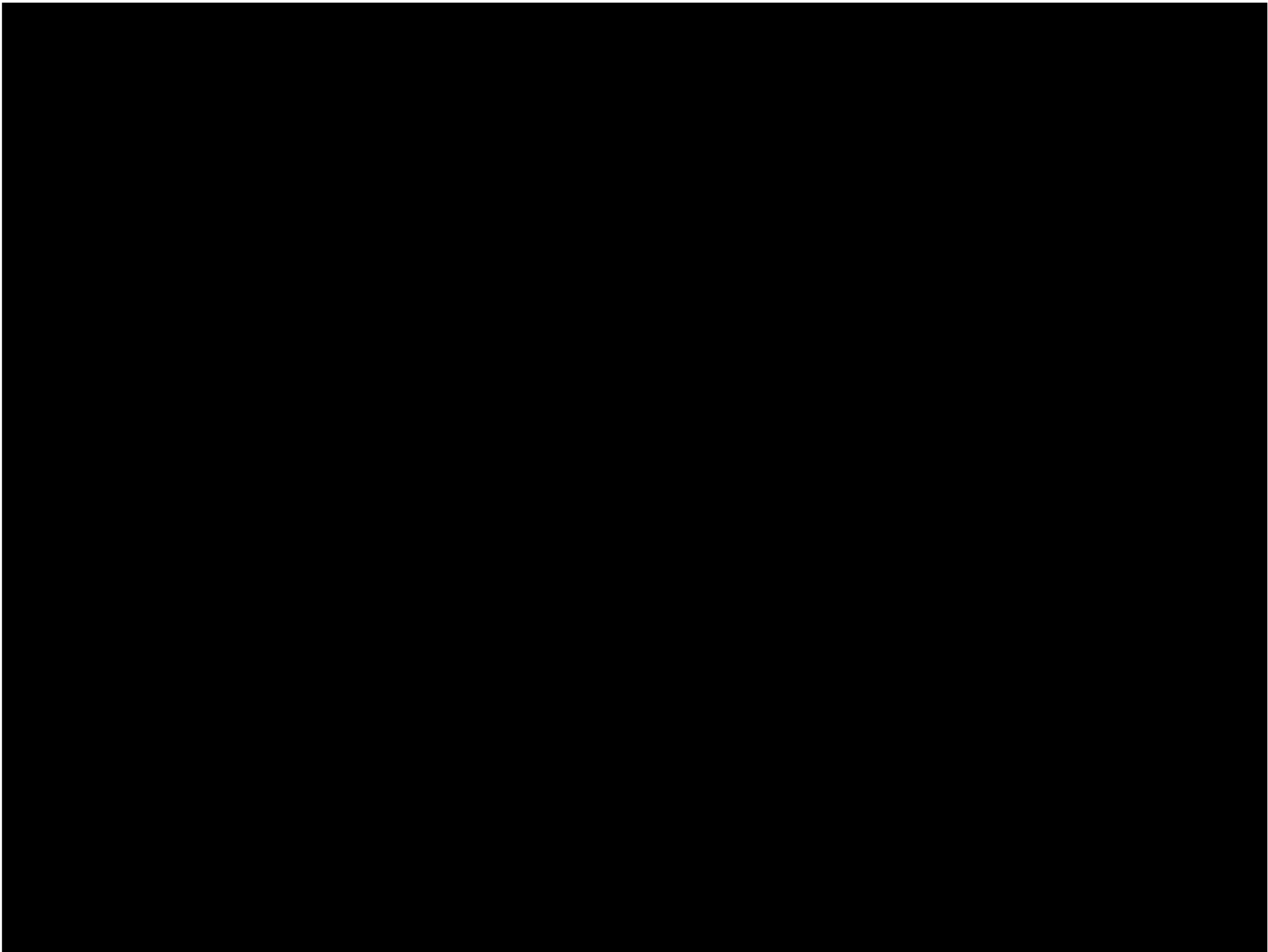
Reproducibility

Two colonies of $\sim 10^{10}$ *P. vortex* bacteria.



Both inoculated from the same "parent" colony.
Growth time ~ 3 days





Part VI: Swarming Intelligence

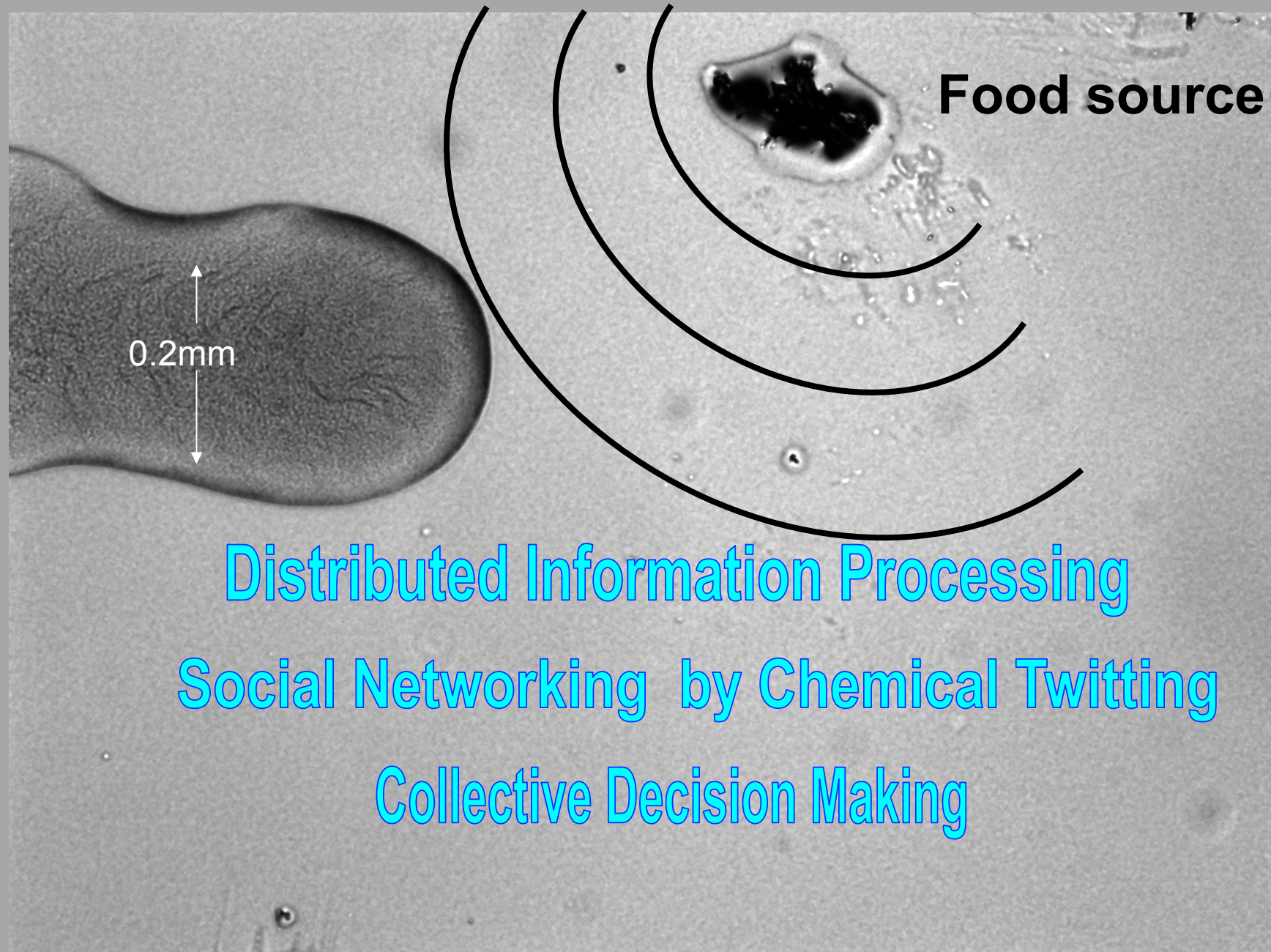
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Ingham and Ben-Jacob, BMC Microbiology 2009

With Oren Kalishman and Colin Ingham



Collective Navigation



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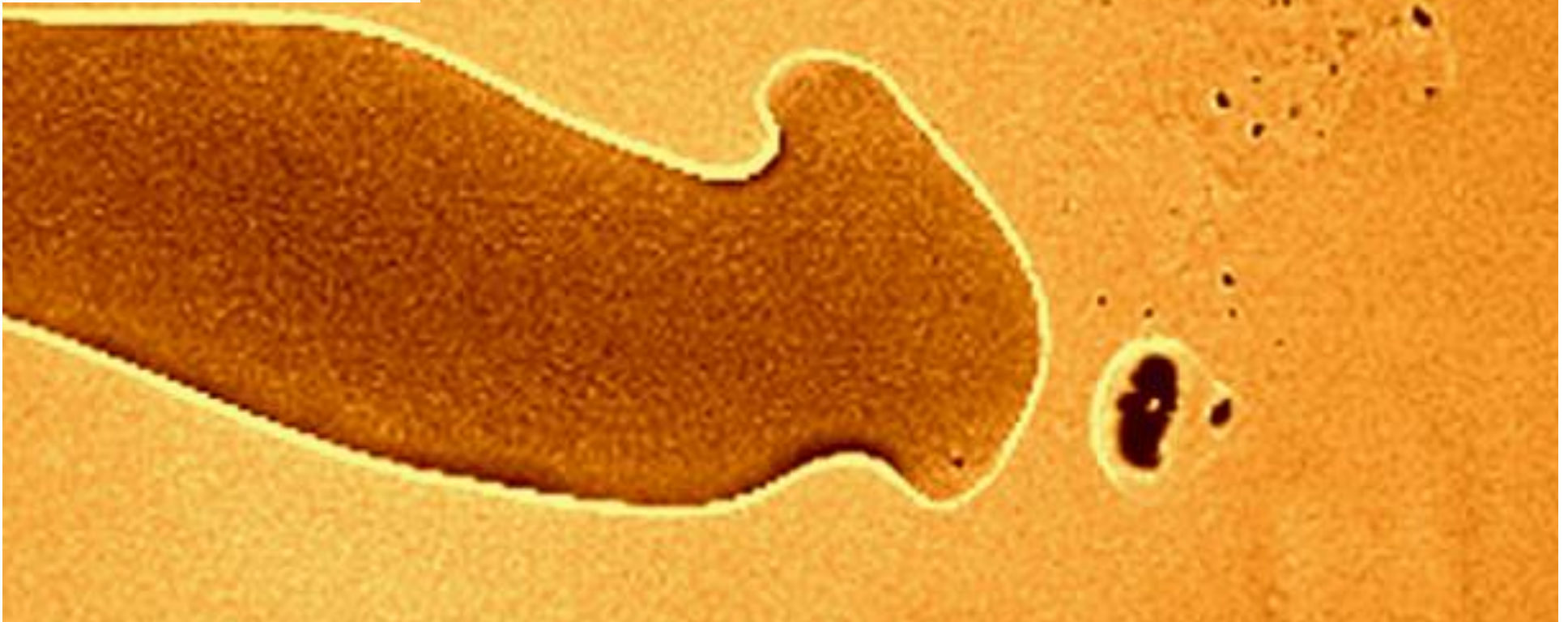
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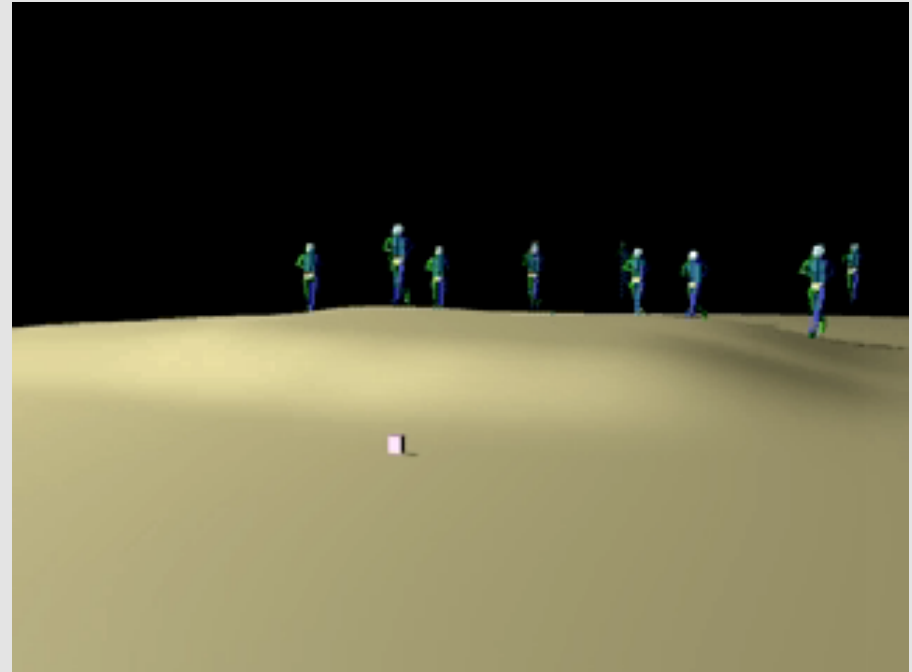
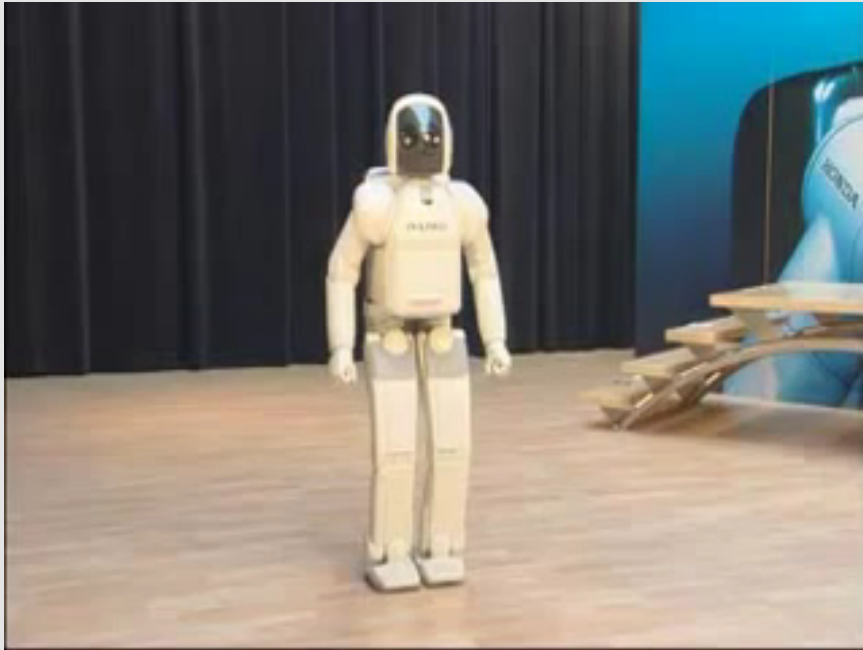


Collective Sensing & Decision making

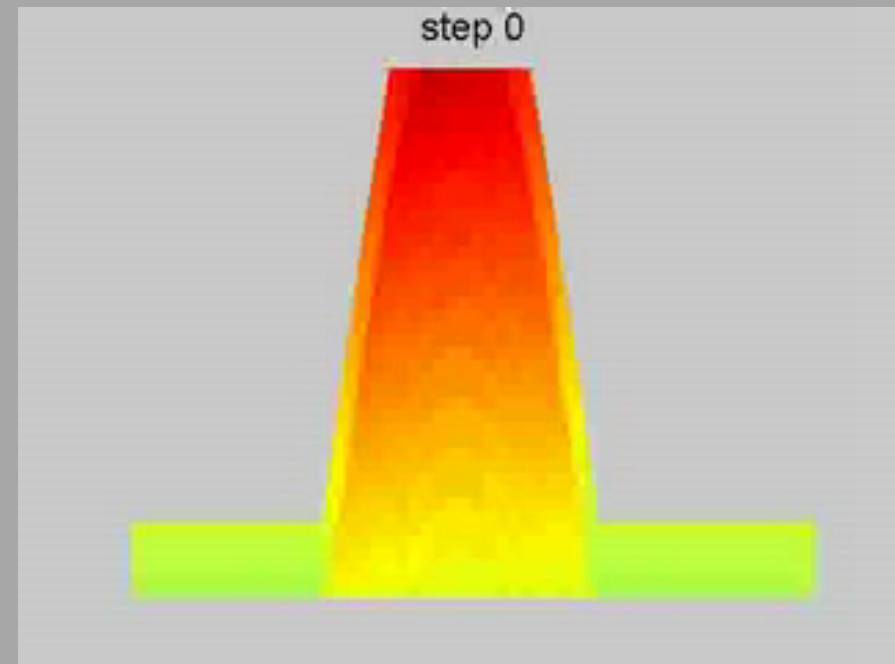
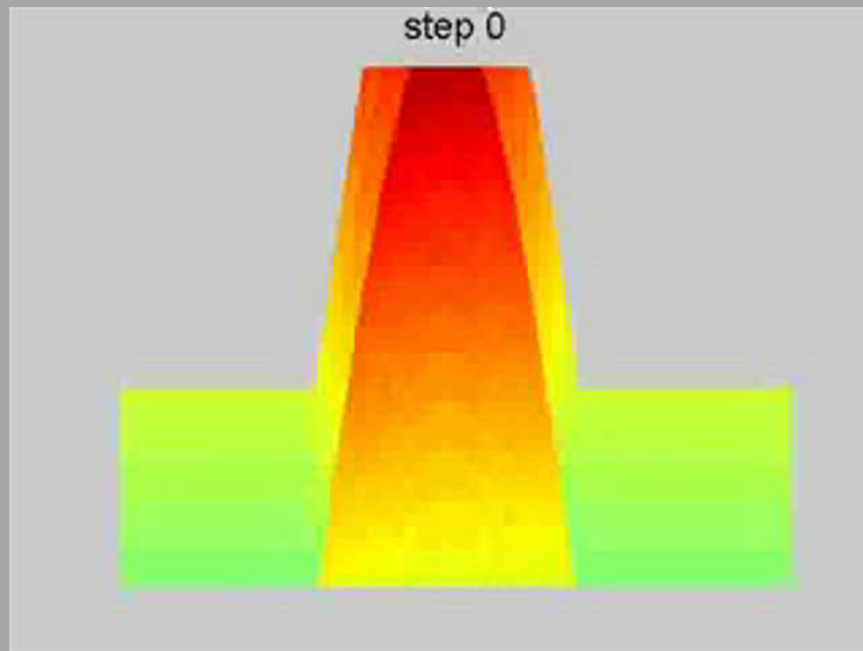
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Collective agent navigation

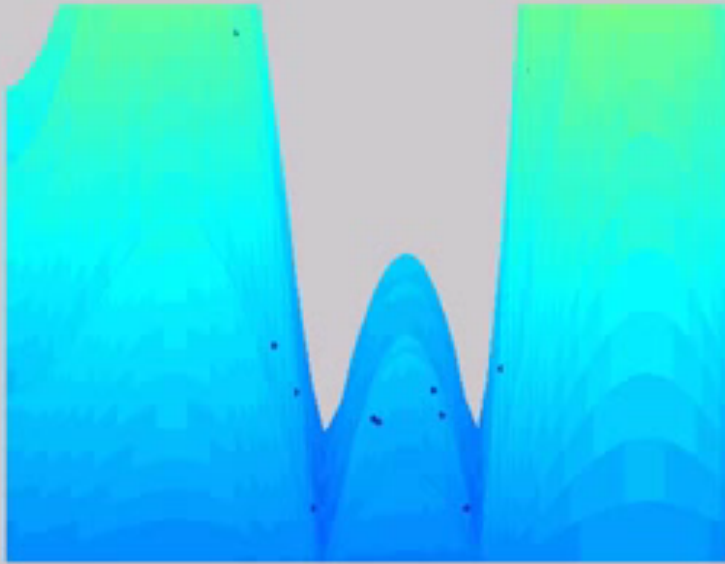


Collective sensing and
Distributed information processing

Highly complex terrain

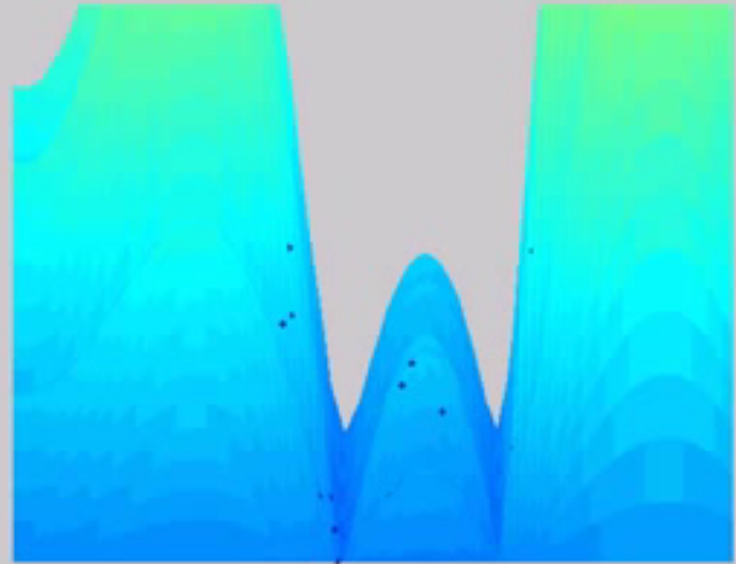
Fixed interactions

step 0



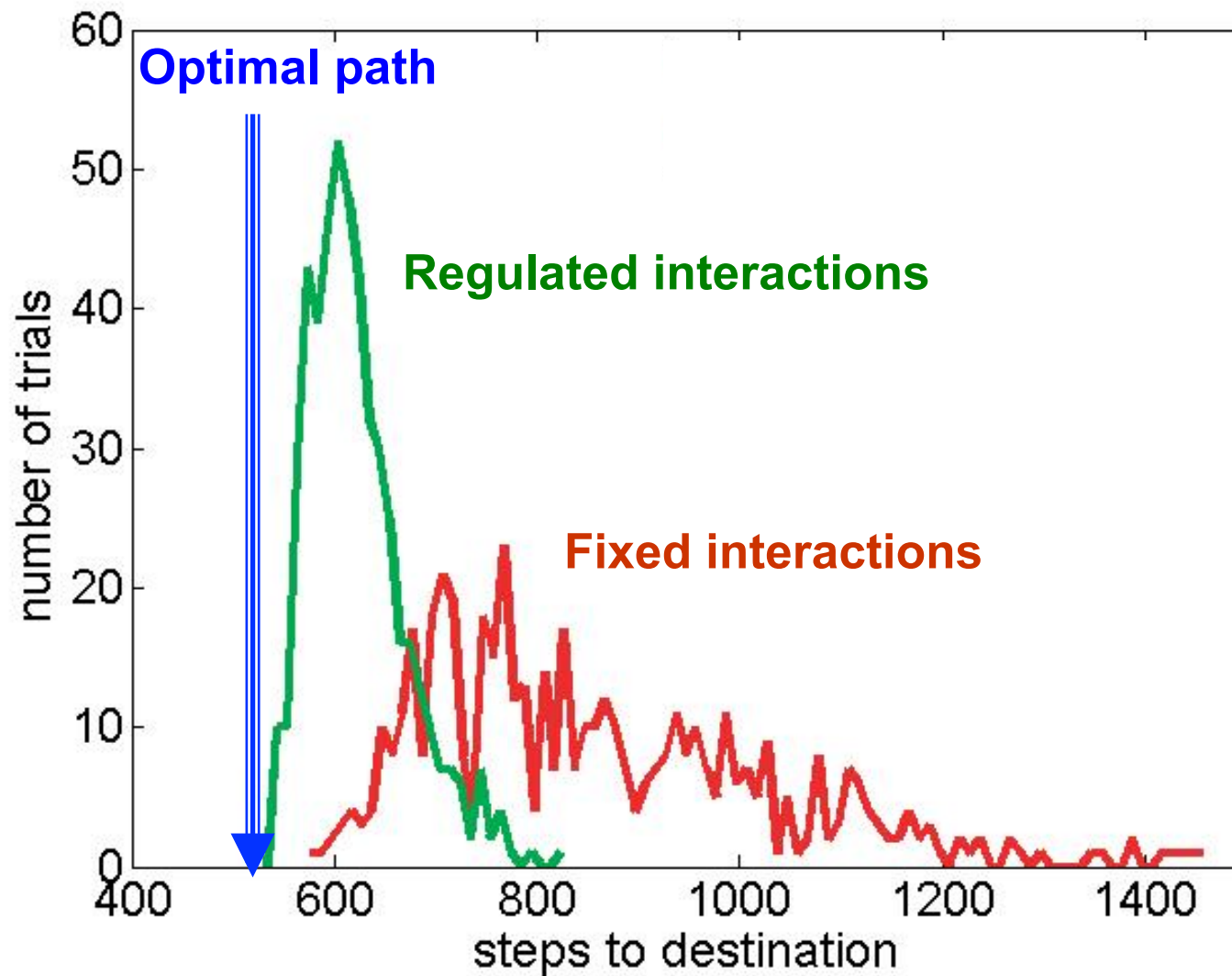
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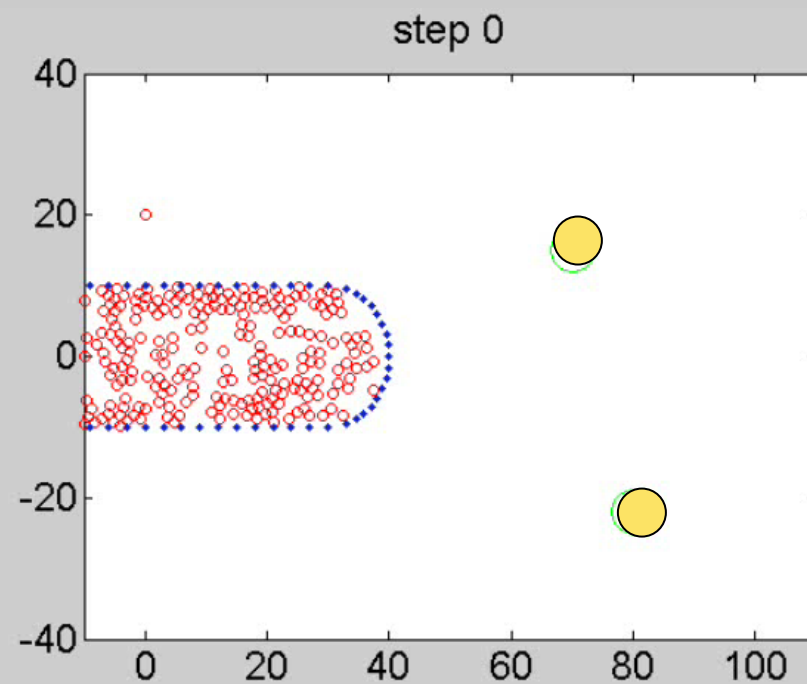
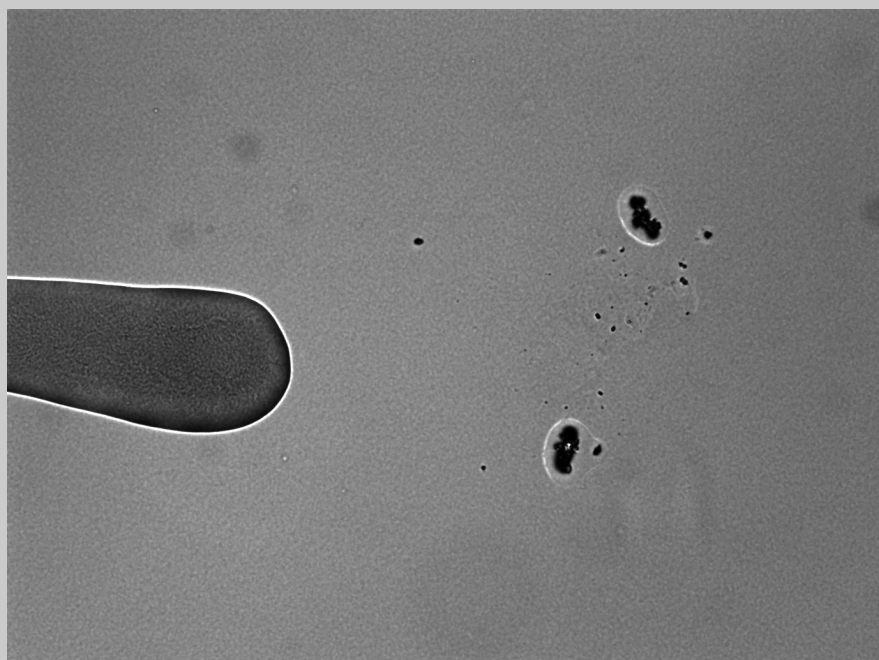
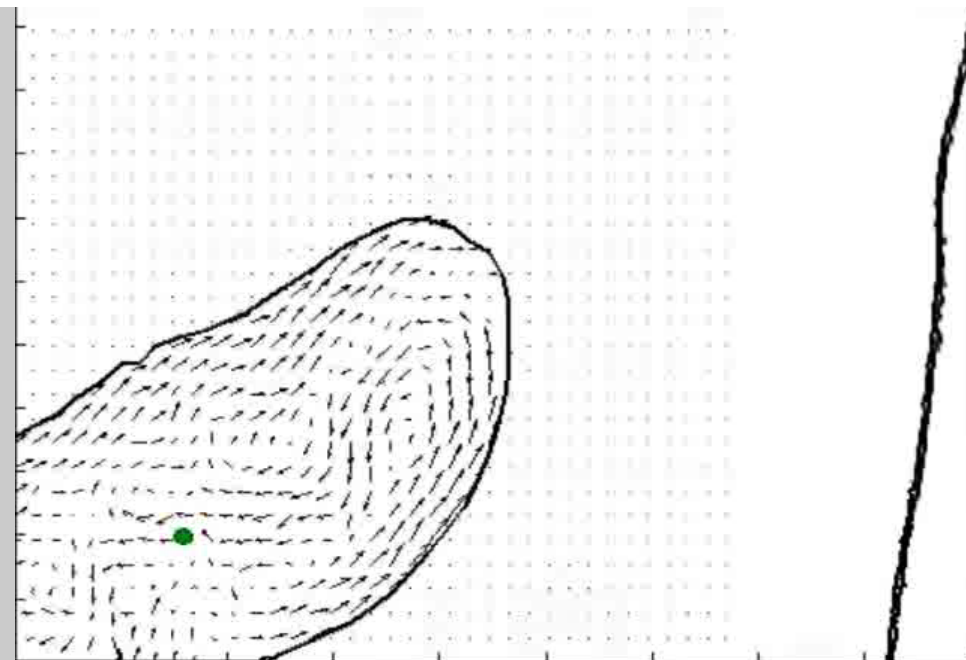
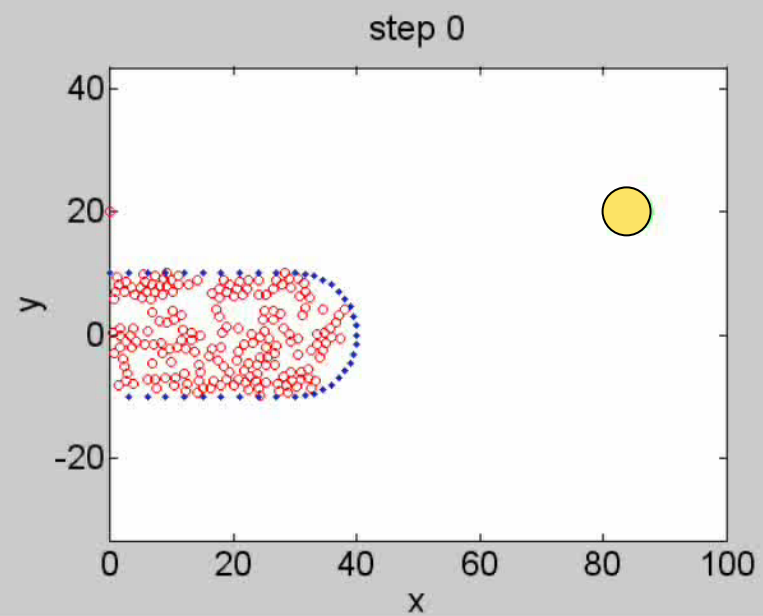
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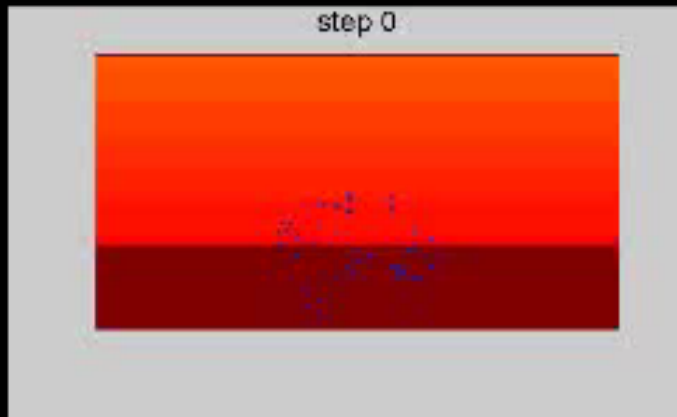
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Quantification of the results

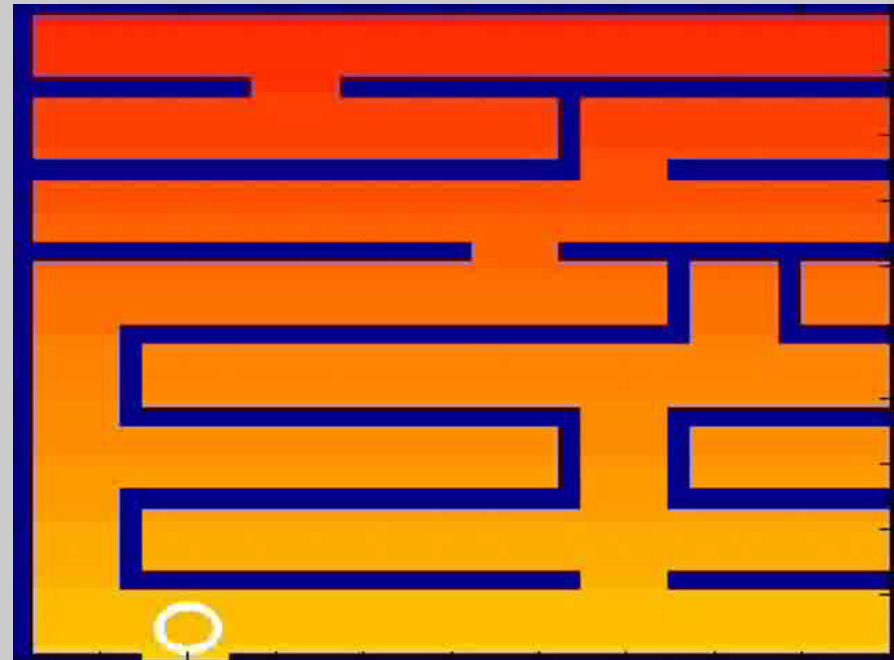
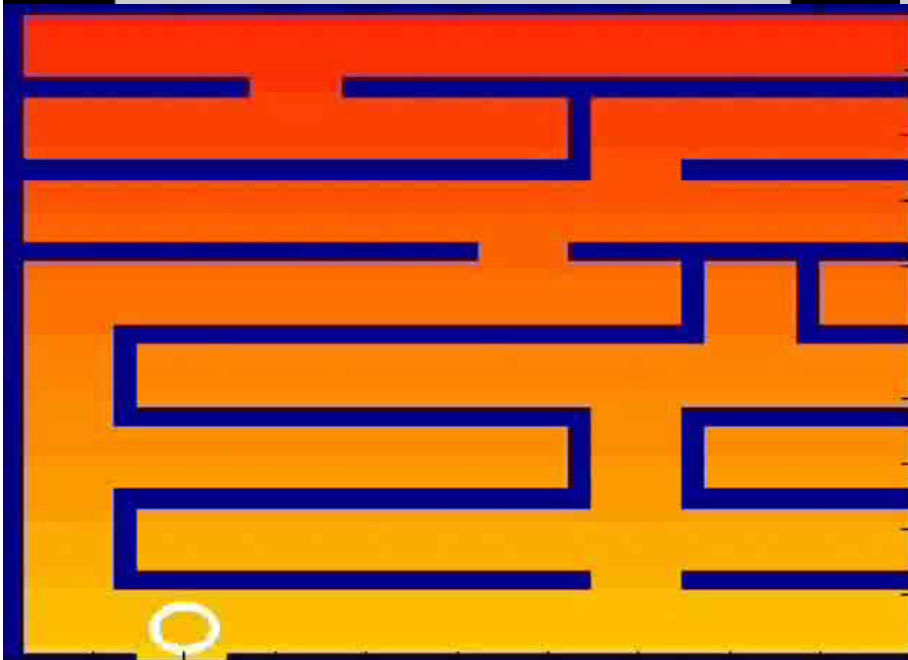




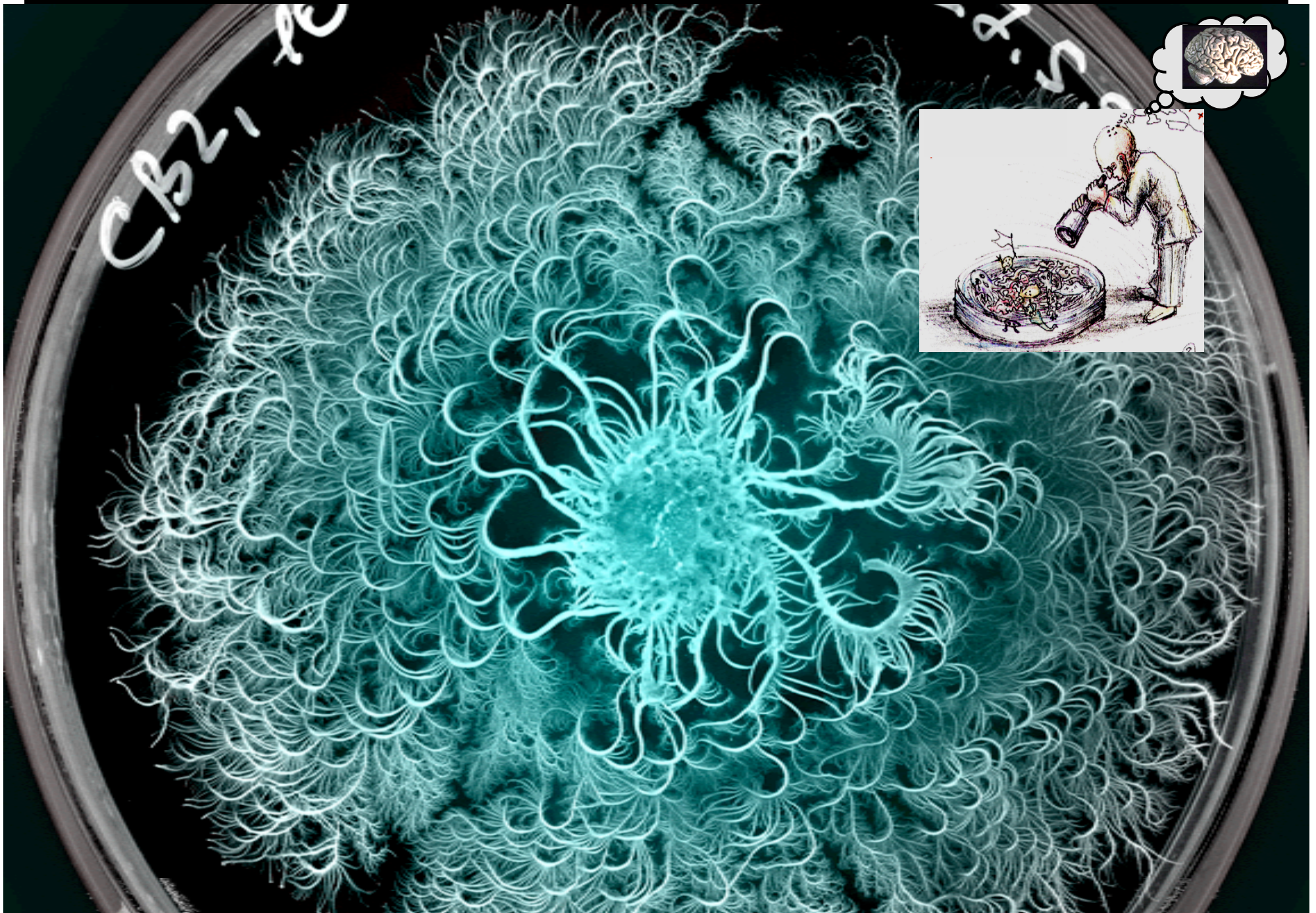
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A bootstrapping mechanism



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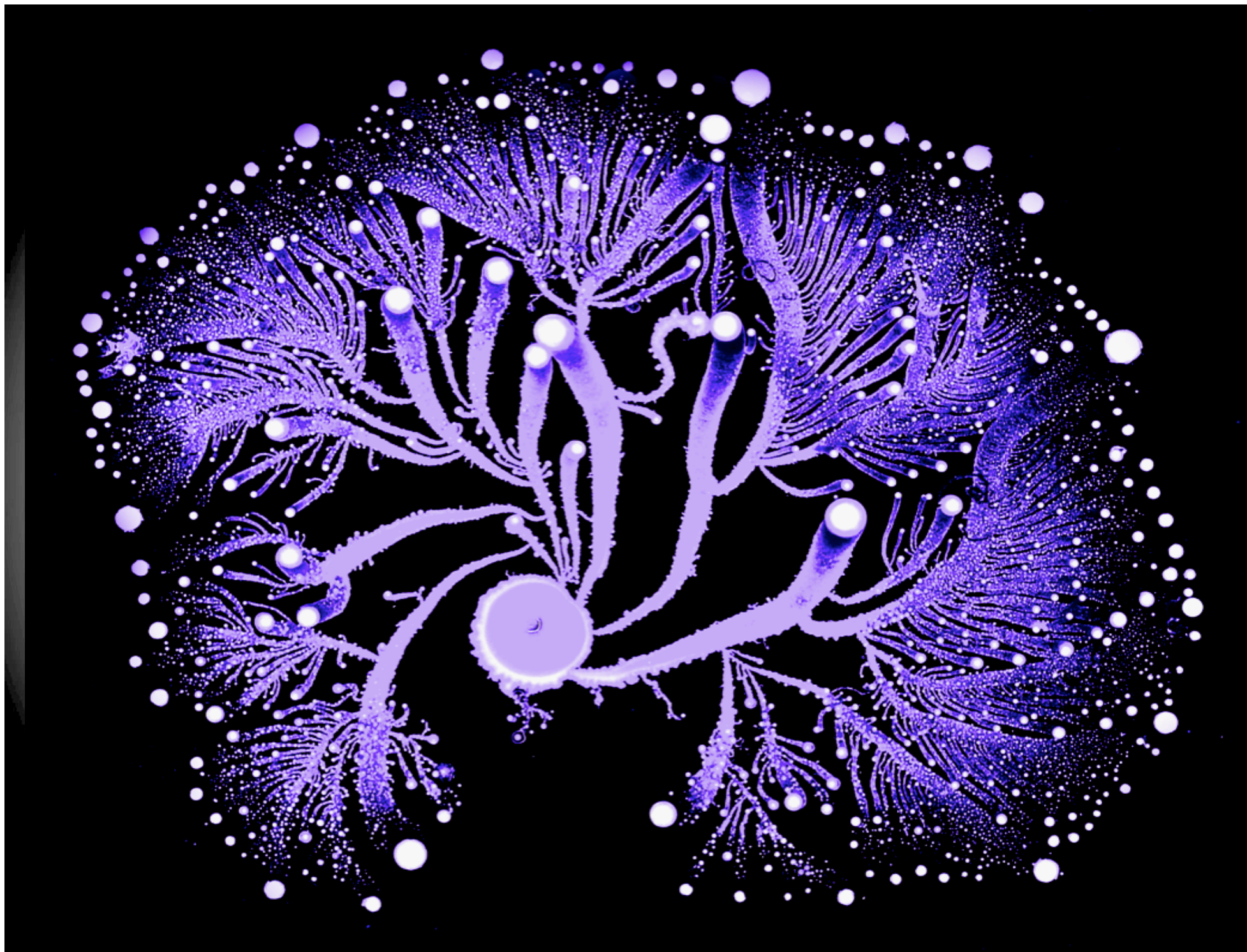
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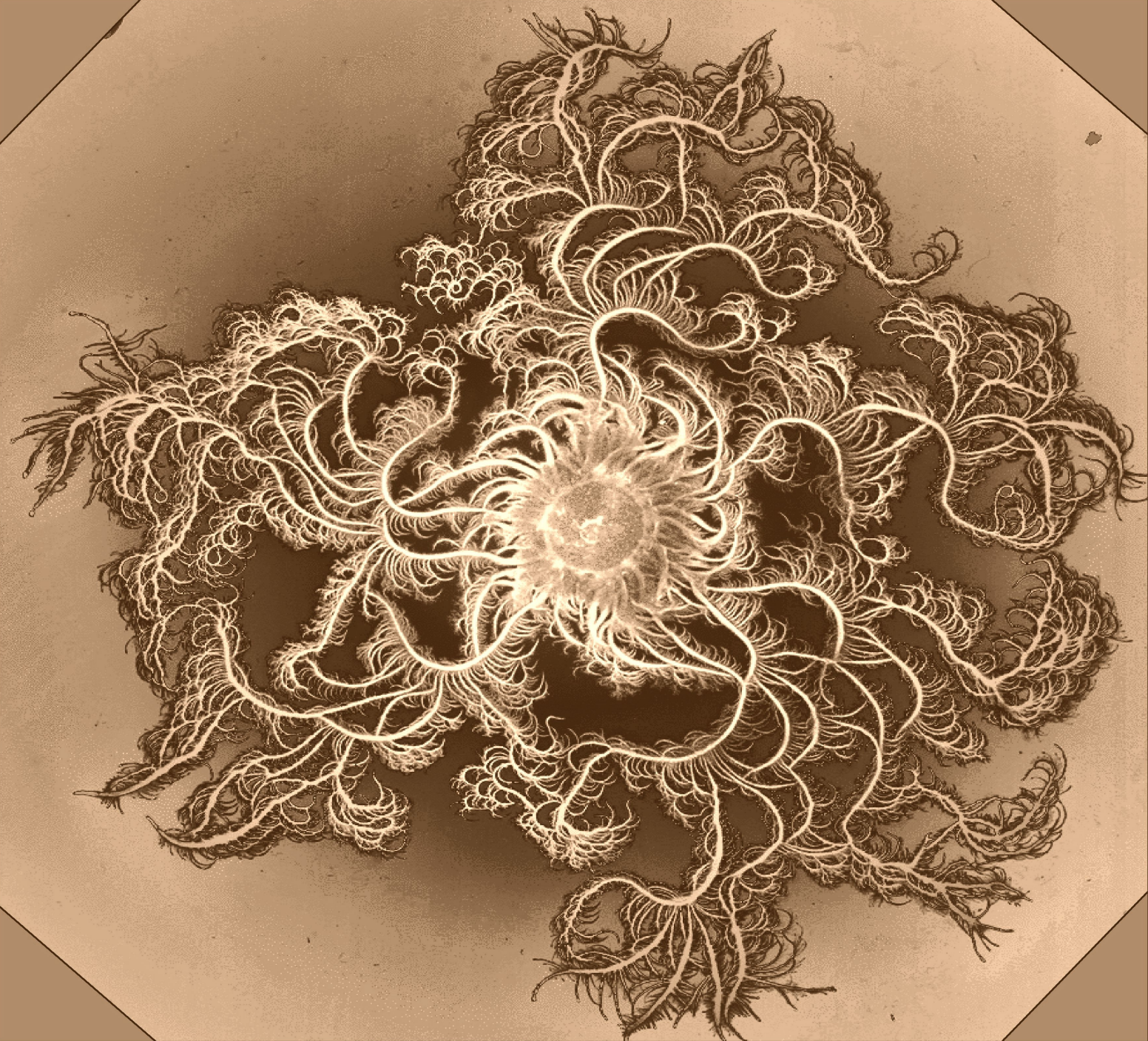


The Bacteria and I - Full Disclosure

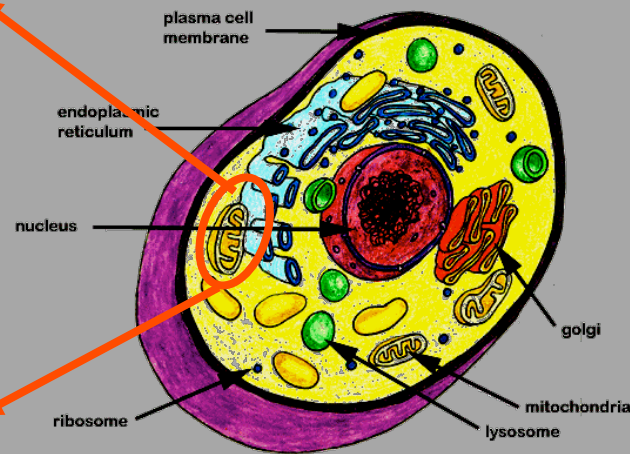
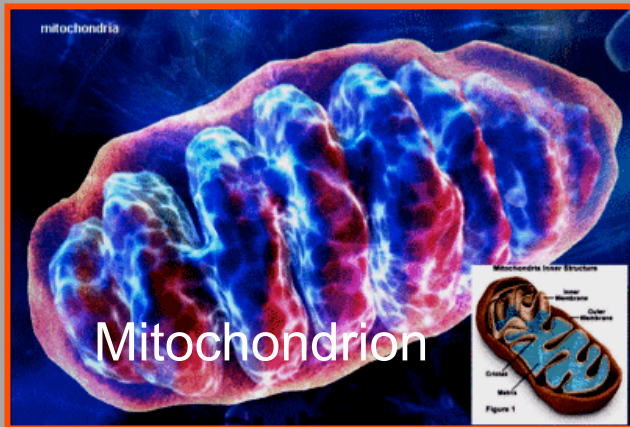
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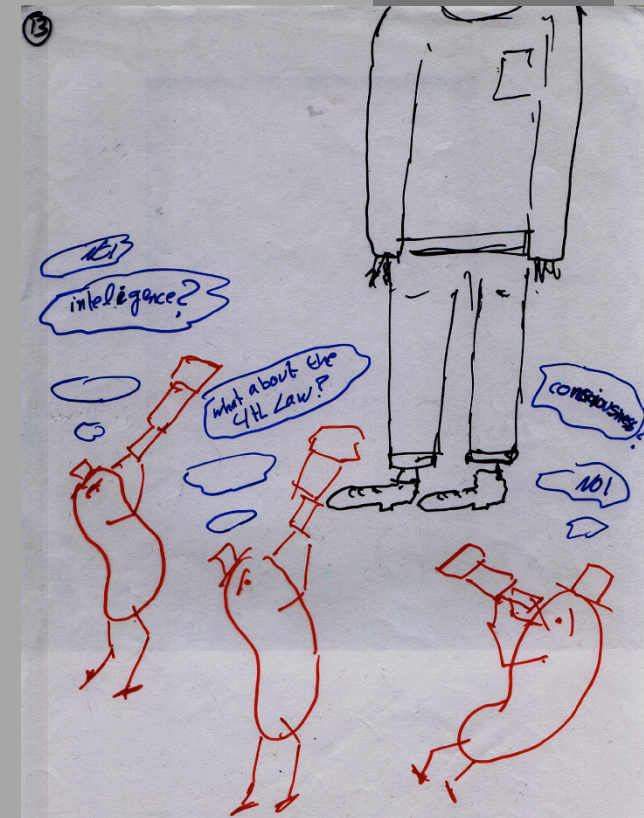
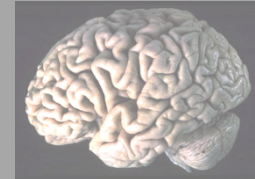


From Bacteria Thou Art



"Intelligence is the Freedom to Err"

Eshel Ben Jacob, Nobel Symposium 2002



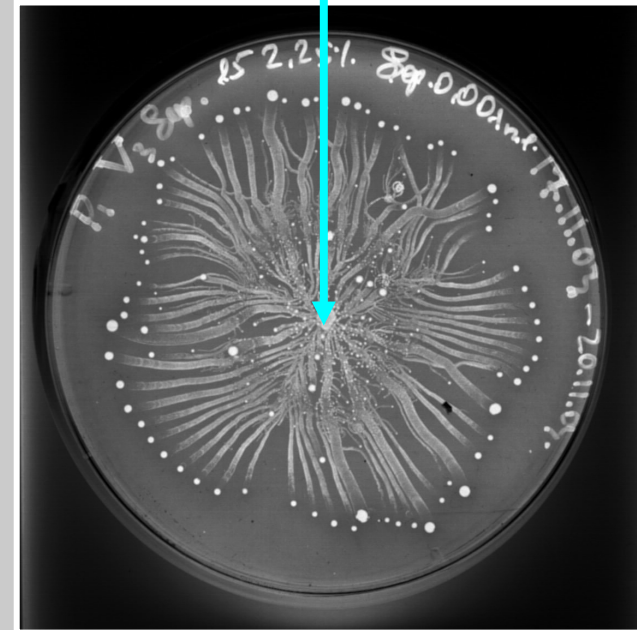
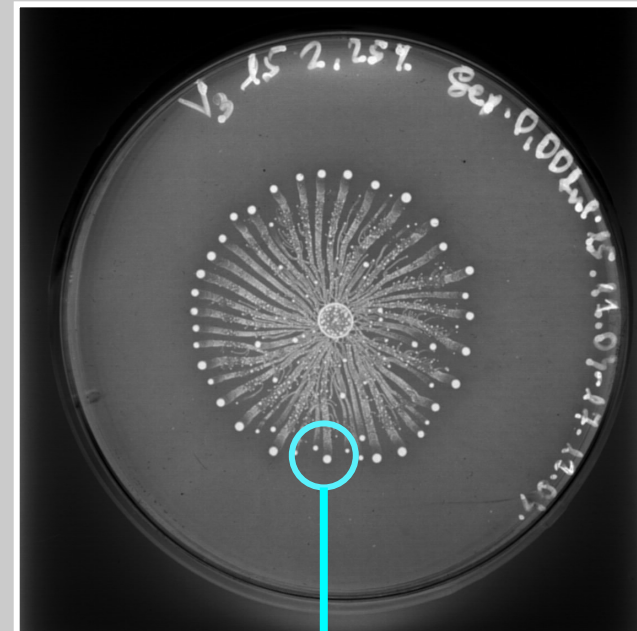
The End

Exposure to antibiotics

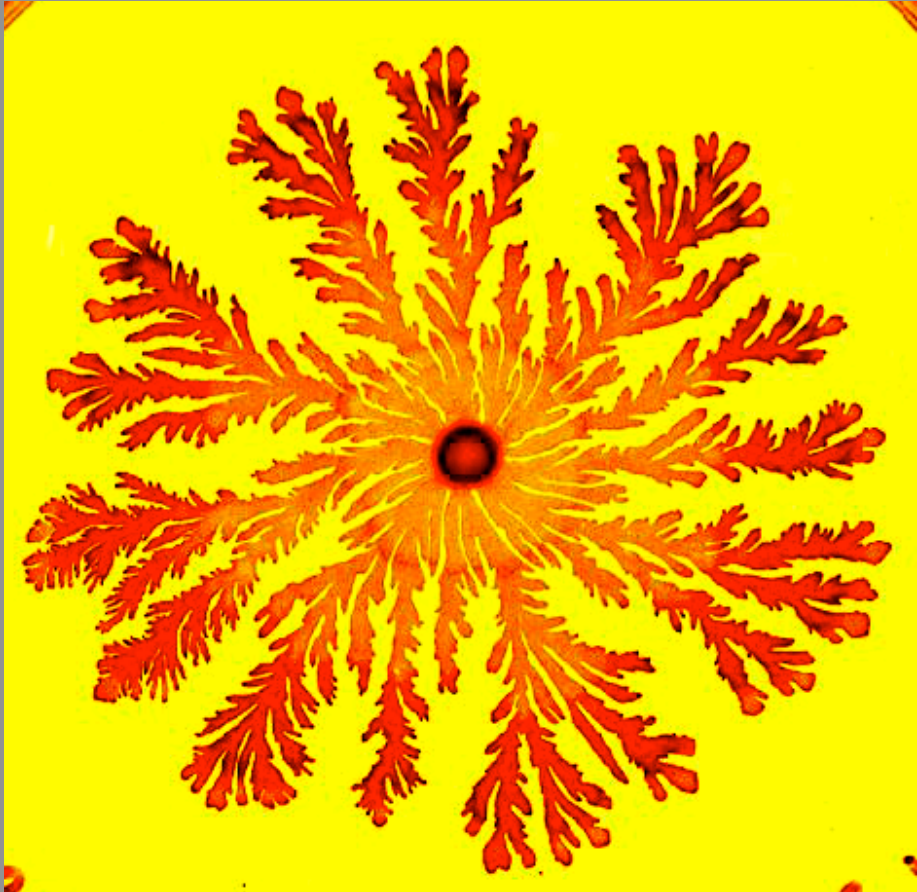
Normal growth



Second exposure



Results of Model Simulations I

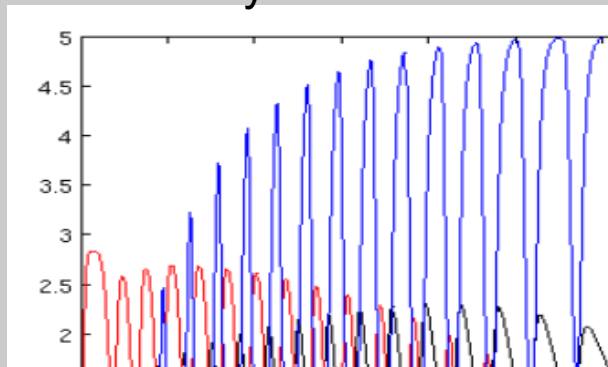


Observations

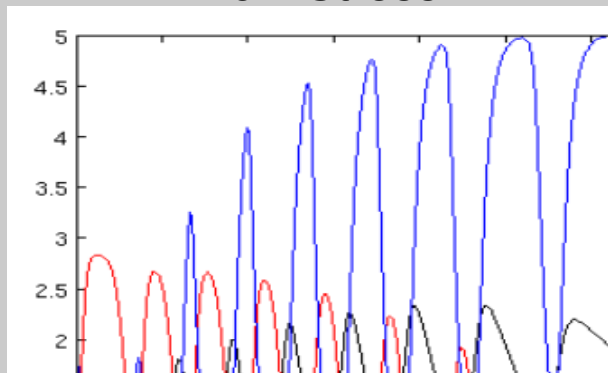


Simulations

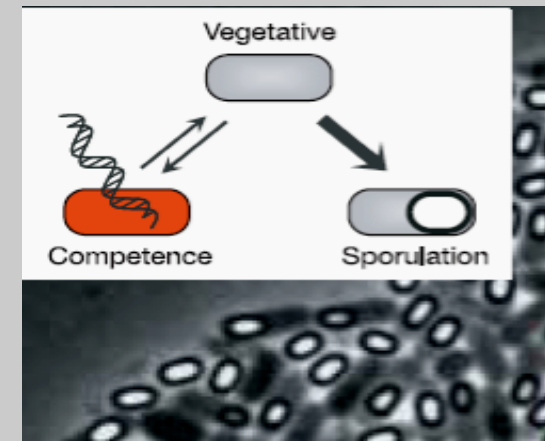
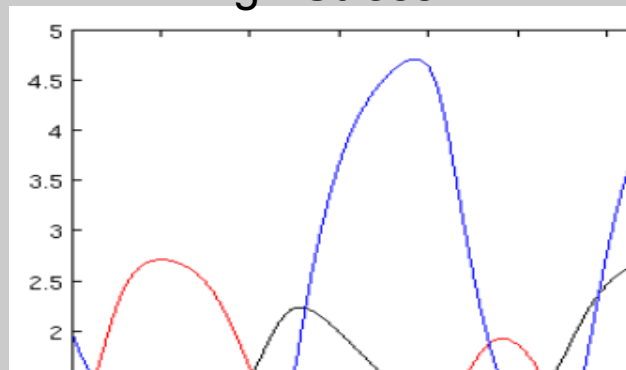
Very Low Stress



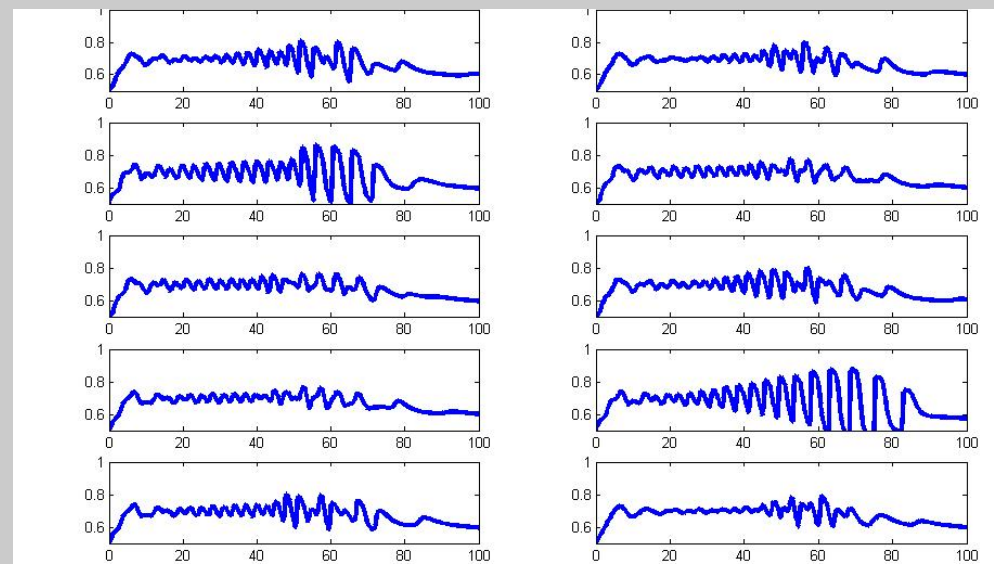
Low Stress



High Stress

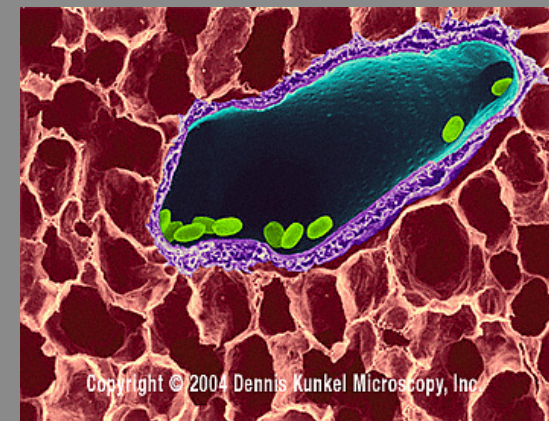
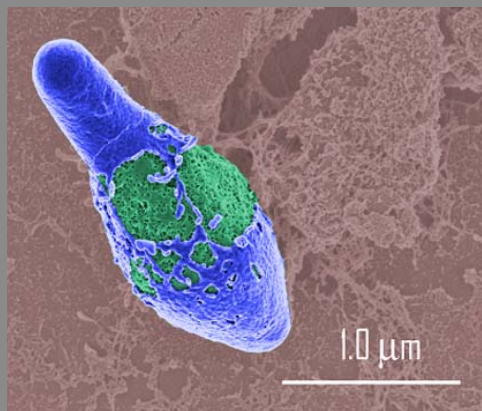
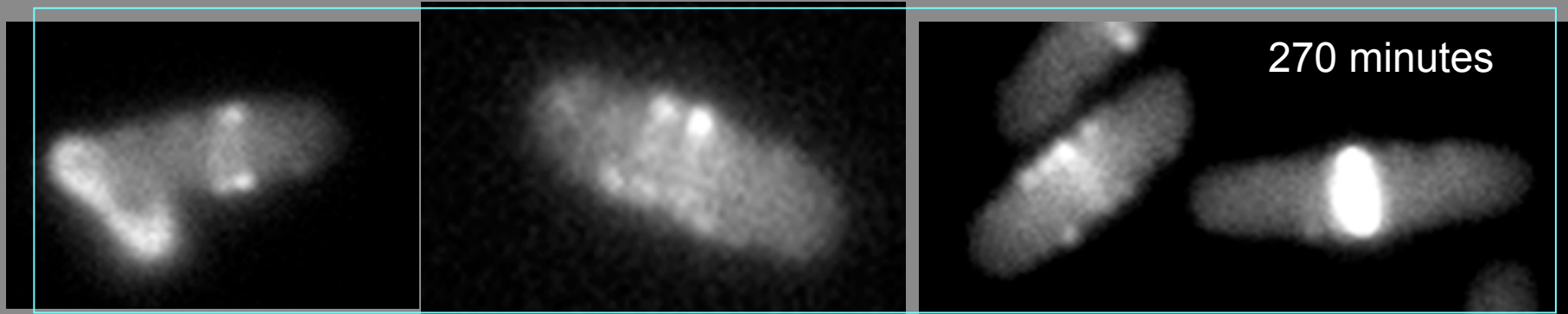


AbrB in Different Cells



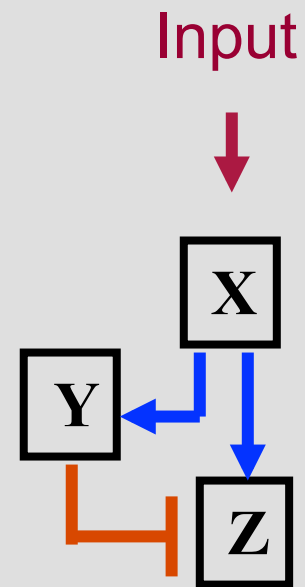
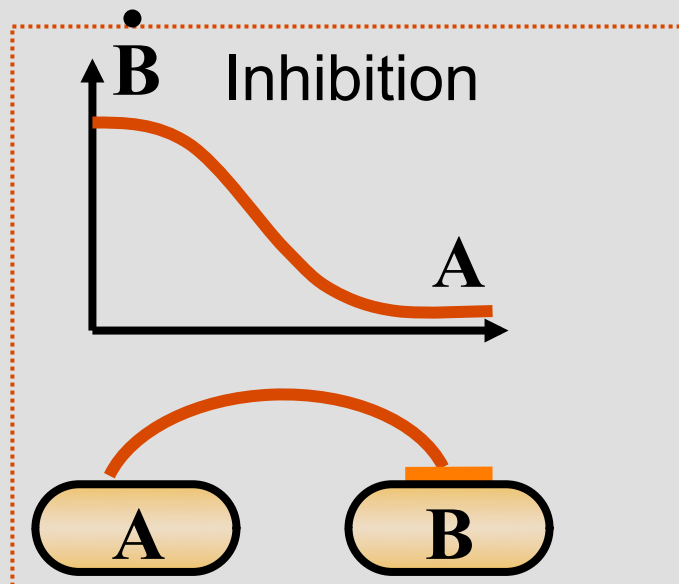
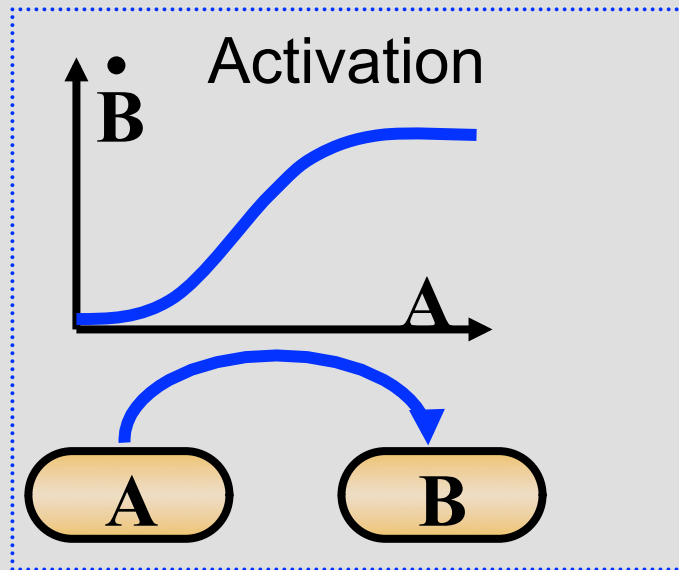
Germination

From Liza Harry UTS Australia

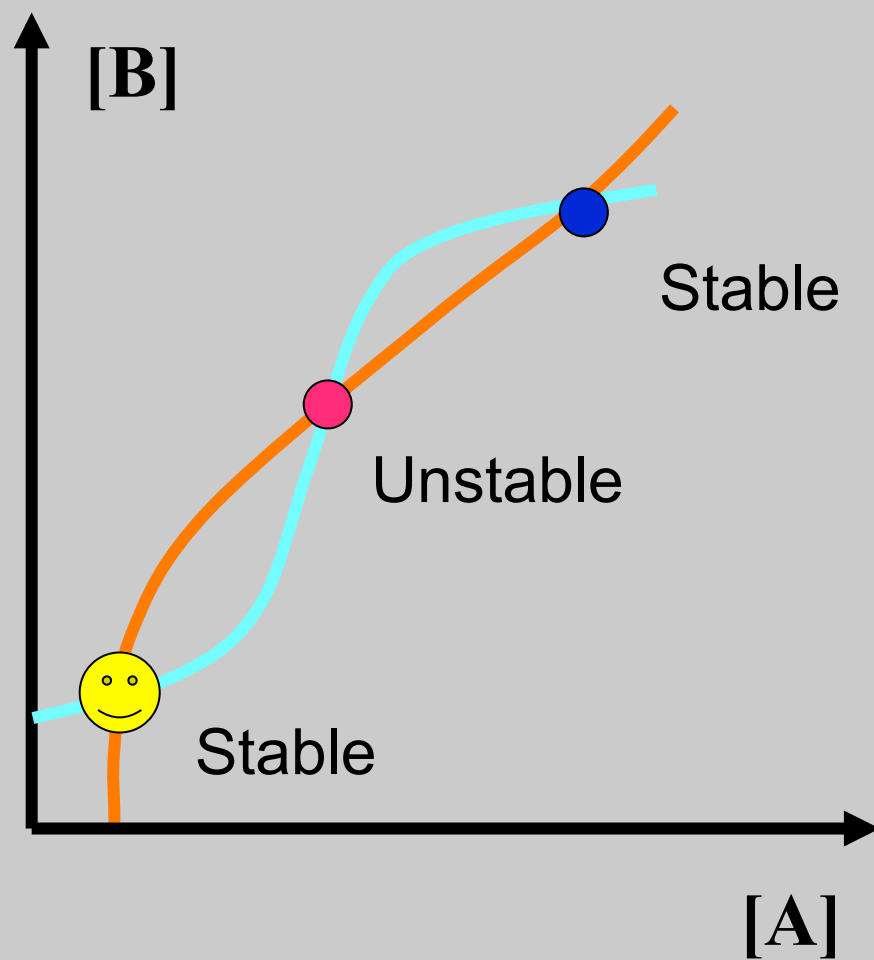
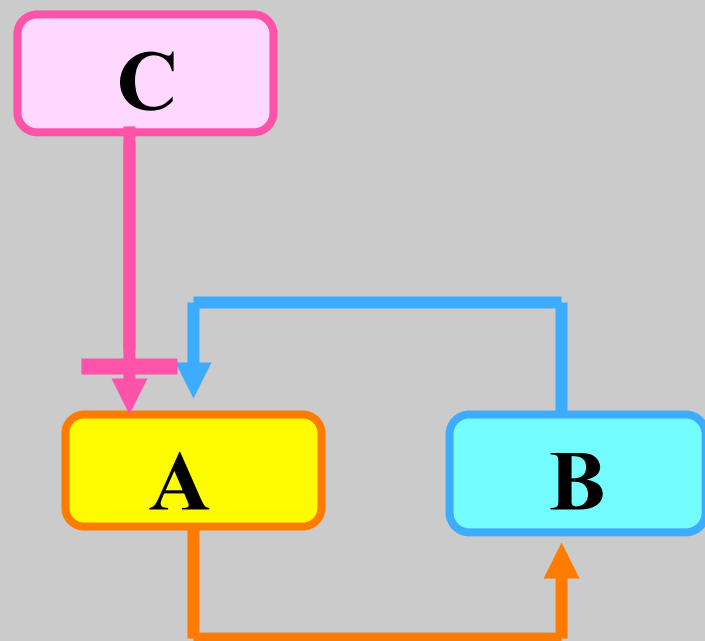


Bacterial Functional Solvability





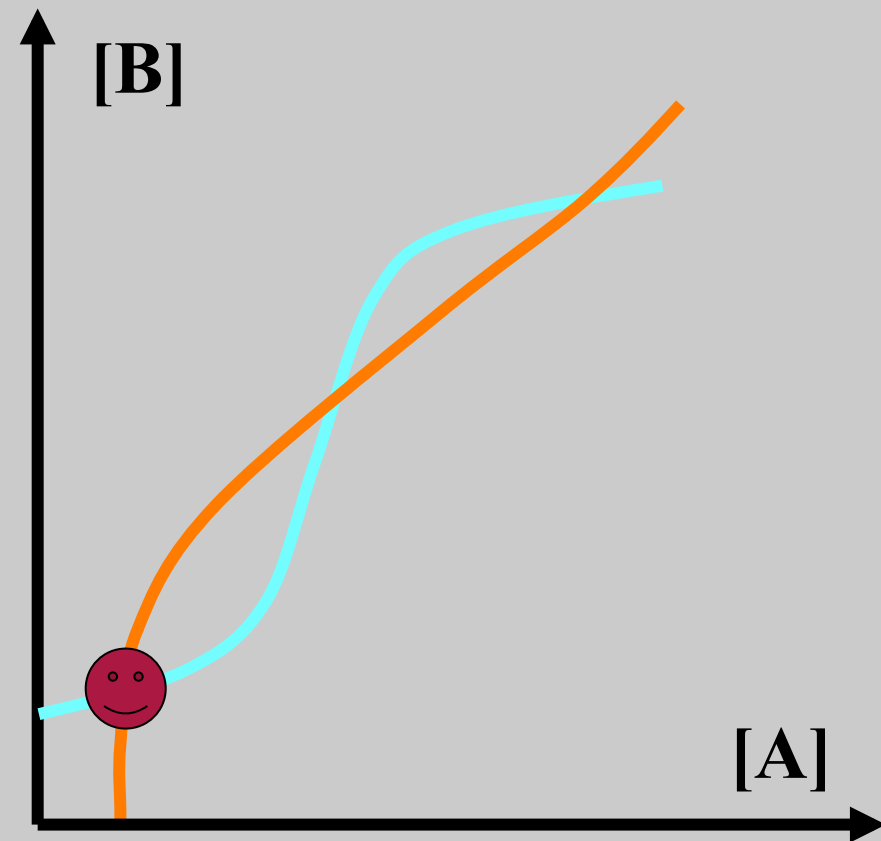
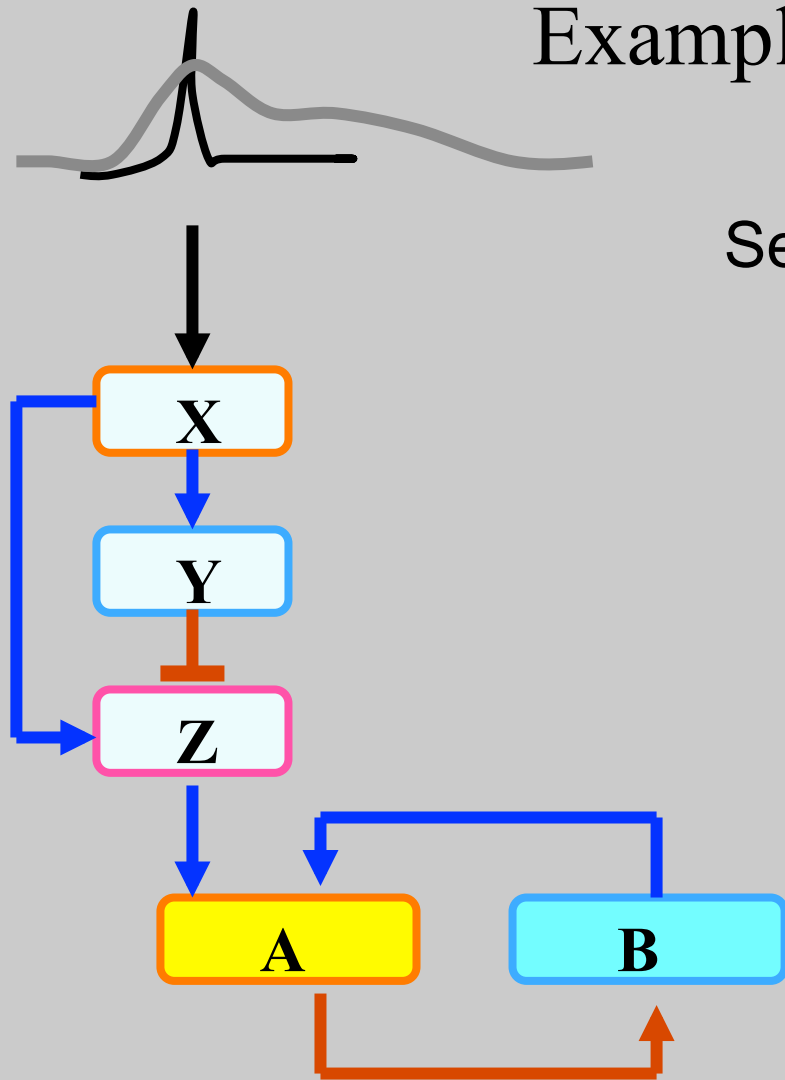
Example of a Flip-flop Circuit



With Daniel Schultz *PNAS* 2010

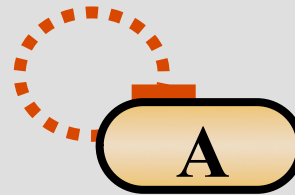
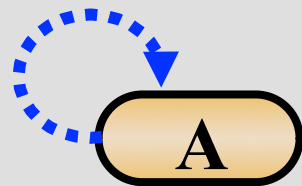
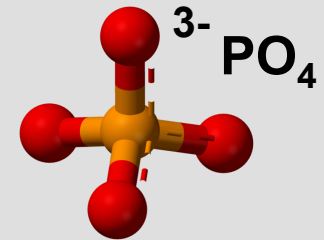
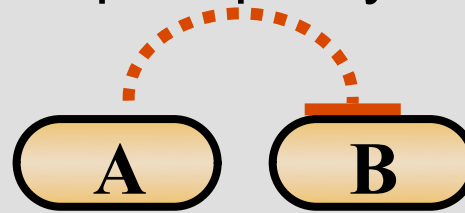
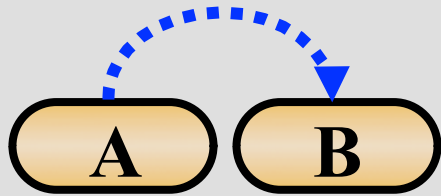
Example of a Functional Role

Filtering noise
Separation of time scales



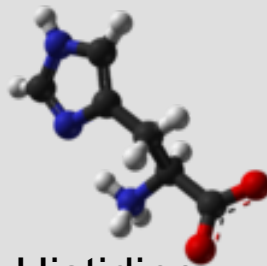
With Daniel Schultz *PNAS* 2010

Phosphorylation and Dephosphorylation

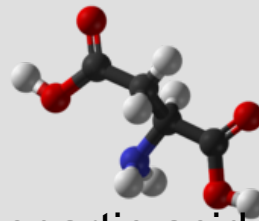


Self-Activation Self-Inhibition

Time scale control by using different Amino Acids



Histidine



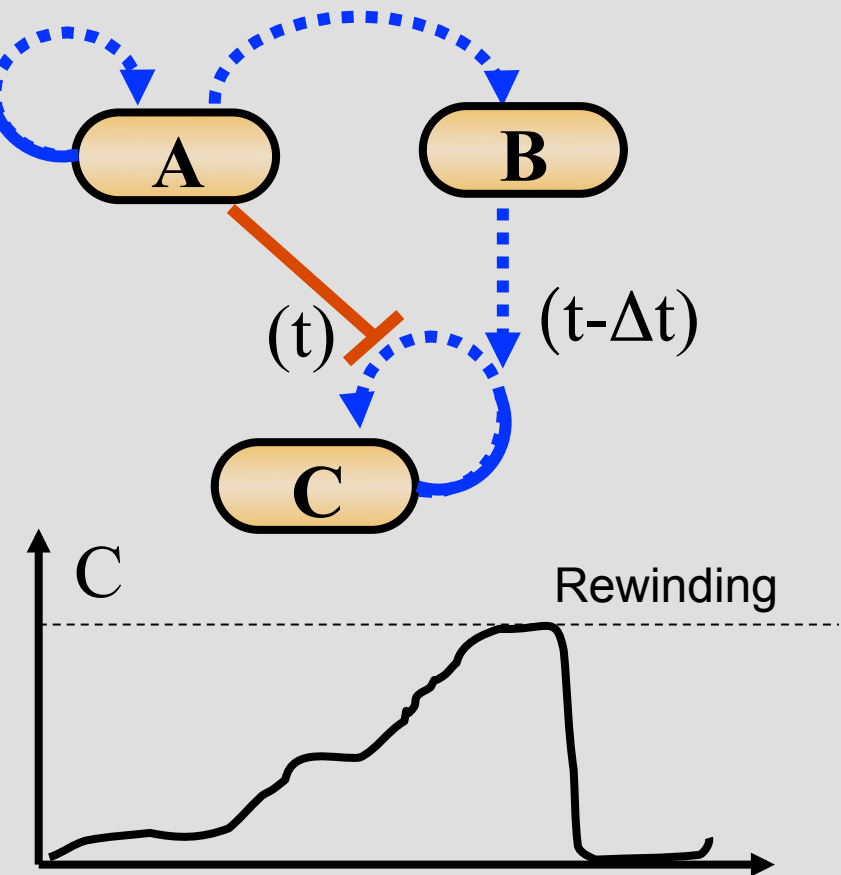
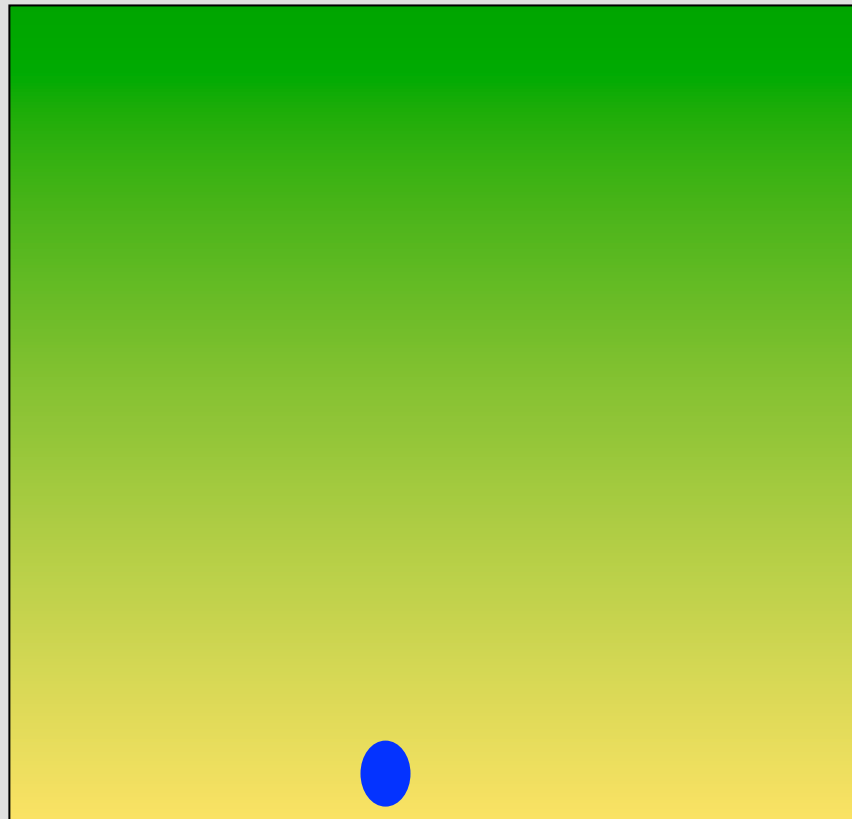
Aspartic acid



Serine

Chemotaxis -

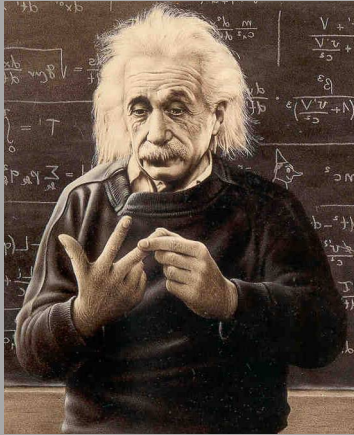
The measured concentration



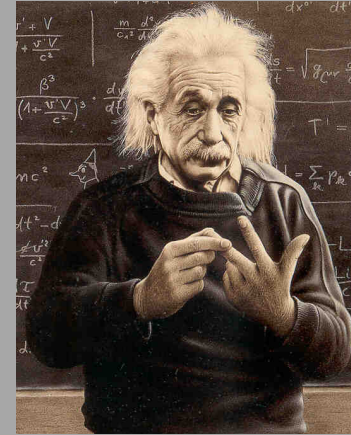
THE JERUSALEM POST - FRONT

Can bacteria teach us how to make life decisions?

TAU physicist says single-cell organisms can show humans how to cope with stress



\$2 - \$100



\$100

\$97

\$96

\$99

\$101

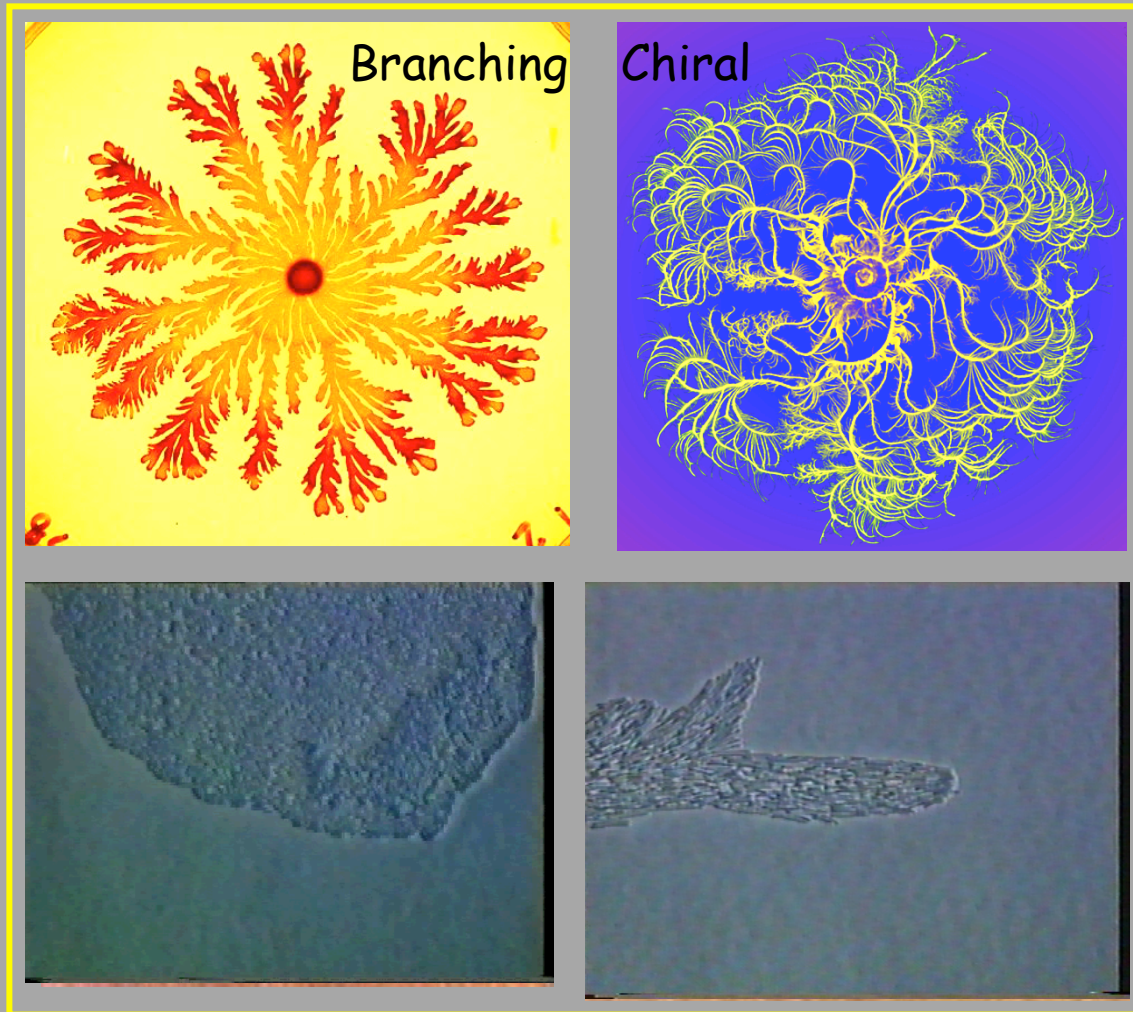
\$98

\$100

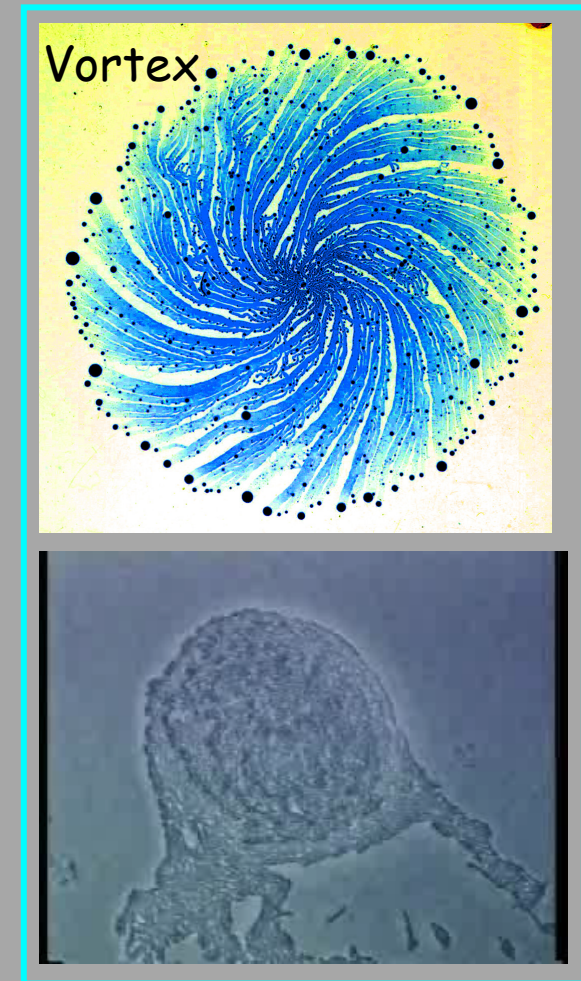
Minimization of Maximum Regret

The Two Bacterial Strains that we Developed

Paenibacillus dendritiformis



Paenibacillus vortex



Both are Gram⁺ lubricating bacteria

Genome sequencing – about 7,000 genes – many surprises