SUMMER SCHOOL LECTURES

Herbert Levine – UCSD Physics

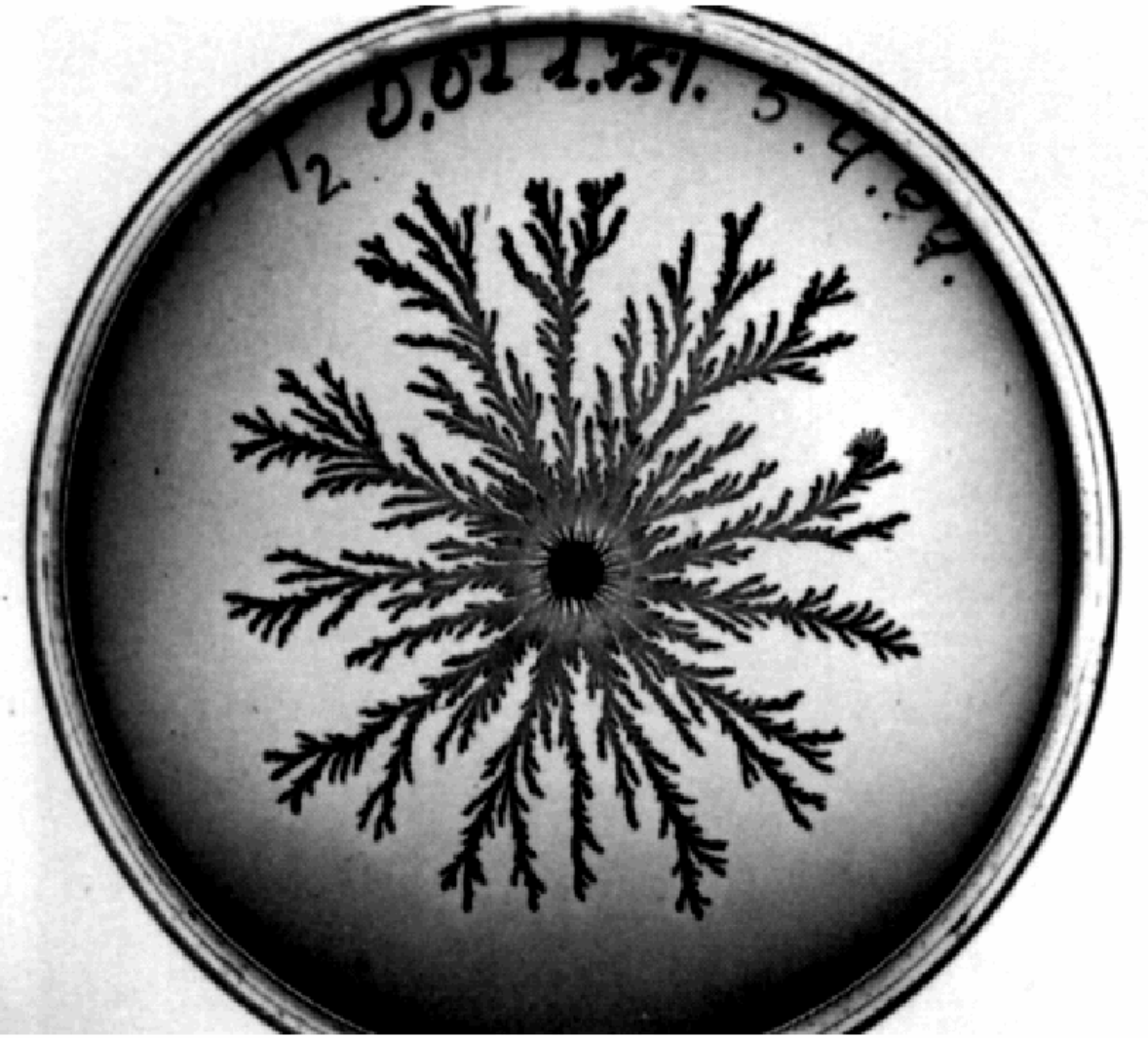
Basic subject: Pattern Formation in Biological Systems

- Bacterial Colonies: Diffusively-induced Branching
- Amoebae Aggregation: Communication via nonlinear waves
- Patterns Inside the Cell: Stochastic effects

- Each topic: introduction to experimental system
  analysis of possible models
  sample of results to date

Goal is to help you understand how physics can help!

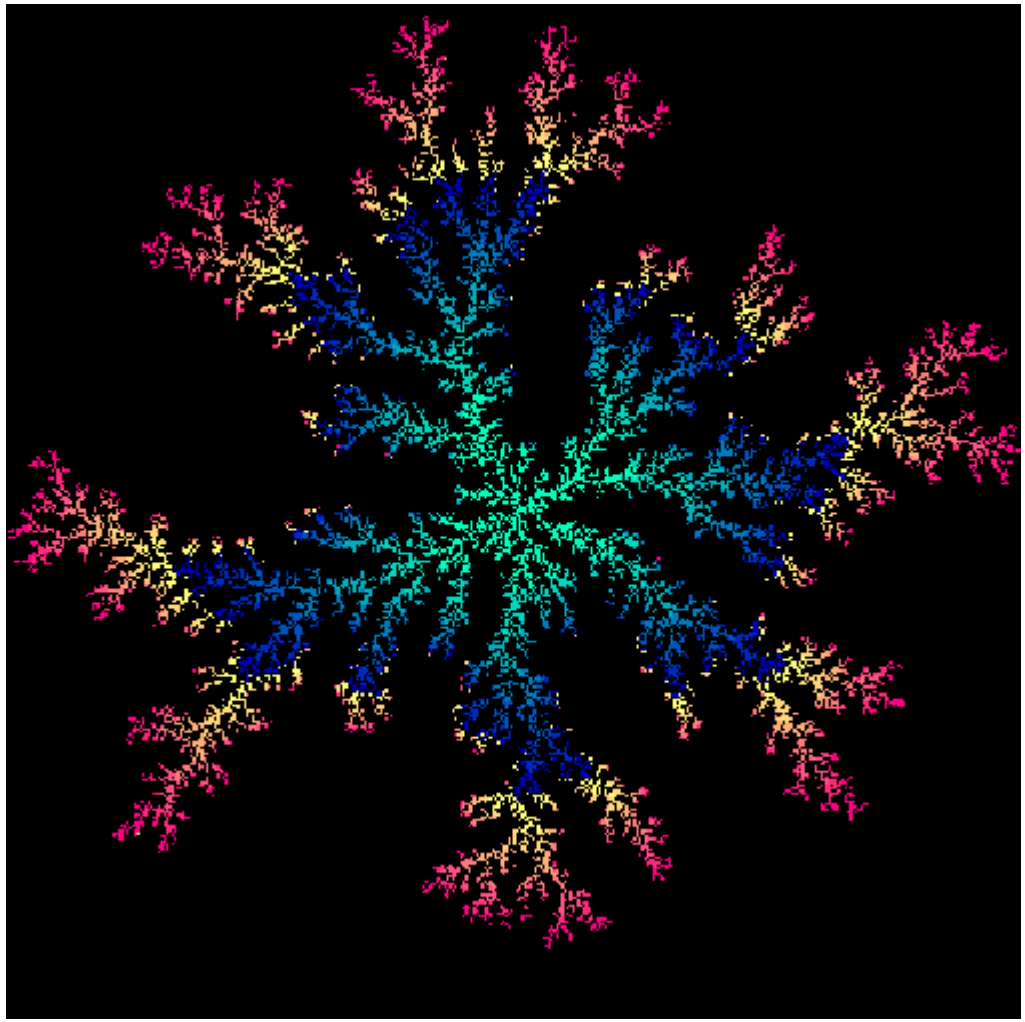
Branched growth in Bacillus*



From lab of E. Ben-Jacob; following earlier work by Japanese group

Growth is limited by the diffusion of nutrient

* and related species!

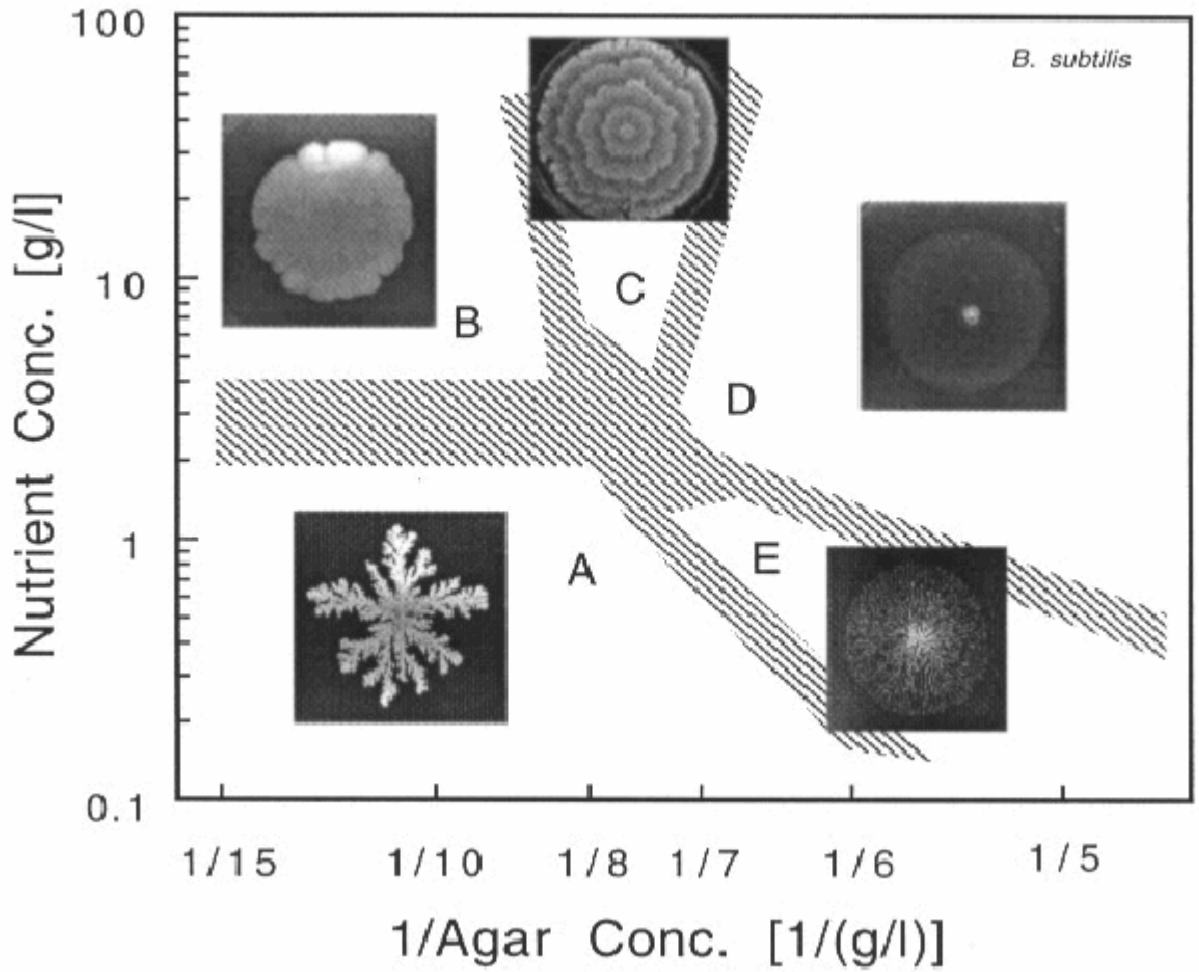


Bacterial branching patterns has physical equivalent

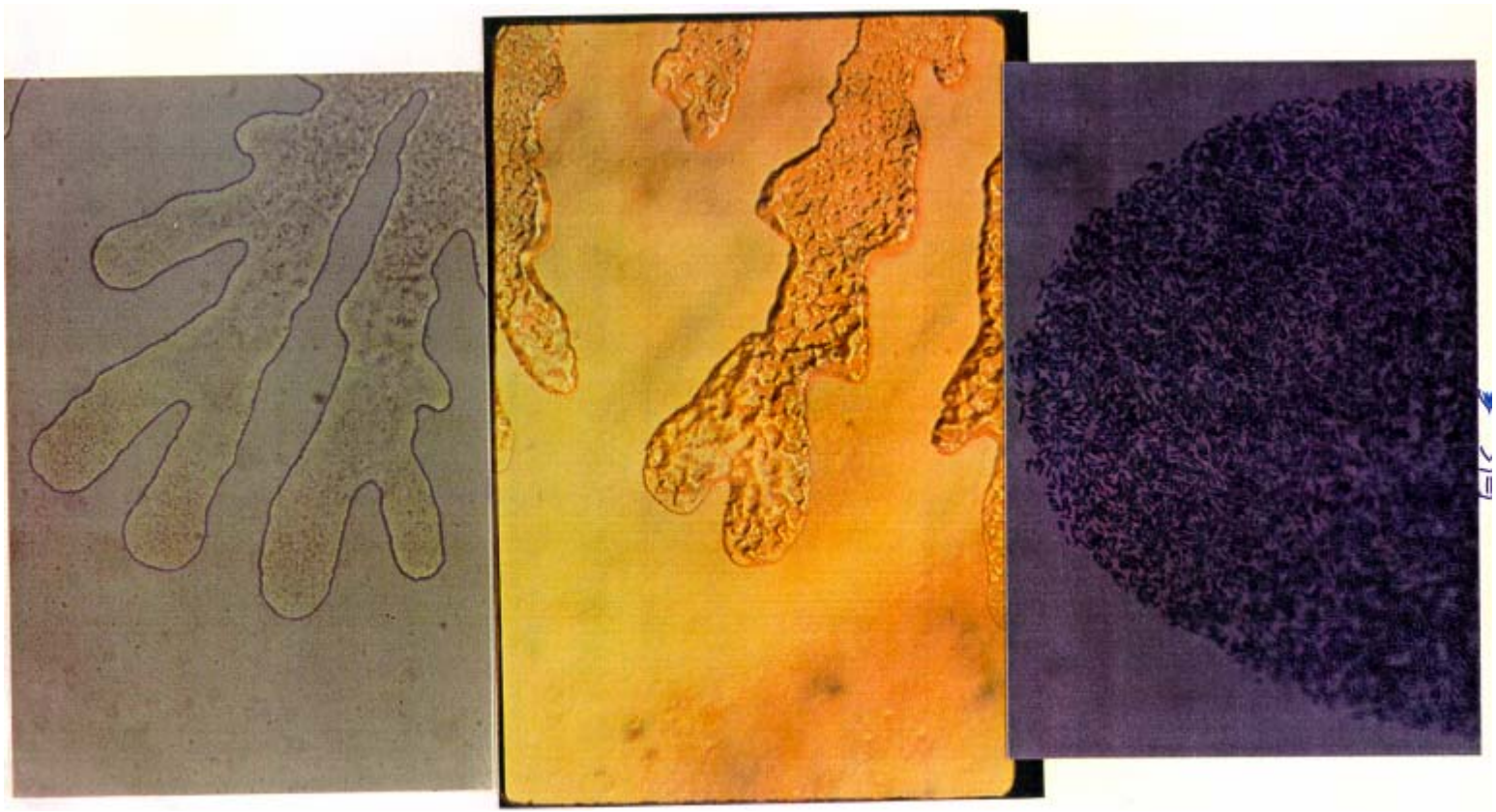
One random walker attaches wherever it hits and another one is released

DLA – Witten and Sander (1981)

Phase diagram for Bacillus

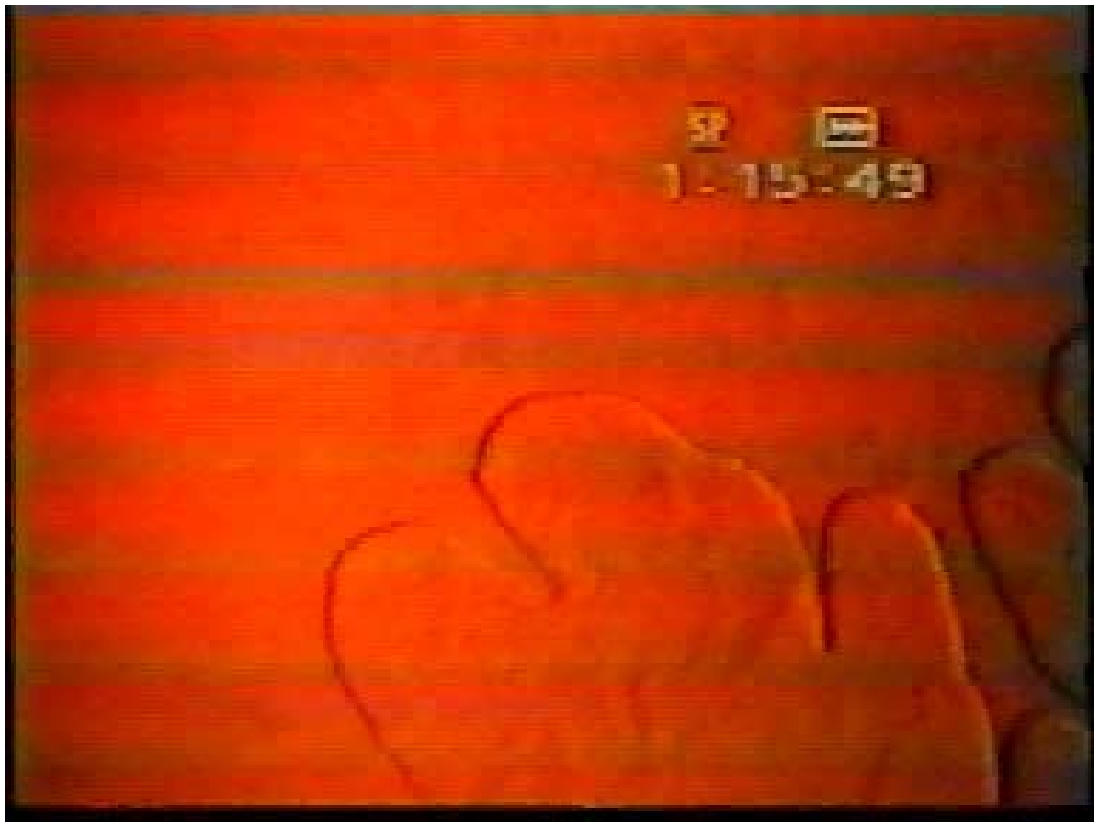


A closer look at the branches



Note: wetting envelope, discrete cells.

The movie version



Courtesy,
Ben-Jacob lab

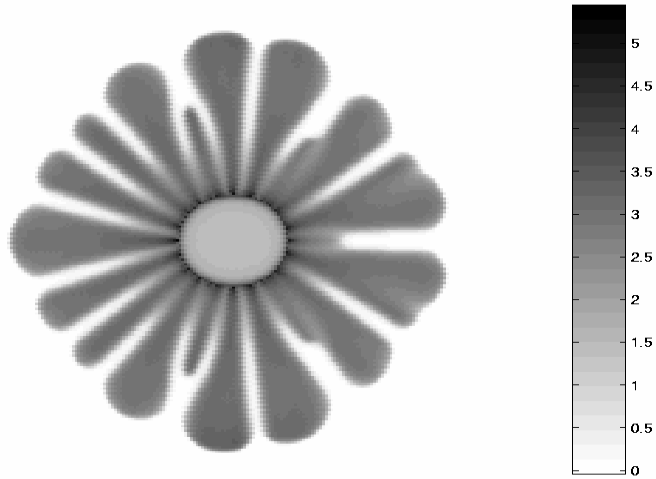
REACTION-DIFUSION MODELING

Let us work through some basic concepts in using coupled PDE's to model pattern formation in expanding colonies

So, how do the bacteria do it?

Cutoff can come via several effects

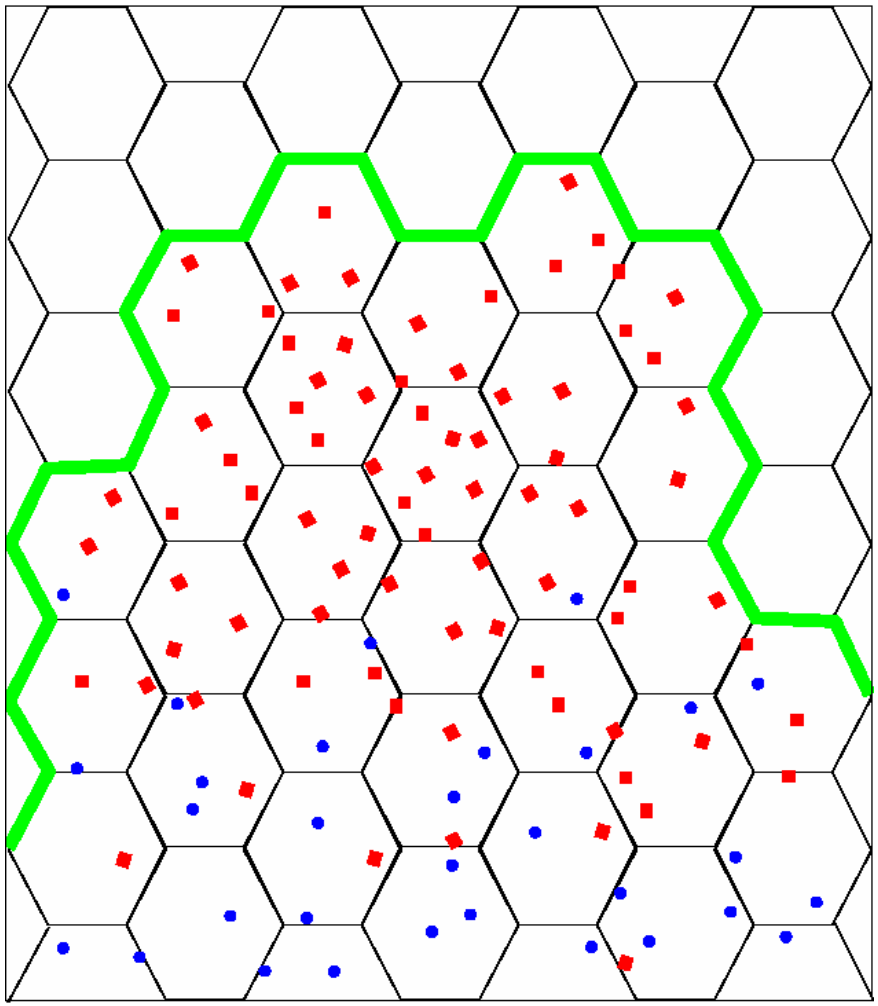
1. Reaction-term cutoff due to finite numbers
2. Diffusion-cutoff due to wetting fluid



Branching!

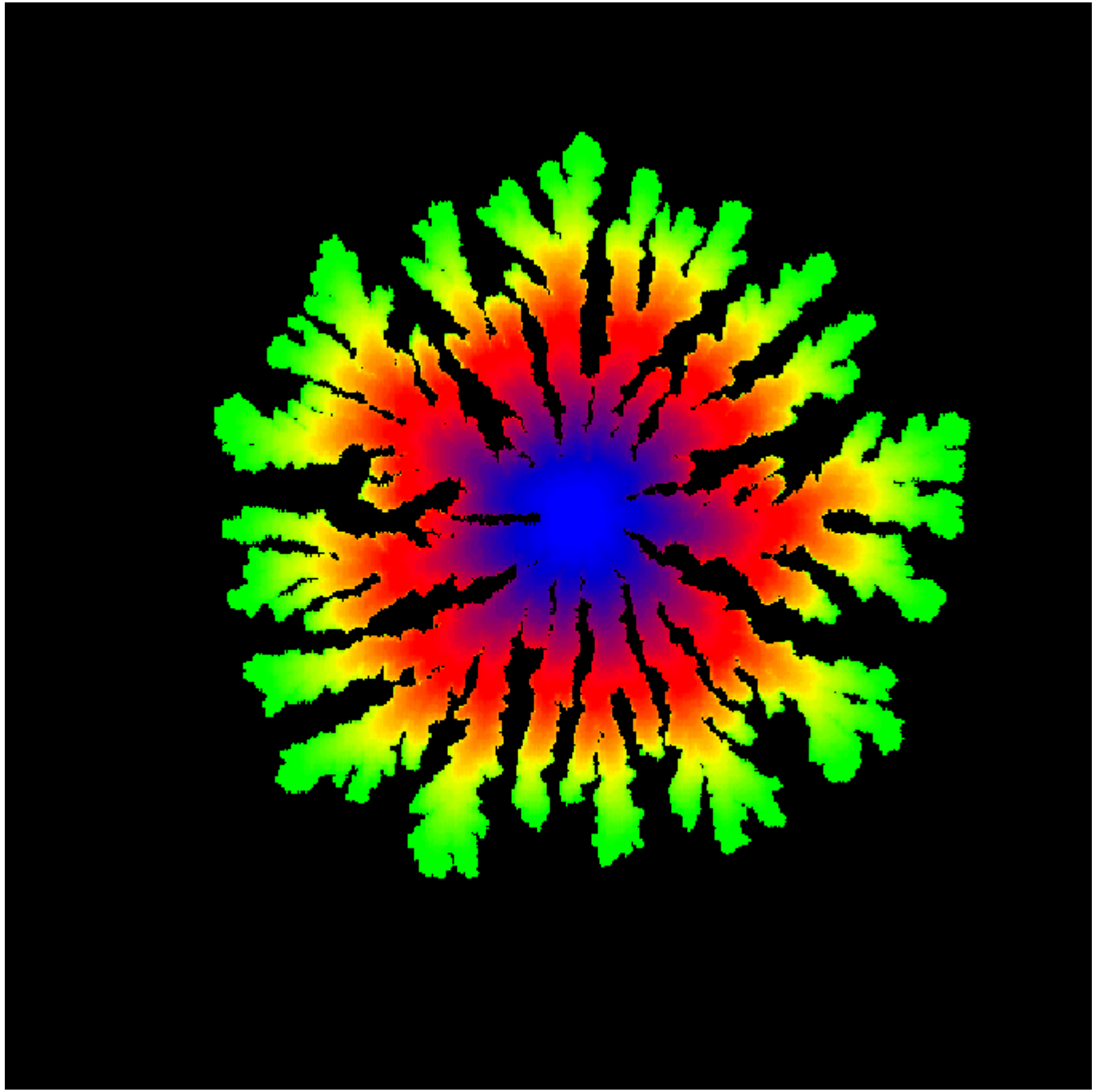
E. Ben-Jacob, I. Cohen and H.Levine; Adv. Physics (2000)

Discrete walker simulations



- Diffusion modeled by random walkers
- Inactivation modeled by usage of internal energy
- Consumption of nutrient needed to raise energy stores

Tradeoffs:
Increased noise vs
Increased flexibility



Testing a semi-quantitative model

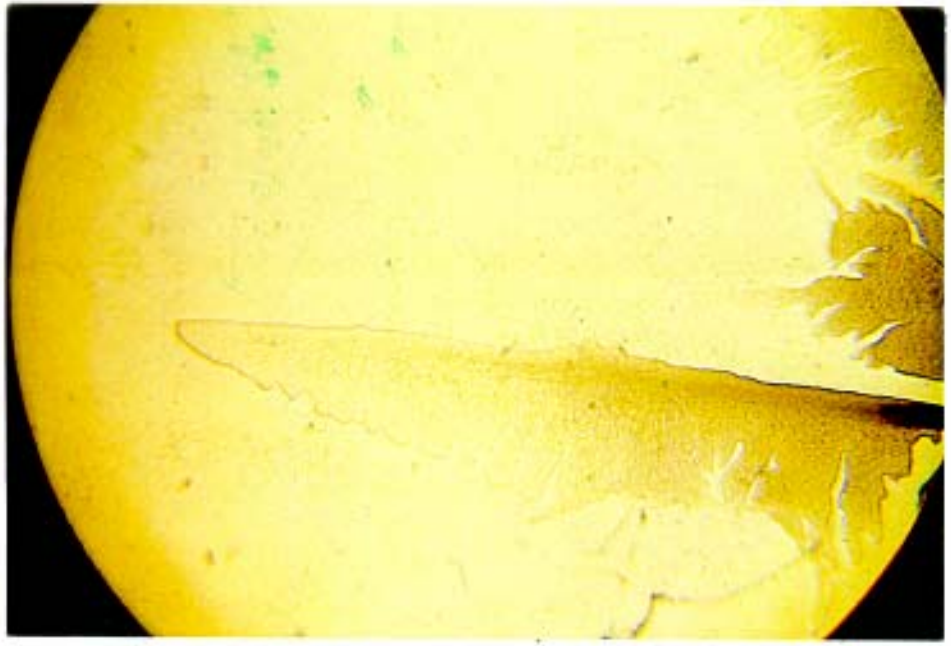
- We need to make nontrivial predictions that don't depend on all the details that are left out of the model – quite an art form!
- Examples

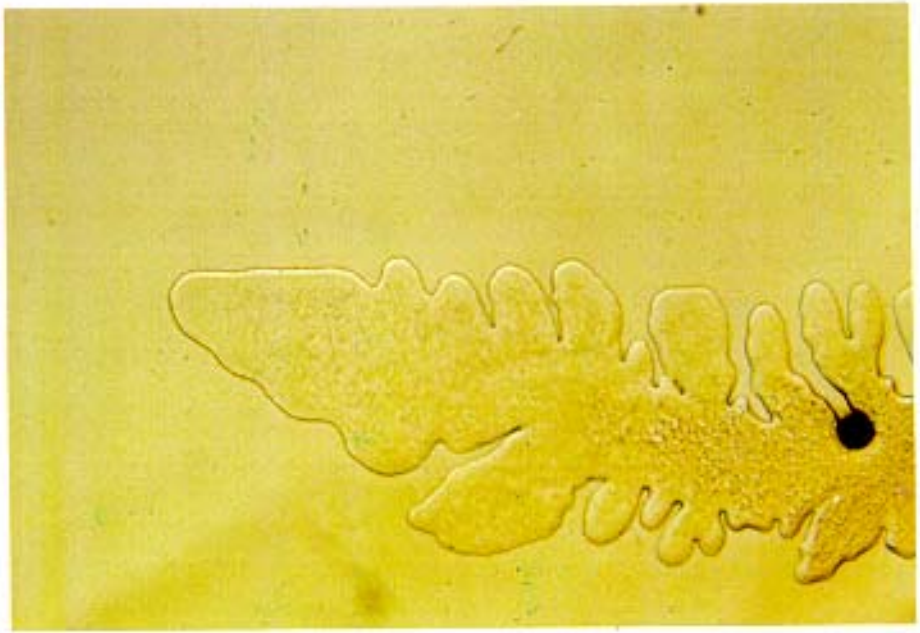
  -phase diagrams

  -effects of perturbations (e.g. anisotropy)

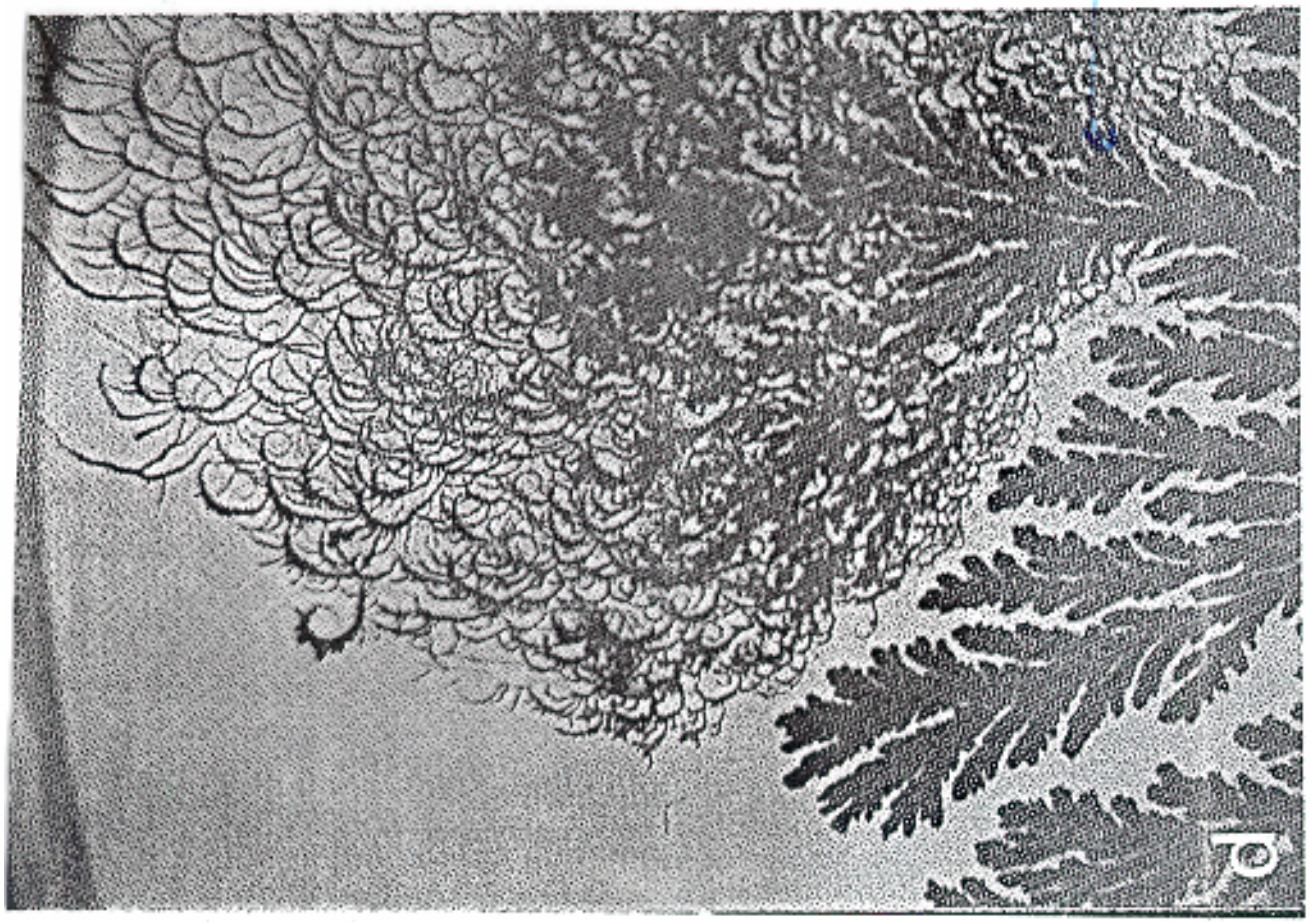
  -similarities in behavior of different species

It would be great to have a full model, but this is just not possible for any biocomplexity scale problem





Cells can do more than molecules!

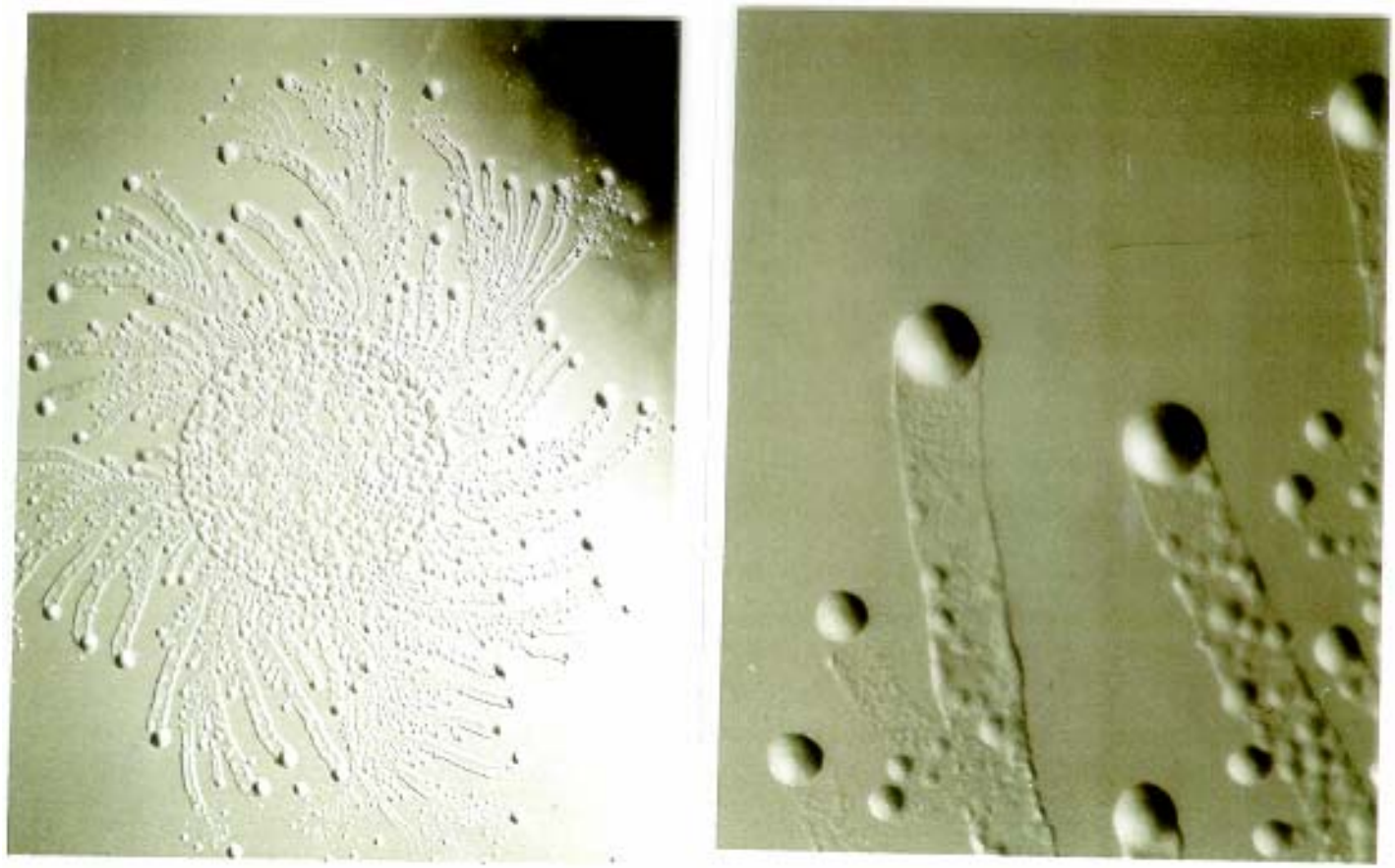


Heritable change

From branching to chiral

Chirality due to the flagellum

Vortex structures in bacteria

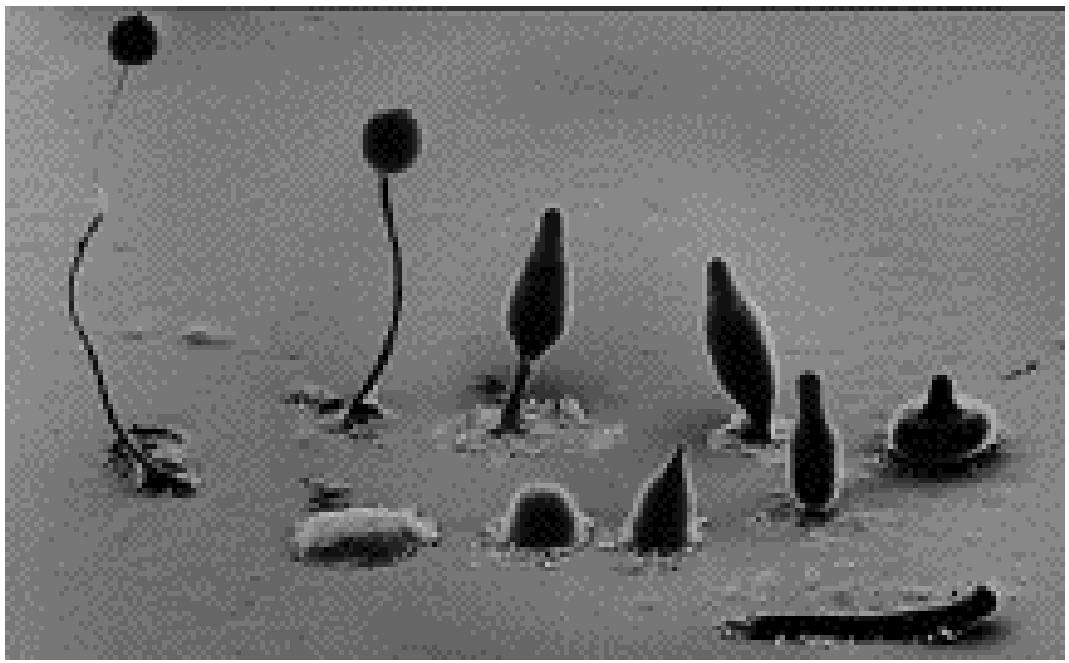


No reason to believe in chemical wave guidance

Conclusions

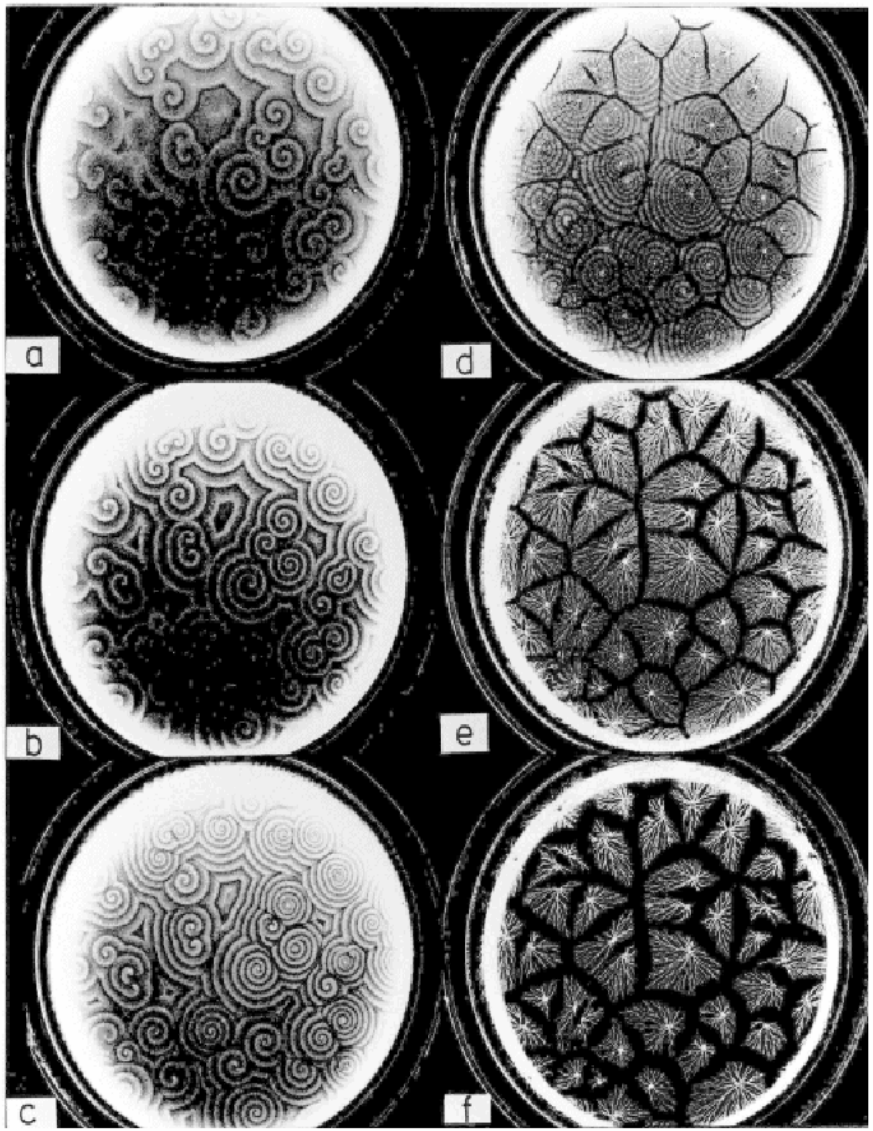
- Bacteria can make an extraordinary series of remarkable patterns in space and time
- One can make progress in understanding these patterns by building on intuition from patterns in nonliving systems and then adding in specific information about the biological system at hand
- We cannot just model everything microscopically since we often don’t know all the ingredients and in any case we don’t know how much resolution is needed (MD simulations – millions of simple molecules over microseconds; here, billions of bacteria over weeks)
- Insight into critical ingredients is necessary and is of course generated by testing simplified models versus experiment.

Dictyostelium amoebae
a motion-dominated lifecycle



After starvation, cells aggregate, differentiate, sort and cooperate to create a functional multicellular organism

24 hour life-cycle of Dictyostelium – courtesy of R.Blanton



Courtesy – P. Newell

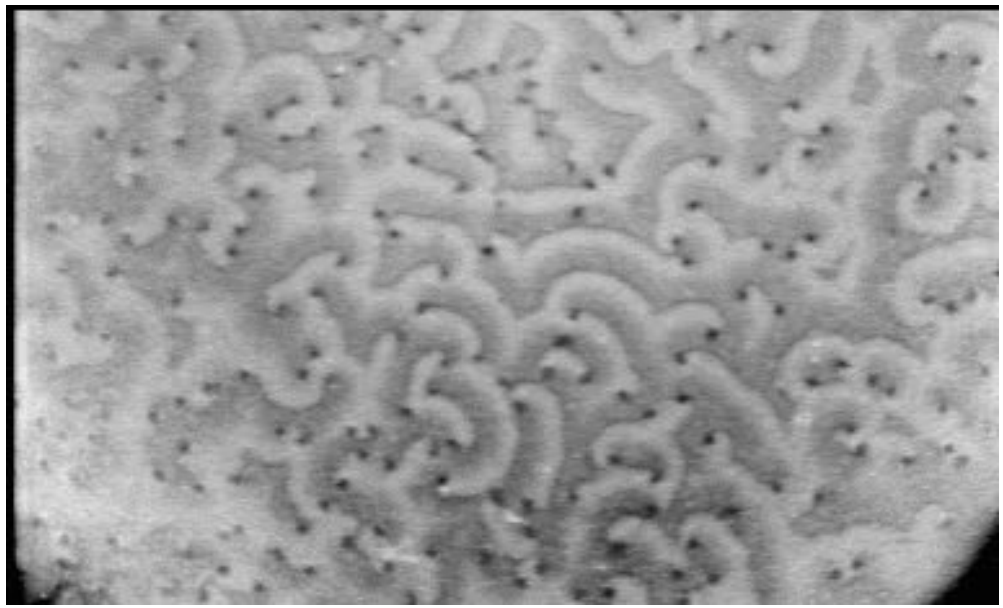
Aggregation stage is fairly well-understood

- cAMP excitable signaling
- Chemotactic response
- Streaming instability

-> mound formation

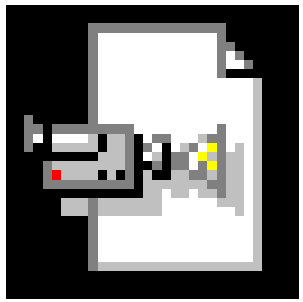
Research focus has shifted to trying to understand the cell biology of chemotaxis to spatio-temporal signals

Aggregation (4h)



Dark field waves of D. discoideum cells.
From F. Siegert and C. J. Weijer, J. Cell Sci. 93, 325-335(1989).

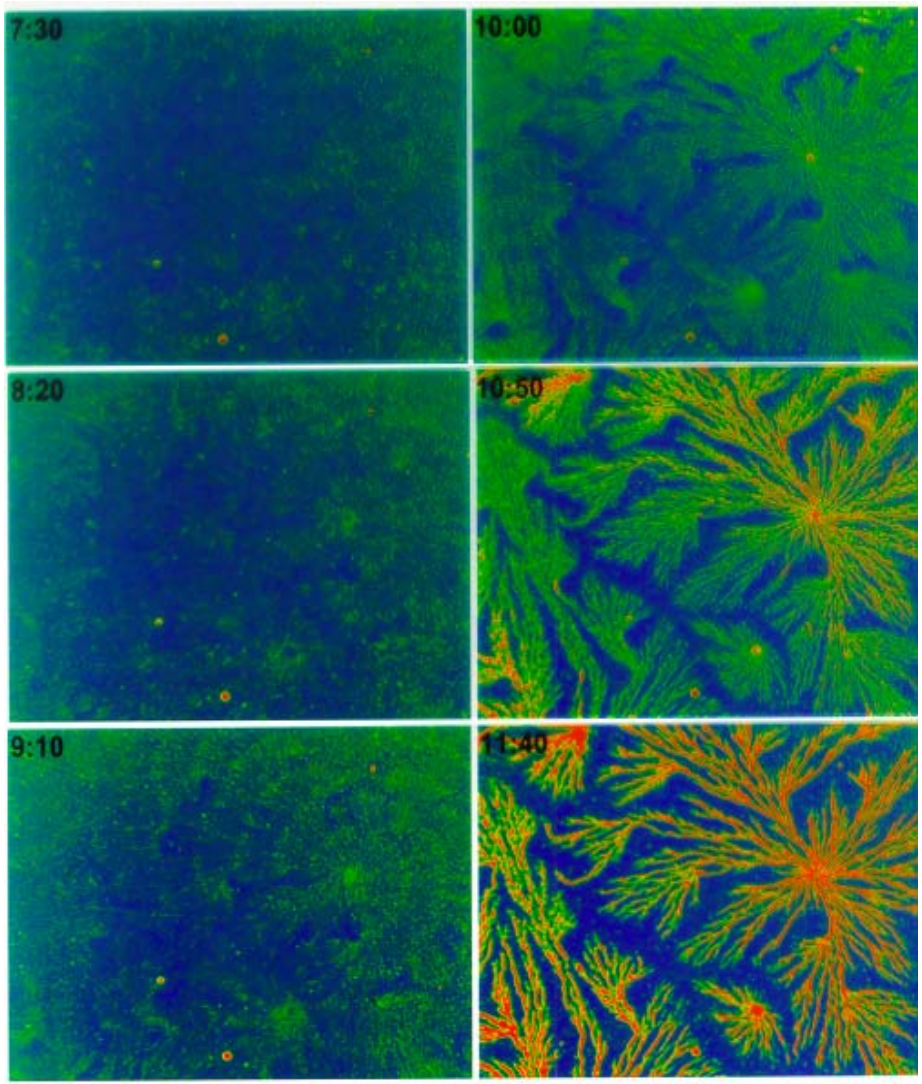
Close-up view of chemotaxis



Video Clip

Courtesy of C. Weijer

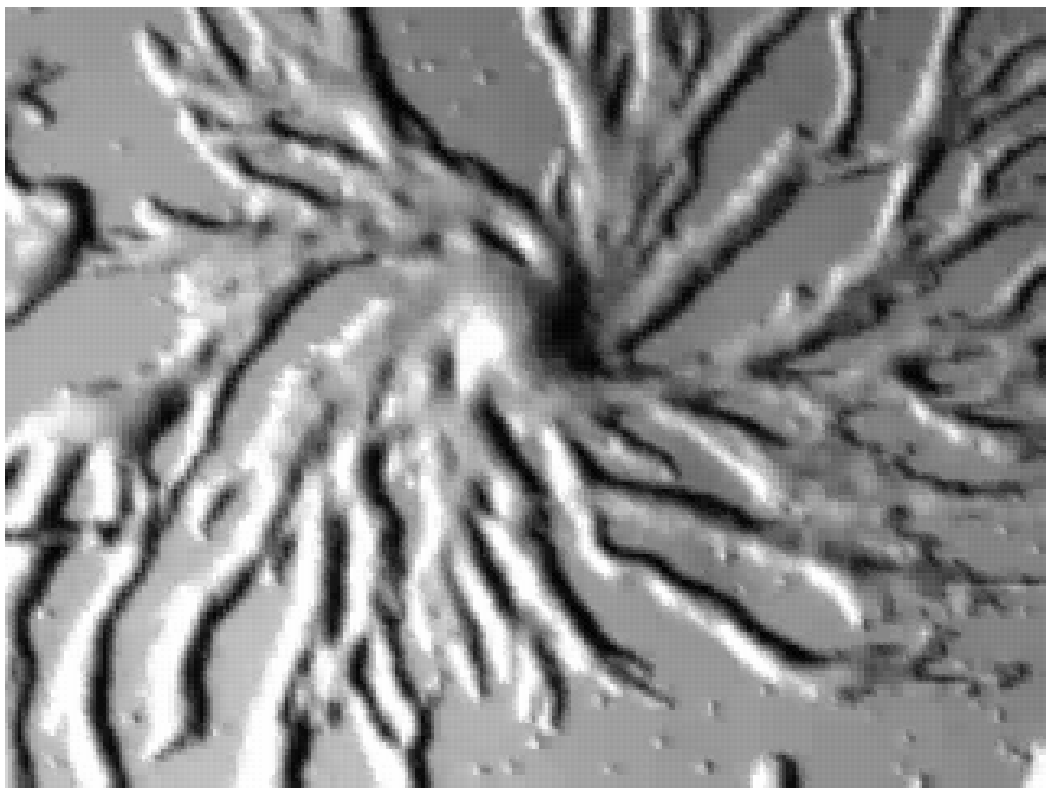
Formation of streaming pattern



Collapse to the mound
is not radially symmetric

Courtesy: R. Kessin

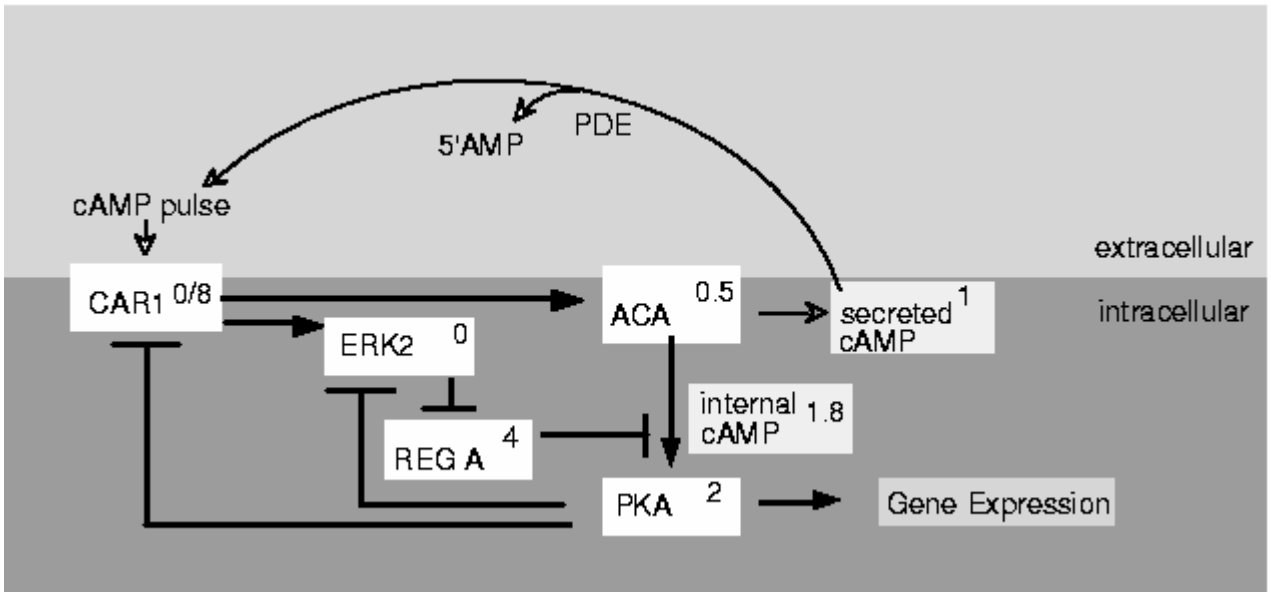
Streaming into the mound



Fruiting body formation

Much is understood about the network underlying cAMP Signaling

- Non-responsive -> Excitable -> oscillatory as cell ages
- Several models exist (each with weaknesses)
- In each cycle, there is a host of measurable changes, including internal cAMP, cGMP rise, Ca influx, actin polymerization ..



Excitable media modeling

How can we use the reaction-diffusion framework to understand the nature of waves in this system?

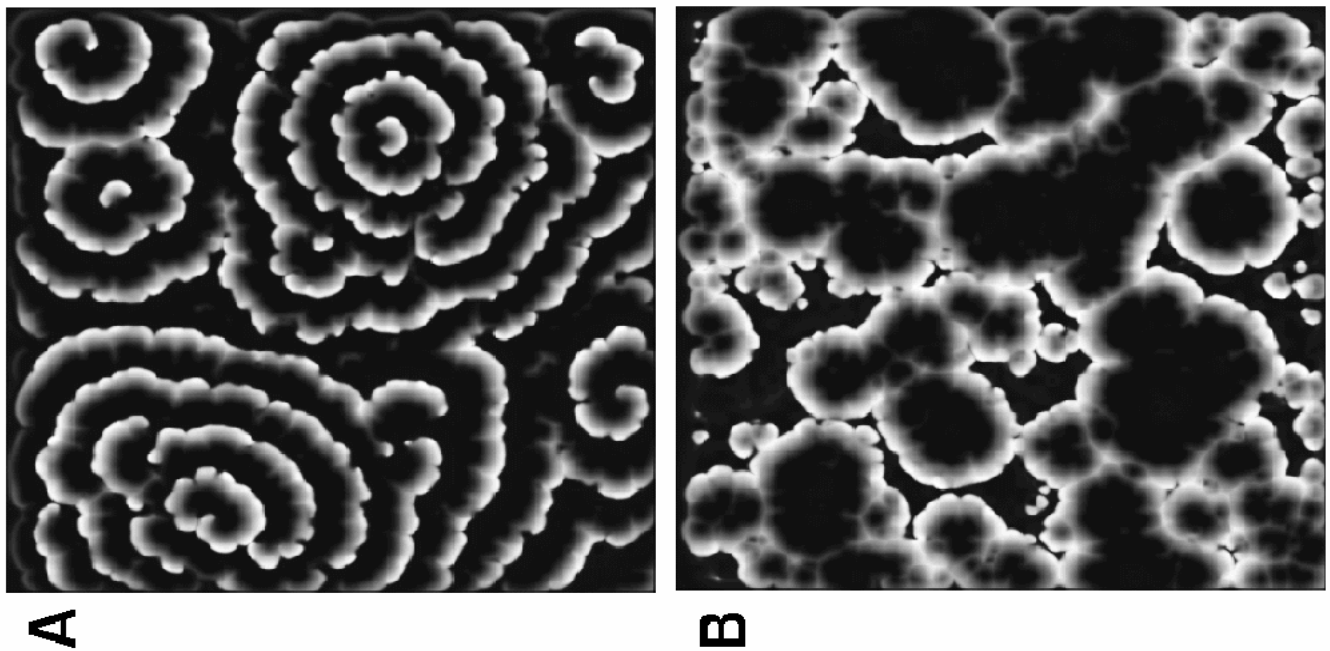
Genetic Feedback Model

We need wave-breaking to get spirals – where does the large inhomogeniety come form?

Our proposal – excitability is varying in time, controlled by the expression of genes controlling the signaling which in turn are coupled to cAMP signals

1. This accounts for observed history of the wavefield; abortive waves -> fully developed spirals
2. This naturally gives wave-breaking during weakly excitable epoch
3. Specific predictions: spiral coarsening via instability and failure of spiral formation after re-setting

Wave-resetting simulation



M. Falcke + H. Levine, PRL 80, 3875 (1998)

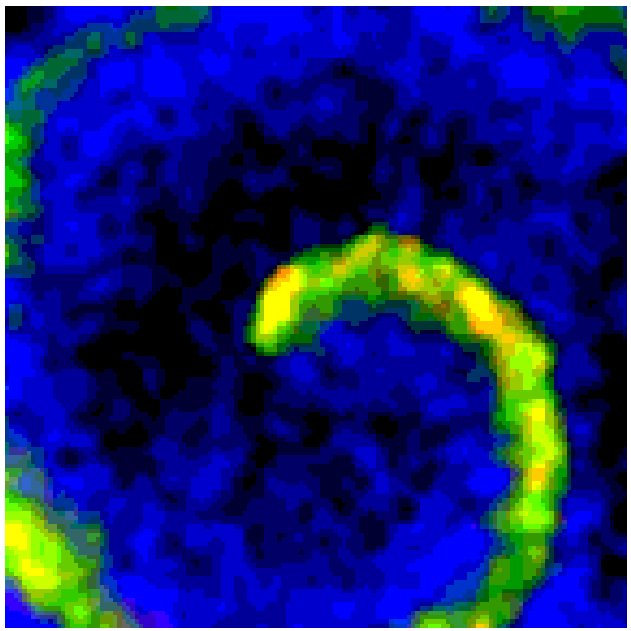
Dicty conclusions

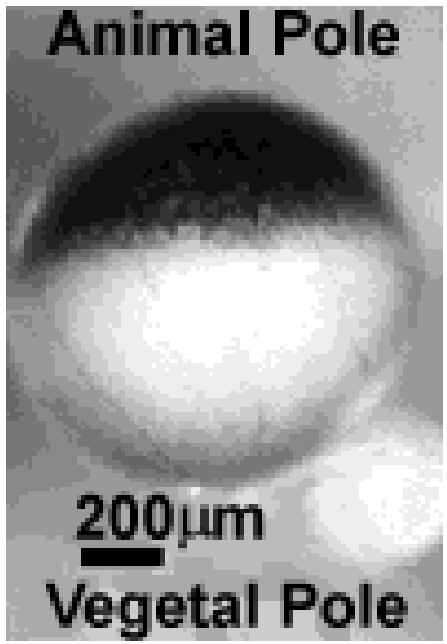
- Again, we can use concepts from physics to help unravel a complex pattern-forming process
- Some biological detail can (and needs to be!) ignored for some questions; but this needs constant revisiting as models are compared to data
- Critical role for experiments which test the underlying mechanisms proposed by models, not just the quantitative details
- Focus is shifting to understanding the single cell response

Stochastic effects in Intracellular Calcium Dynamics

- Some experimental systems
- Stochastic versus deterministic models

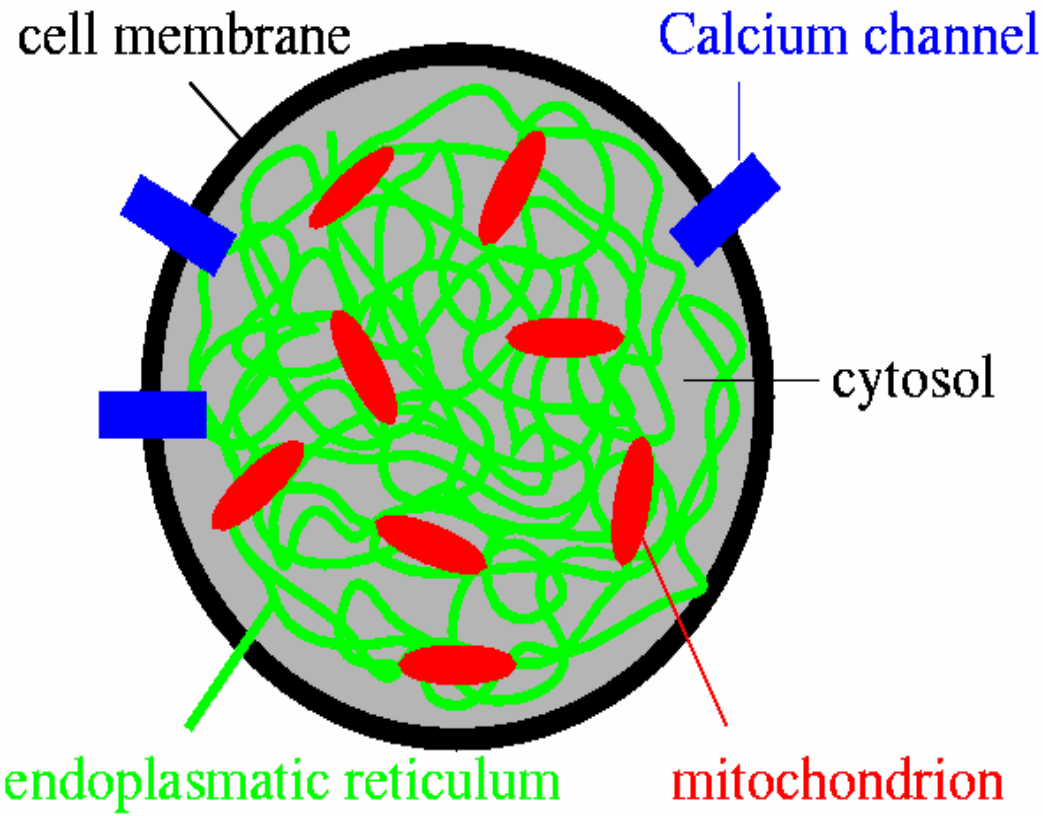
Spiral wave in Xenopus Oocytes





From I. Parker,
UC Irvine

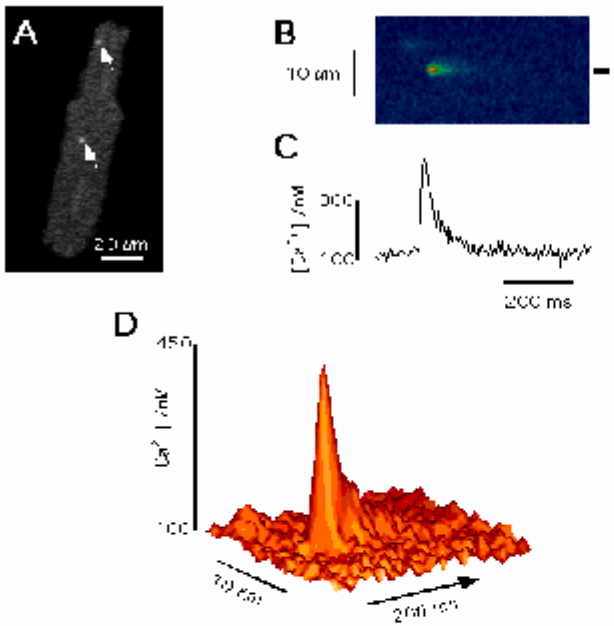
Elements of Calcium handling in a Cell



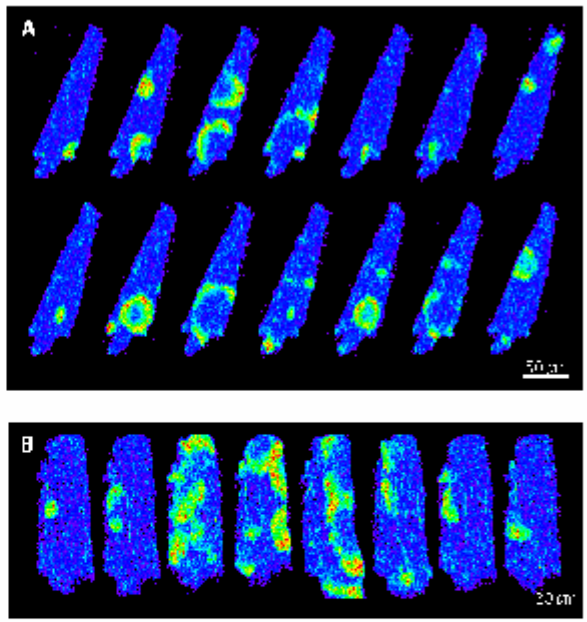
The picture holds for large cells: 0.1-1mm

Mitochondria and the endoplasmatic reticulum are nonlinear Calcium stores.

Calcium dynamics in myocytes



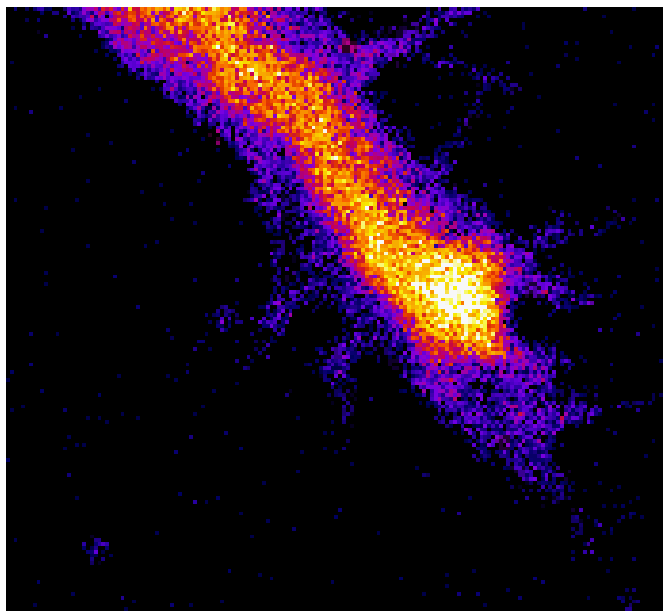
Calcium spark in a cardiac myocyte

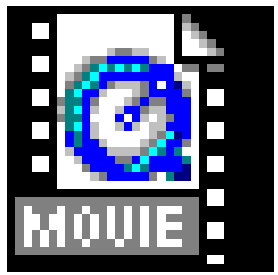


Spontaneous Calcium waves in cardiac myocyte

From: http://www.meddean.luc.edu/lumen/DeptWebs/physio/blatter.html
Web site of L.A.Blatter, Loyola University Chicago

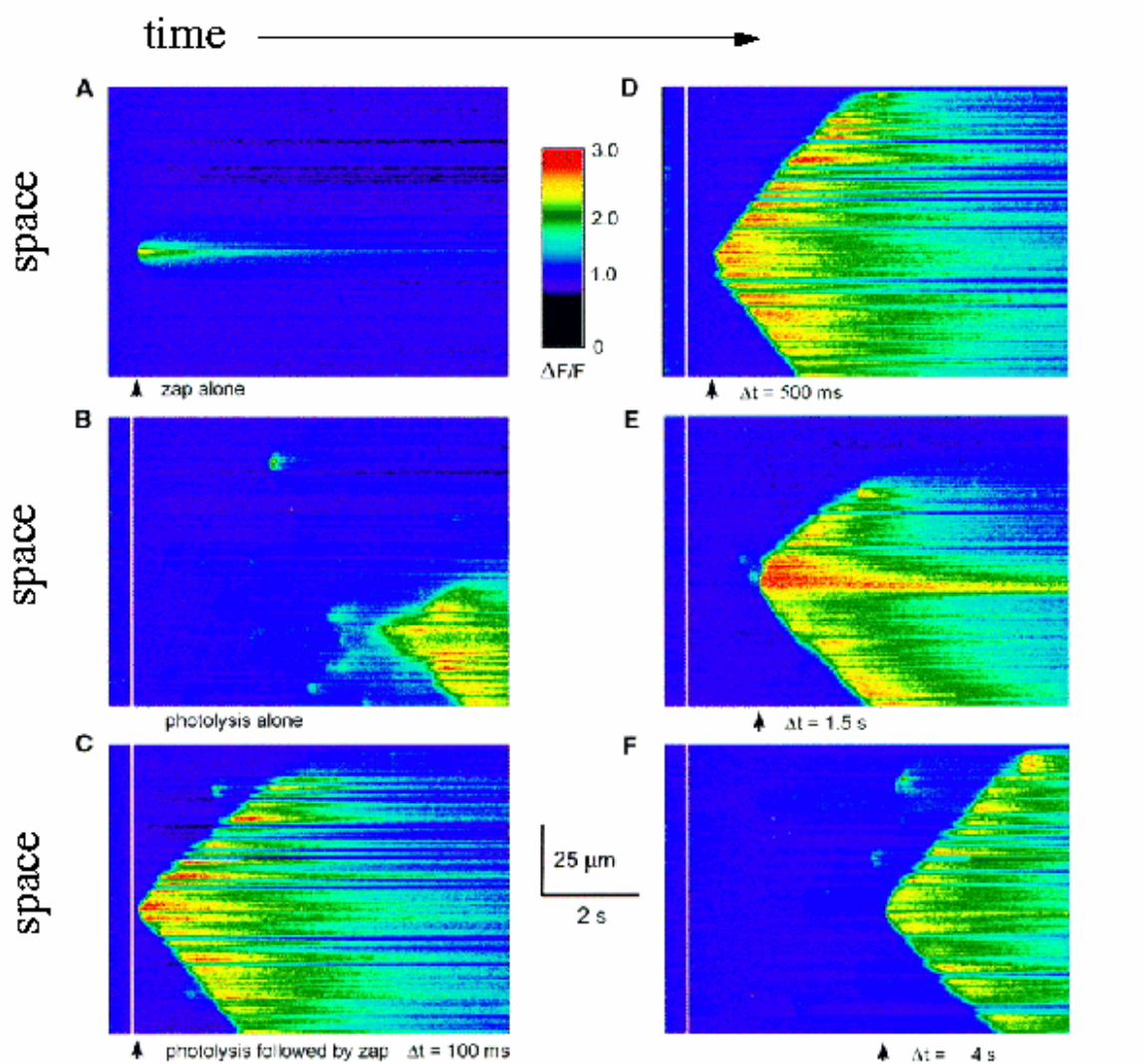
Calcium dynamics in Xenopus neurons (Spitzer lab – UCSD)





QuickTime Movie

Wave Initiation experiment



Ca+ line scans
IP_3 released at line

Marchant et al
EMBO (1999)

Review of oocyte results

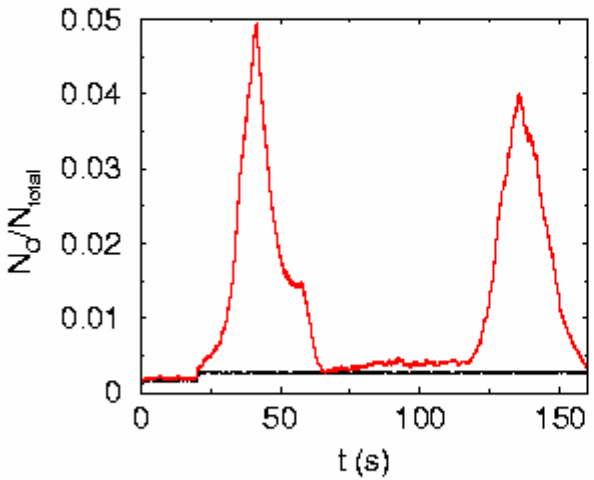
- Many types of nonlinear patterns (puffs, abortive waves, propagating waves ..) can be seen in the Xenopus oocyte system
- Experimentally, there is clear evidence of the importance of stochastic IP_3 channel dynamics such as spontaneous firings and abortive waves
- We have attempted to construct a stochastic model based on the deYoung-Keizer kinetic scheme so as to investigate these phenomena.

Modeling the role of stochasticity

What types of models can shed light on these possible effects that noise (in the form of channel and openings and closings) can have on the pattern-forming dynamics?

Wave Initiation Simulation

fraction of open channels



N=109 } same deterministic limit

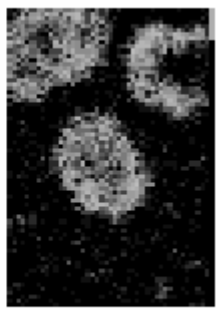
N=27

No wave in deterministic limit !

IP_3 increased from 0.17 to 0.22 μM at t=20s.

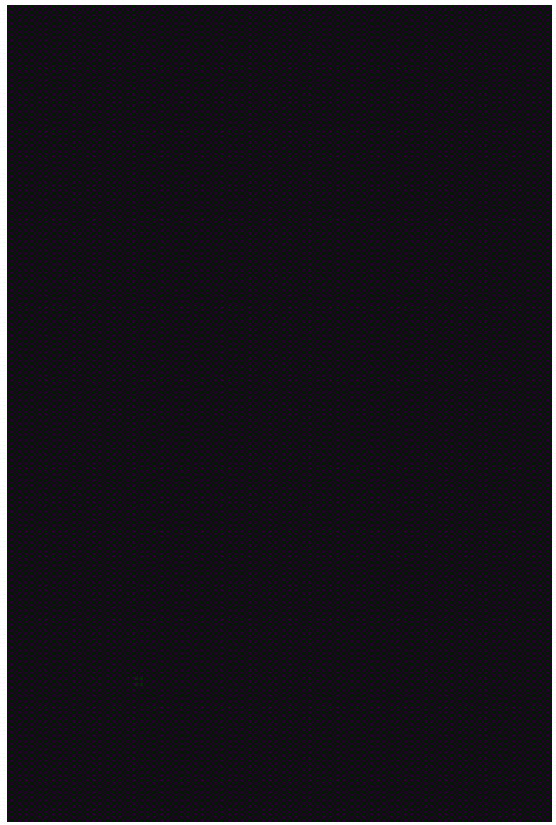
t=24.33s

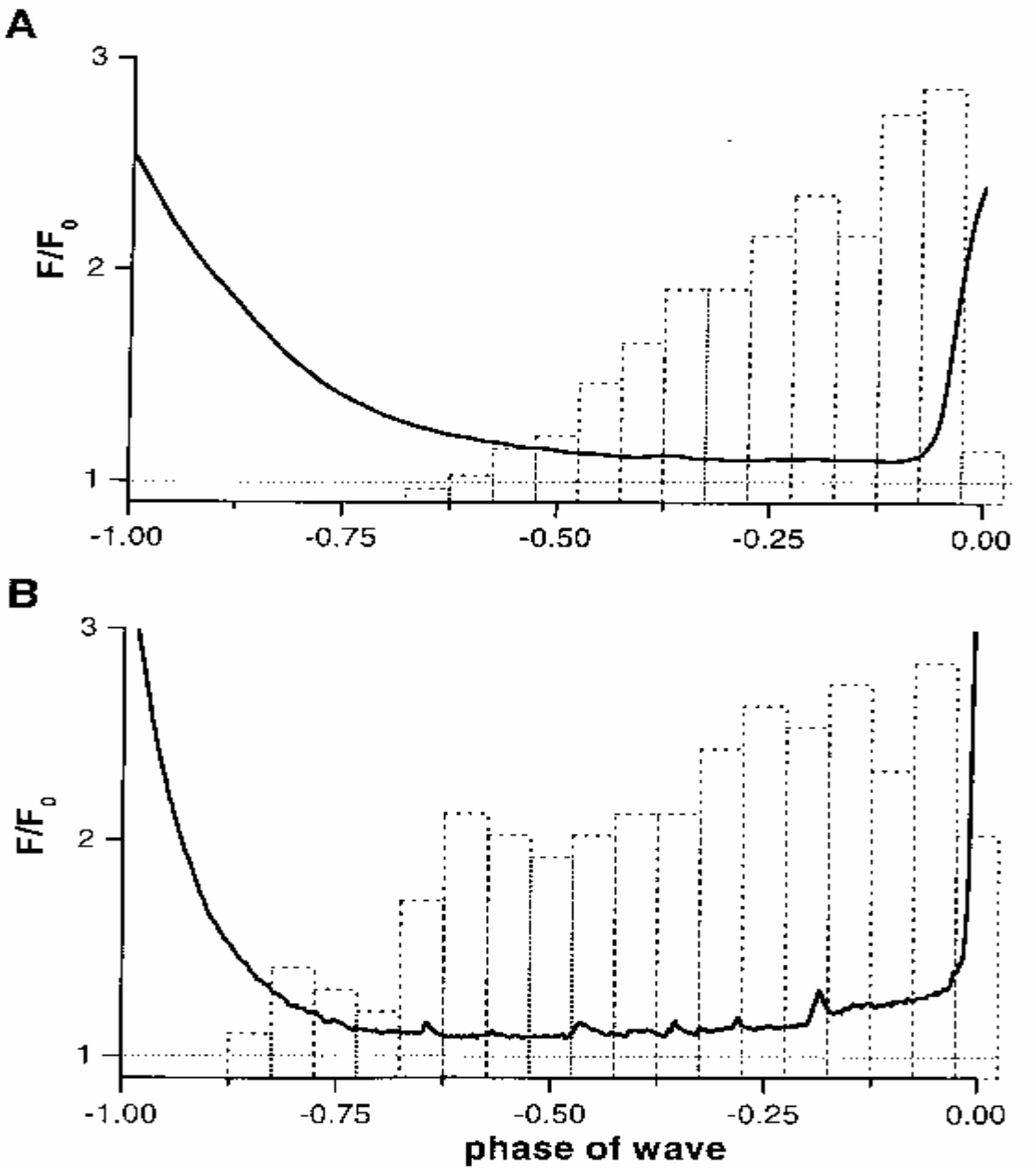
t=28.23s



t=38.20s

The movie version!





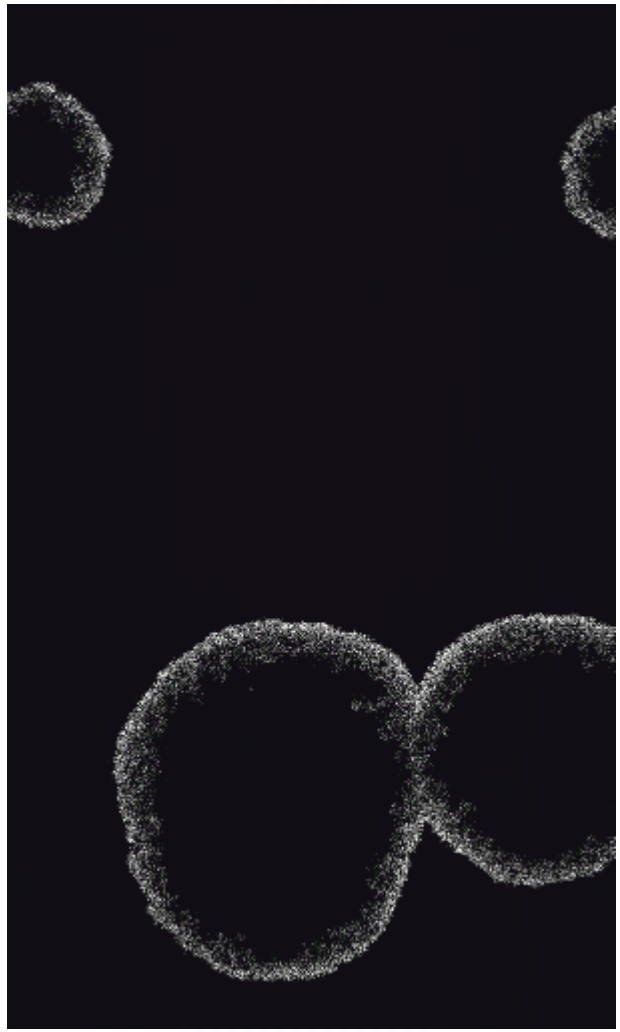
Puff distribution data (Parker et al, UCI)

More excitable – single puff can excite a wave, after recovery period

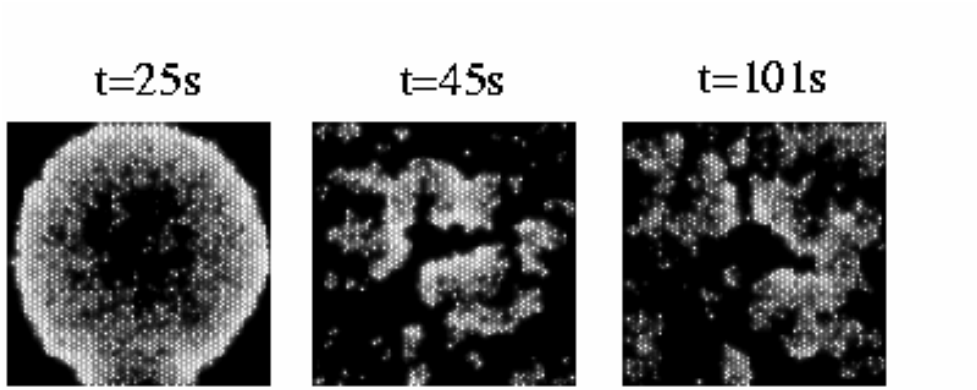
Less excitable: need a cooperative increase in background Ca level

Backfiring in 2 dimensions

Simulation of the stochastic model with an intermediate number of channels



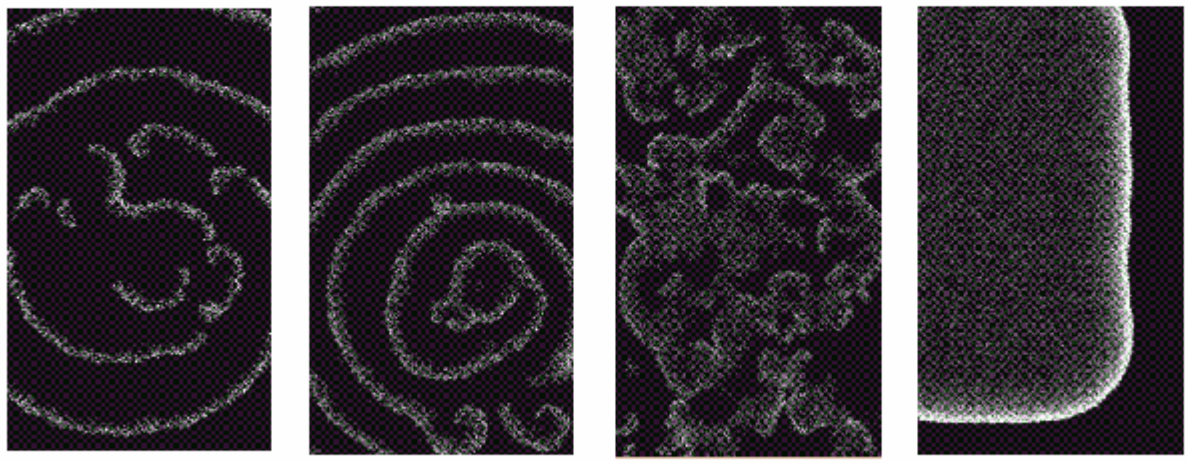
Backfiring can also lead to a spatio-temporal disordered state.



Transition to deterministic behavior

4 simulations, same deterministic limit, IP_3=0.175μM:

shown 1.57 x 1.31 mm^2



N=23 N=35 N=47 N=71