The Physics of Life: Spatial Population Genetics

I. Introduction to spatial population genetics

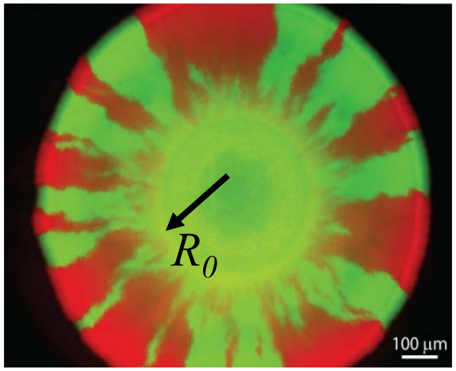
K. Korolev et al., Reviews of modern physics 82, 1691 (2010)

II. Pushed genetic waves and antagonistic interactions

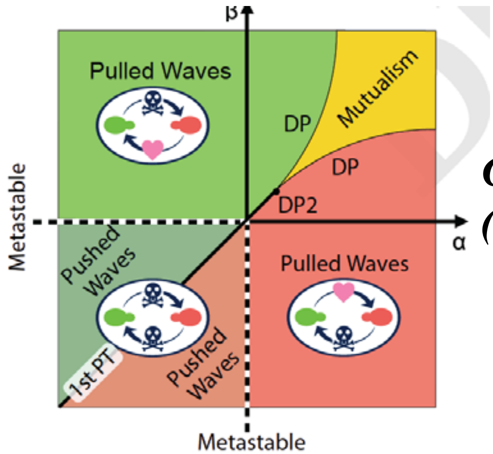
H. Tanaka et al., Proceedings of the National Academy of Sciences 114, 8452 (2017); M. Lavrentovich & drn, arXiv:1907.07865.

III. Microbial interactions and expansions on liquid substrates

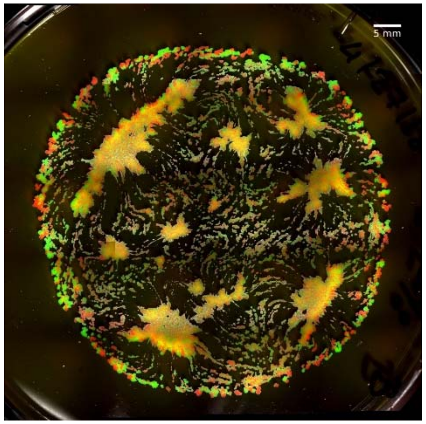
S. Atis et al. Physical Review X9, 021058 (2019): 021058.



P. Aeruginosa (J. Xavier et al.)

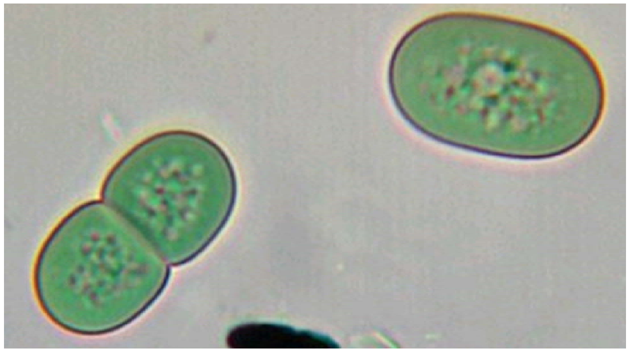


Game theory: (E. Frey et al.)



S. cerevisea (S. Atis et al.)

Motivation: Life probably evolved first in a *liquid* environment



Cyanobacterium *Synechococcus*

- ***~2-3 billion years ago, like today, water covered most of the earth***

- ***Fossilized, oxygen-producing cyanobacteria have been dated at ~2 billion years ago.***

- ***Oxygenic cyanobacteria transformed the atmosphere via photosynthesis***

- ***Their spatial growth and evolutionary competition took place in <u>liquid</u> environments at both high and low Reynolds numbers***

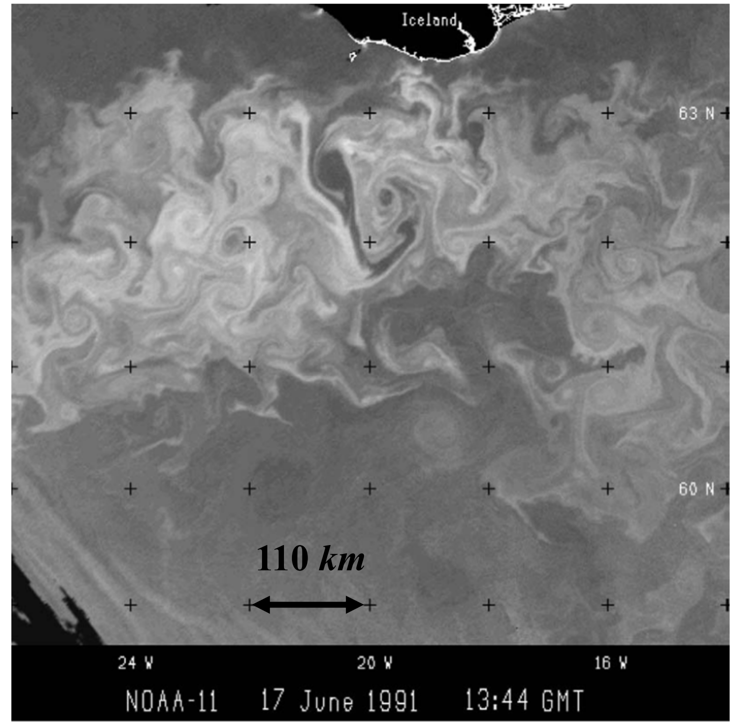
- ***These photosynthetic organisms control their height to resist down welling currents and stay close to the ocean or lake surface.***

Bloom of cyanobacteria
in Lake Atitlán, Guatemala
NASA Earth observatory

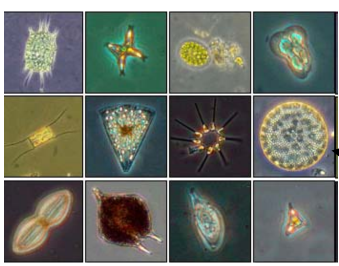
Striated plankton populations in oceanic flows

Phytoplankton blooms at high Reynolds number in the Norwegian Sea and near Iceland

http://visibleearth.nasa.gov/cgi-bin/viewrecord?5278
.see also, Tel. et al. Phys. Rep. **413**, 91 (2005).



A. P. Martin, Prog. Oceanography **57**, 125 (2003)



mixing layer ≈ *25-100* m.

Phytoplankton
(see also zooplankton
& bacterioplankton)

http://earthobservatory.nasa.gov/Experiments/ICE/Channel_Islands/

$Re = LU / \nu = 10^8 - 10^9$

Large eddy turnover time ≈ 50 days

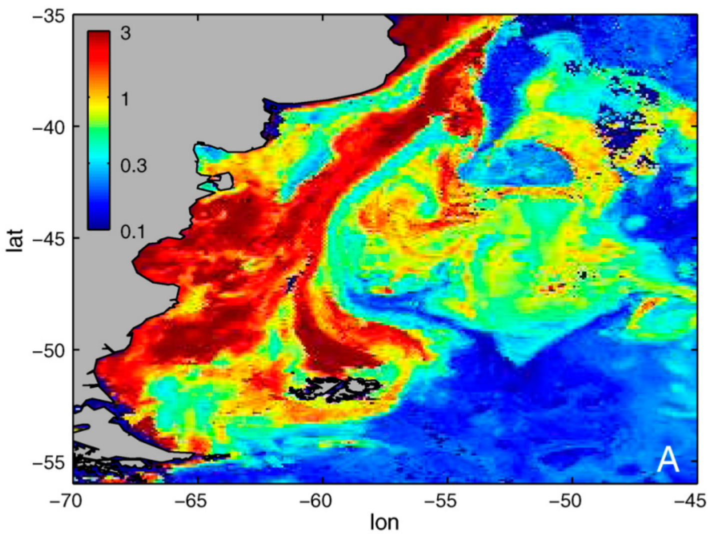
Small eddy turnover time ≈ 5 minutes

Plankton doubling time ≈ 12-24 hours

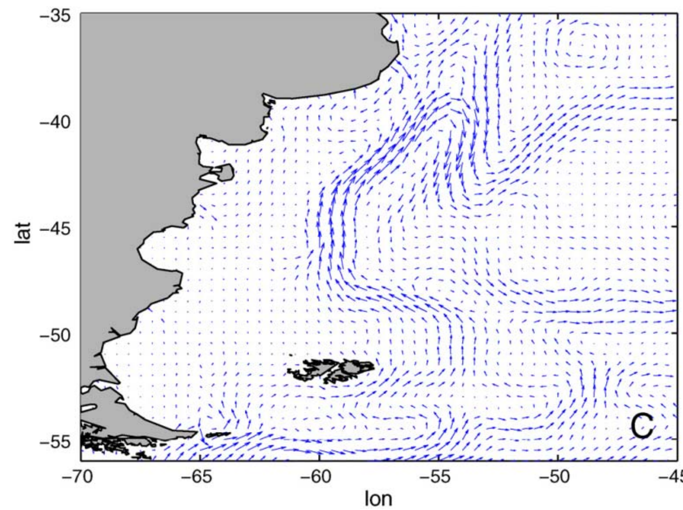
Fluid dynamical niches of phytoplankton types

PNAS 107, 18366 (2010)

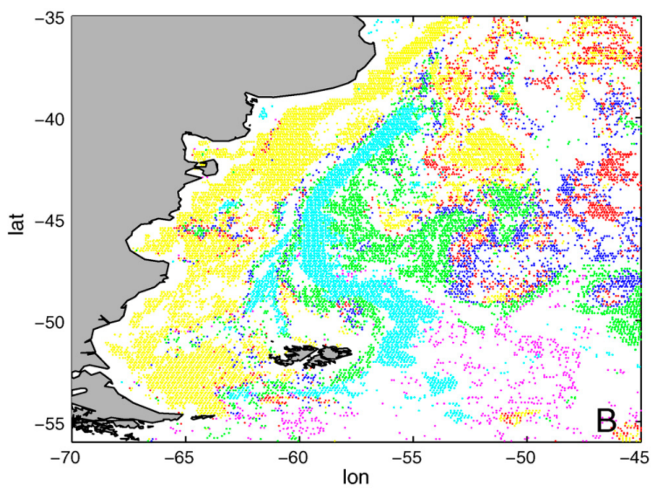
Francesco d'Ovidio[a,b,1], Silvia De Monte[c,d,e,1,2], Séverine Alvain[f], Yves Dandonneau[b], and Marina Lévy[b]



Chlorophyll map



Velocity field from altimetry



Dominant species types

diatoms (green)
Prochlorococcus (red)
Synechococcus (dark blue)
nanoeukaryotes (yellow)
Phaeocystis (magenta)
coccolithophorids (cyan).

Compressible advection of microorganism density *c(x,t)*

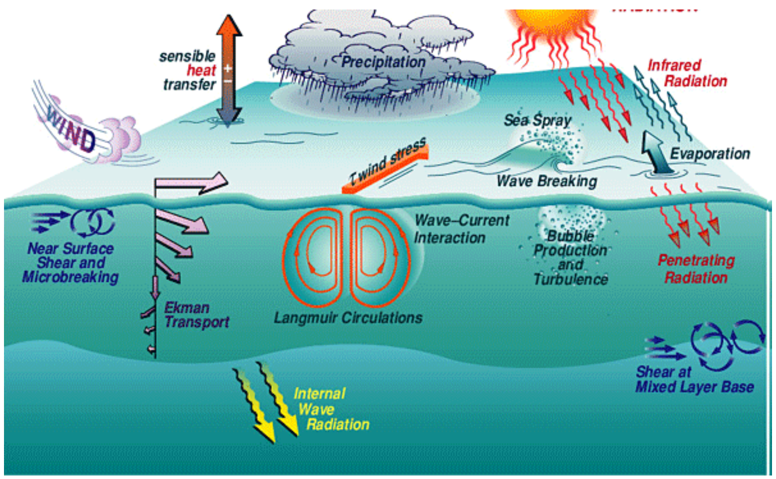
$$\frac{\partial}{\partial t}c(\vec{x},t)+\nabla\cdot[\vec{u}(\vec{x},t)c(\vec{x},t)]=D\nabla^2 c(\vec{x},t)+\mu c(\vec{x},t)[1-c(\vec{x},t)]$$

$$\vec{\nabla}\cdot\vec{u}(\vec{x},t)\neq 0$$

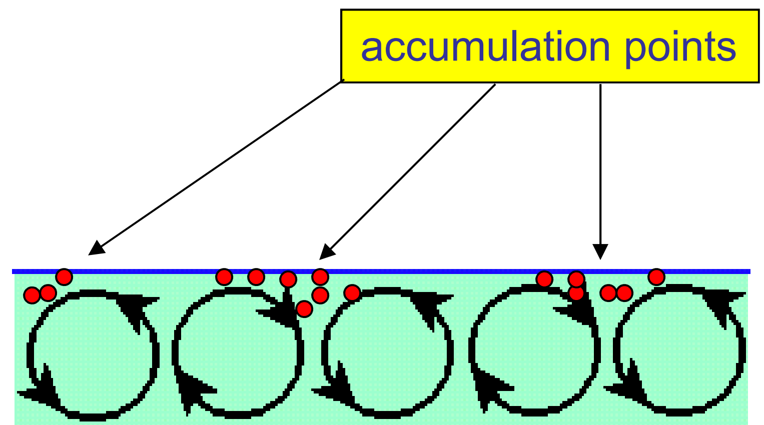
$u(\vec{x},t)$ is an effective $2d$ compressible turbulent velocity field....

μ is the growth rate...

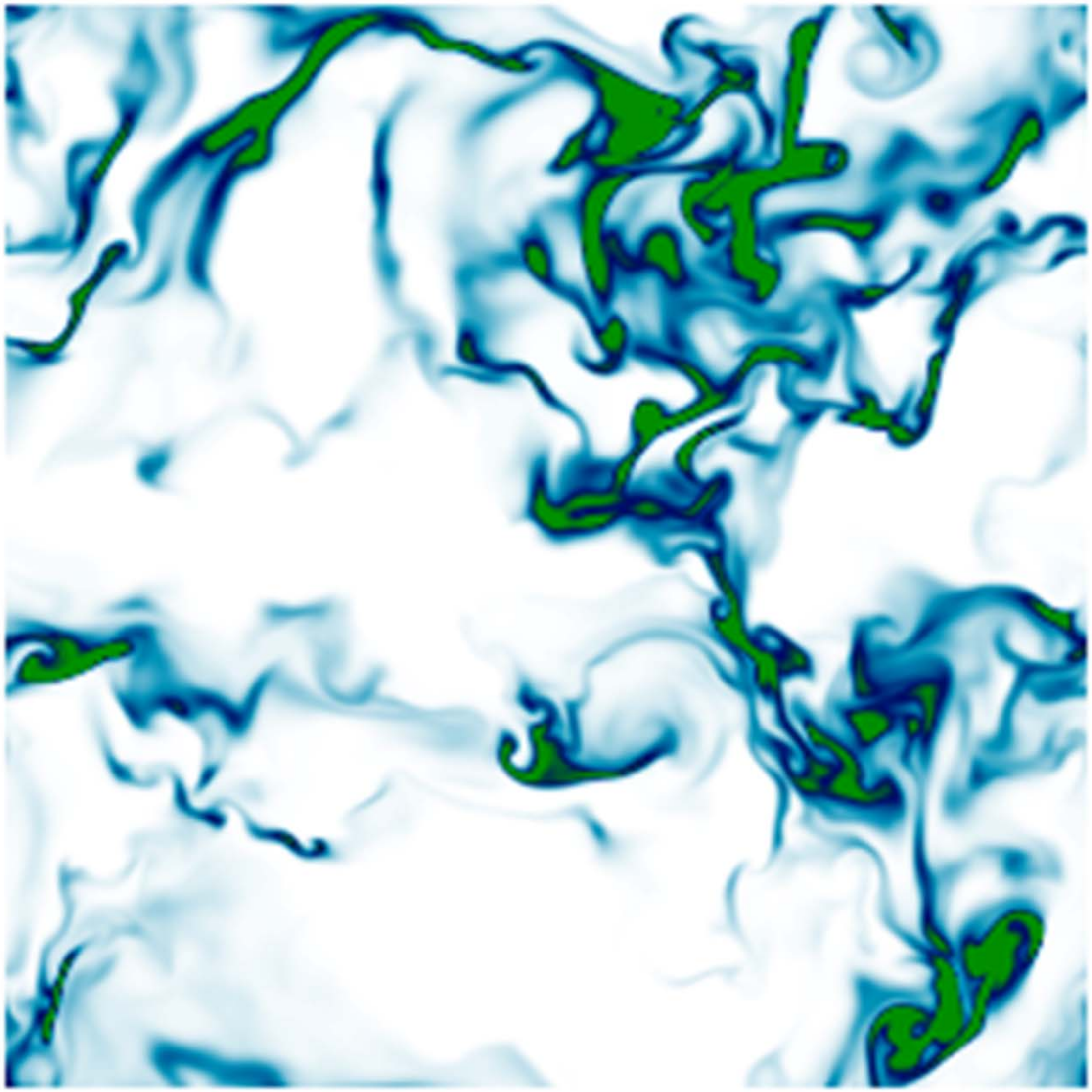
Advection by an effectively compressible two dimensional velocity field results for organisms that actively control their buoyancy to stay close to the ocean surface.



Uop.whoi.edu/projects/projects.htm



Buoyant population dyanamics in Silico (Perlekar, Toschi, Benzi, drn)



$$\frac{\partial \vec{u}}{\partial t} + \vec{u} \cdot \vec{\nabla} \vec{u} = -\frac{1}{\rho} \vec{\nabla} p + \nu \nabla^2 \vec{u} + \vec{f}$$

project onto a 2d plane $\rightarrow \vec{\nabla} \cdot \vec{u}_{2d} \neq 0$

$$\frac{\partial c}{\partial t} + \nabla \cdot (\vec{u}_{2d} c) = D \nabla^2 c + \mu c (1 - c)$$

Reynolds number

$$Re = \frac{u_{\rm rms} L}{\nu}$$

Schmidt number

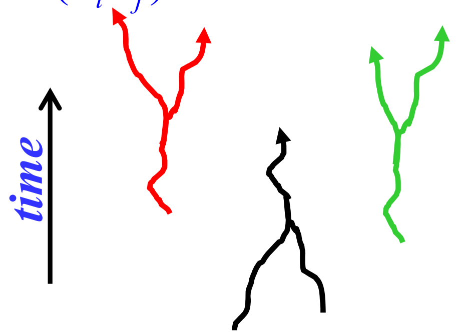
$$Sc = \frac{\nu}{D}$$

Doubling time/eddy turnover time

$$\tau_2 / \tau_{eddy} \sim 1/(\mu \tau_{eddy})$$

Compressible population genetics with two interacting species

Compressible turbulent flow (Re ~10^{5}) $\kappa = < (\vec{\nabla}\cdot\vec{u})^2 > / < (\partial_i u_j)^2 > = 0.17$



Agent-based simulation:
"Survival of the luckiest"

(Pigolotti et al. T*heo. population biology* **84,** 72 (2013)

Wanted: simplified model systems and/or repeatable experiments that explore how fluid flows affect spatial population genetics….

- ***High Reynolds numbers might be hard to achieve in the laboratory, but low Reynolds numbers can also be biologically relevant***
- ***Can we impose flows with reproduction times $\tau_2 \sim 1/\mu << \tau_{eddy}$, where τ_{eddy} is a eddy turnover time?***

Simplified reaction-diffusion model of competition with a prescribed flow field

Compare lecture II:

$\varepsilon_A \leftrightarrow \alpha; \quad \varepsilon_B \leftrightarrow \beta$

Governing equations

go to board

$$\frac{\partial c_A}{\partial t} + \nabla \cdot (\mathbf{u} c_A) = D\nabla^2 c_A + c_A(1 - c_A - c_B + \epsilon_A c_B)$$

$$\frac{\partial c_B}{\partial t} + \nabla \cdot (\mathbf{u} c_B) = D\nabla^2 c_B + c_B(1 - c_B - c_A + \epsilon_B c_A)$$

Flow

$$u_x(x, y) = F[\alpha \sin(2\pi x/L) + (1 - \alpha)\sin(2\pi y/L)]$$

$$u_y(x, y) = F[\alpha \sin(2\pi y/L) + (1 - \alpha)\sin(2\pi x/L)]$$

Parameters

$$D = 10^{-4}, L = 1, \alpha = 0, \epsilon_A = -0.2, \epsilon_B = -0.3$$

Dynamics of Total c_T & A-Fraction f (1)

Scalar

(1) $$\frac{\partial c_A}{\partial t} + \nabla \cdot (\mathbf{u} c_A) = D\nabla^2 c_A + c_A(1 - c_A - c_B + \epsilon_A c_B)$$

(2) $$\frac{\partial c_B}{\partial t} + \nabla \cdot (\mathbf{u} c_B) = D\nabla^2 c_B + c_B(1 - c_B - c_A + \epsilon_B c_A)$$

$\epsilon_A, \epsilon_B < 0$

Flow

$$u_x(x,y) = F[\alpha \sin(2\pi x/L) + (1-\alpha)\sin(2\pi y/L)]$$
$$u_y(x,y) = F[\alpha \sin(2\pi y/L) + (1-\alpha)\sin(2\pi x/L)]$$

Parameters

$$D = 10^{-4}, L = 1, \alpha = 0, \epsilon_A = -0.2, \epsilon_B = -0.3$$

* Change of variables, let $c_T = c_A + c_B$, $f = \frac{c_A}{c_A + c_B} = \frac{c_A}{c_T}$, $\frac{c_B}{c_T} = 1 - f$

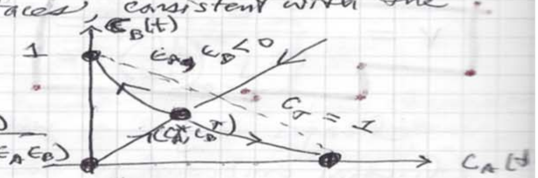
add (1) & (2) $\Rightarrow$ $$\frac{\partial}{\partial t}(c_A + c_B) + \vec{\nabla} \cdot (\vec{u} c_T) = D\nabla^2 c_T + c_T(1 - c_T) + (\epsilon_A + \epsilon_B) c_A c_B$$

$$\frac{\partial}{\partial t}(c_T) + \vec{\nabla} \cdot (\vec{u} c_T) = D\nabla^2 c_T + c_T(1 - c_T) + (\epsilon_A + \epsilon_B) c_T^2 f(1-f)$$

$$\sigma = -\frac{\epsilon_A + \epsilon_B}{2}$$

So... even when $c_T \approx 1$, $$\frac{\partial c_T}{\partial t} \approx -2\sigma f(1-f)$$

So the antagonism parameter σ decreases the total population at A/B interfaces, consistent with the well mixed dynamics associated with Eqs (1) & (2) (see Pigolotti et al.)



(Pigolotti et al. Fig. 2)

Hyperbolic fixed point at $(c_A^*, c_B^*) = \frac{(\epsilon_A, \epsilon_B)}{(\epsilon_A + \epsilon_B - \epsilon_A \epsilon_B)}$

but $c_T \approx 1$, provided $|\epsilon_A + \epsilon_B| << |\epsilon_A \epsilon_B|$

$\Rightarrow$ at the fixed point $c_A^* + c_B^* = 1 + \frac{\epsilon_A \epsilon_B}{|\epsilon_A + \epsilon_B| - \epsilon_A \epsilon_B} = O(\epsilon_A, \epsilon_B)$

* What is the dynamics of $f(\vec{x},t)$? — First we study the <u>well-mixed</u> case...

$$\frac{df}{dt} = \frac{1}{c_T}\frac{dc_A}{dt} - \frac{c_A}{c_T^2}\frac{dc_T}{dt}$$

$$= (1 - c_A - c_B + \epsilon_A c_B) f - \frac{f}{c_T}\left[(1-f)c_T + (\epsilon_A + \epsilon_B) c_T^2 f(1-f)\right]$$

* Everything simplifies provided $\epsilon_A, \epsilon_B \ll 1 \Longleftrightarrow c_T \approx 1$

$$\frac{df}{dt} = \epsilon_A f(1-f) - [\epsilon_A + \epsilon_B] f\, f(1-f), \text{ or}$$

$$\frac{df}{dt} = f(1-f)\left[\epsilon_A - (\epsilon_A + \epsilon_B) f\right] \qquad \begin{cases} \epsilon_A - \epsilon_B = \delta \\ \frac{\epsilon_A + \epsilon_B}{2} = -\sigma \end{cases} \Longleftrightarrow \begin{array}{l} \epsilon_A = \frac{\delta}{2} - \sigma \\ \epsilon_B = -\frac{\delta}{2} - \sigma \end{array}$$

$$\therefore \epsilon_A - (\epsilon_A + \epsilon_B) f = \left(\frac{\delta}{2} - \sigma\right) + 2\sigma f$$

$$= \frac{\delta}{2} + \sigma(2f - 1) \quad \&$$

$$\boxed{\frac{df}{dt} = f(1-f)\left[\frac{\delta}{2} + \sigma(2f-1)\right]}$$

Same equation as Lavrentovich / drn draft paper

* Additional terms when there are spatial gradients...

$$\frac{\partial f}{\partial t} = \frac{-1}{c_T}\vec{\nabla}\cdot(\vec{u}\, c_A) + \frac{D}{c_T}\nabla^2 c_A - \frac{c_A}{c_T^2}\left[-\vec{\nabla}\cdot(\vec{u}\, c_T) + D\nabla^2 c_T\right] + \cdots$$

$$\approx -\vec{\nabla}\cdot(\vec{u}\, c_A) + D\nabla^2 c_A + c_A(\vec{\nabla}\cdot\vec{u}) + \cdots, \text{ if } c_T \approx 1$$

$$\approx -(\vec{u}\cdot\vec{\nabla}) f - f\,\vec{\nabla}\cdot\vec{u} + D\nabla^2 f + f(\vec{\nabla}\cdot\vec{u}) + \cdots, \text{ if } c_T \approx 1$$

$$\Rightarrow \boxed{\frac{\partial f}{\partial t} + (\vec{u}\cdot\vec{\nabla}) f = D\nabla^2 f + f(1-f)\left[\frac{\delta}{2} + \sigma(2f-1)\right]}$$

deterministic generalization of Model A to include flow

Test of nucleation theory in two dimensions

Xiaojue Zhu,
R. Benzi,
F. Toschi & drn

The dynamics of the droplet radius $R(t)$ is given by

$$\frac{dR(t)}{dt} = -\frac{D}{R(t)} + \frac{\delta}{2}\sqrt{\frac{D}{\sigma\tau_g}} \quad \text{(require } R(t) >> w = \text{ interface width)}$$

$\rightarrow$ critical droplet radius $R_c = \gamma / c = (2/\delta)\sqrt{D\sigma}$

$\rightarrow$ dying droplets should vanish with a square root singularity,

$$R(t) = \sqrt{R_0^2 - 2D(t - t_0)},$$

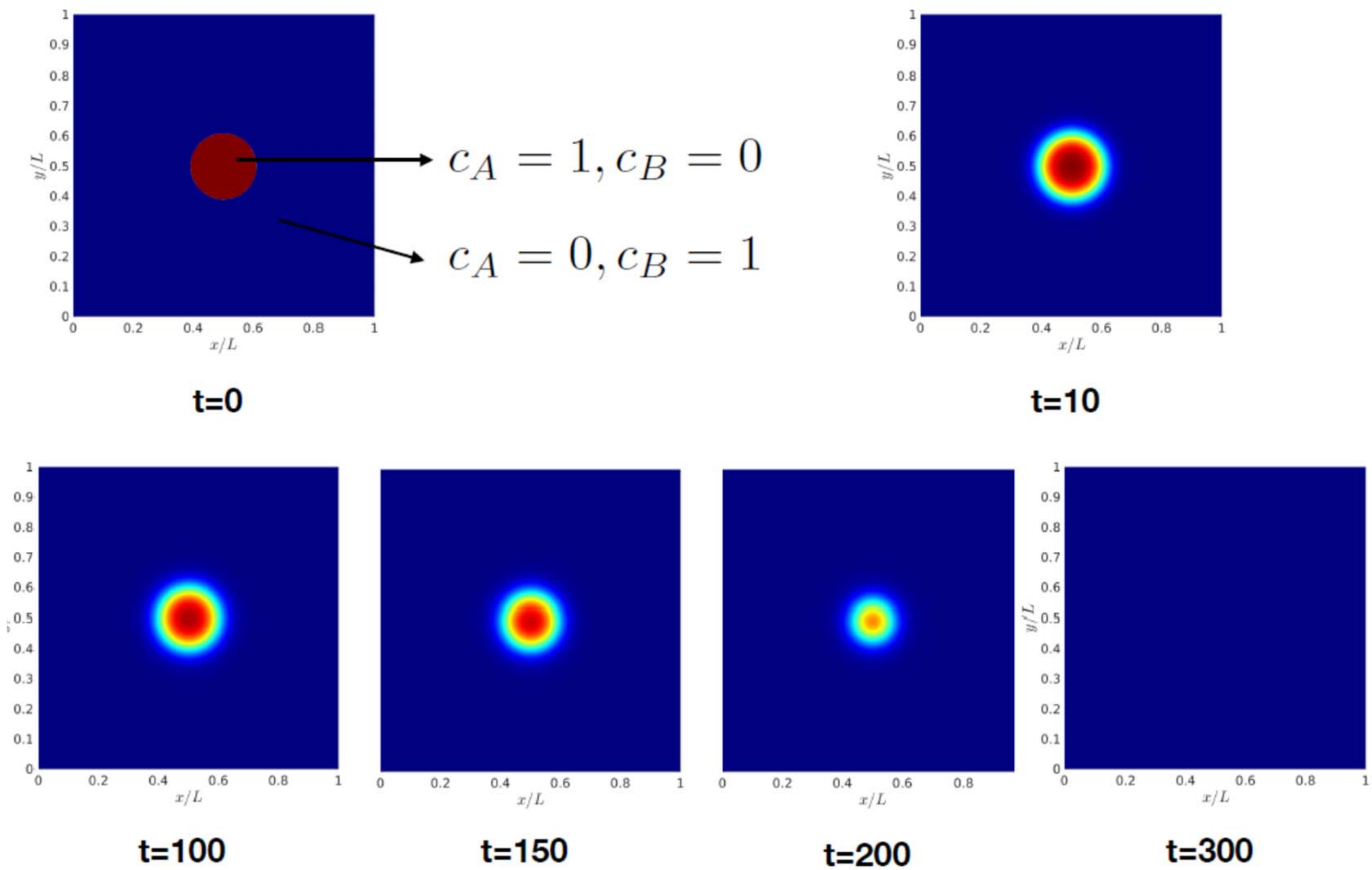
where R_0 is the radius of a dying droplet has well below the maximum R_c at time t_0

$\rightarrow$ Once the droplet is above the maximum, we should eventually have a circular, expanding pushed wave with $R(t) \approx vt, \; v = (\delta/2)\sqrt{D/\sigma\tau_g}$

simulations: selective advantage $= \delta = \varepsilon_A - \varepsilon_B = 0.1$

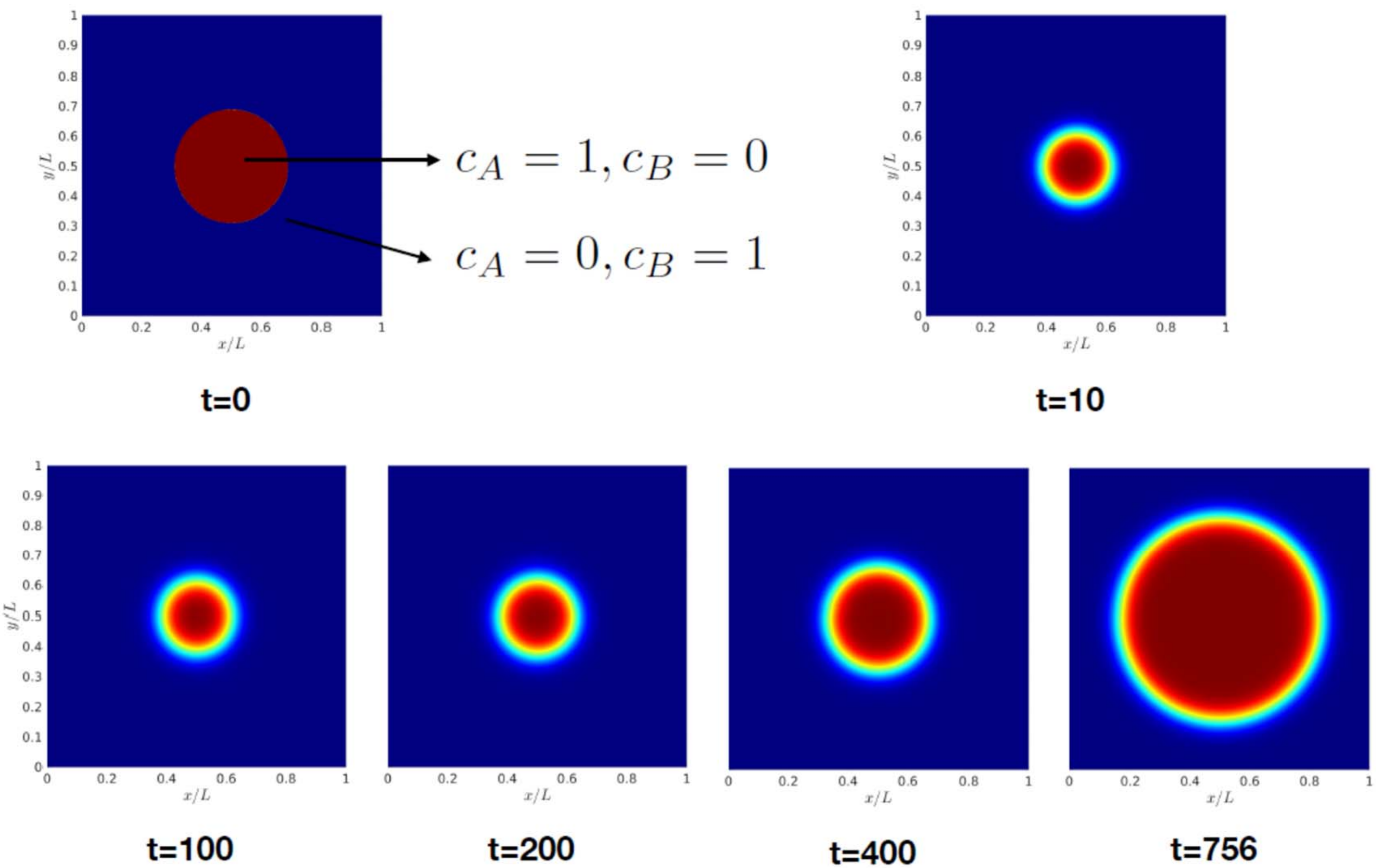
antagonism $= \sigma = -(\varepsilon_A + \varepsilon_B)/2 = 0.25$

1. Initial radius=0.11 without flow



$R < R_c$

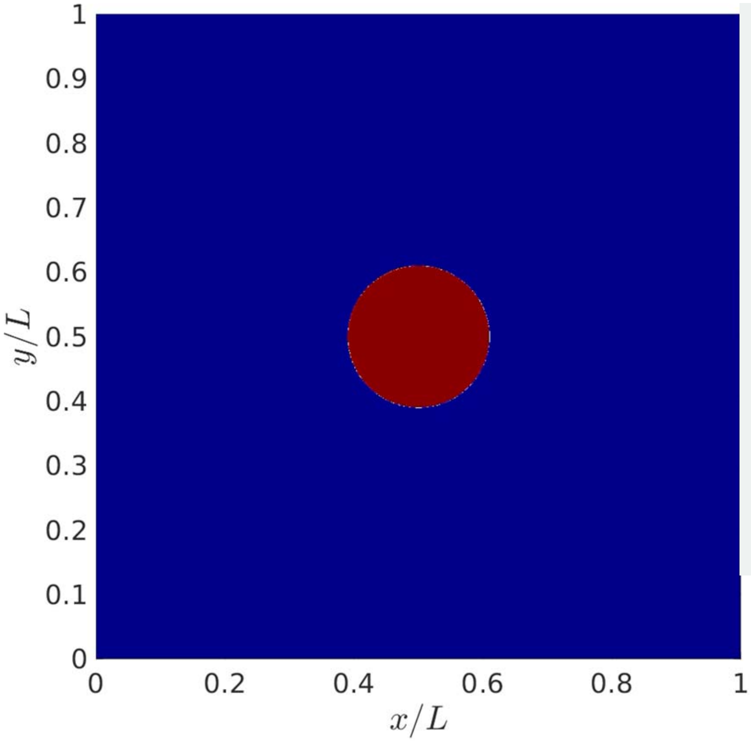
2. Initial radius=0.12 without flow

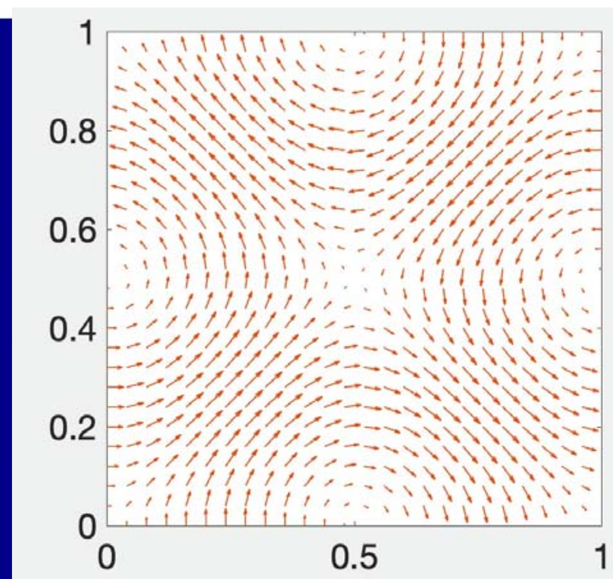


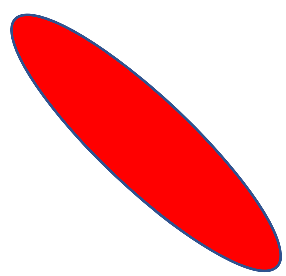
$R > R_c$

The effect of a saddle flow on a (slightly) subcritical droplet of a selectively favored species.

Initial radius=0.11, F=0.0025







•R(t=0) < R_c without flow.

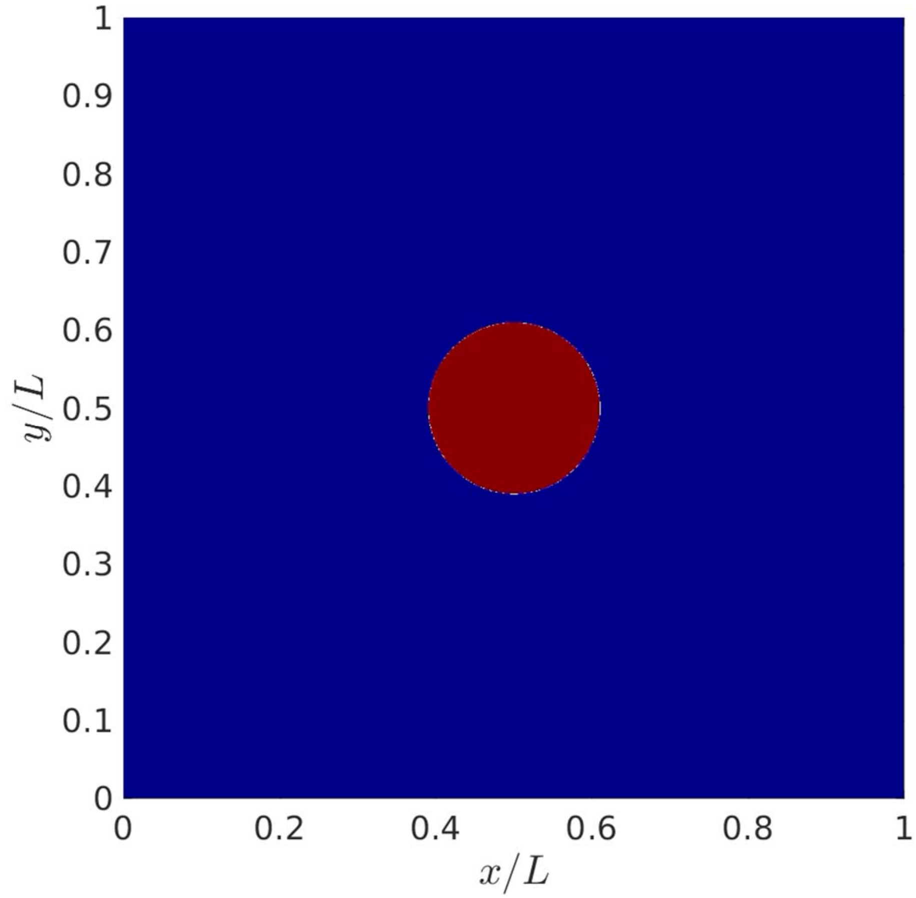
•The saddle flow elongates the droplet, and resulting flat regions are relatively free from the confining effects of line tension.

•Although there is a selective advantage, the <u>inward</u> flows due to the saddle are larger than the <u>outward</u> pushed wave velocity due to the selective advantage.

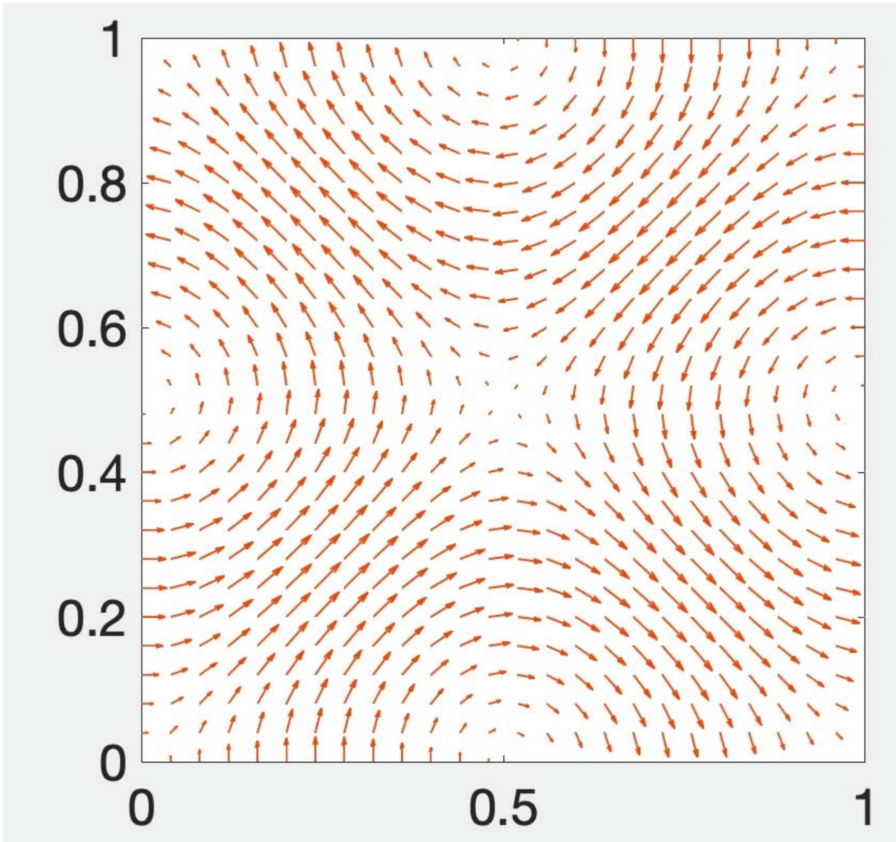
•The net effect is to produce a <u>shorter</u> extinction time.

Initial radius=0.11, F=0.025

(Fluid driving force F at the saddles is now a factor of 10 bigger.

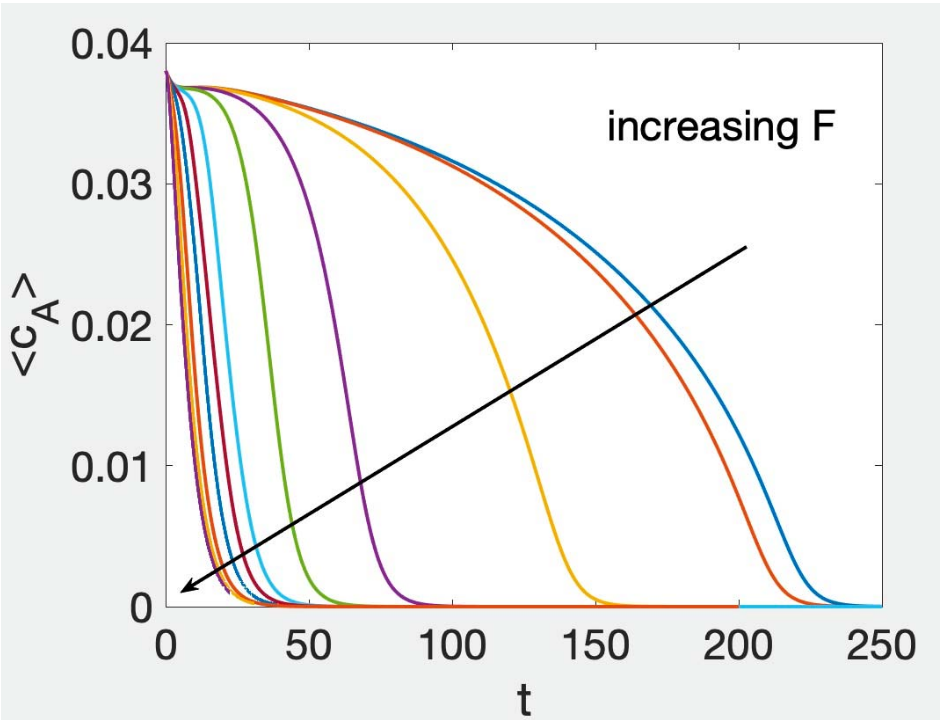


Red droplet of the selectively favored phase dies even more rapidly…



Time series for initial radius=0.11, increasing flow strength F at the saddle

$$c_A(t) = \pi R^2(t); \quad R(t) = \sqrt{R_0^2 - 2D(t - t_0)}$$



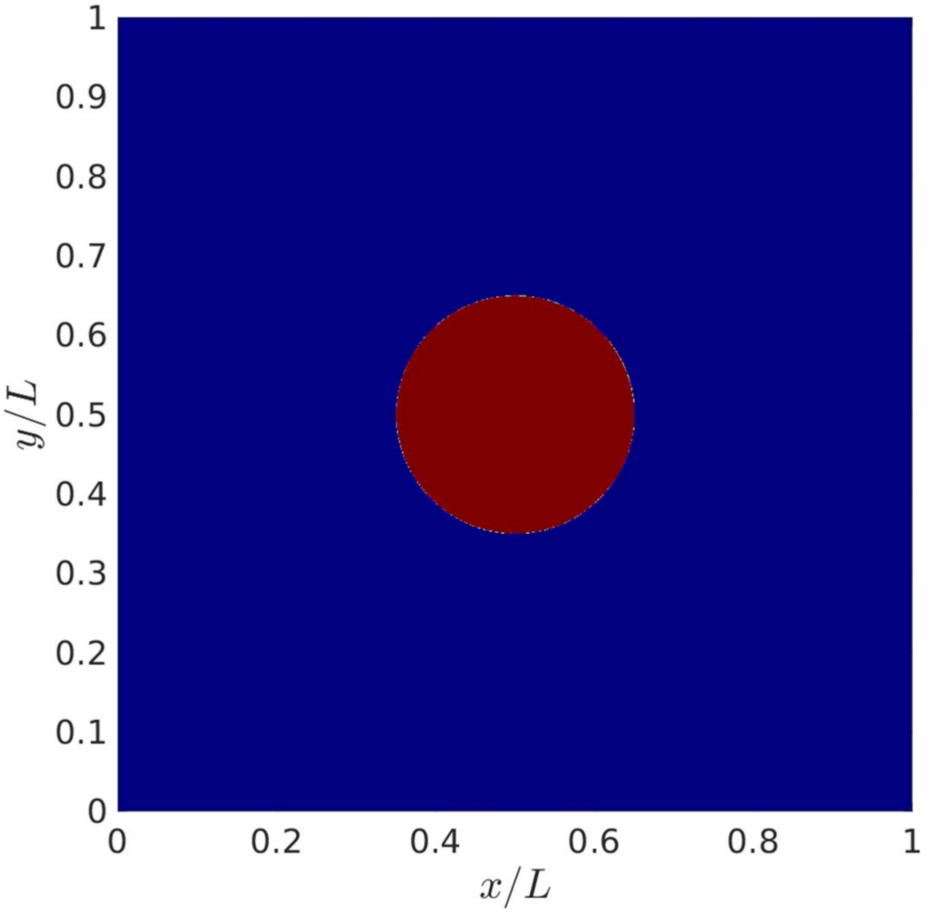
The predicted linear vanishing of $c_A(t)$ is rounded into a foot, due to the smoothing effect of diffusion?

The selectively favored droplet dies even more rapidly when born on a saddle point

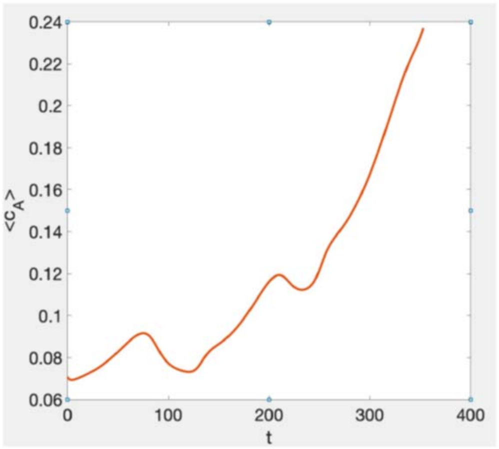
Extinction time $T_E \approx T_0 - AF^2$; $T_E(F)$ must be an even function of F.

Hence, $T_E(F) \approx T_E(0) - AF^2$ for small F....

Larger droplets can be strongly influenced by periodic boundary conditions!!



Saddle flow with very small F

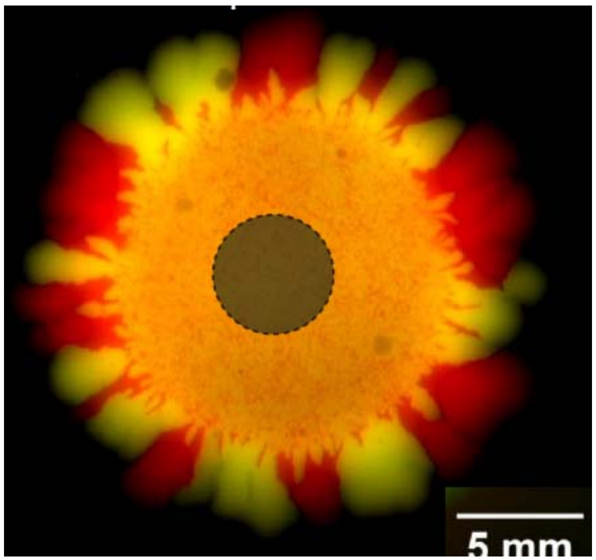


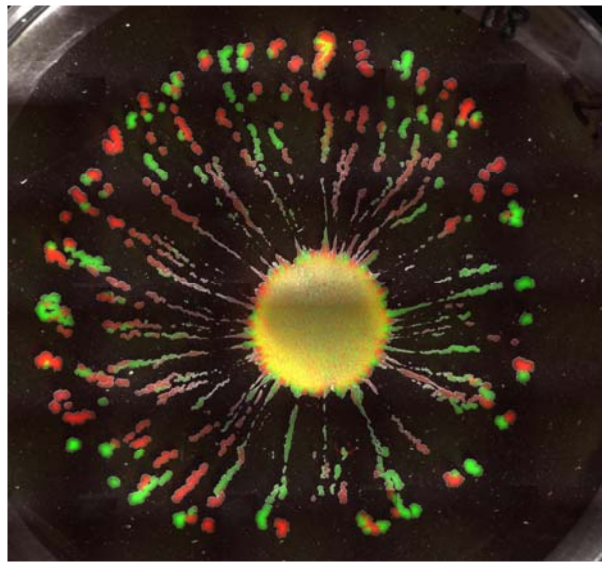
Red variable species is initially at the saddle point. <c_A> grows non-monotonically. Also as time goes by, A splits up and reconnects.

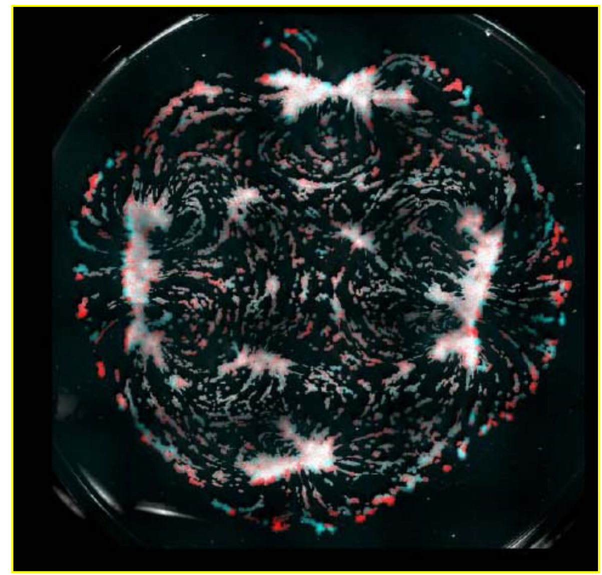
Can we do experiments?

On Growth and Form of Microorganisms on *Liquid* Substrates

"Microbes on the surface of a highly viscous liquid generate buoyant flows that alter colony morphology and evolutionary dynamics"



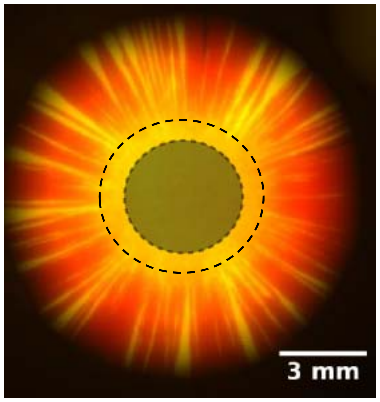




Severine Atis
Bryan Weinstein
Andrew Murray

Microorganisms grown on liquid but highly viscous substrates create their own flows (without pumps and syringes!)

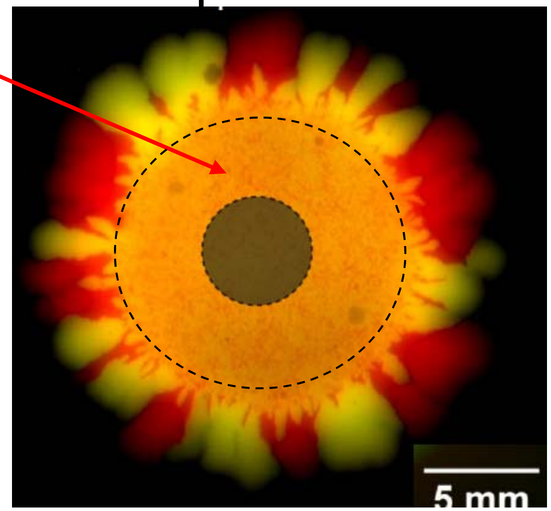
Hard Agar



Genetic demixing of yeast on a 1% hard agar YPD plate (viscosity $\eta = \infty$)

Epoch of genetic demixing stretched out….

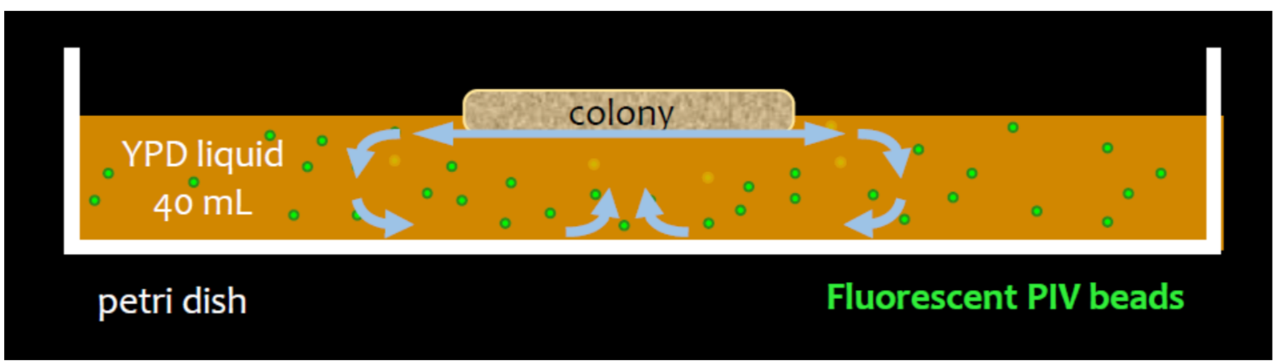
Liquid Media



Yeast on a liquid but highly viscous YPD media with 3% cellulose ($\eta \approx 600$ Pa-s)

Cellulose % (w/v)	Viscosity (Pa·s)
1.8	22 ± 3
2.0	51 ± 6
2.2	81 ± 9
2.4	120 ± 10
2.6	340 ± 50

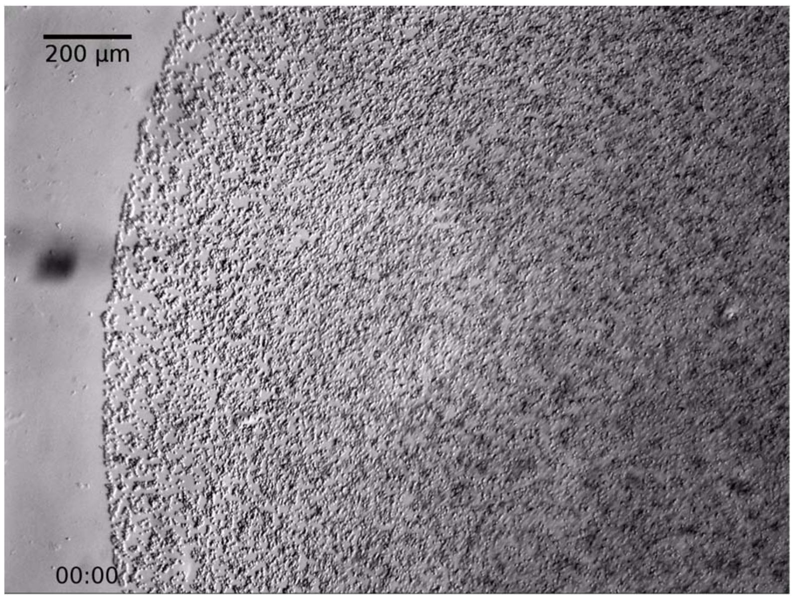
(the viscosity of water is $\eta \approx 10^{-3}$ Pa-s; our viscosities are $10^4 - 10^5$ times larger)



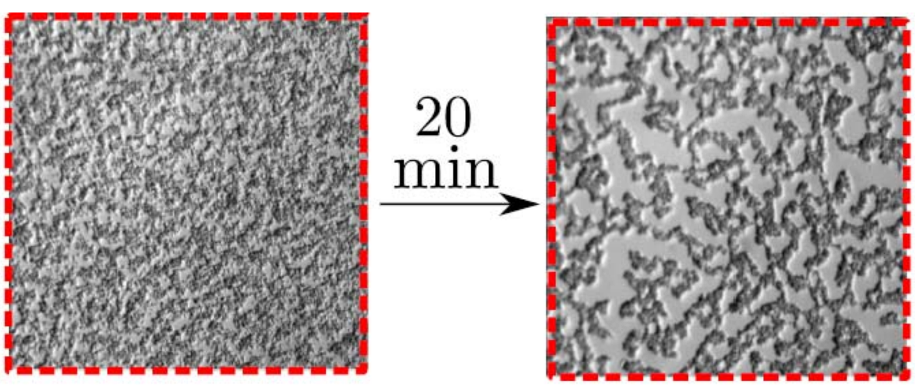
The colony itself generates flows that dilate the growing cell mass radially!

As the time since inoculation elapses, microorganisms on liquid substrates can behave like gases, liquids or solids….

At very early times, the yeast cells exhibit gas-liquid phase separation

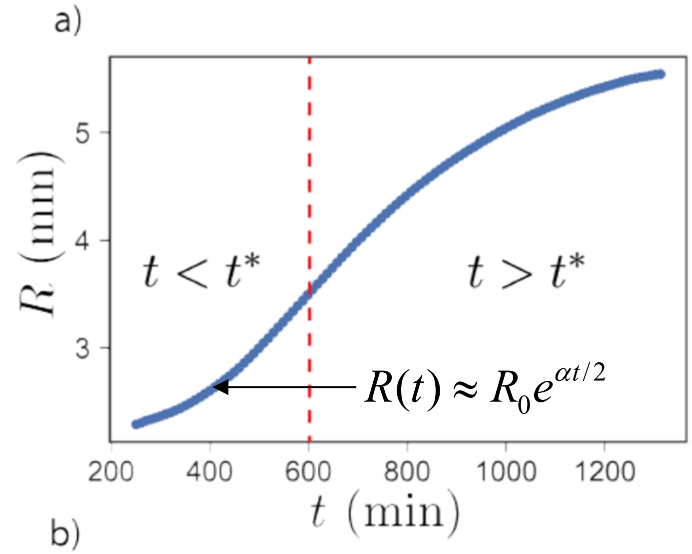


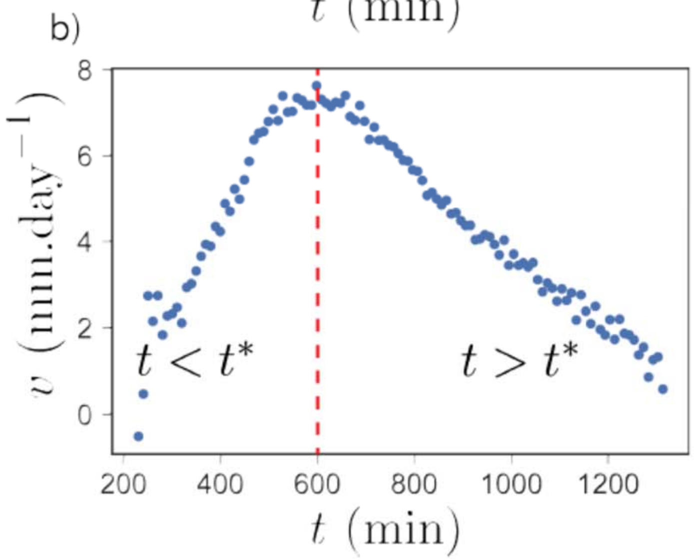
D. Vella and L. Mahadevan, American Journal of Physics 73.9 (2005): 817-825.

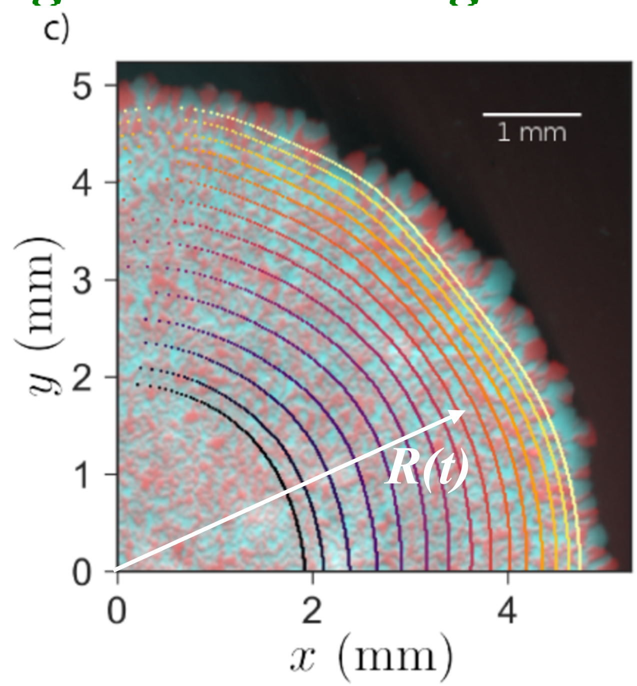


Coarsening or "spinodal decomposition"….

We find initial exponential growth for t < t, followed by a gradually slowing down & genetic demixing at the frontier*





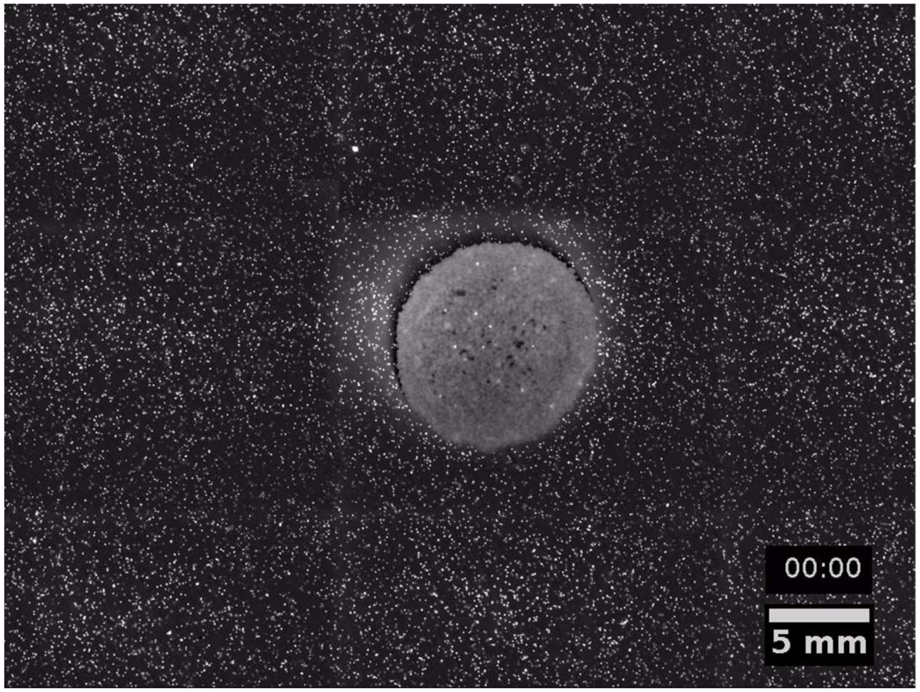


a) Radially averaged yeast colony radius R(t) during the first 24h of growth on a high viscosity liquid substrate with η =600 Pa-sec.

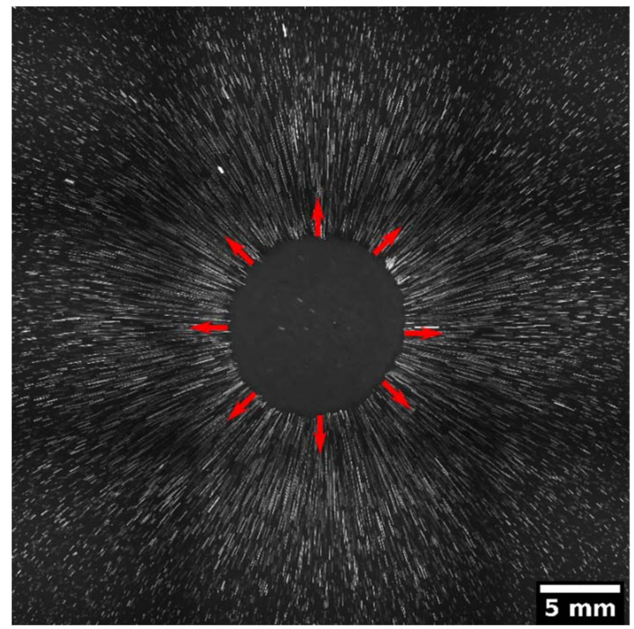
b) The colony front velocity v(t) extracted from R(t), exhibiting: (1) an approximately exponential phase for t < t and (2 a slowly decaying velocity over time for t > t.

c) Consecutive front spatial positions at 40 min intervals during the first 24h of growth.

24-48 hours, $\eta \approx 600$ Pa-S



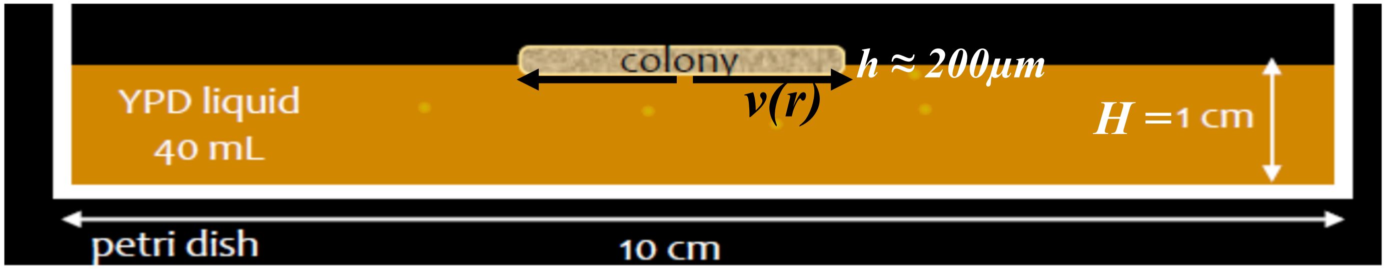
Motion of fluorescent beads around a mature colony reveals that fluid motion is generated beneath the growing colony



One early time mechanism for radial motion is outward pushing when all cells at the interface are actively dividing….

Deformations of features inside colony in a liquid-like regime consistent with a dilational flow (η = 600 Pa-sec)

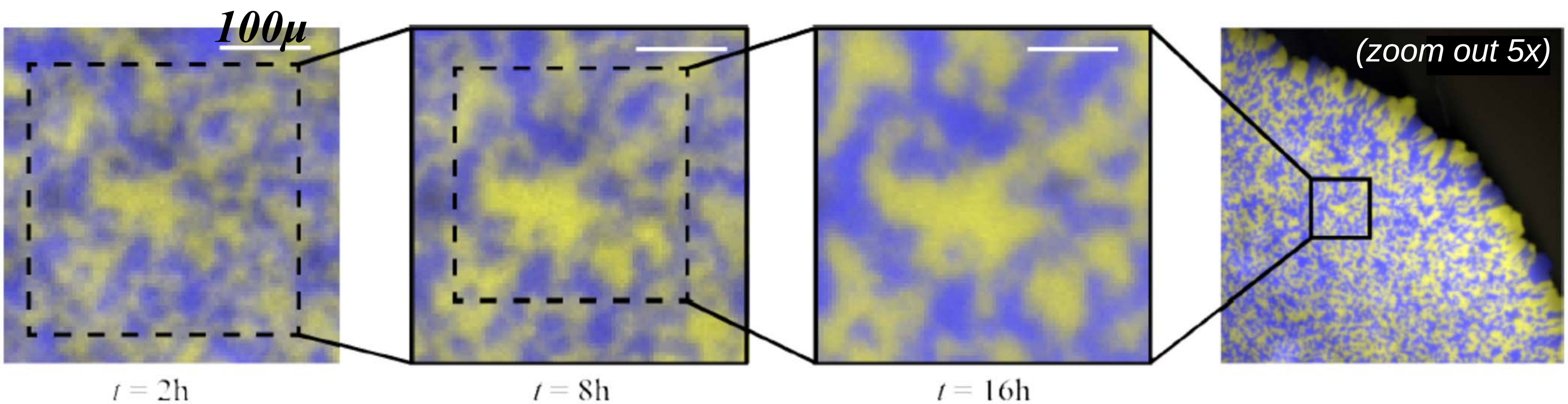
Colony features dilate as if inscribed on an inflating balloon….



Simple model of 2d colony dynamics: $\dfrac{\partial \rho_{2d}}{\partial t} + \vec{\nabla} \cdot (\rho_{2d} \vec{v}_{2d}) = \alpha_1 \rho_{2d}$, ρ_{2d} = cell density

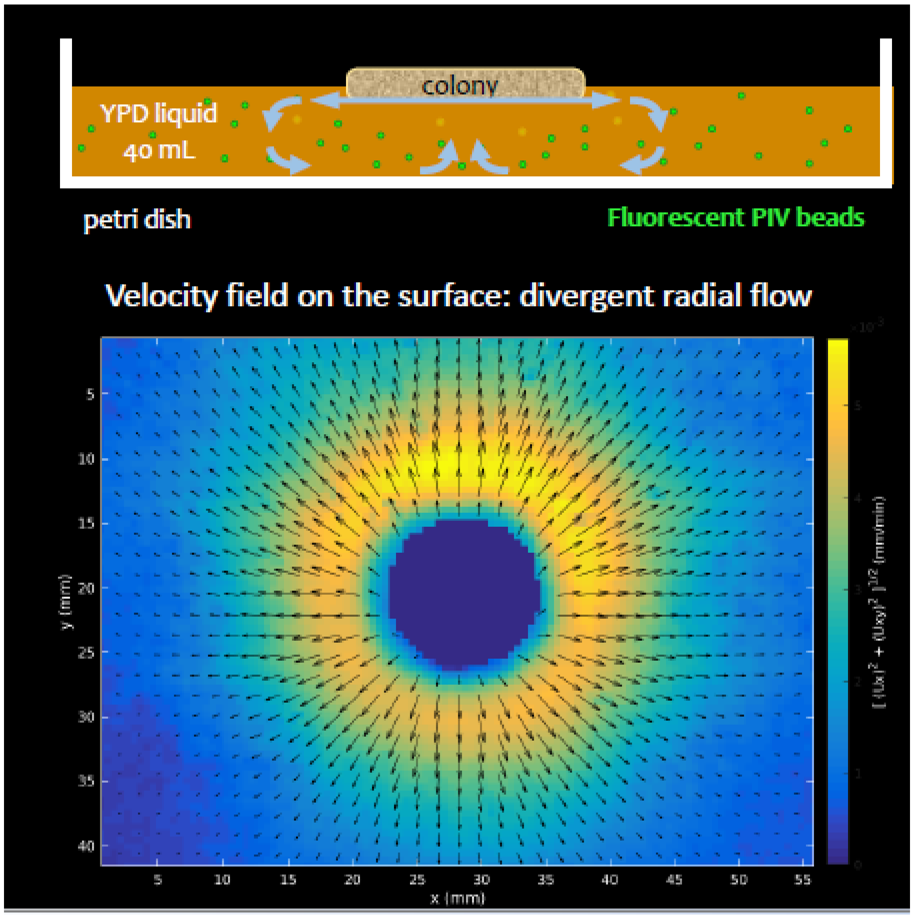
α_1 = growth rate $\rightarrow \vec{\nabla} \cdot \vec{v}_{2d}(r) = \alpha_1$; assume overdamped liquid-like colony dynamics:

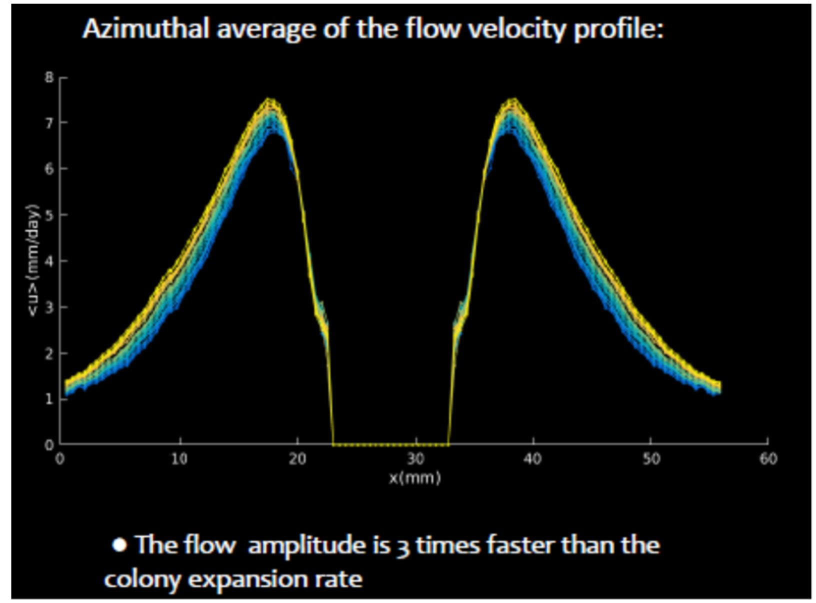
$0 \approx -\vec{\nabla} p_{2d} - \gamma \vec{v}(\vec{r}))$; $\gamma = \eta_s / hH$; $\rightarrow$ $\boxed{\vec{v}_{2d}(\vec{r}) \approx \alpha_1 r \hat{r} / 2}$ dilational velocity field

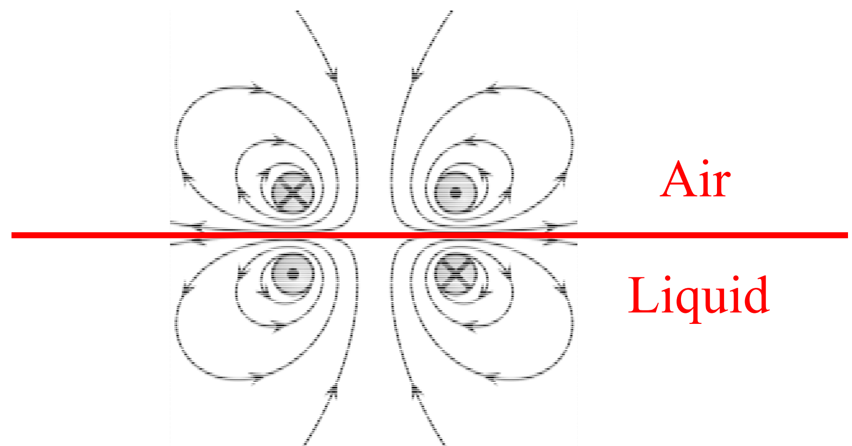


The first three images have the same scale bar = 100 μm. The final picture, with scale bar 500 μm, shows the same feature at the much larger colony scale

In addition to simple outward pushing due to excluded volume interactions, a metabolically-induced vortex ring appears under the colony, enhancing the radial growth rate





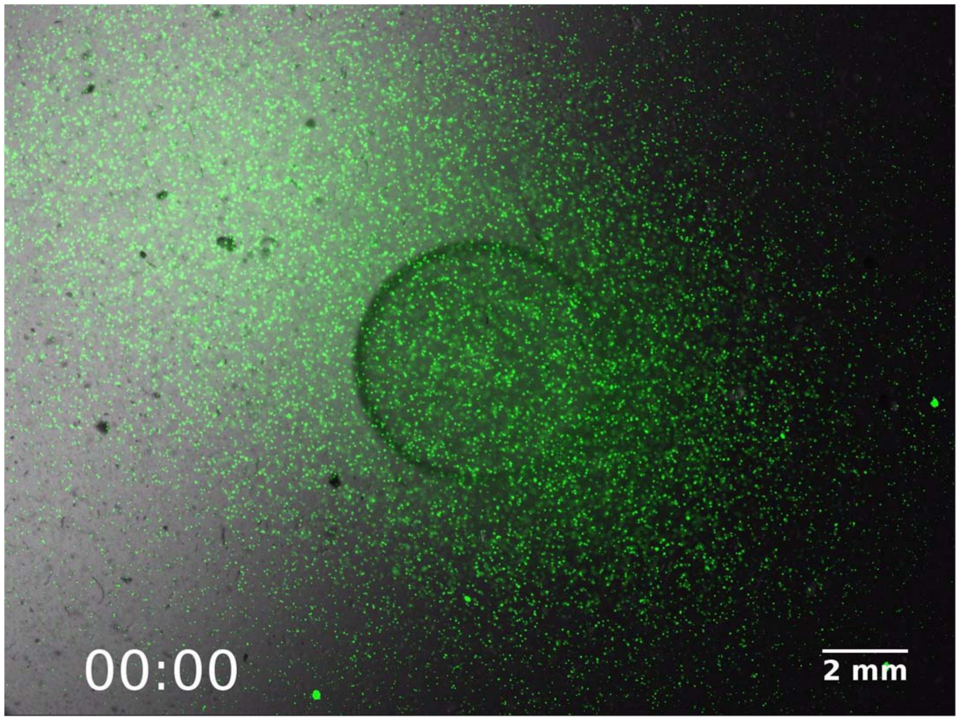


$$\vec{\omega}(\vec{r}) = \vec{\nabla} \times \vec{v}(\vec{r}); \;\; \vec{\nabla} \cdot \vec{v}(\vec{r}) = 0$$

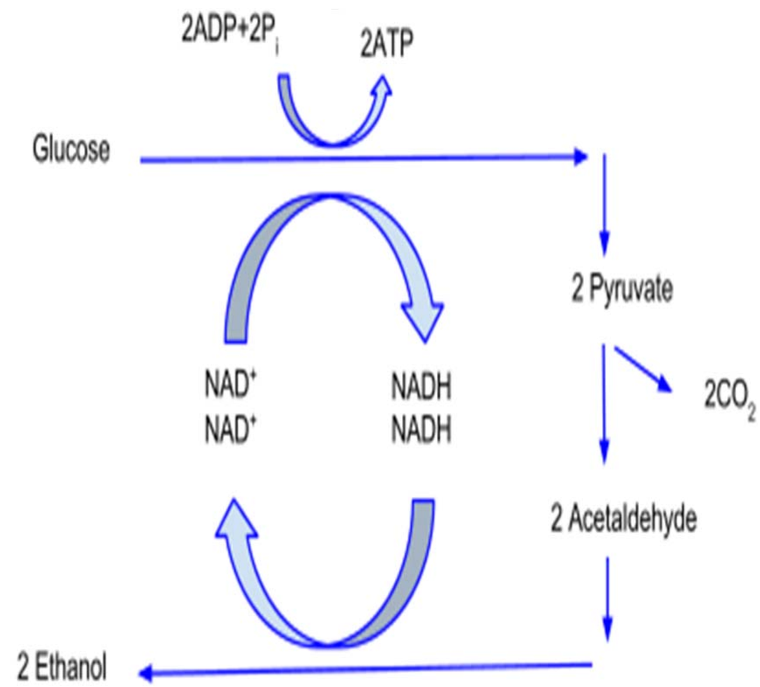
$$\vec{v}(\vec{r}) \approx \alpha_2 r \hat{r} / 2 \quad \Leftarrow \quad \left[\text{compare magnetostatics: } 4\pi \vec{J}(\vec{r})/c = \vec{\nabla} \times \vec{B}(\vec{r}); \; \vec{\nabla} \cdot \vec{B}(\vec{r}) = 0\right]$$

Origin of the enhanced flow beneath colonies growing on liquid substrates?

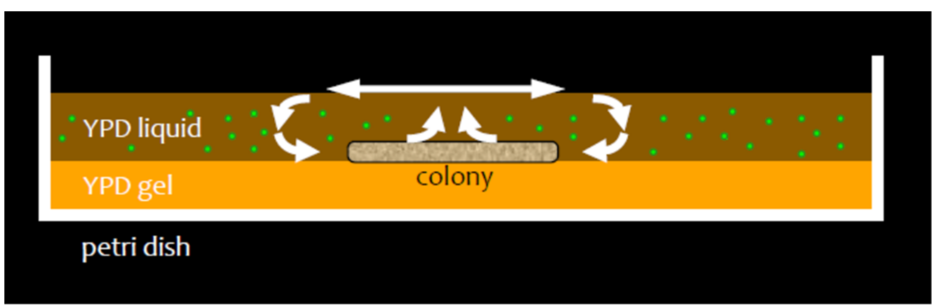
Case I: colony on the <u>bottom</u> of the dish



Anaerobic pathway:
dextrose (~3%) → CO_2 + ethanol

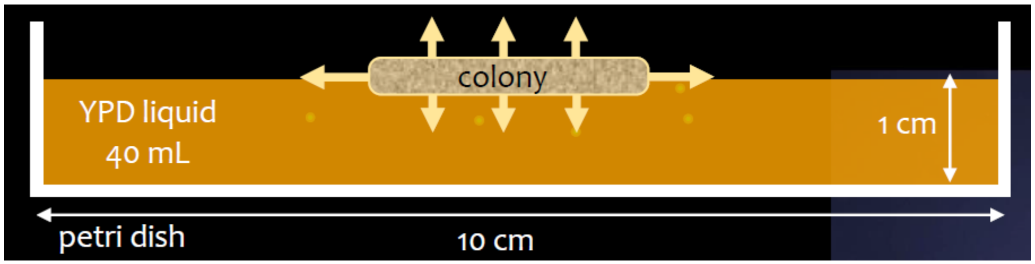


wikipedia



Yeast colony on bottom, dextrose-metabolism-induced CO_2 bubbles!!

Origin of the enhanced flow beneath colonies growing on liquid substrates



- Fluid mechanics

Boussinesq approximation (valid in the limit of small density difference)

$$\frac{\partial \vec{v}}{\partial t} + \vec{v}.\nabla\vec{v} = -\frac{1}{\rho_0}\nabla p + \nu\nabla^2\vec{v} + \frac{\rho}{\rho_0}\vec{g}$$

media density:

$$\rho = \rho_0 + \delta\rho = \rho_0(1 + \beta c)$$

Diffusion equation for the nutrients field

$$\frac{\partial c}{\partial t} + \nabla.(\vec{v}c) = D\nabla^2 c$$

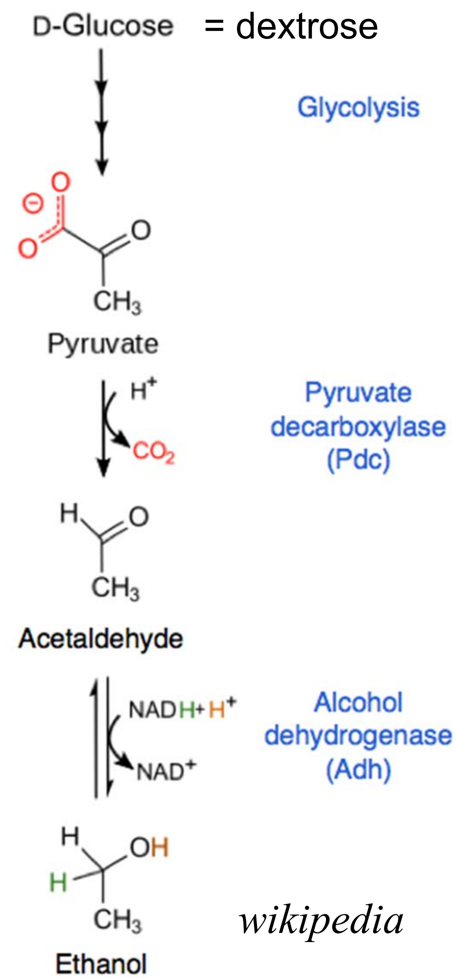
ρ_0 : fluid density

ν : kinematic viscosity

g : gravity

p : pressure

Case II: colony growing at the top of the liquid substrate



wikipedia

Flow simulations

Boundary conditions:

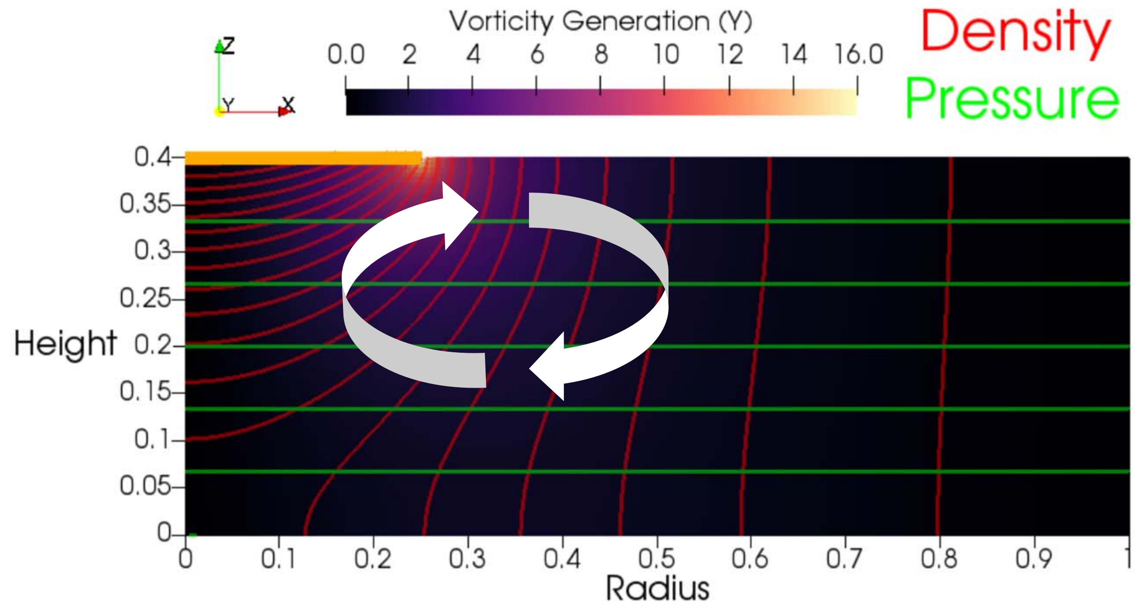
$$\vec{j}_{\mathrm{out}} = \alpha c \vec{n}$$

$$\vec{j}_{\mathrm{diff}} = \rho_0 \beta D \nabla c$$

$$\vec{j}_{\mathrm{out}} = \vec{j}_{\mathrm{diff}}$$

$$\boxed{\nabla c.\vec{n} = \frac{\alpha c}{\rho_0 \beta D}.\vec{n}}$$

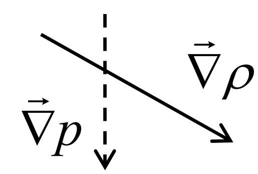
Isobars and isoclines in the <u>absence</u> of flow ($\eta = \infty$)



Take the curl of the Navier-Stokes equations…

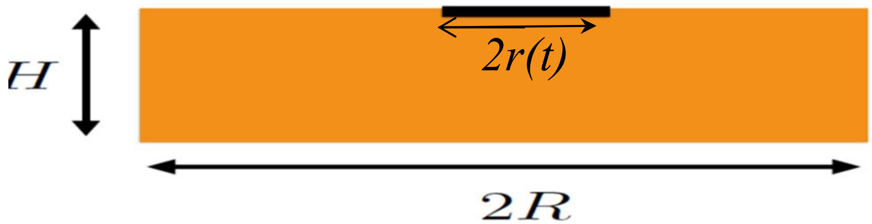
Vorticity equation: $\vec{\omega} = \nabla \times \vec{u}$

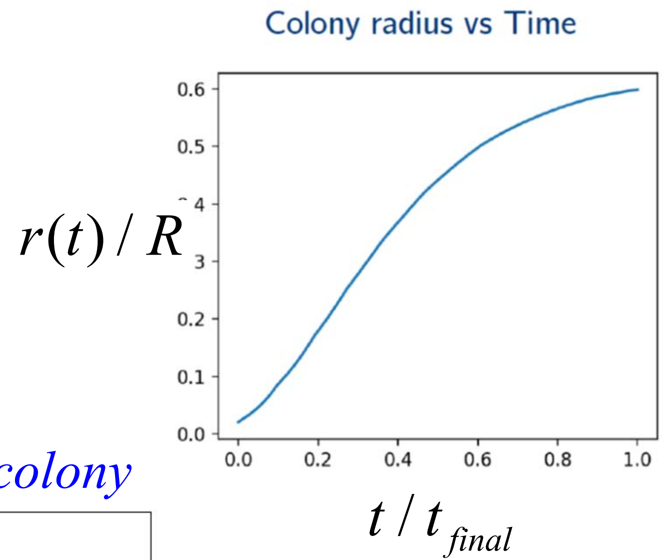
$$\frac{\partial \vec{\omega}}{\partial t} + (\vec{u}.\nabla)\vec{\omega} = (\vec{\omega}.\nabla)\vec{u} + \boxed{\frac{1}{\rho^2}(\nabla \rho \times \nabla p)} + \nu \nabla^2 \vec{\omega}$$



A thresholdless baroclinic instability generates a ring of vorticity beneath the colony….

Dynamics of nutrient depletion & vorticity generation





Nutrient depletion beneath an expanding colony

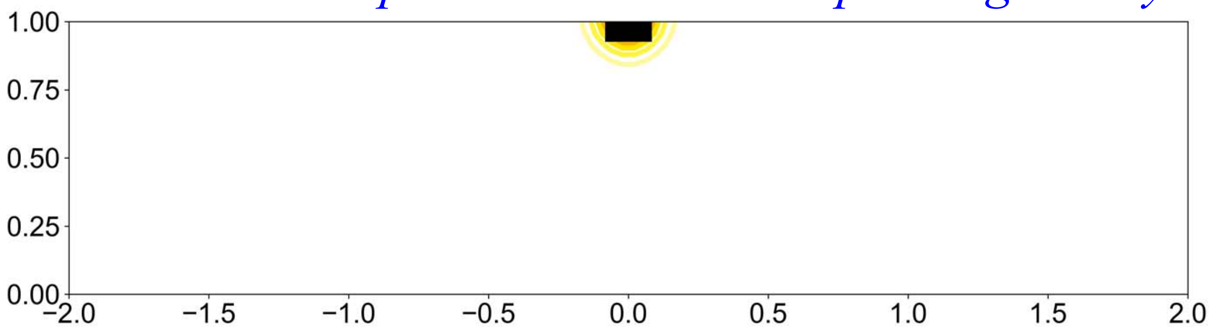
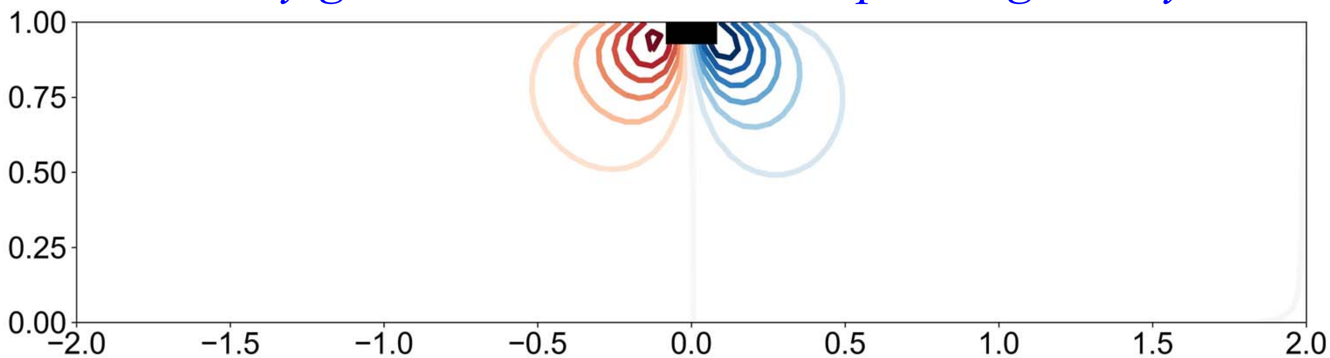


plate radius
R = 2

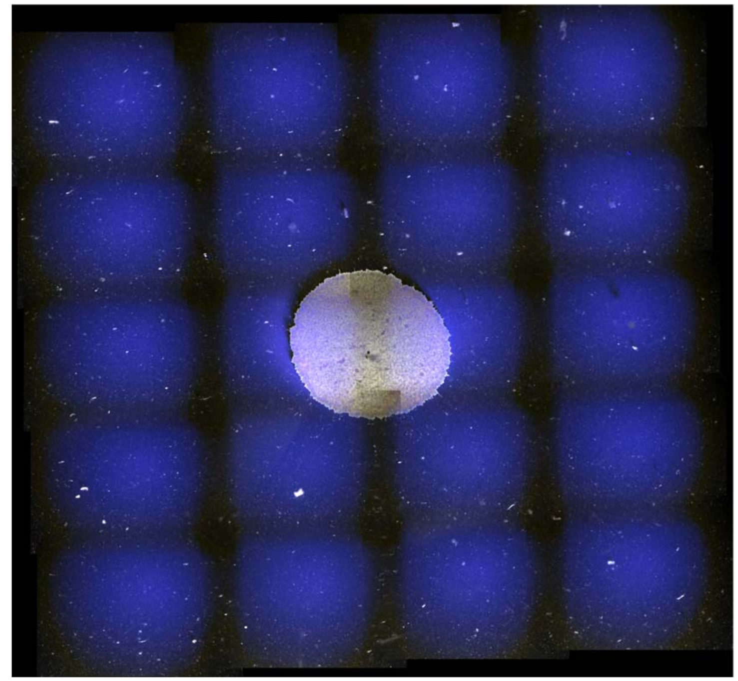
Vorticity generation beneath an expanding colony



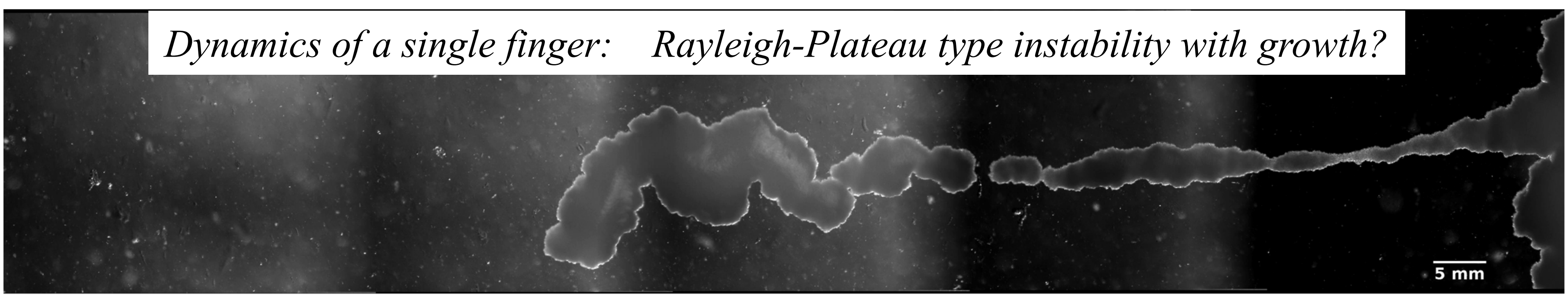
(Vamsi Spandan & Michael Brenner)

Enhancing the radial flow field...

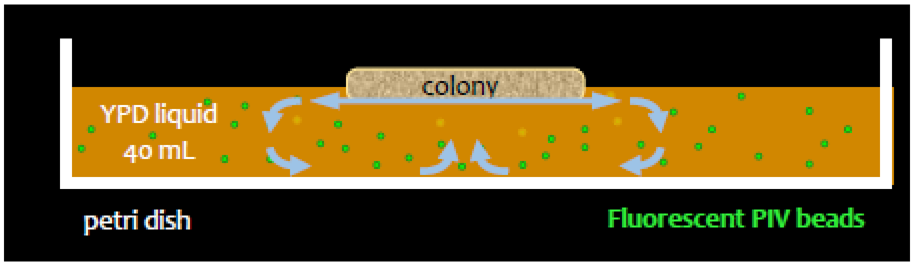
(moderate substrate viscosity η≈450 Pa-s)

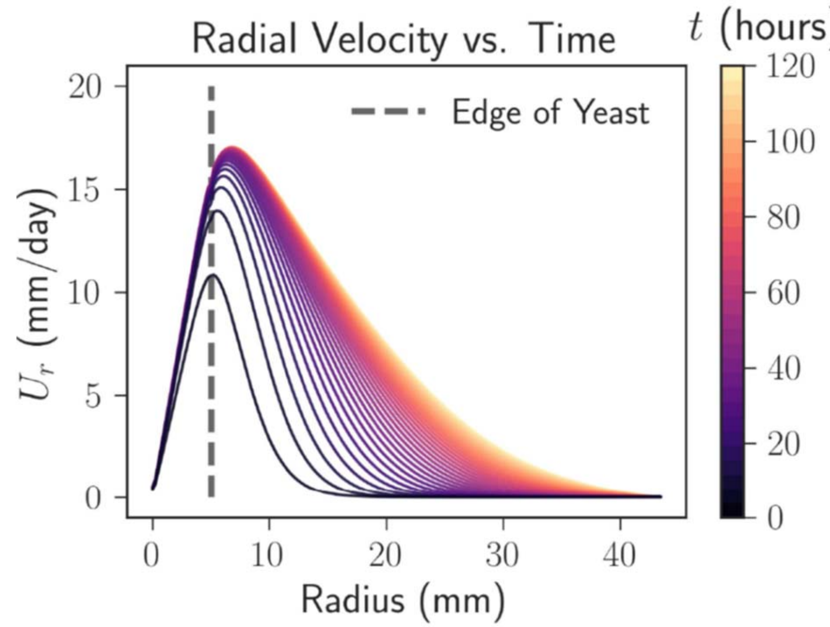


Liquid-like fingering instabilities



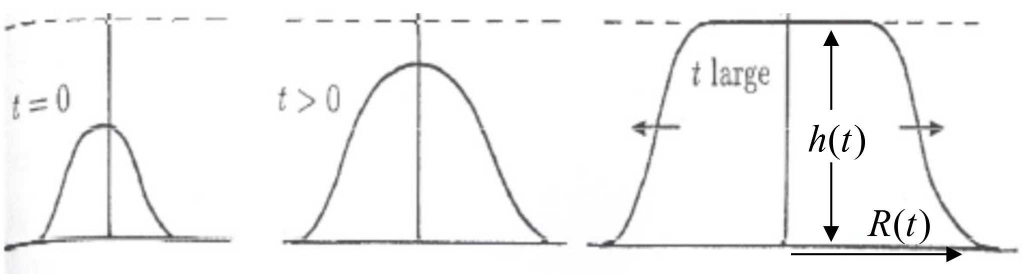
Lubrication approximation for growth with radial stretching in liquid colonies





$$\frac{\partial h(\vec{r},t)}{\partial t}+\vec{\nabla}\cdot\left[h(\vec{r},t)\vec{v}(\vec{r})\right]=D\nabla^2 h(\vec{r},t)+\mu h(\vec{r},t)\left[1-h(\vec{r},t)/h_0\right]$$

$\vec{v}(\vec{r})\approx\alpha r\hat{r}/2;$ α contains effects of both colony pushing & a metabolically generated vortex ring



$r(t)\approx r(0)e^{\alpha t/2}$, exponential growth accompanied by colony thinning

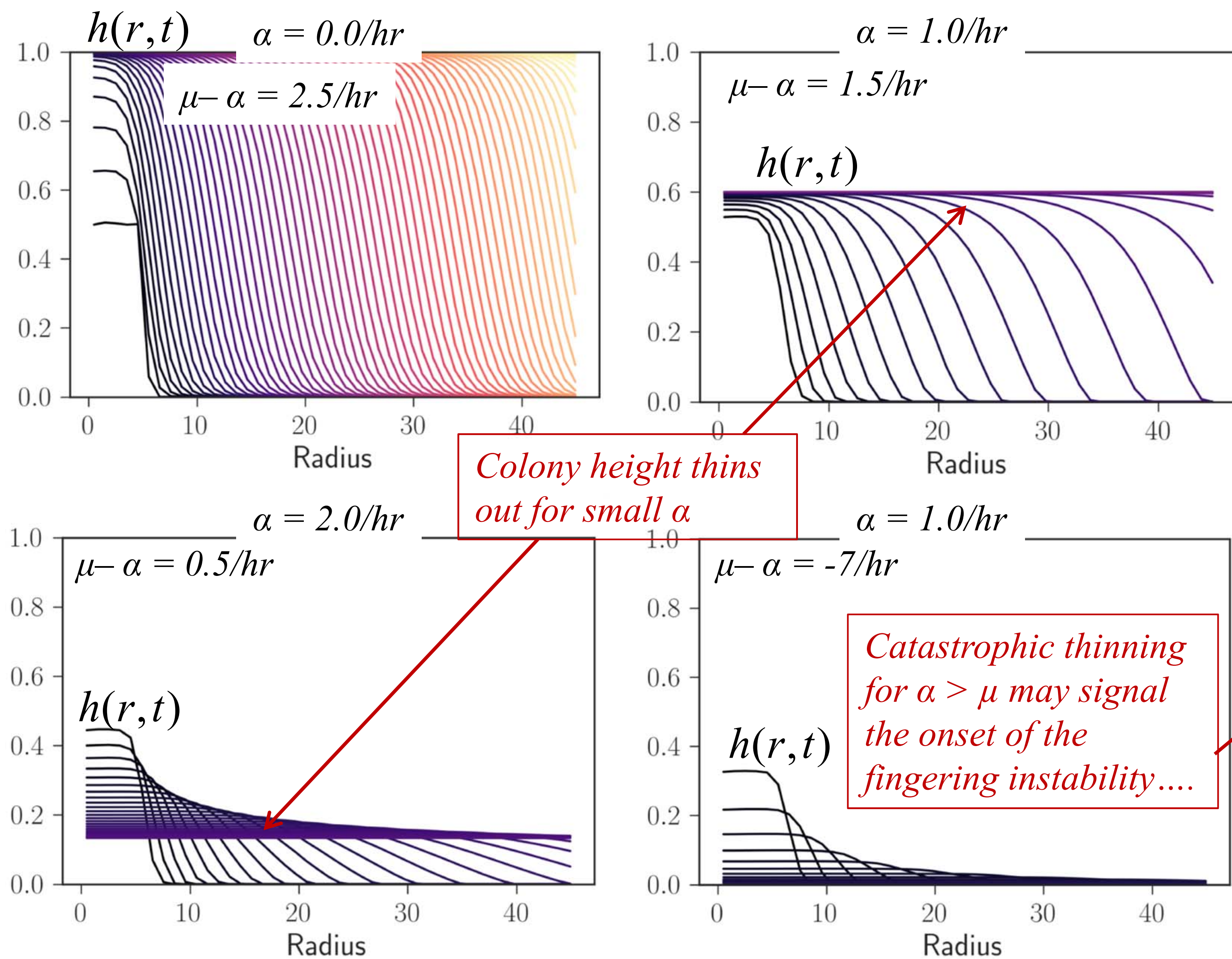
$$h(t)\approx\frac{e^{(\mu-\alpha)t}h(0)}{1+\frac{\mu h(0)}{h_0(\mu-\alpha)}\left[e^{(\mu-\alpha)t}-1\right]},$$

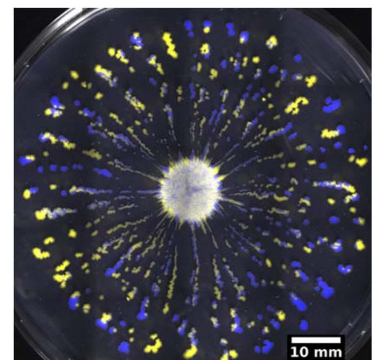
$$\lim_{t\to\infty}h(t)=h^*=h_0(1-\alpha/\mu),\ \ \alpha<\mu$$

$$\lim_{t\to\infty}h_0(t)=0,\ \ \mu<\alpha$$

Radial height profiles with different radial flows v(r)=αr/2

variable $\mu - \alpha$; equal time intervals

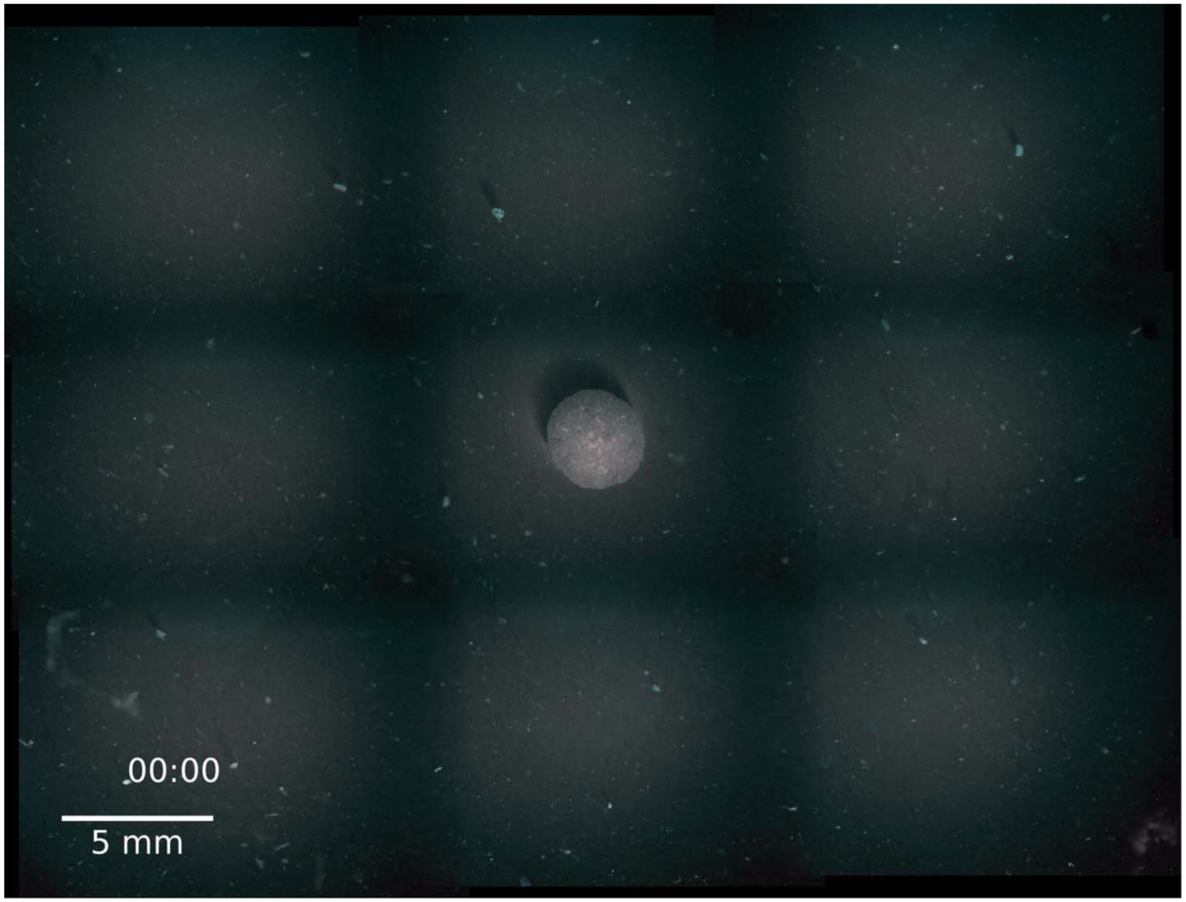




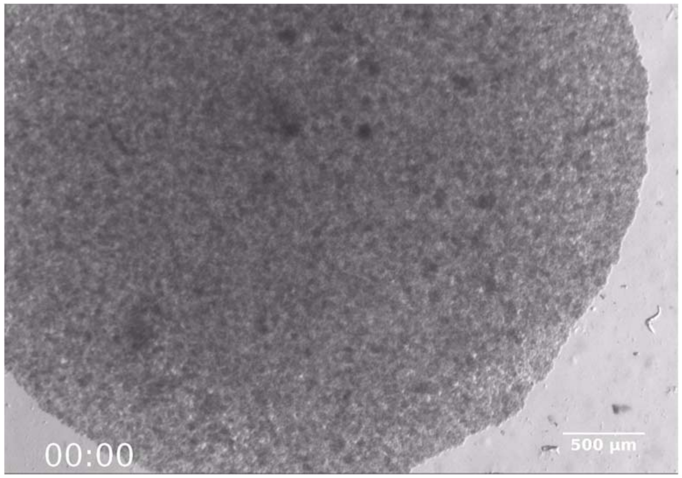
?

Solid-like colony fragmentation

(low substrate viscosity η ≈ 85 Pa-s)

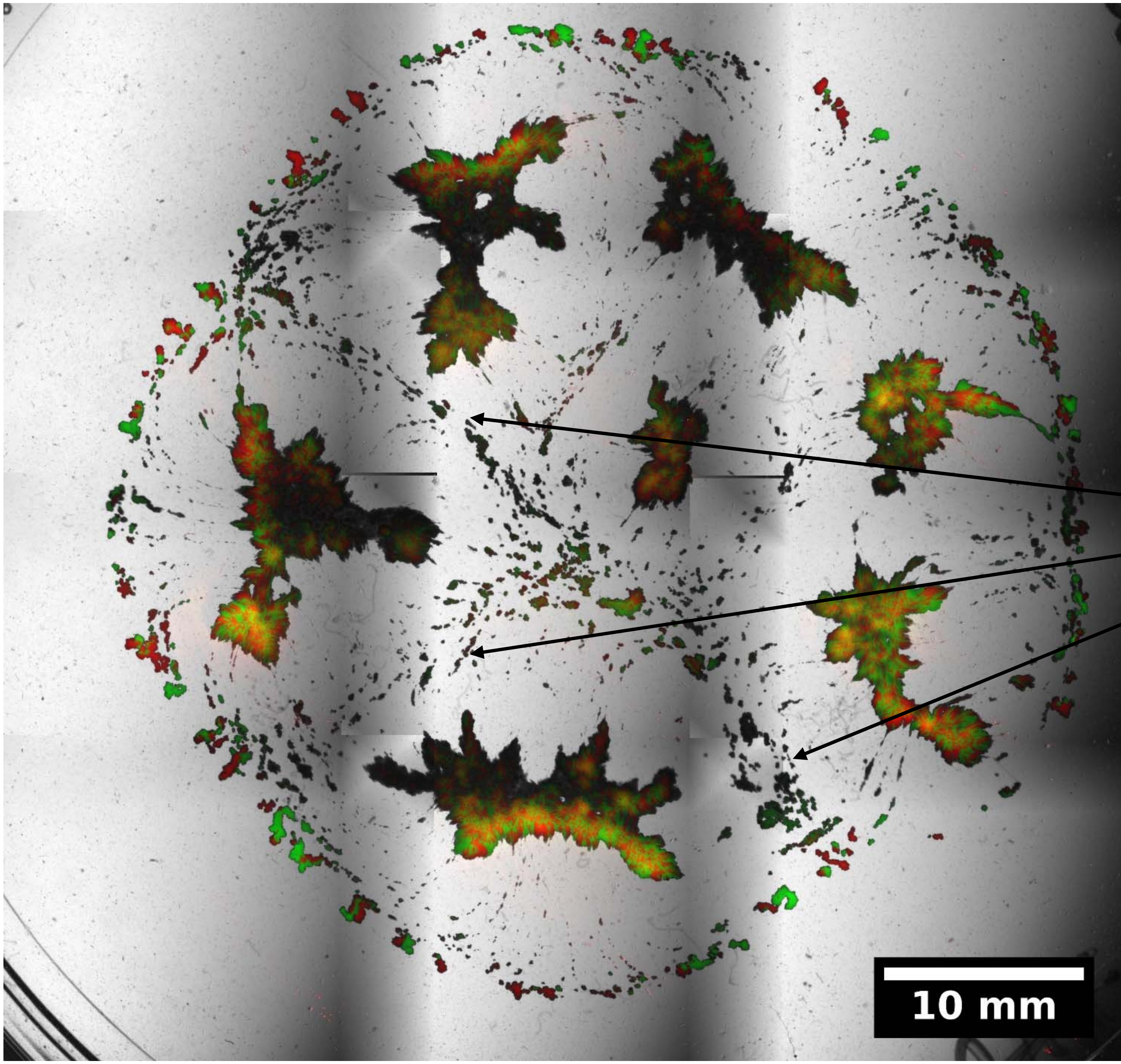


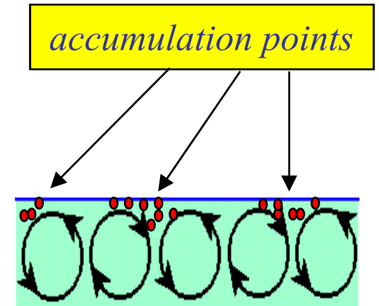
Zoom in reveals necking dynamics….



Colony takes over plate in < 1 day!

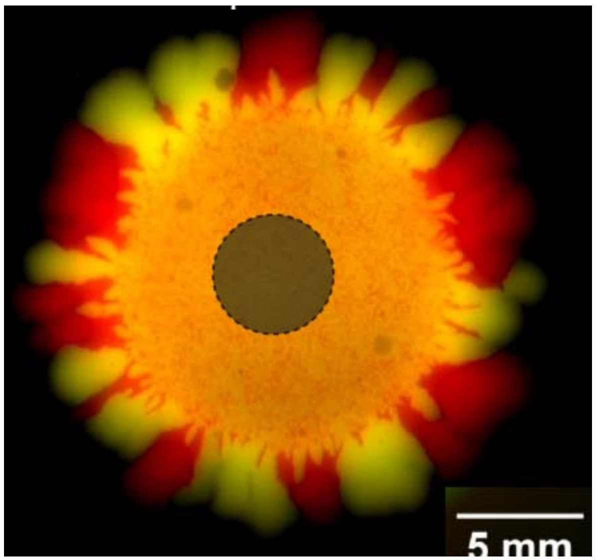
Actually, we expect a submerged vortex ring under <u>each</u> colony fragment….

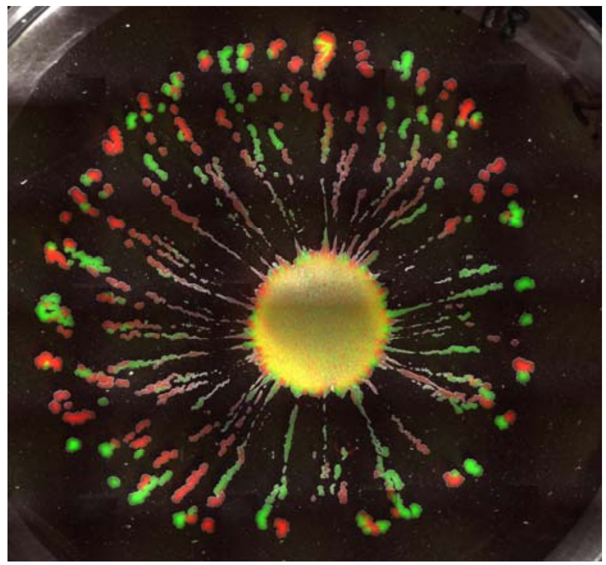


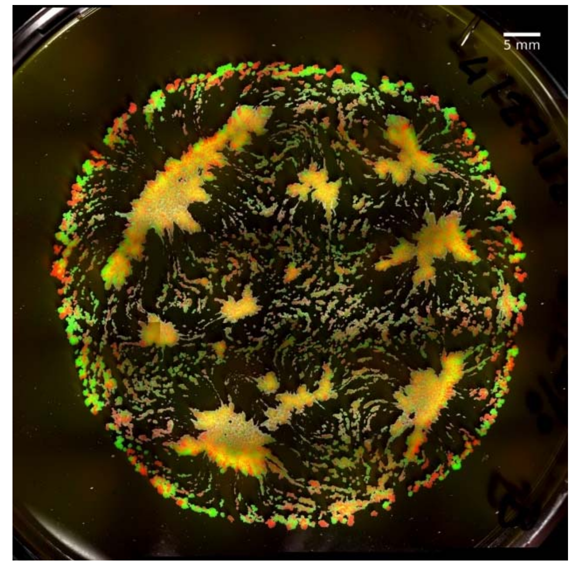


On Growth and Form of Microorganisms on *Liquid* Substrates

"Microbes on the surface of a highly viscous liquid generate buoyant flows that alter colony morphology and evolutionary dynamics"







Thank you!!

Severine Atis
Bryan Weinstein
Andrew Murray