Gene Surfing on Population Waves

The fate of neutral mutations in a spreading population

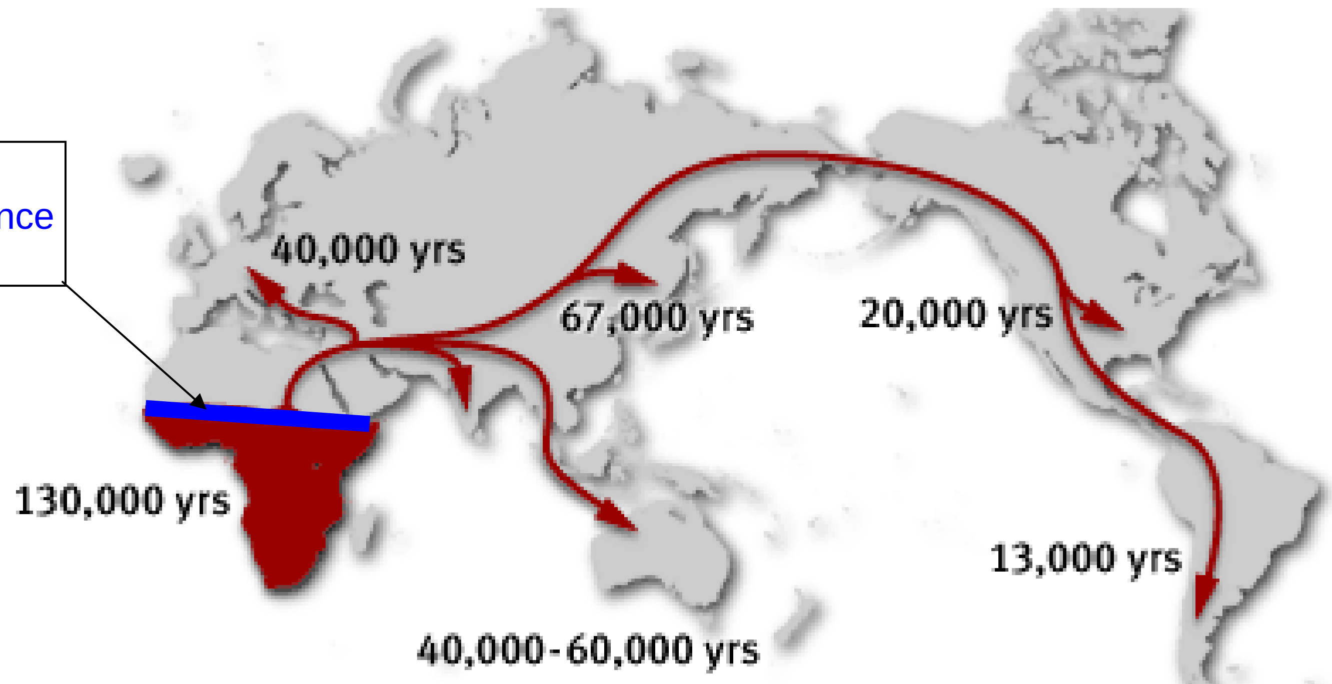
O. Hallatschek and drn

lots of help from the Ramanathan group…..

vs.

Neutral genetic markers can be used to infer direction, timing, and dispersal rates of colonization pathways

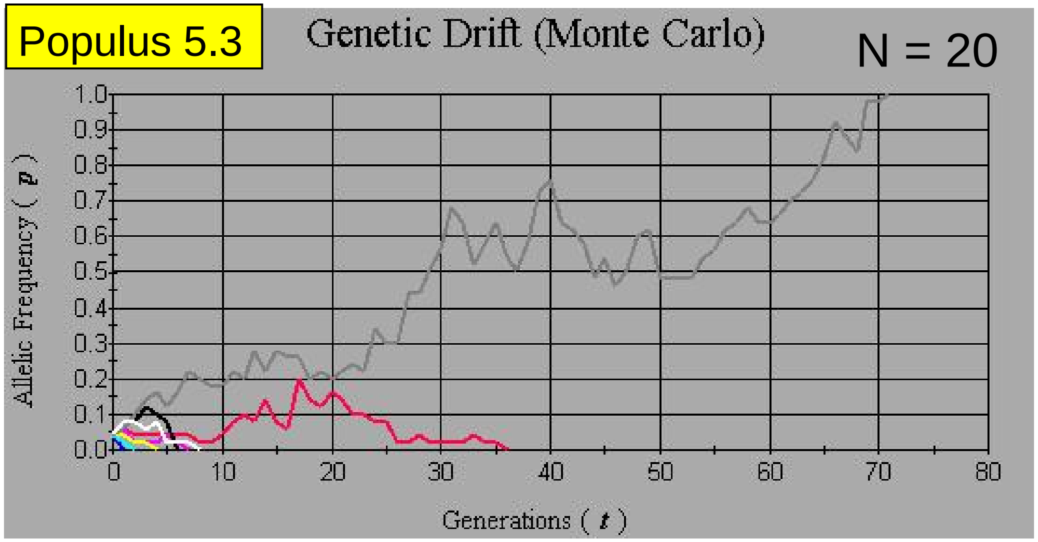
Neutral mutations have the best chance of surviving here



https://www3.nationalgeographic.com/genographic/

“Surfing genes” are the major footprints of humanity’s migrations

Neutral mutations have an advantage at an expanding population front



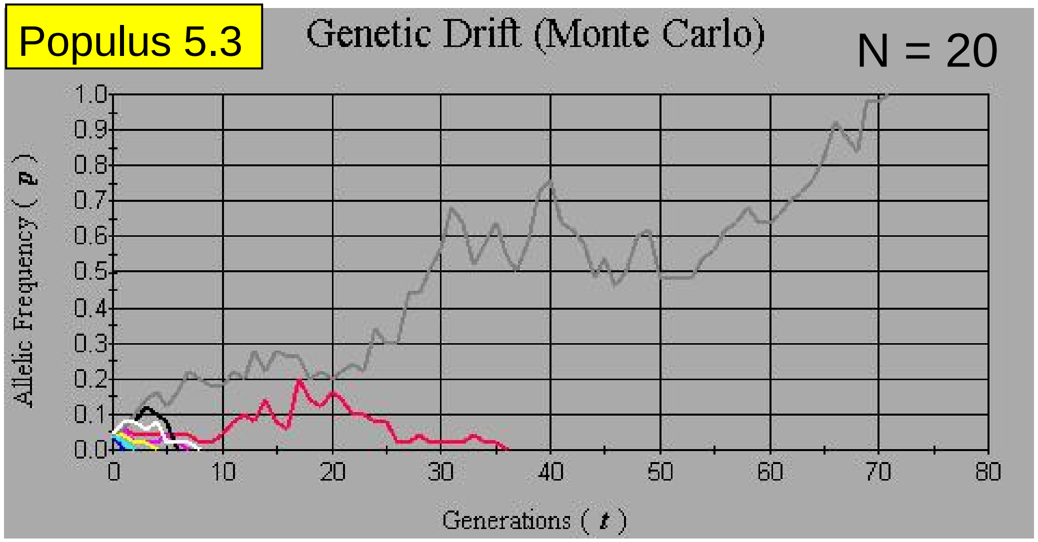
Genetic drift for a neutral mutation

*M. Kimura, Genetics **47**, 713 (1962)*

u(p,t)= probability allele A has frequency p at time t.

•Finite populations go to fixation for long times(using, e.g., Fisher-Wright population sampling)

Neutral mutations have an advantage at an expanding population front



Genetic drift for a <u>neutral</u> mutation

*M. Kimura, Genetics **47**, 713 (1962)*

u(p,t)= probability allele A has frequency p at time t.

•Finite populations go to fixation for long times(using, e.g., Fisher-Wright population sampling)

$$\frac{\partial u(p,t)}{\partial t} = \frac{\partial^2 [D_G \bullet u(p,t)]}{\partial p^2}$$

$$D_G = p(1-p)/(4N)$$

$$u(0,t) = 0;\ u(1,t) = 1$$

•Finite populations go to fixation for long times

•Probability of fixation of a single neutral mutation in a population of size N is just 1/N

•But N is small in the vicinity of an expanding population front!

Introduction to Population Dynamics

$c(t) =$ population of species at time t in region Ω

$$\frac{dc(t)}{dt} = \text{births + saturation + migration}$$

1798 T.R. Matthus $\quad \frac{dc(t)}{dt} = ac(t), \; a > 0$

Introduction to Population Dynamics

$c(t) =$ population of species at time t in region Ω

$$\frac{dc(t)}{dt} = \text{births + saturation + migration}$$

<u>1798</u> T.R. Malthus $\quad \dfrac{dc(t)}{dt} = ac(t), \ a > 0$

<u>1836</u> P.F. Verhulst $\quad \dfrac{dc(t)}{dt} = ac(t) - bc^2(t)$

Introduction to Population Dynamics

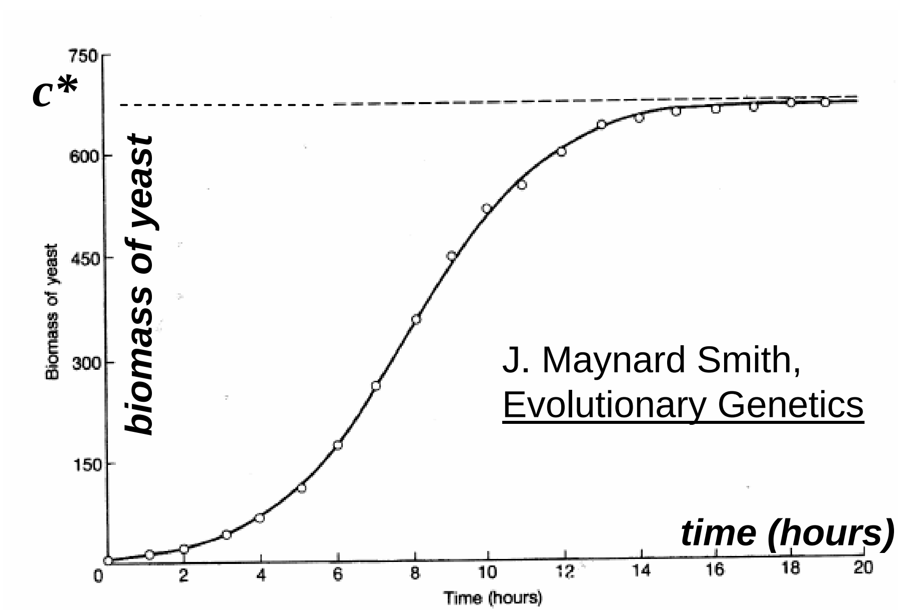
$c(t) =$ population of species at time *t* in region Ω

$$\frac{dc(t)}{dt} = \text{births + saturation + migration}$$

1798 T.R. Matthus $\qquad \frac{dc(t)}{dt} = ac(t), \; a > 0$

1836 P.F. Verhulst $\qquad \frac{dc(t)}{dt} = ac(t) - bc^2(t)$

stable population size: $c^* = a/b$



J. Maynard Smith, Evolutionary Genetics

Fisher Waves and Population Dynamics

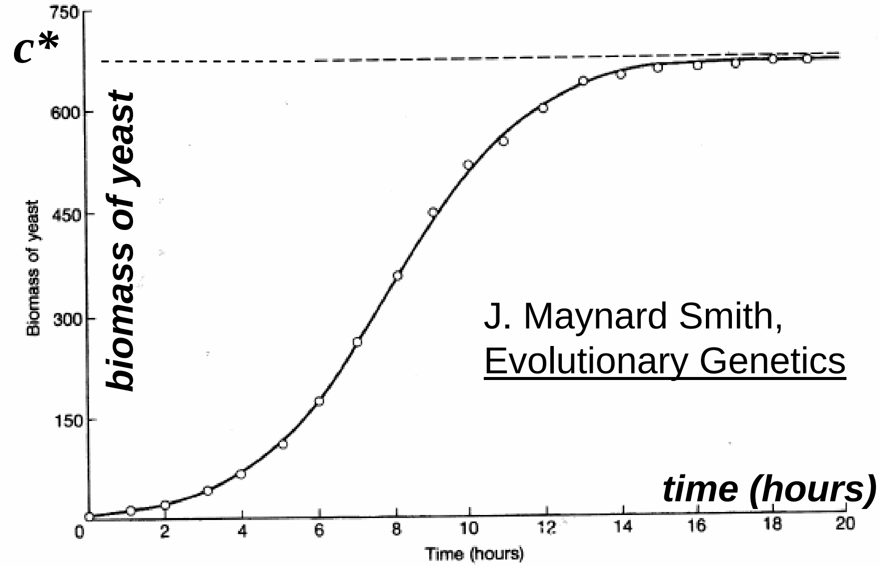
$c(t) =$ population of species at time t in region Ω

$$\frac{dc(t)}{dt} = \text{births + saturation + migration}$$

1798 T.R. Matthus $\qquad \dfrac{dc(t)}{dt} = ac(t),\ a > 0$

1836 P.F. Verhulst $\qquad \dfrac{dc(t)}{dt} = ac(t) - bc^2(t)$

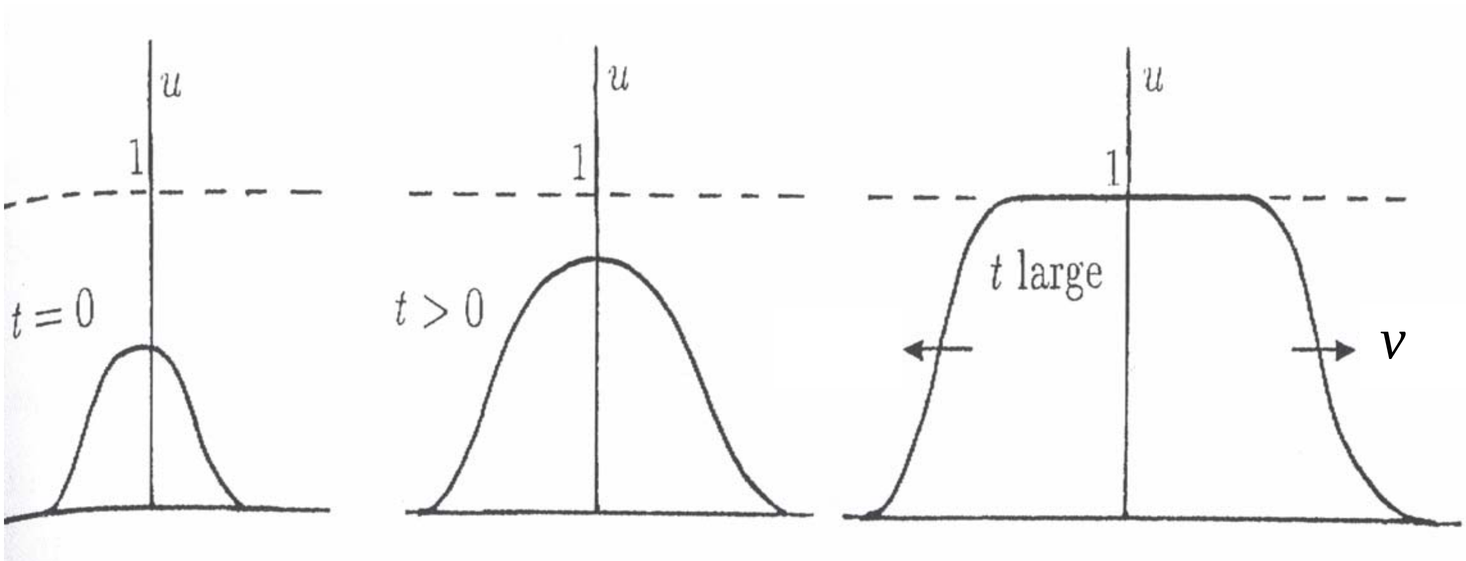
stable population size: $c^* = a/b$



1937 R.A. Fisher $\qquad c = c(\vec{r},t) \qquad \dfrac{\partial c(\vec{r},t)}{\partial t} = D\nabla^2 c(\vec{r},t) + ac(\vec{r},t) - bc^2(\vec{r},t)$

Fisher Waves In One Dimension

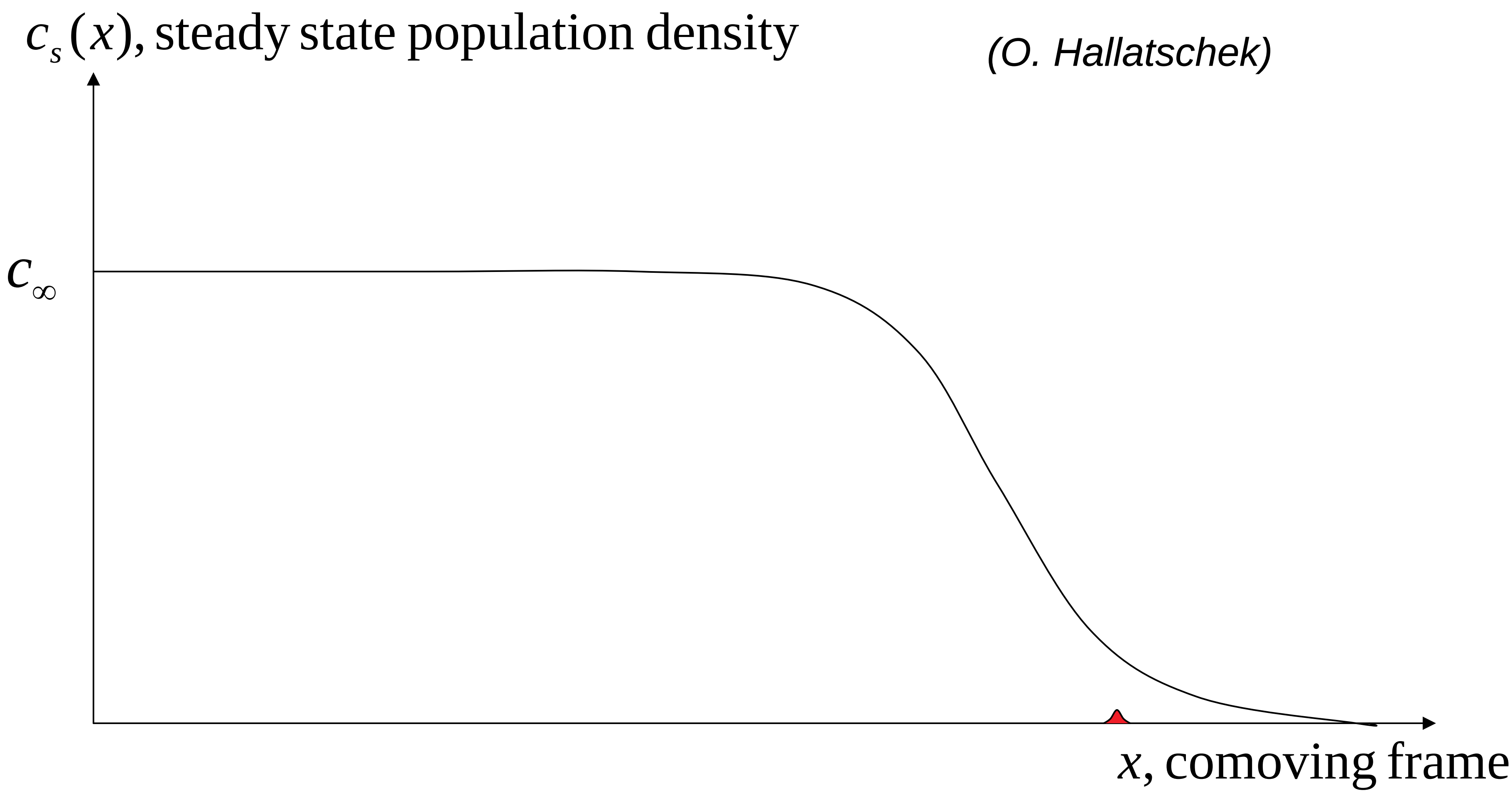
$$\frac{\partial}{\partial t}c(x,t) = D\frac{\partial^2}{\partial x^2}c(x,t) + ac(x,t) - bc^2(x,t); \quad let\ c(x,t) = f(x - vt)$$



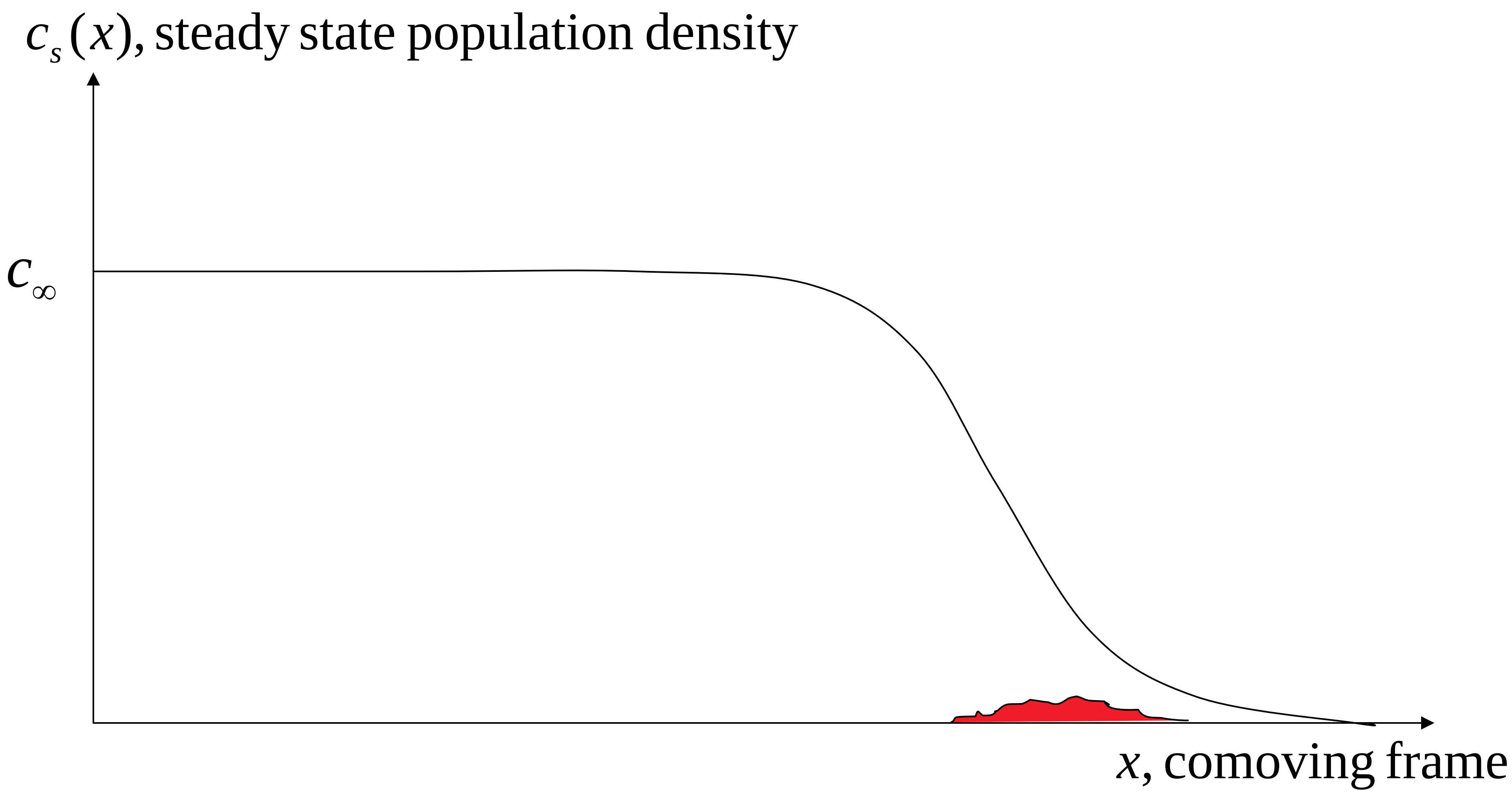
Schematic time development of a wavefront solution of Fisher's equation on the infinite line. (J.D. Murray, Mathematical Biology)

$$Interface\ velocity = 2\sqrt{Da} \qquad Interface\ width = \sqrt{D/a}$$

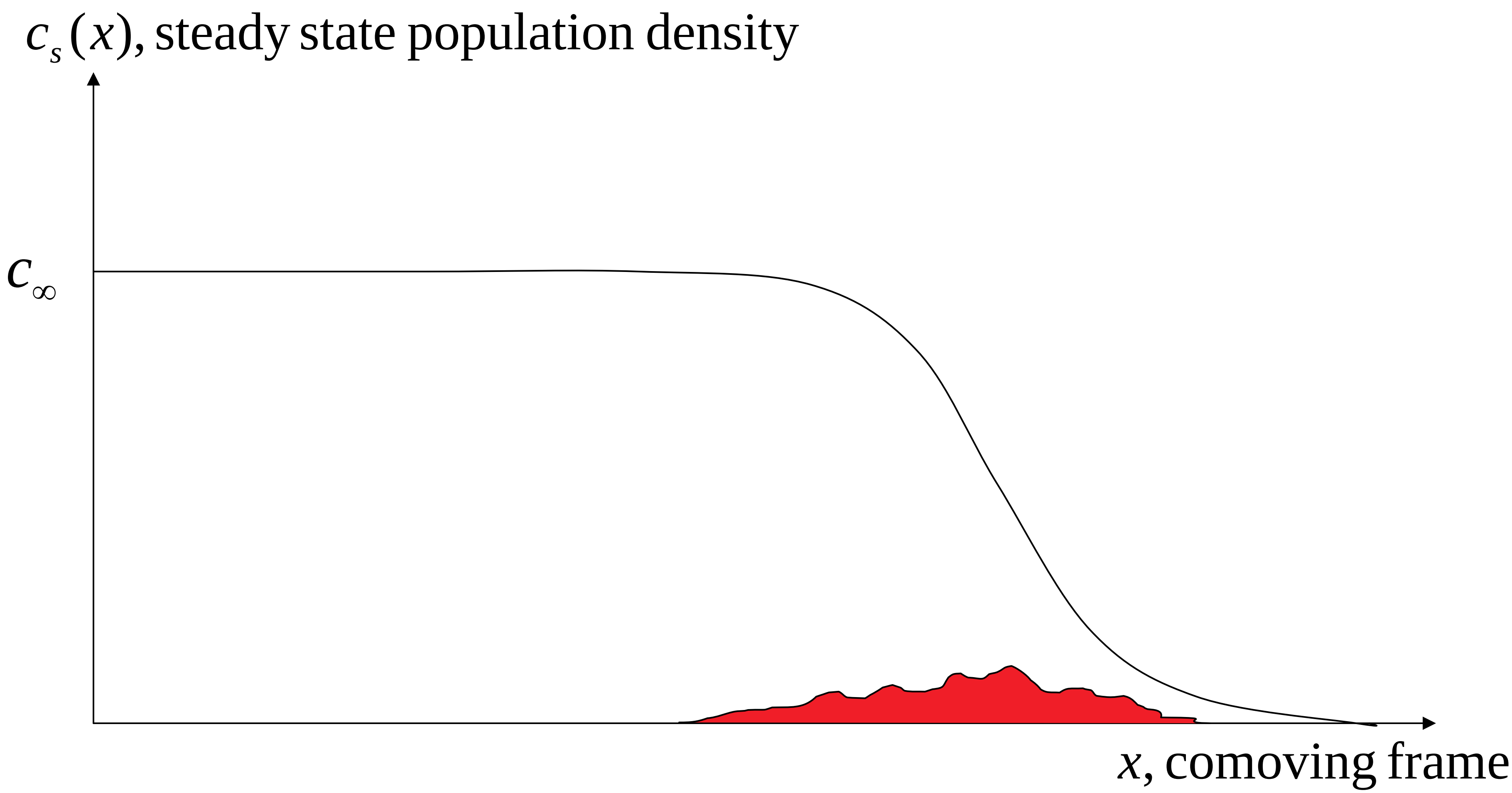
Successful Surfing (1d)



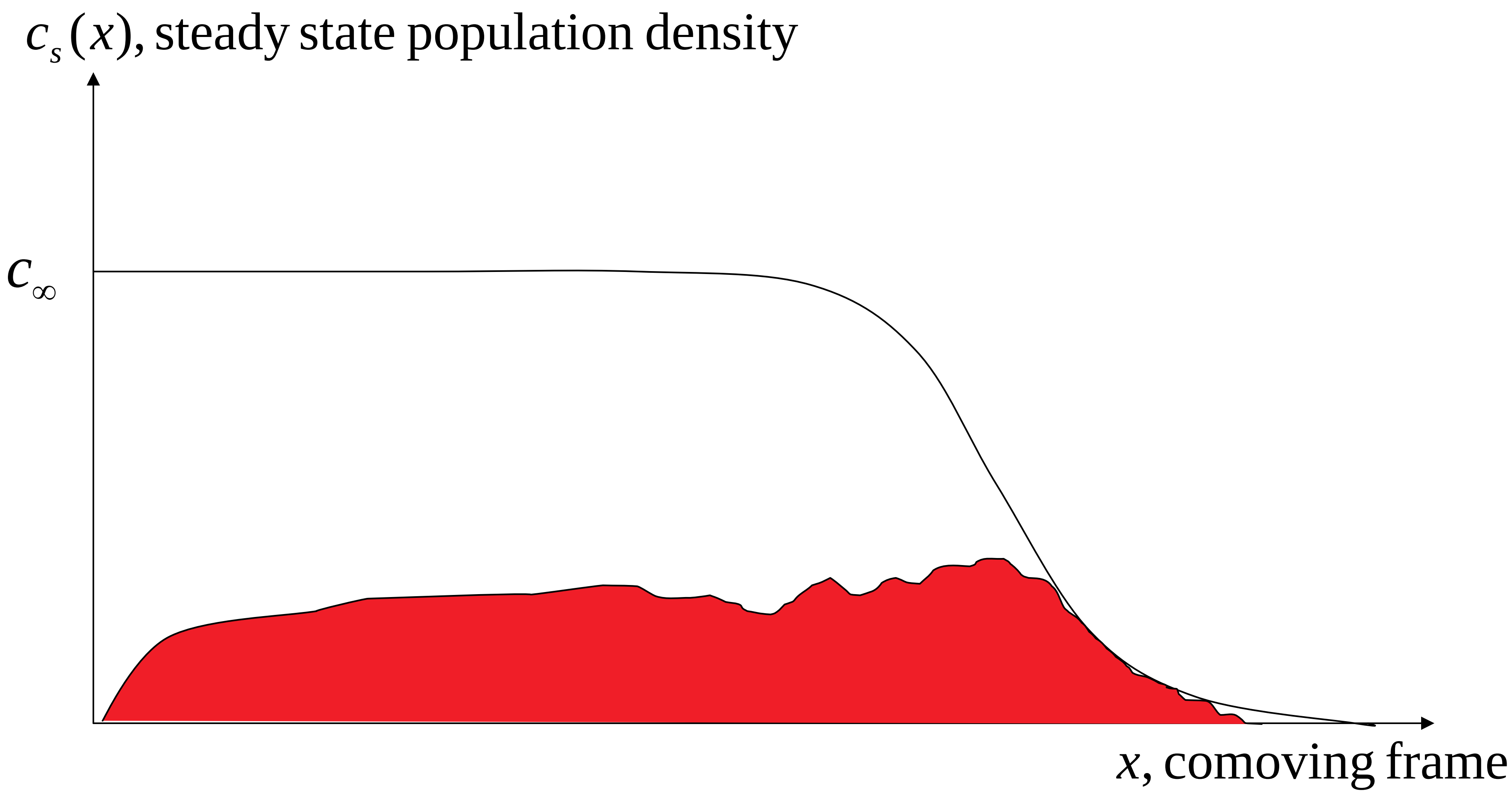
Successful Surfing (1d)



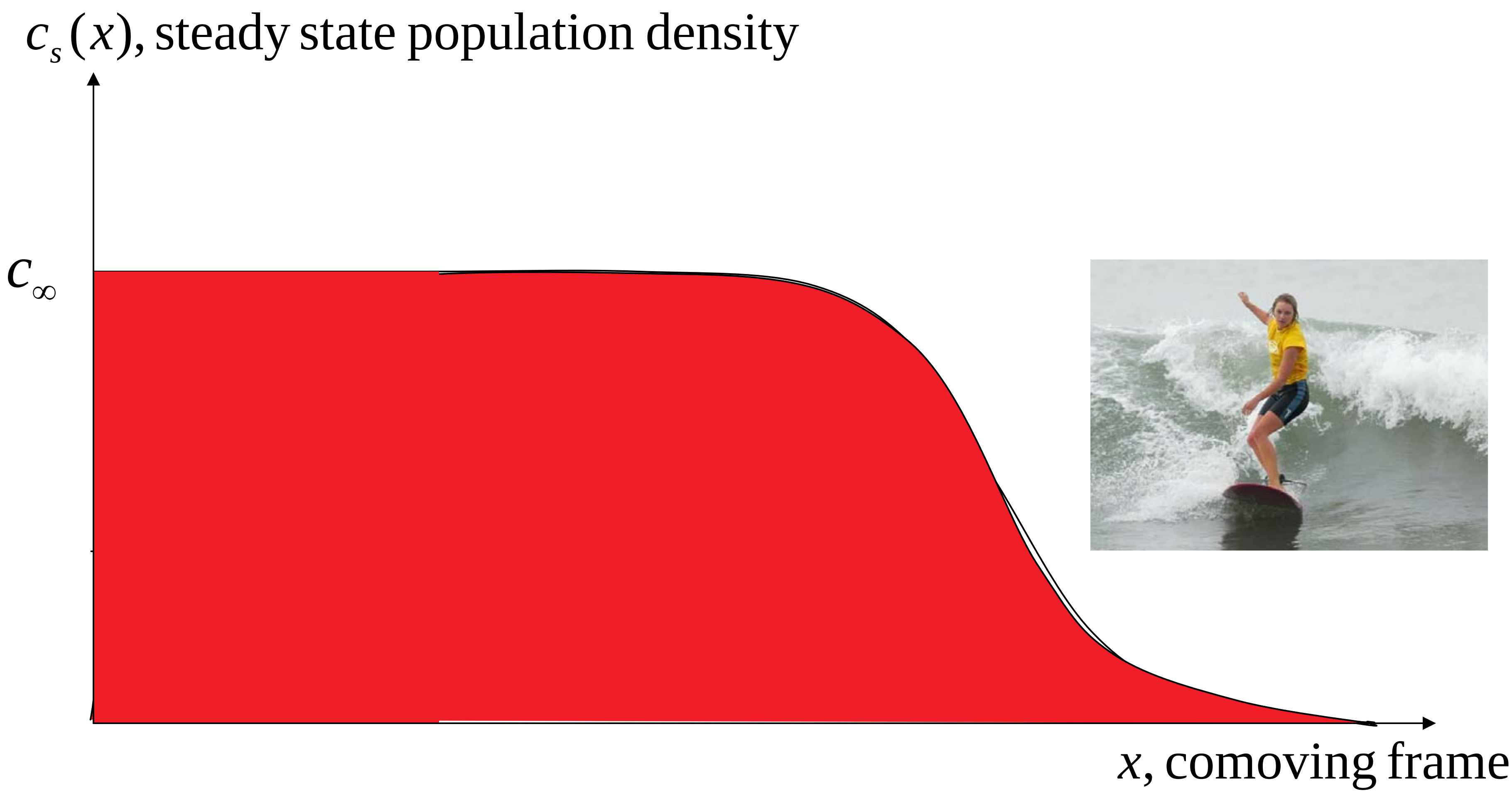
Successful Surfing (1d)



Successful Surfing (1d)

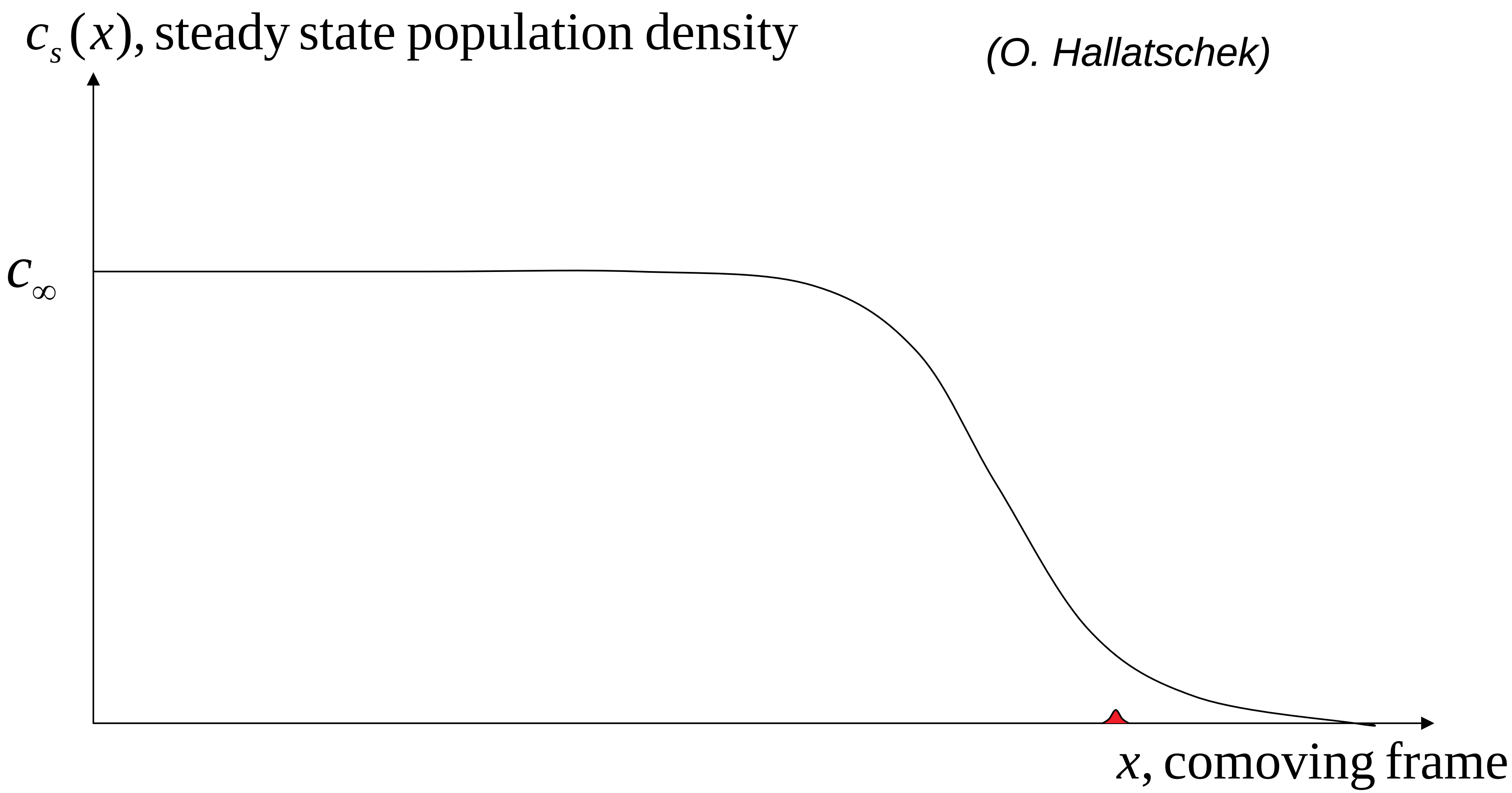


Successful Surfing (1d)

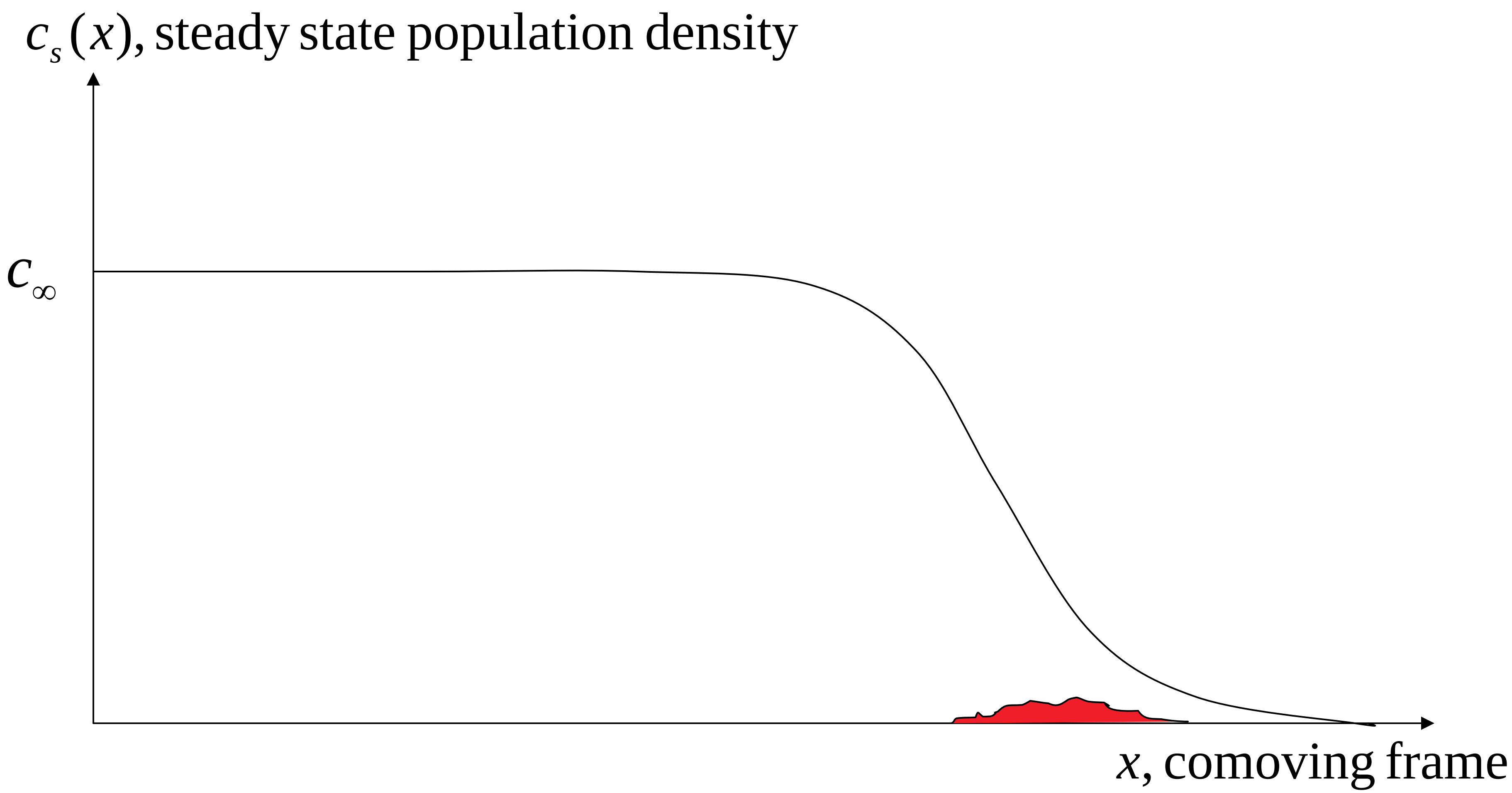


Often however …

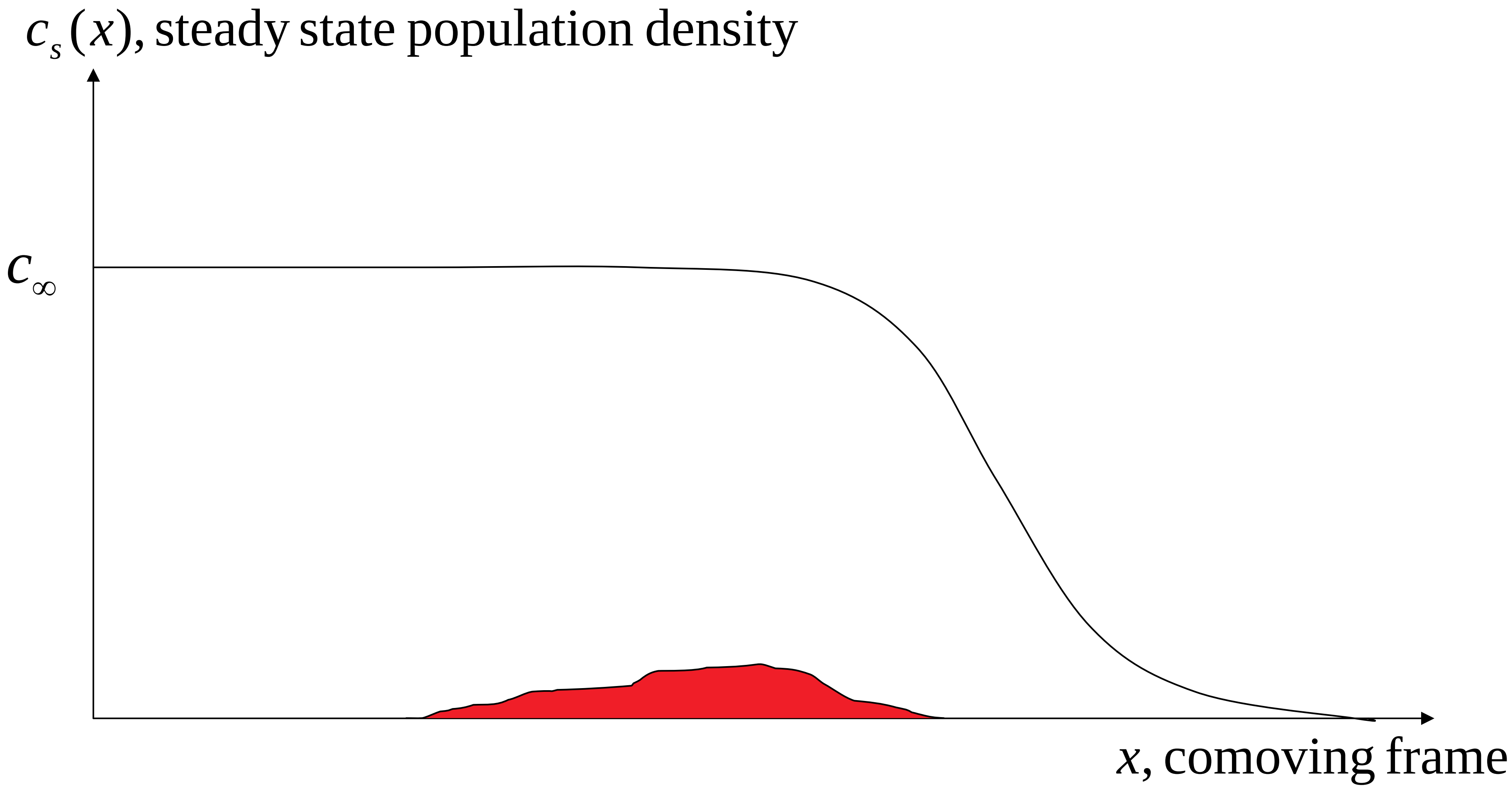
(O. Hallatschek)



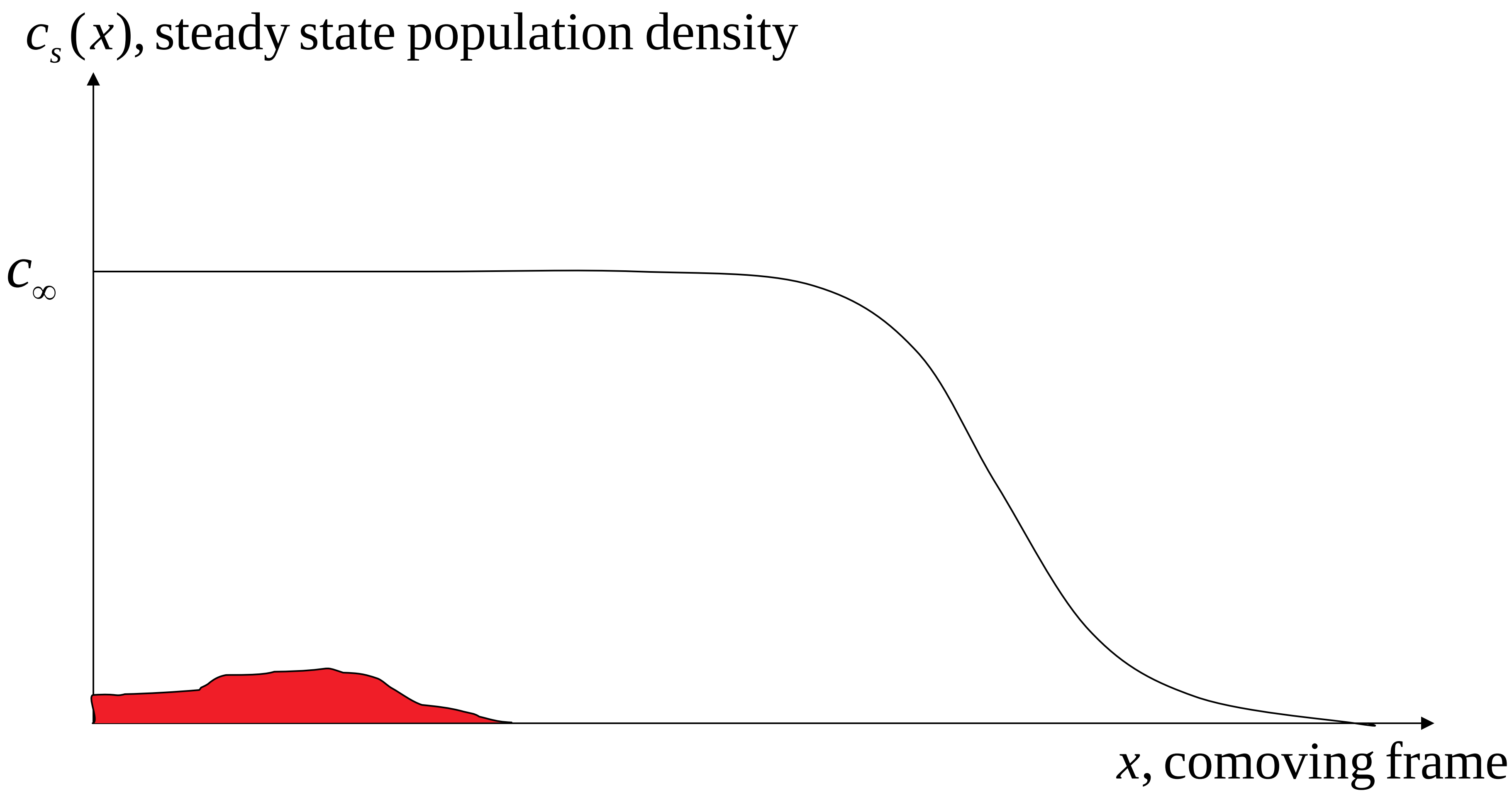
Often however …



Often however …

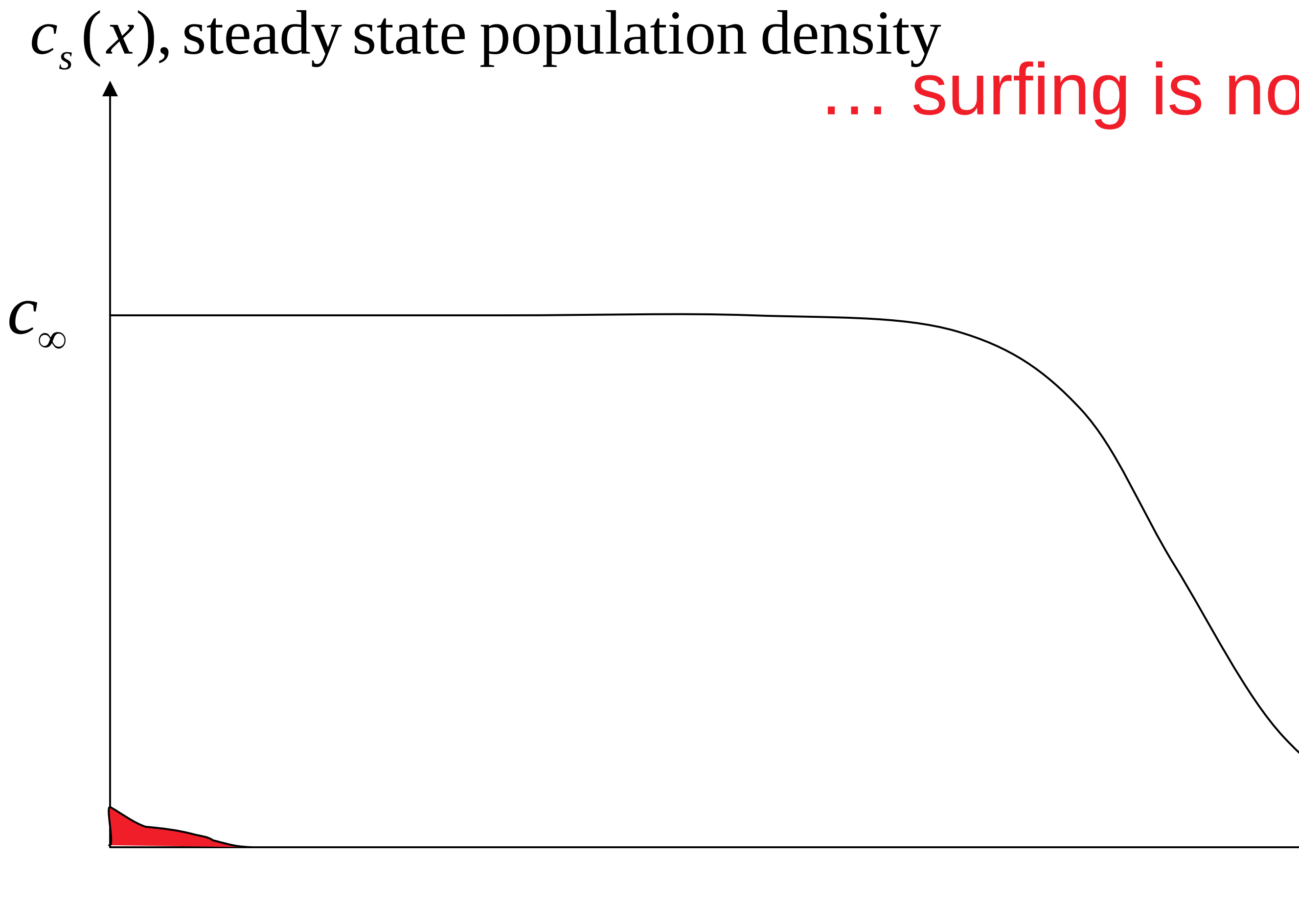


Often however …



Often however …

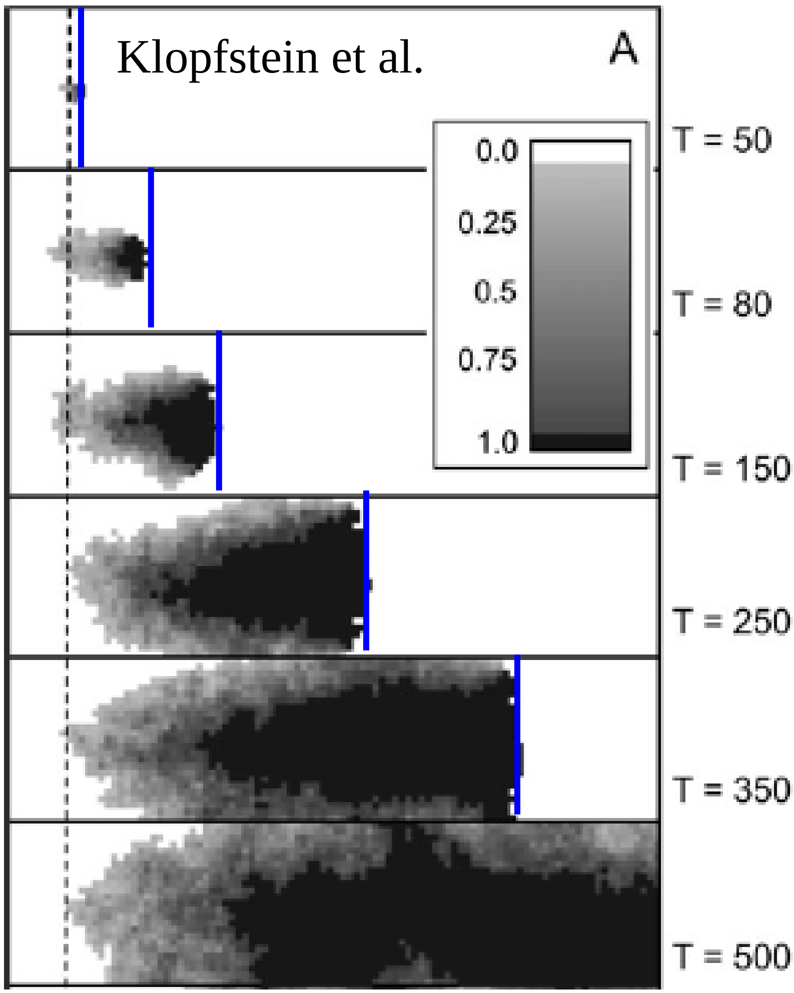
… surfing is not achieved!



*Mutations Surfing on a **Two-Dimensional** Population Wave*

S. Klopfstein, M. Currat, and L. Excoffier, Mol. Biol. Evol. **23**, 482–490 (2006)

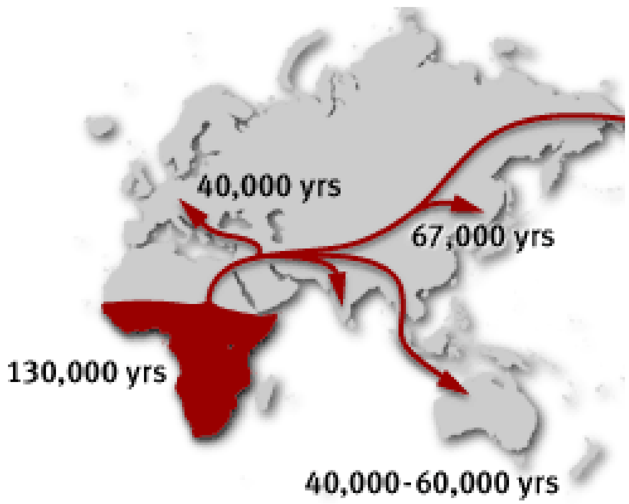
C. A. Edmonds, A. S. Lillie, and L. Cavalli-Sforza PNAS 975–979 (2004)



Effective population size at the front of a wave can be very small….

1. What is the probability of successful surfing?
2. How does this depend on the position of the mutation within the interface?
3. How does a successful mutation spread laterally downstream?
4. How do neutral mutations (initially well mixed) segregate in space when carried along a population wave?

Can Gene Surfing be Studied in Bacteria (or Yeast!)?



*E. J. Stewart et al., PLoS, Biology, **3**, 295 (2005)(Taddei Lab)*

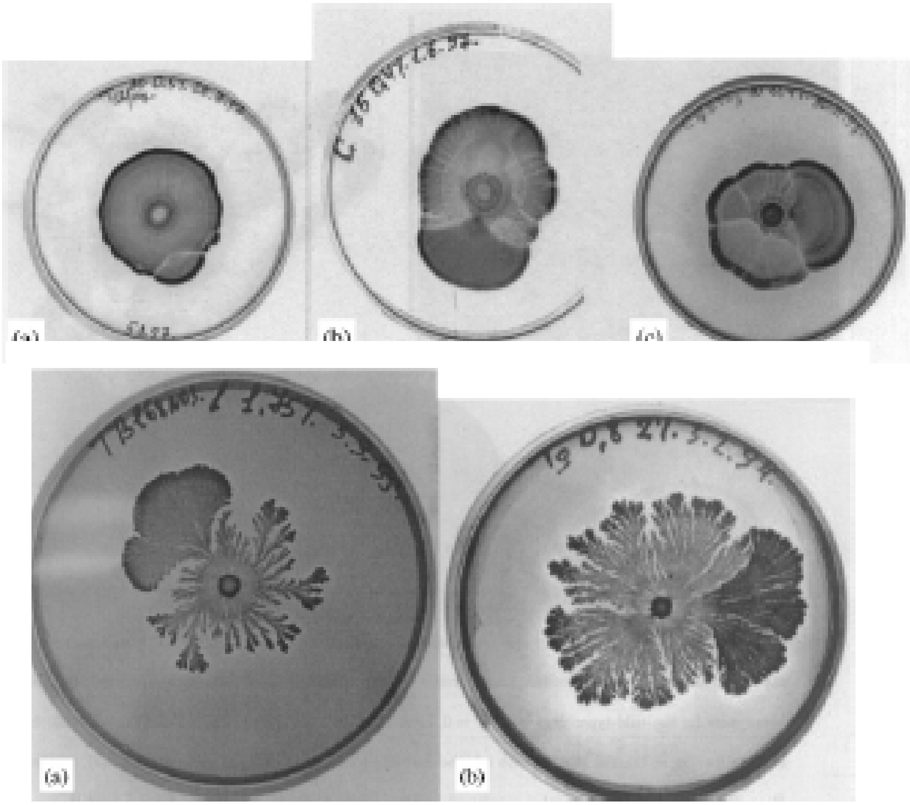
Twitching motility?

	Large mammals (with mitochondria)	E. coli with flagella	E. coli without flagella
t_2	9×10^8 sec. (30 years)	1500 sec.	1500 sec.
l_2	10^6 cm. (10 km.)	10^{-1} cm.	10^{-3} cm.
$D=l_2^2/2t_2$	10^3 cm^2/sec	2×10^{-6} cm^2/sec	7×10^{-10} cm^2/sec
velocity	1×10^{-3} cm/sec	1×10^{-4} cm/sec	1×10^{-6} cm/sec
L(500)	10^4 km	30 cm	0.5 cm

Range expansion in 500 generations

"Surfing" (= Sectoring) in Paenibacillus dendritiformis:

I. G. Ron et al. Physica A320, 485 (2003)



Emerging sectors in compact colonies of P. dendritiformis.

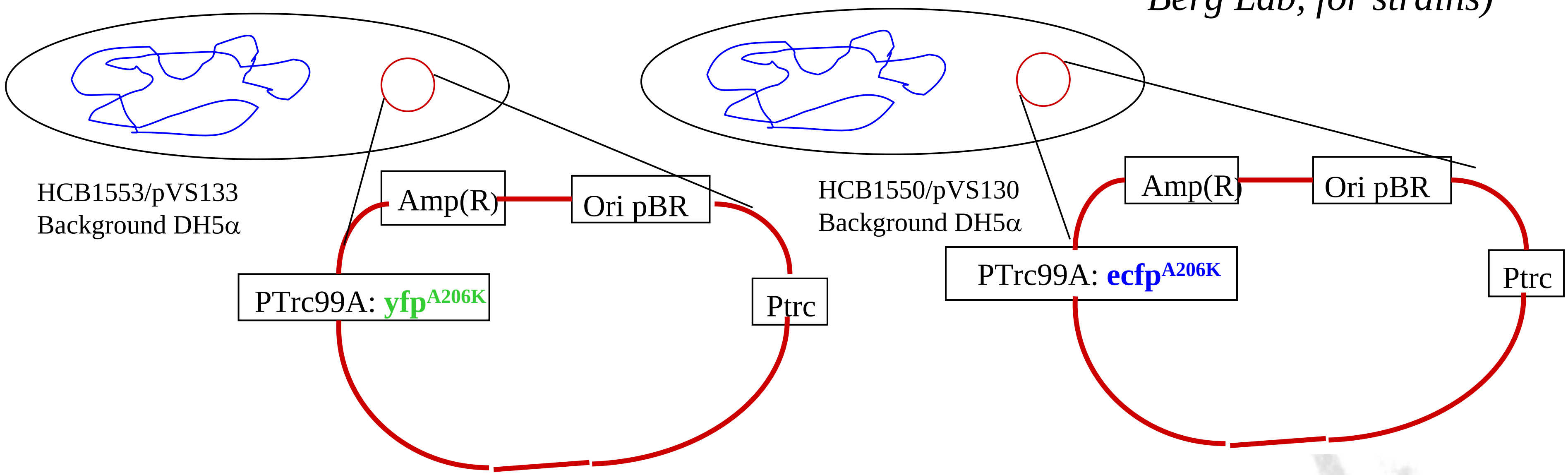
Emerging sectors in branching colonies of P. dendritiformis.

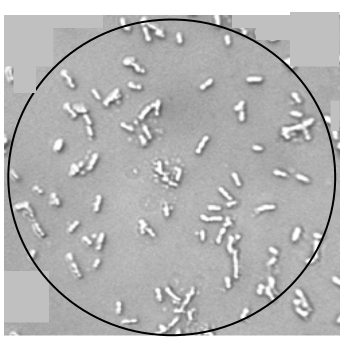
- *Unless mutants have a different growth dynamics (and hence are not neutral!), they will go unnoticed…*

- *Can we create **<u>strictly neutral</u>** mutations at the interface of a bacterial population front, and follow their subsequent dynamics?*

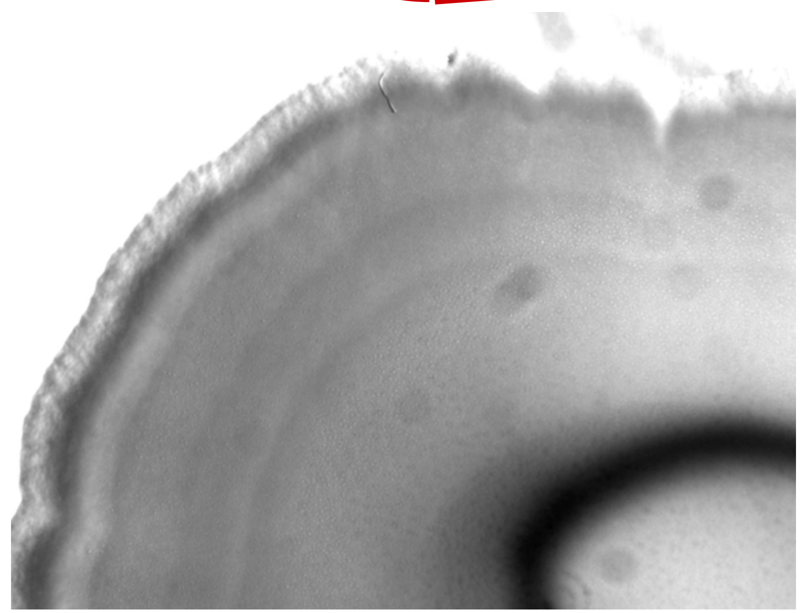
Gene Surfing in nonmotile E. coli

(thanks to Tom Shimizu, Berg Lab, for strains)



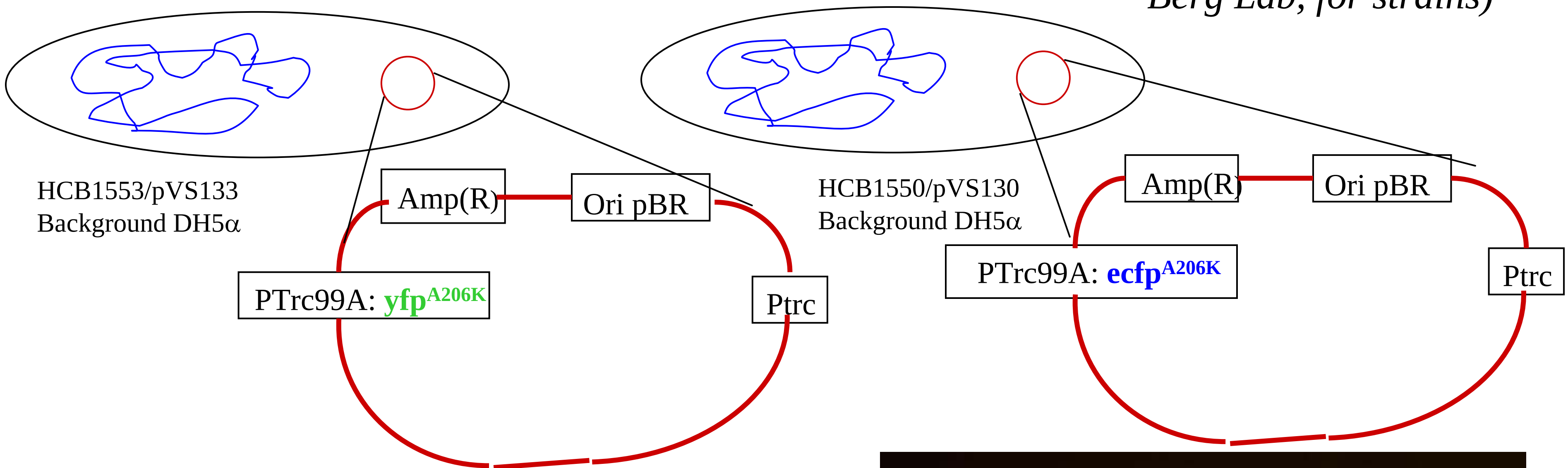


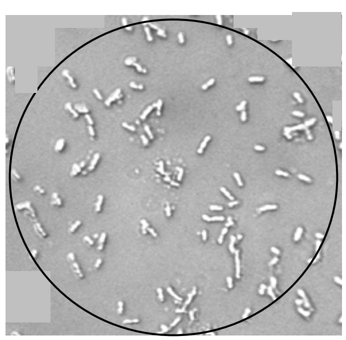
50-50 mixture,
1550/1553



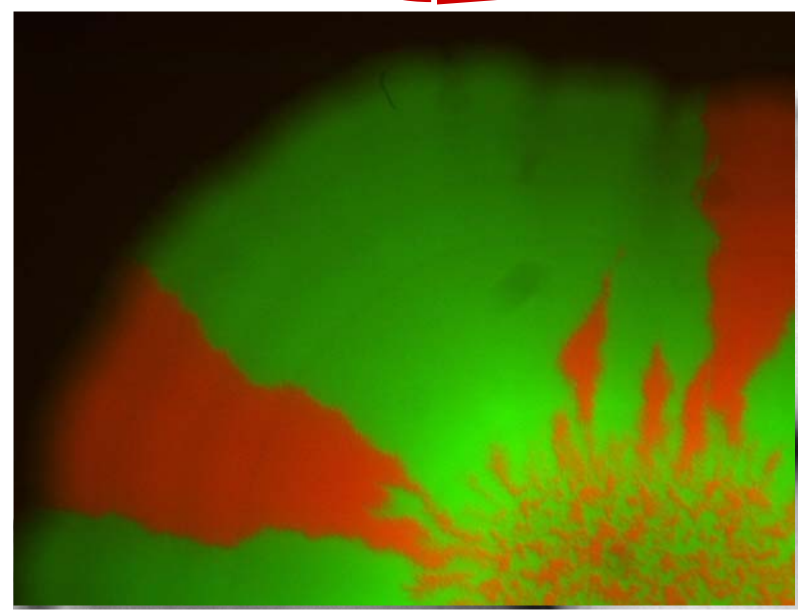
Gene Surfing in nonmotile E. coli

(thanks to Tom Shimizu, Berg Lab, for strains)





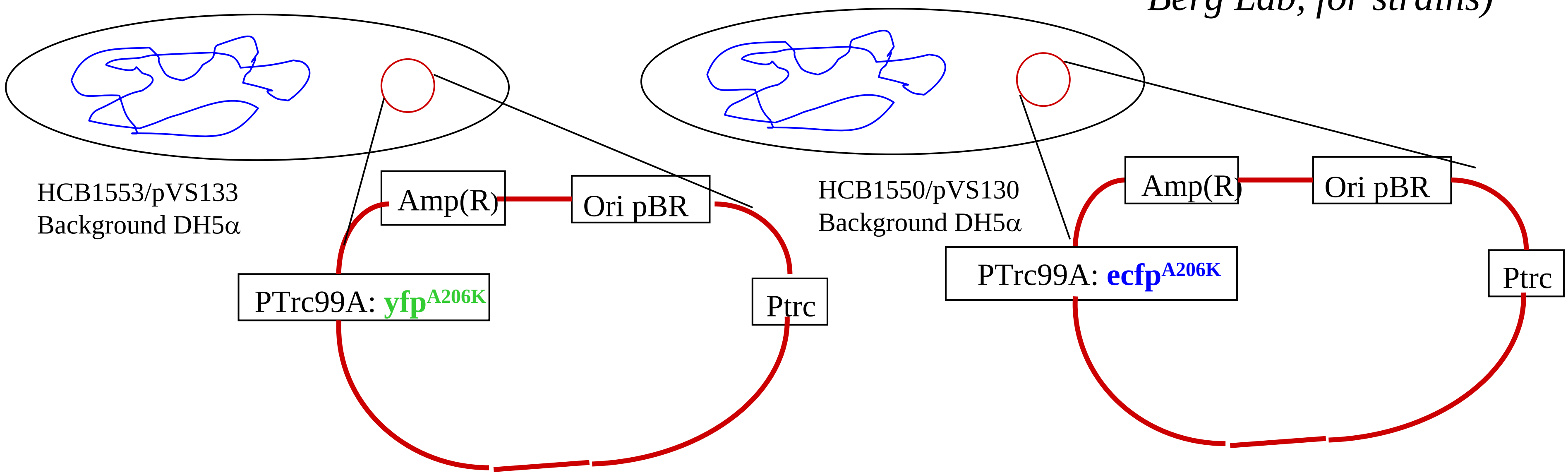
50-50 mixture,
1550/1553

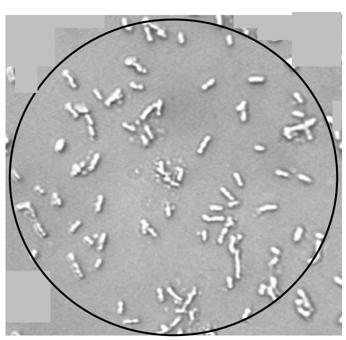


Cyan → Red

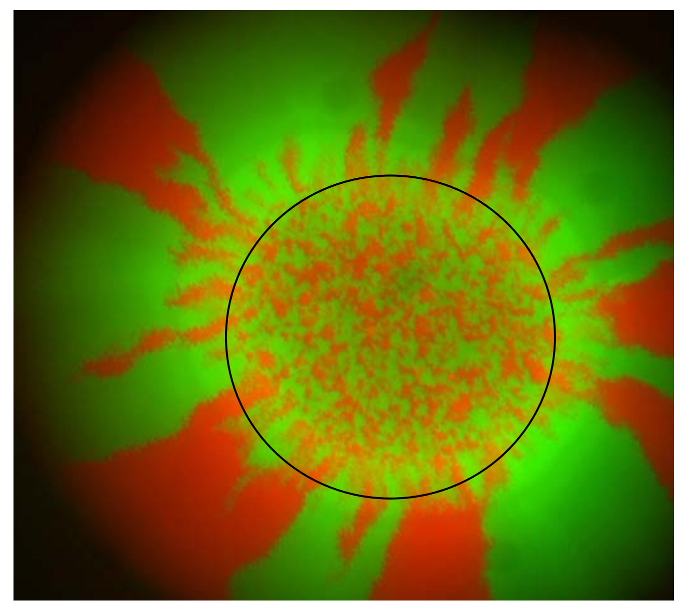
Gene Surfing in nonmotile E. coli

(thanks to Tom Shimizu, Berg Lab, for strains)





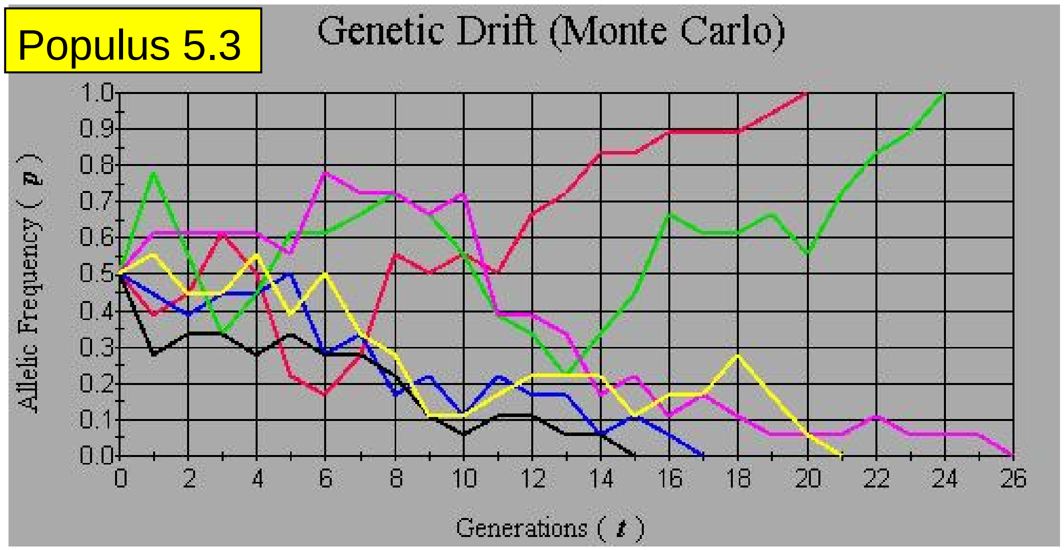
50-50 mixture,
1550/1553



Cyan → Red

Genetic drift is enhanced at the frontier…

Consider a 50-50 “panmictic” solution of N_r red & N_b blue bacteria in a test tube



Let H_n = “heterozygosity”

= probability that two randomly chosen bacteria <u>differ</u> in color

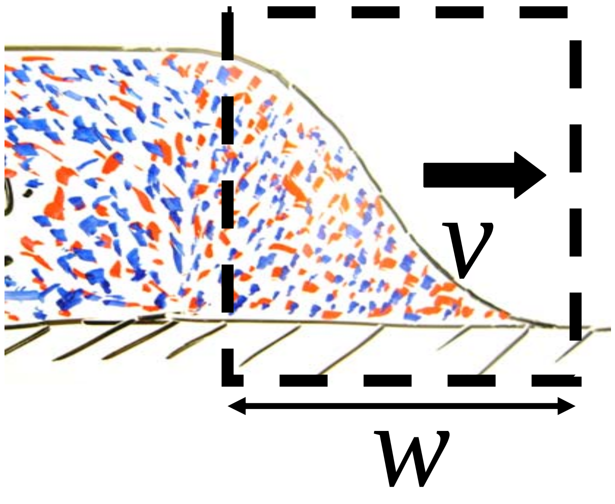
τ = generation time

$$H(t) \approx H_0 e^{-t/\tau N_{eff}}$$

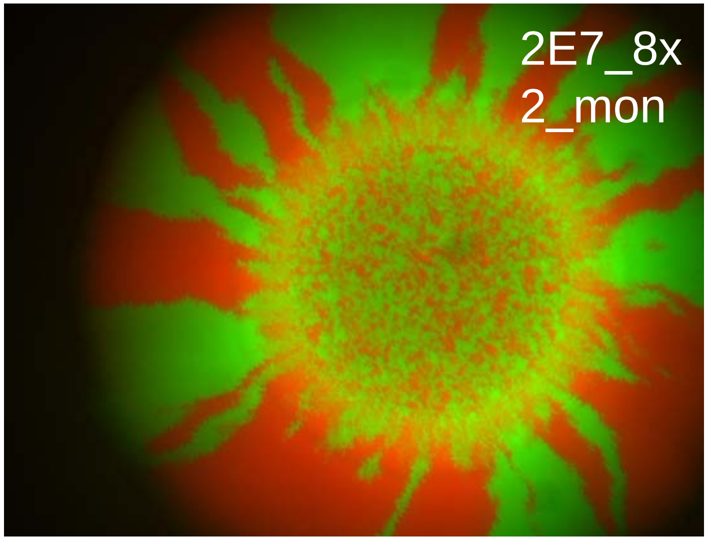
$$N_{eff} = effective\ population\ size$$

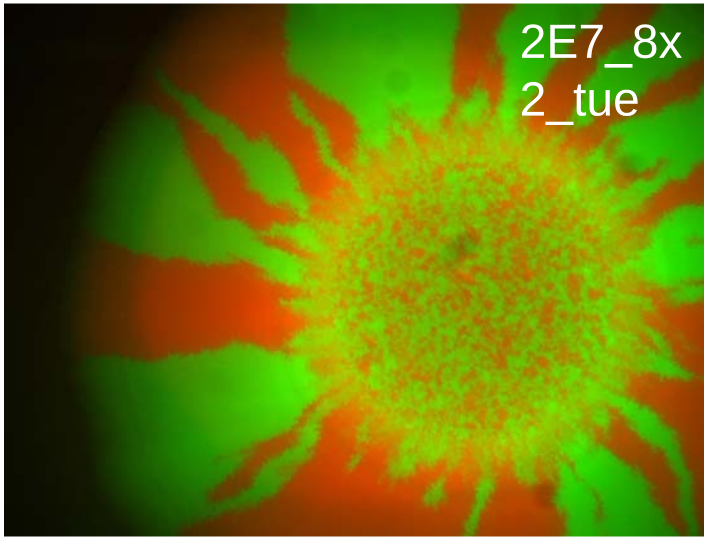
$N_{eff} \approx 10^9$, in an overnight culture, but

$N_{eff} \approx 10$, for immotile bacteria modelled by a Fisher wave

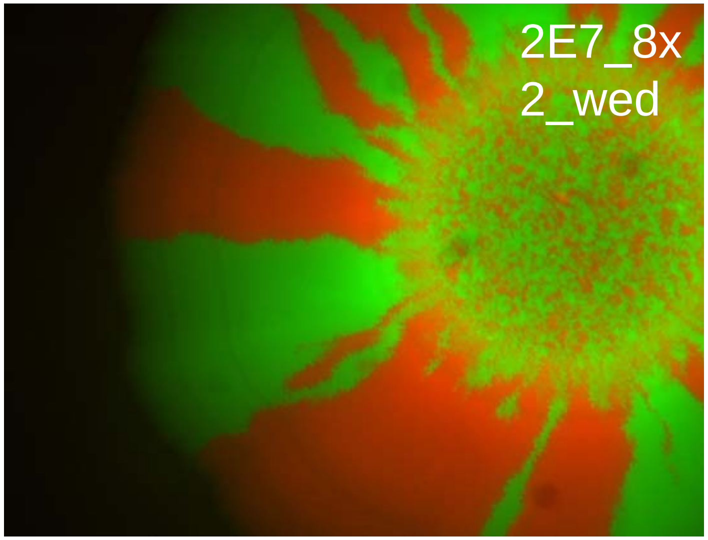


50-50 HCB1550/1553 circular inoculants



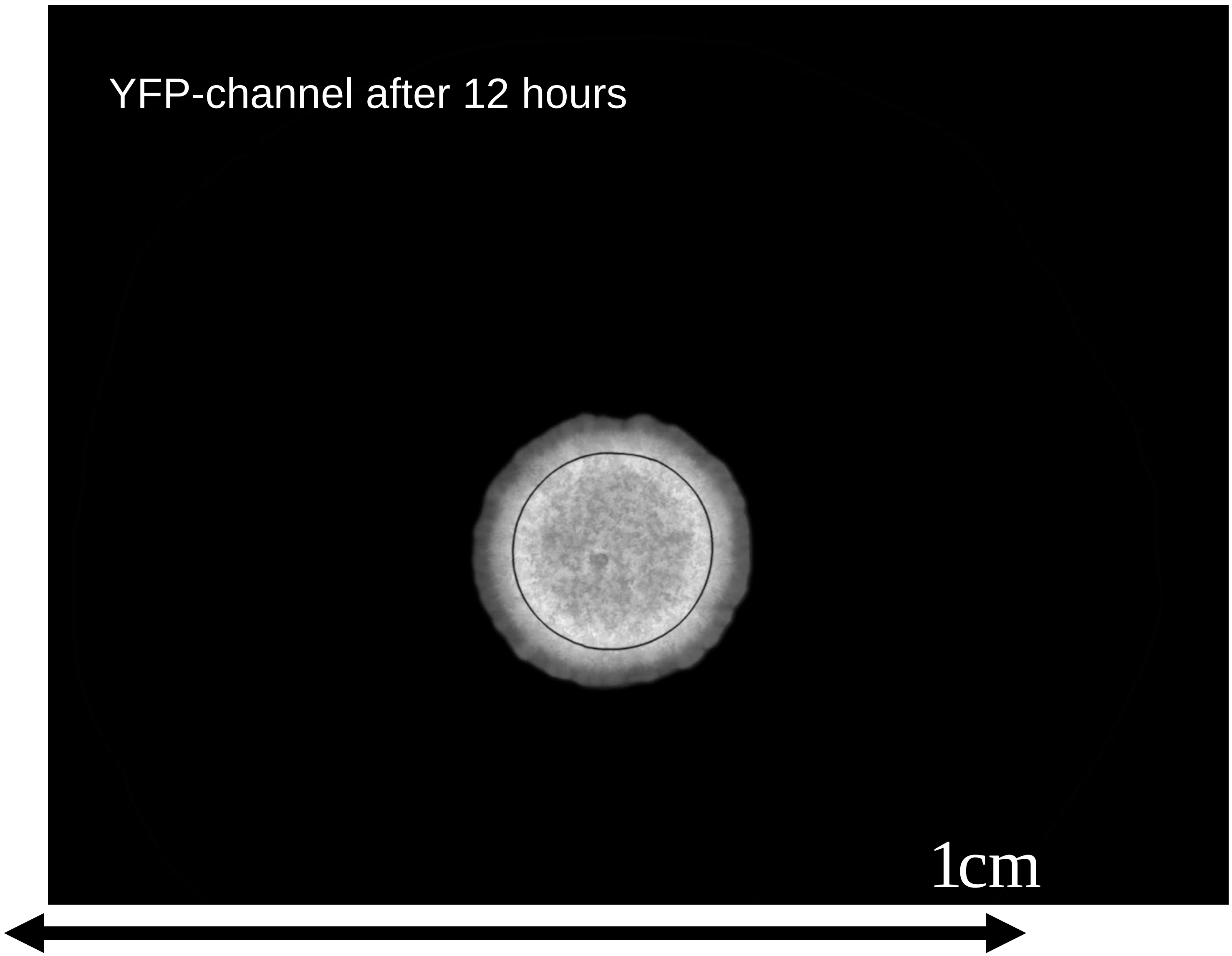


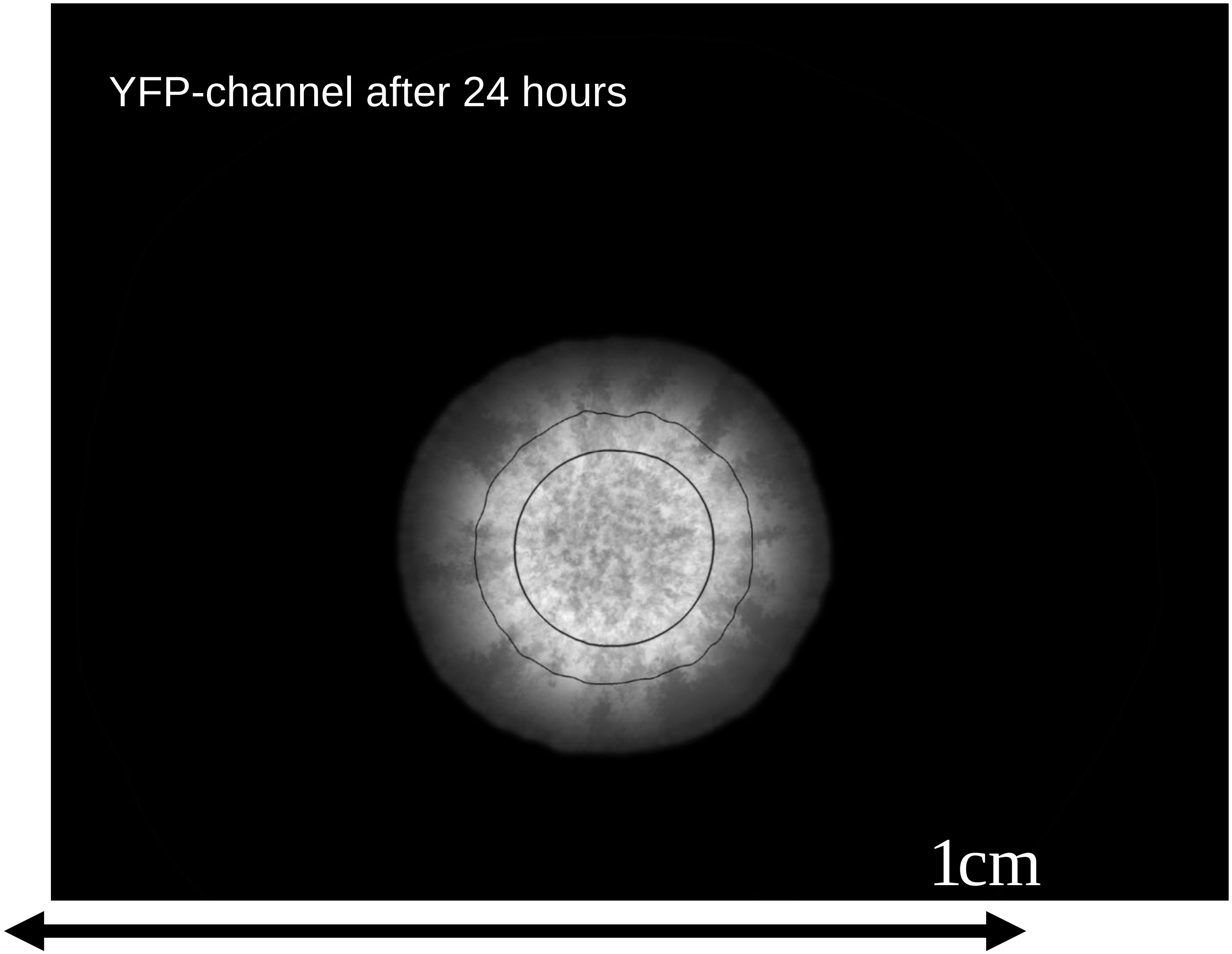
= 2 mm.

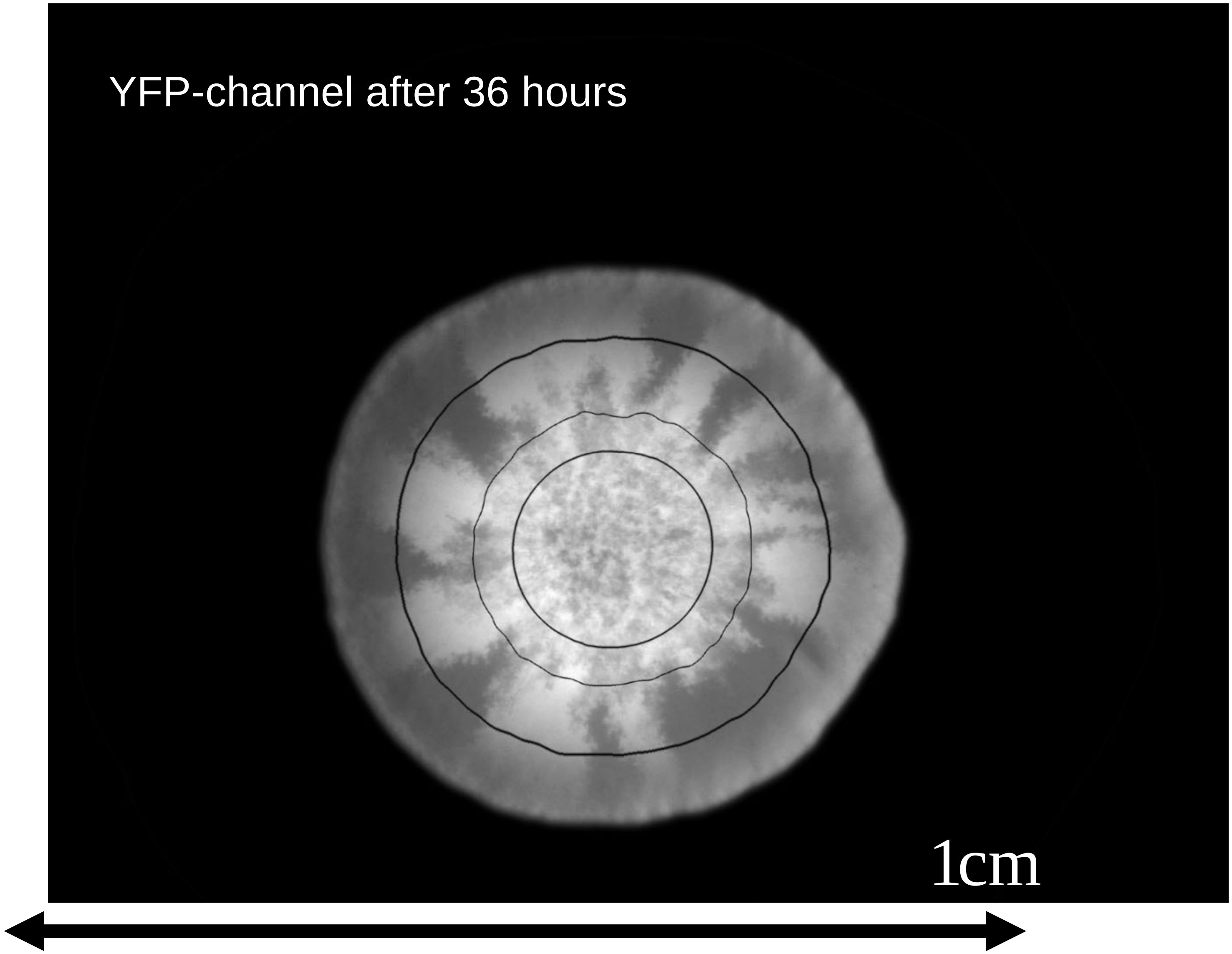


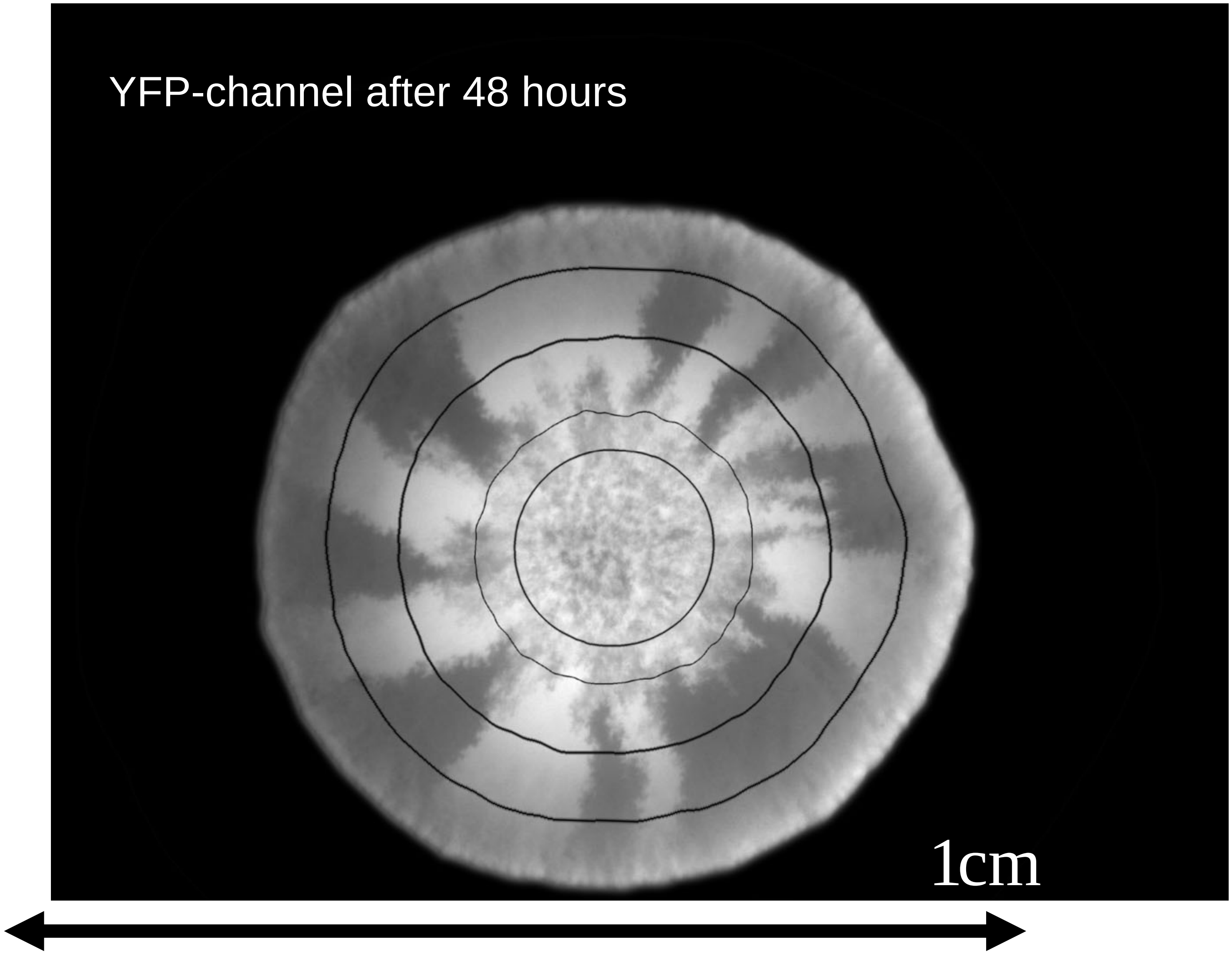
Founder population ≅ 5000

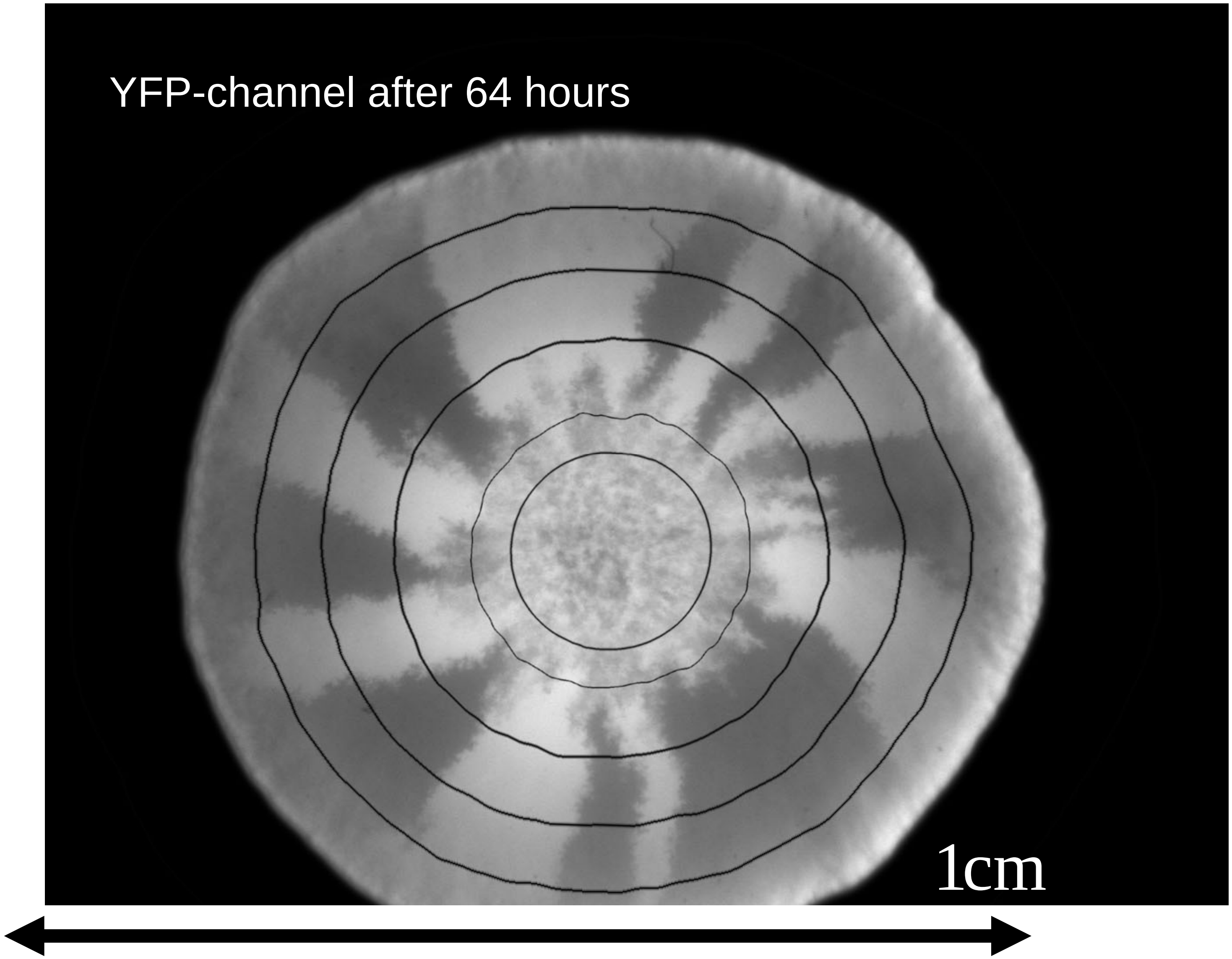
Segregation patterns both in the "homeland" area and radial "sectors" <u>lock in</u> behind wave

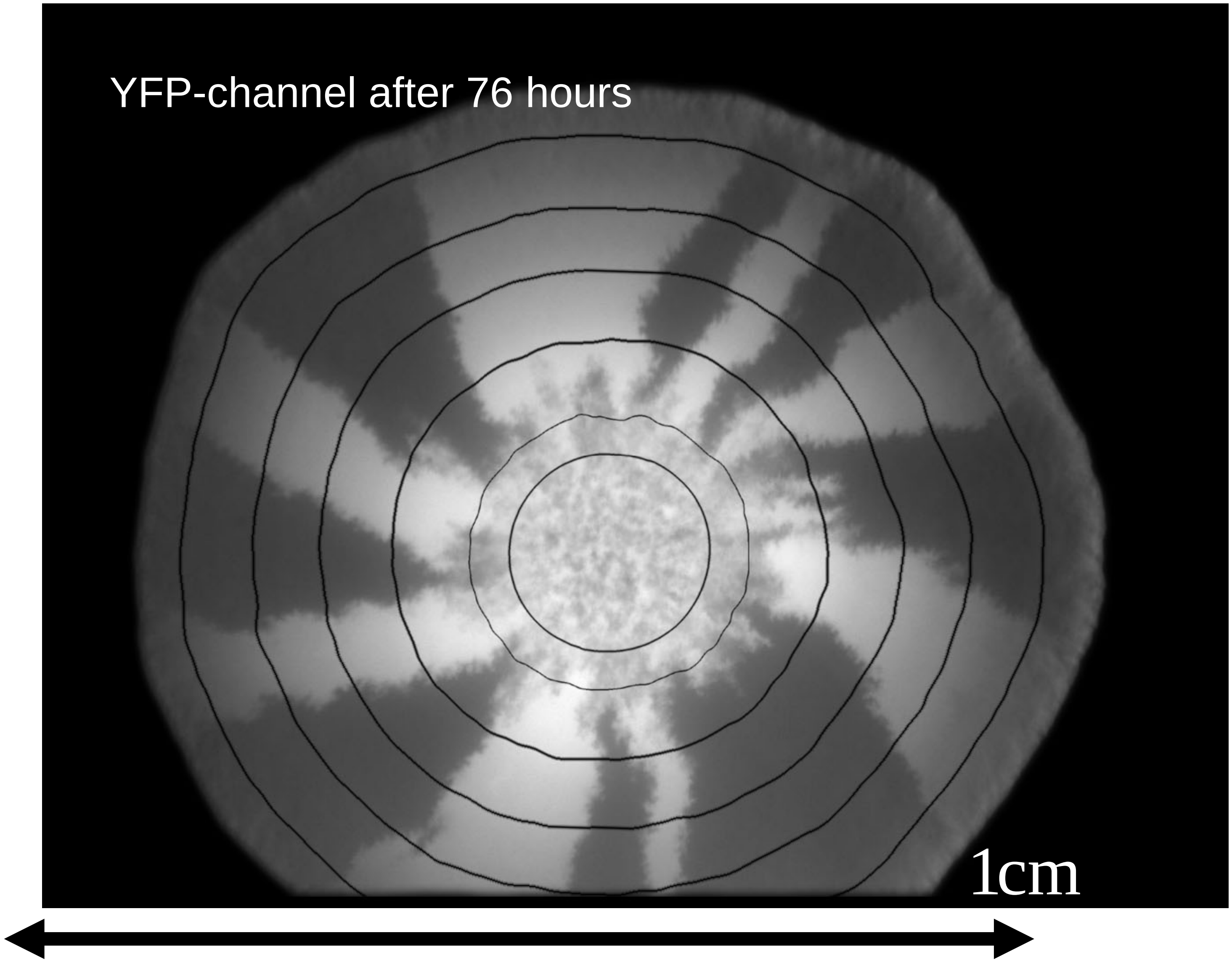

YFP-channel after 12 hours
1cm


YFP-channel after 24 hours
1cm

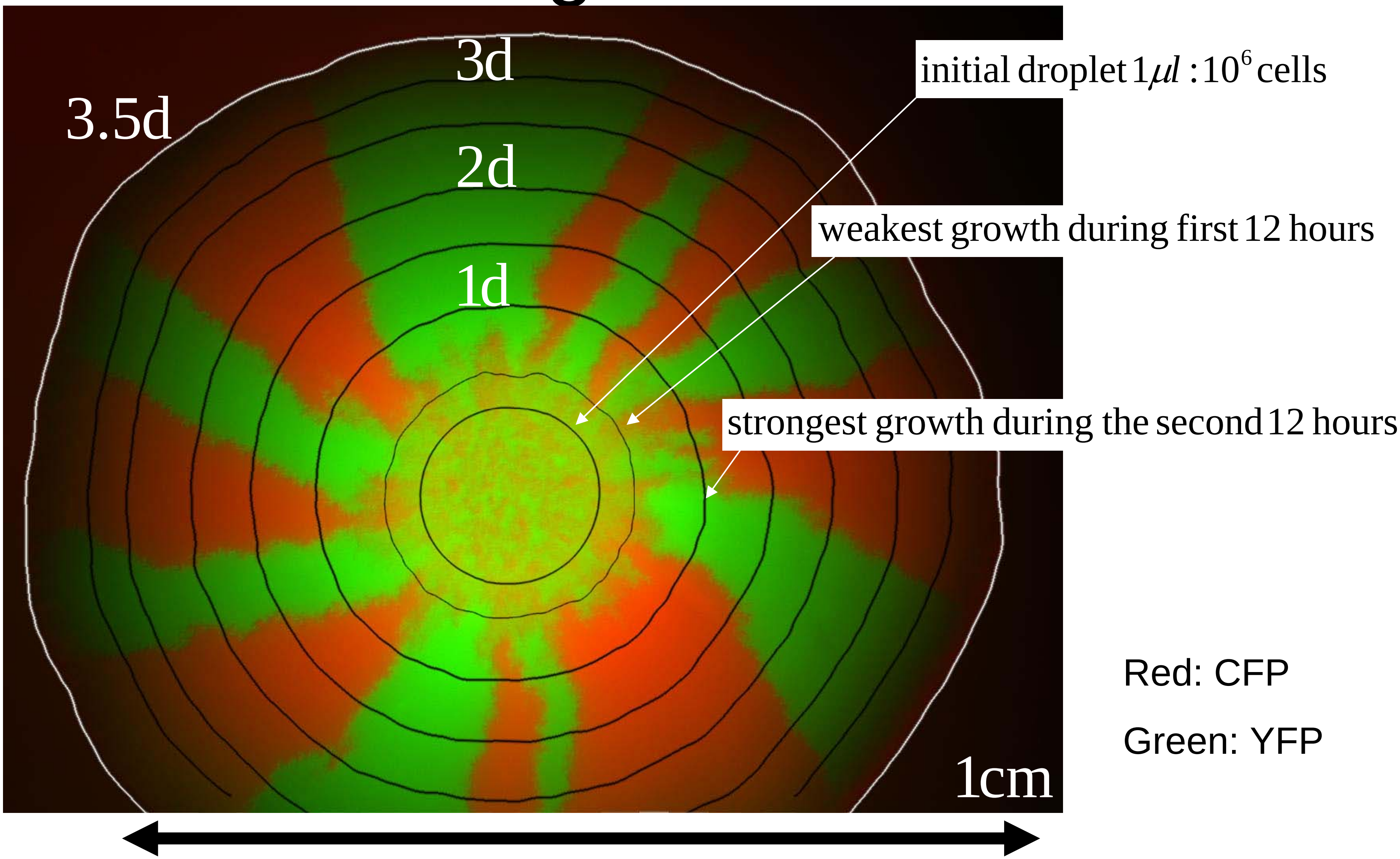

YFP-channel after 36 hours
1cm


YFP-channel after 48 hours
1cm


YFP-channel after 64 hours
1cm


YFP-channel after 76 hours
1cm

Gene surfing in E. coli colonies



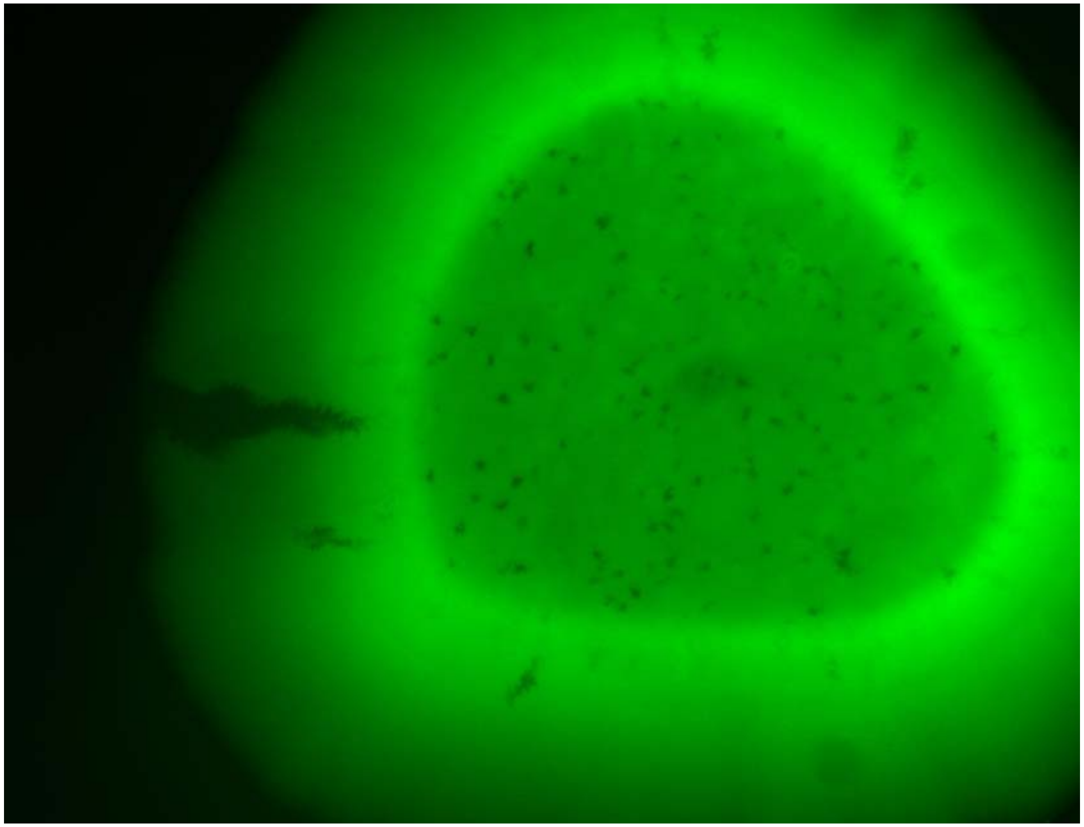
Red: CFP

Green: YFP

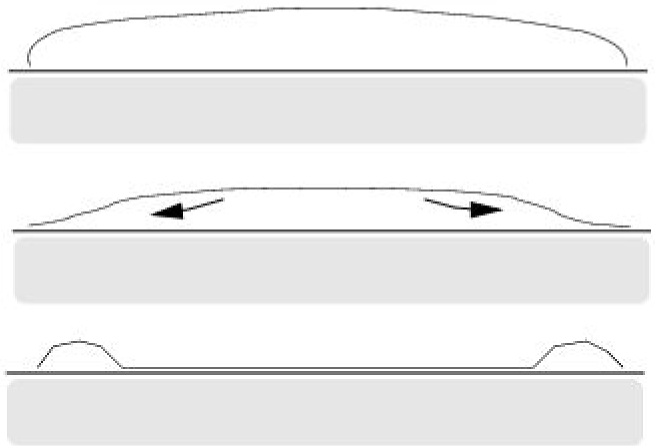
Sector creation in the dilute limit I

98%-2% mixture
green channel only
founder population~5000

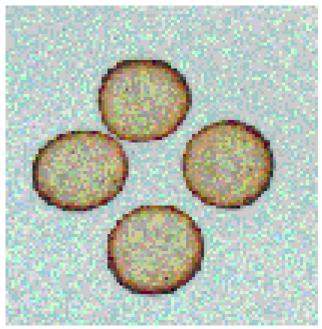
But why is there a bright rim???

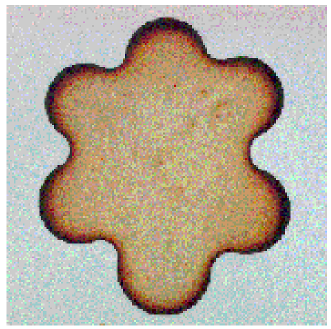


Coffee stain effect



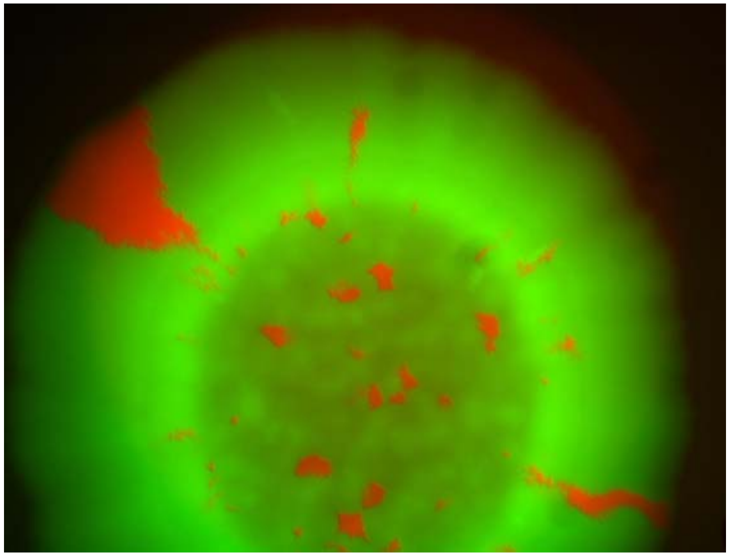
http://visindavefur.hi.is/svar.asp?id=5513



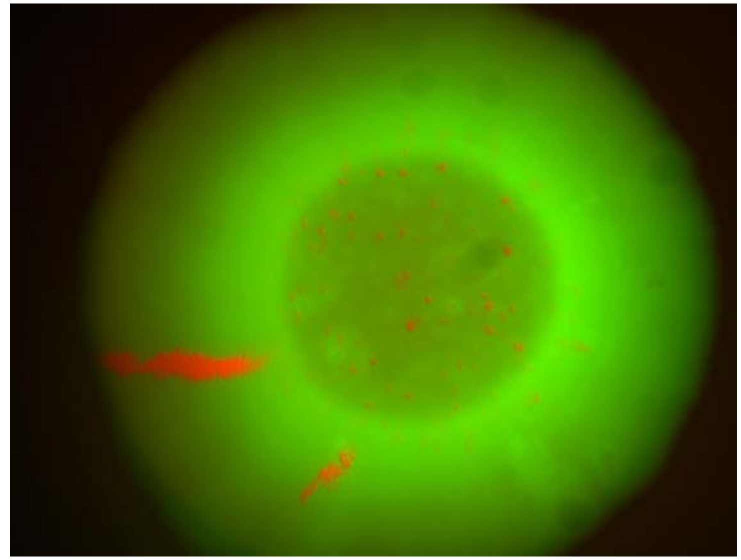


S. Nagel et al. Univ. of Chicago

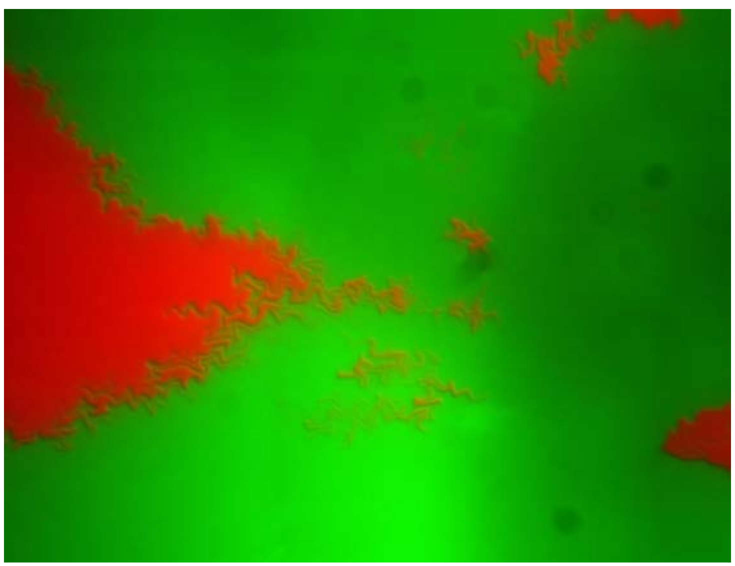
Sector creation in the dilute limit II

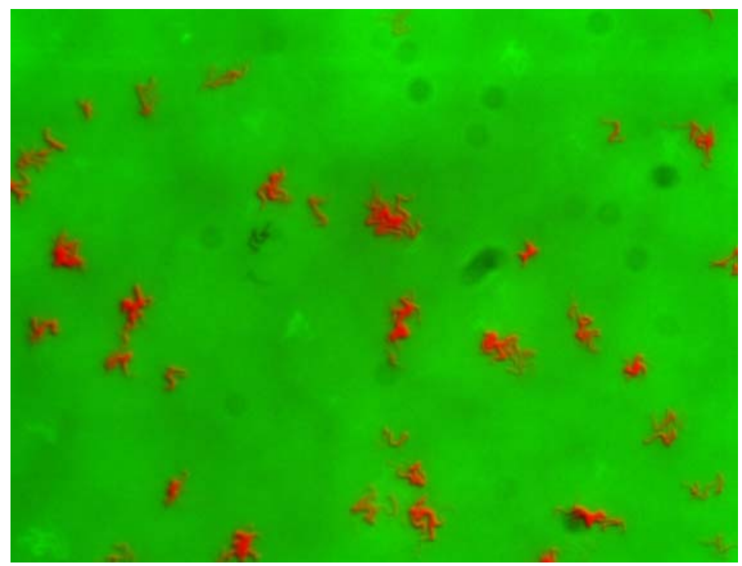


95%-5% mixture, founder population ~ 500



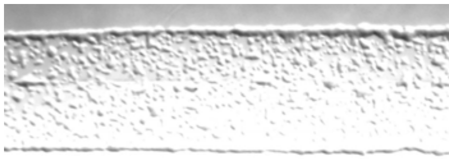
98%-2% mixture, founder population ~ 5000



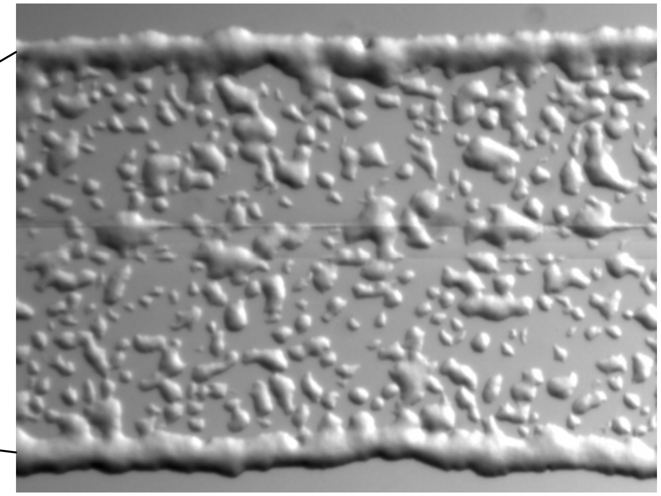


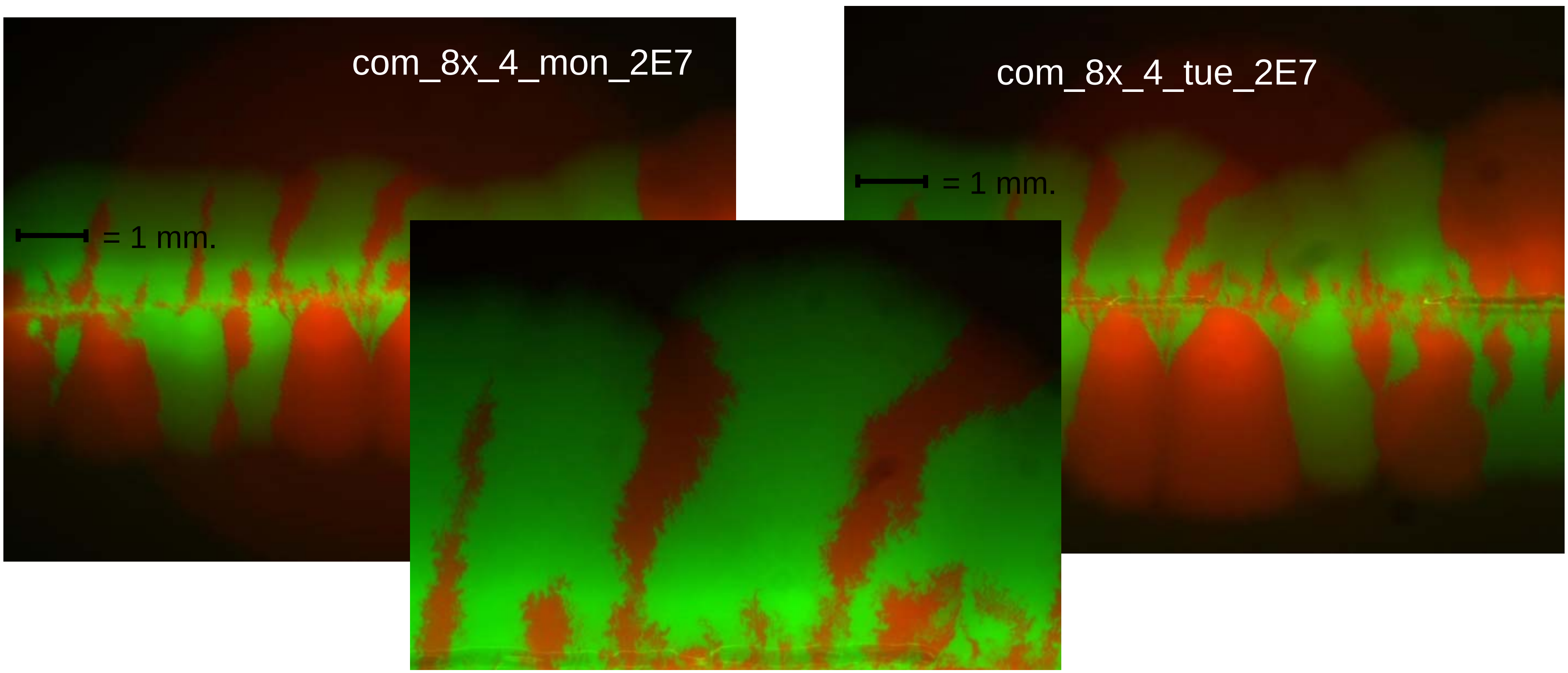
Linear inoculants (razor blade) 50%-50% mixtures

100X, 6h after innoculation

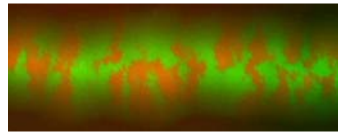


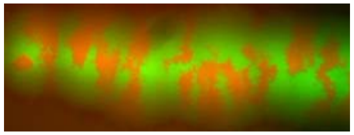
coffee stain effect!

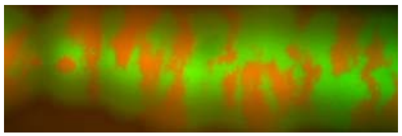


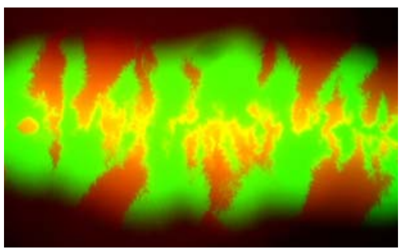


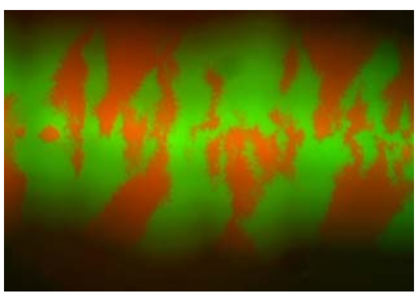
Growth velocity of linear innoculation

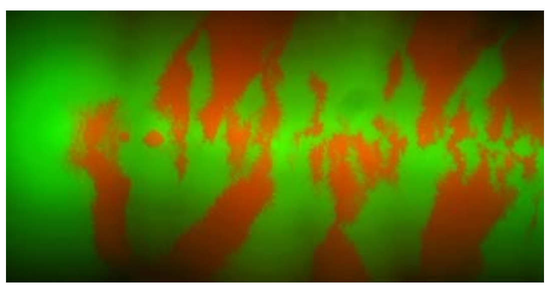


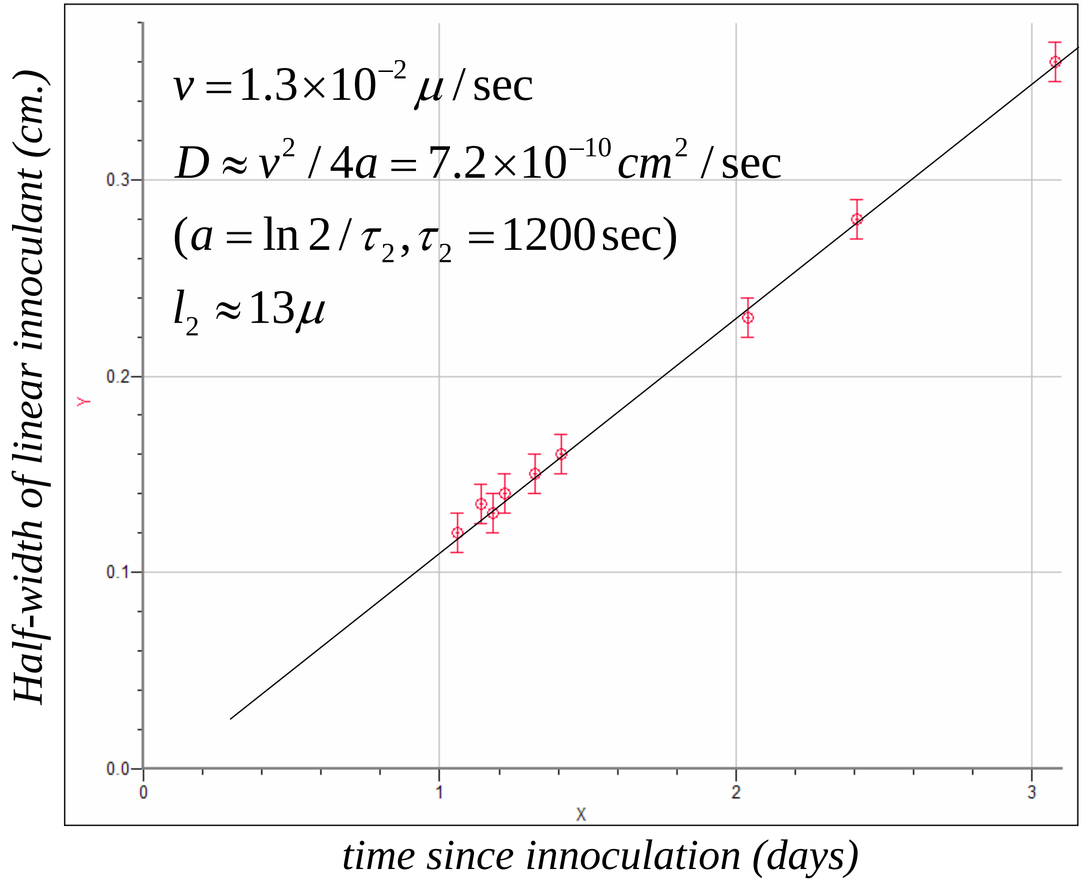






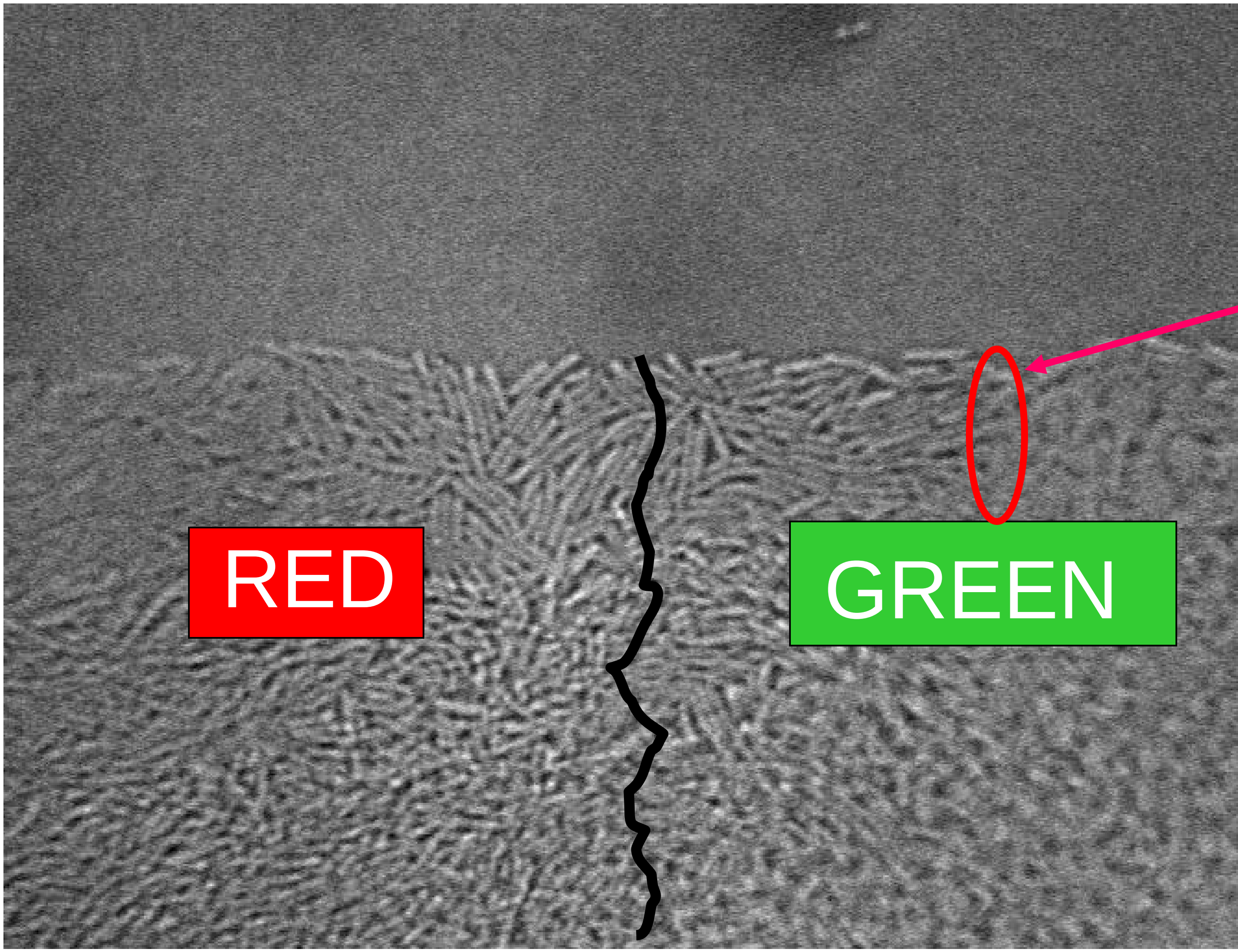






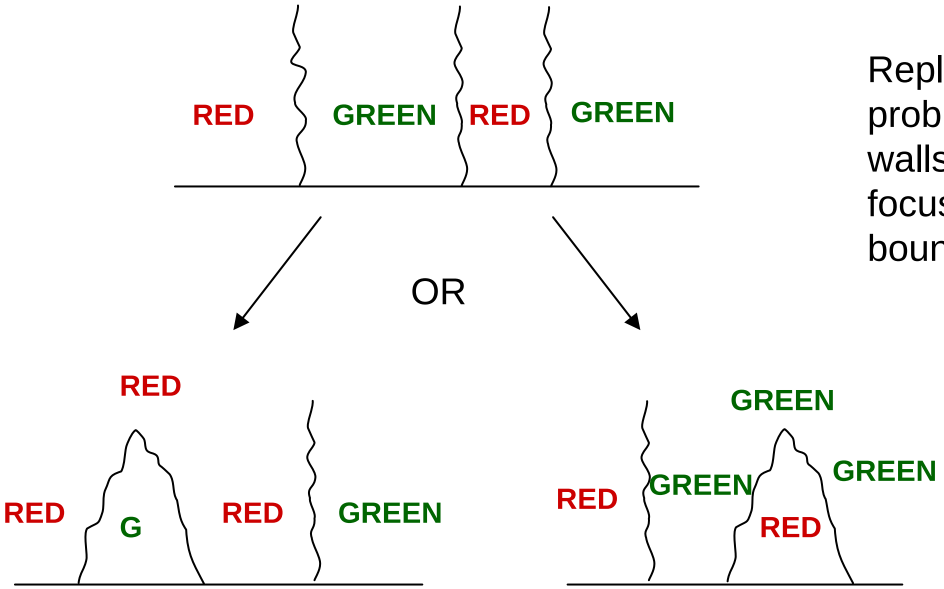
Front moves ~15 cell widths in a generation time…

Are segregation boundaries between neutral mutations in bacteria unbiased random walks?

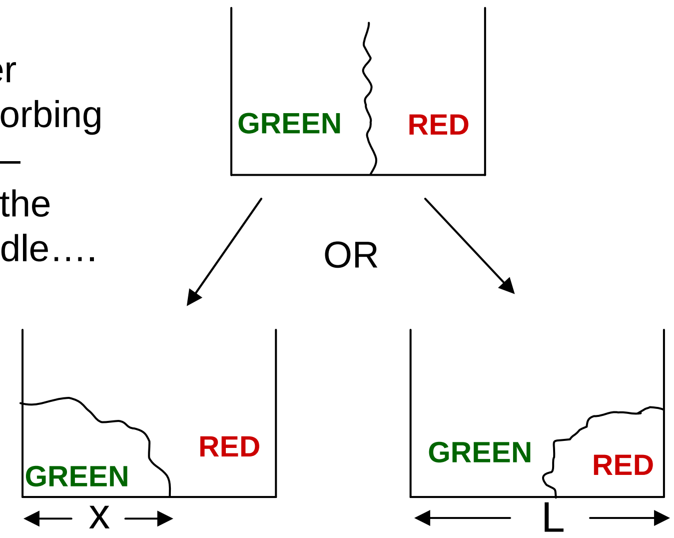


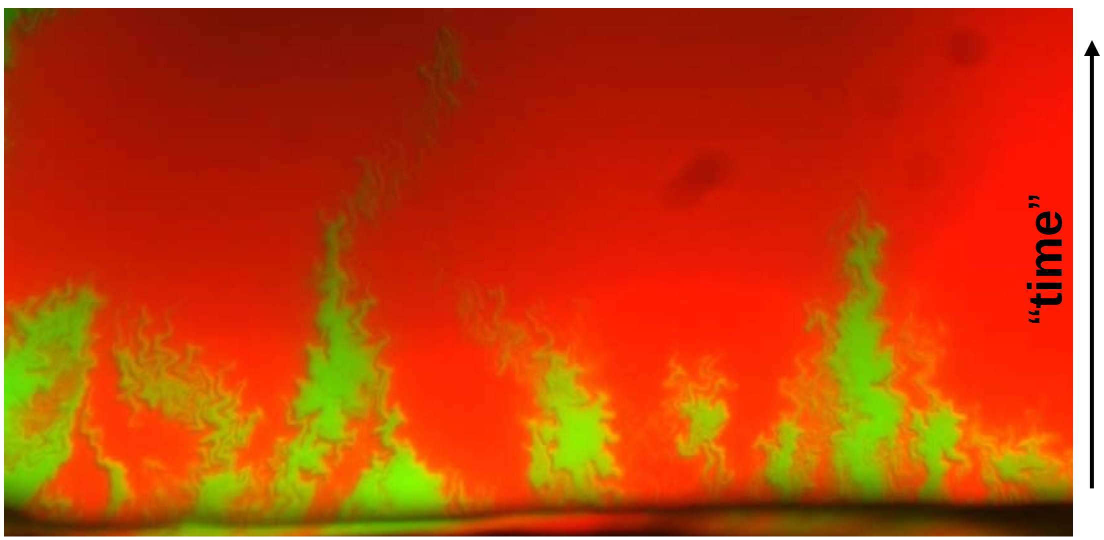
Effective population size ~ 15

Linear Inoculations: Coarsening of Annihilating Random Walks

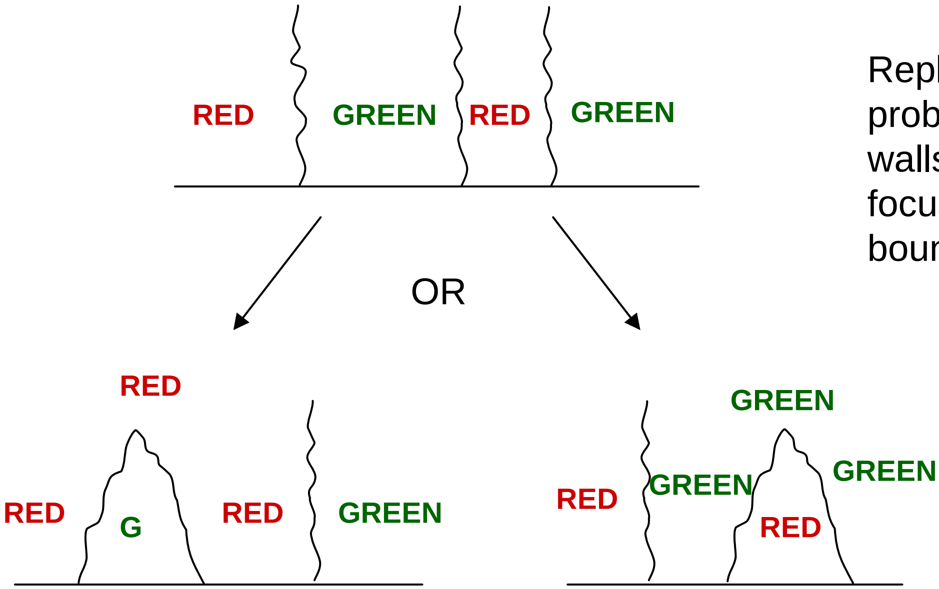


Replace with simpler problem of rigid absorbing walls on either side – focus on the fate of the boundary in the middle….

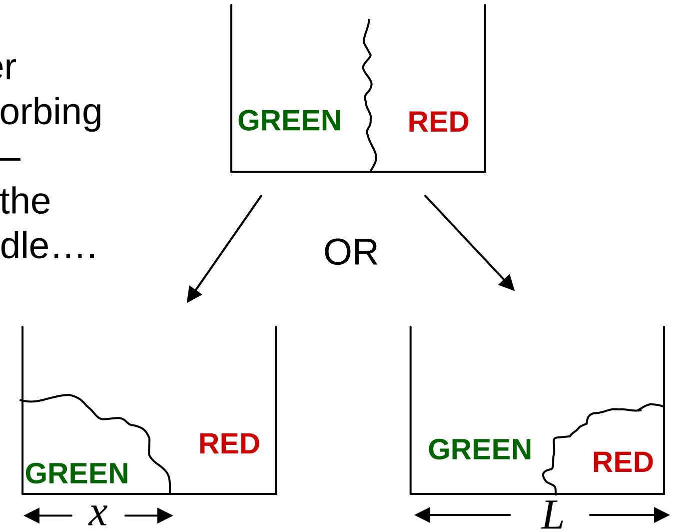


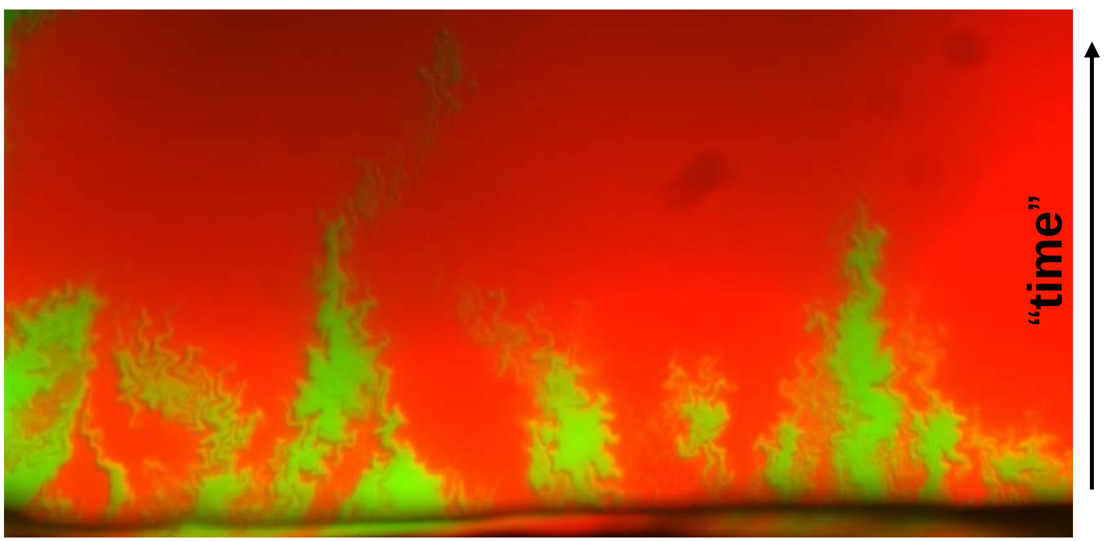


Linear Inoculations: Coarsening of Annihilating Random Walks



Replace with simpler problem of rigid absorbing walls on either side – focus on the fate of the boundary in the middle….



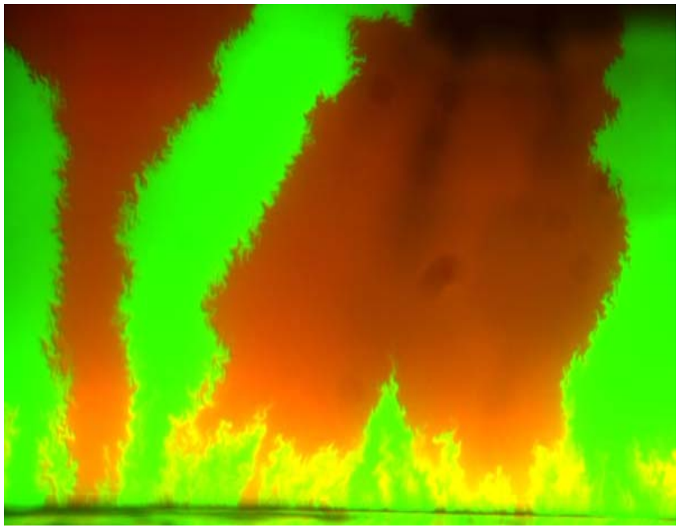


If D_W = wall diffusion constant, length of flares given by….

$$W(x) = \text{ mean distance to capture}$$
$$= x(L-x)/8D_W$$

$$n_w(t) = \text{ density of walls}$$
$$= 1/\sqrt{2D_W t}$$
$$\propto 1/t^{\zeta}, \text{ in general}$$

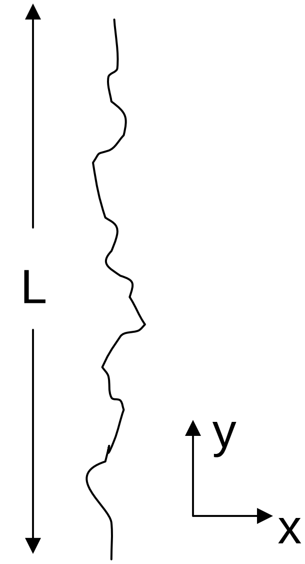
Boundary wandering, linear innoculation

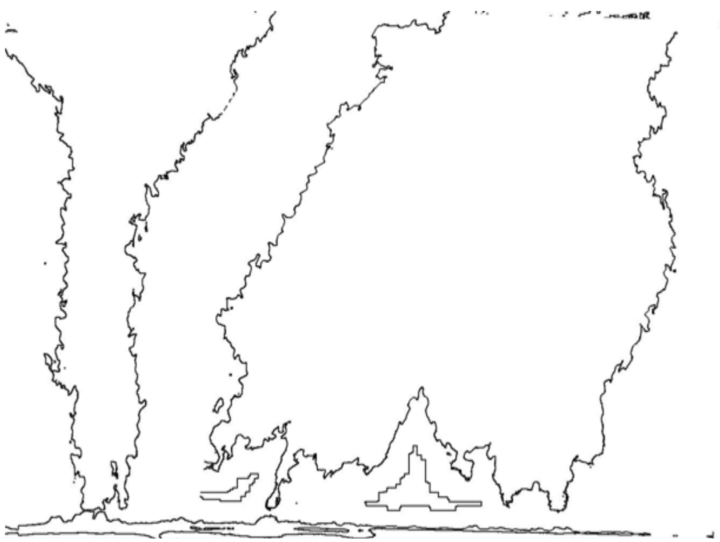


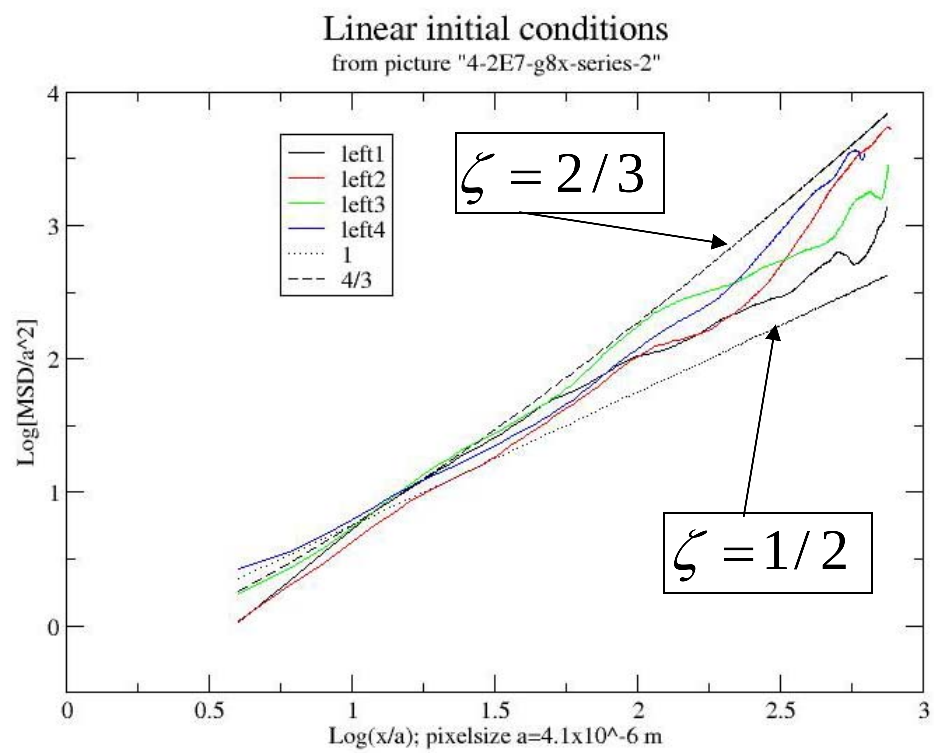
$$<[x(L)-x(0)]^2> \quad \approx const.\times L^{2\zeta}$$

$$\zeta = 1/2, \text{ random walk}$$

$$\zeta = 2/3, \text{ "Eden model"}$$







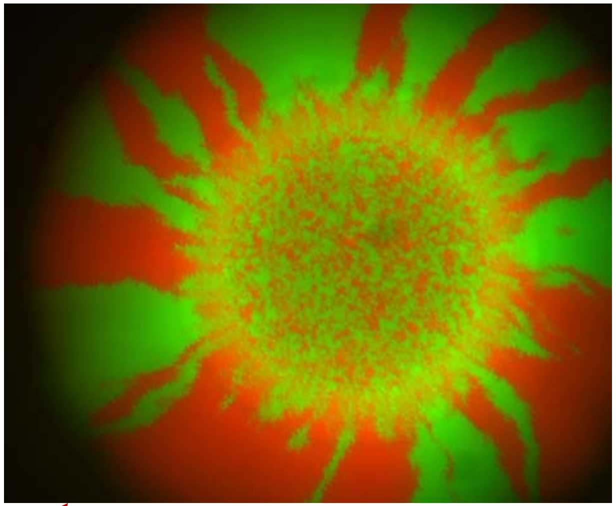
Acknowledgements and Future Directions

Sharad Ramanathan

Thanks to CSB/FAS, Andrew Murray and Erin O'Shea

Thanks to Oskar Hallatschek

Thanks to members of the Ramanathan group

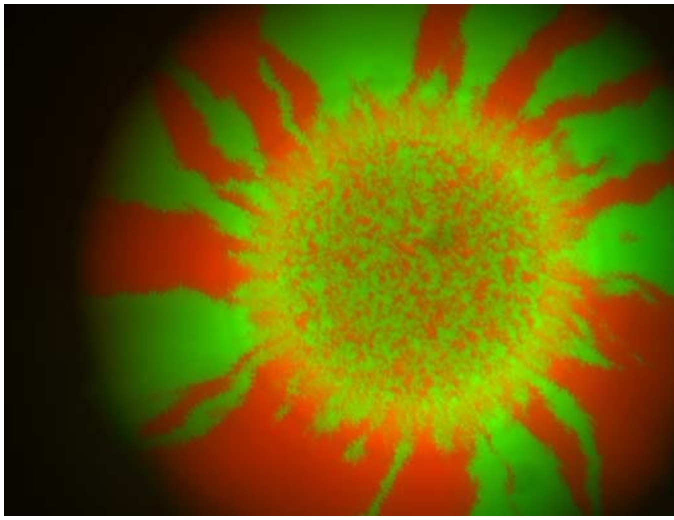


Effect of "Inflation": some sectors never die out!

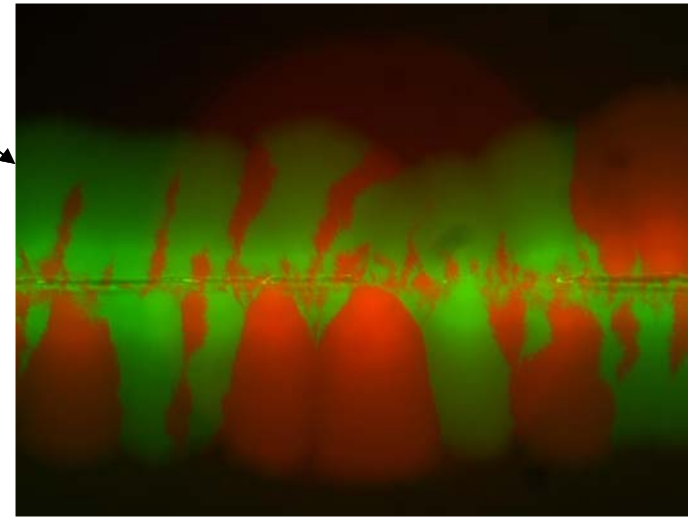
Future Directions

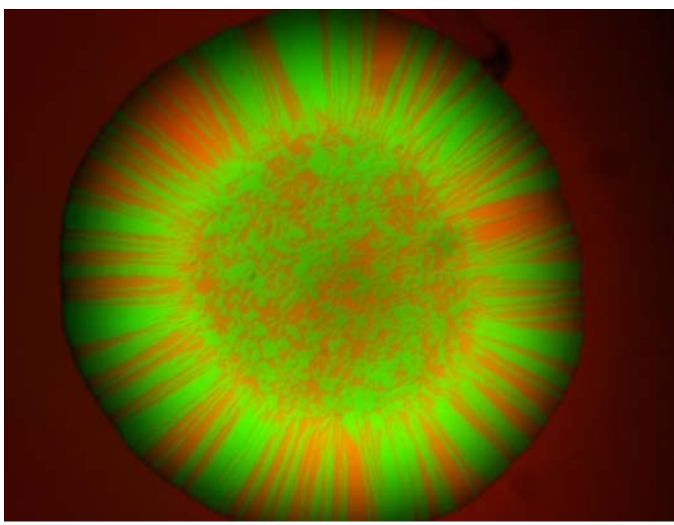
- Effect of 'inflation' and selective pressure on radial inoculations
- Gene surfing in yeast; how do *round* micro-organisms behave?
- Population segregation in *flagellated* bacteria (diffusion constant is larger by four orders of magnitude!)
- Why the crinkled patterns in the early stages? Effect of boundary conditions?

Segregation in E. coli vs. segreation in Mat α haploid yeast

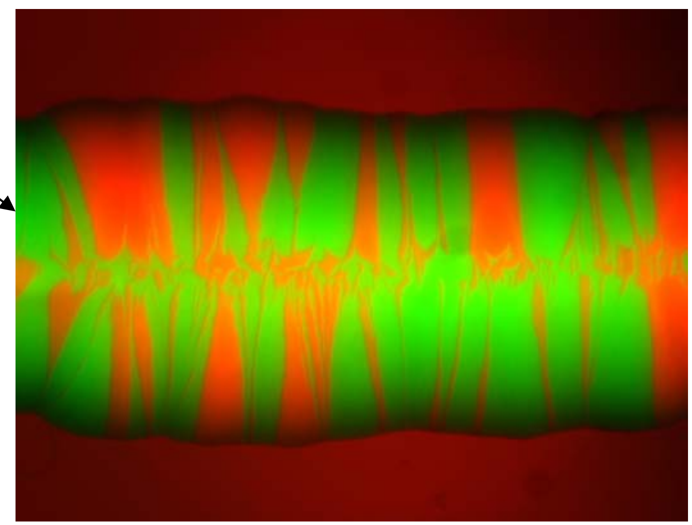


bacteria

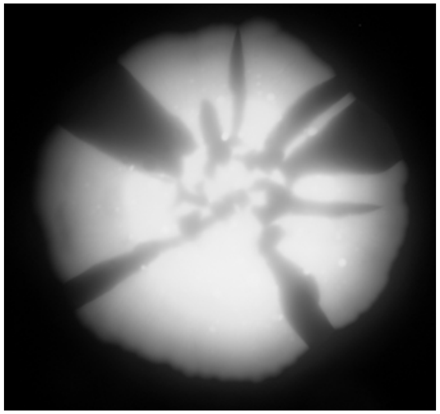


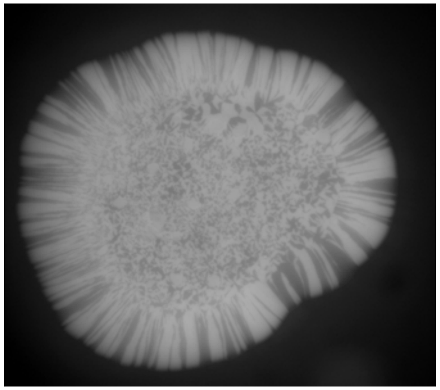


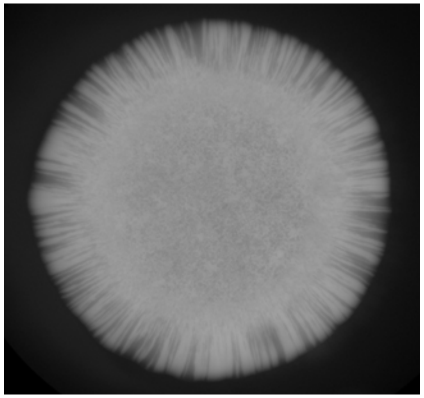
yeast



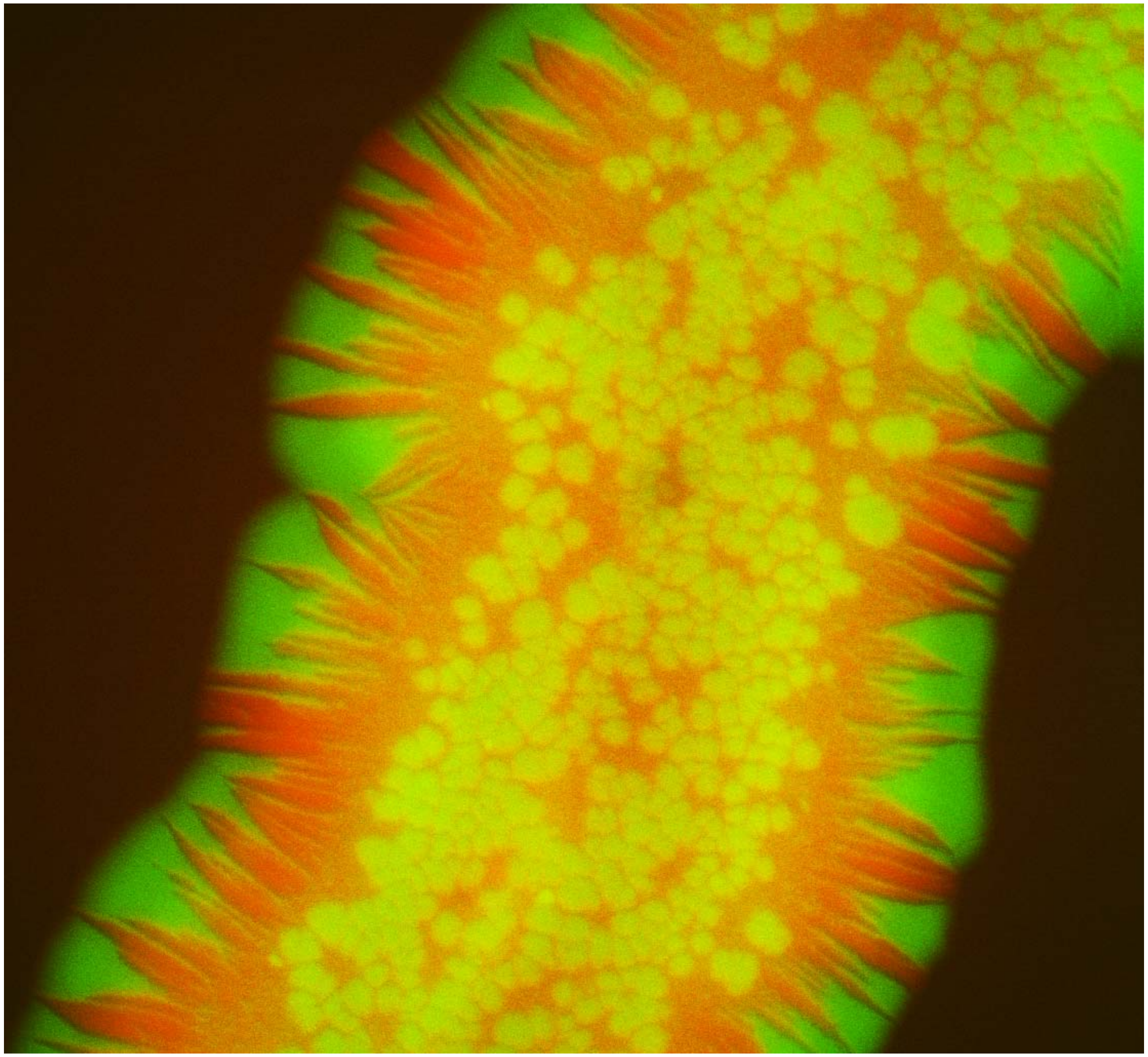
Effective population size probably much large at the frontier…



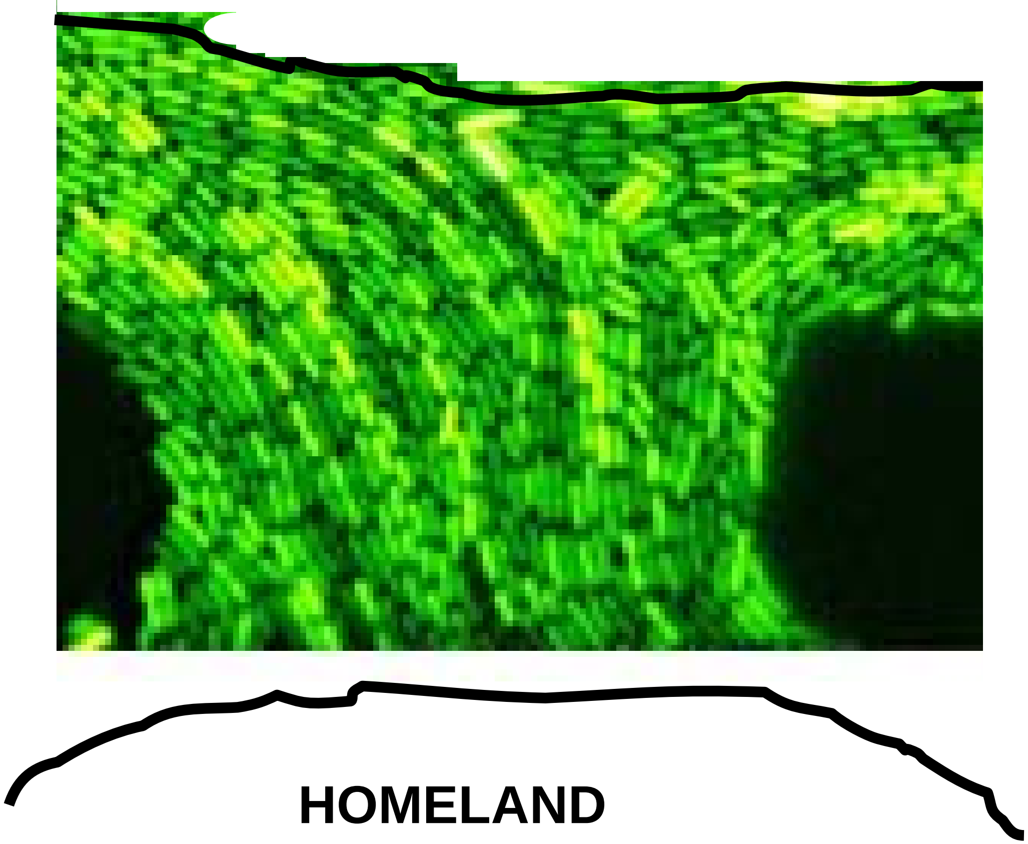


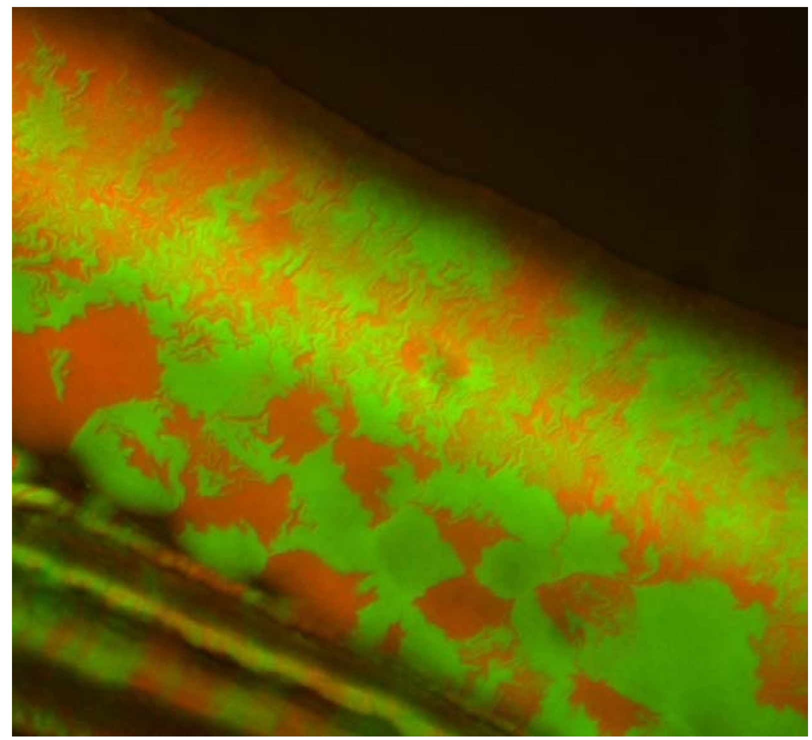


Colored yeast with a selective advantage !



Why are there buckles and folds in the segregation textures?





adapted from, N. Guido et al. Nature V439, 856 (2006). (J. J. Collins Lab, Boston University)