Cooperation and conflict in microbial pathogens

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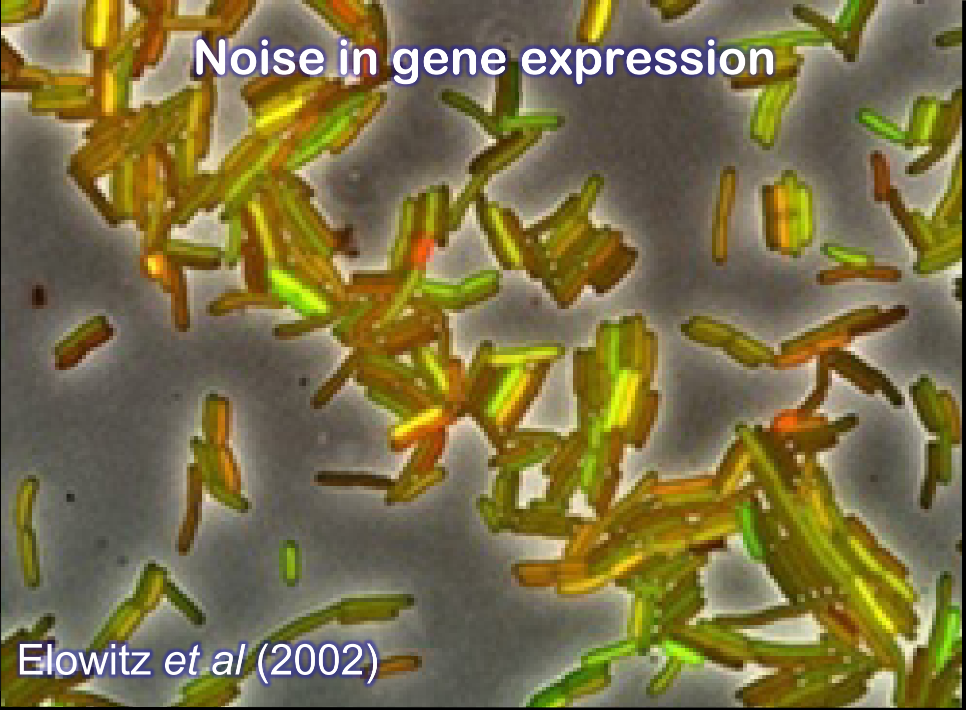
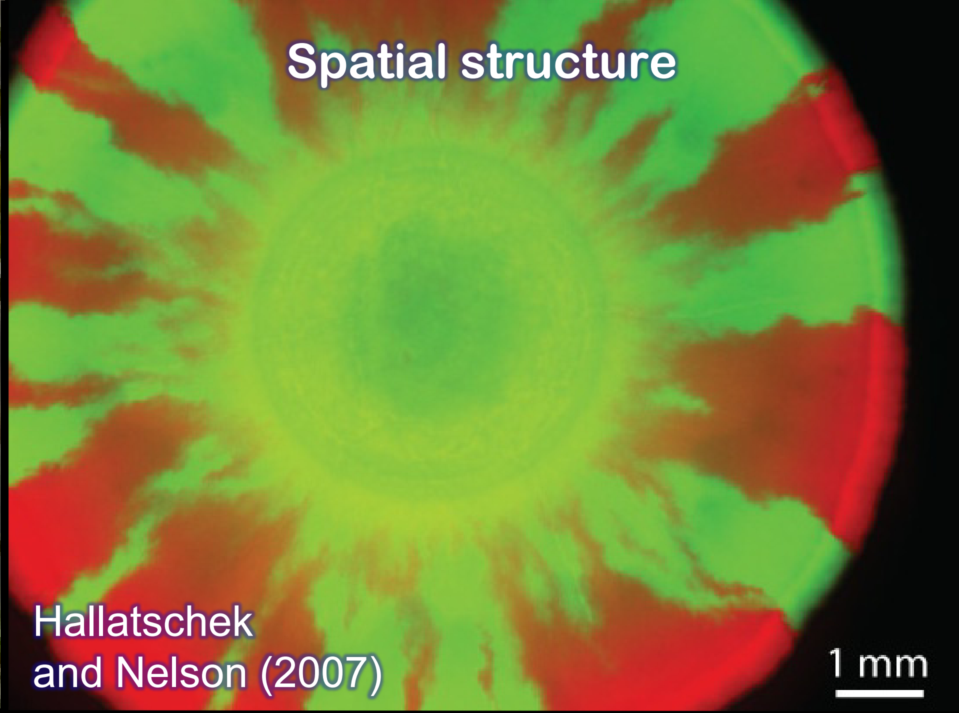


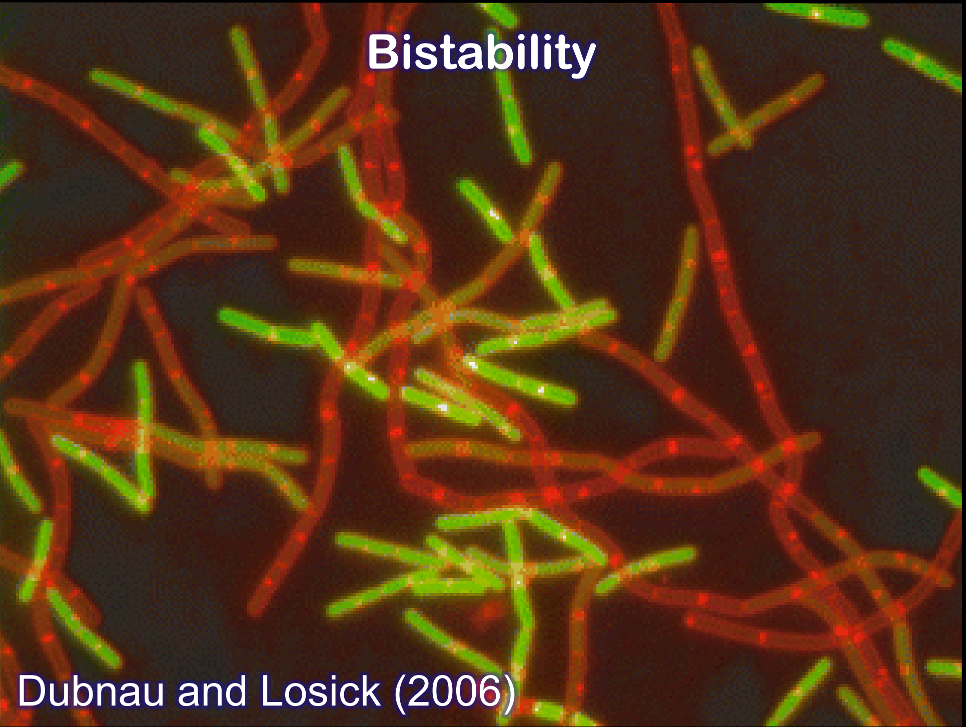
Noise in gene expression

Elowitz *et al* (2002)



Spatial structure

Hallatschek
and Nelson (2007)



Bistability

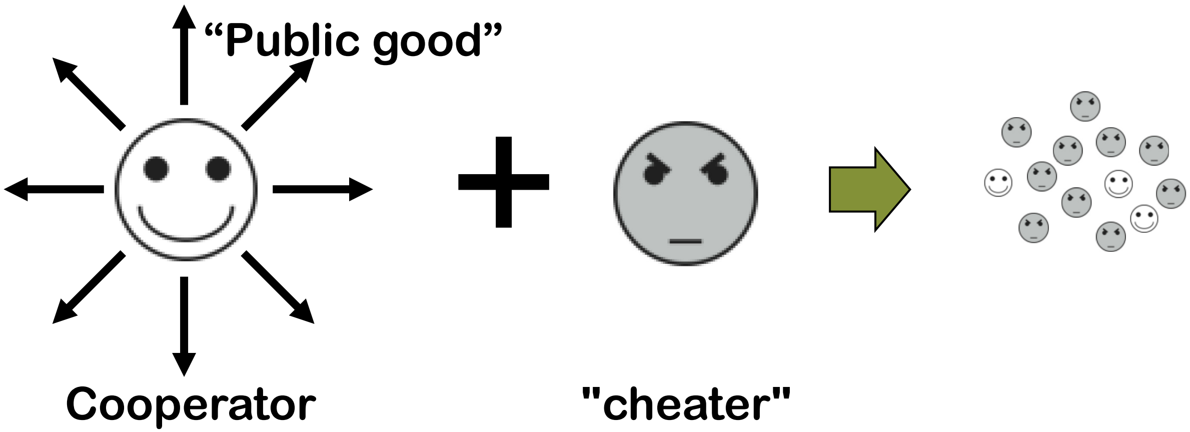
Dubnau and Losick (2006)

"Social" interactions

Bacteria have many examples of social interaction

- Strength by numbers
- Secretion of virulence factors
- Biofilm formation
- Quorum sensing

What prevents evolutionary cheating?

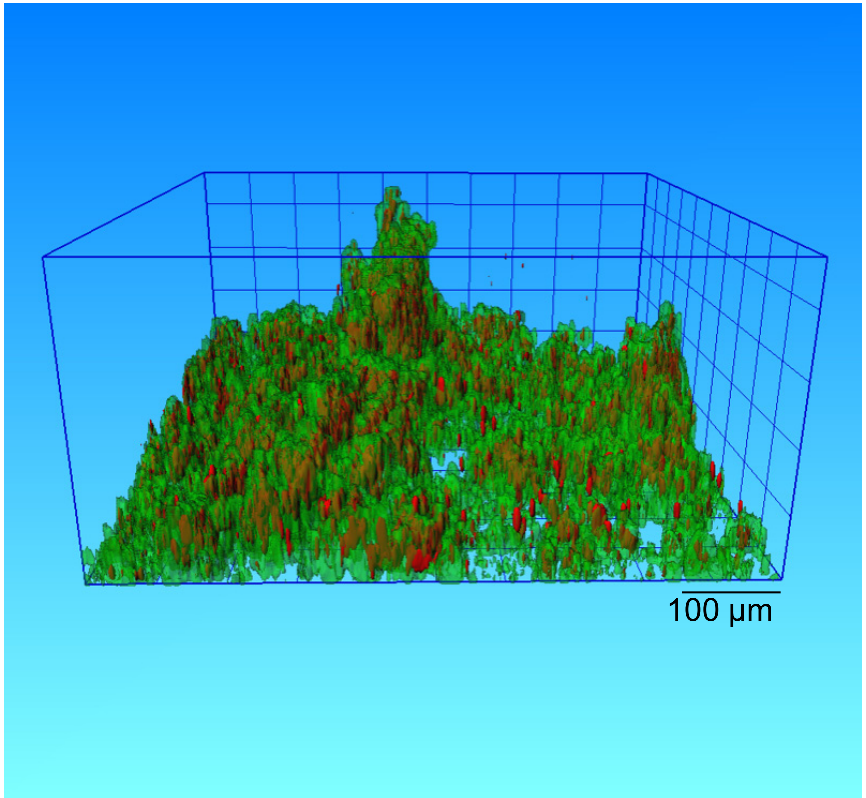


“Public good”

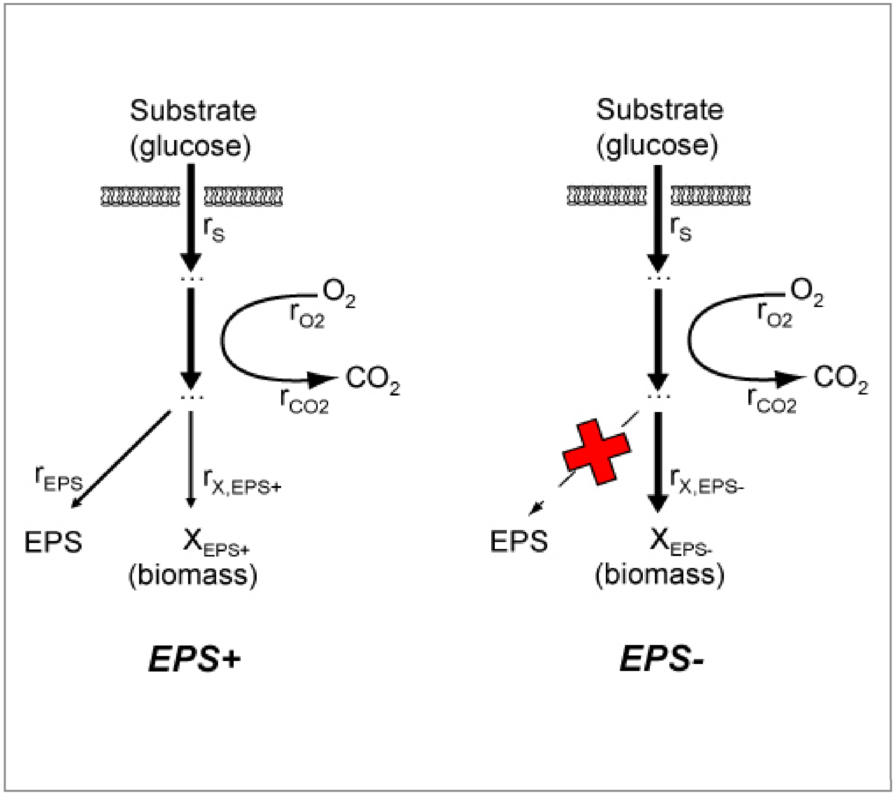
Cooperator

"cheater"

Cells in biofilms are embedded in a matrix of extracellular polymeric substances

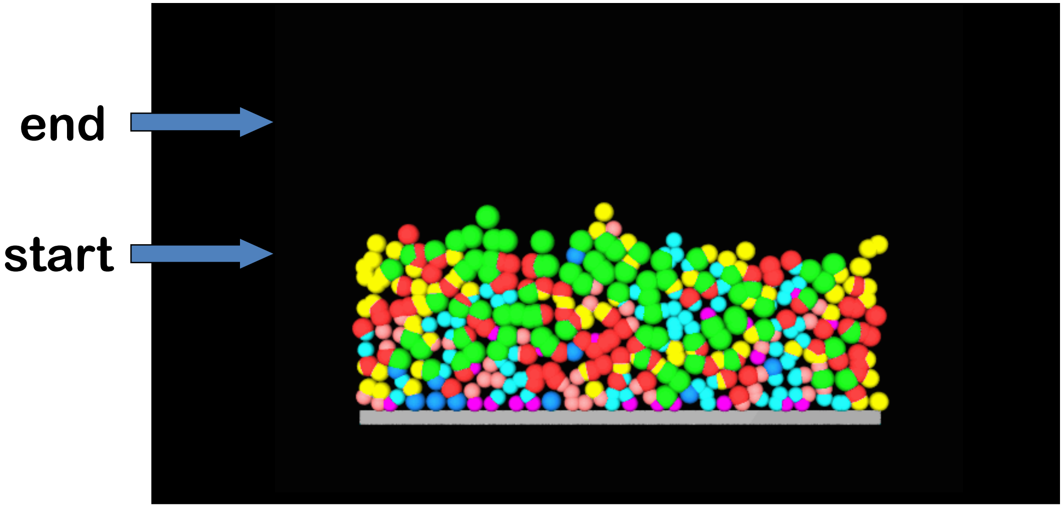


Bacteria (red) and glycoconjugate matrix (green).
Courtesy T. Neu, UFZ Germany.

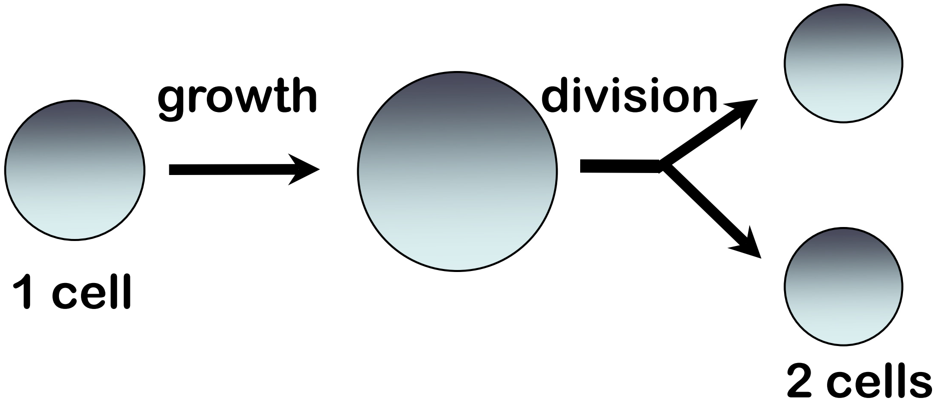


How is polymer secretion robust to "cheating"?

Biofilm dynamics emerge from interactions among cells



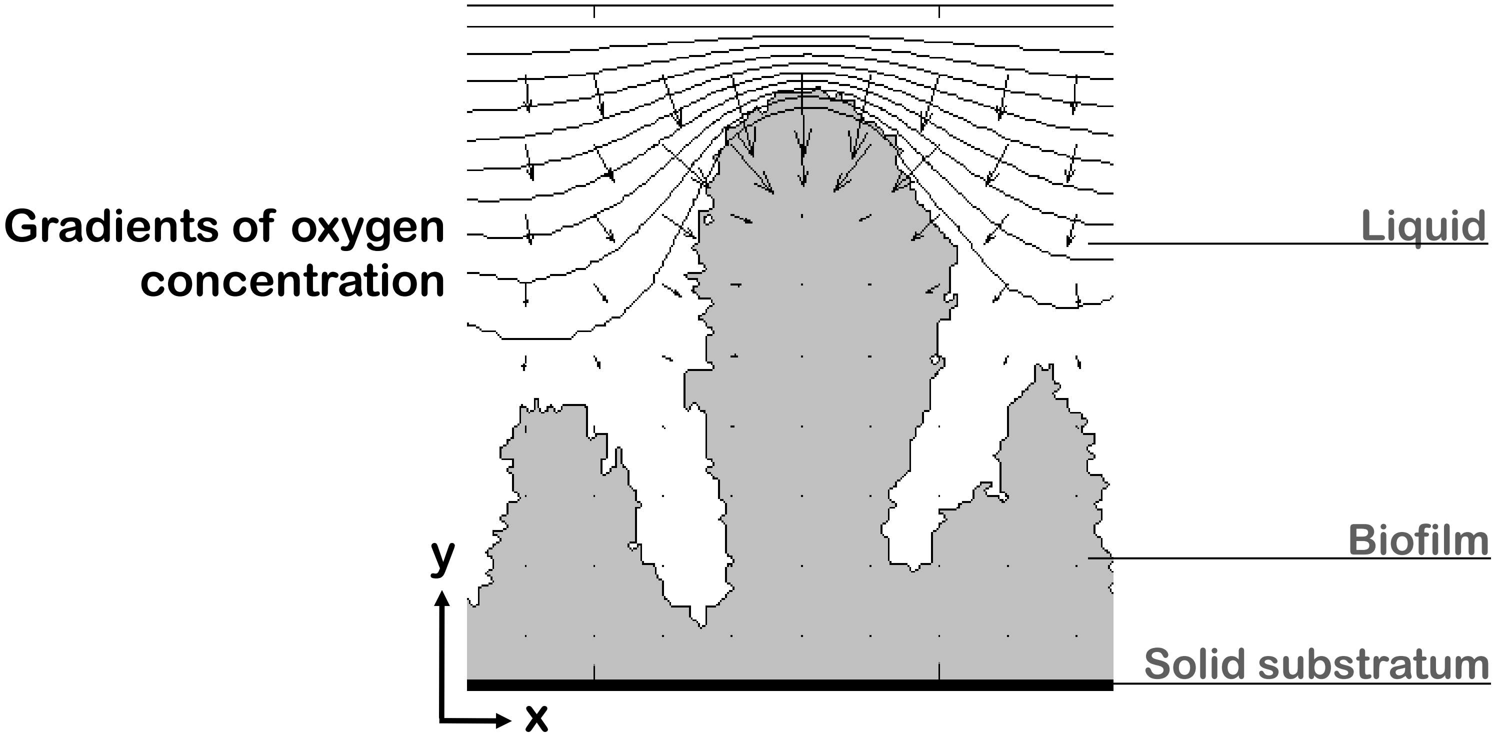
1. Growth 2. Division 3. Spreading



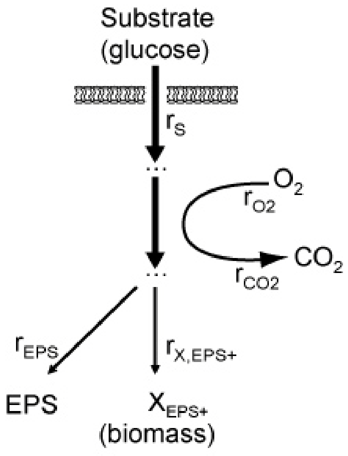
Gradients produce heterogeneous growth

$$\frac{\partial[O_2]}{\partial t} = \underbrace{D_{O2}\left(\frac{\partial^2[O_2]}{\partial x^2}+\frac{\partial^2[O_2]}{\partial y^2}\right)}_{\text{Diffusion}} + \underbrace{r_{O2}}_{\text{Reaction}}$$

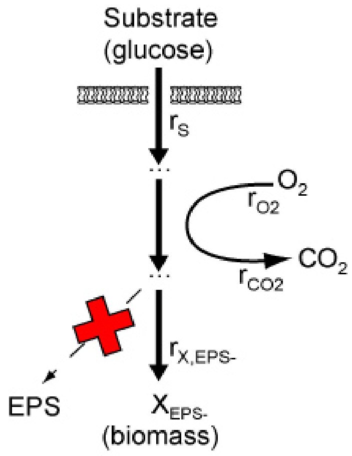
Vertical cross-section through biofilm



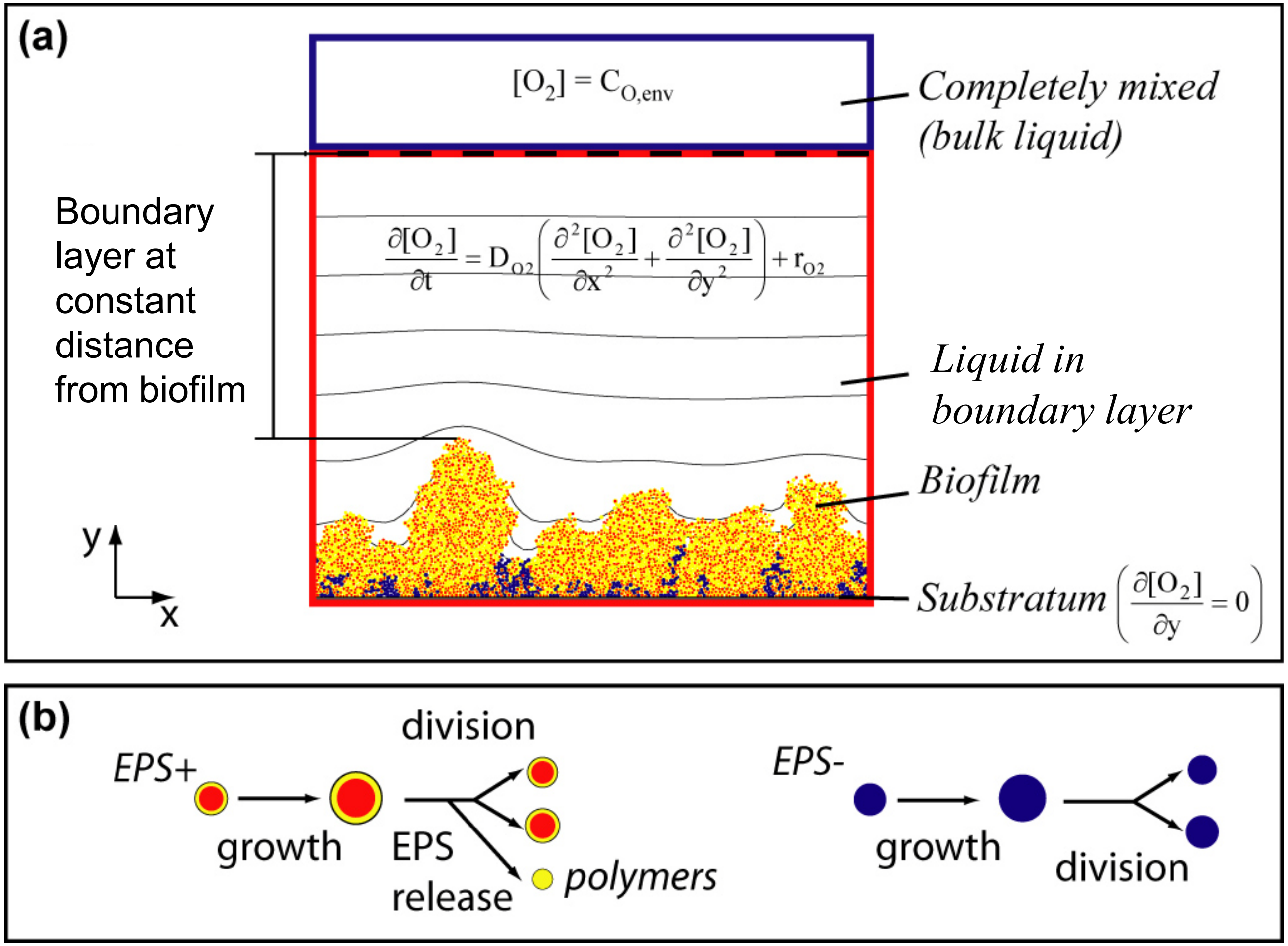
Producers and cheaters compete within the biofilm



EPS+

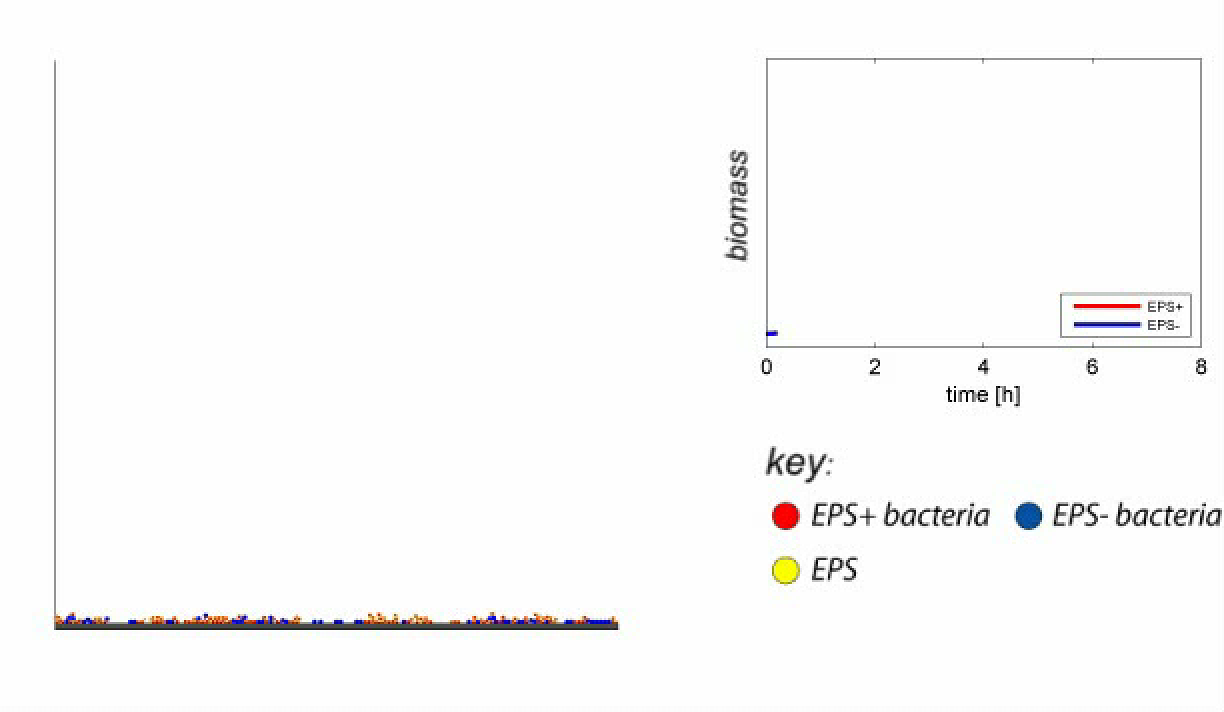


EPS-



Xavier and Foster, ***PNAS*** (2007)

With oxygen gradients OFF "cheaters" win



Xavier and Foster, *PNAS* (2007)

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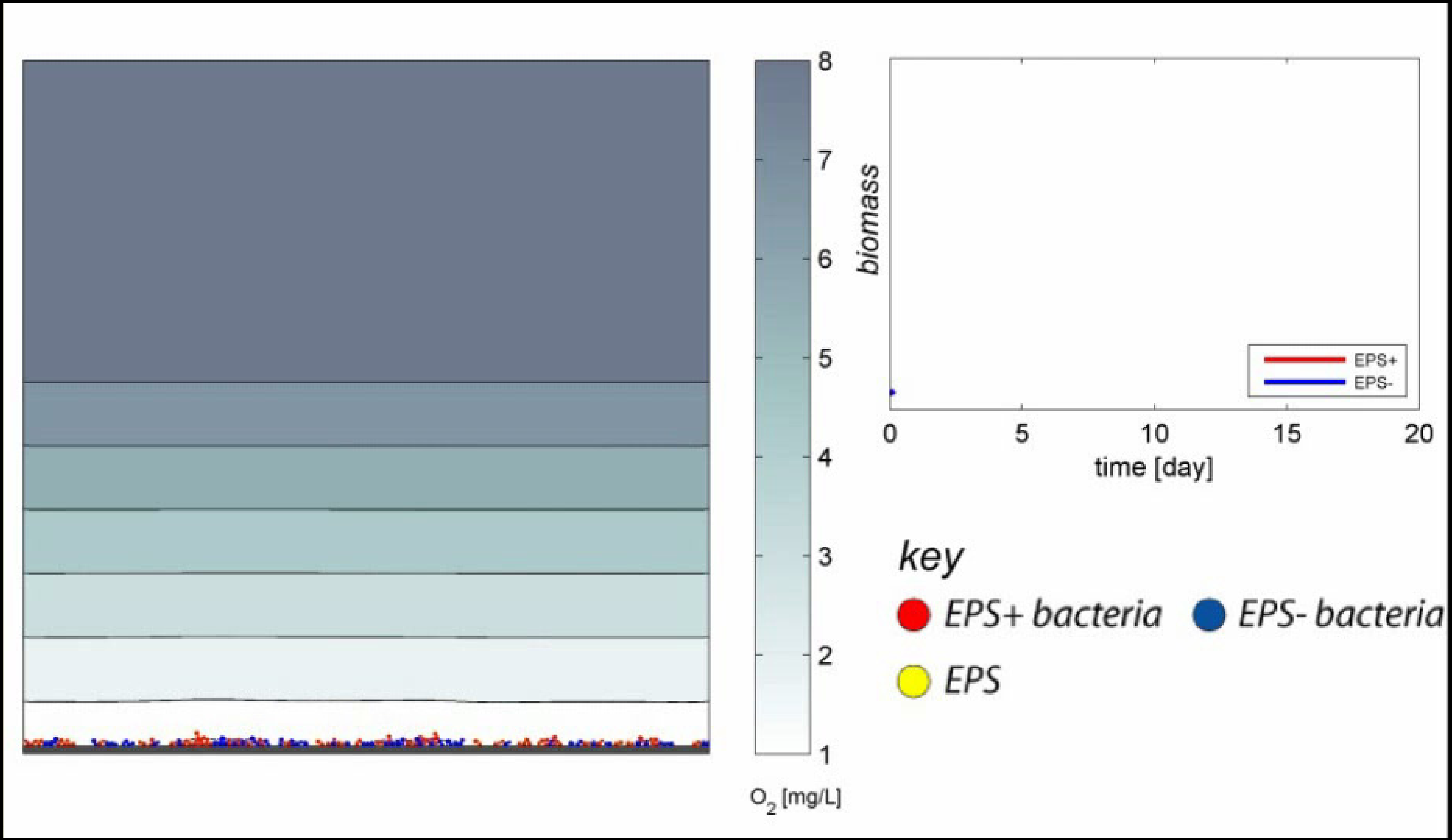
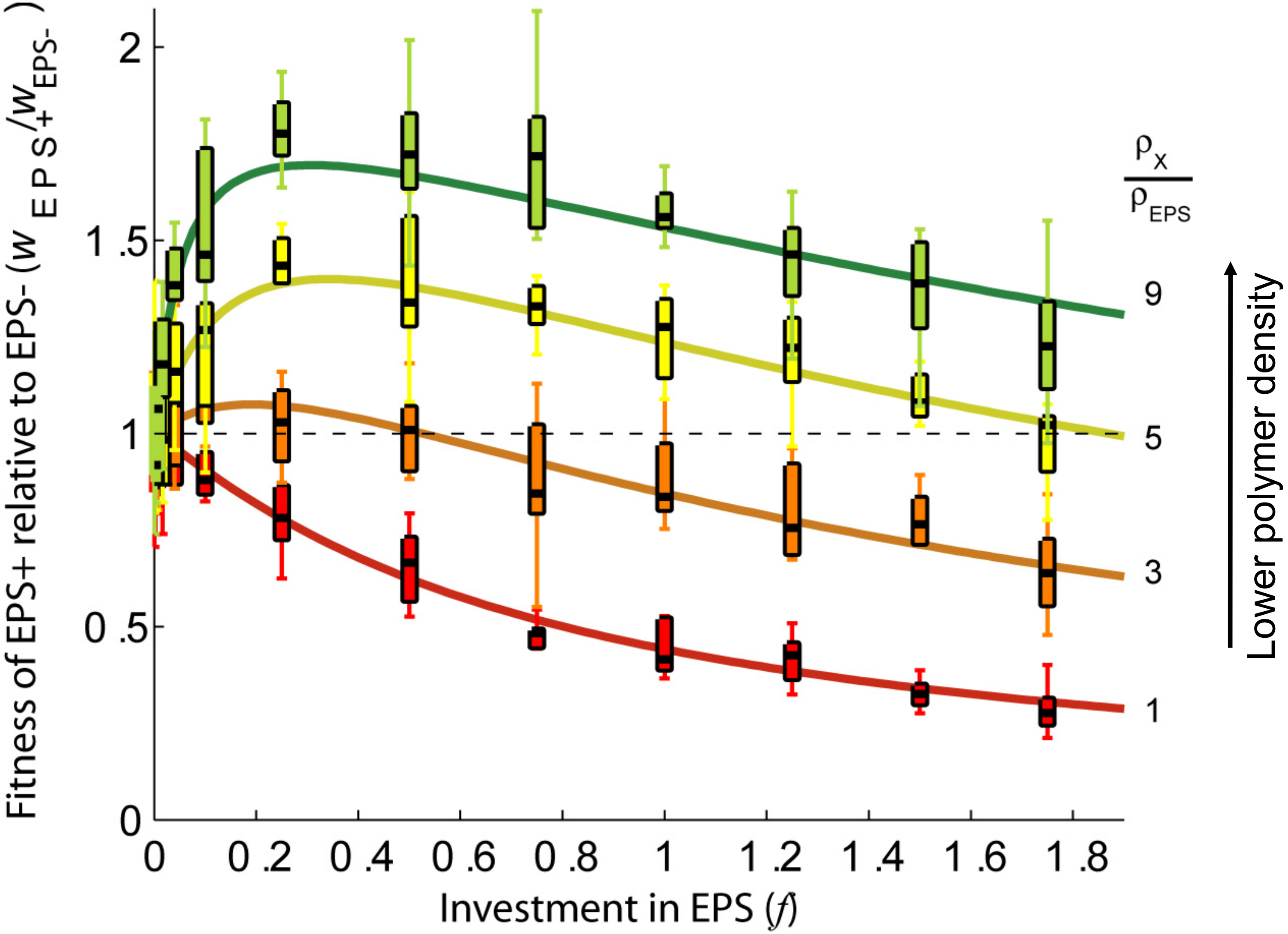


Xavier and Foster, *PNAS* (2007)



Xavier and Foster, *PNAS* (2007)

Extracellular polymers can work as a competitive trait

Cooperative trait

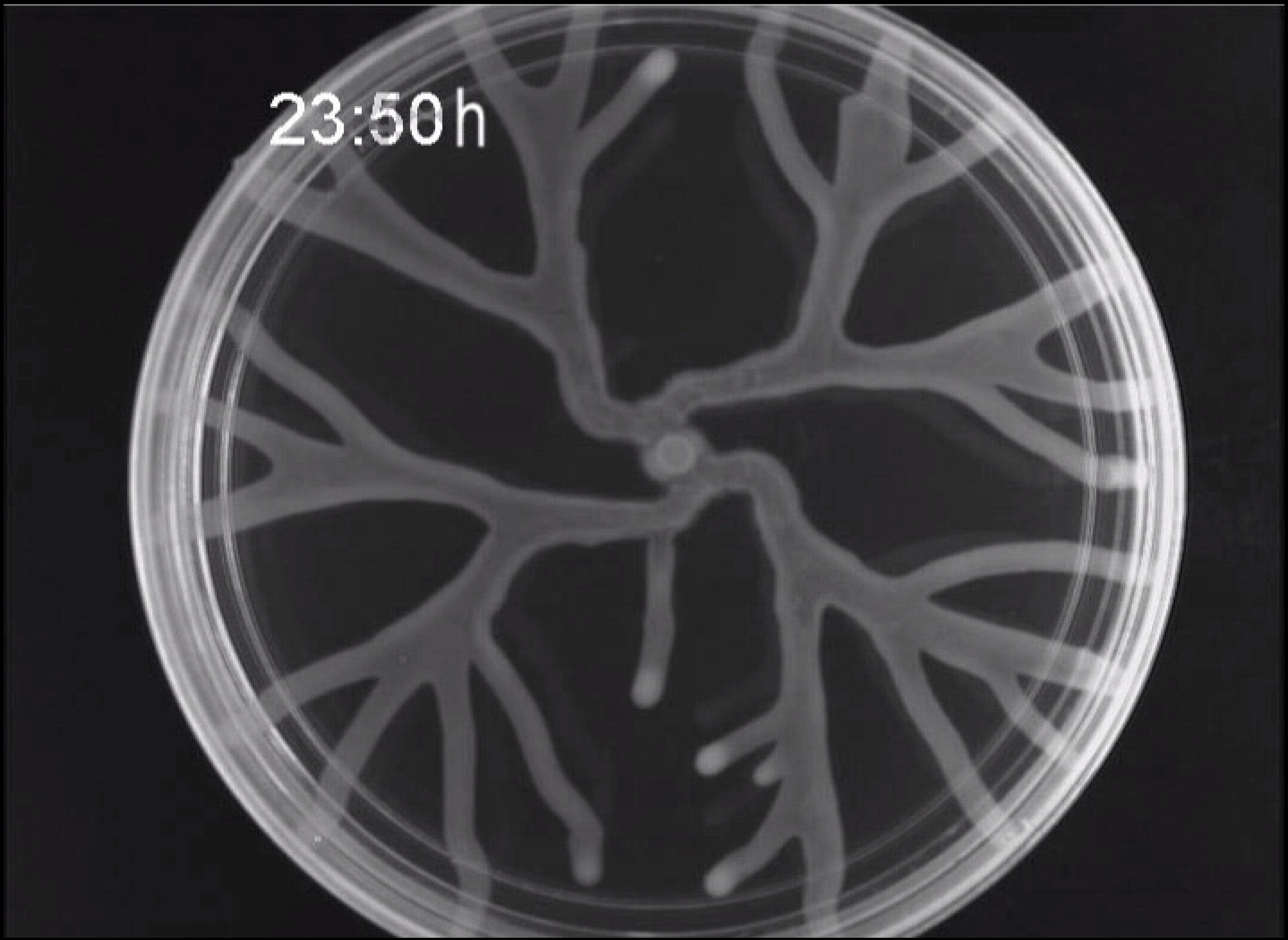
Open to exploitation

Competitive trait

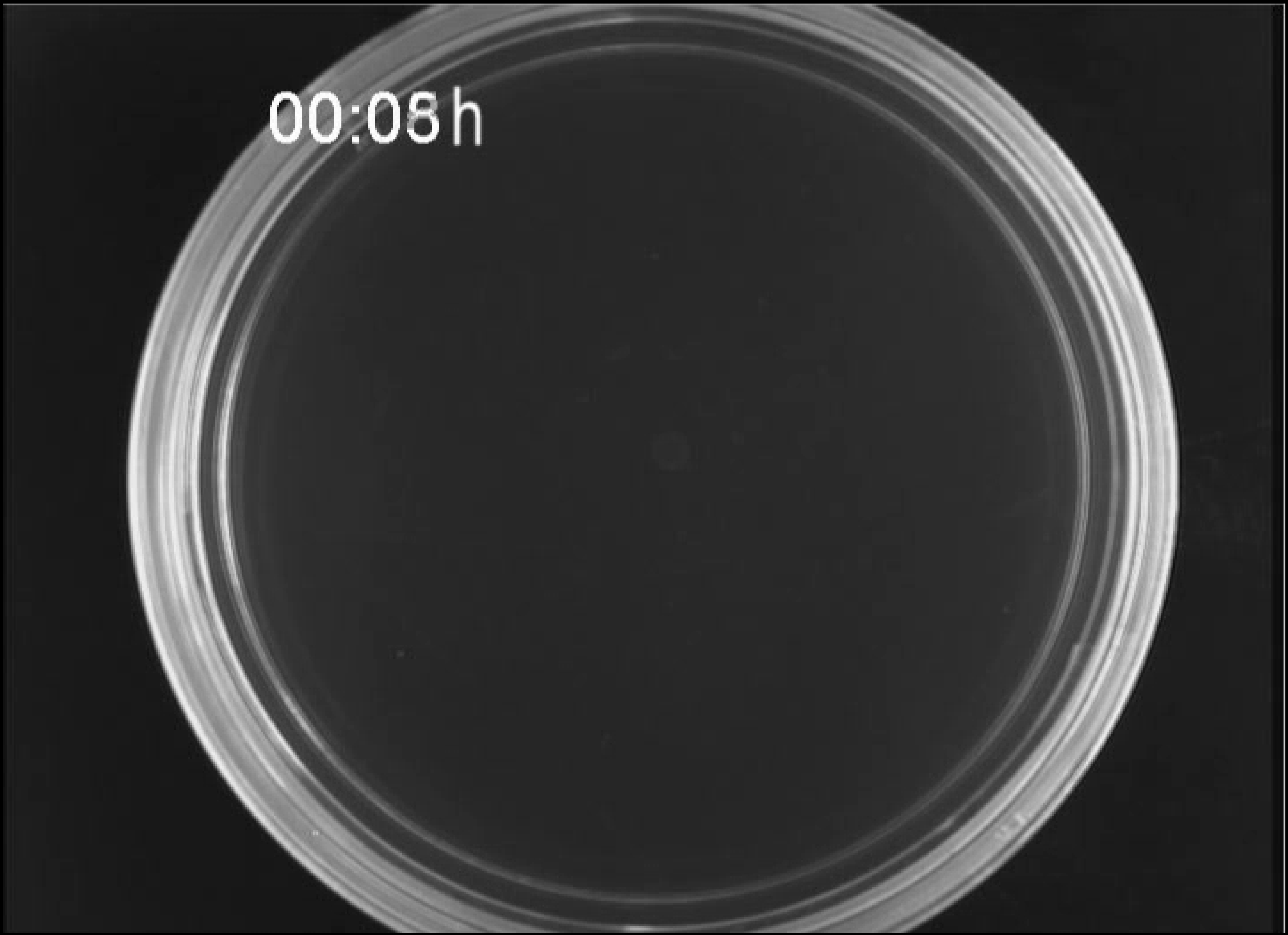
Benefit own lineage

Xavier and Foster, *PNAS* (2007)

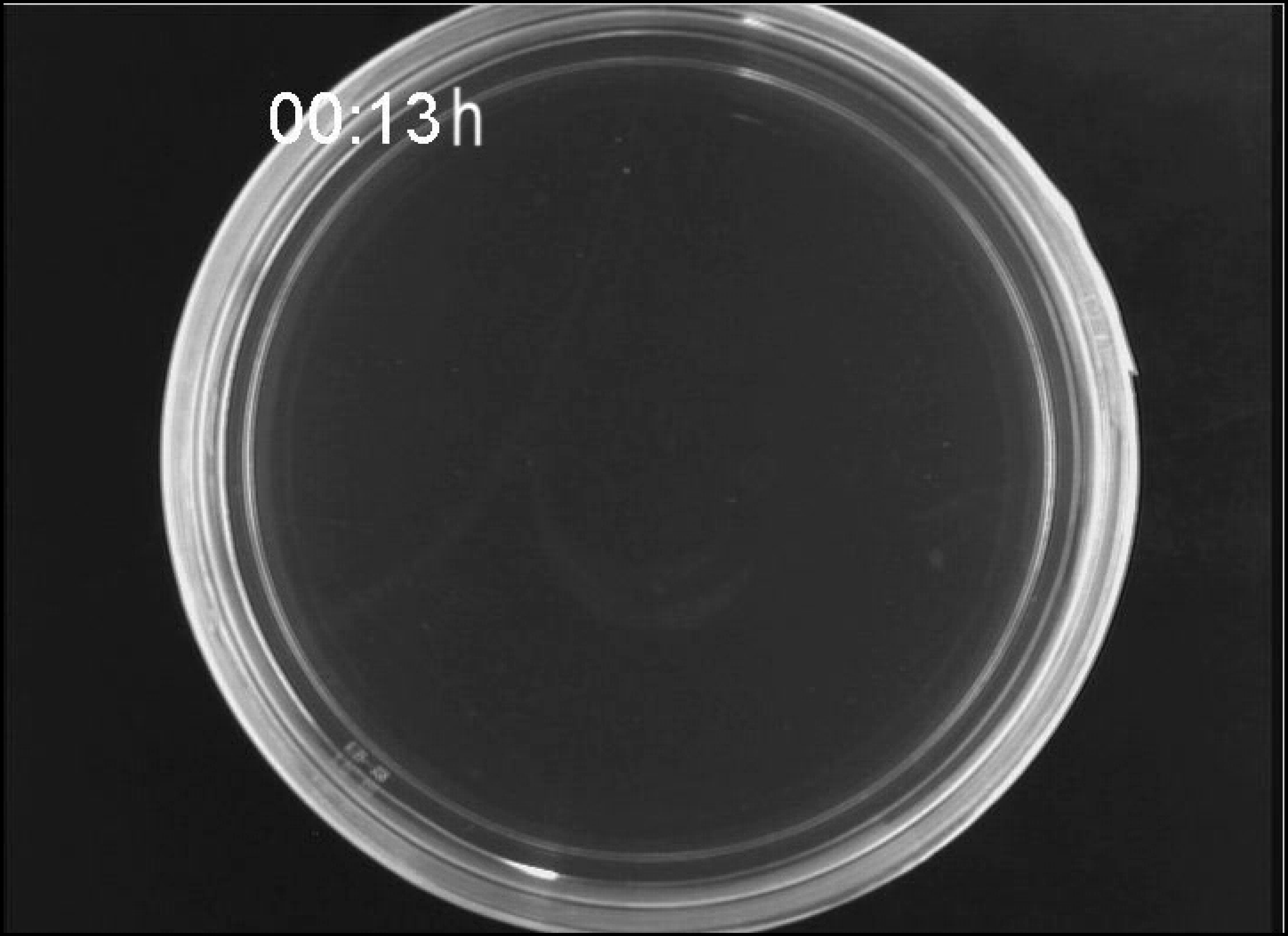
Swarming: collective motility in *Pseudomonas aeruginosa*



Swarming: collective motility in *Pseudomonas aeruginosa*



Swarming colonies have long range repulsion



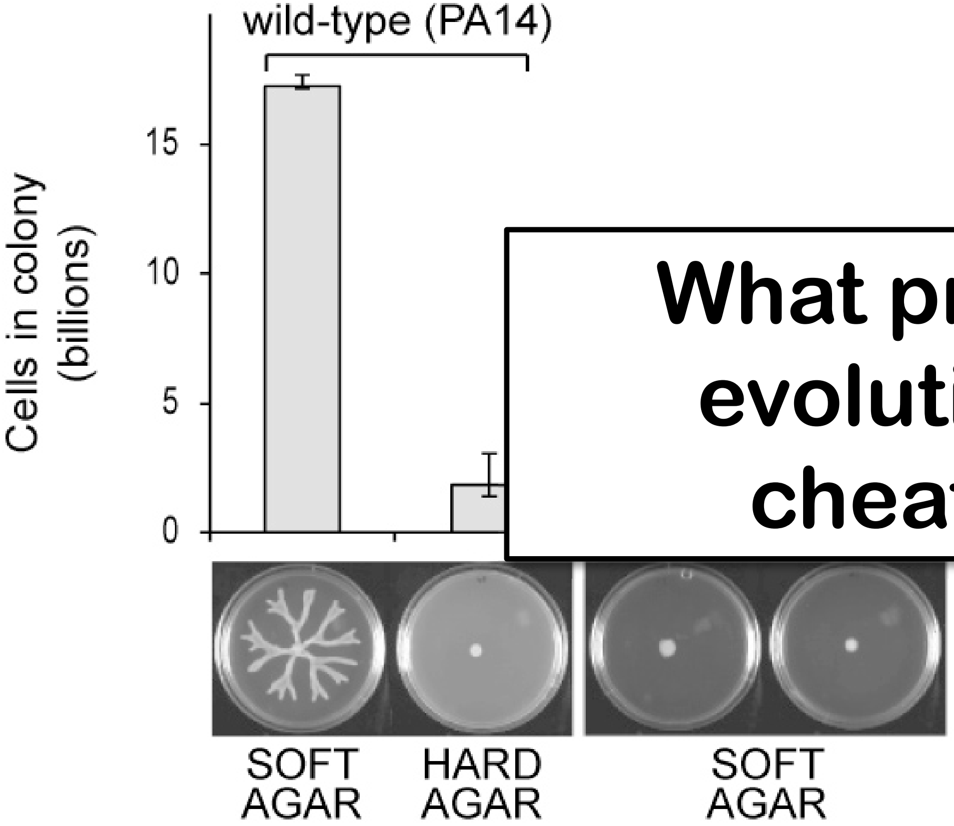
Pseudomonas aeruginosa is a well established model

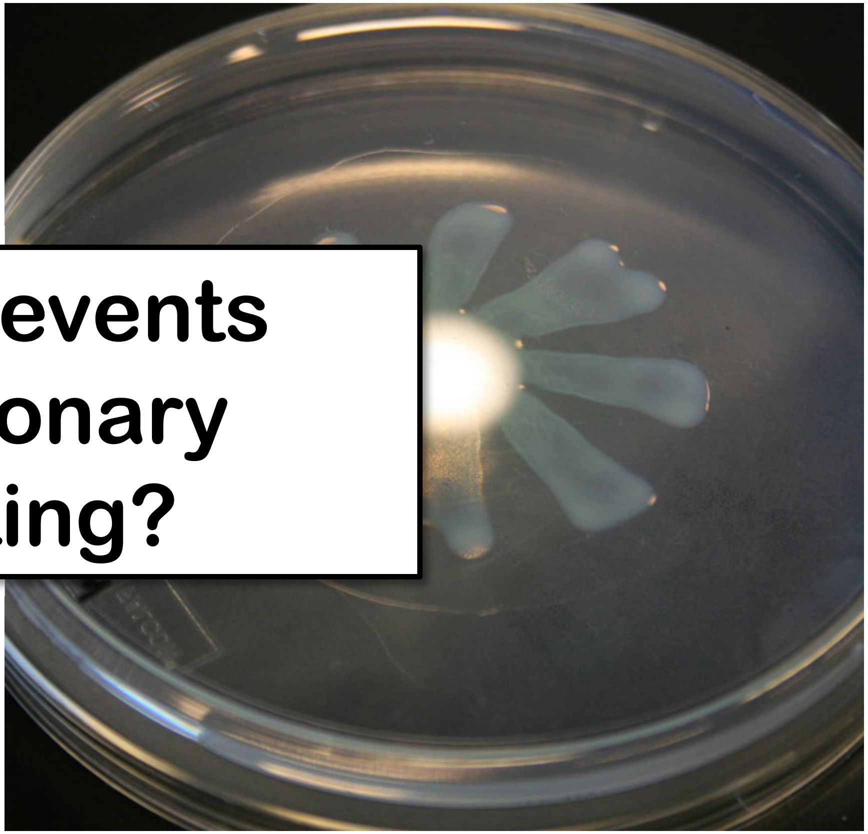
- Sequenced genomes
- Non-redundant libraries of transposon mutants
- Affymetric GeneChip microarrays

- It is an opportunistic pathogen

- Forms biofilms in cystic fibrosis lungs that are hard to treat with antibiotics

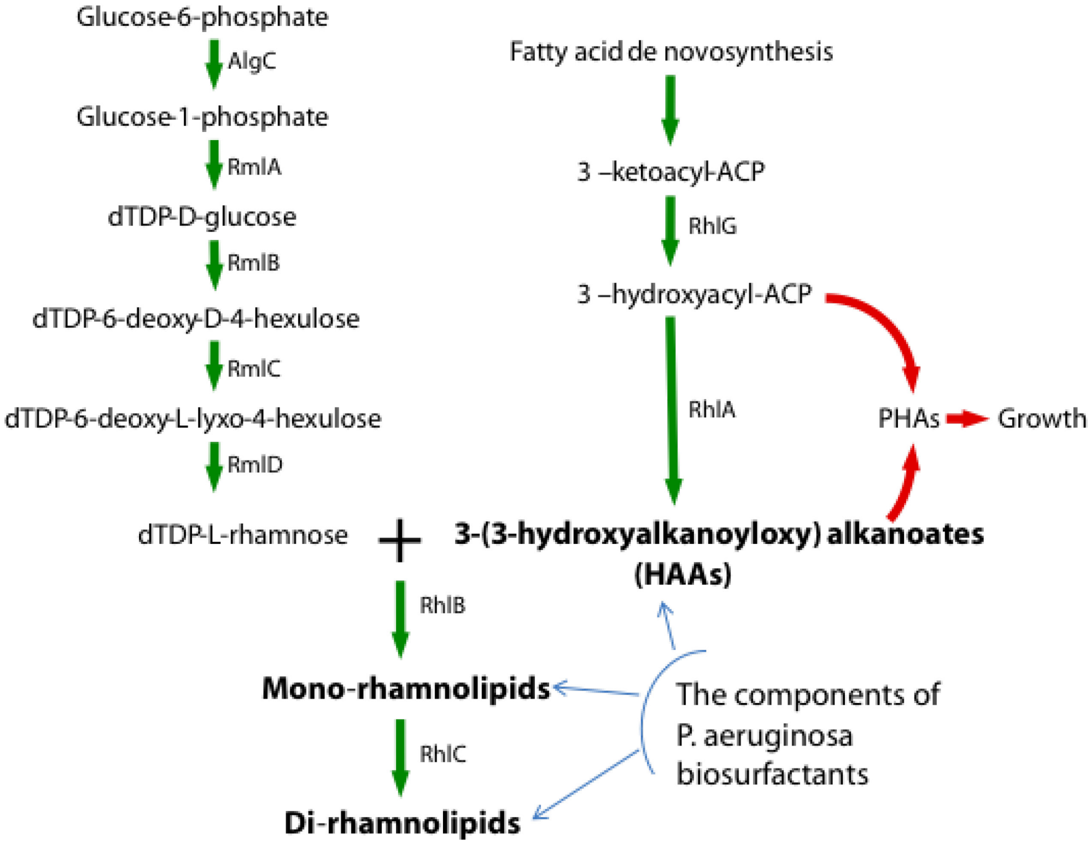
Swarming benefits the colony but requires biosurfactant synthesis by cells





What prevents evolutionary cheating?

Biosurfactant synthesis is well characterized



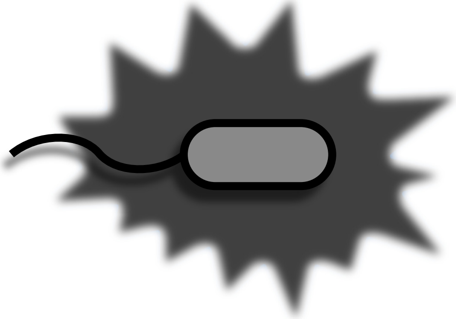
Glucose-6-phosphate
AlgC
Glucose-1-phosphate
RmlA
dTDP-D-glucose
RmlB
dTDP-6-deoxy-D-4-hexulose
RmlC
dTDP-6-deoxy-L-lyxo-4-hexulose
RmlD
dTDP-L-rhamnose

Fatty acid de novosynthesis
3 –ketoacyl-ACP
RhlG
3 –hydroxyacyl-ACP
RhlA
PHAs
Growth

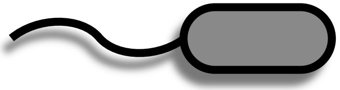
+ **3-(3-hydroxyalkanoyloxy) alkanoates (HAAs)**

RhlB
Mono-rhamnolipids
RhlC
Di-rhamnolipids

The components of P. aeruginosa biosurfactants

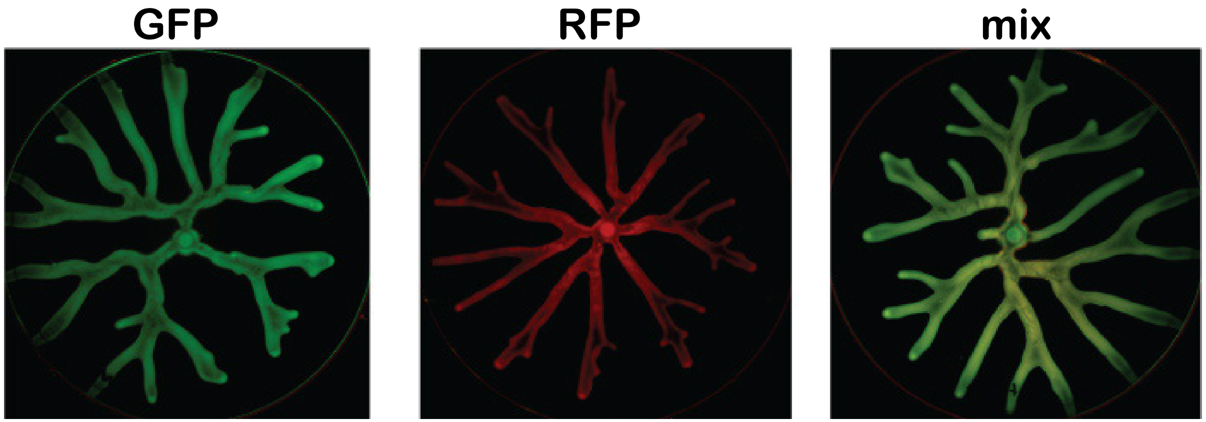


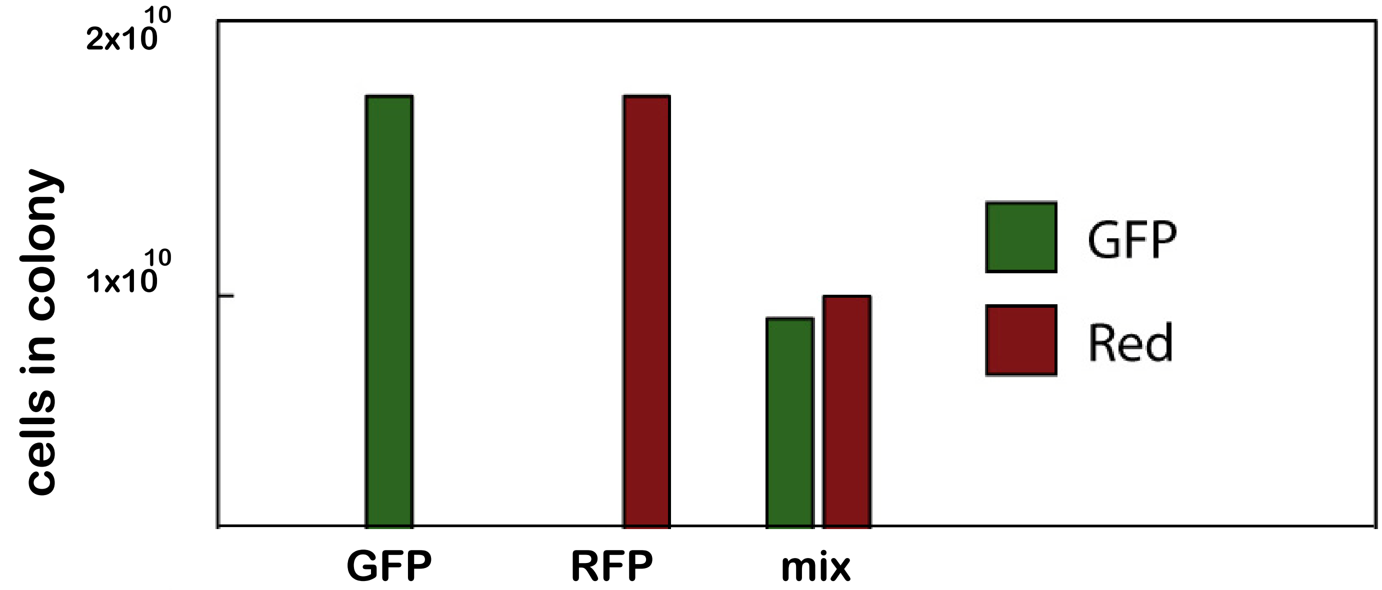
Wild-type



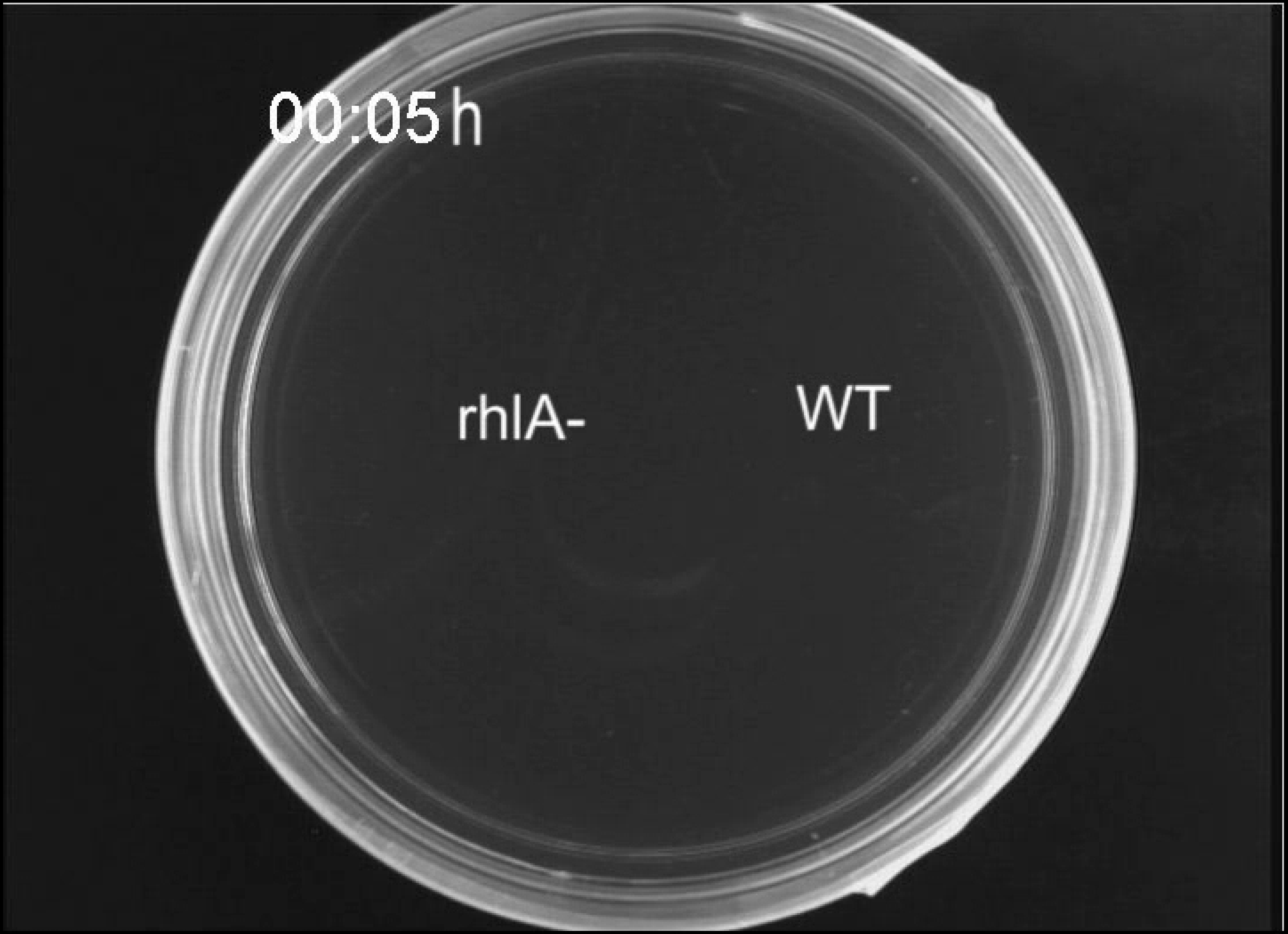
rhlA^{-}
(Non-cooperator)

Different genotypes are distinguishable using neutral colors

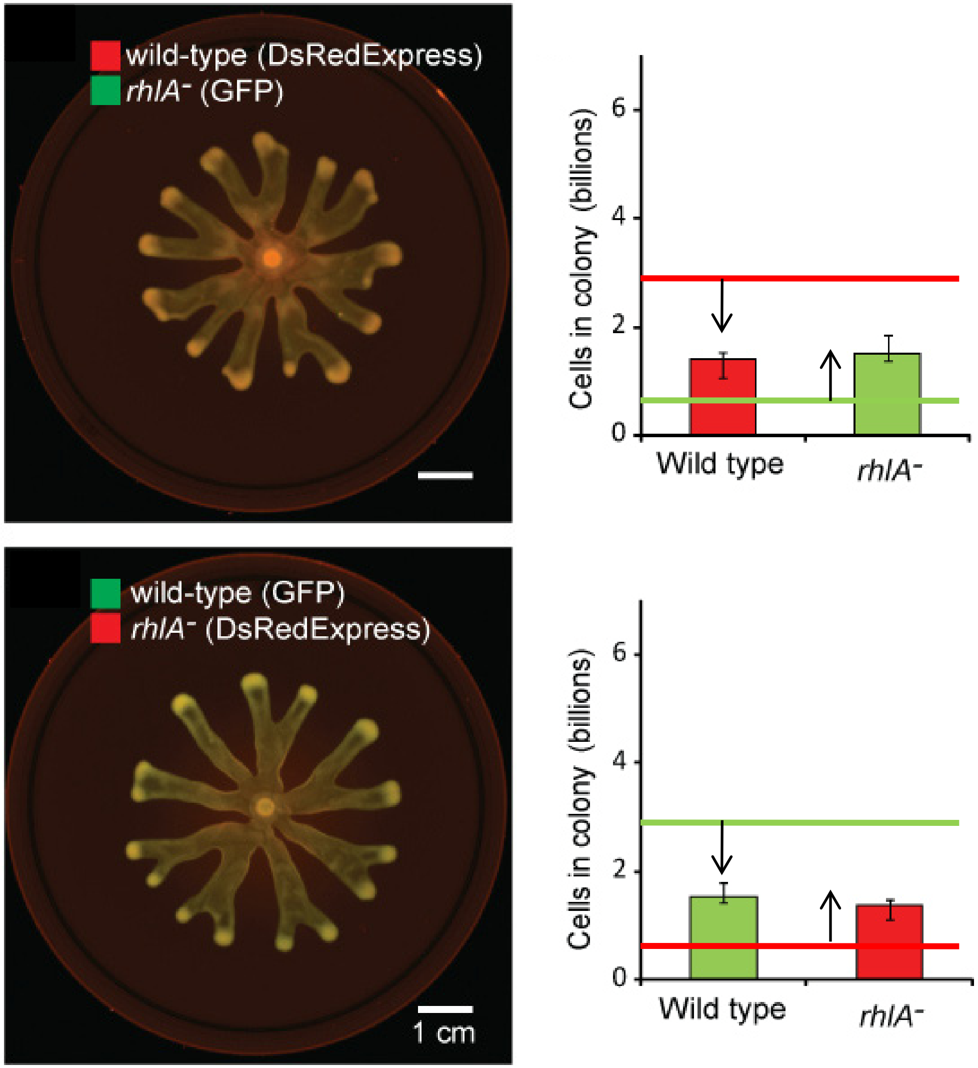




Biosurfactants are a “public good”



Biosurfactant secretion is uncheatable



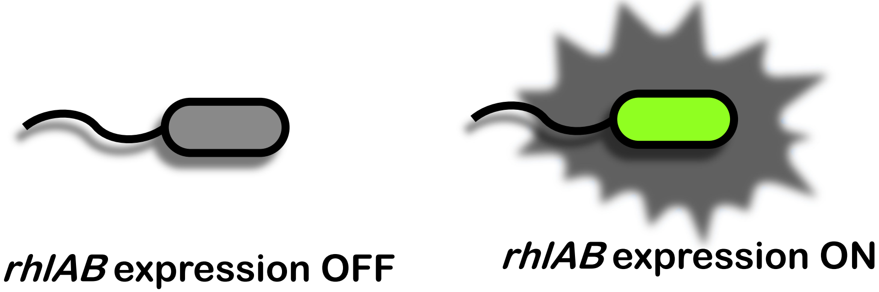
- Non-cooperators do better than when alone…
- …but at expense of wild-type
- Not enough to distinguish who wins, WT or *rhlA*-

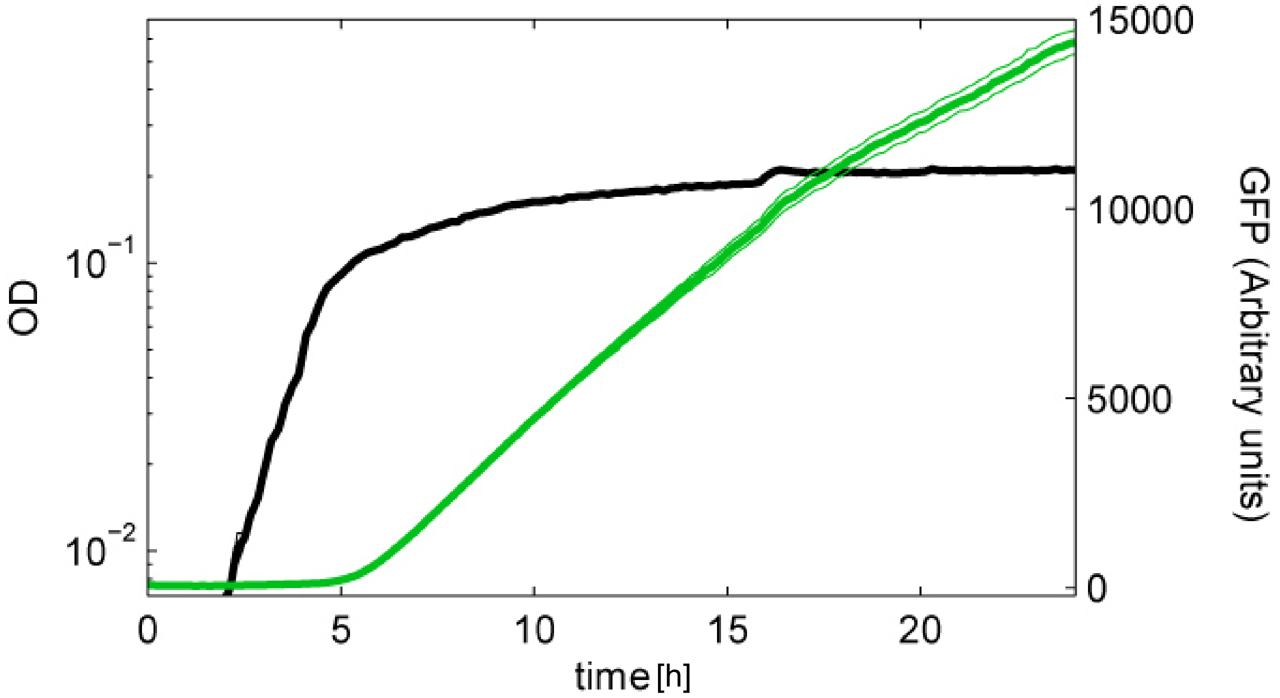
Measured relative fitness:

0.99±0.05

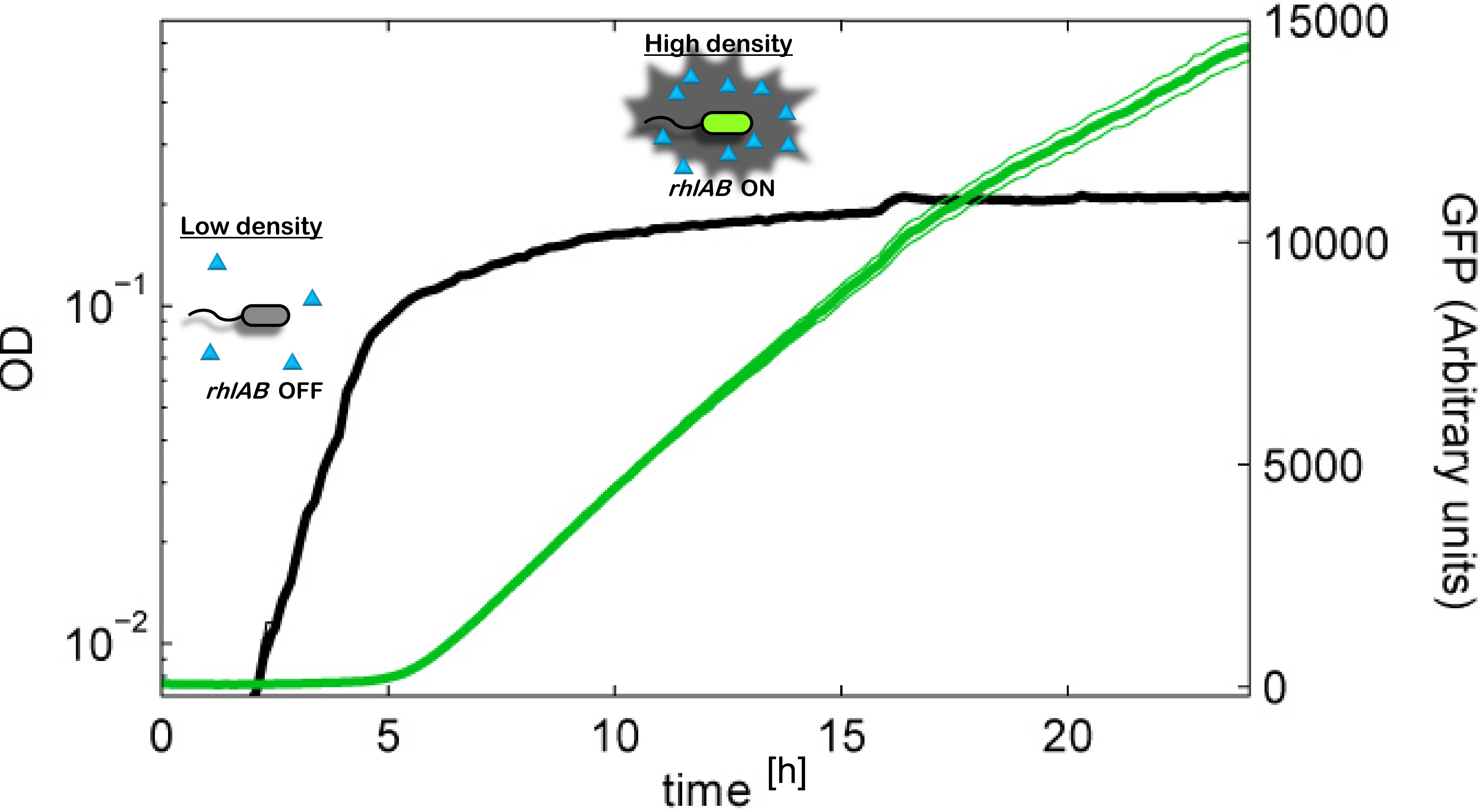
rhlA expression is delayed until stationary phase

P. aeruginosa
PA14 *rhlAB*-GFP

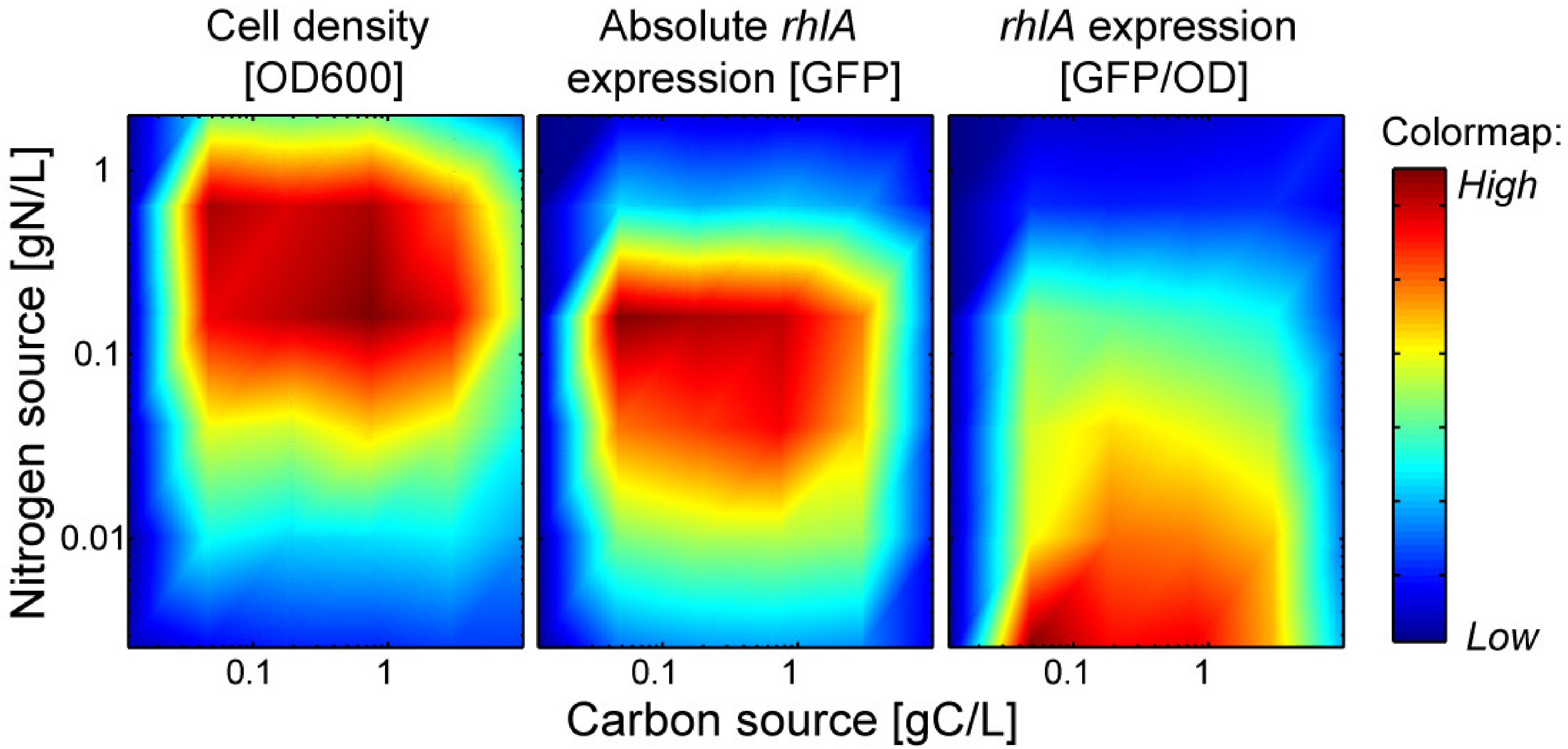




Quorum sensing is necessary yet not sufficient

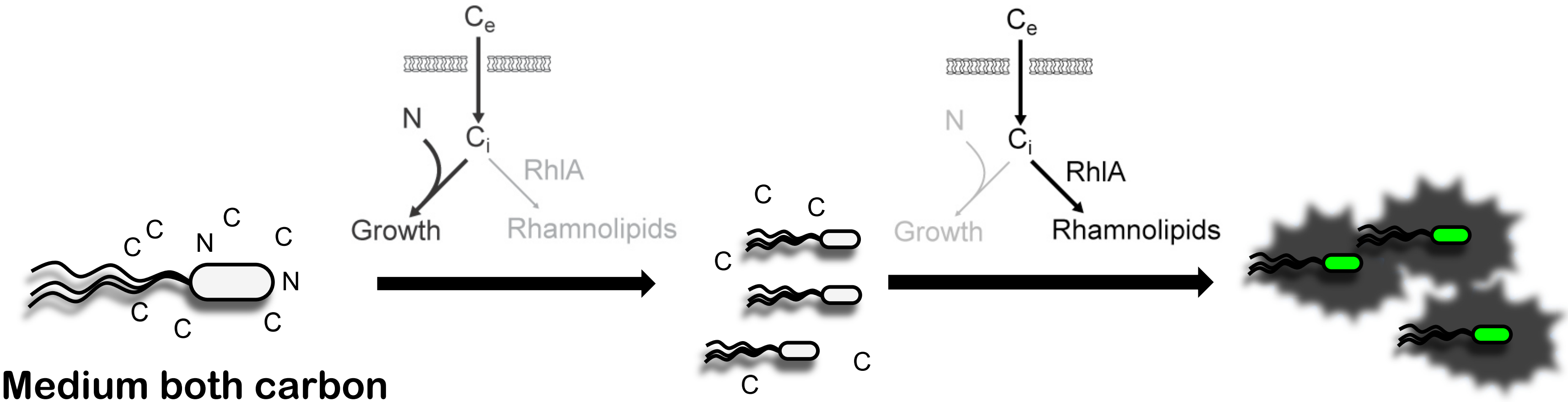


Expression of biosurfactant synthesis is favored at lower nitrogen source levels



Carbon source: Glycerol ($C_3H_5(OH)_3$)
Nitrogen source: $(NH_4)_2SO_4$

rhlA regulation ensures metabolic prudence



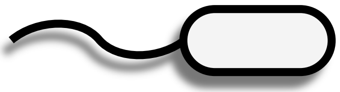
Medium both carbon and nitrogen but carbon is in excess

Cells grow while there's nitrogen…

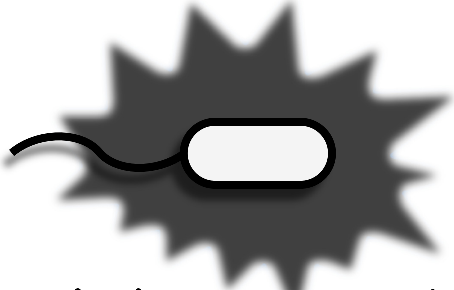
…then use excess carbon to secrete rhamnolipids

But only if there's a quorum

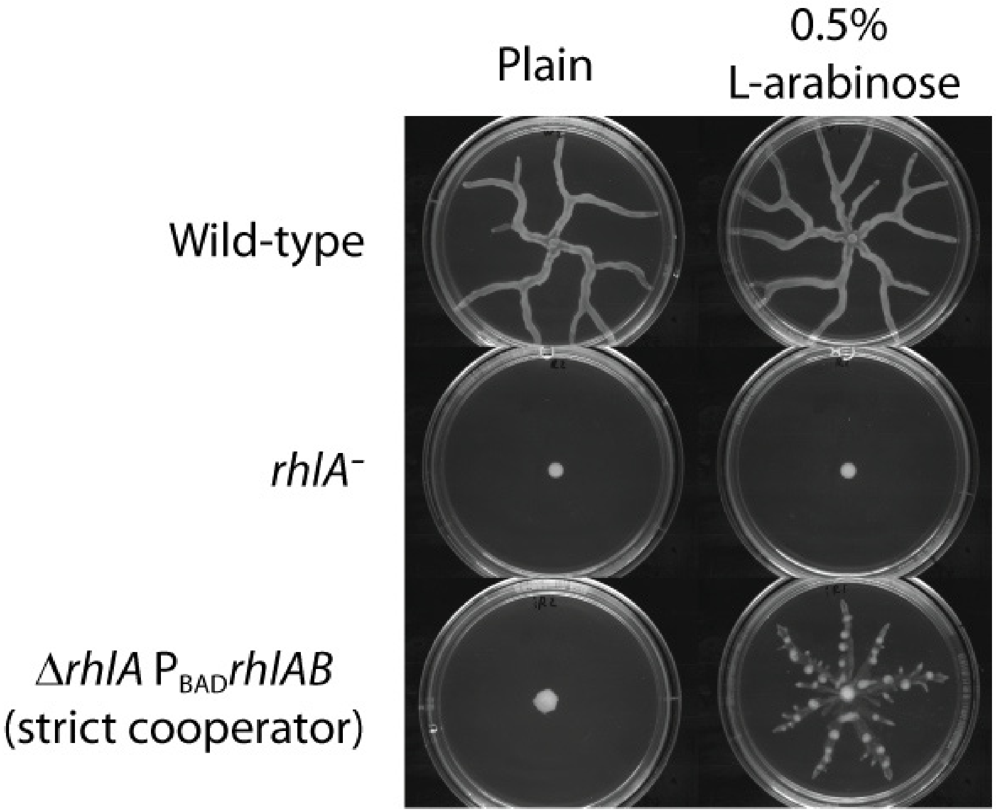
Inducible rhlAB bypasses metabolic pudence mechanism



No inducer (behaves like non-cooperator)

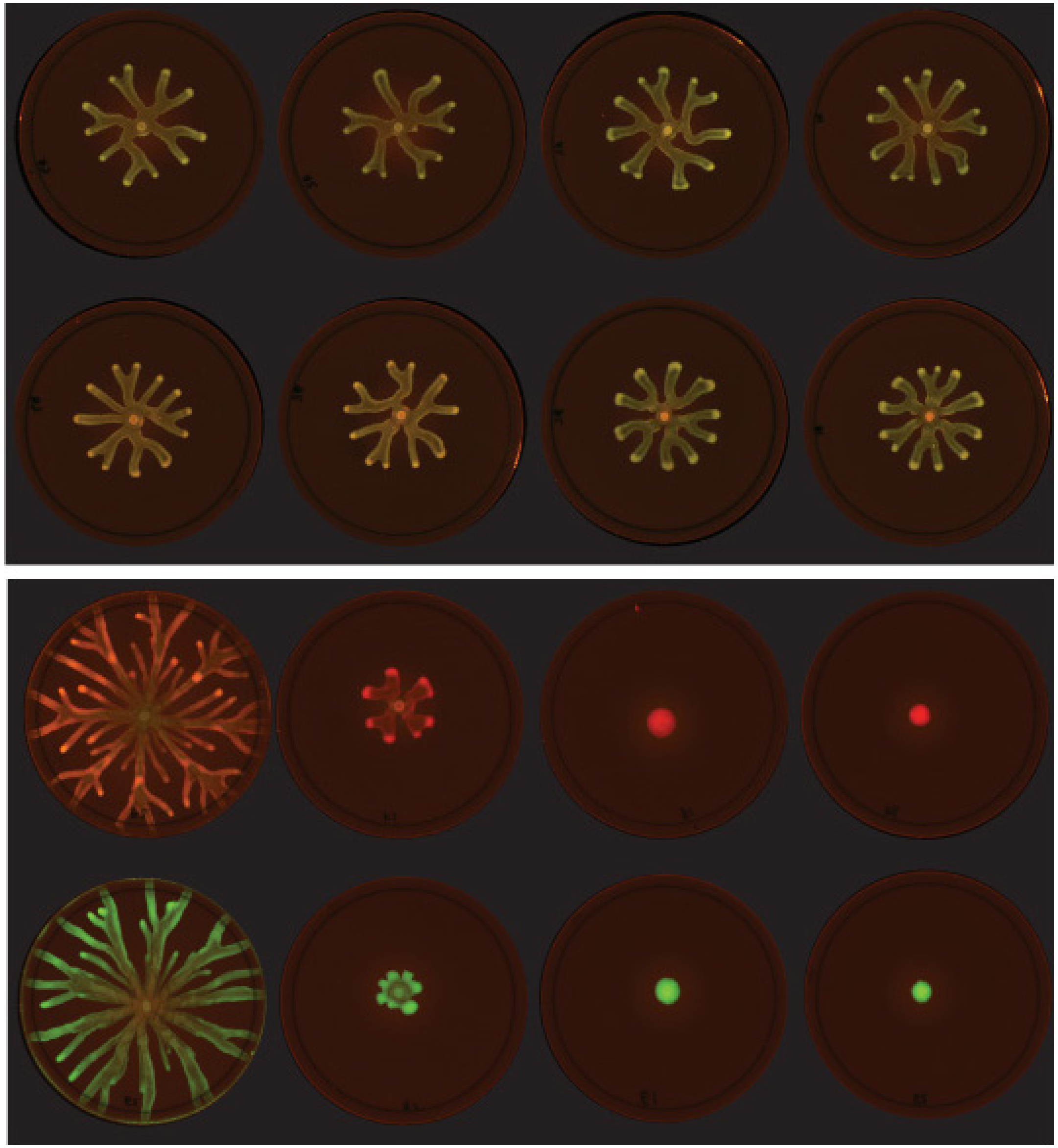


Inducer present (strict cooperator)



Biosurfactant secretion in strict cooperator is cheatable

Day 1 Day 2 Day 3 Day 4



Wild-type (Green)
vs rhlA$^-$ (Red)

Wild-type (Red)
vs rhlA$^-$ (Green)

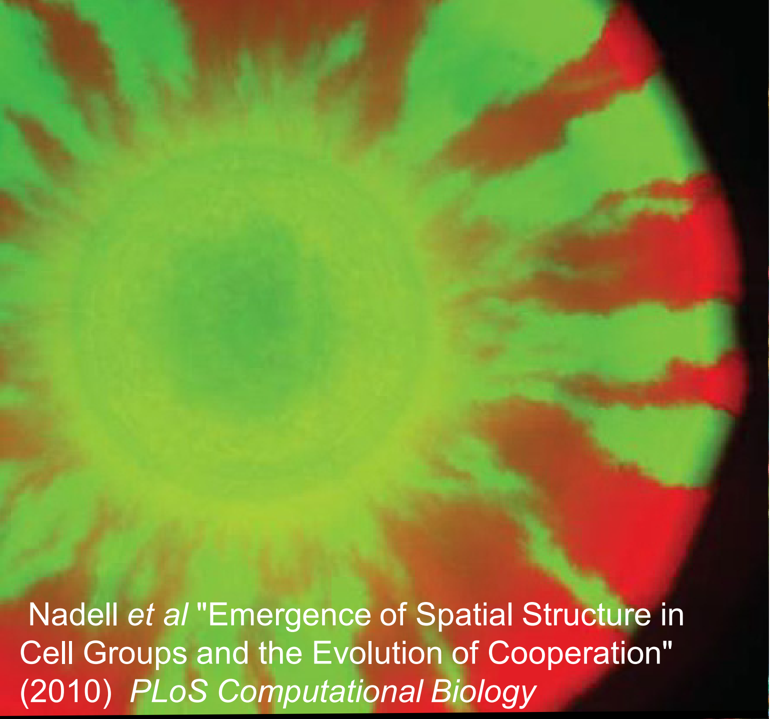
Strict
cooperator (Green)
vs rhlA$^-$ (Red)

Strict
cooperator (Red)
vs rhlA$^-$ (Green)

Summary

Xavier *et al.* Mol Microbiol (2011) 79(1):166-79

- **Bacteria rely on multicellular traits for many tasks**
- **Multicellular cooperative traits are open to exploitation…**
- **…and therefore must have evolved with mechanisms for robustness**
- **We can find the mechanisms stabilizing bacterial multicellularity:**
  - **Physical or biological mechanisms setting populations structure**
  - **Molecular mechanisms (metabolic prudence, quorum sensing, more?)**
- **Can lead to new therapies**



Nadell *et al* "Emergence of Spatial Structure in Cell Groups and the Evolution of Cooperation" (2010) *PLoS Computational Biology*

Xavier *et al* "Social evolution of spatial patterns in bacterial biofilms: when conflict drives disorder." (2009) *The American Naturalist*

Acknowledgments

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