The effect of nutrient-limited growth on floral pattern formation in yeast biofilms

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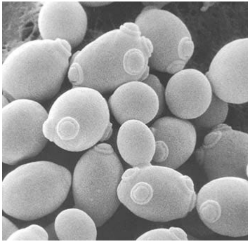
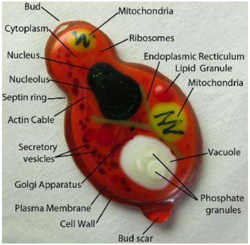
Yeast

- Single-cell fungi ($\sim 10^{-6}$ m).
- *Candida albicans*
  - Human pathogen that grows on medical implants.
  - Candidiasis affects 0.2% per year, mortality rate 30–40%[1].
- *Saccharomyces cerevisiae*
  - Baking and brewing.
  - Model for plant and animal cells.

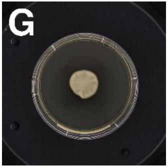




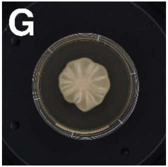
[1] M. S. Lionakis, *Med. Mycol.* 52 (2014), pp. 555–564.

Biofilm formation experiments

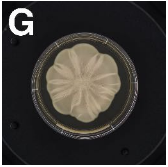
- Yeasts can form **biofilms**: slimy communities of cells and fluid.
- Increase resistance to anti-fungals up to 2000 times[2].
- Pattern formation mechanisms not fully understood
  - **Nutrient-limited growth**.
  - Mechanical forces.
- Want to understand expansion speed and petal formation.



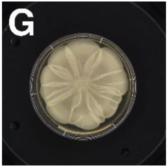
3 days.



5 days.



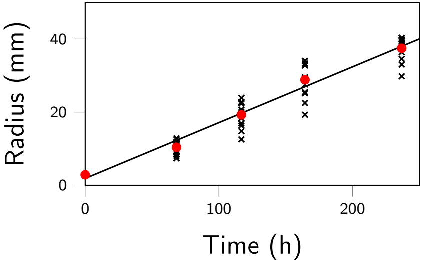
7 days.



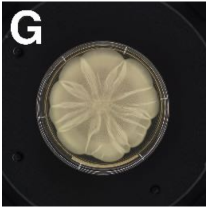
10 days.

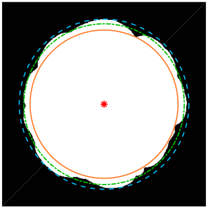
[2] L. M. Martinez and B. C. Fries, *Curr. Fungal Infect. Rep.* 4 (2010), pp. 266–275.

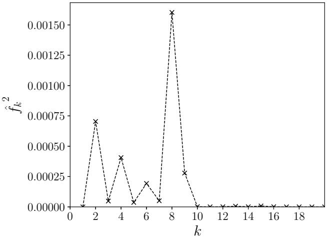
Quantifying floral patterns



- Use angular pair-correlation function to count petals.







Dimensionless model

- Reaction-diffusion system with non-linear cell diffusion[3].

$$\frac{\partial n}{\partial t} = D\nabla \cdot (n\nabla n) + ng,$$
$$\frac{\partial g}{\partial t} = \nabla^2 g - ng.$$

- $n(\boldsymbol{x}, t)$: (**n**umber) cell density.
- $g(\boldsymbol{x}, t)$: **g**lucose concentration.
- D: ratio of cell to nutrient diffusivity.

[3] S. Kitsunezaki, *J. Phys. Soc. Jpn.* 66 (1997), pp. 1544–1550; L. Chen et al., *PLOS Comput. Biol.* 10 (2014), e1003979.

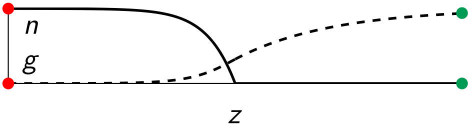
1D travelling wave analysis

- If glucose diffuses much faster than cells: $D = \varepsilon \ll 1$.
- Travelling wave co-ordinate $z = x - vt$, for $v \in \mathbb{R}^+$.
- Define new variable[4] $\zeta = \int_0^z n^{-k}\,\mathrm{d}s$.

$$\frac{\mathrm{d}N}{\mathrm{d}\zeta} = \frac{1}{\varepsilon}\left(v - vN - W - vG\right),$$

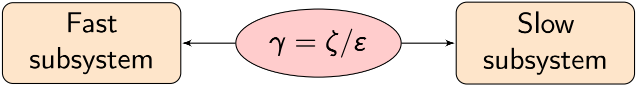
$$\frac{\mathrm{d}G}{\mathrm{d}\zeta} = WN,$$

$$\frac{\mathrm{d}W}{\mathrm{d}\zeta} = N^2G - vWN.$$



[4] D. G. Aronson, Proc. Adv. Sem., Math. Res. Center, Univ. Wisconsin, Madison, Wis. Vol. 44, Academic Press, 1980, pp. 161–176.

Geometric singular perturbation theory (GSPT)



$$\frac{dN}{d\gamma} = v - vN - W - vG, \qquad \varepsilon\frac{dN}{d\zeta} = v - vN - W - vG,$$

$$\frac{dG}{d\gamma} = \varepsilon WN, \qquad \frac{dG}{d\zeta} = WN,$$

$$\frac{dW}{d\gamma} = \varepsilon\left(N^2G - vWN\right). \qquad \frac{dW}{d\zeta} = N^2G - vWN.$$

Geometric singular perturbation theory (GSPT)

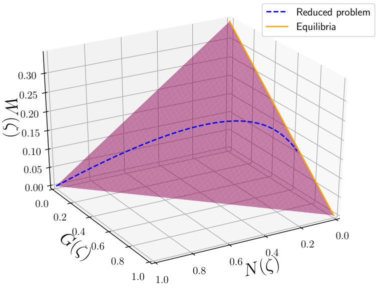
$$\frac{\mathrm{d}N}{\mathrm{d}\gamma} = v - vN - W - vG,$$
$$\frac{\mathrm{d}G}{\mathrm{d}\gamma} = 0,$$
$$\frac{\mathrm{d}W}{\mathrm{d}\gamma} = 0.$$

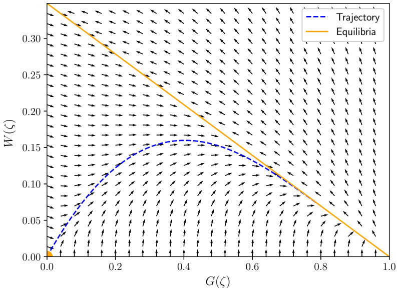
$$0 = v - vN - W - vG,$$
$$\frac{\mathrm{d}G}{\mathrm{d}\zeta} = WN,$$
$$\frac{\mathrm{d}W}{\mathrm{d}\zeta} = N^2G - vWN.$$

Travelling waves for $\varepsilon = 0$

$$\frac{\mathrm{d}N}{\mathrm{d}\gamma} = v - vN - W - vG,$$
$$\frac{\mathrm{d}G}{\mathrm{d}\gamma} = 0,$$
$$\frac{\mathrm{d}W}{\mathrm{d}\gamma} = 0.$$

$$\mathcal{S}_0 : 0 = v - vN - W - vG,$$
$$\frac{\mathrm{d}G}{\mathrm{d}\zeta} = WN,$$
$$\frac{\mathrm{d}W}{\mathrm{d}\zeta} = N^2G - vWN.$$

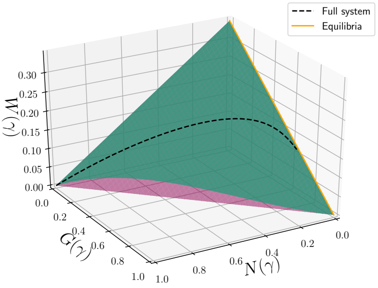




Dynamics for $\varepsilon \neq 0$

- Dynamics occur on a slow manifold $\mathcal{O}(\varepsilon)$ from $\mathcal{S}_0$[5].

$$\mathcal{S}_\varepsilon : W = v(1 - N - G) + \varepsilon \frac{N^2 G}{v} + \mathcal{O}(\varepsilon^2).$$

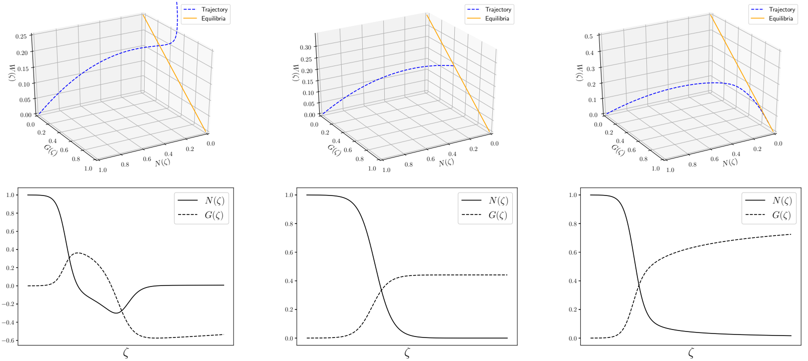


$$\frac{dN}{d\gamma} = v - vN - W - vG,$$
$$\frac{dG}{d\gamma} = \varepsilon W N,$$
$$\frac{dW}{d\gamma} = \varepsilon \left(N^2 G - vWN \right).$$

- Numerically: $d_\varepsilon(W, W_\varepsilon) \sim \varepsilon^{2.02}$.

[5] N. Fenichel, *J. Diff. Eq.* 31 (1979), pp. 53–98; J. Alexander, R. Gardner, and C. K. R. T. Jones, *J. Reine Angew. Math.* 410 (1990), pp. 167–212.

Travelling waves for $D \neq 0$

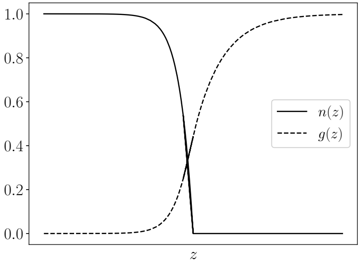


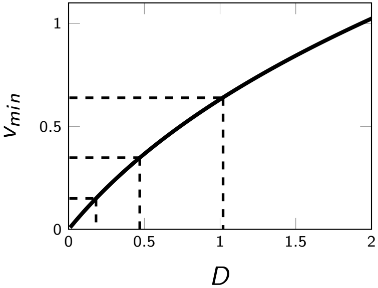
$v = 0.25.$ $v_{min} = 0.348.$ $v = 0.5.$

- Biologically valid travelling waves for $v \geq v_{min}(\varepsilon)$.

Estimating D

- v_{min} gives sharp-fronted solution in original variables[6].
  - Appropriate for finite-sized biofilms.
- $1 - 1$ relationship between v_{min} and D.





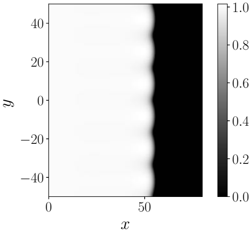
- Experimental data: $D \in [0.181, 1.02]$, and $D_{mean} = 0.47$.

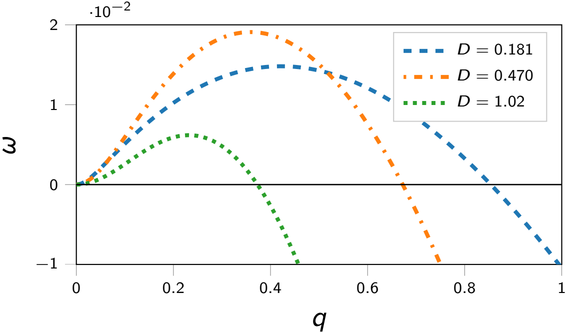
[6] J. Müller and W. van Saarloos, *Phys. Rev. E* 65 (2002), 061111.

2D linear stability analysis

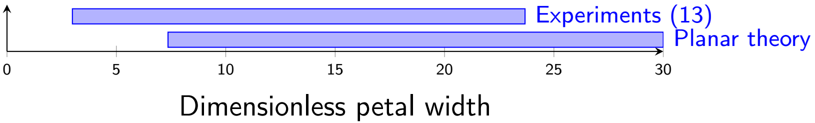
Perturb travelling wave, $\delta \ll 1$

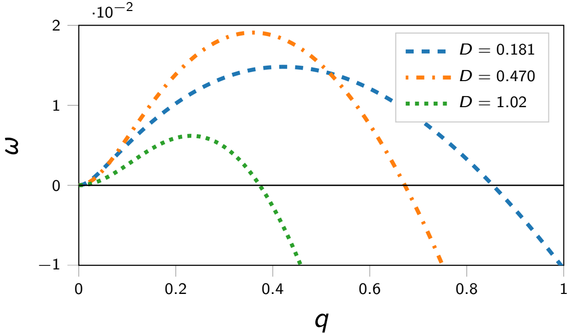
$$\xi \sim x - vt + \delta e^{iqy+\omega t},$$
$$n(\xi, y, t) \sim n_0(\xi) + \delta n_1(\xi) e^{iqy+\omega t},$$
$$g(\xi, y, t) \sim g_0(\xi) + \delta g_1(\xi) e^{iqy+\omega t}.$$



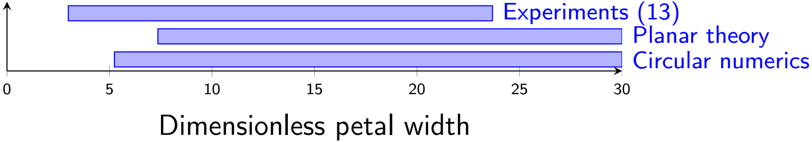


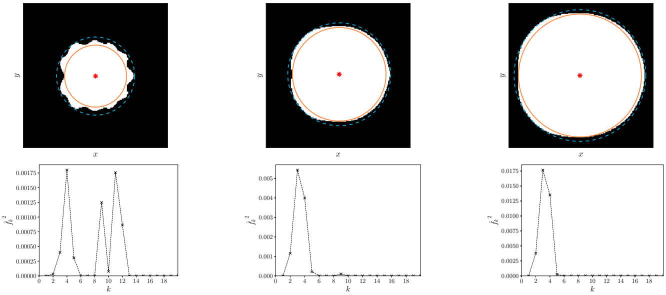
2D linear stability analysis





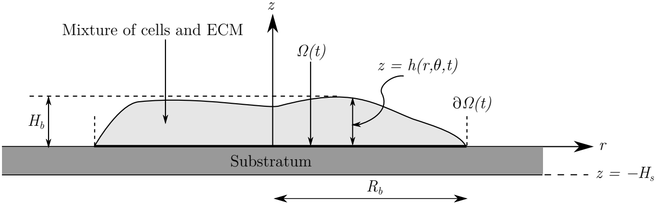
2D linear stability analysis





Summary

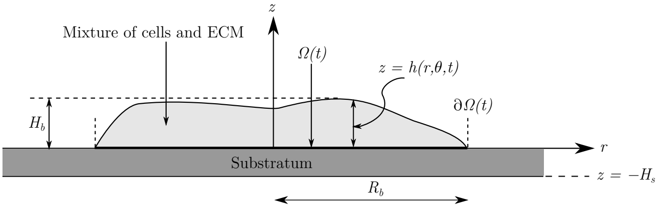
- Pathogenic yeasts form biofilms that help them resist treatment.
- We model biofilm as a reaction–diffusion system with non-linear cell diffusion.
- GSPT helps us describe travelling wave solutions.
- Linear stability analysis suggests nutrient-limited growth is a possible mechanism for petal formation[7].
- Current work: multi-phase, thin-film fluid model.



[7] A. Tam et al., *J. Theor. Biol.* 448 (2018), pp. 122–141.

Multi-phase fluid model

- Treat biofilm as mixture of two viscous fluids (cells, ECM).



- Mass and momentum balance for fluid phases

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \boldsymbol{u}_\alpha) = r_p \chi_\alpha \phi_n g_b, \quad \nabla \cdot (\phi_\alpha \boldsymbol{\sigma}_\alpha) + \boldsymbol{F}_\alpha = 0.$$

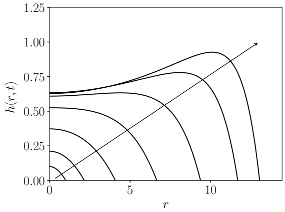
- Nutrient mass balance in substratum and biofilm

$$\frac{\partial g_s}{\partial t} = D_s \nabla^2 g_s, \quad \frac{\partial g_b}{\partial t} + \nabla \cdot (g_b \phi_m \boldsymbol{u}_m) = D_b \nabla^2 g_b - \eta \phi_n g_b.$$

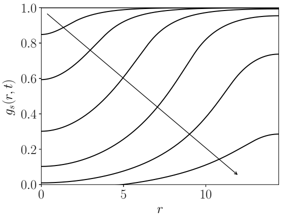
- Thin-film approximation: $H_b/R_b = \varepsilon \ll 1$.

Extensional flow regime: 1D radial solutions

Biofilm profile



Nutrient concentration



Comparison with experiments