A multi-phase extensional flow model for sliding motility in yeast biofilms

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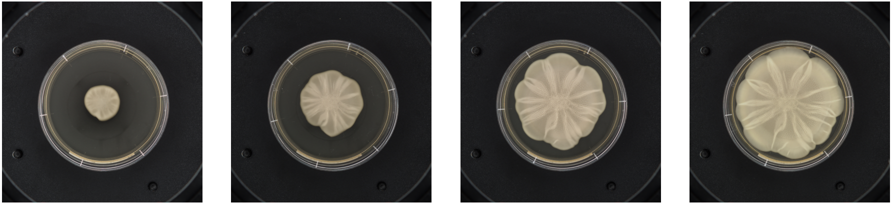
6 February, 2019

Yeast biofilms

- Sticky communities of cells and fluid.
- *Candida albicans*
  - Human pathogen: grows on implanted medical devices.
  - Candidiasis affects 0.2% per year, mortality rate 30–40%[1].
- *Saccharomyces cerevisiae*
  - Baking and brewing.
  - Model organism.
- We can induce biofilm formation in experiments.

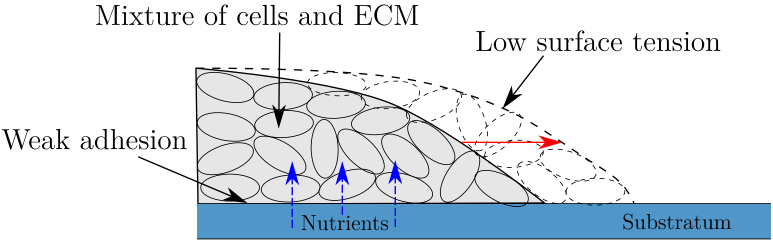


(a) 3 days. (b) 5 days. (c) 7 days. (d) 10 days.

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

Sliding motility

- Cell proliferation generates expansive forces.
- Cell surfaces are hydrophobic[2].
  - Low friction on biofilm–substratum interface[3].
  - Low surface tension[4].
- Biofilm spreads passively as a unit.



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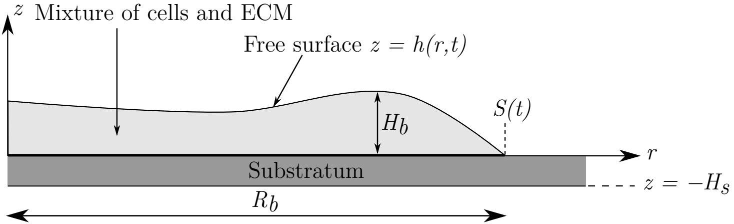
[3] J. Recht et al., *J. Bacteriol.* 182 (2000), pp. 4348–4351.
[4] R. M. Harshey, *Ann. Rev. Microbiol.* 57 (2003), pp. 249–273.

Model assumptions



- Axisymmetric cylindrical geometry.
  - Biofilm occupies $0 \leq r \leq S(t)$ and $0 \leq z \leq h(r,t)$.
- Biofilm is a mixture of two (viscous, Newtonian) fluid phases:
  - Living cells $\phi_n(r,z,t)$ and ECM $\phi_m(r,z,t)$, with $\phi_n + \phi_m = 1$.
  - Similar physical properties: $\rho_n = \rho_m$, $\mu_n = \mu_m$, *etc.*
  - Large interphase drag: $\boldsymbol{u}_n = \boldsymbol{u}_m$.
- Thin aspect ratio

$$\frac{H_s}{R_b} = \varepsilon \ll 1, \qquad \frac{H_b}{R_b} = \mathcal{O}(\varepsilon).$$

Governing equations

- Mass balance (fluid phases)

$$\frac{\partial \phi_n}{\partial t} + \nabla \cdot (\phi_n \boldsymbol{u}) = \psi_n \phi_n g_b - \psi_d \phi_n,$$

$$\frac{\partial \phi_m}{\partial t} + \nabla \cdot (\phi_m \boldsymbol{u}) = \psi_m \phi_n g_b + \psi_d \phi_n.$$

- Mass balance (nutrients in the substratum and biofilm)

$$\frac{\partial g_s}{\partial t} = D_s \nabla^2 g_s,$$

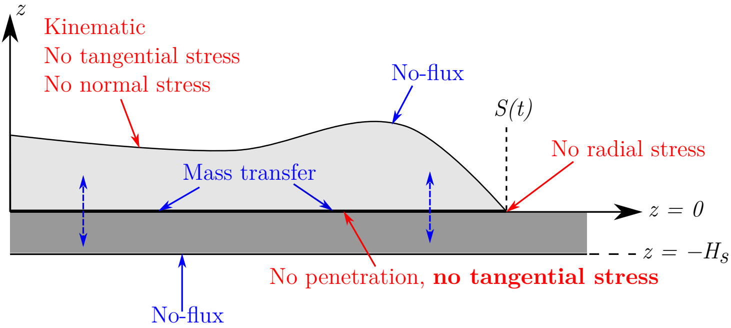
$$\frac{\partial g_b}{\partial t} + \nabla \cdot (g_b \phi_m \boldsymbol{u}) = D_b \nabla^2 g_b - \eta \phi_n g_b.$$

- Momentum balance (fluid mixture)

$$\nabla \cdot \boldsymbol{\sigma} = \boldsymbol{0}.$$

Boundary conditions

- Boundary conditions for nutrients and fluids close the model.



- Nutrient transfer conditions on $z = 0$:

$$D_s \frac{\partial g_s}{\partial z} = -Q \left(g_s - g_b \right), \quad D_b \frac{\partial g_b}{\partial z} = -Q \left(g_s - g_b \right).$$

- No normal stress on the free surface models low surface tension.
- No tangential stress on the substratum models weak adhesion.

Extensional flow scaling

- Scaling based on relevant physics.
  - Thin biofilm (aspect ratio $\varepsilon \ll 1$).
  - Low surface tension.
  - Nutrient-limited growth.
- Variables

$$(r, z) = (R_b \hat{r}, \varepsilon R_b \hat{z}), \quad (u_r, u_z) = (\psi_n G R_b \hat{u_r}, \varepsilon \psi_n G R_b \hat{u_z}),$$

$$t = \frac{\hat{t}}{\psi_n G}, \quad g_s = G \hat{g}_s, \quad g_b = G \hat{g}_b, \quad p = \psi_n G \mu \hat{p}.$$

- Parameters (estimated based on experiments)

$$\Psi_m = \frac{\psi_m}{\psi_n} = 0.11, \quad \Psi_d = \frac{\psi_d G}{\psi_n} = 0,$$

$$D = \frac{D_s}{\psi_n G R_b^2} = 4.34, \quad \mathrm{Pe} = \frac{\psi_n G R_b^2}{D_b} = 0.95, \quad \Upsilon = \frac{\eta R_b^2}{D_b} = 3.15,$$

$$Q_s = \frac{Q R_b}{\varepsilon D_s} = 2.09, \quad Q_b = \frac{Q R_b}{\varepsilon D_b} = 8.65.$$

Thin-film model

- Expand variables

$$h \sim h_0(r,t) + \varepsilon^2 h_1(r,t), \quad \phi_n \sim \phi_{n0}(r,z,t) + \varepsilon^2 \phi_{n1}(r,z,t), \qquad etc.$$

- Dimensionless model (dropping hats)

$$\frac{1}{r}\frac{\partial}{\partial r}(ru_r) + \frac{\partial u_z}{\partial z} = (1+\Psi_m)\,\phi_n g_b,$$

$$\frac{\partial \phi_n}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(ru_r\phi_n) + \frac{\partial}{\partial z}(u_z\phi_n) = \phi_n g_b - \Psi_d \phi_n,$$

$$\frac{\partial g_s}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial g_s}{\partial r}\right) + \frac{1}{\varepsilon^2}\frac{\partial^2 g_s}{\partial z^2}\right]$$

$$\mathrm{Pe}\left(\frac{\partial g_b}{\partial t} + \nabla\cdot[(1-\phi_n)g_b\boldsymbol{u}]\right) = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial g_b}{\partial r}\right) + \frac{1}{\varepsilon^2}\frac{\partial^2 g_b}{\partial z^2} - \Upsilon\phi_n g_b,$$

$$-\frac{\partial p}{\partial r} + \frac{2}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u_r}{\partial r}\right) - \frac{2}{3}\frac{\partial}{\partial r}\left[\frac{1}{r}\frac{\partial}{\partial r}(ru_r) + \frac{\partial u_z}{\partial z}\right] + \frac{\partial}{\partial z}\left(\frac{\partial u_z}{\partial r} + \frac{1}{\varepsilon^2}\frac{\partial u_r}{\partial z}\right) - \frac{2}{r^2}u_r = 0,$$

$$-\frac{\partial p}{\partial z} + 2\frac{\partial^2 u_z}{\partial z^2} - \frac{2}{3}\frac{\partial}{\partial z}\left[\frac{1}{r}\frac{\partial}{\partial r}(ru_r) + \frac{\partial u_z}{\partial z}\right] + \frac{1}{r}\frac{\partial}{\partial r}\left[r\left(\frac{\partial u_r}{\partial z} + \varepsilon^2\frac{\partial u_z}{\partial r}\right)\right] = 0.$$

Thin-film model

- Expand variables

$$h \sim h_0(r,t) + \varepsilon^2 h_1(r,t), \quad \phi_n \sim \phi_{n0}(r,z,t) + \varepsilon^2 \phi_{n1}(r,z,t), \qquad etc.$$

- Simplified leading-order model

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r u_{r0}\right) + \frac{\partial u_{z0}}{\partial z} = \left(1 + \Psi_m\right)\phi_{n0} g_{b0},$$

$$\frac{\partial \phi_{n0}}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}\left(r u_{r0}\phi_{n0}\right) + \frac{\partial}{\partial z}\left(u_{z0}\phi_{n0}\right) = \phi_{n0} g_{b0} - \Psi_d \phi_{n0},$$

$$\frac{\partial^2 g_{s0}}{\partial z^2} = 0,$$

$$\frac{\partial^2 g_{b0}}{\partial z^2} = 0,$$

$$\frac{\partial^2 u_{r0}}{\partial z^2} = 0,$$

$$-\frac{\partial p_0}{\partial z} + \frac{1}{3}\frac{\partial}{\partial z}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r u_{r0}\right) + \frac{\partial u_{z0}}{\partial z}\right] + \frac{\partial^2 u_{z0}}{\partial z^2} = 0.$$

Thin-film model

- Integrating across biofilm depth eliminates z dependence.

$$\bar{\phi}_n = \frac{1}{h}\int_0^h \phi_n \, \mathrm{d}z.$$

- Applying BCs gives a 1D system for $r \in [0, S(t)]$

$$\frac{\partial h_0}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}\left(r u_{r0} h_0\right) = \left(1 + \Psi_m\right)\bar{\phi}_{n0} g_{b0} h_0,$$

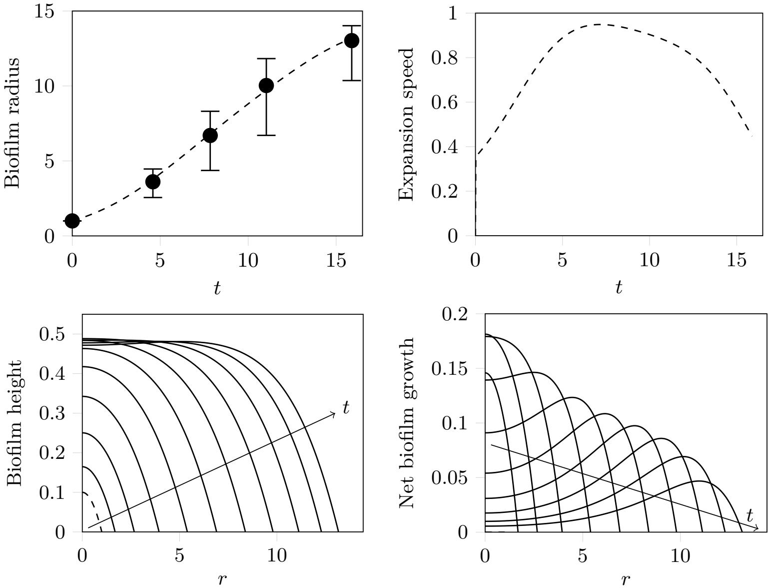
$$\frac{\partial \bar{\phi}_{n0}}{\partial t} + u_{r0}\frac{\partial \bar{\phi}_{n0}}{\partial r} = \bar{\phi}_{n0}\left[g_{b0} - \Psi_d - \left(1 + \Psi_m\right)\bar{\phi}_{n0} g_{b0}\right],$$

$$\frac{\partial g_{s0}}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial g_{s0}}{\partial r}\right) - Q_s\left(g_{s0} - g_{b0}\right)\right],$$

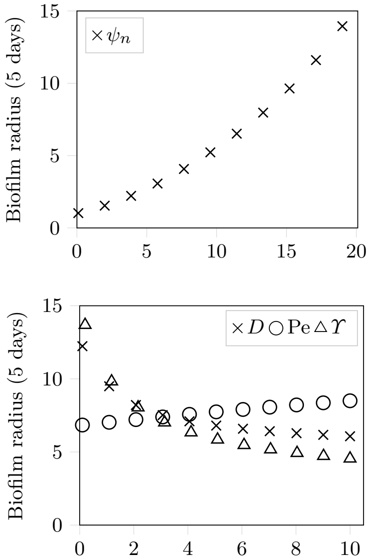
$$\mathrm{Pe}\left[h_0\frac{\partial g_{b0}}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}\left(r u_{r0}\left(1 - \bar{\phi}_{n0}\right) g_{b0} h_0\right)\right] = \frac{1}{r}\frac{\partial}{\partial r}\left(r h_0\frac{\partial g_{b0}}{\partial r}\right) + Q_b\left(g_{s0} - g_{b0}\right) - \Upsilon \bar{\phi}_{n0} g_{b0} h_0,$$

$$2\frac{\partial}{\partial r}\left[\frac{h_0}{r}\frac{\partial}{\partial r}\left(r u_{r0}\right)\right] - \frac{u_{r0}}{r}\frac{\partial h_0}{\partial r} = \left(1 + \Psi_m\right)\frac{\partial}{\partial r}\left(\bar{\phi}_{n0} g_{b0} h_0\right).$$

Numerical solution and comparison with experiments

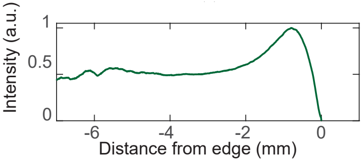


Predicting biofilm size

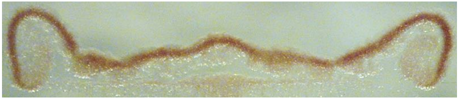


Predicting biofilm shape

- We observe ridge formation in different experimental conditions.

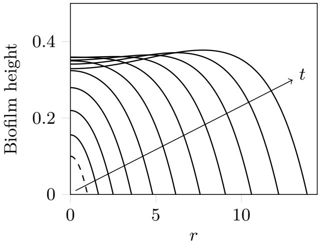


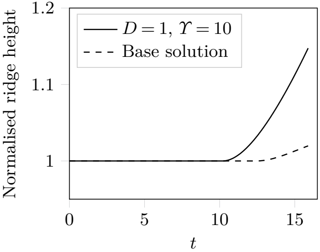
(a) Bacterial biofilm[5].



(b) Yeast colony[6].

- The model can reproduce ridge formation.





[5] S. Srinivasan, C. N. Kaplan, and L. Mahadevan, *bioRxiv* (2018), pre-print.

[6] J. Maršíková et al., *BMC Genom.* 18 (2017), pp. 1–16.

Summary

- We derived a multi-phase model for sliding motility in biofilms.
- The extensional flow thin-film limit simplifies the model.
- Sliding motility can explain experimental results.
- We predict effect of parameters on biofilm size and shape.

Summary

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Acknowledgements:

- University of Adelaide.
- ANZIAM Student Support scheme.
- A. F. Pillow Trust.
- Supervisors and co-authors.

Initial and boundary conditions

Initial conditions:

$$S(0) = 1, \quad h_0(r,0) = H_0\left(1 - r^2\right), \quad \bar{\phi}_{n0}(r,0) = 1, \quad g_{s0}(r,0) = 1, \quad g_{b0}(r,0) = 0.$$

Boundary conditions:

$$\left.\frac{\partial h_0}{\partial r}\right|_{(0,t)} = 0, \quad \left.\frac{\partial \bar{\phi}_{n0}}{\partial r}\right|_{(0,t)} = 0, \quad \left.\frac{\partial g_{s0}}{\partial r}\right|_{(0,t)} = 0, \quad \left.\frac{\partial g_{b0}}{\partial r}\right|_{(0,t)} = 0, \quad u_{r0}(0,t) = 0.$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = u_{r0}\left(S(t),t\right).$$

$$\left.\frac{\partial g_{s0}}{\partial r}\right|_{(R_p,t)} = 0.$$

$$\left.\frac{\partial g_{b0}}{\partial r}\right|_{(S(t),t)} = 0.$$

$$2\frac{\partial u_{r0}}{\partial r} + \frac{u_{r0}}{r} = \left(1 + \Psi_m\right)\bar{\phi}_{n0} g_{b0}, \quad \text{on} \quad (r,t) = \left(S(t),t\right).$$

Numerics and solution for nutrient concentrations

- For g_s, we split the domain into two regions:
  - Biofilm domain, $r \in [0, S(t)]$.
  - Unoccupied Petri dish domain, $r \in [S(t), R]$, where $Q_s = 0$.
- Newton's method ensures g_s and $\partial_r g_s$ are continuous at $S(t)$.
- Solve model using front-fixing Crank–Nicolson scheme

$$\xi = \frac{r}{S(t)}, \quad \text{and} \quad \xi_{outer} = \frac{r - S(t)}{R - S(t)}.$$