Modeling polymorphic transformation of bacterial flagella

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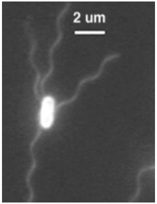
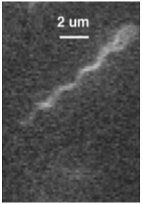
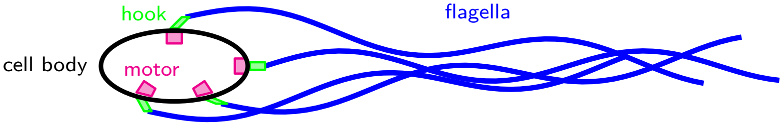
Background





E. coli images from Turner et al., *J. Bacteriol.*, 182(10):2793–2280, 2000.



- *E. coli* and *Salmonella* have several flagella distributed around the cell body.
- Each flagellum is attached to a motor via by a flexible hook.
- Motors can spin clockwise (CW) or counter-clockwise (CCW).

Background

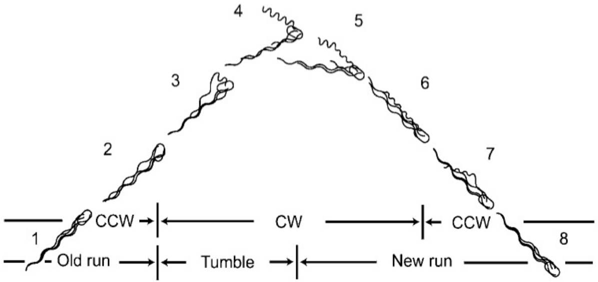


Image from Darnton et al., *Bacteriol.*, 189(5):1756–1764, 2007.

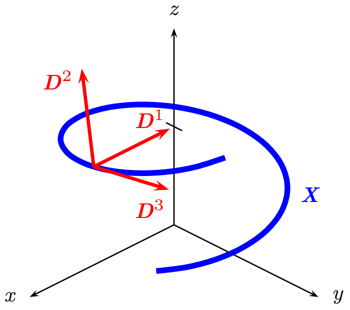
- In "run" phase, all motors turn CCW and flagella bundle together to move forward.
- Each flagellar filament has a left-handed helical shape.
- In "tumble" phase, the cell changes direction.
- One or more flagella spin CW and leave the bundle, temporarily changing shape to a right-handed helix.
- All motors then return to CCW rotation to begin a new run.

Background

Video from `http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php`
Ref: Turner et al., *J. Bacteriol.*, 182(10):2793–2280, 2000.

Mathematical model – Kirchhoff rod theory

- Kirchhoff rod model: Assume a long, thin rod with rest length L.
- Center-line of filament parametrized by $\boldsymbol{X}(s,t)$ where $0 \leq s \leq L$.
- Filament orientation determined by orthonormal vectors $\left\{\boldsymbol{D}^1(s,t),\ \boldsymbol{D}^2(s,t),\ \boldsymbol{D}^3(s,t)\right\}$.



Mathematical model – Energy functionals

- Filament energy functionals

$$E_{\text{shear}} = \frac{1}{2}\int_0^L \left[b_1 \left(\frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^1 \right)^2 + b_2 \left(\frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^2 \right)^2 \right] ds,$$

$$E_{\text{stretch}} = \frac{1}{2}\int_0^L \left[b_3 \left(\frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^3 - 1 \right)^2 \right] ds,$$

$$E_{\text{bend}} = \frac{1}{2}\int_0^L \left[a_1 \left(\Omega_1 - \kappa_1 \right)^2 + a_2 \left(\Omega_2 - \kappa_2 \right)^2 \right] ds,$$

where $\Omega_1 = \frac{\partial \boldsymbol{D}^2}{\partial s} \cdot \boldsymbol{D}^3$ and $\Omega_2 = \frac{\partial \boldsymbol{D}^3}{\partial s} \cdot \boldsymbol{D}^1$, and

$$E_{\text{twist}} = \frac{1}{2}\int_0^L \left[\frac{1}{2} a_3 \left(\Omega_3 - \tau \right)^2 \left(\Omega_3 + \tau \right)^2 + \gamma \left(\frac{\partial \Omega_3}{\partial s} \right)^2 \right] ds,$$

where $\Omega_3 = \frac{\partial \boldsymbol{D}^1}{\partial s} \cdot \boldsymbol{D}^2$. $\Omega_3 > 0 \implies$ right-handed, $\Omega_3 < 0 \implies$ left-handed.

- Bistable twist energy from [Goldstein et al., 2000].
- $\kappa = \sqrt{\kappa_1^2 + \kappa_2^2}$ is the intrinsic curvature
- τ is the intrinsic twist.

Mathematical model – Constitutive relations

- Internal force $\boldsymbol{F}(s,t)$ and moment $\boldsymbol{N}(s,t)$

$$\boldsymbol{F}(s,t) = \sum_{i=1}^{3} F_i \boldsymbol{D}^i \qquad \boldsymbol{N}(s,t) = \sum_{i=1}^{3} N_i \boldsymbol{D}^i$$

- Kirchhoff rod model constitutive relations

$$F_1 = b_1 \frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^1 \qquad F_2 = b_2 \frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^2 \qquad F_3 = b_3 \left(\frac{\partial \boldsymbol{X}}{\partial s} \cdot \boldsymbol{D}^3 - 1 \right)$$

$$N_1 = a_1 (\Omega_1 - \kappa_1) \qquad N_2 = a_2 (\Omega_2 - \kappa_2) \qquad N_3 = a_3\, \Omega_3 \left(\Omega_3^2 - \tau^2 \right) - \gamma \frac{\partial^2 \Omega_3}{\partial s^2}$$

where $\Omega_1 = \frac{\partial \boldsymbol{D}^2}{\partial s} \cdot \boldsymbol{D}^3$, $\Omega_2 = \frac{\partial \boldsymbol{D}^3}{\partial s} \cdot \boldsymbol{D}^1$, and $\Omega_3 = \frac{\partial \boldsymbol{D}^1}{\partial s} \cdot \boldsymbol{D}^2$.

- The above relations can be derived by taking a variational derivative of the energy functionals.
- Force $\boldsymbol{f}(s,t)$ and moment $\boldsymbol{n}(s,t)$, per unit length.

$$0 = \boldsymbol{f} + \frac{\partial \boldsymbol{F}}{\partial s}, \qquad 0 = \boldsymbol{n} + \frac{\partial \boldsymbol{N}}{\partial s} + \left(\frac{\partial \boldsymbol{X}}{\partial s} \times \boldsymbol{F} \right)$$

Regularized Stokes formulation and Kirchhoff rod theory

- Typical length scale $< 20\mu m \implies$ low Reynolds number.
- Stokes equations:

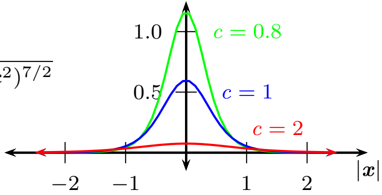
$$0 = -\nabla p + \mu \Delta \boldsymbol{u} + \boldsymbol{g}$$
$$0 = \nabla \cdot \boldsymbol{u}$$

where $\boldsymbol{u}(\boldsymbol{x}, t)$ is the fluid velocity, $p(\boldsymbol{x}, t)$ is the pressure, and μ is viscosity.

- Body force:

$$\boldsymbol{g}(\boldsymbol{x}, t) = \int_0^L \Big(-\boldsymbol{f}(s,t) \Big) \delta_c(\boldsymbol{x} - \boldsymbol{X})\, ds + \frac{1}{2} \nabla \times \int_0^L \Big(-\boldsymbol{n}(s,t) \Big) \delta_c(\boldsymbol{x} - \boldsymbol{X})\, ds$$

where $\delta_c(\boldsymbol{x}) = \dfrac{15 c^4}{8\pi(|\boldsymbol{x}|^2 + c^2)^{7/2}}$

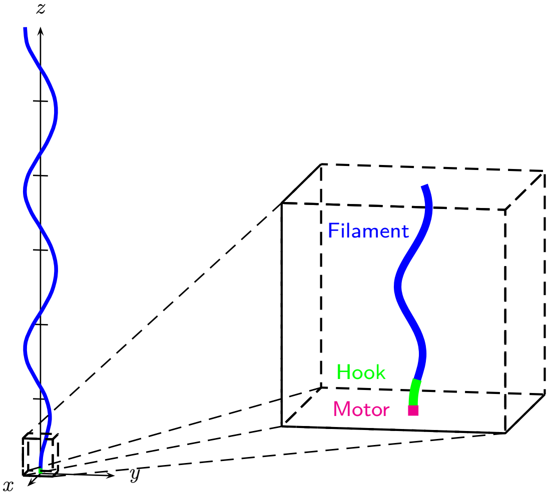


- Filament evolution equations:

$$\frac{\partial \boldsymbol{X}}{\partial t} = \boldsymbol{u}(\boldsymbol{X}, t), \qquad \frac{\partial \boldsymbol{D}^i}{\partial t} = \boldsymbol{w}(\boldsymbol{X}, t) \times \boldsymbol{D}^i, \qquad i = 1, 2, 3$$

where $\boldsymbol{w}(\boldsymbol{x}, t) = \frac{1}{2} \nabla \times \boldsymbol{u}$

Simulation of a single helical filament



Motor rotates either CW or CCW with frequency ω.

Physical parameters

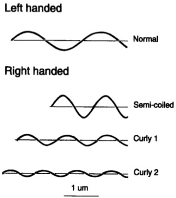
		Filament	Hook
Length	L	$6\ \mu$m	$0.072\ \mu$m
Shear modulus	$b_1,\ b_2$	8.0×10^{-1} g μm/s^2	8.0×10^{-1} g μm/s^2
Stretch modulus	b_3	8.0×10^{-1} g μm/s^2	8.0×10^{-1} g μm/s^2
Bending modulus	$a_1,\ a_2$	3.5×10^{-3} g μm^3/s^2	3.5×10^{-5} g μm^3/s^2
Twist modulus	a_3	1.0×10^{-4} g μm^5/s^2	1.0×10^{-6} g μm^5/s^2
Twist-gradient coefficient	γ	4.0×10^{-6} g μm^3/s^2	0
Intrinsic curvature	κ	$1.3055\ \mu$m^{-1}	0
Intrinsic twist	τ	$-2.1472\ \mu$m^{-1}	0

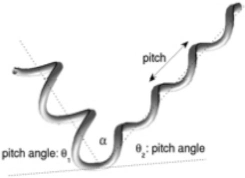
Fluid viscosity	μ	0.01×10^{-4} g/(μm $\cdot$ s)
Motor rotation frequency	ω	100 Hz
Time step	Δt	1.0×10^{-7} s
Filament grid size	Δs	$2.4 \times 10^{-2}\ \mu$m
Regularization parameter	c	$5\Delta s$

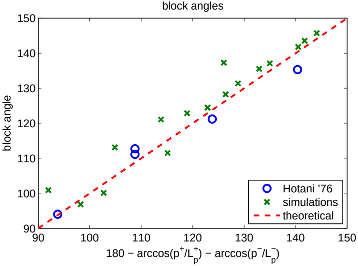
Bistable helix

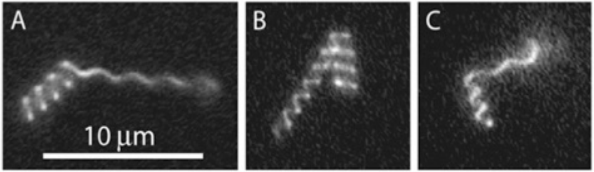
$$E_{\mathsf{twist}} = \frac{1}{2}\int_0^L \left[\frac{1}{2}a_3\left(\Omega_3 - \tau_R\right)^2\left(\Omega_3 + \tau_L\right)^2 + \gamma\left(\frac{\partial\Omega_3}{\partial s}\right)^2\right]\, ds,$$

Bistable helix - block angle



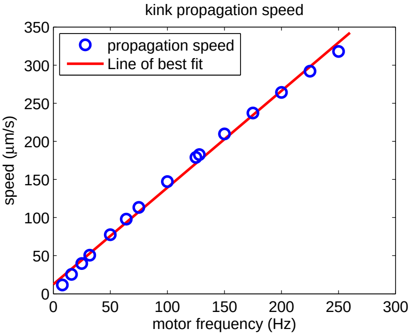


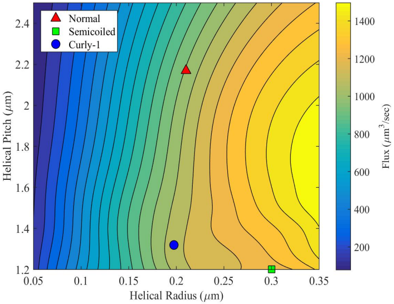




Ref: Turner et al., *J. Bacteriol.*, 182(10):2793–2280, 2000, and Darnton and Berg, *Biophys. J.*, 92:2230–2236, 2007.

Bistable helix

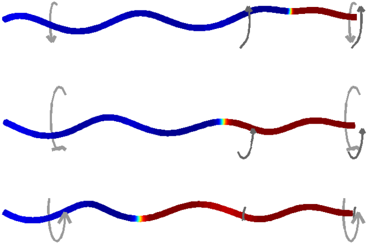




- For typical motor rotation frequency (100 to 200 Hz), a complete polymorphic transformation occurs in < 0.04 seconds in our simulations.
- Semicoiled and curly states push more fluid than normal state.

Bistable helix in viscous flow

- Hotani observed polymorphic transformation when a flagellar filament is subject to a viscous flow [Hotani, 1982].



Ref: Hotani, *J. Mol. Biol.*, 156:791-806, 1982.

Bistable helix in viscous flow

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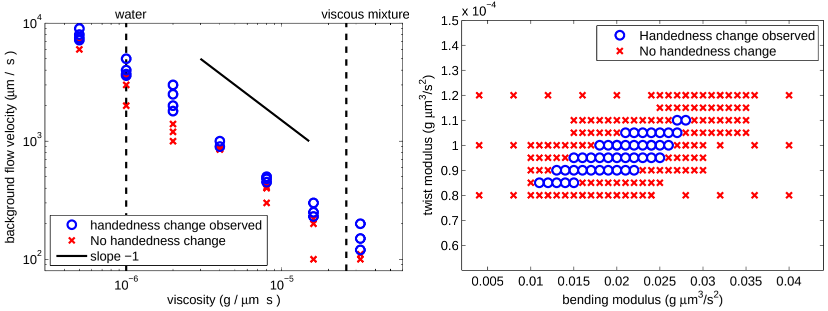

- Velocity threshold is inversely proportional to fluid viscosity.
- Experimental flow speeds are $1–8$ μm/s.

Conclusions and Future Work

Conclusions

- A model of a bacterial flagellum was presented using Kirchhoff rod theory and Stokes' flow.
- Filament is capable of changing handedness with reversal of the motor.
- Performed simulations motivated by experiments by Hotani [Hotani, 1982].

Future Work

- Include more flagella to study bundling behavior.
- Extend the model to include proton-motive force.
- Simulate a free swimming bacterium.