Hammer and Apte (1992) — "Simulation of cell rolling and adhesion on surfaces in shear flow"

April 30, 2018; rev. May 11, 2018

Andrew Watson

1 Summary

This is the first paper on adhesion dynamics. Their goal is to simulate leukocyte rolling by explicitly tracking individual microvilli and receptors, and their bound states. They assume microvilli all have a fixed length, are stiff and oriented normal to the surface of a spherical cell, and support a random number of receptors. All receptors are the same type, and they assume all the receptors are linear springs with force-dependent on and off rates governed by the Dembo model.

They compute rolling velocities for different parameters. They also characterize a few qualitatively different rolling/adhesive behaviors (unbound, rolling, tumbling, transient adhesion, and adhesion) and identify important parameters for rolling.

2 Model Description

2.1 Cell Geometry and Receptors

- Assume the cell is a sphere of radius R_c, which is covered by N_{mv} microvilli with radius R_{mv} and length L_{mv}. Assume the microvilli are rigid, and are oriented normal to the cell surface.
- For calculating the hydrodynamic forces on the cell, it is assumed that the cell is a sphere with radius $R_{\text{ch}} \equiv R_c + L_{\text{mv}}$.
- There are R_T receptors on a cell, and the rolling surface has a ligand density of N_l.
- Assume the adhesion molecules are linear springs.
- Bonds are assumed to form between the center of the tip of a microvillus (denoted $\mathbf{x}_m \equiv (x_m, y_m, z_m)$) and a point on the surface (denoted $\mathbf{x}_0 \equiv (x_0, y_0, z_0)$). Define $\mathbf{x}_b = \mathbf{x}_0 - \mathbf{x}_m$ which gives the orientation and length of the bond.
- The on and off rates of each bond depend on the bond length according to the Dembo model:

$$k_{\text{on}} = k_{\text{on}}^0 \exp\left(-\frac{\sigma_{\text{ts}}(L_{\text{sep}} - \lambda)^2}{2k_bT}\right) \tag{1}$$

$$k_{\text{off}} = k_{\text{off}}^0 \exp\left(\frac{(\sigma - \sigma_{\text{ts}})(L_{\text{sep}} - \lambda)^2}{2k_bT}\right). \tag{2}$$

- Here λ is the equilibrium separation distance, k_bT is the thermal energy, σ is the spring constant, and σ_{ts} is the transition state spring constant.
- Note from equations (1) and (2), if $\sigma - \sigma_{\text{ts}} > 0$ the bonds are slip bonds, but if $\sigma - \sigma_{\text{ts}} < 0$ the bonds are catch bonds.
- They find that $\sigma - \sigma_{\text{ts}}$ has a large effect on cell adhesion in flow.
- They assume that only receptors on microvilli tips are able to bind to the rolling surface, therefore they only track receptors on the tips of microvilli.
- Bonds form normal to the rolling surface, so k_{on} is given by equation (1) with $L_{\text{sep}} \equiv x_m$.
- The off rate of a specific bond depends on the length of the existing bond, and so k_{off} is given by equation (2) with $L_{\text{sep}} \equiv |\mathbf{x}_b|$.
- If receptors are distributed uniformly over the surface of the cell, then the number of receptors on the tip of a single microvillus is Poisson-distributed:

$$P(n) = \frac{\left(\frac{R_T A_{\text{mv}}}{A_c}\right)^n \exp\left(-\frac{R_T A_{\text{mv}}}{A_c}\right)}{n!}. \tag{3}$$

- A_{mv} is the surface area of a single microvillus tip, and A_c is the surface area of the entire cell. So $\frac{R_T A_{\text{mv}}}{A_c}$ is the average number of receptors on a microvillus tip.

- Assume that the time it takes for a given bond to form or break is given by an exponential distribution with mean $1/k_{\text{on}}$ or $1/k_{\text{off}}$. Then the probability that a given bond forms in a time interval Δt is given by

$$P_{\text{on}} = 1 - \exp(-k_{\text{on}}\Delta t), \tag{4}$$

  and the probability of a given bond breaking is the same with k_{off} in place of k_{on}.

- Each bond generates a force and torque on the cell body, and the sum of these forces along with colloidal forces (described in sub-section 2.2) affect the cell velocity.

- We assume the fluid velocity is given by Stokes' equation, and therefore the cell velocity is linearly related to the net force on the cell:

$$\mathbf{U} = \underline{\underline{M}}\mathbf{F}$$

  where $\mathbf{U} = (V_x, V_y, V_z, \Omega_x, \Omega_y, \Omega_z)$ and $\mathbf{F} = (F_x^b + F_x^c, F_y^b + F^s, F_z^b, C_x^b, C_y^b, C_z^b + C^s)$.

- The positions of the microvilli must be tracked as the cell translates and rotates. Spherical coordinates are used to track the microvilli. If a given microvillus has coordinates (θ_m, ϕ_m), then its position evolves according to:

$$\frac{d\phi_m}{dt} = -\sin\theta_m\Omega_x + \cos\theta_m\Omega_y \tag{5}$$

$$\frac{d\theta_m}{dt} = -\frac{\cos\phi_m\cos\theta_m}{\sin\phi_m}\Omega_x - \frac{\cos\phi_m\sin\theta_m}{\sin\phi_m}\Omega_y + \Omega_z. \tag{6}$$

- Both coordinate systems use the cell's frame of reference (see Fig.), so the anchor point $\mathbf{x}_0$ of each bond must be tracked as well:

$$\frac{d\mathbf{x}_0}{dt} = -\mathbf{V} \tag{7}$$

- Cartesian and spherical coordinates are related through the expected equations:

$$x = R_{\text{ch}}\sin\phi\cos\theta$$
$$y = R_{\text{ch}}\sin\phi\sin\theta$$
$$z = R_{\text{ch}}\cos\phi$$

2.2 Bond and Colloidal Forces

- Assume the bonds are linear springs with spring constant σ and rest length λ.

- The force generated by a single bond is given by

$$\mathbf{F}^b = \sigma(|\mathbf{x}_b| - \lambda)\frac{\mathbf{x}_b}{|\mathbf{x}_b|}. \tag{8}$$

- The torque generated by a single bond is given by

$$\mathbf{C}^b = \mathbf{x}_m \times \mathbf{F}^b. \tag{9}$$

- The force due to gravity is approximately

$$F_{\text{gr}} = \frac{4}{3}\pi(\rho_c - \rho_m)R_{\text{ch}}^3 g, \tag{10}$$

  where ρ_c and rho_m are the densities of the cell and the medium, and g is the acceleration due to gravity.

- Colloidal forces decay strongly with distance, and usually the length scale for decay is shorter than the length of the microvilli (sources in Hammer and Apte (1992): Bongrand and Bell, 1984; Israelachvili, 1985).

- Therefore assume that all of the colloidal forces acting on the cell come from the microvilli (except for gravity).

- There are three colloidal forces associated with individual microvilli: van der Waals forces, electrostatic forces, and steric stabilization forces. All of these forces only act normal to the rolling surface, i.e. in the x direction.

- van der Waals force:

$$F_{\text{vdw}} = \frac{A_{\text{H}}A_{\text{mv}}}{6\pi}\sum_{\text{microvilli}} x_m^{-3}. \tag{11}$$

  A_{H} is the Hamaker constant.

- Electrostatic force:

$$F_{\text{el}} = \frac{e^2 z_1 z_2 N_1 N_2 A_{\text{mv}}}{2\epsilon_r\epsilon_o\delta^2}\sinh\delta L_1\sinh\delta L_2\sum_{\text{microvilli}} e^{-\delta x_m}. \tag{12}$$

- Steric stabilization force:

$$F_{\text{ss}} = \left(\lambda_{\text{ss}} A_{\text{mv}} \sum_{\text{microvilli}} x_m^{-2} \right) \mathcal{H}\left(L_g - x_m\right) \tag{13}$$

  where $\mathcal{H}$ is the Heaviside function.

- Then the colloidal force is the sum of the above 4 forces (with the appropriate signs)

3 Results Overview

4 Discussion/Conclusions Overview

Article Evaluation

Reference

Hammer, D. A. and Apte, S. M. (1992). Simulation of cell rolling and adhesion on surfaces in shear flow: general results and analysis of selectin-mediated neutrophil adhesion. *Biophysical Journal*, 63(1):35–57.