— "Modeling Leukocyte Rolling"

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1 Introduction

- Leukocyte rolling is mediated by a continuous series of molecular bonds between the cell and the substrate that rapidly form and dissociate. Some models of rolling are direct models that track the states of important molecules and bonds, and others are semi-analytic or analytic or agent-based models (unsure what this means?).
- Rolling of leukocytes is necessary for firm adhesion. Rolling of leukocytes involves, at a minimum, a selectin and selectin ligand. Selectins bind carbohydrates and are expressed on leukocytes and other cells.
- There are different scales of leukocyte binding/rolling, from the cellular level down to the molecular level ($\sim$ 4 orders of magnitude).
- While the simplest description of rolling involves a single selectin binding to a single ligand, in reality rolling involves several selectins interacting with an unknown number of ligands.
- Rolling velocity is modulated by integrins.
- Mechanical properties of the cell are also important. Rolling of rigid beads, for example, is unstable even at relatively low shear rates (no specific shear rates are given in this section).
- Modeling shows that rolling requires molecular bonds with fast association and dissociation.
- The motion of a rigid sphere in flow next to a wall can be calculated (see Goldman et al., 1967), and the translational velocity of a sphere in flow next to a wall is the hydrodynamic velocity. Rolling cells travel at a much lower velocity than the hydrodynamic velocity.
- A repulsive force is necessary to prevent permanent adhesion of a sphere to the wall.
- There are four basic types of leukocyte rolling models:
  1. Direct models—track receptor-ligand bonds individually, track positions of receptors and ligands, and their association state
  2. Semi-analytic models—track bond density in the cell-substrate contact area using kinetic rate equations
  3. Analytic models—"describe the evolution of the rolling process through individual variables, the evolution of which can be described by mathematical equations."
  4. Agent-based models—"multilevel, object-oriented models, which are typically based on available software toolkits."
- See p. 228 for a brief historical description of the development of leukocyte rolling models. They mention a couple of models where the activity of integrins is included.
- Four important classes of parameters:
  1. Cellular parameters like cell radius and density, properties of the microvilli, and viscoelastic/mechanical properties.
  2. Molecular parameters like receptor and ligand lengths, densities, and bond properties
  3. Environmental parameters like temperature and fluid properties
  4. Algorithmic/Numerical parameters, like time step, mesh size, etc.
- There are three classes of interactions:
  1. Receptor-ligand interactions: the Bell model or the Dembo model and MC simulations
  2. Cell-substrate interactions: forces due to gravity, other cells, electrostatics, and receptor-ligand binding
  3. Cell-fluid interactions.

- With the Dembo model of binding/unbinding,

$$k_f = k_f^0 \exp\left[\frac{-\sigma_{\text{ts}}\left(L_{\text{sep}} - \lambda\right)^2}{2\kappa_B T}\right], \text{ and}$$

$$k_d = k_d^0 \exp\left[\frac{\left(\sigma - \sigma_{\text{ts}}\right)\left(L_{\text{sep}} - \lambda\right)^2}{2\kappa_B T}\right]$$

  where σ_{ts}, σ, λ, and L_{sep} are the transition-state spring constant, the bound-state spring constant, the unstressed bond length, and the separation distance.

- With the Bell model,

$$k_f = k_f^0 \exp\left[\frac{\sigma\left|L_{\text{sep}} - \lambda\right|\left(\delta - 0.5\left|L_{\text{sep}} - \lambda\right|\right)}{\kappa_B T}\right], \text{ and}$$

$$k_d = k_d^0 \exp\left[\frac{\sigma\left|L_{\text{sep}} - \lambda\right|}{\kappa_B T}\right]$$

  where δ is the reactive compliance.

- Then these reaction rates can be used to run Monte Carlo simulations of bond formation and breaking.
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2 Published Modeling Approaches

The authors discuss 6 models:

1. Adhesion dynamics model of Hammer and Apte (1992)
2. Event-tracking model of adhesion (ETMA) of Pospieszalska et al. (2009)
3. A semi-analytic model of Tozeren and Ley (1992)
4. A model of cell deformation in rolling by Khismatullin and Truskey (2004)
5. An analytic model by Zhao et al. (1995)
6. An agent-based model of rolling by Tang et al. (2007)

2.1 Adhesion Dynamics Model by Hammer and Apte (1992)

- Simulates the rolling of a rigid sphere with rigid microvilli protruding normally from the surface
- Have a single class of receptors, randomly distributed over the sphere surface
- Receptor-ligand bonds are modeled with the Dembo model, and bonds form perpendicularly to the substrate and are modeled as Hookean springs.
- They use a fixed time step, and in each step determine whether each bond or potential bond breaks or forms, and update the velocity on the sphere
- This model has been updated and modified several times, substituting the Bell model for the Dembo model, adding integrin receptors, adding deformable microvilli, etc.
- One extension of the model by Krasik et al. (2006) adds activation of integrins
- Another extension by Caputo et al. (2007) introduces an overall ligand on rate given by

$$\left(k_f^0\right)_L = k_0 P n_R \tag{1}$$

  where k_0 is the encounter rate, P is the probability of bond formation, and n_R is the density of substrate receptors. With increasing shear rate, k_0 increases and P decreases.

2.2 Event-Tracking Model of Adhesion by Pospieszalska et al. (2009)

- The cell is modeled as a sphere with flexible microvilli.
- ETMA tracks individual receptors, and so bonds can form at angles other than $90°$, and they track individual microvilli
- Use a variable time step for MC simulation, and pick the first reaction, and ignore the others.

- They ignore translation along the y-axis and rotations about the x- and z-axes
- Track a single type of receptor.
- They found that 30% of bonds do not last long enough to become load-bearing ($\gamma = 50s^{-1}$).
- In a later iteration, they allow microvilli to stretch as well as bend

2.3 Model by Tozeren and Ley (1992)

- The first semi-analytic model of rolling
- They model the leukocyte as a "bumpy" sphere. They assume there is a fluid layer separating the cell and the substrate with a thickness of the length of typical cell protrusions.
- The cells have a uniform rolling velocity V_x and slip velocity V_s, and are separated from the surface with a constant distance h_c.
- All bonds formed at the same time are lumped together into a single bond state
- The forces on a bond can be found from the bond length, and the bond density as a function of x in the contact zone is calculated according to equation (29) (it looks like the steady state of an advection-reaction equation).
- The model describes steady-state rolling for a given shear rate

2.4 Model by Khismatullin and Truskey (2004)

- Model whole-cell deformation in rolling. The leukocyte is modeled as a viscoelastic drop composed of a viscoelastic nucleus surrounded by a viscoelastic cytoplasm. The membrane has a cortical tension, which pulls it into a sphere shape.
- Microvilli are modeled as springs
- The fluid is modeled with the Navier-Stokes equations, as opposed to the Stokes equations used in previous models

2.5 Model by Zhao et al. (1995)

- This is an analytical model of rolling which tracks the distribution of velocities for rolling leukocytes
- Assumption: leukocyte displacement is composed of random step-like jumps at random times
- Assume cells are observed at intervals of Δt, then the observed velocity of a cell at a time t and position x is given by

$$V(x,t) = \frac{x(t+0.5\Delta t) - x(t-0.5\Delta t)}{\Delta t}. \tag{2}$$

- Then $p(V,t)$ satisfies $\frac{\partial p}{\partial t} = -\frac{\partial J}{\partial V}$ where J is a probability flux given by

$$J(V,t) = A(V)p(V,t) - \frac{1}{2}\frac{\partial(B(V)p(V,t))}{\partial V}. \tag{3}$$

where $A(V) = \frac{l_{\text{mean}}/t_{\text{mean}} - V}{\Delta t}$ and $B(V) = 2Vl_{\text{mean}}\left[\frac{1+(\sigma_1/l_{\text{mean}})^2}{(\Delta t)^2}\right]$.

- This describes the transient evolution of leukocyte rolling. The steady state distribution is a γ distribution, that depends on the frame rate of the observations Δt.

2.6 In Silico White Blood Cell Model by Tang et al. (2007)

- This is an agent-based model
- The cell is modeled as a rectangle with rounded edges, and the surface of the cell is divided into 600 subunits. The substrate surface is also divided into subunits of the same size.
- The leukocyte subunits contain 3 agents representing PSGL-1, VLA-4, and CXCR2. The substrate subunits contain 3 agents representing P-selectin, VCAM-1, and GRO-α.
- I don't understand the geometry of this model. Something like rolling is simulated by removing elements from the trailing end

of the cell and adding them to the leading end of the cell, and then elements on the cell and substrate which are adjacent to each other can form bonds.