Course: Biophysics
ProblemSet: 5
Due: 17th April

3rd April, 2014

6.7 *Inner ear*

A. J. Hudspeth and coauthors found a surprising phenomenon while studying signal transduction by the inner ear. Figure 6.13a shows a bundle of stiff fibers (called stereocilia) projecting from a sensory cell. The fibers sway when the surrounding inner-ear

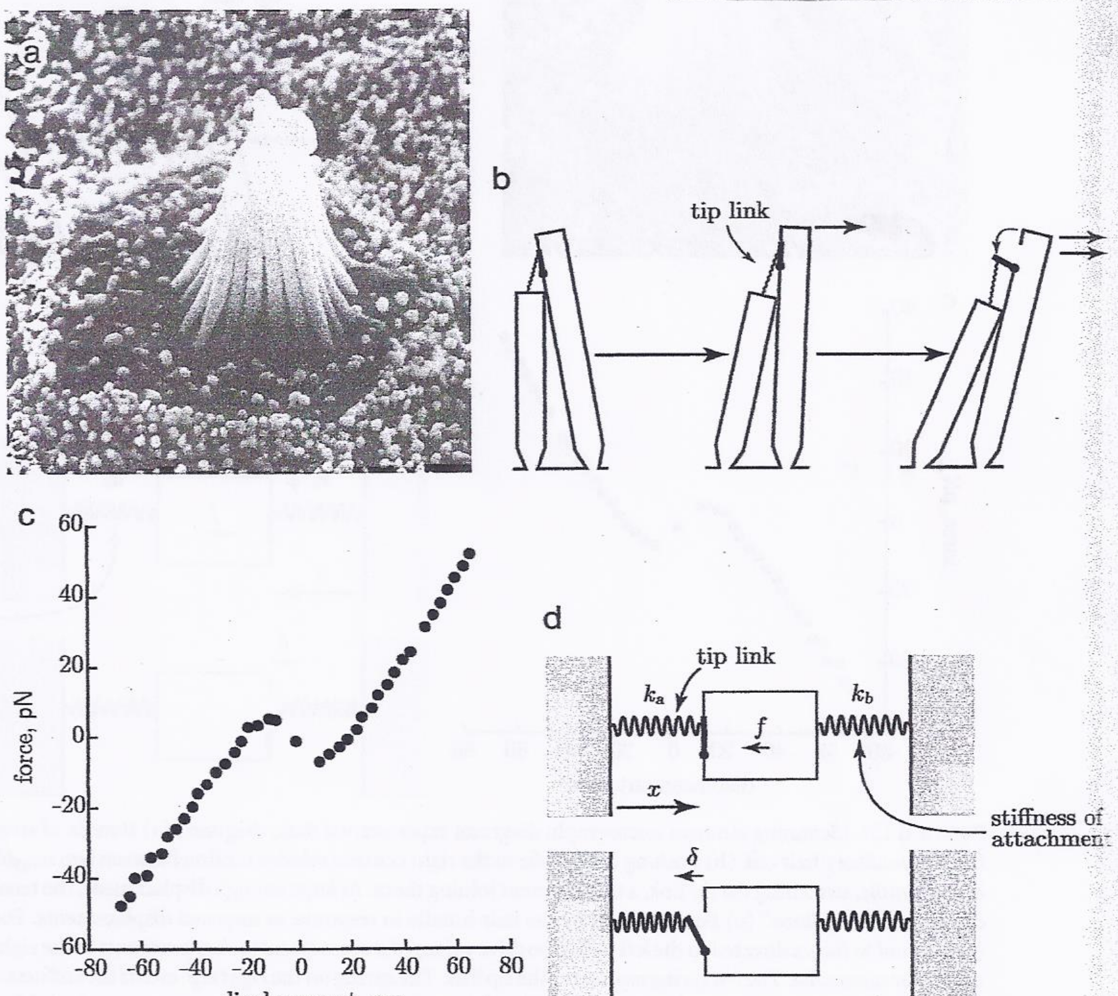

Figure 6.13: (Scanning electron micrograph; diagram; experimental data; diagram) (a) Bundle of stereocilia projecting from an auditory hair cell. (b) Pushing the bundle to the right causes a relative motion between two neighboring stereocilia in the bundle, stretching the tip link, a thin filament joining them. At large enough displacement, the tension in the tip link can open a "trap door." (c) Force exerted by the hair bundle in response to imposed displacements. Positive values of f correspond to forces directed to the left in (b); positive values of x correspond to displacements to the right. (d) Mechanical model for stereocilia. The *left spring* represents the tip link. The spring on the *right* represents the stiffness of the attachment point where the stereocilium joins the main body of the hair cell. The two springs exert a combined force f. The model envisions N of these units in parallel. [(a) Digital image kindly supplied by A. J. Hudspeth; (c) data from Martin et al. 2000.]

fluid moves. Other micrographs (not shown) revealed thin, flexible filaments (called tip links) joining each fiber in the bundle to its neighbor (wiggly line in the sketch, Figure 6.13b).

The experimenters measured the force-displacement relation for the bundle by using a tiny glass fiber to poke it. A feedback circuit maintained a fixed displacement for the bundle's tip and reported back the force needed to maintain this displacement. The surprise is that the experiments gave the complex curve shown in panel (c). A simple spring has a stiffness $k = \frac{df}{dx}$ that is constant (independent of x). The diagram shows that the bundle of stereocilia behaves like a simple spring at large deflections; but in the middle, it has a region of *negative* stiffness!

To explain their observations, the experimenters hypothesized a trap door at one end of the tip link (top right of the wiggly line in Figure 6.13b), and proposed that the trap door was effectively a two-state system.

a. Explain qualitatively how this hypothesis helps us to understand the data.
b. In particular, explain why the bump in the curve is rounded, not sharp.
c. In its actual operation, the hair bundle is not clamped; its displacement can wander at will, subject to applied forces from motion of the surrounding fluid. At zero applied force, the curve shows *three* possible displacements, at about −20, 0, and +20 nm. But really, we will never observe one of these three values. Which one? Why?

6.10 $\boxed{T_2}$ *Gating compliance*

(Continuation of Problem 6.7.) We can model the system in Figure 6.13 quantitatively as follows. We think of the bundle of stereocilia as a collection of N elastic units in parallel. Each element has two springs: One, with spring constant k_a and equilibrium position x_a, represents the elasticity of the tip link filament. The other spring, characterized by k_b and x_b, represents the stiffness of the stereocilium's attachment point (provided by a bundle of actin filaments). See panel (d) of the figure.

The first spring attaches via a hinged element (the "trap door"). When the hinge is in its open state, the attachment point is a distance δ to the left of its closed state relative to the body of the stereocilium. The trap door is itself a two-state system with a free energy change ΔF_0 to jump to its open state.

a. Derive the formula $f_{\text{closed}}(x) = k_a(x - x_a) + k_b(x - x_b)$ for the net force on the stereocilium in the closed state. Rewrite this in the more compact form $f_{\text{closed}} = k(x - x_1)$ and find the effective parameters k and x_1 in terms of the earlier quantities. Then find the analogous formula for the state in which the trap door is open.
b. The total force f_{tot} is the sum of N terms. In $P_{\text{open}}N$ of these terms, the trap door is open; in the remaining $(1 - P_{\text{open}})N$, it is closed. To find the open probability using Equation 6.34 on page 225, we need the free energy difference $\Delta F(x)$ between the system's two states (at fixed x). This difference is a constant, ΔF_0, plus a term involving the energy stored in spring a. Get a formula for $\Delta F(x)$.
c. Assemble the pieces of your answer to get the force $f_{\text{tot}}(x)$ in terms of the unknown parameters N, k_a, k_b, x_a, x_b, δ, and ΔF_1, where $\Delta F_1 \equiv \Delta F_0 + \frac{1}{2}k_a\delta^2$. That's a lot of parameters, but some of them enter only in fixed combination. Show that your answer can be expressed as

$$f_{\text{tot}}(x) = K_{\text{tot}}x + f_0 - \frac{Nz}{1 + e^{-z(x-x_0)/k_BT}},$$

and find the quantities K_{tot}, f_0, z, and x_0 in terms of the earlier parameters.
d. Hudspeth and coauthors fit this model to their data and to other known facts. They found $N = 65$, $K_{\text{tot}} = 1.1\,\text{pN}\,\text{nm}^{-1}$, $x_0 = -2.2\,\text{nm}$, and $f_0 = 25\,\text{pN}$. Graph the formula in (c), using these values. Use various trial values for z, starting from zero and moving upward. What value of z gives a curve resembling the data?
e. The authors also estimated that $k_a = 2 \cdot 10^{-4}\,\text{N}\,\text{m}^{-1}$. Use this value and your answer from (d) to find δ. Is this a reasonable value?