

Discussion/ Problem Set for Detailed vs. Heuristic II

Melcher et al. (1996a, b) examined the effects of focal brainstem lesions on the brainstem auditory evoked potential (BAEP) of cats. Melcher & Kiang (1996) then used the lesion results (combined with other anatomical and physiological data) to deduce which of the many cell populations in the auditory brainstem generate the BAEP. Their conclusions are summarized in Figure 1 below. This problem examines whether some of the conclusions illustrated in Figure 1 could have been reached without performing lesion experiments.

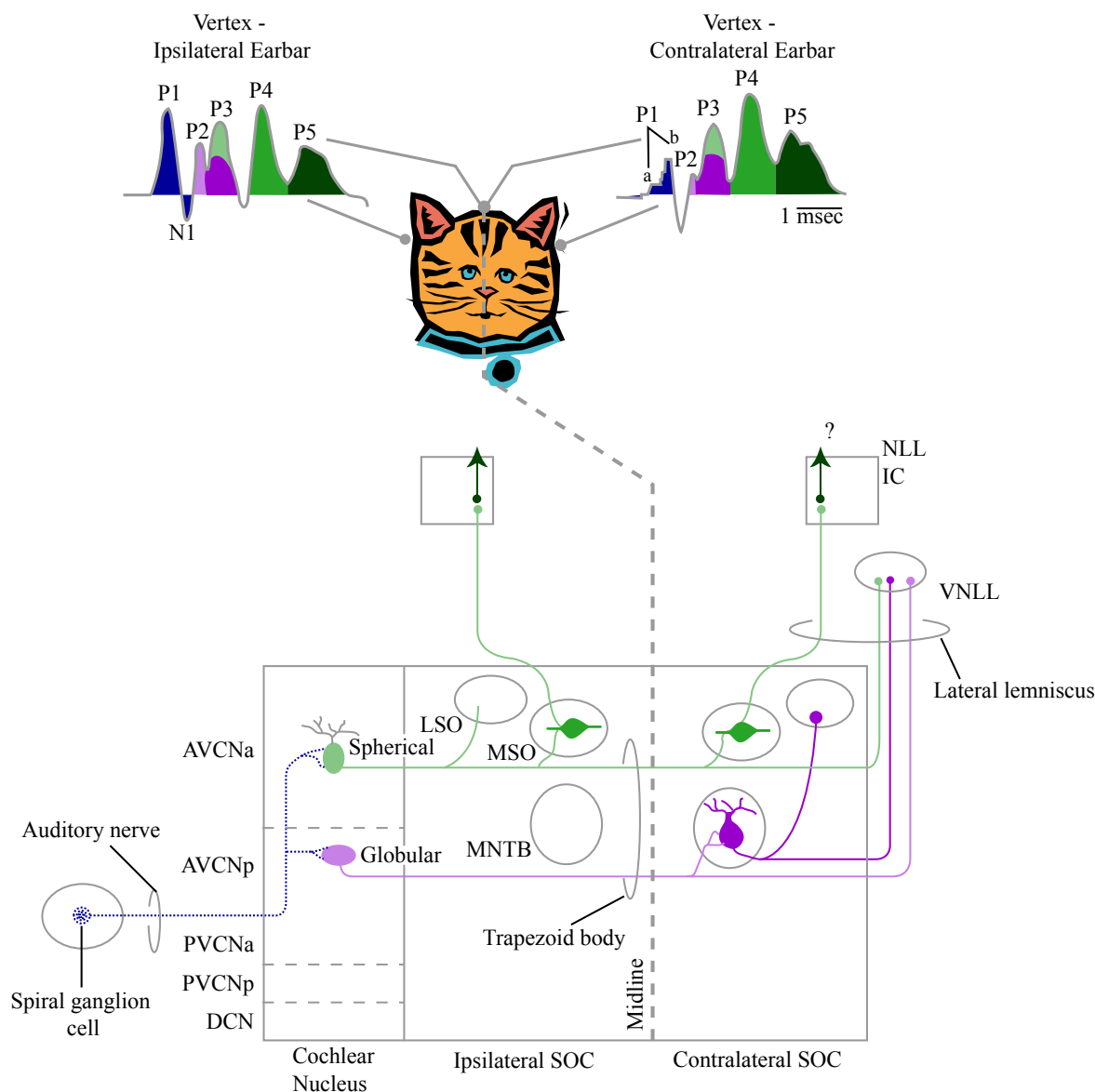


Figure 1: Cellular generators of the click-evoked BAEP in cats. Colors code for the relationships between cell populations and each part of the BAEP waveforms (at top). Code applies only to the labeled positivities (P1, P1a – P5) and negativity (N1). Except for the spiral ganglion cell contribution (blue shading), the BAEP is largely generated by pathways originating with the spherical cells in the AVCNa (three shades of green) and with the globular cells in the AVCNp and PVCNa (two shades of purple).

This problem is presented within a framework for BAEP generation that amounts to a simple adaptation of Goldstein & Kiang's model (1958). In this framework (Figure 2, see following page):

(1) The BAEP equals the sum of potentials produced by each cell population in the brainstem (e.g., spherical cells of the cochlear nucleus, MNTB principal cells.).

(2) The potential produced by each cell population, $V(t)$, is further decomposed into the sum of potentials produced by each cell in the population.

(3) The potential produced by the i th cell, $v_i(t)$, is written as the convolution of two quantities:

(i) the unitary potential produced at the BAEP recording electrodes when the cell discharges once ($u_i(t)$) and,

(ii) the instantaneous rate at which the cell discharges following the BAEP stimulus ($r_i(t)$, essentially the cell's PST histogram).

Part (4) in Figure 2 shows the dependence of $V(t)$ on N (number of cells in the population), $u_i(t)$ and $r_i(t)$.

The first part of this problem arrives at a possible relationship between the fiber diameter of brainstem cells and the amplitude of the unitary potential these cells produce at the BAEP recording electrodes. The second part asks you to use this relationship, along with published anatomical and physiological data for brainstem cells, to deduce "on the back of an envelope", which cell populations contribute most to the BAEP.

Part 1

Figure 3 shows: (top) a diagrammatic cell with many of the morphological features of an auditory brainstem cell, (middle) a cross-sectional view through the cell's myelinated axon, and (bottom) an electrical model for the two consecutive short segments along the axon.

Assume that the following standard scaling relationships apply when extending the electrical model for the axon from one cell to another (Rushton, 1951; Goldman and Albus, 1968):

- The ratio of axon diameter, d , to fiber diameter, D , is constant (~ 0.6 ; Rushton, 1951).
- R_a , the resistance per unit length to axial current flow within the axon, decreases with increasing axon cross-sectional area (i.e., $R_a \sim 1/d^2$).
- The myelin conductance and capacitance per unit length (G_m , C_m) are independent of fiber diameter. Specifically, G_m and $C_m \sim \ln(D/d)$ (the dependence on geometry for the conductance and capacitance between two concentric cylinders).
- Node length is independent of fiber diameter (McDonald and Ohlrich, 1971).
- Channel conductances per unit area and membrane capacitance per unit area of nodal membrane is fixed.
- Inter-nodal length is proportional to fiber diameter (Hursh, 1939).

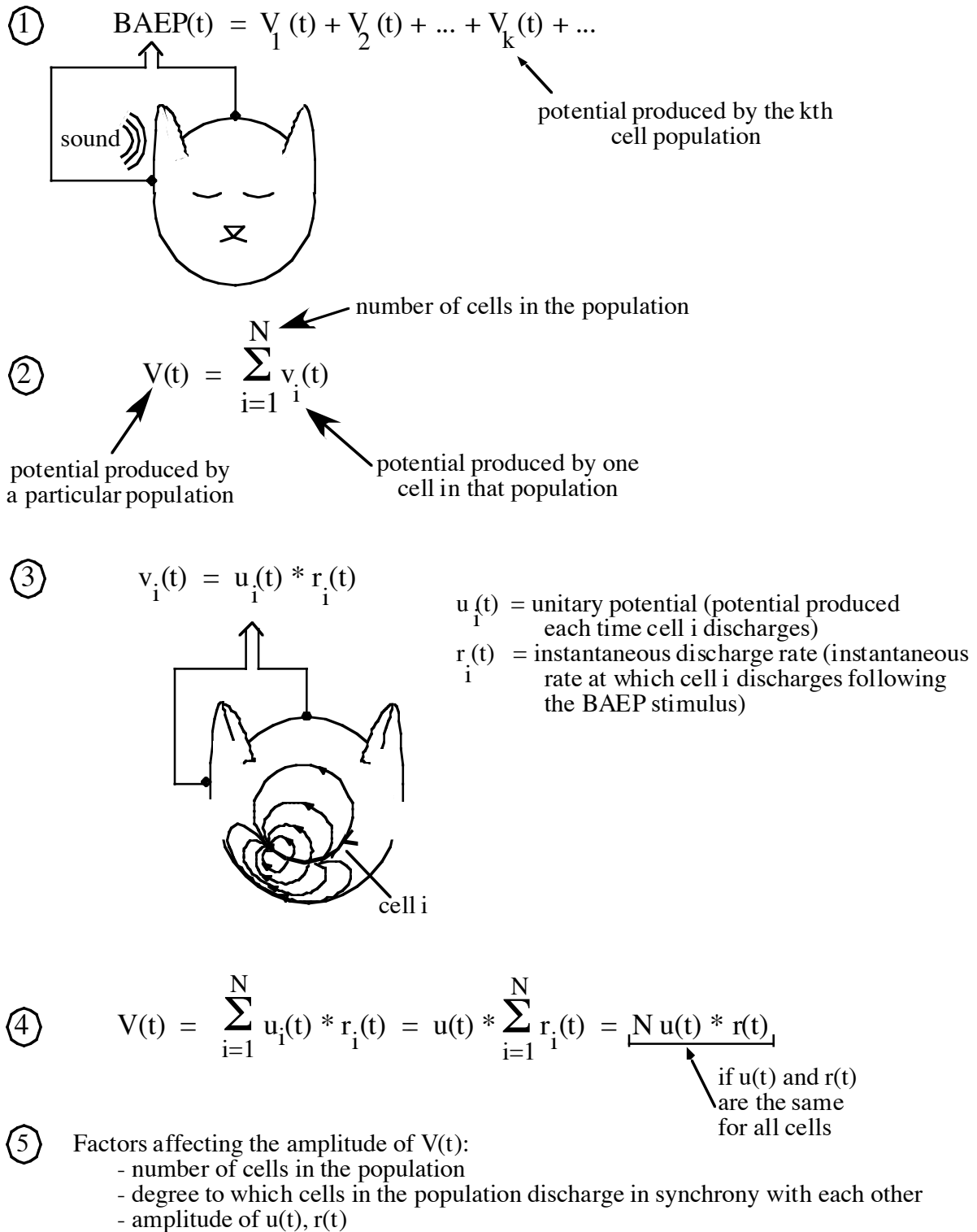


Figure 2: A general model for BAEP generation. (see Goldstein and Kiang, 1958; Wang, 1979; Melcher and Kiang, 1996)

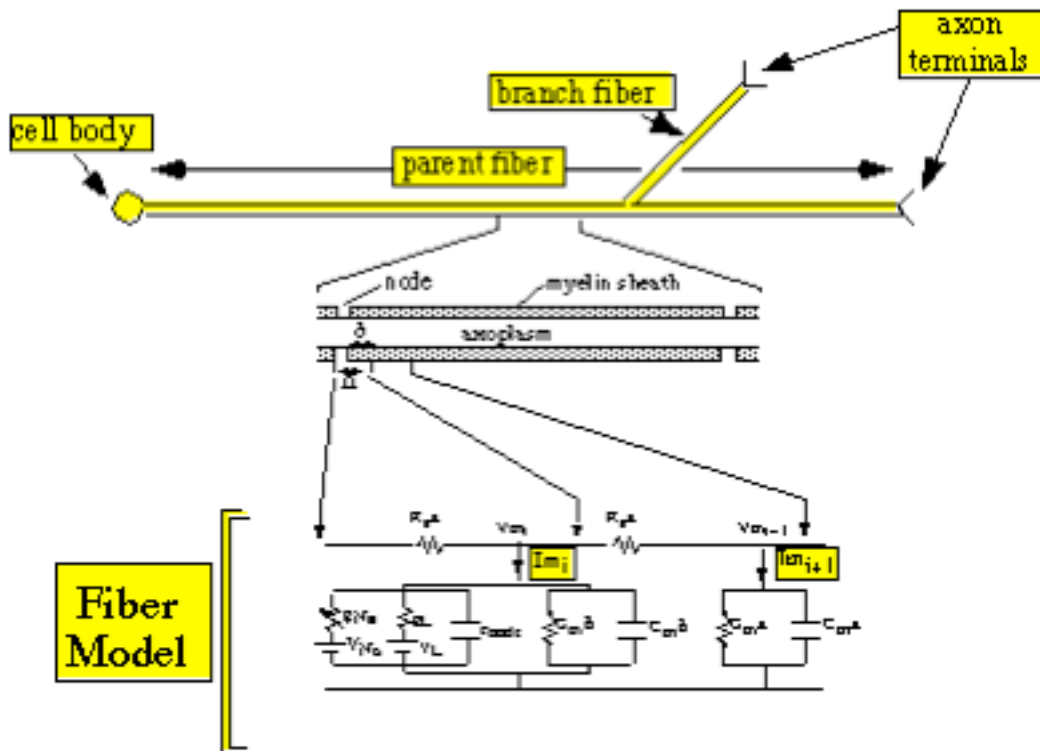


Figure 3: Diagrammatic cell and electrical model for its fiber. In the model (bottom), the fiber has been divided into segments of length Δ . V_m^i and I_m^i are the transmembrane potential and current, respectively, on the i th segment. Membrane of nodes is modeled using a voltage-dependent sodium conductance (g_{Na}), leak conductance (g_L), and capacitance (c_{node}). The remaining parameters are defined in the text. (from Melcher, 1995)

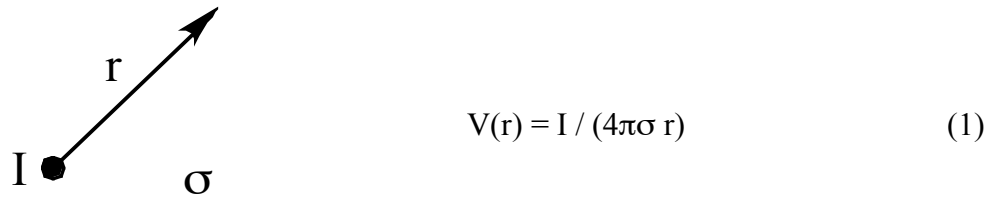
When the relationships above hold, the following are true for two discharging fibers with different diameters:

- The transmembrane potential *waveform* and *amplitude* are identical for corresponding nodes on the two fibers (e.g., the i th (counting from the cell body) on both fibers).
- The nodal current *waveform* is the same at corresponding nodes.

The time delay in the voltage or current waveform is the same from one node to the next. As a result, the well-known proportionality between conduction velocity and fiber diameter occurs because inter-nodal length (and hence the distance traveled by an action potential in a given unit of time) increases with increasing fiber diameter. [Note that the preceding statements strictly apply to a “free-running” action potential (i.e. one that is unaffected by the ends of the cell or any branches.)]

(a) Assume the density of current through nodal membrane (amp/m^2) is the same regardless of fiber diameter (Can you argue why this would be true?). How does the total nodal current depend on fiber diameter?

(b) Now consider the extracellular potential (i.e., unitary potential) produced by a cell like the one in Figure 3. Assume that the unitary potential can be written as a weighted sum of the transmembrane currents on consecutive short segments (length Δ) of the cell. Further assume that the cell lies in an electrical conductor of infinite extent (conductivity σ , units of length/resistance) and that transmembrane current on each segment can be modeled as a point source of current. Eq. (1) describes the potential, V , produced by one segment with current I . r is the distance from the current source. Use dimensional analysis to verify that eq. (1) is correct.



(c) Next, consider the extracellular potential produced by a complete cell (not just one segment). For simplicity, consider a cell with a straight, unbranched fiber. Assume all of the transmembrane current flows through nodes of Ranvier (i.e., the myelin of the internodes is perfectly insulating). The current sources produced by this cell at one instant in time are shown in Figure 4 (bottom). The I_n correspond to the transmembrane current on N consecutive nodes on the fiber (each dot on the z -axis indicates the location of a node). L is the inter-nodal distance. Use eq. (1) to write the potential at point 1 produced by all N current sources.

What is the potential when $z_1 \gg NL$?

Hint 1: $(1 + \delta)^{-1} \approx 1 - \delta$ when $\delta \ll 1$.

Hint 2: Remember that the total transmembrane current must be zero, so

$$\sum_{n=1}^N I_n = 0.$$

Given your answer in (a), what is the relationship between the potential at point 1 and fiber diameter when $z_1 \gg NL$?

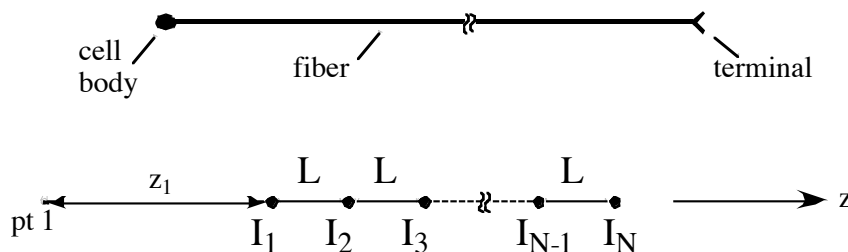


Figure 4

(d) How does your answer compare with the results from Melcher (1995) shown in Figure 5?

(e) Melcher (1995) argues that there is a strong relationship between the fiber diameter of brainstem cells and the amplitude of the unitary potential they produce. Based on your findings in (c), are you inclined to agree or disagree? Could your thoughts on this point be influenced by more detailed unitary potential calculations like those in Figure 5?

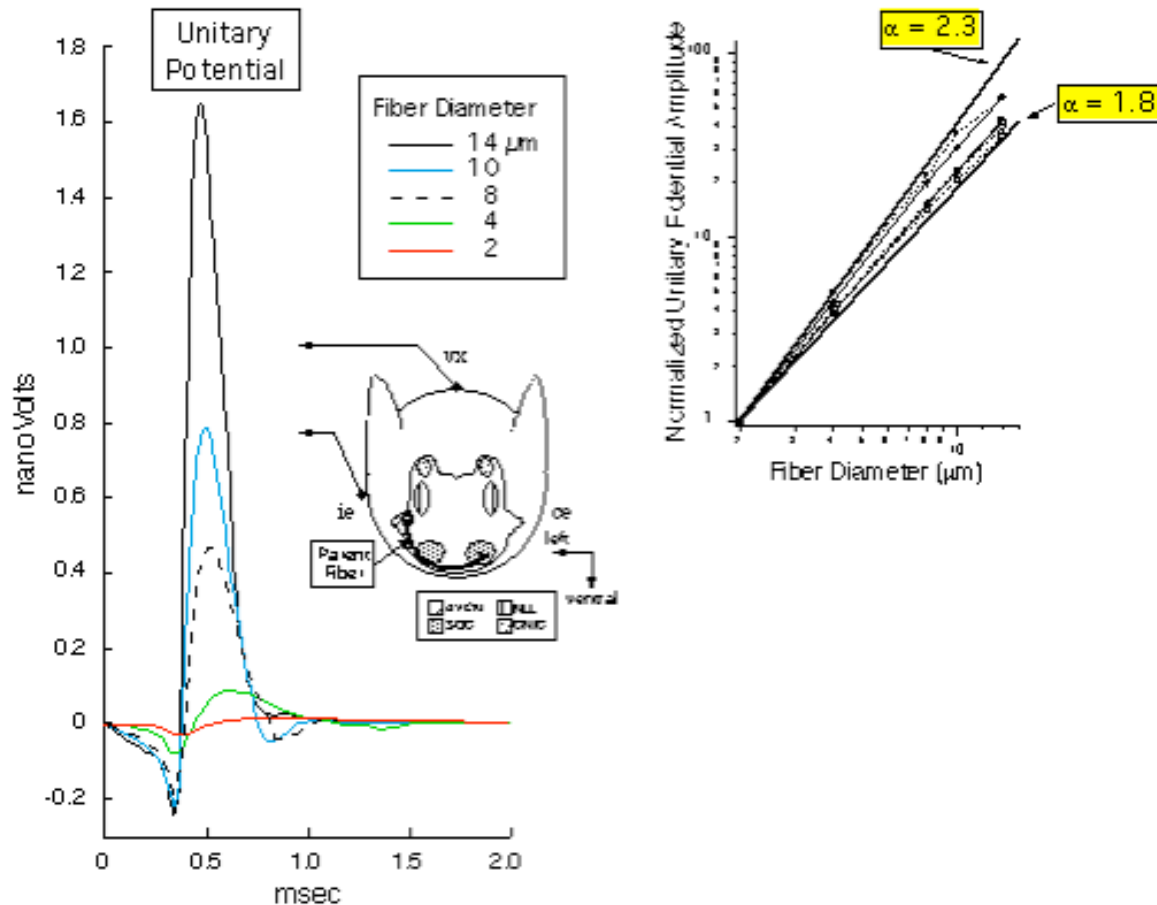


Figure 5: Dependence of unitary potential amplitude on fiber diameter. For reference, note that globular, spherical and multipolar cells of the anteroventral cochlear nucleus have fiber diameters of approximately 10, 4, and 2 μm. **Left:** Unitary potentials calculated using a compartmental model like the one shown at the bottom of Figure 3. The cell model was realistic in that it had a cell body (modeled as in Rothman et al., 1993) and terminals (modeled using a passive conductance and capacitance). Unitary potentials were calculated as a weighted sum of the transmembrane currents on consecutive short segments of the cell. The weighting was inversely proportional to the distance between the segment and the BAEP recording electrodes (vx, vertex; ie, ipsilateral ear). Realistic distances between the cell and BAEP recording electrodes were used. However, the model was unrealistic in that the medium outside the cell was a homogenous conductor of infinite extent (not a realistic model for the head). **Right:** Unitary potential amplitude (peak-to-peak) vs. fiber diameter. Amplitude was proportional to D^α , where α ranged from 1.8 to 2.3 depending on “recording” electrode location, axon terminal location, and axon terminal properties (represented by different symbols and line types).

Part 2

(a) Use the data in Table 1 to estimate the *magnitude* of each listed cell population's contribution to the BAEP. Express the magnitude as a fraction of the magnitude for the globular cell population.

(b) Use the latency data in Table 1 to estimate the BAEP peak (1 - 5) to which each cell population will contribute. [Note: In Figure 1, the BAEP waveforms begin at the time of the click presentation.]

(c) How do your estimates compare with the conclusions for P1 - 3 in Figure 1? If they agree, were the lesion experiments of Melcher et al. (1996a, b) necessary? If they disagree, what might be the source(s) of the discrepancies?

| Cell Population | Fiber Diameter (μm) | Number of Cells | Approx. Latency (ms) for Clicks at 30-50 dB re Threshold |
|-----------------------|----------------------------------|-----------------|--|
| Auditory Nerve | 2 | 50,000 | 0.6 - 1 |
| Spherical Cells | 4 | 28,000 | 2 - 2.5 |
| Globular Cells | 10 | 6,000 | 1.7 - 2.3 |
| AVCN Multipolar Cells | 2 | 35,000 | 2.5 - 3 |
| Octopus cells | < 10 | 1,500 | ~2 |

Table 1: Fiber diameter data are from Brownell, 1975, Liberman and Oliver, 1984. Cell numbers are from Osen, 1970, Melcher, 1993. Latency data are from Kiang et al., 1965, Bourk, 1976. The latencies are for cells with a characteristic frequency > 2 kHz. Latencies for lower CF cells are greater.

References

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