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Using 3D Modeling to Describe the Electromotility of the Outer Hair Cell Protein Prestin, and its Role in Sound Perception Among Mammals

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PDB File: Now using an original PDB file that merges 7S9E (inhibited) with 7S8X (compact; uninhibited) (Two confirmations of the prestin protein exported from PyMOL to Jmol).

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Description: Prestin has been identified as a key motor protein that enables auditory perception in mammals. Located in the plasma membrane of the cochlea's outer hair cells (OHCs), prestin carries out pivotal functions as an anion transporter and voltage sensor. Through a complex process known as electromotility, prestin undergoes voltage-dependent longitudinal contractions and elongations which modulate the shape of OHCs in response to electrical stimulation. Much has yet to be uncovered, however, about the exact biochemical mechanisms by which this transduction operates. Further, it has yet to be described how specific convergent changes in the amino acid residues of prestin endow echolocating mammals with this unique and keen auditory ability. There are currently six distinct models available in the Protein Data Bank which highlight the conformational changes of prestin in the common bottlenose dolphin (*Tursiops truncatus*) based on its binding to a variety of ion ligands. Among them is salicylate, which is known to compete for the protein's anion binding site and induce reversible hearing loss. By using 3D modeling techniques to generate a unique representation of prestin, it is our goal to tell a compelling molecular story regarding the processes which underly these conformational changes. Thus, we aim to contribute to the scientific understanding of prestin's electromotive functions in the OHC membrane.

Model Details:

- Prestin is a homodimer whose two peptide chains each contain 14 transmembrane (TM) α helices.
- PyMOL was used to combine one dimer chain from each of two PDB models: Chain A of 79SE (inhibited with salicylate) and Chain B of 7S8X (compact "sensor up"). This merged model, nicknamed "Frankenstein", was then saved as a new PDB file.
    - A Jmol script was developed and tested on this nascent model, which worked successfully.
- Domains among the two dimers are color-coded, with each domain being colored a lighter shade of the same color on Chain A and a darker shade on Chain B.
- The N and C termini (at Thr13 and Gln722) are marked in blue and red respectively.
- STAS Domain inside the cell: Colored lavenderblush (lighter) on Chain A and lavender (darker) on Chain B
- Core Domain in the cell membrane: Colored lightsalmon (lighter) on Chain A and salmon (darker) on Chain B
- Gate Domain in the cell membrane: Colored azure (lighter) on Chain A and lightblue (darker) on Chain B

- The inhibitor, salicylate (SAL) is shown in spacefill using light cpk colors and held in place at the anion binding site, colored darkviolet.
    - A removable element involving the helices that surround SAL, secured with magnets, will increase visibility of the active site.
- Two key residues that bind to the SAL are shown in spacefill with cpk colors. These are Ser398, which forms hydrogen bonds, and Phe137, which participates in pi stacking.
- Arg399 (located in TM10) is shown in spacefill and light cpk colors. It is known to rotate while prestin oscillates between confirmations.
- 13 convergent amino acid replacements have been identified on the model (colored in gold) that are shared by mammals that can echolocate and are not found in organisms that cannot echolocate (Liu et al, 2010).

Anion binding site	Gln97, Phe101, Phe137, Leu397, Ser398, Arg399 (rotates up and down)
STAS domain	Thr13–Phe76, Gln504–Glu581, Lys615–Gln722
Core domain	Lys77–Arg197, Ser386–Pro436
Gate domain	Phe198–Gly385, Gln437–Gln504
Amino acid replacements in echolocators	Glu40, Ser167, Thr186, Ser308, Thr384, Ala392, Val532, Leu568, Ala601, Thr621, Ser685, Gln689, Asp700

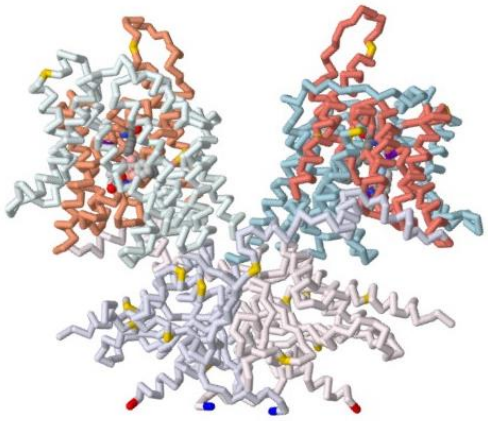

Figure 1. Merged prestin homodimer with Chain A inhibited with SAL on the left and Chain B (compact) on the right

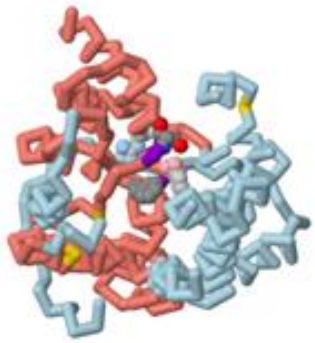

Figure 2. Close up of SAL bound to prestin active site with Phe137, Ser398, and the rotating Arg399 shown in spacefill

Additional References:

Liu, Y., Cotton, J.A., Shen, B., Han, X., Rossiter, S.J., & Zhang, S. (2010). Convergent sequence evolution between echolocating bats and dolphins. *Current Biology, 20*(2), R53–R54. https://doi.org/10.1016/j.cub.2009.11.058