A molecular level prototype for mechanoelectrical transducer in mammalian hair cells

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Mechanoelectrical Transducer

The auditory system is one of the most significant sensory systems for mammals and the sense of hearing is significant to communicate with each other and perceive the surrounding environment. The mechanoelectrical transducer (MET) is a crucial component of mammalian auditory system. It is widely believed that the deflection of hair bundles opens MET channels, located at the bottom of the tip links, to generate electrical signals. The MET channel is a nonselective cation channel with a considerably high permeability of Ca^{2+}. The gating mechanism of the MET channel remains a puzzling issue due to the lack of essential molecular building blocks.

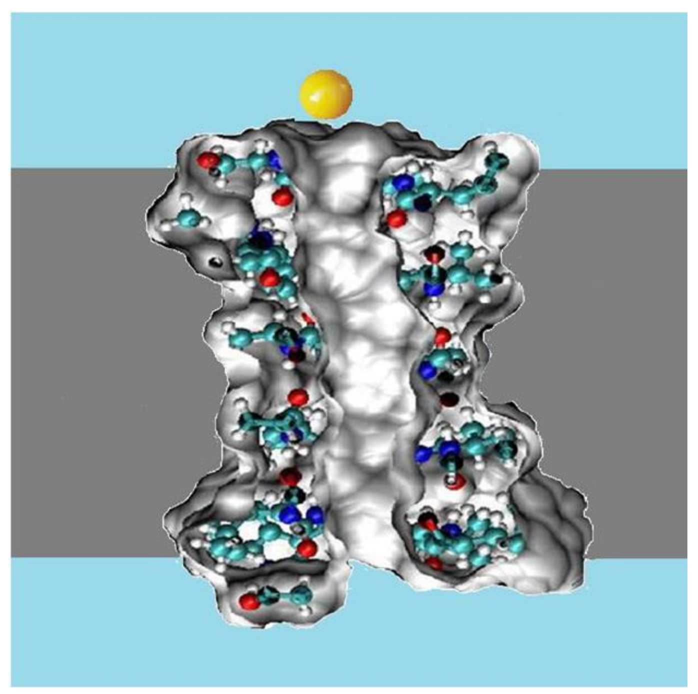


Figure 1: Our molecular level MET prototype consisting of a charged blocker, a realistic ion channel and surrounding membranes

In this work, we propose a molecular level prototype for MET in mammalian hair cells. We employ the Poisson-Nernst-Planck theory for three dimensional numerical simulations in order to validate our proposed prototype. Moreover, we compare our computational results with experimental data.

Coupled Governing Equations

Poisson Equation

$$-\nabla\cdot\left(\varepsilon(\mathbf{r})\nabla\Phi(\mathbf{r})\right) = 4\pi\left(\sum_{k=1}^{N_P} Q_k\delta(\mathbf{r}-\mathbf{r}_k) + \sum_{\beta=1}^{N_m} q_\beta C_\beta(\mathbf{r})\right) \quad (1)$$

Nernst-Planck Equation

$$\frac{\partial C_\beta}{\partial t} = -\nabla\cdot\mathbf{J}_\beta \qquad \mathbf{J}_\beta = -D_\beta(\mathbf{r})\left[\nabla C_\beta(\mathbf{r}) + \frac{q_\beta}{k_B T}C_\beta(\mathbf{r})\nabla\Phi(\mathbf{r})\right]$$

$$\nabla\cdot D_\beta(\mathbf{r})\left[\nabla C_\beta(\mathbf{r}) + \frac{q_\beta}{k_B T}C_\beta(\mathbf{r})\nabla\Phi(\mathbf{r})\right] = 0 \quad (2)$$

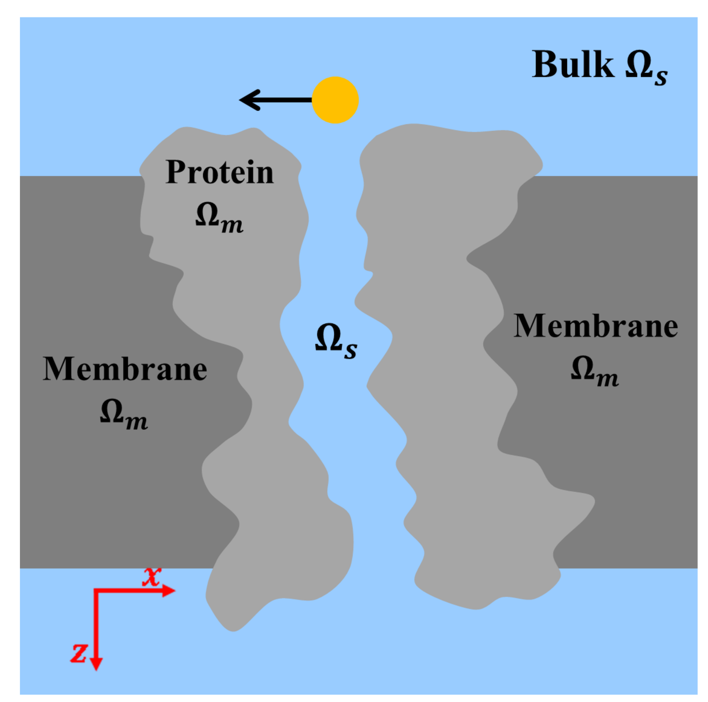
- **$\Phi(\mathbf{r})$:** Electrostatic potential
- **$C_\beta(\mathbf{r})$** and **q_β**: Concentration and charge of βth ion species
- **$\sum_{k=1}^{N_P} Q_k\delta(\mathbf{r}-\mathbf{r}_k)$:** Fixed charges in protein

We solve the Poisson equation (1) and the steady-state form of the Nernst-Planck equation (2) in a self-consistent manner with appropriate initial/boundary conditions.

Computational Algorithms

- **Dirichlet to Neumann Mapping** is a computational technique using Green's function $\Phi^*(\mathbf{r})$ to remove charge singularities in the Poisson equation, which result in the Poisson equation of the regular part $\tilde{\Phi}(\mathbf{r})$.
- **Matched Interface and Boundary (MIB)** is a numerical scheme to solve elliptic equations with discontinuous coefficients and irregular complex geometries by employing fictitious values and auxiliary points.
- **Successive over relaxation (SOR)-like iterative procedure** is a self-consistent manner to solve the coupled PNP equations simultaneously.

Computational Domain



$$\Omega = \Omega_m \cup \Omega_s$$

- **Ω_m**: Biomolecule region
- **Ω_s**: Solvent region

We allow the blocker to move along one direction just outside the channel mouth to express the blocker's gating behavior.

Conclusion

We design an extensive numerical experiment to analyze in detail the electrostatic potential and channel current in response to variations of blocker charge, blocker relative displacement, bulk ion concentration and applied external voltage. We demonstrate an excellent consistency between our model prediction of channel open probability and relative displacement and experimental measurement from rat outer hair cells. Our findings indicate that hair-cell tip links efficiently convey mechanical force to mechanosensitive transduction channels and manage their opening and closing.

Reference

Jinkyoung Park and Guo-Wei Wei, "A molecular level prototype for mechano-electrical transducer in mammalian hair cells", *Journal of Computational Neuroscience*, 35, 231-241, (2013)

Acknowledgement

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Simulation Results

Numerical simulations are carried our for a molecular level prototype for the MET channel.

Effect of the charged blocker

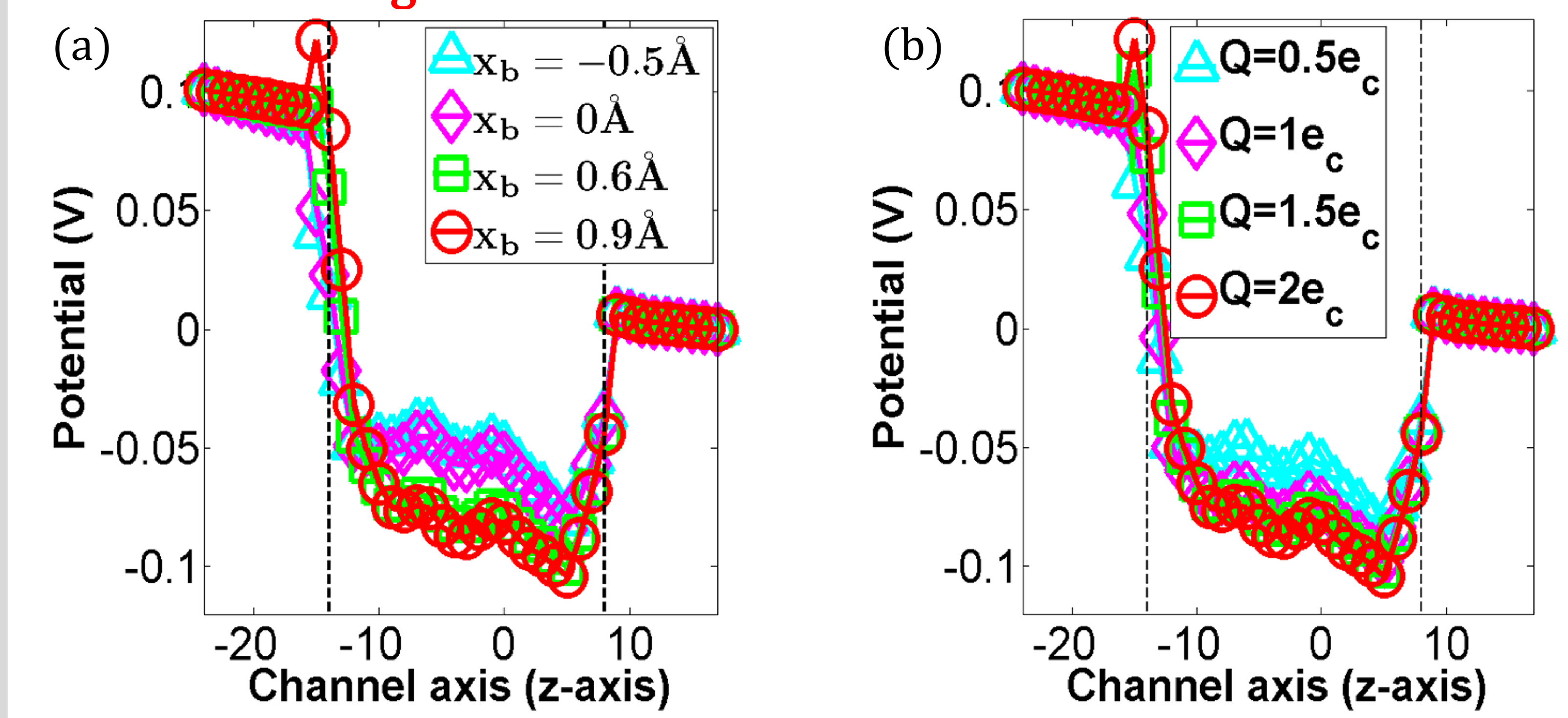

Figure 2: Electrostatic potential profiles (a) at different locations of the blocker and (b) at different charges of the blocker.

The proposed MET prototype shows a desirable gating effect only when the blocker carry sufficient charge and it is located at its optimized position.

Open probability versus blocker relative displacement

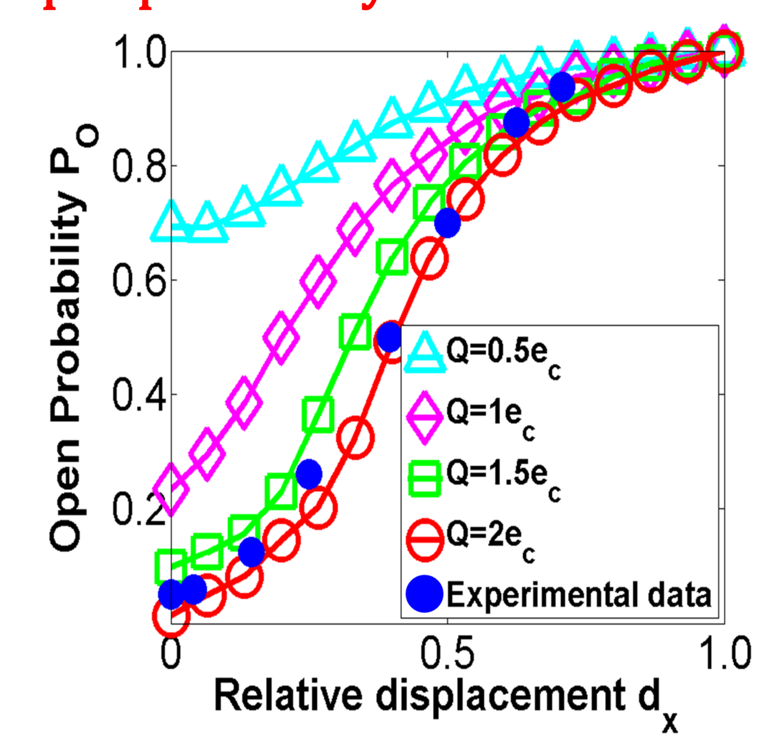

Figure 3: Comparison of our model prediction with experimental finding (Kennedy et al, 2005).

At each blocker charge, the graph forms a sigmodal shape and, especially, the charge $Q = 2e_c$ gives a remarkable agreement with the experimental data.

Robustness

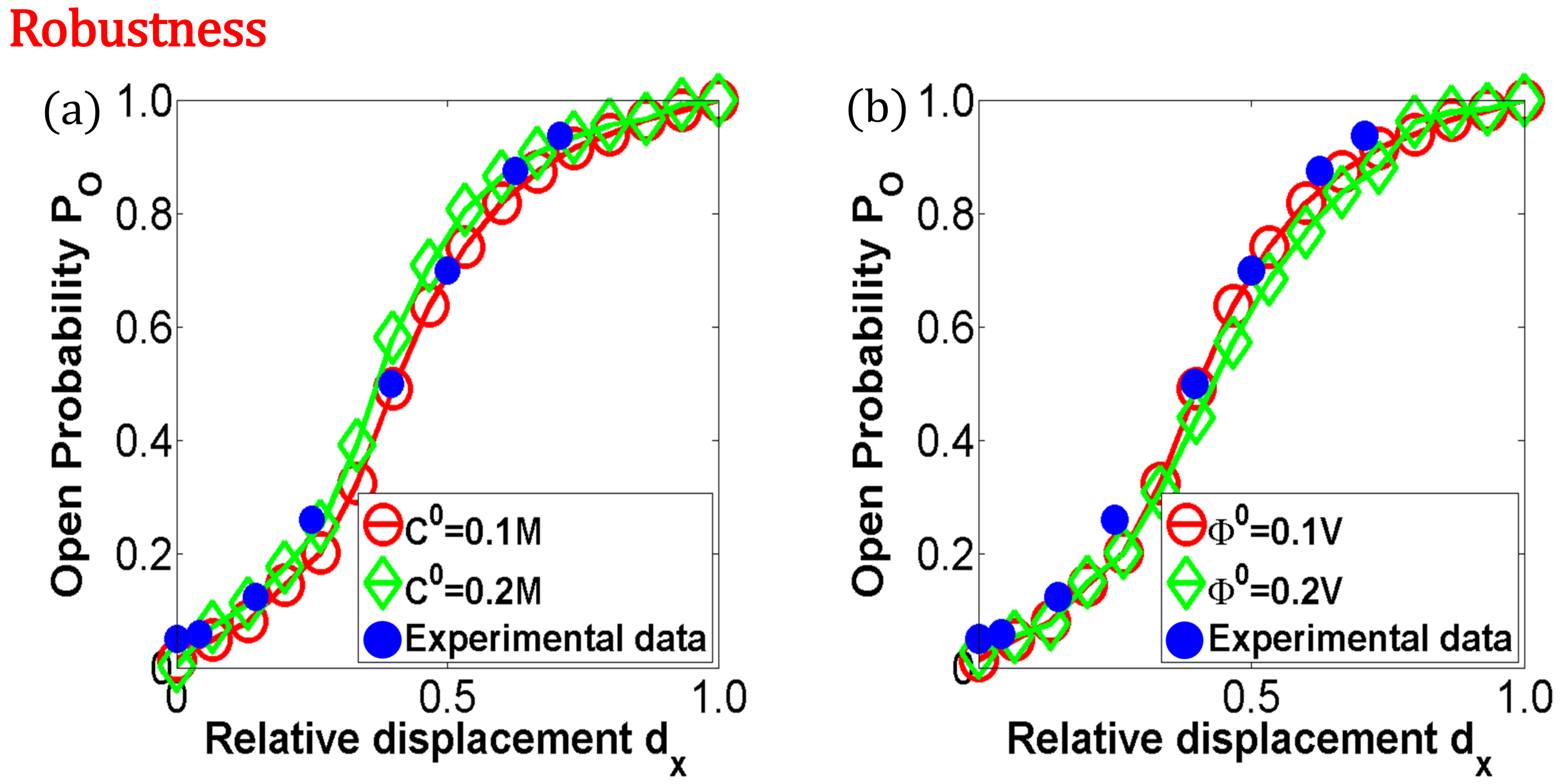

Figure 4: Sensitivity to the change of (a) bulk ion concentration and (b) applied external voltage.

There is still an excellent remarkable consistency although bulk ion concentration or applied voltage is doubled.