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A Novel Approach to Simulating the Gating Transitions of Mechanosensitive Channels

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Membranes have long been known to serve multiple critical roles for cells, including acting as barriers and also as gatekeepers, controlling the flow of materials and information between the cell and the exterior environment. More recently, it has been realized that membranes also act as sensors, responding to mechanical stimuli through modulation of the behavior of a growing number of identified membrane-embedded proteins in all domains of life. Chief among these proteins are so-called mechanosensitive (MS) ion channels, some of which can open under a change in membrane tension. The existence of MS channels was first recognized in auditory hair cells (1) and in embryonic chick skeletal muscle (2). They were later discovered in bacteria as well (3), where they allow these organisms to avoid bursting under the sudden increases in turgor pressure that might occur during, e.g., rainfall by rapidly (within milliseconds) releasing osmolytes from the cell (4).

The first few structures of MS channels were determined in the late 1990s and early 2000s, namely the mechanosensitive channel of large conductance (MscL) and small conductance (MscS) (Fig. 1). Molecular dynamics (MD) simulations were soon after carried out by a number of groups in an attempt to understand how the channels are affected by application of tension, looking particularly for the gating transitions between closed and open states (5–8). The most common computational approach to induce a transition to the open state has been the direct application of external forces to the protein (6,9) or of tension to the membrane (5,10). However, because the simulation timescale (ns) was typically less than the timescale of gating (μs–ms), large forces or tensions were required, making the resulting conformational changes of the proteins open to interpretation.

In this issue of *Biophysical Journal*, Vanegas and colleagues report on a novel approach to generating realistic gating transitions of MS channels in MD simulations, overcoming the limitations normally inherent to the disparate timescales (11). Called locally distributed tension MD (LDT-MD), the approach applies forces to the lipids surrounding the protein; these forces rapidly decay with increasing radial distance from the center of the protein. By applying forces primarily to lipids near the protein, the authors circumvent the inefficiency of force transmission through the softer membrane to the stiffer protein while still capturing the interactions between the two that facilitate gating. They apply LDT-MD to MscL, and within just a few nanoseconds, they are able to generate reversible opening of the pore. In contrast, applying tension to the entire membrane either did not open the pore, ruptured the membrane, or both. Structural properties of the LDT-MD-generated open state of MscL were found to agree with experiments. Taking the method further, the authors combine LDT-MD with metadynamics, determining the free energy as a function of the change in area at different effective membrane tensions; yet again, the open state of MscL matches experimental expectations. In a final example, they demonstrate that LDT-MD can also be used to generate asymmetric forces in the two leaflets, mimicking, e.g., the addition of lysolipids to one leaflet. Comparison with distances measured in FRET experiments reveals a counterintuitive result, namely that adding lysolipids to one side of the membrane causes expansion rather than compression on that side.

The ability to capture the effects of mechanical stimuli on membranes and membrane proteins in MD simulations is needed as much now as it was 15–20 years ago. In addition to the bacterial MS ion channels, eukaryotic MS channels are now being characterized and simulated, e.g., vertebrate Piezo channels (Fig. 1; (12,13)), plant OSCA channels (14), and others (15). The mechanical properties of other

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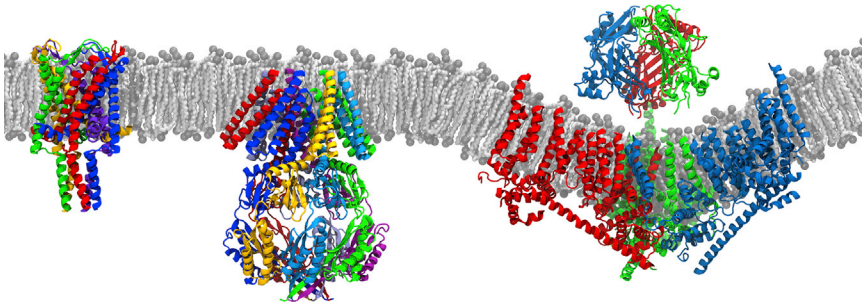

FIGURE 1 Structures of example MS channels against a lipid membrane background (*gray spheres* for head groups and *white sticks* for aliphatic tails). (*Left*) The pentameric bacterial MscL (Protein Data Bank, PDB: 2OAR) is shown. (*Middle*) The heptameric bacterial MscS (PDB: 2OAU) is shown. (*Right*) The trimeric eukaryotic Piezo1 (PDB: 6BPZ). To see this figure in color, go online.

membranes are also of significant interest, such as the Gram-negative bacterial outer membrane (16–18). Simulations of all of these systems will benefit from novel approaches such as LDT-MD.

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REFERENCES

1. Corey, D. P., and A. J. Hudspeth. 1979. Ionic basis of the receptor potential in a vertebrate hair cell. *Nature.* 281:675–677.
2. Guharay, F., and F. Sachs. 1984. Stretch-activated single ion channel currents in tissue-cultured embryonic chick skeletal muscle. *J. Physiol.* 352:685–701.
3. Martinac, B., M. Buechner, …, C. Kung. 1987. Pressure-sensitive ion channel in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA.* 84:2297–2301.
4. Kung, C. 2005. A possible unifying principle for mechanosensation. *Nature.* 436:647–654.
5. Colombo, G., S. J. Marrink, and A. E. Mark. 2003. Simulation of MscL gating in a bilayer under stress. *Biophys. J.* 84:2331–2337.
6. Gullingsrud, J., and K. Schulten. 2003. Gating of MscL studied by steered molecular dynamics. *Biophys. J.* 85:2087–2099.
7. Sotomayor, M., and K. Schulten. 2004. Molecular dynamics study of gating in the mechanosensitive channel of small conductance MscS. *Biophys. J.* 87:3050–3065.
8. Anishkin, A., and S. Sukharev. 2004. Water dynamics and dewetting transitions in the small mechanosensitive channel MscS. *Biophys. J.* 86:2883–2895.
9. Jeon, J., and G. A. Voth. 2008. Gating of the mechanosensitive channel protein MscL: the interplay of membrane and protein. *Biophys. J.* 94:3497–3511.
10. Yefimov, S., E. van der Giessen, …, S. J. Marrink. 2008. Mechanosensitive membrane channels in action. *Biophys. J.* 94:2994–3002.
11. Rajeshwar, T. R., A. Anishkin, …, J. M. Vanegas. 2021. Mechanical activation of MscL revealed by a locally distributed tension molecular dynamics approach. *Biophys. J.* 120:■■■–■■■.
12. Coste, B., J. Mathur, …, A. Patapoutian. 2010. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science.* 330:55–60.
13. Botello-Smith, W. M., W. Jiang, …, Y. Luo. 2019. A mechanism for the activation of the mechanosensitive Piezo1 channel by the small molecule Yoda1. *Nat. Commun.* 10:4503.
14. Zhang, M., D. Wang, …, L. Chen. 2018. Structure of the mechanosensitive OSCA channels. *Nat. Struct. Mol. Biol.* 25:850–858.
15. Kefauver, J. M., A. B. Ward, and A. Patapoutian. 2020. Discoveries in structure and physiology of mechanically activated ion channels. *Nature.* 587:567–576.
16. Hwang, H., N. Paracini, …, J. C. Gumbart. 2018. Distribution of mechanical stress in the *Escherichia coli* cell envelope. *Biochim. Biophys. Acta Biomembr.* 1860:2566–2575.
17. Rojas, E. R., G. Billings, …, K. C. Huang. 2018. The outer membrane is an essential load-bearing element in Gram-negative bacteria. *Nature.* 559:617–621.
18. Lessen, H. J., P. J. Fleming, …, A. J. Sodt. 2018. Building blocks of the outer membrane: calculating a general elastic energy model for β-barrel membrane proteins. *J. Chem. Theory Comput.* 14:4487–4497.