# Protein Shape Change Has a Major Effect on the Gating Energy of a Mechanosensitive Channel

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# SUPPLEMENTARY MATERIAL: Protein shape change has a major effect on the gating energy of a mechanosensitive channel

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# Midplane bending and hydrophobic mismatch

In the main text we have omitted the changes related to the midplane bending energy $\Delta E_{\mathrm{mp}}$ and the hydrophobic mismatch energy $\Delta E_{\mathrm{mm}}$. In this section we make order of magnitude estimates of these energetic changes in the gating of MscL.

First, to determine the midplane bending energy, we calculate the center of mass positions of lipid molecules as a function of distance from the protein boundary. What is relevant here is the component of the center of mass along the bilayer normal direction. For an order of magnitude estimate, we use the equation derived by Wiggins and Phillips (1), $\Delta E_{\mathrm{mp}} = \pi\kappa H'^2 \tilde{G}_H$, where $\kappa$ is the bilayer bending modulus, $H'$ is the derivative of the midplane at the protein boundary, and $\tilde{G}_H$ is a tension dependent number whose values vary between 0 and 4 for realistic tensions. The largest values of $H'^2 \approx 0.1$ as calculated from simulations are achieved for the closed state at tensions 0 and 10 mN/m. Using the values $\kappa \approx 20$ mN/m and $\tilde{G}_H \approx 1$ (corresponding to a tension of 10 mN/m) we find $\Delta E_{\mathrm{mp}} \approx 0.6 k_{\mathrm{B}}T$ for the maximum midplane bending energy observed. Thus, we conclude that the $\Delta E_{\mathrm{mp}}$ term can be neglected from Eq. 4 in the main text.

Since the gating tension of MscL has been shown to depend on lipid tail length (2), the tension-induced thinning of lipid bilayer might play a role in MscL gating. This is described in Eq. 4 in the main text by the $\Delta E_{\mathrm{mm}}$ term. Several models have been introduced to analyze the magnitude of the hydrophopic mismatch energy (1, 3–5). Most of the models calculate the deformation energy of a bilayer assuming that the contact between water and hydrophobic regions is fully covered, and in this spirit predict a quadratic dependence of energy on thickness mismatch. The actual numbers differ somewhat depending on the approximations used in the different models. In this work we consider the order of magnitude most important, thus we have chosen to use the equation discussed by Marsh (5),

$$E_{mm} = N_{\mathrm{L}} \times ((6.1 \pm 0.4)\mathrm{nm}^{-1}) k_{\mathrm{B}}T \frac{(l_{\mathrm{L}} - l_{\mathrm{o}})^2}{l_{\mathrm{o}}}. \qquad \text{(S1)}$$

Here $N_{\mathrm{L}} = 29$ is the approximate number of lipid molecules in the first shell surrounding the protein, $l_{\mathrm{L}}$ is the height of the monolayer next to the protein, and $l_{\mathrm{o}}$ is the height of the unperturbed monolayer. While the bending elasticity term is not fully taken into account in this equation, it would make the energy only slightly larger and would not affect the order of magnitude estimate (5). Also, the mismatch energy seems to follow linear dependence

on thickness mismatch instead of the quadratic dependence predicted by elastic models (5). Yet, this equation has been shown to correctly describe the MscL partitioning coefficient on lipid tail length close to the optimal one (16 carbons) (5), and it seems to explain the dependence of gating tension on bilayer thickness as observed by Perozo et al. (2, 5). In our case, the changes in bilayer thickness are rather small (see below) and we are close to the optimal bilayer thickness. Consequently, we have chosen this equation for our order of magnitude estimation.

To analyze the hydrophobic mismatch, we calculated the thickness of the lipid bilayer as a function of distance from the protein boundary. The deformation is shown in Fig. S1. Table S1 highlights the bulk bilayer thicknesses under different tensions, the thickness difference compared to zero tension, and the energy related to this difference. As there is no hydrophobic mismatch at zero tension, we assume that the hydrophobic thickness of the initial closed state is the same as in a bilayer at zero tension, i.e. 4.44 nm. Thus, the energies in Table S1 correspond to mismatch energies when the initial closed state is embedded in a membrane which has become thinner due to induced tension. These energies correspond to the mismatch energy change in step 1. Importantly, all energies in Table S1 are negligible compared to the energies calculated from pressure profiles; see discussion in the previous sections.

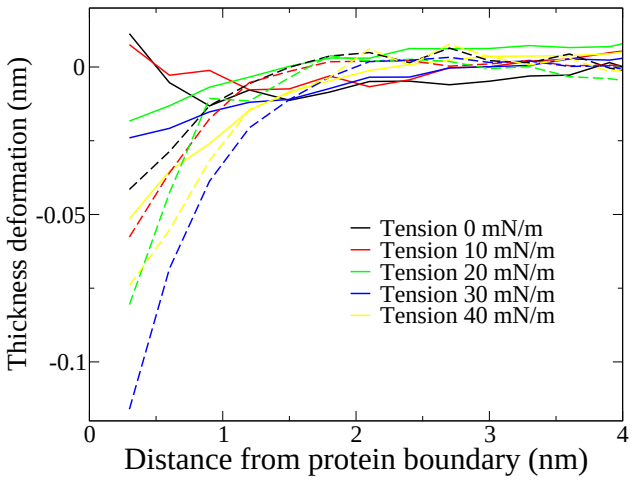


Figure S1: Bulk bilayer thickness under different tensions, and estimates for mismatch energy change. Thickness is here defined as the distance between the coarce-grained beads that represent phosphorous in the lipid headgroup.

Table S1: Bulk bilayer thickness under different tensions, and estimates for mismatch energy change. Thickness is here defined as the distance between the coarce-grained beads that represent phosphorous in the lipid headgroup.

| tension (mN/m) | thickness (nm) | $l_{\mathrm{L}} - l_{\mathrm{o}}$ (nm) | $\Delta E^{1}_{mm} k_{\mathrm{b}} T$ |
|---|---|---|---|
| 0 | 4.44 | 0 | 0 |
| 10 | 4.34 | 0.05 | 0.2 |
| 20 | 4.24 | 0.1 | 0.8 |
| 30 | 4.12 | 0.15 | 1.8 |
| 40 | 3.95 | 0.25 | 5.0 |

The difference in mismatch energy between the closed* and open states corresponds to the mismatch energy difference in step 2. Figure S1 depicts that the open state at 30 mN/m has the largest thickness mismatch, corresponding to a thickness deformation of $(l_{\mathrm{L}} - l_{\mathrm{o}}) \approx 0.05$ nm for a monolayer. Using Eq. S1 with these values we get $E_{mm} \approx 0.2 k_{\mathrm{B}} T$, which is also negligible. Values for the thickness mismatch are in agreement with earlier atomistic molecular dynamics simulations (6–8).

In this section, we have shown that the tension induced gating of MscL in symmetric one-component bilayers is not significantly affected by midplane bending or thickness changes. Whether this conclusion holds more generally remains an open issue. For example, variations in lipid composition can change membrane thickness more than tension, and do affect the gating tension (2). Asymmetric distribution of lipids across a membrane can also play a role in the midplane bending term. These cases remain to be explored elsewhere.

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