Integrating MD simulations with PELDOR/DEER spectroscopy and cryoEM reveals the dynamics and energetics underlying mechanosensation

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Introduction

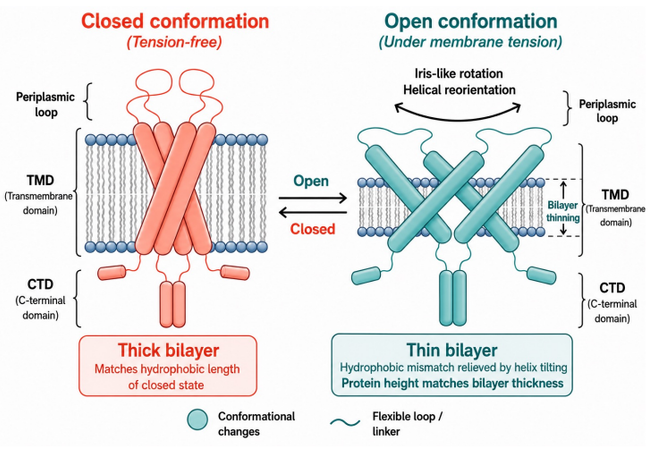

Figure 1: Proposed model of EcMscL opening. Membrane tension drives TM-helix tilting, bilayer thinning, and hydrophobic mismatch relief, stabilising the expanded state.

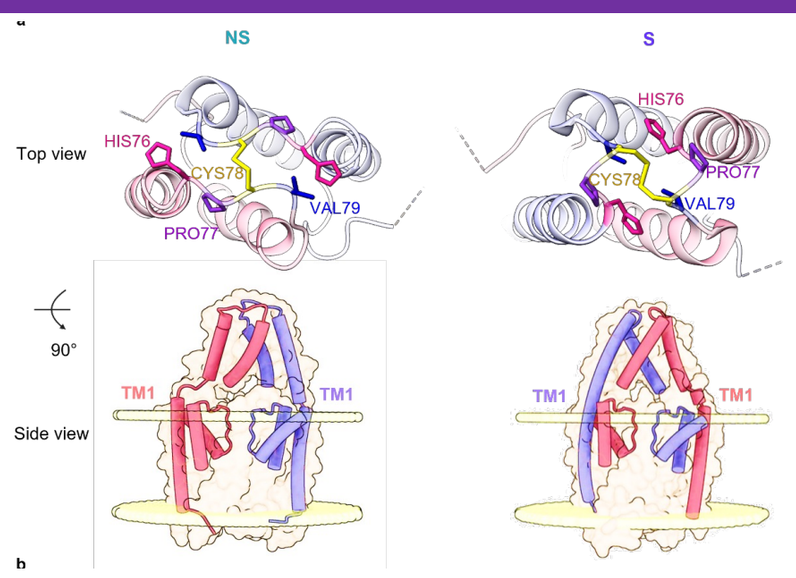

Figure 2: Top and side views of the non-swapped (NS) and swapped (S) conformations of TRAAK. The NS→S transition involves ~180° rotation of TM1 and exchange of cap domains between adjacent monomers.

Motivation and Objectives

- Mechanosensitive ion channels convert membrane mechanical forces into biological responses.
- MscL protects bacteria from osmotic lysis while TRAAK regulates neuronal excitability.
- CryoEM resolves individual conformational states, whereas PELDOR/DEER reveals conformational ensembles
- Molecular dynamics (MD) simulations provide atomic-level insight into the dynamics, energetics
- We integrate MD simulations with cryoEM and PELDOR/DEER spectroscopy to uncover the molecular mechanisms of mechanosensation

Structural Basis and Mechanism of EcMscL Gating

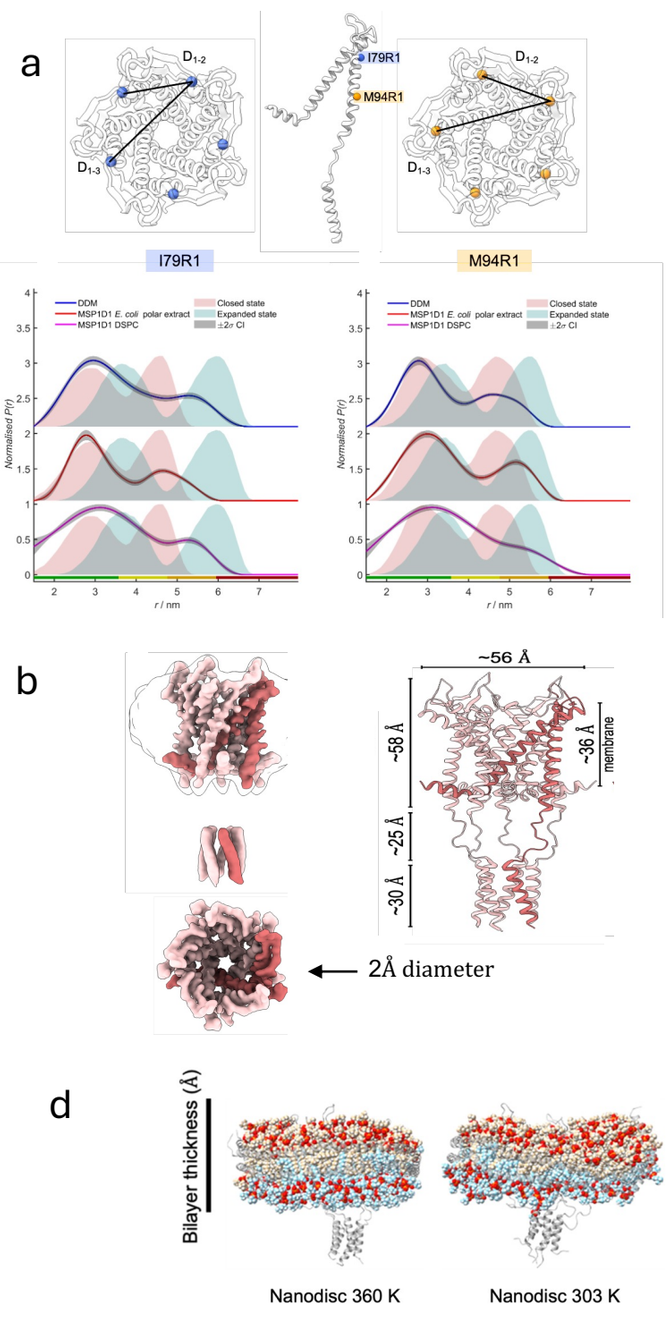

Figure 3: PELDOR reveals expanded EcMscL conformations in DSPC nanodiscs (a). CryoEM resolves corresponding closed (DMPC, salmon) and expanded (DSPC, teal) structures (b). MD simulations show reduced nano-pocket lipid occupancy in the expanded state (c). Nanodiscs promote channel expansion through bilayer thinning and increased acyl-chain interdigitation (d).

Conformational Dynamics and Energetics of Cap-Domain Switching in TRAAK

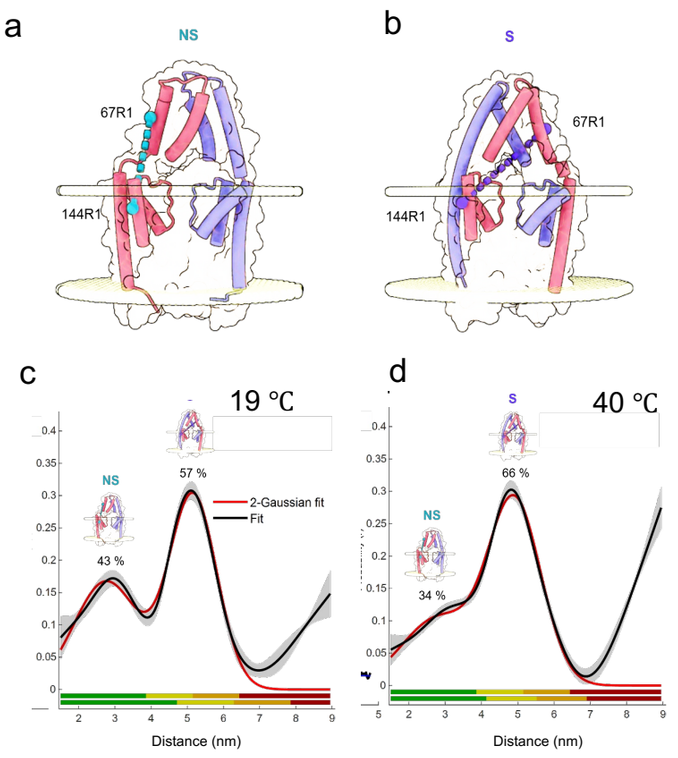

Figure 4: The spin labels on TM1 and TM2 of the same monomer (a,b). The PELDOR distance distributions are shown at temperature of 19 ℃ (c) and 40 ℃ (d) reveals a shift in the population from NS to S.

$$\Delta G = G(N,p,T) - G_{ideal\ gas}(N,p,T) = KTln\left(\langle e^{U/KT}\rangle\right)$$

$$U_{prot-memb} = U_{LJ} + U_{elec}$$

States	Temperature (°C)	Energy (kcal mol^{-1})	Energy difference (kcal mol^{-1})
S	19	-37821 ± 500.2	979 ± 724
	40	-36842 ± 524.3	
NS	19	-42505.2 ± 548.9	2689 ± 819
	40	-39816.2 ± 609.1	

Table 1: MD-derived protein–membrane interaction energies underlying the non-swapped to swapped transition in TRAAK.

Conclusions

- PELDOR identifies EcMscL and TRAAK conformational ensembles.
- CryoEM resolves closed and expanded EcMscL structures.
- MD reveals mechanisms of MscL expansion and TRAAK switching.
- Bilayer thinning and interdigitation promote EcMscL opening.
- Reduced pocket-lipid occupancy facilitates gating.
- Temperature shifts TRAAK cap-state populations.
- Protein–membrane interactions govern TRAAK energetics.
- Membrane mechanics regulate mechanosensation.

References

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