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# Steered Molecular Dynamics study of the Nanomechanical Properties of the Archaeal MscL

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**Abstract:** The mechanosensitive channels of large conductance (MscL) act as nanovalves releasing the pressure in different type of cells. They have also been proposed to be used in the smart liposomal drug delivery in conjunction with superparamagnetic particles, hence the thermal and structural stability of these mechanosensitive channles is of a great importance to us. Due to the fact that local temperature rises in this method, a stiffer channel can serve as a better candidate. In this study, the nanomechanical properties of an Archaeal MscL is investigated using constant force SMD simulations. The Young's modulus obtained for the TM1 of Archaeal MscL is $5.8 \pm 1$ (GPa) and the previously reported value for MtMscL is $3.2 \pm 0.9$ (GPa). In other words, our simulation results indicate that the TM1 helix in the Archaeal MscL is about 80% stiffer than its counterpart in M. tuberculosis which potentially makes it favourable for the new smart liposomal drug delivery.

**Keywords:** Nanomechanical properties; Mechanosensitive channel; Nanovalve; Young's modulus; SMD

## Introduction

There are many proteins embedded in the cell membrane enabling it to perform its desired functions. Of a particular interest, mechanosensitive channels of large conductance (MscL) are a group of integral proteins which are believed to secure the membranes in bacteria in the face of hypoosmotic conditions by acting as a safety nanovalve which releases the turgor pressure [1-3]. The gating mechanism of these channels is of a great importance and there are evidences of bilayer-mediated gating of these channels in which tension from the lipid bilayer leads to a conformational change and channel gating [4, 5].

In addition, recently a new prospect of liposomal drug delivery has been envisioned in which mechanosensitive channels of large conductance can act as a nanovalve which can be triggered by superparamagnetic particles that are attached to their N-terminus [6-8]. In this particular application, one of the major concerns would be the thermal and structural stability of the channel as well as the membrane since increase in temperature is inevitable. Archaea, one of the three domains of life beside Bacteria and Eucarya, being able to live under harsh environmental conditions, may provide us with a reasonable solution. It has been shown that Archaeal lipids (Fig. 1.) are more stable (due to tail branching and ether linkage) than its other counterparts [9, 10]. So in this study nano-mechanical properties of mechanosensitive channel of large conductance of Archaea is studied and the results are compared with its bacterial counterpart (MtMscL) to figure out which channel can be considered as a better candidate for the discussed application.

In this study, steered molecular dynamics (SMD) is used to study one of the $\alpha$-helices (TM1) in an Archaeal MscL homolog from *Methanosarcina acetivorans* (Fig. 1). Using SMD simulations with constant force, helix behavior is investigated with an atomistic resolution.

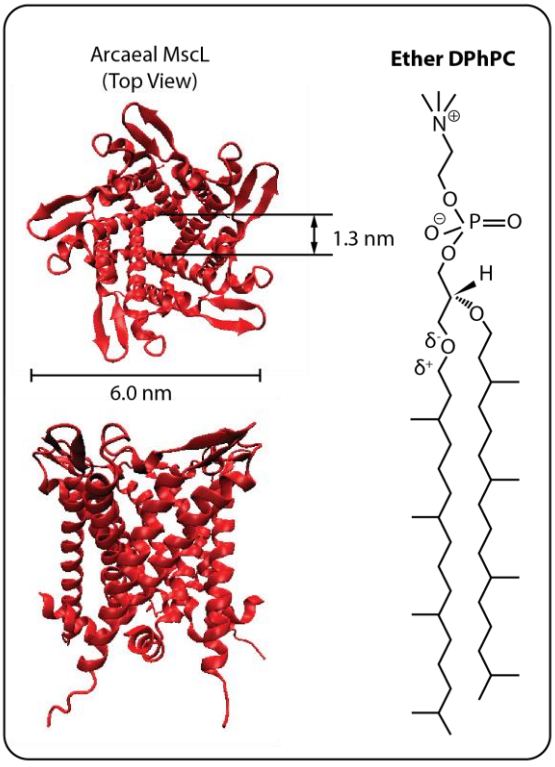


Fig. 1. Schematic of a the Archaeal MscL and the ether-linked lipids found in Achaea.

## Materials and method

In all simulations GPU-accelerated Nanoscale Molecular Dynamics (NAMD) 2.12 package [11-14] was used and all-atom CHARMM36 force field was employed [15]. The coordinates for the TM1 helix of the Archaeal MscL was extracted from its crystal structure (4Y7K) in Protein Data Bank using VMD [16].

In this study, SMD is used to apply a constant external force to one atom of the helix while keeping its other end fixed. In this regard, the ∝ carbons of the first two residues are fixed and their counterpart in the last residue is pulled with a constant force. Since the maximum strain that MscL helices experience during gating is around 6% , we chose our force range to be 0.3-1 $kcal/mol$Å; which is also similar to previous studies [17, 18]. For every force, 3 simulations are carried out each of which is 10 ns long. In every simulation, the helix is allowed to reach an equilibrium length and the strain is calculated by knowing its initial length ($\Delta L/L_0 \times 100$).

For the resultant stress of the helix, the applied constant force is divided by the average cross-sectional area of the helix which can be calculated by estimating its radius of gyration ($r_{gyr}$). In calculation of the $r_{gyr}$ the formula used by Bavi et al. [18] is used and it is worth noting that when the helix is solvated in water this value may change and so here this radius is calculated after the equilibration in the water to be 2.53 Å.

In all simulations, Langevin dynamics was used to maintain the temperature at 300 K and the pressure was controlled through Langevin piston (at 1 bar). The TM1 helix was solvated with water (TIP3P) in a 34× 34×90 Å box using VMD. A 1.0 fs time step is used for the numerical integration and electrostatics were included through Lennard Jones interactions with 10 to 12 Å switch along with particle mesh Ewald (PME) for long-range electrostatics. For the equilibration of the helix in water the process used by Bavi et al. [18] was used and the final coordinates of equilibration was taken as the starting point for the production runs of constant force SMD.

## Results and Discussion

In this study, the nanomechanical properties of an Archaeal MscL channel was investigated and compared to previously studied MtMscL which can act as nanovalves in smart liposomal drug delivery. The constant force SMD simulations have been carried out using force range of 0.3-1 ($^{kcal}/_{mol\,Å}$). For every force the simulation is conducted 3 times and the equilibrium strain is calculated (Fig. 2).

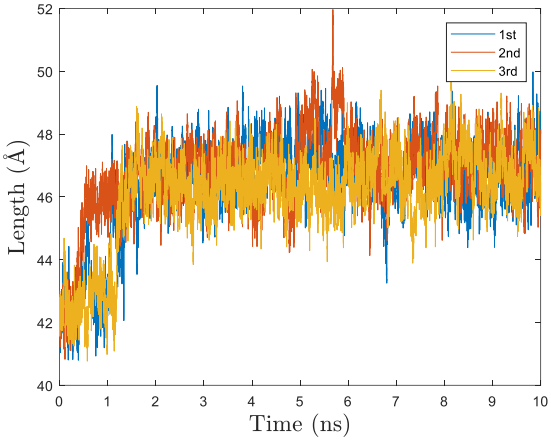


Fig. 2. The evolution of the helix length under unidirectional force of 0.9 ($^{kcal}/_{mol\,Å}$). The simulation is carried out 3 times.

To obtain the Young's modulus of the helix, the stress-strain diagram is plotted and a line is fitted through the points (Fig. 3). The slope of the fitted line indicates that Young's modulus for TM1 helix of the Archaeal Mscl is $5.8 \pm 1$(GPa).

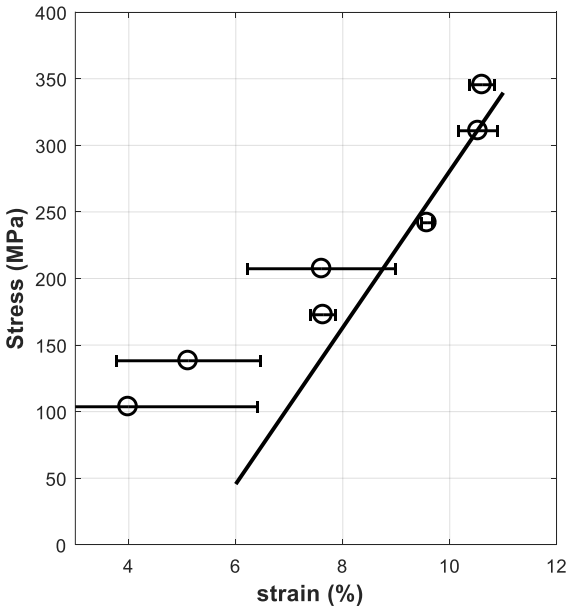


Fig. 3. Archaeal MscL unidirectional traction, stress-strain curve corresponding to 0.3-1 ($^{kcal}/_{mol\,Å}$) force range. Each point represents the averaged value of the 3 simulations and Young's modulus is estimated to be $5.8 \pm 1$ (GPa).

## Conclusions

With the newly introduced horizons for the smart liposomal drug delivery using MscL channels as a nanovalve which undergoes a local temperature rise, the nanomechanical properties of these channels are of great importance to us. In this study the nanomechanical properties of an Archaeal MscL was obtained in order to be compared with that of the previously published MtMscL. Due to the inevitable increase in temperature in the aforementioned application of the MscL, the channel with a higher stiffness can be a favorable alternative. Moreover, the derived parameters from atomistic simulations can be used for mesoscopic bead-spring and hybrid continuum-atomistic models for capturing phenomena occurring in larger length and time scales [19]. The Young's modulus for MtMscl is previously reported to be $3.2 \pm 0.9$ (GPa) [18]. Our results indicate that the TM1 helix of the Archaeal MscL is around 80% stiffer than the MtMscL. In other words, Archaeal MscL has a higher structural stability and can potentially provide us with a better alternative for liposomal drug delivery.

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