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STRUCTURE MODELS OF MECHANOSENSITIVE CHANNEL FROM ACCESSIBILITY DATA
AND MOLECULAR DYNAMICS SIMULATION

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จเรวัตร จักรมณี : แบบจำลองโครงสร้างของเมคานโนเซนซิทีฟแชนแนลจากข้อมูลแอกเซสซิบิลิตีและการจำลองพลวัตเชิงโมเลกุล. (STRUCTURE MODELS OF MECHANOSENSITIVE CHANNEL FROM ACCESSIBILITY DATA AND MOLECULAR DYNAMICS SIMULATION) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร.พรเทพ สมพรพิสุทธิ์, 71 หน้า.

เมคานโนเซนซิทีฟแชนแนลชนิดค่านำไฟฟ้าสูง (MscL) เป็นเมมเบรนโปรตีนประเภทไฮโดรโฟบิกที่ทำหน้าที่เสมือนวาล์วนิรภัยสำหรับควบคุมแรงดันออกสโมติกในเซลล์โปรคาริโอต โปรตีนชนิดนี้รับรู้และแปลงสัญญาณจากสิ่งเร้าเชิงกลไปเป็นการเคลื่อนที่ของโปรตีน MscL มีลักษณะพิเศษในการเปลี่ยนแปลงคอนฟอร์เมชันเพื่อตอบสนองเมมเบรนเทนชัน ในการศึกษาี้ใช้ข้อมูลอีพิอาร์สองกลุ่มสำหรับสร้างคอนฟอร์เมชันของ MscL จากแบคทีเรียชนิดอีโคไล ที่สภาวะปิด (cl-ecoMscL) และสภาวะอินเทอร์มีเดียต (in-ecoMscL) ด้วยวิธี PaDSAR ซึ่งเป็นวิธีการจำลองพลวัตเชิงโมเลกุลแบบมีรีสเตรนที่นำมาจากการทดลอง แบบจำลองของ in-ecoMscL มีสภาพโดยรวมคล้ายคลึงอย่างมากกับแบบจำลอง cl-ecoMscL ซึ่งชี้แนะว่าแบบจำลองนี้อาจจะสอดคล้องกับแชนแนลสภาวะปิดที่ขยายตัวก่อน การเปรียบเทียบเชิงโครงสร้างระหว่าง cl-ecoMscL และ in-ecoMscL ทำให้เห็นว่าการขยับตัวส่วนใหญ่ของท่อนทรานสเมมเบรนอยู่ใกล้เกตไฮโดรโฟบิกที่ประกอบด้วยเรสซิดีวส์ Leu19 และ Val23 เพื่อสำรวจสมบัติเชิงโครงสร้างและพลวัต ได้ทำซิมูเลชันแบบ MD เป็นเวลา 100 นาโนวินาที สำหรับคอนฟอร์เมชันที่สภาวะปิดและสภาวะอินเทอร์มีเดียตในไบเลเยอร์ชนิดพามีโทอิล-โอเลอิล-ฟอสฟาทีดิลโคลีนและโดลาวโรอิล-กลีเซอโร-ฟอสฟาทีดิลโคลีน ตามลำดับ ผลการซิมูเลชันแสดงให้เห็นถึงความเสถียรเชิงโครงสร้างของ MscL ค่าโมบิลิตีเชิงเปรียบเทียบของท่อน TM1 และ TM2 สอดคล้องกับข้อมูลโมบิลิตีจากการทดลอง การเปลี่ยนแปลงความหนาของไบเลเยอร์ที่สังเกตได้จากซิมูเลชันชี้ให้เห็นว่าโปรตีนชักนำให้เกิดการบิดรูปของไบเลเยอร์อันเนื่องมาจากอิทธิพลของไฮโดรโฟบิกมิสแมทช์

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JAREWAT JAKMUNEE: STRUCTURE MODELS OF MECHANOSENSITIVE CHANNEL FROM ACCESSIBILITY DATA AND MOLECULAR DYNAMICS SIMULATION. ADVISOR: ASSOC. PROF. PORNTHEP SOMPORNPIST, Ph.D., 71 pp.

The mechanosensitive channel of large conductance (MscL) is a homopentameric membrane protein that serves as effective osmotic safety valves in prokaryotes. It senses and transduces mechanical stimuli into protein motion. MscL is specifically designed to change its conformation in response to changes in membrane tension. In this study, two different EPR dataset were used in modeling the Escherichia coli MscL channel in its closed (cl-ecoMscL) and intermediate (in-ecoMscL) conformations through PaDSAR, an experimentally restrained molecular dynamics simulation method. The in-ecoMscL model is in overall very similar to the cl-ecoMscL, suggesting the model may be correspond to pre-expanded closed state. Structure comparison between cl-ecoMscL and in-ecoMscL revealed the major transmembrane (TM) movement is located near the hydrophobic gate residues: Leu19 and Val23. To investigate structure and dynamics properties of the protein, 100ns molecular dynamics (MD) simulations of the closed and intermediate state conformations were performed in palmitoyl-oleoyl-phosphatidyl cholines bilayer and dilauroyl-glycero-phosphocholines bilayer, respectively. The results show structure stability of MscL during the course of MD simulations. The relative mobility of TM1 and TM2 segments is consistent with the experimental mobility data. The bilayer thickness change observed from the MD simulations indicates the protein-induced bilayer deformation due to the effect of hydrophobic mismatch.

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CONTENTS

	Page
THAI ABSTRACT	iv
ENGLISH ABSTRACT	v
ACKNOWLEDGEMENTS	vi
CONTENTS	vii
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS	xv
CHAPTER 1 INTRODUCTION	1
1.1 Cell membrane	1
1.2 Ion channel	3
1.3 Mechanosensitive channel	5
1.4 Mechanosensitive channel of large conductance	7
1.5 Osmotic regulation of cell bacteria	9
1.6 Electron Paramagnetic Resonance and Spin Labeling	11
1.7 Literature reviews	12
1.7.1 Lipid-driven conformational changes of Mscl: Hydrophobic mismatch and geometric consequences of bilayer.....	12
1.7.2 Structure refinement of membrane proteins based on SDSL-EPR.....	15
1.8 Inspiration and objectives of this research	16
CHAPTER 2 THEORY.....	19
2.1 Molecular Dynamics.....	19
2.2 Molecular mechanics force fields	21
2.3 Expansion based integration algorithm	26
2.4 The Periodic boundary conditions (PBC)	28
2.5 The Particle Mesh Ewald (PME)	30
CHAPTER 3 METERIALS AND METHOD	31
3.1 Materials	31



	Page
3.1.1 Hardware	31
3.1.2 Software	31
NAMD.....	31
CHARMM	31
Visual molecular dynamics (VMD).....	31
SSH Secure Shell.....	32
APBS (Adaptive Poisson-Boltzmann Solver).....	32
wordom	32
DSSP (Define Secondary Structure of Proteins).....	32
HOLE program	32
3.2. Methodology.....	33
3.2.1 Model building of the MscL in its closed conformation	33
3.2.2 Model building of the MscL in an intermediate conformation.....	37
3.2.3 Molecular dynamics simulations	39
3.2.4 Analysis of MD trajectory.....	41
CHAPTER 4 RESULTS AND DISCUSSION	42
4.1 Sequence alignment	42
4.2 PaDSAR models of cl-ecoMscL and in-ecoMscL	43
4.3 Structural stabilities of the cl-ecoMscL and in-ecoMscL models.....	50
4.3 Inter-subunit distance changes at the hydrophobic gate residues	60
4.4 Protein-induced lipid perturbation.....	62
4.5 Proposed transition model.....	65
CHAPTER 5 CONCLUSION	66
REFERENCES	67
VITA.....	71



2432385467

LIST OF TABLES

TABLE 3.1	Residue number of EcoMscL with an assignment of the EP-types for close state modeling. The assignment was done by an analysis of ΠO_2 , $\Pi NiEDDA$ and ΔH_0^{-1} profiles.....	33
TABLE 3.2	Residue number of EcoMscL with an assignment of the EP-types for the intermediate state modeling. The assignment was done by an analysis of ΠO_2 , $\Pi NiEDDA$ and ΔH_0^{-1} profiles.....	38



LIST OF FIGURES

- FIGURE 1.1** The fluid mosaic model representation of cell membrane or plasma membrane structure. 2
- FIGURE 1.2** Classification of ion channels based on external stimuli. From left to right: voltage-gated ion channels, ligand-gated (extracellular ligand) ion channels, ligand-gated (intracellular ligand) ion channels and mechanically gated ion channels..... 4
- FIGURE 1.3** Typical current traces of MscS (A) and MscK (B) in the presence of MscL(C). Recordings were generated from patches derived from *E. coli* giant spheroplast at -20 mV. MscL is a homopentamer in which each monomer has two TM segments. The open state is characterized by a very large single channel conductance (~ 3.5 nS) and activation tensions close to the lytic limit of biological membranes. MscS, as originally described, is actually the result of two distinct gene products, YggB, which underlies MscS proper, and KefA, which is now known as MscK because of the role of potassium ions in modulating activity. Both channels have similar single channel conductances (~ 1 nS) and are activated at intermediate tensions. MscS activity also shows a distinctive inactivation/adaptation phenomenon. 6
- FIGURE 1.4** Schematic representation of (A) the pentamer structure and (B) the monomer structure of mtbMscL. Three structure domains including transmembrane helices (TM1 and TM2), N-terminal and C-terminal in cytoplasmic domains are illustrated. 8
- FIGURE 1.5** Cellular responses to changes in the osmotic environment. 10
- FIGURE 1.6** Reaction of the methanethiosulfonate spin label (MTSSL) with the sulfhydryl group of a cysteine side chain, generating the spin label side chain. 11
- FIGURE 1.7** A model depicting the evolution of structurally distinct conformations during MscL gating. The top row represents a hypothetical sequence of kinetic events MscL undergoes on its way to the fully open state. Manipulating the lipid environment surrounding the channel can trap at least three of these distinct conformations: (i) the closed state is stable in PC18, (ii) PC14 stabilizes a closed conformation further along the kinetic path and (iii) the fully open state can be locked by addition of conical-shaped lipids (LPC) on one leaflet of the bilayer. The possibility



- remains of stabilizing additional intermediates (such as subconducting states) using even shorter (but more unstable) bilayers..... 13
- FIGURE 1.8** Physical changes in the lipid bilayer and the structural state of MscL. Shown in each case are diagrams of the type of bilayer perturbation (left), the estimated TM pressure profile (middle) and the corresponding functional state of MscL (right). (a) An unperturbed (control) bilayer stabilizes the channel in its closed conformation.(b) Reconstitution of MscL into bilayers of different thickness compresses/expands the pressure profile and biases the threshold of activation through hydrophobic mismatch, possibly stabilizing an intermediate conformation of the channel.(c) Asymmetric incorporation of cone-shaped lipids (i.e. LPC) alters the pressure profile, favoring the fully open state. 14
- FIGURE 1.9** PaDSAR method based on data from SDSL-EPR technique to the structural refinement of membrane proteins through restrained molecular dynamics simulations..... 15
- FIGURE 1.10** EPR data of TM residues in MscL channel..... 17
- FIGURE 2.1** Schematic comparison of time- and length-scales, accessible to different types of simulation techniques (quantum simulations (QM), molecular dynamics (MD), Brownian dynamics (BD) and hydrodynamics/fluid dynamics (HD)). The black dots mark the longest ($\approx 1 \mu\text{s}$) and the biggest ($N > 5 \times 10^9$, $L \approx 0.4 \mu\text{m}$ molecular dynamics simulations). 20
- FIGURE 2.2** Schematic representation of (A) Bond-stretching force, (B) Angle-bending force, (C) Proper torsional force and (D) Improper torsional force. 24
- FIGURE 2.3** The potential energy function, U . that potential energy of each term is the y-axis. (A) The interaction energy of two bonded atoms as a function of the distance of their atomic centers with ideal distance b_0 as harmonic term. (B) The harmonic term, similar in form to (A), but of lower energy, that describes the interaction of two atoms bonded to a third atom as a function of the angle between them with the ideal angle θ_0 . (C) A typical periodic ($n=2$) cosine term with a minimum φ_0 at 0 used to describe both in- and out-of-plane dihedral angle energies. Plots (A–C) share the same range for energy. (D) The van der Waals interaction energy of two atoms with ϵ and r_0 the geometric mean of their respective ϵ and r_0 . (E) Three typical electrostatic interactions. The



- top line idealizes the interaction of charges with like signs while the bottom line idealizes the interaction of two charges with different signs. The sum of (D–E) constitutes the non-bonded interaction energy of two atomic centers..... 25
- FIGURE 2.4** Periodic boundary condition in two dimensions with the primary cell surrounded by its image cells. Molecules that leave the cell will be replaced by their images entering the cell from the opposite side. 29
- FIGURE 3.1** (Left) Show that the distribution properties of NiEDDA and O₂ in bilayer (NiEDDA, nickel ethylene diamine diacetate is hydrophilic. It cannot partition in lipid membrane and O₂ dissolves in membrane). (Right) Schematic representation for definition of pseudo-atoms used by PaDSAR..... 35
- FIGURE 3.2** Flowchart of the method used to generate structural models of EcoMscL in Close and intermediate state respectively and to MD simulation..... 36
- FIGURE 3.3** Structures of Some Lipids..... 37
- FIGURE 3.4** The membrane proteins of two system. (Up), Palmitoyl oleoyl phosphatidyl Cholines (POPC) are membrane bilayer for PC18 and (Down), Dilauroylglycero-phosphocholines (DLPC) for PC12 and TIP3P are force field parameter for water molecules..... 40
- FIGURE 4.1** Primary sequence alignment of MscL channels from various microorganisms: Eco = *Escherichia coli*, Mtb= *Mycobacterium tuberculosis*, Pa= *Pantoea ananatis*, Pf= *Plasmodium falciparum*, Ep= *Erwinia pyrifoliae*. 42
- FIGURE 4.2** The conformations of EcoMscL channel in Close state (Right) and Intermediate state (Left). 43
- FIGURE 4.3** Ramachandran plot calculation of the psi/phi angle distribution of the model (A) Close conformation (B) Intermediate conformation, as computed by PROCHECK program. The cl-ecoMscL and in-ecoMscL structures superimpose with an overall root mean square deviation (RMSD) of about 1.8Å using all backbone atoms, and thus reveal small conformational changes between the two states. Figure 4.4 shows superimposed structural models derived from PaDSAR. As can be seen from the figure, the TM1 region exhibits the most structural deviation



- with RMSD of 1.8Å. Superposition of the two transmembrane domains of the in-ecoMscL onto the corresponding domains of cl-ecoMscL revealed that the cytoplasmic side of the TM1 helix is slightly tilted, resulting in a small increase of the pore diameter. 45
- FIGURE 4.4** Represent TM1 and TM2 helices of Eco-MscL derived from PaDSAR..... 46
- FIGURE 4.5** (A) Represented model of channel in close conformation and intermediate conformation (B) Represented by molecular surface of Eco-MscL on Top view. (C) Graphical presentation of pore diameter profiles of the closed (red line) and the intermediate conformation (blue line). 47
- FIGURE 4.6** Movement of hydrophobic residues possibly involves with gating of Eco-MscL channel. 48
- FIGURE 4.7** Number of closed contact residues along the TM1 and TM2 residues of cl-ecoMscL (black line) and in-ecoMscL (red line) models. 49
- FIGURE 4.8** Backbone RMSD with respect to the starting structure of two MD systems as a function of simulation time. 50
- FIGURE 4.9** The RMSD profiles of the different domain (TM1, TM2, Periplasmic loop, C terminal and N terminal) of two MD system as a function of time..... 52
- FIGURE 4.10** RMSD of individual TM segment (Chain A-E) of two MD systems (Up is a close conformation and Down is a intermediate conformation) as a function of time. 53
- FIGURE 4.11** Average backbone RMSF of closed system (I) (black) and Intermediate system (red). Illustrate the different domains (TM1, TM2, Periplasmic loop, C terminal and N terminal) of proteins. 55
- FIGURE 4.12** Backbone RMSF as a function of residue number of close state (PC18).56
- FIGURE 4.13** Backbone RMSF as a function of residue number of intermediate state (PC12). 57
- FIGURE 4.14** RMSF box plot of accessibility data from EPR (Up) and alpha carbon of two transmembrane helices (Down). The bottom and the top of the box are 25 and 75 percentile. The median is the straight line, and the mean is plotted as a square. 58
- FIGURE 4.15** Show that stability of secondary structure helices of the five transmembrane segments included TM1 and TM2 of close state and intermediate state as a function of simulation time calculated by DSSP. The each color mean : α -helix (red), stand in β -sheet (blue), β -bridge (yellow), β -turn (black), coil (green), unassigned (white). 59



2432385467

- FIGURE 4.16** Color scale represents the distance pair of gated of channel in Eco-MscL in close state and intermediate state. 61
- FIGURE 4.17** Hydrophobic thickness of pure POPC bilayer is about 4 Å greater than that of DLPC bilayer. 63
- FIGURE 4.18** Membrane thickness profiles of POPC and DLPC bilayer obtained from the simulations in the presence of cl-ecoMscL and in-ecoMscL, respectively. The thickness was measured from an average distance between the N-atom of tertiary amine head group. 63
- FIGURE 4.19** The closed gate in the pore at the constriction region occluding the passage of water. (A) Water molecules enter to the pore but do not penetrate throughout the channel. Water occlusion is located near the narrowest region of the pore (orange) constituting of two hydrophobic residues, L19 and V23. (B) Extracellular and cytoplasmic views illustrate these residues forms a hydrophobic plug. 64
- FIGURE 4.20** Proposed mechanism for the closed - intermediate transition. 65



LIST OF ABBREVIATIONS

Ms	Mechanosensitive channels
MscL	Mechanosensitive channels of Large conductance
MscS	Mechanosensitive channels of Small conductance
PD	pore domain
TM	transmembrane
Å	angstrom
°	degree
MD	molecular dynamics
PDB	protein data bank
PSF	protein structure file
VMD	visual molecular dynamics
APBS	adaptive Poisson-Boltzmann solver
PBE	Poisson-Boltzmann equation
PaDSAR	pseudoatom-driven solvent accessibility refinement
EPR	electron paramagnetic resonance
α	alpha
SDSL	site directed spin labeling
V	Valine
L	Leucine
ΔG_{elec}	electrostatic solvation free energy
L_{mem}	range of membrane bilayer thickness
ϵ_{m}	dielectric constant of the membrane
ϵ_{w}	dielectric constant of the water
$\epsilon_{\text{protein}}$	dielectric constant of the protein
POPC	palmitoyl oleoyl phosphatidyl cholines
DLPC	Dilauroylglycero phospho cholines

ns	nanosecond
RMSD	root-mean-square-deviation
RMSF	root-mean-square-fluctuation
3D	three dimensional
Kcal	kilocalorie
mV	milivolt
DSSP	database of secondary structure assignments of all protein
nS	nanosiemens

