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Research Article

Conformational Modulation of Transmembrane Segments of a Protein (CorA) By Effective Media -

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ABSTRACT

Background: The membrane protein CorA from Thermotoga maritima (TmCorA) is known to be a funnel-shaped homopentamer. This magnesium channel protein spans across the membrane and has well-defined functions of its inner (iCorA) and outer (oCorA) membrane segments. It is not feasible to achieve large-scale structural response of CorA embedded in a bilayer lipid membrane in presence of solvent even with large-scale traditional MD simulations. Coarse-graining becomes unavoidable to investigate large-scale structural response. An efficient coarse-grained approach that involves knowledge-based residue-residue interaction, a set of residue interaction with its surrounding in an effective medium, and a bond-fluctuating mechanism with ample degrees of freedom is used to study large-scale structural response of iCorA and oCorA.

Results: Conformational response of the inner (iCorA) and outer (oCorA) segments of a transmembrane protein is studied by a coarse-grain Monte Carlo simulation in effective media for a range of its interaction strength (f) with the protein residues in native and denatured phases. The radius of gyration of iCorA is found to decrease in native phase and increase in denature phase before reaching saturations as a function of interaction strength. The outer membrane segment shows opposite response to effective interaction. Modulation of the protein structure is enhanced by the hydrophobic media. Analysis of the structure factor shows that the inner segment retains its globular conformation for most of the media interaction except at high temperature in a weakly interacting medium; hydrophobic interactions with the effective medium accentuate the structural response. The outer segment retains its random-coil conformations for almost all interaction range and its radius of gyration does not seem to be affected by the hydrophobic media. Self-organizing globular and fibrous segments of iCorA, critical in its conformational modulation, are identified from the residue contact profiles.

Conclusions: The interaction strength of the effective medium in which the protein is embedded has strong influence in modulating its conformation, degree and nature of which depend on the range of temperatures, i.e., low and high range in native and denatured phases, respectively.

Keywords: CorA protein; Effective media; Coarse-grained approach; Monte Carlo

INTRODUCTION

The membrane protein CorA from Thermotoga maritima (TmCorA) consists of 351 residues and is known to be a funnel-shaped homopentamer with a large intracellular N-terminal domain linked to a membrane embedded ion pore. CorA proteins are characterized by two C-terminal transmembrane (TM) segments connected by a short periplasmic loop with well-defined outer (oCorA) and inner (iCorA) membrane segments involving residues 1-290 and 291-351, respectively. Selective response of ion channels such as transport of magnesium ions via CorA protein plays a very important role in controlling the expression of many genes critical in virulence. For example [1] have reported that 'regulation of CorA Mg^{2+} channel function affects the virulence of Salmonella enteric Serovar Typhimurium' in which they explain their data based on the 'regulation of CorA function for optimal virulence'. [2] have also discussed the 'connection between the Mg^{2+} transport channels and bacterial virulence'. In a review on 'the structure and regulation of magnesium selective ion channels', [3] have pointed out that 'complete structural information on eukaryotic Mg^{2+} -transport proteins is currently lacking due to associated technical challenges'. Therefore, we focus on the structural response of the transmembrane segments of CorA protein as our on-going investigations.

In general, protein structures plays a critical role in its prolific yet very specific functions. Very often it is difficult to identify most pertinent structures from its relatively large conformational ensemble [4], a challenging issue in a theoretical analysis. In order to understand and interpret the experimental observations, verifying the expected results, or predicting the unexpected outcomes it is crucial to develop insight into the conformational stability of the protein. Proteins have to be embedded in appropriate environment (solvent, solute, along with a host of other reactive and inert (macromolecular crowding) components to perform its functions *in vitro* or *in vivo* [5-9]. Macromolecular crowding both in and out of cells is the natural reality. A membrane protein is generally embedded in a cell environment consisting of aqueous components with specific yet variable pH, ionic strength, etc., osmolytes and other co-solvents along with reactive and inert crowding agents. Interactions of the protein with its surrounding depend on the interactions and temperature [4-9]. Understanding the structure and dynamics of a single (isolated) protein i.e., in dilute solution is, however, very important in assessing its fundamental characteristics resulting from competing and cooperative interactions among residues. Such investigations provide a base to explore the effects of external interacting constituents in underlying surroundings. As pointed above, the function of a protein depends not only on its residue sequence but also on its interacting and inert surroundings. For example, urea and guanidinium chloride favor unfolded state while Trim Ethylamine N-Oxide (TMAO) glycine, betaine, glycerol, and sugars stabilize the folded state of proteins [5,7]. It is difficult to assess the effect of each crowding element without a clear understanding of structural dynamics in presence of simplified environment that can incorporate the effect of such general components as solvent/solute first.

CorA is a magnesium channel protein (as pointed above) that spans across the membrane and has well-defined functions of its inner (iCorA) and outer (oCorA) membrane segments [10-24]. The thermal response of iCorA and oCorA have been found to have contrasting differences [21]. As mentioned above, the protein must be embedded in an appropriate matrix environment (e.g. membrane, solvent, etc) to perform its specific functions. Majority of the computational modeling of CorA involves all-atom Molecular dynamics simulation of protein embedded in a bilayer lipid membrane in presence of solvent [20]. Even with large-scale computing (involving CPU of the orders of months), it is not feasible to probe large-scale structural response of its components such as protein and membrane. Coarse-graining becomes unavoidable to investigate large-scale structural response of the protein. Instead of representing each element of the membrane and its crowded environment explicitly, it would be good to consider an effective medium first for simplicity. We would like to explore the structural dynamics of a membrane protein CorA in an effective medium [25] that may incorporate some element of solvent/solute without adding steric hindrance of its surrounding. In this article we

use an efficient coarse-grained approach that involves knowledge-based residue-residue interaction, a set of residue interaction with its surrounding in an effective medium, and the bond-fluctuating method on a discrete lattice with ample degrees of freedom [26].

Why this study is critical in understanding the conformational response of CorA and what insight is expected to be gained from this investigation? The membrane environment is known to be dynamic particularly in regard to ion channel gating mechanism. Effects of variability of evolving solvent/solute constituents on the structural response of CorA is not explored to our knowledge. Our goal is to identify how the conformations of inner and outer membrane segments of CorA respond to strength of interaction with its surrounding in native and denatured phases. We have made several interesting observations such as positive and negative response of the radius of gyration of the inner segment of the protein with the surrounding media in native and denatured phases, critical nature of the hydrophobic interaction in modulating extenuating the structural response, and little effect on the response of the outer segment of the protein to its interaction with its surrounding particularly in hydrophobic matrix. Besides the first of its kind, these findings are critical in guiding the future computer simulations and laboratory experiments to specific range of solvent/solute quality. The model and method are presented next followed by results and discussion and a concluding remark.

MATERIALS AND METHODS

Coarse-graining has become a common mechanism in modeling complex protein systems. In this study, we use a coarse-grained representation of the protein chain (all-residue), the underlying host space (cubic lattice), and a mean-field-like surroundings (an effective medium) to capture overall impact of solvent/solute (sol) of a crowded environment. A large fraction of computational modeling do not involve such coarse-graining procedures, therefore, the work presented here may be complementary and may provide an alternative framework to understand the structural evolution of the protein in different surroundings. The transmembrane protein CorA consists of 351 residues with an outer (oCorA) and an inner (iCorA) transmembrane segment with residues 1-290 and 291-351. A protein chain is a set of nodes tethered together in a chain with flexible bonds that can adopt to various configurations in order to explore its conformational phase space; a node represents a residue (coarse-graining its internal structure) occupies a cube of size $(2a)^3$ where a is the lattice constant. CorA is represented by 351 nodes tethered together by covalent (peptide) bonds while the iCorA and oCorA segments by 61 and 290 nodes respectively. The covalent (peptide) bond between consecutive nodes varies between 2 and $\sqrt{(10)}$ in unit of lattice constant with strict implementation of its excluded volume constraints. The degrees of freedom for nodes to move and bonds to fluctuate are limited on a cubic lattice in comparison to continuum host space. However, unlike the minimalist models on a discrete lattice with fixed bond length and limited number of neighboring lattice sites, there are ample degrees of freedom for each nodes to move and covalent bonds to fluctuate here as in a bond-fluctuating polymer chain [26]. This is one of the most efficient and effective method to investigate large-scale problems where one can easily enhance the degrees of freedom by fine-graining [25] and incorporate structural refinements.

The protein chain is initially placed in a random configuration on the cubic lattice; the empty lattice sites act as effective medium. Each node/residue interacts with surrounding nodes of the protein and the underlying host space (empty lattice sites) with a generalized Lennard-Jones potential,

$$U_{ij} = \left[\varepsilon_j \left(\frac{\sigma}{r_j} \right)^{\mathbb{P}} + \varepsilon_j \left(\frac{\sigma}{r_j} \right)^{6} \right], \; r_{ij} < r_c \qquad (1)$$

Where ij is the distance between the residues at site i and j; $r_c=\sqrt{8}$ and $\sigma = 1$ in units of lattice constant. The potential strength, ε_{ij}, is unique for each interactions, residue-residue and residue-solvent. The residue-residue interaction is based on the knowledge-based contact interaction matrix (20×20 for 20 amino acids with 210 independent pairs) of a number of knowledge-based residue-residue interactions we use Betancourt-Thirumalai (BT) [27] matrix which appears to be somewhat improved over the classic Miyazawa-Jernigan (MJ) interaction [28].

Interaction between a residue at a site i and its surrounding environment (empty) site j is unique for each residue type and based on their hydropathy index i.e. $\varepsilon_{ij} = f\varepsilon_r A_{h/p/e}$. The residue-sol interaction is repulsive ($\varepsilon_r = 0.1$) for all hydrophobic (H) residues, attractive ($\varepsilon_r = -0.2$) for all polar (P) residues, and more attractive ($\varepsilon_r = -0.3$) to all electrostatic (E) residues. Although the hydropathy index is binned into three groups for simplicity, the weight $A_{h/p/e}$ of each residue varies within each group (H,P,E) according to its relative hydropathy index (Table 1). That is, the interactions between different types of residues and solsites are unique; the empirical parameter f introduced above modulates environment solute/solvent quality. We have used all hydropathy interactions i.e. hydrophobic, polar, and electrostatic with $f = f_{hpe}$) and hydrophobic ($f = f_h$) interactions alone to assess the differences.

Table 1: Hydropathy H-index and corresponding weights.

Residue	H-Index	Weight ($A_{h/p/e}$)
Ile	4.5	H1 = 1.000
Val	4.2	H2 = 0.933
Leu	3.8	H3 = 0.844
Phe	2.8	H4 = 0.622
Cys	2.5	H5 = 0.556
Met	1.9	H6 = 0.422
Ala	1.8	H7 = 0.400
Gly	−0.4	H8 = 0.089
Thr	−0.7	P1 = 0.200
Ser	−0.8	P2 = 0.229
Trp	−0.9	P3 = 0.257
Tyr	−1.3	P4 = 0.371
Pro	−1.6	P5 = 0.457
His	−3.2	P6 = 0.914
Gln	−3.5	P7 = 1.000
Asn	−3.5	P8 = 1.000
Asp	−3.5	E1 = 0.778
Glu	−3.5	E2 = 0.778
Lys	−3.9	E3 = 0.867
Arg	−4.5	E4 = 1.000

At a fixed temperature (T) and sets of residue-residue and residue-solvent interactions, each residue performs its stochastic movement with the Metropolis algorithm after the excluded volume constraints are satisfied. This procedure involves, (i) selecting a residue/node and one of its neighboring sites randomly, (ii) checking the availability of the proposed site (i.e. the sol site), (iii) making sure that the excluded volume criterion and limits on the bond-length are consequently satisfied before (iv) implementing the hopping probability exp (−ΔE/T) where ΔE is the change in energy between new (proposed) and current configurations and T is the temperature in reduced unit of the Boltzmann constant. In fact all quantities including the phenomenological energy, temperature, interaction strength f are in arbitrary units. Since we are interested in response of the protein structures to temperature and interaction strength, it is not feasible to provide estimates of their absolute values. For a coarse-grained model system like ours, it is feasible to identify such regimes as low and high temperatures (see below) using a calibration based on all atom Molecular Dynamics (MD) simulation. Attempts to move each node once define unit Monte Carlo (MC) step. We examine both local and global physical quantities such as contact and mobility profiles, radius of gyration, and structure factor as a function of residue-sol interaction strength (f). Each simulation is performed for a sufficiently long time (e.g. 5 million time steps) with 100-200 independent samples to calculate these physical quantities. Most of our simulations are performed on 150^3 and 350^3 lattices with iCorA and oCorA, respectively. Although we have used different lattice sizes to check the finite size effects.

RESULTS AND DISCUSSION

In order to assess the structural response of the protein, we analyze both local and global physical quantities. A pair of snapshots of the iCorA at a high and low residue-sol interaction (f_{hpe} = 1.0, 5.0) at a relatively high temperature (T = 0.032) are presented in figure 1 to illustrate the contrast in the size of the protein. Clearly, the visual inspection shows that the size of the protein reduces on increasing the residue-sol interaction strength. The change in size of the protein at different temperatures for a range of residue-solvent interaction strength is not as obvious from the snapshots alone. Therefore, we calculate the average radius of gyration of the proteins.

Effect of the effective medium interaction on the variation of the radius of gyration of iCorA is presented in figure 2 at representative low and high temperatures which may correspond to native and denatured phases respectively of the protein. In native phase (T = 0.012), the radius of gyration increases on increasing the interaction strength before approaching its saturation at high interactions. The response of the changes in radius of gyration to media-interaction are higher on increasing the temperature with maximum changes at a particular temperature (e.g. around T = 0.020). On raising the temperature further e.g. T = 0.024, the response of the radius of gyration to effective interaction appears to remain unchanged. Continued raising the temperature, on the other hand, leads to reversal in response of the radius of gyration to effective media interactions (see the inset figure 2). For example, the radius of gyration decreases continuously with the sol-interaction (f = f_{hpe}) at T = 0.028 before reaching a steady-state value at a critical interaction (f_c~ 2.5). The phase transition characterized by the continuous change in radius of gyration (random-coil to globular) with the interaction strength f is accentuated by the hydrophobic effective (f = f_{hpe}) media at lower critical interaction (f_c~1.5). The continuous phase transition from globular (f = f_{hpe} = 2.0) to random-coil (f = f_{hpe} = 4.0) appears to persist at higher temperature (T = 0.032) at higher critical concentration (f_c~4.5). The response of the radius of gyration of the outer segment (oCorA) of the protein to effective interaction is reverse to that of the inner segment; hydrophobic interactions do not seem to affect the radius of gyration of the outer segment (see supplement figure 1).

The overall spread of the protein structure can be further analyzed by examining the structure factor S(q),

$$S(q) = \langle \frac{1}{N} \left| \sum_{j=1}^{N} e^{-i\vec{q}\cdot r_j} \right|^2 \rangle_{|\vec{q}|}$$

Where r_j is the position of each residue and |q| = 2π/λ is the wave

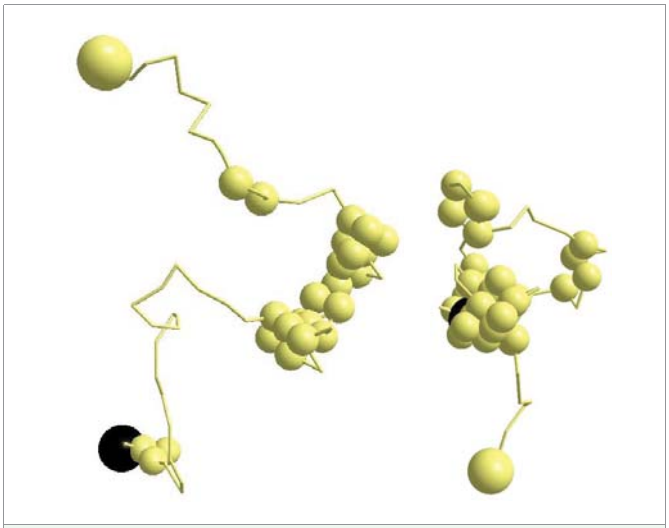

Figure 1: Snapshots of iCorA at the end of 10^7 MCS time on a simulation box of size 150^3 at T = 0.032 with the residue-sol interaction f = f_{hpe} = 1.0 (left), 5.0 (right). Large black sphere represents the first residue and large gold sphere, the 61st residue.

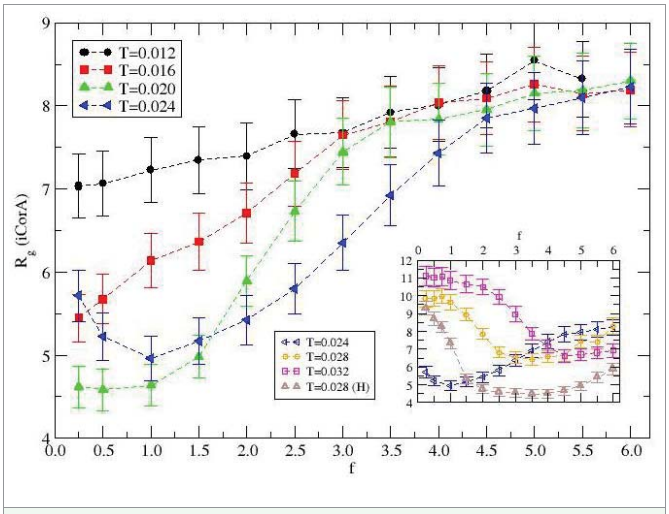

Figure 2: Variation of the radius of gyration of iCorA with the strength (f) of the effective medium interaction at lower (native phase) and higher (denatured phase, inset) temperatures. A set of data with the hydrophobic (H) interaction alone (without contribution from polar interaction) at the temperature T = 0.028. (H) Is included to compare it with corresponding data with full effective Medium interactions i.e., Hydrophobic (H); Polar (P); and Electrostatic (E).

vector of wavelength λ, the spatial spread of residues in the protein's conformation. Using the power-law scaling of the structure factor with the wave vector, $S(q) \propto q^{-1/\gamma}$ or $S(q) \propto \lambda^{1/\gamma}$, one can evaluate the effective dimension D of the protein conformation $N \propto R_g^{1/\gamma}$, $D = 1/\gamma$. Figure 3 shows the variation of the structure factor of iCorA with the wave vector on a log-log scale at temperature T = 0.028 and 0.032 with the effective media interactions $f = f_{hpe} = 2.0, 4.0$. While the protein stays globular (D~ 3) at T = 0.028 in effective media with interaction strength $f = f_{hpe} = 2.0$ and 4.0, a crossover occurs from a random coil (D~ 2) conformation in a medium with $f_{hpe} = 2.0$ to a globular (D~ 3) conformation in a medium with $f = f_{hpe} = 4.0$ at T = 0.032. The outer segment (oCorA) of the transmembrane CorA remains random-coil at these temperatures in effective medium with interaction strength f = 2.0 and 4.0 (see figure S2 of the supplement). At low temperatures, the protein retains its globular structure at all the interaction strengths of the effective medium (see figure S3 of the supplement).

How does the interactions with the effective media affect the self-organizing assembly of residues? Segmental structure can be analyzed by examining the average number (N_n) of residues around each, i.e. the residue contact profiles. Figure 4 shows the variation of the contact profiles of iCorA with the interaction strength ($f = f_{hpe} = 1.0$-6.0) at a temperature T = 0.016. In a low interacting effective medium (f = 1.0), distribution of residues is almost uniform with a relatively high residues contact; the protein conformation is globular. Onset of segmental re-organization seems to occur on increasing the interaction strength (f = 2.0). Increasing the interaction strength with the effective medium (f = 4.0), induces a distinction between segments where the dense segment (residue 39-55, segmental globular structure) seems to anchor the sparse distribution of remaining segments. The segmental phase separation persists at higher effective interactions and higher temperatures which seem consistent with the trends in global physical quantities described above. The contact profile of oCorA shows that the conformation of the protein remains expanded in tenuous random coil conformations (see figure S4) consistent with the observations based on its global physical properties mentioned above changing the interacting medium to purely hydrophobic leads to pinning down structure of the protein in a somewhat frozen configuration (see figures S4 and S2).

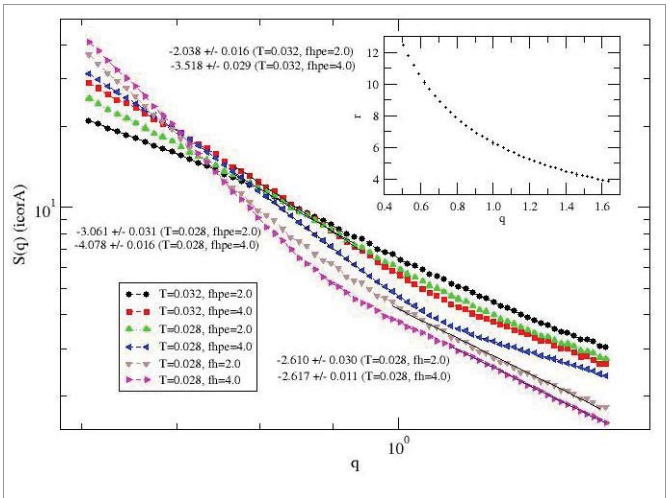

Figure 3: Structure factor S(q) versus the wave vector q at the temperature T = 0.028 and 0.032 of iCorA with the effective media interactions $f = f_{hpe} = 2.0, 4.0$; a data set with the hydrophobic interaction $f = f_{hpe} = 2.0, 4.0$ at the temperature T = 0.028 is also included for the comparison. Slopes are the estimated for the data points appropriate for the size of the protein at specific temperatures and interaction strength. Inset is the spatial (r) scale versus wave vector q.

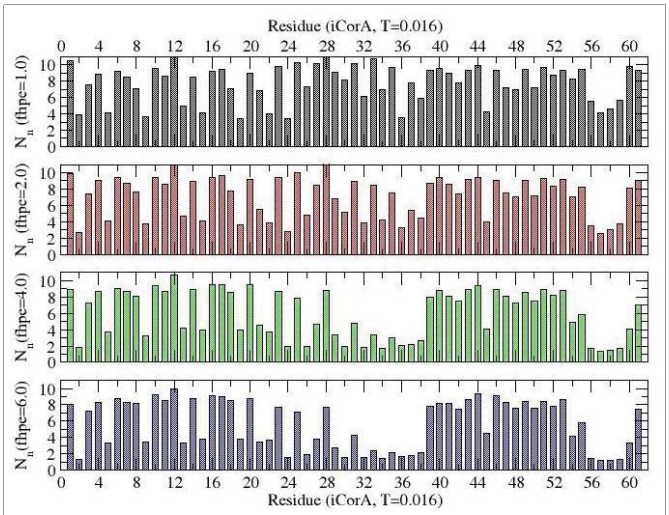

Figure 4: Average number (N_n) of interacting residues of iCorA around each at a temperature T = 0.016 (native phase) at strength of interaction $f = f_{hpe} = 1.0 - 6.0$.

CONCLUSIONS

Conformational response of inner (iCorA) and outer (iCorA) segments of a transmembrane protein (CorA) to its interaction with the effective medium is examined by a coarse-grained Monte Carlo method. We find that the interaction strength (f) of the effective medium in which the protein is embedded has strong influence in modulating its conformation, degree and nature of which depend on the range of temperatures, i.e., low and high range in native and denatured phases respectively. In native phase, we find that the radius of gyration of the inner segment (iCorA) increases on increasing the residue-sol interaction strength until it reaches its saturation. The response of the radius of gyration is enhanced by raising the temperature in the native phase. The response reverses in denatured phase, i.e., the radius of gyration of iCorA decays on increasing the interaction strength (f) before reaching its saturation. The range of effective interaction strength decreases on raising the temperature. The outer segment exhibits opposite trend, i.e., increase of its radius of gyration with the interaction strength in denatured phase while it remains unaffected by a purely hydrophobic effective medium.

Detailed analysis of the structure factor reveals that the inner segment retains its globular conformation in native phase for entire residue-sol interaction strength while it exhibits some variability in the denatured phase. The inner segment does not seem to spread out much even at higher temperature particularly in a relatively strongly interactive effective media, however, it conform to random coil at high temperature in effective media with weak interaction. In presence of hydrophobic media, iCorA conform to a rather complex heterogeneous morphology with an effective dimension D ~ 2.6 which is neither globular nor random coil. The outer segment oCorA retains its random-coil conformation at almost entire range of effective medium interactions at high temperatures.

From the analysis of the local physical quantity such as the residue contact profile, we are able to identify specific segment of iCorA towards one end (e.g. residues 39-55) that conform to a globular solid. The self-assembly of these residues induced by residue-residue and residue-sol interactions seems to anchor the structural spread with

a delicate mixture of micro-globules and fibrous segments towards the opposite end to perform its specific function in ion-channel gating. Contact profile of the outer segment (oCorA) shows a rather uniform distribution of residues to provide it ample flexibility. These findings are critical in understanding the conformational response of the protein with the overall solvent/solute interaction. Interpretations of the most experimental data are speculative; we hope that this study will help in interpreting the experimental data and identifying appropriate cellular media for future experiments.

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