

Research Update

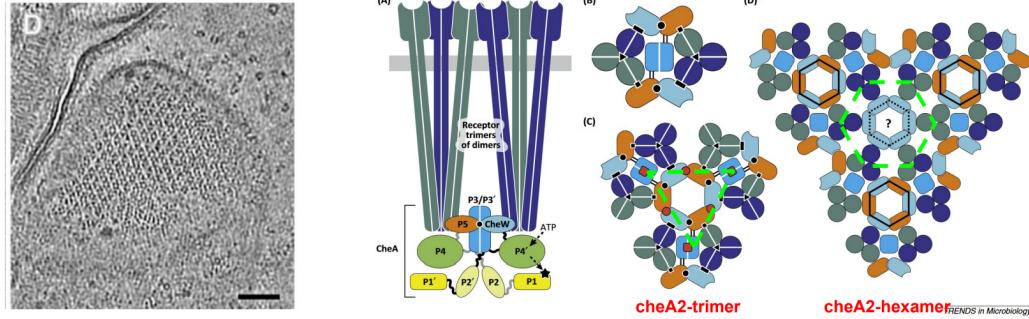
Jian Huang

2024 Sep

1 Study domain-domain interactions of the CheA using Hyres

1.1 Goal and motivation

Bacterial chemotaxis enables mobile bacteria to move toward or away from attractants or repellents. The chemotaxis pathways for sensing surrounding chemicals rely on a chemosensory array of so-called core-signaling units (CSUs),¹ consisting of transmembrane chemoreceptors, the histidine kinase CheA and an adaptor protein CheW. Many copies of the CSUs can form highly ordered array on the surface of bacterial cell membrane. The chemosensory array can integrate cooperatively the sensory signaling from surrounding chemicals to regulate the autophosphorylation activity of the CheA, which will trigger a series of downstream phosphorylation processes (on CheY etc) and eventually modulate the cell's flagella motors.²



- ❖ 2 receptor trimers-of-dimers (physiologically dimers from different kinds of chemoreceptors could mix up);
- ❖ 1 CheA complex:
 - P1: His substrate domain, which will be phosphorylated by the CheA.P4 kinase domain
 - P2: (not super important for kinase regulation and chemotaxis);
 - P3: dimerization domain
 - P4: kinase domain
 - P5: forms heterodimers with CheW. It self shares a fold homologous to CheW
- ❖ 2 CheW: coupling chemoreceptors and CheA through CheA.P5

Figure 1.1: Core Signaling Units on the E. coli cell membrane surface (The left panel) and the model for the CSU structure. Current understandings of those players are listed below the figure.

1.2 Previously on this project

1. Close inspection of the P1/P1' dimerization interface proposed by Tom revealed that the interface has too many unsaturated negatively charged residues, meaning the proposed interface might not be biophysically feasible.

1.3 Hyres simulation setup

Here, I adopted a lower temperature (380 K) for the CheA Hyres simulation while keeping other restraint setups the same.

Table 1.1: Simulation setup and status

CheA dimer System	Temp.	Restraints	Time	Status
"Parallel" P1/P1'	350 K	w P1/P1' restraints	2 us * 6 conf.	Done
"Parallel" P1/P1'	400 K	w P1/P1' restraints	2 us * 6 conf.	Done
"Antiparallel" P1/P1'	350 K	w P1/P1' restraints	2 us * 6 conf.	Done
"Antiparallel" P1/P1'	400 K	w P1/P1' restraints	2 us * 6 conf.	Done
"Parallel" P1/P1'	350 K	w/o P1/P1' restraints	2 us * 6 conf.	Done
"Parallel" P1/P1'	400 K	w/o P1/P1' restraints	2 us * 6 conf.	Done
"Parallel" P1/P1'	380 K	w/o P1/P1' restraints	2 us * 6 conf.	Done

1.4 Distance and contact analysis

To examine the "*trans*-" productive mode where the P1 from one chain would be phosphorylated by the P4 domain from another chain, I tracked the distances between P1-H48 and ATP in the P4 domains.

1. Distance analysis.

I first calculated the distance between P1-H48-C-alpha atom and the P3 atom of the ATP molecule (the ending phosphate group) as a function of simulation time. The measurement directly reflects distance between the substrate and the phosphorylation center, which would represent a "**productive**" contacting mode.

2. Contacting frequency analysis.

On the basis of the above distance analysis, I further examine the pairwise contact frequencies between residues on the P1 and P4 domains when P1 and P4 are contacting in the productive mode. I first used a distance cutoff of 20 Å between P1-H48 and ATP to extract frames where P1 and P4 are productively contacting, and then a contacting cutoff of 15 Å was used for residue-level pairwise contacts.

2 Exploring gating/activation mechanisms of TRP channels

Goal and Motivation

Transient receptor potential (TRP) channels are a large and diverse family of transmembrane ion channels that are critical in sensory perception through polymodal activation by various physical and chemical stimuli.

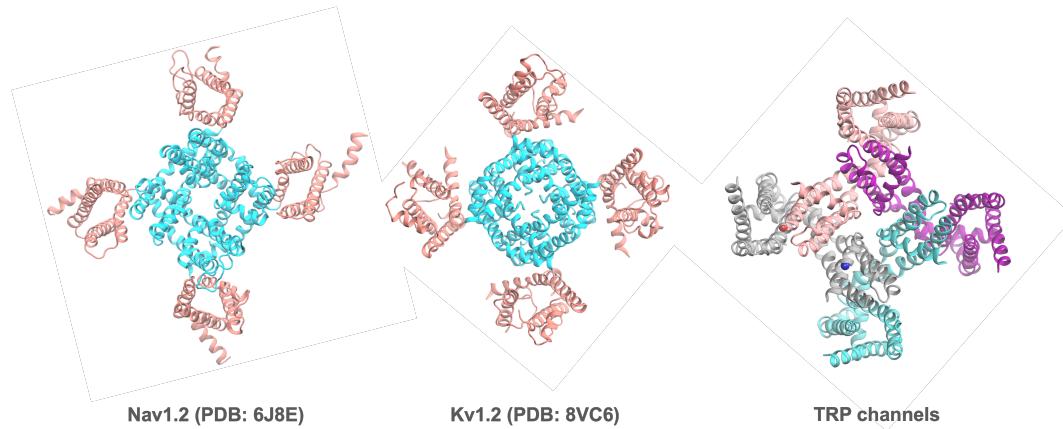


Figure 2.1: The similarity of topologies of voltage-gated ion channels (Nav1.2 and Kv1.2 as two examples shown here) and TRP channels (TRPV4 as an example shown in the right panel). Only the transmembrane region (TM) is shown with the pore region and the voltage sensor domain shown as salmon and cyan color respectively. For TRP channel in the right panel, TMs from four monomers are colored differently in order to show the domain-swapping feature of the topology.

References

- [1] Muok, A. R.; Chua, T. K.; Srivastava, M.; Yang, W.; Maschmann, Z.; Borbat, P. P.; Chong, J.; Zhang, S.; Freed, J. H.; Briegel, A.; Crane, B. R. *Science Signaling* **2020**, *13*, eabc1328.
- [2] Briegel, A.; Ames, P.; Gumbart, J. C.; Oikonomou, C. M.; Parkinson, J. S.; Jensen, G. J. *Molecular Microbiology* **2013**, *89*, 831–841.