A COMPUTATIONAL FREE ENERGY EXPLORATION OF BINDING AND GATING MECHANISMS IN LIGAND-GATING ION CHANNELS

Carla Molteni

King's College London, Physics Department, Strand, WC2R 2LS, London, UK
E-mail: carla.molteni@kcl.ac.uk

Pentameric ligand-gated ion channels (pLGICs) are important biomolecules that mediate fast synaptic transmission. Their malfunction is linked to serious neuronal disorders, including Alzheimer's disease, and they are major targets for drugs; in invertebrates they are involved in insecticide resistance. pLGICs are efficient nano-machines, composed of five subunits arranged around an ion permeable pore embedded in the cell membrane, with an extracellular, a transmembrane and an intracellular domain. The binding of a neurotransmitter to the extracellular domain at the interface between two subunits triggers the opening (gating) of the channel: ions can then flow across the cell membrane. Unfortunately, the complexity of pLGICs and the limited structural information from X-ray crystallography prevent a detailed understanding of how they function. State-of-the-art and novel computational techniques are therefore crucial to build an accurate picture at the atomic level of the mechanisms which drive the activation of pLGICs, complementing the available experimental data.

We have used a combination of computational methods, including homology modeling, ligand-protein docking, molecular dynamics and, for accelerating rare events, metadynamics, with the guidance of mutagenesis electrophysiology experiments, to explore the mechanisms of neurotransmitter/drug binding and the corresponding free energy landscapes in native and mutated systems, focusing in particular on the insect GABA-activated RDL receptor and on the serotonin-activated 5-HT_3 receptor. Moreover, we have investigated a potential *trans-cis* proline switch for the gating of the ion channel.

NOTES