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*Deciphering the allosteric modulation of the purinergic P2X receptors using Markov models*

The family of Purinergic P2X receptors are ligand-gated cation channels which are affected by a number of allosteric modulators. Inducing conformational changes throughout the whole protein, allosteric modulators modify the efficacy and potency of a receptor's orthosteric ligands. We briefly review the literature of mathematical models of P2X receptors and develop modelling paradigms for allosteric modulation of orthosteric systems based on previous models of P2X receptors and the experimental protocols that they depend on. Furthermore, we analyze in detail allosteric modulation of P2X4 receptors by the pharmacological agent Ivermectin and present two plausible types of models. Using an MCMC methodology, we compare the models and the mechanisms by which they reproduce experimental data, concluding that sensitization and desensitization of receptors are not independent of each other, and that the later can occur subsequent to the former. To capture this behaviour, we develop a two layer Markov model that is more compatible with our understanding of allostery and experimentally observed data. Finally, we discuss the possibility that this two layered model represents a shared mechanism governing the dyanmics of all P2X receptors.