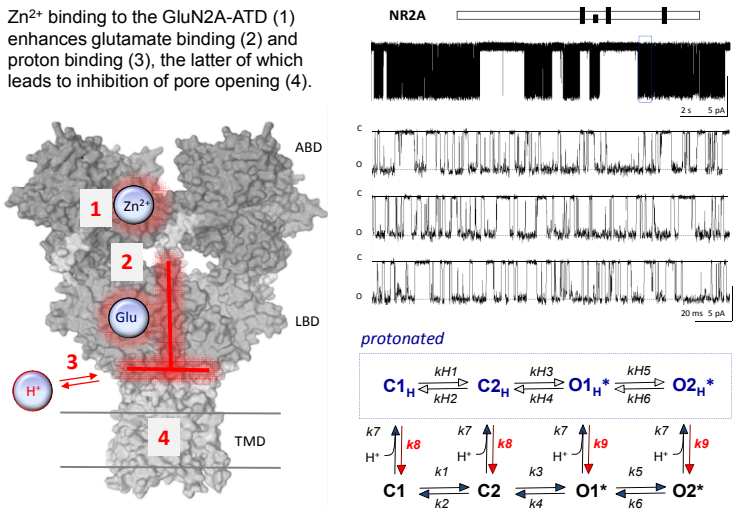
Regulation of glutamate receptors by endogenous modulators

A major focus of our lab is to understand how glutamate receptors can be modulated by endogenous ion such as zinc, magnesium, and protons. To accomplish this, we combine electrophysiological recordings from native and recombinant glutamate receptors with (a) site-directed mutagenesis to determine the site of action, (b) kinetic analysis of single channel recordings from outside-out and cell-attached patches with only a single active channel, (c) evaluation of the response time course for whole cell and excised patch recordings of macroscopic currents, and (d) determination of pharmacological properties for a range of agonists and modulators. The results of these different experimental approaches are combined to develop conceptual models of receptor function that can be used to explore the relationship between receptor structure and modulation. The overarching goal is to eventually merge structurally inspired models with electrophysiological data to arrive at specific and testable hypotheses about glutamate receptor modulation. Understanding in detail receptor gating is critically important for understanding how endogenous modulators influence excitatory synaptic transmission, synaptic plasticity, as well as the mechanism of potential drugs that act at a wide range of glutamate receptors. We anticipate that better understanding of receptor modulation and drug action will lead to new ideas about ways to modulate glutamate receptors for therapeutic gain.



Model of Zn^{2+}-induced inhibition of GluN2A (*left*) and single channel recording from one active GluN1/GluN2A receptor in an outside-out patch in response to maximally effective concentrations of glutamate and glycine (*upper right*). A kinetic model that allowed detection of Zn^{2+}-induced changes in the proton equilibrium from single channel data.