**Project Title:** Biophysical Mechanisms of Glutamate Transport

**Project Abstract:**
Glutamate is the principal transmitter used in excitatory synaptic signaling and its extracellular concentration must be tightly controlled in the brain. Rapid removal of synaptically released glutamate and homeostasis of ambient glutamate are achieved by members of a gene family of excitatory amino acid transporters (EAAT1-5) that are expressed on neurons and astrocytes. Despite significant progress since their cloning, a number of fundamental questions about the molecular mechanisms involved in glutamate transport remain unresolved. A dominant theory postulates that transporters allow access to binding sites for intracellular and extracellular solutes in an alternating cycle, but a structural basis for this mechanism remains unclear. In addition, glutamate uptake is thermodynamically coupled to the transmembrane influx of three Na⁺ ions and one proton and the counter-transport of one K⁺ ion, but the detailed structural and mechanistic basis of the ion interaction and flux coupling are unknown. We propose to use a combination of computational and biophysical approaches to address these questions and generate preliminary data supporting the resubmission of a scored but unfunded NIH application (R01 NS033270-13; Physiology and Biophysics of Glutamate Transport; PI Kavanaugh).