(Popescu and Auerbach, 2004). Therefore, a comprehensive statistical description for the activity of a fully liganded one-channel that includes all three kinetic modes must be represented by a 21-state three-tier model, such that each channel cycles extensively through each tier, described by the 3C2D2O scheme, before it slips stochastically into a mode with distinct open lifetimes but similar 3C2D2O sequence. It was proposed previously that glutamate dissociation occurs with observable probability only from the C_3 states of either mode, and the association and dissociation kinetics of glutamate are similar for all three tiers (Popescu and Auerbach, 2003). Clearly, after incorporating glutamate-binding steps to each of the three tiers, the resulting 27-state model, although grossly simplified relative to the myriad of conformational transitions that most likely accompany gating, is too complex to be practical for quantitative investigations of steady-state one-channel data. Instead, depending on the experimental conditions and the scope of the analyses, simpler models can adequately fit the purpose. One common simplification is to ignore modal behavior and fit a 3C2D2O model to the entire

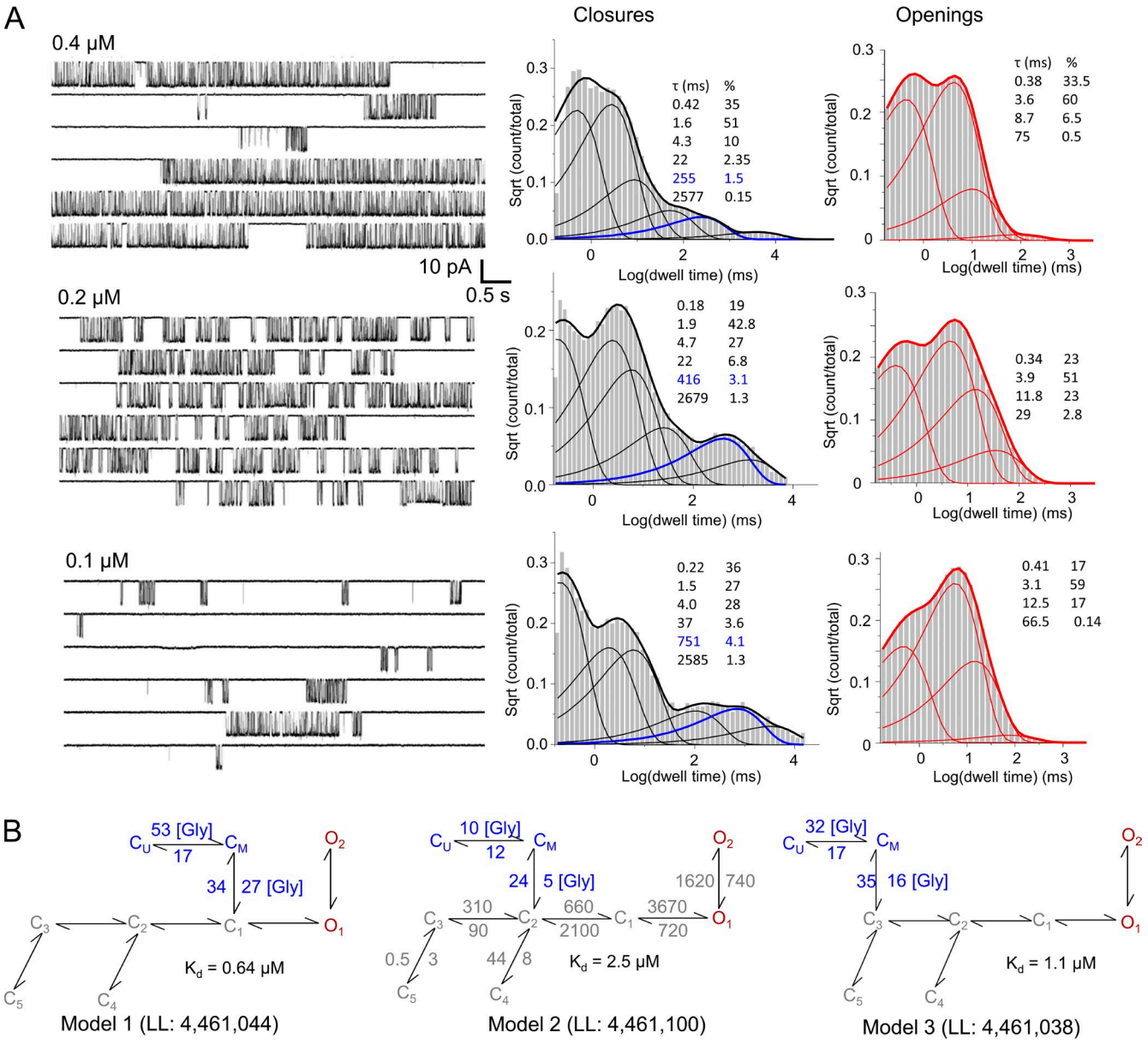

Figure 1. NMDA receptor activity in subsaturating concentrations of glycine and 1 mM glutamate. (A) Representative current traces (left) and histograms of closed (black) and open (red) event durations calculated from data within one full record, in three glycine concentrations, as indicated. The concentration-dependent closed component is highlighted in blue. (B) Three top-ranking models, and their respective LL values, incorporate explicit glycine-binding steps; they were each fitted globally to data obtained with several glycine concentrations ($n = 9$; $>2 \times 10^6$ events). Glycine concentration is in micromolars. Rate constants are in s^{-1}, except for the glycine-binding rate constants, which are in $\mu M^{-1}s^{-1}$.