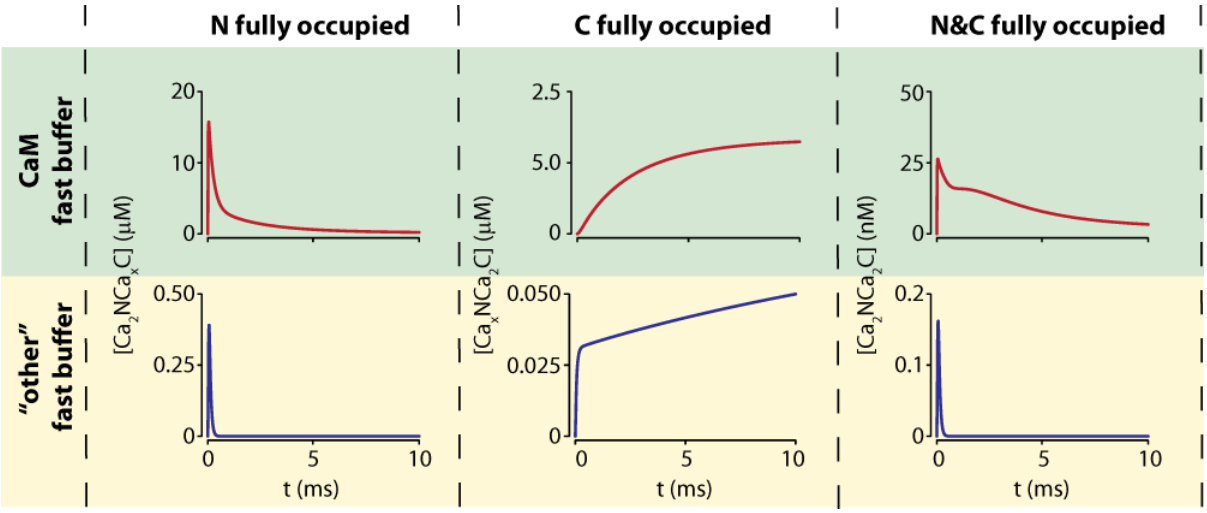

Supplementary Figure 8. **Comparing new CaM kinetics with those used in previous studies.** With the N-lobe having such a high speed of binding and Ca^{2+} 'flowing' from N-lobe to C-lobe to a high affinity CBP (see Fig 2b in main text) much more Ca^{2+} will be bound to CaM then expected with the previously assumed properties of CaM. We simulated a 50 μM increase in total [Ca^{2+}] from an initial condition of 100 nM free [Ca^{2+}]. To compare how CaM is activated having the newly determined properties to its properties described earlier, we simulated the CaM in two ways. We simulated CaM as determined in the present study (top row, CaM fast buffer) to contrast it to CaM with properties used in earlier simulations[34] (bottom row, "other" fast buffer). In earlier simulations 260 μM CaM and 45 μM CB together with 5 μM 'fast buffer' was assumed[34]. To make a fair comparison, we simulated the newly determined CaM properties also at 260 μM CaM and 45 μM CB (but added no 'fast buffer'). It is difficult to define exactly when CaM is "activated" since some processes only need Ca^{2+} binding to the N-lobe or C-lobe whereas other CaM targets need fully occupied CaM (both lobes) to be activated. Therefore, we simulated here the concentrations of fully occupied N-lobes, C-lobes and whole CaM (both lobes) that occur in the first 10 ms after the influx of Ca^{2+}. Please note that the y-axis scales between the old CaM properties (bottom row) and new CaM properties (top row) are one to two orders of magnitude different.