Non-Markovian rate process of TRP ion channel activity

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The Markov state model (MSM) is a popular, simple, phenomenological theoretical tool for describing the hierarchy of time scales involved in protein functional processes, e.g. ion channel gating. A MSM is a particular case of the general non-Markovian model, where the transition from one state to another depends only on the relevant transition rate from one state to the next, and does not include the history of state occupancy within the system, i.e., it only includes reversible, non-dissipative processes. Therefore, it requires knowledge of the structural details of the conformational changes of the channel and, it is not predictive when those details are not known. In the case of ion channels, this simple description fails in real (non-equilibrium) situations, such as local temperature changes or energy losses during channel gating. Overcoming these limitations is key to going beyond a mere phenomenological description, towards a better understanding of the physics underlying the channel dynamics. Here, we show that it is possible to use non-Markovian equations (i.e. offer a general description that includes MSM as a particular case) to develop a relatively simple analytical model that successfully predicts experimental data on the thermodynamic activity out of equilibrium of the temperature-sensitive channels TRPV1 and TRPM8. Our model is able to predict asymmetrical opening and closing rates, infinite processes, "new state creation" and temperature changes throughout the process.