Multiscale Modeling of RAS on Cellular Membranes

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Abstract

Cancer results from modifications to cellular decision-making processes. In normal cells, the protein-mediated signaling networks that control growth and movement are tightly regulated. However, mutations that disrupt or over-activate signaling proteins can drive uncontrolled cell growth resulting in cancer. RAS, a peripheral membrane signaling protein, is mutated in 30% of all cancers, especially those of the pancreas, colon and lung. These oncogenic mutations result in the loss of GTPase activity which in turn causes persistent engagement of effectors and enhanced or continuous growth signaling.

RAS driven cancers have so far eluded effective treatments. The ability to predict the fundamental mechanism of RAS-driven cancer initiation would significantly accelerate the development of novel diagnostics and/or targeted therapies for these cancers. Working towards this predictive understanding, our current goal is to bridge experimental gaps in the understanding of RAS and RAF in the context of the cellular membranes on which they are active. However, conventional simulation approaches cannot address the complexities of RAS-driven cancers due to the orders of magnitude difference in time and length scales associated with membrane vs. protein dynamics. Therefore, we are developing a novel multiscale modeling approach that leverages new experimental data machine learning to explore membrane environments. An unsupervised machine learning ecosystem analyzes coarse scale simulation data and recognizes biologically relevant events and situations and selects appropriate subsystems for fine scale simulation. Our approach includes a feedback loop to continually improve the fidelity of the macro model.

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