MAR13-2012-000520

Abstract for an Invited Paper
for the MAR13 Meeting of
the American Physical Society

From flexibility to cooperativity: multiscale modeling of cadherin-mediated cell adhesion

YINGHAO WU, Albert Einstein College of Medicine

Cadherins constitute a large family of Ca2+-dependent adhesion molecules in the Inter-cellular junctions that play a pivotal role in the assembly of cells into specific three-dimensional tissues. Although the molecular mechanisms underlying cadherin-mediated cell adhesion are still not fully understood, it seems likely that both cis dimers that are formed by binding of extracellular domains of two cadherins on the same cell surface, and trans-dimers formed between cadherins on opposing cell surfaces, are critical to trigger the junction formation. Here we present a new multiscale computational strategy to model the process of junction formation based on the knowledge of cadherin molecular structures and its 3D binding affinities. The cell interfacial region is defined by a simplified system where each of two interacting membrane surfaces is represented as a two-dimensional lattice with each cadherin molecule treated as a randomly diffusing unit. The binding energy for a pair of interacting cadherins in this two-dimensional discrete system is obtained from 3D binding affinities through a renormalization process derived from statistical thermodynamics. The properties of individual cadherins used in the lattice model are based on molecular level simulations. Our results show that within the range of experimentally-measured binding affinities, cadherins condense into junctions driven by the coupling of cis and trans interactions. The key factor appears to be a loss of molecular flexibility during trans dimerization that increases the magnitude of lateral cis interactions. We have also developed stochastic dynamics to study the adhesion of multiple cells. Each cell in the system is described as a mechanical entity and adhesive properties between two cells are derived from the lattice model. The cellular simulations are used to study the specific problems of tissue morphogenesis and tumor metastasis. The consequent question and upcoming challenge is to understand the functional roles of cell adhesion in intracellular signal transduction.