STRETCHING THE CADHERIN MOLECULAR VELCRO® OF CELL-CELL JUNCTIONS

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EXECUTIVE SUMMARY

The extracellular domains of classical cadherins form a Velcro®-like surface that glues cells together in the presence of calcium. This is essential for cell-cell adhesion and multicellular life, but the mechanics of multi-cadherin complexes is poorly understood. Using VMD (visual molecular dynamics) and NAMD (nanoscale molecular dynamics) on Blue Waters we were able to perform atomistic simulations of realistic adhesive systems that included up to twelve cadherin-cadherin bonds with 3.7 million atoms. These simulations revealed how cadherins respond to mechanical stimulation that mimics physiological forces, such as those experienced by tissue stretched by blood pressure, muscle movement, or impact with a foreign object. In addition, we were able to determine the collective behavior of cadherins in the absence of calcium and the relaxation of partially ruptured cadherin lattices as it may occur during wound healing. These simulations shed light on the basic molecular mechanisms that underlie tissue development, mechanics, and repair.

RESEARCH CHALLENGE

Selective and robust adhesion between cells is essential for multicellular life. Classical cadherin proteins are found on the surface of cells and act as molecular Velcro® that glues adhesive cells together [1,2]. The adhesion mediated by cadherins depends on calcium ions and is the basis for the formation of organs and the maintenance of tissue integrity in humans and in multiple species across the animal kingdom. The molecular architecture of a key cadherin protein named E-cad revealed how its extracellular domain protrudes from the cell surface as a hook that engages with another E-cad from an adjacent cell [3]. This E-cad/E-cad complex effectively forms a bond that links adjacent cells together in cell-cell junctions. E-cad also has a transmembrane helix and a cytoplasmic domain that anchors the protein to the actin cytoskeleton, thus restricting its motion in the membrane plane. A single E-cad/E-cad bond is weak, so the strength of E-cad-mediated adhesion derives from multiple E-cad/E-cad bonds arranged in a large and robust lattice (see Fig. 1). Previous studies have provided a detailed description of how single E-cad molecules and bonds behave and respond to force in the presence and the absence of calcium [4–7]. However, very little is known about the collective behavior of a "society" of E-cad molecules in a lattice. Understanding how lattices of E-cad proteins respond to forces is essential to determine how tissue is maintained and broken, how wound healing occurs at the molecular level, and how mutations that change E-cad mechanics lead to disease.

METHODS & CODES

To test how an E-cad lattice responds to forces that mimic the effect of cells being stretched by blood pressure, muscle movement, or impact with a foreign object, we generated atomistic models with lattices containing one to twelve E-cad/E-cad bonds [3]. Mechanical properties of cadherin proteins are best studied in simulations where all atoms in the system, including critical calcium ions, are explicitly modeled, and where the system is hydrated with water molecules and ions that mimic the native physiological environment of cell-cell junctions. Such systems were built and simulated with VMD and NAMD [8,9], a pair of programs for molecular visualization and dynamics simulation created by the Theoretical and Computational Biophysics Group at the University of Illinois at Urbana-Champaign. This software suite can handle large atomistic systems, which in our case encompassed up to 3.7 million atoms. NAMD can efficiently use thousands of cores in Blue Waters, which allowed us to simulate these large systems and use steered molecular dynamics (SMD), a technique in which forces are applied to proteins to test their mechanical response *in silico* [10].

RESULTS & IMPACT

Systems including one, four, and twelve E-cad/E-cad bonds in a lattice arrangement were simulated for twenty or more nanoseconds, in equilibrium and under tension. To make the systems realistic, we also incorporated constraints that mimic cytoplasmic attachment to the cytoskeleton. To the best of our knowledge, these are the first all-atom SMD simulations revealing detailed dynamics of a complete and realistic cadherin lattice. We were able to observe how the initially curved E-cad/E-cad bonds became straight upon application of force, suggesting that cadherins at the cell-cell junction can act as molecular shock absorbers that extend without the E-cad/E-cad bond breaking at low force. As tension increased, we observed E-cad/E-cad bond rupture without any unfolding of the individual E-cad molecules, despite lateral interactions that stabilized the lattice. To test reversibility, we released forces and observed the recovery of curvature for individual E-cad molecules, hinting at the steps required to reestablish cell-cell adhesion after rupture. We also explored the behavior of the lattice in the absence of calcium, which resulted in disordered and floppy E-cad chains. Additional simulations will explore the elastic response of the calcium-free lattice as well as of lattices that are not anchored to the cytoskeleton or that are subjected to shearing stress. Overall, NAMD simulations of cadherin lattices are providing an unprecedented atomistic view of the mechanics of cellular adhesion.

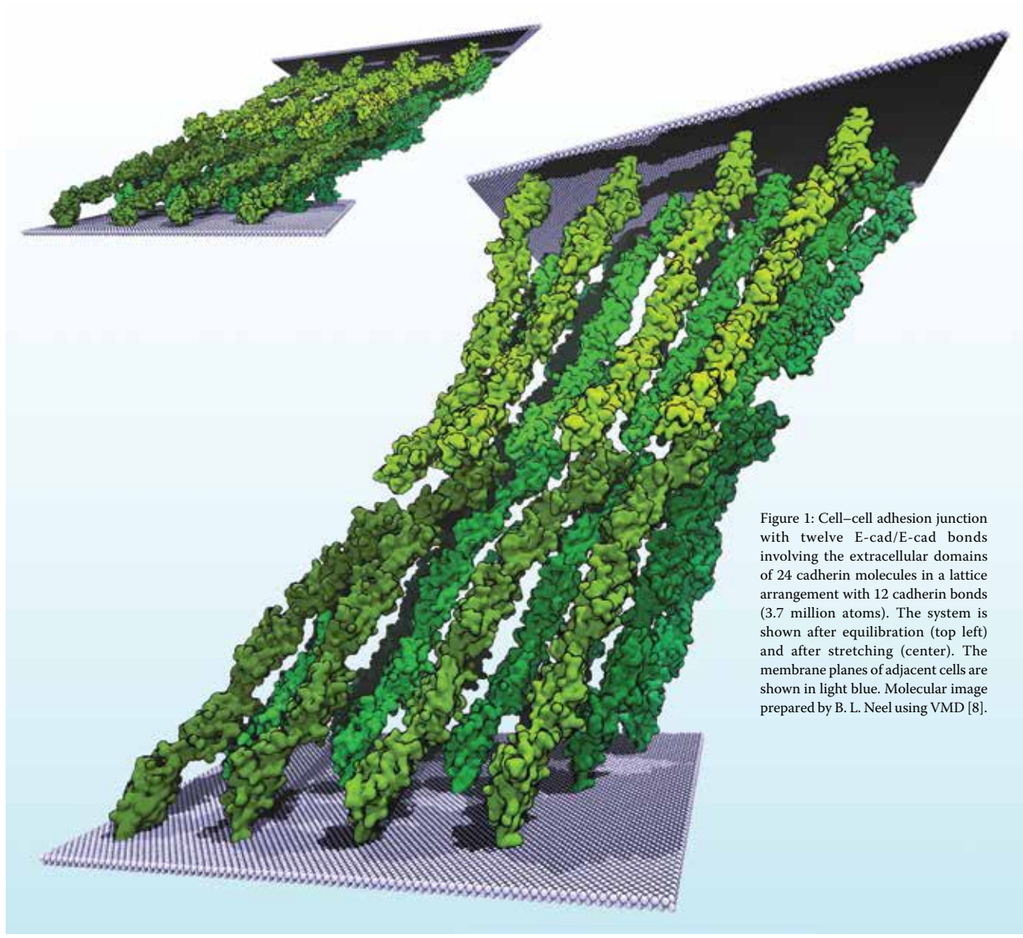

Figure 1: Cell–cell adhesion junction with twelve E-cad/E-cad bonds involving the extracellular domains of 24 cadherin molecules in a lattice arrangement with 12 cadherin bonds (3.7 million atoms). The system is shown after equilibration (top left) and after stretching (center). The membrane planes of adjacent cells are shown in light blue. Molecular image prepared by B. L. Neel using VMD [8].

WHY BLUE WATERS

Molecular dynamics simulations of large atomistic systems are extremely computationally demanding and cannot be divided into smaller independent simulations to be distributed among poorly networked computational resources. Only a fast networked and massively parallel system like Blue Waters can be used to achieve the multi-nanosecond time scales relevant to study the dynamics and elasticity of cadherin complexes.