Towards a Multiscale Mechanical Model of Cell Adhesion Dynamics

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Introduction: Cell-matrix junctions, in particular focal adhesions (FAs), regulate mechanobiological functions, e.g. proliferation, differentiation, and apoptosis[1,2]. Describing the multiscale linkage between substrate and FA mechanics is needed to reveal residue targets for mechanically activated diseases and to design engineered tissues that maintain desired cell health through mechanical cues. Here, we present a multiscale cell adhesion model, from the molecular mechanics of a cell-matrix junction to a 2D continuum model of a cell.

Materials and Methods: All-atom molecular dynamics (MD) simulations of the ectoplasmic integrin-fibronectin (int-FN) complex, a key component of an FA, were run in GROMACS 2018.3[3]. The int-FN structure file was downloaded from the protein data bank[4]. The integrin headpieces and FN chains were isolated in PyMOL[5]. The structure was solvated in a TIP3P water box (18nm x 45nm x 19nm) with 0.15 mM NaCl. Energy was minimized for 15k steps with the steepest gradient descent algorithm, then equilibrated with an NPT ensemble for 1ns at 1 bar and 310K. LYS 559 and GLU 36 at the proximal ends of the integrin headpieces were restrained. PRO 1142 at the distal end of the FN chain was pulled at 10nm/ns using a 50kJ/mol/nm spring with an umbrella potential for 3ns (Fig. 1A). The int-FN length was measured as the average vertical distance between PRO 1142 and each of the two restrained residues. The custom FE model assumes the cell as a thin elastic disk on top of an elastic substrate (Fig. 1C). To account for cell contractility, an active stress field was applied inside the cell. We used a catch-slip bond model of adhesion to determine the number of int-substrate bonds per node in the FE mesh in a force dependent manner[6]. Force-balance in the FE mesh thus includes elastic deformation of the cell cytoskeleton, active contractile stress within the cell, and coupling to the elastic substrate through substrate-int bonds. Crucially, the int-FN complex in the FE model was modeled as a nonlinear spring using a piecewise linear fit to the force-extension curves provided by the MD simulations.

Results and Discussion: The int-FN complex length extended from 19.9nm to 40.2nm after the applied velocity control. The structure held a 109pN/nm stiffness up to 5nm before the proximal portion of the FN unraveled, leading to greater elongation until 15nm (Fig. 1B). After brief stiffening due to a lack of extension, the FN's distal portion began to unravel. The structure's elongation sequence indicated that the integrin headpiece maintains its integrity, carrying the bulk of the load transmission while allowing for free motion and stretching of the FN domains. The stiffness was fed into the FE model. Forces at individual integrins from the coupled FE model are in the range 0-120pN, with average of 20pN (Fig. 1D), within the linear regime of the force-extension results seen in the MD simulations. Our model shows that MD and FE can be coupled to evaluate cell shape and the distribution of integrin forces across the body, providing a useful tool for investigating cell mechanobiology.

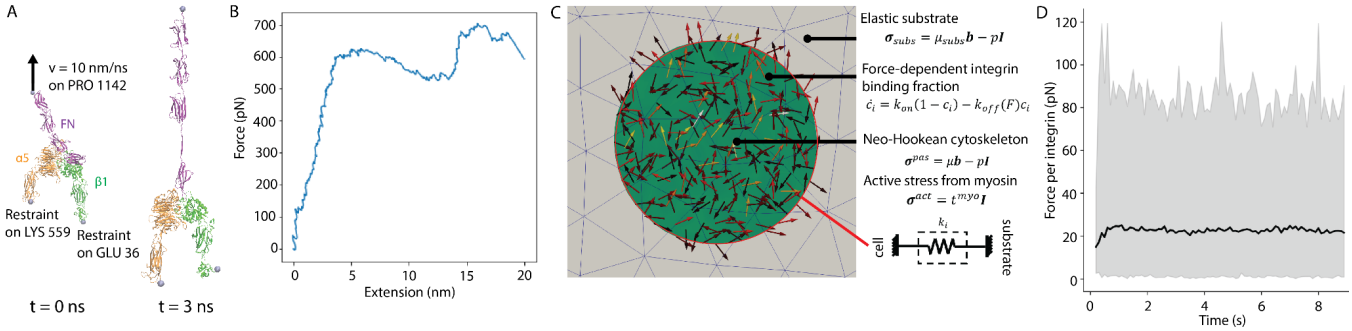

Fig 1: (A) First and last frames of int-FN system with restraints on proximal residues and an applied velocity of 10 nm/ns on PRO 1142. (B) Plot of the force vs. int-FN extension. (C) Mathematical inputs and force outputs (arrows) from the FE model. (D) Force distribution per integrin bond in the FE model.

Conclusion: The multiscale mechanical model lays the groundwork for studying the coupled effects of molecular mechanics and cell morphology. Future studies shall incorporate key membrane dynamics including integrin diffusion and clustering and their effects on membrane curvature fluctuations, while developing 3D geometry.

References: [1]Ingber DE. *Proc. Natl. Acad. Sci.* 2003, 100:1472-1474. [2]Jahed ZH et al. *Internat. Rev. Cell Mol. Biol.* 2014, 110: 2475-2483. [3]Abraham MJ et al. *SoftwareX,* 1-2, 19-25, 2015. [4]Available at: rcsb.org/structure/7nwl [5]Schrodinger L & DeLano W. *PyMOL.* 2020. Available at: http://www.pymol.org/pymol. [6]Cheng et al. *Sci Adv* 2020, 6:eaax1909.