Cell Adhesion and Integrin Mechanosensing *in silico*

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Biomechanics vs Mechanobiology

Biomechanics: The study of mechanical behavior and properties of living systems and biological structures.

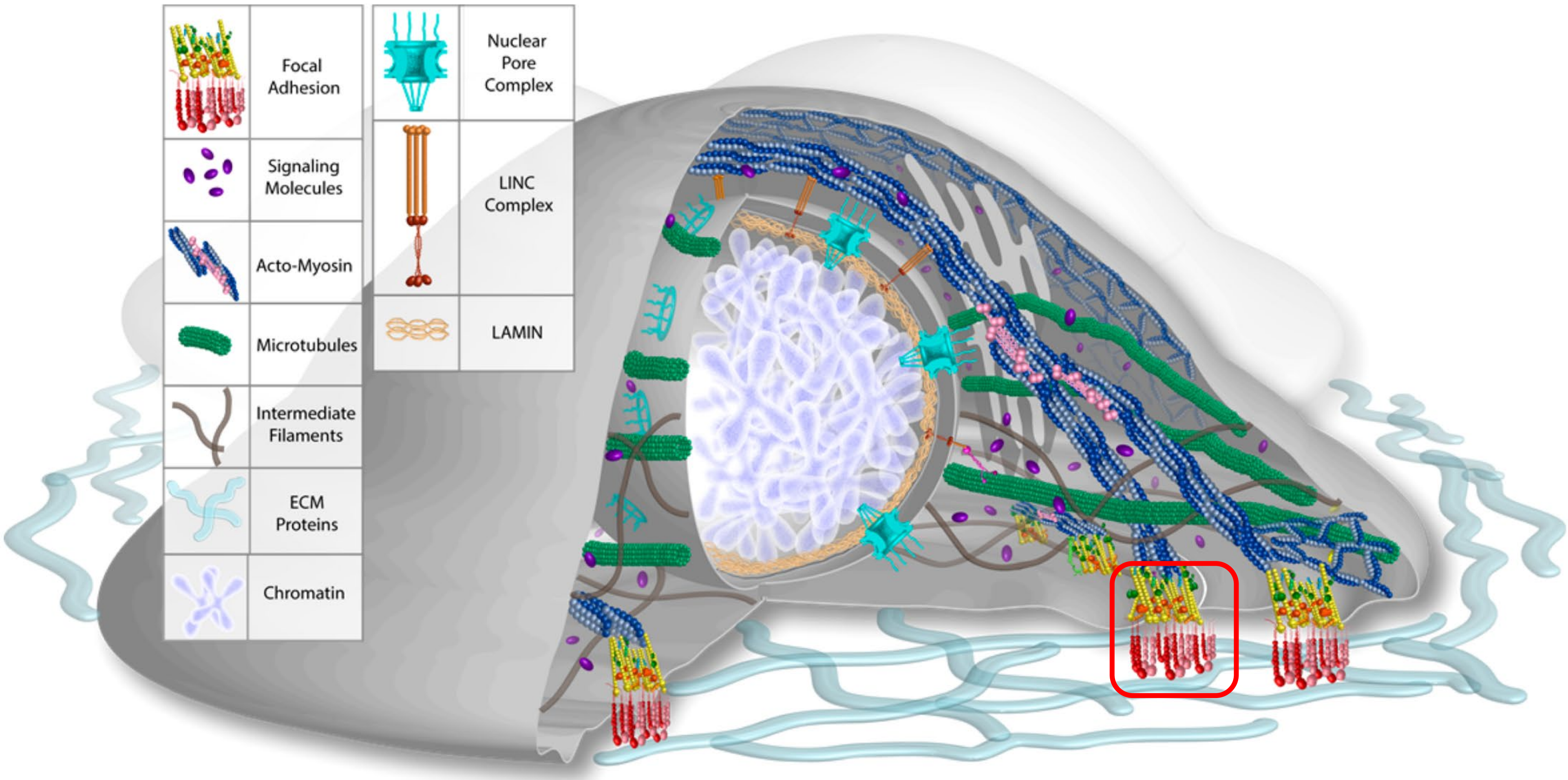
Mechanobiology: The study of how mechanics interacts with and governs the biological behavior of living systems and biological structures.

Biomechanics vs Mechanobiology

Biomechanics: Studying **bio**logy through the lens of **mechanics**.

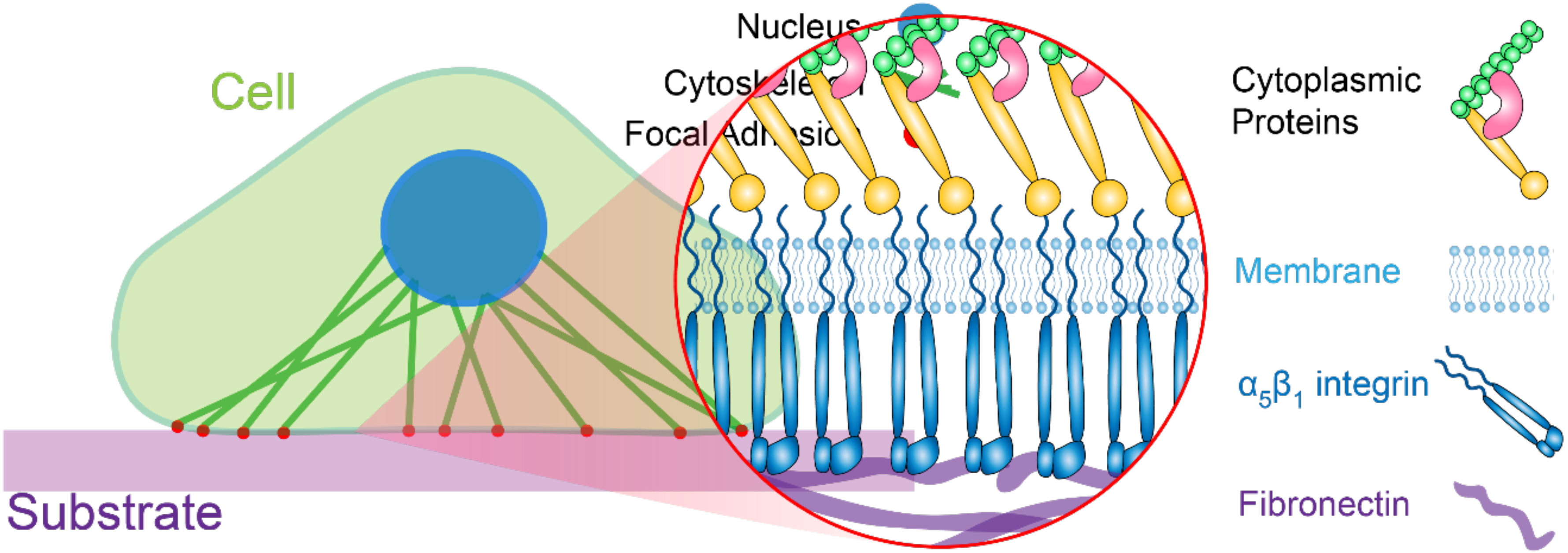
Mechanobiology: Studying how **mechanics** influences **biology**.

The mechanical system of the cell



Shams et al. *ACS Biomaterials Sci & Eng.* 2017.

Integrin is a cell adhesion molecule with an instrumental role in disease and cell biology



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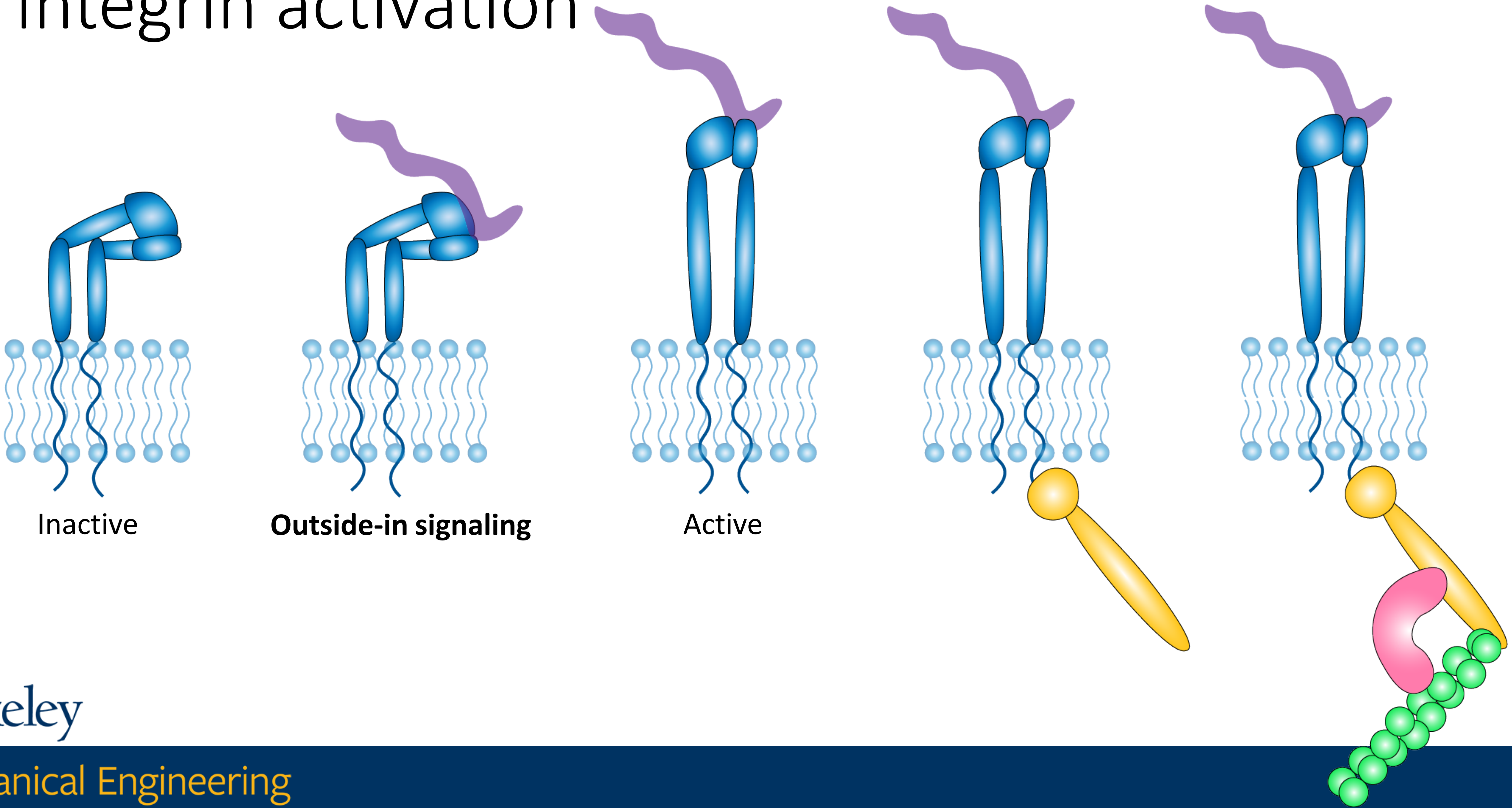
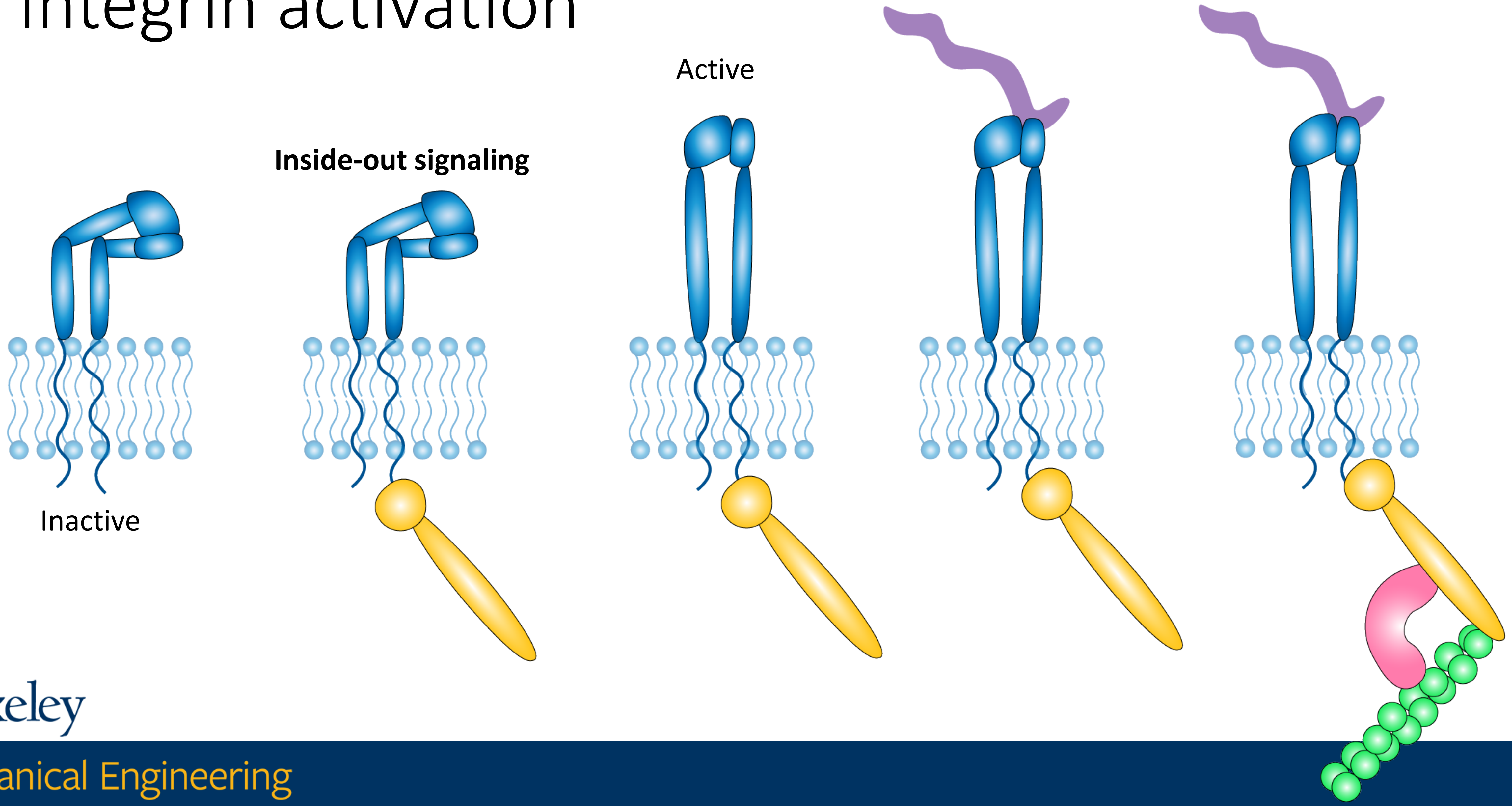
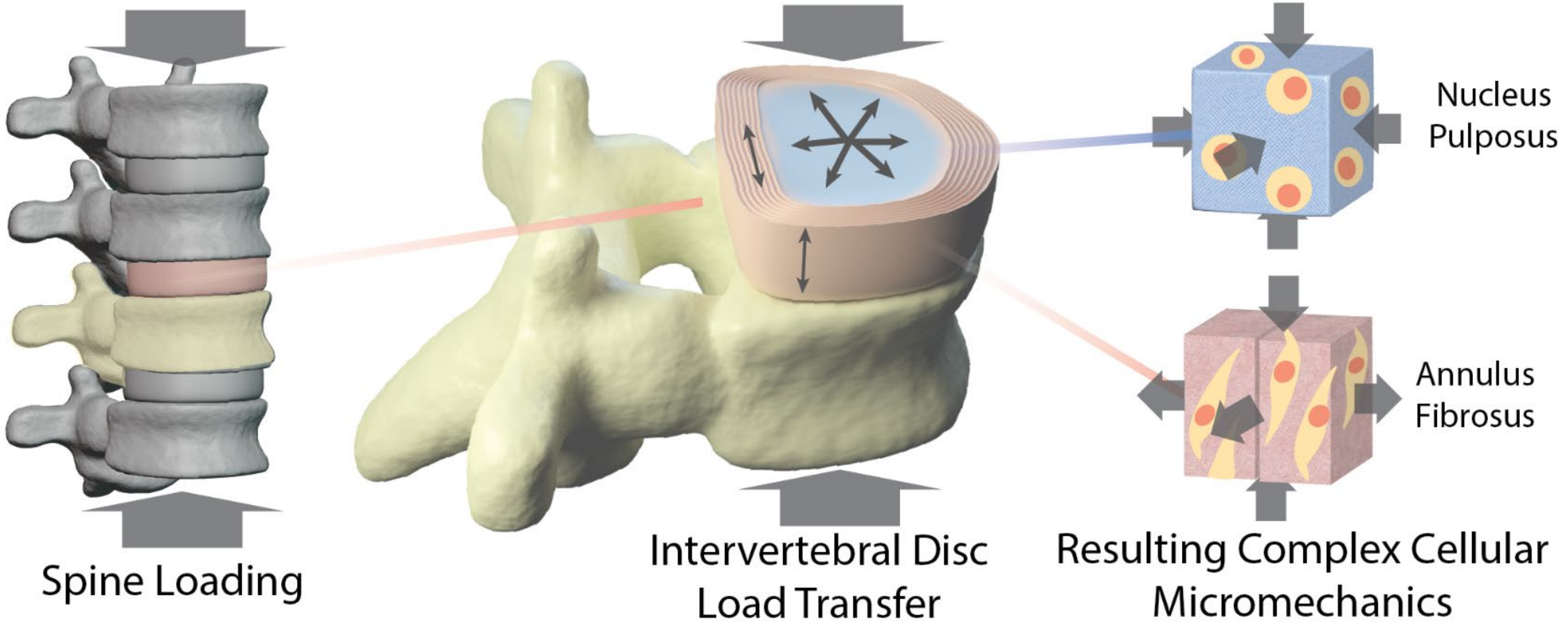
Integrin activation



Integrin activation

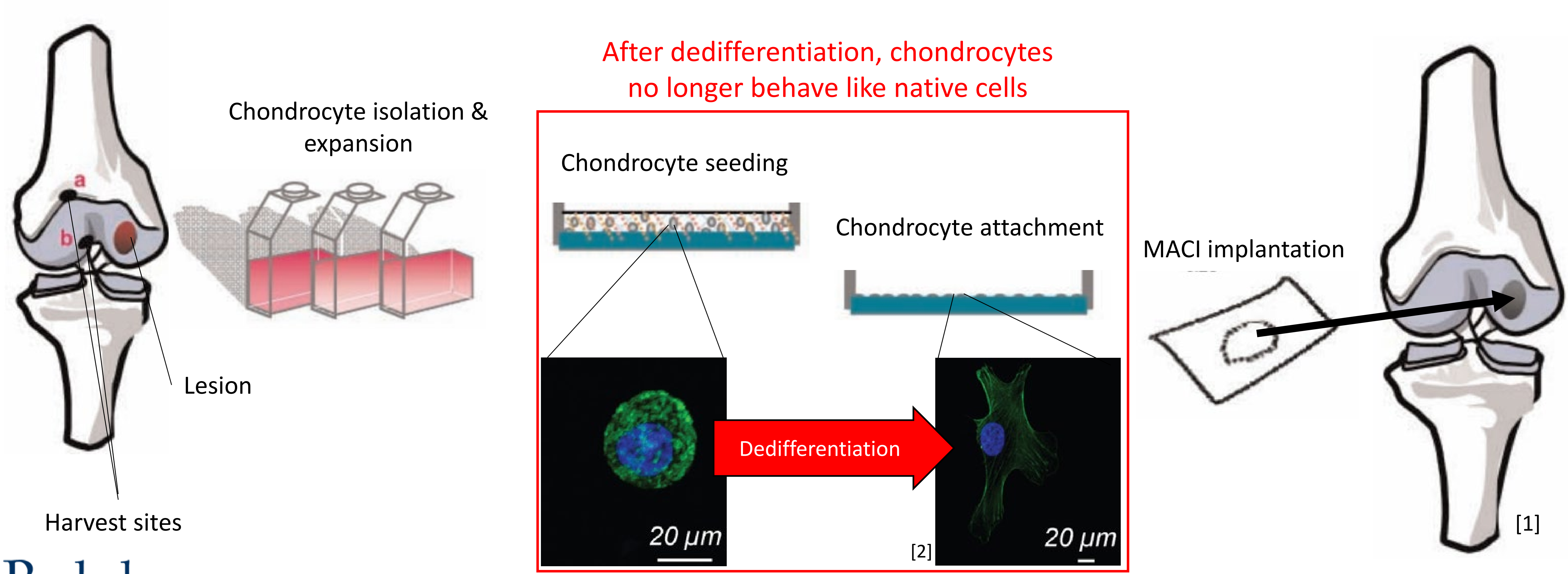


Integrin is a cell adhesion molecule with an instrumental role in disease and cell biology



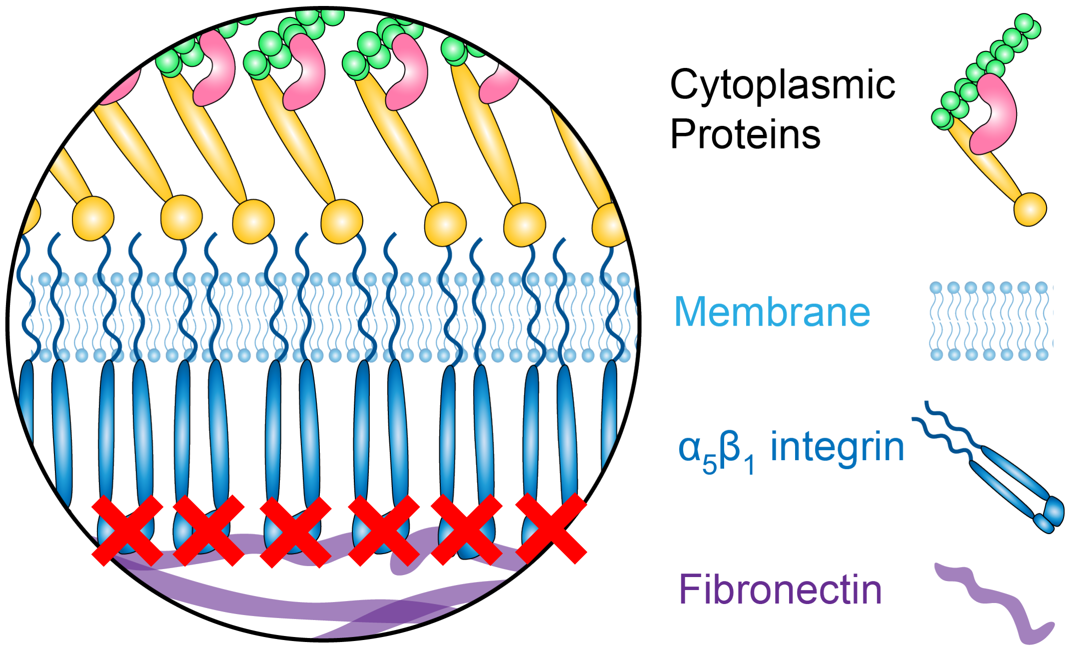
Jonathan McKinley. *Figure used with permission.*

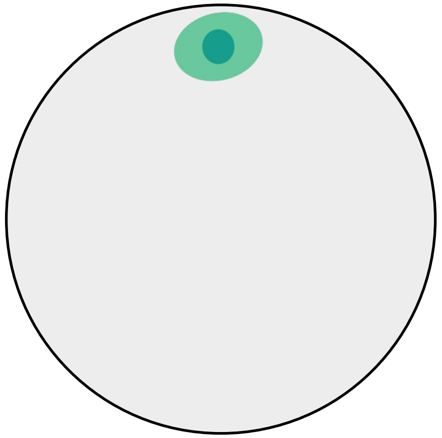
Integrin is a cell adhesion molecule with an instrumental role in disease and cell biology



[1] Brittberg M. *American Journal of Sports Medicine.* 2010. [2] Ghosh et al. *Biophysical Journal.* 2022.

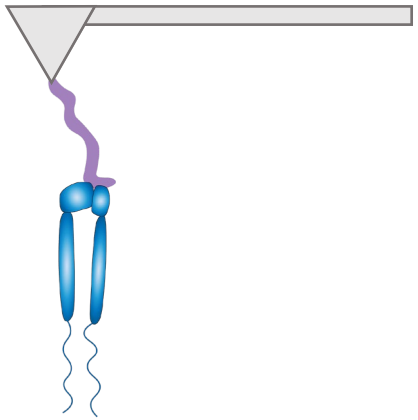
Integrin is a cell adhesion molecule with an instrumental role in disease and cell biology





↓ Cell Adhesion

Friedland et al. *Science.* 2009.



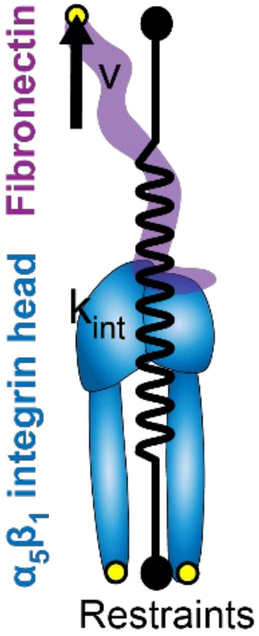
↓ Rupture Force

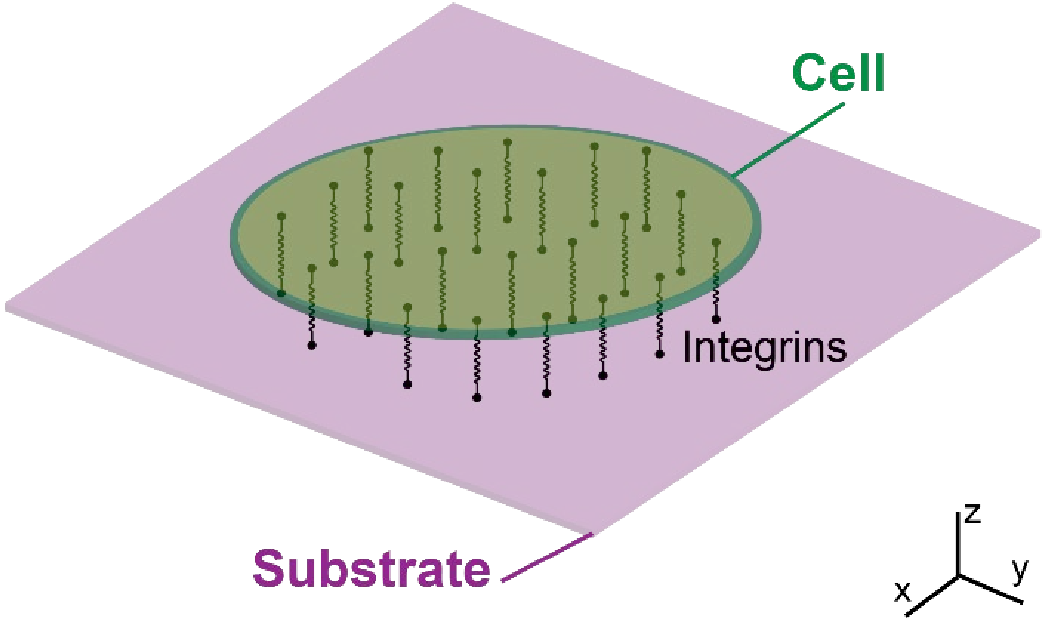
Li et al. *Biophysical.* 2002.

But how does disrupting $\alpha_5\beta_1$ integrin reduce cell adhesion?

What are the multiscale mechanics?

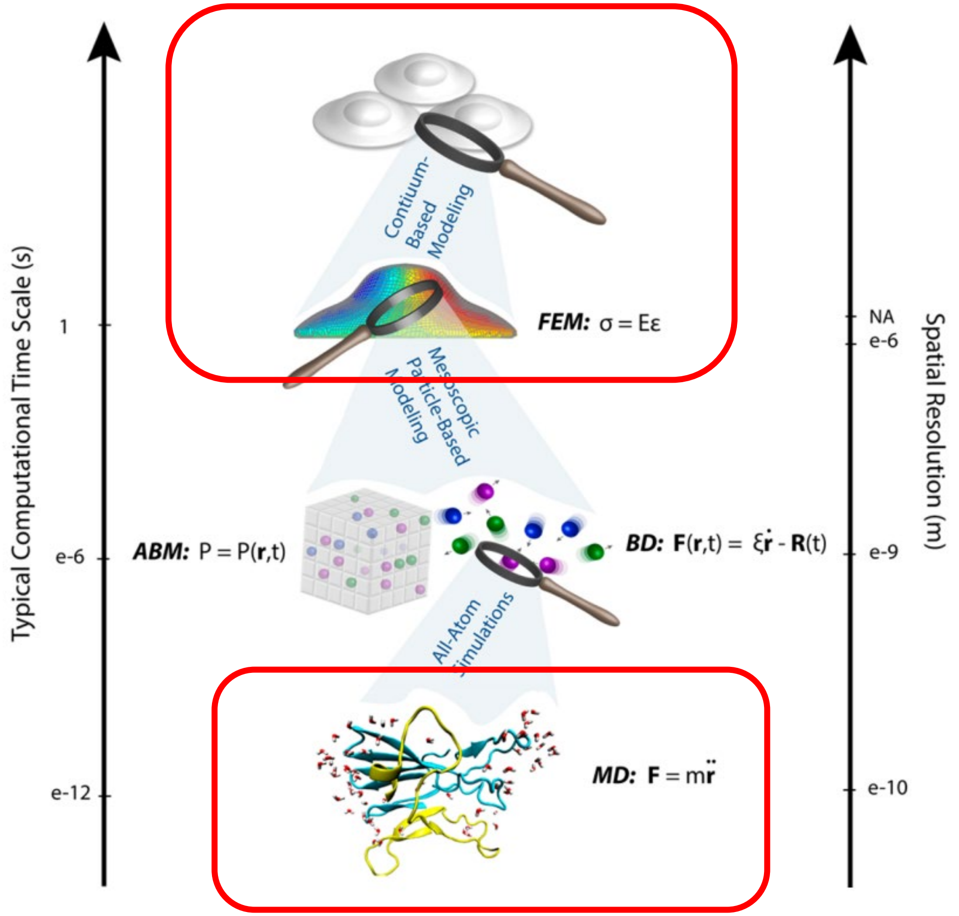
Multiscale model to link the nanomechanics of integrin to the whole-cell micromechanics





Tools we can use to investigate multiscale mechanics

Whole-cell model



Molecular model

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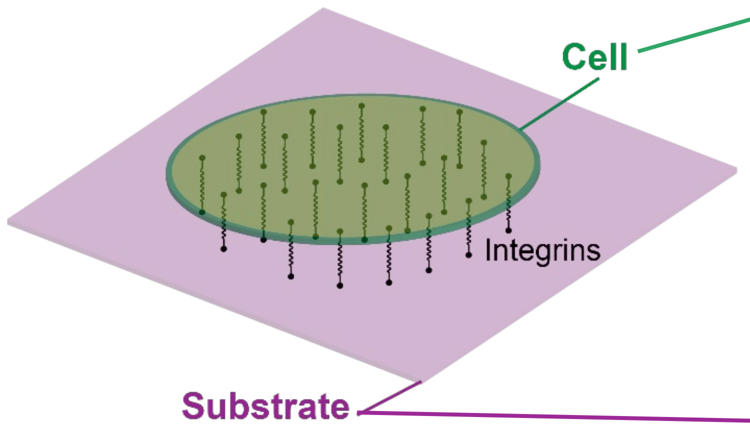
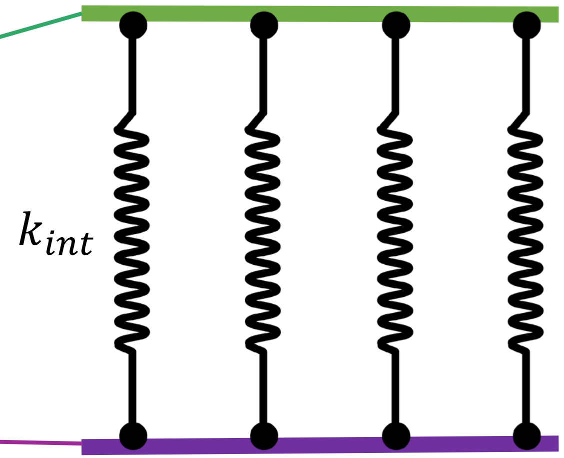
Shams et al. *ACS Biomaterials Sci & Eng.* 2017.

Whole-cell Finite Element Model





External Body Motion

$$\Sigma \boldsymbol{F} = \boldsymbol{f}_{\boldsymbol{ext}} + \nabla \boldsymbol{\sigma} = \rho \boldsymbol{a}$$

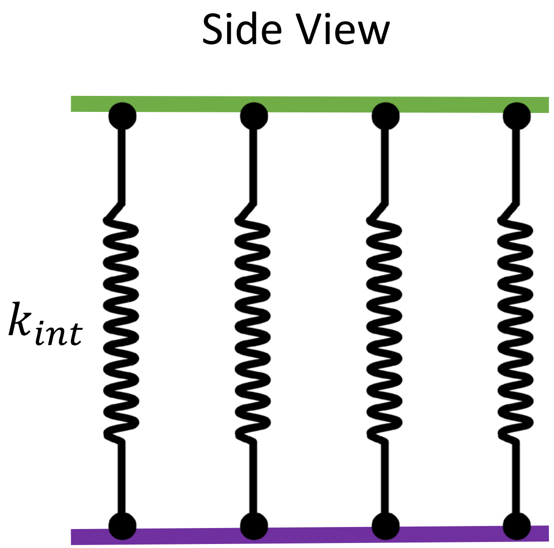
Cell: $\boldsymbol{f}_{\boldsymbol{int}} - \nabla\left(\boldsymbol{\sigma}_c^{pas} + \boldsymbol{\sigma}_c^{act}\right) = \rho_c \boldsymbol{a}_c$

Substrate: $\boldsymbol{f}_{\boldsymbol{int}} - \nabla \boldsymbol{\sigma}_s^{pas} = \rho_s \boldsymbol{a}_s$

Hooke's Law: $\boldsymbol{f}_{\boldsymbol{int}} = N_{int} k_{int} \boldsymbol{u}_{\boldsymbol{int}}$

$$\boldsymbol{f}_{\boldsymbol{int}} = C N_{max} k_{int} \boldsymbol{u}_{\boldsymbol{int}}$$

Whole-cell Finite Element Model



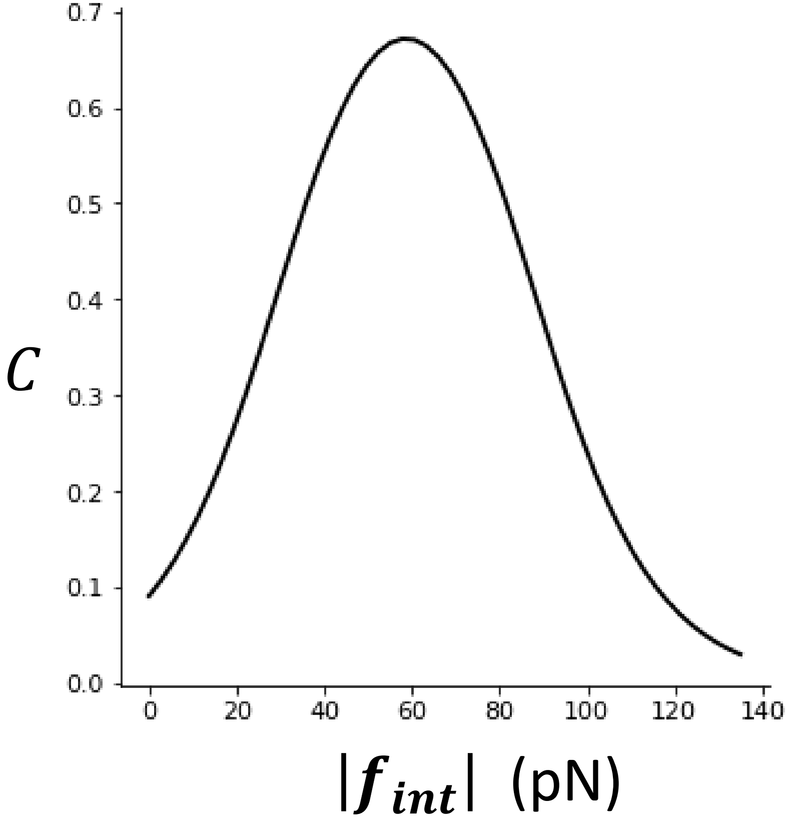
$$\boldsymbol{f}_{\boldsymbol{int}} = C N_{max} k_{int} \boldsymbol{u}_{\boldsymbol{int}}$$

$$C_{t+\Delta t} = C\left(1 - K_{off}\Delta t\right) + K_{on}\Delta t(1 - C)$$

$$K_{off} = K_a e^{\frac{|\boldsymbol{f}_{\boldsymbol{int}}|}{F_a}} + K_b e^{\frac{-|\boldsymbol{f}_{\boldsymbol{int}}|}{F_b}}$$

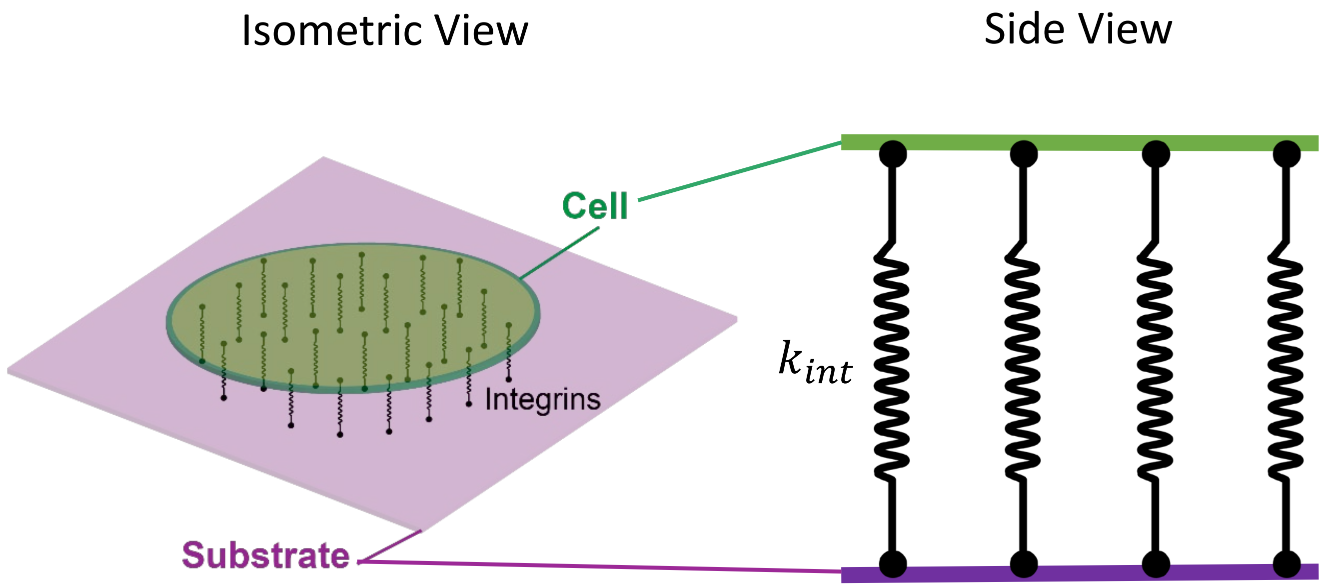
K_a : 0.004 s^{-1} [2]
K_b : 10 s^{-1} [2]
F_a : 15 pN [2]
F_b : 15 pN [2]

K_{on} : 0.002 s^{-1} [1]
Δt : 0.01s

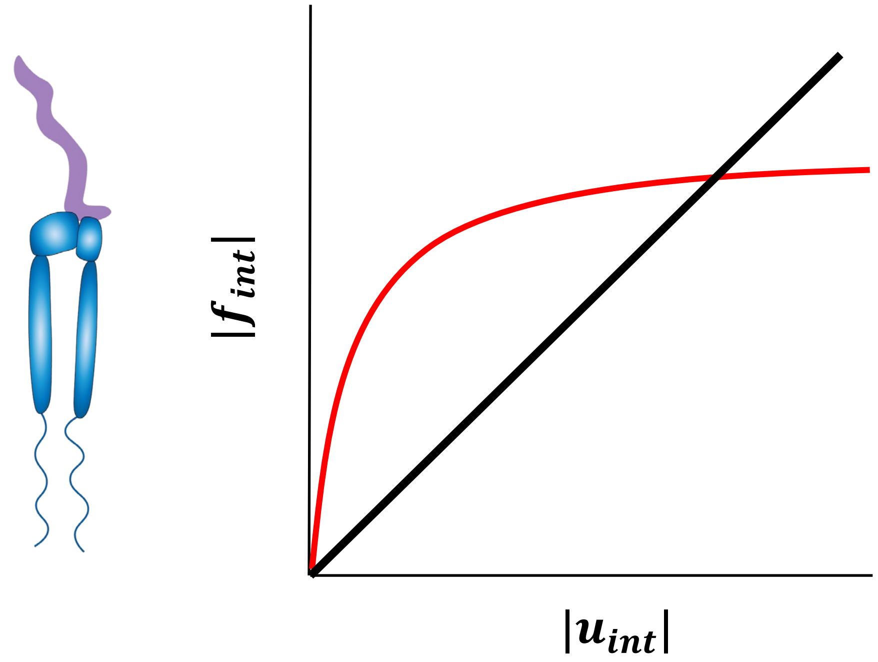


Bell GI. *Science*. 1978.

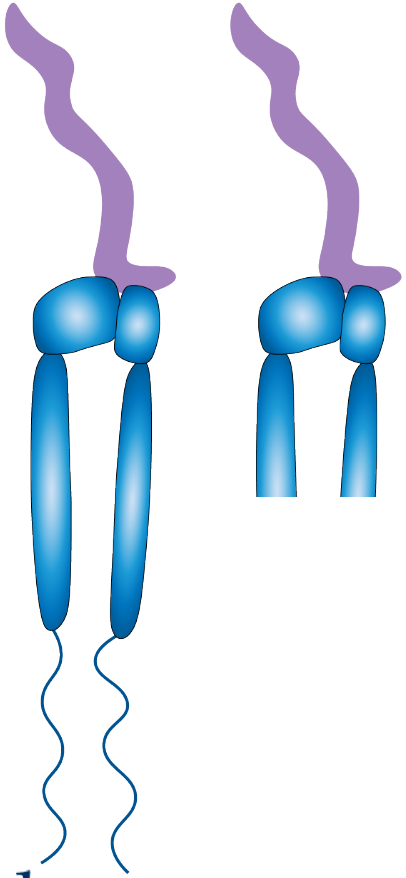
Multiscale Coupling

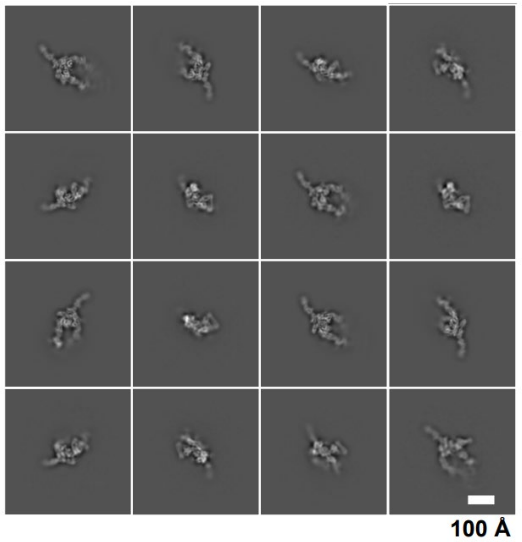


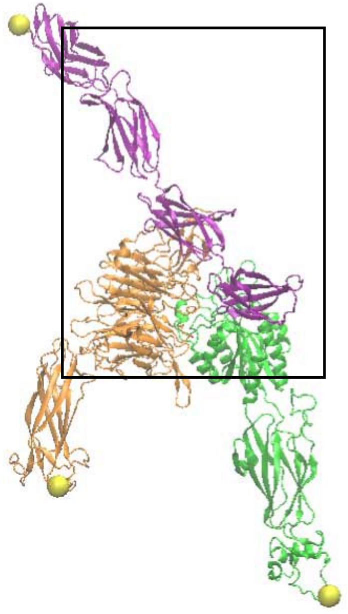
$$\boldsymbol{f}_{\boldsymbol{int}} = C N_{max} k_{int} \boldsymbol{u}_{\boldsymbol{int}}$$

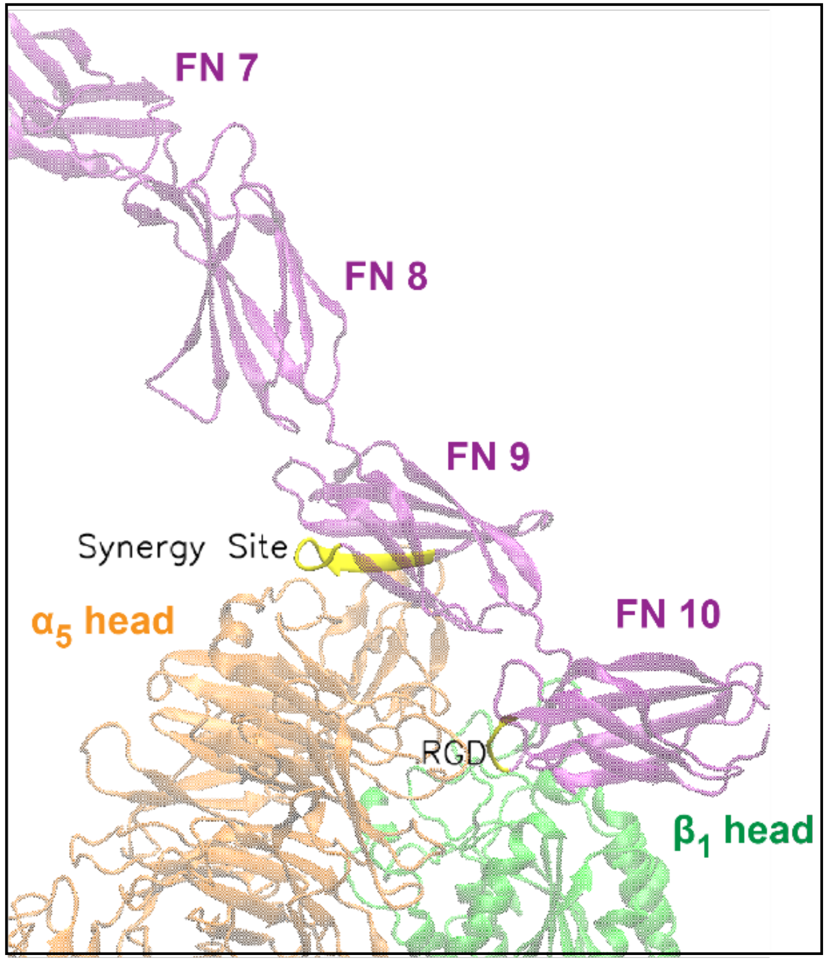


$\alpha_5\beta_1$ integrin-fibronectin structure







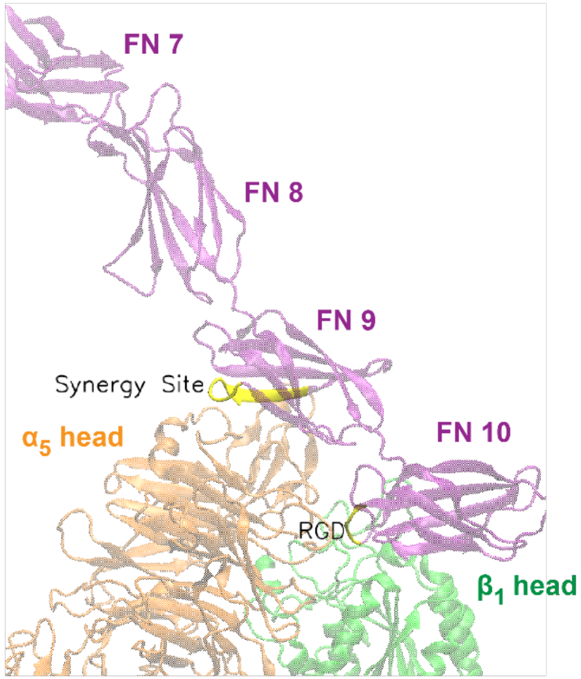


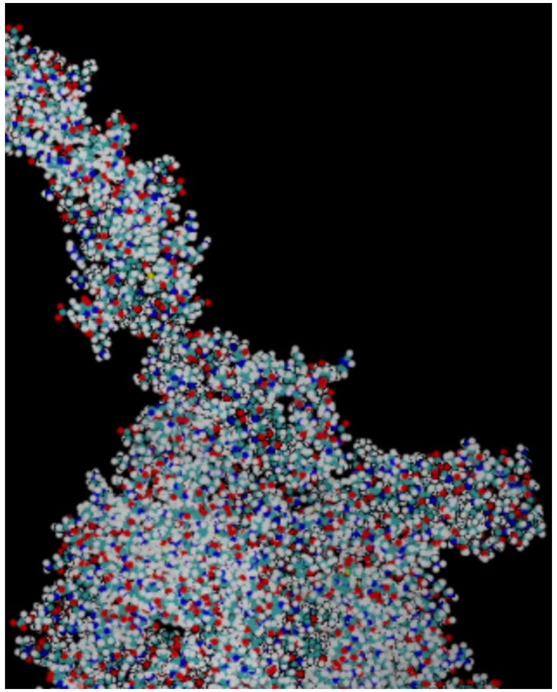
Molecular Dynamics

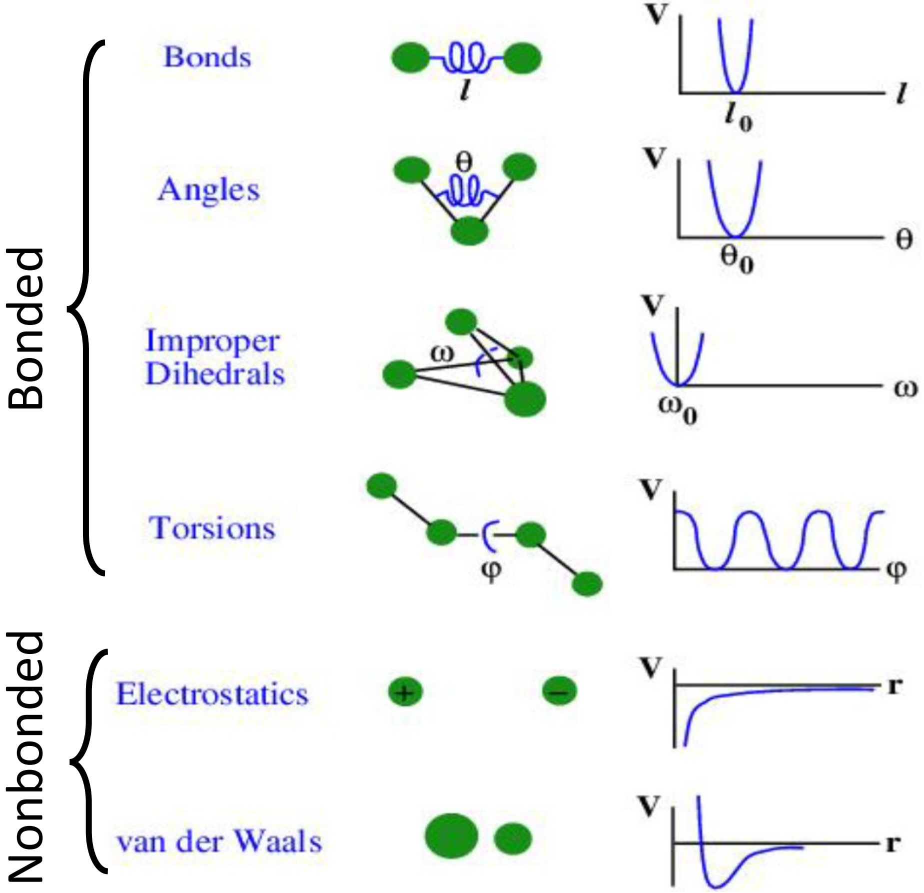
1. Initialize

Positions: $\boldsymbol{r}^N = (\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots \boldsymbol{r}_N)$

Potentials: $V(\boldsymbol{r}^N) = V_{bonded} + V_{nonbonded}$







bioinformatics.niaid.nih.gov/cmm/intro_simulation/intro_simulation.pdf

Molecular Dynamics

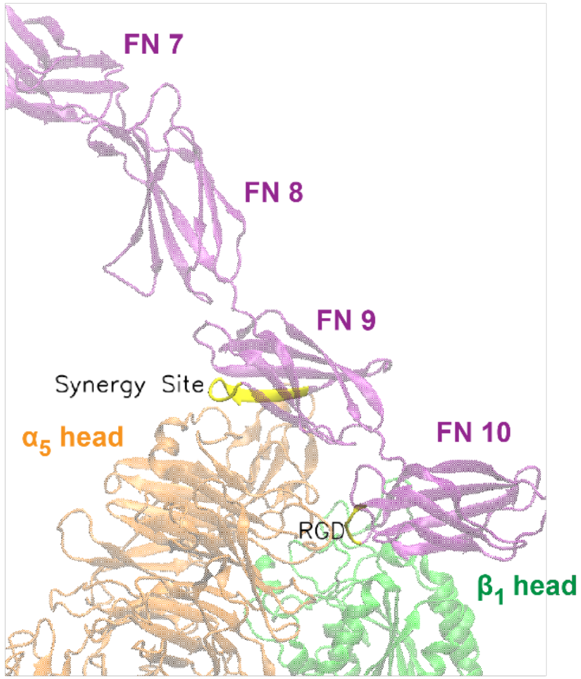
1. Initialize

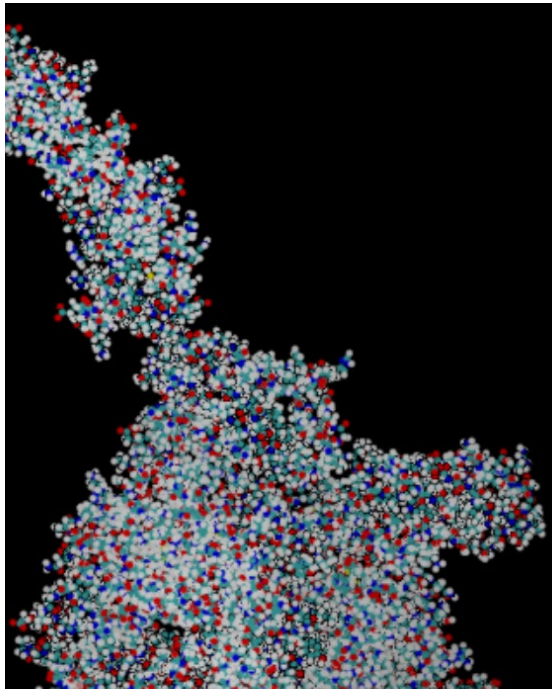
Positions: $\boldsymbol{r}^N = (\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots \boldsymbol{r}_N)$

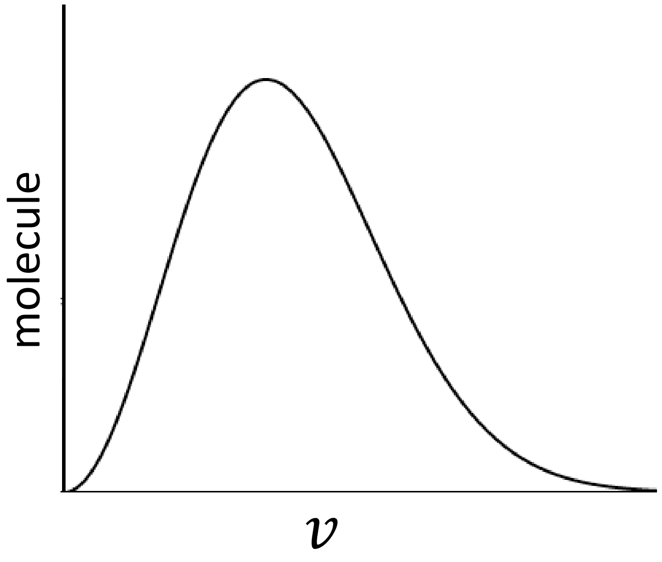
Potentials: $V(\boldsymbol{r}^N) = V_{bonded} + V_{nonbonded}$

Velocities: $\boldsymbol{v}^N = (\boldsymbol{v}_1, \boldsymbol{v}_2, \ldots \boldsymbol{v}_N)$

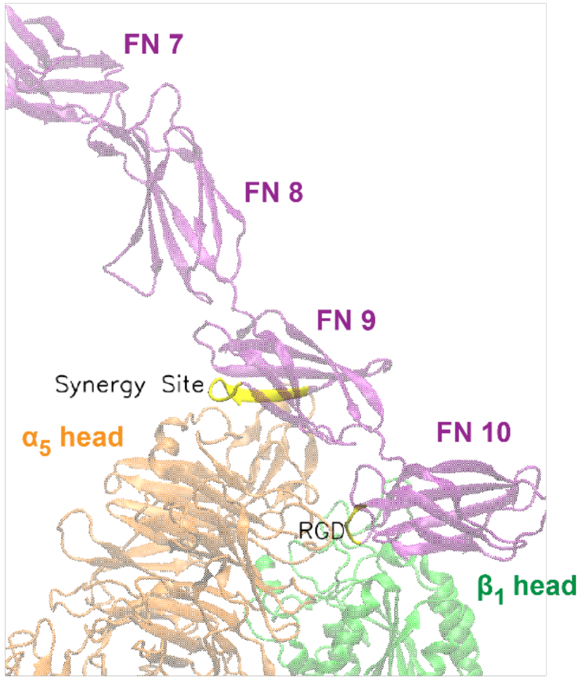
$$p(v_i) = \sqrt{\frac{m_i}{2\pi kT}} \exp\left(-\frac{m_i v_i^2}{2kT}\right)$$

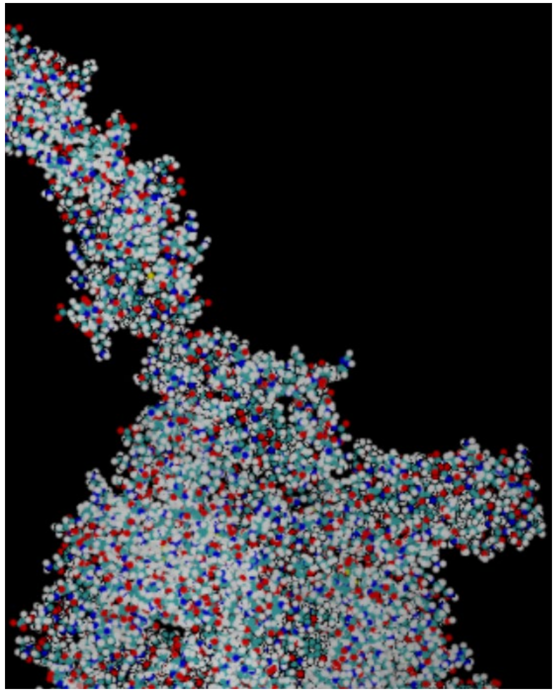






Molecular Dynamics





2. Compute forces & energies

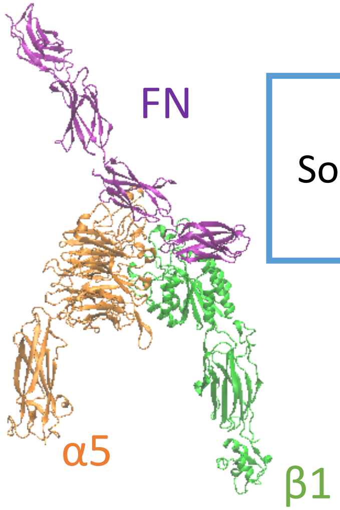
$$\boldsymbol{F}_i = -\frac{\partial V}{\partial \boldsymbol{r}_i}$$

3. Update positions & velocities

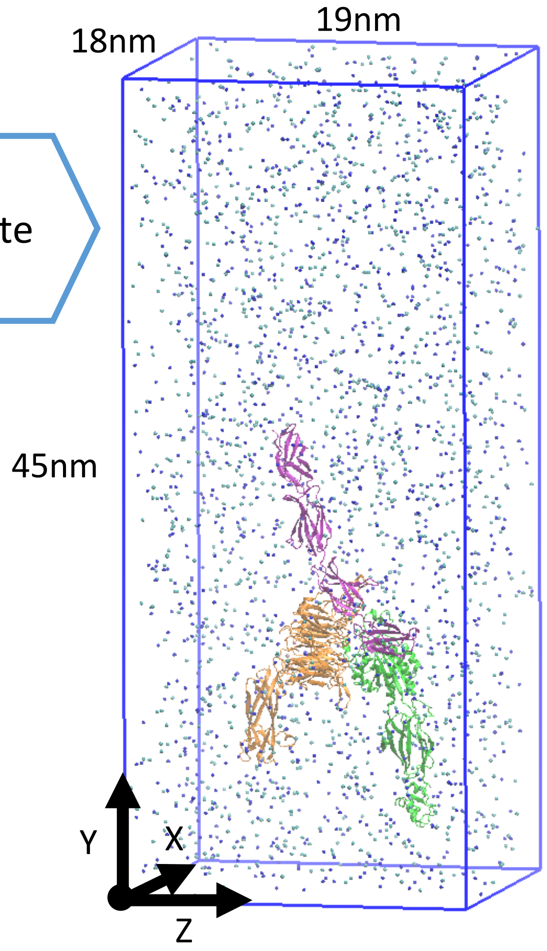
$$\frac{d^2\boldsymbol{r}_i}{dt^2} = \frac{\boldsymbol{F}_i}{m_i} \qquad \frac{d\boldsymbol{r}_i}{dt} = \boldsymbol{v}_i \qquad \frac{d\boldsymbol{v}_i}{dt} = \frac{\boldsymbol{F}_i}{m_i}$$

4. Output trajectory

Molecular Dynamics Workflow

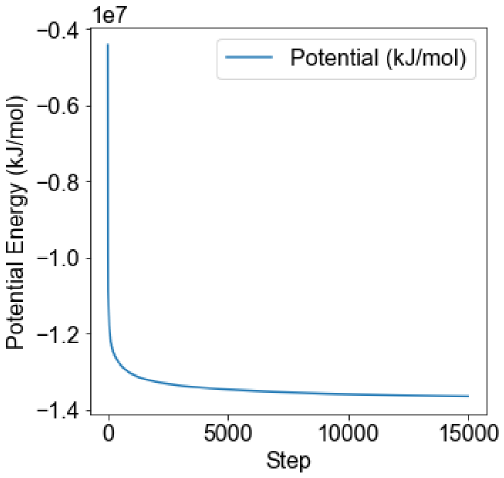


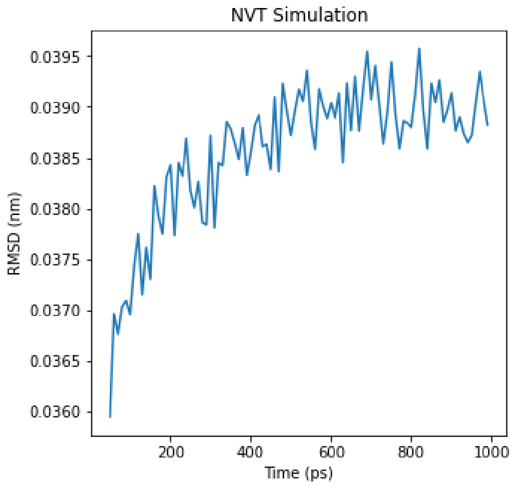
Solvate

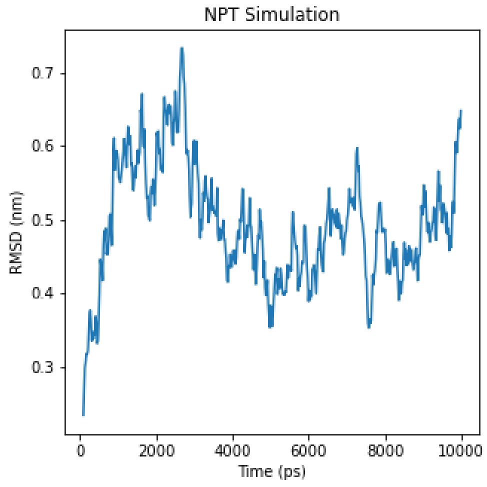


1.5M atoms

Minimization → NVT Equilibration → NPT Equilibration



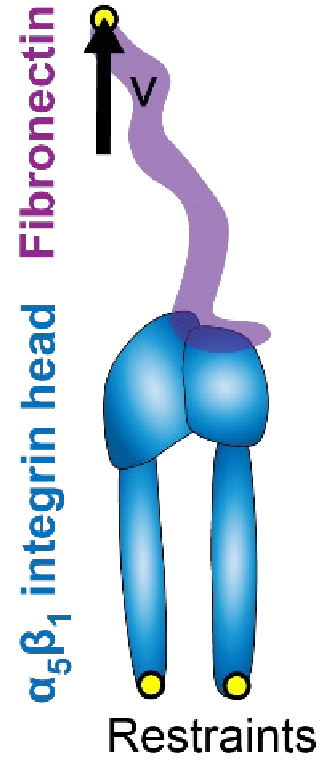


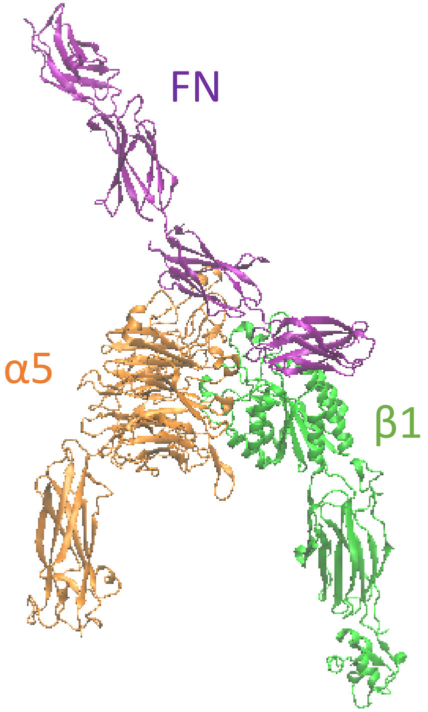


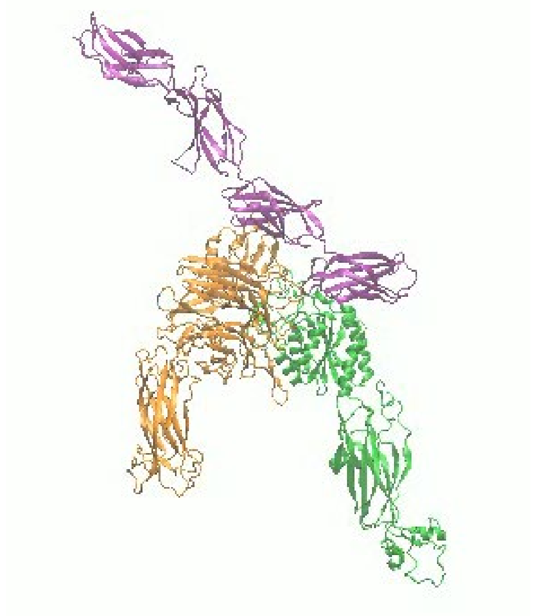
$$RMSD = \sqrt{\frac{1}{M}\sum_{i=1}^{N} m_i \| r_i(t_1) - r_i(t_2) \|^2}$$

N: Atoms P: Pressure
V: Volume T: Temperature

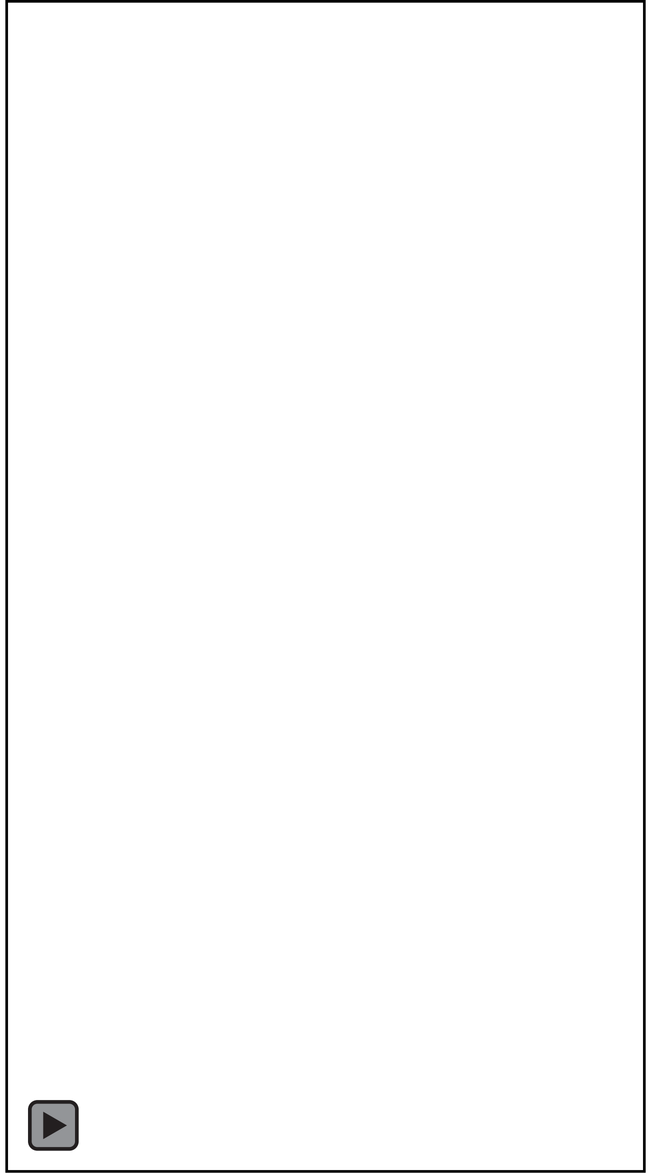
Molecular Dynamics





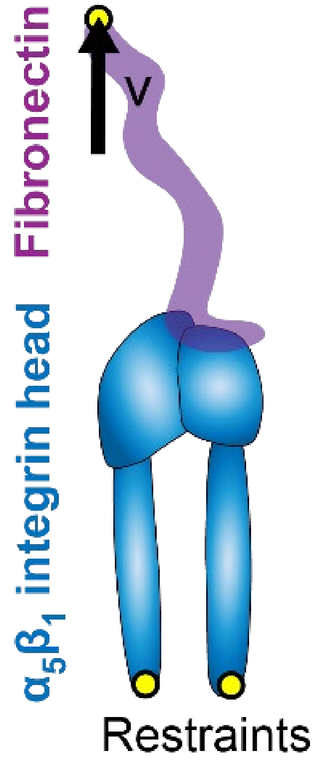


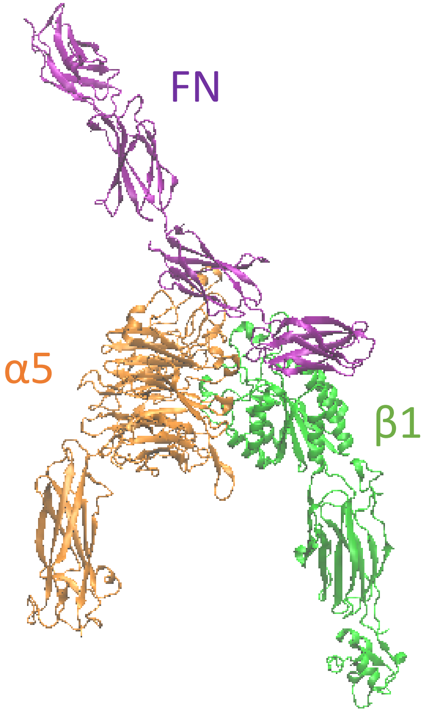
1 nm/ns

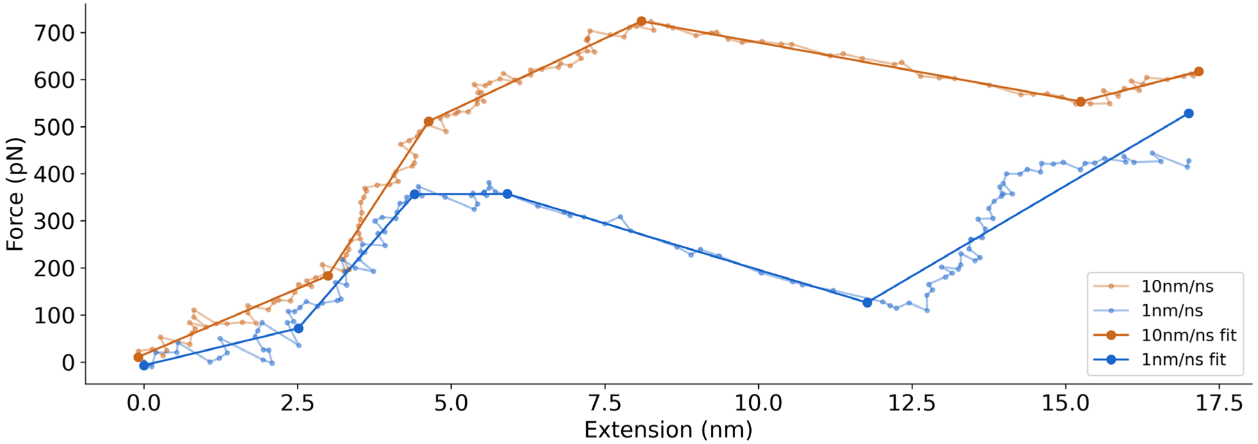


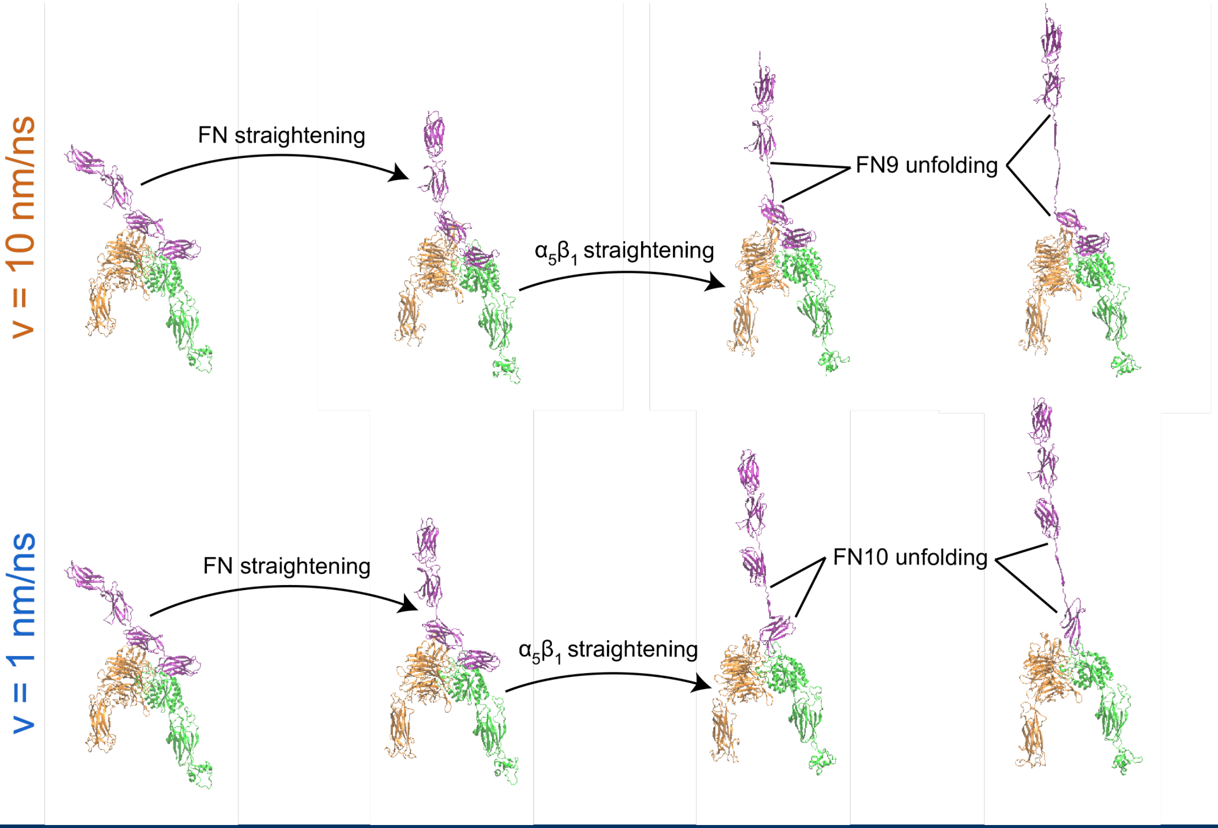
10 nm/ns

Molecular Dynamics



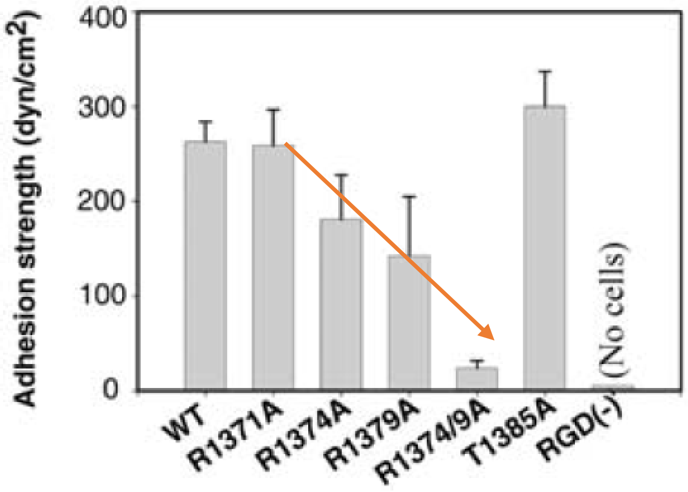




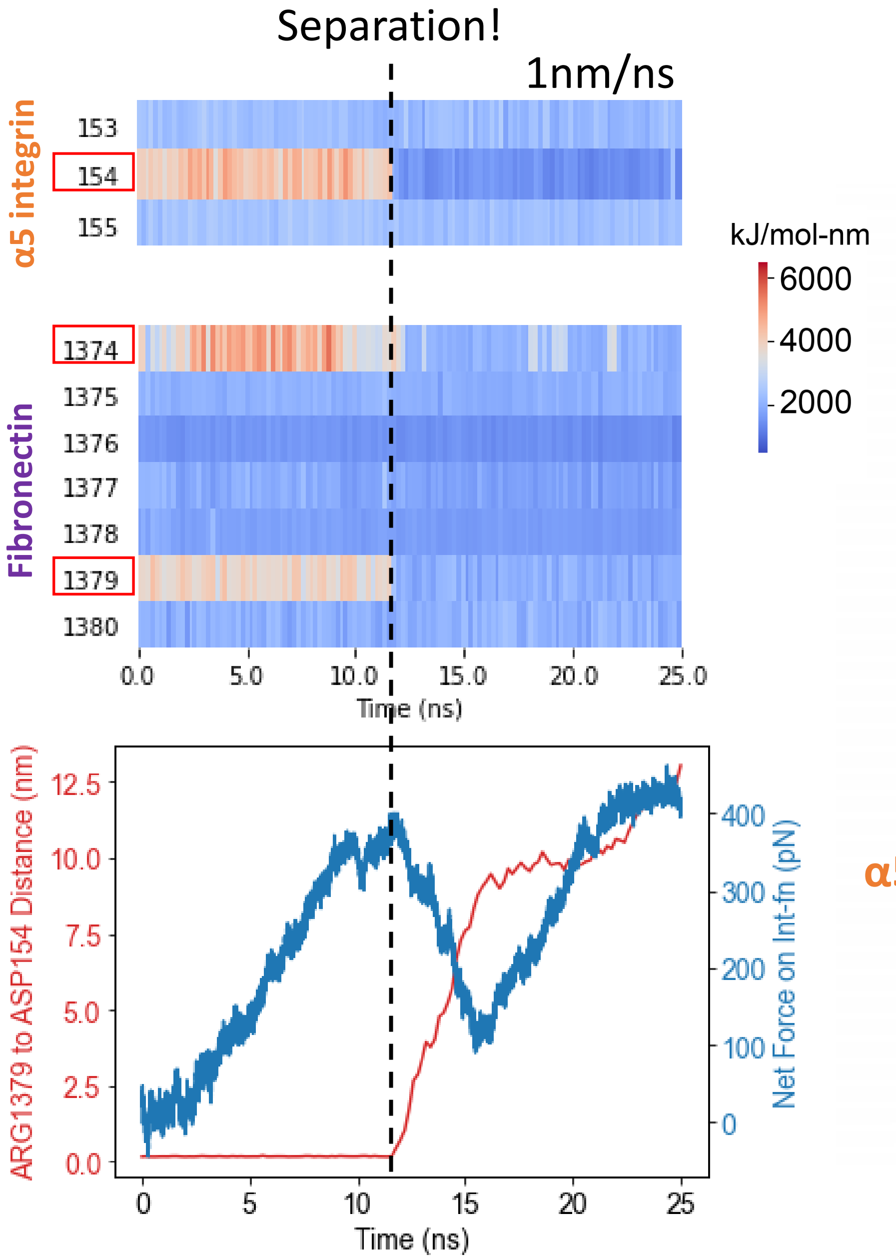


Individual amino acid interactions confirms key adhesion mediators

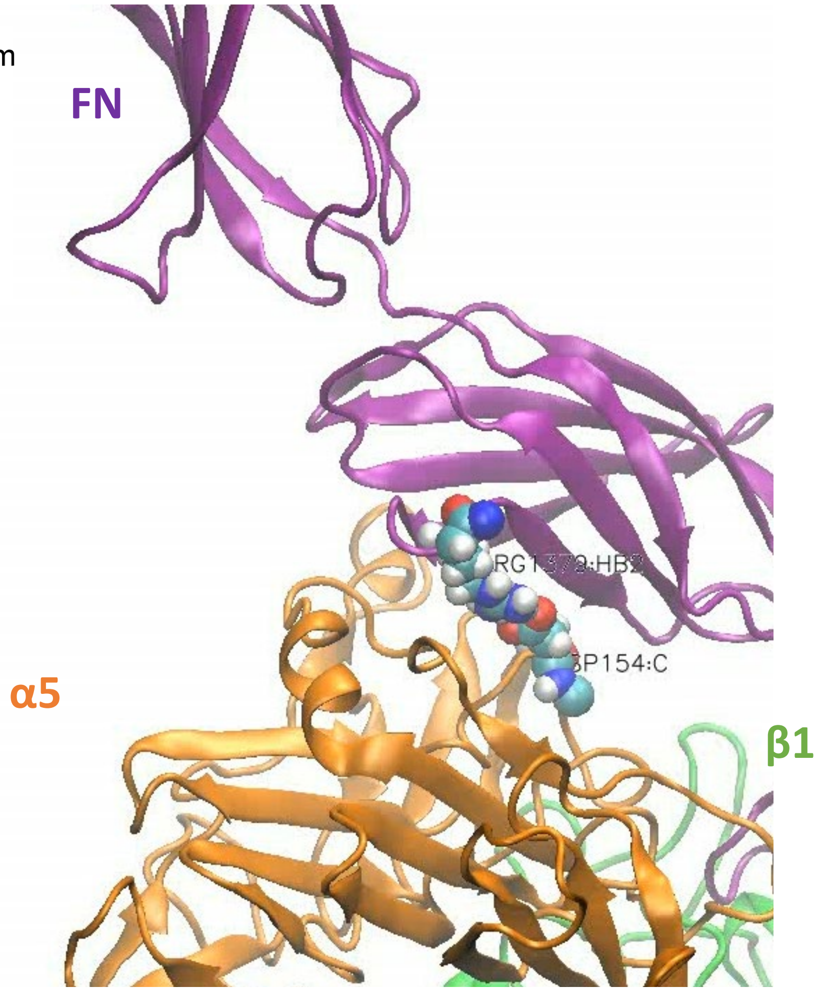
Mutation of 1379 reduces cell adhesion strength per spinning disk assay



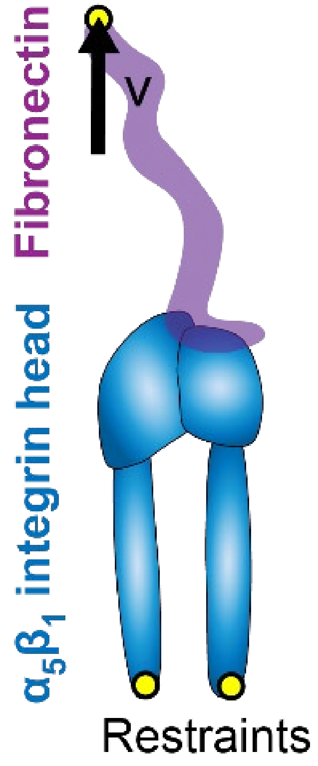
Friedland et al. *Science.* 2009.

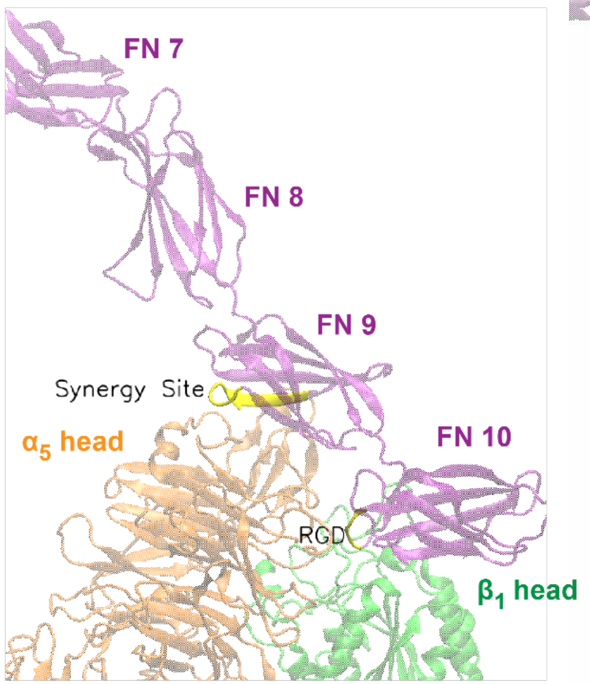


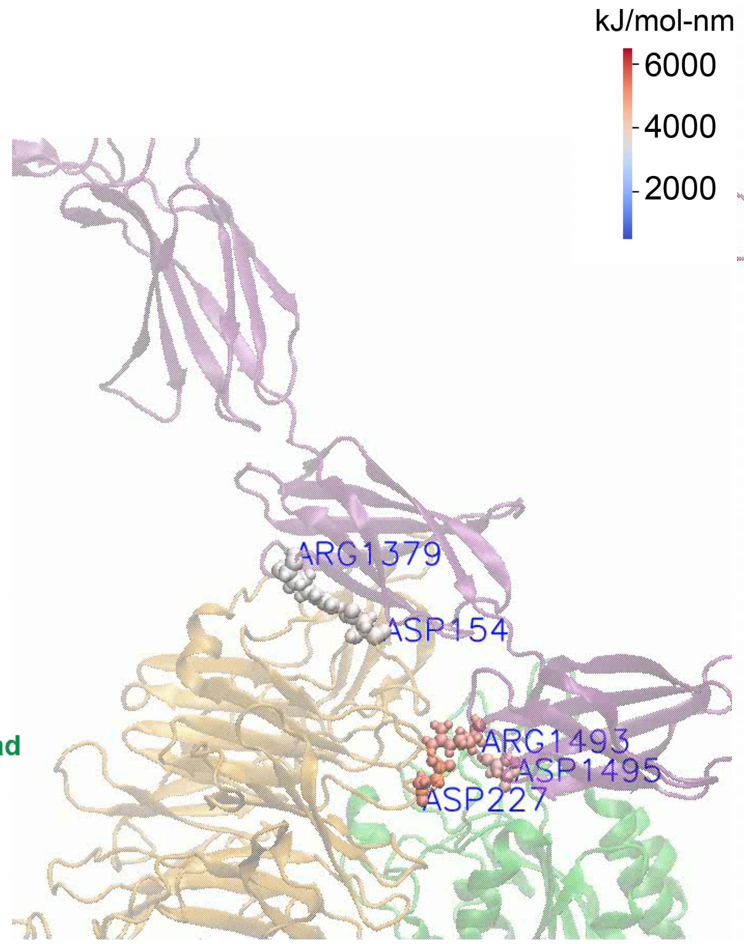
Movie shows moment of separation



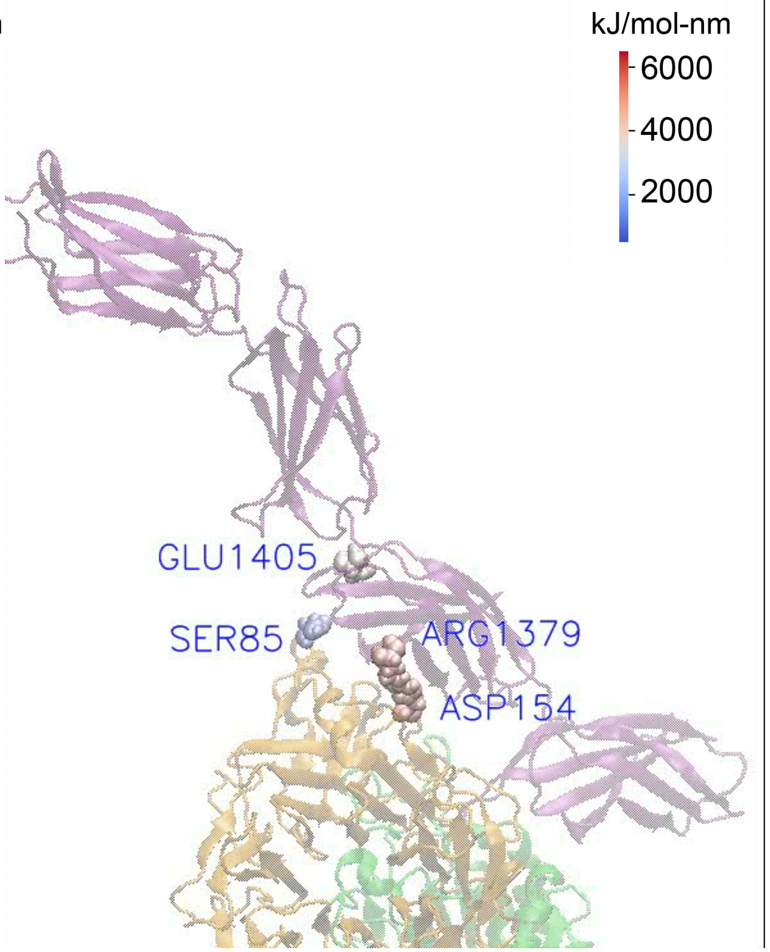
Individual amino acid interactions confirms key adhesion mediators





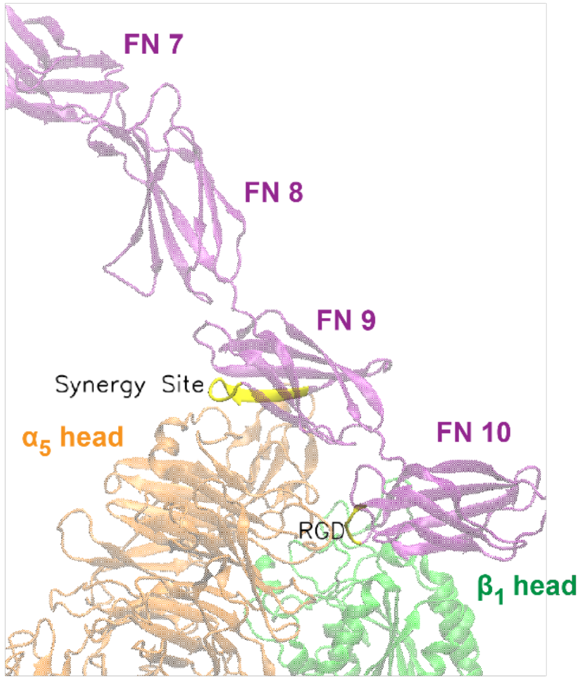


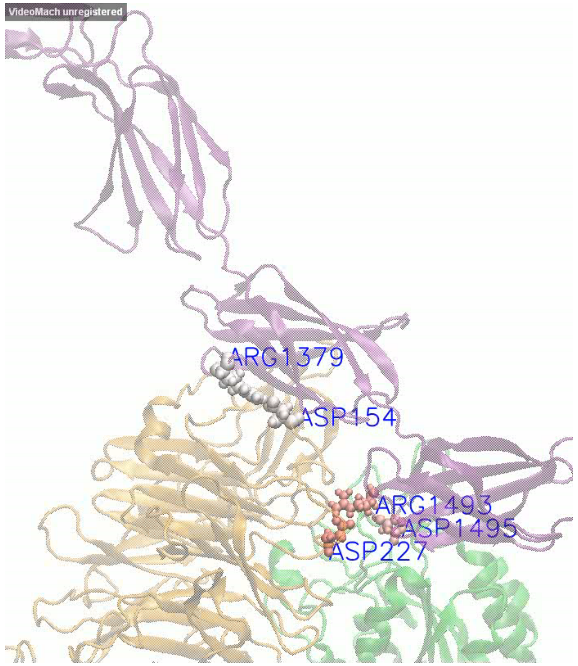
1 nm/ns

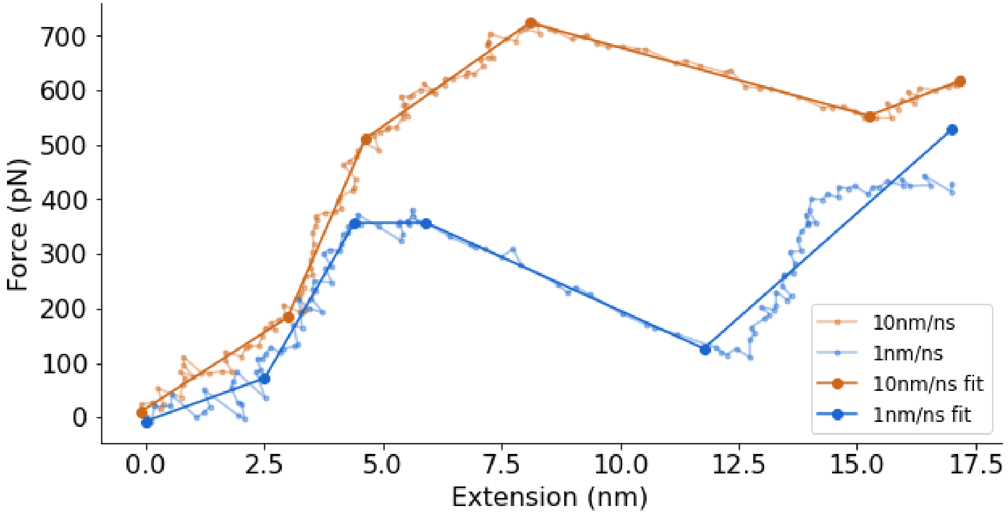


10 nm/ns

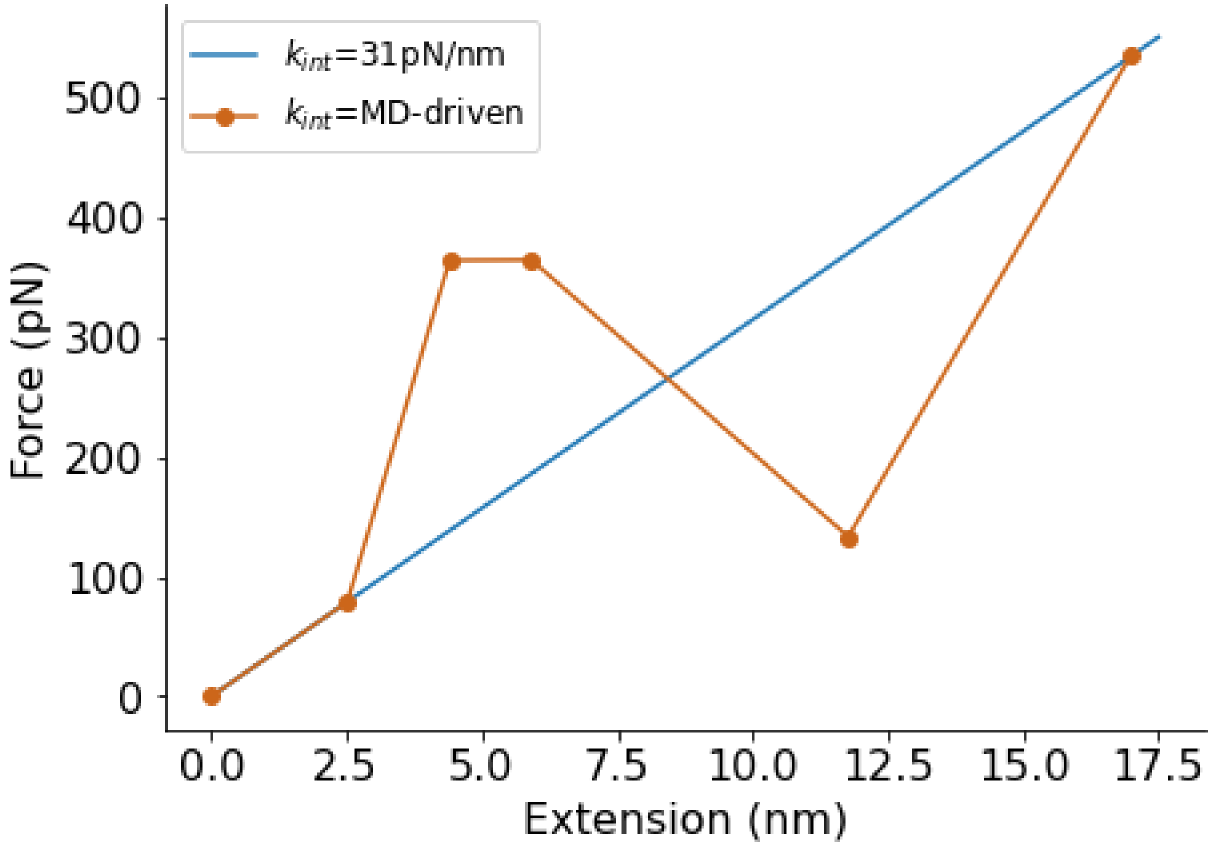
Amino acid interactions at synergy site contribute to the nonlinear force-extension behavior of $\alpha_5\beta_1$-FN

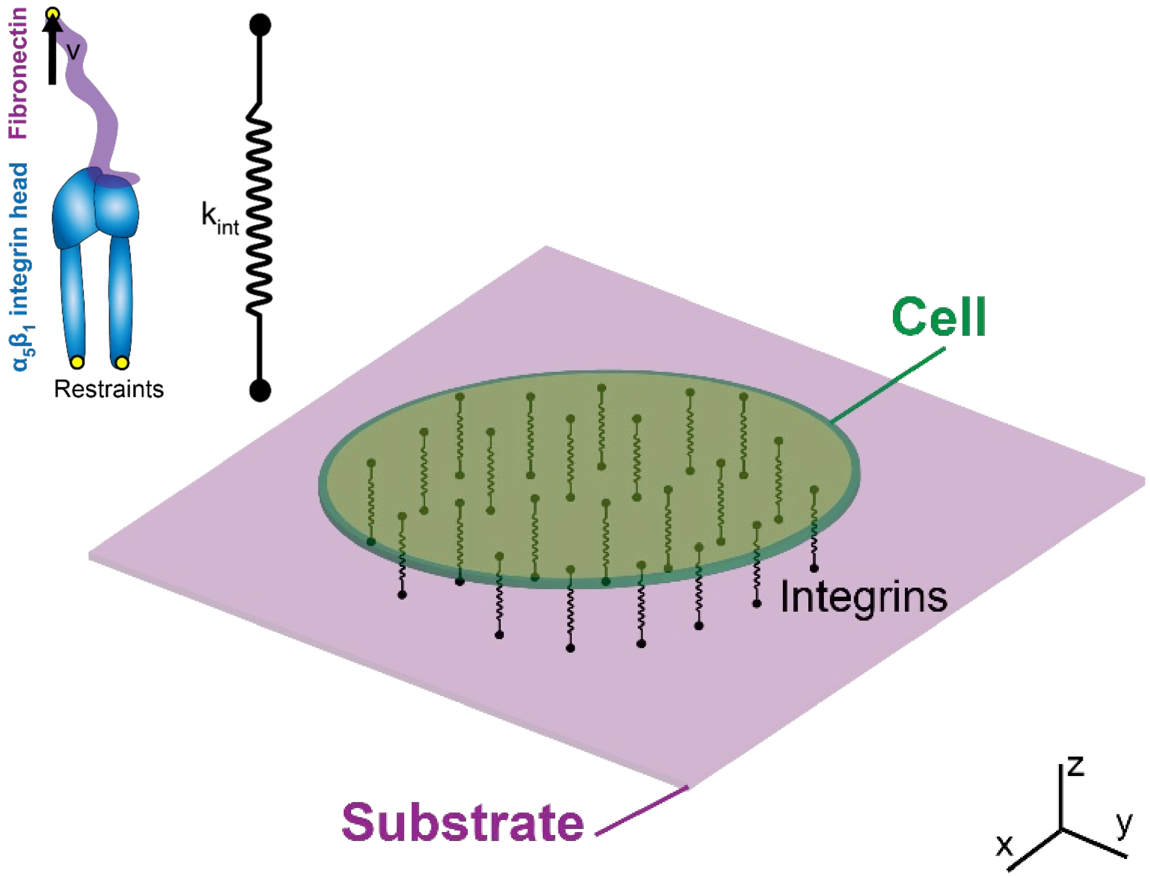




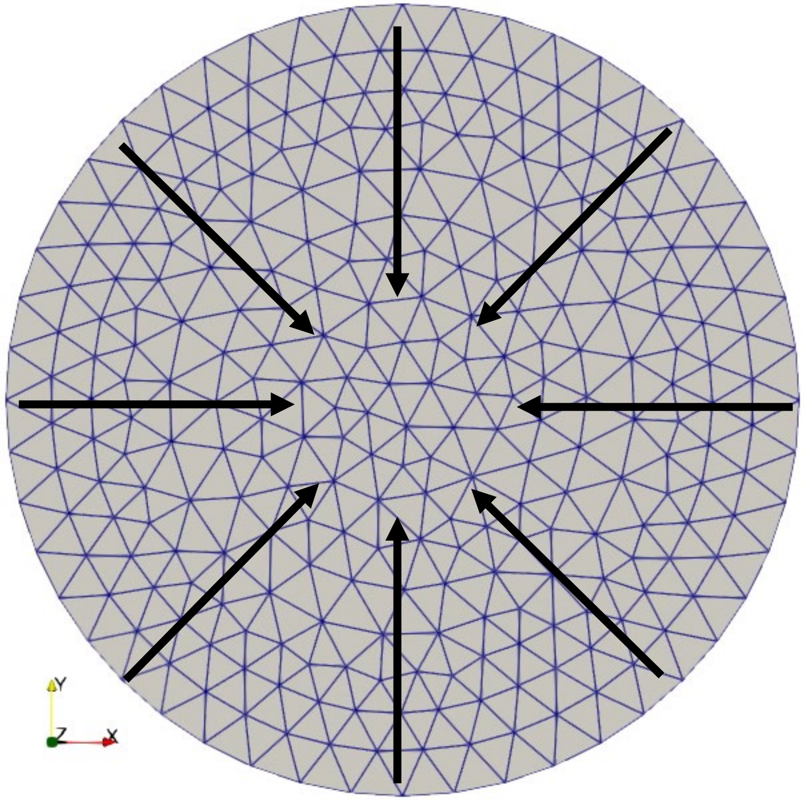


Multiscale coupling



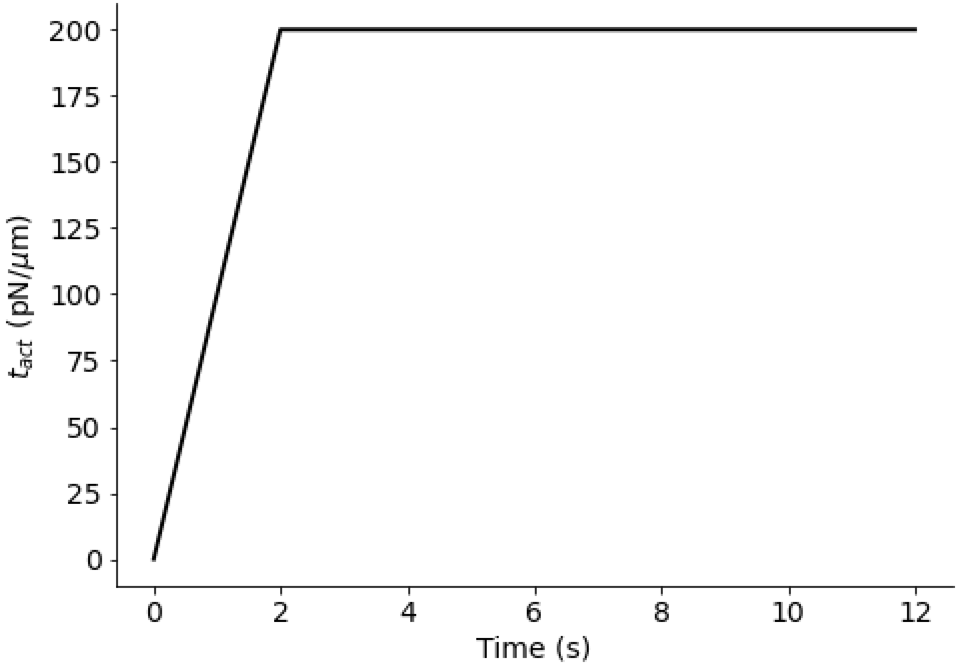


Isotropic cell contractility

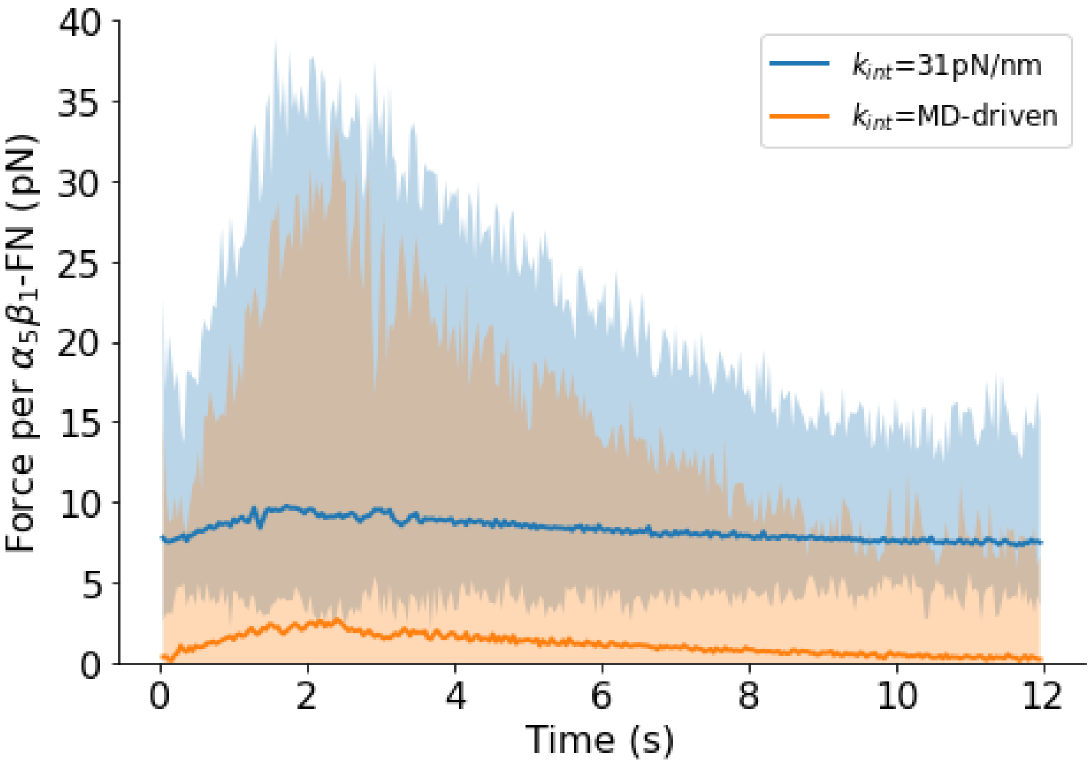


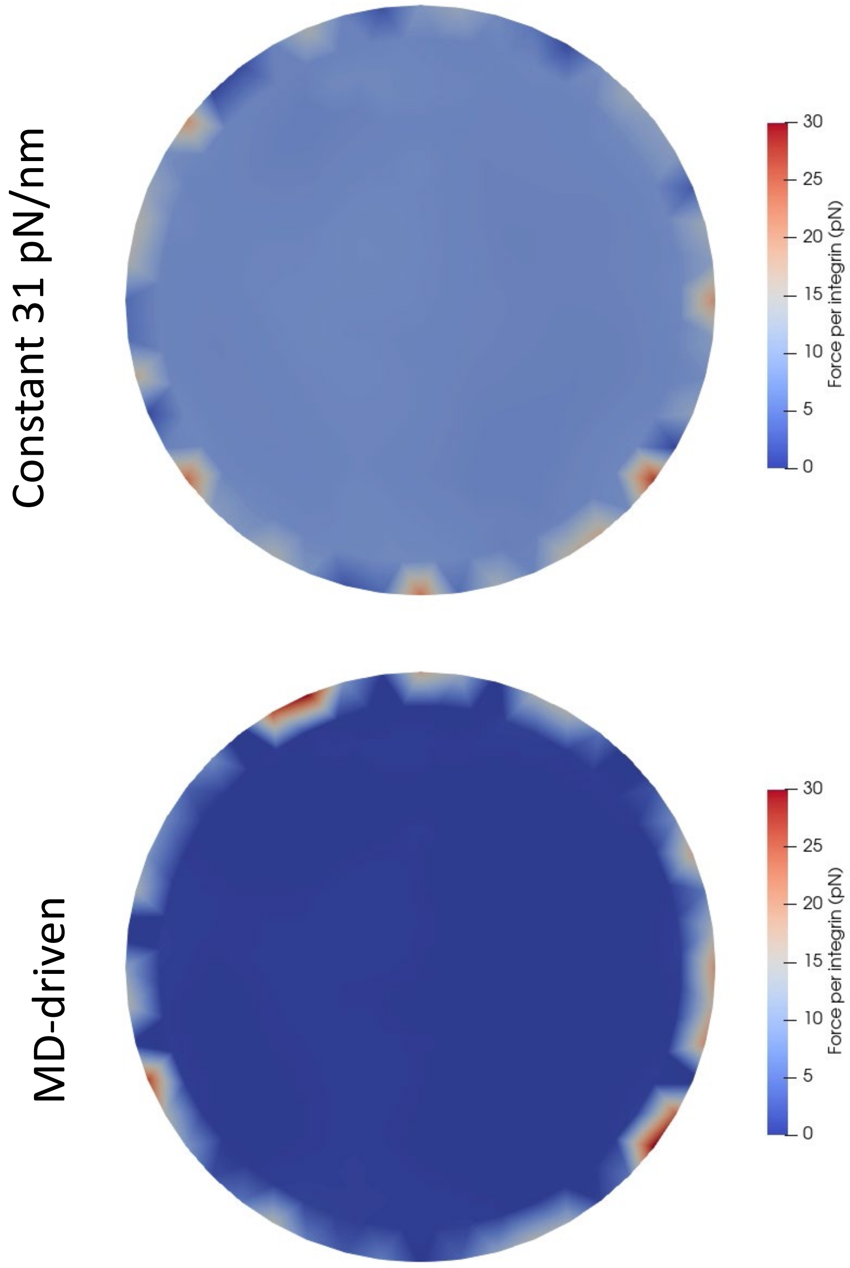
$$\boldsymbol{f}_{\boldsymbol{int}} - \nabla\left(\boldsymbol{\sigma}_c^{pas} + \boldsymbol{\sigma}_c^{act}\right) = \rho_c \boldsymbol{a}_c$$

$$\boldsymbol{\sigma}_c^{act} = t_{act}\boldsymbol{I}$$



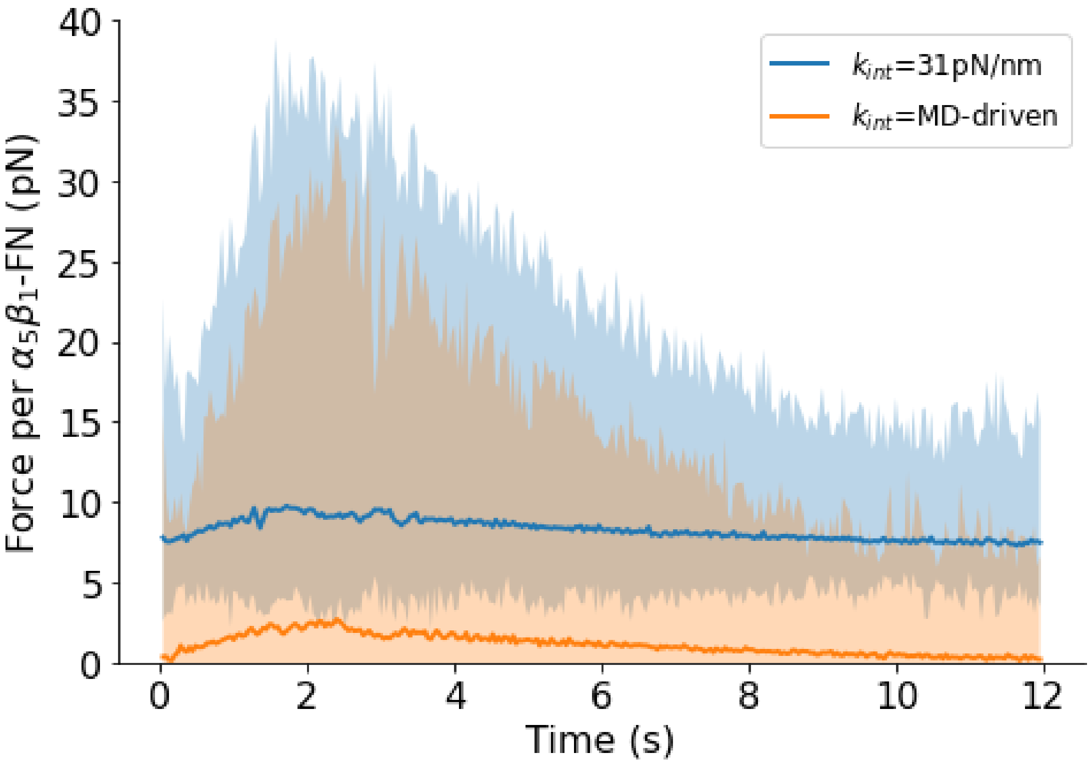
Force per integrin is dampened

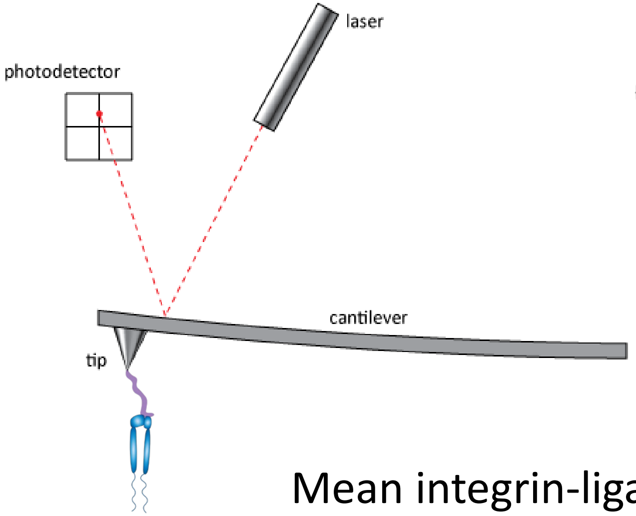


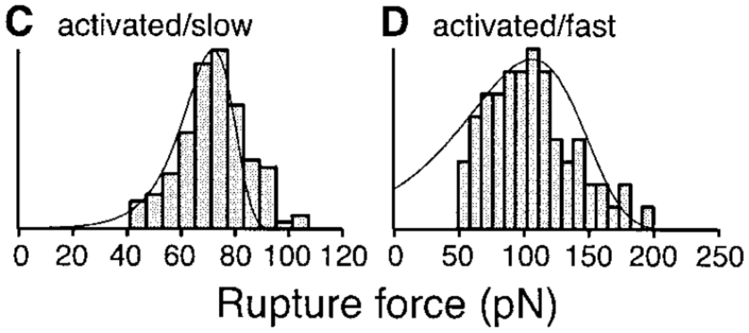


Berkeley

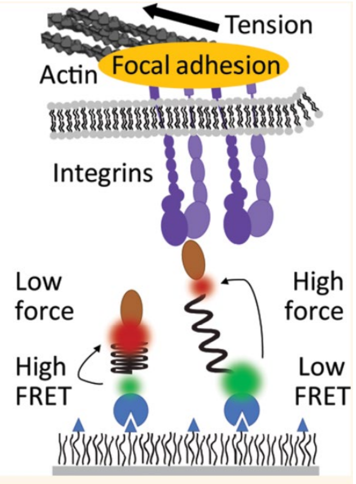
Comparing to FRET-based sensors and AFM

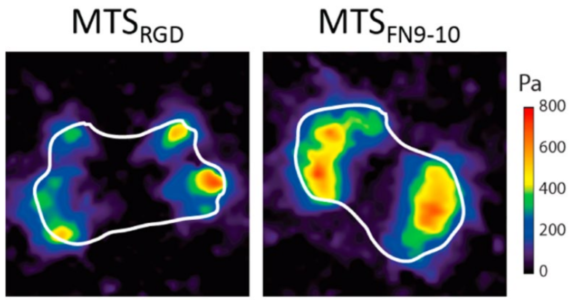


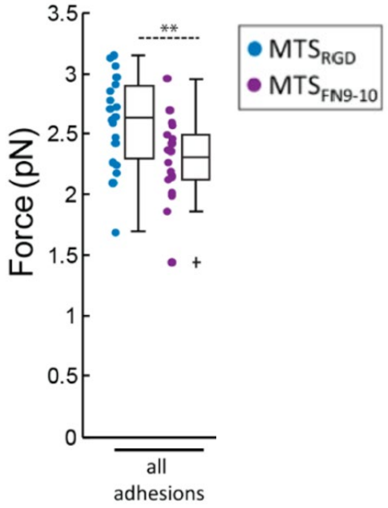




Mean integrin-ligand rupture forces: 70 –100 pN [1]

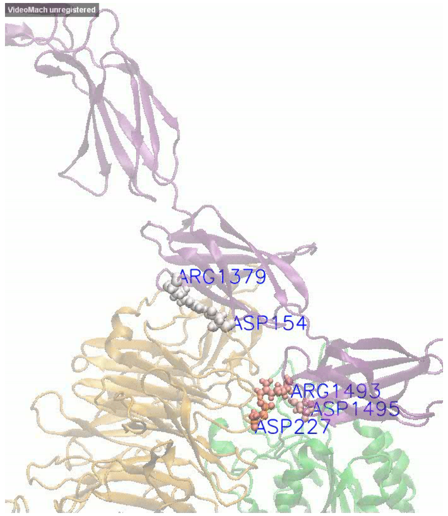


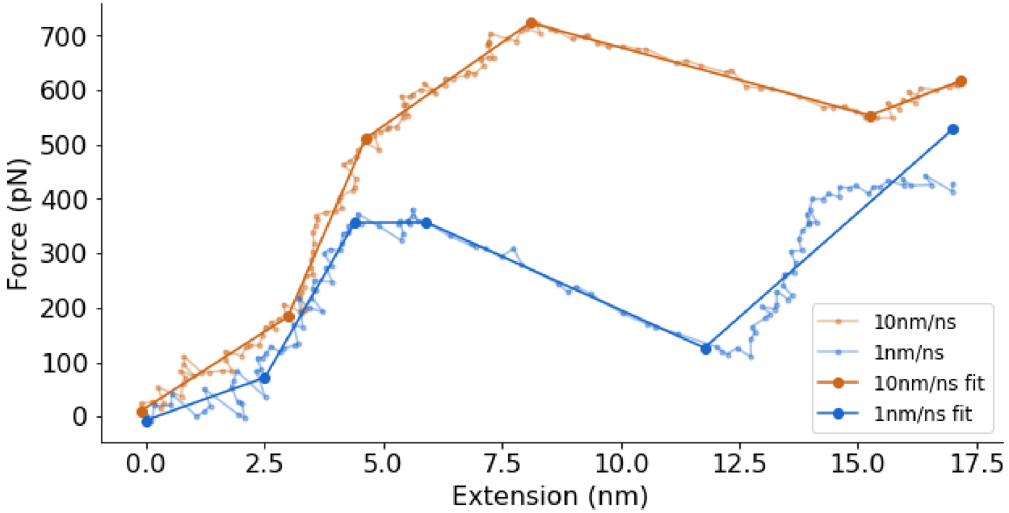


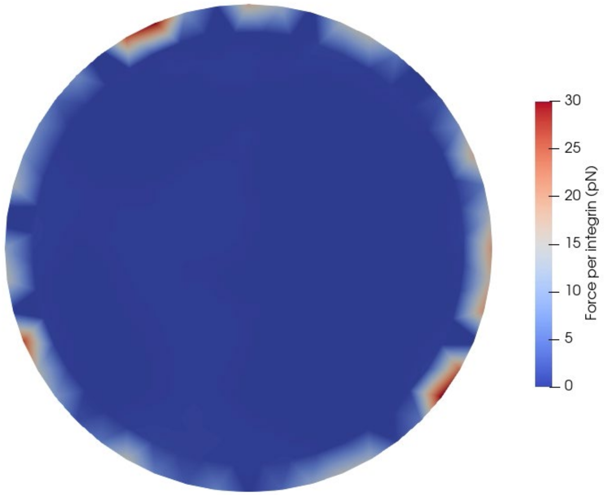


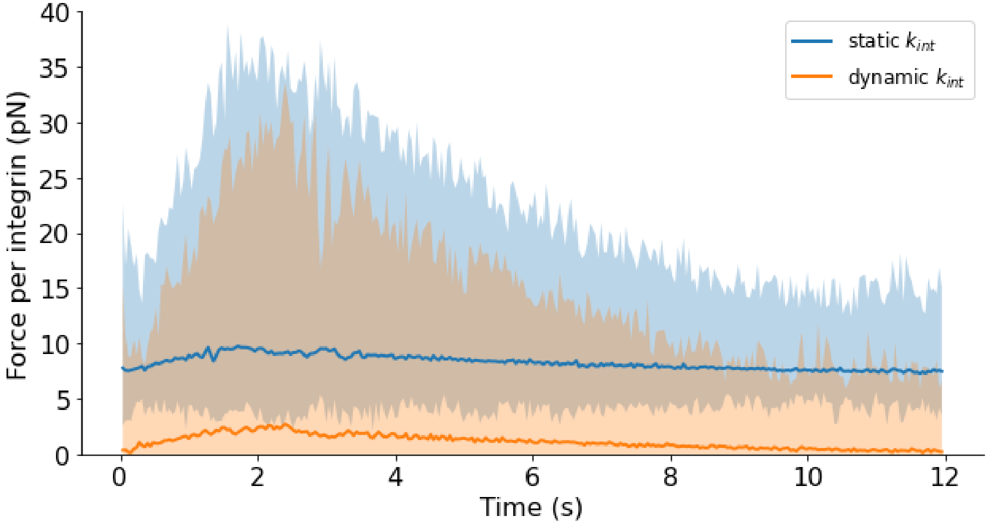
[1] Li et al. *Biophysical Journal.* 2003. [2] Chang et al. *ACS Nano.* 2016.

Amino acid interactions at synergy site contribute to the nonlinear force-extension behavior of $\alpha_5\beta_1$-FN, which can lead to dampened whole-cell adhesion force landscapes



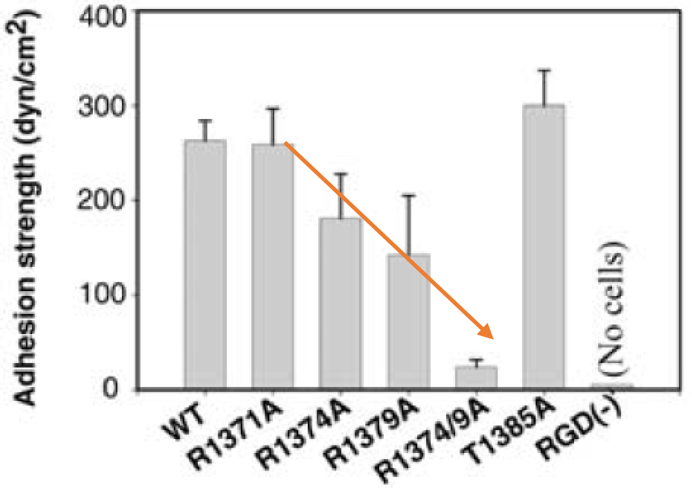




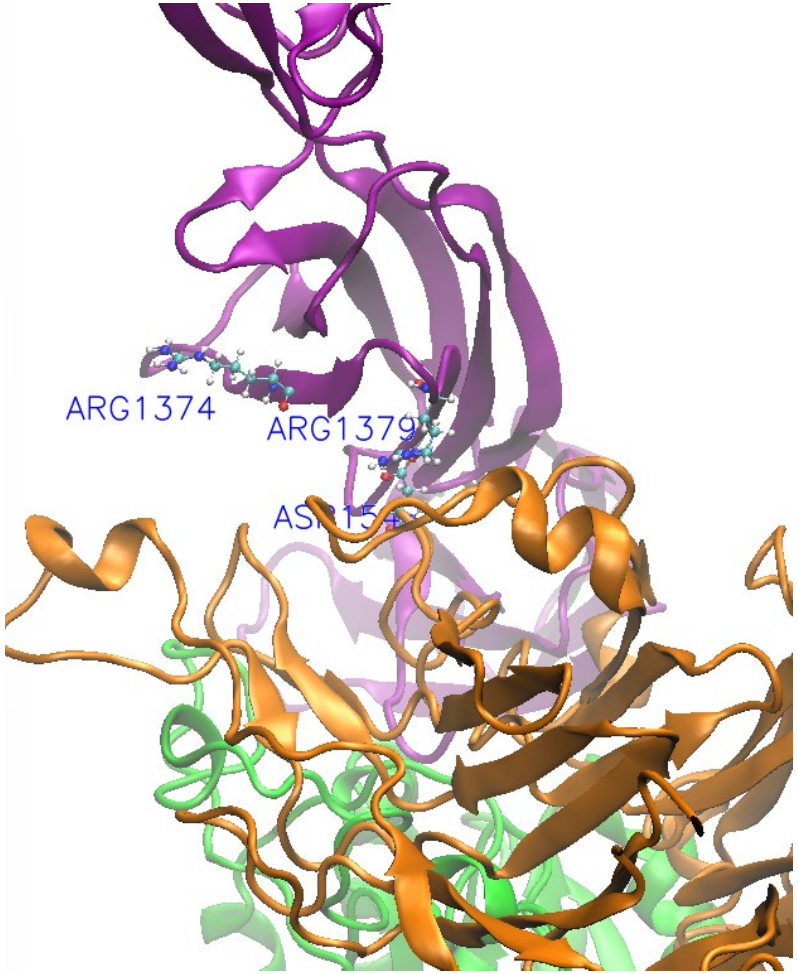


Ongoing Work

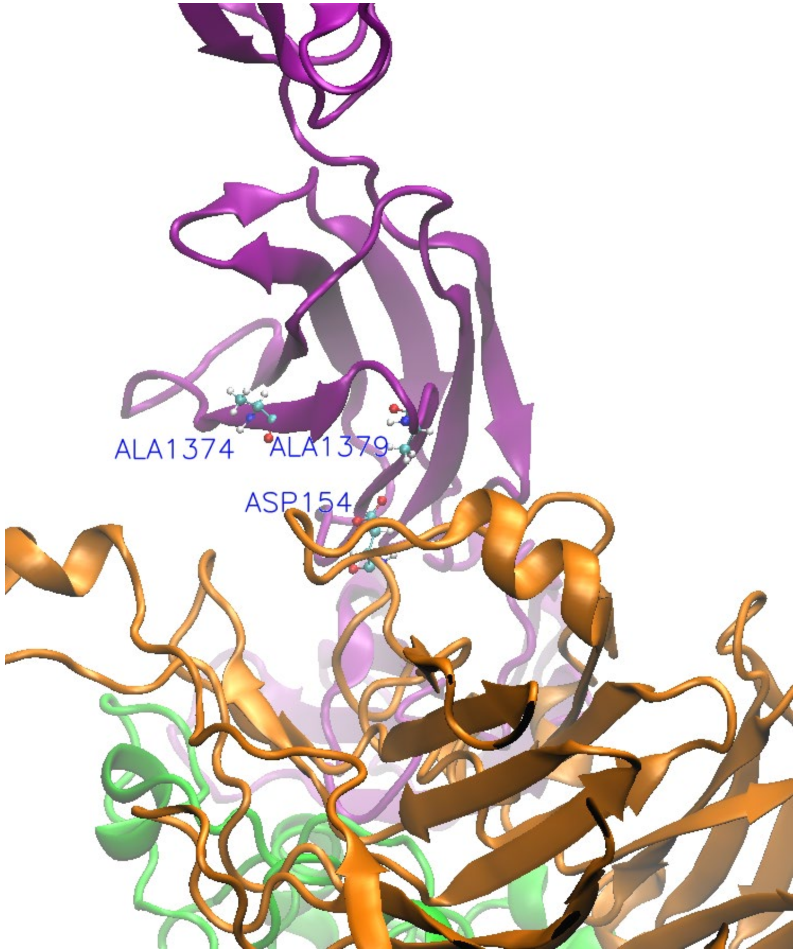
Virtual mutation of R1374/9A



Friedland et al. *Science.* 2009.



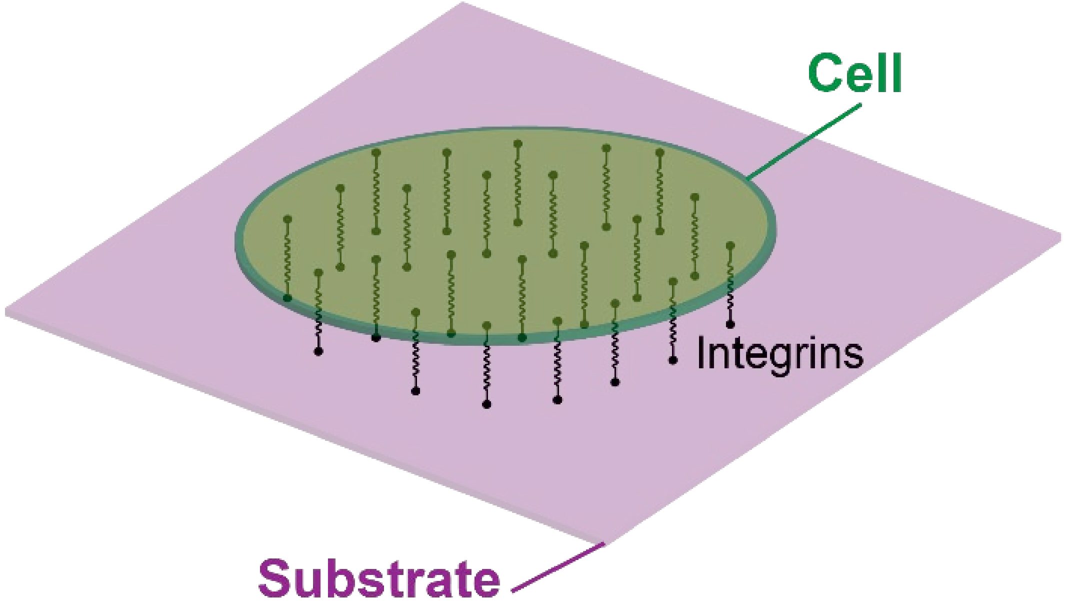
WT

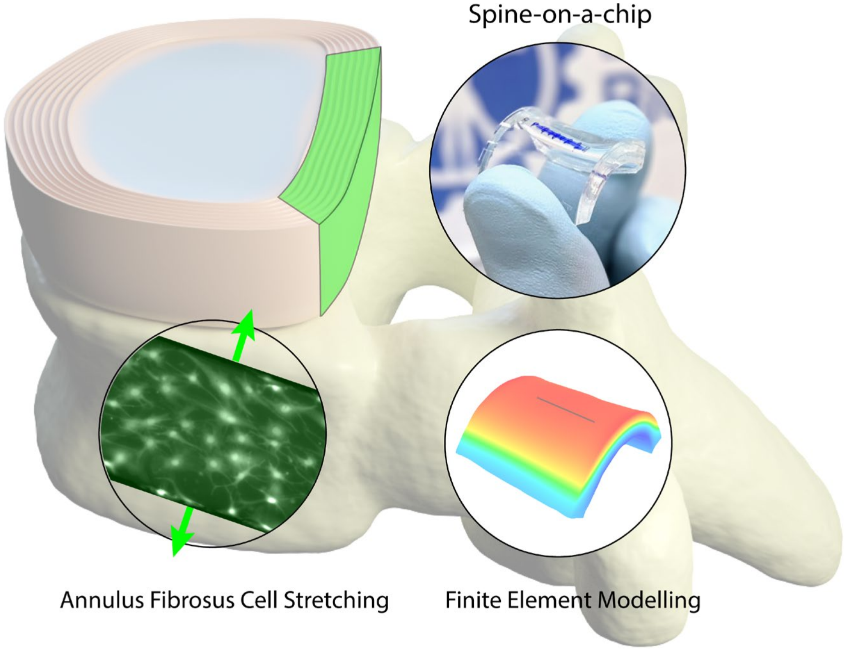


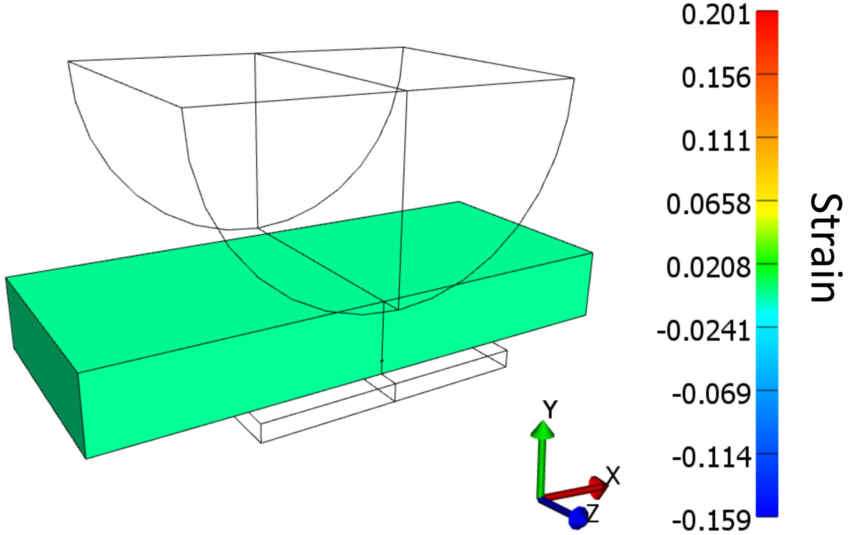
R1374/9A

Ongoing Work

Stretching the substrate

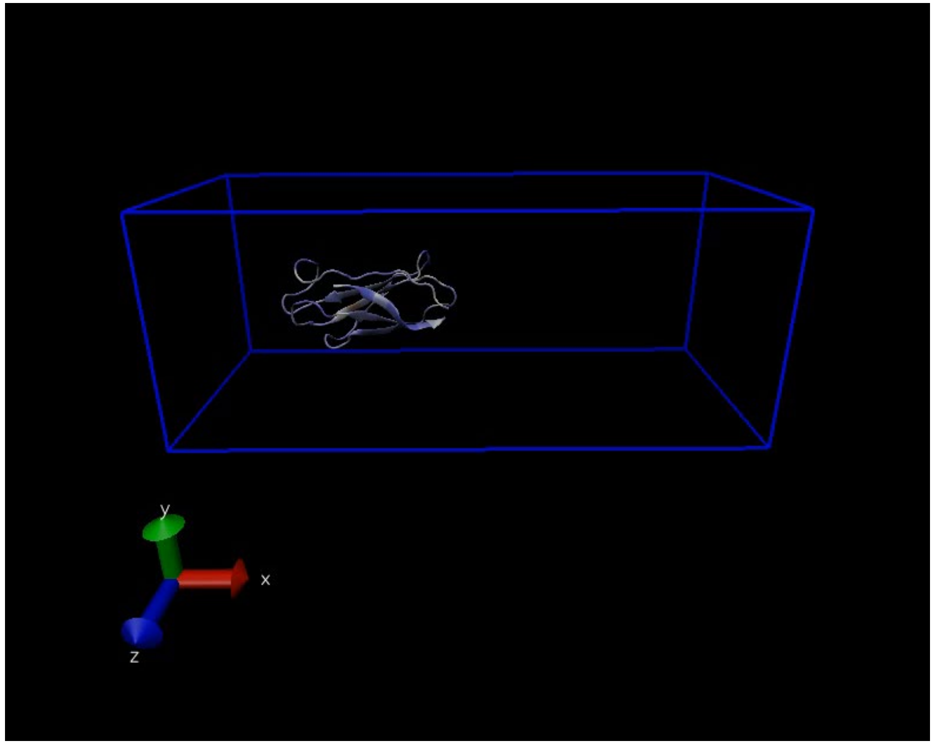






McKinley & Montes. *Biomicrofluidics*. 2022.

Fibronectin Steered Molecular Dynamics and Force Distribution Analysis Demo



Available: github.com/dredremontes/fn_MD_FDA

Berkeley

More info: dredremontes.github.io

Your feedback is appreciated