Computational modeling of cell movements in different scales

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Albert Einstein College of Medicine
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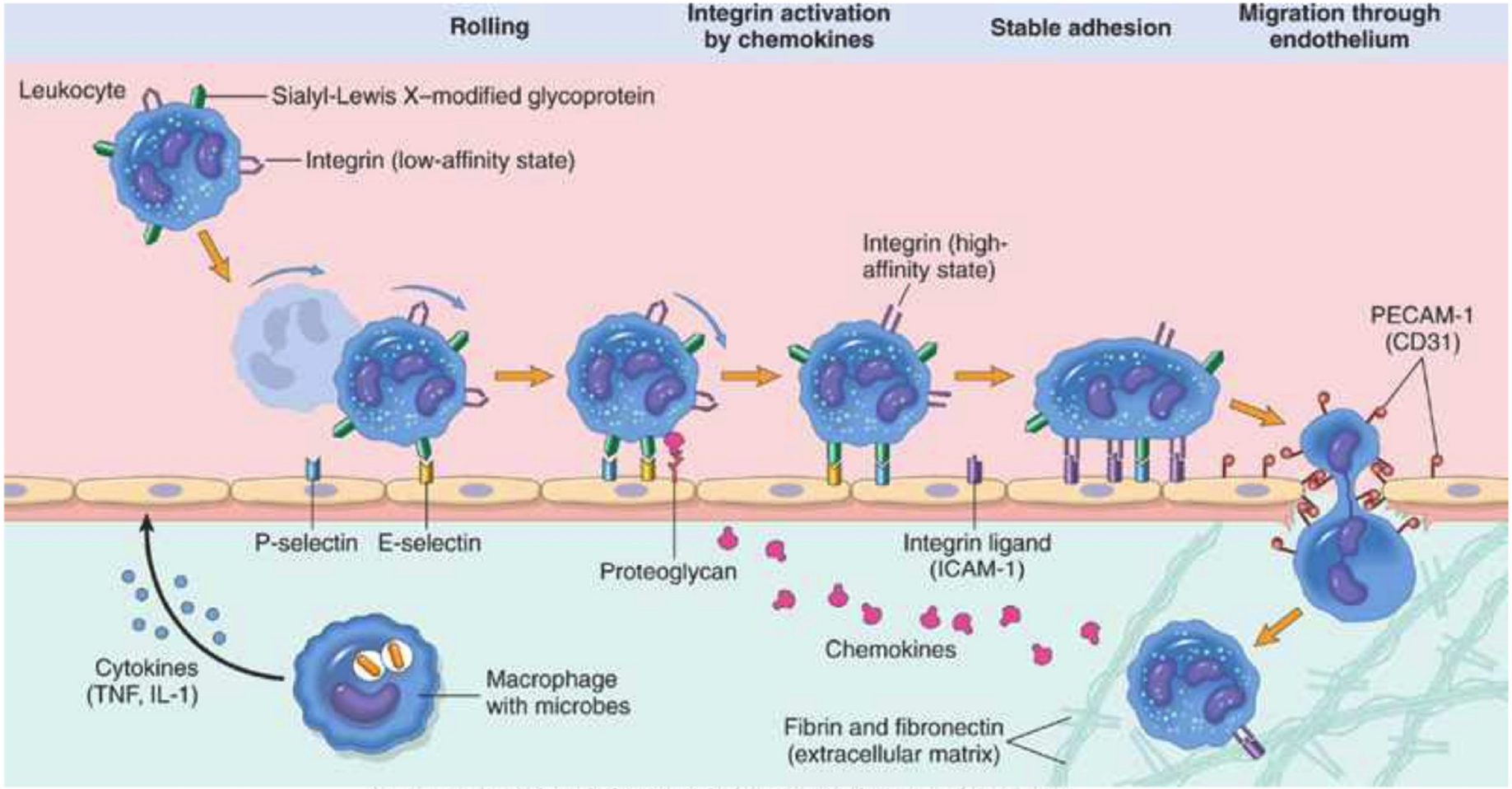
Background



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.

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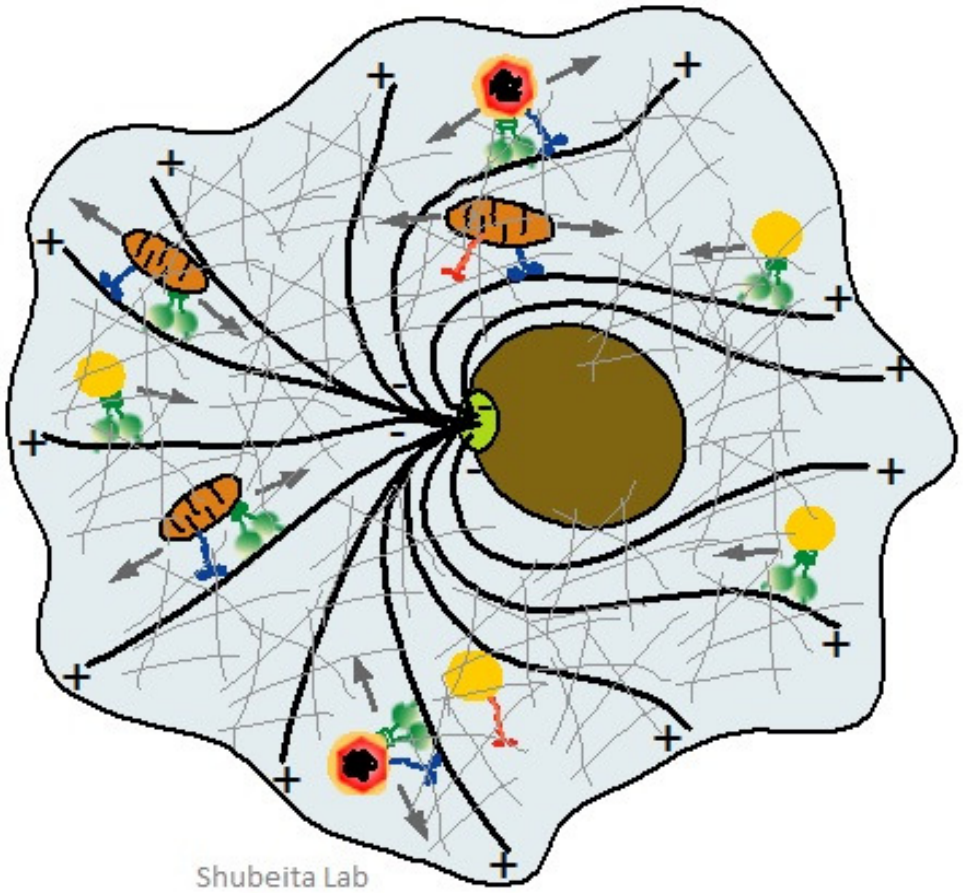

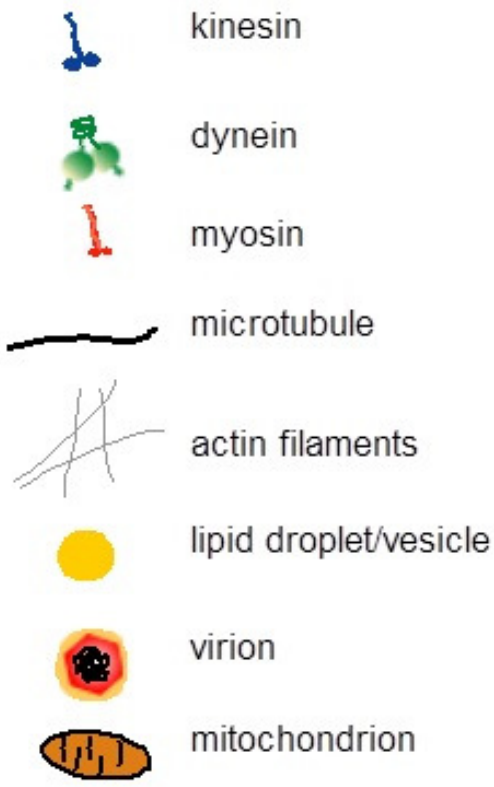

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Outline

- Simulation of molecular motor
- Modeling cytoskeleton
- Simulation of single cell locomotion
- Simulations of movements in multicellular systems

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  - A specific example of Myosin V
  - General model
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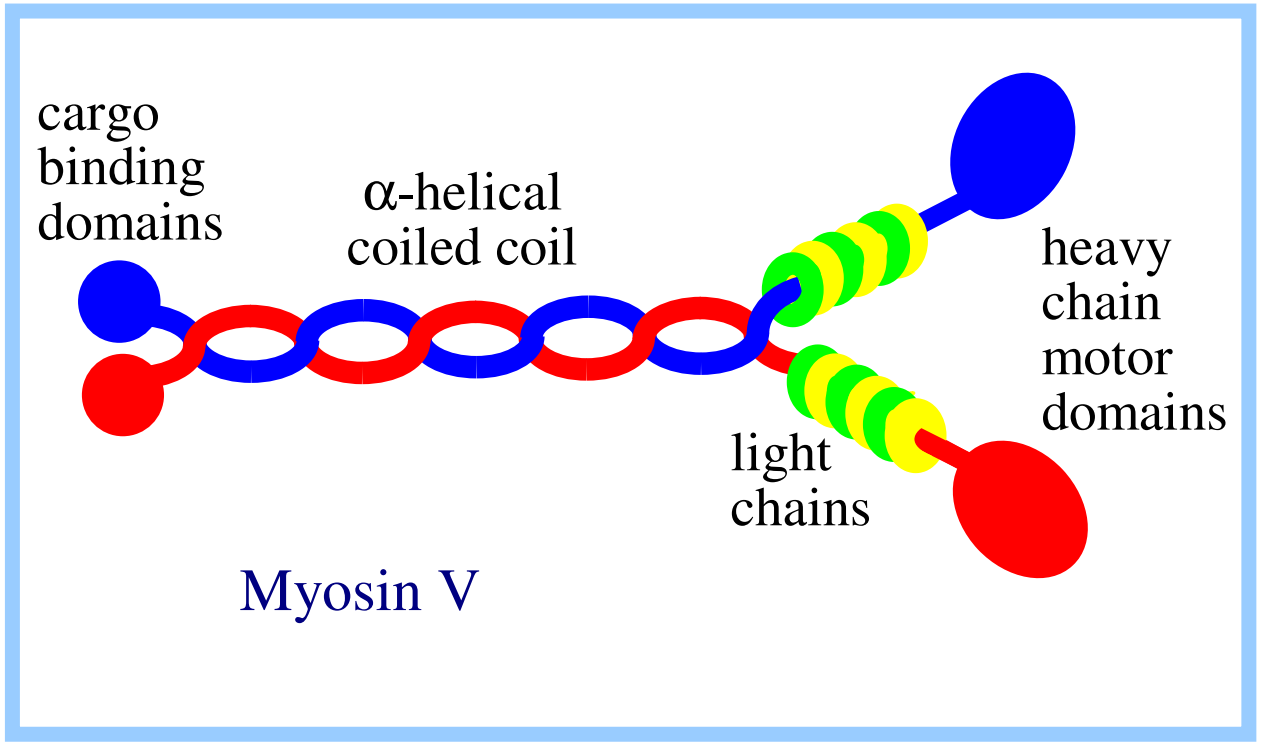
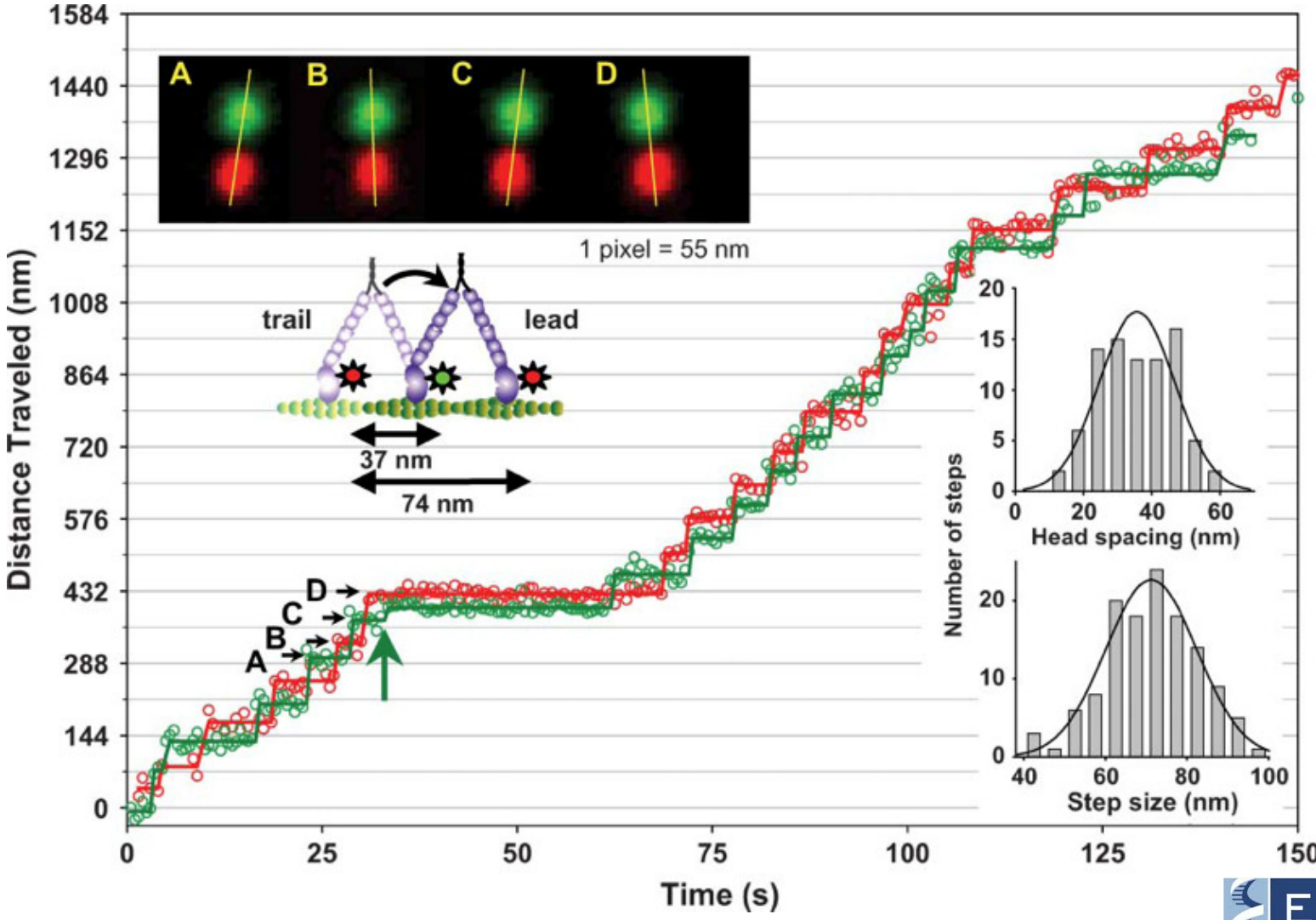


Total internal reflection fluorescence *microscopy* (*TIRF*)



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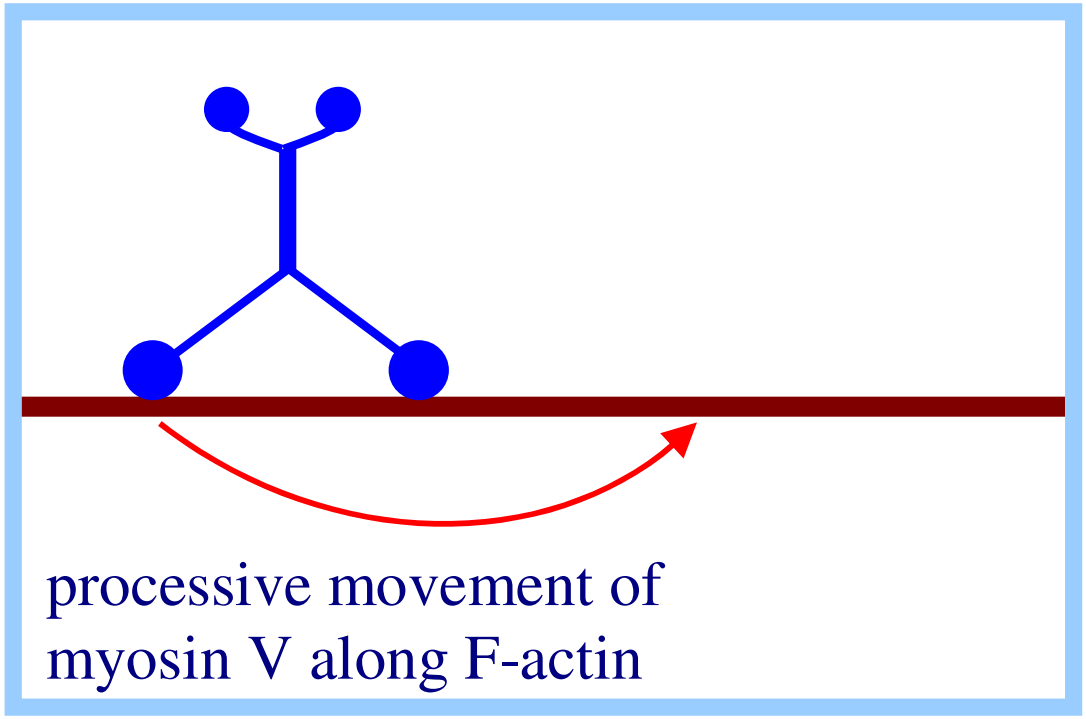
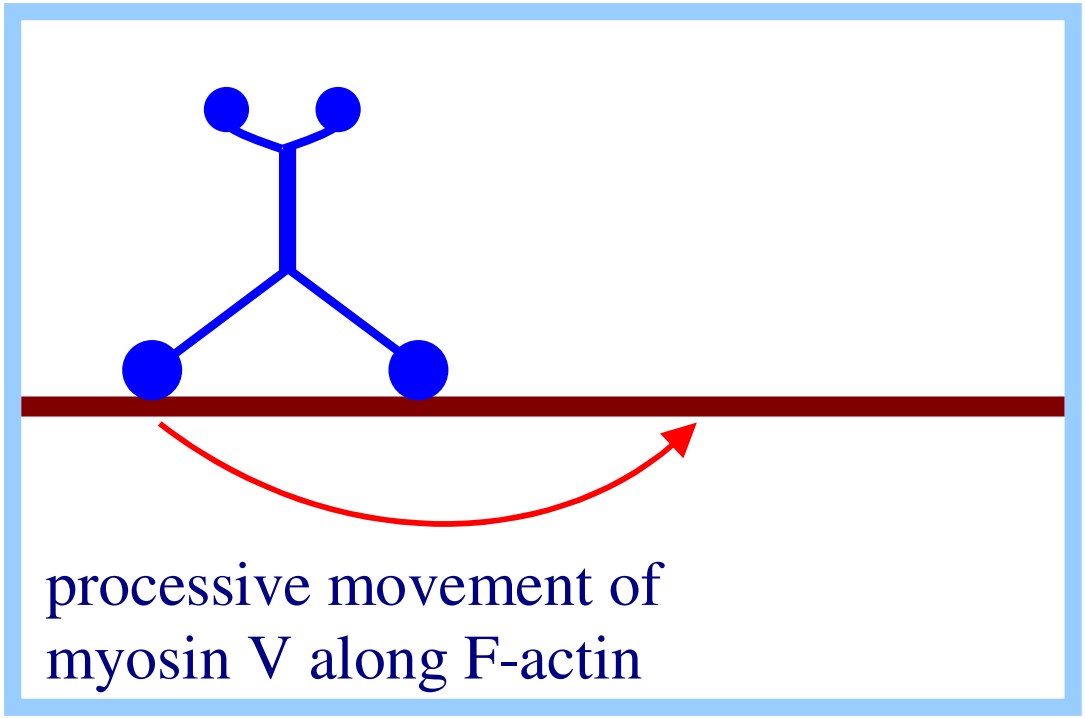


Movement of myosin V along actin is **processive**, meaning that myosin V remains **attached** to an actin filament as it walks along that filament.

In contrast, myosin II is a non-processive motor that detaches from actin at a stage of each reaction cycle.

The processive movement of myosin V is appropriate for its role in transporting organelles along actin fila

In the **hand over hand** stepping mechanism of myosin V, one head domain dissociates from an actin filament only when the other head domain binds to the next subunit with the correct orientation along the helical actin filament.

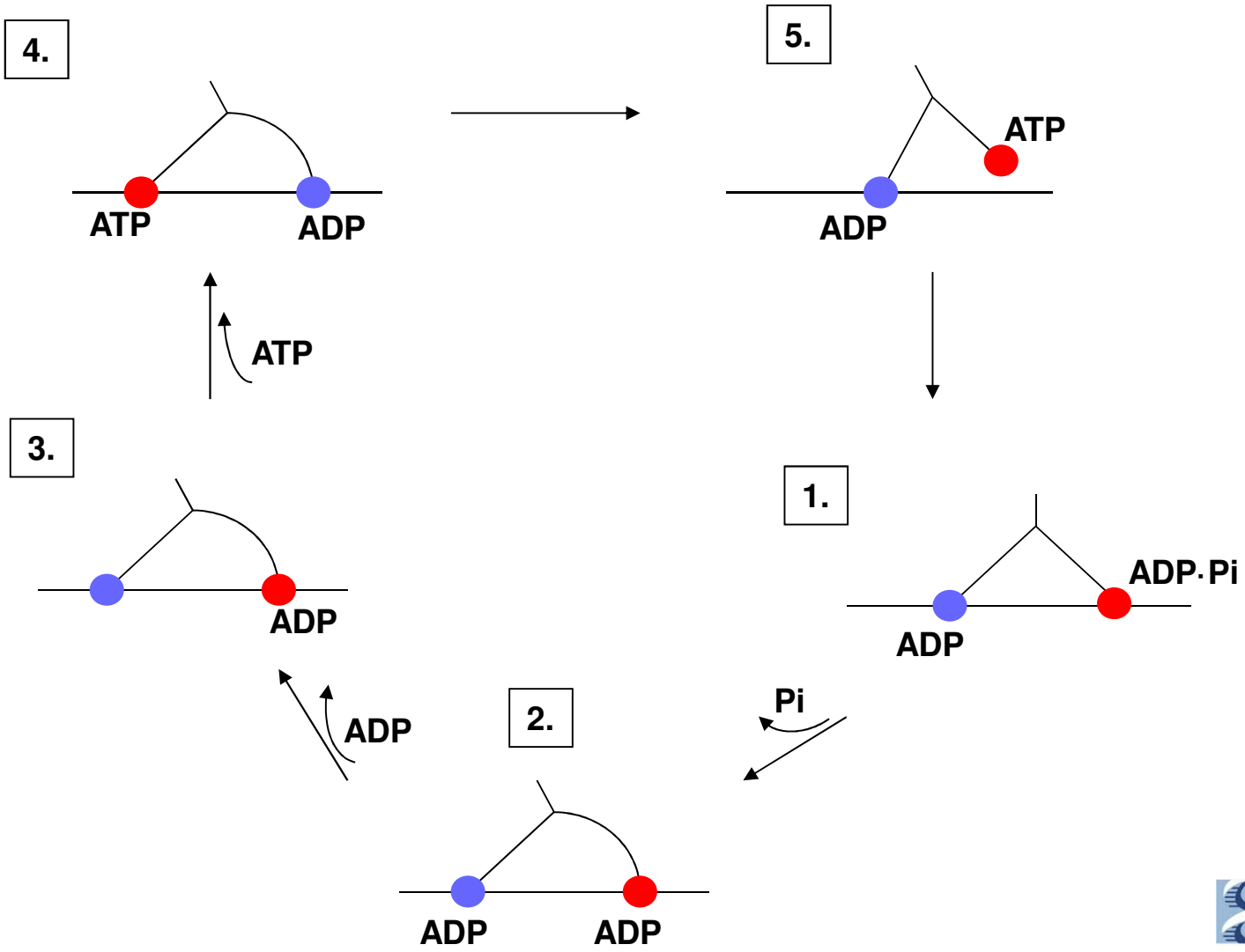


Since there are 13 actin subunits per helical turn, myosin V has a relatively **long step length** of 74 nm.

By stepping the length of the actin helical repeat, myosin V maintains a straight path along an actin filament, rather than spiraling around it.

- Conformational change
- Internal coordination
- Brownian diffusion

Myosin V mechanochemical cycle



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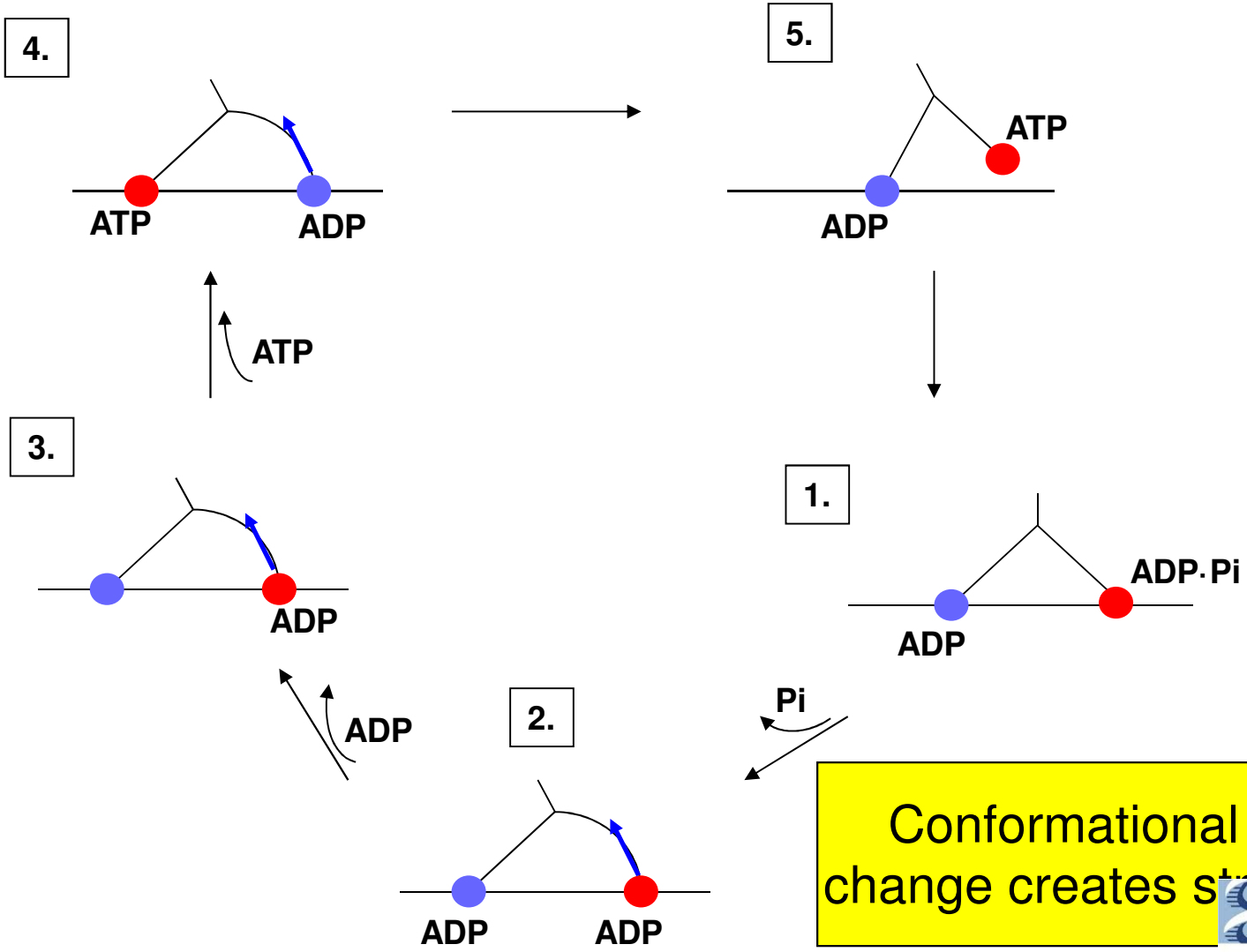
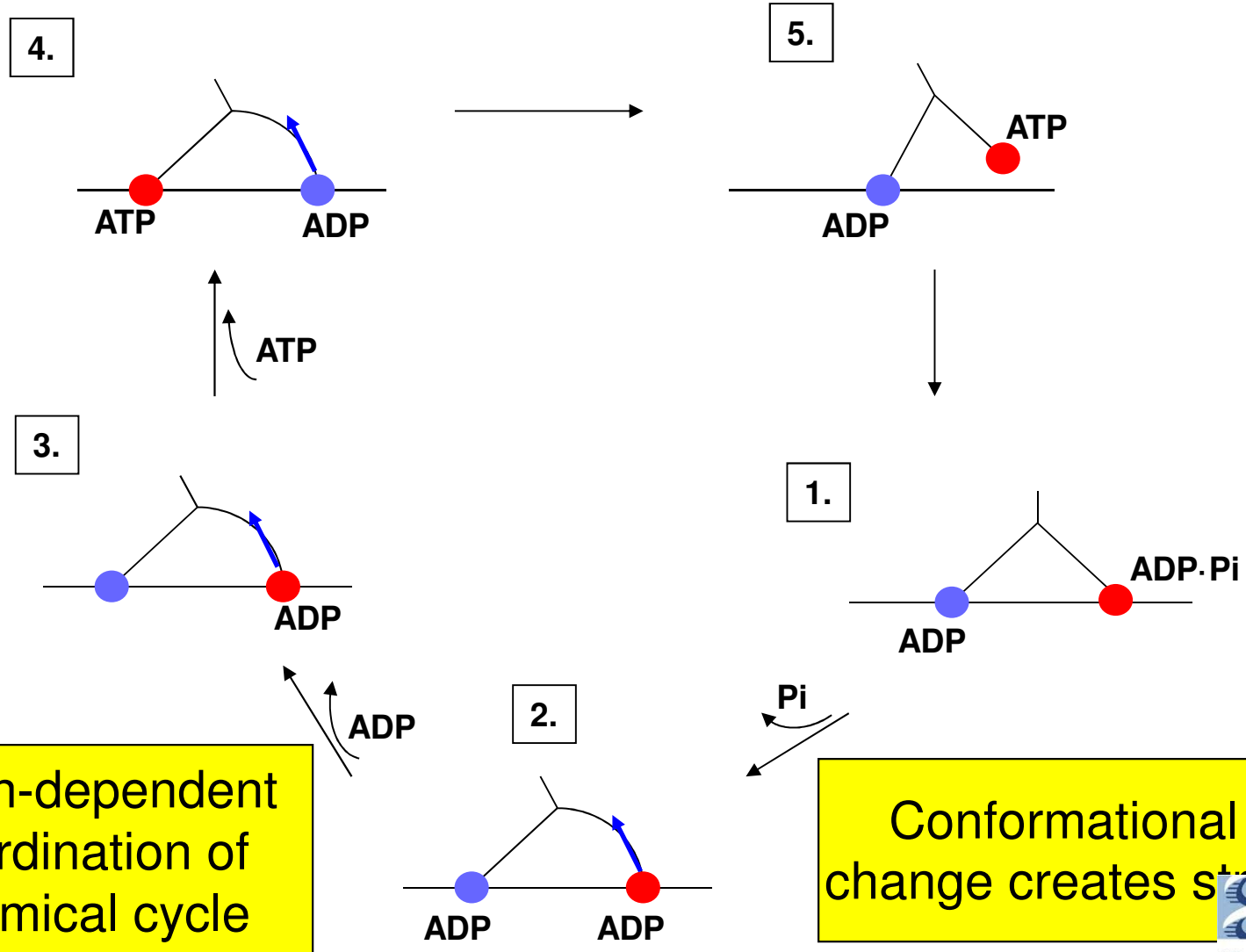
Myosin V mechanochemical cycle



Conformational change creates strain

- Conformational change
- Internal coordination
- Brownian diffusion

Myosin V mechanochemical cycle

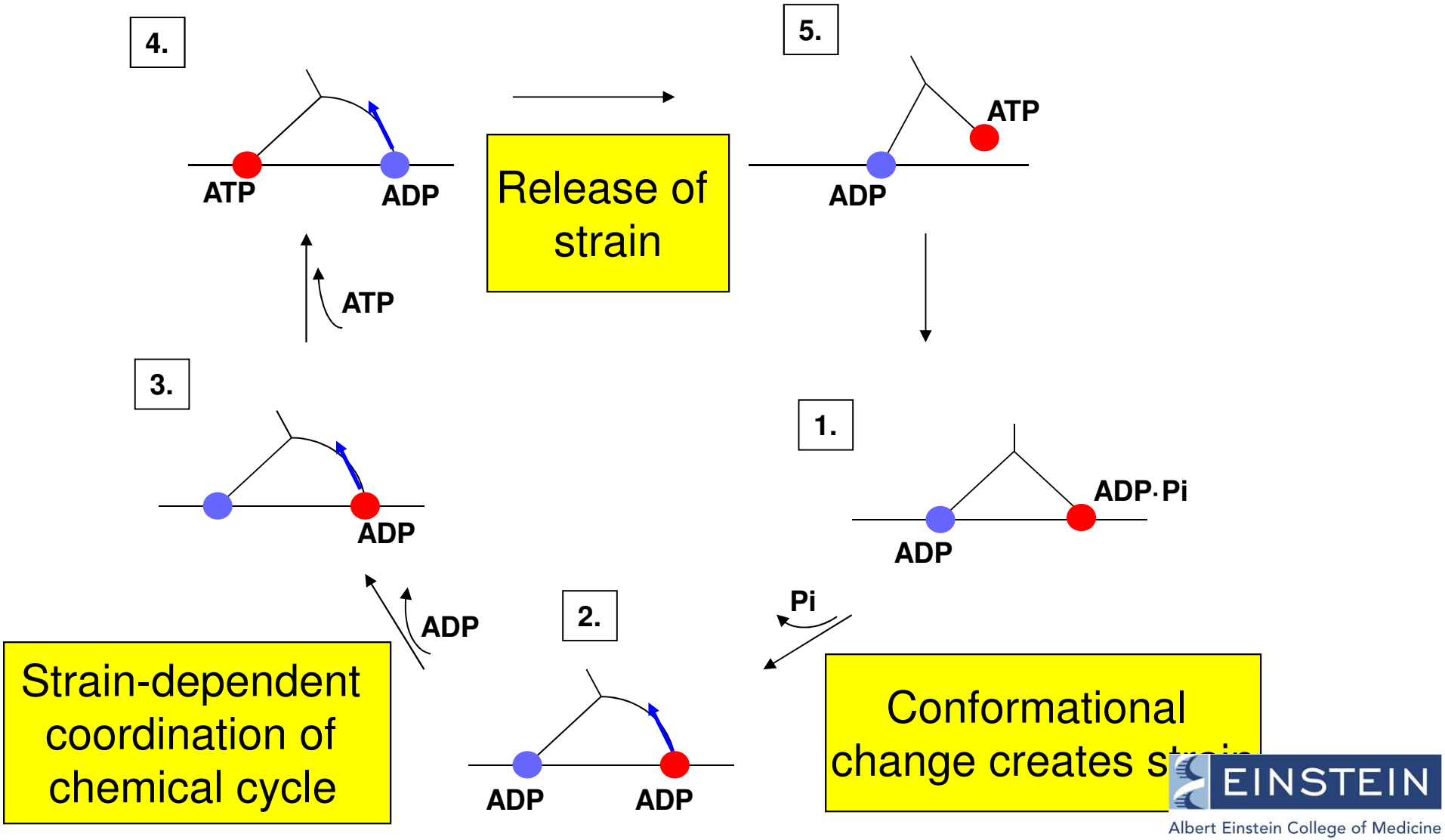


Strain-dependent coordination of chemical cycle

Conformational change creates strain

- Conformational change
- Internal coordination
- Brownian diffusion

Myosin V mechanochemical cycle



- Conformational change
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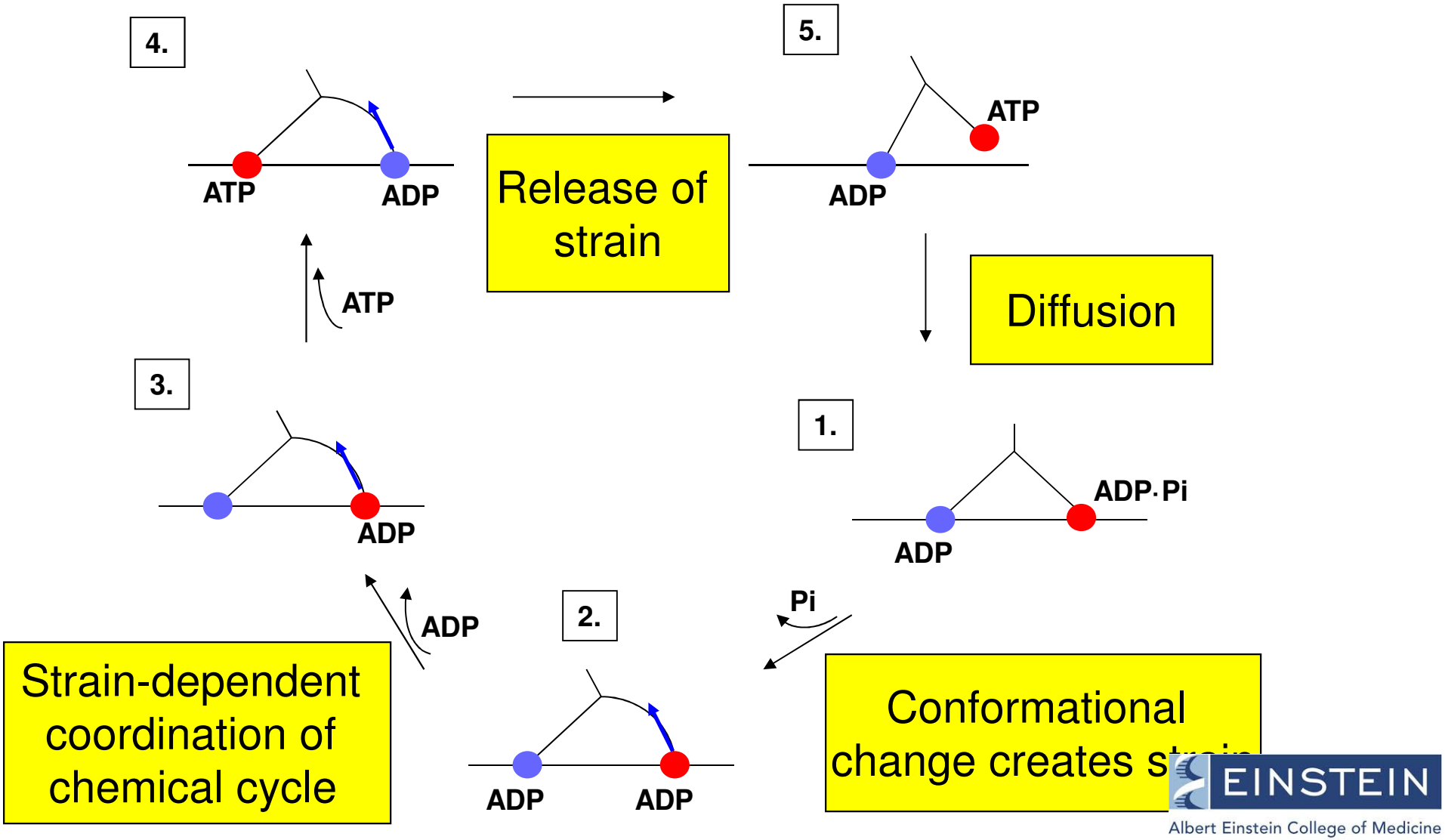
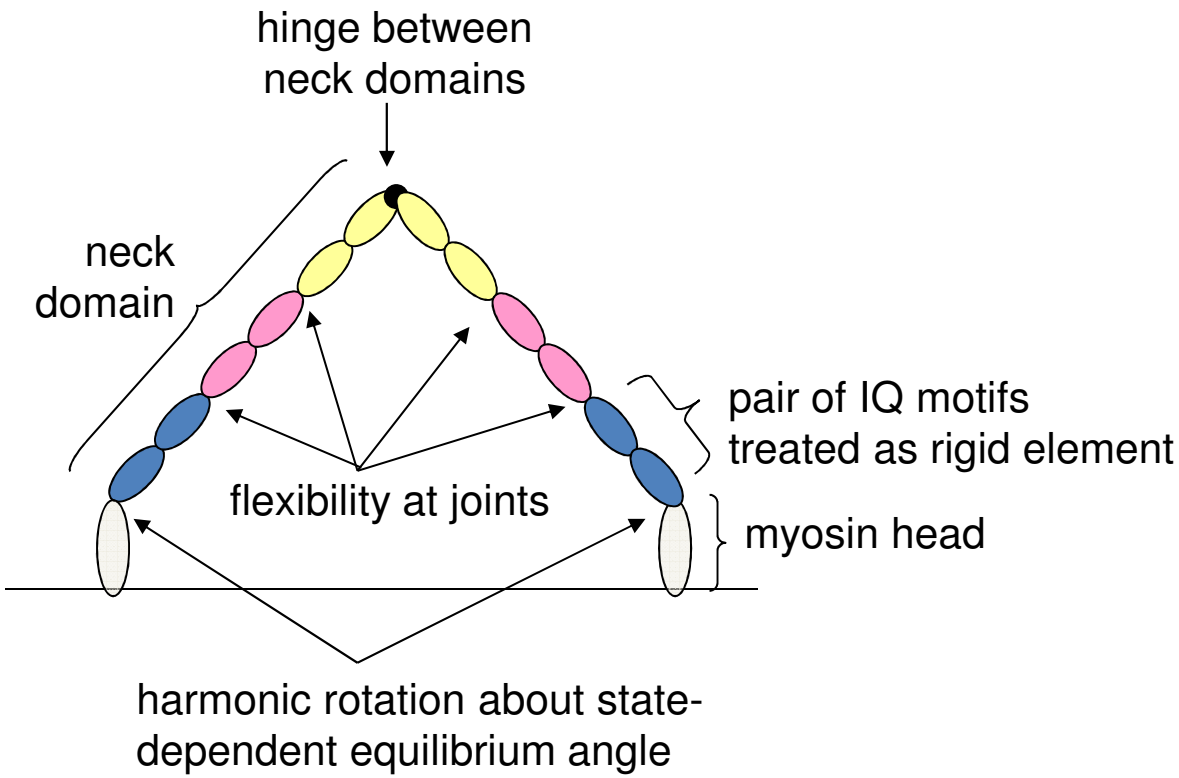
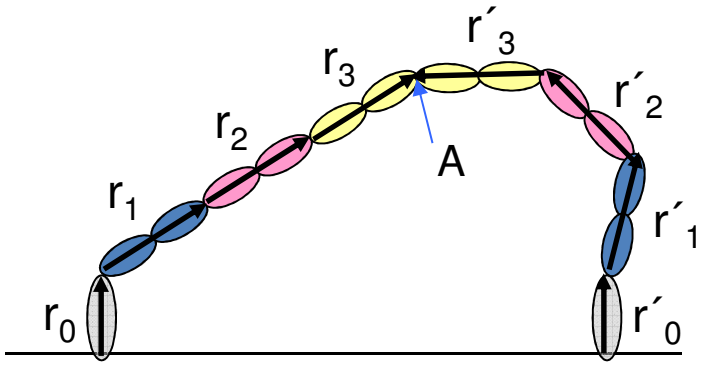
Myosin V mechanochemical cycle



Myosin V: 3D model

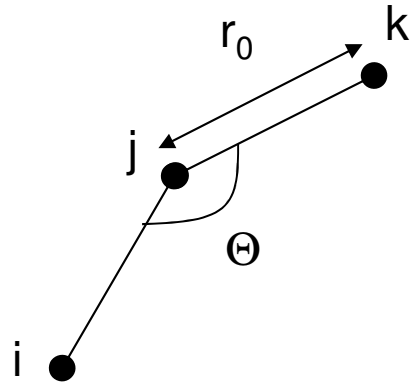


Myosin V 3D model: elasticity of neck domains



Neck domain:
- 3 rigid segments
- flexibility at joints

Bending energy of semiflexible filaments:



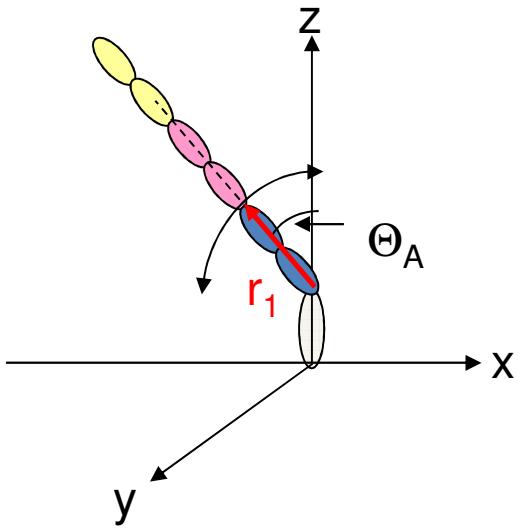
$$V = \tfrac{1}{2} V_0 (\hat{n}_{jk} \cdot \hat{n}_{ji} - cos\theta_{eq})^2$$

$$V_0 \sim \frac{k_B T l_p}{r_0}$$

M. Terrak et. el., PNAS 102, 12718 (2005).
M. Doi and S. F. Edwards, “The Theory of Polymer dynamics”, (1986).

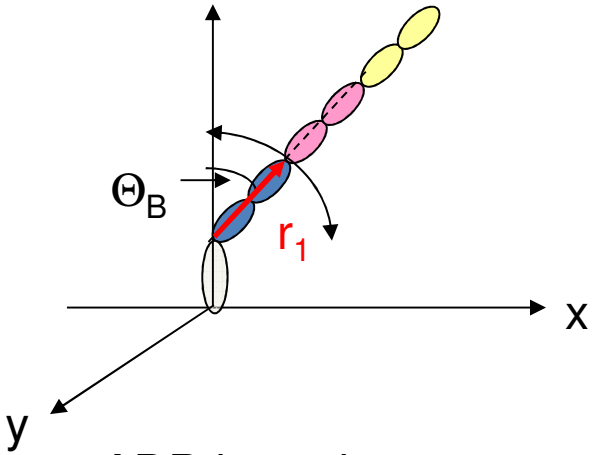
Myosin V 3D model: rotational states

Pre-stroke:



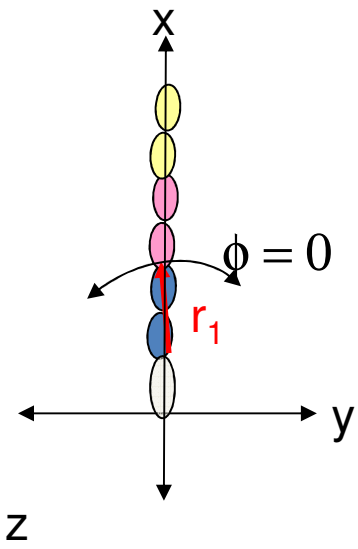
ADP.Pi-bound

Post-stroke:

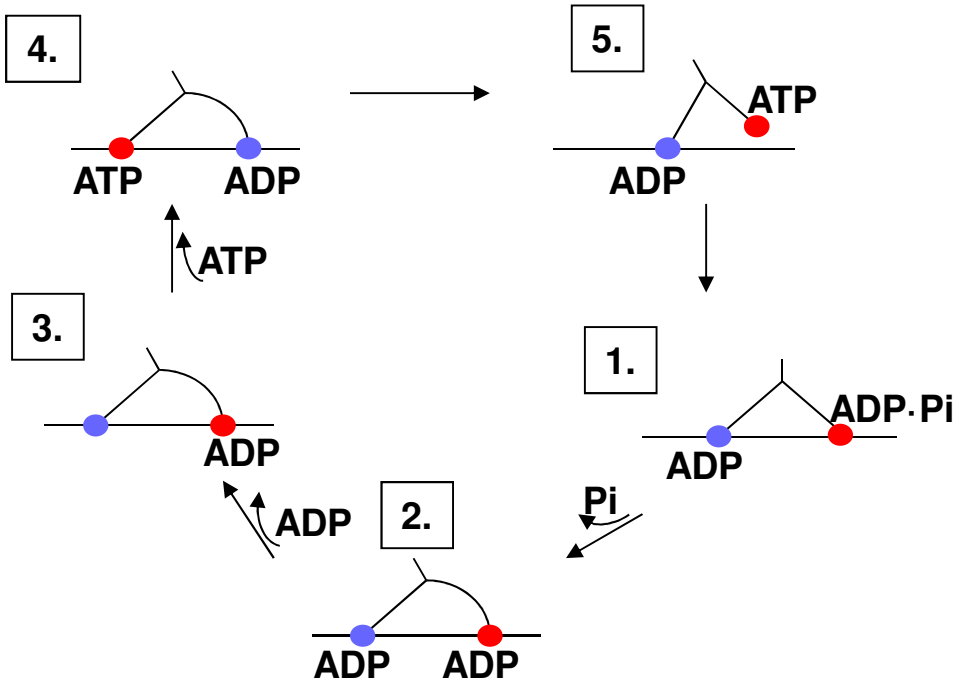


ADP-bound
Empty
ATP-bound

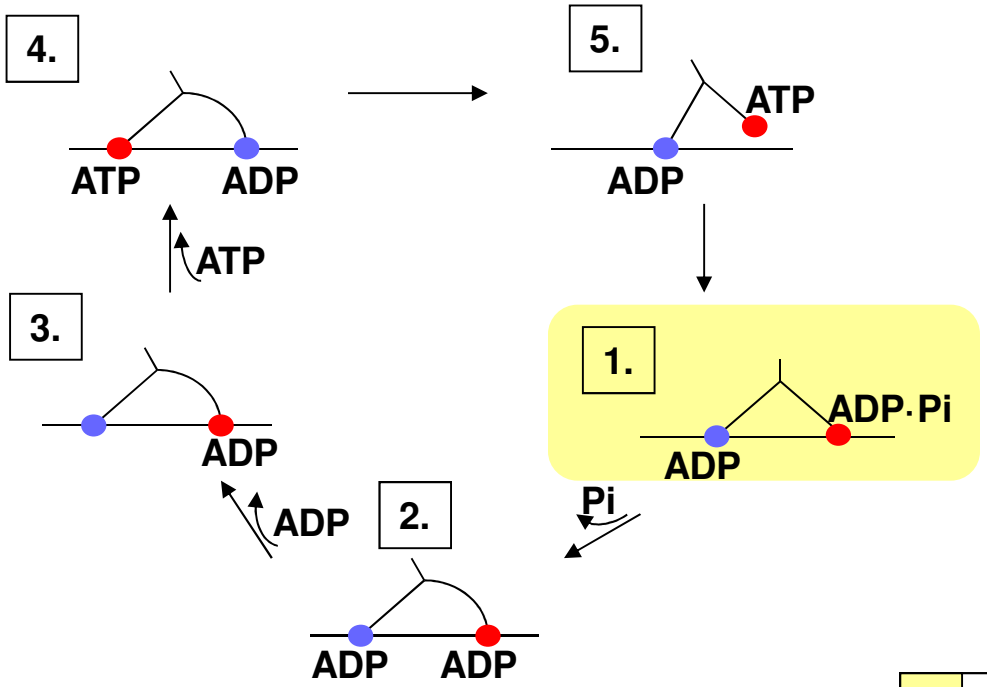
"Bird's eye" view:

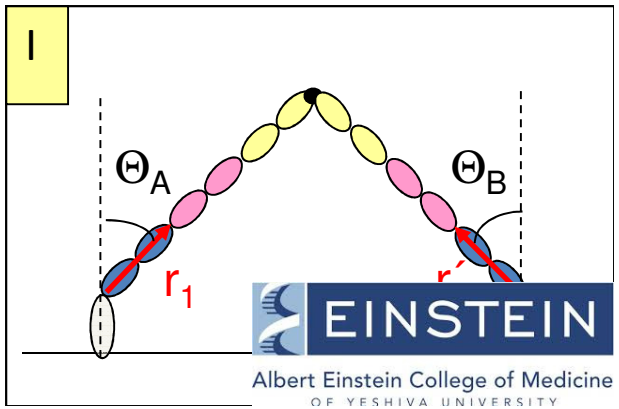


Myosin V 3D model: mechanical cycle



Myosin V 3D model: mechanical cycle





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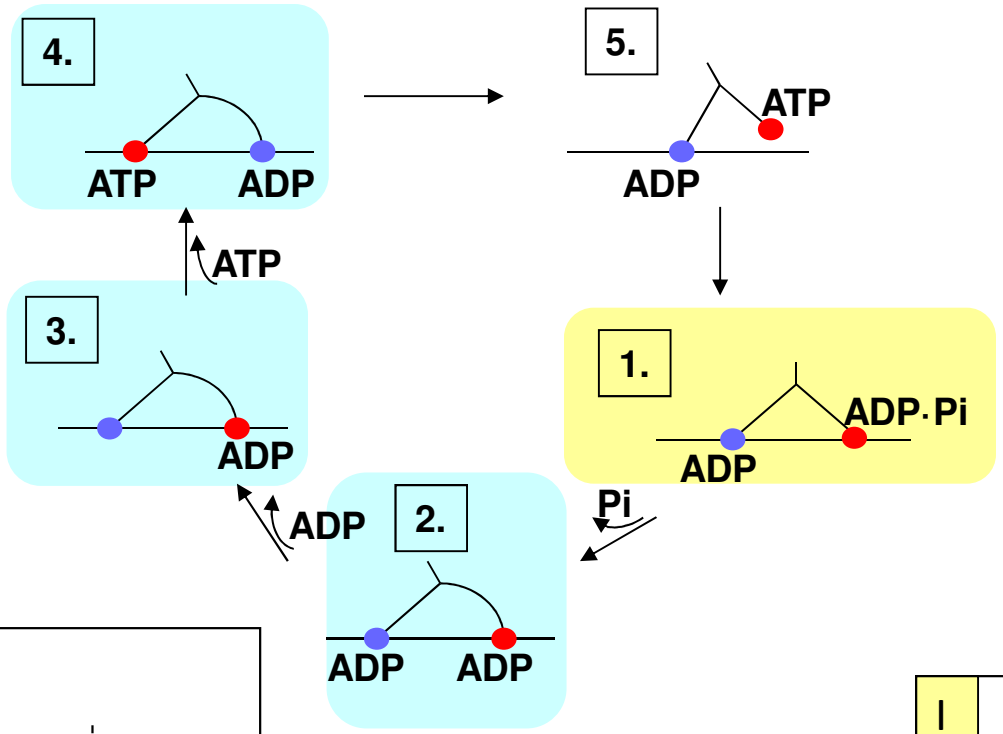
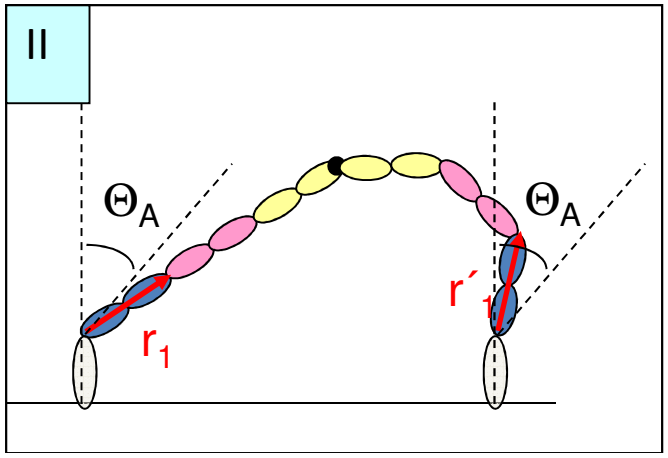
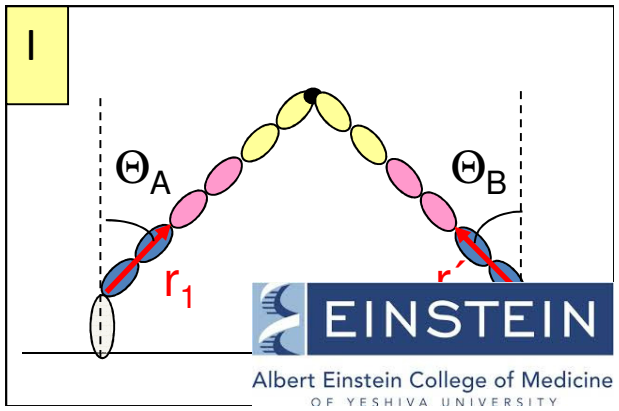
Myosin V 3D model: mechanical cycle







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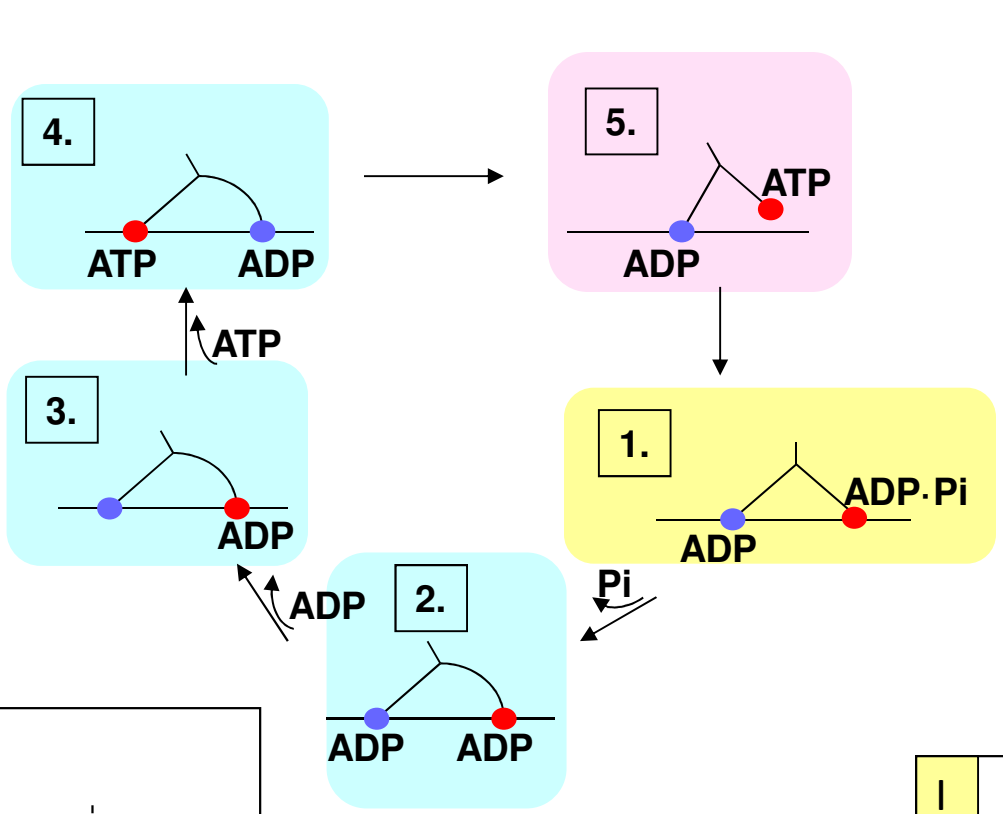

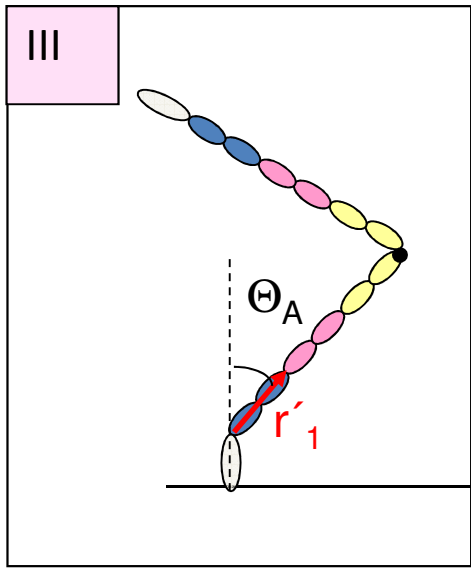

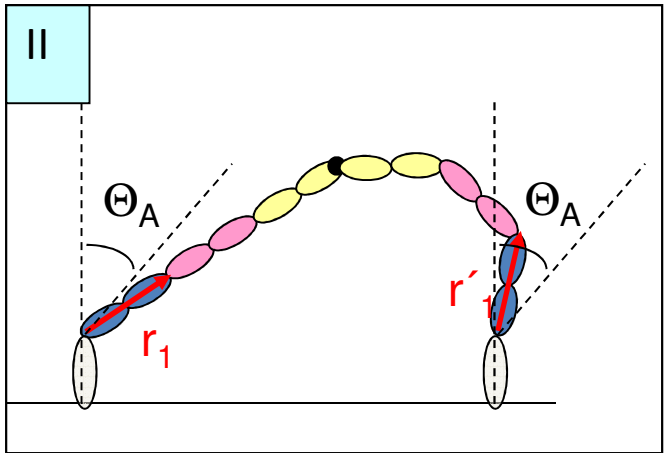

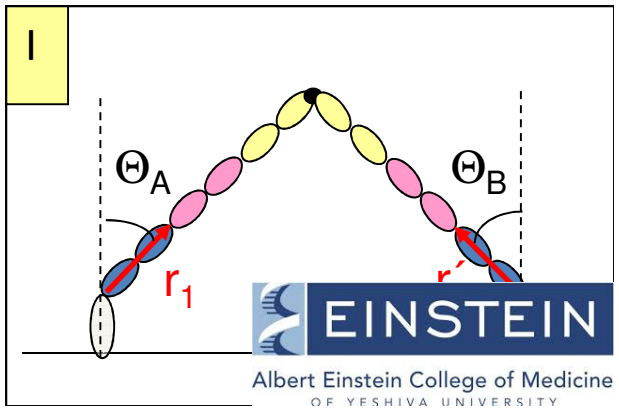

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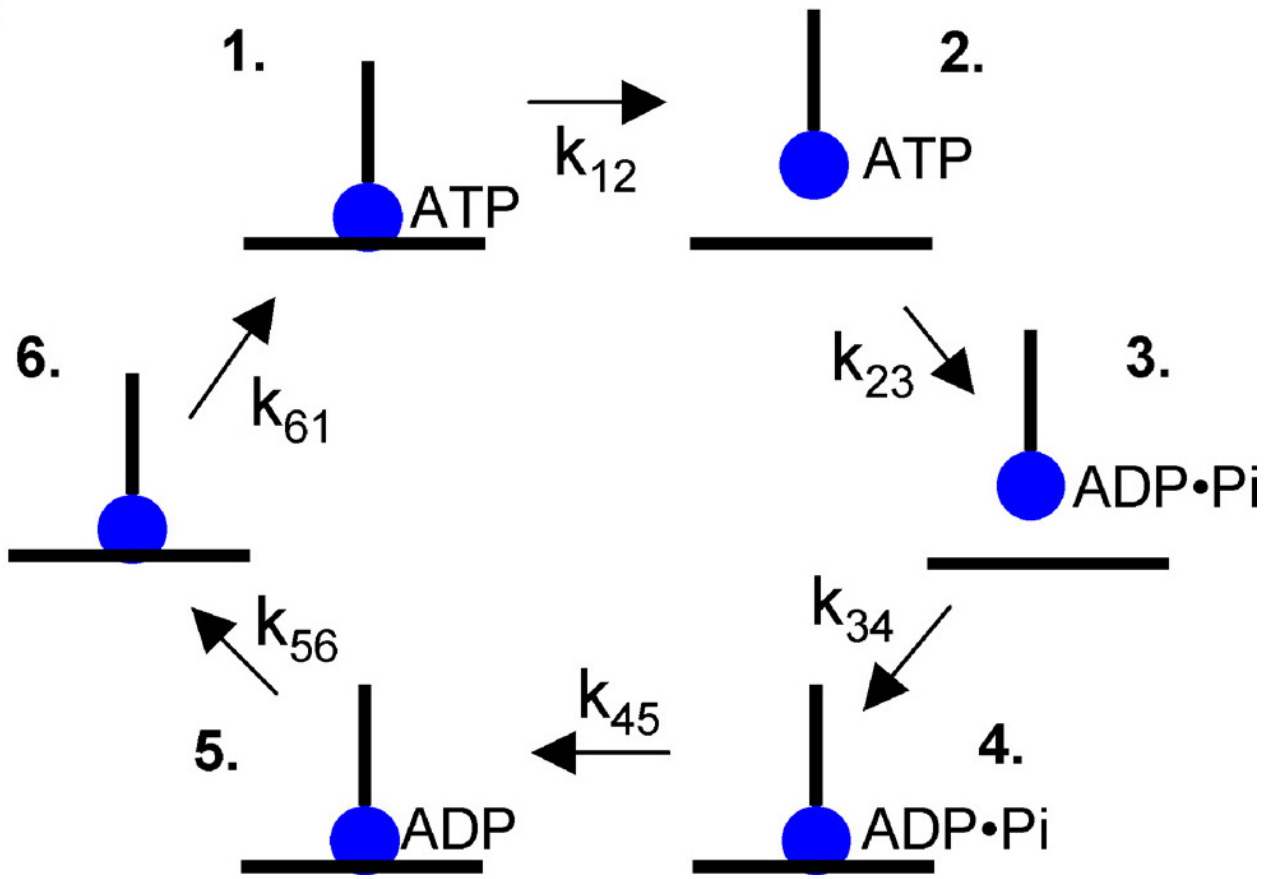
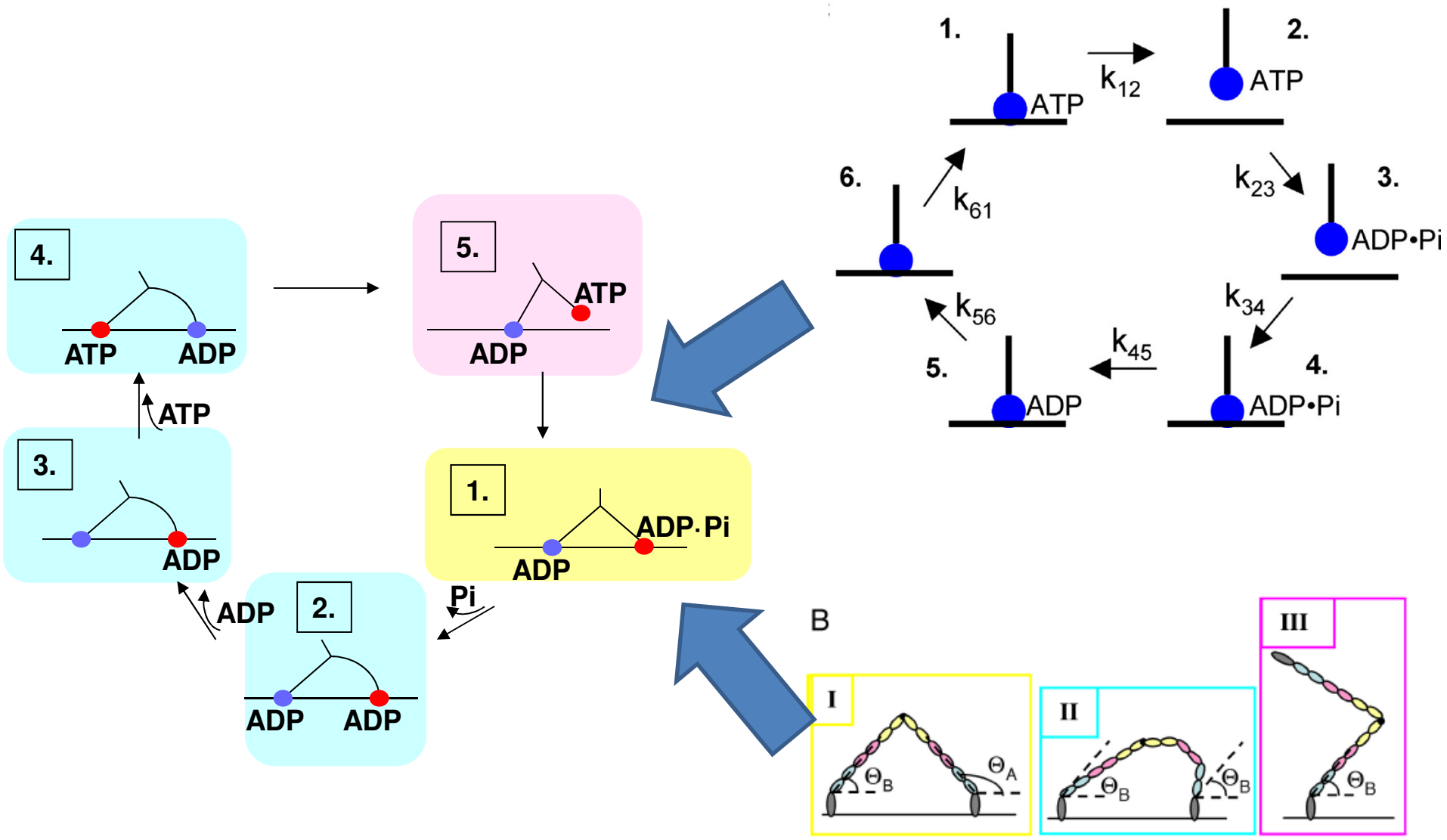
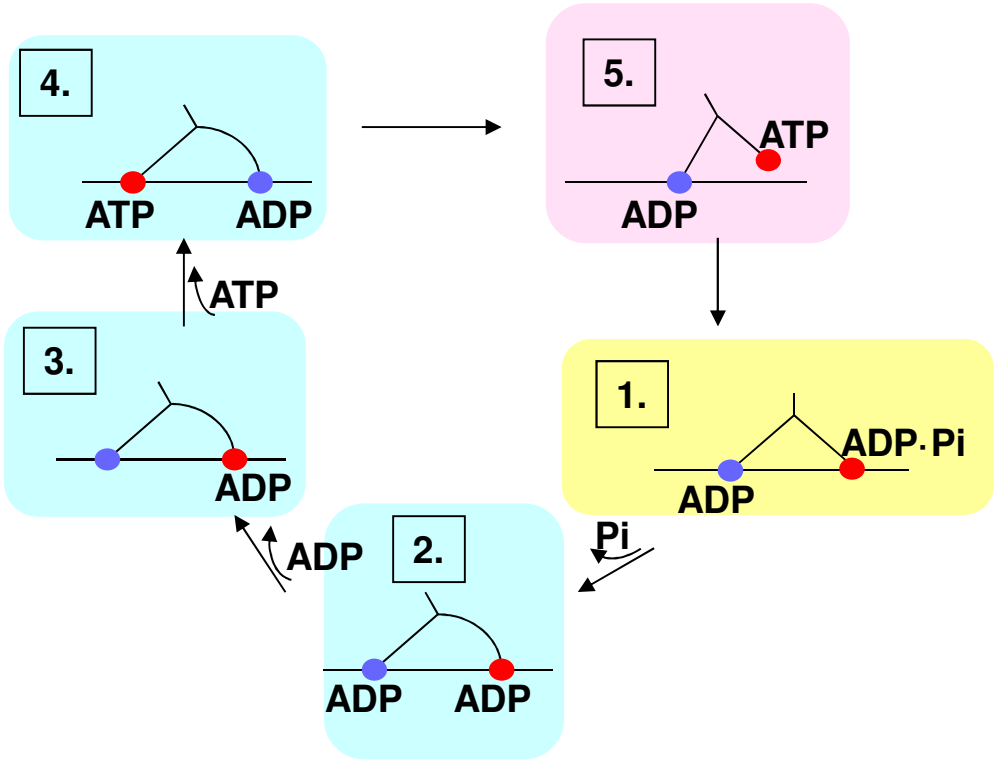
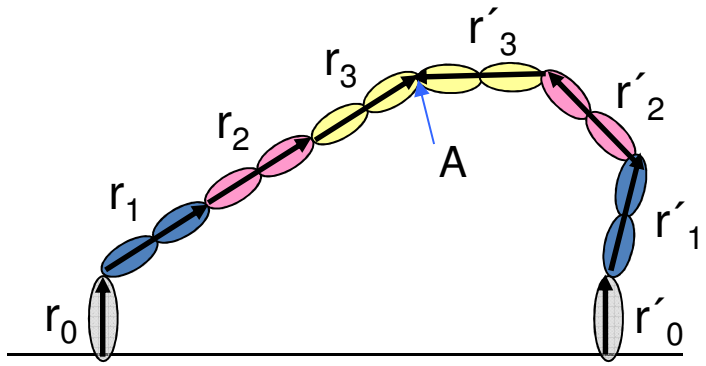


Table 1. Chemical transition rates of a myosin-V monomer

Rate	Value	Source
k_{12}	dt^{-1}	Ref. 18
k_{23}	700 s^{-1}	Ref. 18
k_{34}	Diffusion limited	Model output
k_{45}	200 s^{-1}	Refs. 19 and 21
k_{56}	15 s^{-1}	Refs. 8 and 21
k_{61}	1.6 $\mu M^{-1} \cdot s^{-1}$, [ATP] = 1 mM	Refs. 18 and 31







$$\mathbf{F}_i(\mathbf{r}_i) = 0 = -\gamma_i \dot{\mathbf{r}}_i - \nabla U(\mathbf{r}_i) + \xi_i(t)$$

$$U = \frac{1}{2}\sum_{i=2}^{8} V_i(\cos\phi_i(t) - \cos\phi_i^0)^2 + \frac{1}{2}K\sum_{i=1}^{8}(r_{ij} - r_0)^2$$

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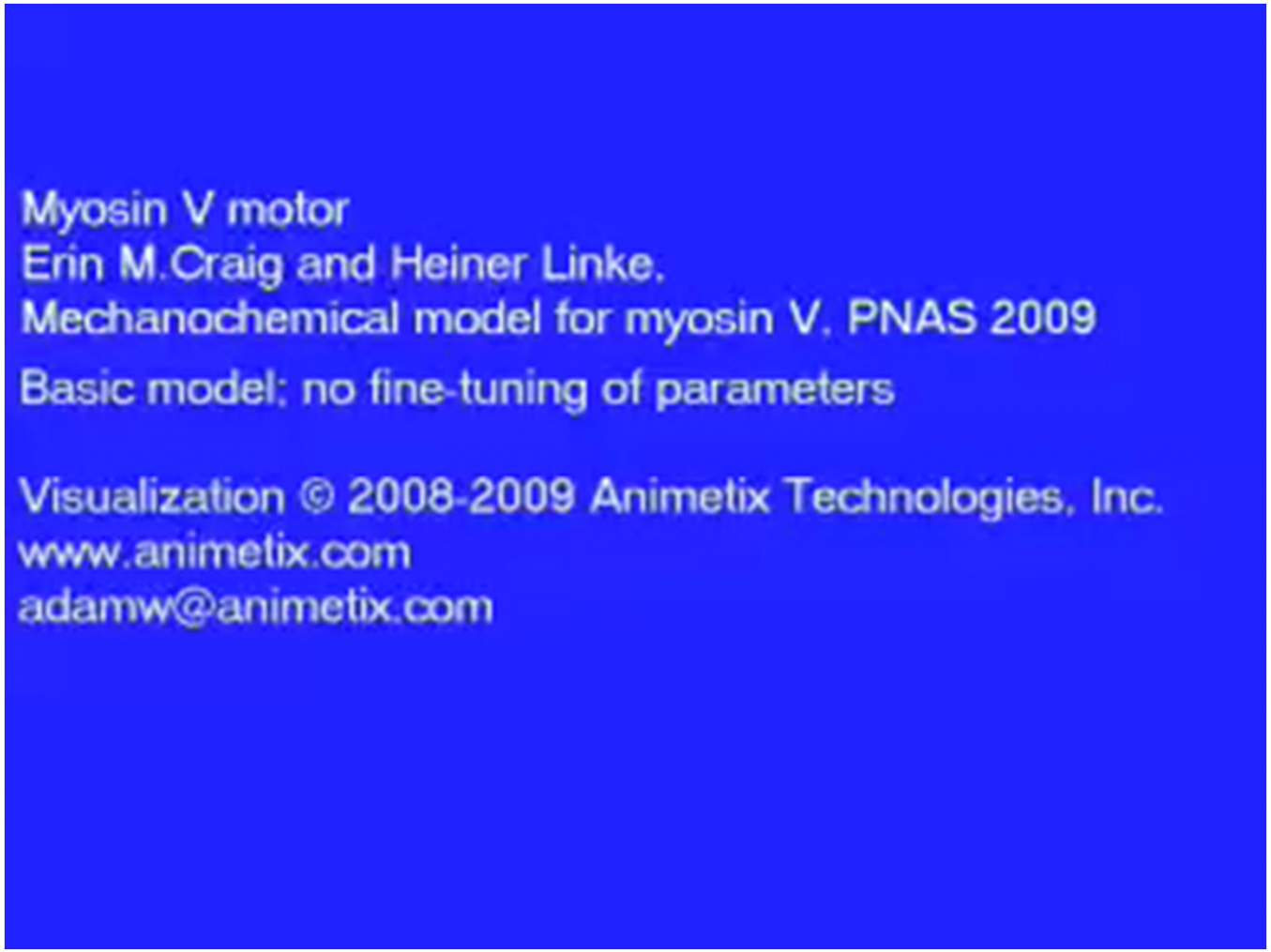

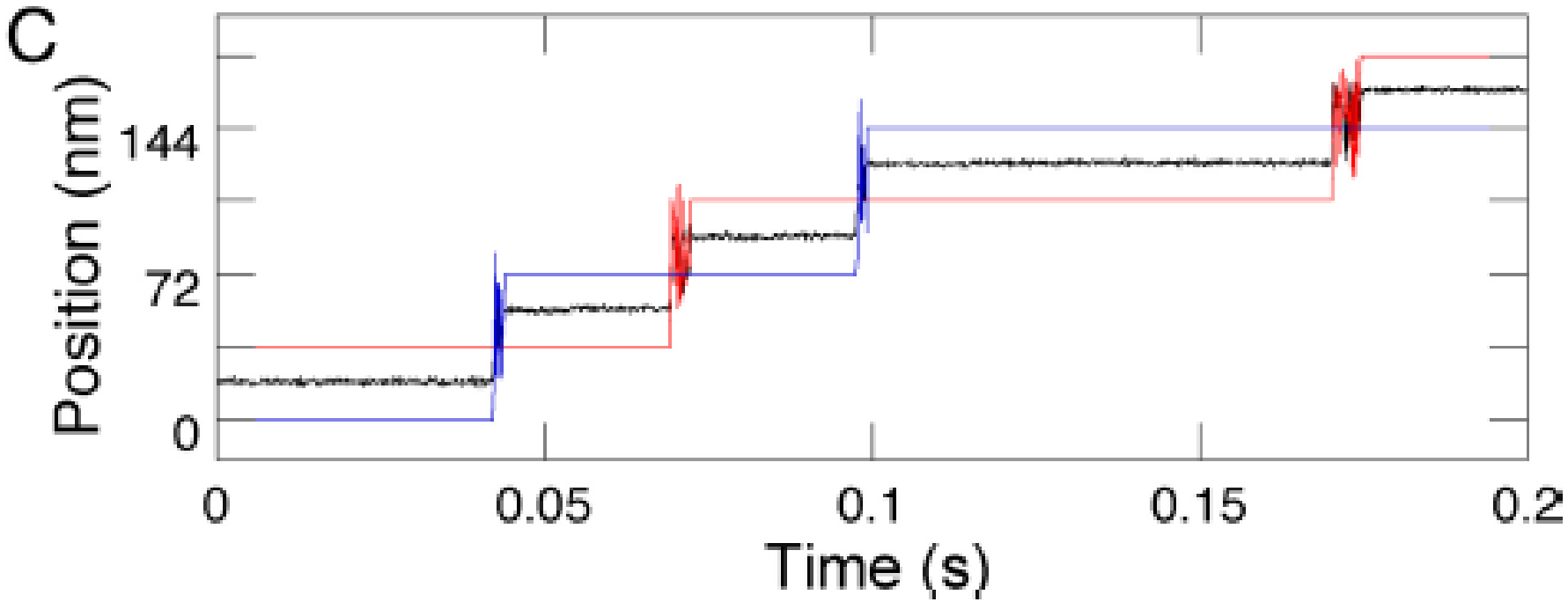

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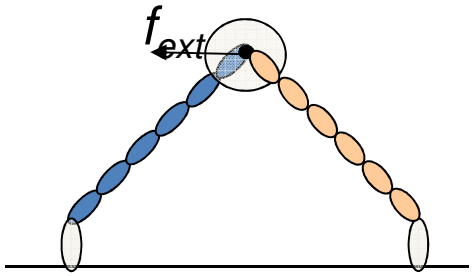
Myosin V 3D model: inputs and outputs



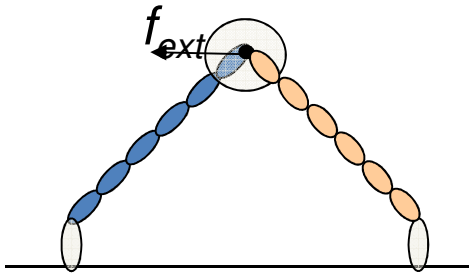
Model Parameters:

- Binding sites
- Neck domain length
- Drag coefficients
- Transition rates
- Neck domain persistence length
- Equilibrium angles
- Rotational stiffness
- Neck domains: free swivel?

Experimentally measured behavior:

- Average step size
- Substep ("prestroke") size, ATP dependence
- Step trajectories, cargo
- Step trajectories, individual heads
- Profile of step average, cargo
- Profile of step average, heads
- correlation of z-position with steps
- correlation of x and z variance with steps
- non-Gaussian fluctuations (failed steps?)
- positional distribution of detached head
- load dependence of velocity and dwell times
- Mechanical processivity (steps per contact)
- Kinetic processivity (1 step per ATP)
- Stepping vs. neck length
- Characteristics of backsteps under load

Mechanistic model can demonstrate which physical assumptions are consistent with known data. This can help address...



- *Mechanics of stepping: what happens during one-head-bound state?*
- *Role of strain in coordinated walking?*
- *Backwards steps under load: processive walking?*
- *Mechanism behind distribution of step sizes for different neck lengths?*

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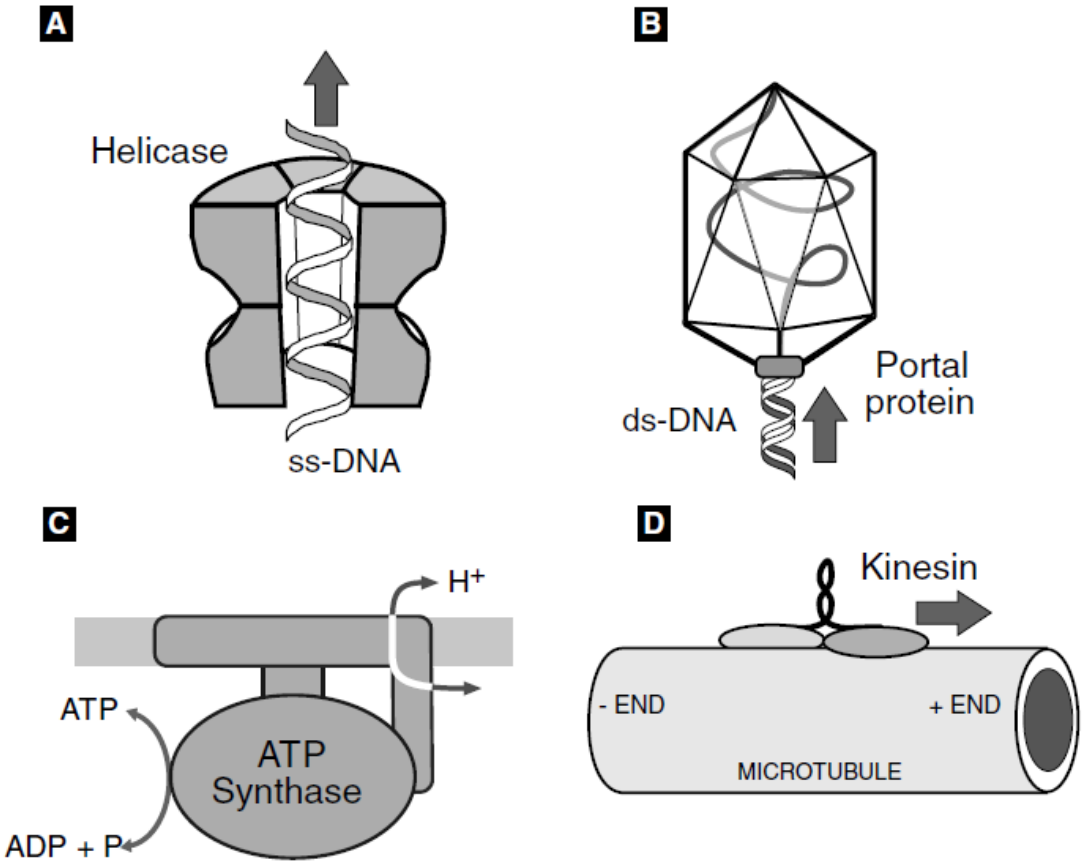


Figure 12.1 Amazing variety of molecular motors: (A) Rotary motor DNA helicase translocates unidirectionally along the DNA strand using nucleotide hydrolysis as a "fuel." (B) Another rotary motor hydrolyzing ATP, bacteriophage portal protein, drives DNA in and out. (C) Reversible rotary motor ATP synthase either produces ATP using ion gradient or pumps protons hydrolyzing ATP. (D) Linear motor kinesin is a "walking enzyme." Utilizing chemical energy stored in ATP, it moves "head-over-head" toward the plus end of the microtubule "track." Some of these motors are discussed in this chapter.

A Mechanochemical Model

spatial

$$\frac{\partial p}{\partial t} = D\left[\underbrace{\frac{\partial}{\partial x}\left(p\frac{\partial(\phi/k_{\mathrm{B}}T)}{\partial x}\right)}_{\text{Drift}} + \underbrace{\frac{\partial^2 p}{\partial x^2}}_{\text{Diffusion}}\right] \quad \text{[Smoluchowski equation].}$$

$$\phi(x,t) = \underbrace{\phi_{\mathrm{I}}(x,t)}_{\text{internally generated forces}} + \underbrace{\phi_{\mathrm{L}}(x,t)}_{\text{external load forces}},$$

reaction

$$\frac{d}{dt}\mathbf{P} = \mathbf{J}_\xi = \mathbf{K}\cdot\mathbf{P}, \quad \mathbf{P} = \begin{pmatrix} p_- \\ p_0 \end{pmatrix}, \quad \mathbf{K} = \begin{pmatrix} k^* & -k^- \\ -k^* & k^- \end{pmatrix}.$$

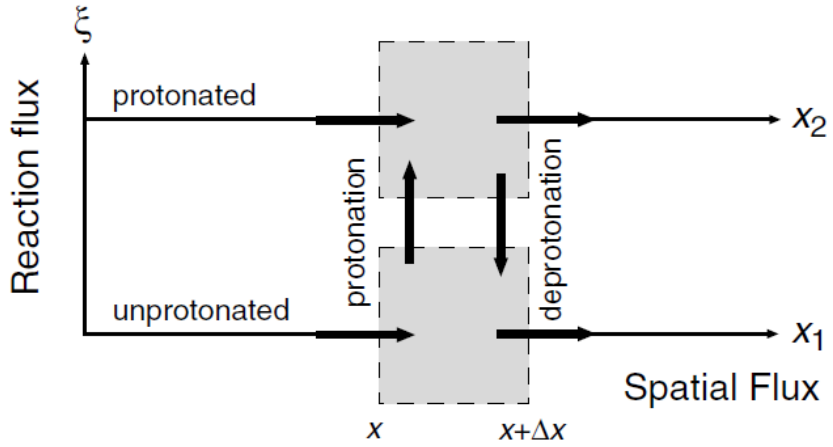
A Mechanochemical Model

Mechano-chemical coupling

$$\frac{\partial}{\partial t}\begin{pmatrix} p_1 \\ p_2 \end{pmatrix} = \text{net flow in space} + \text{net flow along reaction coordinates}$$

$$= -\overbrace{\begin{pmatrix} (\partial/\partial x_1) J_{x_1} \\ (\partial/\partial x_2) J_{x_2} \end{pmatrix}} + \overbrace{\begin{pmatrix} J_{\xi_1} \\ J_{\xi_2} \end{pmatrix}}$$

$$= -D\begin{pmatrix} -(\partial/\partial x_1)[p_1 \partial(\phi_1/k_B T)/\partial x_1 + (\partial p_1/\partial x_1)] \\ -(\partial/\partial x_2)[p_2 \partial(\phi_2/k_B T)/\partial x_2 + (\partial p_2/\partial x_2)] \end{pmatrix} + \begin{pmatrix} k^- p_2 - k^* p_1 \\ k^* p_1 - k^- p_2 \end{pmatrix}$$



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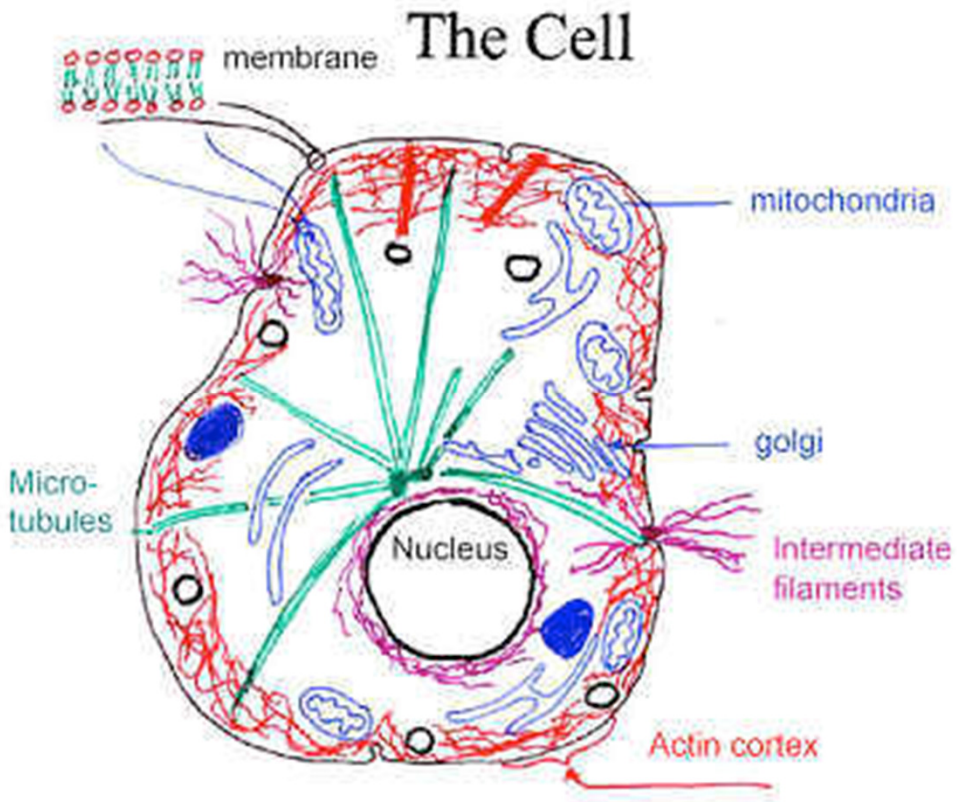
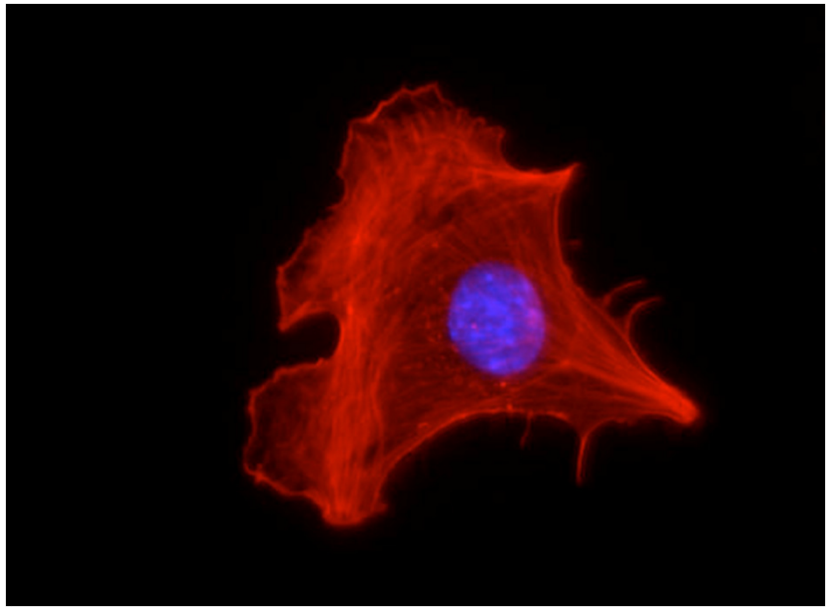
The Cytoskeleton

- Complex, network structure that gives the cell mechanical support and shape



The Cytoskeleton

- Composed of actin filaments, crosslinked to one another to form a network



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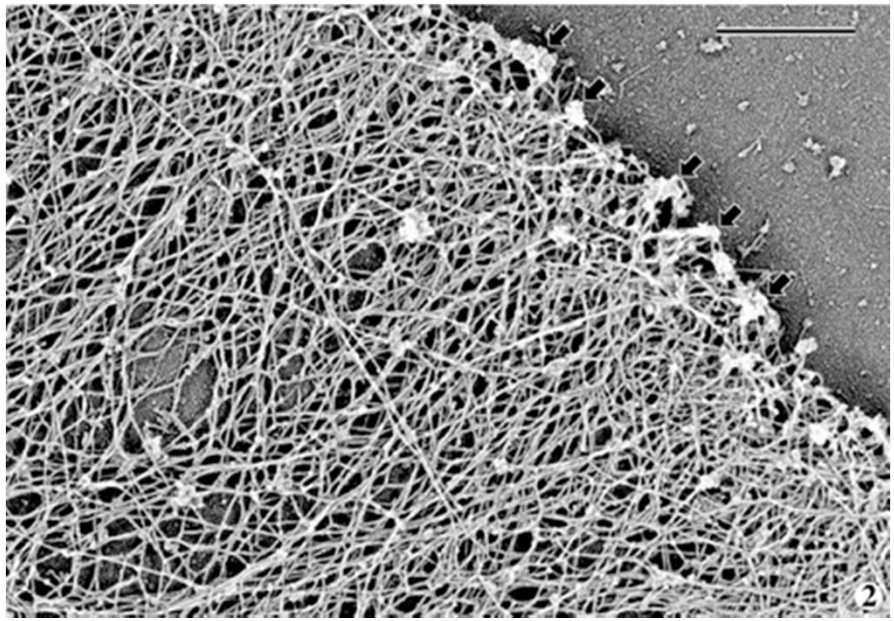

http://scienceblogs.com/transcript/2007/10/last_week_i_s
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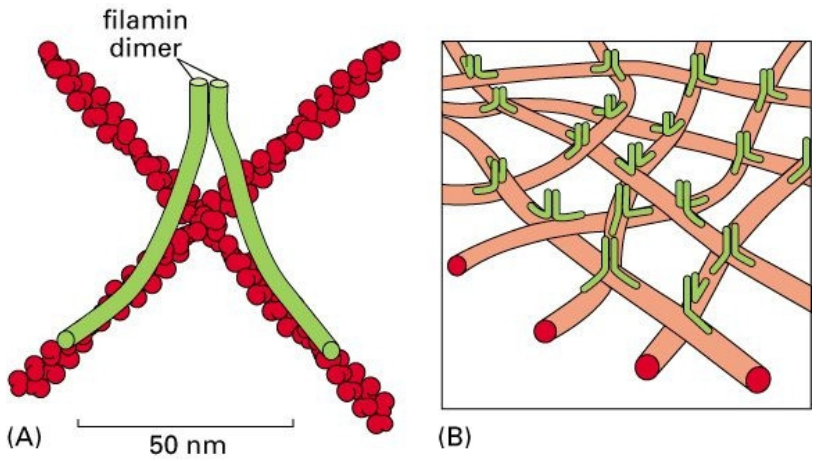
The Cytoskeleton

- Crosslinking proteins: filamin, alpha-actinin
- Approximately 100,000-500,000 , 1 μm long filaments in a cell cytoskeleton



Alberts, Molecular Biology of the Cell

- Can reorganize itself to perform various tasks
- Rearrangement can produce different mechanical properties

Modeling the Cytoskeleton

- 10^5, 1 micron length filaments in cytoskeleton
- Crosslinks every 100 nm
- 10^6 filament segments + 10^5crosslinks
- Discrete model, system of masses and springs
- Size of time step limited by:
  - Space step (length of filament segments)
- Algorithm Speed also limited by number of elements in system

“Rheology of the Cytoskeleton”

- Models range from discrete:
  - Tensegrity and filament based models
- to Continuous:
  - Elastic, Viscoelastic, Porous, Soft Glassy Material
- Credits wide range to scale of phenomenon of interest

Outline

- Simulation of molecular motor
- Modeling cytoskeleton
  - Coarse-grained models
  - Continuum models
  - Localized models
- Simulation of single cell locomotion
- Simulations of movements in multicellular systems

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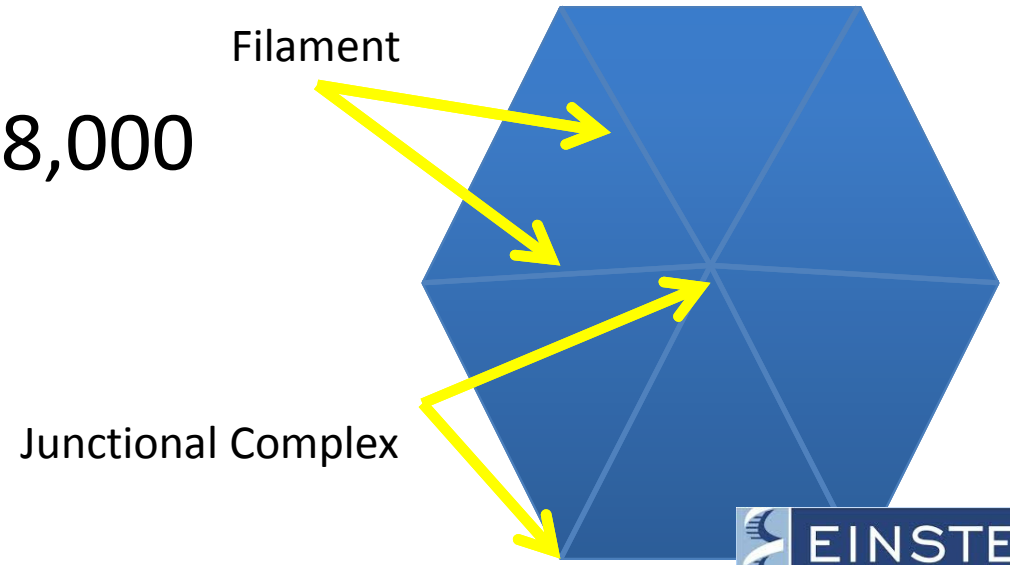
Coarse-Grained Models

- Incorporates averaging and smoothing techniques to create a lower resolution description of the material to be modeled

Coarse-Grained Models

- Li et al created a coarse-grained model of the red blood cell (RBC) cytoskeleton to study its deformation with optical tweezers
- 10^5 filament vertices in the RBC, connected in 6-fold symmetry
- Model includes ~18,000 filament junctions



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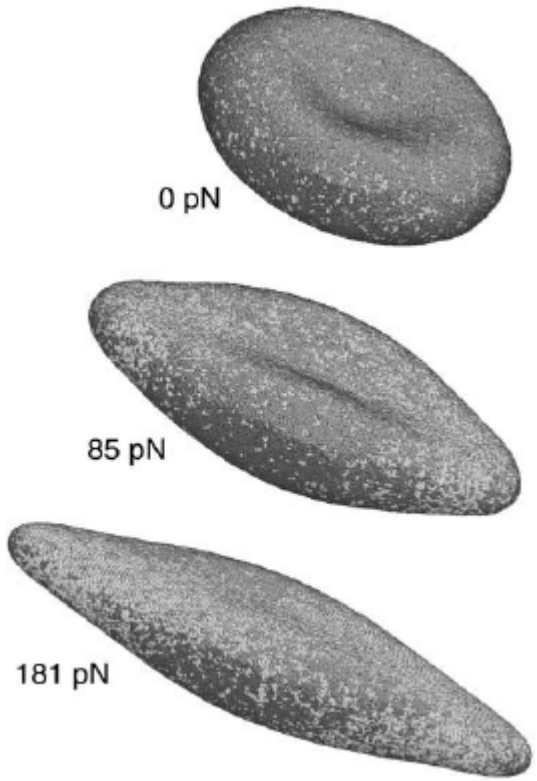
Coarse-Grained Models

- Begin with a RBC-shaped surface (donut shape), covered in filament vertices, connected in the typical 6-fold pattern
- Goal is capture the shape of RBC as it undergoes simulated optical tweezer experiments



Coarse-Grained Models

- Coarse-Grained Molecular Dynamics
- Update vertex positions with $m\ddot{x}_j = F_j$
- Where the forces are given as partial derivatives of the free energy:

$$E = E_{in-plane} + E_{bending} + E_{surface} + E_{Volume}$$

$$F_j = \frac{\partial E}{\partial x_j}$$

Coarse-Grained Models

- Coarse-Graining can be an acceptable modeling method, when the material has a regular, homogeneous structure (like the RBC)
- For inhomogeneous media, this technique will tend to blur or average out interesting heterogeneities

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Continuum Models

- Material is treated as a continuous body
- Disregard material's microstructure
- Motion, Deformation modeled with a constitutive Law

Continuum Models

- Cogan and Guy, two-phase fluid model of the cytosol/cytoskeleton in crawling cells
- Cytoskeleton treated as a highly viscous, polymeric fluid compared to the cytosol, a fluid with water-like properties
- During crawling, cytoskeleton is constantly rearranging itself (crosslinks transient)

Continuum Models

- Two phase fluid model

  c = cytoskeleton, f = fluid cytosol

- Volume fractions of two fluids $\theta_c(x,t), \theta_f(x,t)$
- Velocity of each fluid $u_c(x,t), u_f(x,t)$

- Conservation of Mass

$$(\theta_c)_t + \nabla \cdot (u_c \theta_c) = J$$

$$(\theta_f)_t + \nabla \cdot (u_f \theta_f) = -J$$

Continuum Models

- Via the relation: $\theta_c + \theta_f = 1$
- Incompressibility condition pops out:

$$\nabla \cdot \left(u_c \theta_c + u_f \theta_f \right) = 0$$

Continuum Models

- Conservation of Momentum
  - Low Reynolds Flow, Inertia Neglected
  - Equation = Balance of Forces

$$\nabla \cdot \left(\theta_c T_c \right) + M = 0$$

$$\nabla \cdot \left(\theta_f T_f \right) - M = 0$$

- T = Stress Tensor, M = momentum transfer between the two phases

Continuum Models

- Stress Tensor T of the form: $T_i = p_i I + \sigma_i$
- Transfer of Momentum M of the form:

$$M = P_{cf} \nabla \theta_f - \xi \left(u_f - u_c \right)$$

- First term: force generated by local interactions of the two phases, average of surface forces at interface, may be dependent on chemical interactions

Continuum Models

- Second term: Transfer of momentum due to drag generated of one fluid passing through the other

$$M = P_{cf} \nabla \theta_f - \xi \left(u_f - u_c \right)$$

Continuum Equations

- Equation Set:

$$\theta_c + \theta_f = 1$$

$$\nabla \cdot \left(u_c \theta_c + u_f \theta_f \right) = 0$$

$$\left(\theta_c \right)_t + \nabla \cdot \left(u_c \theta_c \right) = J$$

$$\nabla \cdot \left(\theta_c T_c \right) + M = 0$$

$$\nabla \cdot \left(\theta_f T_f \right) - M = 0$$

$$\theta_c(x,t), \theta_f(x,t)$$

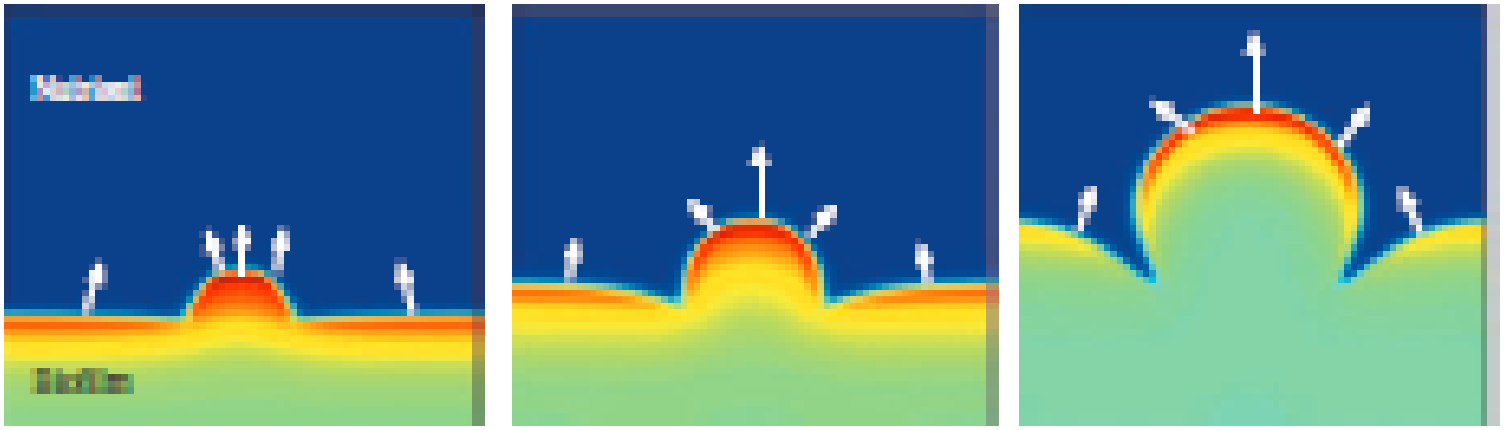

Figure 3. Snapshots of the solution to the multiphase equations, neglecting the external flow. The nutrient diffuses from the top (in the blue region) and is consumed by the bacteria within the biofilm region. The colormap shows regions of high growth (red) in the tips of the initial colony. The higher growth leads to higher osmotic pressure, which in turn, moves the biofilm region. Since the tips have access to more nutrient (via diffusion), the perturbation is reinforced leading to a highly heterogeneous structure. The arrows represent the interface velocity.

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Detailed, Localized Models

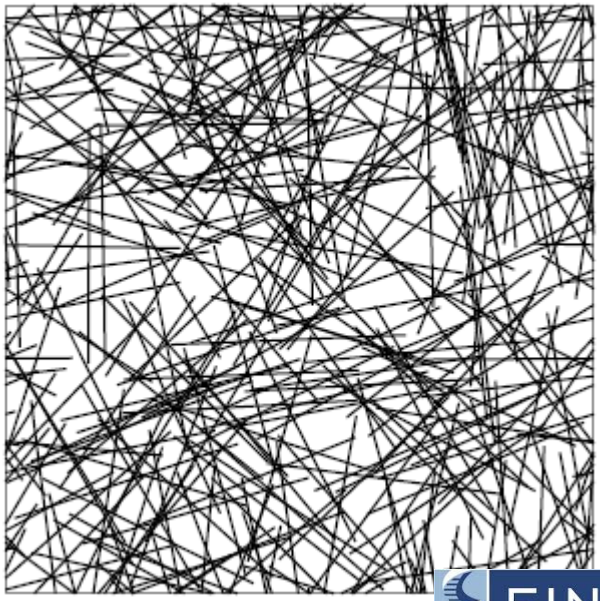
- Focus on thoroughly modeling a portion of the material, representing the discrete elements that make up its structure
- Hope is that understanding how small patch of material behaves will provide insight into a continuum level description of the material

Detailed, Localized Models

- Head, Levine, MacKintosh model of patch of actin network
- Study network response to stress
- Study how network architecture (crosslink connectivity, filament mechanical parameters) affect bulk mechanical properties of the cytoskeleton (shear and Young's modulus)

Detailed, Localized Models

- Create a 2D network of filaments
- Lay down filaments with random orientations and positions until desired density is achieved
- Intersection of two filaments is a crosslink (freely rotating)



Detailed, Localized Models

- Energy of the system:

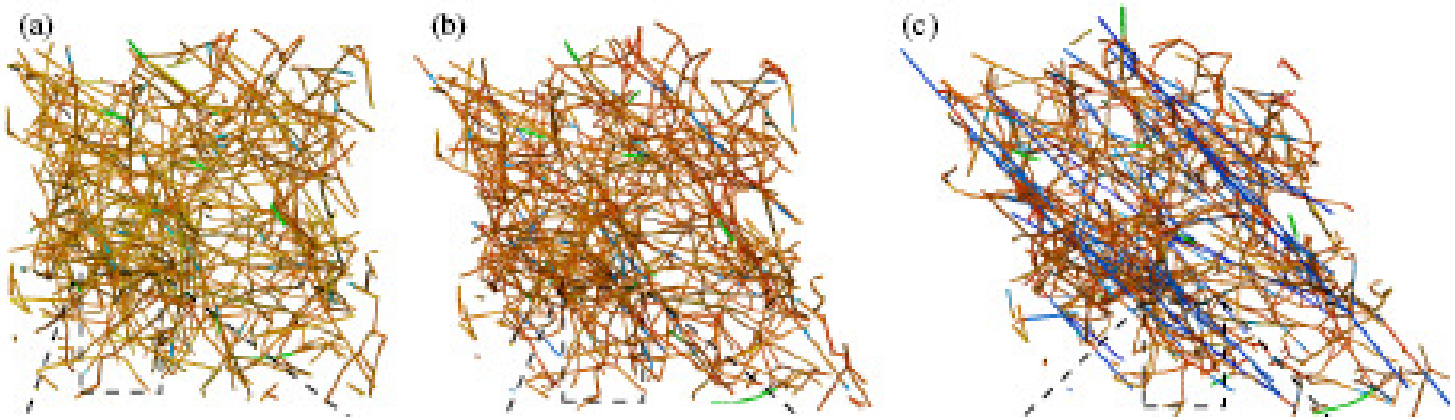
$$E = E_{streching} + E_{bending}$$

$$E = \frac{1}{2}\mu\int\left(\frac{\partial l}{\partial s}\right)^2 ds + \frac{1}{2}\kappa\int\left(\frac{\partial^2 w}{\partial s}\right)^2 ds$$

- Discrete version of this expression, calculated with segment endpoints and midpoints

Detailed, Localized Models

- Shear stress γ applied to the network



- Filaments rearranged via energy minimization, to seek a position of mechanical equilibrium

$$E = \frac{1}{2}\mu\int\left(\frac{\partial l}{\partial s}\right)^2 ds + \frac{1}{2}\kappa\int\left(\frac{\partial^2 w}{\partial s}\right)^2 ds$$

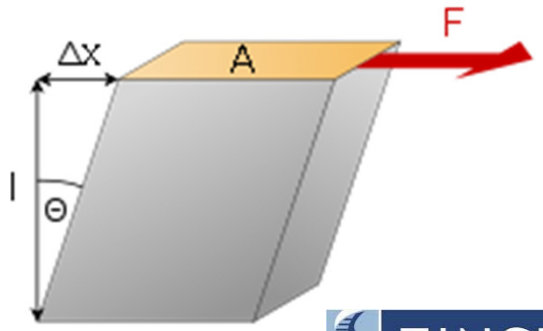
Detailed, Localized Models

- Shear modulus G calculated by utilizing

$$E = G\frac{\gamma^2}{2} \quad \rightarrow \quad G = E\frac{2}{\gamma^2}$$

In materials science, **shear modulus** or **modulus of rigidity**, denoted by *G*, or sometimes *S* or μ, is defined as the ratio of shear stress to the shear strain

$$G \stackrel{\text{def}}{=} \frac{\tau_{xy}}{\gamma_{xy}} = \frac{F/A}{\Delta x/l} = \frac{Fl}{A\Delta x}$$



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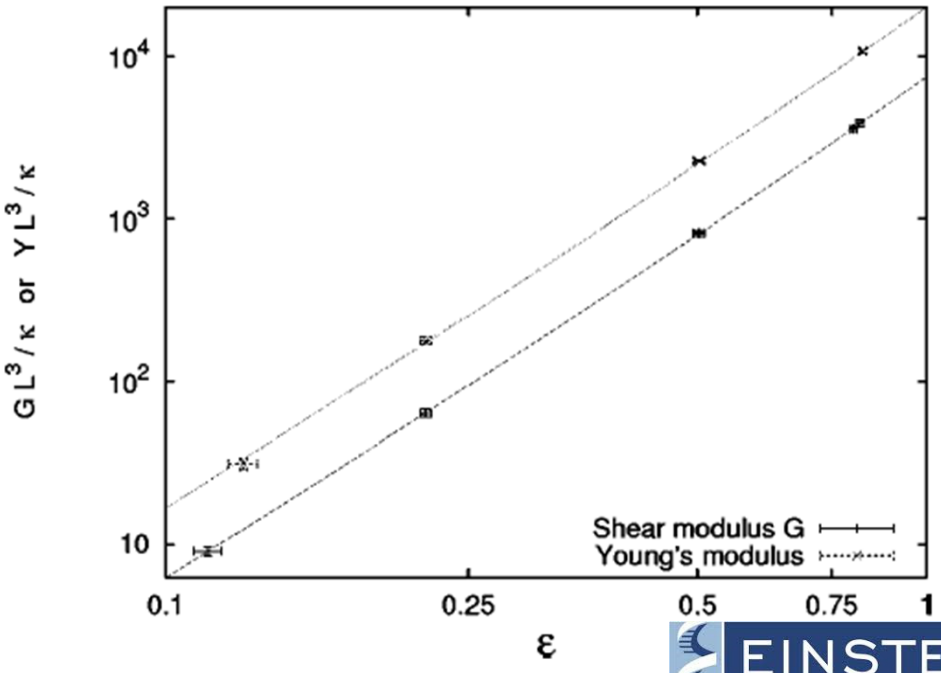
Detailed, Localized Models

- Results from these studies:
  - Networks exhibited strain hardening (as strain is increased, so does elasticity modulus)
  - Filaments tend to align themselves with the axis of strain



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Detailed, Localized Models

- Utilize data to develop a relationship between the strain and the mechanical parameters

$$G = A\varepsilon^{f}(1 + B\varepsilon)$$

- Data represents average mechanical moduli of many generated networks
- Coefficients A and B depend on crosslink density and individual filament moduli

Summary

- Single scale models of a material are justifiable for capturing particular phenomena
- The example presented here, the cytoskeleton, can be described by different equations in different situations
- Assumptions of isotropy were made to some degree in each example model
- Multiscale modeling may be necessary when isotropy cannot be assumed

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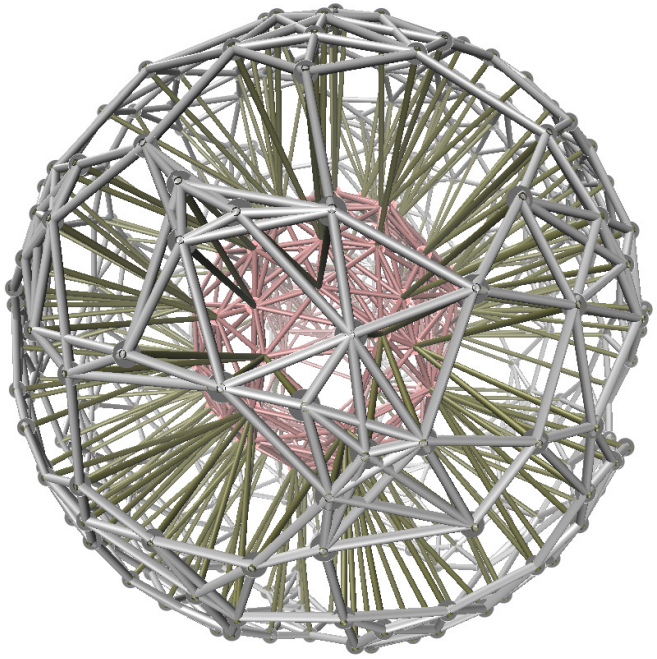
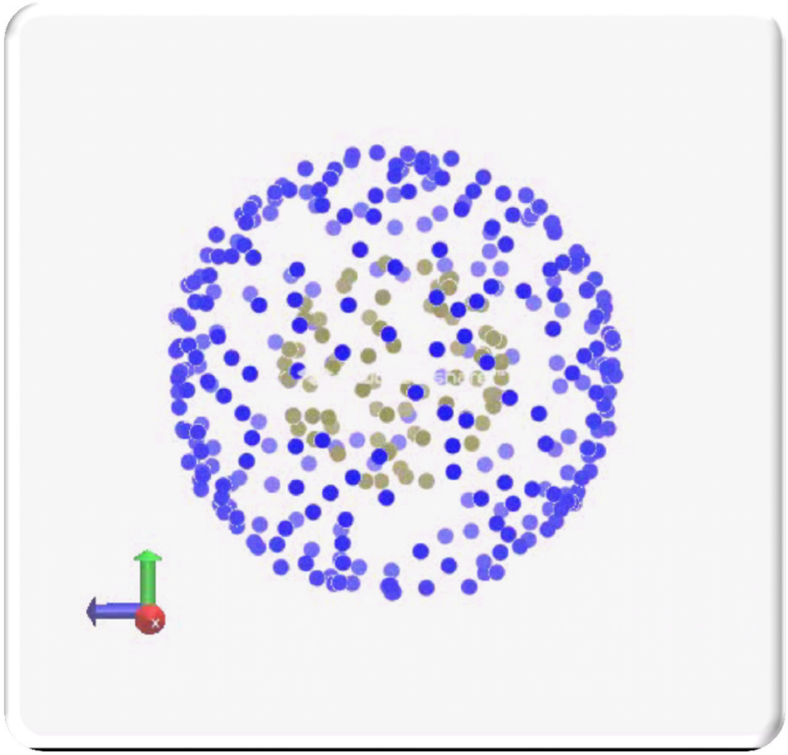
Cell-based Simulations





Crawling Cells

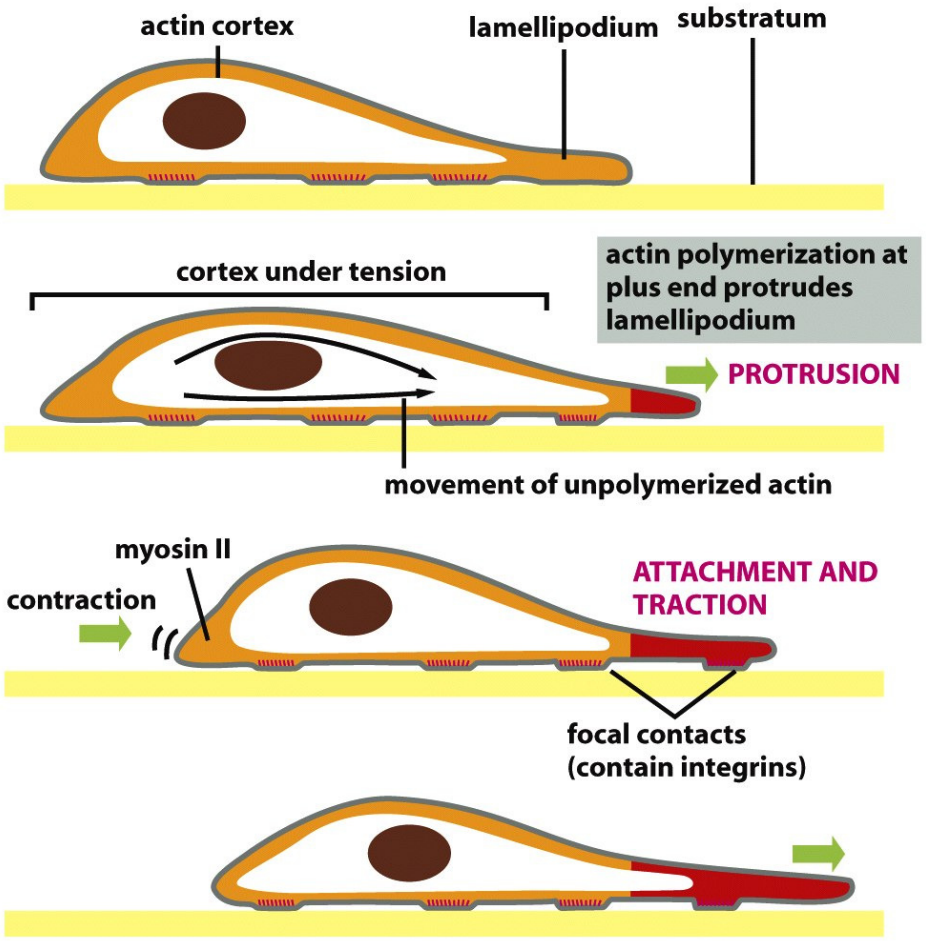
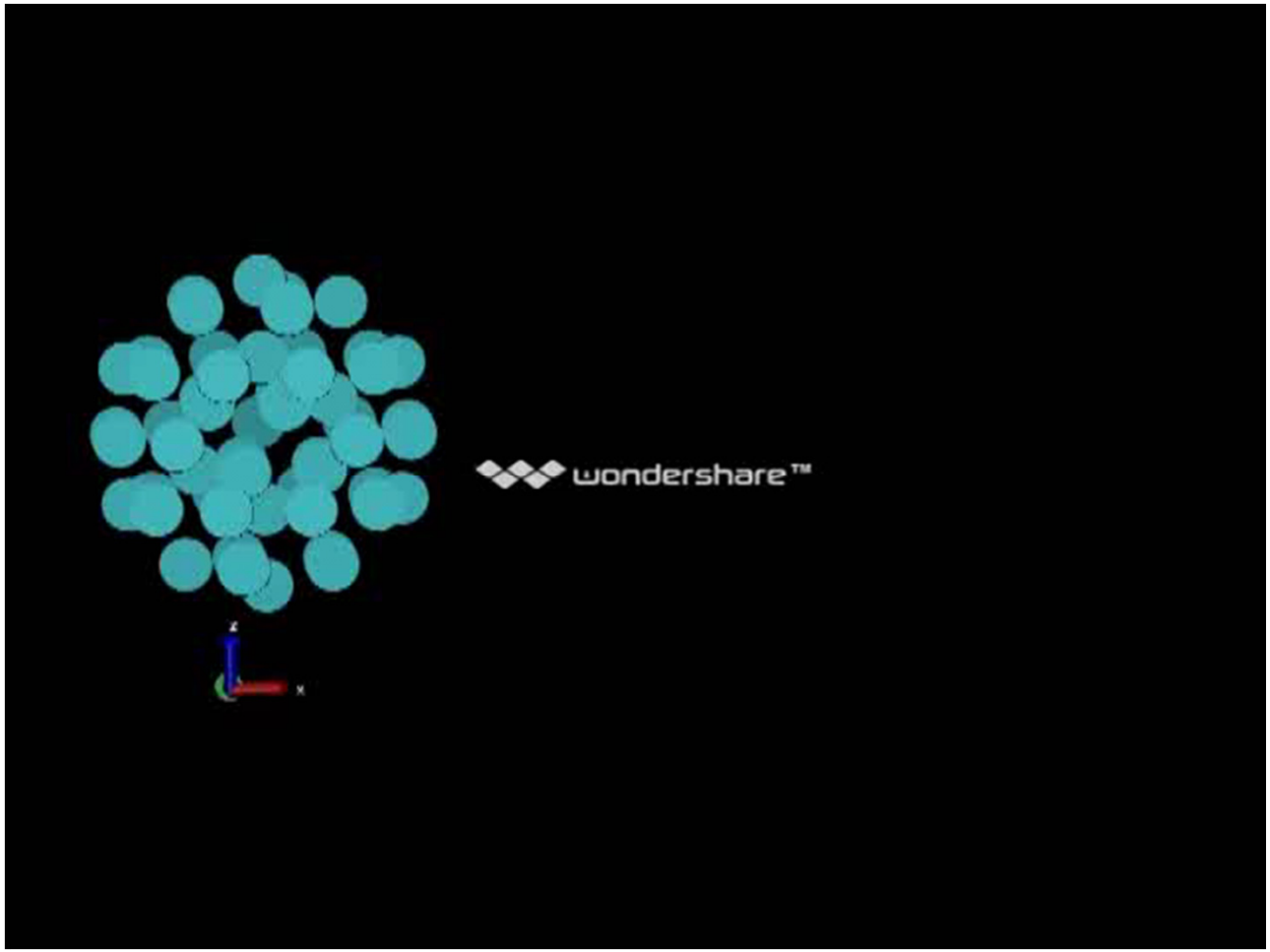


Figure 16-86 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Alberts, Molecular Biology of the Cell

1. Polarization of the cell (defining front vs. back)
2. Protrusion of the leading edge
3. Formation of adhesive contacts with the surface
4. De-adhesion and retraction of the trailing edge



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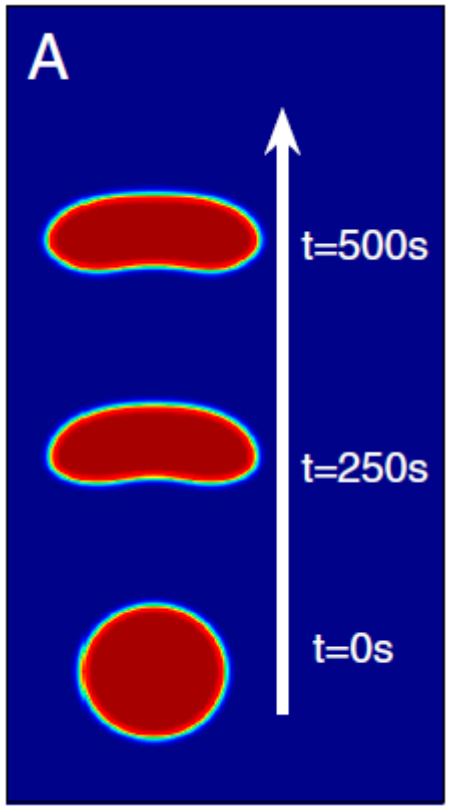
Other methods: phase-field theory

$$\frac{\partial \phi}{\partial t} = -\mathbf{u}\cdot\nabla\phi + \Gamma\left(\epsilon\nabla^2\phi - \frac{G'}{\epsilon} + c\epsilon|\nabla\phi|\right)$$

$$\nu_0\nabla\cdot[\phi(\nabla\mathbf{u} + \nabla\mathbf{u}^T)] + \nabla\cdot\sigma_{\text{myo}} + \nabla\cdot\sigma_{\text{poly}} + \mathbf{F}_{\text{mem}} + \mathbf{F}_{\text{adh}} = 0$$

$$\frac{\partial}{\partial t}(\phi\rho_a) = -\nabla\cdot(\phi\rho_a\mathbf{u}) + D_a\nabla\cdot(\phi\nabla\rho_a) + \phi f(\rho_a, \rho_a^{\text{cyt}})$$

$$\frac{\partial}{\partial t}(\phi\rho_m) = -\nabla\cdot(\phi\rho_m\mathbf{u}) + D_m(\rho_a)\nabla\cdot(\phi\nabla\rho_m)$$



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    - Voronoi tessellation

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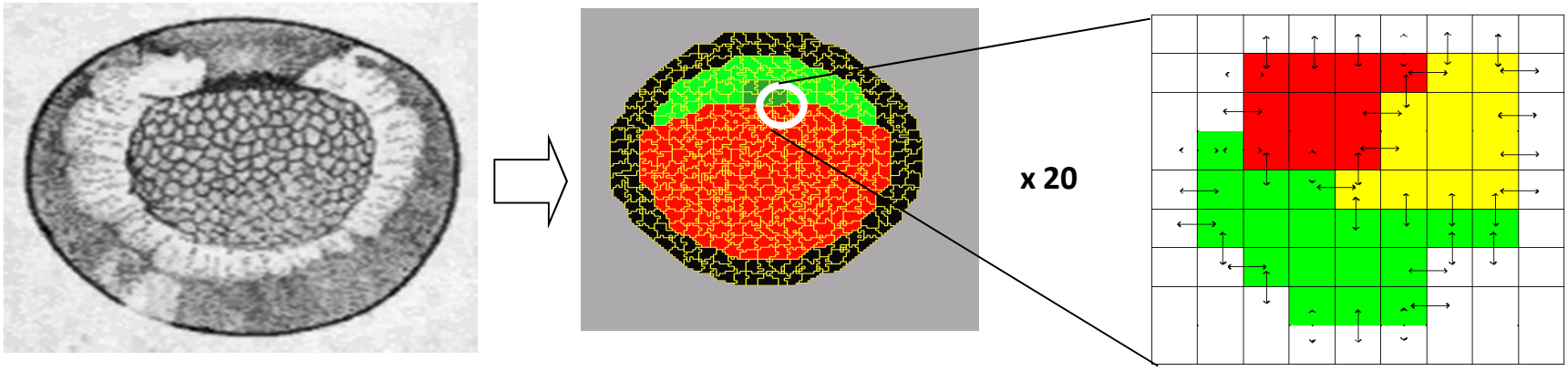
Physical and Mathematical Background

- The Glazier-Graner-Hogeweg Model (*GGH*) is a Metropolis-Type Lattice-Based Pseudo-Hamiltonian Model

- Pseudo-Hamiltonian Lattice-Based Model
- Monte Carlo Sampling

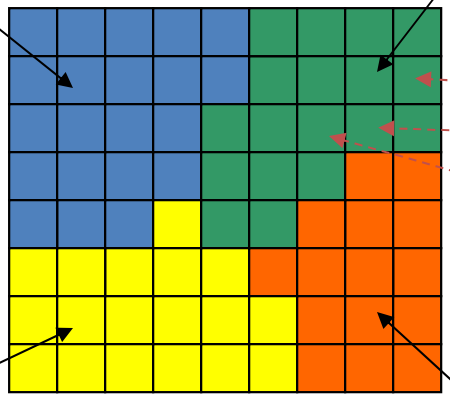
GGH Model Basics

Lattice based model where cells are represented as spatially extended objects occupying several lattice sites



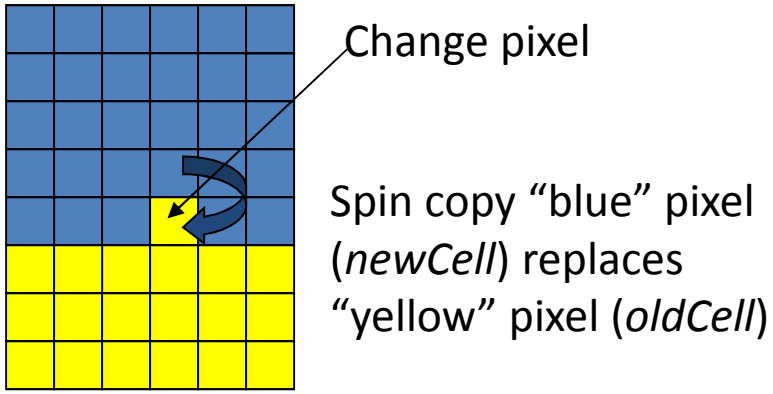
Experiment

Mathematical/Computer Representation



Cell motility – GGH dynamics

GGH is Monte Carlo algorithm where cells randomly are trying to extend their boundaries by overwriting neighboring pixels. This results in **volume increase of expanding** cell and **volume decrease for cell whose pixel is being overwritten**



Not All Pixel Copy Attempts Are Created Equal – Energy of Cellular System

GGH Model is based on energy minimization using Metropolis algorithm. Most biological interactions between cells are encapsulated in the Effective Energy, *H.*

- *H* is generally the sum of many separate terms.
- Each term in *H* encapsulates a single biological mechanism.
- Additional Cell Properties described as **Constraints.**

$$H = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}(1-\delta_{\sigma(x),\sigma(x')}) +$$
$$\lambda_s (s_\sigma - S_\sigma)^2 + \lambda_v (v_\sigma - V_\sigma)^2 +$$
$$E_{chem} + E_{hapt} + \ldots$$

- Metropolis algorithm: probability of configuration change

$$P(\Delta E) = 1, \ \Delta E \leq 0$$
$$P(\Delta E) = e^{-\Delta E/kT}, \ \Delta E > 0$$

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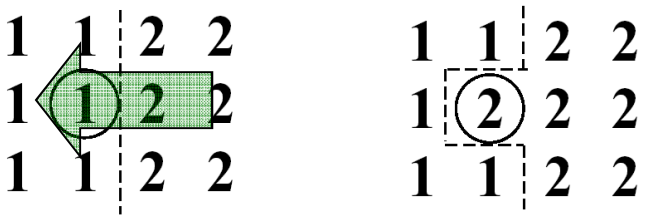
•The key to the GGH is its use of an Effective Energy or Hamiltonian, *H*, and Modified Metropolis Dynamics to provide the Cell Lattice Dynamics.

•This Dynamics means that cells fluctuate, with an Intrinsic Motility *T*, representing their cytoskeletally-induced motility.

•The Cell Lattice evolves at any time to gradually reduce the Effective Energy with a velocity proportional to the gradient of the Energy (Perfect Damping).

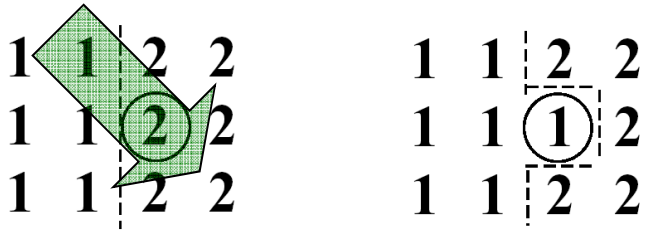
(a)



J_{12} $\quad 3\,J_{21}$

$$\Delta H = 3\,J_{21} - J_{12}$$

(b)



J_{21} $\quad 3\,J_{12}$

$$\Delta H = 3\,J_{12} - J_{21}$$

For a given ΔH, the Acceptance Probability is:

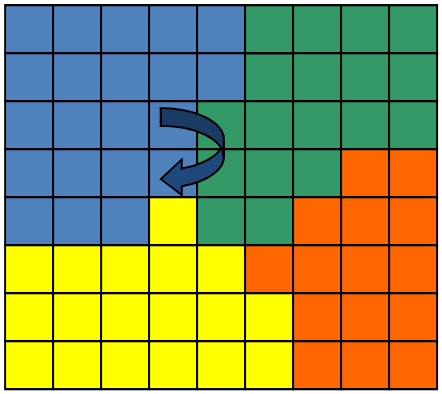
$$H = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}\left(1-\delta_{\sigma(x),\sigma(x')}\right)$$

$$P_{\text{acceptance}}\left(\Delta H\right) = \begin{cases} 1 & \text{if} \quad \Delta H < -Y \\ e^{\frac{-\Delta H + Y}{T}} & \text{if} \quad \Delta H \geq -Y \end{cases}$$

Y is a Dissipation Threshold.

Also introduce concept of Copy or Protrusion Direction $\hat{d}$ which May Affect the Acceptance

invalid attempt



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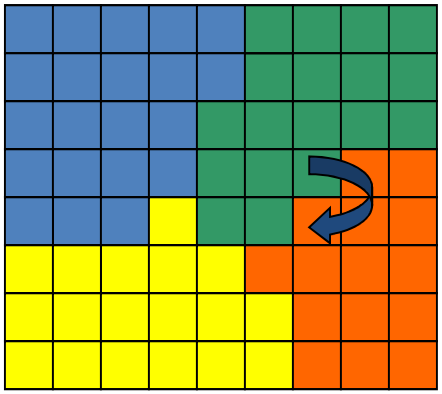

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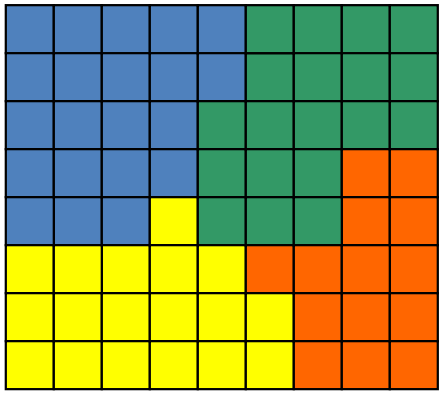

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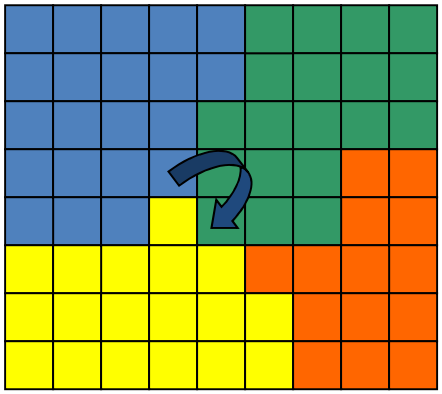

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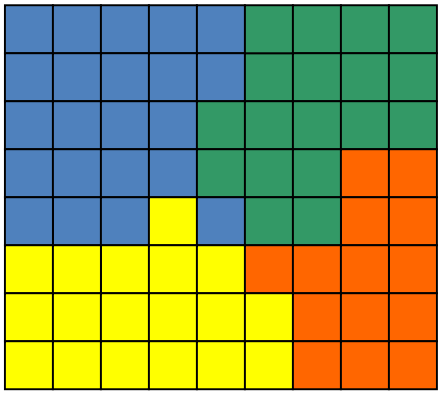

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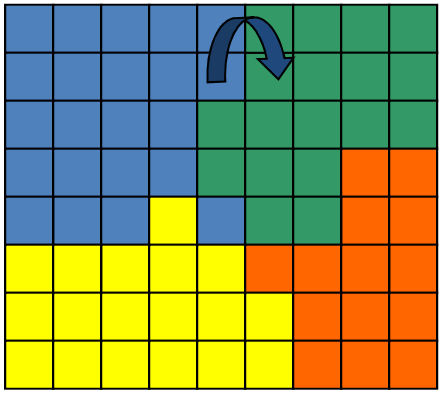
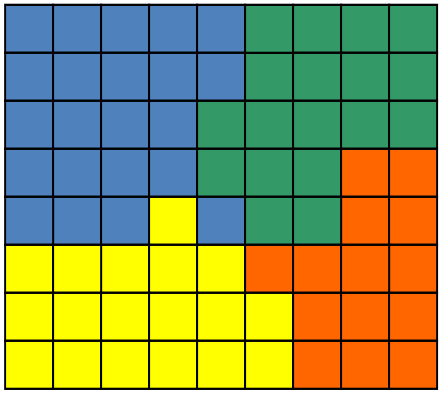


reject



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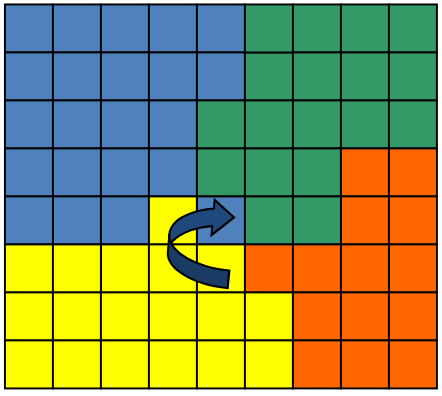

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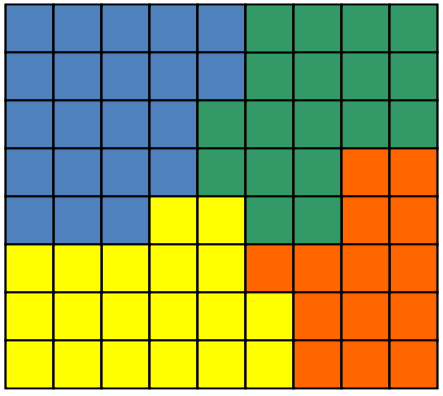


Constraints

- Most Important Constraints:
  - Cell Volume
  - Cell Surface Area
- Additional Examples:
  - Cell Elongation
  - Viscous Drag

Volume Constraints

- Most Cells (except Generalized Cells representing fluid media) have defined volumes.

$$H_{\text{volume}} = \sum_{\sigma} \lambda_{\text{volume}}(\sigma)\left(V(\sigma) - V_{\text{target}}(\sigma)\right)^2$$

- Provides an easy way to implement Cell growth:

$$\frac{dV_{\text{target}}(\sigma)}{\text{dt}} = f(\text{system state}, \text{cell state})$$

- And Cell Death:

$$V_{\text{target}}(\sigma) = 0$$

Surface Constraints

- Many Cells also have defined membrane areas.

$$H_{\text{surface}} = \sum_{\sigma} \lambda_{\text{surface}}(\sigma)\left(S(\sigma) - S_{\text{target}}(\sigma)\right)^2$$

- The ratio: $$R = \frac{\left(V_{\text{target}}(\sigma)\right)^{1/d}}{\left(S_{\text{target}}(\sigma)\right)^{1/d-1}}$$ (*d*=dimension)

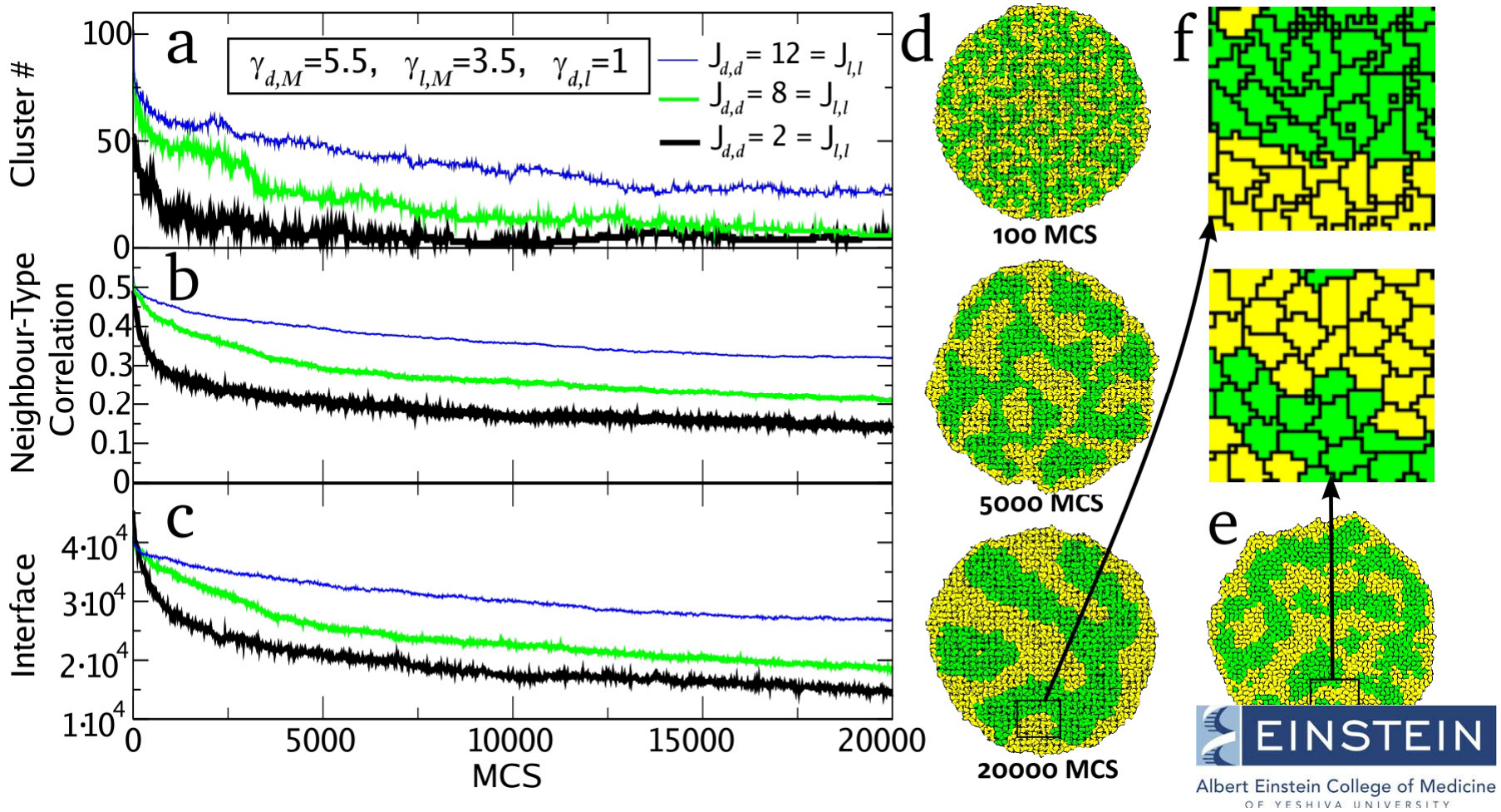
controls the Cell's general shape:

- Small *R* means the Cell is floppy (underinflated basketball)

- Large *R* means the Cell is spherical and rigid.

Cell sorting

$$E = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}\left(1-\delta_{\sigma(x),\sigma(x')}\right) + \lambda_v\left(v_\sigma - V_\sigma\right)^2$$



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Field Equations

- Most Fields evolve via diffusion, secretion, absorption and decay.

$$\frac{\partial C(\vec{i})}{\partial t} = D_c \nabla^2 C(\vec{i}) - \gamma_c C(\vec{i}) + S_c(\sigma(\vec{i})) - A_c(\sigma(\vec{i}))$$

Diffusion Decay Secretion Absorption

- Sometimes we couple two or more Fields via Reaction-Diffusion Equations of Form:

$$\frac{\partial C_1(\vec{i})}{\partial t} = f(C_1, C_2) + D_{c_1} \nabla^2 C_1(\vec{i}) - \gamma_{c_1} C_1(\vec{i}) + S_{c_1}(\sigma(\vec{i})) - A_{c_1}(\sigma(\vec{i}))$$

$$\frac{\partial C_2(\vec{i})}{\partial t} = g(C_1, C_2) + D_{c_2} \nabla^2 C_2(\vec{i}) - \gamma_{c_2} C_2(\vec{i}) + S_{c_2}(\sigma(\vec{i})) - A_{c_2}(\sigma(\vec{i}))$$

In GGH we can couple evolving fields to cell properties/behaviors

- Chemotaxis/Haptotaxis
- Chemical Concentration Dependent Cell Growth rate - mitosis
- Chemical Concentration Dependent Cell Differentiation

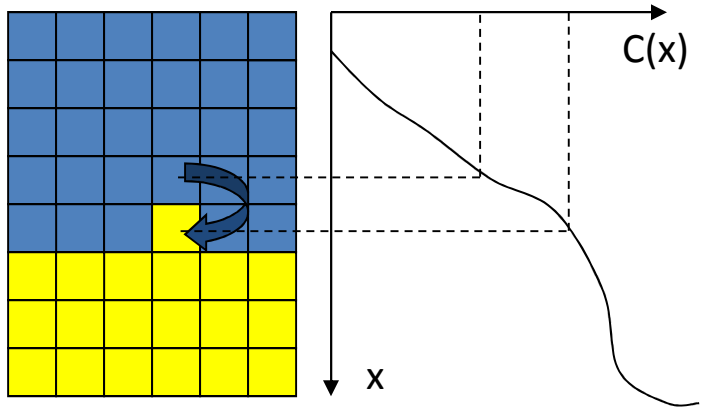
Chemotaxis Term – Most Basic Form

$$\Delta E_{chem} = -\lambda(c(x_{destination}) - c(x_{source}))$$

If concentration at the spin-copy destination pixel ($c(x_{destination})$) is higher than concentration at the spin-copy source ($c(x_{source})$) AND λ is positive then ΔE is negative and such spin copy will be accepted. The cell chemotacts up the concentration gradient

Lower concentration

Higher concentration



Chemorepulsion can be obtained by making λ negative

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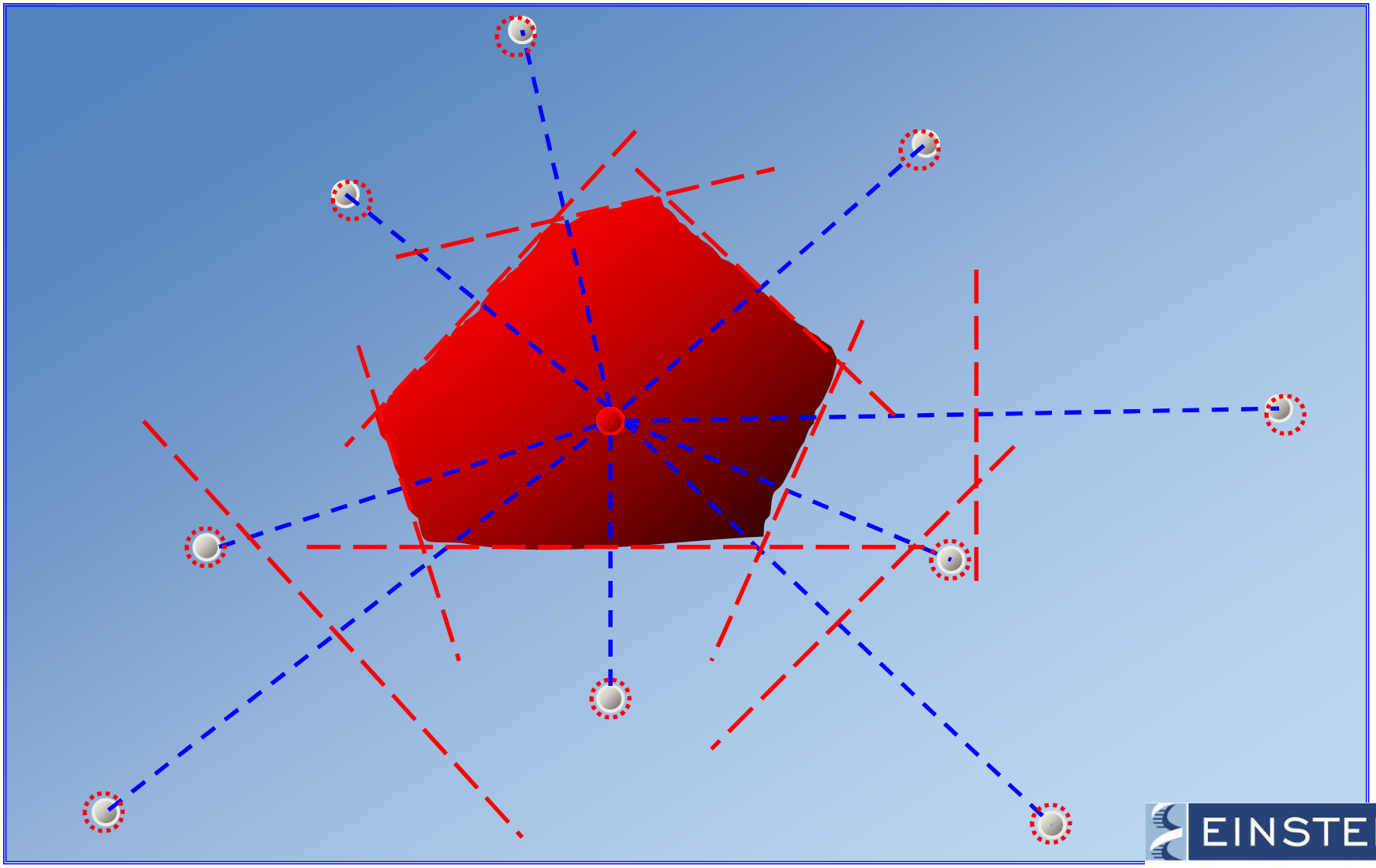
- Simulation of molecular motor
- Modeling cytoskeleton
- Simulation of single cell locomotion
- Simulations of movements in multicellular systems
    - Cell potts model
    - Voronoi tessellation

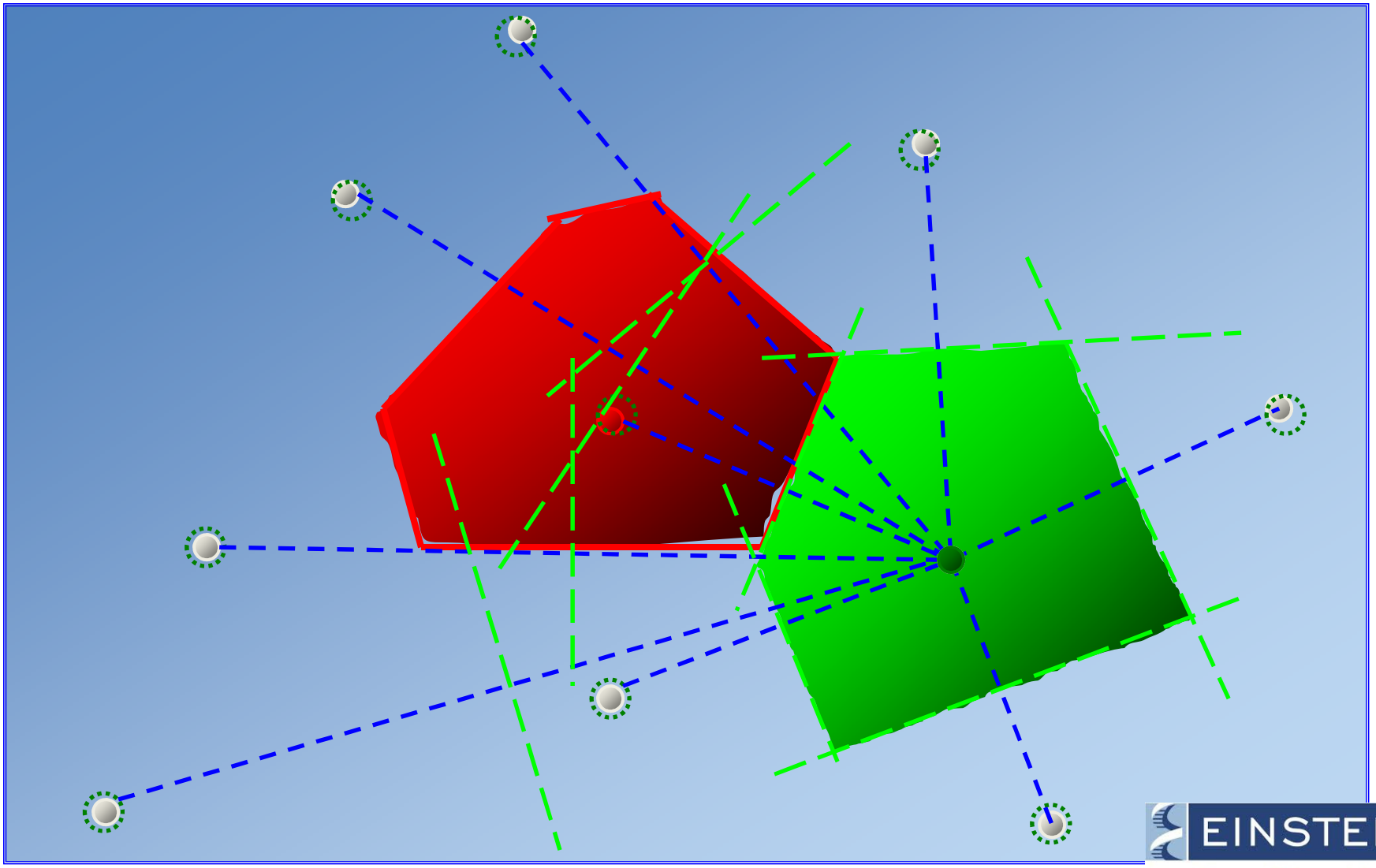
Monte-Carlo Simulation

- Voronoi tessellation as the representation of cell geometry



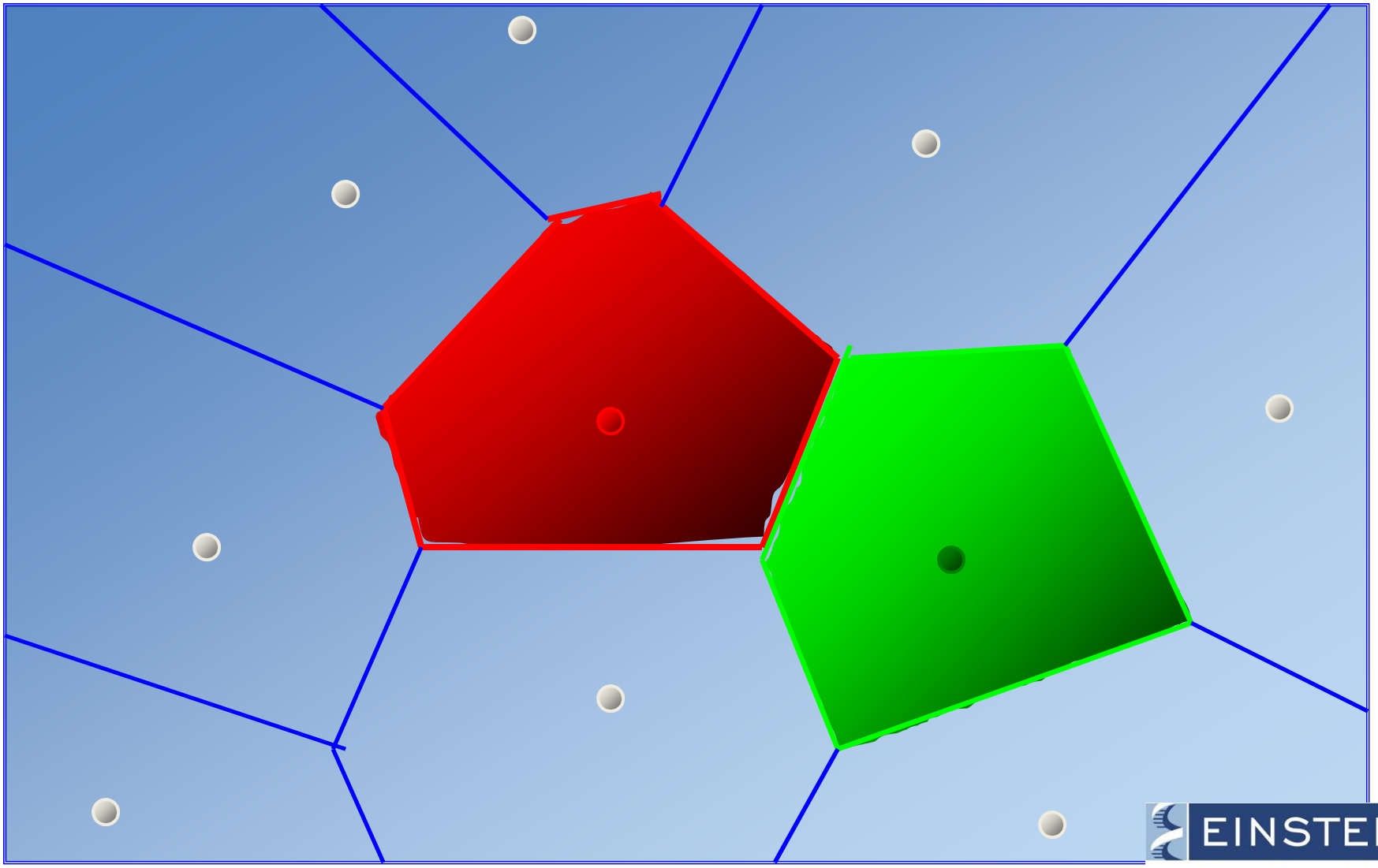
Monte-Carlo Simulation

- Voronoi tessellation as the representation of cell geometry



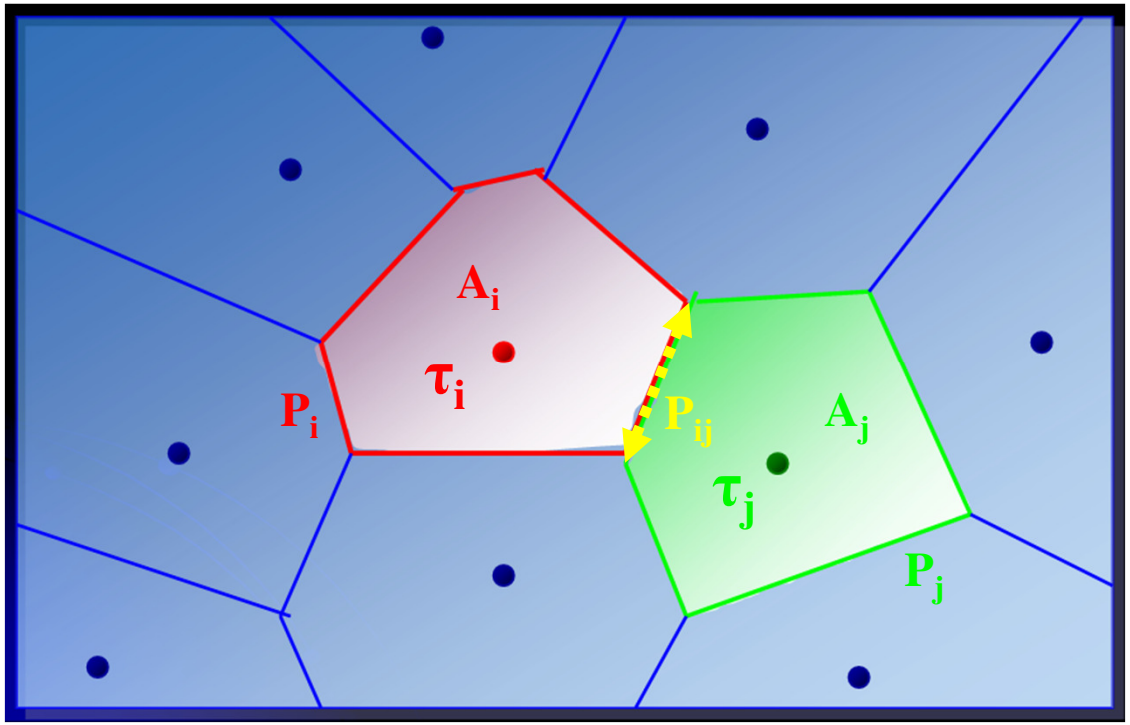
Monte-Carlo Simulation

- Voronoi tessellation as the representation of cell geometry



Monte-Carlo Simulation

- Hamiltonian function describing cell-cell interactions



$$U_{Total} =$$

$$-\sum_{ij} \gamma(\tau_i, \tau_j) P_{ij}$$

$$+$$

$$\lambda_A \sum_i \left(A_i - A_i^0\right)^2$$

$$+$$

$$\lambda_P \sum_i \left(P_i - P_i^0\right)^2$$

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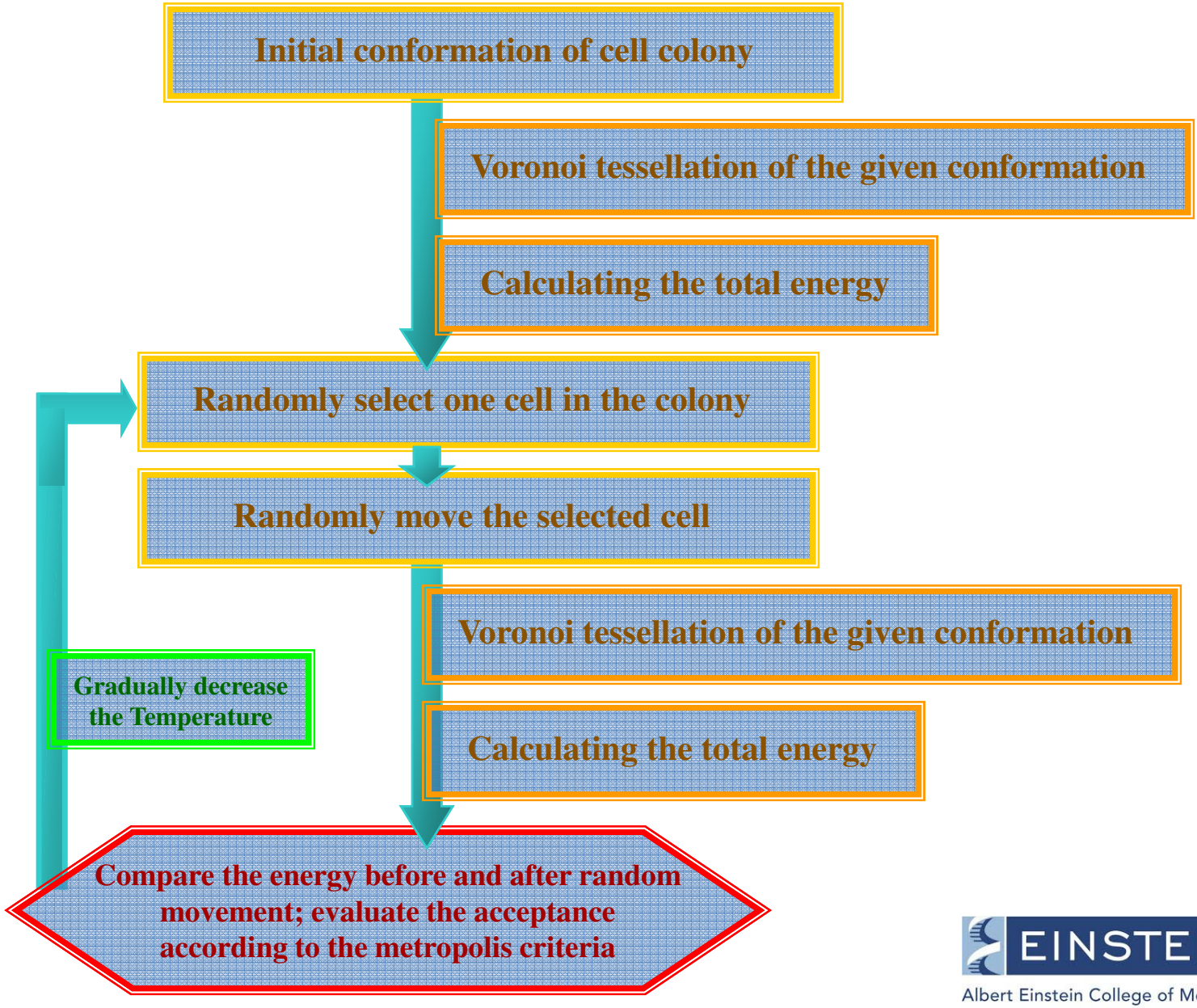
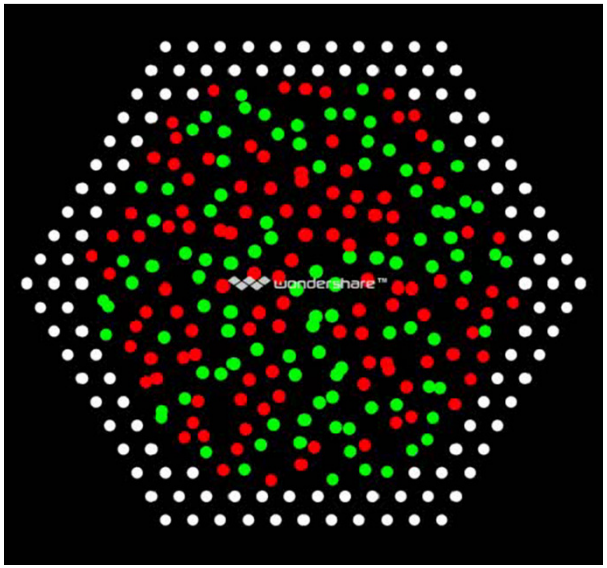
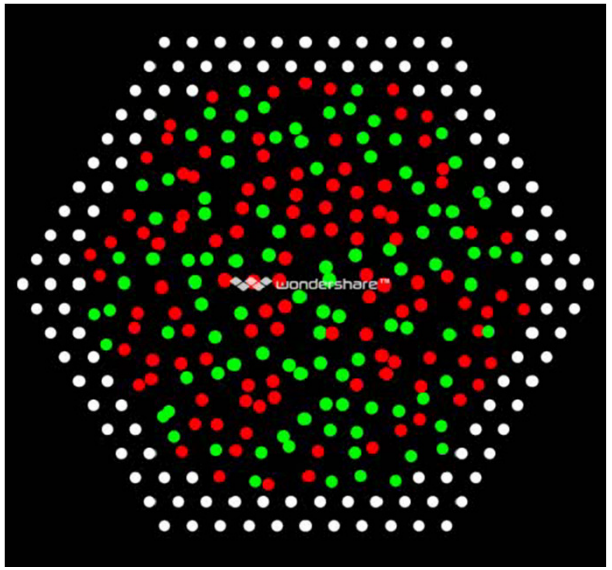
Monte-Carlo Simulation: Flowchart



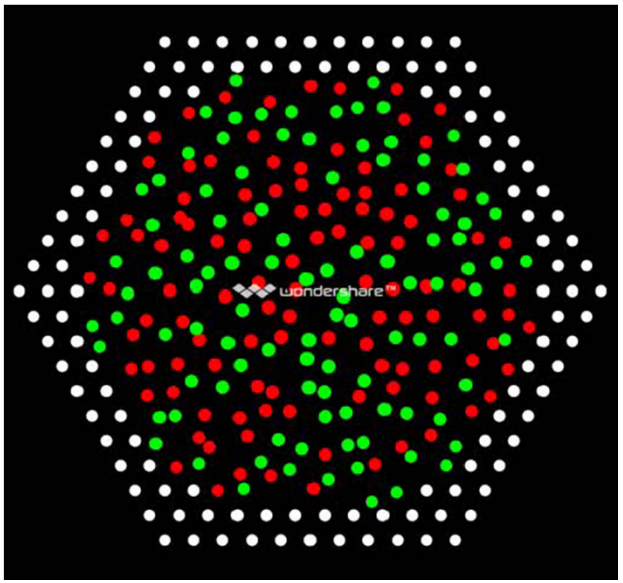
Monte-Carlo Simulation: Results



$\gamma(\tau i,\tau j) > \gamma(\tau i,\tau j) > \gamma(\tau i,\tau j)$



$\gamma(\tau i,\tau j) > \gamma(\tau i,\tau j) > \gamma(\tau i,\tau j)$



$\gamma(\tau i,\tau j) > \gamma(\tau i,\tau j) > \gamma(\tau i,\tau j)$

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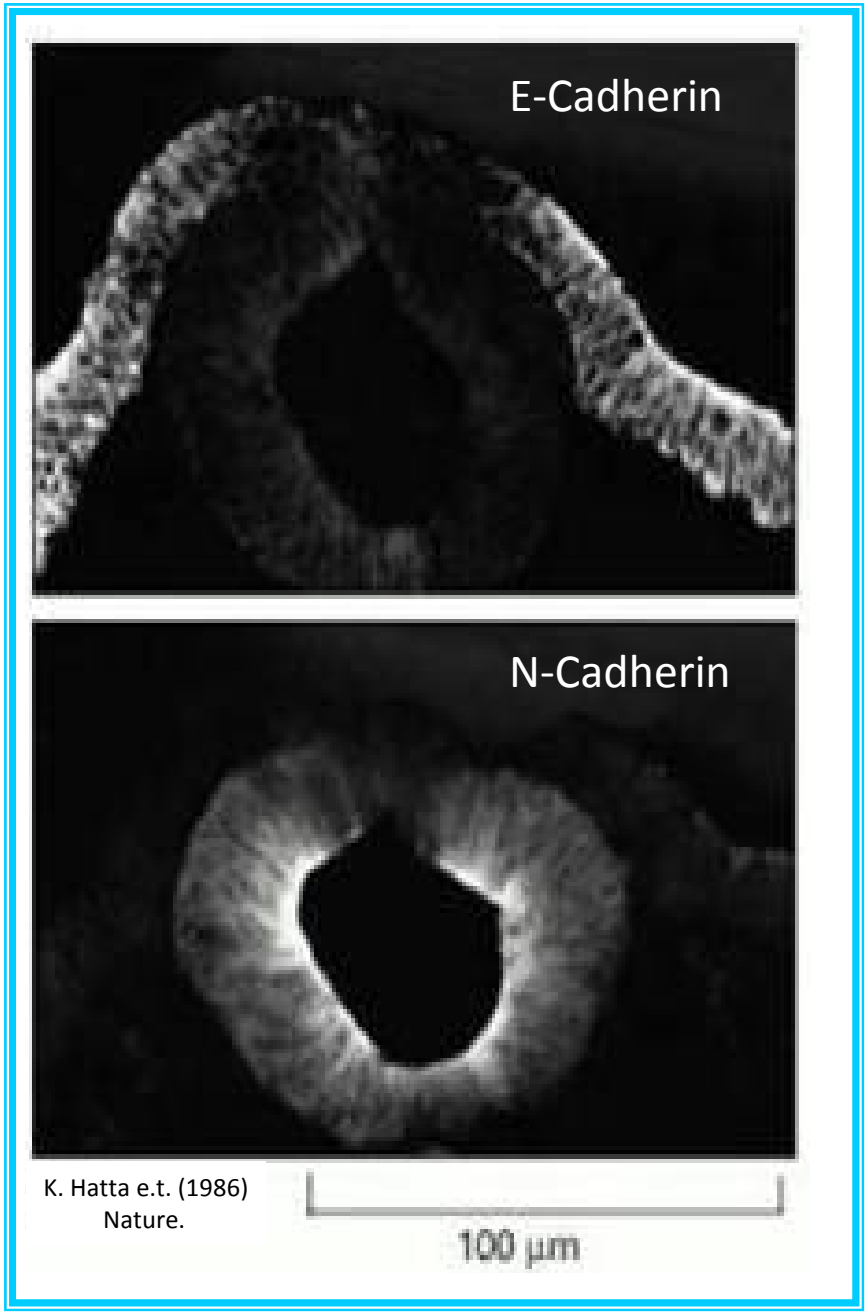

K. Hatta e.t. (1986) Nature.

$$\Delta G_{trans}^{(3D)}(N-cad, N-cad)$$

$$\Delta G_{trans}^{(3D)}(N-cad, E-cad)$$

$$\Delta G_{trans}^{(3D)}(E-cad, E-cad)$$

Surface plasmon resonance

Summary

- Simulation of molecular motor
- Modeling cytoskeleton
- Simulation of single cell locomotion
- Simulations of movements in multicellular systems

Perspective

- How to integrate intracellular signaling, PPI or GR networks?

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