Biological Machines, Cell Mechanics and Nanotechnology Part III

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The protein nano-factory

1. Transcription
2. RNA processing
3. mRNA translation
4. Replication
DNA and RNA polymerases are important biological machines. DNA polymerases (and helicases) are biological motors that function in DNA replication (and repair). RNA polymerase makes a copy of DNA (transcription) and from this copy (mRNA) proteins are designed in the cell (translation).
Transcription is powered by a complicated molecular machine:
The RNA polymerase

RNA polymerase is a copy machine: It moves along the (double stranded) DNA and makes an exact (single stranded) copy (= mRNA)

3 steps:
1) Complicated initiation step
2) Elongation (3’ -> 5’)
3) Termination (RNA released)
The RNA polymerase is a macromolecular machine with a difficult design.

*Example from your reading material!*

- DNA is clamped between two subunits and then the **double helix** is **opened**
- Then a **copy** from a single DNA strand is **made** into a **single strand RNA**
Single molecule methods to study DNA/RNA motors

Immobilized DNA/RNA motor shortens or lengthens the DNA/RNA that can be detected by bead displacements.

DNA or RNA is first stretched by a bead using optical traps, magnetic beads or hydrodynamic flow.

Direct motor movement on stretched DNA/RNA can be detected by attaching a fluorescently labeled bead.

Detection of single base pair stepping by *E. coli* RNA polymerase (RNAP)

Two optical traps:
- One holds the DNA with **strong force**, the other holds the RNAP with **weak force**
- If RNAP moves, the attached bead is displaced (to the right)

Recorded single base pair steps of RNAP
Single molecule methods to study DNA/RNA motors

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Function</th>
<th>No. catalytic subunits</th>
<th>Velocity (bp s$^{-1}$)$^b$</th>
<th>Force (pN)$^c$</th>
<th>Processivity (bp)$^d$</th>
<th>Step size (bp)</th>
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<td><em>E. coli</em> RNA polymerase</td>
<td>RNA polymerase</td>
<td>Transcription</td>
<td>1</td>
<td>16</td>
<td>25</td>
<td>Several kbp</td>
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<td>RNA polymerase</td>
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<td>16</td>
<td>&gt;1000</td>
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<td>Chromosome segregation</td>
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<td>5000</td>
<td>40</td>
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<td>2 or 13</td>
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<td>dsDNA translocase</td>
<td>Viral packaging</td>
<td>5</td>
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<td>57</td>
<td>15 000</td>
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<td>Migrates Holliday junction</td>
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<td>43</td>
<td>25</td>
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<td>HCV NS3</td>
<td>RNA helicase</td>
<td>HCV replication</td>
<td>1 or 2</td>
<td>50</td>
<td>NN</td>
<td>18</td>
<td>11</td>
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<td>dsDNA translocase</td>
<td>Type I restriction enzyme</td>
<td>1</td>
<td>550</td>
<td>&gt;5</td>
<td>5000</td>
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<td>RSC complex</td>
<td>dsDNA translocase</td>
<td>Chromatin remodeling</td>
<td>1</td>
<td>350</td>
<td>&gt;2</td>
<td>400</td>
<td>12</td>
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<td>Rad54</td>
<td>dsDNA translocase</td>
<td>Homologous recombination</td>
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<td>300</td>
<td>NN</td>
<td>12 000</td>
<td>NN</td>
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<tr>
<td>RecBCD</td>
<td>DNA helicase</td>
<td>dsDNA break processing</td>
<td>2</td>
<td>520</td>
<td>8</td>
<td>30 000</td>
<td>&lt;6 or 23</td>
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<td><em>B. subtilis</em> DNA uptake</td>
<td>ssDNA translocase</td>
<td>Horizontal gene transfer</td>
<td>NN</td>
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<td>45</td>
<td>&gt;10 000</td>
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<td>160</td>
<td>NN</td>
<td>17 000</td>
<td>NA</td>
</tr>
</tbody>
</table>

The nuclear pore: the smallest filter in the world
The nuclear pore: a molecular nano-filter
The nuclear pore: a molecular nano-filter

How the nano-sieve works:

- The nuclear pore complex (NPC) is a complicated structure containing about 30 different proteins (nucleoporins)
- The central channel is filled with filamentous hydrophilic polypeptides
- The polypeptides contain hydrophobic regions (FG-repeats = Phenylalanine/Glycin)
- These structures are able to constantly and rapidly re-arrange acting as a sieve for small molecules
- A nuclear transporter can interact with the FG-repeats shuttling other molecules
The bacterial flagellum motor

Not a flagella as found in other (non-bacterial) cells (not made of microtubules)
The bacterial flagellum motor

Example from your reading material!

- Motor composed of **20 proteins**
- **40 genes** needed to make the motor and its flagellum
- **8 torque (turning) generators** driven by proton motion force (no ATP required)
- **1200 protons** needed per turn
- **100 revolutions** per second
- **18,000 RPM** (300 Hz)
- Directional reverse within 1/10 of second
- Efficiency: < 5%
- Power output: $10^{-15}$ Watt (2-3 more efficient than ATP motors)
A proton gradient drives the motor like water drives a turbine

- **Drive shaft** passes thru two rings in the outer membrane. The rings act as bearings. Not involved in force generation
- **C-ring** (cytoplasmic ring) is important for force production and directional reversal
- **MotA** and **MotB** rings form the **proton channels**

Howard, Mechanics of Motor Proteins, 1st Ed.
Electrostatic model of the flagellum motor

Rotor-stator (motor) interaction generates the torque (turning):

Alternating charges on the rotor might be used to drive the motor:
• The lines of charges on the rotor are tilted with respect to the channels
• As positive protons move thru the channels, they attract negative charges on the rotor
• These electrostatic attraction forces might turn the motor

Howard, Mechanics of Motor Proteins, 1st Ed.
Torque-speed relationships

Methods to measure rotation of single motors:

A) **Laser illumination**: flagellum illuminated by a laser thru a small slit (dark bar)

B) **Polystrene beads**: beads attached to flagellum and deflection monitored by laser

C) **Oscillating voltage**: fixed cells are exposed to an oscillating (90°) voltage field

Rotating (90°) electric field around bacterium generates torque in flagellum
• Flagellum motor made of 20 different proteins
• It spans across three layers of membranes: outer membrane, peptidoglycan layer and cytoplasmic membrane
• It consists of various components, such as a rotor, stators, a drive shaft, a plug socket, a rotation-switch regulator, and so on.
• Rotary motor embedded at the base of a **helical filament**
• A short segment (55 nm) connects the motor and the helical propeller = **hook** (universal joint)
• **Flagellin** molecules (synthesized in the cytoplasm) transported to the end of the filament through the channel
• **Flagellin binding** is coordinated by a **rotating cap** (always preparing only one flagellin binding site)
• Cap movements looks like climbing up the helical stairs step by step.

Movie
bacterial_motor.wmv
18:42
The bacterial flagella motor: Evolution or Intelligent design?

Intelligent design (ID) is the concept that some aspects of the natural universe are better explained by an intelligent cause rather than by an undirected process such as natural selection.

- “The bacterial flagellum is an irreducible complex system” (a minimal, not reducible system)
- “This complexity could not have arisen through gradual variation or natural selection”
- “This system is so complex that it can only function when all of their components are present” (could not evolve from a simpler assembly which would be fully functionary)
- Only 50% of components are really necessary (=> indispensable)
- There is not "the" bacterial flagellum: thousands (if not millions) different bacterial flagellum systems exist
- Some are redundant and non-function and used for functions others than motility
- Several proteins have sequence homology indicating a common ancestor
- The flagellum evolved starting from just two proteins (e.g., proto-flagellin)
- Similarities between flagellar and non-flagellar systems exist
- Proto-flagellum could easily arose from pre-existing modules as the ATPase, polymerized filaments, ion-channels and domains of the chemotaxis apparatus

The bacterial flagella motor: Evolution or Intelligent design?
A nano-biomachine powered by highly motile bacteria

- Highly motile gliding bacteria *Mycoplasma mobile* pulled on a micro-rotor fueled by glucose
- How it works:
  - Floating of cells into the circular track
  - Glycoprotein coating on track-bottom helps bacteria attachment
  - Restricting biotin-labeled bacteria movements to streptavidin-coated rotor

![Diagram of the biomachine](image)

Drop bacteria solution here

Rotor placed in ring in a 2nd step

![Image of the biomachine](image)
A nano-biomachine powered by highly motile bacteria

Speed: 3 rpm
Torque: 2-5 \( \times 10^{-16} \) N-m
Stall force: 27 pN

Movie

Movie

Example from your reading material!
Synthetic molecular motors

Biological motors offer great inspiration for the design of artificial motors to achieve controlled movement at the molecular level.

Rotaxane systems:
- A macrocycle (train) can travel along a molecular chain (rail) between two stations (0,1).
- Train’s position depend on the electron composition of the stations and train.

- Translocation of train can be achieved by redox or acid/base stimuli as well as photochemically.
- Translocation is initiated by protonation of station 0 making the interaction between train and station repulsive (train moves to station 1 as a result).
- After deprotonation the system relax back to its initial state (train back to station 0).

Schliwa, Molecular Motors, 1st Ed.
Synthetic molecular muscle

- Two linear intertwined rotaxane units can **contract** and stretch like a muscle
- In the presence of Cu\(^+\) the conformation is **stretched**
- In the presence of Zn\(^{2+}\) the configuration is **contracted**
Molecular muscles

NEMS (Nanoelectromechanical systems) device based on rotaxane coated AFM cantilevers: redox-driven contraction/relaxation of rotaxanes results in a measureable deflection of the laserbeam.
“Magic” movement of a liquid drop driven by rotaxanes

A monolayer of rotaxanes (turned on and off by UV-light) was able to move a liquid drop (1.25 µl) on a steep surface

Berná et al., Nat. Mater., 2005
Computer models of non-biological nano-machines

- Many **macroscopic machines** can be reduced to the nano-level
- Some might work even better (no friction, no wearing/tiring) some might be impossible to design based on their complexity (e.g., atomic power plant)
- Examples of **current modeled nano-constructions** are:
  - Nano Bearing
  - Nano Gear
  - Nano Filter
  - Nano Pump
  - Nano Electromotor/ Nano Car
  - Nano Computer (simple I/O)
- A nano-bearing does **not** need any bearing balls or lubricants
- It works based on **strong covalent bonds** and **weak “van der Waals” repulsive forces**
- **Simulations** are based on reliable software tools already used by Chemists for many years

![Nano-bearings](http://www.e-drexler.com/)
Computer models of non-biological nano-machines

- Planetary gearing is a gear system that consists of one or more outer gears, or planet gears, revolving about a central, or sun gear.
- Planetary gears convert shaft power from one angular frequency to another.

http://nanoengineer-1.com/
Computer models of non-biological nano-machines

Nano-pump

http://www.imm.org/research/parts/pump/
Complex nano-machines

- **Nano-worm drive** assembly containing 11 components made from 25,374 atoms
- Simulations **took 340 hours** to complete (on a regular desk-top computer)

Nano speed gear reducer

15,342 atoms

http://www.e-drexler.com/
Applications, open questions and critique

• It’s **only a matter of time** before nanotechnology (combined with MEMS and optofluidics) can result in the fabrication of **neuroprosthetic devices, artificial retina** etc.
• Very far from now perhaps a brain implant using biological molecules to store data can back-up human memories (which might otherwise be lost due to ageing or degenerative diseases)
• It might be feasible to think of atom-by-atom manufacturing of such components in **nanofactories**
• However: The two machines containing about **25,000 atoms**, are the most complex simulations ever created and they haven’t even been built yet!
• By comparison: An **ion channel** (one of nature’s sophisticated nanomachines) can have a molecular mass approaching **1MD** (Mega Dalton), and contains **millions of atoms**
Nano Factory

Movie
NanoFactory.mov

http://www.e-drexler.com/
What is nature, what is life, what is a machine?

• Since we are composed of units that can be dissect into parts, modules, domains, proteins and atoms the question might arose: Is life artificial?
• Protein motors, intercellular sensors, membrane channels, protein scaffolds etc. leads to an mechanistic understanding of the cell (contrary to vitalist view)
• However: Less fruitful doing biological research is to pull organisms apart and inspecting them piece by piece (reductionism)

• A distinction between natural and artificial goes back at least to Aristotle and Plato but this distinction is becoming increasingly irrelevant: living organisms look more and more like machines, and machines look more and more like living organisms
• The natural/artificial distinction is highly discussed in religion, genetic engineering, food production, virtual realities, computer intelligence, medicine etc.
=> here "natural" is mostly considered beneficial, safe, reliable and trustworthy while "artificial" is basically considered imperfect, immoral, unhealthy, damaging and dangerous
Raymond Kurzweil’s vision

- **Inventor and futurist**: optical character recognition (OCR), text-to-speech and speech recognition technology and electronic keyboard instruments
- **Author** of several books on artificial intelligence (AI), transhumanism, **the technological singularity**, and futurism
- Receiving many awards in including 15 (!) honorary doctoral degrees
- He made many **future (technology) predictions** while many of them became surprisingly reality

The technological singularity (predicted 2005):

**2010-2020**
- $1000 computers have **same processing power as human brains**
- Computers become smaller and increasingly **integrated into everyday life** (clothes, furniture...)
- **Glasses** that beam images onto our retinas to a **produce virtual reality (VR)**
- **VR glasses** have built-in computers with "**virtual assistant**" programs that can **help** us with various daily tasks ("**augmented reality**")

**2020-2030**
- Computers less than 100 nm big
- **Nanomachines** are **used for medical purposes** ("brainscans")
- **Nanobots** capable of entering the bloodstream to "feed" cells and extract their waste (we don’t need to eat anymore)
- Nanotech-based manufacturing everywhere
- **Virtual reality** will be of such a high-quality that it will be **indistinguishable from real reality**
- A **computer** is a “Strong A.I.” (artificial intelligence) and **can think like a human**
Kurzweil’s prediction of a technological singularity

2030-2040

• **Mind uploading** becomes possible: “Copy and paste” a complete human’s mind
• **Nanomachines** in brain control incoming and outgoing signals (can also block internal signals)
  • As a result, **truly full-immersion virtual reality** can be generated
  • Better cognitive, emotional, memory and sensory capabilities
  • Directly interfacing with computers
  • “Telepathically” communicate with other
• “Human body 2.0” consists of a nanotechnological system of nourishment and circulation: no need for many internal organs
• “Human body 3.0”: Improved skeleton and can alter its shape and external appearance

2045-

The singularity

• Technological singularity = artificial intelligences beat human beings as the smartest and most capable life forms on the Earth
• Technological development is taken over by the machines
• Machines enter into an **uncontrolled reaction of self-improvement cycles**
• From this point, **technological advancement is explosive**
Kurzweil’s prediction of a technological singularity

• The elimination of humanity by violent machines is unlikely because it is difficult to say who is (an enhanced) human and who is machine (A.I.) anyway
• A.I.s convert more and more of the Earth's matter into engineered, computational substrate to support even more A.I.s. until the whole Earth is one, gigantic computer
• At this point, the only possible way to increase the number of machines any further is to begin converting all of the matter in the universe into similar massive computers
• This is called the "wake up of the universe": all "dumb" matter (stones, dust, gases, etc.) is converted into intelligent matter
  2099
• Planet-sized computers exist
  2199
• Process of “wake-up of the universe” is completed
• Physical control over the whole universe: clearing the laws of physics possible, therefore time, space and interdimensional travel possible
The critiques

**Douglas R. Hofstadter** (Author of popular book “Goedel, Escher, Bach”):
- "It’s as if you took a lot of very good food and some dog excrement and mix it all up so that you can’t possibly figure out what's good or bad”.
- “It's an intimate mixture of rubbish and good ideas, and it's very hard to distinguish between the two, because these are smart people; they're not stupid."

**Bill Joy** (Cofounder of Sun Microsystems): Agrees with Kurzweil's timeline of future progress, but believes that technologies such as A.I., nanotechnology and advanced biotechnology will create a dark, pessimistic, harmful and depressing (dystopian) world
Integrating single cells into stable tissues

3 principles act to form a tissue from single cells:
1) **Cytoskeleton** not only acts to stabilize single cells but also helps to **connect a cell to a neighbor cell**
2) Specialized (polymeric) proteins make **cell-cell contacts** (**cell adhesion molecules**, CAM)
3) An **matrix outside the cell** (**extracellular matrix**, ECM) acts as a **fibrous filling material** and to glue cells to each other

Single cells need to be stick together in a tissue as bricks in a wall

**The skin is a epithelial tissue**
Integrating single cells into stable tissues

- **Intracellular anchor proteins** connect the cytoskeleton to transmembrane adhesion proteins (CAMs)
- **Transmembrane adhesion proteins** are embedded in the extracellular matrix (ECM)
Integrating single cells into stable tissues

A detailed view

- Intracellular anchor proteins
- Transmembrane adhesion proteins
- Cytoskeletal filaments
- Extracellular matrix
- Cell adhesion molecules (CAMs)
- Actin
- Intermediate filament
- Adhesion receptors
- ECM
Desmosomes are button-like structures connecting two cells

Thick intermediate filament bundles connected to electron dense structures can be seen in EM of two keratinocytes (skin cells) firmly connected to each other.

In the skin disease *pemphigus vulgaris* the protein desmoglein is non-functional, resulting in severe skin blistering.
Gap junctions are 2-3 nm wide “food-channels” between 2 cells

**Gap junctions** form a channel system for the exchange of small metabolites (as ions, sugars, vitamins, ATP etc.) between two cells.

The gap junction channels are formed by the hexagonal protein **connexin**.

Atomic structure of gap junctions:

- **C** = cytosol,
- **M** = membrane bilayer,
- **E** = extracellular gap.
Cell junctions are crucial for tension and mechanical stability of tissues

Since cell junctions integrate a cell’s cytoskeleton and at the same time strongly connect to neighboring cells, shape, rigidity and cell strength are largely increased

<table>
<thead>
<tr>
<th>Functions of cell junctions</th>
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<tr>
<td>JUNCTION</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Anchoring junctions</td>
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<tr>
<td>1. Adherens junctions</td>
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<tr>
<td>2. Desmosomes</td>
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<tr>
<td>3. Hemidesmosomes</td>
</tr>
<tr>
<td>Tight junctions</td>
</tr>
<tr>
<td>Gap junctions</td>
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</table>
ECM (extracellular matrix)

- Extracellular matrix (ECM) is the tissue below an epithelium (single cell layer)
- ECM contains many highly elastic fibers but also the cells that secrete these fibers
- These fibers and cells are embedded in a gel (hyaluronan and proteoglycans)

Fibroblasts embedded in the ECM
ECM contains stiff/non-elastic and highly elastic fibers

**Highly elastic aorta** need to resist strong and alternating blood pressure

- **Elastin** molecules are highly cross-linked by covalent bonds
- An elastin assembly can stretch and relax like a **rubber-band**

Elastic fiber (**elastin**) in the outer layer of the aorta
Hyaluronan resists compression and gives cartilage its gel-like properties

- Major component of cartilage is the **aggrecan aggregate**: huge molecule (MW $2 \times 10^8$) with a size of a bacterium
- Up to 100 **aggrecan** molecules are connected to a **hyaluronan** backbone
Collagens are elastic fibers found in skin and bone

Collagens are complex molecules embedded in the ECM

A single collagen fiber in the gel-forming matrix of cartilage
Cell contact with the ECM (e.g., fibronectin) is important for cell growth (proliferation) and cell survival.

If a cell cannot spread on a larger space on the substrate it will eventually die:

The spreading of ECM proteins on a surface is more important than the concentration of these proteins (in a smaller area).
Literature

**Molecular Cell Biology 6th Edition**
by [Harvey Lodish](#) etc.

Aug 2007

**Cell Biology 2nd Edition**
by [Thomas D. Pollard](#) etc.

Apr 2007

**Molecular Biology of the Cell, 5th Edition**
by [Bruce Alberts](#) etc.

Nov 2007
Free online books


National Center for Biotechnology Information
National Library of Medicine National Institutes of Health

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What is NCBI do?

Established in 1980 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information - all for the better understanding of molecular processes affecting human health and disease. More...

GenBank Celebrating 25 Years

NCBI will hold a scientific meeting to celebrate the 25th anniversary of GenBank.
April 7-8, 2008
Natcher Auditorium, NIH Campus, Bethesda MD

click here for more information

GenBank vs. RefSeq

Confused about the distinctions between GenBank, RefSeq, TPA and UniProt? Click here for a brief description of the databases and their differences.

dbMHC
Cooper, Geoffrey M.

37 items in *WormBook: The Online Review of C. elegans Biology*
The *C. elegans* Research Community; editors
Pasadena (CA): *WormBook*; c2005

35 items in *Modern Genetic Analysis*.
Griffiths, Anthony J.F.; Gelbart, William M.; Miller, Jeffrey H.; Lewontin, Richard C.

34 items in *Molecular Cell Biology*. 4th ed.
Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David;altimore, James D.

Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter
Focused/specialized literature

*Cytoskeleton: Signalling and Cell Regulation (A Practical Approach)*
by Kermit L. Carraway and Carolie A. Carothers Carraway

*Cytoskeleton Methods and Protocols*
by Ray H. Gavin (Editor)

*Cytoskeletal Mechanics: Models and Measurements*
by Mohammad R. K. Mofrad and Roger Kamm

Mar 2000  Jan 2001  Sep 2006
Focused/specialized literature

**G Proteins, Cytoskeleton and Cancer**
by Hiroshi, Ed. Maruta

**Aspects of the Cytoskeleton**
by Seema Khurana

Jan 1998

**Molecular Motors**
by Manfred Schliwa

Mar 2003

Nov 2006
Focused/specialized literature

**Mechanics of Motor Proteins and the Cytoskeleton**
by Jonathon Howard

Feb 2001

**Molecular Motors: Methods and Protocols**
by Ann O. Sperry

Jun 2007

**Guidebook to the Cytoskeletal and Motor Proteins**
by Thomas Kreis and Ronald Vale

Sep 1999
Focused/specialized literature

**Molecular Devices and Machines**  
by [Vincenzo Balzani](#) etc.

**Our Molecular Nature: The Body's Motors, Machines and Messages** by [David S. Goodsell](#)

**Molecular Machines**  
by [T. Ross Kelly](#)

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*Apr 2003*  
*Apr 1996*  
*Feb 2006*
Focused/specialized literature

**Molecular Machines & Motors**
by J.-P. Sauvage

**Intermediate Filaments**
by Jesus Paramio

**Intermediate Filament Cytoskeleton**
by M. Bishr Omary and Pierre A. Coulombe

Jul 2001  |  June 2006  |  Dec 2004
Focused/specialized literature

Molecular Interactions of Actin
by D.D. Thomas and C.G. dos Remedios
Mar 2002

Actin-Binding Proteins and Disease by Cris dos Remedios and Deepak Chhabra
Nov 2007

Actin-Monomer-Binding Proteins
by Pekka Lappalainen
Dec 2006
Focused/specialized literature

**Myosins**
by Lynne M. Coluccio

**The Role of Microtubules in Cell Biology, Neurobiology, and Oncology**
by Antonio Tito Fojo

**Microtubule Protocols**
by Jun Zhou

Dec 2007  
May 2008  
Aug 2007
Review articles

Articles that summarize the hot trends in cell biology (it is free!)

Current Opinion in Cell Biology

Volume 20, Issue 1, Pages 1-110 (February 2008)
Cell structure and dynamics
Edited by Yixian Zheng and Karen Oegema

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   Yixian Zheng and Karen Oegema
   SummaryPlus | Full Text + Links | PDF (100 K) | View Related Articles

4. ESCRT complexes and the biogenesis of multivesicular bodies
   Pages 4-11
   James H Hurley
   SummaryPlus | Full Text + Links | PDF (5399 K) | View Related Articles

5. Structural Insights shed light onto septin assemblies and function
   Pages 12-18
   Yves Barral and Makoto Kinoshita
   SummaryPlus | Full Text + Links | PDF (1033 K) | View Related Articles

6. The bacterial cytoskeleton
   Pages 19-27
Thank you for your attention!

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