# Biological Physics - Molecular Motors

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Experimental and Theoretical Physics
Part III
Michaelmas 2021

Notes version: v0.05
Release name: Evolving Emergence

# Molecular Motors

# 1

## 1.1 Introduction

Living biological systems all share the same properties of being able to transform one kind of energy, normally chemical energy, into another in order to do work. For this purpose, over the course of evolution, cells have developed a large collection of molecular machinaries, each with different purposes. In this chapter, we will focus on one category of these: molecular motors.

We have mentioned at the beginning of the course that the cell is a very crowded environment and diffusion is often not sufficient to deliver molecules across the cells in a biological meaningful timescale. To bypass this problem and others, cells employ molecular motors that move *non randomly*. Non-random movement costs energy and these molecular motors are able to transform chemical energy, often in the form of ATP into kinetic energy.

Molecular motors are often classified as follows with some examples:

- Cytoskeletal motor proeins: myosin, kinesin, dynein
- Polymerization motors: actin, microtubules, RecA
- Ion pumps: Na-K pump
- Rotary motors: ATP-synthase, bacterial flagellar motors
- DNA motors: RNA polymerase, helicases

These motors perform many different functions, such as the contraction of stress fibers that give cells a certain shape and muscle contraction, cell motility, separation of the chromosomes in the two daughter cells, transport of cargo across the cell, etc...

The structure of these motors also come in different shape, however most of them exhibit head-domains, where ATP binds. Hydroplysis of ATP results in a conformational change, which is then guided and amplified into a larger structural change of the whole molecule leading to movement. For instance, kinesin and dynein move along the microtubules, which have a well-defined polarity, which determines the directionality of the movement of these motors. Many motors also have a cargo-binding domain where passive cargo can bind and then be actively transported (Fig. 1.1).

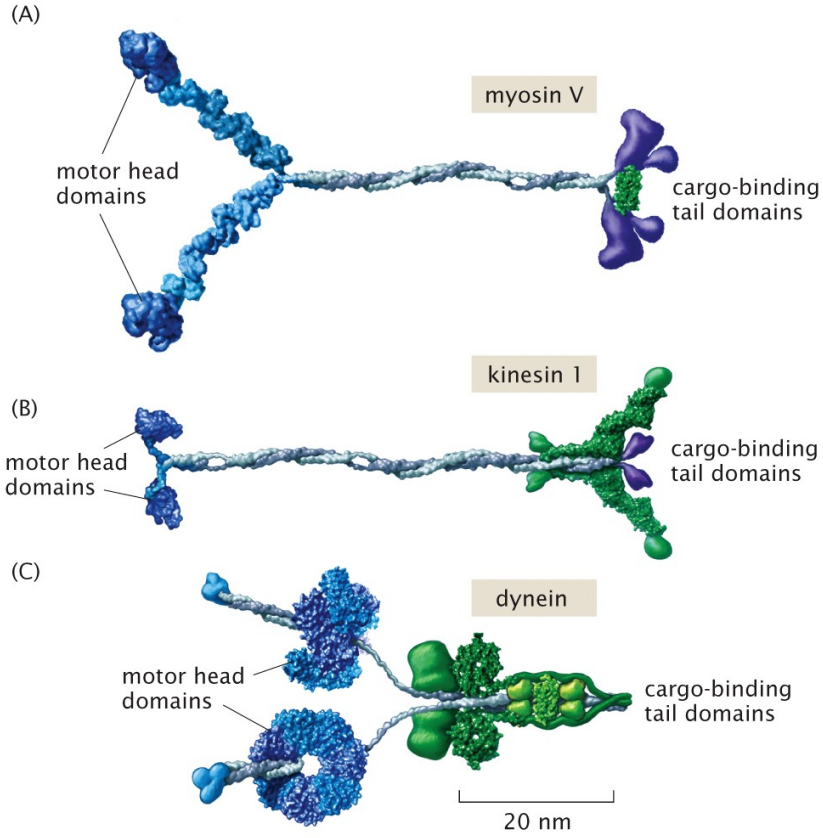


Figure 16.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

**Fig. 1.1 Key classes of translational motors**

## 1.2 Energy source: ATP

Many molecular motors use hydrolysis of ATP as an energy source, which is then converted to motion. One hydrolysis event generates approximatly 20-30$k_BT$ of energy, where $T$ is temperature and $k_B$ is the Boltzmann constant. Not all this energy will be transfered, as the process is not 100% efficient. The products of the chemical reaction, ADP and the orthophosphates, sit at a much lower energy. This is partially because the orthophosphates group is stabilized by multiple resonance structure and the electrostatic repulsion is reduced going from ATP to ADP.

ATP is obtained through the process of cellular respiration by glucose metabolization. One glucose molecule will produce of the order of 30 ATP molecules, by going through glycolysis (+7-9 ATP), the oxidative decarboxylation of pyruvate (+5 ATP), and the Krebs cycle (+20 ATP). In particular, at different points in this process, oxidative phosporilation occurs. It involves the electron transport chain that establishes a proton gradient across the boundary of the inner membrane by oxidizing NADH produced in the Krebs cycles. The resulting proton-motive force is a combination of an electrostatic term caused by the electrical potential

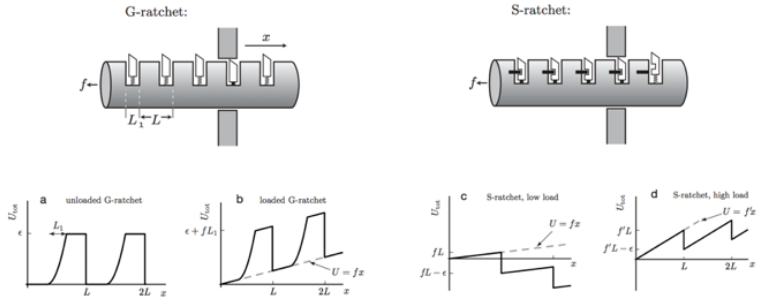


**Fig. 1.2 Schematic of G-ratchet and S-ratchet.**

gradient and a diffusion term caused by a difference in ion concentration.

$$pmf = V_m + \Delta\mu/e$$

## 1.3 Physical models

To model the dynamics of molecular motors we will think of them as random walkers moving in an energy landscape, in which the motor can assume different internal states.

### 1.3.1 Thermal rachet

Molecular machines live in a world dominated by thermal fluctuations. These thermal fluctuations can be exploited to jump over energy barriers.

Imagine a machine that when it encounters an energy bump, only needs to wait some time for a thermal fluctuation to come and allow it to jump over the barrier. We can model this as a shaft with a series of beveled bolts mounted on springs that prevents the shaft to move to the left (G-ratchet in fig. 1.2). The shaft also pulls a load represented by a force $f$ directed to the left. Occasionally, large enough thermal fluctuations will be able to kick the shaft with energy greater than $\epsilon + fL$ required to jump the next bolt and the shaft will move to the right. If you imagine to wrap the shaft around a circle, this machine would be able to constantly extract work from the surrounding thermal motion and thus violate the second law of thermodynamics.

How can we resolve this paradox? As shown in fig 1.2 if $k_BT$ is comparable to $\epsilon$ and sufficient to pull the weight to the right, then it will also be sufficient to allow the shaft to retract because the bolt springs will be subject to thermal fluctuations. So, effectively, the shaft will be pulled in the direction of the force.

However, let's modify the shaft so that there are latches that keep the bolts down if the bolt is to left of the wall, and releases it if it is on the right side (S-ratchet in fig. 1.2). In this case, it will be the potential energy stored in the compressed bolts that will be used to pull a cargo right as long as the springs are stiff enough. Let's formalize this mathematically.

Imagine that the shaft is wrapped around a circle and it has $n$ bolts, $P(x)$ denotes the probability that a ratchet will at be position $x$ at steady-state and we are tracking $M$ ratchets. At each time step $\Delta t$ a ratchet can get a thermal kick that can move it to the right or to the left. There will $MP(x)\Delta x$ ratchets between position $x - \Delta x/2$ and $x + \Delta x/2$ and half of them will step to the right in time $\Delta t$. Similarly, there will be $MP(x+\Delta x)\Delta x$ ratchets between $x + \Delta x/2$ and $x + 3\Delta x/2$ and half of them will step to left in time $\Delta t$. Then the number of ratchets that cross position $x + \Delta x$ from left to right is

$$1/2M[P(x) - P(x + \Delta x)]\Delta x \approx -1/2\Delta x^2 M\frac{dP}{dx} = -DM\frac{dP}{dx}\Delta t.$$

where $D = \Delta x^2/2\Delta t$ is the diffusion coefficient.

Let's define the $F = -dU_{tot}/dx$. In the absence of any diffusive motion, this force would impart a drift velocity given by $v_{drift} = F/\zeta$ where $\zeta$ is the friction coefficient. By using Einstein relation, we can rewrite this as

$$v_{drift} = -\frac{D}{k_b T}\frac{dU_{tot}}{dx}.$$

Then the total number of ratchets crossing $x$ in time $\Delta t$ from the left due to drift will be $MP(x)v_{drift}$. Therefore in total, we have to contributions and the total flux of ratchets from left to right is

$$j^{1D} = -MD(\frac{dP}{dx} + \frac{1}{k_B T}P\frac{dU_{tot}}{dx}).$$

Note that at equilibrium, the flux goes to zero. The equilibrium probability distribution of the ratchets in the external field will be the Boltzmann distribution

$$P_{eq}(x) = P_0 e^{-U_{tot}/k_B T}$$

Because the number of ratchets has to be conserved $\partial_t P = -\partial_x j/M$ and therefore

$$\partial_t P = D[\partial_x(P\partial_x U_{tot}/k_B T) + \partial_x^2 P]$$

called the Smoluchowski equation.

### 1.3.2 Polymerization ratchet

Polymerization motors can also be modeled as ratchets. The basic idea consists in the fact that a growing filament can result in a

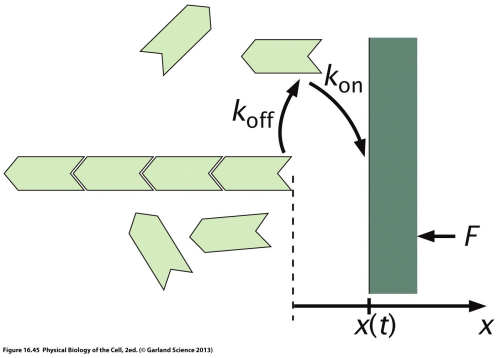


**Fig. 1.3 Sketch of a filament reaching a wall**

pushing force on a resisting barrier by virtue of fluctuations in the position of the barrier or the filament. Imagine a filament that has grown in order to reach a barrier (cell wall). If the barrier or the filament jiggle, then a new monomer may be able to squeeze in (fig. 1.3).

For now, let's neglect the action of the force. Let's assume that each monomer has length $\delta$ and can be inserted if the distance between the tip of the filament and the barrier reaches such size. This is a first passage type problem, which we are going to solve using an analogy. Imaging that you have a particle that is diffusing along a distance $\delta$ and you want to determine the first time it reached position $\delta$ if it starts at 0. The current due to diffusion will be

$$j_0 = -D\partial_x P$$

where $P$ is the probability of finding the particle at position $x$. At steady-state, we know that

$$\partial_x^2 P = 0$$

meaning that $P = Ax + B$. To compute $A$ and $B$, we exploit the fact that $P(x)$ has to be normalized:

$$\int_0^\delta P(x)dx = 1 = A\delta^2/2 + B\delta$$

and that $P(\delta) = 0$. With these two constraints, we find that $A = -2/\delta^2$ and $B = 2\delta$.

The current is then

$$j_0 = -DA = 2D/\delta^2$$

and the first passage time is the inverse of this quantity

$$\tau_1 = \delta^2/2D.$$

Then the rate of polimerization will be

$$v = \delta/\tau_1 = 2D/\delta.$$

Now, if we apply a constant force F, the current will become

$$j_0 = -\partial_x P - P\frac{F}{\zeta}$$

where the friction coefficient $\zeta = k_B T/D$. At steady-state the current is constant and the differential equation has general solution

$$P(x) = Ae^{-Fx/k_B T} - j_0\zeta/F.$$

Similarly to before we use the two constraints $P(\delta) = 0$ and $\int_P(x)dx = 1$ to find $A$ and $j_0$. The result is that the steady-state current is

$$j_0 = [(k_B T\zeta/F^2)(e^{F\delta/k_B T} - 1) - \zeta\delta/F]^{-1}$$

and the growth rate of the filament will be

$$v = \delta j_0 = \frac{D}{\delta}\frac{(F\delta/k_B T)^2}{e^{F\delta/k_B T} - 1 - F\delta/k_B T}.$$

## 1.4 Linear motors

### 1.4.1 One state model

For translational motors, we will start by assuming that the motor has no internal states and simply jumps from one position to another with a forward rate $k_+$ and a backward rate $k_-$ over a discretized one-dimensional filament. These rates are related to the energy potential the motor is moving in $U$, which is related to the force $U = fx$. For the motor to move, the rates $k_-$ and $k_+$ will have to be different.

Let's define $p(n,t)$ the probability of finding the motor at position $n$ at time $t$. Then the probability at time $t + dt$ will be

$$p(n,t+dt) = k_+ dtp(n-1,t)+k_- dtp(n+1,t)+(1-k_+ dt-k_- dt)p(n,t)$$

By sending $dt$ to 0 and defining positions as $x = na$, we find the following master equation:

$$\partial_t p = (k_- - k_+)a\partial_x p + \frac{1}{2}(k_+ + k_-)a^2\partial_x^2 p$$

which corresponds to a diffusion equation with drift with diffusion coefficient $D = (k_+ + k_-)a^2/2$ and drift velocity $V = (k_- - k_+)a$.

The two rates are related to the difference in energy between going forward versus backwards. If ATP hydrolysis allows to take step forward, then

$$\frac{K_+}{k_-} = e^{-\beta\Delta G_h}$$

where $\Delta G_h$ corresponds to the free energy from hydrolysis. In the presence of a force that pulls the motors backwords, than the

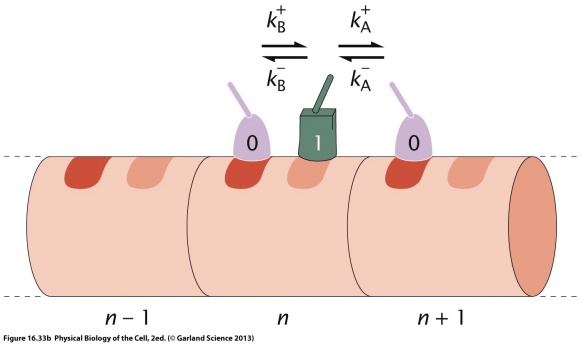


**Fig. 1.4 Schematic of a two-state model**

energy of the step forward will be raised by a factor $Fa$ and the reaction coefficients will satisfy

$$\frac{K_+(F)}{k_-(F)} = e^{-\beta(\Delta G_h + Fa)}$$

The free energy released by hydrolysis is

$$\Delta G_h = \Delta G_0 + k_B T \ln\left(\frac{[ADP][P_i]}{[ATP]}\right)$$

where $\Delta G_0$ is the energy released by breaking a chemical bond in the ATP molecule. This results in

$$\frac{k_+}{k_-} \propto [ATP]$$

which predicts either a velocity that saturates with $[ATP]$ if all the dependence is in the forward direction, or that is linear with $[ATP]$ if all the dependence is in the backward direction.

### 1.4.2 Two state model

Some motors do not seem to follow the simple one state model above and multiple intermediate states have to be considered. The simplest case is a two-state model where the motor, in addition to moving forward and backward, can be in two conformational states and these states have to alternate in order to provide movement.

In this case, the probability distribution $p_i(n,t)$ will refer to the distribution of the two internal states the motor can be in. Let's define $k_A^+$ the rate at which state 1 will convert to state 0 and move forward. Similarly, $k_B^+$ will be the rate at which state 0 will convert to state 1 and move forward. Analogous definitions will be for $k_A^-$ and $k_B^-$ (See fig. 1.4). Then the master equations are

$$\begin{cases} \frac{dp_0}{dt} = k_A^+ p_1 + k_B^- p_1 - k_A^- p_0 - k_B^+ p_0 \\ \frac{dp_1}{dt} = k_A^- p_0 + k_B^+ p_0 - k_A^+ p_1 - k_B^- p_1 \end{cases}$$

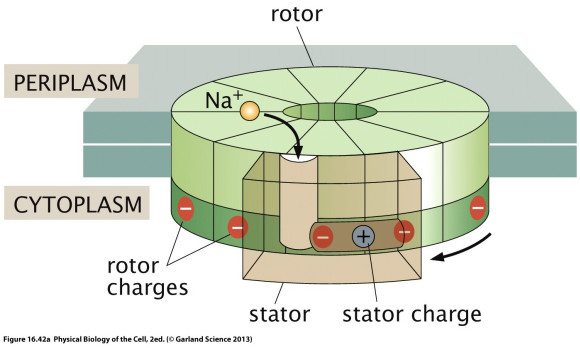


**Fig. 1.5 Typical structure of a rotary motor**

At steady state, we find that

$$(k_A^+ + k_B^-)p_1 = (k_A^- + k_B^+)p_0$$

Because $p_0 + p_1 = 1$ then

$$\begin{cases} p_0 = \frac{k_A^+ + k_B^-}{k_A^+ + k_A^- + k_B^+ + k_B^-} \\ p_1 = \frac{k_A^- + k_B^+}{k_A^+ + k_A^- + k_B^+ + k_B^-} \end{cases}$$

Let's assume that when the motor transitions from 0 to 1 it travels a distance $\delta$ and when going from 1 to 0 it travels a distance $a - \delta$. Then the net velocity will be

$$v = \delta(p_0 k_B^+ - p_1 k_B^-) + (a - \delta)(p_1 k_A^+ - p_0 k_A^-)$$

By replacing the solutions for $p_0$ and $p_1$, we find the average velocity

$$\langle v \rangle = a \frac{k_A^+ k_B^+ - k_A^- k_B^-}{k_A^+ + k_A^- + k_B^+ + k_B^-}$$

Note that the velocity does not depend on the distance $\delta$ traveled by the motor when transitioning between the two states.

## 1.5 Rotary Motors

Similar models to the ones developed in the previous section can be applied to rotary motors by imagining to wrap the track around a circle. Also the motors move through discrete steps that are coupled with energy-realising reactions, such as ATP hydrolysis or transport of ions down an electrical gradient. In rotatory motors, instead of talking of linear speed, we talk about angular speed, instead of force, we talk about torque.

The motor is driven by thermal fluctuations that result in rotational diffusion of the rotor. The diffusion is rectified, leading to directed motion by electrostatic between the charges on the rotor, the stator and the $Na^+$ ions. A rotor charge is captured by

the stator charge, which is opposite in sign. It will then diffuse away until it finds itself in a input channel, where it is exposed to a high concentration of $Na^+$. The driving force is then the free-energy difference experienced by the ion as it travels through the membrane (fig. 1.5).

One special example of rotary motors are bacteria flagella. The energy source of these motors is the proton-motive force. Most models that explain the behavior of these motors try to reproduce the relationship between torque and speed found in experiments. One example of such models by Xing et al describes the kynetic of the motor with four physical ingredients: (i) load and motor are connected through a soft elastic linkage, (ii) motor rotation is tightly coupled to ion flux, (iii) motor rotation is driven by proton driven conformation changes and (iv) the proton channel in the stator is gated by rotor movement.