Chemical Determinism – Motor Proteins

30 March 2019

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One of the main ideas of evolution is that it is based on chance, in particular on random mutations. Over the years of monitoring the genetic and molecular-biology underpinnings of the evolution idea I have come to believe that determinism is more involved than it is normally given credit for. Playing with genetic algorithms in the 1990s demonstrated graphically the power of the cross-over function (aka recombination) to guide natural selection in a population toward optimal outcomes, where the less frequent mutations offered a random noise input that helped the population to reach a global optimum, instead of the local optima often arrived at under the more focused cross-over.

But it was reading Peter Hoffmann's 2012 book *Life's Ratchet* ([1]) that really drove home the role of determinism, which he characterizes as a *ratchet*, a process that filters random behavior into a particular "purposeful" direction. Since Hoffmann is a biophysicist, his presentation is heavily guided by the physical principles of energy conversion, thermodynamics, and entropy, which makes for a fresh approach to a traditionally biological subject. The startling thing Hoffmann's book introduced me to was the subject of molecular machines or motor proteins. These were amazing engines that harnessed the chemical and physical energy within a cell to act like miniature workers hauling materials around and constructing other molecules. The intelligent design crowd would go bonkers.

The source of energy and randomness for the nanoscale activities in a cell is the molecular storm.

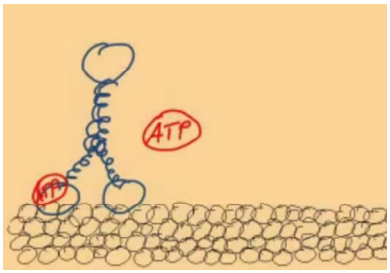
Molecular Storm

I will let Hoffmann's words explain:

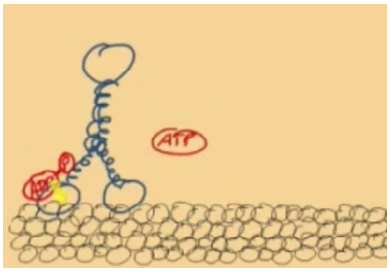
> The tiny scale of atoms and molecules is dominated by continuous motion. Scientists call this continuous motion of atoms and molecules *thermal motion*. Thermal motion does not mean gently floating atoms: At room temperature, air molecules reach speeds in excess of the fastest jet airplane! If we were reduced to the size of a molecule, we would be bombarded by a *molecular storm*—a storm so fierce, it would make a hurricane look like a breeze. Yet, despite their stupendous speeds, molecules in the air do not get very far, because they frequently collide with each other. When this happens, the colliding molecules bounce like tiny billiard balls. The jittery dance that Brown observed and that Einstein explained is the result of this underlying tempest of colliding atoms. ([1] p.72)

> An important difference between a macroscopic storm and our molecular storm is that the molecular storm has no preferred direction. In other words, every collision with a water molecule comes from a random direction. Storms of our everyday experience blow in a more or less constant direction and can perform useful work (for example, move a sailboat or a windmill). At the nanoscale, not only is the molecular storm an overwhelming force, but it is also completely random. It is difficult to imagine how a molecular storm can serve as an energy source for useful work. …
>
> our machine must somehow tame the molecular storm … ([1] p.145)

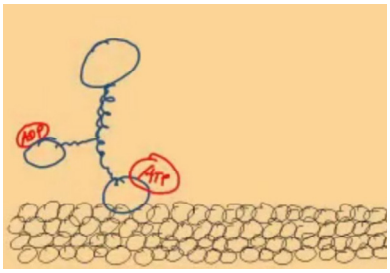
This taming of the molecular storm requires a ratchet mechanism that is able to filter the random motion into a particular channel of action. This is demonstrated by the motor protein kinesin which hauls packages (vesicles filled with nutrients) along microtubules in the cell by "walking" along the microtubule.



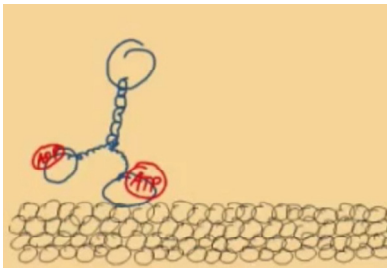
(1) kinesin on microtubule



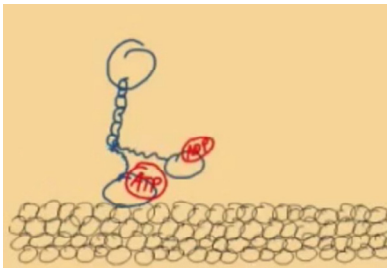
(2) ATP→ADP P↑



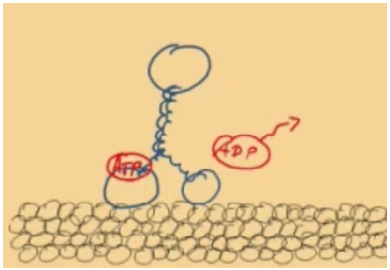
(3) Back foot 1lifts, ATP arrives



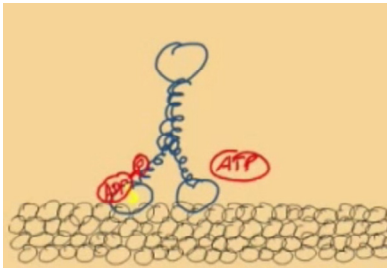
(4) Leg bends toward lead foot 2



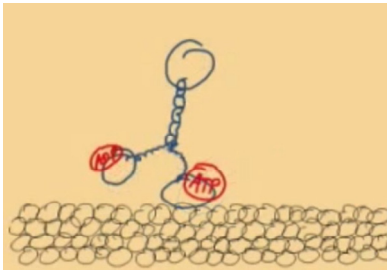
(5) Back foot 1 moves forward



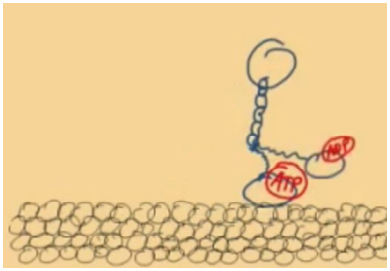
(6) Foot 1 attaches, ADP leaves



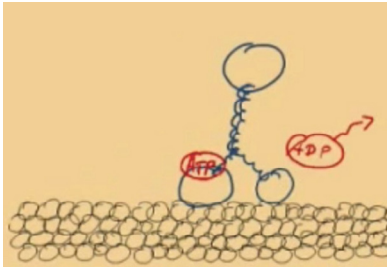
(7) Repeat: ATP→ADP P↑



(8) Back foot 2 lifts, ATP arrives, leg bends toward lead foot 1



(9) Back foot 2 moves forward



(10) Back foot 2 attaches, ADP leaves

Drawings by Peter M. Hoffmann from his video ([2])

Figure 1 Sequence of steps for kinesin walking along microtubule.

Motor Proteins – Kinesin

How the kinesin molecule walks is shown in Figure 1, which is a collection of snapshots from Hoffmann's video talk ([2]). The following is a narration of the kinesin motion given in Hoffmann's book ([1] pp.160-1) with links to my figures from the video rather than to the figures in the book.

> … a molecular motor called kinesin—a fifty-nanometer-long assembly of protein molecules—walks on two feet (or *heads*, as biologists confusingly call them) on a molecular track called a microtubule, always keeping one foot planted to the track. These motors are used to move cargo throughout cells—they are nanosize Sherpas, carrying heavy molecular loads along a one-way track to distant regions of the cell.

To see how kinesin motors work, let's take it step-by-step (literally) [Figure 1]. Initially, both feet are attached to the microtubule, and one of them has bound to an ATP molecule[1] [Figure 1 (1)]. The ATP molecule releases its energy (turning into ADP), and this energy is used to detach the foot from the microtubule [Figure 1 (2)]. Once this foot is detached, the molecular storm initially pushes the foot forward and backward, but it cannot go very far as the other foot is still holding on to the track. Now, the foot still planted on the track takes on an ATP molecule and by an allosteric shape change bends the whole kinesin molecule forward, forcing the dangling foot toward the forward direction [Figure 1 (3)-(5)]. Now, the dangling foot latches on in front of the attached foot, and releases ADP [Figure 1 (6)]. The attached foot degrades its ATP in turn, detaches from the track, and the cycle repeats [Figure 1 (7)].

We find here a [ratchet] mechanism …: The allosteric interaction [is] not allowing the free foot to swing backward as it is randomly pushed by the molecular storm. Once the foot has made a step, the now lagging foot must be released in an irreversible reset step, requiring the breakdown of an ATP molecule to a lower-energy ADP molecule. As long as there is a supply of ATP molecules, the motor will keep walking.

The hallmark of a tightly coupled molecular motor is that it goes through well-defined cycles, using up a fixed number of ATP molecules during each step. Nevertheless, random motion is the drive behind the motor's locomotion, as it ultimately moves the legs of the motor forward—of course, rectified by the allosteric interaction of the motor's legs with ATP.

The heart of the ratchet in this case is the allosteric change of shape of the kinesin molecule when ATP binds to it. In my essay, "Meditation on 'Is' in Mathematics Part II – Mathematical Reality," I likened the chains of if-then reasoning "discovered" by mathematicians to pieces in a jig-saw puzzle that eventually produce an originally hidden, but "determined," puzzle. In a similar way, the fitting of molecules together is like fitting pieces of a puzzle, but in this case the puzzle is three-dimensional and dynamic, that is, fitting one piece can change the shape of the molecular puzzle and cause previously fitted pieces to change or leave. So the ultimate pattern or puzzle is not static and fixed, but constantly changing. Some could argue that the body of mathematics is also changing and new discoveries cause previous ones to be reinterpreted and considered in a different way. In any case, just the biological considerations of Hoffmann's book are sufficiently riveting without resorting to analogies.

Animated videos and lectures greatly help in visualizing and understanding these ideas. The following is a suggested list.

Motor Protein Videos

Short Videos

A Day in the Life of a Motor Protein
(https://www.youtube.com/watch?v=tMKlPDBRJ1E)

This video concentrates on the action of kinesin in brain nerve cells, but in analogy to traveling on streets in a city. It still requires the specificity of a real biological explanation.

Motor Proteins, tiny Pirates in Your Cells
(https://www.youtube.com/watch?v=SgR4ojtPw5Q)

This short talk offers the most detailed biological explanation, but without animations. The narrator is a bit of a jerk and goes very fast, but it does offer the most scientific information.

[1] JOS: ATP = adenosine triphosphate, ADP = adenosine diphosphate

The Inner Life of a Cell. Animation by John Lieber
(Youtube version, Mar 29, 2014 https://www.youtube.com/watch?v=MZ47-G4XKDw)

This is an exciting animation originally made in 2006 that shows the operation of kinesin (Figure 2), as well as a lot of other organelles in the cell and among cells. It is an animation without narration, so you need other videos to explain what is going on ([3]).

Lieber's website: https://www.artofthecell.com/inner-life-of-a-cell/in-the-beginning-there-was-the-inner-life-of-the-cell.

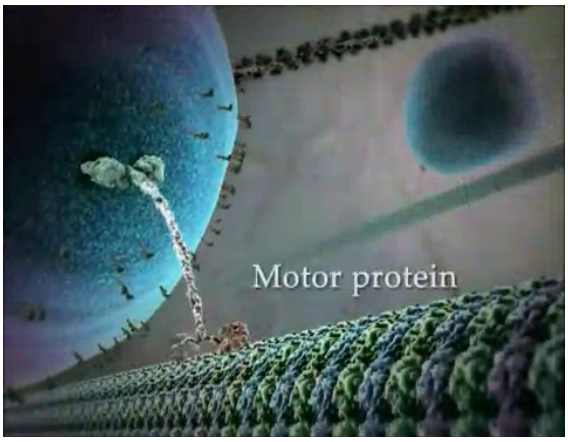


Figure 2 From "The Inner Life of the Cell" John Lieber 2006
https://gfycat.com/giftedpolishedfugu

Longer Video

2015 Lecture 1: Molecular Motor Proteins - Ron Vale (https://www.youtube.com/watch?v=9RUHJhskW00)

This is an excellent 35 minute talk that gives a thorough technical explanation of motor proteins with animations and diagrams. (Other lectures can be found at [4].) From a description of the talk:

> **Part 1:** Molecular motor proteins are fascinating enzymes that power much of the movement performed by living organisms. In this introductory lecture, I will provide an overview of the motors that move along cytoskeletal tracks (kinesin and dynein which move along microtubules and myosin which moves along actin). The talk first describes the broad spectrum of biological roles that kinesin, dynein and myosin play in cells. The talk then discusses how these nanoscale proteins convert energy from ATP hydrolysis into unidirectional motion and force production, and compares common principles of kinesin and myosin. The talk concludes by discussing the role of motor proteins in disease and how drugs that modulate motor protein activity can treat human disease.

References

[1] Hoffmann, Peter M., *Life's Ratchet: How Molecular Machines Extract Order from Chaos*, Basic Books, New York, 2012.

[2] Hoffmann, Peter M., "Life's Ratchet: How Molecular Machines Extract Order from Chaos," Video Talk, 38 min, 8 Sep 2016 (https://www.youtube.com/watch?v=j11sEzaYCUM)

[3] Lieber, John, "The Inner Life of the Cell" Video, January 2018 (http://www.artofthecell.com/the-inner-life-of-the-cell, retrieved 1/21/2019). 2006 Video: https://www.youtube.com/watch?v=MZ47-G4XKDw

[4] Vale, Ron, "Lectures: Molecular Protein Motors," 2015 (https://www.ibiology.org/cell-biology/motor-proteins/)