# Chapter 1.

## Introduction

**1a)** This is an e-book about the constructive effects of thermal energy in biology at the subcellular level. Thermal energy manifests itself as thermal fluctuations, sometimes referred to as thermal noise. Noise is usually a pejorative term, and thus inappropriate from the perspective developed in this e-book. Instead, it will be argued that at the subcellular level thermal fluctuations are responsible for much of the vitality of the cell. They cause the motion of all types of substrate molecules, enabling them to find enzymes that chemically change them. The whole array of such processes is called metabolism and these processes would not occur without the thermal fluctuations. Even the enzyme activity of the protein catalysts is strongly dependent on thermal fluctuations. In this e-book the focus is on one very special type of thermally caused behavior, *rectified Brownian motion* (RBM). What this phrase means will become clear as one reads the e-book.

Brownian motion was written about by Robert Brown [1] in 1828 (and by Adolphe Brongniart [2], so that a French speaking person might call it *Brongniart motion*). When he first observed the jiggly motion of pollen grains suspended in water through a low powered microscope, Brown thought he had discovered the "primitive molecule" of living matter [3]. However, subsequent observations of the same sort with suspended inorganic materials changed his mind. In this e-book, however, it will be argued that he may have been correct after all, i.e. thermal motions are indeed responsible for the vitality of cellular life. We use the word "vitality" in its literal sense and do not intend any connection with the doctrine of *vitalism*. In fact the thesis developed in this e-book is the antithesis of *vitalism*.

**1b)** RBM is a special sort of thermal mechanism. It has a somewhat long history in science, having been introduced in the 1930's, and later by Andrew Huxley in 1957 [4]. However, it went out of favor for awhile. In recent years it has been revived, principally in the context of the mechanism

of function of motor proteins, such as actin and myosin, kinesin and microtubule and dynein and microtubule [5]. In each of these cases, metabolic free energy in the form of ATP (adenosine triphosphate) is used to drive the functional cycle. A competing perspective is that there is a direct chemo-mechanical energy conversion from ATP to *secular* motion. By *secular* we mean a regular sustained motion that is very distinct from the rapid, random Brownian motion. This conversion mechanism is called the *power stroke*. It is commonly suggested in contemporary textbooks [6] that the power stroke is the mechanism by which the ATP cycle causes motion in motor proteins. Nevertheless, careful authors, especially in contemporary journal articles, do express the reservation that the detailed mechanism of the power stroke has yet to be elucidated. In this e-book, it is argued that the failure to find a detailed mechanism for the power stroke is the result of the possibility that the correct mechanism is of a very different kind, i.e. it is based on RBM instead. This conflict in perspective is the motivation for writing this e-book.

The e-book is divided into four main chapters, starting with chapter 1, the Introduction. In chapter 2, various thermal properties are introduced and explained. To make their importance clear, these properties are given for three very different mass scales, a minnow, an E. Coli and ubiquinone. Their masses (in grams) respectively are in the ratio $134::2x10^{-12}::1.4x10^{-21}$. This spans 23 orders of magnitude. As will be shown, thermal fluctuations are insignificant for the minnow, but they are surprisingly large for the E. Coli. Nevertheless, the E. Coli manages to execute secular motion using its flagella. For ubiquinone the thermal fluctuations are enormous and completely dominate its behavior. This is the case for which the introduction of RBM is made. Some of the thermal properties presented in chapter 2 are: Reynold's number, Stokes' drag force, mean free path, mean free time, Brownian path length, Langevin equation, diffusion equation, mean first passage time (MFPT), as well as RBM. When the discussion becomes mathematically technical, the equations are treated in an appendix to the chapter. In this way, a reader untrained in the mathematical fine points can still read the book meaningfully by skipping the appendices, while a more sophisticated reader will benefit from the mathematical details and proofs.

Similarly, the biochemical contexts for some of the examples will also be presented in appendices so that the reader can study them carefully but without losing the train of the central argument.

In chapter 3 the Brownian work theorem is presented and its proof is given in the chapter appendix. This result is the heart of the matter and clearly places the power stroke concept in contrast with RBM. For the E.Coli both mechanisms are at work while for the ubiquinone only RBM can operate. This sets the stage for consideration of which mechanism operates in a number of different sub-cellular processes. The two cases considered in detail in this chapter are the E. Coli and ubiquinone. Each provides a different perspective on the problem of mechanism.

In chapter 4 and its references a detailed look at rotary enzymes, kinesin motion on microtubules, actin and myocin dynamics, flagella and polymerases is taken. It is expected that by this point in the e-book, the reader will see much more clearly the robust presence of thermal motions in sub-cellular processes and how they can provide constructive effects through the mechanism of RBM. In the case of rotary enzymes, RBM appears to be the only possibility. For kinesin on microtubules and for actin and myosin the situation is less definitive. It may be more like the E. Coli case or it may also be exclusively explained by RBM. What is happening with flagella and with polmerases is still an open question.

It will have become clear by the end of the e-book that at the truly nanometer scale, thermal energy is very robust and a dominant source of energy for mechanisms. Harnessing this heat without violation of the second law of thermodynamics depends on RBM. At the macroscopic scale, heat is harnessed for useful work by heat engines. RBM, however, operates very differently from heat engines since it functions in an essentially isothermal environment. The biological use of RBM teaches us that the design of nanometer devices may benefit from RBM as well.

**1c)** To close this introduction, it is necessary to distinguish RBM from another current topic that is popular in the same biological context, that of

Brownian ratchets [7]. As will be shown in chapter two, Brownian motion can be described by the diffusion equation in an appropriate limit. The Brownian ratchet is described by a diffusion process with a potential energy term. This potential energy term in the one dimensional case is depicted by a periodic asymmetric saw-tooth potential. The mechanism of the ratchet depends on the existence of the potential. See the appendix for mathematical details (since this description is at the heart of the matter about which this book is written, all readers are encouraged to study this appendix). In the RBM mechanism there is no potential term, or if there is a potential, it is not necessarily periodic or saw-tooth and is only incidental to the mechanism. What is essential for the RBM mechanism is that the boundary conditions for the diffusion process are asymmetric. This asymmetry is responsible for the rectification, and rectification occurs even when there is no potential term at all. Thus, RBM is not the same thing as a Brownian ratchet. In some literature the phrase "biased Brownian motion" occurs and usually means the same thing as RBM.

## Appendix 1.1: Diffusion in a potential

The diffusion equation in one spatial dimension is

$$\frac{\partial}{\partial t} f(x,t) = \frac{\partial}{\partial x} D\left( \frac{\partial}{\partial x} + \beta \frac{\partial V(x)}{\partial x} \right) f(x,t)$$

in which $f(x,t)$ is the density of the diffusing quantity as a function of position, x, and time, t. D is the diffusion constant and has the units $cm^2/s$. The potential energy is $V(x)$ and the parameter $\beta$ is given by

$$\beta = \frac{1}{kT}$$

in which k is Boltzmann's constant ($1.381 \times 10^{-16}$ ergs/K) and T is the absolute temperature in Kelvins (K). It is straightforward to show that the steady state solution to the diffusion equation is

$$f_{ss}(x) = f_0 \exp\left[-\beta V(x)\right]$$

in which $f_0$ is a normalizing constant. The diffusion flux is defined by

$$flux = -D\left(\frac{\partial}{\partial x} + \beta \frac{\partial V(x)}{\partial x}\right) f(x,t)$$

When the steady state value for $f(x,t)$, $f_{ss}(x)$, is substituted into the right-hand side of the flux equation, the flux vanishes for any potential whatsoever. Consequently a static saw-tooth potential will not generate a flux at steady state. What has been shown in the theory of the Brownian ratchet is that if the saw-tooth potential is alternately turned on and left on for an appropriate short time and then turned off for the same amount of time, a none-zero flux can be generated [7]. Variations on this theme also work. The difficulty with this model in the context of sub-cellular biology is the demonstration of the existence of an on and off saw-tooth potential for the interacting proteins or other molecules. No convincing examples have been published to date.

In the RBM model the diffusion equation operates on a finite domain of the x-axis between x = a and x = b > a. We suppose that biological processes maintain the density constant at both a and b and that the density at a is greater than at b:

$$f(a) > f(b)$$

The steady state solution to the diffusion equation in the absence of any potential term, $V(x)$, is given by

$$f_{ss}(x) = f(a) - \frac{x-a}{b-a}\left(f(a) - f(b)\right)$$

This solution clearly satisfies the asymmetric boundary conditions at x = a and x = b. It is a linear profile that decreases as x goes from a to b. The steady state flux is constant and from a to b:

$$flux = -D\frac{\partial}{\partial x} f_{ss}(x) = D\frac{f(a) - f(b)}{b - a} > 0$$

As will be seen in chapter 2, biological processes, such as metabolism, can produce the asymmetric boundary conditions require for the production of a none-zero flux. Several examples of this mechanism are already known to apply in sub-cellular biology [8].

## References


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