Maximum Entropy and Living Organisms.

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1 Introduction

My interest lies at the intersection of life, inference and engines. At the heart of all things is entropy — in particular **The Maximum Entropy Principle** (MaxEnt), which is a statistical method of producing minimum bias priors in accordance with Bayesian probability.

The basic idea is to recognise that the most fruitful thing an agent can do with a probability distribution is to use it to make a bet. I want to ask, if a bet is repeatedly playing out successfully and reliably, how is the information associated with it encoded into the agent? If living organisms were able to evolve to states of maximum entropy with respect to relevant knowledge on dependable conditions, would this provide an advantage over competing organisms that may exhibit differing biases with respect to the same observations?

These are the general questions I'm interested in, but my focus at the moment is on a non-equilibrium model for the behaviour of the molecular motor protein Kinesin. Over the course of a single stepping-cycle, 1 ATP molecule is hydrolysed and the motor undergoes a diffusive search for the subsequent binding site. This serves to extract work from a thermal reservoir in a cyclical sequence of states that breaks detailed balance.

I am investigating MaxEnt to see if it can be used to quantify the cost of an inference (that is, that a diffusive process succeeds within some time-limit) in terms of solely the properties that define it in the first place (viscosity of the fluid, mass of the constituents, load force etc). If this cost can be compared with the budget liberated during ATP hydrolysis (and all the other biochemical processes along the cycle), it may be possible to find regions of parameter space where the cost exceeds the budget, implying that the protein should stall.

If these regimes of failure overlap with experimental data, this provides a case for the application of MaxEnt to living methods of energy extraction and dissipation more widely.

2 Entropy and Maximum Entropy

Entropy S has deep-set interpretations in a variety of fields but two important ways of describing the quantity are in:

1. *molecular thermodynamics* where it is used to characterise energy dispersal at a certain temperature; to quantify the flow of thermal energy between two states of a system [1].

2. *probability theory* where it serves as a measure of the information required to achieve full certainty; it represents a state of knowledge of a system [2], expressed as a somewhat aggregated function of the probability density p:

$$S(p) = -k_B \sum_i p_i \ln p_i = -k_B \langle \ln p \rangle \tag{1}$$

where k_B is Boltzmann's constant, $\{i\}$ is an exhaustive set of N mutually exclusive alternatives and p_i satisfy $\sum_i^N p_i = 1$.

In the 1950's Edwin T. Jaynes realised that entropy could be used as a basic element of probability theory, allowing one to construct prior probabilities that minimise bias with respect to available information [3]. MaxEnt is essentially an algorithm that provides a way of building a model that optimally represents a state of knowledge. Given information $\boldsymbol{\vartheta}$ in the form of a set of M independent vectors $\{\boldsymbol{\vartheta}_j\}$ with $j = 1, \cdots, M < N$, each with a value for its associated expectation $\langle \boldsymbol{\vartheta}_j \rangle = \sum_i^N p_i \boldsymbol{\vartheta}_{ij}$, the information entropy (1) is maximised to S_{Max} and the Lagrange multiplier method yields a corresponding distribution $p_{\boldsymbol{\vartheta}} \equiv \{p_i\}$:

$$p_i = \frac{e^{-\lambda \cdot \boldsymbol{\vartheta}_i}}{\mathcal{Z}} \tag{2}$$

where $\mathcal{Z} = \sum_i^N e^{-\lambda \cdot \boldsymbol{\vartheta}_i}$ is the normalising partition function and Lagrange multipliers $\lambda = \{\lambda_j\}$ follow scalar-product notation:

$$\lambda \cdot \boldsymbol{\vartheta}_i \equiv \lambda_1 \boldsymbol{\vartheta}_{1i} + \cdots + \lambda_M \boldsymbol{\vartheta}_{Mi} \tag{3}$$

The λ_j are found by solving the set of M coupled differential equations:

$$\langle \boldsymbol{\vartheta}_j \rangle = -\frac{\partial}{\partial \lambda_j} \ln \mathcal{Z} \tag{4}$$

Qualitatively, this method serves to 'flatten out' the distribution as much as possible whilst still maintaining the constraints that have been applied during the maximisation procedure. It ensures that the resultant probabilistic description obtained includes: a) the information contained in the measurements themselves; b) the assumption of an exhaustive set of mutually exclusive outcomes; and c) *absolutely nothing else*.

This maximised entropy can also be used as a basis to define entropy, which makes it useful because, unlike classical definitions from thermodynamics, it is not limited to equilibrium frameworks and concepts, but can be provided arbitrarily given $\boldsymbol{\vartheta}$: a so-called 'hypothesis space' that ideally encapsulates all the essential information of the system in question [4].

3 Research Methods

My interest revolves around the search for hypothesis spaces that can apply to physically relevant processes enacted by living organisms — for instance by modelling the expected rate of a well-defined event, the mean first passage time of arrival or the correlation between dwell times of a system. Then, in conjunction with thermodynamic considerations, I aim to use MaxEnt to make predictions about the behaviour of a biological system in a variety of parameter regimes.

3.1 Kinesin and Rectified Brownian Motion

Kinesin is a molecular motor protein that can be found in all living organisms. It consists of two motor heads which bind sequentially to sections of a long molecular track called a microtubule highway. The protein is responsible for the directed transport of larger molecules within a cell. Due to the extremely low Renoylds number of sub-cellular biology, inertial effects play no significant role in stepping, so instead Kinesin procession harnesses Brownian motion, often acting against an external load force backwards.

The process is works in a cycle [5], with most stages (Figure1) involving biochemical reactions. It is initiated by the supply of the adenosine triphosphate (ATP) arriving at a nucleotide-binding pocket on the anchored motor-head. The protein then undergoes a variety of conformational changes that culminate in the docking of an attached neck-linker to the head, forming a complex known as the 'cover-neck bundle'. This newly-formed complex has the tendency to bend towards the anchored head, and it is considered a critical component for stepping. Full docking is completed in eventual direct contact with the motor core, but the mechanism by which this final process occurs is energetically unfavourable, completed only with the release of free energy from the hydrolysis of ATP, which powers the cycle [6].

Meanwhile, the tethered second head, initially situated 16nm behind the target, dependably makes its way to the next microtubule binding site ahead. Studies on Kinesin have identified two possible mechanisms to convert the chemical energy from hydrolysis into mechanical work. The first is the 'power stroke' model, whereby docking of the linker mechanically forces the tethered head forward some distance. The second is the 'Brownian ratchet' model, involving a biased diffusive search of the tethered head to find the target binding site. These two methods of movement are not mutually exclusive [7] and it is the subject of my work to investigate the contributions of each by modelling the tethered head as a particle that periodically resets [8] to the position of the anchored head, 8nm away from the initial and final binding sites.

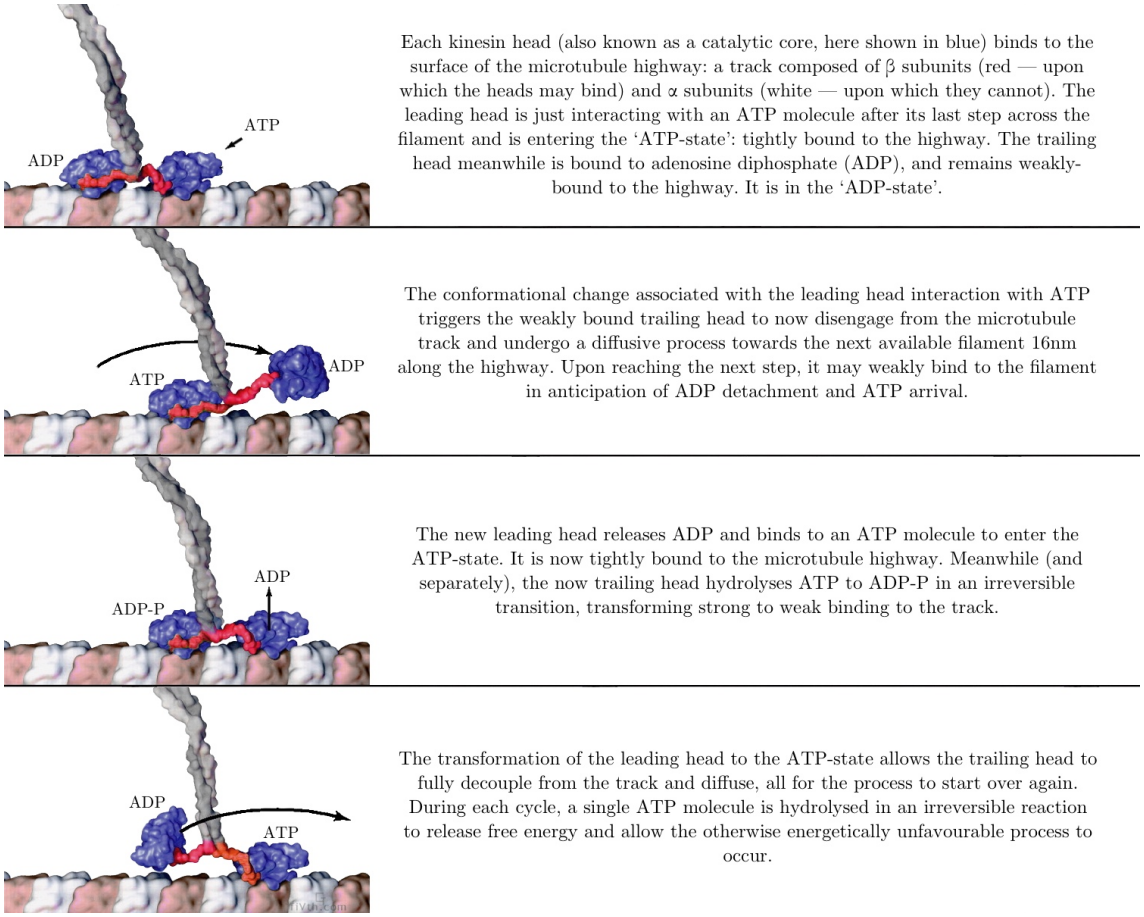

Figure 1: **The Kinesin Stepping Cycle.** The diagram on the left is adapted from [9]. Loads attach to the tall thin section of the protein in grey.

3.2 Irreversible Thermodynamics

Experiments have identified some 'missing' internal dissipation in the motor. Energy is released initially in the form of chemical free-energy (-20kT), some of which is transformed into work to carry the load (3.74kT at 2pN), and the remainder is dissipated into some form of heat. Heat has been known to come from a couple of sources: a simple viscous drag component (0.06kT), and a more complicated non-equilibrium contribution due to the stochastic nature of the diffusing head (0.1kT). However, when experimental researchers went looking for these various forms of dissipation [10], they discovered that 80% of the energy remains unaccounted for, implying an unknown internal source of dissipation that seems to be responsible for the vast majority of the energy budget available.

In terms of thermodynamics, the process is intriguing because it harnesses thermal energy to extract work by enforcing boundary conditions and driving resetting through the expense of metabolic energy. In conjunction with the other processes in the cycle, let's ask: can this be understood as the working stroke of a heat engine which spends time far away from equilibrium?

Crucially, this engine would operate in a fundamentally different way than its Carnot relative. Far from maintaining a constant entropy throughout the cycle, it would be acting to *maximise* entropy during a critical step. This incorporation of information via MaxEnt is equivalent to maximising irreversibly with respect to the hypothesis space $\boldsymbol{\vartheta}$ — a prediction measure which is used to inform a later forecasted outcome. In addition, this engine is being actively driven by an external agent; it does not operate in isolation or apply to closed systems.

A simple non-equilibrium argument in thermodynamics [11] can be re-purposed to provide a starting point for the research outlined here (Figure2). Consider a system in contact with a thermal reservoir, initially in an equilibrium state $p_0 = e^{-\beta\mathcal{H}_0}/\mathcal{Z}_0$ with Hamiltonian $\mathcal{H}_0$. It undergoes 3 general processes in a cycle. These steps are as follows:

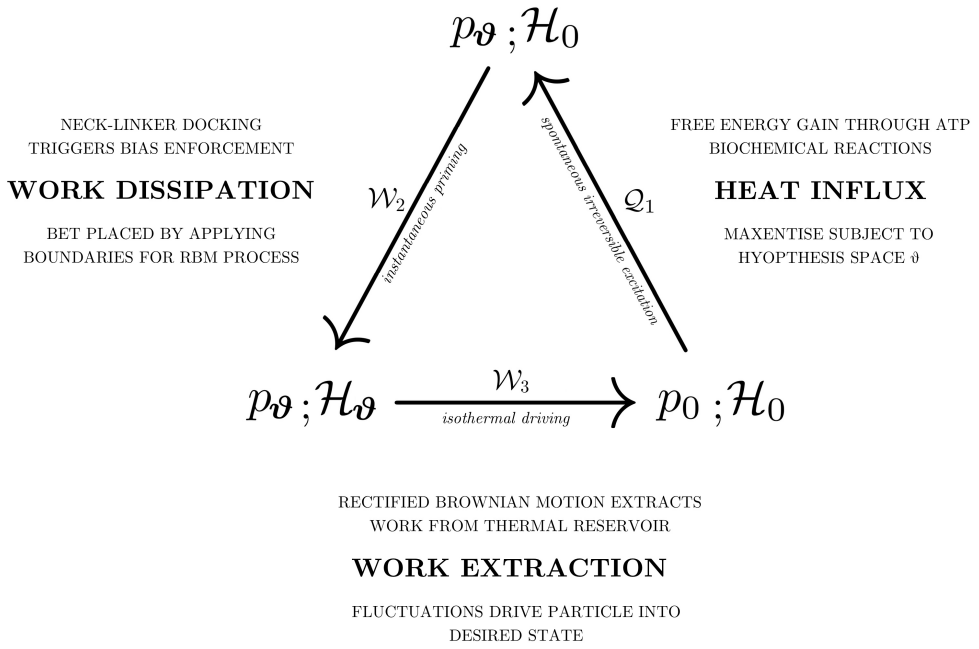

Figure 2: **The Biological Inference Engine** This cycle has been adapted from a simple non-equilibrium free energy argument [11] and is a sketch intended for further investigation.

1. *Spontaneous, irreversible excitation* — A heat $\mathcal{Q}_1 = \langle \mathcal{H}_0 \rangle_{p_{\vartheta}} - \langle \mathcal{H}_0 \rangle_{p_0}$ is transferred from the environment to the system, kicking the state-particle out of equilibrium. Biochemical reactions involving ATP stimulate conformational changes in the protein, expending metabolic energy in preparation for the thermal driving process.

2. *Instantaneous priming* — The system Hamiltonian is transformed $\mathcal{H}_0 \to \mathcal{H}_{\vartheta} \equiv -k_B T \ln p_{\vartheta}$, requiring dissipated work $\mathcal{W}_2 = \langle \mathcal{H}_{\vartheta} \rangle_{p_{\vartheta}} - \langle \mathcal{H}_{\vartheta} \rangle_{p_0}$. In Kinesin, before the diffusive search of the trailing head, the anchored leading head binds with ATP and causes a mechanical element called the neck-linker to dock onto the catalytic core. This mechanism is widely believed to play a key role in directional stepping by providing a forward bias for the diffusive search, harnessing RBM principles by imposing effective boundary conditions that exponentially alter the probabilities of visiting forward vs backward binding sites [12].

3. *Isothermal driving* — The quench triggers the final part of the process. The system is now exposed to thermal fluctuations and driven into the original desired equilibrium state, over which work $\mathcal{W}_3 = F(p_0) - F(p_{\vartheta}) = \langle \mathcal{H}_0 \rangle_{p_0} - TS_0 - \langle \mathcal{H}_{\vartheta} \rangle_{p_{\vartheta}} + TS_{Max}$ is performed. This is the RBM working stroke in action. The system is ready to repeat the cycle all over again.

Clearly the cycle breaks down if $\mathcal{W}_3 > \mathcal{Q}_1 + \mathcal{W}_2$. Or, in other words, the work performed should not exceed the heat paid for the wager plus the work spent to frame the guess.

With Kinesin in mind, $\mathcal{Q}_1$ should correspond directly to hydrolysis and other metabolic reactions which can be modelled using Arrhenius rate reaction methods [13]. $\mathcal{W}_2$ can be considered by looking at both experimental observations [14] and structural modelling of the protein [15]. Neither of these are expected to be particularly load-dependent [16]. $\mathcal{W}_3$ however, is. So the investigation here is concerned with the search for an appropriate hypothesis space: one that wholly encapsulates all the relevant information associated with that diffusive search - consisting of: the first-passage time distributions; the dwell times; the 'pulling-back' load force; the constant temperature of the cell and other fundamental quantities of the system. From there, $\mathcal{W}_3$ is thought be calculable using MaxEnt.

Experimental measurements have found that Kinesin operates up to 5-7pN load force [17] and 5mPa s effective viscosity [18]. The ultimate goal then is to theoretically reproduce these experimentally observed stall values by finding parameters that satisfy $\mathcal{W}_3 > \mathcal{Q}_1 + \mathcal{W}_2$.

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