Energy and Information Transduction In
Strongly-Coupled Systems

by

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Abstract

Molecular machines are stochastic systems that interconvert different forms of energy, such as chemical potential energy and mechanical energy. These machines are generally comprised of many subunits that each perform a specific function. We develop a novel model that captures some of the important behaviours of rotary stochastic coupled systems. This model contains an explicit reference to the degree of coupling between subunits and allows for the investigation of energy transduction as a function of coupling strength. Evolving the system using Fokker-Planck dynamics, we find that the efficiency of this energy transduction is tightly correlated with coupling strength. In addition, recent developments in theoretical studies have established links between information theory and stochastic thermodynamics. Prompted by these developments, we investigate the information-theoretic quantities of nostalgicia and learning rate. We find that, in this model, these quantities lose their link to the thermodynamics of the system, as here we consider the case of symmetric coupling between subsystems whereas these quantities were originally derived for asymmetric coupling.

Keywords: Molecular Machines; Fokker-Planck Dynamics; Efficiency; Information Theory
Acknowledgements

Unlike the rest of this thesis the following section follows no logical trail. It will have had no revisions and so I may be repetitive in what I say; however, it is, personally, the most important to me as it is the place where I get to thank and acknowledge all of the people that have provided me with constant support, friendship, and inspiration as I worked to complete my undergraduate degree at Simon Fraser University.

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Dedication

For my parents Neil & Stella Lucero.
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Chapter 1

Introduction

Living organisms possess a myriad of abilities that make them interesting systems to study. In particular, these organisms possess the ability to obtain energy from their surroundings (either by active or passive action) and convert it into other forms of energy that are useful for self-sustenance. For example, animals chase (and potentially consume) other animals, while plants convert solar energy into energy that sustains them without having to expend the energy for a chase. Common to both of these organisms and their abilities to convert energy is the central contribution of many cooperating molecular machines in order to facilitate this energy conversion. Molecular machines can be found in all of life’s domains. The simplest single-celled prokaryotes to the most complex eukaryotes can accommodate a greater complexity in their genomes by having specialized machines to process and implement the instructions contained within, the influence of these micro- to nano-scale machines cannot be understated [1, 2]. As such this thesis aims to examine some of the physical principles that govern their operation.

1.1 Molecular Machines

Despite the incredible diversity visible on the supracellular level, at the subcellular level, there appear to be only a few key elements that are essential for maintaining and sustaining life. Among these are the genetic code, cellular membranes and molecular machines. These machines are a sub-category of proteins that are capable of converting between different types of energy. One particular type of molecular machines—so-called *mechanochemical* machines—can interconvert two specific types of energy: chemical potential and mechanical motion. These machines often power themselves by consuming adenosine triphosphate (ATP). Each molecule of ATP generates \( \approx 20k_B T \) of free energy as a high-energy bond is broken to convert ATP to its constituent parts of adenosine diphosphate (ADP) and inorganic phosphate (P$_1$),

\[
\text{ATP} \rightarrow \text{ADP} + \text{P}_1.
\]
While we often speak of them as regular machines, there are a few fascinating facts that make molecular machines different than common everyday machines like cars or refrigerators. In particular, thermal fluctuations play a large role in these machines’ operation. Thermal fluctuations are random deviations from the average system state which arise due to non-zero temperatures. These fluctuations are measured by the unit $k_B T$, where $k_B$ is Boltzmann’s constant and $T$ is the absolute temperature of the surroundings. At room temperature, $k_B T = 4.114$ pN nm, which is comparable to the energetic barriers separating different conformational states of a protein. As a result, thermal fluctuations can cause a protein to occasionally go ‘uphill’.

In many living organisms, specifically those containing mitochondria, these energy-bearing ATP molecules are generated by a membrane-bound, rotary mechanochemical motor: F$_o$ F$_1$-ATP synthase. We are particularly interested in modelling this motor in this work.

1.1.1 F$_o$F$_1$-ATP synthase

F$_o$F$_1$-ATP synthase is composed of three components: a membrane-bound component (F$_o$), and a membrane-free component (F$_1$), connected via a central crankshaft. A large hydrogen-ion gradient is established across the inner mitochondrial membrane, and flow of ions down this gradient imparts an electromotive force on the F$_o$ component. This is then transduced into a torque that induces a mechanical rotation of the central crankshaft. This mechanical rotation powers the reactions that occur in the catalytic site of the enzyme, driving forward the synthesis of ATP.

The H$^+$ gradient established over the membrane drives the machine in the direction of the synthesis of ATP. Synthesis of ATP results in a deviation of ATP concentration from its steady-state value which, in turn, establishes a chemical drive to hydrolyze ATP so as to restore the steady-state concentration.

Structurally, it is well known that the F$_1$ component has three identical catalytic sites, and it is also believed that one complete rotation corresponds to potentially three chemical reactions [3].

1.1.2 Reynolds Number for Molecular Machines

The Reynolds number is a characteristic quantity of a fluid that captures the dominant forces acting within that fluid [4]. It is defined as the ratio between inertial fluid forces and viscous fluid forces:

$$\text{Re} \equiv \frac{L \nu \rho_{\text{med}}}{\eta_{\text{med}}},$$

(1.1)

1 This is pronounced “Eff-Oh”
where $L$ is the length of the object, $v$ is the speed, $\rho_{\text{med}}$, and $\eta_{\text{med}}$ denote the density and viscosity of the surrounding medium, respectively. Attaching a 2 µm actin filament to the central crankshaft of ATP synthase, the Reynolds number in water of this filament, rotating at an angular speed of say 100 rotations per second, is $\approx 2 \times 10^{-5}$. For Reynolds numbers much less than unity, the behaviour of the system is utterly dominated by viscous forces (i.e. the instantaneous forces) acting on the object. This object would not retain any memory or persistent motion in this regime. As such, an object that is not pushed persistently will come to rest extremely quickly. While this quoted number serves as a useful benchmark, this is actually only an upper bound on the Reynolds number for objects at this length scale and with this speed of operation: in vivo, the Reynolds number tends to be much lower as the cell is a very crowded place.

1.2 Motivations and Goals

Experiments have found that notable examples of molecular machines can be extremely efficient energy transducers. To acquire directed motion these nanoscale machines operate far out of equilibrium and harness stores of chemical energy. In order to explore these molecular machines and the tradeoffs that they face, we have developed a minimal model of a rotary machine comprised of two subsystems that are energetically coupled together such that the dynamics of one subsystem influences the other (and vice versa), inspired by the molecule $F_{0}F_{1}$-ATP synthase. We vary the strengths of various external gradients, as well as the coupling strength between the systems. We use the Smoluchowski equation (the overdamped Fokker-Planck equation) to evolve probability distributions on tilted energy landscapes, where detailed balance is broken and no analytic solution is known. The search for the Pareto frontier of machine operation leads to the question of whether there is some optimal way to configure the system subject to the system satisfying multiple criteria simultaneously. We create a minimal and general model independent of the molecular details of the $F_{0}F_{1}$ system, so that our model can be applied to other machines that undergo cyclic operation.
Chapter 2

Theoretical Background

Classical thermodynamics is a mathematical framework for describing physical systems characterized by the Gibbs-Boltzmann probability distribution [5]. However, it is ultimately limited in its scope of applicability and is unable to describe systems that are pushed far away from its equilibrium configuration. Thus the study of nonequilibrium thermodynamics aims to generalize classical thermodynamics to systems which no longer satisfy the requirements of equilibrium. This novel theoretical framework thus allows out-of-equilibrium processes to be investigated, and in particular sheds light on different systems such as driven quantum systems or even processes in biological organisms [6]. In this thesis we focus our attention on nonequilibrium driving that provides an external perturbation on an energetically coupled system embedded in a noisy environment.

The realization that thermodynamics has an intersection with information theory has a long history [7]. Initially spurred by discussion regarding Maxwell’s Demon and the challenges it poses, many attempted to find the solution at the turn of the twentieth century. It was not until 1961 that Rudolf Landauer, at the time working for IBM, realized that the erasure of information requires a minimum amount of energy dissipation. Specifically, to erase a bit of information requires $k_B T \ln 2$ of energy. This link between thermodynamics and information theory has been an area of recent research interest [8, 9].

2.1 Entropy and Information

The following section reviews material from Chapter 2 of Elements of Information Theory by Cover & Thomas [10] and establishes the relevant background on information theory.

In order to properly discuss information, we first introduce the concept of entropy and its relationship to random variables. Here, for clarity, we focus our discussion on two random variables; however, this discussion is easily generalized to any number of random variables. A random variable (RV) $X$ is a variable whose possible values are outcomes of a certain stochastic phenomenon. Here we use the notation of a capital letter, say $X$, to denote the random variable in general and a lower case letter, say $X = x$, to denote a specific
realization or outcome of a random variable. All outcomes are drawn from the random variable’s allowed state space $\mathcal{X}$ (ie. $x \in \mathcal{X} \forall x$). In this work we consider continuous state spaces and thus continuous random variables.

The entropy of a RV, $X_1 \sim \rho_1(x_1)^1$, which can assume states in a continuous space of possibilities, $\mathcal{X}_1$, is given by,

$$H(X_1) := - \int_{\mathcal{X}_1} dx_1 \; \rho_1(x_1) \ln \rho_1(x_1) ,$$

(2.1)

where the integral $\int$ denotes an integration over all possible realizations of the RV $X_1 = x_1 \in \mathcal{X}_1$. Entropy is measured here in units known as nats$^2$. If $X_2 \sim \rho_2(x_2)$ is a different RV with another continuous space of possibilities, $\mathcal{X}_2$, the joint entropy between the two RVs, assuming they are jointly distributed as $\rho(x_1, x_2)$, is

$$H(X_1, X_2) := - \int_{\mathcal{X}_1, \mathcal{X}_2} dx_1 dx_2 \; \rho(x_1, x_2) \ln \rho(x_1, x_2) .$$

(2.2)

This can be rewritten as (see Appendix A.1),

$$H(X_1, X_2) = H(X_2|X_1) + H(X_1) ,$$

(2.3)

where we have defined the conditional entropy of $X_2$, $H(X_2|X_1)$, as:

$$H(X_2|X_1) := - \int_{\mathcal{X}_1, \mathcal{X}_2} dx_1 dx_2 \; \rho(x_1, x_2) \ln \frac{\rho(x_2)}{\rho_1(x_1) \rho_2(x_2)} .$$

(2.4)

Equation (2.3) is sometimes known as the chain rule for entropies. By convexity we have that, for any random variables $X_1$ and $X_2$, $H(X_1|X_2) \leq H(X_1)$, with equality only when $X_1$ and $X_2$ are independent. The entropy of a random variable then is the uncertainty that one has about that RV or, viewed in a complementary way, it is a measure of how much information would be required to describe, on average, that RV.

The mutual information between the two random variables $X_1$ and $X_2$ is defined to be:

$$I(X_1, X_2) = \int_{\mathcal{X}_1, \mathcal{X}_2} dx_1 dx_2 \; \rho(x_1, x_2) \ln \frac{\rho(x_1, x_2)}{\rho_1(x_1) \rho_2(x_2)} .$$

(2.5)

---

1 This is read as “The random variable $X_1$ is distributed as $\rho_1(x_1)$”

2 Entropy can be measured in different units depending on what base of logarithm is used. For base $e$, entropy is measured in “nats”. Similarly, for base 10 entropy is measured in “hartleys” while for base 2 entropy is measured in “bits”.

---

5
Employing equations (2.1), (2.2), and (2.3) we can rewrite this as simply,

\[ I(X_1, X_2) = H(X_1) + H(X_2) - H(X_1, X_2) \]  
\[ = H(X_1) - H(X_1 | X_2) \]  
\[ = H(X_2) - H(X_2 | X_1) . \]

Since \( H(X_1 | X_2) \leq H(X_1) \), it must be the case that \( I(X_1, X_2) \geq 0 \). Intuitively, we can think of mutual information as a reduction in the entropy of an RV given knowledge of another RV.

In order to measure a “distance” between two probability distributions, we make use of the relative entropy or Kullback-Leibler (KL) divergence between the two distributions \( \rho(x_1, x_2) \) and \( q(x_1, x_2) \), given by,

\[ D[\rho(x_1, x_2) | | q(x_1, x_2)] = \int_{x_1} \int_{x_2} \rho(x_1, x_2) \ln \frac{\rho(x_1, x_2)}{q(x_1, x_2)}. \]

We utilize here the convention (by continuity) that \( 0 \ln 0 = 0 \) and \( \rho \ln \frac{\rho}{q} = \infty \). We note that relative entropy is non-negative and is 0 if \( \forall \ x_1, x_2, \rho(x_1, x_2) = q(x_1, x_2) \). Strictly speaking, relative entropy can only be loosely intuitively interpreted as a distance as it is not a true mathematical metric, being non-symmetric in \( \rho(x) \) and \( q(x) \) and also disobeying the triangle inequality. Recasting the mutual information in terms of this relative entropy we acquire

\[ I(X_1, X_2) = D[\rho(x_1, x_2) | | \rho_1(x_1) \rho_2(x_2)]. \]

Therefore, mutual information can be seen as a measure of “distance” between the joint distribution \( \rho(x_1, x_2) \) and the product of the marginal distributions \( \rho_1(x_1) \rho_2(x_2) \). In other words, it measures how far the two RVs \( X_1 \) and \( X_2 \) are from being independent.

In order to quantify the limits on information processing we now introduce the data processing inequality. Consider three random variables \( X_1, X_2, \) and \( X_3 \), with respective allowed states \( X_1, X_2, X_3 \). In addition, suppose that \( \rho(x_1, x_3 | x_2) = \rho(x_1 | x_2) \rho(x_3 | x_2) \). In other words, \( X_1 \) and \( X_3 \) are conditionally independent given \( X_2 \). Then the data processing inequality states

\[ I(X_1, X_2) \geq I(X_1, X_3) . \]

Intuitively, if \( X_1 \) ‘knows about’ \( X_3 \) only through the intermediate \( X_2 \),

\[ X_1 \rightarrow X_2 \rightarrow X_3, \]

then the data processing inequality imposes that \( X_1 \) cannot have information about \( X_3 \) that \( X_2 \) does not have about \( X_3 \).
2.2 Information Theoretic Quantities

2.2.1 Nostalgia and Thermodynamics of Prediction

We introduce here a framework that was first proposed by Still et. al. [11], and examined recently more concretely in discrete Markovian models [12]. This framework measures the quality of a predictive model generated by a system responding to a stochastic signal and relates it to the thermodynamics of the system.

The equilibrium free energy is defined as [5],

$$\beta F_{\text{eq}}(x_1) := -\ln \left\{ \int dx_2 \exp \left[ -\beta V_{\text{tot}}(x_1, x_2) \right] \right\}. \quad (2.10)$$

Here, $x_1$ and $x_2$ denote the environment and system variables, respectively. $V_{\text{tot}}(x_1, x_2)$ denotes the total external potential of the system. In nonequilibrium settings, the free energy can be generalized to

$$\beta F_{\text{neq}}(x_1) = \beta F_{\text{eq}}(x_1) + \beta F_{\text{add}}(x_2|x_1), \quad (2.11)$$

where $\beta F_{\text{add}}(x_2|x_1)$ is given by

$$\beta F_{\text{add}}(x_2|x_1) := D \left[ \rho(x_2|x_1)||\pi(x_2|x_1) \right], \quad (2.12)$$

and the conditional equilibrium distribution $\pi(x_2|x_1)$ is

$$\pi(x_2|x_1) = \exp \left( -\beta \left[ V_{\text{tot}}(x_1, x_2) - F_{\text{eq}}(x_1) \right] \right). \quad (2.13)$$

To model the evolution of the system and the environment, a leap-frog alternating timestep is used. The pattern is given by the following:

- **Work Step**: At a fixed system state, $x_2(t)$, at time $t$, the environment evolves

  $$x_1(t) \rightarrow x_1(t + \Delta t)$$

- **Heat Step**: At a fixed environmental state, $x_1(t + \Delta t)$, at time $t + \Delta t$ the system evolves

  $$x_2(t) \rightarrow x_2(t + \Delta t)$$

Thus the Markov Chain,

$$x_2(t) \rightarrow x_1(t) \rightarrow x_1(t + \Delta t), \quad (2.14)$$

is formed from this timestep pattern.
The work done by the environment on the system after a single step of environmental dynamics is

\[ W [x_1(t) \rightarrow x_1(t + \Delta t), x_2(t)] := V_{\text{tot}} [x_1(t + \Delta t), x_2(t)] - V_{\text{tot}} [x_1(t), x_2(t)] . \quad (2.15) \]

Similarly, the heat during a single step of system dynamics can be defined in a similar way as,

\[ Q [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] := V_{\text{tot}} [x_1(t + \Delta t), x_2(t + \Delta t)] - V_{\text{tot}} [x_1(t + \Delta t), x_2(t)] . \quad (2.16) \]

The change in free energy during the work step is:

\[ \Delta F_{\text{neq}} [x_1(t) \rightarrow x_1(t + \Delta t), x_2(t)] := F_{\text{neq}} [x_1(t + \Delta t), x_2(t)] - F_{\text{neq}} [x_1(t), x_2(t)] , \quad (2.17) \]

while the change during a heat step is:

\[ \Delta F_{\text{neq}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] := F_{\text{neq}} [x_1(t + \Delta t), x_2(t + \Delta t)] - F_{\text{neq}} [x_1(t + \Delta t), x_2(t)] . \quad (2.18) \]

The average dissipation over work steps, utilizing the appropriate entropy relations, is given by,

\[ \beta (W_{\text{diss}} [x_1(t) \rightarrow x_1(t + \Delta t), x_2(t)]) = I [x_1(t), x_2(t)] - I [x_1(t + \Delta t), x_2(t)] . \quad (2.19) \]

We identify the right-hand side (RHS) first term as the instantaneous memory, \( I_{\text{mem}}(t) := I [x_1(t), x_2(t)] \), whereas the second term, \( I_{\text{pred}}(t) := I [x_1(t + \Delta t), x_2(t)] \) can be identified as instantaneous predictive power. Noting that

\[ \rho [x_1(t + \Delta t), x_2(t)|x_1(t)] = \rho [x_1(t + \Delta t)|x_1(t)] \rho [x_2(t)|x_1(t)] , \]

which can be directly seen from the Markov Chain formed from the timestep pattern (2.14). Thus (2.9) holds, and as a result \( I_{\text{mem}}(t) - I_{\text{pred}}(t) \geq 0 \). Given this, (2.19) has the following interpretation: if the system is viewed as performing a computation to calculate a predictive model of the environment’s future states, then (2.19) quantifies this model’s unnecessary complexity. As such, this quantity is assigned the stylized name of \( \text{nostalgia} \) [11]. The equation,

\[ \beta (W_{\text{diss}} [x_1(t) \rightarrow x_1(t + \Delta t), x_2(t)]) = I_{\text{mem}}(t) - I_{\text{pred}}(t) \equiv I_{\text{nos}}(t) , \quad (2.20) \]

thus relates thermodynamic dissipation to unnecessary information carried by the predictive model computed via the system’s dynamics.
Similarly, we can define the work dissipated over the relaxation of the system as,

\[ \beta \langle W_{\text{diss}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] \rangle := -\beta \langle \Delta F_{\text{neq}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] \rangle. \]  

(2.21)

The total dissipation over the time step from \( t \) to \( t + \Delta t \) is given by:

\[ \langle W_{\text{diss}}(t) \rangle = \langle W_{\text{diss}} [x_1(t) \rightarrow x_1(t + \Delta t), x_2(t)] \rangle + \langle W_{\text{diss}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] \rangle. \]  

(2.22)

Combining this with (2.20), we obtain the following result:

\[ \beta \langle W_{\text{diss}}(t) \rangle = I_{\text{nos}}(t) - \beta \langle \Delta F_{\text{neq}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] \rangle. \]  

(2.23)

As the relaxation steps, on average, bring the system closer to equilibrium, we can conclude that

\[ \beta \langle \Delta F_{\text{neq}}^{\text{relax}}(t) \rangle := \beta \langle \Delta F_{\text{neq}} [x_1(t + \Delta t), x_2(t) \rightarrow x_2(t + \Delta t)] \rangle \leq 0, \]  

(2.24)

and hence we place the following bound on total dissipation:

\[ \beta \langle W_{\text{diss}}(t) \rangle \geq I_{\text{nos}}(t). \]  

(2.25)

### 2.2.2 Learning Rate

This section follows the development of a framework by Hartich et. al. [13] and subsequent work by Brittain et. al. [14]. The link between thermodynamics and information plays a central role in biochemical sensing. It is possible to argue that, given the limited supply of resources biological systems have, these resources should be optimally placed such that they can be efficiently used by the biological system to sense their environment.

To quantify the performance of a sensor, a quantity known as the learning rate has been proposed as a metric when the signal-sensor system can be described as a bipartite Markov chain [13].

The learning rate is defined as

\[ l_{\text{sys}}(t) := -\frac{\partial}{\partial t'} H [x_1(t)|x_2(t')]. \]  

(2.26)

Using (2.5), we can also rewrite this as

\[ l_{\text{sys}}(t) := -\frac{\partial}{\partial t'} I [x_1(t), x_2(t')]. \]  

(2.27)
Intuitively, this measures the rate at which a sensor, due to its own dynamics, reduces the uncertainty it has regarding the signal. The form of the learning rate in (2.27) is sometimes known in the literature as information flow.

In steady-state, we have the conservation law:

\[
\frac{d}{dt} H [x_1(t)|x_2(t)] := h_x - l_{sys} = 0 ,
\]

(2.28)

where

\[
h_x := \frac{\partial}{\partial t} H [x_1(t')|x_2(t)]
\]

(2.29)

is the rate of reduction of the signal’s Shannon entropy due to its coupling with the sensor [15]. In steady-state, \( H(x_2(t + \Delta t)) = H(x_2(t)) \), so we can write the learning rate in the form

\[
l_{sys} = h_x = \frac{\partial}{\partial t} I_{nos}(t) .
\]

(2.30)

Alternatively, in steady-state, an equivalent description of this learning rate is given by

\[
l_{sys} = \int \int d x_1 d x_2 J_{ss}^2(x_1, x_2) \frac{\partial}{\partial x_2} \ln \left( \frac{\rho_{ss}(x_1, x_2)}{\rho_{ss}(x_2)} \right) ,
\]

(2.31)

where \( J_{ss}^2(x_1, x_2) \) is the steady-state flux of the sensor and \( \rho_{ss}(x_1, x_2) \) is the steady-state joint probability distribution of the sensor and signal. These quantities are discussed further in Sec. 3.4.
Chapter 3

General Model System

3.1 Goals of the Model

Inspired by the mechanochemical machine $F_0F_1$-ATP synthase, we propose a model designed to be a minimal and easily generalized model of a rotary machine with coupled components.

The goal of this model is to explore the tradeoffs that are faced by stochastic machines. In particular, we aim to understand how the strength of coupling between the subsystems affects the optimization of these stochastic motors. Moreover, we seek to characterize the energy transduction through the entire system, as well as to relate the efficiency of such energy flows and dissipation to the information flow through the system. We do this by applying existing information-thermodynamic frameworks to this model to observe the relationship between thermodynamic and information-theoretic quantities in this novel case.

As we wanted a general model, we have attempted to minimize the inclusion of any information that is entirely specific to the $F_0F_1$ machine. However, guided by the properties of $F_0F_1$-ATP synthase, in creating this model the following considerations were made:

**Two coupled subsystems**

The model we present here comprises a system composed of two energetically coupled subsystems. Each of the subsystems can be represented as a single degree of freedom $x_i$.

**Low Reynolds Number regime**

Due to their size, the Reynolds number of most molecular machines are generally very small, as calculated in Section 1.1.2. Therefore, we will consider this regime as it is the one particularly pertinent to the systems that we are interested in studying. Thus we assume that the system we consider obeys overdamped dynamics.
Variable strength of coupling

Generally in modelling coupled molecular motors, a simplifying assumption is invoked that there is rigid (perfect) coupling between the two subsystems is usually made. In this work we seek to relax this assumption to be able to explore the effect of a non-rigid coupling between the subsystems on the system’s performance.

Number of Minima

We assume that the subsystem has $n$ energetically preferred minima, and we may choose to explore how the variation of this $n$ impacts system performance.

3.2 System Definitions

The energy landscape (hereafter simply potential) captures the properties of the considerations discussed above. The total potential is composed of three primary contributions: the intrinsic potentials of the two subsystems as well as the coupling between them. The intrinsic potential possesses an $n$-fold periodic structure and so has the form:

$$V_i^{\text{internal}}(E_{i-1}, x_i, n) = \frac{E_{i-1}}{2} [1 - \cos(nx_i)] . \quad (3.1)$$

The coupling potential is designed so as to favour the minimization of the deviations between the coordinates $x_1$ and $x_2$:

$$V_{\text{couple}}(E_{\text{couple}}, x_1, x_2) = \frac{E_{\text{couple}}}{2} [1 - \cos(x_1 - x_2)] . \quad (3.2)$$

The exact form of the model potential (Fig. 3.1) is then given by

$$V_{\text{tot}}(E_0, x_1, E_1, x_2, E_{\text{couple}}, n) = V_1^{\text{internal}}(E_1, x_1, n) + V_{\text{couple}}(E_{\text{couple}}, x_1, x_2) + V_2^{\text{internal}}(E_2, x_2, n)$$

$$= \frac{1}{2} \{ E_0(1 - \cos[nx_1]) + E_{\text{couple}}(1 - \cos[x_1 - x_2]) + E_1(1 - \cos[nx_2]) \} . \quad (3.3)$$

The energies $\beta E_{i-1}$ sets the height of the energy barriers between the metastable states of a given subunit $i$. The energy $\beta E_{\text{couple}}$ sets the strength of the inter-subunit coupling. For brevity, we henceforth suppress the dependency of the potentials on these energies $E_{i-1}$ and the number of minima $n$.

3.3 System Dynamics

The system dynamics we model using Langevin dynamics with the general form:

$$d\mathbf{X}_t = \mu(\mathbf{X}_t, t) \, dt + \sigma(\mathbf{X}_t, t) \, d\mathbf{W}_t , \quad (3.4)$$
with drift vector $\mu(X_t, t)$ and diffusion coefficient $D(X_t, t) = \sigma^2/2$. This Langevin equation is described by a corresponding Fokker-Planck equation that has the form

$$
\frac{\partial}{\partial t} P(x, t) = \left[ -\sum_{i=1}^{N} \frac{\partial}{\partial x_i} \mu_i(x, t) + \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{\partial^2}{\partial x_i \partial x_j} D_{ij}(x, t) \right] P(x, t), \quad (3.5)
$$

with diffusion tensor $D = \frac{1}{2} \sigma \sigma^T$.

The Langevin equation for each subsystem is given by

$$
\dot{v}_1 = -\gamma_1 v_1 - \frac{1}{m_1} \frac{\partial V_{tot}(x_1, x_2)}{\partial x_1} + \frac{\psi_1}{m_1} + \sqrt{\frac{2\gamma_1 k_B T}{m_1}} \Gamma_1(t), \quad (3.6a)
$$

$$
\dot{v}_2 = -\gamma_2 v_2 - \frac{1}{m_2} \frac{\partial V_{tot}(x_1, x_2)}{\partial x_2} + \frac{\psi_2}{m_2} + \sqrt{\frac{2\gamma_2 k_B T}{m_2}} \Gamma_2(t), \quad (3.6b)
$$
where the total potential is given by:

\[ V_{\text{tot}}(x_1, x_2) = \frac{1}{2} \left\{ E_0 (1 - \cos nx_1) + E_{\text{couple}} (1 - \cos[x_1 - x_2]) + E_1 (1 - \cos nx_2) \right\}, \]  

(3.7)

\( \psi_i \) denotes the effect that an external gradient \( i \) imposes on sub-system \( i \), \( n \) is the number of minima of the potential, and stochastic Langevin forces \( \Gamma_i(t) \) satisfy the relation

\[ \langle \Gamma_\nu(t) \Gamma_\mu(t') \rangle = \frac{2 \gamma_\nu k_B T m_\nu}{m_\mu} \delta_\nu\mu \delta(t - t'). \]  

(3.8)

Taking the overdamped limit \( \gamma t \gg 1 \) (Sec. 1.1.2) and using \( v = \dot{x} \), the Langevin equations simplify to (in matrix-vector form):

\[
\begin{bmatrix}
\begin{pmatrix} x_1 \\ x_2 \end{pmatrix}
\end{bmatrix}
\begin{pmatrix} dx_1 \\ dx_2 \end{pmatrix} =
- \begin{bmatrix}
\begin{pmatrix} \gamma_1 m_1 \\ \gamma_2 m_2 \end{pmatrix}
\end{bmatrix}
\begin{bmatrix}
\begin{pmatrix} \frac{\partial V_{\text{tot}}(x_1, x_2)}{\partial x_1} - \psi_1 \\ \frac{\partial V_{\text{tot}}(x_1, x_2)}{\partial x_2} - \psi_2 \end{pmatrix}
\end{bmatrix}
\end{bmatrix}
\begin{pmatrix} dt \\ dt \end{pmatrix}
+ \begin{bmatrix}
\begin{pmatrix} \sqrt{\frac{2 \gamma_1 k_B T}{m_1 \gamma_1 m_1}} \\ 0 \end{pmatrix}
\begin{pmatrix} \sqrt{\frac{2 \gamma_2 k_B T}{m_2 \gamma_2 m_2}} \end{pmatrix}
\end{bmatrix}
\begin{bmatrix}
\begin{pmatrix} \Gamma_1(t) \\ \Gamma_2(t) \end{pmatrix}
\end{bmatrix}
\begin{pmatrix} dt \\ dt \end{pmatrix}.
\]  

(3.9)

Using (3.4), we identify

\[
\mu_i = \frac{1}{\gamma_i m_i} \frac{\partial V_{\text{tot}}}{\partial x_i},
\]

(3.10a)

\[
D_{ij} = \frac{k_B T}{\gamma_i m_i} \delta_{ij},
\]

(3.10b)

where \( \delta_{ij} \) denotes the Kronecker delta. Hence, the Fokker-Planck equation\(^1\) is given by

\[
\frac{\partial}{\partial t} P(x, t) = \sum_{i=1}^{2} \left[ \frac{\partial}{\partial x_i} (\beta D f_i(x)) + D \frac{\partial^2}{\partial x_i^2} \right] P(x, t),
\]

(3.11)

where \( x = [x_1, x_2]^T \), \( \beta = (k_B T)^{-1} \), \( \beta D_i = (\gamma_i m_i)^{-1} = \beta D \forall \ i \) and the net driving force \( f_i(x) = \frac{\partial V_{\text{tot}}(x)}{\partial x_i} - \psi_i \).

### 3.3.1 Flux and the continuity equation

Since the Fokker-Planck equation evolves a probability distribution forward in time, this necessitates a continuity equation for the probability density so as to conserve probability:

\[
\frac{\partial}{\partial t} P(x, t) = -\nabla \cdot \mathbf{J}(x, t),
\]

(3.12)

\(^1\) In the limit of \( \gamma t \gg 1 \) this is also known as the Smoluchowski equation.
where $\mathbf{J}(\mathbf{x}, t)$ is the probability flux. Comparing (3.12) to (3.11) we can directly identify the probability flux as

$$J_i(\mathbf{x}, t) = -\left[\beta D f_i(\mathbf{x}) + D \frac{\partial}{\partial x_i}\right] P(\mathbf{x}, t). \quad (3.13)$$

### 3.4 Steady state

Due to the influence of the chemical baths, the system is driven out of equilibrium, and thus the steady-state distribution is, in general, not adequately captured by the Gibbs-Boltzmann distribution,

$$\pi(\mathbf{x}) = \frac{1}{Z} \exp(-\beta V_{\text{tot}}(\mathbf{x})). \quad (3.14)$$

However, there still exists a distribution $P^{ss}(\mathbf{x})$ that satisfies [16]

$$J^{ss}_i(\mathbf{x}) \equiv \text{const.} = -\left[\beta D f_i(\mathbf{x}) + D \frac{\partial}{\partial x_i}\right] P^{ss}(\mathbf{x}). \quad (3.15)$$

As any transient behaviours of the system probability distribution that occur before the system reaches steady-state is of little interest in the long-time limit, we evolve the system until this balance condition is met and perform all our subsequent calculations using this steady-state probability $P^{ss}(\mathbf{x})$.

To quantify the net probability that is circulating in a given sub-system at steady-state we integrate over the flux in the following way:

$${\mathcal{J}}^{\text{int}}_i := \frac{1}{||\mathbf{X}_i||} \int_{\mathbf{X}_i, \mathbf{X}_i'} d\mathbf{x}_i d\mathbf{x}_i' J^{ss}_i(\mathbf{x}). \quad (3.16)$$
Chapter 4

Methods

The following methods closely follow the work of [17]. The Fokker-Planck equation (3.11) is a partial differential equation (PDE) that captures the evolution of a probability distribution on a continuous energy landscape. Due to the non-linear nature of the potential as well as the non-equilibrium forcings that are introduced into the equation, analytic approximations, much less exact solutions, are intractable. As such, we turn to numerical methods to evolve the system. To solve a parabolic equation like the Fokker-Planck equation, two methods are generally employed: finite-difference methods and spectral methods. While spectral methods are ideal for high spatial resolution in multiple dimensions, finite-difference methods are conceptually clearer and more straightforward to implement. Here we concluded that for our system, the acceptable computational cost of explicit methods with sufficient resolution did not necessitate using a more advanced method beyond finite differences.

4.1 Numerical scheme

We choose the Forward-Time Central-Space (FTCS) algorithm in order to evolve the Fokker-Planck equation [18]. The FTCS algorithm is an explicit method to solve the PDE. Explicit methods involve the calculation of the future state of the system using the current state of the system. This is in contrast to implicit methods which solve an algebraic equations for the current state and the future state given the imposed boundary conditions and a guess of the solution at some time point [19]. In order to implement numerically, the partial derivatives of (3.11) must be replaced by discrete approximations. The FTCS algorithm solves the time component of the PDE using a Forward-Euler scheme giving a solution of temporal order accuracy $O(\Delta t)$. To solve the spatial component of the PDE this algorithm uses a Central Difference scheme giving a solution of spatial order accuracy $O(\Delta x^2)$. Specifically, the approximation we make in this simulation is given by [18]:

$$\frac{\partial}{\partial t} P(x, t) \approx \frac{P(x, t + \Delta t) - P(x, t)}{\Delta t},$$

(4.1a)
\[
\frac{\partial}{\partial x_i} [f_i(x)P(x,t)] \approx \frac{f_i(x_i + \Delta x, x_{i'})P(x_i + \Delta x, x_{i'}, t) - f_i(x_i - \Delta x, x_{i'})P(x_i - \Delta x, x_{i'}, t)}{2\Delta x},
\]

\[
\frac{\partial^2}{\partial x_i^2} P(x,t) \approx \frac{P(x_i + \Delta x, x_{i'}) - 2P(x_i, x_{i'}) + P(x_i - \Delta x, x_{i'})}{2\Delta x},
\]

where \(i\) denotes the variable the derivative is being taken with respect to, and \(i'\) is the other variable held constant. The complete probability update is given by:

\[
P(x,t + \Delta t) = P(x,t) + \Delta t \left[ \beta D f_1(x_1 + \Delta x, x_2)P(x_1 + \Delta x, x_2, t) - f_1(x_1 - \Delta x, x_2)P(x_1 - \Delta x, x_2, t) \right] \left( \frac{\Delta x}{2} \right) + \Delta t \left[ D P(x_1 + \Delta x, x_2, t) - 2P(x_1, x_2, t) + P(x_1 - \Delta x, x_2, t) \right] \left( \frac{\Delta x}{2} \right) + \Delta t \left[ \beta D f_2(x_1, x_2 + \Delta x)P(x_1, x_2 + \Delta x, t) - f_2(x_1, x_2 - \Delta x)P(x_1, x_2 - \Delta x, t) \right] \left( \frac{\Delta x}{2} \right) + \Delta t \left[ D P(x_1, x_2 + \Delta x, t) - 2P(x_1, x_2, t) + P(x_1, x_2 - \Delta x, t) \right] \left( \frac{\Delta x}{2} \right).
\]

We impose periodic boundary conditions by setting \(P(0) = P(2\pi)\). For stability and uniformity across various energy parameters, we use a timestep discretization of \(\Delta t = 1 \times 10^{-3}\), and spatial discretization of \(\Delta x = 2\pi/360\).

**4.1.1 Calculating flux and power**

The flux given in (3.13) must also be discretized. Again using central difference method for the derivatives we have

\[
J^\text{SS}_i(x) \approx D \left[ -\beta f_i(x)P^\text{ss}(x) - \frac{P^\text{ss}(x_i + \Delta x, x_{i'}) - P^\text{ss}(x_i + \Delta x, x_{i'})}{2\Delta x} \right].
\]

Multiplying by the relevant force \(\psi_i\) converts the flux into the power:

\[
P_i^\text{int} = J_i^\text{int}\psi_i.
\]

**4.1.2 Calculating efficiency and dissipation**

We quantify the efficiency of a stochastic machine as its ability to transduce energy in a directed fashion. That is, the efficiency \(\eta\) measures the ratio of the energy output to the ATP gradient, divided by the energy input into the machine through the influence of the \(H^+\) gradient:

\[
\eta = -\frac{P^\text{out}}{P^\text{int}}.
\]
Intuitively, this quantity is positive when energy is successfully transduced from one gradient affecting the motor to another. Conversely, \( \eta \leq 0 \) if the subsystems each transduce energy from their driving gradients to expelled heat. Given this, we define the *incompetence* \( \Omega \) of this machine as

\[
\Omega := 1 - \eta ,
\]  

where \( \Omega < 1 \) for successful energy transduction and \( \Omega \geq 1 \) for the contrary.

### 4.1.3 Calculating the steady-state distribution

The criterion for the convergence to the steady-state distribution \( P^{ss}(x) \) is given by the total variation distance between the distribution \( P(x, t) \) at time \( t \) and the distribution \( P(x, t+1) \) at time \( t+1 \):

\[
\frac{1}{2} \sum_{m=1}^{M} \sum_{n=1}^{N} |P(x_{1,m}, x_{2,n}, t + 1) - P(x_{1,m}, x_{2,n}, t)| < 1 \times 10^{-16} ,
\]  

where \( M \) and \( N \) denotes the number of discrete values that \( x_1 \) and \( x_2 \) take on, respectively. Intuitively, this criterion checks when the distribution stops changing, despite having been propagated forward in time by one simulation time unit using (4.2).
Chapter 5

Results

Chapter 3 proposed a model for a molecular machine comprised of two coupled cyclic sub-systems and developed this model in general terms so as to allow for different applications. In order to facilitate the discussion in this section, we examine specifically the case when aspects of the proposed model are meant to imitate the behaviours of F₀F₁-ATP synthase. As such we associate the variable $x_1$ to the angular orientation of the F₀ component, whereas $x_2$ we associate with the angular orientation of the F₁ component of the machine. Furthermore, the gradients denoted by $\beta \psi_1$ and $\beta \psi_2$ are hereafter associated with the driving forces imposed by the $\text{H}^+$ and ATP chemical baths, respectively. Throughout, results are presented for intrinsic system barriers $\beta E_0 = \beta E_1 = 4$ and $n = 3$ minima. Fig. 5.1 presents a schematic.

![Figure 5.1: Schematic of the system being simulated. The degrees of freedom of the system are simulated as two particles diffusing in an external potential. The system exchanges energy with a heat bath. Weights denote that work may be done on, or extracted from, the system.](image)

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5.1 Probability Distributions

5.1.1 Equilibrium

Equilibrium dynamics is realized by evolving the system without the effect of the chemical baths (i.e., $\psi_i = 0 \ \forall \ i$). In this case, as there is no forcing that drives the system out of equilibrium, hence the steady-state probability distribution satisfies the Gibbs-Boltzmann distribution (3.14). We propagate the Fokker-Planck equation forward in time until the condition (4.7) is satisfied, producing the probability distributions illustrated for various coupling strengths $\beta E_{\text{couple}}$ in Fig. 5.2. Comparing with Fig. 3.1, the calculated equilibrium probability distribution is peaked where the energy is the lowest, as expected from (3.14).

![Figure 5.2: The equilibrium probability distributions $\pi(x)$ of the system without influence from the chemical baths ($\psi_i = 0 \ \forall \ i$). Heatmap denotes the probability density, with lighter colors corresponding to higher probability. System barrier heights are $\beta E_0 = \beta E_1 = 4$.](image)

5.1.2 Steady state

Introducing the effect of a separate constant forcing on each of the subsystems, we orient the driving forces in opposite directions, thereby modeling the effect of opposing driving forces imposed by the $\text{H}^+$ gradient and the ATP-ADP chemical potential difference on $\text{F}_0\text{F}_1$-ATP synthase enzyme as initially discussed in the Introduction (Sec. 1.1.1). Figure 5.3
shows that the addition of these gradients displaces the distribution to favour alternate angles compared to those that are preferred at equilibrium (Fig. 5.2). In particular, as the driving forces are increased, angles that were once inaccessible become readily accessible. Intuitively, this can be understood as the driving forces provide necessary energetic input to overcome the tendency of the coupling to enforce the subsystems adopting the same angular orientations. As such, the system explores a much wider space than without such energetic impetus (compare top left-most plot and bottom right-most plot in Fig. 5.3). As the coupling strength increases, the driving force required to counteract this coupling also increases.

5.1.3 Distance from equilibrium

We use the relative entropy (2.7) to quantify the effect a given combination of driving forces has on the equilibrium distribution. Figure 5.4 shows this relative entropy as a function of various energetic parameters of the system, including the effects of the two driving forces $\beta \psi_1$ and $\beta \psi_2$, as well as the coupling $E_{\text{couple}}$. The system is driven furthest from equilibrium when the coupling is only a little stronger than the intrinsic system barriers. When the coupling is too weak, or similarly when the coupling is too strong, it evidently causes the system to be closer to equilibrium than it otherwise could be.

5.2 Flux

The net flux (hereafter simply flux) is another quantitative measure of the degree to which a system responds to an external perturbation. Here we define positive flux for $F_o$ as being in the direction of rotation that is imposed on this subsystem by the flow of $\text{H}^+$ ions from the intermembrane space into the matrix of the mitochondria. Similarly, we define positive flux for $F_1$ as being in the direction associated with the synthesis of ATP. A flux of zero indicates that the system does not respond to external perturbations. Figures 5.5 and 5.6 show the response of each of the $F_o$ and $F_1$ subunits, respectively.

For low coupling strengths, a given subsystem is predominantly affected by only those external perturbations that directly act on it. For example, at coupling strengths $\beta E_{\text{couple}} \leq 4$ the flux of subsystem 1 more or less responds only to changes in $\beta \psi_1$ and is essentially insensitive to changes in $\beta \psi_2$. For large coupling, the two opposing driving forces compete. For $\beta E_{\text{couple}} \geq 4$, the effect of the coupling is to lower the overall flux, since one subsystem substantively affects the dynamics of the other subsystem. With very large coupling, flux remains close to zero unless one driving force heavily dominates the other.

Thus, to maximize the flux of a certain subsystem, an effective strategy would be to limit the inter-subsystem coupling. To maximize the overall flux of the joint subsystem, a coupling strength that is only slightly larger than the system barriers should be chosen: choosing too large a coupling strength renders each subsystem dependent on the dynamics
Figure 5.3: The steady-state distribution $\rho^{SS}(x)$ as a function of the angles $x_1$ and $x_2$. H$^+$ driving strength varies across columns of subplots, and ATP driving strength varies across rows. Opposing signs of driving forces denote that the driving forces push the system in different directions. System energy barriers are $\beta_{E_0} = \beta_{E_1} = 4$, and coupling strength is $\beta_{E_{\text{couple}}} = 16$.

of the other. Should these subsystems experience equal-strength driving forces that push them in opposite directions, then the system as a whole experiences no net motion in this regime.
Figure 5.4: The relative entropy between the steady-state distribution and the equilibrium distribution. Within a given subplot the $x$ and $y$-axes denote the value of the strength of the $\text{H}^+$ and ATP driving forces, respectively. Each subplot corresponds to a different value of the coupling strength $\beta E_{\text{couple}}$.

5.3 Thermodynamics at steady state

5.3.1 Efficiency

To calculate the power generated by a subsystem, the flux of that subsystem as well as the driving force acting upon it needs to be known (4.4). The power generated by each subsystem gives the information necessary to calculate the efficiency of the energy transduction.

Figure 5.7 illustrates the efficiency for various driving strengths. For low coupling strength $E_{\text{couple}}$, the efficiency is negative, $\eta \leq 0$. In this regime, as defined in (4.6), all of the energy introduced into the system is dissipated into the environment from unsuccessful transduction. In the large coupling limit, the efficiency saturates to a value equal to the ratio,

$$\lim_{E_{\text{couple}} \to \infty} \eta = \frac{\psi_{\text{out}}}{\psi_{\text{in}}} ,$$

where, akin to (4.5), $\psi_{\text{out}}$ denotes the weaker driving force.
Figure 5.5: The integrated steady-state flux $J_1^{\text{int}}$ of the $F_o$ subunit. Similar presentation of data as in Fig. 5.4.

Figure 5.6: The integrated steady-state flux $J_2^{\text{int}}$ of the $F_1$ subunit. Similar presentation of data as in Fig. 5.4.
Therefore, rigid coupling produces higher efficiency. Lower coupling strength only reduces the efficiency. The coupling evidently must greatly exceed the intrinsic system barriers ($E_{\text{couple}} \gg E_0 = E_1$) in order to produce successful energy transduction.

![Diagram showing the efficiency $\eta$ of the energy transduction between $F_\text{O}$ and $F_1$ subsystems.](image)

Figure 5.7: The efficiency $\eta$ of the energy transduction between $F_\text{O}$ and $F_1$ subsystems. Black boxes indicate equal and opposing driving forces, for which the flux is zero and hence the efficiency is not well defined. Similar presentation of data as in Fig. 5.4.

### 5.4 Tradeoffs

Natural selection drives biological systems to improve themselves for the environment in which they find themselves. We might hypothesize that this environment specifies not only which aspects of the system’s function require optimization, but also the constraints that require consideration during the optimization procedure.

For example, $F_\text{O}F_1$-ATP synthase needs to produce many ATP per second, thus requiring a large flux of the $F_1$ component of the motor. Since the energy that powers the chemical reactions at the $F_1$ component must be transduced from the energy that is stored in the $H^+$ gradient, which only directly affects the $F_\text{O}$ component, then selection should favor higher efficiency. For the efficiency to be large, the coupling between the two subsystems should be as large as possible (see Fig. 5.7); however, this need for strong coupling must be balanced with the consideration that too strong coupling would result in the system being immobilized...
and being unable to maintain its far-from-equilibrium steady-state distance (due to the
effect of the opposing driving forces). Thus, one might expect machine performance to
face this four-way tradeoff between flux, efficiency, strength of coupling, and distance from
equilibrium.

5.5 Information-theoretic quantities

We now examine the links between thermodynamics and information theory within our
model system. In order to facilitate this analysis we take the following viewpoint: the F₁ sub-
unit responds to an external signal from the F₀ subunit, thus we can think of F₀ as a signal
and F₁ as a sensor.

5.5.1 Nostalgia

Having the steady-state probability distribution of the system allows for relatively straight-
forward calculation of some information-theoretic quantities. Fig. 5.8 presents the nostalgia
for different combinations of coupling strength and gradient influences. It is immediately
striking that some combination of the driving forces produce negative nostalgia, whereas in
Still et al. [11] nostalgia was positive definite. Here, future signal states are not conditionally
independent of the current sensor state,

\[ p(x_1[t + \Delta t], x_2(t)|x_1(t)) \neq p[x_1(t + \Delta t)|x_1(t)] p[x_2(t)|x_1(t)] \text{ ,} \tag{5.2} \]

or equivalently, it is not the case that

\[ x_2(t) \rightarrow x_1(t) \rightarrow x_1(t + \Delta t) \]

forms a Markov Chain, since the state of the sensor \( x_2(t) \) directly influences the future
signal state \( x_1(t + \Delta t) \), due to the coupling term \( (3.2) \) in the total system potential \( (3.7) \).
As such, the data-processing inequality need not hold, and nostalgia can be negative. Thus,
in a context such as this where signal and sensor are coupled symmetrically\(^1\), the unwar-
ranted retention of past information (i.e. the nostalgia) becomes decoupled from energetic
inefficiency.

5.5.2 Learning Rate

Fig. 5.9 shows the steady-state learning rate, for different combinations of coupling and
driving strengths. For no- to low-coupling between F₁ (the sensor) and F₀ (the signal), as

\(^1\) As opposed to asymmetric coupling where one affects the other but not the other way around, such
as when the environment affects the system dynamics, but the environment evolves independently of the
system.
we intuitively expect, the sensor cannot learn about the signal at all and hence the learning rate is zero, regardless of the influence of the gradients on the sensor or signal source. If the sensor and signal are strongly coupled, then the learning rate is maximized. It stands to reason that, if the dynamics of the signal greatly affect the sensor’s dynamics, the sensor cannot help but learn about the signal. For intermediate coupling strengths, we see that there are combinations of driving strengths in which the sensor learns about the signal; however, if the external driving force imposed upon it overwhelms the dynamics of the sensor, then the sensor becomes more correlated with the external driving than the signal. As the external driving is oriented oppositely to that of the direction of the signal, a negative learning rate results.

5.6 Information and Thermodynamics

While previous works [11–14] illustrated elegant connections between information-theoretic quantities and thermodynamic bounds, we find that these connections are severed here. This is primarily due to the requirement of the information-theoretic quantities examined here, that the coupling between the sensor and the signal be asymmetric: the signal may affect the dynamics of the sensor but the signal evolves on its own independent dynamics, regardless
of the given state of the sensor. Therefore, we find that naively applying the frameworks established in previous work to this model of signal and sensor does not preserve the desired relations between information and efficiency. A new framework, which incorporates a symmetric coupling of sensor and signal would be required to link thermodynamics and information theory in this context.

### 5.7 Parameter ranges: discussion and limitations

The parameters chosen and region of parameter space explored in this work was restricted by the following considerations:

1. Computational restrictions
2. Focus on regions with interesting and interpretable results
3. Biological relevance

As we are using an FTCS algorithm, the grid size over which we have to do a computation, and by extension the amount of time required to perform this computation, increases as the square of the number of grid points. In order to explore the larger energetic parameters,
a finer grid would be required so as to ensure the stability of the algorithm, however, this becomes untenable at energies above $250 k_B T$. While this energy regime is much higher than what we would expect for biological system, coupling strengths of this magnitude enforce $x_2 \approx x_1$, imposing that the angular orientations of both subsystems are equal at all times, and thus the system reduces from having two degrees of freedom to one, making this system in this limit tractable for analytical study.

The computational time required to relax an initial uniform distribution to the steady-state distribution $\rho^{SS}(x)$, varies depending on the values chosen for the energetic parameters of the system including $\beta E_i$, $\beta E_{\text{couple}}$, and $\beta \psi_i$. Generally the larger values of $\beta E_i$ and $\beta E_{\text{couple}}$ the slower the convergence to steady state. For a fixed set of $\beta E_i$ and $\beta E_{\text{couple}}$, a larger $\beta \psi_i$ for each of the subsystems $i$ increases the rate of convergence. Intuitively, this can be explained in that the larger the driving force $\beta \psi_i$ the more energy is introduced into the system and hence the system is able to explore areas of phase space that would otherwise take a very long time to reach due to that area being associated with high energetic costs. To be consistent, we require the usage of the same convergence criteria (4.7) in the slow convergence cases as fast convergence cases. The cases of slow convergence (large values of $\beta E_i$ and $\beta E_{\text{couple}}$) would therefore would take much too long and as such was not regarded as a priority over other analysis. To accurately reflect $F_0 F_1$-ATP synthase, further work could be performed implementing an algorithm that is unconditionally stable [19] so as to facilitate the use of larger time steps and hence be able to satisfy (4.7) for even the largest system barrier heights.
Chapter 6

Conclusions

This research explored the tradeoffs faced by molecular machines that are comprised of energetically coupled components and explored links proposed between information theory and thermodynamics. To this end, a minimal model was developed, using the $\text{F}_o\text{F}_1$-ATP synthase molecular machine as initial inspiration. This model was designed with the goal of satisfying both generality and interpretability. Specifically, we desired a model that could generate results that were easily mappable to biological molecular machines, in this case $\text{F}_o\text{F}_1$-ATP synthase, yet can also easily generalize to any molecular machine, comprised of two subsystems, of which the full system can be described as having periodic operation. Utilizing standard computational physics techniques, we simulated the dynamics of this model using a Fokker-Planck equation and evolved the system to a steady state. At steady state, we computed the distance from equilibrium, flux, efficiency, and information-theoretic quantities as a function of different combinations of perturbations on the subsystems, as well as the coupling between them.

Our results strongly suggest that there are significant tradeoffs between distance from equilibrium, flux, efficiency, and coupling strength. Specifically, we observe that naively optimizing only one of these quantities, without regards for the others, may lead to overall detrimental outcomes for biological systems that are described adequately by our model. We see in our model that optimizing for efficiency alone enforces that the subsystems must be rigidly coupled; however, we see that by doing so it leaves the overall system closer to equilibrium, thus reducing the nonequilibrium free energy that is available to the system to do work. Moreover, within this context, we find that the traditional frameworks for understanding the connections between thermodynamics and information theory are not, at least naively, applicable. This prompts a question of what modifications are required to the existing frameworks so as to make them adequate to explain the behaviours of the model we have proposed here.
6.1 Future Work

The development of this model opens a swath of directions that one may choose to pursue. The results presented within this work have assumed that the machine has components with three preferred angles. What then would result for different numbers of preferred angles, or for a phase offset between the potentials of the two components of the motor. Does the tradeoff change between the quantities discussed above?

Similarly, what is the correct way to apply the discussed information-thermodynamics framework to this model such that the elegant relationships found between them are preserved? Perhaps extending the number of coupled subsystems to three from two, and introducing asymmetric coupling between the newly introduced subsystem and the current subsystems would allow application of the existing frameworks to this expanded system.
Bibliography


Appendix A

Derivations

A.1 Derivation of Chain Rule for Entropies

\[
H(X_1, X_2) = - \int_{x_1} \int_{x_2} dx_1 dx_2 \ p(x_1, x_2) \ln p(x_1, x_2) \quad (A.1a)
\]

\[
= - \int_{x_1} \int_{x_2} dx_1 dx_2 \ p(x_1, x_2) \ln [p(x_2|x_1)p(x_1)] \quad (A.1b)
\]

\[
= - \int_{x_1} \int_{x_2} dx_1 dx_2 \ p(x_1, x_2) \left[ \ln p(x_2|x_1) + \ln p(x_1) \right] \quad (A.1c)
\]

\[
= \left\{- \int_{x_1} \int_{x_2} dx_1 dx_2 \ p(x_1, x_2) \ln p(x_2|x_1) \right\} + \left\{- \int_{x_1} \int_{x_2} dx_1 dx_2 \ p(x_1, x_2) \ln p(x_1) \right\} \quad (A.1d)
\]

\[
= H(X_2|X_1) + H(X_1) \quad (A.1e)
\]