DESIGN AND CONTROL OF DYNAMICAL SYSTEMS: A CLASSICAL TO QUANTUM PERSPECTIVE

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Mathieu Ouellet

To my parents, Josée Boudreault and Éric Ouellet.

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ABSTRACT

DESIGN AND CONTROL OF DYNAMICAL SYSTEMS: A CLASSICAL TO QUANTUM PERSPECTIVE

Mathieu Ouellet

Lee C. Bassett

The design and control of dynamical systems have long been core objectives of engineering. In this thesis, we tackle the complexities of design and control across paradigms ranging from Boolean models of genetic networks, to thermally driven stochastic systems, to quantum-mechanical systems. These disparate domains share common challenges, including the large dimensionality of the design space and the computational intractability of objective functions. For classical systems, we draw inspiration from optimization heuristics and genetic programming, leveraging the inherent symmetries within these problems. This approach led to the discovery of a novel symmetry in biological systems, which we term dynamical mirror symmetry, and the subsequent design of artificial mechanical structures that emulate the behavior of biological prions. Quantum systems introduce an additional layer of complexity: the exponential growth in the dimensionality of the Hilbert space, which makes classical simulations impractical. As a test platform, we develop control sequences tailored for nitrogen vacancy centers to achieve precise control. Our approach begins with the use of standardized quantum control sequences, demonstrating their capability to infer the parameters of a quantum Hamiltonian. We then develop a more general method inspired by diagrammatic path integrals, which enables full differentiability and supports perturbative expansions for optimization and control.

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CHAPTER 1

INTRODUCTION

1.1. Dynamical systems

Time keeps moving forward, bringing change everywhere. Planets orbit, weather changes, molecules bounce around, and complex chemical reactions break bonds. On the quantum level, electrons, quarks, and gluons do their thing. Statistical mechanics tells us this forward march—known as the 'arrow of time'—is one-way only. So, everything ages and evolves along the way.

It is, therefore, unsurprising that science has tried to explain the diverse temporal behaviors observed in nature. This led to the creation of a broad field known as dynamical systems that focuses on the temporal evolution of systems. Examples of such systems range from simple projectiles traveling through a vacuum to populations of rabbits and foxes on a secluded, thriving island. They also include complex social dynamics like those of the stock market.

Historically, the field of dynamical systems theory began with the early work of ancient astronomers like Hipparchus and Claudius Ptolemy and was later advanced by Johannes Kepler and Isaac Newton, all of whom sought to predict the positions of planets and stars. Inspired by the study of celestial bodies, Poincaré laid the foundational principles of dynamical systems theory, seeking to answer key questions about the behavior of complex systems. He introduced the study of qualitative properties of differential equations, bifurcation theory, and probabilistic concepts like ergodicity. Poincaré also pioneered phase space analysis and the study of limit cycles. Following Poincaré's foundational work, the field of dynamical systems evolved as non-linearly as the systems it studies through the early 20th century. The focus remained on understanding predictable, stable behaviors and refining mathematical tools, bringing ideas from topology, geometry, and differential equations. Researchers began to uncover systems that defied these traditional expectations, displaying irregular and unpredictable behaviors. This led to the emergence of chaos theory in the 1960s, marked by the recognition that deterministic systems could exhibit extreme sensitivity to initial conditions, unpredictability, and complex dynamics that traditional methods struggled to describe. These insights challenged existing paradigms, revealing that even simple systems could evolve in ways that were inherently difficult to predict.

The field continues to evolve today, driven by advances in computational, data-driven, and machinelearning approaches aimed at modeling complex and large-scale dynamical systems. The diversity of systems—from biological networks and climate models to economic systems and engineered processes—each with its unique characteristics and complexities, underscores the field's vast potential and ongoing challenges. This thesis will focus on a wide range of dynamic systems and goals. We will start by studying gene regulatory networks using discrete models, which capture the on-off states of genes and their interactions, providing insights into the underlying dynamics and patterns of gene expression. We will then study simple molecular structures in a thermal bath that mimics the behavior of biological prions, exploring how these structures undergo conformational changes and propagate misfolding through stochastic interactions. Finally, we will study quantum systems, with a particular focus on nitrogen-vacancy (NV) centers coupled to a ¹³C spin bath, examining their dynamics, coherence properties, and potential applications in quantum sensing and information processing.

To study a given system S, we define a state x(t) that evolves in function of time. The state contains all the information necessary to define the evolution of the systems. The state x would contain the positions and velocities in the projectile example. In the case of population dynamics, such as that of rabbits and foxes, the state could be sufficiently described by recording the numbers of each species for a given year and the preceding year. A potentially acceptable state for the stock market would be the order book for each stock, which shows how many stocks are sold at a given price and bought at a given price.

Mathematically, this leads to a state space X where $x \in X$ includes every possible system configu-

ration it can attain or be started with. The dimension of the state space X is determined by the number of variables required to describe the system's state. For instance, the projectile needs 12 real variables to describe its position and orientation with their velocities, making its state space twelve-dimensional $X \subset \mathbb{R}^{12}$. The state space often has a natural topology, typically assumed to be a smooth manifold when dealing with continuous dynamical systems. This thesis addresses various state spaces, most of which are smooth manifolds. An exception is found in Chapter 2, which examines a system on a discrete space.

In state space, a system's state is a point, and its whole trajectory can be visualized as a curve that describes how the state changes over time. This evolution is given by the transition map $\phi(t_1, t_0) : X \to X$ which take the state at time t_0 and evolve it to t_1 where $t_1 > t_0$ such that $x(t_1) = \phi(t_1, t_0, x_0)$. This map should be well-defined in a subset of the state space X. An important property of the transition map is the semi-group property that says that for $t_2 \ge t_1 \ge t_0$, we have

$$\phi(t_0, t_0, x_0) = x_0 \tag{1.1}$$

$$\phi(t_2, t_0, x_0) = \phi(t_2, t_1, \phi(t_1, t_0, x_0)) \tag{1.2}$$

This property implies that the system's evolution over the interval from t_0 to t_2 can be broken down into an evolution from time t_0 to t_1 , followed by the evolution from t_1 to t_2 . Generally, this is the only condition required for a transition map to be valid.

For each system, the map follows some dynamical equation; in the case of the projectile, this is Newtonian mechanics (we assume the projectile is way slower than light). The rabbits and foxes example follow the Lotka-Volterra equations, which model population dynamics. Those two systems are modeled as deterministic, meaning that two copies of those systems starting at the same position will follow the same trajectory. In this thesis, Chapter 2 will use deterministic evolution for biological systems. Chapter 4 and 5 also use a deterministic state evolution of quantum mechanical time evolution, which leads to random projective measurement. While this is believable for the projectile and perhaps a good first approximation for the island system, this is not true for the stock market. Although models are available, the system's evolution remains highly random and can only be partially captured by approaches that account for this inherent randomness. In our case, Chapter 3 will use such a model to consider the coupling of a deterministic system with a random energy source.

In all our modeling attempts, we will be faced with a multitude of problems. One is internal structural inaccuracies, where the model does not consider all the complexity of the real system. For example, asymmetry in the projectile shape leads to neglecting oscillating behaviors and, more importantly, air drag. In our case, we will always be forced to make strong assumptions and simplify our model. We will, for example, consider that gene networks can be modeled through discrete evolution under simple dynamics. While those assumptions will often limit the precision of our model's predictions, they simplify the study and allow us to focus on essential aspects. Another source is measurement noise and parameter uncertainty, where a parameter's exact value is unknown. Parameters, such as the average rate at which foxes catch rabbits, need to be estimated in any modeling endeavor. More often than not, those parameters are learned or fitted on measured data using the model properties. In Chapter 4 and 5, we will present different methodologies for the learning of quantum systems.

Finally, external structural inaccuracies also play an important role. Each model does not perfectly take into account all the dependencies outside it. In the dynamics of a predator-prey system, such as rabbits and foxes, external factors like the availability of vegetation significantly impact rabbit populations, which in turn affects the fox population. Similarly, for a projectile not in a vacuum, the surrounding air significantly influences its trajectory through variations in density and wind speed. For the stock market, the perfect model would take into account every agent in the system, their sentiment on the market, the state of the economic system they operate in, every other financial instrument, and every external factor, such as geopolitical events or the news. This is, of course, an impossible-to-build model. To tackle this problem, the map ϕ can be taken as probabilistic, where a probability density is given for each reachable state in X. Or the system can be isolated, and the external influences can be accounted for with enough precision. This issue will be a primary focus of Chapter 3, where our systems are immersed in an unknown, fluctuating environment that cannot be directly monitored. Consequently, we will represent this environment as a source of random fluctuations.

1.2. Design versus Control

In the initial phase of this study, we focus on defining the necessary state variables and identifying the evolution map $\phi(t_1, t_0)$. This thesis will explore a variety of systems, each characterized by distinct maps and state spaces (see Figure 1.1). In Chapter 2, we study Boolean networks, which represent well-isolated systems for which the states are binary vectors, and the map ϕ is a discontinuous map in time that follows boolean logic rules. Chapter 3 studies mechanical systems in a thermal bath interacting with their environment in a random manner and a continuous time evolution. In this case, the state is simply positions and velocities, and the map ϕ is given by Langevin equations, which we will study. Finally, Chapter 4 and 5 study the quantum spin degree of freedom in not-so-well-isolated interacting systems. As we will discuss in section 1.3, their state is given by the tensor product of each sub-system state, and the Schrödinger equation gives their evolution.

Once the dynamical system is established, we examine its behavior. Dynamical systems are rich in terms of behaviors. This analysis typically includes assessing how small perturbations or alterations in initial conditions affect the system, a process known as stability analysis [3]. Other exciting behaviors consist of attractors or sets of states toward which the system tends to evolve, regardless of the starting conditions [4]. Those states can be simple points where the system goes and stays fixed, called fixed points, or a limit cycle that the system reaches and then cyclically visits.



Figure 1.1: **Projects overview** All projects can be thought of along two axes: one axis spans from the design of systems to the control of existing systems, while the other ranges from studying the systems' intrinsic properties to exploiting these properties for practical use. Following a standard quadrant ordering, we have studied quantum dynamics to gain access to optimizers for control, controlled a quantum system to function as a sensor, designed mechanical systems that exploit prionic dynamical properties, and designed biological gene networks with specific properties to better understand their origins in nature.

Both Chapter 2 and 3 will be interested in such behaviors where the goal is to reach a stable point. We do so by designing the system to reach a specific goal. In the case of the Boolean networks of Chapter 2, the goal is to understand where the long limit cycle appears. To answer that, we study how different system elements interact with each other and relate them to the properties of the map ϕ . In the case of mechanical systems, our goal is to create mechanical systems with two fixed points such that under random interaction, they both stay in those states. However, we require that when those two types of fixed points collide, they both collapse to the same fixed point. This type of dynamic is akin to Prions, a protein that has two stable foldings and can propagate one of its foldings to neighboring proteins of the same kind.

While understanding what causes a system's specific dynamic to appear is of general interest, we often care about how we can influence a system to do what we want. In this case, energy is pumped or taken from the system in specific ways to change its behavior. This energy manipulation aims to maintain the system within desired parameters or to shift it to a more favorable state. Designing systems entails setting up initial conditions and configurations that inherently possess the desired dynamics. Conversely, controlling systems involves actively intervening in ongoing processes to steer the system towards specific outcomes, often in real-time.

For instance, in designing the Boolean networks mentioned earlier, the focus is on structuring the network so that it naturally exhibits long limit cycles without the need for external interference. On the other hand, controlling such a system would look quite different. It would involve adjusting the state of specific nodes, applying external constraints, or changing the rules based on observed behavior to induce or sustain a desired state. This dynamic and responsive approach to influencing the system underscores the primary distinction between design and control: one is about creation with foresight, and the other is about guidance through interaction.

To go back to our simple examples, a control system for the projectile could be some flaps that can be controlled to change the trajectory. On the other hand, designing the projectile's launcher to make it rotate is a design-based approach, where the gyroscopic effect is used to keep the projectile straight. In the case of population dynamics, we could hunt off one or both populations, decreasing their numbers, while a design strategy could be to make a part of the island inhospitable for the foxes. Generally, design involves shaping the systems to naturally lead to the desired effect, while control requires some sort of energy expenditure.

Control means adding an input u(t) to the system's evolution [5, 6]. This control input can be obtained in different ways. In feed-forward or open-loop control, u(t) is predetermined based on a model of the system, aiming to achieve the desired outcome by anticipating the system's response. In feedback or closed-loop control, u(t) is calculated in real time based on the difference between the desired and current states, continuously adjusting to minimize this error. Different approaches relax the rigidity of the control framework, like adaptive control, which modifies u(t) by adjusting the control parameters to handle uncertainties and changing conditions in the systems [7].

Under control, the transition map becomes $x(t_1) = \phi(t_1, t_0, x_0, u(\cdot))$ which now depends on the time-varying vector $u(\cdot)$. This introduces new conditions for the transition map. Notably, only the input applied before the observed time affects the system. For two input signals $u_1(\cdot)$ and $u_2(\cdot)$ such that $u_1(t) = u_2(t) \forall t \leq t_1$ we have that $\phi(t_1, t_0, x_0, u_1(\cdot)) = \phi(t_1, t_0, x_0, u_2(\cdot))$. This means the system is causal, relying solely on previous states and control actions before the observed time point. In other words, tomorrow's actions do not influence the system's state from yesterday.

Both Chapter 4 and 5 inscribe themselves in this control framework as seen in Figure 1.1. In the first case, we control the electronic spin of an NV center so that it acquires information about its surroundings. Then, its state can be read, which gives us information about its surroundings. To do so, we adapt a well-known control framework called dynamic decoupling sequences for sensing tasks. In Chapter 5, we break from this limiting framework and build a new framework that allows us to learn similar control sequences.

This framework is inspired by graph-theoretic ideas, which can represent various systems and their evolution, including the evolution of quantum systems [8], brain networks [9, 10, 11], protein interactions [12, 13], biological [14, 15] and social networks [16, 17, 18]. Here, we apply these concepts to quantum systems, demonstrating their potential to reveal insights into complex dynamics and control within this domain.

1.3. Classical versus Quantum

This thesis examines two main categories of systems: classical systems in the first two chapters and Quantum systems in the following two. This section explores the differences between those two types of systems. We compare the Lagrangian and Hamiltonian frameworks of classical mechanics with quantum mechanics, highlighting the distinctions. This chapter aims to provide a brief introduction.

1.3.1. Boolean dynamic

In the first chapter, we will treat the most straightforward dynamical system to understand but not necessarily the easiest to work with Boolean networks [19, 20]. For boolean networks, the states xcomprise n Boolean variables ($x \in \mathbb{Z}^n$) that can be either 1 (on) or 0 off). The system updates at a discrete time when each node uses its Boolean function (which can be the same for all nodes) and updates its state. This update can be done synchronously, where all the node states are updated simultaneously, or asynchronously, where a subset, potentially chosen randomly, is updated each time [21, 22].

Boolean networks are frequently used to model biological systems [23, 24, 25]. They provide a simple yet powerful framework to model the complex interaction between components like proteins and genes [26]. Detailed quantitative information about those components is hard to get in those systems. The binary approach allows us to capture the essential dynamic without having to fully study their exact quantitative influence on each other.

Each node Boolean function only uses a subset of the other nodes as input. For example, in a system

of 4 nodes, the synchronous update function of node 3 (ϕ_3) could take the form. $\phi_3(t+1, t, x_1, x_3) = x_1 \lor x_2$, meaning that the next state takes the value x_1 or x_2 , 1 if any of them is 1 or 0 otherwise. In this system case, ϕ is independent of the value of t since the system evolution is independent of time.

From ϕ_3 , we see that the update function only needs the values of two nodes to function, node 1 and itself. This allows us to represent an abstraction of the system as a directed graph that shows how the information propagates. In this simple case, node 1 would have an outgoing arrow pointing to node 3, and node 3 would have an ongoing arrow pointing to itself.

The state space of such networks is all the unique combination of on/off states for each of the n nodes denoted \mathbb{Z}^n . Contrary to our previous examples, this space is discrete and contains 2n possible states arranged in n dimensions. This space can be visualized as a directed graph (because of its discreteness), where each arrow represents the transition according to the network's logical rules. Because of the finite nature of space, any state evolves into an attractor. They can be described by their length, meaning the number of transitions before the state cycles back to its initial state in the attractor. Attractors of length one are fixed points where the system remains in a single state indefinitely. Attractors are of interest in biological systems because they represent stable cell states (for fixed points) or cyclic behaviors (lengths greater than 1).

Previous studies have studied the mean length of an attractor in random networks at the critical limit [27, 28, 29]. Those networks are made by selecting K nodes as input nodes for each node and randomizing a Boolean update function that uses those K nodes as input. This is done on all the n nodes of the network. At the critical limit, Boolean networks feature properties at the boundary of the frozen space where small perturbations at one node barely propagate and the chaotic phase where the same perturbations lead to exponential propagation [30]. Criticality is determined by K and the Boolean functions used.

This approach has shed light on the scaling behaviors of the attractor length when n tends to infinity [27, 28, 29, 31, 30]. In Chapter 2, we investigate a similar problem, but we will deal with the finite case with no fixed connection pattern (K is variable). This leads to the problem that the standard tool, namely mean field theory, cannot be used. Therefore, to study what leads to long cycling behaviors, we will turn toward designing networks with such long cycles and study their shared property. This will allow us to conclude the conditions needed in the interaction network's topology to generate long cycles.

1.3.2. From Newton to Langevin

For a classical system, one can use Newtonian formalism to study the evolution of a simple system. This applies to point-like particle systems with constant mass where the forces and accelerations are in a non-relativistic, inertial reference frame. In this case, the state x of the system is given by two vectors, the position $q \in \mathbf{R}^n$ and the velocities $\dot{q} \in \mathbf{R}^n$. In this framework, knowing $\dot{q}(t)$ from $t \in [t_0, t_1]$ and the initial positions $q(t_0)$ we have that $q(t_1) = \int_{t_0}^{t_1} \dot{q}(\tau) d\tau + q_0(t_0)$. Then we only need to find the evolution of $\dot{q}(t)$, which is given simply by the second law of motion $F = m\ddot{q}(t)$. The rotation degrees of freedom can be taken into account in a similar manner by equating the torque τ to the derivative of the angular momentum L such that $\tau = \frac{dL}{dt}$.

Newton's equations are deterministic; they do not capture the reality of microscopy systems. When noise and environmental interactions become significant while staying mostly random, as in molecular dynamics, a better framework, the Langevin framework, is needed. The Langevin framework introduces random forces to represent thermal fluctuations, giving a more accurate picture. Additionally, it includes dissipative forces, like friction, which Newton's framework misses, as it does not represent the exchange with the environment. We will give here a small introduction to this framework and then use it in Chapter 3 to create a mechanical structure analogous to biological prions.

A large particle, which we will call the Brownian particle, is immersed in a bath of much smaller

particles. For example, consider a small dust particle, approximately 200 µm in size, suspended in a steady body of air composed primarily of dinitrogen molecules. This represents a size difference of about six orders of magnitude. In this example, the Brownian particle is small enough to stay airborne and moves randomly due to collisions with much faster gas molecules.

The Brownian particle is still governed by $m\frac{dq}{dt} = F(t)$ where F here includes interaction with the small particle bath. If the dynamic of all those particles was simulated and their positions and velocities were known, this force would not be random. This is, however, quite unpractical, and an approximate form for F would be desirable. Considering only the effect of the bath, Fcan be approximated by two components. First, a friction force $(-\gamma \dot{q})$ prevents the particle from infinitely gaining energy from the surrounding medium. Secondly, a random force $(\xi(t))$ represents the random collision with the small particles of the bath. This led to the Langevin equations of motion for a Brownian particle:

$$\frac{dp}{dt} = F_{det}(t) - \gamma \dot{q} + \xi(t), \qquad (1.3)$$

where $F_{det}(t)$ represents the deterministic forces not due to the bath (gravity, for example).

The random forces $\xi(t)$ is a stochastic variable that needs a little bit of care in defining. For a massive particle at equilibrium, we expect from the equipartition of energy that

$$\langle q^2(t)\rangle = \frac{k_b T}{m},\tag{1.4}$$

where k_b is the Boltzmann constant and T the temperature and $\langle \ldots \rangle$ denote the average over the equilibrium distribution. On average, the force $\xi(t)$ should not break the symmetry of the system such that the average over the distribution of ξ is zero ($\langle \xi(t) \rangle = 0$). Furthermore, the impacts should be instantaneous and not correlated with each other, which can be enforced by specifying the second moment $\langle \xi(t_1)\xi(t_2) \rangle = g\delta(t_1 - t_2)$. This absence of correlation is explained by the difference in timescales between the bath's motion and the Brownian particle.

In chapter 3, we design small mechanical systems composed of springs, masses, and magnets. While the description here captures the essence of a rigorous approach, a detailed analysis is provided in chapter 3. These systems must be stable in two distinct conformations, represented by the states x_1 and x_2 . Stability, in this context, means that for a specific range of temperatures, the evolution of both states, $\phi(t_1, t_0, x_1 = H)$ and $\phi(t_1, t_0, x_2 = P)$, remain close to their initial states. The two states are denoted as the healthy state, H, and the prionic state, P. Their names are derived from the specific dynamics that will be defined and enforced in the following paragraph. We express this stability condition as

$$d(\phi(t_1, t_0, x_0), x_0) < \epsilon \qquad \forall t_1 \ge t_0, \tag{1.5}$$

where d denotes a distance metric defined on the state space, and ϵ specifies the permissible deformation threshold that ensures the state remains recognizable. For example, in the case of a protein, this condition implies that despite the natural fluctuations within a thermal bath, the protein's structure remains within a range that allows it to perform its function.

Furthermore, when considering the combined system (x_1, x_2) , it must exhibit the following properties:

$$d(\phi(t_1, t_0, (H, H)), (H, H)) < \epsilon \qquad \forall t_1 \ge t_0,$$
(1.6)

$$d(\phi(t_1, t_0, (P, P)), (P, P)) < \epsilon \qquad \forall t_1 \ge t_0,$$
(1.7)

$$\lim_{t_1 \to \infty} \phi(t_1, t_0, (H, P)) \to (P, P)$$
(1.8)

These conditions enforce the prionic nature of the dynamics, where pairs of healthy states (H, H)and pairs of prionic states (P, P) remain stable. However, mixed pairs (H, P) inevitably collapse into prionic pairs (P, P). This mechanism ensures the propagation of the diseased, or P, states.

1.3.3. Toward Quantum Mechanics

These two design projects for classical systems provide an excellent testbed for exploring systems characterized by discrete, nonlinear dynamics and Newtonian mechanics under thermal motion, both of which aim to generate complex and interesting behaviors. Having established these foundational principles, we next extend our approach to quantum systems, where the challenges and opportunities of quantum dynamics come into play. To bridge this gap, we first review the classical formalisms that naturally lead into quantum mechanics, highlighting the connections and divergences essential for our exploration.

In classical mechanics, we often prefer to work in a formalism that allows for more general coordination to tackle complex systems and constraints. This approach is captured by the Lagrangian framework, offering a versatile tool for handling varying coordinates and constraints in complex dynamics. The Lagrangian formalism uses the potential and kinetic energy to write the equation of motion directly. This will also allow us to work directly on a scalar quantity, the system's energy, without dealing with the forces, a vector quantity. In this framework, the state $x = (q, \dot{q})$ comprises generalized positions q and their derivatives, where these positions need not represent particle positions exclusively. For instance, in a two-particle system along a line, q_1 could denote the center of mass position, while q_2 could represent the particle separation. Alternatively, in a more unconventional scenario, q_1 could represent the angle subtended by two points with respect to a third non-collinear point. using those generalized coordinates, the kinetic energy $T(q, \dot{q})$ and the potential energy V(q) the Lagrangian can be defined as

$$\mathcal{L}(q,\dot{q}) = T(q,\dot{q}) - V(q). \tag{1.9}$$

In the case where no external or non-conservative input is added to the system, the dynamic of the

system can be written as a system of 2n equations where n is the dimension of q such that

$$\frac{d}{dt}\frac{\partial}{\partial \dot{q}_i}\mathcal{L}(q,\dot{q}) = \frac{\partial}{\partial q_i}\mathcal{L}(q,\dot{q})$$
(1.10)

$$\frac{d}{dt}q_i = \dot{q}_i \tag{1.11}$$

The Lagrangian formulation facilitates the effective handling of constraints. Although this framework is suitable for most classical mechanics problems, quantum mechanics originates from a different framework, namely Hamiltonian mechanics. Hamiltonian mechanics allows for a simpler study of symmetries and energy conservation. As observed in Equation 1.9, the Lagrangian resembles the system's energy but with an opposite sign. Hamiltonian mechanics builds on this insight by reformulating the total energy of the system E = T + V in a useful way. The energy of the system, under some condition on the generalized coordinate that can be found in [32] can be written as

$$E(q, \dot{q}) = \frac{\partial \mathcal{L}}{\partial \dot{q}} \dot{q} - \mathcal{L}(q, \dot{q})$$
(1.12)

This allows us to define the generalized momentum $p = \frac{\partial}{\partial \dot{q}}$. We would like to rewrite the energy in terms of this new variable p and q. This is motivated by the fact that those two are the new independent variables of the energy, the same way q and \dot{q} were independent in the Lagrangian formalism. For clarity, we will write \dot{q} as a function of q and p, which allows us to write the energy (That we will now write as H and not E) as

$$H(q,p) = p\dot{q}(q,p) - \mathcal{L}(q,\dot{q}(q,p)).$$

$$(1.13)$$

This formulation allows us to write Hamilton's equations that can be solved to get the dynamic of

the system

$$\dot{q} = \frac{\partial H(q, p)}{\partial p},\tag{1.14}$$

$$\dot{p} = -\frac{\partial H(q, p)}{\partial q} \tag{1.15}$$

This formalism can be greatly simplified using Poisson's brackets, which also have the advantage of leading to the quantization of quantum mechanics. Poisson's brackets are defined between two functions u(q, p) and v(q, p) by

$$\{u, v\}_{q, p} = \sum_{i} \frac{\partial u}{\partial q_{i}} \frac{\partial v}{\partial p_{i}} - \frac{\partial u}{\partial p_{i}} \frac{\partial v}{\partial q_{i}}$$
(1.16)

The indices on the Poisson bracket can be omitted since they are invariant under the canonical transformation of q and p. We will therefore simply write $\{u, v\}$ for $\{u, v\}_{q,p}$. Any quantity of interest in our classical system can be expressed as a function of the state and the time f(q, p, t). The evolution of this quantity is dictated by the evolution of the system's state, which follows the Hamiltonian formalism. The evolution of f(q, p, t) is then given by

$$\frac{df}{dt} = \frac{\partial f}{\partial t} + \{f, H\}.$$
(1.17)

This is also trivially true for the canonical variable since they are also functions of the state. They can be written as

$$\dot{q}_i = \{p_i, H\},$$
 (1.18)

$$\dot{p}_i = \{p_i, H\}.$$
 (1.19)

While the added complexity of this chapter may seem unnecessary at the moment, it will serve two purposes. First, quantum dynamics naturally emerges within a Hamiltonian framework and follows many of the same equations. Secondly, the reader should now understand that the same dynamical equations can be represented in various ways, each leading to different methods for computing the system's evolution. We will build on this idea to introduce yet another formalism specifically for representing quantum mechanical evolution, though it can still be applied to classical systems.

1.3.4. Quantum mechanics

In the previous section, we began with Newtonian mechanics and generalized the coordinates to develop Lagrangian mechanics. We then extended this approach further by generalizing the momentum, which gives us the Hamiltonian. In all of that framework, the system studied is classical, as is the case for Chapter 2 and 3. In this section, we introduce the systems and framework for the second half of this thesis, which focuses on quantum mechanics. This overview is a basic introduction for readers less familiar with the subject. Readers seeking a comprehensive introduction to quantum mechanics are encouraged to consult the following resources [33, 34, 35, 36].

There are multiple important distinctions between classical and quantum dynamics. In classical physics, as we saw previously, systems have definite states at any given time. Quantum dynamics allows for more complex states where the system can be in a superposition of multiple states before measurement. This allows for highly nontrivial consequences on the evolution of the systems, as is exemplified in the celebrated double slit experiment [37]. In this experiment, an individual particle passing through two slits simultaneously creates an interference pattern typically associated with waves, demonstrating the principle of superposition and challenging classical intuitions [38].

Another important difference is the impact of measurement and the concept of uncertainty. Classical measurements do not fundamentally alter the state of the system; for example, measuring the speed of a projectile can be done without changing its course. In quantum mechanics, measurement affects the system and typically transforms it from a superposition state to a single state. This process is probabilistic and is governed by the uncertainty principle, which prevents us from simultaneously accessing non-commuting variables, such as position and momentum, with perfect precision.

In quantum mechanics, we will go one step forward in generalizing momentum and the position coordinates. In this framework, they are replaced by operators; for example, the one-dimensional position over an axis x will become \hat{x} . While a state in Hamiltonian mechanics was given by (q, p)here, it is now represented by a vector in a Hilbert space $|\psi\rangle$. The operator acts as a measurement on the state $|\psi\rangle$ such that if $|\psi\rangle$ represent a particle at position x then the operator \hat{x} acts like $\hat{x} |\psi\rangle$ The system's state can be finite, as in a system of N spins, or infinite, like that of an electron trapped in a potential well.

This process, called canonical quantization, aims to preserve the structure and symmetries of a classical Hamiltonian while enforcing the commutation relations of quantum mechanics, which we will explain shortly. But first, let's start with a small example of first canonical quantization in the case of a harmonic oscillator. The classical Hamiltonian is given by

$$H(q,p) = E(q,p) = \frac{p^2}{2m} + \frac{1}{2}m\omega^2 x^2$$
(1.20)

and the state of the system can be represented as a 2-dimensional vector (q, p). Under the first canonical quantization p is replaced with the operator $\hat{p} = -i\hbar \frac{\partial}{\partial q}$ and the position q is replaced by the operator \hat{q} that acts as a multiplication operator by q such that for a function f(q) we get $\hat{q}f(q) = qf(q)$. The Hamiltonian, therefore, becomes

$$\hat{H} = -\frac{\hbar^2}{2m}\frac{\partial^2}{\partial q^2} + \frac{1}{2}m\omega^2 \hat{q}^2.$$
(1.21)

The classical Hamiltonian was a function of (q, p), and now we have an operator that needs to operate on the system's state. The state space of the quantum harmonic oscillator is the onedimensional Hilbert space of square-integrable functions, which is the space of complex function in
one variable such that

$$\int_{-\infty}^{\infty} |\psi(x)|^2 dx < \infty \tag{1.22}$$

The time evolution of a quantum state $|\psi(t)\rangle$ is given by the Schrödinger equation

$$i\hbar\frac{\partial}{\partial t}\left|\psi(t)\right\rangle = \hat{H}(t)\left|\psi(t)\right\rangle. \tag{1.23}$$

In time-independent problems where the state is stationary, the equation becomes

$$\hat{H} \left| \psi \right\rangle = E \left| \psi \right\rangle, \tag{1.24}$$

which shows once again the relationship between the Hamiltonian and the energy of the system E.

It is useful to investigate how the Poisson bracket transforms in quantum mechanics. This investigation helps to better understand the link between the classical Hamiltonian formalism, presented in the previous section, and quantum mechanics. Additionally, it reflects the fact that, in quantum mechanics, our variables no longer commute. As mentioned earlier, position and momentum cannot be measured simultaneously with arbitrary precision. They obey the uncertainty principle, which states that

$$\sqrt{\langle \hat{q}^2 \rangle - \langle \hat{q} \rangle^2} \sqrt{\langle \hat{p}^2 \rangle - \langle \hat{p} \rangle^2} \ge \hbar/2 \tag{1.25}$$

where \hbar (Planck's constant) represents the smallest unit of action and $\sqrt{\langle \hat{A}^2 \rangle - \langle \hat{A} \rangle^2}$ is the standard deviation of the operator A. This can be done by changing the Poisson Bracket into a commutator such that

$$\{u, v\} \to \frac{1}{i\hbar} \left[\hat{u}, \hat{v}\right] \tag{1.26}$$

where $[\hat{u}, \hat{v}] = \hat{u}\hat{v} - \hat{v}\hat{u}$. Note that we exchanged the functions u, v for operators \hat{u}, \hat{v} .

These changes gave rise to the Heisenberg picture in quantum mechanics, an alternative framework to the Schrödinger picture that offers valuable analogies with classical Hamiltonian mechanics. In classical mechanics, the evolution of a state function f is given by $\frac{df}{dt} = \frac{\partial f}{\partial t} + \{f, \hat{H}\}$. In the Heisenberg picture, the evolution of an operator A is given by

$$\frac{dA}{dt} = -\frac{i}{\hbar} \left[A, \hat{H} \right] + \frac{\partial A}{\partial t}$$
(1.27)

where each operator, including \hat{H} , is expressed in the Heisenberg picture, causing them to differ slightly from those in the Schrödinger picture. We will not delve into the differences between the Schrödinger and Heisenberg pictures here, as we will return to the Schrödinger picture for the remainder of the chapter. This brief discussion serves to highlight the parallels between classical and quantum mechanics.

Chapter 4 will explore quantum sensing, focusing on determining the magnitude of the term α in a Nucleus Hamiltonian of the form $\hat{H}_N = \hat{H}_{N0} + \alpha \hat{H}_{N1}$. We will achieve this using a small electronic quantum system E described by the Hamiltonian $\hat{H}_E(t)$, which we can both control and measure accurately. The two systems are coupled via a small interaction described by \hat{H}_{NE} , enabling information about the parameter α to transfer to the electron system E that we control. By adjusting the control part of the Hamiltonian, $\hat{H}_{control}(t)$, we can create a resonance whose exact position depends on the value of α , allowing us to measure it accurately. Surprisingly, we will find that the current theory fails to explain the observed resonance, indicating that the Hamiltonian \hat{H}_N is incomplete. This discrepancy will be resolved by introducing a new term that accounts for symmetry breaking due to distortions in the system's crystal lattice.

The final chapter, Chapter 5, presents an implementation of a new representation of the quantum evolution operator. In quantum mechanics, the transition map $\phi(t_1, t_0, |\psi\rangle)$ that evolves the state

 $|\psi\rangle$ from time t_0 to t_1 is a linear operator that is normally denoted $|\psi(t_1)\rangle = \hat{U}(t_1, t_0) |\psi(t_0)\rangle$. In the case of a time-independent Hamiltonian, this map can be computed easily by the exponential operator such that $\hat{U}(t_1, t_0) = \exp\left\{\frac{i(t_1-t_0)}{\hbar}\hat{H}\right\}$. In the time-dependent case is given by :

$$U(t,t_0) = \mathcal{T}\left\{\exp\left(-\frac{i}{\hbar}\int_{t_0}^t H(t')dt'\right)\right\},\tag{1.28}$$

where \mathcal{T} denotes the time-ordering operator. While this expression may appear straightforward, it conceals significant complexity beneath the syntactic convenience of the time-ordering operator. The time-dependent evolution operator can be expanded in a series using the Dyson series as

$$U(t,t_0) = \sum_{n=0}^{\infty} \left(\frac{-i}{\hbar}\right)^n \int_{t_0}^t dt_1 \int_{t_0}^{t_1} dt_2 \cdots \int_{t_0}^{t_{n-1}} H(t_1) H(t_2) \cdots H(t_n).$$
(1.29)

A significant part of quantum computing involves calculating the unitary operator U and adjusting the Hamiltonian H(t) so that U performs a desired task. There are many ways to compute this U, and they can be thought of as analogous to the different representations we previously discussed for classical mechanics. While all methods yield the same results, some offer more advantageous properties. Certain approaches allow for easier approximations in specific systems or handle dissipative effects more effectively.

In the time-independent case, this reduces the computing of the exponential of a matrix, which can be accomplished through various methods. This can be achieved using the Taylor series expansion, eigenvalue decomposition, or the Padé approximation technique, to cite only a few. The Taylor series expansion is particularly interesting because it is equivalent to expressing the evolution as a sum over paths on the graph generated by the Hamiltonian. These walks can be sampled as an approximate method, prioritizing the most significant ones. However, it is challenging to enumerate all the paths and sum their infinite number without performing an infinite number of operations. This makes the approach impractical for control, and the simplicity of computing the exponential becomes ineffective. The situation is even worse in the time-dependent case due to the timeordering operator combined with integrals, which prevents this type of expansion. Despite these challenges, solutions can still be found by making the matrix product continuous and employing Green's functions. In Chapter 5, we will demonstrate that this expression can still be interpreted as a sum over paths on a graph, and we will present an implementation using modern machine learning frameworks.

CHAPTER 2

BREAKING REFLECTION SYMMETRY: EVOLVING LONG DYNAMICAL CYCLES IN BOOLEAN SYSTEMS

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2.1. Introduction

One of the most intriguing characteristics of complex systems is that they evince emergent global functions from local interactions. Gene regulatory networks are a quintessential example, describing the complex network of short time-scale interactions between molecules to produce the long time-scale cycles of reactions that sustain life [39, 40, 41, 42]. Such cyclic behaviors play a fundamental role in many processes, including cell cycles [43], biological clocks [44], cell fate [45], cancer regulation and DNA damage [46], and signaling [47]. It is known that cyclic behavior in random Boolean models arises more often than fixed points and that such behavior is favored by evolution [48]. Despite their significance and prevalence, long cyclic reactions remain far from understood, in part because the process of determining their underlying mechanisms is made difficult by the nonlinear and heterogeneous distribution of interactions. Can we distill simple principles for how specific patterns of local interactions determine long and complex cycles of reactions?

Biological systems have been fruitfully modeled as Boolean networks to shed light on this question. In these models, the state of each component—a gene, protein, or RNA—is described by a binary value, and the interactions between components—binding, chemical reaction, and so on are described by Boolean functions. Prior work has extensively studied the interaction functions [49, 50, 51] to model probabilistic [52] and multi-level [53] interactions or to stabilize existing sequences of reactions [54]. Other work has focused on the intensive study of specific network topologies [40, 41, 55, 56, 57, 58] and local structures that are typically referred to as motifs [59]. However, we still lack a general understanding of how the local interaction topology determines long sequences of cycles, thereby limiting our ability to make principled predictions across different networks about the global effects of local structures.

Here, we provide such an understanding through the analytical and numerical study of Boolean network topology. First, we use an evolutionary algorithm to optimize for network motifs with long cycle lengths and discover the existence of *suppressed motifs* that are almost entirely absent in the evolved networks. Next, we discover that many such evolved networks display a *dynamical reflection symmetry*, such that if the network at state $\vec{x}(t)$ transitions to state $\vec{y} = \vec{x}(t+1)$, then that same network at state $\vec{1} - \vec{x}(t)$ transitions to state $\vec{1} - \vec{y}$. Moreover, we find that the suppressed motifs systematically break this symmetry.

To demonstrate the practical utility of our finding, we apply it to real biological systems and find that reflection symmetry appears naturally in networks that have evolved to support long dynamical cycles, whereas suppressed motifs decrement the length of dynamical cycles. Our findings demonstrate how dynamical symmetries play a crucial role in the observed complexity of biological systems.

2.2. Boolean Network Model

Our Boolean network model follows a typical construction [53] motivated by biologically meaningful functions [20], the notion of threshold logic [60], and multiple models of Boolean networks [61, 62, 48] that have been used successfully in biology. The system state $\vec{x}(t)$ is represented by an n-dimensional Boolean vector in $\mathbb{B}^n = {\text{True, False}}^n$, a finite space of dimension 2^n that we refer as the *state space*. For simplicity, we will often use an integer representation of True as 1 and False as 0. We consider networks where interactions between the nodes are either null, inhibitory, or excitatory.



Figure 2.1: **Boolean network model.** (A)(*left*) Example of an interaction network. Red indicates an inhibitory connection; black indicates an excitatory connection. Curved arrows indicate selfloops. (A)(*bottom*, *right*) Two consecutive temporal states of the network on the left. Connections not in use are shown in grey. The state of each node is shown as a '0' or '1' inside the relevant circle. (A)(*top*, *right*) The full state space of the network is shown on the left. Arrows indicate the temporal progression from state to state. Each state is encoded as the activity of the three nodes (e.g., '(0,1,1)' listed clockwise starting from the top one). (B) A larger interaction network of 6 nodes. The state space of this network will depend upon whether the orange edge is excitatory or inhibitory. In the former case, the state space is as shown in the top beige circle; in the latter case, the state space is as shown in the bottom beige circle. (C) Distribution of maximum cycle length for uniformly sampled networks of 5, 6, 7, and 8. (D) Expected decrement in cycle length (*x*-axis) when a single edge is randomly altered (*y*-axis). (E) Optimized networks for cycle length obtained by random sampling (blue) and by a Pareto evolutionary algorithm (orange).

We represent those interactions by a weighted adjacency matrix, **A** where A_{ij} is 1 for an excitatory edge from node *i* to node *j*, -1 for an inhibitory one, or 0 if there is no interaction (see Figure 2.1. B).

The states of all nodes are updated in discrete time steps; all states are updated at once. At every time step, each node sums the excitatory and inhibitory inputs, and if that sum is greater than 0, then the node becomes active (1); otherwise, it becomes inactive (0). The update rule can be formally specified as follows:

$$x_{i}(t+1) = \begin{cases} 1, & \text{if } \sum_{j} A_{ji} x_{j}(t) > 0 \\ 0, & \text{if } \sum_{j} A_{ji} x_{j}(t) \le 0 \end{cases}$$
(2.1)

and we will write $\tau(\vec{x}(t)) = \vec{x}(t+1)$.

2.3. Numerical Results

2.3.1. Sampling networks

To relate cycling dynamics to the topology of the interaction network, we began by considering random networks. We discovered that most random networks have a short cycle length (Figure 2.1.C), which is reflected in the exponential tail of the cycle-length distribution. The identification of cycles is an NP-hard problem [63]. Hence we limit our study of cycle lengths to networks containing eight or fewer nodes. Long cycles are also extremely rare. For instance, a random network of seven nodes has a cycle of length 19 with an approximate probability of one in a million (see Figure 2.1.C). We have also found that edge density is a determining factor in maximal cycle length, as denser networks are more likely to exhibit long cycles. Furthermore, altering the nature of a single edge (e.g., from excitatory to inhibitory) has a strong destructive effect on the maximal cycle length (see Figure 2.1). We did not observe a correlation between the degree of asymmetry in the connection matrix and the length of cycles; in fact, we found that both the best and worst cycles often exhibit high degrees of symmetry, suggesting that the specific nature of the asymmetry is crucial in determining cycle length.

The apparent simplicity of this Boolean model belies surprising complexity. Unlike Hopfield networks, the lack of symmetry in the interaction matrix $(a_{ij} \neq a_{ji})$ of Boolean networks implies the non-existence of a Lyapunov function, making them difficult to study analytically [64, 65]. Further, the inclusion of self-loops has been shown to increase the number and robustness of attractor states, thereby increasing the complexity of our model's dynamics [66]. For these reasons, such models are remarkably expressive and useful in explaining real biological observations such as cell differentiation [67].

We investigated the association between a network's maximum cycle length and its edge density to identify factors influencing cycle length. Our findings indicate that higher edge density leads to an increase in both average and maximum cycle lengths (see Figure 2.2A). We observe that in random networks, a combination of inhibitory and excitatory edges results in longer cycles (see Figure 2.2B). Furthermore, we found that the average maximum cycle length increases with the presence of excitatory or inhibitory circuits in the interaction network (see Figure 2.2.C). We also found that the specific distribution of excitatory and inhibitory connections, particularly in selfconnections, differentially affected cycle length. Self-inhibition, which we defined as an inhibition circuit of length 1, was positively correlated with a high maximum cycle length. By contrast, selfexcitation, which we defined as an excitatory circuit of length 1, was negatively correlated with a high maximum cycle length (see Figure 2.2.D).

To identify and study highly cyclic networks, we utilized an objective function that balances the maximization of cycle length and the minimization of network density. This trade-off is of significance in various domains. Biological systems often face energetic constraints on interactions or the physical pathways on which they rely [68, 69], while the boundaries of their design limit engineered systems. The goal of minimizing interactions is countered by the goal of facilitating a diverse



Figure 2.2: Topological properties of random networks. (A) The average and largest maximal cycle length as a function of density for an eight-node network. (B) The average maximal cycle length as a function of the number of edges of each type: excitatory and inhibitory. (C) The average maximal cycle length as a function of the average size of physical cycles within the interaction network. Note that the former is a dynamical property and the latter is an interaction property. (D) The average maximal cycle length as a function of the number of the number. All plots use a sample of 400,000 random networks.



Figure 2.3: The role of suppressed motifs in cycle dynamics. (A) Example of suppressed motifs. For the full list, see Appendix 2.7.1. (B) Average cycle length in randomly sampled networks for n = 7 from a uniform distribution over the space of all interaction network topologies (blue) and from a random sample over networks created by gluing suppressed motifs together (see Appendix 2.7.1). (C) Proportion of network with a given cycle length for random sample over networks created by gluing together a randomly selected subset of all motifs (red) and for a random subset of motifs. Here we see that the decrease in cycle length is not caused by the gluing process but by the motifs themselves.

dynamical repertoire [70, 71, 72, 73].

We used a genetic Pareto algorithm [74] that encodes each network's genetic representation as a string of n^2 characters in the set -1, 0, 1 (see also Supp. Figure 2.9. A-B-C). This algorithm finds Pareto efficient solutions without the need to define one objective function encapsulating the two objectives, allowing us to analyze the entire landscape of optimal solutions. Using this genetic algorithm, we evolved random networks along the Pareto front and confirmed that we produced networks with larger maximum cycle lengths than equi-dense random networks (Figure 2.1. E; for further information regarding the structure of Pareto networks, see Supp. Figure 2.9. D-E).

2.3.2. Suppressed motifs

We then investigated the factors contributing to the variation in the set of Pareto optimal networks compared to the general population of networks. We found significant differences in the networks' local topology, which differs markedly between evolved and random networks. We observed that the Pareto front networks' global properties—specifically, their density and average degree—were similar to those of random networks. Yet, their local topology was dramatically different. When considering 3-motifs, i.e., subsets of three nodes in the graph with their connections, we discovered a subgroup of around thirty (out of a possible 3284) 3-motifs that were almost completely absent in the evolved networks (see Figure 2.3.A and Supp. Figure 2.8.A). The existence of these *suppressed motifs* suggests a condition on the network's local connectivity that affects its evolved functionality.

To evaluate the impact of suppressed motifs on cycle length, we artificially created networks containing a high density of suppressed motifs (see the). We found that the average cycle length was significantly lower than expected in random networks for all network densities (p < 0.0001) (Figure 2.3.B). We also found that the density of networks with a given maximum cycle length was lower than expected in random networks (Figure 2.3. C). To determine the specificity of the observed behavior, we next constructed networks containing a high density of randomly selected 3-node motifs. In this new population, we observed only a 20 % decrease in the density of networks with a long cycle length; this is in comparison to a more than 95% decrease for suppressed motifs networks (Figure 2.3. C; see Supp. Figure 2.11 for p-values and confidence intervals). These findings suggest that a decremented cycle length is specific to suppressed motifs and is not purely an artifact of sampling over a limited number of motifs.

2.3.3. Dynamical reflection symmetry drives long cycles

To better understand what drives the existence of suppressed motifs, we exhaustively enumerated all networks for n < 5 (Figure 2.4. A). This becomes rapidly pointless for larger n since the number of networks is approximately given by $\frac{3^{n^2}}{n!}$. For each n < 5, we identified the networks with the



Figure 2.4: The role of symmetries in cycle dynamics. (A) Example networks of up to 4 nodes, with the highest cycle length possible in that network size. (B) The state space of the n = 4 network shown in panel (A). The lines without arrowheads represent the states linked under the reflection symmetry (e.g., '(0,0,0,1)' is linked to '(1,1,1,0)'). The top right schematic shows conceptually how the reflection symmetry affects the system's dynamics where a state x is mapped under time evolution to the state y. (C) Average number of fully symmetric transitions. (D) We sample the average partial symmetry ratio, the fraction of bits that transition symmetrically, for random networks (blue), evolved networks (orange), and suppressed motif networks (red).

maximal cycle length (see Appendix 2.7.1). What do all of these networks have in common? We might naively posit that symmetry in the structure of the interaction is important, and indeed the optimized networks with 1 < n < 4 exhibit structural symmetry. However, we observed that the 4-node networks with the maximum cycle length were not structurally symmetric, motivating the need for a different explanation.

As an alternative, we considered a dynamical reflection symmetry that manifests in the network's state-space representation. Such a reflection symmetry permits the inverse of a sequence of states as another sequence. The inverse state is given by the \neg operator or the standard NOT gate. Under this operator, the state of four Boolean nodes $\vec{x} = (0110)$ becomes the state $\neg \vec{x} = \vec{1} - \vec{x} = (1001)$. Then, when we say *dynamical* reflection symmetry, we mean that if the system's dynamics evolve to map x(t) to x(t+1), then the system's dynamics also evolve to map $\neg x(t)$ to $\neg x(t+1)$ as follows:

$$\tau(x) = y \iff \tau(\neg x) = \neg y. \tag{2.2}$$

We observed dynamical reflection symmetry in the network's state transition diagram in all of the 1 < n < 5 networks found to have maximal cycle lengths (Figure 2.4.A-B).

This observation motivates the question: Might reflection symmetry relate to suppressed motifs, and if so how? We found that the maximum cycle length was significantly lower (Figure 2.4. C) in the suppressed motif networks than in the random networks (pairwise two-sided z-test, p < 0.0001). In contrast, our evolved networks—built to optimize the maximum cycle length—displayed a 3- to 7-fold increase in reflection symmetric transitions compared to random networks. These findings link reflection symmetry with the presence of suppressed motifs and a network's ability to display cyclic behaviors.

To better understand how reflection symmetry might relate to suppressed motifs, we returned to our artificially constructed networks containing a high density of suppressed motifs and measured



Figure 2.5: Reflection symmetry in gene regulation networks. (A) Comparison between the average symmetry ratio for Boolean network models of biological systems and their random counterparts built to maintain the joint distribution of node number and nodes' in-degree. (B) Comparison between the average symmetry ratio of Boolean network models of biological systems separated into categories according to tags in the GINim repository.

the number of reflection-symmetric transitions. The number of perfectly symmetric transitions is small; hence, it is of value to also estimate partial symmetries. Specifically, we estimate the fraction of bits that respects symmetry. Specifically, given a Boolean network of size n, the partial symmetry ratio p_{sr} for this network is given by:

$$p_{sr} = \frac{1}{2^n \cdot n} \sum_{x} \sum_{i} \theta(|f(x)_i - f(\neg x)_i|), \qquad (2.3)$$

where $\theta(x)$ takes the value 1 if x > 0 and is zero elsewhere. With this broader definition of partial symmetry, we observed a similar trend in which evolved networks showed an increase in the partial symmetry ratio, whereas suppressed motif networks showed a decrease (Figure 2.4.D). These findings motivate further investigations into the causes that might drive correlations between dynamical reflection symmetry, suppressed motifs, and long cycles.

2.3.4. Real boolean biological networks support reflection symmetries

Evolved networks that displayed a long maximum cycle length tended to express reflection-symmetric transitions more frequently than random networks. Interestingly, those transitions were not exclusively present inside the cycles but were also found in the non-cyclic part of the state space. This observation suggests that dynamical symmetries may play an even more profound role in evolved networks, and motivates investigation of their presence in broader categories of dynamical networks, both synthetic and natural. We turned to gene regulatory networks to test our hypothesis regarding the presence of reflection symmetries in biology. We used two repositories: the GINsim software [75] and the PyBoolNet python package [76].

The set of Boolean biological networks used contains 70 networks. Networks containing non-binary states were transformed to a binary representation using GINSIM. They have between 3 and 218 nodes, with an average of 33.7 nodes. The average connectivity is in the range of [1.18, 4.82] with an average of 2.55 connections. The 129 random Boolean networks were generated using the BoolNet package with uniform function generation, and uniform linkage based on Kauffman's method [77]. The number of genes was selected to reproduce the distribution found in the real network, and the function generation was done randomly using the homogeneous policy. The average number of inputs was selected to reproduce the average number found in the real networks with the given number of nodes.

Using these data, we observed that Boolean models of biological systems showed markedly more symmetries than random networks (Figure 2.5. A). Specifically, the average number of symmetric transitions in the biological model networks was 64.4%, whereas the average number in random networks was 53.6%. The slight deviation from 50% is due to the finite size of the analyzed networks. Further, the reflection symmetry ratio was significantly greater in the biological networks than in the random networks (two-sided *t*-test, t = 7.068, $p = 4.6 \times 10^{-10}$). In addition to this overall effect, we noted a marked variation across the different models: for 10 of the biological networks, less than 50% of transitions were symmetric; for 29 of them, more than 70% were symmetric; and for 12 of them, more than 80% were symmetric. To better understand this variability, we divided the models into biologically relevant categories using the tags provided in the GINsim repository. The seven most populated categories were retained for analysis (Figure 2.5. B). We observed that the most symmetrical categories were cell signaling, cell fate, cell activation, and cancer, with only a few networks lying under the 50% line.

By considering symmetries in Boolean networks, we illustrate a simple method to determine reflection symmetry and examine the overall development of the system. Notably, this concept of reflection symmetry can also be applied to non-binary state systems and even to systems where only part of the system's evolution is known. As an example, we have included a basic case study using continuously valued scRNA-seq data of cancer cells, demonstrating how these symmetries can be utilized to classify cells that respond to drugs versus those that are drug resistant (see Appendix 2.4).

2.4. Deriving reflection symmetry directly from data

Boolean networks permit a simple, general definition of dynamical symmetry. However, Boolean models are not available for many natural dynamical systems, and creating them requires extensive work. Hence, here we analyze symmetry directly from data, circumventing the challenges of Boolean model construction.

We considered the problem of drug resistance in melanoma at the single-cell level. The state of gene expression can predict which cells will resist therapy and which ones will be sensitive and responsive to therapy. Notably, this prediction is possible before treating the cells with any drug. Thus, we define the state of a cell as a "primed" resistant state if that cell would be resistant upon the application of a drug [78]. For this experiment, we profiled the gene expression of these cells using scRNA-seq. We then divided the cells into two categories: the drug-sensitive cells and the cells primed for drug resistance [78].



Figure 2.6: **Reflection symmetry in cancerous cells.** (A) An illustrative example of the reflection symmetry ratio for four cells that express two genes. (*Left*) The normalized level of expression for all four cells and both genes. (*Right*) A symmetric matrix showing the computed reflection symmetry ratio between every pair of cells. In this example, cells 1 and 3 are highly reflection-symmetric, whereas cells 2 and 4 are not reflection-symmetric (asymmetric). (B) The distribution of the reflection symmetry ratio (\bar{s}) for all pair of cells. The red line indicates the expectation for uncorrelated, normally distributed genes. (C) The probability for a randomly selected pair of cells to have different states (drug-sensitive state/drug-resistant state) as a function of the reflection symmetry ratio \bar{s} . The orange curve shows that the probability for pair of cells with a reflection symmetry ratio \bar{s} higher than x as shown in Inset 1. The blue curve shows the probability for pair of cells with a reflection symmetry ratio \bar{s} higher than x as shown in Inset 2. The red curve shows the probability obtained by random permutations of the labels for both cases. The green line shows the average reflection symmetry ratio over all the pairs of cells.

To apply the idea of symmetry to these data, we normalized the expression of each gene. Specifically, negative (positive) normalized quantities represented a lower (higher) expression level than the average expression found for a given gene in all the cells tested. Genes that are highly expressed in more than 70% of the cell are removed as these are typically housekeeping genes unrelated to the process of interest. We also remove genes that are not expressed in at least 25% of the cells since it becomes too hard to find two cells having the same gene expressed. Genes with zero expression are changed to NaN. Finally, genes with a decreasing expression distribution, i.e. where most expression values are close to 0, are removed because of their lack of suitability for defining a symmetry axis. We then defined a parity metric to determine whether two cells had a symmetric expression at the gene level. This metric quantifies how opposite the same gene expressions are for two different cells. For each gene, the maximum of the distribution of each gene's expression over all cells is defined as the zero expression level. Redefining the zero expression allows us to think of the expression of each gene as being more (positive value) or less (negative value) than the most common quantity found in the cells. The maximum of the distribution was preferred over the average since the distributions have highly zero-inflated counts due to the experimental technique used. The expression value for each gene is then scaled by the standard deviation. Let x be a gene, i, j be a pair of cells, and s(i, j)be the reflection symmetry ratio. We ask for the function s(i, j) to be 1 for a perfectly symmetric expression, i.e. $x_i = -x_j$. We also desire that the function will output a 0 if $|x_i| \approx 0$ and $|x_j| \approx 0$ even if $x_i = -x_j$. This condition allows us to avoid attributing some symmetry properties to noise by requiring a difference of at least 20% of the standard deviation between the two expressions x_i and x_j . Finally, we want the function to output a 0 when x_i and x_j are of the same sign. One possible function with these properties is given by

$$s(i,j) = 1 - \max\left\{ \left| \frac{x_i + x_j}{|x_i| + |x_j| + \epsilon} \right|^{h_1}, \frac{1 - \tanh h_2 \left(r_{x,ij} - r \right)}{2} \right\},\$$

where h_1, h_2 are parameters that select the smoothness of the transition between the values of 0



Figure 2.7: Reflection symmetry ratio s(i, j) given two gene expression values: x_i and x_j . For symmetric values, the ratio is 1 and collapses rapidly to 0 when the two values have the same sign.

and 1, and $r_{x,ij} = \sqrt{x_i^2 + x_j^2}$. The parameters used for the indicator are $h_1 = 1.7$, r = 0.1, $h_2 = 25$, and $\epsilon = 1 \times 10^{-7}$. Figure 2.7 shows the reflection symmetry ratio for these parameters.

We observed that the distribution of the parity metric spanned from 0 (non-symmetric pairs) to 0.4 (symmetric pairs). The distribution was also bi-modal, suggesting the existence of two pair types (see Figure 2.6.B). The expectation value of the parity metric for two normally distributed gene expression measurements is 0.343; by contrast, we find that the observed gene expression measurements are skewed toward non-symmetry. With these data and metrics in hand, we studied the symmetrical opposition of the two different states (drug-sensitive or primed). Specifically, we computed the probability that a pair of cells respecting a given criterion were of different states. When considering all pairs independently from their reflection symmetry, we observed a probability of approximately 35% for a pair to have different states. Therefore, we have approximately a one-in-three chance of picking a drug-sensitive and a primed cell when picking a pair of cells at random in our data set. We expected pairs with a high (low) reflection symmetry ratio to have a higher (lower) probability of residing in different paths (drug-sensitive vs. primed). Our expectation was confirmed: pairs with a low reflection symmetry ratio had a probability of around 25% to be of

different states versus 80% for the high reflection symmetry ratio pairs (see Figure 2.6.C). Broadly, these data demonstrate that reflection symmetry correlates with drug resistance in cancer and could be used to classify a cell as drug-resistant or drug-responsive.

The application of symmetry analysis to gene expression inside melanoma scRNA-seq data is a simple example of the potential of considering symmetry in biology. However, the drug-sensitive and drug-resistant paths were not directly observed in the cells where the gene expression was measured. The labeling was inferred by principal component analysis of the cells' gene expression, where the variance was found to be principally located on one axis. This axis was later found to correlate highly with sensitivity and drug resistance. Additional studies could be conducted on data sets that are not linearly separable using one axis and on data expressing more than a binary category.

2.5. Discussion

2.5.1. Functional Role for Reflection Symmetry.

In this study, we uncovered a new link between the expression of specific motifs and the existence of cycling behavior in Boolean networks. Potential links between these two properties have been reported previously for some gene regulatory networks [79]. For example, prior studies report a link between bi-fan motifs and cycling behavior [79] and find that chaotic motifs are linked to cycling [80]. Building upon these observations, we have shown that abnormally underrepresented motifs have a specific function as reflection-symmetry breakers. This relationship sheds light on how an interaction network with these motifs can maintain long cycles.

2.5.2. Diversity of Dynamical Symmetries.

Here we investigated the problem of dynamical symmetries in Boolean networks. Many other types of symmetries exist. For example, one might seek to understand symmetries in the output function on each node and consider that the function $f_1(\vec{x}) = (x_1 \text{ or } x_2)$ is invariant under permutation of its argument. In fact, output function symmetries at the node level are a powerful way to characterize complex network dynamics [81, 82]. Our work extends these observations by showing that symmetries at the global level can explain some properties of networks with complex dynamics. Another common approach is the study of symmetric properties inside the interaction network, such as fibration symmetry [83, 84]. Our approach differs from these studies in evaluating symmetry in the state space [85], but nevertheless provides insights regarding a specific property of the interaction network. This property does not appear as a symmetry in the structure but as a balancing equation on each node. By taking a different perspective from prior studies, our approach sheds light on new mechanisms of dynamical symmetries and the function of the systems that support them.

2.5.3. Methodological Considerations.

Several methodological considerations are pertinent to our work. First, there remains a conceptual and formal distinction between a system and its Boolean network model. Here, we have shown that biologically inspired Boolean networks display a high level of reflection symmetry and that not all biological processes have the same amount of symmetry. Yet, it remains unknown whether reflection symmetry is intrinsic to the system or a result of the map between a set of experiments and its Boolean network model. Future theoretical work could examine the impact of the mapping process on our findings. Further experimental work could examine the evolution of a simple biological system (e.g., yeast) and confirm the existence of reflection-symmetric states.

Boolean models of biological systems can include more general types of interactions and update rules than the ones we considered. Reflection symmetry can be easily identified in both thresholded and un-thresholded models. Furthermore, since every Boolean model maps binary states to binary states, our reflection symmetry definition is broadly applicable and does not depend on the nature of the updating scheme. The difference in models does affect the ability to analyze motifs since the model determines the possible types of interactions. Further work should examine this potential dependence and the broader impact of the updating schemes and the model on the condition necessary for mirror symmetry. Future work could also seek to generalize and test the theory of dynamical reflection symmetry for more general Boolean networks and multiple updating schemes and to random Boolean networks [57, 86]. Finally, various other deterministic network-based systems exhibit cyclical behavior, and it would be intriguing to investigate whether subclasses of motifs also exist in systems such as coupled maps on networks [87, 88] or evolutionary games on networks [89].

2.6. Conclusion

In identifying the important role of dynamical symmetry in Boolean networks, this work suggests strategies that can be used to engineer complex dynamical systems with particular dynamical features, or to modify an existing system's architecture to influence its properties. In particular, we have shown is is possible to enhance or suppress cycling behaviors by altering only a small subset of edges in a system's interaction network topology. As applied to complex biophysical systems in pharmacology and microbiology, this understanding may aid the design of targeted diagnostics and therapeutics.

Our findings can also improve Boolean network modeling of real systems. In situations where cycling behavior is a defining system characteristic, the search for a suitable Boolean network model can be dramatically simplified by considering the symmetric subspace. This is crucial since it is impractical to explore the complete state space experimentally, even for small networks. Similarly, reflectionsymmetric counterparts of observed trajectories can be added to training data sets, doubling the information available to machine learning models at no extra cost, analogously to mirroring images for neural network training.

In elucidating the formal relationship between reflection symmetry and cyclic behaviors, our work raises intriguing new questions for the scientific community. For example: What causes and regulates dynamical symmetries? Why does the degree of dynamical symmetry vary across different cellular and molecular processes? Which diseases or other perturbations to the system impact this symmetry? Is symmetry explained by evolution or caused by the physics of the system? Answers to these questions will profoundly impact our fundamental understanding of natural dynamical systems.

2.6.1. Data and code availability

All data and code used in the manuscript are available at https://github.com/ouelletmathieu/BMS.

2.7. Appendix

2.7.1. Sampling

We sample the space of Boolean networks in two steps. First, a density is chosen uniformly at random from the range 0.2 to 1. Second, we select elements in the matrix and fill those elements with either a -1 or +1—with equal probability—until we reach the target density. For the biased case, we again begin by choosing a density randomly from 0.2 to 1. Then, we select valid motifs randomly from the set of desired motifs and place them randomly in the interaction network. If we cannot find a position for a given motif, then we discard that motif and randomly draw another from the same set. Once the desired ratio of motifs is achieved, the network is filled with random edges to achieve the global density. Edges used for a motif (empty edges included) are protected and cannot be filled in this part of the process.

2.7.2. Evolved networks

In our evolutionary algorithm, we set the population size to 600 interaction networks with a density taken from a uniform distribution ranging from 0.2 to 1.0. The selection for mating is handled by the NSGA2 algorithm [74]. In each step, 400 new offspring are created using two mating operators (see next section for details). We mutate each edge of the offspring's interaction networks with a probability of P = 0.02. When a component is selected for mutation, its value is changed to one of the two other values in $\{-1, 0, 1\}$. The generation process is then repeated until convergence. The whole process is repeated 30 times.

We use two mating operators that reflect the exploratory and convergent mating strategies, respectively. Both operators are used with equal probability each time we call the mating procedure.



Figure 2.8: Ruppressed motifs and their impact on the propagation of perturbations. (A) Set of suppressed motifs. To improve the readability of this visualization, the set of suppressed motifs was approximately clustered by structural similarity. Each blue circle represents a cluster. The line between motifs inside a cluster shows how motifs in the cluster are related. The beige circle represents the global structure of the motifs inside the blue cluster. (B) Small perturbations propagate more in evolved networks than in random and suppressed motif networks. We sample the average distance between two states which initially differs only by one component after 3 updates (triangle) and after 10 updates (square).

The first mating operator generates two offspring. For each index of the matrix, each offspring gets assigned either the first or second parent's component. If the first offspring receives its component from parent two, then the second offspring receives its component from parent one. Then both matrices are tested for validity; if one is found to be disconnected when considering the interaction matrix as an undirected graph, the process is restarted. The second mating operator generates one offspring at a time. We list the cycle basis of both parents' interaction networks. Then, random cycle structures are picked from the cycle basis to build a new interaction network containing a random mixture of cycles from both parents. Only cycles that agree for all of their common inhibition or excitation edges are selected. If two selected cycles cannot be joined because of disagreeing edges, the process is restarted. We use the first mating operator if the process fails more than 1000 times. Such failures happen but are rare and represent a negligible percentage of the offspring production.

Interestingly, each node in the evolved networks had approximately 20% more incoming excitatory edges than inhibitory edges. The evolved networks also exhibited nearly twice as many physical excitation circuits as the random networks (see Supp. Figure 2.9.D). These features were emergent properties, as the evolutionary algorithm did not explicitly optimize for them. In addition to comparing all evolved networks to all random networks, we separately examined the dynamics of evolved networks that implemented the exploratory versus the convergent mating strategy. We found that convergent mating consistently produced networks with greater maximum cycle length than exploratory mating (see Suppl. Figure 2.9.C). In general, the structure of the two parents does not generate offspring with long cyclic behavior. Even for the convergent mating strategy, most cycles from both parents do not act cooperatively, generating important attractors leading to fixed points.

2.7.3. Motif characterization

To calculate the z-value for the number of expected motifs, we used sampled data to obtain each motif's average expected number and its expected standard deviation. Since the expected number for 3-motifs is always one order of magnitude less than the standard deviation, we consider motifs with an individual z-score of less than -0.1 to be suppressed. This repression typically corresponds to the absence of the motif in the graph. We then consider a given motif to be suppressed in the population if it is tagged as suppressed in at least 50% of the population's individual graphs.

2.7.4. Reflection symmetry

Since for each $n \leq 4$, there was at least one network with the maximal possible cycle length with this symmetry, it is quite tempting to conjecture that there always exists a maximal network with this property. This, of course, cannot be confirmed computationally and could only be realistically verified up to n = 5 without developing a more sophisticated search algorithm.

2.7.5. Robustness

Another frequently cited property of the evolved networks is their robustness to perturbation. We sought to determine if the evolved networks and the suppressed motif networks had distinct levels of robustness. The notion of robustness depends upon a notion of response to perturbation. The distance between the non-perturbed and perturbed states is measured at each time step by the Hamming distance, which only counts the number of non-matching bits. A robust network is one where the distance stays constant or decreases over time. We expect evolved networks to show an increase in robustness, and we expect suppressed motif networks to show a decrease in robustness. The results are surprising: for a large range of edge densities, perturbations to suppressed motif networks do not drive a large divergence in state dynamics in comparison to uniform random networks (Supp. Figure 2.8).

Intuitively, one might imagine that a network's sensitivity to perturbation could depend upon the maximum cycle length, such that the longer the maximum cycle, the greater the tendency for perturbations to drive divergent dynamics. In contrast to this intuition, however, random and suppressed motif networks have quite different average cycle lengths. The difference could then be entirely caused by the presence of long cycles in the evolved population in comparison with the



Figure 2.9: Offspring generation and properties of suppressed motifs. (A) Offspring generation is based on cycle preservation. (B) Example of the approximated Pareto front where green points are optimal in the Pareto sense, and where red points are sub-optimal. (C) Evaluation of the different mating strategies or policies that generate offspring. (D) Ratio of the number of different physical constituents of the Pareto front networks versus random networks. (E) Ratio of the number of different physical constituents for the suppressed motif networks versus the random networks.



Figure 2.10: Time evolution of perturbations. (A) Average Hamming distance from the 1bit perturbed network to the unperturbed network as a function of the time for the Pareto front networks binned by cycle length. (B) Same as in panel (A) but for a maximal cycle length of 16 and plotted separately for Pareto front networks, random networks, and suppressed motif networks.

two other populations. To test this possibility, we have compared networks from each category with the same cycle length. For a given maximum cycle length, evolved networks have a slightly lower distance than the random and the suppressed networks for a given cycle length (see Supp. Figure 2.10.A). The difference however is quite small and is cyclic with the period equal to the cycle length, as expected (see Supp. Figure 2.10.B). Therefore, suppressed motifs and the optimization process have, for a given maximum cycle length, a rather low impact on how the networks handle perturbations.



Figure 2.11: Statistical analysis. (A) The *p*-values for the comparison with the uniformly sampled networks shown in Figure 2.3.D. The *p*-values were capped at 10^{-6} when their values were smaller than this number. (B) Proportion difference between the uniformly sampled networks and the motifs enriched networks with the confidence interval shown as error bars.

CHAPTER 3

MECHANICAL PRIONS: SELF-ASSEMBLING MICROSTRUCTURES

This chapter is in press as Ouellet, Mathieu, Dani S. Bassett, Lee C. Bassett, Kieran A. Murphy, and Shubhankar P. Patankar. "Mechanical prions: Self-assembling microstructures." arXiv preprint arXiv:2402.10939 (2024). I was responsible for conceptualizing the research questions, designing and conducting the experiments, analyzing the data, and drafting the manuscript.

3.1. Introduction

Prions are shape-shifting proteins notorious for their ability to cause deadly transmissible diseases [90, 91]. Among others, these include scrapie in sheep and goats, bovine spongiform encephalopathy in cattle, and Creutzfeld-Jakob disease in humans. Despite such examples of its malignancy, prionic behavior can also be advantageous in certain contexts. Proteins with prionic appendages facilitate the formation and maintenance of long-term memories, while fungi such as yeasts rely on prions to transmit heritable characteristics [92].

The infectious propagation of conformational changes drives prionic behavior [93, 94]. Physical studies of biological prions have primarily taken a macroscale, statistical view, focusing on chemical rate modeling [95, 96]. A microscale physical model that reproduces the key elements of prions—including their ability to exist in distinct conformations, self-assemble into the prion state, and self-replicate—has yet to be developed and examined. In this work, we address this gap by presenting a biologically-inspired mechanical model of prions.

Prions—whether biological or synthetic—must possess several key properties. First, the system must have at least two stable conformations. For consistency with biological prions, we refer to these conformations as healthy (H) and prionic (P) (Figure 3.1A). Second, the P conformation must be able to form stable polymers, and P-P dimers should be more stable than H-H dimers (Figure 3.1B). Third, the H conformation must be able to interact with the P conformation to form an unstable H-P dimer. The H-P dimer, in turn, must be able to convert to a P-P dimer through a reaction that cannot occur solely with monomers; this property is essential to allow a mechanical prion to transmit its misfolded configuration to nearby structures (Figure 3.1C). If these minimal conditions are met, we posit that a propagation mechanism similar to that occurring in biological prions can be replicated in a system of simple mechanical elements that we call *mechanical prions* (Figure 3.1D).

3.2. Prions as bar-joint linkages

We employ a bar-joint linkage model [97] within a thermal bath [98], inspired by prior studies on conformational changes [99, 100, 101]. Each structure comprises N nodes, divided into two groups: exterior nodes, which enable polymer binding, and interior nodes, for structural stability. Interactions between linked nodes are modeled using a harmonic potential common for coarse-grained modeling of proteins [102, 99] and a Lennard-Jones (LJ) 12-6 potential to allow for interactions between nodes across prions [103]. Results are presented in LJ units, where the LJ energy minimum, ε , is set to $0.05K\ell^2$, where K is the harmonic spring constant and ℓ is the length of external bonds. We set the LJ length scale, σ , such that the energy minimum between two nodes occurs at a separation 0.05ℓ . To incorporate thermal fluctuations, we model the system's dynamics using the Langevin formalism in LAMMPS [104].

3.3. Discovering mechanical prions

When searching the space of bar-joint linkages for viable prions, several choices are pertinent: the exterior shape for stable configurations, defining a (possibly non-convex) polygon; the number and position of internal nodes; and the number and lengths of the edges connecting the internal and external nodes.

We constrain our search for mechanical prions to the space of regular pentagons, in this case, a 4torus [105]. With the number of external nodes set to five, we aim to find two distinct configurations



Figure 3.1: Essential prioric properties. (A) The system can exist in two distinct states, known as the prior (P) and healthy (H) conformations. (B) The prior conformation is capable of forming polymers with other priors; the healthy conformation is not. (C) The lock and key process of the prior conformation and the healthy conformation, whereby a dimer is formed. (D) Propagation of the prioric conformation in a mono-disperse solution when one prior is present.

representing the H and P structures. First, we require that the P structure self-binds with lower energy than the H structure. We search for a P polygon where three external nodes can align with three nodes of another P polygon (Figure 3.1B). Second, the binding process must allow the formation of a tower-like structure of P polygons, while the H polygon should resist self-binding to prevent assembly. To ensure that this is the case, we limit the maximum number of interacting nodes between two H polygons to two (Figure 3.1B). Third, we search for a lock-and-key mechanism [106], whereby the P and H polygons interact *via* three external nodes, with the H polygon requiring a small deformation for binding to the P polygon (Figure 3.1C). This imperfection disrupts the rate symmetry between free and bonded states (Figure 3.1D).

To guarantee mechanical rigidity, external nodes defining the polygons must connect to a set of internal nodes [97] (Figure 3.2A), thereby allowing for two stable conformations of a single structure. These conformations have identical energy minima (Figure 3.2B)[101, 107]. The two conformations



Figure 3.2: **Bar-joint mechanical prion model.** (A) Schematic of the structure. (B) Bond energy of the free system evaluated along the reaction path between the H and P conformations for the structure shown in panel (A). (C) Schematic of the P and H conformations interacting. (D) Bond potential energy between the P-H dimer and the P-P dimer evaluated along the reaction path.

are isolated from each other by an activation energy barrier that prevents transitions from one state to another.

The two interacting structures exhibit prominent interactions within the lock-and-key region, whereas other interaction configurations are inhibited by design (Figure 3.2C). The potential energy in the P-P configuration equals that of two separate P structures, an energy minimum. In contrast, the P-H configuration's potential energy is notably higher due to misaligned lock-and-key areas (Figure 3.2D). The barrier's potential energy remains largely unaffected. This reduced activation energy required for P-H to P-P transition drives the prionic effect and alters the symmetry of configuration rates .

Through this search process, we discovered several candidate mechanical prions in the space of pentagonal bar-joint linkages. Although their static energy landscape suggests prionic behavior, it remains essential to evaluate them under dynamic conditions, wherein multiple undesired effects can appear that prevent the transition from P-H to P-P. Examples of these undesired effects include internal node binding issues, additional undesirable stable configurations, and entropy inhibiting the reaction [108]. The prior design phases just described do not address these challenges. Hence, we must evaluate the behavior for the specific pair of configuration states under Langevin dynamics.

3.4. Validating prion properties

We track the dynamics of structures undergoing Langevin dynamics by quantifying the sum of squared differences in their internal angles relative to reference conformations and subsequently assign each structure to the closest reference conformation. In cases where both distances exceed defined thresholds, we classify the structure as denatured, indicating that it has adopted an undesired conformation. These labels are then utilized to analyze the dynamics via a discrete-time Markovian model, from which we derive transition rates through model fitting over a coarse-grained time scale . We investigate the evolution of an ensemble comprising P and H structures and track the concentrations of both interacting (bound P-H and P-P) and non-interacting (free P and H)



Figure 3.3: **Dynamical properties.** (A) The transition rate between the two conformations (P for prion and H for healthy) in the free and bound cases at low temperatures fit with a super-Arrhenius form. The inset shows the deviation from the fitting at higher temperatures. (B) The two curves show the equilibrium distribution of the prion population in the free (in dark purple) and bound (in dark blue) cases given the inverse temperature. The inset shows four examples of the dynamics of each monomer (P and H) inside a dimer (PH) at various temperatures. The temperatures are indicated by arrows beneath the plot. Here, we used the same reaction coordinates as those in Figure 1.C.
structures.

The rates corresponding to the structure discussed in this paper is illustrated in Figure 3.3A. In the free scenario, both the H \rightarrow P and P \rightarrow H rates are indistinguishable within the given margins of uncertainty. In the bound scenario, however, the H \rightarrow P rate becomes up to two orders of magnitude faster, thereby breaking the symmetry. At lower temperatures ($\beta \varepsilon = \frac{\varepsilon}{k_{\rm B}T} > 3 \times 10^4$) P \rightarrow H conversions within the bound state become infrequent, with none observed within the time scale feasible to the simulation. The observed rates indicate that we successfully designed a prionic structure.

Equilibrium distributions, derived from a Markov model based on observed transition rates between the coarse-grained states of the different types of structures, are shown in Figure 3.3B. The stationary distribution is asymmetric; bound systems approach 100% prion conversion, whereas free systems approach only 50% prion conversion. At low temperatures ($\beta \varepsilon > 10^3$), both free configurations are thermodynamically stable, and no other conformations are present. We arrive at equilibrium distributions (Figure 3.3B) by using simulation rates that have been derived from an extended Arrhenius model [109]. The model accurately characterizes dynamic behavior at low temperatures (Figure 3.3A). We observe super-Arrhenius behavior, or lower-than-expected reaction rates, at low temperatures. This effect, also seen in the kinetics of protein folding [110], in collective behaviors [111, 112], and in enzyme-catalyzed reactions [113], is generally related to an increase in the activation energy or a change in the transition state at lower temperatures [114].

The inset of Figure 3.3B displays four time traces that illustrate the conformational changes of the bound structure, all initiated from the P-H conformation. The third trace displays the system at a temperature where unbound transitions are exceedingly rare. In this trace, the bound H visibly transitions to the P conformation, as highlighted in the magnified portion of the plot. We observe a subtle conformational shift in the P structure during the H's transformation, which appears to begin when the initial H structure is halfway through its transition. This timing suggests that the P structure (to which the H binds) actively participates in the conversion process. Furthermore,

the final stability of P-P dimers is not simply an outcome of the stability of individual P and H monomers. This stability of large assemblies in the prionic state is crucial for prion functionality. We note a difference in the level of random fluctuations between the healthy and prion states at all temperatures (see Figure 3.3A inset). These differences are likely due to the empty key-lock site for the healthy configuration, which makes these networks less rigid overall while the prion's degrees of freedom become constrained upon binding.

We observe non-monotonic fluctuations (U-shaped) for the bound configuration at high temperatures that cannot be accurately described by an Arrhenius-type equation (Figure 3.3A, inset). This phenomenon is explained by the ability of the bound networks to attain new, slightly deformed, conformations at high temperatures that are not labeled as denatured. This ability can be seen in the first time trace (Figure 3.3B), where the curves exceed the H conformation and remain stable for an extended period before shifting to the P conformation. This conformation is stabilized by the rigidity imparted by binding with the prion, and the final structure exhibits greater stability at elevated temperatures, resulting in its exclusive presence in the bound state.

3.5. Experimental Validation

To experimentally validate the properties of the mechanical prions we identified, we built a tabletop environment where the dynamics of structural configurations could be evaluated in a proof of concept experiment. We 3D-printed spring-like edges that extend and contract (Figure 3.4A), and we placed magnets at each node to allow interactions across structures. We simulated a thermal bath using a stepper motor that agitates the mechanical structures at varying speeds. Transition rates observed in the free and bound states qualitatively align with our theoretical predictions, showing the expected rate asymmetry (Figure 3.4B). The supplementary information includes videos of the P-H dimer converting to the P-P configuration, along with additional details of the macro-scale model.



Figure 3.4: External mechanism and macroscopic model. (A) (top) Macroscopic model exhibiting the healthy conformation. (bottom) Macroscopic model exhibiting the prion conformation. (B) The transition rate exhibited by the macroscopic model is similar to the transition rate exhibited by simulated structures. The inset shows one of the macroscopic models used in the experiment. Further details can be found in the Supplement.

3.6. The lock-and-key mechanism

The lock-and-key mechanism is crucial for eliciting prionic behavior. Intuitively, the key and lock should have the same geometry to enable the key to align with the lock. However, when two networks with perfect alignment bind to one another, the overall shape of the constituent networks does not change. This fixity is due to the fact that Lennard-Jones potentials exist at significant levels only between matched node pairs, not between distant misaligned nodes. Therefore, the keylock areas must necessarily be misaligned to force internal reorganization in the H monomer. This misalignment of external nodes breaks the symmetry in the rates between the free and the bonded states (see Supplement).

While the external node configurations establish the lock-and-key mechanism, the positioning of internal nodes also plays a crucial role in this mechanism. The internal nodes ensure the stability of the mechanical prion while simultaneously facilitating conformational changes. Their placement greatly influences the transition temperature by changing the structure's stability. We find that prionic behaviors of mechanical structures are robust to a wide range of choices of the precise locations of the internal nodes .

3.7. Discussion

In aggregate form, mechanical prions offer a variety of useful architectures, powerful functions, and capacities for design and control. Prion-like mechanical networks can help build fast and irreversible sensors, leveraging their unique polymerization properties and switching capabilities. The switching rates of these structures can be fine-tuned by designing their binding sites to preferentially promote aggregation over fragmentation [115, 116], with a specific focus on the large-scale structures that are targeted for production. Similar to their biological counterparts that produce amyloid plaques, mechanical prions can assemble into durable 2D sheets (Figure 3.5A) [117] and 1D fibrils (Figure 3.5.B). Such constructions have been explored, for example, using prion-inspired peptides [118, 119, 120, 121, 122]. Monodisperse prion solutions, which restructure after seeding, have potential utility



Figure 3.5: Potential applications. (A) Prions could have multiple binding sites, thereby allowing for higher dimensional structure. Here, a simple 2D sheet is represented. (B) Prions could be utilized in the functionalization of nanoparticles, where a change in conformation could result in a change in solubility or the formation of structures such as fibrils. (C) Prions could be used to create structures that are capable of disassembling themselves, triggered by a change in the conformation of one of their components. (D) The transformation of healthy assembled structures into non-interacting prions can be leveraged as a switching mechanism through the disassembly process.

in scavenging and control processes [120]. Recent advancements in DNA origami have facilitated the fabrication of scaled-down mechanical structures, featuring joints, sliders, and hinges, suggesting the potential for our structure to be constructed using similar methodologies [123, 124, 125].

Prions are often associated with pathological aggregates, but recent studies have also indicated their role in various beneficial biological functions [126, 127] and display complex prion-prion interactions [128]. This work reshapes our understanding of prionic dynamics, suggesting that not all aggregates are pathological, with some having potential functional utility. For instance, "healthy" configurations can be aggregated to design self-disassembling scaffolds (Figure 3.5C). Inspired by these findings, future approaches might introduce prions into synthetic materials, potentially for drug delivery systems where a prion-composed shell safely disintegrates at its target [129] (Figure 3.5D).

In addition to its potential practical utility, our work also offers several directions for further theoretical exploration. While we limit our attention to two-dimensional frames, three-dimensional mechanical structures can similarly be discovered and examined using the techniques we describe here. Symmetries can be imposed to the structures and subsequently utilized as foundational elements for constructing more complex physical or dynamical structures [130, 12]. Future work could also seek to reduce the degree of internal nodes, thereby reducing the potential for obstructions and easing the fabrication of macroscale structures.

3.8. Method

3.8.1. Design of mechanical prions

In this section, we offer a summary of the methodologies employed in this study. For more detailed information, refer to the Supplementary Information .

External nodes

First, we randomly generate pentagons with side length 1. We filter non-simple and pentagons with an internal angle of less than 10 degrees. This filtering process facilitates the creation of shapes that are simpler to manufacture. We require healthy polygons to self-bind poorly and prionic polygons to self-bind strongly. We calculate a fitness value f to achieve this goal, representing the binding affinity between two polygons. To minimize this fitness for pairs of polygons, we use the iterative closest point (ICP) shape registration algorithm [131]. Each polygon is labeled as a potential healthy structure if its fitness is less than or equal to n_H and as a potential prion if its fitness is greater than or equal to n_P . These values ensure healthy structures engage in pairwise node binding, while prions require at least three nodes. Given that all edge lengths are identical and we are dealing with simple pentagons (with non-intersecting edges), each pentagon can always bind to itself at a minimum of two nodes. To prevent their self-assembly, we ensure that these configurations are not stable under our chosen temperature conditions.

Internal nodes

The pentagons we select as candidate mechanical prions are not rigid, possessing several conformational degrees of freedom. We enforce rigidity by adding n_{in} nodes to the interior while avoiding states of self-stress. The n_{in} nodes are incorporated to allow for the existence of two stable conformations . We use a conformational solver to determine the position of the internal nodes to allow transition between both conformations [101]. We try 10000 solutions for each pair with a length discrepancy tolerance of 0.01ℓ , discarding any duplicate solutions.

3.8.2. Energy landscape

We use Lennard-Jones potentials for inter-node interactions and model edges using Hookean spring dynamics. We employ the Nudged Elastic Band (NEB) method [132] as implemented in LAMMPS [104] to compute the static scenario and assess the activation energy between two conformations. The initial configuration is represented by the H monomer (or the HP dimer), and the final configuration is represented by the P monomer (or the PP dimer) for the free (or bonded) case. An initial relaxation step guarantees that the newly associated structures will settle into their nearest energy minima. For both cases (bonded and free), we use a step size of 0.001 with 12 replicas. We remove structures where the activation energy of the free setting is higher than the bonded setting (see Supplementary Information).

3.8.3. Dynamical Analysis

We simulate the dynamics of conformational change using the Langevin formalism in the Largescale Atomic/Molecular Massively Parallel Simulator (LAMMPS). In our simulations, for every candidate pair that shows a promising energy landscape, we analyze their dynamical properties for temperatures ranging from $1e^{-8}\frac{1}{\epsilon}$ to $1e^{-3}\frac{1}{\epsilon}$. We simulate 12000 time points and record the positions of all structures at 600 evenly spaced instances. We double the number of time steps during every run of the simulation until convergence is achieved. Simulations start in one of three configurations, each featuring 30 structures within a 15×15 box. In the first two configurations, we assess the stability of the healthy and prionic structures. The last configuration consists of pairs of prions and healthy structures. We position the pairs near their binding sites to facilitate interaction during simulation. Labels are assigned by computing the distance of each structure at every time point with the prionic and healthy configurations . We compute reaction rates and steady-state ratios from the sequences of labels modeled as Markov processes. Rate curves are adapted to fit a modified Arrhenius equation, as described in [109], of the form:

$$k = k_{\infty} \exp\left[-\frac{E_A}{R(T-T_0)}\right].$$

3.8.4. Macroscopic Model

As a proof-of-concept, we develop a macroscopic model utilizing two types of spring-like edges . All edges were 3D printed using ultraviolet-sensitive resin and assembled with Chicago screws. We fix rare earth magnets to the screws to allow interactions between the external nodes, and add a printed cap for centering. The cap's thickness was calibrated to regulate the holding force between nodes, thereby ensuring that structures remain bound when three nodes interact, but not when only two nodes interact.

To perform experiments to validate prionic behavior, we use an arm of length 100 mm, manipulated by a stepper motor. We use one of the nodes to attach structures to the arm. The stepper motor undergoes oscillations spanning 1 radian for 20 cycles. Between each oscillation set, we reset the conformation, and randomize the angle between the manipulating arm and the structure. We regulate angular speed using the number of steps per second, where each step measures 1.8 degrees. We sweep speeds from 50 to 250 steps per second.

3.9. Appendix

Here, we provide a detailed account of our methods. First, we outline the process of identifying mechanical structures capable of exhibiting prionic behavior. Second, we describe how we identify the minimum energy path between two distinct conformations. Third, we describe the simulation process of validating prionic properties in a thermal bath. Fourth, we discuss the role of external and internal nodes in mechanical prions. Finally, we offer design and experimental details for a macroscopic prion prototype.

3.9.1. Designing mechanical prions

In this section, we detail the process of searching for mechanical prions in the space of mechanical networks. We begin by considering the external shape of potential prions and "healthy" mechanical structures. We then highlight various filtering stages, starting with the external shape, moving to self-binding properties for individual mechanical structures, and finally selecting pairs that exhibit optimal prionic functionality together.

We employ a bar-joint linkage model. We treat a mechanical prion as comprising N interacting nodes of unit mass $(m^* = 1)$ where LJ units are employed. The set of nodes, denoted as $\mathcal{V} = \{1, \dots, N\}$, is embedded in a two-dimensional space. The position of node *i* in molecule *k* is given as $\mathbf{x}_{k}^{(i)}(t)$. We partition the node set into two distinct groups: $\mathcal{V}ext$, representing the exterior nodes responsible for polymer binding, and $\mathcal{V}int$, the interior nodes. We denote the set of connections between nodes as \mathcal{E} , and we set the spring constant, *K*, for connections to 1. An entry $(i, j) \in \mathcal{E}$ implies that node *i* connects to node *j*. An edge (i, j) belongs to the set of exterior edges \mathcal{E}_{ext} if *i* and *j* both belong to the set of exterior nodes \mathcal{V}_{ext} .

External shape

We set the external edge length l to 1.0 and the number of edges to 5. We generate pentagons at random by selecting three arbitrary angles in the range $[0, 2\pi]$. The last two angles are determined based on the first three. We then filter the set of random polygons to ensure that the distance between the starting and ending points of the polygons is under 0.002, filtering them to adhere to the length criteria. While more sophisticated methods exist, our approach is unbiased and sufficient for smaller-sized polygons. The space of all pentagons formed this way is a four torus and can be seen in Figure 3.6.A. In this context, the polygon symbolizes the external interaction structure, which needs to allow for the creation of prion aggregate. Therefore, we introduce conditions to ensure the polygons are simple (non-intersecting) and maintain a minimum internal angle of 10 degrees, as shown in Figure 3.6B (left). This condition on the minimum internal angle ensures that external nodes are not too proximate, given their uniform distance, thereby minimizing excessive interactions.

Self-binding requirements

We require healthy polygons to self-bind poorly and prionic polygons to self-bind strongly. To achieve this distinction, we calculate a fitness value f, representing the binding affinity between two polygons, such that,

$$g(\mathbf{x}_k, \mathbf{x}_l) = \frac{g_{\min}^2}{2} \sum_{i \in \mathcal{V}_{ext}} \sum_{j \in \mathcal{V}_{ext}} \max\left(\frac{1}{d(\mathbf{x}_k^{(i)}, \mathbf{x}_l^{(j)})^2}, g_{\min}\right)$$
(3.1)

$$f(k,l) = \min_{\mathbf{x}_k, \mathbf{x}_l} g(\mathbf{x}_k, \mathbf{x}_l), \tag{3.2}$$

where $d(\mathbf{x}_{k}^{(i)}, \mathbf{x}_{l}^{(j)})$ is the distance between nodes *i* and *j* from structures *k* and *l*, respectively. To cap the contribution to *g* of two bonded nodes, we define g_{\min} as $f_{\min} = \frac{1}{d_{\min}^{2}}$ and set d_{\min} to be 0.001*l*. To minimize this fitness for pairs of polygons, we use the iterative closest points (ICP) shape registration algorithm [131]. For both polygons, we generate a set, S_{k}^{m} , the set of all *m* adjacent nodes. For each node pair (s, s'), where both *s* and *s'* belong to S_{k}^{m} and $m \in \{2, 3, 4\}$, we adjust the position and orientation of \vec{x}_{k} to minimize their overlap. We set the translation of \mathbf{x}_{k} such that the center of mass of the node subset *s* aligns with the center of mass of the node subset *s'* located at \mathbf{x}'_{k} . The rotation is then selected to minimize the least squares distance between the two subsets. The subset size *m* is chosen from the set $\{2, 3, 4\}$ because, for a pentagon, these values represent the only non-trivial bindings that do not result in complete overlaps. For every initial position identified for the pairs (s, s'), we apply the ICP algorithm with a maximum of 20 iterations and a tolerance set to 0.005ℓ . These steps provide us with a comprehensive list of potential self-binding configurations for a polygon.

However, not all self-binding configurations are valid. As such, we systematically eliminate pairs (s, s') that display an overlap area greater than 0.02 for every identified pairing. It is worth highlighting that the step to mitigate overlap is introduced mainly based on our conceptualization of these polygons as rigid structures. Each polygon is labeled as a potential healthy structure if its fitness is less than or equal to n_H and as a potential prion if its fitness is greater than or equal to n_P . For pentagons, we set n_H and n_P to 2.1 and 2.8, respectively. These values ensure healthy structures engage in pairwise node binding, whereas prions require at least a three-node binding. Figure 3.6.C displays the various self-binding levels and their respective fitness values. Given that all edge lengths are identical and we are dealing with simple pentagons (with non-intersecting edges), each pentagon can always bind to itself at a minimum of two nodes. To prevent their assembly, we ensure that these configurations are not stable under our temperature conditions. Figure 3.6.D presents the refined space of polygons, using the color scheme from panel C to indicate their self-binding capabilities.

Inter-binding requirements

Having curated a list of candidate healthy and prionic polygons, we can now identify pairs, (H, P), that adhere to our interaction rules and objectives. Let \mathbf{x}_H and \mathbf{x}_p be the external nodes corresponding to the healthy and prionic polygons, respectively. We use the same fitness methodology we employed for self-binding to evaluate their inter-binding characteristics. We filter pairs according to the following rules:

- 1. $f(H, P) \leq f(P, P)$; this requirement enforces that the binding strength between prions is at least equivalent to the strength of the healthy-prion bond.
- 2. $f(H, P) \leq f(H, H) + \Delta f$; this requirement enforces that the bond between a healthy structure and a prion takes precedence over the self-binding of two healthy structures. This requirement facilitates the lock and key mechanism detailed in the main text (see Figure 3.6.E).
- 3. Paired subsets of bonded nodes in the H P and P P bindings must be identical, thereby enabling healthy structures to transform into prions.

For this study, to ensure imperfect H - P binding, we set $\Delta f = 0.5$.

Placement of internal nodes

The pentagons we select as candidate mechanical prions are not rigid but instead possess conformational degrees of freedom. Nevertheless, they must maintain rigidity to preserve their shape in a



Figure 3.6: **Space exploration and prion design. A.** Pentagon space. Each point denotes a 2D pentagon structure. This space is topologically equivalent to a four-torus. Shadows represent projections on three axes. **B.** Polygon criteria. External polygons must meet two primary conditions: a specified minimal angle and no self-intersections. (Continued.)

Figure 3.6: (Previous page.) **C.** Self-binding criteria. Polygons vary in their capabilities. Lowfitness polygons can primarily interact through pairs of nodes with themselves, whereas high-fitness polygons exhibit more interacting nodes, resulting in enhanced bound stability.**D.** Filtered pentagon space. Polygons in this set adhere to the criteria outlined in panel B and are color-coded consistent with panel C. The space now appears fragmented, with prions frequently located at the ends of elongated filaments. **E.** Boundary Mismatch. The mechanism necessitates a mismatch in the interacting boundaries of the two polygons. This discrepancy elevates the potential energy and facilitates a shift in the pathway. **F.** Internal Nodes. Pairs are derived from the sets of healthy polygons and prions. Internal nodes and edges (depicted in blue) are positioned to ensure zero potential energy for both external conformations. A potential energy barrier separates these two conformations. **G.** Prionic Behavior. The search procedure identifies structures that, similar to prions, prefer a specific conformation during interactions.

bath. We enforce rigidity by adding n_{in} nodes to the interior, thereby reducing the conformational degrees of freedom to zero. To avoid states of self-stress, we connect internal nodes to a smaller subset of external nodes. If H represents the energy of a mechanical structure, then the equation $\frac{\partial H}{\partial \mathbf{x}} = 0$ admits only rigid-body transformations as its solutions [97]. Therefore, if we set $n_{in} = 1$, it follows that $|\mathcal{E}_{H}^{xy}| = 4$. Given that we only consider the space of pentagons, this choice would considerably restrict potential dynamics, as all nodes, barring one, would connect to the sole central node. Therefore, we set the number of internal nodes n_{in} to two. The corresponding number of internal-to-external edges is given by

$$\left|\mathcal{E}_{H}^{xy}\right| = 2n_{in} + n_{ext} - 3,\tag{3.3}$$

where $n_{ext} = 5$ denotes the number of external nodes.

Let \mathbf{y}_H and \mathbf{y}_P denote the positions of internal nodes in the healthy and prionic configurations and let \mathcal{E}^{xy} represent the set of edges connecting internal nodes to external nodes. Given the locations of external nodes, \mathbf{x}_H and \mathbf{x}_P , our goal is to determine \mathbf{y}_H and \mathbf{y}_P , such that,

$$d(\mathbf{x}_{H}^{(i)}, \mathbf{x}_{H}^{(j)}) = d(\mathbf{x}_{P}^{(i)}, \mathbf{x}_{P}^{(j)}) \qquad \forall (i, j) \in \mathcal{E}_{H}^{xy}.$$
(3.4)

By setting this condition, we ensure that every edge in \mathcal{E}^{xy} has a consistent edge length in both the healthy and prionic structures.

We evaluate random edge allocations of \mathcal{E}_{H}^{xy} for every pair H and P. The Maxwell-Calladine equation does not specify node positions or edge lengths, r_{ij} . Therefore, we use a conformational solver to determine \mathbf{y} [101]. We try 10000 solutions for each pair with a length discrepancy tolerance of 0.01ℓ , discarding duplicate solutions. We then sample the identified manifold to ensure complete coverage. In our model, their solutions are independent since the internal nodes do not interact with each other through edges. Consequently, the complete manifold is the product of the manifolds for each individual internal node. Figure 3.9 presents an illustration of such a manifold. The lengths of all edges r_{ij} are consequently established by determining the position of the internal nodes and their connection topology.

3.9.2. Energy landscape

In this section, we detail the process of identifying the minimum energy path between two conformations of a mechanical structure. This analysis aims to pinpoint pairs of structures that show decreased activation energy when interacting with the prionic conformation. We specifically look for pairs of structures, H and P, where the energy barrier to transition from H to P is reduced when a P is bonded to both H and P. If the energy barrier increases or remains the same, it would not lead to the formation of a prion because in these structures, transitioning to the P conformation while bound would not be facilitated (a crucial characteristic of prions). This step is what disrupts the rate symmetry in the system.

We use Lennard-Jones potentials for inter-node interactions and model edges using Hookean spring

dynamics. This non-rigid bar construction enables the system to explore states beyond the zeroenergy manifold at temperatures above absolute zero [99].

The total energy of a set of structures $\{1, \dots, M\}$ is denoted as $H(\mathbf{X}_{1,M})$, where $\mathbf{X}_{[1,m]} = (\mathbf{x}_1, \dots, \mathbf{x}_M)$ represents the kinetic (E_{kin}) , bond (U_{bond}) , and interaction (U_{int}) energies such that

$$H(\mathbf{X}_{[1,M]}) = \sum_{k \in \{1,\dots,m\}} E_{kin}(\mathbf{x}_k) + U(\mathbf{x}_k, \mathbf{X}_{[1,M]}),$$
(3.5)

$$U(\mathbf{x}_k, \mathbf{X}_{[1,M]}) = U_{bond}(\mathbf{x}_k) + U_{int}(\mathbf{x}_k, \mathbf{X}_{[1,M]}),$$
(3.6)

$$E_{kin}(\mathbf{x}_k) = \frac{m}{2} \sum_{i \in \mathcal{V}} \dot{\mathbf{x}}^{(i)} \cdot \dot{\mathbf{x}}^{(i)}, \qquad (3.7)$$

$$U_{bond}(\mathbf{x}_k) = K \sum_{(i,j)\in\mathcal{E}} (d_{kl}^{(i,j)} - r_{ij})^2,$$
(3.8)

$$U_{int}(\mathbf{x}_k, \mathbf{X}_{[1,M]}) = 4\epsilon \sum_{l=1}^{M} \sum_{\substack{i \in \mathcal{V}_k \\ j \in \mathcal{V}_l}} \left(\frac{\sigma}{d_{kl}^{(i,j)}}\right)^{12} - \left(\frac{\sigma}{d_{kl}^{(i,j)}}\right)^6,$$
(3.9)

where $d_{kl}^{(i,j)}$ is the distance between nodes *i* and *j* and r_{ij} is the relaxed length of the corresponding bond. We employ the Nudged Elastic Band (NEB) method [132] as implemented in LAMMPS [104] to compute the static scenario and assess the activation energy between the two conformations. The NEB method is a computational technique to find the most probable transition pathways between an initial and final system state (here, the two conformations). It uses a series of copies of the system (replicas) connected by virtual elastic bands to map the energy landscape between two states, thereby allowing for the identification of the minimum energy path and associated energy barriers. In the bonded scenario, as an initial approximation, we replace bonded nodes with a single node and adjust the mass proportionally. The initial configuration is represented by the HP dimer and the final configuration is by the PP dimer. An initial relaxation step guarantees that the newly associated structures will settle into their nearest energy minimum. For both cases (bonded and free), we use a step size of 0.001 with 12 replicas.

For every pair of candidate polygons and every solution of interior nodes, we compute the free (E_A^{free}) and bound (E_A^{bound}) transition energies. Any structure where

$$E_A^{bound} \ll E_A^{free},\tag{3.10}$$

should act as a prion. However, this may not always be the case due to the limitations of the NEB technique. NEB can get stuck in local minima, especially when multiple pathways exist, or the energy landscape is non-convex. Moreover, the method only offers a static representation of the energy landscape, neglecting any evolution with time. Nonetheless, given that the NEB approach is several orders of magnitude faster than conducting extended dynamic simulations, it proves valuable in screening potential prions. We address these shortcomings through dynamic analysis to verify that the candidate structures discovered by NEB are indeed prions.

3.9.3. Dynamical Analysis

Dynamical simulation We begin by detailing the thermal bath simulation methodology and the structures' dynamics in their respective unbound and bound states. We simulate the dynamics of conformational change using the Langevin formalism as operationalized in the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS). We can write the force on a node i as

$$F^{(i)}(\mathbf{x}_k, \mathbf{X}_{[1,M]}) = -\nabla U_m(\mathbf{x}_k, \mathbf{X}_{[1,M]})$$
$$-\gamma * m * \dot{\mathbf{x}}_k^{(i)} + F_{k,sol}^{(i)},$$

where $\nabla U_m(\mathbf{x}_k, \mathbf{X}_{[1,M]})$ represents the gradient of potential energy of the system. The second term, $\gamma * m * \dot{\mathbf{x}}_k^{(i)}$, represents the frictional drag and/or viscous damping. For normalization, we set the damping coefficient γ to 1. The third term, $F_{k,sol}^{(i)}$, is the force exerted by the imaginary



Figure 3.7: The system's properties. A. Energy landscape attainable from the two conformations (healthy, prion) at the temperature under analysis. Conformations are projected onto the 2D plane using principal components analysis (PCA). The red trajectory indicates the minimum energy path between the two conformations in the free case. B. Illustration of the external shape manifold used to study its impact on prionic properties.

solvent particle that exchanges energy with the nodes through random interactions with a magnitude controlled by the temperature T. This force has a magnitude proportional to $2\gamma Tm$ [104].

In our simulations, for every candidate pair that showed a promising energy landscape, we analyze their dynamical properties for temperatures ranging from $1e^{-8}\frac{1}{\epsilon}$ to $1e^{-3}\frac{1}{\epsilon}$. We simulate 12000 time points and record the positions of all structures at 600 evenly spaced instances. We double the number of time steps during every run of the simulation until convergence is achieved. Simulations start in one of three configurations, each featuring 30 structures within a 15×15 box. In the first two configurations, we assess the stability of the healthy and prionic structures. The last configuration consists of pairs of prions and healthy structures. We position the pairs near their binding sites to facilitate interaction during simulation.

Analyzing trajectories of conformational change In the manuscript, we examine *in silico* trajectories of conformational change. We assign labels to intermediate states during simulations and analyze the resulting coarse-grained sequences assuming the Markov property. The labels denote

one of three general states: healthy, prionic, or denatured. To assign these labels, we compute distances between each intermediate state and the prionic and healthy configurations. For a given structure in conformation c, let Δ be the set of all triplets of connected nodes (i, j, k), and let θ_{ijk}^c be the angle between them. We define the distance D as

$$D(\mathbf{x}_k, c) = \sum_{(ijk)\in\Delta} (\theta_{ijk}^c - \theta_{ijk}^k)^2$$

We first measure the distance between the healthy and prionic states, $D_{max} = D(H, P)$. For structure k, we then measure distances to the healthy and prionic configurations as $D_H = D(\mathbf{x}_k, H)$ and $D_P = D(\mathbf{x}_k, P)$, respectively. If both D_H and D_P exceed D_{max} , we label k as being denatured. Otherwise, we assign the label corresponding to the smaller value between D_H and D_P .

To facilitate visualization of dynamics we perform principal component analysis (PCA) on the set of all conformations. This process allows us to project states at all temperatures to the nearest point on the reaction pathway. Specifically, we compile all θ_{ijk}^c as row vectors into the data matrix containing all time points and apply PCA, defining reaction coordinates as the first principal component. This process is carried out dynamically across our extensive spectrum of analyzed temperatures, all within the same matrix, to capture the complete range of motion. This component accounts for more than 95% of the data variance (see Figure 3.7.A). Despite its utility, this approach requires extended numerical simulations to acquire data for PCA at all temperatures. Therefore, we reserve this method for plotting and use an alternative, simpler approach for simulations.

Rate computation We compute reaction rates and steady-state ratios from coarse-grained sequences of conformational states modeled as Markov processes. Rate curves are adapted to fit a modified Arrhenius equation, as described in [109], of the form:

$$k = k_{\infty} \exp\left[-\frac{E_A}{R(T-T_0)}\right]$$



Figure 3.8: Role of external nodes. The prioric behavior is examined as a function of the mismatch distance, Δ , between the pair of priors and healthy conformations. Each pair features similar internal node positions and minor differences in external geometries compared to the example provided in the paper.

3.9.4. Additional considerations

Properties of the External Node

In this section, we describe how we analyze the impact on the prionic property of the external node. The goal is to study slightly deformed polygons with similar internal structures and assess the effects of such deformations. To achieve this goal, we begin with the initial pairs from the main text and choose polygons close to the prionic external polygon within the filtered manifold (see Figure 3.6.D). The manifold segment resembles an arrowhead, as shown in Figure 3.7, where the vertical axis in the illustration corresponds to the base angle. At the top, the symmetric case is observed, and mirror reflection along the vertical axis appears on either side of the arrowhead. The dimension corresponding to the arrow's thickness is associated with the cusp angle. At this stage, only the external polygon is present. Internal nodes are introduced to minimize the distance to the

original prion. This aim is achieved by navigating the manifold formed by the internal points and selecting the nearest one.

The difference, Δ , is determined by the initial distance between nodes positioned for binding before the actual interaction. A higher value suggests a lesser fit between the two shapes, implying increased stress during their interaction. The difference in activation temperature, called here prionicity, is defined as

$$\Pr(\mathcal{V}, \mathcal{E}) = \frac{T_{free} - T_{bound}}{T_{free} + T_{bound}},\tag{3.11}$$

where T_{free} and T_{bound} represent the minimum temperatures at which over 40% of the limit distribution consists of prions in the free and bound scenarios, respectively. The 40% threshold is selected as it is below the typical 50% (even mixture) observed for the free case.

In Figure 3.8, we plot prionicity, Pr, as a function of the mismatch, Δ , between the key-lock areas for various mechanical prions. All prions share nearly identical internal and external shapes, with the exception of the external lock region. We measure Δ as the smallest distance at which nodes from the key and the lock can be paired in P-H dimers without forcing conformational changes. We find that prionicity increases with increasing key-lock mismatch.

Properties of the Internal Nodes

In this section, we examine the influence of internal nodes on the prionic behavior of mechanical structures. We begin by detailing some of their characteristics and then provide insights into the methodology employed to reach these conclusions.

As mentioned earlier, an important property of the placement of the internal node in our framework is that the lengths of the edges between the internal and external nodes must be the same in both conformations to meet the system's energy requirements. Therefore, given the external shape, the number of internal nodes, and their connections to the external nodes, the internal nodes can only occupy certain positions within the polygon. Figure 3.9.A) displays the potential positions that



Figure 3.9: Role of internal nodes A. The prionicity, a metric used to quantify the reduction in transition temperature caused by the interaction of the dimer compared to that of the individual monomers, as a function of the position of the two internal nodes. B. The transition temperature of the prion. C. The prionicity as a function of the mismatch distance Δ for a pair of prions and healthy conformations with distinct internal nodes and minimal variations in their external shapes.

the internal node can assume for the primary structure discussed in the paper. The internal node's position in the healthy structure dictates its location in the prion and *vice versa*. Furthermore, the positions of the individual internal nodes are independent of one another. In this particular polygon, with its distinct connection pattern to the external node, the potential placement space for internal nodes is largely characterized by near-linear trajectories. Specifically, two separate connected components define the placement set for one node. While these sets are not always strictly linear, they predominantly tend to be. Given that no edges are connecting them and the external polygon is fixed *a priori*, the two systems of equations operate independently. Therefore, the solution space for both nodes in our system is the product of the solution space for each node. Consequently, the design of our example prion has two additional degrees of freedom, which affect its stability and transition temperature.

The system's prioricity exhibits intricate variations based on the internal node's position, yet it maintains a similar magnitude between the two connected components of the domain (see Figure 3.9.B). The white point indicates the position of the structures shown in the paper. Given its closeness to a region with reduced prioricity and more favorable zones, this placement might appear

counterintuitive. However, this choice was driven by two primary factors. First, it was chosen because its transition temperature was within our desired range: not so high as to complicate convergence in large-scale numerical simulation, yet not so low as to render the physical model unstable (see Figure 3.9.C). Second, to construct the physical model, the central nodes must not interfere with one another and remain sufficiently distant throughout the standard range of motion to avoid interaction. While the present selection can be further optimized, it sufficiently demonstrates the effect while potentially leaving room for enhancement. Interestingly, most positions of the interior nodes give rise to valid prions that perform adequately, implying that precise placement of the interior nodes is less critical.

The relation between prioricity and the transition temperature is quite complex, as the internal node placement affects T_{free} and T_{bound} differently. The temperatures T_{free} are shown in Figure 3.9.C, where we observe a stark contrast between the two disconnected regions of the solution space. T_{free} also indicates that the two internal nodes engage in synergic interactions. Thus, even though their placements, based solely on energy levels, appear independent, the final selection must consider their interactions.

3.9.5. Experimental Demonstration

This section provides insights into constructing the macroscopic model and elaborates on the experimental setup employed. We created a macroscopic model for proof of concept, featuring external edges of 57.80 mm in length (see Figure 3.10.A). To accurately replicate our design, we needed to devise edges capable of extending and retracting based on a harmonic potential. Fortunately, the model's performance is not critically dependent on the exact specifications of its components. We chose two types of edges that, while not perfectly matching the desired properties, still ensure the system's functionality. The first type, similar to a spring, contracts readily but exhibits limited extension capabilities (see Figure 3.10.B). The second type, similar to a leaf spring, offers superior extension properties compared to the first but is less robust (see Figure 3.10.C). Either can serve



Figure 3.10: Macroscopic model drawing. A. Edge dimensions with color-differentiated layers shown in the inset in millimeters. The lengths of these edges closely align with the structure presented in the paper. Any variations in length may be attributed to the precision level maintained during the construction phase. The arrangement prevents overlaps and collisions. B. The primary edge type in the model. The central zigzag functions as a rigid spring, with force modulated by the zigzag's thickness (0.8 mm) and the edge's thickness (3 mm). C. The secondary edge type, utilized only once in the actual model, offers a broader range of expansion and contraction. While the entire model could be constructed using this edge type, it would compromise the desired aesthetic appeal. D. For the primary edge type, occasional translations or rotations of the spring component are necessary to prevent collisions.

as the primary edge type for the structure independently, but employing both proved effective. In the physical realm, edges cannot pass through one another, which is a fundamental distinction from our simulation. This characteristic necessitates careful consideration and adaptation in our macroscopic model. We employed edges modified with off-center springs for the central nodes to address this issue, as depicted in Figure 3.10.D. Additionally, we arranged the edges over several layers, as illustrated in Figure 3.10.A, incorporating an unused layer to accommodate the sagging of the central nodes.

All edges were 3d printed using ultraviolet-sensitive resin and assembled with Chicago screws, as depicted in Figure 3.11. 3R mm rare earth magnets were affixed to the screw's bottom to allow interaction between the external nodes, and a printed cap was added for centering. The cap's thickness was calibrated to regulate the holding force between nodes, thereby ensuring that structures remain bound when three nodes interact, but not when only two nodes interact.

In the experimental setup, an arm measuring 100mm in length is manipulated by a stepper motor. The structures are attached to the arm via one of their nodes, leveraging the pre-existing magnet (see Figure 3.11.C). The stepper motor undergoes oscillations spanning 1 radian for 20 cycles in the experimental setup. Between each oscillation set, the conformation is reset, and the angle of the structure around its attachment point to the arm is randomized. In the experiment, the speed is regulated by the number of steps, each measuring 1.8 degrees, ranging from 50 to 250 steps per second. Conformations were manually assessed, given the straightforward nature of the task and the macro structure's distinct transition to the prion conformation. Due to the limited extension range of the edges, the macro model is constrained to transition only between the healthy and prion conformations. Unlike the computational model, the physical version necessitates disassembly for denaturation and is susceptible to breakage under excessive force.



Figure 3.11: Macroscopic model experiment. A. Experimental setup featuring two interacting structures agitated by a stepper motor. B. Schematic of the fully assembled macroscopic model used in the experiment.

CHAPTER 4

QUADRUPOLAR RESONANCE SPECTROSCOPY OF INDIVIDUAL NUCLEI USING A ROOM-TEMPERATURE QUANTUM SENSOR

This chapter is in press as Breitweiser, S. Alex^{*}, Mathieu Ouellet^{*}, Tzu-Yung Huang, Tim H. Taminiau, and Lee C. Bassett. "Quadrupolar resonance spectroscopy of individual nuclei using a room-temperature quantum sensor." arXiv preprint arXiv:2405.14859 (2024) [133]. As the co-first of this paper, I was responsible for conceptualizing the research questions, analyzing the data, and drafting the manuscript.

Nuclear Quadrupole Resonance (NQR) spectroscopy detects interactions between nuclear electric quadrupole moments and local electric field gradients, aiding the study of molecular structures at low bias magnetic field [134, 135, 136]. NQR spectroscopy is widely applied in security for explosive and drug detection [137, 138, 139], pharmaceutical analysis of powders [140, 141, 142], and thermometry [143, 144]. Due to the unique fields experienced by nuclei at each site, set primarily by the valence electrons and, therefore, the corresponding chemical bonds, NQR studies reveal a wealth of information that can be used to identify and characterize molecules and bulk materials. However, due to the small magnetic signal generated by each nucleus, traditional radio-frequency NQR is limited to use with macroscopic samples that contain large nuclear ensembles. The ability to perform NQR on individual nuclear sites would open up the possibility of studying molecule-to-molecule variations and dynamical changes due to local fields and structural changes, *e.g.*, protein folding and drug-target interactions.

Quantum sensors based on optically active defects in semiconductors allow for investigations of much smaller nuclear ensembles. Defect-based quantum sensors such as the diamond nitrogen-vacancy (NV) center host electronic spin states that can be initialized and measured with laser light and manipulated with microwave signals at room temperature. The electron spin qubits interact with proximal nuclear spins through unique magnetic hyperfine couplings that are determined by their positions [145]. Using Dynamical Decoupling (DD) control sequences, it is possible to resonantly amplify these hyperfine couplings [146], allowing high precision characterization and control of individual nuclei [147, 148, 149, 150, 151, 152]. NV-center quantum sensors have been employed along with DD sequences to perform NQR spectroscopy of small nuclear ensembles in deuterated molecules [153] and in hexagonal boron nitride crystals [154, 155]. In other regimes, NV-center ensembles have been used to boost the sensitivity of traditional NQR detectors for macroscopic powder samples [136]. However, accessing individual nuclei and retrieving their quadrupolar Hamiltonian has remained an open challenge.

In this work, we demonstrate DD-based, room-temperature NQR spectroscopy of the nitrogen-14 (^{14}N) nuclei intrinsic to individual NV centers. In this way, the NV centers serve as both quantum sensors and as analogs of individual molecules. The measurements reveal considerable variations in the ^{14}N quadrupolar and hyperfine parameters among different NV centers, as well as a previously unreported term in the nuclear quadrupolar Hamiltonian that results from symmetry breaking. We further observe correlations between the nuclear Hamiltonian parameters and the electronic Zero-Field Splitting (ZFS) parameters, highlighting the potential of NQR spectroscopy to reveal details of local chemical structure and deformations due to electric or strain fields. Finally, we design and implement DD sequences that utilize the ^{14}N quadrupolar Hamiltonian to facilitate initialization and arbitrary quantum control of the ^{14}N nuclear spin.

4.1. Electron-nuclear interactions in diamond NV centers

The NV center (Figure 4.1a) consists of one substitutional ¹⁴N coupled to a vacancy in the diamond lattice. In its negatively charged state, the NV center hosts an electronic spin-1 state that undergoes a spin-dependent optical pumping transition, allowing the spin state to be initialized and read out optically [156]. This electronic spin interacts with the intrinsic ¹⁴N nuclear spin within the NV center ($\approx 99.7\%$ spin-1 ¹⁴N in natural abundance), as well as with ¹³C nuclei in the surrounding



Figure 4.1: Electron-nuclear interactions in ¹⁴NV centers (a) Model of a diamond NV center located within a solid immersion lens, composed of an electronic spin (purple) coupled to a ¹⁴N nucleus (blue).(b) Pictoral representation of the Hamiltonian terms for ¹⁴NV. (c) Schematic of a DD spectroscopy sequence. Initial and final $\frac{\pi}{2}$ pulses are in opposite directions, while decoupling π pulses are XY8 symmetrized. (d) DD NQR features corresponding to the $|m_I = \pm 1\rangle$ to $|m_I = 0\rangle$ transitions (dips marked purple and red) appear in the presence of an off-axis magnetic field (N = 64, B = 193 G). A third series of dips corresponding to the $|m_I = \pm 1\rangle$ transition (marked green) appears due to the quadrupolar asymmetry parameter, even without an off-axis magnetic field. Panel (b) displays the energy levels associated with the peaks. (e) DD spectra for two different NV centers (blue and orange), here with N = 32 pulses repetitions, reflect significant differences in the ¹⁴N quadrupolar Hamiltonian. Data are shown with markers, along with best-fit simulation results as dashed lines.

diamond lattice (spin- $\frac{1}{2}$, $\approx 1.1\%$ natural abundance) and any other nearby nuclear spins. In the isotropic case, ignoring the effects of strain or electric fields, the general Hamiltonian comprising the electron spin interacting with a single nuclear spin is given by

$$H = DS_z^2 + E(S_X^2 - S_Y^2) + \gamma_e \vec{B} \cdot \vec{S} + H_{\text{quad}} + H_{\text{hf}} + \gamma_n \vec{B} \cdot \vec{I}, \qquad (4.1)$$

where $\vec{S} = (S_X, S_Y, S_Z)$ is the electronic spin operator, $\vec{I} = (I_X, I_Y, I_Z)$ is the nuclear spin operator, γ_e (γ_n) is the electronic (nuclear) gyromagnetic ratio, and $B = (B_X, B_Y, B_Z)$ is the external magnetic field. Figure 4.1b shows this Hamiltonian diagrammatically for the specific example of the NV-center's intrinsic ¹⁴N nucleus. The first two terms represent electronic zero-field splitting (ZFS), followed by the Zeeman term for electronic spins. This is succeeded by the nuclear quadrupolar term and hyperfine coupling and the Zeeman term for nuclear spins. The term $H_{\rm hf}$ represents the hyperfine interaction, which takes the general form

$$H_{\rm hf} = \vec{S} \cdot \mathbf{A} \cdot \vec{I} \tag{4.2}$$

where **A** is the hyperfine interaction tensor. For ¹⁴NV, $H_{\rm hf}$ takes the simplified form:

$$H_{\rm hf} = A_Z S_Z I_Z + A_\perp (S_X I_X + S_Y I_Y), \tag{4.3}$$

where A_Z and A_{\perp} are the parallel and perpendicular hyperfine coupling strengths. The second term in Eq. 4.3 generally does not affect the electron-nuclear dynamics due to the large mismatch in energy splitting between the electron and nuclear spin states, leaving the parallel term as the primary hyperfine-coupling effect.

The term H_{quad} represents the nuclear quadrupolar Hamiltonian, which is nonzero for nuclear species

with total nuclear spin $I \ge 1$. The quadrupolar Hamiltonian can, in general, be written as [157]

$$H_{\text{quad}} = \frac{eQV_{ZZ}}{4I(2I-1)} [3I_Z^2 - I(I+1) + \frac{V_{XX} - V_{YY}}{2V_{ZZ}} (I_+^2 + I_-^2)]$$
(4.4)

where e is the electron charge, Q is the quadrupolar moment unique to each nuclear isotope, $V_{ZZ} = \partial^2 V/\partial z^2$ is the electric field gradient along the principal nuclear axis, and V_{XX} and V_{YY} are the electric field gradients in the perpendicular plane. The principal axes are chosen so that $|V_{ZZ}| > |V_{XX}| > |V_{YY}|$, and the electric field gradient is diagonal in this basis. For a particular nucleus, Eq. (4.4) takes the simplified form

$$H_{\text{quad}} = PI_Z^2 + \alpha (I_+^2 + I_-^2), \qquad (4.5)$$

where P and α are constant parameters representing the quadrupolar splitting and asymmetry parameters, respectively.

Although the nuclear quadrupolar Hamiltonian term is distinct from the electronic spin, its effects on the electronic spin can be observed *via* the hyperfine interaction using DD sequences as shown in Figure 4.1c. Transverse terms in $H_{\rm hf}$ (the second term in Eq. 4.3) lead to rotations of the nuclear state that depend on the electron spin projection. DD sequences amplify this interaction since multiple small rotations accumulate when the spacing between pulses is resonant with the hyperfine-shifted frequency of the nuclear Larmor precession, causing resonant series to emerge in DD spectra [146].

Figure 4.1d shows an example of a DD NQR spectrum in which three distinct resonance series can be observed. The series correspond to electron-spin-dependent transitions between the ¹⁴N nuclear states as indicated in Fig. 4.1b. As discussed in the next section, the physics responsible for transitions between nuclear states with $|m_I = 0\rangle \leftrightarrow |m_I = \pm 1\rangle$ is different from those transitions between $|m_I = \pm 1\rangle$ states. Nevertheless, the observation of all three resonance series constitutes a complete measurement of the nuclear quadrupolar Hamiltonian (Eq. 4.5), together with A_Z . Since the DD sequence extends the coherence lifetime of the electronic spin, this method allows extremely precise determination of P for each nucleus and also reveals the existence of small α Hamiltonian terms that had previously not been detected nor considered [156].

4.2. DD NQR spectroscopy

The ¹⁴N nucleus intrinsic to the NV center represents a convenient testbed to illustrate the physics of DD-based NQR. Ideally, the C_{3v} symmetry of the NV center should cause the asymmetry quadrupolar parameter α to vanish. Moreover, in the presence of a purely longitudinal magnetic field ($B_X = B_Y = 0$), the axially-symmetric hyperfine Hamiltonian of Eq. 4.3 does not generate nuclear spin rotations under DD sequences, since the magnetic field direction experienced by the nucleus is independent of the electron spin projection. In real systems with reduced symmetry, however, both of these conditions are relaxed.

In the presence of a weak transverse magnetic field $(B_X \ll B_Z)$ an effective perpendicular hyperfine coupling term appears due to spin mixing [158], leading to an approximate hyperfine Hamiltonian given by

$$H_{\rm hf} \approx A_Z S_Z I_Z + F \frac{\gamma_N B_X A_\perp}{\gamma_e B_Z} S_Z I_X, \tag{4.6}$$

where F is a constant that is particular to the ¹⁴N nuclear isotope [159]. Previous authors have used this effective hyperfine interaction to observe nuclear quadrupolar interactions for NV ensembles using electron spin-echo envelope modulation [160], to perform dc vector magnetometry using single NV centers [159] and to realize high fidelity gates [161]. We use it in order to quantify the quadrupolar Hamiltonian parameters *via* DD NQR spectroscopy. In a DD control sequence with appropriate pulse spacing, the $S_Z I_X$ term in the effective hyperfine Hamiltonian facilitates electronspin-dependent rotations of the ¹⁴N spin (see Figure 4.1c), in analogy with the case for 13C nuclei [146]. The rotations manifest in DD spectra as two distinct resonance series, each corresponding to one of the $|m_I\rangle = 0$ to $|m_I = \pm 1\rangle$ transitions, with spacing given by

$$\tau_k \approx \frac{(2k+1)\pi}{2P \pm A_z \mp \omega_N} \tag{4.7}$$

where $\omega_N = \gamma_N B$.

Figure 4.1e shows the DD NQR spectra obtained by sweeping the pulse spacing near two such transition resonances for two different NV centers. The shift in resonance position reflects differences in P and A_Z for these two NV centers. We use numerical simulations to fit DD NQR spectra acquired using different N around these two resonances; see Supplementary Material I.

Table 4.1 shows NQR spectroscopy results for six NV centers located within the same diamond sample (Supplementary Fig. 3). Interestingly, the values of P and A_Z show a variance one order of magnitude larger than the measurement uncertainty. In particular, NV A exhibits values for P and A_Z that differ by several kHz from the other NVs in this sample. NV A is also the only NV under a diamond solid immersion lens (SIL). These milled structures are used to minimize optical losses caused by total internal reflection and spherical aberration (See Figure 4.1a) [162, 163]. Yet, they are recognized to influence the local strain field at the NV centers [164], consequently affecting the NV Hamiltonian[165, 166].

NV	\mathbf{D} (MHz)	\mathbf{E} (MHz)	$\mathbf{A}_{\mathbf{Z}}$ (kHz)	\mathbf{P} (kHz)	β
А	2859.20(2)	8.33(4)	2168.1(1)	4934.9(1)	0.0016(2)
В	2870.47(2)	7.51(4)	2164.7(1)	4939.5(1)	0.0039(3)
С	2870.39(2)	7.63(4)	2163.5(5)	4939.4(2)	0.0095(4)
D	2870.37(1)	7.58(3)	2165.0(3)	4939.2(1)	0.0175(6)
Е	2872.20(3)	7.58(4)	2162.9(4)	4936.9(2)	0.0205(4)
F	2870.41(2)	7.04(3)	2162.9(4)	4940.7(2)	0.0082(4)

Table 4.1: Electronic ZFS, hyperfine, and ¹⁴N quadrupolar parameters for each NV studied.



Figure 4.2: Forbidden transitions (a) Evolution of the nuclear spin in the $|m_I = \pm 1\rangle$ manifold when the electronic spin is in the state $|m_s = 0\rangle$ (blue) and $|m_s = -1\rangle$ (red) for a tuned DD sequence with N = 12. (b) DD spectroscopy data for NV A (blue points with dashed line) and simulation (solid orange curve) for N = 32. (c) The measured electron spin projection (blue markers) as a function of N for fixed $\tau = 1.372 \,\mu$ s (black marker in (b)) agrees with simulations (solid orange curve). (d) DD spectroscopy data as a function of τ and N, which is fit using simulations (e) to determine the value of α . Error bars in (d) are comparable to those in (b) and (c). (f) Detection limit for α as a function of β for tuned DD sequences with different N; the detection limit is the situation where the signal-to-noise ratio exceeds 1. The noise floor is assumed to be constant at $P(|0\rangle) = 0.2$. The shaded area represents the detection threshold for the sequence applied experimentally. The star marks the value for NV A.

4.3. Forbidden quadrupolar transitions

Although the α_i term in the ¹⁴N quadrupolar Hamiltonian vanishes for the ideal case of C_{3v} symmetry, local perturbations such as strain and electric fields can distort the electronic wavefunctions, leading to nonzero transverse electric-field gradients at the ¹⁴N position. When α is nonzero, the second term in Eq. (4.5) directly couples the $|m_I = -1\rangle$ and $|m_I = +1\rangle$ nuclear states, causing nuclear transitions to occur that are typically symmetry forbidden. Figure 4.2a illustrates these dynamics for a suitably tuned DD sequence, whereby the nuclear spin evolves in the $|m_I = +1\rangle$ manifold according to slightly different rotation axes depending on the electronic spin state; after many pulses, the nuclear spin evolves into orthogonal spin states. The resulting entanglement between electronic and nuclear spins manifests as a reduced signal amplitude for these carefully tuned pulse sequences. DD spectroscopy of NV A (Fig. 4.2b) reveals the presence of these forbidden transitions as a series of sharp, periodic resonances with a spacing given by

$$\tau_k \approx \frac{(2k+1)\pi}{2(A_Z - 2\omega_N)},\tag{4.8}$$

where $\omega_N = \gamma_N B$. The Supplementary material VI includes a derivation of this expression.

In analogy to the typical phenomena of DD resonances (as in Fig. 4.1c), whereby A_{\perp} induces S_z -dependent rotations between states with $\Delta m_I = 1$, here the nonzero α term induces S_z -dependent transitions between $|m_I = \pm 1\rangle$ states. When α is small, many pulses are needed in order to accumulate a measurable rotation angle. Figure 4.2c shows the evolution of the DD signal as a function of N; the contrast is reduced by approximately $\frac{1}{3}$ due to the thermal occupation probability of the uncoupled $|m_I = 0\rangle$ state. By varying both τ and N (Fig. 4.2f) around a particular resonance, we map out the full dynamics of these forbidden quadrupolar resonances. A fit using numerical simulations (Fig. 4.2f) yields a best-fit value of $\alpha = 2\pi \times 2.429(12)$ kHz. The ratio $\alpha/P = 5 \times 10^{-4}$ illustrates how a tiny Hamiltonian parameter can have a substantial impact on nuclear dynamics and be measured with high precision using DD spectroscopy.

The sensitivity of the DD-based measurement is limited by intrinsic decoherence mechanisms (captured by T_2) and by pulse errors [167]. For the sequences we consider, the total experimental sequence times are much shorter than the intrinsic decoherence time (typically $T_2 \approx 1$ ms at room temperature), and the contrast decay is dominated by pulse errors, which we model using an exponential envelope, $e^{-\beta N}$. This envelope constrains the practical detection limit of α , shown in Figure 4.2b as a set of curves for different N as a function of β .

Of the six NV centers we studied, we only observed forbidden transitions for NV A. We propose two reasons for this observation. First, NV A may experience larger-than-average symmetry breaking from transverse strain or electric fields due to its location at the center of a milled SIL, and hence a larger value of α . This is supported by measurements of the electronic ZFS D and E (Table 4.1) are significantly different than for other NV centers in the sample. Moreover, NV A features the smallest β of the sample and, subsequently, the lowest detection limit. Figure 4.2f shows the β values for the other NV centers along with a shaded region corresponding to the N < 64 limit we experimentally investigated; we expect that α for these NV centers is outside the detection region.

4.4. Nuclear initialization and coherent evolution

In addition to their use in sensing, DD sequences can be used to achieve precise control over individual spin states [146, 148, 147]. Combinations of conditional and non-conditional gates can be used to construct protocols for nuclear-spin initialization, unitary control, and entanglement with the electron spin [147]. Figure 4.3a shows a sequence used to probe ¹⁴N spin initialization. Here, two DD sequences functioning as CNOT gates transfer the population from the electron to the nuclear spin states, and a subsequent electron-spin free-precession sequence probes the resulting nuclear population. The electron precession exhibits three oscillation frequencies associated with the ¹⁴N spin states, resolved by the A_Z hyperfine coupling (Fig. 4.3b). The relative amplitudes of these three oscillations, extracted from the power spectrum (Fig. 4.3b) reflect the nuclear spin occupation probabilities. In this case, the DD initialization sequence applied to a forbidden transition of NV


Figure 4.3: Initialization and Coherent Evolution (a) Experimental sequence used to probe initialization of the ¹⁴N nuclear spin. (b) Power spectra of the free-precession data acquired without (orange) and with (blue) a DD-based initialization sequence. (c) $|m_I = +1\rangle$ (blue markers) and $|m_I = -1\rangle$ (orange markers) populations fitted from Ramsey data while varying the amount of green time used to reinitialize the electron state. Exponential fits (dotted lines) show the population difference decaying to the steady state values (solid horizontal lines). (d) Pulse sequence used to measure the free induction decay of the ¹⁴N nuclear spin. The nuclear tomography sequence used is described in the Supplementary Material. (e,f) Oscillations of the X (blue markers) and Y (orange markers) projection of the ¹⁴N nuclear spin within the $|m_I = +1\rangle / |m_I = -1\rangle$ manifold during free evolution while the electron spin is in the (e) $|m_S = 0\rangle$ and (f) $|m_S = -1\rangle$ state.

A transfers population from the $|m_I = -1\rangle$ state directly to $|m_I = +1\rangle$, further confirming the physical interpretation of these resonances. More information about the initialization sequences and free-induction measurements is available in the Supplementary Material.

The data in Fig 4.3b show that the ¹⁴N nuclear spin is partially polarized even without the ¹⁴N initialization sequence. This is due to the off-axis hyperfine interaction in the optically excited state [168]. By sweeping the duration of green illumination used to reset the electron spin, the non-equilibrium nuclear population lasts for several microseconds (Figure 4.3c) before returning to the steady state values, consistent with other studies on the ¹⁴N nuclear spin population [169]. Nuclear tomography on the ¹⁴N using the electronic spin confirms the effectiveness of the initialization sequence (Figure 4.3d). Oscillations in the ¹⁴N nuclear spin projection within the $|m_I = +1\rangle / |m_I = -1\rangle$ manifold during free evolution, observable while the electron spin is in the $|m_S = 0\rangle$ and $|m_S = -1\rangle$ states, are evident in Figures 4.3e and 4.3f.

4.5. Comparisons of NQR and ZFS parameters

Figure 4.4 shows the measured values for the ¹⁴N quadrupolar splitting P and hyperfine coupling A_z plotted against the electronic ZFS parameters D and E for each NV center studied. The measurements are clearly correlated, confirming that the nuclear quadrupolar Hamiltonian is influenced by local strain and electric fields that distort the chemical bonds. As discussed earlier, NV A exhibits ZFS parameters that are significantly shifted from the mean, consistent with a large local strain or electric field. NV A is also the only center for which we observed a nonzero α parameters in the ¹⁴N quadrupolar Hamiltonian. Using Equation 4.4, we obtain $V_{zz} = 1.359(7) \times 10^{22} \text{ V/m}^2$, and the fitted value of α for NV A gives a normalized transverse electric field gradient value of $\frac{V_{xx}-V_{YY}}{V_{zz}} = 0.0181(3)$.

4.6. Conclusion

This study introduced a method to measure the quadropolar Hamiltonian of an individual nucleus using a single electronic spin as a sensor. The method enabled the observation of previously



Figure 4.4: Impact of ZFS parameters (a) Measured P parameters for ¹⁴N, derived from DD spectroscopy, plotted against the electron ZFS parameters D and E electron splitting parameters derived from zero-field ESR data. (b) Measured A_z parameters for ¹⁴N, similarly plotted against D and E. Dashed lines indicate linear fits. Error bars are comparable in size to the markers.

unidentified terms in the ¹⁴N Hamiltonian for NV centers, and elucidated correlations between the electronic and nuclear Hailtonian parameters due to distortions of the defect's structure. Compared to existing techniques, this approach offers numerous advantages. Due to the frequency selectivity of DD spectroscopy, each nucleus is uniquely resolved by its hyperfine coupling to the electron sensor. The measurement is also highly local; its sensitivity decreases rapidly with distance since the hyperfine coupling scales as $\sim 1/d^3$, where d is the sensor-target separation; see the supporting information for further details on sensitivity limits. Recent advances in creating and stabilizing shallow NV centers [170, 171], combined with this approach, can potentially allow nanoscale NQR sensors capable of probing individual nuclei at the single-molecule level. This method can also be used to probe nuclei associated with surface groups, or to fingerprint defects inside the bulk. Functionalized nanodiamonds containing NV centers can be suspended in liquid solutions and probed in biochemical environments for *in situ* and *in vivo* chemical sensing applications [172, 173, 174].

One of the significant advantages of the NV center is its surrounding ¹³C ensemble, which can function as a quantum register [147, 175, 176] and enhance sensing capacity [177]. This approach preserves the ability to utilize such techniques. Since the hyperfine and quadrupolar parameters are much stronger than the Zeeman splitting under our experimental conditions, the resonance positions remain stable over a wide range of magnetic field values. Hence, the magnetic field can be tuned for the convenience of the sample/system under study.

The accurate measurement of the asymmetry of the quadrupolar moment is becoming increasingly crucial for precise control and manipulation of quantum systems [178, 179, 180]. Quadrupolar asymmetry plays a role, for example, in semiconductor quantum dots [181] where it is the source of decoherence, and in nuclear spin squeezing [182] where it can be used for control. The ability to detect even the small magnitude of the asymmetry in systems where it is expected to be zero represents a significant advancement.

Similar to other pulsed quantum spectroscopy techniques, the sensitivity of this NQR technique is

limited by T_2 and pulse errors. Pulse errors can be minimized by implementing more sophisticated control schemes [183, 184]. Although T_2 at room temperature is already close to the T_1 limit, it is possible to adapt NMR sensing protocols that surpass the T_2 limit for use with NQR [185]. Additional techniques such as optimizing NV depth [186], improving sample preparation [187], and employing machine learning to compensate for noise [188] will further boost the sensitivity.

4.7. Methods

The experimental sample and optical setup are as described in [189]. NV A is at the focus of a Solid Immersion Lens (SIL) surrounded by a circular antenna used for microwave control. Other NVs studied were within the antenna's range but not within the SIL's focus, leading to reduced optical readout contrast. Magnetic fields were supplied by a permanent magnet and were measured and aligned using the $|m_S = 0\rangle$ to $|m_S = \pm 1\rangle$ ESR transitions of the electronic spin. Magnetic fields for each experiment are listed in the Supplementary Info. For initializing the spin states, long green laser pulses (20 µs) are used to reset the system, while shorter (100 ns) laser pulses are used to reinitialize only the electron spin.

The experiment timing was controlled by a pair of Arbitrary Waveform Generators (AWGs). One (AWG520 Tektronix) was triggered to start the experiment and controlled the optical excitations and collection paths, including the AOM used to turn on the green (532nm) laser used for readout and initialization, and the data acquisition system (National Instruments, PCIe-6323). The AWG520 was also used to trigger another AWG (AWG7102 Tektronix) which was used to control the IQ modulation of a benchtop signal generator (SG384, Stanford Research Systems), which was fed into a high bandwidth mixer (ZX05-63LH+, Mini-Circuits) to allow fast pulses and a high-isolation switch (ZASWA-2-50DR, Mini-Circuits, allowing) to prevent on-resonance leakage from decohering the spin, both of which are also controlled by the AWG7102. Interpolated pulse spacings are used to increase the resolution beyond the hardware limitations [1]. The output was fed through a USB-controlled microwave attenuator (Rudat 6000-60, Mini-Circuits) and broadband amplifier



Figure 4.5: (a) Pulsed ESR and (b) Ramsey data (blue points) from NV A taken with an on-axis field $(B_Z > 0)$. Fits (solid orange lines) are consistent with a model containing only the nitrogen-14 nuclear spin coupling, with no other strongly coupled spins detected.

(ZHL-16W-43-S+, Mini-Circuits) before being delivered into the sample through a custom SMAconnected PCB, which is, in turn, wire-bonded to the antenna traces.

4.8. Appendix

4.8.1. ESR and Ramsey

With natural isotopic abundance, we expect around 1.1% of the carbon nuclei in the diamond lattice to be carbon-13. In bulk electronics grade samples, this means we expect a "typical" NV center to have a few carbon-13 nuclei coupled in the $2\pi \times 10-100$ kHz range, as well as the NV's intrinsic nitrogen-14 nucleus with $\approx 2\pi \times 2.17$ MHz coupling. It is possible to have more strongly coupled carbon-13 nuclei if one is located within the first few coordination shells around the NV center, which causes both the dipolar and contact couplings to increase. Two simple methods for measuring strong nuclear couplings are electron spin resonance (ESR) and Ramsey type experiments. These related experiments use either a weak, detuned microwave pulse or measure the rotation of a coherent electron superposition state to infer the energy levels of the electron spin. Since these are shifted by the coupling to nuclear spin, different frequencies will be observed. Both of these are limited in resolution by the coherence time of the electron, either under driving (T_2^{Rabi}) or free decay (T_2^*) , which are expected to be similar. 4.5 shows ESR and Ramsey data on NV A with an on axis magnetic field. In 4.5(a), ESR is taken with 1 μ s pulse widths at an amplitude which gives an approximate π rotation, leading to an \approx 1 MHz resolution. While this does not saturate the coherence limit, this avoids broadening of the peaks due to slow spectral drift in the system. In 4.5, the phase of the final $\frac{\pi}{2}$ pulse is swept at 5 MHz to aid in measuring the component oscillation frequencies of the beating signal. Data was taken past $T_2^* \approx 2.4(1) \,\mu$ s and showed no revivals. Both of these datasets are consistent with a model including only the nitrogen-14 nuclear spin and no other strongly coupled nuclei $(|A_Z| \gtrsim \frac{2\pi}{T_2^*} \approx 2\pi \times 300 \,\text{kHz}$, where $|A_Z|$ is the strength of the on-axis component of the electonuclear hyperfine coupling). Datasets for the other NVs studied were similar, either showing no strong couplings or only a few couplings near the T_2^* limit for those with longer coherence times. None showed Carbon-13 couplings stronger than 200 kHz.

4.8.2. Dynamical Decoupling Spectrum

Dynamical decoupling extends the coherence time of the electron spin with refocusing pulses. A single refocusing pulse is enough to extend the coherence time to several hundred μs , greatly increasing the resolution with which nuclear spin dynamics can be detected in spectroscopy. Furthermore, at higher pulse numbers and longer inter-pulse spacings, resonances from individual nuclei become sharper and separate spectrally, allowing resonances from weakly coupled nuclei to be observed. In the case of spin- $\frac{1}{2}$ nuclei such as ${}^{13}C$, the approximate location of individual nuclear spin resonances is given by

$$\tau_k = \frac{(2k-1)\pi}{2\omega_L + A_Z} \tag{4.9}$$

where τ_k is the spacing between pulses at the k-th resonance, ω_L is the nuclear Larmor frequency, and A_Z is the parallel component of the hyperfine coupling for that individual nuclei. Spectroscopy from sweeping τ is then expected to reveal resonances arising from several more weakly coupled C-13 nuclei (with $\frac{2\pi}{T_2^*} \gtrsim |A_Z| \gtrsim \frac{2\pi}{T_2} \approx 2\pi \times 10 \text{ kHz}$) for an NV in natural isotopic abundance diamond, such as those in the sample under study.



Figure 4.6: Dynamical decoupling data (blue points w/ dashed line) taken on NV A with a purely on-axis field ($B_X \approx 0$) shows resonances associated with multiple individual carbon-nuclei (colored arrows), as well as a resonance series associated with a higher energy spin (black arrows). Simulation (solid yellow line) shows this is consistent with an additional term in the nitrogen-14 nuclear quadrupolar Hamiltonian, as well the known carbon-13 nuclei. Data is taken with N = 32 pulses at a magnetic field of 264 Gauss aligned within $\approx 1^{\circ}$ of the NV axis. (Inset) High resolution data (markers) taken for various N around $\tau = 1.372$ us fitted using our in-house simulator (best-fit simulation represented by dashed lines). Based on this we determine $\alpha = 2\pi \times 2.43(2)$ kHz for the Nitrogen-14 nuclear spin.

Indeed, we observe resonances associated with at least four C-13 nuclei within the dynamical decoupling spectroscopy data shown in 4.6, indicated by colored arrows. Additional data was taken at each resonance and fitted in simulation to obtain the hyperfine coupling for each carbon-13. In addition, broad resonances saturating to $P(|0\rangle) = 0.5$ are caused by the electron spin entangling with a large number of nuclei near the carbon-13 Larmor frequency. Here, data is taken with a purely on-axis magnetic field $(B_X \approx 0)$, and therefore, resonances associated with the $m_I = 0$ to $m_I = \pm 1$ nitrogen nuclear spin transition are not expected to appear. However, the data also contain an unexpected, higher-frequency resonance series in addition to the expected carbon-13 resonances. The resonance series corresponds to a frequency of several MHz, and it is stable to the orientation of the external DC magnetic field (up to at least $\pm 3^{\circ}$). Additional data was taken around one of these resonances and fitted to obtain the α and A parameters for the nitrogen-14 nuclear spin Hamiltonian in NV A as described in Fig. 2 of the main text. After fitting the four carbon-13 nuclear resonances and the nitrogen-14 nuclear parameters (including the P and A parameters) the simulations (yellow line) agree well with the dynamical decoupling spectra everywhere except near the carbon-13 Larmor frequency (which is expected as our exact simulations do not account for the nuclear spin bath).

Other NVs studied in this work showed similar carbon-13 resonances but did not display the highfrequency resonances associated with the nitrogen nuclear spin.

4.8.3. Fitting additional Hamiltonian parameters for Nitrogen-14 nuclei

As described in the main text, data was taken for each NV with a slightly off-axis field ($|B_X| > 0$), allowing $m_I = 0$ to $m_I = \pm 1$ nitrogen nuclear spin transitions to occur due to spin mixing. To fit the value of both the hyperfine and quadrupolar parameters of the Nitrogen nuclear spins in the NVs studied, the number of Dynamical Decoupling pulses was swept while looking at a narrow region around a high order resonances for each of the two transitions. The resonances were chosen to avoid features related to Carbon-13 nuclei coupled to each NV. The data for both resonances was



Figure 4.7: Dynamical decoupling data for each NV studied taken with an off-axis field $|B_X| > 0$, showing resonances associated with $|m_I = 0\rangle$ to $|m_I = \pm 1\rangle$ transitions of the Nitrogen-14 nuclear spin as the number of dynamical decoupling pulses is swept. Pulse spacings below the hardware limit ($\approx 1 \text{ ns}$) are achieved using interpolated sequences [1]



Figure 4.8: Sequences used to initialize and read out the nuclear spin state using the electron spin. Dashed gates in the tomography sequence are included or removed depending on the desired nuclear measurement axis.

simultaneously fitted to a simulation based on the Hamiltonian given in the main text for each NV, with the hyperfine and quadrupolar parameters allowed to vary. Additional variation parameters were added to account for the loss of coherence due to pulse imperfections and dephasing of the NV electron spin during the DD sequence. Data for each NV listed in the main text is shown in figure 4.7.

4.8.4. Nuclear Spin Initialization and Tomography Sequences

Based on our fitted simulations, we find that N = 24 pulses at a spacing of $\tau = 1.372$ us gives an approximate $\frac{\pi}{2}$ rotation between the $|m_I = -1\rangle$ and $|m_I = +1\rangle$ states of the Nitrogen-14 nuclear spin conditional on the state of the electron spin within the $|m_S = 0\rangle / |m_S = -1\rangle$ manifold (see Fig1(b) of main text). Furthermore, simulations show that a high-fidelity unconditional Z rotation on the $|m_I = \pm 1\rangle$ manifold of the Nitrogen-14 spin can be implemented using a single pulse on the $|m_S = 0\rangle / |m_S = -1\rangle$ electron spin manifold, due to the small magnitude of the off-axis term in the

nuclear quadrupolar Hamiltonian.

Using these two-qubit gates, we implement nuclear initialization and tomography sequences adapted from [147], as depicted in Fig. 4.8.

4.8.5. Initialized Ramsey

As described in the main text, Ramsey data was taken after initializing the nitrogen nuclear spin using the above sequence to measure the population in each nuclear spin states. The amount of green time used to re-initialize the electron spin is swept to ensure we are not observing a steady-state polarization. Raw Ramsey data for each electron re-initialization length is shown in Fig. 4.9. Data for the steady state Ramsey is repeated from Fig. 4.5 As expected, the nuclear spin populations decay back to the steady state value due to off-axis hyperfine coupling in the excited electronic state, with a characteristic decay time of several μs (similar to other published work [169]).

4.8.6. Full Nitrogen Initialization

Simulations

Simulations throughout the manuscript were performed using exact simulation of the described Hamiltonians, along with the well-known Hamiltonian for the electronic spin of the negatively charged NV center at room temperature. Only spin degrees of freedom are considered, while optical and charge dynamics are assumed to be normalized away by readout calibrations which are interleaved with the experiments. Decoherence dynamics are modeled as a uniform decay of this signal, using the form described in Equation (8) of the main text. Hyperfine and quadrupolar parameters are extracted from data by allowing these parameters to vary in the simulations and fitting the simulation results to the data using general optimization methods.

In Figure 4, simulations are performed without (a) and with (b) Gaussian noise, which is representative of the dominant shot noise in our experiments. In Figure 4(a), the maximum contrast is obtained by sweeping the number of pulses and measuring the largest contrast obtained, where con-



Figure 4.9: Initialized Ramsey experiment for each of the electron re-initialization times, as depicted in Fig3(a) of the main text. Blue markers are data and yellow lines are oscillatory fits used to extract the occupation parameters of the Nitrogen-14 spin. (Insets) Power spectra for each of the Ramsey experiments - the polarization of the Nitrogen-14 spin is apparent from the unequal height of the frequency peaks.

trast is defined as the depth of the resonance peak divided by the total readout contrast (normalized to be 1). In Figure 4(b), simulations were performed and random noise was added in, using a noise amount characteristic of our experiments. For each value of β , the α parameter in the simulation was reduced until the uncertainty in the fit dropped below the current signal.

Resonant Lines for α

The Hamiltonian of the system is given by:

$$H = H_{ZE} + H_{ZN} + H_{hf} + H_{quad}$$
$$H_{quad} := P(I_Z^2) + \alpha(I_+^2 + I_-^2))$$
$$H_{hf} := A_Z S_Z I_Z + A_\perp S_Z I_X$$
$$H_{ZE} := \Omega_E S_Z$$
$$H_{ZN} := \Omega_N I_Z$$

where H_{ZE} and H_{ZN} represent the Zeeman terms for the electronic and nitrogen spins, respectively, H_{quad} denotes the quadrupolar term, and H_{hf} refers to the hyperfine coupling between the two spins.

Under the assumption that the perpendicular hyperfine coupling is negligible, i.e., $A_{\perp} \approx 0$, we can perform a unitary transformation U(t) to eliminate all the fast-rotating components from the system. The transformation is given by $U(t) = e^{-i\Delta_E tS_z} \otimes e^{-i\Delta_N tI_z}$. The transformation is described by $U(t) = e^{-i\Delta_E tS_z} \otimes e^{-i\Delta_N tI_z}$. Under this transformation, the terms H_{ZE} , H_{ZN} , and $H_{hf,Z}$ remain unchanged. Contrary to the isotropic components of the Hamiltonian, the quadrupolar coupling does not commute with the other terms. As a result, it is essential to calculate its contribution to the Hamiltonian explicitly. Using the Baker–Campbell–Hausdorff formula, we get that

$$e^{i\lambda I_z}I_+^2 e^{-i\lambda I_z} = e^{2i\lambda}I_+^2$$
$$e^{i\lambda I_z}I_-^2 e^{-i\lambda I_z} = e^{-2i\lambda}I_-^2$$

Thus, the Hamiltonian expressed in the rotating frame is given by:

$$H' = A_Z S_Z I_Z + P(I_Z^2) + \alpha (e^{2i\Delta_N} I_+^2 + e^{-2i\Delta_N} I_-^2))$$

where we set $\Delta_E = \Omega_E$ and $\Delta_N = \Omega_N$. The term that is dependent on the electronic spin state is solely given by $A_Z S_Z I_Z = A_Z [|1\rangle \langle 1| - |-1\rangle \langle -1|] \otimes I_Z$ which allows us to write the Hamiltonian as

$$H' = |-1\rangle \langle -1| \otimes H_{-1} + |0\rangle \langle 0| \otimes H_0 + |1\rangle \langle 1| \otimes H_1$$

where $H_{-1} = -A_z I_z + H_{ind}$, $H_0 = H_{ind}$, and $H_1 = A_z I_z + H_{ind}$. We have consolidated the timeindependent portion of the Hamiltonian into H_{ind} , which includes the quadrupolar term and is expressed as:

$$H_{ind} = P(I_Z^2) + \alpha (e^{2i\Delta_N} I_+^2 + e^{-2i\Delta_N} I_-^2))$$

The evolution operator $V = \exp\{-iHt\}$ takes the same form

$$V = |-1\rangle \langle -1| \otimes V_{-1} + |0\rangle \langle 0| \otimes V_0 + |1\rangle \langle 1| \otimes V_1,$$

where V_i exclusively influences the nitrogen subspace with spin state *i* and can be formulated as a rotation around an axis \vec{n}_i of angle ϕ_i such that $V_i = \exp\left[-i\phi_i(\vec{I}\cdot\vec{n}_i)\right]$. For a spin 1 system, the trace is computed as

Tr
$$\left[\exp\left[-i\phi_i(\vec{I}\cdot\vec{n})\right]\right] = 1 + 2\cos\phi_i.$$

Our goal is to isolate $\vec{n}_i \cdot \vec{n}_j$ to allow us to find the resonance conditions. To do so, we can use the

fact that $\operatorname{Tr}\left[\exp\left[-i\phi(\vec{I}\cdot\vec{n})\right]I_j\right] = -2i\sin(\phi)n_j$ to generate this expression

$$\vec{n}_{-1} \cdot \vec{n}_0 = 1 + \frac{1}{4} \sum_{j \in \{x, y, z\}} \frac{\operatorname{Tr}\left[(V_{-1} - V_0) I_j \right]]\operatorname{Tr}\left[(V_{-1} I_j) \right]}{1 - \left(\frac{\operatorname{Tr}[V_0] - 1}{2} \right)^2}$$

Under a π -pulse, using the $|-1\rangle$, $|0\rangle$ as an example the electronic spin evolves as follows: $|-1\rangle \rightarrow |0\rangle$, $|+1\rangle \rightarrow |+1\rangle$, and $|0\rangle \rightarrow |-1\rangle$, with the pulse sequence specified by:



This results in the following evolution operators:

$$V_{0} = \exp \left[-i\tau H_{ind}\right] \exp \left[-2i\tau H_{+1}\right] \exp \left[-i\tau H_{ind}\right]$$
$$V_{-1} = \exp \left[-4i\tau H_{-1}\right]$$
$$V_{+1} = \exp \left[-i\tau H_{+1}\right] \exp \left[-2i\tau H_{ind}\right] \exp \left[-i\tau H_{+1}\right].$$

Our objective is to determine the difference in rotation between the +1 and -1 states, which can be computed as $\vec{n}_{-1} \cdot \vec{n}_{+1}$ and the angle of rotation ϕ . It is important to note that our aim is not to maximize the angle ϕ but rather to find the condition that maximizes the difference in the evolution of the states $|+1\rangle\langle+1|$ and $|-1\rangle\langle-1|$. Our goal is, therefore, to minimize the dot product between those two angles:

$$\tau_{res} = \arg\min_{\tau} \left(1 + \frac{1}{4} \sum_{j \in \{x, y, z\}} \frac{\operatorname{Tr}\left[(V_{+1} - V_{-1})I_j \right] \operatorname{Tr}\left[(V_{+1}I_j) \right]}{1 - \left(\frac{\operatorname{Tr}\left[V_{-1} \right] - 1}{2} \right)^2} \right)$$

Minimizing this equation is laborious, yet several small parameters are present in the Hamiltonian. The hyperfine coupling significantly outweighs the Zeeman term $\left(\frac{\Omega_N}{A_Z} \approx 0.04\right)$, allowing for a first-order expansion of the ratio. Similarly, for $\frac{\alpha}{\Omega_N} \approx 0.03$, retaining the term at first order is appropriate, while the term $\frac{\alpha}{A_Z}$ can be safely omitted, as it is approximately 0.001.

CHAPTER 5

A GRAPH-BASED REPRESENTATION OF QUANTUM DYNAMICS AND CONTROL

In quantum mechanics, the evolution operator is indispensable for elucidating the temporal dynamics of quantum states. Its precise computation is paramount, particularly in quantum computing, where it orchestrates qubit manipulations through unitary transformations integral to algorithm execution. Such rigorous control of the evolution operator advances the theoretical underpinnings essential for pioneering developments in quantum technologies [6]. In many quantum applications, the goal is to determine the evolution of a state or a density matrix, achieved through the time evolution operator $\mathcal{U}(t, t_0)$ which is given by

$$\mathcal{U}(t,t_0) = \mathcal{T}\left\{\exp\left[-i\int_{t_0}^t H(\tau)d\tau\right]\right\}$$
(5.1)

where \mathcal{T} is the time-ordering operator. This notation involving the time-ordering operator is largely syntactic sugar for an underlying complex nested integral:

$$\mathcal{U}(t,t_0) = I + \sum_{n=1}^{\infty} (-i)^n \int_{t_0}^t dt_1 \int_{t_0}^{t_1} dt_2 \cdots \int_{t_0}^{t_{n-1}} \dots H(t_1) H(t_2) \dots H(t_n).$$
(5.2)

 $\mathcal{U}(t, t_0)$ generally depends on some parameters \vec{x} , which parameterize a time-dependent control. In numerous tasks, \vec{x} must be optimized to minimize a loss function $\mathcal{L}(\mathcal{U})$, which may, for instance, quantify the deviation from a desired gate and the control cost. Thus, it's crucial to effortlessly calculate the gradient $\frac{\partial \mathcal{L}(\mathcal{U})}{\partial \vec{x}}$ across a broad spectrum of loss functions \mathcal{L} and Hamiltonians.

Quantum computing and sensing typically operate within a discrete state space, where states are assigned qubit values. This discrete nature allows for precise control and manipulation, essential for quantum algorithms and high-precision measurements. Significant efforts have been directed toward spin-based systems to enhance qubit fidelity and operational stability. This led to the development of multiple approaches for simulating and controlling their evolution. One such approach is diagrammatic, representing the evolution as a sum of diagrams that depict interactions between spins.

Diagrammatic approaches, such as the pair-correlation approximation [190, 191, 192], the Linked Cluster Expansion (LCE) [193], the Cluster Correlation Expansion (CCE) [194, 195, 196] and the ring diagram methods [197, 198], are widely employed in the study of spin decoherence in quantum systems [199]. Those methods and their derivatives have been used to study the decoherence of solid-state qubits and organic radicals across various platforms [200, 201, 202, 203, 204]. They offer a robust perturbation expansion that allows summing over groups of Feynman diagrams in increasingly advanced ways, enabling detailed study of the effects of each group, enhancing both performance and interpretability [193].

Inspired by these approaches, we propose a method that is also based on diagrams but applicable to any finite basis Hamiltonian. The method preserves the interpretability of previous diagrammatic techniques and allows treatment to be exact or perturbative. Additionally, our approach is designed to support gradient descent and integrate seamlessly into current machine learning frameworks.

5.1. Hamiltonian as a Graph

A Hamiltonian H can be conceptualized as a graph, a notion that should not seem too surprising [205, 206, 8]. In this graph, the vertices $v \in V$ correspond to the matrix's basis, one vertex v_i for each row or column. The vertices v_i and v_j are connected by an edge $e_{i,j}$ if and only if $H_{ij} \neq 0$ and this edge is given the weight $w(e_{i,j}) = H_{ij}$. Non-zero diagonal elements imply the presence of self-loops in the graph. Figure 5.1 shows an example of a network for a simple Hamiltonian. Although this isomorphic transformation does not confer new information, it facilitates intuitive consideration of paths within state space.

Equations 5.1 and 5.2 function similarly to an exponential operator, emphasizing the product of

the Hamiltonian matrix within an iterated integral. In the time-independent case, the evolution operator is simply given by

$$\mathcal{U}(t,t_0) \equiv \exp\left\{-iH\Delta t\right\} = \sum_{k=0}^{\infty} \frac{(-i\Delta t)^k}{k!} H^k$$
(5.3)

Viewing the Hamiltonian as a graph, the matrix power, under the matrix product, $(H^n)_{ij}$ equals the weighted sum of all paths from node j to i of length k. Thus, $\mathcal{U}(t, t_0)$ represents a summation across all paths, weighted by their lengths and the transitions involved. The straightforward path interpretation in the time-independent scenario naturally suggests representing the time-dependent case of $\mathcal{U}(t, t_0)_{ij}$ as a summation over all paths as well. However, given the time-ordered exponential and time-dependent weights, attention must be paid to the product of weights, which can be done using Volterra composition.

5.2. Evolution Operator Representation

In this section, we detail the process, utilizing Volterra composition alongside the conventional breakdown of a graph into its elemental cycles and paths to compute the time-ordered exponential of 5.2. Let \star be the Volterra composition of the first kind such that for $t_1 > t_0$ we have

$$(f \star g)(t_1, t_0) = \int_{t_0}^{t_1} f(t_1, \tau) g(\tau, t_0) d\tau$$
(5.4)

and let 1_{\star} be the identity of this composition. For the *n* repeated composition of *f* with itself we write $f^{\star n} = f \star \cdots \star f$ (*n* times). In a similar fashion, we write $[1_{\star} - f]^{\star -1}$ for $\sum_{n=0}^{\infty} f^{\star n}$ which we will call the resolvent of *f*. For any function of the form $f(t_1, t_2)\Theta(t_1 - t_2)$, this series is unconditionally convergent everywhere except at the singularities of the function [207].

Then, following [208, 209, 210, 211], $U(t, t_0)$ can be written as



Figure 5.1: Graphical Hamiltonian (A) A Hamiltonian can be interpreted as a weighted graph. (B) Example of the computation tree for the element \mathcal{U}_{11} corresponding to the graph shown in (A). (C) Example of the computation graph for \mathcal{U}_{11}

$$\mathcal{U}_{ji}(t,t_0) = \sum_{p \in \Pi_{i,j}} (-i)^{|p|-1} \int_{t_0}^t \left(\mathcal{G}_{\{i,v_1,\dots,v_{l-1}\},j} \star H_{jv_{l-1}} \right)^{-1} \star \mathcal{G}_{\{i\},v_1} \star H_{v_1,i} \star \mathcal{G}_{\emptyset,i} (t,\tau) d\tau$$
(5.5)

where $\Pi_{i,j}$ denotes the set of all simple paths from node *i* to node *j*, each path *p* being a sequence of vertices $(i, v_1, \ldots, v_{l-1}, j)$ without repeated vertices. $\mathcal{G}_{V,i}$ represents Green's functions for simple cycles, which start and end at node *i* and traverse only through vertices in subset *V*. Like simple paths, these cycles are characterized by visiting each vertex no more than once. The following section will discuss green functions; however, we initially exclude them from Equation 5.5. This omission aims to elucidate the connection to the time-independent scenario described in Equation 5.3. In this case, the equation can then be approximated as

$$\mathcal{U}_{ji}(t,t_0) \approx \sum_{p \in \Pi_{i,j}} (-i)^{|p|-1} \int_{t_0}^t \left(H_{jv_{l-1}} \star \cdots \star H_{v_1,i} \right) (t,\tau) d\tau$$

$$(5.6)$$

This equation retains the concept of a summation over paths, now only on more straightforward paths. The product of steps is incorporated using Volterra composition instead of the simple product. However, as seen in the time-independent case, relying solely on simple paths is inadequate; for instance, for the graph of Figure 5.1A, there is only one simple path in between node 1 and 3 when computing \mathcal{U}_{31} . Using Equation 5.6 to compute \mathcal{U}_{31} would not take into account all the valid paths. The path $1 \rightarrow 2 \rightarrow 1 \rightarrow 2 \rightarrow 3$ exemplifies a valid path missed when considering only simple paths. In this case, this path takes the form $1 \rightarrow \gamma \rightarrow 2 \rightarrow 3$ where γ is an element of Γ_1 , which contains all simple cycles starting from node 1. Green functions are introduced to address those simple cycles and are added between all transitions in Equation 5.5. However, caution is required to prevent double counting as the path $1 \rightarrow 2 \rightarrow 1 \rightarrow 2 \rightarrow 3$ can be represented either as $1 \rightarrow \gamma_1 \rightarrow 2 \rightarrow 3$ or $1 \rightarrow 2 \rightarrow \gamma_2 \rightarrow 3$, where $\gamma_1 \in \Gamma_1$ and $\gamma_2 \in \Gamma_2$. To avoid double-counting, nodes that have been previously visited are excluded from $\mathcal{G}_{V,i}$, justifying the use of a vertex subset V rather than the entire graph. Finally, it is important to note that simple cycles can be composed recursively. A simple cycle from Γ_2 can be disrupted by a simple cycle from Γ_3 if vertex 3 is visited at any point during the first cycle. The Green functions need to add those loops recursively, thereby covering all possible paths. For more details on the enumeration of paths, see [212].

The Green functions $\mathcal{G}_{V,i}$, defined recursively, describe simple cycles originating from vertex v_i , using only vertices within the subset $V \subseteq G$, such that

$$\mathcal{G}_{V,i} = [1_{\star} - \sum_{\gamma \in \Gamma_{G \setminus V,i}} (-i)^{|\gamma| - 1} \mathcal{G}_{\{i, v_1, \dots, v_{l-2}\}, v_{l-1}} \star$$
$$\mathcal{G}_{\{i\}, v_1} \star H_{v_1 i}]^{\star - 1}, \qquad (5.7)$$

where $\Gamma_{G\setminus V,i}$ is the set of cycle starting at node *i* on the graph *G* with the set of node *V* removed and γ is a cycle of the form $\gamma = (i, v_1, \dots, v_{l-1})$. The recursion halts when vertex *i* in $\mathcal{G}_{V,i}$ has no neighboring vertices within *V*, at which point it is specified as

$$\mathcal{G}_{V,i} = \begin{cases} [1_{\star} - H_{ii}]^{\star - 1} & \text{if } H_{ii} \neq 0. \\ \\ 1_{\star} & \text{otherwise.} \end{cases}$$
(5.8)

The recursive process, therefore, terminates after a finite number of steps. Figure 5.1B shows an example of such a process.

Reviewing a Green function with only a self-loop as its simple cycle, $\mathcal{G}_{V,i} = [1_{\star} - H_{ii}]^{\star - 1}$, highlights

the resolvent's role. The resolvent allows for the iterative traversal of its simple cycles in every possible sequence. Here, it aggregates the terms for circling the cycle once (H_{ii}) , twice $(H_{ii} \star H_{ii})$, and so on, ad infinitum. This can be easily seen by the fact that $[1_{\star} - f]^{\star -1} = \sum_{k} f^{\star k}$ For example, if two cycles, denoted as c_1 and c_2 , are reachable, the resolvent $[1_{\star} - c_1 - c_2]^{\star -1}$ aggregate every possible ways of navigating them. This ranges from not traversing any (1_{\star}) to traversing each one independently $c_1 + c_2$, up to every permutation in any order $(c_1c_2 + c_2c_1 + \ldots)$.

This method, employing the Volterra composition, enables the computation of \mathcal{U}_{ji} in terms of all paths $p \in \Pi_{ij}$ from *i* to *j*. This is achieved through an enumeration process incorporating simple paths with simple cycles incorporated between each step. When employing this method, one can calculate partial \mathcal{U} over a subset of paths Π' , which we write $\mathcal{U}_{\Pi'}$. This is achieved by substituting Π with Π' in Equation 5.5. We will leverage this feature to simplify computations and delve into the underlying physics of a measurement process in Section 5.4.4.

5.3. Implementation

The presented representation is admittedly quite unwieldy to deal with. It is barely tractable by hand for simple problems because of the complexity and the shear numbers of nested integral [208]. Furthermore, approximating the resolvent as a series leads to convergence problems and is extremely slow. Discretizing the Volterra composition and finding a tractable way to compute the resolvent is necessary. Since our goal extends beyond merely computing U to include accessing its derivatives with respect to controls and parameters in the Hamiltonian, we must track and compute these derivatives. This can be efficiently achieved using contemporary deep learning frameworks [213]. Even though the representation is finite regarding path and cycle expansion, it results in a combinatorial explosion that must be managed.

5.3.1. Discretized Volterra Composition

Fortunately, the composition 5.4 is, in essence, a continuous analog to the matrix multiplication. This analogy leads to a simple discretization scheme [214, 215, 207]. For a function $f(t_1, t_2)$, which is not a distribution, where both t_1 and t_2 belong to an interval I, we create its discrete analog, a matrix \mathbf{F} , by discretizing the interval I into n_t points $\{t_l\}_{l=0}^{n_t}$ using a step size Δt , as follows:

$$(\mathbf{F})_{ll'} := f(t_l, t_{l'})\Theta(t_l - t_{l'}).$$
(5.9)

This approach enables us to express the discretized Volterra composition, utilizing the basic rectangular method for integral approximation, as follows:

$$(f \star g)(t_l, t_{l'}) = \lim_{\Delta t \to 0} (\mathbf{FG})_{ll'} \Delta t.$$
(5.10)

It also leads to a simple expression for the resolvent

$$[1_{\star} - f]^{\star - 1}(t_l, t_{l'}) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \left(\mathbf{I} - \Delta t \mathbf{F} \right)_{ll'}^{-1}.$$
 (5.11)

Thus, calculating the resolvent equates to determining a matrix inverse, with the precision of the approximation enhanced by reducing the size of Δt . We have outlined the discretization approach for approximation via rectangular integration. However, this can and should be implemented using higher-order methods such as the trapezoidal or Simpson's rule for enhanced accuracy [207].

5.3.2. Computation Tree

First, the Hamiltonian is discretized also on the interval $\{t_i\}_{i=0}^{n_t}$ such that

$$H(t_l, \vec{x}) = H_0 + \sum_{k=1}^{n_H} f_k(t_l, \vec{x}) H_k, \qquad (5.12)$$

where the terms $f_{lk}(\vec{x})$ may denote control parameters or fields parameterized by a vector $\vec{x} \in \mathbb{R}^{n_c}$, parameters within the Hamiltonian, or uncertainties associated with the Hamiltonian. The specific details of $f_{lk}(\vec{x})$ are not crucial at this point; only knowing the nonzero transitions element in H_k and H_0 is important for building the graph. The computation tree, as described by Equation 5.5, can then be straightforwardly implemented. Initially, the non-zero terms of $H(t_l, \vec{x})$ serve to construct graph G, in which an edge between node i and j is established if there exists a pair (t_l, \vec{x}) for which $H(t_l, \vec{x}) \neq 0$. The computation graph of \mathcal{U}_{ji} , following equation 5.5, is built where the needed $\Gamma_{G\setminus V,i}$ are computed on demand until the graph is fully expanded.

At this stage, neither H_{ij} nor \mathcal{G} have been calculated. This computation occurs during a forward pass when \vec{x} is provided as input. The functional elements H_{ij} are transformed in their discrete matrix analog $(\mathbf{H}_{ij})_{ll'}$ such that

$$(\mathbf{H}_{ij})_{ll'} = H_{0,ij}\mathbf{L}_{ll'} + \sum_{k=1}^{n_H} H_{k,ij}(\mathbf{F}_k(\vec{x}))_{ll'}$$
(5.13)

where **L** is a lower triangular matrix of 1 and $(\mathbf{F}_k(\vec{x}))_{ll'} = f_k(t_l, \vec{x})\Theta(t_l - t_{l'})$. Equation 5.13 is input into Equation 5.5 to calculate \mathcal{U} . To allow for the gradient to flow from \mathcal{U}_{ji} to the vector \vec{x} , the function $f_k(t_l, \vec{x})$ needs to be differentiable.

In this work, we achieve this by setting $f_k(t_l, \vec{x}) = \mathbf{B}_k \vec{x}$ where $\mathbf{B}_k \in \mathbb{R}^{n_t, n_c}$ is a matrix that represents the basis used for representing the control. This study implemented linear, Lagrange, and Fourier bases, but the framework is versatile enough to incorporate any other type, including integrating a deep neural network. Unless otherwise stated, the results presented in this paper employ the linear basis, wherein \vec{x} represents the control values at a subset n_c of the n_t time points, with the \mathbf{B}_k performing linear interpolation between these points. If multiple independent control functions are required, the control vectors are combined into \vec{x} , transforming \mathbf{B}_k into a block diagonal matrix.

5.3.3. Taming the Exponential Complexity

The computation tree can also become unwieldy for even small systems (see, for example, Figure 5.1C). This problem can be mitigated using multiple strategies. The initial method, termed *Length-limited Path Computation*, is self-explanatory. To mitigate the explosive complexity, we filter $\Pi_{i,j}$ by removing simple paths exceeding a certain length, where the acceptable threshold varies depending

on the system. Similarly, we limit the computation in the Green functions, which we termed *Recursion-limited cycle computation*. In the case of Green's functions, we cap the recursion depth for computing $\mathcal{G}_{V,i}$ at a threshold, beyond which they are treated as the identity matrix. Similarly, this threshold is employed to restrict the length of cycles in Λ_i , mirroring the approach taken with paths.

These two strategies are straightforward and generally perform well with conservative thresholds. However, they are problem-dependent and do not consider the value of \mathbf{H}_{ij} , potentially rendering a long path significant and a short path negligible. The impact of a path $p \in \Pi_{i,j}$ can be assessed by approximating the norm of the term in the sum of Equation 5.5 which takes the form $\left\|\int_{t_0}^t (\mathcal{G}' \star H' \cdots \star \mathcal{G}'')(t, \tau) d\tau\right\|$ or, at the very least, by establishing an upper bound. This task presents challenges due to the nested inverses inherent within the \mathcal{G} matrices. However, the norm of the composition of paths can be used, which is $\|H' \star \cdots H''' \star H''''\|$. It correlates strongly with the path's impact on \mathcal{U} for low entanglement. Each path can be ranked according to this norm, allowing for effective thresholding.

For large systems, space complexity becomes challenging due to the quadratic growth in storage requirements for matrices and gradients ($\sim n_t^2$), along with a linear increase in the count of such matrices with respect to |V|, which typically scales as the square of the graph's node count. As usual, there's a trade-off: store all data to save time or recompute data each time to conserve memory. In our implementation, frequently reused matrices, notably the main \mathcal{G} , are prioritized for caching. In scenarios where system size prevents caching, all matrices are recalculated dynamically, including the **H**. Furthermore, gradient checkpointing is implemented at each resolvent and Volterra composition, facilitating training through selective storage of intermediate activations and on-demand recomputation. This strategy balances a higher computational cost against reduced memory usage [216]. With this feature activated, the computational load nearly doubles due to minimal gradient storage.

5.4. Applications

This section highlights applications demonstrating the method's strengths and weaknesses, inspired by real-world challenges and showcasing the representation properties. We begin with a straightforward fluxonium example in Section 5.4.1 to demonstrate the method's effectiveness and the automatic differentiation scheme's capability to manage the typically loss functions. Next, in Section 5.4.2, we explore a spin chain example to highlight the method's primary advantage and drawback: the element-wise computation of \mathcal{U} . This is illustrated through a state transfer example where the loss function relies on only a few elements of \mathcal{U} . In Section 5.4.3, we show a useful aspect of the representation as two-dimensional functions, whereby the elements of \mathcal{U} are calculated for any given initial and final times. Finally, in Section 5.4.4, we delve into how examining a particular path within \mathcal{U} aids in crafting measurement strategies, focusing on the application of single-spin nuclear quadrupolar resonance (NQR) involving nitrogen-vacancy (NV) centers in diamonds.

5.4.1. Fluxonium Qubit and Standard Loss Functions

In this section, we illustrate the method's functionality using the extensively studied fluxonium qubit as an example, highlighting its capacity to support all types of loss functions. Figure 2.3 illustrates the examined fluxonium model, which presents the two energy levels in the well representing the qubit alongside the overall architecture of a fluxonium qubit [217]. The Hamiltonian is given by

$$H = f_q \frac{\sigma_z}{2} + a(t) \frac{\sigma_x}{2} \tag{5.14}$$

where f_q is the fluxonium frequency at the frustration point, a(t) is the time dependent control and σ_i is the ith Pauli matrix [218]. The qubit frequency, f_q , is 13.89 MHz, and the amplitude, |a(t)|, is constrained to $\leq 500mHz$, delineating the range within which the energy levels and flux maintain an approximately linear relationship. We aim to develop a Y/2 rotation gate subject to multiple constraints. We aimed for control that minimizes depolarization, approximated as proportional to the T_1 of the fluxonium at a given driving frequency, as follows:



Figure 5.2: A simple fluxonium example (A) Schematic representation of the system featuring the two energy levels utilized for Qubit formation. (B) Paths on the Bloch sphere of the system's state implementing a Y/2 gate for a short 25 ns pulse (1) and a long 79 ns pulse (2). (C) Trace distance (in red) and decoherence, D_1 (in blue), plotted against varying pulse lengths for the optimized pulse. Markers highlight the Bloch spheres depicted in section (B). (D) Time trace of the control signals a(t) over seven different control durations ranging from XX ns to XX ns, displayed in a waterfalled format with alternating line types for readability.

$$D_1 = \int_0^t T_1^{-1}(a(t'))dt'$$
(5.15)

where the function T_1 was obtained experimentally for a constant driving in [218]. To assess the deviation between the final gate at t_m , denoted $\mathcal{U}_{ji}(t_m, t_0)$, and the intended target gate $U_{X/2}$, we utilize the trace distance, which is defined as

$$\operatorname{Tr}(\rho,\sigma) = \frac{1}{2} \operatorname{Tr}\left[\sqrt{(\rho-\sigma)^{\dagger}(\rho-\sigma)}\right].$$
(5.16)

For gradient computations, this is more conveniently calculated as $\frac{1}{2} \sum |\lambda_i|$, where λ_i are the eigenvalues of $\rho - \sigma$. The loss function is formulated as the sum of all individual losses, each weighted by a linear coefficient to reflect the importance attributed to each specific loss.

The total time for the gate is taken as a decision variable. An optimal time exists; however, a gate can be effectively optimized for the most sufficiently long duration. At this optimal duration, simple bang-bang control results in exceptionally high fidelity [219]. However, we introduce additional criteria for the pulse, making this control scheme sub-optimal but more realistic. The initial set of criteria pertains to the pulse's shape, while the second ensures stability amidst fluxonium frequency drifts.

We penalize the L^1 norm of the control $L_a^1 = \int_0^t |a(t)| dt$, the norm of the derivative $L_{da}^1 = \int_0^t |\frac{\partial}{\partial t}a(t)| dt$ and of the second order derivative $L_{d^2a}^1 = \int_0^t |\frac{\partial^2}{\partial t^2}a(t)| dt$. These penalties help lower the heating, ensure stability, and help satisfy the experimental bandwidth constraints on the control a(t). Additionally, we impose a penalty for frequency drift L^{drift} , such that minor frequency variations still result in effective gate performance. To achieve this, we assess the variation in trace distance due to a change in f_q by employing a straightforward partial derivative, such that

$$L_{drift} = \left| \frac{\partial \text{Tr}(\rho, \sigma)}{\partial f_q} \right|.$$
(5.17)

Using all those losses, Figure 5.2BCD illustrates the result of the optimization process. Figure 5.2B displays the trajectories for two distinct pulse durations: one near the optimal gate time (1) and the other significantly longer (2). Figure 5.2C reveals the optimal gate time close to the first arrow, indicating a period when the qubit requires minimal driving, as evidenced by its lowest decoherence. The pulses obtained in Figure 5.2D are consistent with those reported in [218]. The common mechanism involves splitting the pulse into two halves: the first with positive driving and the second with negative driving, featuring a rapid transition at the center. The pulses exhibit signs of driving level quantization, stemming from local minima in $T_1^{-1}(a)$. This occurs because certain driving values slightly outperform those lower or higher in decoherence.

5.4.2. State transfer in Spin Chain

In this section, we demonstrate a key characteristic of the approach. The expansion 5.5 computes individual elements of the operator \mathcal{U} sequentially, rather than the entire operator simultaneously. Depending on the situation, this can either present challenges or offer benefits. It is advantageous for scenarios involving state transfer, where the loss associated with transferring from $|i\rangle$ to $|j\rangle$ can be expressed as

$$||\langle j|\mathcal{U}(t_m, t_0)|i\rangle|| = ||\mathcal{U}_{ji}(t_m, t_0)||$$
(5.18)

only requiring the computation of \mathcal{U}_{ji} .

To illustrate this, we examine state transfer within a spin chain characterized by the Hamiltonian

$$H = \sum_{i=0}^{n_s} \Omega_i S_i^z + \sum_{i=0}^{n_s - 1} \vec{S_i} \cdot \mathbf{A}_i \cdot \vec{S_{i+1}} + a(t) S_1^x,$$
(5.19)

where the initial term represents the Zeeman effect for each spin, while the second term addresses the interactions between spins (See Figure 5.3A). In this scenario, only nearest-neighbor interactions are considered. The final term accounts for the control applied exclusively to the first spin in the chain. The objective is to modify the last spin in the chain from $|0...0\rangle$ to $|0...1\rangle$ by solely



Figure 5.3: Partial computation of \mathcal{U} illustrated: state transfer in a spin chain (A) Graph of the Hamiltonian used in the example (B) Unfaithful depiction of the chain's three-spin state using three Bloch spheres. (C) Expectation values for X (blue), Y (orange), and Z (green) across the three spins. (D) (Left) Control exerted on the first spin results in the rotation of the third spin. (Right) Time evolution of the transfer matrix element's magnitude.

manipulating the first spin. Therefore our target is to maximise $||\mathcal{U}_{40}||$.

As an illustrative example, we consider the case of $n_s = 3$, which can be easily visualized. For this case, the graph G contains 8 nodes and 24 edges, from which 8 are self-loops (see Figure 5.3 A). Figure 5.3 displays the outcomes of optimizing 5.18 under similar norm losses on the pulse a(t) to that used for the fluxonium. In this example, we set \mathbf{A}_I to be diagonal and form an XXZ spin chain. The couplings are given by $J_{xy}^i(S_i^x S_{i+1}^x + S_i^y S_{i+1}^y) + J_z^i S_i^z S_{i+1}^z$, with the coupling constants J_{xy}^i varying across each pairs and J_z^i is kept to 1. The coupling J_{xy}^i is chosen randomly from a normal distribution with mean 1 MHz and standard deviation 0.1 MHz. A random example is shown in Figure 5.3B,C with $J_{xy}^0 = 1.005$ MHz and $J_{xy}^1 = 0.9215$ MHz. The pulse's total duration is fixed at 5 μ s. While not optimized, it is sufficiently lengthy to permit a viable solution. Figure 5.3B, C shows the expectation values and positions on the Bloch sphere for each qubit; though this depiction does not show the entanglement between them, it shows the high-fidelity transfer to state $|001\rangle$.

5.4.3. Subspace Avoidance

This section highlights that $\mathcal{U}_{ji}(t_i, t_j)$ is calculated from any initial time up to any final time within the discretized period, as long as the end comes after the start ($0 \leq i \leq n_t$, $0 \leq j \leq n_t$, and $i \leq j$). This capability allows tracking the entire system trajectory, enabling trajectory-dependent loss functions. Additionally, it is helpful for tasks involving memory effects, especially in non-Markovian systems, which this framework can simulate in vectorized form. For instance, it applies to loss functions concerning two-time correlation functions [220]. We explored a simple example of preventing unwanted transitions through subspace avoidance [221, 222].

In this case, we study a three-level system where a Qubit is stored in two energy levels $|1\rangle$ and $|2\rangle$ with energy ω_1 and ω_2 respectively (See Figure 5.4A). Those two levels are coupled through a laser with frequency ω_L detuned with the level of the state $|2\rangle$ by $\delta_2 = \omega_2 - \omega_L$. We assume an unintended coupling to a third state $|3\rangle$ with energy ω_3 . This state causes a quick loss of coherence and should be

avoided. The Rabi frequency between state $|1\rangle$ and $|2\rangle$ is written as $\Omega_{12}(t) = \Omega_{R,12}(t) + i\Omega_{I,12}(t)$. We represent the Rabi frequency between the first state and the unwanted state as being proportional to $\Omega_{12}(t)$, with a phase difference such that

$$\Omega_{13}(t) = \beta e^{i\xi} \Omega_{12}(t), \tag{5.20}$$

where ξ and β are real constants, with $\beta \ll 1$ to reflect its nature as a minor, undesired coupling. The Hamiltonian is then given by

$$H(t) = \frac{1}{2} \begin{pmatrix} -\delta_2(t) & \Omega_{12}^*(t) & \beta e^{-i\xi} \Omega_{12}^*(t) \\ \Omega_{12}(t) & \delta_2(t) & 0 \\ \beta e^{i\xi} \Omega_{12}(t) & 0 & -2\Delta + \delta_2(t). \end{pmatrix}$$
(5.21)

The goal is to transition the population from state $|1\rangle$ to $|2\rangle$, quantifiable by $||\mathcal{U}_{21}(t_f, t_0)||$ while concurrently minimizing transfer to $|3\rangle$ measured by

$$S_3 = \alpha \int_{t_0}^{t_f} \sum_{i \in 1,2} \langle 3 | \mathcal{U}(\tau, t_0) | i \rangle \, d\tau.$$
 (5.22)

Figure 5.4B illustrates the outcomes of state transfer optimization, disregarding S_3 . It shows the final state transfer as a function of the product $t \cdot \Delta$, indicative of task difficulty. At high Δ values, state $|2\rangle$ can be selectively targeted, avoiding the parasitic state. The inset in Figure 5.4B demonstrates that considering S_3 across various α values results in a nearly constant final population in state $|3\rangle$ post-optimization. However, the transfer to the desired state takes a hit, recovering early for the lowest α but requiring a longer control sequence for higher α (see Figure 5.4C). Longer control is the trade-off for reducing time in the noisy subspace, which diminishes significantly when considering S_3 (see Figure 5.4D). Avoiding the subspace substantially changes the problem, affecting the control strategy and the minimum control time. These factors can be



Figure 5.4: Full differentiability in time evolution: preventing subspace intrusion (A) Energy level diagram of the three-level system, highlighting the undesired state and depicting various couplings. (B) State transfer population between state $|1\rangle$ and $|2\rangle$ showing good transfer for $t \cdot \Delta >$ 0.03 (Inset) Unwanted transition for decreasing α showing the low dependency on the added subspace loss. (C) Ratio of state transfer population with subspace loss normalized to transfer without subspace loss. (D) Ration of subspace population with subspace loss normalized to transfer without subspace loss.

effectively addressed within this framework for more complex systems.

5.4.4. Creating a Measurement Scheme

In our concluding example, we integrate all components to create a sensing scheme based on a Nitrogen-Vacancy (NV) center's electronic spin (S=1). Sensing using NV centers can be implemented in bulk diamonds, nanodiamonds, nanopillars, or cantilevers [223, 224]. These configurations enable the sensing of electric and magnetic fields and the coupling with other spins for NMR [225]. Diamonds can be easily functionalized and are safe for biological applications [172]. Drawing inspiration from a recent study that employs the NV center for gauging the quadrupolar moment of an adjacent nitrogen-14 (¹⁴N) spin (I=1) [2].

Our Hamiltonian is simplified relative to [2], yet captures the same dynamics:

$$H_{\theta}(P,t) = \Omega_E S_z + \gamma_{\perp} S_z I_x + P S_z I_z + \theta(t) H_{ctrl}.$$
(5.23)

The Hamiltonian includes the NV Zeeman term, the NV-¹⁴N hyperfine coupling, the ¹⁴N's quadrupolar term, and the NV spin control. The control part of the Hamiltonian (H_{ctrl}) addresses the transition between the state $|0\rangle$ and $|1\rangle$ of the NV center and takes the form

$$H_{ctrl} = \Omega_C \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0.5 \\ 0 & 0.5 & 0 \end{pmatrix} \otimes \mathbf{1}_{N14}.$$
 (5.24)

The experiment begins by setting the NV center to the $|0\rangle$ state while the nitrogen spin remains in a thermal state (approximated here as completely mixed). The initial state ρ_{init} is given by

$$\rho_{init} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix} \otimes \frac{1}{3} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$
(5.25)
The standard way to control this system is achieved through square pulses (in the most basic setup), which rotate the NV center spin by either $\pi/2$ or π around the X-axis, the control axis, in the $|0\rangle$ and $|1\rangle$ subspace of the NV center. One of the control sequences, comprising these two types of rotations, is known as CPMG ($\theta_{CP}(t,\tau)$) [226] and is illustrated in Figure 5.5A. It consists of Nrepetitions of a π pulse, each separated by a waiting period of duration τ , the only parameter for the sequence. Two $\pi/2$ pulses sandwich this sequence, positioning the NV center in the XY plane before the sequence and subsequently realigning it perpendicular to this plane for measurement purposes. The outcome of the pulse sequence, measured right after the last $\pi/2$ pulse, is shown in 5.5C. When $P \neq 0$ and τ are on resonance, the NV center does not return to its initial state after the sequence. This is marked by significant peaks that become more pronounced as the number of pulse repetitions increases [133]. Thus, this approach can serve as a measurement strategy where the parameter τ is swept, and the positions of the peaks enable the determination of P.

We aim to replicate this approach by learning a one-parameter family of controls, denoted as $\theta_O(t, v)$, where v serves as our one parameter, analogous to τ . However, we add stricter requirements that are of use to the experimentalist. Firstly, our aim is for the resulting signal to present a single peak, the center of which provides information about P. This differs from the CPMG sequence, which produces multiple peaks, to simplify the analysis process. Secondly, we seek a fixed control duration, unlike CPMG, which takes approximately $2\tau N$ seconds, excluding the much shorter $\pi/2$ and π pulses relative to the τ interval.

To accomplish this objective, we create a matrix Θ such that $\Theta_{ij} = \theta_O(t_j, v_i)$. Our goal is to learn this matrix. Θ is of dimension $n_P \times n_t$, with n_P representing the number of distinct pulse sequences to be learned and n_t indicating the time points, as previously described. We discretize the range of P values into n_P values to which the system should be sensitive, aligning this discretization with the number of rows in the matrix Θ and ask for each control $\Theta_{O,i}$ to uniquely respond to its associated P_i .



Figure 5.5: **Designing a measurement scheme** (A) NV center system with the electronic spin (V) and the Nitrogen (N) in the diamond crystal lattice and the CPMG pulse sequence used in [2] (B) Graph of the Hamiltonian showing the two unconnected subspace and the path considered (C) (top) Signal captured via the CPMG pulse sequence during τ sweep, with and without a quadrupolar term. (bottom) The contribution originates from the partial computation along the path illustrated in (B). (D) (left) Control optimized for measuring P (right) signal detection based on the peak within the pulse, centered along the v = P axis. Each row represents a sweep akin to that in (C), with the distinction that the single parameter is no longer time τ but v, a learned dependency.

Establishing a loss function is necessary to optimize the discretized version of θ . This function can be simplified by only studying a path that excites a transition caused by P that leads to measurable outcomes. Identifying the path responsible for this effect is straightforward within our framework, as it allows for the separate visualization of their impacts. Figure 5.5B highlights a path of interest within the Hamiltonian graph, activated when the signal deviates from zero (see Figure 5.5C). The partial \mathcal{U} along this path is expressed as $\mathcal{U}_{path}^{P,\theta}(t_f, t_i)$. We will disregard the time variables in subsequent references, as they remain constant for this problem.

This can be incorporated in a loss function of the form

$$L_{meas}(\Theta) = \sum_{i} \left(-||\mathcal{U}_{path}^{P_i,\Theta_i}|| + \frac{1}{n_P - 1} \sum_{j,j \neq i} ||\mathcal{U}_{path}^{P_i,\Theta_j}|| \right).$$
(5.26)

For an optimal Θ matrix, the first term of the sum would be maximized, showing that pulse *i* is sensitive to P_i , whereas the second sum would be zero, demonstrating the pulse's insensitivity to any other *P* values. Additionally, we incorporate into the loss function the losses L_a^1, L_{da}^1 , and $L_{d^2a}^1$ to ensure smoothness, along with a term that guarantees that the control for each *P* varies smoothly as *P* changes, as follows:

$$L_{meas}(\Theta) = \sum_{i \in \{0, \dots, n_P - 1\}, j} (\Theta_{i,j} - \Theta_{i+1,j})^2$$
(5.27)

Figure 5.5D shows the learned map ϕ in the function of v, which shows a highly structured pulse sequence that is composed of mainly three frequencies (See Supplementary Material). The three frequencies correspond to the three transitions in the path (refer to Supplementary Material). The learned sequences are highly effective for measurement as demonstrated by the linear relationship between P and v with a precisely centered peak, shown in Figure 5.5.E.

5.5. Discussion

In this paper, we introduced an implementation of a graph-based representation for the evolution operator of a Hamiltonian in discrete space. This approach enables the automated gradient to flow seamlessly. Furthermore, we demonstrated that the method permits an in-depth study of each path's impact on the evolution operator. We exemplified the method's accuracy through several examples specifically designed to highlight a particular attribute of the approach.

This method can be used in scenarios of low-coupling, such as a spin interacting with a large bath, where the bath's state over time is not required to be precisely known [227, 194]. It could be applied to optimizing decoupling pulse sequences to limit bath-caused decoherence, representing the method's next logical progression. This is due to the method's resemblance to the perturbative diagrammatic expansion approach, which utilizes specific paths in the Hamiltonian to calculate the dynamics' properties. The principal methods going in this direction include the linked cluster expansion (LCE) [193, 228] and the correlated cluster expansion (CCE) [229, 194]. Both methods employ Feynman-like diagrams within a finite space, where the LCE approach details the summation of all possible diagrams—a highly laborious task—while the CCE method provides a more structured approach to summing, addressing a series of LCE diagrams in a single effort [194]. The approach introduced here is comparable to handling a series of LCE diagrams in CCE fashion but incorporates loops via the Green function, enabling the summation of an even greater number of diagrams in a single step. As demonstrated in the final example, this technique is also valuable for investigating causality and determining which paths are crucial.

Although we do not claim this method to be the ultimate in accuracy, it delivers commendable results with a notably low number of points. This contrasts with iterative methods, where the evolution operator is applied repeatedly [230, 231, 232, 233]. Although the computational tree is significantly more complex to generate than those methods, it enables tracking the dependency of parameters at each timestep, a task challenging to achieve with another scheme. This benefit comes

with the drawback of some inefficiency, as managing the exponential complexity arising from path computation becomes unfeasible without a suitable strategy. It is important to highlight that none of the examples discussed in this paper fall within this regime. However, removing paths becomes necessary with as few as six spins in the chain. Although the automated techniques we introduced suffice for such scenarios, a human-guided approach that considers the system's specificity may be essential for more complex systems. An enhanced framework could be implemented, drawing inspiration from dynamic computation graph research [234]. This framework would dynamically tailor computation paths (specifically, the diverse paths and cycles in the Hamiltonian) for each input, directing computational power toward the input data's most significant aspects. Matrix factorization techniques tailored for the Volterra product could be employed, akin to the Low-rank Factorization methods utilized in Deep Learning [235].

Finally, it is worth noting that this method has applications beyond quantum mechanics, as it fundamentally involves computing time-ordered exponentials, a concept not exclusive to this field. Time-ordered exponentials are utilized across various domains, as linear time-dependent dynamical systems are ubiquitous. Among the most unexpected applications are finance, where time-dependent fractional dynamics are studied [236], biology, which employs Markov Chains [237], and computer science, where methods for compressing temporal networks are developed [238]. Although other solvers have been employed in various applications where control was neither attempted nor necessary, we contend that examining the specific paths and cycles that generate the effects of interest in these cases could provide insightful revelations.

CHAPTER 6

CONCLUDING REMARKS

This thesis explored the concept of dynamic systems, which model how different systems evolve over time in Chapter 1. This includes systems ranging from non-linear discrete and stochastic classical systems to more complex quantum systems. Chapter 2 investigates Boolean networks as a model for understanding biological systems, particularly gene regulation. We identify how the topology of interaction networks influences the emergence of long-limit cycles, which are critical for biological functions. The study demonstrates that specific network configurations lead to predictable, stable, dynamic behaviors. This insight is crucial for designing synthetic biological circuits and understanding pathological conditions like cancer.

Chapter 3 introduces the concept of mechanical prions, which exhibit two stable states similar to biological prions. The research shows how these mechanical systems can be designed to remain stable under random perturbation yet collapse into a single stable state when necessary. This work provides a novel perspective on designing mechanical systems that mimic biological processes, with potential applications in materials science and nanotechnology.

Chapters 4 and 5 shift focus to quantum systems, particularly the control and design of quantum mechanical systems. The research highlights how quantum states can be manipulated and controlled, particularly in spin dynamics in diamond NV centers. The findings underscore the importance of precise control in quantum systems for quantum computing and sensing applications. The thesis also presents a new framework for learning control sequences in quantum systems, which could lead to more efficient and robust quantum technologies.

We explored the distinction and interplay between designing systems to achieve desired outcomes and controlling systems in real-time to guide them toward specific goals. This is examined across various types of systems—from Boolean networks inherently designed to reach specific attractors to quantum systems where precise control sequences are essential for maintaining coherence and achieving desired quantum states. The work underscores that while design involves setting initial conditions and system parameters to guide the system's evolution naturally, control requires active intervention, such as applying external forces or adjusting system parameters dynamically.

6.1. Future Directions

The integration of classical and quantum mechanics concepts and the design versus control framework is not limited to a single field but is applicable across various scientific and engineering disciplines. The study of Boolean networks within this thesis opens new avenues for exploring more complex biological systems. Future research could focus on expanding these models to include multi-layered networks that account for additional biological complexities, such as epigenetic factors. More complex Boolean models beyond the threshold limit could be analyzed. Although these models may complicate the definition of topology and the binarization of edges, they offer the advantage of greater realism. Additionally, continuous models could be explored, potentially addressing some of the challenges posed by the discrete nonlinearities encountered in this study.

The study also paves the way for designing systems that inherently perform specific tasks without the need for external control. This approach was applied in Chapter 3 to develop a mechanical analog to prions. The same framework can be extended to develop more advanced self-assembling materials and nanostructures. In this research, the dynamics depended on a single factor, the temperature, which we cannot control. However, it is conceivable to introduce an additional controllable parameter, such as a magnetic or electric field, that could reset the prion process. Future research could investigate how these principles could be applied to design materials with programmable stability capable of self-repair or transformation under specific conditions.

An intriguing question arises when considering prion-like systems in the context of quantum mechanics and systems presented in Chapter 4 and Chapter 5. Quantum systems evolve unitarily, meaning no information is lost during their evolution. This presents a challenge because, in prionic propagation, a significant portion of the state space must collapse into a specific subset of states. This process inherently involves deleting information and breaking the quantum system's unitarity. However, it is possible to build such a system when considering non-unitary dynamics that appear when it interacts with a bath, similar to the classical case. Therefore, a prionic quantum system could be constructed, although its practical application remains unclear.

Another fascinating direction of inquiry that combines these two projects is the creation of dynamic prions. In the presented prions, their prionic or healthy type is determined by their conformation. However, we could conceptualize these two stable states as dynamical limit cycles similar to those observed in the Boolean systems we studied. In this scenario, for example, the prionic system could be a non-oscillating oscillator, while the healthy one could oscillate at a specific frequency. The non-oscillating state could then propagate through interactions with the oscillating one, offering a novel way to explore dynamic state transitions in prionic systems.

The work on quantum control, particularly in the context of NV centers in diamond, lays the groundwork for more advanced quantum sensing and quantum computing applications. The presented framework for designing sensing systems applies to a broad class of systems. Moreover, the accompanying simulation tool enables the learning of a Hamiltonian through a feedback loop with the experimental setup, allowing for real-time adjustments and optimizing the system's performance. This is achievable with this framework because there is no distinction between the Hamiltonian and the control; both are treated as inputs. This approach allows simultaneous simulation of the dynamics, optimization of the best input based on the current knowledge of the Hamiltonian, and execution of the most informative experiment to update the Hamiltonian based on simulated and observed results.

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