A PROBABILISTIC ANALYSIS OF THE DYNAMICS OF STOCHASTIC EQUATIONS DETERMINED BY THE GILLESPIE ALGORITHM

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1. Introduction

The accurate modelling of the time dynamics of discrete physical systems is integral across the sciences. Such models often involve an approximation of both the system state space as a continuous quantity and the evolution of the system as a deterministic quantity. In systems with a small number of elements, such a model has limited validity, due to the increasing effect of stochasticity in the dynamics, and the increasing granularity of the state space. The Gillespie Algorithm provides a way of modelling these systems in such a way that neither of the aforementioned approximations are necessary. However, this implies a loss of determinism. In this essay, we consider to what extent we can forecast the evolution of Gillespie Algorithm derived models of such systems, and determine behaviours that are independent of inter-trial stochasticity.

Biochemical processes, and, in particular, gene regulatory networks, form a critical class of systems that are amenable to stochastic modelling through the Gillespie Algorithm. Such systems evolve through discrete reaction events, in which both the choice of reaction and the time between reactions are random quantities. In gene regulatory network models, there is no clear concept of mass conservation. In other words, the gain of one system substrate does not necessarily imply the loss of others, and vice versa. This reflects the fact the substrates of such systems are generally messenger RNA molecules, or proteins. The rate of change of these factors may be a product of the state of the system, but the actual production and degradation processes can be carried out by biological machinery external to the system. The Circadian Rhythm Model described in [GOL03] exhibits this property, as does our simplification of the model presented in Appendix B. For this reason, we concentrate on the class of models in which each discrete system evolution takes the form of a gain or loss of one substrate element.

The vast majority of the mathematical machinery we construct is unique to this essay, and is introduced as it comes up, so as not to detract from the overall flow of the exposition. In order that the reader does not get lost in a morass of definitions, we provide an index of terminology, in Appendix D.

Shortly prior to submission of this essay, it was found that our definition of a time-stable Gillespie Simulation is equivalent to that of an ergodic Markov Chain, and that many of the results presented in Chapter 4 and onwards, have generalised counterparts in [FAY95]. However, the proofs of these results are in general unique to this exposition, having been arrived at independently, and it is indicated if this is not the case. Reconstruction of the mathematical apparatus and nomenclature to coincide with that presented in [FAY95], and general Markov Chain theory, was not considered a worthwhile endeavour.
In this section, we construct some of the basic mathematical objects necessary for our subsequent analysis, and provide the explicit form of the Gillespie Algorithm.

**Definition 2.1. Substrate State Space:** We define the substrate state space, \( X \), of a physical system with \( n \) distinct substrate types, as the set of allowable substrate vectors. So an element \( x \in X \) is an \( n \)-dimensional vector, with the value of \( x_i \) denoting the quantity of the \( i^{th} \) substrate of the system. We define the mass of \( x \) to denote the sum of the numbers of its substrate elements. In this essay, we consider physical systems where substrate levels take positive integer values. Therefore, \( X \cong \mathbb{N}^n \). In particular we define, the \( i^{th} \) basis vector of \( X \): \( e^i \), as follows:

\[
e^i_j = \delta_{ij}
\]

Here, \( \delta \) signifies the Kronecker delta function.

**Definition 2.2. System State Space** We define the system state space \( Y \) as the product space \( X \times \mathbb{R}^+ \). A system state \( y \in Y \) is of the form \( (x,t) \), with \( x \in X \), \( t \in \mathbb{R}^+ \), and describes the system having substrate levels corresponding to \( x \), at time \( t \).

**Definition 2.3. Reaction State Space:** We consider physical systems that evolve through the occurrence of \( m \) separate reactions, \( r_1 \ldots r_m \). We define the reaction state space \( Q \) of the system as the discrete set consisting of these reactions. Each reaction can be considered as a function mapping \( X \) to itself. This essay is chiefly concerned with systems where the following assumptions apply:

1. \( m = 2n \)
2. \( r_i(x) = x + e^i \) \( i \in \{1,2,...n\} \)
3. \( r_{i+n}(x) = x - e^i \) \( i \in \{1,2,...n\} \)

**Definition 2.4. Reaction Rate Vector Field:** The reaction rate vector field, \( R \), of a physical system, is a function

\[
R : Y \mapsto \mathbb{R}^m
\]

The value \( R_i(y) \) denotes the rate of occurrence of reaction \( r_i \) in the system, given system state \( y \). Note that reaction rates can only take non-negative values, ie \( R_i(y) \geq 0 \), \( \forall y \in Y \). In this essay, we will be dealing solely with physical systems whose reaction rate vector fields are independent of time, and therefore purely a function of the current substrate levels. Therefore, we will henceforth consider \( R \) as a function with effective domain \( X \). In other words, given \( y \in Y \) such that \( y = (x,t) \) we take \( R(y) = R(x) \), and use the two terms interchangeably. In this essay, the following assumption applies:

1. \( R_i(x) \neq 0 \) \( \forall i \in \{1,...,n\} \)
2. \( R_i(x) = 0 \) \( \iff x_i = 0 \) \( \forall i \in \{n+1,...,2n\} \)

\(^1\)Here, we consider \( \mathbb{N} \) to include 0
Definition 2.5. Gillespie Model: Define a Gillespie model as the pair \((X, R)\) consisting of a substrate state space, and reaction rate vector field. Note that any two physical systems sharing the same Gillespie model have identical dynamics. In this sense, we can consider a Gillespie model to uniquely define a physical system being modelled.

We are now in a position to define the Gillespie Algorithm, which generates a stochastic trajectory of the system state of a Gillespie model in time. In the exposition of the algorithm to come, the following notation is used:

Notation 2.6.

1. \(\lambda(x) = \sum_{i=1}^{i=m} R_i(x) = \|R(x)\|_{L_1}\) (as every rate is by definition non-negative).
   \(\lambda\) corresponds to the total reaction rate of the system.
2. \(I\) is the iteration counter. On the \(i^{th}\) iteration of the Gillespie Algorithm, \(I := i\)

Algorithm 2.7. Classical Gillespie Algorithm [WIL06]

1. **Initialisation**: Set an initial system state \(y_0 = (x_t, t_0)\), and calculate \(R(x_t)\). Set \(I = 1\)
2. **Random Number Generation and Scaling**: Calculate \(\lambda(x_{t_{I-1}})\). Simulate a realisation of the following random variables
   \(u_I \sim U[0, 1] \quad w_I \sim \text{exp}(1)\)
   Define:
   \[\bar{w}_I = \frac{1}{\lambda(x_{t_{I-1}})} \times w_i \quad \bar{u}_I = u_I \times \lambda(x_{t_{I-1}})\]
   Note that \(\bar{w}_I \sim \text{exp}(\lambda(x_{t_{I-1}}))\), and \(\bar{u}_I \sim U[0, \lambda(x_{t_{I-1}})]\)
3. **System Update**: We define the set of intervals \(\{c_k\}_{i=1}^{m}\)
   \[c_k = \sum_{i=1}^{k-1} R_i(x_{t_{I-1}}) + [0, R_k(x_{t_{I-1}})]\]
   Note that:
   (a) \(\bigcup_{i=1}^{m} c_i = [0, \lambda(x_{t_{I-1}})]\)
   (b) \(c_i \cap c_j = \emptyset \quad \forall i, j\)
Therefore \( \tilde{u}_I \) is in exactly one of the set of intervals \( \{c_k\} \). Call this the \( j^{th} \) interval. Set

\[
y_I = (r_j(x_{t_{I-1}}), t_I + w_I)
\]

(4) **Reset:** Store \( y_I \). Set \( I = I + 1 \). Return to step (2)

**Explanation**

The algorithm models each reaction as a poisson process, of rate equal to its respective reaction rate. The sum of reactions is therefore a poisson process with rate equal to the sum of the rates of the respective reactions. Waiting times between reactions are therefore exponentially distributed, and given by the random variables of the form \( \{\tilde{w}_I\} \). After each waiting time, we choose a reaction to simulate. The probability of choosing a reaction is equal to its reaction rate as a proportion of the total reaction rate of the system.

**Definition 2.8.** Define a K step Gillespie Simulation on a Gillespie Model as the sequence: \( \{y_i\}_{i=0}^K \), obtained by performing the Gillespie algorithm K times given an initial system state \( y_0 \). A Gillespie simulation with no step number specified is assumed to be an infinite sequence. Note that simulations are not well defined, due to the inherent stochasticity of the algorithm.

**Definition 2.9.** Define the trajectory, \( x(t) : (t_0,T) \to X \), of a Gillespie Simulation \( \{y_i\}_{i=0}^\infty \) as follows:

\[ x(t) = x_{t_i}, \quad t \in [t_i, t_{i+1}) \]

Define the initial condition of a Gillespie trajectory as the state \( y_0 = (x_0, t_0) \).

In essence, when we iteratively perform the Gillespie algorithm on a Gillespie Model with initial conditions, we get a discrete set of vectors \( \{y_i\} \), which capture every single change occurring in the system during application of the algorithm. This is the Gillespie simulation. The trajectory continuously models the actual time evolution of the system, which is unchanging except at the set of timepoints recorded by the Gillespie simulation.

**Definition 2.10.** Given a point \( x(t') \) on a trajectory, we name \( t' \) as the elapsed (external) time. We also define the internal time \( p \) of a point \( x(t') \) on the trajectory as follows:

\[ p[x(t')] = i : t' \in [t_i, t_{i+1}) \]

Note that the space of internal times is isomorphic to \( \mathbb{N} \). The internal time corresponds to
the number of changes the system state has gone through. We denote the space of internal
times as $\mathbb{T}$.

**Definition 2.11. Random Sequence Space:**
Realisation of an infinitely long Gillespie simulation involves generation of the following
sequences of random variables:
\[
\begin{align*}
\{u_i\}_{i=1}^{\infty} & : u_j \sim U[0, 1] \quad \forall j \in \mathbb{N} \\
\{w_i\}_{i=1}^{\infty} & : w_j \sim \text{exp}(1) \quad \forall j \in \mathbb{N}
\end{align*}
\]
We accordingly define the random sequence space $\Omega$ as follows:
\[
\Omega = U \times W
\]
\[
U = \{u : u = \{u_i\}_{i=1}^{\infty} ; u_i \sim U[0, 1] \}
\]
\[
W = \{w : w = \{w_i\}_{i=1}^{\infty} ; w_i \sim \text{exp}(1) \}
\]

**Proposition 2.12.** A Gillespie Simulation (and thereby a trajectory) on a Gillespie Model
can be uniquely determined, given the pair: $(x_0, \omega)$, where $x_0 \in X$, and $\omega \in \Omega$.

**Proof.** Decompose $\omega$ into the pair of sequences $(u, w)$. The proposition is equivalent to
stating that a Gillespie Simulation is deterministic, given $(x_0, u, w)$. All of the randomness
in the Gillespie algorithm is associated with the generation of the sequences: $w$ and $u$.
Therefore, the result is trivial. We have purposely excluded the provision of an initial
elapsed timepoint $t_0$ in the initial condition $(x_0, u, w)$, since it has no effect on the dynamics
of the Gillespie simulation: and merely serves to translate the simulation in time. \qed

For clarity, we outline an explicit, modified version of the algorithm, which runs determin-
istically, given a triple $(x_0, w, u)$, below.

**Algorithm 2.13. Modified Gillespie Algorithm**

1. **Initialisation:** Generate an element $\omega \in \Omega$
   
   Set initial system state and rates vectors: $y_0$ and $R(y_0)$, and iteration counter $I = 1$

2. **Random Number Scaling:** As in Algorithm 2.7

3. **System Update:** As in Algorithm 2.7

4. **Return to Step 2**
3. The Formulation of Gillespie Simulations as Random Dynamical Systems

**Definition 3.1. Random Dynamical System** [LUD98] A measurable random dynamical system on the measurable space \((X, \mathcal{B})\) over a metric dynamical system \((\Omega, \mathcal{F}, \mathbb{P}, (\theta(t))_{t \in \mathbb{T}})\) with time \(\mathbb{T}\) is a mapping:

\[
\varphi : \mathbb{T} \times \Omega \times X \to X, \quad (t, \omega, x) \mapsto \varphi(t, \omega, x)
\]

with the following properties:

1. **Measurability:** \(\varphi\) is \(\mathcal{B}(\mathbb{T}) \otimes \mathcal{F} \otimes \mathcal{B}, \mathcal{B}\)-measurable
2. **Cocycle Property:** The mappings \(\varphi(t, \omega) := \varphi(t, \omega, \cdot) : X \to X\) form a cocycle over \(\theta(\cdot)\) ie they satisfy:

\[
\begin{align*}
\varphi(0, \omega) &= id_X \quad \forall \omega \in \Omega \\
\varphi(t + s, \omega) &= \varphi(t, \theta(s)\omega) \circ \varphi(s, \omega) \quad \forall s, t \in \mathbb{T} \quad \omega \in \Omega
\end{align*}
\]

Here, we use ‘\(\circ\)’ to denote composition, which canonically defines an action on the left of the semigroup of self mappings, \(X \to X\).

**Theorem 3.2. A Gillespie Simulation on a Gillespie Model can be formulated as a Random Dynamical System**

The proof of this theorem forms the crux of this chapter. We commence by defining the relevant spaces and measured espoused in Definition 3.1. In this chapter, we take for granted the assumptions of Definitions 2.3 and 2.4.

**Definition 3.3.** We define a \(\sigma\)-algebra, \(\mathcal{B}\), on the system state space \(Y\). Recall that \(Y \cong \mathbb{N}^n \times \mathbb{R}^+\) (Definition 2.2). We take \(\mathcal{B}\) to be the product of the Counting and Lebesgue measures on these respective spaces. \(\mathcal{B}\) is well defined, due to existence and uniqueness of the product measure [RUD87].

**Definition 3.4.** We define \((\Omega, \mathcal{F}, \mathcal{V})\) to be the measurable space such that:

1. \(\Omega\) is defined as in 2.11
2. \(\mathcal{F}\) is the \(\sigma\)-algebra generated by sets of the form \(\{(u, w) : (u, w) \in I_i \times J_i \subseteq [0, 1] \times \mathbb{R}^+\}\), where \(I_i\) and \(J_i\) are open intervals, for some \(i \in \mathbb{N}\). Since this is a countable product of Borel \(\sigma\)-algebras (which are generated by open intervals) on the support of each sequence element, we rest assured that it too is a \(\sigma\)-algebra ([RUD87]).
(3) $V(A) = \prod_{i=1}^{\infty} P((u_i, w_i) \in A_i)$.

Here the probability measure, $P$, is that derived from the probability density functions of $u_i$ and $w_i$. $V$, as a countable product of probability measures, is itself a probability measure [RUD87]

**Definition 3.5.** For a given Gillespie Model, we define the ‘flow’ map $\varphi : T \times \Omega \times Y \mapsto Y$, as follows:

$$\varphi(d, (u, w), y_0) = (y_d)$$

Here, $y_d$ is the system state obtained by conducting a $d$-step Gillespie Simulation on the triple $(y_0, u, w)$, which we have previously shown to be deterministic (2.12). $d \in \mathbb{T}$, the space of internal times, which we have previously noted is isomorphic to $\mathbb{N}$.

Note that 2.13 provides an explicit method of computation for the flow map.

**Definition 3.6.** We define a Borel $\sigma$-algebra on $T : \mathcal{B}(T)$, by giving $T$ the discrete topology.

Note that every subset of $T$ is measurable, due to countability of the space combined with the fact that every discrete element of the space is measurable.

**Theorem 3.7.** The Flow map, $\varphi$, is measurable

Our plan of action is to decompose the flow map $\varphi$ into the composition of two functions. One transforms the sequence $u$ of uniform random variables into a sequence of reaction types, and the next converts the initial substrate vector to the final one using this reaction sequence, while calculating the reaction timepoint. The measurability of both of these functions then implies measurability of their composition, $\varphi$. Note that this decomposition is employed for purely theoretical purposes. Applying it algorithmically would be computationally expensive.

**Definition 3.8.** Consider a Gillespie simulation on a model with $m$ reaction types, denoted $r_1...r_m$. We define $S$ as the space of reaction sequences.

$$s \in S \Rightarrow s = \{s_i\}_{i=1}^{\infty} ; \quad s_i \in Q, \forall i$$

We define a measure on $S$ in several stages: We first formalise the notion of distance between two reaction sequences. Let $r_i, r_j$ be two reactions. Then define

$$|r_i - r_j| = \delta_{ij}$$
Here, $\delta_{ij}$ denotes the Kronecker Delta function. Now for arbitrary $q, s \in S$:

$$d(q, s) = \sum_{i=1}^{\infty} \frac{|q_i - s_i|}{2^i}$$

Such metrics on a sequence space are common in fields such as Dynamical Systems, so we neglect to prove that $d$ does indeed define a metric, and refer the reader to, for example [DEV92]. Now that we have a metric, and therefore an induced metrizable topology, on $S$, we note the existence of a Borel $\sigma$-algebra $\mathcal{B}(S)$ generated by open sets in the topology. In other words, $\mathcal{B}(S)$ is generated by balls $B$ of arbitrary radius in $S$. Note the following:

$$B(s, 2^{-k}) = \{ q \in S : \{q_i\}_{i=1}^{k} = \{s_i\}_{i=1}^{k} \}$$

**Definition 3.9.** We define the ‘reaction sequence generating’ function of a Gillespie Model as follows:

$$\psi : T \times \Omega \times Y \mapsto (T \times W \times S \times Y),$$

$$\psi(d, (u, w), y) = (d, w, s, y)$$

Here $s$ is the sequence of reaction types occurring in a Gillespie simulation on the model given initial conditions $(x, w, u)$. Applying Algorithm 2.13 to this triple and storing only the generated reaction sequence would explicitly compute the function. Note that this is essentially a function mapping $U$ to $S$: it acts as the identity function on other subspaces of its domain, and they are included purely in order that it can transmit information to functions it is composed with.

**Definition 3.10.** For a given Gillespie simulation, we define the function $\phi$ as follows

$$\phi : T \times W \times S \times Y \mapsto Y,$$

$$\phi(d, w, y_0) = y_d$$

Here, $y_d$ is the system state reached by performing a $d$-step Gillespie simulation on $y_0$, with the reaction sequence of the simulation specified by $s$, and the reaction timepoints by $w$.

The proofs of results leading to Theorem 3.7 are simplified by the following observations:

1. $\varphi(d, \omega, y) = \phi \circ \psi(d, \omega, y)$, so measurability of $\phi$ and $\psi$ is a sufficient condition for measurability of $\varphi$

2. To prove measurability of a function $f : X \to Y$, with $(Y, \mathcal{B})$ a measurable space, it is sufficient to prove measurability of of arbitrary elements of a generating set for the $\sigma$-algebra $\mathcal{B}$. Here we define a generating set of $\mathcal{B}$ to be a set that generates the whole of $\mathcal{B}$ under $\sigma$-algebra operations. [RUD87]
(3) The $\sigma$-algebra that allows implementation of the Lebesgue measure on $\mathbb{R}^+$ is generated by open intervals. The $\sigma$-algebra required for implementation of the counting measure on a countable space is generated by discrete elements of that space. [RUD87]

(4) The $\sigma$-algebra $\mathcal{B}$ on $Y$ is generated by the product of single elements of $X$, and open intervals on $\mathbb{R}^+$. To prove measurability of a function $f$ that maps onto $Y$, we therefore need only prove measurability of $f^{-1}(x,E)$, for an arbitrary element $x \in X$, and an arbitrary interval $E \in \mathbb{R}^+$

Lemma 3.11. $\psi$ is $\mathcal{B}(T) \otimes \mathcal{F} \otimes \mathcal{B}$ measurable
Not that this is equivalent to showing that $\psi^{-1}(d,\omega,A,y)$ is $\mathcal{B}(T) \otimes \mathcal{F} \otimes \mathcal{B}$ measurable, for any discrete points $d \in T$, $\omega \in \Omega$, $y \in Y$, and open interval $A \in \mathcal{S}$.

Proof. The restriction of the range of $\psi$ to $T \times \Omega \times Y$ is the identity function, so it is sufficient to prove that $\psi^{-1}(A,.)$ is measurable. Decomposing the product spaces $Y$ and $\Omega$ into their constituent factor spaces, we have:

$$\psi^{-1}(A,.) = \{ x \in X, t \in \mathbb{R}^+, d \in T, u \in U, w \in W \text{ such that } \psi|_{S}(d,u,w,x,t) = A \}$$

$$= \mathbb{R}^+ \times W \times \bigcup_{x \in X} \bigcup_{d \in T} \{ u : \psi|_{S}(d,u,x,. ) = A \}$$

The second equality holds due to the fact that internal and elapsed time calculations are independent of reaction sequence choice in the Gillespie Algorithm. Countability of $X$ and $T$ imply that the above double union is countable. It remains to show measurability, for fixed $d \in T$, $x \in X$, of:

$$\{ u \in U : \psi|_{S}(d,u,x,. ) = A \}$$

Any open set in $S$ is a countable union of open balls, so we may assume without loss of generality that $A$ is an open ball. From 3.8, we see that

$$A = \{ q \in S : \{ q_i \}_{i=1}^{k} = \{ s_i \}_{i=1}^{k} \}$$

for some fixed sequence of reactions $\{ s_i \}_{i=1}^{k}$. We know that $s_1 = r_j$, for some $j \in \{ 1,...,m \}$. For a Gillespie simulation with arbitrary initial condition $y_0$, the first reaction is $r_j$ if and only if $u_1$ falls in some interval, of which the size, and start/end points are determined by the computations in 2.13, and the current state of the substrate vector. Let us denote this interval $I_{s_1}$. If the $j^{th}$ reaction rate is 0, then $I_{s_1} = \emptyset$. We inductively define $I_{s_i}$ similarly. Then

$$\{ u \in U : \psi|_{S}(d,u,x,. ) \in A \} = \prod_{i=1}^{k} \{ u : u_i \in I_{s_i} \}$$

From Definition 3.4, we see that this is measurable, since, although we have not analysed the dimensions of each individual $I_{s_i}$, we know each one represents either an interval or the empty set. □
Lemma 3.12. $\phi$ is measurable

Note that this is equivalent to showing that $\phi^{-1}(x, E)$ is $\mathcal{B}(\mathbb{T}) \otimes \mathcal{F} \otimes \mathcal{B}(\mathcal{S}) \otimes \mathcal{B}$ measurable for any $x \in X$ and interval $E \subseteq \mathbb{R}^+$, as $(Y, \mathcal{B})$ is generated by sets of this form.

Proof.

$$\phi^{-1}(x, E) = \bigcup_{x' \in X} \bigcup_{d \in \mathbb{T}} \{ w \in W, t \in \mathbb{R}^+, s \in S : \phi(d, (x', t), w, s) \in (x, E) \}$$

Each of these unions is countable due to the countability of $X$ and $T$. Therefore, measurability of the whole set is equivalent to that of each component element of the double union.

Note that we may assume $t = 0$, without loss of generality, in the above equality. Changing the initial elapsed time value merely translates the final elapsed time value, so does not affect measurability of the function.

Therefore, it remains to show measurability, for fixed $d \in \mathbb{T}$ and $x' \in X$, of:

$$\{ w \in W, s \in S : \phi(d, (x', 0), w, s) \in (x, E) \}$$

(3.3)

At the $i^{th}$ internal time (iteration) step, we calculate the increase in elapsed time by scaling $w_i$ by a factor proportional to the total magnitude of the reaction rates. The form of the scaling function, as shown in Algorithm 2.7, is as follows:

$$\tilde{w}_i = \frac{1}{\lambda(x_{t_i})} \times w_i$$

Note that the map from $w_i$ to $\tilde{w}_i$ (defined separately for each $i$), is therefore continuous over its domain ($\lambda(x_{t_i})$ can only take positive values).

Let us introduce some new notation:

$$G_{k,I} = \{ w \in W : \sum_{i=1}^{k} \tilde{w}_i \in I \}, \quad k \in \mathbb{T}, I \subseteq \mathbb{R}^+ \quad (3.4)$$

$$F_{k,x'} = \{ s \in S : \phi(k, x', s, .) = (x, .) \}, \quad k \in \mathbb{T}, x' \in X \quad (3.5)$$

We observe that 3.3 describes the set $G_{d,E} \times F_{k,x'}$. It remains to show each of these sets is measurable.

We prove measurability of $G_{d,E}$ by induction. First assume $d = 1$, and pick an arbitrary interval $I = (a, b)$ (with $a$ or $b$ possibly equal to $\pm \infty$):

$$G_{1,I} = \{ w : (\tilde{w}_1 > a \cap \tilde{w}_1 < b) \}$$

Continuity of each transformation $w_i \mapsto \tilde{w}_i$ shows that the set of $w_1$ for which the above is true is Borel-measurable. In particular, this property holds for $I = E$, as choice of interval was arbitrary.
Now let us assume that $G_{k-1,I}$ is measurable, for some $k \in \mathbb{N}$, and any open interval $I = (a, b)$:

\[
G_{k,I} = \bigcup_{q \in \mathbb{Q}} \{ G_{k-1,(a-q,\infty)} \cap \{ w_k : w_k \in (q, \infty) \} \} \bigcap \bigcup_{q \in \mathbb{Q}} \{ G_{k-1,(-\infty,b)} \cap \{ w_k : w_k \in (-\infty, q) \} \}
\]

We can see that this is a composition of countable unions and intersections applied to measurable sets, and is therefore itself measurable, thus completing our induction argument.

We now prove measurability of $F_{k,x'}$:

Pick $s \in S$. Note that the elements $\{ s_i \}_{i=k+1}^{\infty}$ of $s$ are independent of whether $s$ is in the set $F_{k,x'}$, which is solely a function of the values $\{ s_i \}_{i=1}^{k}$. After all, the substrate vector of a Gillespie simulation at the $k^{th}$ iteration step is independent of the reactions occurring during subsequent iteration steps.

Now observe that, due to the fact that a given element $s_j \in s$ belongs to one of $m$ possible values, there are at most $m^k$ possible distinct sequences $\{ s_i \}_{i=1}^{k}$. Thus there must be a finite number (possibly zero) of distinct specifications on the set $\{ s_i \}_{i=1}^{k}$ that uniquely define any sequence starting with these values to belong to $F_{k,x'}$. Recall from Definition 3.8 the following:

\[
B(s, 2^{-k}) = \{ q \in S : \{ q_i \}_{i=1}^{k} = \{ s_i \}_{i=1}^{k} \}
\]

We see that $F_{k,x'}$ is consequently a finite union of open balls in $S$, which is measurable by definition, with respect to $B(S)$.

\[\square\]

**Corollary 3.13.** Theorem 3.7 is true

**Definition 3.14.** We define the family of shift maps $\theta(s) : \Omega \rightarrow \Omega$ as follows:

\[
\theta(s)(u, w) = (u', w')
\]

Here, $(u', w')$ is the pair of sequences satisfying the property:

\[
(u'_i, w'_i) = (u_{i+s}, w_{i+s}) \forall i \in \mathbb{N}
\]

**Theorem 3.15.** The Flow map, $\varphi$ (Definition 3.5), satisfies the cocycle property over $\theta(.)$ (Definition 3.1).

**Proof.** We consider the set of mappings $\varphi(t, w) = \varphi(t, w, .) : Y \rightarrow Y$.

\[
\varphi(0, w) = id_Y
\]

(3.6)

This requires no explanation. A cursory observation of the Gillespie algorithm shows that a 0-step Gillespie simulation is equivalent to the identity mapping. It remains to show the following:
\[ \varphi(t + s, \omega) = \varphi(t, \theta(s)\omega) \circ \varphi(s, \omega) \quad \forall s, t \in T \quad \omega \in \Omega \] (3.7)

The LHS of Equation 3.7 defines a mapping from a system state \( y_0 \) to the final value of its \( t + s \) step Gillespie simulation, \( y_{t+s} \). The RHS defines the composition of a \( t \) step and \( s \) step mapping on \( y_0 \). Since a Gillespie simulation proceeds algorithmically, with the results of each iteration stage independent of previous Gillespie states, the RHS also defines a \( t + s \) step mapping. Noting Proposition 2.12, we merely need show that the sequences \( \omega_L \) and \( \omega_R \) used to perform the simulations on the LHS and RHS of Equation (3.7) respectively, are identical.

From the definition of the flow map, \( \omega_L = \omega \), where \( \omega \) is chosen in Equation (3.7).

On inspection, we see that:

\[
(\omega_R)_i^s = (\omega)_i^s \\
(\omega_R)_i^{s+1} = \theta(s)(\omega)_i^\infty = (\omega)_i^{s+1}
\]

So \( \omega_L = \omega_R \), and we are done. \( \Box \)

**Corollary 3.16.** The flow map \( \varphi \) defines a measurable Random Dynamical System

**Definition 3.17.** Generator of the flow We define the generating functions \( \zeta(\omega) \) of the flow map as follows:

\[
\zeta(\omega) = \varphi(1, \omega) : Y \mapsto Y
\]

Current literature focuses on Random Dynamical Systems in which the generating function, as defined above, is an affine map, with respect to the random vector \( \omega \) that it is parameterised by. This is obviously not the case in our situation, which leaves us at a dead end in terms of our current method of analysis, pending further research on less well-behaved Random Dynamical Systems. This inclusion of this chapter was not just in the hope that such research will be carried out, however. Many of the structures and functions we have defined are subsequently used in other situations during the course of the essay.
We now introduce a regulatory condition on a Gillespie Model that we name *time stability*, which allows us to define a measure proportional to the limiting probability density of a Gillespie simulation on its substrate state space. First we must attach a probability measure to the space of Gillespie simulations in order that we can quantify simulation properties in terms of their likelihood of occurrence.

**Definition 4.1. Simulation State Space**
We define the simulation state space of \( y \), \( O_y \), as the space of possible infinitely long Gillespie simulations with initial system state \( y \in Y \). We define the generic simulation state space, \( O \), as

\[
O = \bigcup_{y \in Y} O_y
\]

Recall (Proposition 2.12), that a simulation \( o \in O_y \) is determined completely by the element \( \omega \in \Omega \). Therefore we use the notation \( o_y(\omega) \) to indicate the Gillespie simulation in the space \( O_y \), determined by the random sequence element \( \omega \). It is important to recall that the determination is not unique, so it is possible to have distinct elements \( \omega_1, \omega_2 \in \Omega \), such that \( o_y(\omega_1) = o_y(\omega_2) \).

We define the *k-step* simulation state space of \( y \), \( O_y^k \), as the space of possible \( k \)-step Gillespie simulations with initial system state \( y \).

We will often solely concern ourselves with the substrate vector associated to an element of a simulation \( o \in O_y \). The notation \( o_i|_X \), signifies the substrate vector associated with \( o_i \), the \( i \)th system state of a Gillespie simulation.

**Definition 4.2. \( \sigma \)-algebra on \( O_y \)**
We define a measure, \( O_y \), on \( O_y \) as follows:

\( O_y^k \) consists of a set of sequences of system states, of length \( k \). It is therefore isomorphic to the product of \( k \) copies of the system state space \( Y \). We have already defined a measure \( \mathcal{B} \) on \( Y \) (see Definition 3.3). We define \( O_y^k \) to be the product of \( k \) copies of \( \mathcal{B} \). We then take:

\[
O_y = \bigcap_{i=1}^{\infty} O_y^i
\]

\( O_y \), as a product of \( \sigma \)-algebras, is one itself [RUD87].

**Definition 4.3. We define the decomposition map** \( C_y : O_y \rightarrow \mathcal{F} \) *as follows:*

\[
C_y(o) = \{ \omega \in \Omega : \varphi(i, y, \omega) = o_i \quad \forall i \in \mathbb{T} \}
\]
The construction of the Borel σ-algebra, \( \mathcal{F} \), is found in Definition 3.4.

The decomposition map is named as such due to the fact that it 'decomposes' a Gillespie simulation into the set of possible random vector sequences that would have, when inputted into the Gillespie algorithm, provided the original simulation as an output. It can be considered a 'pseudo'-inverse of the flow map, whose non-injectivity prohibits a true inverse.

**Lemma 4.4.** The range of the decomposition map is indeed \( \mathcal{F} \), the Borel σ-algebra on \( \Omega \).

**Proof.** Pick \( o \in \mathcal{O}_y \). Let \( A_i \) be the set of \( \omega \in \Omega \) such that: \( \varphi(i, y, \omega) = o_i \). Then we have:

1. \( o_i \) is measurable in \((Y, \mathcal{B})\)
2. Measurability of \( \varphi \), the flow map implies \( A_i \) is measurable

Therefore, we have measurability of \( C_y(o) = \bigcap_{i=1}^{\infty} A_i \) \( \square \)

We proceed to prove measurability of the \( C_y \). We furthermore prove that the image of any \( \mathcal{O}_y \)-measurable set, under \( C_y \), is \( \mathcal{F} \)-measurable. This implies that the σ-algebra generated by the pre-images of measurable sets in \( \mathcal{F} \), under the decomposition map, is precisely \( \mathcal{O}_y \). Consequently, we can 'transport' our existing probability measure \( \mathcal{V} \) (see Definition 3.4) on the random sequence space, to a measure on \( \mathcal{O}_y \), through this bijective correspondence.

**Lemma 4.5.** \( \mathcal{O}_y \)-measurability of the decomposition map

**Proof.** It is sufficient to prove measurability of the pre-image of any member of a generating set of \( \mathcal{F} \). Recall that any element \( \omega \in \Omega \) can be expressed as a pair \((u, w)\). We can see from 3.4 that \( \mathcal{F} \) is generated by sets of the form:

\( \{(u, w) : u_i \in J_1, w_i \in J_2, i \in \mathbb{N}\} \)

where \( J_1 \in [0, 1], J_2 \in (0, \infty) \), are open (or closed) intervals.

Pick an arbitrary set \( A \in \mathcal{F} \) of this form:

\( A = \{(u, w) : u_k \in J_1, w_k \in J_2, i\} \)

for open intervals \( J_1, J_2 \) as previously described.

\[ C_y^{-1}(A) = \{ o : \exists (u, w) \in A : \varphi(i, y, u, w) = o_i \ \forall i \in \mathbb{N} \} \]

\[ = \{ o : o_k \in \varphi(k, y, u, w); u_k \in J_1, w_k \in J_2 \} \]

\[ = \{ o : (x_k, t_k) \in \varphi(k, y, u, w); u_k \in J_1, w_k \in J_2 \} \]

Here we recall that \( o = \{(x_i, t_i)\}_{i=1}^{\infty} \)

It is sufficient to show that the set of \((x_k, t_k)\) satisfying the constraint of Equation 4.3 is \( \mathcal{B} \)-measurable, since \( \mathcal{O}_y \) is the countable product of copies of \( \mathcal{B} \).

\( \mathcal{B} \) is the product space of the σ-algebras generated by the counting measure on \( X \), and the Lebesgue measure on \( \mathbb{R}^+ \). Every subset of \( X \) is measurable with respect to the counting
measure, as it as a space of countable cardinality. So we need only prove that the set of \( \{t_k\} \) satisfying the constraint of 4.3 is Lebesgue measurable.

Referring to 2.7, we see that:

\[
t_k = \tilde{w}_k + \sum_{i=1}^{k-1} \tilde{w}_i
\]

where \( \tilde{w}_i = \lambda_i w_i \) for some nonzero constant \( \lambda_i \). Since the support of \( w_i \) is \((0, \infty)\), and the set \( \{w_i\}_{i=1}^{k-1} \) is unconstrained in Equation 4.3, we can see that the support of \( \sum_{i=1}^{k-1} \tilde{w}_i \) is also \((0, \infty)\). Therefore the set of \( \{t_k\} \) satisfying the constraints of Equation 4.3 is equivalent to the following set:

\[
\{g + h : g \in J_2, h \in (0, \infty)\}
\]

This is an interval, so Lebesgue measurable. \( \square \)

**Lemma 4.6.** The image of an \( O_y \)-measurable set under \( C_y \) is \( F \)-measurable

**Proof.** \( O_y \) is the product of countable copies of \( B \), the \( \sigma \)-algebra on \( Y \), the system state space. Therefore, any \( O \)-measurable set \( A \) will be of the form:

\[
A = \prod_{i=1}^{\infty} A_i : \quad A_i \in B \quad \forall i
\]

Now by definition:

\[
C_y(A) = \bigcap_{i=1}^{\infty} \{\omega : \phi(i, y, \omega) \in A_i\}
\]

Each element of the intersection is \( F \)-measurable due to measurability of the flow map \( \phi \) (Theorem 3.7 ). Therefore, \( C_y(A) \) is \( F \)-measurable. \( \square \)

**Definition 4.7.** Probability measure on \( O_y \)

We define the function \( P : O_y \mapsto [0, 1] \) as follows:

\[
P(o) = V(C_y(o))
\]

The bijection under \( C_y \) of members of \( O_y \) and \( F \), (Lemmas 4.5, 4.6), combined with the fact the \( V \) is a probability measure, assures us that \( P \) is a probability measure.

We can now analyse the dynamics of Gillespie simulations probabilistically. In a biochemical system of the type the Gillespie algorithm attempts to model, we inevitably observe stability of the dynamics over time, despite their local stochasticity. We proceed to define this idea rigorously, and demonstrate its consequences.
Definition 4.8. **Time-Stable simulation state space**

For a given \( x \in X, y \in Y \), let

\[
A_{xy} = \left\{ o \in O_y : \bigcap_{n=1}^{\infty} \left( \bigcup_{m=n}^{\infty} \{ o_m : o_m|X = x \} \right) \right\}
\]

In other words, \( A_{xy} \) is the set of simulations in \( O_y \) that return to the substrate vector \( x \) infinitely often. We can see that Equation 4.4 is measurable. We define \( O_y \) to be time-stable (with respect to \( x \)) if there exists \( x \in X \) such that

\[
P(A_{xy}) = 1
\]

Lemma 4.9. Suppose \( O_y \) is time-stable with respect to some substrate vector \( x' \in X \). Then \( O_y \) is time stable with respect to any \( x \in X \). We may therefore alter our definition of time stability to remove dependence on a given substrate vector \( x \in X \).

Proof. For any \( o \in A_{x'y} \), we have a subsequence \( \{ o_{n_i} \}_{i=1}^{\infty} \) of elements of \( o \) whose substrate vector is equal to \( x' \). Let \( K_i \) be the event that there exists \( j \in \{ n_i, \ldots, n_{i+1} \} \) such that \( o_j|X = x \). We can see that \( \{ K_i \} \) are independent, identically distributed random variables, due to the following:

1. The evolution of the substrate vector in the Gillespie algorithm is dependent only on its current state (i.e., it is a Markov chain), due to independence of of sequence elements of sequences in the random sequence space.
2. The only system state \( K_i \) is dependent on is therefore \( o_{n_i} \), whose substrate vector is \( x \), for all \( i \).

The same reasoning assures us that the set of \( \sigma \)-algebras: \( \{ O_y^{n_i} \cap (O_y^{n_i-1})^c \}_{i=1}^{\infty} \) are mutually independent. We also see that

\[
K_i \in O_y^{n_i} \cap (O_y^{n_i-1})^c
\]

Let

\[
G_k = \sigma\left( \bigcup_{i=1}^{\infty} \{ O_y^{n_i} \cap (O_y^{n_i-1})^c \} \right)
\]

Now let \( K \) be the event that, for any \( i \in \mathbb{N} \), with \( i > n_1 \), there exists \( j \in \mathbb{N} \) such that \( j > i \) and \( o_j = x \), with \( j \geq n_1 \). Then

\[
K = A_{xy} = \bigcap_{i=1}^{\infty} \left( \bigcup_{j=n_i}^{\infty} K_j \right) \in \bigcap_{i=1}^{\infty} G_i
\]

So \( A_{xy} \) is a tail event with respect to the aforementioned set of \( \sigma \)-algebras, and, by Kolmogorov’s Zero-One Law [WIL91], has probability 0 or 1.

Now given \( o \in A_{x'y}, i \in \mathbb{N} \), we know that there exists \( j \) such that \( n_j > i \). In addition, \( o_{n_j}|X = x' \) by definition. Due to the assumptions in Definition 2.3, we are assured that there is a finite sequence of reactions that would take the substrate vector from \( x' \) to \( x \).
The probability of each of these reactions occurring is always strictly greater than zero, regardless of the system state, again by assumption. Therefore the product of these positive probabilities, which gives the probability of the aforementioned sequence of reactions occurring, is again greater than 0. This event would imply the occurrence of an element of $o$ with substrate vector $x'$, and index greater than $n_j$. This is an event contained within $K$, and therefore, $A_{xy}$. This shows that $P(A_{xy}) > 0$, so $P(A_{xy}) = 1$. □

The previous lemma shows that, given a time stable simulation state space, any Gillespie simulation will hit every substrate vector infinitely often with probability one. One would think that this does not make sense in the context of a biological system. However, note that the above proof gives no constraints on the time scale required to achieve such time stability.

**Corollary 4.10.** Suppose there exists a time stable simulation state space, $O_y$, on a Gillespie model $(X, R)$. Then every simulation state space on $(X, R)$ is time stable, regardless of initial system state. This allows us to generalise the notion of time stability from a property of a particular simulation state space to one of the whole Gillespie model.

**Proof.** Suppose $O_y$ is time stable. Given arbitrary $y' = (x', t') \in Y$, we are required to show that $O_{y'}$ is time stable. Now we know from Lemma 4.9 that, on $O_y$, $P(A_{x'y}) = 1$. Let

$$H = \{o \in O_y : \exists k \text{ s.t. } o_k|_X = x'\}$$

Time stability ensures that $P(H) = 1$. Therefore $P(H \cap A_{x'y}) = 1$. So any simulation in $O_y$ that hits $x'$, returns to hit $x'$ again infinitely often, with probability one. But this is equivalent to saying that any simulation with initial substrate vector $x'$, returns to hit $x'$ again infinitely often, with probability one, due to memorylessness of the Gillespie algorithm. This implies that $O_{y'}$ is time stable. □

We proceed to prove the almost-sure existence of a limiting probability for elements of a Gillespie simulation on a time stable model to take a given substrate state. This then allows us to define a measure on the substrate state space proportional to the aforementioned limiting probability.

**Definition 4.11.** Given a time stable simulation space $O_y$, an arbitrary fixed $x \in X$, and an element $o \in A_{xy}$ containing a subsequence $\{o_{n_i}\}_{i=1}^{\infty}$ with $o_{n_i}|_X = x$, we define

$$N^o_i = n^o_i - n^o_{i-1}; \quad N^o_1 = n^o_1$$

Note that these random variable $N^o_i$ are independent and identically distributed (with respect to both $o$ and $i$), by a similar argument to that of the independence of $\{K_i\}$ in Lemma 4.9. So their distribution is solely a function of $x$, and not $O_y$. We take the random variable $N^x$ to be a representative random variable of the set. In other words it shares their distribution. We term the distribution of $N^x$ to be the **return distribution** of $x$. 


Lemma 4.12. For a given time stable Gillespie model, if the mean of \( N^{x'} \), \( \mu_{x'} \), is finite for a given \( x' \in X \), then the mean of \( N^x \) is finite for every \( x \in X \). We refer to such a model as strongly time stable. Any time stable Gillespie model that does not satisfy this property is weakly time stable.

Proof. Let \( C_{x'x} \) be the random variable denoting the number of steps a Gillespie simulation starting at \( x' \) takes to reach \( x \). Define \( C_{xx'} \) similarly. Then we see that

\[
\mathbb{E}(N^x) \leq \mathbb{E}(C_{x'x}) + \mathbb{E}(C_{xx'}) + \mathbb{E}(C_{xx'})
\]

(1) \( \mathbb{E}(C_{xx'}) < \infty \):
For a simulation \( o \) with subsequence \( \{o_n\} \) of system states with substrate vector \( x' \), let \( A \) be the event that, for a given \( i \), there exists \( k \in [n_i, n_{i+1}] \) such that \( o_k|_X = x \), with \( p \) its corresponding probability. Then

\[
p \times \mathbb{E}(N^{x'}|A) \leq \mu_{x'}
\]

The reasoning is thus: Let us denote the probability space of \( N^{x'} \) as \( (\Omega, \mathcal{F}, P) \). Then

\[
\mu_{x'} = \int_{\Omega} N^{x'} dP = \int_{A} N^{x'} dP + \int_{\Omega \setminus A} N^{x'} dP
\]

All terms are positive due to non-negativity of the support of \( N^{x'} \). Now if \( \int_{A} N^{x'} dP \geq \frac{1}{p} \times \mu_{x'} \), we have:

\[
\int_{A} N^{x'} dP \geq p \times \int_{A} \mu_{x'} dP = p \times \frac{1}{p} \times \mu_{x'} \quad \downarrow
\]

Now \( C_{xx'} \leq \{N^{x'}|A\} \) by definition, so the result follows.

(2) \( \mathbb{E}(C_{x'x}) < \infty \):

\[
\mathbb{E}(C_{x'x}) = \sum_{i=1}^{\infty} i \times p_i
\]

Here, \( p_i \) is the probability that a Gillespie simulation with initial substrate vector \( x' \) has a substrate vector \( x \) after \( i \) steps. Let \( k \) be the probability that the simulation returns to \( x' \) without hitting \( x \). Then \( k < 1 \), by time stability of the model. We also have

\[
\sum_{i>n \times \mu_{x'}} p_i < k^n
\]

Now take \( \bar{p} = \sup_{i \leq \mu_{x'}} (p_i) \). Then

\[
\mathbb{E}(C_{x'x}) \leq \left( \sum_{i=1}^{\infty} k^i \right) \left( \sum_{i \leq \mu_{x'}} i \times \bar{p} \right) < \infty
\]

\( \square \)
**Theorem 4.13.** Let $O_y$ be a simulation state space on a time stable Gillespie Model $(X, R)$. Fix an arbitrary $x \in X$, and, for a given $o \in O_y$, let

$$B_{n}^{o,x} = \left\{ \frac{1}{n} \times \# \{ 0 \leq k < n : o_k|_X = x \} \right\}$$

Suppose that the model is strongly time stable, so that $N^x$ has finite mean, $\mu$. Recall that $\mu$ is independent of the initial state $y$ of $O_y$. Then we claim that

$$P \left( \left\{ o : \liminf_{n \to \infty} B_{n}^{o,x} = \limsup_{n \to \infty} B_{n}^{o,x} = \frac{1}{\mu} \right\} \right) = 1$$

In other words, the subset of $O_y$ in which $\lim_{n \to \infty} B_{n}^{o,x}$ exists and equals $\frac{1}{\mu}$ has probability one.

Now suppose $N^x$ has infinite mean. Then

$$P ( \{ \liminf_{n \to \infty} B_{n}^{o,x} = 0 \} ) = 1$$

**Proof.**

We deal with the case where $N^x$ has finite mean first:

We are assured that $A_{xy}$ is a set of measure one, by definition. For every $o \in A_{xy}$, there exists $\{ o_i \}_{i=1}^\infty$ with $o_i|_X = x$. Therefore, on this set, by the strong law of large numbers:

$$P \left( A_{xy} \cap \left\{ o : \lim_{i \to \infty} \frac{1}{i} \sum_{k=1}^i N^x_k = \mu \right\}^c \right) = 0$$

This implies

$$P \left( \left\{ o : \lim_{i \to \infty} \frac{1}{i} \sum_{k=1}^i N^x_k = \mu \right\} \right) = 1$$

Now

$$\left\{ \lim_{j \to \infty} B_{j}^{o,x} = \frac{1}{\mu} \right\} = \left\{ \lim_{j \to \infty} \frac{1}{j} \sum_{i=1}^j N^o_i = \mu \right\} = \left\{ \lim_{j \to \infty} \frac{1}{j} \sum_{i=1}^j N^o_i = \mu \right\}$$

Thus proving the theorem.

The proof is more involved where $N^x$ has infinite mean:

A sufficient condition for the claim is that

$$\forall \epsilon > 0 : P \left( \left\{ o : \bigcap_{i=1}^{\infty} \bigcup_{j=1}^{\infty} \{ B_{j}^{o} > \epsilon \} \right\} \right) = 0 \quad (4.5)$$

Now

$$\{ B_{j}^{o} > \epsilon \} = \{ n^o_{c_j} < \epsilon j \} = \left\{ \sum_{i=1}^{c_j} N^o_i < \epsilon j \right\}$$
where \( c_j = [\epsilon_j] + 1 \), the value of \( \epsilon_j \) rounded up to the nearest positive integer

Therefore (4.5) is equivalent to

\[
\forall \epsilon > 0 : \mathcal{P} \left( \left\{ o : \lim_{i \to \infty} \bigcup_{j=i}^{\infty} \left\{ \sum_{k=1}^{c_j} N^o_k < \epsilon_j \right\} \right\} \right) = 0 \quad (4.6)
\]

We note that \( \epsilon_j \leq c_j \). Therefore (4.6) is implied by:

\[
\forall \epsilon > 0 : \mathcal{P} \left( \left\{ o : \lim_{i \to \infty} \bigcup_{j=i}^{\infty} \left\{ \frac{1}{c_j} \sum_{k=1}^{c_j} N^o_k < 1 \right\} \right\} \right) = 0 \quad (4.7)
\]

Regardless of the value of \( c_j \), the random variable \( \tilde{N}^o_{k,j} = \frac{1}{c_j} N^o_k \) will have infinite mean, since this property is invariant under scaling. With our new notation, (4.7) is equivalent to

\[
\forall \epsilon > 0 : \mathcal{P} \left( \left\{ o : \lim_{i \to \infty} \bigcup_{j=i}^{\infty} \left\{ \sum_{k=1}^{c_j} \tilde{N}^o_{k,j} < 1 \right\} \right\} \right) = 0 \quad (4.8)
\]

A sufficient condition for the above is that there exists some value of \( j \) with \( \tilde{N}^o_{k,j} > 1 \), with probability one. Such an occurrence is a tail event, by the same reasoning as given in Lemma 4.9 regarding the set \( K \). Therefore it has either probability 0 or 1. Since any element \( \tilde{N}^o_{k,j} > 1 \) has infinite mean, there is a strictly positive probability that it will be greater than one, ruling out the former option. We are done.

\[ \square \]

**Lemma 4.14.** A random variable with non-negative support must have defined mean, whether finite or infinite.

**Proof.** The expected value of a random variable \( X \) on a probability space \( (\Omega, \mathcal{F}, \mathcal{P}) \) is defined as the Lebesgue integral:

\[
\int_{\Omega} X \, d\mathcal{P}
\]

This does not exist only when both the positive and negative components of the integral both sum to infinity. However, if \( X \) has non-negative support, the above integral has no negative component.

\[ \square \]

**Corollary 4.15.** Any substrate vector on a time-stable Gillespie model must satisfy one of the conditions of Theorem 4.13. So any time stable Gillespie model is either strongly or weakly time stable.
Definition 4.16. Given a strongly time stable Gillespie Model, we we attach a measure \( \mathcal{L} : X \to [0,1] \) as follows [FAY95]:

\[
\mathcal{L}(x) = \frac{1}{\mu_x}
\]

Here, \( \mu_x \) is the mean value of \( N^x \), the return distribution of \( x \). Theorem 4.13 and Corollary 4.15 show us that it is defined for all \( x \in X \). Since it is just a weighted form of the counting measure, we neglect to prove that it does indeed define a measure. We name \( \mathcal{L} \) the **Limiting Probability** of \( X \). Note that this is a probability measure. By Theorem 4.13:

\[
P\left( \bigcap_{x \in X} \{ o : \liminf_{n \to \infty} B_{n}^{o,x} = \limsup_{n \to \infty} B_{n}^{o,x} \} \right) = 1
\]

Taking a simulation \( o \) from the above set, we have:

\[
\mathcal{L}(X) = P\left( \bigcup_{x \in X} B_{n}^{o,x} \right) = 1
\]

5. **A Time Stability Heuristic**

**Notation 5.1.**

1. We take \( d : X \times X \to \mathbb{R}^+ \) to be the \( L_1 \) metric on \( X \). So

\[
d(x, x') = \sum_{i=1}^{n} |x_i - x'_i|
\]

2. We take \( B(x, r) \) to define a closed ball with respect to the \( L_1 \) metric. So

\[
B(x, r) = \{ x' \in X : d(x, x') \leq r \}
\]

**Definition 5.2. Rests**

Consider a Gillespie model \( (X, R) \), with \( A \subset X \). Suppose we have a simulation \( o \in O \), with a finite string of elements: \( \{ o_i \}_{i=k}^{m} \).

1. \( o_k \mid X \notin A \)
2. \( o_i \mid X \in A \ \forall i = \{ k + 1, \ldots, m \} \)
3. \( o_{m+1} \notin A \)

Then we define the string \( \{ o_i \}_{i=k+1}^{m} \) to be a **rest** of \( o \) in \( A \), of length \( m - k \).

Suppose we replace conditions (2) and (3) with:

4. \( o_i \mid X \in A \ \forall i > k \)

Then we refer to the string \( \{ o_i \}_{i=k+1}^{\infty} \) as an **infinite rest** of \( o \) in \( A \).

Define \( x \in A \) as the substrate vector: \( o_k \mid X \). We refer to \( x \) as the **entry point** of the rest.
Lemma 5.3. Suppose we have two results of a subset $A$, with identical entry point $x \in A$. Then the random variables denoting resting length are independent and identically distributed, with defined (possibly infinite) mean.

Proof. Independence and identical distribution are a consequence of the memorylessness of the Gillespie Algorithm. The defined mean is a consequence of 4.14. □

Definition 5.4. Stable Mass Model
We define a Gillespie Model $(X, R)$ to be of stable mass if there exists a subset $N \subset X$ of the form $N = B(x, r)$ such that the following condition is satisfied for all Gillespie simulations $o$:

$$\exists c \in (0.5, 1) : \text{s.t. } o_k|_X \notin N \Rightarrow P\left(d(o_{k+1}|_X, N) < d(o_k|_X, N)\right) > c$$

Here, we assume that the reactions of the system satisfy the assumptions of Definition 2.3.

Theorem 5.5. A Gillespie Model $(X, R)$ of stable mass is also strongly time stable

Proof. We know that the set $N$ is of the form $B(x, r)$ by definition. Let $y = (x, 0)$. For a simulation $o \in O_y$, let us denote by $Q_o$ the expected resting length of $o$ in $X/N$. We prove this is finite in the next lemma. Assuming for now that it is indeed finite, we know that there exists $x \in N$ such that the expected resting time of $o$ in $X/x$ is finite, due to the fact that $N$ contains a finite number of substrate vectors. But this is equivalent to stating that the expected value of the return distribution of $x$ is finite, which implies that the Gillespie model is strongly time stable. □

Lemma 5.6. The expected resting time of a simulation $o$ in $X/N$ exists and is finite in a stable mass model, where $o_1|_X \in N$.

Proof. We know that the set $N$ is of the form $B(x, r)$ by definition. Let $y = (x, 0)$. Then, for a simulation $o \in O_y$, let us define the function:

$$f : O_y \mapsto \mathbb{Z}^N; \quad f(o)_k = d(o_k|_X, x)$$

Here, $\mathbb{Z}^N$ is the sequence space on $\mathbb{Z}$. We can see that $f$ is measurable. Also,

$$f(o)_k > r \Leftrightarrow o_k|_X \notin N$$

Given a rest of $o$ in $X/N$: $\{o_i\}_{i=j}^{j+m}$, with unknown length $m$, we wish to find the expected length $m$ of the rest, assuming that it exists. This transforms to the problem: Given the information that $f(o)_k = r + 1$, what is the expected first return time of $\{f(o)_i\}$ to the
interval \([0,r]\), assuming that it exists?

Define the random variables \(\{Z_i\}_{i=k}^m\) as follows:

\[
Z_i = \begin{cases} 
1 & \text{if } f(o_i) \geq f(o_{i+1}) \\
-1 & \text{if } f(o_i) < f(o_{i+1}) \\
1 & \text{if } i = k
\end{cases}
\]

Then \(S_j = \sum_{i=k}^j Z_i\) is a biased random walk starting at 1. The time of the first expected hitting of \(S_j\) to the point 0 is always greater or equal to the expected value of \(m\), as \(S_j\) is by definition greater or equal to \(f(o_j) - f(o_k)\). As \(i\) tends to infinity, \(S_i\) will, with probability one, eventually be smaller or equal to \(\tilde{S}_i\), where:

\[
\tilde{S}_j = \sum_{i=k}^j \tilde{Z}_i; \quad \tilde{Z}_i = \begin{cases} 
1 & \text{with probability } 1-c \\
-1 & \text{with probability } c \\
1 & \text{if } i = k
\end{cases}
\]

This is due to the fact that the probability of the event \(\{Z_i = -1\}\) is always greater than \(c\), by the definition of mass stability. We now show that a first hitting time exists with probability one for \(\{\tilde{S}_j\}\), which implies that it exists for \(\{S_j\}\) with probability one as well:

Calculation gives us the following:

\[
E(\tilde{S}_n) = 1 + (n - 1)(1 - 2c) \\
Var(\tilde{S}_n) = 1 + (n - 1)(1 - c)(1 + c)^2c
\]

Applying Chebyshev’s Inequality [WIL91], gives:

\[
P \left( |\tilde{S}_n - E(\tilde{S}_n)| \geq k \times \sqrt{Var(\tilde{S}_n)} \right) < \frac{1}{k^2}
\]

Since \(E(S_n)\) decreases at a rate proportional to \(n\) (since \(1 - 2c < 0\)), while \(\sqrt{Var(S_n)}\) increases at a rate proportional to the square root of \(n\), one can see that \(\{\tilde{S}_n\}\) will almost surely hit 0 eventually, as \(n\) increases. So \(m\) exists with probability one.

It remains to show that the expected value of this first hitting time, for the sequence \(\{\tilde{S}_i\}\), is finite. This implies that the same is true for \(\{S_i\}\), which in turn shows that the expected value of \(m\) is finite.

Let \(H\) be the random variable denoting the length of steps required for the random walk \(\tilde{S}_i\) to hit zero, and \(p_i\) be the probability of the event \(\{H = i\}\) (which is only nonzero when \(i\) is odd). Then

\[
p_{2i+1} = \binom{2i + 1}{i}c^{i+1}(1-c)^i
\]

\[
E(H) = \sum_{i=0}^{\infty} i p_i \approx \sum_{i=1}^{\infty} \left( 2i + 1 \right) \left( \frac{2i + 1}{2i} \right)^{\frac{3}{2}} c(4c(1-c))^i \frac{1}{\sqrt{\pi n}} 
\]

Equation 5.1 uses Stirling’s approximation. We note that convergence of the approximation is sufficient to prove that of the original summation, due to the sum of error terms being bounded. Now \(4c(1-c) < 1\), due to the fact that \(c \in (0.5, 1)\). The presence of this exponentially decreasing term assures us that the sum converges. \(\square\)
Example 5.7. **Comparison of Time Stability of Random Walks**

Pólya proved that a random walk on a one or two dimensional integer lattice will return to its starting point with probability one, but that in higher dimensions, the probability of return was strictly smaller than one. Also proven was that the expected return time of the one and two dimensional random walks to their starting point was infinite [POL21]. Subsequent research estimated the probability of return on a three dimensional integer lattice to be approximately 0.34 [GLA77]. In Appendix A, we have formulated Gillespie Models equivalent to the one and three dimensional random walks, just described. With respect to our terminology, the first is weakly time stable, while the second is not time stable at all.

We construct and prove strong time stability of a weakly constrained three dimensional random walk Gillespie model, in Appendix A.4, using Theorem 5.5. The counterintuitive physical interpretation is that an unbiased random walk will meet a given point on the $\mathbb{Z}^3$ lattice with probability less or equal to 0.35, while one in which a weak drift term towards the origin is present outside of a ball around the origin, will meet every point with probability one.

Example 5.8. **A Circadian Model**

Consider our Circadian Model described in Appendix B, and graphed in Figure 3. The probability of a reaction of decreasing mass, given substrate vector $x \in X$ is equal to:

$$\sum_{i=1}^{10} \frac{R_{i+10}(x)}{R_i(x) + R_{i+10}(x)}$$

A sufficient condition for mass stability of the model around a set of the form $B(0,r)$, for some finite $r$, is that the above summation is always greater than some $c > 0.5$, when $x$ is outside of the set $B(0,r)$. Upon algebraic manipulation, this reduces to the following inequality being satisfied, for some $K > 0$, dependent on $r$:

$$(v_2 - v_3)x_1 + v_4x_{10} - \frac{v_1}{1 + x_{10}^2} > K \sum_{i=1}^{10} x_i$$

This inequality is not satisfied mathematically on all but a set of finite mass, as would be required for mass stability around a set of the form previously described. It fails due to the fact that the ratio between the quantities $\sum_{i=2}^{9} x_i$ and $x_1$, is unbounded. However, incorporation of a bound in the Gillespie model, which would be physically realistic, given that $x_1$ levels drive the rate of production of $\{x_2, ..., x_9\}$, would imply mass stability of the model.

Time Stability with respect to External Time

Time stability is defined with respect to internal time; the number of system state changes a Gillespie undergoes. One easily observes that it is preserved under the transformation to external time. What is not so clear, however, is whether strong time stability is invariant under this transformation. In other words, does the (in)finiteness of the expected value of the internal time return distribution determine that of its external counterpart?
Conjecture 5.9. There exist Gillespie models that are only weakly time stable, such that the expected external time between a simulation hitting the same substrate vector is finite.

Reasoning Consider the Modified Random walk given in Appendix A.2. The dynamics are the same as in the unmodified version with respect to internal timestep, and it is therefore weakly time stable. However, the amount of elapsed time between reactions decreases doubly exponentially as the mass of the system increases. It could therefore be possible that the external expected return time between oscillations was finite. A sufficient condition for this to be true would be that there existed an interval $I = [-r, r]$, for some $r \in \mathbb{N}$, such that the expected elapsed resting time of $Z/I$ was finite. A heuristic for the proof would be to show the terms in the expansion of the expected value of this resting time decreased fast enough as $r$ increased, to allow the above to be true for some finite value of $r$. This would then prove it to be true for any value of $r$.

Note that computer simulation may not be a useful tool in the determination of time stability. A seemingly time stable system might in fact have a critical substrate state, unlikely to be reached after a computationally tractable length of time, which, when reached, has a probability of irreversibly changing the dynamics of a simulation in such a way that previously attained substrate states are no longer reached with probability one.

6. A Categorisation of the Concept of Oscillatory Dynamics on a Gillespie Model

The notion of an oscillating system is well defined in the deterministic setting. One merely need find a system state that is repeated after some defined time value, which we call the period of the oscillation. Adding an external noise to a deterministic oscillation does not complicate the definition unduly. The underlying trajectory would be unaffected by the noise values in such a setting, and could easily be uncovered by spectral analysis. In a Gillespie simulation, however, the path of the underlying trajectory will be determined by past noise values, which makes determination of period, and, indeed, what constitutes an oscillatory behaviour, ill defined. In this section we outline some possible means of arriving to such a definition.

Proposition 6.1. Any strongly time stable Gillespie model oscillates in the sense that there is an expected (finite) return time of a simulation on the model to any substrate vector it has already reached.

For a proof of the above proposition, refer to Section 4. Strong time stability, however, is not a sufficient condition for the existence of what we would empirically term an oscillatory model. For instance, a random walk on a finite lattice will revisit every point infinitely often, with a finite expected return time. We would however hardly characterise this as an oscillatory system.

The above proposition shows that the notion of eventual return to the same system state is ill-suited to the stochastic setting. Let us therefore consider another property of deterministic oscillators. A sine wave could be considered the most basic oscillatory system. The
function:

\[ f(x) = \sin(x) \]

has a period of \(2\pi\). We could describe any point on this trajectory by its phase, which would generally be defined as its value modulus \(2\pi\). An alternative definition of phase could be given by constructing a bijective mapping between the phase as previously described, and some other property of the trajectory. We do so by fixing a timestep \(\alpha\) such that the quantity \(f(t + \alpha) - f(t)\) is unique to the value of \(t\), modulus \(2\pi\). One appropriate value of \(\alpha\) is one that corresponds to one quarter of the period. Figure 1 graphs \(f(t + \alpha)\) against \(f(t)\). We see that this results in a perfect circle. We can now define the phase of a point \(f(t)\) by the angle of the point it corresponds to on the circle.

In a similar vein, a Gillespie simulation of the Circadian Model (Appendix B), part of which is plotted in Figure 2, was realised computationally. An algorithm (omitted) was created to determine an average period of oscillation, \(\beta\), for the PER1 protein. We use the word oscillation loosely here, as, since we have not yet constructed an exact definition. The algorithm determined the average spacing between peaks, where multiple vacillations in quick succession around a single local maximum were ignored. Let \(g(t)\) be the trajectory of the Gillespie simulation. Figure 4 provides a graph of \(g(t + \beta)\) against \(g(t)\). We note that the shape of the graph bears only a very superficial resemblance to the circle obtained under the analogous transformation of the sine function (Figure 1). However, a shared property of the graphs is the constant unidirectional change in angle with respect to a central point. This corresponds to the ‘phase’ of each model increasing in the same direction with time. We now construct a possible definition of a stochastic oscillator that is based on the existence of this property.

**Definition 6.2. Phase Function**

Pick \(c \in \mathbb{R}^n\). We define the phase function of \(c\) as follows:

\[
Q^n_c : \mathbb{R}^n \times \mathbb{R}^n \mapsto [0, 2\pi]^n
\]

\[(Q^n_c)_i(a,b) = \text{atan2}((a_i - c_i), (b_i - c_i)) \quad i \in \{1, \ldots, n\}\]

Here, \(\text{atan2}(a,b)\) gives the angle, in radians, between the positive \(x\)-axis and the vector from the origin to the Cartesian co-ordinate \((a, b)\). [MAT12].

**Definition 6.3. Jump Function**

Consider a Gillespie Model \((X, R)\) together with a positive integer \(\alpha\). Pick an \(x \in X\), and take \(y = (x, 0) \in Y\). Given \(o \in O_y\), we take:

\[
J_{\alpha,o} : X \mapsto X
\]

\[J_{\alpha,o}(x) = o_{\alpha}|_X\]

**Definition 6.4. Mapping to the Phase Space**

Consider a Gillespie Model \((X, R)\), where \(X \cong \mathbb{N}^n\) Pick a point \(c \in \mathbb{R}^n/X\), a positive
integer $\alpha \in \mathbb{N}$, and a Gillespie simulation $o$ with $o_1|X = x$. We define a mapping $T_{c,\alpha}$ from $X \times O(x,0)$ to $[0,2\pi)^n$ as follows:

$$T_{c,\alpha}(x,o) = Q^n_c(x,J_{\alpha,o}(x))$$

We also define:

$$H_{c,\alpha}(x) = \mathbb{E}(T(x)) = \int_{o \in O(x,o)} T_{c,\alpha}(x,o) \, dP$$

Our expected value is taken with respect to the probability measure espoused in Definition 4.7. We refer to $\text{Im}(H_{c,\alpha})$ as the phase space with respect to the parameters of $H$.

The $i^{th}$ component of $T_{c,\alpha}(x,o)$, to put it plainly, calculates the difference in angle between the two lines originating at $c_i$, and respectively ending at $x_i$ and the position of $x_i$ after $\alpha$ steps of the simulation $o$. $\mathbb{E}(T(x_i))$ gives the expected value of this angle over the probability space of simulations. We require that both lines are non-trivial (ie not a point), in order for such an angle to exist. The constraint of $c$ to $\mathbb{R}^n/X$ ensures this.

$H$, meanwhile, gives a family of mappings from the substrate vector space $X$ to the phase space $[0,2\pi)^n$, parameterised by the values $c$ and $\alpha$. Note that, since there are only a countable number of elements in $X$, any $H$-mapping is necessarily non-surjective, and any phase space is countable.

**Definition 6.5. Generators on the Phase Space**

Recall the flow map $\varphi$, from Definition 3.5. We define a family of mappings on the phase space, parameterised by values $c \in \mathbb{R}^n/X$, and $\alpha \in \mathbb{N}$, as follows:

$$K_{c,\alpha} : \text{Im}(H_{c,\alpha}) \mapsto [0,2\pi)^n$$

$$K_{c,\alpha}(h) = \left( \mathbb{E}\left(H_{c,\alpha}(\varphi|_X(1,\omega,y))| H_{c,\alpha}(y|_X) = h \right) - h \right) \mod 2\pi$$

Note that the expected value here is taken with respect to the probability measure $\mathcal{V}$ defined on $\Omega$ in Definition 3.4.

Given that a system state is in a given phase, with respect to some $c$ and $\alpha$, the function $K_{c,\alpha}$ outputs the expected value of the change in phase after one step of the Gillespie Algorithm. In an oscillatory system, we would want the direction of this change in phase to be invariant with respect to the original phase. In other words, we want $K$ to be an order preserving map. We give a rigorous definition of an order preserving map below:

**Definition 6.6. Order Preserving Map**

Suppose we pick three arbitrary vectors $h^1, h^2, h^3 \in \mathcal{K} \subset [0,2\pi)^n$, with the $i^{th}$ component of the vector $h^3$ denoted $h^3_i$. We define

$$f : \mathcal{K} \mapsto [0,2\pi)^n$$

to be an order preserving map if, for all $i \in \{1, ..., n\}$:

$$h^1_i > h^2_i > h^3_i \Rightarrow$$
(1) \( f(h_1^j) > f(h_2^j) > f(h_3^j) \) OR
(2) \( f(h_2^j) > f(h_3^j) > f(h_1^j) \) OR
(3) \( f(h_3^j) > f(h_1^j) > f(h_2^j) \)

In other words, the order of the points on the canonical circle formed by identifying the ends of the interval \([0, 2\pi)\), is preserved.

**Definition 6.7. Absolutely Oscillatory System**

We define a strongly time-stable Gillespie Model \((X, R)\) to be an absolutely oscillatory system if there exists \(c \in \mathbb{R}^n/X\), and \(\alpha \in \mathbb{N}\) such that \(K_{c,\alpha}\) is an order preserving map. We name \(K_{c,\alpha}\) a rotation map of the system. Note that it may not be unique.

Note that one could also define a relatively oscillating system by requiring \(K_{c,\alpha}\) to be order preserving on a restriction of its domain to a set of high limiting probability.

The obvious way to form a notion of the period of an absolutely oscillatory system would be to find the average ‘rotation’ realised by the rotation map over its domain. This cannot be done by iterating the rotation map infinitely, and finding the average rotation, a technique often used in a dynamical systems setting (See ‘Poincare Rotation Number’, [DEV92]). The reason is that the domain and range of the map are not equal. We instead proceed as follows:

**Definition 6.8. Measure on the Phase Space**

Assume we have a strongly time-stable Gillespie Model. Recall the Limiting probability measure on \(X\) defined in 4.16. We can transport it to any phase space of the form \(\text{Im}(H_{c,\alpha})\) as follows:

\[
\mathcal{L}(h) = \mathcal{L}\{x \in X : H_{c,\alpha}(x) = h\}
\]

Countability of both spaces makes measurability of the mapping trivial.

**Lemma 6.9.** Suppose \((X, R)\) is an absolutely oscillatory Gillespie model, with a rotation map \(K_{c,\alpha}\). Let us turn the (countable) elements of the phase space into a sequence \(\{h_i\}_{i=1}^{\infty}\). Let us define

\[
S_n = \sum_{i=1}^{n} K_{c,\alpha}(h_i)\mathcal{L}(h_i)
\]

Then \(\lim_{n \to \infty} S_n\) exists and is invariant with respect to permutations of the indexing of the set \(\{h_i\}\).

**Proof.**

\[
\sum_{m} \sum_{m} S_m \leq 2\pi \sum_{m} \mathcal{L}(h_m) \leq 2\pi
\]
Therefore \( \{S_n\} \) is a Cauchy sequence and convergent. Since every term in the summation is non-negative, it is also absolutely convergent, and the limit is therefore independent of the indexing of \( \{h_i\} \).

**Definition 6.10. Period of the Rotation Map of an Absolutely Oscillatory System**

Given a rotation map \( K_{c,\alpha} \), and taking \( S_n \) as in Lemma 6.9, we define the period of the rotation map \( \beta_{c,\alpha} \) of an oscillator as

\[
\lim_{n \to \infty} S_n
\]

**Lemma 6.11.**

Suppose \( K_{c,\alpha} \) is a rotation map. For a simulation \( o \), let

\[
\tilde{S}_k^o = \frac{1}{k} \sum_{i=2}^{k} \left( H_{c,\alpha}(o_i) - H_{c,\alpha}(o_{i-1}) \right)
\]

Then

\[
P(\{o : \lim_{k \to \infty} \tilde{S}_k^o = \beta_{c,\alpha}\}) = 1
\]

**Proof.** Given a subsequence \( \{o_{n_i}\} \) such that \( H_{c,\alpha}(o_{n_i}|X) = h_j \), we are assured, by the strong law of large numbers, that

\[
\lim_{k \to \infty} \frac{1}{k} \sum_{n_i=2}^{k} \left( H_{c,\alpha}(o_{n_i}) - H_{c,\alpha}(o_{n_i-1}) \right) = K_{c,\alpha}(h_j)
\]

with probability one. The result is then a consequence of Theorem 4.13. \( \square \)

**Conjecture 6.12.** Any two rotation maps of an absolutely oscillatory Gillespie Model have the same period

**Reasoning**

Given two rotation maps \( K_{c,\alpha} \) and \( K_{c',\alpha'} \), we would expect, by the strong law of large numbers, that

\[
P\left( \{ o \in O_y : (\lim_{k \to \infty} \frac{1}{k} \sum_{i=1}^{k} K_{c,\alpha}(o_i|X) = \beta_{c,\alpha}) \cap (\lim_{k \to \infty} \frac{1}{k} \sum_{i=1}^{k} K_{c',\alpha'}(o_i|X) = \beta_{c',\alpha'}) \} \right) = 1
\]

for any initial system state \( y \in Y \). If \( \beta_{c,\alpha} \) and \( \beta_{c',\alpha'} \) were different, then the above set of simulations would ‘wrap around’ the points \( c \) and \( c' \) at different rates, in the respective phase spaces. This would be equivalent to the limiting rate of oscillation of a simulation being different with respect to two different viewing points on the substrate state space, which would only be possible if both viewing points were not ‘centred’ inside the expected oscillation trajectory. However, the placing of the points \( c \) and \( c' \) are both necessarily ‘centred’ in such a way, in order for \( K_{c,\alpha} \) and \( K_{c',\alpha'} \) to define rotation maps.
Appendix A. Random Walk Models

A.1. One Dimensional Random Walk.
The following Gillespie Model \((X, R)\) recreates a random walk on the integer lattice:

1. \(X \equiv \mathbb{Z}\)
2. Reactions \(r_1, r_2\) satisfy assumptions of 2.3
3. \(R_1(x) = R_2(x) = 0.5\)

The following Gillespie Model \((X, R)\) recreates a random walk on the integer lattice:

1. \(X \equiv \mathbb{Z}\)
2. Reactions \(r_1, r_2\) satisfy assumptions of 2.3
3. \(R_1(x) = R_2(x) = 0.5(\exp(\exp(\sum_{i=1}^{n} x_i)))\)

A.3. Three Dimensional Random Walk.
The following Gillespie Model \((X, R)\) recreates a random walk on the three dimensional integer lattice:

1. \(X \equiv \mathbb{Z}^3\)
2. Reactions \(r_1, r_2, ..., r_6\) satisfy assumptions of 2.3
3. \(R_i(x) = \frac{1}{6} \forall i \in \{1, 2, ..., 6\}\)

A.4. Three Dimensional Weakly Constrained Random Walk. The following Gillespie Model \((X, R)\) recreates a weakly constrained random walk on the three dimensional integer lattice:

1. \(X \equiv \mathbb{Z}^3\)
2. Reactions \(r_1, r_2, ..., r_6\) satisfy assumptions of 2.3
3. For some \(r \in \mathbb{N}, d \in (0.5, 1)\), we have:
   \[
   R_i(x) = \begin{cases} 
   \frac{1}{6} & x \in B(0, r) \\
   \frac{1-d}{3} & x \notin B(0, r), i \in \{1, 2, 3\} \\
   \frac{d}{3} & x \notin B(0, r), i \in \{4, 5, 6\} 
   \end{cases}
   \]

Lemma A.1. The Three Dimensional Weakly Constrained Random Walk Model is strongly time stable

Proof. By Theorem 5.5, it is sufficient to prove that the model is of stable mass. But this is obvious upon observation of the definition of stable mass; for any Gillespie simulation \(o \in O\), we have:

\[o_k|X \notin N \Rightarrow \mathcal{P}(d(o_{k+1}|X, N) < d(o_k|X, N)) = 3 \left(\frac{d}{3}\right) = d > c\]

for some \(c > 0.5\). \(\Box\)
The existence of the circadian clock, nearly universal to animal species, is hypothesised to derive from a complex autoregulatory gene network, which undergoes one complete oscillation over an approximately 24 hour period [GOLO3]. The expression of the protein PER1 are understood to be involved in this process. Goldbeter et al. [GOL03] propose a 30 parameter model of the dynamics of PER1 expression levels, which they then realise through the Gillespie Algorithm. We simplified this model, while aiming to reflect the overall dynamics of the process. A summary of the simplified processes affecting PER1 regulation is described below, and derived from [MOR08] (in which an alternative simplified model is suggested):

(1) The presence of PER1 MRNA in the cell ribosome instigates translation of a protein we shall term IP1 (‘Intermediate Protein 1’). This is essentially a completely de-phosphorylated version of the PER1 protein.

(2) IP1 undergoes several stages of phosphorylation, at a constant rate that we shall term the protein forward rate, into IP2, IP3, etc.

(3) The final product realised after complete phosphorylation is the PER1 protein. The presence of PER1, which acts as a transcription factor, inhibits transcription of the PER1 MRNA.

Note that both the PER1 protein and PER1 MRNA in this process degrade constantly at a rate proportional to their overall level in the cell.

Upon computational experimentation, I determined that at least 8 intermediate phosphorylation stages were required to induce an obviously oscillatory Gillespie Algorithm realisation of the model. The Gillespie Model \((X, R)\) used is described below, and a graphical simulation is provided (Figure 3):

**CONSTANTS:**

(1) \(\Omega\) (Scaling constant, setting size of the system)
(2) \(v_1 = 30\Omega\) (MRNA transcription rate)
(3) \(v_2 = 36\) (MRNA degradation rate)
(4) \(v_3 = 2\) (MRNA translation rate)
(5) \(v_4 = 0.5\) (Transcription Factor degradation rate)
(6) \(\lambda = 1.666667\) (Phosphorylation rate)

**SUBSTRATES:**

\(X_1\) describes the quantity of PER1 MRNA in the ribosome.
\(X_2, ..., X_9\) describe the quantities of the intermediate proteins in the nucleus.
\(X_{10}\) describes the quantity of the PER1 protein in the nucleus.

\[X = (X_1, X_2, ..., X_{10}) \approx N^{10}\]

**REACTIONS**
The reactions of the system, \( \{r_1, r_2, \ldots, r_{20}\} \), follow the assumptions of Definition 2.3. The reaction rate function, \( R \), is as follows:

\[
\begin{align*}
R_1(x) &= \frac{v_1}{1 + x_4^{10}} \\
R_2(x) &= v_3 \times x_1 \\
R_i(x) &= \lambda \times x_{i-1} & i \in \{3, 4, \ldots, 10\} \\
R_{11}(x) &= v_2 \times x_1 \\
R_{20}(x) &= v_4 \times x_{10}
\end{align*}
\]

**Appendix C. Deterministic Analogues**

**Definition C.1. Deterministic Analogue**

Consider a Gillespie Model \((X, R)\), with \( n \) substrate and \( m \) reaction types. Recall that \( X \cong \mathbb{N}^n \).

We define the deterministic analogue of the Gillespie Model \((X, R)\) to be a pair \((\tilde{R}_n, \tilde{R})\), satisfying the properties:

1. \( \tilde{R} : \mathbb{R}^n \rightarrow \mathbb{R}^m \)
2. \( \tilde{R}(x) = R(x) \quad \forall x \in \mathbb{R}^n \cap X \)
3. Given any initial value problem of the form:
   \[
x'(t) = \tilde{R}(x(t)) \quad (x_0, t_0) \in (\mathbb{R}^n \cap X, \mathbb{R}^+) \]
   We have: \( x_i(t) \geq 0 \quad \forall t > 0, i \in 1 \ldots n \)

We say \( \tilde{R} \) is an extension of \( R \) to \( \mathbb{R}^n \). It is not unique.

We define the deterministic analogue of a Gillespie trajectory, with initial substrate vector \( x_0 \) and elapsed time \( t_0 \), to be a solution of the Initial Value Problem:

\[
x'(t) = \tilde{R}(x(t))
\]

Definition C.1 gives the sense that choosing an appropriate deterministic analogue to a Gillespie Model presents a problem. In practice, most Gillespie Models are derived from pre-existing deterministic analogues, rather than vice versa, sidestepping the problem. In any case, a computationally practicable Gillespie model is likely to have a closed-form expression for the reaction rate vector field, which will admit an obvious continuous extension, as can be seen in, for example, the Circadian Model described in Appendix B.

**Conjecture C.2.** Given any Gillespie Model \((X, R)\), there exists a deterministic analogue \((\mathbb{R}^n, \tilde{R})\) such that \( \tilde{R} \) is both continuous and infinitely differentiable.

A proof of the conjecture is outside the scope of the essay. Suffice to say that, given \( n \) points in \( \mathbb{R}^n \), it is possible to construct a degree \( n \) polynomial passing through each of them. Similarly, given a countable, nowhere-dense, subset of \( \mathbb{R}^n \), it is possible to construct a power series function, which is by definition continuous and infinitely differentiable, that passes through each point.
## Appendix D. Index of Terminology

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Appendix E. Figures

Figure 1. Plot of \( \sin(x) \) against \( \sin(x + \alpha) \); \( \alpha = 0.5\pi \)

![Figure 1](image1.png)

Figure 2. A trajectory of the Deterministic Analogue to the Circadian Model described in Appendix B

![Figure 2](image2.png)
Figure 3. A Gillespie trajectory of the Circadian Model described in Appendix B, with scale parameter $\Omega = 1$.

Figure 4. Plot of $g(t+\beta)$ against $g(t)$. Here, $g(t)$ is the Gillespie trajectory of PER1 protein in a Gillespie simulation of the Circadian model. $\beta = 9.8$. 
Appendix F. A list of definitions and results that have analogues in Markov Chain Theory

Strongly and weakly time stable Gillespie Models correspond to positive recurrent and recurrent ergodic Markov Chains [FAY95]. The construction of these objects involves Lemma 4.9 and Corollary 4.10, which have analogues in [FAY95].

The formulation of Lemma 4.12 was motivated by a similar result in [FAY95].

Theorem 4.13 corresponds to the Ergodic Theorem for Markov Chains [FAY95]

The idea of Definition 4.16 was motivated by an identical result in [FAY95]

All of the proofs of the above results were arrived at completely independently of [FAY95], and do not bear a resemblance to their existing counterparts.
7. Bibliography


[FAY95] Fayolle et al., *Topics in the Constructive Theory of Countable Markov Chains* CUP 1995


[POL21] Pólya G. *Über eine Aufgabe der Wahrscheinlichkeitsrechnung betreffend die Irrfahrt im Strassennetz* Mathematische Annalen, 1921
