

Chapter 2

Methods

We here review in more detail the mathematical formalism underlying the modelling of stochasticity in population systems, which will be used throughout the rest of the thesis. We begin with revisiting the basic mathematical definitions which lead to the concept of homogeneous stochastic process. Those describe the dynamics of the chemical concentrations in a stochastic formalism. Homogeneous processes satisfy the master equation; the fundamental equation for the stochastic dynamics.

An analytic procedure that can always be carried out on the master equation is the deterministic limit, which describes the time evolution of the averages of the state variables. This limit is tantamount to apply the mass action law to the reaction scheme. The deterministic equations give a macroscopic description of the dynamics of the system and are one of the major methodologies for the theoretical study of biological and chemical systems. Their use is exemplified by the book by Murray [1]. This older tradition involved both the study of simple, analytically tractable, models and dynamical systems theory. The former was concerned with the mathematical investigation of specific differential equations of few variables and the latter with general results on stability of attractors, topological notions, bifurcation theory, and so on [2].

In this thesis, we are interested in a parallel methodology for the mathematical analysis of the full stochastic model [3, 4]. This is much less widely appreciated than that for the corresponding deterministic analysis. Using a variant of the Kramers-Moyal expansion [3], discussed in this chapter, stochastic differential equations can be derived from the master equation when the number of molecules is large. As explained in the introduction, the stochasticity originates from the discreteness of the molecules. Techniques from the theory of stochastic processes can be used to attack these equations analytically, just as in the deterministic case.

2.1 Stochastic Formulation of Chemical Systems

The dynamics of a chemical system is mathematically described by a homogeneous process, which is defined in the following. In doing this, we start from the concept of a stochastic variable which is assumed to be known. We then proceed to define the master equation, starting from associating to every chemical reaction a transition rate. The reference for the whole section is the book of van Kampen [4].

2.1.1 Stochastic Processes

A *stochastic process* is a stochastic variable, \mathcal{N} , which depends on time t . In the following, we assume that \mathcal{N} takes discrete values and that the time t is a continuous variable. Each stochastic process can be represented by giving the explicit expression of the function $\mathcal{N}(t)$ or, as done frequently, by means of the *Kolmogorov hierarchy*. This is the set of all the $P_r(n_1, t_1; n_2, t_2; \dots; n_r, t_r)$, indexed by $r \in \mathbb{N}$, which indicate the probability of measuring the values n_1, n_2, \dots, n_r of $\mathcal{N}(t)$ at the times t_1, t_2, \dots, t_r . In the following, we call them probability density functions. The statistical properties of a stochastic process are given by the following averages:

$$\langle \mathcal{N}(t_1) \dots \mathcal{N}(t_r) \rangle = \sum_{n_1, n_2, \dots, n_r} P_r(n_1, t_1; \dots; n_r, t_r) n_1 \dots n_r. \quad (2.1.1)$$

The sum $\sum_{n_1, n_2, \dots, n_r}$ is over all possible n_1, \dots, n_r , which are the values assumed by \mathcal{N} . If \mathcal{N} takes continuous values, an analogous definition to Eq. (2.1.1) holds, but with the sum replaced by an integral.

Note the difference between the stochastic variable \mathcal{N} and the value that it assumes, n . As customarily done in textbooks for physicists, both shall be indicated with n to lighten the notation. The meaning shall be given by the sense of the discussion.

2.1.2 Markovian Processes

For a given stochastic process, we may define the *conditional probabilities*:

$$P_{r|s}(n_1, t_1; \dots; n_r, t_r | m_1, \tau_1; \dots; m_s, \tau_s) = \frac{P_{r+s}(n_1, t_1; \dots; n_r, t_r; m_1, \tau_1; \dots; m_s, \tau_s)}{P_s(m_1, \tau_1, \dots, m_s, \tau_s)}.$$

They express the probability of measuring the values n_1, \dots, n_r at the times t_1, \dots, t_r ; given that we previously measured the values m_1, \dots, m_s , at the times τ_1, \dots, τ_s . Clearly, the times are ordered such that $\tau_1 \leq \tau_2 \leq \dots \leq t_1 \leq \dots \leq t_r$.

A stochastic process is called *Markovian* if the outcome of any future measurement is determined only by the most recent measurement. In other words, the following condition must hold:

$$P_{r|s}(n_1, t_1; \dots; n_r, t_r | m_1, \tau_1; \dots; m_s, \tau_s) = P_{r|1}(n_1, t_1; \dots; n_r, t_r | m_1, \tau_1). \quad (2.1.2)$$

This is called the *Markov property*. The meaning of the Markov property is that the system is memoryless, in the sense that the history of the dynamics does not affect its future. For systems of chemical reactions this is not strictly true, as we know that the laws of physics conserve memory of the past. However, if we suppose that the system is sufficiently mixed, the effects of the memory are relevant on very short timescales, so that the Markov property is reasonably satisfied on the timescales of interest.

Markov processes are fully described by just two elements of the Kolmogorov hierarchy: $P_1(n, t) \equiv P(n, t)$ and $P_{1|1}(n, t | n', t') \equiv P(n, t | n', t')$. In fact, any other probability density function can be expressed using these two, by making use of the Markov property and the definition of the conditional probabilities. Let us consider, for example, P_3 . We have that:

$$\begin{aligned} P_3(n_1, t_1; n_2, t_2; n_3, t_3) &= P(n_3, t_3 | n_2, t_2; n_1, t_1) P_2(n_2, t_2; n_1, t_1) \\ &= P(n_3, t_3 | n_2, t_2) P_2(n_2, t_2; n_1, t_1) \\ &= P(n_3, t_3 | n_2, t_2) P(n_2, t_2 | n_1, t_1) P_1(n_1, t_1). \end{aligned} \quad (2.1.3)$$

This argument generalises straightforwardly to any P_n .

The statistical properties of a Markov process are thus given by the *mean*, $\langle n(t) \rangle$, and the *temporal autocorrelation*, $\langle n(t)n(t_0) \rangle$.

2.1.3 Homogeneous Processes

A stochastic process, Markovian or not, is called *stationary* if every average (2.1.1) is invariant under time translation. In formulae:

$$\langle n(t_1 + \bar{t}) \dots n(t_r + \bar{t}) \rangle = \langle n(t_1) \dots n(t_r) \rangle, \quad \forall \bar{t}, \forall r. \quad (2.1.4)$$

As a consequence, the mean of a stationary process, $\langle n(t) \rangle = \langle n \rangle$, does not depend on time.

Note that if the stochastic process is Markovian and stationary, the conditional probability $P(n, t | n', t') \equiv W_{\Delta t}(n | n')$ depends only on the time difference, $\Delta t = t - t'$. Moreover, $P(n, t) \equiv P_s(n)$ is time-independent and it is called the *stationary distribution*.

In this thesis, we are interested in a class of Markovian stochastic processes with a further condition slightly weaker than stationarity. Specifically, we wish to describe

stationary systems initialised at non-stationary conditions. These processes are called *homogeneous*. They are characterised by having each average (2.1.1), except the first one, invariant under time translation. In such case, the conditional probability $P(n, t|n', t') \equiv W_{\Delta t}(n|n')$ still depends on the time difference Δt , but $P(n, t)$ now retains a dependence on time t .

2.1.4 The Master Equation

The dynamics of an homogeneous process is specified once the transition probabilities per unit of time, or *transition rates*, are given. These indicate the probability per unit time that the system goes from state n' to the state $n \neq n'$.

Suppose $n(t)$ is a homogeneous process, described by the functions $P(n, t)$ and $W_{\Delta t}(n|n')$. Then, the transition rate, T , is defined as:

$$T(n|n') = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} W_{\Delta t}(n|n'), \quad n \neq n'. \quad (2.1.5)$$

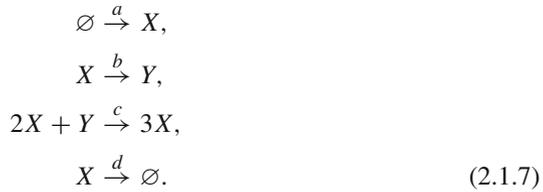
For chemical systems, the explicit expressions for the transition rates can be obtained directly from the chemical reactions. The problem becomes to calculate the probability density function of the number of molecules, $P(n, t)$, given the knowledge of the system at the initial time, $P(n, 0) = \delta_{n, n_0}$. The $P(n, t)$ satisfies an equation which governs the dynamics of homogeneous processes, and is called the *master equation*:

$$\partial_t P(n, t) \equiv \frac{\partial}{\partial t} P(n, t) = \sum_{n' \neq n} T(n|n') P(n', t) - T(n'|n) P(n, t). \quad (2.1.6)$$

Solving the master equation by setting $\partial_t P = 0$, leads to the stationary solution, $P_s(n)$. It has been shown that for a general initial condition: $P(n, t) \rightarrow P_s(n)$, as $t \rightarrow \infty$. In other words, homogeneous processes become stationary at long times.

2.1.5 Choosing the Transition Rates

Chemical systems are specified by means of their chemical reactions, which describe the possible interactions among the molecules. For example, let us suppose that molecules of two chemical species, called respectively X and Y , interact in a cell of volume V . For illustrative purposes we may assume that the chemical reactions are given by the following scheme, called the Brusselator [5]:



In order, these reactions describe: (1) the creation of a new X molecule, (2) an X molecule spontaneously transforming into a Y molecule, (3) two X molecules reacting with a Y , changing it to an X , and (4) X molecules being removed from the system. The rates at which the reactions occur are denoted by a, b, c and d . Each of these reactions are assumed to occur independently, and without memory of the previous states of the system.

Once the reaction scheme has been picked and laid out, the transition rates, T_s , can be chosen. They effectively specify the model. When writing the transition rates, we shall only list the variables that are involved in the reaction.

For the Brusselator, the number of X and Y will be denoted by n_1 and n_2 , respectively. The rate of the transition for a given reaction is proportional to the product of the densities of the reactants that trigger the reaction. For the scheme (2.1.7) they read:

$$\begin{aligned}
T_1(n_1 + 1, n_2 | n_1, n_2) &= a, \\
T_2(n_1 - 1, n_2 + 1 | n_1, n_2) &= b \frac{n_1}{V}, \\
T_3(n_1 + 1, n_2 - 1 | n_1, n_2) &= c \frac{n_1^2 n_2}{V^3}, \\
T_4(n_1 - 1, n_2 | n_1, n_2) &= d \frac{n_1}{V},
\end{aligned}
\tag{2.1.8}$$

where the subscripts on the rates refer to the four reactions (2.1.7).

In some studies, the state of the system is specified using the concentrations instead of the number of molecules. Referring to our example, we denote the concentration for the species X and Y respectively by x and y . They indicate the number of molecules of each species divided by the volume V . In this latter case the transition rates read:

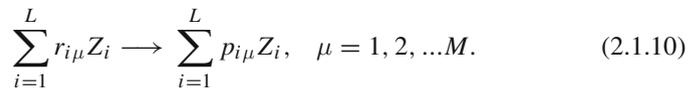
$$\begin{aligned}
T_1(x + \frac{1}{V}, y | x, y) &= a, \\
T_2(x - \frac{1}{V}, y + \frac{1}{V} | x, y) &= bx, \\
T_3(x + \frac{1}{V}, y - \frac{1}{V} | x, y) &= cx^2y, \\
T_4(x - \frac{1}{V}, y | x, y) &= dx.
\end{aligned}
\tag{2.1.9}$$

In the following chapters we will make use of both conventions.

The transition rates for the Brusselator can be substituted into the master equation which can then, together with suitable initial and boundary conditions, be used to solve for the probability density function, $P(n_1, n_2, t)$. They can also be used as the basis for setting up a simulation using the Gillespie algorithm [6, 7], which provides a way to generate random numbers distributed as $P(n_1, n_2, t)$ at time t . This is an exact method for simulating the stochastic process defined by the transition rates (2.1.9). Moreover, the Gillespie algorithm is efficient compared to numerical methods in which the time is sampled. Instead, in the Gillespie algorithm the time at which the next reaction occurs is generated stochastically, thus avoiding simulating the system when no reactions are occurring.

2.1.6 Formalism for a General Network

We now generalise the above formulation so that it applies to a general biochemical network. To do this, suppose that there are L different chemical species in the system. We will denote them by $Z_i, i = 1, \dots, L$ and at a given time there will be n_i molecules of the i -th species, so that the state of the system can be specified by $\mathbf{n} = (n_1, \dots, n_L)$. We suppose that there are M reactions which interconvert species:



Here the numbers $r_{i\mu}$ and $p_{i\mu}$ ($i = 1, \dots, L; \mu = 1, \dots, M$) describe respectively the population of the reactants and the products involved in the reaction. The reactions of the Brusselator, Eqs. (2.1.7), are a simple example of this general set of reactions.

A quantity which is central to the structure of the chemical network is the stoichiometry matrix, $\nu_{i\mu} \equiv r_{i\mu} - p_{i\mu}$, which describes how many molecules of species Z_i are transformed due to the reaction μ . In the notation introduced above for the master equation, $\mathbf{n}' = \mathbf{n} - \boldsymbol{\nu}$, where $\boldsymbol{\nu}_\mu = (\nu_{1\mu}, \dots, \nu_{L\mu})$ is the stoichiometric vector corresponding to reaction μ . Therefore the master equation (2.1.6) may be equivalently written as

$$\frac{\partial P(\mathbf{n}, t)}{\partial t} = \sum_{\mu=1}^M [\mathsf{T}_\mu(\mathbf{n}|\mathbf{n} - \boldsymbol{\nu}_\mu)P(\mathbf{n} - \boldsymbol{\nu}_\mu, t) - \mathsf{T}_\mu(\mathbf{n} + \boldsymbol{\nu}_\mu|\mathbf{n})P(\mathbf{n}, t)]. \quad (2.1.11)$$

Many models of interest involve only a handful of different reactions; in this situation, it is often convenient to rewrite the master equation as a sum over reactions as in Eq. (2.1.11), rather than over pairs of states \mathbf{n} and \mathbf{n}' as in Eq. (2.1.6).

2.2 Approximation Schemes for the Master Equation

We now approximate the master equation in two different regimes, that will be analysed for each example studied in this thesis [8]. They are respectively the deterministic limit and the Fokker-Planck approximation. The former is obtained by taking $V \rightarrow \infty$, and leads to a corresponding system of ordinary differential equations. This describes the system when the number of molecules is macroscopic, so that the effects of the intrinsic noise are negligible. In the latter, the discrete nature of the molecules is retained. The approximation yields a Fokker-Planck equation that is more suitable to analysis than the master equation.

2.2.1 The Deterministic Limit

The deterministic limit for a chemical system can be obtained by applying the law of mass action to the chemical reactions, as we have seen in the previous chapter. However, it can also be systematically derived by a limiting procedure starting from the master equation itself. This is the approach followed in this section.

We begin with multiplying Eq. (2.1.11) by \mathbf{n} , and summing over all possible values of \mathbf{n} . After making the change of variable $\mathbf{n} \rightarrow \mathbf{n} + \boldsymbol{\nu}$ in the first summation, one finds that

$$\frac{d\langle \mathbf{n}(t) \rangle}{dt} = \sum_{\mu=1}^M \nu_{\mu} \langle T_{\mu}(\mathbf{n} + \boldsymbol{\nu}_{\mu} | \mathbf{n}) \rangle, \quad (2.2.1)$$

where the angle brackets define the expectation value:

$$\langle \dots \rangle = \sum_{\mathbf{n}} (\dots) P(\mathbf{n}, t). \quad (2.2.2)$$

In the limit where both the particle numbers and the volume become large, we will take the state variables to be the concentration of the constituents n_i/V , rather than their number n_i . These will be assumed to have a finite limit as $V \rightarrow \infty$. Specifically, the state of the system will be determined by the new variables $y_i = \lim_{V \rightarrow \infty} \frac{\langle n_i \rangle}{V}$, where $i = 1, \dots, L$. From Eq. (2.2.1) we have that

$$\frac{dy_i}{d\tau} = \sum_{\mu=1}^M \nu_{i\mu} f_{\mu}(\mathbf{y}), \quad i = 1, \dots, L, \quad (2.2.3)$$

where $\tau = t/V$ and where

$$\begin{aligned}
f_\mu(\mathbf{y}) &= \lim_{V \rightarrow \infty} \langle T_\mu(\mathbf{n} + \boldsymbol{\nu}_\mu | \mathbf{n}) \rangle \\
&= \lim_{V \rightarrow \infty} T_\mu(\langle \mathbf{n} \rangle + \boldsymbol{\nu}_\mu | \langle \mathbf{n} \rangle) \\
&= \lim_{V \rightarrow \infty} T_\mu(V \mathbf{y} + \boldsymbol{\nu}_\mu | V \mathbf{y}).
\end{aligned} \tag{2.2.4}$$

In the above we have used the fact that in the macroscopic limit the probability distribution functions are Dirac delta functions and so, for instance, $\langle n^m \rangle = \langle n \rangle^m$, for any integer m .

The equation

$$\frac{dy_i}{d\tau} = \mathcal{A}_i(\mathbf{y}), \tag{2.2.5}$$

where

$$\mathcal{A}_i(\mathbf{y}) \equiv \sum_{\mu=1}^M \nu_{i\mu} f_\mu(\mathbf{y}), \quad i = 1, \dots, L, \tag{2.2.6}$$

is the deterministic limit corresponding to the master equation (2.1.11). It can be calculated from a knowledge of the stoichiometric matrix $\nu_{i\mu}$ and the transition rates $T_\mu(\mathbf{n} + \boldsymbol{\nu}_\mu | \mathbf{n})$. For the case of the Brusselator, the transition rates had particularly simple forms in that they were all functions of the species concentration n_i/V . More generally, they might separately be functions of n_i and V , which become functions of the species concentration n_i/V only when both the particle numbers and the volume become large, so that in the limit $V \rightarrow \infty$ they become functions of the macroscopic state variable \mathbf{y} .

2.2.2 The Kramers-Moyal Expansion

The master equation (2.1.11) can be approximated by a Fokker-Planck equation via an expansion due to Kramers and Moyal [3]. As pointed out by van Kampen, the expansion parameter for a chemical system is the inverse of the system size [4]. In our case, this is represented by the inverse of the cell volume, V^{-1} .

We begin by substituting $y_i = n_i/V$ directly into the master equation. Since, as discussed above, our transition rates are all functions of n_i/V we simply replace $T_\mu(\mathbf{n} + \boldsymbol{\nu}_\mu | \mathbf{n})$ by $f_\mu(\mathbf{y})$ in the notation of Eq. (2.1.11). In addition we will denote the probability density function $P(\mathbf{n}, t)$, where \mathbf{n} has been replaced by $V \mathbf{y}$, as $P(\mathbf{y}, t)$. With these changes we may write the master equation (2.1.11) as

$$\frac{\partial P(\mathbf{y}, t)}{\partial t} = \sum_{\mu=1}^M \left[f_\mu\left(\mathbf{y} - \frac{\boldsymbol{\nu}_\mu}{V}\right) P\left(\mathbf{y} - \frac{\boldsymbol{\nu}_\mu}{V}, t\right) - f_\mu(\mathbf{y}) P(\mathbf{y}, t) \right]. \tag{2.2.7}$$

For V large, the steps ν_μ/V are likely to be very small, suggesting that we may expand the functions P and f as Taylor series around \mathbf{y} . Truncating at order $\mathcal{O}(V^{-2})$, we arrive at

$$\begin{aligned} \frac{\partial P(\mathbf{y}, \tau)}{\partial \tau} = & - \sum_{\mu=1}^M \sum_i \nu_{i\mu} \frac{\partial}{\partial y_i} [f_\mu(\mathbf{y})P(\mathbf{y}, \tau)] \\ & + \sum_{\mu=1}^M \frac{1}{2V} \sum_{i,j} \nu_{i\mu} \nu_{j\mu} \frac{\partial^2}{\partial y_i \partial y_j} [f_\mu(\mathbf{y})P(\mathbf{y}, \tau)], \end{aligned}$$

where as before we have absorbed a factor of V into the rescaled time variable $\tau = t/V$. This is a Fokker-Planck equation which can be cast into the standard form [3]

$$\frac{\partial P(\mathbf{y}, \tau)}{\partial \tau} = - \sum_i \frac{\partial}{\partial y_i} [\mathcal{A}_i(\mathbf{y})P(\mathbf{y}, \tau)] + \frac{1}{2V} \sum_{i,j} \frac{\partial^2}{\partial y_i \partial y_j} [\mathcal{B}_{ij}(\mathbf{y})P(\mathbf{y}, \tau)], \quad (2.2.8)$$

where $\mathcal{A}_i(\mathbf{y})$ is defined by Eq. (2.2.6) and where

$$\mathcal{B}_{ij}(\mathbf{y}) = \sum_{\mu=1}^M \nu_{i\mu} \nu_{j\mu} f_\mu(\mathbf{y}), \quad i, j = 1, \dots, L. \quad (2.2.9)$$

In the Fokker-Planck equation (2.2.8), the continuous nature of the state variables indicates that the individual nature of the constituents has been lost. However, the stochasticity due to this discreteness has not: it now manifests itself through the function $\mathcal{B}_{ij}(\mathbf{y})$. We can see this is the case through the presence of the factor $1/V$.

One might ask if this approach is consistent with the derivation of the deterministic limit. As $V \rightarrow \infty$, the Fokker-Planck equation reduces to the Liouville equation [3]

$$\frac{\partial P(\mathbf{y}, \tau)}{\partial \tau} = - \sum_i \frac{\partial}{\partial y_i} [\mathcal{A}_i(\mathbf{y})P(\mathbf{y}, \tau)]. \quad (2.2.10)$$

One can check by direct substitution that the solution to this equation is $P(\mathbf{y}, \tau) = \delta(\mathbf{y}(\tau) - \mathbf{y})$ where δ is the Dirac delta function and where $\mathbf{y}(\tau)$ is the solution of the deterministic limit (2.2.5).

It is also natural to ask if it is useful to include higher order terms in V^{-1} . There are sound mathematical reasons for not going to higher order, for instance the probability density function may become negative [3]. As we will see, for the problems that we are interested in this thesis (and many others) very good agreement with simulations can be found by working with the Fokker-Planck equation (2.2.8).

2.2.3 The Langevin Picture

The Fokker-Planck equation (2.2.8) provides an approximate description of the system but, like the master equation (2.1.11) from which it originated, it is an equation for a probability density function. It is therefore quite distinct from the deterministic limit (2.2.5), which is an equation for the state variables themselves. There does, however, exist an equation for the state variables which is completely equivalent to the Fokker-Planck equation (2.2.8). This is called the Langevin equation and takes the form [3]

$$\frac{dy_i}{d\tau} = \mathcal{A}_i(\mathbf{y}) + \frac{1}{\sqrt{V}} \sum_j \mathcal{G}_{ij}(\mathbf{y}) \eta_j(\tau), \quad (2.2.11)$$

where the $\eta_j(\tau)$ are Gaussian white noises with zero mean and correlator

$$\langle \eta_i(\tau) \eta_j(\tau') \rangle = \delta_{ij} \delta(\tau - \tau'), \quad (2.2.12)$$

and where $\mathcal{G}_{ij}(\mathbf{y})$ is related to $\mathcal{B}_{ij}(\mathbf{y})$ by

$$\mathcal{B}_{ij}(\mathbf{y}) = \sum_k \mathcal{G}_{ik}(\mathbf{y}) \mathcal{G}_{jk}(\mathbf{y}). \quad (2.2.13)$$

Equation (2.2.11) generalises the ordinary differential equation (2.2.5) with the addition of noise terms $\boldsymbol{\eta}(\tau)$ and so is a stochastic differential equation. As we will discuss below we need to specify that it is to be interpreted in the sense of Itô [3]. Notice the direct relationship between this stochastic differential equation and the macroscopic ordinary differential equation: sending $V \rightarrow \infty$ in Eq. (2.2.11) immediately yields equation (2.2.5).

2.2.4 On the Noise Matrix \mathcal{B}

It is important to point out that the matrices $\mathcal{G}_{ij}(\mathbf{y})$, which define the behaviour of the noise, cannot be found from the deterministic equations, and a knowledge of the microscopic stochastic dynamics is essential if one is to understand the effects of noise. It is not permissible in this context to simply add noise terms to the deterministic equations, as some authors have done in the past. The only situation in which it is permissible to do this is if the noise is external to the system, that is, it does not originate from the discreteness of the individuals.

We end this section with two general comments on the Langevin equation (2.2.11). The first is that while there are no strong restrictions on the form of $\mathcal{A}_i(\mathbf{y})$, there are on $\mathcal{B}_{ij}(\mathbf{y})$. From Eq. (2.2.9) we see that the matrix \mathcal{B} is symmetric, but also that for any non-zero vector \mathbf{w} ,

$$\sum_{i,j} w_i \mathcal{B}_{ij} w_j = \sum_{\mu=1}^M (\mathbf{w} \cdot \nu) f_{\mu}(\mathbf{y}) \geq 0, \quad (2.2.14)$$

since $f_{\mu}(\mathbf{y}) \geq 0$. Thus \mathcal{B} is positive semi-definite. It follows that $\mathcal{B} = \mathcal{G} \mathcal{G}^T$ for some non-singular matrix \mathcal{G} , where T denotes transpose. One way of constructing such a matrix is to note that since \mathcal{B} is symmetric, it can be diagonalised by an orthogonal transformation defined through a matrix \mathcal{O}_{ij} [9]. Then since \mathcal{B} is positive semi-definite, its eigenvalues are non-negative, and so [10]

$$\mathcal{B} = \mathcal{O} \Lambda \mathcal{O}^T = \mathcal{G} \mathcal{G}^T, \quad \text{where } \mathcal{G} = \mathcal{O} \Lambda^{1/2}, \quad (2.2.15)$$

and where Λ and $\Lambda^{1/2}$ are the diagonal matrices with respectively the eigenvalues and square root of the eigenvalues of \mathcal{B} as entries. We can take the positive roots of the eigenvalues without loss of generality, since the sign can always be absorbed in the η_j factor in Eq. (2.2.11) (its distribution is Gaussian and so invariant under sign changes). It should also be pointed out that we can go further and make an orthogonal transformation, \mathcal{S} , on the noise, $\zeta_j = \sum_i \mathcal{S}_{ij} \eta_j$, and leave Eq. (2.2.12), and so its distribution, unchanged. The transformation matrix \mathcal{S} can then be used to define a new matrix $\mathcal{G}'_{ij} = \sum_k \mathcal{G}_{ik} \mathcal{S}_{jk}$, so that the form of Eq. (2.2.11) is unchanged. So while the procedure outlined above gives us a way of constructing $\mathcal{G}_{ij}(\mathbf{y})$ from $\mathcal{B}_{ij}(\mathbf{y})$, it is not unique.

The second comment relates to the statement made earlier, that Eq. (2.2.11) is to be interpreted in the Itô sense. The singular nature of white noise means that in some cases stochastic differential equations are not uniquely defined by simply writing down the equation, but have to be supplemented with the additional information on how the singular nature of the process is to be interpreted [3]. This happens when \mathcal{G}_{ij} depends on the state of the system \mathbf{y} ; the noise is then said to be multiplicative. As we will see in the next chapter, this subtlety can be the key to understand some interesting behaviours. It is instead not relevant for the models investigated in Chaps. 4 and 5, since there the \mathcal{G}_{ij} is evaluated at a fixed point of the dynamics.

To conclude, we notice that there exist other techniques similar to the Kramer-Moyal expansion which yield approximations for the master equation. A notable example is the van Kampen expansion [4], that will be used throughout Chaps. 4 and 5 in the study of pattern formation. The van Kampen expansion operates a *linear noise approximation*, so that the resulting Langevin equation has a linear deterministic part and additive noise. This approximation can also be arrived at via the Kramer-Moyal expansion: first, a solution of the deterministic system, Eqs. (2.2.5), is to be chosen; Eq. (2.2.11) is then linearised around the deterministic solution leading to a linear Langevin equation. In Chaps. 4 and 5 we have chosen to adopt the van Kampen expansion instead of the Kramers-Moyal expansion, to standardise the exposition to the majority of the literature about stochastic pattern formation. However, the models studied in these chapters can be equivalently investigated using the technique we have described here.

References

1. J.D. Murray, *Mathematical Biology*, Vol. 2 3rd edn. (Springer, Berlin, 2008)
2. S. Wiggins, *Introduction to Applied Nonlinear Dynamical Systems and Chaos*, 2nd edn. (Springer, Berlin, 2003)
3. C.W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, 4th edn. (Springer, New York, 2009)
4. N.G. van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd edn. (Elsevier Science, Amsterdam, 2007)
5. P. Glansdorff, I. Prigogine, *Thermodynamic Theory of Structure, Stability and Fluctuations* (Wiley-Interscience, Chichester, 1971)
6. D.T. Gillespie, *J. Comput. Phys.* **22**, 403 (1976)
7. D.T. Gillespie, *J. Phys. Chem.* **81**, 2340 (1977)
8. A.J. McKane, T. Biancalani, T. Rogers, *Bull. Math. Biol.* (2013)
9. S. Lang, *Linear Algebra* (Springer, Berlin, 1987)
10. M.L. Mehta, *Matrix Theory* (Hindustan Publishing Corporation, India, 1989)



<http://www.springer.com/978-3-319-07727-7>

The Influence of Demographic Stochasticity on Population
Dynamics

A Mathematical Study of Noise-Induced Bistable States and
Stochastic Patterns

Biancalani, T.

2014, XVII, 113 p. 37 illus., 16 illus. in color., Hardcover

ISBN: 978-3-319-07727-7