

Nonlinear phenomena in biology.

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Chapter 1

Rate equations.

1.1 The Poisson distribution

Let us consider an experiment with two possible outcomes, A and \bar{A} . The probability of A is p and that of \bar{A} is $q = 1 - p$. We now repeat the experiment N times independently. The binomial distribution gives the probability that outcome A appears exactly k times:

$$p_N(k) = \binom{N}{k} p^k (1-p)^{N-k}, \quad k = 0, 1, \dots, N \quad (1.1)$$

By using the Stirling approximation $m! \approx m^m e^{-m} \sqrt{2\pi m}$, valid in the limit $m \rightarrow \infty$, we can derive the Poisson limit, defined as $N \rightarrow \infty$, $p \rightarrow 0$ with $Np \rightarrow \lambda$, finite:

$$p_\lambda(k) = e^{-\lambda} \frac{\lambda^k}{k!} \quad k = 0, 1, \dots, \infty \quad (1.2)$$

This Poisson distribution is one of the most important distributions in nature, probably second to the Gaussian distribution¹. The Poisson distribution has both mean and variance equal to the parameter λ :

$$\langle k \rangle = \sum_{k=0}^{\infty} k p_\lambda(k) = \lambda \quad (1.3)$$

$$\sigma^2 = \langle k^2 \rangle - \langle k \rangle^2 = \lambda \quad (1.4)$$

So $\sigma = \sqrt{\langle k \rangle}$, a typical property of the Poisson distribution.

We can think of the Poisson distribution simply as a convenient limit which simplifies the calculations in many occasions. For instance, the probability that a person was born on a particular day, say January 1st, is $p = 1/365$, approximately. Imagine that we have now a large group of $N = 500$ people. Which is the probability that exactly 3 people were born on January 1st? The correct answer is given by the binomial distribution by

¹It is worth saying that in the limit $\lambda \rightarrow \infty$ the Poisson distribution can be itself approximated by a Gaussian distribution $\frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(k-\mu)^2}{2\sigma^2}}$ of mean $\mu = \lambda$ and variance $\sigma^2 = \lambda$.

considering the events A = “being born on January 1st” with probability $p \approx \frac{1}{365}$ and \bar{A} = “not being born on January 1st” with probability $1 - p \approx \frac{364}{365}$:

$$p_{500}(3) = \binom{500}{3} \left(\frac{1}{365}\right)^3 \left(\frac{364}{365}\right)^{497} = 0.108919\dots \quad (1.5)$$

If we use the Poisson limit, $\lambda = pN \approx 500/365 = 1.37$, we obtain:

$$p_{1.37}(3) = e^{-1.37} \frac{1.37^3}{3!} = 0.108900\dots \quad (1.6)$$

which is good enough. Let us compute now the probability that at least two persons were born on May 11th

$$p_{500}(k \geq 2) = 1 - p_{500}(k \leq 1) = 1 - p_{500}(0) - p_{500}(1) = 1 - e^{-\lambda} - \lambda e^{-\lambda} = 0.3977\dots \quad (1.7)$$

1. A typist makes on average 5 mistakes every 100 words. Find the probability that in a text of 1000 words the typist has made (a) exactly 10 mistakes, (b) at least 10 mistakes.
2. Use the Gaussian approximation to the Poisson distribution to find the probability that in a group of 10000 people, at least 10 people were born on January 1st.
3. Un estudio sobre la influencia de la pldora anticonceptiva sobre el cncer del cuello de tero [El Pas, 28/11/2007, aparecido en Lancet el da anterior] analiza un grupo de 52082 mujeres, 16573 de las cuales haban tomado la pldora anticonceptiva y 35509 haba usado otros mtodos de control de natalidad. El estudio muestra que la incidencia del cncer de tero en el grupo de mujeres que toman la pldora es de 4.5 casos por 1000 mujeres, mientras que en el grupo de las que no toman la pldora es de 3.8 casos por 1000. El artculo titula que “la pldora aumenta el riesgo de cncer de cuello uterino”, concretamente un 18% segn se detalla en el texto. Calcular la tasa global de incidencia del cncer en el grupo de 52082 mujeres. Con ese dato, calcular la probabilidad de que un grupo de 16573 mujeres tomadas al azar de un conjunto de 52082 tenga una tasa de 4.5 por mil o mayor.

There are occasions in which the Poisson limit occurs exactly. Imagine we distribute N dots randomly and uniformly in the interval $[0, T]$ (we will think immediately of this as events occurring randomly in time with a uniform rate, hence the notation). We call $\rho = N/T$ the rate at which points are distributed. We now ask the question: which is the probability that exactly k of the N dots lie in the interval $[t_1, t_1 + t]$? The event A = “one given dot lies in the interval $[t_1, t_1 + t]$ ” has probability $p = \frac{t}{T}$ whereas the event \bar{A} = “the given dot does not lie in the interval $[t_1, t_1 + t]$ ” has probability $q = 1 - p$. It should be clear that the answer to the previous question is given by the binomial

distribution, Eq.(1.1). We now make the limit $N \rightarrow \infty$, $T \rightarrow \infty$ but $\rho = N/T$ finite. This limit corresponds to the distribution in which the events occur uniformly in time with a rate (frequency) ρ . Let us give an example: consider, for instance, the atoms of a β -radiative substance. Each atom emits electrons independently of each other. The probability that one given atom will desintegrate is constant with time and it is not known which atom will desintegrate in a given time. All we observe is the emission of electrons with a given, constant, rate. We can estimate the rate of emission ρ simply by counting the number of electrons N emitted in a time interval T as $\rho = N/T$. The larger T and N , the better our estimate for ρ . Let us now consider the total number of electrons k emitted in the time interval $[t_1, t_1 + t]$. As discussed above it follows exactly the Poisson distribution of parameter $\lambda = \rho N = \frac{t}{T}N = \rho t$,

$$p_{\rho,t}(k) = e^{-\rho t} \frac{(\rho t)^k}{k!}. \quad (1.8)$$

A different, but related question, concerns the probability distribution of the waiting time for the emission of an electron. We start by looking at the radiative substance at $t = 0$ and we ask the probability $f(t)dt$ that a particle will be emitted in the time interval $[t, t + dt]$. Hence, the probability that no particle is emitted in the interval $[0, t]$ is $1 - \int_0^t f(t')dt'$. This must coincide with $p_{\rho,t}(k = 0) = e^{-\rho t}$:

$$1 - \int_0^t f(t')dt' = e^{-\rho t} \quad (1.9)$$

Taking the time derivative we conclude that $f(t) = \rho e^{-\rho t}$, the well known exponential law for radioactive decay which allows to identify $\tau = 1/\rho = T/N$ as the average time between emissions. Let us denote by $\hat{f}(t)dt$ the probability that the next electron is emitted in the interval $(t, t + dt)$ giving that there was an emission at $t = 0$. That implies that no other electron has been emitted in the interval $(0, t)$. Let us denote by X the event "an electron has been emitted in $(t, t + dt)$ ", the probability of this event is $P(X) = f(t)dt$. Let us denote by Y the event "an electron was emitted at $t = 0$ but no other electron has been emitted in $(0, t)$ ". We are asking for the conditional probability

$$\hat{f}(t)dt = P(X|Y) = \frac{P(X, Y)}{P(Y)} \quad (1.10)$$

but X and Y are independent events, since the probability of emission in the interval $(t, t + dt)$ does not depend on whether an electron has been emitted before in the interval $(0, t)$. Hence we have $P(X, Y) = P(X)P(Y)$ and $\hat{f}(t)dt = P(X) = f(t)dt$. This leads to $\hat{f}(t) = f(t)$. In other words, the waiting time between two consecutive emissions follows also the exponential law with the same rate ρ .

1.2 Rate equations

Let us consider now a system that can switch between two states that we name "1" and "2". The event A is now the switching from 1 to 2, and we assume that those

switches occur uniformly and randomly at a rate $\omega(1 \rightarrow 2)$. The inverse process, that of switching from 2 to 1 might or might not occur. If it occurs, its rate $\omega(2 \rightarrow 1)$ has, in principle, no relation whatsoever with the rate $\omega(1 \rightarrow 2)$. If we start at $t = 0$ in state 1, we ask the probabilities $P_1(t)$ and $P_2(t)$ that the system is in state 1 or 2, respectively, at time t . Obviously, they must satisfy $P_1(t) + P_2(t) = 1$. We will derive now a differential equation for $P_1(t)$. The probability that the system is in state 1 at time $t + dt$ has two contributions: that of being in 1 at time t and not having jumped to state 2 during the interval $(t, t + dt)$, and that of being at 2 at time t and having made a jump from 2 to 1 in the interval $(t, t + dt)$. This leads to:

$$P_1(t + dt) = P_1(t)[1 - \omega(1 \rightarrow 2)dt] + P_2(t)\omega(2 \rightarrow 1)dt \quad (1.11)$$

From where we get:

$$\frac{dP_1(t)}{dt} = -\omega(1 \rightarrow 2)P_1(t) + \omega(2 \rightarrow 1)P_2(t) \quad (1.12)$$

The equivalent equation for $P_2(t)$ is:

$$\frac{dP_2(t)}{dt} = -\omega(2 \rightarrow 1)P_2(t) + \omega(1 \rightarrow 2)P_1(t) \quad (1.13)$$

Notice that

$$\frac{d}{dt}[P_1(t) + P_2(t)] = 0 \quad (1.14)$$

since $P_1(t) + P_2(t) = 1$ at all times t . One defines the probability current, $J(1 \rightarrow 2)$ from state 1 to 2 as:

$$J(1 \rightarrow 2) = -\omega(1 \rightarrow 2)P_1(t) + \omega(2 \rightarrow 1)P_2(t) \quad (1.15)$$

and a similar definition leads to $J(2 \rightarrow 1) = -J(1 \rightarrow 2)$.

The generalization to the situation where the system can be in many states $i = 1, 2, 3, \dots$ is straightforward:

$$\frac{dP_i(t)}{dt} = \sum_{j \neq i} [-\omega(i \rightarrow j)P_i(t) + \omega(j \rightarrow i)P_j(t)] \quad (1.16)$$

Or in terms of the currents $J(i \rightarrow j) = -\omega(i \rightarrow j)P_i(t) + \omega(j \rightarrow i)P_j(t)$:

$$\frac{dP_i(t)}{dt} = \sum_{j \neq i} J(i \rightarrow j) \quad (1.17)$$

Although it is not very common in practice, nothing prevents us from considering the more general case where the transition rates depend on time. Hence, the more general rate equations are:

$$\frac{dP_i(t)}{dt} = \sum_{j \neq i} [-\omega(i \rightarrow j; t)P_i(t) + \omega(j \rightarrow i; t)P_j(t)] \quad (1.18)$$

Note that the sum can be replaced by $\sum_{\forall j}$ since the term $j = i$ does not contribute to this sum. To find the solution of these rate equations we need to specify an initial condition $P_i(t = t_0)$.

We stress again that the rate coefficients $\omega_{i \rightarrow j} \equiv \omega(i \rightarrow j)$ do not need to satisfy any relation amongst them². Remember also that the rates $\omega_{i \rightarrow j}$ are not probabilities and do not need to be bounded to the interval $[0, 1]$ (although they are positive quantities). Moreover, ω_{ij} has units of time⁻¹. It is easy now to verify that whatever the coefficients $\omega_{i \rightarrow j}$ it is

$$\frac{d}{dt} \sum_i P_i(t) = 0 \quad (1.19)$$

and, again, we have the normalization condition $\sum_i P_i(t) = 1$ for all times t provided that $\sum_i P_i(t_0) = 1$.

It is usual to define the total escape rate Ω_j from state j as the sum of all rates to all possible states:

$$\Omega_j = \sum_{i \neq j} \omega_{j \rightarrow i} = \sum_{i \neq j} \omega(j \rightarrow i). \quad (1.20)$$

When the total number of states N is finite, it is possible, and useful sometimes, to define the matrix Ω as

$$\begin{aligned} \Omega_{ij} &= \omega(j \rightarrow i) && \text{if } i \neq j \\ \Omega_{ii} &= -\sum_{j \neq i} \omega(i \rightarrow j) \end{aligned} \quad (1.21)$$

such that the rate equations admit the form:

$$\frac{dP_i(t)}{dt} = \sum_j \Omega_{ij} P_j(t) \quad (1.22)$$

The matrix Ω is such that the rows add to zero. This property ensures that the solutions $P_i(t)$ respect the positivity condition $P_i(t) \geq 0$ provided that $P_i(0) \geq 0$. It can also be proven that Ω has a zero eigenvalue $\lambda_1 = 0$ and the others $-\lambda_2, \dots, -\lambda_N$ are real and negative (maybe the real part is negative?). This ensures that the functions $P_i(t)$ can be written as:

$$P_i(t) = P_i^{st} + \sum_{k=2}^N C_{ik} e^{-\lambda_k t} \quad (1.23)$$

with the stationary (or steady state) probabilities $P_i^{st} = \lim_{t \rightarrow \infty} P_i(t)$ are the elements of the eigenvector corresponding to the zero eigenvalue. Irreducibility and ergodicity should be discussed here. It seems that not all initial conditions $P_i(t_0)$ must lead to the stationary distribution unless the process is ergodic.

It would be nice to be able to give the stationary solution P_i^{st} given the transition rates coefficients $\omega_{i \rightarrow j}$. However, this is not possible in general. A simple case in which

²The elements $\omega(i \rightarrow i)$ are not defined and one usually takes $\omega(i \rightarrow i) = 0$ although their precise value is irrelevant in the majority of formulas.

this is possible is that of two states $N = 2$ (that we label as before by state 1 and state 2). In this case the solution is simply found as:

$$\begin{aligned} P_1(t) &= P_1(t_0)e^{-(\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2})(t-t_0)} + \frac{\omega_{2 \rightarrow 1}}{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2}} [1 - e^{-(\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2})(t-t_0)}] \\ P_2(t) &= P_2(t_0)e^{-(\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2})(t-t_0)} + \frac{\omega_{1 \rightarrow 2}}{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2}} [1 - e^{-(\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2})(t-t_0)}] \end{aligned} \quad (1.24)$$

The stationary distribution is:

$$\begin{aligned} P_1^{st} &= \frac{\omega_{2 \rightarrow 1}}{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2}} \\ P_2^{st} &= \frac{\omega_{1 \rightarrow 2}}{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2}} \end{aligned} \quad (1.25)$$

a particularly simple solution. Note that in this case the stationary distribution satisfies

$$\omega(1 \rightarrow 2)P_1^{st} = \omega(2 \rightarrow 1)P_2^{st} \quad (1.26)$$

a property known as *detailed balance condition*. Unfortunately, there is no equivalent explicit expression in the case of having more than 2 states.

An interesting quantity is the probability $P(i, t|j, t_0)$ that the system is in state i at time t given that it was in state j at time t_0 . Do not confuse it with the probability density $f(i, t|j, t_0)$ defined such that $f(i, t|j, t_0)dt$ is the probability that the system is at state j at time t_0 and stays there until it jumps to state i in the time interval $(t, t + dt)$, with no intermediate jumps in the interval (t_0, t) . Since the total escape rate from state j is $\Omega_j = \sum_i \omega(j \rightarrow i)$, the probability density function of the next jump from state j is $\Omega_j e^{-\Omega_j(t-t_0)}$. The probability that the system does not jump out of j in the time interval (t_0, t) is $1 - \int_0^t \Omega_j e^{-\Omega_j t} = e^{-\Omega_j(t-t_0)}$. The probability that it jumps from j to i in the time interval $(t, t + dt)$ is $\omega(j \rightarrow i)dt$. Therefore, the required probability density function is:

$$f(i, t|j, t_0) = \omega(j \rightarrow i)e^{-\Omega_j(t-t_0)} \quad (1.27)$$

On the other hand, $P(j, t|i, t_0)$ is difficult to compute because in the interval $[t_0, t]$ there might have been many jumps to intermediate states. Again, an explicit formula can only be given in the case $N = 2$ where we can reason as follows: the probability that the system is in state 1 at time t is the probability that it was in state 1 at time t_0 times the probability $P(1, t|1, t_0)$ plus the probability that it was in state 2 at t_0 times the probability $P(1, t|2, t_0)$:

$$\begin{aligned} P_1(t) &= P_1(t_0)P(1, t|1, t_0) + P_2(t_0)P(1, t|2, t_0) \\ &= P_1(t_0)P(1, t|1, t_0) + [1 - P_1(t_0)]P(1, t|2, t_0) \\ &= P_1(t_0)[P(1, t|1, t_0) - P(1, t|2, t_0)] + P(1, t|2, t_0) \end{aligned} \quad (1.28)$$

comparing with Eq.(1.24) we get:

$$P(1, t|1, t_0) = \frac{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2} e^{-(\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2})(t-t_0)}}{\omega_{2 \rightarrow 1} + \omega_{1 \rightarrow 2}} \quad (1.29)$$

and, of course, $P(2, t|1, t_0) = 1 - P(1, t|1, t_0)$ and equivalent expressions for $P(1, t|2, t_0)$ and $P(2, t|2, t_0)$. Let us stress, again, that no equivalent solution exists in the case of having $N \geq 3$ states in the system.

Chapter 2

Master equations.

2.1 Master equations

2.1.1 Radioactive decay

We now consider the rate equations from a different point of view. Let us take as an example the β -radioactive substance of the previous chapter. The events are the emission of electrons. Schematically:



where X denotes a radioactive atom and Y the product of the desintegration. Each one of the N atoms of the substance can be in the state 1 (it has not yet emitted an electron) or in state 2 (it has emitted an electron). The transitions are from state 1 to state 2 at a rate $\omega \equiv \omega(1 \rightarrow 2)$. The rate equations are (there are no transitions from 2 to 1):

$$\begin{aligned} \frac{dP_1(t)}{dt} &= -\omega P_1(t) \\ \frac{dP_2(t)}{dt} &= +\omega P_1(t) \end{aligned} \quad (2.2)$$

Let $n_1(t)$ and $n_2(t)$ be the number of atoms in state 1 and 2 respectively at time t . Since the particles that leave state 1 go to state 2, it is $n_1(t) + n_2(t) = N$. The values of $n_1(t)$ and $n_2(t)$ are random variables that can take values with different probabilities. Let us introduce the probability $P(n_1, n_2; t)$ of finding n_1 atoms in state 1 and n_2 atoms in state 2 at time t . We assume that the initial condition is that all N atoms are in state 1 at time $t_0 = 0$. Using Kronecker-delta functions, this initial condition is:

$$P(n_1, n_2; 0) = \delta_{n_1, N} \delta_{n_2, 0} \quad (2.3)$$

The condition $n_1(t) + n_2(t) = N$ means that we can actually simplify notation and focus on the probability $P(n; t)$ of having n particles in state 1 at time t ; the number of particles in state 2 will be simply $N - n$. We now derive a differential equation for $P(n; t)$.

The probability $P(n; t)$ of having n particles in state 1 at time t can change because one particle has left state 1 to go into state 2. A single atom can jump from 1 to 2 in the

time interval $(t, t + dt)$ with a probability ωdt . Therefore, the probability of **any** atom jumping from 1 to 2 is $\omega n dt$ since the atoms jump independently one of the other. The probability that there are n particles in state 1 at time $t + dt$ has two contributions: (i) the event they were $n + 1$ particles at time t and a jump occurred in $(t, t + dt)$ or (ii) they were n particles at time t and no jumps occurred in $(t, t + dt)$. Translated into an equations:

$$P(n; t + dt) = P(n + 1; t)\omega(n + 1)dt + P(n; t)(1 - n\omega dt) + o(dt)^2 \quad (2.4)$$

or, taking the limit $dt \rightarrow 0$:

$$\frac{\partial P(n; t)}{\partial t} = -\omega n P(n; t) + \omega(n + 1)P(n + 1; t) \quad (2.5)$$

This is the master equation of the radioactive process. This is to be solved with the initial condition $P(n; 0) = \delta_{n,N}$. The solution can be found in this case (as well as in other cases) with the help of the generating function $G(s, t)$. This is defined as:

$$G(s, t) = \sum_{n=-\infty}^{\infty} s^n P(n; t) \quad (2.6)$$

(note that in most cases the sum is limited to $n \geq 0$ since $P(n; t) = 0$ for $n < 0$). Multiplying Eq.(2.5) by s^n and summing over n we get:

$$\sum_n s^n \frac{\partial P(n; t)}{\partial t} = -\omega \sum_n n s^n P(n; t) + \omega \sum_n (n + 1) s^n P(n + 1; t) \quad (2.7)$$

which after a simple manipulation replacing $n + 1 \rightarrow n$ in the last terms leads to the differential equation:

$$\frac{\partial G(s, t)}{\partial t} = \omega(1 - s) \frac{\partial G(s, t)}{\partial s} \quad (2.8)$$

The solution is found by Lagrange's method:

$$G(s, t) = \Phi((s - 1)e^{-\omega t}) \quad (2.9)$$

the arbitrary function $\Phi(x)$ is obtained using the initial condition $G(s, 0) = s^N$, or $\Phi(x) = (x + 1)^N$. This leads finally to:

$$G(s, t) = [(s - 1)e^{-\omega t} + 1]^N = [se^{-\omega t} + 1 - e^{-\omega t}]^N \quad (2.10)$$

Note that the condition $G(1, t) = 1$ is equivalent to the normalization condition $\sum_n P_n(t) = 1$. Expanding in taylor series using the binomial expansion

$$G(s, t) = \sum_{n=0}^N \binom{N}{n} [se^{-\omega t}]^n [1 - e^{-\omega t}]^{N-n} \quad (2.11)$$

which, recalling the definition of the generation function, Eq.(2.6), gives the solution for the probabilities:

$$P(n; t) = \binom{N}{n} e^{-n\omega t} [1 - e^{-\omega t}]^{N-n} \quad (2.12)$$

This is nothing by a binomial distribution of parameter $p(t) = e^{-\omega t}$, the expected result. The mean value of particles in state 1 at time t is $Np(t)$:

$$\langle n(t) \rangle = Ne^{-\omega t} \quad (2.13)$$

which is again the well known law of radioactive decay. Alternatively, the mean value can be computed from the generating function as

$$\langle n(t) \rangle = \left. \frac{\partial G(s, t)}{\partial s} \right|_{s=1} \quad (2.14)$$

The variance can be computed in a similar way using

$$\langle n(t)^2 \rangle = \left. \frac{\partial}{\partial s} s \frac{\partial G(s, t)}{\partial s} \right|_{s=1} \quad (2.15)$$

with the well known result for a binomial distribution, $\sigma^2[n(t)] = Np(1 - p)$, or:

$$\sigma^2[n(t)] = Ne^{-\omega t}(1 - e^{-\omega t}) \quad (2.16)$$

We can make connection with the results of the previous chapter by noticing that the number of electrons emitted is $k = N - n$ and the probability $P_{e^-}(k, t)$ of emitting k electrons in the interval $(0, t)$ also follows a binomial distribution:

$$P_{e^-}(k; t) = \binom{N}{k} e^{-(N-k)\omega t} [1 - e^{-\omega t}]^k, \quad n = 0, 1, \dots, N \quad (2.17)$$

of probability $p = 1 - e^{-\omega t}$. In the large N limit, this reduces to the Poisson distribution if we write $\omega = \frac{\rho}{N}$ such that $Np \rightarrow \rho t$ in the limit $N \rightarrow \infty$. So everything agrees if we used that the rate ρ of emission of N atoms is N times the rate of emission ω of a single atom.

2.1.2 Birth and death processes

An important class of master equations respond to the *birth and death* scheme. Let us assume that a system X can lose particles to a reservoir A . Let us call k_1 at the rate at which a particle goes from X to A . So far, this is similar to the previous example of the radioactive substance, but now we include the possibility that particles from A go back to X at a rate k_2 . To simplify matters, we assume that the number of particles of A , n_A , is kept constant (particles are removed or restored to A as necessary, A is a bath of particles).



(following Gillespie, the bar on top of the A means that its population is assumed to be constant).

We want to find the master equation for the probability $P(n; t)$ that there are n particles left in X at time t . We have now three elementary contributions to $P(n; t + dt)$ according to what happened in the time interval $(t, t + dt)$: (i) X had n particles at time t and none was lost to the bath and none was obtained from the bath; (ii) X had $n + 1$ particles in time t and one particle was lost to the bath; (iii) X had $n - 1$ particles and one was transferred from the bath. Combining the probabilities of these four events we get the evolution equation:

$$\begin{aligned} P(n; t + dt) &= P(n; t)[1 - nk_1 dt][1 - n_A k_2 dt] && \text{case (i)} \\ &+ P(n + 1; t)k_1(n + 1)dt && \text{case (ii)} \\ &+ P(n - 1; t)n_A k_2 dt + o(dt)^2 && \text{case (iii)} \end{aligned} \quad (2.19)$$

or, taking the limit $dt \rightarrow 0$ and simplifying notation $k_A \equiv k_2 n_A$:

$$\frac{dP(n; t)}{dt} = -(k_1 n + k_A)P(n; t) + k_1(n + 1)P(n + 1; t) + k_A P(n - 1; t) \quad (2.20)$$

with the initial condition $P(n; 0) = \delta_{n, N}$. This equation is solved again by introducing the generating function $G(s, t)$. The resulting partial differential equation is:

$$\frac{\partial G(s, t)}{\partial t} = k_A(s - 1)G - k_1(s - 1)\frac{\partial G(s, t)}{\partial s} \quad (2.21)$$

Again, the method of Lagrange gives us the general solution:

$$G(s, t) = e^{\frac{k_A}{k_1}(s-1)} \Phi((s - 1)e^{-k_1 t}) \quad (2.22)$$

with $\Phi(x)$ an arbitrary function. Implementing the initial condition $G(s, 0) = s^N$, we obtain: $\phi(x) = (x + 1)^N e^{-\frac{k_A}{k_1} x}$ and the final solution is:

$$G(s, t) = e^{\frac{k_A}{k_1}(s-1)[1-e^{-k_1 t}]} [se^{-k_1 t} + 1 - e^{-k_1 t}]^N \quad (2.23)$$

We could now expand in powers of s to get the probabilities $P_n(t)$. The first moments are easily found from the derivatives of the generating function:

$$\begin{aligned} \langle n(t) \rangle &= Ne^{-k_1 t} + (1 - e^{-k_1 t})\frac{k_A}{k_1} \\ \sigma^2[n(t)] &= Ne^{-k_1 t}(1 - e^{-k_1 t}) + (1 - e^{-k_1 t})\frac{k_A}{k_1} \end{aligned} \quad (2.24)$$

In the stationary limit $t \rightarrow \infty$ we have:

$$G(s, t \rightarrow \infty) = e^{\frac{k_A}{k_1}(s-1)} = e^{-\frac{k_A}{k_1}} \sum_{n=0}^{\infty} \left(\frac{k_A}{k_1}\right)^n \frac{s^n}{n!} \quad (2.25)$$

hence

$$P(n; t \rightarrow \infty) = \frac{e^{-\frac{k_A}{k_1}}}{n!} \left(\frac{k_A}{k_1}\right)^n \quad (2.26)$$

nothing but a Poisson distribution of parameter $\lambda = \frac{k_A}{k_1}$.

2.1.3 Gene transcription

A modification of the above death and birth process has been proposed as a very simple and crude model for gene transcription. The model assumes that a gene A (a portion of DNA) is copied into a messenger-RNA (mRNA) at a rate k_T . The mRNA then degrades at a rate γ . The schematic reactions are:



The master equation describing this process of creation and degradation of mRNA is:

$$\frac{\partial P(n; t)}{\partial t} = k_T P(n-1; t) - k_T P(n; t) + \gamma(n+1)P(n+1; t) - \gamma n P(n; t) \quad (2.28)$$

This equation can be solved using the generating function technique to find that in the steady state the probability of finding n mRNA's is a Poisson distribution of parameter k_T/γ . Hence, the average number of mRNA's molecules is $\langle n \rangle = k_T/\gamma$. Typically, a gen of about 1500 base pairs will take 60s for transcription. That gives us an idea of the order of magnitude of $k_T \approx 1/60s$. The degradation rate is of the order of 4 times smaller, $\gamma \approx 1/240s$. Hence the average number of mRNA's transcribed by a particular gene is of the order of $\langle n \rangle \approx 4$. This is correct experimentally, but the model has a problem: the variability is too high. This is because the fluctuations in the Poisson distributions, as measured by the root mean square $\sigma = \sqrt{\langle n \rangle} \approx 2$, which is a variability of the 50% in the number of mRNA molecules. This is too high.

We might want to include some other effects present in gene expression. We know that mRNA is translated into proteins inside the ribosomes. A codon is a sequence of three nucleotides (Adenin, Thymin, Cytosin or Guanin) and each codon is translated into one of the possible 20 aminoacids (this is the *genetic code*). This translation is mediated by 20 different tRNA's. Each tRNA couples to the right codon to generate the aminoacid. The sequence of aminoacids Hence we have the following process¹: genes create mRNA molecules at a rate k_r . An mRNA molecule can either degrade at a rate γ or produce a protein at a rate k_p . The protein finally degrades at a rate γ_p .

If we introduce the probability $P(r, n; t)$ of having r mRNA's, n proteins at time t , we can write the master equation of the standard dogma as:

$$\begin{aligned} \frac{\partial P(r, n; t)}{\partial t} &= k_r P(r-1, n; t) - k_r P(r, n; t) && \text{transcription} \\ &+ k_p r P(r, n-1; t) - k_p r P(r, n; t) && \text{translation} \\ &+ \gamma_r (r+1) P(r+1, n; t) - \gamma_r r P(r, n; t) && \text{degradation of mRNA} \\ &+ \gamma_p (n+1) P(r, n+1; t) - \gamma_p n P(r, n; t) && \text{degradation of protein} \end{aligned} \quad (2.29)$$

We can use now the generating function technique to compute the mean values and the

¹This whole process is known as the *standard dogma* of molecular biology.

fluctuations in the steady state. The result is

$$\langle r \rangle = \frac{k_r}{\gamma_r} \quad (2.30)$$

$$\sigma^2[r] = \quad (2.31)$$

$$\langle n \rangle = \frac{k_r k_p}{\gamma_r \gamma_p} \quad (2.32)$$

$$\frac{\sigma^2[n]}{\langle n \rangle} = 1 + \frac{k_p}{\gamma_r + \gamma_p} \quad (2.33)$$

The last equation shows that in this model the distribution of proteins is super-Poissonian, since the fluctuations are larger than in the Poisson distribution. This has been named as *noise amplification*. The situation is then even worse than it was in the previous model, as far as the magnitude of the variability is concerned. It is believed that the number of proteins is regulated by a feedback mechanism between different genes. A gene B can regulate the production of gene A by producing proteins that bind to the promoters of gene A.

A recent modification of this model [A. Oudenaïdon, PNAS **98**, 8614 (2001)], includes the presence of inhibitory circuits in gene expression. Basically it amounts to replacing k_r by $k_r(1 - \epsilon n)$ with ϵ a small number (a more realistic approach could be to include some non-linear saturation terms). One can now solve the master equation and after a lengthy calculation find that the average number of proteins decreases to $\langle n \rangle = \frac{k_r}{\gamma_r} \left(1 - \epsilon \frac{k_r}{\gamma_r}\right)$. The variance is then reduced to:

$$\frac{\sigma^2[n]}{\langle n \rangle} = 1 + \frac{k_p}{\gamma_r + \gamma_p} - \epsilon \frac{k_r k_p}{\gamma_r \gamma_p} \quad (2.34)$$

2.1.4 The autocatalytic reaction

2.1.5 The prey-predator Lotka-Volterra model

Rate and master equations are commonly used in other fields, such as population dynamics and the kinetics of chemical reactions (including those occurring in living beings). However, some sort of approximation is usually needed to derive them.

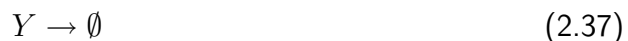
Let us start with the Lotka-Volterra model. We consider an animal species X (the prey, think on rabbits) which reproduces by eating grass, A . The schematic reaction is as follows:



with some rate k_0 . We'll use the notation $k_A = k_0 n_A$. At the same time, the species Y (the predator, think on foxes) reproduces by eating species X . Again schematically:



with a rate k_1 . Finally, the species Y can die of natural causes at a rate k_2 :



Of course, this is a very simplified model of population dynamics, but let us analyze it in some detail.

We denote by $P(n_1, n_2; t)$ the probability that there are n_1 animals of species X and n_2 animals of species Y at time t . The master equation can be obtained by enumerating the elementary processes occurring in the time interval $(t, t + dt)$ that might contribute to $P(n_1, n_2; t + dt)$ namely:

- (i) The population was (n_1, n_2) at time t and no rabbit reproduced and no rabbit was eaten and no fox died.
- (ii) The population was $(n_1 - 1, n_2)$ at time t and a rabbit reproduced.
- (iii) The population was $(n_1, n_2 + 1)$ at time t and a fox died.
- (iv) The population was $(n_1 + 1, n_2 - 1)$ at time t and a fox ate a rabbit and reproduced.

The contributions to the probability are, respectively:

$$\begin{aligned}
 P(n_1, n_2; t + dt) &= P(n_1, n_2; t)[1 - k_A n_1 dt][1 - k_1 n_1 n_2 dt][1 - k_2 n_2 dt] && \text{case (i)} \\
 &+ P(n_1 - 1, n_2; t)k_A(n_1 - 1)dt && \text{case (ii)} \\
 &+ P(n_1, n_2 + 1; t)k_2(n_2 + 1)dt && \text{case (iii)} \\
 &+ P(n_1 + 1, n_2 - 1; t)k_1(n_1 + 1)(n_2 - 1)dt && \text{case (iv)} \\
 &&& (2.38)
 \end{aligned}$$

Taking the limit $dt \rightarrow 0$ we obtain the desired master equation:

$$\begin{aligned}
 \frac{\partial P(n_1, n_2; t)}{\partial t} &= -(k_A n_1 + k_1 n_1 n_2 + k_2 n_2)P(n_1, n_2; t) + k_A(n_1 - 1)P(n_1 - 1, n_2; t) \\
 &+ k_2(n_2 + 1)P(n_1, n_2 + 1; t) + k_1(n_1 + 1)(n_2 - 1)P(n_1 + 1, n_2 - 1; t) \\
 &&& (2.39)
 \end{aligned}$$

In deriving this equation we have made a very strong assumption: that all foxes eat all rabbits with the same rate. Hence the term $k_1 n_1 n_2$ which is directly proportional to the number of pairs of rabbits and foxes. However, this is unlikely to be true in a real situation. Some rabbits will be closer to some foxes and those pairs will have an enhanced probability of leading to the loss of a rabbit and the birth of a fox. This is a *homogeneity* assumption in the sense that the spatial distribution of the animals is completely neglected² in which. It might be close to true in a case in which there is a fast movement, migration, of animals from a place to another, but in general it has to be seen as an unjustified approximation. In any event, it is not reasonable to assume that a prey can be eaten with equal probability by **all** possible predators, so the corresponding term is proportional to $k_1 n_1 n_2$. It is more likely that this term is proportional to the local density of predators, n_2/Ω , being Ω a measure of the volume of the system where prey and predator live. Hence, we correct this term by writing it as $k_1 n_1 n_2/\Omega$. Now k_1 is the rate per unit volume and has units of volume/time. Similarly the corresponding rate for the eating of grass by the prey is proportional to the local concentration of grass, not to the total amount of grass, and we write the corresponding term as $k_A n_A/\Omega$, or k_{ACA} being c_A the concentration of grass. We will use the notation $\bar{k}_1 = k_1/\Omega$ and

²It can also be considered as a kind of mean field approach, since spatial inhomogeneities are not considered. However, we will use shortly the name *mean-field* to denote a situation in which correlations between the populations of prey and predators are neglected.

and $\bar{k}_A = k_A/\Omega$. We will see that only with this rescaling is possible to recover the deterministic equations in the limit of Ω large.

One might try to solve the master equation by introducing the generating function:

$$G(s_1, s_2, t) = \sum_{n_1=-\infty}^{\infty} \sum_{n_2=-\infty}^{\infty} s_1^{n_1} s_2^{n_2} P(n_1, n_2; t) \quad (2.40)$$

The resulting equation for $G(s_1, s_2; t)$ is

$$\frac{\partial G}{\partial t} = -k_A(1-s_1)G + k_2(1-s_2)\frac{\partial G}{\partial s_2} + \bar{k}_1 s_2(s_1-s_2)\frac{\partial^2 G}{\partial s_1 \partial s_2} \quad (2.41)$$

but it is wrong, I am a little bit tired now. In any case, the solution looks hopeless (?).

2.2 General results

The most general master equation appears to be of the form:

$$\frac{\partial P(n, t)}{\partial t} = \sum_k (E^k - 1) [C_k(n) P(n, t)], \quad (2.42)$$

begin $C_k(n)$ some coefficients and E the linear step operator such that $E^k[f(n)] \equiv f(n+k)$ and k runs over the integer numbers. The k -th term of this sum corresponds to the process in which $-k$ particles are created (hence destroyed if $k > 0$) at a rate C_k .

It is possible to obtain the general form of the equation for the generating function $G(s, t) = \sum_n s^n P(n; t)$, starting from:

$$\frac{\partial G}{\partial t} = \sum_k (s^{-k} - 1) \sum_n s^n C_k(n) P(n, t). \quad (2.43)$$

If we now assume the Taylor expansion $C_k(n) = \sum_a C_k^a n^a$ and use that $s^{n+a} = (s \frac{\partial}{\partial s})^a s^n$, we arrive at:

$$\frac{\partial G}{\partial t} = \sum_k (s^{-k} - 1) C_k \left(s \frac{\partial}{\partial s} \right) G(s, t). \quad (2.44)$$

From (2.42) we get the (exact) equations for these first two moments, as:

$$\frac{d\langle n \rangle}{dt} = - \sum_k \langle k C_k(n) \rangle, \quad \frac{d\langle n^2 \rangle}{dt} = \sum_k \langle k(k-2n) C_k(n) \rangle. \quad (2.45)$$

2.3 The mean-field theory

The mean-field theory is interested in the evolution of the mean values, neglecting fluctuations. In some cases, it is possible to obtain exact equations for the evolution of the mean values, but in most cases the evolution equations will necessarily involve some sort of approximation. Let us begin by the radioactive substance. Let us call $X(t)$ the average value of the number of radioactive atoms remaining:

$$X(t) = \sum_n nP(n; t) \quad (2.46)$$

We know that $X(t) = X(0)e^{-\omega t}$, but we want to obtain directly from the master equation a differential equation for $X(t)$. Taking the derivative of the previous equation and substituting Eq.(2.5):

$$\frac{dX(t)}{dt} = \sum_n n \frac{\partial P(n; t)}{\partial t} = \sum_n n [-\omega n P(n; t) + \omega(n+1)P(n+1; t)] \quad (2.47)$$

we now make changes of variables $n+1 \rightarrow n$ in the second term of the sum to obtain:

$$\frac{dX(t)}{dt} = -\omega \sum_n n P(n; t) \quad (2.48)$$

or

$$\frac{dX(t)}{dt} = -\omega X(t) \quad (2.49)$$

the desired mean-field equation, exact in this case.

If we do the same for the birth and death process, we obtain again an exact equation for the mean value:

$$\frac{dX(t)}{dt} = -k_1 X(t) + k_A \quad (2.50)$$

whose solution is

$$X(t) = X(0)e^{-k_1 t} + \frac{k_A}{k_1} (1 - e^{-k_1 t}) \quad (2.51)$$

in agreement with the previous treatment.

Example which is not linear.

We turn now to the pre-predator Lotka-Volterra model. We need to compute two averages $X(t) = \langle n_1(t) \rangle$ and $Y(t) = \langle n_2(t) \rangle$. After some careful calculation one obtains:

$$\begin{aligned} \frac{dX(t)}{dt} &= \bar{k}_A X(t) - \bar{k}_1 \langle n_1(t) n_2(t) \rangle \\ \frac{dY(t)}{dt} &= \bar{k}_1 \langle n_1(t) n_2(t) \rangle - k_2 Y(t) \end{aligned} \quad (2.52)$$

And the equations are not closed. This is typical of non-linear problems. We could now compute the evolution of $\langle n_1(t) n_2(t) \rangle$ but then it would be coupled to higher and higher order moments, a complete mess! Mean-field approach assumes that the populations

are independent and hence $\langle n_1(t)n_2(t) \rangle = \langle n_1(t) \rangle \langle n_2(t) \rangle = X(t)Y(t)$. This is simply not true, but ...

$$\begin{aligned}\frac{dX(t)}{dt} &= \bar{k}_A X(t) - \bar{k}_1 X(t)Y(t) \\ \frac{dY(t)}{dt} &= \bar{k}_1 X(t)Y(t) - k_2 Y(t)\end{aligned}\quad (2.53)$$

Now we can derive the evolution equation for the density of species $x(t) = \frac{X(t)}{\Omega}$, $y(t) = \frac{Y(t)}{\Omega}$. With the above definitions we get:

$$\begin{aligned}\frac{dx(t)}{dt} &= k_A c_A x(t) - k_1 x(t)y(t) \\ \frac{dy(t)}{dt} &= k_1 y(t)x(t) - k_2 y(t)\end{aligned}\quad (2.54)$$

being $c_A = n_A/\Omega$ the concentration of food. Now all the parameters in the equations are intensive. These are the celebrated Lotka-Volterra equations.

2.3.1 The enzymatic reaction

We now look at a very simple enzymatic reaction, where one substrate molecule S binds to the enzyme E which then decays into one product P plus an uncombined enzyme, one might write



In 1913 the two scientists Maud L. Menten (1879-1960) and Leonor Michaelis (1875-1949) published a famous work on the function of invertase (or saccharase). Invertase is an enzyme, found for example in yeast, which catalyses the breakdown of sucrose. What Menten and Michaelis postulated and reasoned was the following: the reaction starts with the relatively fast combination of the complex



and is followed by a rather slow decay into the product and the enzyme



By assuming a high energy barrier for the combination of a product with an enzyme the backwards rate k_{-2} can be neglected. In this way one can write down a set of differential equations for the dynamical variables $s(t), e(t), c(t)$ and $p(t)$, resembling

substrate, enzyme, complex and product concentration respectively:

$$\dot{s}(t) = k_{-1}c(t) - k_1s(t)e(t) \quad (2.58)$$

$$\dot{e}(t) = (k_{-1} + k_2)c(t) - k_1s(t)e(t) \quad (2.59)$$

$$\dot{c}(t) = -(k_{-1} + k_2)c(t) + k_1s(t)e(t) \quad (2.60)$$

$$\dot{p}(t) = k_2c(t) \quad (2.61)$$

After a short time of rapid complex building the rates of complex formation and breakdown will be in a steady state of flow, leading to a constant concentration $c(t)$ meaning $\dot{c}(t) = 0$. The sum of bound and unbound enzyme molecules is constant $c(t) + e(t) = e_0$ and one can eliminate $e(t)$ in (2.60). The steady state concentration of complexes is

$$c(t) = \frac{e_0s(t)}{s(t) + \frac{k_{-1}+k_2}{k_1}} \equiv \frac{e_0s(t)}{s(t) + K_M} \quad (2.62)$$

and K_M is called the Michaelis-Menten constant. When this equation is substituted into the dynamics of the product one finds:

$$\dot{p}(t) = \frac{k_2e_0s(t)}{s(t) + K_M} \equiv V_{max} \frac{s(t)}{s(t) + K_M}, \quad (2.63)$$

which is a form that can easily be compared with an experiment. For large substrate concentrations the production velocity saturates at V_{max} whereas low substrate concentrations lead to velocities of $V_{max}s/K_M$. The constants K_M and V_{max} have been determined for many enzymes.

2.4 Beyond meand-field: The Gaussian approximation

2.5 The Fokker-Planck equation

2.6 The Langevin equation

The mean-field equations give us information only about the average values (with the limitations expressed before in the case of nonlinear terms). There have been some attempts to modify the mean-field equations by including stochastic terms. However, this is not an easy task and some recent papers have addressed this problem [for instance, Aparicio and Solari, "Population dynamics: Poisson approximation and its relation to the Langevin process Phys. Rev. Lett. 86, 4183 (2001)]. Let us consider first the simple radioactive decay. The basic question is: is it possible to modify equation (2.49) to reproduce not just the mean value but also the fluctuations of the original process? In other words, could we write something like:

$$\frac{dn(t)}{dt} = -\omega n(t) + G\xi(t) \quad (2.64)$$

where $\xi(t)$ is white noise $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$ and G is a function to be determined. We would like that the solution of this equation to have the exact mean and variance for the process $n(t)$, namely:

$$\begin{aligned} \langle n(t) \rangle &= n(0)e^{-\omega t} \\ \langle n(t)^2 \rangle - \langle n(t) \rangle^2 &= n(0)e^{-\omega t}(1 - e^{-\omega t}) \end{aligned} \quad (2.65)$$

Let us assume first that $G = G(t)$ is a function of time. The solution of equation (2.64) is in this case:

$$n(t) = n(0)e^{-\omega t} + e^{-\omega t} \int_0^t ds e^{-\omega s} G(s) \xi(s) \quad (2.66)$$

From where it follows:

$$\langle n(t) \rangle = n(0)e^{-\omega t} + e^{-\omega t} \int_0^t ds e^{-\omega s} G(s) \langle \xi(s) \rangle = n(0)e^{-\omega t} \quad (2.67)$$

and

$$\langle n(t)^2 \rangle - \langle n(t) \rangle^2 = \langle (n(t) - n(0)e^{-\omega t})^2 \rangle = e^{-2\omega t} \int_0^t ds \int_0^t du e^{\omega(s+u)} G(s)G(u) \langle \xi(s)\xi(u) \rangle \quad (2.68)$$

replacing $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$ and the left hand side by the desired variance, we obtain:

$$n(0)(e^{\omega t} - 1) = \int_0^t ds e^{2\omega s} G(s)^2 \quad (2.69)$$

and taking the derivative with respect to time it is:

$$G(t)^2 = \omega n(0)e^{-\omega t} \quad (2.70)$$

We conclude that the stochastic differential equation:

$$\frac{dn(t)}{dt} = -\omega n(t) + \sqrt{\omega n(0)e^{-\omega t}} \xi(t) \quad (2.71)$$

has the same moments $\langle n(t) \rangle$ and $\langle n(t)^2 \rangle$ than the original master equation and is, hence, an improvement upon the simple equation (2.49). However, we do not quite like this equation since the initial condition $n(0)$ appears explicitly in it. We can write it in the equivalent way:

$$\frac{dn(t)}{dt} = -\omega n(t) + \sqrt{\omega \langle n(t) \rangle} \xi(t) \quad (2.72)$$

which do not like either because the average value is not known a priori. Finally, we try the following version:

$$\frac{dn(t)}{dt} = -\omega n(t) + \sqrt{\omega n(t)} \xi(t) \quad (2.73)$$

This equation has a multiplicative noise and needs an interpretation rule. It turns out that only in the Itô interpretation, the first two moments coincide with the original process. Hence, we conclude that equation (2.73), interpreted in the Itô sense, is the

stochastic equation that improves upon the mean-field approximation Eq.(2.49). This equation has the same first two moments that the master equation of the radiative process (see the 4th exercise in page 252 of van Kampen's book).

We apply now the same ideas to modify the mean-field equation (2.50) for the birth and death process. We look to modify it by adding some stochastic terms in such a way that the mean value and the variance coincide with the ones obtained from the master equation. We try:

$$\frac{dn(t)}{dt} = -k_1 n(t) + k_A + G\xi(t) \quad (2.74)$$

It is easy to arrive at:

$$\sigma^2[n(t)] = e^{-2k_1 t} \int_0^t ds G(s)^2 e^{2k_1 s} \quad (2.75)$$

and comparing with the desired correlations as given by Eq.(2.24). The result is that $G(t)^2 = Nk_1 e^{-k_1 t} + k_A + k_A(1 - e^{-k_1 t}) = k_1 \langle n(t) \rangle + k_A$. Again, we do not like this expression and we try: $G(t)^2 = k_1 n(t) + k_A$. The resulting stochastic differential equation

$$\frac{dn(t)}{dt} = -k_1 n(t) + k_A + \sqrt{k_1 n(t) + k_A} \xi(t) \quad (2.76)$$

has the same first and second moments than the master process, Eqs.(2.24), when it is interpreted in the Itô sense, as a somewhat lengthy calculation shows.

2.7 The $1/\Omega$ expansion of the master equation

Chapter 3

Numerical simulations of master equations: The Gillespie's algorithm.

3.1 Numerical simulations of master equations.

Given the difficulties one encounters for the analytical treatment of master equations, it is common to resort to numerical simulations of the underlying stochastic process. Let us learn how to proceed. We first begin by the simple example of a two-state system. If we denote by A and B the possible states there will be jumps from A to B at a rate $\omega_{A \rightarrow B}$ and from B to A at a rate $\omega_{B \rightarrow A}$. Remember that, besides being both non-negative numbers, the rates $\omega_{A \rightarrow B}$ and $\omega_{B \rightarrow A}$ have no relation amongst them. The process is schematized by:



The stochastic process is a series of jumps from one of the two states to the other. Imagine that at time t_0 we are at state A . The jump to state B will happen randomly with a probability density function $f_{A \rightarrow B}(t)$ such that $f_{A \rightarrow B}(t)dt$ is the probability that the system remains at state A for a time t and then jumps to state B in the time interval $(t, t + dt)$. This is equal to the probability that no jump occurred in the interval $(t_0, t_0 + t)$ which, according to the discussion in section 1.2, is $e^{-\omega_{A \rightarrow B}t}$, times the probability that a jump does occur in the interval $(t, t + dt)$, which is $\omega_{A \rightarrow B}dt$, or:

$$f_{A \rightarrow B}(t)dt = e^{-\omega_{A \rightarrow B}t} \omega_{A \rightarrow B} dt, \quad (3.2)$$

or

$$f_{A \rightarrow B}(t) = e^{-\omega_{A \rightarrow B}t} \omega_{A \rightarrow B}. \quad (3.3)$$

This is nothing but an exponential distribution. Next thing we have to do is to generate a time of jump $t_{A \rightarrow B}$ using this distribution. This is done by generating a random number u_0 uniformly distributed in the interval $(0, 1)$ and solving the equation

$$u_0 = \int_0^{t_{A \rightarrow B}} f_{A \rightarrow B}(t) dt = 1 - e^{-\omega_{A \rightarrow B}t_{A \rightarrow B}} \quad (3.4)$$

or, using that $1 - u_0$ and u_0 have the same statistical properties:

$$t_{A \rightarrow B} = \frac{-\ln u_0}{\omega_{A \rightarrow B}}. \quad (3.5)$$

At time $t_1 = t_0 + t_{A \rightarrow B}$ we jump from A to B . Now that the state is B we have to compute the time interval $t_{B \rightarrow A}$ to the next jump, this time from B to A . The same reasoning leads to the time of the next jump $t_2 = t_1 + t_{B \rightarrow A}$ where t is obtained from a random number u_1 as

$$t_{B \rightarrow A} = \frac{-\ln u_1}{\omega_{B \rightarrow A}}. \quad (3.6)$$

Now the time of the next jump, from A to B is $t_3 = t_2 + t_{A \rightarrow B}$ where

$$t_{A \rightarrow B} = \frac{-\ln u_2}{\omega_{A \rightarrow B}}, \quad (3.7)$$

and so on.

```
c /home/raul/COHERENCE/rate1.f
  implicit double precision(a-h,o-z)
  tmax=10000.0d0
  t=0.0d0
  wab=0.5d0
  wba=1.0d0
  call dran_ini(12345)
  i=i_dran(2)
  write(66,*) t,i
  do while (t.lt.tmax)
    if (i.eq.1) then
      tn=-dlog(dran_u())/wab
      in=2
    else
      tn=-dlog(dran_u())/wba
      in=1
    endif
    t=t+tn
    write(66,*) t,i
    i=in
    write(66,*) t,i
  enddo
end
```

We now consider the more general case that there are M states labeled by $1, 2, \dots, M$. Imagine that at time t_0 we are at state i_0 . Now there can be jumps to $M - 1$ different states with rates $\omega_{i_0 \rightarrow k}$ for $k = 1, \dots, N$, $k \neq i_0$. If $\omega_{i_0 \rightarrow j} = 0$, then the corresponding jump $t_{i_0 \rightarrow j}$ is not permitted. We generate now $M - 1$ random numbers u_0^k for

$k = 1, \dots, M, k \neq i_0$ and compute the jumping times to every one of these states as:

$$t_{i_0 \rightarrow k} = \frac{-\ln u_0^k}{\omega_{i_0 \rightarrow k}}, \quad k = 1, \dots, M, k \neq i_0 \quad (3.8)$$

The next jump to happen will be the one that occurs in the smallest possible time $t_{i_0 \rightarrow i_1} = \min(t_{i_0 \rightarrow 1}, t_{i_0 \rightarrow 2}, \dots, t_{i_0 \rightarrow M})$. The, at time $t_1 = t_0 + t_{i_0 \rightarrow i_1}$ we jump from i_0 to i_1 . Now that we are at state i_1 , we generate the random numbers u_1^k for $k = 1, \dots, M, k \neq i_1$ and compute the times of possible jumps

$$t_{i_1 \rightarrow k} = \frac{-\ln u_1^k}{\omega_{i_1 \rightarrow k}}, \quad k = 1, \dots, M, k \neq i_1. \quad (3.9)$$

The actual jump $i_1 \rightarrow i_2$ is the one that occurs in the earliest time $t_{i_1 \rightarrow i_2} = \min(t_{i_1 \rightarrow 1}, t_{i_1 \rightarrow 2}, \dots, t_{i_1 \rightarrow M})$. Then, at time $t_2 = t_1 + t_{i_1 \rightarrow i_2}$ the state jumps from i_1 to i_2 . The process starts again at state i_2 at time t_2 .

Here we present a computer program that implements this numerical method:

```
c      /home/raul/COHERENCE/rate2.f
      implicit double precision(a-h,o-z)
      parameter (M=10)
      dimension w(M,M)
      do i=1,M
        do j=1,M
          w(i,j)=abs(i-j)
        enddo
      enddo
      tmax=10000.0d0
      t=0.0d0
      call dran_ini(12345)
      i=i_dran(M)
      write(66,*) t,i
      do while (t.lt.tmax)
        if (i.eq.1) then
          j0=2
        else
          j0=1
        endif
        tn=-dlog(dran_u())/w(i,j0)
        in=j0
        do j=j0+1,M
          if (j.ne.i) then
            if (w(i,j).gt.0.0d0) then
              t1=-dlog(dran_u())/w(i,j)
              if (t1.lt.tn) then
                tn=t1
              endif
            endif
          endif
        enddo
      enddo
```

```

                                in=j
                                endif
                            endif
                        endif
                    enddo
                t=t+tn
                write(66,*) t,i
                i=in
                write(66,*) t,i
            enddo
        end

```

The same problems can be considered from a different point of view. Imagine first that we are interested in the behavior of an ensemble of N independent systems. Each of the systems follows a stochastic dynamics with jumps between two possible states A and B . In order to simulate the behavior of the ensemble, we can either run the above program `rate1` N times and then analyze the data accordingly or we can just focus on the stochastic variable that gives the number n of systems which at time t are in state A . By conservation, the number of systems which are at state B is $N - n$.

From this alternative point of view, the variable n can take any of the $N + 1$ values $n = 0, 1, \dots, N$. So, we consider that the ensemble can be in any of $N + 1$ states labeled by the value of n . This is similar to the second case explained before (program `rate2`). However the problem gets simpler as the only possible transitions allowed are those that increase (or decrease) in one unit the value of n , corresponding to transitions from one system from B to A (or from A to B). The rate of the transition from n to $n + 1$ is $(N - n)\omega_{B \rightarrow A}$ and the rate of the transition from n to $n - 1$ is $n\omega_{A \rightarrow B}$. Then, if at time t_0 we are in state n we have to compute the time $t_{n \rightarrow n+1}$ of the next jump $n \rightarrow n + 1$ and the time $t_{n \rightarrow n-1}$ of the next jump to $n \rightarrow n - 1$ and realize the action implied by the minimum of these two values. Let us now give a specific program that implements this numerical method.

```

c    /home/raul/COHERENCE/rate1b.f
    implicit double precision(a-h,o-z)
    tmax=10000.0d0
    t=0.0d0
    wab=0.5d0
    wba=1.0d0
    call dran_ini(12345)
    n=i_dran(N+1)-1
    write(66,*) t,n
    do while (t.lt.tmax)
        if (n.eq.0) then
            tn=-dlog(dran_u())/ (N*wab)
            in=1
        elseif (n.eq.N)

```

```

tn=-dlog(dran_u())/ (N*wab)
  else
    tn1=-dlog(dran_u()) / ((N-n) *wba)
    tn2=-dlog(dran_u()) / (n*wab)
    if (tn1.lt.tn2) then
      tn=tn1
      in=n-1
    else
      tn=tn2
      in=n+1
    endif
  endif
  t=t+tn
  write(66,*) t,n
  n=in
  write(66,*) t,n
enddo
end

```

An extension of this description can be used in the case that an individual system can be in more than 2 states. Instead of giving now an specific example, we will explain first a modification introduced by Gillespie that leads to a much more efficient programming of the numerical simulations.

3.2 The Gillespie's algorithm.

Gillespie has proposed a very simple but very effective modification of the numerical algorithm. We first take the point of view of considering only one system. This can be in any of M states. Assume that, as before, the system is in the state i_0 at time t_0 . First, one computes the rate of escape from this state i_0 to any other state $j \neq i_0$. This is nothing but $\Omega_{i_0} = \sum_{j \neq i_0} \omega_{i_0 \rightarrow j}$. Then one computes the time interval to the next jump $t_{i_0 \rightarrow i_1}$ using this total rate:

$$t_{i_0 \rightarrow i_1} = \frac{-\ln u_0}{\Omega_{i_0}}. \quad (3.10)$$

Once the time of the next jump has been determined as $t_1 = t_0 + t_{i_0 \rightarrow i_1}$ then we have to determine where to jump, or which is the final state i_1 . The probability $p_{i_0 \rightarrow j}$, of reaching state $j \neq i_0$ is proportional to the rate $\omega_{i_0 \rightarrow j}$, or

$$p_{i_0 \rightarrow j} = \frac{\omega_{i_0 \rightarrow j}}{\Omega_{i_0}} \quad (3.11)$$

It is easy now to determine the final state i_1 by using a random number v_0 uniformly distributed in the interval $(0, 1)$ and finding the smallest i_1 that satisfies $\sum_{j=1}^{i_1} p_{i_0 \rightarrow j} > v_0$.

The program is:

```

c      /home/raul/COHERENCE/rate3.f
      implicit double precision(a-h,o-z)
      parameter (M=100)
      dimension w(M,M),wt(M)
      do i=1,M
      wt(i)=0.0d0
          do j=1,M
              w(i,j)=abs(i-j)
              wt(i)=wt(i)+w(i,j)
          enddo
      enddo
      tmax=10000.0d0
      t=0.0d0
      call dran_ini(12345)
      i=i_dran(M)
      write(66,*) t,i
      do while (t.lt.tmax)
          tn=-dlog(dran_u())/wt(i)
          p=0.0d0
          j=0
          r=dran_u()*wt(i)
          do while (r.gt.p)
              j=j+1
              p=p+w(i,j)
          enddo
          t=t+tn
          write(66,*) t,i
          i=j
          write(66,*) t,i
      enddo
      end

```

If we take now the point of view that there are N (possibly interacting) systems we need to consider the variables that give the number of systems n_k which are on each of the possible states $k = 1, \dots, M$. These variables will change (typically by a small amount) and the rates of the transitions $(n_1, \dots, n_M) \rightarrow (n'_1, \dots, n'_M)$ will depend on the variables (n_1, \dots, n_M) themselves. It is easier if we consider an specific example.

A simple model for the spread of an epidemics is the so-called SIR model: S (for susceptible), I (for infectious) and R (for recovered). In its simplest form a population of N individuals is splitted into these three groups: susceptible people can get the disease, infectious people have the disease and can hence pass the infection to susceptible people. Infected people cure and then they become immune to antoher infection. In this simple version, there are no death or birth of individuals and their total number

remains constant. If n_S, n_I, n_R are, respectively, the number of susceptible, infected and recovered individuals, they verify $n_S + n_I + n_R = N$ the basic ingredients of the model are:

1) A susceptible gets infected after being in contact with an infected. The contact of a susceptible with an infected will occur with probability proportional to n_I/Ω , being Ω a parameter that determines the spatial extension of the population. If we call β the rate at which a given susceptible people gets infected after a contact with an infected people, the overall rate at which one susceptible people will get infected is $\beta n_I/\Omega$. The rate at which **any** susceptible will get infected is then $\beta n_S n_I/\Omega$.

2) An infected individual gets cured and becomes recovered. This happens, for an individual infected, at rate ν .

In step (1), when a susceptible gets infected the numbers vary as: $n_S \rightarrow n_S - 1, n_I \rightarrow n_I + 1$. In step (2), recovery of an infected, the numbers vary as: $n_I \rightarrow n_I - 1, n_R \rightarrow n_R + 1$. It is possible (and convenient) to introduce more steps in the process, such as the death (possibly with different rates) of susceptible, infected and recovered individuals; the birth of susceptible individuals and the entrance of infected individuals from another town. However, for the sake of clarity, we only consider the two previous basic ingredients.

Now it is easy what to do: at the population level, the two jumps are (1) $n_S \rightarrow n_S - 1, n_I \rightarrow n_I + 1$ with rate $\beta n_S n_I/\Omega$ and (2) $n_I \rightarrow n_I - 1, n_R \rightarrow n_R + 1$ with rate νn_I . The reader might find interesting to write down the master equation of the model and to derive the corresponding mean-field equations for the densities $s = n_S/\Omega$, $i = n_I/\Omega$, $r = n_R/\Omega$:

$$\frac{ds}{dt} = -\beta si \quad (3.12)$$

$$\frac{di}{dt} = \beta si - \nu i \quad (3.13)$$

$$\frac{dr}{dt} = \nu i \quad (3.14)$$

The following program implements Gillespie's algorithm for this model:

```
c /home/raul/COHERENCE/epidemics.f
  implicit double precision(a-h,o-z)
  double precision nu
  N=10000
  tmax=10000.0d0
  t=0.0d0
  nu=0.5d0
  beta=1.0d0
  Omega=100.0d0
  call dran_ini(12345)
  ni=i_dran(N+1)-1
  ns=N-ni
  nr=0
  write(66,*) t,ns,ni,nr
```

```
do while (t.lt.tmax)
    if (ni.eq.0) stop
    w1=beta*ns*ni/Omega
    w2=nu*ni
    w=w1+w2
    tn=-dlog(dran_u())/w
    t=t+tn
    write(66,*) t,ns,ni,nr
    if (dran_u().lt.w1/w) then
        ns=ns-1
        ni=ni+1
    else
        ni=ni-1
        nr=nr+1
    endif
    write(66,*) t,ns,ni,nr
enddo
end
```