


Preface

These notes are in part based on a course for advanced students in the applications of stochastic processes held in 1978 at the University of Konstanz. These notes contain the results of recent studies on the stochastic description of ion transport through biological membranes. In particular, they serve as an introduction to an unified theory of fluctuations in complex biological transport systems. We emphasize that the subject of this volume is not to introduce the mathematics of stochastic processes but to present a field of theoretical biophysics in which stochastic methods are important.

In the last years the study of membrane noise has become an important method in biophysics. Valuable information on the ion transport mechanisms in membranes can be obtained from noise analysis. A number of different processes such as the opening and closing of ion channels have been shown to be sources of the measured current or voltage fluctuations. Biological transport systems can be complex. For example, the transport process can be coupled to other processes such as chemical reactions and take place in discontinuous structures of molecular dimensions. Furthermore, since there are strong electric fields or high concentration gradients across biological membranes ion transport processes of biological relevance are mostly processes far from equilibrium. For these reasons the development of new theoretical concepts has been necessary. The concept of transport in discrete systems has turned out to be more appropriate than continuum models.
There are two purposes for these notes: the first is to familiarize the reader with the theoretical background which is necessary for a satisfactory analysis of electrical noise in ion transport through biological membranes. Hence a number of applications of the general concepts to special transport models are discussed; the second is to show that the developed concepts may also be applied for the investigation of general properties of systems in nonequilibrium states. A main result of this study is the invalidity of the fluctuation-dissipation theorem for transport fluctuations at nonequilibrium steady states as consequence of the vectorial character of the considered (electrical) transport processes, while for scalar quantities the fluctuation dissipation theorem can be extended to nonequilibrium states.

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A. Stochastic Processes

Contrariwise to a deterministic process governed by deterministic laws a stochastic or random process is controlled by probabilistic laws. Consider an experimental set-up by which an observable quantity or a set of observable quantities $X(t)$ as a function of time can be measured: If the time course of $X(t)$ is governed by probabilistic laws, different measurements of $X(t)$ with the same experimental set-up at different times or with identical set-ups at the same time may yield different results $X(t)$, representing different possible realizations of $X(t)$. The ensemble of all possible realizations of $X(t)$ is a stochastic (random) process. $X(t)$ is called a random variable, or a set of random variables, respectively. Stochastic processes may be discrete or continuous in $X$ and in time $t$. We will mainly consider processes which are discrete in $X$ (e.g. integers) and continuous in time.

There is a large literature dealing with the mathematical fundamental theory of stochastic processes (e.g. Doob, 1953, Karlin, 1965). However, it is possible to get a knowledge which is sufficient for a great variety of applications in natural sciences, by adopting a less rigorous and more heuristic approach, as has been presented e.g. in the textbook by Bailey (1964). We mainly restrict this introductory part to a summarization of some definitions and facts, the knowledge of which is necessary for those readers who want to follow this volume without further study of mathematical textbooks.
1. Expectation Values, Moments, Variance, Correlations

Of central importance for the theoretical and experimental analysis of stochastic processes are averaged quantities. Though in most cases the experimentalist measures time averages, the theoretical approach is based on ensemble averaged quantities. If the stochastic process is ergodic (see below), ensemble averages and the corresponding time averages are equal. An ensemble average of some function \( f \) of \( X(t) \) is got by averaging over all possible realizations of \( X \) at time \( t \). It is called the expectation value of \( f \) and denoted by \( \langle f \rangle \):

\[
\langle f(X(t)) \rangle : \text{Expectation value of } f \text{ at time } t \quad (A.1.1)
\]

Moments

The most simple ensemble average is the expectation or mean value of \( X(t) \) itself. It is called the first moment of \( X \):

\[
\langle X(t) \rangle : \text{Expectation value of } X, \text{ first moment} \quad (A.1.2)
\]

The mean square value of \( X \) is called the second moment:

\[
\langle X^2(t) \rangle : \text{Mean square value, second moment} \quad (A.1.3)
\]

Generally:

\[
\langle X^k(t) \rangle : k\text{-th moment of } X \quad (A.1.4)
\]

\( k = 1, 2, 3 \ldots \)

Often one is especially interested in the averaged deviations of \( X(t) \) from the mean value \( \langle X(t) \rangle \) or the magnitude of the fluctuations around \( \langle X(t) \rangle \). For this reason one introduces the so-called central moments or cumulants. Of special importance is the second central moment or variance:

\[
\sigma^2(t) = \langle (X(t) - \langle X(t) \rangle)^2 \rangle \quad (A.1.5)
\]
Generally the $k$-th central moment or cumulant is:

$$
\sigma^k(t) = \langle (X(t) - \langle X(t) \rangle)^k \rangle 
$$

(A.1.6)

The $k$-th central moment can always be expressed by the lower order moments. Explicitely for the variance holds the important relation:

$$
\langle (X(t) - \langle X(t) \rangle)^2 \rangle = \langle X^2(t) \rangle - \langle X(t) \rangle^2 
$$

(A.1.7)

The validity of this relation may simply be shown by using the fact that the expectation value of a sum of quantities is equal to the sum of the expectation values of these quantities.

Correlations

Up to now we have considered quantities averaged at one time $t$. Further important information about the mechanisms underlying a stochastic process may be contained in the correlations between the measured quantities at different times. If $X(t)$ represents a single variable, the most important correlation is the autocorrelation function $C(t,s)$, by which an ensemble averaged correlation between $X$ at time $t$ and $X$ at time $(t+s)$ is defined:

$$
C(t,s) = \langle X(t) \ X(t+s) \rangle 
$$

(A.1.8)

Often the autocorrelation function $C_{\Delta X}(t,s)$ of the deviation

$$
\Delta X(t) = X(t) - \langle X(t) \rangle 
$$

(A.1.9)

from the expectation value $\langle X(t) \rangle$ is used, namely

$$
C_{\Delta X}(t,s) = \langle \Delta X(t) \ \Delta X(t+s) \rangle 
$$

(A1.10)
For $s=0$ $C(t,o)$ is the second moment and $C_{\Delta X}(t,o)$ the variance of $X(t)$:

$$C(t,o) = \langle X^2 \rangle$$  \hspace{1cm} (A.1.11)

$$C_{\Delta X}(t,o) = \sigma^2(t)$$

Information about the correlations between different quantities $Y$ and $Z$ may be obtained by the crosscorrelation $C_{YZ}(t,s)$:

$$C_{YZ}(t,s) = \langle Y(t) Z(t+s) \rangle$$  \hspace{1cm} (A.1.12)

The crosscorrelation $C_{YZ}(t,s)$ may be different from the crosscorrelation $C_{ZY}(t,s)$. Further information may be contained in higher order correlations which are obtained by comparison of quantities at more than two different times.

2. Probabilities

We suppose that the reader has an intuitive feeling for the idea of probability: In the experiment of throwing a die the probability of getting a special number is $1/6$. Probabilities are nonnegative and not greater than one.

If the possible values of a random variable $X$ are discrete and denoted by $X_i$, the probability that $X$ assumes the special value $X_i$ is $P(X_i)$. Clearly,

$$\sum_{\text{all } i} P(X_i) = 1,$$  \hspace{1cm} (A.2.1)

expressing the certainty that in one experiment $X$ takes exactly one value $X_i$. 
If the random variable assumes a continuous range of values, then we define the probability density \( p(X) \), where \( p(X) \, dX \) is the probability of finding the value of the random variable in the interval between \( X \) and \( X+dX \). \( p(X) \) satisfies the relation

\[
\int p(X) \, dX = 1 \quad (A.2.2)
\]

Throughout this article probabilities are denoted by \( P \) and probability densities by \( p \). In most cases we shall assume discrete processes and use probabilities \( P \). For a continuous process the corresponding relations are found by replacing \( P(X) \) by \( p(X) \, dX \) and sums by integrals. The probability distribution function \( D(X) \) denotes the probability that the random variable is smaller than \( X \):

\[
D(X_1) = P(X \leq X_1) \quad (A.2.3)
\]

Obviously, for continuous \( X \) the probability density function \( p(x) \) is related to the distribution function \( d(x) \) through

\[
p(X) = \frac{dd(X)}{dX} \quad (A2.4)
\]

### 2.1 Expectation Values and Probabilities

The expectation values may be defined with the use of the probabilities. If we admit time dependence, the expectation value \( \langle X(t) \rangle \) in discrete processes is given from the probability \( P(X,t) \) by

\[
\langle X(t) \rangle = \sum_{\text{all } X} X \, P(X,t) \quad (A.2.5)
\]
The summation has to be taken over all possible values $X$. Note that the time dependence of $\langle X(t) \rangle$ comes in by the time dependence of $P(X,t)$. Correspondingly the moments $\langle X^k(t) \rangle$ are

$$\langle X^k(t) \rangle = \sum_{all \ X} X^k P(X,t)$$

(A.2.6)

Generally, the expectation value $\langle f(X(t)) \rangle$ is

$$\langle f(X(t)) \rangle = \sum_{all \ X} f(X) P(X,t)$$

(A.2.7)

**Conditional and Joint Probabilities**

Often, in time dependent processes one needs the probability that $X$ is the value of the random variable at time $t$ under the condition that the value was $X'$ at time $t'$. This conditional probability is denoted by

$$P(X,t/X',t').$$

It must be distinguished from the joint probability

$$P(X,t; X',t'),$$

which is the probability that at time $t$ the value is $X$ and at time $t'$ the value is $X'$. Between conditional and joint probability holds the relation which is clear from the definitions:

$$P(X,t; X',t') = P(X,t/X',t') P(X',t')$$

(A.2.8)

Correspondingly, also higher order probabilities may be defined.
The autocorrelation function $C(t,s)$ may be expressed by the joint probability:

$$C(t,s) = \left< X(t) X(t+s) \right> = \sum_{X,X'} X \cdot X' \cdot P(X,t; X',t+s)$$

(A.2.9)

**Conditionally Averaged Values**

The introduction of the conditional probability makes possible the definition of conditional averages. Often one is interested in the expectation value of $X$ at time $t$ under the (initial) condition that it was $X'$ at time $t'$. It is given by

$$\left< X(t) \right>_{(X',t')} = \sum_X X P(X,t/X',t')$$

(A.2.10)

Correspondingly, conditional averages for other quantities may be defined. These subensemble averages are important for Markov processes (see part B) where the time course of probabilities is determined by only one initial condition. In case $X$ stands for a set of variables, the probabilities and averages are defined analogously.

3. Binomial, Poisson, Normal Distributions

**Binomial Distribution**

Consider a special experiment, where the probability for a special (positive) result is $P$. Then the probability for another (negative)
result is clearly $(1-P)$. We ask for the probability that in $m$
identical and independent experiments $n$ have positive results. This
probability $P_m(n)$ is given by the binomial law

$$P_m(n) = \binom{m}{n} p^n (1-p)^{m-n} \quad (A.3.1)$$

with

$$\binom{m}{n} = \frac{m!}{n! (m-n)!}$$

In (A.3.1) the possible values $n$ of the random variable are positive
integers. $P_m(n)$ satisfies relation (A.2.1):

$$\sum_{n=0}^{m} P_m(n) = 1 \quad (A.3.2)$$

The summation in (A.3.2) is taken over all possible values $n$. With
the use of relations (A.2.5)-(A.2.6) the expectation values can be
calculated from (A.3.1). The results for the first two moments $\langle n \rangle$, $\langle n^2 \rangle$ and the variance $\sigma^2$ are

$$\langle n \rangle = m P$$

$$\langle n^2 \rangle = m^2 P^2 + m P (1-P) \quad (A.3.3)$$

$$\sigma^2 = m P (1-P) = \langle n \rangle (1-P)$$

Poisson Distribution

The Poisson distribution is derived from the binomial law by the li-
miting process

$$m \to \infty, \quad p \to 0, \quad m P = \langle n \rangle \text{ finite,} \quad (A.3.4)$$
where \( m \) and \( P \) remain the number of identical independent experiments and the probability of a positive result of a single experiment, respectively. The probability \( P(n) \) that \( n \) experiments have positive results is given by the Poisson law:

\[
P(n) = \frac{\langle n \rangle^n}{n!} e^{-\langle n \rangle}
\]

(A.3.5) is used instead of (A.3.1) in cases of a sufficiently great number of experiments. \( P(n) \) satisfies relation (A.2.1):

\[
\sum_{n=0}^{\infty} P(n) = 1
\]

(A.3.6)

Second moment and variance can be directly derived from (A.3.3)

\[
\langle n^2 \rangle = \langle n \rangle^2 + \langle n \rangle
\]

\[
\sigma^2 = \langle n \rangle
\]

(A.3.7)

Normal Distribution

A random variable \( X \) is said to follow a normal distribution if its probability density \( p(X) \) is given by:

\[
p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[ -\frac{(X - \langle X \rangle)^2}{2\sigma^2} \right]
\]

(A.3.8)

\( \langle X \rangle \) : expectation (mean) value, \( \sigma^2 \) : the variance.

The importance of the normal distribution is a consequence of the central-limit-theorem which, roughly speaking, asserts that the normal distribution will result in general, when a large number of independent random variables are summed to obtain one new random variable.
4. Stationarity and Ergodicity

Stationarity

A stochastic process is called stationary, if \( P(X,t) \) is independent of time:

\[
P(X,t) = P(X) \quad (A.4.1)
\]

Otherwise it is called nonstationary. As consequence of (A.4.1) all moments are time-independent. Often a stochastic process is called (weakly) stationary, if the first two moments are time-independent.

The autocorrelation function \( C(t,s) \) in stationary processes is independent of time \( t \) and satisfies the following relations, which may easily be derived from the definition (A.1.8) of \( C(t,s) \) and the definition of stationarity:

\[
\begin{align*}
C(t,s) &= C(0,s) = C(s) \quad &\text{a)} \\
C(s) &= C(-s) = C(|s|) \quad &\text{b)} \quad (A.4.2) \\
|C(s)| &\leq C(0) \geq 0 \quad &\text{c)}
\end{align*}
\]

Ergodicity

Of great practical importance is the special class of ergodic processes. A stationary stochastic process is called ergodic, if the ensemble averages (expectation values) are equal to the corresponding time averages over one realization \( X_i(t) \) of the stochastic process:

\[
\langle f(X) \rangle = \frac{1}{2T} \int_{-T}^{+T} f(X(t)) \, dt \quad (A.4.3)
\]
Time averages in this article are denoted by $\bar{f}$. Especially, the moments are in ergodic processes:

$$\langle X \rangle = \bar{x}_i$$

$$\langle X^k \rangle = \bar{x}_i^k$$ \hspace{1cm} (A.4.4)

$$\sigma^2 = \frac{(x_i - \bar{x}_i)^2}{\bar{x}_i^2}$$

and the autocorrelation function

$$C(s) = \frac{X_i(t) X_i(t+s)}{\bar{x}_i^2}$$ \hspace{1cm} (A.4.5)

We note that ergodicity necessarily implies stationarity.

In experimental investigations of stationary processes mostly ergodicity is assumed. Fortunately this has been successful in most cases. Ergodic processes can be investigated with one experimental set-up (one realization of the stochastic process) and the quantities characterizing the process can be measured by time averaging.

Nevertheless, we must keep in mind that stationarity not necessarily implies ergodicity, e.g. stationary processes may be nonergodic if the realizations $X_i(t)$ depend in some random way on starting conditions. A simple example is the stationary process defined by the realizations

$$X_i(t) = A(i) \sin[\omega t + \theta(i)]$$ \hspace{1cm} (A.4.6)

where amplitude $A(i)$ and phase $\theta(i)$ are random variables.