Stochastic models for systems of interacting ion channels

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We consider a variety of Markov based models for systems of ion channels exhibiting dependence between channels. It is shown how many useful properties which may be calculated for an aggregated single-channel model, or a system of independent channels, can be extended to various types of interacting channel systems. Key structure and results from the theory of aggregated Markov processes are summarized in a convenient matrix form. These are then applied to the superposition of independent and dependent channels, including a patch of channels in a random environment, and a system of channels with spatial interactions. Calculations based on the resultant matrix expressions and intensity arguments can be implemented straightforwardly in a matrix-oriented package such as Matlab. The role of reversibility is also studied. A number of examples illustrate the strengths of the methods and enable numerical comparisons between the different types of systems.

Keywords: aggregated Markov chain; dwell-times; intensities; matrix methods; random environment; receptors; reversibility; spatial dependence; superposition.

1. Introduction

Development of stochastic models for the behaviour of ion channels in biological membranes as a basis for inference about the channel kinetics based on experimental data has been stimulated by the capability for direct observation of single-channel activity using the patch clamp technique. Since, in practice, several channels are often observed in a patch, there is a need for types of models which are satisfactory both for single and for multiple channels.

Initially, experimental evidence from studies of some types of channel supported the idea that the channels in a patch act independently; for example, see Neher et al. (1978)

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and Miller (1982). As a result, most early modelling of multiple channels, including that of Jackson (1985), Kijima & Kijima (1987b), Yeo et al. (1989), Dabrowski et al. (1990) and Fredkin & Rice (1991), dealt with independent (non-interacting) channels. More recently, for several types of channel, there has been growing evidence of interactions between the channels in a patch. For example, Schindler et al. (1984), Yeramian et al. (1986) and Keleshian et al. (2000) discuss such aspects for ACh channels, Kiss & Nagy (1985) consider sodium channels, Tytgat & Hess (1992) and Draber et al. (1993) deal with K+ channels, while chloride channels are discussed in Queyroy & Verdetti (1992), and L-type Ca2+ channels are studied in Mazzanti et al. (1991), Imredy & Yue (1992) and DeFelice (1993).

In contrast to the independence case, there have been few studies dealing with models for interacting channels. In Ball et al. (1994) dependence between channels was introduced through the influence of a random environment; an example of this type is given later in this paper. Keleshian et al. (1994) and Ball et al. (1997) considered a different form of dependence, based on the number of open channels in the patch. Manivannan et al. (1996) have studied a system of interacting identically distributed two-state channels; the channels are in clusters which may associate or dissociate, channels in a cluster are either all open or all closed, and the channels in a cluster open or close simultaneously. Ball & Yeo (2000) considered models incorporating spatial dependence between channels. Other approaches to modelling dependence between channels may be of interest, but it seems important that there should always be some physically reasonable basis for the types of model considered, and our own work has sought to achieve this.

At any given time a channel molecule is usually regarded as being in one of a finite number of kinetically (physicochemically) distinct states linked by well defined transition pathways (see Sakmann & Neher, 1995). Reflecting this, the behaviour of a single channel is commonly modelled by a continuous-time homogeneous finite-state Markov chain (see, for example, Colquhoun & Hawkes, 1982; Fredkin & Rice, 1986; Ball & Rice, 1992). If the channel gating is not coupled to a free energy source, such as a concentration gradient across the membrane, then (cf. Läuger, 1995) the gating behaviour is a time reversible phenomena and any reasonable model should possess this property. At several places in the present paper, we look at conditions for reversibility to hold and consequences of reversibility for a channel system.

Because the states need not all have distinct conductance levels, only some of the transitions between actual states may be directly observable. Thus the model state space is aggregated by a partitioning into classes corresponding to the various conductance levels, so that at any specified time it is possible to observe only which class the process is in. In the simplest case there would be just two classes, conducting (open) and non-conducting (closed); correspondingly, for a patch of channels only the total conductance would be observed, rather than which individual channels were conducting or non-conducting. Such models for ion channels use standard (textbook) theory of finite-state space continuous-time Markov chains (cf. Chapter 3 of Guttorp, 1995), but are non-standard in the particular structure (especially partitioning) that is imposed on the state space, in the questions asked and the properties considered. Actual data may be degraded by noise and by time interval omission, i.e. a failure to record events of very short duration. Aspects of these complications have been addressed elsewhere (see, for example, Roux & Sauvé, 1985; Ball
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& Sansom, 1988; Hawkes et al., 1990, 1992; Ball et al., 1993b) and will not be explored here.

The present paper is concerned with the structure and properties of multichannel models, and with computational methods aimed at obtaining useful properties. Properties of aggregated Markov processes are fundamental, both for studying models for a single channel and for dealing with the superposition resulting from a system consisting of several channels which may interact. The background structure is motivated in Section 2 by simple examples, with possible dependence incorporated through the number of open channels, through a random environment or through spatial interactions. Section 3 is then devoted to reviewing, in a relatively simple context, key aspects of the theory developed in the ion channel setting by Colquhoun & Hawkes (1982, 1987, 1995) and Fredkin et al. (1985); other details and some extensions were given in Ball et al. (1997). It deals with basic structure arising from the aggregation, entry processes and related equilibrium distributions, and joint distributions for class sojourn-times (dwell-times) and associated moments and correlations.

For any of the multiple-channel models considered in this paper, once the equilibrium distribution is known, expressions for the equilibrium mean sojourn times of the superposition at the various levels can be written down by using an argument based on intensities. In fact, an extension of this argument can be used to derive compact expressions for the probability density functions of the various equilibrium level sojourn times for three of the four types of model considered. These techniques, due to Ball & Milne (2000), provide a unified approach to such derivations, and are also presented in Section 3 for a general aggregated Markov process. Other aspects of aggregated Markov processes are, however, required for dealing with joint distributions or non-equilibrium properties.

The general theory is applied in Section 4 to the four types of model for a multichannel system outlined in Section 2, i.e. independent and identically distributed channels (Jackson, 1985; Kijima & Kijima, 1987b; Yeo et al., 1989; Colquhoun & Hawkes, 1990; Fredkin & Rice, 1991), co-operative channels (Keleshian et al., 1994; Ball et al., 1997), spatially dependent channels (Ball & Yeo, 2000) and channels in a random environment (Ball et al., 1994). The references given indicate places where more information about the different types of model may be found. The general matrix expressions given for the properties of the various models, though often forbidding, are in principle straightforward to compute in a package such as Matlab once numerical values have been specified for model parameters. Results of some such calculations are illustrated in Section 5 for the examples introduced earlier. Numerical comparisons between these models are then possible. Although relatively simple two- and three-state models are used in these illustrations, the methods can generally be readily applied to more complex situations. Some concluding remarks are given in Section 6.

2. Background and motivation

In modelling a multichannel system it has been assumed traditionally, as indicated above, that the individual channels behave independently and in a probabilistically identical manner. This way of combining the individual channel models has strong appeal, based on simplicity and convenience, even though it may not always be appropriate. In recent papers (Ball et al., 1994, 1997; Ball & Yeo, 2000) we have explored three different approaches,
each with its own special appeal, to introduce some form of dependence between the individual channel models.

In order to explain the ideas we assume throughout this section that the mechanism for each individual channel is a sequential scheme involving three states,

\[ C_1 \leftrightarrow C_2 \leftrightarrow O_3 \]  

(1)
as has been frequently considered for an agonist-gated (e.g. nicotinic acetylcholine receptor) channel. With appropriate changes to the following discussion it would be possible to substitute for (1) any other scheme, for example the five-state scheme considered by many authors (e.g. Colquhoun & Hawkes, 1982). In such a diagram open (unit conductance) states are indicated by \( O \), and closed (zero conductance) states by \( C \), with subscripts indicating the state label as used in subsequent models.

A mechanism like (1) is usually modelled as a (homogeneous) continuous-time Markov chain, denoted by \( \{X(t); t \geq 0\} \), which gives the state \( X(t) \) that the channel is in at each time \( t \) (see, for example Colquhoun & Hawkes, 1982); for the mechanism of (1) the state space is \{1, 2, 3\}. Transitions between states in such a model are determined by an associated (homogeneous) discrete-time Markov chain (the jump chain), and, given the successive states visited, the sojourn times in individual states are independent, each sojourn time having an exponential distribution with a parameter that depends only on the state being visited.

In the underlying Markov chain model of an ion channel, the actual state \( X(t) \) at time \( t \) may be unobservable; what is, in principle, observable is the aggregated process (see, for example Fredkin et al., 1985) which records the class of states that the underlying process is in at each time. For the mechanism of (1) the relevant classes are \( C = \{1, 2\} \) and \( O = \{3\} \), respectively the classes of closed and open states. The theory of aggregated Markov chains can be used to derive model properties such as probability density functions and moments of class sojourn times, particularly open times and closed times, and their joint properties assuming that the aggregated process is in equilibrium. Except when a class consists of a single state, such sojourn times are usually not exponentially distributed.

The following subsections outline, in a non-technical way, the basic structure of each of the four types of model for a multichannel system, and introduce some relevant notation and terminology. Section 4 will give more formal description of such models as well as some detailed illustrative examples, with numerical examples in Section 5 that will enable comparisons between the various types of model.

### 2.1 Independent and identically distributed channels

This type of model for a multichannel system assumes that the individual channels each have the same conductance and follow the same continuous-time Markov chain model, and also that these channels behave independently. For example, if there were two distinguishable channels, which are labelled channel 1 and channel 2 say, then the state of the system could be described by a two-vector whose components give the respective states of the individual channels. For individual channels following (1) the state space for the full two-channel system has \( 3^2 = 9 \) states, \((1, 1), (1, 2), (1, 3), (2, 1), (2, 2), (2, 3), (3, 1), (3, 2) \) and \( (3, 3) \), where, for example, the state \((1, 3)\) corresponds to channel 1 being in
state 1 and channel 2 in state 3. By exploiting symmetries which arise from channels being normally indistinguishable, and recording information only on the number of channels in each state, it is possible to reduce the size of this state space to 6 states, since the states (1, 2) and (2, 1) are equivalent and can thus be treated as a single state, as can states (1, 3) and (3, 1) and similarly states (2, 3) and (3, 2). In general, the number of system states is \( r^N \), where \( r \) denotes the number of states for an individual channel and \( N \) the number of channels in the system, and this can be reduced to \( \binom{N+r-1}{r} \) different system states if the only information kept is the number of channels in each (channel) state. Such reduction in the size of the system state space, which is more significant with more channels or a larger single-channel state space, has an important impact on the computation speed when dealing with numerical examples. For example, the reduction is from 81 states to 15 in the case of four channels following (1), and this reduction assists computational efficiency because in many formulae the size of matrices involved drops from 81 x 81 to 15 x 15. Whichever of these state spaces is used, the system process is, mathematically, just another continuous-time Markov chain.

For a multichannel system it is often sufficient to summarize the state of the system at a given time \( t \) by the number, \( M(t) \), of channels open at that time. (Since the individual channels were each assumed to have unit conductance, \( M(t) \) gives the overall system conductance at time \( t \).) This defines the superposition process \( \{M(t); t \geq 0\} \). The system state space, full or reduced, can then be partitioned into classes according to the level of the superposition process (that is, the number of channels open). For two channels independent and identically distributed according to (1), the system state space can be partitioned into three classes denoted by \( D_0, D_1 \) and \( D_2 \); for the full system state space these are given by \( D_0 = \{(1, 1), (1, 2), (2, 1), (2, 2)\} \), \( D_1 = \{(1, 3), (3, 1), (2, 3), (3, 2)\} \) and \( D_2 = \{(3, 3)\} \). Figure 1 gives illustrative realizations of two such single-channel processes and the corresponding superposition. For dealing with properties of the superposition process \( \{M(t); t \geq 0\} \) we are led again to an aggregated Markov chain structure, where now the aggregation is defined on the system state space. This aggregated Markov chain structure can be used, as for a single-channel model, to derive distributions and moments of class sojourn times, in particular (joint) distributions for sojourn times of the superposition process at its various levels.

### 2.2 Interacting channels: simple cooperativity

The model for a multichannel system based on independent and identically distributed channels can be extended to a type of model, studied by Keleshian et al. (1994) and Ball et al. (1997), which allows positive or negative cooperativity to be introduced between channels in a way that is physically plausible. For this type of extension, it is supposed that in the presence of another open channel there is a change in one or more transition rates for the other channels of the system. For example, for two channels independent and identically distributed according to (1), suppose that the transition rate from \( C_2 \) to \( O_3 \) (opening rate) for a given channel has two possible values: one, corresponding to the independence case, applies when the other channel is closed; the alternative value applies when the other channel is open. If the alternative opening rate is greater than the base (independence) rate then the two-channel system exhibits positive cooperativity; an alternative opening rate less than the base rate models negative cooperativity. (The case
of equality yields, of course, the independence model.) The transition rate from \( C_1 \) to \( C_2 \) may also be different in the two cases. With \( N \) channels there are more possibilities: the transition rates for any given channel may vary according to the number of other channels which are open (and so have \( N \) possible values).

For such a model, the system process is, again, a continuous-time Markov chain, with the same full, or reduced, state space as for the independence model and transition rates that differ in a simple way from those for that model. The reduced state space is the same because, once again, only the number of channels in each state needs to be recorded. Moreover, as for the independence model, aggregated Markov chain theory based on the same aggregation of the state space can be used to derive the usual types of system properties for the superposition process.

### 2.3 Spatial dependence

The models discussed above for multichannel systems of interacting channels take no account of the spatial configuration of the channels within a patch. Whilst it is likely that spatial aspects might be relevant in some circumstances, it has not been easy to build general models incorporating this feature that are susceptible to analysis, and furthermore at the present time it does not seem possible to obtain appropriate data. The models considered in Ball & Yeo (2000) are an attempt to take account of the spatial relationship of channels in a simple yet plausible way that still yields a mathematically tractable model.

For the simplest possible type of model it can be supposed that the channels are arranged on a ring and that the transition rates for a given channel depend on the number of its (two nearest) neighbours which are open. For two- or three-channel systems this model coincides with the type of interaction model described in the previous subsection, because a given channel and its neighbours then constitute the entire system. To obtain a new type of model at least four channels must be considered. For such models, the system process is once more a continuous-time Markov chain, having full state space as for the independence or simple cooperativity model and transition rates that differ in a simple way from those for
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the independence model. However, for such nearest neighbour models comprising at least four channels the appropriate reduced state space is larger than that for the independence or simple cooperativity model based on the same single-channel model, as will be explained later. Once again, aggregated Markov chain theory, based on the previous aggregation of the state space, can be used to derive properties of the superposition process.

It is possible to consider other spatial configurations, with channels arranged on a line (which is straightforward), or on a lattice (which is more difficult partly because the combinatorial results are not presently available and even the reduced state space can be prohibitively large for numerical calculations). In any of these models longer range interactions may be incorporated.

2.4 Random environment

A different approach to dependence between channels was introduced in Ball et al. (1994), and provides a means of modelling the 'buzz modes' observed, for example, by McManus & Magleby (1988). In this approach the channels of the system are assumed to be dependent only through the influence of a common random environment, perhaps unobservable or reflecting changes not measured, which is itself modelled as a homogeneous continuous-time Markov chain \( \{ X_E(t); \ t \geq 0 \} \) with \( m \) states. For \( N \) channels, the entire system is then described by a process \( \{ (X_E(t), Y_1(t), Y_2(t), \ldots, Y_N(t)); \ t \geq 0 \} \), called the complete process, where the component processes \( \{ Y_i(t); \ t \geq 0 \}, \ i = 1, 2, \ldots, N \) are the individual single-channel processes. Conditional on the environment process the component processes are independent and identically distributed, each according to a continuous-time Markov chain having a transition rate matrix which at time \( t \) may depend on \( e \), the state of the environment process at that time. The complete process is then itself a continuous-time Markov chain with full state space having \( m \times r^N \) elements, that is \( m \) times the number of states for a system of \( N \) independent and identically distributed channels each with \( r \) states. Once again, symmetries allow the full state space to be reduced to one having \( m \times \binom{N + r - 1}{N} \) states.

For example, a random environment model based on a two-state environment process and two three-state channel processes would require 12 states (reduced from 18), of which six have both channels closed, four have one channel closed and one open, and two have both channels open. The transition rates of such a process can be written down in terms of the transition rates for the environment process and those for the homogeneous continuous-time Markov chains \( \{ Y^{(e)}(t); \ t \geq 0 \} \) which for the various environment states \( e \) describe the behaviour of a typical single channel if the environment process were to remain always in state \( e \). (But note that the processes \( \{ Y^{(e)}(t); \ t \geq 0 \} \) are not themselves the single-channel processes.) Aggregation enters, much as before, both at the level of a single-channel process, and in the complete process.

3. Aggregated Markov processes

This section outlines the basic theory and some key properties of aggregated Markov processes. As indicated already in the earlier sections, this theory has a two-fold importance in the ion channel setting: it is used initially in modelling the behaviour of any single channel, and subsequently also in studying the behaviour of the superposition
process resulting from a many-channel system. The theory of aggregated Markov processes was developed especially by Colquhoun & Hawkes (1982, 1987) and Fredkin et al. (1985) in the ion channel literature, and others like Fredkin & Rice (1986), Ball & Sansom (1987, 1988) and Ball et al. (1997) in the probability literature. Our approach here is based on the latter paper, to which reference should be made for further details. Section 3.8 of Guttorp (1995) gives a brief introduction to the basic theory. In what follows, vectors and matrices appear in bold, all vectors are column vectors and $^T$ denotes transpose, this being often used to express row vectors. Moreover, 1 denotes a column vector of ones, $I$ an identity matrix, and $0$ a matrix (vector) of zeros, with dimensions determined by the context.

3.1 Basic theory

Consider a (homogeneous) continuous-time Markov chain $\{Y(t)\} = \{Y(t); \ t \geq 0\}$ with state space $\{1, 2, \ldots, r\}$ and $r \times r$ transition rate matrix $Q = [q_{ij}]$. For $i \neq j$, $q_{ij}$ is the transition rate from state $i$ to state $j$; the diagonal elements satisfy $q_{ii} = -\sum_{i \neq j} q_{ij}$. It is supposed that the chain is irreducible, in the sense that it is possible to move between any pair of states by means of a finite number of transitions. Without such an assumption it would be possible for a chain to stay forever in some subset of states, in which case, if interest centres on the long run behaviour of the process, attention could without loss of generality be focused just on that subset. In some ion channel experiments, such as post-perturbation studies of channel kinetics in the presence of desensitized states, interest centres on the transient behaviour of the channel process, for example Colquhoun et al. (1997) and Merlushkin & Hawkes (1997). Properties of multiple channels incorporating this phenomenon can, at least in principle, be determined using extensions of the methods of this paper.

Transitions between states in the underlying continuous-time chain are determined by an associated discrete-time Markov chain, the jump chain, having transition matrix $P$ with diagonal entries all zero and off-diagonal entries $p_{ij} = (-q_{ii})^{-1}q_{ij}, \ i \neq j$. Thus, for example, the probability that, for fixed $i$ and $j$ with $i \neq j$, the underlying chain jumps from $i$ to $j$ and then back to $i$ again is given by

$(-q_{ii})^{-1}q_{ij}(-q_{jj})^{-1}q_{ji}. \quad (2)$

The process $\{Y(t)\}$, because it has finitely many states and is irreducible, possesses an equilibrium distribution $\pi = [\pi_1, \pi_2, \ldots, \pi_r]^T$ which can be obtained by solving the equations $\pi^T Q = 0$, often called the global balance equations, together with $\sum_{i=1}^r \pi_i = 1$. When started at time $t = 0$ with $\pi$ as its initial distribution, $\{Y(t)\}$ is a stationary process and, in particular, for each $t > 0$ the distribution of $Y(t)$ is again $\pi$. The equilibrium distribution is also the limiting distribution in the sense that its components satisfy $\pi_i = \lim_{t \to \infty} P(Y(t) = i)$.

A continuous-time Markov chain $\{Y(t)\}$ is reversible essentially if its probabilistic properties remain the same when time is reversed. Such a reversible Markov chain is stationary. A stationary Markov chain is reversible if and only if the detailed balance equations $\pi_i q_{ij} = \pi_j q_{ji}, \ i, j \in \{1, 2, \ldots, r\}$, are satisfied for some positive numbers $\pi_i$ summing to one. (This result and other aspects of reversibility are discussed in Section 1.2
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of Kelly (1979).) Its equilibrium distribution is often more conveniently obtained by solving the detailed balance equations supplemented by the equation \( \sum_{i=1}^{n} \pi_i = 1 \), rather than by using the global balance equations. Kolmogorov's criterion allows reversibility to be checked by consideration of the transition rates alone: a process is reversible if and only if for any cycle (closed path) of states the product of the transition rates in one direction around the cycle is equal to the corresponding product in the other direction.

The state space is assumed to be aggregated by division into non-overlapping classes of states. Their significance is that it is possible to observe only which class the chain is in at any given time, and not the individual state. In modelling a single channel the aggregation is typically into two classes, the open states and the closed states; for modelling a many-channel system the classes indicate the total number of open channels, there being one more class than the number of channels in the system (because all channels may be closed); such processes are called aggregated Markov chains. In principle, for a multiple-channel system, either the full or the reduced state space could be used although, for reasons that will be explained later in Section 4.1.1, it will usually be preferable to work with the reduced state space.

In this subsection, the basic properties of such processes are summarized using just two classes, denoted here by A and B, where \( B = A' \) (the complement of A) contains all the states not in A. In principle any finite number of classes could be considered, and this generalization is needed later when dealing with superposition processes. Any partition of the state space induces a partition of the equilibrium distribution \( \pi \) into blocks; with two classes and, for example, \( \pi_A = [\pi_i : i \in A]^T \), the equilibrium distribution can be written, after appropriately reordering the states, as \( \pi^T = [\pi_A^T, \pi_A'^T] \). Furthermore, the transition rate matrix \( Q \) can be expressed, as a partitioned matrix

\[
Q = \begin{bmatrix}
Q_{AA} & Q_{AA'} \\
Q_{A'A} & Q_{A'A'}
\end{bmatrix},
\]

where, for example, the submatrix \( Q_{AA} \) governs transitions between states within A and \( Q_{AA'} \) transitions from states of A to states of \( A' \). Using such a partitioning of \( Q \) it is possible to obtain, in particular, (joint) density functions and moments of the class sojourn times. In order to discuss such results some other fundamental ideas and notation are needed.

For a specified class A consider the times at which the underlying process \( \{Y(t)\} \) commences a sojourn in class A. There is an associated discrete-time Markov chain which at each of the above times gives the state that the underlying continuous-time chain entered at that time. Fredkin et al. (1985) showed that the transition matrix of this discrete-time Markov chain is given by

\[
P_A = Q_A^{-1}Q_AQ_{A'A}^{-1}Q_{A'A}.
\]

(\This form can be motivated as the 'subset' analogue of (2).) Following Ball & Sansom (1988) and Ball et al. (1991), we call the Markov chain with transition matrix given by (4) the class A entry process, or just the A entry process. In another view, it governs the state transitions of the underlying continuous-time chain at the time instants when the latter enters class A. Although the invertibility of, for example, \( Q_{AA} \) is not obvious, it can be established in several ways, in particular by using the result that all the eigenvalues of
a diagonal submatrix such as \( Q_{AA} \) have (strictly) negative real parts. The class \( A' \) entry process can be described in a similar manner. Earlier work of Colquhoun & Hawkes (1982, 1987) showed that such entry processes and their transition matrices play a key role, especially in expressions for sojourn-time densities and correlation functions. In Colquhoun & Hawkes (1987) the matrix \( X_{AA} \) corresponds to our \( P_A \).

The \( A \) entry process is either periodic or aperiodic (cf. p. 2 of Kelly, 1979). Any (irreducible) reversible Markov chain is aperiodic. In the aperiodic case, the \( A \) entry process has an equilibrium distribution, denoted by \( \phi_A \), which can be calculated from \( \phi_A = \alpha_A / (\alpha_A I) \), that is by normalizing \( \alpha_A \) given by

\[
\alpha_A^T = \pi_A^T Q_{A'A},
\]

as in equation (3.63) of Colquhoun & Hawkes (1982). The vector \( \phi_A \) is to be interpreted as giving the equilibrium probabilities that a sojourn of the aggregated process in class \( A \) starts in the various states of that class.

### 3.2 Class sojourn time densities, moments and correlations

Throughout this section it is supposed that the aggregated process is in equilibrium. It is well known (see, for example, (3.64) of Colquhoun & Hawkes, 1982, or (3.11) of Fredkin et al., 1985) that the density function for a sojourn-time \( Z_A \) in class \( A \) can be expressed as

\[
f_{Z_A}(t) = \phi_A^T e^{Q_{AA}t} (-Q_{AA})^t \quad (t \geq 0).
\]

Here \( e^{Q_{AA}t} = \sum_{j=0}^{\infty} t^j Q_{AA}^j / j! \) is the usual matrix exponential; see, for example, p. 169 of Bellman (1970). Equation (6) can often be expressed as a linear combination of exponential densities, as in (1.32) of Colquhoun & Hawkes (1982). (This can be done whenever \( Q_{AA} \) has a complete set of linearly independent real eigenvectors, as is necessarily the case if either (i) the eigenvalues of \( Q_{AA} \) are all real and distinct, or (ii) \( \{Y(t)\} \) is time reversible. Moreover, in the reversible case the coefficients in the above linear combination of exponentials are all positive (see, e.g., Kijima & Kijima, 1987a), so the equilibrium distribution of a typical sojourn-time in class \( A \) is a mixture of negative exponential distributions.) A routine method for deriving (6) is to consider a related continuous-time Markov chain in which the states in \( A' \) are made absorbing states (by setting to zero all elements of \( Q_{AA} \) and \( Q_{A'A} \)) and to calculate the equilibrium time to absorption in this modified chain (see, for example, Colquhoun & Hawkes, 1981; Fredkin et al., 1985). It is immediately obvious from the above-mentioned method for deriving (6) that, like most of the sojourn-time distributions arising in this paper, the distribution given by (6) belongs to the class of phase-type distributions (see, for example, Neuts, 1981).

Equation (6) is a special case of the following result which gives the joint probability density function of the durations of consecutive sojourns of the aggregated process in a specified sequence of classes of some state-space partition. For the sequence \( A_1, A_2, \ldots, A_n \) (in which consecutive classes must be distinct) the required joint density is

\[
f(t_1, t_2, \ldots, t_n) = \phi_{A_1}^T e^{Q_{A_1A_1}t_1} Q_{A_1A_2} e^{Q_{A_2A_2}t_2} Q_{A_2A_3} \cdots Q_{A_{n-1}A_n} e^{Q_{A_nA_n}t_n} (-Q_{A_nA_n})^n_1.
\]
for \( t_1 \geq 0, t_2 \geq 0, \ldots, t_n \geq 0 \) (cf. Fredkin et al., 1985; Ball et al., 1997). This can be established by appropriate generalization of the 'absorbing' chain method indicated for the single class case; a related approach built from corresponding discrete-time results is presented in Chapter 4 of Csenki (1994). An appealing alternative derivation of (7) can be based on the semi-Markov framework of Ball et al. (1991); see Ball et al. (1997) for details. It may be helpful to note that the right-hand side of (7) viewed as a function of the model parameters (the various transition rates) is just the likelihood function based on observations \( t_1, t_2, \ldots, t_n \) of the class sojourn-times in the specified sequence of classes. In the case when the classes each consist of a single state, all vectors and matrices on the right-hand side of (7) reduce to real numbers and the density itself reduces to a better known expression (cf. (3.121) of Guttorp, 1995) giving the joint density function of sojourn-times in successive individual states visited.

Equation (7) is fundamental in that many other (joint) densities, probabilities and moments can be derived, for example by integrating the right-hand side of (7) over appropriate variables; for this reason it is taken as the starting point for all subsequent discussion in this paper. One virtue of this approach is that we are able to use direct calculations based on such densities rather than less intuitive Laplace transform methods. The key result required is

\[
\int_0^\infty t^k e^{Q_{\lambda}t} dt = (-1)^{k+1}k! Q_{\lambda}^{-k+1} \quad (k = 0, 1, 2, \ldots) \tag{8}
\]

for any submatrix \( Q_{\lambda} \) of \( Q \) corresponding to a proper subset \( \lambda \) of the state space.

To derive from (7) the joint probability density of \( Z_A \), the duration of a sojourn of the aggregated process in class \( A \), and \( Z_{A^l} \), the duration of the \( l \)th subsequent sojourn in that class, it is necessary to consider the alternating sequence \( A, A', \ldots, A', A \) consisting of \( l + 1 \) \( A \)'s and \( l \) \( A' \)'s, and use (8) to integrate out all but the two extreme exponential terms on the right-hand side of (7). This yields

\[
f_{Z_A Z_{A^l}}(t, u) = \phi_A^T e^{Q_{\lambda}t} Q_{\lambda} P_{\lambda} e^{Q_{\lambda}u} Q_{\lambda} 1 \quad (t, u \geq 0), \tag{9}
\]

where \( P_{\lambda} \) accounts for the \( l \) returns to \( A \) after the initial sojourn as the required joint density.

From such (joint) density function expressions it is easy to calculate moments. For example, for the duration \( Z_A \) of a sojourn in class \( A \) we obtain from (6) and (8)

\[
E(Z_A^k) = (-1)^k k! \phi_A^T Q_{\lambda}^{-k} 1 \quad (k = 1, 2, \ldots) \tag{10}
\]

and hence

\[
\sigma_A^2 = \text{var}(Z_A) = \phi_A^T (-Q_{\lambda}^{-1})(2I - 1\phi_A^T)(-Q_{\lambda}^{-1}) 1. \tag{11}
\]

Colquhoun & Hawkes (1982, 1987) derived such expressions using Laplace transforms. Similarly, the covariance and hence the correlation between the duration of a sojourn in class \( A \) and that of the \( l \)th subsequent sojourn in that same class can be derived from (9): these correlations are given by

\[
\rho_{AA}(l) = \phi_A^T (-Q_{\lambda}^{-1})(P_{\lambda}' - 1\phi_A^T)(-Q_{\lambda}^{-1}) 1/\sigma_A^2 \quad (l = 1, 2, \ldots). \tag{12}
\]
In the ion channel setting autocorrelation function expressions were first derived by Fredkin et al. (1985), and later by Colquhoun & Hawkes (1987) who also gave cross-correlation expressions in the case of two classes. The structure of such autocorrelation and cross-correlation functions has been considered, under the assumption of reversibility, by several authors; for a summary, and discussion of the practical importance of these ideas, see Ball et al. (1993b).

3.3 Intensities

For an aggregated Markov chain in equilibrium, Ball & Milne (2000) have developed a simple unified approach to the mean sojourn time in a specified class \( A \), and even to the sojourn-time distribution itself. The approach results from viewing the times of entry into class \( A \) as a stationary point process (cf. Cox & Miller, 1965, Chapter 9) and using the theory of such processes to show that \( \mu_A \), the equilibrium mean sojourn time in class \( A \), can be expressed as

\[
\mu_A = \pi_A / \lambda_{A'A}.
\]  

(13)

Here, \( \pi_A \) is the equilibrium probability that the underlying process \( \{ Y(t) \} \) is in class \( A \), and \( \lambda_{A'A} \) is the intensity of the point process of starting times of \( A \) sojourns, i.e. the mean number of such starting times in a time interval of unit length. Note that \( \lambda_{A'A} = \lambda_A' \), since the starting time of a sojourn of one type is always the time of completion of a sojourn of the other type. Essentially, (13) results from the intuitively plausible relationships \( \pi_A = \mu_A / (\mu_A + \mu_A') \) and \( 1/\lambda_{A'A} = \mu_A + \mu_A' \), where the latter quantity is just the mean time between starts of successive \( A \) sojourns. The virtue of (13) is that, once the equilibrium distribution \( \pi \) is known, both \( \pi_A \) and \( \lambda_{A'A} \) are relatively easy to determine; in particular,

\[
\pi_A = \pi_A^T 1 \quad \text{and} \quad \lambda_{A'A} = \pi_A^T Q_{A'A} 1.
\]  

(14)

Furthermore, in view of these expressions, to obtain \( \mu_A \) from (13) it is clearly enough to determine \( \pi \) up to a scalar multiple.

There is an alternative (but related) approach to (13). Define, for example, \( U_A \) to be the remaining lifetime in class \( A \), i.e. the time from the present time until the chain leaves class \( A \), given that this is within a sojourn in \( A \). Then, as is shown in Ball & Milne (2000) (see also Fredkin & Rice, 1991), \( 1/\mu_A = -dP(U_A > t)/dt \big|_{t=0} \). (The same result holds if \( U_A \) is the elapsed lifetime in class \( A \).) Related methods lead to an expression for the density function of a sojourn time \( Z_A \) in, for example, class \( A \):

\[
f_{Z_A}(t) = \mu_A \frac{d^2}{dt^2} P(U_A > t) \quad (t \geq 0).
\]  

(15)

The importance of these results is that an expression for \( P(U_A > t) \) is often easy to write down; then \( \mu_A \), and even \( f_{Z_A}(t) \), can be determined as above.

The general intensity relationship (13) can be applied, as with all the aggregated Markov chain theory, both to a single-channel process and to a multichannel system. In the former case, with \( A \) taken successively as the class of open states and closed states, (13) yields

\[
\mu_O = \pi_O / \lambda_O \quad \text{and} \quad \mu_C = \pi_C / \lambda_C.
\]  

(16)
where $\pi_0, \lambda C, \pi_C$ and $\lambda OC$ are given by appropriate specialization of (14). In the case of a multichannel system, class $A$, taken as $D_s$ for some $s$, indicates the number of open channels. This case will be explored further in the next section.

4. Models for multiple channels

This section outlines the basic structure of each of the four types of multiple-channel model introduced earlier in a general way. In each case, we consider a system of $N$ identically distributed channels, where these channels are individually described by processes $\{Y_1(t)\}, \{Y_2(t)\}, \ldots, \{Y_N(t)\}$ each on $r$ states. These processes are assumed to be identically distributed, although, in principle, this assumption can be relaxed; however, it is important that they need not be assumed independent. Letting $Y(t) = (Y_1(t), Y_2(t), \ldots, Y_N(t))^T$ for each $t$, the system of $N$ channels can then be described by the vector-valued process $\{Y(t); t \geq 0\}$ on the state space $\{1, 2, \ldots, r\}^N$, consisting of all vectors $i = (i_1, i_2, \ldots, i_N)$ where $i_1, i_2, \ldots, i_N$ are respectively the states of the $N$ single channels at a given time and $\{1, 2, \ldots, r\}$ is the state space for a single channel. The full system state space thus has $r^N$ points (states), each an $N$-vector with elements from $\{1, 2, \ldots, r\}$. We call $\{Y(t)\}$ the full system process.

4.1 Independent and identically distributed channels

4.1.1 Definition and illustrative example. Suppose here that the $N$ channels are mutually independent, in addition to being identically distributed, with each being described by an aggregated Markov chain on the state space $\{1, 2, \ldots, r\}$. Then the full system is itself a (vector-valued continuous-time) Markov chain on the state space $\{1, 2, \ldots, r\}^N$, having an $r^N \times r^N$ transition rate matrix $Q$ which can be written down in terms of the transition rates from $Q$, the transition rate matrix for an individual channel. Since the individual chains are independent and identically distributed, the transition rate matrix for the full system chain has a rather simple mathematical structure, being expressible as an $N$-fold Kronecker sum (Fredkin & Rice, 1992a). Albertsen & Hansen (1994) give some explanation for the appearance of such sums in this context. The Kronecker sum representation is also helpful for organizing numerical calculations using a package such as Matlab. However, in later examples we shall work directly from first principles.

The earlier motivational discussion of independent and identically distributed channels, introduced the idea of a reduced state space. The system process considered on the reduced state space is again Markov; we call it the reduced (Markov) chain, and denote it by $\{X(t)\}$. In passing from the full system chain to the reduced chain we are keeping information only on the number of channels in each of the possible channel states and dropping the information on which channel is in which state. This allows the possibility of considerable computational efficiency, through reduction in the size of the transition rate matrix, while still providing adequate information for addressing many questions of interest. Due to independence, the complete or reduced chain is reversible if the single-channel processes are each reversible.

We have earlier introduced the superposition process $\{M(t)\}$ which counts the number of channels open at any time. For $s = 0, 1, \ldots, N$ let $D_s$ denote the set of all states in the
reduced state space yielding level $s$ in the superposition process. Then $\{\mathcal{D}_0, \mathcal{D}_1, \ldots, \mathcal{D}_N\}$ is a partition of the reduced state space. By appropriately ordering the states in the reduced state space, the transition rate matrix $Q$ for the reduced chain can be expressed in corresponding partitioned form as a block tridiagonal matrix. For example, in the case $N = 4$ the matrix $Q$ can be expressed

$$Q = \begin{bmatrix}
Q_{00} & Q_{01} & 0 & 0 \\
Q_{10} & Q_{11} & Q_{12} & 0 \\
0 & Q_{21} & Q_{22} & Q_{23} \\
0 & 0 & Q_{32} & Q_{33} & Q_{34} \\
0 & 0 & 0 & Q_{43} & Q_{44}
\end{bmatrix},$$

(17)

where within any sub-matrix $Q_{SS}$ elements are indexed by the states in $\mathcal{D}_s$. The tridiagonal structure arises because the level of the superposition process can increase or decrease by at most one at any time. Partitionings may be made in various other ways, for example as $\{\mathcal{D}_s, \mathcal{D}'_s\}$. Such partitionings are useful because they allow expressions for moments, correlations and (joint) density functions of sojourn times at any particular level $s$ in the superposition process to be derived from the general theory of aggregated Markov processes using (6), (7) and (10)–(12), where $A$ is replaced by $s$ (notation used, as above, instead of $\mathcal{D}_s$ in the subscripts).

At the disadvantage of involving a larger matrix, it would be possible to work with a corresponding partition of the transition rate matrix, say $Q^c$, for the full system chain. In particular, for fixed $r$ the size of the full state space increases exponentially with $N$, whilst that of the reduced state space increases only polynomially.

**Example** Two three-state channels.

Here the full system chain has $9 (= 3^2)$ states and the reduced chain 6 states, which we order as $(1, 1), (1, 2), (2, 2), (1, 3), (2, 3), (3, 3)$. The classes $\mathcal{D}_0 = \{(1, 1), (1, 2), (2, 2)\}$, $\mathcal{D}_1 = \{(1, 3), (2, 3)\}$, and $\mathcal{D}_2 = \{(3, 3)\}$ then correspond to the three levels 0, 1 and 2 of the superposition process. The transition rate matrix $Q$ for the reduced chain is

$$\begin{array}{cccccc}
-d_1 & 2q_{12} & 0 & 0 & 0 & 0 \\
q_{21} & -d_2 & q_{12} & q_{23} & 0 & 0 \\
0 & 2q_{21} & -d_3 & 0 & 2q_{23} & 0 \\
0 & q_{32} & 0 & -d_4 & q_{12} & 0 \\
0 & 0 & q_{32} & q_{21} & -d_5 & q_{23} \\
0 & 0 & 0 & 0 & 2q_{32} & -d_6
\end{array}$$

the (diagonal) terms $d_1, d_2, \ldots, d_6$ being positive, and defined so that all row sums of $Q$ are zero. When both channels are in the same (for example, open) state, either channel...
could change state, and hence the transition (closing) rate for the system is twice that for a single channel. Such channel systems have been considered, for example, by Colquhoun & Hawkes (1977, 1990) and Yeo et al. (1989). The full system chain is reversible because the single-channel processes are independent and each reversible (as they have no cycles).

4.1.2 Equilibrium properties. The equilibrium distribution for the reduced Markov chain \( \{X(t)\} \) is denoted by \( \pi = [\pi_i] \), where \( \pi_i \) is the equilibrium probability that the system is in state \( i = (i_1, i_2, \ldots, i_N) \). Then the equilibrium probabilities for the superposition process \( \{M(t)\} \) are

\[
\pi_s^{(M)} = \sum_{i \in \mathcal{D}_s} \pi_i \quad (s = 0, 1, \ldots, N).
\]

Both \( \pi \) and \( \pi_s^{(M)} = [\pi_s] \) can be expressed, if required, in terms of the equilibrium distribution, \( \pi^\circ \) say, for the full system chain. Note that because the \( N \) channels are independent we have, in obvious notation, that \( \pi_i^{(c)} = \prod_{k=1}^N \pi_{i_k} \), where, as above, \( \pi = [\pi_1, \pi_2, \ldots, \pi_r]^T \) denotes the equilibrium distribution of a single channel.

As shown in Ball & Milne (2000), the intensity approach outlined earlier can be used to give a simple direct derivation of the mean sojourn time, \( \mu_s \), at level \( s \) of the superposition process. Because the individual channel processes are independent and identically distributed, each with equilibrium probabilities \( \pi_0 \) and \( \pi_c \) of being respectively in the classes of \( \mathcal{O} \) and \( \mathcal{C} \) of open states and closed states, the equilibrium probability of the superposition being at level \( s \) has the well-known binomial form

\[
\pi_s^{(M)} = \binom{N}{s} \pi_0^s \pi_c^{N-s} \quad (s = 0, 1, \ldots, N).
\]

In the notation introduced earlier in this paper for aggregated Markov processes, \( \lambda_{\mathcal{O}} \) is the intensity of the point process of starting times of \( \mathcal{O} \) sojourns, that is the mean number of such starting times in a time interval of unit length, with \( \lambda_{\mathcal{C}} \) defined similarly (and, in fact, \( \lambda_{\mathcal{O}} = \lambda_{\mathcal{C}} \) since the starting time of a sojourn of one type is always the time of completion of a sojourn of the other type). Write \( \lambda_s \), rather than \( \lambda_{\mathcal{O}} \) and \( \lambda_{\mathcal{C}} \), for the intensity of the point process of starting times of level \( s \) sojourns. This can be calculated as

\[
\lambda_s = \binom{N}{s-1} \pi_0^{s-1} \pi_c^{N-s} (N - s + 1) \lambda_{\mathcal{O}} + \binom{N}{s+1} \pi_0^s \pi_c^{N-s-1} (s + 1) \lambda_{\mathcal{C}}.
\]
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intensity relationship $\mu_s = \pi_s^{(M)} / \lambda_s$ for the superposition process becomes

$$\mu_s = \left( \frac{s}{\mu_O} + \frac{N - s}{\mu_C} \right)^{-1} \quad (s = 0, 1, \ldots, N). \quad (21)$$

This result is not so easily obtained using (10). It was proved by other means, and the intensity interpretation conjectured, in Yeo et al. (1989); see their equation (19). An alternative approach was given in Fredkin & Rice (1991). Intensity arguments can be used also to derive extensions of (21) for systems of interacting channels; see, for example, §3 of Ball & Yeo (2000).

Formulae obtained by intensity arguments often, in our experience, yield expressions for the mean level sojourn times simpler to compute than ones obtainable from (10). The same comments apply to derivations of density function expressions obtained from (15). Either (15) or (6) can be applied to the system process (with either the full or reduced state space) to obtain an expression for the density function of a sojourn at level $s$ of the superposition process (cf. (4.1) of Ball et al., 1997). Such an expression can also be obtained from (13b) of Yeo et al. (1989).

4.2 Interacting channels

4.2.1 Definition and illustrative example. Consider an interacting system where some of the transition rates for a given channel at a specified time may depend on the states of the other channels at that time. As a result, the full system chain has a transition rate matrix in which selected non-zero entries are changed, but kept non-zero, thereby preserving irreducibility of that chain; similar comments apply to the transition rate matrix for the reduced chain. There are no simple general results for the reversibility of such interacting channel models; nevertheless Kolmogorov’s criterion can be used to give conditions for particular examples, and Theorem 5.1 of Ball & Yeo (2000) is one result in this direction.

Some numerical examples for a superposition of two-, three- and five-state channels are given in Section 7 of Ball et al. (1997). In these examples it is assumed that only the upward transition rates for the superposition depend on the number of channels open. Various properties concerning moments, correlations and sojourn time density functions were computed using the above results and the Matlab package. Here a similar situation is used to illustrate the numerical methods.

As a simple example we consider three channels, each with three states (labelled 1, 2 and 3) and two classes $O = \{3\}$ (open) and $C = \{1, 2\}$ (closed), as in (1), and having possible transition rates between the states of a single channel as indicated in:

$$\begin{array}{ccc}
1 & q_{12} & 2 \\
q_{21} & q_{23} & 3 \\
q_{21} & q_{23} & q_{32}
\end{array} \quad (22)$$

These transition rates $q_{ij}$ apply when the other channels are closed (class $C$). Note that in representing the states of the Markov chain we are using 1, 2 and 3 as opposed to $C_1$, $C_2$ and $O_3$ as used earlier in, for example, (1). Some of the transition rates may change depending on the number of other channels in the open state (class $O$). Suppose that other channels being open results in a particular channel having a faster opening rate and possibly a slower closing rate. In particular, let the transition rates $q_{12}$, $q_{21}$, $q_{23}$ and $q_{32}$ depend on
whether one ($\tilde{q}_{12}$, $\tilde{q}_{21}$, $\tilde{q}_{23}$, $\tilde{q}_{32}$), or two ($\tilde{q}_{12}$, $\tilde{q}_{21}$, $\tilde{q}_{23}$, $\tilde{q}_{32}$) of the other two channels are open. By applying Kolmogorov's criterion to the cycles $112$, $113$, $123$, $122$, $112$ and $123$, $133$, $233$, $223$, $123$, the multichannel system is reversible only if $q_{12}/q_{21} = \tilde{q}_{12}/\tilde{q}_{21}$. Here, for example, $112$ (short for $(1, 1, 2)$ used previously) indicates two channels are in state 1 and one in state 2; in the reduced chain the order of symbols has no relevance. In fact, this condition is also sufficient for the multichannel system to be reversible, cf. Ball et al. (1997), Theorem 6.1 and Section 7.2. Thus the assumption of reversibility does not impose any restrictions on the form of the dependence of the opening and closing rates ($q_{23}$ and $q_{32}$) on the number of the other channels that are open, although this does not remain true when there are multiple gateways between the open and closed classes of states in a single channel.

The full system chain has 27 ($=3^3$) states. The reduced chain has ten ($=\binom{3}{2}$) states, with classes of four, three, two and one of its states corresponding to the respective levels (number of open channels) 0, 1, 2 and 3 of the superposition process; these classes are {111, 112, 122, 222}, {113, 133, 233}, and {333}. From (6), a level 3 sojourn has a negative exponential distribution with mean $1/(3\tilde{q}_{32})$, while sojourns at levels 2, 1 and 0 have respectively distributions which are linear combinations of 2, 3 and 4 exponentials (provided the eigenvalues of $Q_{22}$, $Q_{11}$ and $Q_{00}$ respectively are real and distinct).

4.2.2 Equilibrium properties. Equilibrium probabilities for the superposition process $\{M(t)\}$ in this setting can be obtained using (18), where the equilibrium distribution, $\pi = [\pi_1]$, of the reduced process can be obtained from the corresponding transition rate matrix in the usual fashion. For reversible processes, simpler results are available (see Ball et al. (1997) and Ball & Yeo (2000)).

Joint distributions, moments and correlations may be found using (6)-(9) and extensions in Ball et al. (1997). For example, the joint density function of the durations of a sojourn at level 3 and the immediately following sojourn at level 2 is

$$f(t, u) = e^{-3\tilde{q}_{32}u}[0, 3\tilde{q}_{32}]e^{Q_{32}w}(-Q_{22})1 \quad (t, u \geq 0),$$

where now $Q_{22}$ is a $2 \times 2$ matrix with diagonal elements $-(2\tilde{q}_{32} + \tilde{q}_{12})$ and $-(\tilde{q}_{21} + 2\tilde{q}_{32} + \tilde{q}_{23})$ and off-diagonal elements $\tilde{q}_{12}$ and $\tilde{q}_{21}$. Thus the durations of these sojourns are independent. However, successive sojourns at other levels are not generally independent; this is because there is more than one gateway between the states at the different levels.

Moments, correlations and density functions of sojourn times at any particular level $s$ in the superposition process can be derived, as indicated above, using (6), (7) and (10)-(12). In particular, the mean length $\mu_s$ of a sojourn at level $s$ is given by (10) (with $k = 1$); to compute $\mu_s$ in this way requires determination of both $\phi_s$ and the inverse of $Q_{ss}$. Intensity arguments can also be used to obtain $\mu_s$ as

$$\mu_s = (\pi \Delta_r)^T 1/((\pi \Delta_r)^T Q_{sr}1) \quad (s = 0, 1, \ldots, n).$$

In general, this calculation will be simpler because it requires the elements of $\pi$ only up to a multiplicative constant, and also no matrix inverse is involved. Expressions for the other properties mentioned above, in particular density functions of sojourn times at a given level, are usually also easier to obtain by intensity arguments.
4.3 Spatial dependence

4.3.1 Introduction. Suppose there is an \( N (\geq 4) \)-channel system \( \{Y(t)\} = \{Y_1(t), \ldots, Y_N(t)\} \) on a ring, such that channels \( N \) and 1 are neighbours and each channel has two classes of states, closed and open. Every channel has exactly two nearest neighbours, and the number of open channels corresponds (proportionally) to the conductivity. The examples of this section are a first step towards studying models based on more complex spatial patterns, for example channels on a grid or a central channel surrounded by a ring of \( N - 1 \) other such channels, in which case the central channel has \( N - 1 \) nearest neighbours and the surrounding channels each have three nearest neighbours. Such models are also relevant in modelling the behaviour of a single channel as a system of interacting subunits, themselves arranged in some spatial pattern; see, for example, the sequential allosteric model of Ball et al. (1993a) and the 'rosette' model of Nayeem et al. (1994).

For purposes of illustration, attention is restricted to channels with one closed state and one open state, denoted respectively by 1 and 2. For extension to the more general case see Ball & Yeo (2000). Suppose that the transition rates \( q_{ij}^{(k)}(i, j = 1, 2; k = 0, 1, 2) \) for any channel may depend on the number \( k \) of nearest neighbours that are open. As in the other examples, it is possible to use symmetries to obtain a reduced (system) state space with substantially fewer states than the \( 2^N \) possible states in the full state space; these are all that is required for evaluating properties of the superposition process, such as equilibrium and level sojourn-time distributions. For the case of \( N = 5 \) the full state space has \( 2^5 = 32 \) states; taking account of symmetries of the ring structure these can be reduced to the eight cases: 11111; 21111, 22111, 22121, 22211, 22221, 22222. Some of these may occur in several ways: in this example, the above states arise respectively in 1;5,5,5,5,5,1 ways, giving 32 in all. For \( N = 7 \) the full state space has \( 2^7 = 128 \) states; these can be reduced to 18: 1111111; 2111111, 2112111, 2121111, 2211111, 2211211, 2212111, 2221111, 2222111, 2222121, 2222211, 2222221; 2222221; 2222222. There are respectively 1;7,7,7,7,14,7,7,7,7,7,7,7,7,7,7,7,7 combinations of these. (In this case these may be evaluated using (26) below, since for \( N \leq 7 \), the states in the reduced state space are characterized by \( N, s, r, b \). This is not the case for \( N \geq 8 \).)

If only the equilibrium distribution of the number of open channels in a reversible system is required, all that is needed for computational purposes is the number of open channels and the number of open neighbour pairs (see (30) below). When \( N = 7 \) there is an effective reduction to 14 configurations of states, as, for example, states denoted 2212111 and 2211211 become equivalent, each having three open channels and one nearest neighbour pair of open channels. In general the reduction is to \( 2 + \lceil N/2 \rceil \lceil (N + 1)/2 \rceil = 2 + (N^2 - \delta)/4 \) configurations, where \( \lfloor x \rfloor \) is the largest integer not greater than \( x \), with \( \delta = 0 \) for even \( N \) and \( \delta = 1 \) for odd \( N \). This is a very large reduction, for example, from 64 to 11 for \( N = 6 \), and from 1028 to 27 for \( N = 10 \).

Some combinatorial results are required for counting the number of states of these various types in the full state space. For \( N \) channels, the number \( M(N, s, r) \) of states with \( s \) open channels and \( r \) pairs of open neighbours is given by Ball & Yeo (2000), together with a proof: \( M(N, s, r) = 1 \) for \( s = r = 0 \) or \( s = r = N \) and, using the convention
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\[
(0) = (-1) = 1,
\]

\[
M(N, s, r) = \frac{N}{s} \binom{s}{r} \binom{N-s-1}{s-r-1}; \quad 1 \leq s \leq N-1, \quad \max(0, 2s-N) \leq r \leq s-1.
\]

(25)

As the transition rate for a channel depends on both its neighbours, the number of cases of the configuration 212 (that is open, closed, open) is also required. For \( N \) channels, let \( M(N, s, r, b) \) be the number of states with \( s \) open, \( r \) pairs of open neighbours and \( b \) closed channels with two open neighbours. Then from (37) of Ball & Yeo (2000) \( M(N, 0, 0, 0) = 1 \) and

\[
M(N, s, r, b) = \frac{N}{s} \binom{s}{r} \binom{N-2s+r-1}{s-r-b-1}; \quad 1 \leq s \leq N, \quad (r, b) \in A(N, s).
\]

(26)

where \( A(N, s) = \{(r, b) : M(N, s, r, b) > 0\} \) is the set of feasible pairs \((r, b)\). Note that \( \sum_r M(N, s, r, b) = M(N, s, r) \) and \( \sum_r M(N, s, r) = \binom{N}{s} \), the number of combinations of states in the full state space with \( s \) channels open.

The transition rate matrix \( Q \) is the basic tool for evaluation of distributional properties of a continuous-time Markov chain. In spatial channel models it is possible, in principle, to write down \( Q \) for the full state space; however using this would be computationally unwieldy for a large number of channels. This problem could be alleviated by working with a reduced state space, but the difficulty is to find a suitable reduction. (We conjecture that a reduced state space can be obtained by attaching to each state in the full state space a vector \((v_0, v_1, \ldots, v_{[N/2]})\), where \( v_0 \) is the number of open channels and, for \( k = 1, 2, \ldots, [N/2] \), \( v_k \) is the number of pairs of open channels that are a distance \( k \) apart, and then treating states with the same vector as a single state in the reduced state space.) One simple case is given below. Nevertheless, many useful properties may be obtained more simply and without detailed knowledge of \( Q \), as will be illustrated. Although some of the results and formulae below may look quite forbidding, they are easy to compute very rapidly for any reasonable number of channels.

To obtain the \( Q \) matrix for (the reduced state space of) the channel system requires finding the possible states with \( s \) increased (decreased) \((s = 0, 1, \ldots, N)\) by one when an opening (closure) occurs. It is useful to draw the network of feasible transitions among the various possible states of the reduced state space. This is shown in Fig. 2 for \( N = 5 \). The eight possible types of state are, the possible transitions and the number of possible transitions of each type (in the full state space) is shown in Fig. 2(a). The states in this case may be described by \((s, r, b)\), and ordered as \((0, 0, 0), (1, 0, 0), (2, 1, 0), (2, 0, 1), (3, 2, 0), (3, 1, 2), (4, 3, 1), (5, 5, 0)\); this is shown in Fig. 2(b) with corresponding transition rates per state in the complete process. The transition rate matrix \( Q \) is then obtained, using this ordering, by combining these results.
For a five-channel two-state spatially dependent system (a) shows the possible states and transitions for the reduced system, together with the number of possible transitions, and (b) the possible states labelled by \((s, r, b)\), the number \(s\) of open channels, the number \(r\) of pairs of open channels, and the number \(b\) of closed channels with two open neighbours, together with the transition rate \(q_i^{(j)}\) per state for a state with \(i\) open neighbours.

\[
Q = \begin{bmatrix}
-d_1 & 5q_{12}^{(0)} & 0 & 0 & 0 & 0 & 0 & 0 \\
q_{21}^{(0)} & -d_2 & 2q_{12}^{(1)} & 2q_{12}^{(0)} & 0 & 0 & 0 & 0 \\
0 & 2q_{21}^{(1)} & -d_3 & 0 & 2q_{12}^{(1)} & q_{12}^{(0)} & 0 & 0 \\
0 & 2q_{21}^{(0)} & 0 & -d_4 & q_{12}^{(2)} & 2q_{12}^{(1)} & 0 & 0 \\
0 & 0 & 2q_{21}^{(1)} & q_{21}^{(2)} & -d_5 & 0 & 2q_{12}^{(1)} & 0 \\
0 & 0 & q_{21}^{(0)} & 2q_{21}^{(1)} & 0 & -d_6 & 2q_{12}^{(2)} & 0 \\
0 & 0 & 0 & 0 & 2q_{21}^{(1)} & 2q_{21}^{(2)} & -d_7 & q_{12}^{(2)} \\
0 & 0 & 0 & 0 & 0 & 0 & 5q_{21}^{(2)} & -d_8 \\
\end{bmatrix}
\]  

where \(d_i\) is the sum of all other elements in the \(i\)th row of the matrix. The sum of the coefficients of the non-diagonal elements in each row of \(Q\) equals 5, as there are five channels that can change state, as seen in Fig. 2.
4.3.2 **Reversibility.** As mentioned earlier, reversibility is a desirable property for a multiple-channel model to possess. General results for reversibility of spatial processes are discussed in Kelly (1979), Chapter 9. For the nearest neighbour channel system a simple necessary and sufficient condition for reversibility is that

\[
\left( q_{12}^{(1)} \right)^2 / \left( q_{12}^{(0)} q_{21}^{(0)} \right) = \left( q_{21}^{(1)} \right)^2 / \left( q_{21}^{(0)} q_{21}^{(2)} \right). \tag{28}
\]

That this is necessary can readily be obtained by applying Kolmogorov’s criterion (see Section 3.1) to any cycle of possible states. For example for \( N = 5 \), the cycle 21111, 22111, 22211, 22221, 22121, 21121, 21111 has products \( q_{12}^{(1)} q_{12}^{(1)} q_{21}^{(1)} q_{21}^{(0)} q_{21}^{(2)} \) and \( q_{12}^{(0)} q_{12}^{(2)} q_{21}^{(1)} q_{21}^{(1)} \), the equality of which yields (28).

To show that (28) is sufficient for reversibility, first note that it implies that

\[
q_{12}^{(k)} = \alpha \beta^k q_{21}^{(k)}, \quad (k = 0, 1, 2), \tag{29}
\]

where \( \alpha = q_{12}^{(0)}/q_{21}^{(0)} \) and \( \beta = \left( q_{12}^{(1)}/q_{21}^{(1)} \right)/\left( q_{12}^{(0)}/q_{21}^{(0)} \right) \). For \( i = (i_1, i_2, \ldots, i_N) \) with \( i_j = 1 \text{ or } 2 \) \( (j = 1, 2, \ldots, N) \), let \( \pi_i \) denote the equilibrium probability that the (full) spatial channel system is in state \( i \). Suppose, cf. Kelly (1979) p. 188, that \( \pi_i \) takes the form

\[
\pi_i = B \alpha^s \beta^r \tag{30}
\]

where, for state \( i, s \) is the number of open channels, \( r \) is the number of pairs of open neighbours, and \( B \) is a normalizing constant. We now show that, with \( \pi_i \) given by (30), the detailed balance equations \( \pi_i q_{ij} = \pi_j q_{ji} \) for all \( i \) and \( j \), are satisfied. Let \( i \) and \( j \) be any two states of the system satisfying \( q_{ij} > 0 \). Then \( i \) and \( j \) differ in only one channel, which, without loss of generality, can be assumed to be closed in state \( i \) and open in state \( j \). For that channel, let \( k \) be the number of its neighbours which are open. Then changing from \( i \) to \( j \) increases \( s \) by 1 and \( r \) by \( k \), and so

\[
\pi_i q_{ij} = B \alpha^s \beta^r q_{12}^{(k)} = B \alpha^{s+1} \beta^{r+k} \left( q_{12}^{(k)}/\alpha \beta^k \right) = \pi_j q_{21}^{(k)} = \pi_j q_{ji}. \tag{31}
\]

Thus the detailed balance equations are satisfied and hence the system is reversible, with equilibrium distribution given by (30). This completes the proof that (28) is also sufficient for reversibility.

If the spatial dependence influences only the opening rates, so \( q_{12}^{(k)} = q_{21}^{(k)} \) for all \( k \), then the right hand side of (28) is unity and necessarily \( q_{12}^{(k)} = \alpha \beta^k, \quad k = 0, 1, 2, \)

4.3.3 **Equilibrium distribution.** For a reversible system, the equilibrium probability for a particular given state \( i = (i_1, \ldots, i_N) \) in the full state space has to be of the form (30). Furthermore, the reversibility condition (28) then yields \( \alpha = q_{12}^{(0)}/q_{21}^{(0)} = \alpha_0/\alpha_1 \) and \( \beta = \beta_0/\beta_1 \), say, where \( q_{12}^{(1)} = \alpha_0 \beta_0, q_{21}^{(1)} = \alpha_1 \beta_1 \). Summing over all possible states in the full state space for a given \( s \) then yields the probability \( \pi(N, s) \) that the channel system in equilibrium has \( s \) open channels as \( \pi(N, 0) = B, \pi(N, N) = B(\alpha \beta)^N, \) and for \( 1 \leq s \leq N - 1 \),

\[
\pi(N, s) = B \alpha^s \sum_r M(N, s, r) \beta^r, \tag{32}
\]
where \( B = \frac{1}{\sum_{s,r} M(N, s, r) \alpha^s \beta^r} \). Moments of this distribution can then be readily evaluated.

### 4.3.4 Equilibrium level sojourn-time distributions.

Let \( b_k(i) \) be the number of closed channels with precisely \( k \) open neighbours for a state \( i \) (in the full state space) with \( s \) open channels, \( r \) pairs of open neighbours and \( b \) closed channels with both neighbours open; thus \( b_2(i) = b \). Then there are \( 2(r - s) \) pairs of neighbouring channels in \( i \) in which one channel is open and the other closed, and in \( 2b \) of these the closed channel has both neighbouring channels open. Thus \( b_1(i) = 2(s - r - b), \) \( b_0(i) = N - s - b_1(i) - b_2(i) = N - 3s + 2r + b \), with \( \sum_k b_k(i) = N - s \). Of the \( N - s \) possible openings from level \( s \), given \((r, b)\), there are \( b_k(i) \) of these with transition rate \( q^{(k)}_{(r,b)} \) (for example, check these in the \( Q \) matrix in (27)).

The transition rates for a channel depend on its number of open neighbours, and so do the corresponding intensities. The intensity \( \lambda_{s,r} \) of the point process of completion times of level \( s \) sojourns can be determined using (15). It is convenient to separate the calculation into two parts by writing \( \lambda_{s,r+1} = \lambda_{s,r-1} + \lambda_{s,r+1} \), the sum of a closing and an opening intensity. By considering all states in a (full) system with \( N - s \) closed channels that have \( k \) open nearest neighbours, \( k = 0, 1, 2 \), the opening intensity is

\[
\lambda_{s,r+1} = \sum_{i: s(i) = s} \pi_i \sum_{k=0}^{2} b_k(i) q^{(k)}_{(r,b)}
\]

\[
= B \alpha^s \sum_{(r,b) \in A(N,s)} M(N, s, r, b) \beta^r v(N, s, r, b)
\]

where \( s(i) \) is the number of open channels under configuration \( i \), and

\[
v(N, s, r, b) = (N - 3s + 2r + b) q^{(0)}_{12} + 2(s - r - b) q^{(1)}_{12} + b q^{(2)}_{12}.
\]

When the closing rate is constant \( q_{21} \), the closing intensity is \( \lambda_{s,r-1} = s \pi(N, s) q_{21} \). The mean equilibrium sojourn time \( \mu_s \) at level \( s \) follows from (13) (see also Ball & Yeo, 2000) as \( \mu_0 = 1/(Nq^{(0)}_{12}) = 1/(N\alpha) \), \( \mu_N = 1/(Nq_{21}) \) and, with \( w(N, s, r, b) = sq_{21} + v(N, s, r, b) \), for \( s = 1, 2, \ldots, N - 1 \),

\[
\mu^{-1}_s = \frac{\sum_{(r,b) \in A(N,s)} M(N, s, r, b) \beta^r w(N, s, r, b)}{\sum_{s' = 1}^N M(N, s', r) \beta^{s'}}.
\]  

(33)

This can readily be modified if the closing rates also depend on the number of open neighbours as can the following paragraph.

For any given configuration \((N, s, r, b)\) of the \( N \) channels in the (full) system and for any given time point, the time until the next event (one channel opening or closing) has an exponential distribution. Summing over the possible configurations enables us to find the distribution of a sojourn time \( Z_s \) at level \( s \). Let \( \tilde{F}_{Z_s}(t) = P(Z_s > t), t \geq 0 \). Then (also from Ball & Yeo, 2000)

\[
\tilde{F}_{Z_0}(t) = \exp(-Nq^{(0)}_{12} t), \quad \tilde{F}_{Z_N}(t) = \exp(-Nq_{21} t), \quad \text{and for } s = 1, 2, \ldots, N - 1,
\]

\[
\tilde{F}_{Z_s}(t) = \frac{\sum_{(r,b) \in A(N,s)} M(N, s, r, b) \beta^r w(N, s, r, b)e^{-w(N,s,r,b)t}}{\sum_{(r,b) \in A(N,s)} M(N, s, r) \beta^r w(N, s, r, b)}.
\]  

(34)
The probability density function $f_{Z_s}(t)$ can be obtained from $\tilde{F}_{Z_s}(t)$ by differentiation. From (34) it can be seen that the density function of $Z_s$ is a mixture of exponentials. The means of $Z_s$, $s = 0, 1, \ldots, N$, cf. (33), can also be calculated directly from (34), as can higher moments.

For the case $N = 5$ considered in the next section with $q_{21}^{(k)} = \xi$, $q_{12}^{(k)} = \alpha \beta_k$, $k = 0, 1, 2$ the values of $M(s, r, b)$, (26), and the $Q$ matrix, (27), are given above. It follows that $B^{-1} = 1 + 5\alpha + 5\alpha^2(1 + \beta)(1 + \alpha\beta) + 5\alpha^4\beta^3 + (\alpha\beta)^5$ and, for example, $\mu_1^{-1} = \xi + 2\alpha(1 + \beta)$, $f_{Z_1}(t) = \frac{1}{\mu_1} e^{-t/\mu_1}$; $\mu_2^{-1} = 2\xi + 3\alpha\beta$,

$$f_{Z_2}(t) = \mu_2 [\beta w_2^2 e^{-\beta w_1 t} + w_2^2 e^{-\beta w_2 t}] / (1 + \beta),$$

(35)

where $w_1 = w(5, 2, 1, 0) = d_3 = 2\xi + \alpha(1 + 2\beta)$, $w_2 = w(5, 2, 0, 1) = d_4 = 2\xi + \alpha(2\beta + \beta^2)$. Other cases may readily be written down, as may joint density functions using (7) and the $Q$ matrix, (27). For example, the joint density of a sojourn at level 4 followed by a sojourn at level 3 is

$$f_{Z_3}(t, u) = 2d_4 \xi e^{-\beta t} (d_5 e^{-d_5 u} + d_6 e^{-d_6 u}), 0 < t, u < \infty$$

(36)

where $d_5 = 3\xi + 2\alpha\beta$, $d_6 = 3\xi + 2\alpha\beta^2$ and $d_7 = (4\xi + \alpha\beta^3)$ while that for levels 5 and 4 is a product of two exponentials with means $1/(5\xi)$ and $1/d_7$.

4.4 Random environment

4.4.1 Definition and illustrative example. A patch of ion channels may be influenced by an external varying environment affecting the transition rates between the states of a channel. Suppose there are $N$ channels, each described for a given state $e$ of the environment by a homogeneous continuous-time Markov chain $\{Y_e(t)\}$, whose transition rate matrix is $Q_e = [q_{ij}^{(e)}]$. Suppose that each channel process has $n_o$ open states and $n_c$ closed states. The environment $\{X_G(t)\}$ is also described by a homogeneous continuous-time Markov chain on $m_e$ states and transition rate matrix $Q^E = [q_{ij}^{E}]$. Necessary and sufficient conditions for reversibility of models of this type were considered by Ball et al. (1994). It was shown that severe restrictions on possible transition rate values were required to maintain reversibility of the full system process, specifically, the environment process $\{X_G(t)\}$ and the processes $\{Y_e^{(0)}(t)\}$, as $e$ varies over all states of the environment, must all be time reversible, and the latter processes must all have identical equilibrium distributions. One situation where this holds is where the transition rates of the single-channel processes are scaled by a common factor as the environment changes state, resulting in a speeding up or slowing down of the processes. We consider now what can happen without such severe reversibility conditions; this may be appropriate when the environment is driven by some external energy source causing changes in the level of stimulus. The transition rate matrix for the complete process $\{X_G(t), Y_1(t), Y_2(t), \ldots, Y_N(t)\}$ may be written down provided simultaneous events are not permitted, even though it becomes very large as the number of channels and/or the number of states per channel or environment increases.

The state space of the complete system may be subdivided into $N + 1$ levels $\{0, 1, \ldots, N\}$ corresponding to the number of open channels. The transition rate matrix $Q = [Q_{ij}], 0 < i, j < N$, corresponds to this subdivision. The problem is now in the same
form as for a superposition of interacting channels and similar properties may be obtained
in the same way. When the environment consists of a single state, the system is equivalent
to \( N \) independent channel processes and results simplify. Furthermore, deviations from
these give some indication of the effect of the environment or channel interaction.

As a simple example we consider a random environment on two states (labelled 1
and 2) and two channels, each with three states (1, 2 and 3) and two classes \( O = \{3\} \)
(open) and \( C = \{1, 2\} \) (closed) and basic transition graph (1), as introduced in the earlier
random environment section; it was noted there that there are 12 states for the complete
process based on the reduced state space. The transition rates are \( q_{ij}, \ (i, j = 1, 2) \)
when the environment is in state 1 (low). When the environment is in state 2 (high) the transition
rates towards opening may change, i.e. to \( \tilde{q}_{12} \) and \( \tilde{q}_{23} \).

4.4.2 Equilibrium properties. As the closing rates are not affected by the environment,
the duration of a sojourn with both channels open reduces to an exponential with mean
1/(2\( q_{32} \)). (This would become a linear combination of two exponentials if \( q_{32} \)
were to change with the environment.) Joint distributions, moments and correlations may be found
using (6)–(9) and extensions in Ball et al. (1997). For example, the joint density function
of the durations of a sojourn at level 2 and the immediately following sojourn at level 1 is

\[
f(t, u) = 2q_{32}e^{-2q_{32}t}[0, 1, 0, 1]e^{Q_{11}u}(-Q_{11})1 \quad (t, u \geq 0),
\]

where

\[
Q_{11} = \begin{bmatrix}
-d7 & q_{12} & q_{12}^E & 0 \\
q_{21} & -d8 & 0 & q_{12}^E \\
q_{21}^E & 0 & -d9 & \tilde{q}_{12} \\
0 & q_{21}^E & q_{21} & -d10
\end{bmatrix}
\]

with \( d7 = q_{12} + q_{12}^E + q_{32}, \ d8 = q_{21} + q_{21}^E + q_{32} + q_{23}, \ d9 = \tilde{q}_{12} + q_{12}^F + q_{32} \)
and \( d10 = q_{21} + q_{12}^E + q_{32} + \tilde{q}_{23} \) (since the row sums of \( Q \) are all zero).

Again, as shown in Ball & Milne (2000), when the full system process is reversible,
the intensity argument can be used in conjunction with conditioning on the state of the
environment to give a simple direct derivation of (21) in this setting. In principle, the
intensity argument can still be used when the full system is not reversible; however, in
practice, there is usually no longer a simple expression for the equilibrium distribution
of the full system process, or consequently for the mean sojourn times, and (21) does not
generally hold for irreversible processes.

5. Numerical examples

The results of the preceding section may readily be applied to evaluate numerically
various properties, such as equilibrium distributions, intensities and level sojourn-time
distributions, for the models described above. Based on a system of five two-state channels
(1 = closed and 2 = open) these are illustrated for a superposition of independent and
identically distributed channels, for superpositions with opening rate dependent on the
number of open channels, for a random environment model and for models with spatial
dependence. For purposes of comparison the mean number \( \nu = \sum_s s \pi_s \) of open channels
is made the same for all four types of model; then equilibrium probabilities $\pi_s$, moments such as the standard deviation $\sigma = \sqrt{\sum_s s^2 \pi_s - \mu^2}$, the density function $f_{Z_s}(t)$ and mean $\mu_s$ of level $s$ sojourn times, etc., may be conveniently compared. Calculations have been carried out in Matlab. Results are illustrated in Table 1 and Fig. 3.

All cases suppose that $q_{21} = 2$. For independent and identically distributed channels, case (a), suppose $q_{12} = 1$. For a single channel the probability that it is open is $p_2 = 1/3$. The number of open channels in the five-channel system in equilibrium has a binomial
A system has five channels, each with two states 1, 2 having closing rate \( q_{21} = 2 \). Cases considered are (a) independent and identically distributed with opening rate \( q_{12} = 1 \); (b1), (b2) and (b3) with opening rate dependent on the number \( s \) of other channels open: 

\[
q_{12}^{(s)} = 0.5379(s + 1), \quad q_{12}^{(s)} = 0.24466 \times 2^s \quad \text{and} \quad q_{12}^{(s)} = 3.5362/(s + 1) \text{ respectively (s = 0, 1, \ldots , 4)}; (c) a random environment on two states with transition rates \( q_{12}^{(s)} = q_{12}^{(s)} = 1 \) and with \( q_{12}^{(1)} = 0.2857, \quad q_{12}^{(2)} = 2.00 \); and (d) spatial interactions on a ring with \( q_{12}^{(s)} = 0.6096 \times 2^s \) where \( (k = 0, 1, 2) \) is the number of open nearest neighbors. Given are the mean \( (\nu) \) and standard deviation \( (\sigma) \) of the equilibrium distribution of the number of open channels, the mean sojourn times \( (\mu_i) \) at level \( i \), and the equilibrium probabilities \( (\pi_i) \) for \( i \) open channels \( (i = 0, 1, \ldots , 5) \).

<table>
<thead>
<tr>
<th>( \nu )</th>
<th>( \sigma )</th>
<th>( \mu_0 )</th>
<th>( \mu_1 )</th>
<th>( \mu_2 )</th>
<th>( \mu_3 )</th>
<th>( \mu_4 )</th>
<th>( \mu_5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>1.6667</td>
<td>1.6667</td>
<td>1.6668</td>
<td>1.6667</td>
<td>1.6667</td>
<td>1.6668</td>
<td></td>
</tr>
<tr>
<td>(b1)</td>
<td>1.0541</td>
<td>1.3700</td>
<td>1.7661</td>
<td>0.8374</td>
<td>1.2347</td>
<td>1.2357</td>
<td></td>
</tr>
<tr>
<td>(b2)</td>
<td>0.2000</td>
<td>0.6496</td>
<td>0.8175</td>
<td>0.0566</td>
<td>0.3446</td>
<td>0.3281</td>
<td></td>
</tr>
<tr>
<td>(b3)</td>
<td>0.1667</td>
<td>0.1756</td>
<td>0.2527</td>
<td>0.1489</td>
<td>0.1769</td>
<td>0.1768</td>
<td></td>
</tr>
<tr>
<td>(c)</td>
<td>0.1429</td>
<td>0.1300</td>
<td>0.1442</td>
<td>0.1503</td>
<td>0.1255</td>
<td>0.1306</td>
<td></td>
</tr>
<tr>
<td>(d)</td>
<td>0.1250</td>
<td>0.1101</td>
<td>0.1009</td>
<td>0.1349</td>
<td>0.1086</td>
<td>0.1081</td>
<td></td>
</tr>
</tbody>
</table>

With a random environment with \( n = 5, p = 1/3 \), and a sojourn at level \( s \) has an exponential distribution with mean \( 1/(q_{12} + s q_{21}) = 1/(s + 5) \). The mean number of open channels in equilibrium is then \( 5/3 \).

For interacting channels with opening rates depending in various ways on the number \( s \) of open channels, three cases are considered: (b1) a linear increase \( q_{12}^{(s)} = 0.3079(s + 1) \), (b2) a geometric increase \( q_{12}^{(s)} = 0.24466 \times 2^s \), and (b3) a decrease \( q_{12}^{(s)} = 3.5362/(s + 1) \), where \( s = 0, 1, \ldots , 4 \). A simple random environment, case (c), on two states with transition rates \( q_{12}^{(s)} = q_{21}^{(s)} = 1 \) (an alternating environment) is used, with the channel opening rate depending on the state of the environment as \( q_{12}^{(1)} = 0.2857, \quad q_{12}^{(2)} = 2.00 \); note that this model is not reversible. For spatial dependence, case (d), the opening rate for a channel depends on the number \( k \) of open neighbors: \( q_{12}^{(s)} = 0.6096 \times 2^k \), \( k = 0, 1, 2 \).

While the mean number \( \nu \) of open channels is the same, by choice, in all cases there are some differences in the standard deviation \( \sigma \). Positive interactions result in increased values of \( \sigma \), the greatest increase being with the case of greatest interaction, namely geometrically increasing opening rates in (b2). The equilibrium distribution of the number
of open channels becomes more spread out, as is to be expected. On the other hand, when
the opening rate decreases with the number of open channels, as in case \(b_3\), \(\sigma\) decreases
and there is less probability in the tails of the distribution of the number of open channels.

The closing rate \(q_{21} = 2\) is fixed in all cases, so a sojourn time at level 5 is
exponential with mean 0.1. Increasing interactions tend to give an increased probability
of longer sojourns at lower levels such as 0 and 1, due to a decreased opening rate,
for example in cases \(b_1\), \(b_2\) and \(d\) a sojourn at level 0 is exponential with mean
\(1/(5q_{12}^{(0)})\), \(q_{12}^{(0)} = 0.3079, 0.24466, 0.6096\) respectively; see Fig. 3. In a given situation, the
relative dispersion (coefficient of variation) \(\sigma/\nu\), and the difference between the situation
observed and the independent and identically distributed case may give some indication of
which interacting model is most appropriate.

6. Concluding remarks

The primary purpose of this paper has been to study the properties of, and to compare,
various models of ion channel systems having some form of interaction between channels.
In particular, three kinds of interaction have received attention; firstly, transition rates
depending on the number of open channels in the system, secondly on spatial interactions
depending on the number of open nearest neighbours to a channel, and thirdly on a
random environment. In each of these situations the state space of the complete system
can be markedly reduced using symmetries, enabling simpler analysis and much faster
computations. A brief description of the required theory of aggregated Markov chains and
intensities has been given, with attention given to how these general methods can be applied
to the particular problems of interest. As reversibility plays an important role in channel
behaviour, attention has been given to conditions for reversibility and to the consequences
of requiring reversibility. A system of five channels, each with two states, has been used to
compare properties of the distributions of the number of open channels and of the duration
of sojourns at particular levels. As the degree of dependence increases there is an increasing
difference, from that of a model of independent and identically distributed channels, in
properties such as standard deviation of the number of open channels and in level sojourn-
time distributions. These properties, together with other experimental evidence, may assist
in describing realistic models and relationships for channel systems. The methods are also
relevant in dealing with other types of channel behaviour, including a single channel with
interacting subunits.

Results for a system of interacting ion channels with transition rates depending on
the number of open channels, and for a system in a random environment, may readily
be computed for channels with several states and/or conductance levels. For a reversible
system of two-state channels exhibiting spatial dependence corresponding results are again
computable for a moderate number of channels; Ball & Yeo (2000) also have some results
for such models where the channels have more than two states. Work in this area has just
begun and much more remains.

For dealing with multiple-channel data there is a need for appropriate statistical
procedures. The literature in this area is less well developed than for analysis of single-
channel data. Analysis based on hidden Markov models has been considered, for example,
by Albertsen & Hansen (1994), Chung et al. (1990), Fredkin & Rice (1992b) and Klein
et al. (1997). Tests for independence, based on renewal properties and the number of
downsteps of the process, have been proposed by Dabrowski et al. (1990) and Dabrowski & McDonald (1992). However, it was noted by Ball et al. (1994) that for the reversible random environment model some of their hypothesis tests will not detect departures from independent and identically distributed channels. There is scope for further work on methods of statistical data analysis for assessing the appropriateness of competing multiple channel models, and estimating parameters in some chosen model.

The methods described in this paper have application in other areas, for example reliability modelling (Csenki, 1994). In reliability the state space may be partitioned into two classes, labelled up or down and corresponding respectively to a system being either operational or non-operational. As for channels, Markov models are usually used, so similar methods based on aggregated Markov models are appropriate, although questions of interest are sometimes rather different (cf. Ball et al., 1997).

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