Conductance Characteristics of Interactive Subunit Membranes

A. H. Bretag and D. I. B. Kerr

School of Pharmacy, South Australian Institute of Technology and Department of Human Physiology and Pharmacology, University of Adelaide, Adelaide

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Subunit Interactions, Membrane Conductance Models

Membrane channels formed by groups of subunits with a special form of interaction between the subunits provide a simple basis for models of membrane conductance. It is shown how the subunit interaction can explain conductance kinetics; particular attention being paid to characteristics of the potassium conductance in the squid piant axon.

We have arrived at an explanation for some of the unique features of ion conductance through cell membranes. Here we show how "induction" and "superposition" of potassium conductance in the squid axon [1, 2] can result from a special form of interaction between subunits of a planar array membrane. Various forms of interaction and co-operativity have been considered previously in attempts to describe potassium conductance [2–11], but few of these have proved any more successful than the original non-interactive Hodgkin-Huxley [12] formulation.

In several cases where claims have been made for potassium conductance models involving membrane subunit or pore interactions [4–9], it has been shown that the mathematical descriptions of the models are approximations only [2–5]. In particular, accurate computations of Adam's model [6] by Hill and Chen [2, 3] have shown his approximation to be invalid and his model to be inadequate.

By contrast, the approximations shared by the models of Bretag, Davis and Kerr [4, 5], Tille [7] and Starzak [8, 9] remain, so far undisputed. The validity of these approximations and their relation to the exact mathematical description of the interaction in these models will be discussed in a forthcoming publication. Meanwhile, further consideration of the form of the interaction has provided a simple mechanistic explanation for the conductance characteristics of the models.

The interaction in these models occurs between nearest neighbour sites in a two dimensional lattice representing the membrane. Sites may exist in two states, active and inactive. The special constraint is that a site cannot undergo a change of state unless it is situated adjacent to a site in the active state.

Requests for reprints should be sent to Dr. A. H. Bretag, School of Pharmacy, South Australian Institute of Technology, North Terrace, *Adelaide*, South Australia 5000.

"Seeding" or "nucleation" is a natural consequence of this form of interaction with the rate of increase in the number of active sites being low while the number of such sites is low and increasing as the number of active sites increases. In other words, if the external determinant of site activation (*e. g.* membrane potential) is increased, then the initial rate of increase in the number of active sites will depend upon the number of such sites existing at that time. Consequently, the models demonstrate "induction" and the duration of the induction period depends on the initial number of activated sites (Fig. 1). Inflexion occurs in the rate of increase when further increase in the number of active sites becomes limited by either the level of the external activation determinant or, eventually, by the shortage of activable sites. This, of course, always assumes that the proportion of active sites is being increased from a low level where not all inactive sites are nearest neighbours of active sites; which leads us to the second important property of these models.

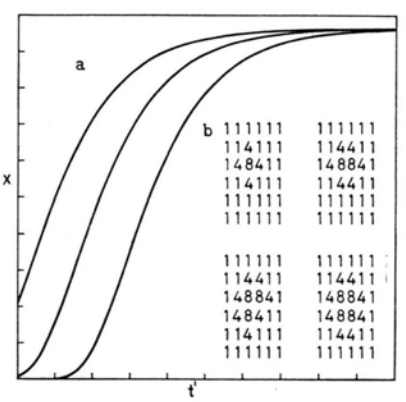


Fig. 1. Induction behaviour. a. Induction illustrated by an arbitrary function

$$x = f(t),$$

where x has been plotted against

$$t' = t - t_0,$$

t_0 being the point chosen for the origin of the abscissa. The smaller the value of x at $t = t_0$, the longer the induction period. b. Induction illustrated by activation in a square lattice where only nearest neighbours may be activated. Beginning with one active site, four further sites may be activated, while beginning with two, three or four; six, at least seven, or at least eight respectively, may be activated. Active sites are indicated by "8", inactive nearest neighbours by "4" and other inactive sites by "1".

Once the proportion of active sites is great enough so that effectively all inactive sites are nearest neighbours of active sites, then further activation is free of our constraint regarding interaction: further activation then being dependent

solely on the level of the external determinant and the availability of activable sites. The rate of activation is thereafter constant at any specified proportion of active sites, for a fixed external determinant.

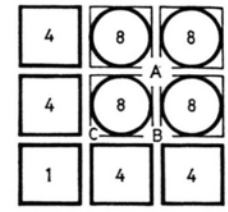
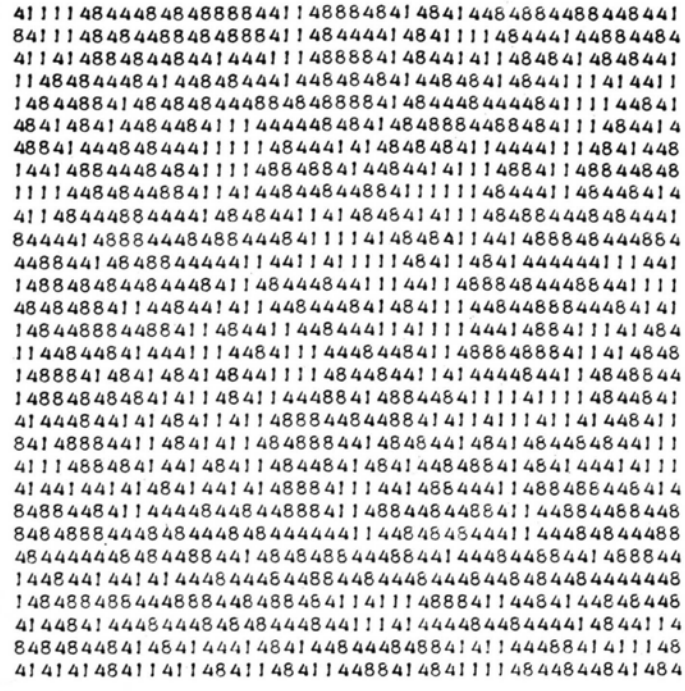


Fig. 2. Square array structure for a potassium-conducting subunit membrane. The rounded form of a subunit indicates the activated state, "8", which, when present in all subunits of a minimum functional group (all subunits adjacent to A), allows the formation of a conducting channel or pore at A. Openings at B and C are considered inadequate for the passage of ions.

a



b

Fig. 3. Parts of two 50×50 square arrays representing potassium-conducting patches of membrane. Subunits are labelled as in Fig. 1. In the first array (a) 26.2% of subunits were randomly set as active. Of those remaining 67.8% were then nearest neighbours of the active subunits. In the second array (b) 55.9% of subunits were randomly set as active. This time 98.8% of the remainder were nearest neighbours. These two cases represent epuilibrium potassium conductances, 0.4% and 9.8% of maximum, respectively, in the BDK square array model.

Thus rates of further activation to a fixed higher level show "superposition". That this is a legitimate property of the Bretag, Davis and Kerr [4] (BDK) potassium conductance model can be illustrated in the following way:

Let us consider a square array for the lattice where four neighbouring sites are required to be simultaneously activated to produce a potassium conductance channel (Fig. 2). Potassium conductance thus depends (if the site distribution is random) on the fourth power of the relative number of active sites. Then, for the resting potassium conductance to be close to that observed experimentally at the normal resting potential [13], it is necessary for the proportion of active sites to be about 25% (*c. f.* $n_0 = 0.24$ for the Hodgkin-Huxley [12] activating particle model). This proportion is already close to that where effectively all inactive sites are nearest neighbours of active sites (Fig. 3). Hence, kinetics for potassium currents, even only slightly above the resting level, will be approximately superimposable for a potential step to a fixed higher potential level. Any initial deviation would rapidly become insignificant as the potassium current increased.

The BDK model is therefore able to fit the experimental data of Cole and Moore [1] with respect to both induction and superposition, even though it does not strictly obey the conditions of stochastic independence of sites imposed by both Hill and Chen [2] and Albano [14]. This is because the working range of the model includes two distinctly different regions: one where there is significant interaction which specifies induction and another where there is no significant interaction which allows superposition.

Although the principles involved in the BDK model are therefore sound, it should be noted that the parameters used in the model were derived by fitting curves to the experimental potassium conductance data of Hogdkin and Huxley [12].

Recent work [15, 16] indicates that such modelling is in error because the conductance curves of Hodgkin and Huxley [12] are not true axolemmal conductance curves; these latter authors having failed to consider potassium ion accumulation in the Schwann Cell Layer (S.C.L.). However, conflicting views of the seriousness of the error are presented [15, 16]. Adam [15] even implies that axolemmal conductance kinetics may indeed not be superimposable and that the superposition of current curves may result from modifications imposed by the S.C.L. We feel that his extreme view is argued against by the experimental results of Cole and Moore [1]. Potassium currents following conditioning hyperpolarisation to various levels were just as superimposable as those following conditioning depolarisation. In the prior case, S.C.L. effects would be identical and inpedendent of the level of conditioning hyperpolarisation, which strongly suggests that axolemmal conductance is superimposable. In fact, Adelman, Palti and Senft [16] take the view that axolemmal conductance is satisfactorily modelled merely by adjusting the maximum conductance $\bar{g}_K$ and the rate constants α_n and β_n in the Hodgkin-Huxley formulation. We are therefore confident that similar minor alterations to our model would enable it also to describe these recent findings as well as maintaining its ability to describe Cole-Moore induction and superposition.

Finally, we feel that the form of interaction specified in the BDK model may also prove more widely applicable: especially if the constraint is relaxed to allow some probability of change of state in those sites not situated adjacent to an active site.

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