Power Spectra and Cooperativity of a Calcium-Regulated Cation Channel

Malcolm W. McGeoch* and Julie E. M. McGeoch‡
*PLEX Corporation, Brookline, Massachusetts 02146, and ‡Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, Massachusetts 02138 USA

ABSTRACT In this article we show that a channel complex of cooperatively interacting subunits can produce a power law spectrum, with the slope of the spectrum depending on the strength of the cooperative interaction. The effects of cooperativity are explored via a computational model of a calcium-regulated cation channel for which new data is presented. The results, which concern "flickering" conductances, are correlated with prior work on critical fluctuations in the Ising model of ferromagnetism.

INTRODUCTION

Many aspects of calcium-regulated channel behavior can be explained by proposing that individual channel subunits, each held shut by a single calcium ion, are coupled tightly in a complex in which the opening of one subunit decreases the calcium binding energy on neighboring subunits. The modeled current fluctuations and spectrum agree with experimental data from a cation channel first identified in skeletal muscle by McGeoch and Guidotti (1992), which conducts both sodium and calcium at hyperpolarizing voltages. This channel has also been found in heart, brain, and oocytes, and plays an important role in the regulation of intracellular sodium (McGeoch and Morielli, submitted for publication). It is gated by cGMP and controlled by divalent cations, prompting comparison with the sensory channels of the eye and nose (Stryer, 1986; Dhallan et al., 1990). The channel current shows a characteristic "flickering", which resembles reported observations of the eye channel (Haynes et al., 1986; Torre et al., 1992; Zimmerman and Baylor, 1986), and it is hard to assign a unitary conductance. The Fourier transform power spectrum of the current record (McGeoch and Guidotti, 1992) is not a Lorentzian curve as would be expected for statistically independent channel events, but exhibits a power law with an exponent between −1 and −2. The existence of such a power law was thought to be a consequence of cooperative interactions between channels (McGeoch and Guidotti, 1992). Power law dependencies with an exponent of −1 have been reported for the eye channel (Haynes et al., 1986; Torre et al., 1992) and interpreted as the sum of two or three Lorentzian distributions each from statistically independent channel types with differing kinetic behavior. The present results suggest an alternative explanation for some of these results in terms of cooperative interactions.

Received for publication 26 July 1993 and in final form 24 September 1993
Address reprint requests to Dr. Julie E. M. McGeoch, Department of Biochemistry and Molecular Biology, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138.

0006-3495/94/01/161/08 $2.00

There already exists an analogue in the Ising model of coupled magnetic spins. Liu and Dilger (1993) have recently discussed the application of the Ising model to cooperative channels and emphasized the enhanced level of fluctuations that cooperativity induces at the channel opening transition. The power spectrum of critical Ising fluctuations has previously been shown by Angles d'Auriac et al. (1982) to obey an inverse power law of slope between −1 and −2, and their results are closest in spirit to the present work, in that they treat a small finite two-dimensional magnetic spin lattice whereas here we are concerned with possibly four channel subunits coupled in a tight circle (2 × 2 lattice).

Arecchi and Lisi (1982) have shown that such power laws arise from systems in which the amplitude of a current takes on different values as a nonlinear dynamical system hops between several basins of attraction. This could correspond in the present context to multiple conductance states of a channel complex. We find that if we require all (four) subunits to be in a "permissive" state before the channel conducts, then the slope of the power spectrum becomes −1, whereas if multiple conductance states can exist (analogous to multiple magnetisation states), the slope tends to −1.7. Both cases may be relevant, because the eye channel has a spectral slope of −1, whereas the cation channel described in the present study shows slopes between −1.4 and −1.8 in different tissues. The −1 slope can arise in a general way in circumstances where an outcome depends on the successful completion of several distinct statistical processes (Montroll and Shlesinger, 1982).

We will consider the coupling of several channel subunits in a small complex, in which the state of one subunit influences the state of its nearest neighbors and propose that the specific means of coupling is via changes in the binding energy of the calcium ions which stabilize the "closed" channel conformation (McGeoch and Guidotti, 1992). DeFelice (1993) has concluded that clustering of functional units could explain the observed cooperativity of L-type calcium channels (which, however, have a different voltage dependence compared with the cGMP-activated cation channel of the present study). When a coupling model is constructed

(below), the resulting power spectrum is found to show a completely characteristic f^{-n} power law, where $1 < n < 1.7$, which is independent of the actual voltage, or calcium concentration, but depends *only* on the coupling parameter. Another well-known consequence of cooperativity displayed by this Ising type of model is enhanced sensitivity to ligands, in this case voltage, calcium concentration and temperature.

THEORETICAL DESCRIPTION

We start our theoretical description by noting that the opening of a channel at hyperpolarizing voltage (Fig. 1) is modulated qualitatively by calcium. If the calcium concentration is increased, the current-voltage plot becomes more "hooked" and the channel requires more voltage to open. This is also seen in the retinal channel (Chen et al., 1993). Just this type of behavior occurs if the calcium binding energy is hypothesized to decrease with increasing transmembrane voltage. We write

$$D(V) = \frac{\alpha}{x_0 + \beta V} \tag{1}$$

where $D(V)$ is the calcium binding potential per unit charge at voltage V and α, x_0, and β are constants. This (point charge potential) form for $D(V)$ would be expected for ionic binding of a Ca^{2+} ion to a protein region with two negatively charged groups, each separated by distance x_0 from the ion, this distance increasing linearly with increased voltage. The possibility of a fixed size calcium site is rejected because insufficient binding energy reduction occurs on the application of the membrane electric field across a site of typical dimensions. The approximately 50 mV binding reduction required to fit the data can, however, be provided by the movement of a multiply charged group part way across the membrane, and communicated to the variable size site, which is near the cytoplasmic side, by a "protein lever."

The channel subunit is assumed to switch from "closed" to "open" in a conformational change that can only occur if the Ca^{2+} ion is off (i.e., the Ca^{2+} ion is no longer "buttoning" the protein together at that location). This kinetic scheme is represented in Fig. 2. Although we speak of subunits having a unique open conductance, it may be that the conductance of the complex is not proportional to the number of "open" subunits, but may require at least two subunits to have changed to an "open" conformation before conductance begins (discussed below). The transition rate from closed to open is in general a function of the calcium concentration and the voltage, and is given by

$$R_0([Ca^{2+}], V) = \gamma_{MOL} P_c \tag{2}$$

where γ_{MOL} is the rate of (thermally induced) conformational change and P_c is the probability that the subunit occupies a Ca^{2+}-free closed state, P_c being equal to the fraction of time that calcium is off.

P_c is equal to the calcium "off" rate (κ_{off}) divided by the sum of the calcium "off" rate and the calcium "on" rate ($\kappa_{off} + \kappa_{on}$). The "off" rate $\kappa_{off} = \nu \exp[-2D(V)q/kT]$ where

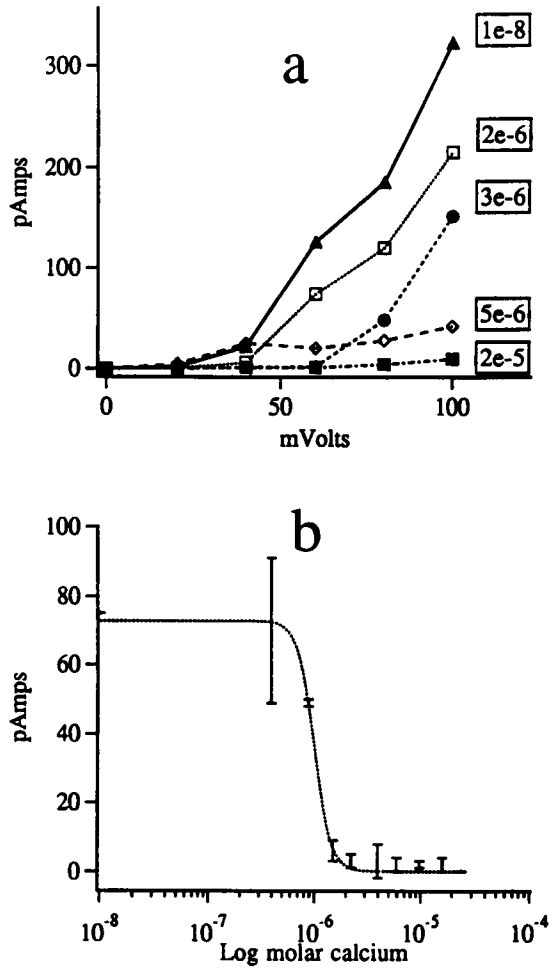

FIGURE 1 (*a*) Measured voltage dependence of cGMP-dependent cation channel current at different calcium concentrations, from (McGeoch and Guidotti, 1992). Skeletal muscle preparation, conditions given in (McGeoch and Guidotti, 1992). (*b*) Measured inhibition of cGMP-dependent cation channel current by calcium at fixed voltage (100 mV), from (McGeoch and Guidotti, 1992). Conditions given in (McGeoch and Guidotti, 1992).

ν is the oscillation frequency of the calcium ion at the site and the exponential term represents the probability of there being sufficient thermal energy to escape from a potential well of depth $2Dq$, q being the unit charge and D, given by Eq. 1, being the interaction potential of calcium with each negative protein group. The "on" rate $\kappa_{on} = k_1[Ca^{2+}]$, where k_1 is determined by diffusion and is only weakly temperature dependent. We therefore obtain for the opening rate

$$R_0([Ca^{2+}], V) = \frac{\gamma_{MOL}}{\left(1 + \frac{k_1[Ca^{2+}]}{\nu} e^{2D(V)q/kT}\right)} \tag{3}$$

Once open, the calcium site will have expanded and the calcium binding potential will be reduced to D' ($<D$) where

$$D'(V) = \frac{\alpha}{x_0' + \beta' V} \tag{4}$$

with $x_0' > x_0$ and $\beta' > \beta$. By an analogous line of reasoning,

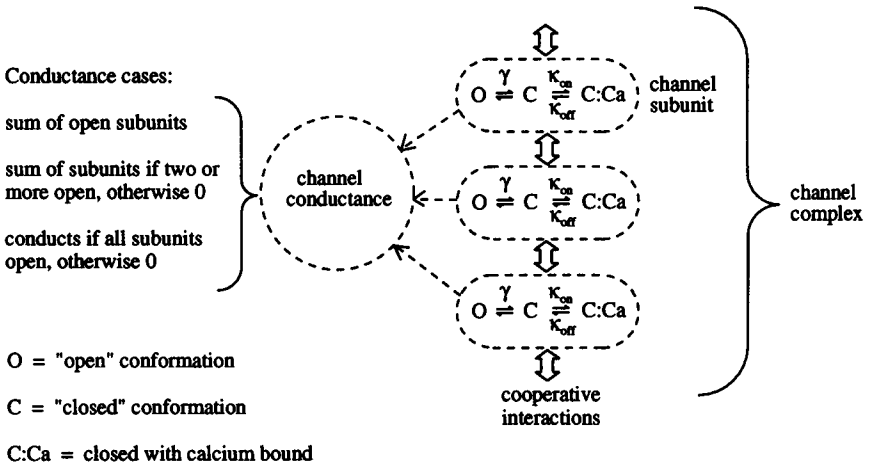

FIGURE 2 Representation of the kinetics of a complex of cooperative calcium-regulated channel subunits.

the transition rate from open to closed is found to be

$$R_c([Ca^{2+}], V) = \frac{\gamma_{MOL}}{\left(1 + \frac{\nu}{k_1[Ca^{2+}]} e^{-2D'(V)q/kT}\right)} \quad (5)$$

For any one channel (sub)unit, Eqs. 3 and 5 describe the open/closed fluctuations in terms of the calcium concentration and voltage. For example, the time averaged current of one unit is given by $SVR_0/(R_0 + R_c)$, where S is the conductance of a channel subunit. For simplicity the opening and closing conformational changes are given the same rate, although in principle there could be an energy difference between the conformations, and indeed such a difference could be voltage dependent. Such energy differences are assumed to be minor compared with the energy involved in the calcium interaction.

The experimental data (Fig. 1) also show an extremely sharp dependence of channel state on the calcium concentration. An average of 3.7 ± 1 Ca^{2+} ions are involved (McGeoch and Guidotti, 1992) in channel inhibition. Either a channel could have more than one calcium binding site, or several channel subunits, each with a single binding site, could interact *cooperatively* in a complex, the opening (for example) of some (sub)units in the complex reducing the calcium binding energy and facilitating the opening of the remaining units. There are several aspects of the channel's behavior that suggest the second case. For one thing, the conductance of "single channel events" is relatively high (150 pS at 50 mM Na, data shown below). The typical conductance of many other channel types is several times smaller than this, so the possibility of correlated opening has to be considered. More importantly, the Fourier transform (power spectrum) of the current ((McGeoch and Guidotti, 1992) and below) is indicative of correlated behavior. Lastly, the time records of the "single channel events" (shown below) appear to show several stages of opening, with a constant fully open state, suggesting the interaction of about four channel subunits in a definite group.

The interaction between subunits can be represented as follows: The assumption is that the interacting (sub)units lie in a planar membrane, "daisy chained" together in a circle and that each unit is influenced by the states of the two neighboring units. The following simple interaction between units is proposed. If the highest calcium binding potential is D, achieved when a unit and its two neighbors are all closed, and the lowest binding is gD, when a unit and its two neighbors are all open (g being a factor less than one), then the binding potential of unit i in the channel complex is

$$D_i = gD + \frac{D}{3}(S_{i-1} + S_i + S_{i+1})(1 - g) \quad (6)$$

where S_i is the state (1 = closed, 0 = open) of unit **i**.

NUMERICAL METHODS

A numerical model of the above system has been run with the trial set of parameters: $x_0 = 5.5 \times 10^{-10}$ m, $\beta = 7.5 \times 10^{-10}$ mV^{-1}, $k_1 = 1 \times 10^{-17}$ m^3 s^{-1}, $\nu = 1 \times 10^{12}$ s^{-1}, $T = 293$ K, and $\alpha = q/(4\pi\epsilon\epsilon_0)$ in MKS units where q is the unit charge, ϵ is the dielectric constant ($\epsilon = 8$) and ϵ_0 is the permittivity of free space. The evolution of the complex was followed in time steps of $1/\gamma_{MOL}$. At each time step the N units in the complex were each given an opportunity to change state. The new state of each channel was determined by comparison of a random number between 0 and 1 with R_0/γ_{MOL} if the channel was originally closed, or with R_c/γ_{MOL} if the channel was originally open. The values of R_0 and R_c for each channel were determined from 3 and 5 using the binding potential given by 6, in which the states of the previous time step were used. In the evaluation of different cases, the evolution of a complex was followed for 4,096 up to 524,000 time steps, depending on the statistical accuracy required.

EXPERIMENTAL METHODS

Rat brain synaptosomal or heart muscle membrane proteins were reconstituted in phospholipid bilayers and patch-clamped, according to the methods described (McGeoch and Guidotti, 1992). The electrolyte concentrations were as

follows: pipette (representing the outside of the cell) 50 mM NaCl. Bath (representing the cytoplasm) 10 mM NaCl and 15 mM MgCl. Both were buffered to pH 7.6 with 5 mM Hepes.

RESULTS AND DISCUSSION

Throughout the presentation of the theoretical data, the membrane voltage is given as a positive number but the normal physiological polarity is implied. Fig. 3 shows computed average current versus calcium concentration for $g = 0.7$, 0.8, and 0.9. As expected, the curves are much more gentle, approaching first order kinetics, as the cooperativity is reduced ($g \rightarrow 1$). On the other hand the current is a steep function of calcium concentration for highly cooperative cases. Comparison with the data of (McGeoch and Guidotti, 1992) indicates that g could be in the range $0.7 < g < 0.8$ for skeletal muscle. Another determination of g comes from the power spectrum of the current fluctuations, discussed below.

Fig. 4 shows I–V plots of the calculated current, obtained by multiplying the open fraction of channel subunits by the voltage, for four calcium concentrations. Above 0.1 μM the I–V plot takes on the characteristic hook shape that is observed experimentally (McGeoch and Guidotti, 1992; Chen et al., 1993).

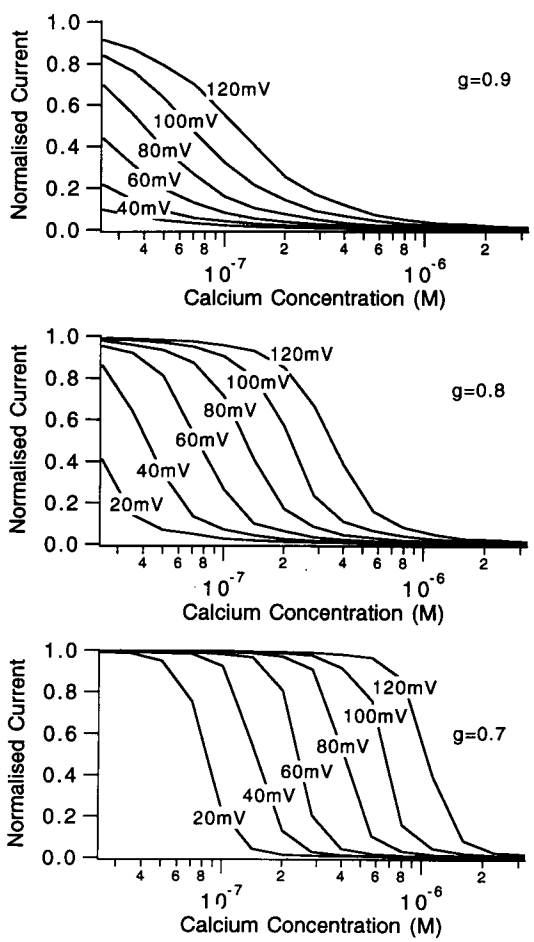

FIGURE 3 Computed average current in relative units as a function of voltage and calcium concentration for weak, moderate, and strong cooperativity ($g = 0.9$, 0.8, and 0.7 respectively, four channels). Current is time averaged over a duration of $4096\gamma_{MOL}^{-1}$.

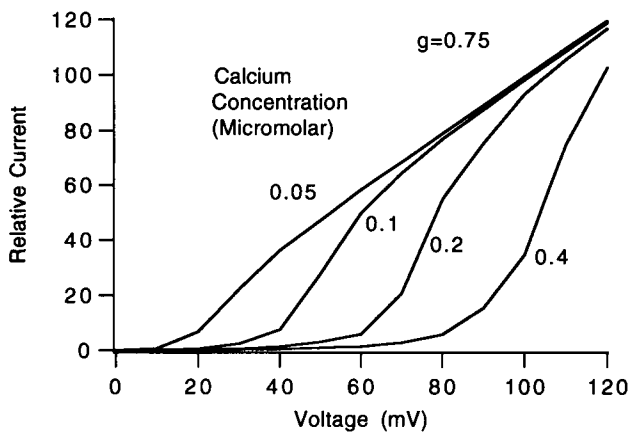

FIGURE 4 Computed average current as a function of voltage for different calcium concentrations. Four-channel complex with cooperativity factor $g = 0.75$.

Up until this point we have assumed that each subunit contributes equally to the conductance when it is in the "open" conformation. Fig. 5 *a* shows the computed time dependence of the cation current for a case having $V = 0.07$ volts, $[Ca^{2+}] = 2 \times 10^{-7}$ M, $g = 0.75$ and four channel units in the model complex. The *experimentally* recorded trace from patch-clamped reconstituted brain channel is shown in Fig. 5 *b* and (expanded) in Fig. 5 *c*. We find that a much better simulation (Fig. 5 *d*) of the experiment is obtained when the conductance is set to zero unless two or more subunits are "open," and only 2, 3, or 4 units of conductance are allowed to occur. In that case the model reproduces the data very realistically, particular points of comparison being the very sudden opening or closing of a whole complex (to a set current maximum) and the flickering of the open current, which is due to one or two of the subunits in a complex momentarily closing and reopening. The experimental fluctuations (Fig. 5 *c*) appear to show that there are four subunits in the complex and that while the complex is conducting one unit drops out frequently and a second unit closes occasionally.

The effect on the simulated current of varying the degree of cooperativity is shown in Fig. 6, in which the cooperativity is increased going through Fig. 6, *a–c*, via the use of $g = 0.85$, 0.75, and 0.65, respectively. A four-subunit channel complex is assumed, and conductance is assumed proportional to the number of open subunits but set to zero for less than two open subunits. There is a dramatic shift toward lower frequency content as cooperativity is increased. This is a reflection of the increased tendency of all subunits to be either closed, or open, with transitions between these two extremes becoming less and less probable as the coupling of subunits is increased. Specifically, when a subunit and its neighbors are all open, the Ca^{2+} binding energy is much reduced (Eq. 6) and the probability of simultaneous re-occupation of a number of Ca^{2+} sites is greatly reduced. The likelihood of a

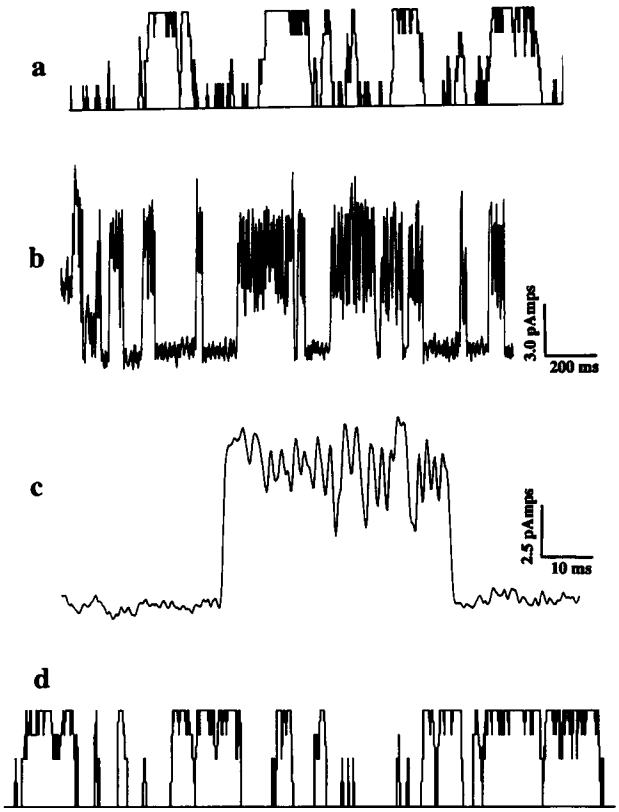

FIGURE 5 (*a*) Computed current through a four-channel cooperative complex with $V = 70$ mV, $[Ca^{2+}] = 2 \times 10^{-7}$ M and binding reduction factor $g = 0.75$ The conductance assumption is that each open subunit contributes equally to the conductance and the whole computed trace spans a time of $960\gamma_{MOL}^{-1}$. (*b*) Measured Na current from patch-clamped brain membrane preparation. Conditions: 60 mV, [Na] = 50 mM, baseline = 0 pAmp. Calcium range is 0.1–0.5 μM. (*c*) Time-expanded trace from the same experiment as trace (*b*). (*d*) Conditions of simulation as in (*a*) except conductance proportional to the number of open subunits begins only for two or more subunits open.

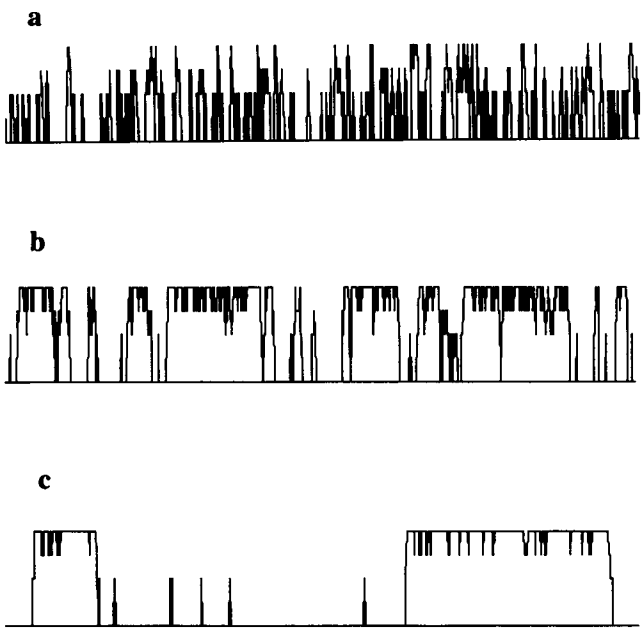

FIGURE 6 Simulated time courses of the channel current at increasing cooperativity, for a conductance proportional to the number of open subunits beginning only when two or more subunits are "open." (*a*) $g = 0.85$, (*b*) $g = 0.75$, (*c*) $g = 0.65$. The time scale is the same in each simulation, the full trace representing $960\gamma_{MOL}^{-1}$.

simultaneous closing transition of a group of subunits therefore becomes very small.

The power spectrum was calculated from extended time sequences (of 4096 points) by fast Fourier transform. Transforms were taken of time sequences in which the average probability of the complex being open was in the range 40% to 60%. After trial variations of calcium concentration and voltage had established that neither of these parameters had a detectable influence on the spectrum, a set of spectra were run at fixed calcium concentration (0.2 μM) in which the desired average state of opening was obtained by variation of the voltage. The spectrum was then studied as a function of the number of channel subunits assumed to be in the complex. In the range of three to eight subunits the spectrum was identical, although the required voltage tended to reduce as the number of units increased. Also, the slope of the spectrum did not depend on how many subunits had to be "open" for conductance but depended *only* on one parameter of the model, the binding energy reduction factor g. The one exception was the case where *all* subunits had to be "open" to allow a conductance, when the spectrum assumed a constant -1 slope as the cooperativity was increased (discussed below in more detail).

Fig. 7 shows four spectra generated as g is decreased from 1 to a small value, i.e., as the cooperativity is increased. In this set it was assumed that the conductance of a channel complex was proportional to the number of subunits open. The spectra carry a certain level of (random) noise due to the use of a finite (4096 point) time sequence. Completely noncooperative behavior ($g = 1$) leads to a flat spectrum, the low-frequency limit of a Lorentzian power spectrum as observed, for example, for the end plate channel of the acetylcholine receptor (Anderson and Stevens, 1973). The present calculation does not reproduce the ν^{-2} high frequency end of the Lorentzian because the opening and closing events take place in a single time step of length γ_{MOL}^{-1}, which is identical to the time unit that is entered into the discrete Fourier transform. As some cooperativity is introduced ($g = 0.85$), the spectrum begins to lose its highest frequencies, and gains in power at lower frequencies. By the time $g = 0.7$, the spectrum obeys a strict power law over more than two orders of magnitude in frequency. The exponent of the power law, shown as a function of cooperativity in Fig. 8 *a*, takes on the value $n = -1.7$ as cooperativity is increased to higher levels ($g < 0.7$). Experimentally measured spectra are shown in Fig. 8 *b* (brain and heart preparations) and Fig. 8 *c* (muscle preparation). Comparing the model spectra with the muscle channel data of (McGeoch and Guidotti, 1992), the measured slope of -1.42 ± 0.14 (mean of six determinations) is seen to correspond to a binding energy reduction factor $g \sim 0.8$,

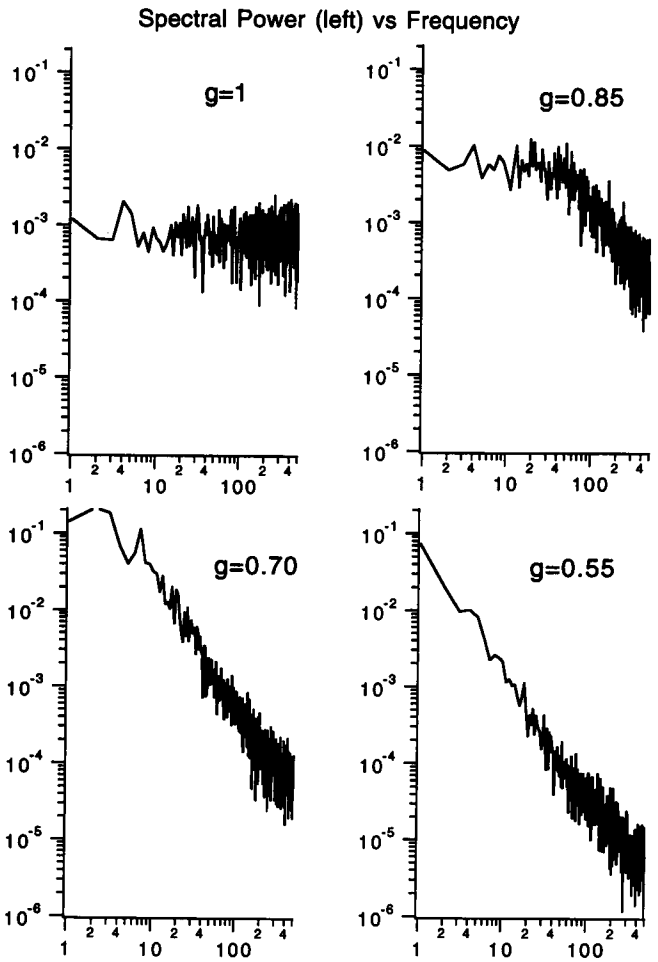

FIGURE 7 Evolution of the power spectrum of channel fluctuations with increasing cooperativity (decreasing g). Transforms of 4096 point time series for a four-channel complex with [Ca] = 0.2 μM at various voltages. The maximum frequency is $\gamma_{MOL}/2$ in each case.

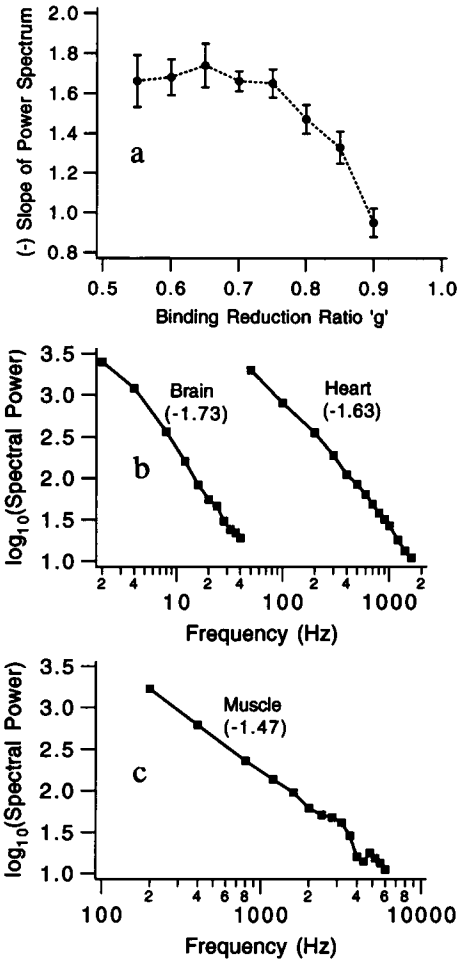

FIGURE 8 (*a*) Negative slope of log(Spectral Power) versus log(Frequency) plots as function of increasing cooperativity (decreasing g). (*b*) Experimental spectral power versus frequency for the brain channel data of Fig. 5b and for time series of heart channel events. (*c*) Experimental spectral power versus Frequency for the muscle preparation (from McGeoch and Guidotti, 1992).

a value consistent with the range deduced above (in muscle) by comparison with the Ca^{2+} inhibition. Heart data, shown in Fig. 8 *b* gave the slope -1.54 ± 0.16 ($n = 6$) (the curve shown has a slope of -1.63). Analysis of the brain channel gave a slope of -1.73, indicating higher cooperativity than in muscle or heart.

It is of interest in connection with the discussion of conductance above that when the program is modified to only allow conductance when two or more subunits are in the "open" state the calculated spectra are unchanged from those presented in Fig. 7. Likewise for the case of only three or four units of conductance. However, if conductance is only allowed when *all* subunits are in the "open" state the calculated slope of the spectrum is -1.0 ± 0.1, in disagreement with the present experiments. The development of this -1 power law is illustrated in Fig. 9. Following Montroll and Shlesinger (1982) one would expect this power law for the frequency of occurrence of an outcome that depended on the successful completion of a number of separate, but linked steps. Here, the separate steps consist of the linked opening of all the subunits. If the subunits do *not* interact, then there is no sense of linkage between the steps and it is not surprising that the flat (white noise) power spectrum is obtained, for in that case we are looking at the overlap of N white noise processes, one for each subunit. There is data (Tytgat and Hess, 1992) for a K^+ channel (not calcium inhibited) that suggests a form of cooperativity in which all four subunits have to be in a "permissive" state in order to allow a transition to unit conductance. It would be interesting to know whether the slope of the power spectrum of this channel was -1.

Often single channel data have been represented in the form of a plot of frequency of occurrence versus pulse duration. Performing this analysis on the cooperative model, we found that this plot was exponential, as expected for a process driven by a true random number generator. The slope of the exponential was, however, a very strong function of the average open fraction (of units), unlike the spectral slope that did not change for open fractions between 10% and 90%. The power spectrum was therefore a much more accurate indicator of cooperativity than the frequency/pulse duration plot.

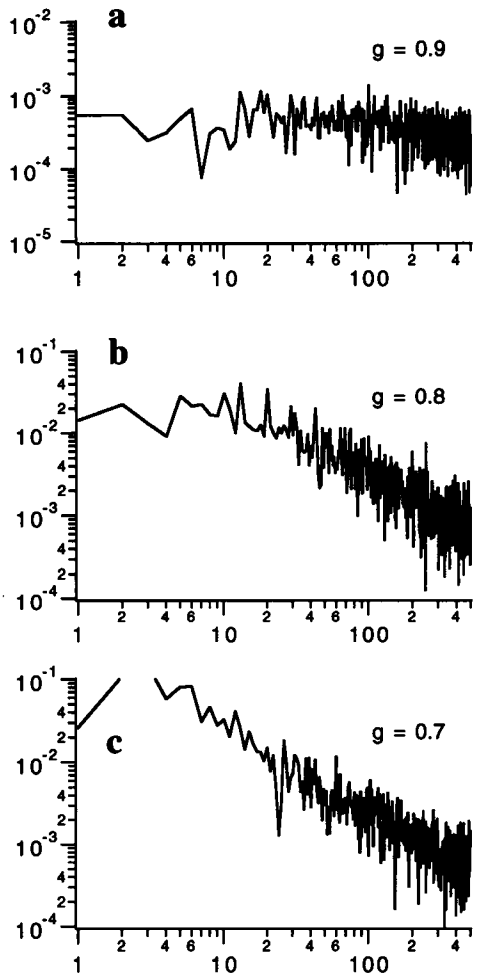

FIGURE 9 Power spectra computed for the case of a four subunit complex at increasing cooperativity, where it is assumed that the complex only conducts when all four subunits are in the "open" state. The maximum frequency is $\gamma_{MOL}/2$ and [Ca] = 0.2 μM. The spectrum evolves to a −1 power law at increasing cooperativity (decreasing g).

It is possible that the existence (Chen et al., 1993) of a subunit that confers "flickering" statistics on the retinal channel could be an example of induced cooperativity, rather than of a second channel species. A corollary of the present results is that in a cooperative Ca^{2+}-regulated channel, any species that competes with Ca^{2+} binding, either directly or allosterically, will have a strong effect on the cooperativity, and hence the channel statistics. The recent indication (Hsu and Molday, 1993) of a competition between cGMP and Ca^{2+} in the retinal channel is possibly of interest in this regard. In (Hsu and Molday, 1993) reduction in cGMP activation of the channel by Ca^{2+} was mediated by calmodulin in an allosteric interaction. The reverse process also must hold, i.e., cGMP binding must reduce the affinity of the calmodulin for Ca^{2+}. That this mechanism does not have Ca^{2+} binding directly to the channel, but to a subsidiary coupled protein does not affect the applicability of our model.

In conclusion, this new framework begins to explain the extraordinarily complex behavior of calcium-controlled, cGMP-dependent cation channels. These channels are apparently ubiquitous in the body and relate to sensory perception and sodium control. We have constructed what we believe is a minimum model of the calcium and voltage dependence of the channel current and shown that it predicts a power law spectrum whose slope is related to the strength of a hypothetical cooperative interaction at the locus of calcium binding. Although this is a specific realization of cooperativity, related to calcium binding, the theory clearly extends to arbitrary cooperative processes involving other ligands. The development of power law spectra in cooperative systems is a general phenomenon, observed in ferromagnetism and other systems of coupled spins in forcing fields. The fact that the cGMP-dependent cation channel exhibits a power law spectrum in many circumstances suggests that a cooperative mode of operation is at work. However, there are other ways in which a spectrum that looks very like a power law spectrum can be generated, notably in the sum of several kinetically different variants of a channel, so it is not possible to say that such a spectrum observed in isolation is proof of cooperativity. In the present case we also take into account the stronger resemblance to experiment of cooperative as opposed to noncooperative time records of the channel current when we suggest that it is very probable that the cGMP-dependent cation channel is cooperative. There appear to be advantages to cooperativity in primary processing for sensory perception. It is expected that a cooperative complex of cGMP-dependent cation channel units should display heightened discrimination for voltage, calcium, and temperature, compared with a single channel subunit.

We thank Dr. D. P. Corey for kindly reading the manuscript and supplying helpful comments.

J. E. M. McGeoch was supported by National Institutes of Health grant DK 27626 to G. Guidotti and by the Office of Naval Research contract N00014-93-1-0722.

REFERENCES

Anderson, C. R., and C. F. Stevens. 1973. Voltage clamp analysis of acetylcholine produced end-plate current fluctuations at frog neuromuscular junction *J. Physiol.* 235:655–691.

Angles d'Auriac, J. C., R. Maynard, and R. Rammal. 1982. Critical dynamics of finite Ising model. *J. Stat. Phys.* 28:307–323.

Arecchi, F. T., and F. Lisi. 1982. Hopping mechanism generating 1/f noise in nonlinear systems. *Phys. Rev. Lett.* 49:94–98.

Chen, T. Y., Y. W. Peng, R. S. Dhallan, B. Ahamed, R. R. Reed, K. W. Yau. 1993. A new subunit of the cyclic nucleotide-gated cation channel in retinal rods. *Nature (Lond.).* 362:764–767.

DeFelice, L. J. 1993. Molecular, and biophysical view of the Ca channel: a hypothesis regarding oligomeric structure, channel clustering, and macroscopic current. *J. Membr. Biol.* 133:191–202.

Dhallan, R. S., K-W. Yau, K. A. Schrader, and R. R. Reed. 1990. Primary structure and functional expression of a cyclic nucleotide-activated channel from olfactory neurons. *Nature (Lond.).* 347:184–187.

Haynes, L. W., A. R. Kay, and K-W. Yau. 1986. Single cyclic GMP-activated channel activity in excised patches of rod outer segment membrane. *Nature (Lond.).* 321:66–70.

Hsu, Y. T., and R. S. Molday. 1993. Modulation of the cGMP-gated channel of rod photoreceptor cells by calmodulin. *Nature (Lond.).* 361:76–79.

Liu, Y., and J. P. Dilger. 1993. Application of the one- and two-dimensional Ising models to studies of cooperativity between ion channels. *Biophys. J.* 64:26–35.

McGeoch, J. E. M., and G. Guidotti. 1992. An insulin-stimulated cation channel in skeletal muscle. Inhibition by calcium causes oscillation. *J. Biol. Chem.* 267:832–842.

Montroll, E. W., and M. F. Shlesinger. 1982. On 1/f noise and other distributions with long tails. *Proc. Natl. Acad. Sci. USA.* 79: 3380–3383.

Stryer, L. 1986. Cyclic GMP cascade of vision. *Ann. Rev. Neurosci.* 9: 87–119.

Torre, V., M. Straforini, F. Sesti, and T. D. Lamb. 1992. Different channel-gating properties of two classes of cyclic GMP-activated channel in vertebrate photoreceptors. *Proc. R. Soc. Lond. B. Biol. Sci.* 250:209–215.

Tytgat, J., and P. Hess. 1992. Evidence for cooperative interactions in potassium channel gating. *Nature (Lond.).* 359:420–423.

Zimmerman, A. L., and D. A. Baylor. 1986. Cyclic GMP-sensitive conductance of retinal rods consists of aqueous pores. *Nature (Lond.).* 321: 70–72.