of fixed negative charges by Ca^{++} or protons. As the shift of g_K curve vs V is 20–40 mV such an effect should shed light on some particular chemical structure in the immediate vicinity of the potassium channel. These few observations may serve others in the attempt to fill the gap which still exists in the full understanding of the functions of the complicated nodal structure. In my opinion, the simple views of an easily accessible bit of excitable membrane with clear delimitations by a myelin-covered inexcitable membrane in the paranodal region does need some amendments. The role of the paranodal loops of myelin as well as the one of the microvilli of Schwann cell cytoplasm is not yet understood and needs elucidation. It is probable, however, that most of the work done on sodium channels is valid. Potassium channels in warmblooded and poikilothermic animals are more difficult to approach and further experimental work is needed into, among other things, the leak problem mentioned in this paper.

* Dedicated to Professor Alexander von Muralt on the occassion of his 80th birthday.

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II. Sodium and potassium channels in myelinated nerve fibers

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The role of sodium and potassium channels in the excitability of the node of Ranvier

The time course of an action potential is determined by time- and voltage-dependent charge movements within and across the cytoplasmic membrane. By means of the voltage-clamp technique it was demonstrated that membrane currents in the node of Ranvier of *Xenopus laevis* can be described by equations (see e.g. Stämpfli and Hille[33]) very similar to the description of membrane current in squid giant axons developed by Hodgkin and Huxley[17]. Also for myelinated nerve fibers of other vertebrates the same kinetic description with only slight modifications can be applied to the membrane currents[7,12]. In general, the total membrane current in the node of Ranvier consists of 4 components:

$$I_{tot} = I_{Na} + I_K + I_C + I_L;$$

in addition to sodium- and potassium-specific currents (I_{Na} and I_K, respectively), capacity current I_C and unspecified leak currents I_L are involved. A further component I_P has been introduced by Fran-

kenhaeuser but can probably be attributed to potassium-selective channels and potassium accumulation (compare Dubois[14]). During an action potential the steep voltage-dependent activation of sodium channels leads to the fast upstroke, while the slower developing inactivation of the sodium conductance repolarizes the membrane potential. Depending on the type of nerve fiber (motor or sensory) and on the type of animal (warm- or coldblooded) the repolarization is more or less supported by activation of potassium currents and by leak currents, both having a reversal potential close to the membrane resting potential.

The present chapter of this multi-author review will primarily deal with recent voltage-clamp methods that yield information on the sodium- and the potassium-selective channels. Though the Hodgkin-Huxley description of ionic membrane currents is only an empirical approximation, the analysis of the different parameters and their dependence on experimental test conditions is still the basis for the development of models for sodium and potassium channels. Therefore, at least a brief definition of the parameters is presented here.

According to the Hodgkin-Huxley description of sodium current, the movement of sodium ions along their electrochemical driving force ($E-E_{Na}$) can be described also in myelinated nerve fibers by:

$$I_{Na} = m^3 h N_{Na} \gamma_{Na} (E - E_{Na}) \quad (1)$$

with γ_{Na} being the conductance of a single sodium channel and N_{Na} the number of sodium channels per node. The conventional voltage- and time-dependent probability of a sodium channel to be in the open state is expressed as m^3h; m represents the activation and h the inactivation process, and these parameters are described by first order kinetics leading to voltage-dependent time constants τ_m and τ_h, respectively. More recent work has demonstrated that the inactivation process in myelinated nerve fibers of frog[8] and rat[25] is better approximated by a sequence of at least 2 inactivated states (see also the chapter by Neumcke).

The potassium current is similarly described by:

$$I_K = n^4 N_K \gamma_K (E - E_K), \quad (2)$$

and its activation is correspondingly determined by first-order kinetics for n with a voltage-dependent time constant τ_n. Also for the potassium channels a slow inactivation process is assumed[29], but this is not to be considered further.

To describe current-voltage relations of sodium and potassium currents in the node of Ranvier a better approximation is often obtained if permeabilities instead of conductances are used. Nevertheless, in the following we continue to use conductances since this is the directly accessible parameter in voltage-clamp experiments, and conversion into permeabilities is based on further assumptions of ion permeation.

The conventional voltage-clamp technique

The development of conventional fast voltage-clamp techniques[33] not only led to a detailed description of the voltage- and time-dependent Hodgkin-Huxley parameters m, h and n, but with the combined application of various ions, drugs, toxins and enzymes model conceptions for the sodium and potassium channels could be elaborated, demonstrating spatially separated and highly selective pore proteins. Such experiments not only contribute to the elucidation of steric and chemical conformations of functionally important components of the channel protein including the selectivity filter and gating structures[16], they also help to develop a detailed understanding of mechanisms of drug and toxin action, and the regulation of channel activity e.g. by protein phosphorylation can be investigated.

The measurement of gating currents

Since the membrane potential regulates the gating of sodium and potassium channels, the channel proteins must possess a structural component that senses the electric field in the membrane. This could either be a dipolar constituent or a charged aminoacid residue; the movement of these charges by alterations in the electric field will lead to alteration in the conformation of the channel protein resulting in activation or inactivation of the channel. Such structures were already postulated by Hodgkin and Huxley[17] and the movement of these charges should give a contribution to intramembraneous current I_C. If the membrane holding potential is set to a hyperpolarizing level which brings all channels into a closed activatable state, then voltage steps symmetric to the holding potential should lead to asymmetric movements of gating charges. Small asymmetric displacement currents were already observed for a long time but only in 1973 a first report appeared describing displacement currents in squid axon that were related to the gating of sodium channels[3]. In myelinated nerve fibers, analysis of such *gating* currents was first performed by Nonner, Rojas & Stämpfli in 1975[28]. Figure 1,A shows records of membrane currents during a depolarizing voltage-clamp pulse; outward currents through potassium-selective channels were blocked by internal cesium ions and externally applied TEA^+ (tetraethylammonium), and symmetrical capacity and leak currents were subtracted. The transient sodium inward current and a tiny, nearly imperceptible, outward-directed and asymmetrical displacement current (see inset fig. 1,A) are left. Since several pharmacological modifications of the sodium current activation also influence these displacement

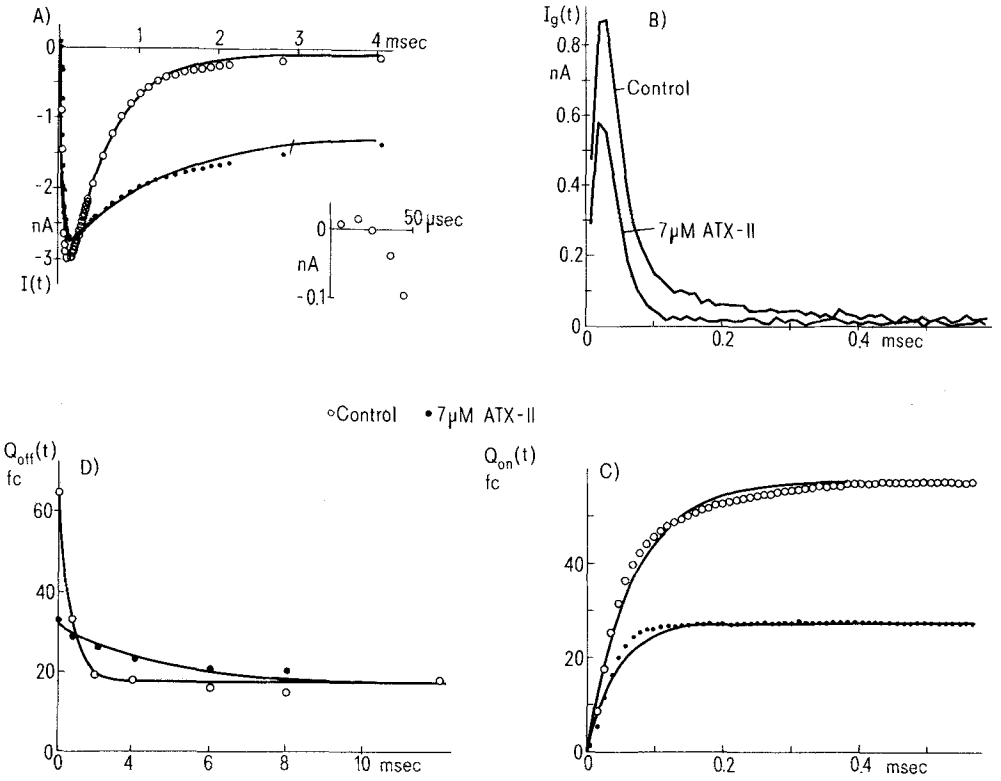

Figure 1. Effect of ATX-II on sodium currents and asymmetrical displacement currents in frog nerve fibers. The control solution had the following composition: 110 mM NaCl, 1.8 mM $CaCl_2$, 4 mM MOPS buffer adjusted to pH 7.2 with NaOH, 10 mM TEA Cl. For the measurement of displacement current sodium was replaced by tetramethylammonium and 300 nM TTX were added. For test solutions 7 µM ATX-II were added to the control solution. Temperature 18 °C. All experiments by Neumcke, Schwarz and Stämpfli, unpublished.
A Sodium current during a depolarizing test potential to +30 mV applied from the holding potential of −90 mV. The lines represent fits of $A(1\text{-}\exp(-t/\tau_m))^3\exp(-t/\tau_h)+C$ to the data points:
Control: A = −4.4 nA τ_m = 44 µsec τ_h = 0.51 msec C = −0.08 nA.
Test: A = −3.1 nA τ_m = 38 µsec τ_h = 1.26 msec C = −1.2 nA.
The inset is a magnified section of the early current in control solution (Exp. G8/3, 10).
B Asymmetrical displacement currents obtained by subtracting the displacement currents elicited by 2 hyperpolarizing pulses of −50 mV from the displacement current elicited by a depolarizing pulse of + 100 mV. The pulses were applied from a holding potential of − 100 mV (Exp. G18/1, 6).
C Charge movements obtained by integration of the currents in figure 1a and by subtraction of a linearly increasing component of charge movement. The lines represent fits of:
$Q_{max}(1\text{-}\exp(-t/\tau_{on}))$ to the data points:
Control: Q_{max} = 57 fC τ_{on} = 65 µsec.
Test: Q_{max} = 28 fC τ_{on} = 45 µsec.
D Immobilization of charge movements during a depolarizing testpulse to +30 mV determined from the asymmetric charge movements elicited by the end of the test pulse (off-response). The lines represent fits of:
$A\exp(-t/\tau_{im})+17.5$ fC to the data points (mean of 2 experiments, Exp. G14/16).
Control: A = 48 fC τ_{im} = 0.35 msec.
Test: A = 14 fC τ_{im} = 2.33 msec.

currents (for review[1,2,20]), there is general agreement that at least a fraction of this displacement current is related to movement of gating particles of sodium channels. Analysis of these *gating* currents from such a record is difficult because of their smallness and their overlapping with the activation of sodium currents. It is believed that application of TTX (tetrodotoxin) blocks the pathway for sodium ions but leaves the gating machinery intact; with the assumption (but see later) that sodium channel gating is uninfluenced after application of TTX, the asymmetrical displacement current (see fig. 1, B) can be investigated in detail. Figure 1, C shows the amount of charge movement obtained by integration of the displacement current of figure 1, B; the time course can be approximated by a fast exponential component which has a time constant similar to τ_m (see figure legend) and is assumed to represent the movement of gating charges of sodium activation. An additional slow component is attributed by some authors to charge movements unrelated to channel gating or may be a component related e.g. to inactivation of sodium channels[34] or to activation of potassium channels[6]. In myelinated nerve fibers this component has not yet been analyzed in detail. Though there are several indications that the fast displacement current represents the gating of the activation of sodium channels, no direct relation between the charge movement and the Hodgkin-

Huxley parameter m (or a power of m) can be drawn. This discrepancy is interpreted by the existence of several activated but not yet conducting states. Several drugs are known to influence the charge movements differently compared to the ionic current[1,2,20]; the toxin II of *Anemonia sulcata* (ATX II), for example, has only minor effects on the amplitude and time constant of sodium current activation (fig. 1,A) but for the displacement currents the amount of charge movement as well as the time constant are drastically reduced (fig. 1, B and C). It is possible that this indicates the existence of conducting states which are not influenced by ATX; comparison of ionic currents and gating currents can, therefore, yield information about the existence of different conducting or non-conducting states. A complication in the interpretation may arise from the possibility that, with drug application, only a fraction of channels becomes modified[23].

In myelinated nerve fibers charge movements that could be related to the inactivation process h have not been discovered with certainty (but see Nonner[27]. Because of the large time constant τ_h compared to τ_m (fig. 1,A) these currents should be even smaller than the gating currents for the activation process m. But another feature of asymmetric displacement currents can be observed that is related to sodium current inactivation. With progressive inactivation of the sodium current during a depolarizing test pulse immobilization of gating currents elicited with the onset of the test pulse (on-response) develops[28]: only for short pulses (200 µsec) the fast charge movement during the on-response equals the charges redistributed after the end of the test pulse (off-response). With increasing pulse duration the off-response declines with a time constant similar to the inactivation time constant τ_h (fig. 1,D)[27]. This coupling of the activation *gating* current with immobilization is taken as evidence for a coupled activation-inactivation mechanism in contrast to the Hodgkin-Huxley formulation[27]. Modification of the sodium current inactivation again influences the immobilization of charge movement. This is exemplified when figures 1,A and 1,D are compared; here, the effect of ATX II on sodium current inactivation and charge immobilization is demonstrated. As is true for the activation process, also the inactivation process cannot directly be related to the immobilization of gating charges, but comparison of the 2 features can again yield information about conducting and non-conducting transition states of a model describing the gating of sodium channels[27]. For such an extended comparison, one should keep in mind that gating currents are always measured with blocked ion movement; thus, possible interactions of permeating ions with gating particles or modifying drug molecules are excluded. For potassium channels for example, it could be demonstrated that the movement of ions influences the kinetics of channel gating (see Swenson and Armstrong[35]), and apparent discrepancies between sodium current inactivation and charge immobilization in the presence of local anesthetics were attributed to competition of sodium ions and drug molecules in channels not blocked by TTX[24].

From the voltage-dependence of the sodium conductance one can calculate the minimum of charges to be moved for the activation of one sodium channel. Accepting that the measured asymmetric displacement current is *gating* current and that all channels act independently with only 2 states (open and closed), then the number of channels per node and the conductance of a single channel can be estimated. Table 1 lists values reported for frog[28] and rabbit[9]; they are of the same order of magnitude, but significant differences are apparent which might be due to differences in the temperature, in ionic composition of the bath solution and in the species. In addition, the assumption of a simple two-state model is probably not suitable (see above) and the effective charge of gating particles is strongly model-dependent[20]. Thus, estimations of the number and conductance of single channels from model-independent calculations are more reliable (see table 2, below).

Single-channel recordings

Some of the above described estimations for the sodium channel parameters are based on the assumption that a channel has only a single conductance level. There are several reasons supporting this idea, but proof could be obtained only if current through single channels could be measured. There is as yet no technique available that allows such detection in the node of Ranvier with its extremly high channel density. But by means of the patch-clamp technique

Table 1

	Frog[28]	Rabbit[24]
Q_{max} (10^3)	860	400
q_{min}	3.5	5
N_{Na} (10^3)	250	80
γ_{Na} (pS)	3	9.8

Q_{max}: Maximum charge movement (unit charges/node); q_{min}: minimum of charges per channel to be moved for sodium activation; obtained from the steepness of the voltage dependence of sodium activation.

Table 2

	Sodium channels		Potassium channels Frog[22]	
	Frog[26]	Rat[25]	Sensory	Motor
N (10^3)	74	21	57	52
γ (pS)	9.8	14.5	4.6	2.7

N: Number of sodium or potassium channels per node; γ: single-channel conductance. All values refer to a holding potential of about − 100 mV and were determined at 15–20 °C.

applied e.g. to cultured muscle cells[32] it could be demonstrated that a single sodium channel is either closed or in a conducting state with a single conductance level. Also, experiments where sodium channels from nerve preparations were reconstituted into artificial membranes sodium channels were found to have only one conducting level[15]. It is beyond the topic of this review to refer to these types of experiments in greater detail, but it should at least be pointed out that a comparison of the results with the results of conventional voltage clamp, measurement of gating currents and noise analysis (see below) will give valuable information for models of ionic channels in myelinated nerve fibers as long as no other techniques are available to study single channels in the node of Ranvier directly.

Analysis of current noise

Despite the lack of a possibility to study single channels in intact nodes of Ranvier and long before single-channel recordings could be performed on other preparations, single-channel parameters were obtained in voltage-clamp experiments by means of fluctuation analysis. It is not the aim of this article to introduce the reader to the theory of the analysis of current fluctuations; only certain results obtained for myelinated nerve fibers by this technique are to be presented. The interested reader is referred to standard textbooks[5] and a more recent review article[19]. Nevertheless, a brief description is given in the following:

The superposition of single-channel openings and closings originating from a large number of channels leads to the time-dependent currents observed under conventional voltage clamp[32]. From current fluctuations originating from the large number of channels in the node of Ranvier, the number of channels per node and the conductance of a single channel can be extracted. In this sense, fluctuations of sodium and potassium currents can be analyzed if current fluctuations from other noise sources are eliminated[13,19]. Assuming that all channels operate independently and are identical with only 1 conducting level, then one can write for the mean current I and the variance var:

$$I = N \cdot i \cdot p \quad (3a) \qquad var = N \cdot i^2 \cdot p(1-p) \quad (3b)$$

with N being the number of channels per node, i the current through a single channel, and p the probability of a channel to be in the open state. In the case of sodium channels, p is represented by m^3h, and in the case of potassium channels by n^4 (compare eqs 1 and 2). That the channels for sodium as well as for potassium ions operate independently may be inferred from the observations that changes in the number of channels per node have only minor influence on the kinetic parameters, though at extremly large channel densities the conductances of single channels may be reduced[26]. There have been no indications that different conductance levels exist for sodium or potassium channels in the node of Ranvier, but recent patch-clamp experiments on other preparations indicate that different populations of sodium channels may exist[18] and that a potassium channel may have more than 1 conducting level[4]. But these deviations are small and should not considerably influence an estimation of N and i from the above equations. Dividing equation 3b by 3a yields:

$$var/I = i \cdot (1-p) \quad (4)$$

thus by determination of var, I and p the single-channel current and the number of channels can be estimated. Eliminating p from equations 3a and 3b leads to:

$$var = i \cdot I - I^2/N \quad (5)$$

Applying this relation to non-stationary currents[31] by fitting the equation to a set of var(t)/I(t) data allows the determination of N and i without previous estimation of p (see also the concluding chapter by Neumcke).

Another approach to analyzing current fluctuations is based on the determination of autocovariance functions or spectral-density functions which are related to each other by Fourier transformation. In contrast to the previous procedure, for this analysis the assumption of a particular description of channel gating is necessary. For a two-state open-closed model the spectral density S(f) is described by a Lorentzian spectrum:

$$S_L = S_0/(1+(f/f_c)^2) \quad (6)$$

The corner frequency f_c is related to the rate constants of the open-closed transition, k_1 and k_{-1}, by $2\pi f_c = (k_1 + k_{-1})$. This special situation is fullfilled for a first-order blocking reaction for an open channel. The blockade of ionic channels in the nodal membrane has not been investigated by this technique, but e.g. the blockade of potassium-selective channels in frog muscle by cesium ions yields such a Lorentzian spectral density[30].

The kinetics of sodium-channel gating can be approximated by the m^3h process; since the inactivation h is a much slower process than the activation m, the spectral density can be described by the sum of an activation (S_m) and an inactivation spectrum (S_h) (fig. 2,A). The m and h processes are defined by first-order reactions, and thus S_h is a simple Lorentzian spectrum with corner frequency $f_c = 1/(2\pi\tau_h)$ and S_m is the sum of three Lorentzian spectra with corner frequencies $f_{c1} = 1/(2\pi\tau_m)$, $f_{c2} = 1/(4\pi\tau_m)$ and $f_{c3} = 1/(6\pi\tau_m)$. So close together are f_{c1}, f_{c2} and f_{c3}, that they cannot be resolved in the spectrum; also by fit

procedures a discrimination of different powers of m is not possible since in the frequency range of three orders of magnitude a distinction of more than 2 corner frequencies is difficult. Therefore, only extreme cases of kinetic models can be deduced from the analysis of spectral density functions.

Another extreme of channel gating is a linear sequence of closed states followed by a linear sequence of open states with equal rate constants for all transitions. In this case the spectral density is described by the diffusion spectrum[19]:

$$S_D = S_1/(1+(f/f_c)^{3/2}) \quad (7)$$

which shows again 1 corner frequency but decays at high frequencies only with a power of 3/2. A reasonable approximation of such a gating scheme is obtained for the description of potassium-current fluctuations which is demonstrated in figure 2,B. While for the Lorentzian spectra the corner frequencies f_c are easily related to macroscopically observable time constants, simple relations cannot be formulated for the corner frequency of a diffusion spectrum[19].

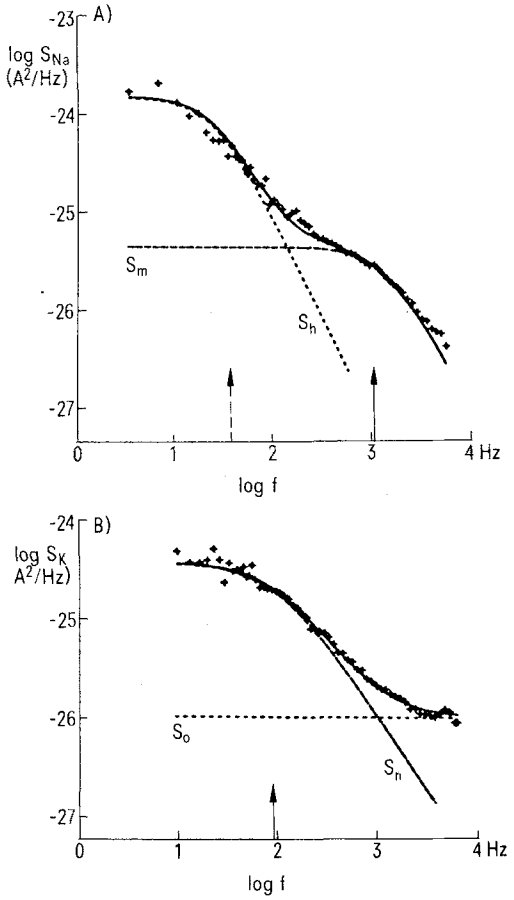

Figure 2. Spectral densities calculated from current fluctuations of frog nerve fibers as described by Conti et al.[13] (taken from Neumcke[19]). *A* Spectral density of sodium current fluctuations during a depolarizing test potential to −30 mV applied from a holding potential of about −100 mV. The solid line represents a fit of Lorentian spectra (see text) to the data points; the location of the corner frequencies corresponding to τ_m and τ_h are indicated by the arrows.
B Spectral density of potassium current fluctuations during a depolarizing testpotential to −46 mV applied from the resting potential of −70 mV. The solid line represents the fit of a diffusion spectrum (eq. 7) plus a frequency-independent background to the data points. The corner frequency is indicated by the arrow.

Since the integral of the spectral density is equal to the variance var, single-channel parameters can again be calculated using equation 3. Calculation of the variance from the spectral density by means of a particular gating model has the advantage that contributions of noise not originating from channel gating are more easily discovered and can be ommitted (see, e.g., fig. 2,B). Single-channel parameters determined by one of the described methods for different myelinated nerve fibers are listed in table 2. All data refer to a holding potential of about 30 mV more negative with respect to the resting potential; this is important to mention since the single-channel conductance as well as the number of activatable channels vary with the holding potential[21]. Scatter in the data reported for sodium channels in nerve fibers of frog may be due to the uncertainty of estimation of p (see eq. 4). For the analysis of non-stationary current fluctuations by equation 5 (see also the chapter by Neumcke) knowledge of p in not necessary, thus comparison of data (table 2) obtained by this method are more reliable and suggest that the single-channel conductance of amphibian sodium channels is slightly smaller than in mammals, but the number of channels per node is higher (compare the chapter by Rosenbluth). Between motor and sensory fibers no differences were found for sodium channels - neither in amphibians (frog) nor in mammals (rat). In contrast, the conductance of single potassium channels in sensory nerve fibers of frog is, by nearly a factor of 2, higher than in motor fibers and may partly account for the differences in action potentials in the two types of nerve fibers.

For the estimation of the parameters of single potassium channels the frequency-independent component S_0 (fig. 2,B) was assumed not to be related to potassium current fluctuations. But if this component were originating from high-frequency closures interrupting open channels (as observed in single-channel recordings of other preparations) the value of the single-channel conductance would be too small and the number of channels per node too high. Since no corner frequency can be observed for S_0 in the frequency range up to 5 kHz, no predictions can be made on its contribution.

Practically no potassium channels are found in intact nodes of Ranvier of mammals; differences in the leak conductance probably contribute in this case to the differences in sensory and motor action potentials. While sodium channels are restricted to the nodal area, potassium channels are also observed in the paranode and internode of frog as well as mammals

after demyelination[10,11] (see also the chapter by Brismar).

Concluding remarks

The interpretation of measurement of displacement currents and current fluctuations is based on assumptions about single-channel properties which can only be verified by single-channel recordings. Even if such experiments could be performed on node of Ranvier the above sections demonstrate that detailed information about kinetic models for sodium and potassium channels can easily be obtained by the described techniques.

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