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Analysing ion channels with hidden Markov models

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Abstract. Ion channel current amplitudes (μ) and open probabilities (P_o) have been analysed so far by defining a 50% threshold to distinguish between open and closed states of the channels. With this standard method (SM) it is very difficult or even impossible to analyse channels of different size in one membrane patch correctly. A stochastical model, named the hidden Markov model (HMM), separates between observation noise and the stochastic process of opening and closing of ion channels. The HMM allows the independent analysis of μ, P_o, and mean dwell times (τ) of different channels in one membrane patch, without defining threshold levels. Using this method errors in the analysis are not summarized like in the SM because all different analysing procedures (e. g. filtering, setting of threshold, fitting processes) are done in one step. Two different K^+ channels in excised basolateral membranes of the cortical collecting duct of rat (CCD) were analysed by the SM and the HMM. The μ value of the intermediate-conductance K^+ channel (i-K^+) was 3.9 ± 0.1 pA (SM) and 3.8 ± 0.2 pA (HMM) for 11 observations. The P_o value of this channel was $10.2 \pm 4.2\%$ (SM) and $10.1 \pm 4.0\%$ (HMM). The mean τ values were 5.4 ± 0.6 ms for the open state and 9.6 ± 2.2 ms and 145 ± 21 ms for the closed states (SM) and 7.8 ± 1.1 ms, 7.7 ± 0.9 ms and 148 ± 24 ms (HMM), respectively. For seven small-conductance K^+ (s-K^+) channels, which were found in the same membrane patches as the i-K^+, an accurate analysis of P_o and τ was not possible with the SM. The μ value was 1.0 ± 0.1 (SM), 0.9 ± 0.1 (HMM) pA. P_o was $16.6 \pm 4.6\%$, the open τ value was 11.1 ± 2.8 ms, and the closed τ value was 34.9 ± 8.5 ms. The HMM allows the analysis of single-channel currents, P_o, and mean τ values when different or more than one ion channel(s) are colocalized in one membrane patch. Where analysis with the SM was possible results did not significantly differ from those obtained with the HMM. Thus for this kind of analysis the method of setting a 50% threshold appears justified.

Key words: Cortical collecting duct – K^+ channel – Rat – Isolated tubule – Patch clamp

Introduction

The analysis of patch-clamp recordings of ion channel currents is problematic when different, or a multitude of channels are present in one membrane patch. So far channel currents have been analysed by standard methods (SM) [4], or slightly modified versions. These methods are limited if different channels are present in one membrane patch, or the membrane contains a multitude of channels. In such cases an accurate analysis is only possible for the current amplitude (μ). To solve these problems a new method was introduced, the hidden Markov model (HMM) [3, 8]. The HMM can be considered as probabilistic functions of Markov chains [1], or as stochastic automatas [10]. HMMs are known in speech recognition as a good tool to distinguish between different words [11]. In ion channel analysis the different parameters of HMM describe the properties of the ion channels. Recently these models were also used to analyse neuronal activity [12]. In the present study HMM was used to analyse patch-clamp recordings of two different K^+ channels of the basolateral membrane of isolated rat cortical collecting duct (CCD) [9]. The results obtained with the HMM are compared to those available with SM.

Materials and methods

The CCDs were isolated from female Wistar rats (Savo, Kisslegg, Germany) with a body weight of 100–200 g. The kidneys were perfused in vivo via the renal artery with sterile culture medium containing 50 000 units/l collagenase and 2000 units/l pronase (both Sigma, Deisenhofen, Germany). After perfusion the kidney was taken out and cortical slices were cut off the kidney. These slices were incubated for 10 min with a Ringer type solution containing the enzymes and gassed by 97% O_2/3% CO_2. This incuba-

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tion procedure yielded different tubule segments which were kept at 4°C. CCD segments were identified by their dimensions and appearance at 40× magnitude. The detailed isolation procedure has been described before [9].

Standard analysis method. Data were recorded with a patch-clamp amplifier and stored on a video recorder. Single-channel currents, open probabilities (P_o) and dwell times (τ) were analysed after low-pass filtering at 1 kHz (8-pole Bessel filter, type 902, Krohn-Hite, Avon, Mass., USA) and A/D-conversion with an AT 486 computer system with a sampling rate of 2 kHz using patch-clamp analysis software developed by ourselves. μ and P_o were determined by setting a baseline optically in the middle of the noise (closed state) and a second line close to the top of the open events of the channel. The single-channel amplitude was defined as the current between open and closed state and the minimum amount of channels present in the patch was estimated before starting the analysis from the number of current levels which were maximally reached during the whole experiment. The threshold was automatically defined as the 50% level of the open state. Each event which was larger than the defined threshold was therefore accepted as an open event and it counted as a closed event if it was smaller. The sum of all times in which the single-channel current was at least 50% of the single-channel μ value divided by the total analysis time equals P_o. The mean τ for open and closed states (τ_o and τ_c, respectively) were analysed by fitting exponential (1 or 2 exponents) curves to the τ histograms. A determination of P_o and τ could only be calculated for the larger ion channel, because the small-conductance K^+ (s-K^+) channel had an amplitude of less than 50% of that of the intermediate-conductance K^+ (i-K^+) channel. Furthermore, an assumption for analysing the τ with the SM was the presence of only one channel in the membrane patch.

Hidden Markov model. The same data as described for the SM were transfered to an IBM Risc 6000 workstation, but now sampled with 10 kHz after low-pass filtering at 10 kHz which is the intrinsic cut-off frequency of the amplifier.

There are two assumptions about the data which must hold if the results are to be meaningful:

1. The measured current should be Gaussian distributed with a mean depending on the state of the ion channels. We tested that for the used amplifier and this is the case if no further filters are used.

2. The measured current is stationary, i. e. amplitudes, etc. do not change during the measurement. Otherwise one calculates an averaged value which might have no meaning.

Data for HMM analysis should be nonfiltered to make sure that the noise is Gaussian distributed. The HMM was fitted to the data. The model given here differs slightly from other known similar models [3]. An HMM consists of an unobservable stationary finite state Markov process $s = (s_1, \ldots, s_T)$, where s_t, $1 \le t \le T$, may be in one of the states $i \in \{1, \ldots, N\}$. Transitions occur with conditional probabilities $a_{ij} = P(j \mid i)$. Together with initial probabilities $\pi_i = P(s_1)$ this defines a Markov chain. Furthermore, a HMM relates a sequence of observations $\underline{\varkappa} = (\varkappa_1, \ldots, \varkappa_T)$ with T as the total length of observation time. For the analysis of ion channels $\varkappa_t$ is the measured current at time t which depends on the respective state s_t, i. e. the observation (= meausred current) is described by the density $P(\varkappa_t \mid s_t)$.

Each state of the Markov process indicates a special number and type of open or closed ion channels, e. g. if there are two different channels: state $i = 1$ means all channels are closed, $i = 2$ the smaller channel is open (the other closed), $i = 3$ the greater channel is open (the other closed), and $i = 4$ both channels are open. So the situation of this example can be described by an HMM with $N = 4$ states. As we said before, we assume each observation $\varkappa_t$ to be a Gaussian distributed random variable,

$$P(\varkappa_t \mid \mu_i, \sigma_i^2) = \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp\left[-\frac{(\varkappa_t - \mu_i)^2}{2\sigma_i^2}\right] \tag{1}$$

with mean μ_i and variance σ_i^2, depending on the respective state $s_t = i$ for all $t \in \{1, \ldots, T\}$. The observation sequence describes a certain channel current with additional noise.

The HMM used here is described by the following parameters $\vec{\lambda}$:

1. Transition probabilities $A = (a_{ij};\ i,j = 1, \ldots, N)$,
2. Initial state probabilities $\Pi = (\pi_i;\ i = 1, \ldots, N)$,
3. Mean currents $M = (\mu_i;\ i = 1, \ldots, N)$, and
4. Variances $\Sigma = (\sigma_i^2;\ i = 1, \ldots, N)$.

The estimation of these parameters was done by a standard algorithm called expectation-maximization (EM) algorithm [5] or in this certain case of HMM it is called Baum-Welch-algorithm [1]. The number of states N of the Markov process has to be presumed before the estimation. The correct estimation of the number of states N can be proven by a statistical test. A comparison of the estimated distribution of the likelihood with the expected distribution of the likelihood of the HMM is the basis of this statistical test [2]. The data of the HMM were fitted to HMM with increasing numbers of states N until the test no longer rejected the HMM.

The EM-algorithm is an iterative maximum likelihood algorithm and is started with:

$$a_{ij} = \begin{cases} 0.9 \text{ for } i = j \\ \dfrac{0.1}{N-1} \text{ for } i \neq j \end{cases} \qquad (i,j \in \{1, \ldots N\}),$$

$$\pi_i = \frac{1}{N} \text{ for } i = 1, \ldots, N$$

The means μ_i are differently chosen near the average of the data and the variances σ_i^2 are set to the total variance of the data.

Iteration is done as follows:

$$\hat{a}_{ij} = \frac{\sum_{t=1}^{T-1} \psi_{ij}(t)}{\sum_{t=1}^{T} \Psi_i(t)}, \tag{2}$$

$$\hat{\pi}_i = \Psi_i(1), \tag{3}$$

$$\hat{\mu}_i = \frac{\sum_{t=1}^{T} \Psi_i(t) \varkappa_t}{\sum_{t=1}^{T} \Psi_i(t)}, \tag{4}$$

$$\hat{\sigma}_i^2 = \frac{\sum_{t=1}^{T} \Psi_i(t)(\varkappa_t - \mu_i)^2}{\sum_{t=1}^{T} \Psi_i(t)}, \tag{5}$$

where $\psi_{ij}(t) = P(s_{t+1} = j, s_t = i \mid \underline{\varkappa}, \vec{\lambda})$ – i. e. the probability being in state i at time t and in state j at time $t + 1$ given the observation $\underline{\varkappa}$ and the model parameters $\vec{\lambda}$ – and $\Psi_i(t) = P(s_t = i \mid \underline{\varkappa}, \vec{\lambda})$. So these equations can be understood intuitively, interpreting the probabilities as frequencies, e. g. Eq. (2) is the sum of all times jumping from state i into state j normalized by the sum of the times staying in state i. The mathematic theory of the EM algorithm guarantees that the iteration converges.

The probabilities $\psi_{ij}(t)$ and $\Psi_i(t)$ can be calculated via the quantities $\alpha_i(t)$ and $\beta_i(t)$ defined for all $i \in \{1, \ldots, N\}$ and $t \in \{1, \ldots, T\}$ by [11]:

$$\alpha_i(t) := \begin{cases} \pi_i \mathrm{P}(\varkappa_1 \mid \mu_i, \sigma_i^2) & \text{for } t = 1 \\ \sum_{j=1}^{N} \alpha_j(t-1) a_{ji} P(\varkappa_t \mid \mu_i, \sigma_i^2) & \text{else,} \end{cases}$$

$$\beta_i(t) := \begin{cases} 1 & \text{for } t = T \\ \sum_{j=1}^{N} a_{ij} P(\varkappa_{t+1} \mid \mu_j, \sigma_j^2) \beta_j(t+1) & \text{else} \end{cases}$$

Table 1. Comparison of the standard method (SM) with the hidden Markov method (HMM) using simulated data

Parameter				
Method	μ (pA)	P_o (%)	τ_o (ms)	τ_c (ms)
Real	1.5	68.4	50.0	20.0
HMM	1.51 ± 0.04	67.9 ± 2.4	47.6 ± 2.3	20.5 ± 0.8
SM (no filter)	1.40 ± 0.17	59.4 ± 5.0	0.29 ± 0.02	0.29 ± 0.02
SM (10 kHz)	1.51 ± 0.05	68.7 ± 4.3	3.6 ± 0.3	3.3 ± 0.1
SM (5 kHz)	1.50 ± 0.04	68.6 ± 2.3	11.8 ± 0.3	10.0 ± 1.0
SM (1 kHz)	1.48 ± 0.09	65.9 ± 2.6	38.5 ± 6.0	20.0 ± 2.4

The analysis with SM was done with filtered data with different cut-off frequencies (in parentheses). In the first row the values of the simulation are shown. Mean dwell times can only be calculated with SM correctly if one uses deep filters. HMM evaluate all values with fewer errors.

μ, Current amplitude; P_o, open probability; τ_o, dwell time in the open state, τ_c, dwell time in the closed state

Following [11], that leads to:

$$\psi_{ij}(t) = \frac{a_{ij}\alpha_i(t)\beta_j(t+1)P(\varkappa_{t+1}\,|\,\mu_j,\sigma_j^2)}{P(\underline{\varkappa}\,|\,\vec{\lambda})}$$

and

$$\Psi_i(t) = \frac{\alpha_i(t)\beta_i(t)}{P(\underline{\varkappa}\,|\,\vec{\lambda})}$$

where the normalization factor$P(\underline{\varkappa}\,|\,\vec{\lambda})$ is the likelihood of the data and can be calculated as:

$$P(\underline{\varkappa}\,|\,\vec{\lambda}) = \sum_{i=1}^{N}\alpha_i(T).$$

For the actual iteration this factor can be dropped in all of Eqs. 2–5. The iterations are stopped when the parameters are not significantly changed anymore.

The single-channel μ value is given by the difference of the estimated current μ_i of the closed state i and μ_j for the open state j. P_o was calculated from the parameters A and Π.

It is possible to calculate the τ values from the parameters of the HMM. But there are some numerical difficulties if there are more than one channel in the same patch, or if there is more than one mean τ for one state. To avoid these problems we suggest a more vivid solution for this problem which introduces another property of HMM and leads to the same results without much more expense. An analysis of τ can be done as for SM. Therefore the most probable state sequence $\underline{s}$ of the HMM – i. e. the different states of the ion channels for the whole measurement – is estimated via the Viterbi algorithm [11, 13]. This algorithm estimates the most probable state for each time taking into consideration the whole observation sequence. Thus, it is more than just asking for the most probable state using Eq. 1 or each sampled value. Having the state sequence, i. e. knowing the state of all ion channels for each time – one can use the procedure as described for SM to estimate the mean τ.

Results

First we tested the algorithm with simulated data (10 sets, 500 000 data points each). We simulated one ion channel with a current amplitude of 1.5 pA, a mean τ in the open state of 50 ms and 20 ms in the closed state and a noise with a standard deviation of 1.5 pA (unfiltered). Table 1 shows the comparison of the results of both methods. With HMM one obtains smaller errors. For the analysis of mean τ with SM one has to use a deep filter to suppress random level crossings whereas the P_o can be estimated independently because the number of random level crossings is independent of the state.

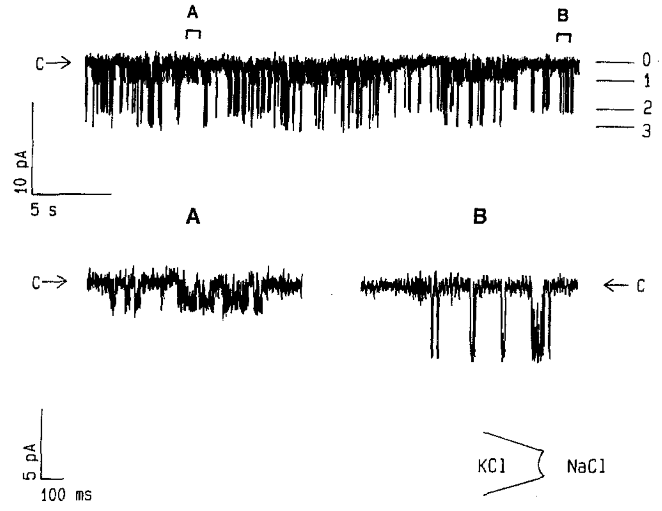

Fig. 1. Original current traces of K$^+$ channels from the basolateral membrane (excised inside-out) of isolated rat cortical collecting duct (CCD), low-pass filtered with a cut-off frequency of 1 kHz. The *upper trace* shows colocalization of a small-conductance K$^+$ (s-K$^+$) channel (*0–1*) and an intermediate-conductane K$^+$ (i-K$^+$) channel (*0–2*). *0–3*, Both channels are open at the same time. The *lower traces* depict examples on an expanded time scale. *Right panel*, i-K$^+$ channel; *left panel*, s-K$^+$ channel. *C →* indicates the closed state of the channels

In the basolateral membrane of rat CCD two different K$^+$ channels were found, a 28-pS (s-K$^+$) and a 85-pS (i-K$^+$) K$^+$ channel (excised with 145 mmol/l KCl in pipette and 145 mmol/l NaCl in bath, 0 mV clamp voltage). Both channels were very active on the cell but the latter one showed only moderate activity when excised in the inside-out configuration. Both K$^+$ channels have been described in more detail recently [9]. An example of the two channels which are often colocalized in one membrane is given in Fig. 1.

The results for 11 different experiments analysed with both methods are compared in Tables 2 and 3. In all cases a recording of 50 s – i. e. 500 000 data points – was used for the analysis with SM and HMM. The amount of channels deduced by the statistical test for N in HMM was always the same as suggested for SM from the filtered data. The μ value of the i-K$^+$ channel was 3.9 ± 0.1 pA (SM) and 3.8 ± 0.2 pA (HMM). P_o of this channel was 10.2 ± 4.2% (SM) and 10.1 ± 4.0% (HMM). The mean τ values were 5.4 ± 0.6 ms for the open state and 9.6 ± 2.2 ms and 145 ± 21 ms for the closed states (SM) and 7.8 ± 1.1 ms, 7.7 ± 0.9 ms, and 148 ± 24 ms (HMM), respectively. There was a large variance in the P_o and the τ between different recordings. This is probably mostly due to the biological run-down of the channel [9] – i. e. P_o decreased and closed τ (τ_c) increased with time. Figure 2

Table 2. Results of the analysis of 11 different recordings of the intermediate-conductance (i-K$^+$) channel with SM and HMM

	SM					HMM				
	μ (pA)	P_o (%)	τ_o (ms)	τ_{c1} (ms)	τ_{c2} (ms)	μ (pA)	P_o (%)	τ_o (ms)	τ_{c1} (ms)	τ_{c2} (ms)
1	3.9	5.0	4.6	22.0	230	4.5	3.1	11.4	9.4	312
2	3.9	7.0	4.5	20.0	190	3.5	9.0	12.5	7.6	130
3	3.9	5.0	4.5	20.0	130	4.0	3.8	10.3	13.1	90
4	4.5	10.0	4.5	7.1	58	3.3	14.6	7.0	8.1	105
5	3.9	8.0	3.9	5.1	77	3.8	7.8	4.3	5.3	95
6	3.5	13.0	4.8	3.2	230	3.3	9.9	6.0	6.4	76
7	3.7	3.0	4.3	5.6	220	3.4	5.1	6.9	3.8	130
8	4.5	51.0	9.4	3.1	97	4.2	48.3	11.7	6.9	115
9	4.0	7.0	8.0	8.9	110	4.8	5.4	8.7	10.4	260
10	4.1	1.5	7.6	4.4	110	3.2	1.8	2.5	9.7	150
11	3.4	2.0	3.1	6.1	–	3.5	2.7	4.5	4.0	90
Σ	3.9	10.2	5.4	9.6	145	3.8	10.1	7.8	7.7	148
SEM	0.1	4.2	0.6	2.2	21	0.2	4.0	1.1	0.9	24

Σ, Mean; P_o, open probability; τ_o, dwell time in open state; τ_{cn}, dwell time in closed state. The mean values were not significantly different in any case between analysis with the SM or the HMM. –, Not evaluable

Table 3. Results of the analysis of seven different recordings of the small-conductance (s-K$^+$) channel with SM and HMM

	SM	HMM			
	μ (pA)	μ (pA)	P_o (%)	τ_o (ms)	τ_c (ms)
1	1.0	0.8	20.6	21.0	27.2
3	1.0	1.2	14.8	19.9	55.0
4	0.9	0.7	19.8	12.1	49.7
6	1.0	0.7	2.2	4.3	60.0
7	0.8	0.5	35.2	5.5	2.3
9	1.8	1.3	20.5	8.7	19.6
11	1.0	1.4	3.2	5.3	30.4
Σ	1.0	0.9	16.6	11.1	34.9
SEM	0.1	0.1	4.6	2.8	8.5

With the SM only μ could be analysed (see text). μ was not significantly different between the two methods

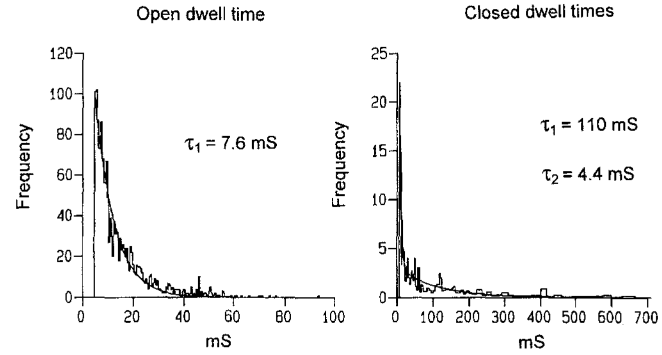

Fig. 2. Open and closed dwell times of an i-K$^+$ channel from the basolateral membrane (excised inside-out) of isolated rat CCD analysed with the SM. The dwell time histograms were fitted by single exponential (τ_1 for open dwell time) or biexponential (τ_1 and τ_2) curves

Table 4. Standard deviation for 11 different recordings analysed with the HMM

	Closed (pA)	s-K$^+$		i-K$^+$
		1 open (pA)	2 open (pA)	open (pA)
1	1.90	1.98		2.11
2	2.46			2.55
3	1.91	2.06	2.14	2.39
4	1.83	1.83	1.89	1.95
5	1.30			1.54
6	1.28	1.46		1.34
7	2.16			2.32
8	1.56	1.57	1.66	1.82
9	1.61	1.65		1.80
10	1.52			1.65
11	1.56	1.72		1.77

There were not data with more than one i-K$^+$ channel

gives an example for the τ of an i-K$^+$ channel after filtering for analysis with SM.

For seven s-K$^+$ channels an analysis of P_o and the mean τ values was not possible with the SM, as the opening of the i-K$^+$ is always analysed as an opening of the s-K$^+$ (see Fig. 1). For the s-K$^+$ channel a μ value of 1.0 ± 0.1 pA was obtained. With the HMM, μ was 0.9 ± 0.1 pA, P_o was 16.6 ± 4.6% and mean open τ (τ_o) reached 11.1 ± 2.8 ms. The mean closed τ value was 34.9 ± 8.5 ms. For one experiment it was impossible to find an accurate transition matrix for the s-K$^+$ channel and this experiment was therefore omitted. All mean values were calculated with both methods and were compared with paired Student's t-test. None of them were significantly different (98% level).

With the HMM it was possible to evaluate the standard deviation of the noise as well.

The noise was slightly larger if channels were open. The difference between the standard deviation of the closed state and the open state of the s-K$^+$ channel was 0.09 ± 0.03 pA, between the closed state and two open channels of this type was 0.13 ± 0.02 pA, and between the closed state and the open state of the i-K$^+$ channel was 0.19 ± 0.03 pA. These values are shown in Table 4.

The absolute magnitude of the noise and its deviation between individual experiments was due to different seal qualities of the membrane. Therefore only the changes of the standard deviation are meaningful.

It is possible to calculate errors for the parameters of each HMM and therefore for the P_o, μ, and τ from a single measurement as well. Nevertheless, the error of these values of a single measurement was always by far less than the variance between different experiments. So this error was neglected in this study.

Discussion

The analysis of single ion channels with the SM of setting current levels for the closed and the open state of the channels and setting a 50% threshold level is certainly the appropriate method to obtain values for the μ, P_o, open and closed τ values. This analysis is mathematically easy and can be done within a reasonable time scale (5–10 min for such an experiment) using a 386/486 personal computer.

When different types of channels – as in the present case – or a multitude of identical channels are present in one membrane patch the SM is either impossible to use or gives at least grossly impaired results. In the present case, recordings of a smaller and a larger channel, which are independent, however, very often appear in one membrane patch. Whenever these channels are colocalized, the error in analysing P_o and τ of the i-K^+ channel was small, as the μ value of the s-K^+ channel is below 50% of that of i-K^+, however, when analysing the s-K^+ the opening of the i-K^+ cannot be distinguished from that of the s-K^+ by the SM. Thus, P_o and τ cannot be exactly analysed. HMM allows, however, the analysis of P_o and τ for the s-K^+ channel currents in the present example as well.

A major advantage of the HMM is the use of data without deep filtering, without defining open and closed state current levels, or setting a threshold level. The HMM can also analyse different kinds of channels and a multitude of channels in one membrane patch. HMM analysis with current hardware and software for these data takes much longer (about 50 h for each recording). This is not acceptable for routine analysis, which is, however, not necessary as SM is obviously sufficient enough. Note, however, that HMM only uses machines time as analysis is done mostly automatically, whereas SM uses man power and machines will be faster soon.

The validity of HMM for analysis of such data was tested with simulated data. The analysis of these data showed that HMM leads to more precise results than SM.

Our first aim was to examine whether the analysis of ion channel parameters with the SM and HMM reveal comparable results for those parameters which can be easily obtained with the SM. This was indeed the case. SM and HMM give equal results for μ, P_o and τ for the i-K^+, and for μ of the s-K^+.

Furthermore HMM allowed in addition to the presented data analysis of channel properties for membranes with a multitude of very active ion channels where individual current levels were no longer visible or for channels which have a current amplitude in the range or below the noise band. The s-K^+ of this study has a μ value of less than the standard deviation of the noise, when no low-pass filters are used (compared Tables 2 and 4). The amplitude of this channel can only be analysed with the SM when data are strongly filtered.

In conclusion, HMM is the most powerful known tool for analysis of single-channel recordings, though the cost is a high amount of computer power and time.

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