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Variances in spectral analysis of membrane noise

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SEZIONE III

(Botanica, zoologia, fisiologia e patologia)

Fisiologia. — *Variances in spectral analysis of membrane noise* (*). Nota di FRANCESCO ANDRIETTI e CARLA CANEGALLO, presentata (**) dal Corrisp. V. CAPRARO.

RIASSUNTO. — Le fluttuazioni di conduttanza di un modello di canale del potassio di una fibra muscolare che segue una cinetica di Hodgkin e Huxley sono state analizzate attraverso l'analisi spettrale indiretta. Sono state confrontate due diverse stime della densità spettrale e le loro rispettive varianze: quella della prima stima considerata è già nota, mentre quella della seconda stima è stata ricavata da noi nelle medesime ipotesi (distribuzione normale). I risultati teorici sono stati confrontati con quelli ottenuti mediante simulazione numerica del processo stazionario in questione. Sono state sviluppate alcune considerazioni sul significato del nostro lavoro per quanto riguarda l'analisi del rumore di membrana: il miglior uso delle stime spettrali, sia dirette che indirette, la lunghezza delle sequenze dei segnali di entrata, l'utilizzazione di « finestre » di vario genere.

INTRODUCTION

Spectral analysis, as well as other kinds of statistical analyses of membrane noise, have been widely used in the past to obtain information about some aspects of biological membranes, as for example an estimate of the number of ionic channels. Spectral analysis has been mainly applied to artificial membranes, neuromuscular junctions, nervous and muscular fibers (a review of this subject has been given by Neher and Stevens, [1]). It has been performed by means of analogue or digital procedures.

The present paper is concerned with this second method and more specifically with the method of decreasing the variance of computed spectra of conductance fluctuations. It does not deal with the different disturbances that arise from the use of amplifiers, data processing, thermal noise and the $1/f$ component associated with the leak ionic pathway (see, for example, Stevens, [2]; Conti, De Felice and Wanke, [3]). Instead what has been considered is a model of potassium ionic channel of muscular fibre, even if the results we have ob-

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(**) Nella seduta del 14 aprile 1984.

tained may be also used in the analysis of other ionic currents for the similarity in the shape of their power spectra ([3], [4], [5]).

The theory and the numerical methods we have used are to a great extent standard in the current literature. Our work consists mainly of their application to a well known stochastic model of ionic current fluctuations, in order to improve its spectral analysis. With regard to the variance of a particular estimate of noise spectrum, $\hat{S}_2(f)$ (see further), we have obtained some results that seem to be original.

The model

Following the well known Hodgkin and Huxley model [6], we assume that the potassium channel permeability depends on the presence of four statistically independent sub-units. Each of them exists in an excited or in a non-excited state with probabilities p_1 and p_0 respectively. When all four sub-units of the channel are in the excited state the channel is open and its conductance is g. Otherwise it is closed and its conductance is zero. As long as we are interested in the statistical aspects of spectral analysis we will not consider other possible schemes of ionic conductance, as that given by Hill and Chen [7] and Chen and Hill [8] for multi-state channels.

In steady-state conditions p_0 and p_1 are time-independent and $p_0 = \beta/(\alpha + \beta)$, $p_1 = \alpha/(\alpha + \beta)$, where α and β are experimentally determined by fitting the voltage-clamp potassium current to that predicted by the Hodgkin and Huxley kinetics. Let us now indicate with P_{01} the probability of finding a channel closed at time t_0 and open at time $t_0 + \Delta t$ and with P_{11} that of finding a channel open at time t_0 and open at time $t_0 + \Delta t$. In steady-state conditions the process is stationary and P_{01} and P_{11} will depend only on the value of Δt. It will be

$$P_{01}(\Delta t) + P_{11}(\Delta t) = P_1 = p_1^4$$

where P_1 is the probability of finding the channel in an open state. Since $P_{11}(\Delta t) = p_1^4 p_{1/1}^4(\Delta t)$, where $p_{1/1}(\Delta t)$ is the conditional probability that one sub-unit be in an excited state at time Δt provided that it is in an excited state at time 0, one has

$$P_{01}(\Delta t) = p_1^4 - p_1^4 p_{1/1}^4(\Delta t) .$$

From the Bayes' formula we have the conditional probability that a channel is open at time t provided that it is closed at time 0

$$P_{1/0}(\Delta t) = \frac{P_{01}(\Delta t)}{P_0} = \frac{p_1^4 - p_1^4 p_{1/1}^4(\Delta t)}{1 - p_1^4}$$

and $p_{1/1}(\Delta t)$ is given by the Hodgkin and Huxley equation [6]

$$p_{1/1}(\Delta t) = \frac{\alpha}{\alpha + \beta} + \left(1 - \frac{\alpha}{\alpha + \beta}\right) \exp\left(-\frac{\Delta t}{\alpha + \beta}\right)$$

The conditional probability $P_{0/1}(\Delta t)$ is

$$P_{0/1}(\Delta t) = 1 - P_{1/1}(\Delta t) = 1 - p^4_{1/1}(\Delta t) .$$

In our simulation we have used a value of $\alpha = 0.05$ msec^{-1}, $\beta = 0.01$ msec^{-1}. These are the rounded values experimentally found in our laboratory (Dr. Peres, personal communication) for the semi-tendinous muscle of *Rana Esculenta* at a membrane potential of -20 mV and they are not far from those given in the literature for the same potential and temperature (about 3 °C) of similar fibres (Adrian, Chandler and Hodgkin, [9]).

In order to avoid aliasing effects in the use of fast Fourier transform algorithms we have taken a sampling interval $\Delta t = 0.4 f_d = 4$ msec (Bendat and Piersol, [10], p. 321), where $f_d = 100$ Hz is the cut-off frequency. This is because the range of interest of spectral analysis of conductance fluctuations, as appears from the current literature, lies approximately between 0 and 100 Hz. The input was generated according to the value of $P_{1/0}(\Delta t)$ and $P_{0/1}(\Delta t)$ of the model and was represented by 2^N points spaced by Δt. N ranged between 7 and 9. The upper limit was due to the limited storage capacity of our microcomputer. The output was represented by 2^N points spaced by $1/(2^N \Delta t)$ in the frequency domain. However our figures will show only a 32 points output from 0 to 60.5 Hz.

The spectral analysis was performed on the zero mean random variable $x(t) = g(t) - gP_1$. According to our model the autocovariance function of $x(t)$ is

$$R(r) = E[x(t)\, x(t + |r|)] = g^2 P_1 P_{1/1}(r) - g^2 P_1^2 .$$

Putting $P_{1/1}(r) = p^1_{1/1}(r)$ one finds after some straightforward calculations

$$R(r) = g^2 P_1^4 \sum_{j=i}^{4} \binom{4}{j} P_1^{4-j} (1 - P_1)^j \exp(-jr/\gamma)$$

where $\gamma = 1/(\alpha + \beta)$.

The power spectrum is

$$S(f) = \int_{-\infty}^{\infty} R(r) \exp(-2\pi i f r)\, dr = g^2 P_1^4 \sum_{j=1}^{4} \binom{4}{j} P_1^{4-j} (1 - P_1)^j \frac{2\gamma/j}{1 + (2\pi f \gamma/j)^2}$$

The power spectrum of potassium conductance fiuctuations has been used for different purposes. One of them is that of determining the number of ionic channels. In fact if n is the number of channels present in a given area of the membrane and if the activities of single channels are statistically independent, then the total power spectrum due to the contribution of all channels is $S^{tot}(f) = nS(f)$. As a value of ng may be experimentally determined by a

measure of the total conductance, fitting the results of the spectral analysis to $S^{tot}(f)$ will give an estimate of n and g.

Spectral analysis has been used also to see if the kinetics of a single potassium or sodium channel is that effectively predicted by the Hodgkin and Huxley model for the average kinetics of many channels, as we have assumed in our analysis ([1], [11]).

Given that the numerical value of g does not affect the statistical properties of the results, in our computations we have taken $g = 1$.

Indirect spectral analysis

We shall consider two different estimates of the autocovariance function

$$\hat{R}_1(r) = (1/T) \int_0^{T-|r|} x(t)\, x(t + |r|)\, dt$$

$$\hat{R}_2(r) = (1/T) \int_0^{T} x(t)\, x(t + |r|)\, dt .$$

The corresponding spectral estimates will be

$$\hat{S}_1(f) = \int_{-T}^{T} \hat{R}_1(r) \exp(-i\, 2\pi f r)\, dr$$

$$\hat{S}_2(f) = \int_{-T}^{T} \hat{R}_2(r) \exp(-i\, 2\pi f r)\, dr .$$

The variance of spectral estimates in general is unknown. But in case of Normal processes one has ([12], p. 415)

$$\mathrm{Var}\,[\hat{S}_1(f)] = (1/T^2)\left\{ \int_{-\infty}^{\infty} S(x) \frac{\sin \pi T (f-x)}{\pi (f-x)} \frac{\sin \pi T (f+x)}{\pi (f+x)}\, dx \right.$$

$$\int_{-\infty}^{\infty} S(y) \frac{\sin \pi T (f+y)}{\pi (f+y)} \frac{\sin \pi T (f-y)}{\pi (f-y)}\, dy +$$

$$\left. + \int_{-\infty}^{\infty} S(x) \frac{\sin^2 \pi T (f-x)}{\pi^2 (f-x)^2}\, dx \int_{-\infty}^{\infty} S(y) \frac{\sin^2 \pi T (f+y)}{\pi^2 (f+y)^2}\, dy \right\} .$$

This result may be simplified for Normal processes whose spectra are approximately constant around the value of f, since the term $S(f)$ may be taken outside the integral. In fact from Jenkins and Watts' formula (A9.1.16) [12], letting $f_1 = f_2 = f$, one has

$$\text{(1)} \qquad \text{Var}\,[\,\hat{S}_1(f)\,] \approx S^2(f)\left\{\frac{\sin 2\pi T f}{2\pi T f} + 1\right\}$$

this result is exact for Normal white noise processes.

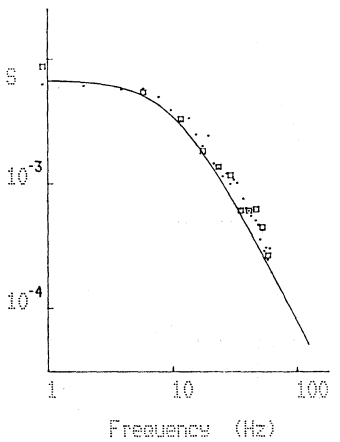

Fig. 1. – (·) Average values of 80 computed spectral estimates $\hat{S}_1(f)$ for N = 7; (□) standard deviations of (·); the continuous line represents $S(f)$. The values at the left of the ordinate axis represent the values corresponding to 0 Hz.

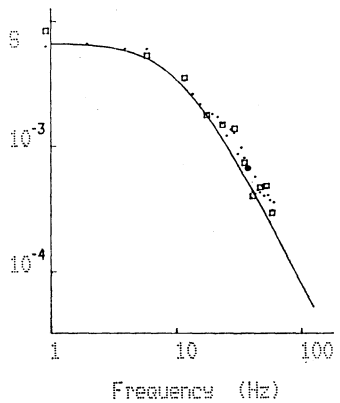

Fig. 2. – As fig. 1 for N = 9.

From Andrietti [13] the variance of $\hat{S}_2(f)$ yields

$$\text{Var}\,[\,\hat{S}_2(f)\,] = (2/T^2)\left\{\int_{-\infty}^{\infty}\frac{\sin^2 2\pi sT}{4\pi^2 s^2}\,ds\int_{-\infty}^{\infty}S(s+g)\,S(s-g)\,\frac{\sin 2\pi(f+g)T}{\pi(f+g)}\right.$$

$$\left.\cdot\,\frac{\sin 2\pi(f-g)T}{\pi(f-g)}\,dg + \int_{-\infty}^{\infty}\frac{\sin^2 2\pi s T}{4\pi^2 s^2}\,ds\int_{-\infty}^{\infty}S(s+g)\,S(s-g)\frac{\sin^2 2\pi(f-g)T}{\pi^2(f-g)^2}\,dg\right\}.$$

For random processes whose spectra are approximately constant around f the term $S(f)$ may be taken outside the integral and for the limit case $f_1 = f_2 = f$, one obtains [13]

$$\text{(2)} \qquad \text{Var}\,[\,\hat{S}_2(f)]\,] \approx S^2(f)\left\{\frac{\sin 4\pi T f}{2\pi T f} + 2\right\}.$$

This result is exact for Normal white noise processes. It shows that the variance of $\hat{S}_2(f)$ is *larger* than that of $\hat{S}_1(f)$ contrary to what could be conjectured on the basis that a greater number of signals should *improve* the variance ([14], p. 67).

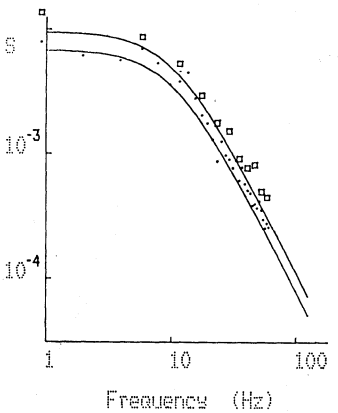

Fig. 3. - (·) Average values of 80 computed spectral estimates $\hat{S}_2(f)$ for $N = 7$; (□) standard deviations of (·); the lower continuous line represents $S(f)$ and the upper one $\sqrt{2}\,S(f)$.

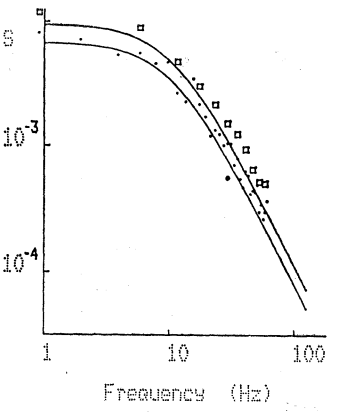

Fig. 4. - As fig. 3 for $N = 9$.

In any case (1) and (2) show that when the value of T is large the standard deviations of $\hat{S}_1(f)$ and $\hat{S}_2(f)$, for spectra approximately constant around f, become

$$\sqrt{\mathrm{Var}\,[\hat{S}_1(f)]} \approx S(f) \tag{3}$$

$$\sqrt{\mathrm{Var}\,[\hat{S}_2(f)]} \approx \sqrt{2}\,S(f)\,. \tag{4}$$

The trigonometric terms in the right hand side of (1) and (2) give rise to some damped oscillations of the variances around the value given by (3) and (4). These oscillations for $f = 2$ are less than 16% for (1) and 8% for (2) for $N = 7$ and decrease when f and N increase. In figs. 1-4 are shown the average values of 80 spectra calculated with the indirect method for $N = 7$, $N = 9$, together with their standard deviations. One may see that the standard deviations are well represented by (3) and (4). The higher values for $f = 0$ are probably due to the trigonometric terms in (1) and (2).

WINDOWS

We will consider the spectral estimates given by

$$\hat{S}_1(f) = \int_{-\infty}^{\infty} \hat{R}_1(r)\, w_l(r) \exp(-i\, 2\pi fr)\, dr$$

$$\hat{S}_2(f) = \int_{-\infty}^{\infty} \hat{R}_2(r)\, w_l(r) \exp(-i\, 2\pi fr)\, dr$$

where $w_l(r)$ is a lag window, with $w_l(r) = 0$ for $r > M$. It may be shown that for Normal processes whose spectra are approximately constant over the width of the lag window, when $M \ll T$, the standard deviation of $\hat{S}_1(f)$ may be approximated (12, p. 418)

$$\sqrt{\mathrm{Var}\,[\hat{S}_1(f)]} \approx \left\{ \frac{S^2(f)}{T} \int_{-M}^{M} w_l^2(u)\, du \right\}^{1/2}. \tag{5}$$

Andrietti [13] has shown that the same formula holds for $\hat{S}_2(f)$ and in this case the result does not require $M \ll T$.

In figs. 5 and 6 one may see the decrease of the standard deviations when boxcar windows are used. We observe that what is important is the relative

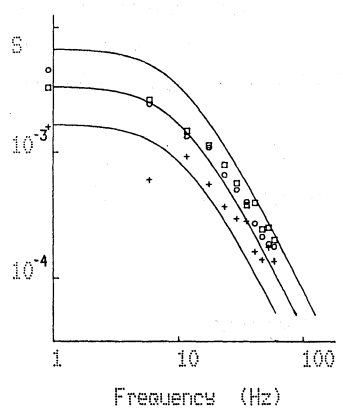

Fig. 5. – Standard deviations of 80 computed spectral estimates $\widehat{S}_1(f)$ with boxcar windows: (○) N = 9, M = 64 Δt; (□) N = 8, M = 32 Δt; (+) N = 9, M = 16 Δt. The upper continuous line represents S (f); the intermediate line represents the predicted standard deviation of (○) and (□); the lower line the predicted standard deviation of (+).

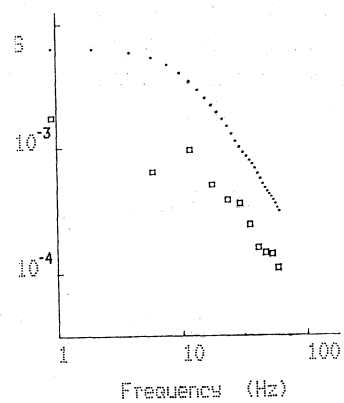

Fig. 6. – (·) Average values of 80 computed spectral estimates $\widehat{S}_2(f)$ with a boxcar window, N = 9, M = 16 Δt; (□) standard deviation of (·).

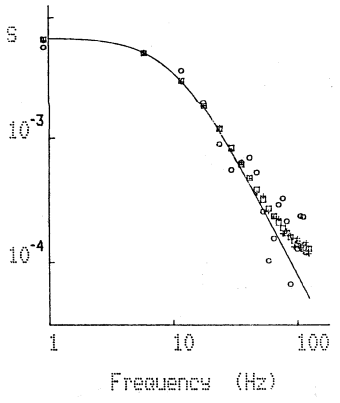

Fig. 7. - Theoretical biased spectra (according to (6)) for N = 7 and boxcar windows: (□) M = 128 Δt; (+) M = 16 Δt; (○) M = 8 Δt. The continuous line represents S (f).

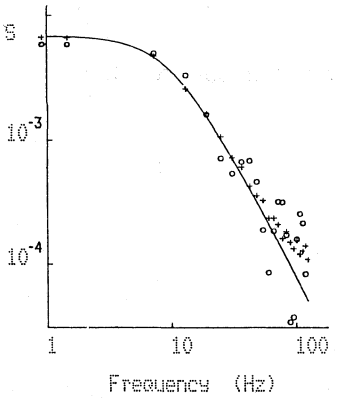

Fig. 8. - Theoretical biased spectra (according to (6)) for N = 9 and boxcar windows: (+) M = 16 Δt; (○) M = 8 Δt. The continuous line presents S (f).

energy of the window, i.e. the ratio between the window area and the record time length, so that approximately the same results are obtained when both M and T are halved. It is also apparent that the variance decrease is rather well predicted by (5) and is about the same for $\hat{S}_1(f)$ or $\hat{S}_2(f)$. In fig. 6 the average values of 80 spectra are also shown. One sees that they can be fitted by a much smoother line that those of figs. 1-4.

To what extent can the window width be reduced? It may be shown that, making the base width of the lag window narrower, the variance of the estimated spectrum decreases and at the same time its bias, i.e. the difference between the expected value of the spectral estimate and S (f), increases [12], p. 246). It will be

$$E[\hat{S}_1(f)] = \int_{-M}^{M} \frac{T - |r|}{T} R(r)\, w_l(r) \exp(-i 2\pi f r)\, dr \tag{6}$$

$$E[\hat{S}_2(f)] = \int_{-M}^{M} R(r)\, w_l(r) \exp(-i 2\pi f r)\, dr\,. \tag{7}$$

The bias of $\hat{S}_1(f)$ is larger than that of $\hat{S}_2(f)$ and $E[\hat{S}_1(f)] \to E[\hat{S}_2(f)]$ when $T \to \infty$. When $w_l(r) = 1$ one obtains the bias for a boxcar window and if moreover M is replaced by T one has the bias for the case in which no windows are used.

We may try to find the maximum boxcar window width for which the bias is not too high. In figs. 7 and 8 the biased spectra are represented according to the discrete formulation of (6). It is apparent that changing from N = 7 to N = 9 does not greatly influence the results. This is due to the fact that

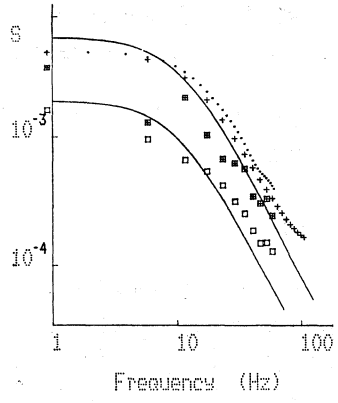

Fig. 9. – Effect of an algebraic window with $\delta = 1$, $N = 7$, $M = 16\ \Delta t$ on the average values of 80 computed spectral estimates $\widehat{S}_1(f)$ (·), on their standard deviations (□) and on the corresponding theoretical biased spectrum (+). Standard deviation of a boxcar window of the same width (▪▪). The lower continuous line represents the predicted value of (□); the upper line represents S (f).

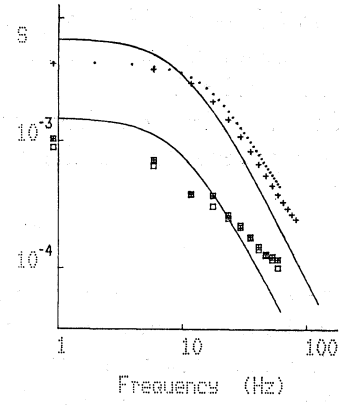

Fig. 10. – Effect of an algebraic window with $\delta = 2$, $N = 7$, $M = 16\ \Delta t$ on the average values of 80 computed spectral estimates $\widehat{S}_1(f)$ (·), on their standard deviation (□) and on the corresponding. theoretical biased spectrum (+). Standard deviation of the same algebraic window for the estimate $\widehat{S}_2(f)$ (▪▪). The lower continuous line represents the predicted value of (□) and (▪▪). The upper line represents S (f).

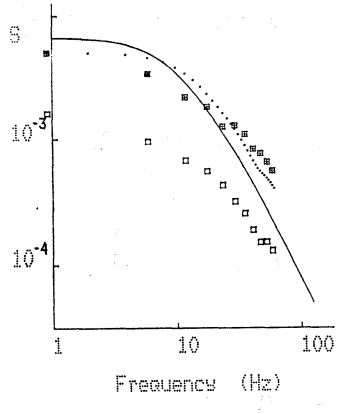

Fig. 11. – (·), (□) As fig. 9 for a different train of input signals; (▪▪) standard deviation calculated from the values of 80 spectral estimates $\widehat{S}_d(f)$, computed through the direct method, with an « equivalent » window (see text). The continuous line represents S (f).

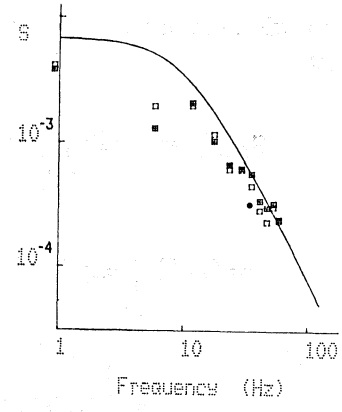

Fig. 12. – Standard deviation for one channel (▪▪) and for 100 channels (□) calculated from the values of 80 computed spectral estimates $\widehat{S}_1(f)$ with a boxcar window, $N = 7$, $M = 16\ \Delta t$. The continuos line represents S (f).

the term $(T - |r|)/T$ is very close to 1 for $|r| \leq M$. Moreover $M = 16\,\Delta t$ seems to be a limit value under which the biased spectrum becomes very distant from the unbiased one.

Our considerations have been confirmed with other kinds of windows. Fig. 9 represents the results obtained with a window

$$w_l(u) = (1 - |r|/M)^{\delta}$$

with $\delta = 1$. One sees that now the decrease of the standard deviations is higher than in the case of boxcar windows. The computed average spectrum is much smoother and closely follows the biased spectrum given by (6). In fig. 10 the case for $\delta = 2$ is shown, together with the standard deviation found for $\hat{S}_2(f)$. One sees that a larger value of δ (and so a decrease of the relative energy of the window) decreases the standard deviation, making the average computed spectra still smoother, and at the same time increases the bias, as we should expect. In any case algebraic windows always show minor standard deviations and higher bias than boxcar windows of the same width.

Direct spectral analysis

When the spectrum estimate is performed by means of the direct method, i.e.

$$S_d(f) = (1/T)\left|\int_0^T x(t)\exp(-i\,2\pi f t)\,dt\right|^2$$

and no windows are used, it is easy to show that $\hat{S}_d(f) = \hat{S}_1(f)$ ([14], p. 77). In fact

$$\hat{S}_d(f) = (1/T)\int_0^T\int_0^T x(t)\,x(v)\exp(-i\,2\pi f(t-v))\,dt\,dv$$

$$= (1/T)\int_{-T}^{T}\exp(-i\,2\pi f r)\left\{\int_0^{T-|r|} x(v)\,x(v+|r|)\,dv\right\}dr$$

$$= \int_{-T}^{T}\hat{R}_1(r)\exp(-i\,2\pi f r)\,dr = \hat{S}_1(f)\,.$$

Instead when a boxcar window is used in the direct case, its effect will be only that of decreasing the number of available data, i.e. of changing N. When other data windows are used, one obtains different results. We do not know of any explicit expression for the variance in this case, when a window $w_d(u)$

is applied to the data to be processed. In fig. 11 the use of a window in both the direct and the indirect method is shown. For the indirect method an algebraic window with $\delta = 1$, $M = 16\,\Delta t$ has been used. In the direct case we used a window « equivalent » to the preceding one, i.e. a window giving the same bias in the direct method of the algebraic window in the indirect one ([14], p. 96). We compared also the effect in direct and indirect method of the same window of the cosine family, largely used in direct spectral analysis ([10], p. 325; [15]).

Our results, not shown here, showed no improvement in the average computed spectra.

DISCUSSION

We wish to develop here some considerations on the practical use of what we have seen above.

When a sequence of data has to be processed, it may be useful to divide the whole sequence into shorter ones in order to obtain better results. We may distinguish between two different cases:

1) the case in which no lag windows are used. In this situation, as we have seen, direct and indirect spectral analyses are equivalent, so that the first method should be preferred, as the computation time is about three times shorter. We have also seen that the variance of the spectra does not depend on the record length. So, the better results, for that which concerns the variance, are obtained with the maximum number of short sequences of signals, for the purpose of averaging on a greater number of spectral estimates. Of course a lower limit to the signal train length will be given by frequency resolution and bias requirement. We found that below the minimum length of $N = 7$, the biased spectrum becomes very different from the unbiased one.

2) The case in which lag windows and the indirect method are used.

In this situation one has a decrease of spectral variance. The same results would be obtained by averaging on the greater number of values obtained from a larger number of shorter signals trains. In this case the processing of longer sequences has to be preferred in order to improve frequency spectral resolution. In principle, in this way the bias should also be improved, but as long as $M \ll T$ the bias depends practically on M and not on T, as we saw above 4.

For what concerns which spectral estimate should be preferred, $\hat{S}_1(f)$ or $\hat{S}_2(f)$, we see no reason in the use of $\hat{S}_2(f)$ when the analysis is digitally performed. When lag windows are used, the variance of $\hat{S}_2(f)$ is the same of that of $\hat{S}_1(f)$, and the improvement of the bias is too low to justify the use of $\hat{S}_2(f)$. We recall that for the computation of $\hat{S}_2(f)$ we are not allowed to use fast Fourier transforms in convolutions and this fact enormously increases the computation time required for the autocovariance function estimate when N is large. Instead, the estimate $\hat{S}_2(f)$ may become of interest in analogue data analysis procedures (see, for example, [10], p. 282).

As we have seen, windows in indirect spectral analysis should be used when the problem to reduce the variance of spectral estimates is important. No systematical attempt has been made to determine the « best » window for what concerns the variance and the bias of on statistical model. We think it should be determined according to the experimental situation and to the particular aim of the research. For example, when spectral analysis is used to determine the number of ionic channels we could take into account the bias making use of (6) and (7).

For what concerns the use of windows in direct spectral analysis, we considered only a few cases in which we found no improvement of the results.

A final point we want to examine is the fact that we have always considered the behaviour of a single channel. In fig. 12 are shown the results obtained with $N = 7$ and a 16 point boxcar window for a single channel and 100 independent channels. In the second case the computed average spectra are divided by 100. Similar results have been obtained both without windows and with other kinds of windows. The main effect of considering many independent channels seems to be that of a multiplicative constant. This is also what we should expect to find on a theoretical basis. In the case of many channels, the sum of many independent open-close processes should only be more « Normal » than a single one.

Things would be different if the activities of single channels were not independent. In this case we would find a higher value of the total power estimated spectrum.

The use of a single channel, instead of many, as one generally does in this kind of modelling, has clearly the advantage of drastically reducing the time of computation.

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