NEGATIVE CAPACITANCE AMPLIFIER FOR MICROELECTRODE INVESTIGATIONS

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In electrophysiological investigations, measurement configurations are preferred which not only supply the single cell potential but are also applicable for further measurement tasks (OOMURA et al. 1966; WAYNER et al. 1967).

In the Biological Research Institute of the Hungarian Academy of Sciences, Tihany, a measurement set-up for solving complex tasks in electrophysiological measurements has been developed which is well suited for multichannel pick-up. The block-diagram of this system utilizing a microelectrode pick-up is shown in Fig. 1. The heart of the system is the low level amplifier with negative capacitance and high input impedance. The input of the amplifier is fed by a measurement bridge which serves to polarize and stimulate the living cell under test, and also to determine the resistance of the microelectrode.

The low level amplifier is followed by an oscilloscope. The amplifier has unity gain, so only the oscilloscope calibration has to be taken into account. A meter for performing amplifier zero adjustment and to determine the resis-

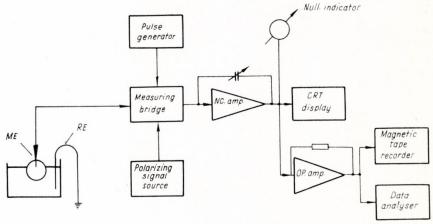


Fig. 1. Block-diagram of measurement set-up used for microelectrode pick-up

tance and tip-potential of the microelectrode is also connected to the low level amplifier output (Schanne et al. 1968). Finally, the low level amplifier feeds a DC amplifier with large negative feedback for high level driving of a signal storage device or an analyser.

The detailed circuit diagram of the system is shown in Fig. 2. An important feature of the system is that two different operating modes are possible. One is the direct operating mode in which the microelectrode is directly connected to the amplifier input. In this case the electrode resistance may

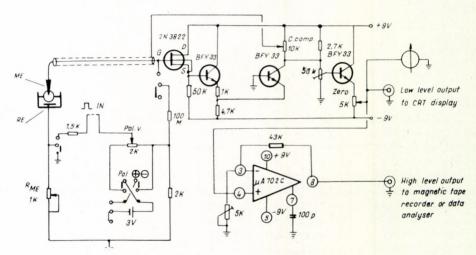


Fig. 2. Circuit diagram of measurement set-up

be neglected compared to the amplifier input resistance, and there is no measurable amplitude loss. This mode is used for recording of spontaneous activity.

In the other operating mode, the measurement bridge is switched to the input. In this case, the cell under test is either stimulated by an external square-wave generator through a suitable Wheatstone-bridge connected to the input, or may be polarized by DC current by using the built-in adjustable current source.

The microelectrode resistance may be checked by the potentiometer serving for the bridge balance which is calibrated in megohm values. Resistances up to 50 megohms may be measured in the bridge arm.

A Texas type 2N3822 N-type field effect transistor is used in the input stage of the low-level amplifier following the bridge, in a source follower configuration (Gosling, 1965; Sevin, 1967). The second transistor is an emitter follower, thus increasing the input resistance of the field effect transistor and as a low impedance current source makes possible the driving of the following common base transistor stage. This has two functions. First, the high amplification allows to realize an adjustable positive feedback to the input for the purpose of neutralizing the capacitance loading the input (Guld, 1962). The feedback loop is capacitively coupled to the input, so the high leakage resistance of the coupling capacitor is an important requirement. Second,

the common base transistor drives the emitter follower supplying the output, comprising the potentiometer for zero adjustment in the emitter circuit.

The low-level amplifier oscilloscope and meter output point drives a Fairchild μ A 702 C DC operational amplifier with non inverting asymmetrical input. The output level of this amplifier is high enough to drive a magnetic signal storage device or an analyser.

The amplifier requires supply voltages of ± 9 volts. Battery operation is made possible by low power consumption, and this made possible a measuring

system with no interfering signals.

Specification data of the negative capacitance amplifier are summarized in $Table\ I$. These have been based on measurement results obtained on 10 actually built amplifiers.

TABLE I

Specification data of the amplifier

$$\label{eq:local_continuity} \begin{split} & \text{Input impedance} \\ & \text{Capacitance compensation referred to the} \\ & \text{input} \\ & \text{Input current I_{GS}} \\ & \text{Frequency response:} \\ & \text{with $R_{\text{ME}}=0$ ohm} \end{split}$$

 $\begin{array}{c} \text{with } R_{\text{ME}} = 10 \text{ megohms} \\ \text{Noise voltage with} \\ R_{\text{ME}} = 10 \text{ megohms} \\ \text{Amplification} \\ \text{Zero adjustmentt} \\ \text{Drift} \end{array}$

Input driving voltage Input overload level Output impedance min. 10^{11} ohms

up to 100 pF max. 10^{-12} amperes

DC to $500 \,\mathrm{kHz}$, flat within $3 \,\mathrm{dB}$ rise time max. $20 \,\mu\mathrm{sec}$

 $\begin{array}{ll} \text{max.} & 120 \; \mu\text{V} \; \text{ p-p} \\ \text{unity} \\ & \pm 100 \; \text{millivolts} \\ 1 \; \text{mV/C}^{\circ} \; \text{ or} \; 1 \; \text{mV/hour} \\ \text{(after one hour warm-up time)} \\ \text{max.} & \pm 1 \; \text{volt} \\ \text{max.} & \pm 50 \; \text{volts} \\ 500 \; \text{ohms} \end{array}$

The pick-up system was measured by the control circuit shown in *Fig.* 3 which proved to be suitable to check the correct system operation during experiments.

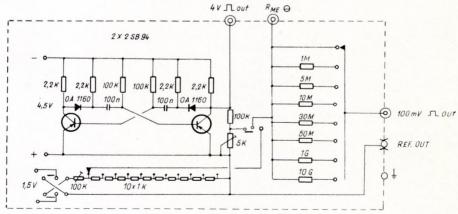


Fig. 3. Circuit diagram of control circuit

The control circuit comprises following parts: an astable multivibrator oscillating at 200 Hz, an adjustable DC voltage standard, and an adjustable high impedance resistance decade. Depending on the measurement problem, either a 100 millivolt square wave or a DC voltage adjustable in 10 mV steps up to 100 mV can be given on the input of the pick-up system through a suitable high resistance. The different parts of the control circuit may also be used independently, as the square-wave signal, the calibrated DC voltage and the high resistance are independently usable.

Measurements performed by using the control circuit of Fig. 3 are summarized in Table II. The block diagram No. 1 in Table II was used to measure the input I_{GS} current of the amplifier. Zeroing the negative capacitance amplifier and using the high resistance of the control circuit voltage

TABLE II

Control measurements carried out on the amplifier $I_{SS} = \frac{V_{GS}}{R}$ $I_{SS} = \frac{V_{GS}}{R}$ R = GRAfter zero adjustments
Ist test temperature balance time
2nd test drift during temperature balance

7. In the control of t

8. Cap. compenzation test circuit

V1 = V2 turn up

4. Gain adjusment with square wave

 V_{GS} was measured, and with the knowledge of R, the current was determined by using the following formula:

$$I_{GS} = \frac{V_{GS}}{R}$$

The amplifier input resistance R_{GS} was measured by using the block-diagram No. 2 in $Table\ II$. The calibrated DC voltage of the control circuit was switched through a high resistance onto the amplifier input, voltages V_1 and V_2 were measured, and knowing R, the input resistance was determined by the formula

$$R_{GS} = \frac{V_2 R}{V_1 - V_2}$$

The stationary transfer characteristic, i.e. the linearity was tested according to block diagram No. 3 in Table II (Telkes, 1968). The calibrated voltage of the control circuit was connected at the amplifier input, and the voltage divider was switched in 10 mV-steps from zero to +100 mV and zero to -100 mV. Measuring V_2 and knowing V_1 , the linearity value was determined for the operating range for our experiments using the formula

$$\operatorname{Lin} = \frac{(V_2 - V_1) \max}{V_1}$$

Block diagram No. 4 in Table II served to calibrate the unity gain of the amplifier. A 100 mV square wave was given on the amplifier input, and an oscilloscope at the output was used to check the equality $V_1 = V_2$.

The amplifier drift under operating conditions was measured by using the block-diagram No. 5 in *Table II*. Adjusting and fixing the zero level of the amplifier with short circuited input, the zero-drift was measured by a digital voltmeter. The time required for reaching thermal equilibrium and the drift after warm-up at room temperature was also measured.

Block diagram No. 6 in Table II served for measuring the output resistance R_{OUT} of the amplifier. A DC voltage from the control circuit was given onto the amplifier input and a voltage V_1 was measured at the output. An adjustable resistance R connected to the output was used to adjust the voltage $V_2 = V_1/2$, and determining the resistance value R required for this condition, the output resistance R_{OUT} was calculated.

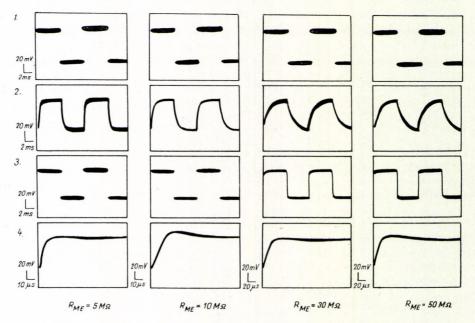
The bridge circuit used to measure the microelectrode resistance was calibrated with the aid of block diagram No. 7 in $Table\ II$. The amplifier was switched into the bridge operating mode, and the high resistance decade of the control circuit was connected to the inputs of the microelectrode and of the reference electrode. The bridge was balanced in all decade steps, and the scale of potentiometer R_{ME} was calibrated in the range of 0 to 50 megohms.

The quality of capacitance compensation was controlled by using the block diagram No. 8 in *Table II*. The square-wave signal of the control circuit was given through the high resistance decade onto the amplifier input. The effects of electrode capacity, cable capacity and other stray capacities loading the input were compensated by a neutralizing circuit. The steps and results of the capacitance compensation investigation are shown by the photographs

of Table III. The four columns of the Table correspond to different series resistance values through which the square wave signal was given on the amplifier input. ($R_{ME}=5$ Mohm, 10 Mohm, 30 Mohm, 50 Mohm). The first row shows the generator square wave signal, the second row shows the amplifier input signal after the resistance without capacitance compensation, and the third row shows the same signal with compensation. Finally, the fourth row shows the expanded leading edge of the square wave in the compensated case.

TABLE III

Responses of capacitance neutralization test with different microelectrode resistances



First row: square vave signal of generator

Second row: amplifier input signal without compensation Third row: amplifier input signal with compensation

Fourth row: expanded view of compensated signal leading edge.

Our control measurements included the investigation of the frequency response and the noise voltage of the amplifier (Schoefeld, 1962). These are summarized in Fig. 4 which shows the frequency responses obtained with different electrode resistances, and also the different noise voltages. All data shown in Fig. 4 are valid for the cases when the amplifier is compensated for the appropriate rise times. The Figure also shows the block-diagram of the measurement set-up.

The photograph of the amplifier is shown by Fig. 5. The unit shown by the photo contains the measurement bridge, the polarizer, the negative

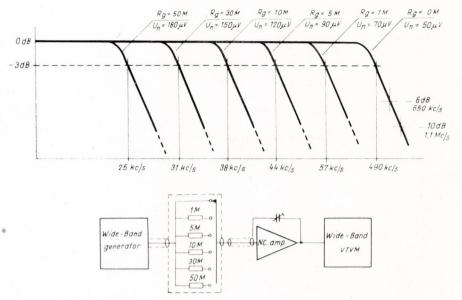


Fig. 4. Amplifier frequency responses with different electrode resistances, and measurement set-up to obtain these responses

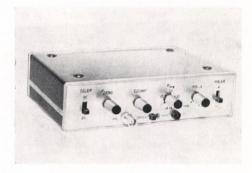


Fig. 5. Photograph of the amplifier for microelectrode pick-up

capacitance amplifier, the DC amplifier and the batteries giving the supply voltages. On the front panel are seen following controls: battery in-out switch, zero adjustment, capacitance compensating, resistance measuring and polarizer voltage adjusting potentiometers, polarity change switch and mode switch. The input BCN connector and the reference electrode input jack are also on the front panel. The high and low level outputs, the connectors for the squarewave generator and the meter are located on the rear panel. Dimensions of the amplifier unit shown in Fig. 5 are $200 \times 130 \times 50$ mm.

Finally, the application fields of the described above system which were actually tried successfully will be enumerated:

1 - In direct operating mode:

— tip-potential investigation of microelectrodes. - measurement of membrane potential in cells,

- recording of spontaneous activity from a single cell or simultaneously from several cells.

- recording in voltage-clamp set-up.

2 - In bridge operating mode:

- measurement of microelectrode resistance,

— polarization by DC current and simultaneous pick-up, - stimulation by square wave and simultaneous pick-up.

- introducing different materials by intracellular iontoforetic mode with simultaneous pick-up.

Summary

A solid state amplifier and different measurement set-ups for micro-

electrode method are investigated by the author.

The preamplifier is supplied with a compensating circuit for neutralization of the input shunt capacity, and has unity gain and high input resistance. The different measurement tasks are handled by a bridge which can be connected to the input. In this way, the object under test may be polarized by DC current or stimulated by a square wave. The measurement bridge also serves for measuring the microelectrode resistance. The visual evaluation of the signals is possible by an oscilloscope connected to the output of the low-level preamplifier. The system has also a high-level output for driving signal storage and signal processing devices.

The control methods of the measurement set-up parameters are summarized in a Table. The parameters have been controlled by a calibrating circuit

which has been also dealt with.

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NEGATÍV KAPACITÁSÚ ERŐSÍTŐ MIKROELEKTRÓDÁS VIZSGÁLATOKHOZ

Véró Mihály

Összefoglalás

A szerző mikroelektród technikához készült félvezetős erősítőt, valamint külön-

böző mérési feladatok elvégzésére alkalmas összeállítást ismertet.

Az előerősítő egységnyi erősítésű, nagy bemenőellenállású és a bemenetet terhelő kapacitás neutralizálására kompenzáló áramkörrel van ellátva. A különböző mérési feladatokat a bemenetre kapcsolható mérőhíd segítségével lehet elvégezni. Így elvezetés közben egyenárammal polarizálni, illetve négyszöghullámmal stimulálni lehet a vizsgált objektumot. Ugyancsak a mérőhíd segítségével lehet megmérni a mikroelektród ellenállását. Az elvezetett jelek vizuális értékelése a kisszintű előerősítő kimenetére kapcsolt oszcilloszkópon történik. Az egyéb jeltárolási és adatfeldolgozási problémák megoldására az elvezető rendszer nagyszintű kimenettel is rendelkezik.

A mérési összeállítás paramétereinek vizsgálati módszerei táblázatban vannak összefoglalva. A paraméterek ellenőrzése a megadott hitelesítő áramkör segítségével

történt.