



The Potentiostat and the Voltage Clamp

by Jackson E. Harrar

In the history of science and technology, there have been many instances when two or more persons have independently created an invention or concept at almost the same time, but for various reasons, one inventor takes precedence or credit. Examples are the telephone, the integrated circuit, calculus in mathematics, and the theory of evolution. Once the invention or concept is introduced, further development soon proceeds along a single path. A rare instance is an innovation that was developed by two different scientists in two different fields at almost the same time, and then widely used for many years in these two fields without the investigators being aware of the other application. This happened in the case of the potentiostat and the voltage clamp, which are basically similar instruments, but whose actual applications are quite dissimilar.

Both the potentiostat and the voltage clamp operate on the principle of negative feedback control. Both instruments employ an amplifier in a feedback arrangement to control the voltage (or electrode potential) in, respectively, an electrolytic cell or a biological specimen. In their simplest forms, they are essentially the same circuit.

In the early 1940s, Archie Hickling at the University of Leicester, England, who was working in the field of electrochemistry, invented the potentiostat and coined the apt name for the device.¹ He used the potentiostat to control the voltage (*i.e.*, the potential) of an electrode to perform electrolysis in an electrolytic cell.

In the late 1940s, at the University of Chicago, Kenneth Cole, with the help of George Marmont, invented an electronic circuit called a voltage clamp,² which was used to investigate ionic conduction in nerves. Concurrently, these voltage clamp techniques were adopted by Alan Hodgkin, Andrew Huxley, and Bernard Katz at Cambridge University in England for their research in this field. In 1963, Hodgkin and Huxley were awarded the Nobel Prize in Physiology or Medicine for this work.

Further development and elaboration of these circuits has been carried on for many years, including the marketing of many commercial instruments—some for electrochemistry and some for biochemistry

and biophysics. In electrochemistry, potentiostats are used for fundamental studies of electrode processes, analytical chemistry, battery research, the synthesis of chemicals, and corrosion research. Variations of the voltage clamp are employed in research on the properties of living biological cells. Adaptations of these instruments have also been made to control the electric current rather than voltage. During most of this time, however, research in these disparate fields of electrochemistry and electrophysiology, and their investigators, has remained virtually independent.

The Potentiostat

Figure 1 shows a simplified version of a potentiostat connected to a three-electrode electrolytic cell. The electrolysis current in the electrolytic cell is provided by the output of the amplifier (Amp) to the cell via the counter electrode (CE). The desired or studied reaction takes place at the working electrode (WE). The reference electrode (RE) senses the potential at the working electrode

and this signal is transmitted to the negative input of the differential amplifier, where it is compared to the desired control voltage (E) at the positive input. The amplifier is a DC-coupled, differential input amplifier. It has a high open-loop gain ($>10^5$), fast response, and its inputs have high input impedances so very little current (nanoamperes) flows in this part of the circuit. The amplifier, by the action of negative feedback, continuously adjusts its output voltage and current to keep the potential measured by the reference electrode equal to the control voltage. The electrolysis current flowing between electrodes CE and WE is measured by additional instrumentation (M) in either the counter electrode part (as shown) or the working electrode part of the circuit.

In electrochemistry, potentiostats are used with working electrodes of inert elements (*e.g.*, platinum, gold, mercury, and carbon), semiconductors, and for corrosion studies, the metal of interest. Sizes range in area from $>100\text{ cm}^2$ for controlled-potential coulometry and electrosynthesis, to very small (radius $<10^3\text{ cm}$) microelectrodes for

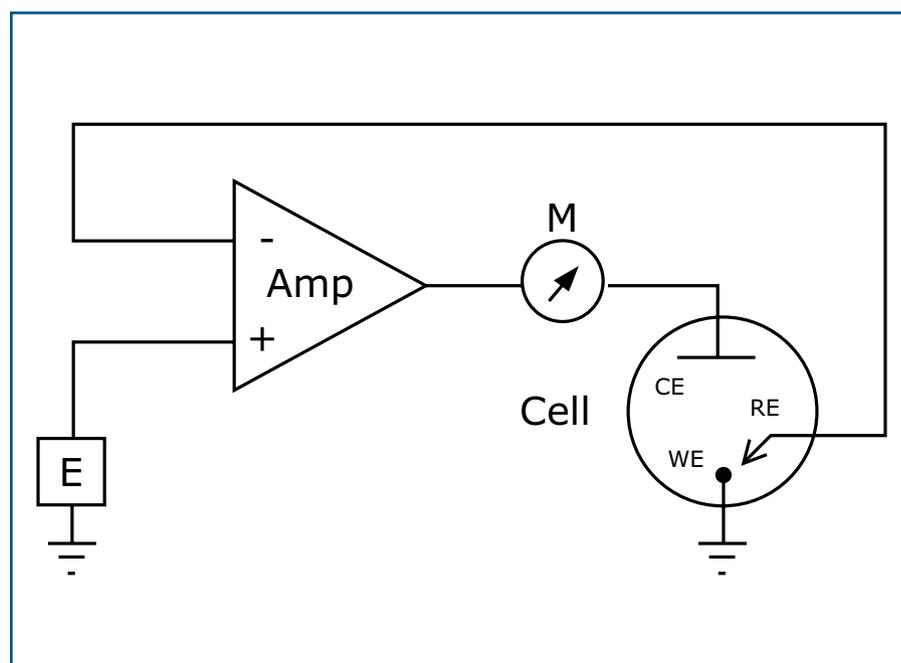


Fig. 1. Simplified potentiostat and three-electrode electrolytic cell.

chemical analysis and fundamental studies.³ Counter electrodes are usually made of platinum, while reference electrodes are most often made of silver, coated with silver chloride, or mercury-mercurous chloride (saturated calomel).

The Voltage Clamp

Figure 2 shows a simplified version of a “two-electrode” voltage clamp connected to an apparatus in which the properties of the membrane of a biological specimen are examined. The specimen in this arrangement is contained in a bathing medium such as saline solution. The electrodes (CE and RE) penetrate the membrane of the specimen. Electrode CE is the current-carrying electrode within the specimen, while the second electrode (RE) senses the potential (with reference to ground) across the membrane. The current flows from electrode CE through the membrane of the specimen to ground. Measurements of the current, in either the amplifier output circuit (M) or the ground circuit, yields information on the properties of the membrane. The electrodes typically are constructed of fine-tipped glass pipets containing a chlorided silver wire or platinum, and the experiments are often performed on a microscope stage.

The similarity of the voltage-clamp configuration to that of the potentiostat is readily apparent. The amplifier/feedback voltage clamp circuit functions the same way it does as a potentiostat to impose a potential equal to the command voltage at the membrane. As in potentiostatic circuits, the current passing through the membrane is measured with auxiliary circuitry not shown in the figure. In the study of nerve cells, early work in voltage clamping revealed information on how sodium and potassium

ions are transported through ion channels in the membrane.^{2,4} Later studies have dealt with calcium and chloride ion flow.

Advances in technique and instrumentation in the field of electrophysiology have led to an apparatus for clamping with a single intracellular electrode, and patch clamping, which enables measuring the properties of single ion channels in a membrane.^{5,6} For the invention of the patch clamp technique, Bert Sakmann and Erwin Neher received the 1991 Nobel Prize in Physiology or Medicine.

Common Problems in the Experiments

Although the electronic circuits of potentiostatic and voltage clamps are similar, the laboratory apparatus and experiments using them are quite different. Nevertheless, some problems that complicate the experiments are present in both fields. Electrophysiologists are always dealing with extremely small microelectrodes which have high resistances that may introduce errors in potential control.⁶ Certain investigations using potentiostats also employ very small working electrodes, and when more exact potential control is required, solution resistances exist that may have to be compensated, particularly at the working electrode.⁷

There are also many electrical capacitance effects that complicate the measurements. First of all, a cell membrane itself constitutes an electrical capacitance that must be charged before the desired potential is established. This is analogous to potentiostatic work in which the working electrode/solution double-layer capacitance must first be charged. There are also “stray” capacitances in both electrolytic and voltage

clamp arrangements that can influence the measurements of high-speed signals.⁶

The stability of the cell/feedback loop in controlling the potential may also be an issue. In the case of potentiostatic measurements, this was examined in terms of classical control-system theory in the 1960s and 1970s,⁷ and has also been addressed for voltage clamp systems.^{6,8} Data interpretation in electrophysiology may also be complicated because the microelectrode contacts a point while the cell is obviously three dimensional. The patch clamp technique is advantageous in this respect because the microelectrode in this configuration is attached directly to an ion channel or small group of ion channels. In both electrochemistry and electrophysiology, quite sophisticated instrumentation has been designed and techniques of data interpretation have been developed to deal with all of these problems.^{5,9}

History

Further development of potentiostatic and voltage clamp instrumentation from the simple circuits described here has proceeded in parallel. The first circuits used amplifiers that were assembled from the individual electronic components (resistors, capacitors, and vacuum tubes). Some early potentiostats also used mechanical servomechanisms. The advent during the 1950s of commercially available, plug-in, modular amplifiers, called operational amplifiers,¹⁰ or “op amps,” made possible many extensions of the basic potentiostat and voltage clamp and more elaborate circuits.^{6,9} At first, using these modular op amps, experimenters who were not trained engineers, but who were versed in electronics, could assemble their own functioning instruments. Quite advanced instruments incorporating integrated-circuit operational amplifiers are now commercially available for many specialized applications in electrochemistry, analytical chemistry, and studies in electrophysiology. These instruments embody features that enable measurement of the electric current during voltage control, or control of the current instead of voltage, operation with very small or very large electrodes, and operation under computer control. Op amps are typically incorporated in the instruments for impedance buffering, current measurement, and resistance compensation.

Returning to a theme of this article, for many years, research in the fields of electrochemistry and electrophysiology has still remained largely independent. Companies marketing instruments and apparatus target one field or the other, but usually not both because the marketing differences are significant. Only a few scientists and engineers in each discipline have been aware of work in the other field. Advances in each field might have occurred somewhat faster if there had been more interaction.

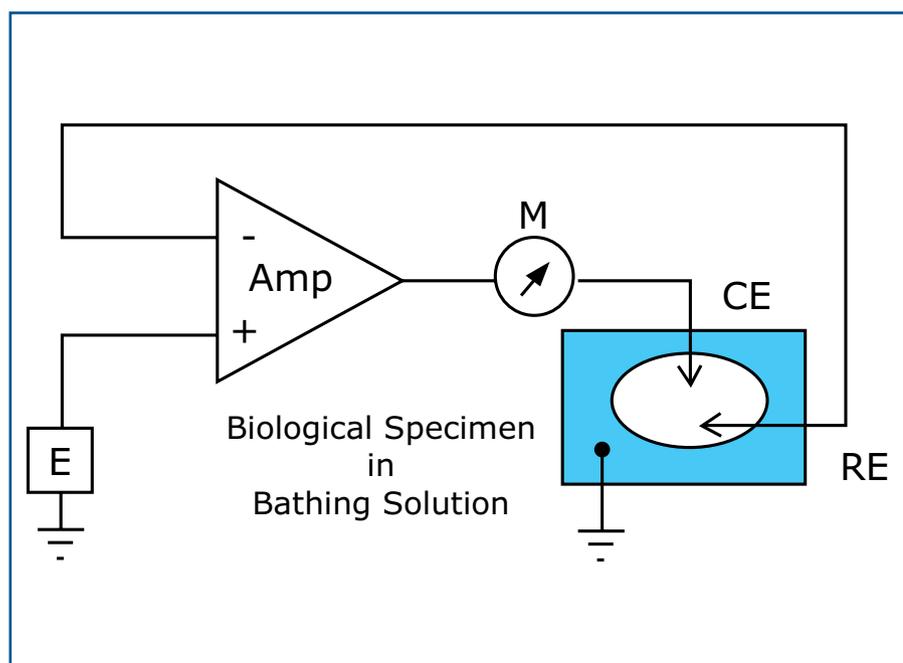


Fig. 2. Simplified two-electrode voltage clamp and biological specimen.

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However, it now appears that some common ground is being cultivated. There is at least one company that the author is aware of that sells both potentiostats and electrophysiology equipment. In analytical electrochemistry, the invention of ion-selective electrodes stimulated research on the properties of laboratory-synthesized membranes. A home glucose monitor is based on electrochemical measurement, and chemical compounds in the brain have been measured using electroanalytical techniques. The technique of cyclic voltammetry has become popular for examining the properties of biological molecules. And at conferences of The Electrochemical Society and the American Chemical Society, there are now many symposia on biomedical research.

About the Author

JACKSON E. HARRAR obtained his PhD in chemistry from the University of Washington in 1958. He retired from a 42-year career at the Lawrence Livermore National Laboratory in 2000. His research was in electroanalytical chemistry and instrumentation, electrosynthesis, and geothermal chemistry. He may be reached at jharrar@mindspring.com. ■

References

1. A. Hickling, *Trans. Faraday Soc.*, **38**, 27 (1942).
2. A. Huxley, "Kenneth S. Cole," Biographical Memoirs, National Academy of Science, Washington, DC, (1996).
3. A. J. Bard and L. R. Faulkner, *Electrochemical Methods*, 2nd ed., J. Wiley, New York, (2000).

4. E. R. Kandel, J. H. Schwartz, and T. M. Jessell, *Essentials of Neural Science and Behavior*, Chapter 10, Appleton & Lange, Norwalk, CT, (1995).
5. T. G. Smith, Jr., H. Lecar, S. J. Redman, and P. W. Gage, Eds., *Voltage and Patch Clamping with Microelectrodes*, American Physiological Society, Bethesda, MD, (1985).
6. *The Axon CNS Guide to Electrophysiology & Biophysics Laboratory Techniques*, Molecular Devices Corporation, Sunnyvale, CA, (2006).
7. D. K. Roe, in *Laboratory Techniques in Electroanalytical Chemistry*, 2nd ed., P. T. Kissinger and W. R. Heineman, Eds., Chapter 7, Marcel Dekker, New York, (1996).
8. A. S. Finkel and P. W. Gage, in Reference 5, Chapter 4.
9. P. T. Kissinger, in Reference 7, Chapter 6.
10. The George A. Philbrick Archives, (2013), <http://www.philbrickarchive.org>.



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