Editorial: Thoughts of a Computerphobe

Leonard S. Gettes, M.D.

IN 1977, Drs. Hondeghem and Katzung\(^1\) reported on their ability to model on a computer the effects of lidocaine and quinidine on the upstroke of the action potential. They used experimental data and concepts concerning the activation, inactivation, and reactivation of the rapid inward channel and the effects of lidocaine and quinidine on these parameters as determined in several laboratories, including their own. The model allowed them to speculate on the site and mechanism of the interaction between the drug and the rapid, sodium-dependent, tetrodotoxin-sensitive ionic channel.

In this issue of Circulation, Hondeghem and Katzung report on their continued observations using this model.\(^2\) They show that the model successfully reproduces the effects of rate, prematurity and partial depolarization on the action potential upstroke. These experimentally determined effects were used to derive the model. Their model predicts the results of steady-state hyperpolarization, an effect not previously tested, and the results of the combined effects of quinidine and lidocaine on the early premature response, which they confirm in a single experiment. As the result of their studies, the investigators suggest that their model can be used to formulate and test hypotheses regarding the actions of combinations of drugs under a variety of clinical situations and, therefore, may be clinically useful. This provocative report brings into focus concerns regarding the appropriate use and possible overuse of the computer in biologic sciences.

In 1962, Noble\(^3\) used a computer to reconstruct the Purkinje fiber action potential. The computed effects of rate changes, applied currents and changes in ionic permeabilities on the action potential were very similar to those determined in the laboratory. This model used modifications of the Hodgkin-Huxley equations to characterize the rapid sodium inward current and potassium outward current which was divided into two components, ik\(_1\) and ik\(_2\). In 1969, Noble and Tsien\(^4\) performed another computer-assisted reconstruction that included the characteristics of newly described additional outward plateau currents i\(_{x1}\) and i\(_{x2}\) and the initial outward transient chloride current. This model also reproduced most of the characteristics of the action potential observed in a variety of experimental situations. In 1975,\(^5\) the model was further upgraded to take into consideration the activation of the sodium inward current in the later stage of the pacemaker potential and the contribution of the slow inward current to the action potential plateau. Again, the model provided a computed action potential that faithfully mimicked experimentally observed behavior.

In 1977, Beeler and Reuter\(^6\) used the computer to model the ventricular action potential. They took into consideration the characteristics of the slow inward current and the effect of the prolonged time constant of the recovery from inactivation of the rapid inward current. This model accounted for the differences between the Purkinje and ventricular fiber action potentials. The metamorphosis of this computerized model illustrates that (1) with proper manipulation, the model is able to reproduce the desired result; (2) it can do so with incomplete data; and (3) careful observation of discrepancies between the model and the experimentally determined observations can lead to the development of new and testable hypotheses. The corollary to the last point is that inattention to seemingly minor discrepancies may lull the observer into a false sense of security regarding the completeness and accuracy of the model.

A computerized model can reproduce biologically observed phenomena if the computer is appropriately programmed. The computer may be called on to solve difficult equations in order to make the model fit the observed response. However, it is unreasonable to assume that the capability of the computer model to reproduce the biologic event is proof of the correctness of the model. Had the early computer models of the Purkinje fiber action potential been accepted as proved that the existing information was complete, it is unlikely that the currents labeled ix\(_1\) or ix\(_2\), the slow inward current, or the reactivation characteristics of the rapid inward current would have been described.

It is reasonable to expect the computer to predict results of experiments in which all conditions are known and correctly interpreted; however, it is unreasonable to expect that a computer model will adequately predict findings in tissues with different characteristics, even if the conditions are similar, or in the same tissues under untested conditions. This is exemplified by the different models needed to reproduce the Purkinje and ventricular fiber action potentials in 1975\(^6\) and 1977,\(^8\) and by an exchange of letters that recently appeared in Circulation Research.\(^7\) This exchange concerned the inability of a computer simulation, using data obtained in the squid axon, to predict results obtained experimentally in the guinea pig papillary muscle.\(^8\) While either the experimental observations or the model was incorrect, it is unreasonable to fault the experimental observations without providing new, experimentally derived data. Similarly, it may be asking too much of the model proposed by Hondeghem and Katzung to generate results that predict a clinical event, because the conditions associated with arrhythmias and the mechanisms of action of the antiarrhythmic drugs in

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vivo are difficult to determine. The importance of the slow inward current in causing slowed conduction, the role of afterdepolarizations, and triggered automaticity in the genesis of the arrhythmia, the cause of depression of the upstroke in the presence of a normal resting potential, the contribution of factors such as acidosis and hypoxia, the possible ability of lysophosphatidyl choline to alter membrane conductance variables, and so on, all require experimental documentation and subsequent inclusion into the computer model. Even then, the resultant prediction may be based on incomplete data and will require experimental validation.

The computer may be used to analyze large amounts of data rapidly, such as those recorded from multiple electrodes within the heart or on the chest wall, provided the signals to be analyzed are easily defined. With this accomplished, it is reasonable to ask the computer to draw isochrone maps or activation sequences. However, it may be unreasonable to expect the computer to discriminate low-voltage, slowly inscribed electrical signals from noise or to decide which of many low-amplitude spikes represent the true activation of the segment in question.

The computer may also be used to assist in the analysis of data generated to test a particular hypothesis, but it is unreasonable to ask the computer to generate the data needed to prove a hypothesis without confirming the results experimentally. Once the computer has predicted a result, it is reasonable that only a limited number of experiments will be needed to establish the validity of the prediction provided the experiments are carefully performed and the results are critically analyzed.

Those of us who grew up in the pre-computer era and have not taken full advantage of the power of the computer should not be frightened by its ability to solve equations, analyze data, draw graphs and predict results, but the biologic scientist should not be tempted to reject tenable hypotheses on the basis of computer-generated results without performing the appropriate experiments. He should be aware of the discarded computer models that dot the scientific literature, and must avoid the temptation to make the question serve the computer rather than the computer serve the question.

References

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