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Preface

The theory of electric current flow in excitable cells has developed extensively since Lord Kelvin first presented the equations for cable transmission a century ago. This development has been particularly rapid during the last 30 years or so, following the first detailed experimental applications of Kelvin's equations to nerve and muscle fibres. As a result, cable theory now plays a central role in many areas of electrophysiology, so that biologists find themselves using mathematical methods of analysis involving techniques considerably more advanced than those with which they are familiar from their undergraduate training. The first aim of this book, therefore, is to give a systematic and explanatory account of the basic mathematical theory that we hope will be of use to research workers in the field as well as in university courses in electrophysiology and in biological mathematics.

When we started writing several years ago this was the sole aim of our work. However, in attempting to write such an account, we encountered a number of areas in which the relevant theory required further development, not only to enable a reasonably systematic account to be given but also to allow us to use the explanatory device of looking at particular problems from different aspects. Where possible, we have attempted the development ourselves, and this second aim has grown as the book was written. As a result, much of the material of the book is new, as a glance at our illustrations will show. If we need to apologize for writing a rather longer and more advanced book than our original aim required, our justification is simply that, in our view, the subject requires such a book. The mathematics of excitation and conduction theory is much more complex, and the experimental work on which it is based is considerably more extensive, than when Bernard Katz wrote his classic review of excitation (*Electric excitation of nerve*) in 1939. Our subject is essentially the same as his, but its content has been greatly transformed and expanded, and we have found it impossible to restrict ourselves to the 100 or so pages that sufficed 35 years ago.

The year 1939 saw the first results of the intracellular recording techniques that were to completely revolutionize the subject after World War II. Katz's book therefore appeared at an ideal moment of time. He was able to review the development of excitation theory (including some of the valuable insights developed during the 1930s) before he and others became so successfully involved in using the new techniques. A watershed had been passed, and for two decades the insights of the 1930s must have paled before the immense power of being able to directly record the events about which the physiologists of the 1930s could only theorize.

We have now reached a somewhat analogous stage of development, although the events about which we now theorize (but wish we could directly record) are molecular rather than cellular. Furthermore, as the new intracellular methods have been applied to progressively more intractable problems in nerve and muscle physiology, so the need to use fairly elaborate, and more highly theoretical, models has returned. Moreover, it is not surprising that some of the insights of the 1930s (for example, Rushton's work on initiation and propagation of the impulse) are proving more useful again. The same problem has returned: even with the new techniques we cannot always record directly all the events we may wish to, and the need to use simplified models of the excitation process itself (not unlike those used in the 1930s) becomes greater when more complex physiological systems are studied. To some extent then the wheel has turned fully round. As a result, we have felt the need to relate some of the older insights to the modern theory of excitation.

We are keenly aware of the fact that the aims of introduction and development co-exist uneasily in the writing of a book. The result is a hybrid. Nonetheless, we have ensured that the introductory and explanatory core is still present as a substantial and identifiable body, although its parts are necessarily interspersed with more advanced development. For the guidance of students interested in our first aim we have indicated in Chapter 1 where the introductory parts are to be found. So far as our second aim is concerned, we cannot say that we are fully satisfied. The developments we have attempted are primarily analytical, largely because we expect the insights gained to be more general than those to be obtained from numerical computer models. However, we have not succeeded in obtaining useful analytical solutions for more than a fraction of the problems that interest electrophysiologists. We present our work as a stimulus to others as much as a record of our own explorations.

Oxford and Yale,
September 1974

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D. N.
R. W. T.

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THIS work originated in the form of circulated notes for graduate lectures and seminars given at Oxford, Homburg (Saar), and Monash. We have also used some of the more introductory material in lectures and tutorials for final-year undergraduates studying Physiological Sciences at Oxford. We have, therefore, benefited from innumerable discussions with colleagues and students. To acknowledge all of these sources of criticism personally is impossible but we should like to acknowledge valuable discussions with Dr. R. H. Adrian, Mr. D. Attwell, Dr. W. K. Chandler, Dr. I. Cohen, Dr. L. L. Costantin, Dr. J. Daut, Dr. R. S. Eisenberg, Professor A. L. Hodgkin, Dr. D. Kernell, Professor D. G. Lampard, Professor K. Morztyn, Dr. K. G. Pearson, Dr. D. Perkel, Dr. W. Rall, Dr. S. J. Redman, Mr. H. Sackin, Dr. M. Schneider, Dr. P. G. Sokolove, and Dr. R. B. Stein. We are also grateful to some of our colleagues for allowing us to see unpublished work and, in some cases, for kindly reading various chapters. Needless to say, the responsibility for remaining errors is ours.

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J. J. B. J.
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R. W. T.

List of notation and definitions

E_m	transmembrane potential expressed as potential of intracellular fluid with respect to that of extracellular fluid (mV).
E_r	resting value of E_m (mV).
V	transmembrane potential expressed as deviation of intracellular potential from resting potential, $V = E_m - E_r$ (mV).
R_i	intracellular resistivity (kΩ cm).
R_m	membrane resistance (kΩ cm^2).
C_m	membrane capacitance (μF cm^{-2}).
Z_m	membrane impedance (kΩ cm^2).
X_m	membrane reactance (kΩ cm^2).
f	frequency (Hz).
ω	radial frequency $= 2\pi f$ (rad).
I_i	membrane ionic (resistance) current (μA cm^{-2}).
I_c	membrane capacity current (μA cm^{-2}).
I_m	total membrane current, usually $I_i + I_c$ (μA cm^{-2}).
I	applied current (μA).
a	fibre radius (one-dimensional theory) (cm).
b	preparation thickness (two-dimensional theory) (cm).
i_i	membrane ionic current per unit length of fibre ($= 2\pi a I_i$) (μA cm^{-1}).
i_c	membrane capacity current per unit length fibre ($= 2\pi a I_c$). (μA cm^{-1}).
i_m	membrane current per unit length fibre ($= 2\pi a I_m$) (μA cm^{-1}).
r_m	membrane resistance per unit length fibre ($= R_m/2\pi a$) (kΩ cm).
r_a	intracellular resistance to axial flow of current along fibre ($= R_i/\pi a^2$) (kΩ cm^{-1}).
c_m	membrane capacitance per unit length fibre ($= 2\pi a C_m$)(μF cm^{-1}).
τ_m	membrane time constant ($= R_m C_m$) (ms).
λ	fibre space constant ($= \sqrt{(R_m a/2R_i)} = \sqrt{(r_m/r_a)}$) (cm).
x	distance along fibre (unidimensional theory) (cm).
X	$= x/\lambda$.
r	distance from point electrode (two-dimensional theory) (cm).
λ_2	two-dimensional space constant (see Chapter 5).
R	$= r/\lambda_2$.
t	time (ms).
T	$= t/\tau_m$.
i_a	intracellular axial current (μA).
R_{in}	input resistance (recorded potential/applied current) (Ω).
Q	charge (nC).

G_m	membrane chord conductance (ms cm^{-2}).
g_m	membrane chord conductance in unit length of fibre (ms cm^{-1}).
θ	conduction velocity (ms^{-1}).
K	$= 2R_i\theta^2C_m/a$ (ms^{-1} or s^{-1}).
$\bar{V}$, $\bar{I}$, etc.	Laplace transforms of V, I, etc.
s	Laplace transform variable.
l	length of fibre.
L	l/λ.

Other symbols are defined as they are introduced.

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13. Mathematical appendix

1. Introductory remarks

THE evolution of electrically excitable membranes in living systems was an essential step in the development of those forms of life which display the complex kinds of behaviour which we associate with the possession of a nervous system. The chemical basis of this excitability is still largely unknown. However, the physical aspects are now very well understood and the theory of current flow in excitable cells is well developed. Unfortunately, many of the important results are still to be found only in the original papers or in fairly specialist reviews and, although some excellent elementary textbooks now exist, there is no systematic account of the more mathematical aspects. We hope that this book will fill this gap.

Virtually all living cells maintain an electrical potential difference between their interiors and the environment, and this potential is one of the factors determining the energy barriers encountered by charged substances entering or leaving the cell. The special characteristic of excitable cells is that the potential may change in response to variations in the chemical environment or in response to current flow. These potential changes (receptor potentials, synaptic potentials, pacemaker potentials, and action potentials) underly the ability of nervous systems to process and to transmit information. They also serve as the triggers of mechanical activity in the case of effector cells such as muscles.

The transmission of information over long distances is carried out by thin projections of nerve cells called nerve axons. Moreover, for anatomical reasons, muscle cells are also often arranged in long fibres. Thus two of the most important kinds of excitable cell have a geometry resembling that of an electric cable. The theory of current flow in electric cables, initially developed for submarine cables by Lord Kelvin (1855, 1856, 1872), was first used in work related to excitable cells towards the end of the nineteenth century by Weber (1873, 1884), Cremer (1899, 1909), and Hermann (1879, 1899, 1905). One of the most important results of this early work was Hermann's suggestion that current flow of the kind described by cable theory may be adequate to maintain nerve impulse propagation. Since then, the theory has frequently been used in the study of nerve and muscle, particularly in work on the responses to electrical stimuli which are small enough to neglect the gross nonlinearities which appear in response to strong stimuli. The theory has also been successfully applied to the mechanism of impulse propagation. This work developed rapidly in the 1930s and 1940s (see Rashevsky 1931; Rushton, 1934, 1937; Monnier 1934; Cole and Curtis 1936, 1939, 1941; Rosenberg 1937*a*, *b*; Hodgkin 1937; Cole and Hodgkin 1939; Katz 1939; Offner, Weinberg, and

Young 1940; Weinberg, 1941; Hodgkin and Rushton 1946; Lorente de Nó 1947) so that by 1946, when Hodgkin and Rushton published their experimental and theoretical analysis of the subthreshold responses of nerve axons to locally applied currents, the nature of the purely passive ('electrotonic') flow of current in nerve axons was largely clarified and some important clues to the nature of the nonlinear properties had emerged. More recently, the most exciting developments in this field have concerned the analysis of the nonlinear properties of excitable cells using the voltage control ('voltage-clamp') technique introduced by Cole and Marmont in 1949. The theoretical interpretation of this work has been based largely on the semi-empirical equations, given by Hodgkin and Huxley in 1952, for describing the time and voltage dependence of the membrane current. However, these developments have continued to require the use of cable theory and of extensions to it that were designed to deal with nonlinear systems and with more complex geometries. The result has been a steady but considerable development of the theory, the importance of which does not depend directly on any particular theory concerning the mechanism of the membrane nonlinearities. Moreover, since Fatt and Katz's (1951) quantitative analysis of the end-plate potential, the theory has also been used in the study of synaptic mechanisms. Therefore it has become an important part of many branches of biophysics and neurophysiology, and it may be useful to graduate students and research workers in these fields to have a more comprehensive introduction to the theory than is at present available.

In this book we attempt to give a systematic account of the theory and its applications. Some of the results are well known and may be found in the physiological literature or in some of the standard mathematical texts (e.g. Carslaw and Jaeger 1959; Jaeger 1951; Luikov 1968). Some of the more recent work may not be so well known. Moreover, the mathematical methods and the notation used have not always been uniform and, largely because the theory has been developed for particular applications, some results of more general importance have not always been obtained or given the attention they may deserve. In view of this situation, we give fairly complete derivations for some of the important and widely-used results, together with references to sources containing the original derivations. Where no references are given we believe the results to be new, but we apologize if we have inadvertently neglected any previous work of importance.

Wherever possible, we have tried to be simple and explanatory rather than complete and general. Some of the consequences of this policy are worth mentioning here, since we may in this way warn our more sophisticated readers where they may expect to find limitations which are largely of our own choosing. First, the derivations given are not always the most general since we believe that most biologists find particular derivations easier to follow. Second, we do not attempt to give a complete review of the physiological applications of importance, but some examples of applications are referred to in order to illustrate the theory. Third, although most of the early development of cable theory was directed towards work with extracellular electrodes, more recent work has often used intracellular electrodes. Since, in many cases, this allows the equations to be simplified, we use this simplification wherever possible. In keeping with this approach, the theory of extracellular fields (see Lorente de Nó 1947; Plonsey 1964; Clark and Plonsey 1966, 1968; Rall and Shepherd 1968; Rosenfalck 1969; Nicholson and Llinas 1971) is omitted. We also omit the theory of three dimensional fields in the vicinity of current sources (see Eisenberg and Johnson 1970).

It may be helpful to readers to have some guidance on how the book might best be used. First, it should be emphasized that we have not written a general introduction to cellular electrophysiology. On the contrary, some familiarity with the subject is assumed, and readers who have no previous knowledge would be well advised to first read an introductory account such as Katz's *Nerve, muscle, and synapse* (1966) or Aidley's *The physiology of excitable cells* (1971). Some parts of the present work will then be found fairly easy to follow. In particular, Chapter 2, many sections of Chapter 3, and Chapters 8, 9, 10, and most of 11 are intended as introductions to the basic principles of linear and nonlinear cable and excitation theory, and some parts of each of these chapters will be found to be relatively elementary. It should be noted that the introductory sections of the book do not necessarily appear at its beginning. We have deliberately deferred some of the introductory material to later chapters dealing with nonlinear cable theory since it is in these chapters that the appropriate applications occur.

Chapters 6 and 7 are concerned with particular applications of cable theory to problems in muscle excitation and the theory of nerve cells. These chapters are written largely as reviews of the present state of the field, and they may well become out of date more quickly than other chapters. We feel, however, that these chapters will give a useful indication of the way in which the theory is used in problems of current interest, and we hope that they will also serve as introductions to these two fields for those who do not have the time to adequately study the complex, and sometimes rather inaccessible, literature. Similarly, Chapter 11 is, to a considerable extent, a survey of the analysis of repetitive firing; as such it is likely to become incomplete as new work takes the analysis further.

Chapters 4, 5, and 12 contain fairly advanced or specialist material, and we suggest that they should be omitted on a first reading. These chapters should prove more useful to those already familiar with the basic principles and to those who need equations for particular problems.

Finally, it will be obvious on perusing the book that some parts assume a fair degree of mathematical knowledge. However, we hope that this will not deter non-mathematical physiologists. In the introductory chapters mentioned above we have tried to explain the derivations in fairly easy stages and, if the reader confines himself to these chapters initially, he should find that little