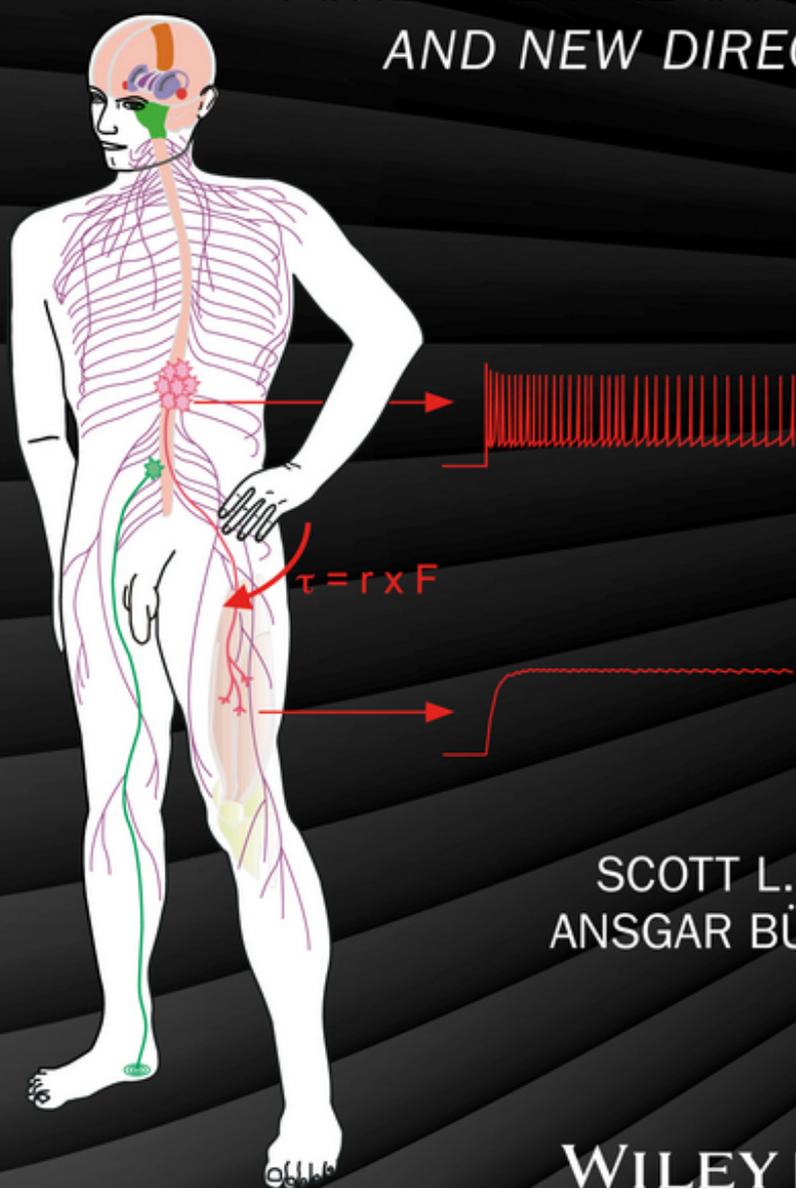


# NEUROBIOLOGY OF MOTOR CONTROL

FUNDAMENTAL CONCEPTS  
AND NEW DIRECTIONS



EDITED BY  
SCOTT L. HOOPER  
ANSGAR BÜSCHGES

WILEY Blackwell



## Neurobiology of Motor Control



# Neurobiology of Motor Control

Fundamental Concepts and New Directions

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## About the Cover

Moving from standing on both feet to standing on one. Higher centers and the basal ganglia “decide” to stand on the right foot, with the basal ganglia (blue shading in brain) playing a central role in suppressing expression of competing behaviors (standing on left foot, kneeling, jumping) (Chapter 7). Motor cortex (orange shading in brain) and brainstem (for facial movements, green shading in head) or spinal cord (for body movements) inter- and motor neuron networks (pink cell bodies in spinal cord) determine what pattern of motor neuron activity will produce the required movements (left hip flexion, changes in trunk and right leg posture to bring body center of mass over right foot) (Chapters 8, 10, 11). Motor neuron activity (upper red trace) induces muscle force production (bottom red trace) and, acting through limb moment arms, the joint torques (curved red arrow and equation) required to generate the movements (Chapter 12). Sensory feedback (green neuron) provides continuous updates of movement success and input necessary to maintain body stability (Chapter 9). Motor learning alters network properties to produce more fluid and effective movement (Chapter 13). Neuron activity and muscle activity and force can be monitored and modified by electrophysiological or molecular biology techniques (Chapters 2–4). Increased insight into the processes at work can be gained with computer simulation (Chapter 5) and evolutionary comparisons (Chapter 6), and applied to develop robots capable of producing more natural and robust movement (Chapter 14).



## 1

## Introduction

Ansgar Büschges<sup>1</sup> and Scott L. Hooper<sup>2</sup>

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It is de rigueur in a review or book on motor control to quote Sherrington's (1924) statement that "To move things is all that mankind can do". Although strictly true, this quotation discounts the central role in human experience of such actionless phenomena as ideation, emotion, and consciousness. However, it is nonetheless true that movement is an absolute requirement for animal survival and reproduction and, as the only observable output of the nervous system, is the defining basis of behavior. Movement is also self-defining, and hence allows analyzing nervous system function on the objective basis of its performance alone without reference to experimenter defined classifications. Disorders of movement also have great clinical importance, and production of functional and robust movement is a central problem in robotics. Because movements must be chosen among, and because almost all motor networks receive sensory input and information about internal state and "decide" how to alter their output in response, studying such networks may also provide insight into how the networks underlying "higher" abilities such as ideation function.

Despite this, many researchers, as well as lay people, take the generation of motor behavior for granted, often rendering it as the outcome of simple and automatic neural processes that can be summarized with large arrows pointing "south" from an animal's brain accompanied by the words "motor system". Only when confronted with particularly outstanding motor performances, e.g., the graceful movements of a dancer or an acrobat, do we appreciate the complexity of generating motor output. This disparity was well captured more than 200 years ago in von Kleist's (1810) essay *Über das Marionetten Theater* (On the Marionette Theater): "He asked me if indeed I hadn't found some of the movements of the puppets...to be exceedingly graceful in the dances. I could not refute this observation," a recognition that led Kleist to elaborate further on the potential mechanistic background of this observation. This text highlights how the ordinariness of movement can prevent us from appreciating how difficult it is to produce (something of which roboticists are well aware), and thus how extraordinary it is that nervous systems can do so.

The last general textbook covering how nervous systems do so, at least with respect to locomotion, was *Neural Control of Locomotion* (Orlovsky et al. 1999). This exceptional book described the neural networks and mechanisms that generate locomotion

in mollusks, insects, anurans, lower vertebrates, mammals, and man. This book was the first comprehensive comparative account of how nervous systems generate locomotion. Such an overview had been lacking for decades and its detail and depth made and make it exceptional.

However, the book's concentration on locomotion meant that it, by design, did not cover the full range of movements animals produce. More importantly, dramatic advances in motor science have occurred since it was published. These advances represent a sea change in that motor research up to the 1990s primarily involved ever more elegant and detailed application of classical anatomical and single unit electrophysiological techniques. In the last two decades, alternatively, a much broader palette of methods has become available or practicable, including multi-unit recordings, molecular neurogenetics, computer simulation, and new approaches for studying how muscles and body anatomy transform motor neuron activity into movement. This broadening of experimental options has been exceptionally fruitful. However, it also means that researchers in motor control must be multi-competent, sufficiently informed and trained to be able to select from these multiple methodological options the optimal approach for the research question at hand.

It is important to make this observation because human nature and the process by which researchers are typically trained (prolonged and intensely concentrated research on a narrowly-defined question in an individual mentor's lab) work against achieving such multi-competence. Instead, as with a person with a hammer seeing every problem as a nail, it leads to researchers using the methods they know in preference to ones that might be better, but about which the researcher only peripherally knows. This is not a new observation, and conscious efforts are being made in training programs to train new researchers across fields. Nonetheless, in our experience barriers still exist between molecular biologists, electrophysiologists, muscle researchers, modelers, biomechanicists, and roboticists. It is a truism that reducing such barriers would serve all well. The question is, how to do so?

This book, in part, is an attempt to contribute to this effort. Its intended audience is all workers in movement production, from molecular biologists to roboticists. Workers in each group will have most knowledge of fields nearest their own ... thus an electrophysiologist from a biology program likely has greatest understanding of molecular biology, and perhaps least of robotics. A biomechanicist likely finds it easier to communicate with a roboticist than a molecular biologist. And in our experience, modelers, at least those whose training was in classical mathematics, always speak a foreign language.

We therefore begin this book with four chapters covering basic knowledge on electrophysiological techniques, methods for large ensemble recordings, neurogenetic and molecular techniques, and computer simulation. These chapters are obviously not intended for experts in the field (although we hope they will be useful for beginning students in their labs, and the molecular biology and simulation chapters include case studies that will interest even experts in the fields). Rather, we hope that these chapters will allow workers outside each chapter's field to better understand and critically assess the field's literature, to understand the later chapters in the book, and encourage workers to reach outside their comfort zone and consider applying different methodological approaches to their research. We believe that writing these chapters, with their at least partially pedagogical nature, was likely a considerable change from the more purely research oriented reviews the authors would be typically asked to

write. We are therefore particularly grateful to the highly distinguished colleagues in the field of motor control who were willing to take on this burden.

Hooper and Schmidt cover classical (i.e., not multi-unit) electrophysiological recording techniques. The first sections of this chapter are practical, and provide the information necessary for readers to understand and interpret intracellular and extracellular recording in the contemporary literature without a detailed explanation of theory. It is very difficult for modern readers to appreciate just how difficult it was for these techniques to be developed. The authors therefore next provide a brief history of extracellular and intracellular recording. The authors end the chapter with a detailed explanation of the theory underlying both recording techniques, and potential pitfalls that can occur with them.

Lebois and Pouzat cover multi-unit recordings...recordings in which electrodes that record the activity of multiple neurons are introduced into nervous tissue. The ability to do so strongly depends on proper electrode design and use, which the authors therefore first cover. Given that these electrodes record the activity of many neurons, advanced techniques are required to identify the individual activities of the many neurons being recorded from. The authors explain these techniques in detail in the chapter's second part.

Schoofs, Pankratz, and Goulding cover the use of molecular genetic tools to study neural network topology and function. They begin with a detailed explanation of the techniques available in invertebrates and vertebrates to observe and alter neuron activity. They then provide four cases studies, two in *Drosophila* and two in mice, in which these techniques were used to make novel findings in motor control that would have been presently impossible to achieve with other methods.

Prinz and Hooper cover computational simulation. The authors first provide a relatively high level overview of both the great power, and also the potential pitfalls, of simulation, making use throughout of case studies relevant to motor control. Because computer simulation may not be a part of the training of many of the book's intended audience, the authors then provide a detailed and basic explanation of how simulation is performed and how it is applied to neurons, synapses, muscles, and biomechanics.

In planning this book we also aimed to reduce another set of barriers: those between workers in different experimental preparations, of which the greatest is between workers in invertebrates and vertebrates. Doing so is important on both historical and scientific grounds. First, many to perhaps most discoveries made in one of these groups have been later found to be also present in the other. Second, recent data suggest a deep homology between (bilaterian) invertebrate and vertebrate motor control structures. This observation suggests that the last common ancestor of these two groups (the urbilaterian) had a relatively complex nervous system from which both bilaterian invertebrate and vertebrate nervous systems developed. It would thus be expected that data from one group would often be relevant to the other. In the later chapters we therefore tried to team researchers in vertebrates and invertebrates, with the comparison between the groups being made implicitly or explicitly. In all cases the results of these across-group collaborations are excellent chapters whose synthesis, we believe, provide a depth and breadth of understanding and insight that could not otherwise have been achieved. We are very grateful to the many open-minded colleagues who were willing to accept this challenge to "work across the divide" in writing these chapters.

In choosing the topics for these chapters we strove to cover the full width of motor control research, areas which, in our opinion, are relevant to all workers, and particularly students and similar upcoming workers, in the field. These topics do not admit to an easy hierarchical ordering, but we tried to begin with the most general (evolution), then turned to the neural basis of movement generation, next to muscles and biomechanics, then to motor learning/plasticity, and finally to the application of these insights to robotics.

Katz and Hale describe motor network evolution. Throughout they intermix explanation of evolutionary concepts and terminology with illustrative case study examples, including cautionary examples in which motor network similarity is solely through convergence. As one would expect, in this chapter the importance of the molecular biology advances discussed above in understanding the evolution of motor circuits is very apparent.

Grillner, Robertson, and Pflüger in their chapters introduce the reader to the neural mechanisms that select which of the movement programs an animal has in its behavioral portfolio to produce. Unlike the other chapters in the book, these chapters are presented separately as vertebrate and invertebrate, with a general introduction. However, the chapters end with discussion of the possible deep homology between the movement selection centers in the two groups.

Harris-Warrick and Ramirez cover the neural networks that generate rhythmic motor acts and identify general principles present across the animal kingdom. In doing so they describe both the importance of synaptic connectivity pattern and cell-specific properties, including the contributions made by specific ion conductances, in rhythm pattern generation. They also describe the effect of modulation in such networks, and the basis of their ability to produce multiple output patterns.

Edwards and Prilutsky cover the role of sensory feedback in modifying and sculpting motor network activity. They begin with a description of control theory and then give case studies of how various types of sensory feedback and input function both in movement generation and the maintenance of posture, emphasizing the common problems and functional solution structures in vertebrates and invertebrates.

Movements are often coordinated, e.g., breathing and locomotion in some gaits. Le Gal, Dubuc, and Smarandache-Wellmann describe the neural mechanisms that underlie these coordinations and the bases of their flexible expression using a wide variety of well-studied case studies. A key insight from this work is the frequent presence of multiple mechanisms subserving these coordinations.

Not all movements are rhythmic. In particular, animals use appendages to reach out to objects in the environment, so-called prehensile movements. Bockemühl describes the theory of prehension with jointed limbs, particularly the redundancy problem (that a motor system can typically fulfill a given reaching task in a very large number of ways) and then both theoretical and neurobiological solutions to this problem. This chapter uses only vertebrate case studies, but the generality of its analysis makes it valuable to workers in all preparations.

Ting and Chiel describe how neural and biomechanical systems interact to produce functional motor behaviors. Central points here are that several new types of redundancy exist on the muscle level, muscle response to neural input is history-dependent and non-linear, and the effect of muscle contraction (and hence motor neuron activity) depends on the contraction state of other muscles and the position of the structure to

which the muscle attaches. This intimate interdependence of nervous system and body state clearly greatly complicates understanding how animals generate movement.

Simmers and Sillar describe motor learning and plasticity in *Xenopus* tadpole swimming and *Aplysia* feeding. As such, their chapter does not cover higher level (motor cortex, cerebellum) involvement in learning complex motor patterns, e.g., to dance. This choice, however, allows them to focus on examples of motor learning in which the basis of the learning can be explained on a cellular level in relatively or very well described motor networks, and in which the learning occurs within these networks.

In the final chapter Buschmann and Trimmer describe how neurobiological and biomechanical research can help design robots that can effectively move through unpredictable environments, covering both rigid limbed (analogous to human or insect limbs) and soft-bodied (analogous to caterpillars or octopus arms) robots. An important part of this chapter is that differences in biological and robotic sensors, force generators, and structural materials complicate applying biological principles to robot design. Nonetheless, this chapter is in a sense a measure of our understanding of biological movement; presumably when we understand the one, we can design the other.

In closing, we want to again thank the authors for their work, and to express our hope that this work will help advance all of our efforts to understand how animals generate movement, particularly the efforts of those beginning their research in this field, who are its future.

## References

- Orlovsky GN, Deliagina TG, Grillner S (1999) *Neural Control of Locomotion*. Oxford, UK: Oxford University Press.
- Sherrington CS (1924) Linacre Lecture, St John's College, Cambridge. In Eccles JC, Gibson WC (eds). *Sherrington: His Life and Thought*. New York, NY: Springer-Verlag.
- von Kleist H (1810) *Über das Marionetten Theater*. Berlin Abendblätter, 4 installments Dec 12–15. Translation *On the Marionette Theatre* by TG Neumiller in *The Drama Review: TDR* (1972) 16:22–26.



## 2

## Electrophysiological Recording Techniques

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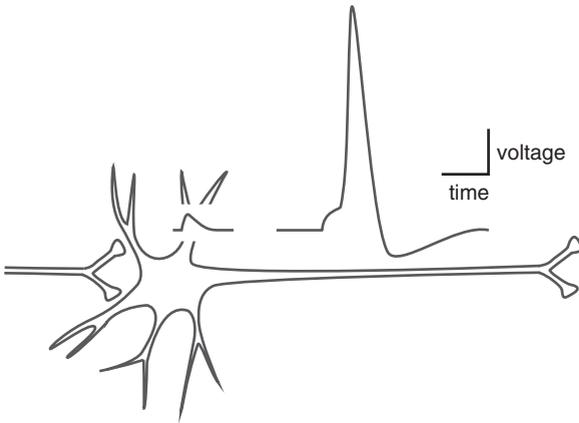
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### 2.1 Introduction

Selective ion transport across membranes, with the resulting development of transmembrane ion concentration and electrical potential differences, occurs in all cells, prokaryotic and eukaryotic. These differences are the bases of respiration and photosynthesis and are a form of energy storage used to power an enormous number of transmembrane transport systems. These differences also provide an environment in which ion (e.g., calcium), ligand, and voltage gated ionotropic channels can evolve. These channels evolved well before the origin of eukaryotes, with bacteria (Kubalski and Martinac 2005; Martinac et al. 2008) having ligand-gated ionotropic channels and voltage-gated Na<sup>+</sup> and K<sup>+</sup> channels, and producing action potential-like electrical spikes (Kralj et al. 2011). The bacterial channels are homologous to vertebrate voltage-gated Na<sup>+</sup> and K<sup>+</sup> channels and were indeed the source material for the crystal structure analysis of these proteins (Doyle et al. 1998; Jiang et al. 2003; Payandeh et al. 2011; Zhang et al. 2012). Transmembrane potentials, and a theoretical ability for more complex types of electrical activity, are thus present in all cells; that this ability is more than theoretical is shown by invertebrate and vertebrate oocytes (Hagiwara and Jaffe 1979) and even plant cells (Fromm and Lautner 2007) generating action potentials.

This ability is most highly evolved in neuron and muscle, with both having excitable membranes, and motor network function and muscle force production critically depending on variation in transmembrane potential. Understanding the generation of motor behavior on the cellular level therefore requires measuring and manipulating neuron and muscle transmembrane potentials (Fig. 2.1). Our goal in this chapter is to provide readers with sufficient understanding of neuron and muscle intracellular and extracellular recording to read this literature with profit.

Sections 2.3 and 2.4 are practically oriented and should be sufficient to understand most modern intracellular and extracellular recording work. Section 2.3 describes contemporary methods for measuring and manipulating neuron and muscle transmembrane potential and current. Section 2.4 discusses contemporary methods for recording electric field potentials generated by neurons, nerves, and muscles. In these recordings the electrodes are placed outside, but in close vicinity, of the cells or nerves, and hence



**Figure 2.1** Neuron schematic. Synaptic input generates graded synaptic potentials in the dendritic region. Information is coded in the axon by action potentials.

are called extracellular recordings. These electrodes can also be used to generate electric fields that elicit action potentials in neurons. Although the theory of the electric field generation (Section 2.6) is the same, extracellular recording from close packed assemblages of large numbers of neurons and axons (e.g., in brain), and analyzing the data so obtained, require specialized techniques. We do not cover these techniques here, which are instead presented in Chapter 3. Section 2.5 provides a brief history of electrophysiological recording. Section 2.6 covers the theory of cell transmembrane potential and action potential generation and intracellular and extracellular recording, and is provided for readers interested in a more detailed understanding of the issues presented in Sections 2.3 through 2.5. Readers not interested in Sections 2.5 and 2.6 can leap from the end of Section 2.4 to 2.6.3.5, *Extracellular Action Potential Summary*, without substantial loss of continuity.

## 2.2 Terminology

Electrophysiology involves measuring electrical potentials and current flows inside, outside, and across the cell membrane. Substantial possibility for confusion exists unless one carefully distinguishes among these different potentials and current flows. This possibility is increased by a failure to distinguish between electrical potential (the work required to bring a test positive charge from infinity, at which the potential is zero, to the point at which the potential is being measured) and voltage (the difference in electrical potential between two points) in much neurobiological writing. For instance, the potential difference across a neuron membrane at rest is technically a voltage, but is very often referred to as the “resting potential”. Very often this difference is immaterial, as the extracellular medium is grounded and thus held at a potential of zero, and hence the intracellular electrical potential equals the transmembrane potential difference (the transmembrane voltage). However, in understanding extracellular recording, it is often important to distinguish between the transmembrane voltage and the electrical potential present at various points in the extracellular medium (see Section 2.6).

To be both unambiguous and maintain typical usage, we use the following conventions. When writing of an electrical potential difference across the cell membrane, we

use “transmembrane potential”. When referring to the potential of a point in space, or to the electrical potentials of the inside or outside of the neuron as individual entities (i.e., relative not to each other, but to ground or infinity) (Section 2.6), we use “potential”. Because they refer to specific, well-defined entities, we use “resting potential” and “action potential” unless it is necessary to specify (Section 2.6) whether it is transmembrane potential difference, or inside or outside potentials, that is being referred to. Current can flow across the neuron membrane, along the membrane’s inside and outside surfaces, and (theoretically) longitudinally inside the membrane itself. Lipid bilayers have very high resistance. Current flow in the last case is therefore negligible and can be ignored. We refer to current flowing across the membrane as “transmembrane current” and describe the direction and amplitude of inside and outside currents as necessary without using special terms.

## 2.3 Intracellular and Patch Clamp Recording

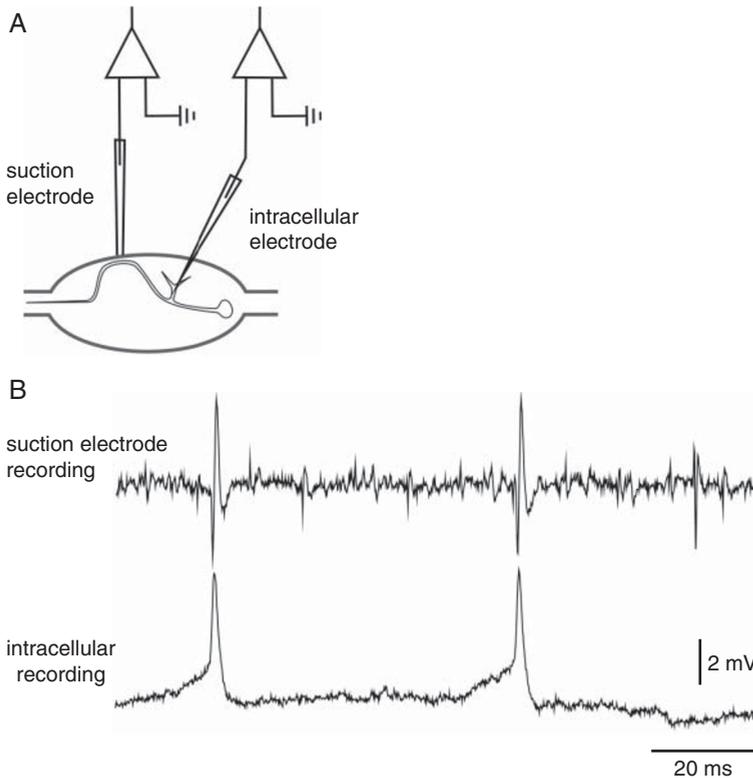
Transmembrane potential and current flow are measured between two points. To measure these entities, we accordingly need pairs of electrodes connected to an appropriate measuring instrument: one electrode with access to the intracellular space and one placed in the extracellular space. The extracellular electrode, the reference electrode, is usually connected to ground, thus setting extracellular potential to 0 mV. An important concern that applies to all intracellular techniques is the cable properties of neurons, which become more pronounced as neuron geometry becomes more extended. For spherical neurons with no or limited processes (isopotential neurons), the transmembrane potential measured by the electrode is a good measure of the transmembrane potential throughout the neuron. For more typical neurons with extensive processes, electrodes measure (Section 2.3.2) or clamp (Section 2.3.3) the transmembrane potential only of the parts of the neuron electrically close to the electrode (see Fig. 2.3).

### 2.3.1 Recording Electrodes

Two approaches are commonly used to gain access to the intracellular side of cells.

*Intracellular Recordings with Sharp Glass Microelectrodes* The cell is impaled with sharp intracellular glass microelectrodes (0.01–0.1  $\mu\text{m}$  tip diameter) that are typically filled with a highly concentrated electrolyte solution (e.g., 3M KCl) (Figs. 2.2, 2.3).

*Whole-Cell Patch Clamp Recordings* This recording configuration is achieved in two steps. First a relatively blunt (compared to sharp intracellular electrodes) (1–2  $\mu\text{m}$  tip diameter) glass electrode is sealed by suction to the membrane, forming a very high ( $G\Omega$ ) resistance between the inside of the pipette and the external solution. At this point the activity of channels in the membrane under the electrode can be measured (see Fig. 2.8E and patch clamp part of Section 2.3.3.2). The membrane patch under the rim of the electrode tip is then ruptured (whole-cell patch-clamp configuration) providing relatively low resistance access to the cytoplasm (Fig. 2.4). Patch electrodes are filled with a solution that, ideally, is isotonic to the cytoplasm. However, it is impossible to match all the other soluble contents of the cytoplasm, and loss of these components to the relatively very large pipette volume (see below) is inevitable.



**Figure 2.2** Extracellular and intracellular recording of a neuron in the abdominal ganglion of a crayfish. (A) Schematic of recording situation. A suction electrode (left) was placed on the surface of the ganglion where the primary dendrite of the neuron of interest was very close to the surface. The neuron was also impaled with an intracellular electrode (right). (B) The first trace shows two action potentials recorded with the suction electrode. The same action potentials were recorded by the intracellular electrode (second trace). Recording courtesy of C. Smarandache-Wellmann.

*Comparison of Two Approaches* Both methods are widely used and have advantages and disadvantages. Sharp intracellular microelectrodes, especially when used in small cells, require small tip diameters to minimize cell damage when the electrode is inserted into the cell. Small tip diameters can create problems because tiny, high resistance electrode tips easily clog during the recording. This can lead to varying electrode resistance and unstable recordings and can cause problems for passing current. The electrodes can also be used to iontophorese charged dyes or indicators into the cells. However, again because of the small tip diameter, iontophoresis of the substances easily clogs the electrode tips.

Another concern with almost all past sharp electrode work is that it has been performed with electrode fill solutions that do not match cytoplasm ionic makeup and typically have ionic strengths far greater than that of cytoplasm. Recent work has shown that high ionic strength electrode fill solutions diffuse even across the small tip diameters of sharp electrodes, and cause large changes in cell properties (Hooper et al. 2015) (see Section 2.6.2 for full discussion of this issue). Adequate sharp electrode current and voltage clamp recordings can be obtained using fill solutions whose ion concentrations