Principles of Nerve Stimulation

This application note provides an introduction to the principles of nerve stimulation, and discusses the use of PowerLab stimulators in experimental physiology.

Written by staff of ADInstruments

Introduction

Excitable tissue may be activated by a wide variety of stimuli, ranging from mechanical trauma to intense magnetic fields. All stimuli work by depolarising the membrane to a threshold voltage level at which the regenerative mechanisms of the action potential take over. In the commonest method of stimulation, a pair of wire electrodes is placed on or near a nerve, and pulses of electric current are passed between the electrodes, under control of an electronic stimulator.

The requirements for efficient and trouble-free stimulation can be understood from Ohm's Law, combined with elementary physiology.

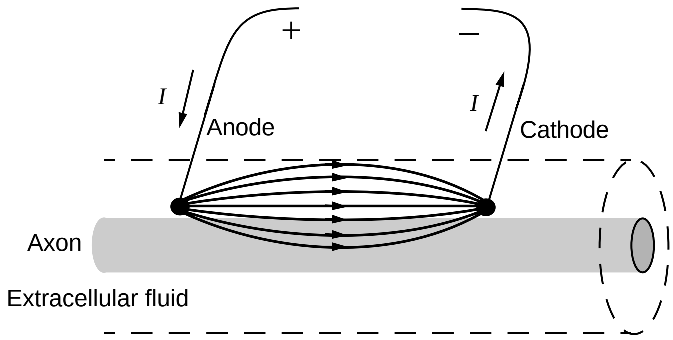

Figure 1. Flow of current between bipolar stimulus electrodes.

Stimulation with external bipolar electrodes

Most of the important principles can be derived from consideration of the arrangement in Figure 1. A single axon is surrounded by a 'coat' of extracellular fluid, and mounted on a pair of perfect electrodes (nonpolarisable and of zero resistance). During the stimulus, a constant current *I* flows between the electrodes. The vector current flux is indicated by arrows. Complete analysis of such a situation requires a detailed mathematical description of the cable properties of the axon, such as was undertaken by Hodgkin and Rushton[1] for a crustacean nerve fibre.

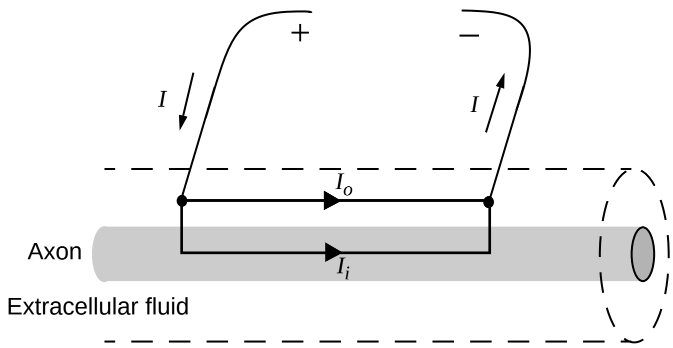

Figure 2. Simplified current flow between electrodes.

For our purposes, a simplified representation (Figure 2) suffices, in which transmembrane current is assumed to flow only at the anode and cathode (in reality it flows at all parts of the axon). If we further ignore capacitive effects, the axon may be represented by a resistive network (Figure 3) in which R_o is the shunt resistance of the external fluid, R_i is the longitudinal resistance of the axoplasm, and R_m is the transmembrane resistance under the cathode or anode. Stimulation will occur when the

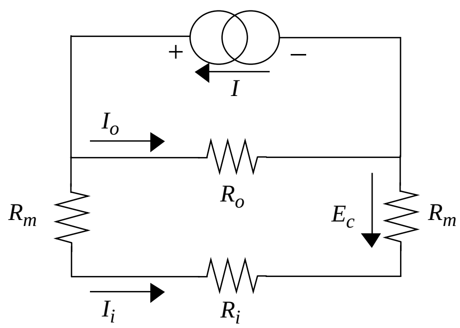

Figure 3. Equivalent circuit of Figure 2.

transmembrane potential at the cathode achieves a depolarising threshold change E_c. Such a change can only occur by virtue of current flow through R_m at the cathode, such that $E_c = I \cdot R_m$. The total stimulus current I is distributed between the axon and the external fluid in inverse proportion to their resistance; it can be shown that

$$E_c = \frac{I \cdot R_m \cdot R_o}{R_i + R_o + 2R_m}$$

Several important results are thus evident. Stimulation of nerves with external electrodes is possible only if a longitudinal intracellular current I_i is caused to flow in the axon. This means that electrode orientation is critical, as described in the section 'Electrode placement' below. Secondly, the effectiveness of the stimulus is greatly affected by the shunt resistance R_o (see 'Efficient stimulation'). Lastly, the effectiveness of a stimulus is proportional to the stimulus current *I*. When time-dependent effects such as capacitance are considered, the duration of a stimulus pulse becomes equally important (see 'Strength-duration curve').

Electrode placement

Three arrangements may be distinguished:

- Bipolar. Both electrodes are close to the nerve (Figure 1).
- Monopolar (also called unipolar). One electrode, normally the anode, is remote from the nerve (Figure 4) so that its size and exact placement are irrelevant.
- Field stimulation. Both electrodes are remote from the nerves (Figure 5). Field stimulation is an inefficient method, typically used to stimulate a nerve plexus in tissue when an individual nerve cannot be exposed.

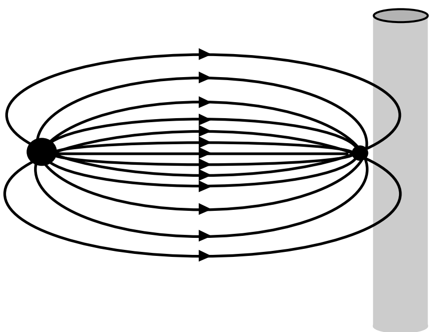

Figure 4. Unipolar stimulation. The anode is distant from the axon, and is usually made larger than the cathode.

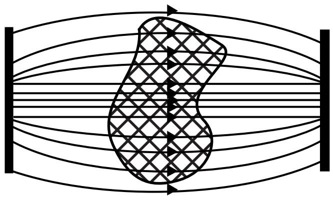

Figure 5. Field stimulation. The electrodes are flat plates. Nerves in the tissue are in varying orientations.

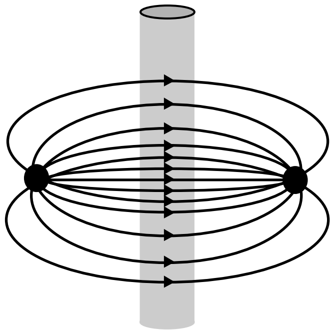

Figure 6. Ineffective symmetrical orientation of electrodes.

Electrodes must be oriented correctly with respect to the nerve fibres. Transverse placement is ineffective (Figure 6), since no longitudinal intracellular current flows in the axon.

Table 1. Current required for stimulation

intracellular	1 nA – 10 nA
grease gap, sucrose gap	0.01 µA – 1 µA
suction electrode	10 µA –1 mA
monopolar with small cathode pushed amongst the nerve fibres	50 µA – 1 mA
bipolar stimulation under paraffin oil	50 µA – 2 mA
bipolar stimulation in volume conductor (saline or tissue)	1 mA – 20 mA
transcutaneous stimulation	2 mA – 20 mA
field stimulation	50 mA – 500 mA

Efficient stimulation

Table 1 shows the approximate current magnitudes required for stimulation under various conditions. Naturally the precise values also depend on the fibre types to be stimulated and on the pulse width.

The range of threshold currents spans six orders of magnitude. The chief reason for this huge range is variation in the extracellular shunt resistance R_o. In the most efficient method, an intracellular microelectrode or whole-cell patch pipette injects current directly into the cell, and R_o is effectively infinite.

Stimulation with external electrodes is much less efficient because most of the stimulus current is wasted by flowing through the shunt resistance R_o. A variety of methods is used to increase efficiency by increasing R_o (Figure 7). In the specialized grease-gap and sucrose-gap methods, an insulating substance replaces most of the extracellular fluid between the electrodes. Simpler methods used in ordinary nerve stimulation include the suction electrode (Figure 8), and the Saxby ring electrode[2], in which all parts of the electrode are insulated except for the inward-facing parts of the rings. Alternatively, a nerve can be suspended in air (either in a humid nerve chamber or coated thinly with silicone gel) or in medicinal-grade paraffin oil.

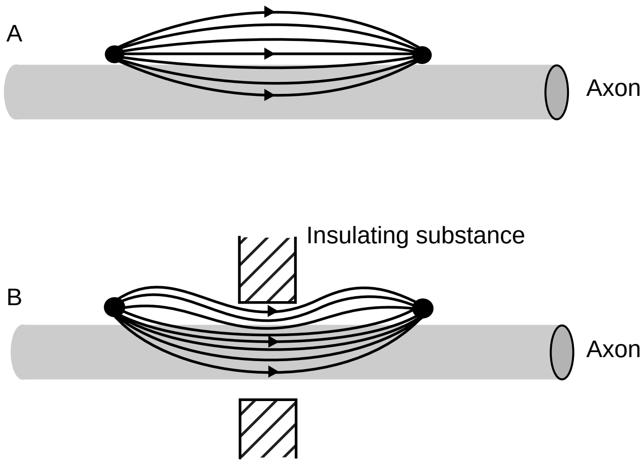

Figure 7. Efficiency of stimulation. (A) Unrestricted flow between bipolar electrodes. (B) Extracellular space between electrodes is obstructed, by one of many methods, increasing R_o so that more current flows in the nerve.

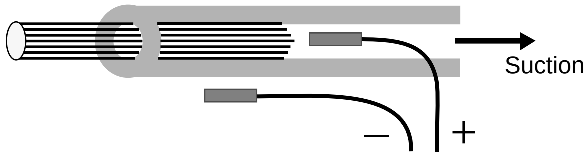

Figure 8. Suction electrode. Gentle suction from the mouth or from a syringe draws the end of the nerve into the glass tube. For greatest efficiency the nerve should be a snug fit. Stimulation occurs outside the glass tube, where cathodal current flows from the nerve. The cathode wire need not approach particularly close to the tip.

Recording and stimulation

A pair of electrodes may be used for extracellular recording as well as for stimulation, merely by connecting them to the input of an amplifier instead of the output of a stimulator. There is an interesting but little-known parallel between the efficiency of stimulation and the efficiency of recording action potentials from the nerve. Any electrode arrangement that is efficient for stimulation gives a large voltage signal in recording, and vice versa. Thus the list in Table 1 is also in order of efficiency of recording, that is of action potential amplitude when the specified electrode arrangement is used for recording.

This is an illustration of the Reciprocity Theorem, which asserts, among other things, that in a passive linear electric circuit the positions of a current source and a voltage-measuring instrument can be interchanged without affecting the voltage recorded. The action potential mechanism can be considered as a current source during recording.

Stimulus polarity

Bipolar stimulation with a small current causes excitation only at the cathode (negative electrode). A propagated impulse arising at the cathode then travels along the axon in both directions (orthodromic and antidromic). Two (usually unwanted) effects may occur at the anode.

Long, strong stimuli may cause anode-break excitation (excitation after the current pulse ends). Such a phenomenon is difficult to recognize or investigate without electrical recording methods. Fortunately, it is unlikely to occur if the stimulus duration is short (<10 ms) and the current intensity is less than 20 times the threshold value.

The other effect is anodal block. Immediately after the stimulus, the membrane near the anode is in a state of reduced excitability. If the stimulus polarity is such that impulses arising at the cathode must propagate past the anode to reach other parts of the preparation, these impulses may fail to pass the anodal region. Since anodal block becomes worse with higher stimulus strengths, a puzzling effect may be seen: the tissue response may fall as the stimulus is increased. To avoid anodal block, the cathode should always be placed nearer the 'business end' of the nerve.

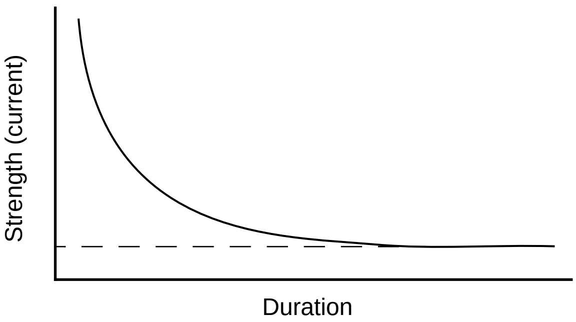

Figure 9. The strength–duration curve for threshold stimulation. The dashed line indicates the rheobase current.

The strength–duration curve

The strength–duration curve for excitation (Figure 9) indicates that stimulus current and duration can be mutually traded off over a certain range. Over this range, the effectiveness of a stimulus is characterized by the product of current and duration, i.e. on the electric charge delivered. For very short pulses this simple relation breaks down because of capacitance of the lead wires. The relation also breaks down for long pulses, as the current approaches the nerve's rheobase value (the minimum effective current).

Nevertheless, over a range extending roughly from 50 µs to 1 ms, changes in duration have a similar effect to changes in the current. For example, if the maximum current from a stimulator is just too small to evoke a particular response with a 0.2 ms pulse, an increase to 0.5 or 1 ms may well be effective.

In nerve stimulation there is rarely much advantage in using pulses longer than 2 ms. For direct stimulation of certain smooth muscles though, a pulse width as long as 10 ms has been recommended[2].

Owing to small fluctuations of excitability, a nerve fibre may not always fire if the stimulus is only slightly above threshold. Dependable stimulation should result if the shock is at least twice the threshold. Intense stimulation may cause tissue damage, but this is unlikely at strengths below 20 times threshold.

Output isolation

The output of some stimulators consists of a voltage pulse referenced to earth potential. In other words, one of the two wires which reach the preparation is grounded. This can be disadvantageous for at least two reasons. One reason is stimulus escape. If the preparation has any other connections to earth, stimulus current may flow in them as well as in the grounded stimulus lead. Unwanted stimulation at sites remote from the stimulus electrodes is then possible, with dire consequences for interpretation of results.

The other reason applies when an electrical response is being recorded with a single-sided (not differential) amplifier, as in intracellular microelectrode or patch techniques. In these cases there is generally a grounded reference electrode, whose job is to supply a reference level (0 V) to the recording amplifier[3]. Passage of stimulus current through this electrode can cause a large and prolonged stimulus artefact, possibly obscuring the response.

An isolated stimulator provides an output with no direct resistive path to ground. Current flowing in one stimulus lead returns to the isolator in the other (Figure 10a), and both problems are prevented.

Similar considerations are applicable in human nerve stimulation, but here there is an even more important reason for stimulus isolation: safety. A properly designed isolator protects against fatal electrocution even if the subject should come in contact with mains voltage.

Constant-current or constant-voltage?

A constant-current stimulator attempts to maintain a specified current between its output terminals, regardless of the load that is connected between the terminals. A constant-voltage stimulator attempts to maintain a specified voltage.

Although both kinds of stimulator can work satisfactorily for nerve stimulation, the constant-current type has the advantage of greater consistency in threshold stimulus strength, because the effectiveness of a stimulus is related directly to the current. Variations in the load (electrode size, contact resistance, and polarisation) do not affect the current from a constant-current stimulator, provided only that they are not so extreme as to cause the stimulator to exceed its compliance voltage.

The current from a constant-voltage stimulator depends as much on the load as on the voltage setting; there is therefore much less consistency in the threshold strength between, and within, experiments. Since polarisation (see below) may develop during a pulse, the current waveform may not be the same shape as the voltage pulse. On the other hand, a constant-voltage output is more suitable for connection as a command signal to other electronic equipment. For example, the PowerLab analog output may be used to supply command signals to voltage clamp amplifiers and the like.

Repetitive constant-current pulses cause more polarisation than constant-voltage pulses, because the polarisation cannot be discharged by backwards current flow between pulses.

Electrodes and polarisation

The junction between a conductive solid phase and an electrolyte solution is known as an electrode. Current flow through any electrode (with one exception) leads to gas formation and polarisation, the latter being a complex phenomenon associated with time-varying overvoltages and rise of electrode resistance. Polarisation may be minimized by keeping the current density low, that is by using an efficient arrangement needing only a small current and by using an electrode with a large surface area.

The exception mentioned above is the case in which the solid phase makes contact with a solution containing some of its own ions. Electric current can here be carried by a reversible chemical reaction. The most commonly used non-polarisable electrode of this type is the silver/silver-chloride electrode, in which the reaction is

$$Ag + Cl^- \leftrightarrow AgCl + e^-$$

A thin coat of AgCl deposited on a silver wire provides a solid store of Cl^- ions. The whole electrode is said to be reversible to chloride ions, in that ionic current in the surrounding solution is carried by Cl^-. Transfer of charge in such an electrode is little impeded by polarisation effects, provided the current density is sufficiently low.

Apart from considerations of polarisability, the choice of electrode material is also governed by the toxicity of many metallic ions (especially copper). Practically, the choice is between plain platinum wires and chloridised silver wires. Most workers use platinum.

PowerLab stimulators

Stimulus Isolator

The ML180 Stimulus Isolator front-end is a versatile unit suitable for both transcutaneous human nerve stimulation and stimulation of isolated nerves. The output is constant-current with three ranges (0–10 mA, 0–1 mA and 0–100 µA), giving fine control of stimulus amplitude. On the lowest range, the resolution (smallest step) is 1 µA. The compliance (maximum output voltage) is 100 V. Pulse widths are 10 µs – 2.5 ms.

Built-in Isolated Stimulators

This kind of stimulator is found in PowerLab models 4ST, 4/20T, and 410, and in the Dual Bio Amp and Stimulator front-end. It is intended for transcutaneous human nerve stimulation. The output is constant-current with one range (0–20 mA), in which the resolution (smallest step) is 100 µA. The resolution is too coarse for investigation of the threshold of isolated nerves. The compliance (maximum output voltage) is 100 V. Pulse widths are 50–200 µs.

Analog outputs

PowerLabs (except the PowerLab/410) have analog outputs, available via the output sockets on the front panel. The outputs are constant voltage and non-isolated, with a range of ±10 V. If both outputs are used, a differential stimulus of ±20 V can be obtained. The maximum current is 25–50 mA.

The analog outputs are unsuitable for transcutaneous nerve stimulation because they are not isolated and because the output voltage is too low. They are also unsuitable for field stimulation.

An important use for the positive analog output is to provide a trigger pulse to an external stimulator. In this application, the pulse width should be set to its minimum, and the amplitude to maximum (10 V).

The analog outputs may be used in various connections for stimulation of an exposed nerve, as shown in Figure 10b–d. The arrangement of Figure 10b is often recommended, apparently by analogy with the well-established arrangement of Figure 10a. But some anodal stimulus current will flow in the earth electrode because the analog outputs are ground-referenced. Although this arrangement is not ideal, it does work for student lab class experiments on the amphibian sciatic nerve. A simple improvement is to remove the ground connection to the nerve (Figure 10c). If the full 20 V differential stimulus is not needed, then the arrangement shown in Figure 10d is recommended.

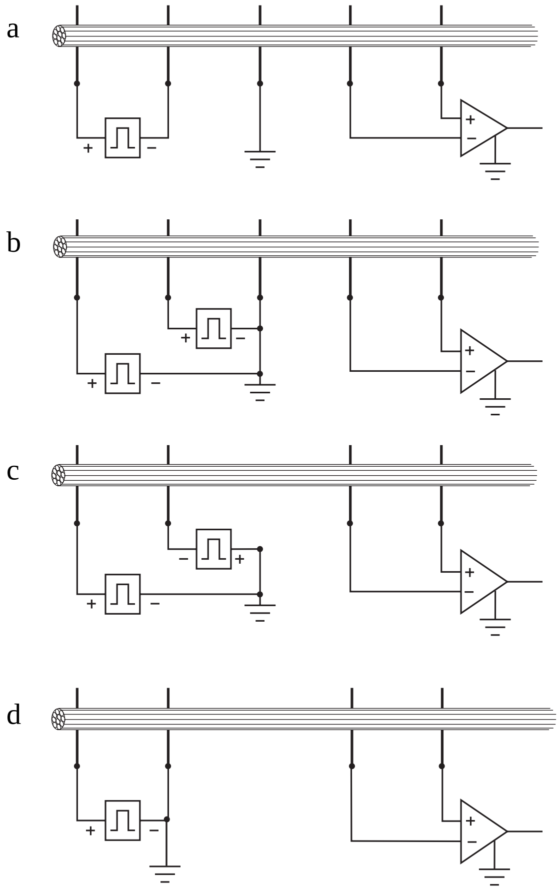

Figure 10. Connections for stimulating a nerve and recording with general-purpose inputs.
(a) arrangement commonly used with an isolated stimulator;
(b) as in (a) but with ground-referenced stimulator (PowerLab analog output); not recommended;
(c) as in (b) but with ground connection to nerve removed;
(d) recommended.

References

1. A. L. Hodgkin and W. A. H. Rushton, 'The electrical constants of a crustacean nerve fibre', *Proceedings of the Royal Society B* 133: 444–479 (1946).

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3. R. D. Purves, *Microelectrode Methods for Intracellular Recording and Ionophoresis* (Academic Press, London, 1981).

Document Number: ALB17c

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