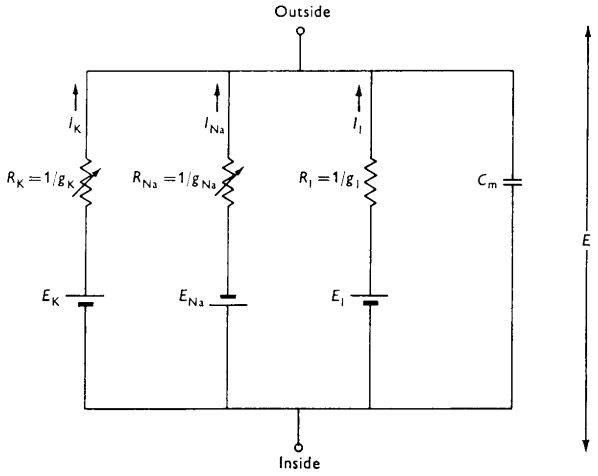
Conceptual model of a patch of electrically excitable membrane. (After Hodgkin and Huxley, 1952*d*.)



At the steady state (resting membrane) when there Is not net current:

$$I_K + I_{Na} + K_{Cl} = 0$$

For K, Na and Cl: $I_K = g_K(E_m - E_K)$

$I_{Na} = g_{Na}(E_m - E_{Na})$

$I_{Cl} = g_{Cl}(E_m - E_{Cl})$

$$\therefore E_m = \frac{g_k}{\sum g} E_k + \frac{g_{Na}}{\sum g} E_{Na} + \frac{g_{Cl}}{\sum g} E_{Cl}$$

Where $\sum g = g_K + g_{Na} + g_{Cl}$

An action potential recorded intracellularly from a squid giant axon. The vertical scale shows the potential (mV) of the internal electrode with respect to the external sea water. The action potential is preceded by a small stimulus artefact. The sine wave at the bottom is a time marker, frequency 500 Hz. (From Hodgkin and Huxley, 1945.)

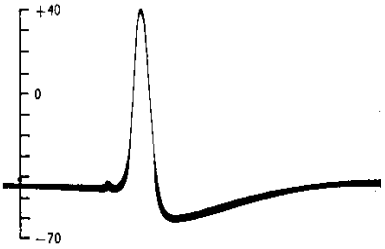
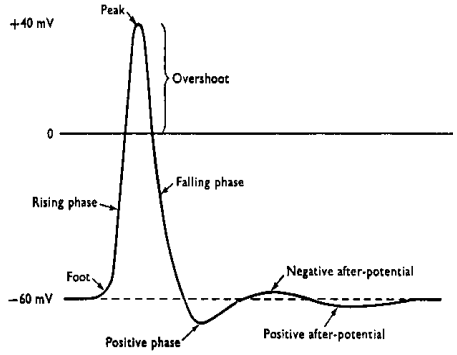


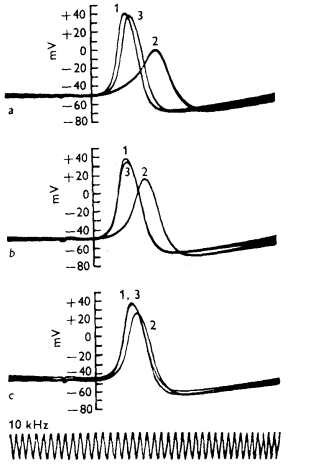
Diagram to show the nomenclature applied to an action potential and the after-potentials which follow it.



The “sodium theory” of the action potential

Action potentials exhibit an overshoot. Thus the peak of the action potential is well above zero. Hodgkin and Katz suggested (in 1949) that this was due to a rapid and selective increase increase in the permeability towards sodium.Thus g_{Na} transiently becomes much greater than g_k .How can this idea be tested?

The effect of reducing the external sodium ion concentration on the size of the action potential in a squid giant axon. In each set of records, record 1 shows the response with the axon in sea water, record 2 in the experimental solution, and record 3 in sea water again. Experimental solutions were made by mixing sea water and isotonic glucose solutions, the proportions of sea water being *a*, 33%; *b*, 50%; and *c*, 70%. (From Hodgkin and Katz, 1949.)



Positive Feedback

Increase in g_{Na}

Depolarization

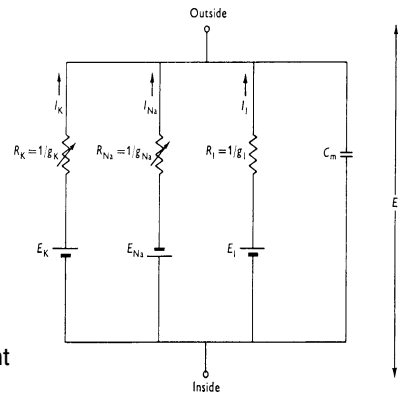
Na flux

Current flowing through the axon membrane is assumed to consist of capacity current and Ionic current.

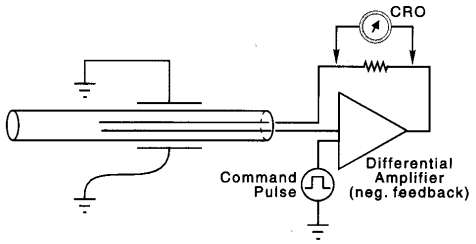
$$I = C_m \frac{dE}{dt} + I_i$$

If the voltage is held constant i.e
The membrane is clamped dE/dt=0
and the membrane current =ionic current
i.e $I=I_i$

Conceptual model of a patch of electrically excitable membrane. (After Hodgkin and Huxley, 1952*d*.)

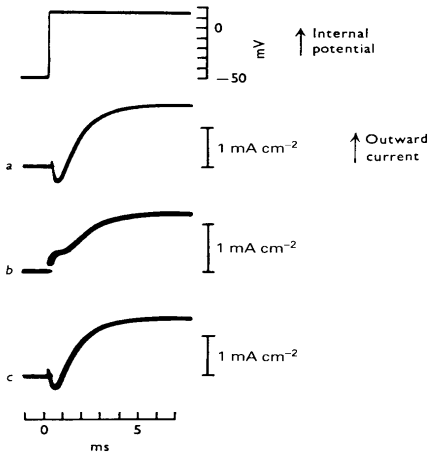


Voltage Clamp

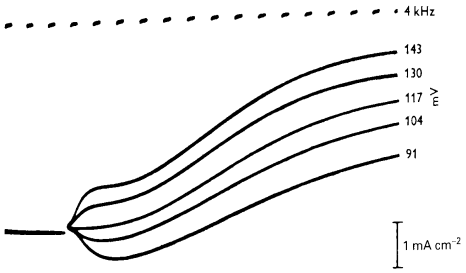


The voltage clamp method used in a squid giant axon. The two wires inserted into the axon are used to measure membrane potential (V) and to pass current (I). The high-gain negative-feedback amplifier compares the command pulse with the membrane potential, and outputs the amount of current necessary to hold the membrane potential constant (or "clamped"). The magnitude of the feedback current can be measured as the IR voltage drop across a resistor and displayed on a cathode-ray oscilloscope (CRO).

Typical records of the membrane current during a voltage clamp experiment. *a* and *c*: In sea water; *b*: in a sodium-free choline chloride solution. (From Hodgkin, 1958, after Hodgkin and Huxley, 1952*a*.)

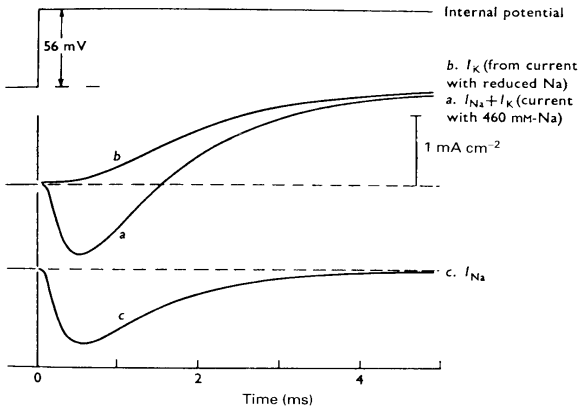


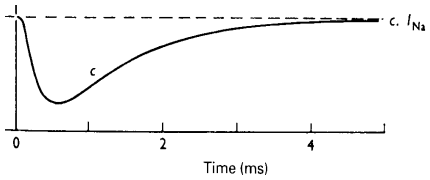
Membrane currents at large depolarizations. Values of V are shown at the right of each record. (From Hodgkin, 1958, after Hodgkin, Huxley and Katz, 1952.)



The potential at which the initial (Na current) is neither inward nor outward is the reversal potential E_{Na} for the Na current i.e about 117 mV.

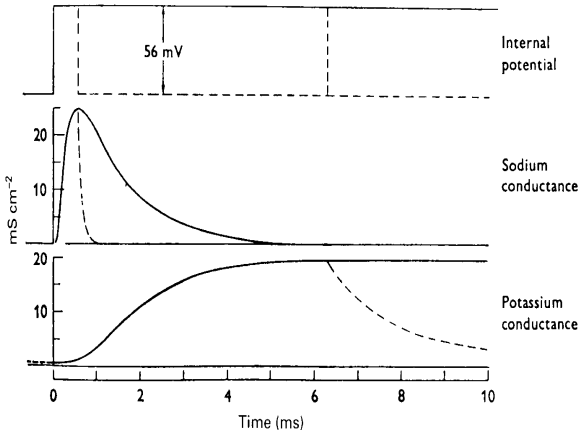
Analysis of the ionic current in a *Loligo* axon during a voltage clamp. Trace *a* shows the response to a depolarization of 56 mV with the axon in sea water. Trace *b* is the response with the axon in a solution comprising

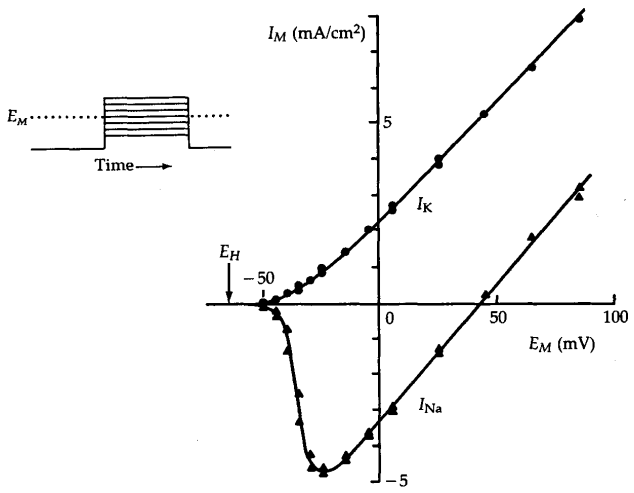




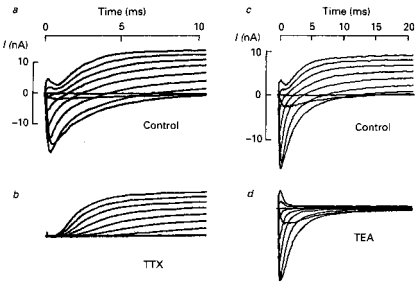
From traces of Na current as a function of time we can obtain g_{Na} by using the equation $I_{Na}=g_{Na}(E-E_{Na})$. E_{Na} is the potential at which the current is nulled.

Ionic conductance changes during a clamped depolarization, derived from the current curves shown in fig. 5.12. The broken curves show the effects of repolarization. (From Hodgkin, 1958, by permission of the Royal Society.)



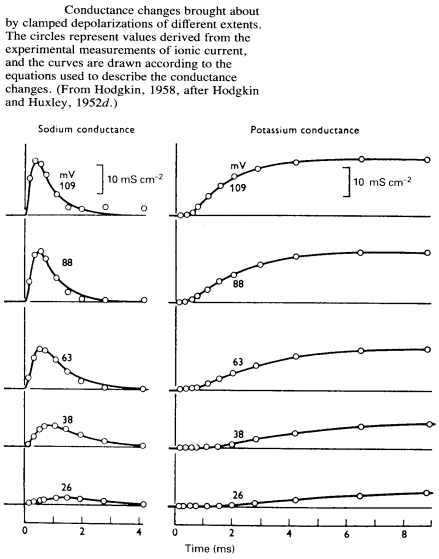


Voltage-clamp records for frog nodes, showing separation of the sodium and potassium currents by the use of selective blocking agents. The membrane potential was clamped at −120 mV for 40 ms before the start of the records, and then depolarised to various levels ranging from −60 to +60 mV in 15 mV steps. Leakage and capacity currents were subtracted by computer. Records in *a* and *c* show the normal response. In *b* the node shown in *a* was treated with 300 nM tetrodotoxin; only the potasssium current remains. In *d* the node shown in *c* was treated with 6 mM TEA; only the sodium current remains. (From Hille, 1984, after Hille, 1966 and 1967.)



If we knew the time and voltage dependence of gNa and gK we could obtain the form the the action potential by numerical integration of the following equation.

$$I_m = C_m dV/dt + g_k(E-E_k) + g_{Na}(E-E_{Na}) + g_l(E-E_l)$$



Conductance changes brought about by clamped depolarizations of different extents. The circles represent values derived from the experimental measurements of ionic current, and the curves are drawn according to the equations used to describe the conductance changes. (From Hodgkin, 1958, after Hodgkin and Huxley, 1952*d*.)

$g_K = \bar{g}_K\, n^4$ n=probability of 4 charged particles being in the correct configuration for conduction.

$g_{Na} = \bar{g}_{Na}\, m^3h$ n=probability of 3 charged particles being In the correct configuration.1-h=probability of inactivation.

n is the potassium activation parameter,m and h are the Na activation and inactivation parameters.

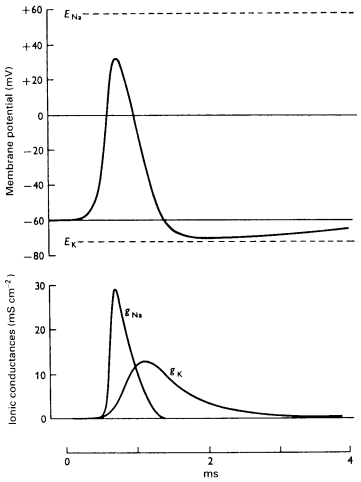
$I_m = C_m dE/dt + I_k + I_{Na} + I_i$

$= C_m dV/dt + g_k(E-E_k) + g_{Na}(E-E_{Na}) + g_l(E-E_l)$

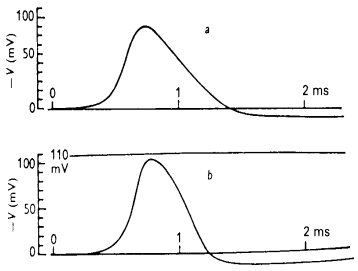
$= C_m dV/dt + \bar{g}_{Na} n^4 (E-E_k) + \bar{g}_{Na} m^3 h\,(E-E_{Na}) + g_l(E-E_l)$

With the voltage and time dependence of m,n and h the Above equation can be solved for V by numerical integration

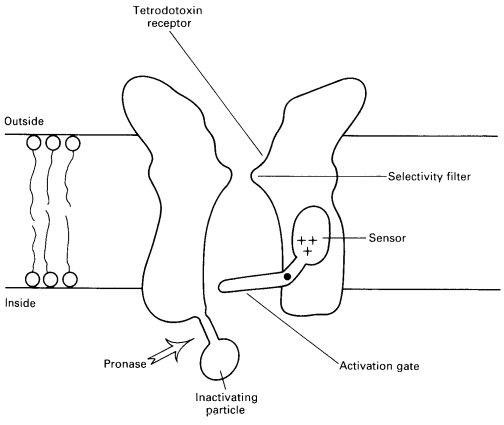
Calculated changes in membrane potential (upper curve) and sodium and potassium conductances (lower curves) during a propagated action potential in a squid giant axon. The scale of the vertical axis is correct, but its position may be slightly inaccurate; it has been drawn here assuming a resting potential of −60 mV. The positions of E_{Na} and E_K are correct with respect to the resting potential. In the original calculations, voltages were measured from the resting potential, as in fig. 5.15. (After Hodgkin and Huxley, 1952*d*; redrawn.)



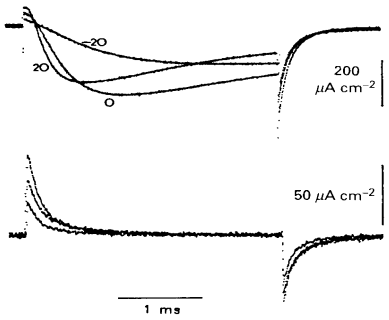
Comparison of computed (*a*) and observed (*b*) propagated action potentials in squid axon at 18.5 °C. The calculated velocity of conduction was 18.8 m s^{-1}; the observed velocity was 21.2 m s^{-1}. (From Hodgkin and Huxley, 1952*d*.)



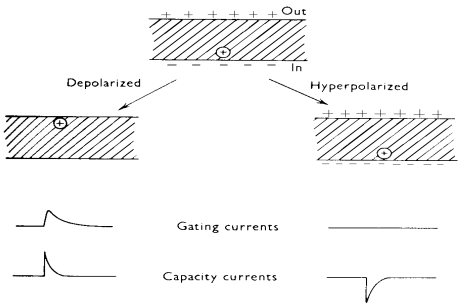
A sketch to show the main features of the sodium channel. (Based partly on diagrams by Armstrong, 1981, and Hille, 1984.)



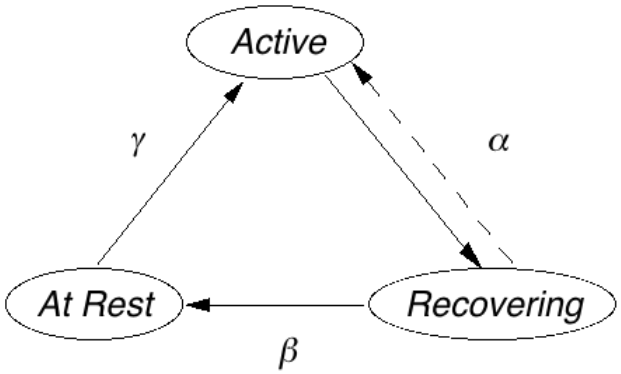
Sodium ionic and gating currents in squid axon, produced during depolarizations under voltage clamp. The upper traces show currents recorded in an artificial sea water with only one fifth of the normal sodium concentration, for depolarizations from −70 mV to −20, 0 and +20 mV. The initial brief outward current is gating current, followed by the much larger inward sodium ionic current. The lower set shows the gating currents alone, after blockage of the sodium ionic currents with tetrodotoxin. Potassium currents were eliminated by using potassium-free solutions for both internal and external media. (From Bezanilla, 1986.)



Schematic diagram showing one way in which gating currents could arise. The capacity currents are much larger than the gating currents.

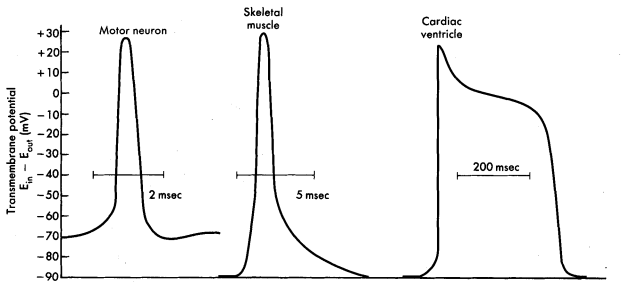


Channel (Gating) Simulations



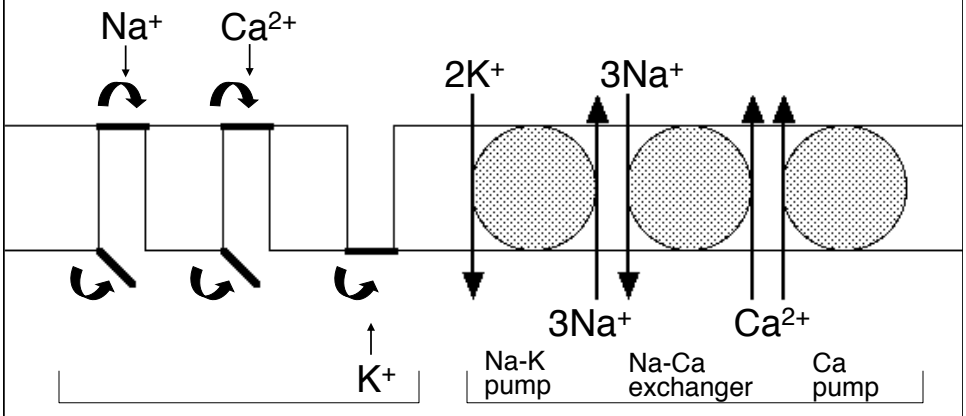
α, β, γ: state transition probabilities, (functions of v and t)

Action Potential from Different Cells



Action potentials from three vertebrate cell types. Note the different time scales.
(Redrawn from Flickinger CJ et al: *Medical cell biology,* Philadelphia, 1979, WB Saunders.)

Cardiac Ion Currents



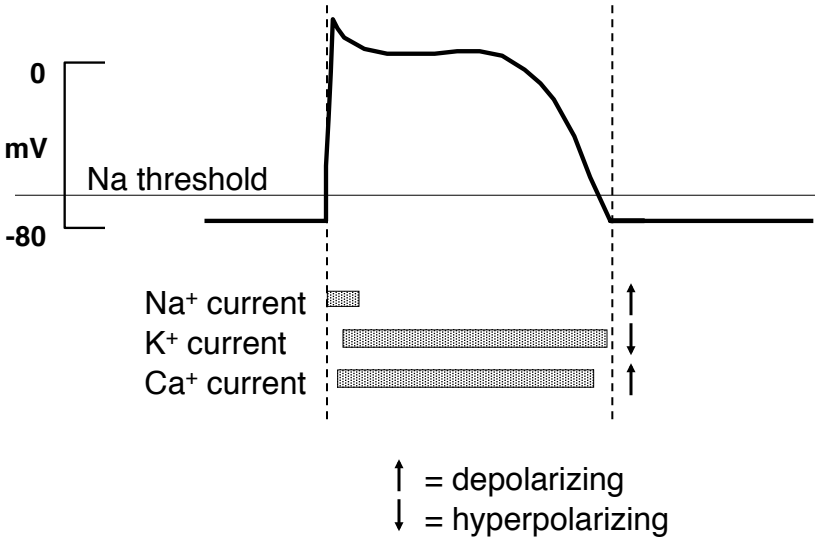
Ion channels

- Passive ion movement
- Driven by concentration and

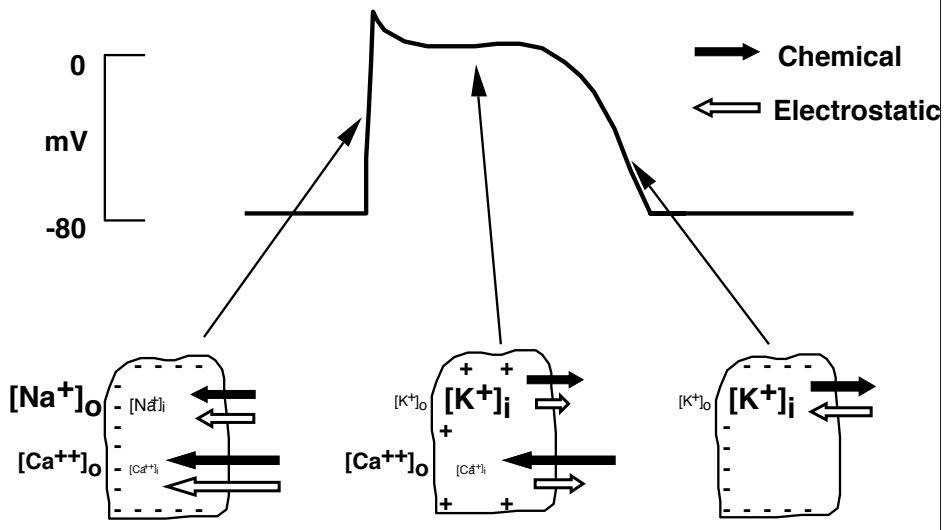
Carrier mediated ion transport

- Na-K and Ca pumps require ATP
- Capable of driving against concentration

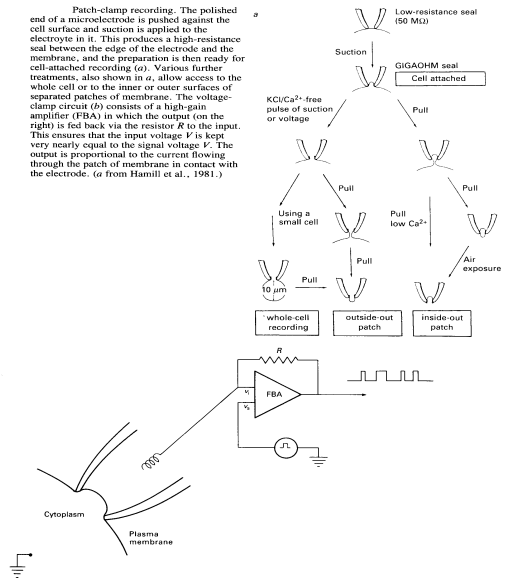
Cardiac Action Potential



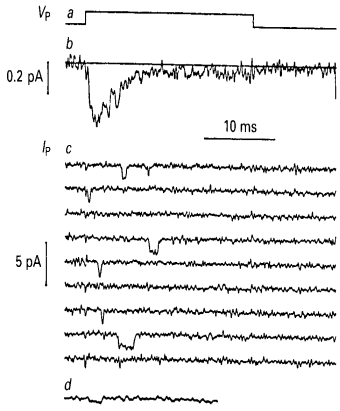
Cardiac Cell Currents



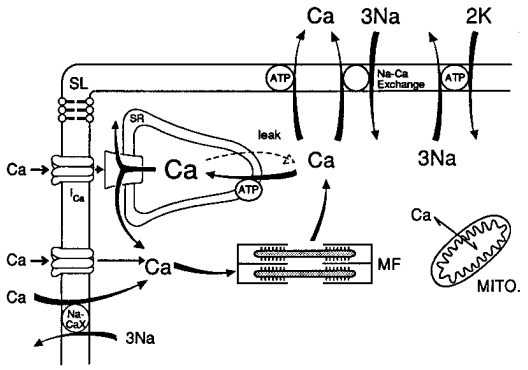
Patch-clamp recording. The polished end of a microelectrode is pushed against the cell surface and suction is applied to the electroyte in it. This produces a high-resistance seal between the edge of the electrode and the membrane, and the preparation is then ready for cell-attached recording (*a*). Various further treatments, also shown in *a*, allow access to the whole cell or to the inner or outer surfaces of separated patches of membrane. The voltage-clamp circuit (*b*) consists of a high-gain amplifier (FBA) in which the output (on the right) is fed back via the resistor *R* to the input. This ensures that the input voltage *V* is kept very nearly equal to the signal voltage *V*. The output is proportional to the current flowing through the patch of membrane in contact with the electrode. (*a* from Hamill et al., 1981.)



Single sodium channel currents from cultured rat muscle cells, recorded with the cell-attached patch-clamp technique. Trace *a* shows the imposed membrane potential, held at $V = -30$ mV (where V = 0 is the resting potential) and depolarized by 40 mV to $V = +10$ mV for about 23 ms at 1 s intervals. Trace *b* shows the average of a set of 300 of current records elicited by these pulses. *c* shows nine successive individual records from this set. Square pulses of inward current (average size 1.6 pA) can be seen in most of the records; these correspond to the opening of individual channels. Trace *d* shows a record taken when two thirds of the sodium ions in the pipette had been replaced with tetramethylammonium ions; the single-channel current is reduced accordingly. (From Sigworth and Neher, 1980.)



Calcium Cycle in Cardiac Muscle



General scheme of Ca cycle in a cardiac myocyte. Ca can enter via Ca channels and Na/Ca exchange. Ca current may also control the SR Ca release by the SR Ca release channel/ ryanodine receptor/ foot protein. Ca is removed from the myofilaments (MF) and cytoplasm by the SR Ca-ATPase pump and the sarcolemmal Ca-ATPase pump and Na/Ca exchange.