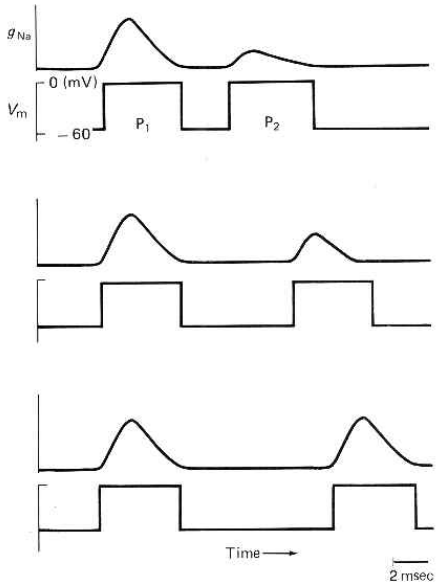
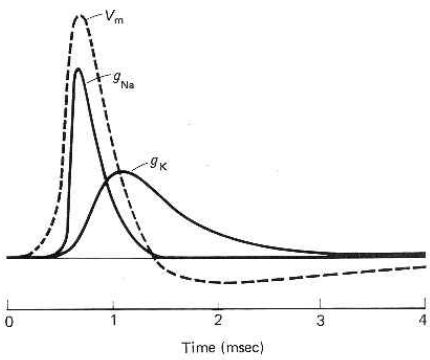


8–6 The second of two depolarizing pulses (P_2) produces a smaller increase in g_{Na} if the interval between the first (P_1) and second is brief, because Na^+ inactivation persists for a few milliseconds after the end of the first activating pulse.

line a). In addition, with maintained depolarization, the Na^+ channels begin to close down, or inactivate, leading to a decay of inward current (Figure 8–4 and Figure 8–5, line b). In contrast, the K^+ channels remain open as long as the membrane is depolarized (Figure 8–5). Each Na^+ channel can exist in three different states thought to represent three different conformations of the Na^+ channel protein: resting, activated, or inactivated. Upon depolarization, the channel goes from the resting (closed) to the activated (open) state. If the depolarization is maintained, the channel switches to the inactivated (closed) state. Once the channel is inactivated, it is refractory: it cannot be activated (opened) by depolarization. The inactivation can be removed only by repolarizing the membrane, which allows the channel to switch from the inactivated to the resting state. This switch takes time because inactivation wanes slowly (Figure 8–6). After the channel has returned to the resting state, it again is available for activation by depolarization.

8–7 The action potential can be reconstructed from the changes in g_{Na} and g_K that result from the opening and closing of Na^+ and K^+ voltage-gated channels. (Adapted from Hodgkin, 1964.)



The Action Potential Can Be Reconstructed from the Individual Electrical Properties of the Neuron

By analyzing the records of depolarizing pulses of various amplitudes and durations, Hodgkin and Huxley generated a complete set of empirical equations that describe the variation of conductances through the Na^+ and the K^+ channels as a function of membrane potential and time. Using these equations and the values of the passive properties of the axon, they were able to compute the predicted shape and the conduction velocity of the propagated action potential. That this calculated waveform agreed almost perfectly with the action potential recorded in the unclamped axon indicates that the data accurately describe the features of the voltage-dependent conductance channels that are essential for the propagation of the action potential.

According to the Hodgkin–Huxley model, an action potential involves the following sequence of events (Figure 8–7). A depolarization of the membrane causes a rapid opening of Na^+ channels (an increase in g_{Na}), resulting in an inward Na^+ current. This current causes further depolarization, which results in more inward current, and the regenerative process leads to the generation of the action potential.[3] Two factors limit the duration of the action potential: (1) The depolarization of the action potential gradually inactivates the Na^+ channels (g_{Na}). (2) The depolarization also opens, with some delay, the voltage-gated K^+ channels, thereby increasing g_K. Consequently the Na^+ current is followed by an outward K^+ current that tends to repolarize the membrane (Figures 8–4 and 8–5).

In most nerve cells, action potentials are followed by a transient hyperpolarization, the hyperpolarizing afterpotential. This brief increase in the negativity of the membrane potential occurs because the K^+ channels that open during the later phase of the action potential do not all close immediately, even after V_m has returned to its resting value. It takes a few milliseconds for all of the voltage-gated K^+ channels to return to the closed state.

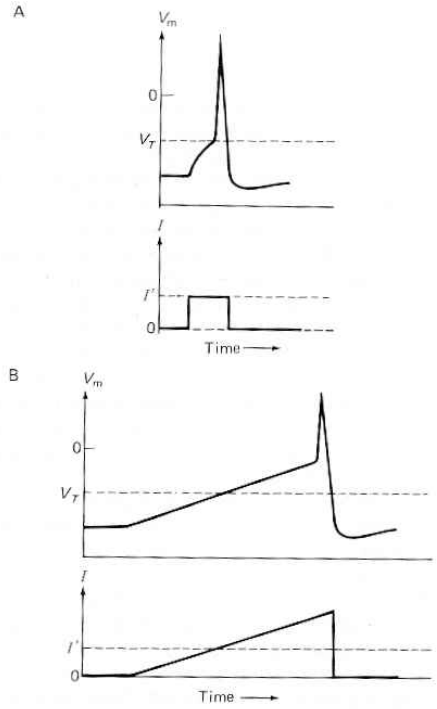
[3] It may at first seem paradoxical that to depolarize the cell experimentally one passes *outward* current across the membrane (see Figure 5–1), while the depolarization during the upstroke of the action potential is attributed to an *inward* Na^+ current. Actually, in both cases *outward* current flows across the passive components, the nongated leakage channels (g_l) and the capacitance (C_m), of the membrane. This outward current across the passive membrane results because current is injected into the cell: in one case through an intracellular electrode (Figure 7–2), and in the other case by the opening of voltage-gated Na^+ channels.

The resulting residual opening of active K^+ channels leads to a greater efflux of K^+ from the cell than occurs in the resting state. This efflux, in turn, causes V_m to hyperpolarize slightly with respect to its normal resting value (Figure 8–7).

The action potential is also followed by a brief period of refractoriness, which can be divided into two phases. The *absolute refractory period* comes immediately after the action potential; during this period, it is impossible to excite the cell no matter how large a stimulating current is applied. This phase is followed directly by the *relative refractory period*, during which it is possible to trigger an action potential, but only by applying stimuli that are stronger than normal. These periods of refractoriness, which together last just a few milliseconds, are both caused by the residual opening of K^+ channels and the residual inactivation of Na^+ channels.

Another feature of the action potential predicted by the Hodgkin–Huxley conductance data is its threshold. Action potentials are all or none in amplitude, and for depolarizations in the range of threshold an additional fraction of a millivolt may be the difference between a subthreshold stimulus and a stimulus that generates a full-blown action potential. This all-or-none behavior may seem surprising when one considers that Na^+ conductance (proportional to the number of Na^+ channels that are open) increases in a strictly graded manner as depolarization is increased (Figure 8–4). With each increment of depolarization, the number of voltage-gated Na^+ channels that flip from the closed to the open state increases in a gradual fashion, thereby causing a gradual increase in the Na^+ influx. What then gives the action potential its threshold? Although a small subthreshold depolarization increases the inward I_{Na}, it also increases two *outward* currents, I_K and I_l, by changing the driving forces that determine their values (see Equation 8–1a). In addition to increasing the driving force for I_K, the depolarization also causes a slow increase in g_K by gradually increasing the number of open K^+ channels (Figure 8–4). As I_K and I_l increase with depolarization, they tend to resist the depolarizing action of the Na^+ influx. The steep voltage sensitivity and rapid kinetics of the Na^+ channel activation process ensure that, as the depolarization proceeds, it will eventually reach a point—the threshold—where the increase in inward I_{Na} outstrips the increase in outward I_K and I_l, and therefore becomes regenerative. Thus a threshold exists because there is a specific value of V_m at which the *net* ionic current ($I_{Na} + I_K + I_l$) just changes from outward to inward, depositing positive charge on the inside of the membrane capacitance.

The data reported by Hodgkin and Huxley also explain why a slowly rising stimulating current may fail to trigger an action potential when it depolarizes the cell to its usual threshold membrane potential, V_T (Figure 8–8). It fails to do so because during a slow approach to V_T the two dynamic processes that oppose the regenerative property of the membrane—inactivation of the Na^+ channels and the activation of the K^+ channels—have a chance to develop significantly before V_T is reached.



8–8 A slowly rising current pulse causes a cell's firing threshold to increase through a process called accommodation. **A.** To reach threshold (V_T) for spike generation, a rectangular (or constant-amplitude) current pulse need have an amplitude of only I'. **B.** If depolarizing current is increased gradually, accommodation occurs and the stimulating current must surpass I' before a spike is initiated.

Therefore, to activate enough Na^+ channels to trigger an action potential, one must depolarize the cell by a greater than normal increment. This increase in threshold resulting from the application of a slowly rising current is called *accommodation*. By decreasing the rate of rise of current even more, one can produce a depolarization so slow that, regardless of how much the cell is depolarized, an action potential is not elicited.

The Na^+ Channel Can Be Characterized in Molecular Terms

The empirical equations derived by Hodgkin and Huxley have been remarkably successful in describing the flow of ions through the Na^+ and K^+ channels that underlies the action potential. However, these equations describe the process of excitation only on a phenomenological level. The data of Hodgkin and Huxley tell us little about the molecular nature of the conductance channels and the mechanisms by which they are activated. Recent work on the Na^+ channel has been directed along these lines.