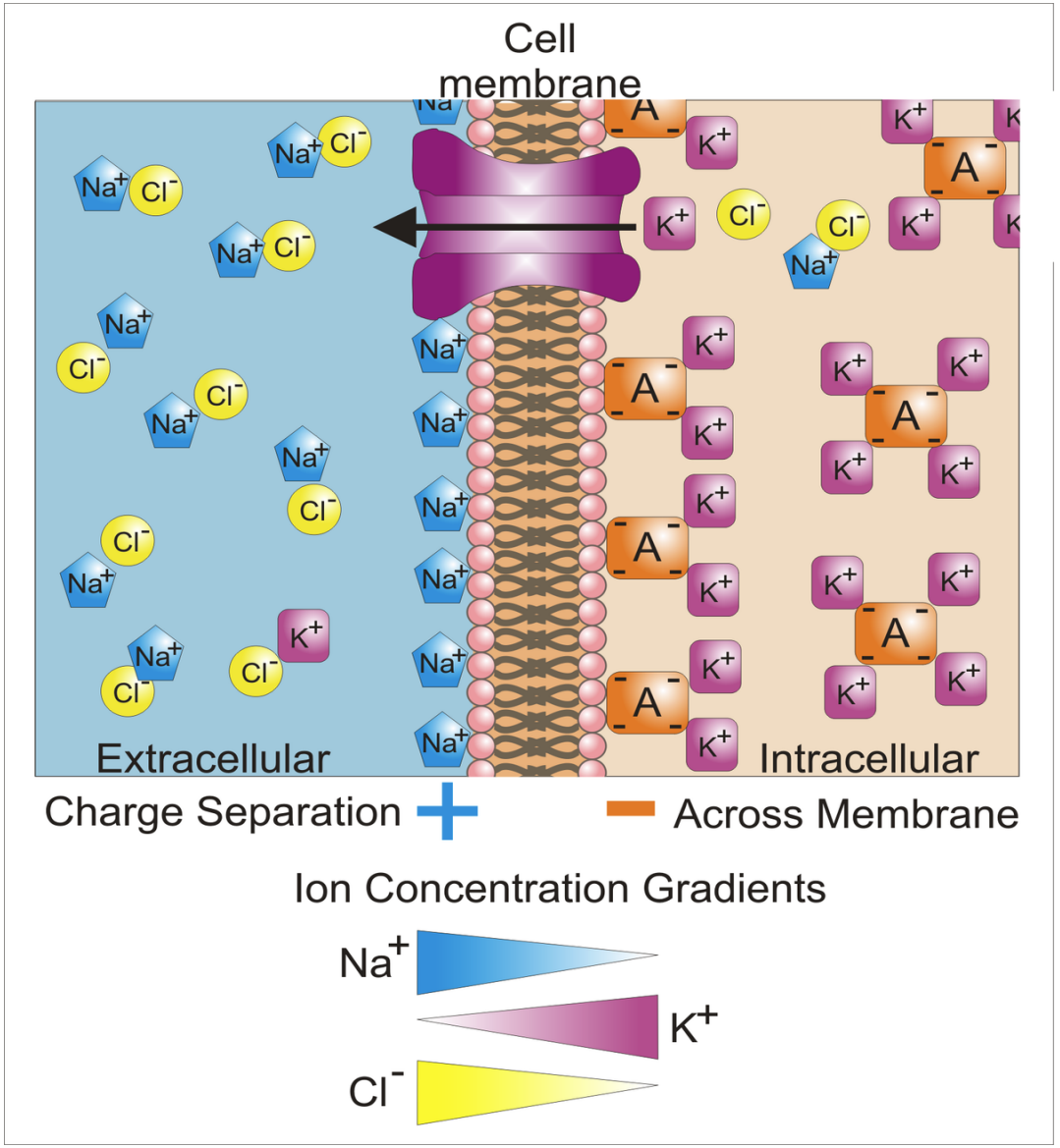
Membrane Potential, Calcium Homeostasis, Signal Transduction

Membrane potential:

In all cells, there is an **electrical potential difference** between the inside of the cell and the surrounding extracellular fluid, caused by the net separation of charge between them. A **very small number** of ions is needed to create the resting membrane potential, 1:1000 is the ratio of ions involved in the maintenance of the membrane potential and ions in the cytosol.



Movement of ions through the membrane:

- ion channels
- transporters
- leaking

Two energetic factors influence the movement of an ion across a membrane.

- The concentration gradient: it applies to uncharged molecules too.
- The electrical potential difference

The total energy change for the movement of an ion across the membrane is the sum of the energy change due to the concentration gradient and the energy change due to electrical potential difference.

These two factors may act in the same direction or in opposite directions.

Depolarization: when the membrane potential becomes less negative

Hyperpolarization: when the membranepotential becomes more negative.

Changes in the Membrane Potential

The opening of an ion channel and the subsequent movement of ions through the channel necessarily changes the membrane potential. This, of course, is because the moving ions are moving charges.

TABLE 1–1 Concentration of some ions inside and outside mammalian spinal motor neurons.

Ion	Concentration (mmol/L of H_2O)		Equilibrium Potential (mV)
	Inside Cell	Outside Cell	
Na+	15.0	150.0	+60
K+	150.0	5.5	–90
Cl–	9.0	125.0	–70

Resting membrane potential = –70 mV

A specific ion moving through an open ion channel causes the membrane potential to move towards the equilibrium potential for that specific ion.

Ca^{2+} homeostasis, Ca^{2+}-mediated cellular functions

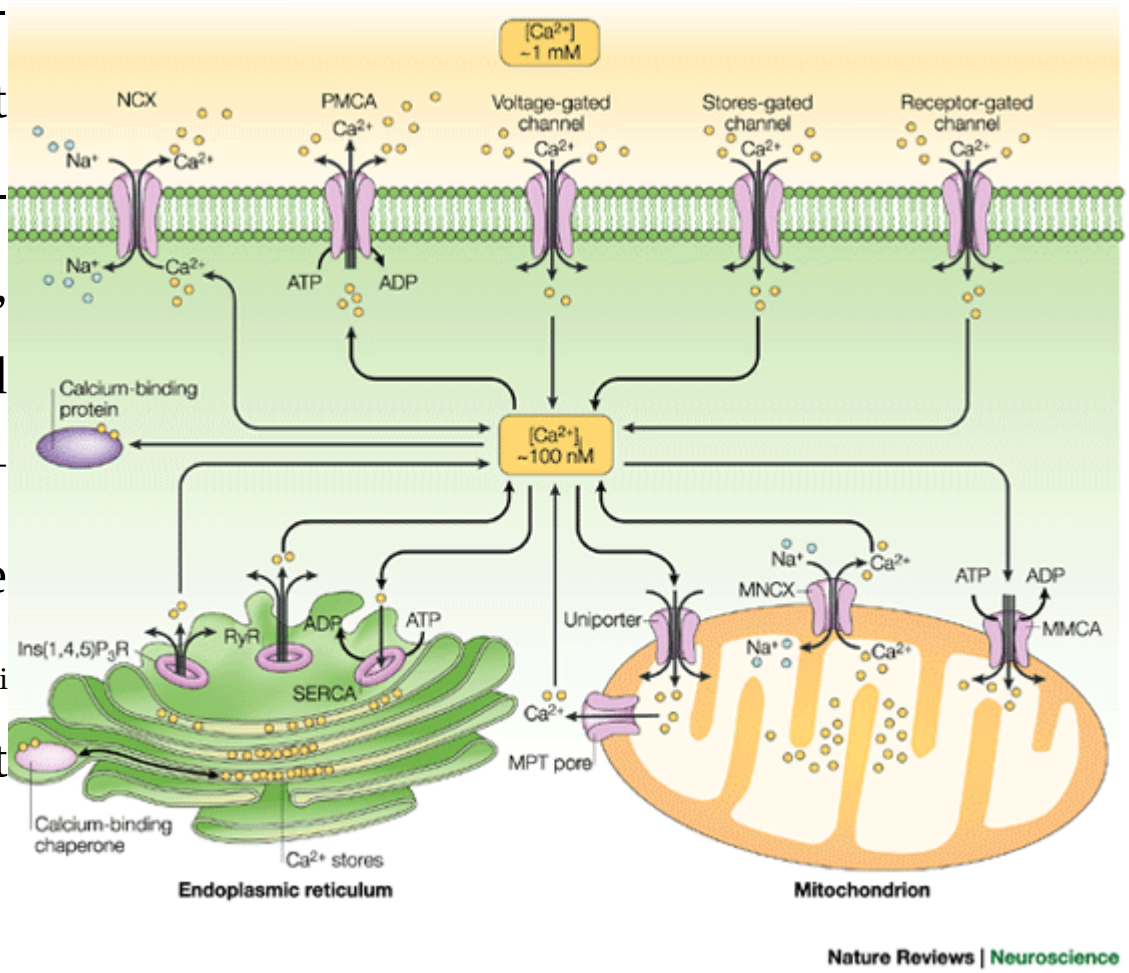
Calcium ion-regulated processes are diverse:
cell motility, gene transcription, muscle contraction, and exocytosis.

Calcium triggers skeletal muscle contraction by binding to troponin C and that calcium can be sequestered in the sarcoplasmic reticulum.

Numerous proteins are modulated directly or indirectly by calcium.

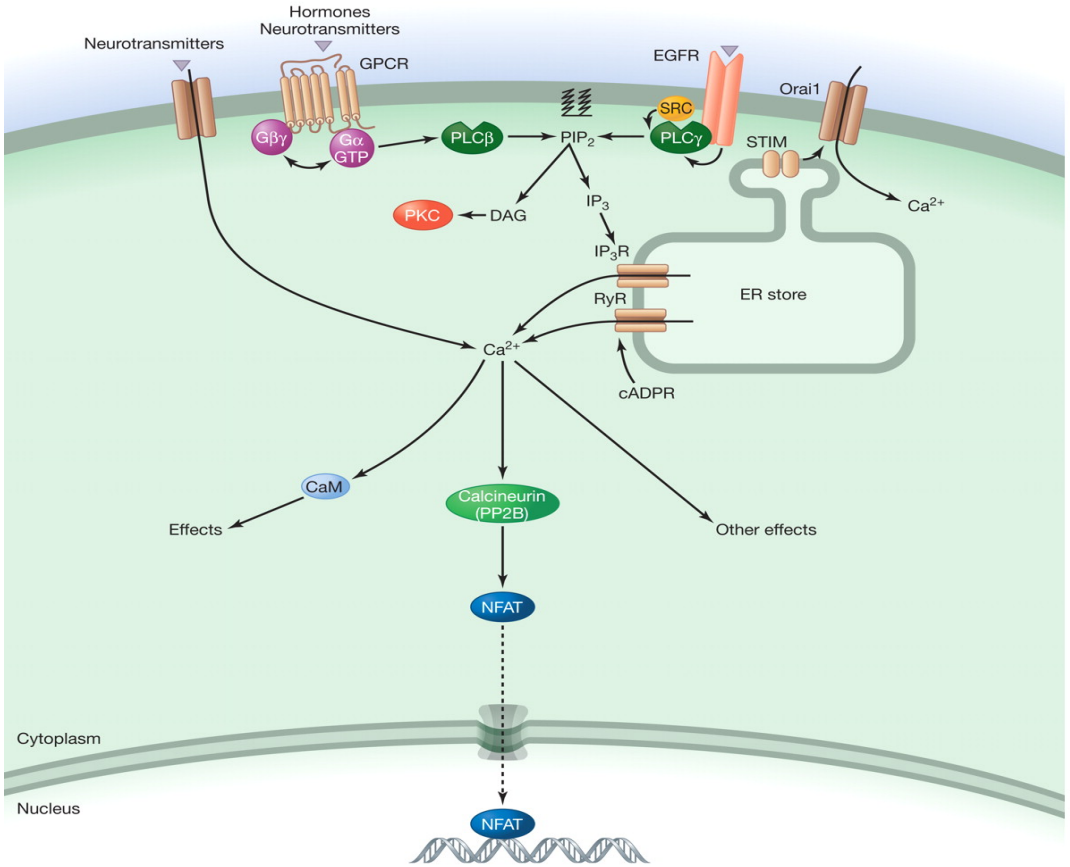
Secretory vesiculi are released following Ca^{2+} entry into the cytosol.

Intracellular calcium ($[Ca^{2+}]_i$) concentration is tightly regulated within narrow limits. $[Ca^{2+}]_i$ increases through Ca^{2+} influx from extracellular pools through various channels (voltage-, ligand- or concentration-gated channels). $[Ca^{2+}]_i$ can also increase through release from endoplasmic reticulum stores, through the ryanodine (RYR), and inositol-trisphosphate receptors. Counter-balancing mechanisms fight to halt $[Ca^{2+}]_i$ increase. The plasma-membrane Ca^{2+} pump (PMCA), Na^+/Ca^{2+} exchanger (NCX) and sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) function to restore normal Ca^{2+} levels. Increased $[Ca^{2+}]_i$ drives Ca^{2+} overload at mitochondria, through PMCA.



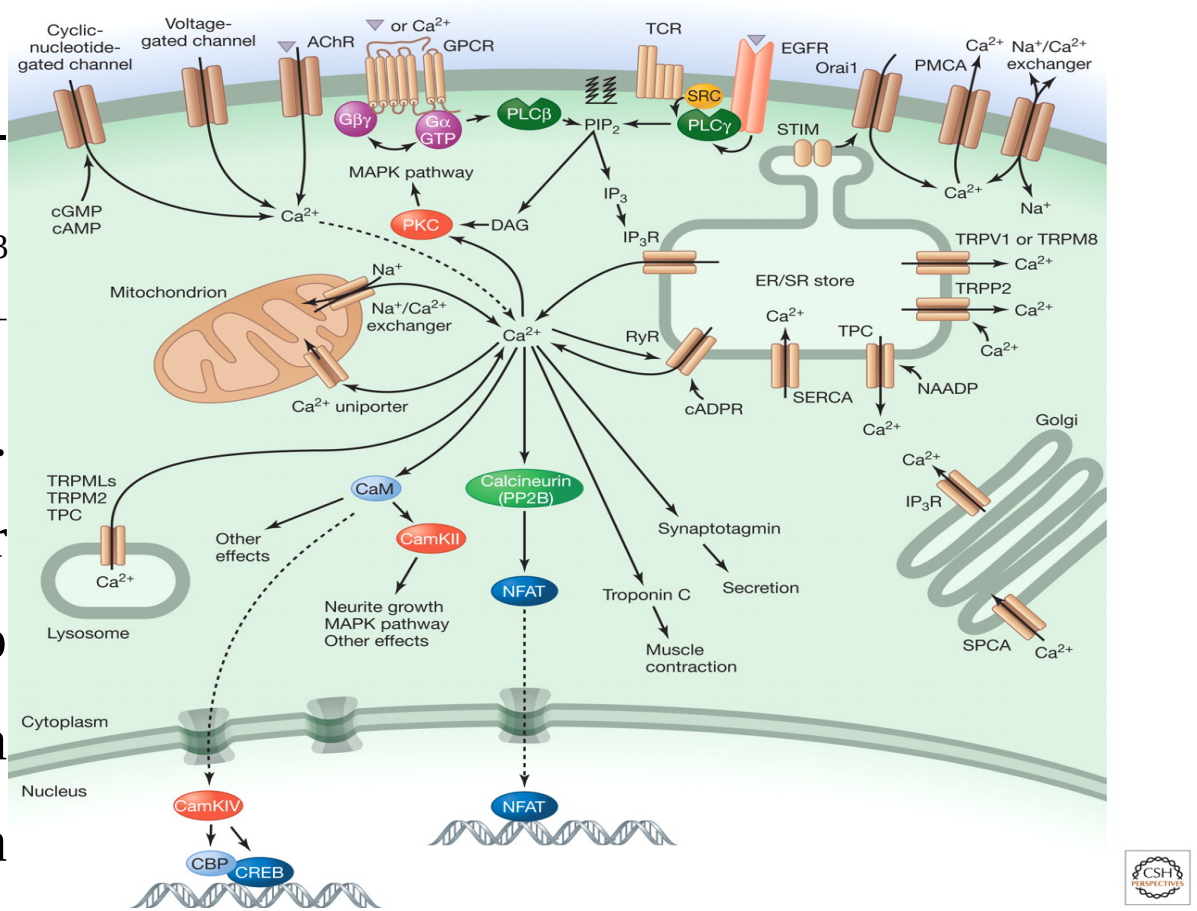
Calcium signals inside cells oscillate:

the cytoplasmic calcium concentration increases, a particular effector is activated, and then the calcium signal is reversed to reset the system.



Cells use channels, pumps, and cytosolic buffers to control calcium levels.

Effect of Ca^{2+} entry:



Hormones bind to G-protein-coupled receptors that leads to IP_3 generation, which releases Ca^{2+} from intracellular stores. Electrical or neurotransmitter stimulation of neurons causes Cto enter cells from outside via different channels. This can increase the average $[Ca^{2+}]_i$ from ~100 nM to ~1 µM. Close to an active channel the Ca^{2+} are used by cells to activate specific process that are generally not sensitive to the bulk $[Ca^{2+}]_i$.

Mediation of Ca^{2+} action:

The actions of Ca^{2+} can be mediated by direct binding of Ca^{2+} to effectors, such as calcineurin, a phosphathase.

It can act via the calmodulin (CaM) a calcium-binding protein. CaM is mobile within cells and can associate with its targets after binding calcium. The interaction of Ca^{2+} with CaM allows it to regulate kinases CaMKII and CaMKIV.

Cell specific Ca^{2+} signaling:

Cardiac myocytes require a rapid (~100ms) whole-cell Ca^{2+} transient to trigger contraction every second.

The rapid Ca^{2+} signals are caused by Ca^{2+} entering through voltage-activated Ca^{2+} channels, which then triggers Ca^{2+} release via ryanodine receptors on the sarcoplasmic reticulum.

Cells that are not electrically excitable typically display Ca^{2+} oscillations that last for ~10s, and can have a periodicity of several minutes, to control gene expression and metabolism.

The slower Ca^{2+} signals typically rely on IP_3, which binds to channels on the ER, or potentially nicotinic acid adenine dinucleotide phosphate-gated (NAADP) Ca^{2+} channels on acidic organelles, leading to release of Ca^{2+} into the cytoplasm.

Ca^{2+} signals can also pass through gap junctions to coordinate activities of neighboring cells.

http://www.cell.com/cell/fulltext/S0092-8674(07)01531-0

Ca^{2+} Acts Locally:

Nonuniformity, cooperativity, and compartmentalization are essential features of cells. Ca^{2+} can diffuse 40μm in 1s in saline solution, while in the cytoplasm Ca^{2+} as a single ion exit only for a short period, fixed and mobile endogenous buffers limit Ca_V-mediated changes in [Ca^{2+}] to 10 μM levels within 20 nm.

The steep Ca^{2+} gradient around entry sites can give rise to nonhomogeneous activation of Ca^{2+} binding proteins with similar Ca^{2+} affinities. Countering these steep gradients are mobile buffers and mobile Ca^{2+}-trigger proteins, which prolong the Ca^{2+} signal and increase its effective length constant. The distributed nature of these Ca^{2+} compartments insures that Ca^{2+} is only briefly free before encountering an extrusion (PMCA, NCX) or uptake (SERCA/MiCa) mechanism.

Intracellular Ca^{2+} compartments are also Ca^{2+} distribution systems.

Skeletal muscle:

The sarcoplasmic reticulum provides Ca^{2+} to the adjacent muscle proteins in a manner that is as efficient and rapid as possible.

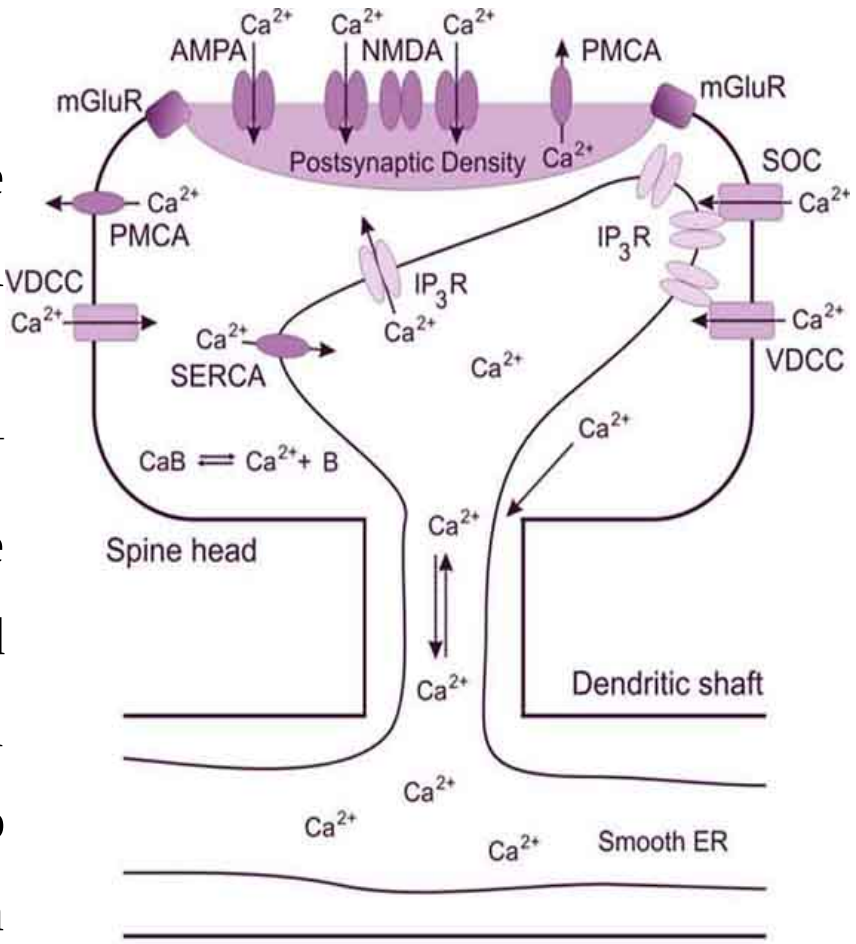
Rapidity: the light-speed messenger, voltage, activates CaV channels. Skeletal muscle CaVs are distributed throughout the T tubule network, which are deep invaginations of the plasma membrane.

Charged residues in CaVs move in response to a change in the transmembrane voltage; the ensuing conformational changes are translated directly to the RyR channels of the sarcoplasmic reticulum. Combining the surface invaginations of the T tubule network, the distributed sarcoplasmic reticulum, and direct coupling between depolarization and RyR channel opening, insures rapid and near simultaneous release of Ca^{2+} to bind adjacent troponin and enable myosin-actin contraction.

Skeletal muscle fibers are fused from multiple single-muscle cells.

Neurons:

Long processes enable localized signaling to be integrated and modified. Even translation and RNA editing might be decentralized.



Dendritic spine: postsynaptic densities house Ca^{2+} sensors regulating synaptic plasticity. The spine head volume is 0.01–1 μm^3, chemically isolated from the main dendrite by the spine neck. When an AP propagates to the spine, free Ca^{2+} rises to ~1μM within ms. The Na/Ca exchanger and Ca pumps rapidly reduce Ca^{2+} levels (τ = 15 ms). Through NMDA receptors the Ca^{2+}-binding sites in calmodulin are filled slowly sequentially. Calmodulin captures transient Ca^{2+} signals and via kinases translates them into more prolonged ones. A crucial feature of signal integrity is the active regulation of spine neck length and diameter.

Mitochondria, Innate Immunity, and Apoptosis

Ca^{2+} regulates mitochondrial function, movement, and viability.

Mitochondria can also store mM Ca^{2+}. Ca^{2+} readily diffuses through large pores in the mitochondrial outer membrane, but it crosses the inner mitochondrial membrane via ion channels and transporters.

The resting electrical gradient from cytoplasm to the interior of mitochondria is −150 to −200 mV. This gradient is created by active transport of protons across the inner mitochondrial membrane.

The Ca^{2+}-sensitive dehydrogenases of the Kreb's cycle are stimulated as increased mitochondrial Ca^{2+} boosts ATP production. Increasing ATP production means more oxygen reduction to water, more leakage of free radicals (ROS: superoxides, peroxides), which oxidize polydesaturated fatty acids in lipids, amino acids, and damage DNA. ROS are also used by innate immunity against bacteria.