

March 2004: The Calcium Pump

The Calcium Pump

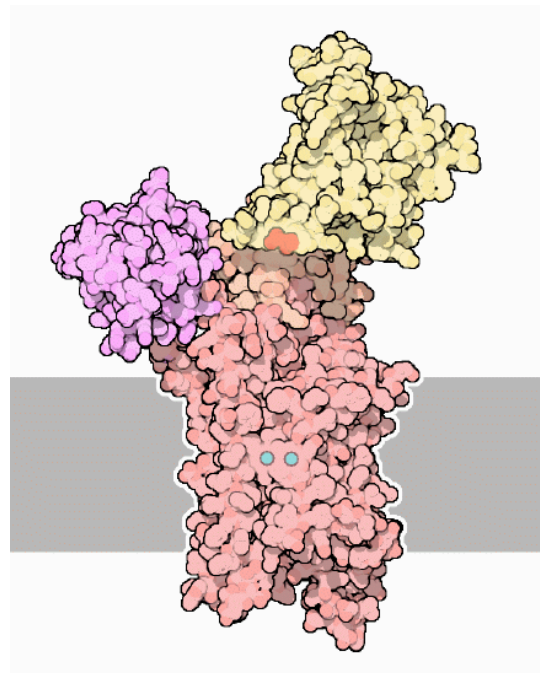
Every time we move a muscle, it requires the combined action of trillions of myosin motors. Our muscle cells use calcium ions to coordinate this massive molecular effort. When a muscle cell is given the signal to contract from its associated nerves, it releases a flood of calcium ions from a special intracellular container, the sarcoplasmic reticulum, that surrounds the bundles of actin and myosin filaments. The calcium ions rapidly spread and bind to tropomyosins on the actin filaments. They shift shape slightly and allow myosin to bind and begin climbing up the filament. These trillions of myosin motors will continue climbing, contracting the muscle, until the calcium is removed.

Relaxation

The calcium pump allows muscles to relax after this frenzied wave of calcium-induced contraction. The pump is found in the membrane of the sarcoplasmic reticulum. In some cases, it is so plentiful that it may make up 90% of the protein there. Powered by ATP, it pumps calcium ions back into the sarcoplasmic reticulum, reducing the calcium level around the actin and myosin filaments and allowing the muscle to relax. Calcium ions are also used for signaling inside other cells, and similar pumps are found in the cell membrane of most cells. They constantly work to reduce the amount of calcium to very low levels, preparing the cell. Then, at a moment's notice, the cell can allow a flood of calcium to enter, spreading the signal to all corners.

Pumping Calcium

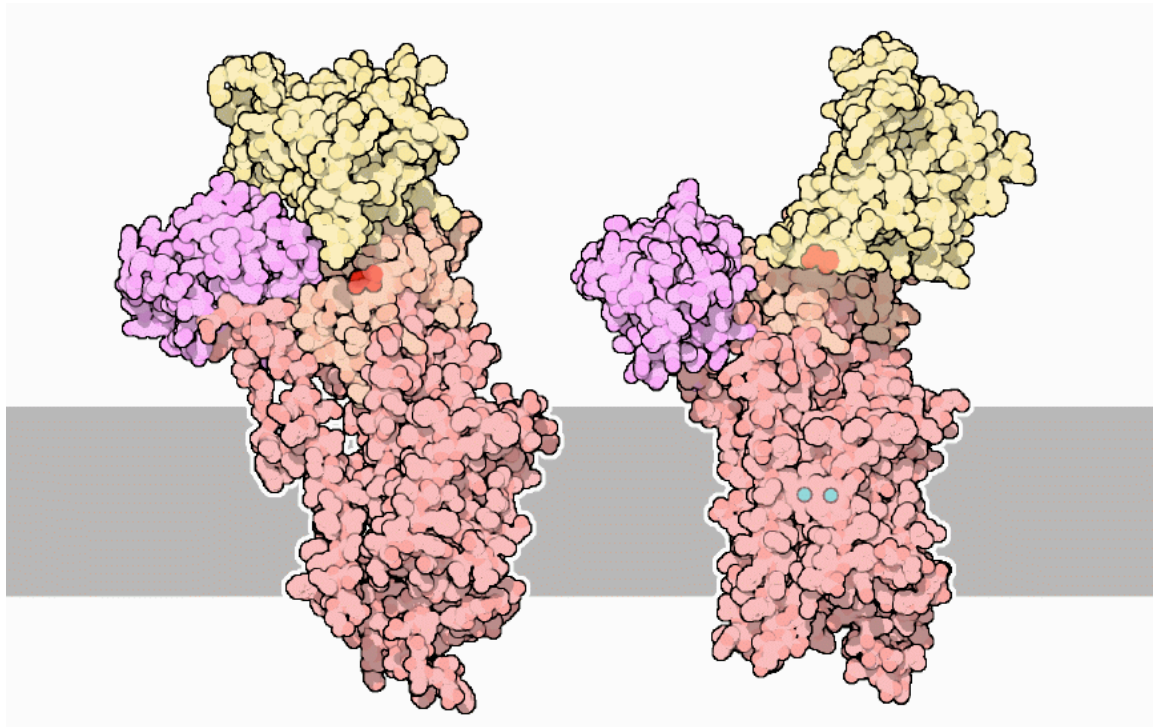
The calcium pump is an amazing machine with several moving parts. It is found in the membrane, as shown here from PDB entry [1eul](#). It has a big domain poking out on the outside of the sarcoplasmic reticulum, and a region that is embedded in the membrane, forming a tunnel to the other side. For each ATP broken, it transfers two calcium ions (shown here in blue) through the membrane, and two or three hydrogen ions back in the opposite direction. As shown on the next page, the calcium pump bends and flexes during the pumping cycle.



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The Pumping Cycle

The calcium pump goes through a cycle of changes in the process of pumping. Four distinct steps have been proposed, and the PDB currently has structures of two of these steps. The structure on the left, from PDB entry [1iwo](#), is the empty state, which presumably has hydrogen ions bound in the transfer site, although they cannot be seen in the crystal structure. It shifts shape into the structure on the right, from PDB entry [1eul](#), allowing calcium ions to enter from the top and replace the hydrogen ions, which travel out upwards into the cytoplasm. The remaining two steps use an ATP molecule to shift the shape so that the calcium will be released downwards. In this process, a phosphate is transferred from the ATP to a special aspartate amino acid in the pump, number 351, shown here in red. As you can see, this aspartate and the presumed ATP binding site (which must be close to the aspartate) are some distance from the tunnel that calcium passes through. The switching is controlled by large motions of the ATP-binding domains, which push and pull on the protein surrounding the tunnel, opening and closing it appropriately.



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Exploring the Structure

The calcium binding site is in a tunnel formed by four alpha helices, which cross straight through the membrane. This illustration, from PDB entry [1eul](#), shows a view down the helices. The two calcium ions, shown as blue-green spheres, are held by a collection of amino acids, shown in balls-and-sticks, that coordinate it from all sides. The protein is far less stable when these calcium ions are removed. It was solved by adding a drug molecule that binds near the calcium-binding site and freezes the protein into a stable, but non functioning, form.

