**pH and Buffers: Buffering in the Blood**

See lecture 21 and 22 notes for acid-base equilibrium and lecture 22 and 23 notes for an introduction to buffers.

A buffer solution is any solution that maintains an approximately constant pH despite small additions of acid and base. The pH of a buffer is maintained by a mixture of weak conjugate acids and bases, which provides a source or sink for protons.

Blood is buffered in the pH range 7.35-7.45
Buffering agents in blood: \( \text{H}_2\text{CO}_3 / \text{HCO}_3^- \) (carbonic acid/bicarbonate)

**Example from Lecture 23 video: Effects on Blood pH from Vitamin B\(_{12}\) Deficiency**

The buffering capacity of a buffered solution can be overcome by the addition of excessive acid or base.

An instance of too much acid affecting the pH of blood occurs in the disease methylmalonic aciduria, a metabolic disorder in which methylmalonic acid builds up in the blood and overcomes the \( \text{H}_2\text{CO}_3 / \text{HCO}_3^- \) buffering capacity.

In healthy individuals, fatty acids (fats) are converted into energy through the series of steps shown below. Enzymes catalyze each of these steps, and the enzyme **methylmalonyl-CoA mutase (MUT), which requires vitamin B\(_{12}\) binding for activity**, catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA. In the absence of sufficient vitamin B\(_{12}\) or in cases where vitamin B\(_{12}\) cannot bind to MUT, methylmalonyl-CoA is instead converted to methylmalonic acid, and buildup of this acid can result in a lowering of blood pH.

![Diagram of fatty acid metabolism](image)

In methylmalonic aciduria, the MUT-catalyzed step cannot occur, resulting in a buildup of acid instead of the conversion of fatty acids into energy.

The disease methylmalonic aciduria can be caused by insufficient vitamin B\(_{12}\) intake. However, it is most often caused by a genetic mutation in the gene encoding the MUT enzyme. A single amino acid substitution from a glycine (the smallest amino acid) to an arginine (a much larger amino acid) can destroy all MUT activity.
Using X-ray crystallography, scientists determined that the glycine-to-arginine mutation occurs in the B<sub>12</sub> binding pocket, blocking vitamin B<sub>12</sub> binding (see pictures A and B below). This explains why it is not effective to treat individuals with methylmalonic aciduria with high doses of B<sub>12</sub>, since the B<sub>12</sub> cannot bind to MUT. Using this information, scientists are now looking into treatment with a truncated B<sub>12</sub> mimic that can bind in the blocked pocket of the mutant MUT enzyme (see picture C below). This truncated B<sub>12</sub> can partially restore MUT activity, and may lead to a successful treatment for methylmalonic aciduria.

The MUT enzyme is shown in white, the arginine residue in the mutant enzyme is shown (blocking the binding pocket) in blue, and vitamin B<sub>12</sub> is shown in red.