5.111 Principles of Chemical Science
Fall 2008

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.

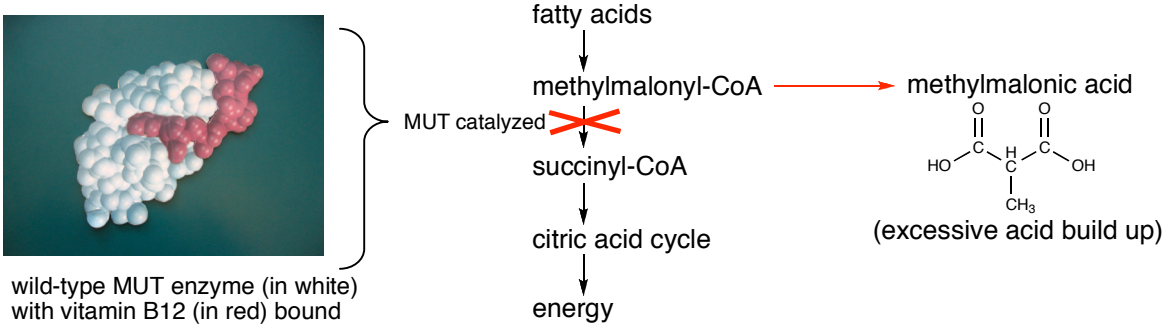
Blood is buffered in the pH range 7.35-7.45
Buffering agents in blood: H_2CO_3/HCO_3^- (carbonic acid/bicarbonate)

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 H_2CO_3/HCO_3^- buffering capacity.

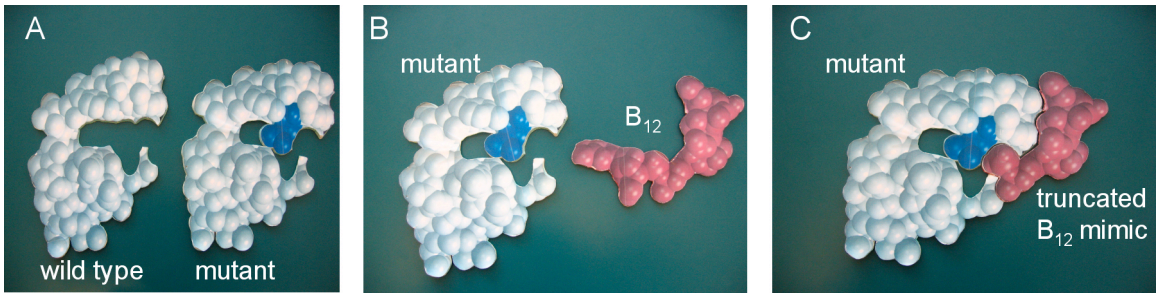
In healthy individuals, fatty acids (fats) are converted into energy through the series of steps shown below. Enzymes catalyze each of these steps, and the enzyme **methylmalonyl-CoA mutase (MUT), which requires vitamin B_{12} binding for activity,** catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA. 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.



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_{12} binding pocket, blocking vitamin B_{12} 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_{12}, since the B_{12} cannot bind to MUT. Using this information, scientists are now looking into treatment with a truncated B_{12} mimic that can bind in the blocked pocket of the mutant MUT enzyme (see picture C below). This truncated B_{12} 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_{12} is shown in red.