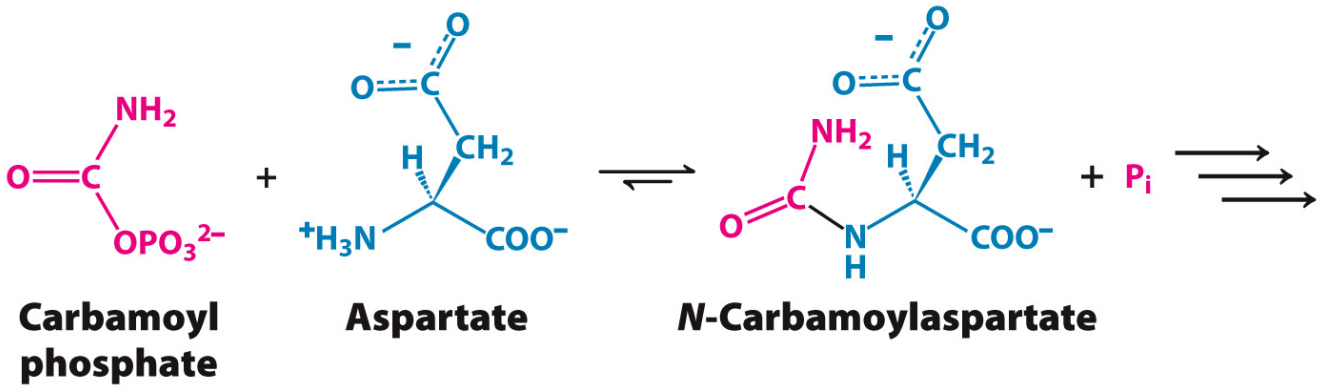
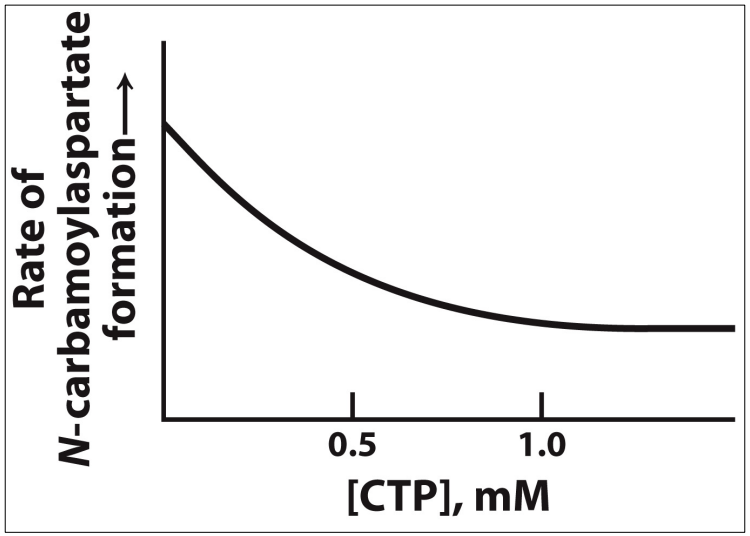
Regulation of enzyme activity

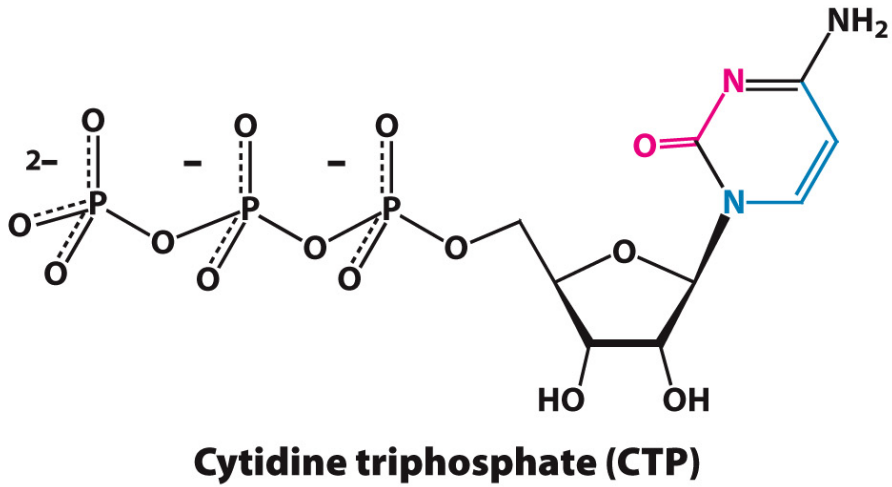
Five means to regulate enzymatic activity:

1. **Allosteric Control.**
2. **Multiple Forms of Enzymes.**
3. **Reversible Covalent Modification.**
4. **Proteolytic Activation.**
5. **Controlling the Amount of Enzyme Present.**

The allosteric enzyme aspartate transcarbamolyase (ATCase) catalyzes the first step in pyrimidine biosynthesis and is inhibited by CTP, the end product of the pathway

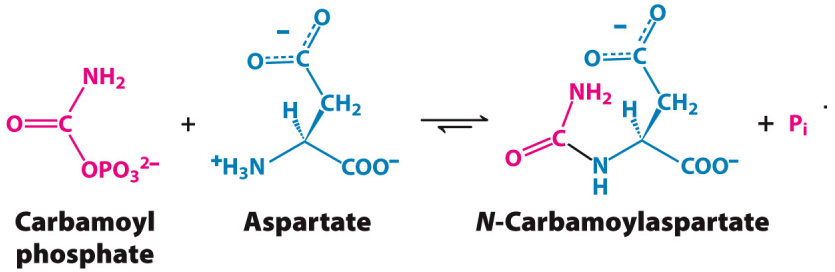


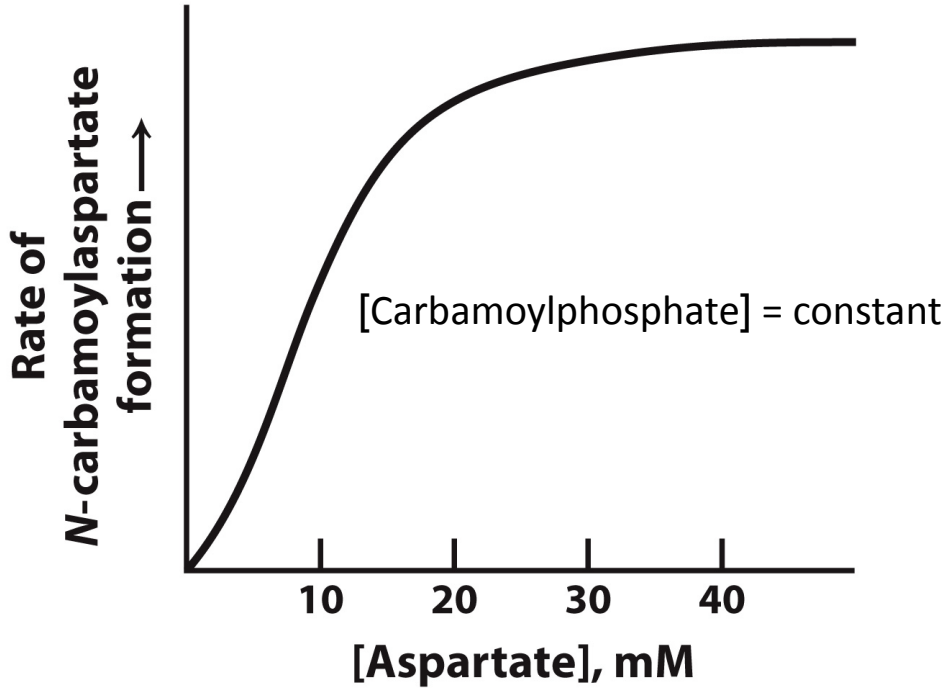




ATCase is an allosteric enzyme

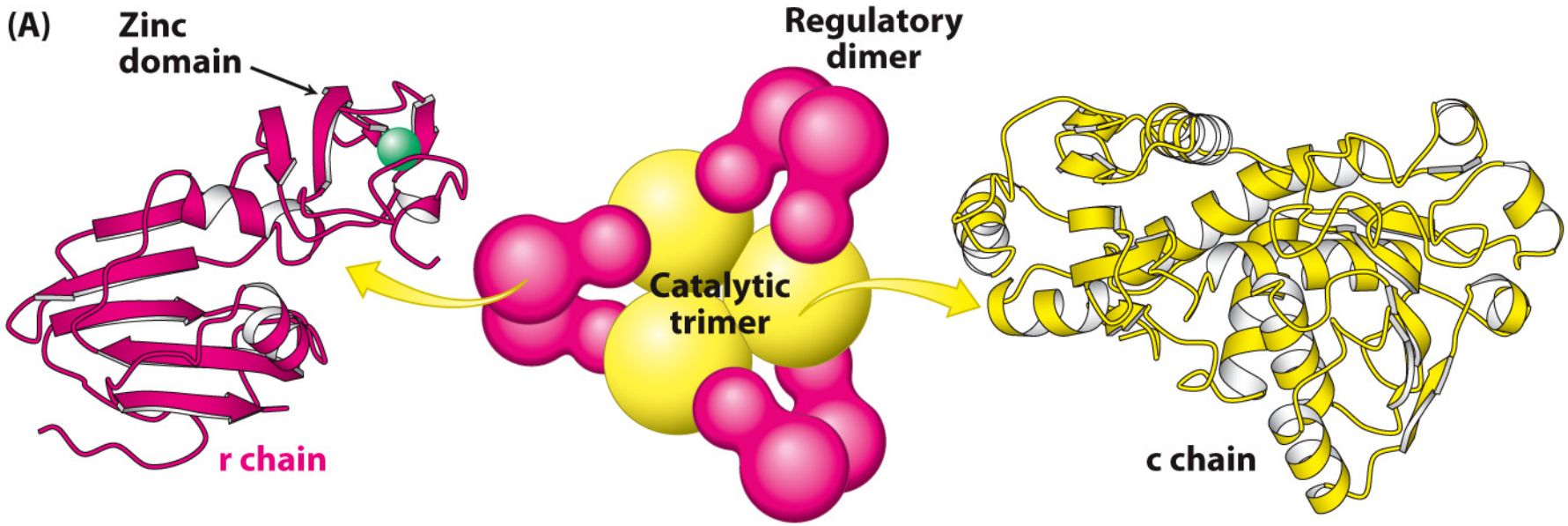
Allosteric enzymes are generally **oligomeric** enzymes with multiple active sites. They show cooperative substrate turnover with a **sigmoidal** dependence of the initial velocity on substrate concentration.





Native ATCase consists of six catalytic and six regulatory subunits (c_6r_6), organized as two catalytic trimers and two regulatory dimers.

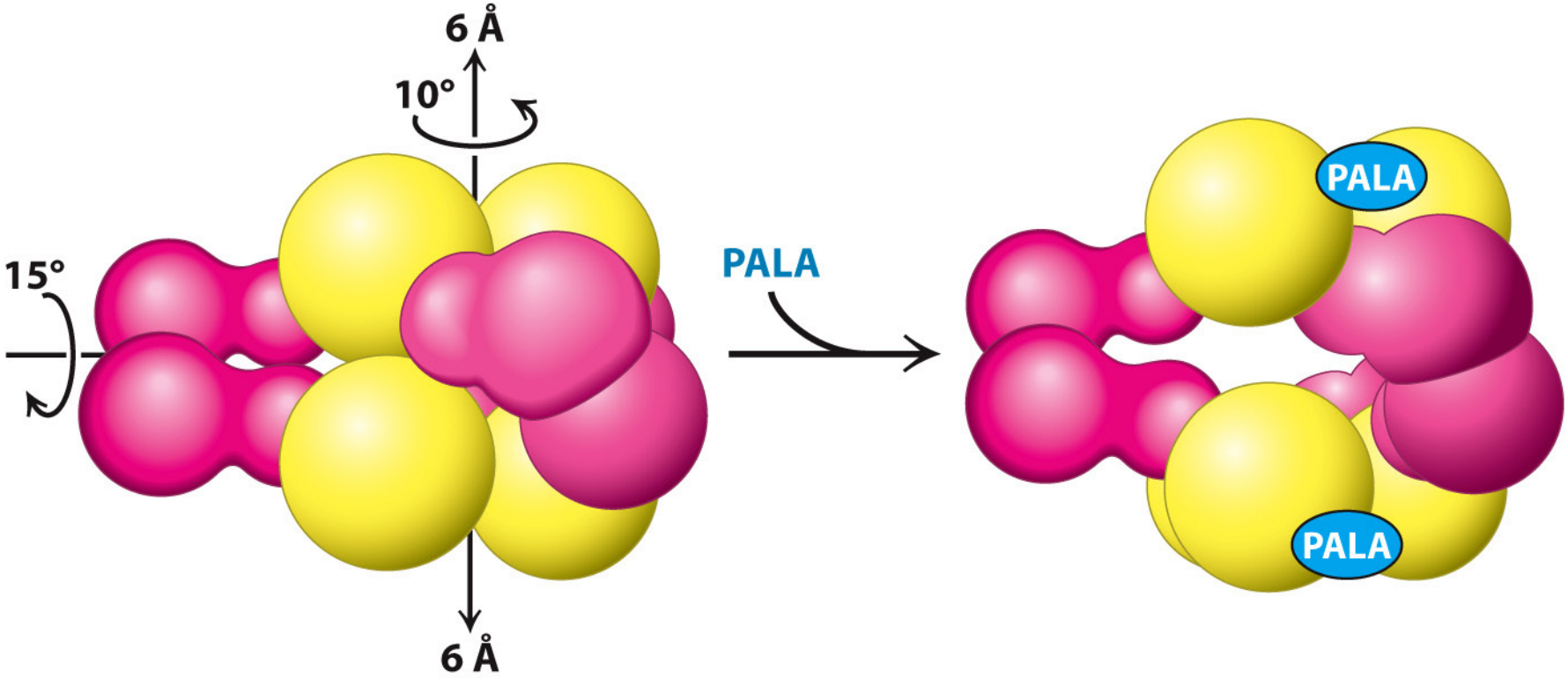
Top view, second catalytic trimer is hidden below



6 active sites, located at the interface between the catalytic subunits of each catalytic trimer
The 3 regulatory dimers connect the catalytic trimers by binding to one catalytic subunit in each trimer

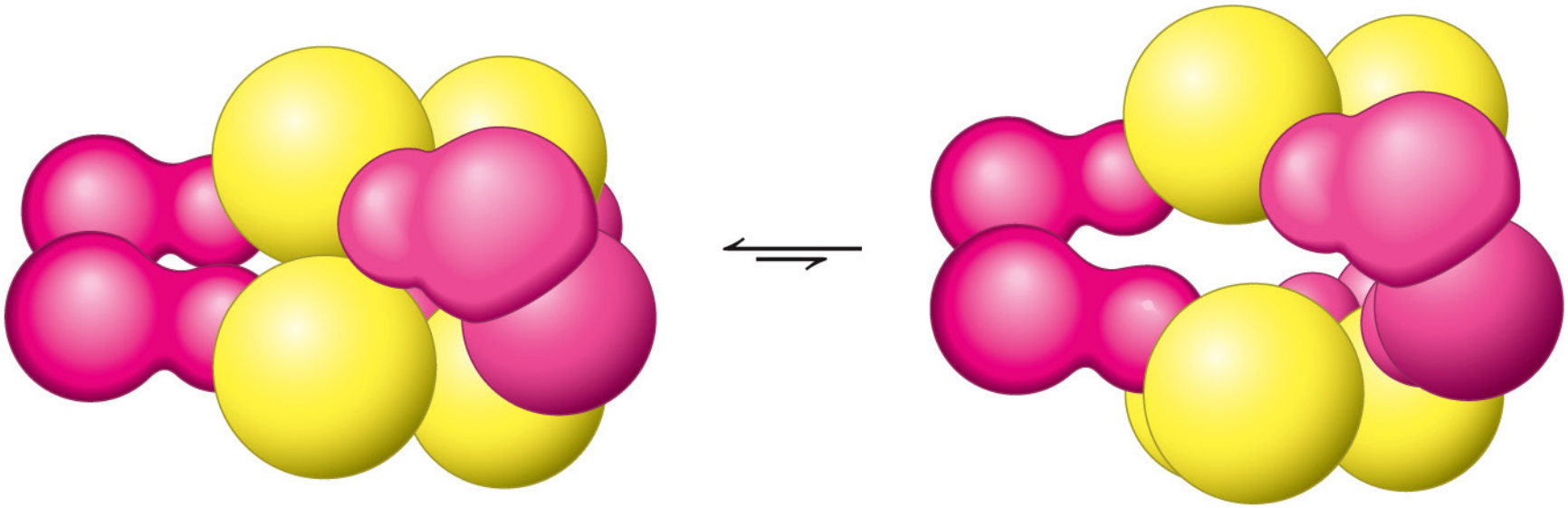
ATCase exists in two conformations; the less active T-state and the more active R-state

Binding of the competitive ATCase inhibitor PALA (substrate analogue) shifts the conformational equilibrium to the R-state.



T state
(less active)

R state
(more active)



More stable in the absence of substrates

Favored by substrate binding

Allosteric coefficient L = T/R

T = 100 - 1000 for most allosteric enzymes

10.1 Aspartate Transcarbamoylase Is Allosterically Inhibited by the End Product of Its Pathway

Allosteric interactions in ATCase are mediated by large changes in quaternary structure

The effect of substrates on allosteric enzymes are called homotropic effects.

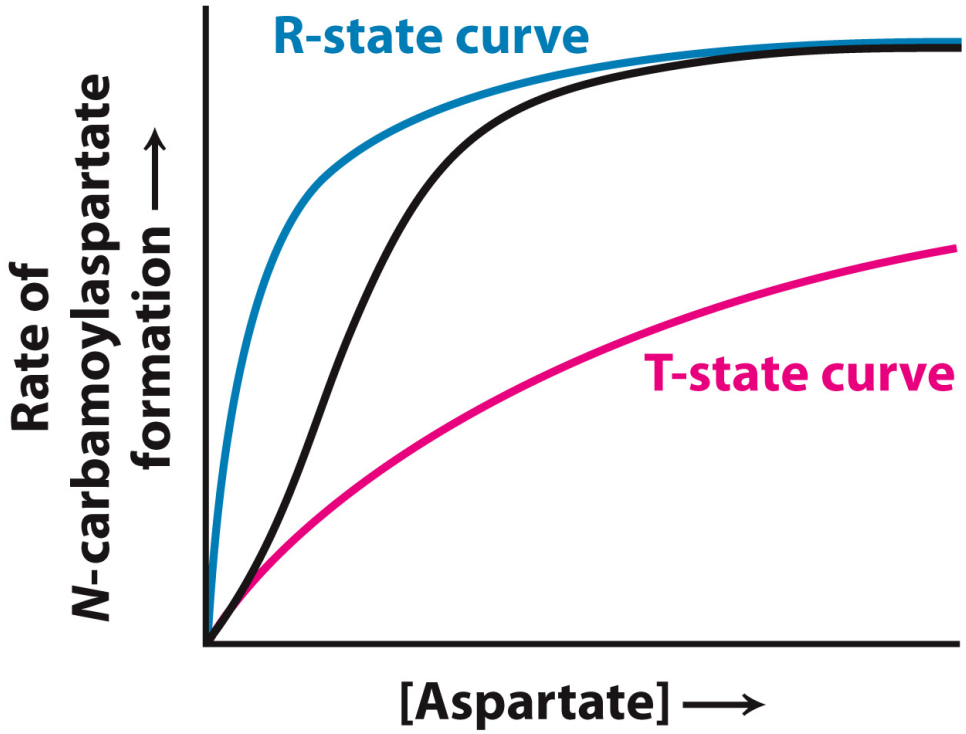
ATCase adheres to the concerted mechanism for allosteric enzymes, which postulates that all active sites are in the same state, either T or R.

The sigmoidal kinetic curve of allosteric enzymes allows increased sensitivity to changes in substrate concentration, or the threshold effect.

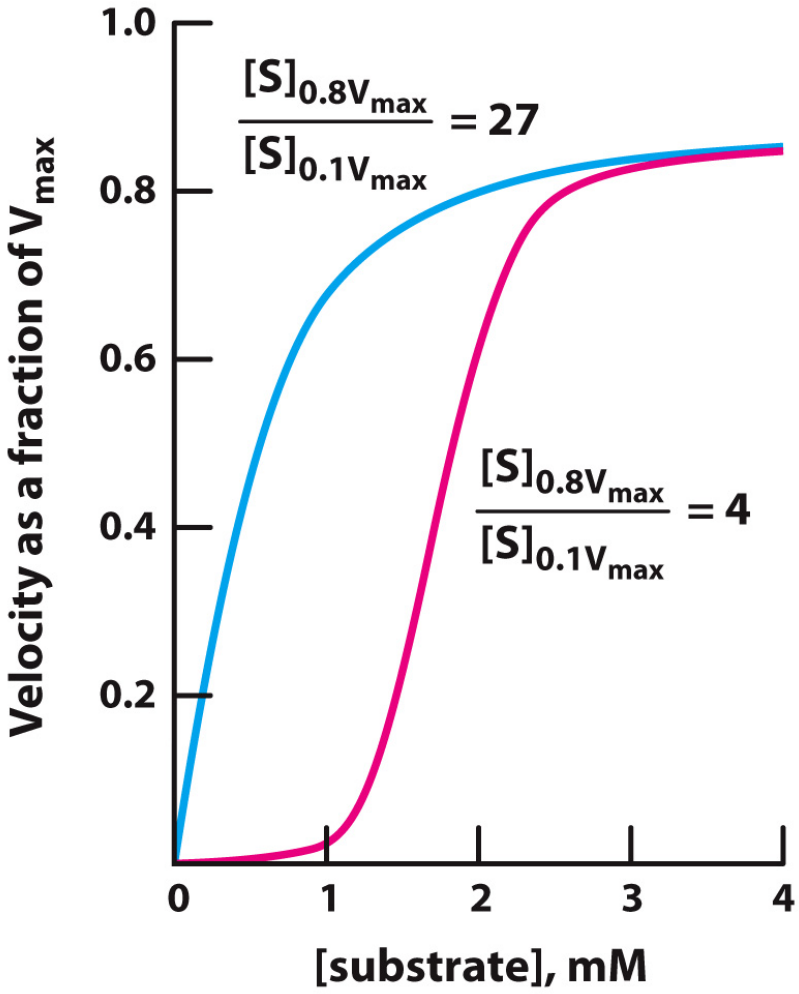
- **All 6 active sites of ATCase are either in the R or T state**

- **Substrate binding favors the more active R state**

- **The sigmoidal dependence of v_i on substrate concentration is a result of a mixture of R and T states, with mainly T at low and mainly R at high substrate concentrations.**



The cooperative effect of substrate binding in ATCase leads to a much steeper dependence of activity on substrate concentration compared to classical (unregulated) Michelis-Menten enzymes.



Allosteric regulators modulate the T-to-R equilibrium

CTP binds to the regulatory dimers of the less active T-state, whereas ATP favors the more active R-state