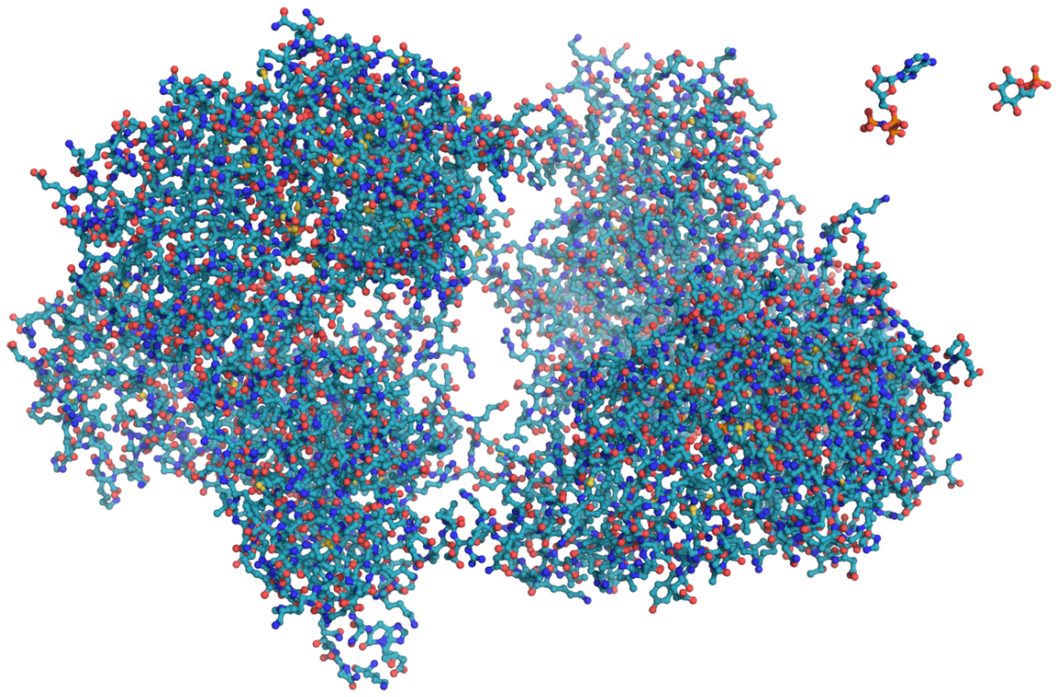
Enzyme Regulation I

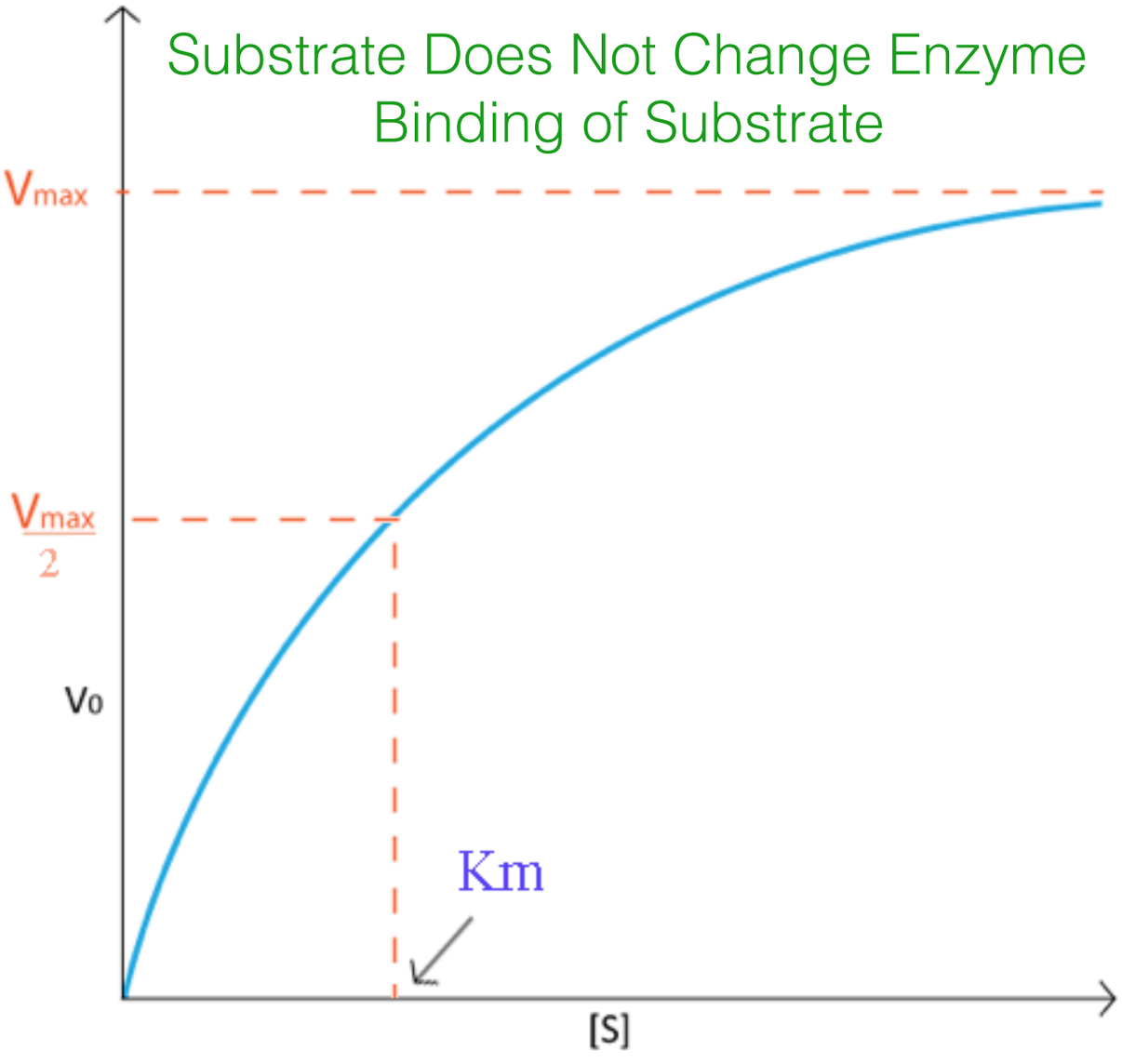
Dr. Kevin Ahern

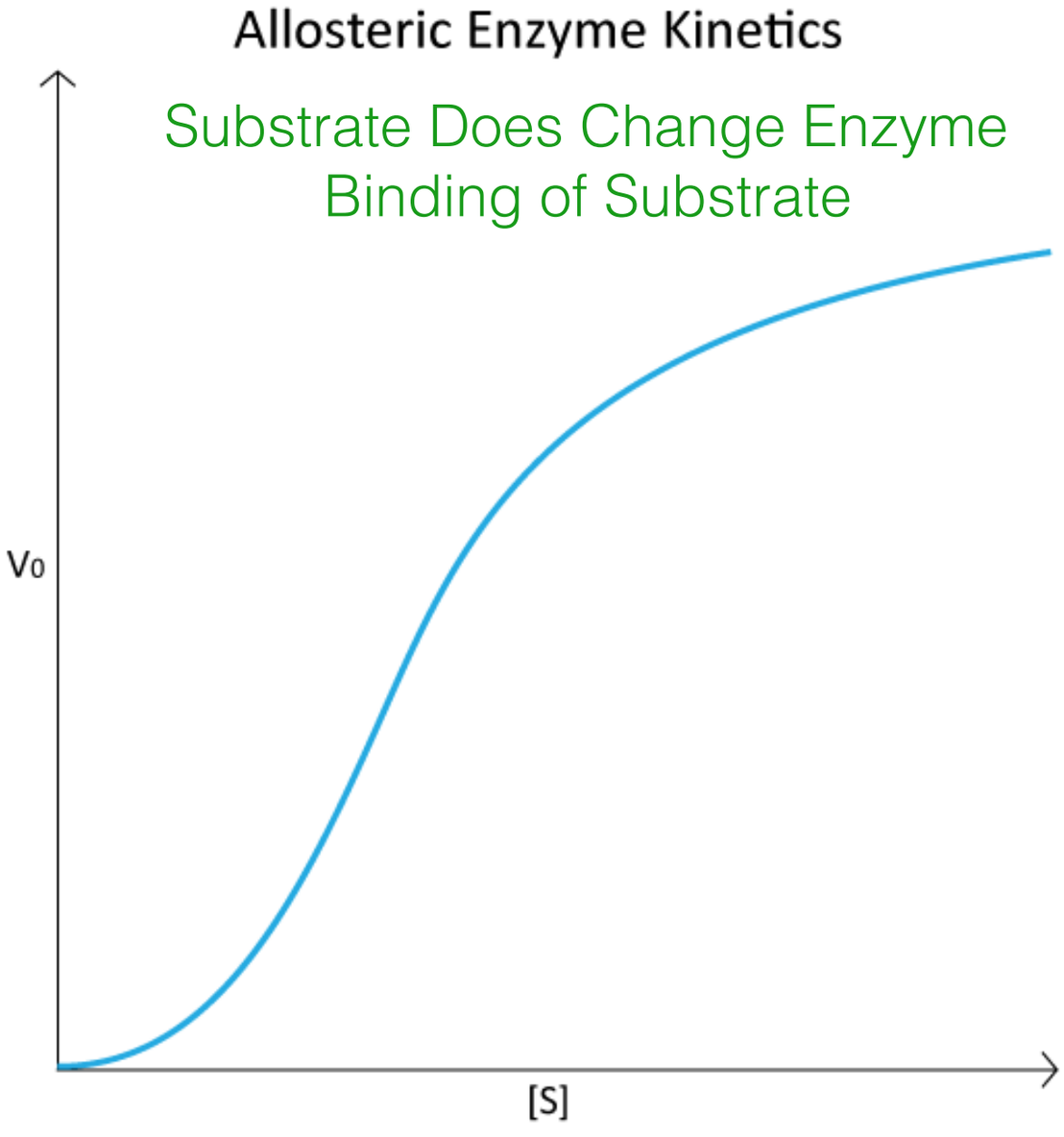
Enzyme Regulation Mechanisms

1. Allosterism
2. Covalent Modification
3. Control of Synthesis
4. Availability of Substrate



Control of Enzyme Activity





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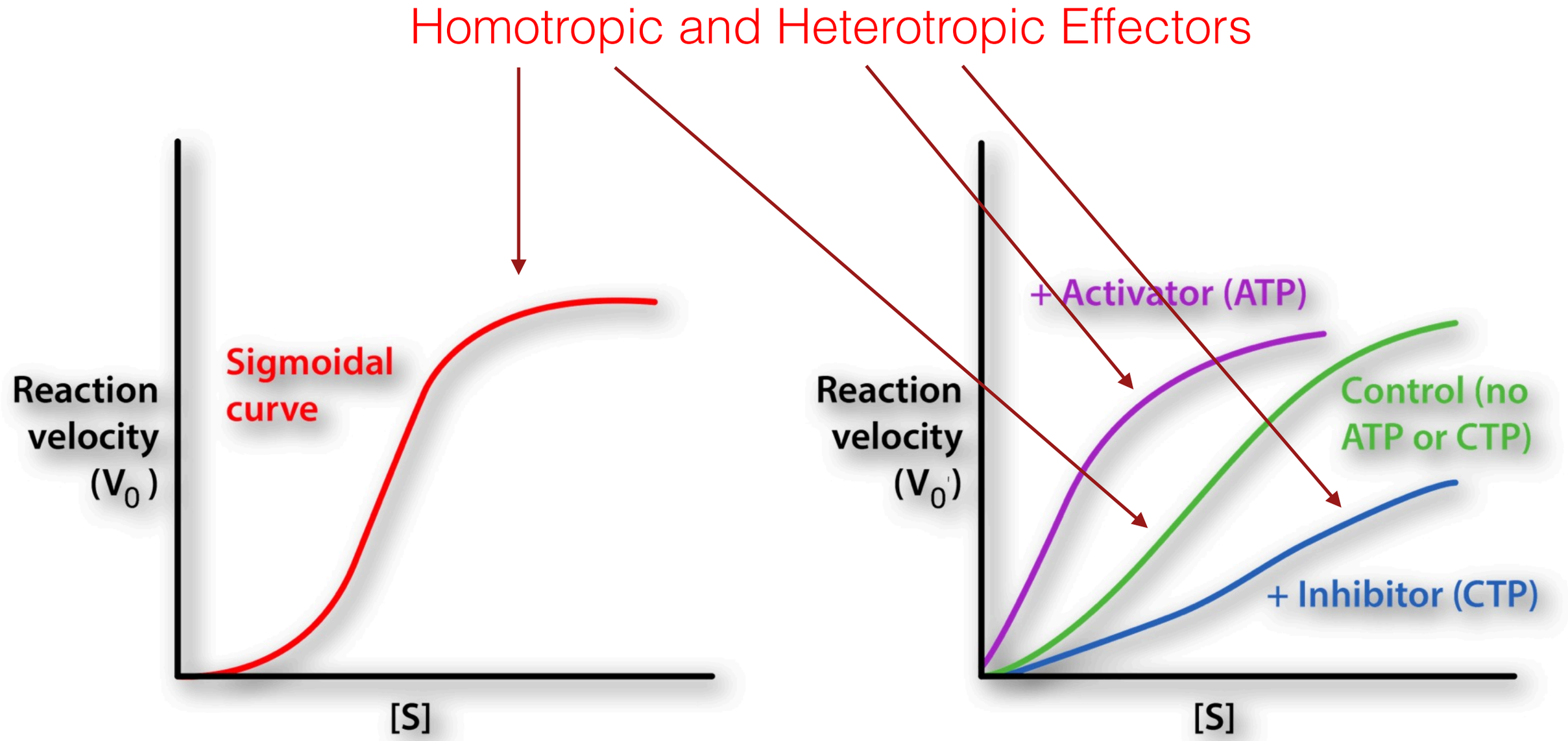
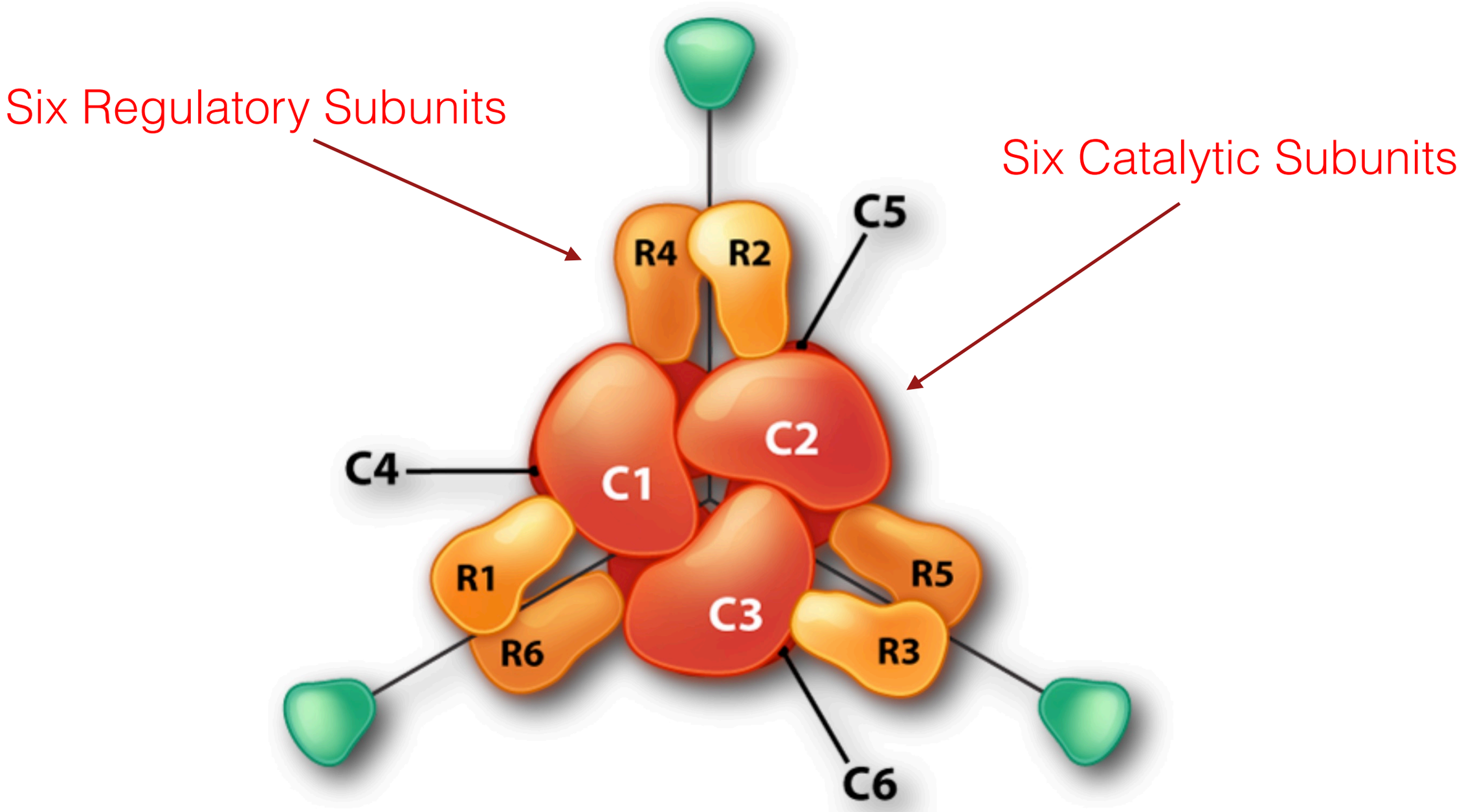


Control of Enzyme Activity

Aspartate Transcarbamoylase (ATCase)



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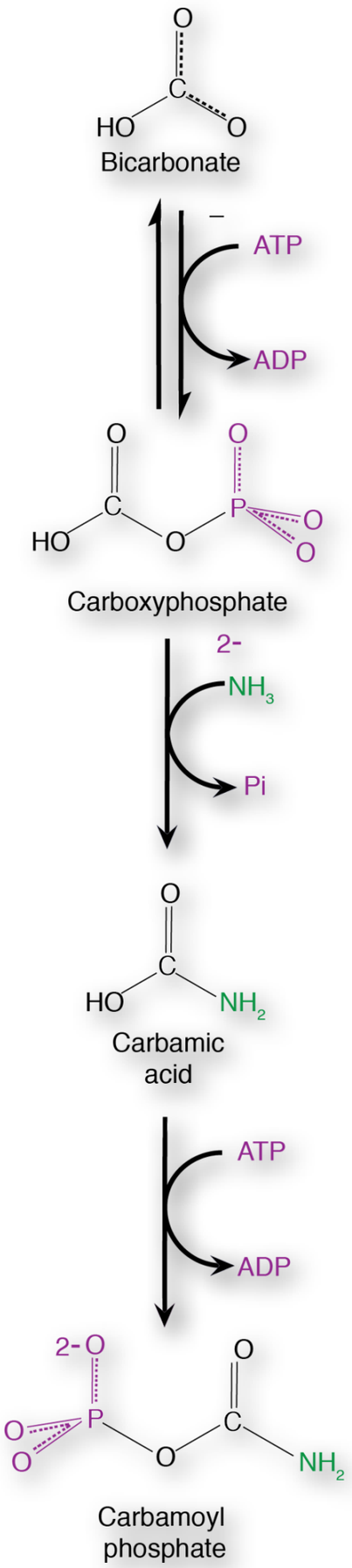

Control of Enzyme Activity

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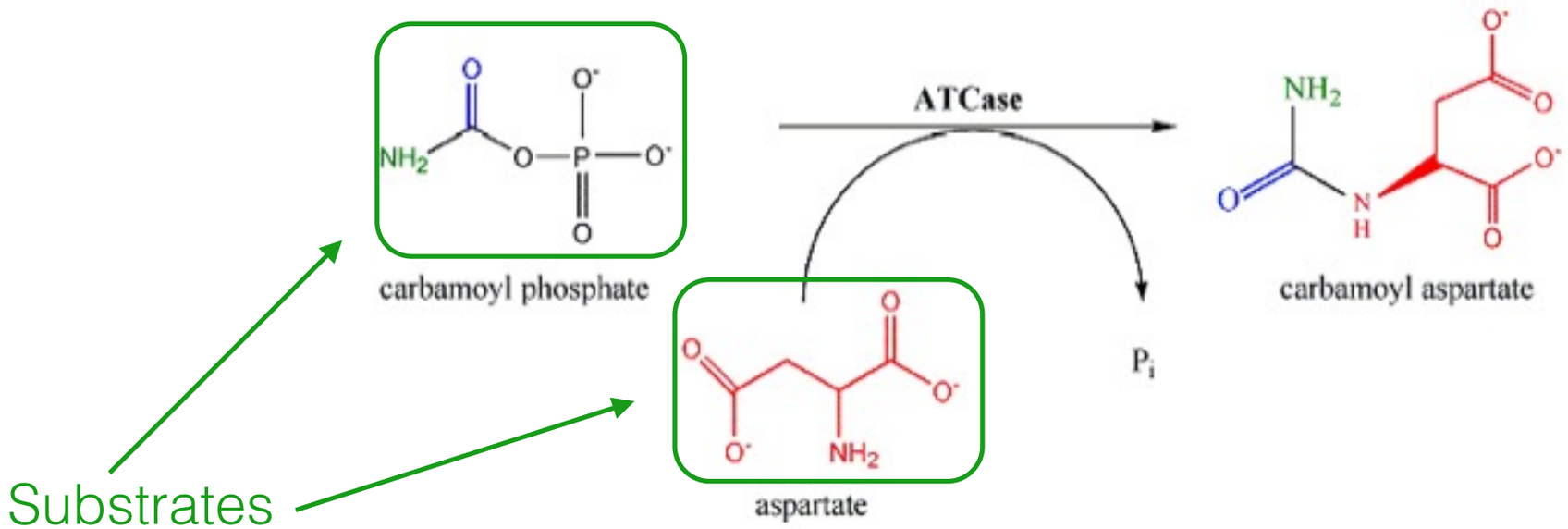
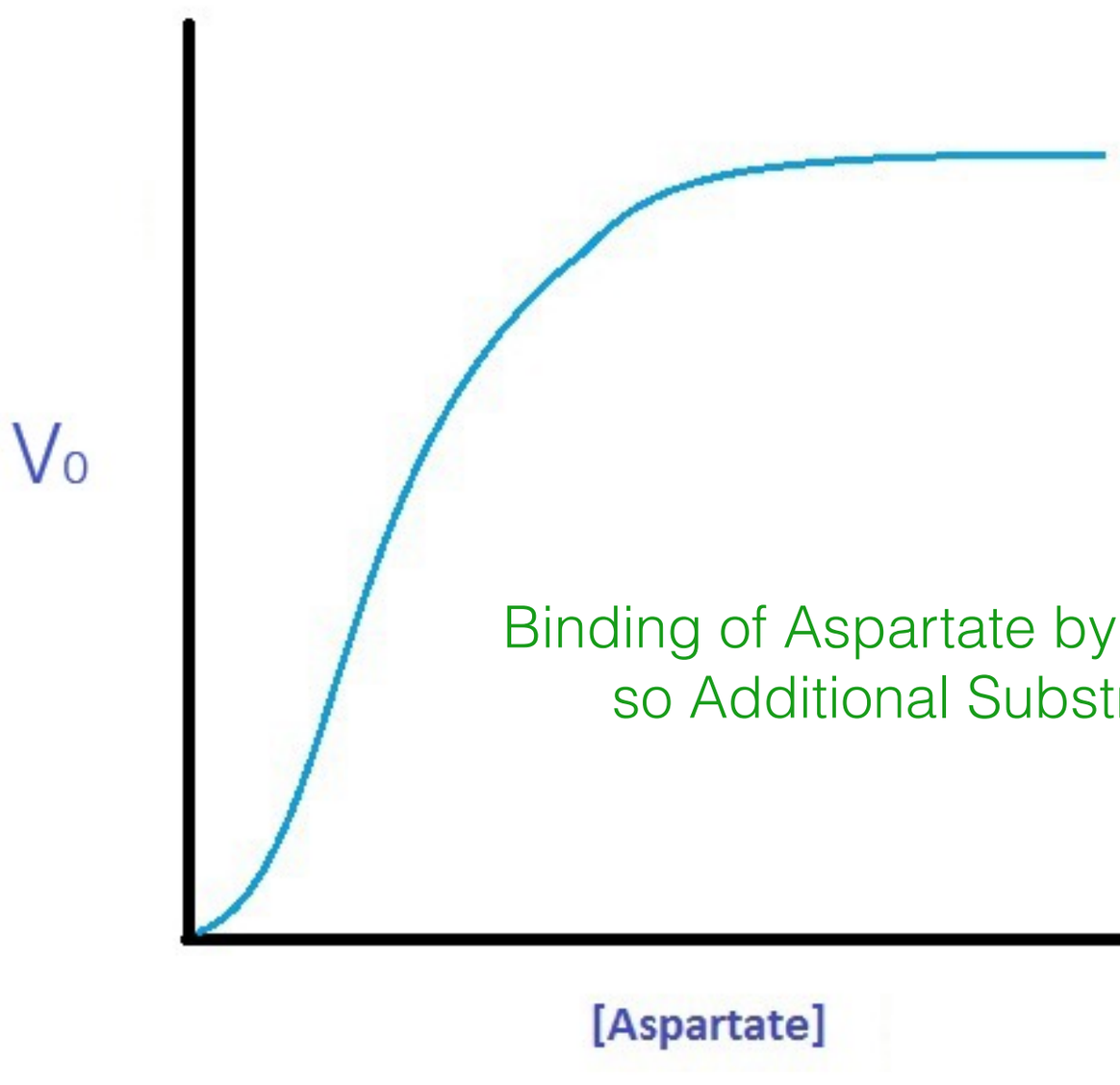


- Aspartate - Amino Acid
- ATP - High Energy, Purine
- CTP - End Product of Pathway

Control of Enzyme Activity

ATCase is Affected by One of its Substrates - Aspartate
Aspartate is a Homotropic Effector of ATCase

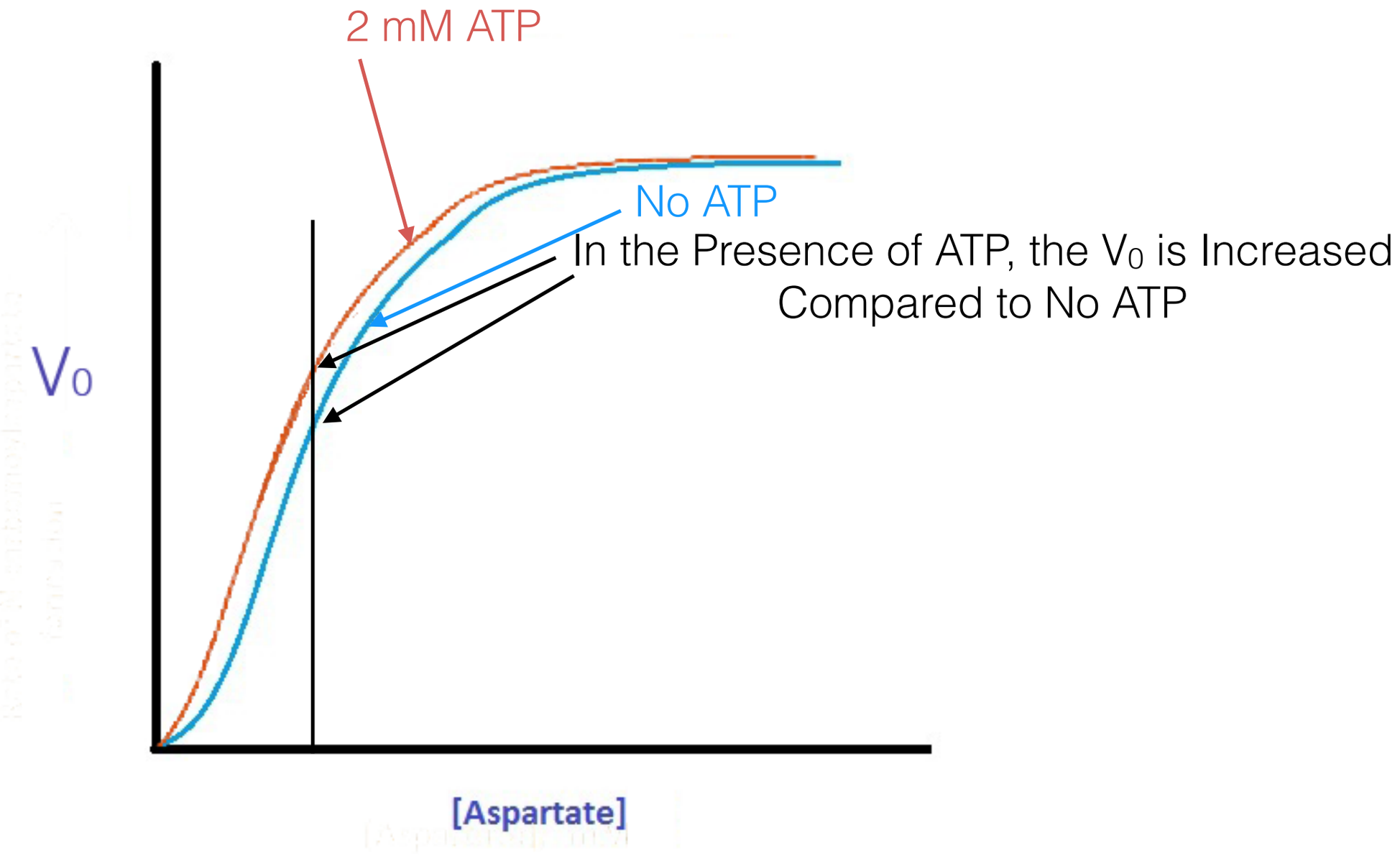


Binding of Aspartate by ATCase Favors the R-State
so Additional Substrate Binding is Favored

Control of Enzyme Activity

- Allosteric Control of ATCase

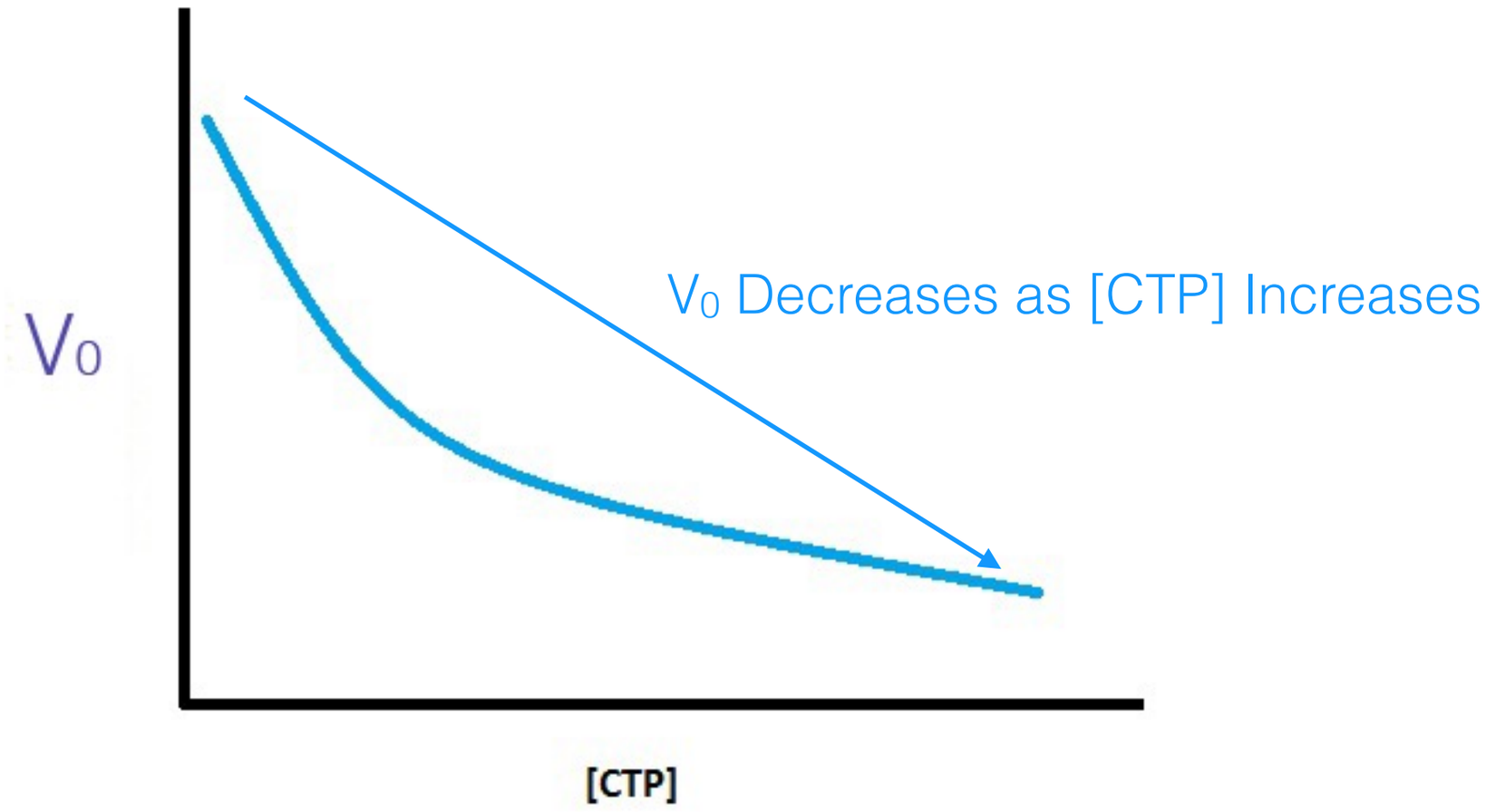
ATP Activates ATCase (Converts to R State)



Control of Enzyme Activity

- Allosteric Control of ATCase

CTP Reduces the Activity of ATCase - Converts to T State



Control of Enzyme Activity

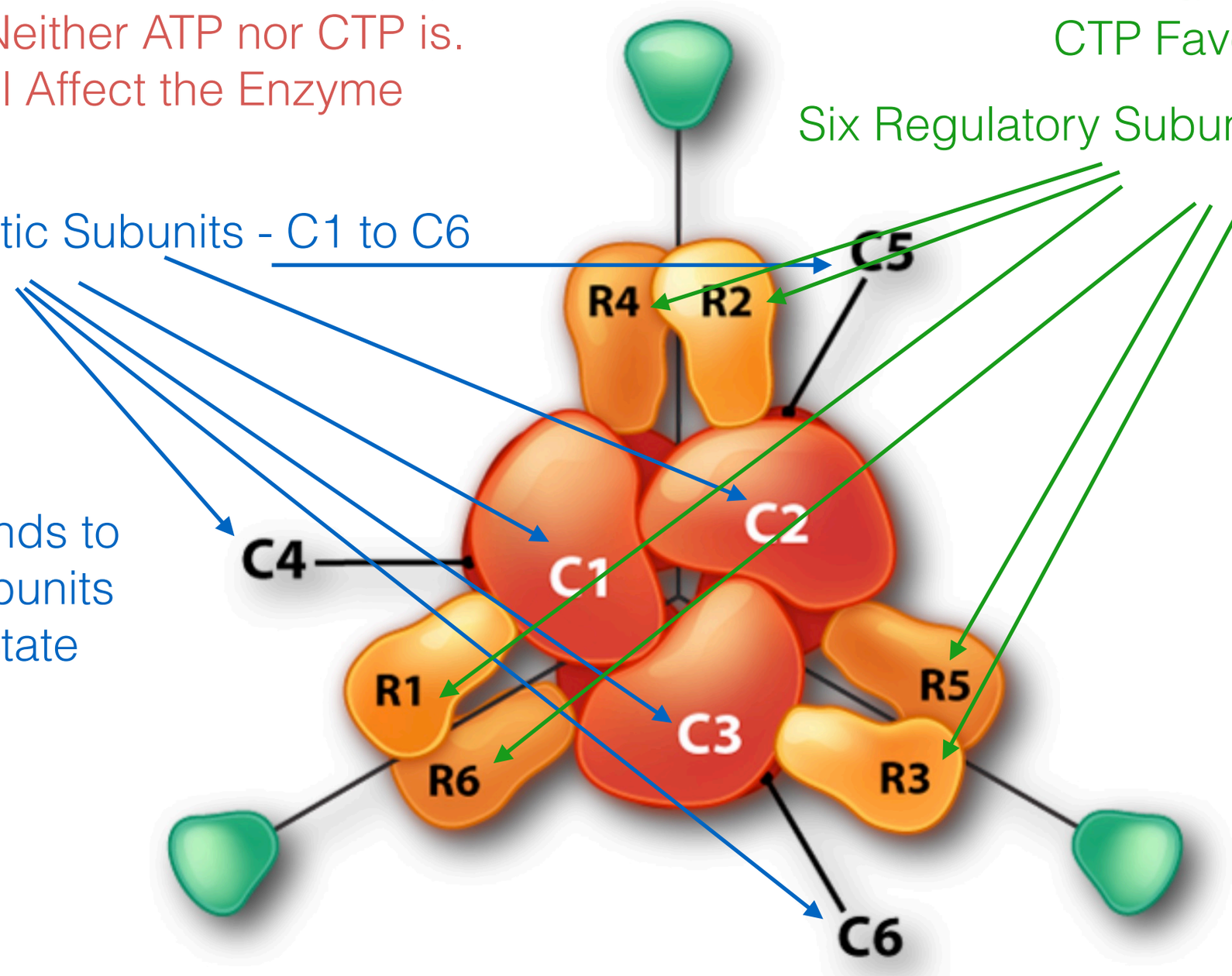
- Allosteric Control

Aspartate is a Substrate,
but Neither ATP nor CTP is.
All Affect the Enzyme

ATP and CTP Bind Regulatory Sites
ATP Favors R State
CTP Favors T State

Six Regulatory Subunits - R1 to R6

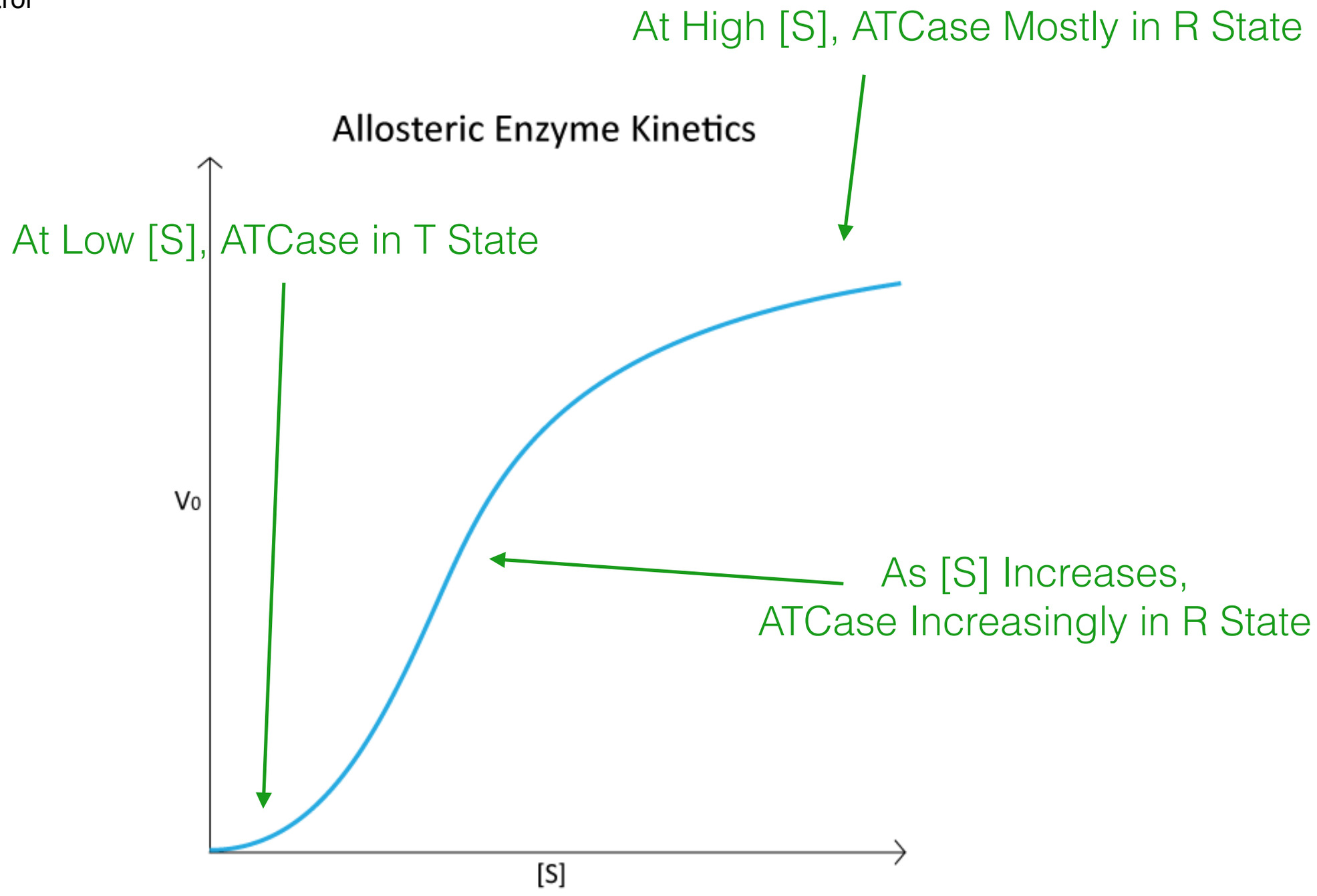
Six Catalytic Subunits - C1 to C6



Aspartate Binds to
Catalytic Subunits
Favors R State

Control of Enzyme Activity

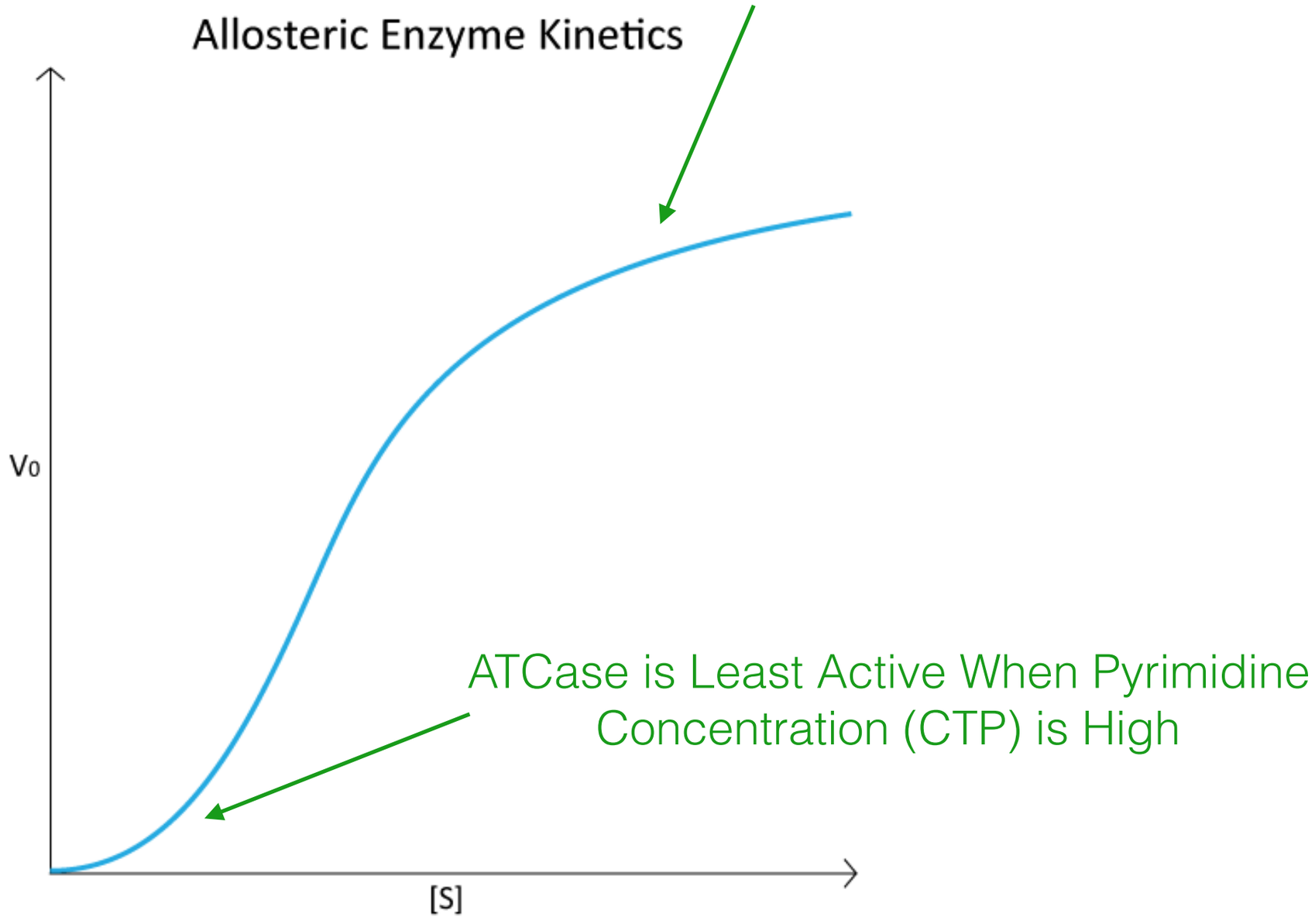
- Allosteric Control



Control of Enzyme Activity

- Allosteric Control

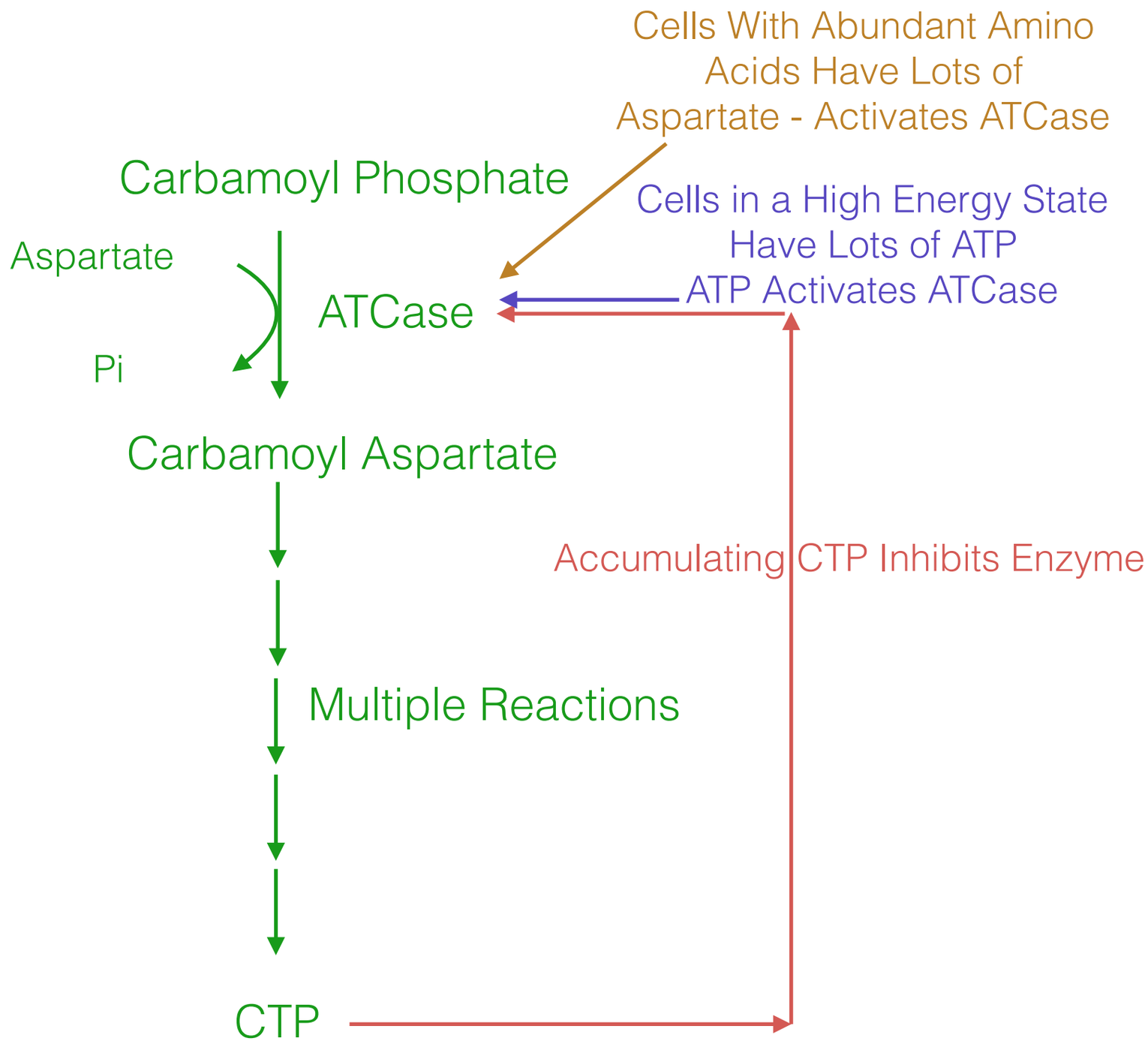
Thus, ATCase is Most Active When Energy (ATP) is High and When Pyrimidines are Low in Concentration Relative to Purines



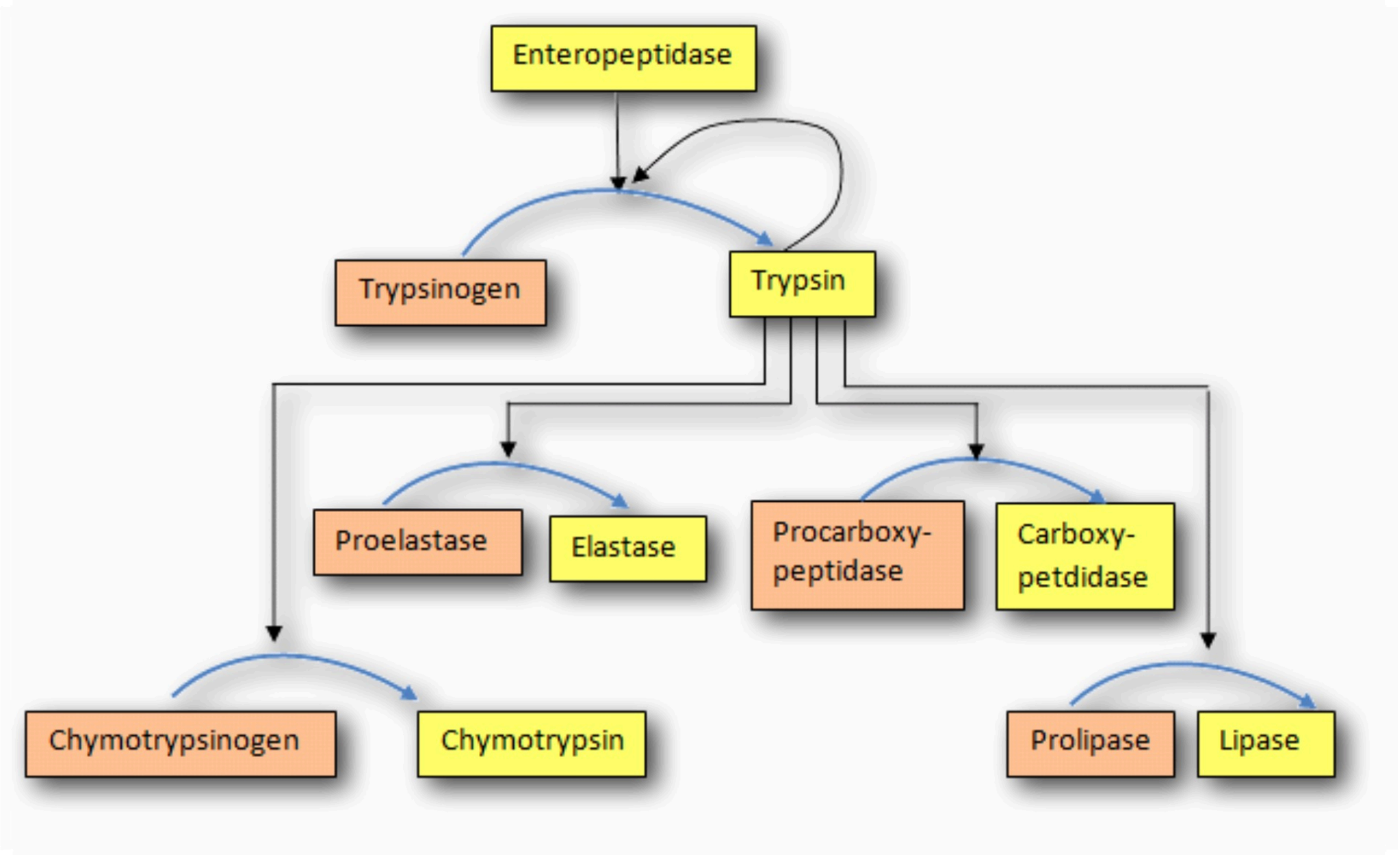
ATCase is Least Active When Pyrimidine Concentration (CTP) is High

Feedback Inhibition

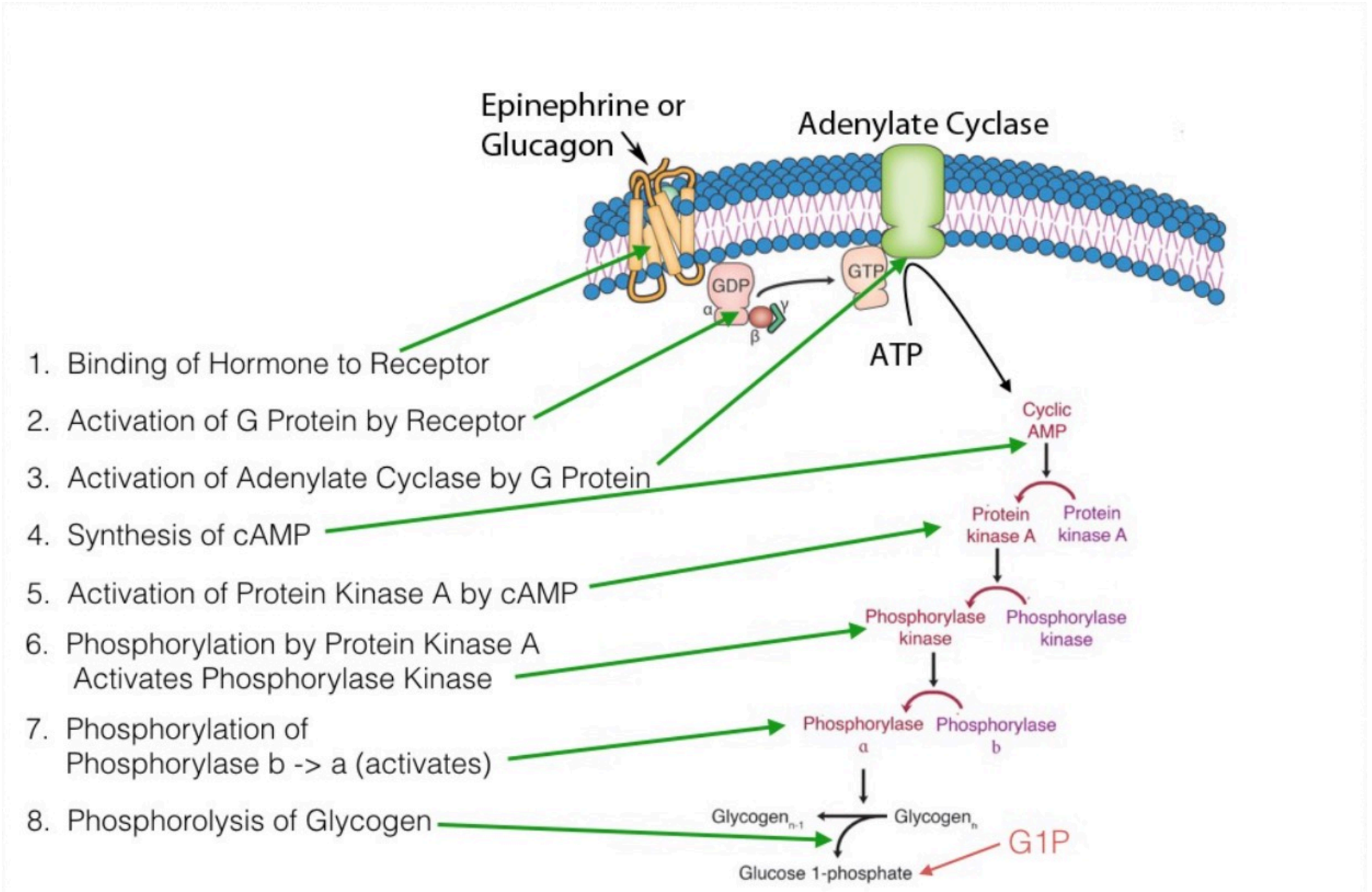
- Aspartate Transcarbamoylase (ATCase)



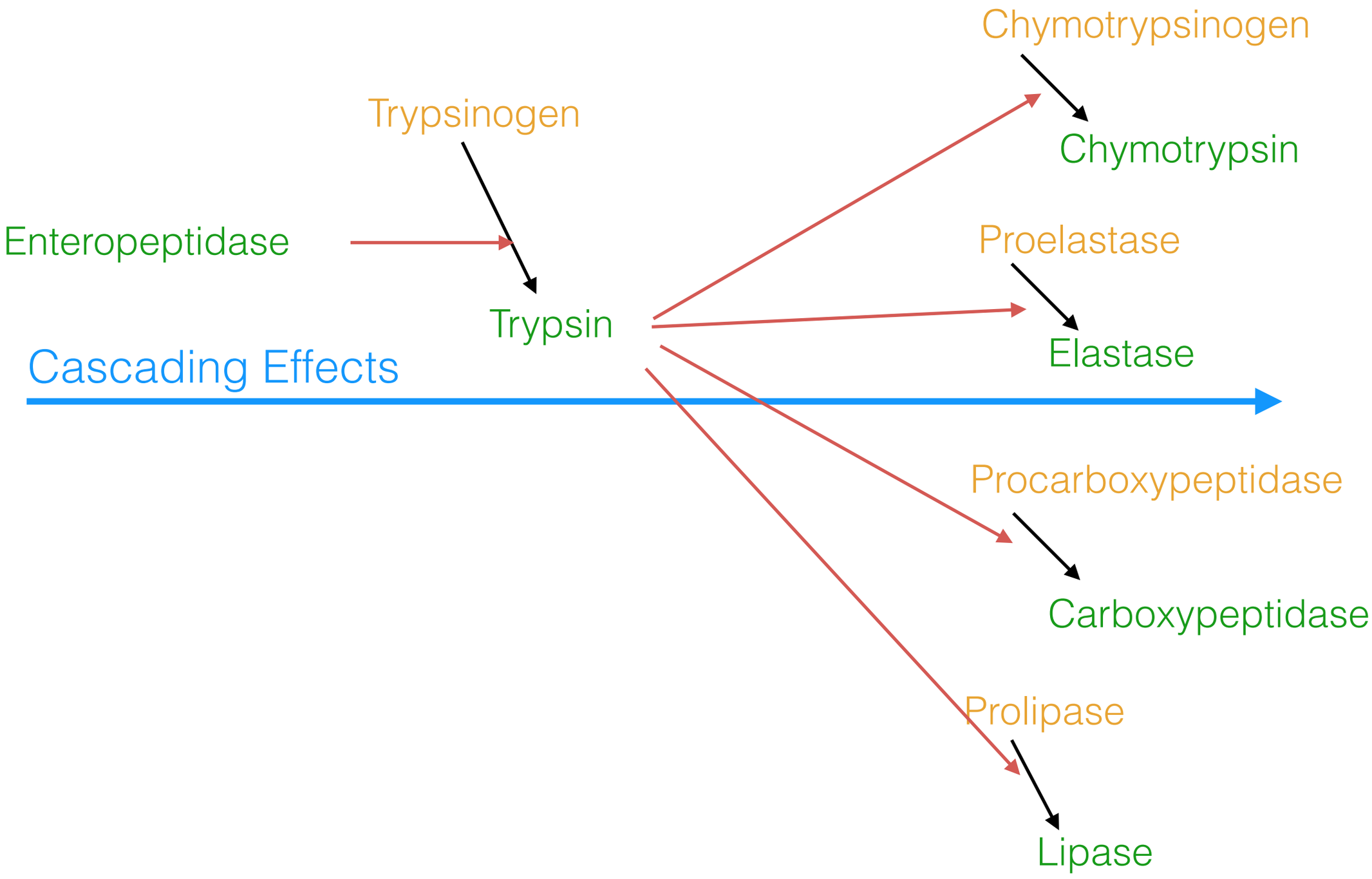
Covalent Modification



Covalent Modification

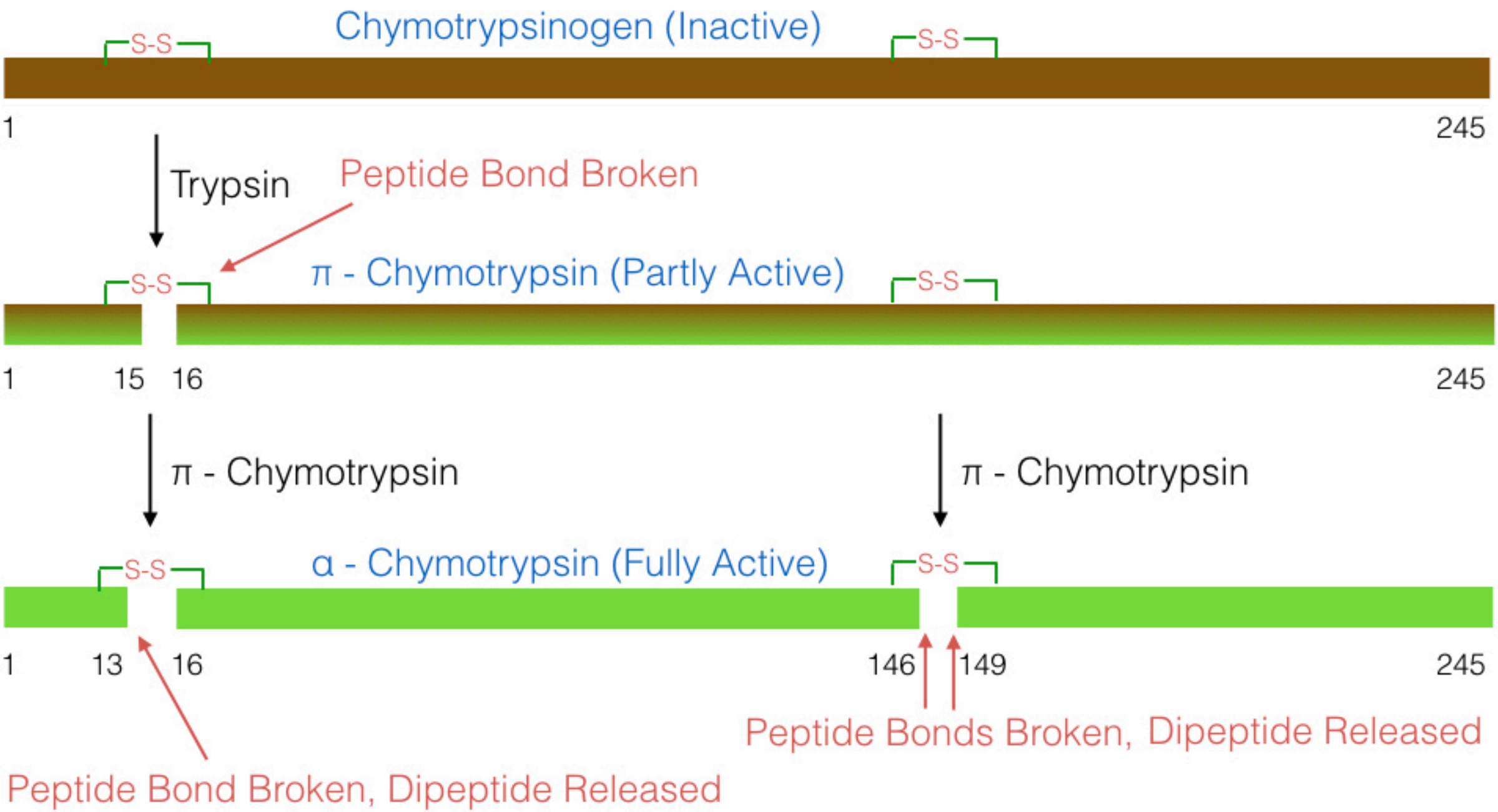


Zymogen Activation



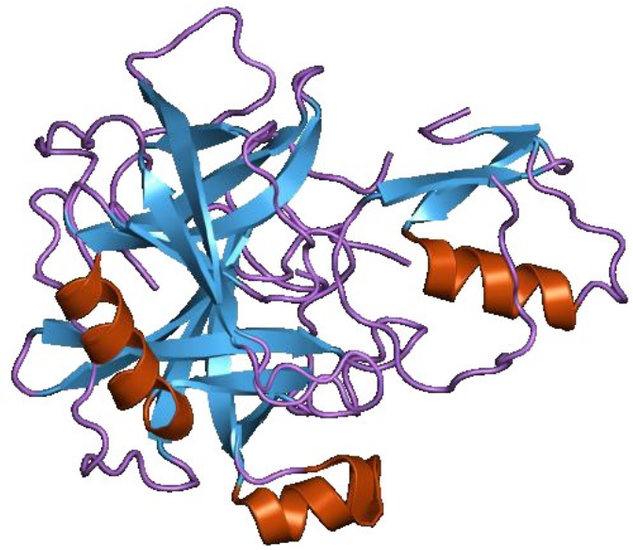
Control of Enzyme of Activity

- Covalent Modification Control



Control of Enzyme of Activity

- Zymogens

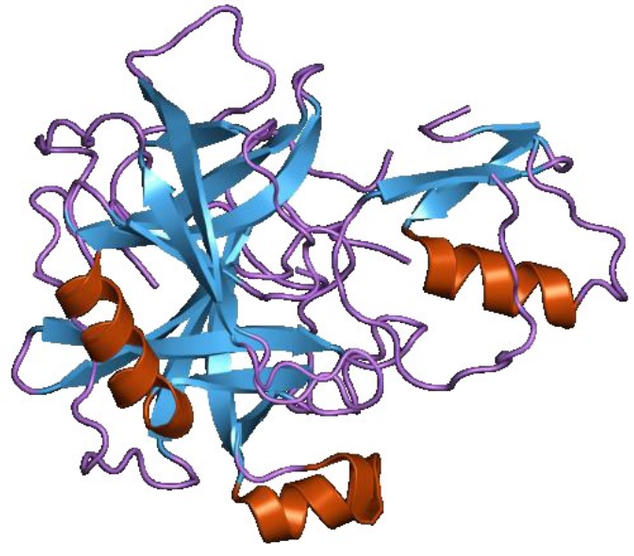


http://www.ebi.ac.uk/

- Protease Precursors
  - Pepsinogen
  - Proenteropeptidase
  - Trypsinogen
  - Chymotrypsinogen
  - Procarboxypeptidases
  - Blood Clotting Proteins
  - Procaspases
  - Proelastase
- Other
  - Pacifastin
  - Plasminogen
  - Angiotensinogen
  - Prolipase
  - Pre-proinsulin

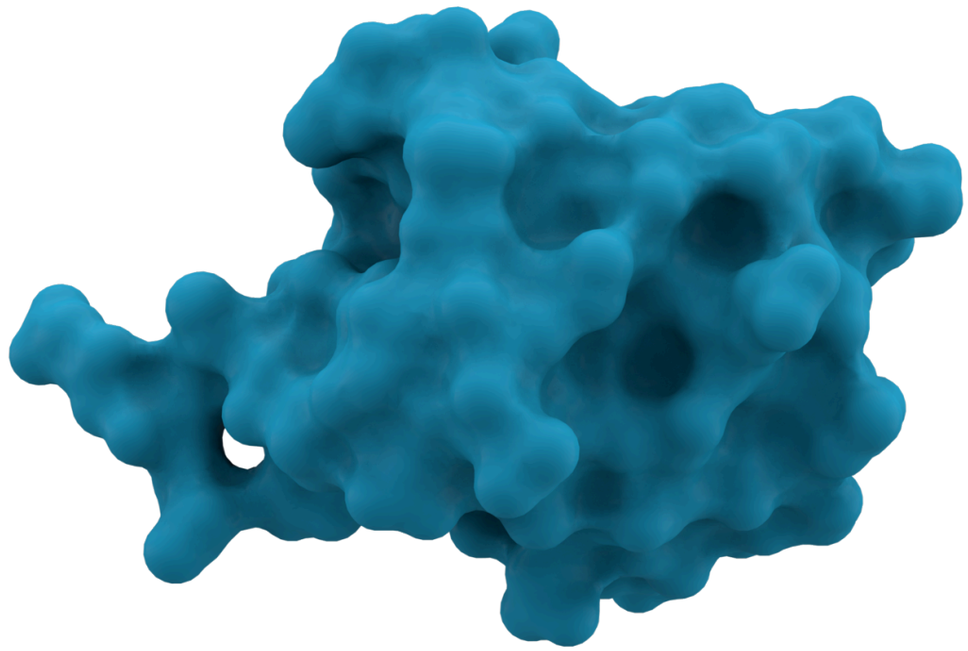
Control of Enzyme of Activity

• Other Covalent Modifications to Proteins



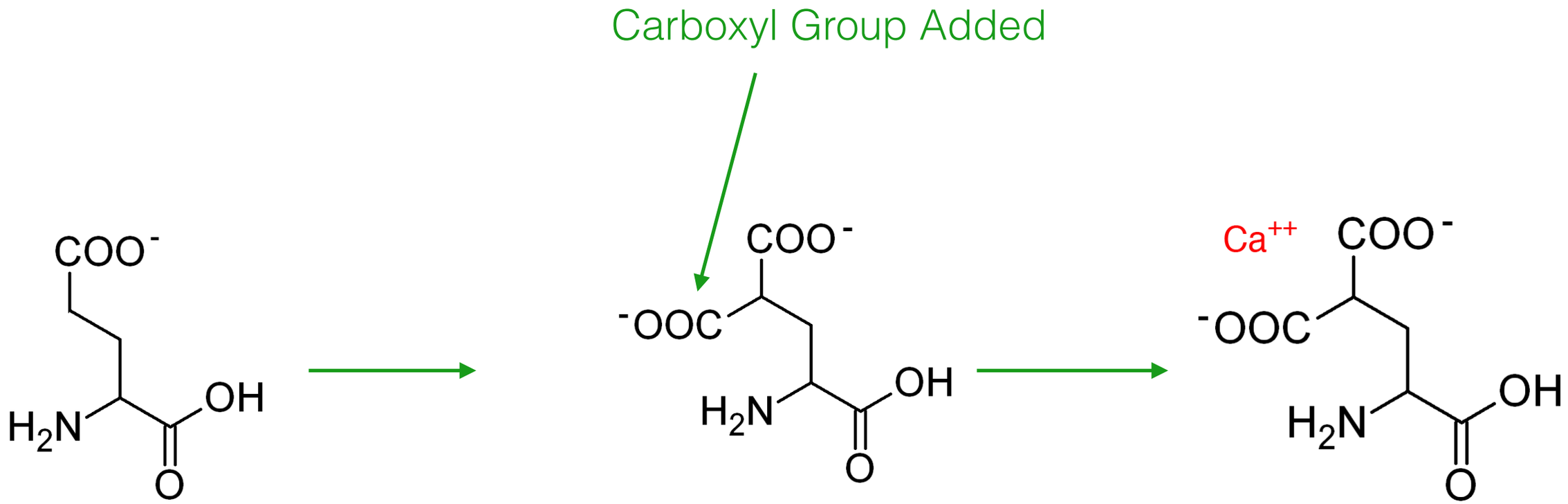
http://www.ebi.ac.uk/

- Phosphorylation - Kinase Cascades
- Acetylation - Histones
- Formylation - All Prokaryotic Proteins
- Acylation - Anchored Membrane Proteins (SRC)
- ADP Ribosylation - Transcription Factors
- Prenylation - Ras
- Sulfation - Serine Protease Inhibitors
- Ubiquitination - Many Proteins
- γ-Carboxylation - Clotting Proteins



Control of Enzyme of Activity

- γ-Carboxylation



Glutamate Side Chain

γ - carboxyglutamate

Protein Wonderland

(to the tune of "*Winter Wonderland*")

Metabolic Melody

Mechan-i-sm . . determines
How an en . . zyme is workin'
Here are the ways
That each elastase
Breaks a peptide bond so easily

Starting with the binding of the substrate
Catalytic triad is the star
Histidine's electron sink reacts to
Pull a proton from a serine's a-r-r-r-r

Then the al . . . koxide ion
Gets elec . . . trons a-flyin
It makes a big fuss
For one nuc-le-us
And breaks and makes a bond with carbonyl

Then the process switches in its action
Water comes to free the carbonyl
Loss of proton yields hydroxide ion
Attacking on the peptide bound there still -ll -ll

Which the en . . . . zyme releases
Otherwise . . . action ceases
The process is done
Until the S1
Binds a substrate starting up again