An Introduction to Metabolism

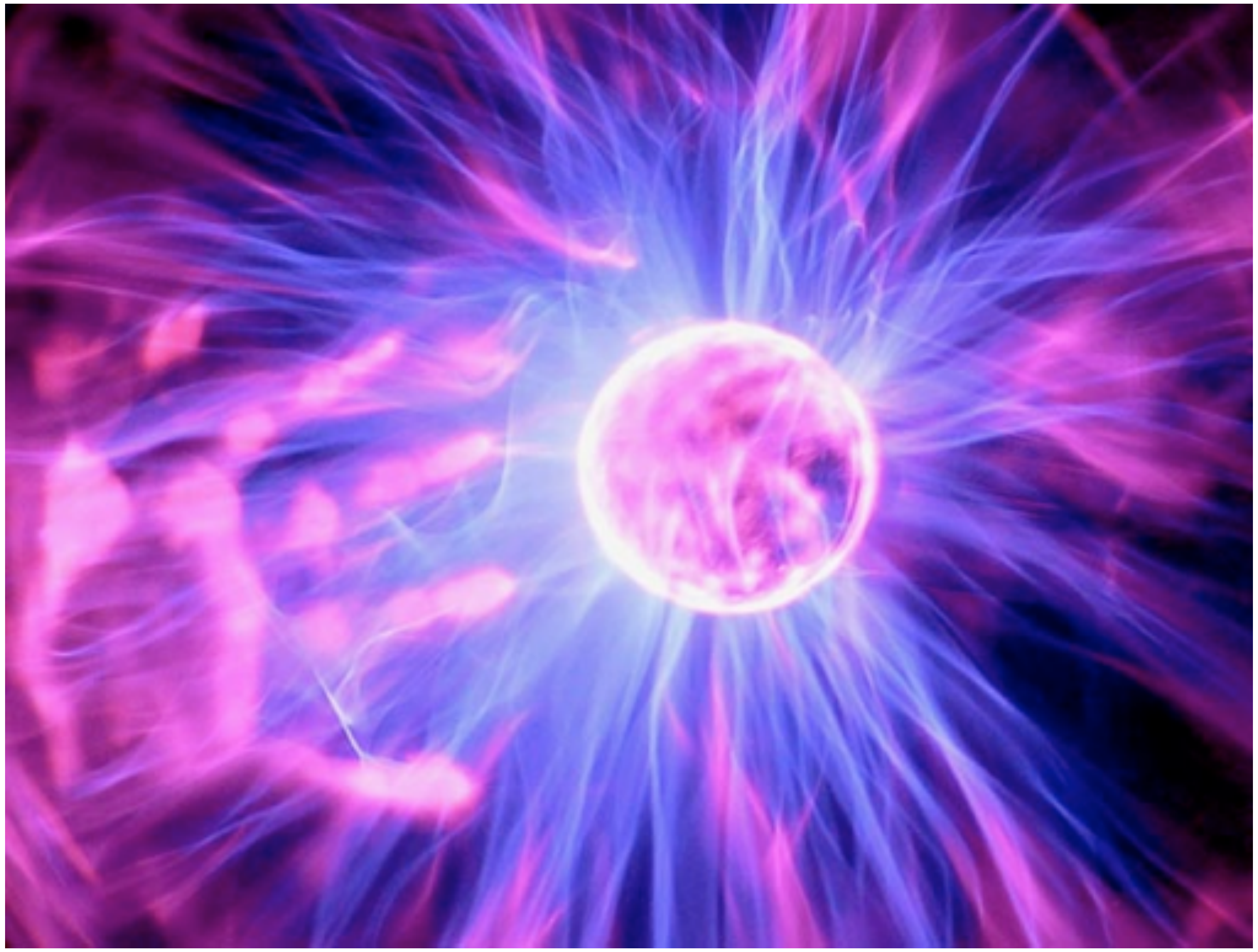
PREFACE

- **The living cell is a chemical factory with thousands of reactions taking place, many of them simultaneously**
- **This chapter is about matter and energy flow during life processes and how that flow is regulated**

(8) Intro to Metabolism

I.

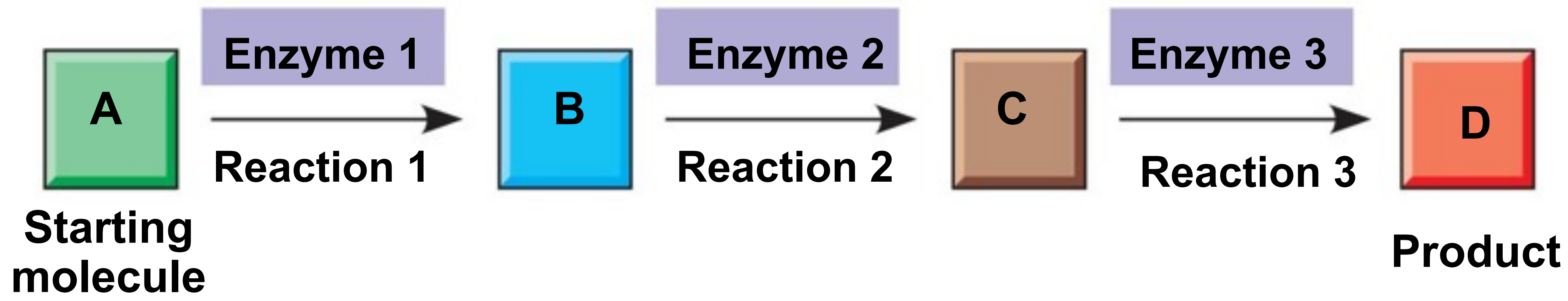
Main Idea: Metabolism, the collection of all cellular reactions, transforms matter and energy.



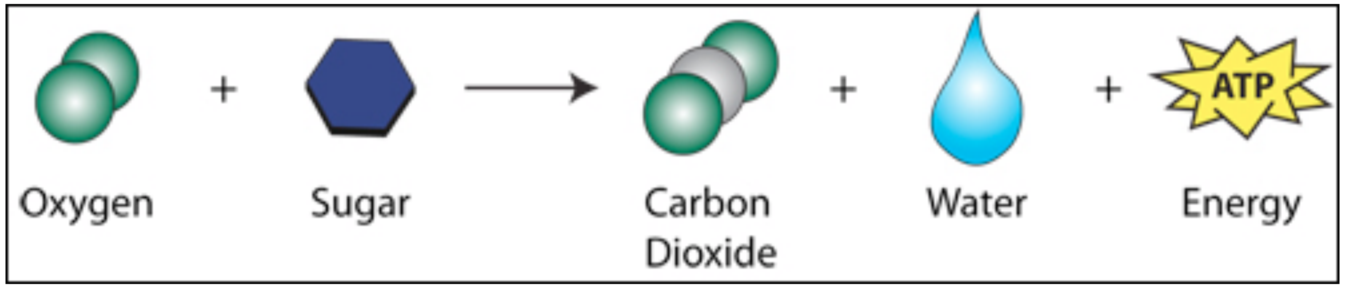
AN ORGANISM'S METABOLISM TRANSFORMS MATTER AND ENERGY, SUBJECT TO THE LAWS OF THERMODYNAMICS

A. Organization of the Chemistry of Life into Metabolic pathways

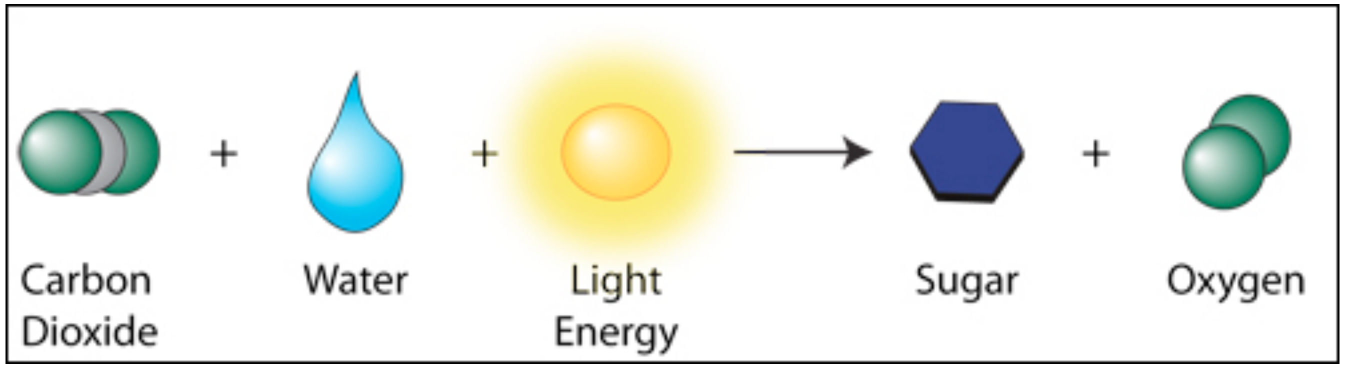
- Metabolic pathways begin with a specific molecule, which is then altered in a series steps, resulting in a certain product.



- **Catabolic Pathways:** release energy by breaking down complex molecules into simpler molecules
  - Ex. Cell Respiration



- **Anabolic Pathways:** consume energy to build complex molecules from simpler molecules
  - Ex. Photosynthesis



Notice the location of "energy" relative to the arrow in the chemical equation.

B. Forms of Energy

- **Energy is**...the capacity to do work, the ability to cause change, the ability to rearrange matter, the ability to move matter against opposing forces.
- **Kinetic Energy** is associated with the motion of objects
  - Moving objects can perform work, by imparting motion onto other objects
- **Heat or Thermal Energy** is kinetic energy associated with the random movement of atoms and molecules

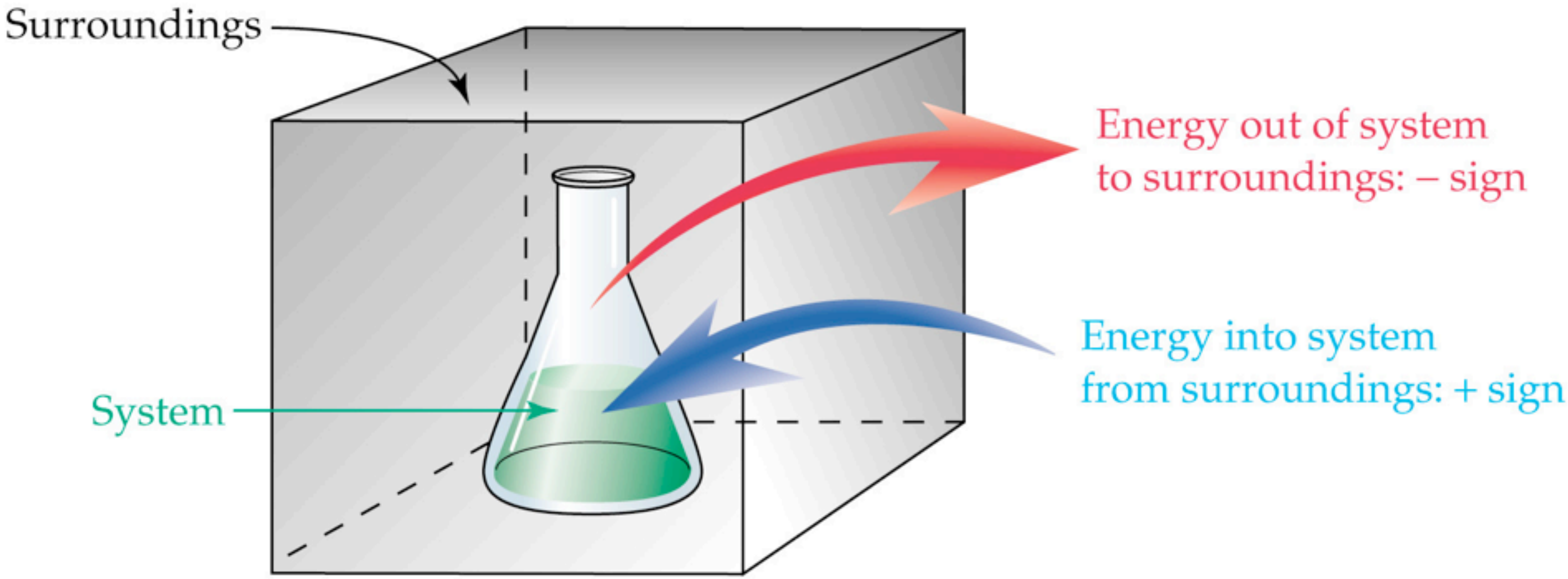
Forms of Energy (continued)

- **Potential Energy** is the energy that matter possesses as a result of its location or structure
- **Chemical Energy** is refers to the potential energy available for release in a chemical reaction.
  - This chemical energy was derived from light during photosynthesis...Organisms are energy transformers.

C. The Laws of Energy Transformation

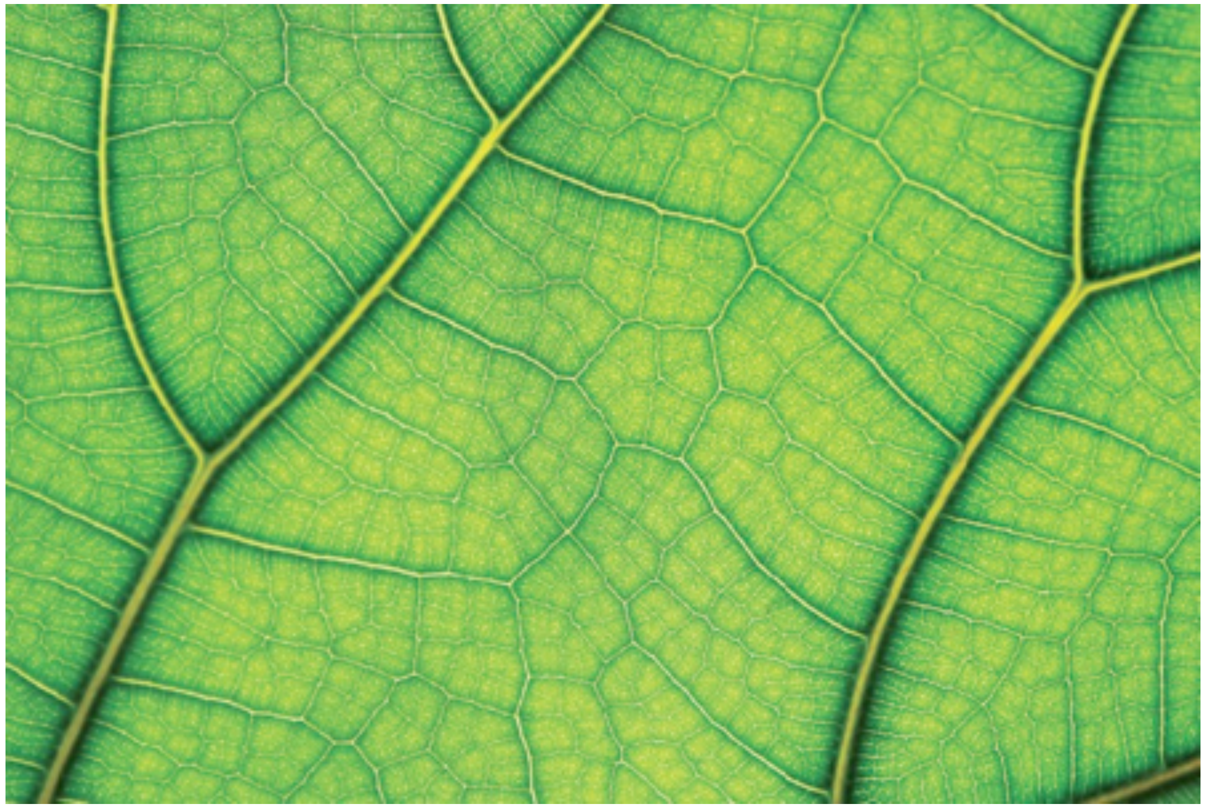
- **Thermodynamics** is the study of energy transformations that occur in a collection of matter.
  - **System**- denotes the matter under study
  - **Surroundings**- everything outside the system
  - **Isolated systems**- where energy and matter are not transferred between the system and surroundings
  - **Open systems**- where energy and matter are transferred between the system and surroundings
- Two laws of thermodynamics govern energy transformations.

$$\Delta E = E_{final} - E_{initial}$$



1. First Law of Thermodynamics

- **First Law of Thermodynamics:** Energy can be transferred and transformed, but it can not be created or destroyed.
  - This is the principle of energy conservation
  - *The electric company and plants are energy transformers*



2. Second Law of Thermodynamics

- **Second Law of Thermodynamics:** Every energy transfer or transformation increases the entropy (disorder) of the universe
  - With energy transfer or transformation some energy is becomes unavailable to do work
  - Most of the is lost to the surroundings as heat.
- **Spontaneous processes** occur without an input of energy, in order for this to take place the process increase the disorder of the universe
  - Spontaneous does not imply speed but rather a process that is energetically favorable.
    - Ex. rusting nail

3. Biological Order and Disorder

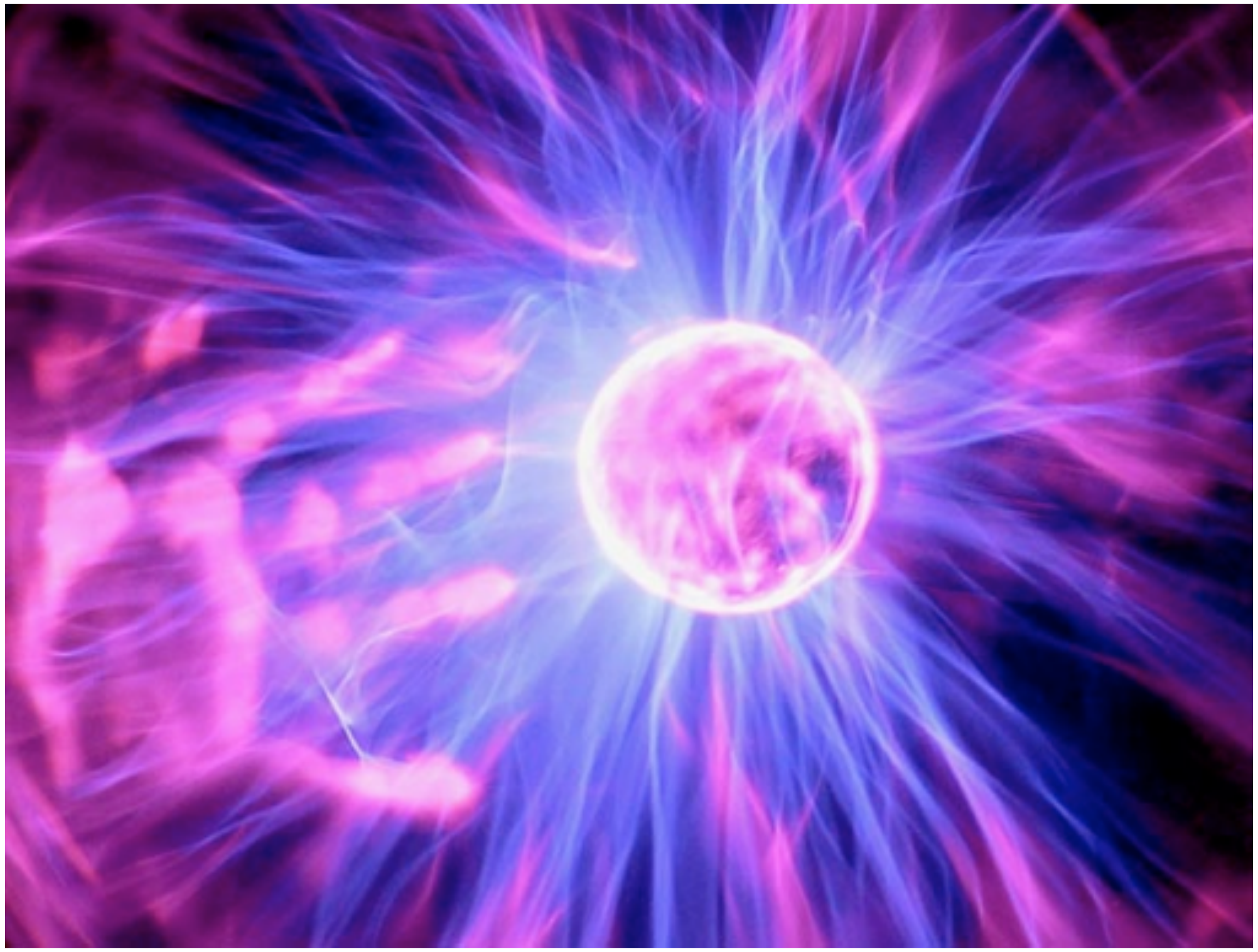
- **Cells** create ordered structures from less organized starting materials.
- **Organisms** are complex ordered structures from less organized starting material
  - Fibonacci Numbers
- **Complex organisms evolved from simpler organisms.** This does in any way violate the second law of thermodynamics. The entropy of a system can decrease as long as the entropy of its surroundings increase.

Organisms are islands of low entropy in an sea of increasing entropy.

(8) Intro to Metabolism

II.

Main Idea: Biologists want to know which reactions occur spontaneously and which require an input of energy.



THE FREE-ENERGY CHANGE OF A REACTION TELLS US WHETHER OR NOT THE REACTION OCCURS SPONTANEOUSLY

A. Free-Energy Change, ΔG

- **Free Energy:** is the portion of a system's energy that can perform work
- Change in Free Energy = (change in total energy) - (temperature)(change in entropy)

$$\Delta G = \Delta H - (T)(\Delta S)$$

B. Free Energy, Stability & Equilibrium

- Once we know ΔG we can predict if a reaction is spontaneous.

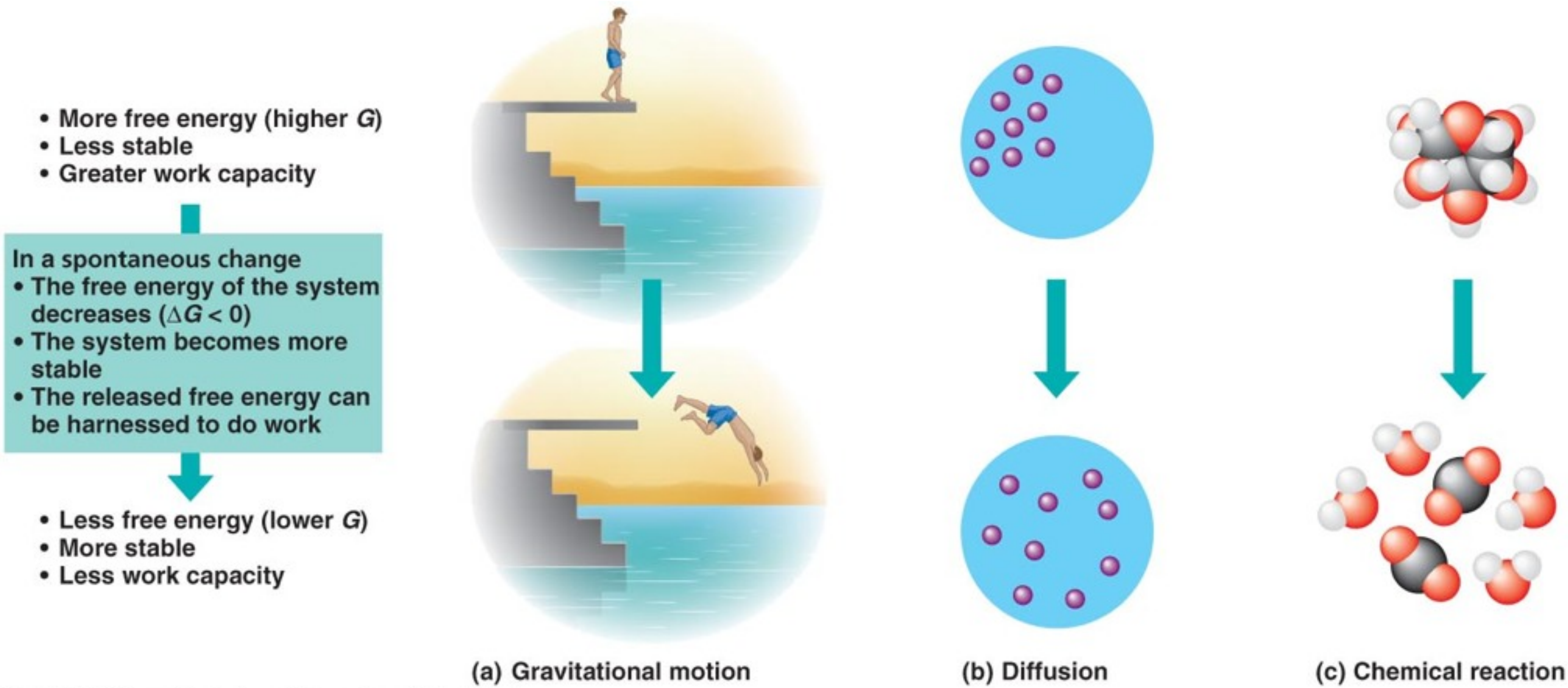
$\Delta G<0$ reaction is spontaneous

$\Delta G>0$ reaction is nonspontaneous

- We can think of free energy as a measure of a system's instability-its tendency to change to a more stable state
- Unless something prevents it systems will move towards greater stability
- Maximum stability is described by the term *equilibrium.*
- Systems naturally move towards equilibrium but never spontaneously move away from equilibrium.
- Most chemical reactions are reversible and will naturally eventually reach equilibrium
- However...A process is spontaneous and can do work only when it is moving away from equilibrium

Free Energy, Stability & Equilibrium

- Maximum stability is described by the term *equilibrium.*
- Systems naturally move towards equilibrium but never spontaneously move away from equilibrium.
- Free energy decreases as reactions move towards equilibrium
- Most chemical reactions are reversible and will naturally eventually reach equilibrium
- However...A process is spontaneous and can do work only when it is moving away from equilibrium
- As a result cells must constantly "push" reactions away from equilibrium, otherwise free energy decreases, work can not get done and the cell dies


• More free energy (higher G)
• Less stable
• Greater work capacity
In a spontaneous change
• The free energy of the system decreases (ΔG < 0)
• The system becomes more stable
• The released free energy can be harnessed to do work
• Less free energy (lower G)
• More stable
• Less work capacity
(a) Gravitational motion
(b) Diffusion
(c) Chemical reaction

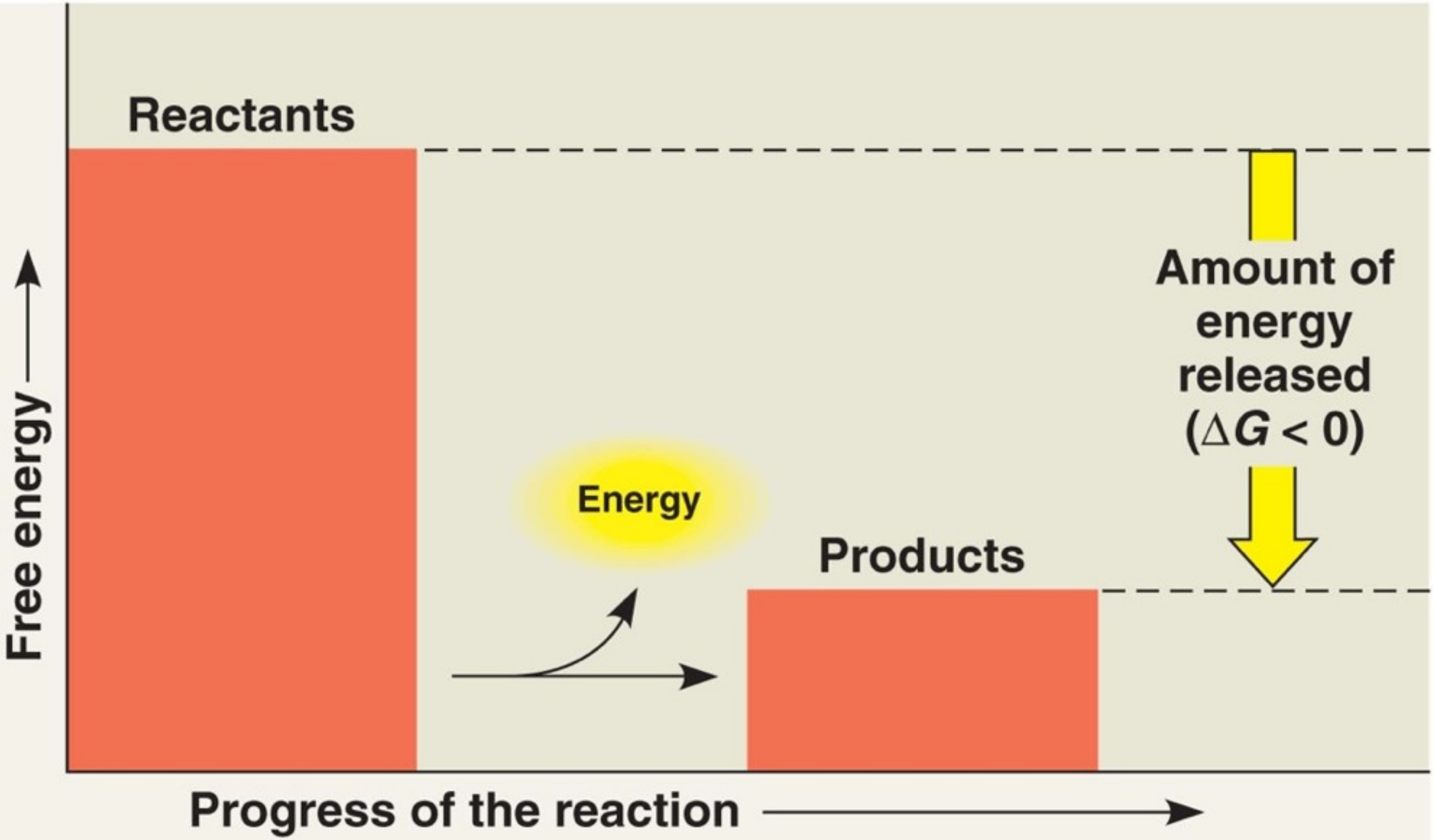
C. Free Energy & Metabolism

1. Exergonic & Endergonic Reactions

- Based upon free energy reactions are classified as either...
- **Exergonic Reactions:** proceed with a net *release* of free energy
  - $\triangle$G decreases
  - $\triangle$G is negative
  - $\triangle$G's magnitude represents max amount of work
  - Reaction is spontaneous

$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O$$

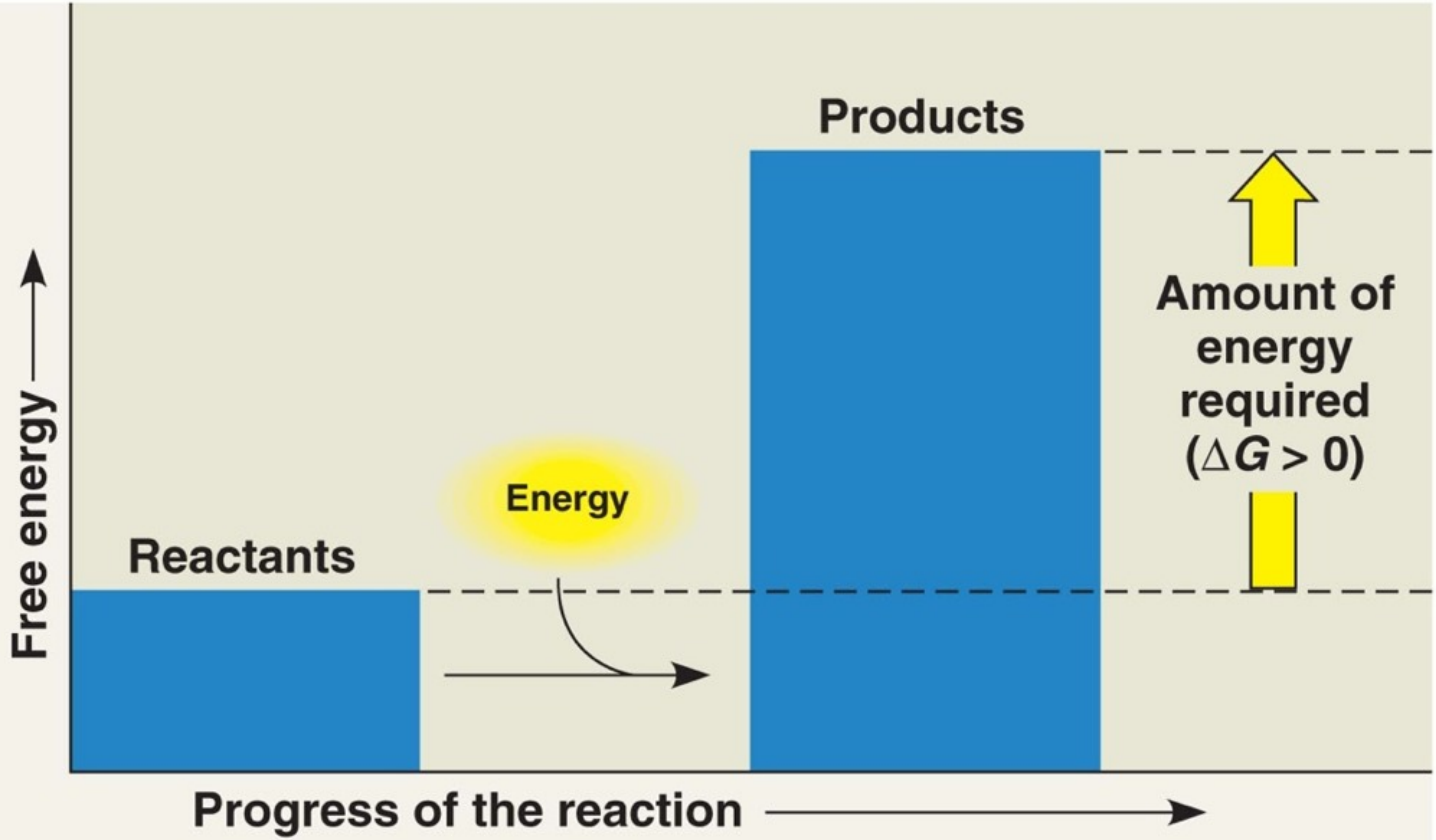
$$\triangle G = -686\ \text{kcal/mol}$$



(a) Exergonic reaction: energy released

Exergonic & Endergonic Reactions continued

- Based upon free energy reactions are classified as either...
- **Endergonic Reactions:** absorb free energy from its surroundings
  - $\triangle$G increases
  - $\triangle$G is positive
  - $\triangle$G's magnitude represents amount of work needed
  - Reaction is nonspontaneous

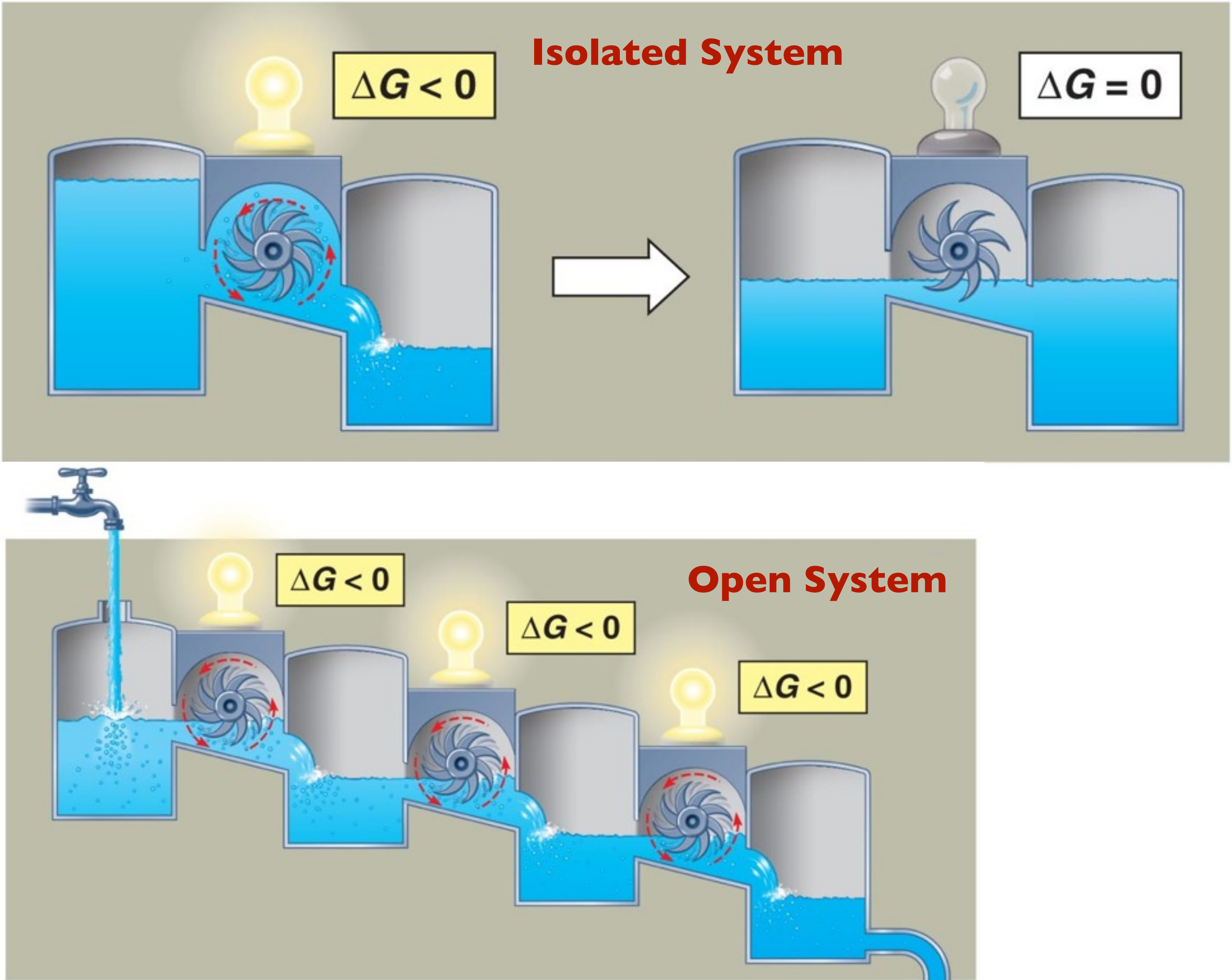


(b) Endergonic reaction: energy required

[redacted]

2. Equilibrium & Metabolism

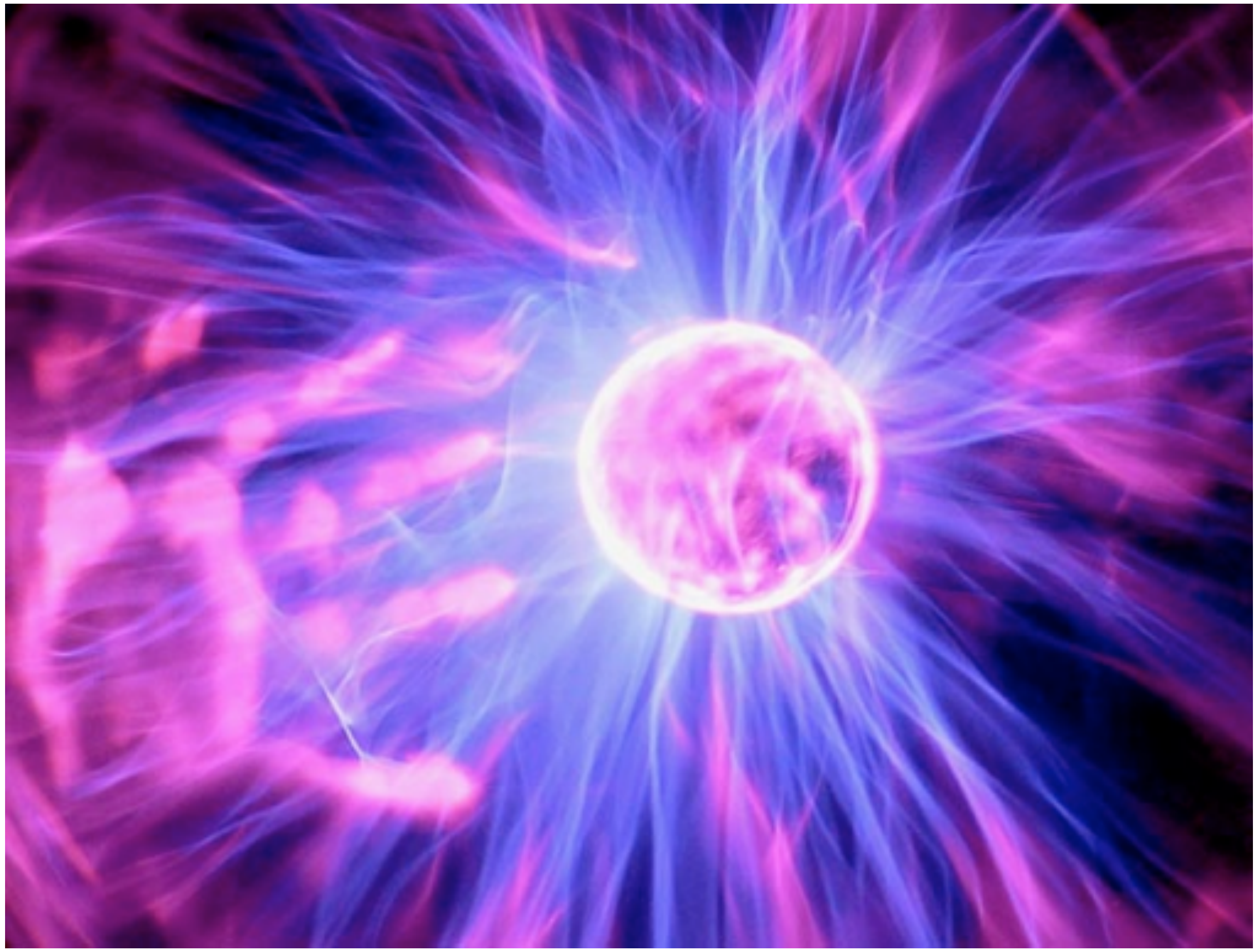
- Recall that isolated systems eventually reach equilibrium and can do no work
- Recall if a cell has reached equilibrium it is dead
- **The fact that metabolism as a whole is never at equilibrium is one of the defining features of life.**
- The constant flow of materials in and out of the cell keeps the metabolic pathways from ever reaching equilibrium


Isolated System
ΔG < 0
ΔG = 0
Open System
ΔG < 0
ΔG < 0
ΔG < 0

(8) Intro to Metabolism

III.

Main Idea: The cell uses the energy released from exergonic reactions to power the endergonic reactions.

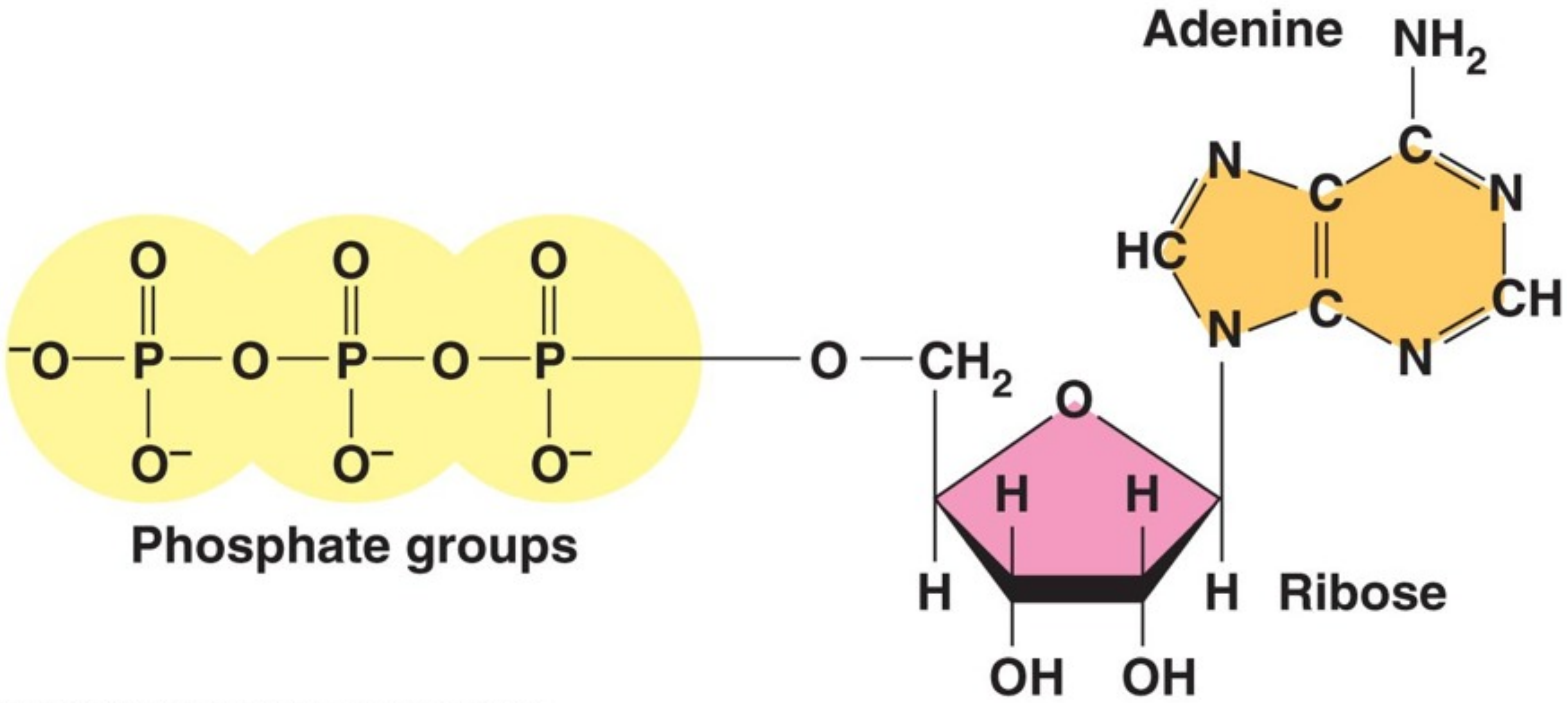


ATP POWERS CELLULAR WORK BY COUPLING EXERGONIC REACTIONS TO ENDERGONIC REACTIONS

- The cell does three main types of work:
  - Chemical
  - Transport
  - Mechanical

A. The Structure & Hydrolysis of ATP

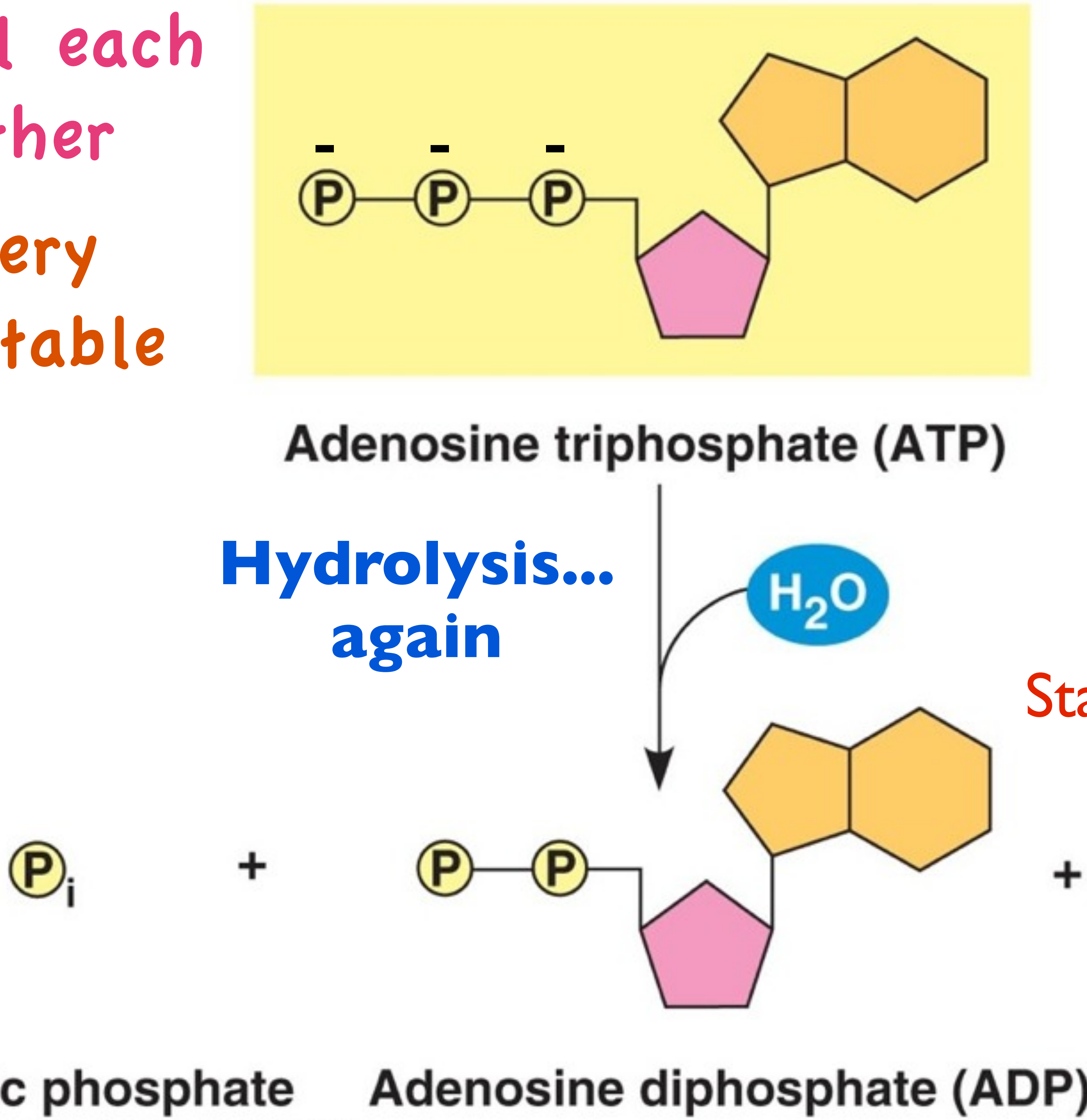
- ATP used as a subunit for RNA synthesis as well as energy coupling



The Structure & Hydrolysis of ATP

repel each other

very unstable



Hydrolysis... again

Standard Conditions

-7.3kcal/mol

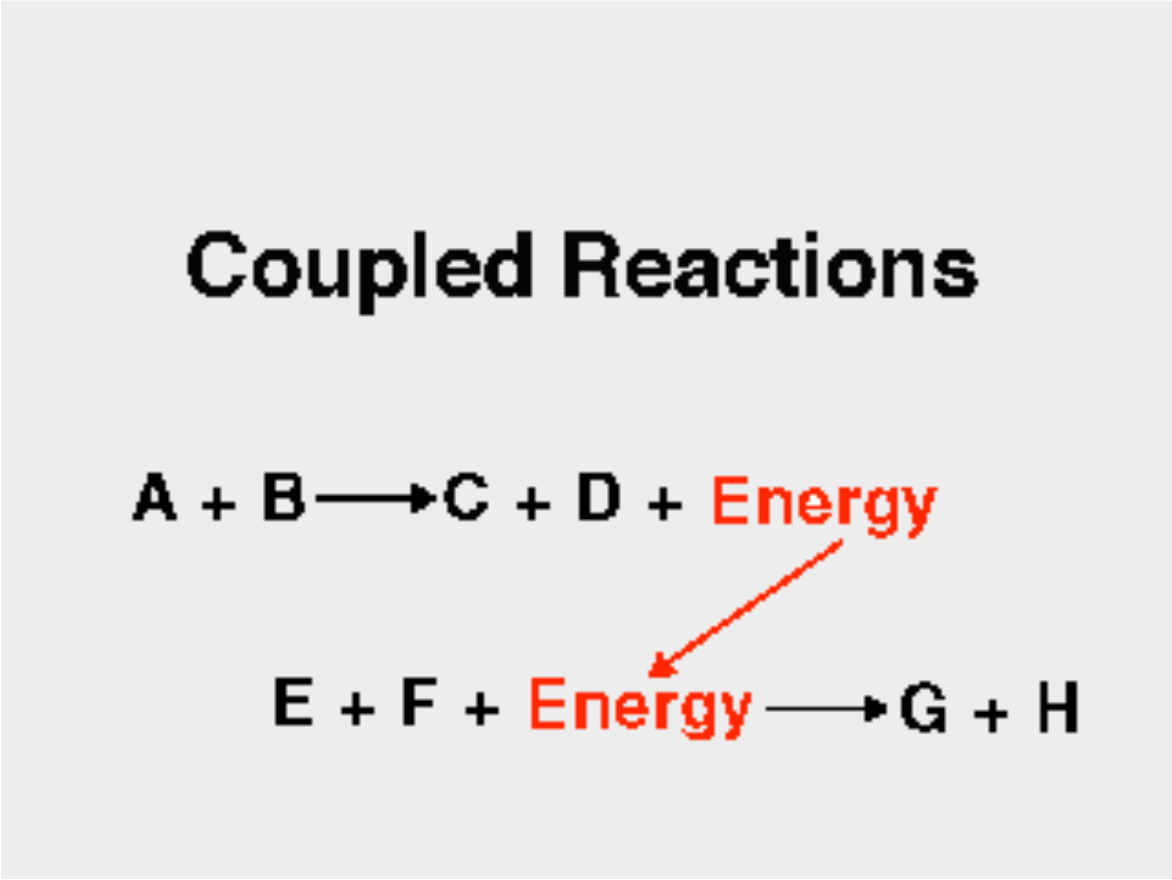
Energy

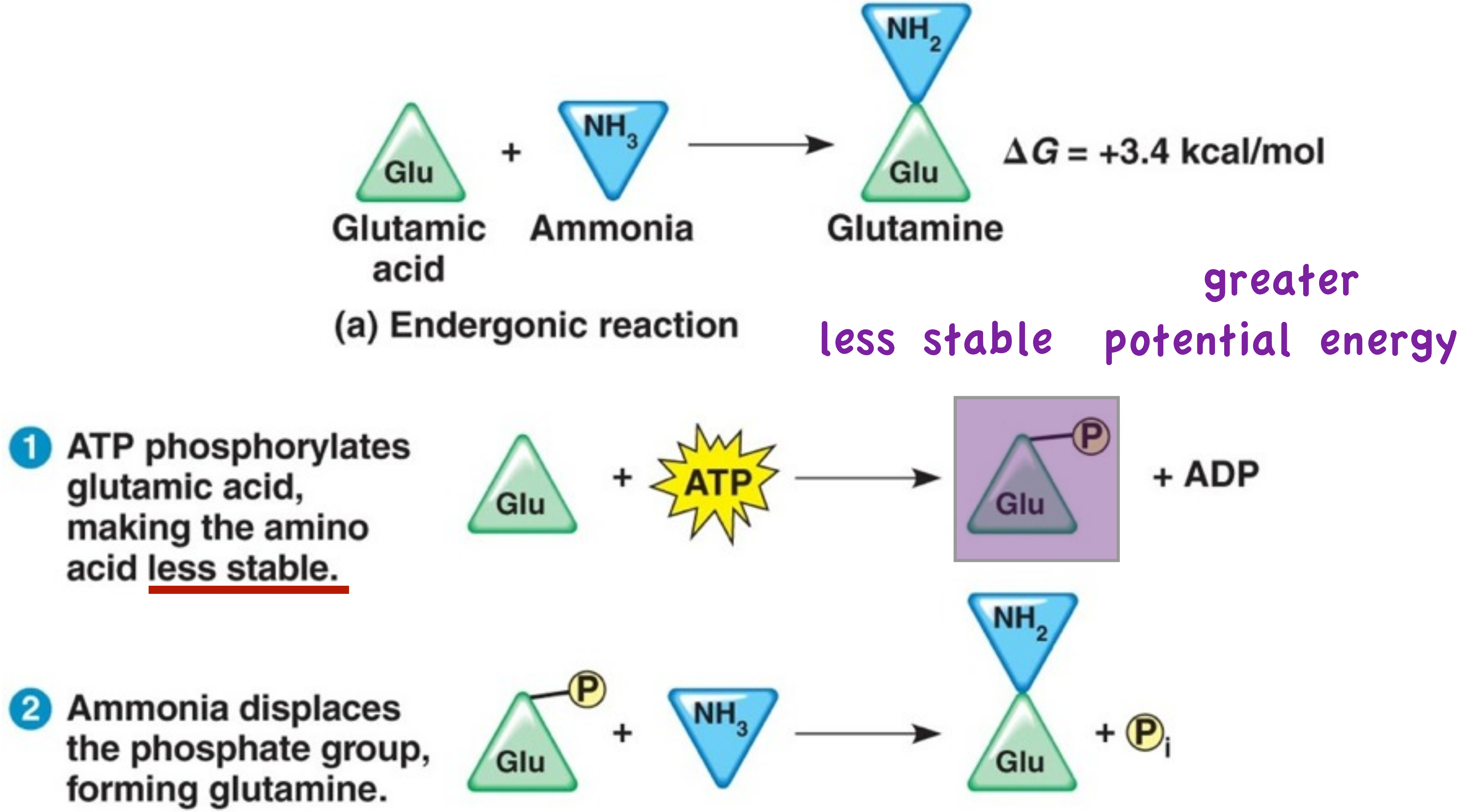
-13kcal/mol

Cell Conditions

B. How the Hydrolysis of ATP Performs Work

- When ATP is hydrolyzed in a test tube, the release of free energy merely heats up the surroundings.
- At times this may be useful for an organism to warm itself
- However at other times this heat could be dangerous
- *Instead cells prefer to harness the energy released from ATP hydrolysis and use it power endergonic reactions and cellular work.*





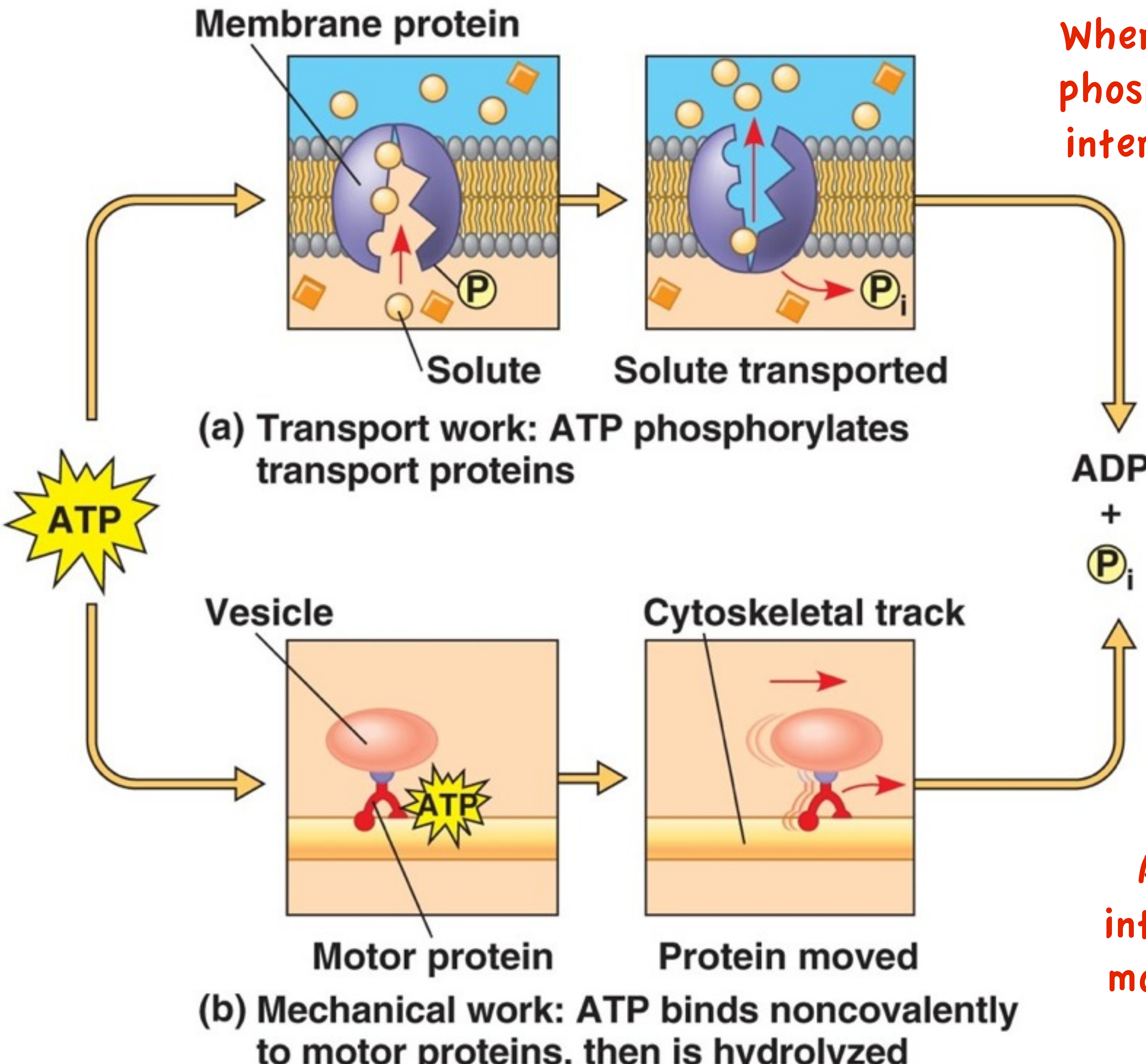
(a) Endergonic reaction

(b) Coupled with ATP hydrolysis, an exergonic reaction

Glu + NH_3 $\longrightarrow$ Glu— NH_2		ΔG = +3.4 kcal/mol
ATP $\longrightarrow$ ADP + P_i		ΔG = -7.3 kcal/mol
		Net ΔG = -3.9 kcal/mol

(c) Overall free-energy change

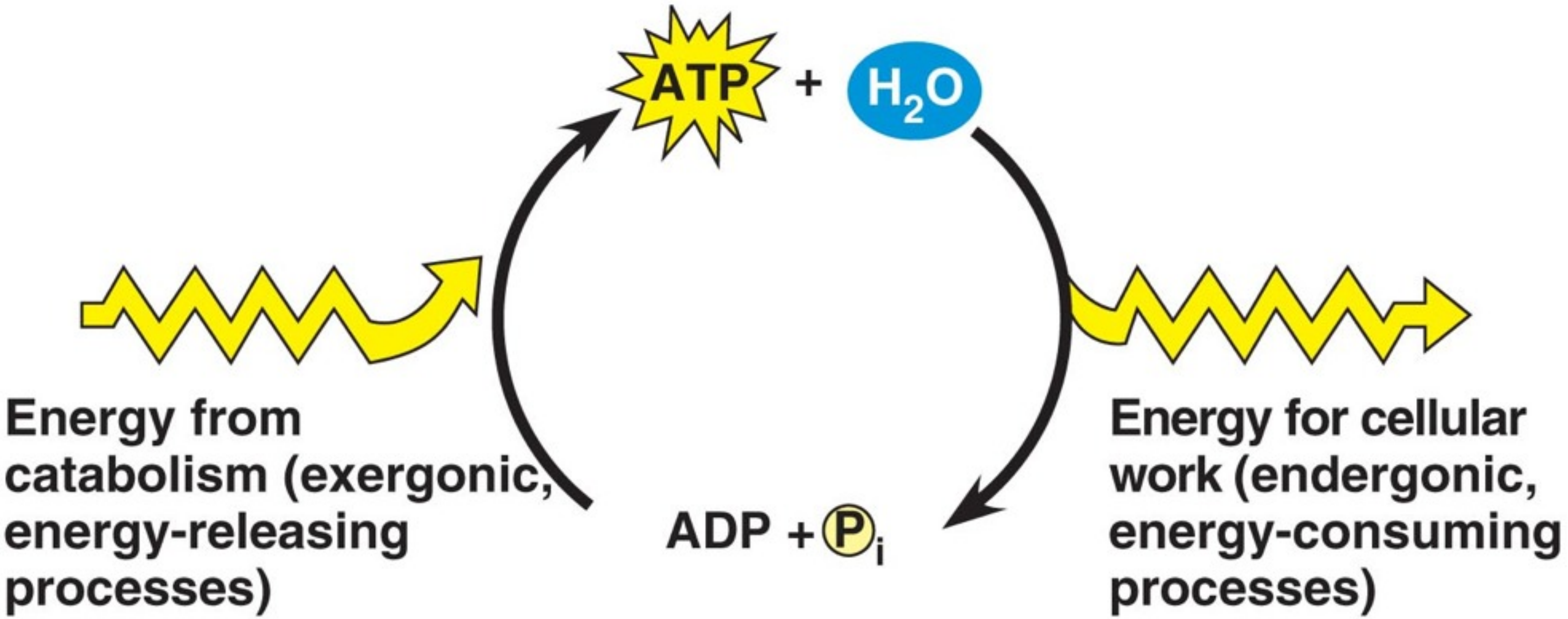
Where are the phosphorylated intermediates?



Are these intermediates more or less stable?

C. The Regeneration of ATP

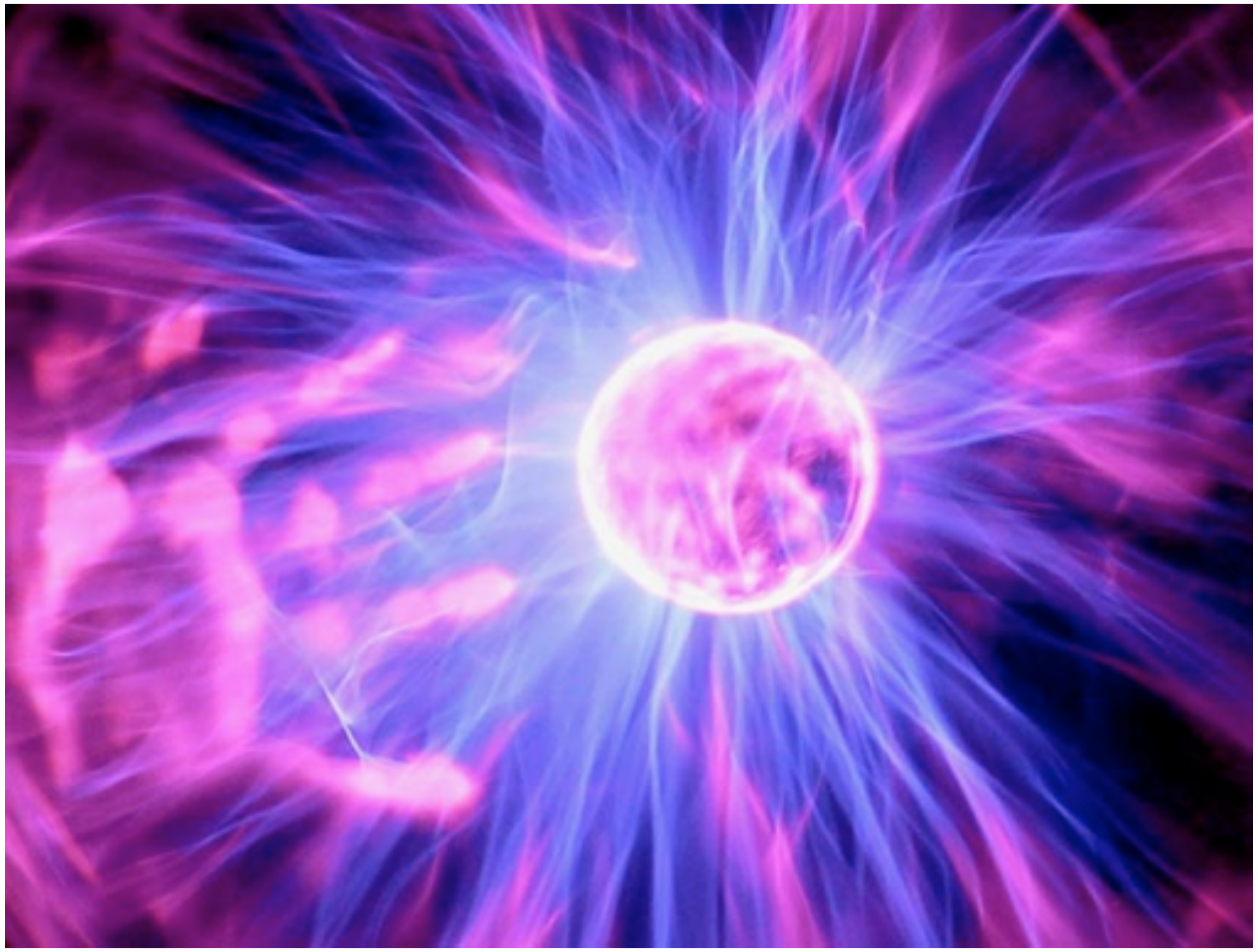
- ATP is hydrolyzed continuously.
- ATP is renewable and can be regenerated
- The ATP cycle below can consume and regenerate 10 million per second



(8) Intro to Metabolism

IV.

Main Idea: Enzymes speed up the rate of chemical reactions in cells.

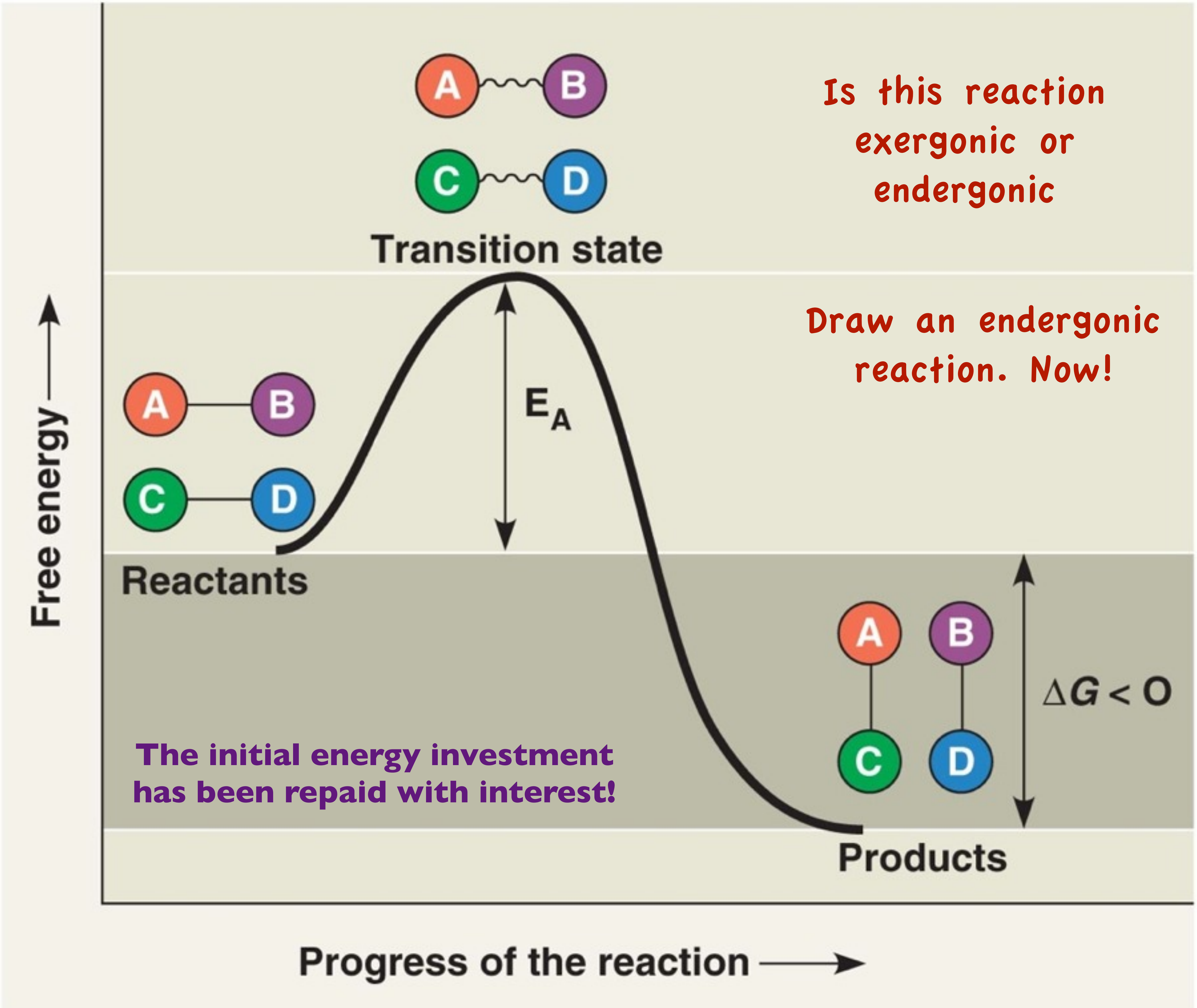


ENZYMES SPEED UP METABOLIC REACTIONS BY LOWERING THE ACTIVATION ENERGY

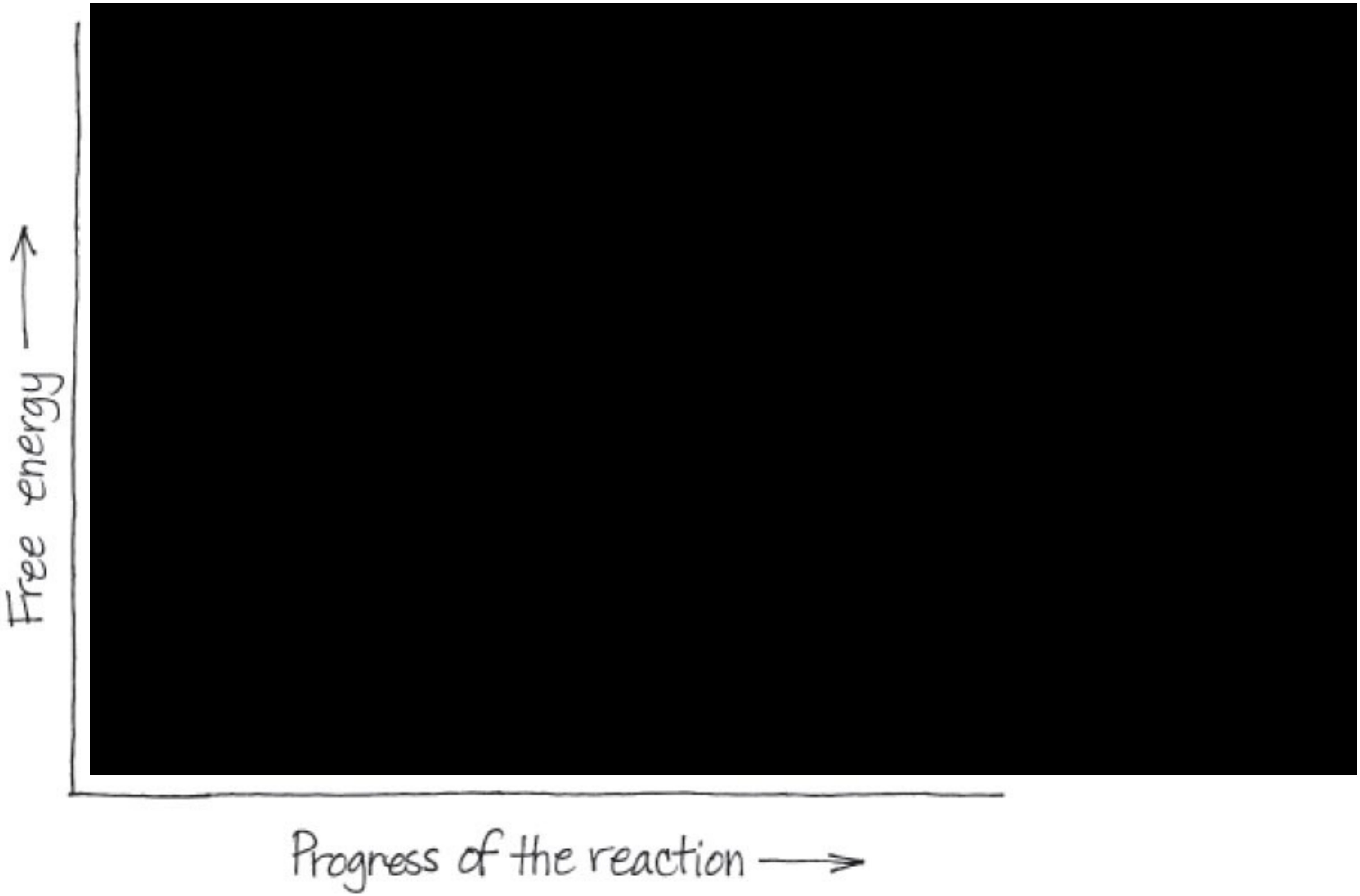
- The Laws of Thermodynamics can tell us if reactions are likely spontaneous but say nothing about the rate of reactions.
- **Enzyme**: a macromolecule that acts like a **catalyst**, a chemical that speeds up a reaction without being consumed by the reaction

A. The Activation Energy Barrier

- Every chemical reaction between molecules involves making and breaking bonds.
- Changing molecules involves contorting them into a less stable conformation.
  - Remember it takes energy to contort the molecule!
- The initial energy investment used to contort the molecule is called the **activation energy**.
- Thermal energy accelerates molecules so they collide more forcefully and/or more frequently.
  - Once the molecules absorb a certain amount of energy they become unstable to the point where the bonds can break. This unstable condition is called the **transition state**.


Transition state
Is this reaction exergonic or endergonic
Draw an endergonic reaction. Now!
E_A
Free energy
Reactants
ΔG < O
The initial energy investment has been repaid with interest!
Products
Progress of the reaction

Answer



One last note:

Some reactions have such a low activation energy that room temperature is sufficient for molecules to reach their transition state

In most cases however the activation energy is high the transition state is rarely reached and the reaction hardly

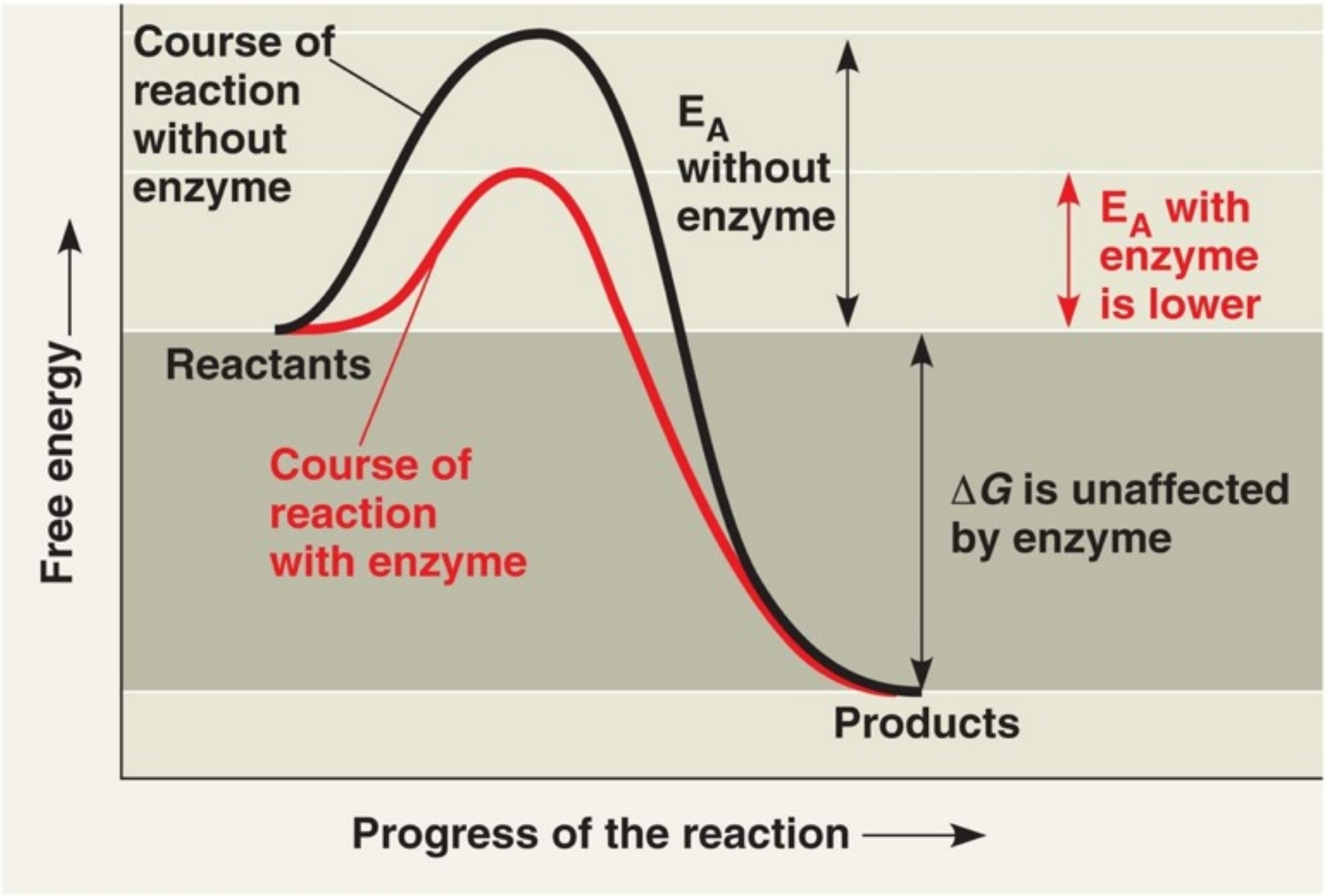
B. How Enzymes Lower the Activation Energy Barrier

- Complex molecules such as proteins are rich in free energy and have the potential to decompose spontaneously.
- These molecules persist because the temperature of typical cells is not sufficiently high enough for molecules to overcome the activation energy.

How Enzymes Lower the Activation Energy Barrier

- Heat, of course, will help molecules reach their transition state but this solution is inappropriate for biological systems.
  - First... high temps denature protein and kills cells
  - Second...heat would speed up all reactions, not just the ones needed
- Enzymes solve both of these problems.

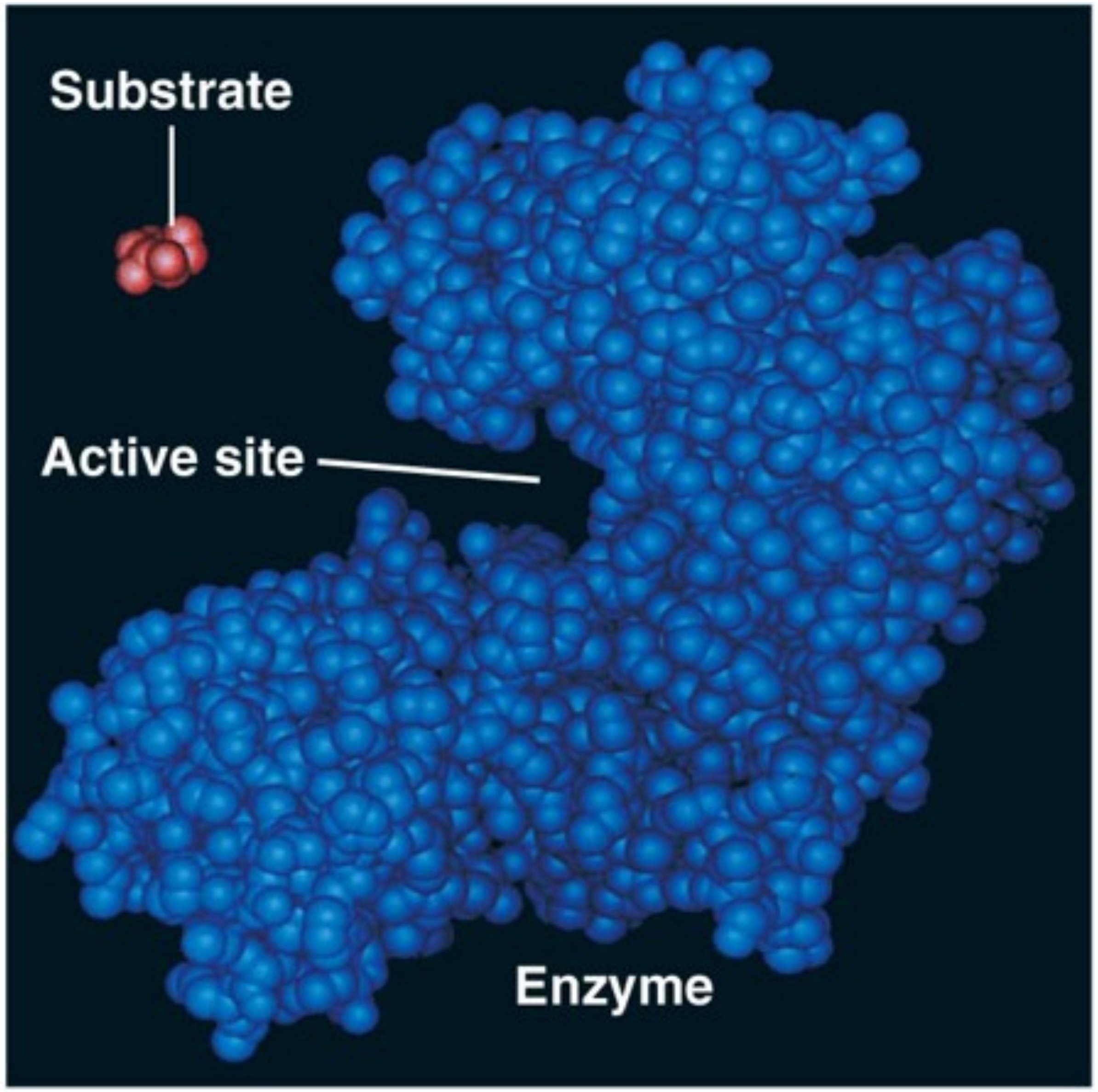
- **Enzymes catalyze reactions by lowering the activation energy**
- **Enzymes are specific for the reactions they catalyze**



Also note: enzymes only speed up the rate of reactions that would occur anyways

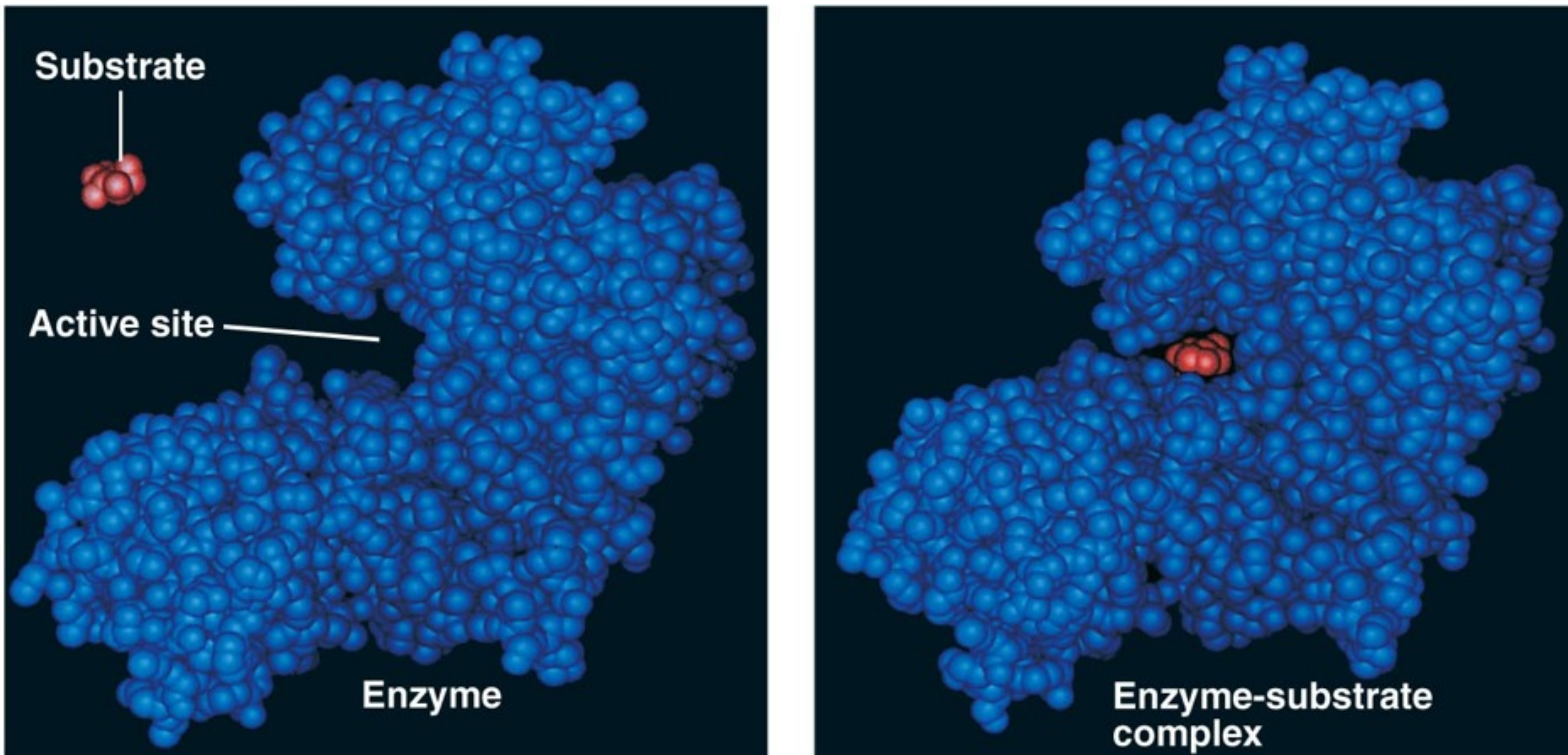
C. Substrate Specificity of Enzymes

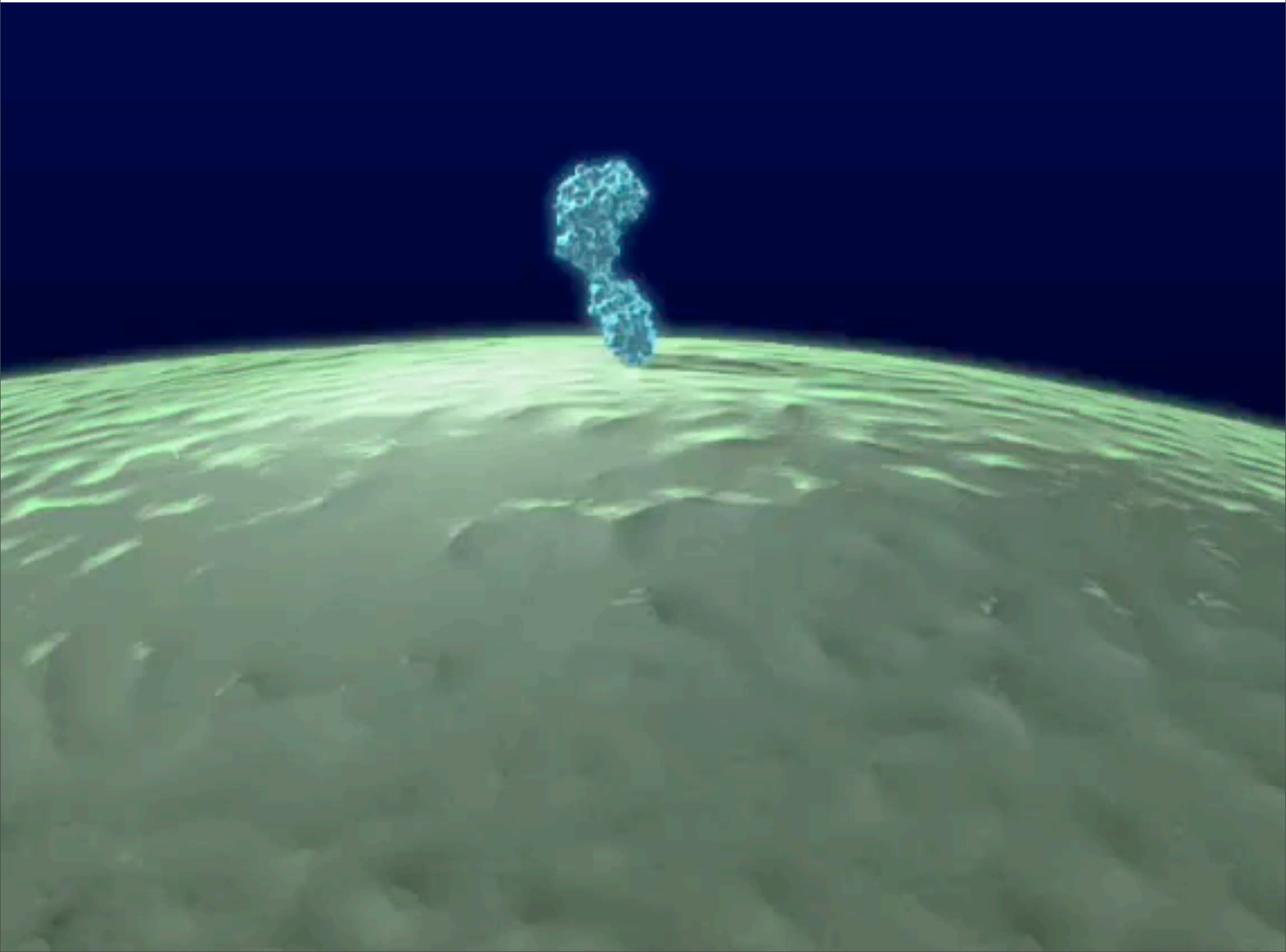
- **Substrate:** the reactant an enzyme acts upon.
  - Most enzymes are proteins
  - Most enzymes end in *-ase*
- **Active site:** is typically a pocket or groove on the surface of the enzyme where catalysis occurs.



Substrate Specificity of Enzymes

- Enzymes are not stiff, they alternate between continually between subtly different shapes
- **Induced fit**: as the substrate moves into the active site, the enzyme moves into another conformation that snugly fits the substrate





D. Catalysis in an Enzyme's Active Site

- Very small amounts enzyme can have a huge metabolic impact.
  - A single enzyme typically acts upon about a thousand substrate molecules per second, some even faster!
- Most metabolic reactions are reversible and enzymes can catalyze in either direction, depending on which direction has a ($-\triangle G$).
  - This in turn depends on the relative concentrations of reactants and products

Catalysis in an Enzyme's Active Site

Enzymes use a variety of mechanisms that lower activation energy and speed up reactions

- **First**, enzymes provide a **template** for two substrate molecules **to orient** themselves in way that promotes their union.
- **Second**, enzymes may stretch a substrate, **stressing their bonds** so that they reach their transition state.
- **Third**, enzyme's active site may provide a **micro-environment** that is more conducive to a particular type of reaction.
- **Fourth**, the mechanism of catalysis is the **direct participation** of the active site in the chemical reaction.

Catalysis in an Enzyme's Active Site

- **Rate of reaction...** is partly a function of the in initial concentration of the substrate.
  - Positive correlation between rate and substrate concentration
  - However there is a limit to how fast a reaction can be pushed
- The point at which the substrate concentration is so great that all the active sites on the enzymes are filled is called **saturation**.
  - When enzymes are saturated the only way to increase rate of product is to add more enzymes.

E. Effects of Local Conditions on Enzyme activity

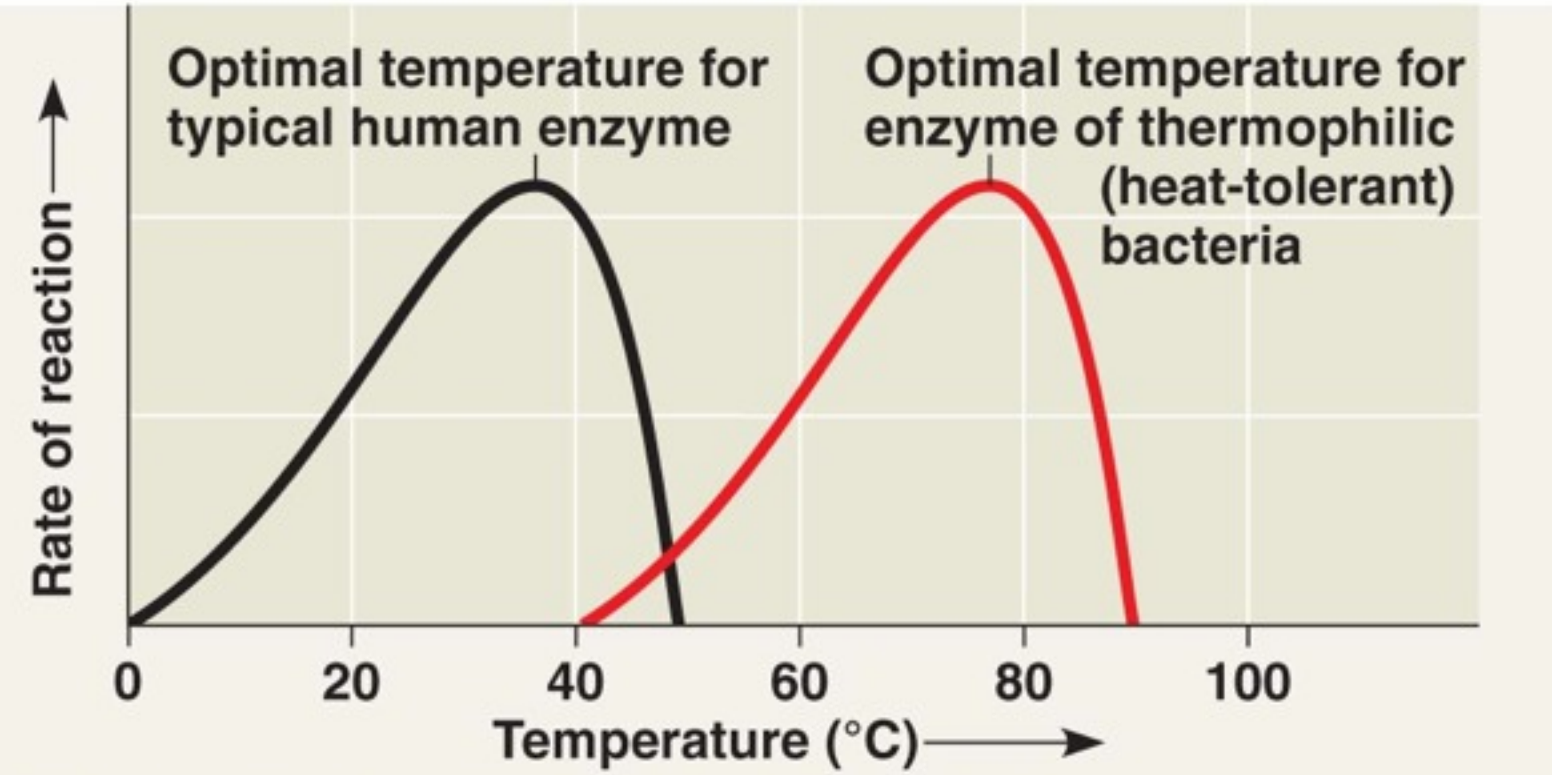
- The activity of an enzyme is affected by general environmental factors such as temperature, pH, chemicals, etc.
- Enzymes work better under some conditions than under other conditions.

1. Effects of Temperature and pH

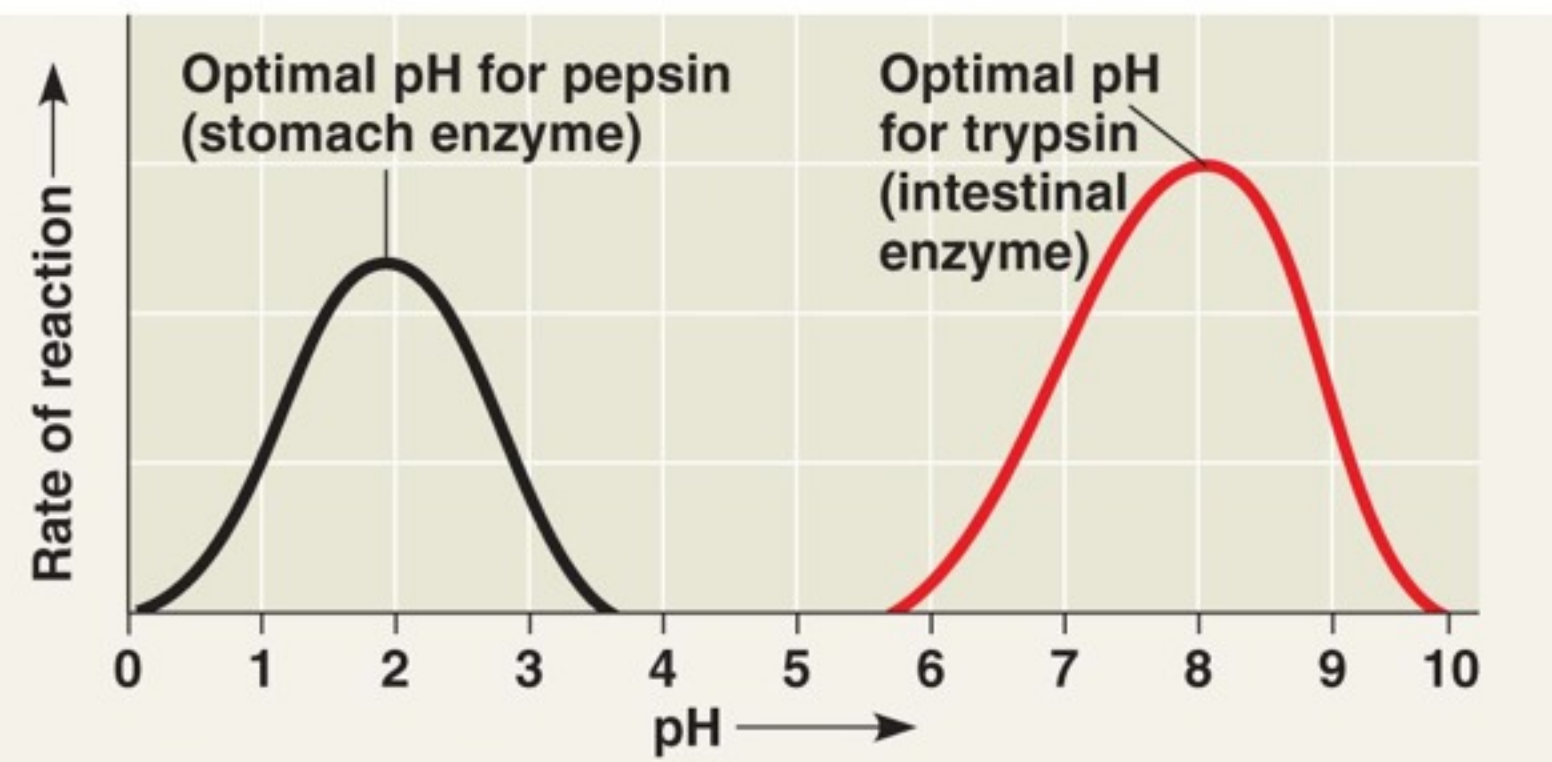
- The rate of enzyme activity is directly correlated with temperature, up to a point.
    - *Each enzyme has an optimum temperature*
    - *Most enzymes work best around the normal body temperature*

Effects of Temperature and pH

- The rate of enzyme activity is dependent upon pH, like temperature enzymes have optimum pH's.
  - *Acidic environments can denature proteins!*



(a) Optimal temperature for two enzymes



(b) Optimal pH for two enzymes

2. Cofactors

- Many enzymes require nonprotein helpers for catalytic activity.

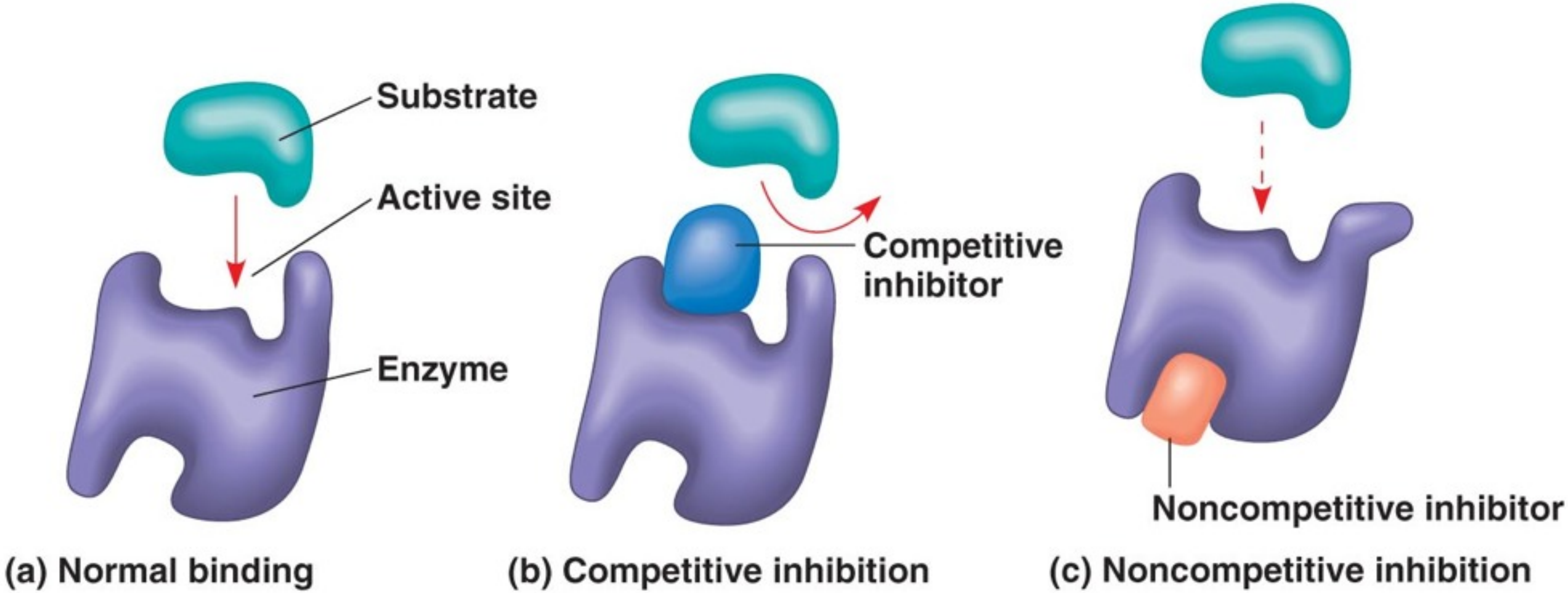
- **Cofactors:**
  - Inorganic
  - Minerals (metal ions)
  - Can bind tightly as permanent residents
  - Can bind loosely and reversibly

- **Coenzymes:**
  - Organic
  - Vitamins
  - Can bind tightly as permanent residents
  - Can bind loosely and reversibly

3. Enzyme Inhibitors

- Certain chemicals selectively inhibit the action of specific enzymes...**inhibitors**
- If the inhibitor binds covalently the inhibition is irreversible.
- If the inhibitor binds with weak interactions the inhibition is reversible.
  - Some reversible inhibitors compete with the substrate for the active site, these mimics called **Competitive Inhibitors** decrease the productivity of the enzyme.
    - *The inhibition can be overcome by adding more substrate!*

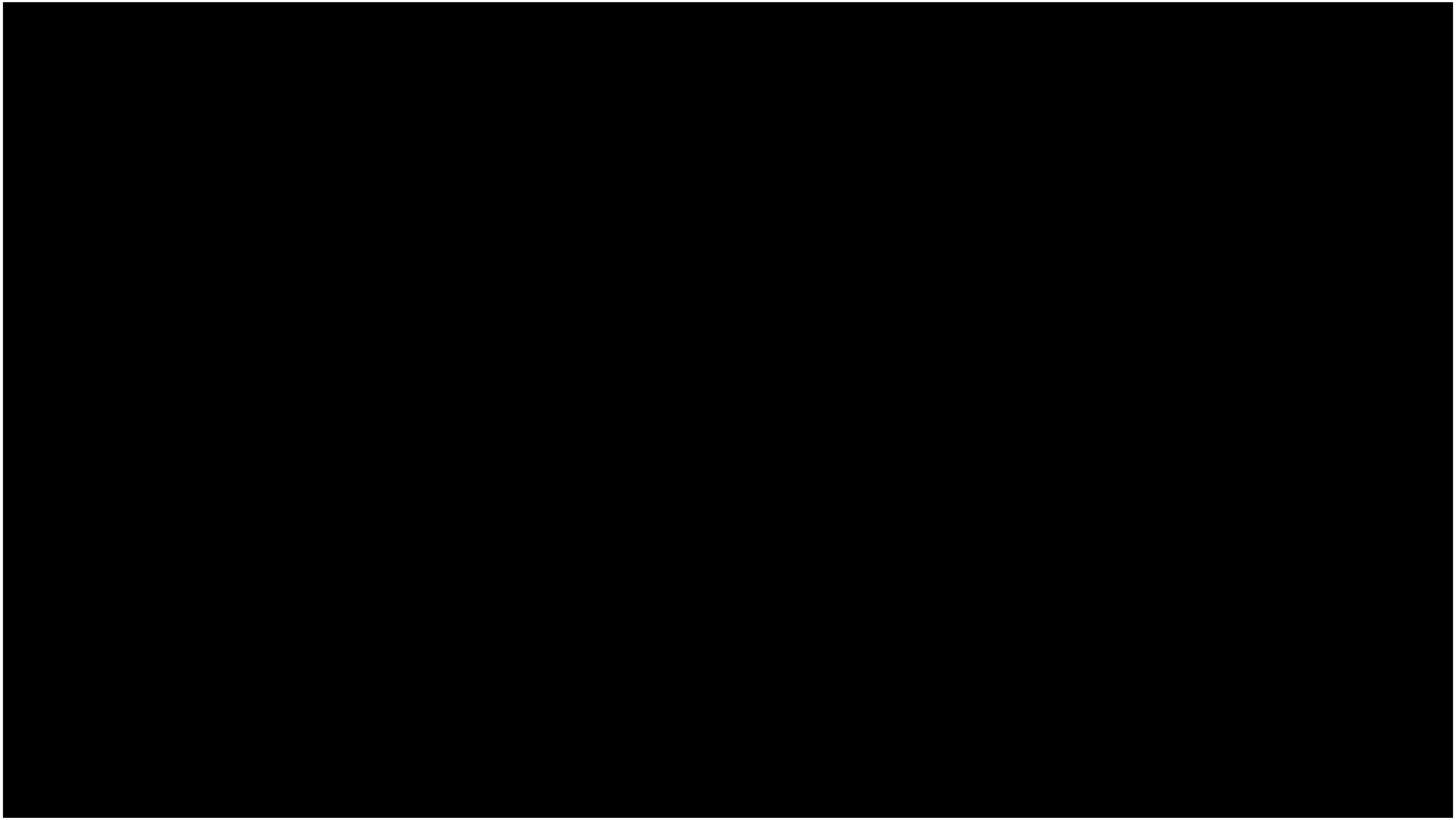
- **NonCompetitive Inhibitors** decrease the productivity of the enzyme but they do not compete with substrates for the active site, instead they bind to another part of enzyme which results in a change of in the shape of the active site.

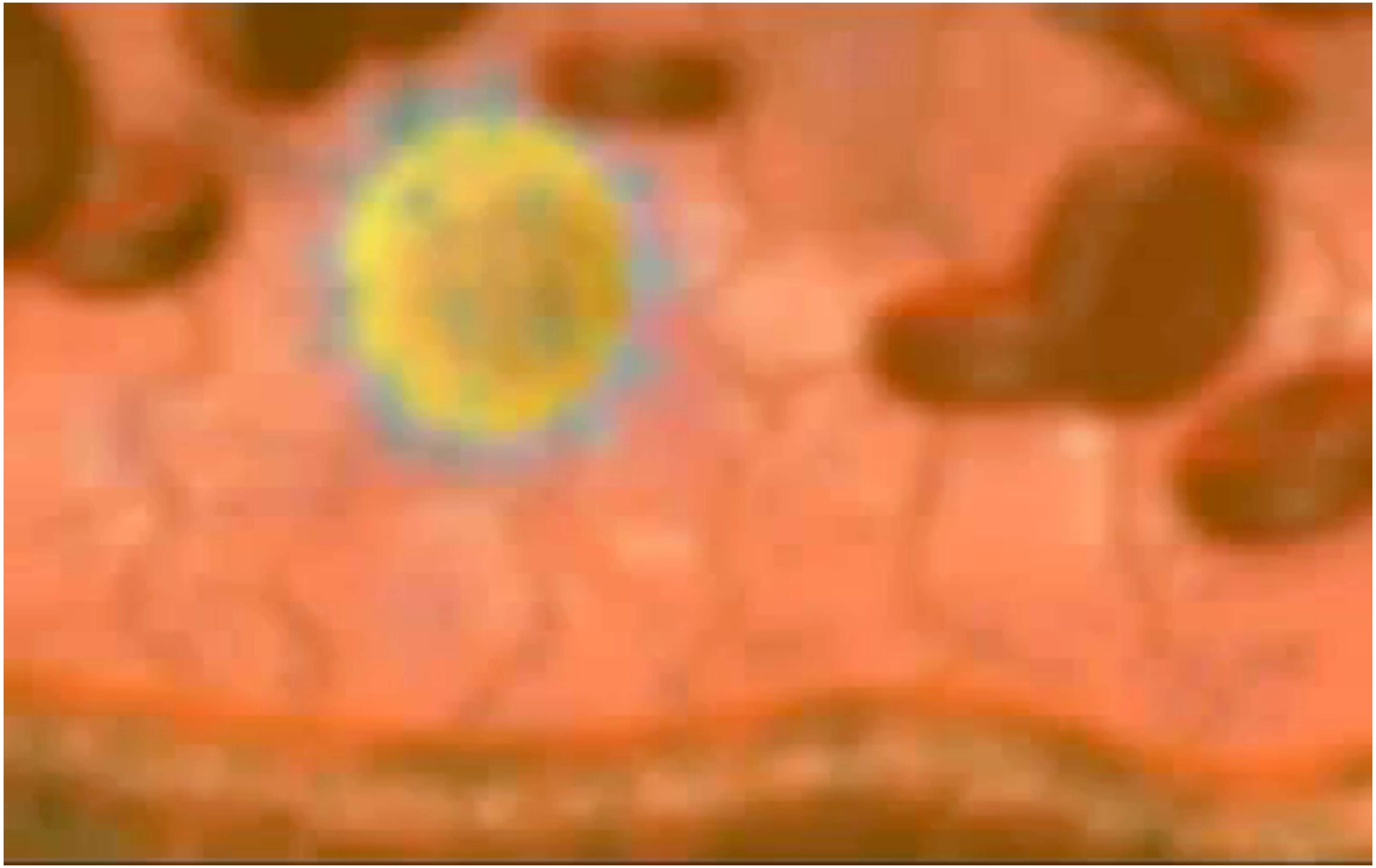


Poisons and Toxins

- **Poisons and toxins are often irreversible inhibitors**
- *Sarin a nerve gas.*
- *DDT a pesticide.*
- *Penicillin an antibiotic*
- Keep this in mind...molecules naturally present in the cell often regulate enzyme activity by acting as inhibitors. Such regulation is essential to cellular metabolism.

A Review of Enzymes





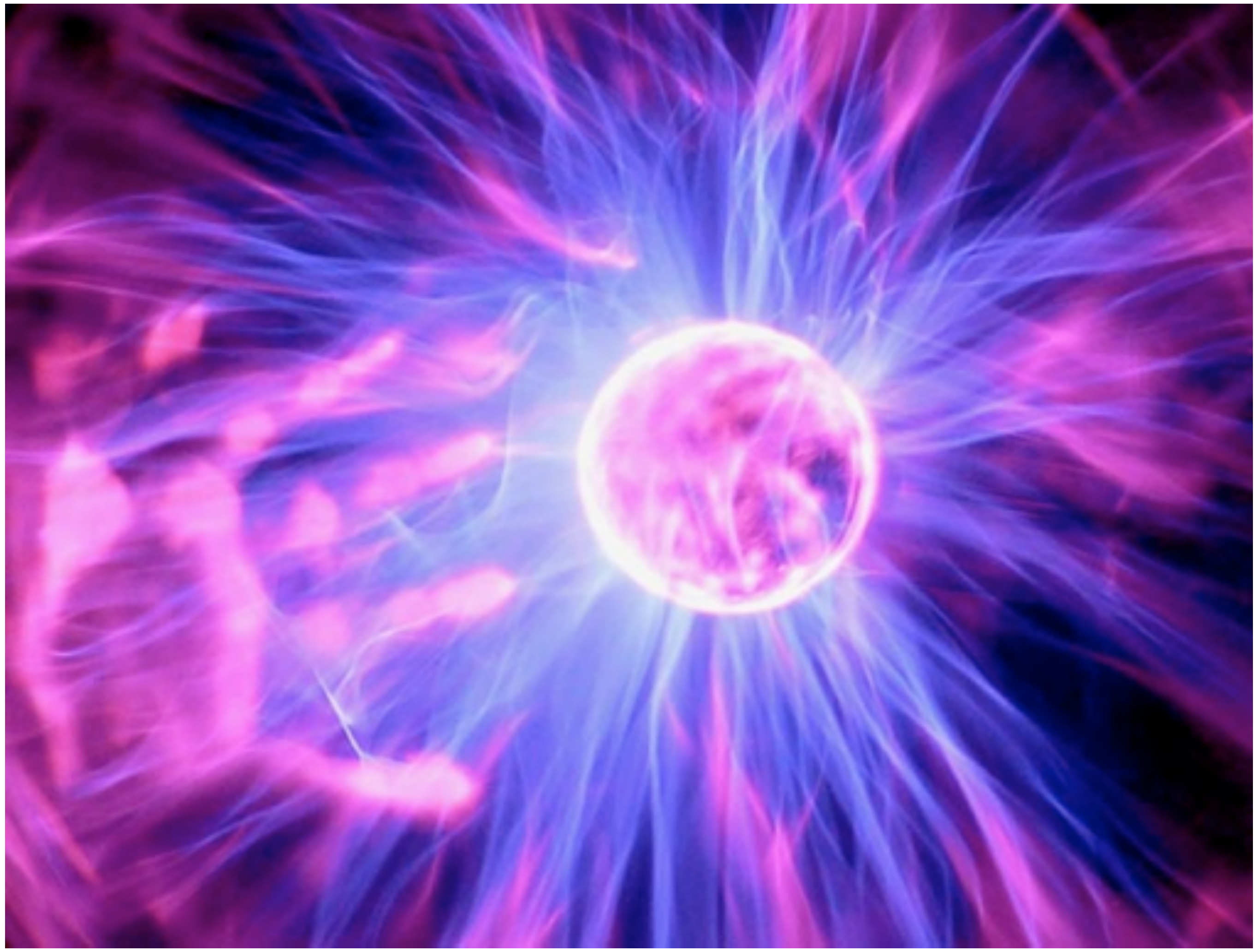
F. The Evolution of Enzymes

- Biochemists have discovered and named over 4000 different enzymes in various species, there are likely many more.
- How did so many enzymes come into existence?
- *Mutation in a gene.*
- *Changes amino acid sequence in enzyme.*
- *Some changes effect the active site*
- *Alteration leads to novel activity or binds a new substrate*
- *New function benefits organism*
- *Natural selection favors mutated enzyme*
- *Mutated enzyme persists in population*

(8) Intro to Metabolism

V.

Main Idea: Cells must regulate metabolic pathways, by controlling *when* and *where* certain chemical reactions take place.



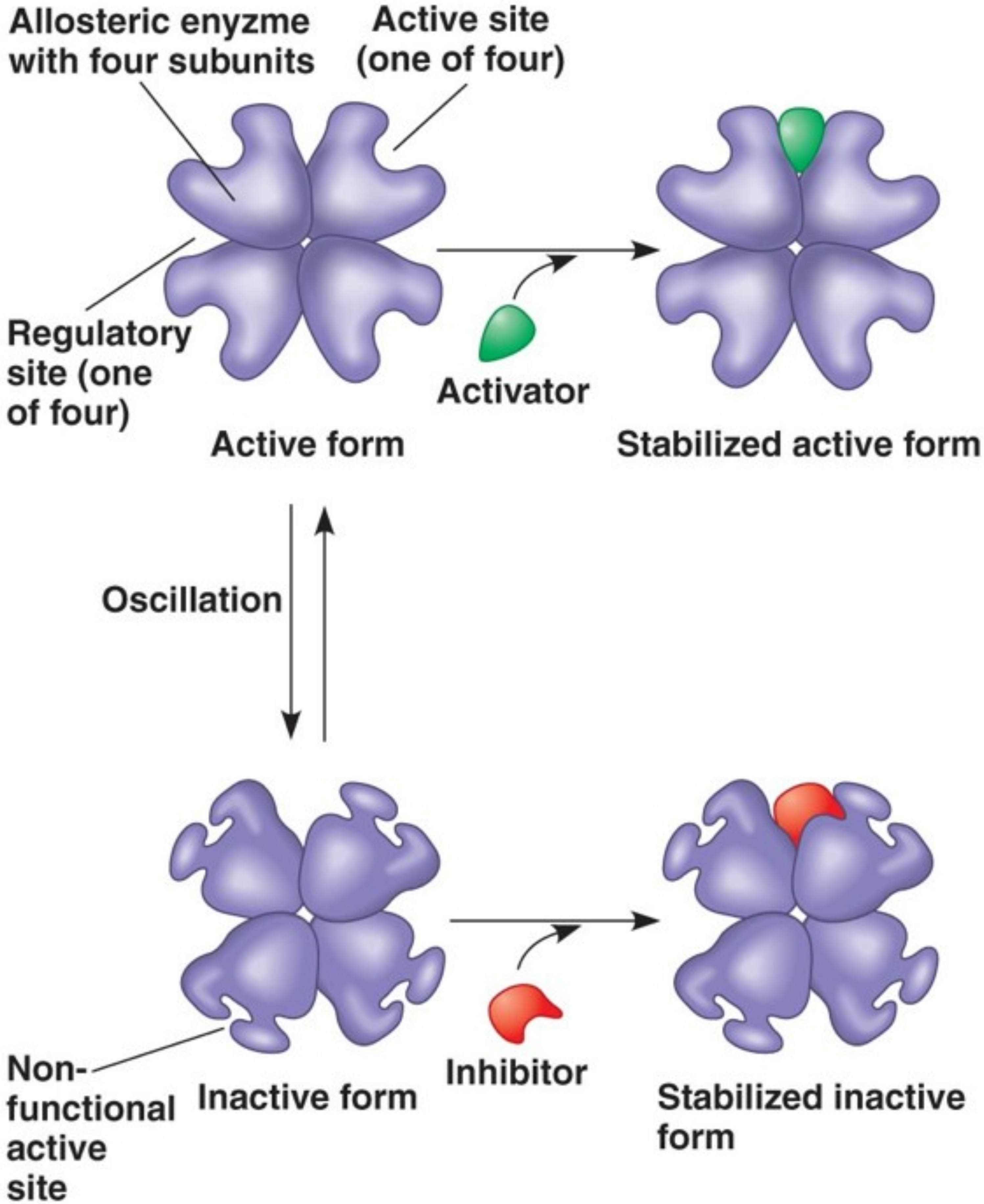
REGULATION OF ENZYME ACTIVITY HELPS CONTROL METABOLISM

A. Allosteric Regulation of Enzymes

- Allosteric Regulation involves molecules that naturally regulate enzyme activity, by behaving like reversible noncompetitive inhibitors.
- These molecules bind to the enzyme, alter its active site and therefore its activity.

1. Allosteric Activation & Inhibition

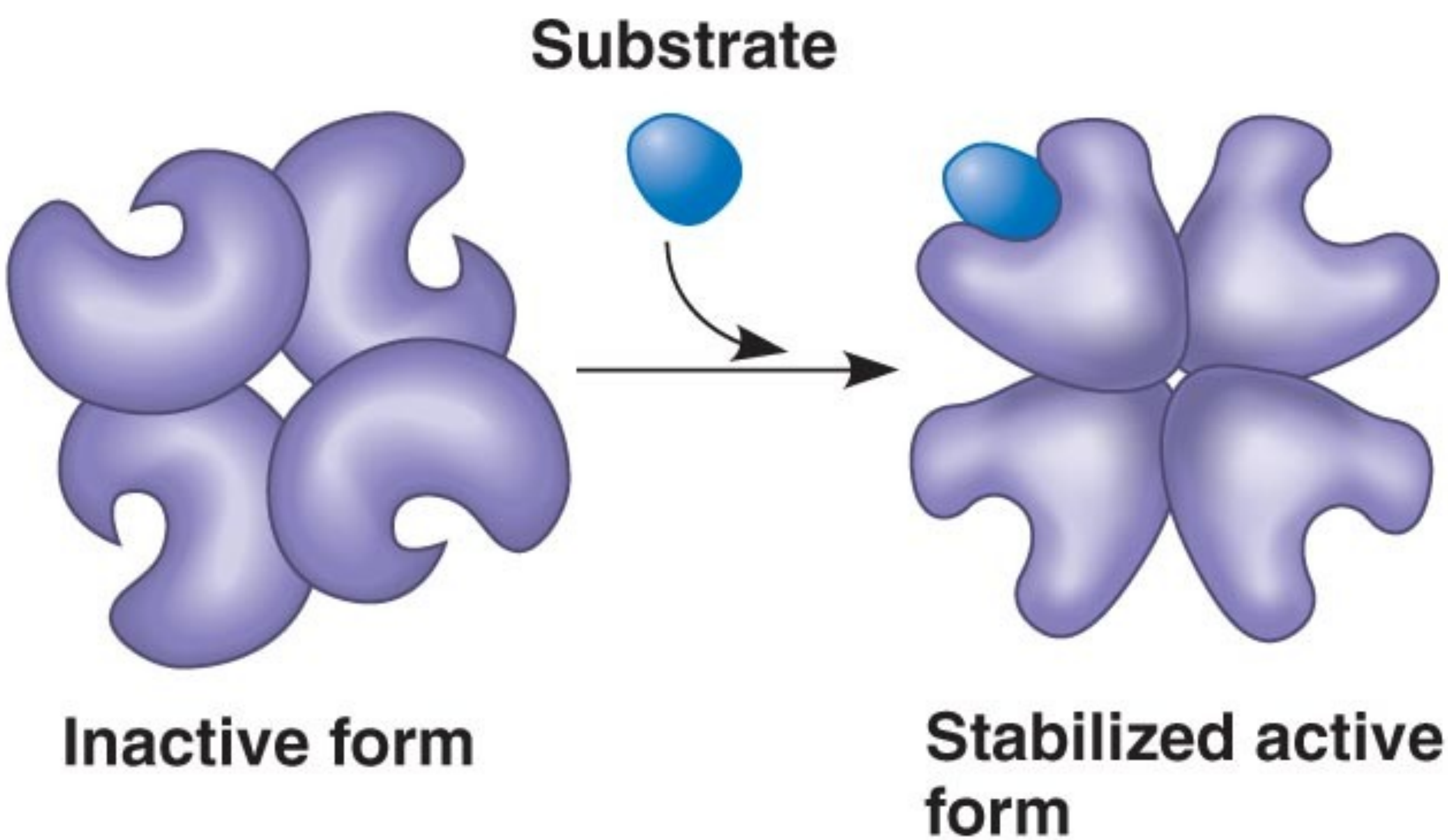
- Most enzymes allosterically regulated have multiple subunits.
- The simplest kind of regulation involves activation or inhibition by binding a molecule to a *regulatory site*.
    - *Activators* stabilize shape and keeps the enzyme functioning
    - *Inhibitors* stabilize the inactive form and prevents the enzyme from functioning
- Fluctuating concentrations of these regulators can result in a sophisticated pattern of response in the activity of enzymes.



(a) Allosteric activators and inhibitors

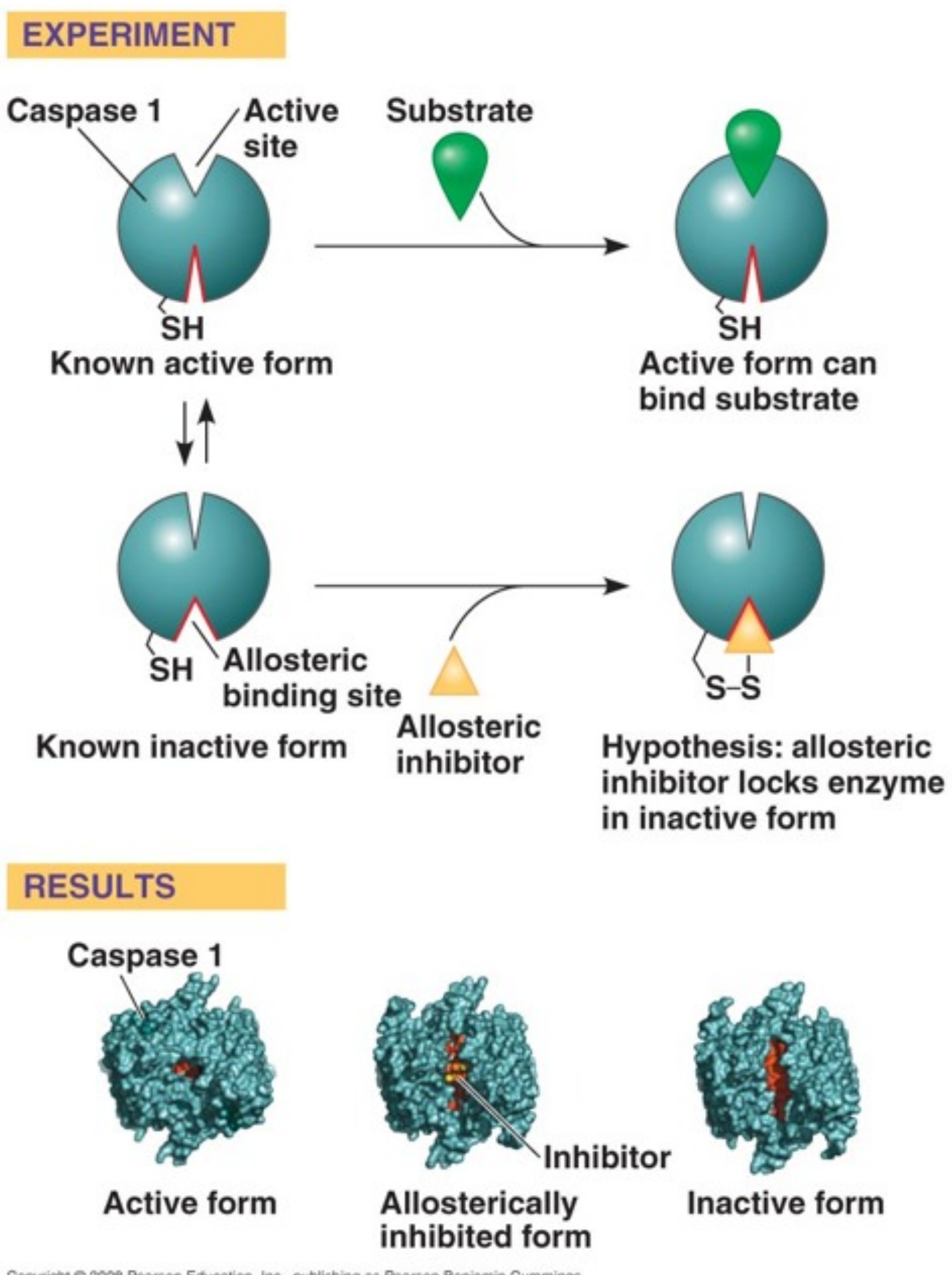
Allosteric Activation & Inhibition

- **Cooperativity**, is another kind of allosteric activation where a substrate binds to one active site in a multisubunit enzyme triggering a shape change in other active sites that are more receptive to binding thereby increasing the catalytic activity.



(b) Cooperativity: another type of allosteric activation

2. Identification of Allosteric Regulators



Researchers want a find a way to silent Caspase 1 activty

Screened over 8000 compounds for possible binding to Caspase 1

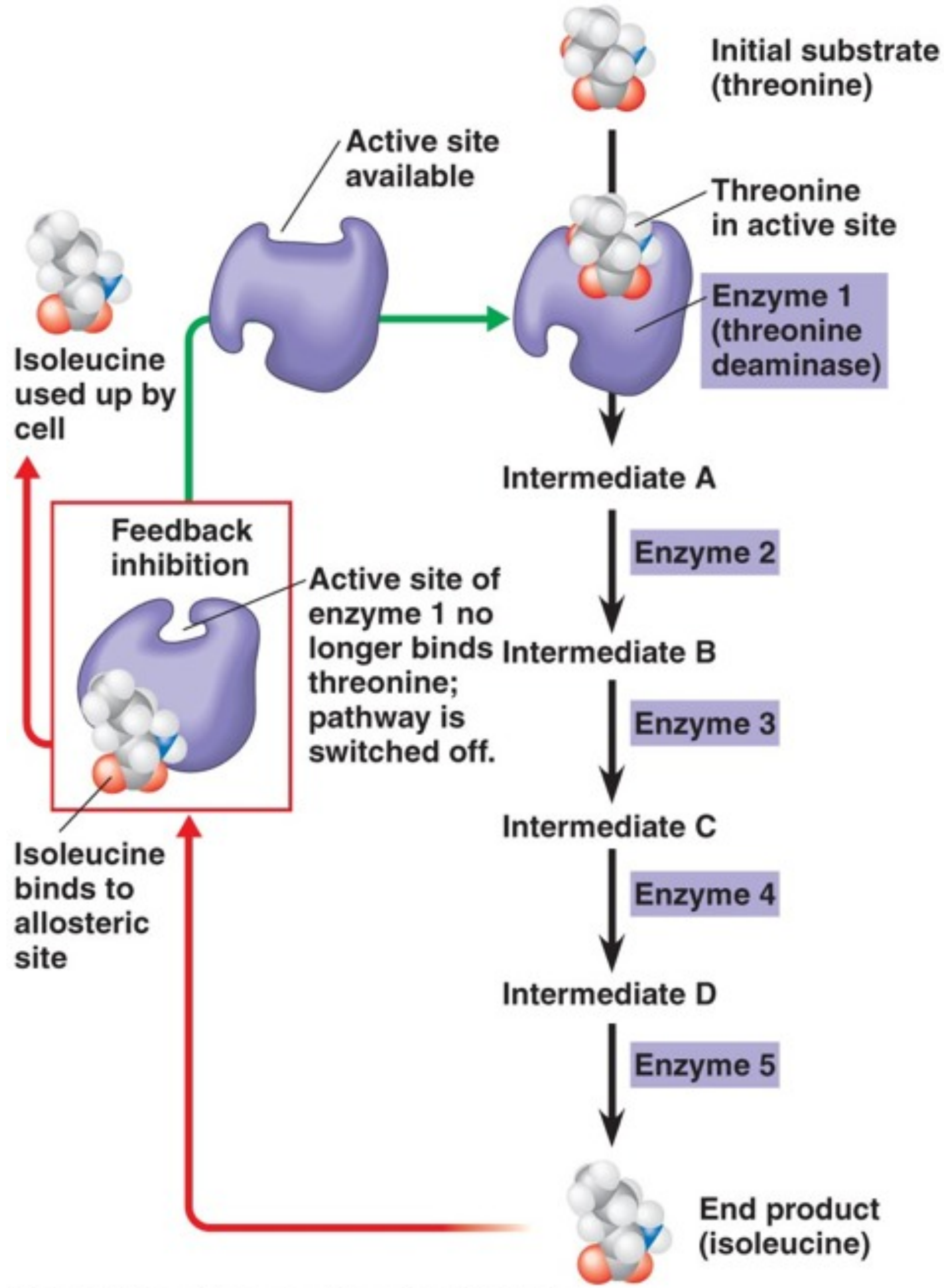
X-ray diffraction was used to analyze structure

14 compounds were identified to inhibit Caspase 1

These inhibitors can be used to control enzyme activity

3. Feedback Inhibition

- **Feedback Inhibition**, a metabolic pathway is switched off by the inhibitory binding of its end product to an enzyme that acts early in the pathway



Feedback Inhibition of Biochemical Pathways

Play | Pause | Audio | Text

Many of the enzyme-catalyzed reactions that occur in a cell, such as those involved in the biosynthesis of an amino acid, are carried out in a specific sequence called a biochemical pathway.

B. Specific Localization of Enzymes Within the Cell

- The cell is not a bag of chemicals with thousands of enzymes and substrates in a random mix.
- The cell is compartmentalized, and cellular structures help bring order to metabolic pathways.