# Glycolysis

Glycolysis is the first step in the breakdown of glucose to extract energy for cellular metabolism. Glycolysis consists of an energy-requiring phase followed by an energy-releasing phase.

## Introduction

Suppose that we gave one molecule of glucose to you and one molecule of glucose to *Lactobacillus acidophilus*—the friendly bacterium that turns milk into yogurt.

Overall, the metabolism of glucose in one of your cells would be pretty different from its metabolism in *Lactobacillus*—check out the fermentation article for more details. Yet, the first steps would be the same in both cases: both you and the bacterium would need to split the glucose molecule in two by putting it through glycolysis[1].

## What is glycolysis?

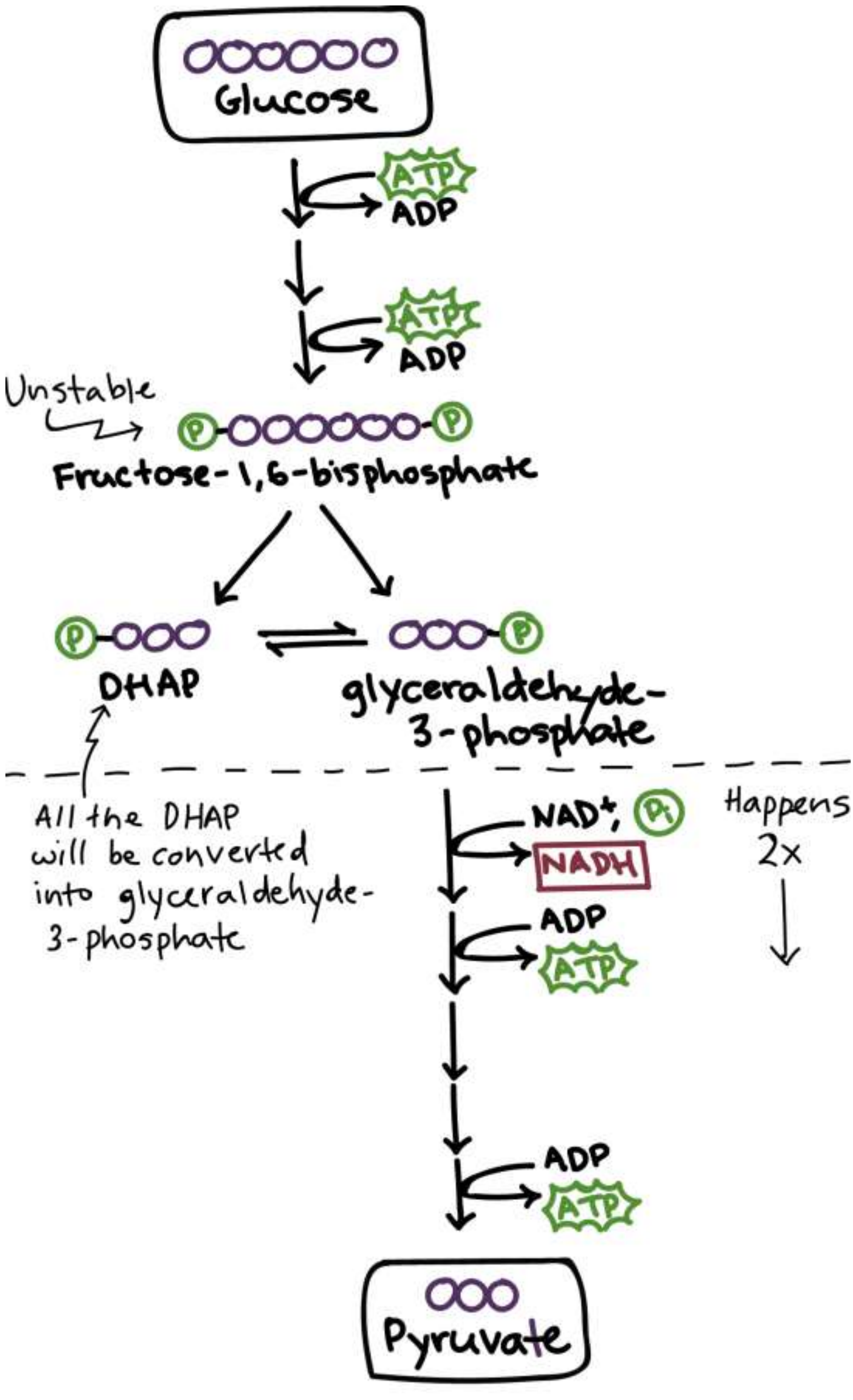
**Glycolysis** is a series of reactions that and extract energy from glucose by splitting it into two three-carbon molecules called pyruvates. Glycolysis is an ancient metabolic pathway, meaning that it evolved long ago, and it is found in the great majority of organisms alive today[2,3].

In organisms that perform cellular respiration, glycolysis is the first stage of this process. However, glycolysis doesn't require oxygen, and many anaerobic organisms—organisms that do not use oxygen—also have this pathway.

## Highlights of glycolysis

Glycolysis has ten steps, and depending on your interests—and the classes you're taking—you may want to know the details of all of them. However, you may also be looking for a greatest hits version of glycolysis, something that highlights the key steps and principles without tracing the fate of every single atom. Let's start with a simplified version of the pathway that does just that. Glycolysis takes place in the cytosol of a cell, and it can be broken down into two main phases: the energy-requiring phase, above the dotted line in the image below, and the energy-releasing phase, below the dotted line.

- **Energy-requiring phase.** In this phase, the starting molecule of glucose gets rearranged, and two phosphate groups are attached to it. The phosphate groups make the modified sugar—now called fructose-1,6-bisphosphate—unstable, allowing it to split in half and form two phosphate-bearing three-carbon sugars. Because the phosphates used in these steps come from ATP, two ATP molecules get used up.




Simplified diagram of glycolysis.

Energy investment phase. Glucose is first converted to fructose-1,6-bisphosphate in a series of steps that use up two ATP. Then, unstable fructose-1,6-bisphosphate splits in two, forming two three-carbon molecules called DHAP and glyceraldehyde-3-phosphae. Glyceraldehyde-3-phosphate can continue with the next steps of the pathway, and DHAP can be readily converted into glyceraldehyde-3-phosphate.

Energy payoff phase. In a series of steps that produce one NADH and two ATP, a glyceraldehyde-3-phosphate molecule is converted into a pyruvate molecule. This happens twice for each molecule of glucose since glucose is split into two three-carbon molecules, both of which will go through the final steps of the pathway.
The three-carbon sugars formed when the unstable sugar breaks down are different from each other. Only one—glyceraldehyde-3-phosphate—can enter the following step. However, the unfavourable sugar, DHAP can be easily converted into the favourable one, so both finish the pathway in the end

- **Energy-releasing phase.** In this phase, each three-carbon sugar is converted into another three-carbon molecule, pyruvate, through a series of reactions. In these reactions, two ATP molecules and one NADH molecule are made. Because this phase takes place twice, once for each of the two three-carbon sugars, it makes four ATP and two NADH overall.

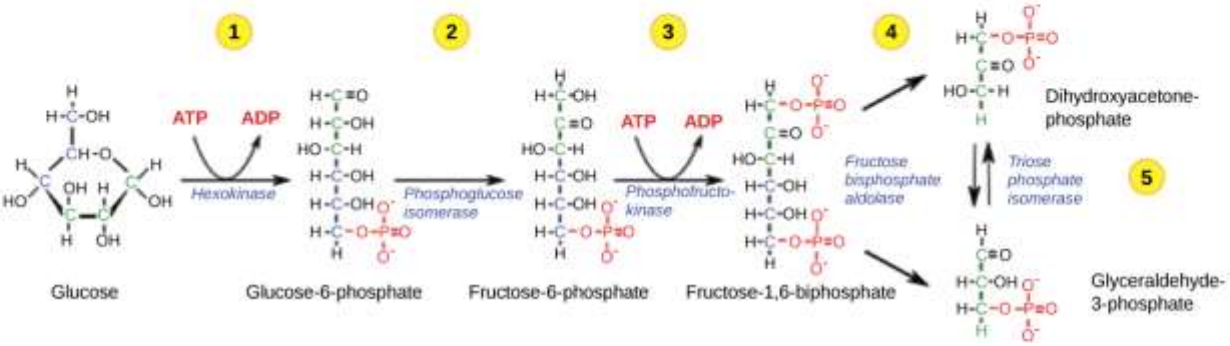
Each reaction in glycolysis is catalysed by its own enzyme. The most important enzyme for regulation of glycolysis is **phosphofructokinase**, which catalyses formation of the unstable, two-phosphate sugar molecule, fructose-1,6-bisphosphate[4]. Phosphofructokinase speeds up or slows down glycolysis in response to the energy needs of the cell.

Overall, glycolysis converts one six-carbon molecule of glucose into two three-carbon molecules of pyruvate. The net products of this process are two molecules of ATP (4 ATP produced 2 ATP used up) and two molecules of NADH.

## Detailed steps: Energy-requiring phase

We've already seen what happens on a broad level during the energy-requiring phase of glycolysis. Two ATP\text{ATP}ATPA, T, Ps are spent to form an unstable sugar with two phosphate groups, which then splits to form two three-carbon molecules that are isomers of each other.

Next, we'll look at the individual steps in greater detail. Each step is catalysed by its own specific enzyme, whose name is indicated above the reaction arrow in the diagram below.




Detailed steps of the first half of glycolysis.

1. Glucose is converted to glucose-6-phosphate by hexokinase. This step converts one ATP to ADP.

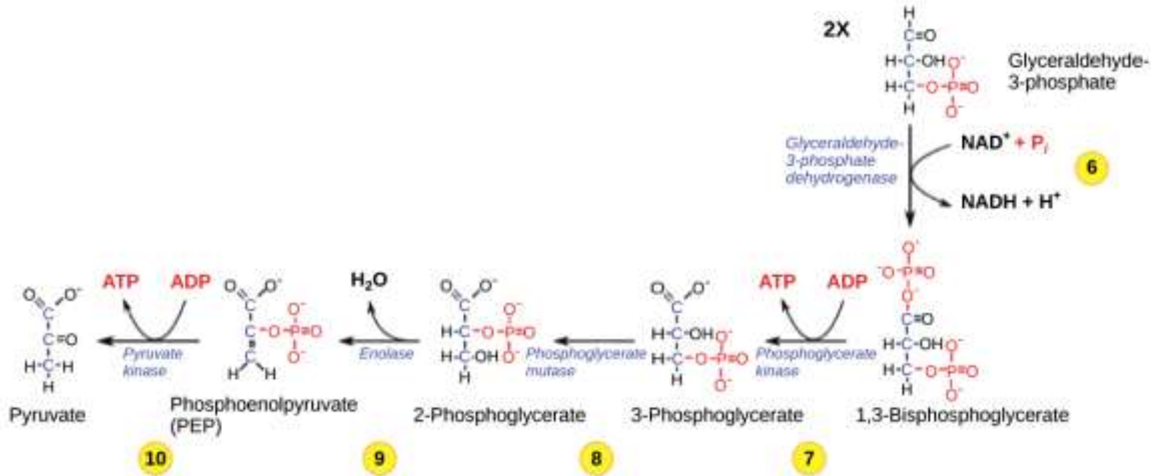
2. Glucose-6-phosphate is converted into fructose-6-phosphate by phosphoglucose isomerise.
3. Fructose-6-phosphate is converted into fructose-1,6-bisphosphate by phosphofructokinase. This step converts one ATP to ADP.
4. Fructose-1,6-bisphosphate is split into two three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate (DHAP). The enzyme that catalyses this step is fructose bisphosphate aldolase.
5. The DHAP is converted into glyceralde-3-phosphate by an enzyme called triose phosphate isomerise. This reaction can go in either direction, but because glyceraldehyde-3-phosphate is continually being used up in the rest of the pathway, the equilibrium favours conversion of DHAP to glyceraldehyde-3-phosphate.

**Step 1.** A phosphate group is transferred from ATP to glucose, making glucose-6-phosphate. Glucose-6-phosphate is more reactive than glucose, and the addition of the phosphate also traps glucose inside the cell since glucose with a phosphate can't readily cross the membrane.
**Step 2.** Glucose-6-phosphate is converted into its isomer, fructose-6-phosphate.
**Step 3.** A phosphate group is transferred from ATP to fructose-6-phosphate, producing fructose-1,6-bisphosphate. This step is catalysed by the enzyme phosphofructokinase, which can be regulated to speed up or slow down the glycolysis pathway.
**Step 4.** Fructose-1,6-bisphosphate splits to form two three-carbon sugars: dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate. They are isomers of each other, but only one—glyceraldehyde-3-phosphate—can directly continue through the next steps of glycolysis.
**Step 5.** DHAP is converted into glyceraldehyde-3-phosphate. The two molecules exist in equilibrium, but the equilibrium is "pulled" strongly downward, in the scheme of the diagram above, as glyceraldehyde-3-phosphate is used up. Thus, all of the DHAP is eventually converted.

## Detailed steps: Energy-releasing phase

In the second half of glycolysis, the three-carbon sugars formed in the first half of the process go through a series of additional transformations, ultimately turning into pyruvate. In the process, four ATP molecules are produced, along with two molecules of NADH.

Here, we'll look in more detail at the reactions that lead to these products. The reactions shown below happen twice for each glucose molecule since a glucose splits into two three-carbon molecules, both of which will eventually proceed through the pathway.




Detailed steps of the second half of glycolysis. All of these reactions will happen twice for one molecule of glucose.

6. Glyceraldehyde-3-phosphate is converted into 1,3-bisphosphoglycerate. This is a redox reaction in which NAD+ is converted to NADH (with the release of an H+ ion). An inorganic phosphate is also a reactant for this reaction, which is catalysed by glyceraldehyde-3-phosphate dehydrogenase.
7. 1,3-bisphosphoglycerate is converted to 3-phosphoglycerate by phosphoglycerate kinase. This step converts an ADP to an ATP.
8. 3-phosphoglycerate is converted to 2-phosphoglycerate by phosphoglycerate mutase.
9. 2-phosphoglycerate is converted to phosphoenolpyruvate (PEP) by enolase. This reaction releases a water molecule.
10. Phosphoenolpyruvate (PEP) is converted to pyruvate by pyruvate kinase. An ADP is converted to an ATP in this reaction.

**Step 6.** Glyceraldehyde-3-phosphate, one of the three-carbon sugars formed in the initial phase, loses two electrons and two protons, reducing NAD+ to NADH and producing an H+. This reaction releases energy, which is used to attach another phosphate to the sugar, forming 1,3-bisphosphoglycerate.
**Step 7.** 1,3-bisphosphoglycerate donates one of its phosphate groups to ADP making a molecule of ATP and turning into 3-phosphoglycerate in the process.
**Step 8.** 3-phosphoglycerate is converted into its isomer, 2-phosphoglycerate.
**Step 9.** 2-phosphoglycerate loses a molecule of water, becoming phosphoenolpyruvate (PEP is an unstable molecule, poised to lose its phosphate group in the final step of glycolysis.
**Step 10.** PEP readily donates its phosphate group to ADP, making a second molecule of ATP. As it loses its phosphate, PEP is converted pyruvate, the end product of glycolysis.

## What happens to pyruvate and NADH?

At the end of glycolysis, we're left with two ATP, two NADH and two pyruvate molecules. If oxygen is available, the pyruvate can be broken down (oxidized) all the way to carbon dioxide in cellular respiration, making many molecules of ATP. You can learn how this works in the videos and articles on pyruvate oxidation, the citric acid cycle, and oxidative phosphorylation.
What happens to the NADH? It can't just sit around in the cell, piling up. That's because cells have only a certain number of $NAD^+$ molecules, which cycle back and forth between oxidized ($NAD^+$) and reduced (NADH) states:

$$NAD + 2e^{-2} + 2H + 2 \rightleftharpoons NADH+$$

Glycolysis needs $NAD^+$ to accept electrons as part of a specific reaction. If there's no $NAD^+$ around (because it's all stuck in its NADH form), this reaction can't happen and glycolysis will come to a halt. So, all cells need a way to turn NADH back into $NAD^+$ to keep glycolysis going.

There are two basic ways of accomplishing this. When oxygen is present, NADH can pass its electrons into the electron transport chain, regenerating $NAD^+$ for use in glycolysis.

When oxygen is absent, cells may use other, simpler pathways to regenerate NAD+. In these pathways, NADH donates its electrons to an acceptor molecule in a reaction that doesn't make ATP but does regenerate $NAD^+$ so glycolysis can continue. This process is called f**ermentation**..

Fermentation is a primary metabolic strategy for lots of bacteria—including our friend from the introduction, *Lactobacillus acidophilus*[1]. Even some cells in your body, such as red blood cells, rely on fermentation to make their ATP.