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Independent Study Mentorship

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**Research Assessment #4**

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"Metabolic Engineering." Biotechnology: Changing Life Through Science, UXL, 2012. Science in Context, Accessed 29 Sept. 2017.

Michaels, Pamela V. "Metabolic Engineering." Biotechnology: In Context, edited by Brenda Wilmoth Lerner and K. Lee Lerner, Gale, 2012. In Context Series. Science in Context, Accessed 29 Sept. 2017.

**Assessment:**

Usually, when I try to think of topics to explore for my research assessment, I tend to pick topics I have previous knowledge about. This time, I wanted to push myself and research a subject I do not know about. Eventually, I came upon Metabolic Engineering. At first, I thought it was a career topic completely separate from chemical engineering but I noticed how they are interconnected. Since I have no prior knowledge regarding this topic, the articles I selected are specifically over the general overview metabolic engineering.

The first article, "Metabolic Engineering", initially interested me because of the picture it contained. The scientist in the picture appears to be observing this bright orange substance which was intriguing he had no safety goggles which was the first thing you should have while conducting an experiment. According to this article, microbiology, cell biology, biochemistry, mathematical sciences, and chemical engineering are heavily used. When I first read this, my initial thought was to go back and research something else because it would be difficult for me to process the jargon used in these are articles if I do not know much about these subjects. However, I believe that this would be the best way to get a glimpse of everything at once. Using my background from my biology and chemistry classes, I was able to grasp the scientific foundation and why it works the way it does. The main goal these scientists have is to improve human life. This goal related to my personality which made me realize it could potentially be the topic I finalize on for my ISM journey. Since most of this field revolves around biochemistry, it is very critical to completely understand the basics and always be ready to learn more and adapt to the topic at hand because on new current events.

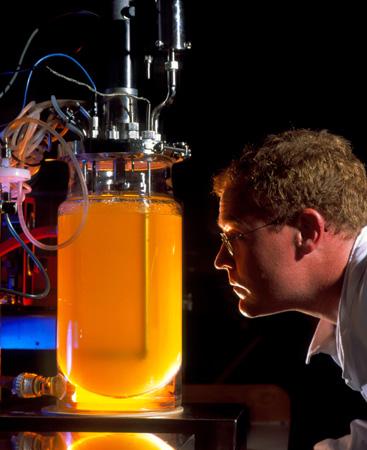
After interpreting the development of metabolic engineering, I felt that there were some discontinuities with my understanding. It pushed me to learn more about the history of this topic and its impacts. In another article also called “Metabolic Engineering”, I noticed how in depth the author explains the scientists involved in creating this field. I came to the realization that even though we have advanced technology, there are so much more advances left to make in this field. It's a fairly new professional career and began growing during the 1970s. Moving forward, I came upon DOE's Joint BioEnergy Institute (JBEI), who is introducing environmentally friendly biosynthetic diesel fuel. This invention could potentially change the world globally. If this new clean fuel source soon becomes usable by everyday consumers, the pollution released by our growing population will start to decrease and help sustain the world for future generations. There are other biofuels that will improve the environment but because they were not metabolically engineered, it would require redesigned automobiles to be compatible with the fuel. If there are more people who are interested and pursue this career path, it would be extremely beneficial to the greater good. I realized many people who have a loving nature tend to become doctors because they want to help people. If this topic was a bit more widely known, it would give people more options to choose a career. If people start to have a bigger interest in metabolic engineering, it would help out the world faster and be more conservative when it comes to our natural resources.

The research I have conducted gave me an in-depth insight of the metabolic engineering. I discovered the personal connections I have made with this topic and I noticed how I interested I am. I have gained valuable information and am excited for this career in the future for what it has to bring. While this research may have been surface level, the passion and determination of these professionals are apparent. In this research, I got to build upon that learn the general outlook as well as notice how a topic that has inspired me to be more environmentally friendly than I already am because of all the hard work they put into their new solutions to improve the world and lifestyle of humans. The challenge is highly visible with this research and I have been inspired to keep pushing forward on my journey and maybe help make a difference in the world like metabolical engineers.

**Article 1:**

**Metabolic Engineering**

*Biotechnology: Changing Life Through Science*, 2012



## **Description**

Numerous chemical reactions take place in the human body on a daily basis. Most of these reactions occur repeatedly in the same body systems. For instance, the digestive system controls the breakdown of food, whereas the circulatory system ensures proper blood circulation in the body. These biological systems are a series of chemical reactions. The combined effect of all the chemical reactions in the human body is referred to as [metabolism](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll). Proper metabolism is important to general health and growth.

Metabolic engineering consists of techniques that allow us to better understand metabolic processes that can be altered to benefit mankind. Metabolic engineering has the potential to contribute immensely towards the growth of health care, medical sciences, and various industries.

Metabolic engineering can be used to improve food production for such products as cheese, wine, and beer. It is helpful in finding cures for diseases, for the mass production of antibiotics, to improve agricultural practices, and to enable effective means of energy production. Metabolic engineering can also assist in the development of ecologically-friendly ways for cleaning up the environment.

## **Scientific Foundations**

All living bodies, including [plants](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll) and animals, are made of cells. Each cell in a body is programmed to carry out a number of chemical reactions. Metabolism comprises all of these reactions. There are two different types of metabolic processes. Anabolic reactions take place to form a compound (chemical molecule), while catabolic reactions are responsible for the breakdown of compounds. [Enzymes](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll) are substances that catalyze (or speed up) metabolic reactions.

Metabolic reactions typically follow set sequences called metabolic pathways. Scientists study these pathways to understand the functioning of cells, tissues, organs, and eventually the complete body system. Enzymes catalyze each step in a cellular pathway, so determining the specific enzymes participating in a reaction is important. Metabolic engineering involves discovering and analyzing such metabolic pathways.

## **Development**

Since the time English naturalist Charles Darwin (1809–1882) introduced his theory of [evolution](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll), people have known that minor changes occur from one generation to another. Although they share several similarities, children are different from their parents. Some of their differences are better suited for survival. Some do not have any effect, whereas others may be harmful. Nature always prefers those changes (also known as mutations) that increase survival rates of an organism. During the natural course of evolution, mutations accumulate over millions of years to such an extent that the organism showing modifications stops resembling the parent species and becomes a new species.

Metabolic engineering is a relatively new science that is developed on the underlying principles of evolution. It allows scientists to create mutations and study their effects in a much shorter span of time and in a laboratory setup. By modifying the genetic composition of cells, scientists can enhance desired mutations that either improve quality or increase production of various bioproducts (two examples are cheese and medicines) for industrial use.

Cells and their components are so small that it is difficult to study them in detail. Studying the genetic information in cells did not become possible until the advent of some sophisticated techniques such as the polymerase chain reaction (PCR), in which the smallest quantities of genetic material can be amplified to an extent where they can be easily examined.

Invented in 1985, PCR enables scientists to clone (copy) and investigate the [genes](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll) responsible for the creation of various compounds the body uses. PCR also aids analysis of the complete genetic material of several organisms, allowing scientists to look at genetic differences across a population.

## **Current Issues**

Metabolic engineering helped create several beneficial bioproducts—products derived through living systems. Microorganisms and single-celled creatures are much simpler than their multi-cellular counterparts and have less genetic material and fewer biochemical reactions to be investigated. Consequently, researchers are more successful in engineering metabolic pathways in microorganisms.

The primary objective of metabolic engineering is to improve human life. It is being used to create varieties of plants that are resistant to pest infestation, yield a higher quantity of produce, or generate more nutritious goods. Metabolic engineering has also been used to study heart and liver diseases.

Apart from the complexity of organisms, other issues have slowed the progress in metabolic engineering. Sometimes, scientists who discover certain beneficial microbes also get legal protections that restrict others from performing investigative studies on the newly discovered microorganism. In other instances, it is not possible to study the metabolic pathways of some microorganisms because they cannot be cultured in the laboratory for various reasons.

## **Metabolic Engineering as a Comprehensive Subject**

Metabolic engineering is a multidisciplinary area requiring knowledge and implementation of other principles including recombinant deoxyribonucleic acid ([DNA](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll)) technology (in which DNA from different organisms is combined), microbiology, cell [biology](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll), [biochemistry](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll), mathematical sciences, and chemical engineering.

## **How was Erythromycin Discovered?**

Erythromycin, a common antibiotic for treating infections caused by bacteria, was discovered from a bacterium in 1952. Its structure was identified in 1965, and the process of its creation was published in 1981. However, it was only in the 1990s that its manufacture was completely understood. With the new information gained, researchers have now found a laboratory method for mass-producing erythromycin.

## **Words to Know**

**Anabolic**

To build the body. Often used to describe a group of [hormones](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll) sometimes abused by [athletes](https://docs.google.com/document/d/1ekiyqd2IWrqTYd2xaTleW-pc0C41cbH2hdNgNbxdpKo/edit#bookmark=id.30j0zll) in training to temporarily increase the size of their muscles.

#### **Catabolic**

To break down. The breakdown of complex molecules into simpler molecules.

#### **Catalyst**

Any agent that accelerates a chemical reaction without entering the reaction or being changed by it.

#### **Metabolism**

Chemical changes in body tissue that convert nutrients into energy for use by all vital bodily functions.

**Article 2:**

## **Metabolic Engineering**

*Biotechnology: In Context*, 2012

Introduction

Metabolic engineering uses [recombinant DNA](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) technology in order to alter [metabolism](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) and metabolic flux. This multidisciplinary, evolving scientific field utilizes created microorganisms as well as transformed bacteria and [enzymes](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) in order to alter, enhance, or otherwise shift metabolic processes.

Metabolic engineering seeks to change the metabolism inside cells in order to achieve a specific goal, whether that is the alteration of the course of a disease process, production of a commercial chemical product, creation of a diagnostic test, pollution degradation and land-use reclamation, or production of clean-burning renewable vehicular fuel. Much of the current research in the field is aimed at either using the techniques of metabolic engineering to create viable solutions for specific issues or development and implementation of systems and tools for use in engineering specific types of microorganisms.

## **Words to Know**

**Biofuels**

A form of fuel created from biomass. Biofuels are produced through the use of renewable resources. The three most common types of biofuel are bioethanol as a replacement for traditional fossil fuels, biodiesel as a “green” replacement for diesel fuel, and biogas used instead of natural gas.

#### **Biomass**

Organic matter that can be reused or recycled into a variety of types of renewable energy resources.

#### **Flux**

The flow of energy through a particular system or electronic medium. In metabolic engineering, flux is defined as the rate of turnover of molecules in a metabolic pathway. Enzymes regulate the rate of flux.

#### **Recombinant** [**DNA**](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) **Technology**

When a DNA segment is isolated and added to a different DNA strand, generally in another organism and the two (or more) strands join together, they are said to recombine. This process is accomplished through [genetic engineering](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) and [biotechnology](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs).

#### [**Synthetic Biology**](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs)

From the Synthetic Biology Engineering Research Center (SynBERC) it is a maturing scientific discipline that combines science and engineering in order to design and build novel biological functions and systems. Among its seminal characteristics are predictable off-the-shelf parts and devices with standard connections, robust biological chassis that readily accept said parts and devices, standards for assembling components into increasingly sophisticated and functional systems, and open-source availability and development of parts, devices, and chassis.

## **Historical Background and Scientific Foundations**

The development of recombinant DNA technology was foundational for the multidisciplinary field of metabolic engineering. In 1869 Johann Friedrich Miescher (1844–1895), in his research involving human white blood cells, discovered a weakly acidic substance he called nuclein in the nuclei of the cells. In 1944 Colin MacLeod (1909–1972), Maclyn McCarty (1911–2005), and Oswald Avery (1877–1955) verified that the genetic material from Miescher's studies was DNA. In 1953 James D. Watson (1928–) and Francis Crick (1916–2004) proved that DNA base pairs provided the codes for the transmission of genetic information and that DNA exists in the structure of a double helix. The first recombinant DNA (rDNA) molecule was produced by Paul Berg (1926–) in 1970, using what he referred to as a cut-and-splice technique. He combined DNA from a monkey virus with a lambda bacteriophage. Herbert Boyer (1936–), Annie Chang, and Stanley N. Cohen (1935–) used recombinant DNA technology to create novel organisms combining the DNA of two different species in 1972: the African clawed toad and the [*Escherichia coli*](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) bacteria. They proved that the changes to the *E. coli* DNA were both permanent and heritable. Organisms combining the DNA of two or more species are called transgenic, and the manner in which they are created is referred to as genetic engineering. Recombinant DNA technology is a driving force in the fields of biotechnology, medicine, agriculture, and metabolic engineering.

The development of biotechnology is another crucial precursor for metabolic engineering. In 1909 Archibald Garrod (1857–1936) of the United Kingdom hypothesized that [genes](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) play a significant role in the creation of [proteins](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) necessary for the chemical reactions critical to the processes of metabolism. In 1966 the [genetic code](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) was discovered; Hamilton Smith (1931–) of the United States isolated the first restriction enzyme in 1970. This was critical for both rDNA technology and the development of metabolic engineering: In order for successful creation of transgenic organisms, it is essential that the desired DNA sequences be successfully cut and rejoined.

Metabolic engineering is a growing field, having gotten its start with the advent of recombinant DNA technology in the 1970s. It is multidisciplinary, combining precise and detailed analysis of metabolic and other pathways with the techniques of biotechnology in order to enhance functioning at the cellular level through the strategic and targeted use of genetic engineering and cellular modification. An integral aspect of metabolic engineering is the measurement and analysis of metabolic fluxes in order to understand their role in the control of both metabolic function and cellular physiology. Metabolic engineering has very significant applications relevant to medicine, fuel technology, chemical production, materials science, pharmaceuticals, and biology, all at the cellular level. The field combines the sciences, techniques, and tenets of engineering and mathematical analysis and uses them to gain a better understanding of possible ways to manipulate and control metabolic flux as a means of making the best choices of target sites for genetic engineering.

## **Impacts and Issues**



Metabolic engineering utilizes biology and the principles of biotechnology in conjunction with organic and synthetic chemistry for the production of renewable fuels, medical diagnosis and treatment, and the development of non-petroleum-based chemicals. It utilizes rDNA technology to produce genetically modified microbes capable of transforming plant cellulose into clean, renewable fuels from completely renewable resources. The United States Department of Energy (DOE) is funding three institutes around the country whose primary task is to utilize the principles of biotechnology and metabolic engineering in order to develop economically feasible, highly efficient, and renewable, non-fossil fuel based, environmentally-positive, sustainably-produced biofuels. Genetically-engineered microbes are highly efficient at converting biomass into non-toxically created, renewable, inexpensive, and reliably produced chemicals.

In September 2011 the DOE's Joint BioEnergy Institute (JBEI) announced the identification of a potential new form of green, renewable, and environmentally friendly biosynthetic diesel fuel, potentially replacing Number 2 diesel fuel. Advanced biofuels are [liquid fuels](https://docs.google.com/document/d/1MihdLvRLPn2QNfSKFN430UCFDxmCiyHLrDZ8rqbUrRs/edit#bookmark=id.gjdgxs) synthesized from organic biomass and could be used as drop-ins for all types of major transportation vehicles. They are clean and renewable and have the potential to replace petroleum-based fuels, effectively reducing the emissions carbon-footprint and positively impacting the environment and global climate stability. One major difference between the metabolically-engineered biofuels and currently existing biofuels has to do with the drop-in concept. Current biofuels require retooling of transportation systems, whereas metabolically-engineered biofuels will be able to work seamlessly with existing systems in trucks, cars, trains, and jet planes.

Many commercially-used chemicals are based on petroleum, which is not economical, renewable, or environmentally friendly. Metabolic engineers are working to create the same chemicals by altering the metabolism of microbes rather than utilizing petrochemicals. The expectation is that these chemicals, when polymerized, will make structurally more sound biodegradable polymers.

Synthetic biology is another important area for metabolic engineering; it facilitates production of synthetic DNA for construction of synthetic microbial pathways. A primary application of synthetic biology involves restructuring metabolic pathways to increase efficiency, which is also a primary objective of metabolic engineering.

Many human diseases are metabolically based, such as cancer, obesity, and diabetes. If the metabolic rates and fluxes are studied and mapped, it may be possible to alter their pathways using metabolic engineering technology and reverse the outcome of the disease processes. Scientists at the University of California at Los Angeles (UCLA) are utilizing the principles of metabolic engineering to study obesity in mice. They have created a paradigm in which a non-native metabolic pathway via a glyoxylate shunt into mouse liver impacted the metabolism of fatty acid. The experimental group of mice did not become obese despite consuming the same diet that caused obesity in their matched-pair group. This work suggests considerable benefit to studying metabolism in higher order mammals through the construction of non-native pathways.

Another team used metabolic engineering with yeast and *E. coli* bacteria to microbially produce the highly effective (greater than a 90 percent cure rate) anti-malarial drug artemisinin. It is being optimized and scaled for use as a cost-effective treatment for malaria in Africa and Asia, where the need is greatest. Between 300 and 500 million people are affected by malaria every year, and one to two million people die due to lack of available, affordable treatment. Most of those impacted by malaria are infants and young children in developing countries.

In addition to the development of anti-malarial drugs, work is being done to create oxidized terpene-based pharmaceuticals. Terpenes are derived from conifers, particularly some species of pine tree, making them a highly renewable and cost-effective resource. The National Institutes of Health (NIH) is funding metabolic engineering research aimed at developing oxidized terpene-based drugs potentially effective as treatments for hepatitis and human immunodeficiency virus (HIV).