Biotechnology and the role of Chemical Engineers

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1 مجال التكنولوجيا الحيوية

1-1 يمكن النظر إلى التكنولوجيا الحيوية أو Biotechnology باعتبارها نتاجاً لتطبيق المفاهيم الهندسية engineering concepts على العمليات البيولوجية biological processes.

In its broadest definition, biotechnology is the application of biological techniques and engineered organisms to make products or modify plants and animals to carry desired traits. This definition also extends to use of various human cells and other body parts to produce desirable products. The term "bioindustry" refers to the cluster of companies that produce engineered biological products and their supporting businesses. "Biotechnology" refers to the use of the biological sciences (such as gene manipulation), often in combination with other sciences (such as materials sciences, nanotechnology, and computer software), to discover, evaluate and develop products for bioindustry.

2-1 توجد من المؤشرات ما يدفع بالكثيرين إلى الاعتقاد بأن مجال التكنولوجيا الحيوية بمثل الثورة العلمية التالية والتى قد تؤثر على مستقبل البشرية بقدر يزيد على تأثير الثورة الصناعية الأولى والثورة التى نجمت عن دخول الكمبيوتر فى كافة المجالات.

3-1 أهم ما فى التكنولوجيا الحيوية بصورتها الحديثة أنها مؤسسة على معرفة علمية فى مجال البيولوجيا الجزيئية molecular biology تمكنها من تحديد وتغيير ونقل المادة الجينية التى تتحكم فى صفات وخصائص الكائنات الحية

The new revolution is based on advances in molecular biology that permit the identification, alteration, and transfer of genetic materials that control fundamental characteristics of organisms. The ability to manipulate genetic material to achieve specified outcomes in living organisms (and in some cases their offspring) promises major changes in many aspects of modern life.

4-1 تصنف الصناعات الحيوية Bioindustry firms حسب مجال عملها إلى ما يلى:

أ. المنتجات العلاجية Therapeutics:

وهى المنتجات التى تستخدم فى علاج الأمراض أو خفض احتمالات حدوثها

Biotechnology regularly produces remarkable new medical treatments and applications for improving human health. These include the following preventive agents or treatments for:

Acute Growth Deficiency
Hepatitis B (vaccine and therapeutic)
Anemia
Diabetes mellitus
Acute myocardial infarction (heart attack)
Cystic Fibrosis
AIDS-related Kaposi's sarcoma
Hairy cell leukemia
Kidney transplant rejection

ب. المنتجات الوقائية Diagnostics:

وهى المنتجات التى تستخدم فى الاختبارات المعملية لتشخيص الأمراض أو تحديد الحالة الصحية

Biotechnology products have made it easier to detect and diagnose illnesses. Many of these new techniques are easier to use and some, such as pregnancy testing, can even be used at home. More than 400 clinical diagnostic devices using biotechnology products are in use today. The most important are screening techniques to protect the blood supply against contamination by AIDS and hepatitis B and C viruses.

ج. المنتجات الزراعية Agricultural:

وهى المنتجات المرتبطة بالزراعة والثروة الحيوانية وتشمل:

Genetic engineering العمليات المتعلقة بالتعديل والنقل الجينى

Veterinary activities العمليات المرتبطة بالتربية الحيوانية والداجنة

Food processing عمليات التصنيع الغذائى

The current work in plant biotechnology emphasizes modification of plant specific characteristics such as resistance to weeds, pests, herbicides, and pesticides, tolerance to stress, and improved nutritional content. Other work focuses on improving traits important to agriculture such as frost resistance and nitrogen fixation. According to the Biotechnology Industry organization, all of these activities are directed at improving the yield and reliability of plants in the face of pests, reducing the cost of farming by reducing the need for costly herbicides, improving crop quality, and increasing crop diversity by developing entirely new crops.

Food-processing research currently focuses on growth and fermentation by yeast and bacteria. These methods are well known technologies used in cheese and bread making. Biotechnology applications include producing fermentation starter cultures with specific taste, texture or other characteristics; creating plant tissue for the production of plant-derived ingredients (starches for example); and improving waste management (such as oil or other waste digesting bacteria). "In principle," one report asserts, "any commodity that is consumed in an undifferentiated or highly process form could be produced in this manner, and product substitution could be easily introduced…. In short, agricultural production in the field could be supplemented by cell and tissue culture factories."

د. التنظيف البيئى الحيوى Bioremediation والمجالات التكنولوجية المتقدمة New high technology applications:

التنظيف البيئى الحيوى Bioremediation هو مجال استخدام كائنات حية organisms لتنظيف التربة أو المياه الملوثة:

"Bioremediation" involves the use of microorganisms to degrade various types of environmental pollution, such as waste oil and heavy metals, to produce environmentally safe byproducts. This method was used to clean oil spills and might be used to decontaminate military bases or to remove heavy metals from soil. It might also be used to clean up nuclear waste.

المجالات التكنولوجية المتقدمة تهدف إلى إنتاج مواد جديدة أو إنتاج الطاقة من المصادر الجديدة وذلك عن طريق الربط بين مجال التكنولوجيا الحيوية وبين مجالات:

- الإلكترونيات الدقيقة microelectronics
- التعامل مع طبقات المادة المتناهية فى الصغر nanotechnology
- الصناعات المتقدمة تكنولوجياً high tech. Industries

Biotechnology may offer efficient ways to produce renewable energy by using microorganisms, modified plants, plant material, municipal and animal wastes, and other sources to produce different types of fuels and gases. Research is underway exploring the use of organisms to enhance the recovery of fossil fuels, to improve coal desulfurization, and to convert coal to gasoline.

هـ. مجال توفير احتياجات الصناعات الحيوية Bioindustry Suppliers:

ويشمل هذا المجال توريد الخامات أو المعدات للصناعات الحيوية، تشمل هذه التوريدات:

Enzymes
Re-agents
Specialized software
Technical instruments

Bioindustry Example: The Market for Enzymes

The following extracts from one of the recent Biotechnology Annual Reports. Some major opportunities for enzymes produced by fermentation:

- "The world-wide market for industrial enzymes was about US$1.8billion in 1998 and is projected to reach US$3 billion in 2008. the projections include only growth in traditional enzyme markets and exclude new applications in the chemical industry or for bioremediation. Most enzymes are sold to the food industry (45 percent) followed by detergents (35 percent) and textiles (11 percent)…
- Prices for enzymes vary greatly from US$ 1 per kilogram for food enzymes to more than US$1,000 per kilogram for specialty enzymes…
- The discovery and commercialisation of extremo-enzymes will create many new enzyme catalysts within new industrial applications, expanding the market to US$7 billion with five years…
- Recent progress with enzymes also has been made in the paper and pulp industry. Biocatalysts have been used for treating wastewater and new enzymes have been used successfully in removing ink from recycled paper and breaking down wood fibres (xylanases and cellulases)…
- Enzymes will also have a tremendous impact on chiral chemistry, important in the production of pharmaceutical and agricultural products. In 1997, sales for chiral drugs were US$90 billion or about 30 percent of total drug sales…
- One of the natural sources of plastic is bacteria, many species of which make plastics very similar to polyester. Biotechnology has given researchers the tools to take the process a step further. Companies such as Monsanto and DuPont have recently succeeded in transferring plastic-producing genes from bacteria into plants. Bioplastic could be made from barley, corn, oats, rice, soy, or wheat…
- As we engineer enzymes or microorganisms with new functions, we create opportunities to develop new biopolymers leading to biomaterial with unknown properties. These unknown materials could offer environmental and economic advantages over today's conventional fabrics, plastics, paper, rubber, or even construction materials…".

Bioprocessing Example: Polyester from Starch

Propanediol is the key starting material for new kind of polyester fibre, polypropylene terephthalate. This polymer has properties unique for a polyester fibre such as stretch recovery, resiliency, toughness and easy dye capability without the use of chemical modifiers. DuPont, in association with Genencor International, has developed a process that uses GMO to convert low-cost sugar from cornstarch into propanediol at high yield in a fermentor. DuPont believes this technology represents the world's lowest cost route to a future key intermediate and has backed this judgment with the construction of new processing factories based on this bioprocessing technology.

2 مثال للتوضيح – إنتـاج دواء باستخدام التكنولوجيا الحيوية:

لكون بعض المركبات – ومنها الدوائية – شديد التعقيد فى بنائها الجزيئى فإن عملية تخليقها باستخدام الطرق التقليدية للكيمياء العضوية تصبح مهمة صعبة للغاية ويصبح بديل استخدام الكائنات الحية الدقيقة microorganisms حلاً ملائماً، توجد حالياً عمليات صناعية تتم على المستوى التجارى لإنتاج مركبات دوائية عالية القيمة باستخدام التفاعلات الحيوية فى وجود كائنات دقيقة معدلة جينياً فيما يلى أحد الأمثلة للتوضيح:

The Role of Chemical Engineering in Biotechnology

Many useful materials have complicated structures which makes their chemical synthesis difficult but they have long been produced by utilizing microorganisms in processes such as fermentation and cell culture. In recent years the production of many high-value pharmaceuticals, has become possible by the use of bacteria that have been engineered using gene technology, and of cells with desired characteristics obtained by cell fusion. The biochemical industry is expanding rapidly as a means of producing valuable chemicals. To take one example; Interferon, which is now widely used for the treatments of cancer and hepatitis, is produced by the use of recombinant bacteria as shown in Figure (9.1). Among them a strain with high productivity was screened and culture conditions suited to their growth were determined. Production processes and equipment were then designed, operated and optimized to produce interferon effectively. Formation of by-products, however, was unavoidable and so it was necessary to separate and purify interferon to the degree of purity that was necessary to satisfy the pharmacopoeia activity and safety requirements.

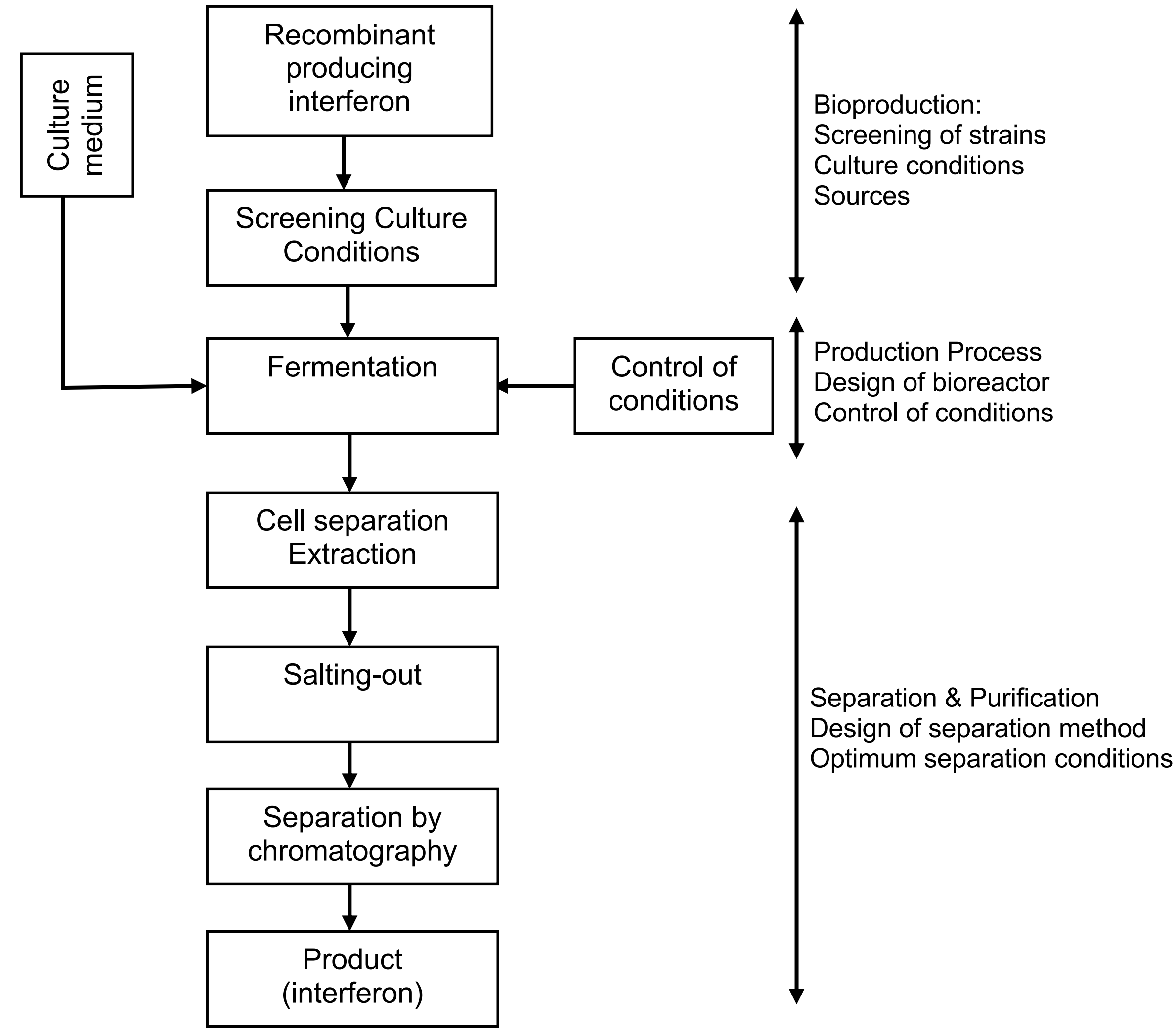

Figure (1) Production of interferon by recombinant microorganisms

3 دور المهندس الكيميائى – فرع التخصص فى الهندسة الكيميائية الحيوية :Biochemical Engineering

Chemical engineering plays an important role in the biochemical industries. The production processes consist of physical, chemical and biological conversions together with mass transfer processes; the role of chemical engineers is to design and operate the processes needed for effective and efficient production. In both the conventional and biochemical industries new processes constantly need to be devised. Most of the products of the biochemical industry are either foodstuffs or medical products and pharmaceuticals which directly affect our lives and so high purity and safety are essential during production. To satisfy these requirements, separation processes have become increasingly important and account for a large part of production costs.

Biochemical engineering is a multidisciplinary field:

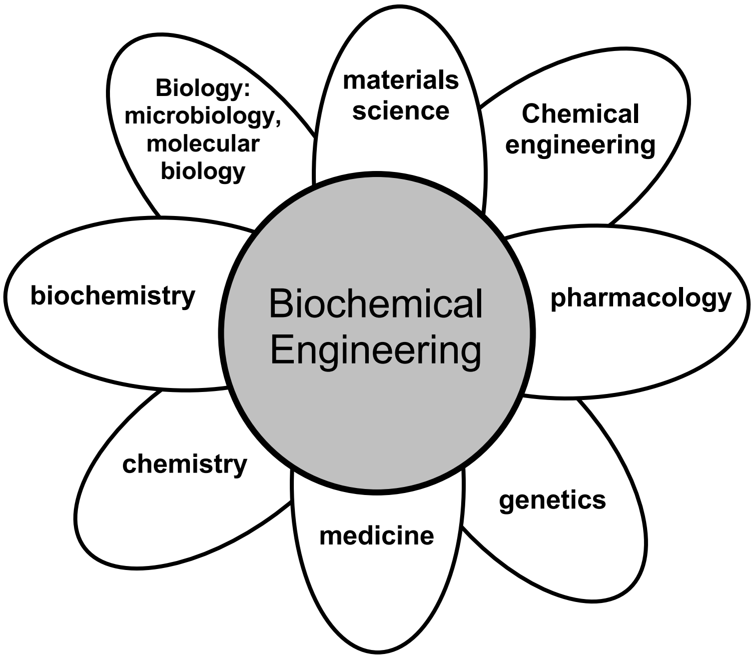

Figure (2) Biochemical Engineering and Related Disciplines

Related disciplines, and also areas of specialization of biochemical engineering:

1. metabolic engineering, including metabolic modelling
2. bioprocess engineering, including process control
3. bioseparations
4. bioinformatics
5. biomaterials engineering
6. tissue engineering
7. vessel design (e.g. reactors)

Areas of biochemical engineering cover research at the scale of the biocatalyst development (microbe, insect cell, mammalian cell, plant cells, enzyme) from the genetic level to the culture development, including reactor design and manufacturing plant.

An example of what a biochemical engineer might do:

A biologist selects a microbe to produce acetic acid from carbon monoxide, hydrogen and carbon dioxide gas (syn gas). In order to sell the product, a biochemical engineer can evaluate the following:

What is the key constraint in the process; i.e. what are the problems to be solved before the process can be profitable?

Cost of starting materials	+	**Cost of production**	<	**selling price of the product(s)**

Feedstock (market price)

1. labor
2. utilities
3. capital depreciation
4. material transport
5. separation & purification
6. reactor operation (utilities)
7. shipping and packaging
8. waste disposal
9. advertising and marketing
10. bad batches
11. others?

Also factor:
12. investment cost
13. research & development
14. capital equipment

Large companies have experience in estimating these costs before starting a project based on data collected from previous projects (also known as *rule of thumb*).

Which of the components described above require engineering?

4. material transport: chemical & industrial engineers
5. separation & purification: require scale-up and design
6. reactor operation: requires engineers and scientists
8. waste disposal: requires engineers, microbiologists
13. research & development
14. capital equipment: design and start-up

4 مثال توضيحى –دور المهندس الكيميائى فى تصميم المفاعلات الحيوية :Bioreactors

تعتبر مهمتى تصميم المفاعلات الحيوية bioreactors وطرق الفصل separation techniques هى الأهم والأكثر صعوبة من بين جميع المهام التى يضطلع بها المهندس الكيميائى فى مجال التكنولوجيا الحيوية. سوف نركز فيما يلى على المفاعلات الحيوية bioreactors بتقديم بعض المعلومات الأولية:

4.1 What is a Bioreactor?

When the prefix “bio-“ is used, it has the meaning of “function possessed by living creatures’. Thus, bioreactors are the reactors that convert or produce materials using functions naturally done by living creatures. Since fermenters that produce traditional products such as beer, wine and soy sauce have existed for centuries, they are not considered true bioreactors; rather it is reactors that utilize new materials and methods that are so classified and are part of our new and advanced technology. Reactors using immobilized enzymes, microorganisms are animal or plant cells and those applying new methodologies such as genetic manipulation or cell fusion are typical bioreactors.

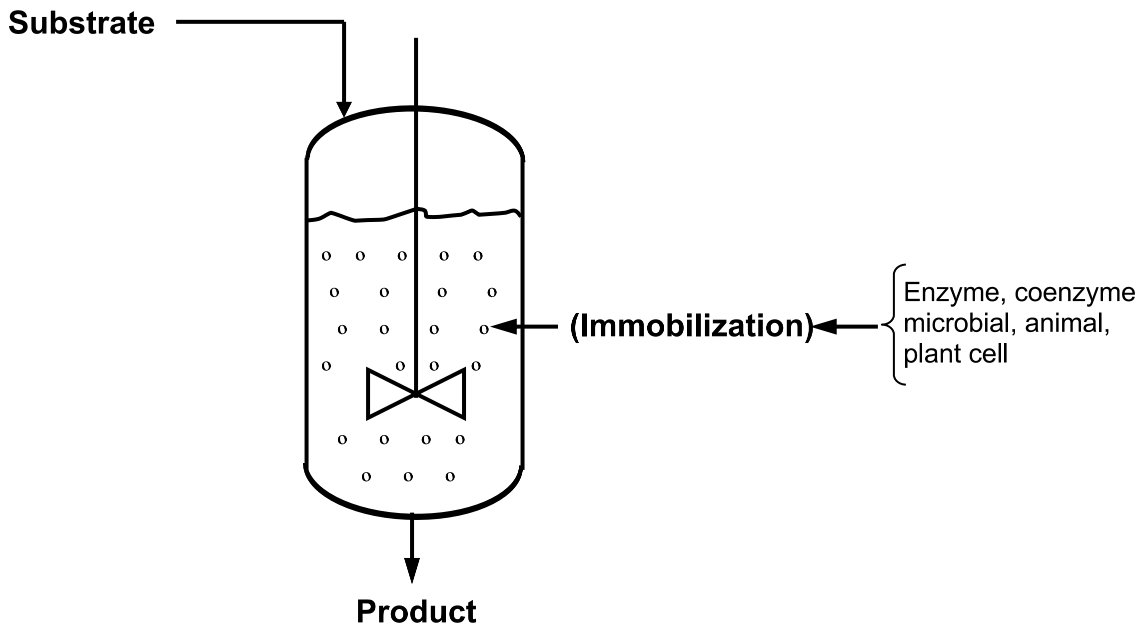

Figure (3) Bioreactor

4.2 What can be done in Bioreactors?

Bioreactors, then, are reactors used to produce materials with new or advanced technology by the application of biological functions. The biological functions are provided by enzymes, microorganisms and animal or plant cells which , as a group, may be referred to as biocatalysts. When microorganisms are used, manipulation of DNA is frequently employed while when cells are used, cell fusion techniques can be applied. Table 9.1 shows examples of products obtained from bioreactors including some currently under investigation.

Reactions using biological functions are catalyzed by enzymes. They may be divided into several types according to the form of catalysts being used, for example, isolated free enzymes and those existing in microorganisms are animal or plant cells. The performance of such reaction systems is not simple, but reactions using more than two enzymes or coenzymes can be carried out invitro, i.e. outside living systems.

Table 1 Examples of products produced in bioreactors

	Biocatalyst	Products
Enzymes	Glucose isomerase Rennin Aminoacylase Amylase, invertase Glucoamylase Thermolysin Fumarase Aspartase	Fructose Cheese L-amino acids Converted sugar Glucose Aspartame L-malic acid L-aspartic acid
Microorganisms	*Escherichia coli* (recombinant DNA) *Bacillus subtilis* Yeast *Aspergillus* sp. *Lactobacillus* sp. *Acetobacter* sp. *Streptomoyces* sp. *Clostridium* sp.	Interferon, interleukin, insulin etc. protease, amylase, etc. ethanol citiric acid lactic acid acetic acid antibiotics acetone, butanol
Animal cells	Human cell Mammalian cell	Interferon, interleukin Vaccin diagnostic agent Monoclonal antibody Prostaglandin
Plant cells	*Catharansus roseus* *Nicotiana tabacum* *Papaver somniferum* *Digitalis lanata* *Daucas carrota* *Panax ginseng* *Lithospermum erthrorhizon*	Ajmalicin Yubiquinone, nicotine Codeine Digoxin Antocyanin, perrigrogenin Saponins Shikonin
Insect cells	*Spodoptera frugiperda*	Antiseptic virus, proteins

When it is difficult to extract several enzymes catalyzing reactions or to use enzymes in bioreactors because the enzymes are unstable, whole living microorganisms or cells are used. In this case the catalysts are enzymes included in the viable body. For example in the case of ethanol fermentation, ethanol is produced by the Embden-Meyerhof cycle using yeast (Figure 9.4). Animal or plant cells are normally used to produce materials that microorganisms cannot produce. It is, however, now becoming possible to make microorganisms produce proteins originally produced by animal or plant cells by applying recombinant DNA (r-DNA) techniques. Alkaloids produced by plant cells are in general difficult to produce by microorganisms even by genetic manipulation. Although the growth rates of animal and plant cells are slow compared with microorganisms and careful handling is necessary, there are many products that are produced solely by animal or plant cells. Extensive research on the application of these cells is being undertaken and as a result the development of many more biocatalysts can be expected for future applications.

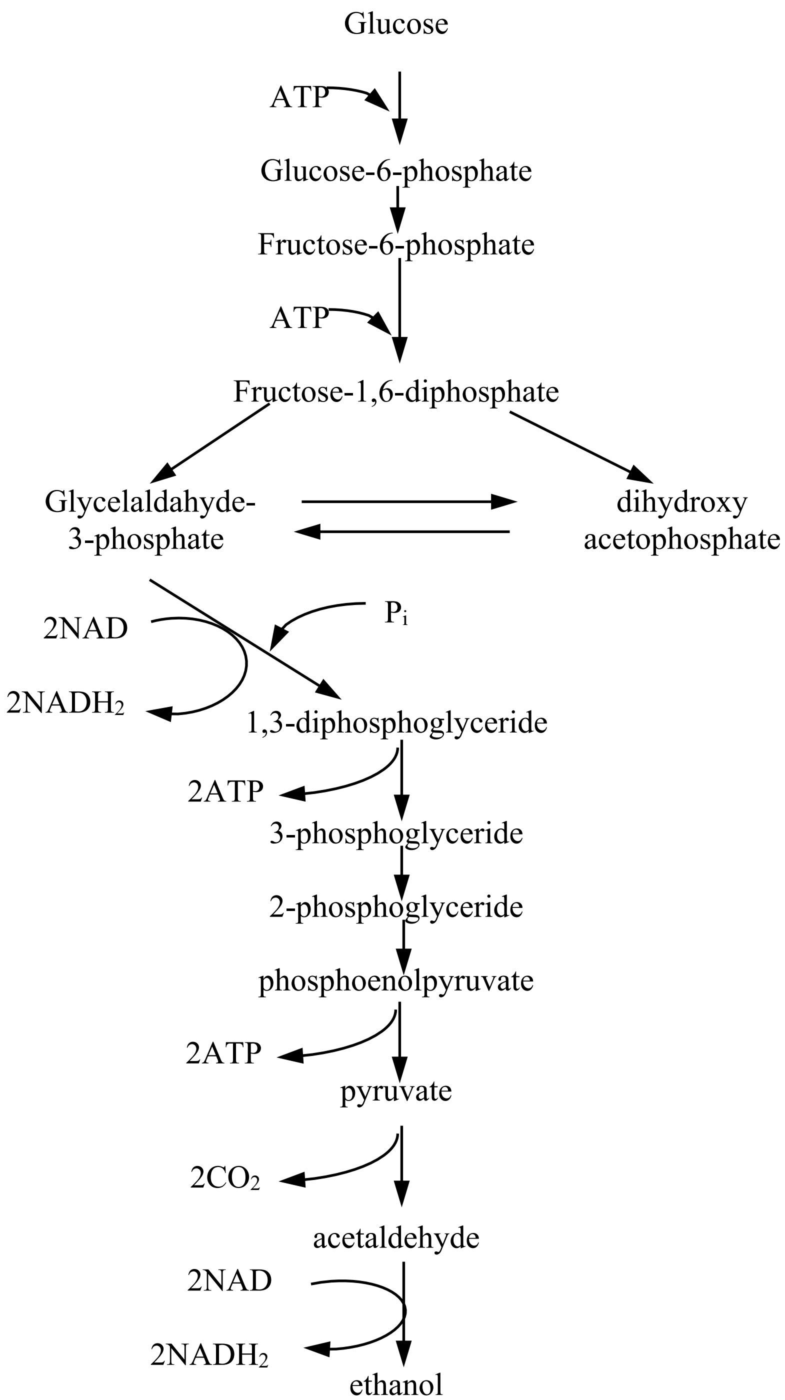

Figure (4) The Embden-Meyerhof cycle (note: P_i=H_3PO_4)

4.3 What is the difference between bioreactors and other reactors?

Bioreactors represent one of the new key technologies as we moved in the 21st century. What significant differences do they have when compared to other reactors? Let us consider their characteristics.

Bioreactors use enzymes which originate from living organisms, so the reaction conditions in bioreactors are generally mild. In many cases they operate at or close to room temperature although enzymes from microorganisms living in hot springs may work most actively at temperatures of 80ºC or even higher. Selection of a particular biocatalyst therefore defines the conditions at which the reactor is operated. In any case, the optimum temperature, pH and other conditions are usually in a narrow range and it is necessary to control bioreactors to be operated at or near room temperature, removing the heat of reaction and obtaining a uniform temperature throughout the reactor is often difficult and requires careful design.

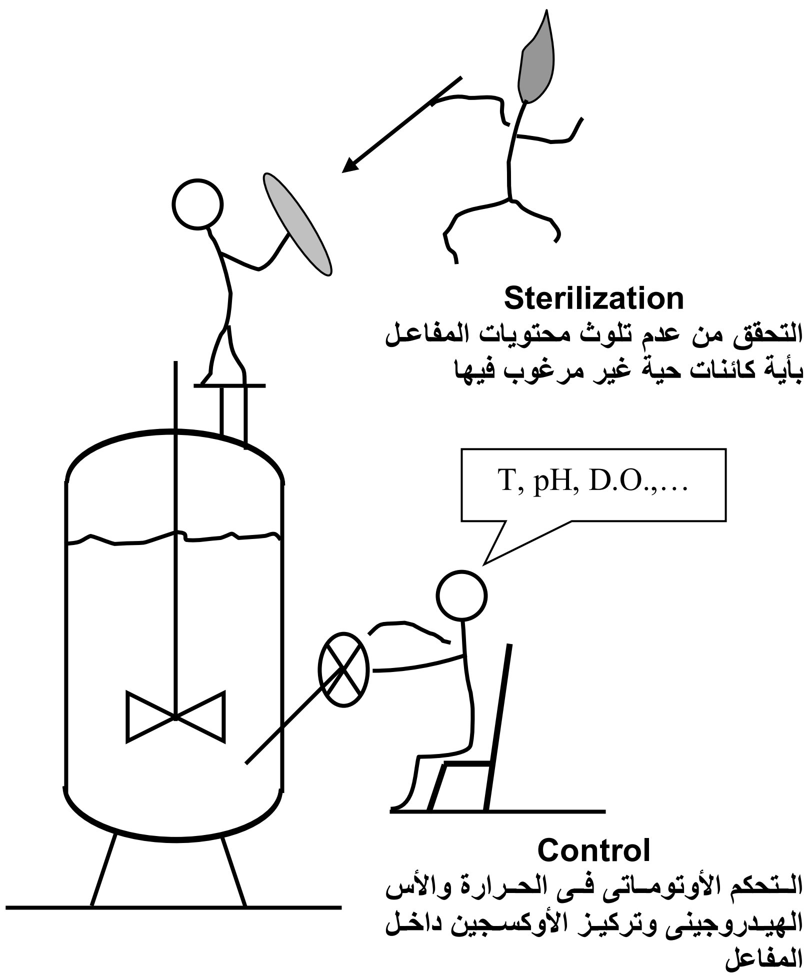

Figure (5) Control and sterilization is important in bioreactors (T = temperature, D.O. = dissolved oxygen)

A principal task in the operation of bioreactors is the prevention of contamination by surrounding microorganisms. The inside of a bioreactor is designed to be suitable for microorganisms to grow, so those foreign microorganisms with high growth rates will grow rapidly while the desired microorganisms or cells may die. Careful sterilization of the equipment an feedstocks is therefore essential.

Reaction rates using biocatalysts such as microorganisms and animal or plant cells are generally slow compared with those carried out on conventional solid catalysts because reactions proceed slowly in living creatures. If, however, we consider reaction rates per unit mass of enzymes (which may be referred to as the turn-over number) the reaction rates are often much faster than those on solid catalysts. This is because enzymes exist in living bodies in a very dilute state and so although biochemical reactions seem to be slow, very fast reaction rates can be realized if enzymes can be purified and used at high concentrations.

Another characteristic of biocatalysts is their high selectivity for reactants. Enzymes recognize specific substrates, form reaction intermediates with them and synthesize products. They do not form intermediates with other materials, so in principle side reactions do not occur. However, many enzymes take part in bioreactions occurring in microorganisms or in other cells and in practice side reactions are often observed in bioreactors. Enzymes sometimes misrecognise materials as their own specific substrates and catalyze a reaction as if the substances were similar to the substrates. But even if such a situation does occur, the selectivity is very high compared with other catalytic reactions.

Notes on Bacteria:

Bacteria are single-celled microorganisms that lack a nuclear membrane, are metabolically active and divide by binary fission. Medically they are a major cause of disease. Superficially, bacteria appear to be relatively simple forms of life; in fact, they are sophisticated and highly adaptable. Many bacteria multiply at rapid rates, and different species can utilize an enormous variety of hydrocarbon substrates, including phenol, rubber, and petroleum. These organisms exist widely in both parasitic and free-living forms. Because they are ubiquitous and have a remarkable capacity to adapt to changing environments by selection of spontaneous mutants, the importance of bacteria in every fields of medicine and biotechnology cannot be overstated.