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GENERAL INTRODUCTION:

Artificial immune systems (AIS) emerged in the last years as a new computational paradigm in artificial intelligence. They belong to a group of biologically inspired systems like artificial neural networks, DNA computations, evolutionary algorithms, but they have also been compared to other soft computing paradigms like fuzzy systems and probabilistic reasoning .

Immune system in general is a complex of cells, molecules, and organs proven capable of performing tasks like pattern recognition, learning, self-organization, and memory acquisition, generation of diversity, noise tolerance, anomaly detection, generalization, distributed detection, and optimization. Artificial immune systems are defined as adaptive systems, inspired by theoretical immunology and observed immune functions, principles and models. Newly developed computational techniques based on immune-logical principles and immune engineering concepts are used for solving computational problems using metaphors from innate immune systems and self/non-self-discrimination. They have properties like adaptively, diversity, robustness, distributivity, predator-prey pattern, etc .

The use of workers in the field of scientific research and development in many technical areas such as robotics, control, optimization and protection from Internet piracy and other fields. For our part we will try to apply this system to improve, the conductivity in the ultrafiltration is a necessary part in the dialysis machines.

At the end of this project, we are trying to understand several points:

What is artificial immune system?

What are the improvements provided by the immune system? The extent of their impact in the conductivity?

The project is divided into three chapters:

Chapter I: Artificial immune system .

Chapter II: dialysis.

Chapter III: Application of the algorithm of the immune system.

CHAPTER(I): Artificial Immune System

I.1 Introduction :

The study of human's body always attracted much attention because of its complexity. Our field of research is mainly based on the extraction of useful metaphors from biological systems to create effective solutions to complex problems. The most significant developments from the human model were the «neural networks» inspired by the functioning of the brain, and «evolutionary algorithms " inspired by the theory of Darwinian evolution.

However, more recently, there has been a growing interest in the use of another biological system that is «immune system" as a source of inspiration for solving complex problems.

Biological immune system has processing capabilities of information including the identification of the model, learning, memory and parallel distributed processing. For this and other reasons, the immune system has attracted significant interest for its use as a metaphor for inspiration in the calculation. This field of research is known as artificial immune systems in this chapter a detailed explanation of this immune system.

I.2 NATURAL IMMUNE SYSTEMS: [1]

All living organisms are capable of presenting some type of defence against foreign attack. The evolution of species that resulted in the emergence of the vertebrates also led to the evolution of the immune system of this species. The vertebrate immune system is particularly interesting due to its several computational capabilities, as will be discussed throughout this section.

The immune system of vertebrates is composed of a great variety of molecules, cells, and organs spread all over the body. There is no central organ controlling the functioning of the immune system, and there are several elements in transit and in different compartments performing complementary roles. The main task of the immune system is to survey the organism in the search for malfunctioning cells from their own body (e.g., cancer and tumor cells), and foreign disease causing elements (e.g., viruses and bacteria). Every element that can be recognized by the immune system is called an antigen (Ag). The cells that originally belong to our body and are harmless to its functioning are termed self (or self-antigens), while the disease causing elements are named non-self (or non-self-antigens). The immune system, thus, has to be capable of distinguishing between what is self-from what is non-self; a process called self/non-self-discrimination, and performed basically through pattern recognition events.

From a pattern recognition perspective, the most appealing characteristic of the IS is the presence of receptor molecules, on the surface of immune cells, capable of recognizing an almost

limitless range of antigenic patterns. One can identify two major groups of immune cells, known as B-cells and T-cells. These two types of cells are rather similar, but differ with relation to how they recognize antigens and by their functional roles. B-cells are capable of recognizing antigens free in solution (e.g., in the blood stream), while T-cells require antigens to be presented by other accessory cells.

I.2.1 A Brief History: [2]

Immunology is a relatively new science. Its origin is addressed to Edward Jenner, who discovered, approximately 200 years ago, in 1796, that the vaccinia, or cowpox, induced protection against human smallpox, a frequently lethal disease (Janeway Jr. & Travers, 1997). Jenner baptized his process vaccination, an expression that still describes the inoculation of healthy individuals with weakened, or attenuated samples of agents that cause diseases, aiming at obtaining protection against these diseases.

When Jenner introduced the vaccination, nothing was known about the ethnological agent of immunology. In the nineteenth century, Robert Koch proved that infectious diseases were caused by pathogenic microorganisms, each of which was responsible for a certain pathology.

In the 1880 decade, Louis Pasteur designed a vaccine against the chicken-pox and developed an anti-rage, which was very successful in its first inoculation of a child bitten by a mad dog. So, many practical triumphs yielded the search for immune protection mechanisms. At that same time, Elie Metchnikoff discovered phagocytosis and emphasized cellular aspects.

In 1890, Emil von Behring and Shibasaburo Kitasato found that the serum of inoculated individuals contained substances, called antibodies that bind specifically to the infectious agents.

Paul Ehrlich was intrigued by the explosive increase in antibody production after exposure to antigen and attempted to account for this phenomenon by formulating his side-chain theory.

In the early 1900, Jules Bordet and Karl Landsteiner brought to discussion the notion of immunological specificity. It was shown that the immune system was capable of producing specific antibodies against artificially synthesized chemicals that had never existed in the world.

The theoretical proposals originated during the period 1930-1950, were mainly sub-cellular. It was focused the biosynthesis of antibody molecules, made by cells. The conclusion was that the antigen must bring into the cell information concerning the complementary structure of the antibody molecule, introducing a theory called template instruction theory. The first well-known works on the template theory were performed by Breinl and Haurowitz, and further developed and advocated by the Nobel Prize winner Linus Pauling.

The following twenty years, 1950-1970, saw the decline of these early antigen-template (instructive) theories of antibody formation, in favor of selective theories. The prototype of these theories was the clonal selection theory, proposed by McFarlane Burnet (1959).

Other Nobel Prize winners performed striking theoretical studies, in the period of 1970-1990: Niels K. Jerne (1974), with his network idea, and Susumu Tonegawa (1983), studying the structure and diversity of receptors.

In the last few years, most of the work in immunology is focusing on: apoptosis, antigen presentation, cytokines, immune regulation, memory, autoimmune diseases, DNA vaccines, intracellular and intercellular signaling, and maturation of the immune response.

Table 1 summarizes the main ideas and researchers in the immunology field. A reader interested in the history of immunology might refer to Jerne (1974), Bell & Perelson (1978), and Cziko (1995).

Aims	Period	Pioneers	Notions
Application	1796-1870	Jenner Koch	Immunization Pathology
	1870-1890	Pasteur Metchinikoff	Immunization Phagocytosis
Description	1890-1910	von Behring & KITASATO Ehrlich	Antibodies Cell receptors
	1910-1930	Bordet Landsteiner	Specificity Haptens
Mechanisms (System)	1930-1950	Breidl & Haurowitz Linus Pauling	Antibody synthesis Antigen template
	1950-1980	Burnet Niels Jerne	Clonal selection Network and Cooperation
Molecular	1980-1990	Susumu Tonegawa	Structure and diversity of receptors

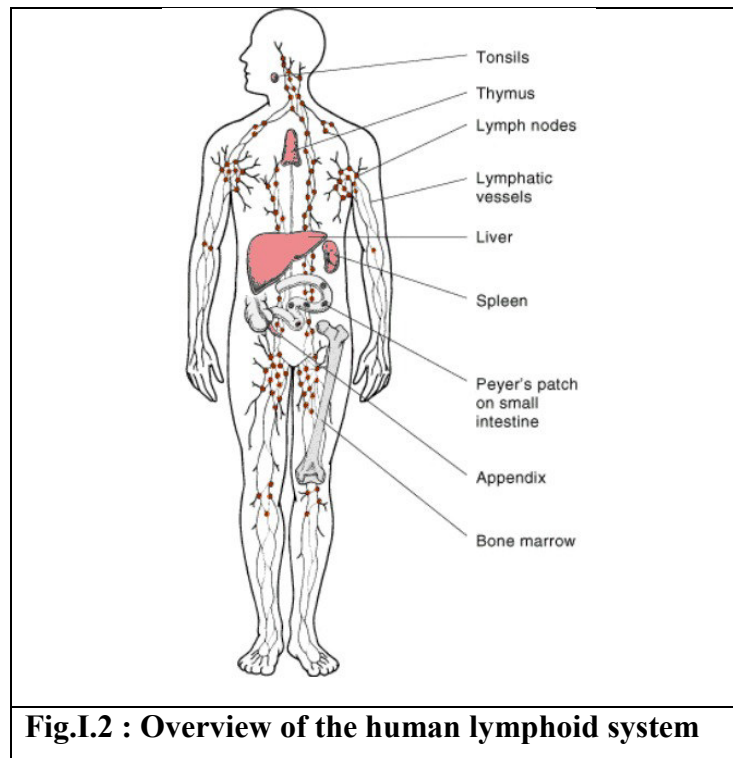
Fig.I.1: History of immunology (adapted from Jerne, 1974).

I.2.2 Immunological concepts:

I.2.2.1 Immune System Organs: [3]

These organs of the immune system produce develop and disseminate the lymphocytes, one of five types of white blood cells, which will recognize and fight infection and diseases.

The blood and lymphatic vessels are an important part of the lymphoid organs because they carry the lymphocytes to and from different parts of the body.



I.2.2.1.a Lymphoid Organs: [3]

Bone marrow: This is the soft tissue in the hollow centre of bones. All blood cells including most immune cells, are produced within the bone marrow from special cells called stem cells. Once they have matured they migrate to various parts of the immune system via the lymphatic system.

Thymus: This pinkish grey gland is located behind the breastbone. Its main function is to transform the white blood cells into the various type of T-cells which are able to mount an attack on the organisms. The thymus is most active up to adolescence, after which it begins to grow smaller.

Tonsils: Lymph tissue are also found around the entrance to the throat, the most obvious being the tonsil. Tonsils trap and destroy bacteria and germs that we inhale or swallow. They show signs of infection when they have white patches or a pale yellow substance covering them.

Spleen: This fist-size, spongy and deep red organ is located on the left side of the abdominal cavity just behind the lower rib. It cleanses our blood by filtering used-up and defective red blood cells. It also cleanses the phagocytes that fight infection. Large numbers of lymphocytes and antibodies also reside here on the lookout for invaders.

I.2.2.1.b Lymphatic System:

Lymph: This clear fluid seeps from our blood vessel into our tissues, collecting cell debris, bacteria and unwanted stuff along the way. Most of these fluid flows back into the blood system while the rest circulates back to the heart.

Lymph nodes: These are gland like organs found in many sites in the body, including under the arms, behind the ears, in the neck, abdomen and the groin. The lymph nodes are home to macrophages, T cells and B cells.

I.2.2.2 Immune cells: [4]

T-Cells: T lymphocytes are usually divided into two major subsets that are functionally and phenotypically (identifiably) different. The T helper subset, also called the CD4+ T cell, is a pertinent coordinator of immune regulation. The main function of the T helper cell is to augment or potentiate immune responses by the secretion of specialized factors that activate other white blood cells to fight off infection.

Natural Killer Cells: Natural killer cells, often referred to as NK cells, are similar to the killer T cell subset (CD8+ T cells).

B Cells: The major function of B lymphocytes is the production of antibodies in response to foreign proteins of bacteria, viruses, and tumour cells.

Macrophages: Macrophages are important in the regulation of immune responses. They are often referred to as scavengers or antigen-presenting cells (APC) because they pick up and ingest foreign materials and present these antigens to other cells of the immune system such as T cells and B cells. This is one of the important first steps in the initiation of an immune response.

Stimulated macrophages exhibit increased levels of phagocytosis and are also secretory.

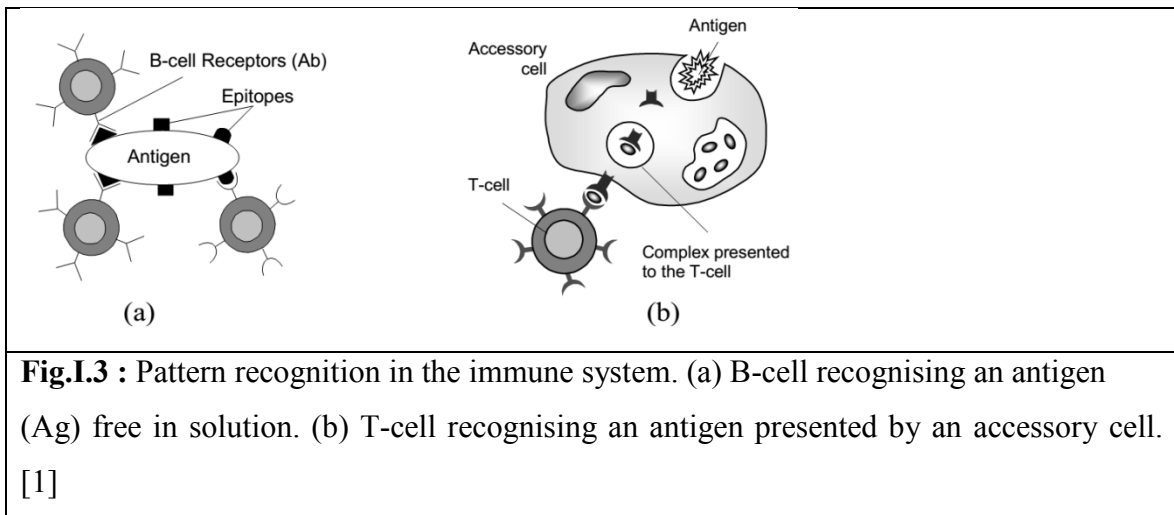
Dendritic Cells: Another cell type, addressed only recently, is the dendritic cell. Dendritic cells, which also originate in the bone marrow, function as antigen presenting cells (APC).

I.2.2.3 Antigens:

In immunology, an antigen is a substance foreign to the body (for example, a bacterium) which, once in the body, attracts and is bound to by a respective and specific antibody. Each of

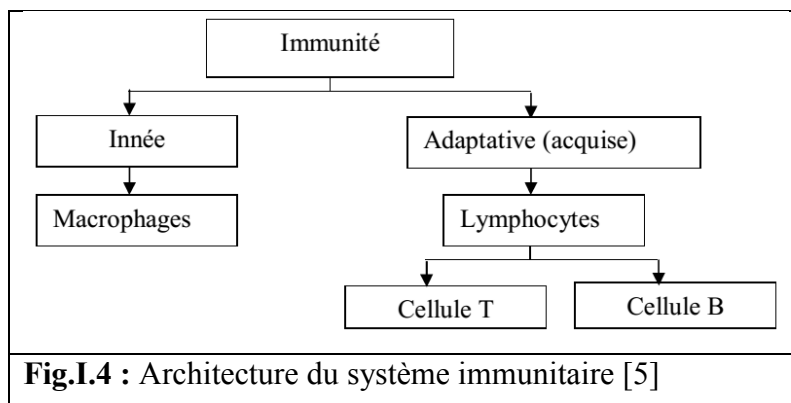
diverse types of antibodies binds to a specific antigen by its variable region interaction (CDR loops), an analogy being the fit between a lock and a key.

Fig. 1(a) illustrates that antigens are covered with molecules, named epitopes. These allow them to be recognized by the receptor molecules on the surface of B-cells, called antibodies (Ab). In contrast, Fig. 1(b) shows how for an antigen to be recognized by a T-cell receptor, it has to be processed and presented by an accessory cell.



I.2.3 Architecture of the immune system:

The body's defence against the external environment has a so-called innate immune or natural, that is to say, exists in the absence of contact with the antigen, called adaptive or acquired immunity, and that means appearing after the connection of an organism and particles of foreign antigens. [5]



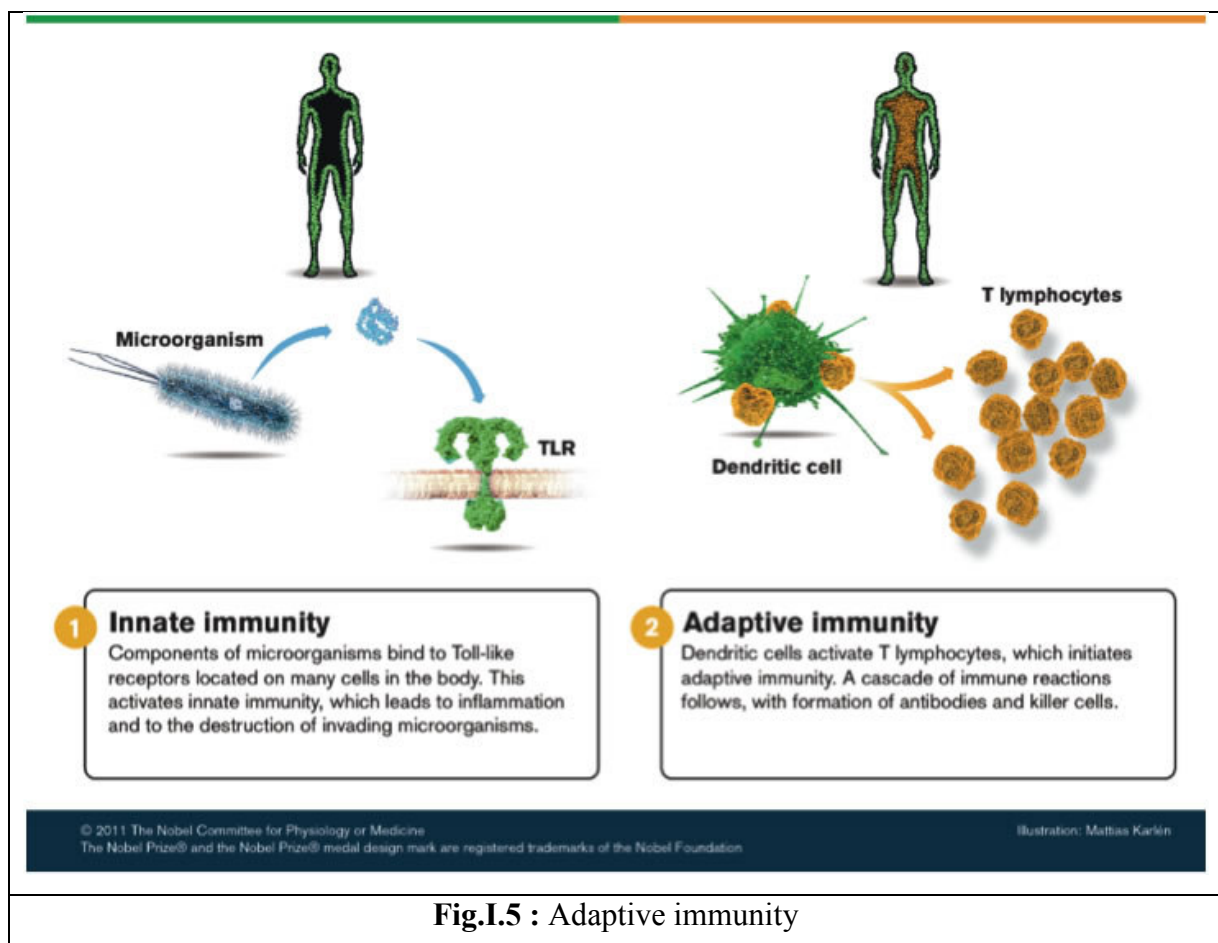
I.2.3.1 Innate immunity:

Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include physical barriers

such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body. The innate immune response is activated by chemical properties of the antigen. [6]

I.2.3.2 Adaptive immunity:

Adaptive immunity refers to antigen-specific immune response. The adaptive immune response is more complex than the innate. The antigen first must be processed and recognized. Once an antigen has been recognized, the adaptive immune system creates an army of immune cells specifically designed to attack that antigen. Adaptive immunity also includes a "memory" that makes future responses against a specific antigen more efficient. [6]



I.2.4 How the Immune System Protects the Body: [1]

As discussed previously, our body is protected by a diverse army of cells and molecules that work in concert, where the ultimate target of all immune responses is an antigen (Ag), which is usually a foreign molecule from a bacterium or other invader. Figure 6 presents a simplified version of the basic immune mechanisms of defence.

Specialized antigen presenting cells (APCs), such as macrophages, roam the body, ingesting and digesting the antigens they find and fragmenting them into antigenic peptides (Nossal, 1993)

(I). Pieces of these peptides are joined to major histocompatibility complex (MHC) molecules and are displayed on the surface of the cell. Other white blood cells, called T cells or T lymphocytes, have receptor molecules that enable each of them to recognize a different peptide-MHC combination (II). T cells activated by that recognition divide and secrete lymphokines, or chemical signals, that mobilize other components of the immune system (III).

The B lymphocytes, which also have receptor molecules of a single specificity on their surface, respond to those signals. Unlike the receptors of T cells, however, those of B cells can recognize parts of antigens free in solution, without MHC molecules (IV). When activated, the B cells divide and differentiate into plasma cells that secrete antibody proteins, which are soluble forms of their receptors (V). By binding to the antigens they find, antibodies can neutralize them (VI) or precipitate their destruction by complement enzymes or by scavenging cells. Some T and B cells become memory cells that persist in the circulation and boost the immune system's readiness to eliminate the same antigen if it presents itself in the future. Because the genes for antibodies in B cells frequently suffer mutation and editing, the antibody response improves after repeated immunizations, this phenomenon is called affinity maturation and will be discussed further in the text.

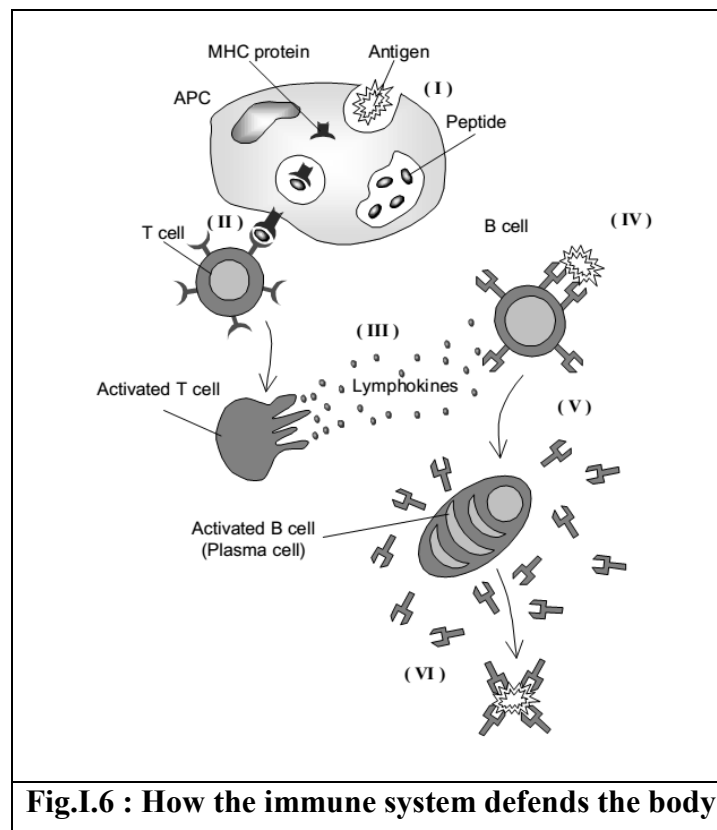


Fig.I.6 : How the immune system defends the body

I.2.5 Immune theories:

Behaviour and immune system reactions are governed primarily by immune theories:

I.2.5.1 Clonal selection:

Theory was proposed by Burnet (1959). The theory is used to explain basic response of adaptive immune system to antigenic stimulus. It establishes the idea that only those cells capable of recognizing an antigen will proliferate while other cells are selected against. Clonal selection operates on both B and T cells. B cells, when their antibodies bind with an antigen, are activated and differentiated into plasma or memory cells. Prior to this process, clones of B cells are produced and undergo somatic hyper mutation. As a result, diversity is introduced into the B cell population. Plasma cells produce antigen-specific antibodies that work against antigen. Memory cells remain with the host and promote a rapid secondary response (Castro and Timmis, 2003).

I.2.5.2 Negative Selection: [1]

The concept of a negative signal following certain lymphocyte-antigen interactions, allows for the control of those lymphocytes being anti-self. Negative selection of a lymphocyte describes the process whereby a lymphocyte-antigen interaction results in the death or anergy of that lymphocyte. The immune cell is simply purged from the repertoire. Location plays a role in negative selection: the primary lymphoid organs are designed to largely exclude foreign antigens and to preserve the self-antigens, whereas the secondary lymphoid organs are designed to filter out and concentrate foreign material, and to promote co-stimulatory intercellular immune reactions (Zinkernagel & Kelly, 1997).

The negative selection of T-cells has been broadly used by the AIS community as a model to perform anomaly detection. Basically, the negative selection of T-cells that occurs within the thymus is based on the following considerations. The thymus is comprised of a myriad of molecules that primarily present self-molecules to the naïve T-cells (immature T-cells just produced and with no function yet).

The interactions of immature T-cells with the self-molecules results in the death of all those naïve T-cells that recognize the self-molecules. This means that only T-cells that do not recognize self-molecules are allowed to survive and become functional T-cells.

I.2.5.2.a Negative T cell Selection:

The negative T cell selection can occur within the thymus or on the periphery.

Negative thymic selection is based on the following considerations. The thymus is comprised of a myriad of class I and class II MHC-bearing APCs, including macrophages, dendritic cells, and specialized epithelial cells. Because the thymus is protected by the maternal immune system and by a blood-thymic barrier, these APCs primarily present self-peptide/ MHC complexes (self-MHC ligands) to the emerging T cell repertoire. Negative thymic selection stems from interactions of immature self-reactive thymocytes with self-MHC ligands on thymic APC, and results in activation dependent cell's death to purge potentially auto-reactive T cells from the repertoire. T cells bearing "useless" TCRs that do not exhibit significant interactions with any self-MHC ligand are also lost from the repertoire. Negative thymic selection, however, is not perfect, and some self-reactive T cells escape into the periphery as fully immunocompetent cells, posing the threat of autoimmune diseases.

The inductive signal for T cell activation requires more than TCR cross-linking. For the T cells on the periphery, several adjunct processes such as the binding of a variety of cell adhesion molecules are necessary for T cell activation. In the absence of co-stimulatory activity, union of TCR and MHC-T cell epitope may deliver a down-regulatory signal to the T cell. The innate immunity is responsible for delivering a great amount of co-stimulatory signals (like B7.1 and B7.2) for the adaptive immunity.

I.2.5.2.b Negative B cell Selection:

T cell tolerance alone would be insufficient protection against autoimmunity. Immature B cells within the bone marrow are especially sensitive to tolerance induction, and mature B cells can also be rendered tolerant if they encounter antigen in the absence of T cell help and co-stimulatory influences, but only at higher antigen concentrations.

I.2.5.3 Positive Selection:

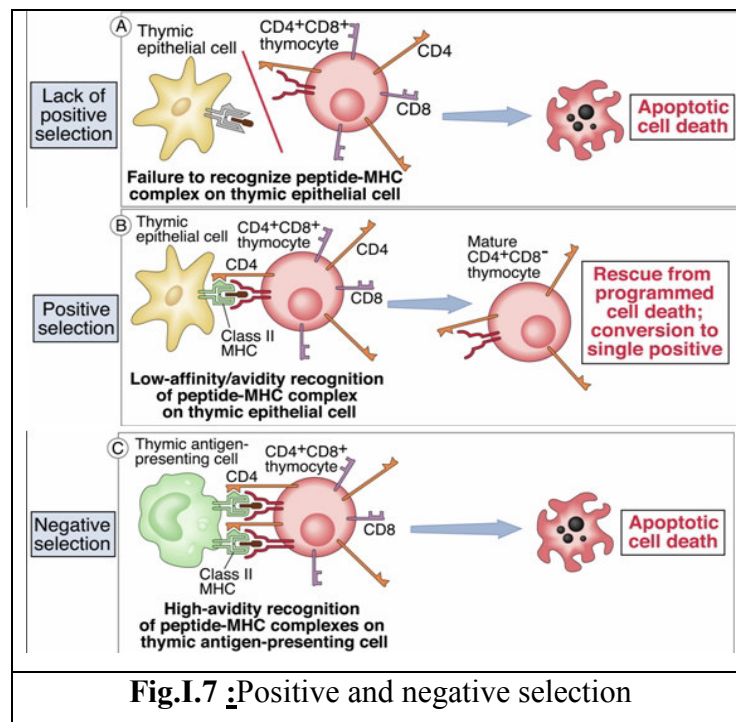
Lymphocytes that are especially effective in recognizing foreign peptides presented by self-MHC molecules suffer positive selection, a process which is responsible for controlling survival and differentiation of the repertoires (Anderson et al., 1999).

In several cases, positive selection initiated by receptor ligation involves rescue from cell death. Rescue of pre-T and pre-B lymphocytes appears similar in that, in each case, the receptor consists of the first produced chain of the antigen receptor, expressed by mature cells, plus other

developmentally regulated proteins. These receptors are coupled to signal-transducing molecules and perhaps exert their function by binding to ligands thus far unknown (von Boehmer, 1994).

The generated signals result in rescue from cell death and maturation that are associated with suppression of rearrangement of TCR heavy chain and immunoglobulin light chain. In certain aspects, positive selection of immature T cell and positive selection of mature B cells by the immunoglobulin receptor in germinal centers appear rather similar. In the former, cells are rescued from cell death, and further receptor gene rearrangement ceases following ligation of the TCR by self-ligands on thymic epithelium. In the latter, cells are rescued from cell death, and somatic hyper mutation ceases following immunoglobulin receptor binding to foreign proteins presented by APCs in germinal centers.

Positive thymic selection also enables exclusive expression of either CD4 or CD8 on T cells that bear TCR with a predilection to interact with peptides on either class II or class I MHC proteins, respectively.



I.2.6 The immune network: [7]

In the early 1970s an eminent Danish immunologist working in Switzerland triggered a revolution in our understanding of the immune system. Niels Jerne proposed that cells and molecules of the immune system not only recognize foreign substances, but also recognize, respond to and are regulated by each other. It followed that we should regard the immune system as a network of interacting cells and antibodies.

This perspective is known as the idiotypic network theory, or more simply the immune network theory. The idea is that the cells of the immune system are functionally connected via variable components with enormous diversity (V regions), with each cell being connected to a small subset of the rest via interactions between V regions. Important properties of this system, including memory, are then properties of the network of cells as a whole, rather than of the individual cells. This was a revolutionary paradigm for immunology, and much progress has since been made towards understanding the immune system in these terms.

I.3 ARTIFICIAL IMMUNE SYSTEMS:

I.3.1 History:[8]

AIS emerged in the mid-1980s with articles authored by Farmer, Packard and Perelson (1986) and Bersini and Varela (1990) on immune networks. However, it was only in the mid-1990s that AIS became a field in its own right. Forrest et al. (on negative selection) and Kephart et al. published their first papers on AIS in 1994, and Dasgupta conducted extensive studies on Negative Selection Algorithms. Hunt and Cooke started the works on Immune Network models in 1995; Timmis and Neal continued this work and made some improvements. De Castro & Von Zuben's and Nicosia & Cutello's work (on clonal selection) became notable in 2002. The first book on Artificial Immune Systems was edited by Dasgupta in 1999.

Currently, new ideas along AIS lines, such as danger theory and algorithms inspired by the innate immune system, are also being explored. Although some believe that these new ideas do not yet offer any truly 'new' abstract, over and above existing AIS algorithms. This, however, is hotly debated, and the debate provides one of the main driving forces for AIS development at the moment. Other recent developments involve the exploration of degeneracy in AIS models, which is motivated by its hypothesized role in open ended learning and evolution.

Originally AIS set out to find efficient abstractions of processes found in the immune system but, more recently, it is becoming interested in modelling the biological processes and in applying immune algorithms to bioinformatics problems.

In 2008, Dasgupta and Nino published a textbook on Immunological Computation which presents a compendium of up-to-date work related to immunity-based techniques and describes a wide variety of applications.

I.3.2 Definition :[8]

The field of Artificial Immune Systems (AIS) is concerned with abstracting the structure and function of the immune system to computational systems, and investigating the application of these systems towards solving computational problems from mathematics, engineering, and information technology. AIS is a sub-field of Biologically-inspired computing, and Natural computation, with interests in Machine Learning and belonging to the broader field of Artificial Intelligence.

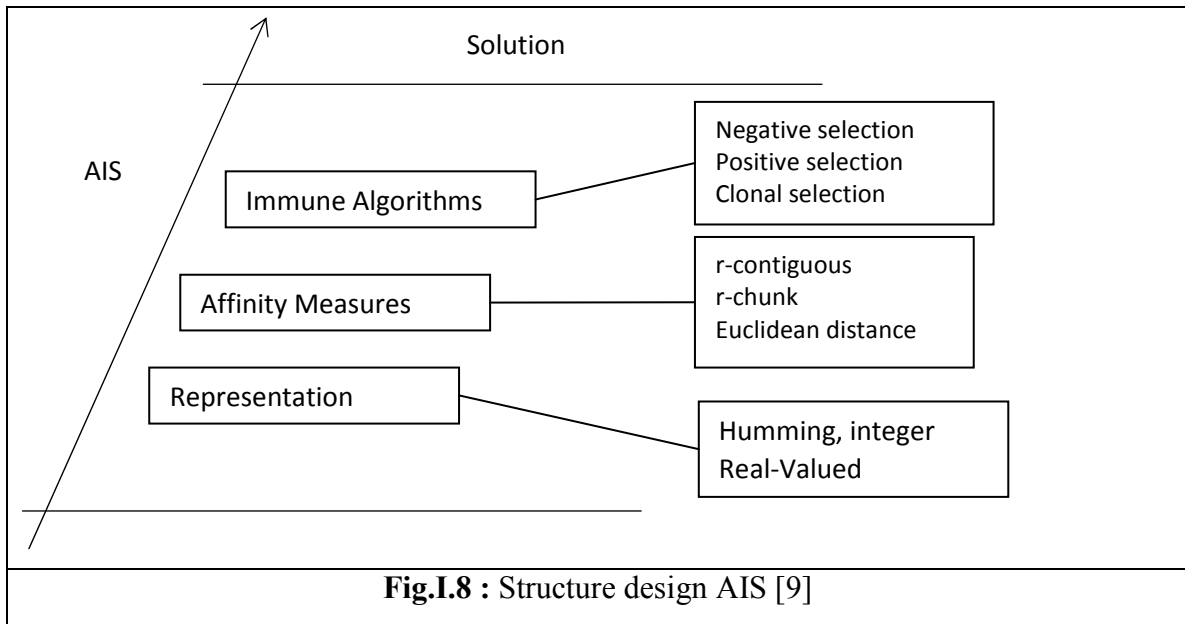
Artificial Immune Systems (AIS) are adaptive systems, inspired by theoretical immunology and observed immune functions, principles and models, which are applied to problem solving.

AIS is distinct from computational immunology and theoretical biology that are concerned with simulating immunology using computational and mathematical models towards better understanding the immune system, although such models initiated the field of AIS and continue to provide a fertile ground for inspiration. Finally, the field of AIS is not concerned with the investigation of the immune system as a substrate computation, such as DNA computing.

I.3.3 Modelling of artificial immune systems:

Framework to design biologically inspired algorithm requires, at least, the following basic elements:

- A representation for the components of the system.
- A set of mechanisms to evaluate the interaction of individuals with the environment and each other. The environment is usually simulated by a set of input stimuli, one or more fitness function(s), or other mean(s).
- Procedures of adaptation that govern the dynamics of the system, i.e. how its behaviour varies over time.



I.3.3.1 Representation:

T and B cells are the most important cells in the immune system. They contain useful for the recognition of intruders surface receptors, whose shapes are complementary to the shape of antigen. Cells and immune molecules are elements that must be modelled and used in the proposed artificial immune system models.

It is assumed that each antigen is specifically with all antibodies which supplements exist in a small region of encirclement. This region is characterized by a parameter "S" called affinity threshold. The result of the definition of the affinity threshold Vs is the volume of which is called the identification region.

I.3.3.2 Affinity measures :

The affinity between an antibody and an antigen is on their distance, antigen A is represented by a vector = <Ag1, Ag2,... Ag, AgL>, an antibody is in turn represented by a vector = Ab <Ab1, Ab2... Abl>.

To measure the completeness between the antigen and the antibody, several techniques can be used. More often one resorts to the use of the distances. Different distances exist, the most used are:

- Euclidean distance: $D = \sqrt{\sum_{i=1}^n (Ab_i - Ag_i)^2}$ Equ.I.1

- The Manhattan distance: $D = \sum_{i=1}^n |Ab_i - Ag_i|$ Equ.I.2

- The Hamming distance: $D = \sum_{i=1}^n \delta^i$ où $\delta = \begin{cases} 1, & Ab_i \neq Ag_i \\ 0, & \text{sinon} \end{cases}$ Equ.I.3

I.3.4 Algorithms of artificial immune system:

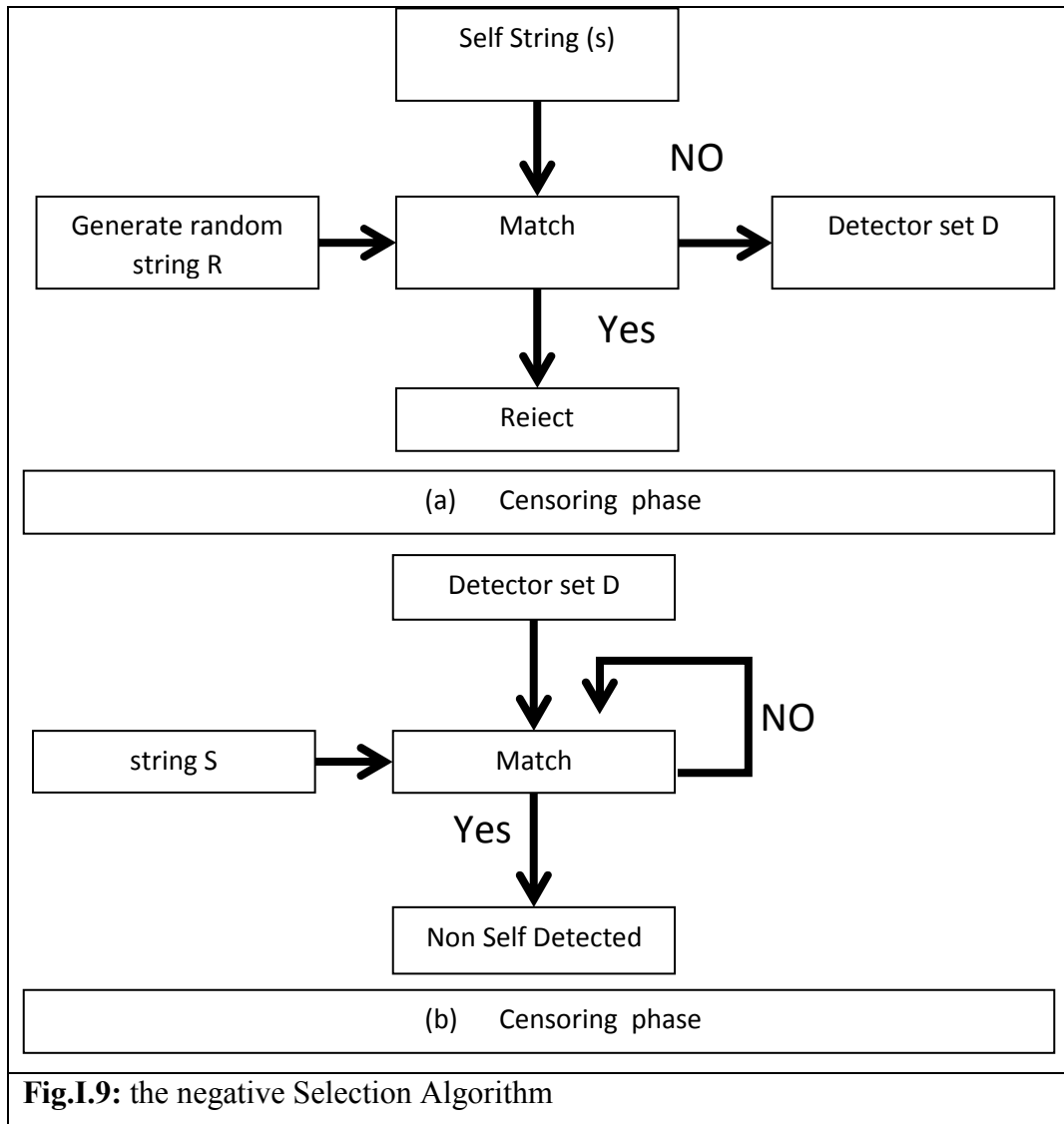
I.3.4.1 The negative selection algorithm: [10]

The negative selection algorithm is a supervised learning algorithm introduced by Forrest and al to computer security, network security and anomalies detection problems. It is based on the discriminatory mechanism of the natural system. The aim of the negative selection algorithm is to classify a bit or string representations of real-world data, termed antigen, as normal or anomalous. In nature, Antigen is anything which is not part of the body itself.

The algorithm processes in two steps: learning and testing. The basic idea of the negative selection algorithm is to generate a number of detectors in the complementary space. Then, apply these detectors to classify new, unseen, data as self or non self.

The algorithm can be summarized in the following steps:

- Define self as a set of S elements of length l over a finite alphabet: a collection that needs to be protected or monitored.
- Then generate a set of D detectors, which does not match any element in S. Instead of exact or perfect matching, the method uses a partial matching rule, in which two strings match if and only if they are identical at least at r contiguous positions, where r is a chosen parameter.
- Monitor S form changes by continually matching the detectors in D against S. A schematically representation of the algorithm can be found in **Fig.I.9**. In the initial description of the algorithm, candidate detectors are generated randomly and then tested to see if they match any self-string. If a match is found, the candidate is rejected .This process is repeated until a desired number of detectors is generated.



I.3.4.2 Algorithm ClonalG: [11]

Provides an overview of the steps of the CLONALG algorithm:

1. **Initialisation** — The first step of the CLONALG technique is initialisation, which involves preparing an antibody pool of fixed size N. This pool is then partitioned into two components, a memory antibody section in that eventually becomes representative of the algorithms solution and a remaining antibody pool r used for introducing additional diversity into the system.

2. **Loop** — The algorithm then proceeds by executing a number of iterations of exposing the system to all known antigens. A single round of exposure or iteration is referred to as a

generation. The number of generations G the system executes is user configurable, though the system can use a problem specific stopping condition.

a. **Select Antigen** — A single antigen is selected at random without replacement (for the current generation) from the pool of antigens

b. **Exposure** — The system is exposed to the selected antigen. Affinity values are calculated for all antibodies against the antigen. Affinity is a measure of similarity, and is problem dependent. It is common to use Hamming distance.

c. **Selection** — A set of n antibodies are selected from the entire antibody pool that have the highest affinity with the antigen.

d. **Cloning** — The set of selected antibodies are then cloned in proportion to their affinity (rank based).

e. **Affinity Maturation (mutation)** — The clone (set of duplicate antigens) are then subjected to an affinity maturation process to better match the antigen in question. Here, the degree of maturation is inversely proportional to their parent's affinity (rank based), meaning that the greater the affinity, the lower the mutation.

f. **Clone Exposure** — The clone is then exposed to the antigen, and affinity measures are calculated.

g. **Candidature** — The antibody or antibodies with the highest affinity in the clone are then selected as candidate memory antibodies for placement into m . If the affinity of a candidate memory cell is higher than that of the highest stimulated antigen from the memory pool n_i , then it replaces said antigen. Group replacements occur in a similar, but batched manner.

h. **Replacement** — Finally, the d individuals in the remaining r antigen pool with the lowest affinity are replaced with new random antibodies.

3. **Finish** — After the completion of the training regime, the memory n_i component of the antigen pool is then taken as the algorithms solution. Depending on the problem domain, the solution may be a single best individual antigen or the collective of all antigens in the pool.

I.4 Conclusion:

The immune system is complex but very powerful; it can detect many different types of pathogens, even unknown one, and thanks to a strong interaction between all the different actors

of the immune system, the pathogens can be destroyed. As the immune system has some very interesting features, a new artificial intelligence paradigm called the artificial immune system was created, is of course an interesting candidate to apply AIS In the field of dialysis. It is that we will cover in the next chapter of the note.

CHAPTER (II): HEMODIALYSIS

II.1 Introduction :

In medicine, dialysis (from Greek "dialysis", meaning dissolution, "dia", meaning through, and "lysis", meaning loosening) is a process for removing waste and excess water from the blood, and is primarily used to provide an artificial replacement for lost kidney function in people with renal failure. Dialysis may be used for those with an acute disturbance in kidney function (acute kidney injury, previously acute renal failure) or for those with progressive but chronically worsening kidney function—a state known as chronic kidney disease stage 5 (previously chronic renal failure or end-stage kidney disease). The latter form may develop over months or years, but in contrast to acute kidney injury is not usually reversible, and dialysis is regarded as a "holding measure" until a renal transplant can be performed, or sometimes as the only supportive measure in those for whom a transplant would be inappropriate.

The kidneys have important roles in maintaining health. When healthy, the kidneys maintain the body's internal equilibrium of water and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, sulfate). Those acidic metabolism products that the body cannot get rid of via respiration are also excreted through the kidneys.

The kidneys also function as a part of the endocrine system producing erythropoietin and calcitriol. Erythropoietin is involved in the production of red blood cells and calcitriol plays a role in bone formation. Dialysis is an imperfect treatment to replace kidney function because it does not correct the endocrine functions of the kidney. Dialysis treatments replace some of these functions through diffusion (waste removal) and ultrafiltration (fluid removal). [12]

Try in this chapter, a detailed explanation of dialysis and the way it works.

II.2 Kidney: [13]

Kidney is a paired organ whose functions include removing waste products from the blood and regulating the amount of fluid in the body. The basic units of the kidneys are microscopically thin structures called nephrons, which filter the blood and cause wastes to be removed in the form of urine. To get her with the bladder, two ureters, and the single urethra, the kidneys make up the body's urinary system. Human beings, as well as members of all other vertebrate species, typically have two kidneys.

Like kidney beans, the body's kidneys are dark red in colour and have a shape in which one side is convex, or rounded, and the other is concave, or indented. The kidneys of adult humans are about 10 to 13 cm (4 to 5 in) long and about 5 to 7.5 cm (2 to 3 in) wide—about the size of a computer mouse.

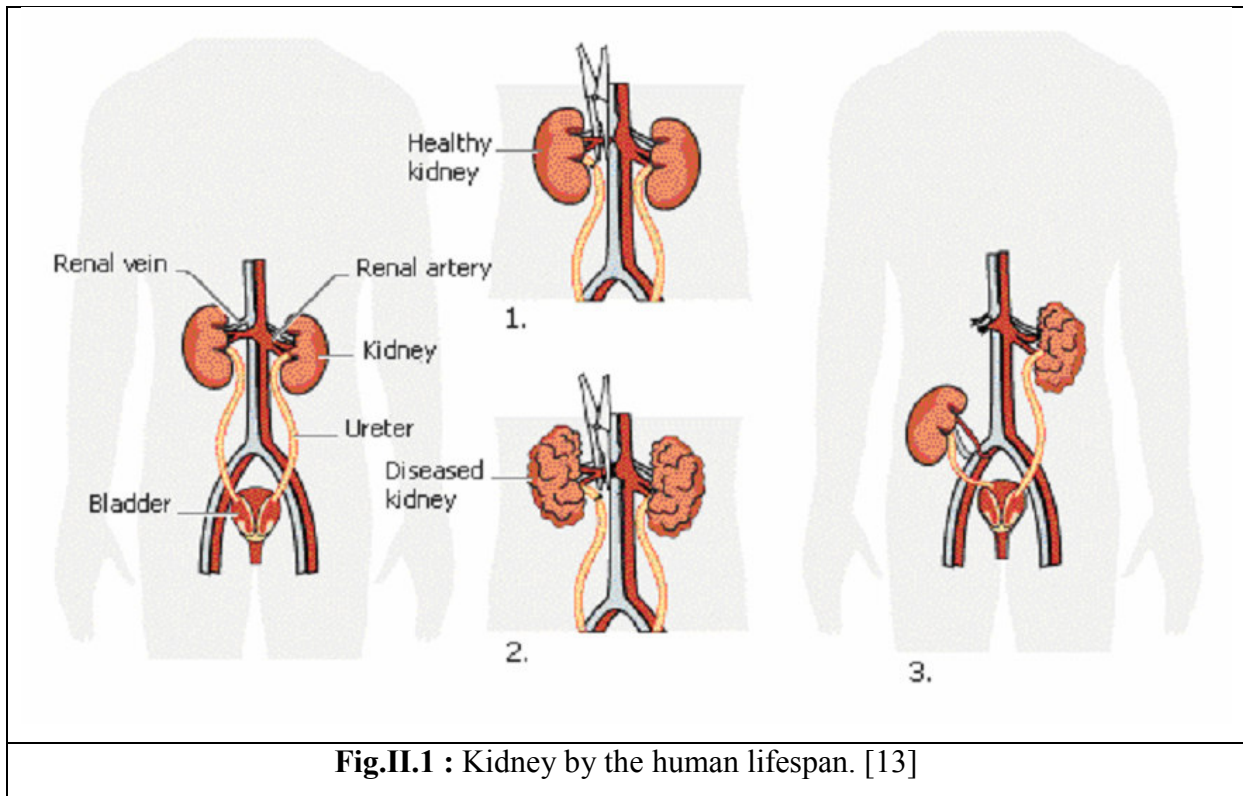


Fig.II.1 : Kidney by the human lifespan. [13]

The kidneys lie against the rear wall of the abdomen, on either side of the spine. They are situated below the middle of the back, beneath the liver on the right and the spleen on the left.

Each kidney is encased in a transparent, fibrous membrane called a renal capsule, which helps protect it against trauma and infection. The concave part of the kidney attaches to two of the body's crucial blood vessels—the renal artery, the renal vein—and the ureter, a tube like structure that carries urine to the bladder.

A primary function of kidneys is the removal of poisonous wastes from the blood. Chief among these wastes are the nitrogen-containing compounds urea and uric acid, which result from the breakdown of proteins and nucleic acids. Life-threatening illnesses occur when too many of these waste products accumulate in the bloodstream. Fortunately, a healthy kidney can easily rid the body of these substances.

II.3 KIDNEY DISEASES: [13]

Diseases of the kidney range from mild infection to life-threatening kidney failure. The most common form of kidney disease is an inflammation of the kidney, called pyelonephritis. Most such inflammations are caused by a bacterial infection that starts in the bladder and spreads to the kidney. Sometimes an obstruction that interferes with the flow of urine in the urinary tract can cause the disease. Symptoms of pyelonephritis include fever, chills, and back pain.

Antibiotic drugs are usually given to fight the infection, which can scar the kidneys and impair their function if left untreated.

Glomerulonephritis, another common kidney disease, is characterized by inflammation of some of the kidney's glomeruli (glomerulus is a round cluster of interconnected capillaries found in the cortex of a kidney, which remove body waste to be excreted as urine) .

This condition may occur when the body's immune system is impaired. Antibodies and other substances form large particles in the bloodstream that become trapped in the glomeruli. This causes inflammation and prevents the glomeruli from working properly. Symptoms may include blood in the urine, swelling of body tissues, and the presence of protein in the urine, as determined by laboratory tests. Glomerulonephritis often clears up without treatment. When treatment is necessary, it may include a special diet, immunosuppressant drugs, or plasmapheresis, a procedure that removes the portion of the blood that contains antibodies.

Other common kidney disorders include kidney stones, which are small, crystallized substances, such as calcium, that form in the kidney or other parts of the urinary tract. Smaller kidney stones can pass out of the body on their own, although this can be painful. Larger stones may require surgery, or they may be broken into smaller pieces with sound waves in a procedure called ultrasonic lithotripsy.

The kidneys may be harmed whenever injury or disease affects the rest of the body. For example, diabetes mellitus (a disease caused by a malfunctioning pancreas that produces little or no insulin) can result in impaired blood flow through the kidneys. The bacteria that cause tuberculosis can travel from the lungs and infect the kidneys. Injured muscles can release large amounts of protein into the bloodstream, blocking the nephrons. Drug use, including long-term use of some prescription medications as well as illegal drugs, can also cause kidney damage. Certain birth defects may cause the kidneys to have abnormal shapes or to function improperly.

Treatment of severe kidney disease may include kidney dialysis, a procedure in which blood is circulated through a machine that removes wastes and excess fluid from the bloodstream. Some patients use dialysis for a short time, while their kidneys recover from injury or disease. Others must use dialysis for their entire lives or until they undergo a kidney transplant. Kidney transplants are the most common of all transplant operations and have excellent success rates. Unfortunately, there are not enough kidneys available for the people who need them. More than 38,000 people in the United States alone wait for a kidney transplant each year, and fewer than 12,000 of them receive this life sustaining organ.

II.4 History of dialysis: [14]

Kidneys keep our blood clean. If they stop working, toxins accumulate in the blood and can lead to death. Kidney dialysis machines, known as artificial kidneys, can replace kidney function. They remove toxins before pumping clean blood back into the body.

The first artificial kidney machine was developed by Willem Kolff in 1943. He had limited materials during wartime, so he used cellophane sausage wrapping attached to a wooden rotating drum. The first 15 people hooked up to the machine died. However, drum dialyzers saved many lives. Kolff improved his machine and pioneered other devices.

The 1950s and 1960s saw new designs for dialysis machines. Some were for use in the home as well as hospital. Home dialysis was more convenient for patients and could be carried out more frequently, so it improved patient health. However, home dialysis machines were expensive and complex to use and clean.

In the 1950s people thought machines could not manage long-term kidney failure. Long-term dialysis damaged patients' veins and arteries. This made it difficult for them to use dialysis machines. In 1960, American doctor Belding Scribner invented the Teflon shunt. Patients now had a permanent connector fitted to their arm that linked them to a dialysis machine without the blood clotting. This gave hope to patients waiting for an organ transplant.

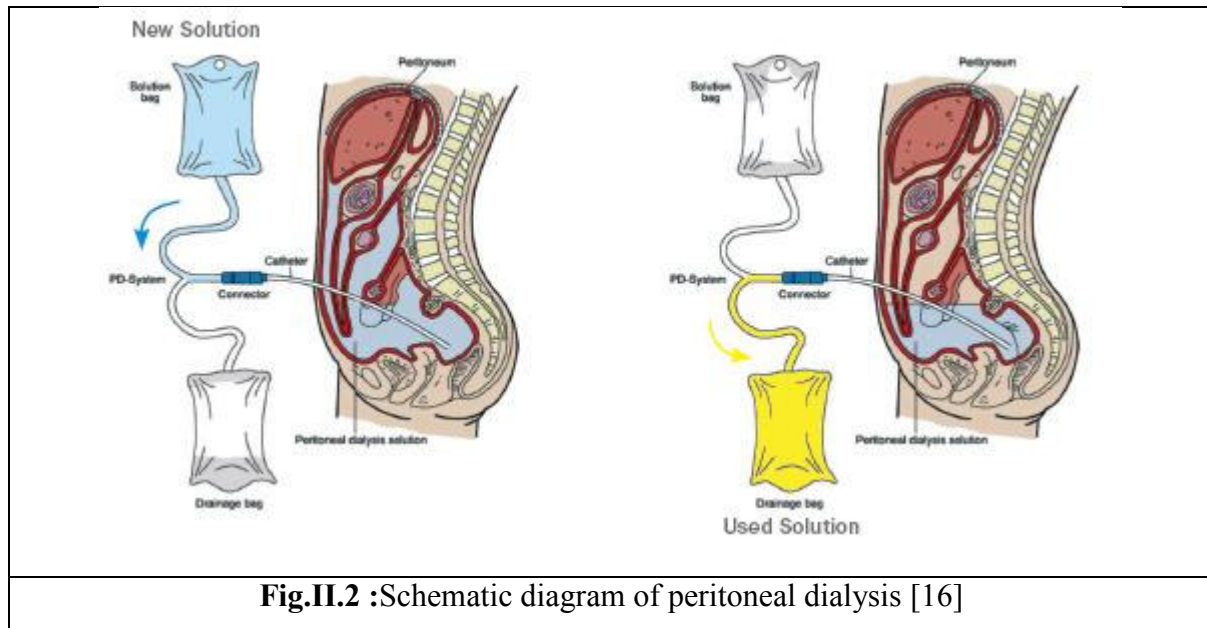
II.5 Types of the dialysis:

Dialysis is a therapy that removes water and toxins from the body. Dialysis is typically applied in patients with acute or chronic kidney failure. The major forms of dialysis are:

II.5.1 Peritoneal Dialysis : [15]

Dialysis is a treatment for kidney failure that helps filter waste products from the blood when the kidneys are not working properly. Peritoneal dialysis (PD) uses a membrane in the abdomen (the peritoneal membrane) as a natural filter to clear wastes and extra fluid from the body and to keep chemical levels in the body as close to normal as possible.

Peritoneal dialysis does not require travel to a dialysis centre. The dialysis process (called an exchange) can be done at home, often at night during sleep. But it must be done on a continuous, daily basis.



The first step in peritoneal dialysis is called the Fill, in which the dialysis solution enters the peritoneal cavity. The second step is the Dwell. During the Dwell step, while the solution is in the peritoneal cavity, extra fluid and waste from the body travel across the peritoneal membrane into the dialysis fluid. The final step is the Drain, in which the dialysis solution is drained after a few hours and replaced with new solution.

There are different types of peritoneal dialysis:

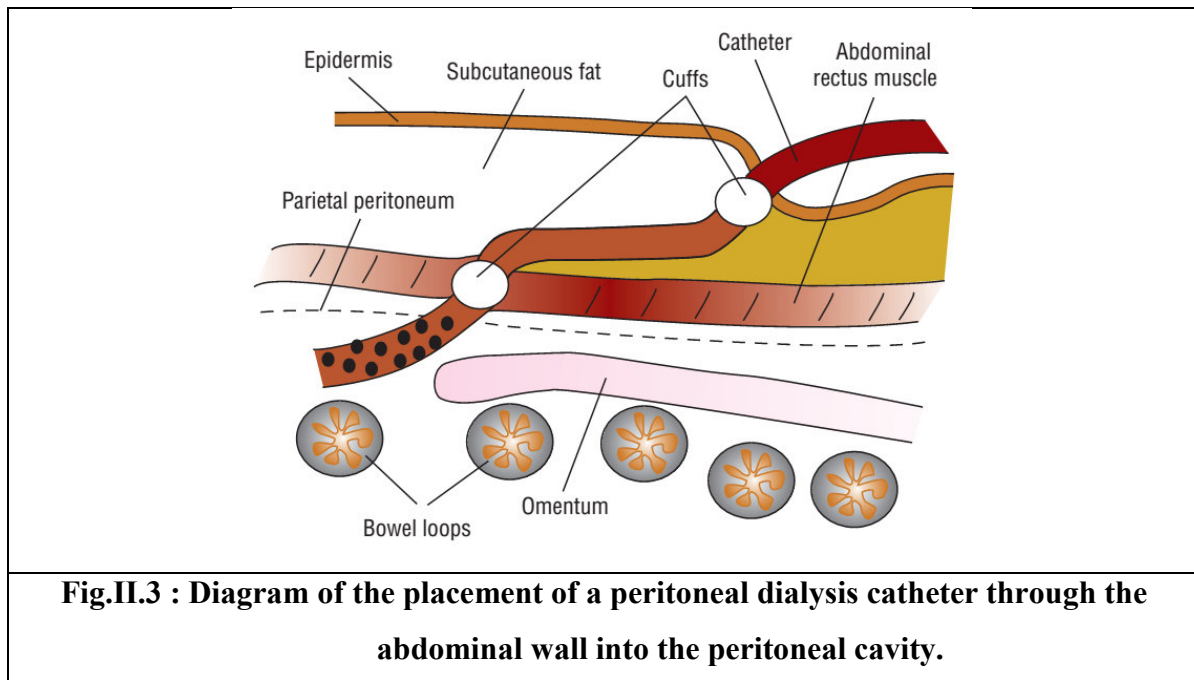
Continuous ambulatory peritoneal dialysis (CAPD) is the form of peritoneal dialysis that most people use. During CAPD, the dialysis solution stays in the belly for about 4 to 6 hours. Most people do 3 or 4 exchanges during the day and one in the evening that stays overnight. During the dwell time, the person is able to do normal daily activities.

Continuous cycling peritoneal dialysis (CCPD) uses a machine that automatically fills and drains the solution from the belly. The machine performs 3 to 5 exchanges while the person sleeps. In the morning, one exchange is left in the belly. Usually one exchange is done in the middle of the day.

• **Principles of peritoneal dialysis:** [15]

Access to the peritoneal cavity is via the placement of an indwelling catheter. Many types are available and **Fig.II.3** shows a typical example. Most catheters are manufactured from silastic, which is soft, flexible, and biocompatible. A typical adult catheter is approximately 40 to 45 cm long, 20 to 22 cm of which are inside the peritoneal cavity.

Placement of the catheter is such that the distal end lies low in a pelvic gutter. The center section of the catheter has one or two cuffs made of a porous material. This section is tunneled inside the anterior abdominal wall so that the cuffs provide mechanical support and stability to the catheter, a mechanical barrier to skin organisms, and prevent their migration along the catheter into the peritoneal cavity. The cuffs are placed at different sites surrounding the abdominal rectus muscle.



The remainder of the central section of the catheter is tunneled subcutaneously before exiting the abdominal surface, usually a few centimeters below and to one side of the umbilicus.

The placement of the catheter exit site is one of the factors related to the development or prevention of exit-site infections and peritonitis. The external section of most peritoneal catheters ends with a Luer-Lok connector, which can be connected to a variety of administration sets. These catheters can be used immediately if necessary, provided small initial volumes are instilled; however, a maturation period of 2 to 6 weeks is preferred.

II.5.2 Haemodialysis: [14]

Dialysis is a mechanical process that partly does the work that healthy kidneys would do. Hemodialysis uses a man-made membrane (dialyzer) to filter wastes, remove extra fluid from the blood, restore the proper balance of chemicals in the blood, and eliminate extra fluid (edema) from the body.

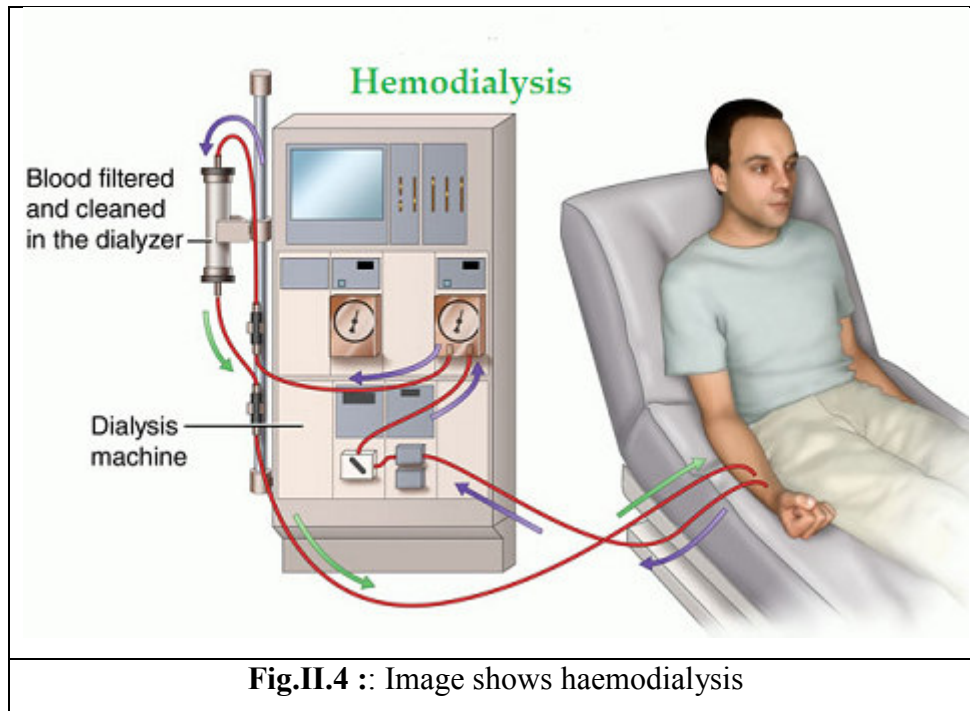


Fig.II.4 :: Image shows haemodialysis

Before hemodialysis treatments can begin, a doctor will need to create an access where blood can flow in and out of the body (dialysis access). This is usually done by joining an artery and a vein in the forearm or by using a small tube to connect an artery and a vein.

Hemodialysis is usually done in a hospital or dialysis centre on a set schedule. It is usually done 3 days a week and takes 3 to 5 hours a day. In some cases, hemodialysis can be done at home. Home haemodialysis can be done on more days of the week. Some types of home haemodialysis are done during the night.

II.5.2.1 PRINCIPLES OF HEMODIALYSIS:[17]

Haemodialysis consists of the perfusion of blood and a physiologic salt solution on opposite sides of a semipermeable membrane.

Multiple substances, such as water, urea, creatinine, uremic toxins, and drugs, move from the blood into the dialysate, by either passive diffusion or convection as the result of ultrafiltration. Diffusion is the movement of substances along a concentration gradient; the rate of diffusion depends on the difference between the concentration of solute in blood and dialysate, solute characteristics, the dialyzer membrane composition, and blood and dialysate flow rates. Ultrafiltration is the movement of water across the dialyzer membrane as a consequence of hydrostatic or osmotic pressure and is the primary means for removal of excess

body water. Convection occurs when dissolved solutes are “dragged” across a membrane with fluid transport (as long as the pores in the dialyzer are large enough to allow them to pass). Convection can be maximized by increasing the hydrostatic pressure gradient across the dialysis membrane, or by changing to a dialyzer that is more permeable to water transport.

These two processes can be controlled independently, and thus a patient’s haemodialysis prescription can be individualized to attain the desired degree of solute and fluid removal.

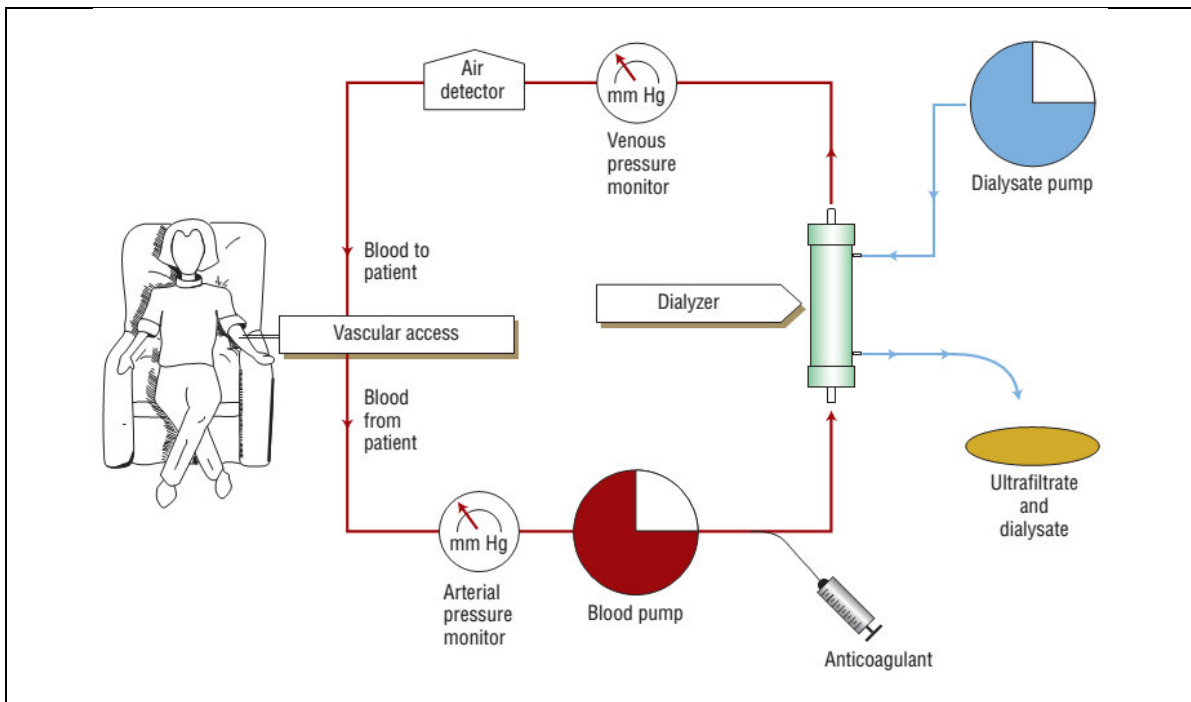


Fig.II.5 : In haemodialysis, the patient’s blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at a rate of 500 to 1,000 mL/min through the dialyzer counter-current to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment. [17]

II.5.2.2 Haemodialysis Machine: [18]

The two principle components of a haemodialysis machine system are the dialyzer (artificial kidney) and the extra-corporeal system. The 'dialyzer' is a series of semi permeable membranes, arranged to form paths for blood to pass next to dialysis fluid on opposite sides of the membrane, flowing in opposite directions.

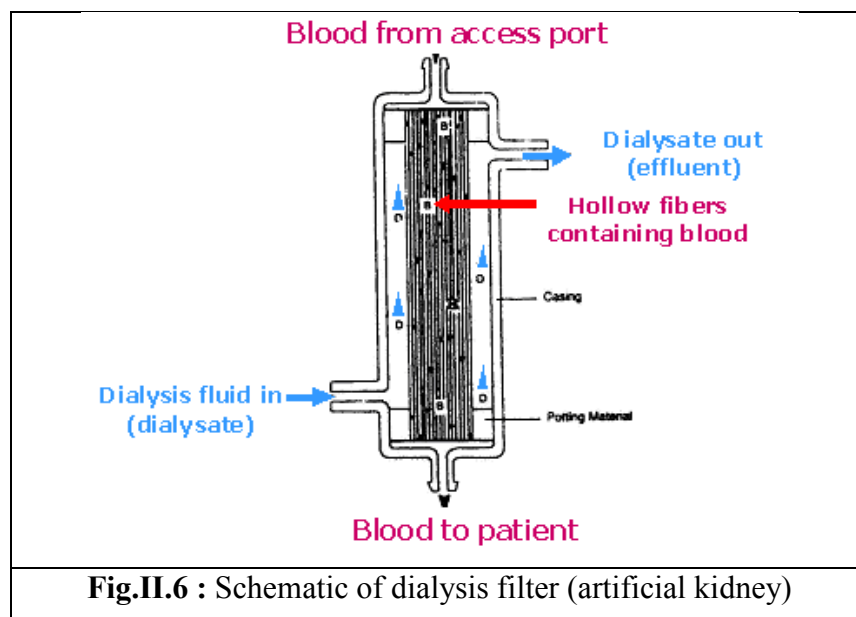
The 'extracorporeal system' refers to blood being drawn from a needle ('A'-needle) by a pump, passing through the dialyzer and returning to the patient through another needle ('V'-needle).

The system has a series of fail-safe mechanisms to prevent a number of possible complications. There is an arterial pressure monitor to protect the fistula from excess negative pressure. There is a bubble trap to prevent air embolus and a venous pressure monitor to detect and prevent blood loss.

The flow rates of blood and dialysate fluid, plus composition of dialysate and length of dialysis are individualized for each patient. The dialysis fluid is made up of specific (individualized) concentrations of electrolytes with treated water. Meticulous preparation of water for dialysis is essential as contamination of water with microorganisms and chemicals is dangerous.

II.5.3 Artificial Kidneys: [19]

The dialysis filter is referred to as an artificial kidney. Blood is pulled from the patient and carried into the filter. Once inside, the blood travels through many tiny tubules called hollow fibers. Water and solutes can pass across the semi-permeable membrane between the blood and the fluid that surrounds the hollow fibers. Any fluid or solutes that enters the filter canister will be drained out as waste.



Note how the dialysis filter has structural similarities to the nephron unit. Blood arrives at the filter via the access tubing (afferent arteriole). Blood enters the small hollow fibers within the filter (glomerulus). Water and solutes diffuse across the semi-permeable membrane of the hollow fibers and collect in the canister (Bowman's capsule). Collected fluid (filtrate or effluent) is then

removed via the drainage tubing (collecting tubule). Blood that remains in the hollow fibers is returned to the patient via the return side of the filter (effluent arterial).

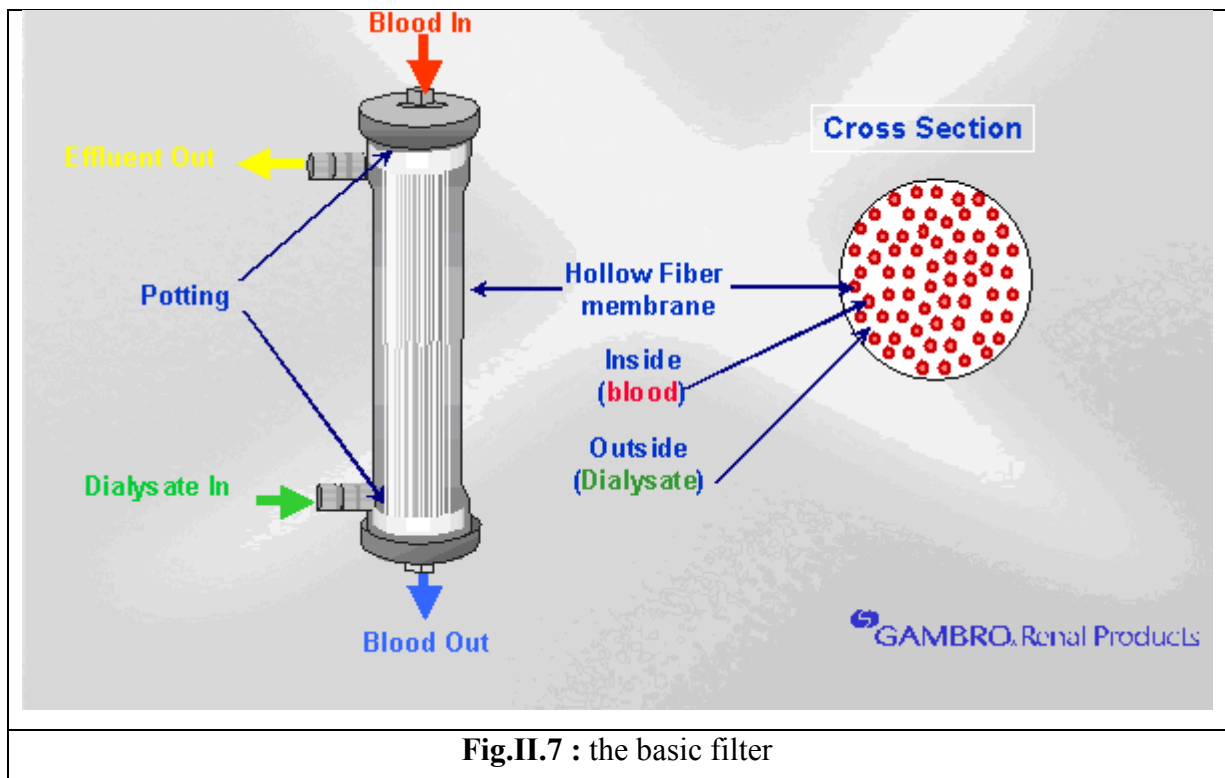


Fig.II.7 : the basic filter

Although similarities exist between the nephron unit and the artificial kidney, the artificial kidney has limited capabilities. In the nephron unit, filtered water and waste enters the proximal tubule. Because the nephron unit removes significantly more water and solutes than needed, most of the water and electrolytes that enter the tubule system are reabsorbed.

Unlike the nephron unit, the artificial kidney cannot reabsorb water or solutes that enter the filter canister. Any filtrate that enters the filter canister will be removed via the drainage tubule. Consequently, one of the differences in the artificial kidney is the absence of the proximal tubule, loop of henle and distal tubule where water and solute reabsorption and secretion occurs. Thus, the drainage tubule that exits the filter is similar to the collecting tubule of the nephron unit, not the proximal tubule. To compensate for the inability to reabsorb water and solutes following removal from the blood, the artificial kidney is manipulated to restrict the actual removal to only surplus water and wastes. This is done by adjusting dialysis solutions and ultrafiltration rates. If more water or solutes are removed than desired, they may need to be given back via intravenous infusions.

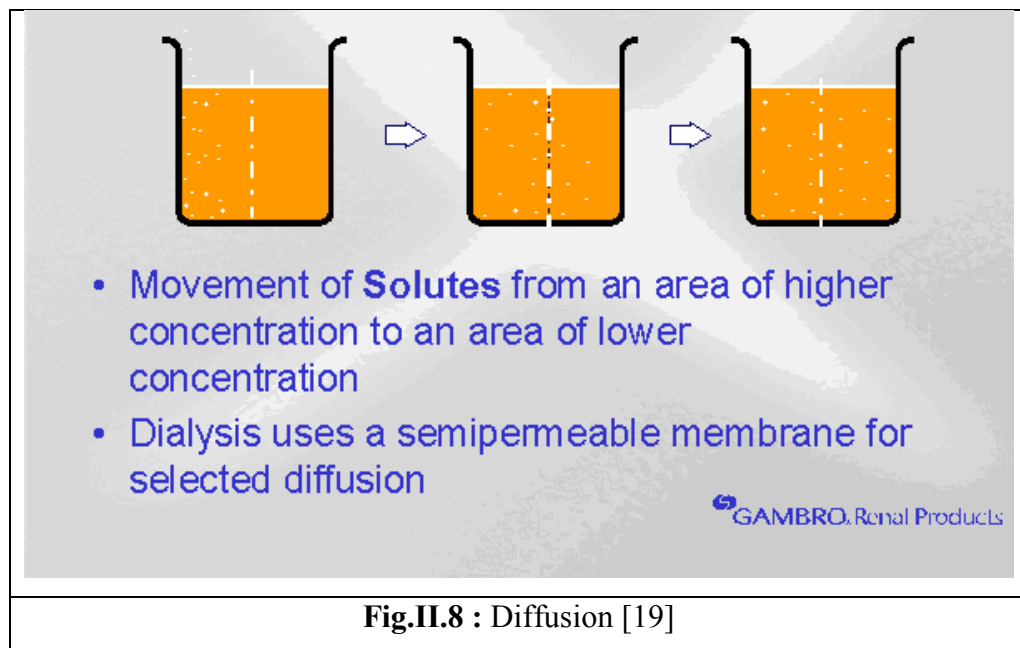
The artificial kidney does not replace other important kidney functions, including stimulation of red blood cell production (erythropoietin), blood pressure and sodium regulation

(renin) and calcium uptake by the GI tract (vitamin D synthesis). The nephron normally traps and recycles bicarbonate to maintain acid base balance. Bicarb is given to patients during haemodialysis to compensate for bicarb deficits.

The principles used during haemodialysis are reviewed below:

II.5.3.1 **Diffusion:** [19]

Diffusion is the movement of particles (solutes) across a semi-permeable membrane. Diffusion is the movement from the side with the highest concentration of particles, to the side with the lowest concentration.



II.5.3.2 **DIALYSIS FLUID (DIALYSATE):** [19]

Dialysate is the fluid that is pumped into the filter canister, surrounding the hollow fibers. The concentration of solutes in the dialysis fluid determines diffusion gradients. The removal of surplus solutes from the blood is achieved by infusing dialysate fluid that contains a lower solute concentration than the serum concentration (e.g. dialysate does not contain urea or creatinine).

To maintain normal serum electrolyte levels, dialysate fluid contains sodium, chloride and magnesium levels that are equal to serum concentrations (thus, removal of these electrolytes should only occur if the blood level exceeds normal serum concentrations). In renal failure, potassium is often high at the start of a treatment, therefore, we may begin dialysis with a low concentration of potassium in the dialysate. Because potassium is easily removed during dialysis, and continued dialysis will be required to ensure removal of other wastes such as urea and

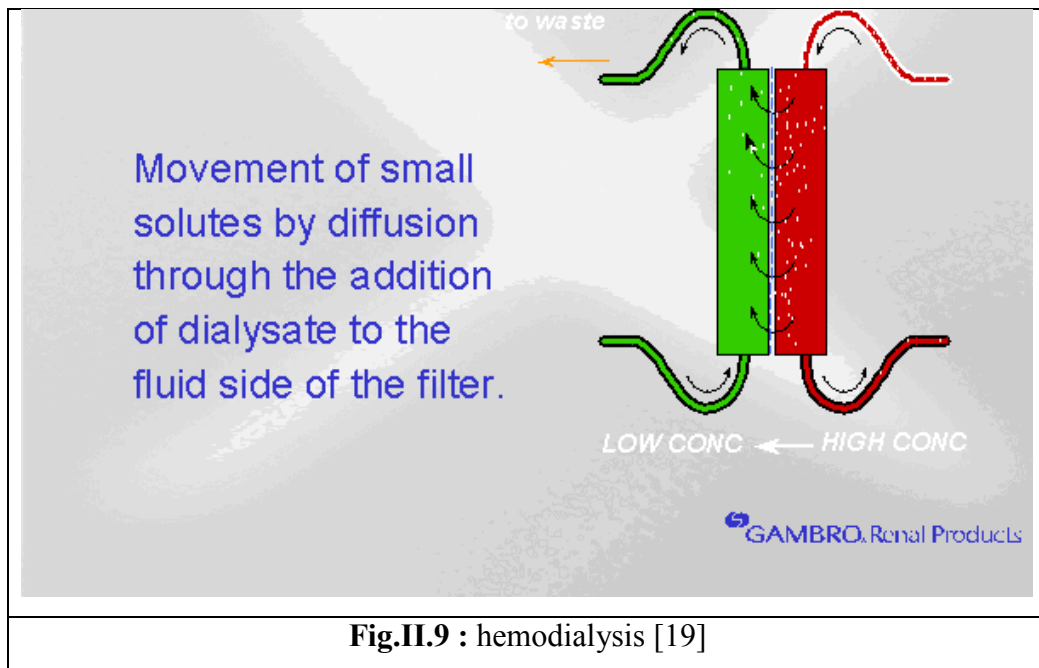
creatinine, potassium concentrations in the dialysate often require upward adjustment as the potassium level in the blood falls. Although in theory, potassium levels should not fall below 4 mmol/L in the serum if the dialysate contains 4 mmol/L, a number of factors influence serum potassium levels in critical care. Insulin therapy and the use of sympathomimetic drugs promotes the movement of potassium from the blood into the cells. This can lower serum levels. Additionally, potassium loss through the GI tract can increase the potential for hypokalemia. Low magnesium levels will also suppress the serum potassium levels, therefore, magnesium deficits should be replaced as needed. Additionally, high hemofiltration rates can lead to additional potassium clearance. Potassium levels must be monitored closely and adjusted to maintain normal serum concentrations.

In renal failure, serum bicarbonate levels are generally low, therefore, a source of bicarbonate is added to the dialysate to facilitate diffusion of bicarbonate into the blood. Lactate based formulas provide one source (e.g., Gambro's LG formulas). Higher concentrations of lactate in the dialysate promote diffusion into the blood. If hepatic function is normal, lactate is quickly converted to bicarbonate in the liver. Prisma^(TM) and Prismaflex^(TM) both use premixed bags of sterile dialysate. Lactate based preparations have a long stability, making them less expensive to prepare. Because bicarbonate is only stable for a short period in solution, it must be added to the dialysis bags before using.

If the patient is unable to convert lactate to bicarb at a rate that is fast enough, serum lactate levels will rise. This occurs in both hepatic insufficiency and shock states were the patient already has excess lactate production due to anaerobic metabolism. In these instances, a bicarb containing product is used to deliver bicarbonate (e.g. B.O or Normocarb).

If 1 L of dialysate is administered per hour, one L of dialysate fluid will collect in the drainage collection bag per hour. This will be in addition to any fluid removed; dialysate doesn't normally cross into the bloodstream.

Concentration gradients play a major role in diffusion. These will be explored further in the discussion on clearance. The other factor that influences diffusion is the type of filter used. Diffusion of solutes cannot occur across a concentration gradient if the pore size is too small to permit passage.

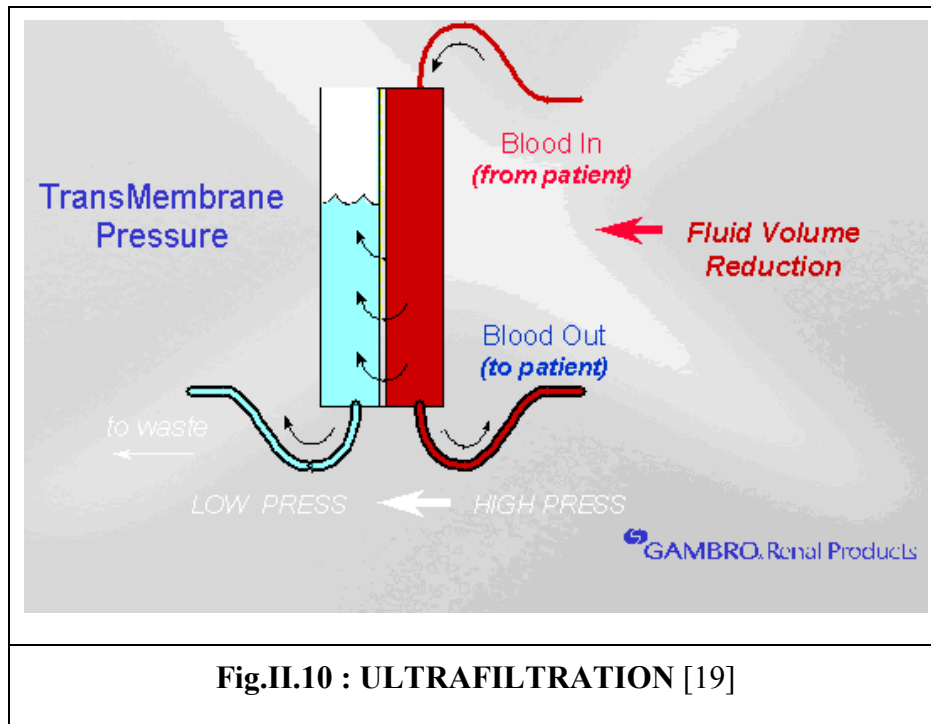


II.5.3.3 ULTRAFILTRATION: [19]

Ultrafiltration is the movement of water across a semi-permeable membrane because of a pressure gradient (hydrostatic, osmotic or oncotic). The increased blood pressure in the glomerulus creates a favorable driving pressure to force water across the glomerular membrane.

Blood pressure within the hollow fibers is positive, while the pressure outside the hollow fibers is lower. Increased negativity can be generated outside the hollow fibers by the effluent pump by either increasing the fluid removal rate, or by increasing the replacement flow rate. The difference between the blood pressure in the hollow fibers and the surrounding pressure is the Trans-Membrane Pressure (TMP). The TMP determines the ultra-filtrate production.

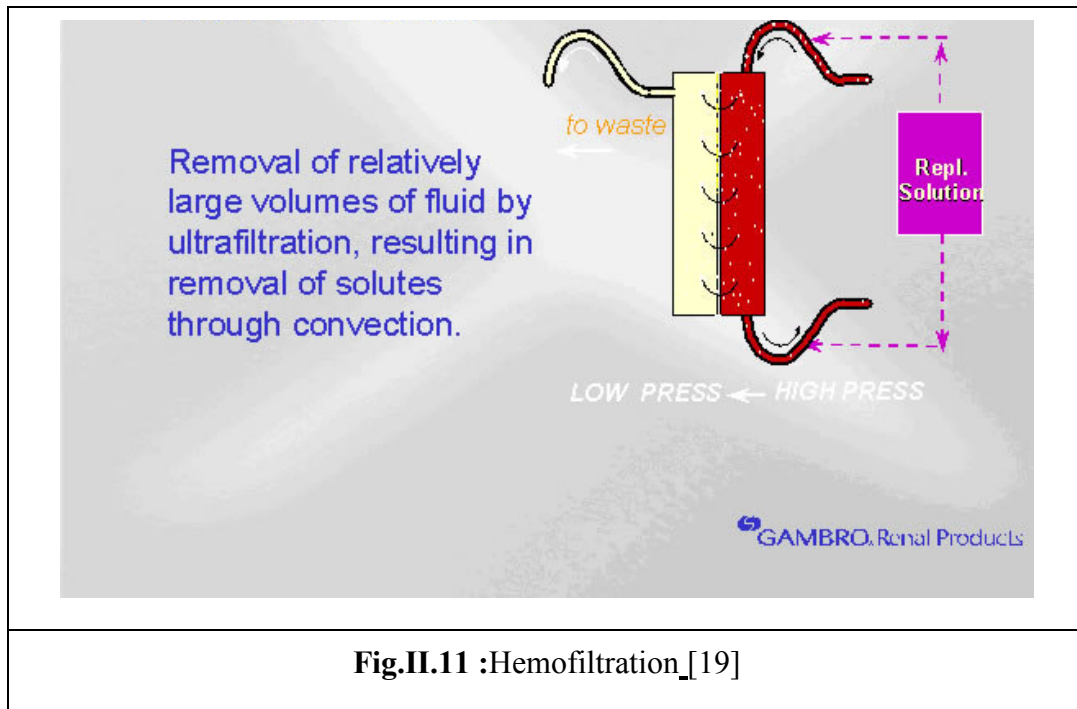
Different filter membrane properties can produce different ultrafiltration rates at a constant TMP. A filter that is more permeable to water will allow more water to travel across the membrane at a given TMP. A filter with a high permeability to water is called a high flux membrane.



II.5.3.4 HEMOFILTRATION: [19]

In haemodialysis circuits, pulling large volumes of water across the semi-permeable membrane creates a convective current that "drags" additional solutes. While diffusion is effective at removing most small molecules, convection enhances the removal of small and mid-sized molecules. Thus, convection can be added to haemodialysis therapy to enhance solute removal. To prevent hypovolemia, any water removed during hemofiltration must be returned to the blood before it reaches the patient. This is called "replacement" fluid. Hemofiltration rates of 1 L/hr mean that one litre of fluid is removed from the patient's blood and eliminated in the drainage fluid AND 1 L of replacement fluid is returned to the circuit before it reaches the patient. We set hemofiltration rates by adjusting replacement rates. Any fluid removed during hemofiltration is given back to maintain a net neutral fluid balance. Replacement fluid must be sterile intravenous fluids with concentrations of electrolytes similar to plasma.

For example, if the CRRT therapy includes a hemofiltration rate of 1 L per hour, and the fluid removal is set at 200 ml per hour, 1200 ml will be pulled from the patient and introduced into the drainage collection bag each hour. Because the 1 L of hemofiltration is replaced, the net fluid removed is 200 ml. Whether hemofiltration is used or not, the net fluid removed is equal to the fluid removal setting.



II.5.3.5 PREDILUTION VERSUS POSTDILUTION HEMOFILTRATION: [19]

Replacement fluids can be returned either pre or post filter. This is referred to as predilution or post dilution sets. Predilution means that the replacement solution is returned to the blood before it reaches the filter, diluting the blood in the hollow fibers. Postdilution means that the replacement fluid is returned to the blood after the filter (but before the return side of the access catheter). Predilution dilutes the blood in the filter, reducing clotting. Postdilution concentrates the blood in the filter, enhancing clearance.

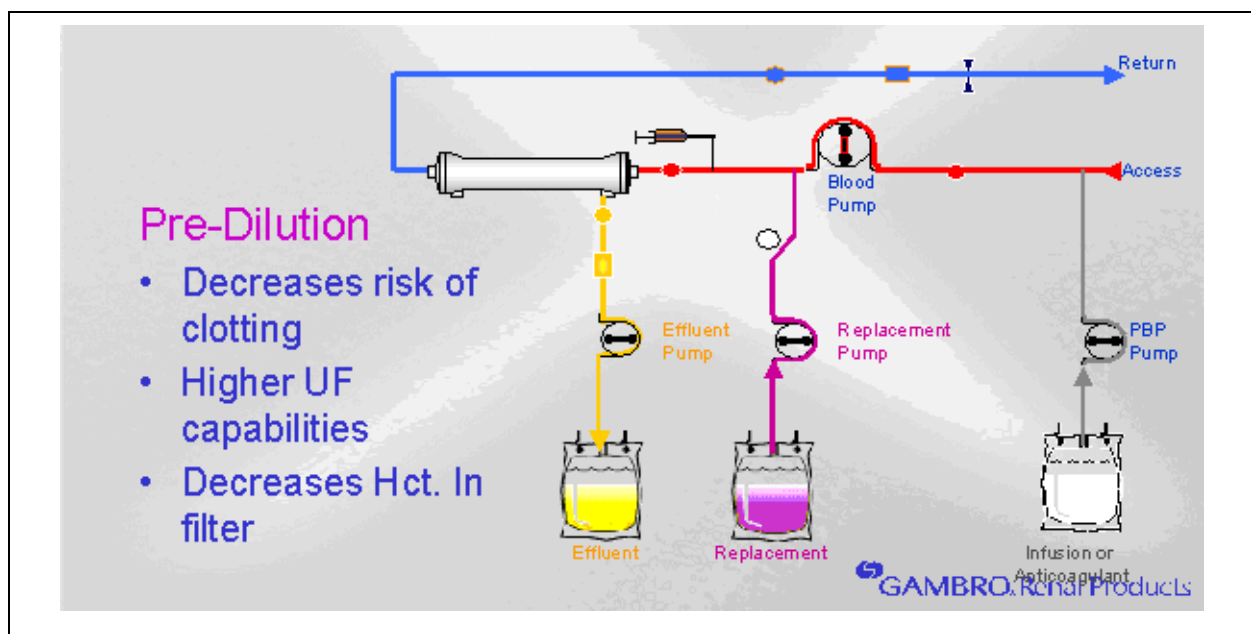
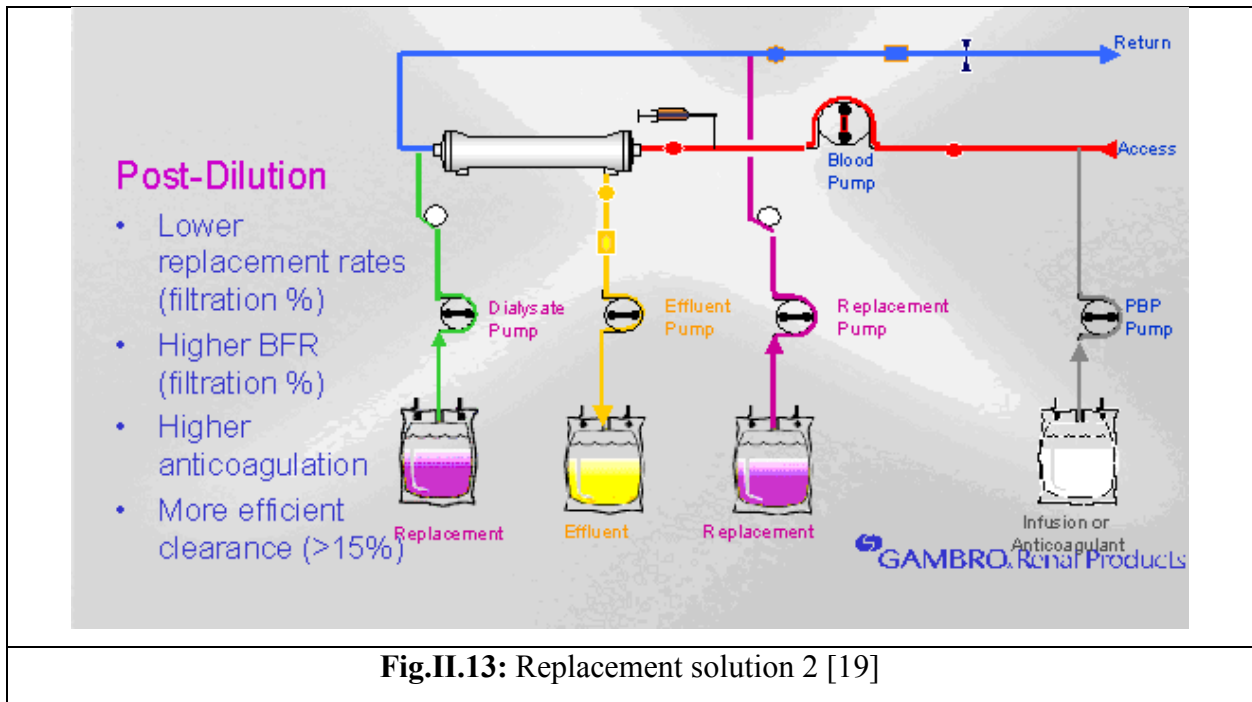


Fig.II.12 : Replacement solution 1 [19]



II.5.3.6 CLEARANCE: [19]

Creatinine is a by-product of muscle protein metabolism that is completely filtered by the glomerulus and 100% eliminated. None of the filtered creatinine is reabsorbed from the tubules nor is any additional creatinine secreted into the tubule lumen post glomerulus. This makes it the best indicator of renal failure. Because it is completely eliminated during normal renal function, measurement of creatinine clearance is the best measure of glomerular filtration.

Urea is another by-product of protein metabolism, however, it is a by-product of all protein metabolism (not just muscle protein metabolism). It is filtered into the glomerular filtrate. Unlike creatinine, a percentage of filtered urea is reabsorbed from the tubules. Consequently, urea levels can become increased in the presence of a normal creatinine level. For example, urea can increase due to increased urea production (e.g., anabolic or catabolic states) or increased tubule reabsorption of urea (e.g., due to dehydration). Creatinine only increases when renal filtration decreases, or the production of creatinine becomes so high that it exceeds glomerular filtration capabilities. Excessive creatinine production can occur when significant muscle death has occurred, for example in rhabdomyolysis.

Clearance is the rate at which solutes are cleared from the body. Clearance is abbreviated by the letter **K**. The clearance (or K) of a solute is the volume of blood from which the substance is completely removed per unit time (Gambro training manual). It is calculated as follows:

$$K = \text{excretion rate of solute} / \text{blood concentration of solute} \dots \dots \dots \text{Equ.II.1}$$

To translate this to dialysis: if a dialyzer has the ability to clear 170 ml/min of urea at a blood flow rate of 200 ml/min, it means that for every 200 ml of blood that flows through the filter, 170 ml will be returned urea free. The remaining 30 ml will have the same concentration of urea as the blood entering the filter. The 200 ml of blood being returned each minute to the systemic circuit will have significantly less urea than without dialysis, but will still have to mix in with the systemic volume. Thus, blood must continually circulate through the filter before the total systemic level will begin to fall.

The following formula can be used to calculate the clearance of a solute in ml/min at the dialysis membrane. To calculate the rate of clearance of a solute, the following formula can be used, where Q(blood)in is the flow of blood into the filter, Q(blood)out is the flow of blood out of the filter, C(blood)in is the concentration of the solute in the pre-filter serum and C(blood) is the concentration of the solute in the post filter blood. Q(blood)in and Q(blood)out are the same and equal to the blood flow rate.

$$K = \frac{Q(\text{blood})_{in} \times C(\text{blood})_{in} - Q(\text{blood})_{out} \times C(\text{blood})_{out}}{C(\text{blood})_{in}} \text{ ml/min} \dots \text{Equ.II.2}$$

This can be simplified to:

$$K = \frac{Q(\text{blood})_{in} \times (C(\text{blood})_{in} - C(\text{blood})_{out})}{C(\text{blood})_{in}} \text{ ml/min} \dots \text{Equ.II.3}$$

II.6 different types of generator haemodialysis:

- **Hemodialysis machine (with hemodiafiltration) Landwind Medical JH-2000** [20]



Fig.II.14: Hemodialysis machine (with hemodiafiltration) Landwind Medical JH-2000

Characteristics of the generator	
<p>Main technical parameter</p> <ul style="list-style-type: none"> • Volume (length x width x height) 310mm x 340mm x 1570mm . Weight: about 90kg Power supply voltage: AC220V±10% Frequency: 50HZ — 60 HZ Power: 1500W • Blood pump/spare pump: Flux 15'—340ml/min (06mm) 20-460ml/min (P8mm) • Heparin pump: Flux: 0.1ml/h 10ml/h(±5%) Precise: 0.1ml/h Injector size: 20ml/30ml/50ml 10ml/20ml/30ml(selectable) • Arterial pressure: display scope: -300mmHg +300mmHg (±10mmHg) . Venous pressure: display scope: -50mmHg--+300mmHg (±10mm Hg) 	<ul style="list-style-type: none"> • Dialysate flow: 300ml/min -800ml/min linearity adjustable (+ 10%) (-5%) Temperature: 35.0C--39.0°C Resolving rate: 0.1°C Conductivity: 13mS/cm-15.5mS/cm (±0.1 mS/cm) • Heating board temperature for substitution liquid: controlling scope: 35t —39t(±0.5C) • UF flow scope: 0—1800ml/h(±30ml/h) 0 --4000ml/h(optional) • ISO UF flow scope: 0 -2000ml/h(±30l/h) • TMP: Scope: -100mm Hg ‘—+600mmH(±20mmHg) Blood leakage monitor: over 1ml blood per liter dialysate(flow: 500ml/min) ‘ Blood level monitor: ultrasonic sensor ‘ Air bubble monitor: Infrared and response threshold value: Single air bubble of 200 μl exists when blood flux 's 200ml/min . Inflow pressure: 0 MPa-0.6MPa ‘ Inflow temperature: 5°C ‘—30 °C . Environment temperature: 10°C —30°C, Relative humidity ≤ 70% • Rinse/disinfection: chemical disinfection(citric acid, peracetic acid and oxalic acid) • Hot rinse: 80 °C ‘ Back-up power supply: last for 15-30 min after electric-cut.(optional)

- **Générateur d'hémodialyse Weilisheng Biotech W-T2008-B** [21]



Fig.II.15: Hemodialysis machine Weilisheng Biotech W-T2008-B

Characteristics of the generator	
<p>Introduction</p> <p>Size & Weight Size: 380mm×400mm×1380mm (L*W*H)</p> <p>Area: 500*520 mm</p> <p>Weight: 88KG</p> <p>Power Supply AC220V, 50Hz / 60Hz, 10A</p> <p>Input power: 1500W</p> <p>Back-up battery: 30 minutes (optional)</p> <p>Water input pressure: 0.15 MPa ~ 0.6 MPa 21.75 P.S.I. ~ 87 P.S.I.</p> <p>Water input temperature: 10°C ~ 30°C</p> <p>Working environment: temperature 10°C ~ 30°C</p>	<p>Heparin Pump</p> <p>Syringe size: 20, 30, 50 ml</p> <p>Flow range: 0 ml/h ~ 10 ml/h</p> <p>Resolution ratio: 0.1ml</p> <p>Precision: ±5%</p> <p>Sanitize</p> <p>1.Hot decalcification :</p> <p>Time: about 20 minutes</p> <p>Temperature: 30~60°C, 500ml/min.</p> <p>2.Chemical disinfection :</p> <p>Time: about 45 minutes</p>

<p>at relative humidity of no more than 70%.</p> <p>Dialysate</p> <p>Dialysate temperature: preset range 34.0°C ~ 39.0°C</p> <p>Dialysate flux: 300~800 ml/min</p> <p>Dialysate concentration: 12.1 mS/cm ~ 16.0 mS/cm, ±0.1 mS/cm</p> <p>Dialysate mixing ratio: can set variety ratio.</p> <p>UF rate Flow range: 0 ml/h ~ 4000 ml/h</p> <p>Resolution ratio: 1ml</p> <p>Precision: ±30 ml/h</p> <p>Extracorporeal Part</p> <p>Venous pressure: -180 mmHg ~ +600 mmHg, ±10 mmHg</p> <p>Arterial pressure : -380 mmHg ~ +400 mmHg, ±10 mmHg</p> <p>TMP pressure : -180 mmHg ~ +600 mmHg, ±20 mmHg</p> <p>Blood pump flow range: 20 ml/min ~ 400 ml/min (diameter:Φ6 mm)</p> <p>Spare pump flow range: 30 ml/min ~ 600 ml/min (diameter:Φ8 mm)</p> <p>Resolution ratio: 1 ml</p> <p>Precision: error range ±10ml or 10% of reading</p>	<p>Temperature: 30~40°C, 500ml/min.</p> <p>3. Heat disinfection :</p> <p>Time: about 60 minutes</p> <p>Temperature: >85°C, 300ml/min.</p> <p>Storage Environment Storage temperature should be between 5°C ~ 40°C, at relative humidity of no more than 80%.</p> <p>Monitoring System</p> <p>Dialysate temperature: preset range 34.0°C ~ 39.0°C, ±0.5°C</p> <p>Blood leak detection: Photochromic Alarm when erythrocyte specific volume is 0.32±0.02 or blood leak volume is equal or more than 1ml per liter of dialysate</p> <p>Bubble detection: ultrasonic Alarm when a single air bubble volume is more than 200µl at 200ml/min blood flow</p> <p>Conductivity: acoustic-optic, ±0.5%</p>
--	---

II.7 Conclusion:

Dialysis is of great importance too, is the most important treatment for kidney disease, without which accumulate large amounts of toxins and harmful substances in the human body, leading to causing the deaths of large numbers of people, the components of this device is strange that performs the function of a large very much like a normal kidney, However, it is inadequate and has a lot of defects, such as slow and the amount of material waste it, which leads

to many diseases as well as high costs, every part of it has special requirements and special conditions for operation.

CHAPTER (III): APPLICATION

III.1 Introduction :

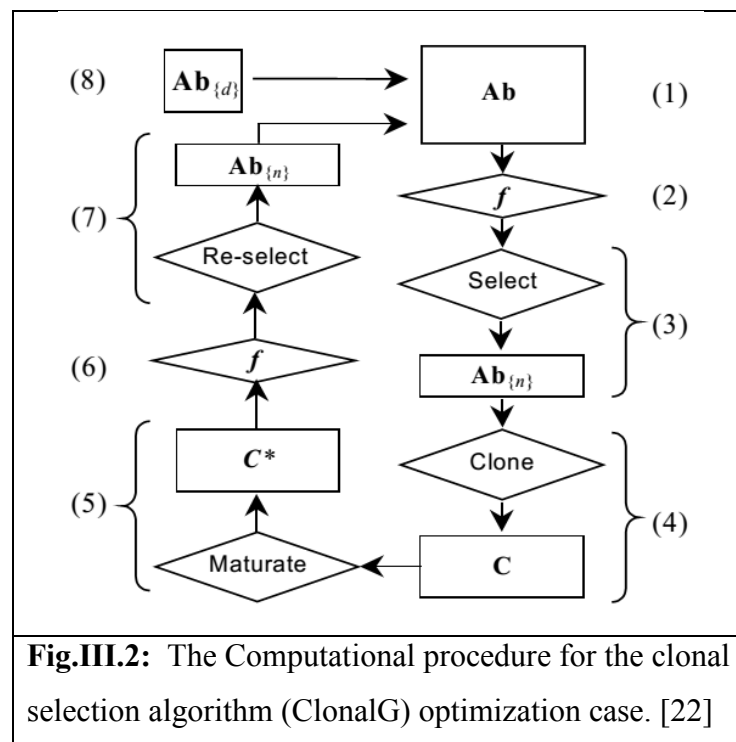
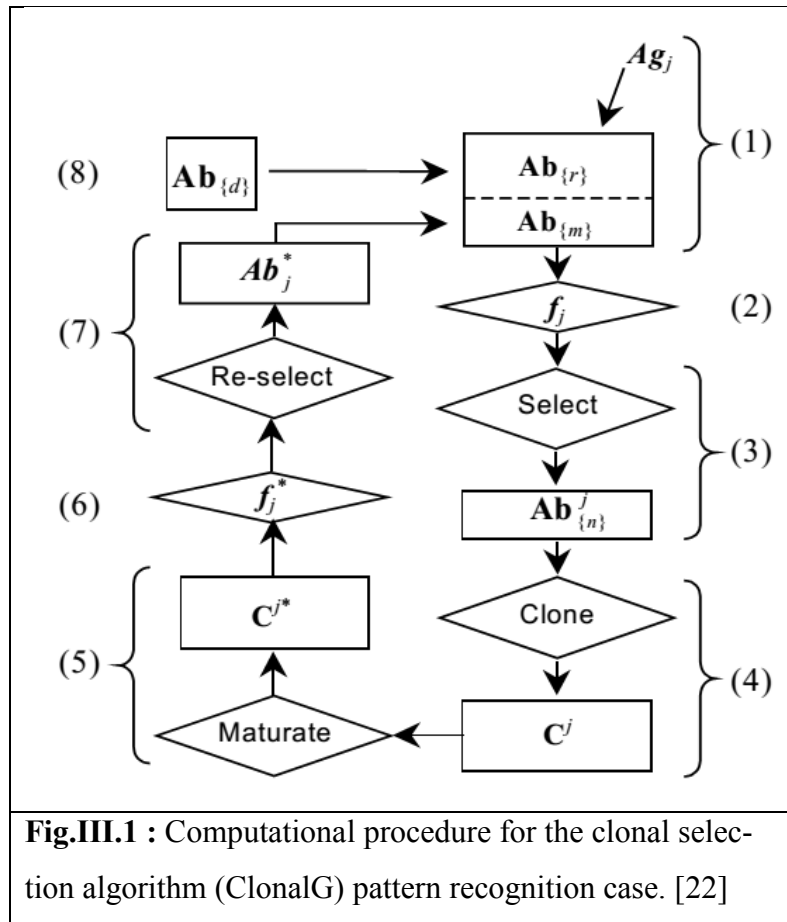
In the field of artificial intelligence was developed algorithms inspired by the many natural phenomena, and was among these algorithms immune system artificial which is one of the most important algorithms which has the ability to improvement in many areas, has been suggested by programming and simulations using MATLAB, to simulations to improve conductivity in ultrafiltration in a dialysis machine. All of which we'll cover in this chapter.

III.2 Optimisation by Immune Algorithm :

In artificial immune systems, clonal selection algorithms are a class of algorithms inspired by the clonal selection theory of acquired immunity, which explains how to improve the B-lymphocytes and T response to antigens over time is called affinity maturation. These algorithms focus on the attributes of Darwinian Theory, where the selection is inspired by the affinity of antigen-antibody reactions, inspired reproduction through cell division, and is inspired by somatic hyper-mutation difference. Is applied to clonal selection algorithms to improve the most common and pattern recognition areas.

The scientists (de Castro and Von Zuben) exploiting choose clonal and studied, and They convert it to an algorithm CLONALG: (The CLONal selection ALGORITHM), and can provide us with many ways and new in solving a lot of problems in many areas , and involves finding optimal solutions either at the peak or in the pelvis in several jobs interspersed with restrictions.

We have to apply this algorithm in MATLAB software, which is one of the best platforms of scientific programming in the world, has given us our good results in our tests.



The algorithm begins with the generation of an antibodies population. Each antibody corresponds to a candidate solution:

1. A set of antigens Ag is presented to the antibodies population Ab;
2. The affinity measure f of the antibodies in relation to the antigens is calculated;
3. The n highest affinity antibodies to the antigens are selected to be cloned, generating the antibody subset Ab_{n} ;
4. The antibodies selected will be cloned according to their affinity to the antigens (as higher the affinity more clones it will generate) by using Equation Equ.III.1, producing a C clones population;

$$numClones = round\left(\frac{\beta \cdot n}{i}\right) \dots \dots \dots \text{Equ.III.1}$$

β : is a clonal multiplication factor.

n: is the total amount of antibody.

i: is the antibody current ranking based on its affinity .

5. The C clones population is subjected to an affinity maturation process at an inversely proportional rate to the affinity of the clone (as higher the affinity, lower the mutation rate), by using Equation Equ.III.2, and a new population of clones C*is produced;

$$p = \left(\frac{1}{\rho}\right) \cdot \exp(-f) \dots \dots \dots \text{Equ.III.2}$$

ρ : is a parameter of the algorithm that defines the mutation rate of an antibody.

f: is the normalized affinity function of the antibody to the antigen.

6. The C*clones population is evaluated and its affinity measure f* in relation to the antigens is calculated;
7. The n matured antibodies of the highest affinity are selected to compose the next population generation, since its affinity is greater than its original antibodies;
8. The d worst antibodies are removed from the population and replaced by new randomly generated antibodies.

This process repeats until a stop condition (numbered generations) is reached.

MATLAB program:

MATLAB (matrix laboratory) is a multi-paradigm numerical computing environment and fourth-generation programming language. Developed by MathWorks, MATLAB allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs written in other languages, including C, C++, Java, and FORTRAN.

Although MATLAB is intended primarily for numerical computing, an optional toolbox uses the MuPAD symbolic engine, allowing access to symbolic computing capabilities. An

additional package, Simulink, adds graphical multi-domain simulation and Model-Based Design for dynamic and embedded systems.

In 2004, MATLAB had around one million users across industry and academia. MATLAB users come from various backgrounds of engineering, science, and economics. MATLAB is widely used in academic and research institutions as well as industrial enterprises. [23]

Specifications computer simulation:

CPU: Intel core i3-2120 3.3GHz –M.Cash :3 Mb

RAM: 8 GO – 1600 MHz

GPU: NVIDIA GTX 650 Ti - 1 GO – CUDA.CORE:736

MATLAB R2012b 64bit

Microsoft Windows 7 64bit

Perform MATLAB Computations on CUDA GPUs

Using MATLAB for GPU computing lets you accelerate your applications with GPUs more easily than by using C or Fortran. With the familiar MATLAB language you can take advantage of the CUDA GPU computing technology without having to learn the intricacies of GPU architectures or low-level GPU computing libraries. [24]

III.3 Consider a simple function of experience:

After we finished converting artificial immune system algorithm (ClonalG) program in MATLAB software, we employ a number of optimization functions known to the workers in the field of scientific research. We use it to determine the validity of the results when we use them is true or not.

III.3.1 Maximization function test:

III.3.1.a Function: $f(x)=15*x-x^2$

X	F(X)
1	14
2	26
3	36
4	44
5	50
6	54
7	56
8	56
9	54
10	50
11	44
12	36
13	26
14	14
15	0

Fig.III.3 : The result of calculating the function F(X) in Microsoft excel

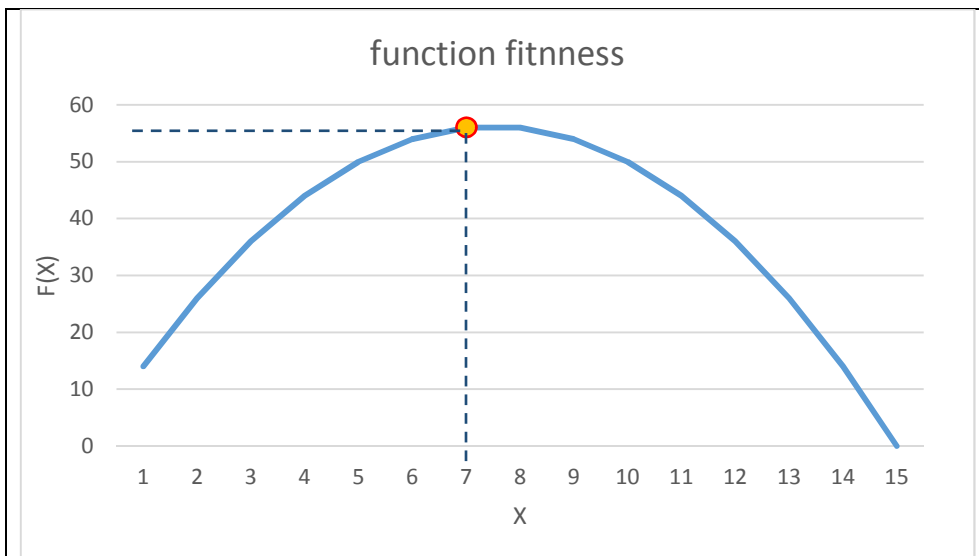


Fig.III.4 :Trace function F(X) in Microsoft excel

III.3.1.b Testing function F(X) in MATLAB:

The size of the initial Random population = 50, and repetition cycle number =50

And the clonal multiplication factor = 20.

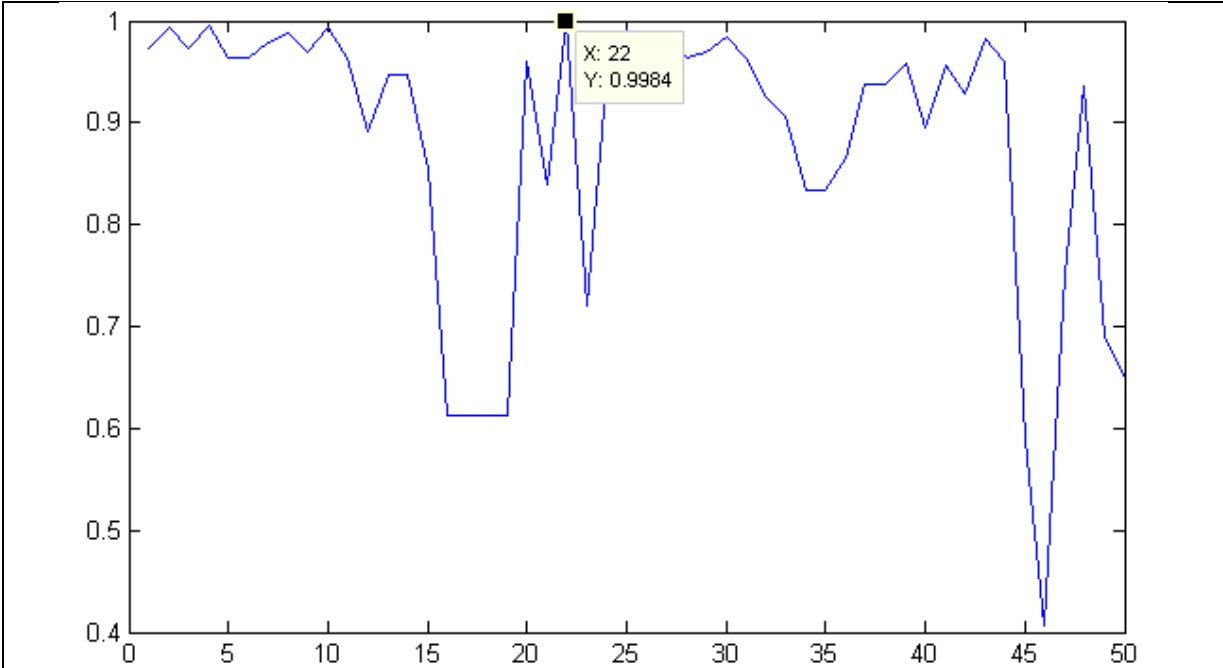


Fig.III.5: Trace the global-best solutions and best the global-best for F(X) in MATLAB

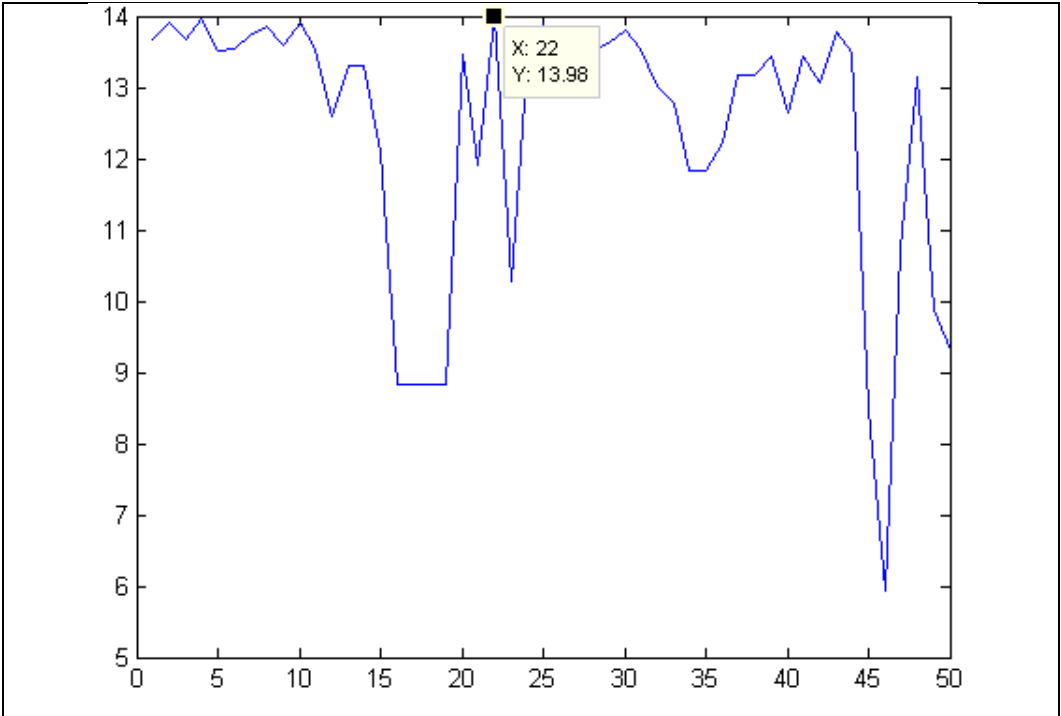


Fig.III.6: Trace the Bests solutions and Best the Best for F(X) in MATLAB

```

0.6482

GlobalMBest =

0.9984

fFGlobF =

13.9789
    
```

Fig.III.7: global-best and best solution for F(X) in MATLAB

Notes:

According to the results shown. We find that the program runs well as giving value sizes by the function F (X). Good results.

III.3.2 Minimization function test:

III.3.2.a Alpine Function test:

$f_{Alpine}(x) = \sum_{i=1}^n |x_i \sin(x_i) + 0.1x_i|$ Equ.III.3
 Minimum global: $f(x^*) = 0$, at $x^* = (0, \dots, 0)$

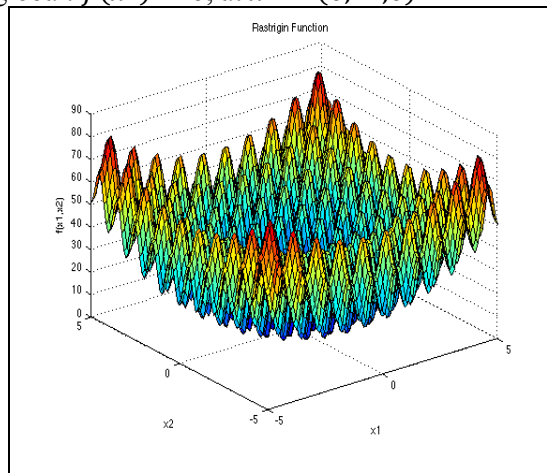


Fig.III.8 : Alpine function

X	F(X)
1	0,941470985
2	2,018594854
3	0,723360024
4	2,627209981
5	4,294621373
6	1,076492989
7	5,298906191
8	8,714865973
9	4,609066367
10	4,440211109
11	9,899892272
12	5,238875016
13	6,762171479
14	15,26850298
15	11,2543176
16	3,006453067
17	14,64375736
18	11,71777044
19	4,747666984
20	20,25890501

Fig.III.9: The result of calculating the function Alpine in Microsoft excel

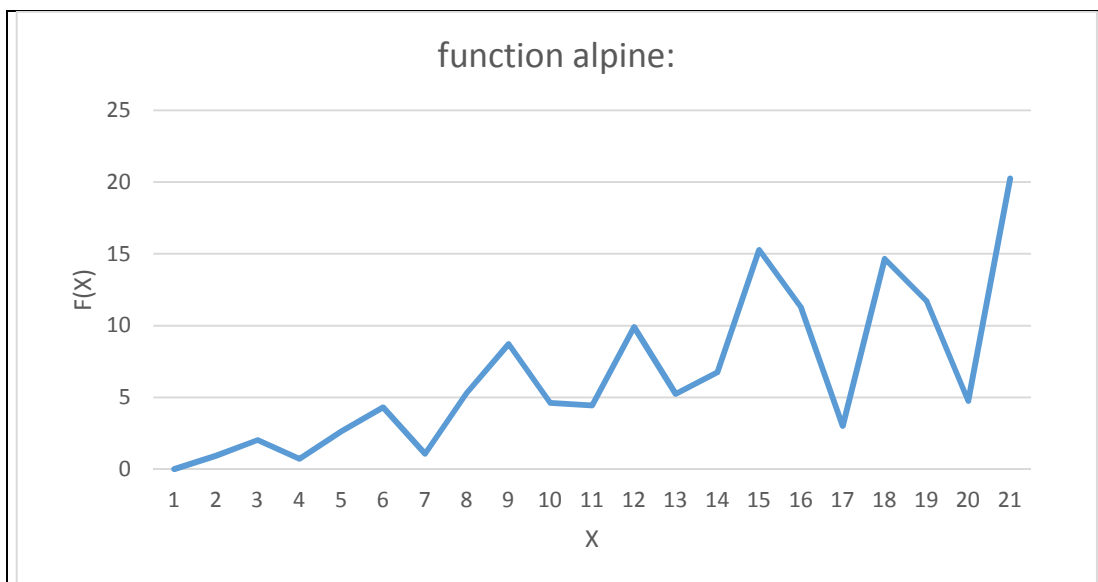


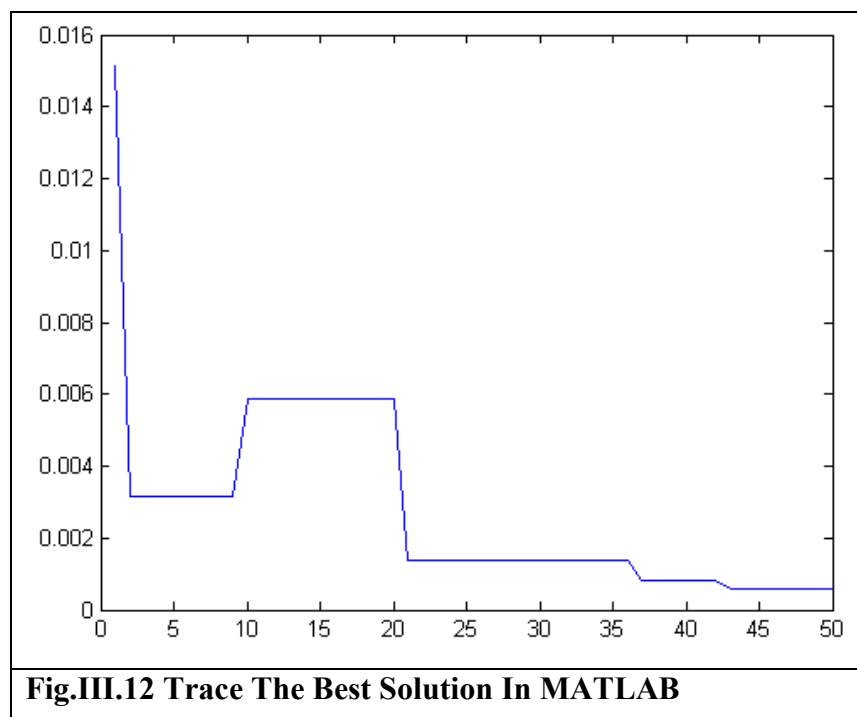
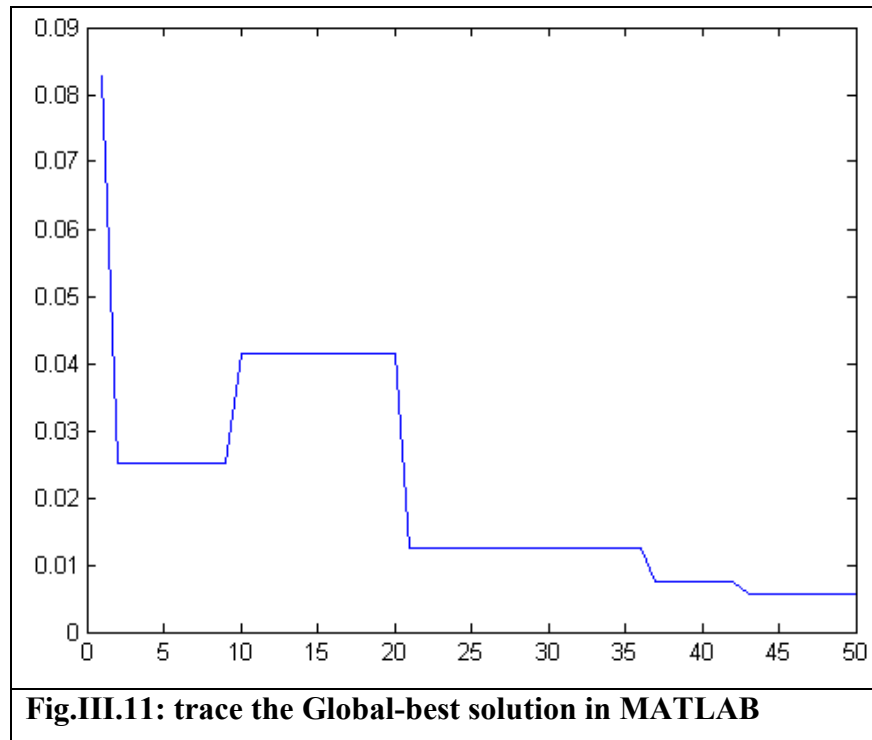
Fig.III.10: Trace function Alpine in Microsoft excel

Testing Alpine function in MATLAB:

Dimension number =1:

The number population initial Random = 50, and repetition cycle number =50

And the clonal multiplication factor = 20.



```

0.0057

GlobalMBest =

0.0057

fFGlobF =

6.0731e-04

fx >>
    
```

Fig.III.13 : global-best and best solution for Alpine in MATLAB

III.3.2.b Rastrigin Function test:

Rastrigin : $f(x) = 10d + \sum_{i=1}^d [x_i^2 - 10 \cos(2\pi x_i)]$Equ.III.4

Minimum global: $f(x^*) = 0$, at $x^* = (0, \dots, 0)$

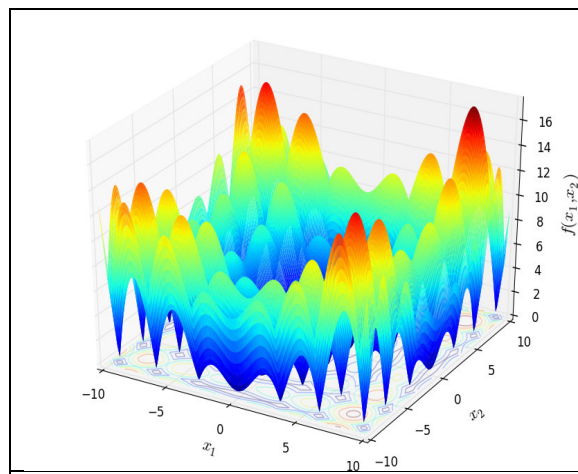


Fig.III.14: Rastrigin

X	F(X)
0	0
1	50
2	200
3	450
4	800
5	1250
6	1800
7	2450
8	3200
9	4050
10	5000
11	6050
12	7200
13	8450
14	9800
15	11250

Fig.III.15: The result of calculating the function Rastrigin in Microsoft excel

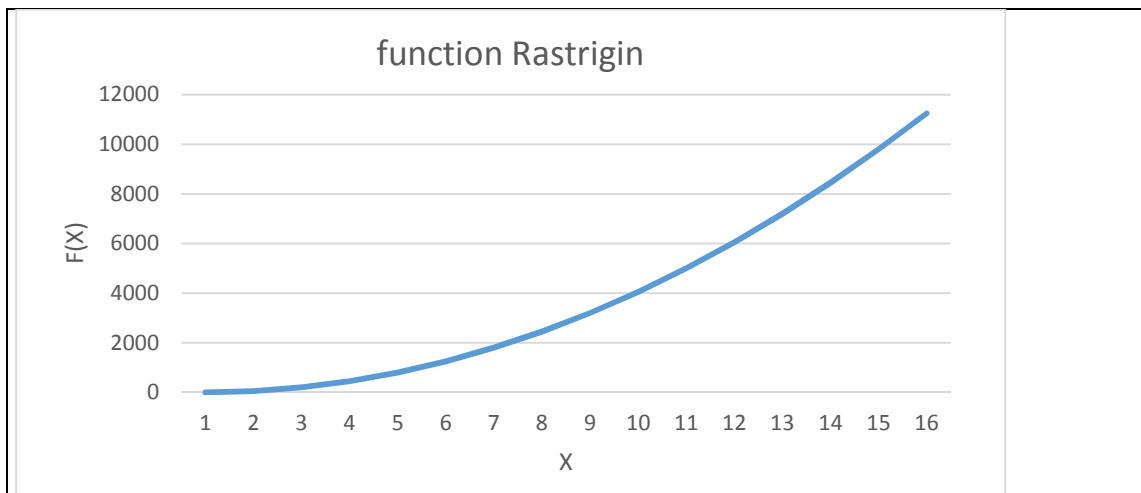


Fig.III.16:Trace the result of calculating the function Rastrigin in Microsoft excel

Testing Rastrigin function in MATLAB:

Dimension number =3:

The number population initial Random = 50, and repetition cycle number =50
 And the clonal multiplication factor = 20.

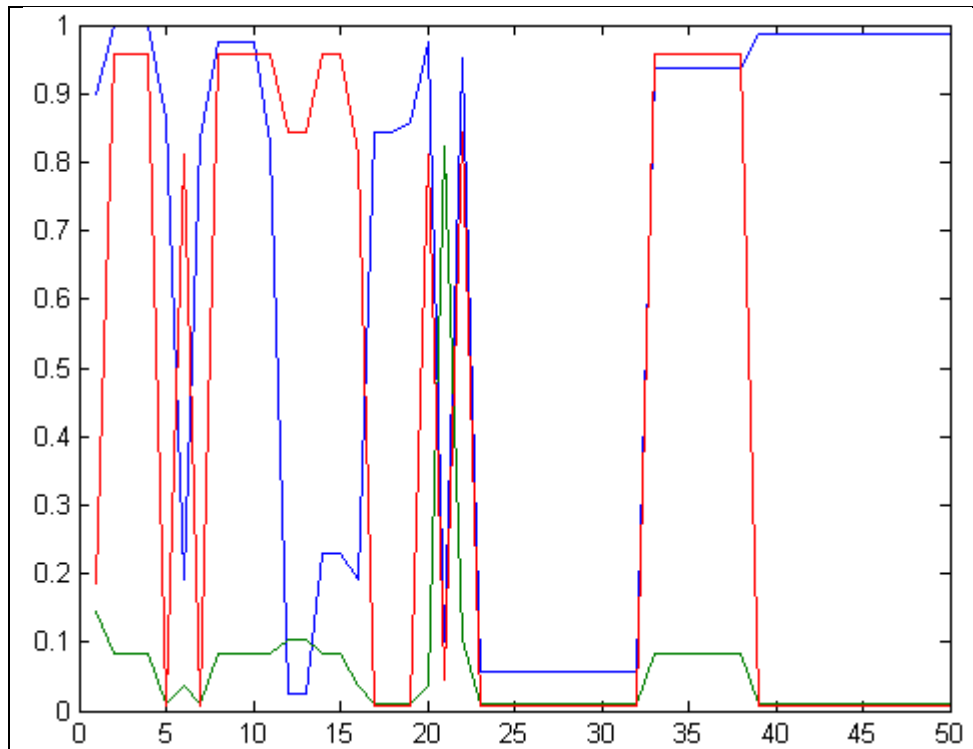


Fig.III.17: trace the Global-best solution for Rastrigin in MATLAB

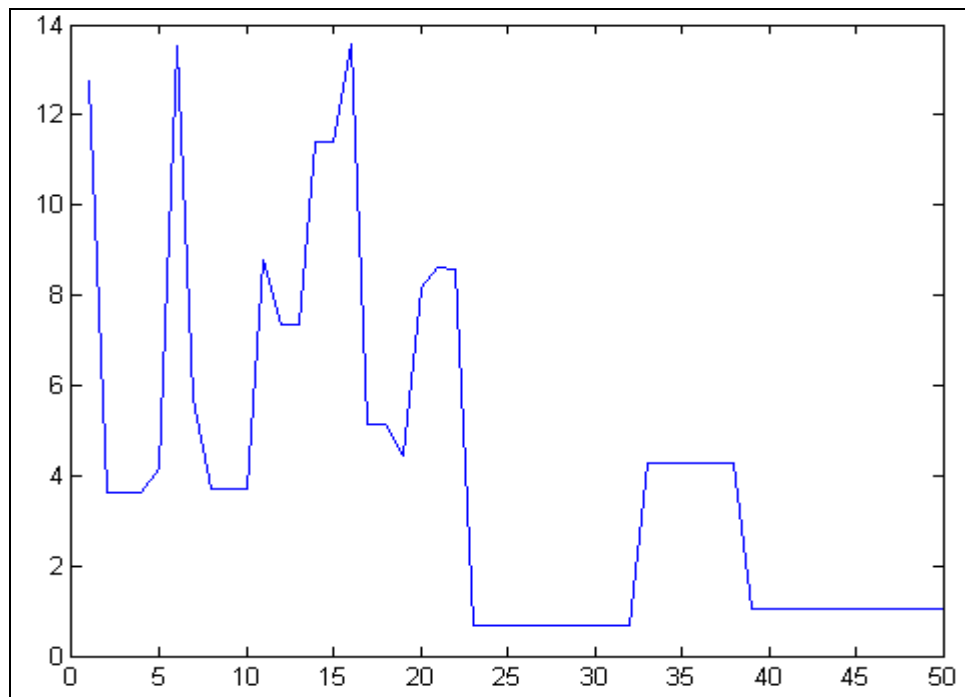
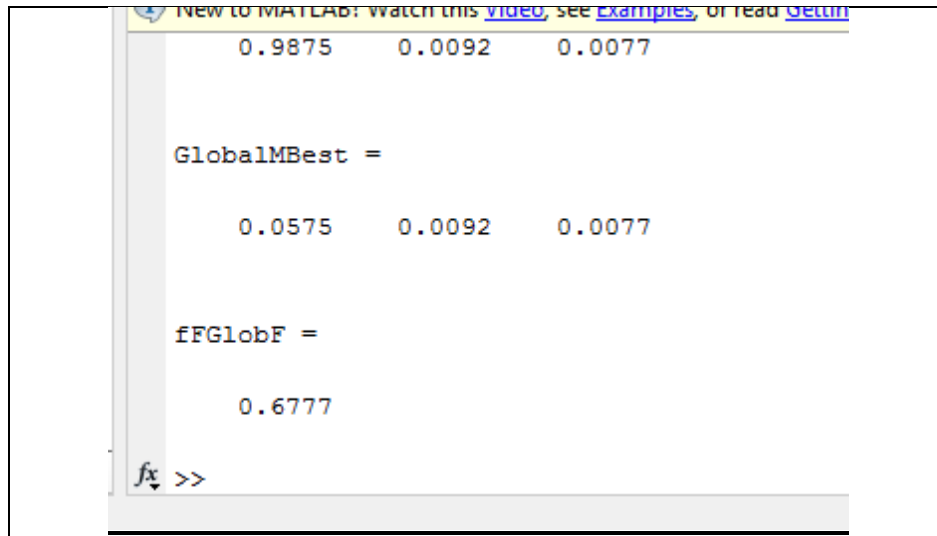


Fig.III.18: trace the best solution for Rastrigin in MATLAB



```

0.9875    0.0092    0.0077

GlobalMBest =

    0.0575    0.0092    0.0077

fFGlobF =

    0.6777

fx >>

```

Fig.III.19: best and global best solution for Rastrigin in MATLAB

NOTES:

For the Fig.III.15 ;Fig.III.7; Fig.III.21 Good results in terms of values that are similar to the results of the values and functions give the values of major and minor according to the function of each figure.

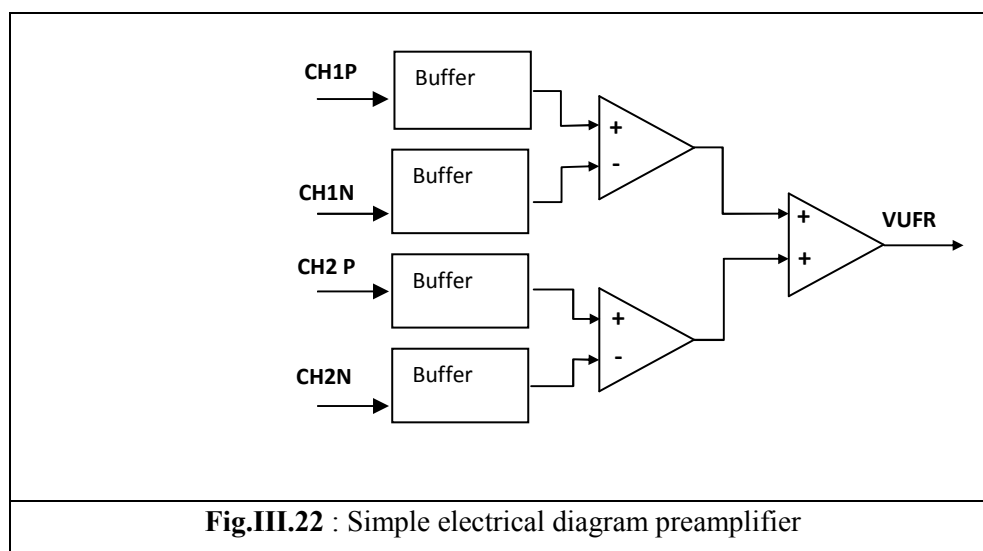
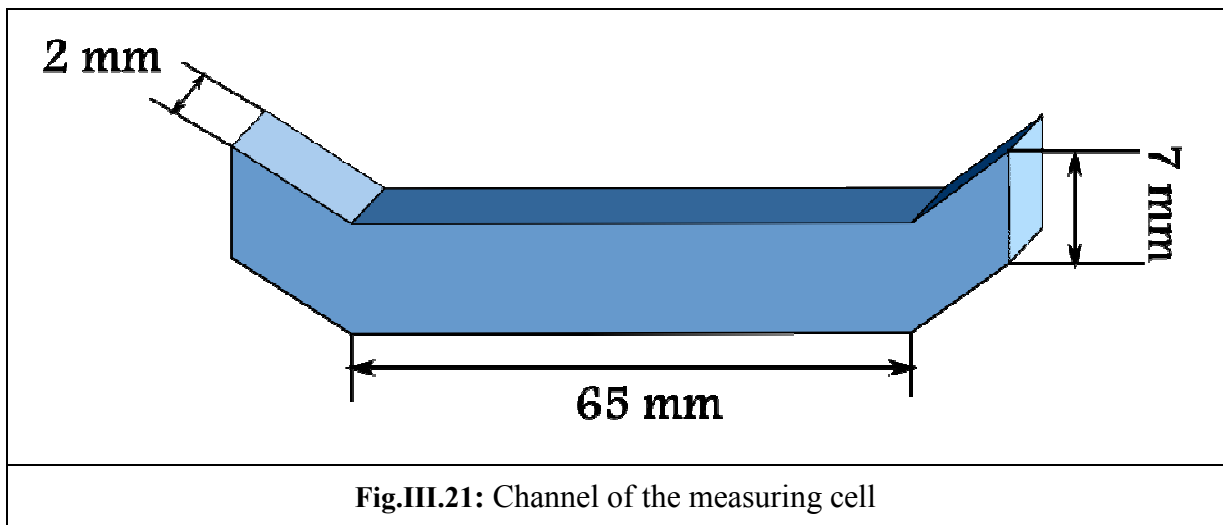
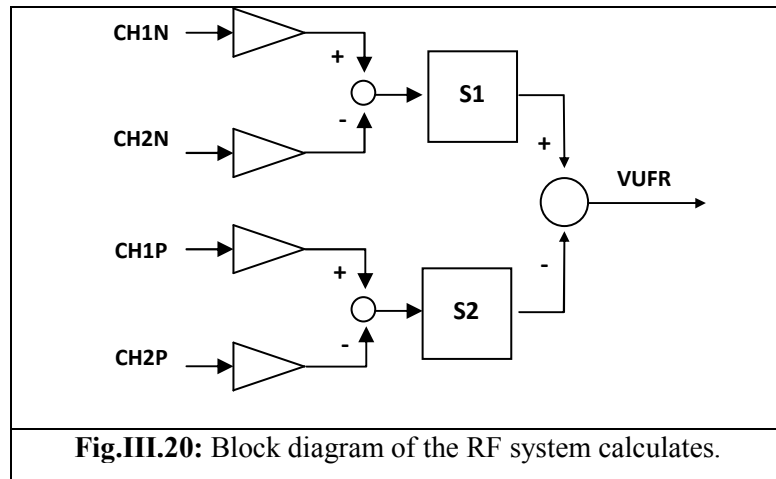
III.4 The Ultrafiltration module (FCM):**III.4.1 The module definition:**

This module is a module mainly calculated. He is responsible for determining UF rate and pressure transmembrane resultant against current starting in the capillary between blood and dialysate.

With a measurement cell attacked by an electromagnetic field arises a potential difference in the two channels of the cell and the difference between these two potentials we give the desired UFR, and the thus calculated is carried out. Both channels are crossed, by a dialysate and the other by the liquid leaving the capillary (carrying the liquid waste). It can be seen that there is a very close relationship between the DFM and FCM modules.

III.4.2 Modelling:

In this section, we try to simplify the representation of our system block diagrams where modelling becomes easier:



In the measuring cell, there are two channels in each channel where a potential difference is imposed by electrodes inserted in the channels. The potential difference between these two is the ultrafiltration rate (UFR) desired. For this reason the electric circuit calculates was modeled in order to introduce the desired improvements.

The electric circuit is a set of operational amplifier circuits connected in cascade. Each electrode is connected to a circuit. Electrodes have the positive voltage circuit that look like, and for those in the negative voltage.

The values of the passive circuit elements are as follows:

R=100 KΩ, R1=220 KΩ, R2=15 KΩ, R3=1 MΩ, C= 1μF, C1= 6.8μF, C2= 100pF.

Channel 1: the positive 1 circuits that constitute the channel are:

a follower, a differential amplifier respectively. The sampled area of the channel voltage VF1 is governed by the following equation:

$$VF_1(s) = \frac{0.33 s^2 + 235 s}{(1+s)(0.33 s^2 + 235 s + 44)} \cdot VCHP_1 - \frac{220 s}{(1+s)(0.33 s^2 + 235 s + 44)} \cdot VCHN_1 \dots\dots \text{Equ.III.5}$$

Where: VCHP1 VCHN1 and voltages are taken by the positive and negative electrodes.

Same for channel 2:

$$VF_2(s) = \frac{0.33 s^2 + 235 s}{(1+s)(0.33 s^2 + 235 s + 44)} \cdot VCHP_2 - \frac{220 s}{(1+s)(0.33 s^2 + 235 s + 44)} \cdot VCHN_2 \dots\dots \text{Equ.III.6}$$

For calculation of the voltage corresponding to UFR voltages VF1 and VF2, pass through another set of circuits consisting of: a non-inverting amplifier, and a differential amplifier circuit CR respectively cascaded, the voltage obtained from the equation has the following form:

$$VUFR(s) = VF_1(s) - VF_2(s) \dots\dots\dots \text{Equ.III.7}$$

System Result from MATLAB:

$$VUFR(s) = \frac{s^3 + 0.7121s^2}{s^4 + 0.7141s^3 + 0.001439s^2 + 7.388 \times 10^{-7}s + 1.33 \times 10^{-11}} \dots\dots\dots \text{Equ.III.8}$$

III.4.3 Conductivity control system from Ultrafiltration:

To monitor the conductivity of ultrafiltration we proposed the servo system shown Fig.III.25

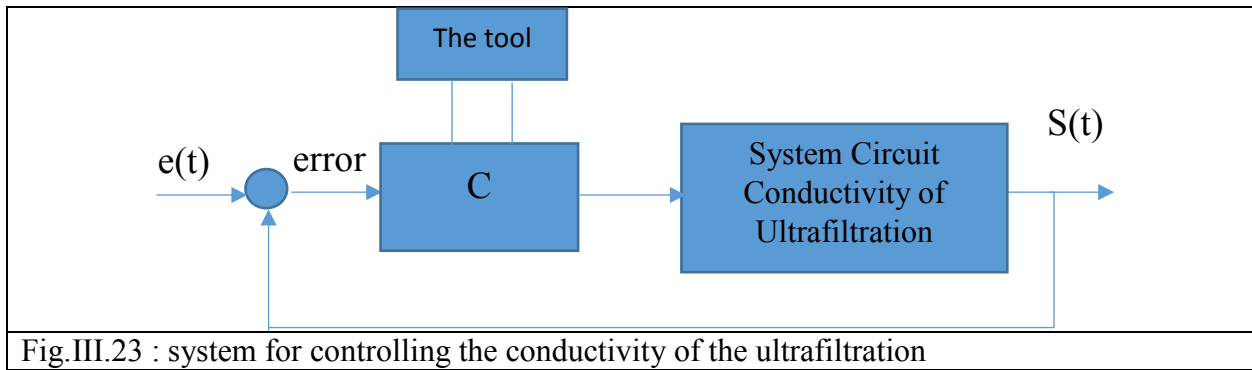


Fig.III.23 : system for controlling the conductivity of the ultrafiltration

C: PID controller we will use it to control the conductivity of ultrafiltration system

The tool (AIS) to estimate the parameters of correction.

III.5 MATLAB simulation of the control system of the conductivity of the ultrafiltration::

In this section, we simulate the system conductivity MATLAB Simulink, and we will consider four types of loops and compare the results.

III.5.1 System on open loop:

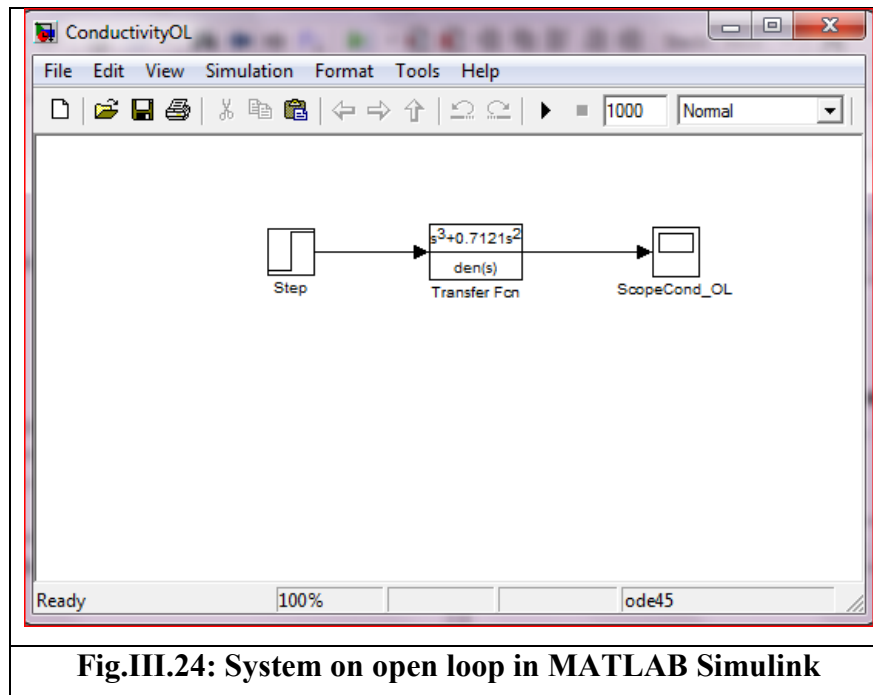


Fig.III.24: System on open loop in MATLAB Simulink

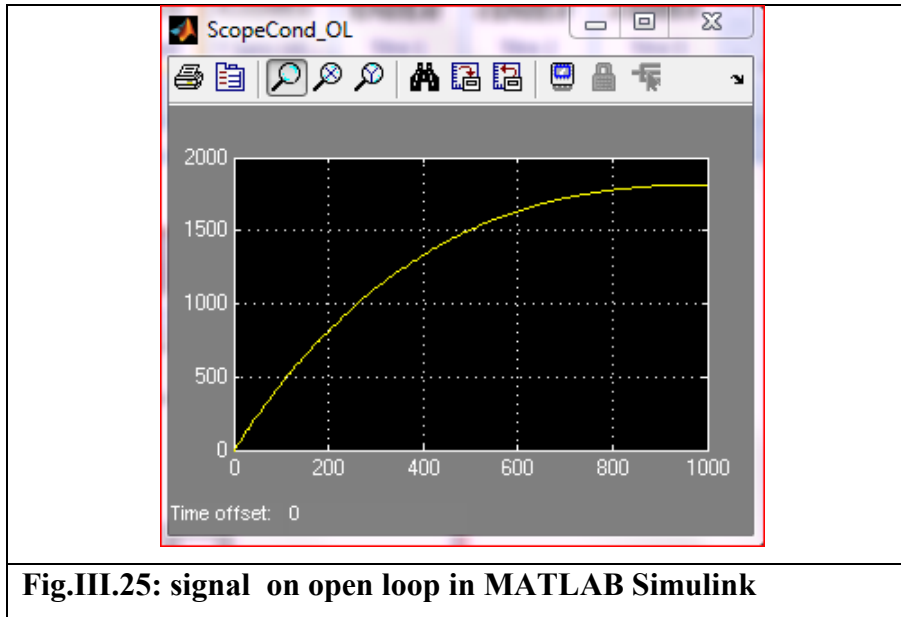


Fig.III.25: signal on open loop in MATLAB Simulink

We find that the signal taking **Fig.III.25** a great time to arrival at the desired value.

Therefore, we find that the system in this case failed to catastrophic failure because it did not meet the required expectations.

III.5.2 System on closed loop:

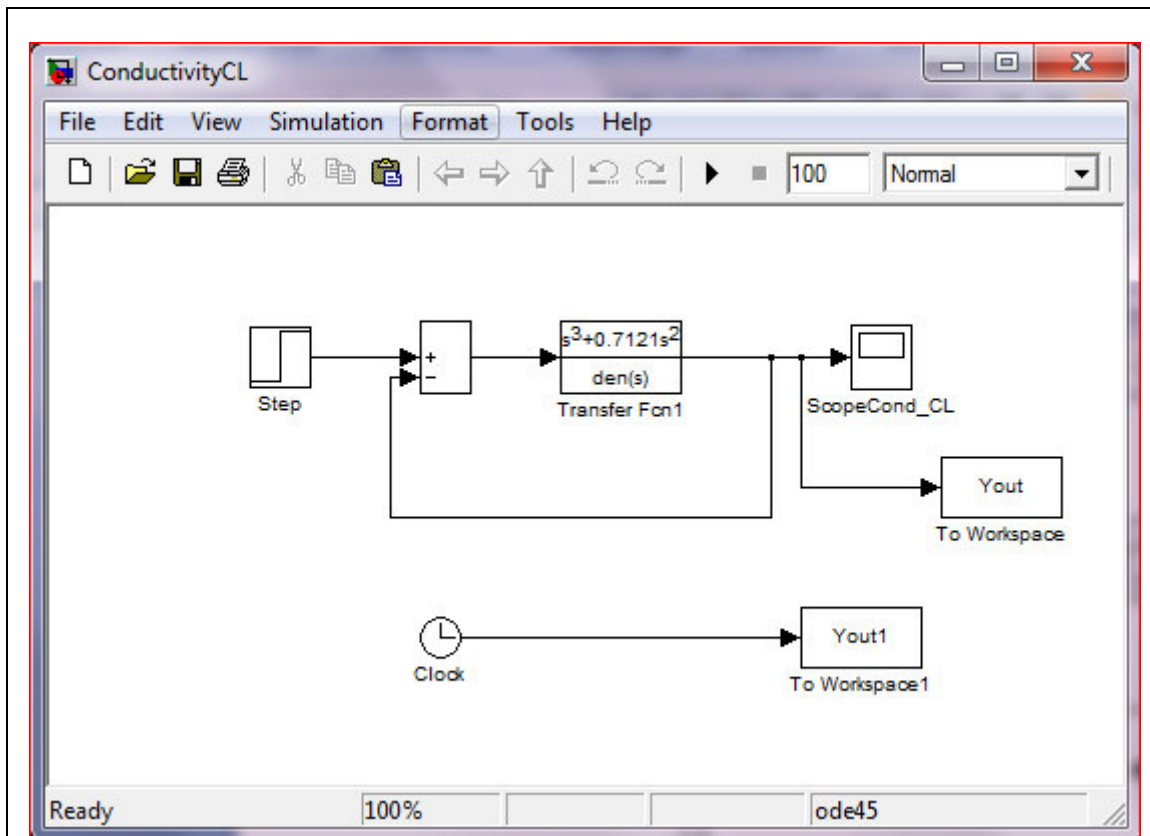


Fig.III.26: System on closed loop in MATLAB Simulink

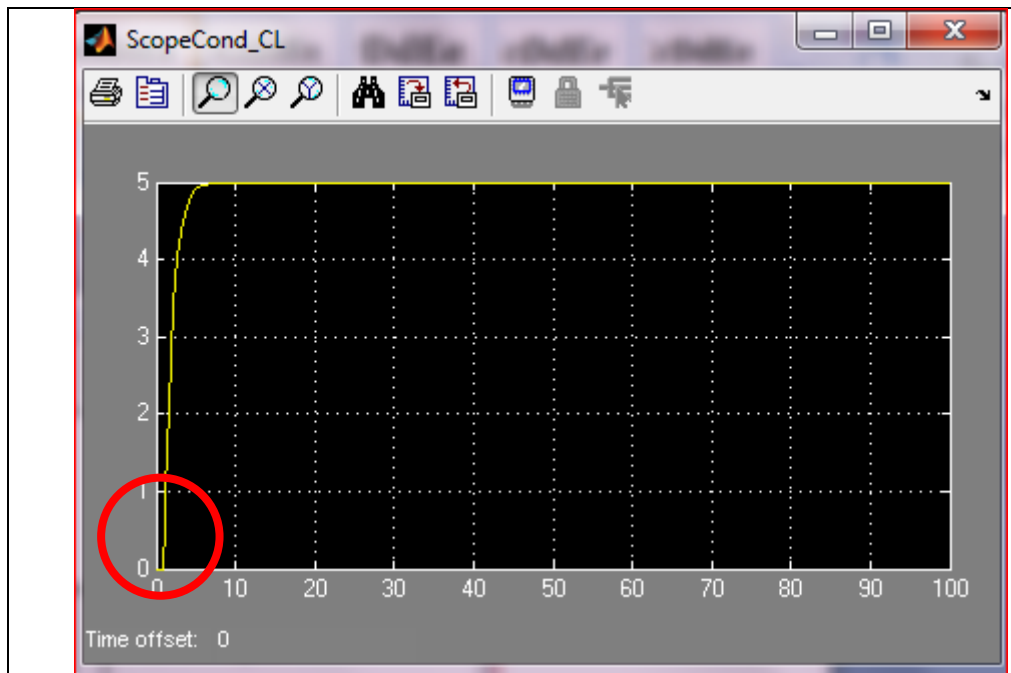


Fig.III.27: signal on closed loop in MATLAB Simulink

From Fig.III.27 we find that the response time of the signal gave a small but he came late for appearing.

III.5.3 System with proposed PID:

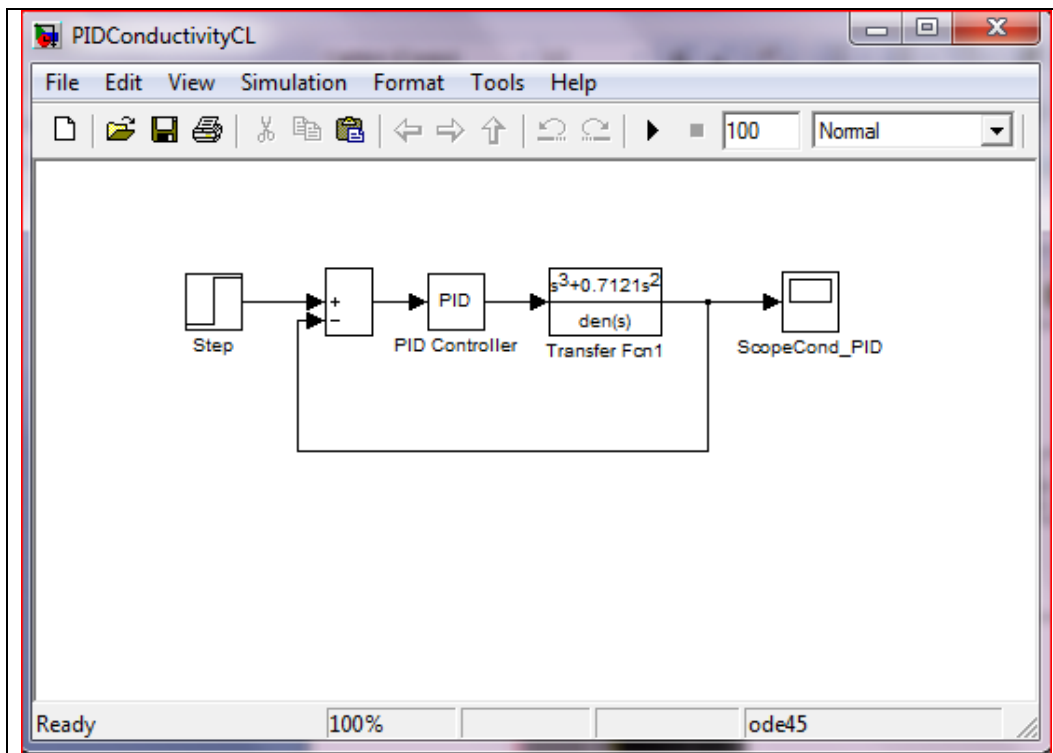


Fig.III.28: System with proposed PID in MATLAB Simulink



Fig.III.29: signal with proposed PID in MATLAB Simulink

In Fig.III.29 we find that the response time was fairly good in addition to the presence of noise and do not forget the existence of the delay in the appearance of the curve and this shows us the flaws in this case, in addition to the stability of the delayed signal.

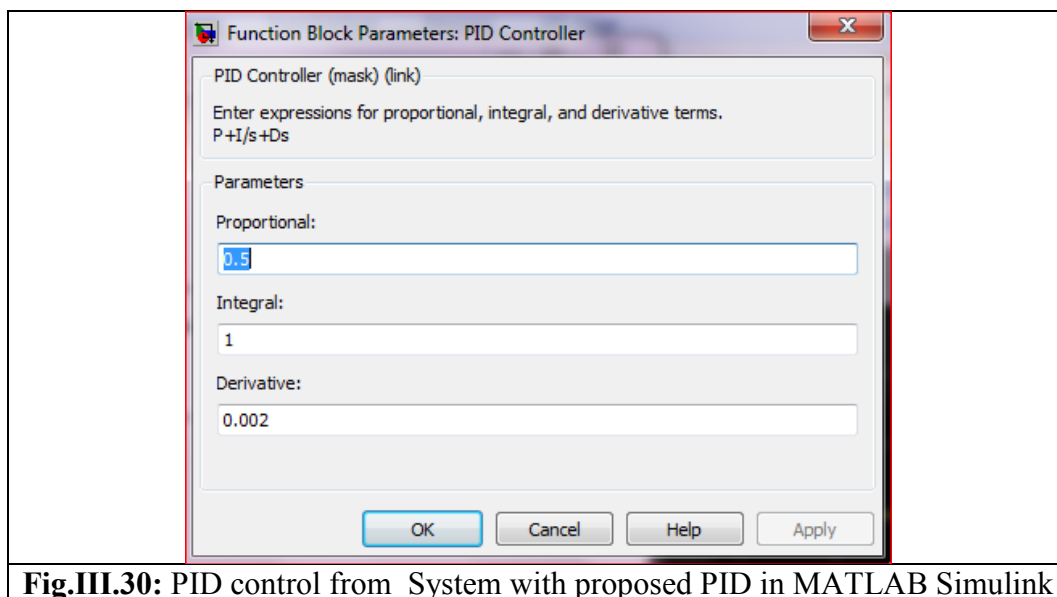


Fig.III.30: PID control from System with proposed PID in MATLAB Simulink

It also shows us **Fig.III.30** the PID values we develop every time until we find the appropriate value for the emergence of values in **Fig.III.29**

This method is useless because we will not be able to find the values at the right time always. Making it also failed.

III.5.4 System with AIS PID tuning:

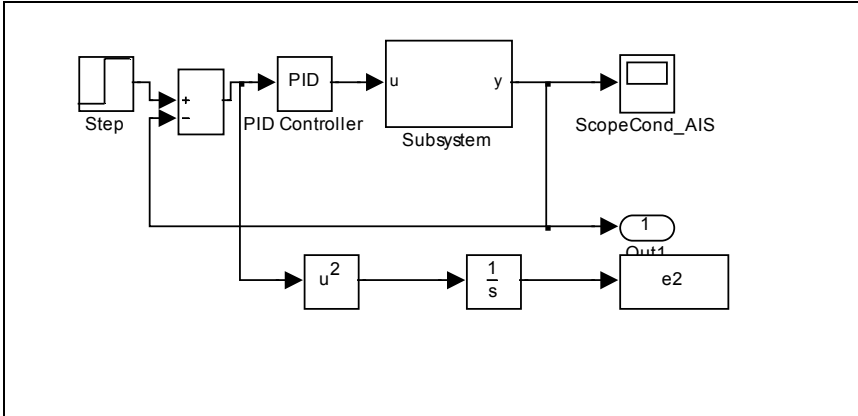


Fig.III.31: System with AIS_PID tuning in MATLAB Simulink

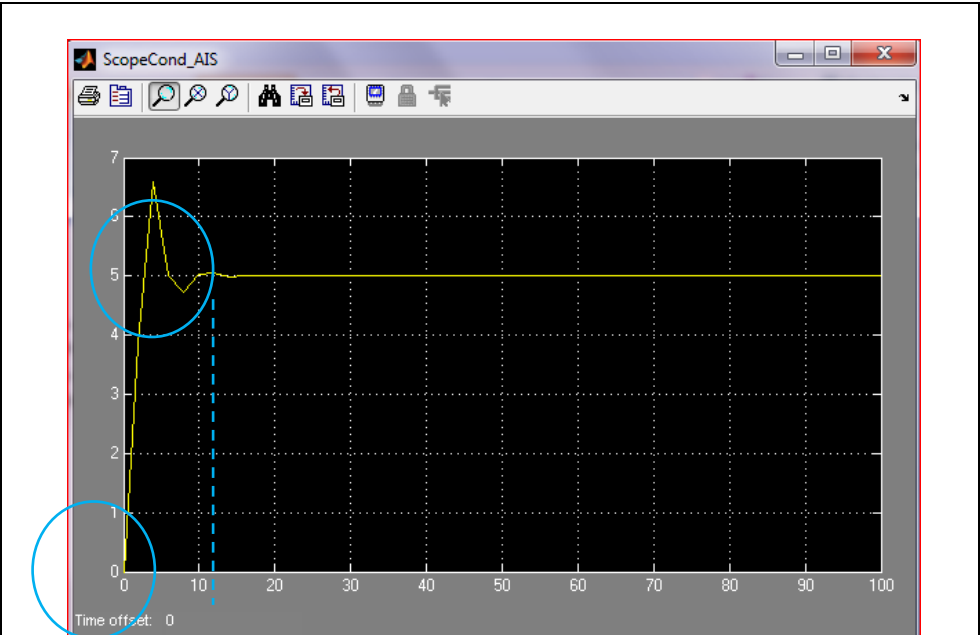
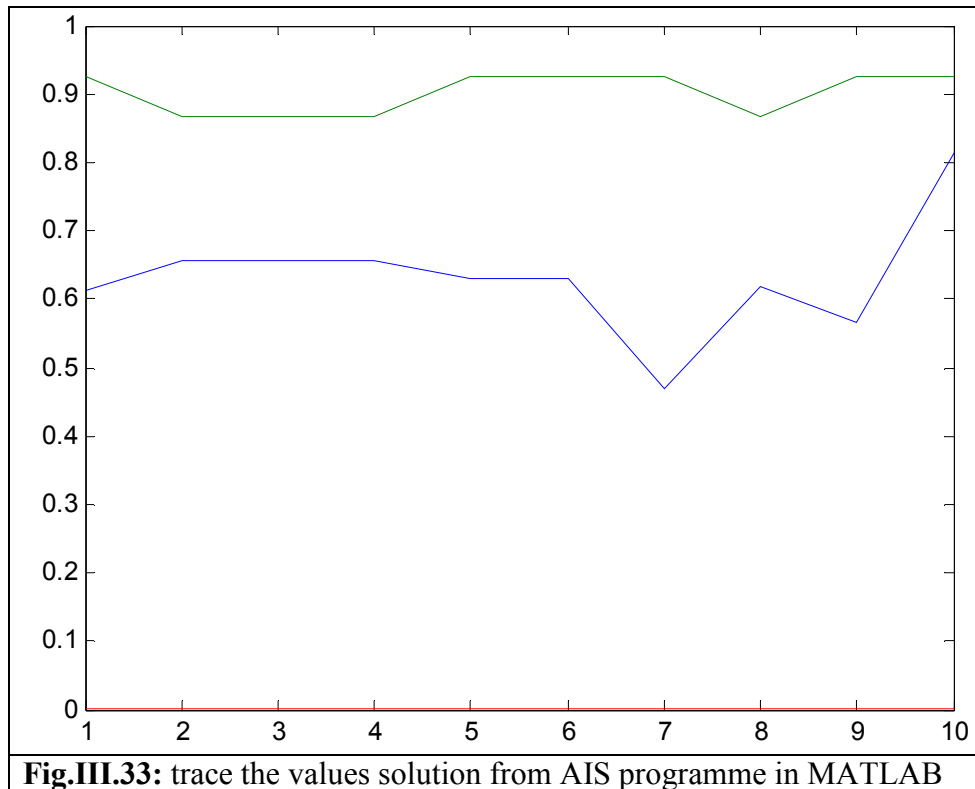


Fig.III.32: Signal with AIS_PID tuning in MATLAB Simulink



```

In AISConductivity at 75

GlobalMBest =

    0.6289    0.9266    0.0015

fx >>
Start
    
```

Fig.III.34: the global best solution from AIS in MATLAB

When Fig.III.32 our observation , we find that the signal appeared directly at zero and the value rose to 6.5 and then decreased to the value of up to 5 with a little bit of confusion to settle in a very short time while the signal in Fig.III.29 that took a long time , in addition to the delay in emerge. Which indicates that the system with the artificial immune system gave very good results, that is, it has improved in conductivity and that is what we are looking forward to it since the beginning. In addition, the PID values in the system with the artificial immune system come directly and without modification, and comes on automatically and this in reverse Fig.III.36 PID values that we have selected each time in the previous type. Here we find that the system with the immune system of artificial superiority over other species, making it the better, in terms of the speed of conductivity and stability, and quality and this is what proves to us that the system with the immune system of artificial has been significantly improved and this is what we look forward to in the introduction to our project.

III.6 GENERAL CONCLUSION:

Artificial immune system has shown efficacy in the field of artificial intelligence. It belongs to the group of systems inspired by nature. And this system, which has been applied to wide range of diverse cells and molecules problems, has proven to be able to recognize patterns and learning, diversity and optimization ... and others. Newly developed computational techniques based on immune-logical principles and immune engineering concepts are used for solving computational problems using metaphors from innate immune systems and self / non-self-discrimination.

Through our project, we demonstrated that the artificial immune system played a major role in the optimization process and through the simulations, we have done with some other methods that have proved their failure in front of this system, which has proved to be effective again as it had already been applied in other areas. Such algorithm helps much in the development of medical devices that help patients on the performance of their duties.

It was demonstrated, through the development of several algorithms, that with simple systemic views of the immune system, we can manage to engineer different computational techniques in other fields.

We wish to be the application of such projects, this project will be the beginning of other projects, and these projects targeted and applied to other devices in all fields, especially in the medical field because it is the only outlet for patients, as well as makes the technology moving at a faster pace than usual.

Conclusion perspective:

Since this project has been successful in terms of simulations and gave good results in improving the conductivity in the ultrafiltration is hoped, would be the application of these simulations in fact by the electronic circuit built inside the dialysis machine, because this will greatly help in the development of this device and present the results of a successful additional to the above.

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University of Mohamed Khider- Biskra

Faculty of Science & Technology
Department of Electrical Engineering
Sector: Electronic

Option : Telecommunication

Ref:.....

**Memory End of Studies
For graduation**

MASTER

Theme

**Introduction of an artificial immune
system for an intelligent ultra-
filtering control of a patient to realize
a hemodialysis operation**

Presented by:

AMMARI Abdessamed

Before the jury:

Mrs. Fedias Meriem

Dr. TOUMI ABIDA

Mrs.Nebar Hanane

**Presented
Supervisor
Examiner**

Academic Year: 2013 / 2014

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University of Mohamed Khider- Biskra

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Sector: Electronics

Option : Telecommunication

MASTER

Theme

**Introduction of an artificial immune
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a hemodialysis operation**

Presented by:

AMMARI Abdessamed

signature

Favorable opinion of the supervisor:

Dr. TOUMI Abida

Favorable opinion of the President of the Jury

Mrs. Fedias Meriem

Signature

Stamp and signature

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MASTER

Theme

Introduction of an artificial immune system for an intelligent ultra-filtering control of a patient to realize a hemodialysis operation

Presented by: AMMARI Abdessamed

Supervisor by : Dr. TOUMI Abida

Abstract (English and Arabic)

The artificial intelligence gave a strong impetus to the development of the world in all fields, although most of this is exemplified by the project inspired by your immune system in human beings, thanks to this we apply it to improve the functioning of ultrafiltration in a dialysis machine has brought positive results and successful. It has shown us that the algorithms taken from nature have a significant impact on human life.

المخلص:

إن الذكاء الاصطناعي أعطى دفعة قوية في تطوير العالم في جميع الميادين وإن من أهم أمثله هو هذا المشروع المستوحى من نظام المناعة الخاص بالإنسان، فبفضل هذا قمنا بتطبيقه لتحسين عمل الترشيح الفائق في جهاز غسيل الكلى فقد أتى بنتائج إيجابية وناجحة. فقد برهننا أن الخوارزميات المأخوذة من الطبيعة لها تأثير كبير في حياة الإنسان.