

**ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ:
«ΑΝΑΠΤΥΞΗ ΝΕΩΝ ΦΑΡΜΑΚΩΝ: ΕΡΕΥΝΑ,
ΚΥΚΛΟΦΟΡΙΑ ΚΑΙ ΠΡΟΣΒΑΣΗ»**

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ΙΑΤΡΙΚΗ ΣΧΟΛΗ**

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APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN BIOMEDICAL SCIENCES

ΚΑΒΙΔΟΠΟΥΛΟΥ ΑΓΛΑΪΑ

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

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Abstract

In this dissertation is presented the contribution of AI in biomedical sciences and particularly in drug development, image analysis, healthcare, radiomics and clinical trials. It will be demonstrated the general theoretical context behind the evolution of Artificial Intelligence, as well as its applications. The first chapter, analyzes the history of Artificial Intelligence starting with its definition. The second chapter includes a review of the literature underlining some of the most important milestones of the creation of Artificial Intelligence. As AI has been conducive to the development of many fields it has been characterized by many experts as the biggest innovation of the century. Thus, the third chapter presents the different methods of machine learning used in those fields. In the last chapter of the thesis, chapter 4, is represented a discussion about the findings of the thesis as well as about some new ways that Artificial Intelligence could be beneficial.

Περίληψη

Η παρακάτω διπλωματική εργασία αποτελεί μια εκτεταμένη βιβλιογραφική ανασκόπηση των Εφαρμογών της Τεχνητής Νοημοσύνης στις Βιοϊατρικές Επιστήμες. Πιο αναλυτικά, εστιάζει στις εφαρμογές της Τεχνητής Νοημοσύνης στην Ανάπτυξη Νέων Φαρμάκων, στην Ανάλυση Εικόνων (Image Analysis), στην Ιατρική Φροντίδα (Healthcare), στα Radiomics και στις Κλινικές Δοκιμές (Clinical Trials). Η Τεχνητή Νοημοσύνη έχει αποτελέσει ακρογωνιαίό λίθο στην ανάπτυξη πολλών άλλων επιστημών και σύμφωνα με πλήθος ειδικών και ερευνητών θεωρείτο η μεγαλύτερη ανακάλυψη του αιώνα. Στο πρώτο κεφάλαιο αναλύεται η ιστορία της Τεχνητής Νοημοσύνης καθώς και ο ορισμός αυτής. Στο επόμενο κεφάλαιο γίνεται η αναζήτηση της βιβλιογραφίας στην οποία παρουσιάζονται τα πρώτα βήματα που έγιναν ώστε να δημιουργηθεί η επιστήμη που γνωρίζουμε σήμερα. Έπειτα αναλύονται οι εφαρμογές αυτής σε διάφορους τομείς καθώς και η συμβολή της στην περαιτέρω ανάπτυξη τους. Τέλος, στο τελευταίο κεφάλαιο, κεφάλαιο 4, γίνεται η συζήτηση πάνω σε ό,τι ειπώθηκε προηγουμένως καθώς και προτείνονται νέοι δρόμοι ανάπτυξης της επιστήμης της Τεχνητής Νοημοσύνης.

1. Introduction

1.1 Definition of Artificial Intelligence

“A branch of computer science dealing with the simulation of intelligent behavior in computers / The capability of a machine to imitate intelligent human behavior” - Merriam-Webster^[1]

The main purpose of Artificial Intelligence is to design, synthesize, and train computational systems to perform tasks commonly seen as intelligent^[11]. According to Kok et al.^[2], rather than searching for a common definition of Artificial Intelligence, it would be wise to think of the definition of artificially intelligent systems as classified below:

- systems that think like humans
- systems that act like humans
- systems that think rationally
- systems that act rationally.

1.2. History of Artificial Intelligence

Before the Common Era, in the Sixth century, Homer introduced automata from the workshops of the Greek god Hephaestus in his poem The Iliad^[3]. Later, around the fifth century, Aristotle presented the epistemological basis about the division of knowledge into categories; theory as the most critical and art as less important^[3]. Additionally, he pioneered the syllogistic logic which is the first formal deductive reasoning system. In Common Era, at the late first century, Heron of Alexander built mythical automata and many others mechanical marvels. In the Fifteenth - Sixteenth century, Paracelsus was the first to introduce the magnetic or sympathetic system of medicine, the basis of magnetic healing^[4].

Around 1495, Leonardo da Vinci was already familiar with the perception of a

machine that can imitate a human and his first robot designs can testify that^[5]. In 1637, René Descartes wrote a philosophical and autobiographical treatise: *“Discourse on the Method of Rightly Conducting One’s Reason and of Seeking Truth in the Sciences”*^[3] which codifies the mind and body problem. In 1937, Alan Turing proposed an abstract universal computing machine. In 1941, German intelligence messages were encrypted by Turing and his colleagues at Bletchley Park in England^[3]. In the 1940s and 1950s, the discipline of Artificial Intelligence started to enchant the interest of scientists in different fields like computer scientists and mathematicians. McCulloch and Pitts’ paper^[95]: *“A logical calculus of the ideas Immanent in Nervous Activity”* (1943) was the first paper in modeling neurons with algorithms. In 1950, Alan Turing’s paper^[10]: *“Computing Machinery and Intelligence”* proposed the imitation game.

Since then, many scientists started to study and develop the science of robotics. Joseph F. Engelberger^[6] (founder and president of Unimation, Inc., the world’s first industrial robotics manufacturer which he launched in 1956) and Victor Scheinman^[7] (American engineer who conceived and designed the first successful electrically powered, computer-controlled robotic arm in 1969) are only some of the pioneers in the field of robotics. Sixteen years later the invention of the imitation game, Joseph Weizenbaum created a computer program named ELIZA which successfully passed the imitation game^[5].

Artificial Intelligence (AI) was firstly initiated at Dartmouth College in 1956 and it combines three different academic fields: **psychology**, **philosophy** and **computer science**^[8]. As Buchanan, B.G.^[9] cleverly stated, *“AI is not just about robots. It is also about understanding the nature of intelligent thought and action using computers as experimental devices”*.

Artificial Intelligence is the amalgamation of values from many disciplines such as **engineering** (Norbert Wiener's work on cybernetics including feedback and control), **biology** (W. Ross Ashby and Warren McCulloch and Walter Pitts's work on neural networks in simple organisms), **experimental psychology** (Newell and Simon, *Human Problem Solving* (1972)), **communication theory** (Claude E. Shannon: Founder of Information Theory), **game theory** (John Von Neumann and Oskar Morgenstern, *Theory of Games and Economic Behavior* (1944)), **mathematics** and **statistics** (Irving J. "Good, Speculations Concerning the First Ultraintelligent Machine," *Advances in Computers*, 6 (1965)), **logic** and **philosophy** (Alan Turing, Alonzo Church, and Carl Hempel), and **linguistics** (Noam Chomsky, *Theory Of Universal Grammar* (1960s))^[9].

2. Literature review

2.1 The Imitation Game

Alan Turing was the first to introduce the question: “*Can machines think?*” Using that as a starting point, Turing described the question in terms of a game known as the “*imitation game*”. As it is presented in his seminal paper in the philosophy journal *Mind*^[10]:

“It is played with three people, a man (A), a woman (B), and an interrogator (C) who may be of either sex. The interrogator stays in a room apart from the other two. The object of the game for the interrogator is to determine which of the other two is the man and which is the woman. He knows them by labels X and Y, and at the end of the game he says either ‘X is A and Y is B’ or ‘X is B and Y is A’. The interrogator is allowed to put questions to A and B thus:

C: Will X please tell me the length of his or her hair?

Now suppose X is actually A, then A must answer. It is A’s object in the game to try and cause C to make the wrong identification. His answer might therefore be:

“My hair is shingled, and the longest strands are about nine inches long.”

In order the tones of voice not to help the interrogator the answers should be written, or better still, typewritten. The ideal arrangement is to have a teleprinter communicating between the two rooms. Alternatively, the question and answers can be repeated by an intermediary. The object of the game for the third player (B) is to help the interrogator. The best strategy for her is probably to give truthful answers. She can add such things as “*I am the woman, don’t listen to him!*” to her answers, but it will avail nothing as the man can make similar remarks.

“What will happen when a machine takes the part of A in this game?”, “Will the interrogator decide wrongly as often when the game is played like this as he does

when the game is played between a man and a woman?". These questions replace the original question which is: "*Can machines think?*" To answer that question, Turing then alter the imitation game by having machine in (Human) A's position. Now the task for C is to choose which of A and B is human. Schematically it looks like this:

(Fig. 1)^[5]

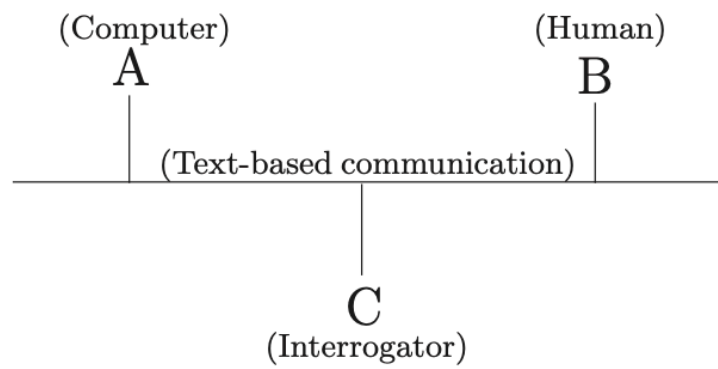


Fig. 1. The Imitation Game: The goal of the interrogator is to determine which of the two participants (A or B) is the machine and which is the human. There are physical boundaries between the participants, and the communication is accomplished via text.^[5]

In other words, machine's task was to deceive a human interrogator into believing that it is human. Engineering the test in this way it enhances the level of difficulty for the computer, but totally avoids the question, "*Can computers think?*"^[9]

In 1950 there was a critical moment in the history of AI with Turing publishing a seminal paper in the philosophy journal *Mind*^[10]. In that paper, patterned ideas were presented that assumed the possibility of programming an electronic computer to perform intelligently. Of course, there was included a description of the landmark imitation game that we know as Turing's Test^[9]. Additionally, Vannevar Bush's paper in the *Atlantic Monthly* that was published in 1945, is outlined a farsighted vision of capabilities^[9].

2.2 Consciousness in computers

Roger Penrose, one of the greatest mathematicians, stated at his famous book *“The Emperor’s New Mind”* [87] that strong AI is impossible. As a strong protester of the idea that a computer could be conscious, Penrose justified his opinion by presenting detailed analysis of many topics in mathematics such as Turing machines and computability theory, the Mandelbrot set, complex numbers, Gödel’s theorem, recursive function theory, complexity theory and Platonism versus intuitionism as well as in classical Einsteinian physics and quantum physics, cosmology, and neuroscience.[87]

At his book he attempts to prove that the nature of the physics that might based on conscious thought processes cannot be accurately simulated by any computer [87]. That is because, the brain seems to make use of non-computational physical processes in some crucial way when consciousness comes into play. For that reason, the computer cannot simulate properly some aspects of the brain’s action. In strong Artificial Intelligence is believed that computer’s actions are the same as the brain’s including conscious perceptions that emerging from computations[87]. Nevertheless, the main viewpoint of Penrose is that computers can solve a difficult task that requires intelligence but they cannot truly understand the task.

2.3 Machine Learning

The first paper written on machine learning published in 1957 from the American mathematician and researcher Ray Solomonoff under the name: "*An Inductive Inference Machine*"^[94]. In that paper, Solomonoff described machine learning as "*the set of instructions that have been prepared by which certain problems in inductive inference can be solved*".

Another definition of machine learning is the following: Machine learning is a branch of artificial intelligence research that employs a variety of statistical, probabilistic and optimization tools to "learn" from past examples and then to use that prior training to classify new data, identify new patterns or predict novel trends^[13]. Each learning process consists of two phases: (i) the estimation of unknown dependencies in a system from a given dataset and (ii) the use of estimated dependencies to predict new outputs of the system.^[14]

There are two main common types of ML methods known as (i) unsupervised learning and (ii) supervised learning. In unsupervised learning methods, labeled examples are not provided and there is no notion of the output during the learning process. Consequently, the learning scheme/model has to find patterns or discover the groups of the input data. On the other side, supervised learning is considered as a labeled set of training data that is used to estimate or map the input data to the desired output^[12]. These labeled examples are the training set that the program tries to learn about or to learn how to map the input data to the desired output. For instance, a labeled training set might be a set of corrupted images of the number "8".

(Fig. 2)^[15]

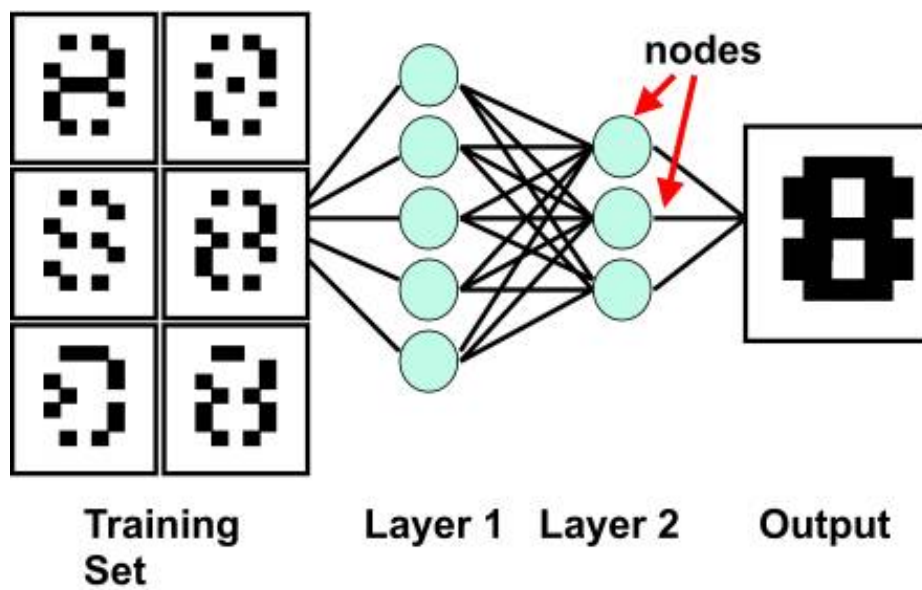


Fig. 2. An example of how a machine learner is trained to recognize images using a training set (a corrupted image of the number “8”) which is labeled or identified as the number “8”.^[15]

This procedure can be thought as a classification problem. The classification task refers to a learning process that categorizes the data into a set of finite classes^[12].

As Kourou *et al.*, 2015^[12] stated, in the past decades, new strategies for the early prediction of cancer treatment have developed by scientists. All these new technologies in the field of medicine make it possible for large amounts of cancer data to be collected and also to be available to the medical research community. For that reason, Machine Learning (ML) methods have become a popular tool for medical researchers. Identification of the patterns and the relationships between them can be discovered by these techniques and they are also able to effectively predict future outcomes of a cancer type.

Regression and clustering are two other common ML tasks. The first one is referred to a learning function that maps the data into a real-value variable. Ultimately, for each new sample the value of a predictive variable can be estimated based on this process. The second one, clustering, is a common unsupervised task in which one tries to find the categories or clusters in order to describe the data items. Derived from this process, each new sample can be assigned to one of the identified clusters concerning the similar characteristics that they share. Semi-supervised learning is another type of ML methods that have been widely applied. It is a combination of supervised and unsupervised learning and incorporates labeled and unlabeled data in order to construct an accurate learning model. Generally, this type of learning is used when there are more unlabeled datasets than labeled.^[12]

A ML method has data samples as basic components. Every sample is described with several features and every feature consists of different types of values. Moreover, knowing already the specific type of data being used, allows the

right selection of tools and techniques that can be used for their analysis. Consequently, the main objective of ML techniques is to produce a model which can be used to perform classification, prediction, estimation or any other similar task.^[12]

3. AI Applications in Biomedical Sciences - Results

3.1. Expert Systems

Expert systems by definition are capable of providing expert conclusions about specialized areas. Some applications of expert systems are; diagnosing faults in military systems (radars, aircrafts), taxonomically classify members of a particular species, advice on possible chemical structures, evaluate potential ore deposits, diagnose diseases, etc^[11]. There are two key components in the design of every expert system; the representation of knowledge and the usage of this expertise while drawing conclusions^[11]. Knowledge can be represented as a large set of simple rules as well as in structures called *frames* and *scripts*.

How crucial was this to AI? In an interview in 1985, when the Editors of the Artificial Intelligence Journal asked key AI scientists for their views of the most important happenings in AI over the previous decade, Allen Newell responded^[16]:

“There is no doubt, as far as I am concerned, that the development of expert systems is the major advance in the field during the past decade....The emergence of expert systems has transformed the enterprise of AI, not only because it has been the main driver of the current wave of commercialization of AI, but because it has set the major scientific problems for AI for the next few years...”

3.1.1 DENDRAL and META-DENDRAL

One of the earliest systems to exploit domain-specific knowledge in problem solving and also the "the mother of all expert systems" was DENDRAL. It was developed at Stanford in the late 1960s^[16] and it is considered as the first expert system because it automated the decision-making process^[19].

DENDRAL is one of the first and most notable AI application that analyses the mass spectra of organic molecules by deducing their structure to their chemical

formulas and mass spectrographic information from the chemical bonds present in the molecules. Its primary aim was to study hypothesis formation and discovery in science^[18]. That application induced new rules of mass spectral fragmentation. DENDRAL's characteristic is applying the heuristic knowledge of expert chemists to the structure elucidation problem^[16]. The idea for that project was a team effort.

At first, Feigenbaum was looking for a working environment that will examine processes of empirical induction (of models and theories from data). Then a geneticist named Lederberg, whose work in 1965 on exobiology included the mass spectra of amino acids, proposed the task of analyzing mass spectra. Last but not least, Buchanan joined the attempt as a scientist of philosophy of science mixed with AI^[22]. DENDRAL's methods proved remarkably effective as they were able to find the correct structure out of millions of possibilities after only a few trials. The approach was proved so successful that descendants of the system are used in chemical and pharmaceutical laboratories throughout the world.

Heuristic DENDRAL and META-DENDRAL, are two major programs that included in DENDRAL project^[20]. The whole program was written in Lisp programming language.^[19]

In 1970 approximately, META-DENDRAL was created^[22]. The reason why scientists decided to create META-DENDRAL is because there was a problem of extracting domain-specific rules from experts, utilised by DENDRAL^[21]. Programs that will transfer interactive knowledge needed experts with enough specific knowledge in some areas of chemistry in order to make a high performance problem solving program^[23] and there were not many scientists able to do that. As a result, the initiation of the formation of an automatic rule called META-DENDRAL was inevitable.

META-DENDRAL was the catalyst that driven to the rebirth of the machine

learning area and that was due to three factors: knowledge, generalization and demonstrably significant results.^[22]

The current META-DENDRAL program^[24,25] is able to give chemists the opportunity to determine the dependency of mass spectrometric fragmentation on substructural features, having in mind the hypothesis that molecular fragmentations are related to topological graph structural features of molecules. The aim is to build a program that could indicate qualitative explanations of the characteristic fragmentations as well as re-arrangements among a set of molecules.^[21]

As Buchanan and Feigenbaum stated^[22], the extension of DENDRAL was the MYCIN, then the EMYCIN (the software generalization) and then applications in medicine, engineering, molecular biology, x-ray crystallography, submarine detection, etc. All these developments constituted a system-building experimental AI effort. That effort sustained in a period over fifteen years. All in all, a new sector of AI was born, as well as a sector of the software industry^[22].

3.1.2 MYCIN

MYCIN was developed at Stanford in the mid-1970s. It was one of the first programs to aim at the problems of rationale with uncertain or incomplete information and it can also be characterised as one of the first backward chaining expert systems^[17]. MYCIN is portrayed as the extension of DENDRAL^[21] and it constitutes the establishment of the methodology of contemporary expert systems. It uses expert medical knowledge to identify and prescribe treatment for spinal meningitis and bacterial infections of the blood.

More specifically, the system had to be user friendly and also had to provide regularly reliable advice^[71]. Additionally, it had to be capable of using inaccurate or incomplete information (i.e. definitive laboratory data, medical documents etc.) and to

maintain a great amount of specific information that may be used in the future. Last but not least, MYCIN had the ability to give explanations of its reasoning^[17] and answer all questions made by physicians^[71].

Graphically, the MYCIN system comprises three major subprograms, as shown in **Figure 3**^[71]. These parts are: the Consultation Program which is the core of the system and it cooperates with the physician to acquire information about the patient and make diagnoses and suggest therapeutic schemes. After that, the Explanation Program follows, and provides explanations and justifications for the actions taken by the program. Lastly, the Knowledge-Acquisition Program is only utilized by experts to update the knowledge base of the system.

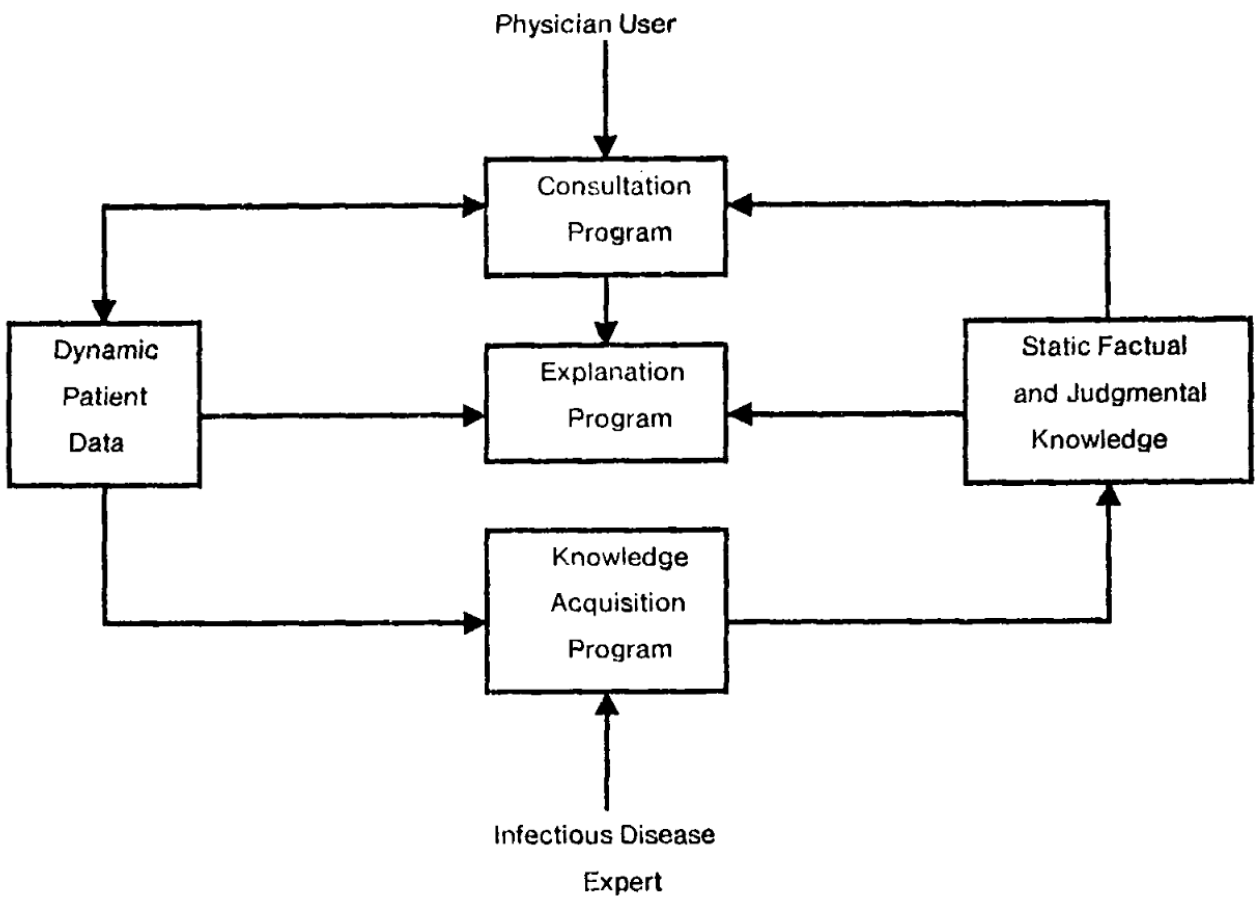


Fig. 3. Organization of the MYCIN system. The arrows indicate the information flow between modules, knowledge base, and users.^[71]

3.2 Robotics

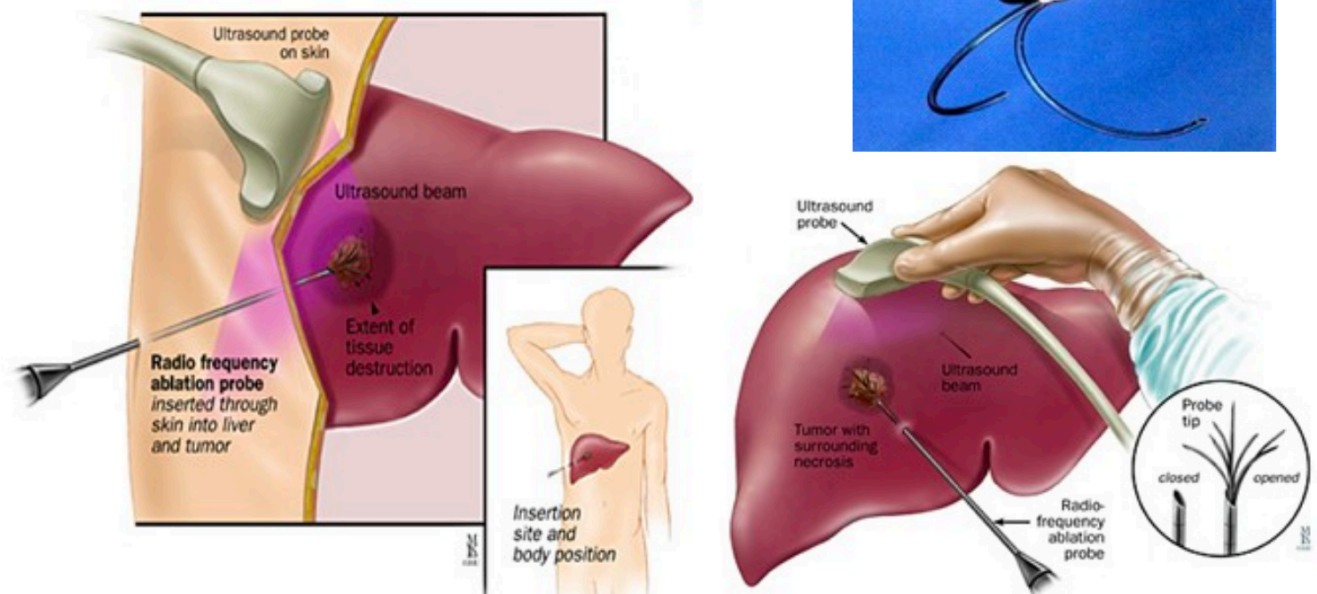
One of the most important feature of designing a flexible and responsive robots is planning. For scientists to achieve that, writing a program that can intelligently explore the ideal path of executing an order without being affected by the huge number of possibilities is the only way. Moreover, that requires sophisticated techniques for representing spatial knowledge and controlling search through possible environments^[11].

In today's world, many innovations have been made in robotics and especially in biomedical sciences. Thus, the global numbers of robotic surgeries are increasing. Leverages such as short hospitalization periods, limited postoperative recovery time, safety for patients at particular risk (diabetic, with an increased body mass index (BMI > 35), prompt robotic surgery for the treatment of cancer of internal organs a standard regimen^[48]. More specifically, even though the reasons for their enduring popularity are many and complex, the need for innovation is the motivating force. Robotic surgery is considered as a minimally invasive precision surgery. But how that can be done? Innovative systems will influence the robot, which will operate as a data-driven platform, to make decisions with the aid of integrating advances in imaging, artificial intelligence and machine learning.^[47]

3.2.1 Radiofrequency Ablation (RFA)

Another application of robotics in healthcare is in radiofrequency ablation (RFA) of liver cancer^[47]. The radiofrequency ablation technique is mostly used in the therapy of cancer of internal organs^[47] and it is a minimally invasive surgery. The method consists of high efficiency produced by a large selection of electrode shapes and modes of exposure that are inserted through the liver tissue into the tumor, with ultrasound guidance, and burns out the tumor. **(Fig. 4)**^[49]

RFA Experience In Nicosia General Hospital (CLM)



P. Hadjicostas,,M.Dietis, C. Antreou / Surgical Department

Fig.4. RFA method schematically.[49]

It is important for this method to be completed at the first attempt, as accurately as possible, with no damage to the vascular secretion elements of the liver. The problem is that it requires the surgeon to maintain the immobility of the ablator electrode for a long time (20 to 40 minutes) in some cases, which requires great effort^[49]. A solution to that problem would be the replacement of the surgeon with a robotic manipulator. A robotic manipulator has many assets such as great accuracy of the position and orientation of the electrode related to the expected path of motion, minimization of the amplitude of oscillations in movement process, fixation in the desired position at the time of the operation and the ability to remove the electrode exactly through the input channel so as to minimize additional damage^[49]. Also, robotic insertion is more stable regarding needle posture at a given angle during needle targeting and insertion than a surgeon.

3.2.2 Augmented reality robotic surgery

Vision-based tracking system for augmented reality to localize recurrent laryngeal nerve during robotic thyroid surgery^[50] constitutes another innovation in robotics. Robotic thyroid surgery is a popular type of surgery since it is scarless. The reason why scientists decided to create a robot to utilize that type of surgery is mainly because an injury to the recurrent laryngeal nerve (RLN), which is located rear to the thyroid glands and it is difficult to identify, can result in vocal cord paralysis, aspiration, and thus poor quality of life.^[51]

This new type of robotic surgery based on Augmented reality (AR). That technique, allows virtual organs to be overlaid onto the actual organs during the surgery^[50]. Even though AR seems really useful, in surgery is not popular due to the inconvenient of the manually relocation of the AR images according to robot's camera movement. The solution to that problem came from Lee et. al.^[50] who created a

vision-based tracking system that lets the AR image to move in compliance with the actual organ. **(Fig. 5)**^[50]

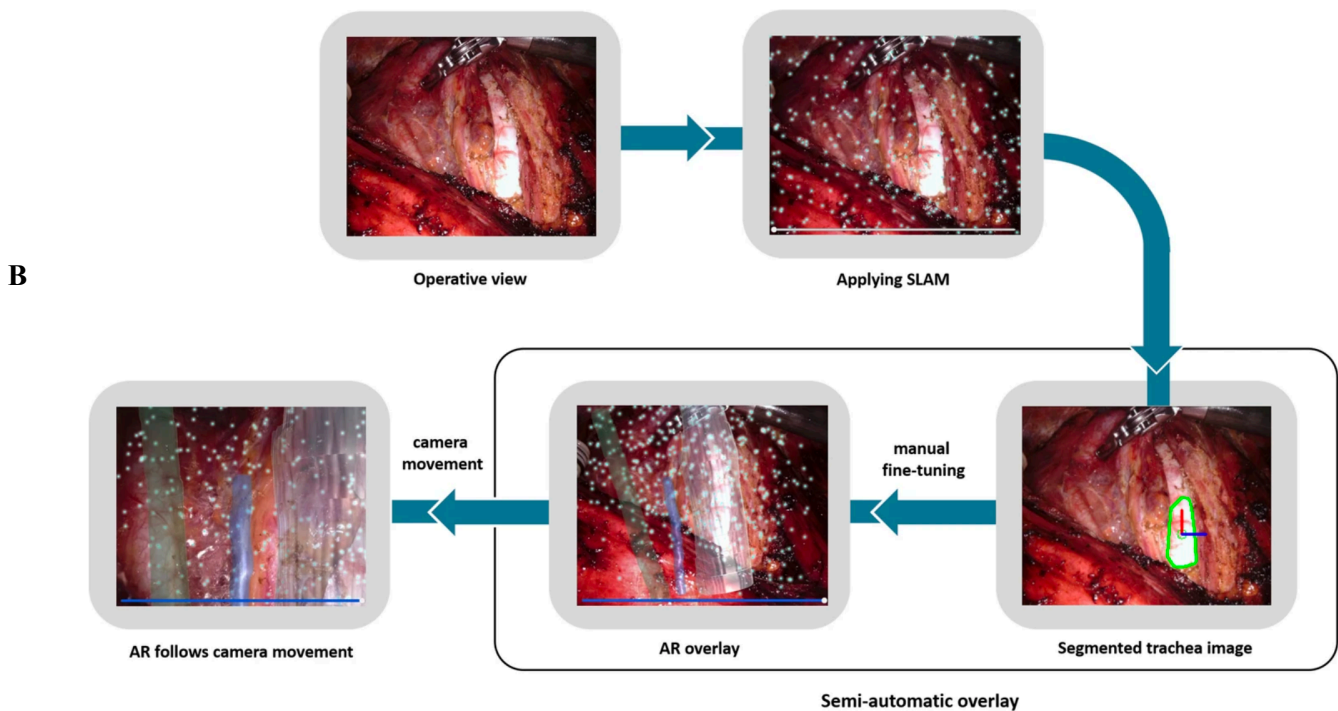
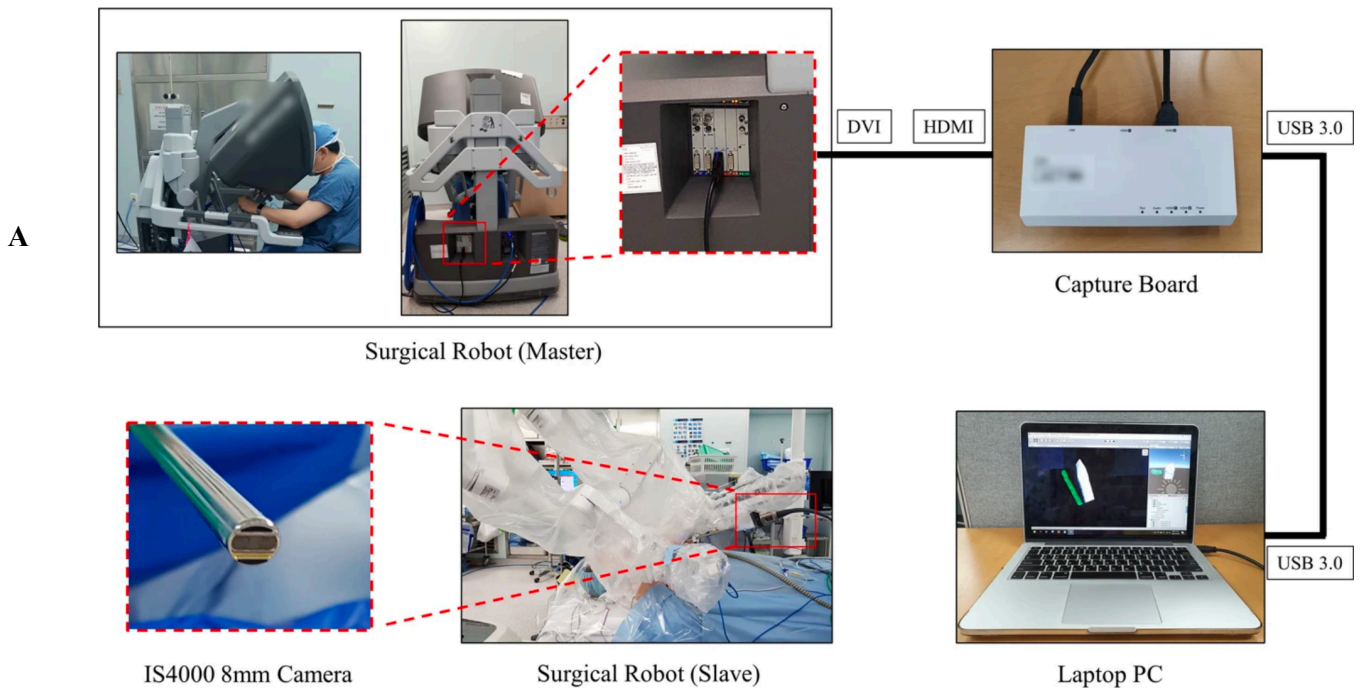


Fig.5. A. The hardware of tracking system used in robotic surgery. The surgical robot screen is branched out and connected to a laptop computer operating a vision-based tracking system.

B. The process of AR application on the operative image using vision-based tracking system.^[50]

3.2.3 Robotic guidance systems

Another application of the robotics in surgery is a robotic guidance system for navigated spine surgery. Navigation and robotics in spine surgery is a combination that possibly can recognize and maintain bone entry position and planned trajectory. One of the most crucial steps in spine surgeries associated with thoracolumbar posterior fixation is the insertion of pedicle screws. That is because both neural and vascular structures are close to the pedicles. As a result, the great demand for increased accuracy, reduced complication rates, and lowered radiation exposure to the surgical personnel resulted in an escalated use of robots in minimally invasive spine (MIS) surgery.^[55]

A custom robotic arm that was integrated into a hybrid operating room (OR) equipped with an augmented reality surgical navigation system (ARSN), which was used for planning screw paths and directing the robot, was introduced by Burström *et. al.* ^[54] (**Fig. 6, Fig. 7**). This is a new robot-guided system autonomously adjusted according to the planned screw trajectory. In order to identify the levels to be treated, fluoroscopy is used. Then, the robot is mounted on the table rail system and it is instantly functional without any need for calibration because of the integration to the ARSN. Additionally, the instrument guide on the robot accepts adapters for standard surgical instruments, such as drills, Jamshidi needles, pedicle probes, etc.^[54]

Nevertheless, the invasion of the specialist is inevitable because the insertion of the Jamshidi needle into the pedicle is done manually^[54]. Next step, is the accuracy measurements that have to be performed on verification cone beam. These are computed tomographies alongside the superimposed planned paths.^[54]

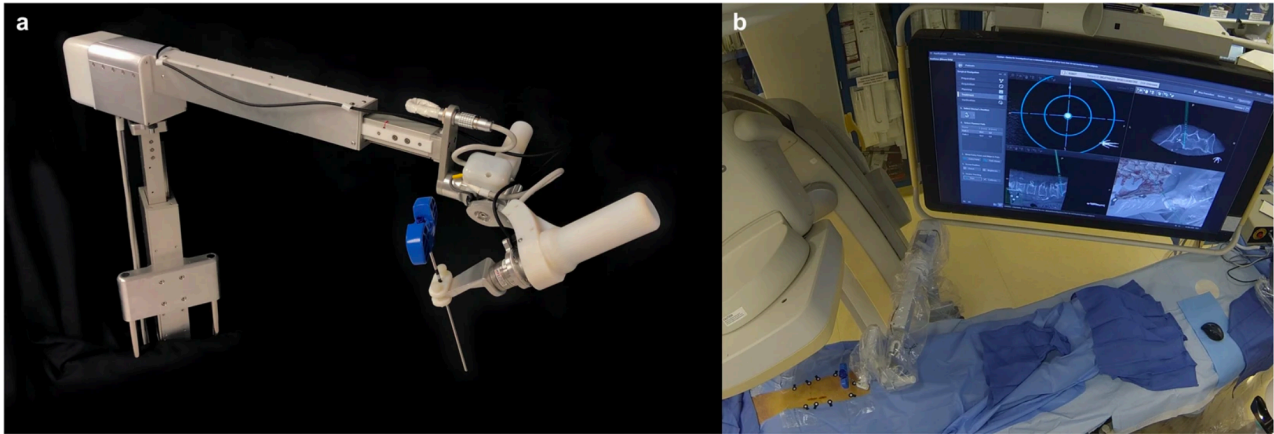


Fig. 6. (a) Layout of the robotic arm with a Jamshidi needle (blue) in the instrument adapter is depicted in. **(b)**The entire surgical setup in the operating room is seen with the robot, C-arm and navigation interface on a monitor.[54]

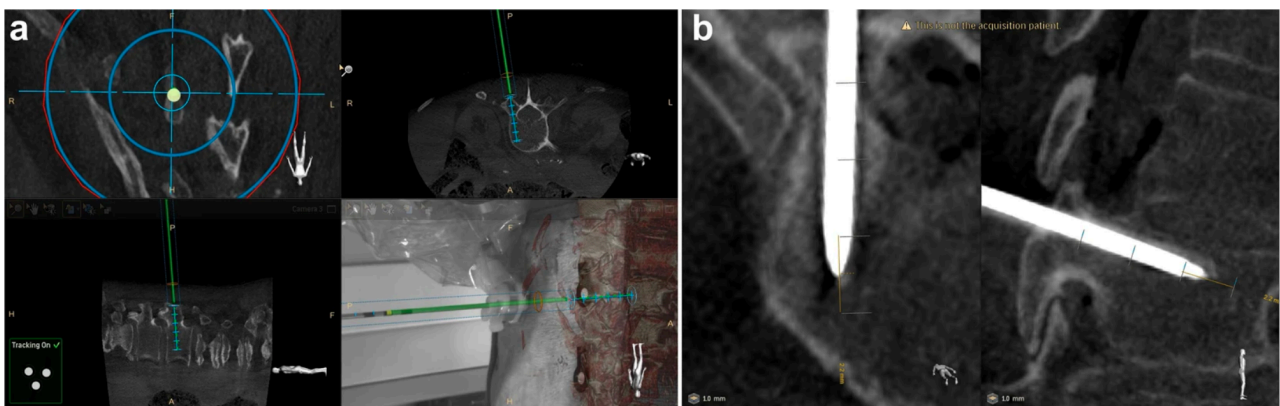


Fig. 7. Representation of the surgical navigation interface during robot assisted surgery:

(a), top left shows a coronal view along the pedicle trajectory, top right shows an axial view with the navigated Jamshidi in green, bottom left a sagittal view, and bottom right a camera feed with an augmented reality overlay depicting the underlying anatomy.

(b) A post-operative computed tomography scan of a placed Jamshidi needle is illustrated. Axial view to the left and sagittal view to the right.^[54]

As it is already mentioned before, medical robots are created to provide accuracy, safety and effectiveness by overcoming the limitations of human ingenuity and consciousness^[52]. Image guidance has been proved as a way to 'equip' medical robotic systems with the intelligence and flexibility in order to operate highly-demanding interventional tasks on soft tissues autonomously but supervised from trained practitioners.^[52]

More particularly, robotic guidance for autonomous vascular access constitutes the first step in a plethora of diagnostic and therapeutic practices, such as drawing blood, regulate fluids and medications, introducing endovascular devices and checking physiological status^[52]. But, such an innovation does not come with no cost, the difficulties of vascular access resulted in the development of imaging technologies divided into four main categories: **tactile pressure-based imaging** (provides maps of tissue elastic response with sensitivities of several pascals^[53]), **optical coherence tomography and photoacoustic tomography**, **near-infrared (NIR) optical imaging** (utilizes 700–1,000 nm light from lasers or light-emitting diodes (LEDs) to image superficial vessels within 5 mm of the tissue surface without precisely estimate the depth of the vessel beneath the skin^[51]), and **ultrasound (US) imaging** (higher vascular access and lower complication rates compared to blind cannulation^[51]). The problem with these imaging-based methods is that they are depended on the practitioner. On the other hand, commercial robotic catheter systems, which are approved by FDA, even though they are not image-guided, can successfully have access to intravascular navigation.

Yet, medical robots have demonstrated the ability to manipulate percutaneous instruments into soft tissue anatomy and robotic technologies can operate autonomously and achieve critical tasks with minimal supervision when resources are

limited. Chen *et. al.*^[51] created a portable robotic device that can inject needles and catheters into deformable tissues such as blood vessels to draw blood or deliver fluids autonomously. **(Fig. 8)**^[52]. Then, the robotic cannulation will be directed by predictions from a series of deep convolutional neural networks (DNNs) that encode spatiotemporal information from multimodal image sequences to guide real-time servoing. The device therefore, will be able to segment, classify, localize and track peripheral vessels while in motion and taking into consideration the anatomical variability of each patient. Last step, is the evaluation of image-guided robotic tracking to manual performance *in vitro* (tissue-mimicking phantoms mimicking wide demographic variability) and *in vivo* (anaesthetized rat models of superficial venous access). The outcome was in favor of the device since it can improve success rates and procedure times compared to manual cannulations by trained operators.^[52]

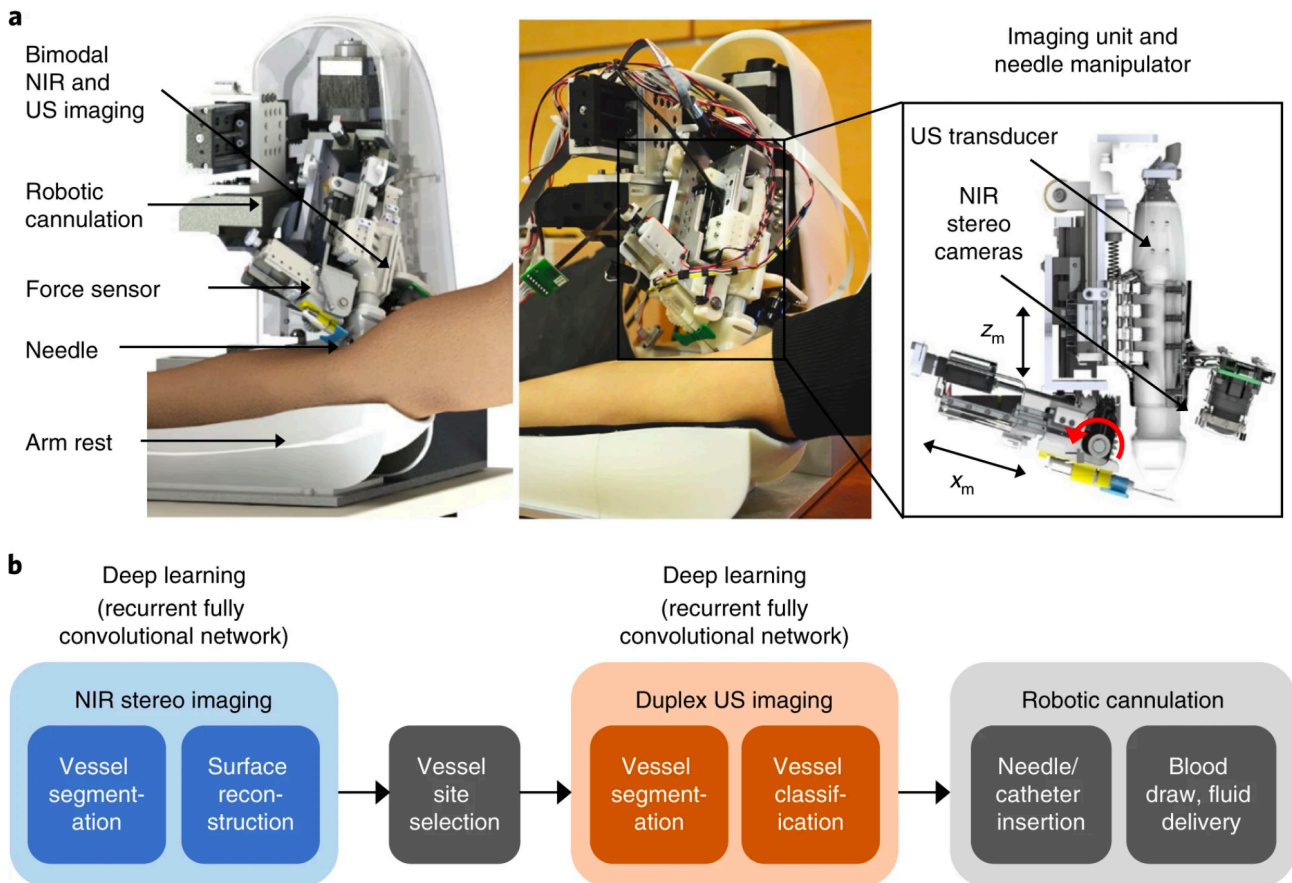


Fig. 8. (a) The device couples bimodal 3D vessel imaging and adaptive robotic instrument manipulation within a compact shell. The robot comprises a six-degrees-of-freedom (6-DOF) base positioning unit and a 3-DOF distal manipulator that performs autonomous cannulation under NIR and US image guidance.

(b) End-to-end workflow for robotic vascular access. The robotic guidance is driven by a pair of trained deep convolutional neural networks operating on continuous NIR and US imaging sequences.^[52]

3.2.4 Da Vinci surgical system

Another application in robotic surgery is in maxillofacial surgery for the treatment of head and neck tumors and non-malignant diseases. In that kind of surgery, large incisions are taken place and can be approached in two ways; transmandibular and transpharyngeal. Procedures like that can induce great discomfort, as well as significant surgical morbidity, speech dysfunction and indigestion from the dissection of large amounts of normal tissue. In order to surpass these obstacles, Liu *et. al.*^[56] created a robotic surgical system that introduced transoral robotic surgery (TORS). TORS first applied clinically in maxillofacial surgery to remove a vallecular cyst by McLeod and Melder^[57]. It can be used in stage T1 and T2 oropharyngeal cancer and it is also FDA- approved since 2009. According to Liu *et. al.*^[56] the **da Vinci** surgical system is currently acknowledged as the most successful robotic surgery system.

One more benefit of procedures with robotic assistance is that they can be accomplished with less blood loss, fewer complications, less hospitalization and more improved cosmetic results than standard open techniques.^[58]

The first **da Vinci**^[59] robot was created in 1999 by Intuitive Surgical. It was consisted of three major parts: a surgeon's console that enables handling of the corresponding instruments with master controls, a robotic cart on the patient's side and a high-definition 3D vision tower^[59]. The **da Vinci** system intended to recreate the open surgery atmosphere, thus it was preferred by the open surgeon.

The surgeon performs the surgery while seated. The console also enables him to have a high-definition real-time view inside the patient. The robotic cart is consisted of three or four arms: one arm knobs the endoscopic camera, while the other two or three arms hold the EndoWrist instruments that provide enhanced

degrees of freedom and superior 3D imaging. In this way, large-scale movements such as those needed for dissecting and suturing are accomplished. Furthermore, the camera operate in the system, enabling the specialist to see a true-to-life stereoscopic image of the anatomy of the patient, which is transmitted to both the surgeon's console and the vision tower beside the surgical assistant^[59]. Last but not least, the vision tower present a broad perspective and visualization of the process to the surgical assistant at the patient's side. **(Fig. 9)**^[56]

Taking all these into consideration, robotic surgery may hold promise in the treatment of craniofacial conditions, such as head and neck neoplasms, cleft palate and craniofacial asymmetry, among others.

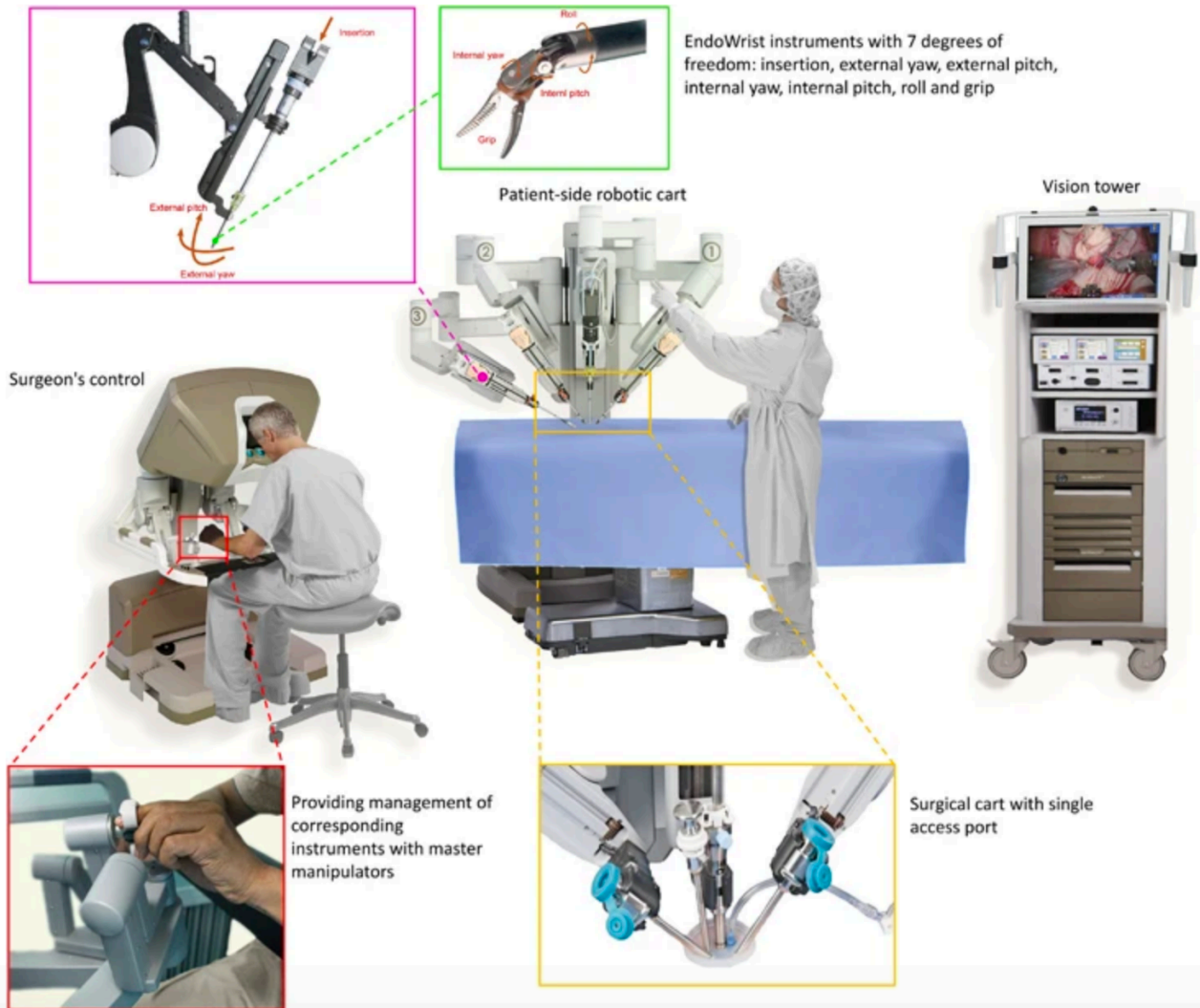


Fig. 9. Schematic representation of the Robotic surgery operating room.^[56]

3.3 Computational drug design

In today's world, research in AI has been focused on deep learning^[27] which is a subfield of machine learning. A characteristic of that new research field is that its artificial neural networks are mimicking the structure of the human brain.

Since DENDRAL and META-DENDRAL, chemists started to involve in AI applications. They used its abilities to rethink some of their theories (DENDRAL induced new rules of mass spectral fragmentation) and also to explore new fields such as chemoinformatics. That new field includes an environment with computational drug design tools, with a range from classical structure-based quantitative structure–activity relationship techniques (QSAR)^[28], matched molecular pairs^[29] to free-energy perturbation^[30]. Machine-learning tools, such as QSAR modeling, that can analyze potential biological active molecules from a pool of candidate compounds rapidly and low-cost were created. Thus, drug discovery changed drastically into the era of “big data” and machine learning approaches progressed into deep learning approaches. That new era, promises a more powerful and efficient way to work with the great amount of data produced by the modern drug discovery approaches^[46]. All these improvements, lead to drug discovery via artificial intelligence. In general, drug discovery can be divided into four major stages: *target selection and validation, compound screening and lead optimization, preclinical studies and clinical trials*. **(Fig.10)**^[43]

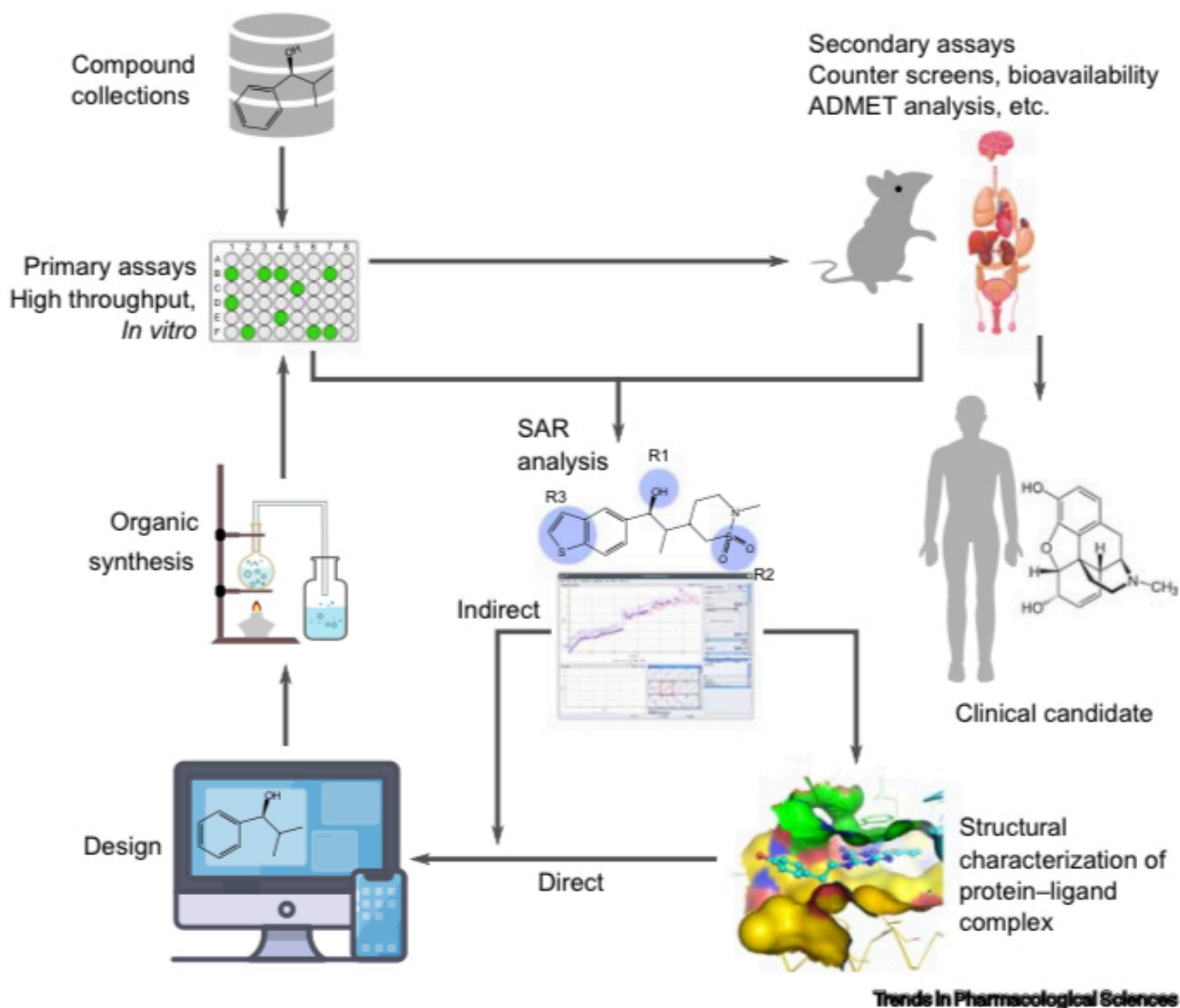


Fig. 10. A Representative Pipeline of Drug Discovery.

Compounds identification by screening compound collections via primary assays and secondary assays that include counter-screens and ADMET (absorption, distribution, metabolism, excretion, and toxicity) studies, structure–activity relationship (SAR) and *in silico* studies in combination with cellular functional tests are used in an repetitious cycle to improve the functional properties of the drug candidates. After that, new drug candidates with desirable characteristics are synthesized via organic synthesis. Lastly, the selected drug candidate which has now passed all preclinical tests successfully is given to human patients in a clinical trial.^[43]

The first step, consists the study of the disease-target in order to identify the desirable molecule. That can be achieved by cellular and genetic evaluation of the molecule, genomic and proteomic analysis, and bioinformatic predictions^[43].

Step two, is the formation and testing of the ideal compound. To distinguish the compound, molecular libraries and methods such as combinatorial chemistry, high-throughput screening and virtual screening are used. Afterwards, structure–activity and *in silico* studies in combination with cellular functional tests are used repetitively to enhance the functional characteristics of newly synthesized drug candidates. Lastly, in order to test the compound *in vivo*, studies, such as pharmacokinetic investigations and toxicity tests are conducted in animal models.^[43]

Step three, is the administration of the drug candidate which has now successfully passed all preclinical tests to patients in a clinical trial. Clinical trials include three Phases: **Phase I**, drug safety (testing a small number of human subjects), **Phase II**, drug efficacy (testing with a small number of people affected by the targeted disease) and **Phase III**, efficacy studies (testing with a larger number of patients)^[43]. Considering that safety and efficacy of the drug candidate are evident in the clinical phases, the compound is examined by agencies such as the FDA and EMA for approval and commercialization.^[43]

More specifically, designing new molecules and planning synthesis with AI would be achieved if the system has the fundamental intelligence to produce autonomously innovative molecular representations that are structurally similar to drugs and chemically-wise^[26]. In other words, AI has been used to develop completely new lead compounds that exhibit desired activity *in silico*^[35]. The computational *de novo* design in a combination with AI would create a ‘computer chemist’ who will learn from known and useful compounds and enable the production

of chemically correct and synthesizable structures with a planned biological activity^[35]. Furthermore, molecular graph convolution methods^[31], variational autoencoders^[32] and recurrent neural networks (RNN)^[33] are only some of the greater achievements of these efforts.

According to Olivecrona *et al.*^[34], an experiment for designing new molecules is consisted of the training of an RNN on simplified molecular-input line-entry system (SMILES) representations from the ChEMBL database^[26]. After that, the pre-trained RNNs, which have been tuned by policy-based reinforcement learning, were used to create new sequences. The learning procedure for these sequences that follow the conditional probability distributions, is done by the training set. As a result, from the sequences generated by the network, 94% corresponded to valid molecular structures, of which 90% were new^[26]. Next steps after the molecular structure inputs are available, is the activity prediction of the compound property by machine learning and neural network algorithms.^[27]

As Gisbert Schneider^[37] stated: *“Advanced machine learning requires large well-annotated datasets that need to be compiled or generated. Also, the chemical structure of a drug alone rarely accounts for the observed pharmacological effect in a simple fashion. Most drugs have multiple biological targets and activities, and the irrelative importance is highly dependent on the individual genetic profile of patients, and a range of other factors. In certain areas of drug design we are confronted with inherently ill-posed problems owing to a multitude of often unknown contributing factors”*.

Schneider's group^[37] made an effort using this approach by creating a nonhuman 'drug designer'. He stated: *“Modern machine-learning methods are very fast and can consider several design goals in parallel. So, our drug design software*

was trained to recognize important features and characteristics of known drugs. The obtained models were then used to automatically assemble new molecules with these learned desired properties from scratch^[37].

Other neural network-based project is Atomwise^[38]. It was invented by Abraham Heifets and Izhar Wallach in California, USA and it uses machine learning technology to screen compounds fast. It applies the same technology as in 2D image as well as speech recognition, all utilized to molecular recognition (3D image recognition)^[36]. Unfortunately, the human intervention is inevitable.

PaccMann, INtERAcT and PIMKL from IBM Research, are some of the open-source, deep-learning projects.^[35]

3.3.1 PaccMann

PaccMann is an innovative approach for the prediction of anticancer compound sensitivity (cancer cell-drug sensitivity) by means of a multi-modal attention-based neural network. More specifically, that project is consisted of three backbones of drug sensitivity; the molecular structure of compounds, transcriptomic profiles of cancer cells and prior knowledge about interactions among proteins within cells^[39]. **(Fig. 11)**^[41]

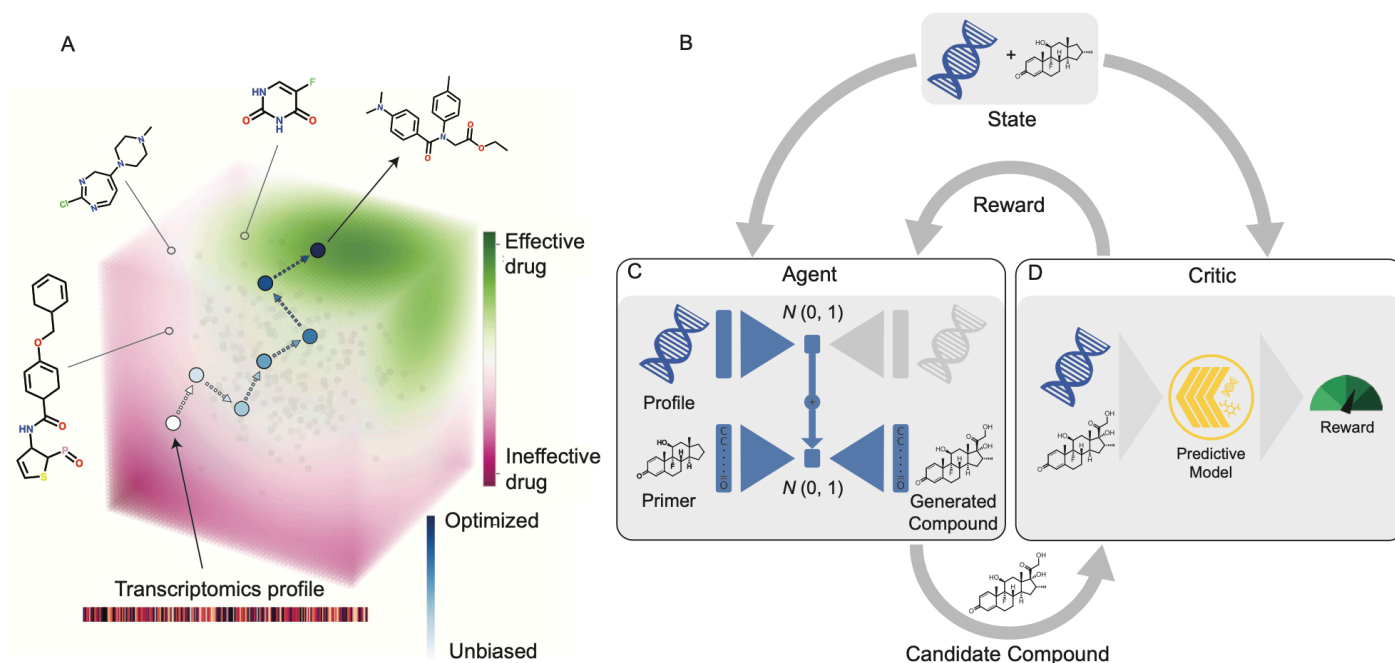


Fig. 11. The proposed framework for anticancer compound design against specific cancer profiles.

(A) The model is going through the chemical space in order to find effective compounds. From an unbiased molecule generator, compounds are sampled and screened in-silico versus the transcriptomic profiles of interest.

As a result, only the manifolds with the most effective compounds used for sampling from generator.

(B) The 'agent' (aka the conditional compound generator) is incorporated through two, initially separate Variational Autoencoders (VAEs). The compound generation begins with a wanted biomolecular profile such as a transcriptomic profile. Moreover, the profile is encoded into the latent space of gene expression profiles, through a pre-trained omics VAE.

(C) The molecular decoder of a solely pre-trained molecule VAE is decoding the latent representation of the profile to produce a candidate compound.

(D) The candidate compound is evaluated by a critic which is represented by a multimodal drug sensitivity prediction model that ingests the compound and the target profile of interest. The IC₅₀ efficacy, as predicted by the critic, is interpreted as reward.^[41]

3.3.2 INtERAcT

INtERAcT is reviewing cancer research publications and derive interactions by applying unsupervised machine learning^[35]. It is evident that, more and more biomedical publications are blooming, emerging a rich source of new knowledge. Thus, many biomedical facts are not accessible right away and therefore it is time-consuming for the researcher to identify them. So, INtERAcT in a completely unsupervised way and by extracting protein-protein interactions from a bulk of biomedical articles related to a broad range of scientific domains, helps the researcher to accomplish his study. More specifically, it makes use of vector representation of words which have previously been rated on a bulk of domain specific knowledge, and perform a new metric that estimates an interaction score between two molecules in the space where the corresponding words are embedded^[40]. This metric exceeds every other method used by far. It is also highly robust regarding to parameter choices, hence leading to the recognition of known molecular interactions in every cancer types studied^[40]. **(Fig. 12)**^[40]

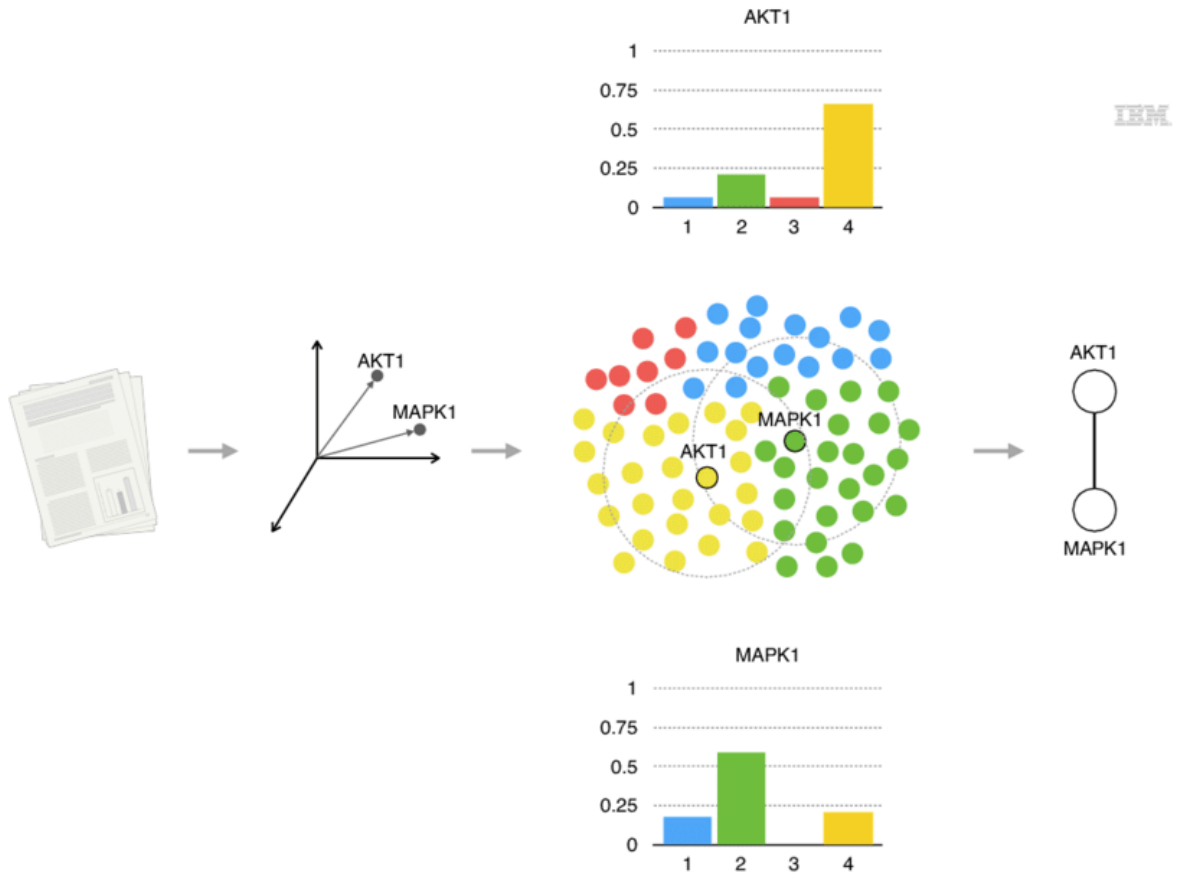


Fig. 12. Schematic representation of INtERAct.^[40]

3.3.3 PIMKL

PIMKL or **Pathway Induced Multiple Kernel Learning**, is a machine-learning algorithm able to predict phenotype from multiomic data^[35]. More specifically, this groundbreaking methodology is able to classify samples, at the same time, providing a pathway-based molecular fingerprint of the signature that underlies the classification. It uses multi-modal molecular measurements, based on the optimization of a mixture of pathway-induced kernels. These kernels are created by using prior knowledge as a form of a molecular interaction network and a set of annotated genes sets. After that, the pathway-induced kernels links is optimized aiming to classify a phenotype of interest. Last but not least, PIMKL identifies which molecular mechanisms are beneficial for the prediction of the considered phenotype as it shown in **Figure 13**^[42]:

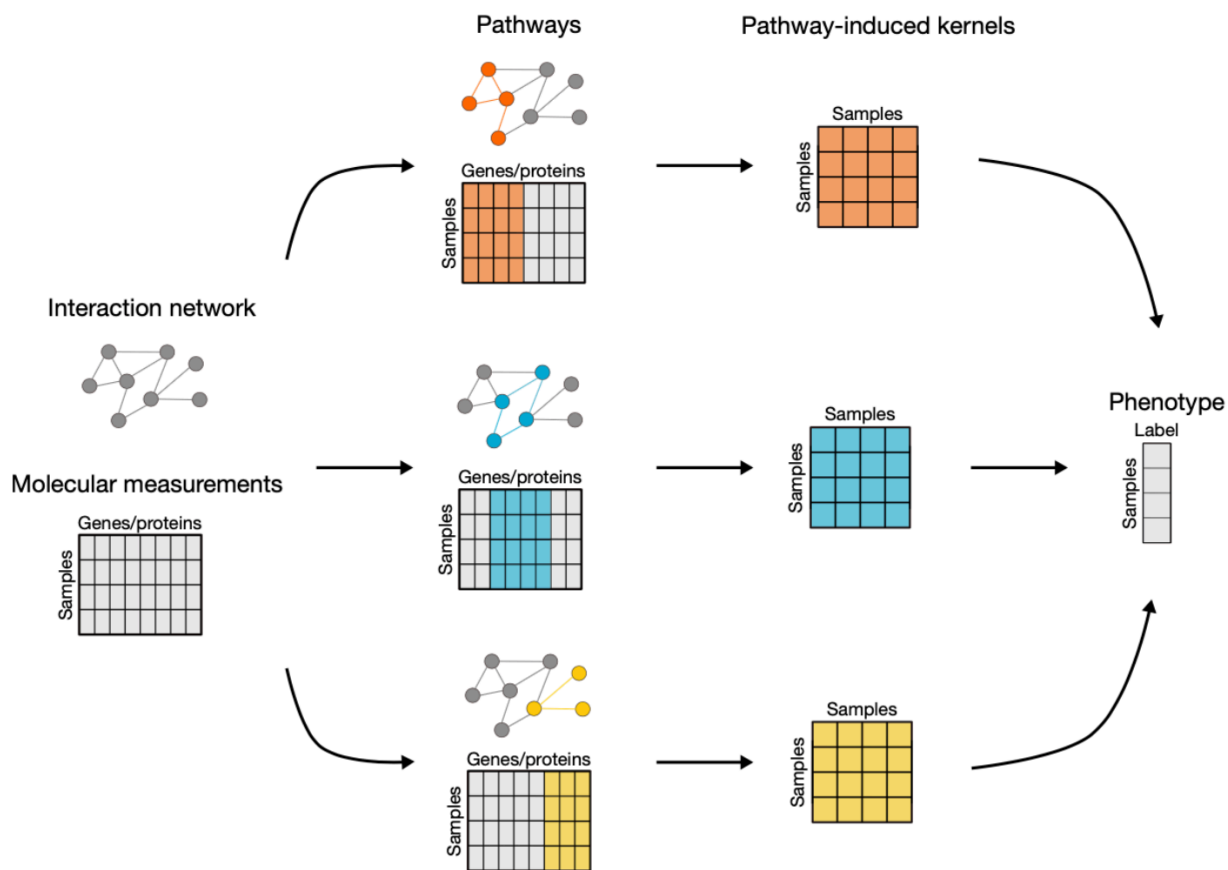


Fig. 13. PIMKL concept.

Molecular interactions are described by a network topology while similar sub-networks can be utilized to generate a mixture of pathway-induced kernels. The convex combination of kernels is then optimized to predict a phenotype of interest. The weights of the mixture assign an importance to each selected pathway, thereby shedding light on the molecular mechanisms that contribute to the specific phenotype.^[42]

3.3.4 Deep Neural Networks

Another interesting approach in drug development area is the classification of various drugs to therapeutic categories only by their transcriptional profiles via training **Deep Neural Networks (DNN)** on large transcriptional response datasets^[44]. DNNs are flexible multilayer systems of connected and interacting artificial neurons with several hidden layers, that execute various data transformations^[44]. Although, accomplishing state-of-the-art results and surpassing human accuracy is evident, the adoption of deep learning in biomedicine has been comparatively slow^[45]. Furthermore, significant levels of classification accuracy have been accomplished by traditional machine learning approaches but at the price of manually selected and tuned features^[44]. On the other hand, the greatest benefit of Neural Networks is the automatic feature of learning from massive data sets^[44]. **(Fig. 14)** ^[44]

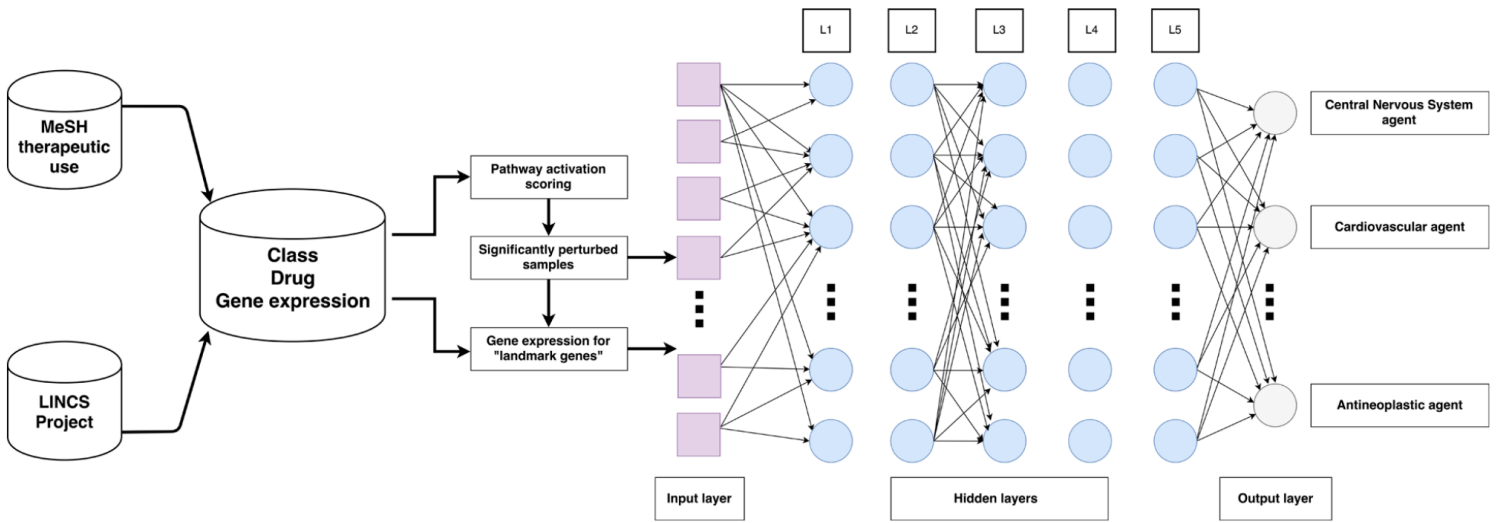


Fig. 14. DNNs concept.^[44]

According to Aliper *et al.*^[44], they used samples of 678 drugs across A549, MCF-7 and PC-3 cell lines from the LINCS Project and linked those to 12 therapeutic use categories derived from MeSH. To train the DNN, they used gene level transcriptomic data and transcriptomic data processed by using a pathway activation scoring algorithm for a pooled dataset of samples perturbed with different concentrations of the drug for 6 and 24 hours. DNN achieved high classification accuracy in both pathway and gene level data, even though the accuracy based on pathway level data was significantly better^[44]. **(Fig. 15)** ^[44]

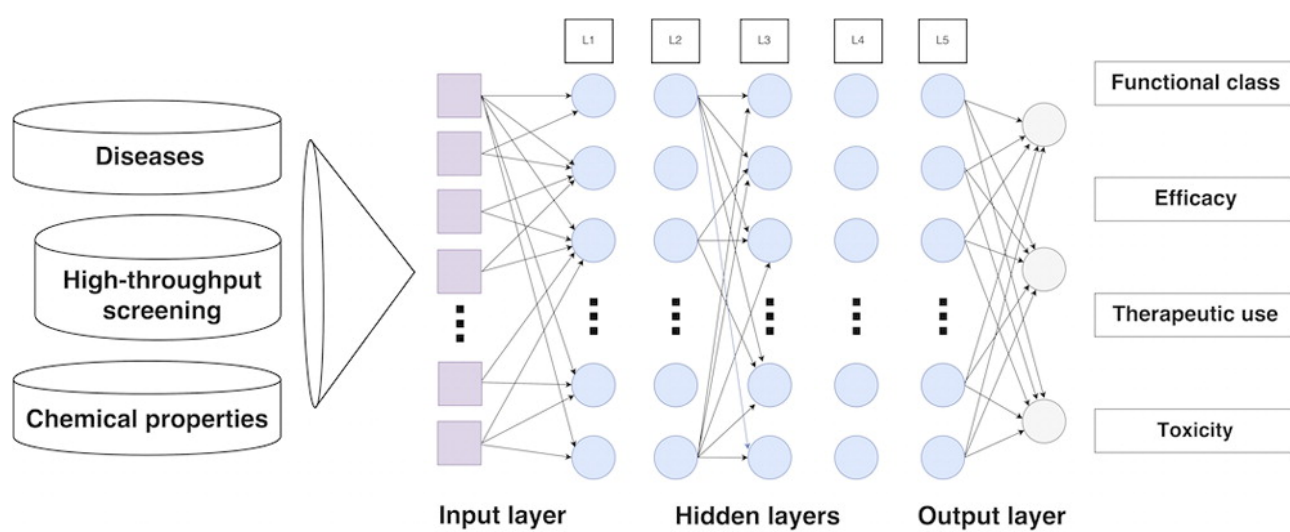


Fig. 15. Study design. Gene expression data from LINCS Project was linked to 12 MeSH therapeutic use categories. DNN was trained separately on gene expression level data for “landmark genes” and pathway activation scores for significantly perturbed samples, forming input layers of 977 and 271 neural nodes, respectively.^[44]

3.3.5 Protein structure prediction

Proteins comprised of sequences of amino acids and have four well defined levels of structure; *primary*, *secondary*, *tertiary* and *quaternary*. The way proteins are folded and structured can play a vital role for the body's proper function. For that reason, rigid quality control mechanisms are in charge of coordinating the rates of protein synthesis with degradation in order to prevent the formulation of intracellular aggregates. If that regulation fails, a pathogenic mechanism, is responsible for increased levels of misfolded and aggregated proteins^[91].

These aggregated proteins are commonly embodied with alpha-synuclein (α S) proteins which are the major component of Lewy bodies^[92]. Additionally, alpha-synuclein (α S) proteins' aggregate deposition constitute a pathogenic hallmark of all synucleinopathathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA)^[92]. Thus, it is important to be able to predict the structure of the proteins in order to understand the mechanism of these pathological conditions and cure them.

A typical pipeline for Protein Structure Prediction proposes intermediate prediction steps that called Protein Structure Annotations (PSA). Several PSA that are among others; torsion angles or contact density, and variations of the aforementioned ones such as half-sphere exposure and distance maps. A pipeline for the prediction of protein structure is represented in **Figure 16**^[89].

More precisely, the prediction of the structure of a protein can lead to the detection of the three-dimensional shape of a protein from its amino acid sequence. Additionally, by examining the correlated variation of homologous sequences, which helps in the prediction of protein structures, it is feasible to figure which amino acid residues are in contact.^[91]

In order to induce accurate predictions of the distances between pairs of residues, a neural network should be trained. These predictions, are going to be used for the development of a potential of mean force that could precisely present the shape of a protein. The resulted potential, could be optimized by using a gradient descent algorithm in order to produce structures without complex sampling procedures. The occurring system, that is called **AlphaFold**, can accomplish high precision even though for sequences that have fewer homologous sequences.^[90]

More specifically, the **AlphaFold** system is using three deep-learning-based methods for free modeling (FM) protein structure prediction. These methods described as follow^[88]:

- 1. Prediction of the distance between pairs of residues within a protein.*
- 2. Direct estimation of the accuracy of a candidate structure (termed the GDT-net).*
- 3. Direct production of protein structures.*

The first one is explained before. The second one, the GDT-net, as it is explained in **Figure 17**^[88], is trained in a distributed and continuous environment. Candidate structures are generated from actors that run simulated annealing along with the latest GDT-net for all proteins in the training set^[88]. At the same time, the GDT-net is trained by the learners on candidates sampled from the actors.^[88]

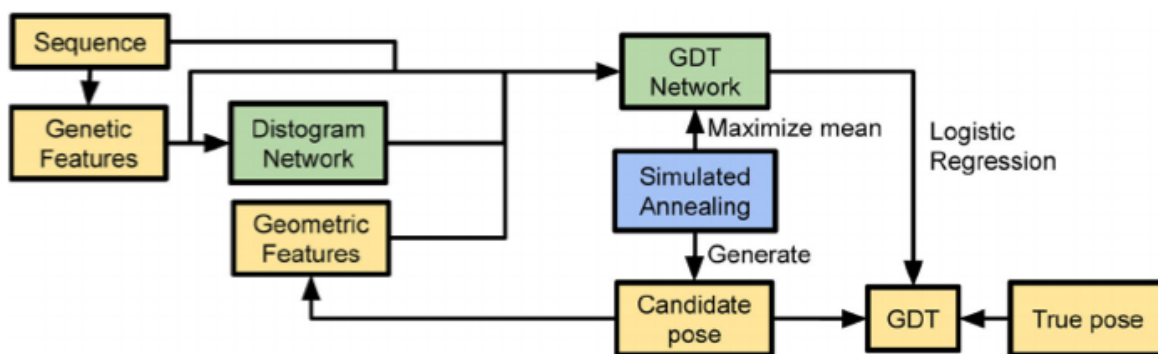


Fig. 17. A schematic of the GDT-net system (A). Feature extraction stages are shown in yellow, structure-prediction neural network in green, and structure realization in blue.^[88]

To sum up, Protein Structure Prediction systems are consisted of multiple specialized components with Deep Learning systems having an important role in them. Even though there has been significant advancement in this area over the last few years, particularly in the prediction of contact and distance maps, the structural, evolutionary and co-evolutionary information are still underdeveloped. Additionally, the dependence of the structure prediction pipelines on advanced and delicate techniques to recognize similarity between known and unknown structures and sequences, it is not clear if the predictions genuinely represent low energy structures^[89].

3.4 Image Analysis

A very useful examination tool in medical practice is image analysis and more specifically in chest radiography. Chest radiography is very valuable for the diagnosis of a disease because by examining it, specialists can decide whether a patient has a clinical condition -and what kind- or not. So, the automated detection of a chest disease, judging by the chest radiography, is one of the new trends in medical imaging research^[61]. Computer-aided detection (CAD) systems focuses on the artificial intelligence technology in the screening of specific disease (pulmonary nodules, tuberculosis, and interstitial lung diseases).^[61]

Chest X-ray or CXR is a diagnostic tool that is used mostly in medical practice and has a leading role in the diagnosis of lung diseases^[61]. Also, the cost of chest X-rays is very low and they can be easily operated. Currently, expert radiologists use X-rays to detect illnesses like lung disease and early lung cancer. But, the accurate interpreting of the information is a great challenge due to the overlapping of the tissue structures in the chest X-ray. Hence, computer-aided detection (CAD) systems can help experts to detect doubtful lesions that cannot be easily noticed, and so to enhance the precision of their detection.^[61]

The method that is followed in CAD systems is mainly separated into: image preprocessing, extracting Region Of Interest (ROI) regions, extracting ROI features and classifying disease according to the features. Furthermore, Artificial Intelligence has introduced new methods. More specifically, deep learning primarily replaced the process of feature extraction and disease classification in the traditional CAD systems. Additionally, it was also widely used in image segmentation and bone suppression of chest X-ray^[61].

Deep learning advances in medical imaging and large database construction

have exceeded trained experts in a plethora of medical imaging tasks such as pneumonia diagnosis, diabetic retinopathy detection, skin cancer classification, arrhythmia detection, and bleeding identification^[61].

Some of the most common diseases in chest radiographs are shown in **Figure 18**^[61]. CAD systems require many chest radiographs for the training, validation, testing and performance comparisons. Therefore, the creation of a large annotated medical image dataset is needed, but that is not easy and so, many researchers depend on publicly available CXR datasets^[61] such as Indiana dataset^[62], KIT dataset^[63], MC dataset^[64], JSRT dataset^{[65],[66]}, Shenzhen dataset^[64] and Chest X-ray 14 dataset^[67].

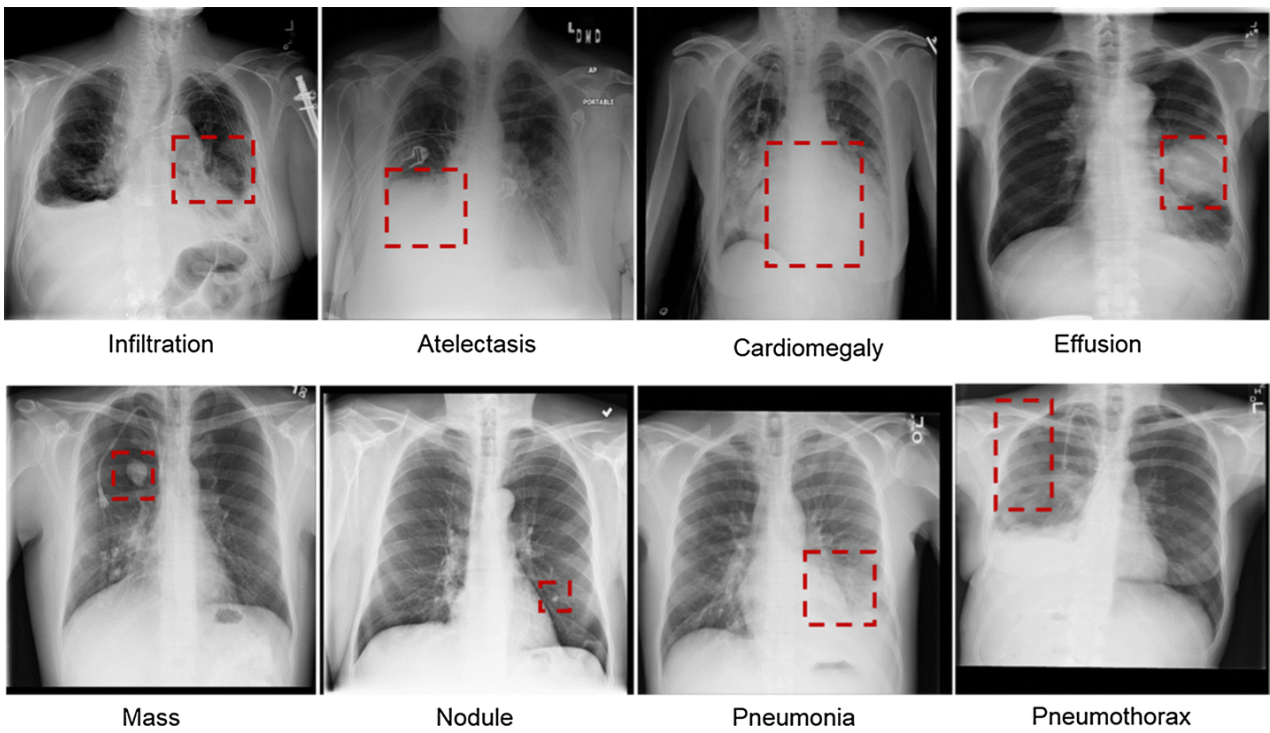


Fig. 18. Eight common diseases like the infiltration, atelectasis, cardiac hypertrophy, effusion, lumps, nodules, pneumonia, and pneumothorax observed in the chest radiographs.^[61]

Chest X-Rays Computer-aided detection algorithms are able to identify various diseases, and they are playing a crucial role as a second opinion for medical experts. Also, medical experts can have their workload minimised by computer-aided detection algorithms which can review many Chest X-Rays quickly.

Another application of AI in medical imaging is discrimination between pulmonary micro-nodules and non-nodules from computed tomography (CT) images^[68] with CNN models. As The National Lung Screening Trial Research Team^[69] stated, the main aim of early low-dose CT screening for lung cancer in high risk individuals could reduce lung cancer mortality by 20%.

More specifically, the detection of pulmonary nodules from CT images referred as crucial indicator of lung cancer. Particularly, pulmonary nodules can be described as small masses of tissue in the lung. They have round or oval shape and a diameter less or equal to 30 mm and in regard to their diameters they can be divided into three categories; micro-nodules (< 3 mm), small nodules (3–9 mm) and nodules (10–30 mm).^[68]

How deep convolutional neural networks (CNNs) have contributed to the detection and classification of the pulmonary nodules?

These automated pulmonary nodule detection systems basically include two steps: first, the screening of the candidate and second, the reduction of false positive. For the first step, the threshold should be set to the intensity and morphological parameters so the crude candidates can be examined. Then, for the second step, due to the tolerance of the threshold value for high sensitivity, a large number of false positives are produced. For that reason, the advanced classifiers are needed to reduce the false positive rate.^[68]

The main method that have been used is the following:

LIDC / IDRI dataset

In this method, the database is made up of 1018 CT scans derived from 1010 different patients where the scans of eight patients had been duplicated by inadvertence^[68]. All the CT images required are obtained from a publicly accessible medical images database named the Lung Image Database Consortium and Image Database Resource Initiative (LIDC/IDRI).^[70]

Firstly, in order to be attained more accurate and efficient results, every scan was analyzed individually by four medical experts of different institutions with the unique aim of annotating the existing lung nodules, which is also called the “blinded reading”^[68]. Then, the results were combined and forwarded to each of the four medical experts. That allowed them to look both their own annotations and the ones marked by the other three co-workers and decide about the existing lung nodules. This is also known as “unblinded reading”^[68]. An example of lung CT image containing a nodule is shown in **Figure 19**^[68]. Nodules are separated in Nodules (3–30 mm), Micro-nodules (< 3 mm) and Non-nodules (> or equal 3 mm)^[68].

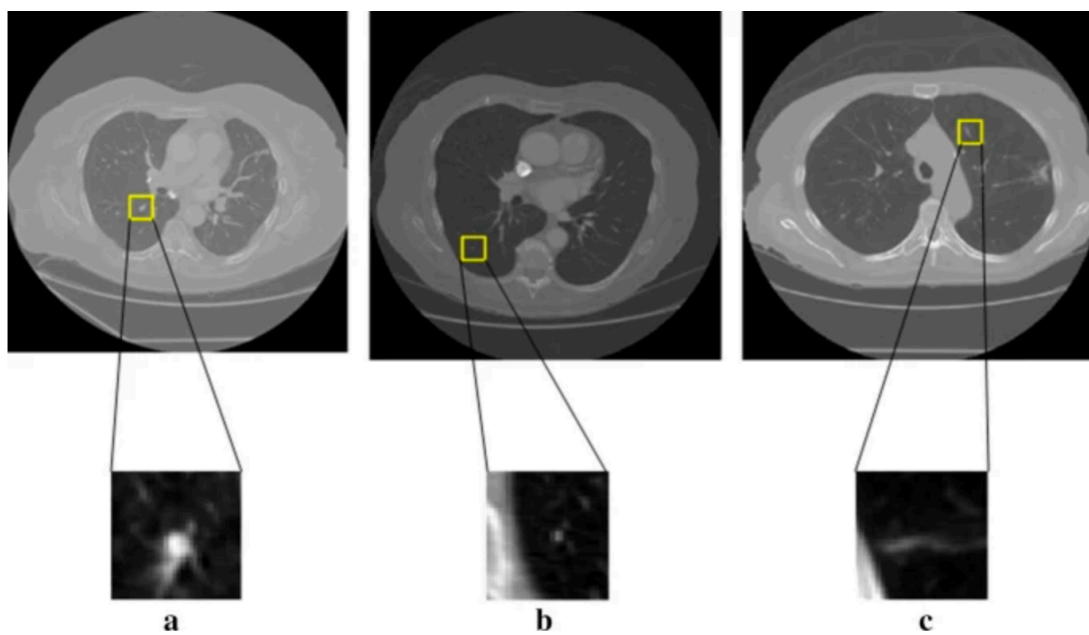


Fig. 19. Examples of the suspected lesions and non-nodules identified in the LIDC/IDRI dataset.

a Nodules ($3 \text{ mm} \leq \text{diameter} < 30 \text{ mm}$); **b** micro-nodules (diameter $< 3 \text{ mm}$);

c non-nodules ($3 \text{ mm} \leq \text{diameter}$).^[68]

CNN models

Since micro-nodules and non-nodules are both very small objects, three CNN models with small filters and different depths were designed and presented in **Figure 20**^[68]. As showed, the first CNN model (M_1) comprises one convolutional layer (C_1) and one MaxPooling (MP) layer succeeded by a fully connected (FC) layer, a dropout (D) layer and two fully connected (FC) layers including the Softmax layer^[68]. The second CNN model (M_2) consists of two convolutional layers (C_1 and C_2). The first one (C_1) is followed by a rectified linear activation (ReLU) layer and a MaxPooling (MP) layer. After that, the second convolutional layer (C_2) is followed by a dropout layer (D) and two fully connected (FC) Mlayers including the Softmax layer. Last but not least, the third CNN model (M_3) is consisted of four convolutional layers (C_1, C_2, C_3, C_4). Each of the first three convolutional layers is followed by a MaxPooling (MP) layer. The last convolutional (C_4) layer is followed by a dropout (D) layer and two fully connected (FC) layers including the Softmax layer.

Three CNN models were developed in order to differentiate micro-nodules and non-nodules from CT images. The main utilization of these models is to eliminate the false positives in automated pulmonary nodule detection^[68].

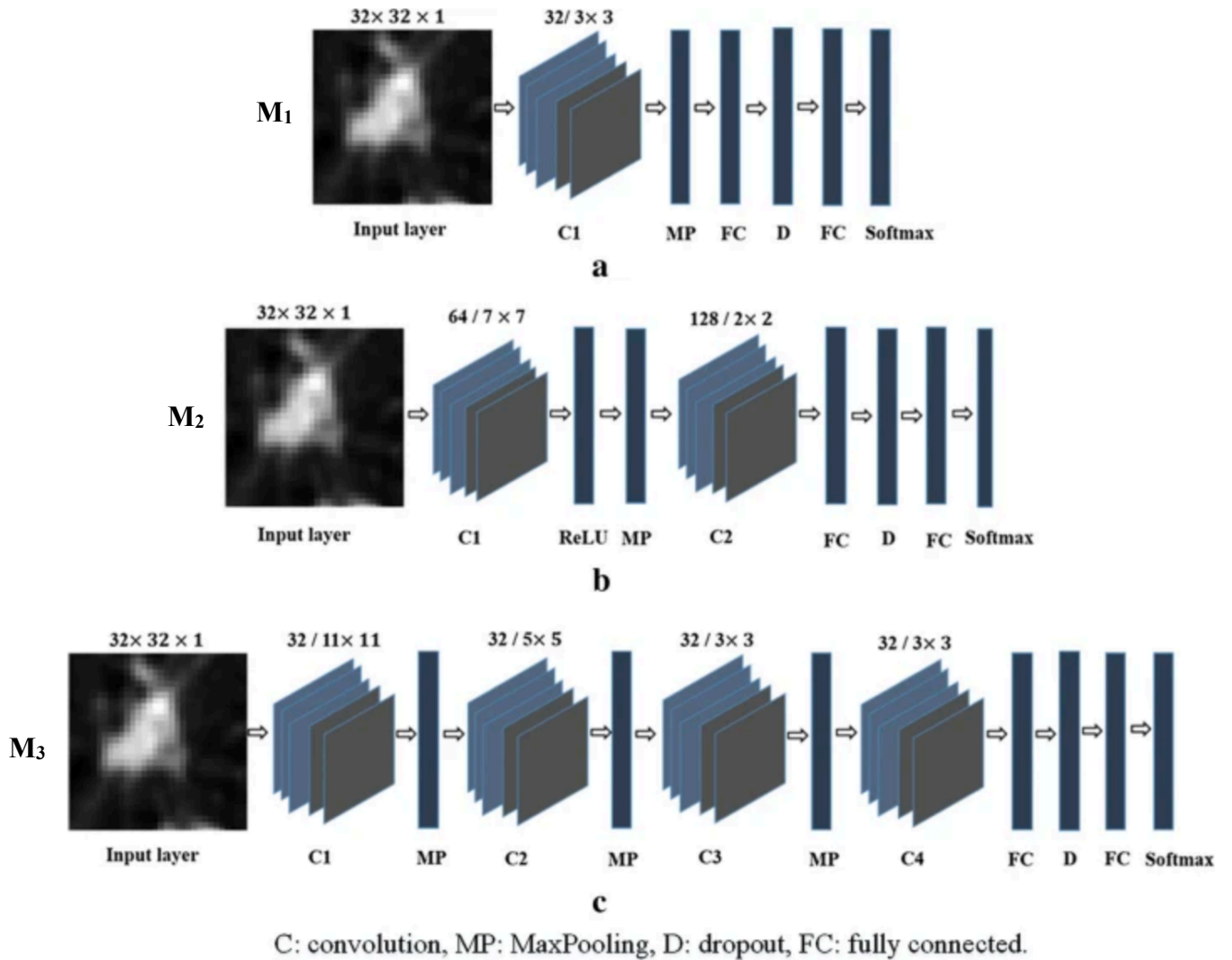


Fig.20. The architectures of the proposed three CNN models. **a** The first CNN model (M_1); **b** the second CNN model (M_2); **c** the third CNN model (M_3).^[68]

3.5 Radiomics and Radiogenomics

The term 'Precision oncology' is referring to the customization of cancer care. A patient experienced a customized cancer care will have practices and/or therapies tailored to him/her. In this way, it can be achieved maximization of the success of preventive and therapeutic interventions with minimum side effects^[75]. The biggest part of precision oncology related research has gathered in the molecular characterization of tumors with the use of genomics based approaches. Nevertheless, that requires tissue extraction by tumor biopsies and even though many approaches based on genomics have been applied successfully in clinical oncology, some inherent limitations to biopsy based assays exist^[75]. Different than biopsies, medical imaging is non-invasive and can give information associated with the entire tumor phenotype, as well as the intra-tumor heterogeneity^[75]. Recent advances in high-resolution image acquisition machines along with computational hardware provide the precise and efficient quantification of tumor phenotypic characteristics.^[75]

The new age of precision medicine is directed in a new emerging translational field of research called Radiomics. This novel area is aiming to detect associations between qualitative and quantitative information derived from clinical images and clinical data, with or without associated gene expression to support evidence-based clinical decision-making^[71]. More specifically, the main goal is to discover new imaging biomarkers, by high-throughput extraction of quantitative image features like shape, histogram and texture that captures tumor heterogeneity.^[72]

Imaging techniques can give information about the tumor non-invasively and also provide information about the underlying genetic makeup^[74]. Radiomics can be applied to a great variety of standard-of-care clinical images like CT, MRI or PET and

it can be used in plenty clinical practices; diagnosis, prediction of prognosis, and evaluation of treatment response^[72]. Additionally, a great advantage of Radiomics' analyses is that they can be performed in tumor regions, metastatic lesions, as well as in normal tissues.^[71]

The radiomic process can be broken down to multiple serial steps including image acquisition, tumor segmentation, feature extraction, predictive modeling, and model validation as is shown in **Figure 21**.^[72]

Each and every step has definable inputs and outputs. Also, careful evaluation is essential for the creation of robust and reliable models. In that way, models will be transferred into clinical practice for the purposes of prognosis, non-invasive disease tracking, and evaluation of disease response to treatment. ^[71]

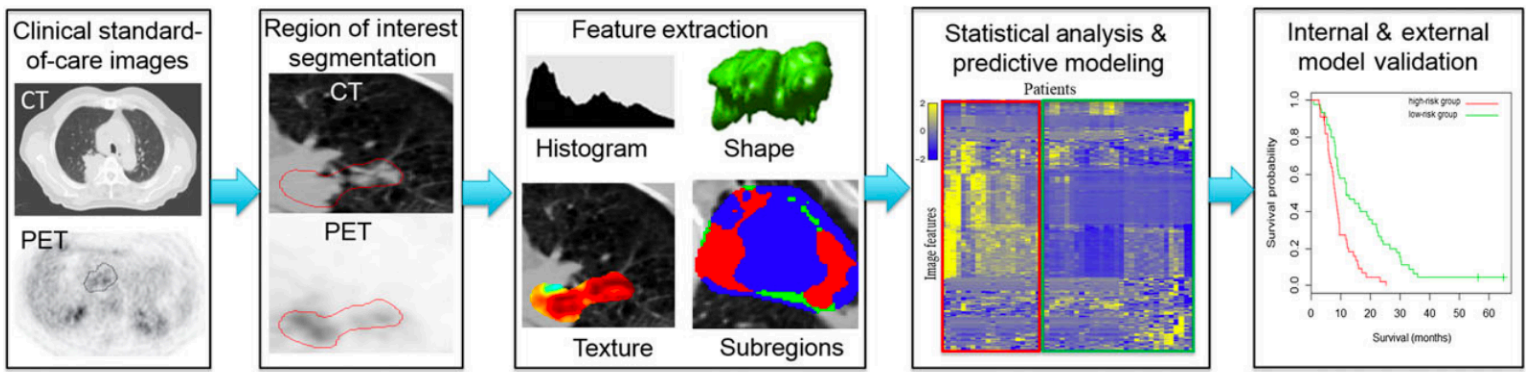


Fig. 21. Workflow of a typical radiomic study.[72]

The main idea that is hidden behind the process is that both morphological and functional clinical images include qualitative and quantitative information that may reveal the underlying pathophysiology of a tissue. When combined with appropriate statistical or bioinformatics tools, models can be developed that will potentially improve prediction accuracy of clinical outcomes [72].

The calculation of the quantitative features of the Radiomics can be done by a software which takes the medical images as an input. Also, many tools have been developed in order the software to be user-friendly in terms of use and to perform well in terms of calculation time. But still, the attentive check of the quality of the input data as well as the selection of the optimal parameters are still questioning and thus a reliable and robust output cannot be guaranteed without a question[71].

Another important thing to have in mind is, that parameters such as the type of image acquisition, post processing, and segmentation can affect the quality of features extracted, their association with clinical data, and also the model derived from them[71].

A related field to Radiomics is Radiogenomics. It is an emerging research field focusing on building multi-scale associations between medical imaging and gene expression data in order to identify the underlying biological basis of imaging phenotypes[73]. More specifically, that field is associated with the relations between radiomic features at the tissue scale and underlying molecular features at the genomic, transcriptomic or proteomic level. **(Fig. 22)**[73]

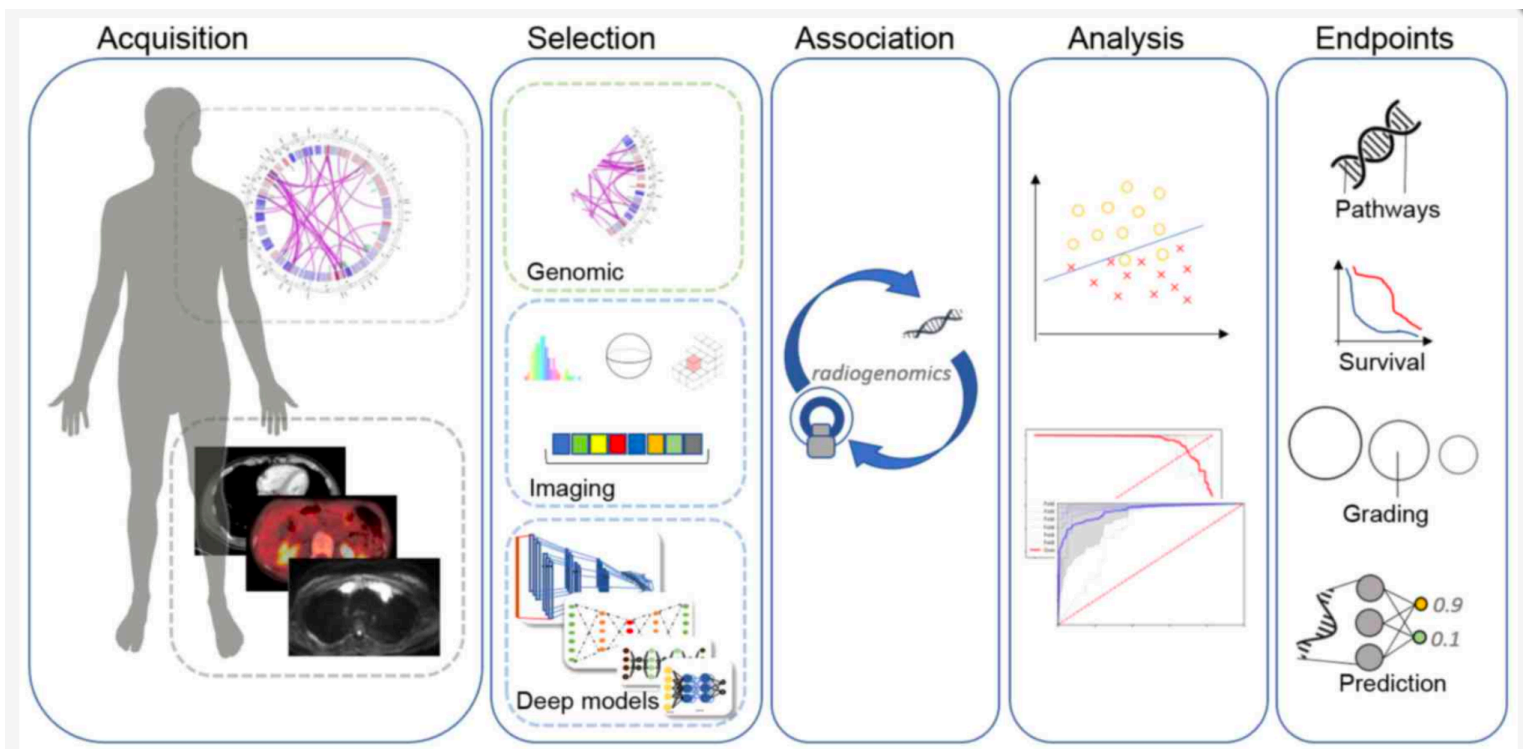


Fig. 22. The pipeline of radiogenomics.

A predetermined data acquisition protocol for genomic and imaging data, feature extraction and feature selection based on statistical analysis is included. The association and modeling of these highly discriminative biomarkers holds the potential to enhance robustness in decision support systems. [73]

These molecular/genetic alterations cause changes at the tissue level that can be detected computationally regarding radiological appearance by properties such as tissue shape and texture. Suchlike changes can yet be very subtle or invisible to the human eye. As a consequence, artificial intelligence (AI) techniques such as deep learning have provided the means to detect and decode these changes/patterns in medical images and link them with molecular/genetic characteristics. In this way, the development of robust decision support systems and hybrid prognostic, predictive and diagnostic signatures is achieved.^[73]

Furthermore, radiogenomics can also improve diagnosis, the non-invasive prediction of molecular background and survival prediction in oncology through association of genomic data with radiomics' features obtained from a non-invasive design shedding light on underlying oncogenic mechanisms^[73]. Radiomics and radiogenomics are two fields that have significant growth in the past few years. Nevertheless, a lot of radiomic studies recognised new imaging signatures that have displayed improved diagnostic, prognostic or predictive performance in comparison to currently used imaging metrics, like tumor size, in many oncologic applications.^[72]

An interesting example of Radiogenomics is their application in breast cancer by using dynamic contrast enhanced MRI and gene expression profiling. The main goal of this application was to examine the capability of an automated, quantitative radiomics platform on magnetic resonance (MR) breast imaging to presume underlying activity of clinically relevant gene pathways acquired from RNA sequencing of invasive breast cancers prior to therapy.^[74]

According to Yeh, A.C. *et al.*^[74] study, radiomic and gene expression data from 47 cases were obtained. **(Fig. 23)**^[74]. At first, the analysis of clinical DCE-MRI images of these cases together with corresponding gene expression data derived from RNA

sequencing resulted in 119 gene expression pathways that had at least one significant association with a radiomic phenotype. To analyze which pathway categories had the largest number of associations with radiomic phenotypes, the average number of significant associations per pathway were examined. The result was that by using MR imaging it is feasible to identify tumors that are more immunologically active. More precisely, MR imaging of breast tumors can infer underlying gene expression by using RNA sequencing.^[74]

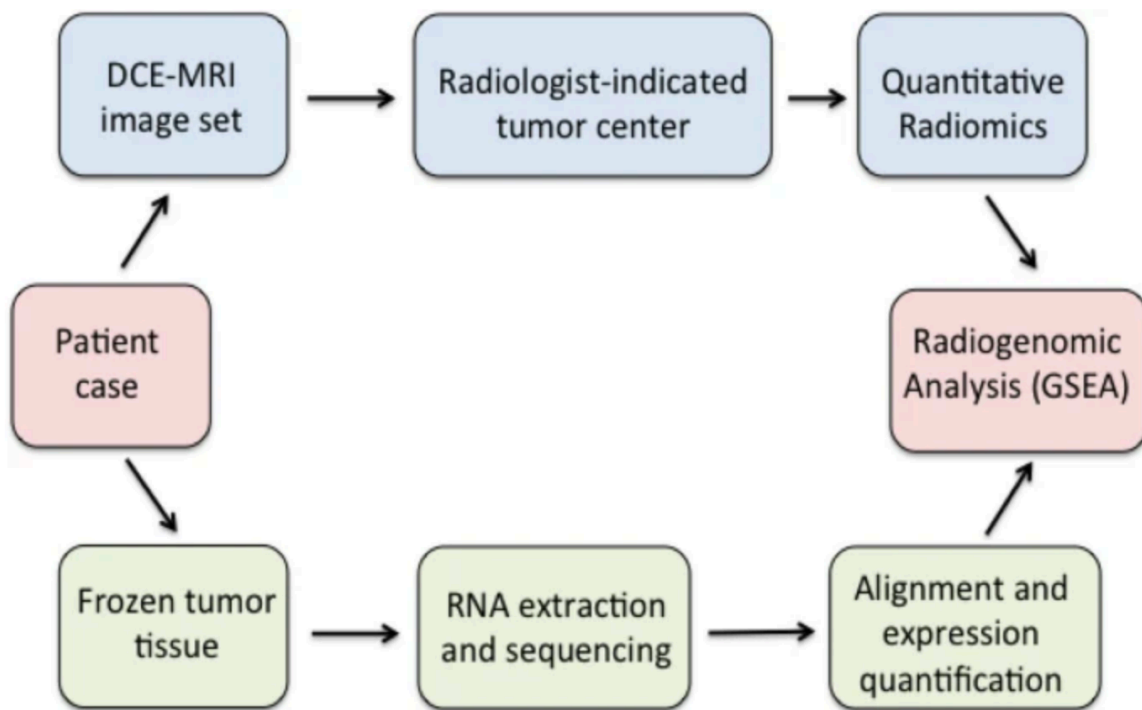


Fig. 23. Schematic of radiogenomic pipeline and analysis. From each case we obtained fresh frozen tumor tissue as well as the corresponding set of dynamic contrast-enhanced MRI images of that tumor. Frozen tissue was then processed for total RNA extraction, sequencing, and expression quantification while the images were subjected to quantitative radiomic analysis after a staff radiologist indicated the tumor center for input. Final radiogenomic analysis combined these two datasets for gene set enrichment analysis.^[74]

Another example of how Radiomics can contribute to medicine is by investigating the machine-learning approaches for prognostic radiomic biomarkers. How can that be achieved? An important characteristic of Radiomics is that it can extract and mine a great number of medical imaging features and thus quantify tumor phenotypic characteristics^[75]. But that is not the way to succeed. It also needs highly accurate and solid machine-learning approaches.

In machine learning, computational methods/models are using data to enhance performance or make accurate predictions^[75]. Hence, different machine-learning models should be compared for radiomics based on clinical biomarkers. A very important process in machine learning is classification. It is considered as a supervised learning task of deriving a function from labeled training data^[75]. As training data, a set of examples is noted, where each example is expressed as a pair of an input vector (features) and a desired output value (target or category label)^[75]. These training data are analyzed by a classification algorithm (classifier) so as to derive a hypothesis (function) that will be utilized for predicting the labels of unseen observations ^[75]. In order to investigate the machine-learning approaches, Parmar *et al.*^[75] studied for prognostic radiomic biomarkers with a total of 440 radiomic features being extracted from the segmented tumor regions of the pre-treatment CT images.

(Fig. 24)^[75]

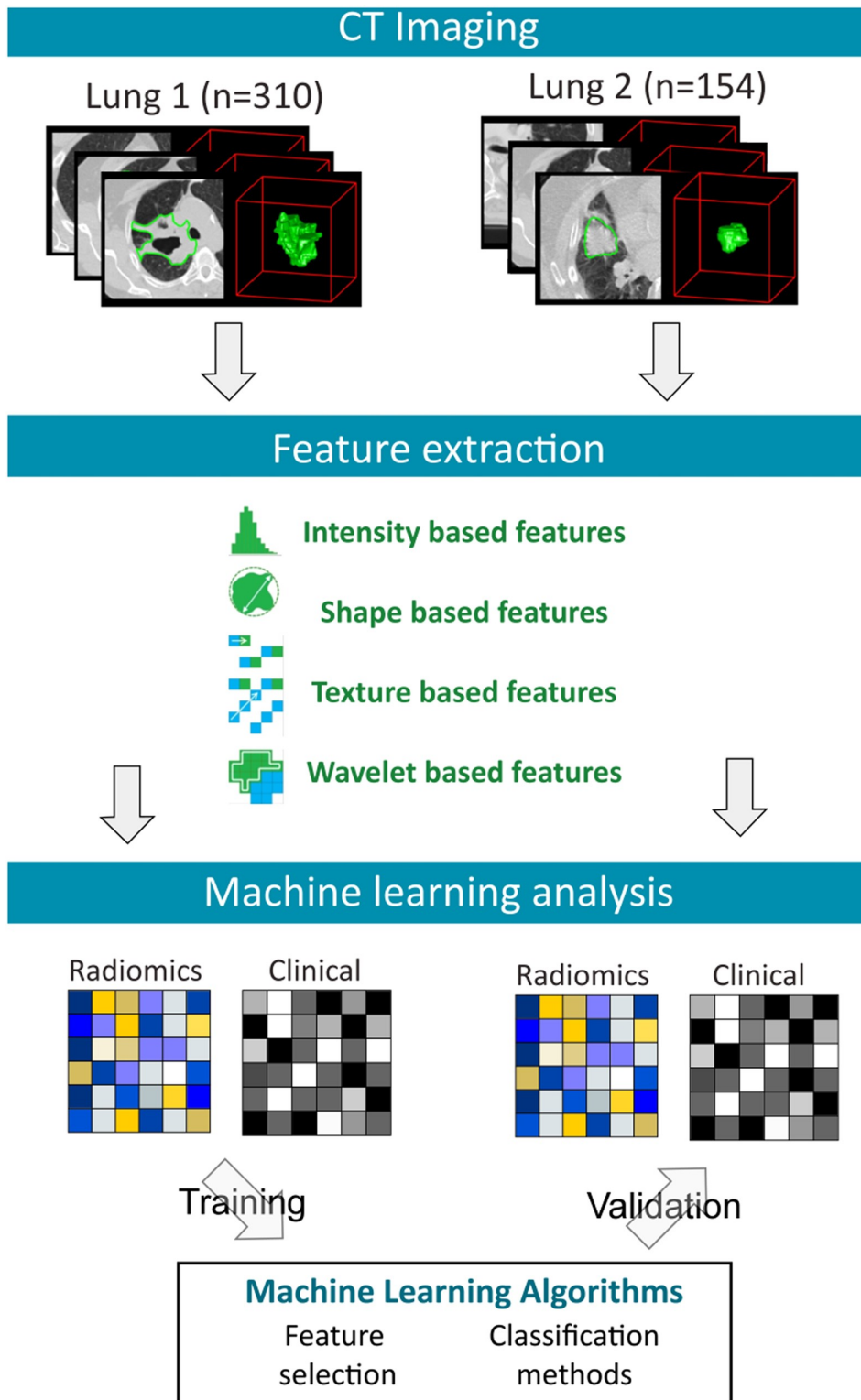


Fig. 24. The pipeline of the study.^[75]

A company that applies radiomics is **Enlitic**. It was created at San Francisco, CA and its main purpose is to develop a deep learning tool for radiologists that enhances their reading and analysis^[84]. It is engaged to satisfy and even better to surpass applicable regulatory, statutory, and quality requirements, in support of improving patient healthcare^[83]. **Enlitic** incorporates deep learning AI in radiology in three different ways.

Firstly, it operates quality assessments or a second read posterior the initial interpretation on the images and the report. Secondly, it emphasizes to incoming studies in order to prioritize and appropriately route through the organization and last but not least to provide real-time diagnostic support alongside a radiologist^[84]. Their mission is to create products that will help healthcare professionals measure, detect, characterize, track, and triage anomalies in radiological images in order to diagnose anomalies in less time and with greater precision^[84].

How this company works? A trained deep learning model is detecting visual patterns in a chest X-ray for a differential diagnosis. Also, **Enlitic's** AI model is able to find malignancies in low-dose chest CT lung cancer screening studies up to two years earlier than radiologists.^[84]

3.6 Clinical Trials

In the process of drug development, clinical trials is one of the most crucial and critical steps. The clinical development phase is responsible for ensuring the efficacy and safety of new medicines. It is formed from four phases as it is presented in **Figure 25**.^[77]

The drug pipeline is difficult to be managed and thus it is challenging to adeptly proceed to costly and time-consuming clinical trials as rapidly as possible. Subsequently, every delay in the process to get out the market means millions of dollars in lost revenues for a blockbuster drug.

Most of the time, in clinical trials, all the information needed is gathered by human services suppliers amid patient visits without direct information from patients. All that information is collected from individualized computing gadgets (advanced cells and tablets) which billions of individuals are using. In this way, those data from every patient in a continuous and convenient way is entered to the devices and apps and stored on their own cell phones. Especially, information for non-transferable ailments, such as hypertension and diabetes can be collected and conveying accurately through wearable medicinal gadgets. Next, all collected information will be publishing from cloud based clinical trial frameworks in order the results and registries of examiners and patients to be accessible in web. ^[78]

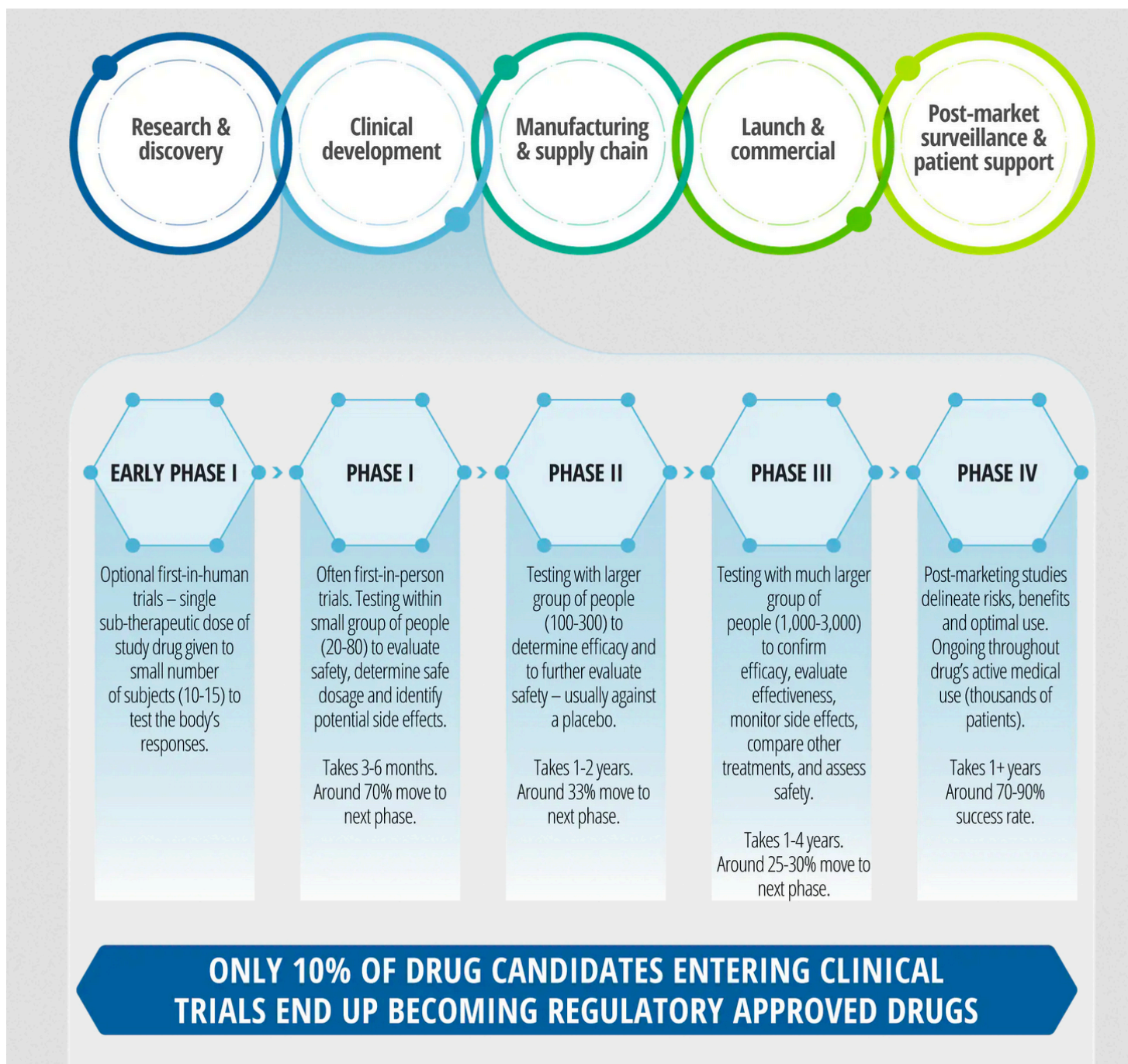


Fig. 25. The traditional approach to clinical development is a lengthy process with only 10 per cent success rate. [77]

To make things easier, AI has also been applied in the design of clinical trials. At each and every clinical trial a protocol is followed and describes precisely how the study will be conducted. If any problem occurs and modifications to the current protocol are necessary, months of delays and hundreds of thousands of dollars may be added to the total cost^[76]. (**Fig. 26**)^[76]. In order to avoid such a situation, all the prior information needed for the design of a trial should be taken from numerous sources, along with comparable studies, clinical data and regulatory information. For that purpose, AI-powered software is able to process all of that information faster, as well as to gather more data than a professional.^[76]

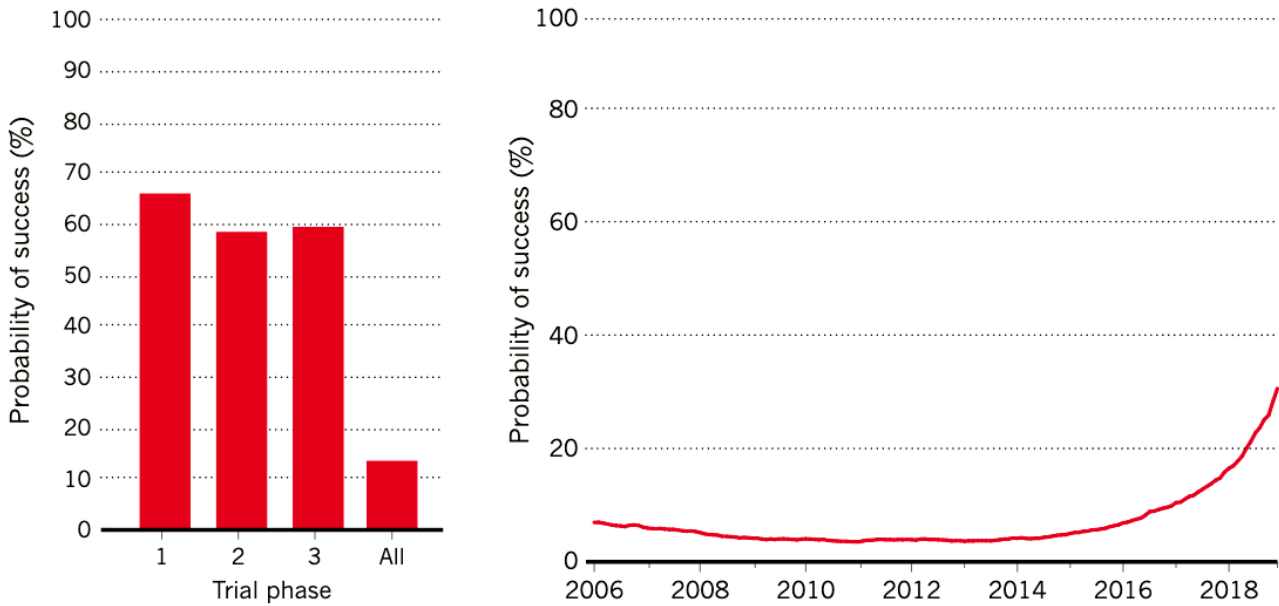


Fig. 26. THE STATE OF CLINICAL TRIALS. The success rates of clinical trials are low. Between January 2000 and October 2015, just 13.8% of drug candidates successfully navigated all three stages of clinical testing (left).

Success rates declined for much of this period, but since 2015 it seems the trend has begun to reverse (right).

Shaded area represents the estimated probabilities of success if all clinical trials yet to be completed failed (lower bound) or if all succeeded (upper bound).^[76]

Trials.ai, a start-up company in San Diego, California, is specialized in designing better trials protocols via its AI tool. More specifically, by using Natural Language Processing (NLP) and other AI techniques collects and analyses publicly available data like journal papers and drug labels. Then, by using those data, the company's software designs the customer's proposed trial, based on aspects such as the strictness of its eligibility criteria and the affect those could have on outcomes like cost, length or participant retention. [76]

Furthermore, an important thing to have in mind is that even trials with well-designed protocols must rely on participants to follow instructions. Again, AI has given the solution to that problem. **AiCure**, a data-analysis company in New York City provides a platform that allows people to use their smartphones to record videos of themselves taking medication. Afterwards, **AiCure's** software is using computer-vision algorithms that analyses those images and identifying the person and the pill, confirming whether it was taken.[76]

3.7. Healthcare

The current successful uses of artificial intelligence in healthcare system constitute a result of the fast-growing accessibility of healthcare medical data and the advances in the big data diagnostic techniques^[80]. In today's world, healthcare tends to be more personal, predictive, preventative and participatory^[79]. Also, the modern healthcare technology by introducing pioneering products and services, helps people live healthier and longer lives. Nevertheless, the aim of artificial intelligence (AI) in healthcare is to examine and determine patterns in large and complex datasets in less time and more accurate than before.^[80]

The major applications of AI in healthcare and research can be divided in four categories. In the first three categories lie all the applications that efficiently treat big data and issue quick access to data so as to solve issues linked to healthcare^[79]. These applications include; living assistance for elderly and disabled people, natural language processing techniques and fundamental research activities. The fourth category of AI applications includes the diagnosis, detection and prediction of diseases.^[79]

In the first category, AI health apps have the potential to empower people to evaluate their own symptoms and care for themselves when possible^[80]. More specifically, in the area of assisted living for elderly and disabled people, AI applications that use interactive smart robotic systems are opening the way for improvements in life quality, increased sense of dignity and independence^[79]. Particularly, scientists developed smart home functions and tools, such as intelligent solution models based on wireless sensor networks, data mining, and AI, for people with loss of autonomy (PLA).^[79]

“Smart communication architecture” systems for “ambient assisted living”

(AAL) have allowed AI to process information that have been collected not from one but from different communication channels or technologies. That development helps the user to determine the appearance of events in the network environment and thus the need of assistance for elderly people.^[79]

SALSA intelligent agent can help elders with daily medication activities. Also, machine learning in motion analysis and gait study can warn the user for hazardous actions and activate preventative measures. In this case, sensors gather data about the ambient environment and human behavior so as to be analyzed by cloud computing or edge intelligence. Then, a decision is made regarding the actions that have to be taken. These actions include alarm activation or preventive measures. Also, a significant extension of the expert system for memory rehabilitation (ES-MR) for amateur users is an expert system based on AI combined with mobile devices and personal digital assistants (PDAs) that is able to give aid to people with lasting memory damage by improving their memory capabilities^[79]. In **Figure 27**^[79] the model for AAL is showed.

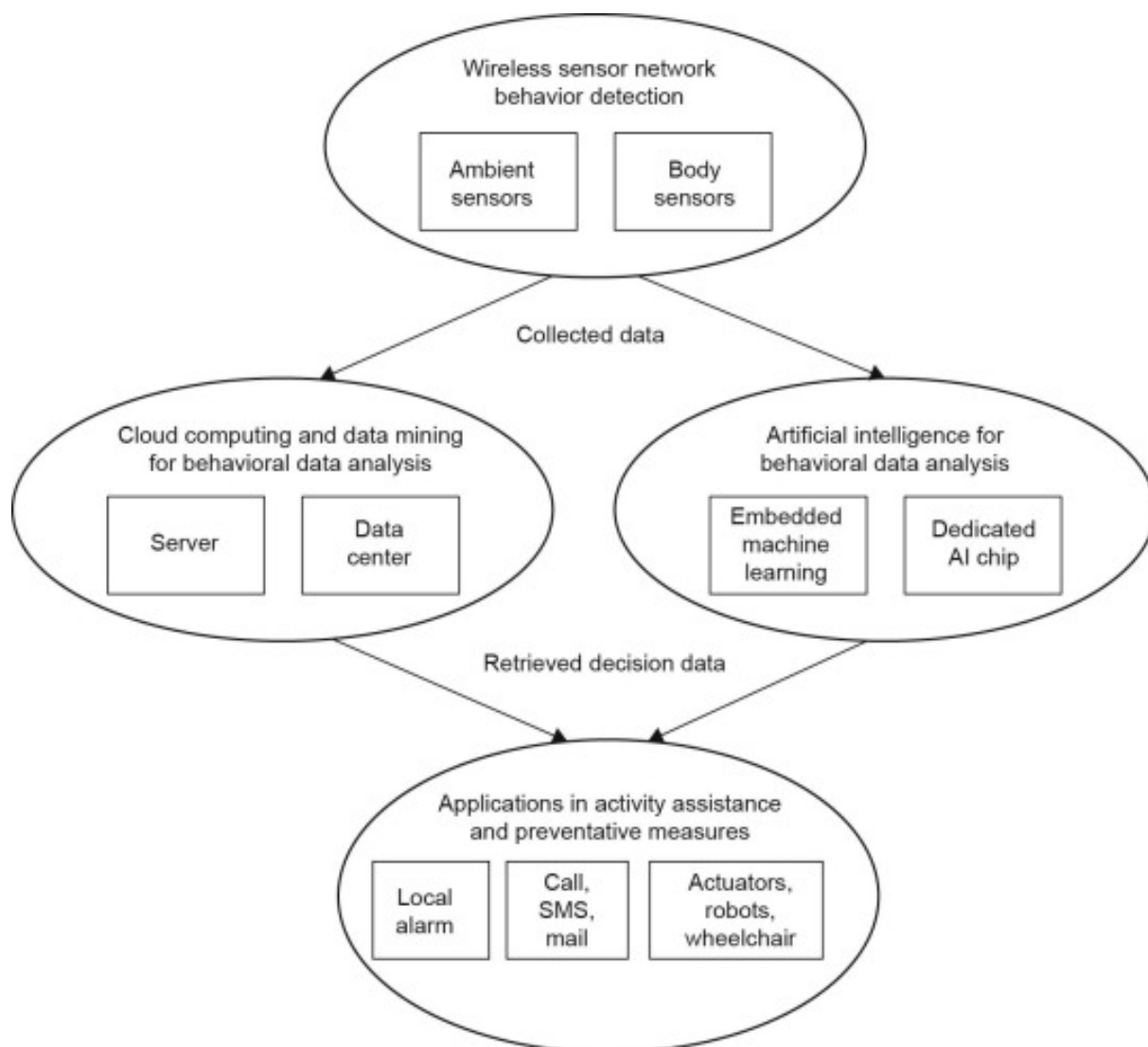


Fig. 27. The proposed model of AAL.^[79]

Another category is the development of human–machine interfaces (**HMI**s) based on facial expression analysis, trained neural networks (NNs). **HMI**s require the use of specific image-processing steps to recognize human facial expressions as commands^[79]. This application allowed people with disabilities to control wheelchairs and robot assistance vehicles without a joystick or sensors attached to the body^[79]. Some applications of such systems are:

RUDO, is an ambient intelligence system (**AmI**) for blind people that provides assistance in home environment. It consisted of several modules that support or ensure recognition of approaching people, alert when other household members are moving in the flat, work on a computer, supervision of (sighted) children, cooperation of a sighted and a blind person (e.g., when studying), control of heating and zonal regulation by a blind person^[81]. (**Fig. 28**)^[81]

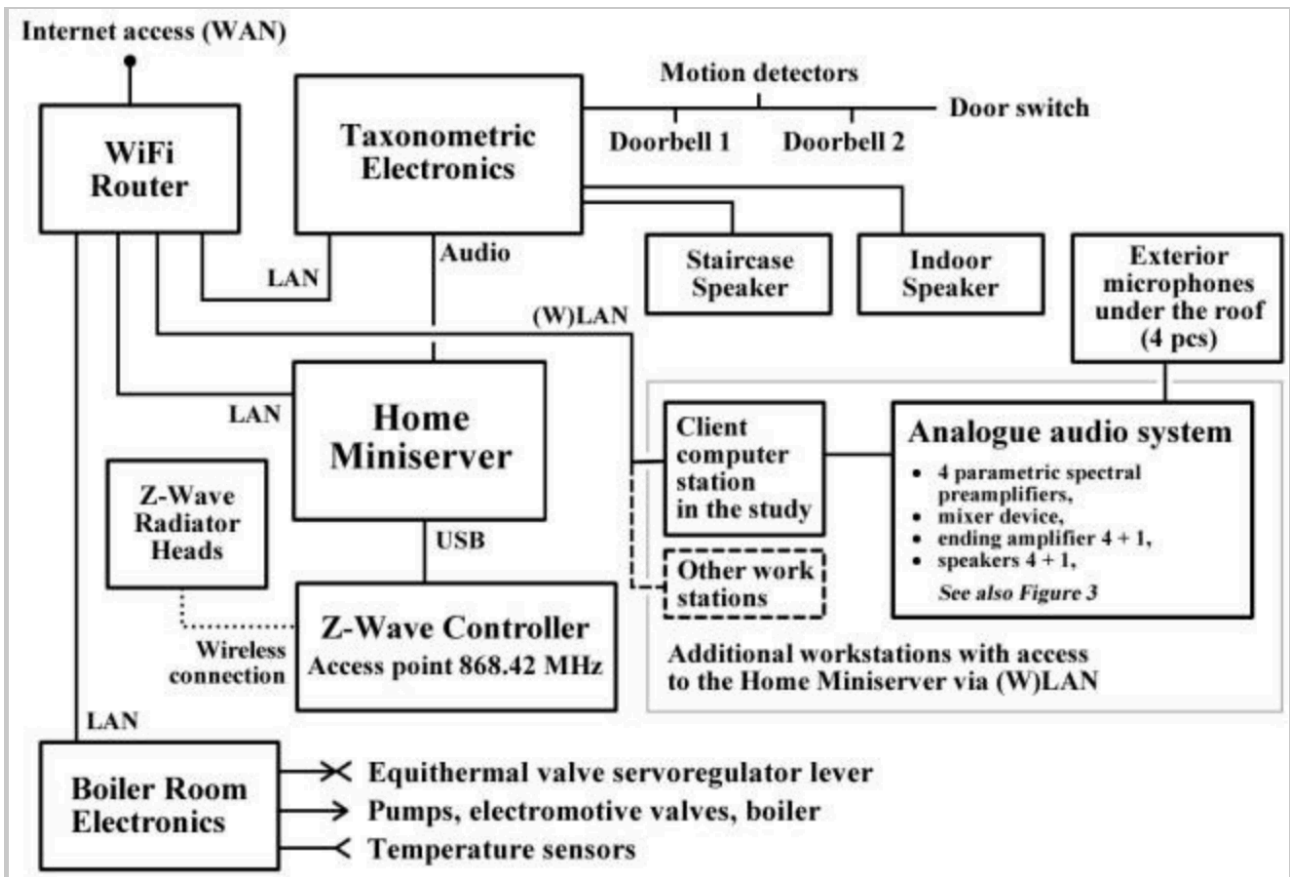


Fig.28. Block diagram of the main hardware components of RUDO system. This is the form in which the prototype of the system has been implemented in a detached house.^[81]

Smart Care, an intelligent assistant which provides aid to an expecting mother to take care of herself, is a smart device based tool which aims to decrease maternal mortality and birth of malnourished child. It consisted of a cloud based system, where all the information will be reserved in the global database. Furthermore, the system also uses local database of the device.^[82]

How it works? All the information stored in the application is synced whenever it connects with the internet. If not connected, the user can use the system with the information stored in the local database. From all that information stored in the cloud database, expert doctors, gynecologists and other social organizations will monitor the conditions of the expecting mothers. Last step, all the information will be shared with the concerned experts and researchers to enhance the maternity conditions of our country. **(Fig. 29)**^[82]

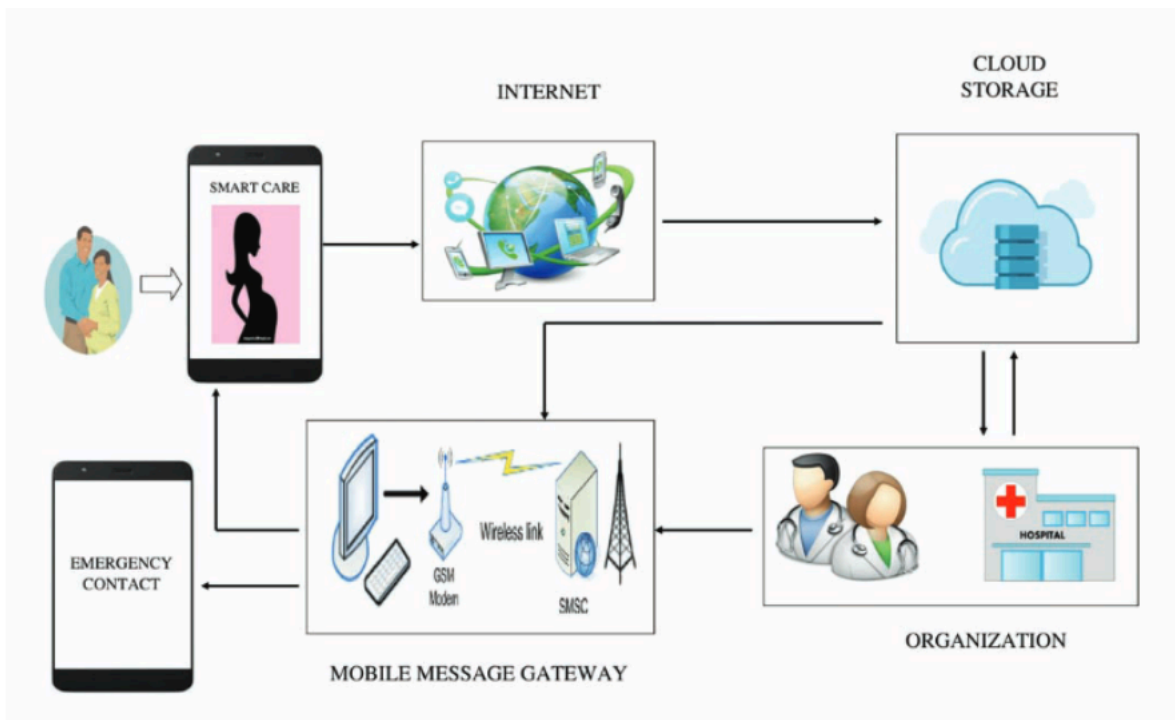


Fig. 29. The System Architecture of Smart Care.[82]

The fourth category of AI applications contains intelligent agents called the **Computational Modeling Assistant (CMA)**. These help biomedical researchers to build simulation models from the conceptual models they have in mind that can be executed. In **Figure 30**^[79] a broad view of the process flow and interactions between a CMA and human researchers is showed. The CMA is equipped with a vast of knowledge, methods, and databases. As an input the CMA is getting biological models which are represent researcher's hypothesis. CMA's intelligence gives it the opportunity to incorporate all this knowledge and these models and then convert the hypothesis of the researchers into concrete simulation models. The best models are selected and the CMA generates simulation codes. Hence, CMA allows a substantially accelerated research process and enhanced productivity. ^[79]

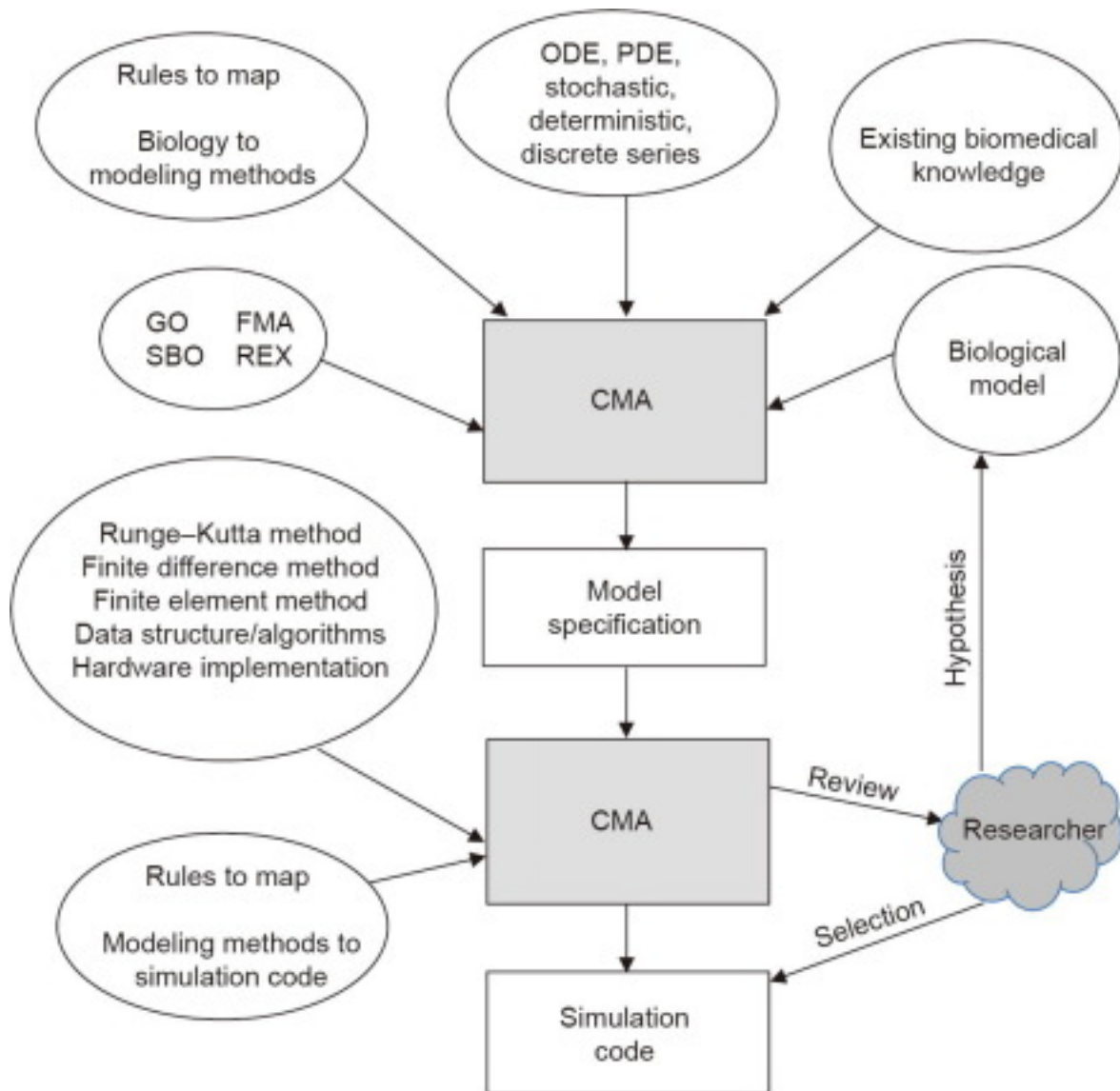


Fig. 30. A general perspective of process flow and interactions between a CMA and human researchers in view of various ontologies and knowledge databases. ODE: ordinary differential equation; PDE: partial differential equation; GO: gene oncology; FMA: foundational model of anatomy ontology; SBO: systems biology ontology; REX: physicochemical process ontology.^[79]

One more application of AI in healthcare is in natural language processing (**NLP**) for biomedical applications. More specifically, in the area of biomedical question-answering (**BioQA**). The main goal of the above is to detect quickly and precisely answers to questions made by the user from a plethora of documents and datasets.^[79]

To achieve that, the classification into different categories from the answer of the biomedical questions must be done. The reason why this classification should be completed is because the appropriate information has to be extracted. ML can categorize biomedical questions into four basic types with a veracity close to 90%. Later on, an intelligent biomedical document retrieval system can efficiently retrieve sections of the documents that are most likely to contain the answers to the biomedical questions.^[79]

Another usage of AI in biomedical research is the examination and indexing of academic literature. In this way, the difficult and challenging task of reviewing the literature regarding a given topic of interest, could be done with the help of a semantic graph-based AI approach instead of a biomedical researcher. Furthermore, when literature review is finished, ranking of the related literature can be accomplished if the number of research papers is beyond readability. That can give the researchers the opportunity to compose and test to-the-point scientific hypotheses.^[79]

Besides those applications mentioned before, one of the most important demand for AI in biomedicine exists in the diagnostics of diseases. In vitro diagnostics with the use of biosensors and biochips such as gene expression, a very important diagnostic tool, can be analyzed by ML. Then, AI interprets microarray data to classify and detect abnormalities. Other application is diagnosing cardiovascular

diseases in the early stage. That includes integrated AI, biosensors and related point-of-care testing (**POCT**) systems. Also, prediction of the survival rates of cancer patients it is possible with AI.^[79]

In seizure prediction, medical imaging (two-dimensional) and signal (one-dimensional) processing are two other diagnostic techniques. In one-dimensional signal processing AI has been applied to biomedical signal feature extraction, such as electroencephalography (**EEG**), electromyography (**EMG**), and electrocardiography (**ECG**). An important application of EEG is epileptic seizure prediction.^[79]

A really innovative company that aims in patients diagnosis is **Buoy Health, Inc.** It operates as an AI-driven health assistant that helps patients self-diagnose and triage to the right care. The main purpose of the company is to make self-diagnosis and navigating the healthcare system simple and easy.^[85]

PathAI is also an AI company that is advances high-end technology that can diagnose and treat some of today's most challenging diseases. More specifically, **PathAI** is developing technology that helps pathologists to recognize the symptoms and make fast and precise diagnoses for every patient, every time. Besides the diagnosis of the patient, **PathAI** aims to help identify patients that will benefit from innovative therapies, and thus to lead medicine to more scalable and personalized form.^[86]

4. Discussion

AI applications can be used in almost every profession and can replace old and cost-effective practices. In this study, all the research in AI applications has been concentrated in biomedical sciences. The development of AI in biomedical sciences is escalating exponentially day after day. Image processing, medical prognosis, precision medicine, drug development, clinical trials and advanced healthcare are only some of them. More specifically, image processing can lead the way in more detailed and precise prognosis and diagnosis of a condition based solely on images from diagnostic tools. Medical prognosis and precision medicine can be achieved by using important biomarkers derived from Radiomics and Radiogenomics. Radiomics and robotics in surgery are two fields that were not existed some years back. Drug development via machine learning and prediction of the protein structure using deep learning can lead the way to many more high-end discoveries in the field of drug development. More specifically, by increasing the number of known protein structures, AlphaFold could open new ways for research and treatments for until now incurable illnesses such as Alzheimer's and Parkinson's. Additionally, designing clinical trials can be much easier and more successful than before by using Artificial Intelligence's tools. Last but not least, healthcare is more accessible and efficient than ever with the help of AI. Still, there are a lot of things to be done in order to achieve the best results.

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Synopsis

The aim of this thesis is to identify some of the applications of Artificial Intelligence in Biomedical Sciences. The journey begins around Homer's era when the first "*automata*" were introduced. According to Kalligeropoulos *et al.*^[93] the word "automata" is a Homeric word as it is presented frequently in the Iliad and Odyssey.

Artificial Intelligence (AI) was firstly initiated at Dartmouth College in 1956 and it combines three different academic fields: psychology, philosophy and computer science^[8]. As Buchanan, B.G.^[9] cleverly stated, "*AI is not just about robots. It is also about understanding the nature of intelligent thought and action using computers as experimental devices*".

AI is the amalgamation of values from many disciplines such as **engineering** (Norbert Wiener's work on cybernetics including feedback and control), **biology** (W. Ross Ashby and Warren McCulloch and Walter Pitts's work on neural networks in simple organisms), **experimental psychology** (Newell and Simon, Human Problem Solving (1972)), **communication theory** (Claude E. Shannon: Founder of Information Theory), **game theory** (John Von Neumann and Oskar Morgenstern, Theory of Games and Economic Behavior (1944)), **mathematics** and **statistics** (Irving J. Good, Speculations Concerning the First Ultraintelligent Machine," *Advances in Computers*, 6. (1965)), **logic** and **philosophy** (Alan Turing, Alonzo Church, and Carl Hempel), and **linguistics** (Noam Chomsky, Theory Of Universal Grammar (1960s))^[9].

In 1950 there was a critical moment in the history of AI with Turing publishing a seminal paper in the philosophy journal *Mind*^[10]. In that paper, patterned ideas were presented that assumed the possibility of programming an electronic computer to perform intelligently. Of course, there was included a description of the landmark

imitation game that we know as Turing's Test^[9]. Additionally, Vannevar Bush's paper in the *Atlantic Monthly* that was published in 1945, is outlined a farsighted vision of capabilities^[9].

On the other side, Roger Penrose, one of the greatest mathematicians, stated at his famous book *"The Emperor's New Mind"*^[87] that strong AI is impossible. As a strong protester of the idea that a computer could be conscious, Penrose justified his opinion by presenting detailed analysis of many topics in mathematics such as Turing machines and computability theory, the Mandelbrot set, complex numbers, Gödel's theorem, recursive function theory, complexity theory and Platonism versus intuitionism as well as in classical Einsteinian physics and quantum physics, cosmology, and neuroscience.^[87]

As a part of Artificial Intelligence, Machine Learning, was introduced for the first time in 1957 into a paper published in from the American mathematician and researcher Ray Solomonoff under the name: *"An Inductive Inference Machine"*^[94]. In that paper, Solomonoff described machine learning as *"the set of instructions that have been prepared by which certain problems in inductive inference can be solved"*.

Machine learning opened the way for the creation of Expert Systems. By definition, they are capable of providing expert conclusions about specialized areas. Some applications of expert systems are; diagnosing faults in military systems (radars, aircrafts), taxonomically classify members of a particular species, advice on possible chemical structures, evaluate potential ore deposits, diagnose diseases, etc^[11]. One of the earliest systems to exploit domain-specific knowledge in problem solving and also the "the mother of all expert systems" was DENDRAL^[16]. It is one of the first and most notable AI application that analyses the mass spectra of organic molecules by deducing their structure to their chemical formulas and mass

spectrographic information from the chemical bonds present in the molecules^[18].

Later on, META-DENDRAL was created. The current META-DENDRAL program^[24,25] is able to give chemists the opportunity to determine the dependency of mass spectrometric fragmentation on substructural features, having in mind the hypothesis that molecular fragmentations are related to topological graph structural features of molecules. The aim is to build a program that could indicate qualitative explanations of the characteristic fragmentations as well as re-arrangements among a set of molecules^[21].

MYCIN was developed at Stanford in the mid-1970s. It was one of the first programs to aim at the problems of rationale with uncertain or incomplete information and it can also be characterised as one of the first backward chaining expert systems^[17].

After the expert systems robots were introduced. In today's world, many innovations have been made in robotics and especially in biomedical sciences. Thus, the global numbers of robotic surgeries are increasing. Leverages such as short hospitalization periods, limited postoperative recovery time, safety for patients at particular risk (diabetic, with an increased body mass index (BMI > 35), prompt robotic surgery for the treatment of cancer of internal organs a standard regimen^[48].

Some of the applications of robotics in healthcare are in **Radiofrequency ablation (RFA)**^[47], which is mostly used in the therapy of cancer of internal organs^[47] and it is a minimally invasive surgery, in **Vision-based tracking system for augmented reality** to localize recurrent laryngeal nerve during robotic thyroid surgery^[50], which allows virtual organs to be overlaid onto the actual organs during the surgery^[50] and in **Maxillofacial surgery** for the treatment of head and neck tumors and non-malignant diseases^[56]. Additionally, a **robotic guidance system** for

navigated spine surgery^[55] and **robotic guidance system** for autonomous vascular access^[52] are some other applications.

A very useful examination tool in medical practice is image analysis and more specifically in chest radiography. Computer-aided detection (CAD) systems focus on the artificial intelligence technology in the screening of specific disease (pulmonary nodules, tuberculosis, and interstitial lung diseases).^[61]

The term 'Precision oncology' is referring to the customization of cancer care. The biggest part of precision oncology related research has gathered in the molecular characterization of tumors with the use of genomics based approaches. Medical imaging is non-invasive and can give information associated with the entire tumor phenotype, as well as the intra-tumor heterogeneity^[75]. Recent advances in high-resolution image acquisition machines along with computational hardware provide the precise and efficient quantification of tumor phenotypic characteristics.^[75]

Radiomics is a novel area that is aiming to detect associations between qualitative and quantitative information derived from clinical images and clinical data, with or without associated gene expression to support evidence-based clinical decision-making^[71]. More specifically, the main goal is to discover new imaging biomarkers, by high-throughput extraction of quantitative image features like shape, histogram and texture that captures tumor heterogeneity^[72]. Additionally, a great advantage of Radiomics' analyses is that they can be performed in tumor regions, metastatic lesions, as well as in normal tissues^[71].

Computational drug design tools have been used to develop completely new lead compounds that exhibit desired activity *in silico*^[35]. The computational *de novo* design in a combination with AI would create a 'computer chemist' who will learn from known and useful compounds and enable the production of chemically correct and

synthesizable structures with a planned biological activity^[35]. Furthermore, molecular graph convolution methods^[31], variational autoencoders^[32] and recurrent neural networks (RNN)^[33] are only some of the greater achievements of these efforts.

Some of these deep learning projects that have been used for drug development are **Atomwise**^[37], **PaccMann**, **INtERAcT** and **PIMKL** from IBM Research^[35].

Protein structure prediction is a new emerging field that uses Artificial Intelligence and can lead to new drug development. More precisely, the prediction of the structure of a protein can lead to the detection of the three-dimensional shape of a protein from its amino acid sequence^[91] and thus to reveal the mechanism of pathological conditions such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA)^[92].

Nevertheless, in the process of drug development, clinical trials is one of the most crucial and critical steps. The clinical development phase is responsible for ensuring the efficacy and safety of new medicines.^[77] The drug pipeline is difficult to be managed and thus it is challenging to adeptly proceed to costly and time-consuming clinical trials as rapidly as possible. To make things easier, AI has also been applied in the design of clinical trials. At each and every clinical trial a protocol is followed and describes precisely how the study will be conducted^[76]. For that purpose, AI-powered software is able to process all of that information faster, as well as to gather more data than a professional.^[76] **Trials.ai**, a start-up company in San Diego, California, is specialized in designing better trials protocols via its AI tool.^[76] Furthermore, an important thing to have in mind is that even trials with well-designed protocols must rely on participants to follow instructions. Again, AI has given the solution to that problem. **AiCure**, a data-analysis company in New York City provides

a platform that allows people to use their smartphones to record videos of themselves taking medication. Afterwards, **AiCure**'s software is using computer-vision algorithms that analyse those images and identifying the person and the pill, confirming whether it was taken.^[76]

Furthermore, the aim of artificial intelligence (AI) in healthcare is to examine and determine patterns in large and complex datasets in less time and more accurate than before^[80]. The major applications of AI in healthcare and research can be divided in four categories. In the first three categories lie all the applications that efficiently treat big data and issue quick access to data so as to solve issues linked to healthcare^[79]. These applications include; living assistance for elderly and disabled people, natural language processing techniques, and fundamental research activities. The fourth category of AI applications includes the diagnosis, detection and prediction of diseases.^[79]

“Smart communication architecture” systems for “ambient assisted living” (**AAL**) have allowed AI to process information that have been collected not from one but from different communication channels or technologies. That development helps the user to determine the appearance of events in the network environment and thus the need of assistance for elderly people.^[79] **SALSA** intelligent agent can help elders with daily medication activities^[79]. Another category is the development of human-machine interfaces (HMIs) based on facial expression analysis, trained neural networks (NNs). This application allowed people with disabilities to control wheelchairs and robot assistance vehicles without a joystick or sensors attached to the body^[79]. Some applications of such systems are: **RUDO**, an ambient intelligence system (Aml) for blind people that provides assistance in home environment^[81] and **Smart Care**, an intelligent assistant which provides aid to an expecting mother to

take care of herself^[82]. The fourth category of AI applications contains intelligent agents called the **Computational Modeling Assistant (CMA)**. These help biomedical researchers to build simulation models from the conceptual models they have in mind that can be executed^[79]. One more application of AI in healthcare is in natural language processing for biomedical applications. More specifically, in the area of biomedical question-answering (**BioQA**)^[79]. Also, examination and indexing of academic literature is another usage of AI in biomedical research.^[79]

Besides those applications mentioned before, one of the most important demand for AI in biomedicine exists in the diagnostics of diseases. In vitro diagnostics with the use of biosensors and biochips such as gene expression, a very important diagnostic tool, can be analyzed by ML. That includes integrated AI, biosensors and related point-of-care testing (**POCT**) systems.^[79]

In seizure prediction, medical imaging (two-dimensional) and signal (one-dimensional) processing are two other diagnostic techniques. In one-dimensional signal processing AI has been applied to biomedical signal feature extraction, such as electroencephalography (EEG), electromyography (EMG), and electrocardiography (ECG). An important application of EEG is epileptic seizure prediction.^[79]

A really innovative company that aims in patients diagnosis is **Buoy Health, Inc.** It operates as an AI-driven health assistant that helps patients self-diagnose and triage to the right care. The main purpose of the company is to make self-diagnosis and navigating the healthcare system simple and easy.^[85]

Last but not least, **PathAI** is also an AI company that is advances high-end technology that can diagnose and treat some of today's most challenging diseases. Besides the diagnosis of the patient, **PathAI** aims to help identify patients that will

benefit from innovative therapies, and thus to lead medicine to more scalable and personalized form.^[86]

Taking everything into consideration, even though Artificial Intelligence is a prominent field, some limitations still exist. Bioethics, is an important limitation that has occur as a result of the massive amounts of data collected for medical or not purposes. Last but not least, misapplication is another limitation that researchers should be aware of.