Review Article

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Journal Of Medical Physics And Applied Sciences
ISSN 2574-285X

2016
Vol. 1 No. 1: 5

DOI: 10.21767/2574-285X.100005

Impact of Physics on Medical Sciences and Applications: Lasers and Nanotechnology

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Citation: El-Sherbini TM. Impact of Physics on Medical Sciences and Applications: Lasers and Nanotechnology. Insights Med Phys. 2016, 1:1.

Abstract

This review article focuses on the latest advances in medical sciences that followed recent developments in physics. The focus here will be on the developments in those disciplines of physics namely; lasers and nanotechnology that are related to the research at the Laboratory of Lasers and New Materials (LLNM) of Cairo University and have direct connection to the field of Medical Physics. Laser induced breakdown spectroscopy (LIBS) has proven to be a powerful technique as a rapid and accurate tool for the identification and the analysis of microorganisms and human clinical specimens. It was applied in (LLNM) for the diagnosis and classification of liver cancer. New short wave length laser lines have been identified in (LLNM) which are important for the development of X-ray lasers that will have great impact on medical sciences and applications. Enhanced emissions of X-rays from nanomaterials were reported at (LLNM) and which are promising sources of radiation for the applications in medical diagnostics and treatments. The recent developments in lasers and nanotechnology have revolutionized both the research in biomedical science and the methods for medical diagnostics and treatments.

Keywords: LIBS technique in biomedical applications; Medical physics; Nanotechnology in medicine; Optical tomography; X-ray lasers

Received: February 20, 2016; **Accepted:** March 02, 2016; **Published:** March 08, 2016

Introduction

Medical Physics is the branch of Natural Sciences that deals with the application of physics in medicine. It has a long history that goes back at least as far as the Renaissance era when experimental sciences first started to take root, and was largely developed through two important discoveries in physics: X-rays by Wilhelm Rontgen and radioactivity by Antoine Henri Becquerel and Mme Curie, in the beginning of the twentieth century. From the middle of the twentieth century until now, many striking discoveries in physics have been made which have had great impact in the advancements of medical sciences and especially in medical diagnostics and treatments.

In this review article, some of these impacts and developments will be discussed within the framework of the research conducted at the Laboratory of Lasers and New Materials (LLNM) of Cairo University and which encompass:

- Laser Induced Breakdown Spectroscopy in medical sciences and applications.
- Computerized tomography and X-ray lasers in medical sciences and applications.
- Nanotechnology in medical sciences and applications.

Laser Induced Breakdown Spectroscopy in Medical Sciences and Applications

Laser Induced Breakdown Spectroscopy (LIBS) is a form of optical emission spectroscopy [1-3]. It is a technique based on utilizing light emitted from plasma that is generated via interaction of high power laser beams with matter (solids, liquids or gases). Assuming that light emitted is sufficiently influenced by the characteristic parameters of the plasma, the atomic spectroscopic analysis of the emitted light shows considerable information about the elemental structure and the basic physical processes in plasmas [4].

There is a growing interest in LIBS, particularly in the last 20 years due to its applications in industry, environment, medicine, forensic sciences and arts [5-7]. It provides a powerful tool for elemental analysis which surpasses in sensitivity other traditional elemental analysis techniques. Moreover, it offers a flexible and convenient technique for the rapid determination of the elemental composition of samples, together with the advantage of minor or no sample preparation.

Recently, LIBS has been applied to biological and medical systems, and extensively in the analysis of human tissue samples. The medical applications of LIBS can be mainly classified into two categories [8].

- The analysis of human clinical specimens (e.g. teeth, bones, urinary bladder and gall stones, liver tissues or other tissue samples)
- The analysis of microorganisms (e.g. bacteria, moulds, yeasts and viruses)

Concerning the first category, Patlak implemented the LIBS technique in order to study the role of various elements in the formation of gallstones (formed under the emphysema and mucosal state of gall bladder) [9]. The samples were collected from the Purvanchal region of Uttar Pradesh, India. The investigators were interested in exploring the elemental difference between gallstone compositions formed under habitat, nutrition and other environmental conditions. The study reveals the higher occurrence of gallstones in female patients. However, for male patients they found that it is more prevalent for those who were having the habit of tobacco, chewing, smoking or drinking alcohols. They also extended the applications of LIBS technique for in- situ study of deciduous tooth and *in vivo* study of human nail. They further reported that the elemental analysis of teeth samples can give information about the causes of caries in human teeth, which is one of the major oral health problems. Another biomedical application of LIBS was carried out in our laboratory of lasers and new materials (LLNM) at Cairo University. This was the diagnosis and classification of liver cancer using the LIBS technique [10]. Radiation from ND: YAG laser at 532 nm with 5.7×10^8 W/cm^2 was used to initiate plasma on the surface of liver tissue. The light emitted was analyzed where it allowed the detection of trace elements in malignant tissues. The optical fiber used to collect the radiation emitted from the samples, was a multimode quartz with a 25 µm inner diameter that was connected to an Echelle type spectrograph. The spectrograph was coupled to an intensified charge coupled device (ICCD) camera with which the light collected can be scanned over the wavelengths of interest **(Figure 1).** The system was controlled by Kestrel-Spec software to acquire images from the supported camera. The system detection covered a wavelength range from 200 to 1200 nm in single shot.

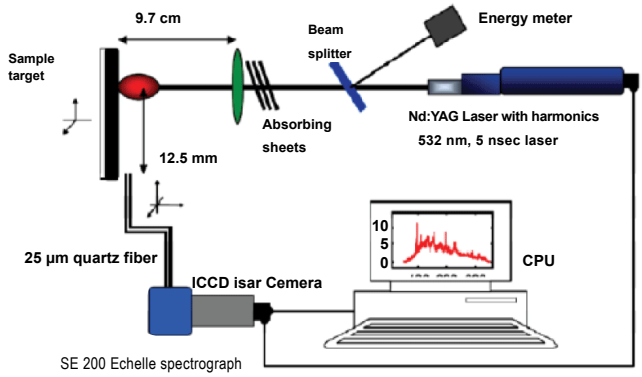

Figure 1 The setup of LIBS experiment.

The identification of the different elements was carried out using a spam 16 software spectrum analyzer. The wavelengths of the emitted spectrum were calibrated using light from a low pressure Hg- lamp, while a deuterium halogen lamp was used in calibrating the emission spectral intensities (relative sensitivity) over the entire wavelength scale. The trace elements Mg, K, Ca, Na, Fe, Mn and Cu were identified with different concentrations in the liver tissues under study. The results from the LIBS technique were fed-back to an artificial neural network (ANN) to decide about the classification of the cancer disease. The neural network that was constructed at (LLNM), is most suitable for the differentiation between normal and malignant samples. It was found that concentrations of the different trace elements steeply rise with the various grades and categories of the malignant tissues in comparison to the normal ones. The following conclusions were deducted when applying the LIBS technique in the study:

- It is a simple and promising technique capable of diagnosing malignant cells and tissues.
- It reduces the possibility of contamination as well as standard errors.
- It is capable of detecting trace elements with very low concentrations in the range of one part per million.
- It is a minimally invasive technique, since a small sized sample can lead to good results.
- It gives online quantification for all trace elements in a tissue simultaneously.

The second category of LIBS applications uses the technique for identifying microorganisms such as bacteria, moulds, yeasts, spores on surfaces and viruses which are responsible for human diseases [11-15]. LIBS application as a diagnostic technique that can rapidly detect and identify pathogenic microorganism is therefore of utmost interest to the medical community. It is currently used to identify pathogenic bacteria, specifically for clinical applications in hospital microbiology laboratories or military field hospitals. LIBS- based identification of bacteria is also applied to non-clinical industrial applications. In the food-processing industry, LIBS is used for the rapid identification of bacteria responsible for food borne contamination, such as *salmonella enteric* serovar *typhimurium* [16]. LIBS technique for biomedical analysis has more practical advantages over other spectrochemical techniques such as inductively coupled plasma mass spectrometry (ICP-MS), mass-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) and atomic absorption spectroscopy (AAS). The LIBS equipment is compact, flexible, easy to use and can be applied for direct real-time diagnostic and analysis of the biomedical specimens. Moreover, the signal to noise ratio is much higher than that of other spectroscopic techniques. The LIBS technique can be extended in the near future to cover broad range of biomedical applications including [16]:

- *In vivo or invitro* versatile and wide variety of "optical biopsies".
- *In vivo* identification of ulcerated tissues.

- *In vivo* or *in vitro* stone analysis (e.g. kidney and gall bladder stones).
- Real- time identification of caries dental tissue (cavities).
- *In vivo* measurements with high spatial resolution of heavy metal concentrations in tissues (e.g. in different parts of bone, in joints or in different regions of the liver).
- Identification of bacteria in human fluid specimens.

Computerized Tomography and X-Ray Lasers in Medical Sciences and Applications

X-ray tomography is a branch of medical radiology, used as a diagnostic technique [17,18]. It is well known that X-rays are not absorbed equally well by different parts of the body. Heavy elements in the body such as calcium are much better absorbers of X-rays than light elements such as carbon, oxygen, and hydrogen [19]. Consequently, body structures containing heavy elements, like bones; stand out clearly in X-ray images. The soft tissues (e.g. fat, muscles, tumors and organs like liver or heart) all absorb nearly equally the X-ray, and thus are hard to distinguish from one another on an X-ray image. On an ordinary X-ray image the shadows of all the objects in the path of the X-ray beam are superimposed, and thus the shadows of normal structures may mash or interfere with the shadows that indicate the disease [19]. In order to distinguish shadows indicating diseases, the X-ray images should be taken from different directions, such as from the back, the sides and under an oblique angle. Taking X-ray images of slices of the body (body section radiography) is known as "tomography".

X-ray imaging was dramatically improved by the invention of the computerized tomography (CT) by Godfrey Hounsfield in 1972 [20]. This invention led him, together with Allan Cormack, to earn a Nobel Prize in medicine in 1979. The X-ray (CT) imaging is similar to that taken by a planar camera, however, with two additional features. Firstly, the camera is constructed so that the head can rotate either stepwise or continuously about the patient to acquire multiple views. Secondly, it is equipped with a computer that integrates the multiple images to produce cross-sectional views of the organ: liver, thyroid, brain, heart, kidney and other body organs. The more advanced (CT) camera designs have more than one head or are constructed with a ring of detectors whereas, in the case of the single and multiple head cameras, the heads are mechanically rotated around the patient to obtain the multiple projection views [21]. When the image slices are resembled by computer software, the result is a very detailed multidimensional view of the body's interior. For some (CT) exams, an intravenous contrast injection is required to enhance visibility in the area of the body being examined. In 1998, (CT) was revolutionized with the introduction of the first four-slice spiral (CT) scanners. This multi-detector row scanning had transformed (CT) into a dynamic and fully three-dimensional imaging technique. (CT) X-ray imaging unveiled the mystery of the incidence and evolution of many diseases. For example, CT together with the development of appropriate computer algorithms, made it possible to locate micro calcifications in digitized mammograms, which led to the early detection of breast cancer. In fact, X-ray computed tomography had a fundamental impact on medicine. A new milestone in medical physics is the introduction of optical tomography, which is a form of computed tomography (CT) that creates a digital volumetric model of an object by reconstructing images made from light transmitted and scattered through an object [22]. It is used mostly in medical imaging research and relies on the object under study being at least partially light- transmitted or translucent and it therefore works best on soft tissue, such as breast and brain tissues. Further developments in computed tomography were the invention of optical coherence tomography (OCT) that uses light to capture micrometer resolution, three- dimensional images from within optical scattering biological tissues [23]. This medical imaging technique is based on low- coherence interferometry, typically employing near- infrared light. The use of relatively long wavelength light allows it to penetrate into the scattering medium. The light sources employed in (OCT), include super-luminescent diodes, ultra short pulsed lasers and super-continuum lasers. This imaging technique has the ability of achieving sub- micrometer resolution over a wide range of wavelengths, 100 nm, together with the advantage of high signal-to-noise ratio, permitting fast signal acquisition. Nowadays, optical coherence tomography (OCT) in medical diagnostics is considered a prominent imaging technique that can give high resolution, cross- sectional and three-dimensional images of bio- medical tissues in real time, using the coherence properties of laser light [23]. It has several and diverse applications in medical diagnostics, such as in ophthalmology and optometry where it can be used to obtain detailed images from within the retina [24,25]. It has been also used recently, in interventional cardiology to help diagnose coronary artery disease [26]. Moreover, it has been proven promising in dermatology to improve the diagnostic process and offers a potential option for imaging of the dermal structures with faster and deeper reaching systems [27,28]. OCT allows the reconstruction of the images from the upper skin layers, in a similar way as ultrasound does, but with much higher spatial resolution. It can be used to illustrate single layers and their vertical and horizontal expansion [29]. Imaging depth is usually about 1 mm, but is dependent on the specific properties of the tissues [30].

The advances in laser physics have also considerable impact on medicine and biomedical research. Soon after the advent of lasers in 1960 they found their way into biomedical sciences and medical applications, such as ophthalmology, dermatology, cosmetic surgery, oncology, dentistry and many areas of medicine [31-36]. Compared with the traditional light sources used in medicine, lasers operate within a very narrow wavelength range and the light emitted is coherent. They have much higher intensities and power densities and moreover, they are capable of operating at specific wavelength. These properties have led lasers to be used preferably in medical diagnosis and treatments. In the medical community, interest grows as laser physics is developing ways to expand the optical range of lasers to the shorter wavelength regions, i.e. to the extreme ultraviolet (XUV) and the X-ray regions of the electromagnetic spectrum. The first demonstration of an X- ray laser was at the Lawrence Livermore National Laboratory (LLNL) in 1985 [37,38]. The beam was

produced with a wavelength of the order of 5 nm, which is 100 times shorter than that of visible light. The photon wavelengths of the X- rays produced are 100 times shorter than those of the optical photons, which mean that they are 100 times as energetic as the optical photons. This requires a pumping energy for the X- ray laser of about 1000 times the energy needed for pumping optical lasers that work in the visible region [38]. In the (LLNL) beams of high energy neodymium, glass – lasers (Nova Lasers producing kilo joule pulses, lasting for a nano- second) were used to pump a thin foil of selenium to produce a coherent beam of X- ray [38]. When the Nova beam strikes the selenium foils, it vaporizes them completely to create plasma of neon- like selenium ions. The excited neon-like selenium ions in the plasma emit a coherent soft X-ray beam from the 3p–3s transition with a wavelength of 21 nm **(Figure 2).**

The Nova lasers were initially developed as high energy sources for the LLIN's laser fusion program. These huge and high energy lasers produce large amount of heat and have to be cooled after every pulse, and for that reason they are not suitable as pumping sources for X- ray lasers in medical applications. Nowadays, tabletop X- ray lasers are produced using less energy while no cooling off period is required [39]. The idea behind the development of these types of lasers is based on the possibility of creating X- ray laser beam using extremely short picoseconds pulse, which would require less energy (5-joule). In 1998 Dunn have demonstrated X-ray laser amplification for the 14.7 nm transition in the nickel-like palladium scheme, using a tabletop apparatus. They developed the method of laser chirped- pulse amplification, where a very short pulse is expanded before it travels through the amplifier and then compresses to its original duration before the laser beam is focused on the target [40]. After the demonstrations of X-ray lasing from plasmas of neon-like ions of selenium and nickel-like ions of palladium, extensive work - both theoretical and experimental was carried out by physicists in different research laboratories in order to investigate the possibilities to produce X-ray lasing from other atomic transition mechanisms [41-43]. The study of transition probabilities and radiative lifetimes of laser levels in atomic systems was initiated by El- Sherbini in the physics department of the faculty of science at Cairo University. He carried out multi-configuration Hartree-Fock (MCHF) calculations for singly ionized krypton in order to determine the lifetimes of laser levels in this ion. The results

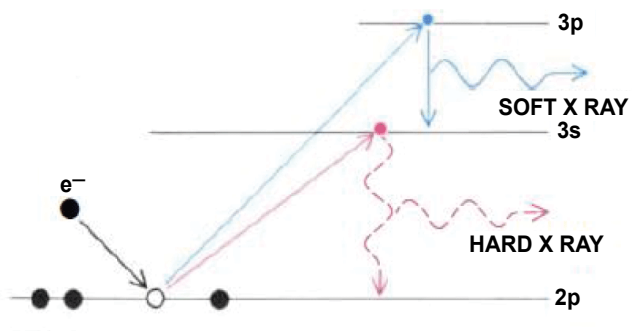

Figure 2 Energy level scheme of neon-like selenium.

showed that some of these levels are metastable [44-46]. He suggested a two-step excitation from the ground state of the ion to the $4p^4 5p$ level involving some intermediate metastable states as a possible excitation mechanism **(Figure 3).**

His work was further developed by the atomic physics group at the Laboratory of Lasers and New Materials (LLNM) at Cairo University, in order to study the possibility of laser emission from excited electrons in atomic iso-electronic sequences. These studies are essential, not only for a better understanding of atomic structure and ionizing phenomena, but they also provide new laser lines which could be extended into the X- ray spectral region [47,48]. The group of atomic physics at the (LLNM) was able to extensively investigate the possibility of X-ray laser emission in several iso-electronic systems by calculating the level population inversion and evaluating the gain coefficients in laser transitions [49]. The investigations include: He, Be, B, C, Ne, Na, mg, Al, Si, Ca, S, Sc and Ni iso-electronic sequences [50-70]. Most of the heavy members of the iso-electronic sequences studied radiate in the soft X-ray spectral region with wave lengths between 5 and 50 nm. The stimulated emission that was reported in these ions, indicate that some of the transitions are promising and could lead to progress towards the development of soft X-ray laser devices. Once X-ray lasers become reliable, efficient and economical, they will have several important applications in medicine and biomedical sciences. Their short wavelength, coherence and extreme brightness should allow for the exploration of living organisms and structures much smaller than one can see with optical methods. Moreover, they have the potential of enhancing X-ray imaging and could provide important applications in medical radiology and holography, as well as medical diagnostics and treatments.

Nanotechnology in Medical Sciences and Applications

The term nanotechnology was first envisioned by the distinguished physicist Richard Feynman in his illuminating lecture entitled "There is plenty of room at the bottom", that he gave in 1959 at the California Institute of Technology. In his lecture, he discussed the possibility of direct manipulation of individual atoms to be used as a powerful tool for synthesis. However, at that time the practical methods of implementing Feynman's ideas had not yet been discovered [71,72]. Originating from the Greek word for "dwarf" (*nános*), "nano" describes physical length scales that are in the order of a millionth of a millimeter. By convention, nanotechnology is taken as the scale range 1 to 100 nm, following the definition used by the National Nanotechnology Initiative in the US, where the sizes of most atoms and molecules of medical interest lie within this range. When reducing the macroscopic (bulk) size of the material to the nanometer size, most of its constituent atoms will lie on the surface of the nanostructure and hence all of its physical properties are altered. Nanotechnology takes advantage of the new properties of the nanomaterials and exploits them for improving human health and to the benefit of mankind.

The breakthrough that led to the practical realization of nanotechnology came in the 1980's. This was with the invention

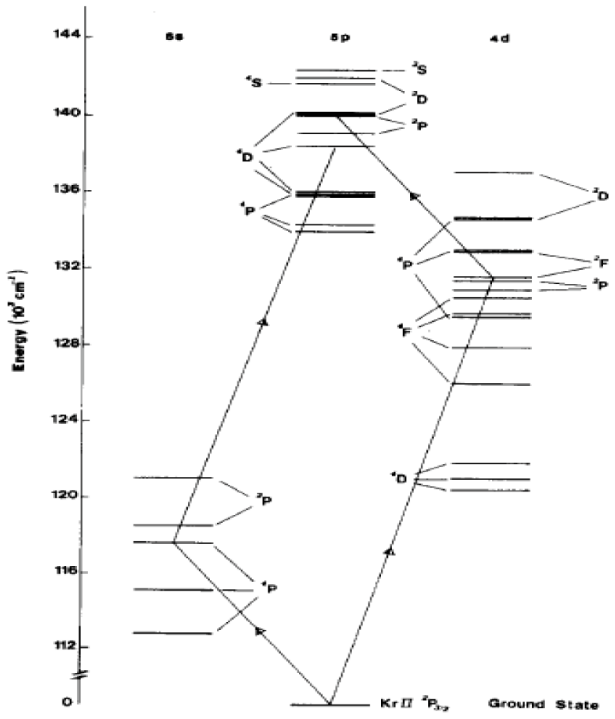

Figure 3 Energy level of singly ionized krypton, showing the two-step excitation from the $4p^5$ ($^2P_{3/2}$) ground state to the $4p^45p$ upper states.

of the scanning tunneling microscope (STM) in 1982, by Gerd Binning and Heinrich Rohrer [73]. Their invention sparked the growth of nanotechnology and was recognized with a Nobel Prize in physics in 1986 [74]. Soon afterwards, it was followed by the invention of the atomic force microscope (AFM), by Gerd Binning and Calvin Quate in 1986 [75]. With both the (STM) and the (AFM) devices, it became possible to observe structures on the atomic scale [76,77] and moreover, to manipulate individual atoms [77,78].

The use of nanotechnology in medical sciences and applications, known as nanomedicine, is a rapidly expanding field. Although this field is still in its infant stage, there is a growing interest among the medical community for the medical applications of nanomaterials and nanotechnology due to its ability to bring more progress and breakthroughs in diagnostics, treatments and prevention of diseases [79]. Now adays, nanotechnology and nanomaterials have a wide spectrum of medical applications, including targeted drug delivery, radio therapy and cancer treatment, nano-biosensors and nano-medical imaging:

Targeted (controlled) drug delivery

It is used for cancer, tumors or other types of diseases where the effect of drugs is optimized while toxic side effects are reduced. A technique that employs nanoparticles to deliver drugs to specific types of cells is currently under development, with some applications already being used. Nanoparticles are controlled and attracted to diseased cells, which leads to a direct attack and treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of the disease [80]. For example, nanoparticles that release drugs when subjected to shear force were tested and used to dissolve clots that blocked arteries [81]. Researchers at the University of Illinois have demonstrated that gelatin nanoparticles can be used to deliver drugs to damaged brain tissues [82]. At the Massachusetts Institute of Technology (MIT), researchers use nanoparticles to deliver vaccines [83]. The nanoparticles protect the vaccine, allowing it more time to trigger a stronger immune response. Methods are being developed to release insulin through a sponge-like matrix that contains insulin as well as nanocapsules with an enzyme. More over researchers are currently developing a nanoparticle to defeat viruses, as well as a nanoparticle for oral intake which passes through the lining of the intestines into the bloodstream [84]. This should allow drugs that must now be delivered as an injection, to be taken in pill form. In the application of liposomes as drug carriers, the localized release of their content (such as cytotoxic agents) is stimulated through exposure to ultrasound, heat or change in pH. One example is Caelyx, a liposome carrier containing the cancer drug doxorubicin [85]. Recently, complex drug delivery mechanisms are being developed that have the ability to get drugs through cell membranes and into cytoplasm [86].

Radio therapy and cancer treatment

The nanotechnology could play an effective role in radiation oncology. Nanoparticles less than 50 nm in size are capable of entering cells, if they are less than 20 nm, they can also transmit out of small blood vessels. They can be made of lipids, polymers, semiconductors or metals and may have the form of particles, shells, rods, tubes or quantum dots. Their nano-scale allows them to preferentially penetrate and be retained by biological cells and tissues. It is well known that tumors stimulate the growth of new blood vessels in their neighborhoods that can supply them with oxygen and other nutrients to sustain their rapid cell replication and growth [87]. Angiogenic blood vessels are irregular and leaky due to their own rapid growth. They have more and large gaps in their walls than healthy blood vessels. The gap sizes vary depending on where the tumor is in the body and on its stage of development, but they generally range from a few hundred nanometers to a few microns [88]. In contrast, the pores in normal blood vessels are just 2-6 nm in size. Nanoparticles between 10 and 300 nm in diameter have just the right size to pass through gaps in the blood vessels, thus supplying tumors, but they do not significantly penetrate healthy tissues [87]. By loading the particles with chemotherapy drugs–established cancer killers–one can deliver the drugs to tumor cells without damaging healthy cells. Two nanotechnology reformulations of chemotherapeutics, Abraxane and Doxil, have been approved by the US Food and Drug Administration (FDA) and are currently being used to the benefit of cancer patients. Many more anticancer nanomedicines are under clinical development, of which some are based on very different principles than chemotherapy. AuroShellfor example is gold nanoshells that uses passive targeting via enhanced permeability and retain effect to reach tumor sites [89]. Once the particle is in the tumor, Near-Infra Red (NIR) laser light is applied, which heats the particle and

thermally destroys the tumor and the surrounding blood vessels without significant damage to healthy tissues [87]. AuroShell is currently being tested in a phase I clinical trial for head and neck cancers. Eric Deutsch from the Institute Gustave-Roussy in France investigated the possibility to increase the efficacy of radiation therapy by using high-density nanoparticles. Together with his colleagues, he has shown that gold nanoparticles can enhance the efficacy of low-energy X-rays in irradiated cells [90]. Target heat therapy has also been developed to destroy breast cancer tumors. Here, antibodies that are strongly attracted to proteins produced in one type of breast cancer cell were attached to nanotubes, causing for the nanotubes to accumulate on the tumor. Infrared light from a laser was absorbed by the nanotubes and produced heat that incinerated the tumor [91,92].

Semiconductor nanostructures called quantum dots have been shown to increase the sensitivity of cells to ionizing radiation [93]. They increase the absorption of incident X-ray or gamma ray radiation, inducing electron ejection and generating free radicals. These free radicals increase cellular damage and, ultimately, induce cell death. Quantum dots can also be used in combination-cancer treatments which enhances the effects of conformal radiation delivery with the help of photodynamic therapy (PDT). Medical physicists from the University of Puerto Rico (USA), experimentally demonstrated how quantum dots are an ideal “mediator” in such multimodality regimes [94]. Wensha Yang and his group showed that when high doses of radiation strike quantum dots, they become luminescent and the light emitted triggers the cancer-killing activity of a Photo Dynamic Therapy (PDT) photo-sensitizer called Photofrin (a drug that is absorbed selectively by cancer cells) [95].

Nano-biosensors and Nano-medical imaging

A biosensor is an analytical device used for the detection of an analyte, that combines a biological component with a physiochemical detector [96,97]. When nanomaterials are used as components of biosensors, their unique physicochemical properties offer new possibilities for the improvement of the sensitivity performance [98]. The field of nanobiosensing is quite promising, especially in areas that could not be accomplished by conventional bulk materials. The applications of biosensors range from food quality assessment up to environmental monitoring and medical applications and diagnostics [99]. In the medical applications and diagnostics nanomaterials are playing an important role in the development of efficient biosensors which can analyze the minute details of biological interactions with extreme precision and sensitivity [100]. A key component of biosensing is the transduction mechanism which is responsible for converting the responses of bioanalyte interactions in an identifiable and reproducible manner, using the conversion of specific biochemical reaction energy, into an electrical form through the use of the transduction mechanism. Nanomaterials are indispensable incumbents in this dimension as they have high surface area to volume ratios which allow the surface to be used in a better and far more diversely functional manner [99]. Moreover, their electrochemical properties are the important assets for the biosensor technology. In brief, a biosensor is defined as a sensing device (a measurement system) designed specifically for estimation of a material by using the biological interactions and then assessing these interactions into a readable form with the help of a transduction and electromechanical interpretation. Therefore, the main components of a biosensor are the bioreceptor, the transducer and the detector. The main function of the biosensor is to sense a biological specific material such as antibodies, proteins, enzymes, immunological molecules etc. Nanobiosensors can be classified according to the type and nature of the nanomaterials incorporated in the biosensing application that are involved in enhancing and improving the sensing mechanism [99]. For instance, nanoparticle based biosensors include all the sensors which employ metallic nanoparticles as the enhancers of the sensing biochemical signals. Similarly, nanobiosensors are called nanotube-based sensors if they involve carbon nanotubes as enhancers of the reaction specificity and efficiency while biosensors using nanowires as charge transport and carriers are termed as nanowire biosensors. Likewise, there are quantum dots-based sensors which employ quantum dots as the contrast agents for improving optical responses [99].

Medical applications of nanobiosensors are versatile and multifunctional. Cui and Lieber have reported the performance of biosensors based on silicon nanowires doped with boron and used them for the detection of biological and chemical species [101]. Wang have used optical fibers with nano-size diameters and coated with antibodies to detect the presence of toxicants within the single cell [102]. Lieber group at Harvard University has developed a complex one dimensional architecture comprising at least 200 independent electrical nanowire assemblies that has been used to perform a low level detection of serum- bone cancer antigens. Nanomaterials with unique optical properties such as quantum dots, with different emission wavelengths can be excited by a single excitation source while organic dyes with different emission wavelengths must be excited by multiple excitation sources [98]. Demands for simultaneous detection of more targets in single assay, drives the development of inorganic nanocrystal-based fluorescent probes to replace organic fluorophores. Moreover, there are numerous clinical applications that are concerned with the use of nanobiosensors in routine. These applications include the detection of glucose in diabetic patients, the detection of urinary tract bacterial infections, the detection of HIV-AIDS and the diagnosis of cancer [103-109]. Recent advances in medical sensing involve the development of glucose biosensors that utilize nanotubes as immobilizing surfaces for enzyme glucose oxidize; this enzyme is used for the estimation of glucose from the several body fluids. Traditionally, the sensors using enzymes predicted the presence of glucose from major body tissues, but the use of nanotubes as assemblies for immobilization has led to the estimation of glucose from even scare body fluids such as tears and even saliva [99]. In one such arrangement, single-walled nanotubes have been effectively employed for enzymatic detection of glucose, and this innovation has also yielded significant increase in the enzyme activities [110]. It is clear from the previous examples, that nanomaterials have proved to be highly beneficial for brightening the sensing technology and have improved the diagnostic and detection procedures. They have also provided faster diagnostics that

enabled more rapid analysis and evaluation protocols, and in this way they have definitely revolutionized the bio-sensing mechanisms.

Nanotechnology has the potential of yielding considerable progress in medical diagnostics, with the ultimate goal of identifying diseases at the earliest stage possible (even up to the level of a single cell). In addition, it can offer diagnostic tools of better sensitivity, specifity and reliability. One of the tools to achieve this goal, is nano-imaging (known as molecular imaging) which has largely enhanced the effectiveness of *in vivo* diagnostics. The imaging techniques cover advanced optical imaging and spectroscopy, nuclear imaging with radioactive tracers, magnetic resonance imaging, ultrasound and optical and X-ray imaging. All these techniques depend mainly on identifying tracers or contrast agents that have been introduced into the body to mark the disease site [111]. The goal is to create highly sensitive and reliable detection agents that can also deliver and monitor therapy. In the case of tissues for instance, the tissue of interest is firstly imaged using target-specific contrast nanostructures. Then, the targeting nanostructures are combined with a pharmacologically active agent that can be used for therapy. Finally, monitoring of the results of this therapy over time is done by sequential imaging [99]. The *in vivo* imaging characterization of the complex behaviors of disease in time and space gives us information about the location, the size, the speed of development, the amount of molecular processes that are contributing, the means of treatment and the way it responds to therapy. Specific and sensitive site-targeted contrast agents are employed in molecular imaging due to the fact that molecules are too small to be imaged directly with noninvasive techniques [112]. Unlike traditional blood pool contrast agents, a site-targeted agent is intended to enhance a selected biomarker that otherwise might be impossible to distinguish from surrounding normal tissue. A wide range of particles or molecules is currently used for medical imaging. However, recent developments focus on using nanoparticles as tracers or contrast agents. Fluorescent nanocrystals such as quantum dots are nanoparticles which, depending on their coating and their physical and chemical properties, can target a specific tissue or cell and be made to fluorescence for imaging purposes. They offer a more intense fluorescent light emission, longer fluorescence lifetimes and increased multiplexing capabilities compared to conventional materials [111].

Targeted detection of cellular apoptosis with the use of technetium-labeled annexin, according to Wickline and Lanza is now in clinical trials on the basis of binding to membrane phosphatidyl serine epitopes that are exposed during apoptosis [112,113]. Other nuclear constructs appear useful for monitoring transfection events by imaging proteins that are expressed after reporter gene transcription. In this context, Wickline and Lanza give the example of the herpes virus kinase genes that can be used as a reporter construct in association with a therapeutic gene by phosphorylating certain exogenously supplied radio labeled probes that are then trapped inside of cells where they can be imaged [112,114]. Targeted perfluorocarbon nanoparticles were the first reported molecular imaging agent for ultrasound applications and were shown to increase reflectivity from fibrin thrombi *in-vivo* by two orders of magnitude or more [115-117]. Targeting to vascular epitopes such as tissue factor, whose expression is induced in smooth muscle cells *in-vivo* after angioplasty, is possible due to the fact that these particles can penetrate through micro fissures into the vascular media [118,119].

The exponential growth of biocompatible nanotechnology now promises to expand the horizon for molecular imaging and therapy with a host of new agents. Besides the use of nano-agents for *in-vivo* imaging of molecules or cells, the use of nanoscale agents for diagnosis and manipulation may lead to an improvement of surgical techniques in the clinic. This may be achieved, for example, through a better mapping of cancer distribution using near-infrared imaging. Moreover, the ability to incorporate drugs or gens into detectable site-targeted nano-systems represents a new paradigm in therapeutics that could usher in an era of image-based drug delivery and dosing [112]. In the nineties of last century and the beginning of this century, biomedical optical imaging witnessed breakthroughs in the development of imaging techniques, with the invention of the Scanning Near-Field Optical Microscopy (SNOM) and the Stochastic Optical Reconstruction Microscopy (STORM). These techniques are developed mainly for nanostructure investigations. It is known that the resolution (i.e. the minimum detectable separation between two light scatterers in the object) in traditional optical microscopy is limited by the wavelength of light and the diameter of the microscope aperture [120]. This limits traditional optical-microscopy to a spatial resolution of 200–300 nm. This resolution is relatively low and not sufficient for the imaging and observing of biomedical structures in detail and hence many details could be lost. (SNOM) and (STORM) techniques overcome the diffraction limit of the traditional optical microscopy and generate high resolution optical images that could reach 10 nm. (SNOM) allows the optical detection of the most miniscule surface structures of transparent as well as opaque samples. Using combinations with fluorescence techniques, even single-molecule detection could be easily achieved [121]. Instead of using a small aperture as in the traditional optical microscope, in (SNOM) a metal tip is used to provide a local excitation. This sharp metal tip is placed in the focus of a laser beam and hence an effect called “local field enhancement” will cause the electric field to become roughly 1000 times stronger. This enhancement is localized to the tip, which has a typical diameter of 10 nm. As this tip is scanned over the surface, an image can be formed with a resolution as fine as the tip [122]. A super-resolution imaging method based on the sequential localization of photo-switchable fluorescent probes has recently been invented [123,124]. Following Zhuang these photo-switchable probes can be optically switched between a fluorescent and dark state. In this manner, their fluorescence emission can be controlled over time, such that different molecules are turned on during different time windows [125]. This additional control in the time domain allows molecules with spatially overlapping images to be separated in time, and consequently allows their positions to be precisely determined. The high-precision localization of individual fluorescent molecules process is repeated to allow more molecules to be localized. Once enough localization has been accumulated, a high-resolution

image can then be constructed from the measured positions of the probes. The resolution of the final image is no longer limited by diffraction, but by the precision of each localization. Multicolor-three dimensional (STORM) makes it now possible to image cellular structures with near molecular-scale resolution [125].

Among the highlights in materials science and nanotechnology is the discovery of graphene in 2004 by the eminent physicists Andre Geim and Konstantin Novoselov at Manchester University (UK). They received the Nobel Prize in Physics in 2010 for their work on isolating graphene for the first time and investigating its unique and peculiar properties [126,127]. Graphene is just a one atom thick-two dimensional sheet of carbon atoms arranged in a honeycomb like lattice. It has remarkable mechanical, physical and chemical properties, and hence has found numerous potential applications in a wide range of areas, including biomedical sciences [128-130]. It has recently been used in various medical applications, which include biosensing, medical imaging, drug delivery, and cancer therapies [131-133]. Chief among its medical applications might be the revolutionary new DNA sequencing which accelerates genomics. Cees Dekker and his research group at the Kavli Institute of Nanoscience in the Netherlands were the first team to demonstrate in 2010 the DNA motion through graphene nanopores [134]. They created a series of pores (holes) ranging from 5 to 25 nm in diameter by placing flakes of graphene over a silicon nitride membrane and drilling nanosized holes in the graphene using an electron beam. By applying a voltage of 200 mV across the graphene membrane, which channeled the flow of ions through the pore and registered as an electrical current signal, a series of spikes were observed in the electric current that scales the pore. These spikes correspond to drops in conductance when DNA strands slide across the pore via a biochemical process known as translocation **(Figure 4)**. In 2013 they demonstrated how to tailor the hydrophobicity of graphene for its use as nanopores for DNA translocation and it was shown that single-stranded DNA could be detected in graphene nanopores with excellent nanopore durability and reproducibility [135]. In 2015 Dekker and his group suggested replacing the monolayer of graphene nanopore by a multilayer graphene in order to reduce the noise in the ionic current through graphene nanopores [136]. Their work is considered the first step towards ultrafast genomic screening [137]. In the mean time, research teams from the department of physics at Harvard University and the MIT have demonstrated that graphene can act as an artificial membrane separating two liquid reservoirs [138]. They showed that although graphene membrane prevented ions and water from flowing through it due to its very thin nanosize pores, the membrane could attract different ions and other chemicals to its two atomically close surfaces. It could therefore be used for chemical sensing and detection of single molecules. Hence, when the researchers added long DNA chains to the liquid, they were electrically pulled one by one through the graphene nanopore and the nucleotide bases, which are the letters of the genetic code, could be identified [139]. Graphene nanopore sequencing provides very inexpensive and rapid DNA sequencing and has potential to boost personalized health care. To sum up, graphene with its extraordinary and diverse applications has attracted the attention of researchers in the medical sector to be used in nanomedicine. In biosensing several researches utilized the strongly binding energy of nucleotide bases in DNA to graphene surface on the one hand, with the effective fluorescence-quenching ability of grapheme on the other hand, to develop novel graphene-based DNA detection platforms [140-142]. Fan and and his research group reported a graphene oxide-based multicolor DNA probe for rapid, sensitive and selective detection of DNA targets in solutions. Other researchers found that graphene could deliver oligonucleotides, such as molecular beacons and aptamers, into living cells for in situ probing of biomolecules [140-143]. Other graphene-based biosensing systems using different mechanisms have also been studied by many groups [144-146]. According to Feng and Liu owing to its ultra- high surface area and excellent electron mobility, graphene or graphene- based composite materials were used to modify electrodes in the electrodes in the electrochemical sensing of various biomolecules, including glucose, DNA and proteins, with high sensitivities [129,147-149]. In tissue engineering, graphene has been used as an enhancing agent to improve the mechanical properties of biodegradable polymeric nanocomposites for engineering bone tissue applications [150]. In bioimaging, functionalized and surfactant dispersed graphene solutions have been designed as blood pool MRI contrast agents [151]. Iodine and manganese incorporating graphene nanoparticles have served as multimodal MRI-CT contrast agents [152]. Graphene micro- and nano- particles have served as contrast agents for photo-acoustic and thermo-acoustic tomography [153]. Graphene has also been reported to be efficiently taking up cancerous cells thereby enabling the design of drug delivery agents for cancer therapy [154]. Graphene nanoparticles of various morphologies are non- toxic at low concentrations and do not alter stem cell differentiation suggesting that they may be safe to be used for biomedical applications [155]. The interaction between protein and graphene

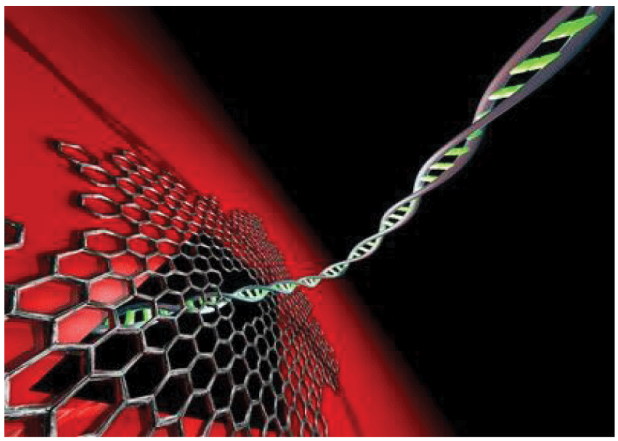

Figure 4 Artistic rendering of a DNA molecule traversing through a small whole (gap) made in an atomic layer of graphene that is located on a Si/S (coutesy: Cees D, Lab TU Delfet/Terr).

or graphene derivatives has been thoroughly discussed, and the toxicological profile of graphene and graphene derivatives in various biological and biomedical applications has been introduced [130]. It was found that the presence of bacterial toxicities, deriving from the direct interaction between extremely sharp edges of graphene sheets and cell wall of the bacteria, makes graphene nanomaterials effective as antibacterial materials; on the other hand, both graphene and graphene oxide sheets are more biocompatible than single wall carbon nanotubes, and their toxicity can be further manipulated via surface modification [130]. It has been also reported that graphene could enhance PCR by increasing the yield of DNA product. Experiments revealed that graphene's thermal conductivity could be the main factor behind this result [156]. In 2014, graphene-based transparent (in the frequency range between infrared and ultraviolet) and flexible, implantable medical sensor microarrays were announced that allow the viewing of brain tissue hidden by implants (optical transparency was > 90%). Applications include also demonstrated, opto-genetic activation of focal cortical areas, *in vivo* imaging of cortical vasculature via fluorescence microscopy and three-dimensional optical coherence tomography [157]. In fact using graphene or graphene- based materials in medical imaging provide unrivaled image clarity. In drug delivery and cancer therapy, graphene was first explored and investigated by the group of Hogji Dai at Stanford University (USA) in 2008 [132,158]. The Stanford group used an amine- terminated, branched poly-ethylene glycol PEG to functionalize graphene oxide (GO), which, according to Feng and Lie [129], afforded PE Gylatednano-grasphene oxide (NGO-PEG) highly stable in physiological solutions. Aromatic anti-cancer drugs (e.g. SN38 and doxorubicin) were effectively loaded on the graphene for intracellular drug delivery. Ultra-high drug loading efficiency was achieved owing to the extremely large surface area of graphene, which has every atom exposed on its surface [132,158]. There are several other research groups that have also paid attention to the graphene-based drug loading and delivery systems and a number of interesting results have been published [159,160]. The *in vivo* study of graphene in animals was initiated by the group of Lianzhu Feng and Zhuang Liu at the Institute of Functional Nano and Soft Materials at Soochow University in China [129]. In their work PEGylated nano-graphene was labeled by a near infrared (NIR) fluorescence dye for *in vivo* fluorescence imaging. The *in vivo* behaviors of NGO-PEG were investigated in several different xenograft tumor mouse models, showing remarkably high passive uptake of graphene in tumors [161]. Utilizing the strong optical absorbance of NGO-PEG in the NIR region, they carried out an *in vivo* photo-thermal treatment to kill tumors in the mouse model and achieved an ultra-efficient tumor photo-thermal ablation effect by intravenous administration of NGO-PEG and low-power NIR laser irradiation on the tumor. This was the first success of using graphene for *in vivo* cancer therapy. Afterwards, another group further showed that nano-graphene was significantly better than carbon nanotubes in inducing photo-thermal death of U251 human glioma cells *in vitro* [133]. Recently, researchers at Monash University (Malaysia), found that the sheet of graphene oxide (GO) can be transformed into liquid crystal droplets spontaneously [162]. Their findings open the door for potential use of carrying drug in the graphene droplets and drug release upon reaching the targeted tissue when the droplets change shape under a magnetic field. Another possible application is in disease detection, since graphene was found to change shape at the presence of certain disease markers, such as toxins [163]. A graphene "flying carpet" was demonstrated to deliver two anti-cancer drugs sequentially to the lung tumor cells (A549) in a mouse model [164].

Doxorubicin (DOX) is embedded onto the graphene sheet, while the molecules of tumor necrosis factor-related apoptosis–inducing ligand (TRAIL) are linked to nanostructure via short peptide chains **(Figure 5).** Injected intravenously, the graphene strips with the drug playload preferentially concentrate to the cancer cells due to common blood vessel leakage around the tumor. Receptors on the cancer cell membrane bind (TRAIL) and cell surface enzymes clip the peptide and thus release the drug onto the cell surface. Without the bulky (TRAIL), the graphene strips with the embedded (DOX) are swallowed into the cells. The intracellular acidic environmental promotes DOX's release from graphene. TRAIL in the cell surface triggers the apoptosis while (DOX) attacks the nucleus. These two drugs work synergistically and were found to be more effective than either drug alone [165]. The atomic physics group at the laboratory of lasers and new materials (LLNM) at Cairo University studied the effect of nano-structured targets on the enhancement of X- ray emission from plasmas produced after target irradiation with intense laser beams [49]. The enhanced X- rays could be used in medical radiology and diagnostics. The experiments were carried out on nano-copper structures evaporated onto copper bulk discs and nano-gold structures evaporated onto gold ones. Comparison of both studies in the case of nano-structured targets and bulk targets were performed at different laser fluencies (1×10^9 - 1×10^{12} W/cm^2) on the target. A 20% increase of the X-ray emission for nano-gold with respect to bulk gold was observed, however, the X-ray emission in the nano-copper and bulk copper was the same [166]. The researchers of the group also performed a comparative study of plasmas produced from nano and bulk ZnO targets. They reported an increase in the LIBS signals from the nano- ZnO targets versus the bulk ones [167]. The measurements

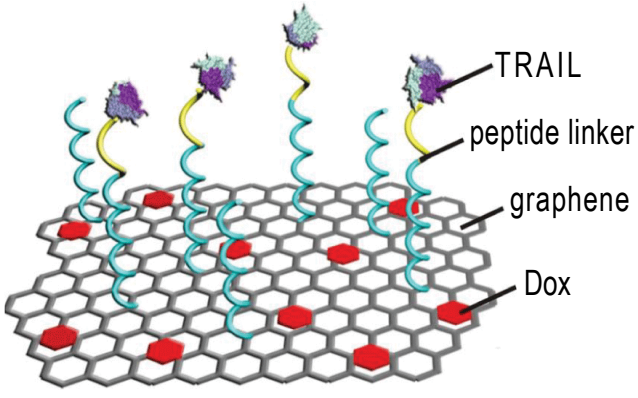

Figure 5 "Flying Carpet" technique usesgraphene to deliver two anticancer drugs sequentially to cancer cells.

were done for the Zn I-lines and were repeated at different delay times in the range from 1 to 5 μs and at constant irradiation level with fixed gate time of 1 μs. The average enhancement over the different Zn I-lines was found to increase exponentially up to 8-fold with delay time. The studies were further extended to a set of other nanomaterials and bulk targets (Fe_3O_4, Ag_2O, SiO_2, TiO_2 and Al_2O_3), which were investigated at laser fluencies in the range of 2.5 W/cm^2 up to 86 W/cm^2. The investigations revealed salient enhanced spectral emission from the nanoparticle targets of the compounds to that from their bulky counterparts [168]. Therefore, the results suggest that using nanoparticles as targets in LIBS technique could increase its sensitivity in elemental analysis and hence improve its applications in biological and medical systems.

Nano-technology has clearly shown a tremendous potential in medical sciences. Its impact on the advances in the medical field is considerable through its many promising applications in the area of cancer treatment, the treatment of infectious, cardiovascular, neurological, lung and blood diseases, diabetes and dentistry. Moreover, the various nanomaterials that it will provide, may be used to further develop tissue engineering and cell repair and for the purpose of generating devices as nanorobots, nanochips, nanoimplants and prostheses [169-171].

Conclusion

The review article discusses the impact of physics in medical fields in so far as it is related to the research conducted at the Laboratory of Lasers and New Materials (LLNM) of Cairo University. In fact progress in physics has influenced, improved, and has direct impact on almost all topics in biology and medicine. Within the scope of this review it was impossible to cover all these fields. We did not discuss for example its impact on many medical topics, such as: Nuclear Magnetic Imaging (NMI), Positron Emission Tomography (PET), Nuclear Medicine (NM), Ultrasonography (USG), Electrocardiography (ECG), Echoencephalography, Ophthalmoscopy, Endoscopy, lasers in medicine and surgery etc.

Perhaps the most profound impact physics could have on medical sciences lies in the field of nanotechnology, where progress is being made at rapid pace. Physicists are currently working towards the construction and development of molecular assemblers and nanorobots, which are machines that could re-order matter at molecular and atomic scales. The advent of these smart nanomedical devices will bring about a revolution in future medicine and will radically change the way medicine has been practiced for centuries, opening new horizons especially in the fields of diagnostics and treatments, to the benefit of human health.

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