Annals of Materials Science & Engineering

Austin Publishing Group

Open Access Full Text Article

Editorial

Some Reflections on the Impact of Physics, Materials Science, and Engineering on Biology and Medecine

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Received: September 03, 2014; **Accepted:** September 25, 2014; **Published:** October 01, 2014

"Human health has always been determined on the nanometer scale; this is where the structure and properties of the machines of life work in every one of the cells in every living thing. The practical impact of nanoscience on human health will be huge." Richard E. Smalley, 1996 Nobel Laureate.

The aim of biomedical research is to uncover new knowledge that will lead to better health, as well as to develop the basic principles of biology, i.e. the rules of living systems. All research and technology indicators suggest that biotechnology and information technology (IT), coupled with the convergence of microsystems and nanotechnologies, are closely aligned with global and societal priorities, and primary drivers of economic growth. They will eventually dominate the future. Biotechnology is already transforming health care and agriculture, and opening up enormous possibilities for sustainable resource management. IT is the driving force in every industry today, transforming many of them and enabling new areas of research, such as the human genome, and enterprise. Both IT and biotechnology are challenging and transforming the world's underlying social, economic, and political structures. Within this context, there is also a long tradition of physics-based techniques making important contributions to biology and medecine. Biology and engineering have a complex, often discordant, relationship. Living systems are intrinsically messy, so most biologists spend a lot of time analyzing untidy subjects such as variation, ecological interactions and the multitudes of tangled genetic, developmental and metabolic pathways that organisms use. In biology, noise is often a kind of signal, and generalizable principles are hard to find. By contrast, physicists and engineers can take a more reductionist[1] approach to the world, deducing and testing the inherent principles and mechanisms by which things fail, work or can be made to work. Despite these differences, the two fields are vitally important to one another[2]. The physical world poses many basic challenges to all living creatures, which in turn have evolved an astonishing array of solutions. Many of them perform so well that we marvel at their superiority to human-made devices.

Recent advances in computer performance and affordability have accelerated their application to understanding biological phenomena [1]. The emergence of quantitative biology poses special challenges to biologists and to physicists eager to make a contribution. In these notes, we shall eventually describe recent developments which illustrate some interdisciplinary, biological issues in materials science, physics and electrical engineering. More precisely, this paper presents a range of examples that illustrate the important role that numerical simulation plays in the modeling of the electrical response of biological cells. These and other examples provide compelling evidence and arguments for emphasizing biological sciences in materials science, physics, and engineering curricula and the implementation of a bio-materials paradigm to facilitate the emergence of innovative interdisciplinarity involving the biological sciences, materials sciences, computer science, and engineering (Figure 1).

Natural systems are typically highly complex, and so also are the signals derived from them. This is especially true of soft, e.g. cell, membranes, and rigid, e.g. shells, bones, biological materials. Smart biological structures are ultimate composite materials based on polymers and minerals, which can have a variety of properties depending on their structure at many length scales. Biological organisms have structure at many scales, involve feedback, and are highly non-linear, open, driven systems that operate away from thermodynamic equilibrium. The physics of such systems is not well understood. The mechanical properties of cells are largely determined by the cytoskeleton network, a hybrid polymer gel consisting of several kinds of different filamentous proteins, consisting of filamentous actin (F-actin), microtubules and intermediate filaments[3]. Soft-condensed-matter physics, and specifically polymer physics, has helped to shed some light on this structure and the emergence of its mechanical properties. But the cytoskeleton is not just some "packaging" material. It is kept far from equilibrium by the coupling of its polymerization to the hydrolysis of adenosine triphosphate (ATP), the molecule that supplies energy to living organisms. Cells generate forces by contracting the cytoskeleton, i.e. their "inner muscles", composed largely of actin networks and bundles, as mentioned above, and actuated by myosin motor proteins [2]. These networks are not simple linear, elastic solids; they can exhibit highly nonlinear elasticity and a thermal dynamics driven by ATP-dependent processes. The cytoskeletal network is predominantly under tension; its stiffness increases with tension and thereby increases the forces it can support [3-6]. The cytoskeleton is coupled to the external environment via

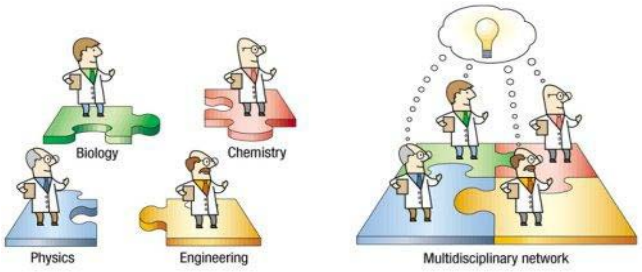

Figure 1: A cartoon illustrating the interdisciplinarity involving the biological sciences, materials sciences, computer science, and engineering.

Citation: Brosseau C. Some Reflections on the Impact of Physics, Materials Science, and Engineering on Biology and Medecine. Ann J Materials Sci Eng. 2014;1(3): 8.

specialized adhesion contacts, the focal adhesions where cellular stress sensors are believed to be localized.

There has been much fruitful collaboration between physicists and biologists over the years-most famously in elucidating the structure of DNA and in developing techniques for medical imaging[4]. Among the different contributions that physics made to biology six important issues should be emphasized:

(i) Understanding of the mechanisms regulating macroscopic behavior in relation to the microscopic material distribution

Analogous properties regulate the mechanical and electrical responses of the human body and its components as other disordered composite materials. The physical and physiological functions of biological composite materials, i.e. cells, tissues, and bones, are highly dependent on the structural, spatial, and chemical interactions of its major components: the membrane, and the cytoplasm. Previous studies have indicated hierarchical and highly ordered structures in a number of biological materials based on small-angle x-ray and neutron scattering, transmission electron microscopy, and atomic force microscopy [7]. It is instructive (with reference to Table I) to note how many physics-based methods have been applied to view living bodies, without the disruption of anatomical dissection, permits to visualize very small components of living things and at different levels of resolution. The methods of macro-imaging include conventional X-radiology, tomography scanning, ultrasound (Doppler echography), and magnetic resonance imaging. The impact of these procedures on medical practice continues to grow as new techniques appear. Micro-imaging began with the use of the light microscope, but has progressed with electron microscopy, and nuclear magnetic resonance to mention but a few, which permit much higher levels of resolution.

A study by the National Materials Advisory Board [8] dealt with the broad area of biology as a guide for new materials technology, and that study has been followed by books and reports of symposia on biomimicry and bio-inspired materials [9,10]. An important issue that arises in looking at natural materials and structures is the question "are the systems optimized?" and the answer is probably "yes and no". No, because of the limitations in the choice of elements (C, H, O, P, Ca, Si, etc) and ions those are found in the natural environment. We know that, for engineering purposes, we are able to select and use stronger and more durable materials for structure, as well as having more voltage endurance, and we may need them to function over much wider temperature regimes. On the other hand, we should recognize that natural structures are designed to survive in environments that have restricted mechanical loads and electrical fields, fairly narrow temperature regimes, and so on. The living plant or animal that cannot adapt its structure and properties to those environments or to changes in them does not survive.

(ii) Inspiration from nature to design biological and biomimetic materials

Natural materials are composites generally based on polymers and minerals which can have a variety of properties depending on their structure at many length scales. Materials solutions developed by biological organisms to provide materials with outstanding properties have received a lot of attention of late and are considered as invaluable sources of inspiration by the materials scientists community, e.g. butterfly wings, spider silk, gecko feet [11]. These creatures and biological structures eventually possess skills and attributes beyond conventional engineering. As a consequence, scientists began to ask an important question [11]. How do we reformulate biological designs in man-made structure and create bio-inspired advanced materials that are structurally and functionally optimized, that can build themselves, repair themselves, and eventually evolve? Recent advances in methods of nanoscale fabrication, characterization, and simulation have created new opportunities for manipulating and mimicking the intrinsically nanostructured biological materials. Biomimetic materials research cannot simply rely on observation and structural description of natural materials alone for a transfer of ideas and concepts. A major challenge in bio-inspired materials science is to understand the underlying design principles and physicochemical mechanisms that determine the optimized structured organization in biological systems at the molecular, cellular, tissue, and organism level, and its relationship to function. It may be also emphasized that the optimal solution of an engineering problem can lead to a quite different material than the biological material serving as inspiration, even if the guiding physicochemical principles are the same. This may be due, on the one hand, to the different boundary conditions and constraints imposed on natural materials by the biological environment, and, on the other hand, to the inability of the current state of knowledge of the interactions between the internal constituents of the systems.

(iii) Cross-fertilization and convergence of nanotechnologies with biotechnologies

It is important to understand the emergence of materials science and engineering as a "new synthesis of disciplines." After only a decade of development, materials science and engineering, while still in some degree of disciplinary uncertainty, was emerging as a model for interdisciplinarity and multidisciplinarity which prominently linked to various engineering disciplines, chemistry, physics, and mathematics. Its continued evolution along the lines of emergence of biophysics, combining biology and physics, or geochemistry, combining geology and chemistry, was questioned, but neither biomaterials nor bio-materials (the spectrum of biological sciences and materials sciences interdisciplinarity) was a prominent issue. By the end of the 1980s, a further assessment of the progress of materials science and engineering was made in the context of an effort "to conduct a comprehensive materials research and technology assessment for the next decade." The result was a publication titled *Materials Science and Engineering for the 1990's: Maintaining Competitiveness in the Age of Materials*[2]. Here, inherently interdisciplinary areas included biomaterials prominently, but the true interdisciplinary issues of bio-materials education and research were not prominent, despite the fact that the synergistic elements which now defined materials science and engineering structure, properties, synthesis/processing, and performance of materials—could find clear examples of bio-materials: prostheses, artificial organs, biosensors, drug delivery, cell separation, MRI contrast enhancement, hyperthermic heating of biological materials (either for cell destruction or to increase the efficacy of associated treatments such as chemotherapy)[5], wound management, and a plethora of medical equipment and devices. In addition, bioleaching and related biomaterials processing and

Table 1: Correlations between physics, materials science, engineering, and medecine.

Physics	Medecine and Biology
Statics (mechanics)	Orthopaedics
Dynamics (mechanics)	Heart motion, cell motility
Elasticity and strength of materials	Orthopaedics, elasticity of DNA, "auxetic" living tissue
Fluid statics	Blood pressure
Fluid dynamics	Blood flow in vascular systems, lubrication of cartilage in joints
Surface tension	Capillary action
Sound and acoustics	Stethoscope, ultrasound, acoustic microscope, Doppler echography
Electricity	All life processes, ion transfer at membranes, the invertebrate superposition eyes-structures behave like metamaterial with negative refractive index
Dielectrics	Scanning dielectric microscope
Magnetism	Nuclear magnetic resonance (NMR), magnetic resonance imaging (MRI)
Light and optics, polarization and coherence, optical microrheology	Light microscopy, laser therapy, fibre optics, optical tomography
Heat and thermodynamics	Heat balance
Kinetic theory and statistical mechanics	Brownian motion, osmosis, diffusion of gases
Atomic physics and spectroscopy	Chemical shift in NMR imaging, lasers in medecine
Fluorescence imaging	Motion of proteins such as myosin or actin
Molecular physics	Genetics, antibodies, protein structure, electron microscope
Ultraviolet and infrared energy	Skin treatment and imaging
X-rays	Radiology
Quantum mechanics	Electron diffraction microscope
Relativity	Synchrotron radiation imaging
Crystallography	Structure of proteins
Solid-state physics and semiconductors	Computers in medecine, scintigraphy
Statistical physics	Self-similarity and scale invariance of biological networks
Nuclear physics	Radioisotope labelling, nuclear medecine, radiation therapy
Radioactivity	Positron emission topography
Elementary particle physics	Pion therapy
Accelerators, cyclotrons, etc	Tumour therapy, Hodgkin's disease
Astronomy and astrophysics	Discovery of helium
Signal processing, time series analysis	Diagnostic applications of the cardiovascular system and brain
Electronics	Molecular electronics
Materials science	Synthetic structural composites, bio-inspired structures, bioresorbable scaffolding for repairs, fracture mechanisms in mineralized biological tissues, like bone and dentin, artificial skin,biomedical adhesives inspired by marine glues,

processes were emerging along with biomimetics applied to materials-related innovations.

By the end of the 1990s, nanotechnology and nanomaterials became the emerging science and engineering initiatives worldwide, and more recent evolution of these concepts has touted convergent new technologies: the synergistic combination of nanotechnology, biotechnology, information technology, and cognitive sciences[3]. These convergences elicit additional and imperative interdisciplinarity involving public health and the environmental sciences and engineering, especially as these relate to the manufacture and proliferation of nanomaterials, and in particular nanoparticulate materials. Here the biological and especially bio-materials implications bode prominently. This paper will review a few research examples or case histories of biological issues and interdisciplinary applications in materials sciences and engineering. These examples span more than three decades, including novel biomimetic materials developments and the development of systematic if not systemic assays to evaluate the cytotoxic potential for emerging nanoparticulate materials applications. In addition to demonstrating the applications of fundamental biological phenomena in materials extraction, processing, and performance (as related, for example, to degradation or corrosion), this article will illustrate the characterization of biological and biomaterials microstructures as these relate to properties, processes, and performance. These examples and applications involving biological materials sciences will provide the basis for a bio-materials paradigm and the emphasis of the biological sciences in materials science and engineering curricula.

(4i) Contributions of physicists to discover the principles of heredity

Sixty years ago, Delbruck [13] put forward an important difference between physics and biology. In his own words," The animal or plant or micro-organism he [the biologist] is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity. Even the molecular species and the chemical reactions which he encounters are the fashions of today to be replaced by others as evolution goes on. The organism he [the biologist] is working with is not a particular expression of an ideal organism, but one thread in the infinite web of all living forms, all interrelated and all interdependent. The physicist has been reared in a different atmosphere. The materials and phenomena he [the physicist] works with are the same here and now as they were at all times and as they are on the most distant star." Sixty years ago, Delbruck and his "phage school" were interested by some fundamental questions:

What is the physical form in which hereditary information is stored? How is it reproduced when a cell divides, or when particle invades a cell and eventually multiplies itself into it? How does the information change when mutations occur? This school of thought was a group of former physicists and some biologists who shared his passion for reducing the problem of heredity to simple rules, physical entities and conserved energy by studying the replication and genetic behavior of bacterial viruses (phages) in their hosts. Two important contributions of this group were the identification of the DNA as genetic material through X-ray crystallography, and the deciphering of the genetic code as triplets chosen from a set of four nucleotides. Recently, this led to projects to sequence the human genome-the entire blueprint of every cell-to understands the processes by which the genes of an organism are expressed. Such information can help to understand, for example, why some cells develop in muscle tissue, while others become brain cells.

(5i) Contemporary problems in the biomedical sciences that present challenges to physicists are those of statistical physics.

A central goal of contemporary quantitative biology is to contribute to a quantitative, functional understanding of biological systems, using concepts and methods of statistical physics, e.g. complexity, emergence of order from disorder. Stanley and co-workers [14] have described several examples of recent progress in applying the powerful machinery of statistical physics to biological systems, e.g. the fractal features characterized by the long-range correlations found recently in DNA sequences containing non-coding material. Our genome is not just a collection of genes but a strongly correlated system shaped by multiple interactions between genes. Molecular information processing takes place through a number of networks governing the regulatory interactions between genes, the interaction between proteins, metabolic pathways in the cell, etc. Hence, as it has become clear in recent years, biological function cannot be understood at the level of single genes but requires the study of their interactions at the level of the entire genome. To understand various aspects of this "many-body" system, broadly based research programs are engaged worldwide involving the statistics of sequences and molecules, the structure and dynamics of bio-molecular networks, and the statistical dynamics of populations. Building a quantitative theory requires the confluence of ideas from molecular genetics, evolution biology, biophysics, statistical mechanics, and bioinformatics.

(6i) Computational methods to model field stimulation of biological cells: the importance of multiscale multiphysics simulation strategy

Heterogeneities are intrinsic in biological systems. Biological materials research cannot simply rely on observation and structural description of natural materials alone for a transfer of ideas and concepts. A grand challenge in biological materials science is to understand the underlying design principles and physical mechanisms that determine the optimized structural organization in biological systems at the molecular, cellular, tissue, and organism levels, and its relationship to function. Within this perspective, field simulation of biological cells has a wide range of applications, e.g. diagnostics of human diseases [15], elecrochemotherapy of tumors [15-16], gene transfection [16-20], cardiac defibrillation [21], design of biological and biomimetic materials [11], electroporation [22-26][6].

Mechanical forces induced by flow have also great influences on cells. In particular, shear stress can modify cell shape and regulate a number of functions, such as the intracellular distribution of Ca^{2+} ions, the release of NO, the expression of intercellular adhesion molecules, etc [27]. The human erythrocyte (red blood cell) demonstrates extraordinary ability to undergo reversible large deformation and fluidity. A cytoskeletal dynamics simulation framework that allows active remodeling of the 3D cytoskeleton via breakable as well as reformable associations of the junction complex and spectrin tetramer was worked out by Li and co-workers [28]. In addition, the introduction of microelectrode technology has facilitated the development of methods for manipulating, trapping, and separating bio-particles, from bacteria to viruses and macromolecules such as nucleic acids and proteins [29-31].

The development of quantitative methods of characterizing living matter has been heavily investigated over the last few decades. Much of the early work on the measurement and modeling of the dielectric properties of biological cells that can be approximated by rigid particles was done by the seminal researches by Cole[7] [32] and Fricke [33]. Cells have a highly heterogeneous structure, containing many different materials with different dielectric properties. One important output of the study of the dielectric properties of biological cells has been the discovery of the molecular thickness of the cell membrane by Höber in the beginning of the 1910s [34-35]. The approach usually taken to model them is to replace the particle with a hypothetical particle of known size, shape, and distribution of charges and/or materials. These classical models of cells based on shelled spheres or ellipsoids have been successfully employed to interpret some experiments involving single cells or colloidal suspensions [36-37]. An interesting overview of these late studies can be found in Schwan [38] and Foster and Schwan [39]. When cells deviate from simple geometries, or when the interfaces separating the different constituents do not coincide with a surface of constant coordinates (within a certain set of coordinate types), the electrostatic problem must be solved by numerical methods. Even for ellipsoids, this constraint requires the surface of the membrane to be confocal with the core, producing a shell of non-uniform thickness. As this very thin membrane is a region of high field amplification such non-uniformity may leads to inaccuracy of the electric field distribution.

For the purpose of modeling the wave transport in biological systems, computer simulations play a central role. Several approaches have been brought forward. Among the most widely used techniques, one can mention boundary element (BE) [40-44], finite element (FE) [45-48], and finite difference (FD) [49-51] methods. These methods solve numerically Laplace's equation with periodic boundaries under quasi-electrostatic condition of electric field stimulation. Technically, as will be discussed in Sec. III below, there are a number of challenges in pursuing this investigation, chief among them is how to deal with the separation of scales between the nanometer sized membrane and the micron sized cell. Each of these has its own advantages and limitations. When the cellular media are assumed to have piecewise homogeneous and isotropic complex permittivities, the electric potential equation simply reduces to the Laplace equation. The numerical solution of this partial differential equation in the form of FD involves a kind of polynomial approximation in nodes of a convenient grid. Thus, the existence of very small domains makes it

necessary to use a very dense grid compared to standard FD or FE methods. The FE method partitions the different cellular regions into simple elements, such as triangles in 2D and tetrahedrons in 3D. The use of adaptative meshing techniques and extensive computer resources are necessary since the number of equations to solve is prohibitively large. Using a BE method, only bounding surfaces of the geometry need to be discretized which reduces the memory space. In any FE, FD, or BE method, the unknowns to be determined are the values of the electric potential at the nodes of a 3D grid or at the subareas of a 2D surface mesh. From the potential distribution, the effective dielectric properties (permittivity, conductivity, polarizability) can be determined after specific treatments. For example, Brosseau and Beroual [52] computed the effective permittivity of dielectric heterostructures by obtaining first the potential and its derivatives at the nodes of a mesh, and then computing the electrostatic energy by integration. In a different way, Sekine [53] employed the BE method, and performed a fitting procedure by equating the calculated potential to hat produced by a dipole with principal components of polarizability to be determined. Sancho and co-workers [54] used a variant of the BE method based on an integral equation for the polarization charge density induced on the dielectric surfaces within the quasistatic approximation. Since the numerical discretization of this integral equation does not involve any type of polynomial interpolation, the surface mesh consists of a reasonably small number of elements, thus producing a linear system of equations which can be easily solved. Two advantages were put forward by the authors: on the one hand, this method does not suffer from numerical instabilities, and on the other hand, it provides a direct computation of the (Maxwell) stresses produced by the electric field [55].

To overcome the difficulties of these standard techniques, some circuit-based numerical methods, e.g. the equivalent circuit (EC) methods [56-59], and the transport lattice (TL) method [60] have been recently developed for analysis of the frequency and time domain EFITP of biological cells in an external electric field. These methods are based on spatially distributed transport networks, which are solved by Kirchhoff's laws to determine the potential distribution, i.e. spatial representation using the method of equivalent circuits. The EC method originally introduced by Fear and Stuchly [50] was initially used to model the response of cells connected via gap junctions. In the EC method, the cytoplasm and the extracellular medium are represented by resistances, which are connected in parallel by membrane impedance, and the membrane is represented by a parallel resistance-capacitance unit. Similar to the FD method, the EC approach uses Cartesian grids, but with two levels of resolution: a fine grid is built around the membrane while a coarse grid occupies the main area away from the membranes. The TL method is equivalent to a FE analysis, in that they both solve complicated partial differential equations.

More recently, Green and Jones [61] have suggested a method to extract the dipole moment of differently shaped particles (sphere, bisected sphere, ellipsoid, truncated cylinder, and erythrocyte cell) from numerical solutions of the EFITP when the particle is placed in an external uniform applied electric field. Gurtovenko and Vattulainen [62] used molecular dynamics simulations to investigate the EFITP that is found to originate from the interplay between lipid membrane asymmetry and the asymmetric distribution of monovalent salt ions on the two sides of the membrane.

Electroporation needs to be investigated more to fully exploit its potential and physical modeling is an interesting option [63-66]. Computational models can assist in optimizing parametric studies, the results of which can be verified using reduced number of actual experiments. Electroporation of cells depend on a number of parameters, such as the applied voltage, duration of the pulse, number and shape of pulses, and other experimental quantities, such as the conductivity of the medium, temperature, and other cellular and environmental factors. Within this perspective, the numerical analysis of Krassowska and co-workers [67] provides considerable insight into the understanding of the electroporation process. For example, these authors investigated the formation and the evolution of pores for the purpose of modeling the DNA uptake mediated by electroporation. Based on the C^{++} programming language, Shil and co-workers [68] investigated the EFITP porous shelled spherical cells by including a random distribution of cholesterol in the membrane.

Last but not least, the growing public concerns about possible human health hazards caused by exposure to RF fields, e.g. wireless communication devices, broadcasting transmitters, and various microwave apparatus [69-74], and electrical injury [75] motivate the research concerning the modeling of the transport and interaction of electromagnetic fields in biological structures.

Foot notes:

[1]The reductionist approach to science-the idea that physics explains chemistry, chemistry explains biology, and so forth has its limits. It is the right model for almost all the science we have discovered so far, but it is not necessarily the whole story. Cracks in the reductionist edifice include quantum entanglement, emergent phenomena, and criticality.

[2]The key to the DNA discovery was the significant individual partnership between Watson (a biologist) and Crick (a physicist) which helped them to find a common language and gave rise to the idea of DNA replication and the foundations for molecular biology.

[3]Actin is the most abundant protein found in eukaryotic cells. It comprises 10% of the total protein mass in muscle cells and up to 5% in nonmuscle cells. Microtubules are 25 nm diameter cylindrical structures comprised generally of 13 protofilaments, each consisting of tubulin dimer subunits, 8 nm in length, aligned lengthwise parallel to the microtubule axis. The protofilaments are bound laterally to form a sheet that closes to form a cylindrical microtubule.

[4]Less successful has been physicists' long-cherished hope that quantum mechanics could offer a new framework for understanding living systems, i.e. in the late 1940s and 1950s it was fashionable to suppose that quantum mechanics held the key to the mystery of life. Flushed with their success in explaining the properties of non-living matter, the founders of quantum mechanics hoped their theory was both weird enough and powerful enough to explain the peculiar living state of matter too. Bohr, Heisenberg, Wigner offered speculations, while Schrödinger's famous book *What is Life*? Published in 1944, paved the way for the birth of molecular biology in the 1950s. Half a century later, no clear-cut "life principle" has emerged from the quantum realm that would single out the living state as in any way

special. Classical ball-and-stick models seem adequate for most explanations in molecular biology. In spite of this, there is clear and accumulating evidence that quantum mechanics plays a key role in biology. Unfortunately, biological systems are so complex that it is hard to separate "pure" quantum effects from the shifting melee of essentially classical processes that are also present. There is thus plenty of scope for disagreement about the extent to which life utilizes non-trivial quantum processes.

[5]A review of recent clinical results for magnetic hyperthermia treatments of brain and prostate cancer via direct injection, and developments in medical sensing technologies involving a new generation of magnetic resonance imaging contrast agents has been given by Pankhurst and co-workers [12].

[6]As the medical field moves from treatment of diseases with drugs to treatment with genes, safe and efficient gene delivery systems are needed to make this transition. Within this perspective, electroporation represents a safe, non-viral, and efficient gene delivery system. This involves the application of short duration (10-50 ms), high intensity (100-200 Vcm^{-1}) pulses such that they transiently permeabilize the cell membrane to enable uptake of xenomolecules such as drugs and genes. More specifically, *in vivo* electroporation is of special interest because it is the most efficient non-viral gene delivery, low-cost, ease of realization, and safety. Recently, it was shown that nanosecond pulsed electric field can also affect the cell constituents, i.e. nucleus, mitochondria, without altering the membrane. Cancerous tumors can be reduced in size by applying a limited number of voltage pulses of high rising time.

[7]Cole made major contributions to the measurement and interpretation of dielectric spectra in general, e.g. the Cole-Cole plot. His work on the low-frequency properties of nerve tissues led directly to the elucidation of the mechanism of ion conduction in nerves end indirectly to the patch-clamp techniques that are so successful in the investigation of nerve conduction. Cole's book [32] contains an historical survey of the main contributions dealing with the bulk electrical properties of biological materials covering the 1920s through the 1940s.

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Ann J Materials Sci Eng - Volume 1 Issue 3 - 2014
ISSN : 2471-0245 | www.austinpublishinggroup.com

Citation: Brosseau C. Some Reflections on the Impact of Physics, Materials Science, and Engineering on Biology and Medecine. Ann J Materials Sci Eng. 2014;1(3): 8.