Plasma Medicine

Alexander Fridman | Gary Friedman

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Contents

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Alexander Fridman and Gary Friedman
Drexel University, Philadelphia, PA, USA

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Preface

Plasma medicine has inspired the last decade of the authors' professional activities at Drexel Plasma Institute of the Drexel University. Plasma medicine is a very exciting and new multidisciplinary branch of modern science and technology. Even the term ‘plasma medicine’ has only been in existence since the start of the 21st century. Plasma medicine embraces physics required to develop novel plasma discharges relevant for medical applications, medicine to apply the technology not only in vitro but also in vivo testing and, last but not least, biology to understand the complicated biochemical processes involved in plasma interaction with living tissues.

While an understanding of the mechanisms by which non-thermal plasma interacts with living systems has begun to emerge only recently, a significant number of journal publications and even reviews focused on plasma medicine have appeared during the last 5–10 years. Several prestigious journals have published special issues dedicated to the topic, the new *Plasma Medicine* journal has been recently inaugurated, multiple world symposiums have created special sessions in this new field and plasma medical workshops have been organized in the USA, Germany, France, Korea, Japan, China and other countries. Four successful International Conferences on Plasma Medicine (ICPM) took place during the last 7 years in the USA, Germany and France; the 5th ICPM is planned to be held in Japan. Finally, the International Society on Plasma Medicine has been organized to coordinate the efforts of physicist, chemists, biologists, engineers, medical doctors and representatives of the industry working in this new field.

Despite the tremendous interest in plasma medicine, no single monograph has published in this field. There is no book where recent developments in plasma medicine, both technological and scientific, are described in a fashion accessible to the highly interdisciplinary audience of doctors, physicists, biologists, chemists and other scientists, university students and professors, engineers and medical practitioners. This is exactly the goal of the present *Plasma Medicine* book. The book is written for numerous scientists and medical practitioners, students, professors and industrial professionals who are involved today in plasma medicine.

When writing the book, we kept in mind the multidisciplinary nature of the field of plasma medicine. Physicists, chemists and engineers should be able to learn the different terminology of their biologist and medical practitioner partners, and vice versa. The book is beneficial to sides and should promote more effective development of the field of plasma medicine. The subject of plasma medicine has recently been included in the academic curriculum of universities, and we hope that the book will be helpful in this regard to students (as well as professors) involved in plasma-medical education.

Plasma Medicine consists of 11 chapters; Chapters 1–5 are focused on the **fundamentals of plasma medicine** and Chapter 6–11 are focused on **applied plasma medicine**.

Chapter 1 introduces the subject of plasma medicine. Chapter 2 describes the fundamental physical and chemical processes in plasmas relevant to its interaction with living tissues, providing a basic introduction to plasma medicine. Chapter 3 describes fundamental biology relevant to an understanding of the major principles of plasma interaction with living tissues. This topic covers the basic biological and medical introduction to plasma medicine, and will help physicists and engineers understand that even simple living organisms are much more complicated than electric devices. Chapter 4 describes plasma physics and engineering of the systems and devices relevant for medical applications. This chapter covers physical, chemical and engineering aspects of major electric discharges used for plasma–medical applications. In chapter 5, a description of the biophysical and biochemical mechanisms of plasma interaction with living tissues is provided. This chapter enables an understanding of the kinetics of plasma interaction with eukaryotic and prokaryotic cells, starting from gas phase and surface processes stimulated by active plasma species and including the consequent biochemical processes inside the cells.

Chapters 6 and 7 describe plasma sterilization of inanimate surfaces, as well as plasma sterilization of water and air. These chapters cover multiple applications of different low-pressure and atmospheric-pressure non-thermal discharges for disinfection and sterilization of different surfaces (e.g. medical instruments, food, space-crafts etc.); natural, drinking and industrial water; and large-volume air flows. Chapter 8 is focused on plasma-induced cauterization and blood coagulation. Plasma control of blood composition and relevant plasma treatment of blood diseases is also discussed in this chapter. Chapter 9 describes plasma treatment and healing of different wounds and diseases, in particular, plasma abatement of skin, dental and internal infections, treatment and healing of wounds and plasma treatment of oncological (cancerous), gastrointestinal, cardiovascular and other diseases. Chapter 10 describes plasma pharmacology, which suggests preliminary plasma treatment of water or special organic or inorganic solutions. These plasma-treated solutions can then be utilized for sterilization or healing purposes. The last chapter is focused on basic aspects of plasma-medical tissue engineering. This topic covers major modern aspects of plasma treatment of biomaterials and plasma-supported tissue engineering. This very important topic of applied plasma medicine is not directly related to plasma interaction with living tissue. This part of modern plasma medicine is very interesting, significant and relatively better developed (in particular, by our colleagues from University of Bari) than other branches; only a concise review of the subject is provided in this book.

Instructors can access PowerPoint files of the illustrations presented within this text, for teaching, at http://booksupport.wiley.com.

Alexander Fridman and Gary Friedman
Philadelphia

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1

Introduction to Fundamental and Applied Aspects of Plasma Medicine

1.1 Plasma medicine as a novel branch of medical technology

New ideas bring new hopes: plasma medicine is definitely one of those. Recent developments in physics and engineering have resulted in many important medical advances. The various medical technologies that have been widely described in the existing literature include applications of ionizing radiation, lasers, ultrasound, magnetism, and others. Plasma technology is a relative newcomer to the field of medicine. Very recent exponential developments in physical electronics and pulsed power engineering have promoted consequent significant developments in non-thermal atmospheric-pressure plasma science and engineering. Space-uniform and well-controlled cold atmospheric-pressure plasma sources have become a reality, creating the opportunity to safely and controllably apply plasma to animal and human bodies. This has instigated the creation of a novel and exciting area of medical technolgy: plasma medicine.

Experimental work conducted at several major universities, research centers, and hospitals around the world over the last decade demonstrates that non-thermal plasma can provide breakthrough solutions to challenging medical problems. It is effective in sterilization of different surfaces including living tissues, disinfects large-scale air and water streams, deactivates dangerous pathogens including those in food and drinks, and is able to stop serious bleeding without damaging healthy tissue. Non-thermal plasma can be directly used to promote wound healing and to treat multiple diseases including skin, gastrointestinal, cardiovascular, and dental diseases, as well as different forms of cancer. It has also proven effective in the treatment of blood, controlling its properties. Non-thermal discharges have also proven to be very useful in the treatment of different biomaterials and in tissue engineering, tissue analysis and diagnostics of diseases. Research indicates that non-thermal plasma may prove to be useful in pharmacology by changing properties of existing drugs and creating new medicines. Non-thermal plasma, developed recently due to the rapid progress in electronics, is clearly a promising new tool which should be provided to medical doctors to resolve medical problems. Plasma medicine, the subject of this book, is a source of great interest today.

When talking about the novel plasma sources which it is possible to apply to human and animal bodies, as well as for the treatment of cells and tissues in detailed biomedical experiments, we have to stress the *safety* and *controllability* of these novel plasma devices. As an example, the floating-electrode dielectric barrier discharge (FE-DBD) plasma source widely used for medical applications, in particular in Drexel University, applies c. 30–40 kV directly to the human body (see one of the authors of this book in Figure 1.1). Obviously, safety is the main issue in this case. Of no less importance is the controllability of the plasma parameters. The uniform cold atmospheric-pressure plasmas as well as some other plasma-medical devices developed recently can be effectively controlled; this is important not only for prescribing specific doses of medical treatment, but also for investigation of the mechanisms of plasma-medical treatment. Without detailed understanding of physical, chemical, and biomedical mechanisms, plasma tools have little chance of successful application in medicine.

Figure 1.1 *Non-thermal short-pulsed 40 kV FE-DBD plasma sustained directly between a dielectric-coated electrode and a human body*.

Non-thermal plasma is very far from thermodynamic equilibrium, which is discussed below. Such strongly non-equilibrium medium can be very ‘creative’ in its interactions with biomolecules. As first demonstrated in the 1950s by

Stanley Miller (see Figure 1.2) and his colleagues from the University of Chicago, plasma is even able to generate amino acids from methane and inorganics. It is very much possible that plasma, being a strongly non-equilibrium and multi-parametric medium, can even be responsible for the creation of life itself. Recent experiments prove that controllable changes of DNA after non-thermal plasma treatment are very sensitive to plasma parameters. This explains the great importance of the controllability of plasma parameters and a deep understanding of mechanisms for successful progress of plasma-medical science. The success of plasma medicine requires a detailed understanding of physical, chemical, and biomedical mechanisms of the strongly non-equilibrium plasma interaction with cells and living tissues. Without a fundamental understanding, plasma medicine is at risk of become a modernized medieval magic (see Figure 1.3).

Figure 1.2 *In the 1950s, Stanley Miller of the University of Chicago synthesized amino acids in plasma from methane and inorganic compounds*.

Figure 1.3 *International Society for Plasma Medicine (ISPM) signifies crucial importance of deep and detailed research focused on fundamental understanding of physical, chemical and biological bases of plasma medicine.*

Plasma medicine is a multidisciplinary branch of modern science and technology. It embraces physics (required to develop novel plasma discharges relevant for medical applications), medicine (to apply the technology for not only in vitro but also in vivo testing), and last but not least biology (to understand the complicated biochemical processes involved in plasma interaction with living tissues). While an understanding of the mechanisms by which non-thermal plasma can interact with living systems has begun to emerge only recently, a significant number of original journal publications and even reviews have appeared since the mid-2000s. Several prestigious journals have published special issues dedicated to the plasma medicine, the new *Plasma Medicine* journal has been recently launched, multiple world symposiums have created special sessions in this new field, and plasma-medical workshops have been organized in the USA, Germany, France, Korea, Slovakia, and other countries. The most important world forum of plasma-medical research is the International Conferences on Plasma Medicine (ICPM). Four of these biannual conferences have already been successfully organized: ICPM-1 in Corpus Christi, Texas, USA; ICPM-2 in San-Antonia, Texas, USA; ICPM-3 in Greifswald, Germany; and finally ICPM-4 in Orleans, France in 2012. Finally, the International Society on Plasma Medicine was launched this year (2012) to coordinate the efforts of physicist, chemists, biologists, engineers, medical doctors and representatives of the industry in the new field of plasma medicine.

Hopefully, this book will be helpful to this entire and very multidisciplinary group of researchers and industry representatives. Plasma scientists and medical doctors speak different languages; they even have two different meanings for the word ‘plasma’ itself. Plasma scientists, medical doctors and biologists often have very different approaches to fundamental knowledge as well as practical applicability, but this book recognizes that they are united by a mutual interest in this new field of plasma medicine and by the common idea that development of plasma medicine brings new opportunities for treating human conditions.

1.2 Why plasma can be a useful tool in medicine

While the term ‘medicine’ in the title of the book does not require a special introduction, the term ‘plasma’ may require some elucidation (especially for medical practitioners). Plasma is an ionized gas and a distinct fourth state of matter. ‘Ionized’ means that at least one electron is not bound to an atom or molecule, converting them into positively charged ions. As temperature increases, atoms and molecules become more energetic and the state of matter transforms in the sequence: solid to liquid, liquid to gas and finally gas to plasma, which justifies the label of ‘fourth state of matter’.

The free electric charges, electrons and ions make plasma electrically conductive (with magnitudes of conductivity sometimes exceeding that of gold and copper), internally interactive, and strongly responsive to electromagnetic fields. Ionized gas is defined as plasma when it is electrically neutral (electron density is balanced by that of positive ions) and contains a significant number of electrically charged particles, sufficient to affect its electrical properties and behavior. In addition to being important in many aspects of our daily lives, plasmas are estimated to constitute more than 99% of the known universe.

The term ‘plasma’ was first introduced by Irving Langmuir in 1928 when the multi-component, strongly interacting ionized gas reminded him of blood plasma; the term ‘plasma’ itself therefore has a strong relation to medicine. This can however be confusing: for example, read the discussions regarding plasma treatment of blood plasma in Chapter 8 of this book. Defining the term plasma, Irving Langmuir wrote: “Except near the electrodes, where there are sheaths containing very few electrons, the ionized gas contains ions and electrons in about equal numbers so that the resultant space charge is very small. We shall use the name **plasma** to describe this region containing balanced charges of ions and electrons”. Plasmas occur naturally, but can also be effectively produced in laboratory settings and in industrial or hospital operations, providing opportunities for numerous applications including thermonuclear synthesis, electronics, lasers, fluorescent lamps, cauterization and tissue ablation during surgeries, and many others. We remind the reader that most computer and cell-phone hardware is based on plasma technology, not to forget about the plasma TV. In this book, we will focus on the fundamental and practical aspects of plasma applications to medicine, biology, and related disciplines, which represent today probably the most novel and exciting component of plasma science and engineering. Plasma is widely used in practice today. Generally, plasma offers three major features which are attractive for major practical applications.

1. *Temperatures* and energy densities of some plasma components can significantly exceed those in conventional technologies. These temperatures can easily exceed the level of c. 10 000 K. For example, if melted ceramics are needed to make relevant coatings, requiring temperatures above 3000 K, there is no choice but to use plasma. In medical settings, high temperatures and energy densities can be useful for cauterization and tissue ablation during surgery, for example.

2. Plasmas are able to produce a *very high concentration of energetic and chemically active species* (e.g., electrons, positive and negative ions, atoms and radicals, excited atoms and molecules, as well as photons that span wide spectral ranges). A high concentration of active species is crucial for important plasma applications such as plasma-assisted ignition and combustion (probably the oldest plasma application) and plasma generation of ozone for water cleaning. In medical settings, generation of the high concentration of excited and reactive species can be useful for sterilization of surfaces, air, and water streams, as well as for tissue engineering.

3. Plasma systems can be very far from thermodynamic equilibrium, providing an *extremely high concentration of the chemically active species while maintaining bulk temperatures as low as room temperature*. This feature determines exclusiveness of plasma use in microelectronics and semiconductor industries: most elements of modern computers, cell phones, television equipment, cold lighting, and other electronic devices are manufactured using cold plasma technology. This important feature also determines the wide application of cold plasma in treatment of polymers: most textiles for our clothes, photographic paper, wrapping materials and so on are today plasma treated. In medical settings, the generation of an extremely high concentration of the chemically active species, while maintaining bulk temperatures as low as room temperature, can be useful for: non-thermal blood coagulation; corrections of blood composition and properties; sterilization of skin and other living tissues; healing wounds; and treating diseases not effectively treated before.

The three specific plasma features described above permit significant intensification of traditional chemical and biochemical processes, improvements in their efficiency, and often successful stimulation of chemical and biochemical reactions that are not possible using conventional techniques.

1.3 Natural and man-made, completely and weakly ionized plasmas

Plasma comprises the majority of the mass in the known universe: the solar corona, solar wind, nebula, and the Earth's ionosphere are all plasmas. The most readily recognized form of natural plasma phenomenon in the Earth's atmosphere is lightning. The breakthrough experiments with this natural form of plasma were performed long ago by Benjamin Franklin (Figure 1.4), which explains the special interest in plasma research in the Philadelphia area where the authors of this book are based (Drexel Plasma Institute, Drexel University).

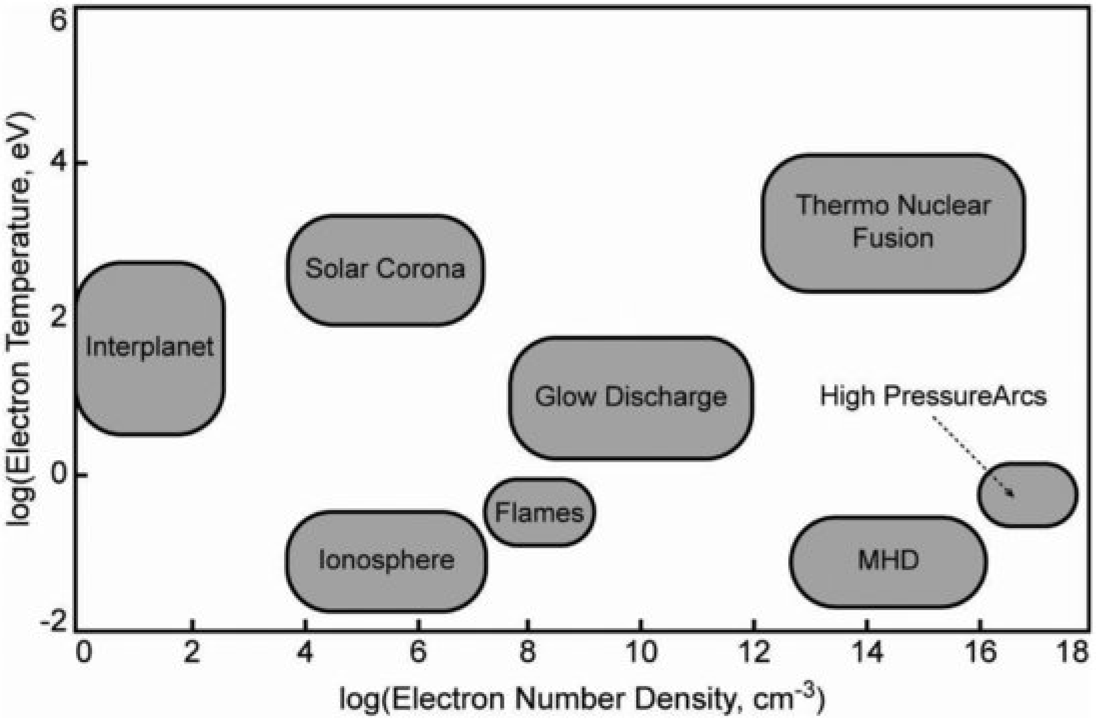
Figure 1.4 *Benjamin Franklin successfully performed the first experiments with the atmospheric plasma phenomenon of lightning*.

At altitudes of approximately 100 km, the atmosphere no longer remains non-conducting due to significant ionization and formation of plasma by solar radiation. As one progresses further into near-space altitudes, the Earth's magnetic field interacts with charged particles streaming from the sun. These particles are diverted and often become trapped by the Earth's magnetic field. The trapped particles are most dense near the poles, creating the beautifully rendered Aurora Borealis (Figure 1.5). Lightning and the Aurora Borealis are the most common forms of natural plasmas observed on earth.

Figure 1.5 *Aurora borealis.*

Natural and man-made or manufactured plasmas (generated in gas discharges) occur over a wide range of pressures, electron temperatures, and electron densities (see Figure 1.6). Temperatures of manufactured plasmas range from slightly above room temperature to temperatures comparable to the interior of stars, with electron densities that span over 15 orders of magnitude. Most plasmas of practical significance, however, have electron temperatures of 1–20 eV with electron densities in the range 10^6–10^{18} cm^{-3} (high temperatures are conventionally expressed in electron-volts, with 1 eV *c.* 11 600 K).

Figure 1.6 *General chart of plasma temperatures and densities.*



Not all particles need to be ionized in plasma; a common condition in plasma chemistry is for the gases to be only partially ionized. The ionization degree (ratio of density of major charged species to that of neutral gas) in conventional plasma-chemical systems is in the range 10^{-7}–10^{-4}. When the ionization degree is close to unity, such plasma is referred to as *completely ionized plasma*. Completely ionized plasmas are conventional for thermonuclear plasma systems (tokomaks, stellarators, plasma pinches, focuses, etc.). When ionization degree is low, the plasma is called *weakly ionized plasma*. Weakly ionized plasmas and the important chemical and biochemical processes stimulated in such plasmas is the focus of this book.

Both natural and manufactured or man-made laboratory plasmas are quasi-neutral, which means that concentrations of positively charged particles (positive ions) and negatively charged particles (electrons and negative ions) are well balanced. Langmuir was one of the pioneers who studied gas discharges, and defined plasma to be a region not influenced by its boundaries. The transition zone between the plasma and its boundaries was termed the plasma *sheath*. The properties of the sheath differ from those of the plasma and these boundaries influence the motion of the charge particles in this sheath. They form an electrical screen for the plasma from influences of the boundary. Very important concepts group plasma physics, plasma chemistry, and plasma medicine into two major classes – those of thermal and non-thermal plasmas – which are discussed in the following section.

1.4 Plasma as a non-equilibrium multi-temperature system

Temperature in plasma is determined by the average energies of the plasma particles (neutral and charged) and their relevant degrees of freedom (translational, rotational, vibrational, and those related to electronic excitation). As multi-component systems, plasmas are therefore able to exhibit multiple temperatures. In electric discharges common for plasmas generated in the laboratory, energy from the electric field is first accumulated by the electrons through collisions; it is subsequently transferred from the electrons to the heavy particles. Electrons receive energy from the electric field during their mean free path. During the following collision with a heavy particle, they only lose a small portion of that energy (because electrons are much lighter than the heavy particles). That is why electron temperature in plasma is initially higher than that of heavy particles. Subsequently, collisions of electrons with heavy particles (Joule heating) can equilibrate their temperatures unless time or energy are not sufficient for the equilibration (such as the situation in coronas and pulsed discharges), or there is an intensive cooling mechanism preventing heating of the entire gas (as for wall-cooled low-pressure discharges).

The temperature difference between electrons and heavy neutral particles due to Joule heating in the collisional weakly ionized plasma is conventionally proportional to the square of the ratio of the electric field (E) to the pressure (p). Only in the case of small values of E/p, the temperatures of electrons and heavy particles approach each other. This is a basic requirement for the so-called local thermodynamic equilibrium (LTE) in plasma. Additionally, LTE conditions require chemical equilibrium as well as restrictions on the gradients. The LTE plasma follows major laws of the equilibrium thermodynamics and can be characterized by a single temperature at each point of space. Ionization and chemical processes in such plasmas are determined by temperature (and only indirectly by the electric fields through Joule heating). The quasi-equilibrium plasma of this kind is usually called *thermal plasma*. In nature, thermal plasmas can be represented by solar plasma (see Figure 1.7).

Figure 1.7 *Solar plasma.*