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,

Plasma Medicine, First Edition. Alexander Fridman and Gary Friedman.

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

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.

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).

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,

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

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.*

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).

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.

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).

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)

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

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.

Figure 1.5 *Aurora borealis.*

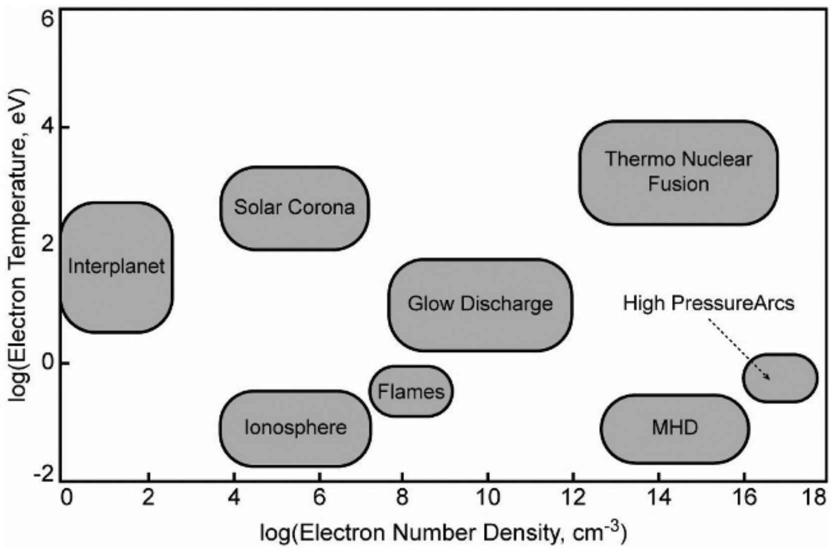

Figure 1.6 *General chart of plasma temperatures and densities.*

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).

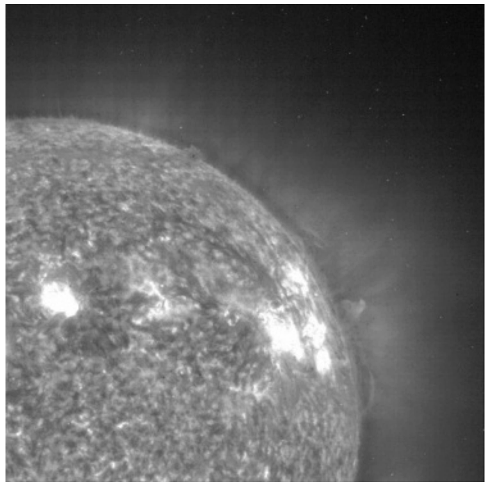

Figure 1.7 *Solar plasma.*

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).

Numerous plasmas are sustained very far from the thermodynamic equilibrium and are characterized by multiple temperatures related to different plasma particles and different degrees of freedom. The electron temperature often significantly exceeds those of heavy particles ($T_e \gg T_0$). Ionization and chemical processes in such non-equilibrium plasmas are directly determined by electron temperature, and are therefore not very sensitive to thermal processes and temperature of the gas. The non-equilibrium plasma of this kind is usually referred to as *non-thermal plasma*. Non-thermal plasmas in nature are represented by the Aurora Borealis (see Figure 1.5) as opposed to thermal plasmas which are represented by lightening.

Although the relation between different plasma temperatures in non-thermal plasmas can be complex, it can be conventionally presented in the collisional weakly ionized plasmas as: $T_e > T_v > T_r \approx T_i \approx T_0$. Electron temperature T_e is the highest in the system, followed by the temperature of vibrational excitation of molecules T_v. The lowest temperature is usually shared in plasma by heavy neutrals (T_0, temperature of translational degrees of freedom or simply bulk gas temperature), ions (T_i), and rotational degrees of freedom of molecules (T_r). In many non-thermal plasma systems, electron temperature is *c*. 1 eV (*c*. 10 000 K), while gas temperature is close to room temperature.

Non-thermal plasmas are usually generated either at low pressures, at lower power levels, or in a different kind of pulsed discharge systems. The engineering aspects and application realms are quite different for thermal and non-thermal plasmas. Thermal plasmas are usually more powerful (up to 30 MW and above), while non-thermal plasmas are more selective and can be used in delicate applications without degrading the surrounding environment. However, these diverse forms of ionized gases share many common characteristics.

It is interesting to note that both thermal and non-thermal plasmas usually have the highest temperature (T_e in one case and T_0 in the other) of the order of magnitude of 1 eV, which is c. 10% of the total energy required for ionization (c. 10 eV). This reflects the general axiom formulated by Zeldovich and Frank-Kamenetsky for atoms and small molecules in chemical kinetics: the temperature required for a chemical process is typically c. 10% of the total required energy, which is the Arrhenius activation energy. Plasma temperatures can be somewhat identified as the 'down payment' for the ionization process (since a similar rule i.e. that of 10% is usually applied to calculate a down payment for a mortgage).

Thermal and non-thermal plasmas have their own specific niches for biological and medical applications. High temperatures and high energy densities typical of thermal plasmas determine their applications for cauterization and tissue ablation during surgeries. Such devices are widely used today in medical practice; some of them even combine the above-mentioned features with tissue sterilization. Thermal plasma in air is also very productive in the generation of NO, which determines its application in the so-called plasma-induced NO-therapy effective in plasma treatment of wounds and different diseases. Non-thermal plasma permits the generation of an extremely high concentration of the chemically active species, while maintaining bulk temperatures as low as room temperature. It determines the specific application niche of the non-thermal plasma, which is usually: non-thermal blood coagulation and corrections of blood composition and properties; sterilization of skin and other living tissues; sterilization of medical instruments and other fragile materials and devices; processing of biopolymers; tissue engineering; and finally non-thermal plasma healing of wounds and different diseases not effectively treated before.

1.5 Gas discharges as plasma sources for biology and medicine

Plasma medicine is based on a sequence of plasma-chemical and biochemical processes involving ionized gases. A plasma source, which in most laboratory conditions is a gas discharge, therefore represents a physical and engineering basis of the plasma medicine. For simplicity, an electric discharge as a plasma source in general can be viewed as two electrodes inserted into a glass tube and connected to a power supply. The tube can be filled with various gases or evacuated. As the voltage applied across the two electrodes increases, the current suddenly increases sharply at a threshold voltage required for sufficiently intensive electron avalanches. If the pressure is low (of the order a few Torr) and the external circuit has a large resistance to prohibit a large current, a glow discharge develops. This is the low-current high-voltage discharge widely used to generate non-thermal plasmas. A similar discharge is the basis of operation for fluorescent lamps, a common plasma discharge device. The glow discharge can be considered as a major example of the low-pressure non-thermal plasma sources (see Figure 1.8). Low-pressure plasma discharges can be effective as UV sources or sources of some active species for sterilization. They can be also effective for the treatment of biopolymers and in tissue engineering. It should be mentioned that, to keep treatment areas clean from the products of erosion of electrodes, low-pressure plasma-medical technologies are often based on electrode-less low-pressure plasma sources such as low-pressure radio-frequency plasma sources.

Historically, some important developments in the area of plasma medicine probably started with the work on surface treatment and subsequent surface interactions with cells (e.g. the work carried out by the groups of Riccardo D'Agostino, Pietro Favia and Michael Wertheimer) and sterilization using low-pressure non-thermal plasma (e.g. the work carried out by the group led by Michel Moisan).

Most plasma-medical applications require operation at atmospheric pressure, therefore use of atmospheric-pressure plasma discharges. Igor Alexeff and Mounir Laroussi were some of the first researchers to employ atmospheric-pressure plasma for sterilization, while Eva Stoffels was probably one of the first to apply such discharges directly to cells. Dr. Richard Satava, who managed various projects at the Defense Advanced Research Projects Agency (DARPA), helped develop initial applications of non-thermal plasma in medicine in the United States.

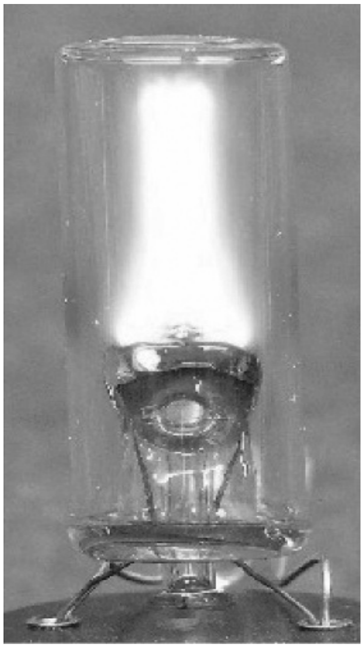

Figure 1.8 *Glow discharge.*

Probably the simplest example of such discharges is the corona discharge (see Figure 1.9). A non-thermal corona discharge occurs at high pressures (including atmospheric pressure) in regions of sharply non-uniform electric fields. The field near one or both electrodes must be stronger than in the rest of the gas. This occurs near sharp points, edges or small diameter wires. These tend to be low-power plasma sources, limited by the onset of electrical breakdown of the gas. However, it is possible to circumvent this restriction through

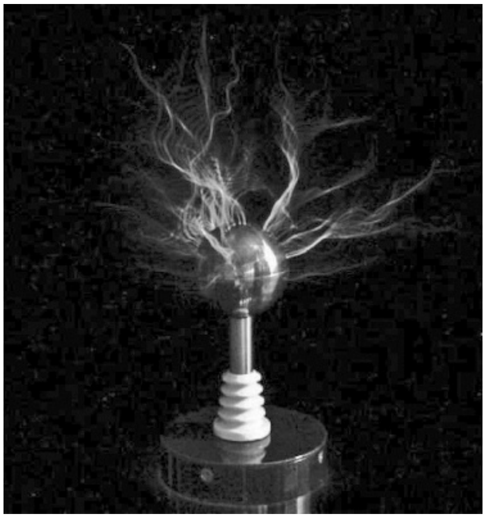

Figure 1.9 *Corona discharge.*

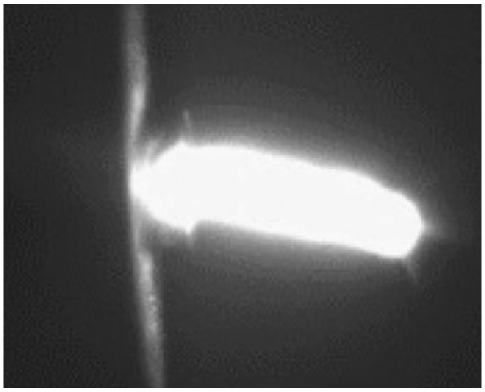

Figure 1.10 *Arc discharge.*

the use of pulsating power supplies. Electron temperature in the corona discharges can exceed 1 eV, while gas temperatures remain at the level of room temperature. The corona discharges are widely applied in the treatment of polymer materials: most synthetic fabrics used for clothing are treated using corona-like discharges to provide sufficient adhesion prior to dye applications.

The corona discharge can be considered as a major example of the atmospheric-pressure non-thermal plasma sources (see Figure 1.9). Atmospheric-pressure non-thermal plasma discharges can be effective in non-thermal blood coagulation and corrections of blood composition and properties; sterilization of skin and other living tissues; sterilization of medical instruments and other fragile materials and devices; processing of biopolymers; tissue engineering; and healing of wounds and different diseases. It should be mentioned that to keep treatment areas free from the products of erosion of electrodes and to provide uniform (or focused) treatment, other more complicated atmospheric pressure discharges such as dielectric barrier discharge (DBD) or atmospheric pressure glow (APG) plasma jet are normally used in medical applications.

For conditions that involve high pressures (i.e. of the order of an atmosphere) and when the external circuit resistance is low, a thermal arc discharge can be organized between two electrodes. Thermal arcs usually carry large currents, greater than 1 A at voltages of the order of tens of volts. Furthermore, they release large amounts of thermal energy at very high temperatures, often exceeding 10 000 K. The arcs are often coupled with a gas flow to form high-temperature plasma jets. The arc discharges are well known not only to scientists and engineers, but also to the general public because of their wide application in welding devices. The arc discharge can be considered as a major example of a thermal plasma source (see Figure 1.10). As mentioned above, arc discharges are widely used in medicine as cauterization and tissue ablation devices.

Thermal discharges can also be used to generate active species and UV for medical applications. This approach has been pursued, for example, by the groups headed by Gregor Morfill at the Max Plank Institute in Munich, Germany and Anatoly Shekhter in Moscow, Russia.

Other electric discharges widely applied in plasma engineering include non-equilibrium low-pressure radio-frequency (RF) discharges that play key roles in sophisticated etching and deposition processes of modern microelectronics, as well as in the treatment of polymer materials. More and more chemical processes are organized in gliding arc discharges (powerful generators of non-equilibrium atmospheric-pressure plasma), especially with plasma stabilization in reverse vortex 'tornado' flow (see Figure 1.11). The gliding arc 'tornado' discharges provide the unique combination of high power typical of arc discharges with a relatively high level of non-equilibrium typical of non-thermal atmospheric-pressure discharges. Regarding biomedical applications, the gliding arc 'tornado' discharges have been effectively used for sterilization of liquids and for plasma treatment of water and water solutions for sterilization of skin and wounds.

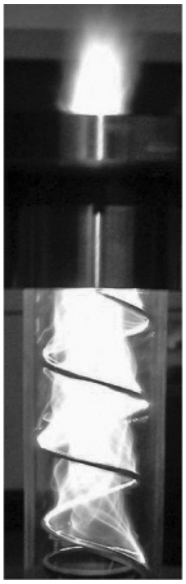

Figure 1.11 Gliding arc discharge stabilized in the 'tornado' gas flow.

Some electric discharges which are not conventional plasma sources attract significant interest for biological and medical applications. Of such non-traditional but practically interesting biomedical plasma discharges, we can point out the non-thermal high-voltage atmospheric-pressure FE-DBD, which is able to use the human body as a second electrode without damaging the living tissue. Such a discharge, developed independently as a plasma-medical tool by Wolfgang Viol and the authors of this book, obviously provides important opportunities for direct plasma applications in biology and medicine (Figure 1.12). Similar discharges have been developed by a number of different groups including that of Klaus-Dieter Weltmann in Greifwald, Germany, Jean-Michel Pouvesle in Orleans, France and David Graves at the University of California, Berkley.

Another example of this kind is related to atmospheric-pressure non-thermal plasma helium jets (see Figure 1.13), developed by a number of different groups including Mounir Laroussi in the US, Michael Kong

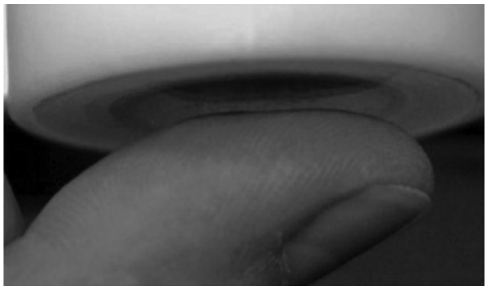

Figure 1.12 Floating-electrode dielectric barrier discharge (FE-DBD) with a finger as a second electrode.

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Figure 1.13 *Professor Mounir Laroussi of Old Dominion University working with the non-thermal atmospheric-pressure plasma jet, a convenient tool for topical focused plasma treatment of living tissues (see color plate).*

in UK, Jean-Michel Pouvesle in France, Jae Koo Lee in South Korea. All these plasma sources, and especially those widely applied in plasma medicine, are discussed in detail in Chapter 4.

1.6 Plasma chemistry as the fundamental basis of plasma medicine

Chemically active plasma is a multi-component system that is highly reactive due to large concentrations of charged particles (electrons, negative and positive ions); excited atoms and molecules (electronic and vibrational excitations make a major contribution); active atoms and radicals; and UV-photons. Each component of the chemically active plasma plays its own specific role in plasma-chemical kinetics. For example, electrons are usually first to receive the energy from the electric field and then distribute it between other plasma components and specific degrees of freedom of the system. Changing the parameters of the electron gas (density, temperature, electron energy distribution function or EEDF) often allows the plasma-chemical processes to be controlled and optimized.

Ions are charged heavy particles that are able to make a significant contribution to plasma-chemical kinetics either due to their high energy (as in the case of sputtering and reactive ion etching) or to their ability to suppress activation barriers of chemical reactions. This second feature of the plasma ions results in the so-called ion- or plasma-catalysis, which is particularly essential in plasma-assisted ignition and flame stabilization; fuel conversion; hydrogen production; exhaust gas cleaning; and even in the direct plasma treatment of living tissue.

Vibrational excitation of molecules often makes a major contribution to the plasma-chemical kinetics because the plasma electrons with energies around 1 eV primarily transfer most of the energy in gases such as N_2, CO, CO_2, and H_2 into vibrational excitation. Stimulation of plasma-chemical processes through vibrational excitation allows the highest values of energy efficiency to be reached. Electronic excitation of atoms and molecules can also play a significant role, especially when the lifetime of the excited particles is quite long (as in the case of the metastable electronically excited atoms and molecules). As an example, we can mention plasma-generated metastable electronically excited oxygen molecules $O_2(^1\Delta_g)$ (singlet oxygen), which effectively participate in the plasma-stimulated oxidation process in polymer processing and biological and medical applications.

The contribution of atoms and radicals is obviously significant. For example, O-atoms and OH radicals effectively generated in atmospheric air discharges can play key roles in numerous plasma-stimulated oxidation processes. Plasma-generated photons also play key roles in a wide range of applications from plasma light sources to UV sterilization of water.

Plasma is not only a multi-component and multi-parametric system, but it can also be very far from thermodynamic equilibrium. Non-thermal plasmas are often strongly non-equilibrium systems. Concentrations of the active species described above can exceed many orders of magnitude of the concentrations achieved in quasi-equilibrium systems at the same gas temperature. Successful control of plasma permits the chemical or biochemical process to be steered in a particular direction and through an optimal mechanism. Control of a plasma-chemical system requires detailed understanding of elementary processes and kinetics of the chemically active plasma. Major fundamentals of plasma physics, elementary processes in plasma, and plasma kinetics are discussed in Chapter 2.

1.7 Non-thermal plasma interaction with cells and living tissues

As mentioned above, the mechanisms of chemical processes in plasma are complex. The complexity of mechanisms of plasma interaction with cells and living tissues is however much higher. Probably the easiest way to approach this challenging topic is to compare the biological effect of non-thermal plasma, which has been researched for less than a decade, with the biological effect of ionizing radiation, which has been intensively investigated for more than half a century.

Initially, there is a fundamental similarity between the biomolecular action of ionizing radiation (IR) and of non-equilibrium plasma. To a significant extent, both actions influence biological molecules and living organisms through generation of reactive oxygen species (ROS). Since methods of studying IR have been extensively developed, they can be conveniently adapted to investigate the effects of non-equilibrium plasma. Results of such biochemical investigations will be discussed in detail later in Chapter 5.

However, there are also important differences in the mechanisms by which IR and non-equilibrium plasma affect biological systems. For one thing, non-equilibrium plasma can generate many important species that IR usually does not. This includes reactive nitrogen species (RNS), large amount of freely moving charges (mostly positive and negative ions), and strong electric fields. Studying the mechanism of the non-equilibrium plasma treatment therefore has to involve characterization of the effects of these additional species. Even more importantly, IR is a penetrating radiation that generates ROS directly inside cells and, to some extent, causes direct damage to biological molecules within cells.

Non-equilibrium plasma, on the other hand, does not directly generate reactive species inside cells. Rather, it acts by initiating chains of reactions that begin in the plasma generation region. The ‘plasma effect’ then proceeds through the extracellular region (biological medium), modifying biomolecules which subsequently initiate signaling, modify cell membranes, or diffuse across them to create observable effects on living organisms (see Figure 1.14). For simplicity, the plasma-medical effect can be compared to a three-layer sandwich (illustrated by the Figure 1.14). Primary active species are generated inside the plasma (first layer) and are then are transported from the gas-phase into the intermediate biological medium (second liquid layer), from where the active species reach cells and trigger sophisticated intracellular biochemistry through multiple signaling mechanisms (third layer). Only the first steps toward an understanding of complex mechanism at

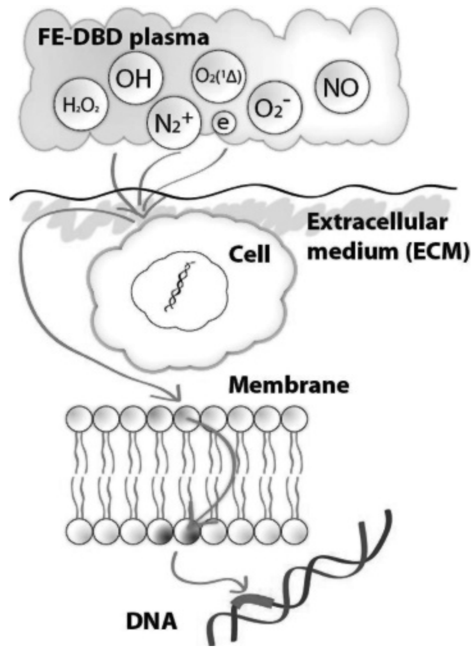

Figure 1.14 *Overall sequence of the non-equilibrium plasma-induced biomolecular processes: charges and active species (OH, H_2O_2, N_2^+, O_2^-, NO, $O_2(^1\Delta)$, etc.) from non-thermal plasma act on the cell membrane through the extracellular medium (ECM) leading to intracellular effects (e.g., protein modification, changes in transcription rates, DNA-related effects, etc.).*

each of these three levels of plasma interaction with cells and living tissues have been made; these will be reviewed in Chapter 5.

1.8 Applied plasma medicine

Plasma technologies successfully compete with conventional approaches in many practical applications, for example: thermal plasma deposition of protective coatings; plasma stabilization of flames; plasma conversion of fuels; plasma light sources; plasma cleaning of exhaust gases; and plasma sterilization of water. All these plasma technologies are practically interesting, commercially viable, and have made an important contribution to the development of our society.

The most exciting applications of plasma, however, have no conventional analogies and no (or almost no) competition. A good relevant example is plasma applications in microelectronics, such as etching of deep trenches (0.2 μm wide and 4 μm deep) in single-crystal silicon (very important in the fabrication of integrated circuits). The capabilities of plasma processing in microelectronics are extraordinary and unique; without plasma processing, we would not have achieved such powerful and compact computers and cell phones. When all alternatives fail, plasma remains as a viable and valuable tool. Selective modulation of regimes, power, density, and temperatures enable plasma to meet challenges and solve problems which cannot be solved by alternative technologies. There are other applications where plasma processes are not only highly efficient, but actually unique. For example, there are no other technologies which are able to compete with plasma for production of ozone (for more than 100 years); we should also keep in mind thermonuclear plasma as a unique major source of energy in the future.

In a similar way, plasma medicine attracts significant interest today because of the opportunities to tackle unresolved medical problems and to treat previously untreatable diseases. As a strongly non-equilibrium multi-parametric medium, plasma is able to shift the paradigm in therapeutics, wound-healing, and disease control. Some of the earlier applications of plasma in medicine relied mainly on its thermal effects. Heat and high temperature have been exploited in medicine for a long time for the purposes of tissue removal, sterilization, and cauterization (cessation of bleeding). Warriors have cauterized wounds by bringing them in contact with red hot metal objects and even flame (plasma) since ancient times.

Electrocautery is a more modern technique which applies controlled heat to surface layers of tissue by passing a sufficiently high current through it. Contact of tissue with the metal surface of a cautery device often results in adhesion of charred tissue to the metal, however. Subsequent removal of the metal can peel the charred tissue away, re-starting bleeding. Some of the earlier applications of plasma in medicine provided an alternative to metal-contact electrocautery. In argon plasma coagulation (APC, also sometimes called argon beam coagulation), highly conductive plasma replaced the metal contacts in order to pass a current through tissue, hence avoiding the difficulty with tissue adhesion. Hot plasma is also employed to cut tissue, although the exact mechanism by which this cutting occurs remains unclear. Heat delivered by plasma has also been employed recently for cosmetic re-structuring of tissue.

What differentiates more recent research on applications of plasma in medicine is the exploitation of the non-thermal effects. Why are non-thermal effects of plasma so interesting and promising? The main reason is that non-thermal plasma effects can be tuned for various sub-lethal purposes such as genetic transfection, cell detachment, wound healing, and others. Moreover, non-thermal effects can be selective in achieving a desired result for some living matter, while having little effect on the surrounding tissue. This is the case, for example, with recent plasma blood coagulation and bacteria deactivation, which does not cause toxicity in the surrounding living tissue.

Many examples demonstrating the effectiveness of plasma wound healing and treatments of different diseases are discussed in Chapter 9. Here, we quote an example of when a human life has been saved as a result of plasma treatment: the plasma treatment of corneal infections. In this regard, a special microplasma system has been developed for local medical treatment of skin diseases, and especially for the treatment of corneal infections (Gostev and Dobrynin, 2006). Details regarding this discharge are provided in Chapter 4 (see pin-to-hole spark discharge or PHD).

A series of in vitro experiments on bacterial cultures and in vivo experiments on rabbit eyes using this plasma discharge were conducted by Misyn *et al*. (2000). The experiments affirm the strong bactericidal effect of this microdischarge with minimal and reversible changes (if any) in biological tissues, even in such delicate tissues as cornea. During the investigation of plasma treatment of ulcerous dermatitis of rabbit cornea, two important observations were made: (1) plasma treatment has a pronounced and immediate bactericidal effect, and (2) the treatment has an effect on wound pathology and the rate of tissue regeneration and wound healing process.

These results provided a strong grounding for the successful application of the medical microplasma system (Gostev and Dobrynin, 2006) for treatment of a human patient with complicated ulcerous eyelid wounds, depicted in Figure 1.15. Necrotic phlegm on the surface of the upper eyelid was treated by an air plasma plume of 3 mm diameter for 5 seconds once every few days. By the fifth day of treatment (two 5-second plasma treatment sessions), the eyelid edema and inflammation were reduced. By the sixth day (third session), the treated area was free of edema and inflammation and a rose granular tissue appeared. Three more plasma treatments were administered (six in total), and the patient was discharged from the hospital six days after the final treatment (Figure 1.15).

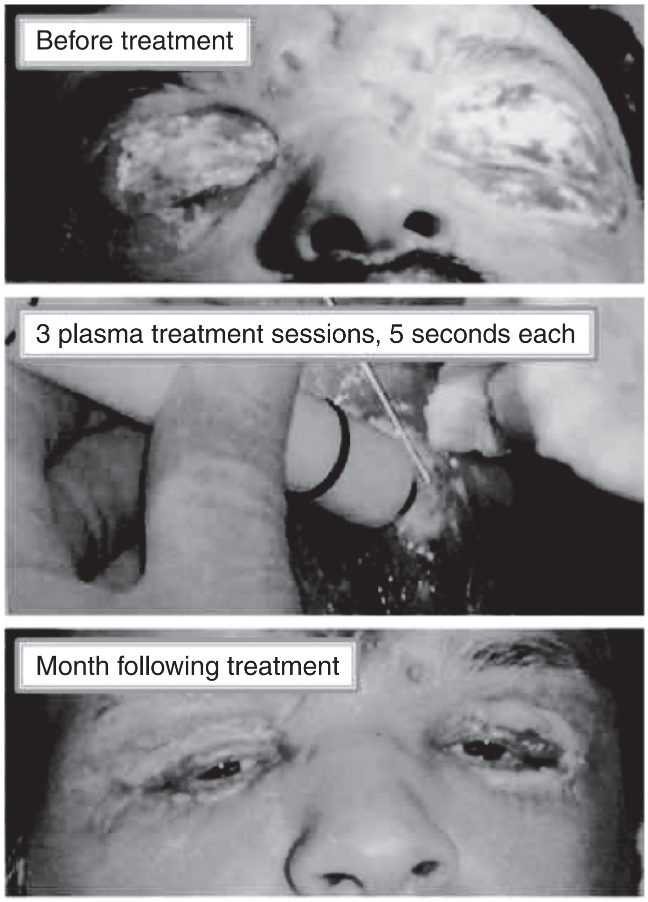

Figure 1.15 *Result of plasma treatment sessions (top: before; lower: after) of plasma treatment (middle) of a complicated ulcerous eyelid wound (see color plate).*

From these initial thoughts on the exciting and motivating results of the application of plasma medicine, the following chapters will discuss in detail the fundamentals of plasma medicine (first the fundamentals related to plasma physics and chemistry, and then basic medicine fundamentals).