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Grand challenges in low temperature plasmas

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Low temperature plasmas (LTPs) enable to create a highly reactive environment at near ambient temperatures due to the energetic electrons with typical kinetic energies in the range of 1 to 10 eV (1 eV = 11600K), which are being used in applications ranging from plasma etching of electronic chips and additive manufacturing to plasma-assisted combustion. LTPs are at the core of many advanced technologies. Without LTPs, many of the conveniences of modern society would simply not exist. New applications of LTPs are continuously being proposed. Researchers are facing many grand challenges before these new applications can be translated to practice. In this paper, we will discuss the challenges being faced in the field of LTPs, in particular for atmospheric pressure plasmas, with a focus on health, energy and sustainability.

KEYWORDS

low temperature plasmas (LTP), plasma etching (PE), plasma-assisted combustion, atmospheric pressure plasmas, plasma for health, plasma for energy conversion, sustainability

1 Introduction

The definition of low temperature plasmas (LTPs) is primarily related to the temperatures of its species. High temperature plasmas have electron temperatures on the order of 10^8 K (10 keV) or higher. This type of plasma is more relevant to nuclear fusion for clean energy production. The sun is a natural fusion plasma reactor. Two of the largest man-made high-temperature plasma devices are the International Thermonuclear Experimental Reactor (ITER) investigating magnetically confined fusion and the National Ignition Facility (NIF) investigating inertially confined fusion. In contrast, laboratory generated LTPs have an electron temperature on the order of 10 eV (1 eV = 11600K) or lower, with gas temperatures that range from room temperature to several thousand Kelvin. Plasmas having the gas temperature, and often the ion temperature, much lower than the electron temperature are classified as nonequilibrium LTPs. Plasmas having gas temperatures close or equal to their electron temperature are in thermal equilibrium and are referred to as thermal LTPs.

Nonequilibrium LTPs produce greater chemical reactivity than is possible at the same gas temperature because of their higher electron temperatures. The higher electron temperature enables electron impact excitation of atoms and molecules to higher electronic and vibrational states, while they can also break chemical bonds to create radicals. In this way, certain chemical reactions can be enhanced and chemical products can be produced at relatively low gas temperatures. The essence of nonequilibrium LTPs is transferring energy from electric fields to chemical bonds so that new reactive species can be produced. For a given gas composition, the rate of production of such chemically active species depends on the electron energy distribution function (EEDF), which further initially determines the excitation temperature and vibrational temperature. Plasma chemical reactions following the initial electron impact events then determine the reactivity of the system.

Diverse applications of nonequilibrium LTPs surround us in our daily life, e.g., computer chips are manufactured by LTPs-enabled processing (e.g., etching, deposition), high performance optics used in telescopes and coatings in eyeglasses are produced by LTPs-enhanced film deposition. Satellites use plasma thrusters for repositioning and station keeping.

The essence of thermal plasmas is transferring electrical energy to thermal energy. The concentrations of nearly all species, including electrons, ions, atoms, molecules and radicals, are largely given by equilibrium relationships, including Saha's equation. That said, there are also non-equilibrium regions of these plasmas, typically at the boundaries near walls. The applications of thermal LTPs include hazard waste treatment, welding, cutting, and spray coatings.

Research in LTPs is often focused on 1) the development of new plasma sources for various applications, 2) plasma diagnostics to characterize and investigate plasma processes, and 3) plasma simulations to gain insights into the mechanisms of plasma generation, with the ultimate goal to achieve predictive capabilities for a variety of applications. In this article, we discuss many remaining challenges for these research areas.

All LTPs studies are performed to advance a large range of applications and develop new applications. In this article we focus on the challenges related to several emerging applications, including 1) plasma for energy storage/conversion, 2) plasma for nanomaterials production and processing, 3) several fundamental questions of plasma medicine such as penetration depth of plasma, definition of plasma dose, the role of electric field, 4) plasma for decontamination, 5) plasma for cancer treatment, and 6) plasma technology implementation in cosmetics. For each topic, one or two experts, as indicated below, have been asked to write a short perspective. These write ups are the perspective of these individual authors and can be focused on the author's particular interest. A broader more comprehensive list of challenges and applications can be found in the 2022 Plasma Roadmap [1].

2 Challenge in LTPs Sources (X. Lu and D. Liu, HuaZhong University of Science and Technology, P.R. China)

Plasma sources are the key for the plasma applications. A typical plasma source includes three parts, i.e., the power supply used to drive the plasma, the electrode configuration, and the working gas. Because plasmas generated by different plasma sources are different, some desirable effects may be achieved by one plasma source treatment but not by the other. It is thus crucial to develop several different plasma sources for each targeted application. This is especially true for understanding the fundamental mechanism of the plasma effects.

The research community has acknowledged the importance of such need. The reactive agents (RA) of plasma include 1) reactive chemical species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and 2) reactive physical agents including charged particles, UV, and so on [2, 3]. One plasma source might predominantly generate one type of RA, while producing only small amounts of other RAs.

From the applications point of view, the preferred RA for various applications for example in the field of plasma medicine, such as killing bacteria, inducing cancer cell apoptosis, promoting stem cell differentiation, and enhancing transdermal drug delivery, might be also different.

Furthermore, currently most plasma sources used for plasma medicine use noble working gases, which is acceptable when they are used in a hospital environment but might be cost prohibitive for many other applications. On the other hand, if air can be used as a main working gas, then the potential plasma applications will be greatly broadened. Although several plasma jet devices operated in air have been reported [4–6], new plasma devices using air as a working gas are still urgently needed.

In addition, currently, many types of plasma sources are being investigated for applications of renewable energy storage/gas conversion, including dielectric barrier discharges (DBD), microwave (MW) and gliding arc (GA) plasmas, ns-pulsed plasmas, atmospheric pressure glow discharges (APGD) and spark plasmas. However, the energy efficiency of some of these plasma sources is still too low for commercial practice and thus developing new or improved plasma sources and power supplies for such applications is also needed [7].

Finally, researchers are pursuing to generate homogeneous cold atmospheric pressure air plasma at large gap distances, which is required for diverse applications such as surface treatment. However, it remains challenging [7–9].

3 Challenge in LTPs Diagnostics (P. Bruggemann, University of Minnesota, United States, and S. Reuter, Polytechnique Montréal, Canada)

In view of the complexity of LTPs, diagnostic are key enablers of advances in both science and technology in the LTP field. The state-of-the-art in plasma diagnostics has made considerable progress in the last decade not only by the development of new diagnostics but also through improvements of existing capabilities by leveraging technological advances. While new techniques such as EFISH allow spatially and temporally resolved measurement of electric fields [10], continuous improvements in detector sensitivity have benefited for example Thomson scattering [11]. Real time data collection at increasing frame rate capabilities enable characterizing stochastic filamentary plasmas [12] but also the use of data science methods in the analysis of diagnostics [13]. Nonetheless, many challenges remain, and we highlight a few critical needs in plasma diagnostics that in our opinion will significantly contribute to the advancement of our research field, particularly for atmospheric pressure plasmas.

3.1 Energy deposition, dissipation and species mapping

Energy deposition in LTPs occurs mainly from electric fields to electrons on picosecond timescales. However, the energy dissipation is driven by collisional processes including elastic and inelastic electron-neutral collisions, relaxation or recombination of excited states and interactions with surfaces spanning timescales from nanoseconds to seconds. A solid understanding of these processes is critical to control the non-equilibrium energy deposition into beneficial reactions and species and requires detailed measurements of multiple plasma parameters and species. Experimental validation of models with extensive reaction sets of 100s of species, including excited states, only recently started to emerge and few studies include more than a handful of different species or excited states measurements [14]. The analysis of experimental data often relies on assumptions based on partial equilibrium, which is not a priori applicable for such conditions. In addition, several measurement challenges remain, such as the measurement of 1) the tail of the electron energy distribution function to include energies enabling electronic excitation and ionization [15], 2) ultrafast energy transfer involving hot atom processes and quenching of excited states [16] and 3) high vibrational levels for example in N_2 which are believed to play a key role in enhancing chemical reaction rates [17].

3.2 Time/spatially resolved measurements

The implementation of diagnostics requires a priori a good understanding of the relevant time and length scales as information on transients and gradients could be lost otherwise. In addition, most diagnostics require signal averaging/accumulation which requires excellent plasma stability. Great progress in stabilizing atmospheric pressure plasmas has been achieved by ensuring discharge reproducibility [18]. Furthermore, the development of novel single-shot or real-time diagnostic techniques is particularly important for stochastic filamentary plasmas. In addition, spatial gradients in atmospheric pressure plasmas, particularly near interfaces, can approach length scales similar to the diffraction limit and while vital for the study of species fluxes to substrates can be extremely challenging to measure. Most diagnostics that are able to measure a broad range of species can only provide line of sight or line integrated densities [19]. Since most practical plasmas are inhomogeneous, a full spatial analysis requires additional information about species and temperature distributions and the research field could benefit from extending diagnostics with high spatial resolution to a broader range of species beyond atoms and diatomic molecules.

3.3 Reference sources and model comparison

The plasma community performs research on a large variety of homemade plasma sources, and therefore, comparison of data is often challenging. We strongly support the development of reference sources such as the *GEC-reference cell* [20] and the *COST jet* [2] that can be implemented in different research groups to allow faster progress and access to already existing and complementary diagnostics. To date, the great variability of atmospheric pressure plasmas is however not represented in the existing reference sources and reference experiments for example for plasma filaments in addition to diffuse discharges might be timely. Furthermore, the detailed description of plasma reactors and operation conditions is critical to allow for the comparison with models. It is important to consider when designing plasma sources for advanced diagnostics that 3D models remain rare [21] and simplified geometries that can be represented in 2D [22] or 1D [23] will be easier accessible for modelling.

3.4 Diagnostics of interfaces and substrates

While most plasma-based applications rely on the interaction of plasmas with solids or liquids, material surface characterization and measurements of reactive species in liquids are mainly performed *ex situ*. Many processes underpinning plasma modification of substrates involve short-lived species including charged species, hence a more detailed understanding from plasma-surface interactions might benefit from the development of *in situ* diagnostics compatible with the complex plasma environment and able to diagnose the dynamic change in plasma-material interactions. Current *in situ* diagnostics include various infrared techniques but a broader range of species-specific techniques with higher sensitivity or selectivity might benefit our research field [1]. The challenge for probing liquids is even larger as short-lived reactive species penetrate a finite distance into the liquid on a nm to μm scale depending on the lifetime of the radicals [1, 24]. In many cases the plasma-induced liquid phase chemistry is dominated by this highly reactive near interfacial layer which remains largely unexplored with few exceptions [25].

In conclusion, while a broad range of plasma diagnostic capabilities exists, additional efforts for new diagnostic development are needed to satisfy the diagnostic needs of new application developments and fundamental science in our research field. Many plasma diagnostics are invasive and indirect measurements often require knowledge of the plasma processes and models to interpret results. In many cases complementary diagnostics remain a necessity to accurately apply diagnostics in complex low temperature plasma environments. Diagnostic techniques heavily rely on cross-sectional data and existing gaps in databases need to be filled, especially so for the increasingly complex gas mixtures used for a large range of novel applications. Future developments in this area could highly benefit from collaborations with the Atomic, Molecular and Optical (AMO) community.

4 Challenge in LTPs Simulation (G. Naidis, Russian Academy of Sciences, Russia)

Plasma sources used in various applications produce equilibrium or non-equilibrium plasmas. Numerical codes for simulations of equilibrium plasmas are usually based on the fluid dynamic approach [26, 27]. As input data for these codes, thermodynamic and transport characteristics versus the gas temperature and pressure are used. Fluid models are also widely applied for simulations of non-equilibrium plasmas. In this case, knowledge of transport and kinetic coefficients for electrons is required. These coefficients are typically evaluated by solving the Boltzmann equation for the electron energy distribution function (EEDF), e.g., using the open-access platform LXCat [28]. At strong vibrational excitation of gas molecules, the Boltzmann equation is to be solved together with the system of balance equations for the densities of vibrationally excited states [29].

In conditions when non-local effects caused by strong non-uniformity and/or fast variation of plasma parameters become important, more sophisticated particle approaches, such as particle-in-cell/Monte-Carlo models, are applied [30, 31]. One of the challenges in plasma simulations is the disparity of length and time scales typical for various physical and chemical processes. To meet this challenge, hybrid models have been developed, dividing computations in modules [32, 33]. In particular, hybrid modelling allows combining particle and fluid approaches.

In computations of complex plasma systems, global (spatially averaged) models are often used, working with kinetic schemes that include up to several hundred species and several thousand reactions [34]. These models are useful for identifying leading reactions and species and reducing kinetic schemes, thus making them applicable for spatially resolved kinetic and fluid computations. A challenge in modeling complex chemical transformations in non-equilibrium plasmas is the lack or insufficient reliability of the data on reaction rate constants, especially for processes involving vibrationally and electronically excited species.

For modelling of steady-state discharges, both time-dependent solvers, attaining steady state by relaxation from an initial state, and stationary solvers, obtaining solution of steady-state equations by iterations, are applied. The stationary solvers are typically less time-consuming and have advantages when studying stability of different modes of steady-state discharges and transitions between them [35].

5 Plasma application

5.1 Challenges in plasma for renewable energy storage/gas conversion (A. Bogaerts, University of Antwerp, Belgium)

Renewable energy storage is one of the grand challenges of this century, due to the growing contribution of renewable electricity from e.g., solar and wind, which produces peak powers. Plasma reactors are powered by electricity, and quickly switched on/off, and therefore in principle ideally suited for renewable energy storage. Moreover, they can convert greenhouse gases, such as CO_2 and CH_4, into value-added chemicals or renewable fuels, and thereby also contribute to the problem of global warming. In fact, plasma technology can catch three birds with one stone: 1) by converting the greenhouse gases, it reduces their concentrations (or their emissions) in the atmosphere, 2) it produces value-added chemicals or fuels from greenhouse gases instead of from fossil fuels, thereby reducing our dependence on fossil fuels and reducing also CO_2 emissions, and 3) by using renewable electricity, it also avoids CO_2 emissions.

Most of the research focuses on CO_2 and CH_4 conversion (e.g. [36–39]), but also on N_2 fixation into NH_3 and NO_x (e.g., [39–43]), as well as NH_3 decomposition for H_2 production (e.g., [44]). CO_2 splitting leads to CO feedstock that can be combined with H_2 into syngas (CO/H_2 mixture) for Fischer-Tropsch synthesis of hydrocarbons. CH_4 conversion is of great interest for H_2 synthesis, but also for olefin production (mainly ethylene, C_2H_4). The combined CO_2 and CH_4 conversion, also called dry reforming of methane (DRM), mainly leads to syngas (CO/H_2), but can also directly form higher hydrocarbons or oxygenates, like methanol, ethanol, formaldehyde, formic acid, etc, if suitable catalysts can be designed, but even without catalysts, this might be possible by careful reactor design and choice of the operating conditions, as recently demonstrated [45]. N_2 fixation is being studied for both NH_3 and NO_x production, as alternatives for the energy-intensive Haber-Bosch and Ostwald processes. Many types of plasma reactors are being investigated, but most work is performed with dielectric barrier discharges (DBD), microwave (MW) and gliding arc (GA) plasmas, ns-pulsed plasmas, atmospheric pressure glow discharges (APGD) and spark plasmas (see details in [36–45]).

While the application of plasma for renewable energy storage and gas conversion is clearly one of the emerging applications of this century, also due to the urgent need for electrification of the chemical industry, this application still faces some challenges that need to be overcome before it can be applied at large scale, e.g., in the chemical industry. These challenges include the need to further enhance the 1) conversion, 2) energy efficiency, and 3) product selectivity.

Conversion and energy efficiency are related to each other, as the energy efficiency is typically defined based on the conversion obtained at a certain energy input compared to the reaction enthalpy (only applicable for endothermic reactions, like CO_2 splitting and DRM) [37]. Hence, a high conversion typically gives rise to a high energy efficiency, although this is not always the case, i.e., when the conversion rises less than linearly with the energy input, the energy efficiency will drop. In that case, a compromise needs to be made whether one prefers a higher conversion or a higher energy efficiency, depending on the application. The conversion (and thus also energy efficiency) is often limited by the limited fraction of gas passing through the plasma in some reactors (e.g., GA plasmas [46]), and especially by recombination of the products (back-reactions) when the gas temperature drops only slowly after the reactor [47]. Major efforts are therefore needed for reactor design improvements, focusing on gas flow dynamics, to make sure that all the gas is treated by the plasma and that reaction products are quickly removed and/or cooled directly after the reactor (fast quenching) to avoid back-reactions [48, 49].

In addition, the energy efficiency is determined by how much energy is needed to reach a certain conversion, and thus by the reaction mechanisms. The latter are different for the different plasma types. DBD plasmas typically operate at higher reduced electric fields (i.e., ratio of electric field over gas number density) than e.g., MW, GA or APGD plasmas (i.e., around 200 Td for DBD vs. 50–100 Td for the latter types, where $1\ Td = 10^{-21}\ V\ m^2$) [50]. These higher reduced electric fields create electrons with somewhat higher temperatures, which give rise to electron impact electronic excitation and ionization, rather than vibrational excitation. The latter is more common at reduced electric fields of 50–100 Td, and is known as the most efficient dissociation mechanism [50]. Indeed, vibrational-induced dissociation proceeds by population of the lower vibrational levels, which gradually populate the higher levels by vibrational-vibrational relaxation until the dissociation limit is reached, i.e., so-called ladder climbing. This vibrational pathway is theoretically the most common in MW, GA and APGD plasmas, but in practice, these plasma types are characterized by relatively high gas temperatures (up to 3000 K and even higher; hence, they are also called warm plasmas), so that vibrational-translational relaxation becomes important and causes depopulation of the vibrational levels. This reduces the importance of this energy-efficient vibrational dissociation pathway. At the same time, this process causes further gas heating, making vibrational-translational relaxation even more important. In practice, the dissociation of CO_2, CH_4 and N_2 in these warm plasmas proceeds largely by thermal chemistry [51, 52], but nevertheless, they are typically characterized by much better energy efficiency than DBD plasmas, as e.g, demonstrated in [37, 39]. Nevertheless, further research is needed, to go beyond the thermal efficiency limit, e.g., by exploiting the reaction of O atoms with CO_2 [53].

The third challenge of plasma technology for renewable energy storage and gas conversion is product selectivity, which is related to the high reactivity of plasmas, producing many different products, and it is known that product separation would add a major cost to the overall process. To improve the selectivity, plasma can be combined with catalysts, in so-called plasma catalysis [54–56]. This can be performed in one stage, where the catalysts are directly integrated in the plasma, for which DBD plasmas are most suitable, due to their lower temperature (slightly above room temperature). The alternative is two-stage plasma catalysis, where the catalysts are typically placed after the plasma. This is a more suitable option for MW, GA and APGD plasmas, which typically have too high gas temperature for catalysts to be integrated inside the plasma (although there are examples where it has been demonstrated to be successful), but the high temperature at the gas outlet can still be used to activate (thermal) catalysts placed after the plasma. Plasma catalysis is very promising, but clearly more research is needed, especially to design the most suitable catalysts tailored to the plasma conditions. This is especially true for one-stage plasma catalysis, where short-lived plasma species (e.g., radicals, vibrationally and electronically excited species) come in contact with the catalyst, and thus, the mechanisms are different from thermal catalysis, and hence, other catalysts must be designed. Studies on simple reactions, such as NH_3 synthesis, have revealed novel insights, e.g., on the role of (vibrationally) excited N_2 and plasma-produced radicals, making other catalysts potentially more interesting than in thermal catalysis or even showing that the kind of metal is not so important [57, 58]. In addition, CO_2 hydrogenation to CH_3OH or CH_4 (methanation) has already demonstrated promising results (e.g., [59]). However, plasma catalysis is very complicated and still far from understood. Therefore, more fundamental research, both computationally and experimentally (e.g., by *in-situ* diagnostics) is needed.

In general, it is clear that plasma technology is very promising for renewable energy storage by gas conversion, but more fundamental research is needed to exploit the full potential of this important application. Finally, we will have to demonstrate that plasma reactors can be sufficiently scaled up, in order to provide the scale needed to replace processes with a high CO_2 footprint, to find a successful entry in the present chemical industry.

5.2 Challenge in plasma nanoscience and nanotechnology (K. Ostrikov, Queensland University of Technology, Australia)

Over the last decades, nanomaterials and nanoscale materials processing have emerged among the leading technological platforms of the century. Diverse forms of nanomaterials spanning the common states of matter (gas, liquid, solid, plasma) and extremely wide elemental composition have firmly become a cornerstone of materials, devices, systems for applications spanning almost all aspects of human society—from health and wellbeing to zero-carbon renewable energy, space exploration, quantum information, and many more. This explosion of material types, structures and applications created the strong need for efficient, reliable, and precise fabrication approaches.

Building upon the truly outstanding decades-long industrial track record of low-temperature plasma processing in microelectronics, plasma nanoscience and nanotechnology have formed a truly unique and competitive niche among the vast number of existing and emerging materials processing technologies [60, 61]. Plasmas have been applied for the synthesis and processing of a broad range of nanomaterials, with pioneering synthesis of fullerenes and carbon nanotubes. Since then, nanomaterials of all dimensionalities from zero-dimensional quantum dots to three-dimensional nanostructures made of a very broad range of materials according to their structure (e.g., amorphous, crystalline), phase (e.g., liquid, colloidal, solid, mixed-phase), state (soft or hard matter), elemental compositions (e.g., oxides, nitrides, phosphides, etc.) have been synthesized and applied to produce functional materials and devices in diverse areas. The plasma conditions also range from very mild, room-temperature atmospheric-pressure plasma jets to extreme conditions when fusion (e.g., plasma focus) or cryogenic plasmas are involved. The plasma itself has been reduced well into the micrometre domain, and microplasmas have been successfully utilized to produce diverse nanomaterials [62]. Under extreme ultra-high-energy-density conditions, even nanoplasmas can be generated, e.g., through the targeted explosion of nanoparticles [63]. The most common competitive advantages of nanoscale plasma processing include but by far are not limited to: 1) precision which has been further advanced through the recent advent of atomic scale processing including both atomic layer etching and deposition; 2) energy efficiency achievable through lower-temperature operation and ability to instantly be switched on and off, even with nanosecond precision; 3) diverse and unique plasma-specific effects such as induced by ion energies and fluxes, electric charging of the surfaces, selective processing of few atomic layers near the surface, etc. These and many other benefits of sole or hybrid use of plasmas with other processing techniques are presented in a very large body of literature over the last couple of decades.

Looking into the future, plasma nanoscience and nanotechnology face very important challenges which present unprecedented opportunities for further advances and even closer collaborations across diverse fields of research and applications. These challenges and opportunities are numerous and span all the areas where traditional nanotechnology commonly contributes, perhaps too many to even list them in the available space. Only one set of challenges and opportunities related to the global effort to achieve zero-carbon-emissions world is highlighted here. Recently, plasma-enabled scalable roll-to-roll process of functional nanocarbon production maps the way to contribute to the re-carbon (e.g., re-use of greenhouse gas emissions such as CO_2 and CH_4 gases)—up-carbon (e.g., convert greenhouse gas emissions into high-value carbon nanomaterials)—de-carbon (e.g., reduce carbon footprint of plasma processing and utilizing the carbon nanomaterials in clean energy technologies) sustainable and circular-economy inspired concept [64]. Further insights into the application of plasma-electrified and plasma-nanoscience-enabled up-carbonization for low-carbon clean energy applications have recently been summarized [65]. Overall, the outlook for plasma nanotechnology is optimistic and the extent of its broad adoption will depend on the ability of the plasma community to keep the ever-accelerating pace and diversification of nanomaterials-related opportunities presented by our rapidly changing world.

5.3 Challenges in plasma medicine

5.3.1 Several fundamental questions of plasma medicine (X. Lu, Huazhong University of Science and Technology, China)

The research scope of plasma medicine entails the biological effect of plasma on organisms, which include bacteria, viruses, tissues, and the human body. The applications of plasma medicine include cleaning and disinfecting of medical apparatus and instruments, root canal treatment, promoting wound healing, cancer treatment, promoting stem cell differentiation, enhancing transdermal drug delivery, and so on. However, there are several key questions that need to be answered before the plasma can be used in clinics. In the following, some of these questions are discussed.

5.3.1.1 The penetration depth of plasmas in tissue

When a plasma is used for the applications mentioned above, one key question arises, i.e., how deep can the reactive agents (RAs) generated by the plasma penetrate into tissue? If the plasma-induced effects can only penetrate tens of nanometer thickness like that in common materials processing applications (e.g., plastics and polymers) where plasmas can only directly modify the uppermost surface layers, then the applications of plasma medicine would be very limited.

Fortunately, studies on the penetration depth by using different models, including water-based models, biological media models, gel-based models, animal skin models, 3D cell models, and living tissue models, show that plasma can effectively deliver H_2O_2 and nitric oxide derivatives (NOD) NO_2^- and NO_3^- into models from tens of micrometers to millimeters range [3, 66–74].

In addition, the concept of plasma RAs penetration is a combination of the two major local effects: 1) direct penetration of plasma-generated RAs, and 2) relay of the effects, cells directly stimulated by the plasma treatment can also produce RAs, which may amplify the original RAs effects. The original RAs are transmitted in tissue by cell-to-cell communication *via* paracrine and direct contact signaling. In this way, plasma-generated RAs indeed cause and relay significant biological effects within and even beyond the tissues directly exposed to the plasma. This way, cells not directly exposed to the plasma could be affected by the plasma treatment through the cell-to-cell communication; often referred to as the "bystander effect" [75–79]. The role of cell-to-cell communication in plasma health care and medicine remains to be elucidated.

Bystander effects originating from the initial cutaneous plasma RA signals can lead to systemic responses such as induction of the immune response. RONS and other less-reactive molecules, are the key plasma RAs involved in the immune response. RONS are important regulatory molecules of the immune response. For example, NO can affect the production of more than 20 cytokines from various cells involved in the immune system and its responses. RONS also influence the migration of immune cells and regulate the expression of chemokine receptors. However, this knowledge is presently at the infancy stage and coordinated cross-disciplinary efforts are therefore warranted to advance this critical area.

5.3.1.2 Effect of electric field

It is widely accepted that biological effects of direct plasma treatment are due to the combination of both physical and chemical reactive agents. Lots of work has been devoted to the roles of chemical reactive agents. The biological effects of chemical reactive agents, such as O, O (^{1}D), O_2^-, O_2 ($^1\Delta_g$), O_3, OH, NO, NO_2^-, NO_3^-, $ONOO^-$, etc. have been investigated.

On the other hand, there are only very limit studies on the biological effect of the physical reactive agents of plasma, such as the effect of electric field. Kushner's group simulated the electric field distribution of cells when a plasma jet is used to treat cells covered by thin layer of liquid [80]. It is found that when the luminous plasma is in contact with the water layer, electric fields exceeding tens of kV/cm are induced in cell membranes and up to 10 kV/cm in the cell nucleus and cytoplasm. The high electric fields may induce pores within the cell membranes in a process which is similar to electroporation that increases the permeability of the barrier to the reactive species, this is actually confirmed by molecular dynamic simulation from Bogaert's group [81].

However, to the best of our knowledge, no measurement of plasma-induced electric fields in tissue has been reported. Furthermore, when plasma is used to treat intact skin, the outside stratum corneum layer of the skin, which is made of "dead" cells and has much different conductivity compared with the corium layer, will play an important role in the distribution of the electric field. All these important points need further investigations.

5.3.1.3 Definition of plasma dose

Different plasma treatment doses are responsible for different cellular effects, including lethal influences (higher doses) and non-lethal influences (low doses) on cell behavior. Unfortunately, there is no clear definition of plasma dose so far. Some groups refer to the plasma treatment duration as dose [82, 83]. However, the treatment duration is not the essence of the plasma dose. Besides, the energy deposited into the plasma per area has been proposed by other researchers [84, 85]. However, different plasma biological effects have been obtained by using different plasma sources while under the same power and treatment time.

Recently, Lu's group proposed a definition of equivalent total oxidation potential (ETOP) as a possible plasma dose concept [86]. The ETOP concept involves three key points, i.e., 1) H: the equivalent total oxidation potential of the RONS, 2) T: the equivalent total oxidation potential associated with the reactive agents unrelated to RONS, such as electric field and

UV/VUV, and 3) the equivalent total oxidation potential related synergistic effects between the H and T factors. Due to lack of mechanistic insights and limited data, significant additional work is needed and alternative more clinical applied approaches to determine a dose concept are being explored.

5.3.2 Challenge of low temperature plasma for decontamination (M. Laroussi, Old Dominion University, United States)

With the rise in antibiotic resistance and viral-driven pandemics, biological decontamination has become a crucial issue affecting public health and safety. Since the mid-1990s atmospheric pressure LTPs has been proposed as a technology that can meet the above challenges. However, the interaction of LTPs with microorganisms (bacteria, biofilms, viruses, fungi, etc.) is multiphase, making the process very complex. This is especially the case for biofilms (bacteria community embedded within an extracellular polymeric matrix) and in the case of viruses encased in liquid droplets and aerosols. Because of the complexity of this interaction a number of scientific challenges remain unresolved [87]. The main challenges include the understanding and controlling the various LTPs physical/chemical processes and elucidating the biological effects on the target at the subcellular and molecular levels (effects on lipids, proteins, DNA, etc.). In addition, the interaction of LTPs with targets gives rise to unpredictable behaviour that may be difficult to control. This is because the target itself influences the plasma characteristics depending on its surface morphology, conductivity, the medium supporting it (e.g., dry target vs. wet target, tissue, wound, etc.) [88]. As is the case for other medical applications of LTPs two of the key challenges that need to be overcome soon are the evaluation of the dose and the scalability of the process. There have been many definitions of the plasma dose (exposure time, power), but a more appropriate definition would be related to biochemical mechanisms, such as the ETOP, as mentioned in previous section [86]. The scalability challenge becomes especially crucial for industrial and environmental applications such as the decontamination of crops, food, food packages, water, etc. To conclude, although our understanding of the plasma-cell interactions has come a long way in the past few years, a deeper understanding is still needed if LTPs is to become a widely used technology in the healthcare arena, including the fight against pathogenic microorganisms that have been acquiring more and more resistance against the best available antibiotics [89].

5.3.3 Challenge of plasma for cancer therapy (M. Keidar, George Washington University, United States)

Nowadays, cold atmospheric plasma (CAP) application in cancer therapy consists of two methods: direct killing of cancer cells by CAP and stimulation of immune responses by inducing controlled oxidative stress in cancer cells. To this end, the novelty of CAP lies in its multi-factorial effects that include reactive oxygen and nitrogen species (ROS/RNS) produced in the plasma, physical factors like emitted electromagnetic waves and the electric fields that are formed when plasma impinges on tissue [2, 90, 91]. One of the unique features of plasmas compared to other sources of reactivity is the ability to rapidly change the reactive species production pathways in the CAP, thereby enabling feedback systems that customize in real time the reactivity delivered to cancer cells [92]. Plasmas can also self-organize to form coherent structures that modulate the electric field, along with the production and delivery of RONS and charged particles [93]. An intelligent CAP system [94] might be capable to scan the cellular responses to CAP and modify discharge conditions in real-time *via* a feedback mechanism based on machine learning [95, 96]. A real-time control of CAP is capable of optimizing the killing effect on cancer cells or tissues while protecting normal cells or tissues. The adaptive plasma approach may ultimately lead to a personalized CAP-based cancer therapeutic that could be adapted for treatment of other diseases.

CAP treatment of cancer cells and tissue might be stimulating or toxic, depending on the treatment conditions. For instance, both chemical and physical stimuli can lead to sensitization of cancer cells to chemotherapy [97, 98]. Moreover, a recent study demonstrated that glioblastoma cell lines U87MG and A172 could be sensitized to cytotoxicity of temozolomide (TMZ), a drug used for treatment of brain tumors, by the electromagnetic emission from a helium discharge tube [99].

To date, numerous studies of CAP *in vitro*, 2D cell culture models, and the use of 3D, in-ovo, and animal models that are very much in alignment with the cutting-edge approaches in oncology therapeutics are increasingly being reported [86]. Moreover, an initial proof-of-concept clinical case study has already been performed [100] demonstrating the great potential of CAP for cancer therapy. CAP may also be used as an adjunct therapy to standard of care surgery by treating exposed tumor tissues or the remnants of tumor tissue during surgery. CAP as an adjunct therapy was tested clinically for the first time in a patient with stage 4 colon cancer at Baton Rouge General Medical Center in Baton Rouge, Louisiana, immediately after surgery to remove the tumor [90]. A phase I safety clinical trial was completed in 2021 that involved 20 patients to evaluate the safety of the procedure [101].

Important development in CAP cancer therapy is associated with increasing evidence that CAP can trigger unique immune responses and immunogenic cell death [102]. Immunogenic cancer cell death (ICD) might be elicited in response to various stimuli including the ones associated with CAP [103]. The importance of various aspects such as immunity, immunogenicity and antigen presentation, ICD, and vaccination for CAP cancer treatment has been extensively reviewed recently [104]. Understanding of the mechanism associated with plasma-induced oxidative stress that elicits ICD is still largely lacking thus warranting further investigation.

A key challenge remains in identification of CAP mechanism of action on cancer cells. While many papers reported the cause-and-effect relationship between various individual chemical species and tumor toxicity, it is still unclear how much the physical factors might contribute to the cellular responses [105]. Recall that when cancer cells or tissues are directly exposed to plasma, they experience both physical and chemical effectors simultaneously and as such, the observed biological response could be attributed to the synergistic effect of the physical and chemical factors.

5.4 Opportunities and challenges for plasma technology implementation in cosmetics (E. Robert and J.M. Pouvesle, University of Orléans, France)

Inherent with a large number of plasma medicine therapeutic approaches, the study and applications of the interaction of plasma with skin tissue is of key importance [106] for safety reasons, and is timely for the cosmetic technology. This latter sector is indeed demanding on new physical tools, besides microneedles, LED light, iontophoresis based devices, likely to promote cosmetic formula topical application, to control skin penetration and skin cell stimulation, to reduce the use of chemical compounds, to implement active substance from bio-sourced plants or ingredients, for smart packaging, and much more.

Today, DBD-based devices, e.g., Plabeau G4$^+$ Plasma Skin Rejuvenation Device [107], have been manufactured for cosmetic care but, to the best of our knowledge, their mode of action and safety (e.g., in term of ozone generation) have not been fully documented in the literature. Nevertheless, cold plasmas can play a major role associated with their well-known on-demand delivery of reactive species and transient electric fields, their impact in pH modulation and their disinfecting properties. A first critical challenge to implement plasma technology in cosmetics is to achieve safe, tissue tolerable, user friendly and pleasant plasma delivery. As everyone's skin is different, depending on ethnic origin, age, body area, . . ., a second challenge is to target personalized cosmetic care. The latter need might represent an opportunity for plasma technology, especially when associated with the actual huge effort focused on plasma-target interaction study and control, and the today's development of non-invasive skin characterization based on optical spectroscopies and imaging which might be coupled with plasma diagnostics [108].

A unique opportunity for plasma skin treatment is the transient modulation of skin cutaneous barrier characteristics. It has been recently demonstrated that plasma can transiently modulate skin hydrophilicity, skin pH and trans-epidermal water loss during periods of a few minutes and simultaneously trigger a critical enhancement of skin cell permeabilization and speed up cosmetic molecule penetration kinetics in human explants [109, 110]. All these demonstrations open great opportunities for cosmetic ingredients safe and controlled penetration, and may allow for the use of lower amount or at least for a more efficient delivery of chemical substance in skin tissue while keeping their same benefits for cosmetic care. Direct plasma application has also been shown to allow for skin cell stimulation, collagen secretion increase and for its potent disinfecting features. There the challenge is to determine the right plasma composition and application time to achieve controlled stimulation and to preserve skin integrity and skin microbiome at the base of the skin barrier function.

All these opportunities still require a very demanding development, as one should consider home cosmetic care as a daily and combined "treatment". The daily application of plasma for any therapeutic application has so far not been so much investigated as well as combined action of plasma with chemical ingredients (solution, cream, gel), while combined action of plasma with chemotherapeutic drug, and with disinfecting solution is already documented.

Besides skin treatment, plasma can also be envisioned for the functionalization of cosmetic ingredients, for the efficient and selective extraction of cosmetic active ingredients from bio sourced resources, and for innovative packaging development. While numerous challenges have to be faced, plasma technology may be in-line with today's consumer demand for cosmetics including naturalness, green technology, limitation of the use of chemicals, and personalized care.

6 Conclusion

Collectively, the individual contributions of this editorial suggest that LTPs science and technology represents a fertile and fast developing field of research. LTPs research has rapidly responded, and continues to respond, to grand challenges facing humankind such as health and wellbeing, food and water, energy, resources, sustainability, and climate change. LTPs are the basis of applications in all of these, and several other areas, of the world's economy and society. Each application contains specific processes that are either enabled or enhanced by plasma, which in turn requires the development of the relevant plasma sources and processes by translating fundamental research to practice. The LTPs research community is engaging in multidisciplinary research to speed the rate of translation. The examples of key application areas of LTPs discussed in this article provide guidance for the community in how fundamental insights into the plasma chemistry and physics can be translated to society benefiting applications. The increasing number, diversity, and scale of societal grand challenges emphasize the need for both fundamental and applied research. There are needs for advances at both ends of the collaborative spectrum. Startling advances, even multidisciplinary advances, have resulted from the efforts of single researchers (and their research groups). Many of these advances have produced the foundational knowledge of the field. At the same time, besting societal grand challenges through translational research will require the collective and collaborative efforts of the international multidisciplinary community involved in fundamental research and applied development.

Author contributions

All author listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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