Reactive Species in Non-equilibrium Atmospheric-Pressure Plasmas: Generation, Transport, and Biological Effects

X. Lu^{1,2,*}, G. V. Naidis³, M. Laroussi⁴, S. Reuter⁵, D. B. Graves⁶, and K. Ostrikov^{7,8,9}

¹ State Key Laboratory of Advanced Electromagnetic Engineering and Technology,
Huazhong University of Science and Technology, Wuhan, Hubei 430030, P. R. China

² IFSA Collaborative Innovation Center, Shanghai Jiao Tong University, Shanghai 200240,
P.R. China

³ Joint Institute for High Temperatures, Russian Academy of Sciences, Moscow 125412,
Russia

⁴ Plasma Engineering & Medicine Institute, Old Dominion University, Norfolk, VA 23529,
USA

⁵ Leibniz Institute for Plasma Science and Technology, Felix-Hausdorff-Strasse 2, 17489
Greifswald, Germany

⁶ Department of Chemical and Biomolecular Engineering, University of California, Berkeley,
CA 94720, USA

⁷ Institute for Future Environments and School of Physics, Chemistry, and Mechanical
Engineering, Queensland University of Technology, Brisbane, QLD 4000, Australia

⁸ Commonwealth Scientific and Industrial Research Organization, P.O.Box 218, Lindfield,
NSW 2070, Australia

⁹ School of Physics, The University of Sydney, Sydney, NSW 2006, Australia

*Corresponding author. Electronic mail: luxinpei@hotmail.com

Abstract

Non-equilibrium atmospheric-pressure plasmas have recently become a topical area of research owing to their diverse applications in health care and medicine, environmental remediation and pollution control, materials processing, electrochemistry, nanotechnology and other fields. This review focuses on the reactive electrons and ionic, atomic, molecular, and radical species that are produced in these plasmas and then transported from the point of generation to the point of interaction with the material, medium, living cells or tissues being processed. The most important mechanisms of generation and transport of the key species in the plasmas of atmospheric-pressure plasma jets and other non-equilibrium atmospheric-pressure plasmas are introduced and examined from the viewpoint of their applications in plasma hygiene and medicine and other relevant fields. Sophisticated high-precision, time-resolved plasma diagnostics approaches and techniques are presented and their applications to monitor the reactive species and plasma dynamics in the plasma jets and other discharges, both in the gas phase and during the plasma interaction with liquid media, are critically reviewed. The large amount of experimental data is supported by the theoretical models of reactive species generation and transport in the plasmas, surrounding gaseous environments, and plasma interaction with liquid media. These models are presented and their limitations are discussed. Special attention is paid to biological effects of the plasma-generated reactive oxygen and nitrogen (and some other) species in basic biological processes such as cell metabolism, proliferation, survival, etc. as well as plasma applications in bacterial inactivation, wound healing, cancer treatment and some others. Challenges and opportunities for theoretical and experimental research are discussed and the authors' vision for the emerging convergence trends across several disciplines and application domains are presented to stimulate critical discussions and collaborations in the future.

1. Introduction

1.1 Scope and structure

1.2 N-APPJs – a brief overview

1.3 Plasma medicine - a brief introduction

1.3.1 Brief historical perspective

1.3.2 The biomedical applications of N-APPs

1.3.2.1 Effects of N-APPs on prokaryotes

1.3.2.2 Effects of N-APPs on eukaryotes

2. Modelling of production of reactive species in N-APPJs

3. Basic experimental observations and diagnostics

3.1 Fast imaging

3.2 Laser-induced fluorescence

3.2.1 Single-photon absorption laser-induced fluorescence

3.2.2 Two-photon absorption laser-induced fluorescence

3.3 Scattering techniques

3.3.1 Rayleigh scattering

3.3.2 Thomson and Raman scattering

3.4 Optical emission spectroscopy

3.4.1 Information gained from line broadening

3.4.1.1 Natural line broadening

3.4.1.2 Doppler broadening

3.4.1.3 Collisional broadening

3.4.1.4 Stark broadening

3.4.2. Combination of optical emission spectroscopy and modelling

3.4.3. Rotational and vibrational temperature

3.5 Optical absorption spectroscopy

3.5.1 Ozone

3.5.2 UV broadband absorption of OH density

3.5.3 Cavity ring-down spectroscopy

3.5 Selected non-optical techniques

3.5.1 Mass spectrometry

3.5.2 Flow visualization

3.5.3 Electron paramagnetic resonance spectroscopy

4. Temporal and spatial behaviour of key reactive species

4.1 Electron density (n_e)

4.2 O atoms

4.2.1 Effect of admixture of O₂/air on O concentration

4.2.2 Diffusion effect of shielding gas on O production

4.3 OH radical

4.3.1 Effect of H₂O admixture on OH concentration

4.3.2 Effect of gas flow on OH concentration

4.3.3 Effect of O₂ on OH production

4.3.4 Effect of the treated samples on OH concentration

4.3.4.1 Effect of humidity of treatment sample on OH distribution

4.3.4.2 Effect of sample conductivity on OH distribution

4.3.4.3. Effect of the amplitude of the applied voltage on OH distribution

4.3.4.4. The effect of gas flow on OH distribution

4.3.4.5. The effect of the surface characteristics on OH distribution

4.3.5 Effect of the surrounding gas on OH production

4.4 Ozone (O₃)

1 **4.5 Singlet delta oxygen ($O_2(^1\Delta_g)$) species**

2 **4.6 Atomic nitrogen**

3 **4.7 Nitric oxide (NO) species**

4 **4.8 $N_2(A^3\Sigma_u^+)$ metastable**

5 **4.9 Metastable He and Ar states**

6 **5. Reactive species: numerical modelling**

7 **5.1. Generation of reactive species in HF N-APPJs**

8 **5.2. Generation of reactive species in RF N-APPJs**

9 5.2.1. Plasma jets with planar metallic electrodes

10 5.2.2. Needle-type plasma jets

11 **6. Reactive species interaction with liquid**

12 **6.1 Negative ions**

13 **6.2 Positive ions**

14 **6.3 ROS**

15 **6.4 RNS**

16 **7. Biological effects of reactive species**

17 **7.1 Reactive species therapeutics**

18 **7.2 Cell adaptive response to RONS**

19 **7.3 Plasma-generated RONS interacting with cells and tissues**

20 **8. Challenges and outlook**

21 **8.1 Challenges and opportunities**

22 **8.2 Future trends and outlook**

23 **9. Conclusion**

24 **Acknowledgments**

25 **References**

1. Introduction

Reactive atomic, molecular, and radical species play a major role in many chemical, biological, and other processes. The processes these species participate range from formation of nanometer-sized solid objects to effective control of physiological processes in living organisms. Of particular interest are reactive oxygen and nitrogen species (RONS) that are abundantly present or can easily be produced from ambient air. These species can then be delivered to the specific locations where their action is required. For example, this could be a surface of a solid nano-structured material which needs to be delicately oxidized in a microscopic localized area or a tissue or liquid culture medium containing living cells to be processed to induce the desired biological response (e.g., cell proliferation, differentiation or programmed death).

In the above two examples a significant precision is required in terms of controlled delivery of RONS (and some other) species to the surface and even into the interior of the non-living (nano-structured material) and living (cell medium or tissue) matter. This precision can be achieved using a dedicated device, which not only generates these species but also delivers them to the specified locations, with the required doses and precision.

This review focuses on the production of RONS and other reactive species, using non-equilibrium atmospheric-pressure plasma jet (N-APPJ) devices, and their delivery to liquid media that contain living cells, primarily aimed for application in the rapidly emerging field of plasma medicine. Even though many discussions are applicable to a much broader range of atmospheric-pressure plasmas, the N-APPJs have been chosen as one of the most common and effective types of the devices for which all the most important stages of the species production, transport, and interactions with liquids are well-studied and abundantly documented in the literature to allow for a critical and reasonably exhaustive review. This specific focus determines the scope and structure of this review.

1.1. Scope and structure

This review aims to introduce the variety of processes associated with the generation of reactive species using non-equilibrium atmospheric-pressure plasma jet (N-APPJ) devices followed by the transport of these species from the point of generation in the plasma to the point of interaction with biological objects including cells and tissues as sketched in Fig.1.

As can be seen from Fig.1, generation and transport of the reactive species proceed in several stages. The species are produced in the plasma and then pass through the discharge afterglow before coming into contact with liquid media containing biological objects including cells, tissues, biologically relevant macromolecules such as enzymes, proteins, etc. The time scales and the prevailing elementary processes involved in the production and delivery of the reactive species vary significantly from one stage to another. For example, a typical duration of the elementary primary processes involved in the species creation, transformation, excitation, and ionization (e.g., through collisions with other species) is in the nanosecond to microsecond range, while the primary reactive species including electrons, ions, and excited species are generated. During the afterglow, some secondary reactive species such as O_3 , NO , and NO_2 are generated. It typically takes microseconds to milliseconds for the reactive species to pass through the afterglow area of the plasma jet to reach the surface of the liquid medium containing biological material. During this time, some primary species disappear while other secondary species are generated.

On the other hand, when a plasma jet directly interacts with the surface of the liquid medium containing biological material, besides the relatively long-lifetime radicals mentioned above, the short-lifetime radicals including electrons, positive and negative ions, and some excited species could also play some roles in the treatment of biological material [1].

Therefore, multiple transformations take place until the plasma-generated species reach the biological target. Importantly, on the one hand, some biological objects (e.g., cells) produce RONS through normal physiological processes and release into the medium. On the other hand, species generated by the plasma may pass through the liquid and penetrate into the cells and join the similar species that are produced inside the cells. These processes are inter-dependent making it very difficult to identify the specific channels of the species production in the liquid medium and inside the cells. Indeed, species generated by the plasma and delivered to the liquid media affect the species production inside and nearby the cells, while the species released by the cells into the medium, interact with the plasma-generated species and modify the kinetics of chemical reactions in the medium. The complexity and multitude of the chemical reactions and energy exchange processes leads to the typical duration of chemical and biochemical processes in the liquid media of approximately milliseconds to minutes. The biochemical and biological processes inside the cells and the processes of cell transformation are even longer commonly lasting from seconds to days, as sketched in [Fig.1](#).

The species delivered from the plasma to the biological objects interact across different regions in the gaseous and liquid states as shown in [Fig.1](#). This knowledge is critical to enable effective applications of such plasmas in biology, hygiene, and medicine [2] as well as other areas including materials processing and nanotechnology [3]. This is why in the following [Sec.1.2](#) we introduce non-equilibrium atmospheric-pressure plasma jets (N-APPJs) and some of their key attributes that lead to effective and controlled interactions of such plasmas with biological objects. Afterwards, in [Sec.1.3](#) we briefly discuss the most common effects induced by N-APPJs and other non-equilibrium N-APPs on prokaryotic (bacterial) and eukaryotic (mammalian) cells. Wherever possible, accent is made on the specific effects of RONSs (e.g., NO, O₃, OH, H₂O₂, etc.) generated by the plasma on various types of cells

1 such as bacterial pathogens or malignant cancer cells. These examples suggest that N-APPJs
2 have emerged as effective tools for the production and delivery of reactive species, both in
3 the charge-neutral and ionized forms. The N-APPJs represent a broader class of atmospheric-
4 pressure plasma streamer discharges and are often termed guided ionization waves or guided
5 streamers [4].
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12 The focus in this review lies in the diverse approaches and specific techniques for the
13 numerical (Sec.2) and experimental (Sec.3) studies of the propagating plasma jets and the
14 species generated in such jets, from the point of generation to the afterglow (experimental
15 Sec.4 and theoretical Sec.5) and to the liquid media (Sec.6) containing biological material.
16 This is followed by the discussion of some of the possible mechanisms of biological effects
17 involving reactive species of particular interest in plasma medicine applications (Sec.7). The
18 final Sec.8 provides a brief summary of the challenges and opportunities in both the
19 theoretical and experimental studies of N-APPJs and biological effects they cause. The
20 review concludes with a brief discussion of the future trends and outlook for the development
21 of this interesting and rapidly emerging field of research.
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38 **1.2. N-APPJs – a brief overview**

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40 The quest to generate non-equilibrium, low-temperature plasmas at atmospheric
41 pressure started in the early 20th century. In the 1930s, von Engel tried to generate such
42 plasma by controlling the temperature of the cathode [5]. However, it was only in the late
43 1980s and early 1990s when reports on successful generation of stable, relatively large
44 volume, non-equilibrium, diffuse atmospheric-pressure plasmas started to emerge [6-8].
45 These early works used the dielectric barrier discharge configuration and He as the operating
46 gas. Sinusoidal excitation with voltages in the kV range and frequencies in the kHz range
47 were used. In late 1990s and early 2000s, in order to enhance the plasma chemistry, fast rise
48 time voltage pulses with pulse widths in the nanosecond-to-microsecond range were used.
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1 These pulses more effectively couple energy to the electron population resulting in better
2 control of the electron energy distribution function (EEDF) and therefore better control of the
3 plasma chemistry [9-12]. These plasma discharges are relevant to plasma processing
4 including applications in biology and medicine that emerged in the mid-1990s [13,14]. It is
5 presently commonly accepted that non-equilibrium atmospheric-pressure plasmas (N-APPs)
6 generate reactive species that can be transported to biological targets and induce certain
7 effects. Earlier works mostly aimed at inactivation of bacterial cells for applications in
8 sterilization, hygiene and wound healing.

19 As research on the biological and medical applications of plasmas advanced, the
20 demand has much increased for devices that can deliver reactive species well beyond the
21 volumes limited by the electrodes or discharge tubes where the plasma is generated. This
22 need has led to the development of plasma sources that are able to deliver the plasma plumes
23 into the surrounding environment. These devices came to be known as non-equilibrium
24 atmospheric-pressure plasma jets (N-APPJs) [15-31].

34 Various plasma jets and torches had previously been developed and used for a range of
35 other applications such as surface modifications or gas reforming. However, the gas
36 temperature in these jets and torches was often too high to be used on soft materials such as
37 easy-to-melt polymers or biological cells and tissues. For instance, the RF atmospheric-
38 pressure plasma jet developed in the late 1990s by Selwyn and co-workers was successfully
39 used to kill bacteria [32]. However, the gas temperature T_g in this N-APPJ device was
40 relatively high ($T_g > 70^\circ\text{C}$). While this discharge still belongs to the class of low-temperature
41 plasmas (because of the very low electron energy compared, e.g., to high-temperature fusion
42 plasmas), it cannot be applied to treat skin or soft tissues without causing serious thermal
43 damage (e.g., burns).

Other plasma jet configurations, developed during the last decade, generated biologically tolerable plasmas with the gas temperatures not exceeding 40°C [15,33]. Most of these devices use noble (e.g., He or Ar) operating gases with or without admixtures of oxygen or air. Using such gases or gas mixtures, low-temperature plasma plumes up to several centimeters in length have been routinely generated. This was achieved using continuous wave or pulsed power delivery modes and frequencies ranging from DC to RF and even microwave [15]. The length of the pulse-driven plasma plumes depends on the applied voltage, the pulse width, repetition rate, pulse rise time, and gas flow rate. The plasma plumes can have small cross-sections at their tips thus producing localized effects with the precision as high as a few tens of micrometers. This is a very useful feature for high-precision biomedical treatments.

Figure 2 shows some typical plasma jet configurations that have been used to generate plasmas that are suitable for biological applications. Some other configurations such as single-electrode devices have also been developed.

Importantly, plasma jets are not continuous plasma glows, as they appear to the naked eye, but are made of plasma bullets, propagating at very high velocities, up to 10^5 m/s [34-36]. Over the last decade extensive experimental and modeling work has been carried out to understand how the plasma bullets are generated, why they travel at such high velocities, and why they stop and quench centimeters away from the device nozzle [36-48]. The dynamics of the plasma bullets can be explained by the model that takes into account the high density of seed electrons and photo-ionization processes [16, 35].

Further studies revealed that strong electric fields at the head of the bullet play a crucial role in their propagation. The strength of this electric field was measured by several groups to be 15-20 kV/cm in average [49-51]. As such, the plasma bullets are fast ionization waves propagating in a guided fashion within the channel formed in the gas flow. This is why this

type of electrical breakdown is commonly known as guided ionization waves [4]. Extensive coverage of the physics of guided ionization waves can be found in a recent review [4]. Figure 3 shows a typical example of the plasma bullet propagation.

Because the plasma bullets are produced in a repeatable and predictable way, plasma jets can be applied with spatial and temporal controllability required for common biomedical applications that are introduced in the following section.

1.3 Plasma medicine - a brief introduction

1.3.1 Brief historical perspective

Plasma medicine is currently a mature and rapidly developing field of research [52-56] which took its origin in early 1990s. Following earlier works on the inactivation of bacteria by N-APPs [13,14,32], the US Air Force Office of Scientific Research (AFOSR) established a research program to evaluate the effects of low-temperature atmospheric-pressure plasmas on biological cells. This program aimed to study the efficacy of plasmas to destroy pathogens and the possibility of applying these plasmas to disinfect wounds and facilitate healing. The envisaged applications were decontamination of biotic and abiotic surfaces and media suitable for deployment in battlefield hospitals to disinfect and treat the wounds.

Parallel to the work done in the US were experiments conducted in Russia where the plasma was used as a source of nitric oxide (NO) for wound therapy. These experiments became known as “Plasmadynamic Therapy” of wounds [57]. *In vivo* trials on mice and humans suggested that the plasma-based therapy enhanced phagocytosis and accelerated the proliferation of fibroblasts.

By the early 2000s, it was revealed that low doses of N-APP exposure can induce effects such as cell detachment or even apoptosis in some eukaryotic cell lines [58]. The RF plasmas used in this study were produced at the tip of a thin metallic needle.

1 These and some other groundbreaking results have stimulated the new multidisciplinary
2 field which is presently known as Plasma Medicine. Interested reader may refer to non-
3 exhaustive representative publications [[59-91](#)].
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5 *1.3.2 The biomedical applications of N-APPs*

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7 As mentioned above, research on the biomedical applications of low-temperature
8 atmospheric-pressure plasmas was initially focused on sterilizing harmful microorganisms
9 (e.g., bacteria, fungi, spores) on both biotic and abiotic surfaces. It was established that N-
10 APPs produce a mixture (often termed cocktail) of highly-reactive chemical species including
11 reactive oxygen species (ROS) such as O, O₂⁻, O₃ and OH and reactive nitrogen species
12 (RNS) such as NO and NO₂. These species and some of their reaction products are presently
13 well known to exhibit strongly oxidative properties and can trigger signaling pathways in
14 living cells. These species play important roles in cell physiology, metabolism and growth,
15 immune responses, ageing and several other cell processes. Some of these functions and the
16 effects of the plasma exposure are discussed in [Sec.7](#) below.
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19 Experiments on eukaryotic cells demonstrate that under some conditions, N-APPs
20 appear to cause little damage to living animal and plant tissues. For example, skin fibroblast
21 cells usually remain viable under relatively mild doses of the plasma exposure that can be
22 lethal to bacterial cells. The proliferation of fibroblasts is a critical step in the wound healing
23 process. The demonstrated ability of plasmas to kill antibiotic-resistant bacteria and to
24 accelerate the proliferation of specific tissue cells opens the possibility to use plasmas to
25 assist in chronic wound healing. Importantly, this ability has been related to the plasma-
26 generated biologically-relevant reactive species briefly mentioned above.
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29 N-APPs can also induce selective death of cancer cells while leaving normal cells
30 intact. It is very likely that this process is mediated by the plasma-generated reactive species,
31 for example through the activation of specific signaling pathways that involve a cascade of
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intracellular biochemical reactions eventually leading to cancer cell death. These results suggest that plasmas represent an effective and highly-promising tool in certain cancer therapies, perhaps in combination with other anti-cancer modalities such as surgery, radiation therapy and chemotherapy.

The biomedical applications of N-APPs are wide and continue experiencing rapid growth. Because the main topic of this review is on reactive species generated by N-APPJs rather than on various biomedical applications of N-APPJs, the following part of this section will only present a few selected examples of the effects of N-APPs on prokaryotic, eukaryotic, and cancer cell.

1.3.2.1 Effects of N-APPs on prokaryotes

The inactivation of bacteria was the first biological application of N-APPs. Dielectric barrier discharges (DBD) were mostly used in the early trials, while N-APPJs became more and more popular with time, as the obvious benefits of the N-APPJs were recognized by the community. These and some other N-APP discharges have been successfully applied for inactivation of both gram-positive and gram-negative bacteria with various degrees of success. [Figures 4 and 5](#) present typical results obtained by a DBD source and by a plasma jet, respectively.

Quite similar results were obtained for other types of bacteria. The level of log reduction or the size of the inactivation zone strongly depended on the type of bacteria, the initial concentration (bio-burden), and on the medium on which the cells were seeded. Importantly, sufficiently long exposure to N-APPJ leads to effective inactivation of sporulated gram-positive bacteria, which are otherwise very difficult to kill. It was also frequently observed that similar doses of plasma exposure affect planktonic bacterial cells much stronger than biofilms. This result is reasonable because biofilms are formed when a

community of bacterial cells self-organizes to protect itself by forming an extracellular glue-like polysaccharide film. In this case, reasonably long exposure times (typically of the order of tens of minutes) lead to the effective (yet not always complete) biofilm destruction [94,95].

1.3.2.2 Effects of N-APPs on eukaryotes

The sub-cellular structures of Eukaryotes are quite different compared to prokaryotes. A crucial difference is the existence of a nuclear membrane in eukaryotic cells. In addition, many sub-cellular units important for cell function are contained within membrane-bound organelles. Therefore, eukaryotes, such as mammalian cells, respond to extracellular physical and chemical stresses in a different manner than prokaryotes, such as bacteria, do. Here, we introduce two examples that illustrate the effects of N-APPJs on two eukaryotic cells: healthy fibroblast and cancerous (squamous cell carcinoma) cells.

Treatment of the fibroblast cells using different plasma exposure times (doses) has led to significant phenotypic changes [96]. Importantly, these changes have been related to an increased flux of reactive species into the media that modify the intracellular signaling cascades leading to the altered cellular states [96].

A quite similar treatment was applied to human bladder cancer cell line SCaBER [97]. Figure 6 shows the results of the SCaBER cancer cell viability. The counts immediately after plasma jet-treatment (labeled 0 h in the figure) reveal no dead cells which suggest that there was no immediate physical effects and that the interaction between the plasma-generated chemical reactive species and cancerous cells requires sufficient time to show an effect. However, at 24 hours post-plasma treatment the viability of cells reduced to around 50% and to 75% for 2 min and 5 min plasma exposure, respectively. Therefore, the higher the dose of the plasma exposure the lower is the survival rate of the cells. Indeed, 5 min-long plasma

1 treatment diminished the viability of SCaBER cells to approximately 10% observed at 48
2 hours after the plasma treatment [97].
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4 The experimental results discussed above show that N-APPs affect biological cells
5 (prokaryotes and eukaryotes) in a *dose-dependent manner*. The response of eukaryotic cells is
6 not immediate but delayed, which indicates that the N-APPs do not immediately act on the
7 cells with “brute force” (e.g., physical or chemical) but rather initiate cascades of biochemical
8 events. These events take effect over typical time scales for relevant biological processes
9 summarized in Fig.1. The above examples and plentiful results of other researchers suggest
10 that the reactive oxygen and nitrogen species and their reaction by-products the most likely
11 agents that cause the observed effects of N-APPs on living cells.
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24 This is why the following sections present the details of the theoretical and
25 experimental studies aimed to quantify the composition, concentration and fluxes of these
26 reactive species. This knowledge is indispensable for better understanding of the complex
27 interactions of the plasmas with liquids containing biological material.
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36 **2. Modelling of production of reactive species in N-APPJs**

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38 Knowledge of number densities and fluxes of reactive species generated in N-APPJs is
39 crucial for understanding the mechanisms of interaction of the plasma jets with biological
40 objects. The number of the generated species is very large which makes it very difficult to
41 obtain complete experimental information on the chemical composition of the gas in the jet
42 effluent. The obvious advantage of numerical modeling is in the possibility to simultaneously
43 calculate the densities of the whole set of the discharge species.
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53 A general problem of modelling the N-APPJ properties includes the need to consider
54 various physical and chemical phenomena, such as the gas flow, electrodynamic processes,
55 discharge dynamics and kinetics, chemical transformations, etc. Combined simulation of
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these phenomena requires a lot of computational time and is inconvenient in cases when the effects of various factors on the dynamics and structure of N-APPJs are to be analysed. Fortunately, it is possible, to separate some of the mentioned phenomena with sufficient accuracy. In particular, the pattern of the gas flow in the plasma jets is affected by the discharge rather weakly and can be modelled independently. Calculation of mixing of plasma forming gases (usually He or Ar) with surrounding gas (usually air), is based on the solution of the coupled set of stationary Navier–Stokes and diffusion equations [4] and provides the spatial distributions of molar fractions of the neutral species (He, Ar, N₂, O₂, H₂O) in the directions along and across the jet. These spatial distributions are used in the modeling of the discharge properties.

Another factor which helps simplifying the N-APPJ simulations is a rather low energy input in the discharge. As a rule, gas heating due to Joule energy input is not strong and the molar fractions of the produced reactive species are relatively low. It allows one to simulate the discharge while neglecting the increase of the gas temperature and the formation of reactive species. The discharge modeling is based on solving non-stationary balance equations for charged species and Poisson equation for the electric field [4]. The obtained spatio-temporal distributions of the density of electrons and of the electric field can then be used for calculation of the production of primary reactive species (those generated by electron impact) and their subsequent chemical transformations.

There are two major types of N-APPJs showing quite different physical phenomena [33]. In RF (radio frequency) N-APPJs, the plasma is generated by capacitively coupled RF discharges between metallic electrodes, at frequencies in the tens of megahertz or even gigahertz range. Primary reactive species in these jets are produced inside the discharge volume. Another type, HF (high frequency) N-APPJs are formed by barrier discharges in gas flows in thin dielectric tubes by applying sinusoidally varying voltage or repetitive voltage

pulses with frequencies in the kilohertz range (typically around 10^4 Hz). As mentioned in [Sec.1](#), the HF N-APPJs are composed of bullet-like plasma volumes (“plasma bullets”) – streamers propagating along the jet [4]. In this case the generation of primary reactive species occurs not only between the electrodes but also in the effluent region.

Note that the time of gas movement along the jet (the residence time), given by the ratio of the jet length to the mean gas velocity, is typically 10^{-3} - 10^{-2} s and is much larger than the repetition frequency of the applied voltage pulses. In other words, a large number of discharge pulses pass through the gas during its propagation along the jet. In RF N-APPJs the variation of densities of reactive species during the RF or pulse repetition period is typically small. This allows one to use the phase averaged excitation rates, which accelerates the calculations.

However, this approach is not applicable for simulations of HF N-APPJs where the densities of reactive species can vary substantially between the pulses. In this case each of the pulses should be simulated individually. A possible simplification in this case is due to the weak dependence of discharge parameters on the densities of reactive species mentioned above. Consequently, the source terms in the balance equations for the densities of primary species can be assumed to be the same for each of the pulses. These source terms are evaluated in the process of simulation of a single discharge pulse (propagation of a single streamer) and are used in the subsequent simulations of chemical transformations during a sequence of repetitive pulses.

Kinetic schemes used in calculations of the production of reactive species in N-APPJs usually include several hundred reactions involving several tens of components: He, Ar, N, O, and H atoms and molecular species composed of these atoms (in ground and excited states), various atomic and molecular ion species and electrons. Kinetic schemes involving these species are presented e.g. in [\[98-105\]](#). A critical analysis of the chemistry models for He-O₂

1 mixtures is given in [106]. Detailed information on the rate constants of numerous chemical
2 reactions involving neutral species, both in ground and excited states, is compiled in the
3 NIST Chemical Kinetics Database [107].
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7 Rate constants of excitation, dissociation and ionization of neutral species by electron
8 impact are obtained by averaging the corresponding cross-sections over the electron energy
9 distribution function (EEDF). The latter is obtained by solving the Boltzmann equation (e.g.,
10 by using the BOLSIG+ code [108]) for the given reduced electric field and composition of
11 background species in the gas mixture. Another approach evaluates these rate constants as
12 functions of the local electron temperature, the latter being obtained by solving the electron
13 energy balance equation.
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24 To simulate the generation of reactive species, models of various complexity are used.
25 The simplest are 0D (zero-dimensional, volume-averaged) global models approximating the
26 species densities as being nearly uniform in the plasma bulk [109]. The advantage of 0D
27 models lies in the relatively small computational demands for solving the kinetic equations,
28 allowing for the analysis of the dependence of the species densities on various input
29 parameters and on the model assumptions. Besides, in order to know the main channels of
30 generation of the species, one could turn off some specific channels (set the reaction rate
31 constants to zero) to see their effects on the densities of these species. In this way, the main
32 reaction paths for the generation of the species can be distinguished.
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46 In 0D models, the number densities n_j of reactive species are evaluated by solving the
47 balance equations:
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$$51 \quad \frac{dn_j}{dt} = R_j + F_j - n_j/\tau_j \quad , \quad (1)$$

52 where the terms R_j (non-zero for primary reactive species) are the rates of production of
53 species by electron impact and F_j are the net rates of generation/loss of species in chemical
54 reactions. The last term on the right-hand side of equation (1) describes the loss of species
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due to diffusion outside the discharge volume and gas flow through the reactor. Solution of the set of equations (1) at known values of the source terms R_j (the latter being evaluated by solving the electron energy balance equation or by calculating the EEDF) allows one to obtain the temporal dynamics of the plasma composition.

In calculations of densities of reactive species generated in N-APPJs, various modifications of the 0D model are used. The electron energy balance equation, together with the set of equations (1), is used in [110] for the evaluation of the species densities versus the energy input. In [100] the plasma composition is evaluated by assuming the electron number density n_e constant in time. The electron temperature which determines the rate constants in the source terms R_j is chosen such that $dn_e/dt = 0$. In [104,111] the terms R_j are determined using the results of 1D discharge modeling [112]. Temporal evolution of reactive species in the afterglow (with zero source terms R_j) is described using 0D model [113], whereas the initial densities of species are evaluated using the measured absorption data. Spectral data-based estimates for the electron density and EEDF in the discharge region are used for calculation of chemical composition [114]. In calculation [115] of production of reactive species in HF N-APPJs by a sequence of discharge pulses, a 0D model is used with source terms $R_j(t) = R_{j0} \sum_k \delta(t - k\tau)$, $k = 0, 1, 2, \dots$ (here τ is the repetition period and δ is the Dirac delta function); the values R_{j0} are obtained by simulation of streamer propagation along the jet. Such form of the temporal dependence of the source terms reflects the fact that the time of generation of primary reactive species by electron impact, in the region of strong electric field in streamer head, in a single pulse is several orders of magnitude shorter than the repetition period.

Using 0D models, it is possible to represent the temporal evolution of the species densities as their dependence on the axial coordinate z along the jet (plug flow

approximation), replacing terms dn_j/dt with Vdn_j/dz in equations (1), where V is the mean gas flow velocity. A scheme of this approach for RF N-APPJs, where primary active species are produced in the discharge region between the inlet and the nozzle, is presented in Fig.7. For RF N-APPJs, where primary active species are produced by propagating streamers both in the discharge tube and in the effluent, the afterglow region starts from the position where the streamers stop.

The plug flow approximation, with source terms R_j being known functions of z , allows one to describe the variation of the species densities along z both in the discharge region and in the afterglow. The plug flow approximation is applicable also in cases when the composition of background components varies along z due to mixing in the effluent of the plasma forming gas with the surrounding gas.

In [105,116-118] the plug flow approximation is used for the evaluation of axial distributions of reactive species densities in a needle-type RF N-APPJ, defining a profile of the power density (the source term in the electron energy balance equation) along z . In [119], the distribution of densities of reactive species along the z direction (averaged over the jet cross section) is calculated in the framework of the plug flow approximation. The species are produced in HF N-APPJs by a sequence of discharge pulses and the calculations are carried using the source terms obtained through two-dimensional (2D) streamer simulations.

For the description of spatial distributions of the generated reactive species, 1D (one-dimensional) or 2D models are used. In [102,112,120] the simulation of RF discharges between the parallel-plate electrodes in a transverse gas flow is performed using a 1D model (assuming that the variation of the discharge parameters along the flow is negligible). The balance equations for the reactive species j are:

$$\partial n_j / \partial t = R_j + F_j + D_j \partial^2 n_j / \partial x^2 \quad , \quad (2)$$

where D_j are the diffusion coefficients; the coordinate x is directed between the electrodes,

normally to the gas flow. In the framework of this approach, the species densities are calculated versus the inter-electrode position.

2D models give information on the distributions of the produced reactive species j both along and across planar or cylindrical plasma jets. The corresponding balance equations are

$$\partial n_j / \partial t = R_j + F_j - \nabla \cdot (n_j \mathbf{V} - D_j \nabla n_j) \quad , \quad (3)$$

where $\mathbf{V}$ is the gas velocity vector. In [121,122], 2D simulation of RF N-APPJs with the parallel-plate electrodes is performed using nonPDPSIM fluid dynamics code [123]. The densities of the plasma components both in the discharge core between the electrodes and in the effluent are calculated. In [124,125] equations (3) are solved, using COMSOL software, in the effluent region (with zero R_j terms), for the preset species densities at the boundary separating the discharge and the effluent. 1D simulation of the RF discharge between parallel-plate electrodes together with 2D simulation of the gas flow and chemical kinetics in the effluent is carried out in [126] using COMSOL.

2D simulations of the production of active species by a single pulse (single streamer) in HF N-APPJs are performed in [127-132]. Equations describing streamer propagation, with the account of mixing of the plasma forming gas with surrounding air, are solved together with kinetic equations (3). In [133], 2D modelling of the production of reactive species by a sequence of propagating streamers is performed. These and several other presently available results of the numerical modelling of N-APPJ properties, propagation and interactions with various materials are usually in a reasonably good agreement with the results of the basic experimental observations and discharge diagnostics presented in the following section.

3. Basic experimental observations and diagnostics

The last two decades have seen major advances in the development and experimental studies of N-APPJs [33,58,134-140]. One of the important properties of N-APPJs is their

high chemical reactivity at low gas temperatures and even at room temperature [141]. These properties are essential when plasmas interact with biological systems. As mentioned in Sec.1, in applications such as plasma medicine, knowledge fluxes of the discharge species and the relevant elementary processes is essential [141-143]. N-APPJs are usually small with typical dimensions from micrometre to millimetre and non-uniform distributions of the species densities and other parameters. Common plasma jets can access small cavities while the associated fluxes of reactive species are very difficult to measure and calculate. More importantly, the strongly non-equilibrium state of the plasma invalidates the use of many common diagnostic techniques and their evaluation procedures that rely on the equilibrium state assumptions.

As N-APPJs have small dimensions and significant non-uniformity [144], invasive techniques with low spatial resolution are not suitable as they yield incorrect mean values and significantly disturb the plasma properties. Non-invasive optical diagnostic techniques are thus the methods of choice for the diagnostics of N-APPJs [144-149]. These techniques include optical emission spectroscopy, laser-based methods such as laser induced fluorescence techniques, scattering techniques such as Rayleigh-, Raman- and Thomson scattering, optical absorption spectroscopy measurements [145-147,150]. Other commonly used techniques are known from chemical analysis such as mass spectrometry, gas chromatography or electron paramagnetic resonance spectroscopy, and some others. In the following, selected diagnostic techniques are introduced. Each of these techniques uniquely delivers specific plasma and species parameters.

3.1 Fast imaging

Phase-resolved imaging or optical emission spectroscopy can be used to image dynamic processes with picosecond time resolution at MHz acquisition rates. By using gated and

1 triggered intensified charge coupled device (ICCD) cameras, dynamic processes in plasmas
2 can be imaged [41]. This technique is used to detect and monitor plasma bullets with pico- to
3 nanosecond precision [35] and study the streamer dynamics in N-APPJs. The measurement is
4 performed by gating the acquisition time of an ICCD camera down to picoseconds to gain the
5 high time resolution. This acquisition gate is then shifted with respect to the electrical
6 excitation phase. In one acquired image, photons from multiple excitation cycles are
7 accumulated. The resulting image is an averaged emission image from a certain time point in
8 the plasma excitation. Acquisition of multiple datasets results in a dynamic movie of the
9 excitation process throughout the excitation cycle [151,152].

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22 If the plasmas are unstable and show stochastic behaviour in time, this technique cannot
23 be applied, as the averaging process relies on reproducible plasma dynamics and constant
24 triggering parameters. In such cases, cross-correlation spectroscopy can be applied. This
25 spectroscopy correlates an electric event to an optical event and can thus also capture
26 stochastic processes of the plasma breakdown. It is clear that averaging processes reduce the
27 precision of the information acquired and single-shot-resolved techniques need to be
28 developed [153].

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39 Measurements with the high time resolution are possible by the use of streak cameras.
40 These measurements make it possible to monitor highly-dynamic breakdown processes [154].
41 However, the streak cameras do not allow for the precise imaging in both x - and y - spatial
42 dimensions simultaneously.

50 51 **3.2 Laser-induced fluorescence**

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Reviews of laser-induced fluorescence (LIF) spectroscopy applied to plasmas [150,155]
and flames [156] provide comprehensive information on this diagnostic technique. LIF is
based on the principle that wavelength tunable laser radiation is used to transfer atoms or

1 molecules from one energy state $\langle 1 \rangle$ to another, higher energy state $\langle 3 \rangle$. From this state, the
2 excited species transits to an energy level of lower energy $\langle 2 \rangle$, emitting fluorescent radiation
3 during the transition. When the properties of the excitation laser beam and the effects of the
4 quenching species and energy dissipation processes are known, this fluorescent radiation
5 yields information about the population density of energy state $\langle 1 \rangle$. Therefore, LIF can yield
6 valuable information about the densities of the atomic and molecular ground or excited states.
7 While the experimental complexity of the LIF detection systems is high, they provide high
8 sensitivity at high spatial and temporal resolution.
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10 In the following, two specific laser techniques, namely the single-photon laser induced
11 fluorescence as well as two-photon laser induced fluorescence spectroscopy, are presented.
12 These techniques are relevant to the diagnostics of the plasmas that are used for interactions
13 with living cells and tissues.
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15 *3.2.1 Single-photon absorption laser-induced fluorescence*

16 Single-photon laser induced fluorescence spectroscopy uses one photon per excitation
17 of the probed atom or molecule. This poses the problem that in optically thick plasmas,
18 fluorescence photons can be re-absorbed, which obscures the measurements. Furthermore,
19 the use of single-photon transitions limits the available transition energies. Light atoms such
20 as hydrogen, oxygen or nitrogen for example have their ground state transition at energies
21 higher than 6.5 eV, which makes the use of vacuum ultraviolet (VUV) laser systems
22 necessary, should LIF be the method of choice. While this has indeed been done e.g. for O-
23 atoms and H-atoms [157], the experimental challenges to generate and transport the radiation
24 are high and VUV radiation is even less suitable for the diagnostics of N-APPJs. In these
25 cases, two-photon-LIF (TALIF) technique can be used, which will be described in the next
26 section.
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LIF spectroscopy has the advantage over TALIF that it is experimentally simpler as the emitted fluorescence depends only linearly on the laser intensity (opposed to quadratic dependence for TALIF). This eases data evaluation for the case of LIF spectroscopy. On the other hand, the fact that LIF spectroscopy is predominantly used for molecule detection, complicates data evaluation. Briefly, the rotational and vibrational energy dissipation as well as laser scattering noise and collisional quenching obscure the measurements, as will be described below. The most dominant species that are detected by LIF and are relevant to plasma medicine are the hydroxyl radical (OH) and the nitric oxide radical (NO). Furthermore, the species that are detected indirectly through quenching are oxygen, nitrogen, or water molecules [158].

In cold plasmas, non-equilibrium processes and non-Boltzmann distributions make the situation much more complex compared to neutral gases and flames. In single-photon LIF, the fluorescent photon can be of the same energy as the incident laser photon. This poses the problem that scattered laser radiation obscures the signal and needs to be removed or otherwise separated from the fluorescent signal, e.g. by only evaluating the emission after the laser pulse, if the fluorescence lifetime is long enough. To gain absolute values from LIF measurements, energy dissipation mechanisms, optical and geometrical parameters need to be taken into account. Energy level population is strongly influenced by rotational and vibrational energy transfer (RET and VET, respectively) as well as by collisional quenching processes that compete with fluorescent transition detected as LIF signal (see **Error! Reference source not found.**).

The population n_2 of the excited state depends on the absorption rate of the lower energy state $\langle 1 \rangle$, as well as on the stimulated and spontaneous emission of the excited state $\langle 2 \rangle$ as well as the quenching rate according to the rate equation:

$$\frac{dn_2(t)}{dt} = B_{12}I(t)f_B n_1(t) - [B_{21}I(t) - A_2 + Q]n_2(t), \quad (4)$$

where I is the time-dependent laser intensity, B_{12} and B_{21} are the Einstein coefficients for absorption and stimulated emission whereas A_2 is the spontaneous emission coefficient summed over all transitions from the excited to the lower level. The Boltzmann factor f_B denotes the population of the ground state according to the quantum number of the rotational quantum state and the rotational temperature. Q denotes the collisional quenching summed over all quenching species according to $Q = \sum n_i k_i$ with the density n_i and quench coefficient k_i of quenching species i . The collisional quenching term Q depends on the gas temperature and composition and includes all depopulating mechanisms such as those based on electronic and vibrational energy transfer.

In some cases, a few assumptions can be made, which simplify the energy level structure to a simple two-level system. If the following conditions are met, the reduced model of the system leads to reliable quantitative results. For linear LIF, the laser intensity has to be low so that the population of the lower energy state remains nearly constant. Then, stimulated emission can be neglected, which eliminates B_{21} from equation (4) and saturation of the LIF signal does not occur. Rotational energy transfer is fast so that the lifetime of the pumped state is dominated by the lifetime of the vibrational energy band. To avoid the signal loss due to rotational energy transfer, LIF detection is performed broadband to record the entire rotational energy states. Vibrational energy transfer, potentially leading to a loss in signal or different lifetimes can be neglected. Moreover, the rotational-vibrational population of the ground state should be in equilibrium with the gas temperature. Under this condition, the population of the pumped level can be used to calculate the total ground state density by the Boltzmann equation using only the gas temperature.

A typical LIF setup is shown in **Error! Reference source not found..** The LIF signal reaching the detector at observation of 90° to the exciting laser beam is determined by the intersecting volume element V_c of the laser beam and the optical path of collection optics.

With this setup, a high spatial resolution in fractions of a millimetre in every direction can be achieved. The LIF signal for a simplified two-level energy system with the above assumptions is (cf. e.g. [156]):

$$S_{LIF} = \frac{\Omega}{4\pi} \int A_2 \varepsilon n_2 \Gamma(\lambda) dV_c, \quad (5)$$

where Ω is the solid angle of the detection optics, ε is the wavelength dependent efficiency of the detection system, Γ the line profile of the transition. To account for the spectrally broadened nature of both the laser radiation and the absorption transition, a dimensionless overlap fraction has been proposed [159] and can be used to modify traditional monochromatic fluorescence theory. According to [159], the fraction represents the loss from the optimum interaction that is due to both detuning of the centre frequencies and the different spectral distributions of the laser irradiance and the absorption transition.

When stimulated emission is negligible, the solution to equation (4) is:

$$n_2(t) = B_{12} n_1 \int_0^t I(\tau) e^{-(A_2+Q)(t-\tau)} d\tau \quad (6)$$

Inserting (6) into (5) yields an expression for S_{LIF} for which all parameters are known apart from the quenching and optical parameters of the system. These parameters need to be determined in a calibration procedure.

Each LIF system consists of the wavelength- and geometry-dependent components. The volume of detection and the quantum efficiency of the detector as well as the wavelength-dependent transmission function of the optical elements need a calibration procedure in order to determine the influence of the system on the detected fluorescence signal. There are various means of calibration possibilities briefly described below.

In single-photon LIF, calibration of the optical properties of the system especially under the assumptions described above is relatively simple. In simple cases, the species density can be derived from dynamic measurements in the afterglow of the discharge, evaluating the

relative species density evolution using the chemical kinetics model [160-163]. To calibrate LIF precisely, two fundamentally different approaches are possible.

First, LIF is performed on a known species concentration, determined e.g. by absorption spectroscopy, which allows to calculate optical parameters from this calibration. Likewise, titration can be used to determine the species densities, which will be described in the section on TALIF spectroscopy.

Second, a LIF-independent signal, which is also linearly proportional to the laser intensity, is recorded in order to determine the optical system parameters. The most common approach for this is based on Rayleigh scattering [164]. Here, the scattering signal on a reference gas of known quantity is recorded as a function of laser energy [165]. The Rayleigh signal can be detected, resolved in space and then taken as a reference signal [165]. Comparison of Rayleigh based approaches with chemical kinetics modelling show the advantage of using scattering for optical calibration [160,166, 167].

If the experimental conditions do not allow major simplifications in the energy state models, higher-complexity models need to be used to interpret and quantify the LIF signal. For example, two- [166], three- [168], five- [155], and recently six-level [166] models based on [169] have been used. The six-level model describes the laser excitation from the ground level and the stimulated emission. These models include rotational (RET), vibrational (VET) and electronic (Q) energy transfer reactions. **Error! Reference source not found.** shows the energy levels and transitions involved in the five- and six-level models [155,166].

Interestingly, in comparison with the four-level model, the six-level LIF model does not provide the more accurate value of OH density in the Ar N-APPJ [166]. Comprehensive interpretation of this effect would allow researchers to use the models with the minimum appropriate number of the energy levels for accurate measurements of reactive radical densities.

The first laser induced fluorescence spectroscopy measurement in atmospheric pressure plasmas on OH has been performed in [170]. LIF on supersonic plasma jets at reduced pressure has been used for NO measurements [171]. Several biologically relevant molecules such as CH [137], CN [138], NO [33,139,140], and OH have also been investigated by LIF. In addition, LIF has also recently been used for rotational temperature diagnostics [172] and gas flow patterns [173]. More details of the selected results of LIF diagnostics are presented in Sec. 4.

3.2.2 Two-photon absorption laser-induced fluorescence

Especially for light atoms, which have their electronic transitions to the ground state in the range above 6.5 eV, LIF spectroscopy requires the use of high-energy VUV photons. However, two problems are present for this approach. First, media are not always transparent enough for VUV photons making the probed volume optically thick. Second, it is experimentally challenging to provide an oxygen-free environment for the laser pathway to allow the VUV radiation to reach the plasma. For these reasons, it is simpler to use two UV-photons for such excitation schemes rather than one VUV photon. With high enough laser intensity, it becomes possible to detect a TALIF signal from light atoms. This process is nonlinear which makes the signal interpretation and quantification more complex than for the single-photon LIF case.

A strong disadvantage of TALIF is the loss of the possibility to calibrate the excitation and detection system with Rayleigh scattering. In multi-photon processes, the linear relation between the Rayleigh scattering intensity and the laser energy, as is the case for linear LIF, cannot be assumed. Therefore other approaches to calibrate the TALIF signal need to be used.

The first approach is to compare the TALIF signal to the one on a known species density. This can either be done by a reference plasma discharge, for which the respective species density is known or by other methods to determine the species densities. For transient and intermediate species, this can pose a problem. One approach to calibrate oxygen TALIF measurements [174] is based on a microwave plasma initiated dissociation of molecular oxygen to generate atomic oxygen and then guide it into a flow channel. Nitric oxide was added to the flow to react with the atomic oxygen to form NO according to the following reaction [174]:

At a point further downstream, where all NO_2 could be expected to have reacted, a TALIF measurement was performed. The TALIF signal decreases with rising NO_2 concentration. As soon as the NO concentration equals the concentration of atomic oxygen, the O density is determined (see Fig.11).

A different approach without any addition or modification to an existing setup has been proposed [175]. This approach is based on the measurement of the collisional quenching of the laser-excited state ($3p^3 P_2$) in a pure O_2 system in which a high, but variable dissociation degree can be achieved [175]. Since the quenching rate for O is much lower compared to the one of O_2 , the measurements can be correlated to the O density.

The most common approach for calibration of TALIF signals is based on the use of TALIF measurements on a known density of a noble gas [176]. As this gas does not decay in concentration and the density can thus be determined by the ideal gas law, the resulting TALIF signal can be correlated to the known species concentration. Thus, the optical constants of the system can be determined and the species density of the studied species n_x can be calculated, when collisional quenching and ionization can be neglected, according to [176]:

$$n_x = \gamma \frac{a_{21}(\text{NG})}{a_{21}(X)} \frac{\hat{\sigma}^{(2)}(\text{NG})}{\hat{\sigma}^{(2)}(X)} \frac{I(\text{NG})}{I(X)} n_{\text{NG}} \quad , \quad (7)$$

where a_{21} is the branching ratio of the fluorescence transition of the noble gas (NG) and the studied species (X), and $\hat{\sigma}^{(2)}$ is the two-photon excitation cross-section. Furthermore, I is the normalized fluorescence intensity. The factor γ contains the wavelength-dependent system properties at the wavelength of the probed species. If the excitation and fluorescence wavelengths are close enough, $\gamma \sim 1$. In [177], several excitation schemes for hydrogen, nitrogen (in comparison with krypton) and oxygen in comparison with xenon were studied (see **Error! Reference source not found.**).

At atmospheric pressure, the natural lifetime of the transition from the excited state to the ground state is strongly reduced by collisional quenching. This has to be accounted for and quench coefficients have to be included in equation (7) according to [138]:

$$a_{ik} = \frac{A_{ik}}{\sum_{k < i} A_{ik} + \sum_q k_q^i n_q} \quad , \quad (8)$$

where k_q are the quench coefficients of species q at density n_q . These are also temperature dependent. When these factors are determined, the concentration of the species can be obtained.

3.3 Scattering techniques

Fluorescence and emission measurements are usually non-invasive and have high spatial and time resolution. However, they rely on several model assumptions and lack accuracy or the possibility to probe (e.g., electron parameters or direct gas temperature measurements). For these parameters, scattering techniques are particularly useful. Scattering can be elastic scattering from heavy particles (Rayleigh), or from electrons (Thomson) or inelastic scattering from molecules (Raman). A simultaneous measurement of all scattering signals in atmospheric-pressure plasmas can yield electron temperature and density as well as

gas temperature, partial air pressure and the N₂/O₂ ratio with high spatial resolution and absolute calibration [178].

3.3.1 Rayleigh scattering

Rayleigh scattering is elastic scattering of usually laser radiation by atoms or molecules or other particles smaller than the wavelength of radiation. Rayleigh scattering can be simply applied to the diagnostic of temperature or density of gases. Rayleigh scattering originates from the interaction of the oscillating electric field of a light wave on the localized charges of the probed particles. Due to the polarizability of the scattering particles, the charges move with the frequency of the incident light and result in dipole radiation emitted from the particle, which is observed as scattered light. The signal is proportional to the number of scattering particles n given by the ideal gas law

$$n = \frac{p}{k_B T_G} \quad , \quad (9)$$

where k_B is the Boltzmann constant, and T_G is the gas temperature at the pressure p . To deduce the gas temperature from Rayleigh scattering, a reference measurement at a known gas temperature has to be taken. The gas temperature can be determined using $T_{gas} I_{plas} = T_{ref} I_{ref}$. If a stable species such as for example Ar is probed, I_{plas} can be the intensity of the Rayleigh scattering on the species with the plasma switched on and I_{ref} is the intensity of the scattering on the species with the plasma switched off. Assuming room temperature in the latter case, the gas temperature in the plasma can be determined. Different gases have a different differential Rayleigh cross-section [179]. Therefore, a reference spectrum should be optimally performed in the same gas composition.

The neutral gas density can be obtained from the Rayleigh according to [180]:

$$n_g = \frac{S_{Pl+St}-S_{St}}{S_{ref+St}-S_{St}} n_{ref} \quad (10)$$

where n_{ref} is a known gas density injected into the plasma chamber determined by a fixed

1 pressure and (room) temperature. Here, S_{pl} is the plasma Rayleigh signal, S_{st} is stray light
2 determined with a reference measurement at zero pressure, and S_{ref} is the signal of a
3 reference gas at a given temperature and pressure.
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9 *3.3.2 Thomson and Raman scattering*

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11 Among the most important parameters of atmospheric-pressure discharges, the electron
12 density and temperature are probably the least accessible. These parameters can be measured
13 in low-pressure plasmas by using Langmuir probes. For small-size collision-dominated N-
14 APPJs these measurements have not produced convincing results due to the lack of
15 applicable theories. A variety of methods is used to determine electron properties, some of
16 which are also described here. However, these techniques have to rely on several assumptions
17 or model calculations.
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28 One method that can determine electron energies and densities with sufficient accuracy
29 in N-APPJs is Thomson scattering. Recently, an overview on Thomson scattering on N-
30 APPJs has been published [181]. A review of the method used for atmospheric pressure
31 plasmas can also be found in [180] as well as in [182] and [183].
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38 Two major problems make Thomson scattering measurements intricate. Both arise from
39 the low efficiency with which the scattering signal can be detected. First, the scattering signal
40 itself is extremely weak. In [180], the ratio of laser photon flux to detected Thomson
41 scattered photons was reported. Of a 20W laser with a photon flux of several 10^{19} photons/s,
42 only several 10^5 photons/s are Thomson scattered (at an electron density of 10^{18} m^{-3}). From
43 these photons, only 10^3 photons/s are collected by an optical device with 10 cm diameter and
44 a focal length of 60 cm. Taking the transmission probability of a detection system with
45 lenses, spectrograph and detector into account, of the initial 10^{19} photons/s, only some 10
46 photons/s are detected.
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The difference of 18 orders of magnitude causes the second problem. Indeed, in Thomson scattering, the inelastically scattered photons are observed at slightly different wavelengths compared to the laser wavelength. Due to the extremely high photon flux from the laser, the laser light is much stronger than the signal being measured. Therefore, Thomson scattering experimental setups are characterized by complex spectroscopic systems designed to filter the central laser wavelengths with steep filter edges and strong optical density. Mostly, triple grating spectrographs are used, where the laser radiation is filtered by negative apertures and other scattered light is also blocked by walls and apertures inside the spectrographic systems. Other possibilities include the use of a vapour cell containing a gas that absorbs the wavelength of the laser radiation.

In order to calibrate the scattering signal, the measured power of the scattered laser light in the plasma per unit of wavelength P_λ is calculated according to:

$$P_\lambda = n \cdot \xi \cdot \Delta\Omega \cdot P_i \frac{d\sigma}{d\Omega} \cdot S_\lambda(\lambda) \quad , \quad (11)$$

where n is the scattering particle density, P_i the incident laser power, S_λ includes the spectral distribution as a function of the wavelength, ξ is a constant including the efficiency of the optics and detection system as well as the length of the detection volume, $\Delta\Omega$ is the solid angle of detection and $d\sigma/d\Omega$ is the differential cross-section. Details can be found e.g. in [178,180-183].

As Thomson scattering signals are Doppler broadened due to the high velocity of the electrons, the electron temperature can be determined from the broadened line profile of the scattering signal [178]:

$$T_e = \frac{m_e c^2}{4k_B} \left(\frac{\Delta\lambda}{\lambda_l} \right)^2 \quad , \quad (12)$$

where $\Delta\lambda$ the FWHM of the Thomson scattering signal profile, λ_l is the laser wavelength, m_e is the electron mass, c is the speed of light and k_B is the Boltzmann constant.

The resulting equation for the electron density is

$$n_e = n_g \frac{P_\lambda^T}{P^R} \frac{d\sigma^R/d\Omega}{d\sigma^T/d\Omega} , \quad (13)$$

where P^T and P^R are the powers of the scattered Thompson and Raman signals, respectively, and n_g is the gas density. In Eq. (13), terms $d\sigma^R/d\Omega$ and $d\sigma^T/d\Omega$ represent the Raman and Thomson scattering cross sections, respectively.

3.4 Optical emission spectroscopy

Due to its experimental simplicity, optical emission spectroscopy is the most commonly used diagnostic technique for characterisation of the plasma sources. Optical emission spectroscopy probes only the excited levels because it measures the radiation emitted by the excited atoms or molecules in the plasma. At low pressures or in plasmas in thermal equilibrium, interpretation of optical emission spectra is feasible. Due to the plasma conditions, the population density of the probed energy state is related to lower states via the Saha equation and the Boltzmann distribution. For N-APPJs, the situation is different. The strong non-equilibrium makes it difficult to interpret the measured spectra and to receive the absolute values of the ground-state densities. Nevertheless, a lot of information can be gained from OES even at atmospheric pressure. The information can be derived from the absolute and relative line intensities, the line widths, the appearance of certain lines attributed to forbidden states or the emission continuum radiation. The following section briefly introduces the established approaches to analyse optical emission spectra.

3.4.1 Information gained from line broadening

The spectral width of an optical emission line is a source of valuable information about the radiating species. The analysis of the line width is complicated by the several processes that influence it. As some processes result in a Lorentzian line profile and some in a Gaussian profile, the analysis of the line profile type or the Lorentzian versus the Gaussian part can already give the first clue on the processes involved. This is determined by the part of line

1 broadening that affects every element present in the observed volume in the same way, called
2 homogeneous line broadening, and by inhomogeneous broadening arising from an average
3 effect that is different for each particle in the observed volume. In optical emission
4 spectroscopy, the dominant line broadening mechanisms are natural broadening, Doppler
5 broadening, resonance broadening, van der Waals broadening, and Stark broadening. For
6 more in-depth information and fundamentals, we refer the reader to publications [146,147,
7 184-187] and references therein. In the following, the information that can be obtained from
8 line broadening measurements is discussed.
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22 *3.4.1.1 Natural line broadening*

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24 Natural line broadening is a homogeneous line broadening mechanism. The broadening
25 is due to the finite lifetime τ of the excited state of the emitting species. This arises from the
26 Heisenberg uncertainty where uncertainty in the time domain results in an uncertainty of the
27 corresponding energy so that the energy transition is smeared over a range of contributing
28 energies. The line shape resulting from the homogeneous broadening is Lorentzian. As the
29 line broadening is very small, in the order of 10^{-4} , it can usually be neglected in the study of
30 N-APPJs.
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43 *3.4.1.2 Doppler broadening*

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45 This emission line broadening results from the Doppler effect, where the frequency
46 emitted from a moving particle is shifted during a transition depending on the velocity of the
47 emitting particle relative to the propagation of the radiation.
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54 The increase of the full width at half maximum (FWHM) of a Gaussian line Δv_{Dopp} due
55 to the Doppler broadening is [188]
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$$\Delta v_{Dopp} = 2v_0 \sqrt{\frac{2 \ln 2 k_B T}{mc^2}}, \quad (14)$$

where m is the mass of a moving particle, and T is the temperature.

3.4.1.3 Collisional broadening

At atmospheric pressure, most processes in plasmas are dominated by collisional processes. A collision process with an exciting particle effectively reduces the lifetime of the excited state resulting in a broadening of the emission line in the same way as the finite natural lifetime results in a broadening. The collisional broadening increases with the operating pressure. Because of the higher collision frequencies, the species are collisionally de-excited over much shorter time intervals.

For N-APPJs, whose gas temperatures are low, the broadening coefficient can be expressed as [188-190]:

$$\frac{\Delta v}{N} = K(J_G, J_R) \frac{r_e}{\pi} \sqrt{\frac{g_G}{g_R}} \frac{f_R}{\nu_R}, \quad (15)$$

where f_R and ν_R are the oscillator strength and the wavenumber of the resonant transition, g is the statistical weight of the ground (G) and resonant (R) states, respectively, whereas r_e is the classical electron radius. N is the absolute ground state density, $K(J_G, J_R)$ is a numerical coefficient of the order of 1, which depends on the total angular momentum of the ground state J_G and of the resonant state J_R . The line broadening can be expressed in terms of wavelength [190]:

$$\Delta \lambda = 9.3492 \times 10^{-14} \sqrt{\frac{g_G}{g_R}} \lambda_R f_R N, \quad (16)$$

where λ and λ_R are the wavelengths of the line under the observation and the resonant line, respectively, and $\Delta \lambda$ is expressed in units of cm.

3.4.1.4 Stark broadening

Stark broadening of optical emission lines can be used to determine electron densities in non-equilibrium atmospheric-pressure plasmas. This effect has extensively been discussed in literature [141,146,148,150,181,187,188,191-203].

Due to the available calculations, the hydrogen alpha and beta lines are most commonly used to determine the electron density in the 10^{14} – 10^{18} cm⁻³ range [195]. Furthermore, the H_β line is rather insensitive to temperature changes or the ion dynamic effect [196]. A calibrating expression for the full width at half maximum is [196]:

$$H_{\beta} = 4800 \text{ nm} \times \left(\frac{n_e}{10^{23} \text{ m}^{-3}} \right)^{0.68116} \quad (17)$$

Experimentally, the stark broadening contribution to the line broadening can be determined by de-convoluting the Voigt profile with the respective broadening contributions. The measurement procedures are described in [187].

The Gaussian contribution to the line profile is calculated according to

$$\Delta\lambda_{1/2}^G = \sqrt{\Delta\lambda_I^2 + \Delta\lambda_D^2} \quad , \quad (18)$$

where $\Delta\lambda_I$ is the instrumental profile and $\Delta\lambda_D$ is the contribution of the Doppler broadening according to equation (14). If the instrumental broadening dominates the Gaussian line shape, the Stark broadening can be neglected [197].

The Lorentzian contribution is calculated according to

$$\Delta\lambda_{1/2}^L = \Delta\lambda_v + \Delta\lambda_R + \Delta\lambda_S \quad (19)$$

where $\Delta\lambda_v$ is the van der Waals broadening profile width, $\Delta\lambda_R$ is the broadening due to resonance effects, and $\Delta\lambda_S$ is the Stark broadening.

The experimentally observed FWHM width is then:

$$\Delta\lambda_{exp} = 0.5\Delta\lambda_{1/2}^L + \sqrt{(0.5\Delta\lambda_{1/2}^L)^2 + (0.5\Delta\lambda_{1/2}^G)^2} \quad (20)$$

As equation (20) is only an approximation, it can be valid only for certain conditions. A decision scheme evaluating the validity of the FWHM approximation is given in [187].

1 It is worth emphasizing that in atmospheric-pressure plasmas the high gradients and small
2 dimensions can result in a line broadening that is due to averaging over more than one
3 electron density originating from different positions in the discharge [198]. Besides, Stark
4 broadening of emission lines has been used for atmospheric-pressure discharges also using Ar
5 emission lines [199].
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11 3.4.2 *Combination of optical emission spectroscopy and modelling*

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13 At electron densities of less than 10^{13} cm^{-3} Stark broadening is not a reliable method to
14 determine the electronic properties, as other broadening mechanisms dominate the line shape.
15
16 Next to using continuum radiation [187,204,205], another way to determine the electron
17 properties is the use of collisional radiative models (CRM). By relating the line ratios of the
18 selected emission lines to a CRM, the electronic properties can be determined [206]. This is
19 often applied in plasmas, where local thermal equilibrium can be assumed [207]. Again the
20 advantages over the competing techniques are the non-invasiveness and the high spatial
21 resolution (albeit line of sight constricted). For example, in the diagnostics of a low-pressure
22 non-equilibrium Ar discharge, the CRM includes kinetic processes determining the
23 population densities of the first four ($1s_{5-2}$ - Paschen notation) and next ten ($2p_{10-1}$ - Paschen
24 notation) excited levels, belonging to the $3p^5 4s$ and $3p^5 4p$ Ar level configurations,
25 respectively [208]. The approach has been extended to atmospheric pressure [202].
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46 In this approach, the ratio of the population of selected 2p levels strongly depends on
47 the electron density. With the Einstein coefficients for spontaneous emission, the population
48 is proportional to the optical emission of the respective line. By taking the ratio of the
49 coefficients corresponding to the two transitions, other constants are eliminated.
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55 A different approach of combining optical emission spectroscopy with modelling is
56 used e.g. in [209] to obtain the absolute values of the atomic oxygen densities. The
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diagnostics based modelling (DBM) was used to investigate a He rf atmospheric-pressure plasma jet. While two-photon laser induced spectroscopy yields reliable density results of atomic oxygen (see above), this technique is complex and requires access for the laser beam and the observation optics. The DBM combines one-dimensional numerical simulation based on fluid equations with kinetic treatment of the electrons [120,209,210].

The approach is based on actinometry, where two optical emission lines are compared in their intensities. One of the lines originates from the species that is investigated, while the other one originates from an actinometer species of the known (e.g., measured by other means) density. It is assumed that: 1) the excitation of the two emission lines is due to electron impact excitation from the ground state; and 2) primary decay is due to photon emission. The third assumption implies that: 3) the electron impact excitation cross sections of both transitions are similar in threshold and shape as a function of electron energy; in this case the line intensity ratio is proportional to the density ratio of the two species [211].

At atmospheric pressure, however, these assumptions are not always accurate. This applies to condition 2) because at atmospheric pressure, the rates of collisional de-excitation can be higher than the optical transition rates. Condition 3) is also questionable, as for the O($3p^3P$) and Ar($2p_1$) states observed in [209], the electron impact excitation thresholds have a difference of 2.5 eV. This difference can be expected to be significant at atmospheric pressure. This is why spatio-temporal characteristics deduced from modelling were used to obtain the time- and space-resolved electron dynamics. From this, the effective excitation rate coefficients for the observed transitions are determined and further used to derive the atomic oxygen density taking into account relevant processes including dissociative attachment [209].

3.4.3 Rotational and vibrational temperatures

1 A common method to evaluate the temperature of a discharge is to use molecular
2 emission. The use of rotational structures of vibrational bands of molecules is one of the
3 means to obtain such information. It can be applied in the cases, where the observed state is
4 produced by electron impact excitation from the ground state of the molecule and the
5 rotational temperature of the excited and observed state is in equilibrium with the rotational
6 temperature of the ground state. If this rotational temperature of the ground state is in
7 equilibrium with the gas temperature, the gas temperature can be determined. The specific
8 details of this method can be found elsewhere [[146,148,186](#)].

9
10 If the spectra are not completely resolved or the rotational temperature of the excited
11 state is only partially thermalized, a fit of a simulated spectrum can improve the accuracy and
12 validity of the experiment. In the latter case, a two-temperature fit can give a better
13 agreement of the simulation and the experiment [[214](#)].

31 **3.5 Optical absorption spectroscopy**

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33 The simplest and most direct way to determine the absolute species densities is
34 absorption spectroscopy. Compared to other techniques also described in this section, such as
35 optical emission spectroscopy, laser induced fluorescence spectroscopy or mass spectrometry
36 (see Sec. [3.6.1](#)), absorption spectroscopy is a calibration-free technique. Comprehensive
37 coverage of this diagnostic technique applied to atmospheric-pressure plasma jets can be
38 found elsewhere [[188](#)].

39
40 However, absorption spectroscopy has two significant disadvantages that have to be
41 overcome. First, the technique can only deliver line of sight densities and second, the
42 sensitivity of the absorption spectroscopy is lower compared to other techniques.
43 Nevertheless, there is plenty of information on the probed species and the environment of the
44 species that can be gained through the absorption spectroscopy. With higher sensitivity and

more stable light sources, the absorption spectroscopy becomes increasingly more relevant to the diagnostics of N-APPJs.

The absorption spectroscopy is based on the Beer-Lambert law, which describes the absorption of light by an absorbing medium. The wavelength-dependent intensity I_0 of the incident light is related to the density of an absorbing species distributed homogeneously along the light pathway on the length L by:

$$I(\lambda) = I_0(\lambda)e^{-N\sigma(\lambda)L} = I_0(\lambda)e^{-k(\lambda)L}, \quad (21)$$

where $I(\lambda)$ is the transmitted radiation, $\sigma(\lambda)$ represents the wavelength-dependent absorption cross-section, and $k(\lambda)$ is the wavelength-dependent absorption coefficient (see e.g. [188]).

From the absorbance A , the absorber density can be calculated:

$$A(\lambda) = -\ln\left(\frac{I}{I_0}\right) = N\sigma(\lambda)L \quad (22)$$

As the absorption features are usually spread over a wider range of wavelengths around the central wavelength and the line profile is influenced by broadening mechanisms as described above, the integrated absorption coefficient over an absorption line, k_λ , gives a more reliable measure of the absorbance [188]:

$$\frac{1}{L} \int_{-\infty}^{\infty} -\ln\left(\frac{I}{I_0}\right) d\lambda = \sigma_{int}N = k_\lambda = \int_{line} k(\lambda)d\lambda \quad (23)$$

where σ_{int} is the integrated cross-section and is defined as:

$$\sigma_{int} = \int_{-\infty}^{\infty} \sigma(\lambda)d\lambda \quad (24)$$

3.5.1. Ozone

Absorption spectroscopy is widely used for the study of atmospheric-pressure plasmas. Species with a large absorption cross-section in the UV are studied most frequently due to the experimental simplicity. One challenge, however, is the large number of competing processes with significant absorption in the UV spectral range [188, 215, 216].

1 In N-APPs operated in air, ozone (O_3) usually is one of the most abundant species with
2 the highest absorption cross section at around 250 nm. Thus, the simplest approach is to use a
3 mercury lamp with its dominant emission line at 254 nm at the central absorption wavelength
4 of the ozone Hartley bands. More complex measurements use other light sources such as in
5 [217,218], where the distribution of ozone was measured in a pulsed corona discharge array.
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12 Meanwhile ozone generation in plasma jets has been widely studied by UV absorption
13 spectroscopy (see e.g. [151, 188, 219].) Due to the strong overlap of absorption cross-sections
14 of different molecules and due to the possibility of photochemical reactions, it should be
15 cross checked, if the acquired signal actually originates from O_3 molecules [220]. The
16 necessity for Abel inversion to gain spatially resolved data as well as taking into account the
17 temperature makes the evaluation of the measurements more complex [221-226].
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29 3.5.2. *UV broadband absorption of OH density*

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31 The absorption cross-section of OH in the UV spectral range is relatively small [227,
32 228]. For that reason, OH absorption spectroscopy has to be extremely precise or other
33 measures have to be taken to ensure a high signal to noise ratio as for example by using
34 cavity ring down setups [229] (see also Sec.3.5.3), or by studying plasmas with a long plasma
35 region to gain a large absorption length such as a large N-APPJ [138] with sufficient
36 absorption length for determining OH [163]. Time-resolved OH measurements are also
37 possible using the resonant absorption spectroscopy [230]. The use of new devices such as
38 UV LEDs that have recently become available makes the absorption spectroscopy more
39 reliable. The properties of LED emission require a wavelength selection at the detector as is
40 usual for broadband detection. With this approach, other measurements such as LIF
41 measurements of OH can be calibrated [231,232].
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3.5.3. Cavity ring-down spectroscopy

In cavity-enhanced absorption spectroscopy, the light is guided into a cavity with two highly-reflective mirrors with a reflectivity of greater than 0.999. The light inside the cavity travels back and forth several hundred times, thus increasing the absorption length by several orders of magnitude. The exit mirror of the cavity has a slightly lower reflectivity allowing a minute fraction of the incident photons to exit the cavity. Cavity enhanced absorption spectroscopy incorporates several techniques [233] including cavity ring-down (CRD) spectroscopy. As described in a recent paper [234], when a light pulse enters the cavity, the signal at the exit of the cavity is therefore a decaying signal of the subsequent sequence of pulses each with a lower intensity than the previous one. The pulse peak values follow an exponential decay, which is dependent on the reflectivity of the cavity. The resulting decay time is characteristic for each cavity. When an absorbing medium is introduced into the cavity, this decay time is reduced further and the absorption coefficient can be determined. If the number of pulses is large, or the pulse duration is more than two times larger than the time to cross the cavity, the exit pulse peak values follow the continuous exponential decay function shown in **Error! Reference source not found..**

The intensity $I(t)$ can be described by [234]:

$$I(t) = I_0 \cdot e^{-\frac{c}{L}|\ln(R)|t} = I_0 e^{-\frac{t}{\tau_0}} \quad (25)$$

I_0 is the incident light intensity, L is the cavity length, R the reflectivity of the mirrors and c is a constant depending on the time a light beam takes to travel back and forth in a cavity of length L . Here, τ_0 characterizes the lifetime of a laser pulse in a cavity and depends on the transmission coefficient of the mirrors of the cavity without any absorbing medium. If an absorbing medium of length l is introduced into the cavity, the effective pulse lifetime is reduced and the absorber density N can be calculated by [234]:

$$N = 16\pi^2 \frac{\tau_{21}}{\lambda_{12}^2} \frac{w_1}{w_2} \frac{L}{l} \int \frac{1}{\lambda^2} \left(\frac{1}{\tau(\lambda)} - \frac{1}{\tau_0} \right) d\lambda \quad , \quad (26)$$

where τ_{21} is the lifetime of the excited state, λ_{12} is the wavelength of the resonance transition, and w_i the statistical weight of state i . The absorption line is then probed by measuring the wavelength-dependent lifetime $\tau(\lambda)$.

The CRD spectroscopy is not restricted to monochromatic laser light, but has been proven to work also with white non-coherent light [235]. Due to its excellent sensitivity, cavity-enhanced methods, especially cavity ring down spectroscopy have found broad application in diagnostics of low-pressure plasmas [236-238]. This technique is increasingly being used for the studies of N-APPJs [234, 239]. High time resolution and possible space resolution are advantages of the high-sensitivity method [146, 239].

3.6. Selected non-optical techniques

The multiphase systems of interest to plasma medicine sometimes require diagnostic techniques that do not rely on optical spectroscopy. For example, study of the interaction of plasmas with liquids necessitates the use of other diagnostic techniques [240]. In the following, the diagnostics of highly-soluble species such as ions, highly-reactive species such as radicals are introduced and the interactions of different states of matter within the fluid mechanics framework are described.

3.6.1. Mass spectrometry

Molecular beam mass spectrometry (MBMS) is a technique for diagnostics of plasma-jet-generated charged and neutral atomic and molecular species [241-245]. In MBMS, the probed species are usually sampled through a small orifice into a three-step differential pumping stage [241]. The second and third pumping stages are connected through skimmers, which select a particle beam to enter the ionizing chamber and the detector. The aim is to produce a collisionless particle beam that can be measured with mass spectrometry techniques.

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However, many processes disturb the ratio of the probed species composition and need to be considered. First, the orifice has to be small enough so that the plasma itself cannot enter the opening and generate further reactive species within the mass spectrometer. The size of the orifice is determined by the plasma sheath thickness so that at atmospheric pressure, the opening should be in the order of several tens of micrometers. Furthermore, the volume from which the species are sampled is stretched by the suction force of the vacuum pumps. Also collisions within the orifice with the walls or with the other particles disturb the particle composition. Within the orifice, the particles are accelerated and may form a Mach cone. In this case, the first skimmer should be placed within the “zone of silence” to sample the desired collisionless particle beam. If the background pressure is low enough, the particles’ mean free path is long enough that the second stage catches “collision-free” particles directly. Within the mass spectrometer, diffusion and velocity of the particles differ depending on the specific weight of the species. Especially in He discharges this has a large impact as the atomic weight of He differs strongly to that of molecular species such as nitrogen or oxygen.

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For these reasons, MBMS cannot deliver absolute or relative species densities without calibration. When this calibration is performed, e.g. by placing a chamber with a known species composition in front of the orifice, absolute concentrations can be measured.

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Neutral species are detected by ionizing the gas while varying the electron energy. The maximum ionization is usually observed at electron energy of 70 eV. These high electron energies not only ionize but also dissociate the gas, thus affecting the particle composition. An ion will therefore be accompanied by further ions resulting from dissociative ionization. This so-called cracking pattern is electron energy- and species-specific. At the known cracking pattern, the original species composition can be deduced as a superposition of the cracking patterns of each detected species (see, e.g. [172]).

This also explains why ions are easier to detect by MBMS. Indeed, plasma-generated ions do not need to be further ionized in the spectrometer and can thus be detected directly. The MBMS is operated with the ionizing chamber switched off and the ion lenses adjusted.

The third mode of detection is the so-called threshold ionization spectroscopy, where the ionizing electron energy is swept from zero to the maximum value and the spectrum is observed. Usually, a signal is expected at the ionization energy threshold of the detected species. The electrons will ionize the ground state particles. In the plasma, excited species are present. These species can be detected with threshold ionization spectroscopy, as they appear in the spectrum earlier than the ground-state species. This has been done for molecular nitrogen [245].

3.6.2. Flow visualization

While in low-pressure plasmas gas flow effects are not dominant processes, this is very different at atmospheric pressure. In plasma jets operated in ambient air, air species quickly diffuse into the effluent. In [243] an analytical solution for the diffusion equation has been developed, assuming that species diffusing in from the side of the jet nozzle predominantly reach a given point by moving along a straight line. By mapping the pathways of these species to a given flow field, diffusion patterns for arbitrary flow fields can be easily calculated. This path mapping approximation can be applied to analyze, e.g. absorption measurements [246] or to evaluate heat transport [222] or diffusion-based quenching of LIF signals [173]. However, as the situation is usually more complex and involves turbulence and plasma-flow interactions, reliable measurements of the flow parameters are required.

The simplest approach to determine the flow pattern is to use Schlieren diagnostics. The Schlieren diagnostics relies on the change in a light pathway induced by a change in refractive index. This can be induced either by changing the particle composition or by density changes, e.g. through temperature changes.

A Schlieren setup usually consists of a point light source (e.g., laser), collimated to a beam of parallel light, which is imaged onto a 2D detector. A knife-edge blocks the light that passes through the focal point. When the light is deflected by changes in refraction as for example by a plasma jet, this deflected light will appear on the detector. A background-subtracted image will show the change in optical density and can be used to determine particle density or gas temperature. For plasma Schlieren measurements, green light is recommended, as N-APPJs emit little light in this spectral range [247-249]. In addition, shadowgraphy and ICCD imaging can also be used to determine the energy dissipation processes in a plasma jet's effluent [250]. Finally, in order to determine the flow field with the velocity vectors, particle imaging velocimetry (PIV) has been employed [251].

While Schlieren images are line of sight images, they can nevertheless reveal important information about the plasma discharges. This can be improved further by using high-precision tomography techniques.

3.6.3. *Electron paramagnetic resonance spectroscopy*

Electron paramagnetic resonance spectroscopy (EPR), also called electron spin resonance (ESR) spectroscopy has been used for the detection of radicals generated by N-APPJs. EPR spectroscopy determines the splitting of degenerate energy levels into several sublevels within a magnetic field due to the Zeeman effect. The resulting spectra are characteristic for each radical. In a magnetic field, the electron's magnetic moment m_s can align itself either parallel or anti-parallel to the field. The magnetic moment is then $m_s=1/2$ for parallel and $m_s = -1/2$ for anti-parallel alignment each having different energy calculated by:

$$E = m_s g_e \mu_B B_0 \quad , \quad (27)$$

1 where g_e is the Landé factor linking the magnetic moment of the electron to the spin angular
2 momentum quantum number (2.0023 for a free electron), $\mu_B = e\hbar/2m_e$ is the Bohr magneton
3 and B_0 is the magnetic field. For the two states of parallel and anti-parallel alignment of the
4 electron's magnetic moment, the energy difference of the two resulting energy states is
5 proportional to the applied magnetic field according to $\Delta E = g_e \mu_B B_0$. In EPR spectroscopy, the
6 magnetic field matches the criterion for resonance energy, an absorption line is observed.
7 EPR spectroscopy is a well-known surface characterisation technique (see e.g. [252-256])
8 and has recently been used for diagnostics of plasma discharges of relevance to applications
9 in plasma health care and medicine [257-261].

21 Detecting transient species in liquids requires further care, as radicals such as OH have
22 a low lifetime and diagnostics rarely can be performed *in situ*, but requires liquid handling
23 steps until measurements can be started. A technique called spin-trapping has been developed
24 [262-264]. In this technique, nitroso or nitron compounds form a relatively stable spin
25 adduct, which is paramagnetic and thus EPR active. This technique stabilizes radicals with a
26 typical lifetime of μs to lifetimes of the spin adduct of minutes to hours, which is sufficient to
27 perform EPR studies *ex situ*.

38 The experimental procedure is to add the spin trap before or after the plasma treatment
39 to the plasma treated medium, place the medium after the plasma treatment in a glass cuvette,
40 which is inserted into the resonator of the EPR spectrometer [265]. The choice of the
41 appropriate spin trap is essential for the quality of the measurements as it drastically reduces
42 background noise and spurious signals [266, 267].

50 Not only the spin trap but also the used liquid strongly influence the measurement
51 results [267]. However, the possible effect of the liquid medium may be more directly related
52 to the prevailing reaction kinetic processes rather than EPR excitation. Enzymatic activation
53 can help verify the results [268]. As a remote technique, EPR can determine the effect of the

1 plasma jet generated VUV radiation on radical generation in a small enclosed volume of
2 liquid [269].
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4 The following section will show specific examples of application of the above
5 discussed diagnostic techniques to measure the plasma properties and densities of the key
6 reactive species in N-APPJ plasma discharges.
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10 **4. Temporal and spatial behaviour of key reactive species**

11 The specific focus of this section is on the spatial distributions and temporal dynamics
12 of densities of the key reactive species of particular interest for plasma medicine applications.
13 The discussion starts with the lightest species – electrons, followed by oxygen atoms, OH
14 radicals, ozone, other reactive oxygen species, atomic nitrogen, nitric oxide, and concludes
15 with metastable nitrogen, He and Ar species. These species have diverse roles in sustaining
16 chemical reactivity of the N-APPJ discharges, plasma activated media, interactions with
17 biological material, as well as in numerous biological processes. Relevant examples will be
18 presented in [Sec. 6 and 7](#).
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38 **4.1. Electrons**

39 For plasmas generated by electric excitation, the energy is first coupled to electrons.
40 Then the electrons transfer some of their energy to atomic, molecular and radical species (for
41 simplicity also collectively termed heavy particles) through collisions, which results in
42 further ionization, dissociation, excitation, and other elementary processes.
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50 Electron density is one of the most important parameters of any plasma. However, only
51 a few measurements of the electron density of non-equilibrium atmospheric-pressure plasma
52 jets have been carried out. This is due to the lack of reliable electron density diagnostic
53 methods for non-equilibrium atmospheric-pressure plasmas. In addition, N-APPJs normally
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1 have relatively small dimensions (diameter in mm range) and their electron densities are
2 relatively low, which makes the measurements even more difficult [270].
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4 Recently, a new technique by using the Rayleigh microwave scattering (RMS) to
5 measure the electron density of a plasma jet has been reported [271]. Figure 14 shows the
6 schematics of the RMS experimental setup and the experimental results. The plasma jet was
7 driven by a kHz AC power supply. The plasma plume was produced in He flowing through
8 the Pyrex syringe equipped with a pair of high-voltage electrodes. Figure 15 shows that the
9 electron density reaches about $(5-10) \times 10^{13} \text{ cm}^{-3}$ after the discharge initiation and then
10 decays within a characteristic time of a few microseconds. It needs to be pointed out that the
11 measured electron density corresponds to the value averaged along the entire plasma column
12 from the syringe exit. In other words, the spatial resolution of this measurement is low.
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26 Since the cross-section of N-APPJs is usually small, to better understand the plasma
27 behavior, high spatial resolution of the electron density distribution measurement is required.
28 A spatially resolved method for measuring the local densities and temperature of the plasma
29 by using laser scattering has recently been reported [178].
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36 The plasma jet is driven by a 2.45 GHz microwave source (surfatron) in a ceramic tube
37 with an inner diameter of 0.8 mm. Ar is used as a working gas with a flow rate of 1.0 L/min.
38 Figure 16 shows the radial profiles of the electron temperature and electron density with a
39 spatial resolution of 50 μm . The electron density reaches the order of magnitude of $10^{13} -$
40 10^{14} cm^{-3} . It is worth pointing out that the electron density decreases toward the edge, while
41 the electron temperature shows the opposite trend.
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51 Furthermore, Fig.17 shows the radial profiles of the electron density at different axial
52 positions. The maximum electron density in the axial direction is found at about 2 mm from
53 the tube end. We emphasize that the lowest electron density at which pure Thomson
54 scattering can be applied in these types of atmospheric plasmas is about $5 \times 10^{18} \text{ m}^{-3}$. The gas
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temperature of the plasma measured by Rayleigh scattering reaches as high as 600 K.

Another method that can provide the electron density measurements with high spatial resolution has been applied recently [272]. This method relies on using CO₂-laser heterodyne interferometry at the 10.6 μm wavelength. In this N-APPJ device, He gas was fed into the inlet of the micro-hollow cathode and effused out of the anode hole at a flow rate of 6 L/min. A pulsed DC power supply was used to excite the plasma. The power supply provided repetitive positive pulses with the amplitude up to 1.2 kV and the pulse width 400-500 μs.

Figure 18 shows the measured electron density [272]. The peak value of the electron density of the plasma jet exceeds $2 \times 10^{14} \text{ cm}^{-3}$. This diagnostic technique has a sensitivity of about 10^{13} cm^{-3} (at an optical length of 1 mm) and a spatial resolution better than 100 μm. It is worth noting that in CO₂-laser heterodyne interferometry a large contribution of heavy particles (atoms or molecules) to the change in the refractive index is expected due to Joule heating of the operating gas. Hence, this contribution must be separated from the signal to accurately measure the electron density. It should be pointed out that the electron density of N-APPJs decreases quickly after the plasma bullets disappear. In other words, all the electron density measurements must also have high temporal resolution.

Besides the experimental measurements, the electron density of N-APPJs can also be obtained by using numerical modeling. Several groups reported the numerical modeling results of the electron density of N-APPJs to be of the order of $10^{11} - 10^{13} \text{ cm}^{-3}$ depending on the experimental conditions and specific point of calculation [37,39,40,54,273].

4.2 O atoms

Noble gases represent a popular choice among the commonly used working/carrying gases for most of the plasma jet devices. On the other hand, in order to achieve the desired

effect for various applications, admixture of O₂/air is normally used to obtain reactive oxygen species (ROS).

Due to the diffusion of the ambient air, the generation of reactive oxygen species in the plasma jet device can be significantly affected. In general, there are two ways to eliminate the diffusion of the ambient air. The first method is placing the plasma jet in a container, which is filled with a purified gas rather than air. This approach would diminish the main advantage of the plasma jets to operate in open air. The second method is using a shielding gas to insulate the working gas from the ambient air. This is why the focus in this section will be on the effect of admixture O₂/air and the diffusion effect of the ambient air on the O atom concentration.

4.2.1 Effect of admixture of O₂/air on O concentration

It is believed that, in a noble gas, the electron energy distribution function (EEDF) is not significantly changed for small admixtures of molecules. Thus, the dissociation increases with an increasing amount of O₂ in the plasma. But for large concentrations of molecules, significant energy losses due to rotational and vibrational molecular excitations and the electron attachment to the molecules are inevitable. These losses change the EEDF and reduce the amount of the energy which can be used for the dissociation. Consequently, at a certain critical molecular concentration, the dissociation degree of the plasma may decrease. This prediction is confirmed experimentally [274] as shown in Fig.19. The O atom density increases with a steep slope from the detection limit (about $2 \times 10^{12} \text{ cm}^{-3}$) at 0.2% of O₂ to $1.4 \times 10^{14} \text{ cm}^{-3}$ at about 0.6% O₂ admixture. Beyond this value, the density slowly decreases to $5 \times 10^{13} \text{ cm}^{-3}$ at 1.8% O₂ admixture.

Figure 20 shows the spatial distribution of O atoms in the effluent of the plasma jet. It shows that the highest O atom density is achieved close to the nozzle. At a distance of

1 approximately 10 mm on the z-axis the density still has a value of 10^{14} cm^{-3} and further
2 decreases to a few 10^{13} cm^{-3} at the 65 mm distance [274,275].
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4 A microwave plasma jet usually delivers more power to the plasma plumes than a
5 typical plasma plume driven by kHz AC voltages, which results in a higher gas temperature
6 and a higher O atom concentration. Figure 21 shows the TALIF measurements of the O atom
7 concentrations for He mixed with different air concentrations with microwave power of 30W
8 [276]. Next to the nozzle, the O atom concentration is the highest when three to six percent of
9 air is added. At the distance of more than 5 mm away from the nozzle, the O atom
10 concentration is the highest when about one percent of air is added. This difference could be
11 due to the diffusion of ambient air because more air is diffused into the plasma plume at
12 longer distances from the nozzle.
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26 It is worth pointing out that the O concentration of the microwave plasma jet is more
27 than two orders of magnitude higher compared to the RF jet discussed above. One of the
28 reasons is because the gas temperature of the plasma is about 1200 K, while the gas
29 temperature of the RF jet is slightly above 300 K. Moreover, the total O atom density might
30 be even higher than the measured one because TALIF only measures the O atom ground state
31 density, while the excited states and metastables of O are not detected, which could be
32 significant since the gas temperature is so high.
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45 4.2.2 *Effect of diffusion of shielding gas on O production*

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48 When a plasma jet propagates in ambient air, the diffusion of the ambient air will affect
49 the reactive species generation. There are two ways to control the diffusion of the ambient air
50 [277-282]. One way is by placing the plasma jet inside a sealed container, which is filled with
51 the desired gas. Another way is by adding a shielding gas, which forms a “curtain” flow
52 around the effluent of the plasma jet, shielding it from the ambient air.
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Figure 22 shows the O LIF signal maps in a RF plasma jet where the plasma jet propagates inside a container filled with air or Ar [277]. It shows that, when the container is filled with Ar, the zone of O generation is longer along the discharge axis than in ambient air. However, a higher maximum intensity of the TALIF signal is observed in ambient air, which is almost three times higher than inside the chamber filled with Ar. Thus, air diffusion into the discharge plays an important role in the production of active species and leads to an increase in their concentration in the discharge core.

A schematic of a typical experimental setup for a plasma jet with the shielding gas is shown in Fig.23 [282]. Several gases such as Ar, N₂, or O₂ could act as a shielding gas. This gas “curtain” protects the plasma jet effluent from diffusion of air species, and also allows controlling the effluent reactive species composition by adjusting the mixture of the shielding gas. One example is shown in Fig.24, when O₂ is used as the shielding gas, the emission of the second positive system of N₂ is below the detection limit, but the emission intensity of O atoms is the highest.

The shielding gas may also affect the concentration of biologically relevant reactive species in liquid solutions. An example related to the concentrations of nitrite and nitrate which play specific roles in the treatment of biological samples is presented in Fig.25 [143]. Without any shielding during the plasma treatment, a concentration of 168-nM nitrite and 161-nM nitrate in the liquid is observed. With nitrogen shielding gas, lower concentrations of plasma-generated nitrate and nitrite are measured. They are 82-nM (NO₂⁻) and 75-nM (NO₃⁻), respectively, which is less than a half of the concentrations under no shielding conditions.

Furthermore, when oxygen is used as shielding gas, the formation of nitrite can be almost prevented (9 nM), while nitrate shows a low concentration of only 20 nM. Thus the gas “curtain” can be used to control the concentration of reactive nitrogen species. In addition, cell viability experiments show that with the increase of O₂ fraction in the shielding gas, the

1 NO_2^- production decreases, and so does the cell viability. It is thus likely that NO_2^- does not
2 play the main role in the cell viability in this case [113,143].
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7 **4.3 OH radicals**

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9 The concentration of OH radicals generated in pulsed discharges in water, in
10 combustion and other processes has been studied by many research groups. Although there
11 are some investigations on the effect of different process parameters on OH concentration in
12 the plasma jets, these studies are far from being complete. This is why the results of related
13 studies, such as dielectric barrier discharges (DBDs) in a discharge gap, will be discussed in
14 this section as well. These discharges produce quite similar types of plasma species and thus
15 could help understanding the processes in the plasma jets of our primary focus here.
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27 *4.3.1 Effect of H_2O admixture on OH concentration*

28 Figure 26 shows the variation of the OH density at 1 mm from the nozzle of the plasma
29 jet (kINPen) with the concentration of the water added to Ar [166]. The position close to the
30 nozzle is chosen to minimize the effect of the air admixture on the Ar effluent. One can
31 see that the OH density levels off in the range 6500–26000 ppm. This value is similar for
32 atomic O density in He– O_2 RF plasmas discussed in Sec.4.2.1, where O atom density
33 reaches its maximum value when 0.6% molecular oxygen admixture is added [274]. The
34 explanation of this phenomenon involves the effect of the electron energy distribution
35 function (EEDF), which is quite similar to the discussion in the O atom case.
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51 *4.3.2 Effect of gas flow on OH concentration*

52 The gas flow affects the OH concentration in two ways. On one hand, the gas flow has
53 a significant effect on the air diffusion into the working gas stream. Because of humidity of
54 ambient air, it will further affect the H_2O distribution and thus the OH distribution of the
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1 plasma jet device. On the other hand, because of the relatively long lifetime of OH species,
2 the gas flow could also affect the OH distribution. Figure 27 shows the mole fraction of air in
3 the Ar working gas stream of a RF plasma jet [283]. It can be clearly seen that the higher is
4 the flow rate, the longer is the Ar gas stream with the low air fraction. However, when the gas
5 flow is increased to 4 L/min, the gas flow changes from the laminar to the turbulent mode and
6 the length of the Ar gas stream with the low air fraction decreases significantly.

14 Figure 28 shows that the measured OH distribution has a similar appearance to the
15 distribution shown in Fig.27 [283]. It needs to be pointed out that a part of the tubing for
16 supplying Ar gas is made of silicone, which could release a significant amount of H₂O
17 (hundreds ppm) to the working gas during the discharge. This is the reason why the OH
18 concentration at the nozzle of the plasma jet is very high. Furthermore, the gas temperature of
19 this plasma jet is much higher than room temperature. It varies from 400 to 900 K depending
20 on the gas flow rate and the electric power.

31 In applications, plasma jets usually face an object (e.g., a piece of biological or non-
32 biological material) placed in front of the plasma plume. Figure 29 shows the radial
33 distribution of the OH density when a glass plate is placed at 10 mm away from the nozzle
34 for different He flow rates. The position of the OH maximum density moves outwards as the
35 He flow rate increases. This is because the He flow rate affects the surrounding gas diffusion
36 and hence the propagation of the plasma bullet. It has been reported that OH density
37 distribution is at its maximum on the outer surface of the He plasma jet, corresponding to the
38 propagation of the doughnut-shaped plasma bullet [285].

51 This is different from the results presented in Fig.29 where the OH density has a peak
52 on the center axis of the plasma jet at low He flow rates. This could be due to the difference
53 of the gas flow dynamics. In [285], the inner diameter of the quartz tube is 2 mm and the He
54 flow rate of 2–4 L/min is used, while in [284] the quartz tube has an inner diameter of 4 mm

and the He flow rate is only 1.5 L/min. Thus the He flow velocity at the quartz nozzle in [284] is about 10 times lower compared to [285]. Due to the high flow velocity in the latter case, ambient air could not diffuse into the center of the effluent region. Thus the ionization rate in the center is lower than away from the center. As a result, the plasma bullet has a ring shape because the air impurity is too low in the center [55]. On the other hand, the plasma jet has a low flow velocity which allows the ambient air to diffuse deep into the He effluent. As a result, the plasma bullet with the ball-like shape has the spherical shape OH distribution [284].

Figure 30 shows the concentration of OH species as a function of Ar flow rate of another RF plasma jet. At low flow rates, Ar is quickly diluted by ambient air which prevents the discharge from elongation outside the quartz capillary. Therefore, at low Ar flow rates the active discharge did not reach the measurement point and the OH concentration in the effluent was low. The increase in Ar flow results in a sharp increase in OH concentration.

This can be explained as follows [167]. When the RF power delivered to the plasma was 80 W, the visible active discharge reached the measurement point when the flow rate was approximately 0.3 L/min. Then, the OH concentration reached its maximum at the Ar flow of 0.4 L/min. A further increase in the Ar flow rates led to a decrease in OH species concentration. Since the RF power delivered to the discharge was constant during the whole experiment, the decrease in OH concentration can be explained by the fact that the discharge elongation caused by an increase in Ar flow rate led to a decrease in the power density along the discharge length.

4.3.3 Effect of O_2 on OH production

Since no results on the effect of O_2 on OH generation in a plasma jet have been reported, the effect of O_2 on OH generation in other types of N-APPs will be discussed below. In an Ar DBD, it was found that the OH density increases when the O_2 concentration

increases as shown in Fig.31. The OH density peaks at 3% O₂, and decreases with further O₂ addition. The decrease in OH is attributed to O₂ being an attaching gas (and thus an increased loss of electrons at higher oxygen concentrations), and to destruction of OH by ozone: OH + O₃ → HO₂ + O₂. Numerical modeling studies of the reactive species chemistry of an RF driven capacitively coupled glow discharges also show that small additions of O₂ to He - H₂O gas mixture increase the OH production [287,288].

Similarly, Fig.32 shows the time-resolved OH density for different O₂ admixtures in a 2 mm gap discharge between the pin-to-pin electrodes. When O₂ is added, about one order of magnitude higher OH density is observed at 100 μs. The OH density reaches its maximum when the added O₂ concentration is around 0.1%, which is about the same as the concentration of H₂O.

In the early afterglow, the OH density shows similar trends to the case when no O₂ is added. In the late afterglow, however, a substantial increase of OH concentration is observed when O₂ is added. The time-resolved OH density is simulated with a zero-dimensional model [289]. It is found that OH is strongly quenched by O (through the reaction which creates H and O₂: OH + O → O₂ + H). This causes a temporary reduction in the destruction of OH. On the other hand, the H atoms lead to the production of HO₂ and H₂O₂ species. The reactions of H and O with HO₂ are important production mechanisms of OH. After tens of μs, a significant amount of OH radicals is generated through H + HO₂ → OH + OH and O + HO₂ → OH + O₂, this is consistent with the results shown in Fig. 32. However, Fig.33 shows a sudden decrease of the OH density at low O₂ addition for all H₂O concentrations investigated, which contrasts with the trend discussed above. The difference of these observations could be due to the excitation sources used and, consequently, the resulting EEDF. The results shown in Fig. 32 are produced by applying a nanosecond pulse voltage while in Fig. 33, a kHz AC voltage is used.

4.3.4 *Effect of the treated samples on OH concentration*

In the field of biomedical applications, many publications report on the strong potential of N-APPJs for cell behavior modifications in cancer treatment, wound healing or sterilization. However, plasma jet characterizations are typically performed when the jets expand freely in air. Only recently the influence of the targeted surfaces has been considered [158, 291-295].

When a plasma jet is used to treat biological samples, such as mammalian cells or bacteria, the cells are covered by a thin layer of liquid or are on agar media. The water in the liquid or agar media will affect the plasma environment and thus the generation of OH. This in turn could result in a significant difference of OH concentration and distribution.

When human skin treatment is aimed, the skin conductivity among different people and across different areas of the body of the same person could be different. For example, the conductivity of a dry skin could be significantly different from a wet skin. Thus, when a plasma jet is used to treat a human being, the human being is a part of the discharge circuit, which in turn affects the discharge behaviour and the OH concentration. When liquid solution is used to simulate a human being with the similar conductivity, the OH distribution can also be very different because of the differences of the roughness of the skin surface. Furthermore, even for the same treatment surface, when other parameters, such as the gas flow rate and the amplitude of the applied voltage are different, the OH distribution could also be different.

Therefore, in this section, these effects, including the humidity, conductivity, and roughness of the treatment surface on the OH distribution will be discussed. Besides, for the same treatment surface, the gas flow rate and the amplitude of the applied voltage on the OH distribution for the same treatment surface will also be presented.

4.3.4.1. *Effect of humidity of the treated samples on OH distribution*

To study the effect of humidity of the treated sample on the OH generation in dry-air plasmas, firstly, humidity distribution of the gas stream is measured based on the decay of NO LIF signals. Figure 34 shows that a low-humidity region is formed near the nozzle while a high-humidity region is formed near the water/agar surface. The thickness of the low-humidity region reduces with increasing the gas flow rate for both surfaces. It is 0.1–0.5 mm for the flow rates above 0.3 L/min. It also shows that the water evaporation from the agar medium is slightly less than from the water. Humidity at 0.1 mm distance from the agar medium surface is approximately 70% of the humidity level measured at the same distance above the water surface. This indicates that water evaporation should be considered even when agar medium is used.

When a nanosecond pulsed high voltage is applied to the device the plasma is generated between the nozzle and the water/agar surface. The OH generated by the plasma is measured by LIF. Figure 35 shows the distribution of OH emission. When the flow rate increases, the N₂(C) emission increases, whereas the OH density decreases. These observations indicate that the decrease in OH density at higher flow rates is due to the lower humidity rather than a weaker discharge. One should note that the inner diameter of the nozzle is 4 mm and the gas flow rate is only 0.3 L/min, thus the gas flow velocity of the above experiment is much lower compared to the works by other authors. Thus, the humidity of the gas in many plasma jets could be much lower than in the above examples.

4.3.4.2. Effect of sample conductivity on OH distribution

To investigate the effect of conductivity of the treated samples on the distribution of OH species, distilled and saline water were used to study the extreme cases of low and high electrical conductivity (σ), respectively. A correlation between the shape of the photographs and OH distribution in the maps are shown in Fig.36. The optical emission of such plasmas is

dominated by N_2 [4], which is significantly different from the distribution of OH radicals. As can be seen in Fig.36(a), a high peak of the OH density of $1.7 \times 10^{14} \text{ cm}^{-3}$ corresponds to the diffuse conical shape emission close to the target surface. On the contrary, with higher-conductivity solutions, more OH radicals are found closer to the target (see Fig.36(b)). Comparison of OH distributions and the maximum densities $[OH]_{\max} \sim 9 \times 10^{13} \text{ cm}^{-3}$ and $\sim 1.7 \times 10^{14} \text{ cm}^{-3}$ for saline and distilled water solutions, respectively, suggests that the target conductivity has to be taken into account to calculate the OH production rate. The high OH concentration on the liquid surface is believed to be due to the secondary plasma discharge [158].

For comparison, Fig.37 shows the results for the case of the free (unobstructed) propagation of the plasma jet. It is noticed that the OH density is very high close to the nozzle side rather than on the sample surface in the case discussed above. As shown in Fig.37(d), the intensity of He^* emission decreases gradually along the axis while more air/ H_2O is diffused into the He flow stream as shown in Fig.37(b) and (c). In the downstream (from $z = 8$), where the air proportion is much higher, the He^* emission is much weaker. A comparison of (a) and (d) suggests that there exists an optimum proportion of water vapor to produce OH radicals.

In addition, the treatment object conductivity could also affect the discharge behavior, which further affects the gas dynamics, thus the H_2O distribution. The observation shown in Fig.38 confirms the assumption. For distilled water, H_2O does not penetrate into the propagation channel except in the vicinity of the surface where around 25% of the water vapor is concentrated. This is consistent with the results of OH measurements, where the maximum OH density is achieved in the region where humid air mixes with the He flow. For the higher conductivity solution, however, some H_2O can be observed inside the channel from $z = 8 \text{ mm}$. More interestingly, the surfaces representing the specific values of OH densities appear to be disturbed in the impinging plasma zone. This results in a larger H_2O

fraction (at $x = 0$) which increases from 15% at $z = 8$ mm to 25% at $z = 11$ mm. These values are consistent with the previously determined H_2O percentage needed for the optimum OH radical production.

4.3.4.3. Effect of the amplitude of the applied voltage on OH distribution

Figures 39 and 40 show the distribution of OH species for the amplitudes of the applied voltage of 14 kV and 10 kV, respectively [158]. A conducting grounded target was placed at $z = 12$ mm. Firstly, Fig. 39 reveals that the OH density is around $1 \times 10^{13} \text{ cm}^{-3}$ at the tube outlet and increases to about 10^{14} cm^{-3} around 7 to 10 mm downstream. Investigation of the air distribution (Fig.39(b)) reveals the channeling of the He flow which covers the entire 12 mm gap as compared to the free jet case. On the other hand, when the applied voltage is reduced to 10 kV, a spatial shift of the OH maximum density can be observed toward the target. The possibility to maximize OH production in the vicinity of the target suggests that a voltage of 10 kV (rather than, e.g. 14 kV) is most appropriate for biomedical applications that rely on biological effects of reactive OH species.

4.3.4.4. The effect of gas flow on OH distribution

Since the gas flow could affect the surrounding gas diffusion, it could also affect the contribution of water from the target surface. Figure 41 shows the results for He flow rate of 2 L/min instead of 1 L/min [158]. Under such conditions, air and water vapor almost do not penetrate into the He channel. Thus, mainly impurities contained in the buffer gas contribute to the OH radical production. As seen in Fig.41(b,c), the He flow pushes all other gases away from the propagation axis when the air proportion is between 0.5 and 4% while the H_2O fraction is between 1 and 10%. The maximum of 10% of H_2O (around 1400 ppm compared to 3 ppm in the buffer gas) which is measured at $x = 0$ mm along the gap implies that some water is coming from gas pipes. The production of OH radicals in the vicinity of the target

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$([\text{OH}]_{\text{max}} \sim 4 \times 10^{13} \text{ cm}^{-3})$ is much weaker than at the 1 L/min gas flow rate ($[\text{OH}]_{\text{max}} \sim 2 \times 10^{14} \text{ cm}^{-3}$). This observation could be due to the fact that the optimum H_2O proportion is not reached.

4.3.4.5. *Effect of the surface characteristics on OH distribution*

In the following, the effects of three different types of treatment samples on OH distribution are discussed. The three types of samples are a glass plate as a dry surface, a melamine sponge with the absorbed distilled water as a wet surface and rat skin as a biological surface. To maintain the appropriate humidity level on the rat skin, a melamine sponge containing the absorbed phosphate buffered saline (PBS) is placed under the rat skin.

Figures 42 and 43 show the two-dimensional distribution of the air mixture ratio and OH in the plasma jet [284]. It can be seen from Fig.42 that there is a high-concentration He channel along the axis between the nozzle and the glass surface. It is seen in Fig.43 that the radial distribution of OH density shows a maximum on the center axis of the plasma jet; the axial distribution shows two peaks at the quartz tube nozzle and on the glass surface. Besides, the two-dimensional distribution of OH density shown in Fig.43 suggests that there are two OH production regions, namely upstream in the quartz tube and downstream near/on the surface. In the upper stream, most of OH radicals are produced through the dissociation of water vapor contained in the He gas flow in the quartz tube, whereas in the lower stream the OH radicals are generated through the dissociation of water vapor molecules contained in the ambient air diffused into the effluent and water vapor from the surface.

Figure 44 shows the OH density distribution on the three surfaces. From Fig.44, it is seen that OH density on the surface increases depending on the humidity level of the surface. The maximum OH density on the wet surface is $2.0 \times 10^{13} \text{ cm}^{-3}$ at the center of the plasma jet, which is two times higher than on the rat skin and three times higher compared to the dry

surface.

These results also indicate that the amount of ROS surface loss depends on the surface conditions characterized by the roughness and the surface area [284]. When a rough surface such as rat skin is used, the surface has a larger surface area than the glass surface or the sponge surface. Consequently, on the rat skin, the rates of OH and O radical surface loss become higher than on the sponge surface, resulting in a slight difference in their density distribution.

4.3.5 Effect of the surrounding gas on OH production

In order to better understand the effect of air diffusion, Fig. 45 and 46 show the results of two-dimensional mapping of the LIF signals in open air and in the Ar-filled chamber, respectively [277]. In the case of air as ambient gas, the LIF signal is concentrated in the vicinity of the central streamline, with a discharge diameter around 1.5 mm. On the other hand, the discharge in ambient Ar is approximately two times wider, with a diameter of 3.0 mm at a low water concentration. The maximum intensity of the OH LIF signal is approximately two times higher in the plasma operated in open air than in the chamber filled with Ar. It is observed that the maximum of the OH density is located at a distance of about 2 mm from the nozzle in ambient air [277].

The main mechanisms of OH production in this region in the Ar plasma with small addition of H₂O are electron impact reaction $e + H_2O \rightarrow OH + H + e$ and reactions with Ar metastables $Ar^m + H_2O \rightarrow OH + H + Ar$ [293,294]. For the region with a low electron temperature, the water ion dissociative recombination $e + H_2O^+ \rightarrow OH + H$ can also play an important role in the production of OH radicals [295].

4.4 Ozone

Ozone (O_3) is a reactive oxidant and has many industrial and consumer applications. Its high oxidizing potential can cause damage to mucous and respiratory tissues in animals, and also tissues in plants, at concentrations of about 100 ppb and above. This makes ozone a potential respiratory hazard and pollutant. Ozone is detectable by many people at concentrations of as little as 10 ppb in air. Ozone is widely used for killing microorganisms in air and water sources. Many urban potable water systems kill bacteria using ozone instead of the more common chlorine. Ozone has a very high oxidation potential, does not form organochlorine compounds, and does not leave residues in the water after the treatment. Once it has decayed, it leaves no taste or odor in drinking water.

A plasma jet can also generate O_3 when a small amount of O_2 is added to the working gas or when the ambient gas is the surrounding air. O_3 concentration can be reliably measured by UV absorption spectroscopy because it has very large UV absorption cross-section, which is about $1.15 \times 10^{-17} \text{ cm}^2$ measured at 254 nm UV excitation wavelength and a gas temperature of 295 K. A number of measurements of O_3 concentration have been conducted in atmospheric-pressure non-equilibrium plasmas including corona and DBD discharges. However, detailed studies on ozone generation by plasma jets are presently limited [125,151,219,221,296].

Figure 47 shows the spatially resolved absorption profile of ozone molecules in the pulsed RF plasma jet device [221]. The distribution of the ozone density features two distinctively different zones. In the zone close to the nozzle, the peak density of ozone is located in the ionizing plasma approximately 1 mm off the axis. In the second zone further downstream and outside the ionizing plasma, the maximum density of ozone is on the axis of symmetry. The maximum density of O_3 is $2.1 \times 10^{15} \text{ cm}^{-3}$ is measured at the axial position $z =$

13 mm from the nozzle.

This observation can be better understood by carrying the spatially-resolved gas temperature measurements (Fig.48) [221]. A comparison of the results presented in Figs. 47 and 48 reveals a clear correlation between the gas temperature and the ozone density. In the hot plasma region, the ozone density is lower compared with the colder effluent and the radial edges of the plasma plume, where the gas temperature is lower than at the axis of symmetry. This is because the ozone generation and destruction processes strongly depend on the background temperature. In the core of the plasma, the O₃ molecules are produced from O and O₂ species through three-body reactions. In the effluent downstream, where the O density is significantly reduced, O₃ is produced less efficiently and the destruction of ozone molecules is due to long-lived species such as NO and O₂.

Interestingly, in the experiments [221] the gas temperature was reported to be much higher than in many other plasma jet devices, while the ozone generation is strongly temperature dependent. Consequently, the spatial distribution of the ozone molecules in other plasma jet devices could be significantly different from the case discussed above.

4.5 Singlet delta oxygen (O₂(¹Δ_g)) species

Singlet delta oxygen (SDO, O₂(¹Δ_g)) is another important ROS with the excitation energy of 0.98 eV. SDO's most remarkable feature is its extremely long radiative lifetime of above 75 min in the gas phase [297]. SDO is a highly-reactive molecule which plays major roles in numerous biophysical and biochemical processes in diverse biological systems [298,299], as well as in gas and liquid chemistry. SDO not only produces oxidative damage in many biological targets [300,301] but is also a primary active species in the selective killing of tumor cells in the emerging cancer therapy [302-304].

1 N-APPJ plasmas can also generate SDO species. However, reliable measurement of the
2 SDO concentration is a significant challenge. Infrared emission at a wavelength of 1.27 μm is
3 one of the footprints indicative of the SDO's presence. This emission can be used for
4 measuring the SDO concentration. But the intensity of the measured signals is very weak
5 because the radiative transition is forbidden for the electric dipole emission whereas only
6 magnetic dipole radiation is possible [305]. Thus the determination of the absolute SDO
7 number density by measuring the weak signal at 1.27 μm resulting from the radiative de-
8 excitation of SDO is very challenging. There are only few reports on the measurement of
9 SDO generated by N-APPJs [306].

21 Figure 49 shows the SDO density as a function of the applied power of an RF N-APPJ
22 [306]. As can be seen from Fig.49, the concentration of SDO increases non-linearly with the
23 increase of the applied power. Besides, a higher O_2 admixture shifts the curve to the higher-
24 power side. The overall SDO concentration can reach the order of 10^{15} cm^{-3} . It is worth
25 mentioning that the RF N-APPJ operates in a typical α -mode discharge and switches to a γ -
26 mode discharge at higher powers. When the power is increased even further, the plasma
27 becomes inhomogeneous and unstable.

37 Figure 50 shows the SDO concentration as a function of the pulse repetition rate for a
38 typical kHz N-APPJ device [306]. From this figure, it is seen that the SDO concentration
39 increases almost linearly with the increase of the pulse repetition rate. This can be explained
40 by noting that while the pulse repetition rate is increased, the applied voltage, and hence the
41 E/N ratio remain nearly the same. Consequently, the electron temperature does not change
42 either. Therefore, higher pulse repetition rates only lead to the observed higher SDO
43 concentrations.

54 Figures 51(a,b) show the opposite trends in the evolution of the SDO density as a
55 function of the total gas flow, measured in the effluent of the RF and the kHz devices,

respectively. For the kHz N-APPJ case, its SDO density increases with the increase of the gas flow rate while it decreases in the case of the RF N-APPJ. It is believed that the increase of the gas flow induces two competing effects. First, the increase of the gas flow reduces the transit time of the species to the measurement cell and shortens their residence time in the cell. Since O_3 molecules are the major SDO quenching species in the effluent [307], faster transport and shorter residence times weaken SDO quenching before their detection in the measurement cell. Second, for kHz N-APPJ, the gas temperature remains nearly constant for different gas flow rates. However, higher gas flow rates could result in the increase of the plasma volume and the dissipated power, which eventually lead to the higher SDO concentrations. On the other hand, the gas flow significantly affects the gas temperature of the RF N-APPJ. This effect may even lead to the discharge transition from the α -mode to the γ -mode when the gas flow rates are varied. Therefore, higher gas flow rates could result in lower gas temperatures, higher O_3 densities and, consequently, faster SDO destruction in the RF plasma jets.

4.6 Atomic nitrogen

Atomic nitrogen radicals (N) could also play an important role in various applications of N-APPJs. However, studies on the measurement of N concentration of N-APPJs are very limited [308]. Measurements on the N concentration of a RF N-APPJ were performed using a two-photon absorption laser-induced fluorescence [308]. 206.65 nm photons were absorbed by the ground-state N atoms and 744 nm fluorescence signals were detected. A maximum N concentration was observed for an admixture of 0.25 vol % N_2 , as shown in Fig.52.

To our knowledge, measurements of the absolute values of the atomic nitrogen concentration in N-APPJs have not been reported. On the other hand, measurements of the atomic nitrogen density in a N_2 pulsed positive corona discharge by using two-photon

absorption laser-induced fluorescence have been reported [309]. The comparison of the measured and calculated decay curves of the N density after the discharge in Fig.53 reveals that the N density near the tip of the point electrode is about 500 ppm immediately after the discharge pulse. It decreases about 40% after 300 μ s.

4.7 Nitric oxide (NO) species

It is well known that atmospheric-pressure plasmas can generate nitric oxide (NO). On the other hand, cells also produce NO, which acts as a messenger in most mammalian organs. The NO radicals participate in vascular homeostasis, neurotransmission, antimicrobial defense, as well as immune system regulation and host defense processes. This reactive gas can cause apoptosis, necrosis or, alternatively, protect the cells from death, depending on the cell type, radical concentration, as well as the duration and specific areas of the exposure.

NO production methods have been studied in combustion systems [310, 311]. The most important mechanism of generation of NO is through the Zel'dovich reactions $N_2 + O \rightarrow NO + N$ and $N + O_2 \rightarrow NO + O$. In low-pressure plasmas, the first reaction plays the dominant role while at atmospheric- pressure conditions the second reaction is more important [312]. Further studies found that long-lifetime metastable states, such as $N_2(X^1\Sigma, v)$, $N_2(A^3\Sigma)$ and $O_2(b^1\Sigma)$ could also play a dominant role in the NO formation. In all cases, a significant NO decay dominated either by the reverse Zel'dovich reaction $NO + O \rightarrow N + O_2$ or by the conversion of NO into NO_2 through the reaction with O_3 [313].

In the following, the NO concentration measurements are discussed. There are several methods available that can be used to measure the NO concentrations, including the mass spectrometry [314], optical absorption spectroscopy [315], optical emission spectroscopy [316], and laser-induced fluorescence (LIF) [310]. We emphasize that the first three methods

are not *in situ* spatially-resolved NO measurements. Only the LIF spectroscopy can provide the time- and position-resolved measurements.

Figure 54 shows the dependence of the NO species concentration generated by a kINPen device on the air percentage for different Ar gas flow rates [316]. At higher gas flow rates, the NO concentration decreases. Besides, the NO concentration exhibits a maximum as a function of air admixture at approximately 0.1-0.2% of air in the flow. The NO density rises nearly linearly with the increase of the air flow at small air admixtures. The air admixture can thus be used to control the production of NO radicals in the plasma jets.

In Fig.54, compressed dry air is used. On the other hand, due to humidity, the surrounding air always contains some H₂O. The air humidity could affect the NO concentration, as verified by the experiments with air admixture at different proportions of wet Ar flow [316]. As shown in Fig.55, in comparison with ‘dry’ conditions, the ‘wet’ Ar leads to a noticeable amount of NO at 0.5-1% of air. This finding indicates that humidity enhances the generation of NO with air admixtures. However, excessive amounts of H₂O effectively quench the NO generation, e.g., through the following reactions:

LIF spectroscopy has been used to measure the concentrations of NO species generated by an RF plasma jet [317]. Figure 56 shows the 2D profiles of the NO concentration at ground state while the axial profiles for different plasma powers are shown in Fig.57. From Fig.56, one can see that the maximum of NO concentration is at the tube edge, thus most of the NO species are formed inside the tube. Regarding the effect of the power, the higher is the power delivered to the plasma, the larger is the plasma volume and the higher are the maxima of the NO concentration. Besides, it is worth pointing out that, as the plasma effluent has typically a smaller diameter compared with the tube diameter, the discharges are not always

axially symmetric. This is a possible reason of the observation of asymmetric structures in Fig.56.

The air concentration also affects the spatial distribution of NO species, as can be seen in Fig.58 where the NO density *versus* the axial position for different air concentration is plotted. With the increase of the air concentration, the NO density increases while the plasma shrinks in size and it becomes more difficult to sustain the discharge. This can be regarded as an artifact of the NO production. The optimum air concentration for the highest NO production is around 2%. For the case of pure Ar, the generation of NO species is mostly due to the diffusion of ambient air.

4.8 $N_2(A^3\Sigma_u^+)$ metastable

Nitrogen molecules in metastable states play an important role in gas discharge kinetics. These species have long radiative lifetime (2 s) and high excitation energy (6.2 eV) and can induce various reactions in the discharge afterglow. Since no reports on the measurement of $N_2(A^3\Sigma_u^+)$ absolute density in N-APPJs are presently available in the literature, experimental results on $N_2(A^3\Sigma_u^+)$ absolute density in a positive pulsed corona discharge [318] are discussed. The density of $N_2(A^3\Sigma_u^+)$ metastable in N_2 pulsed positive corona discharge between a pin HV electrode and a plate ground electrode is measured by using time-resolved laser-induced fluorescence (LIF). The $N_2(A^3\Sigma_u^+, v''=0)$ state is excited to $N_2(B^3\Pi_g, v'=4)$ by 618 nm dye laser irradiation, then the fluorescence from the $N_2(B^3\Pi_g, v'=4) \rightarrow (A^3\Sigma_u^+, v''=1)$ band is measured. Figure 59 shows the temporal variation of the normalized $N_2(A^3\Sigma_u^+)$ density after the discharge. By fitting the experimental decay curve of the normalized $N_2(A^3\Sigma_u^+)$ density with the calculated curve, the $N_2(A^3\Sigma_u^+)$ density immediately after the discharge is estimated to be slightly less than $6 \times 10^{13} \text{ cm}^{-3}$ at the midpoint of the 12 mm discharge gap.

4.9 Metastable He and Ar states

When used as a working gas of a plasma jet, noble (mainly He or Ar) gases feature metastable states with the relatively high excitation energy. This is why these species may play an important role in the plasma chemical or even in the ionization processes. It is thus very important to know the concentration of the metastable states of the noble gases. In addition, when two different noble gas mixtures are used instead of just one type of a noble gas, the reactions could turn more complicated because of the reactions between diverse metastable states of the different noble gases. The addition of Ar leads to the production of metastable species, such as $\text{Ar}(1s_5)$. These species can store energy from the discharge and possibly enable the effective afterglow plasma chemistry. In the following, the measurements of the concentration of He metastable state in a plasma jet in pure He and in He diluted with 5% Ar are presented.

Figure 60 shows the spatially and temporally resolved distributions of the He^m absorption of a plasma jet driven by positive voltage pulse phase [319]. It shows the temporal evolution of the line-integrated He^m density with a time step of 50 ns. From the figure, it is seen that the high-density region of He^m stretches along the He gas flow. The velocity of the tip is approximately 50 km/s, which is consistent with the propagation velocity of the bullet-like emission observed by the ICCD camera [319]. It is worth pointing out that the He^m density distribution shows a longer tail compared to the profile of the streamer emission. This could be explained by noting that the lifetime of the metastable atoms is longer than the excited species.

The radial distributions of the absolute He^m densities measured in the positive voltage phase are shown in Fig.61. It is seen that the He^m density of the jet has a ring-like hollow shape at the centre. This is similar with the time-resolved observations by the ICCD camera

[36]. The radius of the ring and the peak density gradually decrease with the distance from the tube nozzle. Indeed, the density is about $4.5 \times 10^{11} \text{ cm}^{-3}$ at 1 mm and decreases to $2 \times 10^{11} \text{ cm}^{-3}$ at 10 mm away from the nozzle.

Figure 62 shows the time evolution of the He metastable state concentration. It clearly shows that the He metastable state concentration is higher near the nozzle. At $z = 1 \text{ mm}$, the concentration of He metastable states is still significant at about $3 \mu\text{s}$, which is more than $1 \mu\text{s}$ after it reaches its peak value.

Figure 63 shows the time evolution of the He^m absorption signals in the positive voltage phase measured at several applied voltage V_{0p} . The delay time of the appearance of absorption decreases with the increase in the peak applied voltage, which is possibly due to the shorter ignition delay time. It is interesting to point out that the peak value of the signal does not show any significant change for different peak applied voltages.

The diameter of the tube also affects the radial distributions of He^m density in the positive voltage phase as shown in Fig.64 which shows the data for each tube corresponding to the moment it reaches their peak density. The peak density in each tube is more or less the same in the range of $(3.5 \pm 0.5) \times 10^{11} \text{ cm}^{-3}$. It is noted that the thickness of the ring is approximately 0.4 mm in all the three cases.

The findings discussed above appear to be quite different for the plasma jet sustained in He + 5% Ar working gas [320]. The temporal evolution of the line-integrated $\text{Ar}(1s_5)$ column density obtained by diode laser absorption spectroscopy and the photo-multiplier tube (PMT) signal tracking emission originating from the $811 \text{ nm } 2p_9 \rightarrow 1s_5$ transition is shown in Fig.65 [320]. Both the PMT emission and the Ar^m density measurements show three distinct metastable production regimes. The results in this figure show that the temporal behaviors of the Ar^m species are different. Hence, the production mechanism at different positions in the plasma plume is also different. At 1 and 3 mm from the nozzle, the density of the Ar

metastable state increases quickly within 300 ns, then slowly increases to its peak value at about 700 ns before it starts to decline. On the other hand, at 10 mm, the Ar^m density increases to the peak value in about tens of ns and then quickly decreases to nearly zero over approximately 300 ns.

According to Fig.65, the effective lifetime of the Ar^m in the region close to the nozzle is significantly extended, which could enable plasma-chemical reactions beyond the relatively short timescale of the initial ionization front. Figure 66 corroborates this point by comparing the decay of the Ar^m column density with the decay of 337 nm emission from $\text{N}_2(\text{C}^3\Pi_u)$ species, which can be excited through the following reaction:

The decay rates of $\text{N}_2(\text{C}^3\Pi_u)$ and Ar^m emissions differ by less than 10%. Since the collisional quenching lifetime of $\text{N}_2(\text{C}^3\Pi_u)$ in the air at atmospheric pressure [321] is much shorter than the observed collisional quenching lifetime of Ar^m the extended afterglow emission from $\text{N}_2(\text{C}^3\Pi_u)$ must be primarily supported by the energy transfer from Ar^m .

The density of metastable Ar^m species remains around 10^{11} cm^{-2} for up to 10 μs after the initiation of the discharge. This indicates that Ar^m can drive the plasma chemistry long after the initial ionization front has passed. However, further away from the nozzle, the effective lifetime of Ar^m and, consequently $\text{N}_2(\text{C}^3\Pi_u)$ was significantly reduced because of air entrainment into the plasma channel.

By comparing this result with the measurements of He (2^3S_1) metastable number densities in a pure He plasma jet presented above, the most obvious difference between these datasets is the significantly longer duration of Ar^m production in the region close to the nozzle in the He/Ar mixture. This effect was not observed for metastable production in either pure gas configuration [322]. The longer effective lifetime of Ar^m in this configuration is the result of the enhanced species reproduction in the residual plasma channel, which is apparently not

as effective in the case of pure He or Ar gases. The longer effective lifetime of Ar (1S_5) in the He/Ar plasma jet significantly extended the timescale for the afterglow plasma chemistry.

As mentioned above, the number of the reactive species generated by N-APPJs is very large; on the other hand, the diagnostic methods are very limited, which makes it very difficult to obtain complete chemical compositions in the jet effluent by experimental methods. This brings us to the next section which shows that it is possible to simultaneously calculate the densities of the whole set of the reactive species, by using numerical modeling and simulations.

5. Reactive species: numerical modelling

Rate constants of reactions producing primary reactive species in collisions of hot electrons with neutral components are governed by the electron temperature, the latter depending on the local values of gas mixture composition and the reduced electric field. In RF N-APPJs, under conditions when the plasma is generated by discharges between plane metallic electrodes, the electron temperature and density, and hence the rates of generation of primary species, in the discharge region are nearly uniform. Conditions are quite different in HF N-APPJs, where both mixture composition and electric field vary strongly both along and across the jet. In this case, primary reactive species are produced mostly in local regions of high electric field – in streamer heads. These fields are typically several times higher than the electric fields in RF discharges between metallic electrodes. As a consequence, main channels of production of reactive species in RF and HF N-APPJs can be quite different. For example, the difference between mechanisms of production of OH in He-H₂O mixtures in RF discharges and in HF N-APPJs is discussed in [115].

Formation of primary reactive species triggers a chain of chemical transformations, involving both neutral and charged components, resulting in generation of a number of

various species. Detailed kinetic schemes, referred to in [Sec.2](#), include up to thousands of processes. The rate constants for most of these processes are not well documented. Typical examples concerning uncertainty of some rate constants are given in [\[106\]](#) and discussed below.

5.1. Generation of reactive species in HF N-APPJs

In most simulations of HF N-APPJs, production of reactive species by a single discharge pulse (during the propagation of a single streamer) is considered. Note that parameters of streamers in HF N-APPJs vary substantially depending on the jet radius, gas flow rate, applied voltage, electrode configuration, etc. [\[323\]](#), resulting in the variation of the composition of generated species. The latter depends also on the content of molecular components, such as O₂, H₂O, air, etc., admixed to plasma forming gas (He or Ar) and on the humidity of surrounding air. The difference between the assumptions made and models used leads to the broad range of the calculated values of compositions of reactive species, which sometimes can differ by several orders of magnitude.

[Figure 67](#) shows profiles of the densities of species produced by a single streamer in He jet impinging on dielectric surface in surrounding air [\[127\]](#). The peak species densities in the streamer are (in cm⁻³) about 10¹⁶ for O, 10¹⁴ for N, 10¹⁵ for O₂(a¹Δ), 10¹⁴ for O₃ and 10¹⁴ for electrons. At evaluation of the density of O atoms, both dissociation of O₂ molecules by electron impact:

and the process

of quenching of electronically excited nitrogen molecules N₂^{*} (in A³Σ, B³Π, and other triplet

and singlet states) produced by electron impact:

are taken into account. Nitrogen atoms and excited oxygen molecules are produced in the reactions:

and

Ozone molecules are generated mainly in the process:

Note that during the simulation time of 100 ns only a small part of the produced O atoms is converted into O₃ [127]. At later times a much larger O₃ density can be expected in the effluent.

About three orders of magnitude lower peak values of the electron density n_e (about $2 \times 10^{11} \text{ cm}^{-3}$) and the density of O atoms n_O (about $5 \times 10^{12} \text{ cm}^{-3}$) in the effluent of a plane jet, of He + 0.5% O₂, have been calculated in [131]. As in [127], the peak n_O values are more than an order of magnitude higher compared to n_e .

Another relation between n_e and n_O is obtained in simulations [128]. It was found that at the electron density in the effluent of about 10^{12} cm^{-3} the order of magnitude of the densities of oxygen atoms in ground and excited states is the same as can be seen in Fig.68. The values of n_O are likely to be underestimated because one of the most important reactions (R7) was not included in the kinetic scheme that was used.

Figure 69 shows the calculated radially averaged densities of primary active species, along the jet axis z , produced by a single streamer in a plasma jet of He + 1% humid air (with water molar fraction of 2%) flowing into air with the same water content [119]. To evaluate

the density n_O of oxygen species the contributions of reactions (R5)-(R7) are included. It is assumed that the second path of reactions (R9) and (R10) is dominant and produces one atom in the ground state $N(^4S)$ and another one in the excited state $N(^2D)$. The obtained densities of N, $O_2(a^1\Delta)$, $O(^1D)$ and electrons are around 10^{12} cm^{-3} , while n_O is an order of magnitude higher.

In simulations [132], based on the same kinetic scheme as above [128], the effect of addition of air to He on the densities of oxygen-containing species produced by a single streamer is studied. It is shown that with higher air content in the plasma forming gas the densities of O, $O(^1D)$ and $O_2(a^1\Delta)$ increase in the region inside the tube (nearly proportionally to the molar fraction of added air) but do not change noticeably in the effluent (Fig.70). The evaluated peak densities of O, $O(^1D)$ and electrons in the effluent are about 10^{13} cm^{-3} (higher than in [128], probably due to higher applied voltage). The peak density of $O_2(a^1\Delta)$ is an order of magnitude lower.

The calculated densities of reactive species, produced by a single negative streamer, at the axis of plasma jet of He + 0.2% O_2 flowing into air containing 0.5% H_2O are shown in Fig.71 [133]. The densities of O, $O_2(a^1\Delta)$ and electrons in the effluent, increasing with the applied voltage, are of the same order, the N_2^* density being several times higher. Note that the calculation time, 80 ns, is smaller than the time of quenching of N_2^* in reaction (R7) producing additional amount of O atoms. The calculated OH density is an order of magnitude lower. The ratio of the peak density of $O_2(a^1\Delta)$ to that of electrons, around unity, agrees with that obtained in [119], being an order of magnitude higher than in [132] and an order of magnitude smaller than in [127].

The results of modelling [129] of the plasma chemical processes in streamer propagation along the He jet (with 100 ppm H_2O) flowing into air (with 3% H_2O), reveal that the peak densities of OH species and electrons in the effluent are close to each other, and are

approximately $2 \times 10^{12} \text{ cm}^{-3}$. The relative OH density is higher than calculated elsewhere [133], probably because the H_2O molar fraction is six times larger. OH species are generated upon the dissociation of water molecules (reaction (R2)), recombination of H_2O^+ ions (produced both at H_2O ionization by electron impact and in the Penning reaction of H_2O with excited He atoms) with electrons

and through the reaction

which produces two OH radicals.

Figure 72 shows the effect of addition of 0.5% N_2 , O_2 or air to plasma forming gas on the densities of OH and electrons. Substantial increase of OH density upon addition of O_2 is probably caused by the increased amount of $\text{O}(^1\text{D})$ producing OH radicals through reaction (R14).

Simulation of a sequence of streamers in He plasma jets, with the account of slow chemical transformations between the current pulses, gives a variety of produced reactive species. In Fig.73, the calculated axial distributions of radially averaged species densities, at the average gas flow rate of 6 m/s and repetition frequency of 10 kHz, are shown [119]. Oscillations of the densities of short-living species reflect their variation with time: steep increase during the discharge pulses and decrease between the pulses. Primary reactive species are produced in the region of streamer propagation, at $z < 3.5$ cm. Larger z values correspond to the afterglow region, where the densities of short-living species (O, OH, N, H, HO_2) decrease along the axis. The densities of some of the primary reactive species, such as O, $\text{O}_2(^1\Delta)$ and N, reach peak values at some distance from the streamer starting position, $z = 0$ (accumulation of these species takes place). The densities of other primary reactive species, such as H atoms, excited O, N and He atoms (the latter three not shown in the figure), with lifetimes smaller than the repetition period, decrease strongly between the pulses.

Figure 74 shows the calculated axial profiles of the densities of species produced by a sequence of streamers at the repetition frequency of 10 kHz [133]. In these conditions, streamers propagate over the distance of around 1 cm, depending on the applied voltage, so most of the region shown in Fig.71, up to 5.5 cm, presents the afterglow zone.

Relations between the densities of OH, O₃, H₂O₂ and their peak values at the maximum applied voltage shown in Fig.74 are similar to those calculated in [119] (Fig.73). However, NO density is an order of magnitude lower than in [119]. The latter is probably underestimated in [133] because the important channel of NO production:

was not included in the calculations.

The results of modeling [115] of OH production inside the tube by repetitive streamers propagating along the plasma jet sustained in He with H₂O addition, at various values of H₂O molar fraction $X_{\text{H}_2\text{O}}$, are presented in Fig.75. With the increase of the number of discharge pulses (discharge duration) the OH density at given $X_{\text{H}_2\text{O}}$ increases initially and then reaches the peak values at 10-20th pulse, similarly to the results of measurements [129]. The peak values of OH density increase with the increase of $X_{\text{H}_2\text{O}}$ to about 200 ppm, and saturate at larger $X_{\text{H}_2\text{O}}$, in agreement with the experimental data [324]. Here we note that the saturation is related to the dominant role of recombination reaction (R13) in OH production; the contribution of dissociation (R2) is much smaller.)

The results of simulations described above show that the densities of the produced reactive species can vary in a wide range, depending on such factors as the amplitude, polarity and repetition frequency of the applied voltage pulses, composition of the plasma forming gas, humidity of surrounding air, tube radius, and gas flow velocity. Less sensitive to these factors (changing in narrower limits) are the relations between the calculated densities of various species. Most of the densities increase with the amplitude of applied voltage V and

with the repetition frequency f . These findings are in line with the available experimental data. For example, the character of variation of OH density with U and f obtained in simulation [119] is similar to that measured in [325].

The density of O atoms produced by a single streamer, measured to be in the range 10^{13} - 10^{14} cm⁻³ [326], as well as the peak electron density ($\sim 10^{13}$ cm⁻³) measured in [327], are of the same order of magnitude as most of the simulation results described above. Measurements [284] of the densities of O atoms and OH molecules produced by repetitive streamers in the effluent give the values around 10^{14} cm⁻³ and 5×10^{12} cm⁻³, respectively, in a reasonable agreement with the results of simulations [119,133].

5.2. Generation of reactive species in RF N-APPJs

5.2.1. Plasma jets with planar metallic electrodes

Kinetic processes in RF N-APPJs have been modelled for two discharge configurations. In the first one the plasma forming gas flows through a thin discharge gap between two planar metallic electrodes. Figure 76 shows distributions of O and O₃ densities along the flow, both in the discharge region and in the effluent, for various values of the efficiency γ of recombination of O atoms and destruction of O₃ molecules at the walls, obtained in [114] using a 0D plug flow approach. In these simulations, the electron density and mean energy governing the production of reactive species were estimated from the measured spectral data. The calculated O density (up to 10^{16} cm⁻³) and O₃ density (2-3 times lower) in the discharge region agree with the experimental results. These results show the strong effect of losses at the walls, especially for O₃ species.

The density of O atoms in the discharge core, calculated in [102] in the framework of 1D model, accounting for variation of the plasma parameters in the direction normal to the electrode surfaces, in RF N-APPJ in He with 0.5% O₂, *versus* the discharge power is shown

in Fig.77. Both the measured and the calculated density values increase almost linearly with the power, being in the range 10^{15} - 10^{16} cm⁻³ [102].

The distributions of reactive species along the flow of RF N-APPJ in He with 0.5% O₂, at the power deposition of 0.5 W, calculated using a 2D model [122], are presented in Fig.78. The obtained O and O₃ densities in the discharge core are rather close to those shown in Figs. 76 and 77. Since in this case the jet flows into He atmosphere (the effluent region is not limited by walls), the decrease of O and O₃ densities in the effluent is much slower than that shown in Fig.76.

The calculated peak density of electrons n_e , about 2×10^{10} cm⁻³, is five orders of magnitude lower than the peak density of O atoms n_O . Note that the ratio n_O/n_e in RF N-APPJs is 4-5 orders greater than that in HF N-APPJs (see Sec.5.1). The reason is in the difference in the character of production of reactive species in the two kinds of plasma jets. In RF N-APPJs the species are generated during the whole time (of several milliseconds) of gas movement along the discharge region, while in HF N-APPJs production of primary reactive species occurs mainly in streamer head regions, during very short time intervals.

A 0D global model involving a detailed kinetic scheme is used for the calculation of reactive species densities in the discharge region and in the afterglow of RF N-APPJ [111]. The source terms, governing the production of primary reactive species in the discharge core, are evaluated by using 1D approximation [102]. For the whole afterglow region, the same air impurity level is assumed as in the core plasma region.

The calculated species densities (Fig.79) vary along the discharge region similar to the trends shown in Figs. 76 and 78. In the afterglow, a decrease of the densities of O, H, N atoms and OH, HO₂ radicals takes place, similar to that calculated for HF N-APPJs (Fig.73). The relative (in comparison with the produced O and O₃) amount of hydrogen- and nitrogen-containing species (OH, NO etc.) is much smaller compared to HF N-APPJs. The reason is in

very low molar fractions of N₂ and H₂O in the plasma forming gas.

Article [111] presents detailed information on the relative roles of various kinetic processes in generation and loss of reactive species. Typically several leading reactions exist for each of the species. Hence, as a rule, the balance of species is not very sensitive to the variation of rate constants of individual processes. Because of this, simulations performed under similar conditions using quite different kinetic schemes produce results of the same order of magnitude. Note, for example that reactions

are among the leading reactions that govern O₃ balance in the afterglow [111]. Both of these reactions are not included in some commonly accepted kinetic schemes (e.g., those used in [102,122]). However, the calculated values of O₃ density obtained in all of the mentioned simulations are rather close to each other.

The profiles of the densities of O and O₃ in the effluent of He (with oxygen admixture) RF N-APPJ flowing into He or air have been calculated using a 2D flow model [125], where the experimental values of the species densities are taken at the nozzle. The profiles obtained for the jet flowing into He agree with the experiment. For the jet flowing into air (Fig.80), the model, marked as model 1 in the figure, gives a very fast decay of O density with the distance from the nozzle. The authors assume that some other process produces O and O₃ in the effluent. For example, reaction O₂* + O₂ → O + O₃, involving unidentified excited molecules O₂* with the energy threshold exceeding 4.1 eV was incorporated into model 2. Note that model 2 does not predict the observed fast decrease of O₃ density at distances exceeding 20 mm. The character of the observed profiles of O and O₃ densities can be related to radial non-uniformity of the gas flow velocity and mixture composition. This point requires future research.

The 1D model of an RF discharge between planar electrodes coupled to the 2D model of the reacting and mixing jet is used in [126] for simulation of interaction of an RF N-APPJ with a surface placed normal to the jet axis. The plasma jet is sustained in a He flow with a small admixture of O₂ that expands into surrounding air. Figure 81 shows the spatial distributions of O and O₃ densities. Surface profiles show narrow peaks for O and broader distributions for O₃. The calculated O density at the surface decreases while O₃ density increases with the increase of the distance from the device to the surface.

5.2.2. Needle-type plasma jets

Another, needle-type, configuration of RF N-APPJ is similar to that used for HF plasma jets. Propagation of guided streamers in these jets (when reactive species are generated in a pulsed manner, during very short time intervals) has been observed at voltage frequencies up to 1 MHz [151]. At much higher frequencies typically used in these plasma jets, generation of reactive species is more uniform in time and it is accurate to use the values averaged over the repetition period. However, in comparison with the above configuration with planar electrodes, the spatial distributions of the plasma parameters in the discharge region are strongly non-uniform. In the available computations of chemical processes in needle-type RF N-APPJs (see below), the discharge region is not simulated self-consistently, and semi-empirical approaches are used instead.

In simulations [105,116-118] of the production of reactive species in needle-type Ar RF N-APPJs (for the configuration similar to that described in [270]), 2D fluid dynamics model (considering only background gas species: Ar, O₂, N₂, H₂O) is used, coupled with 0D flow model describing chemical transformations. The source terms in the balance equations for neutral and charged species are evaluated by defining an axial profile of the power density that determines the electron temperature. An example of axial distributions of the plasma

characteristics in Ar jet flowing into ambient humid air, calculated in [116], is shown in Fig.82. The afterglow region (far effluent) starts at the distance ~ 1.2 cm from the nozzle, where the power density drops to zero. Like in HF N-APPJs, primary reactive species are produced by electron impact not only inside the interior of the device, but also in the near effluent, in air-Ar mixture. Note that the gas temperature in this case is much higher than in the plasma jets considered above, reaching the value of 600 K at the needle electrode.

Figure 83 shows the axial profiles of reactive species densities calculated under these conditions. The peak densities of O, O₃ and O₂(a¹Δ), in the range 10^{15} - 10^{16} cm⁻³, are of the same order as those produced in RF N-APPJs with planar electrodes (see Fig.79). However, the densities of nitrogen- and hydrogen-containing species (NO, NO₂, OH, and HO₂) are much larger than those shown in Fig.79. In needle-type RF N-APPJs these species are produced in the effluent, at sufficiently large molar fractions of N₂ and H₂O in the mixture, while in RF N-APPJs with planar electrodes the primary reactive species are produced in the discharge region between the electrodes, at very low N₂ and H₂O content. The character of variation of the species densities in the afterglow is similar to that calculated for HF N-APPJs and for RF N-APPJs with planar electrodes.

The densities of neutral reactive species in needle-type RF N-APPJs presented in Fig.82 are higher than those in HF N-APPJs (note that the power input is also higher), though the relations between the densities of various species are rather similar to those in HF N-APPJs (where reactive species are also produced in the effluent). However, similar to RF N-APPJs with planar electrodes, the relative density of electrons is much lower than in HF N-APPJs, due to the difference in the character of generation of reactive species mentioned above.

The effects of admixtures to Ar of H₂O, N₂ or O₂ on the amount of produced reactive species are considered in [117,118]. The results of simulation agree qualitatively with the measured data.

In [105,116] a detailed analysis of the relative roles of various kinetic processes in generation and loss of reactive species is performed. As in [111], the kinetic scheme used involves over a thousand reactions, with not all of them being well documented. Moreover, some statements in the literature appear to be conflicting. For example, in [116] the reaction $N_2(A^3\Sigma) + O \rightarrow NO + N$ is indicated as one of the main processes producing NO, while, according to the review paper [328], there is no evidence for this reaction to lead to NO formation. Fortunately, similar to the RF N-APPJs with planar electrodes discussed above, the species balance is governed by several leading reactions and is not very sensitive to the variation of rate constants of individual processes.

In [113,240], 2D fluid dynamics model coupled with 0D kinetic model is used for simulation of chemical processes in the afterglow of Ar RF N-APPJ for various shielding gas compositions. The initial densities of reactive species are evaluated using the measured absorption data. Figure 84 shows the calculated species densities *versus* time. Note that they are more than an order of magnitude lower than those obtained in [116] (Fig.83), probably because of the much lower power input. The relations between the peak densities of O, O₃ and OH species calculated in [113] are similar to those obtained in [116]. The relative NO density is substantially lower, likely because the kinetic scheme [113] does not include the important channel of NO production (R14).

The above HF N-APPJs, RF N-APPJs with planar electrodes, and needle-type RF N-APPJs use different plasma forming gases: He in the first and second types of jets and Ar in the third case. Plasma parameters in both HF N-APPJs [4] and needle-type RF N-APPJs [270] depend on the plasma forming gas, hence replacing He with Ar changes the composition of the produced reactive species. The major difference between the kinetic schemes involving He and Ar is related to the difference in the excitation energies of metastable atoms He* and Ar*. While collisions of He* with air components (molecules N₂,

O₂, H₂O) generate electrons and positive ions, collisions of Ar* with these molecules lead to their dissociation or excitation.

Under conditions when primary reactive species are mainly produced in the reactions involving electrons and air components (the number density of the produced He* and Ar* species being relatively low) the dominant channels of generation and loss of reactive species in He and Ar jets are quite similar. Such conditions can be expected when primary reactive species are produced mainly in the effluent, at relatively high air content. For RF N-APPJs with planar electrodes, at low molecular admixtures in the plasma forming gas, the difference between the dominant production channels in He and Ar jets can be much more significant.

Knowledge of the densities, energies and reactivity of the species generated by atmospheric-pressure plasma discharges is important to understand and quantify the interactions of such plasmas with liquids examined in the following section.

6. Reactive species interaction with liquid

For plasma medicine applications such as wound healing, most wounds in their early stages are covered with a water-like liquid resembling blood serum which contains 93% water and 7% proteins [329]. The thickness of the liquid layer is typically a few hundred micrometers. Thus the reactive species generated by an N-APPJ will first react with the liquid layer before interacting with biological systems. It is thus important to understand the mechanisms of how N-APPJs deliver reactive species to the cells and tissues through the intermediate liquid layer.

Because of the lack of reliable diagnostic methods to obtain the concentrations of all (or even most of) the reactive species in the liquid phase, relevant studies are mainly based on computer simulations. Up to now two methods have been used to simulate the processes of plasma interaction with liquid. The first method is based on a global model. It assumes that uniform plasmas are generated on the liquid surface while the concentrations of all the

(charged and neutral) reactive species are constant. It is assumed that the plasma species are in a steady state and are randomly placed on the liquid surface at the moment $t = 0$. Neutral species are assumed to enter the liquid with their thermal velocities.

The charged species are assumed to enter liquid following the (ambipolar) field so that the charge neutrality of the liquid is maintained. In addition, all the reactive species in the liquid are assumed to be well mixed and diffusion of the species in the liquid is not taken into account. The outward flux of reactive species from the liquid to the gas phase is determined based on the assumption that, in a steady state, it balances the incoming flux of the same species. The gaseous species entering the liquid are assumed to be dissolved into the liquid without any barrier (no reflection from the liquid surface). In other words, the sticking coefficients of gaseous species at the liquid surface are assumed to be unity.

However, the global model cannot provide the spatial distribution of reactive species in liquid. For the species with short lifetimes in liquid such as electrons, the global model cannot provide accurate information because those species can only dissolve into a thin layer. Moreover, their concentrations decrease quickly after they enter the liquid. To obtain the spatial distribution of such species, a two-dimensional (2D) model has been reported recently [330]. In this 2D model, the Poisson's equation, transport equations for charged and neutral species, the electron energy conservation equation and radiation transport are solved by direct time integration. The Boltzmann's equation is solved for electron transport and rate coefficients, which are functions of the average electron energy.

The same equations are solved in the liquid. In order to properly include the larger dielectric constant of the liquid, an atomic polarizability is specified for each species so that the number-density-weighted polarizability yields the proper dielectric constant. Transport coefficients for neutral and charged species, and absorption cross-sections, are determined by the local densities. The rate of transport of the gas phase species into the liquid is determined

by using the Henry's law. A schematic of the simulation geometry is shown in Fig.85. Details of the model, simulation geometry and the parameters used can be found elsewhere [330].

In the rest of this section, the simulation results based on 2D models will be discussed. For long-lifetime reactive species, the simulation results based on a global model will also be presented.

6.1 Negative ions

Because the mobility of an electron in liquid e_{aq} is at least 10^4 times smaller than in the gas phase, there is net negative charging on the water surface. During the first discharge pulse, there are no other species in the water other than dissolved oxygen, denoted O_{2aq} . As a result, during the first early afterglow, e_{aq} primarily attaches to O_{2aq} to form O_{2aq}^- . The electron attachment occurs within a few μs .

During the inter-pulse and terminal afterglows, NO_x from the gas phase diffuses into the water (see Fig.86). The diffusion of NO into the liquid enables charge exchange between NO_{aq} and O_{2aq}^- to form NO_{3aq}^- . During later discharge pulses and during the terminal afterglow, nitric acid, HNO_3 is formed in the gas phase and diffuses into the water. NO_{3aq}^- is then also generated by the hydrolysis of HNO_{3aq} . During the terminal afterglow, the end products of the hydrolysis and charge exchange result in O_{2aq}^- and NO_{3aq}^- being the dominant negative ions. These ions diffuse through the $200 \mu m$ water layer to reach the tissue. At the end of the 1 s after the three discharge pulses, the combined densities O_{2aq}^- and NO_{3aq}^- above the tissue are $2.5 \times 10^{13} \text{ cm}^{-3}$.

6.2 Positive ions

The gas-phase positive ions dissolve and quickly exchange charge to form $H_2O_{aq}^+$. Besides, the gas-phase H_2O^+ directly dissolves to form $H_2O_{aq}^+$. The production of $H_2O_{aq}^+$ is

significantly enhanced by photoionization, which contributes 62% to the initial production of $\text{H}_2\text{O}_{\text{aq}}^+$, a process that is enabled by the plasma touching the water surface. In this case the plasma-generated VUV reaches the water surface. As shown in Fig.87, the $\text{H}_2\text{O}_{\text{aq}}^+$ penetrates only a few micrometres into the water before forming hydronium $\text{H}_3\text{O}_{\text{aq}}^+$, a reaction that also produces OH_{aq} . $\text{H}_3\text{O}_{\text{aq}}^+$ is the terminal positive ion, which drifts through the water layer to the tissue. At the end of the terminal 1 s afterglow, the density of $\text{H}_3\text{O}_{\text{aq}}^+$ above the tissue is $2.3 \times 10^{14} \text{ cm}^{-3}$.

6.3 ROS

Unlike charged species discussed above, which largely recombine or neutralize prior to diffusing into the liquid, the lifetimes of neutral radicals are much longer so that these reactive species are able to diffuse into the water without significant losses.

One of the possible interactions of ROS with cell membranes is the peroxidation of the membrane lipids. OH_{aq} and $\text{H}_2\text{O}_{2\text{aq}}$ are highly-reactive radicals, with oxidizing potentials of 2.8 eV and 1.78 eV, respectively. The densities of OH_{aq} and $\text{H}_2\text{O}_{2\text{aq}}$ in liquid during the period from the end of the current pulse to the end of the terminal afterglow are shown in Fig.88. OH_{aq} species could originate from diffusion and salvation processes, charge exchange, and photo-dissociation. However, because the mean free path for charge exchange and photo-dissociation in water is typically 20-30 μm , so the majority of the OH_{aq} species are produced at the top of the liquid. The maximum density of OH_{aq} at the top of the water layer is $1.6 \times 10^{15} \text{ cm}^{-3}$ at 10 μs after the discharge pulse. In addition, because the diffusion through the water layer is slow, the majority of OH_{aq} species react to form $\text{H}_2\text{O}_{2\text{aq}}$ before they can reach the tissue. On the other hand, $\text{H}_2\text{O}_{2\text{aq}}$ has a lower oxidizing potential than OH_{aq} . $\text{H}_2\text{O}_{2\text{aq}}$ can diffuse through the water layer to reach the tissue. At the end of the terminal afterglow, the density of $\text{H}_2\text{O}_{2\text{aq}}$ at the tissue is $5.5 \times 10^{13} \text{ cm}^{-3}$.

The above results are for three discharge pulses only. For multiple discharge pulses, Fig.89 shows the global model simulation results of 100 μL liquid treated by the plasma for 60 s [331]. It shows that OH and H_2O_2 concentration reaches as high as 10^{-4} M (mol/L), which is on the order of 10^{17} cm^{-3} and thus much higher than the case of three discharge pulses. On the other hand, the ONO_2^- concentration, which will be discussed in the following, is only slightly higher than the three-pulse case. However, the $\text{HO}_{2\text{aq}}$ and $\text{O}_{3\text{aq}}$ concentrations, on the contrary, are much lower than in the case of the three pulses.

Regarding the generation of $\text{H}_2\text{O}_{2\text{aq}}$ in liquid, Fig.90 shows the experimental result for the H_2O_2 net production rates of the gas and liquid phases for different feed gas humidity settings. Interestingly, both curves are in a remarkable agreement. This means that the H_2O_2 net production rate in the gas and liquid phases are the same for the studied humidity conditions. Moreover, this confirms that the presence of H_2O_2 molecules in the gas phase directly influences the liquid-phase $\text{H}_2\text{O}_{2\text{aq}}$ concentration. Although this positive correlation does not prove that liquid-phase $\text{H}_2\text{O}_{2\text{aq}}$ molecules originate from gas-phase H_2O_2 , it evidences that the solubility processes play a major role in generating $\text{H}_2\text{O}_{2\text{aq}}$ in liquid.

O_3 has an oxidizing potential of 2.07 eV. The densities of $\text{HO}_{2\text{aq}}$ and $\text{O}_{3\text{aq}}$ are shown in Fig.91 at different times during the afterglow periods. One can see that the maximum density of the $\text{O}_{3\text{aq}}$ species is of the order of 10^{17} cm^{-3} , which is larger than the density of $\text{H}_2\text{O}_{2\text{aq}}$. Furthermore, $\text{O}_{3\text{aq}}$ species in the water mostly originate from the diffusion of O_3 from the gas phase.

As shown in Fig.91, $\text{HO}_{2\text{aq}}$ species is predominantly formed at the top of the water layer by H_{aq} combining with dissolved $\text{O}_{2\text{aq}}$. Importantly, $\text{HO}_{2\text{aq}}$ is a transient species. It is consumed by hydrolysing into $\text{H}_3\text{O}^+_{\text{aq}}$ and $\text{O}^-_{2\text{aq}}$, or by combining with NO_{aq} to form $\text{HNO}_{3\text{aq}}$. The maximum density of $\text{HO}_{2\text{aq}}$ is $2 \times 10^{15} \text{ cm}^{-3}$.

It is worth pointing out that the rate of solvation of O atoms is negligible. This is due to

the large consumption of O atoms in the gas phase to produce O₃. On the other hand, the generation of O_{aq} due to the dissociation of H₂O_{aq} is very low because either photo-dissociation or electron-impact dissociation of O_{aq} requires energy higher than 13.5 eV [333].

6.4 RNS

The nitrogen oxide chemistry in the water is initiated by gas-phase species diffusion into the water. There is a variety of nitrogen oxide species (e.g., NO, NO₂, N₂O, N₂O₃, N₂O₄, N₂O₅) produced in the gas discharge, which is initiated by the formation of NO. Importantly, the OH density increases with successive pulses due to the dissociation of water. As a result of their reactions with NO and NO₂, more and more HNO₂, HNO₃, and HOONO species are produced. Besides, HOONO can be produced through the both NO₂ + OH and NO + HO₂ reaction pathways. All of the nitrogen oxide species from the gas phase diffuse into the water layer and slowly convert into HNO_{xaq} (e.g., HNO_{2aq}, HNO_{3aq} and HOONO_{aq}). HNO_{3aq} and HOONO_{aq} quickly hydrolyse in water to form H₃O_{aq}⁺, NO_{3aq}⁻ and ONOO_{aq}⁻. After the analysis of a complex chain of hydrolyzing reactions, it is found that H₃O_{aq}⁺, NO_{3aq}⁻ and ONOO_{aq}⁻ are the major species that result from RNS diffusion into the water layer. Figure 92 shows the NO_{3aq}⁻ and ONOO_{aq}⁻ concentrations during the pulses and at the end of the terminal afterglow. At the end of the 1 s afterglow, the density of NO_{3aq}⁻ above the tissue is 4×10¹³ cm⁻³ and the ONOO_{aq}⁻ density is 2×10¹³ cm⁻³.

The simulation results based on a global model are also presented for comparison. It is assumed that the densities of the reactive species generated by a plasma jet are time-independent and are uniformly distributed in the gas phase. Figure 93 shows the simulated densities as functions of time when both OH and NO are assumed to be dissolved into the water [334]. It is seen that a variety of species such as NO₃⁻, ONOOH, and O₂⁻ are generated in the water. Besides, the water becomes acidic due to the generation of nitric acid, which is

consistent with the experimental observations [335].

The ability to control and specifically modify liquids using plasmas is very important to better understand the induced biological activity of liquid media. Plasma-activated media (PAM) presently represent one of the most promising directions in plasma medicine research because these media can be used for various treatments days of even weeks after the initial plasma activation [336]. The PAM contain a variety of biologically relevant and reactive species which in turn may induce biological effects on living cells and tissues. These species may penetrate into intracellular space and act alongside with the species generated by the cells to cause various effects ranging from altered metabolism and programmed cell death to specific genetic mutations that affect a variety of cellular responses such as stem cell differentiation or inhibition of proliferation of cancer cells. Some of these biological effects resulting, e.g., from plasma-induced oxidative stress are discussed in the following section.

7. Biological effects of reactive species

It is a remarkable fact that small molecules containing reactive oxygen and nitrogen (RONS), including nitric oxide (NO), superoxide (O_2^-), hydrogen peroxide (H_2O_2); singlet oxygen (1O_2); ozone (O_3) and even hydroxyl radical (OH) can and do play important roles in biological systems [67]. Most key biochemical processes were originally thought to be completely dominated by large molecules such as proteins, carbohydrates and lipids. Within the last several decades, however, RONS have been discovered to act as part of the complex system of cellular communication in aerobic biology. One important piece of early evidence that RONS are part of natural cellular processes was the discovery of superoxide dismutase [337] - an enzyme that functions by converting O_2^- to H_2O_2 . Studies of the biological roles of nitric oxide (NO) demonstrated that macrophages generate nitrite (NO_2^-) and nitrate (NO_3^-) anions [338]. Several later studies showed that NO (or a closely related product) is necessary for macrophages acting against either microorganisms or tumours. In 1998, Furchgott,

1 Ignarro and Murad received the Nobel Prize in Medicine or Physiology ‘for their discoveries
2 concerning NO as a signaling molecule in the cardiovascular system’. The importance of
3
4 nitric oxide and its related chemistry was then well established in biochemistry and medicine.
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6 The interest in nitric oxide biochemistry is hard to exaggerate – the current NO literature is
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8
9 estimated to be on the order of 100,000 articles [339].
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12 The early concept of ‘oxidative stress,’ although later to be significantly revised,
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14 considered that an imbalance between oxidizing and reducing agents in cells could lead to
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16 damage, including ageing and many diseases. The main idea was that chemically damaging,
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18 oxidizing radicals needed to be eliminated, ideally with ‘extra’ antioxidants. This led to a
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20 decades-long view that dietary antioxidants are uniformly healthy. However, more recent
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22 research has shown that antioxidants do not generally prolong life and may even be
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24 counterproductive in some cases [340].
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29 RONS are now known to interact with other signaling molecules, usually by reacting
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31 with and therefore changing the composition and structure of functional groups on proteins or
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33 lipids. These structural changes can in turn alter the way the macromolecules (e.g. enzymes)
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35 fold and react with other proteins, thereby altering key processes such as gene expression.
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39 One well-known example concerns the cysteine group. Cysteine is the only amino acid
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41 that contains a sulphur-hydrogen thiol bond, (denoted –SH) in its side group. Proteins with
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43 thiol groups (P-SH) can use this group as part of the way they are involved in signaling. For
44
45 example, proteins with thiol groups can form a disulfide S–S bond when two such groups
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47 react together through an oxidation reaction. Such a reaction changes the shape or
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49 conformation of the protein, and therefore changes the way the protein folds and interacts
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51 with other proteins. This conformational change in turn can affect many other protein
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53 functions, including, in some cases, gene expression.
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58 The current view of oxidation-reduction (redox) biochemistry is that the processes and
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1 the associated chemical species have been a key part of cellular biochemistry since the
2 beginning of aerobic life [341]. Their actions and characteristics are involved in all important
3 signaling networks. It is too simple to imagine that the role of one set of species in this
4 network is only negative and the other is only positive. However, while it is recognized that
5 RONS are key species, excessively high concentrations for long periods are clearly linked
6 with many diseases states and even ageing, as noted below.

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8 The fact that chemical reactions with oxygen-containing species are intrinsically
9 important actors in aerobic biology is often related to cellular oxidative metabolism.
10 Reactions involving RONS therefore allow a coupling between metabolic processes and other
11 cellular functions [342]. Indeed, it is known that one of the most prolific sources of reactive
12 oxygen in cells are mitochondria, the location of key cellular metabolic processes. [Figure 94](#)
13 illustrates how increasing the levels of mitochondrial ROS ‘stress’ first results in increased
14 cellular proliferation and differentiation, followed by gene expression promoting protective
15 antioxidants, then by cell death and associated biomolecular damage [343]. [Table 1](#) lists both
16 positive (physiological) and negative (pathophysiological) effects associated with the actions
17 of RONS [344]. RONS are known to generally act in dual roles, both favourable and
18 unfavourable.

Physiological effects	Pathophysiological effects
Insulin action/secretion	Atherosclerosis
Growth hormones	Diabetes
Activation of kinases	Hypertension
Transcription factors	Cancer
Regulation of transporters, ion channels	Neurodegenerative disease
Control of proteinases	Cataracts
Activation of heat shock proteins	Reproductive disorders
Altering cytoskeleton	
Cell adhesion and spreading	
Shear stress	
Response to noxious stimuli	
Regulator of cellular PH	
Immune functions	
Cell proliferation	
Blood pressure	
Oxygen sensing	
Wound healing	

Table 1. Physiological and pathophysiological effects of RONS [344].

An important physiological role of RONS is in the immune response – both directly interacting with invading microorganisms and with tumours, and indirectly as signaling agents. White blood cells (e.g. macrophages and neutrophils) attack infecting microorganisms via phagocytosis. These cells are known to create and use RONS, many of which are known to also be created in plasmas operating in air at atmospheric pressure. It is possible that plasma effects and immune system effects are analogous [56,345]. Other therapies that are known to generate RONS to attack infections include antibiotics; photodynamic therapy; medicinal honey; and nitric oxide-releasing molecules [346].

Similar functions for RONS have been observed in all of aerobic biology, including in plants. It is apparent that many of the same considerations concerning the dual role of RONS in health and disease apply to plants as well as animals. Reactive species are now known to be central players in both plant signaling [347] and plant immune responses to infection [348,349]. The latter authors write: ‘Production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) occurs rapidly in response to attempted pathogen invasion of potential

1 host plants. Such reduction–oxidation (redox) changes are sensed and transmitted to engage
2 immune function, including the hypersensitive response, a programmed execution of challenged
3 plant cells’ [349].
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7 The potentially dangerous nature of RONS – due to their highly reactive nature –
8 originally obscured their important functional roles in aerobic biology. It is certainly true that
9 excessive concentrations of RONS are associated with many diseases and pathological
10 conditions. However, there is evidence that in at least some cases the organisms deliberately
11 generate and use RONS as part of their natural stress response mechanisms. In this
12 perspective, the presence of excessive cellular RONS may be more evidence of an underlying
13 state of disease or infection rather than the original cause of the malady itself.
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24 As noted above, RONS can be damaging if present for too long and/or in too high a
25 concentration. This idea is illustrated in Fig.95. If baseline levels of RONS are exceeded for
26 only a short time, the effects are not significant. However, continuous, chronically high levels
27 of oxidative stress lead to damaging effects [350]. Inflammatory responses utilize RONS, for
28 example, but inflammation must be terminated fairly quickly or the protective response may
29 itself become damaging. This has obvious implications for the therapeutic use of RONS-
30 generating plasma: exposures must be limited in dose or damage may overwhelm positive
31 therapeutic effects.
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45 **7.1 Reactive species therapeutics**

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47 One of the most important observations that help support the hypothesis that plasma-
48 generated RONS can themselves be therapeutic is that there are known, well-established
49 examples of therapies that utilize these species. Furthermore, the applications for which these
50 species have been shown to be effective – e.g., antimicrobial action; promotion of wound
51 healing; and anti-cancer effects - are also those for which plasma therapy has shown efficacy.
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1 The correlation between RONS and therapy becomes stronger as more evidence accumulates
2 connecting the two.
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4 One example of known plasma-generated species that can be therapeutic is the nitrite
5 (NO_2^-) anion. This specie is now known to occur naturally and has also been used as a kind of
6 drug. This species is one of the most commonly observed species in water exposed to air
7 plasmas, so some of the therapeutic effects of the plasmas may be related to the effects of this
8 species. Nitrite can be formed when nitric oxide is oxidized and if nitrite itself is oxidized, the
9 nitrate anion (NO_3^-) is formed [351]. Nitrite shows potentially therapeutic effects for a variety
10 of diseases and conditions, ranging from ischemia-reperfusion injury to hypertension to
11 inflammatory bowel disease, among others.
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14 Other important examples of the therapeutic roles of RONS come from the field of
15 cancer treatment. It is now well known that many of the established anti-cancer therapies,
16 including radiation therapy, photodynamic therapy and even some forms of chemotherapy, act
17 through a pro-oxidant mechanism [56, 336,352]. Radiation- (or radio-) therapy is known to
18 involve the direct and indirect creation of various reactive species [353]. Photodynamic
19 therapy (PDT) is generally thought to follow from the creation of photo-generated excited
20 oxygen molecules ($^1\text{O}_2$) after photo-excitation of ingested drugs that can be localized in
21 tumours. Sufficient concentration of ground state O_2 present in cellular fluids is necessary for
22 PDT to work [354]. Many authors have discussed the role of oxidative stress induced by
23 many chemotherapeutic anti-cancer drugs, including [355] and [356] among many others.
24 Furthermore, resistance to cancer therapies is known to often involve tumour anti-oxidant
25 mechanisms [357].
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28 These results all suggest that the observed anti-cancer effects of plasma stem at least in
29 part from plasma-generated RONS. Nitric oxide and other reactive nitrogen species have also
30 been shown to act as effective anti-cancer agents [358,359]. As discussed below, however, as
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1 in radiation therapy, many of the RONS responsible for killing or inhibiting tumours may be
2 generated by the cells themselves, long after the application of the plasma. That is, the
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4 adaptive biological response of the organism probably must be considered as a first order
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6 effect in any therapeutic response to treatments such as plasma medicine therapy.
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10 11 12 **7.2 Cell adaptive response to RONS** 13

14 The question of the role of plasma-generated RONS in observed therapeutic effects
15 must take into the account the fact that reactive species are, by definition, relatively short
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17 lived due to their reactivity with other species. Furthermore, the plasma generally acts on a
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19 surface (such as skin or a wound) over a relatively short period of time, perhaps only a few
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21 seconds to minutes at a time. How can the effects of the plasma be seen over longer distances
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23 and times, as is observed, for example, in treating centimeter-diameter tumors through the
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25 skin of mice [360,361]? One possibility is that the RONS trigger an adaptive biological
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27 response that occurs over longer time and length scales [362].
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33 In a recent proposed model of the mechanisms of plasma medical therapy [362], RONS
34 generated by gas phase plasma enter an adjacent cellular or fluid phase and react initially
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36 with protein and other bio-macromolecules forming longer-lived and biologically active
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38 species. Exposure times are short (seconds to minutes) and limited to areas of perhaps a few
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40 cm². The short term and local application of RONS may mimic the innate immune responses
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42 to infection or injury and could initiate communication of stress to adjacent cells and tissue.
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44 The longer lived species that result from the initial reactions between plasma-generated
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46 RONS may enter adjacent cells and stimulate a relatively long-lived cellular stress response.
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53 Subsequent cell-cell communication could transmit the information to tissues some
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55 distance from the original plasma application and might even stimulate an adaptive immune
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57 response [363]. The therapeutic effects of plasma are proposed to be initiated by this initial
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1 burst-like trigger induced by cellular RONS stress. A related idea was proposed by Naviaux
2 [364], who suggested that older ideas about the negative effects of cellular ‘oxidative stress’
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4 should rather be thought of as ‘oxidative shielding’. Naviaux [364] suggests that cells
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6 respond to stresses, including infection and tumors, by producing RONS themselves. Indeed,
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8 this idea is not so different from the idea that plants use endogenously created RONS to
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10 protect themselves directly and indirectly from invading pathogens [349], as noted above.
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18 **7.3. Plasma-generated RONS interacting with cells and tissues**

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21 As noted in the introduction to this article, the slowest of the processes involved in the
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23 interactions between N-APPJ generated reactive species and cells and tissues are the
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25 biochemical and biological processes within living systems. These responses are thought to
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27 range from on the order of seconds to days and are without doubt the least well understood
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29 aspect of the overall process. Even the identity of the reactive species that enter cells are
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31 seldom known since reactive species will generally react with other biological
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33 macromolecules that will enter into complex biochemical processes within cells. The
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35 resulting biological processes are part of the normal machinery of the cells and these
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37 processes are not well understood at present.
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44 Most commonly, *in vitro* studies have demonstrated the connection or correlation
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46 between plasma dose and observed cellular effects [365]. As noted above, ROS are thought to
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48 play important roles in cell lipid peroxidation, among other effects. OH is very reactive, but
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50 its reactivity limits its penetration into condensed phases to perhaps a few hundred microns at
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52 most. H₂O₂, mostly formed from OH, is far more stable with a much longer lifetime and is
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54 known to have strong effects on mammalian cells [366]. Other plasma-generated RONS
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56 species that were found to correlate with biological effects include O₂⁻, ¹O₂, NO₂⁻, NO₃⁻, and
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1 ONOO⁻. A recent observation raises the intriguing possibility that reactive chlorine species
2 may be important reactive precursors in plasma biology. It was found that Ar/O₂ plasma-
3 generated O atoms react with chloride (Cl⁻) in solution, yielding Cl₂⁻ or ClO⁻ [366]. It is noted
4 that reactive chlorine species have a relatively short lifetime under normal cellular conditions
5 and will therefore decay relatively quickly to a less reactive form.
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13 There has been considerable progress achieved in the last several years by various
14 groups in understanding some of the complex processes initiated by plasma-generated RONS
15 within real biological cells [367], but one important and novel direction has been to explore
16 model cell membranes and cell structures. Of course, in using biological cells and tissue, one
17 has the advantage of realism, but at the expense of considerable complexity. The use of
18 model cells and tissue allows for much better controlled experiments with the obvious
19 disadvantage that the model systems are not identical to biological systems. For example, it
20 was found that plasma-generated ROS can be transported across model phospholipid
21 membranes in aqueous cell culture medium [368]. The interactions between plasma-
22 generated ROS and serum components, possibly generating alkyl-peroxide radicals (i.e.
23 ROO[•]), were also shown to be likely of considerable importance in this work.
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41 In another recent example [369], research on plasma-tissue interactions has been
42 reported by using a 1mm thick gelatin film as a surrogate model for real tissue. This film was
43 placed on top of wells filled with PBS (pH 7.4). Each well also contained fluorescent or
44 colorimetric reporters to allow detection of the presence of various RONS in the medium
45 following plasma exposure to the top of the surrogate tissue. A He N-APPJ was used as the
46 plasma source. The remarkable observation of this study was that the presence of a protein to
47 either the gelatin ‘tissue’ or to the PBS below the gelatin layer acts to either raise or inhibit
48 RONS effects depending upon the O₂ concentration. The importance of the presence of
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1 dissolved O_2 as well as protein again suggested to these authors that an alkyl-peroxide was
2 involved. The proposed mechanism is that the plasma-generated RONS will abstract an H
3 atom from the protein hydrocarbon forming a C-centered alkyl radical ($R^\cdot$). This species reacts
4 readily with O_2 in solution to form the alkyl-peroxide $ROO^\cdot$ radical noted above, leading
5 probably to a relatively stable protein hydroperoxide $ROOH$. This class of species has a
6 relatively long lifetime under physiological conditions and might initiate the cell adaptive
7 response envisioned by the oxy-nitroso induced cell shielding model described above.
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18 **7.4 RONS in biochemistry and biology**

19 Understanding the interactions between plasma-generated RONS and tissues and/or
20 cells is still very much in its early stages, but there have been several decades of research in
21 biology, biochemistry and medicine exploring how RONS interact in biological systems.
22 Some key themes have emerged in this large and complex field and we summarize a few of
23 these ideas here.
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33 Perhaps the most important ROS that act as signaling molecule are H_2O_2 and O_2^- .
34 H_2O_2 is a fairly weak oxidizing agent under normal conditions, but in the presence of
35 transition metal ions, especially ferrous ion (Fe^{2+}), H_2O_2 readily decomposes to form highly
36 reactive OH radical. Many potential biological consequences of this and related reactions
37 have been documented [370]
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47 A common biological pathway to form these compounds is NADPH oxidase (NO_X).
48 NO_X will create O_2^- and superoxide dismutase (SOD) converts O_2^- to H_2O_2 . It is thought that
49 the main targets of H_2O_2 are thiol (-SH) groups on proteins, as noted above. Most commonly,
50 the cysteine amino acid is the source of the SH thiol group. H_2O_2 is known to induce two
51 thiol groups to react with each other to form a S-S (disulfide) bond. This happens in the case
52 of the important antioxidant enzyme glutathione (GSH), for example. Thiol groups can also
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1 be further oxidized to form sulfenic acids, or –SOH groups. Thiol groups can be oxidized
2 further to form sulfinic acids (-SO₂H) and then sulfonic acids (-SO₃H). It seems likely that
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4 plasma-generated H₂O₂ and/or O₂⁻ will react with thiol groups in cellular/tissue proteins in a
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6 similar manner.
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10 In biological systems, nitric oxide (NO) is created enzymatically by nitric oxide
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12 synthase enzymes and while it is a fairly weak oxidant by itself, it reacts very rapidly with O₂⁻
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14 to form peroxynitrite, ONOO⁻. Peroxynitrite will engage in many different reactions and has
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16 itself received almost as much attention as NO [371]. ONOO⁻ will react readily with
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18 dissolved CO₂ to form the radicals CO₃⁻ and NO₂, both of which can react further. NO can
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20 also be oxidized to form NO⁺, and this compound is known to react readily with thiol groups
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22 to form S-nitrosothiols (-SNO groups). For example, it is known that red blood cells will
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24 release S-nitrosothiols when O₂ levels are low in the blood in order to cause the blood vessels
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26 to dilate [372]. Once again, there is every reason to assume that plasma-generated species
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28 such as ONOO⁻, NO, CO₃⁻, NO₂ and O₂⁻ will behave biochemically in the same ways if they
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30 are created or delivered to cells and tissue in such a way that they are able to find the relevant
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32 biological reaction targets.
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41 Biological systems also have numerous chemical means to protect themselves from
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43 reactive RONS or perhaps to exploit their reactivity for some biological function:
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45 antioxidants and radical scavengers. Winterbourne defines an antioxidant as ‘any substance
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47 that delays, prevents or removes oxidative damage to a target molecule’ [373]. A radical
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49 scavenger will react with radicals, but these reactions may or may not lead to protection since
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51 the resulting reaction product can itself be damaging. Ascorbic acid (vitamin C) is an
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53 important water-soluble radical scavenging antioxidant. NAC (N-acetylcysteine) is
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55 commonly used to react with RONS in cells, thus serving as an important negative control in
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1 biological studies that attempt to identify the role of RONS. Other scavengers commonly
2 used include the biological enzymes superoxide dismutase (SOD) and catalase, mentioned
3 above, that convert O_2^- and H_2O_2 , respectively.
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8 Vitamin E (most commonly α -tocopherol), is a key lipid-soluble antioxidant. The
9 most common and well-known antioxidant enzyme is glutathione (GSH), as noted above. The
10 biochemical complexity and often coupled, synergistic activities of antioxidant radical
11 scavengers makes cell culture studies potentially misleading [373].
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18 It is important to note the various clever methods that biochemists have developed to
19 detect either RONS themselves or their reaction products. We briefly review several of these
20 methods here. Directly detecting RONS in cells and tissues is tricky because these species
21 often have short lifetimes and react quickly in the complex cellular environment.
22 Nevertheless, some useful techniques have emerged, especially those associated with
23 fluorescent probes. Wardman summarizes the situation regarding the use of fluorescent or
24 chemiluminescent probes to detect RONS in biological systems [374]. Fluorescent probes
25 include dihydrofluoresceins, dihydrorhodamines, hydroethidine and other reduced dyes.
26 Luminescent probes, often for detecting O_2^- , include compounds such as lucigenin and
27 luminol. Wardman points out that there are multiple challenges and potential limitations to
28 using these probes [374]. These include: understanding reaction mechanisms, controlling or
29 at least anticipating the effects of intermediate reactants, accounting for competing or
30 confounding reactions, accounting for likely intracellular concentrations and distribution
31 between organelles, and understanding susceptibility to effects arising from the environment.
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54 Electron paramagnetic resonance spectroscopy (EPR) detects radicals directly, but
55 generally this technique is used in conjunction with so-called 'spin traps.' For example,
56 DMPO (5,5-dimethyl-1-pyrroline-N-oxide) has been used extensively to detect the presence
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of OH radical. These compounds react, more or less selectively, with radicals of interest, creating a relatively long-lived radical species that can be detected more conveniently. These tools have been used in recent years to detect radicals created in liquids exposed to plasmas [375-377].

Study of the reaction products between RONS and biological macromolecules such as proteins and lipids has also seen great advances. The field of ‘proteomics’ attempts to identify the entire set of proteins that exist in an organism such as human beings. There are vastly more proteins than genes, by perhaps a factor of hundreds. A similar field is lipidomics, the study of the entire set of biologically relevant lipid compounds. An important subset of proteomics is ‘redox proteomics,’ the field that concerns itself with post translational modification associated with reactions with RONS. An important goal in redox proteomics and lipidomics is to measure the structural changes to proteins and lipids that have reacted with RONS.

Mass spectrometry of biological molecules has seen great advances in the last several decades, including applications to redox proteomics and lipidomics [378-380]. Mass spectrometric ionization techniques in wide biochemical use include electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI).

8. Challenges and outlook

The non-exhaustive examples presented in this review suggest that atmospheric-pressure plasmas and the reactive species generated in the plasmas represent an exciting and rapidly expanding and evolving multidisciplinary field of research. The multidisciplinary character of this research presents numerous significant challenges which in turn open new and sometimes unprecedented opportunities. The opportunities in turn define the future trends

and perspectives which not only open new avenues for science excellence and application development across several disciplines but also offer exciting promise for convergence, cross-fertilization of the fields and development of the many presently elusive synergies between physical, chemical, and biological effects. Some of these challenges, opportunities and trends in this field are discussed in this section.

8.1 Challenges and opportunities

When defining the challenges facing the research community, it is important to emphasize several features of the research field covered by this review.

First, the field is multidisciplinary as it is based on the knowledge, approaches, methods and techniques from physical, chemical, biological and engineering sciences.

Second, this field targets multiple applications spanning from more traditional sterilization in hygiene, food processing and medical treatments to more recent applications in cancer therapy, stem cell-based biomedical technologies, and bio-nanotechnology.

Third, this research is “multi-phase” as it involves all four states of matter, for example, living cells in a solid state, physiological media in a liquid state, reactive species in a gas phase, and a propagating streamer head in the plasma phase. Moreover, under real conditions relevant to plasma medicine and other relevant applications, these phases are inter-mixed and consequently, interdependent.

Fourth, the problem of bridging the processes of reactive species generation in atmospheric-pressure plasmas and delivering these species to the surfaces and even into the inner space of living cells is formidably complex as it requires detailed studies of a large number of physical, chemical, and biological phenomena and elementary processes that are characterized by the many parameters that in turn span many orders of magnitude. [Figure 1](#) manifests the multi-scale nature of the problems considered.

1 Fifth, these problems require side-by-side experimental and theoretical studies, with each
2 of them having the physics-, chemistry-, and biology-related components.
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4 With no doubt, these general features of the field suggest an overwhelming complexity of
5 the research involved, which explains the relatively limited knowledge presently available in
6 certain areas. These areas will offer numerous challenges and will represent stand-out
7 opportunities for future research and development.
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10 To be more focused with respect to the specific topic of the review, below we will
11 highlight the challenges and opportunities in experimental and theoretical/numerical research,
12 and wherever possible align these discussions with the selected reactive species that were
13 identified in this review of particular relevance and importance to the research and the
14 emerging applications. Importantly, the experimental and numerical studies are not only
15 carried to cross-examine the results obtained using theory and experimentation separately, but
16 also provide valuable input in the areas where these techniques fail while being used
17 separately.
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20 This opens opportunities for *synergistic studies* where the new knowledge obtained using
21 experimental and theoretical approaches simultaneously by far outweighs the knowledge that
22 can be obtained while using them separately. This is why in the following we do not separate
23 the challenges and opportunities into “experimental” or “theoretical/numerical” but rather
24 structure them to reflect the need for better understanding of some specific phenomena or
25 plasma-related effects.
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28 The key focal point in the studies of reactive species generated by atmospheric-pressure
29 plasmas is the diagnostics of the discharges, surrounding gas phase, and the studies of the
30 relevant transport phenomena and the interactions of the reactive species with the liquid
31 media, living cells and tissues, and other objects being treated. From the diagnostics point of
32 view, several challenges have to be met.
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1 As was stressed several times in the review, the characteristics of APPJs are very non-
2 uniform in space and also vary with time over relatively short time scales. The non-
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4 uniformity creates strong gradients of the specific parameters such as species densities which
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6 in turn affects the reaction chemical kinetics, in particular, the reaction pathways that lead to
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8 the generation of any specific species in the required reactive (e.g., radical, excited, etc.)
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10 states. The present-day plasma diagnostics technology usually provide the averaged values of
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12 the species concentrations, whereas numerical models often under- or overestimate the
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14 densities. One of the main reasons of the significant lack of precision is in the high sensitivity
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16 of the outcomes of the modeling to the chosen reaction pathways and species involved, with
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18 the numbers of such species sometimes reaching several hundreds or even more.
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24 Moreover, several examples in this review suggest that omission of some specific
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26 reaction pathways for the reactive species production often lead to major discrepancies
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28 between the experimental and numerical results. This opens opportunities for more focused
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30 studies to identify, both experimentally and theoretically, the leading channels of the species
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32 production, transport and loss and, consequently, for utilizing this knowledge to optimize the
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34 performance of the plasma jets in specific applications.
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39 One of the obvious existing difficulties is related to the fact that most of the existing
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41 numerical models rely on the reaction rate coefficients that in turn depend on many
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43 environment-specific factors. These factors are in most cases not known especially under
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45 non-equilibrium conditions that are intrinsic to the APPJs and many other APPs. When
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47 plasmas interact with liquids, accounting for these factors becomes even more challenging.
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52 This is why new (possibly radically new) diagnostic approaches, methods, and
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54 instruments are vitally needed. For example, simple and fast diagnostic techniques for real-
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56 time and space-resolved monitoring of the fast dynamics of electrons and the associated
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58 electric fields need to be developed and validated against more complex and already
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established techniques. To resolve complex interfacial phenomena during the plasma-liquid interactions, new interface diagnostic techniques are sought to resolve the often turbulent interaction zones at phase boundaries.

A formidable challenge presents in relating the fluxes of the plasma-generated species to the chemical, bio-chemical, and physiological processes in liquid media that contain living cells. The results discussed in [Secs.4 and 5](#) suggest that it is presently possible to measure and calculate, with reasonable accuracy, the fluxes of the major reactive species at the points of their contact with the liquid media or solid surfaces being treated. However, the complexity of salvation and transformations of these species in the liquid media limits the presently available knowledge and understanding of the elementary plasma-induced/assisted processes in the liquid phase. The recent advances summarized in [Sec.6](#) bring significant optimism into the issue, especially because of the multiple opportunities that become available with the advent of more and more suitable diagnostic instruments and techniques adopted from other fields including physical chemistry, electrochemistry, nuclear physics, optics and some others.

However, even if the fluxes of species generated in the plasma phase and eventually delivered into the biological cells and tissues are known, the overwhelming complexity of biological responses presently prevent researchers from directly relating the processes in the atmospheric-pressure plasmas and inside the cells. Indeed, as discussed in [Sec.7](#), the cells actively generate a range of species that not only range in complexity of their atomic organization (from simple molecules and radicals to macromolecules such as enzymes, proteins, protein complexes etc.) but also engage in a range of intracellular signaling cascades that determine the cells's fate choice (e.g., proliferation, differentiation, programmed death and many other options). Some of these species (e.g., reactive oxygen and nitrogen species,

1 RONS) are produced inside the cells as a part of their response to the plasma-induced stress
2 originating due to the specific physical (e.g., heat) and chemical (e.g., reactions) factors.
3

4 Therefore, even though concentrations of some of the most common RONS can presently
5 be routinely measured both in the intracellular space and in the extracellular environments by
6 using common electrochemical and biochemical means, it is still an unsurmountable task to
7 single out the points of origin of the species - in simple terms if they were transported from
8 the plasma jet or were generated by the cell's immune system's machinery. This problem has
9 been widely recognized by the community as a paramount challenge in the plasma medicine
10 and related fields of research in the coming years.
11

12 Let us now focus on the challenges and opportunities related to the reactive species
13 generated in APPJs and discussed in detail in [Secs.3-5](#). It is worth emphasizing that the
14 measurements discussed in this review are carried out for different plasma jet devices and
15 driven by different power supply. In other words, device-to-device variability may affect the
16 outcomes of the measurements and their interpretations. In order to understand more about
17 the physics and the plasma chemistry processes of N-APPJs, the available diagnostics should
18 be applied to the most common or a few of the most typical N-APPJ devices.
19

20 For the electron density measurements presented in this review, the obtained electron
21 densities usually appear close to the upper edge of the simulation results. One of the reasons
22 might be because the plasmas that were measured are either driven by fast rising pulsed
23 voltages or by RF or microwave power supplies. Such plasmas are commonly hypothesized
24 to have higher electron densities than those driven by kHz AC power supplies. On the other
25 hand, most of the available numerical modeling and simulations focus on the plasma plumes
26 driven by kHz AC power supplies. Therefore, experiments on the measurements of the
27 electron densities of the plasma plumes driven by kHz AC power supplies are needed.
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However, if the electron densities in these plumes are on the order of 10^{11} - 10^{12}cm^{-3} , then the diagnostic methods discussed in this review are not applicable.

Besides, the electron density measurements presented in this review are mostly performed during the discharge phase when the plasmas are generated and sustained. However, most of these plasma discharges are pulsed where the discharge currents appear in a pulsed mode. We are not aware of any reliable measurements that quantify the decay behavior of the electron density during the plasma-off phase. The off-phase features much lower electron densities which presents another challenge and opportunity to develop more sensitive techniques for time-resolved electron measurements in low-density, non-stationary reactive environments.

Regarding the optimization of the O atom concentration, the available studies are at the early stage and are far from being complete. The effects of the surrounding gas, the humidity of the surround air, the conductivity and humidity of the treatment objects, the gas flow rate, the applied voltage amplitude, frequency, and other parameters, on the O atom concentration are presently not available. Further studies will help optimize N-APPJ design and operation in specific applications that rely on reactive oxygen atoms.

Regarding OH radicals generation, there are many unanswered questions. For example, some results show that OH concentrations reach their maximum when H_2O concentrations are at around several thousand ppm. On the other hand, results presented by other groups show that OH concentration reaches its maximum when H_2O concentration are around several hundred ppm. One possible reason could be because the difference of the power delivered to the plasma. It is noticed that, when RF power supply is used, higher power is usually delivered to the plasma compared to the kHz pulsed DC or AC power supply case; this is believed to lead to higher OH concentrations and different OH concentrations at different humidity levels characterized by relative concentrations of H_2O vapor. Furthermore, in

1 realistic applications when a solid target is placed in front of a plasma jet, the discharge, gas
2 flow dynamics, and hence, the OH distribution becomes more complicated and difficult to
3 monitor. Further studies, especially numerical simulations are required to clearly understand
4 the mechanisms and quantify the production rates of OH radicals.
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9 The excited species, including the $O_2(1\Delta_g)$, $N_2(A^3\Sigma_u^+)$, and metastable state He and Ar,
10 besides their direct effects on biological objects, could significantly contribute to the plasma-
11 assisted chemical and biochemical processes. However, as mentioned above, reliable
12 diagnostics of their concentrations and spatial distributions are very limited, not to mention
13 the expected optimization of their generation and subsequent transport.
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22 Atomic nitrogen species are among the most difficult species to generate. Indeed,
23 because of the high bond energy of the N_2 triple bond, significant energy is needed to break a
24 N_2 molecule into two N atoms compared to dissociation of O_2 molecules into O atoms. This
25 is why the concentration of nitrogen atoms in N-APPJs is expected to be much lower than the
26 concentration of oxygen atoms under the same discharge conditions. This might be one of the
27 reasons why the role of nitrogen atoms has not attracted sufficient attention whereas the
28 studies reported to date are quite rare. Nevertheless, N atoms are expected to participate in
29 many chemical and biochemical reactions of relevance to the plasma health care and
30 medicine applications.
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44 NO species, as mentioned above, plays several important roles in biological systems. It
45 can quickly dissolve into water when the object to be treated is wet. Thus not only the gas-
46 phase, but also liquid-phase NO species should be measured experimentally and their
47 concentration quantified by numerical models.
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53 Regarding plasma-liquid interaction, only a few works have been conducted to date and
54 the information available suggests that the options and achieved level of control of such
55 interactions and the arising chemical and biochemical effects require substantial improvement.
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For example, the 2D simulation of the accumulation of reactive species during the APPJ interaction with liquids discussed in [Sec.6](#) is limited to only three pulses. This starkly contrasts with the real-world experiments, where even for a treatment time of few seconds with a frequency of kHz, thousands of pulses are applied. Therefore, the accumulation of the reactive species in the liquid could be much higher than presented in this review.

Besides, some of the reactive species, which only appear at low concentrations for three pulses, could have much higher concentrations when the number of pulses is much higher. This may even change the prevailing reaction pathways and chemical kinetics in the liquid media used for the treatment of biological objects. Therefore, further studies of the accumulation effects of reactive species in relevant liquid media are warranted.

In addition, the 2D model discussed in [Sec.6](#) does not include the effect of the gas flow on the liquid flow dynamics. In the model, the liquid layer is treated by assuming the liquid in a steady state and that all the species penetrate the liquid layer through diffusion. When N-APPJs are used, there is gas flow and the gas flow will disturb the liquid layer and induce the flow of the liquid. This effect will obviously affect the distribution of the species distribution inside the liquid layer and requires careful consideration in the future.

More comprehensive studies are required to better understand biological effects of RONS (see [Sec.7](#)), especially in plasma medicine applications. Unfortunately, the current research is very limited and requires extensive collaborations among researchers from diverse fields, including plasma physics, solution chemistry, bio-chemistry, molecular biology, and some others. The obvious need to conduct multidisciplinary research leads to the expected future trends in this rapidly emerging research field that are discussed in the following section.

8.2 Future trends and outlook

1 In brief, the future trends will embrace the expansion of the existing numerical
2 modeling and experimental techniques both in breadth and depth, while many new techniques
3 are expected to emerge, especially those that rely on information exchange between the
4 numerical and experimental modes of study. Both the experimental and numerical studies
5 will evolve towards better understanding of the plasma dynamics and chemical kinetics in
6 APPJs and the associated transport and interfacial phenomena upon their interactions with
7 gasous, liquid and solid media.
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10 Below are just a few research directions that in our opinion require specific attention:
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- 13 (i) development, diagnostics and simulation of plasma jet arrays – given the pressing
14 demands of process scale-up and parallelizing in view of potential industrial
15 applications;
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- 17 (ii) studies of the effects of plasmas on the gas dynamics in N-APPJs;
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- 19 (iii) development of kinetic and photoionization models for various compositions of
20 plasma forming gases, along with appropriate (e.g., with sufficient spatial and
21 temporal resolution) diagnostic techniques and instrumentation;
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- 23 (iv) quantifying the accumulation effects of multiple discharge pulses rather than
24 single or few voltage pulses – which is a common issue in pulsed discharge
25 applications either in gaseous or liquid environments;
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- 27 (v) revealing the leading channels of production and loss for various reactive species,
28 followed by focusing both the experimental and numerical studies on these
29 specific channels and species involved;
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- 31 (vi) extensive parametric investigations of the effects of variation of these parameters
32 (e.g., plasma forming gas, applied power, temperature, etc.) on the composition
33 and reactivity of the reactive species produced.
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1 These points are certainly not exhaustive and have been selected among the most interesting
2 specific topics discussed in the review.
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5 Perhaps the most important trend observed in the development of this research field is
6 *convergence* which we have already seen in cross-fertilization and synergies between the
7 experimental and numerical studies. Convergence is one of the most important megatrends
8 presently experienced by several industry sectors globally. Given the multidisciplinary nature
9 of the research field of this review, one can also expect a significant convergence with other
10 relevant fields of plasma science and applications.
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21 For example, convergence with the plasma nanoscience research may be underpinned
22 by several common factors, concepts, and approaches. For example, spanning several orders
23 of magnitude in time scales introduced in [Fig.1](#) is conceptually similar to bridging
24 macroscopic and nanoscale phenomena in nanostructure synthesis and processing using low-
25 temperature plasmas [\[381\]](#). Furthermore, plasma treatment of solid (e.g., polymer) surfaces,
26 with microscopic and even nanoscale precision [\[382\]](#) and the arising precise tailoring of
27 surface energy may help exploring a wider range of biological effects of atmospheric-
28 pressure plasmas on living cells. Synergistic actions of APPs with plasma-produced or treated
29 nanoparticles may in turn lead to new research areas at the interface between the plasma
30 medicine and nano-medicine which presently rely on quite different approaches [\[383\]](#).
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46 There are multiple opportunities for collaboration and convergence with biological
47 and biomedical sciences including but not limited to clinical and preventative medicine,
48 molecular biology, biochemistry etc. This opportunity may materialize through the
49 establishment of a common data exchange, processing and interpretation that will relate
50 physic-chemical data with modern biological data analysis and processing approaches based
51 on bioinformatics, big data, and a host of “-omics” approaches. Examples of the advanced “-
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ohmics” approaches directly relevant to plasma health care and medicine research include genomics, transcriptomics, proteomics, metabolomics and some others.

Finally, it is worth emphasizing that the first plasma jets are currently tried in clinical applications, for instance, plasma jets in argon. These treatments are becoming increasingly popular among medical doctors and translational medicine researchers, as they acknowledge a certain degree of similarity and some extra features of the plasma jets compared to laser- and electron-beam-based techniques already used in clinical practice. The promising therapeutic results including ongoing clinical trials provide further confidence and enthusiasm in the use of plasmas in health care, medicine, and related applications.

9. Conclusion

This review has critically examined the production of the key reactive species in atmospheric-pressure plasmas and interaction of these species with liquid media and biological materials of direct relevance to applications of such plasmas in a rapidly emerging field of research presently known as biological and medical applications of plasmas. This field is for simplicity often addressed as plasma medicine, which in fact includes a broader research scope well beyond plasma applications in medicine.

The examples of species generation, mutual transformation and transport across plasma, gas, and liquid environments to the treatment objects (e.g., living cells in a liquid medium) critically examined in this article suggest that this is a very exciting multidisciplinary field of research full of challenges and opportunities for future scientific research and development of commercial applications. The advances achieved to date, in particular in the production, diagnostics of the plasmas and basic understanding of the multi-scale, multi-phase processes involved bring a reasonable optimism to expect that a much better understanding of the whole sequence of interactions of atmospheric-pressure plasmas with living cells and potentially

tissues may be achieved in the coming years. This achievement is only possible through the concerted multi-disciplinary international collaborative effort.

Importantly, the level of confidence in the utility and efficacy of non-equilibrium atmospheric-pressure plasma tools and approaches is continuously increasing, not only because of the reliability but also of the safety of the plasma systems. Plasma medicine is widely recognized as a mature and established field of research with many results currently being translated into clinical applications including wound therapy and palliative medicine. The hopes are high and the recent and ongoing studies raise the hope that plasmas might eventually emerge as a game changer in cancer treatment.

This optimism is supported by the advances made by several research groups around the world, which suggest that synergistic effects of plasmas and common cancer therapies may lead to the as yet elusive selectivity and efficacy of tumor recession in aggressive clinical oncology treatments. This and several other examples of synergies between the effects of plasmas and other materials such as nanoparticles in nanotechnology or nano-medicine processes suggest that non-equilibrium atmospheric-pressure plasma devices may have excellent prospects to eventually become commonplace industrial and consumer products widely accepted in several fields of human activity.

Finally, we hope that this review will stimulate extensive discussions among researchers specializing in the fields as seemingly unbridgeable as the physics of gas discharges and bio-informatics.

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fig-1-plasmajet-liquid-cell.jpg

fig-2-schematic of several plasma jet devices.jpg

fig-3-plasma bullet.jpg

fig-4-e-coli-killing efficiency.jpg

fig-5-killing-petri-dish-image.jpg

Cell viability at post-treatment hours Cells treated in media

fig-7-flow-chart-of-simulation.jpg

fig-8-energy-schematic-of-molecular-for-lif.jpg

fig-9-typical-lif-setup.jpg

fig-10-multiple-energy-level-for-lif.jpg

fig-11-calibrate-o-atom-by-no2-trtration.jpg

fig-12-calibration-o-by-other-gas.jpg

fig-13-cavity-ring-down-spectroscopy.jpg

fig-14-experiment-setup-microwave-plasma.jpg

fig-15-temporal-behavior-of-electron-density-of-a-plasma-jet.jpg

fig-16-spatial-behavior-of-te-ne.jpg

fig-17-2d-ne-behavior.jpg

fig-18-radial-distribution-ne.jpg

fig-19-o2-on-o-density.jpg

fig-20-2d-distribution-of-o-density.jpg

fig-21-air-on-o-atom-concentration-distribution.jpg

fig-23-schematic-of-introducing-curtain-gas.jpg

fig-24-2d-of-n2-and-o-emission.jpg

fig-25-nitrite-nitrate-in-liquid-treated-by-kinpen.jpg

fig-26-oh-for-different-water-concentration-for-kinpen.jpg

fig-27-air-in-ar-flow-by-experiment-and-simulation.jpg

fig-28-oh-distribution-plasma-emission-for-different-ar-flow.jpg

fig-29-oh-radial-distribution-for-different-he-flow.jpg

fig-30-oh-at-2mm-from-nozzle-for-different-ar-flow.jpg

fig-31-oh-for-different-o2.jpg

fig-32-temporal-behavior-of-oh-for-different-o2.jpg

fig-33-oh-for-different-o2-h2o-concentration.jpg

fig-34-relative-humididy-2d-distribution.jpg

fig-35-2d-distribution-of-oh.jpg

(a) Distilled water

(b) Saline water

Distilled water

Saline water

fig-41-oh-air-h2o-for-distilled-water-object.jpg

fig-42-air-2d-diffusion-distribution.jpg

fig-43-2d-distribution-oh.jpg

Discharge in Air

Discharge in Ar

fig-47-o3-distribution.jpg

fig-48-temperature-distribution.jpg

fig-49-sdo-for-different-power-and-o2.jpg

fig-51-sdo-for-different-flow-rate.jpg

fig-52-n-atom-concentration-for-different-n2-concentration.jpg

fig-54-air-concentration-on-no-for-different-flow.jpg

fig-55-effect-air-on-no-for-different-huminty.jpg

fig-56-2d-profile-of-no.jpg

fig-57-axial-profile-of-no-for-different-power.jpg

fig-58-axial-profile-of-no-for-different-air.jpg

fig-59-temporal-behavior-of-n2a-state.jpg

fig-60-spatialtemporal-behavior-he-metastable-state.jpg

fig-61-radial-distribution-of-he-metastable-state.jpg

fig-62-temporal-behavior-of-he-metastable-state.jpg

fig-63-temporal-behavior-of-he-metastable-for-different-voltage.jpg

fig-64-radial-distribution-of-he-metastable-state.jpg

fig-66-ar-metastable-state-and-n2c-emission-decay-behavior.jpg

fig-67-radical-species-concentration-at-different-time.jpg

fig-68-simulation-of-radical-species-concentration-at-a-given-time.jpg

fig-69-radial-average-density-of-reactive-species.jpg

fig-70-o-and-o2a-for-different-he-purity.jpg

fig-71-axial-distribution-of-different-reactive-species-for-different-applied-voltage.jpg

fig-72-oh-e-distribution.jpg

fig-73-radial-average-reactive-species-concentration.jpg

fig-75-oh-build-up-after-many-pulse.jpg

fig-76-spatial-distribution-of-o-o3.jpg

fig-77-o-density-for-different-power.jpg

fig-78-reactive-species-concentration-along-plasma-jet.jpg

fig-79-temporal-behavior-major-plasma-species.jpg

fig-80-o-o3-vs-distance-from-nozzle.jpg

fig-81-o-o3-2d-map.jpg

fig-82-plasma-characteristic-as-distance-from-nozzle.jpg

fig-83-reactive-species-density-along-distance-from-nozzle.jpg

fig-84-temporal-behavior-of-reactive-species.jpg

fig-86-e-and-other-negative-ions.jpg

5 ns

100 ns

5 μs

0.1 ms

30 μs

5 ms

0.1 s

1 s

fig-89-temporal-behavior-of-reactive-species.jpg

fig-90-tracking plasma generated h2o2 from gas into liquid phase.tif

fig-91-plasma-interacting with liquid covered tissue.jpg

fig-93-simulation-of-reactive-species-temporal-behavior.jpg