

POLYTECHNIQUE MONTRÉAL

affiliée à l'Université de Montréal

**Microfluidic devices as diagnostic tools for plasma-liquid and plasma-bio
interactions**

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Mémoire présenté en vue de l'obtention du diplôme de *Maîtrise ès sciences appliquées*
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Ce mémoire intitulé :

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interactions**

présenté par **Julien BISSONNETTE-DULUDE**

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RÉSUMÉ

Au cours des deux dernières décennies, les plasmas à basse température et à pression atmosphérique ont reçu un intérêt croissant de la part de chercheurs en technologies biomédicales. Ces plasmas peuvent influencer les processus biologiques naturels par le biais des photons qu'ils émettent et des espèces chimiques réactives qu'ils produisent. De nombreuses espèces chimiques produites par les plasmas en contact avec des gaz atmosphériques sont les mêmes que celles impliquées dans divers processus biologiques, dont la signalisation cellulaire. Aujourd'hui, les applications biomédicales du plasma incluent le traitement de plaies chroniques, le traitement de cellules et tissus cancéreux, la stérilisation et la décontamination.

Afin d'accélérer la transition vers des traitements cliniques utilisant le plasma, les chercheurs de la communauté biomédicale sont à la recherche de modèles biologiques reproductibles, fiables et bien établis pour étudier les interactions entre des systèmes biologiques et les plasmas. À cet effet, nous croyons que l'utilisation de dispositifs microfluidiques offre des opportunités pour de telles recherches puisque leur utilisation permet déjà de reproduire efficacement et à faible coût des expériences de laboratoire dans différents domaines, dont la chimie analytique, la biochimie et la biologie.

Ainsi, l'objectif central du projet est le développement d'une plateforme qui combine un dispositif microfluidique à une source de plasma afin de fournir de nouveaux outils pour l'étude des interactions plasma-liquide et pour utiliser la microfluidique dans un contexte de recherche en médecine par plasma. Pour ce faire, une nouvelle plateforme plasma-microfluidique a été développée permettant de mettre en contact un plasma d'hélium et de vapeur d'eau avec un liquide circulant dans un dispositif microfluidique. Cette plateforme combine le COST-Jet, une source de plasma de référence, avec des dispositifs microfluidiques fabriqués par impression 3D. Ces derniers ont été développés pour créer un écoulement de liquide et de gaz permettant à la fois une opération stable de la plateforme et une optimisation du transport des espèces chimiques générées par le plasma vers le liquide.

La source de plasma a été caractérisée électriquement par une mesure de la dissipation de puissance de la décharge plasma. Les sources de plasma miniatures, comme le COST-Jet, ont de faibles capacitances menant facilement à de larges erreurs lors d'une mesure de puissance dissipée. Pour contrer ce problème, une méthode d'adaptation d'impédance a été adoptée permettant la mesure de la puissance dissipée par le plasma avec une incertitude de moins de 15%. De plus, la production et le transport d'espèces chimiques réactives vers le liquide circulant dans la plateforme ont été confirmés en mesurant la concentration de

peroxyde d'hydrogène. Cette concentration mesurée varie de 0 à 25 μM selon les conditions expérimentales.

Finalement, afin d'améliorer notre compréhension des processus de production et de transport d'espèces chimiques réactives dans la plateforme plasma-microfluidique, un modèle a été développé. Ce dernier combine un modèle de dynamique des fluides bidimensionnel dans le COST-Jet et le liquide ainsi qu'un modèle de cinétique chimique en dimension zéro (fonction du temps uniquement) dans le plasma. Cette nouvelle approche quasi-2D permet de modéliser un grand nombre de réactions en dimension zéro tout en conservant de l'information spatiale grâce à des simulations de transport d'espèces chimiques en deux dimensions, le tout, en un temps de calcul raisonnable. Les simulations permettent d'estimer la concentration de peroxyde d'hydrogène dans le liquide microfluidique après le traitement plasma avec une différence de moins de 50% par rapport aux données expérimentales; un résultat très satisfaisant considérant les différentes approximations adoptées par le modèle.

Le développement d'une nouvelle plateforme plasma-microfluidique et d'un modèle simplifié décrivant les processus physiques et chimiques essentiels qui s'y déroulent constitue les bases pour l'utilisation de dispositifs microfluidiques comme outil de diagnostic physique, chimique et biologique pour les recherches sur le plasma. Bien que la plateforme ait été développée dans l'optique d'applications biomédicales, nous croyons que l'utilisation de la microfluidique pourrait aussi avoir un impact positif dans d'autres domaines d'applications du plasma où les interactions plasmas-liquides jouent un rôle important comme le traitement des eaux usées ou l'agriculture assistée par plasma.

ABSTRACT

In the last two decades, non-thermal and atmospheric pressure plasmas have received increasing interest from researchers in biomedical technologies. These plasmas can influence natural biological processes through the photons they emit and the reactive chemical species they produce. Many of the chemical species produced by plasmas in contact with atmospheric gases are the same as those involved in various biological processes including cell signaling. Today, biomedical applications of plasma include treatment of chronic wounds, treatment of cancerous cells and tissues, sterilization and decontamination.

To accelerate the transition to plasma treatment in a clinical context, researchers of the plasma medicine community need reliable, reproducible and well-established biological models to study the interactions between biological systems and plasmas. To this end, we believe that the use of microfluidic devices offers relevant opportunities for such research as microfluidic devices already allow for efficient and low-cost replication of laboratory experiments in various fields of research including analytical chemistry, biochemistry and biology.

Thus, the central objective of the project is the development of a platform that combines a microfluidic device with a reference plasma source to provide new tools for fundamental plasma-liquid interactions studies and to enable the use of microfluidics in the context of plasma medicine research. To this end, a new plasma-microfluidic platform has been developed to couple a helium plasma source with a liquid flowing in a microfluidic device. This platform combines the COST-Jet, a reference plasma source, with 3D printed microfluidic devices. The microfluidic devices were developed to form a flow of liquid and gas that allows both a stable operation of the platform and an optimization of the transport of the plasma-generated reactive species to the liquid.

The plasma source was electrically characterized by measuring the plasma discharge power dissipation. Miniature plasma sources, such as the COST-Jet, have small capacitances which easily lead to large uncertainties in the power dissipation measurement. To tackle this problem, an impedance matching method has been adopted allowing a power measurement uncertainty of less than 15%. Moreover, the production and transport of reactive chemical species to the liquid flowing in the platform was confirmed by hydrogen peroxide concentration measurements. This measured concentration varies from 0 to 25 μM depending on the experimental conditions.

Finally, to improve our understanding of the key production and transport pathways of reactive species in the plasma-microfluidic platform, a simulation model was developed. This

model combines a two-dimensional fluid dynamics model inside the COST-Jet plasma and effluent channel and inside the liquid together with a zero-dimensional (function of time only) reaction kinetics model in the plasma and effluent channel. This new quasi-2D approach allows to model a large number of reactions in zero-dimension while preserving spatial information through two-dimensional chemical species transport simulations, in a reasonable computational time. The simulations allow to estimate the hydrogen peroxide concentration in the microfluidic liquid after the plasma treatment with a difference of less than 50% compared to the experimental data; a very satisfactory result considering the different approximations adopted by the model.

The development of a new plasma-microfluidic platform and a simplified model describing the essential physical and chemical processes that take place within it provides the foundation for the use of microfluidic devices as a physical, chemical and biological diagnostic tool for plasma research. Although the platform was developed with biomedical applications in mind, we believe that the use of microfluidics could also have a positive impact in other areas of plasma applications where plasma-liquid interactions play an important role, such as wastewater treatment or plasma assisted agriculture.

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LIST OF SYMBOLS AND ACRONYMS

0D	zero dimension
1D	one dimension
2D	two dimensions
3D	three dimensions
DBD	dielectric barrier discharge
EEDF	electron energy distribution function
NTP	non-thermal plasma
PPD	plasma power dissipation
ppm	parts per million
redox	oxidation-reduction
RF	radio frequency
RMS	root mean square
RONs	reactive oxygen and nitrogen species
slm	standard liter per minute
a	radius of the cylindrical cross-section [m]
A	Chapman-Enskog empirical constant $[\frac{\text{Pa} \cdot \text{m}^4}{\text{K}^{3/2} \text{s}} \sqrt{\frac{\text{kg}}{\text{mol}}}]$
$A_{channel}$	cross section area of the channel [m ²]
$A_{chimney}$	cross section area of the chimney [m ²]
$a_{s,i}^L$	stoichiometric coefficient of species s in reaction i on the left side of the reaction
$a_{s,i}^R$	stoichiometric coefficient of species s in reaction i on the right side of the reaction
$\alpha_{j,i}$	stoichiometric coefficient of species j in reaction i
c_g	concentration in the gas [mol/m ³]
c_i	concentration of specie i [mol/m ³]
$c_{aq,i}$	concentration of specie i in the liquid [mol/m ³]
c_l	concentration in the liquid [mol/m ³]
D	diffusion coefficient [m ² /s]
D_i	diffusion coefficient of specie i [m ² /s]
$D_{aq,i}$	diffusion coefficient of specie i in the liquid [m ² /s]
Δp	pressure variation across a fluidic channel [Pa]

ΔP_{avg}	uncertainty on average power dissipated during one electrical period [W]
e	elementary charge [C]
E	electric field [V/m]
ε_1	Lennard-Jones parameter (energy) of helium [J]
ε_2	Lennard-Jones parameter (energy) of specie of interest [J]
ε_{th}	threshold energy of the reaction [J]
$f(\varepsilon)$	electron energy distribution function [$J^{-3/2}$]
ϕ	phase angle between current and voltage [rad]
ϕ_c	contact angle between the liquid and the microfluidic device's walls [rad]
g	gravitational acceleration [m/s^2]
γ	surface tension [N/m]
h	height of the liquid chimney [m]
η	fluid viscosity [Pa·s]
$I(t)$	time varying current [A]
I_{RMS}	root mean square current [A]
I_{off}	RMS current without a plasma discharge [A]
I_{on}	current with a plasma discharge [A]
$\vec{J}_l$	specie fluxes at the liquid interface [$kg/(m^2 \cdot s)$]
$\vec{J}_g$	specie fluxes at the gas interface [$kg/(m^2 \cdot s)$]
k_b	Boltzmann constant [J/K]
k_i	reaction rate of reaction i (varying units)
ℓ	length of the fluidic channel [m]
L	characteristic length [m]
$L_{channel}$	length of the fluidic channel [m]
m	number of reaction
M_i	molar mass of specie i [kg/mol]
n_e	electron density [$1/m^3$]
n_j	density of specie j [$1/m^3$]
n_s	density of species s [$1/m^3$]
Ω	temperature-dependent collision integral
p	pressure [Pa]
p^*	pressure at the bottom of the chimney [Pa]
p_{cap}	capillary pressure [Pa]
p_g	gravitational pressure [Pa]

p_{hyd}	hydrodynamic pressure [Pa]
P_{avg}	average power dissipated during one electrical period [W]
$P_{channel,x}$	mechanical power consumed to impose a liquid flow rate in a channel x [W]
Pe	Péclet number
P_{off}	dissipated power without a plasma discharge [W]
P_{plasma}	power dissipation in the plasma discharge [W]
$P_{surface}$	power consumed for the formation of the air-water interface [W]
$\wp_{chimney}$	perimeter of the chimney [m]
$\wp_{channel}$	perimeter of the channel [m]
Q	fluidic flow rate [m ³ /s]
Q_3	imposed flow rate in channel 3 [m ³ /s]
Q_{air}	flow rate of air [m ³ /s]
$Q_{fluid\ 1}$	flow rate of fluid 1 [m ³ /s]
$Q_{fluid\ 2}$	flow rate of fluid 2 [m ³ /s]
Q_{water}	flow rate of water [m ³ /s]
$R_{air,x}$	fluidic resistance of channel x for air [Pa·s/m ³]
$R_{aq,i}$	reaction source term of specie i in the liquid [mol/s]
R_{fluid}	fluidic resistance [Pa·s/m ³]
R_L	resistivity of the inductor [Ω]
$R_{water,x}$	fluidic resistance of channel x for water [Pa·s/m ³]
ρ	liquid density [kg/m ³]
S_i	source term of specie i [mol/s]
σ	plasma conductivity [1/ Ω]
σ_1	Lennard-Jones parameter (distance) of helium [m]
σ_2	Lennard-Jones parameter (distance) of specie of interest [m]
σ_i	cross-section of collision i [m ²]
T	temperature [K]
v	average bulk velocity [m/s]
$\vec{v}$	velocity vector field [m/s]
$v(\varepsilon)$	electron velocity [m/s]
$\vec{v}_{aq}$	velocity vector field in liquid [m/s]
v_d	electron drift velocity [m/s]
$V(t)$	time varying voltage [V]
V_{RMS}	root mean square voltage [V]

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CHAPTER 1 INTRODUCTION

The medical community is in a constant state of search for novel therapies to address the most challenging illnesses. The use of plasma, an ionized gas, close to ambient temperature and pressure brought new hopes in the last three decades to cure complex medical conditions such as chronic wound or cancer. The use of plasma for biomedical applications is often referred as the field of plasma medicine. While the term plasma medicine appeared in the scientific literature in the 2000s [4], the first biological experiments involving plasma were conducted in the mid-1990s. In 1996, Laroussi showed that plasma devices operated at atmospheric pressure and low gas temperature can inactivate bacteria [5]. In the early 2000s, Eva Steoffels *et al.* conducted experiments on cells exposed to a plasma and showed that a plasma treatment can lead to cell apoptosis [6, 7]. From there, increased attention from the plasma physics community was given to biomedical applications. In the following years, the plasma medicine research community grew to become highly multidisciplinary and vibrant. Today, the actors of the plasma medicine community come from different backgrounds: physicists, chemists, engineers, biologists, and clinicians.

The innovation path from the idea to the prototype, animal studies, human studies, certification and ultimately, clinical application is long, complex and costly. Researchers of the biomedical community are in constant need of reliable and faster approaches. The field of plasma medicine is not an exception to this rule. Often, novel treatments tested *in vitro* and *in vivo* will not show similar efficacy toward a specific condition simply because the *in vitro* model does not accurately represent the *in vivo* disease's environment. In the search for accurate and well-established biological models for studies in the plasma medicine field, biological models embedded in microfluidic devices could play an important role. Microfluidic devices have already proven themselves useful for testing different chemotherapy, radiotherapy and immunotherapy treatments [8]. The potential of reproducibility and parallelizability that microfluidic devices offer would make them ideal for studying the effects of plasma on biological systems.

In this Master's thesis, a unique and novel platform that combines a reference plasma source with a home-made microfluidic device is developed and used in a study of plasma-liquid interactions. The developed plasma-microfluidic platform is studied with different diagnostic methods. The plasma source is analysed electrically in terms of plasma power dissipation, and the plasma treated liquid is analysed with colorimetric assays. To understand key plasma-chemical pathways enabled by the plasma-liquid interactions, a plasma reaction kinetics and

fluid dynamics model is developed with a new quasi-2D approach. The simulation results are validated and compared to experimental liquid diagnostic data. To set the theoretical basis for the understanding of this manuscript, key concepts of plasma and microfluidic are first reviewed.

1.1 Literature review

1.1.1 Non-thermal plasma and its applications

The term plasma refers to a partially or fully ionized gas and is a state of matter, as are solid, liquid and gas [9, 10]. Plasma exists in a state of quasi-neutrality (the electric charge of the plasma volume is locally neutral) and shows collective behaviors (plasma properties do not arise from a single particle) [11]. From an application point of view, classifying the different plasmas that exist can be very useful. Plasmas can be classified by the pressure of the gas in which it is formed. Some plasmas exist at low pressure (most semiconductors are made with low-pressure plasma processes), some plasmas exist at atmospheric pressure (plasma for biomedical applications are typically atmospheric pressure plasmas) and some plasmas exist at high pressure (plasma in high-intensity light sources) [12]. A plasma can also be categorized by the way electrical power is applied. Laboratory plasmas can be ignited with direct current (DC), low-frequency, radio-frequency (RF) or microwave signals. Another common way to classify plasma is by the temperature of the heavy particles (ions and neutrals) it contains. Plasmas can exist at ambient and even lower temperatures, aurora borealis as an example, and other plasmas, in stars for example, are at extremely high temperatures. This temperature classification is closely related to classifying a plasma through thermodynamic equilibrium. In an equilibrium plasma, all particles, generally electrons, ions and neutrals, are at thermal equilibrium while in a non-equilibrium plasma, lighter particles (electrons) can be at very high temperatures, while heavy particles are at much lower temperatures. Due to the focus on biomedical applications of plasma, this thesis will describe plasma generated at atmospheric pressure and at a gas temperature close to room temperature. We will refer to these plasmas as non-thermal plasma (NTP). non-thermal plasma (NTP)s are often also called non-equilibrium plasmas as they are out of thermodynamic equilibrium. The electrons in NTPs are at a much higher temperature than the ions and neutrals. This makes them interesting in the context of plasma medicine because they are highly reactive chemically, since they contain high energy electrons, but can be operated at a gas temperature compatible with biological systems. The use of NTP in the context of plasma medicine grew in the last several years and today, biomedical applications of plasma include:

- decontamination and sterilization,
- plasma wound healing,
- plasma for cancer treatment,
- plasma treatment of surface for biocompatibility,
- plasma for dentistry.

These different topics were reviewed exhaustively by the community [4, 13–22].

The effects of NTP on biological systems originate from the chemical species it generates and the radiation it emits [23]. A NTP operated in atmospheric gases or in contact with atmospheric gases, generates reactive oxygen and nitrogen species (RONS) that can be radicals, e.g. OH , HO_2 , O_2^- , NO , NO_2 , NO_3 , or non-radicals, e.g. H_2O_2 , O_3 , ONOO^- , O_2NOO^- , ONOOH , HNO_2 , HNO_3 , N_2O_3 , N_2O_4 , N_2O_5 [24]. Interestingly, many of the RONS generated by NTPs are also involved in various cell processes. They are key players in oxidation-reduction (redox) reactions happening in biological systems and it is through these redox reactions that cell signaling is possible [24]. By altering the redox chemistry in a biological system, NTPs can have a variety of effects such as inactivation of viruses and bacteria, triggering immune response in chronic wound and set off apoptosis selectively in cancer cells [23].

1.1.2 Non-thermal plasma sources

Different plasma sources have been developed in the past 20 years in the context of plasma medicine. The first extensively studied plasma source for biomedical application was probably the plasma needle by Stoffels *et al.* [25]. It consists of a thin metal needle powered with a RF signal and covered by a dielectric material. In an atmosphere of helium with a small admixture of air, the plasma needle sustains an electrical discharge that acts as a source of RONS. It is through the transport of these RONS toward a biological system that desired outcomes can be induced by the NTP treatment. Since the invention of the plasma needle, tens of different NTP sources for biomedical applications have been developed in different research groups and companies. While they all have different designs and operation procedures, they can typically be categorized in two main groups [26]. The first one is dielectric barrier discharge (DBD) sources, in which a discharge is created between a powered (high voltage) electrode and a sample to be treated that acts electrically as a ground. A dielectric material is placed on the powered electrode and acts as a barrier (hence the term dielectric barrier discharge) to the formation of an equilibrium discharge which could be of high temperature. The plasma needle [25] enters this first category. In a DBD, the plasma is confined

between two electrodes. To overcome this discharge confinement, a second category of NTP sources have emerged: plasma jets. In plasma jets, a gas flow, typically consisting of a noble gas with an admixture of reactive gases (molecular oxygen, molecular nitrogen, water vapor, etc.) is blown between two electrodes. The low-temperature ionized gas flows out of the inter-electrode volume to form a reactive zone, often visible. This so called plasma plume, highly active chemically, is used to treat biological samples placed downstream [20].

While many biomedical NTP devices have been developed both for research and commercial purposes, few have been widely adopted by the plasma medicine community. The following is a short list of some of the plasma sources that are commonly used for biomedical purposes. The aim of the list is not to present an exhaustive catalogue of all NTP sources, but to give some key examples of devices that are found both commercially and in the scientific literature.

The COST-Jet

This list starts with the COST reference plasma jet as it will be of high interest for the current Master's thesis. The COST-Jet is a capacitively-coupled plasma jet developed at the Ruhr University Bochum [27]. It produces a NTP discharge in a 30 mm long channel with a cross section of $1 \times 1 \text{ mm}^2$ (see Figure 1.1 a)). The plasma-forming gas, injected at a typical flow rate of 1.5 standard liter per minute (slm), is helium with small admixtures of reactive gases. The device is powered by a 13.56 MHz RF signal and the plasma dissipated power is in the order of 1 W [27]. The COST-Jet has the advantage of relatively simple design and geometry making it relatively easy to build, modify and model with computational simulation tools.

The kINPen

The kINPen is a plasma jet developed at the INP Greifswald in collaboration with neoplas GmbH, a German company. It might be the most extensively researched plasma jet [28]. The plasma jet is powered by a 1 MHz signal that ignites a plasma-forming gas composed of a noble gas, typically argon, with or without reactive gases in small admixture. It is in use mainly for chronic wound healing, disinfection of surfaces or biological tissues and cancer treatment research [29].

J-Plasma system

The J-Plasma system is a RF helium plasma source developed by ApyxMedical in the United States. This plasma device has been cleared by the Food and Drug Administration in the

United States for cutting and ablation of soft tissues in surgical procedures, but has also been used in studies on *in vitro* prostate cancer [30].

PlasmaDerm

The PlasmaDerm, developed by CINOGY GmbH in Germany, is a DBD plasma source where the powered electrode is covered with plastic that acts as a dielectric barrier and where the human body acts as the ground [28]. It is mainly used in chronic wound healing, skin disease treatment and surgical wound treatment [31].

Convertible Plasma Jet

This short list of NTP devices ends with the Convertible Plasma Jet which was initially developed at McGill University [32] and recently commercialized by NexPlasmaGen based in Montréal (see Figure 1.1 b)). The device consists of a capillary electrode powered by a 13.56 MHz signal surrounded by a glass dielectric and metallic ground. It is operated with a helium plasma-forming gas and was recently used for the selective killing of breast cancer cells [33, 34].

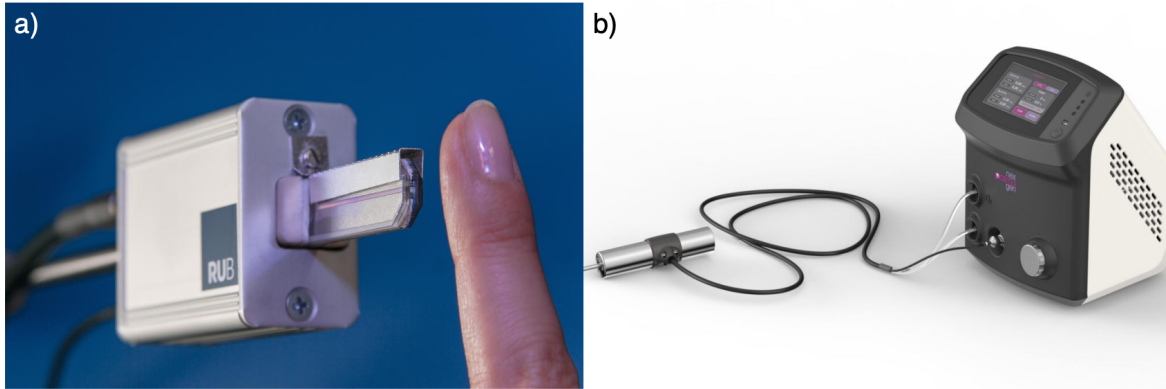


Figure 1.1 NTP sources commercially available or widely used by the plasma medicine community. a) COST-Jet b) Convertible Plasma Jet. a), b) are reproduced with permission from [1] and [2] respectively.

1.1.3 Plasma oncology

While hundreds of scientific papers on plasma oncology have been published in the past 20 years [35], many of them being highly promising, the development of an efficient and well-understood plasma cancer treatment still remains a challenge. No clinical cancer treatment using NTP has yet been approved by a major federal health agency. Plasma-based cancer treatments can, in general, be classified into two main categories: direct plasma treatments and indirect plasma treatments [36]. In a direct plasma treatment, an ionized gas is placed directly in contact with the biological sample to be treated while in an indirect treatment, a medium, typically a biologically relevant solution like a saline solution, is treated by plasma and the treated liquid¹ is then brought in contact with a biological sample. While they seem to be similar, the RONS that are delivered to a biological system during a direct or indirect treatment can vary greatly. In a direct plasma treatment, short-lived RONS, such as radicals, can play a role in the plasma-bio interactions, while in an indirect plasma treatment only longer-lived species are brought in contact with the biological sample [36]. Long-lived NTP-generated RONS that have been considered as playing a role in anti-cancer effects are few (e.g. H_2O_2 , NO_2^- , NO_3^- , ONOO^-) [20] and can also generally be introduced in a liquid by other simpler and cheaper means than a plasma treatment. This typically makes direct plasma treatment of higher interest.

The interest, in the context of cancer treatment, for NTP comes from its selectivity toward malignant cells. *In vivo* and *in vitro* research has shown that application of a NTP treatment can selectively kill cancer cell and induce limited damages to healthy cells [36]. In the last years, research has been conducted to elucidate the mechanisms that explain the selectivity of plasma treatment toward cancer cells [28]. Modification of cell signaling by plasma is thought to play an important role since the contact with NTP affects the signalling pathways in a cancerous environment. It has been shown that plasma treatments can downregulate the proliferation and survival signalling of cancer cells [36]. Oxidative stresses are also an avenue explored to explain the selective behavior of NTP in a cancerous cell environment: cancer cells and non-malignant cells do not react uniformly to oxidative stresses. As mentioned, a NTP produces a variety of radical and non-radical RONS, e.g. O , O_3 , OH , H_2O_2 , HO_2 , NO , ONOOH , all of which can be brought in contact with a biological system to be treated. The RONS induce oxidative damages to the cells and, if high enough concentration are used, the oxidative damage can lead to cell death. However, the antioxidative defense mechanism varies between healthy and cancerous cells. Malignant cells are often more sensitive to oxidative

¹Many terms are used in the literature to name a liquid that was brought in contact with a NTP. The term plasma treated liquid, plasma activated liquid and plasma conditioned liquids are often used by the community. In this thesis they will be referred to as plasma treated liquids.

stress for various reasons [28]. For example, cell membranes are typically more resistant to the diffusion of free radicals when they contain high amount of cholesterol. As a malignant cell membrane usually contains less cholesterol than a healthy cell, it is more sensitive to oxidative stress through diffusion of free radicals [37]. Hence, by applying the right amount of oxidative stresses with NTP, it is possible to selectively induce cell death in cancer cells.

Another avenue explored to explain the selectivity of NTP toward cancerous cells is through its immunotherapeutic effects. Living organisms have a natural line of defense toward cancer propagation: its immune system [38]. An effective immune response selectively attacks malignant cells. Activating or modifying immune responses toward cancerous cells is a cancer treatment path called immunotherapy which has been of high clinical values for different types of cancer that were historically challenging to treat [39]. As NTPs are known to trigger certain immune pathways, in the context of wound healing for example [15], they can also modify the immune response in a tumorous environment leading to selective killing of cancerous cells [28].

Much progress has been achieved in the last years to understand the origin and selectivity of NTP-based cancer treatments, but many questions still need to be addressed. While many cancer cell lines react highly selectively to NTP treatments, some cell lines show a weak selective behavior or a negative selective behavior [40]. To understand the underlying mechanisms in the selectivity of NTP cancer treatments, researchers of the plasma medicine community need biological models that are reproducible, parallelisable and that replicate key biological features found *in vivo*. All these characteristics would accelerate the transition to clinical applications of NTPs in the context of cancer treatment. In that regard, microfluidic-based biological model could help the plasma medicine community address many open questions.

1.1.4 Non-thermal plasmas and microfluidics

Microfluidics refers to the manipulation of small volumes of liquids through channels of typically millimeter and sub-millimeter size. Controlling liquid at this scale enables taking advantage of liquid behaviors that can be different than those happening at macroscopic scale such as capillary forces, viscous forces and diffusion. Microfluidic devices are referred to as laboratory-on-a-chip technologies as they are often developed to reproduce laboratory experiments on a small footprint. In addition, they can be produced and used in large quantity for a reduced cost compared to standard laboratory processes because of their small size and lower needed reagent intake. Because they yield such advantages, microfluidic devices have been used as a tool for drug discovery for a variety of diseases [41].

Furthermore, because of their reproducibility and parallelisability, microfluidic devices have

been used increasingly in oncology research [42]. Inside these microfluidic devices, cells can be cultured in three dimensions. These 3D cell cultures are of high interest because they feature key characteristics of *in vivo* tissues that conventional two-dimensional cell cultures do not offer. Microfluidic 3D cell cultures have been used as a test platform for different chemotherapy, radiotherapy and immunotherapy treatments [8, 43, 44].

The use of microfluidic devices offers a very relevant pathway for accurate and well-established biological models. However, the combination of a NTP with a microfluidic device is a field that has not been much explored by the scientific community, especially in the context of cancer treatment. Plasma microfluidic technology can generally refer to NTP confined in a microchannel (the COST-Jet is a good example of a microchannel plasma [27]) [45], plasma sources embedded in microfluidic devices [46–48] and microfluidic plasma arrays [49]. Lin *et al.* recently reviewed key plasma-microfluidic works [50].

1.1.5 Diagnostics of non-thermal plasmas and plasma treated liquids

The field of plasma diagnostics has the objective of improving the understanding of the state of a plasma through physical observations [51]. To understand underlying mechanisms of the NTP treatment, it is necessary to gain knowledge on the reactive species the NTP source generates and the radiation it emits. This is achieved by plasma diagnostics. Through the understanding of the production of plasma-generated RONS and biological mechanisms associated with these RONS, it is possible to tailor and optimize a biological application. Plasma diagnostics is a very vast field, but diagnostic techniques can generally be part of one of two categories. The first one is probing methods, where a physical probe is used to measure a physical quantity (temperature, voltage, current, etc.) inside or in the surrounding of the plasma to deduce information on the plasma discharge state (electron energy, power dissipation, enthalpy, etc.). The second category of plasma diagnostic techniques is optical methods. Through the observation of electromagnetic waves that are emitted (emission spectroscopy), absorbed (absorption spectroscopy), absorbed and re-emitted (fluorescence techniques) or scattered (scattering techniques) by the plasma discharge, it is possible to learn information about the gas temperature, electron energy distribution, species distribution and transport (neutrals, ions, radicals) [52].

Plasma power dissipation of small-size plasma sources

The plasma power dissipation (PPD) is one of the most fundamental and important plasma parameters. It is frequently one of the first fairly complex measurements achieved when using and/or developing a novel plasma source. The PPD measurement contains key information

about the discharge state and is a very useful input to a simulation model. However, PPD measurements can easily be inaccurate and special care must be taken when performing such electrical diagnostic [53], especially when dealing with miniature NTP sources.

Electrical diagnostics of miniature NTP sources evolved in the past years but still varies significantly among research group. Godyak and Piejak [54] proposed three decades ago the so-called “subtractive method” which has been found very useful for PPD measurement of miniature NTP sources. The basic principles of this method is to retrieve the power dissipated in the plasma discharge by subtracting the power dissipated in the matching network from the power dissipated in both the discharge and matching network (the latter being often far from negligible). The subtractive method has been developed for low-pressure RF discharges, but can be applied for atmospheric pressure miniature discharges. Godyak and Piejak also proposed to compare the subtractive method’s result with a direct current and voltage measurement across the discharge ($P = VI \cos \phi$, where V and I are the RMS voltage and current respectively and ϕ is the phase angle between current and voltage) [54]. However, the latter method of Godyak and Piejak often cannot be applied directly for miniature NTP sources: Léveillé and Coulombe [55] demonstrated that for miniature discharges, the capacitance of the plasma source is small (due to small interelectrode distance) and it is often very close to the capacitance of the commercial voltage probes. Hence, assuming the voltage probe to be passive is no longer valid. They proposed a method where the probe effects on the electrical circuit are considered to retrieve the power dissipated in the plasma discharge only. This method, which needs prior experiments for the characterization of the voltage probe, leads to error on power measurement that can reach 40% and higher, mainly because of the phase angle between the current and voltage. Hoffmann *et al.* [56] proposed, in the context of an atmospheric NTP source, to use a simple matching² network consisting of only an inductor. By measuring the voltage before the inductor and the current flowing through both the inductor and the plasma device, they could accurately (since the phase angle is close to zero when effective coupling is achieved, the error terms related to the phase angle is small: see appendix B) measure the power dissipated in both the inductor and the plasma discharge. Using the subtractive method, they were able to retrieve the power dissipated in the plasma discharge only. In this method, the coupling of the power supply and plasma source is optimized by tuning the frequency of the signal. Hence the method must be modified if one wants to use it at an arbitrary frequency (such as with a commercial 13.56 MHz power supply). Very similar methods have been used recently [15]. Marinov and

²Many simple matching unit used in the literature for miniature NTP atmospheric sources do not set the real part of the impedance to 50 Ω , but only cancel the imaginary part of the impedance. Hence, strictly speaking, they do not match the impedance. Nevertheless, they will be referred to as matching units as other designation might be confusing.

Braithwaite [57] proposed to use both an inductor and a variable capacitor as a coupling unit. By varying the capacitance value, one can match the power supply to the plasma source at an arbitrary frequency. The power measurements of Marinov and Braithwaite were performed with the commercial probe OctIV. This expensive device has the disadvantage of having to be calibrated at a specific frequency making it potentially complex to be used at an arbitrary frequency. Other publications use directional couplers [58] or built-in probes [27] to measure the PPD. These methods require specific equipment or specific electrical circuit design which can be expensive and time consuming.

Taking profit of the advantages of the different methods of power measurement developed in the last years, a method of PPD measurement for NTP atmospheric sources will be presented in chapter 2 (and further details can be found in appendix B).

COST-Jet diagnostics

The COST reference plasma jet was designed with the aim of offering a standardized NTP plasma source and it was adopted and characterized by many research groups around the world. It is based on the microscale atmospheric pressure plasma jet [59,60], that is itself based on the atmospheric pressure plasma jet developed by Selwyn *et al.* [61]. Marinov and Braithwaite reviewed the electrical characteristics of the COST-Jet in terms of plasma ignition voltages, plasma power dissipation and equivalent circuit modelling for different gas composition and plasma discharge modes [57]. They showed that the plasma source can dissipate between 0.1 and 1.4 W in pure helium and that this value increases when reactive gases are added in the feed gas. Further electrical diagnostics with different methods for measuring the plasma power dissipation of the COST-Jet were also presented elsewhere [15,62]. The gas temperature and gas flow dynamics of the COST-Jet were studied by Kelly *et al.* [63]. In terms of plasma chemistry, the plasma-generated reactive species of the COST-Jet were studied by different research groups with optical diagnostics. The density of key reactive oxygen species, such as O and OH radicals, in the effluent (the zone without active plasma where species recombine) of the COST-Jet with humidified helium as plasma-forming gas were measured by means of two photons absorption laser induced fluorescence [64]. These results showed that O and OH can be found in concentration of 10^{13} and 10^{14} cm^{-3} , respectively, and that both their concentrations decay rapidly downstream of the active plasma zone. The production of reactive nitrogen species, such as NO and N_2O , in the effluent of the COST-Jet with a helium and molecular nitrogen plasma-forming gas was also studied with laser induced fluorescence and absorption spectroscopy [65,66].

Plasma treated liquid diagnostics

When brought in contact with a liquid, plasma-generated species induce a cascade of reactions that lead to a modified chemistry in the treated liquid. A thorough review of plasma-liquid interactions was presented by Bruggeman *et al.* [67]. Figure 1.2 shows a schematic of important plasma-liquid interactions processes. As seen in Figure 1.2, some long-lived plasma-generated species exist both in the liquid bulk and at the liquid interface (H_2O_2 , HO_2 , NO_2^- , NO_3^-) while short-lived species exist only at the liquid interface (OH , O , H , etc.). The methods used to detect short-lived species are different than those used to detect longer-lived species. The detection of short-lived species in liquid is usually done indirectly: a chemical that strongly and quickly reacts with the species to be detected is added to the liquid to form a more stable compound which is then detected. The most common indirect detection techniques include the use of terephthalic acid for OH radicals detection with fluorescence spectroscopy [68] and the use of DMPO spin trap to detect H, OH or O_2^- (DMPO-H, DMPO-OH, or DMPO-OOH) with electron paramagnetic resonance spectroscopy [69–71]. The most commonly detected long-lived species in plasma treated liquid include H_2O_2 , NO_2^- and NO_3^- [67]. In the context of the current thesis, only H_2O_2 will be detected. The two most widely used methods for H_2O_2 detection in liquid are probably the AmplexTM Red and the titanium oxysulfate methods. In the AmplexTM Red method, H_2O_2 reacts with horseradish peroxidase to form a product that is detected through fluorescence spectroscopy while in the titanium oxysulfate method, H_2O_2 reacts with titanium ions to form pertitanic acid, yellow in color, which is then detected colorimetrically by absorption spectroscopy. Even if the AmplexTM Red method can detect H_2O_2 with a higher precision, the titanium oxysulfate method was chosen for this thesis work for its easier implementability and sufficient precision.

1.1.6 COST-Jet and plasma-liquid interactions modelling

Plasma computational modelling accelerates the understanding of the physical and chemical mechanisms happening in a plasma device and can help improve its performance. Plasma modelling is generally based on an understanding of many different fields of physics: mechanics, electromagnetic and particle physics are at the base of any modelling attempt of a plasma device. When working with a plasma out of thermodynamic equilibrium, i.e. NTP, statistical physics and chemical reaction kinetics also becomes of high interest [72]. As a full plasma model is of high complexity, it is common to separate the modelling problem in a few sub-models. These sub-models usually include [73]:

- a model to solve the electromagnetic fields through Maxwell’s equations,

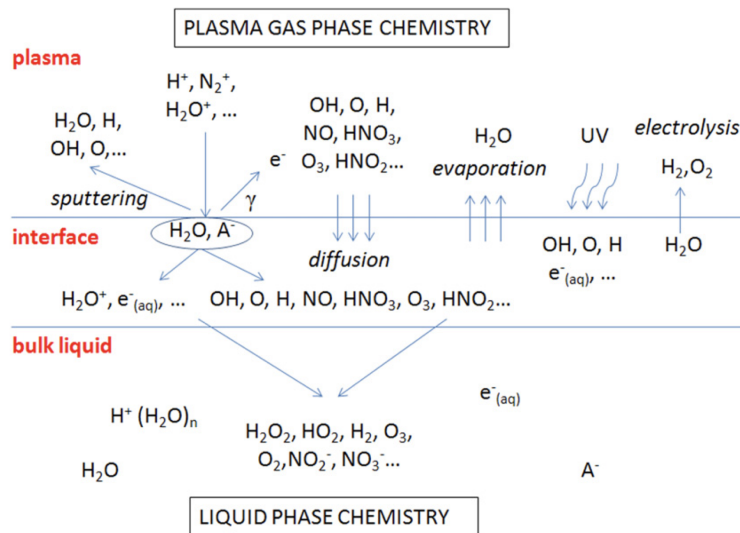


Figure 1.2 Schematic of important plasma-liquid interactions chemical and physical processes. Reproduced with permission from [3].

- a model solving for the gas flow velocity field, gas pressure and gas temperature through Navier-Stokes equations and the heat equation,
- a model solving for the electron energy distribution function (EEDF) through the Boltzmann equation,
- and a reaction kinetics solver to follow the evolution of the density of the different species included in the plasma model.

These different sub-models can be solved in time only, or with one, two or three spatial dimensions depending on the level of complexity of the system to be modelled.

A large number of plasma simulation tools exist and an exhaustive list of codes and software would be too long, but some key plasma simulation framework are worth mentioning. In terms of commercially available simulation tools, COMSOL Multiphysics [74] and ANSYS Fluent [75] are probably the most widely used softwares [72]. ANSYS Fluent is focused on fluid simulation and is mainly used to model thermal plasma processes while COMSOL Multiphysics offers tools to model plasma discharge out of thermal equilibrium. Some non-commercial plasma modeling tools have also been broadly adopted, especially in a research context. nonPDPSIM, a simulation framework developed by the group of Prof. Mark Kushner at the University of Michigan, might be one of the most widely known non-commercial plasma simulation tool and it was harnessed in hundreds of scientific publications. An introduction to this modelling tool can be found in [76]. nonPDPSIM includes many modules

that solve for different physical and chemical variables such as electrons temperature and energy, fluid dynamics, plasma kinetics and surface kinetics. CRANE [77], an open-source simulation tool for plasma modelling based in the MOOSE finite element framework is also gaining popularity in the plasma modelling community. For specific plasma simulation tasks, some modelling tools were widely adopted by the simulation community. BOLSIG+ [78] is one of them. It is a Boltzmann equation solver that can provide different data on uniform plasmas including the EEDF and the reaction rates for electron-impact reactions in plasma out of thermodynamic equilibrium. The calculation achieved in BOLSIG+ are based on plasma parameters and reaction cross sections. The LisbOn KInetics (LOKI) [79], developed in MATLAB, is also a Boltzmann solver and it is gaining popularity for plasma simulation. Another free access simulation software, abundantly utilized in academic and industrial research context, is ZDPlaskin. It is a zero-dimensional plasma kinetics solver that uses a set of chemical reactions with their corresponding reaction rates or electron-impact reaction cross sections to solve the time evolution of chemical species present in a uniform plasma [80]. ZDPlaskin incorporates BOLSIG+, for calculating electron-impact reaction rates through the EEDF. This brief simulation tools overview ends by mentioning the LXCAT project [81] that aims at evaluating and sharing important data that are at the base of plasma simulations. The data available on LXCAT can be used with the different simulation tools that were previously presented.

In this Master's thesis, some of the presented simulation tools (COMSOL, ZDPlaskin and BOLSIG+) will be used to model the active plasma, plasma effluent and plasma-liquid interactions for the COST reference plasma jet. The following presents a short overview of simulation works that were performed on the COST-Jet and in the context of plasma-liquid interactions.

Modelling of the COST-Jet

For biomedical applications, the plasma chemistry is of high interest as the desired effects of NTP on biological systems come, in large part, from the chemical species the NTP generates. To study the evolution of the plasma-generated species in the COST-Jet, 1D modelling is the most common approach [71, 82–84]. The studies are typically based on 0D reaction kinetics solvers where the time variable is coupled to the physical distance in the COST-Jet plasma channel by the average velocity of the plasma-forming gas. This approach to coupling the time to the distance is often referred to as a plug flow model. The main advantage of this type of model is the short computational time: 0D and plug flow models can solve for a large quantity of chemical and electron-impact reactions (often above 1000) in a short time [85].

The obvious drawback of 0D and plug flow models is the absence of spatial information [73]. However, multidimensional plasma simulations ask for much greater computational resources and simplifying approximations are essential to achieve reasonable computation times. In the realm of the COST-Jet, simplifications that are used include:

- setting the concentration of key reactive species at the exit nozzle of the COST-Jet and simulating only a limited reaction set in the plasma effluent [86,87],
- using a multi-time-scale approach [88],
- and using a combination of more than one modeling approaches (hybrid technique) [89].

The nonPDPSIM has also been used in the context of the COST-Jet for a 2D simulation, but with a reduced number of species and reactions [90].

Modelling of plasma-liquid interactions

The interactions between a plasma jet and a liquid have been increasingly studied in the last years including through modelling works [67]. The goal of these plasma-liquid modelling studies is to understand what chemical species are generated in a liquid when it is brought in contact with a plasma or with the effluent of a plasma. Lindsay *et al.* studied with a COMSOL Multiphysics model the interactions between a pulsed streamer discharge and a liquid-filled vessel in terms of fluid dynamics, heat transfer and key chemical species production and transport both in the gas phase and in the liquid [91]. The number of species included in the model was, however, limited and no electron-impact reactions were considered for faster computation time. Heffny *et al.* used a fluid dynamics model where they fixed the concentration of reactive species at the exit of the COST-Jet. They studied the transport of reactive oxygen species in the water for a COST-Jet placed 4 mm above a 3 ml water volume [86]. Mohamedes *et al.* used the nonPDPSIM to study the interactions between a helium plasma jet and water in a well plate, but the presented simulation results could not be compared to experimental work [92]. Heirman *et al.* developed a model that combines 0D reaction kinetics with 2D reaction-diffusion-convection to model the interactions of the KINPen with a well of a 12 well-plate and the results were compared to experimental liquid diagnostics of key reactive species [85]. The last three mentioned works were studies of plasma jet interacting with large volume (more than 1 ml) of liquid. The plasma treatment of small liquid volumes, water droplets, was also studied by Kruszelnicki *et al.* [93] and Oinuma *et al.* [94]. However, to the best of the author's knowledge, no modeling work has been conducted to study the interactions between small volumes of liquid and the COST-Jet

plasma channel and compared with analogue experimental work as will be presented in this manuscript.

1.2 Goals and outline

The field of plasma medicine for oncology has greatly evolved in the last few years, but a full understanding of the physical, chemical and biological mechanisms of the relevant effects a NTP has on a biological system still remains to be achieved. We think that the use of microfluidic devices could be of great interest to study the interactions of NTPs with liquids and biological models. For biological experiments, the coupling between a plasma source and a microfluidic device would enable the use of standard and well-established biological models embedded in microfluidic devices. The precise control of small volumes of liquids would also enable the study of plasma-liquid interactions with a high spatial resolution. However, standardized platform that allows the combination of a reference plasma source and a microfluidic device are lacking. This Master's thesis work addresses this challenge by developing tools that give the ability to use microfluidic devices in the context of plasma-liquid interactions research and ultimately in plasma medicine research. To tackle this challenge, three objectives were adopted:

1. Develop a platform that allows a reference plasma source to treat a liquid circulating in a microfluidic device.
2. Characterize the plasma source and the transport of plasma-generated reactive species in the plasma-microfluidic platform.
3. Develop a computational simulation tool to explain the main plasma species production and transport pathways in the plasma-microfluidic platform.

Chapter 2 will attend to the first two objectives by presenting an article submitted to the *Plasma Sources Science and Technology* journal. In this article, the novel plasma-microfluidic platform developed during this Master's thesis is presented and characterized. To tackle the third objective of this thesis, the reaction kinetics and fluid dynamics inside the plasma-microfluidic platform are modelled with a new quasi-2D approach in chapter 3. Finally, chapter 5 summarizes the work achieved in this thesis and discusses the perspectives and challenges of plasma-microfluidic.

CHAPTER 2 ARTICLE 1 : COUPLING THE COST REFERENCE PLASMA JET TO A MICROFLUIDIC DEVICE: A NEW DIAGNOSTIC TOOL FOR PLASMA-LIQUID INTERACTIONS

2.1 Presentation of the article

The content of the article presented in this chapter fulfills the first two goals of this Master's thesis.

1- Develop a platform that allows a reference plasma source to treat a liquid circulating in a microfluidic device.

To achieve this first goal, a novel device, called the "plasma-microfluidic platform" was designed. As the name suggests, the developed platform combines a plasma source and a microfluidic device. Geometrically and electrically, the operation of the plasma source of the developed plasma-microfluidic platform is identical to the COST-Jet. However, the mechanical design of the whole device was adapted to enable a contact between the plasma channel and a microfluidic device. Figure 2.1 summarizes the mechanical design of the plasma-microfluidic platform and provides a background and insights on the key design choices. The plasma-microfluidic platform contains the following components:

1. The bottom part which is a CNC-machined block of polyoxymethylene plastic that serves as a holder for different components of the plasma-microfluidic platform. The hole at the bottom of this part allows for optical access.
2. The microfluidic devices which were 3D printed with the Asiga Pico2 27 3D printer using UV sensible resin (GR1-clear resin - Pro3Dure - A1000300). Supplementary information on the construction and operation of the microfluidic devices can be found in appendix A.
3. The electrodes which were cut with a high-pressure water jet from a sheet of stainless steel 316.
4. A microscope slide which acts as a glass window. The platform was designed to fit microscope glass slides ($25 \times 75 \text{ mm}^2$).
5. The top holder which was also CNC-machined from a block of polyoxymethylene plastic.

6. Plastic screws and nuts to attach the top and bottom parts together and metal screws and nuts for the electrical connections.

The six components are shown in figure 2.1. They are added one after the other to the different illustrations of the figure to clarify the assembly.

2- Characterize the plasma source and the transport of plasma-generated reactive species in the plasma-microfluidic platform.

To achieve this second goal, the dissipated power of the plasma discharge along with the hydrogen peroxide concentration in the liquid treated by the plasma-microfluidic platform is measured. Supplementary information on the power measurement method can be found in appendix B.

The authors of this chapter's article include the author of this Master's thesis, who performed all the experimental work, data analysis and produced the figures, two Professors of the Department of Engineering Physics at Polytechnique Montréal, Thomas Gervais and Stephan Reuter, and one Professor at the Department of Chemical Engineering at McGill University, Sylvain Coulombe. The article was submitted to the *Plasma Sources Science and Technology* journal.

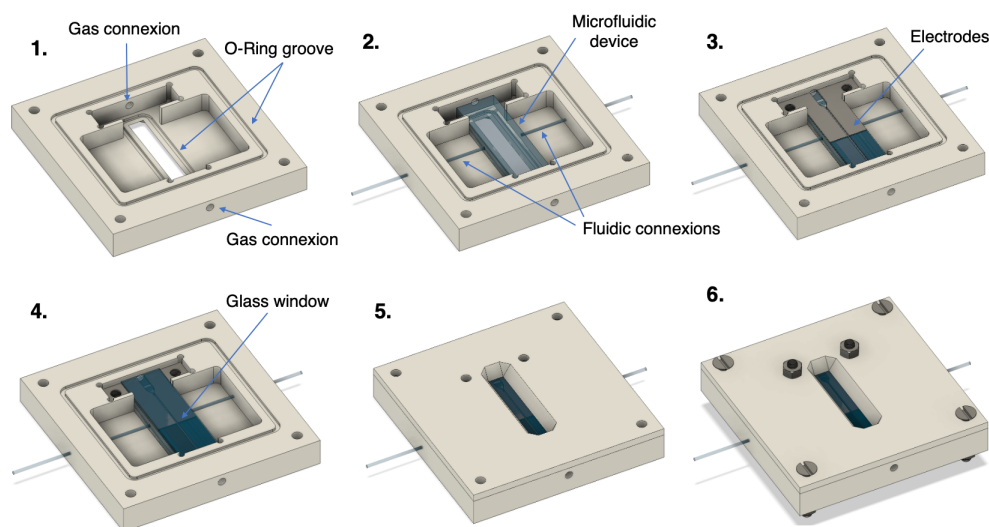


Figure 2.1 Assembly and key design features of the plasma-microfluidic platform.

2.2 Coupling the COST reference plasma jet to a microfluidic device: a new diagnostic tool for plasma-liquid interactions

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2.2.1 Abstract

In plasma medicine, understanding the interactions between plasma-generated reactive species and a biological system is key to any effective treatment. However, standardized platform that allows the study of the reactive species effects on biological models are lacking. We hypothesize here that use of microfluidic devices would unlock many possibilities to investigate the transport of reactive species in plasma-treated liquids and, ultimately, to measure the effects of these species on biological systems. To this end, our approach combines a capacitively coupled RF plasma jet, known as the COST reference plasma jet, with 3D printed microfluidic devices. This novel pairing is achieved by carefully controlling capillary effects within the microfluidic device at the plasma-liquid interaction zone. The generation and transport of reactive species from the plasma to the liquid inside the microfluidic device are analyzed using a colorimetric hydrogen peroxide concentration assay. A capillary flow model is provided to explain the two main regimes of operations observed in the device and their merits are discussed. Overall, the proposed plasma-microfluidic prototype shows great potential for the fundamental study of plasma-liquid interactions and opens the way to the use of standard microfluidic devices with reference biomedical plasma sources.

2.2.2 Introduction

Non-thermal plasmas (NTP) produce highly reactive species that can have a variety of effects on biological organisms spanning from chronic wound healing to selective killing of cancer cells [95]. Today, biomedical applications of plasma include decontamination, sterilization,

plasma wound healing, plasma for cancer treatment, plasma treatment of surfaces for biocompatibility and plasma for dentistry [4, 13, 14, 16–22].

The field of microfluidic has so far provided many solutions in analytical chemistry and chemical synthesis to speed up analysis, use less reagent, or perform continuous flow reagent generation and characterization [96]. By using networks of sub-millimeter channels to manipulate small volumes of liquids, one can take advantage of phenomena dominant at the microscale, such as capillary forces, viscous forces and diffusion to control flows and reagent transport with unrivaled precision [97, 98]. Microfluidic devices can be produced and operated in large quantity for a lower cost than conventional laboratory processes because of their small size, the reduced reagent intake they need to be operated and the automatization potential they offer. Due to these advantages, they have also been used as tools for drug development [43] and more recently in oncology research. Inside microfluidic devices, cells can be cultured in three dimensions. These 3D cell cultures often feature key characteristics of *in vivo* tissues that conventional 2D cell cultures do not offer, making them a relevant biological model. 3D cell cultures embedded in microfluidic devices have been used as a test platform for different chemotherapy, radiotherapy and immunotherapy treatments [8, 43, 44]. As the plasma medicine community is in the pursuit of accurate and well-established biological models to address key questions of plasma oncology, the use of microfluidic devices could offer solutions from plasma-treated liquid characterization all the way to medical plasma treatment development.

Today’s plasma-microfluidic technologies include NTP confined in a microchannel [27, 45], microfluidic plasma arrays which are the arrangement of several small-size plasma sources in a close proximity [49] and NTP sources directly embedded in microfluidic devices [46–48]. Some of the most relevant plasma-microfluidic works have been reviewed by Lin *et al.* [50]. However, the efficient combination of a reference and well-characterized NTP plasma jet with a microfluidic device in an all-in-one platform has not yet been performed. In this article, we report on the coupling of a reference plasma source, the COST-Jet, with microfluidic devices. The COST reference plasma jet [27], was designed in a collective effort with the aim of standardizing a plasma source. It was chosen as a reference plasma jet because of its relative ease of diagnostic and the access to a vast amount of modeling and experimental results. The microfluidic devices were prototyped, with the help of 3D printing, to optimize both the operation stability and the transport of plasma-generated species. The efficient generation and transport of reactive species were investigated with a hydrogen peroxide concentration assay.

The motivation behind the coupling of a biomedical plasma source with microfluidic devices

is twofold. First, to yield a plasma-liquid interactions diagnostic tool that offers both a high spatial resolution and a high degree of control of the plasma-liquid interaction zone. Second, to exploit, in future research, standard microfluidic devices to study the interactions of a NTP with a biological model.

2.2.3 Plasma source

Design

We designed and assembled a plasma source based on the COST reference plasma jet specifications [27]. It consists of a radiofrequency (13.56 MHz) capacitively-coupled plasma jet produced between two stainless steel plate electrodes. The plasma-jet forming channel is 30 mm long with a 1x1 mm² cross section. Helium, the main plasma-forming gas, is fed at a typical flow rate of 1.5 standard liters per minutes (slm), with small admixtures of reactive gases. We use a digital function generator (Singlent SDG2082X) and a broadband RF amplifier (Kalmus - 505C) to generate the 13.56 MHz signal. Matching of the complex part of the plasma load impedance is achieved by using a simple series inductor. This simple method, initially proposed by Hofmann [56] and further integrated with the COST-Jet [15,58], enables accurate measurement of the power dissipated in the plasma. We fabricated the inductor using a toroidal ferrite core (Fair-Rite - 5968002701). The amount of wire turns was chosen to minimize the reactance of the whole impedance load (plasma device and inductor) at the excitation frequency.

Figure 2.2 illustrates the electrical circuit. A Rogowski coil current probe (Tektronix CT-2) and a passive voltage probe (Singlent PP510) are used to measure the current and voltage across the matched plasma source (plasma source and inductance). Both probes are connected to a digital oscilloscope (Singlent SDS1104X-U). The difference in length of the voltage and current probe wires introduces a significant artificial time delay (Δt) at 13.56 MHz. This time delay leads to a phase angle that varies according to the frequency of RF excitation ($\Delta\theta = f\Delta t$) [55]. We measured the artificial phase angle with a 50 Ω load, and corrected the results from this point on. A Matlab code is used to correct and analyse the data.

Figure 2.3 shows the plasma source, feed gas lines and liquid setup. We used helium (Air Liquid, 99.999%) with and without controlled amounts of water vapor. The helium and humidified helium flow rates were controlled by mass flow controllers (MKS 1179C). For the experiments, a total flow rate (pure and humidified helium) of 1.5 slm was used. A simple thermostatic glass bubbler was used to humidify the He stream. The bubbler was kept

inside a temperature-controlled bath (Thermo Scientific RTE 740) set at 10° C. The gas line downstream of the bubbler was kept at 70°C with a heating tape to avoid any condensation of water vapor. To establish the humidity level, a calibration experiment was performed by weighting the water in the bubbler before and after helium was flowed inside for different flow rates and times. Liquid flow in the microfluidic devices was imposed from a distilled water (DW) reservoir by a syringe pump (New Era NE4000). Details on the design and operation of the microfluidic devices are presented in Section 2.2.4.

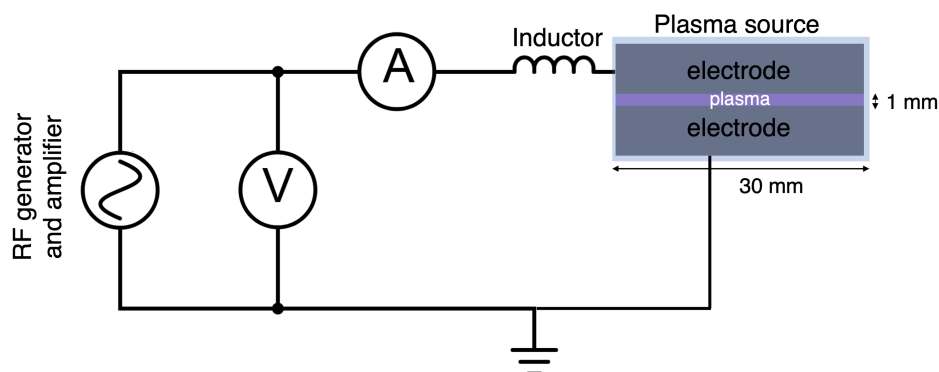


Figure 2.2 Schematic of the electrical circuit.

Experimental set-up

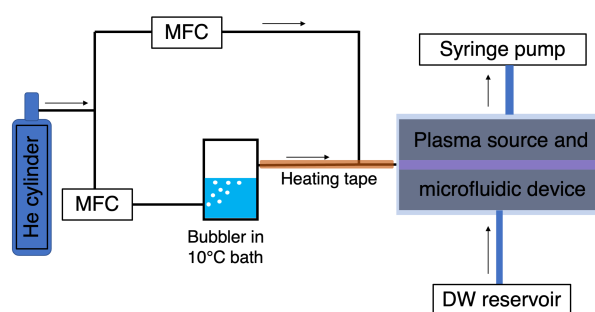


Figure 2.3 Plasma feed gas setup and fluidic setup. The helium is humidified using a thermostatic glass bubbler.

Plasma dissipated power

Plasma power dissipation (PPD) is one of the most fundamental and important plasma parameter and is frequently one of the first fairly complex measurements performed when using and/or developing a novel plasma source. The PPD measurement contains key information about the discharge state. However, PPD measurements can easily be inaccurate and special care must be taken when performing such electrical diagnostics [53], especially when dealing with miniature NTP sources.

The average power dissipated during one electrical period is defined as:

$$P_{avg} = \frac{1}{T} \int_0^T V(t) \cdot I(t) dt,$$

where T is the period, $V(t)$ the time varying voltage and $I(t)$ the time varying current. For a sinusoidal voltage waveform and a linear current response, the average power is:

$$P_{avg} = V_{RMS} \cdot I_{RMS} \cdot \cos\phi \quad (2.1)$$

where V_{RMS} is the root mean square voltage, I_{RMS} is the root mean square current, and ϕ is the phase angle between the current and voltage. This phase angle, ϕ , arises from the load impedance to which the voltage is applied: $Z_{load} = |Z| e^{i\phi}$. An error analysis of Equation 2.1 leads to:

$$\begin{aligned} \Delta P_{avg}^2 &= \left(\frac{\partial P_{avg}}{\partial V_{RMS}} \cdot \Delta V_{RMS} \right)^2 + \left(\frac{\partial P_{avg}}{\partial I_{RMS}} \cdot \Delta I_{RMS} \right)^2 + \left(\frac{\partial P_{avg}}{\partial \phi} \cdot \Delta \phi \right)^2 \\ \Rightarrow \frac{\Delta P_{avg}^2}{P_{avg}^2} &= \left(\frac{\Delta V_{RMS}}{V_{RMS}} \right)^2 + \left(\frac{\Delta I_{RMS}}{I_{RMS}} \right)^2 + (\tan(\phi) \Delta \phi)^2 \end{aligned} \quad (2.2)$$

The last term of Equation 2.2 contains $\tan(\phi)$, whose value increases rapidly when the phase angle is close to $\pm 90^\circ$. This can become problematic when measuring the delivered power to a highly capacitive load like miniature plasma sources. To overcome this challenge, Hoffmann *et al.* [56] proposed, in the context of an atmospheric NTP source, to use a simple coupling network consisting of only an inductor. A non-ideal inductor, like the one used for the impedance coupling in this publication, has a resistivity. This resistive behavior comes from two sources: the non-zero resistance of the wires from which the inductance is made and the heating of the inductor's material through magnetic loss. As current is flowing through the resistive part of the impedance, power is dissipated. Hence, to isolate the power dissipated in

the plasma discharge, the value of the resistive part of the inductor, R_L , needs to be known. Figure 2.4 shows the equivalent circuit representation of the device with (*on*) and without (*off*) the presence of a plasma discharge. In the *off* configuration, power is only dissipated in R_L . The quickest way to determine the value of R_L is probably to measure the power dissipation without igniting the plasma (*off* configuration). The relation between the power and R_L will then be $P_{off} = R_L \cdot I_{off}^2$, where I_{off} is the measured RMS current without a plasma discharge (*off* configuration) and P_{off} the corresponding power. From this, the power dissipation in the discharge can be deduced by the subtractive method [54]:

$$P_{plasma} = V_{on} \cdot I_{on} \cdot \cos\phi - R_L \cdot I_{on}^2 \quad (2.3)$$

R_L is found by the regression of $P_{off} = R_L \cdot I_{off}^2$, V_{on} and I_{on} are the RMS voltage and current with the plasma ignited (*on* configuration).

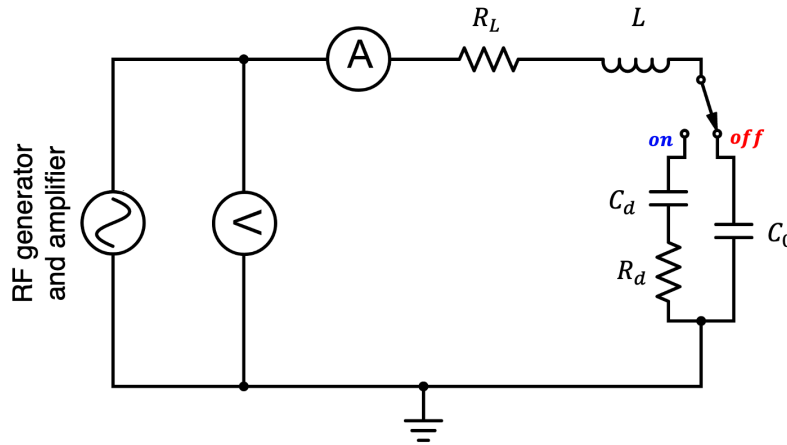


Figure 2.4 Equivalent circuit of the plasma source with (*on*) and without (*off*) plasma discharge. When no plasma is ignited (*off*), the plasma source acts as a capacitor, C_0 , and no power is dissipated in the plasma source. When plasma is ignited (*on*), power is dissipated in the discharge and the plasma source is modelled as a capacitor, C_d , in series with a resistor, R_d .

2.2.4 Microfluidic coupling

The difficulty in combining plasma sources with microfluidic devices arises from the special properties of liquids when manipulated in small volumes. In microfluidic regimes, the capillary forces play an important role: if not adequately confined liquids tend to spread inside small openings. Hence, creating an opening that allows plasma-liquid interactions

while avoiding liquid infiltration in the plasma channel poses a challenge. The following presents how the COST-Jet was combined to a microfluidic device. The proposed plasma-microfluidic coupling enables creating a plasma-liquid interaction zone at a desired position in a controllable and reproducible manner.

Fluidic resistance, flow rate and pressure in microfluidic devices

The microfluidic devices developed for the proposed plasma-microfluidic coupling have two main objectives. The first one is to allow liquid circulation for plasma treatment and the second is to obtain high control on the position of the plasma-liquid interaction zone. The liquid circulation is made possible by imposing a flow rate, Q , while the position of the plasma-liquid interface is controlled by adjusting the pressure, p , in the microfluidic channels (see figure 2.5). These two parameters, Q and p , are connected by the Hagen-Poiseuille law [99]:

$$\Delta p = R_{fluid} \cdot Q \quad (2.4)$$

where R_{fluid} is the fluidic resistance of the microfluidic channel and Δp is the pressure variation across this channel. Equation 2.4 is interpreted as follows: imposing a flow rate Q in a channel of fluidic resistance R_{fluid} leads to a pressure drop across the channel of Δp . A strong analogy exists between the Hagen-Poiseuille law and Ohm's law, $\Delta V = RI$, that connects the voltage drop across a resistance (ΔV) to the current flowing through it (I) by the electrical resistance of the wire (R). R_{fluid} can be customized by changing the geometry of the microfluidic channel. For example, a cylindrical channel has a fluidic resistance given by $R_{cylindrical} = 8\eta\ell / (\pi a^4)$, where η is the circulating fluid viscosity, ℓ is the length of the channel and a is the radius of the cylindrical cross section. The latter equation shows that one can impose Δp at a certain Q by controlling R_{fluid} .

Microfluidic devices design

Figure 2.5 presents a simple schematic of the plasma microfluidic coupling. The plasma zone is ignited on top of the microfluidic device which consists of three main channels. The first one, on the left, is connected to a liquid reservoir and has a hydraulic resistance $R_{hyd,1}$. The second, on the right, is connected to a syringe pump and has a hydraulic resistance $R_{hyd,2}$. In between them, a third channel, that will be called the chimney, allows contact between the plasma zone and the liquid circulating in the microfluidic device. Because of small channel sizes in the microfluidic device, capillary forces are significant. Without adequate control,

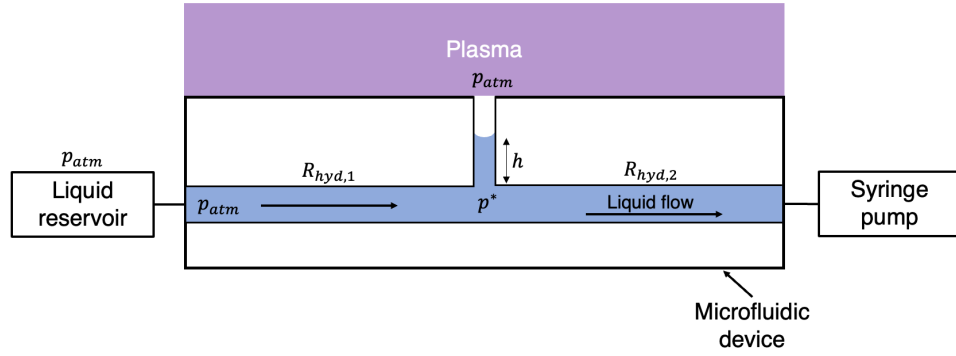


Figure 2.5 Plasma-microfluidic coupling. The liquid interface height, h , can be controlled by varying p^* through the flow rate Q and/or the hydraulic resistance $R_{hyd,1}$.

the circulating water in the microfluidic device would creep inside the plasma channel and lead to changes in the plasma properties making it almost impossible to obtain reproducible experiments. Moreover, exposing the surface of the device to a plasma discharge increases its surface energy, which tends to maximize capillary pressure. If this effect is not considered at the design stage, flow will spill out of the microchannel via capillary action and disrupt the device operation. To avoid such problem, the microfluidic devices are designed to control the position of the liquid interface at the plasma channel. This is achieved by controlling the pressure under the liquid interface such as to offset capillary pressure, also known as Laplace pressure. The capillary pressure is given by:

$$p_{cap} = \frac{\gamma \cos(\phi_c) \wp_{chimney}}{A_{chimney}},$$

where γ is the liquid surface tension, ϕ_c is the contact angle between the liquid and the microfluidic device's walls, $\wp_{chimney}$ is the perimeter of the chimney and $A_{chimney}$ is the cross section area of the chimney. The hydrodynamic pressure, the pressure drop associated to Hagen-Poiseuille's law, is given by:

$$p_{hyd} = R_{water,1} \cdot Q,$$

where Q is the flow rate of the circulating liquid and $R_{water,1}$ is the fluidic resistance of the channel between the liquid reservoir and the chimney for water. The gravitational pressure that originates from the liquid column's weight of the chimney is given by:

$$p_g = \rho gh,$$

where ρ is the liquid density, g is the gravitational acceleration and h is the height of the liquid chimney. The liquid reservoir and the plasma channel are at atmospheric pressure, p_{atm} . At the bottom of the chimney, the pressure is given by:

$$p^* = p_{atm} - p_{hyd} = p_{atm} + p_g - p_{cap}$$

$$\Rightarrow p_{cap} = p_{hyd} + p_g \quad (2.5)$$

From Equation 2.5, we can deduce two regimes of operation. When $p_{cap} > p_{hyd} + p_g$, the capillary forces are dominant, and a liquid chimney exists. In this regime, only liquid is flowing in the microfluidic channel. This first regime is illustrated in Figure 2.6 (a). When $p_{cap} < p_{hyd} + p_g$, the hydrodynamic pressure combined with the gravity is dominant and no liquid chimney exists. In this case, both liquid and gas are flowing in the microfluidic device which offers a second regime of operation. This second regime is illustrated in Figure 2.6 (b) and will be further discussed in section 2.2.6. The microfluidic device is designed to control p_{hyd} through $R_{water,1}$ at a desired liquid flow rate Q .

In microfluidic, a T-junction is a junction of three channels and is probably one of the most common junctions. Figure 2.7 a) shows the schematic of a T-junction. T-junctions can be used to create a flow composed of two different liquids (such as water and oil), or a flow of one liquid and one gas (such as water and air). In a T-junction where the flow rates $Q_{fluid\ 1}$ and $Q_{fluid\ 2}$ are imposed (see Figure 2.7), it is possible to predict the size of the bubbles or droplets formed by each fluid based on the properties of the fluids, the geometrical sizes of the T-junction and the values of $Q_{fluid\ 1}$ and $Q_{fluid\ 2}$ [100]. These types of bubble formation experiments are well known and have been extensively studied by the microfluidic community. The junction that enables the coupling between the microfluidic device and the plasma channel in our system resembles the just mentioned T-junction at one key difference: only one flow rate is imposed, Q_3 in Figure 2.7, and the value of $Q_{fluid\ 1}$ and $Q_{fluid\ 2}$ will change depending on the value of Q_3 . Hence, even if models exist to predict the gas-liquid or liquid-liquid flow formation in a T-junction, they cannot be directly applied to our device.

In the complete plasma-microfluidic platform, the plasma source is positioned on top of the microfluidic device with the plasma channel aligned with the opening of the microfluidic device (see Figure 2.6). A glass plate is then added above the plasma channel and the

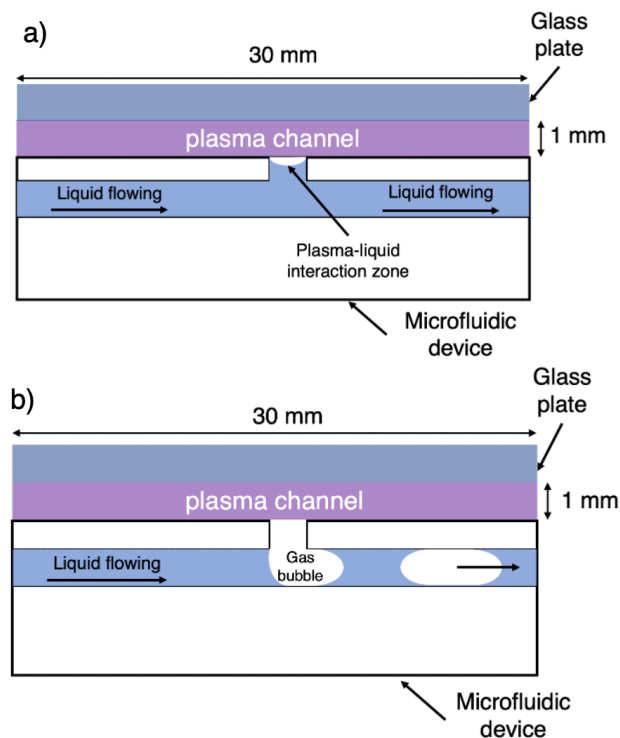


Figure 2.6 Schematic of the two operation regimes of the microfluidic devices. a) Single-phase flow ($p_{hyd} < p_{cap} - p_g$). b) Multiphase flow ($p_{hyd} > p_{cap} - p_g$).

electrodes. The opening of the microfluidic device that creates the interactions between the liquid and the plasma-generated reactive species can be placed at different positions. Figure 2.8 a) and c) shows the opening (in the center of the red circles) directly under the plasma active zone. In c), a plasma is ignited. In b), the opening is positioned in the plasma effluent zone, 3 mm from the end of the active plasma zone. Hence, the position of this liquid interaction zone can be modified to study the spatial evolution of the plasma chemistry and its interactions with liquid.

The microfluidic devices are designed in a CAD software (Fusion 360) and are 3D printed with a 27-micron resolution printer (Pico 2 HD, Asiga, Australia) using UV sensible resin (GR1-clear resin - Pro3Dure - A1000300).

2.2.5 Plasma-liquid interactions and H_2O_2 concentration assay

Liquid samples were plasma treated with the plasma-microfluidic platform and the liquid was diagnosed with a hydrogen peroxide concentration colorimetric assay. For the plasma treatments, the microfluidic devices were operated in the multiphase flow regime with distilled

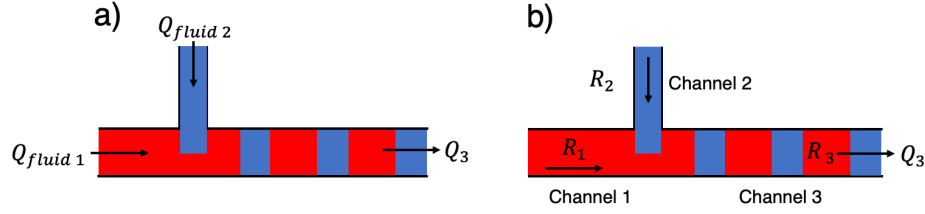


Figure 2.7 A T-junction. a) Imposed flows in the channels. b) Fluidic resistance of the different channels.

water as circulating liquid. For each experiment, the plasma dissipated power, the plasma feed gas humidity and the flow rate imposed by the syringe pump was kept constant for the treatment duration. At the end of the plasma treatment, the concentration of H_2O_2 in the liquid was determined colorimetrically. A solution of 2.5 g of titanium oxysulfate ($TiOSO_4$) in 100 mL of 2 M sulfuric acid solution was used to produce pertitanic acid, which is yellow in color, when reacting with H_2O_2 . In 96-well plate, 160 μL of plasma treated liquid was mixed with 80 μL of the titanium oxysulfate solution and 40 μL of 30 mM sodium azide solution (for stabilisation of the solution). The absorbances of the samples were measured on a Tecan Infinite 200 PRO plate reader at 407 nm. Calibration of the absorbance was achieved by replacing the plasma treated solution with solutions of H_2O_2 of known concentration. Figure 2.9 shows the data and calibration curve for the measurement of H_2O_2 concentration. Detection of H_2O_2 through titanium oxysulfate is typically used for solutions of H_2O_2 of higher concentration than the one analysed in this manuscript. This explains the significant uncertainty on the measurements. Nevertheless, the method was found sufficient to observe key trends on the H_2O_2 concentration variation for different experimental parameters.

2.2.6 Results and discussion

Power measurement

Figure 2.10 shows power measurement results from the method presented in section 2.2.3. The red dots represent the power dissipation without ignited plasma (*off* configuration of Figure 2.4). As previously mentioned, when no plasma is ignited, the power is dissipated almost exclusively in the resistive part of the matching inductor, R_L . This explains the quadratic behaviour of the dissipated power with the current ($P_{off} = R_L \cdot I_{off}^2$). The red line represents the quadratic regression of the power with the current and the black and blue dots represent the power dissipated both in the plasma discharge and the matching inductor (*on* configuration). With the regression and the total dissipated power, the plasma power

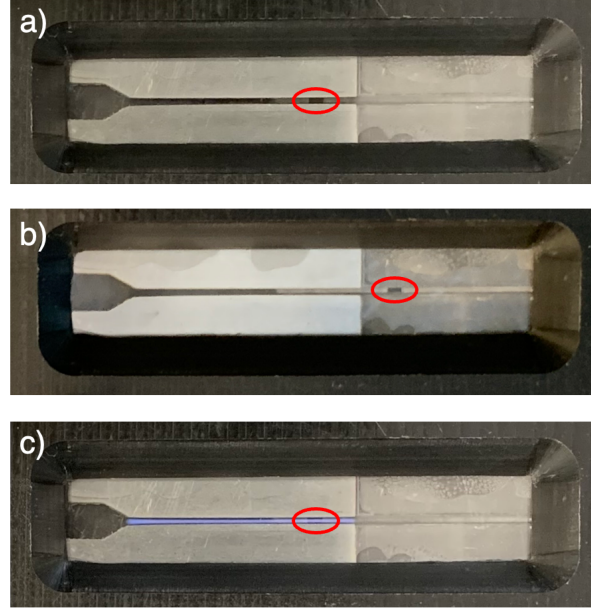


Figure 2.8 Plasma source electrodes on top of the microfluidic device. In a), the opening of the microfluidic device is positioned under the plasma active zone while in b), the opening is in the plasma effluent. In c), the plasma is ignited, and the opening is under the plasma active zone.

dissipation is calculated with Equation 2.3. In Figure 2.10, the black and blue dots represent the total dissipated power with a plasma forming gas of pure helium and with a plasma forming gas of pure helium mixed with an admixture of H_2O of 2100 ppm. Both for pure helium and humidified helium, the point of minimal power is taken slightly after a visible plasma ignition and the point of maximal power is taken slightly before the transition to an arc plasma. Hence, we see that higher power density is needed to ignite the plasma in humidified helium. Analogously, humidified helium can hold a higher power density before transitioning to an arc discharge.

Microfluidic operation

Liquid circulation in the microfluidic devices is possible in two principal regimes of operation. The first one is a single-phase flow: only liquid is flowing in the microfluidic channels ($p_{hyd} < p_{cap} - p_g$ in Equation 2.5). In this regime, the microfluidic device's geometry and the liquid flow rate are chosen to bring plasma-liquid interface at a fixed position. Figure 2.11 shows pictures of tap water with food coloring (for better image contrast) flowing in a 3D printed microfluidic device in this single-phase liquid flow. In a), the gas-liquid interface is held at

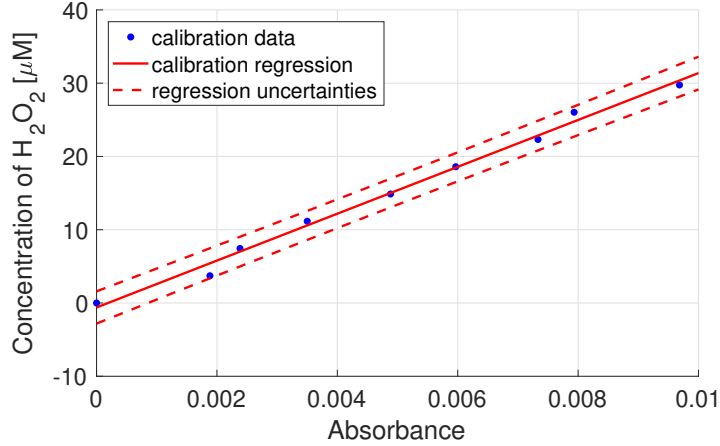


Figure 2.9 H₂O₂ concentration of the samples function of the absorbance. The absorbance of samples of known concentration were measured for calibration.

the upper limit of the microfluidic device, while in b) and c) the gas-liquid interfaces are at lower positions. In Figure 2.11, the height of the gas-liquid interface is controlled only by changing the imposed liquid flow rate in the microfluidic device. The second regime of operation is a multiphase flow. In this regime, both gas and liquid are circulating in the microfluidic device. Multiphase flow is achieved at higher flow rate than single-phase flow when $p_{hyd} > p_{cap} - p_g$ in Equation 2.5. Figure 2.12 shows pictures of the multiphase flow at three different stages of the gas bubble formation in the microfluidic device. In a), a gas bubble starts forming in the fluidic channel. The bubble grows and elongates as seen in b) until it is squeezed on the device's wall and liquid flows again as seen in c). From there, the process repeats itself and another bubble starts to be formed. In this second regime of operation the ratio between gas and liquid that circulates in the microfluidic channels can be controlled by the fluidic resistance of the channel between the liquid reservoir and the opening of the device (R_1 of Figure 2.7) or by the flow rate that is imposed in the microfluidic device (Q_3 of Figure 2.7). The multiphase flow offers two key advantages. The first one is operation stability. An exact control of the gas-liquid interface like in the single-phase flow is particularly sensitive to changes such as flow rates or contact angle. Small instabilities can lead to liquid being dragged in the plasma channel which is strongly undesired as previously mentioned. The second advantage of the multiphase flow is the increased transport of plasma-generated reactive species compared to the single-phase regime. Indeed, the formation of the water droplets in the multiphase flow increases the diffusion transport in the droplets through convection and recirculation movement [101] while these recirculation movements do not take place in the single-phase flow.

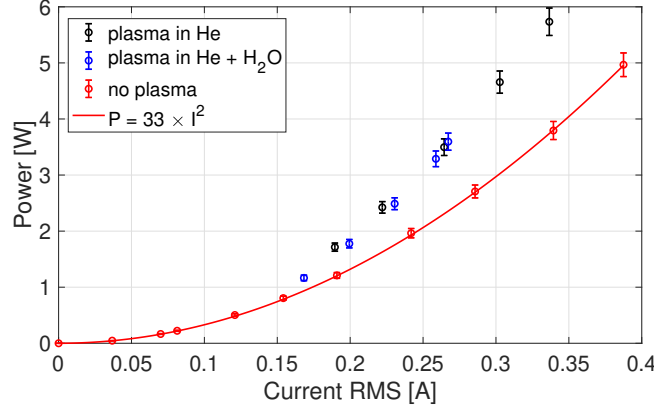


Figure 2.10 Power dissipation with and without an ignited plasma function of the RMS current. The power dissipated in the plasma discharge is given by the difference between the red curve and the power with an ignited plasma.

In Figures 2.11 and 2.12, the same microfluidic device with the same liquid is used and only the imposed liquid flow rate is varied. Figure 2.13 shows the gas bubbles and liquid droplets formed by a multiphase flow at different flow rates. From these experimental observations, we conclude that it is possible to control the size of the gas bubbles and liquid droplets. To explain and predict the gas-liquid flow formation in the microfluidic device, we tried to implement a simple model of the system. Even if the model is overly simplified, several key points could be identified on the formation of the gas bubbles-liquid droplets flow. This led to a hypothesis on multiphase regime formation process. A more complete model and further experimental results would be needed to obtain a satisfactory model. Nevertheless, the following presents some fundamentals on the gas-liquid flow formation processes.

In our microfluidic device, *fluid 1* of Figure 2.7 is water while *fluid 2* is air and the imposed flow rate by the syringe pump would be Q_3 . In the following, we approach the problem with Onsager's variational principal [102–104], which consists of minimizing the Rayleighian. The latter being the sum of the rate of energy dissipation in the system divided by two and the rate of change of the interfacial free energy. We know from experimental results that at low values of Q_3 , only water is flowing in channel 3. It is the first flow regime, when $p_{hyd} < p_{cap} - p_g$. The power consumed to impose this flow before the T-junction is $P_{channel\ 1} = R_{water,1} \cdot Q_{water}^2 = R_{water,1} \cdot Q_3^2$, where $R_{water,1}$ is the fluidic resistance of channel 1 for water. For higher values of Q_3 we see experimentally that both water and air is flowing in channel 3. It is the second regime, when $p_{hyd} > p_{cap} - p_g$. The mechanical power consumed by the system to impose this multiphase flow before the T-junction is $P_{channels\ 1\&2} = R_{water,1} \cdot Q_{water}^2 + R_{air,2} \cdot Q_{air}^2 \approx R_{water,1} \cdot Q_{water}^2$, where $R_{air,2}$ is the fluidic

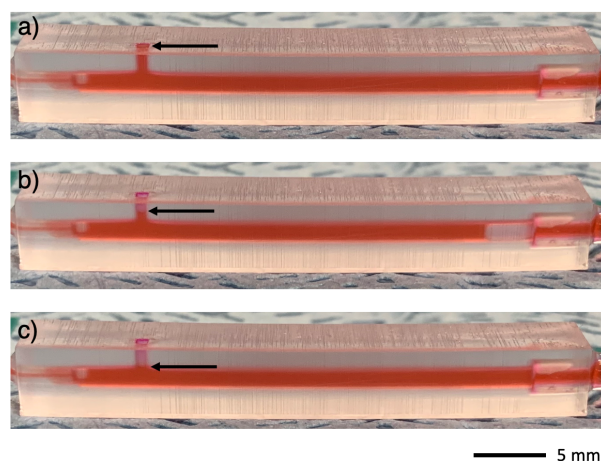


Figure 2.11 Pictures of a microfluidic device operated in the single-phase flow. The height of the liquid interface is varied by changing the flow rate. The black arrows point to the position of the air-liquid interface.

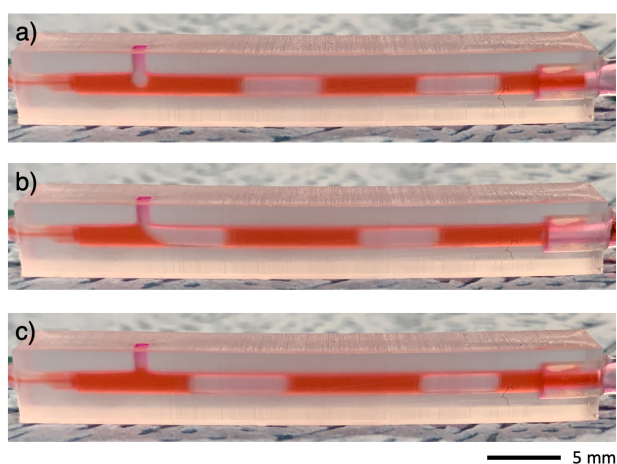


Figure 2.12 Pictures of a microfluidic device operated in the multiphase flow. Pictures a) to c) shows the different steps of the formation of the bubble in the microfluidic device.

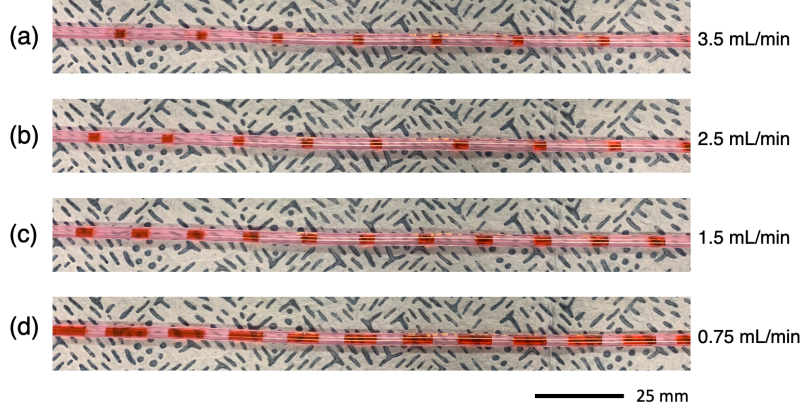


Figure 2.13 Gas-liquid flow at four different flow rates. At higher imposed flow rate, more air is dragged into the channel.

resistance of channel 2 for air. The last approximation is applied because the viscosity of air is 2 orders of magnitude smaller than the one of water and because in our microfluidic devices, channel 1 is much longer than channel 2 making $R_{air,2}$ negligible. For similar arguments, the power dissipated by the system for the flow in channel 3 can be approximated by $P_{channel\ 3} = R_{water,3} \cdot Q_{water}^2 + R_{air,3} \cdot Q_{air}^2 \approx R_{water,3} \cdot Q_{water}^2$, where $R_{water,3}$ is the fluidic resistance of channel 3 for water and $R_{air,3}$ is the fluidic resistance of channel 3 for air. The production of an air bubble in the water also comes at an energy cost because of the formation of an air-water interface. The power consumed for the formation of this interface is given by $P_{surface} = \gamma \cdot \frac{d}{dt}(A)$, where γ is the surface tension of water and $\frac{d}{dt}(A)$ is the time variation of the air-water interface area. For a channel of perimeter $\wp_{channel}$ and a cross section area of $A_{channel}$, the power needed to create the air-water interface is given by $P_{surface} = \gamma \cdot \wp_{channel} \cdot \frac{Q_{air}}{A_{channel}}$. Hence the Rayleighian of the system is given by:

$$\begin{aligned} \mathcal{R} &= \frac{1}{2}P_{channels\ 1\&2} + \frac{1}{2}P_{channel\ 3} + P_{surface} \\ &= \frac{1}{2}(R_{water,1} + R_{water,3}) \cdot Q_{water}^2 + \gamma \cdot \wp_{channel} \cdot \frac{Q_{air}}{A_{channel}} \end{aligned} \quad (2.6)$$

For the experimentally used flow rates and for the microfluidic channel sizes both terms $(R_{water,1} + R_{water,3}) \cdot Q_{water}^2$ and $\gamma \cdot \wp_{channel} \cdot \frac{Q_{air}}{A_{channel}}$ of Equation 2.6 are of similar orders of magnitude in value. The system will tend to minimize the Rayleighian $\left(\frac{\partial \mathcal{R}}{\partial Q_{water}} = \frac{\partial \mathcal{R}}{\partial Q_{air}} = 0\right)$ the total power dissipation under the imposed constraint $Q_{water} + Q_{air} = Q_3$:

$$\mathcal{R} = \frac{1}{2} (R_{water,1} + R_{water,3}) \cdot Q_{water}^2 + \gamma \cdot \wp_{channel} \cdot \frac{Q_3 - Q_{water}}{A_{channel}}$$

$$\Rightarrow \frac{\partial \mathcal{R}}{\partial Q_{water}} = 0 = (R_{water,1} + R_{water,3}) \cdot Q_{water} - \frac{\gamma \wp_{channel}}{A_{channel}} \quad (2.7)$$

From Equation 2.7 we can deduce the flow rates that minimize the power consumption:

$$Q_{water} = \frac{\gamma \wp_{channel}}{(R_{water,1} + R_{water,3}) A_{channel}} \quad (2.8)$$

$$Q_{air} = Q_3 - \frac{\gamma \wp_{channel}}{(R_{water,1} + R_{water,3}) A_{channel}} \quad (2.9)$$

In Figure 2.13, we can see qualitatively that at higher imposed flow rates (Q_3), with all other parameters kept constant, more air is dragged in channel 3 (Q_{water}) as predicted by Equation 2.9. Furthermore, we observed experimentally that using liquids with different surface tensions leads to a change in the average values of Q_{water} and Q_{air} . We compared the bubble formation using water ($\gamma = 72$ mN/m) with using a solution of 70% ethanol in water ($\gamma = 37$ mN/m). We observed a higher flow rate of air with the ethanol solution as predicted by Equation 2.9. Finally, by changing the liquid channel sizes and hence its fluidic resistance we also observed a change in the average values of Q_{water} and Q_{air} : higher fluidic resistance was favoring higher values of Q_{air} . These observations remain qualitative as our theoretical approach that leads to Equations 2.8 and 2.9 has not yet been compared with sufficient experimental data. Our simplified model also conspicuously neglects corner flow leakage around air bubbles during their formation [104]. However, this simplified model infers accurately that the formation of a multiphase air-water flow comes from a competition between the energy consumption associated with creating an air-water interface and the energy consumption associated with imposing a water flow in a microfluidic channel.

H₂O₂ concentration assay

The effects of the variation of feed gas humidity and plasma power dissipation on H₂O₂ production and transport in the circulating liquid of the microfluidic device were studied (Figure 2.14 and 2.15) with the microfluidic devices operated in the multiphase flow regime. For each of them, the concentration of H₂O₂ was compared for the opening of the microfluidic device directly under the active plasma and under the plasma effluent, 3 mm downstream of the active plasma, as seen on Figure 2.8.

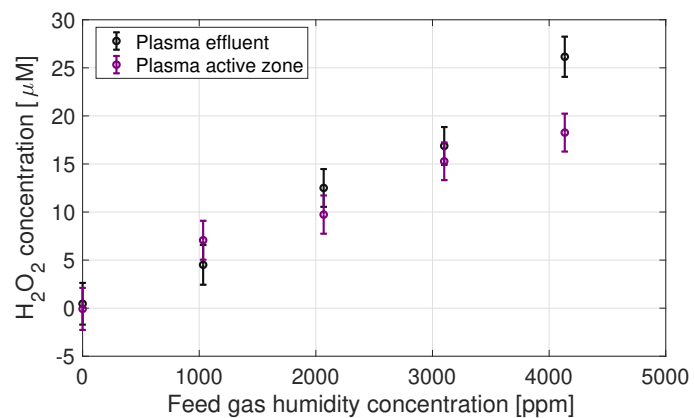


Figure 2.14 H₂O₂ concentration function of the humidity in the feed gas.

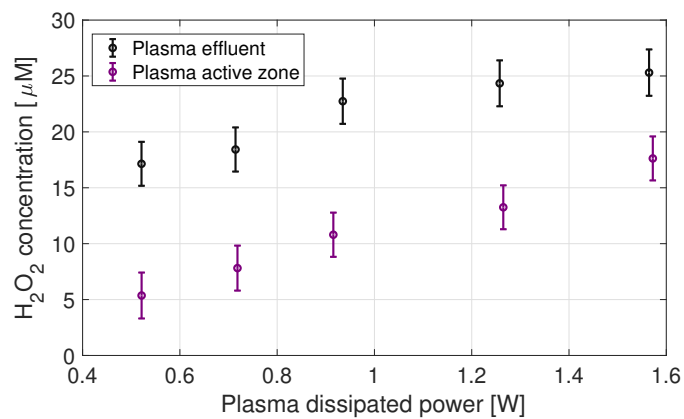


Figure 2.15 H₂O₂ concentration function of the power dissipated in the plasma discharge.

Figure 2.14 illustrates the variation of H_2O_2 concentration in the plasma treated liquid when the concentration of humidity in the feed gas is changed. For each point on this graph, the power dissipated in the plasma was kept constant at 1.4 ± 0.1 W. The final concentration of H_2O_2 in the treated liquid increases with the humidity in the feed gas. Since the main production path of H_2O_2 is through the combination of two OH radicals [71], a higher production of OH radical leads to a higher production of H_2O_2 . As humidity is increased in the plasma feed gas, more OH radicals are formed by dissociation of water molecules through electron-impact reaction ($e + \text{H}_2\text{O} \rightarrow \text{H} + \text{OH}$) which in turn leads to higher H_2O_2 concentration in the liquid. Furthermore, the presence of H_2O_2 is systematically higher for the interaction point in the plasma effluent. This is explained by two main reaction pathways. Firstly, as mentioned, because OH radicals' recombination is the main production pathway of H_2O_2 and OH radicals quickly recombine in the plasma effluent. Secondly, because the main destruction pathway of H_2O_2 is through an electron-impact reaction ($e + \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O} + \text{O}^-$), which no longer takes place in the plasma effluent. When the plasma is operated in pure helium, i.e., with a <3 ppm impurity concentration of humidity, the final H_2O_2 concentration in the treated liquid is lower than the detection limit, suggesting that OH radicals are mainly formed from the dissociation of water molecules originally in the plasma-forming gas and not from additional humidity added by evaporation of water circulating in the microfluidic device.

Figure 2.15 shows the variation of H_2O_2 concentration in the plasma treated liquid for a change of plasma dissipated power. The humidity of the feed gas was kept at 4100 ppm. Both with the opening of the microfluidic device under the active plasma and under the plasma effluent, the increase of power dissipated in the plasma leads to an increase of H_2O_2 concentration in the treated liquid. This could be explained by two reaction pathways. The first one is the increased evaporation of the water circulating in the microfluidic device when the power, and hence the gas temperature, is increased. However, as mentioned, result of Figure 2.14 suggests that the effect on H_2O_2 concentration of evaporation from the water in the microfluidic device is low. The second pathway, and the most probable, is an increased dissociation rate of water molecules with higher plasma power. Higher power thus leads to higher production of OH radicals by the plasma which in turn leads to a higher H_2O_2 concentration in the plasma, plasma effluent and in the treated liquid.

2.2.7 Conclusion

In this manuscript, the COST reference plasma jet was for the first time coupled with microfluidic devices. The interface between the plasma channel and the circulating liquid in

the microfluidic device was controlled by engineering the microfluidic channels' geometry and the imposed flow rate by a syringe pump. The use of 3D printing for the fabrication of microfluidic devices makes their prototyping fairly easy and rapid. The proposed plasma-microfluidic coupling opens the way to new plasma-liquid and plasma-bio interactions studies. The efficient control of liquids on a small scale enables the interactions between liquid and plasma-generated reactive species with a high spatial resolution. We know that for miniature NTP jet sources, plasma chemistry is highly spatially dependent, i.e., reactive species concentration varies greatly in the plasma jet and its surroundings. The proposed method could help understand how this spatial variation can influence the chemistry of liquid in contact with plasma jets. We developed microfluidic devices that allow stable operation of the platform and we think that the formation of the liquid droplet-gas bubble train in the multiphase flow is probably the best approach to maximize the transport of reactive species in the microfluidic devices (see Chapter 3 and Appendix C). Moreover, controlling the flow rate in the microfluidic device also means one can control the velocity of the circulating liquid. This can be of high interest for liquid reaction kinetics analysis since by controlling the velocity, the reactions' time delays can be easily coupled to liquid path distances in the microfluidic device. Furthermore, the proposed plasma-microfluidic platform could open the way to the coupling of existing microfluidic device, used for biological applications such as cancer treatment studies, with reference NTP sources. We think that understanding and tailoring the production and transport pathways of plasma-generated reactive species will play a key role in future research of NTP for biomedical applications and that the combination of NTP sources with microfluidics could be of help in these studies.

Acknowledgements

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CHAPTER 3 COUPLING THE COST REFERENCE PLASMA JET TO A MICROFLUIDIC DEVICE: A COMPUTATIONAL STUDY

The content of this chapter fulfills the third and last goal of this Master’s thesis:

3- Develop a computational simulation tool to explain the main plasma species production and transport pathways in the plasma-microfluidic platform.

The work presented in this chapter was, in large part, performed during an internship with the research group PLASMANT of Prof. Dr. Annemie Bogaerts at University of Antwerp in Belgium. In this chapter, we report on the implementation of a computational model to study the plasma-generated chemistry inside the plasma-microfluidic platform presented in chapter 2. The model takes advantage of the highly unidirectional flow inside the COST-Jet to model the reaction kinetics with a 0D-plug flow model while retaining 2D spatial information through fluid dynamics simulations. This is achieved by using both ZDPlaskin [80] and COMSOL Multiphysics [74] with a similar approach to the work presented in [85]. The simulation approach combining 0D and 2D modeling is introduced together with the results it provides in terms of production and transport of key reactive species. These results are compared with experimental measurements and the limits of the modelling approach are discussed.

As we also plan to submit the results presented in this chapter for publication in *Plasma Sources Science and Technology* journal in the next weeks, it is presented in an article form.

3.1 Model overview

The plasma source inside the plasma-microfluidic platform is based on the COST reference plasma jet [27], which consists of a radiofrequency (13.56 MHz) capacitively-coupled plasma jet produced between two stainless steel plate electrodes. The plasma jet-forming channel is 30 mm long with a 1x1 mm² cross section. Helium is the main plasma-forming gas, and it is combined with small admixtures of water vapor. The plasma-microfluidic platform, presented in chapter 3, is modelled as a plasma channel of 30 mm length, with a cross section of 1 mm by 1 mm followed by a plasma effluent channel of the exact same size. This plasma and effluent channels are put in contact with a small water volume of 2 mm x 1.4 mm and of 1 mm width, which represents the water droplets circulating in the microfluidic device.

The gas-liquid interface can be placed at arbitrary positions in the channel, both under the plasma active zone or under the plasma effluent. The free liquid surface is separated from the plasma or effluent channel by a gap of 0.1 mm. Figure 3.1 shows the schematics of the computational model geometry for a plasma-liquid interaction zone positioned (a) under the plasma active zone and (b) under the plasma effluent. The modelled system's geometry is a cross section of the 3D geometry expanding out of the plane.

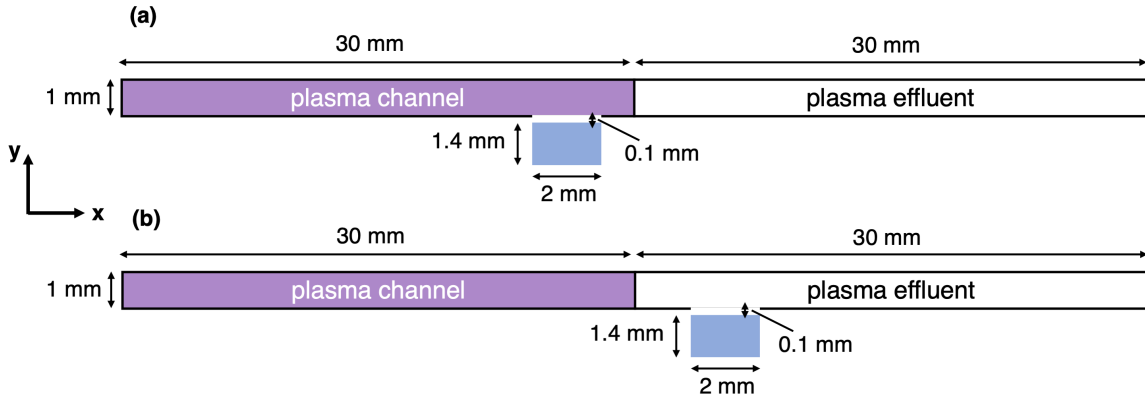


Figure 3.1 Schematic of the geometry used for the simulation model. (a) the liquid volume is placed under the active plasma zone. (b) the liquid is placed under the plasma effluent.

Figure 3.2 shows a flowchart representation of the computational model. The blue colored steps are described in detail in the respective sections of this chapter. Our approach uses a combination of 0D simulations implemented with ZDPlaskin [80] and 2D simulations computed with COMSOL Multiphysics [74]. This approach is used to reduce computing time: full 2D or 3D simulations would be too long to solve with the most recent computers. The chemistry model inside the plasma active zone consists of over 1000 reactions, many of them being electron-impact reactions. For these reactions, the Boltzmann equation must be solved to find the reaction rates. Using both 0D and 2D modelling in parallel enables solving complex chemistry while keeping dimensional information, all of this in a reasonable computational time. The key approximations taken by our modelling approach will be discussed in this chapter.

The first step (I) of the modelling is to simulate the humidified helium flow inside the plasma

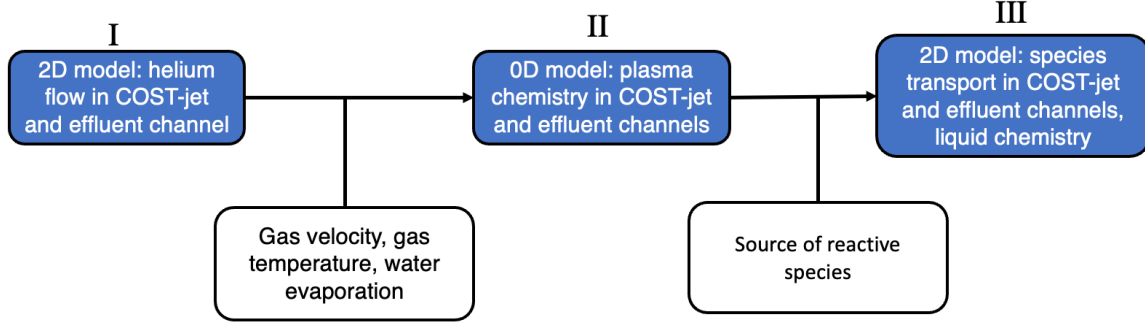


Figure 3.2 Computational flowchart.

and effluent channels in 2D. This step provides spatially-resolved information on the gas velocity, the gas temperature and the humidity concentration in the plasma and effluent channel. This information is needed for the 0D-plug flow plasma chemistry simulations (step II). As it will be presented later, the results of this first 2D model show that the gas flow in the plasma and effluent channel is laminar with a bulk average velocity of $v = 25$ m/s (Reynold number of $Re \sim 200$). The diffusion coefficients of the plasma-generated species have a typical value of $D = 2 \times 10^{-5}$ m²/s (see Table 3.1 with Section 3.4.1). Assuming a characteristic length of $L = 0.1$ mm, we obtain for the plasma channel flow a Péclet number of $Pe = \frac{Lv}{D} = 125$. As this value is much higher than 1 we take advantage of the fact that the transport through diffusion in the direction perpendicular to the gas flow (crosswind diffusion) is much smaller than the laminar flow convective transport to make a key approximation for our modelling approach: the plasma and effluent channel can be broken down into thinner domains, which will be we called “bins”, as shown in figure 3.3. In our approach, each bin is modeled as an independent 0D-plug flow system in step II. For each bin, a different temperature and humidity profile, that is provided by the 2D humidified helium flow simulation (step I), is applied to solve the corresponding chemistry inside a 0D-plug flow simulation. The results of each bin are then used in step (III) as inputs for a second two-dimensional COMSOL model which considers a limited number of plasma-generated species. The COMSOL model considers the transport of plasma-generated species to the liquid along with the reaction kinetics inside the liquid. In the following sections, each step of this simulation procedure is discussed in further details. Figure 3.2 summarizes the computational approach:

- I. A first 2D model simulates the plasma and effluent channel, without solving for any chemistry, to provide spatially-resolved information on gas velocity, gas temperature and humidity concentration. (Section 3.2)

- II. The simulation domain is split in thin bins. The chemistry and reactive species evolution in each bin is solved independently in a 0D-plug flow simulation using the results provided by the first 2D model. (Section 3.3)
- III. A second 2D model uses the results of each bin's 0D-plug flow simulation to model the evolution of plasma reactive species in two dimensions in the plasma channel, effluent channel and inside the liquid. (Section 3.4)

3.2 2D model for velocity, temperature and humidity

The first 2D model is built using COMSOL Multiphysics (version 6.0) [74]. It uses three physics modules: “Laminar Flow”, “Heat Transfer in Fluids” and “Transport of Concentrated Species”. The laminar flow module is used to compute the velocity distribution of the feed gas inside the plasma and effluent channel. A flow rate of 1.5 slm is used at the inlet. The steady state velocity distribution inside the channel is computed by solving the Navier-Stokes equations. The mesh was built using COMSOL’s built-in meshing tools for fluid dynamics. The solution for the velocities is then used as input for the heat transfer and transport of species modules. The heat transfer module is used to compute the temperatures inside the plasma and effluent channel. The temperature at the inlet is fixed. In the plasma section of the channel a constant volumetric heat source is considered: the plasma power dissipation (typically 1 W) divided by the plasma volume ($30 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$). Hence, we assume that almost all the energy consumed by the plasma is dissipated as heat. An interfacial heat flux is considered at the liquid interface resulting from the water evaporation. All other boundaries, except for the outlet, are thermally insulated. The transport of concentrated species module is used to compute the humidity content along the plasma and effluent

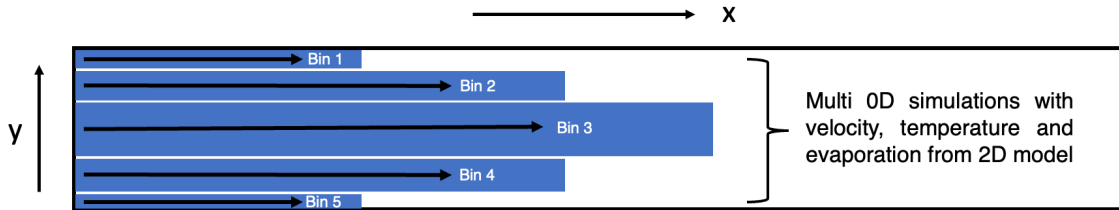


Figure 3.3 The plasma and effluent channel is separated in different bins. The chemical kinetics of each bins is solved by a different 0D model with different parameters of gas velocity, gas temperature and humidity concentration. Only 5 bins are illustrated on the figure for simplicity while in the solved model, 11 bins were used.

channel. The gas inlet has a humidity fixed at a concentration matching the experimental conditions (4500 ppm). The humidity concentration at the gas-liquid interface is kept at 100% relative humidity, the corresponding concentration given by Antoine's Law [105]. No humidity flux is considered at the other boundaries except for the outlet. The convective transport of humidity is computed with the solution of the laminar flow module while the diffusion of humidity in helium is calculated with the mass diffusivity of H₂O in helium.

3.2.1 Inputs for ZDPlaskin's simulations

Before the model solves any plasma chemistry, the main parameters that influence the reaction kinetics evolution such as temperature and humidity content are calculated. These parameters vary spatially in the plasma and effluent channel. To consider these variations, the results from the humidified helium gas flow 2D simulation are used. For the velocity, the average velocity of each bin is used in the corresponding 0D-plug flow simulation. The plasma-forming gas velocity enables the coupling between time and distance in each 0D-plug flow simulation. For each bin, the temperature along the x-axis from the previous 2D model is implemented in the 0D-plug flow simulation. As each bin is not infinitely thin, the y-averaged values are used along the x-axis (plug flow axis). Humidity is introduced slightly differently in the 0D simulations than the temperature. Since the reaction kinetics influences the concentration of H₂O along the x-axis, the concentration of H₂O cannot be fixed (as the temperature was). Instead, the model considers the variation of H₂O concentration along the x-axis. This variation arises from mixing of the evaporated water at the liquid interface with the humidified helium. To consider it, the spatial derivative of the H₂O concentration along the x-axis is used to feed the different 0D-plug flow simulations.

3.3 0D model for reactive species production

The 0D simulations are performed using ZDPlaskin, a freeware that solves complex sets of conservation equations from arbitrary complex sets of chemical reactions:

$$\frac{\partial n_s}{\partial t} = \sum_{i=1}^m \left[(a_{s,i}^R - a_{s,i}^L) k_i \prod_j n_j^{\alpha_{j,i}} \right] \quad (3.1)$$

Where, n_s is the density of species s , m is the number of reactions, $a_{s,i}^R$ and $a_{s,i}^L$ are the stoichiometric coefficient of species s in reaction i on the right side and left side of the reaction, respectively, k_i is the reaction rate of the i^{th} reaction and $n_j^{\alpha_{j,i}}$ is the density of the j^{th} reactant of reaction i elevated to the power equal to its stoichiometric coefficient $\alpha_{j,i}$ [80].

In our model, ZDPlaskin solves the chemistry for a set of 1437 reactions and 90 species (plus electrons) taken from [106]. The reaction rates of heavy species (non-electronic) reactions are either constant or gas-temperature dependent. The reaction rates of electron-impact reactions are calculated through:

$$k_i = \int_{\varepsilon_{th}}^{\infty} \sigma_i(\varepsilon) \nu(\varepsilon) f(\varepsilon) d\varepsilon$$

where ε_{th} is the threshold energy of the reaction, σ_i is the cross section of collision i , ν is the electron velocity, f is the EEDF and ε is the energy. The EEDF is found by solving the Boltzmann equation in ZDPlaskin by the built-in solver BOLSIG+. To do so, the Boltzmann solver uses a set of electron-impact cross sections, gas temperature, reduced electric field and electron density. The reduced electric field is kept constant at a value given by the local-field approximation:

$$E = \sqrt{P/\sigma}$$

where P is the average power density taken as the plasma power dissipation (typically 1W) over the plasma channel volume ($1 \times 1 \times 30 \text{ mm}^3$), and σ is the plasma conductivity calculated with:

$$\sigma = \frac{ev_d n_e}{E}$$

where e is the elementary charge, v_d is the electron drift velocity, n_e is the electron density and E is the electric field. For the results presented in this chapter, the plasma and effluent channel is split into 11 bins. Each bin has a length (dimension along the x-axis) of 60 mm: 30 mm of active plasma and 30 mm of effluent. The four outermost bins (2 at the upper and 2 at the lower edge) are 50 μm -wide (dimension along the y-axis), the central bin is 200 μm -wide and the remaining bins are 100 μm -wide. For each of these 11 bins, one independent 0D-plug flow simulation is performed.

3.4 2D model for transport of plasma generated species

3.4.1 Transport of species in the plasma channel and effluent channel

In the plasma and effluent channel, the concentration of each reactive species of interest is solved in 2D through the convection-diffusion equation:

$$\frac{\partial c_i}{\partial t} = \nabla \cdot (D_i \nabla c_i) - \nabla \cdot (\vec{v} c_i) + S_i \quad (3.2)$$

Where c_i is the concentration of the i^{th} species, D_i is the diffusivity in helium of the i^{th} species, $\vec{v}$ is the velocity vector field solved as presented in section 3.2 and S_i is the source term of the i^{th} specie. In COMSOL, the convection-diffusion equation is solved with the “Transport of Diluted Species” module. The mesh was built using COMSOL’s built-in meshing tools to obtain convergence with the available random-access memory (RAM). The diffusivity of each species, D_i is calculated directly in COMSOL through the Chapman–Enskog theory [107]:

$$D_i = A \frac{T^{3/2}}{p \left(\frac{\sigma_1 + \sigma_2}{2} \right)^2 \Omega} \sqrt{\frac{1}{M_1} + \frac{1}{M_2}}$$

where D_i is the diffusivity in helium of specie i , A is an empirical constant whose value is $A = 5.956 \times 10^{-18} \frac{\text{Pa} \cdot \text{m}^4}{\text{K}^{3/2} \text{s}} \sqrt{\frac{\text{kg}}{\text{mol}}}$, T is the temperature in K, M_1 and M_2 are the molar masses of the helium and the species of interest, respectively, in kg/mol. p is the pressure in Pa and Ω is the temperature-dependent collision integral given by [107]:

$$\Omega = \frac{1.0636}{T^{*1.15610}} + \frac{0.19300}{e^{0.47635T^*}} + \frac{1.03587}{e^{1.52996T^*}} + \frac{1.76474}{e^{3.89411T^*}}$$

where $T^* = \frac{k_b T}{\sqrt{\varepsilon_1 \varepsilon_2}}$. σ_1 , σ_2 , ε_1 and ε_2 are the Lennard-Jones parameters of helium and the species of interest. The temperature profile obtained from the humidified helium gas flow COMSOL model is used to calculate the diffusivities. Table 3.1 presents the Lennard-Jones parameters for the species of interest used in the model [108–110].

S_i in Equation 3.2, the source term, is found, for each species included in the 2D model, with the results of the 0D-plug flow simulations of each bin. Figure 3.4(a) shows an illustrative example of the spatial distribution of the H_2O_2 , OH and O densities obtained with the 0D-plug flow simulation for the central bin. From these density calculations, the density variation along the x-axis of the different species can be found by taking the spatial derivative $\frac{dn_s}{dx}$. Figure 3.4(b) shows an example of the species density variation along the x-axis (the derivative of Figure 3.4(a)) for H_2O_2 , OH and O. This calculation, $\frac{dn_s}{dx}$, is used in turn as an input for the 2D model: for each bin in the domain, the data $\frac{dn_s}{dx}$ acts as a source of reactive species in the convection-diffusion equation:

$$S_i = \frac{dn_s}{dx} \cdot \frac{dx}{dt} = \vec{v} \cdot \frac{dn_s}{dx} \quad (3.3)$$

Table 3.1 Lennard-Jones parameters of gas species. For HNO, the values of HO₂ were used because no information was available.

Species	σ [m]	ϵ [J]	Ref.
He	2.6×10^{-10}	1.4×10^{-22}	[111]
H ₂ O	2.6×10^{-10}	1.1×10^{-20}	[111]
N	3.3×10^{-10}	9.9×10^{-22}	[111]
N ₂	3.8×10^{-10}	9.9×10^{-22}	[111]
O	3.1×10^{-10}	1.5×10^{-21}	[111]
O ₂	3.5×10^{-10}	1.5×10^{-21}	[111]
O ₃	3.9×10^{-10}	2.9×10^{-21}	[112]
NO	3.5×10^{-10}	1.6×10^{-21}	[111]
NO ₂	3.8×10^{-10}	2.9×10^{-21}	[112]
NO ₃	3.8×10^{-10}	5.5×10^{-21}	[113]
N ₂ O	3.8×10^{-10}	3.2×10^{-21}	[111]
H	2.7×10^{-10}	5.1×10^{-22}	[111]
H ₂	2.8×10^{-10}	8.2×10^{-22}	[111]
HNO	3.4×10^{-10}	4.0×10^{-21}	[HO2]
HNO ₂	3.6×10^{-10}	3.8×10^{-21}	[113]
HNO ₃	3.9×10^{-10}	5.4×10^{-21}	[113]
HO ₂	3.4×10^{-10}	4.0×10^{-21}	[113]
H ₂ O ₂	4.2×10^{-10}	3.9×10^{-21}	[111]
OH	3.1×10^{-10}	1.1×10^{-21}	[111]
NH	3.3×10^{-10}	9.0×10^{-22}	[111]

In practice, for each bin and species implemented in the 2D model, $\frac{dn_s}{dx}$ is found from the discrete derivative of the corresponding 0D-plug flow simulation result for specie n_s . $\frac{dn_s}{dx}$ is fed as an interpolation function together with the expression of Equation 3.3 to the COMSOL model to form the source term in a “Out-of-Plane Flux” node. This approach enables the use of a 0D kinetics solver to solve the complex chemistry in the plasma channel. This approach greatly reduces the computation time while retaining the spatial information needed for the resolution of the convection-diffusion equations in 2D. Of course, this approach comes at a cost: species diffusion perpendicular to the 0D-plug flow axis (crosswind diffusion) is completely uncoupled from the reaction kinetics. The error associated to this uncoupling will be further discussed in Section 3.5.

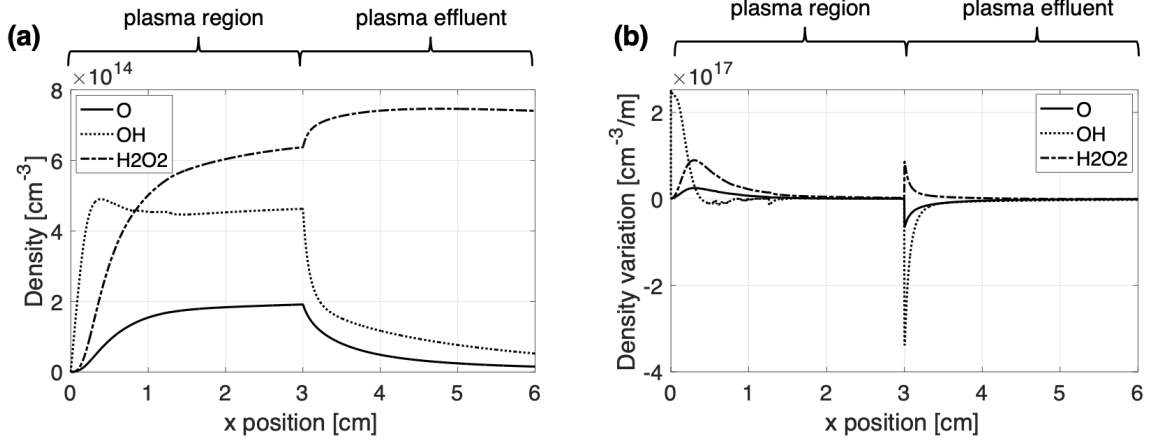


Figure 3.4 0D-plug flow simulation results example for the central bin. In (a) the density evolution along the x-axis for different species and in (b), the corresponding spatial derivative.

3.4.2 Transport of species at the gas-liquid interface

The transport of reactive species at the interface is implemented through Henry's law, a partition condition that defines the ratio of concentrations at the interface:

$$c_l = H \cdot c_g$$

where c_l and c_g are the concentrations in the liquid and gas phases and H is Henry's constant. Also, flux continuity across the interface implies that:

$$\vec{J}_l = -\vec{J}_g,$$

Where $\vec{J}_l$ and $\vec{J}_g$ are the specie fluxes at the liquid and gas interface respectively. The temperature-dependent Henry's constants for the species implemented in the 2D model that are present both in the gas phase and liquid phase are taken from [85].

3.4.3 Reaction-transport processes in the liquid phase

The transport of species in the liquid phase is computed using COMSOL's "Diluted Species Concentration" module coupled to a "Chemistry" module that solves the reaction-diffusion-convection equation for 25 different species and 52 reactions:

$$\frac{\partial c_{aq,i}}{\partial t} = \nabla \cdot (D_{aq,i} \nabla c_{aq,i}) - \vec{v}_{aq} \cdot \nabla c_{aq,i} + R_{aq,i} \quad (3.4)$$

where $c_{aq,i}$ is the concentration of the i^{th} species in the aqueous solution, $D_{aq,i}$ is the diffusivity in water of the i^{th} specie, $\vec{v}_{aq}$ is the velocity vector field and $R_{aq,i}$ is the source or loss term of the i^{th} species for all chemical reactions considered. Initially, the liquid is considered as distilled water: all species' concentrations are set to zero except for OH and H_3O^+ which are set at a concentration of 10^{-7} M. The in-liquid chemical reaction set and the diffusivity of the aqueous species are taken from [85].

The liquid volume of the model represents a snapshot of the actual experimental situation. In reality, a dual-phase flow consisting of a steady moving train of liquid droplets separated by gas bubbles is produced (see Figure 3.5) as explained in chapter 2. The formation of this dual-phase arrangement is highly dynamic, yet very reproducible. As the dynamic formation of the liquid droplet-gas bubble train is complex to simulate, we limited our model to the time lapse when the plasma stream contacts the liquid phase. A convective flow inside the liquid droplet arises from the shear forces exerted by the microfluidic channel walls [101]. To include this movement in the model, the top and bottom boundaries of the liquid volume are considered as sliding walls which velocity is set to the average liquid velocity of the droplet. In the results presented here this velocity is 1.67 cm/s. This value refers to the average water droplet velocity in the plasma-microfluidic experiment when a flow rate of $16.7 \mu\text{l/s}$ (1 ml/min) is used. The two other walls have a slip condition as they represent an air-water interface. Figure 3.5 illustrates the experimentally-observed liquid droplet-gas bubble train formation (a) and how the movement inside the liquid volume was modelled (b).

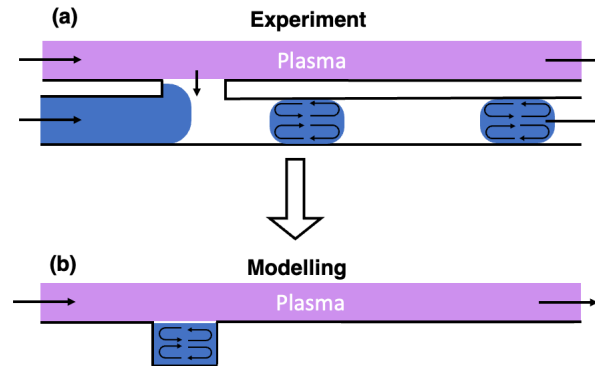
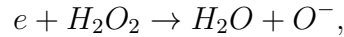


Figure 3.5 Schematic of the steadily-moving liquid droplet-gas bubble train observed experimentally (a). In the model, all the boundaries are stationary (b).

3.5 Results and discussion

The 2D model we developed for the species production and transport in the plasma-microfluidic device considers 18 species in the gas phase and 25 species in the liquid. Table 3.2 summarizes the species implemented in the 2D model. The 25 liquid species were taken directly from [85]. Among these species, only 18 can also exist in the gas phase: these are the 18 species that were included in the gas phase of the 2D model. The results of two distinct models will be presented. The first model considers a liquid volume contacting the plasma-forming zone, spreading from 24 to 26 mm from the main gas inlet. The second one uses a liquid volume in contact with the plasma effluent and is located between 33 and 35 mm from the main gas inlet. In both cases, the plasma power dissipation is taken as 1 W and the feed gas is humid helium (4500 ppm of H_2O) with oxygen (1 ppm) and nitrogen (4 ppm) impurities fed at 1.5 slm. Figure 3.6 shows the result of the first 2D simulation as presented in Section 3.2. These are the results that are used to provide the velocity, temperature and humidity concentration to the 0D-plug flow simulations for each of the 11 bins used in this model. Figure 3.7 shows the results of the velocity field inside the liquid.

Figure 3.8 shows the evolution of H_2O_2 concentration for the plasma-liquid (a) and plasma-effluent (b) contact arrangements. The model predicts higher H_2O_2 concentrations when the plasma effluent contacts the liquid compared to when the liquid contacts with the plasma-forming zone. This is explained by two reasons. First, the simulation shows that the main destruction pathway of H_2O_2 is through an electron-impact reaction:



which no longer takes place in the plasma effluent. Moreover, the main production pathway of H_2O_2 is through the recombination of two OH radicals. Figure 3.9 shows the evolution of OH radicals both in the plasma-forming region and in the plasma effluent. The OH radicals are quickly depleted outside of the plasma-forming region to form H_2O_2 .

Table 3.2 Species implemented in the 2D model.

Gas phase species
$O_2, N_2, H_2, O, N, H, OH, H_2O_2, HO_2, O_3, NO, N_2O, NO_2, NO_3, HNO, HNO_2, HNO_3, NH$
Liquid phase species
$O_2, N_2, H_2, O, N, H, OH, H_2O_2, HO_2, O_3, NO, N_2O, NO_2, NO_3, HNO, HNO_2, HNO_3, NH, OH^-, O_2^-, ONOOH, ONOO^-, H_3O^+, NO_2^-, NO_3^-$

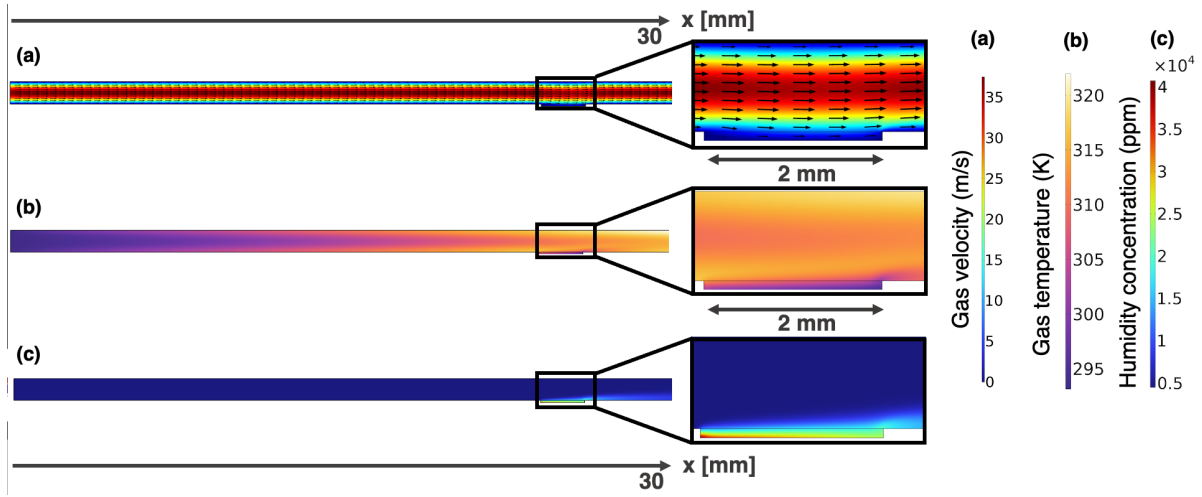


Figure 3.6 Gas velocity (a), gas temperature (b) and humidity concentration profile (c) in the COST-jet channel.

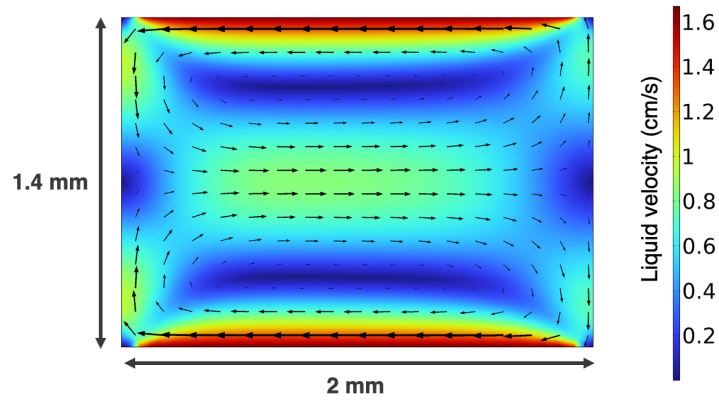


Figure 3.7 Velocity vector field inside the liquid volume.

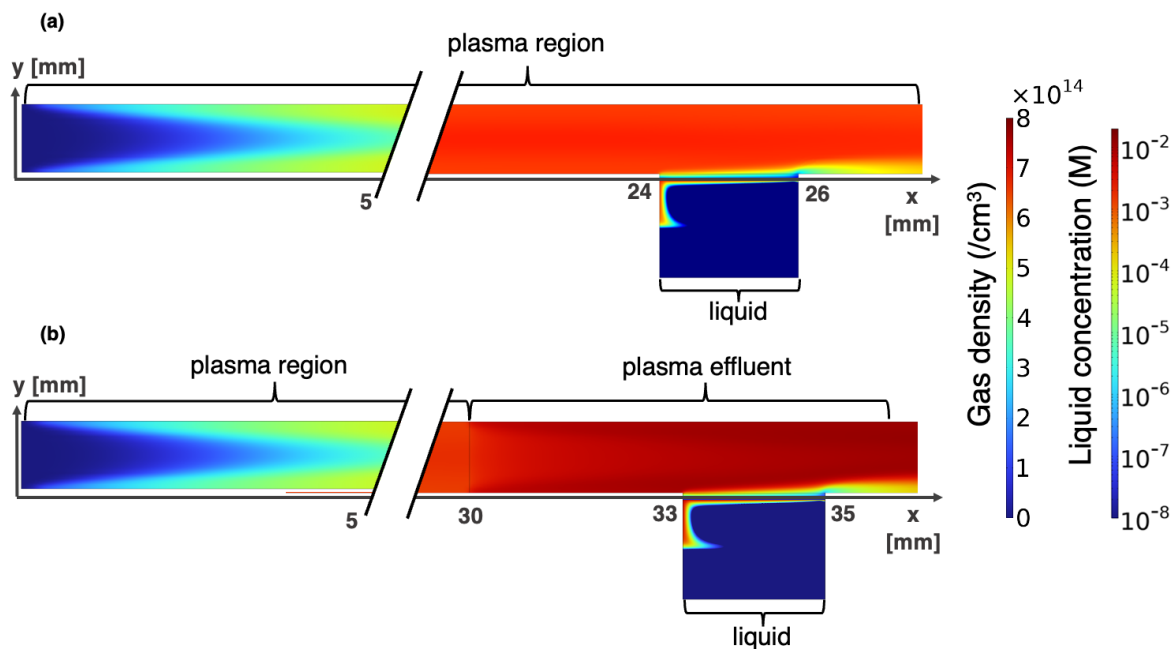


Figure 3.8 H_2O_2 concentration in plasma, plasma effluent and in the liquid for a plasma-liquid interaction zone located in the (a) plasma-forming zone and (b) plasma effluent.

As previously mentioned, the goal of this computational work was to explain the experimental results reported in chapter 2. In this experiment, the imposed liquid flow rate in the microfluidic device was $16.7 \mu\text{l/s}$ (1 ml/min) corresponding to an average velocity of 1.67 cm/s . With this velocity, the liquid droplets travel through the 2 mm opening of the microfluidic device in 0.12 second which can be transposed in the model as a liquid treatment time of 0.12 second . Hence, the experimental results were compared with a simulation of a liquid treatment time of 0.12 second . The H_2O_2 concentration was measured experimentally with the titanium oxysulfate method presented in chapter 2. For a plasma power dissipation of 1 W and a microfluidic water flow rate of $16.7 \mu\text{l/s}$ (1 ml/min), the concentration of H_2O_2 in the treated liquid was experimentally measured for a liquid interaction zone under the plasma-forming region and under the plasma effluent and compared with the average H_2O_2 concentration in the liquid provided by the simulation. Figure 3.10 shows the results in terms of H_2O_2 concentration both for the experiment and simulation. The model predicts higher concentration of H_2O_2 than the experimental values, but with a reasonable margin: both experimental and modelling differs by less than 50% which is satisfactory considering the different approximations that were used. The simulation values presented in Figure 3.10 are the average concentrations inside the liquid volume after a treatment time of 0.12 s . Further simulations showed that once the contact with the plasma or plasma effluent is removed, the average concentration variation of H_2O_2 is less than 1% for at least 90 seconds , which exper-

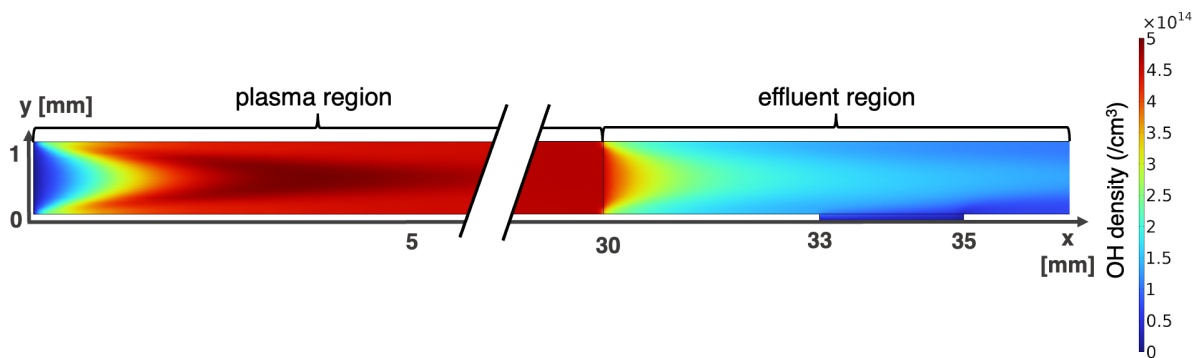


Figure 3.9 OH radicals' concentration in the plasma and the plasma effluent.

imentally is approximately the time between liquid treatment with the plasma-microfluidic platform and the moment where the treated liquid is analyzed. Therefore, the value after the 0.12 s treatment was taken for direct comparison with experimental values.

One of the central simplifications used to model the plasma and effluent channel was to split the domain in bins and to solve an independent 0D-plug flow simulation for each of them. Through this approximation, the effect of the transport of species between the different bins on the reaction kinetics is neglected. To investigate the error associated with this approximation, further simulations were run. To estimate the minimum and maximum values of the average concentration of H_2O_2 in the liquid, the species flux ($\frac{dn_s}{dx}$) in the entire plasma and effluent channel was taken as the flux of the bin of minimum and maximum production of H_2O_2 , respectively. This gives a limit on the H_2O_2 production as we do not expect that the crosstalk between the bins would lead to a reaction kinetics that produces more H_2O_2 than the bin of maximal production or less H_2O_2 than the bin of minimal production. This extremum value investigation is quite straightforward for H_2O_2 in the liquid, because it strongly correlates with the production of H_2O_2 in the plasma and effluent channel. However, for investigation of other species, it might be necessary to look deeper into the production and destruction mechanisms to obtain minimum and maximum values. For example, ONOOH is not formed in the gas phase, but only in the liquid through different reactions (such as $\text{NO}_{aq} + \text{HO}_{2aq} \rightarrow \text{ONOOH}_{aq}$ or $\text{NO}_{2aq} + \text{OH}_{aq} \rightarrow \text{ONOOH}_{aq}$). Hence an estimation of the maximum and minimum concentration values of this specie requires a more thorough analysis.

The model predicts higher concentration of H_2O_2 than the experimental values, but with a reasonable margin: both experimental and modelling differs by less than 50%. Still, the disagreement can be explained by different limits in the modeling approach. The most obvious one is the stationary boundary approximation. In the model, all boundaries of the

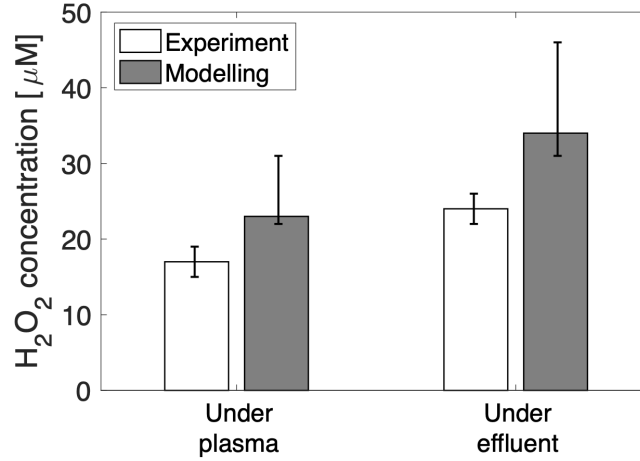


Figure 3.10 Experimental and modelling comparison of H_2O_2 transport in the liquid volume.

liquid are fixed in space while in reality, it is a dynamic system where the boundaries of the liquid droplet are constantly moving. Also, the exact behavior of the small gap between the plasma channel and the liquid is unknown. Its height, which is set to $100\ \mu\text{m}$, might have a different value. Moreover, a verification is required whether there is plasma in the gap and if it makes direct contact with the liquid. In the current model, no chemistry is directly modeled in this gap: the species are only transported (by convection and diffusion) from the plasma channel to this region and no chemistry is directly solved. Furthermore, the species transport at the liquid interface through Henry's law will influence the chemical species concentration in the plasma-forming and plasma effluent regions which in turn might influence the reaction kinetics. This is not taken into account in the model, i.e., there is no feedback loop to the 0D models from species transport at the liquid interface. Also, the use of Henry's law constants might lead to a modelling limit: the Henry's constants we find in the literature comes from systems at equilibrium and the system we modelled in this work is not at equilibrium. However, no better implementation of the partition condition for reactive species between the gas and the liquid than Henry's law exists. Lastly, the power density which is used to calculate the EEDF is taken as an average value for the whole plasma region. In reality it will vary spatially within the plasma channel.

These different limits in our modelling approach might explain the discrepancies between modelling and experimental results. Nevertheless, our model still provides information on the main production and transport pathways of reactive species from the plasma region to the liquid in the microfluidic device.

3.6 Chapter's summary

We presented a first modelling approach to simulate the COST reference plasma jet in contact with a microfluidic device. Taking advantage of the fast computation time of 0D modelling, we combined 0D-plug flow chemical kinetics simulations with 2D fluid dynamics-species transport simulations to obtain a quasi-2D model that provides spatially resolved information on the production and transport of reactive species produced by the COST-Jet plasma discharge. This combined approach was based on the uncoupling of the plasma and plasma effluent reaction kinetics from the crosswind transport processes. The error associated with this approximation was discussed for the transport of hydrogen peroxide in the liquid, and the modelling results were compared with experimental data. The prediction of hydrogen peroxide concentration in the liquid is in good agreement with experimental results, given the simplifying assumptions made. Key limits on the modelling approach were discussed trying to elucidate this discrepancy. The discussed results mainly focused on hydrogen peroxide to have experimental comparison ground. Nevertheless, the presented model still has the potential to give insight on the production and transport of other plasma-generated reactive species. Moreover, the proposed modelling approach could be applied to simulate the complex chemistry of other plasma sources of highly unidirectional gas flow at high Péclet number. The computational work presented here combined with the plasma-microfluidic platform presented previously sets the basis, both in terms of experimental work (chapter 2) and computational work (current chapter), for the use of standard and novel microfluidic devices in the context of plasma medicine.

CHAPTER 4 GENERAL DISCUSSION

The central objective of this Master's thesis was the development of a novel plasma-microfluidic platform to provide new tools for the use of microfluidic devices in the context of plasma medicine research. To tackle this challenge, three specific objectives were put forward:

1. Develop a platform that allows a reference plasma source to treat a liquid circulating in a microfluidic device.
2. Characterize the plasma source and the transport of plasma-generated reactive species in the plasma-microfluidic platform.
3. Develop a computational simulation tool to explain the main plasma species production and transport pathways in the plasma-microfluidic platform.

The work that has been carried out for each of these three specific objectives are summarized and discussed in the following paragraphs and in figure 4.1.

4.1 Development of the plasma-microfluidic platform

The plasma-microfluidic platform is, at its core, the combination of the COST reference plasma jet and a 3D printed microfluidic device. The COST-Jet was chosen as basis for the platform for three main reasons. Firstly, because it has been widely used and studied by several research groups of the NTP community as a reference plasma source and is thus very well characterized. Secondly, because its relatively simple design facilitates its implementation in the plasma-microfluidic platform. Thirdly, the simplicity of its design allows major simplifying assumptions which renders its modeling manageable. The geometry and power delivery of the COST-Jet were unaltered in the plasma-microfluidic platform. Only the mechanical design was changed to enable the coupling of the plasma source to a microfluidic device.

For this thesis, novel microfluidic devices were designed to allow interactions between the plasma or plasma effluent and a liquid circulating inside the microfluidic devices. The operation of the microfluidic devices was possible in two regimes. In the first one, the single-phase liquid flow, the position of the interface between the flowing liquid and the plasma source channel was adjusted by carefully controlling the pressure within the microfluidic device. This was achieved by changing the flow rate of the flowing liquid and the hydraulic resistance of

Objective 1: Develop a platform that allows a reference plasma source to treat a liquid circulating in a microfluidic device.

- Development of an adapted design of the COST-Jet to enable its coupling with microfluidic devices.
- Development of novel home-made 3D printed microfluidic devices that optimize the stability of the plasma-liquid interaction zone and optimize the transport of reactive species.
- Design of a compact and all-in-one plasma-microfluidic platform (gas connexion, liquid connexion, plasma source, microfluidic device, optical access).

Objective 2: Characterize the plasma source and the transport of plasma-generated reactive species in the plasma-microfluidic platform.

- Implementation of an accurate and reliable plasma power dissipation measurement method for the miniature plasma source.
- Experimental analysis of the transport of reactive species based on hydrogen peroxide concentration assays of the plasma treated liquid.

Objective 3: Develop a computational simulation tool to explain the main plasma species production and transport pathways in the plasma-microfluidic platform.

- Development of a new quasi-2D approach to combines 0D reaction kinetics modelling and 2D fluid dynamics modelling applicable to unidirectional flow of high Péclet number.
- Modelling of the transport of 18 gas species and 25 liquid species in a 2D model.
- Comparison of the modelling results with experimental data for hydrogen peroxide: difference of less than 50%.

Figure 4.1 Accomplished work in each of the three specific objectives of this Master's thesis

the microfluidic channels. However, as explained in chapter 2, in this single-phase flow, the transport of reactive species is lacking and a satisfactory operation stability is difficult to obtain, especially in the context of plasma-induced hydrophilic surfaces. To overcome these limitations, a second regime of operation of the microfluidic devices was used: the gas-liquid flow. In this arrangement, both gas bubbles and liquid droplets are circulating, in alternation, in the fluidic channels. The formation of water droplets allows for higher stability in the coupling of the plasma channel with the microfluidic device. Very suitably, it also increases the transport of reactive species within the liquid since a convective movement is created in the water droplets. In both operation regimes, the opening that allows the plasma-liquid interactions can easily be set at different positions. This enables to probe plasma-liquid interactions with a high spatial resolution due to the small and controllable size of the opening. As the plasma chemistry highly varies spatially, it is also possible to tailor the liquid chemistry in the microfluidic device by changing the position of the plasma-liquid interaction zone.

By efficiently combining the COST-Jet with microfluidic devices, a novel plasma-microfluidic platform was created which enables the use of microfluidic technologies with a reference plasma source. This combination of plasma and microfluidic led to major advantages. Firstly, it allows plasma-liquid interaction diagnostics that are reproducible and parallelizable. Secondly, the laminar liquid flow regime, easily obtained with microfluidic devices, is ideally suited for liquid reaction kinetics studies as reaction time can easily be translated to a position in the fluidic channel with the average velocity of the laminar flow. Hence, the plasma-microfluidic combination could be applied to reaction kinetics studies in plasma-liquid interaction processes. This approach brings the design concept of the COST-Jet to a next level, combining a simple plasma channel geometry with an equally simple liquid phase geometry. Finally, the use of microfluidics is well established in biomedical analysis and promises to be of high interest in the context of plasma medicine. Biological models embedded in microfluidic devices have been used in the context of cancer research to test chemotherapy, radiotherapy and immunotherapy treatment and we presume that they are equally relevant to test cancer treatment based on NTP. The presented plasma-microfluidic platform offers a strong prototype for such future studies.

4.2 Characterization of the plasma-microfluidic platform

For a thorough understanding of the plasma-microfluidic platform, the plasma source was electrically characterized, and the liquid treated in the platform was analysed to establish its concentration of hydrogen peroxide. In terms of electrical characterization, an optimized method to measure the plasma power dissipation was implemented. As the high capacitive

load of small-sized plasma sources can lead to large errors on the plasma power dissipation measurement, a simple matching network, consisting of a home-made adjustable inductor, was used. With the subtractive method it was possible to measure the plasma power dissipation with an error of less than 15% (see equation 2.2).

To analyze the transport of plasma-generated reactive species in the liquid circulating in the microfluidic device, the concentration of hydrogen peroxide was measured for different experimental conditions with a colorimetric method. The hydrogen peroxide concentration assays showed that the production of hydrogen peroxide increases both with the plasma power dissipation and humidity content of the plasma-forming gas. Furthermore, when the plasma-liquid interaction zone is placed in the plasma effluent, the transport of hydrogen peroxide in the liquid is systematically higher. This was explained by the plasma reaction kinetics. In the plasma effluent, the OH radicals quickly recombine to form H_2O_2 and the main destruction pathway of H_2O_2 , which is through electron impact, no longer takes place away from the active plasma zone. Because of these reaction paths, we observed a higher concentration of H_2O_2 when the interaction zone is placed in the plasma effluent.

4.3 Development of a simulation model of the plasma-microfluidic platform

To improve our understanding of the production and transport pathways of plasma-generated reactive species in the plasma-microfluidic platform, a simulation model was developed. Since a complete 2D or 3D model would be too intensive in terms of computational time, a novel quasi-2D model was used. The model was developed with the combination of 2D fluid dynamics simulations and 0D reaction kinetics as described in chapter 3. This combination was made possible through a new approach that divides the computational domain into thinner parts, called bins, for which the chemistry is solved through 0D-plug flow models. This approach was justified by the high Péclet number of the plasma gas flow. The proposed method used standard simulation tools: ZDPlaskin to solve the plasma reaction kinetics and COMSOL for the fluid dynamics and transport processes.

The model was able to predict the concentration of H_2O_2 in the treated liquid with a difference of less than 50% compared with experimental results. This is satisfactory considering the different approximations that were made to model the complex mechanisms happening inside the plasma-microfluidic platform. These approximations were essential to model the system, but they are also probably responsible for the discrepancies between the modelling and experimental results. Since these discrepancies were reasonable, we think the method could be applied to model other plasma processes that imply a highly unidirectional flow of high Péclet number.

CHAPTER 5 CONCLUSION

Microfluidic technologies have so far provided many solutions in analytical chemistry and biology and the combination of a reference plasma source, such as the COST-Jet, with microfluidic devices opens the way to novel diagnostic tools for plasma-liquid processes. With the work presented in this thesis, we showed that it is possible to combine microfluidic devices with atmospheric pressure plasma sources and that this combination can be a powerful diagnostic tool for plasma processes that involve liquids. So far, we performed concentration assays of only one species, hydrogen peroxide, in the liquid treated by the plasma-microfluidic platform. Even if the detection of H_2O_2 was sufficient to explain key reaction pathways, the detection of other species would further improve our understanding of the production and transport pathways of reactive species in the plasma-microfluidic platform. The concentration of NO_2^- and NO_3^- , other long-lived liquid species that can be detected with standard methods, could be measured to follow the transport of reactive nitrogen species in the liquid. For such studies, molecular nitrogen would have to be added to the plasma-forming gas. Moreover, the detection of short-lived species, such as OH or O_2^- with spin traps and electron paramagnetic spectroscopy, could improve our understanding of the transport of radicals and ions to the liquid. The detection of reactive species in the liquid could also be combined with optical diagnostic of reactive species present in the plasma itself. While the plasma-microfluidic platform was designed to offer an optical access to the plasma discharge, no experiment on the detection of species in the plasma channel has been conducted for this work. Monitoring the presence of reactive species both in the liquid and in the plasma itself would offer much insight on the transport pathways of these species at the liquid interface. This data would be of high interest for any application that implies both plasma and liquid (plasma for wastewater treatment, plasma for agriculture or plasma medicine for example).

To improve our understanding of the physical and chemical processes in the plasma-microfluidic platform, further modelling work could also be conducted. As explained in chapter 3, the simulations used stationary boundaries to represent the liquid volume flowing in the microfluidic device. Further insight on the liquid droplets' formation could be gained through simulation and the results could help understand how the dynamic formation of water droplets influences the transport of reactive species in the liquid.

The different diagnostic and modelling possibilities presented in the previous paragraphs could be applied to the plasma-microfluidic platform that was used in the context of this thesis. Additionally, small modifications of the current plasma-microfluidic platform could

enable the use of existing microfluidic devices in the context of NTP research. This could be particularly interesting in the field of plasma medicine. As mentioned, microfluidic devices have been used for research on chemotherapy, radiotherapy and immunotherapy treatment and some devices are being used more and more for personalized medicine in a clinical context. These existing microfluidic devices for biomedical applications could be used, with the help of the developed plasma-microfluidic platform, for plasma oncology research. One of the key challenges in using biological models embedded in microfluidic devices for plasma medicine is the complexity of applying a direct plasma treatment to the biological model. With a direct treatment, short-lived species can be brought in contact with the biological system while in an indirect treatment (a plasma treatment of a liquid that is then brought in contact with a biological system), only longer-lived species can have a biological effect. The use of plasma is of high interest in the context of biological applications because it offers the possibility to create short-lived reactive species *in situ*. However, a direct access to the biological model inside the microfluidic device is not always possible with existing biological microfluidic systems. Hence, these microfluidic devices would probably have to be adapted to be used with reference plasma sources in the plasma-microfluidic platform. Nevertheless, we believe that well-established biological model embedded in microfluidic devices could become key research tools in the plasma oncology field.

As of now, the work achieved for the plasma-microfluidic platform was performed mainly by engineers, physicists and chemists. To truly have an impact in plasma medicine, future work conducted in the plasma-microfluidic field must include biologists and eventually clinicians. Only through highly multidisciplinary teamwork will microfluidic devices help answer key open research questions of plasma medicine.

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APPENDIX A SUPPLEMENTARY INFORMATION ON THE MICROFLUIDIC DEVICES CONSTRUCTION AND OPERATION.

The fluidic circuits used for the experiments presented in chapter 2 consists of three main parts :

- A plastic tube of high hydraulic resistance that creates a pressure drop between the liquid inlet and the microfluidic device.
- A plastic tube that enables the connection between the microfluidic device and a syringe (for liquid pumping).
- A 3D printed microfluidic device that enables the connection between the two plastic tubes and allows, through an opening, a contact with the plasma-generated reactive species.

Figure A.1 is a 3D rendering of a typical microfluidic device used in the context of this thesis. On top of the microfluidic device an opening allows the formation of a gas-liquid flow and the interaction between the liquid and the plasma-generated species. The microfluidic devices were 3D printed with a 27 micron resolution printer (the Asiga Pico2 27 3D) using UV sensible resin (GR1-clear resin - Pro3Dure - A1000300) according to the protocol in place in the Microfluidic for Oncology Laboratory of Prof. Thomas Gervais for the fabrication of 3D printed molds. Once printed, to help remove the excess of resin in the channels of the microfluidic device, isopropanol was pumped in the channel using a syringe.

On two sides of the microfluidic device of figure A.1, two holes were designed for a connection with a plastic tube. The smallest connection is for the plastic tube of high hydraulic resistance leading to the liquid reservoir. For the experiments presented in this thesis, this tube had an inner diameter of 1/16 of an inch and a length of 30 cm. This was found sufficient to produce the desired gas-liquid flow with a flow rate of 1 ml/min. The other connection's purpose was to link the microfluidic device to another plastic tube (of lower hydraulic resistance) connected to the syringe for pumping of the liquid. The two tubes were glued to the microfluidic device using UV sensible glue.

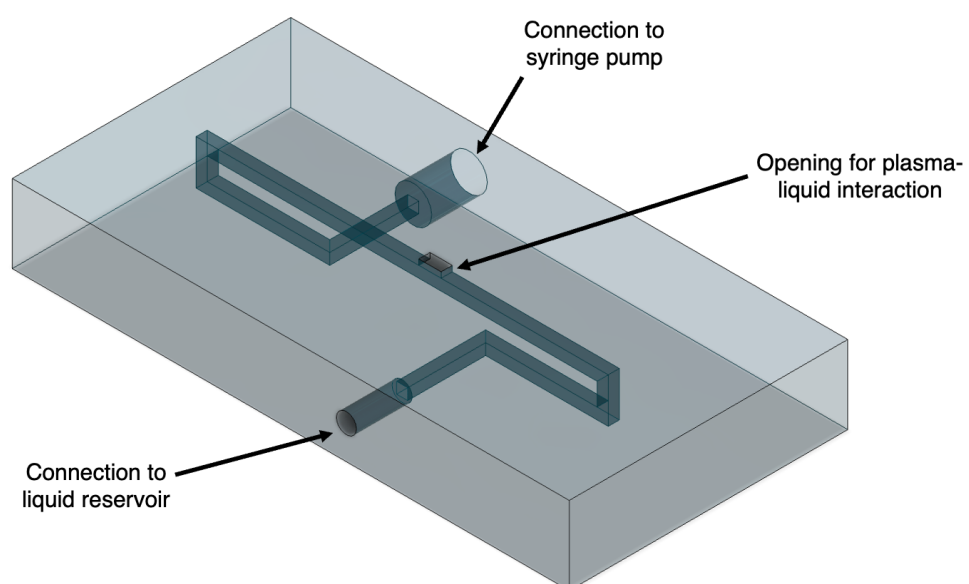


Figure A.1 Example of a microfluidic device for creating a plasma-liquid interaction.

APPENDIX B COMPLEMENTARY INFORMATION ON PLASMA DISCHARGE POWER MEASUREMENTS OF SMALL-SIZED PLASMA SOURCE

The measurement of the plasma dissipated power of small-size plasma sources has to be approached carefully. The article in chapter 2 presents briefly the method used to measure the power dissipated the COST-jet-like plasma source of the plasma-microfluidic platform. The aim of the current appendix is to give more details on this method and general insight on the power measurement of small-sized, highly capacitive, plasma sources.

Circuit representation of plasma sources

Equivalent circuit model is a very powerful tool to represent the relationship between the voltage applied across a plasma device and the resulting current flowing through it [55, 57, 111]. Much of the plasma electrical behavior can be learned through relatively simple circuit models. The most concise, yet accurate and meaningful representation of a capacitively coupled plasma discharge is the combination, in series, of a capacitor with a resistor (see figure B.1 (a)). The capacitor component arises from the plasma sheath region while the resistive component mainly comes from the electron heating by collision within the plasma sheaths [12].

Power measurement and error

The average power dissipated during one electrical period is defined as :

$$P_{avg} = \frac{1}{T} \int_0^T V(t) \cdot I(t) dt, \quad (\text{B.1})$$

where T is the period, $V(t)$ the time varying voltage and $I(t)$ the time varying current.

For a sinusoidal voltage waveform and a linear current response, the average power is :

$$P_{avg} = V_{RMS} \cdot I_{RMS} \cdot \cos(\phi), \quad (\text{B.2})$$

where V_{RMS} is the root mean square voltage, I_{RMS} is the root mean square current, and ϕ is the phase angle between the current and voltage. This phase angle, ϕ , arises from the load impedance to which the voltage is applied: $Z_{load} = |Z|e^{i\phi}$. An error analysis of equation B.2

leads to :

$$\Delta P_{avg}^2 = \left(\frac{\partial P_{avg}}{\partial V_{RMS}} \cdot \Delta V_{RMS} \right)^2 + \left(\frac{\partial P_{avg}}{\partial I_{RMS}} \cdot \Delta I_{RMS} \right)^2 + \left(\frac{\partial P_{avg}}{\partial \phi} \cdot \Delta \phi \right)^2 \quad (B.3)$$

$$\Rightarrow \frac{\Delta P_{avg}^2}{P_{avg}^2} = \left(\frac{\Delta V_{RMS}}{V_{RMS}} \right)^2 + \left(\frac{\Delta I_{RMS}}{I_{RMS}} \right)^2 + (\tan(\phi) \Delta \phi)^2 \quad (B.4)$$

The last term of equation B.4 contains $\tan(\phi)$, whose value increases rapidly when the phase angle is close to $\pm 90^\circ$. This can easily become problematic when measuring the delivered power to a highly capacitive load like a miniature NTP sources. However, diminishing the value of the phase angle would reduce the error ($|\tan(\phi)| \rightarrow 0$ for $|\phi| \rightarrow 0$). To decrease the capacitive load, one can use an inductor in series with the miniature NTP source (see figure B.1 (b)) as proposed in [56]. The presence of the inductance decreases the absolute value of the imaginary part of the impedance ($Im(Z_{\text{With Inductance}}) = \omega L - |Im(Z_{\text{plasma source}})|$) and hence the phase angle decreases ($\tan(\phi) = \frac{Im(Z)}{Re(Z)}$) giving rise to a smaller error related to the measurement of the phase angle. For example, assuming a 1% error on the voltage and current measurement and a phase angle reading error of 3° , equation B.4 leads to a relative error of 60% for a phase shift of 85° and of 6% for a phase shift of 50° .

Resistive impedance of an inductance

A non-ideal inductor has a resistivity. This resistive behavior comes from two sources: the non-zero resistance of the wires from which the inductance is made and the heating of the inductor's material through magnetic loss (i.e. friction from the movement of the magnetic dipole in the inductor). Hence, a real inductor is represented as a perfect inductor in series

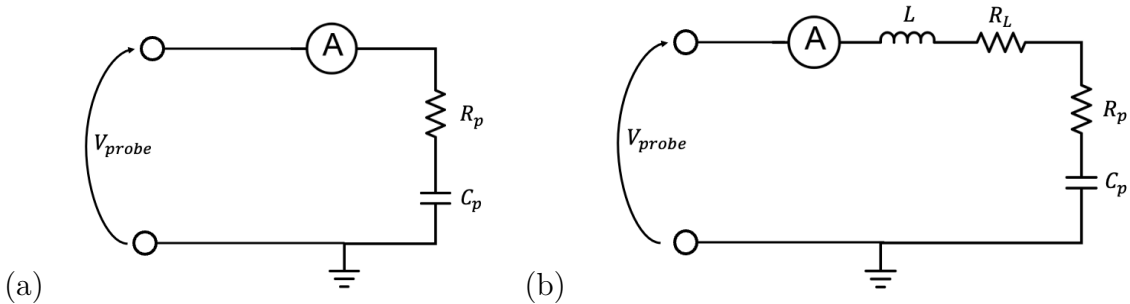


Figure B.1 (a) Circuit representation of a simple capacitive discharge device setup. C_p and R_p represent the plasma discharge. (b) Circuit representation of a PPD measurement setup with an inductance.

with a resistor in our electrical circuit model (see figure B.1 (b)).

As current is flowing through the resistive part of the impedance, power is dissipated. As a result, to isolate the power dissipated in the plasma discharge, the value of the resistive part of the inductor, R_L , needs to be known. The quickest way to determine this value is probably to measure the pre-breakdown power dissipation in the circuit. The relation between the power and R_L will then be $P_{off} = R_L \cdot I_{off}^2$, where I_{off} is the measured RMS current without a plasma discharge and P_{off} the corresponding power. From this, the power dissipation in the discharge can be deduced by the subtractive method [54] :

$$P_{plasma} = V_{on} \cdot I_{on} \cdot \cos(\phi) - R_L \cdot I_{on}^2. \quad (B.5)$$

R_L is found by the regression of $P_{off} = R_L \cdot I_{off}^2$. V_{on} and I_{on} are the RMS voltage and current with the plasma ignited.

Circuit model of the plasma source

The plasma electrical setup presented in chapter 2 (see figure 2.2) can be modeled by the circuit represented in figure B.2. When the plasma is ignited (*on*) the discharge gap is represented by a resistor (R_p) and a capacitor (C_p) in series and when no plasma is ignited (*off*), the inter-electrode gap forms a capacitor (C_{gap}). In both cases, a stray capacitance (C_s) is present due to the proximity between the different electrical components.

When the plasma is *off*, the load impedance is given by (see figure B.2 (a)):

$$Z_{off} = R_L + i \frac{\omega^2 L (C_{gap} + C_s) - 1}{\omega (C_{gap} + C_s)} \quad (B.6)$$

From equation B.6, we deduce the phase with plasma *off*:

$$\phi_{off} = \tan^{-1} \left(\frac{\text{Im}(Z_{off})}{\text{Re}(Z_{off})} \right) = \tan^{-1} \left(\frac{\omega L (C_{gap} + C_s) - 1}{R_L (C_{gap} + C_s)} \right) \quad (B.7)$$

When the plasma is *on*, the expression for the load impedance and phase angle becomes (see figure B.2 (b)):

$$Z_{on} = R_L + \frac{\omega^2 R_p C_p^2}{X} + i \left(\omega L - \frac{\omega^3 R_p C_p C_s + \omega (C_p + C_s)}{X} \right) \quad (B.8)$$

$$\phi_{on} = \tan^{-1} \left(\frac{Im(Z_{ON})}{Re(Z_{ON})} \right) = \tan^{-1} \left(\frac{X\omega L - \omega^3 R_p C_p C_s + \omega(C_p + C_s)}{R_L X + \omega^2 R_p C_p^2} \right), \quad (B.9)$$

where

$$X = \omega^4 R_p^2 C_p^2 C_s^2 + \omega^2 (C_p + C_s)^2 \quad (B.10)$$

As seen in equation B.7 and B.9, the phase angle depends on the value of the added inductance, L . Figure B.3 shows the variation of the phase angle as a function of the inductance value. The setup used for the measurements of this figure is the same as in chapter 2 (see figure 2.2) except that the plasma source is electrically powered by a 13.56 MHz power generator (Dressler - Cesar 1310) instead of the combination of a function generator with a RF amplifier. The inductance value is changed by adjusting the number of wire turn around the ferrite core and it is measured using a vector network analyzer (NanoVNA V2). As seen in figure B.3, for small ($<25 \mu\text{H}$) and big ($>50 \mu\text{H}$) inductance value, the load impedance phase angle is close to $\pm 90^\circ$ which gives rise to a high error of the PPD measurement. However, figure B.3 shows that for L around 35 to 40, the phase angle approaches zero.

Source of error

The error terms of the PPD measurement is given by equation B.4. The error related to the voltage and the current, ΔV_{RMS} and ΔI_{RMS} , is limited by the accuracy of the probe and of the oscilloscope. Voltage and current probes are typically rated with an accuracy of 1-5% while oscilloscope accuracy is limited by the vertical resolution (typically 8-bit) and the noise (usually expressed as a fraction of the division's scale) [112]. The error term related to the phase angle, $\Delta\phi$, is mainly limited by the sample rate of the oscilloscope. The reading of the zero crossing point of the sinusoidal waveform leads to an error on the phase angle of

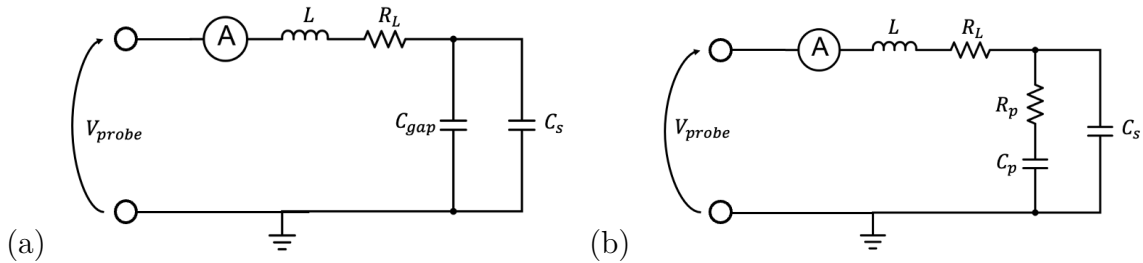


Figure B.2 Circuit representation of the plasma electrical setup. (a) Plasma *off*. (b) Plasma *on*.

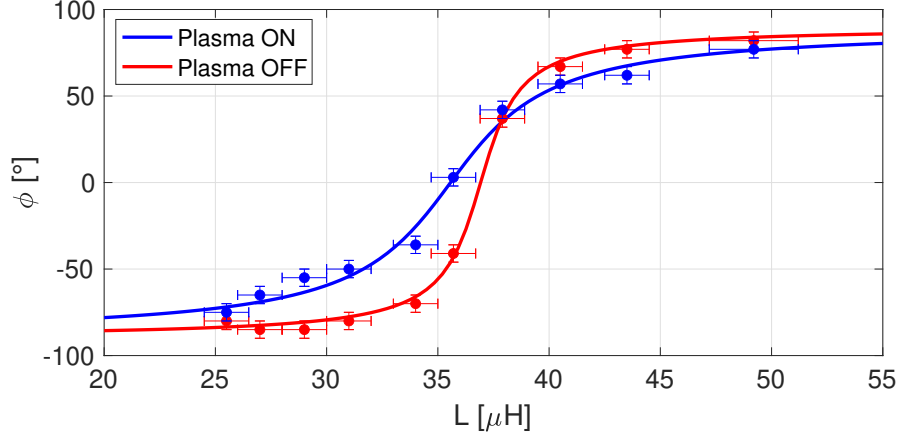


Figure B.3 Phase angle dependence on the inductance value: experimental and fitted values.

$\Delta\phi = (360^\circ)f/S$ where f is the frequency and S is the sample rate of the oscilloscope. For a frequency of 13.56 MHz and sample rate of 10^9 samples per second, $\Delta\phi = 4.9^\circ$. Other factors influencing the accuracy of the phase angle measurement, such as the influence of harmonics on the measured signal or the influence of the relative position of the current and voltage probe between measurements, are much smaller and are therefore neglected. A Fourier transform analysis of the signal showed that the second and higher harmonics compose less than 0.1% of the signal (note that the use of another power supply might introduce a more significant impact of the harmonics). Changing the relative position of the voltage and current probe between different measurements also influences the phase angle. However, assuming a relative permittivity of the cable of 2.3 [58], the wavelength is ~ 10 m at 13.56 MHz. For variation of the order of 1 cm on the relative position of the voltage and current probe, this effect is therefore negligible.

Optimal impedance matching

The impedance matching is achieved by changing the value of the inductance L (i.e. changing the number of wire turn around the ferrite cores). Since the circuit properties change with the plasma ignition, the coupling (i.e. canceling the imaginary part of the circuit impedance) will be influenced by the ignition of the plasma and it is therefore not possible to achieve perfect coupling with and without the plasma discharge. Even if perfect coupling cannot be achieved, small impedance load phase angle (and hence small plasma power dissipation measurement error) can be rapidly obtained. An estimation of the needed inductance can be made with an estimation of the capacitance of the plasma source discharge gap, but fine-tuning of the inductor's value should be obtained by minimizing the phase angle between the

voltage and the current.

APPENDIX C COMPARISON OF THE TWO MICROFLUIDIC FLOW REGIMES ON THE TRANSPORT OF REACTIVE SPECIES.

In chapter 2, two flow regimes were presented: the single-phase liquid flow and the multiphase gas-liquid flow. The multiphase flow was chosen for higher operation stability, but also for the increased transport of reactive species it offers. To illustrate the latter, the following presents two simple simulations, solved in COMSOL Multiphysics, for the transport of an arbitrary reactive species with the single-phase and with the multiphase flow.

In the single-phase flow, liquid is circulating in the microfluidic channel in a laminar flow regime and is in contact with the plasma or effluent channel. This interface acts as a source of reactive species. To investigate the transport of reactive species in the liquid, a fixed concentration will be assumed at the plasma/effluent-liquid interface and the average concentration at the outlet of the channel will be calculated. Figure C.1 (a) shows the geometry of the simulation. It is a 2D cross section of the experiment presented in chapter 2. Figure C.1 (b) shows the laminar velocity field inside the microfluidic channel as solved through the steady-state Navier-Stokes equations for an inlet of 1 ml/min. All walls are considered as "No slip" boundaries except for the plasma/effluent-liquid interface which is a "Slip" boundary. The velocity field is used to solve the convection-diffusion equation for an arbitrary specie. The solution is illustrated in figure C.1 (c). For the convection-diffusion equation, the plasma/effluent-liquid interface is fixed at a concentration of 1 arbitrary unit (a.u.) and the diffusion coefficient is taken as $D = 2 \times 10^{-9} \text{ m}^2/\text{s}$, a typical diffusion coefficient value for liquid reactive species. The solution of the convection-diffusion equation for the single-phase flow shows that the average concentration at the outlet once a steady-state is reached is 0.0035 a.u.

A similar simulation is performed for the multiphase flow. In this case we investigate the transport of reactive species in a water droplet, analogously to the simulations achieved in chapter 3. Figure C.2 (a) shows the geometry of the simulation. It is the same geometry as the simulation of chapter 3, but considering the liquid droplet only. Figure C.2 (b) shows the velocity field inside the liquid droplet. Again, it is the same liquid droplet's velocity field as presented in chapter 3 (for an imposed flow-rate of 1 ml/min). This velocity field is used to solve the convection-diffusion equation for an arbitrary specie whose solution is illustrated in figure C.2 (c). As in the single-phase simulation, the plasma/effluent-liquid interface is fixed at a concentration of 1 arbitrary unit (a.u.) and the diffusion coefficient is taken as $D = 2 \times 10^{-9} \text{ m}^2/\text{s}$ to solve the convection-diffusion equation. The solution of the convection-

diffusion equation for the multiphase flow shows that the average concentration in the liquid droplet after 0.12 s, the time it takes for the liquid droplet to travel the microfluidic opening (see chapter 3 for details), is 0.016 a.u which is 4.6 times higher than the single-phase flow.

These two simple simulations show that the multiphase flow increases the transport of reactive species in the liquid: according to these simulations the average concentration of reactive species in the liquid is almost 5 times higher in the multiphase flow compared to the single-phase flow. The increased transport of species combined with the improved operation stability justifies the use of the single-phase flow.

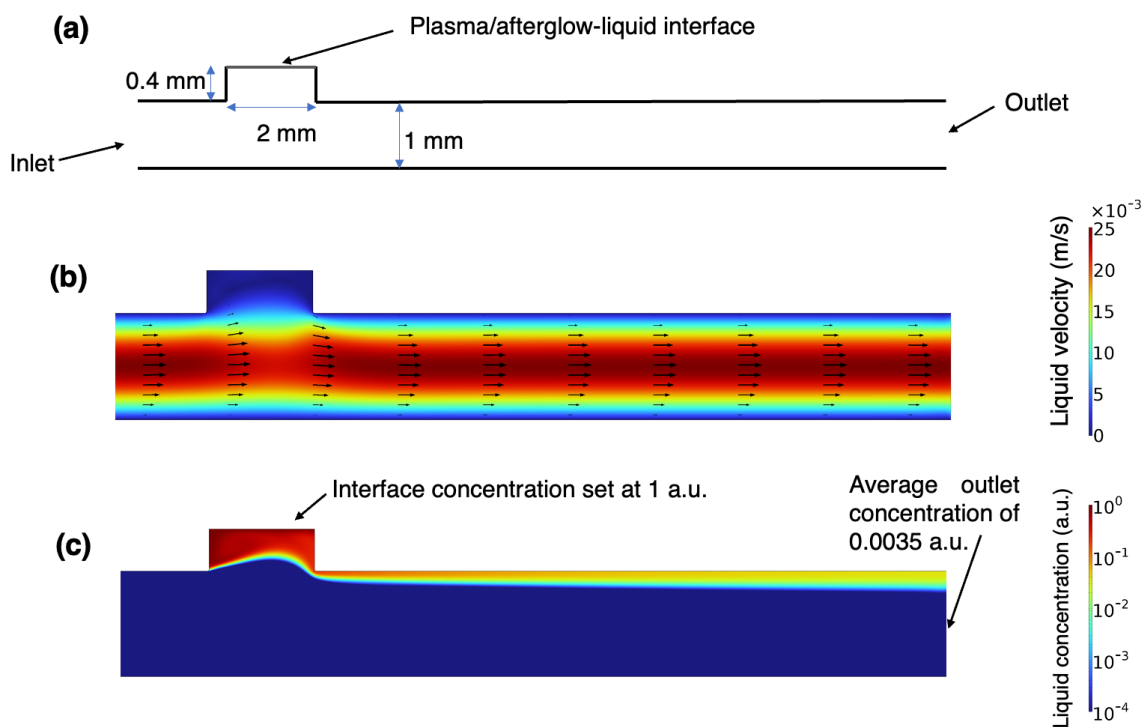


Figure C.1 Simulation of transport of an arbitrary species with the single-phase flow. (a) Simulation geometry. (b) Velocity field. (c) Arbitrary species concentration.

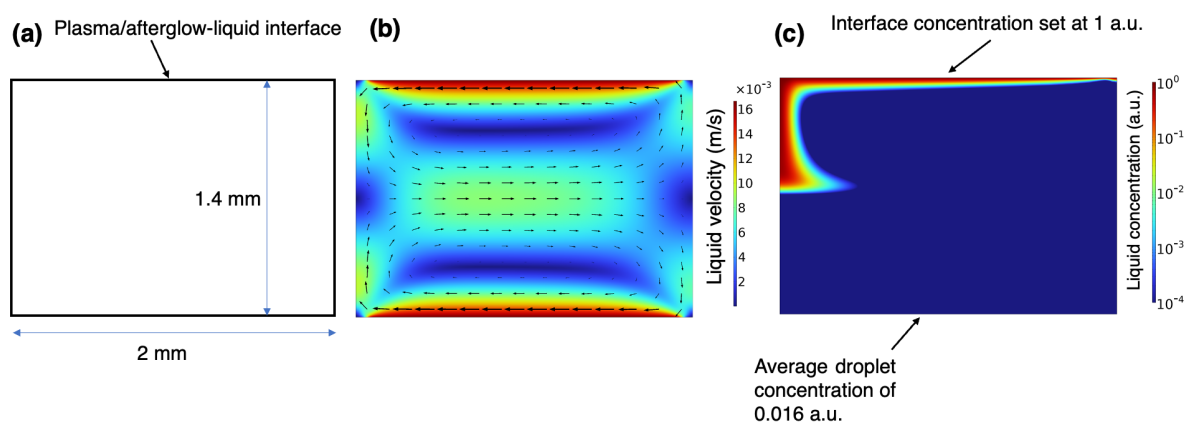


Figure C.2 Simulation of transport of an arbitrary species with the multiphase flow. (a) Simulation geometry. (b) Velocity field. (c) Arbitrary species concentration.