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Unaccounted bias in plasma *in vitro* experiments and the translation to *in vivo*: key issues and challenges

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The potential beneficial impact of plasma is being investigated for many biotechnological and medical applications. However, translating promising *in vitro* results to *in vivo* (bio)medical outcomes remains a challenging task. One of the major challenges in the translation of plasma technologies to *in vivo,* and ultimately clinical use, is the lack in the fine control necessary for an efficient and safe use of plasma sources in medical applications; this we attribute to the mutual interaction between plasma and target [1]. Many key fundamental questions on the mechanisms taking place at the interface between plasma and (bio) targets still need to be addressed. While there is an abundance of literature on the biological effects of plasma treatment, there are only a few reports on the physico-chemical characterization of the treatment process. Even considering a very simple scenario using a plasma jet to treat a 2D culture of cells in a plastic multi-well plate, it is not known in detail how the physical environment of the micro-well may influence the biological effects of the plasma. Recent research has reported how the geometry of the multi-well plate, as well as the electrical characteristics of the support on which it stands, can have a significant impact on the experiment and its reproducibility [1, 2]. Furthermore, the presence or absence of a liquid and small variations in its depth/volume can completely change the nature and the distribution of the bioactive plasma-generated RONS reaching the bottom of the well [3].
Surprisingly, even in small liquid volumes (e.g. 0.2 – 2 ml) typical of biomedical *in vitro* experiments, the impinging plasma jet on the biological liquid can induce the formation of fast and complex electro fluid dynamic (EFD) flows. These flows are affected by plasma parameters such as polarity and can lead to vortex recirculation. Whereas biological effects will always be the focus of plasma medicine, it is important for the advancement of this field to achieve a deeper understanding and a greater awareness of the physico-chemical processes taking place during our plasma biomedical experiments.

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