Recent Progress in Plasma Medicine Research

プラズマの医療応用研究最先端

Satoshi Hamaguchi
浜口智志

Graduate School of Engineering, Osaka University
2-1 Yamadaoka, Suita, Osaka 565-0871, Japan
大阪大学大学院工学研究科 〒565-0871 大阪府吹田市山田丘2-1

Low-temperature atmospheric-pressure plasma (APP) may serve as a source of chemically reactive species and be used for medical treatment such as blood coagulation, wound healing, cancer treatment, and sterilization. Since most living tissues and cells are immersed in liquids (such as blood or culture media), chemically reactive species generated by APPs in the gas phase are transported to the liquid phase and typically converted to different types of reactive species therein before affecting living bodies. In this presentation, recent progresses in medical applications of APPs will be briefly reviewed and then generation, transport, and possible biological effects of chemically reactive species in liquids generated by APP application will be discussed.

1. Introduction

Low temperature plasmas have been applied to a wide range of industrial processes such as fabrication of micro and nano-scale structures on the surfaces of semiconductor chips and thin film deposition for surface coating of various materials. Recently, as one of such applications, use of low-temperature plasmas for medical treatment and material processing for medical applications has attracted much attention in the plasma research community.

In general, research in plasma medicine may be categorized into three subfields. One of them is surface modification/treatment of biomedical materials [1-3]. For example, surfaces of petri dishes (made of polystyrene) are typically pretreated by oxygen plasmas. Surface coating of metal artificial joints by hydroxyapatite is often done with plasma spraying with the use of thermal plasmas. Surface polymerization by plasma CVD (chemical vapor deposition) is also widely studied for the formation of biocompatible films.

Another subfield that is also widely studied is plasma sterilization [4-6]. Including commercial products such as plasma-based air purifiers, this subfield has seen much technological development in recent years in areas beyond medical equipment although the fundamental mechanisms of bactericidal effects by plasmas have yet to be understood better. Furthermore, there are other sources for infectious diseases that are still difficult to inactivate by plasmas, such as spore forming bacteria, viruses, and prions, and inactivation of them is still a topic of active research in this subfield. Usually difficulty of treating such infection sources by plasmas lies in the fact that, in reality, inactivation of them needs to be done without damaging the environments (such as human bodies or medical equipment) where they exist, and often in a cost effective manner.

The third is study on therapeutic or clinical use of plasmas. In this subfield, use of low-temperature, non-cauterizing plasmas for different types of treatment such as blood coagulation, angiogenesis, wound healing, and cancer treatment, has been much of the focus for scientific and technological development.

The origin of such biological effects is reactive species generated by plasmas. Under typical discharge conditions in air, plasma efficiently generates reactive oxygen species (ROS) /reactive nitrogen species (RNS) such as atomic oxygen O, hydroxyl radical OH, hydroperoxyl (or perhydroxyl) radical HOO, singlet oxygen $^1O_2$, and nitric oxide (or nitrogen monoxide) NO. Such chemically reactive species are also generated from endogenous sources in living bodies and play crucial roles in controlling cell signaling pathways and maintaining homeostasis. In this sense, it is not surprising that exogenous ROS/RNS generated by gas plasmas can have some significant effects on living cells and tissues under certain conditions.

2. Reactive species in liquids

In plasma-based therapy, a living tissue is exposed to a low-temperature APP, where there is almost always a liquid layer, such as blood, lymph, and interstitial fluid, that separates the gas plasma and the tissue. In what follows, we briefly discuss simple numerical simulation of generation and transport of chemically reactive species in pure water.

The conceptual diagram of the system we consider in this study is shown in Fig. 1. It is assumed that a plasma is generated in air. Charged species as well as other chemically reactive charge-neutral species that are generated by plasma discharge are assumed to be uniformly distributed in the gas phase. The gas phase species are assumed to be in steady state and, at time t = 0, they are assumed to be exposed to the water surface suddenly. Charge neutral species are assumed to enter water at their thermal velocities whereas charged species are assumed to enter water following the (ambipolar) field so that the charge neutrality of water should be maintained. In this study, we use data of gas phase species from published literatures (such as [8]).

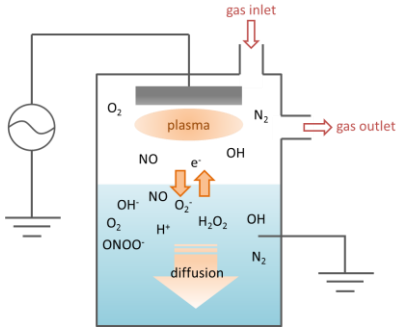

Fig.1. A conceptual diagram of the system

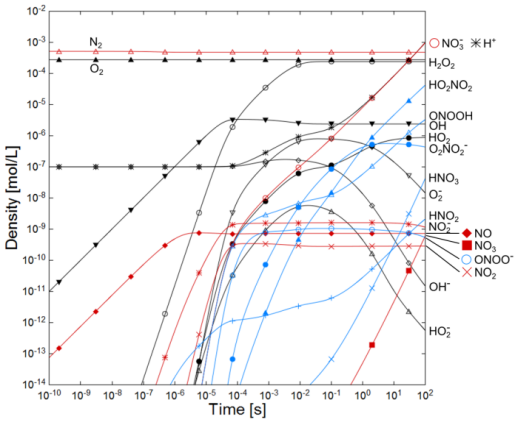

Fig.2. Simulated densities as functions of time when only OH radicals and NO are assumed to dissolved into water. .

In the simulation presented here, chemical species in water are transported by diffusion and drift due to the electric field generated by other charged species as well as the externally applied field such as the sheath field of the plasma. Motion of species is considered only in the depth direction in liquid, for the sake of simplicity. In the global model, where no transport is considered, the medium is assumed to be well.

In a global model, if only hydroxyl radicals (OH) and nitric oxide (NO) molecules generated by a plasma are assumed to be dissolved into water, the numerical simulation has shown that the concentrations of all chemical species, including ROS/RNS generated in water vary as shown in Fig. 2. Especially notable is that the water becomes acidic due to the generation of nitric acid, which is consistent with earlier experimental observations [8].

3. Conclusions

When a liquid is exposed to an APP that generates various kinds of charged and charge-neutral chemically reactive species in the gas phase, many of those species dissolve into the liquid and are transformed to different types of ROS/RNS therein. It is these ROS/RNS in the liquid phase that directly affect living cells if an low-temperature APP is applied to living tissues since there is almost always a liquid layer, such as blood, lymph, and interstitial fluid, lying between the gas phase and tissue. Sample numerical simulation of various reactive species, including hydrogenated electrons and ROS/RNS species, in pure water has been demonstrated.

Acknowledgments

The author acknowledges Dr. K. Ikuse and Mr. T. Kanazawa for performing the numerical simulations discussed in this article.

References

[1] B. D. Ratner, *et al. Biomedical Engineering Desk Reference*, Academic Press, 2009.

[2] A. Milella, R. Di Mundo, F. Palumbo, P. Favia, F. Fracassi, R. d'Agostino, *Plasma Process. Polym.* **6** (2009) 460.

[3] P. K. Chu, J. Y. Chen, L. P. Wang, and N. Huang, *Mat. Sci. Eng. R* **36** (2002) 143.

[4] J. Ehlbeck, U. Schnabel, M. Polak, J. Winter, Th. von Woedtke, R. Brandenburg, T. von dem Hagen, and K.-D. Weltmann, *J. Phys. D: Appl. Phys.* **44** (2011) 013002.

[5] M. Laroussi, *Plasma Process. Polym.* **2** (2005) 391.

[6] H. Yasuda, T. Miura, H. Kurita, K. Takashima, and A. Mizuno, *Plasma Process. Polym.* **7** (2010) 301.

[7] R. Sensenig, S. Kalghatgi, E. Cerchar, G. Fridman, A. Shershevsky, B. Torabi, K. P. Arjunan, E. Podolsky, A. Fridman, G. Friedman, J. A. Clifford and A. D. Brooks: Annals of Biomedical Engineering. **39** (2011) 674.

[8] S. Ikawa, K. Kitano, and S. Hamaguchi, Plasma Process. Polym. **7** (2010) 33.