2013 EU-SPRI FORUM CONFERENCE
MANAGEMENT OF INNOVATION POLICIES

Proceedings of the 2013 EU-SPRI Forum Conference
Madrid 10-12 April 2013
ISBN 978-84-695-7408-9 ORAL PRESENTATION

Title

Evolutionary growth of knowledge and new technological directions of non-thermal plasma technology in medicine

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Abstract

The present paper analyzes the evolution of scientific production and patenting, main proxies of scientific and technological breakthroughs, concerning the specific field of non-thermal plasma for biomedical applications in order to detect directions and promising technological trajectories. The scientific directions of non-thermal plasma in medicine play a critical role because they might generate important innovations that could change the clinical practice. Occurrences of scientific products and patents are retrieved with Boolean queries on SciVerse database after a meticulous procedure to delineate the most promising applications in biomedical sciences. Data are analyzed with two methodological approaches: an exponential model of growth and regression analysis. Results show high rates of scientific growth for applications of non-thermal plasma in disinfection, anticancer treatments, dermatology, whereas for surgery, although values of occurrences are similar to the other research fields, it shows a different trend that after the 2005 is decreasing due to the peculiar application to materials for implantation. Some arguments are discussed at the end of the paper.

Keywords

Non Thermal Plasma, Technological Trajectories, Plasma, Cancer, Medicine.

Note
JEL classification: O30; I31

Acknowledgements
Mario Coccia thanks the colleagues of the Georgia Institute of Technology for scientific support. In addition, he gratefully acknowledges financial support from the CNR - National Research Council of Italy for visiting at Yale University and Georgia Institute of Technology where this research has been developed. Ugo Finardi acknowledges the help and spur of Proff. S. Coluccia and L. Battezzati (University of Torino, Italy). We also thank Ceris-CNR staff and Prof. S. Rolfo of CERIS-CNR for supporting this research field. The usual disclaimer holds, however.

The authors in parentheses (MC: Mario Coccia and UF: Ugo Finardi) have made substantial contributions to the following tasks of research: Conception (MC); Design (MC and UF); theoretical framework (MC and UF); acquisition of data (UF); modeling and analysis of data (MC); interpretation of data (MC and UF); drafting of the manuscript (MC and UF); critical revision of the manuscript for important intellectual content (MC); statistical analysis (MC), supervision (MC).

1. Introduction

Plasma is a peculiar state of the matter, similar to gas, in which a certain fraction of the particles are ionized. According to Fridman (2008, p.1) a: “ionized gas is usually called plasma when it is electrically neutral [...] and contains a significant number of electrically charged particles, sufficient to affect its electrical properties and behaviour”. Technological applications of plasma physics and chemistry are many: TV, mobile phones, synthetic fibres, ozone-plasma technology for potable water, gas lasers, air-cleaning systems, hydrogen production, fuel-cell technology, etc.

This vast number of applications depends also on current technologies that have allowed the production of plasmas at low temperature and at low pressure (Tendero *et al.* 2006). Low-pressure and low-temperature (cold) plasmas are able to interact with the matter without damaging its surface as high-temperature plasmas might do. Thus their characters of high reactivity and pervasivity (given their gaseous nature) can be used profitably for a vast number of applications, such as surface modification of materials like polymers and oxides, or more complex applications like those of green chemistry (Denes and Manolache 2004; Mollah *et al.* 2000). Plasma technologies have a vast number of possible applications in biology and medicine, such as in surgery, sterilization of devices, destruction of pathogens, engineering of biomaterials, chemoprevention, etc (Fridman *et al.*, 2008; Weltmann *et al.*, 2010). “Plasma medicine as an independent medical field is emerging worldwide in a way comparable to the development of laser technology years ago” (Ferreira et al., 2012). Plasma medicine can be applied for surface modification (*e.g.* in biomaterials), bio-decontamination and for therapeutic applications (in this case only atmospheric-pressure plasmas can be used). In fact, living matter is not damaged by its interaction, and thus its characteristics can be exploited for therapeutic uses without main side effects for patients and with better results (i.e. effective treatments) than older technologies.

The purpose of this paper is to analyze the evolutionary growth of non-thermal plasma in order to detect fruitful applications for medical treatments that in the present look more promising. In particular, the aim of this analysis is to pinpoint emerging technological trajectory that present the highest growth and thus proceed more fruitfully than others.

The present work is organized as follow. The next section contains a theoretical framework introducing and discussing those plasma applications that are analyzed in the experimental work. In the third section research methodology is presented, while the fourth contains the description of results. In the fifth and last section results are discussed and conclusions are drawn.

2. Theoretical background

It must first be noted that the word "Plasma" is not unambiguous, as it indicates not only the above described state of the matter but also the liquid component of blood[1]. The present study focuses on plasma as a neutral ionised gas, made by particles – free radicals and excited or non-excited molecules, positive and negative ions, electrons, atoms, photons – in permanent interaction (Moreau et al., 2008, p. 611). Plasmas exist in nature in several contexts (like in polar aurorae) and can be obtained artificially via different methods, such as thermal or non-thermal.

Thermal plasmas are obtained at high pressure and with the use of electrical currents of a substantial power (up to 50 MW): "Thermal plasma processes have a long history of industrialization, of which a notable application is coating metallic substrates with hydroxyapatite (HA) for orthopaedic implantation. Despite its industrial efficiency, thermal plasma deposition results in undesirable changes to thermally sensitive substrates such as HA” (Tan et al., 2012).

Non-thermal plasmas are obtained at lower pressures and use less power. Recently, a new technology can represent a third category: *non-thermal atmospheric plasma*, so-called cold plasma. This plasma is intermediate between the two others and in general is included in the set of the non-thermal plasmas because is formed near atmospheric pressure and ambient temperature: “The temperature of non-thermal atmospheric plasma […] is low, at around room temperature” (Kim et al., 2010, p. 530).

Low-temperature non-equilibrium plasmas play an increasing role in biomedical applications, though user friendly sources need to be developed. For instance, microwave generated atmospheric-pressure plasmas enable lower facility and process costs in a variety of plasma processing and manufacturing techniques (Ferreira et al., 2012, *passim*).

In particular, medical applications of non-thermal plasmas are of two main typologies: “direct and indirect plasma treatment, differentiated by the amount of charged species applied to the surface of the living tissue” (Tan et al., 2012).

- Direct treatment generates a non-thermal, atmospheric-pressure plasma in direct contact with the living tissue, which is used as one of the discharge electrodes. The living tissue, in “direct plasma treatment”, is in direct contact with the plasma and this technique can be mainly applied in skin sterilization, blood coagulation, in assisting wound healing and tissue regeneration.
- On the other hand, indirect plasma treatment is represented by atmospheric pressure plasma jets. This approach creates the plasma remotely and delivers its afterglow by a jet to the desired location; the sample is placed at some distance

[1] Due care has been taken during database building procedure to overcome this homonymy.

from the plasma and only exposed to the formed reactive species (cf. Fridman et al., 2007; Laroussi, 2009; Shashurin *et al.*, 2008).

In order to introduce the topics that are analyzed and discussed in this study the following paragraphs present a selection of some key biomedical applications of cold plasmas in scientific literature and patenting activity.

Applications in the cure of cancers

Non-thermal atmospheric-pressure plasmas can be applied in medicine to induce growth arrest in tumour cells and could have vast applications in immunology or cancer therapies. In fact, the main role of indirect plasma treatment on cell apoptosis and necrosis has been discovered recently. Haertel et al. (2011) argue that: “Plasma is also able to induce apoptosis, which is an important feature when treating cancer cells” (cf. also Kim et al. 2010).

Keidar *et al.* (2011) study the effect of cold plasma on several lines of cancer cells both *in-vitro* and *in-vivo*. The study: “shows […] new response of cancer cells upon treatment with cold plasma jets” (p. 1300). Results display that some cancer cells could be selectively ablated by plasma jets leaving unaffected their corresponding normal cells. Involved mechanisms could be plasma-induced apoptosis and decrease of velocity of cell migration.

Hofmann *et al.* (2010) report the use of Cold Plasma Coagulation (CPC) in the treatment of patients presenting malignant pleural mesothelioma, a cancer provoked by the exposition to asbestos, for which no real cure exists so far. CPC was used in combination with chemotherapics perfusion in order to avoid pleural effusion and cardiotoxic effects and to sterilize the site, thus achieving better quality of life for the patients.

Vandamme *et al.* (2012) perform *in-vivo* tests evaluating the effect of non-thermal plasmas on cancer cell lines. According to their results plasma generates reactive oxygen species that interact with DNA of cancer cells, inducing cell apoptosis. The analysis of how non-thermal atmospheric pressure plasma influences mononuclear cells is also important to understand into plasma–immune cells interactions (Haertel et al., 2011a). However, the molecular mechanisms in plasma-induced cell growth arrest are not well understood. Kim et al. (2010, p. 530) analyze the feasibility of non-thermal atmospheric plasma treatment for cancer therapy and examine the mechanism by which plasma induces anti-proliferative properties and cell death in human colorectal cancer cells. Non-thermal atmospheric plasma is less invasive and more selective to cancer cells as a targeted means of treatment for cancer patients. In particular, the technology is an apt anti-cancer treatment for established or pre-neoplastic defects of the: "esophagus, bladder and bowel, which are anatomically difficult areas for traditional surgical and radiotherapy approaches" (Kim et al., 2010, p. 537). However, these innovative techniques may have some limitations and generate fruitful effects mainly in superficial premalignant defects and early superficial cancer for disinfecting and removing microscopic residual cancer (Kim et al., 2010, p. 537).

Applications in the suppression of pathogens and as disinfectant

Advances in non-thermal atmospheric plasma have also led to applications in treatments to suppress pathogens and infections (Stoffels et al., 2006) or sterilize tissues (Shashurin et al., 2008; Moisan *et al.*, 2001; 2002). Involved mechanisms are several: "In the case of medium and low-pressure discharges, the inactivation mechanisms are the DNA destruction by UV irradiation and the erosion of the micro-organism through intrinsic photodesorption and etching (eventually enhanced by UV radiation)" (p. 18, Moisan, 2001). Two or three distinct phases characterize plasma inactivation of bacteria and spores (p. 357, Moisan, 2002). Bactericidal effects of cold plasmas on two different types of bacteria have been investigated by Morris *et al.* (2009). Results show that exposing bacteria to cold plasma, it kills vegetative cells of both bacteria, while spores are killed only for one of the two. Instead, Xu *et al.* (2011) study effectiveness of atmospheric-pressure non-thermal plasma towards bacteria embedded in biofilms, such as the *Neisseria gonorrhoeae*; in this case, biofilms bacteria are particularly difficult to remove, but plasma seems effective towards destruction of such bacteria. Mechanisms of bacteria inactivation are also studied by Joshi *et al.* (2011). According to their observations: "Plasma treatment causes morphological changes in E. coli that are peculiar to oxidative stress and eventual death" (p. 1055) and "Plasma-induced oxidants attack the cell membrane and depolarize it in E. coli" (p. 1058). Instead, Brun *et al.* (2012) investigate the use of Plasma for the disinfection of ocular cells and tissues: results show effective action towards both bacteria and fungi.

In addition, Burts *et al.* (2009) show the use of atmospheric non-thermal plasma as a disinfectant for objects contaminated with methicillin-resistant Staphylococcus aureus. Hence, generation of plasma is a promising method for disinfection of objects or surfaces that warrants further study in hospital settings. Terrier *et al.* (2009) study the efficiency of cold oxigen plasmas as disinfectant for airborne viruses, with particular regard to influenza viruses, in nebulized sospensions. Results show positive effects: "gas plasma […] is responsible for an important decrease of the viral titer for all the three respiratory viruses" (p. 122). This effect is mainly attributed to the presence of Ozone in the plasma.

Applications in surgery: surface modifications of materials for transplantation and orthopaedics

The use of plasmas in surgery is strongly connected to surface modifications of materials for transplantation of various body parts, and particularly in orthopaedics (often performed with the use of hot plasmas). For instance, Chen *et al.* (2009) study antibacterial effect of silver-containing titanium coatings for bone-substitution Titanium-based prostheses, prepared via a plasma spray technique. Results display antibacterial activity mainly due to the presence of nanostructured silver. Jamieson *et al.* (2011) study, instead, mechanical properties of spongy coatings of prostheses realized with Plasma spraying.

Schrader *et al.* (2012) study the effects on osteointegration of Titanium prostheses where a bioactive nanometric surface ceramic coating, realized with Plasma chemical oxidation, is enriched with bioactive elements (Calcium and Phosphorus) and tested on rats. The surface resulted supports osteointegration and implant fixation. A similar device has been tested by Ripamonti et al. (2012) with a particular attention to its geometry.

Surmenev (2012) performs a review of plasma-assisted methods for the fabrication of coatings based on Calcium Phospates. Several Plasma methods are described (e.g. Radio-frequency magnetron sputtering, Plasma spraying, Pulsed lased deposition, Ion beam-assisted deposition) as well as the characteristics of obtained coatings. Positive results of the techniques are also shown. Finally, Tan et al. (2012) analyze plasma generated by applying energy to a gas resulting in a mixture of ions, electrons and neutral species. They investigate the influence on osteogenic lineage cells or bone tissue and applications in surgical repair of hard tissue. This study shows that atmospheric pressure plasma is a potent tool for modifying the biological function of a material without causing thermal damage, such that adhesion molecules and drugs might be deposited on the original coating to improve performance.

Application in dermatology

Silk fibroin fibres can be surface-modified with the use of Plasmas in order to be used for skin regeneration treatment: surface modifications depend on the gas used for

Plasma generation (Jeong *et al.*, 2009). In fact, another important medical field of application of Cold Plasmas is dermatology and wound healing. Lademann *et al.* (2011) report the use of Plasmas for drug delivery through the skin barrier in an *in-vitro* experiment. No thermal damage was observed and "the treatment of the skin surface with tissue-tolerable plasma is an efficient method for stimulating the penetration of topically applied substances through the skin barrier with a low risk of infection" (p. 490).

Isbari *et al.* (2011) show the use of Cold Atmospheric Argon Plasma as a treatment to cure rare Hailey-Hailey Disease, caused by gene mutation and that nowadays is still difficult to cure. This was done to treat the infection provoked by the disease and to test the effects on the disease of reactive oxygen species. Effectiveness of the therapy shows that it offers a novel treatment option for affected patients.

Procedures for control of wound bleeding and wound healing with the use of Plasmas are reported by Nastuta *et al.* (2011) and by Kuo *et al.* (2012). Their experiments, performed *in-vivo* on animals, show positive effects, with shorter healing time after Plasma application.

This background is important to analyze the technological trajectories of non-thermal plasma in medicine. Next section presents the methodology of research.

3. Research method

The main interest of this paper is to pinpoint current research fields of non-thermal plasma that support technological trajectories of groundbreaking applications in medicine. Of course, this is a complex issue affected by several factors. Thus this work proposes a straightforward approach that tries to detect emerging scientific fields and associated technological trajectories of non-thermal plasma in medicine. Nelson (2008, p. 489) considers: "that a strong body of scientific understanding enables technological progress to be rapid and sustained […] the research in the engineering disciplines and applications oriented sciences aims to develop understanding of what is going on in the operation of the relevant field of practice, so as to illuminate how to advance it". Moreover, Grupp (2000, p. 143) argues that: "innovation literature centres more on technical advance and less on scientific change".

As a matter of fact, it is important to ascertain that scientific advances and changes can be considered as ice-breakers for new scientific research fields, creating new pathways for future patterns of technological innovation. In order to investigate the directions and intensity of scientific research in those research fields that may drive future technological pathways, we use a methodology based on the analysis of numbers of scientific outputs (mainly journal articles, but also conference papers, book chapters etc.) and patents. Data have been retrieved with the use of the database SciVerse® (2012) by Elsevier carrying out a search of critical keywords.

SciVerse® has been preferred for the present study as it encompasses both scientific products and patents (together with web documents); it is in fact a meta-database, retrieving data from other databases (for instance Scopus® and Pubmed®) for scientific production, and from WIPO, EPO, USPTO, JPO and other European and non-European patent offices for patent applications. Database has been built retrieving occurrences according to Boolean sets of keywords and carefully counting the number of scientific products/patents per each year in order to avoid the spurious count of duplicates. Data have been retrieved on June 2012 exploiting the search-and-retrieve system of SciVerse®, inserting in the search window composite queries and using the "title-abs-key" code, thus enabling search only in Title, Abstract or Keywords of scientific products. Data were collected up to 2011 (as 2012 scientific production is still in progress) and go back up to 1974. Queries are reported in Appendix 1 in Table 1A. The analysis has been performed on data from 1990 onwards only, when the quantity of scientific/technological products starts to be more consistent. As a general rule data mining has been performed including (when needed) keywords into quotation marks (*i.e.* “search for the exact phrase2).

Search queries have been realized combining (with the Boolean operator “AND”) for each query two groups of keywords and Boolean operators.

The first group of keywords is common to all queries. It is relative to plasma and it contains all its most relevant definitions. This group of keywords has been realized with due care avoiding to incorporate citations of scientific products and patents on “blood plasma”. Several tests have been performed before getting to the final queries.

The second group of keywords is specific for each query, and encompasses all the terms that are relevant for the specific subject, obtained via study of scientific literature and checked via several preliminary queries on Scopus® (2012), which also support relevant keywords on different topics.

After performing the queries, results have been checked to control duplicates and spurious data. Table 1 in Appendix 1 contains all keywords sets used for our database.

Data mining has been performed in June 2012, and is focused on the time horizon 1990 – 2011 for scientific research products (articles, books and related works) and patents.

As an acceleration of scientific activity in some research fields is a first main signal of scientific accumulation and continuous advances, it is critical to measure and analyse the *rates of scientific and technological growth* that indicate the evolutionary growth of technological trajectories in the medium-long term. The rate of scientific advances is measured by the number of scientific products, whereas technological advances are measured by the number of patents. An *exponential* model is a fruitful approach to measure the patterns of critical scientific fields based on the following *assumptions* (Coccia 2012):

1: $_{a}P$ is the number of scientific articles at t=initial (e.g. 1996)

2: $_{t}P$ is the number of scientific articles at 2011

3: t is the period analyzed

4: scientific articles are a proxy of the scientific knowledge under way

The model is:

$_{t}P = {}_{0}P \cdot e^{rt}$ where e is the base of natural logarithm (2.71828…).

Hence $\frac{_{t}P}{_{0}P} = e^{rt}$; $Log\frac{_{t}P}{_{0}P} = r \cdot t$;

$$r = \frac{Log\left(\frac{_{t}P}{_{0}P}\right)}{t}. \qquad [1]$$

r= rate of scientific (or technological) advances

This method can offer an analytical framework for detecting promising scientific trends that may support main technological trajectories and radical innovations that will impact the healthcare.

In addition, data have also been analyzed by an econometric model based on time series to better understand new directions and compare the results with previous approach (based on Eq.[1]). As some distributions are not normal, a logarithm transformation has been applied to have apt distributions for parametric estimates.

In particular, the functional relationship is:

Scientific-technological output (articles) of non thermal plasma applications in medicine = f (Time)

The specification is based on a simple regression model:

$$Ln\, y_{i,t} = \lambda_0 + \lambda_1 Time + u_{i,t} \qquad \text{(growth model)} \qquad [2]$$

where the *t* subscript indicates the time, $u_{i,t}$ = error term

This equation [2] is estimated by Ordinary Least Squares (OLS), using the statistics software SPSS (Statistical Package for the Social Sciences). Moreover, results show R Square statistic, which is a measure of the strength of association between the observed and predicted values of the dependent variable. The large R Square values indicate strong relationships for models. Adjusted R Square is a "corrected" measure due to the fact that R Square statistic penalizes models with large numbers of parameters. The ANOVA table tests the acceptability of the model from a statistical perspective: ANOVA table is a useful test of the model's ability to explain any variation in the dependent variable. The significance value of the *F* statistic is less than 0.05, which means that the variation explained by the model is not due to chance.

Next section presents the main results.

4. Results

Statistical analysis is based on two samples respectively of 1,081 scientific products and of 154 patents. These samples are the basis to apply models for the analysis of the scientific and technological knowledge growth based on scientific outputs; this enables to detect promising scientific pathways of such key technologies.

Figure 1 reports graphically the number of scientific products per year for the analyzed topics. It must be noted that for Surgery applications of non-thermal plasma, SciVerse data start in 1997.

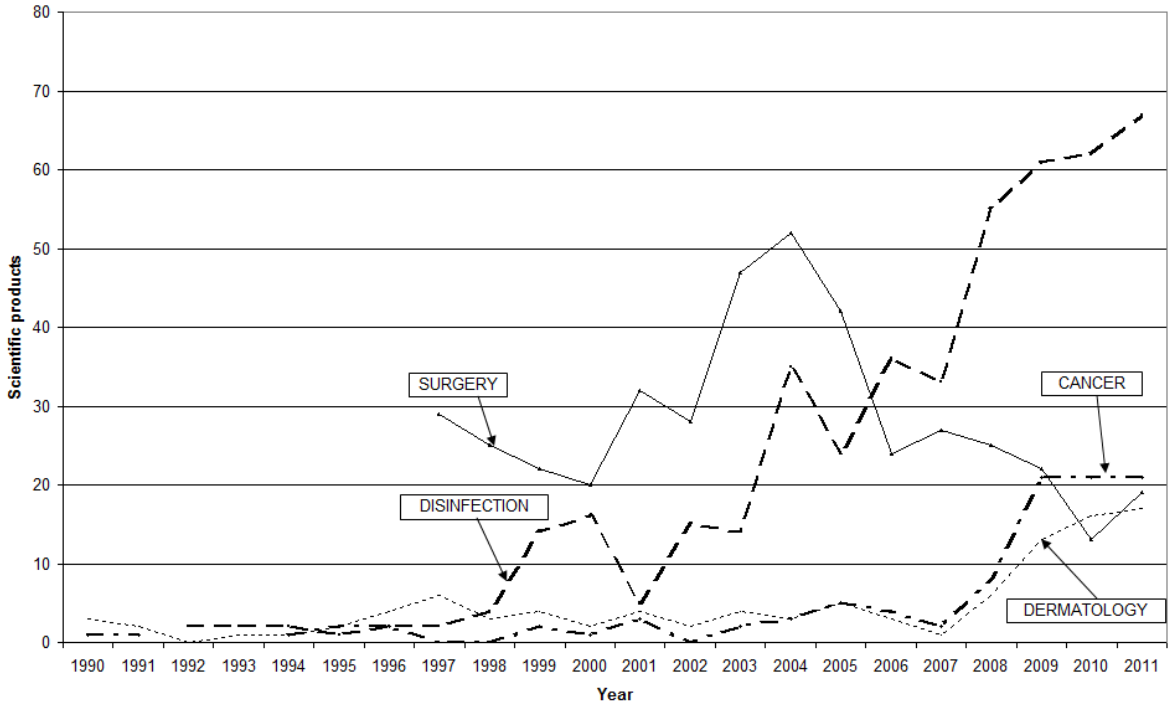

Figure 1 – Trends of scientific products of non-thermal plasma per main applications

Figure 1 shows that the scientific evolution in surgery follows a pathway which is rather different from that of the other topics. In fact, while cancer, disinfection and dermatology applications present a more or less continuous growth in scientific production from 1990 onwards, applications of non-thermal plasma in surgery have a peak of publications around mid-2000s and then a decrease, though still presenting a rather high production at the end of the period. This fact might be due to the specific topic of most part of the literature regarding application of plasma for purposes of surgery. A closer analysis of the scientific products shows that most applications are related to the use of plasma for surface modification of materials or object to be used in surgery for the substitution of body parts (e.g. bone parts) or for implantations (such as, nets for surgical uses[2]). This might prove that the technological trajectory of such applications of non-thermal plasma is following a different pathway, more linked to the trajectory of the

[2] Such nets are used to retain organs in their position after heavy surgical operations.

materials development rather than to the specific trajectories presented by other non-thermal plasma medical applications.

Table 1 reports the evolutionary rates of growth of scientific products for the main explored topics: non-thermal plasma for the cure of cancer, for bacterial disinfection, for surgical applications and for dermatology applications. Such topics have been chosen in literature as the most promising in the field (as theoretical framework shows) and those presenting the widest scientific production in the last years. Such rates of growth are a strong indicator highlighting the emerging directions of these research fields and technological trajectories that may support vital applications in medicine in the future. Data of patents are low and we cannot calculate the rate of scientific growth. The last column has only the sum of patents over time.

Table 1. Rates of scientific growth of scientific fields in non thermal plasma in medicine (Data based on scientific articles and patents by SciVerse, 2012)

TOPIC	1st year	Sum of Articles	Years	Pt/Po	r (articles)	Sum of patents
Cancer	1981-2011	91	22	20	13.617	5
Disinfection	1979-2011	457	24	67	17.519	104
Surgery	1998-2011	427	15	0.655	–2.819	35
Dermatology/ skin regeneration	1974-2011	106	25	17	11.333	10

Non-thermal plasma applications for disinfection present the highest growth rate (more than 17 %), followed by applications for the cure of cancer (almost 13 % growth) and by dermatological applications (more than 11 %). All three research trajectories show a growing rate of scientific production and thus might drive innovations and research in medicine in the not-too-distant future. Conversely applications in surgery show a negative trend (almost -3 %).

Table 2 contains descriptive statistics for patents, whereas table 3 contain those for articles. Patents shows that the higher arithmetic mean over time is relative to the applications of non thermal plasma for disinfection (6.1 patents), followed by dermatology (2.5) and applications in surgery (2.06 patents). Applications for the cure of cancer present a much lower result (1.25).

Table 2 - Descriptive Statistics (patents)

		Cancer	Disinfection	Surgery	Dermatology
Cases	Valid	4	17	16	4
	Missing	43	30	31	43
Mean		1.250	6.117	2.062	2.500
Std. Error of Mean		0.250	0.954	0.432	0.957
Std. Deviation		0.500	3.935	1.730	1.915
Skewness		2.000	0.061	1.213	0.855
Std. Error of Skewness		1.014	0.550	0.564	1.014
Kurtosis		4.000	-1.197	0.413	-1.289
Std. Error of Kurtosis		2.619	1.063	1.091	2.619
Sum		5	104	33	10

As far as scientific products are concerned (table 3), higher arithmetic mean of scientific output is that of plasma application in disinfection (more than 14 articles per year), surgery (more than13 articles), whereas applications in dermatology and cure of cancer have much lower values. Nevertheless, standard deviation is also higher (high dispersion of values). In addition, some distributions are not normal; in this case the logarithmic transformation is an apt approach to have normal distributions and apply parametric estimates for analyzing by, econometric models, these time series (table 4).

Table 3 - Descriptive Statistics (articles)

		Cancer	Disinfection	Surgery	Dermatology
Cases	Valid	34	32	31	31
	Missing	13	15	16	16
Mean		2.676	14.281	13.774	3.419
Std. Deviation		5.226	21.007	16.225	4.372
Skewness		2.751	1.505	0.779	2.152
Std. Error of Skewness		0.403	0.414	0.421	0.421
Kurtosis		6.643	1.023	-0.473	4.333
Std. Error of Kurtosis		0.788	0.809	0.821	0.821

		Cancer	Disinfection	Surgery	Dermatology
Cases	Valid	34	32	31	31
	Missing	13	15	16	16
Mean		2.676	14.281	13.774	3.419
Std. Deviation		5.226	21.007	16.225	4.372
Skewness		2.751	1.505	0.779	2.152
Std. Error of Skewness		0.403	0.414	0.421	0.421
Kurtosis		6.643	1.023	-0.473	4.333
Std. Error of Kurtosis		0.788	0.809	0.821	0.821
Sum		91	457	427	106

Table 4 Descriptive Statistics (Logarithmic values of articles)

		LnCancer	LnDisinfecta	LnSurgery	LnDermathology
Cases	Valid	24	24	22	22
	Missing	23	23	25	25
Mean		0.772	2.007	2.241	1.217
Std. Error of Mean		0.199	0.3156	0.340	0.172
Std. Deviation		0.976	1.548	1.594	0.806
Skewness		1.320	0.064	-0.721	0.477
Std. Error of Skewness		0.472	0.472	0.491	0.491
Kurtosis		0.884	-1.648	-1.445	-0.001
Std. Error of Kurtosis		0.918	0.918	0.953	0.953
Sum		18.53	48.18	49.30	26.77

The econometric models of simple regression are applied to the scientific output represented by articles. The model is not applied to patent time series because this technological output is low and not suitable for econometric estimates. Models are estimated by Ordinary Least Squares (OLS) using SPSS statistics software.

First of all, it must be noted, from results reported in table 5, that the econometric models explain a high variance in the data (see adjusted R square), except for model 4 (Dermatology applications). In addition, the parametric estimates of these models are unbiased, and the significance and the overall explanatory power of coefficients are excellent.

Table 5: Parametric estimates considering scientific outputs (articles) over 1960-2011

Dep. variable / Models	Estimated relationship	Goodness of fit	ANOVA	Applications of non-thermal plasma
1. *LnCancer* y_t=	–202.12*** + *0101* x_t*** (34.13) (0.017)	R^2 *adj =0.60* *S=0.62*	*F=35.34 (sig.0.00)*	*Cancer therapy*
2. *LnDisinf* y_t=	–375.02*** + *0.189* x_t*** (34.34) (0.017)	R^2 *adj =0.84* *S=0.62*	*F=120.52 (sig.0.00)*	*Disinfection*
3. *LnSurgery* y_t=	–358.28*** + *0.180* x_t*** (67.28) (0.034)	R^2 *adj =0.57* *S=1.05*	*F=28.72 (sig.0.00)*	*Surgery treatments*
4. *LnDerma* y_t=	–143.83** + *0.073* x_t***	R^2 *adj =0.34*	*F=11.91 (sig. 0.003)*	*Dermatology Treat.*

Note: The independent variable is time; The dependent variable is the number of scientific publications (over 1970-2011) of non thermal plasma applied in medicine. The second column is the estimate of the constant. Underneath it, in parentheses, its standard error. The third column is the estimate of β. Underneath it, in parentheses, its standard error. The fourth column has adjusted R^2 of the regression and below it, the standard error of the regression. The fifth column has the results of the Fisher test, to its right the significance. In the last column the typology of applications by non thermal plasma. t=time, *** Parameter is Significant at 0.001; ** Parameter is Significant at 0.05.

In particular, Table 5 shows that the higher coefficient of regression is that of non thermal plasma applied for disinfection and surgery. Data show that scientific outputs concerning applications of non thermal plasma in medicine for disinfection have an expected increase of approximately 19% per year, 18% in surgery treatments, and about 10% in cancer therapies. Lower increase per year is represented by Dermatology, although the latter estimated relationship has a low explanatory power.

Appendix 2 contains figures reporting the geometric representation of curves estimated with the regression model presented in table 5 for the different typologies of medical applications of non-thermal plasma.

Discussion and concluding remarks

Current socio-economic change, associated to the continuous advances of current scientific trajectories, is very active and gives strong possibilities to open up new opportunities for basic and applied research, as well as technological applications.

Innovation in biomedical field is particularly important as it bears the promise of better health for large shares of population and of better lifestyle. Economic implications, due to the high cost of care of diseases, are also rather strong in this research field.

Micro-technological revolutions in medicine (such as targeted therapies, nanomedicine, etc.) driven by new technological paradigms[3] have been generating a revolution in clinical practice, increasing the overall survival of patients, quality of life and improving the wellbeing of societies (Coccia 2012).

The study here has analyzed the scientific-technological trajectories of the clinical applications of non-thermal plasmas that are one of the vital scientific fields that presenting most technological advances, as witnessed by the present research. We have analyzed main technological trajectories of non-thermal plasma and showed the intensive evolutionary growth of scientific research and technological applications in patenting in some emerging research fields. The empirical evidence, based on numbers of scientific products and patents (chosen as indicators of evolutionary growth of science and technology), shows the following results:

- biomedical applications of non-thermal plasma present a high rate of growth both in scientific production and in patenting;
- Rates of growth differ according to applications in medicine;

3 First of all, it is important to state the technological paradigms that is " 'model' and 'pattern' of solution of selected technological problems, based on selected principles derived from the natural science and on selected material technologies" (Dosi, 1982, p. 152, original emphasis).

- Rates of growth of scientific evolution of non thermal plasma applied in medicine are well described both by a exponential growth model and by a regression model based on time series, though results slightly differ;
- Rates of growth, measured by the exponential model (Eq.[1]), are higher for applications of non-thermal plasma in disinfection and anticancer treatments, while surgical applications present a negative growth rate;
- Rates of growth, estimated by regression analysis (Eq.[2]), are higher for applications of non-thermal plasma in disinfection and surgery;
- geometric representation (figure 1) shows increasing trends of non-thermal applications in medicine, except applications in surgery that show a maximum around in 2003 and then decrease since 2004 or thereabouts. This difference in the evolution of scientific-technological production can be explained paying a closer look to the content of the scientific articles encompassed in the query. Most part of them is about applications of plasmas for surface modification of materials for body implantation: thus the technological trajectory followed is rather that of the materials than that of plasmas for biomedicine.

The high evolutionary growth of non-thermal plasma applied in medicine is due to its ability to interact in several ways with the living matter without damaging it, and to modify its surface when needed, and can be also a cheaper solution when scale economies are applied and overall costs for healthcare are considered. This paper shows that non-thermal plasma is an apt groundbreaking technology for disinfection and decontamination. This fact is also confirmed by other researches applied for food industry showing that non-thermal plasma seems to be a promising technology for decontamination of fresh food from bacteria Staphylococcus aureus, Listeria monocytogenes and Pseudomonas aeruginosa, respectively (Coccia and Finardi, 2012). This groundbreaking character is confirmed also by the fact that scientific-technological innovation clusters (encompassing several stakeholders), are being created and supported in order to promote innovative activities in the field of biomedical use of non-thermal plasmas (see Gebhardt, 2012 for the German case).

Nevertheless, it must be noted that such promising scientific-technological trajectories in medicine, with high rates of growth, have a number of occurrences (scientific products and patents) lower than other relevant fields where non-thermal plasmas are applied, such as applications for conservation of fresh foods (cf. Coccia and Finardi, 2012). Thus it can be said that such applications of non-thermal plasma in medicine are strongly promising but are also in their infancy, and thus at the beginning of their evolutionary patterns of technological innovation. But it is also true that biomedical applications of new plasma technologies are strategic, because of the possible improvement of life conditions and the economic outcome that they might have in term of efficacy treatments and savings from expenses in hospitalization. Current evolution due to applications of non-thermal plasma can become soon a key element in the field of biomedicine.

Although it is difficult to cover and analyse all scientific information concerning these emerging research fields, we hope that this paper can provide the fundamental technological trajectories of non-thermal plasma that could improve the clinical practice as well as the quality of life and wellbeing of future societies. Nevertheless, this study deserves further investigations based on more comprehensive models and data.

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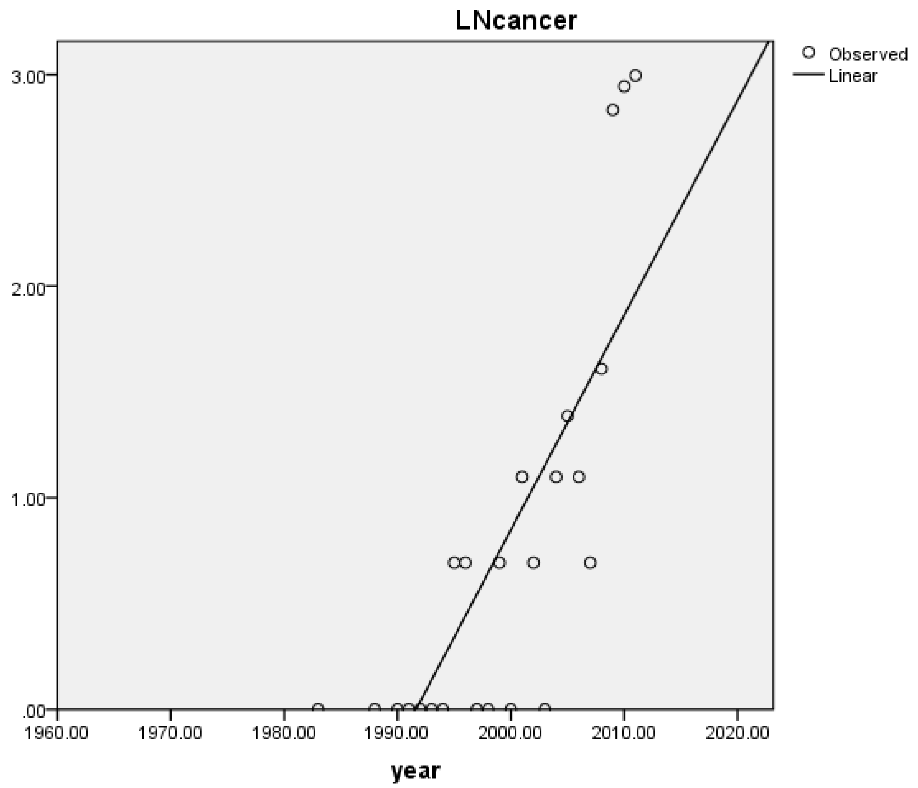
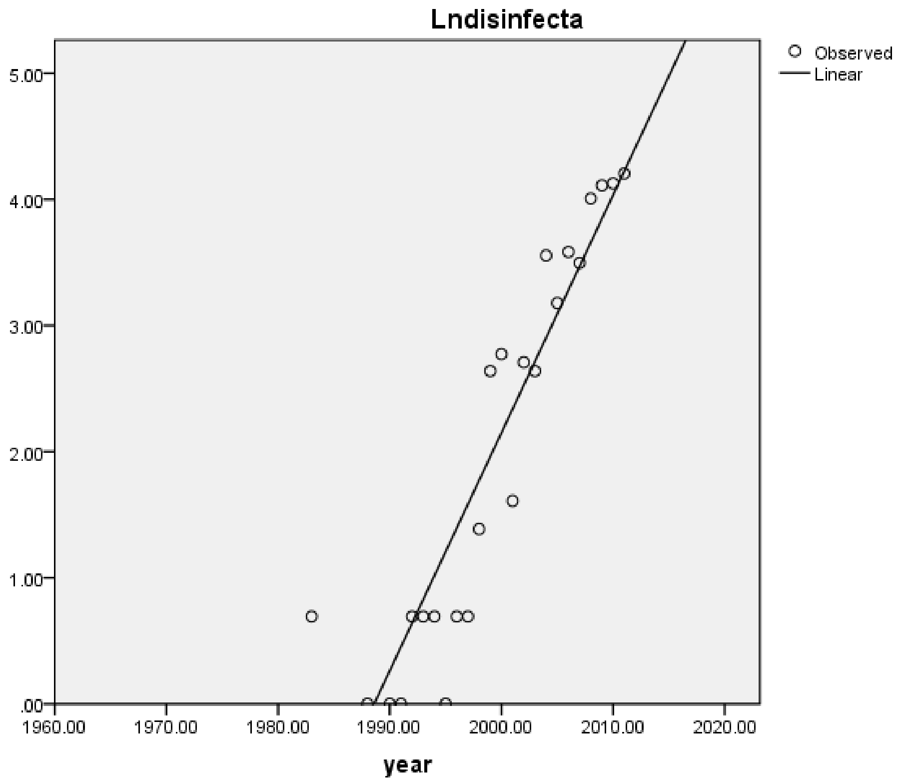
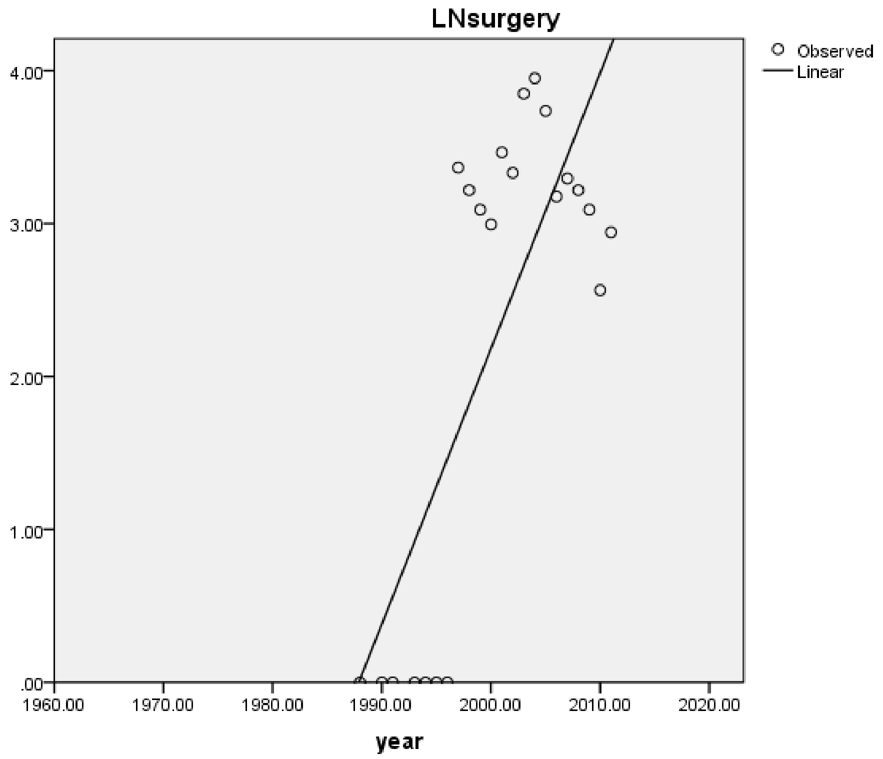
Appendix 1

Table 1A – list of Boolean sets of keywords and of medical areas of investigation
Cure of cancer: title-abs-key(("non-thermal plasma*" OR "non thermal plasma*" OR "cold plasma*" OR "plasma jet*" OR "atmospheric pressure plasma*" OR "atmospheric pressure cold plasma*" OR "atmospheric plasma*" OR "plasma plume*" OR "Plasma spray*" OR "plasma torch*") AND (cancer* OR tumor* OR "tumoral cell*" OR "tumor cell*" OR "tumour cell*" OR neoplas* OR "anticancer treatment*" OR "metastasis" OR "*carcinoma" OR "melanoma"))
Disinfection of objects from pathogens: title-abs-key(("non-thermal plasma*" OR "non thermal plasma*" OR "cold plasma*" OR "plasma jet*" OR "atmospheric pressure plasma*" OR "atmospheric pressure cold plasma*" OR "atmospheric plasma*" OR "plasma plume*" OR "Plasma spray*" OR "plasma torch*") AND (sterilization OR sterilisation OR germici* OR bacterici* OR "bacteria removal" OR "bacterial infection" OR decontamination OR biodecontamination OR bio-decontamination OR "anti-bacterial agents" OR "antiinfective agent" OR listeria OR "staphylococcus aureus" OR salmonella OR "escherichia coli" OR "pseudomonas aeruginosa"))
Surgery: title-abs-key(("non-thermal plasma*" OR "non thermal plasma*" OR "cold plasma*" OR "plasma jet*" OR "atmospheric pressure plasma*" OR "atmospheric pressure cold plasma*" OR "atmospheric plasma*" OR "plasma plume*" OR "Plasma spray*" OR "plasma torch*") AND (surgery OR surgical OR laparoscop* OR laparotomy))
Dermatology and skin regeneration: title-abs-key(("non-thermal plasma*" OR "non thermal plasma*" OR "cold plasma*" OR "plasma jet*" OR "atmospheric pressure plasma*" OR "atmospheric pressure cold plasma*" OR "atmospheric plasma*" OR "plasma plume*" OR "Plasma spray*" OR "plasma torch*") AND ("skin disease*" OR "skin sterilization*" OR "wound* healing" OR "skin burn*" OR "skin ulcer*" OR "wound* patholog*" OR "cutane* patholog*" OR "skin Neoplasm*" OR psoriasis OR erythema OR "skin infection*" OR epidermis OR dermatitis OR "wound infection"))

Appendix 2: Curves estimated by regression analysis (OLS method)






LNsurgery
Observed
Linear
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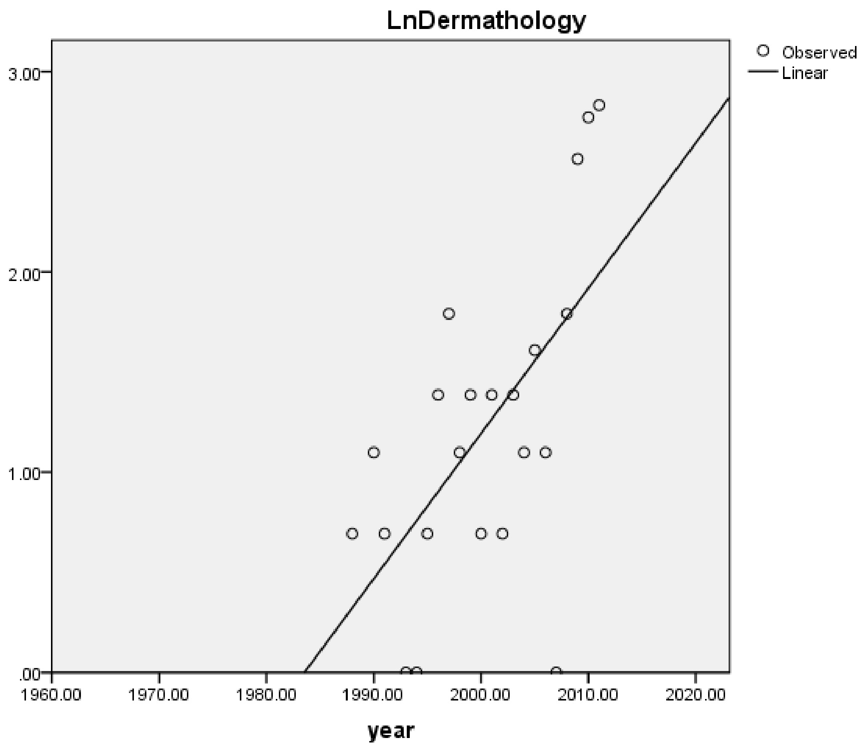
3.00
2.00
1.00
.00
1960.00
1970.00
1980.00
1990.00
2000.00
2010.00
2020.00
year


LnDermathology
Observed
Linear
3.00
2.00
1.00
.00
1960.00
1970.00
1980.00
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2020.00
year