// NO.19-011 | 02/2021

DISCUSSION PAPER

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Anatomy of the Medical Innovation Process – What are the Consequences of Replicability Issues on Innovation?

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Anatomy of the Medical Innovation Process - What are the Consequences of Replicability Issues on Innovation?

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This draft: February 2021
First draft: April 2019

Abstract

The study looks at the impact of replicability issues in preclinical testing on the medical innovation process. The case study focuses on the development of liposomal chemotherapy, which exemplifies the difficulties of replicating experiments in preclinical settings. Despite those issues, liposomes achieved their translation in the clinic. To solve this puzzle, the case study introduces an original methodology to understand how the lack of scientific guidance is overcome to spur medical innovation. The results show that the involvement of researchers along the innovation process helped to accumulate knowledge in different experimental conditions. Properties and research practices involved in scientific experiments when liposomes were used as research tools helped to expand the knowledge base. Recombining those bodies of knowledge with clinical observations helped to overcome the uncertainty about the design to select. The resulting formulations built upon merging well-understood features of liposomes or to combine those with existing complementary technologies to enhance their therapeutic effect.

Keywords: replicability, medical innovation, medical technology

JEL Classification: L65, O33, O34

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Acknowledgements: The data collection achieved in 2014 was supported by the grant DFG Research Training Group 1411. The author would like to thank Francois Perruchas for his support regarding data mining techniques and Davide Consoli for his feedback on the preliminary version of the study. Last but not least, I would like to thank David Deamer and Theresa Allen for their time in discussing the results.

1 Introduction

The ongoing replication crisis affects a wide range of scientific fields and seems particularly important within preclinical research (Ioannidis 2005; Freedman *et al.* 2017; Fanelli 2018). Even if numerous scientific organisations have started to tackle replication issues via specific training and norms in the evaluation of grant proposals (see the NIH initiative on reproducibility)[1], their impact is still in the early stages in preclinical research (Freedman *et al.* 2017). The limited replicability of preclinical studies has shown affecting the pace and the costs of innovation efforts by increasing the delay and costs of lifesaving therapies (Freedman *et al.* 2015). Replicability issues alter the capacity to accumulate knowledge by impeding the identification of common patterns across experiments (Nightingale 2004; Nelson 2008). In this context, science can hardly guide technological efforts in a linear fashion and the medical innovation process must adapt by relying on alternative sources of knowledge (Gelijns & Rosenberg 1994; Nelson *et al.* 2011). This case study proposes to understand how a technology plagued by replicability issues in preclinical settings - liposomes - could achieve their translation from the bench to the bedside. The results show that the difficulties linked to isolating the actual effect of liposomal treatments from their preclinical settings resulted in multiplied competing assumptions and technological designs. Resolving the technological uncertainty was the result of original knowledge recombinations that arose from clinical observations, as well as technological properties that were accumulated outside the realm of health care. The initial use of liposomes as research tools played a leading role in this process by adapting existing methods and well-understood properties to solve medical technological bottlenecks.

The contribution of the paper to the medical innovation literature is threefold: first, by introducing new measures this paper illustrates the concepts of "testing regimes" developed by Yaqub & Nightingale (2012); Yaqub (2017) and Yaqub (2018). Building upon the specificities of medical publications, the delineation of the testing regimes differentiates between simple, intermediate, and complex experimental conditions (i.e. laboratory conditions without medical purposes, preclinical settings with animal testing, and clinical settings). Second, mapping the knowledge dynamics by differentiating the distinct contexts

[1] https://grants.nih.gov/policy/reproducibility/index.htm

of scientific research depicts the non-linear and dynamic characteristics of the medical innovation process described in Gelijns & Rosenberg (1994) and Nelson *et al.* (2011). Third, the results reveal that the innovation strategies to cope with radical uncertainty in the development of medical devices (i.e. merging features (Barberá-Tomás & Consoli 2012), combined use of complementary technologies (Mina *et al.* 2007)) are used in pharmaceuticals. The remainder of this paper is structured as follows: section 2 details the contextual background of the case, section 3 introduces the data source and methodology. Section 4 summarizes the main results of the citation analysis and section 5 discusses those with the specificity of institutions of the case. Section 6 concludes.

2 Contextual background

Replicability in a strict and narrow sense refers to using the exact data and methodology involved in a study to check the reliability of the results originally found. In a broader sense, replication rather refers to an extension of the key results found in different settings (e.g. using other data or methodologies). Replication is thereby a key feature of science by defining the boundaries of theories through the empirical confirmation - or refutation - of previous findings. In the context of preclinical research, being able to replicate the key findings generated upstream in the lab is necessary considering their goal: collecting data to evaluate the risks and benefits associated to a given medical innovation before entering clinical trials. The nature of preclinical research explains to some extent why replicability is limited and why preclinical studies are less likely to be replicated than studies from other disciplines.

2.1 The limited power of science and the importance of testing

In contrast to other sciences, biomedical phenomena are harder to study: disease mechanisms involve multiples interactions between several pathways such as genes, proteins, and cells (Dougherty & Dunne 2012). These interactions might be non-linear, interdependent, and different across individuals (West & Nightingale 2009). The complexity and dynamic nature of the human body make the study of a specific disease mechanism difficult. Consequently, scientists must work in the lab with the use of scientific models to abstract

much from the complexity of reality (Nelson 2003). Learning from experiments relies on a large set of simplifying assumptions about the studied disease mechanism. In this sense, experimenting in the lab predicts or simulates more than replicates the understanding of pathologies (Nelson 2003). Simplifications of the complexity of the human body in the lab may be valid under these conditions, but in the real world clinicians may only check those for a subset of patients. Several therapies have shown to have distinct effects on patients due to ethnic genetic differences underestimated in the lab (Hunt 2008). In this context, the limited or partial fundamental understanding of a pathology, hardly guides innovation efforts in a linear fashion (Gelijns & Rosenberg 1994). Extensive testing activities in preclinical and clinical conditions are needed to refine the assumptions made about medical technology properties.

Preclinical testing is a key step in learning about technologies by evaluating their properties in a controlled environment (e.g. standardised experimental settings). Replicating experiments in this controlled environment implies that a specific mechanism of action can be isolated from the experimental settings. As a result, the behaviour of a medical technology under a given set of conditions can be predicted (Nightingale 2004; Nelson 2008; Yaqub & Nightingale 2012). Experiments conducted in more complex conditions (e.g. clinical trials, where the environment is less difficult to control but more realistic) assess the relevancy of the predictions made in preclinical testing. Defining preclinical conditions relies on a trade-off between simplifying the complexity of the human body and the capacity to provide realistic findings (Yaqub & Nightingale 2012). The assumptions and research infrastructure which characterise the preclinical stage play a crucial role in learning about a given treatment or device. Improvements in the testing infrastructure fasten the pace of technological developments (Thomke *et al.* 1998; Nightingale 2000; Yaqub & Nightingale 2012). Biases from the experimental settings have shown to affect the rate and the direction of technological progress (Yaqub 2017, 2018). Similarly, disentangling the effect of a medical technology from the preclinical conditions is not always easy. A given drug effect can be dependent on the metabolic, or immunological, state of an animal in preclinical settings (Hunter 2017). Interdependence between the studied technology and the experimental conditions can thereby limit the capacity to replicate experiments and, hence, learn

about its properties to innovate. The following section draws upon the history of liposomal cancer chemotherapy to illustrate how interdependence in the preclinical settings creates numerous sources of variations across experiments, which ultimately reduces the chance to replicate the initial findings.

2.2 Liposomes experiments across settings

The lack of detailed and complete protocols used in preclinical studies have been put to the front as significant sources of replicability issues (Hunter 2017). Beyond selective reporting, interdependence that arises from the interaction(s) between the studied technology and the preclinical protocols or settings, reduces de facto the chances of replicating experiments. The case study illustrates this phenomenon with the development of liposomal cancer chemotherapy in the following two subsections. The first subsection summarises the initial use of liposomes as research tools in cell biology experiments, whilst the second subsection expands on the difficulties linked to their use in preclinical settings.

2.2.1 From research tools to chemotherapy

Like other medical technologies, liposomes started their career outside the realm of health care as a research tool (Spetz 1995; Blume 1995). Liposomes consist of a vesicle made of at least one layer of lipid operating at the nanoscale. Discovered by Alec Bangham in 1965, their proximity to the cell membrane made them a prime candidate to become a scientific model in cell biology (Gregoriadis 2018). For this reason, liposomes entered the realm of the laboratory as a research tool in order to test various cell membrane properties (Weinstein 1987). After studying their capacity to resist various pH and temperature changes, liposomes extended their role as research tools by carrying different substances, which enabled testing the presence or absence of biological compounds (Gomez-Hens & Fernandez-Romero 2006). In this context, the use of liposomes as protein carriers laid the groundwork for the concept of cancer "passive targeting" (Matsumura & Maeda 1986). The observations made in animal models that liposomes cluster around the tumour cells rationalised the use of liposomes for cancer chemotherapy and enhanced research efforts (Weinstein 1987).

2.2.2 Towards preclinical testing and replication issues

Despite the fact that the potential of liposomes was established, the limited explanatory power of experiments acted as a burden on the technological developments as if it was "impossible to make definitive experiments" (Weinstein 1987, 90). The formulation and preparation steps involved in the production of liposomes can determine their performance (Wagner & Vorauer-Uhl 2011). Consequently, a change in the input(s) or the sequence of the steps taken in liposomes preparation has led to ambiguous results across experiments. The different scientific communities involved in using liposomes as research tools relied on distinct approaches and apparatus, which enhanced the sources of variations in experiments (Weinstein 1987). Furthermore, the characteristics of the loaded drug in liposomes affect and interact with liposomes properties as well. This combination of drug-liposomes formulation properties constitutes additional sources of variation in the results obtained from preclinical testing.

Furthermore, the different sources of variations in the preparation of liposomes formulations created some interdependence in experiments. This made it difficult to disentangle which step, or interaction with the formulation and/or experimental settings, was responsible for generating confounding results. The limited capacity to replicate experiments impeded the identification of a successful formulation and the reasons behind it. Despite these replication issues, the first market approval related to cancer chemotherapy was achieved in 1995. To understand how researchers were able to overcome these issues, section 3 introduces a bibliometric approach to pin point the sources of insights involved in the main sequence of problem-solving which are documented in section 4.

3 Data and Methodology

The analysis focuses on the US research efforts in liposomal cancer chemotherapy to account for the importance of national institutions within the health sector (Consoli & Mina 2009). The case study combines publication and patent data to uncover the knowledge dynamics occurring over the medical innovation process. The former documents the set of relevant problems to solve and the latter describes the solutions that prevail as a result

(Mina *et al.* 2007). The analysis of the knowledge dynamics differentiates the contexts in which knowledge has been produced to measure the importance of learning by using in experiments to innovate. Even if not successful in replicating experiments, specific methods, or preparation routine, can constitute a source of "background knowledge" (Pavitt 1998) to solve technological bottlenecks.

3.1 Method: citation network analysis

Citation network analysis has been the reference method in understanding the dynamic of medical innovation knowledge (Mina *et al.* 2007; Consoli & Ramlogan 2008; Barberá-Tomás & Consoli 2012). The Main Path algorithm is an appropriate way to observe the main sequence of medical problem-solving (Consoli & Mina 2009). The Main Path simplifies key scientific and technological developments by reflecting the most important junctions of knowledge, assuming that knowledge flows through citations (more details about the methodology is available in subsection 6.3 in the appendix). This trajectory depicts a knowledge space, in which knowledge is accumulated in layers. Like in genealogy, each layer represents a generation of knowledge reflecting the scientific, or technological, state of art related to a given period. The latter assumes that knowledge flows through citations: a node refers to a piece of knowledge (patent or publication) and a citation represents an arc linking two nodes.

3.2 Data sources: publications and patents

Publication data combines records from PubMed and Web of Science. The former provides relevant information on defining the experimental contexts in which liposomes were used (i.e. publication type, Medical Subject Headings (MeSH)) and the latter the cited references and the detailed authors' affiliations. The search query and the main trends are detailed in the appendix (see Figure 4). The sample is composed of 22,683 publications released between 1972 and 2014. With their respective references, 500,864 publications connected through 1,030,630 citations and making up the publication network (see subsection 6.1.1 in the appendix for more details). The delineation between the different sources of insights relies on the MeSH and publication types characterising scientific publications on PubMed. Table 1 introduces the MeSH terms used to determine the knowledge accu-

mulated in the laboratory when liposomes were used as research tools and the publication types used to delineate between preclinical and clinical experiments involving liposomes for medical purposes. I selected publication types based on their definition in the NIH library to tag all sources of clinical observations and the different animal models used in preclinical testing. With regard to the selection of the MeSH term, I selected those that referred directly to the definition of liposomes based on the NIH glossary, which provides different synonyms and concepts[2]. Here, I assume that the publications with liposomes related MeSH only relate to research findings without specific medical purposes.

Table 1: Delineation of experimental contexts

Experimental settings	MeSh, Publication types
In vitro: simplified conditions	Membranes, Artificial; Membrane Lipids; Cell Membrane; Membranes; Phospholipids; Lipid Bilayers [MeSH]
In vivo: intermediate conditions	mice, rats, dogs, primates [Publication type]
Clinical: complex conditions	clinical trials, phase I; clinical trials, phase II; clinical trials, phase III; clinical trials, phase IV; randomized clinical trials; validation studies; case report; evaluation studies; multicenter and observational studies [Publication type]

The patent data comes from the Patent Network Dataverse dataset (Li *et al.* 2014). This dataset provides harmonised and cleaned inventors' names associated to USPT0 patents from 1975 to 2010. The strategy of delineating the sample is disclosed in subsection 6.1.2 in the appendix. The sample consists of 2399 patents granted from 1975 to 2006. The patent network is composed of the set of selected patents and their respective references (10,730 patents in total), connected by 30,193 citations (see subsection 6.1.2 in the appendix for more details). I paired author-inventors' activity to track the sources of relevant knowledge and thus solve technological bottlenecks. I used a two years' time-window (e.g. before or after filing a liposomal patent) and differentiate inventors' equipped with an experimental background through different colours on Figure 1 (see subsection 6.2 for more details in the appendix). If experiments are hardly replicable, this makes it difficult to pin point the mechanism responsible for failures or successes. However, being involved in experiments

[2]Data collection was achieved in 2014 following the classification and hierarchy provided by the MeSH tree edited in 2014. Replicating the same search query today may provide a few variations in the MeSH terms. For more details, see https://www.ncbi.nlm.nih.gov/mesh/68008081

may shed light on a few liposomes properties. The step(s) taken to prepare liposomes or related experiments provide insights about into liposomes designs and their underpinning properties. Those properties may inspire solutions to solve technological bottlenecks by representing a "small latent stock of knowledge" in individuals conducting experiments (Agrawal 2006).

4 Results

The results of the Main Path analysis simplify the evolution of scientific and technological advances in two main trajectories composed of 255 patents (Figure 1) and 173 publications (Figure 2) respectively. The research efforts mapped on Figures 1 and 2 show the importance of combining insights from different experimental contexts: Figure 2 shows the key role of authors involved in early liposomal experiments and those from clinical settings in re-orienting research efforts. Similarly, Figure 1 illustrates the importance of author-inventors in initiating the first formulations for preclinical testing and for medical use and later, in refining those. Even if less visible than on Figure 1, inputs from the use of liposomes as research tools were used to solve numerous technological bottlenecks. Relying on well-understood properties accumulated in simplified conditions of use (research tools) helped to overcome the uncertainty linked to the formulation for chemotherapeutic use. Building upon these properties expanded the knowledge base towards disconnected bodies of knowledge to solve medical bottlenecks.

The interpretation of the results builds upon the citation network analysis (e.g. contexts of experiments in Figure 2 and inventors' publication activity in Figure 1) and the contents of abstracts associated to the patents and publications composing these two trajectories. The key results were cross-validated by reviews from the field (Weinstein 1987; Barenholz 1998; Gomez-Hens & Fernandez-Romero 2006; Wagner & Vorauer-Uhl 2011; Allen & Cullis 2013; Gregoriadis 2018) and two experts from the field (T.Allen and D.Deamer). Table 2 summarises the main problems, sources of insights, and solutions prevailing over time in adapting the purpose of liposomes to cancer chemotherapy.

4.1 Recombining knowledge across experimental contexts

Evidence from experiments on animals shows the potential of using liposomes in cancer chemotherapy. However, this evidence lacked validation in preclinical testing (see subsection 2.2.2). The main issue that needed to be resolved concerned the stability of liposomes in the bloodstream. Their initial use as a cell membrane model inspired the first design that tackled this stability issue by coating liposomes with cholesterol (Barenholz 1998). This led to the emergence of "conventional liposomes" (see Figure 1 and cluster A on Figure 2). Besides enhancing their resistance, a relevant formulation should also fulfil commercial objectives to limit production costs. Technological efforts focused on solving three related issues: stability, sterilization, and scaling-up methods (see the cluster C on Figure 1). The related scientific practices (i.e. experimental designs, methodologies) of using liposomes as research tools inspired how to solve technological bottlenecks: for example, methods to split liposomes in microbiology provided the basis to produce liposomes within a given size range at the industrial scale (Wagner & Vorauer-Uhl 2011).

4.2 Clinical observations: refining use and new applications

After positive results in preclinical testing, conventional liposomes entered in clinical trials in 1987 but exhibited a limited therapeutic efficiency in terms of stability and targeting power. Without scientific insights to explain this failure, clinical trials helped to re-orient the direction of scientific and technological efforts. The medical researchers involved in clinical trials decided to observe in real-settings which formulation was the most appropriate one (conventional vs Stealth liposomes). Stealth liposomes (see Figure 1) came from new advances in the field of new polymers (PEG) in the late 1980s (see Figure 1 and cluster B on Figure 2). However, no neat results emerged from preclinical studies regarding their higher stability vis-a-vis other designs. Clinical observations shed light on the clearance mechanism related to the lack of conventional liposomes stability (see Figure 2). This property was then examined in the laboratory: covering the liposome surface in PEG makes them "invisible" in the blood circulation, avoiding their clearance.

Table 2: Main sequence of problem-solving over time

	Cluster	**Sources of insights**	**Design and use**
Problems	**A**		
	1. Can liposomes fulfil a medical purpose? 2. How to design liposomes resistant enough for diagnostic purposes? Which is the most appropriate formulation?	In vitro and in vivo, clinical observations In vitro and in vivo In vitro and in vivo	vaccine in liver disease different designs different designs
	B		
	How to design liposomes resistant enough for chemotherapeutic application?	Material sciences (polymer)	Stealth liposomes (cancer)
	C		
	Which is the most appropriate formulation? Focus on sterilization, stability and scaling-up	Clinical observations	Stealth liposomes (cancer)
	D		
	How to refine and to expand liposomal chemotherapeutic applications?	Chemical and drugs, Clinical observations	Stealth liposomes (different cancerous diseases and beyond cancer)
	E		
	Can liposomes achieve active tumour targeting?	In vitro, in vivo, immunology	Immunoliposomes (active targeting in chemotherapeutic use)
	F		
	Can liposomes achieve active tumour targeting?	In vitro, in vivo	Theranostics (active targeting in chemotherapeutic use)

Stealth liposomes were used to achieve the first accelerated market approval - Doxil® - which aims to fight against an orphan form of cancer (see cluster C on Figure 2). After its market approval, several observations from clinical practice showed that stealth liposomes tend to cluster around the tumour cell without merging with it (see cluster E in Figure 2). In absence of scientific justification to favour specific formulations, this clinical observation led to two main types of technological alternatives that combine complementary technologies to enhance therapeutic efficiency. The first regime is based on relying on specific drug properties to increase the therapeutic effects (see clusters D in Figures 1 and 2). On the contrary, clusters E and F describe different technological designs that actively aim to target tumour cells by exploiting insights gained from diagnostics. Both trajectories (diagnostics and treatment) merge in the clusters E/F in Figure 1 via the emergence of "immunoliposomes" (e.g. design coated with molecules to bind to cancerous cells) and "theranostics" (e.g. designs with features from diagnostics and pharmaceuticals). Both approaches draw upon the previous knowledge accumulated in the first career of liposomes. Immunoliposomes rely on basic knowledge regarding cell markers and ligands, while theranostics formulations turn properties observed in cell biology (e.g. membrane leakage with pH, gradients, temperature change) into drug-controlled release solutions. This source of inspiration explains why author-inventors are more numerous in these developments by recombining insights from experiments towards medical applications.

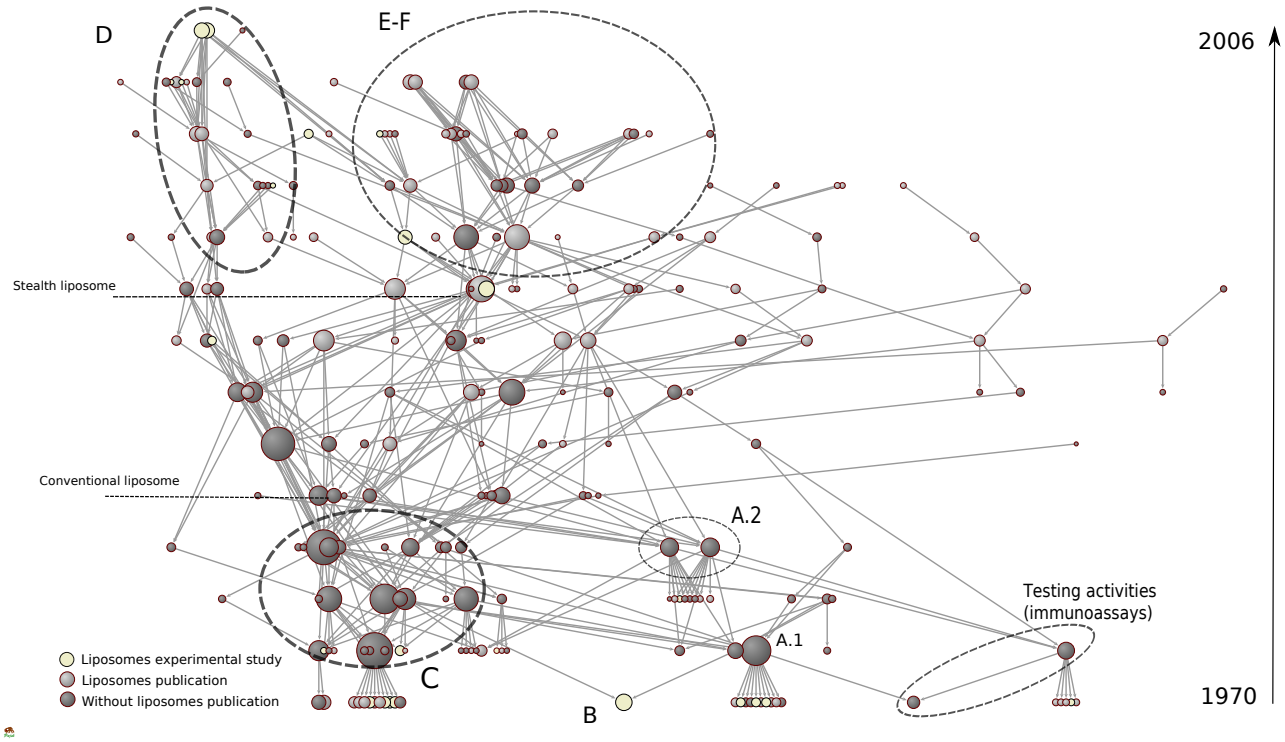

Figure 1: Main technological solutions and inventors' source of insights to develop liposomal chemotherapy

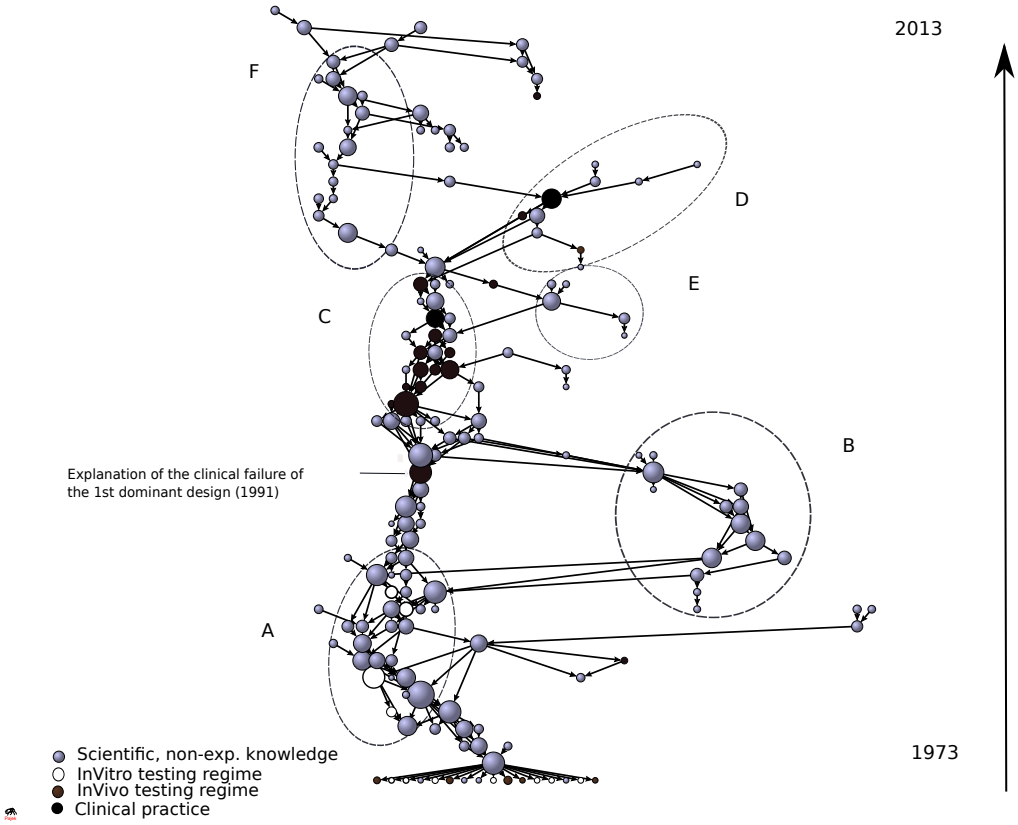

Figure 2: Main problems and contexts of research activities in adapting liposomes to cancer chemotherapy

5 Discussion

The analysis of the sequence of problem-solving shows that the different bodies of knowledge involved for research purposes - and not medical ones - were used to solve technological bottlenecks. These properties were involved as "background knowledge" (Pavitt 1998): tacit skills underlying liposomal experiments were recombined to solve medical technological problems. This echoes findings made in previous contributions (Nelson 2008; Rosenberg 2009; Price 1984), which suggest that instruments represent carriers of technical knowledge across disciplines and organisational boundaries. The uncertainty that remained after the market approval gave a strong role to complementary technologies to improve cancer chemotherapeutic applications. Previous contributions linked to medical devices show that trial and errors were used to adapt technologies for medical purposes (Gelijns & Rosenberg 1999). If a radical uncertainty remains about the design to favour, merging technological features (Barberá-Tomás & Consoli 2012) and combining existing and complementary technologies (Mina *et al.* 2007) represent two strategies to cope with this. This case study shows that therapeutic developments can draw upon the same logic. If science cannot guide technological efforts, complementary technological bodies are integrated or merged. Relying on known properties reduces the uncertainty that arises from the lack of replication in preclinical testing. Beyond the replicability issues, the belief that liposomes will fail due to toxicity issues reduced the involvement of big pharmaceutical companies in technological efforts. An earlier failure of a competing drug delivery technology (e.g. polyclonal antibodies) called into question the use of such technologies among a large range of health agents (Gregoriadis 2018). This also explains the scientists' persistence from the early days of liposomal research in fuelling technological efforts. Finally, clinical trials have played a crucial role in redirecting technological efforts. The translation to the clinic has been the result of several factors summarised in the two paragraphs below.

The access to the bedside - Drug development is an expensive process due to the intensive period of testing activity in preclinical and clinical settings. Testing acts as a proof of concept of the intended use and is heavily regulated by national agencies, such as the Food Drug Administration in the USA. This is particularly the case for anticancer drug development due to the nature of the compounds involved. Those imply a trade-off

between therapeutic benefits (e.g. tumour shrinkage) and the toxicity issues linked to this type of molecule. Liposomal formulation did not lead to additional complex testing guidelines, except for the emergence of a test in vitro to demonstrate their therapeutic benefits (Narang & Desai 2009). This reduced the additional amount of testing activities combined with the Orphan Disease clinical trials criteria, which eased the access to clinical learning.

The acceptance in the clinic - The changing career of liposomes benefited from a wide acceptance from medical practitioners. The delivery of liposomal chemotherapy did not modify the clinical routine used (injection) and the existing standard to evaluate the treatment success (e.g. tumour shrinkage). By following the same clinical routine, the introduction of liposomal chemotherapy did not legitimise another rival medical specialty that could have been a barrier of adoption (Gelijns & Rosenberg 1999). Furthermore, Gregoriadis (2018) stresses the importance of the establishment of a dedicated research group in clinical settings in the 1970s in initiating an early dialogue between the bench and the bedside (see Cluster A.1 in Figure 1).

6 Conclusion

The study introduces a new methodology to understand how a technology plagued by replicability issues could achieve its translation to the clinic. Its application in a case study highlights the importance of bridging insights across experimental settings and, particularly, clinical feedback. By doing so, technological efforts can be redirected to cope with the uncertainty linked to the lack of replicability. The analysis maps the dynamic and non-linear characteristics of the medical innovation process described in Gelijns & Rosenberg (1994) and Nelson *et al.* (2011). The methodology developed constitutes a first step in measuring the importance of testing regimes within the medical innovation process. The qualitative analysis of the results suggests that the delineation between the different experimental testing contexts underestimates the actual role played by testing in simplified and intermediate conditions (e.g. in vitro use for scientific purposes vs animal testing). The structure and composition of citations in preclinical studies further enhance

this underestimation[3]. Further medical innovation studies may consider additional MeSH and publication types to increase the number of relevant studies in preclinical testing. However, relying on the MeSH tree structure to delineate technologies and the importance of testing in simplified conditions is an interesting avenue for further medical innovation studies.

The study extends the innovation strategies found among medical devices to pharmaceuticals by illustrating that merging features and complementary technologies play a leading role in coping with uncertainty (Mina *et al.* 2007; Barberá-Tomás & Consoli 2012). In order to do so, bridging the bench and the bedside was necessary to recombine properties observed in different settings in an innovative way. While the case study stresses the importance of building networks across experimental settings, publishing is another important channel of knowledge diffusion. The workload related to teaching, patient care, and research reduces the amount of time that clinicians have to publish their findings. Impact factors in clinical journals are further enhancing this by reducing incentives to codify observations (Brown 2007). Consequently, clinicians bear the cost of diffusion only if they consider the related scientific contribution as being valuable enough (von Hippel *et al.* 2017). The current scientific organisation, incentives, and reward system question the capacity of benefiting from clinical feedback. Further studies may better consider these institutional aspects on the dynamics of medical innovation process.

[3]Preclinical and clinical references are mostly composed of protocols and toxicity guidelines with less scientific references than other disciplines. The assumptions linked to citation analysis are then likely to decrease their importance.

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Appendix

6.1 Delineation of the samples

The empirical analysis of the case study relies on publication and patent data that have been crossed via the author-inventors' activities. The figure below summarizes the key steps and respective sample sizes:

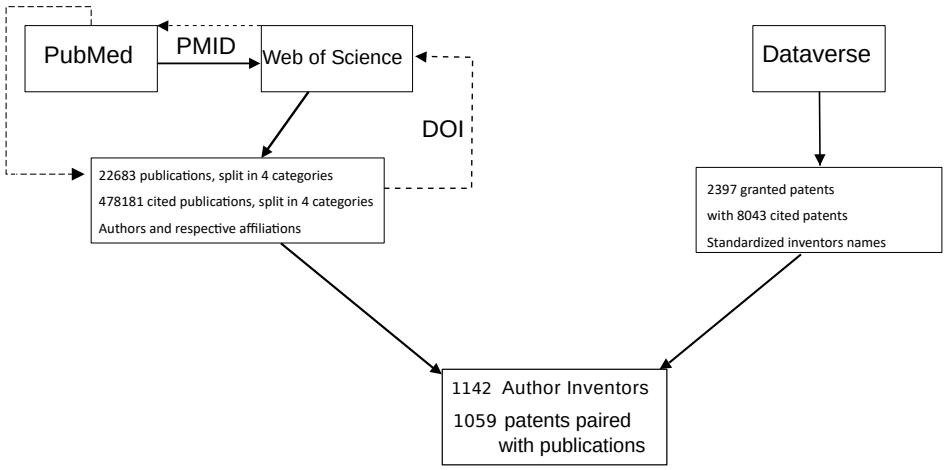


Figure 3: Data collection strategy

6.1.1 Publications

The publication sample was collected by using Web of Science and PubMed reocrds in November 2014. Publications have been selected by combining a set of MeSH terms that refers to liposomes and cancer therapeutics. Considering the number of disciplines involved in liposomal research, the strategy to delineate publications aims at focusing the search towards the most relevant knowledge pieces used in the developments of cancer chemotherapy. The MeSH terms used are based on the MeSH tree edited in 2014 and were mostly selected based on the synonyms and related concepts to liposomes. Only one term has been added (e.g. "enhanced permeability and retention effect") due to its importance in the clinical applications of liposomes based on historical reviews (Weinstein 1987). Only US authors' contributions were considered to be able to increase the chances to match the authors' information with patents. The following keywords have been to used to delineate the set of publications related to develop cancer chemotherapy:

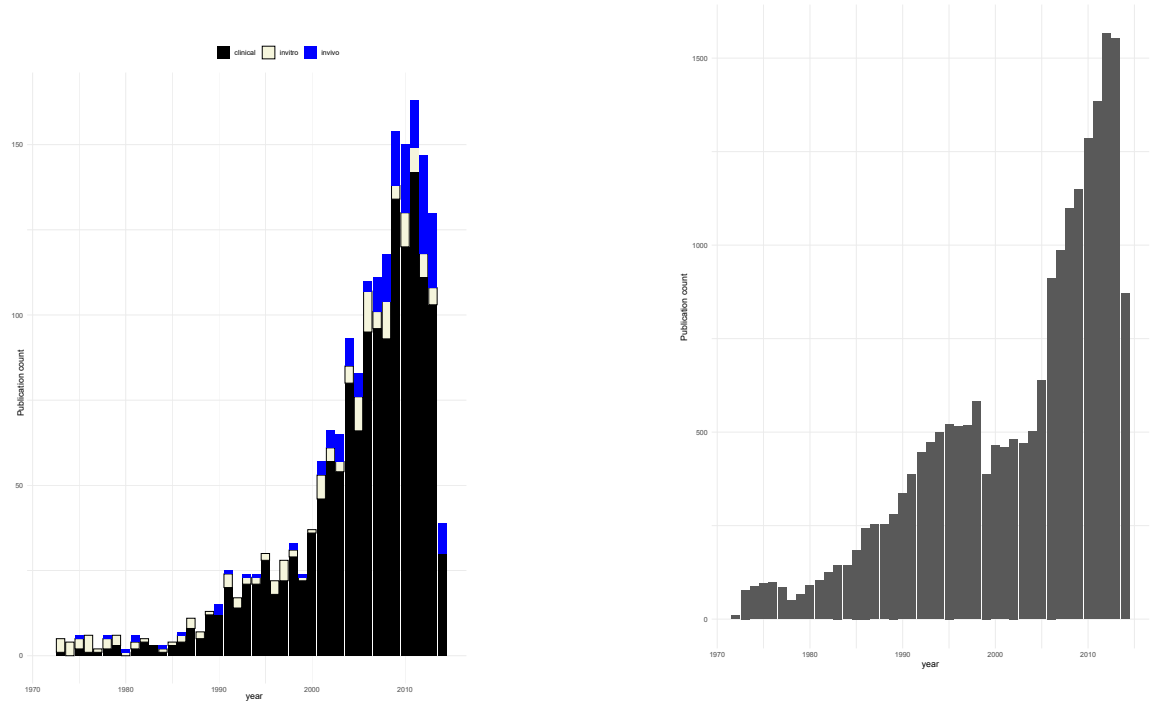
("Liposomes"[MeSH] OR "Liposomes"[Pharmacological Action] OR "Phospholipids"[Mesh] OR "SPI-77,liposomal"[Supplementary Concept])

AND

("Antineoplastic Agents"[Pharmacological Action] OR "Antineoplastic Protocols"[MeSH] OR "genes, Tumor Suppressor"[MeSH] OR "early detection of cancer"[MeSH] OR "cancer vaccines"[MeSH] OR "chemotherapy, cancer, regional perfusion"[MeSH] OR "neoplasms"[MeSH] OR "enhanced permeability retention" [all fields])

Figure 4 introduces the main trends in publishing across experimental and non-experimental contexts. The early days of liposomal research reflects the numerous fields involved by covering all contexts of experiments (i.e. laboratory, preclinical, and clinical). The publication activity follows the dynamics of knowledge over the innovation process: the failure in clinical trials in 1987 stimulated the need for answers regarding the underpinning mechanism. Similarly, the scientific investigations following the first market approval slow down before increasing in the 2000s during which clinical observations question the capacity of lipo-

somes to cluster at the tumour level. On the contrary, experimental knowledge plays a leading role in the early days of liposomes research, either as a research tool, or connected to clinical investigations (vaccines). The production of experimental knowledge intensifies after the market approval ("post implementation period" Gelijns *et al.* (1998)) to refine existing formulations.



(a) Experimental settings

(b) Without experimental purposes

Figure 4: Publication trends over time

6.1.2 Patent data

The Patent Network Dataverse is available online on the Harvard depository[4]. The 2011 version has been used. As shown in previous contributions (Gelijns & Rosenberg 1999; Nelson *et al.* 2011), incorporating related technological advances in the medical field is an important innovation pathway. Following this argument, patents have been extracted if their main, or one of their secondary, technological class(es) refers to 424/450 that explictly consist of lipid bilayers which corresponds to the physical definition of liposomes. Overall, 2722 patents have been granted between 1975 and 2010 with a technological application related to liposomes. Among them, 1209 have the class 424/450 while 1513 refer to this class as a secondary technologies categories. In this subset, the majority of applications refer to 424 and 514 (Drug, bio-affecting and body treating compositions), and 435 (Chemistry: molecular biology and microbiology). Despite a large scope of technological classes associated to liposomes, their relative importance in the sample is secondary vis-à-vis the three above mentioned (see Figure 5 for more details). The analysis focuses on the period 1975-2006 to increase the comparability of the citations patterns across the different

[4] https://dataverse.harvard.edu/dataset.xhtml?persistentId=hdl:1902.1/15705

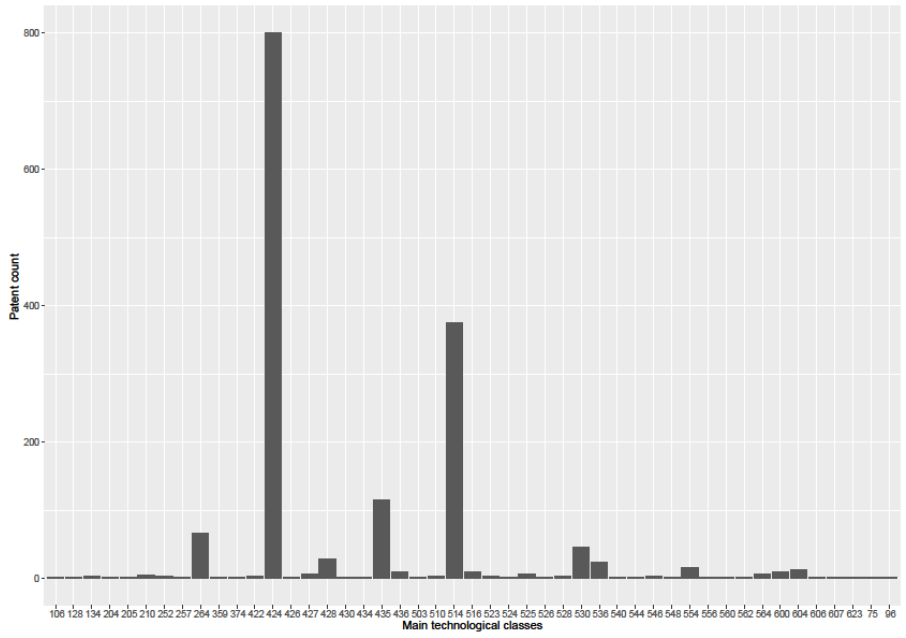


Figure 5: Distribution of main technological classes in liposome patenting

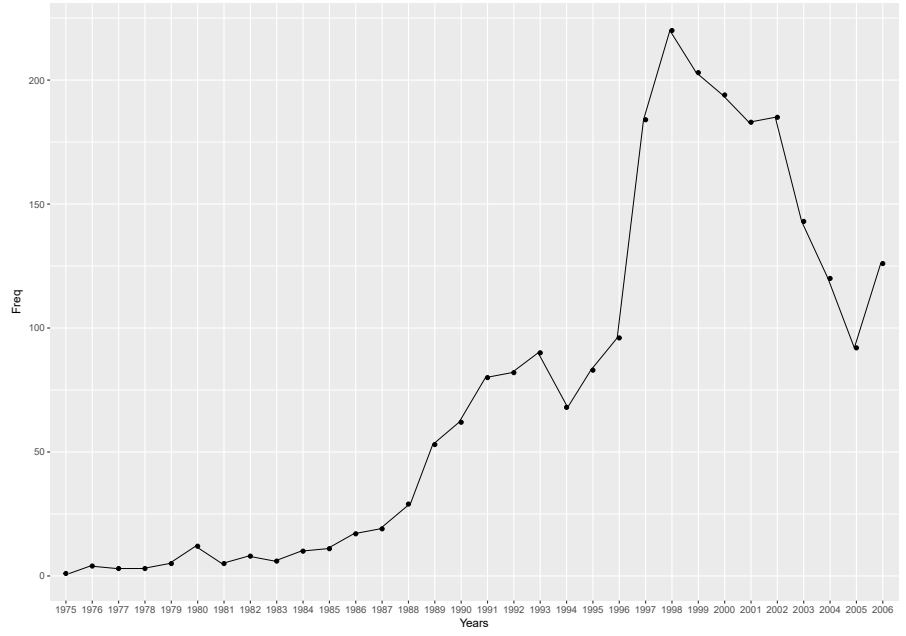


Figure 6: Distribution of granted patents over time

generations of technological efforts over time (see Figure 6). A 5 years time-window is assumed to be necessary to provide enough time to a patent to be significantly cited. The strong initial increase in patenting activity relates with the first accelerated approval in 1995 (Doxil). The decline that occurred short after in the 2000s is linked to a boom of spin-off technologies (Mozafari & Khosravi-Darani 2007) which changed the definition of liposomes as lipid bilayers and their belonging to the 424/450 class. The citation network analysis relies on 2399 patents citing 8333 distinct patents. This network of 10730 patents is connected by 30193 arcs (citations) leading to an averaged connectivity of 5.63.

6.2 Pairing publication and patents

The related inventors' information (i.e. first name, middle name if existing, last name) from the patent data is used to match the author' information by looking at authors with US affiliations only. Doing so bounds the matching exercise to one country (e.g. the USA) and one technological field to reduce the risk of homonymy in pairing patents and publications. To do so, I rely on a 2 years time-window between the inventor's patent application and a related paper co-authored by this inventor. A difference in the release of a paper related to a patent could reflect a journal (or field) specificity, or specific agreement with industry for example. I find 1142 distinct author-inventors (see the Figure 7), associated to 1059 patent applications with at least one related publication.The patent-publication pairing identifies 1855 publications involving inventors. When multiple publications were paired to a patent, their respective types (e.g. experimental vs non-experimental purpose) are aggregated at the patent level. If a patent is paired to at least one experimental publication, the patent is assumed being inspired by insights from experiments to balance the over-representation of non-experimental publications within the sample. Aggregated at the patent level, 193 patents draw upon insights from experiments and 866 without specific experimental purposes. Within the most important technological trajectories presented in Figure 1, I find 111 patents linked to a publication, 27 with experimental related purposes in the lab or the clinic, and 84 without experimental purpose.

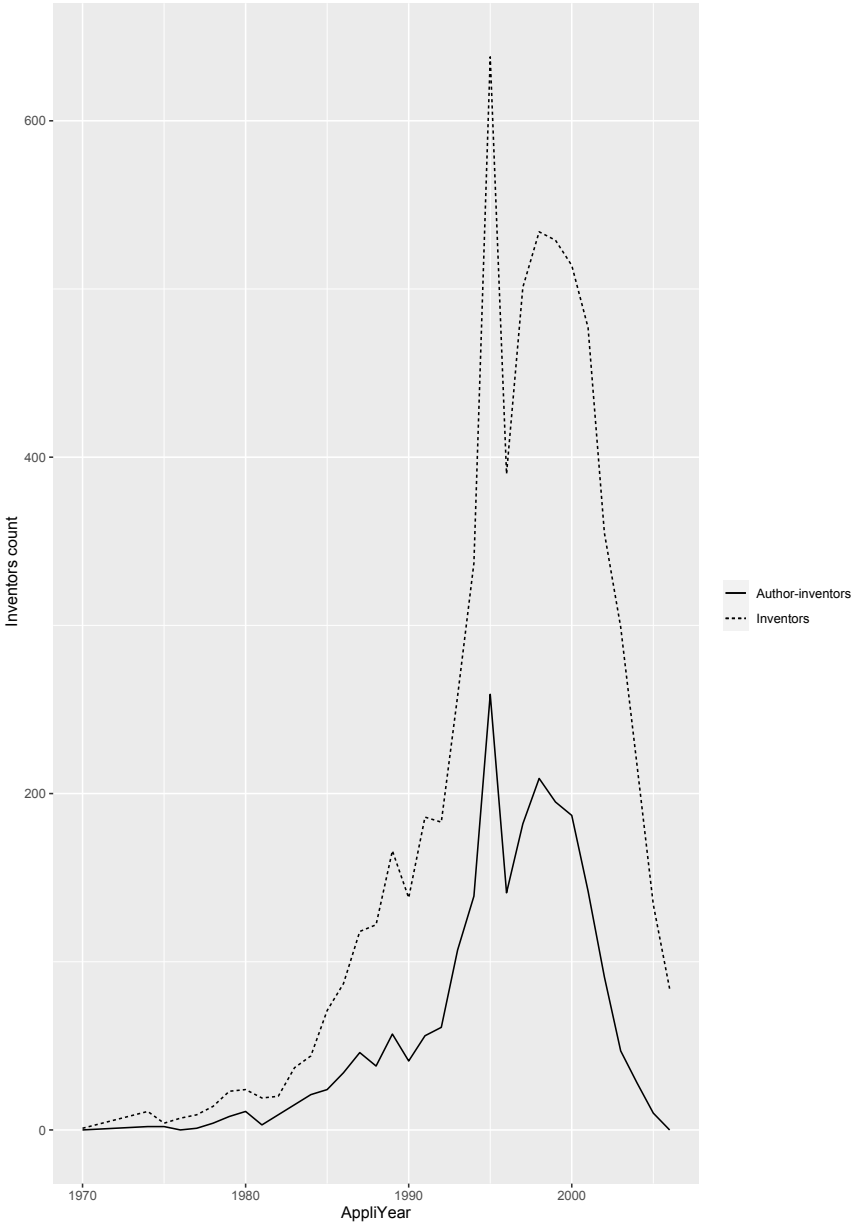


Figure 7: Distribution of inventors and author-inventors over time

6.3 Citation network analysis: The Search Path Count in defining the structural properties of the network

The Search Path Count method has been developed by Batagelj and is available on Pajek software[5]. This procedure relies on a previous approach elaborated by Hummon & Dereian (1989) who develop and compare different methods to assess the importance of a node within a given network. The Search Path Count is the most efficient method, and the least dependent approach regarding the network size (De Nooy *et al.* 2018). First, the Search Path Count detects all vertices that are "sources" (nodes which only cite) and "sinks" (nodes which only receive citations) according to the structure of citations. The algorithm computes the total number of paths between all sources and vertices based on their respective citations. Then, the algorithm assigns a value to the different paths by measuring the number of times a given path is followed. The frequency of passing through a given path is determined by the structure of the citations within the network. This step defines the transversal counts of the arcs between the different nodes to define the most important nodes of the network (Main Path). The size of the nodes is defined according to their relative importance within the network.

6.3.1 Main trajectory in scientific and technological advances

The main path (MP hereafter) analysis simplifies the sequence of problem-solving that faces the medical actors over time. The MP algorithm identifies the highest weights among the different paths described in the previous section to detect the most important pieces of knowledge. When the largest transversal weight is found, the algorithm selects the arc with the highest weights in its neighbourhood. The algorithm processes backward, starting from the latest period, until reaching the earliest period. The implicit assumption is the following: "a citation that is needed in paths between many articles [patents] is more crucial than a citation that is hardly needed for linking articles [patents]" (De Nooy *et al.* 2018, 282). The MP is supposed to reflect the most important junctions of knowledge, assuming that knowledge flows through citations.

[5] http://mrvar.fdv.uni-lj.si/pajek/

6.3.2 Main Path: limitation and extension

Despite its popularity in innovation studies, the MP approach represents an oversimplification of the main developments and provides a very narrow-focused perspective about the main developments of a given field. This extreme simplification can be overcome by relaxing the maximization approach: the extended version of the MP (main subnetwork or self-organized map) contains important pieces of knowledge which are ignored by the maximization approach. This extended version underlines the different paths explored to solve a given problem, such as dead-ends or variations of solutions, which are on average less cited. In this study, a threshold of 0.02 for publications and 0.003 for patents have been used. 21 disconnected patents have been removed from Exhibit 3 because their interpretation is limited without being connected to other nodes within the network. Their emergence in the results is mostly explained by the line cut chosen which focuses on the most important citations but does not insure that all nodes will be connected with the rest of the network.

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