

WHATEVER WORKS: UNCERTAINTY AND TECHNOLOGICAL HYBRIDS IN MEDICAL INNOVATION.

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ABSTRACT

The persistent clinical uncertainty that characterizes medical innovation provides important insights beyond the health arena and for the broader framework of evolutionary approaches to technological change. This paper focuses on the intimate connection between uncertainty and the process of hybridization, defined as the embodiment of multiple competing operational principles within a single device. We argue this type of solution and the associated problem solving emerge as a response to persistent clinical uncertainty about the performance of competing operational principles. Stated in conditional programming language, hybridization corresponds to “if you do not know which one is better then choose all”.

The history of the intervertebral artificial disc, a surgical prosthesis used in the treatment of spinal pain, offers important insights into the hybridization of technologies under persistent uncertainty. The paper presents the case of the only hybrid artificial disc that has been approved for use in regular clinical practice.

1. INTRODUCTION: CLINICAL UNCERTAINTY AND MEDICAL INNOVATION.

Scholarly interest on the dynamics of innovation in medical science and practice has been burgeoning for well over a decade. Early work in the 1960s corroborated the notion that the spectrum of activities underpinning technology creation and diffusion, in medicine and in many other areas, proceeded in a linear and unidirectional fashion from

basic research through to adoption and use. Over the years such a view attracted considerable criticism. First, the link between R&D and technology adoption portrayed as one-way route neglects the influence of end-users who, instead, have been observed to be better at articulating needs and devising alternatives to meet them (Von Hippel, 1976); furthermore, developments in science and technology are embedded in specific contexts of use which drive the direction and the timing of invention (Rosenberg, 1976); as such contexts likely features specific constraints, learning develops unevenly across areas of expertise (Nelson, 2003). In turn, such constrained interdependencies cast significant uncertainty on the adoption and development of new technologies as perhaps best captured by the existence of translational gaps. Finally, the production and legitimization of medical knowledge are embedded also in the long-term developments of individual disciplines and therefore reflect the social relevance that is attached to health problems by different professional communities at specific points in time (Blume, 1992; Gelijns et al, 2001). From this it follows that the design and implementation of novel medical solutions depends on the creation of agreement, or harmonisation of disagreement, within and across different professional groups (Rosenberg, 1989; Webster, 2002). By and large these remarks contribute to shift the frame of reference towards the remit of studies on innovation and technological change.

From this perspective medical innovation is understood as implementation of solutions to emerging problems; such solutions are rarely if ever uniquely circumscribed events but rather trajectories of improvement sequences along which procedures are progressively refined and extended in their scope of application (Dosi, 1982). By extending their range of application and improving practice solutions challenge existing know-how or open the way to previously unexplored domains. A key notion in this approach is the long-term learning process that drives the exploration of emergent design spaces and the application of contingent know-how (Metcalf et al. 2005; Mina et al. 2007; Consoli and Ramlogan, 2008). As new unforeseen hurdles emerge on the way to the practical implementation of solutions, medical know-how calls upon different types of practitioners carrying experiences and competences and fuelling different visions. This implies that the power of theoretical understanding in relation to medical problems is often severely circumscribed, and that practice and experience play a major role in shaping the growth of knowledge in many medical fields. Indeed it is not uncommon that innovation sequences halt when the contingent problem is beyond the

existing capabilities or possibly awaiting a breakthrough in some hitherto unrelated body of knowledge to restore momentum to the innovation sequence. Accordingly a central ingredient in the study of medical innovation is the appreciation of problem-solving as engine of knowledge growth. Paraphrasing Simon (1969), problem-solving in medicine entails pursuing clearly defined goals (e.g. cure or prevent illness) through routes that Dosi and Egidi (1991) would call ‘procedurally uncertain’.

In this framework the nature of the problem, or better the assortment of problem typologies, shapes the task structure, that is, the clinical modalities toward which efforts are directed (Elstein et al, 1978). But problem-solving is also multi-dimensional whereby as some problems are solved others range into view and become new foci of innovative efforts within the broad objective to improve the efficacy of the overarching procedure. Advances in medical know-how involve hierarchic search whereby meta-problems (e.g. heart failure, blindness) set the broad goal and channel subsequent efforts in search of a solution and, possibly but not imperatively, an explanation on disease. To operationalise this concept we propose that the medical problem-solving heuristic involves the definition of meta-hypotheses, or working frameworks, that circumscribe the broad operative principles of the disease area at hand. The history of medicine shows that search processes within such meta-spaces likely generates multiple sub-hypotheses, some contradicting some complementing each other, some stemming as articulation of specific features within the broader model others speculating on observations that do not fit within the prevailing meta-hypothesis. It is not infrequent that sub-hypotheses develop into meta-hypotheses once demonstrated that perceived irregularities fit into a coherent revision of disease (Rosenberg, 1990). Because ex-post selection among different paradigms is a lengthy process hypotheses and styles of practice tend to co-exist over periods before some are discarded off in the long-run, or before two hypotheses are merged into one (Elstein et al, 1978).

Recent work on medical innovation draws insights from the history of engineering, especially works by Constant (1980) on the turbine power and by Vincenti (1990) on aeronautics design (see Consoli and Mina, 2009 for a review). The appealing concept therein is that of an autonomous engineering epistemology, that is, of a body of technical knowledge not subservient or derivative of science but organized according to its own dynamics, principally that of problem-solving. Nelson (2003; with Gelijns, 2010) transliterates these concepts into the realm of medicine by arguing that traditional

scientific inquiry on biochemical processes offers no more than a point of reference for medical research, and that the route through to workable solutions relies mostly on the development of capabilities to testing, implementing and diffusing novel diagnostic and therapeutic techniques. In this view scientific instrumentation has a central role in that it enables replicable experimentation thus guiding emergent modalities of inquiry (De Solla Price, 1984; Rosenberg, 1992; Gelijns and Rosenberg, 1994). This strand of research marks a significant point of discontinuity with the traditional literature on health technology diffusion by arguing that successful clinical modalities are independent from advances on basic scientific understanding concerning the nature and the causes of disease (Nelson, 2003; 2008; Nightingale, 2004). Inherent in this approach is also the uncertainty that permeates the endeavor of both cognitive and practical discovery: borrowing from Metcalfe (2010), innovation scholars portray technology as inseparable from the limitations of human agency.

Whatever the level of state-of-the-art, solutions to health problems ultimately have to stand the test of the clinical environment. This implies among other things that current understanding of a medical issue be translated into a set of specifications for clinical performance. Some of such specifications are explicit and consist in sets of parameters for characteristics, like blood pressure levels, to which instrumentation for measurement can be easily; other types of specifications relate to operational aspects, like how to make a surgical incision, whose operational characteristics are ill-specified and therefore are not amenable to scaling. Such cases call for recursive learning in practice and systematization until a set of criteria can be established (Vincenti, 1990).

This paper is concerned with the uncertainty that permeates the operation of medical technologies when some type of performance characteristic is ill-specified, and with one of the practical strategies that are adopted to overcome such uncertainty, hybridization – defined here as the embodiment of competing operational principles within a single device. The “operational principle” of a technology describes how it achieves its general goals¹; as acutely observed by Murmann and Frenken (2006:939), operational principles allow categorization of a set of artifacts into general product classes. It is argued here that hybridization is a form of problem solving that emerges as a response to persistent

¹ For example, the base principle of the first successful human flight was proposed by Cayley in 1809 to: “separate lift from propulsion by using a fixed wing and propelling it forward with motor power. The central idea was that moving a rigid surface through resisting air would provide the upward force countering gravity.

clinical uncertainty about the differential performance of the competing principles of a therapeutic solution. The problem-solving spaces of hypothesis and therapeutic principles allow the use of different “operators”² to achieve the goal state (Klhar and Simon, 1999; Baldwin and Clark, 2000) Although it is not clear that scientific hypothesis can be hybridized,³ we argue that one operator at hand in the therapeutic technology space is to join different principles in a single device, i.e., to produce an hybrid.

Studies of technological hybridization can be classified in two temporal perspectives. First, the broader perspective considers hybridization as a phenomena occurring during technological transitions, for example the hybrids between sailing ships and steamships which appear in mid XIX century, prior to the hegemony of the steam sailing (Geels, 2002) or in the transition between steam and electric power for manufacturing industries in late XIX century (Devine, 1983). Second, in a narrower time scale, hybridization has been considered as a process of *niche evolution* in a technological system. Hybrids emerge as new technologies which are developed in ‘niches’ of special applications belonging to broader technological systems. For example, Islas (1997) describe how gas turbines were developed at the first time as an auxiliary device⁴ of steam turbines, creating hybrid power stations of electricity generation. Geels (2002) describe some forms of ships created in 1820’s as hybrids between sailing ships and steamships where steam engines entered in the sailing ship as an auxiliary device. Pistorious and Utterback (1997:72) describe these hybrids as a temporary form of symbiosis between the old and the new technology. In this symbiotic relationship, the new technology has a positive effect on the old technology, helping the latter to improve its performance in a special application. At the same time, the new technology can be further developed in the niche. The symbiotic relationship disappears with time, or even inverse its terms. Examples of the former are steamships, which finally eliminates sails from their configuration. Examples of the later are co-generated power stations, where

² Operators are “actions that change existing structures into new structures in well-defined ways. They are like verbs in a language or functions in mathematics: by their powers of conversion (this turns in to that), they define a set of trajectories, paths or routes by which the system can change” (Baldwin and Clark, 2000:129)

³ As they could be *strongly divergent* (Bonaccorsi, 2008). i.e., they cannot be true together.

⁴ The auxiliary function was to super-charge the conventional power station boilers with the heat contained in the exhaust gas of the gas turbine (Islas, 1997)

gas turbines take the role of the main component and stem turbines the role of the auxiliary device.

Although the first perspective of hybridization as a transition can be easily generalized to all technological fields, some perplexity exists for what concerns lack of generality of the symbiotic niche evolution perspective. First, it can be applied only to technological systems since niches can only be developed inside these kinds of broader systems. More importantly the niche perspective has mainly been associated to energy generation systems (e.g. for transport or manufacturing) where “demonstration effects” are easier to conceive and measure (Islas, 1999; de Bresson, 1991)⁵. We argue for a more general roles for hybridization - besides their apparitions as symbiotic niches in technological systems- if we account for the fundamental role of persistent uncertainty in medical innovation. The long lapses of absence of clinical knowledge about some ill-specified aspects of the performance of therapeutic operational principles can offer insights about the design strategies used in all the technology fields where this “demonstration effects” are not available for long periods. Further, because it is focused at single medical device level where hybridization can be understood in relation to the operational principle and not relegated to special applications.

As Joel Mokyr (1998) pointed out in his work about medical innovation, a strategy to face uncertainty is to have “available”⁶ different operational principles which are of not real use in the current conditions but can be useful in the case of future changes. Hybridization is a way to have efficiently “available” all operational principles – even those that are apparently incompatible - which can contribute in the face of persistent uncertainty by joining all them together in a single device⁷. Let us make a very simple

⁵ One of the most famous “demonstrations” of this kind was a bet about the performance of the first full-scale working railway steam locomotive in Pennydarren, in 1804 (Weightman, 2010). Looking at more specific cases, Islas (1999:134) mentions gas turbines which were introduced in the energy system of aeroplanes as a special application (in the super-charge of the main conventional engine) because its use was often producing a 35% increase in the output power of the aircraft.

⁶ Of course, Mokyr acknowledge that the set of “available” operational principles to use in face of changing environment is “not a just a set of blueprints that firms and individuals can pick and choose from freely, but an underlying knowledge set, far more complex and multidimensional” (Mokyr, 1998:131).

⁷ Our concept of hybridization is slightly different than the “availability” concept of Mokyr. The example given by Mokyr to illustrate his concept is the one of “junk” DNA. DNA contains big parts of “junk” code, in the sense that it does not have any apparent function in the phenotype. But when environmental conditions change, this DNA can be “useful”: “The human gene uses only about 1 percent of the DNA; the rest seems to fulfill no obvious function, but changes in it may at some point in the future become

exercise of formalization. In a if-then logic, the niche theory of hybridization as temporal symbiosis during technological transitions says: “If the new operational principles has demonstrated its competence in one element of the system, then use it”. Our view of hybridization is more general and more centered in uncertainty. In a “if-then” logic, our concept of hybridization goes “if you do not know which operational principle is better, then choose all”.

The rest of this work is structured as follows. Due to the central role of uncertainty in our framework, next section is dedicated to study the clinical and technological uncertainties related with the artificial intervertebral disc, a device used in surgical treatment of spinal pain. Section 3 is dedicated to study hybridization in the artificial disc in two ways. First, we perform an in depth case study of the most important hybrid disc design to illustrate the fundamental relationship between hybridization and uncertainty. Second, we use a patent database to identify the role of hybridization in the history of the artificial disc. Section 4 concludes.

2. UNCERTAINTY AND THE ARTIFICIAL DISC

Degenerative disc disease (DDD) concerns the painful effects of physiological changes in the discs separating the vertebrae. This degenerative process, due to ageing but also individual propensity, is the main cause of back pain and disability in the United States (Errico, 2005). Arthroplasty is the surgical replacement of the degenerated and painful disc with an artificial prosthesis.

The rationale for the artificial disc design is rooted in spine biomechanics which “provide the foundation for the disciplines of spine medicine and spine surgery” (Naderi et al., 2007:392). Modern methodologies appeared in the second part of the 20th century included laboratory tests with cadaveric, synthetic or animal models and computer simulations of healthy, diseased and instrumented -with surgical implants- spine segments (Naderi et al., 2007). However, clinical experience has been relevant since at least since 1935 when Pauwels published a treatise on the surgical osteotomy of femoral neck, a procedure based in a biomechanical rationale (Maquet, 1980). The importance of the clinical knowledge stands out clearly in the preface of the handbook of spinal

useful” (Mokyr, 1990:123, note 7). Our concept of hybridization at least suppose that the operational principles joined in the hybrid device have more than purely random possibilities to success.

biomechanics, conveniently titled “Clinical Biomechanics of the Spine”, in particular where it states that clinical biomechanics “combine clinical experience and observations with scientific data in order to improve patient care” (White and Panjabi, 1990: xiii).

The rationale for the design of the spinal artificial disc (Figure 1) stems from the deleterious biomechanical consequences of DDD. Although disc degeneration is not totally understood there are two dominant explanations, one chemical and the other biomechanical, (Bono and Garfin, 2004).

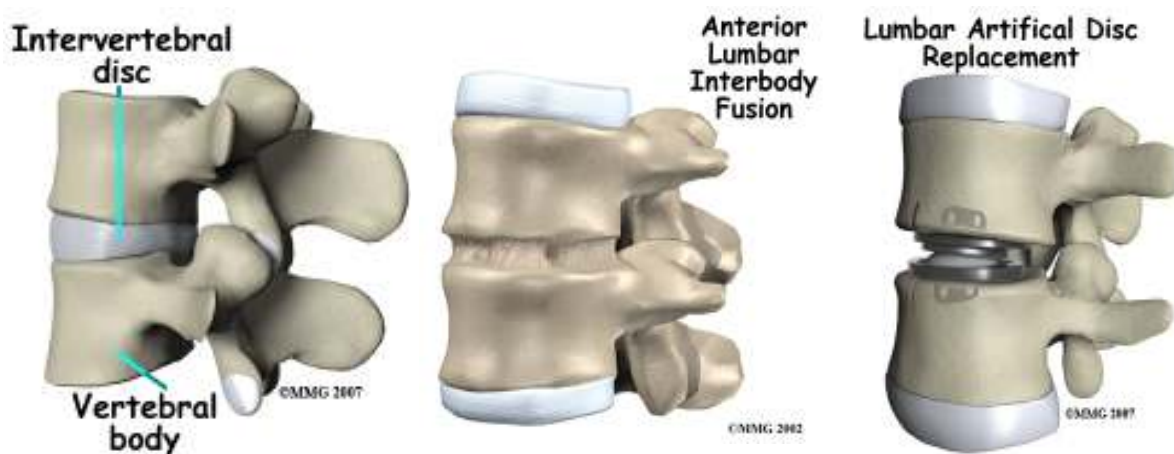


Figure 1: From left to right: a vertebral segment made up of two vertebrae and the intervertebral disc; the arthrodesis or osseous fusion; the arthroplasty or substitution of the disc with an implant (Source: <http://www.eorthopod.com/>)

The mechanic meta-hypothesis comprises two complementary explanations: the first is known as kinematic and refers to the movement of the spinal disc without taking into account the forces that produce the motion, the other is dynamic and is concerned with the combined effect of motion *and* loads. According to the kinematic explanation emerged at the beginning of the 1970s (Mulholland, 2008) DDD caused abnormal movement in the disc which in turn triggered pain. The rationale of the artificial disc therefore is to restore normal movement by supporting a failing structure. Besides few trials between the 1960s and the 1970s (Spalzschi et al., 2002) artificial discs have been adopted in European clinics only after 1989⁸. The use of X-rays to assess the implanted

⁸ The first artificial disc was approved to use in US in 2004, although an IDE (investigation device exemption) was conducted in late 80's, when the first European artificial disc were implanted. This clinical trial ultimately failed. We will account for the geographical aspects of invention of in our narration of the evolution of the artificial disc.

disc allowed greater availability⁹ of clinical data (Griffith, 1994). Randomized clinical trials routinely include comparative assessments of mobility pre- and post-surgery as well as evaluations of quality of life and disability scores. The correlation between mobility and good clinical results facilitates inferences about the role of the restoring of spinal motion through artificial disc implantation (Zigler et al., 2007; Heller et al., 2009).

The second biomechanical explanation is based on a strong emphasis of the anatomic disc's dynamic properties, specifically the load absorption of its cartilaginous articulation. To mimic anatomic load absorption, the theory goes, the artificial disc should reproduce the viscoelastic properties of a healthy disc. Early indications of the importance of this specific aspect in the disc functionality date back to the early 1970s (Urbaniak et al., 1973.) but although it is demonstrated in isolated natural discs (Virgin, 1951) clinical uncertainty persists about the effective load absorption in an anatomic vertebra-disc-vertebra segment like the one depicted in Figure 1. More specifically, the uncertainty concerns the specification of clinical standards to assess this specific disc property and, a fortiori, its restoring through surgery. This is likely due to the difficulty of measurement of load absorption in clinical and even laboratory environments. In 2003, Le Huec et al. (2003:347) affirmed that there were not “any available data” about load absorption properties of the human intervertebral disc. Since then, to the best of our knowledge the only laboratory study which has analyzed the role of load absorption in the normal disc and compared it with the artificial disc dynamic behavior is relatively recent (Dahl, et al., 2006). This study used invasive force sensors installed in cadaveric model of spine units instrumented with artificial discs (Figure 2). The difficulty of installing this equipment inside the human body can explain the total lack of clinical knowledge about the load absorptions properties of the natural and the artificial disc.

⁹ The standard radiographic method currently used to describe spinal angular motion was described by Cobb in 1958.



Figure 2. Testing equipment used by Dahl et al. (2006).

Uncertainty about the load absorption properties of the natural and artificial disc lies at the core of the design rationale of the two different operational principles that have been proposed for surgical replacement. The operational principle that first reached regular clinical use is the one which we refer to as ‘hip-like’. This operational principle is based on the design developed by Sir John Charnley in the 1960s for hip prostheses (Büttner-Janz, 2003). Charnley ball-and-socket configuration transform the substitution of the hip articulation with a prosthetic implant in one of the most successful surgeries in the world. The success of the hip implant soon spreads through other artificial articulations –as the knee or the shoulder- which adopted the Charnely principles. These developments created both the orthopaedic surgery medical specialization and the industry in charge of supply the surgical implants for this kind of interventions as we know them today (Miller, 2002). The artificial discs which follow these principles have rigid contact surfaces in the form of a ball-and-socket articulation, and are made of similar materials to hip prostheses, i.e. metal or relatively rigid plastic, such as the UHMWPE (Figure 3).

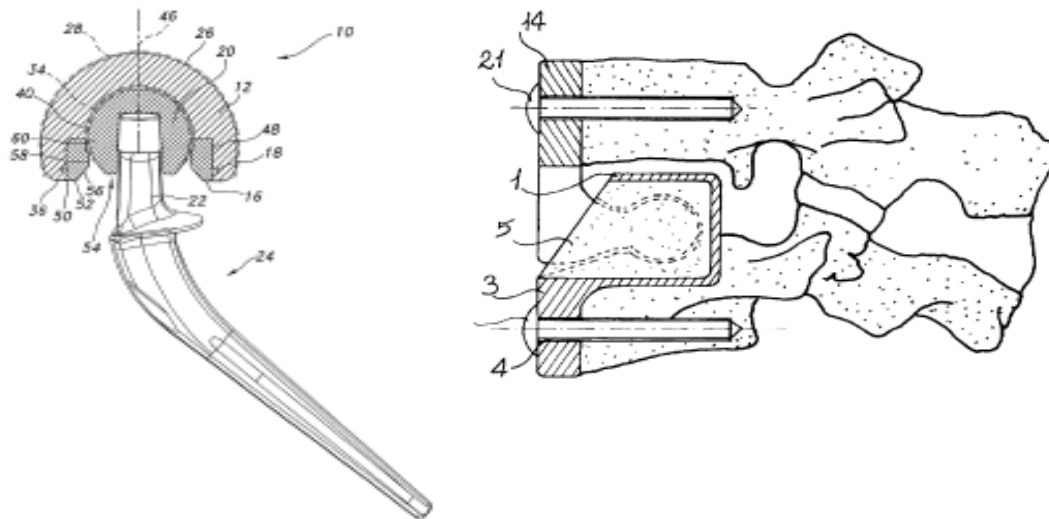


Figure 3. On the left, a hip prosthesis. On the right, a disc prosthesis following the ‘ball-and-socket’ principle of hip implants (Source: US6986792 and US5755796).

Although these discs provide mobility to the intervertebral segment, the use of the rigid surfaces made these kinds of discs incapable of any effective load absorption (Le Huec et al., 2003). The SB Charité hip-like artificial disc was the first artificial disc to be commercialized, both in Europe and US. In Europe was used since 1989 (David, 2002), and in US was finally accepted for clinical use in 2004 (FDA, 2004).

The alternative operational principle, which we call ‘mimetic’, only began to be used in normal clinical practice in Europe in 2007 and is still not approved for use in US. Although mimetic discs have persistently failed to reach the sphere of regular clinical use until 2007, in the last 3 decades numerous R&D projects have been dedicated to the development of discs based on this operational principle, mainly in US (Szpalski et al., 2002; O’Reilly, 2008).

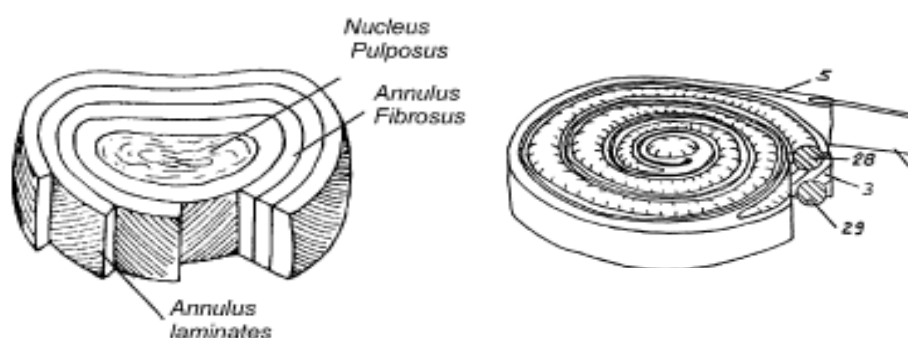


Figure 4. The diagram on the left shows an anatomic intervertebral disc. The diagram in the center shows a “mimetic design” based on the reproduction of the viscoelastic properties of the anatomical disc, using materials such as synthetic elastomers (Source: Eijkelkamp, 2002, and US6610094).

Mimetic-type artificial discs attempt to imitate the articulation properties of the anatomical disc not only in its movement, but also in its load absorption properties (Figure 4). However, as we have seen there has been a persistent uncertainty about the effective load absorption of the natural and artificial discs. The theoretical arguments favoring one or other operational principles are marked by this fundamental uncertainty. For advocates of the hip-like disc, the absorption of load in the anatomical disc (if it exists) is irrelevant, and the prosthetic restoration of movement is sufficient (Mayer, 2005). For advocates of the mimetic disc, artificial discs that do not absorb load lead to biomechanical problems and related painful symptoms which often implied re-operation (Lee and Goel, 2004).

Apart from the uncertainty about this specific aspect of artificial disc performance (load absorption), until now -to the best of our knowledge- there are no more general clinical or laboratory studies comparing the performance of the two operational principles of the artificial disc. This can be due because the research efforts of developers and clinicians have been dedicated to prove the efficacy and safety of the artificial disc comparing it with the procedure which has been the surgical gold standard of DDD treatment until the apparition of the disc prosthesis, i.e., arthrodesis or bone fusion of two vertebrae through the intervertebral space (Figure 1). Advocates of the artificial disc argue that bone fusion cause biomechanical alterations which could lead to degeneration in the adjacent discs (the so-called ‘adjacent disc degeneration syndrome’) and the need for more surgical intervention. It has been argued that artificial disc devices can cannibalize the fusion devices market related with surgical treatment of DDD (Biondo and Lown, 2004). Several randomized studies with control group -which provide the highest degree of clinical evidence (Freeman et al., 2006)- have been devoted to compare the clinical outcomes of bone fusion and artificial disc procedures¹⁰.

3. HYBRIDIZATION AND THE ARTIFICIAL DISC

3.1 A case study about a hybrid disc

As we have seen in our theoretical framework, hybridization can emerge in situations of persistent uncertainty. In the case of the artificial disc, we are interested in the

¹⁰ In its evidence-based guidance for the use of the artificial disc, the National Institute for Health and Clinical Excellence (NICE) identified 5 randomized controlled trials comparing artificial disc and fusion (NICE, 2009; NICE, 2010).

hybridization related to the uncertainty about the differential performances of the hip-like and mimetic principles. The classification of artificial discs into two operational principles similar to the ones we use appears in several studies about the history and design of the artificial disc. Bono and Garfin (2004) use the terms ‘articulated non-elastic discs’ and ‘elastic discs (with load absorption)’. Lee and Goel (2004) opt for ‘kinematic discs’ and ‘kinematic and absorption of load discs’. Szpalski et al. (2002) call them ‘artifacts destined to restore the kinematic functions’ and ‘artifacts destined to restore the viscoelastic functions’ respectively. But these last authors also unambiguously affirm that in the history of the artificial disc ‘of course some devices attempt to combine both principles’ (Szpalski, 2002:S67). Other documents that provide more detail on technological aspects also refer to the hybridization of the two principles, hip-like and mimetic. The state of the art review of patent US5314477 mention the possibility of “the combination of these two research routes” in the design of the artificial disc. The same section of patent US7563286 explicitly includes in its classification a hybrid category which incorporate different design principles.

We will expose our criteria to understand hybridization in the artificial disc studying the case of the Bryan artificial disc, the only hybrid artificial disc which has been approved for clinical use. We have validated our interpretations between the relationship between uncertainty and hybridization in interviews with 4 engineers involved in various ways with the design of artificial discs¹¹. The original idea that would lead to the Bryan disc was conceived by the North-American neurosurgeon Vincent Bryan. In the initial stage of the project, Bryan contacted Alex Kuntzle, a mechanical engineer from the metallurgic industry. In 1994, both applied for a patent which can be considered the first result of their investigation. In 1995, Bryan and Kuntz contacted several venture capital firms for funding the creation in 1997 of Spinal Dynamics (Boyd, 2002), a start-up devoted to the development of the Bryan Disc. In 1999, a representative of the company Medtronic Sofamor Danek (MSD) and Vincent Bryan meet during the annual meeting of the American Association of Spine, to arrange the sale of 14.7% capital of Spinal Dynamics to MSD, the largest proportion of the latter company in the hands of a single shareholder (Medtronic Sofamor Danek, 2002). In 2000 the Bryan disc undertook a

¹¹ One of these individuals was involved in the development of the Bryan disc in late 1990’s. Other was involved as a design engineer in one of the most important mimetic projects of the late 80’s, the Acroflex artificial disc. The other two are R&D engineers currently working in new artificial disc developments, one hip-like and the other one mimetic.

clinical study for obtaining the CE mark. In 2002 CE mark was conceded and the implant began to be used commercially in Europe, while began the clinical testing necessary to apply for FDA marketing approval in the United States (Biondo and Lown, 2004). That same year, 2002, MSD finally acquired Spinal Dynamics for 269.5 million dollars (New York Times, 2002). In 2009 Bryan disc was approved by FDA for its commercial use in US (FDA, 2009). Until 2010, there have been close to 35000 operations using this implant (data from interview).

We will study the hybrid configuration as depicted in the US patent 7025787, filled in 2002, the most recent published patent related with the Bryan artificial disc in our database¹². This patent has a configuration typical of the mimetic operational principle:¹³ one elastomer¹⁴ and two small metal plates that act as the disc-bone interface, trying to ensure the stability of the implant, like in the US5071437 patent related with the Acroflex disc, one of the most representative mimetic projects of the 1980's (Figure 5, left). Acroflex was tested in several experimental human trials, in 1988-1989, 1993-1994 and 1998-2000 (Fraser et al., 2004), but all these trials experimented failures related with the elastomers, provoking a general concern about the behavior of this elastomeric biomaterials in a sandwich configuration (Lee and Goel, 2004).

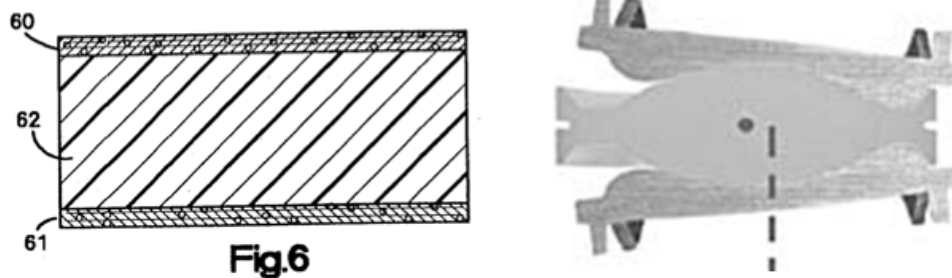


Figure 5. To the left, a classic elastomer/vertebral plates configuration of a mimetic patent related with the Acroflex project; to the right, a typical hip-like configuration (Source: US5071437; Link, 2002).

¹² The characteristics of our database are detailed in the next section.

¹³ E.g. in patent US3867728, the oldest US patent of the mimetic operational principle.

¹⁴ Elastomer refers to materials with mechanical properties (e.g. hysteresis) similar to rubber.

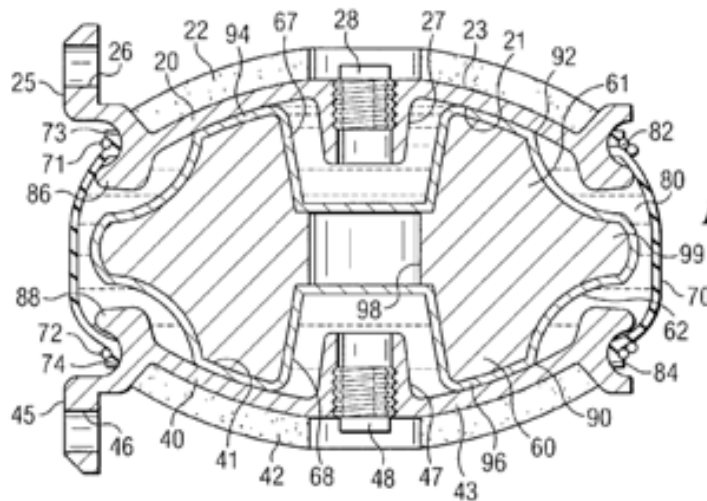


Figure 6. (Source: US7025787). Element 99 function is to absorb load, as in mimetic operational principle patents. However, instead of being joined to small plates 20 and 40, they move over them, as in hip-like patents. Element 70 is a membrane designed to avoid migration of particles from the movement of the articulation between 99 and 20-40.

But the design of the Bryan Disc also incorporates an important novelty with respect to the typical mimetic configuration, which is that the small plates can rotate relative to the elastomer, creating a ball-and-socket articulation as in hip-like artificial discs (Figure 5, right) while, in mimetic operational principle discs, the small plates usually are joined to the elastomers within in the same mould - or by means of a specific process, such as vulcanization - which leaves no possibility for relative rotation (Figure 6).

Hip-like projects were gaining momentum in the early 90's., at the same time the first bad results of the Acroflex project were published (Enker et al., 1993). First multicenter prospective results (non randomized) of the SB Charité disc, a lumbar hip-like design, were published (Griffith et al., 1994). In 1995 the Frenchay hospital in Bristol, UK, one of the most prestigious centres in the world for neck surgery, made public good experimental human results with a cervical prosthesis which also followed the hip-like principle (Cummins, 1998). It was in the middle of the concerning about the performance of the sandwich configuration of the mimetic principle and the apparition of the good results about the hip-like principle when the Bryan disc was conceived. As we have said in section 1, we understand hybridization as a way to have efficiently “available” all the operational principles –even the apparently incompatible- which can be of any help in the face of persistent uncertainty, by joining all them together in a

single device. Although apparently the hypothetical load absorption properties of the mimetic disc seemed to better reproduce the behavior of the natural disc, as we have seen there were no clinical data available which can demonstrate this circumstance. Besides, the hip-like principle was demonstrating its good clinical behavior in terms of quality of life of the patients and mobility of the instrumented level. Hybridization in the Bryan disc is an attempt to join the clinical advantages of the hip-like disc with the possible future advantage which could emerge if load absorption importance were finally demonstrated.

The hybrid character of the design can be recognized in a published interview with Dr. Bryan. There, the inventor affirmed that his intention was “to change the nature of the joint from an arthroial joint to restore something similar to diarthrodial joint” (Mutescu, 2002:8). Diarthrodial joints (or synovial joints), such as hip or knee, joints are freely moveable joints. Arthroial joints (or cartilaginous joint), as the spinal disc, only allow slight movements. Thus, Bryan is clearly describing a hip-like artificial disc. But at, the same time, Bryan claims that the artificial disc has to provide “cushion as the normal vertebral disc” (Mutescu, 2002:8). This last property, typical of the mimetic design can be found more clearly in the "Background" section of US7025787 patent (invented by Bryan, Kuntzler and other 6 individuals and owned by Medtronic) where is stated that the implant "should also provide elasticity and damping sufficient to absorb shocks and stresses imposed on it in a manner similar to that of the natural disc"¹⁵.

Figure 7 represents the hip-like, mimetic and hybrid principles in a design-service space (Frenken and Nuvolari, 2004; Castaldi et al., 2009). Design elements “represent the internal structure of the artefact and, in most cases, are the dimensions that designers take into consideration (e.g., in the case of the car, type of engine, type of suspensions, weight, etc.). Service characteristics, instead, are the “services” actually delivered by the artefact in which users are interested (in the case of the car, speed, reliability, comfort, etc.)” (Castaldi et al., 2009:550). The design and service spaces are connected by several relationships between their elements (Frenken, 2006). In the artificial disc, the services provided by the technology can be mobility, load absorption and the stability of the whole construct (Lee and Goel, 2004). The vertebral endplates are the design

¹⁵ In this patent also is stated that the goal of the invention is to transform a natural arthroial joint like the spinal disc in a artificial diarthrodial joint.

element providing the stability of the bone-implant interface (Bono and Garfin, 2004). In the hip-like principle, the ball-and-socket articulation is the design element providing the mobility of the intervertebral space. In the mimetic principle, the elastomer sandwich configuration provides both mobility and load absorption. But the elastic layer has also a deleterious influence on “stability” (dotted arrow in the map of the mimetic principle in Figure 7), reflecting the failures of the elastomer in the Acroflex disc, which compromised the stability of the implant. As we said before, in the mimetic design the elastomer and plate were joined in the same mould, leaving no possibility for relative rotation. This constraint created excessive loads on the elastomer and provoked its fracture and the failure of the whole construct (Fraser, 2004). The hybrid principle joins the ball-and-socket and the elastomer sandwich elements in a single device, providing mobility and load absorption like the mimetic principle but in a different way, as the vertebral plates are not joined to the elastomer but articulated in a ball-and-socket joint. Thus, the mimetic kind of failure of the elastomer, which compromises the stability of the disc-vertebrae construct in the mimetic principle, is avoided.

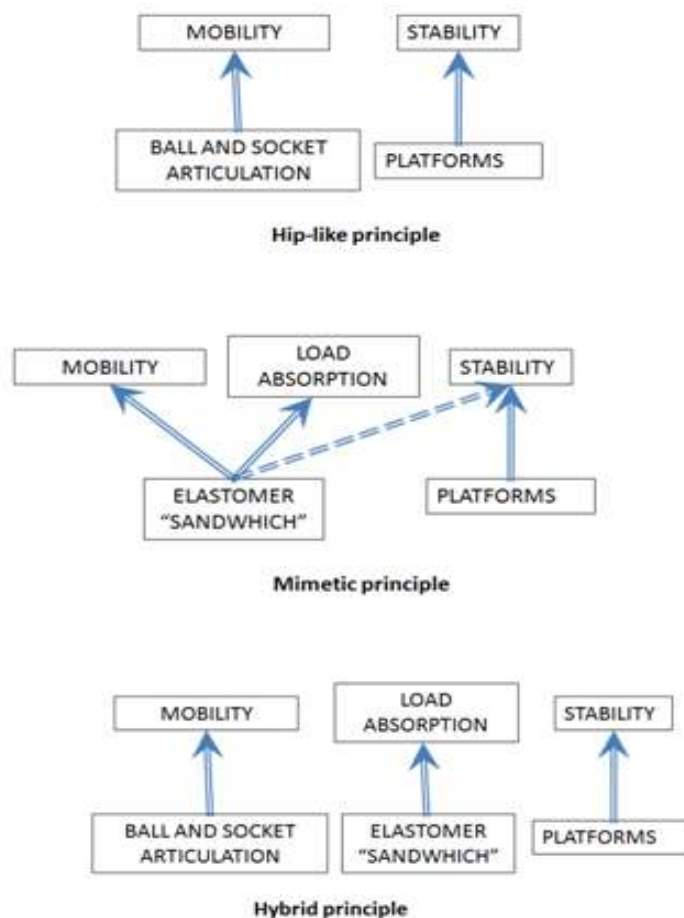


Figure 7. Design-service maps of the hip-like, mimetic and hybrid principles.

Of course, hybridization could not be done ‘automatically’: it needed a special design effort for joining in the same device two different principles. In Figure 6 appears a membrane (part 70) that is attached to vertebral plates. The function of the membrane is to prevent the migration of plastic particles from the hip-like articulation to the surrounding biological tissues. This migration was one of the major problems of the hip prosthesis prior to the introduction of UHMWPE as the plastic material to pair with the metal part of the articulation. The migrated plastic particles provoked dramatic allergic reactions which resulted in the systematic failure of hip implants. UHMWPE use transformed hip substitution from an almost experimental procedure into one of the most successful surgical procedures in the world (Gómez and Morcuende, 2004).



Figure 8. The Bryan artificial disc. Only the metallic vertebral plates and the external membrane can be seen .Source: Anderson et al., 2004)

But UHMWPE is a rigid plastic, incapable of providing significant load absorption (Le Huec et al., 2003). Thus, if the Bryan hybrid design wanted to include an hypothetical load absorption it needed another and more elastic material, as polyurethane. However, there were doubts about the biocompatibility of the particles of the employed polyurethane, which seemed to provoke a worse biological response than the UHMWPE particles (Naidu, 2007). The Bryan design had to include a membrane to avoid the deleterious effect of these polyurethane particles (Figure 8), creating an isolated capsule (Anderson et al., 2003). Hybridization meant also an extra design effort and a growth of complexity of the implant.

3.2 Hybridization through time

To further investigate the occurrence of hybridization in the history of the artificial disc we will use a methodology for analyzing patent citation networks, namely connectivity analysis (Hummon and Doreian, 1988; Verspagen, 2007; Fontana et al., 2009; Martinelli, 2008). In other work we explain the construction of a database of artificial disc patents and extensively apply connectivity analysis to the history of the artificial disc (Barberá et al., 2011)¹⁶. To sum up, connectivity analysis selected from the database the sequence of the most important patents in the evolution of the artificial disc (the top path, in red in Figures 9, 10 and 11). We considered that ‘a patent would be regarded as important if it opened the way to a successful line of further innovation’ (Trajtenberg, 1990: 184). We argued that in medical technologies this importance come precisely of the existence of any clinical evidence confirming the reliability of the knowledge content of the patent (Vincenti, 2000). This important and reliable knowledge signal the trajectory for further research. But prior to the first introduction in the market (i.e., the first innovation), by definition the importance cannot come from the feedback of clinical use; it comes exclusively from the laboratory trials with synthetic or animal models. After the first introduction in the market, the importance comes from the crucial feedback that comes from clinical use.

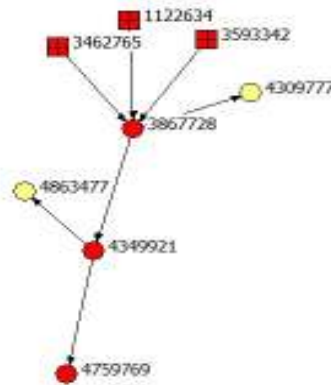


Figure 9: The Network of the Evolution of Top Paths (NETP) 1973-1987

¹⁶ We built our database using keyword searches and found 201 US patents granted for artificial discs before 2004. We searched for citations among these 201 patents. We use US patents for our artificial disc search as they are the only ones used in connectivity analysis so far.

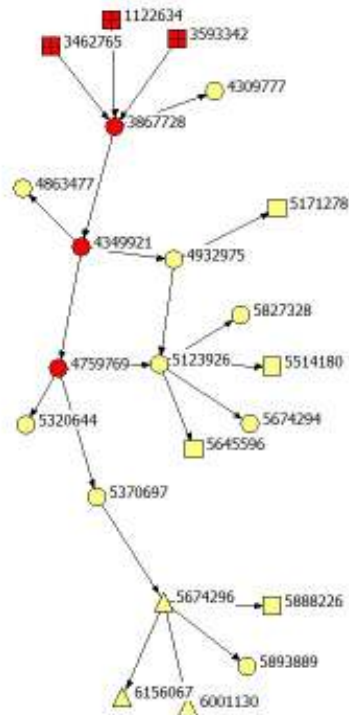


Figure 10: The Network of the Evolution of Top Paths (NETP) 1973-1997

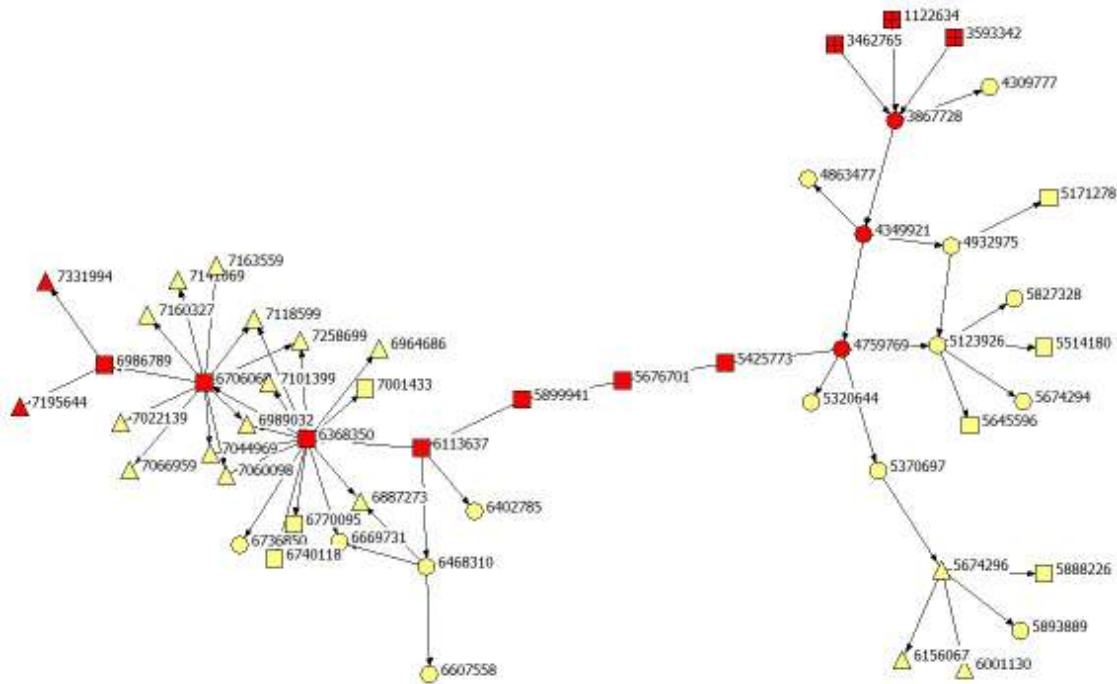


Figure 11: The Network of the Evolution of Top Paths (NETP) 1973-2004

To study the history of the artificial disc with the map of citations, we classified the patents in the network in hip-like (squares), mimetic (circles) or hybrid (triangles), following the technical criteria exposed in the Bryan case. In prior sections we showed

that in US the first phase of the evolution of the artificial disc –prior from the first market introduction of the SB Charité, a hip-like design, in Europe- was based on mimetic designs. These designs (the red circle patents in Figure 9) were important because gave the first feedback from the laboratory use of the discs. This knowledge could be recollected also by the hip-like developers, as it provided general insights about the simulation of the surgical procedure in the laboratory environment. For example, the patent inventors of the mimetic patent US4759769 -which holds a central role in the articulation of the network- are also the authors (Hedman et al.,1991) of the most highly cited scientific article in the patent database, which describes the mechanical tests devised to trial the artificial disc prosthesis described in the patent. It proposes the parameters for experimentation related to this prosthesis, but also others for artificial discs in general; the technical specifications for these tests were adopted 15 years later by rule F2356 of the American Society for Testing and Materials (ASTM) to regulate the mechanical behavior of all artificial discs (Dooris et al.,2005).

However, as we have seen, the most important US mimetic projects ultimately were aborted because of bad results in trials. Meanwhile, the first good results published of the use in Europe of the hip-like operational principle were published. Reflecting these changes, the trajectory of the top path was redirected from the mimetic to the hip-like operational principle (red square patents), which were clearly dominant in the top path since 1998 (Figure 11).

According to this interpretation the yellow patents are dead-ends which did not open the way to a successful line of further innovation. In Figure 10 we can see that inventors during the period 1987-1997 were exploring diverse possibilities: mimetic designs (yellow circle patents), hip-like designs (yellow square patents) and some hybrid configurations, represented by the three yellow triangles of the bottom of the figure, US patents 5674296, 6001130, 6156067. Patent US5674296 is the first patent associated to the Bryan disc project. Patents US6001130 and US6156067 are continuations-in-part of this first patent¹⁷. As we can see in Figure 11, finally this hybrid exploration was not reflected in the top path, which after 1997 was focused in hip-like patents. Last two hybrid patents are probably there due to the truncation of the patent data in the last years

¹⁷ Continuations permit an applicant to refill a pending patent application. Continuations-in-part are special kind of continuations which includes a substantial portion or all of the parent application and adds matter not disclosed in that application, although the benefit of early priority is awarded only for the original disclosures contained in the new application (Hegde et al., 2010).

(Verspagen, 2007) and do not necessarily mean a shift in the importance of hybrid designs.

Hybrid designs continue to flourish in the 2004-1997 stage, although not belonging to the top path. In figure 11 we can see numerous hybrid patents around the top path in this stage. These patents belong to three¹⁸ hybrid development projects (as in the Bryan patents, there were several continuations). The temporal evolution of the three operational principles of the patent network (hip-like, mimetic and hybrid) is represented in Figure 12.

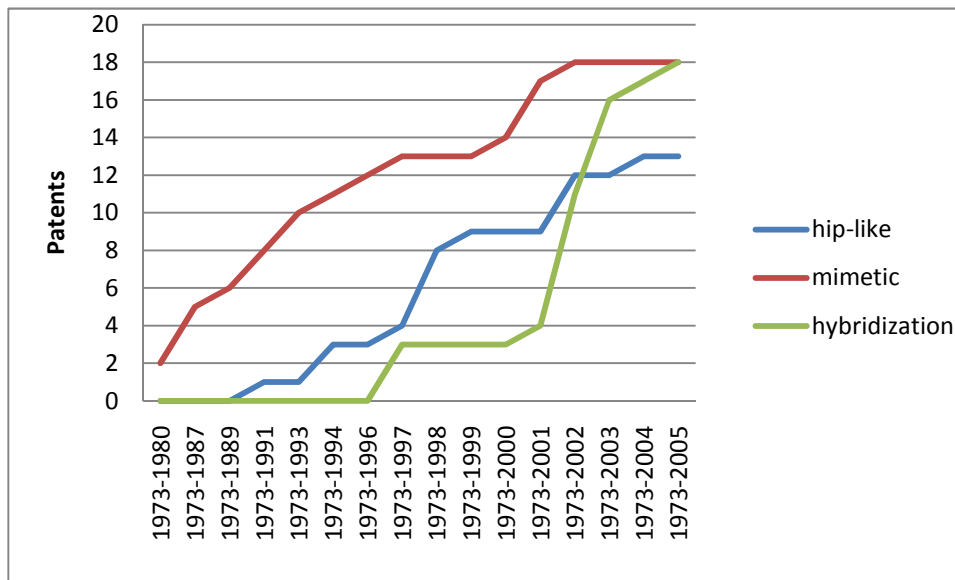


Figure 12. Mimetic, hip-like and hybrid patents through time.

As we have seen in Section 1.2, hybridization is often considered as an epiphenomena occurring during technological transitions. Our interpretation of the evolution of the network is that the hybridization effort represented by the apparition of the Bryan patents in the mid 90's was a transition of the invention activity between the dominance of mimetic projects in the 1980's and first part of the 1990's and the dominance of the

¹⁸ One of these projects was finally approved for clinical use as a hip-like design. We include it in the hybrid operational principle because the patents associated to the project include, apart from the hip-like realization, other realizations designed to include a load absorption effect.

hip-like patents after that. In first part of 2000's hybridization continued in other projects, but did not achieve clinical importance. Two important circumstances must be stressed about this interpretation. First, this is an interpretation for the 1973-2004 period. The history of the artificial disc is not still finished: in recent years, there has been a renaissance of mimetic designs, and two of them were approved for its use in Europe (in 2007 and 2009) and are currently performing pre-approval experimental trials in the US. This circumstance is not reflected in our citations map. Even it can be conceived that the persistent market success of the Bryan¹⁹ disc is a hybrid signal typical of a period of transition which is still not finished. Second, this transition interpretation is limited to the inventive activity in US, where mimetic projects were dominant in the 80's and where the Bryan project was developed. In Europe developers have been traditionally using the hip-like principle during all the period studied.

4. DISCUSSION.

As we understand it, technological hybridization –or the embodiment of multiple competing operational principles within a single device- is a problem-solving strategy used in the search for solutions in a extremely uncertain knowledge space. We showed that the ill-specified nature of many of the problems which medical technology faces offers an excellent opportunity to observe the hybridization process.

Let us grind our conclusive thoughts within the broader framework of engineering epistemology of Constant (1980) and Vincenti (1990). The notion of “Presumptive anomaly” proposed by Constant (1980:15-21) illustrates the role of aerodynamic findings in the transition from engine-propeller system to the turbine system. “By the middle 1920s, aerodynamics indicated that its own laws underwent violent change as the velocity of objects through the air approached the speed of sound. The incapacity of conventional aerodynamic theory to describe such conditions clearly implied that the propeller, the other part of the engine-propeller system, would not function at near-sonic speeds” (Constant, 1980:15). Therein, a “presumptive anomaly” creates a horizon for the development of a radical different system, i.e., the turbine, which could work in such conditions. It can be argued that the two deleterious biomechanical consequences -

¹⁹ In a industry report (Biondo and Lown, 2004), the Bryan disc was the second in a list of 9 lumbar/cervical artificial discs sold worldwide in the period 2000-2004, and the most sold cervical disc worldwide.

kinematic and dynamic- of arthrodesis or the extraction of a painful disc and its substitution with a bone bridge between two adjacent vertebrae (Figure 1), appear as “presumptive anomalies” fostering the development of the artificial disc. These kinematic and dynamic alterations provoked by arthrodesis can cause an “anomaly” in the normal behavior of the adjacent vertebral levels and the need of reoperation.

The kinematic anomaly related to fusion, i.e., the normal motion of the anatomic disc and the abnormal motion of the fusion-instrumented and adjacent discs can be determined by radiographic examination of the spinal column. However, as we have seen the basic hypothesis related with the load absorption properties has not been proved clinically so far. The “presumptive anomaly” in the case of these dynamic conditions is much more ill-specified than in the aerodynamic case or, in the artificial disc context, the kinematics of the anatomic disc. In our view this uncertainty can explain the variety of design efforts in the artificial disc case. In this case, some developments have obliterated the presumptive dynamic conditions and have adopted an operational principle from a very different articulation (the hip) which however seemed to provide both mobility and a satisficing (Simon, 1956) degree of clinical safety.

We argue that hybridization is a design strategy conceived to deal with these ill-specified conditions. Vincenti (1990:51-108) study about flying-quality specifications for Aircraft engineering deals with a conceptually similar problem: the need for these specifications became apparent at the beginning of the 1920s but no clear criteria existed as on how to measure and codify systematically these characteristics. Vincenti describes how engineering research gave way to a body of practice strongly complementary but not subdued to scientific knowledge about aerodynamics. As a result, a whole set of instruments were developed and test flying communities contributed to transform an ill-specified problem in a well-defined catalogue of specifications. In the case of the artificial disc, parallel efforts can be identified in the laboratory studies aimed at calibrating the dynamic properties of the anatomic and artificial discs (Dahl et al., 2006; Le Huec et al., 2003). At the same time the work of Vincenti does not deal with the airplane *design* community efforts during the period where the specifications for designing airplanes with acceptable flying conditions were not available. This paper has argued that hybridization is a design strategy applied precisely in these ill-specified conditions, as in the case of the dynamic properties of the

spinal disc. In the absence of clear-cut specifications designers can choose to embody all the operational principles in a single device with the proviso that some may turn out to be useful in the future. Under this perspective, the hybridization of the artificial disc represents an attempt to join the clinical advantages of the hip-like disc with possible future advantages of integrating the principle of load absorption even though no conclusive evidence exists on its real importance.

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