Measuring exaptation and its impact on innovation, search and problem-solving

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Abstract

Exaptation, the emergence of latent functionality in existing artifacts, is an underexplored mechanism of novelty generation in innovation. In this paper we measure the frequency of exaptation in the pharmaceutical industry. We find that about forty-two percent of new functions derived from existing drugs have an exaptive nature. We think that this constitutes the first measure of exaptation in any industry. We also link exaptation with radical innovation and find that most radical innovations in our sample are exaptive. Also nearly all radical innovations occur in market areas very distant from the drug's original market. We propose that exaptive innovation constitutes a different search mechanism and problem-solving approach from deliberate innovation and discuss the role of context and serendipity in innovation.

Keywords: exaptation, innovation, radical innovation, pharmaceutical industry, search, problem solving

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1. Introduction

Many essential discoveries in the history of science and innovation were the result of the often serendipitous emergence of new functions in existing artifacts when they were exposed to new contexts. The drug Marsilid originally designed to fight tuberculosis happened to greatly improve the mood of the patients taking it and became the first anti-depressant. This observation led to a paradigm change in our understanding of mental health—depression could be treated with synthetic chemicals—and to the establishment of a new field in the pharmaceutical industry. Similarly, Viagra was found useful against the problem of erectile dysfunction although it was developed as an anti-hypertensive drug. This discovery gave birth to a multibillion-dollar market of 'blue-pills' as the drug became the fastest selling in history. With its help, Pfizer became the fifth most profitable company in the U.S. (Loe 2004). The scientific and economic significance of these and numerous other examples emphasizes the need to better understand the usually serendipitous emergence of new functions in existing artifacts and its underexplored role in innovation. In this paper we attempt to measure the frequency and impact of this process in the pharmaceutical industry and its importance for firm strategy and the organization of the innovation process in firms.

Recent research has suggested to explore *exaptation* as an important mechanism of novelty generation (Andriani and Carignani 2014, Cattani 2006, Dew et al. 2004, Kauffman 2000). Exaptation is defined as 'the process by which features acquire functions for which they were not originally adapted or selected' (Oxford Dictionary). Anecdotal evidence shows that exaptation is important in innovation as many inventions, some of which radical, have been exaptive in nature. For instance, in the pharmaceutical industry, many breakthroughs and paradigm changes in treatment resulted from exaptations of previously introduced drugs. The microwave oven resulted from the discovery of a latent function of the radar magnetron (Osepchuk 1984) and the first amplifier was 'exapted' from De Forrest's Audion, originally designed for radio detection (Nebeker 2009). Exaptation thus constitutes a mechanism through which unexpected solutions 'push' the emergence of novel problems, instead of being 'pulled' from ex-ante problem formulation and search. To date, however, no study has quantified the frequency and impact of exaptation in innovation and assessed its role as an emergent mechanism of opportunity discovery. Is exaptation just 'an interesting but minor wrinkle' in

evolutionary theory as stated by Dawkins (cited in Gould 2002, p. 1019), or a fundamental mechanisms in the evolution of new technologies as Kauffman suggests (2000)?

Exaptation is important for several reasons. First, it is related to core issues in current organizational debates such as the processes through which firms are able to spot distant (and superior) opportunities on search landscapes, as well as those aspects related to the un-prestateable nature of these landscapes (Felin et al. 2014). Second, exaptation is related to serendipity (Dew 2009, Meyers 2007). Serendipity acts on existing entities by revealing some unforeseen possibilities and connections hidden in them as they become exposed to new contexts. In other words, serendipity uncovers potential exaptations. Thus, a measure of exaptation is also indirectly a measure of serendipity in innovation. While serendipity, by definition, is not intentional, policymakers and organizations may implement processes that favor 'the prepared mind'. Third, as exaptation refers to the discovery of a 'latent' functionality in an existing artifact, measuring its frequency helps us estimate the latent value in existing artifacts. Extracting such latent value is, theoretically, cheaper than creating new artifacts for new functionalities as the creation process itself is costly. Moreover, our approach gives scholars a base to assess the importance of exaptation in innovation. With a few exceptions (Cattani 2005, Ching 2016, Mastrogiorgio and Gilsing 2016), the research methods utilized so far are mostly qualitative and rely on anecdotal examples. They are therefore unable to provide a scale of the phenomenon. Measuring exaptation also improves our understanding of radical innovation (Andriani and Carignani 2014, Levinthal 1998). In Appendix 1 we report a selected list of exaptations that have shaped the evolution of the pharmaceutical industry. The first antiseptic, anesthetic, antibiotic, antidepressant, sedative, antipsychotic drugs were not invented but exapted from products already available in the market or in laboratories. Thus, exaptation is a source of radical innovation.

Our research resonates with broader and recurring questions in innovation, strategy and organizational theory, such as the recent tension between the importance of 'foresight versus luck' (Cattani 2006, Garud et al. 1997) or the old tension between 'deliberate versus emergent' strategic processes, where emergent processes are those 'realized despite, or in the absence of, intentions' (Mintzberg and Waters 1985). These tensions have re-emerged in two recent debates. Gavetti (2012)

has emphasized the role played by superior cognitive abilities, foresight and analogical thinking in the search for valuable opportunities. Winter (2012) instead stresses that serendipity and contextual factors are more likely to lead to valuable solutions. More recently, von Hippel and von Krogh (2016) have distinguished between traditional problem-solving (where problem formulation precedes search for solutions) versus the simultaneous identification of new problem-solution-pairs (NSP). Their perspective is critiqued by Felin and Zenger (2016), who predicate the primacy of a normative theory in problem-solving. We show that the exaptation perspective contributes to both debates. In particular, with regard to the first debate, our results show the limitations of analogical thinking and the intrinsic importance of contextual factors. Our paper also reframes the NSP contribution within the more general inverse innovation process (Wiener 1993) and anchors it within exaptation.

The rest of the paper is organized as follows. In section 2 we further explain the concept and theoretical significance of exaptation and review the extant literature. In section 3 we describe the empirical framework. Section 4 presents the results which are then discussed in section 5. In section 6 we discuss the main implications and section 7 presents the main limitations and concludes.

2. Literature Review

Alexander defines design as 'the process of inventing things which display new physical order, organization, form, in response to function' (Alexander 1964, p. 1): that is, form-follows-function. In this approach, firms develop new products after having identified a promising function that fulfills a market need. However, in many historical examples the order of the process is altered and a new function follows, not precedes, an existing form. For instance, the microwave oven wasn't developed after the idea of cooking by microwave occurred (form-follows-function). Spencer, an engineer working at Raytheon, serendipitously discovered in 1945 that a magnetron, a radar component, was responsible for the melting of a candy bar in his pocket and could be used for cooking (function-follows-form). Raytheon modified the magnetron for its new function and in 1947 introduced the first microwave oven (Osepchuk 1984). Similarly, the first anti-depressant drug didn't result from a process aiming to design a drug to alleviate depression symptoms. In fact, the idea that synthetic chemicals could influence the brain's physiology and pathology was heresy at the beginning of the

1950s (Tone 2008). The antidepressant function was serendipitously discovered when a drug designed to treat tuberculosis made patients euphoric. It was a piece of radar that generated the function of cooking-by-microwaves, and it was an anti-tuberculotic drug that generated the anti-depressant function. Several other examples are reported in Appendix 1.

In evolutionary sciences the function-follows-form process is known as exaptation (Gould and Vrba 1982). Exaptation has gained increasing attention in the innovation literature (Andriani and Carignani 2014, Bonaccorsi 2011, Cattani 2006, Gould and Vrba 1982). Gould and Vrba (1982) contrasted exaptation—the emergence of a new function for an existing trait—with adaptation, defined as the improvement of a trait through natural selection driven by a pre-existing fitness function. In the words of Gould and Vrba (1982: 6): 'We suggest that such characters, evolved for other usages (or for no function at all), and later 'coopted' for their current role, be called *exaptations*. [...] They are fit for their current role, hence *aptus*, but they were not designed for it, and are therefore not *ad aptus*, or pushed towards fitness. They owe their fitness to features present for other reasons, and are therefore *fit (aptus) by reason of (ex)* their form, or *ex aptus*'. The source of exaptation is the discovery of 'latent functions' of existing technologies, but discovery by itself is not sufficient to cause an evolutionary change. In several cases functional change is followed by a process of modification of the original artifact to optimize it for its new function. In the case of more radical exaptations, the second phase includes also the construction of a new niche for the artifact embodying the exapted function (Andriani and Cohen 2013, Dew and Sarasvathy 2016).

How many latent functions can an artifact have? Is it possible to anticipate—and therefore to 'pre-state'—all the functions that a product or artifact can engender? One of the most interesting aspects of exaptation is the role of 'un-prestateability': according to Kauffman (2000)—see also (Felin et al. 2014, Longo et al. 2012)—, the set of functions of any product depends on a complex interaction between the product, the context and the users. However, as the number of these interactions is un-definable, the number of functions is equally un-definable and therefore un-prestateable. Another interesting and yet neglected aspect is the role played by contextual factors in the search and discovery of valuable opportunities: as noted recently (Felin et al. 2014, p. 4), a recurring tension is that between 'organism centric' approaches—or human agency, broadly

conceived—and 'how much emphasis ought to be placed on the environment'. As we will see, this tension occupies a central place in the innovation, strategy, and organizational theory debate, and exaptation may represent the starting point for a new perspective.

Anecdotal evidence suggests that exaptation is also related to the emergence of innovations with a radical nature. Although the definition of radical innovation is hotly contested, there is consensus that it is based on a high degree of product innovativeness, which is 'a measure of the potential discontinuity a product (process or service) can generate in the marketing and/or technological process' (Garcia and Calantone 2002, p. 113). Moreover, it impacts both the macro and micro-environment (at the industry- and firm-level respectively). An important question, then, is whether exaptations have a radical nature. The answer hinges on the degree of novelty of the exaptation's emergent functions. Functions that are new to the world—such as the antidepressant functions of Marsilid or the microwave oven—have the potential to kick-start new industrial sectors and are therefore radical. In other cases, the underlying function may be new with respect to the technology, or the firm, but not new in absolute. This is the case, for instance, of the Gillette razor (Andriani and Carignani 2014).

Most of the literature assumes that new-to-the-world functions can be only performed through the development of new technology, software or hardware. The idea that a new function requires the development of new technology rests on the assumption that technology is effectively embodied functionality. In other words, it rests on the assumption that the function is contained in the technology. What the 'embodied' view misses, however, is that a function can also arise relationally through the exposure of current artifacts to new contexts. In this case, in an actor-network fashion (Latour 2005), the functionality becomes embodied not in the artifact per se but in the set of relations between artifacts, actors and context. Therefore, the modification or design of new technology is not necessary for the emergence of new functions.

The discussion in the previous paragraph raises the important and related issue of whether technological development, overall, is a necessary pre-condition for radical innovation. Levinthal (1998) proposes the concept of 'speciation' to explain the sudden rise of new technology-based markets absent substantial technology development. Cattani (2006), discussing technological

capabilities, shows that the emergence of the fiber optics industry was due to the redeployment of capabilities developed in unrelated sectors. In general, these scholars have noted that the assumption that radical innovations demand a parallel development of markets and technologies is not strictly necessary, as these innovations can arise by co-opting technologies developed in other sectors.

Our empirical setting, innovation in the pharma industry, is one in which new uses of existing artifacts have been widely documented anecdotally with an extensive focus on the role of serendipity (Ban 2006, Comroe Jr 1977, Li 2006, Meyers 2007). Such literature, however, does not theoretically explore or quantify the phenomenon of exaptation. The literature on drug repurposing (or repositioning) (Dudley et al. 2011), translational medicine (Woolf 2008) and off-label drugs (Radley et al. 2006) does implicitly discusses some facets of exaptation. For instance, DeMonaco et al. (2006) focus on drugs' emergent uses and give an estimate of functional novelty. However, their article aims at disentangling the role of users or manufacturers (Von Hippel 2005) in the origin of new drugs rather than functional shift per se.

3. Empirical Framework

Exaptation is difficult to measure for two main reasons: first, there is no experience about how to measure it. Second, measuring exaptation involves assessing whether an existing artifact has been associated to a new function. Such attribution is problematic not only because the concept of function is itself difficult to define exactly (Andriani and Carignani 2017), but also because a function is a relational property that depends on the artifact-context interaction. Let us analyze five stylized examples: 1) a designer imagines to use a cake pan as a flying toy; 2) children play by throwing cake pans at each other; 3) cake pans are sold at a profit as flying disks and customers buy them; 4) an entrepreneurial designer redesigns a cake pan and invents the frisbee without commercializing it; 5) the frisbee is sold and creates a new niche in the toy market. Which case(s) qualifies for exaptation? Case 1 in itself is inconsequential. Case 2 is more complex: were the children throwing cake pans as they could have thrown snowballs or rugby balls or were they throwing cake pans as frisbees? How do we fix the threshold between the two uses? Case 3 is particularly interesting: the artifact is unmodified, but the fact that it is sold as a toy reveals the emergence of a new market. In case 4, the

original artifact has been modified to optimize the new function's performance but no new market has been created. Case 5 resembles case 2 but the new function is now embedded in a redesigned artifact. Which one is an exaptation and what evidence do we need to prove it?

The original definition of exaptation by Gould and Vrba (1982) predicates that an entity has to be co-opted for a new function and that the co-option has to increase the entity's fitness (or the fitness of the organism/module of which the entity is a part). Fitness in biology is related to differential survival and reproduction, which in economic terms can be interpreted as variation in (or emergence of new) market demand. From this viewpoint, cases 1 and 4 are not exaptations because no market is either modified or created ex novo, whereas cases 3 and 5 qualify. Case 2 is uncertain. Notice that, in this approach, intentionality doesn't play a role: what we measure is not an agent noticing a new behavior but the emergence of economic demand. This helps because intentionality is notoriously difficult to measure. Our approach grounds exaptation in the choices of a population of users and can then be more objectively documented. Therefore, in this paper we measure exaptation in terms of deviation of users' selection from the original function. The modification of users' selection criteria engenders a change in the artifact's market, resulting either in a modified market or, in the more extreme cases, in the appearance of a new market.

Having grounded our measure of exaptation on selection and not on intentionality, the next steps in order to measure exaptation concern the following tasks: counting the number of new or modified markets based on a set of existing artifacts, and deciding whether a modified market is based on an exaptation or an adaptation. To do so we need the following elements: a representative sample of artifacts from a specific economic sector; the complete list of functions for which the artifacts were first introduced into their respective market; the complete list of the emergent functions the artifacts performed after market introduction; the timing of emergent functions in order to assign temporal priority between entry and emergent functions.

3.1 Setting

The pharmaceutical industry

The pharmaceutical industry constitutes an appropriate setting to measure exaptation because of four features: first, the artifacts (drugs) are uniquely and unambiguously identifiable and defined. Second,

the pharma industry is the only one (we know of) in which products' functions are classified and systematized in internationally recognized databases: this allows researchers to unambiguously identify the spectrum of functions for which the drug is being used. Third, drugs' access to market is heavily regulated whereas their subsequent uses are not. Entry point regulation implies that the initial drug function(s) is uniquely specified and can therefore be used as a benchmark vis-a-vis the subsequent functions that emerge through the so-called off-label uses. Fourth, needs—in this case diseases—are also uniquely classified in international databases. These four properties of the industry enable researchers to discriminate between entry and emergent uses.

The specific setting for our measure is the U.S. pharmaceutical market. The FDA (Food and Drug Administration), the U.S. agency for the protection of public health, regulates the pharmaceutical industry by approving drugs for specific uses. Once drugs are FDA-approved, they enter the market. Availability radically expands the range of agents (such as clinicians, patients and other pharma companies) experimenting with the artifact and this engenders innovation (DeMonaco et al. 2006). Experimentation, through exposure to different contexts, i.e. people with different physiology and concurrent diseases, uncovers new positive side effects yielding new uses for drugs, called off-label uses as they are not officially evaluated and approved by the FDA. Doctors are allowed to prescribe drugs for off-label uses, but pharmaceutical companies are barred from advertising them (Ventola 2009). In the U.S., off-label prescriptions account for about 21% of all prescriptions on average but in some fields, such as cardiac medications and anticonvulsants, this can go up to 46% (Radley et al. 2006). Considering that in 2011 U.S. spending for prescription drugs was about $322 billion (Anonymous 2012), the off-label drug market can be estimated at $68 billion.

3.2 Sample and Data

Our sample consists of all new molecular entity drugs (NMEs) approved by the FDA in the period 1998-2000, for a total of 83 NMEs. Two drugs were withdrawn over safety concerns (Vioxx and Cilostazol) and are excluded from the analysis. We chose the 1998-2000 sample to allow time for emergent uses to arise and stabilize. New uses emerge in multiple ways: scientific analysis of drug action or advances in disease understanding can give rise to new drug applications; drug uses are extended to similar conditions; clinical observations discover new unsuspected functions (Gelijns

1998). Therefore, time is needed for the full range of uses to emerge and for false positives to be weeded out. To understand when the number of uses stabilizes, we used the drugs approved in 1998 and ran our analysis with samples of emergent uses at two different points in time: 2003 and 2013. Although the number of emergent uses expanded by 20%, the ratio exaptations/emergent uses didn't substantially change. This confirmed that the 1998-2013 window is appropriate.

A widely used tool for the identification of drug uses is the commercial database DrugDex, developed by MicroMedex (DeMonaco et al. 2006; Tillman et al. 2009). DrugDex is a weekly updated comprehensive compendium of drugs and includes FDA-approved and off-label uses. The inclusion of new uses in DrugDex is based on a review of the available literature published in peer-reviewed journals and other sources, such as FDA documents, regulatory standards, professional health organizations, and other relevant materials. DrugDex specifies whether a use is FDA-approved. The entry use does not always correspond to the FDA-approved use. We can document 18 drugs in our sample in which the NME was approved in other countries prior to the FDA approval. In these cases, we used the pre-FDA approval use as the entry use. This implies that the FDA-approved uses qualify as emergent if they don't match the entry use in the original country.

3.3 Measures

Assessing exaptation by measuring distance on the ICD-9-CM database. The literature on exaptation uses a dichotomous set to discriminate between exaptation and adaptation. However, as implied in our stylized examples, the decision of whether two functions (of the same artifact) are sufficiently different is based on judgment and there are borderline cases in which the decision may be somehow arbitrary. To alleviate this problem, we introduced a measure of the functional distance between entry and emergent use. To do so, we mapped the entry and emergent use onto a space that expresses the current users' needs and measured their distance. As a need map we used the 'gold standard' of disease classification, i.e. the World Health Organization's International Classification of Diseases. To be more precise, we used the ICD-9 Clinical Modification (known as ICD-9-CM). It is a version modified by the U.S. National Center for Health Statistics (NCHS) and it has been the standard disease classification tool for epidemiology, health management and clinical purposes in the U.S. until October 2015 (Topaz 2013). It maps diseases on the basis of anatomy and pathogenesis. The

classification forms a tree-like structure of nested categories. At the top of the structure there are 17 general classes, covering the entire set of diseases. Each class is further subdivided in sub-classes, which contains further sub-classes. Each disease is assigned a code, from 001 to 999. In some cases, additional digits are added to offer a more detailed classification of the disease. An illustration of the measure of distance is provided in Figure 1.

<<< Please insert Figure 1 about here >>>

The distance between entry and emergent use can be categorized in three groups depending on the level of bifurcation crossed in the map:

A. *Large distance*: the uses fall in two different general classes. This distance involves crossing a first-level bifurcation. This is the case of Tolcapone presented in Figure 1.

B. *Intermediate distance*: the uses fall in two sub-classes belonging to the same general class. This distance corresponds to crossing a second-level bifurcation only.

C. *Short distance*: both uses fall in the same sub-class, corresponding to crossing a third or lower bifurcation level.

In order to measure the distance, we followed these steps:

1. For each NME we obtained from DrugDex the text strings describing the entry use (usually this corresponds to the FDA approved use) and emergent use(s). In general, each NME is associated with one or more approved uses and multiple emergent uses. We excluded from the analysis those emergent uses classified by DrugDex as ineffective.
2. We associated entry and emergent uses to their respective diseases on the ICD-9-CM.
3. In order to calculate the distance between the entry and emergent use, we counted the number of bifurcations that separate the entry use code from the emergent use code in the ICD-9-CM (see Figure 1). In general, each DrugDex use may map onto one or more disease codes in the ICD-9-CM database. To avoid cases of multiple counting, we considered for each DrugDex use (entry and emergent) all the possible pairs of FDA to off-label codes, calculated the distances between them and then selected the minimum distance. Therefore, a conservative choice was made since a shorter distance is less likely to be classified as an exaptation.

4. An emergent use is exaptive if its distance from the entry use is large or intermediate because it corresponds to markets that are distinct enough as to be not in competition with one another.

The distance approach relies on two major assumptions: first, it assumes that the entry use is the only use known at the moment of regulatory approval; second, it assumes that the map used to measure distance constitutes a realistic proxy for pharmaceutical markets. Clearly the entry use constitutes in general only one among all the options that drug designers could have chosen to file for approval. Obviously, uses that were already known at the moment of filing cannot qualify for exaptations. To reconstruct the state of knowledge about uses known to the filing company at the moment of filing, we used publications and patents as follows.

- *Publications*. We used publications to determine the state of knowledge of the alternative uses at the time of filing. To clarify this point, we searched PubMed, a free search engine provided by the U.S. National Library of Medicine containing the largest database of references, abstracts and papers in the life sciences. For each emergent use, classified as exaptive, we searched for papers that referred to the emergent use in association with the specific NME. If the earliest paper appeared before the time of entry (whether FDA or earlier in other countries), we consider that the use is not exaptive, as the NME-use association was already in the public domain. Publications preceded time of entry in 26 cases, which were consequently considered as non-exaptive.

- *Patents*. The rationale behind the patent analysis is that, while scientific publications tend to reflect public knowledge, patents may also reflect the original private knowledge and intention for use of the firm at the time of filing. To conduct this analysis, we used the Orange Book by the FDA, which lists the patents associated with each drug and provides this drug with market exclusivity*. For each drug's patent granted before approval, we obtained its technological classes. We then checked if the uses classified as exaptive were already present—and thus envisioned—in the 'secondary' USPTO and IPC technological classes, following an approach similar to that of Nerkar et al. (2004). However, the analysis did not influence our results substantially.

Alternative measure of exaptation. The distance approach is independent of our knowledge of drugs: its reliance on external databases constitutes its main strength, as the procedure is objective and

can, to a certain extent, be automated. It can however suffer from some systematic weaknesses. First, the ICD-9-CM may erroneously classify an emergent use as an exaptation due to insensitivity to the complexity of interaction and level of analysis. For example, a drug used to treat a collateral symptom such as pain associated with cancer may be classified in the 'neoplasm' category and hence appear as an anticancer drug. The opposite case is also possible: uses classified in the same subcategory (hence low distance) may belong to entirely different markets. Second, diseases that appear in different classes based on a specific taxonomic approach (i.e. ICD-9-CM) may be contiguous in an alternative taxonomic approach. To compensate for the shortcomings of the distance approach, we adopted a qualitative approach based on the mechanism of action, i.e. the specific interactions between the active molecule and the organism that enables the pharmacological effect of the drug, and conducted extensive research on each drug entry-emergent use pair. In this case entry and emergent markets are assessed by direct analysis of each of the drug uses by two coders. In case of disagreement between the coders, further research was done until consensus was achieved. The procedure was the following:

1. As with the distance approach, we started from the description of the uses obtained from the DrugDex database.
2. Then we used available sources, such as academic articles, medical databases, PubMed, Wikipedia articles, DrugDex documentation of uses, books, FDA documents, etc. to directly gauge the market difference between the entry and emergent uses. To do this we looked at the mechanism of action, disease description and, when available, historical evidence of drug use.
3. On the basis of this analysis, we coded the use with a binary variable Y/N (Y: exaptation confirmed / N: non-exaptation).

Radical innovation analysis. In addition to measuring the frequency of exaptation we also aim to evaluate the occurrence of radical and incremental innovations within our sample of emergent uses. Following Garcia and Calantone (2002), we used a triadic classification of the degree of newness of a use. The radicalness of use depends on the way in which the need was satisfied prior to the arrival of this drug in this market rather than the mechanism of action of the drug itself.

A. *Radical*: uses that are new-to-the-world. Specifically, this means new or radically improved treatments for previously untreated or poorly treated diseases. The unit of analysis is the population of users characterized by a specific need. Radical uses may activate cascades of further uses i.e. open up new research opportunities.

B. *Semi-radical uses*: uses that introduce significant improvement over current treatments. The unit of analysis is micro, typically a sub-population. For instance, this refers to uses that address the needs of patients who are (or have become) insensitive to existing treatments and whose conditions significantly improve upon discovery of the new use.

C. *Incremental***:** uses that are neither new-to-the-world, nor constitute significant advancement over current treatments, but add to the existing population of treatments.

The degree of newness was evaluated by an analysis of the original publications that discussed the use at the time of its appearance**. The assessment was done on human rather than animal or cultured cell-based evidence.

4. Results

The results are divided into four sets. We first show and compare the results based on the two different approaches of assessing exaptation—the distance approach and the qualitative approach based on case-by-case-in-depth assessment. Next, we report the aggregated results for the entire sample using the qualitative approach. We then present the results by drug and finally focus on the radical innovation results.

Distance versus in-depth approach. Comparing the two approaches, we note that: 1) the distance approach classifies more emergent uses as exaptations than the qualitative approach; 2) the farther the distance, the more likely the distance measure agrees with the qualitative measure. In 162 cases, both approaches agree that a specific use is exaptive. In 62 cases, the distance approach considers a use exaptive and the qualitative approach non-exaptive. In 20 other cases, the distance approach considers uses as non-exaptive while the qualitative analysis considers them exaptive as seen in Table 1.

<<< Please insert Table 1 about here >>>

On average, 71% of the large distance jumps are also exaptations based on the qualitative approach but only about 19% of the intermediate distance jumps are also exaptations according to our second approach, indicating that the threshold between exaptive and non-exaptive uses falls at the intermediate distance level. Overall, these results show that the distance approach is a useful first indicator of exaptiveness but that controls are necessary to support accuracy. Indeed, the fact that 9% of exaptations occur even in the local group illustrates the limitations of the use of the ICD-9-CM map as discussed in the methodology section.

Aggregated results. Because the qualitative approach is the more conservative estimator of the frequency of exaptation, the rest of the paper uses the results of the qualitative approach. Table 2 presents a synthesis of our aggregated results.

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It divides uses into two categories: entry and emergent. Exaptations are a subgroup of emergent uses. The entry uses correspond to the uses for which the drug was originally approved by the FDA or in a few cases (18 cases) by a different regulatory agency prior to FDA approval. The emergent uses arise after the drug is introduced in the market and both users and companies can experiment with it. The table shows that our sample includes 83 NMEs from 1998 until 2000 with 151 entry uses and 430 emergent uses—with an average of 5.2 emergent uses per drug—over the period 1998-2013. We also note that each drug, on average, has 2.2 exaptive uses with a range of 0 to 45 exaptations per drug. About 42% of the emergent uses, that is 179, are exaptive. We also observe standard deviations about twice the size of the mean indicating that, while some drugs have no or few exaptations, others are 'promiscuous' and attack multiple new diseases. In fact, 46 drugs have no exaptations and 13 drugs have no new uses post approval.

Drug-level results. The distributions of emergent and exaptive uses per drug is highly asymmetric and long-tailed, probably of the power-law type as shown in Figure 2.

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A Shapiro-Wilk statistical test indicates the non-normality of both series. Relying on the statistical framework proposed by Clauset et al. (2009), we obtained a 'P-value' of 0.63 for emergent uses and of 0.79 for exaptive uses. This indicates that the power-law hypothesis could not be rejected for either

series. Overall, this test is important because in power law distributions extremes are not outliers but are naturally expected, as in the case of thalidomide in our sample. We also calculated a Spearman correlation between the two series, which resulted in a value of 0.66.

Characterizations of exaptations: radical innovation analysis. we characterize exaptations in terms of distance and radicalness. We remind the reader that distance indicates the difference between the entry and the emergent uses as measured on the need space of the ICD-9-CM map. Radicalness, on the other hand, describes the impact of the emergent use on the market it addresses. We divide the emergent uses in three categories: radical, semi-radical and incremental. 4.6% of emergent uses are radical and 8.6% classify as semi-radical. Of the exaptive uses, 10.4% are radical and 8.8% are semi-radical. The radical innovation number is comparable with other measures of radical innovation (see next section). Figure 3 describes the relationship between exaptive and radical uses.

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We notice a strong correlation between radical and exaptive uses. Almost all radical uses, about 95%, are exaptive whereas incremental uses are in the majority non exaptive. This is an interesting result that we will discuss in the following section. Finally, we correlate radicalness with distance. Figure 4 shows that there is a relation of direct proportionality between distance and radicalness.

<<< Please insert Figure 4 about here >>>

That is, the greater the distance, the higher the probability that the use is radical. For example, we see that about 85% of radical uses are separated by a large distance from the entry use while only about 40% of the non-radical uses are separated by a large distance. Furthermore, no radical uses are in the short distance group. In the next section we will discuss the implication of this result.

5. Discussion of Results

Our paper focuses on the emergence of exaptations following the market introduction of drugs. Our results can be summarized as follows: a) each drug generates on average 2.2 exaptations (with a standard deviation of 5.51, and it generates about 3.0 additional non-exaptive uses); b) a fraction of exaptations, about 10%, are radical.

Regarding point a), exaptations are a part of the larger category of emergent uses, which can be divided between exaptive and adaptive uses. Adaptive emergent uses are generated by the radiation of entry uses toward adjacent niches. The radiation can be explained by the fact that uses designed for a target are likely to work for adjacent targets (that rely on the same or similar pathways). It follows that these uses are functionally similar to the entry use and the process that leads to their emergence is mostly deliberate (Gelijns 1998). Exaptive uses, on the other hand, are functionally novel and about 71% of them correspond to large jumps from the entry use. Exaptive uses arise mostly through an unplanned process of radiation toward non-adjacent niches and not through a deliberate process of search via adjacent niches. Figure 2 shows that the distribution of emergent uses exhibits a highly skewed nature. About 45% of drugs exhibit exaptations, with the majority of exaptations belonging to a few drugs at the head of the distribution. About 9% of drugs show no emergent uses.

Regarding point b), our results also point that a significant number of exaptations result in radical innovations, as 10.4% of exaptations are radical (and 8.8% semi-radical, while the percentages of radical and semi-radical uses over emergent uses are respectively 4.6% and 8.6%). These numbers are roughly aligned with studies in other sectors that find about 10% of innovations to be radical (Barczak et al. 2009, Garcia and Calantone 2002). It is worth stressing that our results apply only to functions that arise after market introduction and that do not necessitate product modification (previous literature has focused on exaptation with product modification). We remind that the radical analysis is independent from the exaptive one—radical uses are such because they have an impact on the market they reach while exaptations relate to the drug's degree of functional novelty with respect to its original market. Interestingly, radical uses strongly correlate with long jumps. This raises the issue of why radical innovations happen when technologies are transferred to very different markets.

The case of thalidomide, the most extreme event in our database, provides an interesting illustration of both points discussed above: thalidomide was approved in 1998 by the FDA but it was originally introduced in 1956 in Germany as a sedative. Thalidomide was withdrawn in 1962 because it caused severe malformation of fetuses (phocomelia) and represents the worst tragedy of post-WWII pharmacology history (Stephens and Brynner 2009). In 1964 Dr. Sheskin, in the search for a drug to sedate a terminally ill patient afflicted by erythema nodosum leprosum (a condition associated with

leprosy that causes unendurable pain), tried thalidomide with unexpected results: not only the pain but the disease itself disappeared (Sheskin 1965). Because of this discovery, 90% of the leprosy hospitals around the world were shut down (Stephens and Brynner 2009), radically changing the treatment of leprosy. Several years later, thalidomide turned out to be effective against several conditions associated with AIDS, such as aphthous ulcers and wasting (Stephens and Brynner 2009). Thalidomide was shown to be effective in 1988 in graft-versus-host disease, in 1994 in diseases associated with angiogenesis, in 2000 in multiple myeloma (Rehman et al. 2011): 'to date, thalidomide has been used to treat 130 disorders, for some of which it is the only effective means of arresting a patient's progressive deterioration' (Stephens and Brynner 2009, p. 164). All the exaptive uses of thalidomide in our database—seven of which are radical—are characterized by long jumps with respect to the entry use. Most of the emergent uses are based on new molecular pathways—at least seven different pathways have been discovered—none of which were anticipated (Rehman et al. 2011). Therefore, the thalidomide case shows that the exposure of a drug developed for a specific purpose to novel and different contexts may lead to the unexpected discovery of radical breakthroughs based on new mechanisms of action and phenomena.

Overall, as our results indicate and the thalidomide case exemplifies, it is plausible that long jumps across the functional space of artifacts are associated with the discovery of new phenomena-based exaptations. Whereas local search around the set of known functions of an artifact may trigger the discovery of a new function within the set allowed by the current phenomenon, the activation of a new phenomenon is associated with a jump across radically different contexts. This point matters because, as Arthur (2009) shows, the most radical innovations are those based on new phenomena, that is, natural effects recently discovered or never before utilized to do work. New phenomena, such as those underlying the turbine jet, recombinant DNA or antidepressant enable new functional possibilities simply unimaginable before their discovery, which then become the foundation for entirely new markets. It follows that exaptations can be divided in two sets, depending on whether they are based on new phenomena or not. For instance, Marsilid was developed as an anti-tuberculotic but became the first psychiatric medicine in history. The discovery that Marsilid made tuberculotic patients euphoric (the exapted function) led to the discovery of a new phenomenon: that chemical

imbalances of neurotransmitters played a role in depression (Mukhurjee 2012). Marsilid's action is based on two radically different phenomena: as an antibacterial against the mycobacterium tuberculosis and as a neurotransmitter modulator in the antidepressant function. Upon this exaptation the idea that artificial chemical substances may influence the brain was introduced, psychoanalysis was relegated to a complementary approach to psychiatric conditions and an entirely new market was created ex nihilo. Exaptations that are based on (and lead to) the discovery of new-to-the-world phenomena are at the root of some of the most radical innovations. These exaptations are very rare. The majority of exaptations rely on the same underlying phenomenon.

The potential of exaptation to the expansion of the pharmaceutical industry is significant. The distinction between non-exaptive and exaptive uses helps understand the potential of emergent uses in addressing diseases neglected by mainstream pharmaceutical industry, such as orphan diseases (rare diseases) and those dominant in emergent and third world economies but absent in developed economies. Non-exaptive uses search the need space in the proximity of focal drugs' uses, and so they tend to address diseases relatively similar to diseases typical of developed markets. As return on investment considerations skew strategic decisions of pharma companies toward diseases dominant in rich countries (Gelijns 1998, Roin 2014), it follows that non-exaptive uses also address similar conditions. In contrast, exaptive uses search the need space far away from the focal use and hence explore regions of the need space that are more likely to include orphan and neglected diseases, i.e. diseases left neglected by the dominant business model. However, lower expected returns to investment have slowed R&D efforts in these areas. The non-exaptive uses of a drug designed for an Alzheimer's disease, mostly prevalent in countries with long life expectancy, will most likely refer to other diseases that are related to Alzheimer's. A potential exaptive use of an Alzheimer's drug, however, could target malaria or leprosy, despite the overall lower investment of resources in such neglected diseases. Overall, our results and examples shed light on an important and yet underexplored mechanism for the discovery of novel opportunities—new functions and markets—in the pharma industry. As we will see in the next section, this has important implications for recent debates in the fields of innovation, strategy and organizational theory.

6. Implications

Implications for the debates in innovation, strategy and organizational theory

Our study has important implications for two recent and inter-related debates: the Gavetti versus Winter debate (GW from now on), and the von Hippel and von Krogh versus Felin and Zenger debate (HKFZ from now on). The GW debate builds on Gavetti's (2012) behavioral theory of the firm, which is then criticized by Winter (2012) for its lack of attention to contextual factors and serendipity. The HKFZ debate builds on von Hippel and von Krogh' (2016) approach to problem-solving based on the simultaneous emergence of 'need-solution pairs', which is then criticized by Felin and Zenger (2016) for failing to frame their phenomenological observation within a general theory of value creation. Risking to oversimplify complex issues, we see commonality between Gavetti (2012) and Felin and Zenger (2016) in their emphasis on the importance of superior cognitive abilities and foresight for the discovery of new problem solutions (and, more generally, of distant opportunities). On the other hand, Winter (2012) and von Hippel and von Krogh (2016) tend to emphasize the role played by serendipity and contextual factors as major drivers of organizational decision-making.

The GW debate. Gavetti (2012) argues that a firm's ability to spot distant opportunities***, which are potentially less contested and more rewarding than local ones, is what leads to achieving superior value. He focuses on the role of superior cognitive abilities and foresight in strategic decision-making as opposed to the role of contextual factors and serendipity proposed by Winter (2012). His proposed model of the mind to spot and build markets around distant opportunities is mainly associative and relies on analogy (Gavetti et al. 2005). On the other side of this debate, Winter (2012) stresses that serendipity and contextual factors in search are more likely to lead to valuable opportunity identification. Their disagreement reflects similar fundamental and recurring tensions in the organizational literature, such as that between foresight and luck (Cattani 2006, Garud et al. 1997). Our results are relevant to both points of contention emphasized by Gavetti (2012). First, we show that radical exaptations—those that satisfy previously unsatisfied needs—occur almost exclusively in distant markets, lending indirect support to Gavetti's proposition that such markets are more likely to be less contested. We offer two reasons to explain why distant markets are more likely to be less contested. First, we propose that the greater the distance, the higher the probability of finding

unexplored—and therefore less contested—areas. Our results show that 46% of emergent uses explore areas different from the one for which the drug had been approved. This search is usually undirected and so more likely than targeted search to land in unexplored or unexploited areas. Second, the greater the distance, the higher the probability that the emergent function relies on a different phenomenon (or mechanism of action) from the one underlying the original function, which may allow the satisfaction of previously unsatisfied needs or even the discovery of new needs and help the firm to become a first-mover.

Gavetti (2012) contends that associative thinking or analogy is the main mental process for the navigation of the complex opportunity space. Analogy is a cognitive process that enables agents to transfer knowledge from a base domain to a target domain when those domains share certain commonalities to allow for knowledge to be transferred across them (Gentner 1983). The literature on exaptation has recently emphasized that limiting factors constrain the power of analogy for the identification of distant opportunities. Limiting factors are particularly related to the problematic identification of target domains, either because the potential size of the target domain of functions is so vast that analogical search can only explore an infinitesimal area of the space (Kauffman 2000, Wagner 2011), or because under certain conditions certain areas of the function space are cognitively 'invisible' to analogical search due to fundamental un-prestateability (Felin et al. 2016). Notably, search via exaptation does not rely on the pre-existence of a target domain but on the emergence of new functions based on artifact-context interaction. Exaptation effectively 'enables' a jump into distant and active areas of the space.

The problematic identification of target domains is further accentuated by factors such as those mentioned in the previous section: new underlying mechanisms and phenomena. As discussed earlier, exaptations can be divided into two sets: those that rely on the same phenomenon as the original function and those based on a different phenomenon. If the exapted and the original function share the same underlying phenomenon, then it is theoretically possible to foresee the exapted function by means of cognitive mechanisms such as analogy or deduction. For instance, the radar was exapted for (and gave rise to) the new field of radio-astronomy. The commonality of the underlying phenomenon in radio-astronomy and in the original use of radars for military purposes, together with the

widespread knowledge of quantum physics, could have permitted the deduction of the potential of radars for radio-astronomy on purely theoretical grounds (Buderi 1997). But, if exaptations rely on a different and previously unknown underlying phenomenon, then it is inherently impossible to arrive at the exaptation via analogy or deduction. Some (rare) exaptations have the potential to create entirely new markets and industries by revealing new phenomena. In other words, they reveal that 'we don't know what we don't know'. The above-mentioned example of Marsilid illustrates the point. Marsilid was originally designed to fight tuberculosis, but then it was discovered to act as an antidepressant drug thanks to the new phenomenon of neurotransmitter imbalance (Mukhurjee 2012) that is different from the phenomenon underlying its original anti-tuberculotic effect. Marsilid exemplifies two other important observations about exaptations relying on new phenomena: first, the fact that they happen by serendipity; second, that these new phenomena open up new areas of knowledge and trajectories of research, innovation and commerce—in this case, the idea that psychiatric diseases were treatable by synthetic chemicals and the multibillion dollar market for antidepressants. Overall, the problematic nature of identifying target domains emphasizes the limits of analogical search as a cognitive theory for the discovery of distant opportunities.

Search via exaptation, indeed, is different as it does not rely on the 'pre-existence' of a target domain but on the 'emergence' of a target domain through artifact-context interactions that give rise to new functions, occasionally underlined by new phenomena. The emergence of ideas leading to distant opportunities is driven not by exogenous factors such as strategy and marketing considerations against which new technologies are either developed or adapted to, but mostly by factors endogenous to the technology and the contexts to which the technology is exposed. In our discussion of function, we pointed out that a function can be understood as embedded either in the artifact itself or in a network formed by novel connections established between the focal artifact and its technological context. In this latter view (function as relation), by endogenous factors we refer to properties called affordances (Felin et al. 2016, Gibson 1986) that are inherent to the technology-context interactions and when acted upon by an agent 'drive' the expansion of the technology into new markets. 'Affordances are properties of things taken with reference to an observer, but not properties of the experience of the observer' (Gibson 1986, p. 129). Thalidomide affords the cure of leprosy by means

of specific biochemical properties within the context of a sick patient. The microwave oven affords cooking by means of its specific energy source. A screw-type wine press affords book printing. Affordances reveal underexplored or unknown links: for instance, drug designers were not aware that Marsilid linked bacterial biology and neurobiology but Marsilid afforded such bridging and, as a result, it drove the expansion of the drug in the new domain of antidepressants.

The HKFZ debate. This debate concerns the role of serendipity and contextual factors in the broader domain of problem-solving. von Hippel and von Krogh (2016) observe that problem-solving may proceed by two routes. In the first, the identification of a need triggers the formulation of a problem that drives the search process for a solution: the order is need-problem formulation-solution. In the second, exposure to information-rich contexts may trigger a serendipitous association between an existing solution and a need, whose satisfaction the agent was not intentionally pursuing. Problem-solving through identifying 'need-solution-pairs' (NSP hereafter) presents the advantage of not implicitly preselecting the area of the solution space by defining the problem too narrowly. Felin and Zenger (2016), whilst not denying that serendipity and context play a role, maintain that 'the goal of the problem-finding and problem-solving perspective is to develop a comparative, strategic, and normative theory of value creation that is analytic and actionable for a focal firm in its efforts to create value'. Such theory, according to them, 'can be seen as a counterpoint to the recent emphasis placed on serendipity and luck in strategy' (p. 224). They are further dissatisfied with the fact that the NSP approach 'fails to provide a normative (or descriptive) theory of when a firm should defer to the serendipitous discovery offered in need-solution pairs and when a focal firm should take up problem-finding and problem-solving itself' (Felin and Zenger 2016, p. 223).

We contend that the irreducible uncertainty associated with market and technological evolution makes the strategy-guiding theory proposed by Felin and Zenger (2016) highly limited. Such theory presupposes that a firm is able to discriminate between situations in which serendipity may or may not play a role. Our results show that a large fraction of innovations that follow market introduction and especially high-impact ones are inherently unpredictable. We concur that organizations need criteria to allocate resources, prioritize investment and rank options for decision-making. However, usually such decisions are context-dependent and therefore they tend to *follow* serendipitous innovations and

not precede them. For instance, in 1945 managers at the military contractor Raytheon were aware that military spending slow-down would shift the market from military to civilian. But they didn't anticipate that they already possessed a breakthrough civilian technology, the microwave oven. It was only after the discovery that the military magnetron was also a microwave oven that they set the strategy for the entry in the kitchen appliances business. Then Felin and Zenger (2016) point out, correctly, that serendipitous discovery (including the emergence of need-solution pairs) depends on the intuition and cognitive attention of the discoverers. However, they then conflate attention with their firm-centric theory. They write that 'our observations and perceptions of our surroundings (and of value), are mind and theory-laden. […] Similarly, theories that guide value creation and value capture direct our attention and help to reveal new ways of seeing potential value in solutions […] that others may fail to see' (Felin and Zenger 2016, p. 226). The problem with this conflation is that the cognitive substrate that channels attention and the observed results often bear no relationships. The substrate that led Galileo to turn Aristotelian physics on its head was the medieval theory of impetus, a wrong theory. Fleming's observation of penicillin rested on his previous discovery of an enzyme (lysozyme). He initially interpreted penicillin as a more effective lysozyme. That cognitive substrate lead Fleming to miss the potential of penicillin (Fleming 1929), which was discovered more than ten years later, partially by chance again. In other words, 'chance favors the prepared mind' but preparedness doesn't mean a normative theory of what is expected.

In their critique, Felin and Zenger (2016) finally point out that most of the NSP examples refer to rather mundane situations in which both need and solutions are well-defined. Under this condition the need-solution landscape is static, whereby the challenge is to find novel uses for solutions that can deliver superior value. In order to do so, 'mechanisms behind the emergence of these new uses and functions need to be identified' (Felin and Zenger 2016, p. 227).

We think that exaptation and our results can provide some clarity about these issues. In particular, we think that: first, the NSP approach can be shown to be part of a larger set: inverse and direct problem solving; second, the predominant mechanism behind NSP is exaptation. Regarding the first point, von Hippel and von Krogh (2016) write that 'the field of problem-solving research generally assumes that formulation of a problem to be solved precedes the search for a solution' (p.

210). We call this approach type 1 problem-solving. The opposite of such a process, according to them, is one that scans a metaphorical need landscape and solution landscape and finds pairs that match one another. In NSP, 'relevant need and potentially useful solution come packaged together […] and are often discovered together' (p. 214).

We observe, as von Hippel and von Krogh (2016) stress, that unbounded exploration is a hard cognitive task and that exploration is intrinsically constraint-bounded. We suggest that exaptation, by focusing attention on artifacts as solutions to unintended problems, may provide that starting constraint: if type 1 search moves from need to solution via problem formulation, the logical reverse for problem-solving that skips the problem formulation step is to move from a pre-existing solution to a need. We call this approach type 2 problem-solving. An analysis of NSP examples reported in their paper shows that solution precedes need. The first (speculative) example concerns a payroll software system. An employee notices a payroll software and realizes that he/she can apply it to solve an emergent need. The direction is from solution to need. The second example concerns the invention of the rolling suitcase. The inventor noticed a potential solution (the ability to push a heavy machine thanks to wheels) and transferred it to his own problem (ability to effortlessly pull heavy suitcases in airports by adding wheels). In this case, the innovation consists in the co-option of an existing solution followed by recombinant innovation to yield a new solution, in short from solution to need.

The NSP identification refers to the cognitive moment in which need and solution are recognized as congruent and matched. From this cognitive viewpoint von Hippel and von Krogh (2016) are right to argue that 'a need-solution pair problem-solving process is presently unknown to problem-solving literature and formal problem-solving practice. We think it flourished in real life, but can offer no evidence beyond illustrative examples at this point' (von Hippel and von Krogh 2016, p. 208). The above generalized approach to NSP (which includes the solution-to-need route and the cognitive matching issue) was anticipated by Wiener, the founder of cybernetics. Wiener called it the 'inverse process of invention' and noticed that often scientists 'turn around and ask not merely, "how can I solve this problem?" but, "now that I have come to a result, what problem have I solved?" The use of reverse question is of tremendous value precisely at the deepest parts of science, but it is even important when it comes to particular engineering problems' (Wiener 1993, p. 22). He added that 'the

social and economic importance of the inverse invention will compare with that of the direct invention'. (Wiener 1993, p. 93). Overall, type 2 processes are numerous in the history of science and technology. For instance, 'many of the essential medical discoveries in history came about not because someone came up with a hypothesis, tested it, and discovered that it was correct, but more typically because someone stumbled upon an answer, after some creative thought, figured out what problem had been inadvertently solved' (Meyers 2007, p. 300). In the management literature, several scholars have pointed out that the relationship between problem-setting and solution is complex and does not follow an ordered process. Cohen, March and Olsen (1972) developed a 'garbage can' view of organizational choice and suggested that an organization "is a collection of choices looking for problems, issues and feelings looking for decision situations in which they might be aired, solutions looking for issues to which they might be the answer, and decision makers looking for work" (Cohen et al., 1972, p. 195). Schön's theory of reflective design (Schön, 1983) also sheds light on the problem-solution relationship. Van de Ven et al. (Van de Ven, Polley, Garud, & Venkataraman, 1999) have argued that the innovation journey is more uncertain and complex than what is assumed in traditional models of innovation and propose a theory of iterative cycles of divergence and convergence in innovation.

von Hippel and von Krogh (2016) show that the NSP phenomenon exists and it matters but do not discuss its sources. We build on their observation (albeit generalized as type 2 problem-solving) and show that a fundamental source of type 2 problem-solving is exaptation, and that it matters especially for wicked problems. Our argument that exaptations provide a crucial source of NSP hinges on the multi-functionality of solutions (based on Kauffman's un-prestatability idea). In general, solutions can be 'pulled' from a need by way of problem formulation or they can 'push' the emergence of new needs via exaptation. The latter type of solutions, that we call unexpected solutions, are effectively invisible until the emergence of a new NSP shows their existence (in the following paragraph we show how unexpected solutions are related to radical innovations). Invisible, however, doesn't mean non-existent. This statement rests on two arguments. First, our results show that solutions introduced to solve a specific need generate a given number of other solutions that

apply to different needs, some of which may be unexpected. Second, unexpected solutions turn out to solve different problems because, as discussed earlier, they contain features that when placed in an appropriate environment afford the emergence of a new behavior that links the unexpected solution to a new need and are perceived by an observer as a new NSP. As affordances are defined in relation to a context and an observer, until the two materialize the unexpected solution is effectively invisible.

von Hippel and von Krogh (2016) speculate that the NSP approach may also generate new-to-the-world innovation. We concur with this and note that innovations that started entirely new technological trajectories are paradigm-changing and are associated with what we call unrealistic needs. Let's call 'realistic' those needs for which a satisfaction is envisaged as technically possible and 'unrealistic' those needs whose satisfaction is deemed impossible with currently available technical means or those needs not yet conceived. Space exploration before rocket propulsion, wrinkle elimination via noninvasive techniques before Botox, treatment of depression via synthetic chemicals before Marsilid, are all examples of such needs. If the development of the means to satisfy such needs is deemed impossible (outside of the current paradigm and/or technological trajectory), then the conversion of the need into a problem formulation does not occur (at least in the official research mechanisms, although a few deviants do pursue out-of-paradigm research). Consequently, such needs are not perceived as giving rise to opportunities and the attainment of unrealistic needs cannot proceed via problem formulation. Unrealistic needs satisfaction, therefore, is more likely to occur by type 2 problem-solving via serendipity and exaptation. As these needs are largely outside of the perceived adjacent-possible, the demonstration that such needs can be fulfilled usually occurs through unintended actions. An existing solution to something else (a technology, a theory, etc.) provides an unexpected discovery that turns an unrealistic need into a realistic need.

Other implications

Our results show that artifacts developed for a purpose generate further functions, which may be used for the development of further niches based on the same (or modified) artifact. In this paper we quantify this phenomenon and notice that each artifact triggers on average about 2.2 exaptations, of which a fraction will be radical. We also stress that radical exaptations are likely to bring about discovery of new phenomena. Put differently, each artifact holds a number of options which

organizations may convert into new markets. Following Cattani (2006), we call them *shadow options* because they exist only in a probabilistic sense and their value is non quantifiable. They represent options on innovation projects that the organization can choose to exert as long as they control the underlying artifacts and can claim ownership of the emergent functions. Framing the issue of the identification of distant opportunities in terms of shadow options of current artifacts provides a strategic tool for innovation policy.

We stressed that exaptive distant opportunities emerge through observation of artifacts' affordances. At the cognitive level this calls for the capacity to observe unusual patterns and associate them with novel functions of the artifact. The rationality dimension that the 'behavioral theory of strategy' insists on does play a role, but it is more concerned with the process of choosing which shadow option to pursue rather than generating shadow options in the first place. Taleb (2012) has coined the term *optionality* to describe a strategy where options are generated serendipitously and rationality is used to select the ones to pursue.

How can organizations accelerate the generation of shadow options? Essentially this can be done by *multiplying the contexts* to which organizational resources and capabilities are exposed. By context we mean the set of environmental features that can interact with the technology to generate a new function, where the interaction occurs via affordances. Multiplication is best performed by adopting hybrid organizational models that mix producer and single user/community innovators**** (Baldwin and von Hippel 2011). Hybrid models escape the constraints associated with targeted research because of three reasons: first, they can bridge more contexts than specialized professionals; second, their institutional environment allows them more freedom to notice unexpected patterns, follow the trail of affordances and escape the bounds of specialization; third, their incentive system is more diversified. The heterogeneity of hybrid models matches well the requisite diversity of exaptive innovation. What do we mean by exposure to contexts? This is typically what user innovation excels at, and it can be achieved by encouraging the largest possible base of users to experiment with artifacts. As the number of users is vastly larger than the number of designers, the range of exploration they can achieve is consequently bigger. The process of democratization of the tools of production also puts in the users' hands technologies that were once restricted to the professionals.

The context multiplication can be achieved by designing organizations that exploit the following three organizational design aspects: recombinant modularity, self-organizing bottom-up innovation and access to distributed networks. The first feature ensures that available resources can be partitioned and assembled in limited-life projects where their value in a new context (the project) can be explored. The second is epitomized by the 15% rule at 3M (Gundling 2000) or one-day-a-week rule at Google. Employees are encouraged to apply their idiosyncratic mix of knowledge and experience to conceive and develop projects that may create value for them and for the organization. As the history of 3M and Google shows, the interaction between the employees' cognitive diversity (Page 2008) and the organizational resources and capabilities becomes a significant contributor to innovation via the exaptation of existing resources and capabilities. The third has to do with creating a permeable interface between the organizational resources and capabilities and external networks. Initiatives such as cooperation with lead-users and innovation communities (Von Hippel 2005), innovation tournaments (Terwiesch and Ulrich 2009), innovation markets (Page 2008), co-design and crowdsourcing (Anderson 2012) and innovation platforms (Chouduri et al. 2016) enable the expansion of the intelligence that can access organizational resources and capabilities, and therefore increase the possibility of new function development. A fourth has to do with the role of entrepreneurs, especially of the effectual type (Dew et al. 2008, Dew and Sarasvathy 2016), and organizational venturing such as the creation of spin-outs and start-ups that explore the diversity of uses of existing artifacts and then market them (Read et al. 2010).

7. Limitations and Conclusions

In the following, we present some limitations of the current study and we discuss the issue of generalizability to other industries.

First, our results are based on the sample of 83 drugs approved by the FDA over three years (1998-2000), a number that is consistent with the average number of 27 approved drugs per year. This constitutes a relatively small sample (about 6%) of the population of approximately1500 NME drugs approved by the FDA. Increasing the sample size will undoubtedly provide additional information and help better calibrate the results. However, the sample follows a long-tailed distribution, most likely a

power law one. In such distributions the four moments are unstable, and in the case of the power law distribution there is no convergence to the mean. This indicates that increasing the sample size may neither change the nature of the result nor diminish their variance.

Second, our results are based on two databases: DrugDex, from which we extracted drugs' original and emergent uses, and the ICD-9-CM, from which we extracted the needs that the drugs target. We also used the ICD-9-CM as a general space to map uses and measure distance. How reliable are our two main sources? DrugDex is a commercial database widely used by practitioners. DrugDex, however, does not include all uses of drugs. Due to the inherently difficult task of collecting broadly scattered information about uses, DrugDex necessarily under-reports the number of uses. In fact, additional uses can be found in the medical literature but many also remain unreported (von Hippel et al. 2016). The existence of additional emergent uses (the number of entry uses is definitely known), rather than detracting from our measure, simply indicates that ratios such as emergent/entry uses and exaptive/entry uses constitute a lower boundary of the phenomenon. In other words, we may underestimate the exaptation phenomenon. The ICD-9 is the official database of the WHO regarding diseases and health procedures. It is the result of a worldwide collaboration among health authorities and experts. The U.S. developed a national version, called the ICD-9-CM, which has been 'the required standard for billing and clinical purposes' since the late 1970s until October 2015 (Topaz M 2013). This database covers the whole period of our research. Using the ICD-9-CM to measure distance between entry and emergent uses represents, in a sense, an exaptation of the database. However, as the ICD is the best available classification of diseases and is designed to group them into categories based on disease similarities, our use is generally consistent with its structure.

Third, our measure of exaptation treats the entry use as the benchmark from which to measure the distance to emergent uses. We put in significant effort to reconstruct the state of knowledge (public and company-based) at the time of the entry use via publications and patent analysis. Although we cannot exclude that some emergent uses were known at the entry time, we are confident that the impact of this should be limited. In fact, a study by DeMonaco et al. (2006) based on one of the years of our sample (1998) that also used DrugDex as its source of emergent uses, shows that most emergent uses (after market introduction) were discovered by users and not manufacturers. This

confirms that our results are robust. Of course, every classification, and even more so in such a complex field as the medical one, requires interpretation and hence is subject to revision.

Are our results generalizable to other industries? Only speculative answers can be given to this question. We expect that, although the numbers will certainly differ across different industries, the following general features will also be found in other sectors: first, a significant fraction of discovery of new functions happens by the exaptation route; second, a non-negligible fraction of exaptive functions are radical; third, most of the exaptations are discovered by users. Several elements support our arguments. First of all, exaptation discovery depends on the role of user innovators (DeMonaco et al. 2006). Does the pharma industry differ from other industry with regards to the role of users? von Hippel and his coauthors (Von Hippel 2005) show that in several sectors a large percentage of innovations are developed by users. Users modify existing products and use them in functionally novel ways to suit their idiosyncratic needs. As these needs emerge from the mix of personal experiences, mental frames, education and activities, they form new contexts that are likely to redefine the ways products are used. That is, they are likely to trigger exaptations. This applies to the pharma industry, in which approved drugs can be experimented with by users (essentially clinicians, family doctors and patients) who are free to explore the full range of potential uses. As there is no reason to think that the number and role of users of the pharmaceutical industry products is smaller or less central than in other industries, user innovation in pharma does not significantly differ from other sectors where users play an important role. Secondly, exaptations are at their core novel artifact-function associations. Such novel associations derive from the exposure of existing artifacts to new contexts. In complex systems, such as organisms, industrial ecosystems and organizations, the number of new contexts to which an artifact can be exposed is uncountable and the latent functions of an artifact are un-prestateable (Longo et al. 2012). Therefore, the number of artifact-context associations is fundamentally unknowable. In this respect, the pharma industry does not differ from other industries. Thirdly, R&D is presumed to be guided by the linearity of the goal-driven approach. The reality, however, is that randomness, luck, serendipity and chance play a fundamental role even in science-driven sectors. In principle, as there is ample evidence about the role of unintended events in innovation in most sectors, there is no reason to expect that the exaptation channel is fundamentally

different in the pharmaceutical industry than in other industrial sectors. In conclusion, exaptation reveals a fundamental property of complex systems: the property according to which a function is an emergent property of the interaction between artifact and context. We offer a measure of the frequency by which this emergent property generates new variety in the economy.

Endnotes

* We acquired the patent information from the DrugPatentWatch Database and through a disclosure through the Freedom of Information Act directly from the FDA.

** For instance Thalidomide was extensively used to treat lupus erythematosus, a disfiguring skin disease (see, for instance, Knop et al. 1983). Recently, however, Thalidomide derivatives such as lenalidomide and immunosuppressive drugs such as the recently approved belimumab are used as first-line options. A research that focused on today's drugs may fail to notice the role of Thalidomide.

*** To be precise, Gavetti refers to cognitively distant opportunities. Our analysis is based instead on the concept of market distance. Although market distance and cognitive distance are distinct, plausibly their rate of change is related. Moreover, Gavetti and the Behavioral Theory of Strategy argue that distant opportunities are generated by behavioral failures that can be analysed along three dimensions: rationality, plasticity and shaping. Rationality is mainly concerned with the identification of distant opportunities. We concentrate on rationality and on opportunity identification.

**** By hybrid organizational models we refer to structures that mix the three fundamental innovation organizational models identified by Baldwin and von Hippel (2011): producer innovator, single-user innovator and community innovator.

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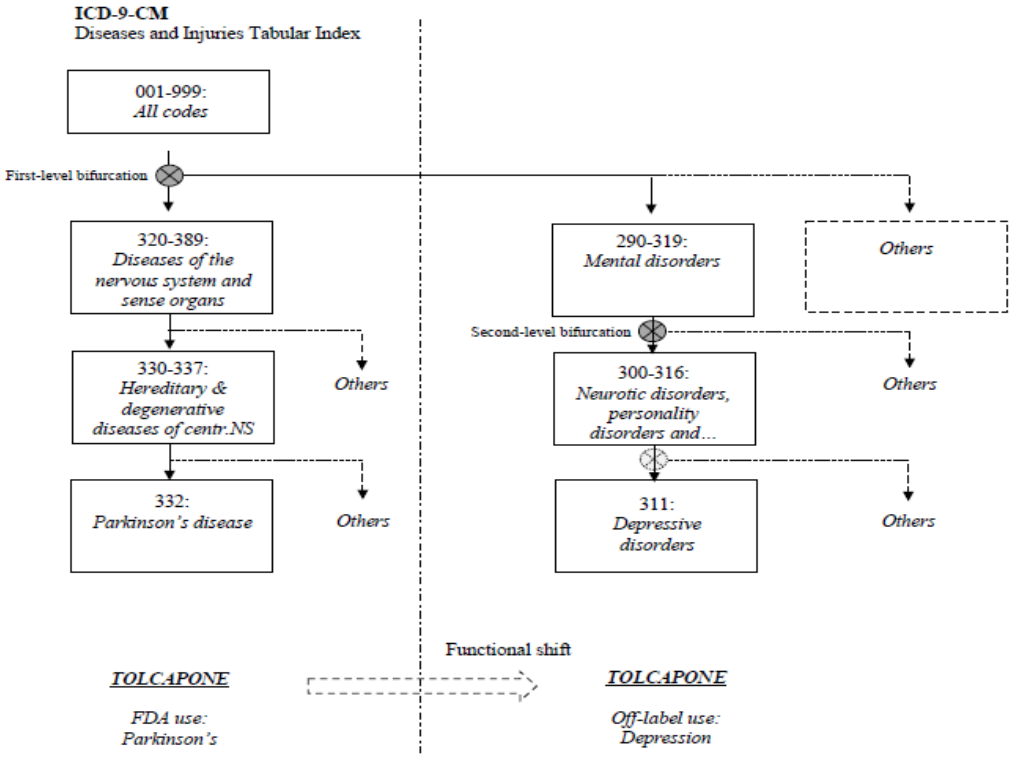
Figure 1. *Exaptation as distance on the ICD-9-CM database* **



** The subset of the ICD-9-CM for two uses (FDA and off-label) of the drug tolcapone. Tolcapone is FDA-approved for Parkinson's disease and is used off-label for depression. Parkinson is assigned code 332 in the ICD-9-CM and is part of sub-class 330-337 ('hereditary and degenerative diseases of central nervous system'), which belongs to class 320-389 ('diseases of the nervous system and sense organs'). The ICD-9-CM assigns the code 311 to depressive disorders, which are included in sub-class 300-316 ('neurotic disorders, personality disorders, and other non-psychotic mental disorders'). In turn, the 300-316 subclass is part of the 290-316 class ('mental disorders'). Both 320-389 and 290-316 are part of the 001-999 total set of diseases and injuries. The distance is assessed by measuring the path on the ICD-9-CM between the FDA-approved and the off-label uses

Figure 2. *The long tail of emergent and exaptive uses (dotted and full lines, respectively)*

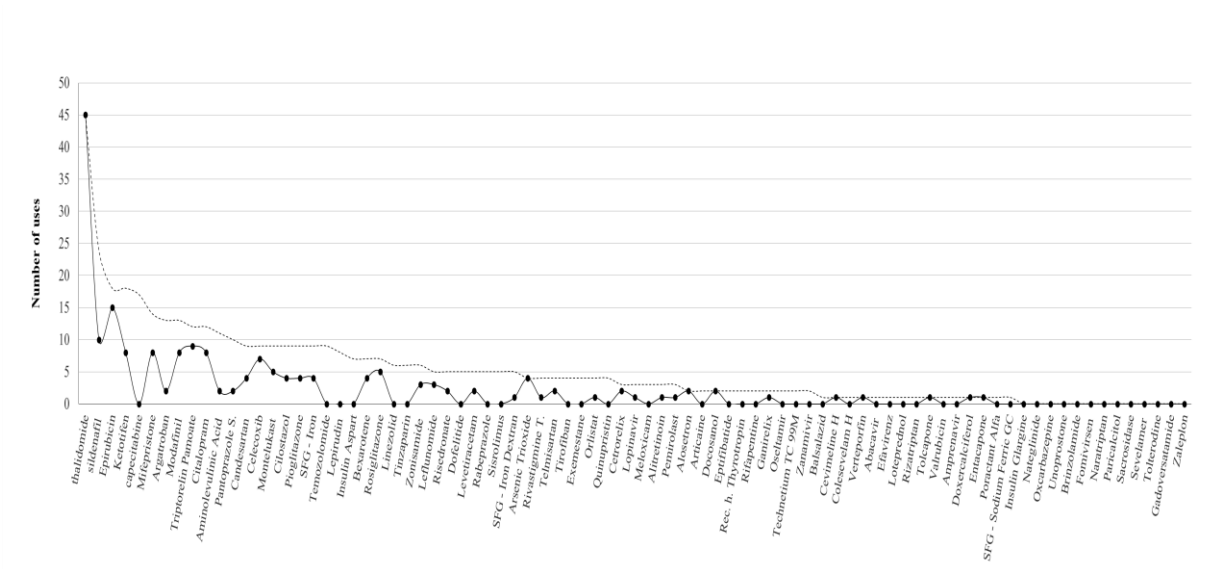


Table 1. *Comparison of the distance versus case approach for measuring exaptation*

	Exaptations: case approach	Non-exaptations: case approach	Total-exaptations: dist. approach
Exaptations: distance approach	162	62	224
Non-exaptations: distance approach	20		
Total-exaptations: case approach	182		

Table 2. *Main results*

YEAR	N°. of NMEs	N°. of Entry Uses	N°. of Emergent Uses	N°. of Exaptations	Exaptation/ Emergent Uses	Exaptation /All Uses	Emergent Uses/ NMEs	Exaptation /Entry Uses	Exaptation /NMEs
2000	24	42	101	46	36%	26%	4.21	1.03	1.50
1999	30	52	153	51	34%	26%	5.10	1.06	1.73
1998	29	57	176	82	53%	42%	6.07	2.04	3.24
All	83	151	430	179	42%	33%	5.18	1.40	2.19

Figure 3. *Percentage distribution of radical/semi-radical/non-radical uses versus exaptive/non-exaptive uses: almost all radical uses are exaptive*

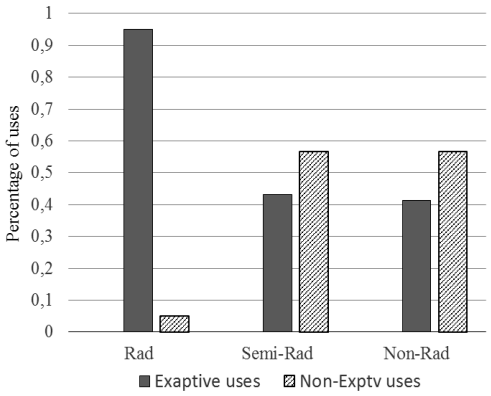
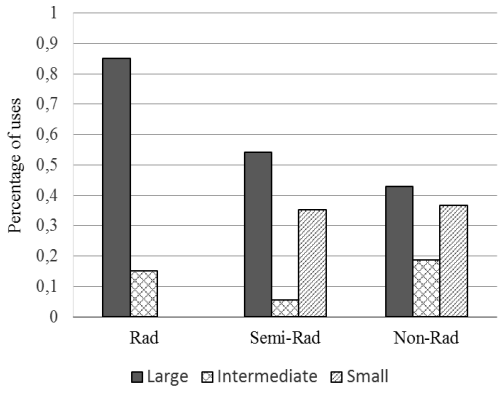


Figure 4. *Percentage distribution of radical/semi-radical/non-radical uses versus large/intermediate/small distance: almost all radical uses are associated with large distance jumps*



APPENDIX 1

Case	Original function	Exapted function	Comments
Laughing gas	Funfair entertainment	First anesthetic	Nitrous oxide (NO) used as laughing gas in funfairs. Anesthetic property discovered serendipitously by Pristley in 1800 and rediscovered by Horace Wells at a fairground in the 1840s, who used it for painless tooth extractions (Li 2006).
Methylene blue	Dye for textile industry	Staining agent in microbiology; first fully synthetic drug	"Ehrlich began using MB, the first aniline dye, to stain bacteria in 1880. By 1885, upon injecting it into a living frog, …, its nerve fibers were stained blue. Could the chemical dye, he reasoned, affect biological function to interfere with nervous transmission and exert an analgesic, or pain-killing, action in people? In 1891 Ehrlich tried MB for malaria. MB worked in mild cases. Nevertheless this represented the first instance of a synthetic drug being successfully used against a specific disease" (Meyers 2007, p. 41). "MB was the very first fully synthetic drug used in medicine. In 1891 it was applied … for the treatment of malaria" (Schirmer et al. 2011, p. e8).
Prontosil (Rubrum) then Sulfanilamide	Brick-red azo dye (textile industry)	First effective antibiotics (synthetic)	Used in textile industry, patented and branded as *Prontosil* (Meyers 2007), "which had been produced in tons by the dye industry for decades without anyone looking into its antibacterial properties" (Li 2006, p. 51). *Prontosil* was discovered to have antibiotics effect by Domagk (Nobel Prize, 1939) at Bayer. Active substance is sulfanilamide.
Mustargen	Mustard gas, chemical weapon	First cancer chemoterapic agent approved by FDA (1949)	According to the American Cancer Society: "from this disaster [Nazi bombing of Bari harbor in 1943], a chemical agent with anticancer activity was serendipitously discovered" (Meyers 2007, p. 126). See also Infield (1976) and Mukherjee (Mukherjee 2010).
Chlorpromazine	Antihistamine and potentiator of anaesthesia	First antipsychotic	In the early 1950s Laborit discovered the psychiatric effects of Chlorpromazine when he noted that: *"*our patients are calm, relaxed and euphoric even after major operations; they appear to really suffer less*"* (Meyers 2007, p. 267). "Chlorpromazine revolutionized the specialty of psychiatry. It brought legitimacy to the concept of biological psychiatry by demonstrating that a drug could influence the course of a major psychosis" (Maxwell and Eckardt 1990).
Antabuse	Rubber vulcanization	First anti-alcoholism drug	In I949 Danish pharmacologists Jacobsen and Hald ingested the vermifuge to prove safety. Then they noticed an unpleasant interaction with alcohol (Kragh 2008).
AZT	Cancer and herpes	First HIV drug	Developed as anticancer drug in 1964, 1970S, Wellcome acquired AZT to treat herpes (Li 2006).
Botox	Strabismus and other conditions	Botox Cosmetic	Orphan drug for the treatment of strabismus, hemifacial spasms, and blepharospasm (DeMonaco et al. 2006).