Measuring Exaptation in the Pharmaceutical Industry[1]

Abstract

Exaptation, the emergence of latent functionality in existing artefacts, is an important mechanism of innovation. In this paper we propose a method to measure the frequency of exaptation. We apply it to the pharmaceutical sector and offer the first measure of the frequency of exaptation in an industry. We show that exaptation accounts for about half of all innovations in the uses of drugs. We also show that some exaptations have a radical character and trigger cascades of innovation. By considering exaptation in their innovation process, organizations can change their investment decisions and product development practices and extract more value from existing products through use development.

1. Introduction

Innovation is a novel recombination or transformation of resources and ways of using them that creates value through a match to consumers´ needs and wants. Most of the research on innovation has focused on innovation as New Product Development and assumed that value is predominantly created through the introduction of new products (or services). With a few exceptions firms have also followed that pattern – new products have been matched to and equated with a single market.

In this paper, we propose an alternative approach -we anticipate that some products introduced for a specific market will later become used to address different needs or wants in a *different* market.

[1] Pierpaolo Andriani (corresponding author)
Kedge Business School, Department of Strategy
pierpaolo.andriani@kedgebs.com

Ayfer Ali
Universidad Carlos III de Madrid, Department of Business Administration
ayfer.ali@uc3m.es

Mariano Mastrogiorgio
University of Antwerp, Antwerp Centre of Evolutionary Demography (ACED)
mariano.mastrogiorgio@uantwerpen.be

Importantly, we posit that this emergent functionality is an innovation because it creates value in a novel way even if the product remains the same.

This alternative view can have implications for how organizations invest in innovation and extract value from their inventions. Latent product functionality can also enable organizations to adapt to changing environments thus making them sustainable and resilient. A product that was adapted for a specific market condition may have a different functionality that can be exploited if the original market disappears. In fact, an analogous version of this process of innovation exists in evolutionary biology and is termed 'exaptation' – a name that we borrow in this paper. It 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 not only in evolutionary biology but also in technology development. Many technological innovations, some of which radical, have been the result of exaptation (Andriani and Carignani 2014, Cattani 2006, Dew et al. 2004, Kauffman 2000). For instance, the microwave oven resulted from the discovery of a latent function of the radar magnetron and the first amplifier was exapted from De Forrest's Audion, originally designed for radio detection (Nebeker 2009). Exaptation has been crucial in the emergence of new industries. The modern pharmaceutical and chemical industries emerged as the result of multiple instances of exaptation of coal tar (Andriani and Carignani 2014).

To date, however, no study has quantified the frequency and the impact of exaptation in innovation. 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 stated by Kauffman? In this paper, we address this issue by measuring the frequency of exaptation in a specific technological sector: the pharmaceutical industry. We expect that our results, while not of the exact same size, are broadly generalizable to other industries.

Measuring the frequency of exaptation matters for several reasons. First, as noted earlier, exaptation refers to the discovery of a 'latent' functionality in an existing artefact. Measuring the

frequency of exaptation can help us estimate the latent value in existing artefacts. Extracting such latent value is, theoretically, cheaper than creating new artefacts for new functionalities as the creation process itself is costly.

Second, measuring exaptation improves our understanding of radical innovation (Andriani and Carignani 2014; Levinthal 1998) and the origin of new industries. In Table 1 we report a selected list of exaptations that have shaped the evolution of the pharmaceutical industry. The table shows that many fundamental breakthroughs in drug discovery are exaptive. The first antiseptic, anesthetic, antibiotic, antidepressant, sedative, antipsychotic, anti-alcohol addiction, cancer chemotherapy agent, erectile dysfunction drug, HIV drug were not invented but exapted from products already available in the market or in laboratories. Thus, exaptation is a source of a radical innovation and triggers the emergence of new industries and scientific trajectories.

Third, our proposed methodology gives scholars a solid base to assess the importance of exaptation in innovation. The research methods utilized so far are mostly qualitative and rely on the selection of specific examples. They are therefore unable to provide a scale of the phenomenon.

Fourth, our paper decouples innovation from new product development and proposes a value based view of innovation where development of new products is not always necessary for addressing customer needs or wants. This separation of new product development from innovation implies that value can be achieved without designing new solutions as the solution may be already available. This new way of thinking can then be expanded by researching and identifying processes that can help firms extract more value from their current products.

Finally, exaptation is related to serendipity (Dew 2009; Merton 2004), which acts on existing entities by revealing some unforeseen possibilities and connections hidden in them. In other words, serendipity uncovers potential exaptations. Thus, a measure of the frequency of exaptation is also indirectly a measure of serendipity in innovation (Ban 2006; Comroe Jr 1977; Duffin 2000; Li 2006; Meyers 2007). While serendipity, by definition, is not intentional, policymakers and organizations

may implement processes that could "favor the prepared mind". One such process, advocated by Nobel laureate Luria is 'controlled sloppiness' in scientific research (Merton 2004, p. 192).

The literature shows that exaptation: a) is important in the history of multiple industries (Dew et al. 2004); b) affects both whole artefacts and internal modules (Andriani and Carignani 2014); c) interacts with adaptive processes to trigger cascades of innovations (Andriani and Cohen 2013, Lane 2011); and d) extends to technological capabilities (Cattani 2006). All these findings show that exaptation is important. But *how important* is exaptation? What is the percentage of innovations due to exaptation? The evidence presented in the literature on exaptation and technological innovation is mainly anecdotal. Without a quantification that demonstrates the relevance of this phenomenon, it is difficult to argue for respectively a change in innovation policy at the macro level and a change in R&D management practices at the micro level. In this paper, we propose the first systematic measure of the frequency of exaptation in technological innovation. By applying it, we find that in the pharmaceutical industry approximately half of the new uses of existing drugs are due to exaptation.

The rest of the paper is organized as follows. In Section 2, we introduce the concept of exaptation and explain its theoretical significance. In Section 3 we describe the empirical framework. In Section 4 and 5 we present and discuss our results. Section 6 concludes and presents some implications for innovation and organizations.

2. Literature Review

Exaptation

Exaptation in evolutionary biology refers to biological "characters evolved for other usages (or for no function at all), and later on 'coopted' for their current role" (Gould and Vrba 1982, p. 6). For example, birds' wings originally served to climb trees or capture preys and they were later on co-opted for flight (Gatesy and Baier 2009). Gould and Vrba (1982) contrasted exaptation—the

emergence of a new function for an existing trait—with the concept of adaptation, defined as the improvement of a trait through natural selection driven by a pre-existing fitness function.

Exaptation has gained increasing attention in the innovation literature (Andriani and Carignani 2014, Cattani 2005, Dew et al. 2004, Kauffman 2000). In the innovation literature, an exaptation refers to a technology or artefact that is fit for its current function thanks to features that were selected for old functions (or no function at all) and were later co-opted for the current one.

Despite the increasing interest, the literature on exaptation is still scant. Levinthal (1998) proposes the concept of 'speciation' to explain the sudden rise of market-changing innovations. He notes that the emergence of new technology-based markets is not necessarily accompanied by a parallel process of technology development, implying that the technologies that came to define new market trajectories were often developed for different applications.

The source of exaptation lies in the discovery of 'latent functions' of existing technologies (Bonaccorsi 2011). Dew et al. (2004) claim that the number of potential functions of any technology depends on a complex interaction between the technology and its context, which is influenced by the actions of users or inventors that try to combine the technology with new domains of use, markets and industries. This means that the total number of functions is un-prestateable and un-knowable (Felin et al. 2014, Longo et al. 2012). A subset of functions emerges through an adaptive channel, whereas other functions emerge through an exaptive channel. It follows that the exaptation potential is subject to combinatorial explosion and that the number of potential applications of existing technologies is inherently larger than what designers and inventors can conceive.

Cattani (2005, 2006) examines whether the technological knowledge base of a firm is predominantly the result of strategic foresight or if it rather consists in 'pre-adapted' capabilities that were accumulated in the past for different applications. In particular, he shows how the accumulation of capabilities in glass production allowed glass-manufacturers such as Corning to enter the fiber optics industry, where optical glass fibers started to be used for long distance communication. Andriani and Carignani (2014) delve into the micro-level aspects of exaptation, developing a framework for exaptation and modularity that takes into account the level at which exaptation takes

place within a modular architecture. They distinguish between 'internal', 'radical' and 'external' exaptation: an internal exaptation is the exaptation of an internal module of a technology, absent any change in the function of the whole technology; a radical exaptation is the exaptation of an internal module of a technology which leads, through horizontal transfer, to the emergence of a new technology, characterized by a new function built around the exapted module; an external exaptation is the exaptation of a whole technology: a new function is discovered for it, with little or no variation with respect to the architecture of the original technology. As radical and external exaptations introduce new functions in the economy, they may give rise to radical innovations. The exaptations we study in this paper belong mostly to the external category. External exaptations are more common in the pharmaceutical industry than in other industrial sectors because drugs are non-assembled products.

The relationship between an 'adaptive' technology, i.e. developed for its current function, and an exaptive technology, developed for a function other than the current one, is complex. Exaptation, as a fundamental process of innovation, often triggers adaptive responses, which, as Jacobs (1969, 1985) shows, may become self-reinforcing and assume the character of avalanches. Levinthal (1998) theorizes about an exaptive–adaptive cycle in the context of the wireless market; Lane (2011) elaborates an adaptive–exaptive model of innovation—which he calls 'exaptive bootstrapping'—based on technology adoption that includes technological, organizational, and societal considerations. His model is 'adaptive-exaptive' since the innovation that activates a cascade is adaptive. In contrast, Andriani and Cohen (2013) show that in both biology and technology innovation cascades may be triggered by exaptations. These cascades are exaptive-adaptive.

Overall, previous research on exaptation has focused on theoretical aspects and has been mainly conducted through case studies (Cattani 2006), theoretical frameworks (Andriani and Cohen 2013; Andriani and Carignani 2014; Dew et al. 2004) or computer simulations (Villani Bonacini, S., Ferrari, D., Serra, R. and Lane, D. 2007). In this paper, we are extending this research by measuring the incidence of exaptation in an industry.

3. Empirical Framework

3.1. Setting

The Pharmaceutical Industry

The pharmaceutical industry and its main product—drugs—create an ideal setting to measure exaptations because of the existence of functional databases, entry point regulation and classification of needs. First, the pharma industry is the only one we are aware of in which drugs' functions are classified and systematized in internationally recognized databases. This allows researchers to unambiguously identify the complete spectrum of functions for which the drug is being used. Second, drugs' access to market is heavily regulated whereas their subsequent uses are not. Entry point regulation implies that the initial drug function is uniquely specified and can therefore be used as a benchmark vis-a-vis the subsequent functions that emerge through off-label uses. Third, needs—in this case diseases—are also uniquely classified in international databases. In short, these three properties of the industry enable researchers to discriminate between adaptive and exaptive functions. The former is defined as functions for which the drug was developed. The latter refers to latent functions in existing drugs, which do not drive drug development and apply to markets different from the adaptive one

Drugs' Route to Market

FDA Regulation. The FDA, the agency of the US Department of Health and Human Services responsible for the protection of public health through the regulation of food, tobacco-related and pharmaceutical products, regulates the pharmaceutical industry by approving selected drugs for specific uses. In order to determine the approved function of a drug, the FDA reviews clinical trial results submitted by companies. If these results show that a drug is safe and efficacious for a particular disease, then the drug is approved for that use.

Off-Label Prescriptions. Once drugs are FDA-approved, they enter the market. As with every other artefact, availability radically expands the range of agents (such as clinicians, patient and other pharma companies) experimenting with the artefact and this engenders innovation (DeMonaco et al. 2006). Experimentation yields new uses for drugs, called off-label uses because these specific uses 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 US, 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, US spending for prescription drugs was about $322 billion (Anon 2012), the off-label drug market can be tentatively estimated at $68 billion.

Off-label constitutes an important innovation channel in the pharmaceutical sector. In a seminal paper, DeMonaco et al. (2006) find that about more than half of off-label uses are discovered by users (and not by manufacturers). Furthermore, they find that user-led innovation is characterized by a higher degree of functional novelty. Despite its obvious importance, research on off-label is curiously minimal and the earliest paper to systematically quantify the market was only published in 2006 (Radley et al. 2006).

3.2 Sample

Our sample consists of the new molecular entity drugs (NMEs) approved by the FDA in 1998. On average, the FDA approves 27 such drugs per year typically for a single use (Roin 2014). In 1998 the FDA approved 29 relevant NMEs (the total number of approved NMEs was 30 but one of them was a radioactive imaging agent used for diagnostic purposes and not to treat disease).

We chose the 1998 sample to allow for comparability with the DeMonaco et al. (2006) paper that looks at the role of clinicians in the discovery of off-label uses. Although their paper had a different purpose and used different methods from ours, some indicators overlap thereby providing an indirect validation of some of our results.

3.3 Measures

On Exaptation and Functional Novelty

Measuring exaptation involves an assessment of the functional novelty between two uses of the same artefact. The original (adaptive) use is the one for which the drug was developed and subsequently approved by the FDA. The emergent function represents a new use different from the one the drug was developed for. The question is whether the new use is sufficiently different from the original one to claim that the artefact's functional space has bifurcated and an exaptation has occurred.

Theoretically, function is a difficult concept to define unequivocally (Vermaas and Houkes 2006, De Winter 2010). As a result, one can approach functional novelty in two different ways: either on the basis of designers' intentionality (in our case pharmaceutical companies) or on the basis of users' selection (such as clinicians). In the first case, where function is defined based on intentionality, exaptation can be defined in terms of deviation from designers' intentionality. But intentionality is difficult to trace and document accurately.

In the second case, functional novelty is assessed in terms of a change in users' selection, which then generates a new or modified market for the artefact. In this case, exaptation is assessed by a comparative analysis of the characteristics of the original and the exapted market. The latter is the approach we use in this paper. Therefore, in this paper we define exaptation in terms of deviation of users' selection from the original function.

Assessing Exaptation by Measuring Distance

The approach we use to measure exaptation is based on the calculation of the 'distance' between the FDA-approved use (s) and the off-label use (s). A widely used tool for the identification of drug uses is the commercial database DrugDex (developed by MicroMedex). 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 the review of the available literature published in peer-

reviewed journals and other sources, such as FDA documents, regulatory standards, professional health organizations, and so on.

The distance between FDA and off-label uses is measured by mapping the uses onto the 'gold standard' of disease classification, i.e. the World Health Organization's International Classification of Diseases. To be more precise, we use 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 is currently the standard diagnostic tool for epidemiology, health management and clinical purposes in the US. It maps diseases to corresponding broader categories that group them on the basis of anatomy and pathogenesis. The classification forms a tree-like structure. Each disease is assigned a code, which can be up to five characters, where the first characters define the most generic category and the following characters progressively place the disease inside more specific baskets (subcategories).

An intuitive idea of the measure of distance is provided in figure 1. *Tolcapone* is FDA-approved for Parkinson's disease and is used off-label for depression. Parkinson's disease 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 ('mental disorders') class. 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.

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

In order to measure the distance, we followed these steps (details are shown in figure 2):

A. We obtain from DrugDex, for each NME, the text strings describing the FDA and off-label indications. In general, each NME is associated with one or more FDA-approved uses and multiple off-labels uses. We exclude from the analysis those off-label uses classified by

DrugDex as ineffective. The FDA-approved uses correspond to our originally approved uses, whereas the off-label uses correspond to post market-introduction emergent uses.

B. We match both FDA and off-label indications to their underlying diseases as reported in the International Classification of Diseases, version ICD-9-CM.

C. In order to calculate the distance between the FDA-approved use and an off-label use, we count the number of bifurcations that separate the FDA-approved code from the off-label code in the ICD-9-CM (see figure 1 for an example). We weigh the bifurcations according to the level at which they are located within the nested tree structure. A higher level bifurcation (first or second digit in the string) indicates a partition in more general and distant classes than a lower level one. Therefore, we assign a weight of 0.5 to the first-order bifurcation, and 0.25 to the second-order and so on. 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 consider for each DrugDex use (FDA and off-label) all the possible pairs of FDA-off label codes, calculate the distances between them and then select the minimum distance. Therefore, a conservative choice is made since a shorter distance is less likely to be classified as an exaptation.

D. The threshold to discriminate between adaptive and exaptive uses is set at the second bifurcation level of the ICD-9-CM. Although the choice of the threshold is somewhat arbitrary we feel that our decision is reasonable and conservative for the following reasons: first, the second level classes are very broad and the large majority of drugs used to treat diseases in each second level class are not in market competition with one another. Second, DeMonaco et al. (2006) using the same sample (but a different methodology) arrive at the estimate that approximately 60% of off-label uses are functionally novel. Although they do not clearly discuss the concept of functional novelty, it seems reasonably resonant with the concept of exaptation. Our result, 57% (see next section) is strikingly similar. Third, the comparison between the two methods we use to assess exaptation (distance and in-depth methods—see below for details about the second one) shows a maximum of conflicting results around the 0.25 threshold (see Figure) but substantial agreement above and below the

0.25 threshold. As the second method is not based on distance, this constitutes an indirect confirmation that the threshold is rightly set.

E. We repeat this process for all FDA-approved and off-label uses at two points in time: 2003 and 2013.

<<< Please insert Figure 2 about here >>>

The distance method suffers from some disadvantages that are inherent in the ICD-9-CM classification:

1. It may erroneously classify an off-label use as an exaptation due to insensitivity to mechanism of action. 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.
2. 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.
3. Class 16 is a catch-all group ('symptoms, signs and ill-defined conditions'). Hence distance from and to class 16 is meaningless and ignored in our study.
4. The distance method 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 is however also its weakness, as it is not possible to perform any in-depth analysis based on mechanism of action and/or disease pathway.

Alternative measure of exaptation frequency as a robustness check. To compensate for the shortcomings of the distance method and verify its accuracy, we adopted a more qualitative method based on the mechanism of action of the drug and conducted through extensive research on each drug. According to this qualitative method, FDA and off-label markets are assessed by direct analysis of each of the drug uses. The procedure is the following:

1. As with the distance method, we start from the description of the uses obtained from the DrugDex database.
2. Then we use available sources, such as academic articles, medical databases, Wikipedia articles, books, FDA documents, etc. in order to directly gauge the market difference between the FDA and off-label uses. To do this we look at the mechanism of action, disease description and, when available, historical evidence of drug use.
3. On the basis of this analysis, we code the use with a binary variable Y/N (Y: exaptation confirmed / N: non-exaptation).

In case of conflict between the two methods (the distance and the qualitative) on whether there is exaptation or not, the determination of the qualitative method prevails. Figure 2 maps exaptations based on the two different methods.

4. Results

4.1. Aggregated Results

The preliminary results are shown in Table 1 and Figure 3. The table reports the aggregated results of the number of off-label and exaptive uses for respectively the 2003 and 2013 snapshots. There are several differences between the 2003 and 2013 samples (see Table 1). First, off label uses drop out of the list, new ones appear and some 2003 off label uses are approved by the FDA in the meantime (see table 1 for details). Second, certain drugs show a large increase in the emergence of new uses. The growth of off-label uses seems to fall in two different classes: on the one hand, we find drugs such as '*thalidomide'* for which growth in uses is divergent as new uses tend to be substantially functionally different from the original use, hence exaptations (from 36 to 42 uses between 2003 and 2013, all of them exaptations). On the other hand, we find drugs such as '*capecitabine'* for which growth is entirely adaptive (from 4 to 17 uses in 10 years). The purely adaptive growth is easily explained by the high toxicity of chemotherapy drugs, which prevents their utilization outside of cancer therapy thus limiting experimentation and emergence of exaptations. If the growth of adaptive

off-labels of *capecitabine* is excluded, the 2003 and 2013 ratio of exaptation to overall new uses is virtually the same.

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

These results indicate that exaptation is an important innovation channel and accounts for approximately 45% of new use innovations in pharma.

Figure 3 shows that about 77% of exaptive uses involve a first-order bifurcation, exhibiting a large distance between originally developed and emergent uses. This indicates that for the majority of exaptive uses the off-label use is not only different but dramatically different from the FDA-approved use.

<<< Please insert Figure 3 about here >>>

4.2 Drug-level results

In figure 4 we show results for off-label and exaptive uses at the drug level for the 2013 sample, which are broadly similar for the 2003 sample. The distributions of all off-label and exaptive uses are highly asymmetric and long-tailed. This is confirmed by a normality test, which confirms that they are not normal. Figure 5 shows a double logarithmic cumulative size-frequency graph of off-label uses per drug. Although the scarcity of points doesn't permit to draw firm conclusions, a KS (Kolmogorov-Smirnov) test confirms that the distribution may follow a power-law type (Newman 2005). As it is typical of long-tailed distributions, we note the presence of extreme events such as *thalidomide*, characterized by a surprising number of 42 off-label uses, all of which are exaptive. In general, we expect that each drug is characterized by a mix of adaptive/exaptive new uses. We also note a correlation between the number of all off-label and exaptive off-label uses (R^2=0.849 for 2003 and R^2=0.760 for 2013).

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

<<< Please insert Figure 5 about here >>>

5. Discussion

We start our discussion section with a short case on '*thalidomide'*. The history of this drug encapsulates the essential aspects of our results.

a. ***A brief history of thalidomide***

Thalidomide probably represents the worst tragedy of post-WWII pharmacology history (Stephens and Brynner 2009). Originally developed as a tranquillizer and morning sickness drug (sold, from 1957, over-the-counter, after seriously deficient animal and human tests), this widely successful drug showed dramatic side effects, such as permanent destruction of peripheral nerves and severe malformation of fetuses (phocomelia). As a result, the drug was withdrawn from the market in 1962. In 1964, in Marseille, Dr. Sheskin was looking for a drug to alleviate the unendurable pain of a condition associated with leprosy: erythema nodosum leprosum (ENL). After exhausting all available drugs, he stumbled upon a discarded bottle of *thalidomide*. Having nothing to lose with a terminally ill patient, he tried it. The results went beyond any reasonable expectation: not only the pain but the disease itself disappeared. Because of this discovery, 90% of the leprosy hospitals around the world were shut down. Several years later, because some leprosy patients had tuberculosis, and some tuberculosis patients had AIDS (Stephens and Brynner 2009, p. 138), *thalidomide* turned out to be effective against several conditions associated with AIDS, such as aphthous ulcers and wasting. Once approved for one condition in 1998, *thalidomide* could be used for unrelated conditions off-label: "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).

The *thalidomide* story shows the three essential features of our results: first, drugs may have divergent and unrelated functions which are often discovered via a serendipitous route. Second, these new uses can be divided into incremental and radical innovations: some uses represent an incremental improvement over existing treatments, whereby others offer treatment for previously incurable diseases. Third, the tight link between adaptive and exaptive developmental routes generates cascades of innovation. *Thalidomide* was originally developed, adaptively, as a tranquillizer. The multiple exaptations that ensued after the drug's withdrawal from market in 1962 led to research programs

devoted to uncover its mechanism of action. This understanding was then used to develop new drugs (as effective as *thalidomide* but without its terrifying side effects), that in turn enabled the treatment of new diseases. The exaptive/adaptive improvements therefore act to generate cascades of innovations.

b. Radical Exaptations

The impact of exaptations reported in this paper varies greatly between two extremes: radical and incremental. We consider radical those exaptations that 1) offer a treatment for a previously intractable or poorly treated disease; 2) may reveal new scientific and technological trajectories deriving from the discovery of unsuspected possibilities hidden in existing artefacts; and 3) may lead to a cascade of ensuing innovations. The discovery of antisepsis, sedatives, anti-depressants and anesthetics reported in Appendix 1 falls in this category. For instance *thalidomide*, after the initial catastrophe of phocomelia, collected more than 40 off-label uses. In particular, we find evidence of cascades of exaptive off-label uses. Incremental improvements, on the other hand, add to the current stock of drugs for a specific disease.

The most significant example of the former in our database is represented by *thalidomide* (see above). Radical exaptive uses generate new markets and revenue streams. We find about 11 examples of radical exaptations in our database, which are illustrated in the table below.

<<< Please insert Table 2 about here >>>

Some radical exaptations that appeared as off-label prescriptions have been subsequently approved by the FDA. We found 2 such cases: *thalidomide* for 'multiple myeloma' and 'erythema nosodum leprosum'.

Radical off-label exaptations indicate that the off-label channel constitutes more than a simple diversification mechanism for FDA-approved drugs. It constitutes a distinct channel of radical innovation, which starts from the usually serendipitous discovery of unsuspected potential in an existing drug and then often leads to systematic research meant to uncover the science behind the discovery. The example of *thalidomide* clarifies this point: the exaptive discovery of *thalidomide*'s

effectiveness against diseases characterized by inflammatory and auto-immune properties led to systematic research to identify the chemical pathways affected by *thalidomide*. Research clarified that it disrupted two growth factors and related chemical pathways. This discovery caused the selective expansion of the application range of *thalidomide* to diseases in which these growth factors were over-expressed. The serendipitous discovery that *thalidomide* also had antiangiogenesis properties suggested its utilization as an anti-cancer drug (Stephens and Brynner 2009). In Figure 6 we show the cascade of papers that was triggered by D'Amato, Loughnan, Flynn, & Folkman (1994)'s historical paper on antiangiogenesis. These examples show that a radical off-label exaptation may trigger a cascade of further applications, some of which derive from the focused application of the science behind the exaptation, whereas others are suggested by proximity with the exaptation.

<<<please insert Figure 6 about here>>>

c. Potential outcomes of investment in exaptive discovery

Our results show that exaptation is an important determinant of scientific discovery and technological development. For the first time we can quantify that the percentage of innovations that follow an exaptive route is approximately 45%. These results raise some questions: the off-label and exaptive channels have so far been predominantly utilized by users, thus confining exaptive discovery to a channel with very limited resources. What would happen if research in off-label and exaptive uses became mainstream? In other words, what is the potential of exaptation for organization?

Several scholars (Dudley et al. 2011, Meyers 2007, Roin 2014, Scannell et al. 2012) claim that the rate of innovation in the pharmaceutical industry has been declining in the past decades despite a massive increase in spending. Scannell et al. (2012) writes about an inverse Moore's law in pharma productivity: spending per approved new drug doubles approximately every 9 years. Multiple explanatory causes are offered: scarcity of available targets (Le Fanu 2011), safety costs (Meyers 2007) and, as Dudley et al (2011, p. 1) write, lack of investment in off-label use development: "major reason for reduced productivity is the lack of systematic evaluation of additional indications that each

drug can target, both during the drug's development phase and subsequent to its arrival on the market".

DeMonaco et al. (2006) contrast the inefficiency of the traditional new drug development, that can take up to 15 years and can cost up to 1.5-1.8 billion per drug (Mestre-Ferrandiz et al. 2012), with the effectiveness, rapidity and low cost of field discovery via the off-label route. Roin reports that off-label development may take as little as three years and cost at most 300 millions. DeMonaco et al. (2006, p. 12) write: "Would it therefore not make both clinical and economic sense to study and improve and support the process by which clinicians discover and report new applications for existing drugs?"

Anecdotal evidence suggests that investing in off-label research may yield a higher pharmaceutical productivity, deliver breakthrough innovation and at the same time reduce new drug development cost. Harvard professor Benjamin Roin (2014, p. 4) writes: "There is hope that developing new uses for existing drugs could "convert cancer into a treatable chronic disease." There is also a growing "expectation that a substantial percentage of rare diseases if not all 8000 rare diseases might be treatable with drugs in the current pharmacopeia". This view is shared by scholars and practitioners alike (DeMonaco et al. 2006, Dudley et al. 2011, Hemphill 2012, Radley et al. 2006, Walton et al. 2009).

Our exaptation results enable us to develop this reasoning further. We attempt to estimate the importance of investing in use development in the following way:

1. The total number of NMEs approved by the FDA between 1940 and 2011 is 1527. This is a lower boundary for all available NME drugs in the world which includes drugs approved in other countries.
2. The average number of uses per drug is 18 (Walton et al. 2009). This number implies that the lower boundary for the total number of uses for existing NMEs is approximately 27000. This number gives us an estimate of the potential supply of solutions available to treat diseases. We call the set of uses the solution space.
3. Our results based on the 1998 sample of DrugDex database show that about 45% of uses are exaptive. Among the exaptations, about 23% of solutions cross the 2nd bifurcation, that is,

they fall in the same ICD-9-CM general class, whereby the remaining 77% cross the 1st order bifurcation and fall into a different general class. We call the entire set of diseases and its organization into classes in the ICD-9-CM the 'need space', as it represent the entire set of addressable problems and potential sources of revenues for the pharmaceutical industry. In Figure 7 we show a subset of the need space, namely classes 7 ('diseases of the circulatory systems') and 8 ('diseases of the respiratory system'). In the figure we show the second level partition of diseases for class 8. A drug specifically introduced for a target in class 8 has an average of 18 latent uses. These uses effectively explore the need space: off-label adaptive uses explore the immediate proximity of the focal drug that is the subclasses 'pneumonia and influenza' (codes 480-488). This means that they will address conditions similar to the focal drug's FDA-approved uses. Exaptive uses on the other hand explore beyond the adaptive area (in this case the 'pneumonia and influenza sub-subclass') and cross either the 2nd or 1st bifurcation. In the former case, they explore other subclasses within class 8 (in Figure 7 this corresponds to all subclasses except 480-488). In the latter case, exaptive uses explore the entire need space outside of class 8.

<<< Please insert Figure 7 about here >>>

4. We can now try to match the solution space with the need space. The solution space can be partitioned in three sets: the adaptive set, 1st order exaptive set and 2nd order exaptive set. The adaptive set explores the proximity of the focal use. About 55% of uses fall in this category. Sildenafil (commercial name: Viagra) is a good example. It has 24 new uses 17 of which are adaptive, i.e. explore uses proximal to the FDA-approved use. These 17 new uses mostly cover conditions proximate to the original erectile dysfunction problem, such as erectile dysfunction caused by other diseases. In contrast, exaptive uses do not explore by proximity but jump across the need space to conditions that may be completely unrelated to the focal use. As about 45% of uses are exaptive and about 75% of them cross a first order bifurcation, exaptive uses constitute an exploration mechanism that reach areas far apart from the focal use. Moreover, a fraction of 1st order bifurcation uses—about 11%—are radical in nature, that is they represent cures for previously intractable diseases, significant advances over existing

therapies, or open up new scientific trajectories. This translates into a number of about 1300 potential radical treatments, of the like of *viagra* or *thalidomide*.

5. What part of the solution space has so far been explored? Given the estimate of 18 uses per drug, the lower boundary of uses in the solution space is about 27000. An estimate of the extent of the solution space explored so far can be obtained by contrasting the estimate of 18 uses per drug (from which we obtain the extent of the solution space) with the average number of off-label uses reported in the DrugDex database. For the sample of NMEs approved in 1998, this number is 5.9. It follows that on the basis of our sample only about a third of the solution space has been explored.
6. In Figure 8 we show an alternative classification of disease (the need space) based on the expected returns from investment in new drugs. Profit maximization-driven investments concentrate on the internal circle, that is, on common diseases in rich markets. Breast or prostate cancer, diabetes and dementia constitute obvious targets. The second set—first ring in figure 8—is populated by 'orphan' diseases. These are rare conditions that have not been 'adopted' by the pharmaceutical industry due to the lack of financial incentive. In the third set, outer concentric ring in figure 8, there are diseases widespread in third world countries but absent in developed markets. The distinction between adaptive and exaptive uses helps understand the potential of off-label uses in this field. Because adaptive uses search the need space in the proximity of focal drugs, they tend to explore the inner circle, that is developed markets' diseases. However, by converse, exaptive uses search far away from the focal use in the need space and hence explore the whole need space, including orphan and third world diseases. Therefore, exaptive off-labels can potentially address neglected diseases. Similarly, this can help address underinvestment in orphan diseases. How many exaptive uses lie unexplored? A minimum boundary can be calculated by multiplying the lower boundary of the solution space times the percentage of first order exaptive uses. That gives a lower boundary of 9300 exaptive uses. The potential for cure of several diseases, especially of the orphan and third-world types, without development of new drugs, becomes self-evident.

In conclusions, we have tried to estimate the potential of exaptive discovery and shown that if relevant investment and attention were devoted to it, its impact would be much bigger than what our measure (based on the users as innovators) has revealed.

<<< Please insert Figure 8 about here >>>

6. Conclusions and ideas for further research

Our paper shows that exaptive processes account for about half of all post-approval innovations in the pharmaceutical industry. Moreover it indicates that exaptations significantly contribute to radical innovation and cascades of change.

In the following, we present some limitations of the current study, we discuss the issue of generalizability to other industries and finish with some implications for innovation theory and practical decision-making driving investment decisions in innovation.

Limitations

Our results are based on the sample of 29 drugs approved by the FDA in 1998, a number that is close to the average number of 27 approved drugs a year. In our sample, we have an extreme event (i.e. low frequency/high impact) – *thalidomide*, which heavily affects the overall number of off-label and exaptive uses. Is *thalidomide* an outlier we should get rid of? Our analysis indicates that the distribution of off-label uses is long-tailed (probably power-law). In these distributions, extreme events are not outliers but on the contrary they form a necessary part of the distribution.

Our measure of exaptation treats the FDA-approved use as the benchmark from which to measure the distance to off-label uses. We implicitly assume that the FDA-approved use is the only one developed by the organization that filed for FDA approval. However, except for rare cases (where historical accounts are available), additional uses discovered by the manufacturer are unknown to us. Hence, we cannot exclude that some uses we classify as off-label were discovered by the organization that filed for FDA approval. The only evidence about this point comes from a previous study

(DeMonaco et al. 2006) that shows that most off-labels were discovered by users and not manufacturers.

Are our results generalizable?

Are these results generalizable to other industries? Only speculative answers can be given to this question. We expect that, although the numbers will certainly be different across different industries, the following general features will also be found in other sectors:

1. a significant fraction of discovery of new applications happens by the exaptation route;
2. a non-negligible fraction of exaptive discoveries are radical;
3. a non-negligible fraction of exaptive discoveries generate cascades of further innovations.

Several elements support our argument.

Off-label discovery depends predominantly on the role of user innovators. Does the pharma industry differ from other industry with regards to the role of users? Von Hippel and his coauthors (Von Hippel 1988, 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. In the highly regulated pharma industry, supply variety is strongly limited by regulatory approval. Consequently this limits the role of users in the supply of new drugs. However, FDA-approved drugs face significantly less regulations in the off-label market, where users (essentially clinicians, family doctors and patients) are free to explore the full range of potential uses. In one word, regulation limits supply variety but not uses variety. From the viewpoint of uses variety, innovation in pharma does not differ from other sectors where users play an important role.

Exaptations are at their core novel artefact-function associations. Such novel associations derive from the exposure of existing artefacts to new contexts. But, as in complex systems, such as organisms, industrial ecosystems and organizations, the number of new contexts to which an artefact

can be exposed is uncountable and the latent uses of an artefact are un-prestateable (Longo et al. 2012), it follows that the number of artefact-context associations is fundamentally unknowable. This is independent from the type of industrial sector.

R&D is presumed to be guided by the linearity of the goal-driven approach. The reality, however, is that serendipity and chance play a fundamental role, even in science-driven sectors. Anecdotal evidence suggests that serendipity acts on existing structures, ideas, artefacts, biological entities or institutions, revealing some unforeseen possibilities and connections hidden in them. In other words, serendipity reveals potential exaptations. In principle, as there is no reason to expect that the role of serendipity is fundamentally different across industrial sectors, there is no essential reason to expect that serendipity-driven exaptation be different across industrial sectors.

Implications for innovation and organizations

In this section we discuss two important implications of our research for innovation theory and investment decisions in innovation projects.

a. Exaptation and financial returns

The development of the first anti-depressant (Marsilid) points to an implication of exaptive discovery, which may bear consequences on decision-making processes that drive investment decisions in innovation. Marsilid was developed as an anti-tuberculosis drug and its success exceeded the most optimistic expectations. However, Marsilid also generated an unexpected application as an anti-depressant: in fact, it was the first antidepressant in history. This new use resulted in an unexpected revenue stream whose development cost was zero. In general in any industrial sector, we observe that products that generate new unanticipated uses produce two different revenues streams: a revenue stream generated by investment in the planned use, and a second revenue stream generated by unanticipated uses. It follows that the return on investment for an adaptive project may exceed expectations due to the presence of a stochastic revenue term: the exaptive term.

If investment in a project is likely to yield returns from exaptive discoveries, should the probability of such returns be embedded in the investment decision-making process? This could be

achieved by considering two terms: the Return on Investment (ROI) generated by planned use(s), and the ROI generated by exaptive discoveries. The first term is the object of analysis of conventional financial risk analysis tools. But how to deal with the second term?

A starting point could be to calculate an estimate of the probability of exaptation and its statistical properties. Our preliminary results indicate that exaptations follow a long-tailed distribution, probably power law. Such distributions are characterized by the instability of their main moments. This means that the statistical properties of single events may not be knowable with statistical significance. However, the type of event distribution is knowable and this may help plan investment decisions. For instance, De Vany (2004) shows that, in the movie industry, information about the type of long-tailed distribution (e.g. the slope of a power law distribution) gives relevant information about the nature of uncertainty of the phenomenon under inquiry and, consequently, helps plan investment decisions.

The situation of the pharma industry indicates the potential for such an approach. The aggregate value of emergent uses accounts for about 21% of pharma revenues, of which, according to our calculations, about 60% are exaptive. This is a substantial fraction of revenues and should be included as an additional term in the ROI calculations. However, two qualifiers have to be added: first, the incidence of emergent uses varies widely across subsectors; second, within the exaptive uses there is a subclass, the radical uses, that exhibit the potential to generate exceptional returns, such as, Aspirin, *botox, minoxidil* and, in our database, *viagra* and *thalidomide*.

In aggregate, the emergent uses may substantially contribute to the innovativeness, creativity and financial wellbeing of a social system. The measure presented in this paper constitutes the first attempt to quantify such a contributor to innovation.

b. New product development and new use development

At a broader level, the existence and magnitude of the frequency of exaptation described in this paper leads to an important observation–innovation depends on both new product development and new uses development, NPD and NUD respectively. Moreover, new uses represent an important

innovation channel that gives rise to significant revenue streams that do not require substantial product modification. However, in organizations as well as in innovation research, there is a pervasive assumption that innovation is the same as NPD emphasized by the lack of mainstream studies documenting the number of new uses per technological artefact.

Building on the distinction between NPD and NUD together with the distinction between adaptive and exaptive processes, we propose the following taxonomy for future research (see figure 9):

<<< Please insert Figure 9 about here>>>

1. Adaptive development of new artefacts (example: the Manhattan project).
2. Adaptive development of new uses (example: *viagra* extension to the treatment of erectile dysfunction caused by non-related pathologies).
3. Exaptive development of new uses (example: Marsilid, the first anti-depressant exapted from Marsilid, the anti-tuberculosis drug).
4. Exaptive development of new artefacts (example: the microwave oven exapted from the magnetron, a radar component).

If new uses are important, how can organizations accelerate their creation? Essentially this can be done by multiplying the contexts to which organizational assets (among which there are technologies, capabilities and resources) are exposed. 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 the one day a week 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 and the organizational assets becomes a significant

contributor to innovation via the exaptation of existing assets. The third has to do with creating a permeable interface between the organizational assets and external networks. Initiatives such as cooperation with lead-users and innovation communities (Von Hippel et al. 1999), innovation tournaments (Terwiesch and Ulrich 2009), innovation markets (Huston and Sakkab 2006), co-design and crowdsourcing (Anderson 2012) and innovation platforms (Eisenmann et al. 2006) enable the expansion of the intelligence that can access organizational assets, and therefore increase the possibility of NUD.

In conclusion, exaptation reveals a fundamental property of complex systems, that is, that a function is an emergent property of the interaction between artefact and context. We offer a measure of the frequency by which this emergent property generates new variety in the economy.

References

Anderson, C. 2012. *Makers: The New Industrial Revolution*. New York, Random House.

Andriani, P., G. Carignani. 2014. Modular exaptation: a missing link in the synthesis of artificial forms. *Res. Policy* **43**(8) 1608–1620.

Andriani, P., J. Cohen. 2013. From exaptation to radical niche construction in biological and technological complex systems. *Complexity* **18**(5) 7–14.

Anon. 2012. *The Global Use of Medicines: Outlook Through 2016*. Parsippany, NJ. Available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS Institute for Healthcare Informatics/Global Use of Meds 2011/Medicines_Outlook_Through_2016_Report.pdf.

Ban, T. A. 2006. The role of serendipity in drug discovery. *Dialogues Clin. Neurosci.* **8**(3) 335–344.

Bonaccorsi, A. 2011. A functional theory of technology and technological change. C. Antonelli, ed. *Handb. Econ. Complex. Technol. Chang.* Cheltenham , Elgar, 286–337.

Bosworth, D. M. 1959. Iproniazid: a brief review of its introduction and clinical use. *Ann. New York Acad. Sci.* 809–819.

Cattani, G. 2005. Preadaptation, Firm Heterogeneity, and Technological Performance: A Study on the Evolution of Fiber Optics, 1970?1995. *Organ. Sci.* **16**(6) 563–580.

Cattani, G. 2006. Technological pre-adaptation, speciation, and emergence of new technologies: how Corning invented and developed fiber optics. *Ind. Corp. Chang.* **15**(2) 285–318.

Comroe Jr, J. H. 1977. Roast pig and scientific discovery. Part I. *Am. Rev. Respir. Dis.* **115**(5) 853.

DeMonaco, H. J., A. Ali, E. Von Hippel. 2006. The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies. *Pharmacotherapy* **26**(3) 323–332.

Dew, N. 2009. Serendipity in Entrepreneurship. *Organ. Stud.* **30**(7) 735–753.

Dew, N., S. D. Sarasvathy, S. Venkataraman. 2004. The economic implications of exaptation. *J. Evol. Econ.* **14**(1) 69–84.

Dudley, J., T. Deshpande, A. Butte. 2011. Exploiting drug–disease relationships for computational drug repositioning. *Brief. Bioinform.* Available at:

http://bib.oxfordjournals.org/content/early/2011/06/20/bib.bbr013.short [Accessed November 10, 2014].

Duffin, J. 2000. Poisoning the Spindle: Serendipity and Discovery of the Anti-Tumor Properties of the Vinca Alkaloids. *Can. Bull. Med. Hist. Can. d'histoire la médecine* **17**(1) 155–192.

Eisenmann, T., G. Parker, M. W. Van Alstyne. 2006. Strategies for two-sided markets. *Harv. Bus. Rev.* **84**(10) 92–101.

Le Fanu, J. 2011. *The rise and fall of modern medicine*. London, Little, Brown Book Group. Available at: http://www.jameslefanu.com/books#1 [Accessed November 24, 2014].

Felin, T., S. Kauffman, R. Koppl, G. Longo. 2014. Economic Opportunity and Evolution: Beyond Landscapes and Bounded Rationality. *Strateg. Entrep. J.* **8**(4) 269–282.

Fleming, A. 1929. On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of B. Influenzae. *Br. J. Exp. Pathol.* **10**(3) 226–236.

Gatesy, S. M., D. B. Baier. 2009. The origin of the avian flight stroke: a kinematic and kinetic perspective.

Gould, S. J. 2002. *"The" Structure of Evolutionary Theory*. Harvard University Press.

Gould, S. J., E. S. Vrba. 1982. Exaptation - a missing term in the science of form. *Paleobiology* **8** 4–15.

Gundling, E. 2000. *The 3M way to innovation: balancing people and profit*. Tokyo, Kodansha International.

Hemphill, T. A. 2012. The NIH Promotes Drug Repurposing and Rescue. *Res. Technol. Manag.* **55**(6) 6–7.

Von Hippel, E. 1988. *The sources of innovation*. Oxford, Oxford University Press.

Von Hippel, E. 2005. *Democratizing Innovation*. Cambridge: MA, MIT Press.

Von Hippel, E., S. Thomke, M. Sonnack. 1999. Creating Breakthroughs at 3M. *Harv. Bus. Rev.* (September-October).

Huston, L., N. Sakkab. 2006. Connect & Develop: inside P&G's new model for innovation. *Harv. Bus. Rev.* 58–66.

Infield, G. B. 1976. *Disaster at Bari*. London, New English Library.

Jacobs. 1969. *The economies of cities*. New York, Random House.

Jacobs, J. 1985. *Cities and the wealth of nations*. New York, Random House.

Kauffman, S. 2000. *Investigations*. Oxford, Oxford University Press.

Kragh, H. 2008. From disulfiram to antabuse: The invention of a drug. *Bull. Hist. Chem.* **33**(2) 82–88.

Lane, D. A. 2011. Complexity and Innovation Dynamics. C. Antonelli, ed. *Handb. Econ. Complex. Technol. Chang.* Cheltenham, Edward Elgar.

Levinthal, D. 1998. The Slow Pace of Rapid Technological Change: Gradualism and Punctuation in Technological Change. *Ind. Corp. Chang.* **7**(2) 217–247.

Li, J. J. 2006. *Laughing gas, Viagra end Libitor: the human stories behind the drugs we use*. Oxford, Oxford University Press.

Longo, G., M. Montevil, S. Kauffman. 2012. No entailing laws, but enablement in the evolution of the biosphere. *Proocedings Fourteenth Intenational Conf. Genet. Evol. Comput. Conf. Companion*. 1379–1392.

Maxwell, R. A., S. B. Eckardt. 1990. Chlorpromazine. R. A. Maxwell, S. B. Eckardt, eds. *Drug Discov. a Caseb. Anal.* New York, Springer, 111–122.

Merton, R. K. 2004. *The travels and adventures of serendipity: a study in sociological semantics and the sociology of science*. Princeton: NJ, Princeton University Press.

Mestre-Ferrandiz, J., J. Sussex, A. Towse. 2012. *The R&D cost of a new medicine*. Available at: http://news.ohe.org/wp-content/uploads/2012/11/RD-Cost-Exec-Sum-+-Contents.pdf [Accessed November 24, 2014].

Meyers, M. A. 2007. *Happy accidents: serendipity in major medical breakthroughs in the twentieth century*. New York, Arcade.

Mukherjee, S. 2010. *The emperor of all maladies: a biography of cancer* . New York, Simon and Schuster.

Mukhurjee, S. 2012. Post-prozac nation: the science and history of treating depression. *New York Times*.

Nebeker, F. 2009. *Dawn of the electronic age: Electrical technologies in the shaping of the modern world, 1914 to 1945*. New York, John Wiley.

Newman, M. E. J. 2005. Power Laws, Pareto Distributions and Zipf's Law. Available at: http://arxiv.org/PS_cache/cond-mat/pdf/0412/0412004.

Radley, D. C., S. N. Finkelstein, R. S. Stafford. 2006. OFf-label prescribing among office-based physicians. *Arch. Intern. Med.* **166**(9) 1021–1026.

Roin, B. N. 2014. Solving the Problem of New Uses. *Michigan State Law Rev.* **forthcomin**.

Rouleau, F., H. Laborit. 1982. *L'alchimie de la découverte*. B. Grasset.

Scannell, J. W., A. Blanckley, H. Boldon, B. Warrington. 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* **11**(3) 191–200.

Schirmer, R. H., H. P. Adlera M., E. Mandelkow. 2011. "Lest we forget you — methylene blue . . ." *Neurobiol. Aging* **32**(2325) 2325.e7–2325.e16.

Stephens, T. D., R. Brynner. 2009. *Dark remedy: The impact of thalidomide and its revival as a vital medicine*. Basic Books.

Terwiesch, C., K. T. Ulrich. 2009. *Innovation Tournaments: Creating and Selecting Exceptional Opportunities*. Cambridge, MA, Harvard Business Press.

Ventola, C. L. 2009. Off-label drug information: regulation, distribution, evaluation, and related controversies. *P T* **34**(8) 428–40.

Vermaas, P. E., W. Houkes. 2006. Technical functions: A drawbridge between the intentional and structural natures of technical artefacts. *Stud. Hist. Philos. Sci. Part A* **37**(1) 5–18.

Villani Bonacini, S., Ferrari, D., Serra, R. and Lane, D., M. 2007. An agent-based model of exaptive processes. *Eur. Manag. Rev.* **4**(4) 141–151.

Waine Jones, A. 2010. *Perspectives in drug discovery*. Linköping: Sweden, Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine.

Walton, S. M., G. T. Schumock, L. Ky-Van, G. C. Alexander, D. Meltzer, R. S. Stafford. 2009. *Developing Evidence- Based Research Priorities for Off-Label Drug Use*. Available at: available at effectivehealthcare.ahrq.gov/reports/final.cfm.

De Winter, J. 2010. *A Pragmatic Account of Functions*. Ghent http://logica.ugent.be/centrum/preprints/De_Winter_-_Functional_Explanation__DRAFT_24_.pdf (accessed 12/04/2014), Ghent University.

Appendix 1

Case	Original function	Exapted function	Comment
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, Waine Jones 2010)
Carbolic acid	Agricultural antiparasites	First antisepsis product	Discovered by Joseph Lister in the 1860s. (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)
Penicillin	Antiseptic and lab tool to isolate viruses (influenza)	First large spectrum antibiotic (natural)	"In addition to its possible use in the treatment of bacterial infections [Fleming referred to external use], penicillin is certainly useful to the bacteriologist for its power of inhibiting unwanted microbes in bacterial cultures so that penicillin insensitive bacteria can readily be isolated" (Fleming 1929, p. 236). Florey and Chain in Oxford didn't contemplate medical uses at the beginning of their research: "we started our work on the isolation and purification, not in the hope of finding some new antibacterial chemotherapeutic drug, but to isolate an enzyme which we hoped would [inactivate a chemical] common on the surface of many pathogenic bacteria" (Meyers 2007, p. 71).
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 (marketed as ***Phenergan)***	Antipsycothic (Chlorpromazine – commercialized as ***Thorazine, Largactil, Megaphen)*** 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) See also (Rouleau and Laborit 1982) "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	Originally used for rubber vulcanization, then exapted in medicine (Disulfiram) as a	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).

	vermifuge		
Marsilid (iproniazid)	Tuberculosis	First antidepressant	Antidepressant effect discovered in 1952 when researchers observed patients became "inappropriately happy" (Ban 2006, Bosworth 1959, Mukhurjee 2012)
AZT	Cancer and herpes treatment	First HIV drug	Developed as anticancer drug in 1964, 1970S, Wellcome acquired AZT to treat herpes (Li 2006).
Viagra	Sildenafil citrate for angina (coronary heart disease)	First oral erectile dysfunction drug	"Ian Osterloth learned that men during phase trial II sometimes suffered an unticipated side effect, …, referred in clinical trials as "unexpected benefits": the drug catalyzed their erections" (Li 2006).
Botox	Strabismus and other conditions	Botox Cosmetic (Botulinum Toxin A).	Orphan drug (approved 1989) for the treatment of strabismus, hemifacial spasms, and blepharospasm (DeMonaco et al. 2006).

Tables and figures

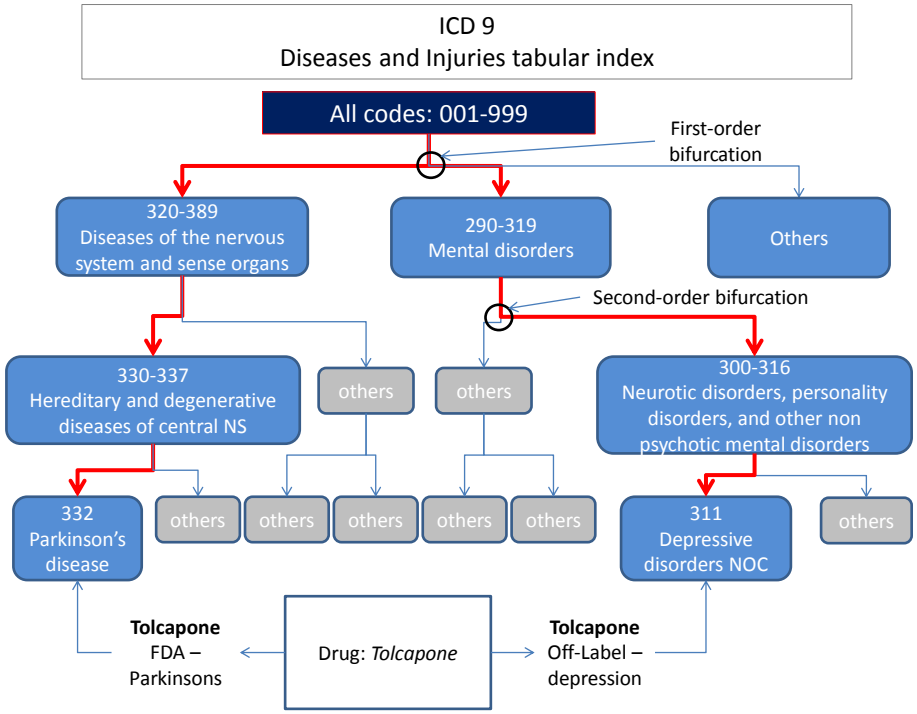

Figure 1 – The subset of the ICD-9-CM for two uses (respectively FDA and off-label) of the drug *tolcapone.* Notice how the measure of exaptation as distance emerges spontaneously from this representation.

A. Identify designed and emergent functions

Designed function	Emergent function
For each NME select FDA uses F_i. (F_i corresponds to a descriptive text string) F_i with i = 1,…, n	For each NME select offlabel uses O_j (O_i corresponds to a descriptive text string) from Micromedex database O_j with j = 1,…, m

B. Map F_i and O_j on ICD 9 database in order to assign most comprehensive set of diseases to function

Designed function	Emergent function
For each NME and index i, convert F_i into ICD 9 code set (Numeric string of up to 5 digits; each successive digit indicating correspondent nested level in tree) $F_i = (r_p s_p t_p x_p y_p)^F$; for p = 1,…,g	For each NME and index j, convert O_i into ICD 9 codes $O_i = (r_q s_q t_q x_q y_q)^O$; for q = 1,…,h

C. Calculate distance

For each pair *p/q for* p = 1,…,g and q = 1,…,h, compare $F_{ip} = (r_p s_p t_p x_p y_p)^F$ and $O_{iq} = (r_q s_q t_q x_q y_q)^O$ and select pair for which ICD-9-CM class difference is minimum.
Then, assign weight to O_{iq} [w_1=0.5 $w_2 = w_1/2$; etc] to obtain
$O_{iqw} = (w_1 r_q + w_2 s_q + w_3 t_q + w_4 x_q + w_5 y_q)$
and calculate metric distance for selected O_{iqw}.

Figure 2 – The figure shows the algorithm used to calculate the distance between FDA-approved and off-label use. Notice that the procedure of conversion of off-label codes from Micromedex to ICD-9-CM (step B) involves a potential degeneracy: one Micromedex descriptor may be converted in multiple (indexes *p* and *q*) ICD 9 codes. Likewise for FDA descriptors. This is why in step C we select the pair *p/q* characterized by the minimum class difference in the ICD-9-CM database. For instance, given an NME, if the code relative to an FDA-approved use *i* falls in class 6 and the codes for an off-label use *j* falls respectively in class 6 and 7, the off-label use in class 6 is retained. Then weights are assigned to the off-label use and distance between the origin of the ICD-9-CM and the position of the off-label use in the tree is calculated. The distance method inevitably involves an element of judgment in setting the threshold between exaptation and adaptation. We set the bar at the level of second-order bifurcation, that is, at the second digit in the ICD-9-CM classification.

type	number of cases	number of exaptations	uncertain cases	ratio exaptations/total
OFF-LABEL 2003	**136**	**78**		**57%**
OFF-LABEL 2013	**170**	**89**		**52%**
FDA 2003	**40**	**1**		**3%**
FDA 2013	**56**	**4**	**2**	**7%**
total: off label and FDA 2003	**176**	**79**		**45%**
total: off label and FDA 2013	**226**	**93**	**2**	**41%**
total: offlabel and FDA 2013 (without capecitabine)	**213**	**93**	**2**	**44%**

Table 1 - Two snapshots (2003 and 2013) of the number of off-label, FDA-approved and exaptive uses. Although the numbers are based on the sample of NMEs approved in 1998, off-label, FDA and exaptive uses change in the two snapshots. This is due to three 'flows': a) 35 off-label uses present in 2003 were not present or were significantly modified in 2013; b) 65 additional off-label uses were present in 2013; c) 5 of the 2003off-label uses were approved by the FDA in the period 2003-2013. The table divides the exaptations among off-labels and FDA uses. Some FDA uses are classified as exaptation, as the NME may have been introduced in other countries for a different use prior to the FDA approval. This is the case of thalidomide in 2003 and four newly FDA-approveduses in the 2003-2013 time period. As discussed in the text, the difference between the 2003 and 2013 numbers is mostly due to the expansion of off-label uses of *capecitabine*. However, the high toxicity of this drug effectively prevents its utililization outside of the cancer area, thereby precluding the emergence of exaptive uses. If the 13 new *capecitabine* off-label uses are removed, the statistics between 2003 and 2013 are virtually the same.

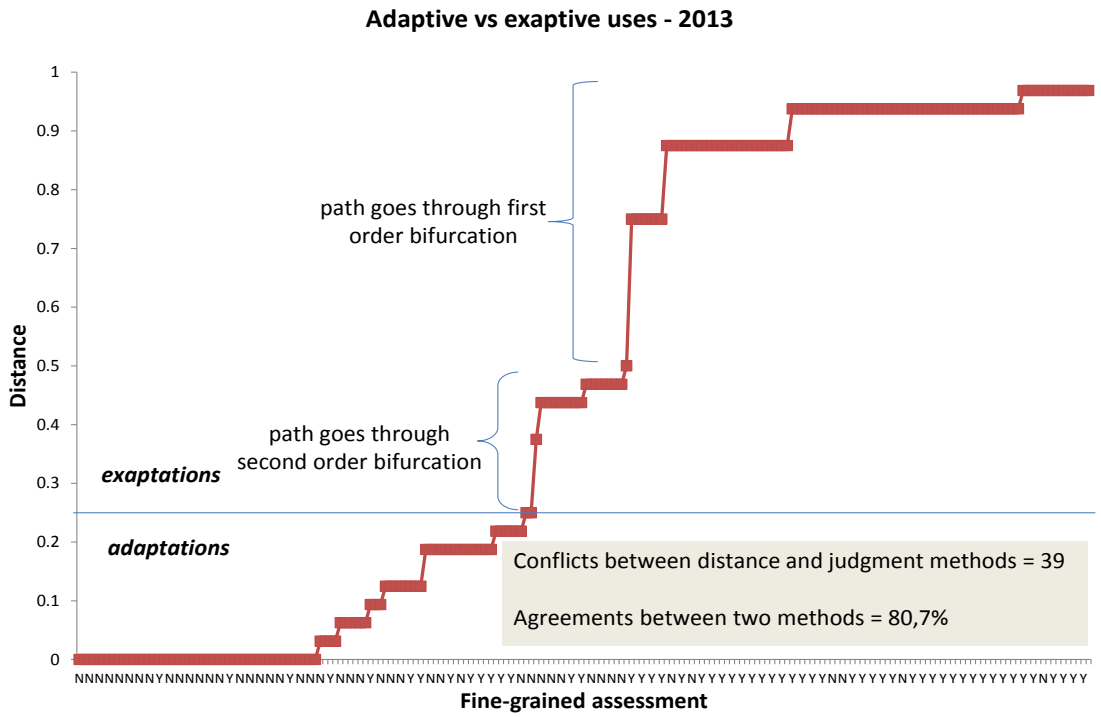

Figure 3 - Exaptive and adaptive uses calculated according to two methods: distance (algorythmic) and qualitative (based on in-depth fine-grained assessment of mechnism of action and market). The vertical axis reports the distance between FDA-approved and off-label uses. We consider as exaptive off-label uses that involve at least a second-order bifurcation, that is, a weighted distance of 0,25. The horizontal axis reports an independent, qualitative measure of exaptation, based on assessing exaptation via an analysis of mechanism of action and market. Percentage of agreement between the two methods is 80%. Most conflicts between the two methods cluster around the distance threshold of 0,25— an indirect confirmation that 0,25 is a real threshold.

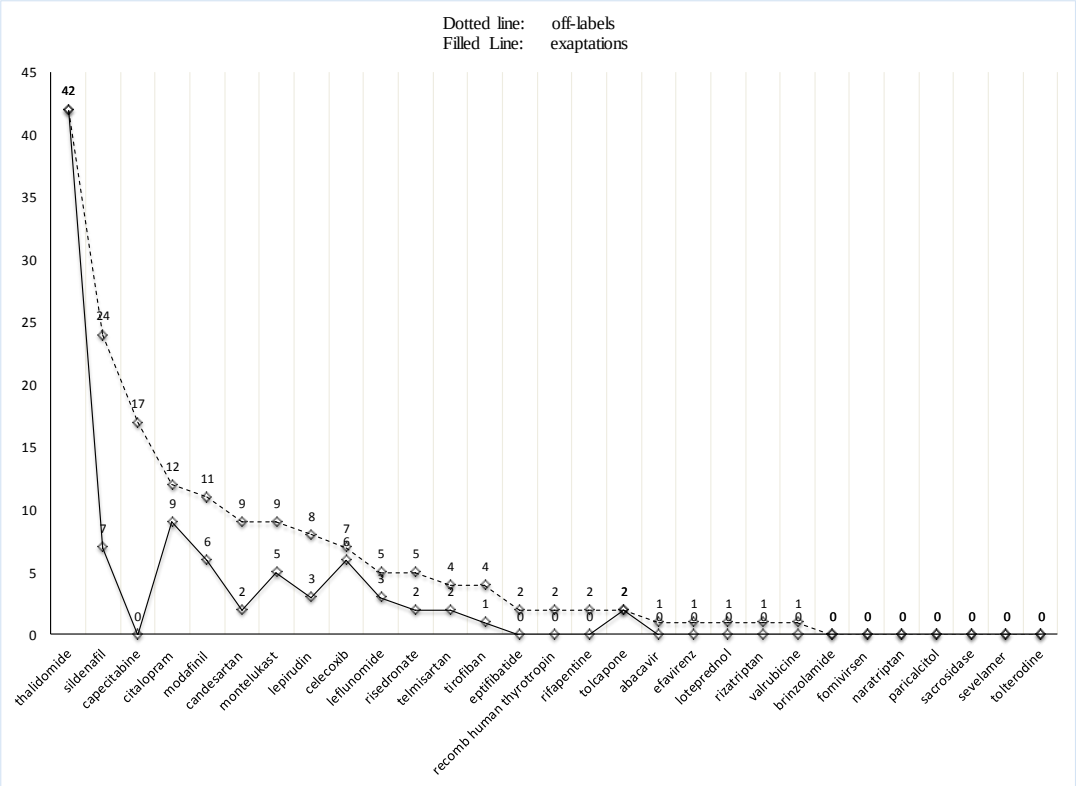

Figure 4 - Frequency of off-label and exaptive uses per drug. The distribution is very asymmetrical and long-tailed. As it is typical of long-tailed distributions, the head of the distribution contains some 'extreme events', namely *thalidomide* and *sildenafil* (*viagra*).

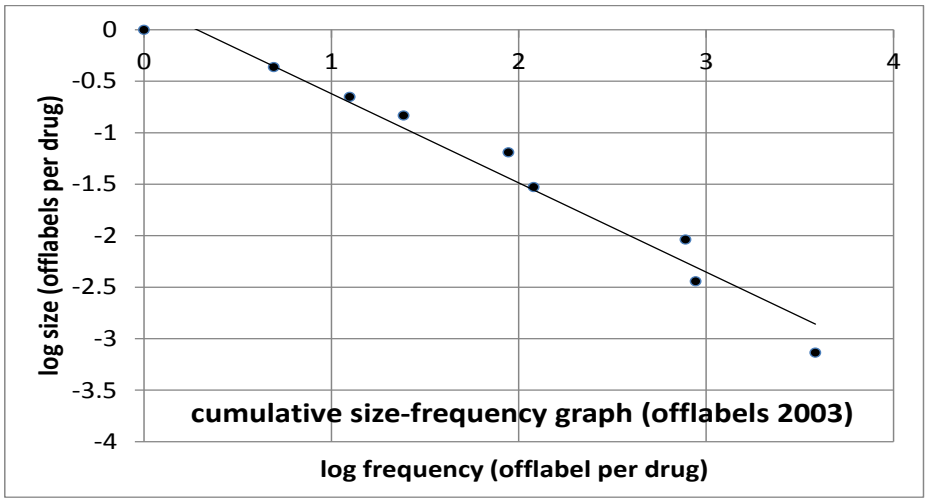

Figure 5 - Cumulative size-frequency distribution of off-label uses (2003) per drug. A KS test does not exclude a power law distribution. Size-frequency distribution for 2013 and for exaptation-only values show similar results.

NME	FDA (F) or off-label (O)FDA approved use	off-label use 2003	off-label use 2013
celecoxib	O	not present	colorectal adenoma
celecoxib	O	not present	familial multiple polyposis syndrome

citalopram	O	binge-eating disorder	same
thalidomide	O	lupus erythematosus	same
thalidomide	O	mesenteric panniculitis	disappeared
thalidomide	F (approved for erythema nodosum leprosum)		
thalidomide	O	not present	cachexia associated with AIDS
thalidomide	O	kaposi's sarcoma - AIDS related	same
thalidomide	O	aphthous ulcers	same
thalidomide	O	not present	aphthous ulcer of mouth - HIV infection - ulcer of esophagus
thalidomide	O	not present	iridocyclitis
thalidomide	O	multiple myeloma	same

Table 2 - Description of radical exaptive uses.

D'Amato RJ, Loughnan MS, Flynn E, Folkman J. (1994) "Thalidomide is an inhibitor of angiogenesis." *Proceedings of the National Academy of Sciences* 91.9: 4082-4085.

Citation (forward): 2327

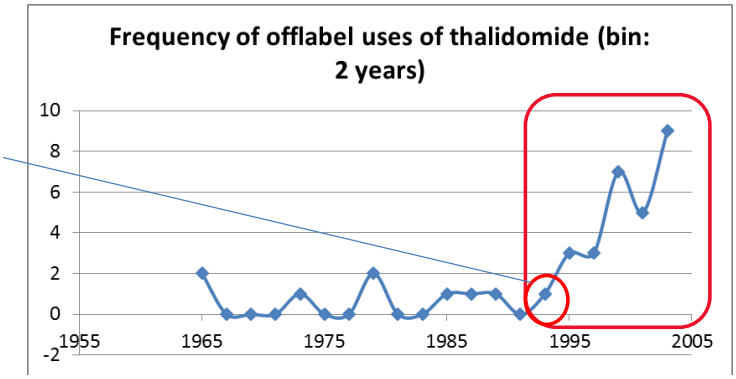

Figure 7 - Number of articles published on thalidomide. A 1994 article discovering the anti-angiogenesis properties of thalidomide results in a cascade of new research on the drug that results in the discovering of multiple new uses discovery

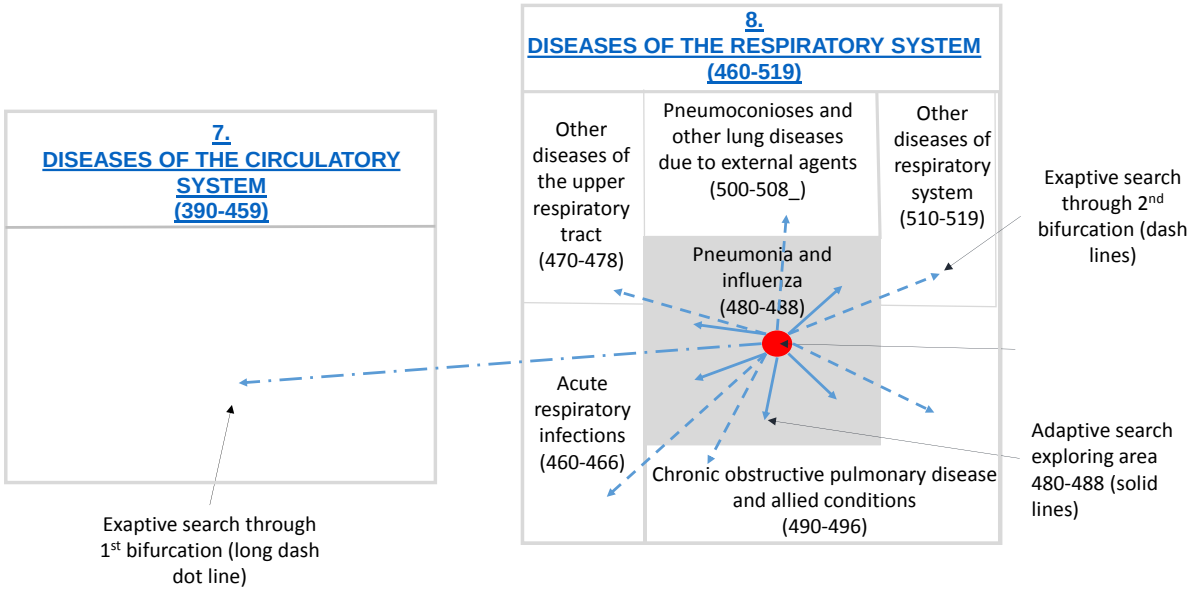

Figure 7 - The entire ICD-9-CM database classifies diseases from 1 to 999. For simplicity, the figure shows only two (out of the total of 17) ICD-9-CM classes pertaining to the first level classification. The classes are, respectively, class 7 *diseases of the circulatory systems* and class 8 *diseases of the respiratory systems*. For class 8 we report the second level classification, which partitions respiratory system diseases into 6 further sub-classes. We do not show further nested sub-subclasses. The red circle represents a hypothetical new (NME) drug designed for a condition that falls in the sub-class *pneumonia and influenza*. This condition will be classified by a number (or more) between 480 and 488. This drug's emergent (off-label) uses can be divided in three categories depending on the distance from the focal drug (red circle). Based on our earlier calculations, about 450% of new uses will be adaptive meaning that they will effectively explore the proximity of the reference drug in the space 480-488. They are indicated by solid lines starting from the focal drug. About 10-15% will be exaptive crossing 2nd order bifurcations: i.e. they cross the boundary between the *pneumonia and influence* sub-class and the other sub-classes in class 8 (460-519). The third class of exaptive uses will cross 1st order bifurcation and explore classes (other than 8) of the entire need space (long dash dot line).

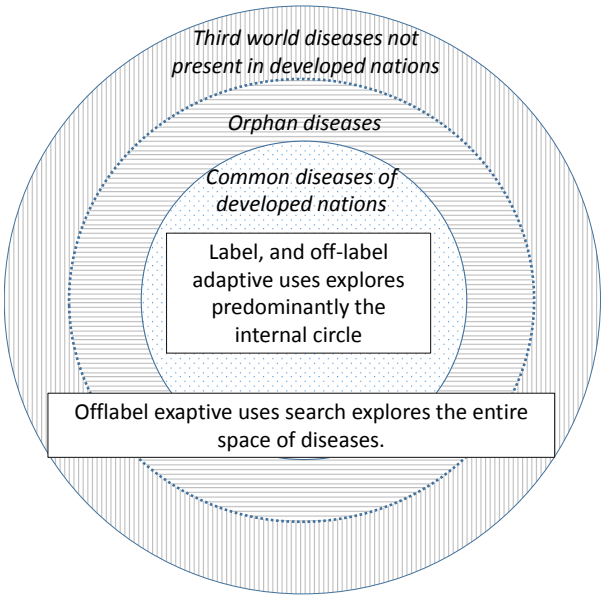

Figure 8 - This figure classifies diseases on the basis of potential economic return. Common diseases of industrialised countries constitute the major target of pharmaceutical investment. O*rphan* diseases are rare diseases; they are usually not 'adopted' by major pharmaceutical companies. Finally, diseases present in third world countries but virtually absent in industrialised countries, do not fulfil the conditions of adequate returns

for pharmaceutical investment. Because most drugs are developed for diseases in the central circle, it follows that off-label adaptive uses will largely fall in the same circle. However, by definition, exaptive uses are not constrained by proximity and hence will explore the entire extent of the need space. Our study shows that more exaptive uses are radical and as such address previously unmet needs. They are therefore more likely to provide solutions to diseases present in the outer two circles.

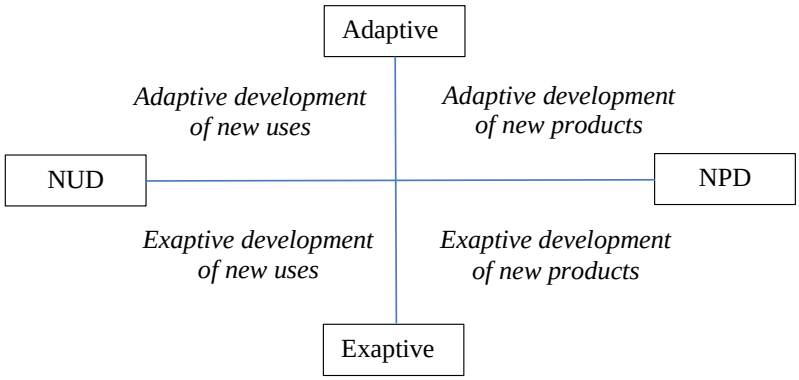

Figure 9 - A taxonomy of innovations based on the nature of development (adaptive vs exaptive) and the output of development (uses vs products).