Studies in History and Philosophy of Science 73 (2019) 1–7

Contents lists available at ScienceDirect

Studies in History and Philosophy of Science

journal homepage: www.elsevier.com/locate/shpsa

Scientific autonomy and the unpredictability of scientific inquiry: The unexpected might not be where you would expect

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HIGHLIGHTS

- The paper challenges common views about scientific unpredictability.
- Three epistemological conditions favoring the occurrence of the unexpected in a scientific inquiry are proposed.
- Call for a shift of focus in debate about science policies away from considerations on freedom of research agenda.
- Call for a focus on appropriate organizational features of science favoring flexibility and diversity.

1. Introduction

"I didn't start my research thinking that I would increase the storage capacity of hard drives. The final landscape is never visible from the starting point". This statement made by the physicist Albert Fert (2007), winner of the 2007 Nobel Prize for his work on the giant magnetoresistance effect, expresses a very common belief, especially among scientists, about the unpredictable nature of the development and results of a research program. Unpredictability is thus valued as the hallmark of pioneering, creative research: major scientific discoveries–or so the story goes–are often unplanned discoveries, made by chance, which then open whole new domains of inquiry.[1] Independently of the issue of their historical soundness, such considerations are often invoked in public debates on policies of research oversight and funding as grounds for defense of scientific autonomy: scientists should be left free to follow their curiosity and to set the orientation of their inquiry accordingly, rather than being asked to develop research programs addressing issues defined by others. Polanyi gives a somewhat lyrical form of this defense in his classical essay "The Republic of Science" (1962, p. 62): "Any attempt at guiding research towards a purpose other than its own is an attempt to deflect it from the advancement of science". He adds that "you can kill or mutilate the advance of science, you cannot shape it. For it can advance only by essentially unpredictable steps, pursuing problems of its own, and the practical benefits of these advances will be incidental and hence doubly unpredictable". In Polanyi's view, the supposedly unpredictable nature of scientific development militates for an internal definition of research priorities: a problem should be considered important in light of considerations internal to a given field of scientific inquiry and not (or at least, not primarily) in light of considerations deemed external to it (such as potential practical applications or, more broadly, utility in light of the needs and concerns, both practical and epistemic, of society). The orientation of the inquiry by such external considerations is thus deemed epistemically counterproductive and vain: one should not attempt to predict the unpredictable.

What is at stake here is the appropriate mode of setting the research agenda. In a nutshell, if scientific unpredictability, and hence the epistemic fecundity of science, is indeed hampered when the agenda is shaped by external considerations, then oversight of research should be kept to a minimum and "blind-delegation" (Wilholt & Glimell, 2011, p. 358) appears as the best way to go: the funders of science have to accept that they have very limited rights over the directions taken by the scientific communities to which they give money.[2] But is it really the case that a research whose agenda is set according to external considerations is less hospitable to the full flourishing of the unexpected than a research whose agenda is freely set internally by scientists? The present paper will challenge this common view by proposing three epistemological conditions that influence the occurrence of the unexpected in the course of a scientific inquiry, in light of which we will submit that a scientific inquiry whose agenda is set externally, or in part externally, may actually favor the occurrence of the unexpected. We will then argue that the issue of the *occurrence* of the unexpected should

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[1] Braben (2008), Couée (2013), Cadogan (2014).

[2] See also for instance Braben (2008, p. 14), and Resnik (2009, p. 84), for a defense of scientific autonomy grounded on considerations on the unpredictability of scientific developments. Of course, scientific autonomy can also be defended on various other grounds, see for instance Ruphy (2017).

https://doi.org/10.1016/j.shpsa.2018.08.002
Received 8 October 2017; Received in revised form 13 June 2018; Accepted 9 August 2018

be clearly distinguished from the issue of the *management* of the unexpected. Once this distinction is made, we advocate a shift in the debate on scientific autonomy away from considerations on freedom of research agenda and towards considerations on organizational features of science, such as flexibility and diversity. When discussing this shift in the final part of our paper, our aim is primarily to set a more relevant and cogent basis for this debate, and not to defend one way of setting the research agenda over another.

2. Preliminary terminological remarks

So far, notions such as "*internal* definition" of research priorities, "problems *of its own*", have been contrasted with notions such as "*external* considerations" (in the setting of science agenda). This contrast can be reformulated more precisely as a conceptual distinction between what we will call in the rest of the paper "endogenous" problems or factors vs. "exogenous" ones. An endogenous problem is a problem encountered and defined within the course of a scientific inquiry. It is internal to the dynamics of the scientific inquiry and its relevance and interest is evaluated solely by researchers involved in the inquiry, according to standards and needs internal to their community. For instance, an emerging question can be deemed important when its resolution is expected to affect other obstacles or pending issues within the concerned scientific field. By contrast, an exogenous problem is identified and formulated outside (or at least partly outside) a scientific field, incorporating interests and expectations of various components of society (and not only of scientific communities). Typically, challenges such as "curing cancer" or developing "secure, clean and efficient energy" or "inclusive, innovative and reflective societies"[3] constitute exogenous problems to be addressed by research, whereas the issue of the existence of the Higgs boson in particle physics is a typical example of an endogenous problem.

Note that our distinction between endogenous problems or factors and exogenous ones is not equivalent to the widespread distinction made between "basic" or "fundamental" science and "applied" science. First, our distinction does not (strictly) cover a distinction between the epistemic and the practical. Endogenous problems can be practical, non-epistemic problems and exogenous problems can be epistemic problems. Non-epistemic, practical endogenous problems are often technical or experimental obstacles encountered in the course of the scientific inquiry (whose aims can be purely epistemic). Consider for instance Thomas H. Morgan's classical research program in genetics in the 1930s. When trying to evaluate the distances between genes on Drosophila chromosomes by measuring cross-over rates in the transmission of the corresponding characters, Morgan's team had to control the natural variability of the cross-over rates (Waters, 2008, p. 715). Solving this endogenous problem (encountered within the course of the inquiry) required developing various experimental tricks (breeding females of the same age, using cross-over modifiers, maintaining a precise temperature, etc). This endogenous problem was thus essentially a practical problem, and not an epistemic one to the extent that its resolution did not bring in itself new knowledge on the transmission of hereditary characters. As regards now exogenous problems, questions on the origin of the universe or the origin of life qualify as examples of epistemic, exogenous problems to the extent that such problems have not been identified and formulated only by scientific communities: they (obviously) cater to the interests of the wider society.

To be sure, debates on the autonomy of science often build on the "basic" or "fundamental" vs. "applied" distinction. But this is unfortunate for at least two reasons. First, the very relevance today of categorizing science as "basic" or "applied" on the basis of distinct aims (increase knowledge vs. practical utility) has been challenged, and rightly so, by various authors (e.g. Kitcher, 2001, 2011; Morrison, 2011; Stokes, 1997). Stokes argues, for instance, that the usual opposition between practical concerns and progress of fundamental knowledge is too simplistic. Some research guided by practical problems may lead to an increase of knowledge because the resolution of the problems requires new fundamental insights. A paradigmatic case of such "use-inspired basic" research, as Stokes (1997, p. 73) calls it, is Pasteur's fundamental contributions in microbiology and immunology that were driven by the need to cure disease such as rabies. Moreover, the category of "basic science" should not be taken as a mere descriptive category. Schauz (2014), for instance, offers very interesting historical insights on how the very concept of basic research (as opposed to applied science) emerged as an analytical category in the late 19th and early 20th centuries, showing that it was not at the beginning opposed to the demand of utility from society. Second, when discussing epistemological conditions bearing on the occurrence of the unexpected, it will turn out that the conceptual distinction between endogenous problems or factors and exogenous ones is indeed more cogent and relevant.[4]

3. Two kinds of scientific unpredictability

Appeals to the unpredictability of scientific results actually refer to various kinds of situation, and these need to be clearly distinguished. First, the notion of the unpredictability of scientific results can relate to unforeseen practical applications of fundamental knowledge. Second, it can refer to a feature of the dynamic of science itself–that is, to the unpredictable development of a line of inquiry that leads to a new, unanticipated line of research and discovery. Let us examine and illustrate these two kinds of scientific unpredictability.

3.1. Unpredictability as unforeseen practical applications

Cases of unpredictability in the sense of unforeseen applications have been very well documented by historians of science and are often put forward in public discourse valorizing scientific unpredictability. A much-cited example is the laser, a widely used technological device today that was made possible by pure theoretical developments in quantum physics during the first half of the 20th century. The laser is often presented as a paradigmatic case of an unforeseen application of fundamental knowledge: the first description of the phenomenon of *Light Amplification by Stimulated Emission of Radiati*on appeared only in 1958 (Schawlow & Townes, 1958), and was presented as a theoretical deduction from quantum physics. The corresponding technological device was developed two years later by Theodore Maiman (1960) and was evidently not a foreseen application guiding the initial development of quantum mechanics. Appeals to this kind of scientific unpredictability go hand in hand with the following view on the relationship between increase of knowledge and practical applications: research is needed to generate a reservoir of fundamental knowledge, which then allows the development of applications. This view was typically defended by Vannevar Bush, who made an explicit appeal to what is now generally called the linear model of innovation (Edgerton, 2004; Freeman, 1996):

> Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn. New products and new processes do not appear full-grown (Bush, 1945, p. 20).

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[3] These are examples of the broad "societal challenges" that research is expected to address in the frame of the European Horizon 2020 program.

[4] It should be noted that our distinction, which is mainly conceptual, does not presuppose or imply that research programs can be sorted by the kind of problems that they address (endogenous vs. exogenous). In other words, it is perfectly compatible with the acknowledgment that most research programs today mix the two kinds of problems.

The development of the A-bomb in the frame of the Manhattan project is another well-known illustration of this kind of valorization of the production of new knowledge: discoveries concerning the fundamental structure of matter is what, later on, allowed military applications (Bush, 1945, p. 20). In the present paper, we will not further discuss this first type of scientific unpredictability since it does not raise the issue that concerns us here, to wit, the epistemological conditions bearing on the occurrence of the unexpected in the course of a given scientific inquiry. We will rather focus on the second (also widespread) understanding of scientific unpredictability, which does.

3.2. *Unpredictability as unforeseen new lines of research and discoveries*

When referring to a feature of the dynamic of a line of research, "scientific unpredictability" designates the occurrence of unexpected results in the course of the inquiry that open up new lines of research and discoveries. A well-known historical illustration of this type of unpredictability is the accidental observation by Alexander Fleming of the blocking effect of a fungus on the proliferation of bacterial colonies (Fleming, 1929) that led to the development of the first antibiotic. Another frequently-mentioned example is the discovery of radioactivity by Henri Becquerel (1896): when working with a crystal containing uranium, Becquerel noted that the crystal had fogged a photographic plate that he had inadvertently left next to the mineral. This observation led him to posit that uranium emitted its own radiations. Another, perhaps less well-known, historical illustration of this kind of unpredictability is the discovery of the chemotherapeutic cisplatin molecule by scientists initially working on the effects of an electric field on bacteria growth (Rosenberg, Van Camp, Grimley, & Thomson, 1967). They observed that cell division was inhibited because of the unexpected formation of a chemical compound of chlorine, hydrogen, and nitrogen with the platinum atoms contained in the electrode. This chemical compound, the cisplatin, was then successfully tested as an anti-proliferative agent against tumoral cells. As with the first kind, this second kind of scientific unpredictability is also frequently invoked to valorize and promote novelty and freedom in science. But less attention has been given to those characteristics of a scientific inquiry that make it more (or less) conducive to surprising results. In other words, what remain under-analyzed are the epistemological conditions bearing on the *occurrence* of the unexpected.

4. Three epistemological features influencing the occurrence of the unexpected

Let us first spell out more precisely what we mean in this paper by "unexpected". We call unexpected a result (observation, outcome of an experiment) that is not only surprising at first sight, but cannot be accounted for within the theoretical or, more largely, the epistemic framework in which the empirical inquiry has been conceived and conducted. This kind of exteriority is what leads scientists to contemplate moving away from the initial explanatory framework and opening up new lines of inquiry in search of an alternative that could accommodate the surprising results. When, then, are such unexpected results more likely to occur in the course of an empirical inquiry?

The general thrust of our proposition is that the occurrence of an unexpected result is linked to our interventions in the world being partially *uncontrolled* and to the degree of diversification of these interventions. This general idea leads us to propose three specific (and related) epistemological conditions bearing on the occurrence of unexpected results: leeway for the manifestation of uncontrolled factors; diversity of the objects under study and of experimental approaches; and hegemony and plasticity of the theoretical background.

4.1. *Leeway for the manifestation of uncontrolled factors*

Manifestation of uncontrolled factors is characteristic of many historical cases of scientific unpredictability. The two well-known examples evoked earlier can be easily analyzed in this manner.[5] Becquerel registered that some unknown, uncontrolled factor (and not light) left its marks on the photographic plate and Fleming registered the effect of some unknown, uncontrolled entities on the Petri dishes. Such manifestations of unknown, uncontrolled factors can be directly linked to the degree of isolation of the object under study.

It is now a well-known feature of some contemporary experimental sciences that many of their objects under study are "created" in the laboratory rather than existing "as such" in the real world. When drawing our attention to this epistemologically-important feature, Hacking (e.g 1983, chap. 13) specified that we should not read this notion of "creation" of phenomena as if *we* were *making* the phenomenon, suggesting instead that a phenomenon is "created" to the extent that it does not exist outside the highly regimented environment of the laboratory. This is typically the case for a phenomenon like the Hall effect: it did not exist "until, with great ingenuity, [Hall] had discovered how to *isolate*, *purify* it, create it in the laboratory" (Hacking, 1983, p. 226, *our italics*). In other words, Hall created in 1879 the material arrangement - a current passing through a conductor at right angles to a magnetic field – for the effect to occur, and "if anywhere in nature there [were] this arrangement, *with no intervening causes,* then the Hall effect [would] occur" (1983, p. 226, *our italics).* Isolation, purification, and control of intervening causes (i.e. control of physical parameters) are noticeable features of an experimental protocol that tend to limit the number of causal pathways which can influence the response to our experimental investigation of the object or phenomenon under study. Unknown causal pathways existing in the real world are thus inoperative (or less operative) in highly controlled laboratory conditions, thereby limiting the occurrence of unexpected results. Inversely, a low degree of isolation and control favors the manifestation of unknown causal pathways, hence the occurrence of unexpected results. The discovery of the cisplatin molecule mentioned earlier is another good illustration, along with Fleming's or Becquerel's discoveries, of the relevance of the degree of isolation. The platinum atom and the electric field interacted in an unplanned way to generate a chemical species, and this had a causal influence on bacteria. The "bacteria/electric field" couple was the original object of the study. Because of the imperfect isolation of this system, an unexpected causal pathway acted on it, and the "bacteria/cisplatin" couple became the new system under study, which gave rise to an unexpected discovery.

4.2. *Diversity of objects under study and of experimental approaches*

The second relevant feature – the degree of diversity of the objects under study and of the experimental approaches employed - follows mechanically, so to speak, from the previous considerations. Indeed, multiplying the types of objects and the types of experimental approaches used to study them increases the probability that some uncontrolled factors intervene and that some unknown causal pathways become manifest.

4.3. *Hegemony and plasticity of the theoretical background*

Another type of relevant feature concerns the theoretical framework in which the empirical inquiry is conducted. The general idea is that a well-established theoretical framework may hinder the occurrence of the unexpected when it is in a hegemonic, monopolistic position, that is, when it constitutes the dominant theoretical framework of inquiry in a given field. Let's spell out why by drawing on Hacking's analyses of processes of mutual adjustment between theoretical ingredients, apparatus, and data that are characteristic of the laboratory sciences. As Hacking aptly remarks: "As a laboratory science matures, it develops a

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[5] We thank one of our anonymous referees for pointing that out.

body of types of theory and types of apparatus and types of analysis that are mutually adjusted to each other" (Hacking, 1992, p. 30). The main insight from Hacking's work relevant to our issue of the occurrence of the unexpected is that a well-established theoretical framework determines the type of questions that can be investigated experimentally, guides the design of apparatus, and defines the type of data produced. Thus, by constraining the type of experimental procedures developed and the type of data generated, a theoretical framework which is in a hegemonic, monopolistic position in a given field tends to *homogenize* the experiments conducted to investigate the phenomena studied in the field. And since a diversity of experimental approaches increases the possible sources of emergence of unexpected results (see our second criteria 4.2), we can conclude that by reducing this diversity, theoretical hegemony reduces the opportunities for the occurrence of unforeseen results. The case of the etiology of cancer provides an interesting illustration of the way such theoretical hegemony can reduce experimental diversity and hence unexpectedness according to our second criteria. First developed in the 1970s, the classical theory of cancer, the Somatic Mutations Theory (SMT), rapidly became the dominant theoretical research framework on carcinogenesis (Mukherjee, 2011), with the ambition of accounting for all types of cancer (despite having been challenged for fifteen years or so by a new theoretical approach, the Tissue Organization Field Theory (TOFT) (Sonnenschein & Soto, 2000)). This hegemony of SMT led to a high degree of homogenization in experimental inquiry: in the context of molecular biology, the experimental procedures adopted were all dedicated to a very standardized search for genetic mutations.

When making explicit above what we mean in this paper by "unexpected results", we specified that, to count as unexpected, a result that is surprising at first sight has furthermore to be recognized as "exterior" – that is, non-integratable with the background theoretical framework in which the inquiry takes place. Consider again scientists working within a well-established theoretical framework. When faced with a surprising result, they will be reluctant to let go of the framework in order to search for an alternative, and for good epistemological reasons: there is (obviously) a high epistemic cost to abandoning a well-established, successful theoretical framework. The right move is rather to try to accommodate the surprising result by adopting, if necessary, some *ad hoc* hypothesis or by tinkering with certain elements of the existing theoretical framework so that the result loses its "exteriority" and can thus be integrated. Indeed, given the recognized plasticity and integrative power of well-established theoretical frameworks,[6] when a (at first sight) surprising result occurs, it rarely leads to a new line of inquiry being considered in order to find an alternative explanatory framework. It is more likely that the surprising result will be integrated within the existing framework. This is clearly what happened for instance in the field of the etiology of cancer just discussed earlier. Many - if not all - surprising observations were made compatible with SMT by using *ad hoc* hypotheses (Soto & Sonnenschein, 2011). For instance, it was observed that various types of cancer were exhibiting a large-scale disorganization of the genome. This observation was surprising, to the extent that it could not be matched with SMT's fundamental postulate of punctual mutations. To integrate it in the framework of SMT, the existence of an original genetic instability of the cancer cells was then postulated (Rajagopalan, Nowak, Vogelstein, & Lengauer, 2003). An observation that could have led to a radical criticism of the explicative framework used in cancerology was simply re-integrated within the prevalent model. To sum up, the degree of hegemony and plasticity of the theoretical background in which an inquiry is conducted appear thus as another epistemological condition bearing on the occurrence of the unexpected.

In light of our three criteria, we will now investigate the impact on the occurrence of the unexpected of an external setting of the research agenda, that is, when research is expected to address exogenous problems. We will first examine whether the importation of exogenous problems may increase the diversity of objects under study and of experimental approaches (our second criteria), and then discuss to what extent it is linked to low degrees of control and isolation of experimental settings (our first criteria).

5. Exogenous problems and the occurrence of the unexpected

Since exogenous problems, by definition, incorporate interests and needs external (or at least partially external) to scientific communities, they may not coincide with research questions that would have emerged in light of the internal dynamics of a given field. Addressing exogenous problems may, then, for instance, prompt the development of local empirical models, in the absence of a well-established theoretical background (typically in the early phases of the development of a scientific field). The biomedical sciences, which often address exogenous problems, provide interesting examples of such local modelling. Consider for instance the case in oncology of the development of radiotherapy protocols in the first half of the 20th century. The aim was to intervene on cancer in order to cure it, despite the absence of any general model describing the mechanism of carcinogenesis. This program led to the development of a variety of exploratory approaches using X-rays against cancer (Pinell, 1992, p. 59). As there were no standardized protocols, many experimental procedures were tested, such as changing the density of X-rays received, the distance of emission, the frequency of the radiotherapy sessions, etc. In order to improve the efficiency of these therapeutic methods, scientists tried to build various local models describing the action of X-rays on cancer, corresponding to the variety of experimental procedures implemented. Grubbe (1949) formulated a model based on the inflammatory reaction to explain the effects of radiotherapy on cancer, according to which the inflammation of the surrounding tissue due to the effects of X-rays was responsible for the decrease of tumoral mass. Grubbe's model reflects his specific use of X-rays, which consisted in applying very high doses in order to generate an inflammatory response. At the same time, and using more moderate doses, Bergonié and Tribondeau developed a model based on the proliferation of the cells in tumoral context, which led to the "Bergonié law" stating that X-rays have a higher impact on proliferating cells than on quiescent ones (Bergonié & Tribondeau, 1959).

This historical episode in oncology is typical of phases where local models proliferate in the absence of a general explanatory framework and under the pressure of exogenous needs and expectations. In these cases, exogenous interests (curing cancer, in our example) encourage the importation of new problems and new objects which may not otherwise have been considered as holding much interest in light of the internal dynamics of the field. Bohme, Van Den Daele, Hohlfeld, Krohn and Schafer (1983) propose the notion of a "pre-paradigmatic" phase to describe these stages of theoretically-blind and mainly empirical apprehension of poorly understood phenomena, where "external factors may and do play a significant role in orienting research" (Bohme et al., 1983, p. vi).[7] To illustrate this significant role, Bohme et al. (1983) analyze the impact of research on fermentation, notably through Pasteur's work, on the development of microbiology and enzymology as scientific disciplines. At the beginning of the nineteenth century, fermentation processes were at the core of many practical activities (beer-brewing, wine and vinegar making, and baking) leading to "a large

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[6] Classical references on these ideas of plasticity or integrative power are, of course, Kuhn's description of scientists being busy working on resolving anomalies in normal science (Kuhn, 1962) and Lakatos' concept of the "protective belt" of a research program (Lakatos, 1978).

[7] The notion of a "pre-paradigmatic" phase shares many features with the Kuhnian notion of "prenormal" science but includes in addition this orienting role played by external practical factors.

number of recognized experimental techniques" (Bohme et al., 1983, p. 57). According to Bohme et al. (1983), the emergence in the 1830s of a rich scientific literature on fermentation led to the co-existence of three different "theoretical approaches" to the explanation of this phenomenon. These approaches, each developed in a specific empirical context, generated many scientific controversies before being unified in the framework of microbiology and enzymology. These historical episodes (in early phases of oncology and of fermentation research) both illustrate how the pressure of exogenous problems can lead to a proliferation of local models and associated specific experimental protocols, hence favoring the occurrence of the unexpected, according to our second criteria.

Moreover, when a research program addresses exogenous problems, new research questions are introduced, which are not chosen primarily because of their tractability with respect to well-established theoretical backgrounds or well-controlled experimental practices.[8] Consequently, such research programs typically aim at directly intervening on a process or phenomenon while often disposing of only a partial knowledge of the causal chains involved and without being able to isolate it from various causal influences exerted by the rest of the physical world.[9] Such "contextualized causal relations", as Carrier calls them (2004, p. 4), go hand in hand with a relatively low degree of control displayed by the experimental protocols (our first criteria). The etiology of cancer again provides interesting illustrations of our claim. Indeed, many current cancer therapies are based on contextualized causal relations. Typically, if a cellular agent is found to be massively expressed in cancer cells, drugs are designed to inhibit it, even if the whole causal chain determining its action is not known. For instance, a large number of proteins promoting angiogenesis (the growth of blood vessels), notably VEGF (Vascular Endothelial Growth Factor), were found in tumoral cells, leading to the design of anti-VEGF molecules (Sitohy, 2012). These molecules are used without considering the complete causal chain in which the VEGF is embedded - only their known action on angiogenesis is considered. The clinical tests have led to an unexpected observation: the use of an anti-VEGF molecule (Avastin) can stimulate tumor growth (Lieu et al., 2013)[10]. This example shows that the use of contextualized causal relations to address an exogenous problem (curing cancer) promotes the appearance of surprising facts by allowing unknown mechanisms to intervene in the experimental procedure.

The discovery of the RNA (Ribonucleic acid) interference phenomenon (a breakthrough in our understanding of gene regulation (Mello & Conte, 2004)), provides another telling instance of exogenous problems leading to unexpected observations through the use of contextual causal relations.[11] A team of researchers (Napoli, Lemieux, & Jorgensen, 1990) working for an agrotechnology company (the DNA Plant Technology Company) were trying to enhance the color of petunias by introducing a copy of the gene naturally coding for the chalcone synthase (the enzyme responsible for the synthesis of the purple pigment). For that purpose, they used the contextual causal relation linking a gene G to the expression of the associated protein P. On the basis of this relation, the authors made the assumption that the introduction of an artificial gene would increase the amount of intracellular chalcone synthase, and thus the amount of purple pigment. Surprisingly, they observed the exact opposite effect: the petals became white because of the extinction of the purple coloration. This phenomenon, called "co-suppression", was due to an (at the time) unknown causal mechanism. Napoli et al. (1990) surprising result opened a new line of intensive research investigating the phenomenon of co-suppression. A link to the known mechanism of genetic regulation by anti-sense RNA (small pieces of RNA bringing the complementary sequence of a given messenger RNA) was later established (Bosher & Labouesse, 2000) and a few years later, Mello and Conte (2004) elucidated the nature of the unknown causal pathway: in some circumstances, the cells produce RNA molecules, which interfere with messenger RNA to inhibit their translation into proteins. This RNA-interference (RNAi) process constitutes a biological mechanism of regulation of genetic expression which is now intensively studied in biological and biomedical sciences.

A last consideration in favor of the hospitality of exogenous research programs to the unexpected appeals to our third criteria (hegemony and plasticity of the theoretical background). When discussing this criterion, we pointed out that scientists working within well-established theoretical backgrounds may tend to attenuate the surprising and problematic dimension of a result by trying to incorporate it within the framework. We suggest that the pressure of an exogenous problem may pull in the opposite direction for the following reason. As explained at the beginning of section 5, the need to address exogenous problems may arise in the absence of a well-established theoretical framework to do it. In the course of a scientific inquiry addressing such exogenous (often pressing) problems, the incentive to integrate a surprising observation into an existing theoretical framework is simply lacking and the surprising observation tends to be considered as a sign that the "local" strategy proposed to solve it has failed. The surprising observation is thus more likely to be considered as a real issue to deal with. Its unexpectedness is therefore accentuated, rather than erased, by integration within an existing framework.

Let us take stock here. In light of the epistemological conditions that we proposed in section 4, it turns out that the importation of exogenous problems may actually favor the occurrence of the unexpected, by diversifying the objects under study and the local models and experimental protocols used (our second criteria), by leading to intervene in poorly known and controlled objects and causal mechanism (our first criteria) and by limiting the tendency to integrate a surprising result within an existing, dominant epistemic framework.

6. Some reflections on the management of the unexpected

Our focus so far has been on the epistemological features of a scientific inquiry that are conducive to the *occurrence* of unexpected results. But this is only half the story when one is interested in the general conditions favoring the full flourishing of the unexpected. The other half of the story concerns the optimization of follow-up once surprising results calling for more investigation have been found. In contrast with the former, which mainly concerns epistemological considerations, the latter concerns institutional structures and the policies regulating the oversight of scientific communities. The issue is as follows: what are the organizational features of science that will allow and even encourage fruitful follow-ups? The flexibility of the inquiry is a first, straightforwardly desirable feature. A scientist, or a group of scientists, should be able to change the direction of research to follow up on unexpected results and explore new territories. But this is only a minimal condition, which leaves open the difficult question of when it is actually justified

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[8] Our point here on tractability echoes Carrier's comparative analysis of basis vs. applied science, when Carrier emphasizes that in the context of basic science, "empirical tests often proceed better by focusing on the pure cases, the idealized ones, because such cases typically yield a more direct access to the processes considered fundamental by the theory at hand" whereas "[…] applied science is denied the privilege of epistemic research to select its problems according to their tractability (…). Practical challenges typically involve a more intricate intertwinement of factors and are thus harder to put under control" (Carrier, 2004, p. 4).

[9] Note that this feature is related to the previous one (use of local models).

[10] Interestingly, this observation led to new research programs that aimed at identifying the molecular causal pathways giving rise to this tumoral resistance phenomenon. Notably, it has strongly oriented the research toward precise understanding of the VEGF pathways (Moens, Goveia, Stapor, Cantelmo, & Carmeliet, 2014). For instance, the study of the mechanisms of expression in cancer cells of various kinds of VEGF agents is becoming an important element of research (Li et al., 2014), and this allows the construction of new fundamental knowledge about the action of the VEGF proteins.

[11] For a more detailed presentation of this case study, see Bedessem (forthcoming).

to do so: it is certainly not the case that all unexpected results deserve to be thoroughly investigated and can lead to epistemic pay-offs (more on this below). This minimal condition also leaves open the issue of what kind of institutional oversight allowing flexibility might *actually* favor efficient and successful research strategies, given our current insights into the functioning of scientific communities.

In want of a full-fledged treatment of these open and timely issues, let us here outline what seem to us to be appropriate and promising ways of dealing with them. Bear in mind first that for proponents of scientific autonomy such as Polanyi, defending the freedom of the research agenda naturally implies a rejection of all forms of centralized planning or oversight of scientific communities: " […] the pursuit of science by independent self-coordinated initiatives assures the most efficient possible organization of scientific progress" (Polanyi, 1962, p. 56). Polanyi's views on the governance of science fits within his generic theory of the self-organization of free societies, stating that polycentric orders, which multiply the number of decision centers by according great freedom to individuals (or to limited groups of individuals), score better than centralized forms of planning by increasing the capacity of complex social systems to handle a flux of new and unpredictable events (Polanyi, 1951, p. 111, p. 154).[12] However, in the specific case of scientific communities (and independently of judgments of Polanyi's broader political views), this is still an open debate and much more needs to be said to justify the claim that leaving individual scientists free to follow up (or not) on surprising results optimizes the full flourishing of the unexpected. On the one hand, Kitcher's well-kown views (Kitcher, 1990) on the epistemic advantages of leaving individual scientists to be guided by their quest for credit or reward may buttress the core assumption of a Polanyi-style defense of scientific autonomy (for in that case, scientists are more willing to engage in risky projects).[13] But on the other hand, more recent developments in the investigation of the division of cognitive labor may challenge it on various grounds. For instance, studies based on computer simulations suggest that "leaving scientists to their own devices" might actually increase conservative research strategies (Kummerfeld & Zollman, 2016). In other words, in the absence of external incentives and even in a (ideal) realm of free individuals, scientists would favor "exploitation" over "exploration". This suggests that some appropriate form of institutional control over scientific communities (e.g. forms that actively support risky science) might be preferable to "blind delegation" in order to optimize the full flourishing of the unexpected.

7. Conclusion

Our primary purpose in this paper has been to challenge, in the context of current public debates about policies of research oversight and funding, the cogency of an argument that is widely used to ground resistance to any external orientation of scientific research. We have argued that an appeal to the unpredictable nature of scientific developments does not constitute a sound argumentative strategy when defending scientific autonomy. To establish this point, we first proposed three epistemological conditions bearing on the occurrence of unexpected results in the course of a scientific inquiry. Secondly, in light of our three conditions, we discussed the impact on the occurrence of the unexpected of external setting of research agenda and we concluded that the importation of exogenous problems may actually favor it. But epistemological considerations concerning the occurrence of the unexpected do not exhaust the question of its full flourishing in science: we suggest that a clear distinction be made between the matter of the occurrence of the unexpected and the matter of its management, and we claim that this second issue (concerning which organizational features of science actually favor fruitful follow-ups) also needs to be investigated. In this paper we only hint at a full response, suggesting that "leaving scientists to their own devices" might not be the best organizational option to optimize the flexibility and diversity needed for the full flourishing of the unexpected. It is undoubtedly the case that a lot more work needs to be done on this topic, yet we hope to have at least made a convincing case in favor of a shift of focus in debates about policies of research oversight and funding from considerations of autonomy and the freedom of scientific agenda to considerations of what epistemologically-appropriate organizational features of science can actually favor flexibility and diversity.

Funding

This work was supported financially by the French National Research Agency under grant n° ANR-14-CE31-0003-01 (DEMOCRASCI project: www.democrasci.com).

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[12] On the link between Polanyi's defense of liberalism and his philosophy of science, see for instance Mirowski (1997).

[13] We thank one of our anonymous referees for suggesting this point.

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