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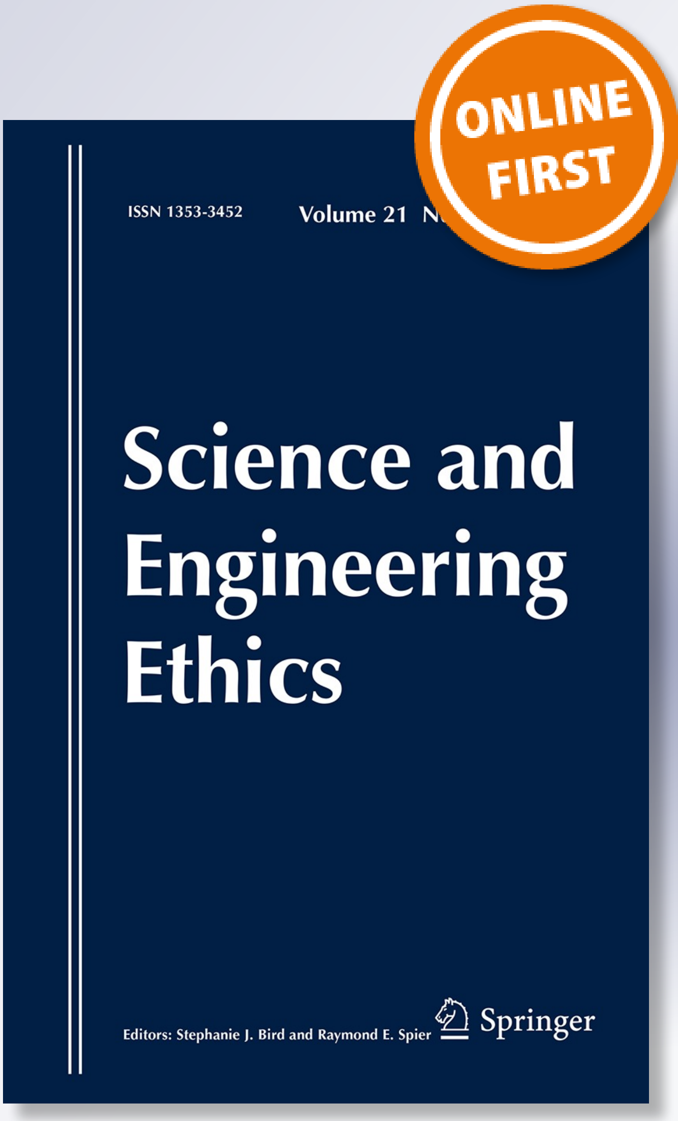

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What is *Proof of Concept* Research and how does it Generate Epistemic and Ethical Categories for Future Scientific Practice?

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Abstract "Proof of concept" is a phrase frequently used in descriptions of research sought in program announcements, in experimental studies, and in the marketing of new technologies. It is often coupled with either a short definition or none at all, its meaning assumed to be fully understood. This is problematic. As a phrase with potential implications for research and technology, its assumed meaning requires some analysis to avoid it becoming a descriptive category that refers to all things scientifically exciting. I provide a short analysis of proof of concept research and offer an example of it within synthetic biology. I suggest that not only are there activities that circumscribe new epistemological categories but there are also associated normative ethical categories or principles linked to the research. I examine these and provide an outline for an alternative ethical account to describe these activities that I refer to as "extended agency ethics". This view is used to explain how the type of research described as proof of concept also provides an attendant proof of principle that is the result of decision-making that extends across practitioners, their tools, techniques, and the problem solving activities of other research groups.

Keywords Epistemic categories · Extended agency · Normative ethics · Re-engineering · Proof of principle · Synthetic biology

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Although there has been much philosophical investigation into the disciplinary foundations of synthetic biology, the diversity of knowledge-making distinctions, methodologies, tools, and resultant products of these (cf. Morange 2009; O'Malley et al. 2008; O'Malley 2009, 2010; Keller 2009; Stich 2006), articulation of the meaning and ethical impacts of some key concepts used within it remain unanalyzed. I focus on one of these: *proof of concept*.

"Proof of concept" is a phrase that has been used frequently in descriptions of the type of research sought in program announcements from funding institutions; project proposals; the dissemination of these investigative and experimental studies; and in the marketing and patenting of new technologies.[1] However, the phrase is often coupled with either a short definition or none at all, its meaning assumed to be fully understood as research that establishes a prototype.[2] This is problematic. As a phrase with potential implications for developing research, protocols, and technological applications, its assumed but embedded meaning requires some analysis to avoid it becoming a descriptive category of research that refers to all things new and scientifically exciting.

I ask and attempt to answer the question: what kind of knowledge does proof of concept research provide? I provide a short analysis of what is proof of concept research, offer an example of it, and map out the relevant relationships between epistemic and ethical categories. I suggest that proof of concept research is articulated in situ, through the activities of scientific investigation. I examine proof of concept in one set of scientific practices—in the demarcation of new categories of knowledge-making within synthetic biology. In the second half of the paper, I contend that not only are there activities of demarcation that circumscribe new epistemological categories but there are ethical categories that are circumscribed by the activities of this research as well. In doing so, proof of concept implies the research (or scientific experimental practices arising from it) described as such provides a formative ethical as well as an epistemological foundation for future experimentation and scientific practice. Following this analysis, I conclude with an outline for a naturalistic epistemology and contextualist ethics for proof of concept research. This includes a sketch of a role-based account of normative ethical valuations that I refer to as "extended agency".[3] This account is intended to provide a conception of proof of concept that makes sense of it as an epistemological, metaphysical, and valuative notion. I claim that the type of research described as proof of concept is extended across environments, agents, and other research groups. Its epistemic status is variously situated in the use of tools, techniques, and

[1] Despite its prominent use and description within synthetic biology and biological engineering, the notion of *proof of concept research* is not restricted to these and has been used in other fields of research as well.

[2] One of the more lengthy definitions can be found in the National Science Foundation's Program Solicitation: *Accelerating Innovation Research-Technology Translation* from the Directorate for Engineering, Industrial Innovation and Partnerships: "A proof-of-concept is the realization of a certain method or idea to ascertain its scientific or technological parameters. A proof-of-concept should be understood sufficiently so that potential application areas can be identified and a follow-on working prototype designed." (National Science Foundation 2014, 14-569).

[3] In this, I apply Clark's (1995, 1998, 2010; and Clark and Chalmers 1998) extended mind thesis to normative valuational claims in ethics.

problem-solving endeavours of practitioners. Its natural metaphysics lies in its category and discipline building activities. And it has normative and valuative impact insofar as it demarcates boundaries of epistemic classes that affect behavior and future research.

What Does It Mean to Say That Research Shows *Proof of Concept*?

In recent use, "proof of concept" describes research in the beginning stages, at the cutting edge of new applications or technologies, and is a buzzword used to mark out scientific research as potentially extendable and/or scalable. It is often defined within a particular context or field of study (e.g. synthetic biology, pharmacology, biochemistry, business). My aim is to analyze the meaning of this phrase in practice. According to the Oxford English Dictionary entry, "proof of concept" is a noun phrase attributable to "evidence (usually deriving from an experiment or pilot project) demonstrating that a design concept, business idea, etc., is feasible" (Oxford English Dictionary 2014).

But what does it mean to say that research shows proof of concept? Trying to articulate what is meant by this phrase requires consideration of how we acquire knowledge more generally and how we know it as knowledge. What is the *concept* that underlies the research—and why is it important? Very generally, proof of concept research presents a discovery about our knowledge of the world and the structure of existence. The *concept* in "proof of concept" appears to refer to any idea that may apply to a class of phenomena. The *proof* seems to be a possibility proof that is shown to obtain in experimental practice. It proves that the causal connection hypothesized, structure proposed, function suggested, or methodological approach taken in the research obtains in at least one actual case—in the test case. The notion of proof of concept research is framed in terms of a particular kind of research that aims to answer a question whose answer has wide applicability in areas beyond that tested. In so doing, the research provides justification in practice of the potential transportability of that research (e.g. the methodology used, process described, pattern instantiated, prototypical application, intervention strategy performed, model or diagrammatic represented). The research may represent a suggested framework or organization of a particular biological structure, chemical pathway, or architectural design. For instance, it may tell us something about how biological systems work, how they function, by what mechanism, or what kinds of things or entities could be produced given certain start up conditions or inputs.

Scientific Practice, Belief, and Categories of Knowledge-making in Synthetic Biology

The recent focus on scientific practice within philosophy of science has turned attention to the experimental activities of science rather than solely on scientific theorizing (insofar as these are at all separable) (Hacking 1982). This shift, referred to as the "practice turn", has provided answers, (or at least more informed lines of questioning), to some long-discussed epistemological problems within philosophy (Chang 2004, 2007, 2009, 2011; Soler 2012; Soler et al. 2014, see also the Society for Philosophy of Science in Practice 2014, and Kendig forthcoming). Philosophy of science in practice challenges previous theory-first or theory-privileged approaches that assume scientific practice is always causally subsequent, epistemologically derivative, or fully prefigured by scientific theory. Positioned along these lines of investigation, this paper takes practice itself to be the source of knowledge and in some cases causally prior to, or the epistemological driver or source of, new advances.

This practice shift provides more than just a new frame within which to understand the goings on of science. Looking at practice and the activities of which it is composed yields answers to what makes justified beliefs justified. It suggests that assessing whether a subject's beliefs are justified requires looking at the processes by which he or she forms beliefs. For proof of concept research, a subject might use her engineering activities to judge whether her beliefs are justified or not. Understood within this frame of practice, justification is not determined solely by the subject's self-reflective representational stance—the belief x is justified insofar as it is based on intuitional experience by y (the subject) that x is true. Instead, in the frame of practice, justified beliefs are formed through active intervening and modification of devices and pathways, in the modelling and experimental investigation, and in the engineering activities of researchers. Put another way, the practices of scientists shape the categories of knowledge and change what makes justified beliefs justified.

For example, three epistemological categories have been shaped by diverse practices in synthetic biology (cf. Morange 2009; O'Malley et al. 2008; O'Malley 2009; Keller 2009). These categories demarcate diverse knowledge-making distinctions that lead to different questions being asked, different methods used, different knowledge acquired through these, and different products or outcomes. The first of these categories is whole genome engineering. Craig Venter's Synthetic Genomics successful synthesis of an entire bacterial genome, Mycoplasma mycoides JCVI-syn1.0, is the most well publicized example of this (Gibson et al. 2010; Hylton 2012). The second is the engineered construction of functional parts, processes, pathways, devices, and systems (Brent 2004; Endy 2005; Haynes et al. 2008). The current attempts to modify metabolic pathways in bacteria, yeast, and algae to generate biofuels are examples of this category (Kendig 2014a). The third epistemological category is that of synthetic experimental evolution or protocell creation (Erwin and Davidson 2009; Morange 2009). Synthetic biology research of this type seeks to understand the process of evolution, biological organization, and the nature of modularity.

To illuminate the role of proof of concept research in synthetic biology, I focus on the second of the three epistemological categories outlined in the above: the knowledge-making practices involved in the re-engineering of small devices, pathways, and systems. Proof of concept research pursued within this category of synthetic biology has produced experimental research that generates highly transferrable knowledge, engineering principles, and know-how that has been used in the conception and development of a wide range of products in a variety of industries. It has been successful in the construction of microbial products which promise to offer cheaper pharmaceuticals such as the antimalarial synthetic drug artemisinin, engineering microbes capable of cleaning up oil spills, and the manufacture of biosensors that can detect the presence of toxic arsenic contamination in drinking water (Amyris Biotechnologies 2013; Kendig 2014a).

This kind of synthetic biology research concentrates on the design, manufacture, and modification of new biomolecular parts and metabolic pathways using engineering techniques and computational models. By employing knowledge of operational pathways such as circuits, oscillators, and digital logic gates, it uses these to understand, model, rewire, reprogram, and re-engineer biological networks and modules. Standard biological parts with known functions are catalogued in a number of registries (e.g. Massachusetts Institute of Technology Registry of Standard Biological Parts). Biological parts can then be selected from the catalogue and assembled in a variety of combinations to construct a system or pathway in a chassis microbe such as *E. coli*.

Proof of Concept: Cyanobacteria Re-engineered for Potential Biofuel Production

The search for a chassis organism can itself amount to proof of concept research. For example, multiple organisms have been utilized and tested in the pursuit of finding a suitable microbe for research into the production of synthetic biofuels. Cyanobacteria appear to be a promising candidates. Cyanobacteria, like Synechocystic sp. PCC 6803, can provide a highly efficient organic system for producing biofuels as they can convert solar energy, water, and carbon dioxide into biofuel molecules (Wang et al. 2013).

Cyanobacteria are also thought to be particularly good candidates because they possess naturally occurring biosynthetic pathways that produce alkanes (key components of gasoline, diesel, and jet fuel). At present, research into the use of cyanobacteria for synthetic biofuel production is still in the very early stages and well behind that of algae research. However, research focused on reconfiguring these to create an organism that produces alkanes/alkene at a rate that is double that of the wild type has been shown to be possible. Synechocystis mutants have been constructed that overexpress alkane biosynthetic genes. This research demonstrates proof of concept for the potential use of cyanobacteria for biofuel production. If their photosynthetic pathways were re-engineered, cyanobacteria may be able to produce alkanes/alkenes at a highly efficient rate (Wang et al. 2013).

How might we best understand the range of experimental research to which this cyanobacteria-based biofuel research applies *as* a proof of concept? The general knowledge-making category that this research is a kind of is that of DNA-based devices and systems. This epistemological category of synthetic biology research is circumscribed by its own embedded practice metaphysics—one whose premise is biological modularity. The premise of biological modularity is an ontological claim that is borne out in the practice of this kind of research. We understand that the biological world is modular because we can build a dry lab mathematical model and then physically manipulate different parts of organisms in the wet lab in ways that would only work if there were discrete parts that were functionally interchangeable. The actual interchangeability of functional parts is shown to be possible in practice and exemplified through the use of different assembly methods (e.g. BioBrick Assembly and Golden Gate assembly) and by the proliferation of devices built from these (e.g. the bacterial biosensors, oscillators, and switches) used in industry as well as the DNA-based devices built by student research teams in iGEM competitions since 2003 (Knight 2003; Genome Consortium for Active Teaching (GCAT) Synbio wiki 2013; Eckdahl et al. 2015).

To say that research in this category shows proof of concept means that the causal hypotheses are possible. The *proof* is an experiment or set of experiments that are intended to represent a test case for the hypothesized theoretical framework (e.g. given input p, q is produced). If the test or exemplar experiment shows that p produces q, it is dubbed proof that p can produce q. In doing so the experiment affirms the hypothetical universal statement, "if p, then q", by showing that in at least one case (A) given p, q is produced. The proof is at bottom a proof of possibility by means of one actual case. Put another way, the proof of the hypothetical model is in the putting into practice.

The claim that the research shows proof—that the metabolic pathway of Synechocystis mutants can be engineered to produce biofuel—applies to the category of all cyanobacteria with engineerable modules (or even all microbes) whose metabolic pathways are similarly re-engineerable to overexpress alkane. The range of the proof, (and the concept's potential application), might best be considered as all members of a kind functionally circumscribed by the category of research being pursued—in this case organisms with engineerable modules suitable to be manipulated by practitioners to produce biofuel.

Generally construed, the underlying assumption in the attribution of a claim that any piece of experimental research shows proof of concept is: *if it works here, it will also works in all cases like this.* In this way, proof of concept research is research that is projectable—it suggests that if this obtains in the test cases then it will obtain in other like cases. Simply stated, proof of concept research makes a claim that extends over a category of like cases where *like cases* are those that exemplify the same causal mechanisms, structure, distribution, process, degree of variability, function, or other feature that is exemplified in the test cases.

Ethical Categorization: Lumpers and Splitters

I now move from discussing the meaning of proof of concept research and the scalable and extendable epistemic categories that it circumscribes to investigating how there might be new ethical categories that are also introduced with proof of concept research. Ethical discussion surrounding synthetic biology has typically suggested that the ethical issues that synthetic biology addresses are the same as those in other emerging technologies—they are fundamentally contiguous with those that have been and continue to be discussed (Preston 2008). In many of these, the epistemological distinctions outlined above (cf. Morange 2009; O'Malley et al. 2008; O'Malley 2009, 2010; Keller 2009) are ignored altogether by what could be referred to by detractors of the view as *ethical lumping*. For instance, Christopher Preston (2008) treats synthetic biology as a homogeneous field, disregarding the distinctive modes of investigation of whole-genome engineering and small-device construction when discussing ethical matters. Erik Parens, Josephine Johnston, and Jacob Moses (2008, 2009) go further, proffering a general lumped view of ethics:

> genetic engineering, nanotechnology, information technology and synthetic biology are so intimately interconnected that it might not make sense to spend much time making neat distinctions among them—at least for the sake of thinking about the ethical questions (Parens et al. 2009: 11)

This lumped view of ethics, intended to be applicable to all emerging technologies, is justified by the apparent similarity of issues between synthetic biology and other emerging technologies. The authors suggest that a "further balkanization of bioethics", or what I call "ethical splitting", is unneeded and should be avoided (Parens, Johnston, and Moses 2008). This resistance to *ethical splitting* is expressed throughout their work:

> Several putatively distinct areas of emerging science and technology are converging, making it ever less useful to try to draw clear borders among them. As emerging technologies converge, it becomes clearer that the ethical issues raised by these technologies are at core similar and familiar. It would be a waste of resources to take up the ethical questions in parallel; i.e., it is not profitable to invent a "new kind" of ethics for each new technology. Instead, we need to get better at productively engaging the familiar ethical questions that cut across those emerging—and converging—technologies (Parens, Johnston, and Moses 2009: 4).

My view can be seen as being in opposition to these. I suggest that emerging technologies each present fundamentally new sets of ethical issues. Motivation for this kind of context dependent ethics is grounded on a sentiment that ethical categories track epistemological ones. This takes the earlier discussion of philosophy of science in practice approach seriously. As discussion of the preceding example in synthetic biology aimed to show, the experimentation performed in proof of concept research leads to new epistemological categories that introduce new questions, methods of investigation, and tools. I now suggest that this research may also introduce new context dependent ethical issues that are endemic to each of these categories.

Assuming continuity across new scientific fields, modes of investigation, knowledge-making practices, and technologies following the ethical lumping approach seems to ignore ethically relevant epistemological distinctions that are non-contiguous with those of other fields of study. This general view is appropriate if we consider our knowledge of ethics to be complete. The lumped view's strength is that it allows us to apply solutions from one set of ethical problems to solve analogous ones in another. It provides a shortcut from problem to solution that circumvents the need for exhaustive research in a new area or extensive ethical discussion within it. We needn't study the engineering practices necessary for small DNA-based devices in synthetic biology to discover the dilemmas arising from it.

We know what they are because they are *just like* those we've already resolved in nanotechnology and genetic engineering. This transferability of ethical solutions is desirable but may not be suitable for all problems arising within a particular field of study.

Ethical splitting may be preferable when new context specific problems need to be addressed within the field. The suggestion muted here is that the circumscription of new epistemic categories generates new ethical categories that may generate novel ethical dilemmas. This role of category generation as framing the space of knowledge has been widely discussed in terms of discipline-building. Categories of knowledge demarcate the kinds of things that are the subject of study for that discipline, e.g. the periodic table of elements, plate tectonics, and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (cf. Dupré 2006). Proof of concept research, insofar as it has generated diverse knowledge-making categories has created new subdisciplines of synthetic biology. Knowledge-making categories do not just demarcate epistemic categories but can be thought of as having ethical riders that are used to decide how we act towards something. Knowledge-making can generate knowledge of what something is, how it works, as well as knowledge of how to act. If our moral behaviour is informed by what kinds of things we are interacting with, it may be our different knowledge-making approaches that may be specifically relevant in making ethical valuations and moral distinctions.

What are Ethical Categories and Why Should We Care?

Proof of concept research has potential ethical as well as legal, social, and environmental implications. Some of these can be witnessed in the attempts to understand the nature of synthetic biology and recent discussions concerning how we should treat the products of it (e.g. Association for molecular pathology V. Myriad genetics, Inc, et al. 2013). The recent Supreme Court decision focused on whether "products of nature" be treated the same as "human-made" inventions. What was at issue was what kinds of these are patentable.[4] If products of nature are of a different kind and belong to a different category than those products which are made by humans then the reasons justifying the patentability of one do not necessarily extend to the patentability of the other.

The questions I posed in the previous sections with regard to ethical splitting and lumping and the generation of new ethical and epistemological categories are prerequisite to resolving these and other ethical dilemmas. They provide knowledge

[4] In 2014, the U.S. Patent and Trademark Office provided the *Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena and Natural Products* (Hirshfeld 2014). In this, a balancing test was suggested to decide whether a claim is "significantly different" from that which is made to be a judicial exception to patentability. That is, whether that which is to be patented has been changed sufficiently to make it different from the naturally occurring phenomena or product. But, of course, the decidability of "significantly different" is decidable only with regard to knowledge of what it is different-from, or different-in-what-way to. Like the 2013 decision, this assumes products of nature and products of humans are ontological distinct and arbitrable.

of the ethical categories of biologically engineered products, how these ethical categorizations come to be, and how should they be used.

In addition to the ethical, legal, and social impacts, public understanding of new research (within synthetic biology in particular) is often mired with perceived threats of what is unknown and uncontrollable. Recent articles, reports and editorials express concern in terms of what is unnatural, and references to science fiction such as *Frankenstein*, *The Island of Dr. Moreau*, *GATTACA*, untoward environmental effects, super-species, eugenics, bioterrorism, and a general uncomfortability about scientists *playing God* or overstepping some ground or engineers subverting evolution are commonplace. So too are general worries about uncertainty, responsibility, and regulation, for instance:

> The concern that humans might be overreaching when we create organisms that never before existed can be a safety concern, but it also returns us to disagreements about what is our proper role in the natural world (a debate largely about non-physical harms or harms to well-being) (Parens et al. 2009).[5]

Initially research within synthetic biology (as well as other kinds of bioengineering) often enjoys favourable reports and reception by the public. This initial favourable reception gives way to an uneasiness and elicits a kind of creepiness for some early opponents (Colvin 2004; Marchant et al. 2010). Growing concern that something (whatever it is) is not how it usually is, where it usually is, or doing what it usually does. This unease is typically expressed in terms of the stuff's unnaturalness.

The initial interest in bioengineering and then the feeling of general creepiness has been described quite aptly as the "wow-to-yuck factor" (Colvin 2004; Marchant et al. 2010). These intuitive aversions may come from the idea that these research products are unnatural and what is unnatural is a threat to what is natural. That it is unnatural is usually considered the ultimate justification for its immorality. The creation and/or redesign of organic materials into synthetic organisms, components and systems are considered intermediate entities. Barnes and Dupré (2008) suggest that it is their intermediate nature that leads to the "yuck" response:

> "yuk" is the routine, immediate, unrationalized response to dirt, but as anthropologists stress, dirt is not a particular sort of matter, it is matter out of place, matter that pollutes, matter that purely by virtue of where it is encountered signifies disorder. The worm in the soup is yuk, not the worm in the garden, and for some of us the same is true of the mud on the carpet; body parts that would elicit no attention at their normal points of attachment may induce repulsion and anxiety if encountered elsewhere; even health-giving

[5] It should be noted that this concern is premised on a misunderstanding of the nature of being in two ways. Novelty is endemic in both reproduction and development. That an organism never existed cannot on its own be a source for concern as each new organism that comes into being (through either sexual or asexual reproduction) never existed before and so is in some sense the first of its kind. Further, organisms constantly change their cellular, epigenetic, and physiological makeup throughout their lifetime (cf. Kendig 2014b).

> implantations of blood or bodily organs may engender analogous disquiet, particularly if species transfer is involved (Barnes and Dupré 2008, 208).

Re-engineered biological parts for chassis microbes that produce new products, such as the earlier case of a DNA device and pathway re-engineering, generate mixture organisms insofar as they can include BioBricks derived from a number of different organisms. Organisms which are redesigned are between various species. They don't neatly fit into our existing taxonomy of species. And so are threats to biological order. The *yuck factor* may be considered an unpleasant aesthetic response that encourages avoidance of species that are synthetically constructed transgenic mosaics, hybrids, or chimeras.[6] These organisms may frustrate our moral intuitions due to the potential liminality of their classification as wholes due to the presence of parts of various origins belonging to different biological categories. Ultimately, small DNA-based devices and systems synthetic biology is perceived as being disruptive to natural order because the products of it go against a sense of internal order of an organism belonging to a single categorization of species classification. Synthetic organisms and parts are modifications that would be considered to subvert their natural categorization insofar as they are considered anomalous human made changes.[7] Knowledge of how we behave towards that individual or product is frustrated because it crosses multiple epistemic (and moral) categories:

> Our responses to disorder and anomaly are strongly socially structured…they are elicited by threats to our dominant systems of classification and the generally accepted ways of applying them. Structured in this way they are protective of the existing institutional order (Barnes and Dupré 2008, 212).

These qualms about the classification of the products of human invention or alteration are qualms that have ethical impacts. This leads us to questions that rely on knowing what kind of thing something is and to what category they belong: how do I know what something is? and how do I know how to act towards this thing, individual, being, or product? Knowledge of *what it is* provides information to us about how we are to behave towards it or in our relationship with it. Is it a moral subject?, a moral object?, or something worthy of our moral consideration? Arguably, these kinds of questions are only answerable once we know what kind of thing we are talking about. Put another way, once we know *what* it is, we start thinking about how we should act towards it. Insofar as ethics is about how we should behave towards others or ourselves, ethical engagement is always at least a two-place relationship (x,y). This holds even if we are treating ourselves (or a part of ourselves) as that entity with which our ethical consideration, or behaviour

[6] It should be recognized that this aesthetic response is not one that is universally shared. There is a wide variability of responses to these entities that goes largely unanalyzed in the discussion of the "yuck" factor. The diversity of responses can be the result of one's training, scientific discipline, or culture. The upshot? Those moral intuitions perceived to follow from the aesthetic response of liminality-avoidance are also not universally shared.

[7] Of course the subverting of *natural* categories has had a long history in selective breeding in agriculture, horticulture, and among pet breeders as well.

towards, is in question. Knowledge of what x is enables us to then figure out how we should behave towards x. If we know how we behave towards other things in the same category as x, then we know how to behave towards x.

Epistemic Categories and Categories of Valuation

Epistemological categorization of the kinds of knowledge in synthetic biology initially appears to be orthogonal to the normative or valuational claims used to inform ethical behaviour or support moral considerations. But I suggest that the epistemic notion of proof of concept research that is used to demarcate categories of non-normative knowledge has a normative ethical analogue—a *proof of principle*—that supervenes upon it. Both articulate proofs that sanction different forms of justified belief. But whereas the first delimits a range of scientific knowledge, the second refers to the valuative and ethical implications arising from these. Proofs of concept and proofs of principle demarcate different forms of knowledge, but they share commonalities of origin and extension. Both are proofs formed through experimental practices, both arise as the consequence of categorization, and both are the result of forms of extended agency.

Proof of concept claims and the epistemic categories they demarcate make differences in the various approaches, processes, or products used in a field. These differences lead to different questions being asked, different methods used, different knowledge acquired through these, and different outcomes (e.g. platform technologies, engineered pathways, or biomedical products). That is, they claim that what is extendable is dependent on what category it belongs to. Research embeds knowledge within a category. This knowledge can be either epistemological (proof of concept) or ethical (proof of principle).

But how might we evaluate moral extendability and projectability? If relying on aesthetic judgments like the *yuck factor* or avoidance of anti-technology just-so stories as the basis for ethical judgments about synthetic biology is problematic,[8] does this mean we must unreflectively embrace all technology in order to avoid being called a Luddite?[9] No. Insofar as proofs of principle are projectability claims, both types of discourse require ethical speculation (cf. Nordmann 2007). The difficulty is in deciding which speculated future possibilities can be grounds for ethical decision-making and which cannot. It seems likely that adjudication of permissible ethical speculation requires careful understanding of the research being pursued rather than reliance on a broadly-conceived of all-or-nothing approach.

Although there may be some generalized ethical principles that apply across all categories without regard to context, there seems to be evidence that some are definable and knowable only within the narrow context of a particular category, (as

8 This is not to discount the role of thought experiments or the use of literary narratives (such as those played out in science fiction). The later discussion of extended agency ethics would suggest that these could play a role but their role would be shared with articulated network of agents involved within the system.

9 Doing so would be to assume a false dichotomy that suggests one must either be wholly for or wholly against technology of all types.

the discussion of the legitimacy or illegitimacy of ethical speculation suggests). However, the absence of universality of at least some ethical claims runs counter to many normative theories that base the determination of what is ethical and what is not on the application of a particular rule or aim to judge what is moral in terms of its universalizability. For instance, Immanuel Kant's categorical imperative, Jeremy Bentham's hedonic calculus, John Stuart Mill's principle of utility, and *the Golden Rule* all provide universal rules that can be used to decide whether any behaviour or action is morally right or wrong by applying that rule.

In these approaches, moral imperatives are revealed in the application of the ethical theory to the situation or action. What underlies these rule-based approaches is that ethical considerations flow from the theory to the action or practice of some type of behaviour—not from the behaviour or thing to be given moral consideration. Although not advocating the particular rule-based ethical theories mentioned in the above, David Hume's discussion in *A Treatise of Human Nature* speaks to the inability to find value in the world and makes the observation that if ethics exists it exists outside of the objects, relationships, or actions to which we ascribe morality or immorality:

> Take any action that you think is vicious … examine it in all respects, and try to find what is the matter of fact, or real existence about it that you call evil or vice … you will never find it, till you examine your own self in the matter and find a sentiment of disapproval, which arises in you, toward this action. Here you will find a matter of fact; but it is the object of feeling, not of reason (Hume 1740).

For Hume, ethical judgments are judgments of approval (approbative) or disapproval (disapprovative). They are moral sentiments. His claim is that the objects, actions, and relationships of the world have no intrinsic value. His approach is based on an empiricist view of the mind. The valuation of a thing, action, or entity is something that only lies in us and is the result of moral contemplation. This view suggests that empirical investigations on their own are not sufficient to resolve ethical dilemmas.

Another justification for the impermissibility of assuming ethical prescriptions and valuations can be read-off empirical descriptions is that if we do so we commit a category mistake.[10] Thinking that value can be found merely in the accurate empirical description of objects, actions, and relationships in the world confuses what *is the case* with what *ought to be* the case. That is, it misappropriates the answer to the *what is it*-question as the answer to the *how should it be*-question. Simply put, these impermissibility claims say that ethical reasoning cannot be derived from empirical investigations. But what do these claims commit us to avoiding? Is it a commitment to the strict orthogonality of epistemic and moral reasoning? Does it eliminate the possibility of objective moral judgments in ethics? In the remaining sections, I suggest it does not.

[10] This is usually discussed in the context of the inadmissibility of claiming an ought from an is (the naturalistic fallacy).

An easy solution to this problem would be to suggest that proof of principle may imply different moral prescriptions on what we should or should not do. Our responsibility of action may be to consider possible future consequences of a particular or general situation (based on a kind of act or rule-based utilitarianism). It could also be in considering what a moral agent should do based on reflecting on what a fair or just person would do—that is, someone that exemplifies a just character (virtue ethics). The first of these approaches could be understood as invoking a duty of reasonable attentiveness to possible future impacts of the research. The second, a kind of ethics of care that is displayed as a trait of character. A third option, an after-the-fact or "backward looking" judgment of whether the course of action was morally correct (see Doorn 2012). Proof of principle may require not just consideration after-the-fact or consideration of possible future consequences using deontological or consequentialist approaches to ethics, but may also require agent-based virtue approaches. Consideration of which approach, (or which combination of approaches), may be determined with regard to the particulars of the research activities undertaken. How this works will be fleshed out in the remaining sections.

Extended Agency Ethics

The context-driven alternative that I suggest can be described as a naturalistic agent-based approach to ethics. Because this view relies on the extended-mind thesis in cognitive science (Clark 1995; Clark and Chalmers 1998), I refer to it as "extended agency".

According to the extended mind thesis, thinking is not exclusively something that happens in the brain, it is something that is spatiotemporally extended (Clark and Chalmers 1998; Clark 2010). Mind includes brain but also includes tools used to aid thinking (e.g. language, culture, pencils, calculators, search engines, mobile phone apps, and other people). Knowledge is not just epistemologically embedded according to this view, but it shapes and is reciprocally shaped by our experiences in the world:

> we use intelligence to structure our environment so that we can succeed with less intelligence…it is the human brain plus these chunks of external scaffolding that finally constitutes the smart, rational inference engine that we call mind (Clark 1998, 180).

I use this extended mind thesis to suggest how ethical decision making is ineliminably connected to the research practiced in groups. Normative ethical evaluations are the result of loops of ethical reflectiveness that—in a multi-agent system—construct the grounds for objective knowledge through intersubjective ethical judgements.

Simply put, normative ethical evaluations rely on what people think, what they do, how they do it, and how they communicate it to others. These evaluations are dependent on the epistemic capabilities of individuals multiply instantiated in systems of practice. The systems of practice include human agents, but also their physical manipulations (e.g. measuring, weighing, running gels), mathematical modelling, proxied or remote tool use, objects of study (e.g. chassis organisms, BioBricks), and the extended social communities that they work within (e.g. research networks that span multiple institutions, iGEM competitions, international research networks).

Extended agency ethics does not assume that intentionality is the sole domain of the brain nor that the body merely follows through with what the brain tells it to do. Instead, agency is not restricted to brain or limited by the boundary of the individual human organism's skin. It can extend to the social research network one participates within with its requisite values and practices. Extended agency provides a conception of proof of principle that attempts to make sense of it as research that is extended across both environments and agents and consists of epistemological, metaphysical, and evaluative judgments.

So, what would a normative ethical decision-making process look like using extended agency ethics? In pursuing research to find a suitable organism to be used as a chassis for biofuel production, a team of researchers would use knowledge acquired from the related areas of research outputs of projects focussing on cyanobacteria, algae, and metabolism. They may use this broad investigative approach to narrow down the range of possible candidates for a chassis organism. They may initially investigate the current algae research and the metabolic pathway of the highly familiar, well-researched green algae, Chlamydomonas reinhardtii. Knowledge of the successes and problems associated with the reengineering of algae as a source of biofuel may lead to the choice of a cyanobacteria instead. Once a chassis is selected, they may focus attention on the synthetic construction of pathways that overexpress alkane biosynthetic genes. Following this, they may begin the task of generating stocks of the newly reengineered form of Synechocystic sp. In order to plan the most efficient scale-up ventures, economists as well as microbiologists may be contracted. Once enough product is produced, they may outsource some beta tests to chemical engineers for kinematic viscosity analysis of the cyanobacteria-based biofuel product. They may request assistance in testing combustibility from colleagues specializing in physical chemistry. Limitations on what can be known and what can be done may come from the reciprocal knowledge exchanged through these interactions. The normative ethical decisions and projectable outcomes (in terms of both proofs of concept and proofs of principle) are obtained through and by these interactions. Knowledge of the organism being used, the marketability of the product, the scale of production, and the social and environmental impacts are all linked to the particular organism used. That is, the ethics of biofuel production varies depending on the organism used, the scaling applied, the prospects for environmental controls, expected social effects, and impact on world economics. Extended agency ethics describes the integrated approach to ethical decision making as one that requires careful consideration of integrated research and technological activities in order to reasonably predict possible outcomes. Ethical decisions concerning the potential use of Synechocystic-based biofuel is not something that comes as purely either backward looking assessment or forward speculation.

The determination of what should be done is not something that can be judged solely on the basis of weighing up consequences of action, nor on the basis of rule-following—categorical or otherwise. Instead, ethical considerations—such as the permissibility of the development of some new technology (e.g. cyanobacterial-based biofuels)—are determined according to the current research, the experiential data amassed, the practitioners' knowledge-making activities, and the potential for scaling up production of the biofuel products by industry. This means that the locus of normative agency and intentionality is distributed across the activities of research groups, tools, and the development of products.

Extended agency provides an externalist view of justification. Justification for beliefs come not from the mind-inside-the-head version of internalism (as some set of brain-bounded intuitionism or reflective perception). Instead, a form of active externalism that distributes cognition and agency across spatiotemporal research practices is suggested to explain the nature of proof of concept research. The ability to form research questions and pursue this kind of research depends on aspects of the technosocial environment in a way that is constitutive in the structuring of the research as knowledge producing and as extendable as a proof.[11]

> Any objects or persons can be reasonably thought of in terms of disassembly and reassembly; no "natural" architectures constrain system design…The entire universe of objects that can be known scientifically must be formulated as problems in communications engineering or theories of the text. Both are cyborg semiologies (Haraway 1985/2006, 129).

> Technologies and scientific discourses can be partially understood as formalizations, i.e., as frozen moments, of the fluid social interactions constituting them, but they should also be viewed as instruments for enforcing meaning. The boundary is permeable between tool and myth, instrument and concept, historical systems of social relations and historical anatomies of possible bodies, including objects of knowledge (Haraway 1985/2006, 130).

Extended agency radically revises what makes justified beliefs justified. Justification can be on the basis of reflection on mental states, but according to extended agency, what is taken to be mental is not restricted to the brain but instead goes beyond the skull and can extend to tools, practices, processes, and other researchers and research groups. Both epistemic credit and ethical culpability are distributed notions that extend beyond the individual human agent. If the extended mind thesis is taking seriously, mental states (usually restricted to the brain by internalist evidentialists) are extended not only beyond the brain and skin of the individual but to include other spatiotemporally distinct biological, technological, and socially extended entities. With this extended cognition, a requisite extended agency and normative ethics based on this actively externalist theory of evidence follows.

Extended Agency as a Role-based Ethics

Extended agency can be understood to be a kind of role-based approach to ethics that demarcates categories of valuation analogous to those epistemic categories (outlined in the first half of this paper). That is, to act in a role is to act according to

[11] This could be seen as a new application of Robert Wilson's (2004, 2005) social manifestation thesis.

a category of activity or to follow a model or prototypic way of acting. It may be profitably understood as being akin to an Aristotelian notion of virtue or a context-driven valuation. The intimacy of epistemic and ethical knowing is explicitly articulated by a number of virtue ethicists (see in particular Swanton's 2003, 249 "virtues as prototypes"). Instead of understanding morality as being based on a set of rules, this approach takes virtues to be frameworks. These frameworks are built from interactions and in-practice experience that both shapes and is shaped by future interactions in the world (Swanton 2003, 279). Christine Swanton's "virtues as prototypes" can be seen as a more restricted version of my extended agency ethics. Whereas Swanton limits knowledge of the world to agent-based interactions, I extend it further to include agent-object based interactions. That is, interactions between humans but also between humans and their objects of investigation are permitted (cf. Haraway 1985; Wimsatt 2007).

Epistemological categories do not map directly onto those of ethics, but they are informative in ways that shapes future behaviour. Ethical categories rely on the epistemological categories insofar as they introduce groupings of organisms, parts, pathways, or products with similar roles. Moral roles like epistemic roles are extendable. Whereas epistemic categories shape disciplines and demarcate diverse knowledge-making distinctions, these collaterally formed role categories that scaffold normative value attributions. Knowing the role something plays means we know what valuation to attribute to it which in turn guides our behaviour. We know how to treat it because we know what kind of role it plays within the process, procedure, or conceptual framework. Assessment of permissible behaviour is contextually embedded insofar as it depends on extended agency across a system of practices. It is decidable given the technological options present, the problems posed, the policies, protocols, and social infrastructure.

Conclusion

In the foregoing, I have answered the question initially posed in the title and at the beginning of this paper: what is *proof of concept* research and how does it generate epistemic and ethical categories for future experimentation and scientific practice in synthetic biology? I began the first half of the paper by characterizing proof of concept research as providing transferable knowledge-making categories through the activities of scientific investigation. Simply stated, I suggested that proof of concept research is research that is framed in terms of a particular kind of research that provides justification in practice of the potential transportability of knowledge acquired through the experimental test case.

Following this characterization, I explained how this works using an example of cyanobacteria re-engineered for potential biofuel production. This approach emphasized the role of scientific practice as central to the generation of categories of knowledge. I suggested that this practice shift changes what makes justified beliefs justified—if we focus on practice, we can understand justified beliefs as being formed through active intervening and modification of devices and pathways and in the engineering activities of researchers. The upshot? Proof of concept claims and the epistemic categories they demarcate make differences in the various approaches, processes, or products of a field. These differences lead to different questions being asked, different methods used, different knowledge acquired through these, and different outcomes.

In the second half, I argued that there was not just an epistemic notion of proof of concept research, but that there is also a normative ethical analogue—a proof of principle. Both proofs are formed through experimental practices and both arise as the consequence of categorization. I then outlined a role-based account of normative ethical valuations that I referred to as "extended agency ethics". Returning to the example of synthetic biofuel research, I illustrated what this ethical alternative would look like in situ. The aim of this paper was to articulate the meaning and use of proof of concept in practice—a project that has so far been missing in the literature on synthetic biology research and the philosophy thereof. In characterizing the epistemological and ethical impact such research has, and in proposing an account of extended agency ethics to better describe the transferrable categories of knowledge-making and ethical decision making activities that are generated by it, this research lays a foundation upon which other philosophical work articulating the meaning and scope of proof of concept and proof of principle activities may be developed.

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