Ref. Ares(2021)7008883 - 15/11/2021

HYBRIDA

D1.2: Identification and discussion of conceptual uncertainties relating to organoids, chimeric entities, and hybrids

Maxence Gaillard, Charles Pence, Mylène Botbol-Baum
UCLouvain

Embedding a comprehensive ethical dimension to organoid-based research and relating technologies

HYBRIDA

Deliverable factsheet:

Project Title:	HYBRIDA
Title of Deliverable:	Identification and discussion of conceptual uncertainties relating to organoids, chimeric entities, and hybrids
Work Package:	WP 1
Due date according to contract:	M8
Actual delivery date	Nov 15, 2021
Authors:	Maxence Gaillard, Charles Pence, Mylène Botbol-Baum (UCL)
Reviewers/comments received from:	Jan-Helge Solbakk, Bjørn Hoffman, Henrik Vogt (UiO); Sara Green (CU); Søren Holm (MAN); Mario Picozzi (UNINS); Mads P. Sørensen, Tine Ravn (AU); Bernard Baertschi, Jean-Luc Galzi, Jacques Haiech, Corinne Sebastiani (Inserm); Christine Mummery (LUMC); Panagiotis Kavouras (NTUA)

ABSTRACT:	This document reviews the main conceptual uncertainties pertaining to the ethical and scientific literature on organoid research. First, we highlight the importance and potentialities of a discussion of concepts before entering the ethical debate. Then we discuss briefly the concept of a hybrid—at the core of the HYBRIDA project—in relation with organoids and chimeras. Finally, we provide a list of conceptual distinctions that have been or will be mobilized to discuss the ontology of the entities generated in the course of organoid research, and we show how these concepts from philosophy, science and common sense can be applied to organoids in future discussions.

Keyword List:	Organoids; hybrids; chimeras; stem cells; bioethics; metaphors; conceptual innovation.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

Consortium:

	ROLE	NAME	Short Name	Country
1.	Coordinator of WP1	Université catholique de Louvain	UCL	Belgium
2.	Partner	University of Oslo	UiO	Norway
3.	Partner	National Technical University of Athens	NTUA	Greece
4.	Partner	University of Manchester	MAN	United Kingdom
5.	Partner	Aarhus University	AU	Denmark
6.	Partner	Leiden University Medical Center	LUMC	The Netherlands
7.	Partner	French National Institute for Health and Medical Research	Inserm	France
8.	Partner	Insubria University	UNINS	Italy

Revision history:

VERSION	DATE	Revised by	Reason
Intermediate report	May 18	Maxence Gaillard, Charles Pence, Mylène Botbol-Baum (UCL)	Draft of intermediate report (title: Conceptual uncertainties pertaining to the ontological status of organoids as hybrids. An exercise in conceptual mapping)
Int. rep.		Jan-Helge (UiO), Sara Green (CU)	Comments on first draft
Int. rep. final	June 2	MG, CP, MBB (UCL)	
		Bernard Baertschi (Inserm), Søren Holm (MAN), Bjørn Hofmann (UiO), Mario Picozzi (UNINS), Mads P. Sørensen (AU), Jean-Luc Galzi, Jacques Haiech, Corinne Sebastiani (Inserm)	Comments on intermediate report
Full report	Oct 18	MG, CP, MBB (UCL)	Final manuscript
		Jan-Helge Solbakk (UiO), Henrik Vogt (UiO), Sara Green (CU), Christine Mummery (LUMC), Panagiotis Kavouras (NTUA)	Comments on the final manuscript
	Oct 29	Mads P. Sørensen and Tine Ravn (AU)	Final manuscript review
Final version	Nov 15	MG, CP, MBB (UCL)	

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

EXECUTIVE SUMMARY

The goal of this report is to identify the main concepts underlying the ethical debate on organoid research with a focus on emerging conceptual uncertainties. In the first part, we discuss to what extent the conceptual discussion can nourish the debate in ethics. We argue that conceptual uncertainty occurs frequently in common language, as we do not always know what we mean by using certain terms. It is most frequent in public discussion, as discussants rarely agree on terms and their definitions, which can be problematic when looking for a common position on debated issues. Perhaps more surprisingly, there is also conceptual uncertainty in scientific research, as scientific concepts evolve and circulate among researchers. This is especially the case for ongoing research, such as organoid research. The term 'organoid' can be seen as a metaphor grounding a new research field which is still in the exploration stage. In this sense, the uncertainty in the concept of organoid conveys the uncertainty of scientific research itself. Then, we defend a model of hybridity to discuss the ontological issues raised by organoid research and related technologies: as organoids cannot easily be classified or categorized, we first have to list the usual categories that we would use to think about them. The laboratory entities developed in the course of organoid research are disruptive and conceptually challenging because they do not fit into well-known conceptual distinctions. This is not to say that we are not equipped to think about them, as philosophy—for centuries—and bioethics—more recently—have developed a language and built concepts to categorize the entities of our world. But here, as with many contemporary biotechnologies, our common landmarks are distorted. This being said, the public discussion will probably still refer to common concepts and conceptual distinctions. As a consequence, we propose here a list of ten conceptual distinctions that, if properly used, can capture most of the ambiguities and uncertainties raised by the entities generated in organoid research. We raise successively the following points where the hybridity of organoids is manifest. (i) From a legal viewpoint, human organoids are things, but they might also be related to persons in specific or transgressive manners that should be investigated. (ii) Organoids are objects of research and development, yet they might become subjects with rights. (iii) For many scientists, organoids are more than a mere cell culture, but they are not full organs, and even less organisms. (iv) Are organoids living entities, or should we identify them as mechanisms? (v) Referring to another classical philosophical distinction, one could ask: are they natural entities or artefacts? (vi) Organoids belong to science, as ways to gain knowledge, and they are also technologies, that is, objects designed to have an impact on the world we live in. (vii) They belong at the same time to the category of research tools and to the category of potential clinical devices. (viii) As tools for research and clinic, organoids are mere means, but they can also be seen as ends from the perspective of technological development or regenerative medicine. (ix) We tend to think of organoids as actual biotechnological entities that have a certain nature, but they are also in the becoming. (x) Certain kinds of organoids are chimeras that tend to blur the distinction, entrenched in common sense, between human and animal. The purpose of this list and discussion is to nourish the reflection of other WPs in the HYBRIDA project and pave the way for deliverable D1.4.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

Contents

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

1 Philosophy, public language, and scientific language

1.1 Philosophy and conceptual uncertainty

The critical role of philosophy in the HYBRIDA project

HYBRIDA is mainly aimed at considering some peculiar laboratory entities and at developing a code of conduct for researchers, helping them to decide what should and what should not be done with these entities. Its origin and destination are thus scientific research. Of course, ethics will interfere somewhere in the process: if the code of conduct hopes to tell researchers what they ought to do and how they ought to do it, at least some justification of its normative positions, grounding these positions in reasons and principles, will be required. For instance, bioethics is well accustomed to the wide range of considerations implied by a possible discussion on whether or not it is acceptable (and under which conditions) to inflict pain on a sentient entity.

Yet philosophy can do more than evaluate normative arguments as applied to predefined objects of inquiry. One of the first steps of the HYBRIDA project is to host a discussion about the ontology of organoids and to provide a map of hybrid entities of use in contemporary biotechnology.[1] After all, we may not even agree on what an organoid is. Indeed, even among scientists there are debates on the meaning of 'organoid' and the best way to refer to them and to related entities. In other words, the ontology of organoids is still a matter of discussion. This is obviously problematic if we want to have a discussion on the regulation of organoid research. As hypothesized in WP1, philosophy can bring something to this discussion. Another assumption of the HYBRIDA project is that the discussion should be as broad as possible and engage with the public. For that, we need to develop a common language that is beyond the technical language of scientific research. Some philosophical reflection on the usual concepts mobilized in this discussion is indispensable here as well.

If we say that "We need to develop organoid research because we want to know more about these entities," or that "Organoids are technologies that should be banned," we are forming judgments based at least in part on assumptions about the concepts we used, such as organoids, knowledge, technology, etc. We have intuitions about the meaning of those terms: it seems to us that we know what we mean by nature when we say that "organoids are (or aren't) natural." If asked to elaborate on the topic, sometimes we will be able to make these assumptions explicit; sometimes we will not.

---

[1] See D1.3 for a discussion on the concept of an organoid per se. See section 2 of this document for a discussion of the concept of hybridity.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

Is conceptual uncertainty a barrier to rational discussion?

It is a common and reasonable claim that the concepts we use in our discussions and debates should be made explicit and that all parties should agree on a common meaning. Indeed, no common position can be reached (and, actually, no proper debate will ever occur), if we do not speak of the same subject matter. This is a point that philosophy has made since its beginning: a rational discussion should be founded on robust concepts. In the absence of such a foundation, every statement formulated during the discussion might fall apart as well. For a large part of the discipline, it is precisely one of the tasks of philosophy: to clarify, define, or refine, concepts.

For instance, a number of Plato's dialogues are articulated around the quest for a definition: What is justice? (*Republic*) What is virtue? (*Meno*) That is, if we agree that there is something such as justice, then we can agree on some properties that will be shared by just acts, and we can then use those properties to identify any act as just or unjust. The problem with Socrates' interlocutors in Plato's dialogues is precisely this: they want to jump to the conclusions, like Meno, who asks *can virtue be taught?* before considering what virtue is, or what we call virtue. The study of the way we use language to better elucidate and characterize concepts is a long-standing project of philosophy from Plato to conceptual analysis. Definitions can be seen as a way to resolve conceptual uncertainty, and, as such, provide the building blocks for a rational discourse.

This being said, definitions alone cannot resolve all the potential issues of rational discourse. It would be presumptuous to hope that any definition process, even if definitions were rigorously adopted by all discussants, will remove all the potential ambiguities and misunderstandings that are likely to arise in the discussion. Further, agreeing on a common definition of basic concepts is not an easy task. Collective efforts might not lead to a consensus or a definitive resolution on what the meaning of X is and should be for all time. As in Plato's dialogues, one can always find a counterexample, i.e., some instance that does not fit the definition. Centuries of conceptual discussions on justice and virtue in philosophy have not allowed us to reach an agreement on the nature of justice and virtue. Without entering the details and difficulties of this conception of philosophy as foundational, conceptual work, we can say that, at least, as long as a project like HYBRIDA entails a large discussion involving many stakeholders, the global discussion would benefit from an effort to share a minimal common language and from a dose of self-awareness regarding the ambiguity of the concepts of interest.

1.2 Conceptual uncertainty in science and science communication

Is there uncertainty in scientific language?

At this point, one objection might be that HYBRIDA will mostly deal with scientific concepts and that while common and philosophical language is often vague, scientific language is taken to be clear and precise. Along these lines, we could endorse a distinction between common concepts (or folk concepts) and scientific concepts. Laypersons form their intuitions and judgments upon folk concepts. The latter can be inferred through categorization tasks but remain, most of the time, implicit. A folk concept cannot be expected to be fully coherent—we might even not rely on "definitions" to categorize objects. Indeed, most research in psychology shows that our common concepts do not follow the definition model (they

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

would be more akin to prototypes, for instance). On this approach, it would not be worth discussing folk concepts, as we are left to the realm of personal and fluctuating intuitions, but scientific concepts might be different. In contrast to folk concepts, scientific concepts are defined according to a theoretical framework. They can also be derived from scientific investigation: it is through an empirical inquiry that we learned that water is H_2O. Contrary both to the misunderstandings of common language and to the infinite disputes of conceptual analysis, scientific concepts would have a precise meaning preventing scientific discourse from confusion and misunderstandings.

The problem with this idea is that the boundary between obscure, confused folk concepts and definite, precise scientific concepts is not as simple as we would like it to be. Historian of science Evelyn Fox-Keller unfolds the concept of a 'gene' by insisting on the shifts of meaning from the emergence of the concept in the beginning of the twentieth century until the Human Genome Project. Even at one point in time, everyone in the field would agree that there is "no single fact of the matter about what the gene is."[2] Yet polysemy might not be a problem for science: in scientific publications, the experimental procedures and the theoretical context help the reader decide on the meaning of the term. It is even necessary that concepts evolve or take on different meanings locally, as scientists are exploring partially unknown phenomena and need to build bridges between different experimental contexts. But among the undesirable consequences of this state of affairs are the possibility that some aspects of the concept become dominant and prevail over other features, or even prevent the advancement of science in various communities. According to Fox-Keller, this is what occurred with the concept of a gene, laden with determinism and reductionism, even if the most recent advances in genomics suggest that the idea of a single, linear process from one genotype to one phenotype is simplistic.

> *The image of genes as clear and distinct causal agents, constituting the basis of all aspects of organismic life, has become so deeply embedded in both popular and scientific thought that it will take far more than good intentions, diligence, or conceptual critique to dislodge it. So, too, the image of a genetic program—although of more recent vintage—has by now become equally embedded in our ways of thinking, along with its attendant conviction (as Jacob and Monod first put it) that "the genome contains not only a series of blue-prints, but a coordinated program of protein synthesis and the means of controlling its execution."*[3]

We can see through this example that scientific concepts are not inherently safe from any and all uncertainty. Scientific concepts can evolve, be polysemic, and convey misplaced ideas when circulating. As a consequence, even if 'organoid' is a term that emerged in the scientific literature, it should also be questioned and clarified before it can be put to use without carrying potential ambiguities in ethical or public debate.

Why are there metaphors in science?

An (in)famous case of conceptual imprecision in the field of science studies (history, STS…) is the use of metaphors in science and science communication.[4] Metaphors are often embedded in scientific discourse

[2] Evelyn Fox-Keller, *The Century of the Gene*, 2000, Harvard University Press.
[3] Fox-Keller, op. cit., conclusion, p.136.
[4] Andrew Ortony ed., *Metaphor and Thought*, 1993, Cambridge University Press; Evelyn Fox-Keller, *Refiguring life, Metaphors of twentieth-century biology*, 1995, Columbia University Press; Sabine Maasen, Everett Mendelsohn,

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 101006012).

itself. In a nutshell, the lesson from all the work that has been done on metaphors in science, and in biology in particular, is that metaphors are powerful cognitive tools (otherwise they would not have been used at all), with potential negative side-effects for reasoning and communication, such as giving rise to misunderstandings, conveying misplaced images, perceptions, and emotions, etc.

A metaphor is the use of one term for another, based on the idea that the concepts behind share a common feature. Usually, the interest behind the use of the metaphor is to replace an abstract or unfamiliar term by a concrete, or familiar one. A computer virus refers to a malignant software susceptible to damage a computer: it is obviously not a virus in the biological sense, but it shares some features with a biological virus that make it easy for us to understand what a computer virus is and to use this term in common language. Metaphors are of pedagogical interest, they are also a powerful tool of communication as they help putting images and labels on a reality that would have been difficult to describe otherwise.

Metaphors are more than a simple tool for communication. They are often used by scientists to convey new ideas, for instance at an early stage of exploration. Some would even argue that new scientific theories must necessarily rest on metaphors.[5] In this sense, metaphors, as a unique cognitive tool to formulate complex ideas, would shape scientific breakthroughs. They are used to develop hypotheses and interpret results, and also to communicate discoveries in a shared language, even between peers. Often, a metaphor precedes the proper definition of concepts that emerge later in the course of research. Take for instance 'stem cells' – the label in itself rests on a double metaphor: the metaphor of the cell (a room) at the origin of cell theory, and the idea of origin, source, that can be found in the 'stem' label (a term involving also concrete images). However, the scientific community has today a good understanding of what a cell is, and that there are specific procedures to identify 'stem cells' in the laboratory. In a way, the expression of 'stem cell' might rest on a metaphor at the beginning, but it has since crystalized into a definite, scientific concept. Yet we cannot totally get rid of uncertainty inherited through common language. There is definitely some conceptual uncertainty in the theoretical discussion around stem cells.[6] What kind of property is stemness? What does it mean to be a stem cell? As long as there are different theoretical approaches to stem cells, there will be different concepts of stem cells. Arguably, distinctions between different theoretical approaches or conceptions of stem cells are somehow obscured by the use of the generic term 'stem cell.'

Indeed, the use of metaphors has also its drawbacks: a metaphor can become misguiding for the same reason that it is useful (intuitive, easy to memorize, emotionally laden…). To take just one example, many studies of science have questioned the engineering metaphor in biology. As Descartes did, it might be useful up to a certain point to think of organisms as mechanisms, but the sustained use of the parallel

---

Peter Weingart, *Biology as society, Society as biology : Metaphors*, 1995, Springer; Evelyn Fox Keller, *Making Sense of Life: Explaining Biological Development with Models, Metaphors, and Machines*, 2002, Harvard University Press; Theodor Brown, *Making Truth, Metaphor in Science*, 2003, University of Illinois Press.

[5] Andrew Reynolds, *The Third Lens : Metaphor and the Creation of Modern Cell Biology*, 2018, University of Chicago Press.

[6] Melinda Fagan, *Philosophy of Stem Cell Biology*, 2013, Palgrave; Lucie Laplane, *Cancer Stem Cells*, 2016, Harvard University Press.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

can be pernicious in the long run and have negative effects on scientific reasoning or on ethical consideration of science.[7]

The difficult use of metaphors in bioethics

O'Keefe and colleagues argue specifically that metaphors have an impact on bioethics[8]. For obvious reasons, 'gene editing' is often preferred in public discourse over technical wordings such as 'alteration of a sequence of nucleotides through the technology CRISPR-Cas9.' The 'gene editing' metaphor is based on the idea that the genome is like a text that one could improve through biotechnology. However, using these text metaphors conveys the idea that we know the grammatical or semantic function of all components that are being "edited" in the genome, which is certainly not true. Authors argue that metaphors "do not accurately describe what CRISPR does" and give the impression of being much more precise than what scientists actually know and can do. The danger is then of an ill-advised bioethical assessment, as the risk/benefit balance appears biased.

> *For science, bioethics, and the public, a key question is, how can our language be honest about the uncertainties in how we will use and develop the technology, and what promise and risk its use holds, without employing terms that trigger gut reaction rather than thoughtful deliberation?*[9]

Beyond imprecision, there is the risk that metaphors convey images that are inappropriate with regard to the phenomena of interest. For instance, the import of military vocabulary in biology[10] or in medicine can have counterproductive, negative effects on the understanding of biological systems.[11] The same confusing outcomes can be observed with economic vocabulary: a biobank is surely a place for storage, but referring to it as a "bank" brings along a lot of concepts that we might not want to apply to biological samples[12].

1.3 Contribution to HYBRIDA

As a consequence, conceptual uncertainty can be problematic for bioethics and lead to situations where ethical discussion and analysis is biased by misunderstandings based on language. This being said, what can one expect from philosophy or conceptual analysis in this regard?

---

[7] George Canguilhem, *La connaissance de la vie*, 1965, Vrin; Daniel Nicholson, Organisms ≠ Machines, *Studies in History and Philosophy of Biological and Biomedical Sciences*, 2013, 44:669-78; Marteen Boudry and Massimo Pigliucci, The mismeasure of machine: Synthetic biology and the trouble with engineering metaphors, *Studies in History and Philosophy of Biological and Biomedical Sciences*, 2013, 44: 660-8; Joachim Boldt, Machine metaphors and ethics in synthetic biology, *Life Sciences, Society and Policy*, 2018, 14:12.

[8] Meaghan O'Keefe et al., "Editing" Genes: A Case Study About How Language Matters in Bioethics, *The American Journal of Bioethics*, 2015, 15(12): 3–10.

[9] O'Keefe, op.cit.

[10] Brendon Larson, The war of the roses: demilitarizing invasion biology, *Frontiers in the Ecology and the Environment*, 2005, 3(9): 495–500.

[11] Bernadette Bensaude-Vincent and Sacha Loeve, Metaphors in nanomedicine: the case of targeted drug delivery, *NanoEthics*, 2014, 8(1):1-17.

[12] Bjørn Hofmann, Jan-Helge Solbakk, and Søren Holm, Analogical reasoning in handling emerging technologies: The case of umbilical cord blood biobanking, *The American Journal of Bioethics*, 2006, 6(6):49–57.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

An obvious remark is that we have to be careful with words. Even if we cannot reason or communicate without metaphors or uncertain concepts, we should reflect upon the possibilities and blind spots associated with our terminological choices. The choice of the word is just the beginning of the process of constitution of an object of discussion, even in the absence of a proper definition. It is certainly better to avoid getting off on the wrong foot. The purpose of this document and of WP1 and WP2 more generally is to identify ambiguities and difficulties in the organoid and ethics literature and to question the assumptions about the nature of the things that we are talking about. Based on the outcomes of WP1 and WP2, D1.4 will propose a tentative framework that will help situate organoids on a map of concepts useful for the general discussion. But before we do so, let us sketch briefly the consequences. Once we identify a term as problematic, what should we do? Suppose that we agree after review and debate that 'organoid' is an inappropriate term, leading to more confusions than it brings understanding in the discussion, what are the options open to us?[13]

How to settle the terms of the discussion?

i) First, one could consider discarding the term. For if it is a source of confusion and misunderstandings when we want to talk about contemporary science, we should stop using 'mini-organs,' or 'organ-in-a-dish,' or even 'organoid'. We could make a public stance in this regard and apply this rule to our own writings. The difficulty is that we still need some label to refer to the entities we want to discuss, so one cannot discard a term without replacing it in some way.

ii) Second, one could consider replacing some terms by others. For instance, we could say that 'microphysiological systems' is more appropriate than 'organoids' in most contexts, especially as an umbrella term for organs-on-chip, organoids, and models of development such as gastruloids. The difficulty here is that 'microphysiological systems' is a rather complex and long term, akin to jargon. As 'organoid' is much easier and pleasant to use, one can expect that organoid will still prevail in most documents and discussions.

iii) Third, there remains still the option of doing nothing. Certain terms are already in use in scientific discourse and in science communication. Given the difficulty of changing this fact of the matter, we should embrace the terms of the discussion as they are. For instance, there have been many debates on the validity of the label 'synthetic biology' itself, yet the expression has been kept, partially because the term has been around for a century[14].

iv) Fourth, if we want to go beyond skepticism, we could try to refine the nomenclature and improve our understanding of the concept, at least in a given context. There is the option of keeping the word itself, but slightly modifying the concept behind it. For instance, we could clearly state that organoids and gastruloids are different entities and that it is wrong to refer to gastruloids as organoids (see D1.3 and D1.4 for a discussion).

---

[13] Herman Cappelen and David Plunkett, A Guided Tour of Conceptual Engineering and Conceptual Ethics, in *Conceptual Engineering and Conceptual Ethics*, 2020, Oxford University Press, 1-26.

[14] Carmen McLeod and Brigitte Nerlich, Synthetic biology, metaphors and responsibility, *Life Sciences, Society and Policy*, 2017, 13:13.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

2 Hybrids, organoids, and chimeras as scientific and common concepts

2.1 Organoids between metaphors and concepts

Is organoid a metaphor or a scientific concept?

The concept of an organoid looks like a proper scientific concept, developed in the scientific literature only, with a corresponding definition (see D1.3 for a discussion). For most scientists, an organoid is a model of a developing organ. A model is an approximation of a real thing that allows for control and manipulation in experiments. When scientists cannot have a grasp on a natural object (because it is too big, impossible to observe, for ethical reasons, and so on), they try to build a model of it, so that they can work on this model as a proxy for the real object of interest. The term organoid has no equivalent in common language. However, this does not mean that laypersons reading or hearing for the first time the term 'organoid' would not have intuitions about what organoids are. This is especially because we all know, or think we know, what an organ is. Literally, *organ-oid* refers to something *similar to an organ*. Other terms encountered in the literature conveying the same idea are "organ-like", a cellular culture "mimicking" an organ, "mini-organs," "a model of an organ."

The suffix '–oid' (or 'id') comes from Greek *eidos*, and it is often used to refer to an entity which has the shape, the form, of something.[15] For instance, an 'android' refers to a machine that looks like a man (a human being). There has been plenty of '–oids' terms in science, especially in description and classification of entities. This is especially true of anatomy: for instance, the sigmoid colon is an organ with sigma (ς) shape. This is also true of astronomy, a science based on observation as well. The interesting fact about astronomy is that, beyond the label, astronomers have debated for years the proper definition and criteria of "asteroids" (in contrast to "planets" or "meteoroids" for instance). This suggests that identifying a class of entity based on the relation of resemblance does not give a criterion specific enough to categorize firmly different kinds of entities.

In a sense, there is an intuitive understanding of what a X-oid is: it is something that looks like X. At the observational level, resemblance is a visual property, something that everyone can see. While being intuitive, resemblance does not offer us a precise definition. There are different manners of "being similar to" or "looking like." A son can look like his mother because they have the same prominent nose (they share an essential physical feature), or because he is reluctant when spending money (they share a character trait), and so on. Resemblance is undetermined: a lot of things can "look like" an organ, or "have the shape" of an organ, without being of any significance for our debate on biotechnological entities. The very term of an 'organoid,' based on this suffix, might contribute to conceptual uncertainty in the discussion. That is, we have an immediate understanding of the term that could be quickly at odds with

[15] It can also express the fact that the entity belongs to a specific class or a certain kind, while the relation to the class is not totally specified. For instance, a hominoid is a member of a species that shares some characteristics with humans.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

the specific definitions that can be found in the scientific literature. In this sense, 'organoid' is only a metaphor that should not be taken too literally. If this is the correct interpretation, this raises a further question: how far can we push the analogy between an organ and an organoid? Research is an enterprise of testing ideas and models, by figuring out the expectations generated by a hypothesis. Organoids are still objects to be explored and defined, and the scientific vocabulary itself has to convey this underlying uncertainty. If we consider visual resemblance as being the primary basis for similarity, an organoid can be understood as a small organ, something that should look like a complete organ of the (human) body. Hence the images of perfect, full-grown mini-organs in dishes.[16] Yet this is far from the real laboratory experimentation with cellular cultures and even far from many potential conceptual developments in organoid research.[17] The objects compared are still heterogenous: an organoid needs to remain something other than an organ. The metaphor is a source of understanding, because it conveys meaning from one object to the other; it should be impossible to equate two things—the organ and the organoid—that are only metaphorically related.

2.2 Hybridity as a guide to conceptual analysis

While the focus of HYBRIDA is on the ethics of organoid research and related technologies, it has been established in the project proposal that organoids are to be understood as 'hybrids.' In this sense, hybridity is a general framework that we can apply to all kinds of biotechnological entities.

"Hybrid" is a concept of common understanding and is also widely used in some parts of science. At its most general level, it refers to something of mixed nature. Hybrids are individuals in which different natural kinds converge, or, in other words, an individual falling under several categories which are often thought of as mutually exclusive. For instance, when Greek mythology describes the Minotaur as being a bull and a man at the same time, this obviously poses a challenge to our basic conceptions of species and biological organisms—we are used to thinking that no individual can belong to two different species. In such a case, it seems tempting to ask: to which category does the individual really belong?

As the entities forged by contemporary biotechnologies are often difficult to position with respect to many concepts we are used to mobilizing in order to name things and form judgments (such as nature, life, person, artefact…), the notion of hybridity has seen widespread use among sociologists and philosophers to describe these new entities.[18] Other concepts have also been proposed to express the idea that hybridity is a general characteristic of contemporary biotechnological products. For instance,

---

[16] For an illustrative figure representing just that (a variety of organs growing in petri dishes) see for instance Cassandra Willyard, The boom in mini stomachs, brains, breasts, kidneys and more, *Nature*, 2015, 523, 520–522.

[17] In the scientific concept of organoid, there is of course more than visual resemblance. Other widespread criteria for a biological entity to be classified as an organoid are notably the ability to perform at least one function of the target organ. An entity that shares a functional property of an organ can be labelled organ-like, yet it is in a very different way than a structural, or visual resemblance (see D1.3 for a discussion).

[18] For instance: Bruno Latour, *We Have Never Been Modern*, 1993 [1991], Harvard University Press. Application of the notion of hybridity to organoids is explicitly made in Boers, van Delden, Bredenoord, Organoids as hybrids: ethical implications for the exchange of human tissues, *Journal of Medical Ethics*, 2019, 45, 131-139.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

the syntagm bio-objects[19] underlines the entanglement of life and materiality, while the concept of 'ubject'[20] has been forged to qualify entities that are between subjects and objects.

Organoids, chimeras, hybrids

Contrary to 'organoid,' hybrid and chimeras offer examples of terms that have a specific, different meaning in science, although they have dubious relationships with common language. Hybrid is a concept in biology, referring to an animal that occurs by the mating of two different species[21]. The concept of chimera used in biological science conforms also to a precise definition: an animal composed of cells with two different DNA sets. Yet, the word 'chimera' itself is borrowed from mythology and refers to imaginary creatures.[22] As concepts circulate, 'hybrid' is often mentioned as well in the general scientific literature and the media as an umbrella term for various kinds of new entities that are difficult to categorize, including chimeras.[23]

The common word and the scientific concept could be mistaken for one another, leading to a prejudicial uncertainty in the discussion. This enmeshment of common terms and scientific concepts might be considered as problematic. Should science use common language at all? Using a term that has an equivalent as a folk concept can be a source of confusion, or of misplaced intuitions. The concept of a chimera is a good example of that. As there is a common concept of chimera, grounded in mythology and representing terrifying creatures, there is the risk that misplaced intuitions and emotions would occur when discussing the scientific concept. The simple reference to the label 'chimera,' even if one is aware of the scientific definition, would raise implicit assumptions and images of full-grown dangerous animals exhibiting different body parts—while the laboratory reality is cell cultures in a dish.

What does it imply, to claim that organoids are hybrid entities?

The label of 'hybrid' for biotechnological entities is still only a starting point for the analysis. Consider any entity that we might want to call a hybrid. We still would have to ask: Of what X and what Y is it a hybrid? In which way is this entity a hybrid of X and Y (the Minotaur has a bull's head and a man's body, but a creature with a human's head on a bull's body would also be a hybrid of the same species, although a very different creature)? What does it change, for this entity, to be of hybrid nature? Does it change its properties? Its functions? What does it change regarding the way we relate to it? How should we consider this hybrid? Does it acquire a specific status in regard to its complex nature? Hybrids might raise uncertainties on two levels.

Firstly, uncertainty can arise when we do not know how to ascribe the entity to a familiar category. The entity potentially falls under several categories, and it is not easy to decide to which category the entity belongs, or even if it would fit only one category. The problem is that these categories are precisely the concepts we mobilize to form judgments of the objects that we encounter. For instance, to know that the entity X is a human being implies that we have to treat X with respect, that X bears dignity, and so on.

---

[19] Niki Vermeulen, Sakari Tamminen, Andrew Webster (ed.), *Bio-objects: Life in the 21st century*, 2017, Routledge.
[20] Klaus Hoeyer, *Exchanging Human Bodily Material: Rethinking Bodies and Markets*, 2013, Springer.
[21] For disambiguation and discussion on hybrids and chimeras, see the CHIMBRIDS report: Taupitz and Weschka eds., *CHIMBRIDS, Chimeras and Hybrids in Comparative European and International Research*, 2009, Springer.
[22] See D1.1 for an analysis of the mythological background of chimeras and hybrids.
[23] See for instance, Sara Reardon, Hybrid zoo: Introducing pig–human embryos and a rat–mouse, *Nature News,* 2017.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

From the ontological status of X, we can derive some of its properties, what we expect from X, and sometimes its moral status, giving us insights into how we should treat X. As a consequence, not knowing how to categorize some entities is going to disturb our epistemological and moral reasoning: it is a source of uncertainty in itself.

Secondly, our usual concepts might not be fit for the understanding of new objects, such as the products of contemporary biotechnologies. E.g., we used to think of entities as being either natural or artificial, but we have to think otherwise because more and more entities are natural and artificial at the same time. More radically, traditional distinctions of philosophical and moral analysis might become redundant. E.g., one could argue that the distinction between nature and artifice was, perhaps, never relevant for categorizing properly the entities we encounter (even if we only recently became aware of this possible irrelevance).

In some cases, uncertainty can be resolved by recognizing that an entity can fall within several categories at the same time. But, again, one would have to consider the implications of that. In other cases, we will resolve the hybridity issue by ascribing the entity to a main category, although acknowledging that it is connected to others as well. But all this resolution process is still dependent on our ability to take hybridity into account.

3 Ten conceptual uncertainties pertaining to the ontological status of organoids as hybrids

One potential way to clarify the status of organoids given their extensive 'hybridity' is to explore explicitly the ways in which common conceptual distinctions break down when applied to this complex case. In this section, we provide a list of ten conceptual distinctions that are briefly defined in very general terms and applied to organoids. By reviewing some of the classical conceptual distinctions that can be applied to organoids, we provide a first conceptual map to be mobilized to form ontological judgments about organoids and in future discussions on ethical and regulatory issues raised by these entities.

The conceptual distinctions listed below rely on common sense, on canonical, philosophical concepts, and on more recent theoretical developments in philosophy of science:

1. From a legal viewpoint, human organoids are **things**, but they might also be related to **persons** in specific manners that should be investigated.
2. Organoids are **objects** of research and development, yet they might become **subjects**.
3. For many scientists, organoids are more than a mere **cell culture**, but they are not full **organs**, and even less **organisms**.
4. Are organoids **living entities**, or should we identify them as **mechanisms**?
5. Referring to another classical philosophical distinction, one could ask: are they **natural entities** or **artefacts**?
6. Organoids belong to **science**, as ways to gain knowledge, and they are also **technologies**, that is, objects designed to have an impact on the world we live in.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 101006012).

7. They belong at the same time to the category of **research** tools and to the category of potential **clinical** devices.
8. As tools for research and clinic, organoids are mere **means**, but they can also be seen as **ends** from the perspective of technological development or regenerative medicine.
9. We tend to think of organoids as **actual biotechnological entities** that have a certain nature, but most research using organoids is focused on their development and thus conceives them as part of a larger **process oriented toward the future**.
10. Certain kinds of organoids, such as chimeras, tend to blur the distinction, entrenched in common sense, between **human** and **animal**.

3.1 Person and Thing

Concepts

The distinction between persons and things traces back to Roman law. Persons and things belong to different categories. Depending on whether entities belong to one category or the other, they shall be treated in different ways. For instance, respect might be due to persons, but not to things; things can be bought and destroyed, not persons, and so on. Categorization also implies that entities are included in a specific set of relationships depending on their category: it takes several persons to conclude a contract; a person can own and use things, not the other way around; and so on.

Hegel remarks that from a Roman law viewpoint, being a person is the same as having the legal status of a person.[24] That is, it is not the property of being a person that gives a specific position regarding the law. There are no clear criteria, based on science or a list of external properties, to determine whether an entity is a person or a thing. Nonetheless, what is defined as a person has such and such legal properties. For the law, the definition of the person is obvious, or performative. A "legal person" for instance is not necessarily an individual human subject, it can refer to a company or a State, and in this respect, a legal person can possess goods, be held responsible for its action, and so on.

When it comes to humans, the distinction between persons and things is obvious up to a certain point, which is a reason for its wide diffusion and common mobilization in bioethics debates: We tend to think of persons as human beings and of things as physical objects that can be seen, touched, or circumscribed. But the dichotomy has been debated since the beginning, as even for the Romans themselves and the legal systems that were derived from this model, the legal taxonomy of persons and things never prevented the existence of in-between cases difficult to decide. Typical persons are human beings, but that is not to say that all human beings have been identified as persons in the history of law. Slaves or children, and even women, would in some respect fall under the category of things, and there were discussions about so-called "monsters" (children deprived of human shape).[25]

Furthermore, the dichotomy leads to paradoxes and ambiguous cases: What about ideas, which are not external, cannot be touched, but are definitely not identical to the person they come from? What about artworks or cultural symbols, which may deserve specific consideration? What about body parts, which are external but seem to belong intrinsically to a person? All these entities are definitely neither

[24] Hegel, *Elements of the Philosophy of Right*, 1820.
[25] Eric Reiter, Rethinking Civil-Law Taxonomy: Persons, Things, and the Problem of Domat's Monster, *LSU Law Center Journal of Civil Law Studies*, 2008, 1.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

persons nor could they be completely assimilated to things, as they are connected to persons in a specific way.[26] As a consequence, a number of ethical questions emerge, such as: Can these entities be possessed or commodified under a contract? Should we treat them with respect? Many entities of concern in biotechnology do not fit neatly into this framework, as they "cannot be considered either persons or mere things"[27] and still have to be subject to regulation, a classic example being human embryos.

Application to organoids

Some organoids, based on human stem cells, are derived from biological material that was part of the body of a person (oocytes, stem cells, tumors…) or an embryo. That does not give an organoid the status of a person any more than the fact that at a to-be-transplanted kidney was part of the body of its donor makes the kidney itself a person. However, it does incline us not to treat them as 'mere things' that could be commodified, commercialized, or destroyed. Why would we be reluctant to call an organoid derived from human cells a mere thing?

3.2 Subject and Object

Concepts

From a legal standpoint, the definition of the person is performative, i.e., what is defined as a person has such and such legal properties. Attempts to justify the distinction between persons and things have led to the ontological distinction between subjects and objects. To claim that an entity is a subject means that this entity possesses a first-person point of view. In other words, it has a subjectivity, a consciousness. On the contrary, there is no first-person point of view in an object.

According to the classical philosophical vocabulary developed by Kant and Hegel, a subject has free will, or reason. It can make plans for the future and control its behavior according to what it judges appropriate. Thanks to this ability, a subject can assume responsibilities and follow rules, and then a specific legal or moral status ensues. By contrast, it makes no sense to ask an entity that has neither reason nor free will to follow rules and to determine how it should behave, as it will behave according to its nature regardless. For instance, one cannot forbid a volcano to erupt.

A moral consequence is that a subject should have rights and duties, as it has an intrinsic moral value and it cannot be considered only through its instrumental value. [28] In this perspective, being recognized as a subject is highly relevant for the defense of an entity's moral and legal status. For instance, if all human beings are subjects, then being human should automatically give access to human rights.

In another sense, one can equate subjectivity, or first-person-viewpoint, with sentience. The subject might not be able to speak for itself or possess reason, but it has an experience, a first-person viewpoint. The ability to suffer, to feel, is enough to argue that a form of subjectivity has developed. A gradualist approach could arguably distinguish different stages of subjectivity, with sentience being a first, basic feature, then evolving in reason and free will. A common view is to consider entities that possess sentience as rights-holders. On this view, an entity that has feelings, is able to feel pain and can build

[26] Klaus Hoeyer, *Exchanging Human Bodily Material: Rethinking Bodies and Market*, Springer, 2013.
[27] Jan-Helge Solbakk, Persons versus things, *Nature*, 2011, 478: 40-41.
[28] Kant, *Critique of Practical Reason*, 1788.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

HYBRIDA

relationships with other subjects should be attributed with some rights (even if not considered as a person by the law).[29] Especially, their ability to feel pain is a justification to attribute certain rights to animals.

Application to organoids

Depending upon our perspective, organoids can be seen as subjects or as objects.[30] This distinction would be especially relevant when discussing brain organoids.[31] Reason, free will, and sentience are properties whose emergence is related to the nervous system. Sentience requires a complex sensory system and central processing that turns electric signals into a kind of consciousness. Reason is, in a way, a faculty of the brain.[32] Thanks to the complexity of the brain, the product of a long evolution, some animals, including human beings, have developed a very special ability to process information before reaching a decision, to make plans for the future, to follow a planned sequence of actions, possibly to adjust their actions according to the situation. Others will insist on high-level consciousness and claim that consciousness makes us human and subjects of rights and duties: most of the time we know what we are doing, and we are in control of our behavior. Whether one insists on sentience freedom, reason, or consciousness, all these features are made possible by the existence of a complex nervous system in the human body.

One might consider first the possibility that a complex nervous system *in vitro* manifests some of the functions of a nervous system, e.g. reaches a certain threshold such that sentience emerges. Another possibility is that a form of consciousness, or even free will, emerges. If this is ever the case, we might want to give organoids that same status as entities that share the same properties. For instance, a sentient organoid should be treated as a sentient animal is in the laboratory. Or, more far-fetched, a conscious, fully reasonable organoid should be treated as a person involved in a clinical trial. In other words, attributing subjectivity would entail rights for brain organoids. An important point would be the assessment of the degree of consciousness involved in laboratory entities, and we would need to make distinctions between different conceptions and degrees of consciousness in this regard.

3.3 Cell-culture and Organ(ism)

Concepts

Cell culture is a well-known object from laboratory biology, gaining in importance throughout the twentieth century. Provided that the right conditions are met, a cell culture can stay "alive" for an indefinite time, like the "immortal cell line" of Henrietta Lacks (HL) established in the 1950's.[33] Thanks to this technology, cells are grown outside the organism from which they originate. An organism is an autonomous entity composed of different functional parts, limited by spatial and temporal boundaries. The organism has integrity, unity, cohesion: it is a whole, while a cell culture is just a collection of cells. Complex organisms are composed of organs fulfilling specific functions. Organs can be identified by their shape and their structure, which make them capable of fulfilling their functions. Following the progress in medicine, we are more inclined to look at organs as independent from the organism: we can store them,

---

[29] Bentham, *An Introduction to the Principles of Morals and Legislation*, 1780.

[30] The idea that organoids are hybrids possessing both "subject-like values" and "object-like values" is defended in Boers et al., Organoids as hybrids, op.cit.

[31] Andrea Lavazza and Frederico Pizzetti, Human cerebral organoids as a new legal and ethical challenge, *Journal of Law and the Biosciences*, 2020, 7: 1.

[32] John Searle, *Freedom & Neurobiology*, 2007, Columbia University Press.

[33] Hannah Landecker, *Culturing Life, How Cells Became Technologies*, 2007, Harvard University Press.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

transplant them into another body, and if everything goes well they are still able to fulfill their functions. Thus, organs are more than a bunch of cells, they also have a unity, a shape. Full organs are made of several types of cells, that is, in terms of development, cells have undergone a process of differentiation. This is a major difference between today's organoids and classical cell cultures.

Application to organoids

A strictly minimal definition would state that organoids are three-dimensional cell cultures. Admittedly, these would be cell cultures which have grown a little longer than usual, and some improvements would have been introduced in the methodology, but organoids would remain essentially cell cultures. Issues related to cell cultures in general would also apply to the culture of organoids: possible commodification of biological materials; property of the cell line taking into account the interests of donors, researchers, and industry; issues of privacy, as organoids have the same genetic material as donors; issues raised by storage, identification, and anonymization; epistemic relations to donors in the case of patient-specific drug screening, etc.

However, as the methodology to grow organoids has improved, they look more like proto-organs. Through differentiation of tissues and self-organization, organoids take progressively the shape of organs, although approximately and at a small scale. If they can be identified as organs, there is the hope that one day, they could fulfill organs' functions. Even if contested, the vocabulary of organoids as "mini-organs"[34] is a witness to this trend. As new uses are envisioned for these entities that are not mere cell cultures, such as organs for transplant, new ethical issues are raised.

Sometimes, organoids can even be considered as proto-organisms, autonomous entities in which different parts have different functions and contribute to the whole. For example, embryoid bodies model the embryo, which is an organism in development. A mammal embryo is a potential organism, not viable outside the womb, with no autonomy with respect to its environment, but it is a step toward a full organism. Other examples include "assembloids," where different organoids are connected. In this kind of experiment, different parts articulate and exchange information. This definitely moves beyond cell culture, and raises more complex issues.

3.4 Life and Mechanism

Concepts

Can we say that organoids are living entities, or are they just mechanisms imitating the development of life? According to the mechanistic point of view, all events occurring in nature should be explained by the causes that preceded them. Describing nature as a mechanism is to describe how things work. Finality, teleology, or divine intervention are banned from the scientific vocabulary. Although the mechanistic point of view is often considered as the gold standard for all sciences since the 17th century, biology has always been at odds with this requirement. Biology deals indeed with living beings (*βίοι*, in Ancient Greek), and it seems that entities that are alive share supplementary properties that simple mechanisms do not possess. Growth, self-organization, and self-repair, among others, are properties of living beings that cannot be found in pure mechanisms.

[34] James Davis and Melanie Lawrence, *Organoids and Mini-Organs*, 2018, Academic Press.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

Application to organoids

Organoids offer mechanistic models of development: thanks to organoids, researchers can observe how an organ develops step by step. Furthermore, by emulating development *in vitro*, we learn how the mechanism unfolds in detail. The production of organoids has provided crucial experiments, providing a definitive answer to many issues—for instance, in the nature of growth factors. A parallel can be drawn with synthetic biology, an enterprise building mechanisms from material that traditionally belongs to what we call life (including genetic material). Organoid biology is close to the dream of engineering life (see next distinction).

Human organoids are (part of) living entities as well. As they originate from the body of a living person, they share properties with that person, especially DNA. No matter how engineered and manipulated the cell culture in the lab may be, the resulting organoid will still have the DNA of the donor of the cell line. Organoids are not mechanisms made from scratch, in the way that a car made of recycled metal from a laundry machine would not keep anything of the original laundry machine that has been recycled. Culturing organoids creates more of a palimpsest, rewriting on something that has already been written. In this case, privacy may be the most problematic issue: how do organoids relate to their living donors? Another issue would be the respect due to life in general. Some claim that, even if not sentient or rational, all forms of life deserve consideration: what forms of life are organoids and what consideration is subsequently due to them?

3.5 Nature and Artefact

Concepts

'Artificial' usually refers to entities created by human beings—so-called artefacts, which are often things, commodities. Most artefacts are designed according to a plan, and they are constructed or produced from raw materials. These things are produced for specific purposes: to be used, sold, and so on. By contrast, natural phenomena are supposed to occur by themselves, and natural objects develop by themselves. Something 'natural' does not require human intervention to occur or grow. How this distinction overlaps with the previous one (life and mechanism) is a matter of debate: Proponents of synthetic biology argue that there is room for an "artificial life," but the extent to which human creations have the ability to go beyond nature is a matter of debate.[35]

Application to organoids

Notice that saying 'mini-gut' or 'mini-brain' is not the same as saying 'artificial intestine' or 'artificial brain.' With 'artificial X,' we might be inclined to think of parts made of steel or plastic, which are unnatural materials (that cannot be found as such in nature). An important property of organoids (even a definitional one) is that they should look like the natural thing, the real organ, as they are organ-oids. However, there are many ways to 'look like' an organ. Is it the shape that matters? The structure? The function?

Organoids are often presented as developing by themselves from stem cells, and researchers are only observing their development as a natural phenomenon.[36] In this sense, organoids are discovered, and not invented, by researchers. By contrast, organs-on-a-chip do not have the appearance of natural

[35] Bruno Latour, Love your monsters, *Breakthrough Journal*, 2011, 2.

[36] See D1.3 for further analysis.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

organs and are often presented as requiring complex engineering. Even if they model their functions, they do not have the shape or the external appearance of organs. They are compounds of non-natural material (the 'chip') and biological cells. A scientific model is an artefact designed to study a specific problem. A good model does not have to look like the real thing, it does not have to be natural, as we mostly learn from a model by constructing it and manipulating it.[37]

Natural things and artefacts might be considered of different value. This can be interpreted in two ways. On the one hand, some might attach an inherent value to Nature, and a laboratory artefact might deserve less consideration than its natural counterpart. On the other hand, an artefact is the product of human work, it results from effort, investment, which might be a source of value. The fact that organoids are produced by a methodology, that has to be invented, defined, and refined, leads us to consider them in relation to property and patentability. Where do organoids stand on this line? Is an organoid a natural thing that we have successfully captured in the lab but that in the end belongs to nature, hence to all of us? Or is it a product of human ingenuity, an artefact made by researchers, the fruit of painful efforts and investments of R&D, that belongs to its creators who deserved to be paid for it?

3.6 Science and Technology

Concepts

Organoids are entities that span different domains, some focused on knowledge production and others more application-focused. In this sense, organoids are used in the field of science and in the field of technology. The two domains can refer to different contexts and different goals. In science, human beings develop knowledge of nature, describe how things are. In the case of biology, scientists want to understand the mechanisms of life: how it develops, how it ends, how it evolves. Technology aims at producing things, acting upon nature in the most efficient way. It aims at fulfilling all kinds of human needs, while 'pure science' is only based on the pursuit of knowledge (that is, curiosity). According to the classical distinction between science and engineering, science is looking for laws of nature, while engineering applies these laws, especially to build new things. However, one does not need to know everything in order to act efficiently upon nature. Of course, science and technology are entangled in many ways and this distinction holds only at the abstract level.

Application to organoids

Organoids are objects of science when they are seen as ways of gaining knowledge. This is for instance the case when embryoid bodies are studied as models of development. Researchers focusing on this object want to understand embryo development, and as a consequence, they develop *in vitro* models to have a better grasp on the phenomenon of interest. In this perspective, organoids are theoretical objects. Our understanding of nature and the human body are making progress thanks to these models.

It sheds a different light on organoids to say that they are biotechnologies. The important points would be that we can produce them safely and efficiently, and that they fulfill the functions that we have in mind for making them in the first place. Criteria for selecting a good product might be cost, reproducibility, traceability… (while the main criterion for a good scientific model is its ability to teach us

[37] Tarja Knuuttila, Modelling and representing: an artefactual approach to model-based representation, *Studies in History and Philosophy of Science*, 2011, 42:262-271.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

something about the reality that it is supposed to model). Consider for instance organoids as possible organs for transplants in the future. Here we have a biotechnological product: it might enter the market, be commercialized, and we have to ask questions about production. Is it safe? How many lives can it save? How much does the development cost? Furthermore, we do not need to know all the biological mechanisms in detail (how it works) before entering the application stage. If it works, a biotechnology is not necessarily improved by knowing more—as we do not necessarily understand all the mechanisms behind the many technological products that we use.

3.7 Research and Clinic

Concepts

Research is an enterprise aiming at discovery, novelty, innovation. With regard to the previous distinction, research can refer to scientific research or technological research (or a mix of both). The clinic refers to care, treatments. It is aimed at improving the well-being of patients. Of course, there is 'clinical research,' i.e., looking for innovation in care, but at the abstract level, one can make the distinction between a research priority and a clinical priority. On a very concrete level, even in the very same hospital, rules and protocols differ for clinical procedures and research activities. The pursuit of clinical research implies a delicate articulation of the priorities and temporalities of both research and care.

Application to organoids

An organoid can be a tool for research, as said earlier, a model of development in embryo research. It can also be considered as a tool of technological research when we are looking at producing the best possible organoid. Asking questions about the clinical destination of the organoid, its use as a clinical device, for diagnostic or therapy, is embracing another perspective, that is, considering the organoid as a clinical device, and not as a research tool.

This distinction will matter when pondering the expectations of patients or potential tissue or embryo donors for organoids, raising issues of misplaced hopes, therapeutic misconception, fair or unfair inducement for participation, and so on.

3.8 Means and Ends

Concepts

As just said, organoids are tools for research and the clinic. Being a tool corresponds to a particular ontological status. Indeed, a tool is designed for a specific purpose: Its existence is justified by its functionality. In other words, the existence of the tool is not a primary goal and its justification cannot be found in the existence of the tool itself. Saying of something that it is "just a tool" is precisely pointing out the fact that instrumental value is a kind of inferior value because it is subordinated to something else. Most tools, once used, are to be dismantled or discarded. This is for instance one of the differences between mere tools and artworks or religious artefacts, which possess a symbolic, intrinsic value.

Application to organoids

We are often inclined to think of organoids as tools. As tools for research (models of development); as tools for the clinic (drug screening for an individual patient; possible organs for organ transplant). A good tool is a tool that works, achieving the goal that it is expected to achieve. Several alternative tools could be envisioned, but the criteria determining the choice of the tool remain subordinated to the final goal. If

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 101006012).

we consider an organoid as a potential organ for transplant, the organoid is a tool for recovery. The only criterion on deciding whether to use this tool or not should be: is this means efficient to achieve this goal?

At the same time, an organoid is not "just a tool." For instance, it might have a value in itself, as a part of the body, as attached to a person (as has already been said). Yet we can consider the value of organoids as tools in another way. For philosophers of technology, interfering with the status of a tool is a manifestation of the ignorance of technological culture. Craftsmen have a respect for their tools that is beyond that owed to simple objects. Persons working with tools know how important they are, how they matter to the achievement of the goal, and that more often than not, means and ends are not defined separately but conjointly. The definition of the tool as a means for a predetermined end has to be revised: the means often force us to re-think the end and sometimes lead to another end. We commonly fix the goals of medicine according to what is at our disposal. With changing tools, what is considered as a reasonable objective in medicine will change as well. Hence regular shifts of what is considered 'normal' or 'exceptional' in health, what deserves to be treated or not, depend on technological progress.

3.9 Actual and Becoming

Concepts

This section deals with a fundamental distinction in ontology, that is, the very nature of things and their relation to time. We can introduce a distinction between, on the one hand, actual objects in the present and, on the other, their becoming, what we think they are going to be in the future, or the kind of result that the current historical process is leading us to. Ethical discussions do not only bear on actual things that are present, here and now, in a specific laboratory, hospital, or biobank: they encompass more general ideas about what these things will become in the future. We do not refer to actual things, but also to virtual things, related to our vision of what the future will be. In the ethical debate, these visions of what organoids will become in the future are as important as what they are concretely today.[38]

Another line of thought would be to insist on the fact that biological phenomena are historical events, anchored in a specific temporality. In this sense, it would be wrong to think of biological events as "things." We are indeed used to thinking of nature as composed of *things* or *substances*, and most questions asked until now in this document are of the style: 'what kind of entity is an organoid?' But not every constituent of the world is a thing or a substance, that is, an entity that is fixed and has a determined nature. The entities of biology can be seen not only as things but as processes or activities[39]: "Things are abstractions from an ever-changing reality. Reality consists of a hierarchy of intertwined processes. If life is change, then the activities driving this change are what we must explain." According to this framework, the apparent stability of the organism relies on it being composed of many processes at different levels.

Now, does it change something to look at something as a process instead of looking at it as an entity? It certainly does from an epistemological point of view: the focus of the scientific inquiry, the problems, the concepts, are not the same when scientists adopt a processual ontology. From a moral point of view as well, the insistence on the *moral status of entities* makes often little sense when considering biological processes that have to be understood from their origins to their destination. For instance, we are used to considering 'the embryo' as an entity, and then we ascribe a status to this entity—

[38] Distinction suggested by Henrik Vogt, see the work on vision assessment in WP2.

[39] Daniel Nicholson & John Dupré, *Towards a Processual Philosophy of Biology*, 2018, Oxford University Press. Quote from the Foreword from Johannes Jaeger.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

at least this is often the way that the moral debate goes. Yet moral and legal stances towards embryos do differ regarding their positions in the development process and their relationships to many other agents: Where does 'the embryo' come from (natural fecundation, IVF, clone…)? What is its destination (supernumerary, parental project…)? In most legal contexts today, all this relational/processual information defines the legal status of any embryo regarding the law, and there is no specific status attached to an entity as an inalienable property of an ever-standing object.

Application to organoids

Actual organoids are models that can be found in many laboratories. Visions of organoids, or organoids-as-visions in the future tense, are just ideas. Although we do not know if they are going to be achieved at some point in time, such visions drive research and ethical discussions. For instance, organoids as organs for organ transplant, developed from patient stem cells in an artificial culture or in an animal's body, are for now only visions of the future. According to most researchers, they are not likely to happen in the very near future. Yet our ethical discussion has to make room for these entities, to explore possibilities and regulate them, without considering them in the same way that we might approach actual cell cultures in existing laboratories.

A provisional lesson is that maybe the debate should not be focused on organoids as actual things. As already noted, organoids are not one unambiguous kind of thing—organoid is rather an umbrella term for many realities, actual and becoming.

The application of the distinction between entity and process can also lead to the remark that a one-day organoid may not be the same thing as a one-week organoid, or a one-month organoid. Perhaps we should instead focus on living matter's property of taking shape, self-organizing, rather than self-organized entities. Organization is a process, and shapes and functions occur in time. To take only one example, the label of a 'gastruloid' might be confusing. Especially, it would be misplaced to ask what kind of *thing* a gastruloid *is*, because the very definition of a gastruloid is a model mimicking the *process* of gastrulation. In a way, there is no such thing as a gastruloid.

At least we should ask: What kind of 'things' do we want in our ontology? Interestingly, the qualification of biotechnological entities as 'hybrids' still relies on the implicit endorsement of a substance ontology. While acknowledging that classical substance ontology is not fit for carving nature at its joints, we still want to replace it with an upgraded substance ontology—but couldn't we do better without it?

3.10 Human and Animal

Concepts

Developing human organs in animals for organ transplant or chimeric organoids also challenges a classical boundary. Not that human and animal are two mutually exclusive categories—after all humans are animals, even for Aristotle—but it seems impossible for an individual to belong to two different species at the same time: Species are meant to be mutually exclusive categories. Hence it might be difficult to situate, biologically and ethically, single organisms with genetically distinct cells from different species (interspecies chimeras). The boundary between humans and other animals is allegedly crucial, manifest for instance in free will and reason, morality, high level of consciousness, language, symbolic thought, culture, technology… As a consequence, we usually give full moral status to human beings and other moral statuses for animals (depending on context). Many social institutions "depend upon the moral distinction drawn between human and nonhuman animals" argue Robert and Baylis. According to these authors, the

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

mere existence of chimeras, entities that could not be classified as either humans or animals, would cause "moral confusion."[40] Some think that drawing such major anthropological consequences from a localized laboratory practice is far-fetched[41].

Application to organoids

Some organoids are simply derived from human materials, others are derived from rodents or animal models. In that sense, there would be two categories of organoids. Specific attention should be paid to organoids made from human material, as they raise issues of privacy, property… (as already mentioned), while organoids made from animal material would be subject to the rules of animal research. Now, it might be confusing to consider entities that share properties, or biological material, of both humans and animals. How should chimeric organoids be considered? With the protection due to human biomaterials, or with the contextual rules of animal research? How should we consider a human organoid implanted in an animal body?[42] Does the xenograft still represent the patient or is it becoming an experimental animal model?

4 Conclusion: taking organoid ontological hybridity seriously

The difficulty, as it emerges now, is to take this notion of hybridity seriously. Hybridity means that we usually deal with conceptual categories which are poorly adapted to the ontological status of the entities we need to discuss. At this point, it can be tempting to get rid of any attempt to think *what things are* (ontology), relying instead on science on the one side and on regulation on the other. Do we really need to know what things are to interact with them and regulate them? However, one must not give up looking for the nature of these entities: this would be throwing ontology away with the bathwater of conceptual uncertainty. All ethical discussions are based on assumptions about the nature of the things that we are talking about. And all these assumptions can be questioned. We can even question the idea that the matter of discussions are things, or entities (see the entity/process distinction, section 3.8).

A minimal amount of scientific information is required for anyone who wants to take part in a rational discussion about objects that are defined and even created by science (as organoids are). But at the same time, scientific information alone is not enough, we need also concepts—like those we list here—to encompass laboratory practices, ethical deliberations, and law. This basic vocabulary of person/thing/object/nature/technology/clinic… will emerge in the debate whatever we, as partners in a general project aimed at fostering discussion on the ethical issues raised by organoids, think or say about

[40] Jason Scott Robert and Françoise Baylis, Crossing species boundaries, *American Journal of Bioethics*, 2003, 3(3): 1-13; Dietmar Hübner, Human-Animal Chimeras and Hybrids: An Ethical Paradox behind Moral Confusion? *Journal of Medicine and Philosophy*, 2018, 43(2) 187-210.

[41] See the full issue, *The American Journal of Bioethics*, 2003, 3(3).

[42] Abed Mansour et al., An in vivo model of functional and vascularized human brain organoids, *Nature Biotechnology*, 2018 36(5): 432–441.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).

the relevance of these concepts. One cannot easily pinpoint organoids on a pre-existing map of concepts, especially since there might be many realities behind this term and the corresponding science and technology are constantly moving.

How to navigate with the multiparametric conceptual map?

Even if none of the conceptual distinctions listed above is perfect to categorize the entities of interest, taken together these distinctions might help to situate organoids and compare them, as not all organoids might have the same status, or fall on the same side of the various distinctions.

Consider an entity A, created in a laboratory, that falls under the common label of organoid or that we want to include in our ethical assessment as an organoid related technology. Using the map to describe A would be equivalent to asking, for each distinction successively: Is this distinction relevant to the description of the ontological status of A? If yes, regarding this distinction, where would you like to put A along the axis drawn by the distinction? On a scale from 1 to 10, would you say that A is a natural thing (1) or an artefact (10), and what does this imply for ethics? Then, would you say that A is more of an object (1) or more of a subject (10)? And so on. There is also the opt-out choice of judging that the distinction is not relevant here.

For instance, a brain organoid is likely to raise discussions focused on subject/object, person/thing, or means/ends distinction, while an intestinal organoid is not going to pose many new challenges regarding these distinctions. Yet this intestinal organoid will raise issues of the relation between research and clinic. A gastruloid might raise discussions on its position regarding the nature/artefact axis, and discussions about chimera embryos will mention the human/animal distinction. In further work, these conceptual distinctions, along with feedback from WP2, WP3, and WP4, will be used as a multiparametric map to discuss the ontological status of various entities generated in organoid-based research.

This project has received funding from the European Union's HORIZON 2020 Research and Innovation programme (Grant No 10100601 2).