The long life of unicorns

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The goal of science is normally to better understand physical reality, i.e. the real world around us, and not fictional creatures such as unicorns. Technology-oriented research, including much of nanotechnology often aims not, or not solely, to understand phenomena, but also to produce objects. These objects can be devices, nanoparticles and engineered surfaces with specific properties that enable either immediate or future applications. Thus, the introduction section of most ACS Nano articles lists a wide variety of applications as the rationale for the work. Those applications constitute entirely legitimate justifications if they do really exist. However, sometimes, they are like unicorns (Figure 1), i.e. they are mythical, and there is no realistic scenario where the objects produced in the article would lead to the proposed application. Arguably that does not constitute studying unicorns because whilst the envisioned applications may indeed be far-fetched, the nano-objects or devices that they describe do exist. It may therefore be true to say that we might learn something useful by studying them. This counterargument does not entirely mitigate the deceptive advertising of improbable applications to justify research; this remains problematic. There is a category of research article even more akin to the study of unicorns than studies justified by unrealistic applications. That category is composed of articles where the phenomenon, and/or the objects themselves, and not only their proposed applications, are mythical. Our focus in this perspective is on this latter category using modelling the passage of nanoparticles through lipid membranes as an example. There are plenty of unicorns in other areas of nanoscience as humorously illustrated by the recent ACS Nano article reporting on the performance of HU-GO-BD (Hummers Graphene Oxide Bird Droppings) for electrocatalytic applications.¹

In this Perspective, co-authored by a philosopher and a scientist, we aim to provide some philosophical and scientific insights into the long life of unicorns, i.e. how deep misconceptions can often persist, and some for a long time, in the scientific literature. We first introduce our example and then we use it to discuss three aspects that underpin the long life of unicorns: the role of article introductions and references in sustaining the myth, the role of models and theories in this context, and, finally the impact of failures in rigorous experimental validation.
Belief in the existence and curative properties of unicorns was common in the European Middle Age and Renaissance. The debate over their existence lasted well into the 18th century. The concept of nanoparticles, thanks to their small size, or special structures, somehow magically getting into cells, thus causing toxicity or opening new ways to deliver drugs is powerful. It has been effectively conveyed to the general public understanding of science via hundreds of press releases stressing alternatively the benefits or the risks. The overwhelming evidence is however, that nanoparticles do not diffuse through membranes and that they enter cells by endocytosis. Gold colloids were already used as a tool (contrast agent) sixty years ago to study this biological phenomenon (Figure 2a). The suggestion in 2005 of non-endocytotic transport of nanoparticles was rapidly challenged (Figure 2b), but the powerful and inspiring idea, i.e. the unicorn, has lingered despite the lack of evidence. The fact that nanoparticles cannot easily enter cells is an evidence from a biological and evolutionary standpoint: cells have to protect themselves from viruses. This disappointing physical reality has not prevented the publication of a large number of theoretical articles studying the diffusion of nanoparticles through membranes as if that hypothetical phenomenon were relevant to drug delivery and nanoparticle toxicity. We will argue that these articles, instead of helping the understanding of interactions between nanoparticles and cells, sustain the unicorn, i.e. they add to the confusion over a simple scientific question, namely “do nanoparticles enter cells by diffusing through lipid membranes?”, which happens to have a simple answer, established for several decades: “no, they don’t”.

**Figure 1:** The Unicorns, "le bestiaire fantastique", 16th Century tapestry (Château de La Trémollière, France).
Figure 2. Nanoparticles enter cells by endocytosis and not by diffusion through membranes. a) Gold nanoparticles in endosomes, Harford et al, 1957; b) Representative rate of transport of 7, 10 and 15 nm gold nanoparticles across lipid membranes; Banerji and Hayes, 2007.

Critical discourse in scientific and philosophy journals.

Demonstrating in sufficient detail how and where the articles studying unicorns go wrong requires a forensic dissection of the text and of the evidence. This is actively discouraged in scientific journals; interestingly the opposite is true in philosophy. Indeed philosophy is built on the kind of analytical engagement that comes from critical discourse. In philosophy journals ideas are challenged, rebuked, and even sometimes ridiculed. Most arguments in philosophy build on the structure, or the wreckage, provided by the arguments of another. As Priest notes, ‘philosophy is precisely that intellectual inquiry in which anything is open to critical challenge and scrutiny’. Without this capacity to challenge arguments and truth claims, the identity of philosophy would be compromised. This is not to say that the philosopher will always recognise their own biases, nor even that they will want to, let alone that they will enjoy the process of being challenged. It’s also worth noting that critical discourse without due care to the other can become highly personal and/or alienate those who might already occupy precarious outsider positions to the discipline. What remains key, however, is that the principle of critical discourse remains at the heart of any sincere philosophical engagement. To the extent that a philosopher is capable of such, the impetus must be that any argument they make, or as made by any other philosopher, should withstand sustained critical and analytical scrutiny.

Laplane et al suggest that the application of philosophical methods to scientific endeavours might help to remedy some of the weaknesses that thereby arise. There is of course plenty to add regarding the benefits to philosophy that comes from engagement with science. While we intend to discuss this point in a philosophy journal in due course, for the moment our focus remains the unicorn. We surmise that the lack of open and public discussion of the evidence that supports scientific claims is one of the reasons for the prosperity of unicorns. Here, new spaces for discussions such as Twitter, PubPeer, blogs and online international journal clubs constitute interesting alternative avenues. It is not enough that scientific endeavour shares many of the analytical tools found in philosophy if the disciplinary traditions of the former limit the scope for their application. These new critical spaces make possible the application of logical and conceptual analysis to specific theoretical claims which are often unwelcome in traditional scientific journals.
How introductions sustain the unicorn?

Introductions of scientific articles are structured texts, which follow specific norms. They do more than introducing the topic: they justify the research and give an overview of the findings. How then do authors build the case for studying unicorns in the introductions of their articles? Let us consider again the case of the “nanoparticles-diffuse-through-membranes” unicorn.

First, authors need to establish plausibility. They may, for example,7 note that some small organic compounds can diffuse through lipid membranes. This is correct, although there is an increasing body of evidence that even for small molecular weight organic compounds intracellular uptake occurs via protein transporters, not via diffusion through the lipid layer.21 Or, they may allude to transfection agents, where a small fraction of DNA complexes reach the cytosol, but not by diffusion through the membrane.8,9 Or they may refer to the (non-controversial) insertion of hydrophobic particles in lipid membrane.22 In this way, they would offer a credible foundation for the claims that follow. Just as the unicorn is made more likely by virtue of the fact that it is a simple construction of real animals in a plausible way, i.e. other land mammals exist that are broadly similar to unicorns (horses), some mammals have horns (rhinos), while some have tusks that twist (narwhals).

Second, authors will always make a case for the importance of the research by listing applications of nanomaterials in biology and medicine. Often this case is made by citing, not articles reporting applications in biology and medicine, but instead chemistry articles reporting on the development of nanoparticles and making promises of future applications.23,24 Promises abound and more research is always necessary. It is therefore easy to write such introductions. The use of cumulative research, for instance in the aggregation of citations to defend a claim about causal relations, plays a key role in scientific theory-building. It is not without limitations, however (cf. research on meta-analysis in social and psychological sciences25,26), and it is important to note that the culmination of knowledge, which can advance the field, is not the same as an accumulation of citations that point to beliefs or expectations about highly speculative applications. Especially where these speculative accounts support further speculation. This latter approach can tend towards a ‘path dependency’ process of knowledge building, described by Peacock as a process of knowledge construction dependent on ‘historical contingencies’.27 The examples we consider in this paper are particularly problematic because the ‘path dependent’ approach relies on the accumulation of highly speculative unicorn applications, which are in turn used to support further claims for unicorn applications. All of which brings into question ‘the validity (and justifiability)’ of the scientific knowledge that such approaches generate.27

Third, they may claim that there is experimental evidence for diffusion of nanoparticles through membranes. However, a non-exhaustive analysis reveals two distinct patterns: 1) articles, e.g.7,10–12 where the claim is presented as common knowledge, i.e. it is not backed up by any reference to experimental evidence; and, 2) articles, e.g.8,13,28, where the introduction gives the impression that such experimental evidence exists but, on close inspection, that is not what the references provided show.9,22,29 There are also several theoretical articles30–34 devoted to the modelling of stripy nanoparticles diffusion through membranes but both the existence of those structures and their special properties are disputed.35–37 As Russell notes, ‘a true belief is not knowledge when it is deduced from a false belief’.38 This is especially important for analysing ‘common knowledge’ accounts that benefit from uncertain foundations and weak analytical processes of construction, as we demonstrate here.

Finally, authors will conclude their introduction by justifying their work in relation to other publications studying the nanoparticle-diffuse-through-membrane unicorn by noting that all those
previous theoretical efforts at studying diffusion of nanoparticles through membranes have shortcomings so more research is necessary.

How theoretical models sustain unicorns?

On the one hand a model serves as useful means to arrive at probabilistic laws, for instance to represent situations where nature is reliable. A material model is useful to describe something in physical terms, such as when snooker balls are employed in a demonstration of relations, while a formal model can be used to describe a process which may not have a specific object or property, for instance by showing a brain structure as modelled on computer. But the logical possibility of any of these models does not guarantee the physical possibility of the idea that is demonstrated, i.e. that the thing that is modelled exists. Because a model may show some necessary conditions in the relation between objects (i.e. conditions that must be present), this is not the same as showing what would be the sufficient conditions (i.e. the full remit of necessary conditions) for those relations or objects to actually exist. In other words, to think of something is no guarantee of its existence, just as to think of the unicorn does not mean that somewhere in the world a unicorn must physically exist. Thus, dozens of theoretical articles about nanoparticles permeating through membranes does not mean that the phenomenon occurs in reality; yet, they assume and reinforce the impression and illusion that it does.

Nevertheless, a model offers the possibility for the scientific and the verifiable. It presents ideas that are quantifiable and objective, and promises something unambiguous and ascertainable. Yet a model is only as good as the data and the method of its construction. More than this, while a model contains within it the possibility for testing and experimentation, it remains vulnerable to the accuracy of the content as understood, interpreted and depicted by researchers. This is similar to a map which is more or less accurate depending on multiple factors, including scaling, interpretation, boundaries (often political), and the selection or omission of data deemed to be more or less useful or valuable, or pertinent to a particular need or situation. As Quine explains, the totality of human knowledge, as well as beliefs, is ‘a man-made fabric which impinges on experience only along the edges,’ such that ‘science is like a field of force whose boundary conditions are experience’. In other words, our experiences, choices, and perceptions all have a role to play in the data that we select, and the model that we represent. That is particularly evident in the case of the nanoparticles-diffuse-through-membrane theoretical articles: when the models do refer to physical reality, it is often through the selection of anecdotal results in support of the unicorn whilst ignoring the overwhelming evidence, accumulated over several decades (Figure 2) that nanoparticles enter cells by endocytosis.

The utility of a model always remains to be seen. Kant (A244/B302) describes this when he suggests that we cannot substitute the mere logical possibility of an idea or concept, namely that the concept does not contradict itself, for the transcendental possibility of a thing, namely, that there is or ought to be an object that corresponds to the concept. To confuse these would be to draw a category mistake, whereby you confuse the category of ‘logically possible’, with what must be the case. We suggest that this type of mistake is common and that the large number of articles providing models of nanoparticles diffusion through membranes (the ‘logically possible’) sustain the mistaken idea that this phenomenon is real.

A scientific theory must make predictions of parameters that can be measured experimentally thus providing stringent tests of its validity. The more tests a theory satisfies without being falsified, the more our confidence in it can legitimately increase. However, some scientific articles introduce theoretical models that propose a mechanistic interpretation of a phenomenon without confrontation
with experiments. This engenders the kind of conceptual errors that we describe above. That a paper includes experimental results does not guarantee that other pitfalls are avoided. Biases, for example, are unavoidable. Especially as biases include the processes by which researchers select, discard and evaluate data, as well as the way in which such data are reported.\(^4\) Confirmation bias among researchers arises from a very human tendency to prioritise confirmatory details and to have preferences related to the success of one’s work.\(^4\) Plus there is what Cairney describes as the ‘social dimension to scientific popularity and endurance’, which includes the fashionability of concepts.\(^4\)

The above analysis illustrates how scientific articles can contribute to sustain deep misconceptions or unicorns. We predict that a systematic analysis (beyond the scope of this Perspective) would find that it is very common for introductions to confuse applications of nanomaterials with promises of such applications by citing articles making promises as evidence of the existence of those applications. We suggest that theoretical models of unicorns reinforce belief in their existence (even when the models do not match with experimental evidence), a category error that confuses the logical possibility of something with its existence. In closing, we briefly mention another source of confusion: ambiguity in terms. What is meant when we say that nanoparticles diffuse through membranes? The usual meaning of such a sentence is that the objects belonging to the category “nanoparticle” have the property of diffusing through membranes. Therefore, the precise definition of what is – and what is not – a nanoparticle is essential. If, as is usually the case, one means objects which have at least one dimension smaller than 100 nm, then we can say with certainty that nanoparticles do not cross membranes by diffusion through membranes (see for example Figure 2). The boundaries of the category “nanoparticles” are disputed, but in any case, it is clearly a very broad ensemble of objects with extremely varied properties. Thus, for example, the hydrophobic macromolecules described as nanoparticles by Liu et al, are extremely different from hydrophilic gold nanoparticles studied by Banerji and Hayes.\(^6\) To improve our understanding, it is more helpful to establish how properties such as permeability vary as a function of the size (or other characteristics) of molecules or particles rather than attempt to define the special properties of nanoparticles, a category of objects that is so broad that it cannot have any other special property than being a nanoparticle.

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