



Masking, extrinsicness, and the nature of dispositions: the role of niche signals in muscle stem cells

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Received: 22 June 2022 / Accepted: 20 March 2023 / Published online: 26 April 2023
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Abstract

I investigate the intrinsic/extrinsic nature of stemness in muscle stem cells (MSC) by relying on recent research on quiescence, with the aim of shedding light on the nature of dispositions and deriving some consequences about stem cells. First, I argue why the study of quiescence is the best available way to establish any claim about the intrinsicness/extrinsicness of stemness at least in some stem cells. Drawing on that, I argue that MSC's stem capacities result from the combination of intrinsic cues plus extrinsic factors from the stem cell niche, making stemness an extrinsic disposition in MSC. Importantly, it is shown that the niche allows the instantiation of stemness in MSC by acting as a *masker* of its manifestation. This shows that stemness is, at least in MSC, what I call an extrinsically structurally masked disposition (SMD); that is, a disposition whose instantiation requires, as a condition of possibility, the interaction between the bearer and a masker. Finally, I conclude by suggesting some potential consequences of this observation for the philosophical study of dispositions and for stem cell research.

Keywords Stem cell · Capacity · Power · Disposition · Dispositional antidotes · Metaphysics of science · Ontology

1 Introduction

Stem cells are a subset of undifferentiated cells that reside in the body of an organism. In contrast with tissue-forming or somatic cells, which are defined by their phenotype, their relative location in the body of the organism, or their patterns of genetic expression, stem cells are defined by their range of potential behaviour(s). Standard

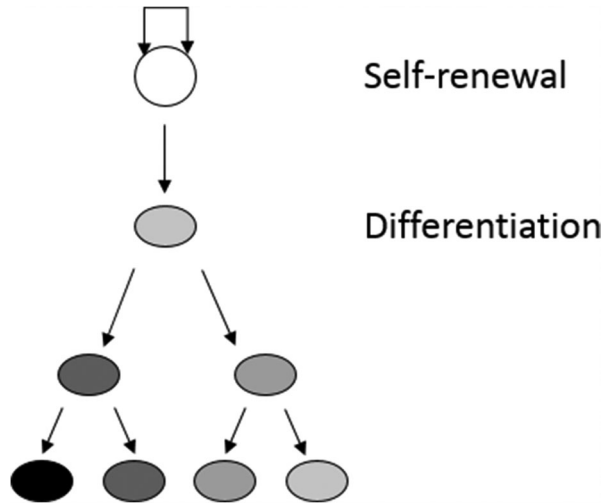
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Fig. 1 Basic abstract schema of stemness. Adapted from Fagan, 2013b



definitions characterize stem cells as undifferentiated cells that have the capacity to self-renew (producing other stem cells) and generate a committed lineage of cells which differentiate to produce somatic cells (Burgess, 2013; Slack, 2018; International Society for Stem Cell Research, 2020; EuroStemCell, 2020) (Fig. 1). Insofar as stem cells are defined appealing to their capacities, they possess one of the typical hallmarks of dispositionality, namely, being referred by a dispositional locution. In addition, the definition of stemness refers to a concrete pattern of manifestation (self-renewing, differentiating), and most research on the nature of stemness explicitly refers to triggering or stimulus conditions (*when injured, when damaged*, etc.). Stemness seems to be a property characterized by its functional-causal role, and hence it seems to be the type of property that philosophers would usually characterize as a disposition (Mumford, 1998, p. 77; McKittrick, 2018; see Hüttemann and Kaiser, 2013, 2018 for the consideration of stemness as a disposition).¹

A controversial hypothesis about stemness, the so-called “niche hypothesis”, states that stemness is a property a subset of cells *in close association* with a specific stem cell microenvironment called the “niche” (Schofield, 1978; Ferraro et al., 2010; Lander et al., 2012). The niche hypothesis suggests two ways of conceiving the dispositional nature of stem cells: a weak interpretation, according to which the niche provides the stimulus conditions that cause the manifestation of stemness; a strong interpretation, which suggests that the capacity, i.e., stemness, is not a property of a specific cell or cell type, but rather an extrinsic or relational property of (almost) every cell that is localized in that microenvironment. The weak interpretation of the

¹ Along the paper, I will use *stem cell property* and *stemness* interchangeably, as I am interested in investigating the metaphysical nature of the property. This does not commit myself to any view concerning the state vs. entity debate (Zipori 2004, 2009), which is orthogonal to my question.

niche hypothesis suggests that stemness is an intrinsic dispositional property that is triggered by the niche. The strong interpretation, however, suggests that stemness is an extrinsic dispositional property. Across the paper, the notion of “intrinsicness” will be used to refer to non-relational properties of the object (i.e., properties of the object whose instantiation does not depend on the environment), whereas “extrinsicness” will refer to relational or environment-dependent properties of the object (Marshall and Weatherston, 2018). In other words, extrinsic properties encompass aspects of the object instantiating the disposition as well as aspects of the relationship between the object and its environment.

These two interpretations raise an ontological question: is stemness an intrinsic disposition, or is it extrinsic? If stemness is an extrinsic property of the cells, the microenvironment plays a key role in its instantiation: if the microenvironment changes, the cell would stop instantiating the property *even without synchronically suffering any internal change* (e.g., change in its genetic expression). On the other hand, if stemness is an intrinsic property of cells, then a cell would instantiate it irrespectively of the properties of its microenvironment. That is, the microenvironment may change and cause that the cell fails to manifest the property; yet if the disposition is intrinsic, the cell would still bear the disposition which would be potentially triggered if the microenvironmental conditions change. Note that the question here is ontological and not epistemological because, as I will explain in detail later (see §3) testing stemness involves placing the cell in an experimental eliciting environment. Therefore, appealing exclusively to experimental tests for answering the question does not seem feasible.

This paper investigates the conditions of instantiation of stemness in muscle stem cells (MSC) to determine whether MSC stemness is an intrinsic or an extrinsic disposition. Drawing on an ontological interpretation of Fagan’s (2013c) “stem cell uncertainty principle” and on some recent research on how quiescence works in MSC, I argue that contemporary evidence supports the extrinsic alternative, and does so in virtue of the role that the niche plays as a *masker* which is required for the instantiation of stemness in MSC. Interestingly, this observation allows me to apply the concept of structurally masked dispositions (SMD) to stem cells. A SMD is a disposition whose instantiation requires, as a condition of possibility, the interaction between the bearer and a masker (Suárez, unpublished manuscript). Across the paper, and given that 1) stemness is usually conceived as the property of a *cell* to be a *stem cell*, and 2) the issue of extrinsicity primarily concerns how a *cell* instantiates the property, it will be assumed that cells, instead of cell lineages, or even the whole organism, are the primary candidates to bear the property.

Note that the treatment of a biological disposition as extrinsic is not new. Love (2003) has already convincingly argued that evolvability is an extrinsic disposition. More recently, Brigandt et al. (2023) have argued that evolvability is sometimes an extrinsic disposition, contending that its consideration as an extrinsic or an intrinsic disposition depends on a methodological choice on the scientists in deciding

whether environmental components are treated as background conditions, stimulus conditions or part of the conditions of instantiation of evolvability.² In this sense, Brigandt et al. (2023) seem to perceive that deciding whether a disposition is (or not) extrinsic is grounded on a methodological choice of the scientists, which is at the same time dependent on the ontological complexity of the property. While I understand their reasons for resolving the issue in terms of scientific methodology, in this paper I adopt the strongest position that some properties are ontologically extrinsic, i.e., their extrinsicness does not depend on the methodological choices of the scientists. And, *mutatis mutandis*, they are not a result of how scientists theorize or model the property. At most, all of these would only *reveal* that the property is extrinsic. Secondly, the specific consequences I derive about the extrinsicity of stemness (namely, that it is an extrinsically SMD) seem strikingly new, and possibly not true of other biological properties such as evolvability.

Methodologically, I follow the recent trend that aims to reinvigorate the role of potentiality in contemporary philosophy of biology (Austin & Nuño de la Rosa, 2019; Austin, 2017; Nuño de la Rosa, 2016), as well as the role of scientific practice in providing novel sources of research for traditional philosophical concepts (Engelhard et al., 2021; Guay & Pradeu, 2016; Kaiser, 2019; Triviño & Suárez, 2020; Triviño, 2022). My strategy will consist in relying on some contemporary research on stemness—i.e., how scientists investigate its nature—to derive philosophical conclusions about the nature of dispositions. Hence, the paper will rely on empirical sources—*epistemology*—to make my claims about the intrinsic/extrinsic nature of muscle stem cells—*ontology*. In the end, I will add some speculations about the consequences of the paper for future empirical research on stem cells.

§2 introduces the key notions from the literature on dispositions that I will assume in conducting my analysis. §3-§4 of the paper argue why quiescence is the best available way to establish any claim about the intrinsicness/extrinsicness of stemness at least in some stem cells. Building on that, §5 analyses the role that the niche plays in stemness in MSC and §6 draws on this discussion to argue that stemness is an extrinsic property whose extrinsicness derives from the role of the niche as a masker. This makes stemness a SMD. Finally, in §7, I present my conclusions for the philosophical analysis of dispositions and speculate some potential empirical implications of my research for the scientific investigation of stemness.

2 Dispositions, extrinsicness and masking

Dispositional properties, also called *capacities* or *powers*, are a class of properties characterized by their functional-causal roles. Classical examples of dispositional properties defined by their functional-causal roles include radioactivity (an element is radioactive if it is prone to decay), fragility (a glass is fragile if it can easily break),

² Literally, they speak of the causal basis to refer to what I prefer to call the conditions of instantiation of the disposition. To avoid confusion, I have translated their use of “causal basis” for my use of conditions of instantiation.

and recognisability (Boris Johnson is recognisable if people can easily recognise him in the streets).

A classical way of analysing dispositions is through the so-called “simple conditional analysis” (SCA), which paraphrasing Choi and Fara (2018), can be introduced as follows:

(SCA) An object o is disposed to a specific manifestation when certain triggering or stimulus conditions were to affect o iff, o would exhibit this manifestation if it were the case that certain triggering or stimulus conditions affected o .

While the SCA does not explicitly mention that the object bears a disposition D , but rather that it is disposed to a certain manifestation, it seems clear that if one accepts the existence of properties then it follows that the SCA is describing the conditions for an object to bear a disposition. Even though the SCA has been seriously questioned (Choi & Fara, 2018; Handfield, 2009), it pragmatically allows to minimally distinguish several different components that need to be recognised in studying the nature of dispositions. I partially build on Hüttemann and Kaiser (2018) in acknowledging that these include:

- (a) The bearer of the disposition, i.e., the object o that is said to bear D and that manifests D .
- (b) The conditions of instantiation of D ($Cinst$), i.e., the properties that o ought to have so that o instantiates D . If D were an intrinsic disposition, then these properties would include only intrinsic features of o ; alternatively, if D were extrinsic, then some of the properties would be relational features of o , and hence the environment needs to be in a certain relation to o for o to bear D .³
- (c) The conditions of manifestation of D ($Cman$), i.e., the events, processes or entities that cause o to manifest D . In the SCA, this role would be played by the stimulus or triggering conditions, but other analyses include also sustaining conditions, especially if one assumes that the manifestation is a causal process—see (e).
- (d) The manifestation of D , i.e., the effect that is brought about when the conditions of manifestation of D affect an object o that bears D , and nothing interferes with o or D .

Additionally, if one assumes that there is a non-empty set of causal events that lead from the moment in which the bearer of D receives the stimulus to the moment when D manifests, then a fifth element can be distinguished:

³ The conditions of instantiation of D should not be conceptually conflated with the causal basis of D , defined as what together with the manifestation conditions of D , is sufficient for o to manifest D (Prior et al., 1982). See Contessa (2012) for a persuasive distinction between the two concepts. In this paper, I will not discuss the problem about the causal basis, although if someone is not persuaded by Contessa’s distinction, she can simply understand the conditions of instantiation of D as spelling out the causal basis of D . For a thoughtful discussion of the concept of causal basis, and how it has been understood in the debate about dispositions, see Ferreira and Hundertmark (unpublished manuscript).

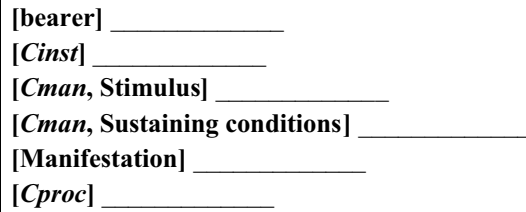


Fig. 2 Basic model of a dispositional property. Note that the blank spaces are expected to be completed with the details of the case study

- (e) The causal process leading to the manifestation of D ($Cproc$), which refers to the set of events that occur between the moment when the stimulus affects the bearer of D , and the moment when D is fully manifested. Some of these causal processes require of some elicitors during the manifestation process to be fully completed. I will refer to the latter as sustaining conditions.

Thus, a basic model for studying the characteristics—or nature—of dispositional properties would look like this (Fig. 2)⁴:

In this paper, I will divorce the *Cinst* of a disposition from the *Cproc*, in considering that they reply to different questions about the nature of dispositions. Take the fragility of a glass, or the recognisability of Boris Johnson. *Cinst* concerns why the glass *is* fragile or why Boris Johnson *is* recognisable. In a sense, it can be considered a question about the “essence” of the property-instantiation, but with the proviso that if one is an anti-essentialist—as I am (Suárez, 2016)—then the same property may be instantiated by means of different “essences” (or, to put it differently, the property is multiply realizable because there are multiple ways that the bearer of the property could be structurally different while still having the same property, see Wimsatt, 2007). Plausible answers to this question would include “because of its (micro)physical structure”, for the glass, or “because (relatively random) citizens recognise him repeatedly through the streets of Leeds”, for Mr. Johnson. *Cproc*, though, concerns how the glass or Boris Johnson *manifest* these dispositions when the appropriate conditions of manifestation obtain. Plausible answers would include “because a process that damages the sides of glass started after it was struck and didn’t stop until the glass broke”, for the glass, or “because his easily identifiable hairstyle triggers mental states in (relatively random) citizens of Leeds leading them to recognise him”, for Mr. Johnson.

Note that *Cproc* leading to the breaking may also occur in a non-fragile object, and Boris Johnson’s hairstyle may be had by someone else and confuse the citizens of Leeds, even though this other person is not recognisable. However, the same is not true about *Cinst* of fragility and recognisability: if an object has the appropriate

⁴ While the framework may seem very abstract at this point, it will become clearer in §5 when I apply it to shed light on a stem cell experiment.

physical (micro)structure or if a person is repeatedly recognised in the street, the object is fragile, and the person is recognisable—even while she may have a better taste for hairstyles than Mr. Johnson and the causal process leading to her recognisability is different.

Because this is so, it is possible to discover ways of interacting with *Cproc* so that the latter does not occur, *even while the object still bears the disposition*. For instance, one can carefully wrap a glass with a special material that absorbs (part of) the energy of a struck so that even if I struck the glass, this does not break. Or Boris Johnson may wear a hat or dye his hair so that even if we see him, we do not recognise him, or at least not so easily. In these cases, the glass would still be fragile, and Mr. Johnson would still be recognisable, and the disposition is said to be *masked*, or *antidoted* (Bird, 1998).⁵

Having made these distinctions, it is now possible to appreciate that the question about the extrinsicity of a disposition primarily concerns *Cinst*, as by definition most manifestations of a disposition would minimally include an external trigger (cf. radioactivity, spontaneous particle decay; see Hauska, 2015). A property is intrinsic iff its instantiation in an object *o* does not depend on features of *o*'s environment, or relational properties of *o*, whereas it is extrinsic otherwise. The fragility of the glass depends on its (micro)structure alone, whereas the recognisability of Boris Johnson depends, among other things, on what other people in his environment know about him—that's why he is likely not recognisable somewhere outside the Commonwealth. Fragility is an intrinsic disposition and recognisability is an extrinsic disposition.⁶

I must make a final point concerning the *identification* of dispositions—and how this conditions their nature, including their extrinsicity—which relates to my general argumentative strategy of relying on empirical evidence to draw metaphysical conclusions. Traditionally, examples of dispositions include cases where one can rely on her background knowledge—including her intuitions based on this knowledge, or knowledge of the scientific theories that postulate the existence of the disposition—or on independent methods for testing whether an object has or lacks the disposition.⁷

When we see a (drinking) glass, we can presume that it will be fragile because we have seen hundreds of (drinking) glasses, or because we know it is a Duralex and know about the objects elaborated by this company. So, we can intuitively assume,

⁵ In traditional analyses, the masker is sometimes supposed to interfere with the stimuli, insofar as the SCA analysis only recognised the stimuli among the conditions of manifestation. However, if one admits that manifestations are processual, and require sustaining conditions (Hüttemann & Kaiser 2018), then it is perfectly conceivable that a masker is an element that interferes with the stimuli, or with the sustaining conditions. I will assume this view of masking in the remaining of the paper.

⁶ If someone is unconvinced about the case for recognisability, or any other extrinsic disposition—excluding stemness—I may use, see McKittrick (2003, 2018), where all the examples are taken from.

⁷ The term *intuition* will be used across the paper to refer to any metaphysical implication that could be derived from our background knowledge, including everyday knowledge, knowledge about scientific theories or experimental knowledge. A premise of the paper is that the source for this background knowledge in the case of stemness is experimental (§3 for justification). This method is in agreement with the tenets of inductive metaphysics/metaphysics of biology that I adopt in the paper.

based on our background knowledge, what will happen to the new (drinking) glass. Alternatively, we may have tested that it is made of *glass*, which is a fragile material according to our best knowledge—scientific or not.

When we think about cases like recognisability, we can imagine a process by which a person becomes recognisable—e.g., daily appearances on the news, playing for a famous football team, etc.—and derive intuitions for a specific person in a concrete environment on this basis—e.g., Boris Johnson will be recognisable in any country of the Commonwealth. Or we can rely on our previous experiences with that person—e.g., how people reacted when they saw Mr. Johnson last month in Leeds—to infer how people will react to her in the future. What matters to make the attribution in these cases is *the (expected or past) reaction*, but not the causal process leading to it.

Note however that there is a big contrast with regards to identification between fragility and recognisability. A possible way of testing recognisability consists in testing *several manifestations of the property*, potentially across environments. This method does not require presupposing any background knowledge about its bearer, but only about the manifestation of the disposition.⁸ In the case of fragility, in contrast, some background knowledge that goes beyond the knowledge of the manifestation of the property is always required to determine whether a new object will or will not be fragile. Fragility cannot be tested by testing its manifestation, or the bearer of the property will be destroyed—hence the property will not be instantiated *in that object* anymore. A priori, this does not seem to pose a big problem provided one can rely on some basic intuitions about how a perfect duplicate of a fragile object will be like. A common—and plausibly correct—assumption is that two objects will be equally fragile if they are made of the same material, e.g., glass, as we know that the (micro)structural properties of glass are such that glass-made objects are fragile.⁹

§3 will show that none of these strategies *seems* open for the case of stemness, hence generating the ontological deadlock. Note that for making the argument I will need to rely on some epistemic evidence. The reader must however note that the *apparently epistemological arguments* I will introduce there depend on this crucial premise about the identification of dispositions.

3 The ontological deadlock

Stem cells are defined by their capacities to self-renew and differentiate. This may be called the stem cell concept:

⁸ Given that my only presupposition about dispositions is that they are functional-causal concepts, knowledge of their manifestation is at least minimally presupposed by definition *if one knows the disposition*.

⁹ One may think that these different strategies depend on the intrinsicness/extrinsicness of the property, but this is not correct. The disposition to dissolve the coins in my pocket is an extrinsic property of nitric acid—depending on the contents of my pocket—which can be inferred by background knowledge about my coins, but cannot be tested by seeing its manifestation—or I would run out of coins. Cowardice, in contrast, is an intrinsic property that can be tested by its repeated manifestation.

[SC Concept] A stem cell is defined by means of their potential, i.e., what they can become *in the future*, after the cell has reproduced

[SC Concept] expresses a dispositional locution, characterizing the property by appealing to its functional-causal role. Its use suggests that stemness is a dispositional property, and I think this conclusion is correct.

A plausible objection to this conclusion, though, would state that stemness is not *only* a disposition, but different types of properties. The latter approach is adopted by Laplane, who proposes a fourfold classification of stemness (Laplane, 2016; Laplane & Solary, 2019). In her account, stemness can be a categorical, a dispositional, a relational (extrinsic), or a systemic property/type. Grounded on this classification, Laplane suggests different target interventions, especially oriented to the treatment of cancer, depending on the type of stem cells that are being treated. The way how Laplane uses the concept of *disposition*, however, strongly differs from mine. She takes dispositions to be *intrinsic* properties. This constitutes a metaphysically loaded view on dispositions, which is perfectly suited for Laplane's goal of using clearly defined metaphysical categories *to assist in the clarification of scientific debates or in the development of scientific hypothesis*, in the tradition of philosophy "in" science (Laplane et al., 2019; Pradeu et al., 2021). Therefore, Laplane would reformulate my question about the extrinsicness of stemness as a question concerning its relationality or its systematicity.

I do not have any objection to Laplane's characterization, provided it is conceived in terms of her specific goals. But my goal in this paper is not understanding stemness to assist scientific research, but rather understanding stemness to shed light *on the metaphysical question about the nature of dispositions*, in the tradition of inductive metaphysics (Engelhard et al., 2021; Kaiser, 2019) or metaphysics for biology (Suárez & Triviño, 2020; Triviño & Suárez, 2020; Triviño, 2022).¹⁰ Hence, instead of taking the *intrinsicness* of dispositions for granted—as Laplane does—I take the *dispositional* nature of stemness as my starting hypothesis.¹¹ My assumption for doing so is that dispositions are properties referred by functional-causal concepts (Mumford, 1998, p. 77; Choi & Fara, 2018; McKittrick, 2018), and [SC Concept] clearly expresses a concept of this type.

If stemness is a disposition, then it would seem that its nature—including its *Cinst*—can be studied using the conventional philosophical methods that have been employed for studying dispositional properties. But, irrespectively of the conceptual intuitiveness of such a conclusion, matters are slightly more complex when it comes to attributing properties to stem cells. On the one hand, there seem to be non-reliable sources to generate some background knowledge about stemness. First, in contrast with other dispositional properties (e.g., fragility, recognisability), there are no reliable intuitions about stemness that one can trust.

¹⁰ Note that these two traditions are in fact traditions in the philosophy of science, provided that one considers that philosophy of science must also be concerned with questions about metaphysics and not only with questions about epistemology.

¹¹ In another draft, currently under review, I thoroughly discuss the biological consequences of my dispositional approach to stemness.

Stemness is a biological property, and thus our intuitions about it derive mainly from scientific practice. Second, stem cell research is mostly experimentally-driven, instead of theory-driven. Hence, our intuitions about stemness cannot derive from the study of the logical consistency or the implications of a stem cell theory: they must derive from the knowledge that stem cell experiments provide.

On the other hand, the experimental study of stem cell properties poses some evidential challenges (or constraints) that need to be faced before any serious conceptual analysis of the *Cinst* of stemness can be carried out. These constraints derive from both experimental results about the nature of stemness, and the grounding assumptions that drive stem cell research (Fagan, 2013a, 2013c, 2015; Laplane, 2016). The combination of these constraints with the observation that intuitions about dispositions must rely either on background knowledge, or on the examination of several manifestations of the property, generates a serious obstacle for understanding the ontological role played by the environment in the case of stemness.

Fagan (2013a, 2013c) refers to this challenge as “stem cell uncertainty principle” or “stem cell experimental relativity” and argues that it derives from [SC Concept] alone. I think she is correct, insofar as the challenge is conceived primarily as an epistemological challenge for stem cell research. In fact, a general problem of dispositions concerns how to gain epistemic access to them, and the case of stemness is especially salient because it requires cell reproduction, which entails the destruction of the cell. But I am not convinced that the *ontological* problem for stemness *as a disposition* derives from the [SC Concept] alone, for otherwise it would be a challenge for any disposition whose manifestation entails the destruction of its bearer (see also §4). Assumptions about how to form our intuitions about the metaphysics of dispositions, and about how stem cell experiments may assist us in doing so, also play a role in reaching the ontological conclusion. That’s why I refer to this challenge as the “ontological deadlock”, which I argue consists in the impossibility of ontologically determining whether stemness is an extrinsic or an intrinsic disposition. In short:

P1. The intrinsic/extrinsic nature of stemness can only be ontologically determined by means of background knowledge—e.g., about (micro)structural or phenotypic properties—or by independent testing methods, §2.

P2. No background knowledge—e.g., about (micro)structural or phenotypic properties—can ensure stemness attribution, by [SC Selection].

P3. No independent testing method can ensure stemness attribution, by [Pa-Case-1, Case-2].

Pa. To ensure stemness ascription by independent methods one needs to rely in knowledge about perfect duplicates or repeated manifestation of stemness, §2.

Case-1. If we know that a cell is a perfect duplicate of a known stem cell by any independent method, then we can infer it will be a stem cell.

P1'. To know that a cell is a perfect duplicate of a known stem cell, we need background knowledge—e.g., about (micro)structural or phenotypic properties—about stemness attribution.

P2'. We do not know if a cell is a perfect duplicate of a known stem cell, by [P1' & P2].

Case-2. If we can repeatedly test the manifestation of stemness by the same bearer, then we can infer that the cell is a stem cell.

P3'. Repeated manifestation in one object requires that the object manifests the property more than once.

P4'. Stemness can only be manifested once in one bearer, because stemness manifestation entails the ontological destruction of the object that bears stemness, by [SC Concept] + [SC Reproduction].

P5'. We cannot repeat the manifestation of stemness in the same bearer, by [P3' & P4'].

C. Hence, the intrinsic/extrinsic nature of stemness cannot be ontologically determined.¹²

P1 and Pa derive from my conception of the identity conditions of dispositions as presented in §2. I will now argue why P2 and P4' hold in the case of stem cells by analysing how stem cell experiments work.

Stem cell experiments start by extracting a set of cells from a specific tissue of a multicellular organismal source whose capacities will be tested. There are no pre-established criteria for this extraction, i.e., there is no specific stem cell signature that is looked for while selecting the candidate population in the organismal source. Rather, the stem cell signature may be discovered (*ideally*) when the experiment ends. To put it more formally:

[SC Selection] There are no a priori criteria for selecting a cell as a candidate stem cell

One reason why [SC Selection] plays such a crucial role in stem cell experiments is that there is no set of necessary and sufficient (micro)structural properties—e.g., genetic markers, patterns of genetic expression, etc.—shared by stem cells and only by stem cells. On the one hand, stem cells are phenotypically defined as undifferentiated cells. While this may allow a basic selection, there are so many intermediate stages between a fully differentiated cell and an undifferentiated one that phenotypic markers are of little help. On the other hand, experiments to determine whether stemness can be characterized by a clear molecular signature have so far failed: the genes found as typical of stemness across stem cell experiments differ; some of these genes are also expressed by progenitor and daughter cells, which are not stem cells (Laplaine, 2016, pp. 115–120). Hence, the possibility of relying on (micro)structural properties that single out stem cells and only stem cells seems spurious.

Once selection has occurred, stem cell experiments will be designed for measuring stem cell capacities, i.e., they measure whether some of the cells of a given candidate

¹² Note that the whole argument depends on [SC Environment], for if some cells would happen to manifest stemness in no eliciting environment, there would be strong reasons to think it is an intrinsic disposition.

stem cell population self-renew and differentiate. Self-renewal and differentiation are products of cell division; thus, stem cell experiments are always structured in terms of *reproductive relations* among cells. Cell reproduction occurs by a process of binary fission (mitosis), in which a given cell splits into two daughter cells. The process of cell reproduction necessarily entails the destruction of the mother cell, which no longer exists after the reproductive event has taken place (Laplaine, 2016, p. 108). We can formalize this principle of stem cells experiments as follows:

[SC Reproduction] Stem cells reproduce by binary division, and binary division entails that the cell that reproduces does not exist anymore

The way in which stem cell experiments test the satisfaction of the properties of self-renewal and differentiation by a candidate stem cell population is not absolute (i.e., there is no shared standard which remains invariable across every experiment), but relative to a specific experimental context as well as the methods used in that context. Stem cell methods always include variables such as the temporal duration of the experiment (e.g., 30 cell generations/reproductive events), and characters or traits of interest that will be measured in the cell population (e.g., actin and myosin synthesis). Stem cell experiments are hence designed in such a way that these variables can be measured with precision, and the experiment design will ideally allow to determine whether a candidate cell population has satisfactorily self-renewed or differentiated under the specific conditions established by the experimental context.

The experimental setup where stem cells experiments are carried out requires that the extracted candidate stem cells are placed in one eliciting environment, where they can express their capacities. Eliciting environments may be artificially designed (in vitro experiments), or naturally existing (in vivo experiments), and are required to test whether some of the cells of the candidate stem cell population can manifest stemness. The environment plays hence a fundamental role in stem cell experiments, which can be formalized as:

[SC Environment] Stem cells are placed in an environment where the expression of their capacities can be tested

Candidate stem cells are required to be placed in eliciting environments to test their capacities, which raises the metaphysical question about the role of the environment: does the environment *trigger* the manifestation of the capacity, or does it *generate* the capacity? In other words, is stemness an intrinsic disposition, with the eliciting environment acting as a stimulus of the capacity, or is it rather an extrinsic property, such that stem cells only instantiate it when interacting with the appropriate environment? This requires examining *whether some components of the niche are included among the Cinst of stemness or rather all of them are mere stimulus that cause its manifestation*. Stem cell experiments, unfortunately, cannot provide any information for satisfactorily replying to this question, because there is no background knowledge to tell stem cells apart from non-stem cells [SC Selection], nor there is a way of testing stemness across environments for the same

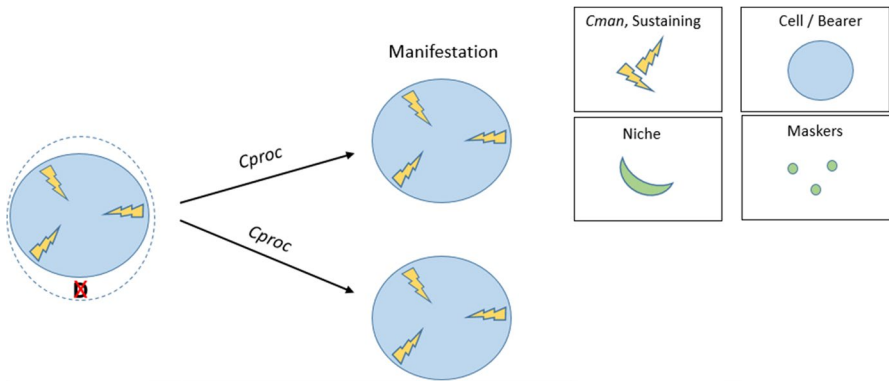


Fig. 3 The ontological deadlock in stemness. Because the cell immediately reproduces, there is no disposition being instantiated

cell due to [SC Reproduction]. Hence, we are trapped in an ontological deadlock (Fig. 3).

Recall that the deadlock is ontological, not epistemological. The problem is not that we cannot know *how to show* intrinsicness, or *how to test* extrinsicness. The challenge is that, because the ontology of stemness is ultimately undeterminable, its nature does not seem specific and/or different from the nature of non-stem cells. Note that the ontological deadlock is a general problem of stemness, and consequently a problem of MSC. The latter will however be the subject of my solution.

Fagan (2013b, p. 955; 2017) envisions a plausible empirical escape from the ontological deadlock. She argues that if stemness is attributed to the starting point of a cell *lineage*, rather than to a single cell, the deadlock disappears. Drawing on that assumption, she argues that research on organoids provides a good source fully examining stem cell capabilities (Fagan, 2018, 2020). Fagan’s response is plausible, and I think it is a good way of overcoming some of the challenges adduced before, at least insofar as they concern experimental research, which is her main aim. However, ontologically, it still leaves the question about intrinsicness unanswered because she fails to explain how the starting cell in the lineage acquired stemness. If the cell acquired it *before* it formed the lineage, we are back to the original problem. If, on the contrary, the cell acquired stemness *after* the lineage was formed, then the object will instantiate the property once it has disappeared. This seems metaphysically unsustainable: If a “Thatcherian” political party is created in the UK today, it does not follow that Margaret Thatcher has acquired the disposition to influence the creation of a political party *today*. At most, one can argue that her disposition has *manifested* today. But either she had the disposition before she passed away, or she never had it, and the bearer of the disposition was something else—e.g., the biographies recorded about her life and work, or her political legacy. Organoid research, hence, provides important information about stemness but does not allow to answer

the question about intrinsicness/extrinsicness. As this is the primary question I aim to answer, I exclude this option here.¹³

Note that the ontological deadlock is an important challenge for defenders of the “niche hypothesis”, as well as a fundamental constraint for understanding the nature of stemness. Concerning the former, if the intrinsicness/extrinsicness of stemness cannot be known due to internal constraints, it turns out that their hypothesis will never be testable. Concerning the latter, if it is impossible to establish faithful criteria to overcome the ontological deadlock in a way that allows discovering what the ontology of stemness is, it seems that we will never know anything about its conditions of instantiation. The only way of solving these issues would be by finding a way of circumventing the constraints that limit stem cell research (§4), and deriving the ontological lessons that follow for the nature of stemness as a disposition (§5, §6).

4 Overcoming the ontological deadlock: the case of quiescence

The study of quiescence provides a valuable tool to overcome the ontological deadlock and understand the *Cinst*—and the intrinsicness/extrinsicness—of some stem cells. For this to happen, the population of quiescent cells being studied needs to fulfil these three criteria:

- (C1) [SC Selection] must be partially overcome for the population of quiescent cells.
- (C2) The quiescent cells need to be shown to be stem cells that are kept in a quiescent state to preserve their stemness, so that quiescence is informative about stemness.
- (C3) [SC Reproduction] must be required not to happen to test quiescence, which allows testing [SC Environment] across environments.

The combination of these criteria allows overcoming the deadlock by generating an independent method that provides enough background knowledge to ensure stemness attribution, at least in these subpopulations of stem cells that are kept in the quiescence state to preserve their stemness. Another way of making the same point would be by noting that quiescence offers a way to access the “essence” of stemness (§2), hence for knowing how some perfect duplicates are. This would show that P2 and P3, *Case 1*, are false. Importantly, my proposal is a way of overcoming the ontological deadlock while keeping an experimental approach to stemness, i.e., uncommitted to any specific theory or conception about what stemness is. In the

¹³ One reviewer has pointed out that the differences between my treatment and Fagan’s lies in the type of stem cells under investigation: muscle stem cells vs. pluripotent stem cells. I think this may be partially correct, as the solution I envision may only be accessible for the former, but not the later. But this is a question open to empirical investigation: if the role I will later attribute to maskers is correct, then it is possible to investigate whether pluripotent stem cells can be masked in different niches and, therefore, it is possible to determine which environments would be eliciting environments. I am skeptical that this would be so, though, given the internal complexities of different stem cell types, and thus I accept that the ontological deadlock cannot be solved for every type of stem cell. But this later claim needs to be empirically demonstrated, and doing so lies however outside the scope of this paper.

reminding, I will introduce quiescence and argue why the satisfaction of these criteria is empirically feasible and it ontologically allows overcoming the deadlock.

Quiescence is a stage or phase within the cell cycle (G_0) during which the cells are in a dormant state, characterized by the lack of cellular reproductive activity.¹⁴ It occurs right after the mother cell has stopped dividing (i.e., after cytokinesis) and before the daughter cells has entered its own division cycle, characterized by the initial protein synthesis of the interphase. Quiescence differs from senescence because, while both are stages of cell cycle arrest, only the former is reversible. Quiescence cells can therefore re-enter the cell cycle again if the appropriate conditions occur, while senescent cells cannot divide further, which ultimately leads to their degeneration and death.

Recent research on quiescence suggests that it is actively maintained through the interaction between internal and external cues from the cell's microenvironment (niche). This active maintenance derives from the fact that quiescent stem cells need to be both dormant and simultaneously ready to be quickly re-activated at any moment, which have led some authors to define quiescence as a "poised state" primed for differentiation (Cheung & Rando, 2013).

Quiescence is not unique to stem cells, though. It has been reported in differentiated cells such as neurons, or hepatocytes. One may think that because quiescence is not unique to stem cells, the chance of appealing to quiescence to solve the ontological deadlock is spurious. But this conclusion would only be partially correct because it silences the fact that undifferentiated quiescent cells are frequently localized in specific parts of the body—the hair follicle (within the bulge), the intestines, among the populations of blood-forming cells, etc.—where it is necessary to maintain a subpopulation of cells dormant but ready to be activated in case of injury or damage. This localization allows that the selection of quiescent cells may be guided by some background knowledge, specifically about those tissues where regeneration or repair is constantly required to occur. This basic selection would at least ensure that the cells that are taken are not just non-stem quiescent cells, but quiescent cells with the potential to manifest their stemness if properly activated, at least in some tissues. It thus seems that, at least in some tissues, [SC Selection] may be *partially overcome* when it comes to the selection of quiescent cells and, particularly, these quiescent cells that may simultaneously be stem cells (C1).

A reason that reinforces not just the selection, but also the nomological (i.e., not accidental) relationship between stemness and quiescence is due to the functional role of the latter for the preservation of the former. I said that subpopulations of quiescent stem cells usually reside in parts of the body of multicellular organisms—mostly vertebrates—where they may be required for tissue repair and/or regeneration. In these tissues, the necessity of maintaining stem cells in a quiescent state is due to the need of preserving a pool of unaltered cells always ready for entering the reproductive cycle when certain damages occur. This has to do with the nuances of cell reproduction. Every cycle of cell reproduction increases the probability of

¹⁴ My analysis of quiescence is a summary of Li and Bhatia (2011), Cheung & Rando (2013), Cho et al. (2019), and van Velthoven & Rando (2019).

genomic decay, and its consequential phenotypic effects—aberrant phenotypes, apoptosis, senescence. If stem cells were constantly reproducing and forming lineages, their reproductive machinery will get damaged, leading to the loss of their self-renewing and differentiation potentials, and compromising the organism's capacity for tissue repair. The organism's capacity of keeping its stem cells in a quiescent state provides the advantage of preserving their role, without having to pay the costs of their constant reproduction. In this sense, quiescence is used to preserve the capacities of stem cells, and thus some quiescent cells are quiescent *because they are stem cells*, which makes the selection to be based in biological properties that are nomologically connected (C2).

Note that one may be sceptical of the kind of connection I have drawn between stemness and quiescence, as I seem to have conflated two properties and misunderstood the [SC Concept]. Recall that [SC Concept] states that stemness is defined by its potential, i.e., by what the cell *will become in the future*. One could then argue that appealing to quiescence, which connects to what the cell is *now*, is of no help with understanding the concept of quiescence. This type of criticism seems to underlie Fagan's (2013a, 2013c) argument that [SC Concept] alone generates the type of problems I described in §3. Note that as it stands, this type of criticism conflates two types of question: one about the *Cinst* of the disposition expressed by [SC Concept], the other about the manifestation of the objects that fulfil [SC Concept] (§2). If we assume that [SC Concept] expresses stemness and the latter is a disposition, then these two questions come apart, especially under the common presupposition that some objects may have dispositions that they do not manifest. My point is thus that if there is the type of nomological relationship between quiescence and stemness that I have described, at least for a subset of cells that can be empirically discovered, then the study of quiescence can reveal something about the *Cinst* of stemness, insofar as these quiescent cells will be so in virtue of being stem cells—thus, they are *simultaneously* stem cells.

Zipori (2009, p. 157) and Clevers (2015) suppose another source of potential problems to (C2). They have criticized, I think persuasively, the relevance of quiescence to understand stemness, as they suspect its importance may be reduced in relation to the relevance of other characteristics of stemness, and even point out that not every stem cell needs to enter a quiescence phase. Their argument is not necessarily incorrect if restricted to the specific area of scientific research about stemness, including its nature, or if the question about the nature of stemness is understood as the possibility of finding universal property *of every stem cell*. But note that I am not offering quiescence as a strategy to solve the type of problems that Zipori and Clevers are interested in, which seem to be broader in scope. I appeal to quiescence, under the specific criteria that I have isolated in my analysis, to metaphysically overcome the ontological deadlock in a way that allows making some claims about *Cinst* of stemness. I am conscious that my solution is not without problems if it is understood as a general way of understanding stemness in every potential stem cell, or if it is valued by its experimental implications. But I do not intend to extend the conclusion of my study beyond what it establishes, and hence their concerns do not apply.

Finally, there is an even deeper concern concerning my appeal to quiescence. If the relationship between quiescence and stemness is not 1:1, but merely

probabilistic, then one may contend it is impossible to break the ontological deadlock by appealing to quiescence for, in the end, the cell must reproduce to determine its intrinsicness/extrinsicness. The reason is clear: if only a subset of the quiescent cells are really stem cells, then deriving conclusions about the latter from the former is, at best, problematic.¹⁵ This is a sensible concern, but I think it is based on a misunderstanding of the ontological deadlock. The ontological deadlock does not concern directly whether a cell is or not a stem cell, but rather whether stemness is an intrinsic or an extrinsic property. While it is true that one would need a 1:1 connection between the properties for showing the former, the same is not true for the latter. It is enough to show that the quiescent stem cells in a specific niche are so intrinsically (or extrinsically), because then one can be certain that the subset of those that are also stem cells will necessarily be so as well.

The satisfaction of (C1) and (C2) in isolation would be enough to use quiescence as the basis for making ontological claims about the conditions of instantiation of stemness iff quiescence could be tested without an eliciting environment. But recall that I said quiescence is an actively maintained state that results from the interaction between a cell and its niche. So, testing quiescence does not avoid [SC Environment]. But it does avoid [SC Reproduction], because quiescence is precisely characterized as a temporal, reversible and primed—i.e., ready to re-enter the reproductive cycle—state of cellular reproductive arrest. Testing quiescence therefore requires testing whether the cell is in such a state by analysing its interactions with its niche; but it does not require the destruction of the quiescent cell, which can be preserved over time. This is mainly because, by definition, testing quiescence requires [SC Reproduction] not to occur. Then quiescence can be tested for the same cell across different environments—or even several times in the same environment—in a way that will allow discovering whether the cell is quiescent and whether it is a stem cell in that environment (C3).

One may object that this premise presupposes that one can easily discover quiescent cells. But matters are more complex, as it is sometimes hard to tell them apart from senescent cells. Recall that the difference is that quiescent cells are in a poised state, which allows them to re-enter the reproductive cycle, while senescent cells are not. This is a serious objection, but it is epistemological, not ontological. I do not presuppose the distinction is easy. My claim rather presupposes the conditionality: if the distinction can be made *for some cells*, which would allow the test to be carried out, then quiescence offers a chance for overcoming the deadlock. It is enough, for my metaphysical interests, that this can be done just in one subpopulation of cells in one tissue, as this would allow studying the problem I aim to study.

Finally, one may argue that the problem of concentrating on quiescence, instead of in stemness, is that I would be changing the disposition that I am characterizing. But note that this would only be correct if I were identifying both properties, or ontologically reducing the latter to the former. My take on quiescence, however, is primarily epistemological. In the form of an argument: given that one needs an

¹⁵ I thank an anonymous reviewer for raising this objection.

[bearer] Quiescent stem cell in the niche
[Cinst] Extrinsic, niche cell interaction mediated through Wnt4, Rho GTPase, Rho kinase (ROCK-Rho axis)
[Cman, Stimulus] BaCl ₂ injury; any other injury in natural occurring populations
[Cman, Sustaining conditions] Cell elements that allow cell division: YAP, <i>MyoD</i>
[Manifestation] Asymmetric division
[Cproc] Stem cell activation

Fig. 4 Model of MSC stemness in mice as discovered by Eliazer et al. (2019)

epistemic proxy for deriving any claim about the ontology of a dispositional property (§2), and given that relying on the repeated manifestation of the property or on knowledge about perfect duplicates seems impossible in the case of stemness (§3), then we need an alternative. My point is that quiescence is an alternative epistemic proxy for making claims about the ontology of stemness as a dispositional property. But I am not claiming that to know the ontology of stemness we need to know the ontology of quiescence. Rather, I am suggesting that we must investigate quiescence to have epistemic access to the ontology of stemness.

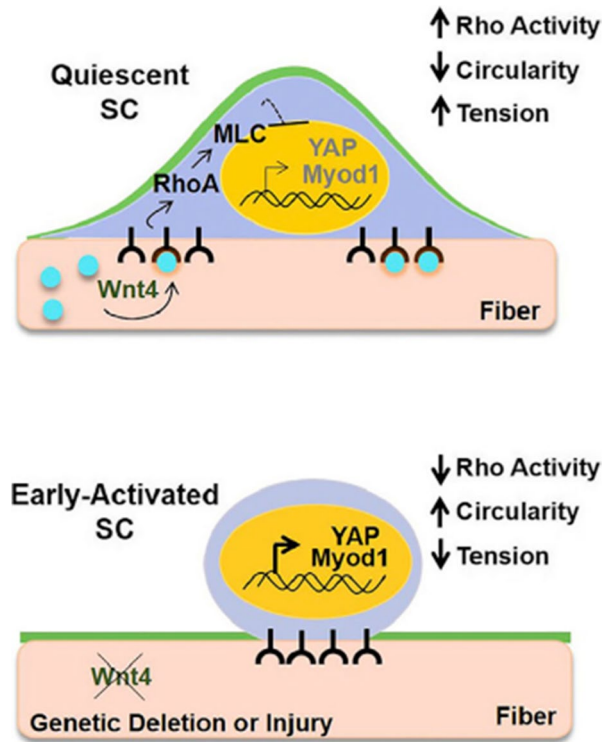
5 Niche signals in muscle stem cells

I analyse the ontological role that the niche plays in MSC stemness. To do so, I rely on Eliazer et al.'s (2019) study of the role played by niche signals in the activation/deactivation of stemness in quiescent MSC in mice.¹⁶ Figure 4 provides a basic model of the nature of stemness of the cells in their study, in a way that advances the metaphysical conclusions I will defend in this section.

Recall that stemness manifests in asymmetric cell division. Stem cell activation refers to the moment when the original cell starts synthesizing the proteins that make it enter in the interphase. Metaphysically, stem cell activation is the moment when *Cproc* begins. In the very moment that this happens, the mother quiescent stem cell as such ceases to exist, as it starts becoming two daughter cells. Before *Cproc* starts, the stem cell resides in the niche as a quiescent stem cell. Understanding the *Cinst* of stemness in this case thus requires understanding how the quiescent cells are maintained in such state. The role of the niche in this maintenance will determine whether the stemness instantiated by these cells is intrinsic or extrinsic. There are three possibilities:

¹⁶ This case study is chosen because the specific subpopulation of quiescent stem cells studied by Eliazer et al. Satisfy (C1)-(C3).

Fig. 5 Role of the niche during *Cinst* (up) and during *Cproc* (down). From Eliazer et al. (2019), graphic abstract. Printed with permission from Cell Stem Cell



(H1) If the niche is a stimulus in stem cell activation, or part of the sustaining conditions of stemness then stemness does not in principle depend on the niche and is intrinsic—assuming no other extrinsic element beyond the niche plays a role in the instantiation. In this case, the niche is part of the *Cman* of stemness.

(H2) If the niche establishes a relationship of dependency with stemness—i.e., the cell is a stem cell in the niche and only in the niche, such that removing the niche causes the bearer to stop instantiating the property—then stemness is extrinsic. In this case, the niche is part of the *Cinst* of stemness.

(H3) If none of these two options is true, because there is no interaction—of dependency or regarding *Cman*—between the niche and the cell, then the niche plays no role in stemness—yet one cannot assure whether it is extrinsic or intrinsic, as this may depend on other elements in the organism.¹⁷

Based on the evidence derived from Eliazer et al., I argue that (H1) should be discarded. Additionally, I argue that Wnt4 from the niche is involved in some bio-molecular processes occurring in the stem cells that reside inside the niche, showing that (H3) is also false. Drawing on this, in §6 I will show that (H2) is the most

¹⁷ In this case, Laplane would argue that stemness is a systemic property.

plausible interpretation of the role of the niche in the instantiation of stemness, provided the action of the niche is interpreted as a case of masking.

Let's now determine the role of the niche in Eliazer et al.'s by looking at their experiments. MSC activation in mice begins after a BaCl_2 injury is experimentally provoked, which triggers a cascade of effects that terminates in MSC division leading to tissue repair. Metaphysically, BaCl_2 injury is the stimulus that causes stemness to manifest. *Cproc* has several phases, and lasts certain time, during which the internal elements of the cell provide the sustaining conditions that are required for cell division. These include the conditions required for DNA replication, spindle formation, or the generation of the replication fork, among others.

Studying the metaphysical role of the niche during *Cproc* and *Cinst* requires knowing the mechanistic details of the biomolecular processes that occur before and after BaCl_2 injury, and during *Cproc*, as knowledge of the biomolecular elements involved in *Cproc* allow discarding their role as *Cinst*, given that the object disappears as soon as *Cproc* starts due to the characteristics of cell reproduction. Figure 5 schematically illustrates what happens in the niche, and in the cells, before and after the injury, and how this influences *Cproc*.

Eliazer et al. observed a drastic reduction in the levels of Wnt4 expression after BaCl_2 injury. Concretely, 18, 24 and 48 h after tissue injury in mice, the levels of expressed Wnt4 in the muscle had decreased between the 45% and the 65%. This provides preliminary evidence that Wnt4 transcript plays a key role in maintaining quiescence and stemness of MSC in the niche, and potentially also a role in inducing their activation after injury. But note that this observation may be misleading, as the reduction of Wnt4 expression may be an effect of a common cause, rather than something directly related to stem cell activation. Note that, if Wnt4 reduction were an effect of a common cause, one could not conclude anything substantial about its potential role in the *Cinst* of stemness, as it may simply not interact with the stem cells. To discard this option, Eliazer et al. tested whether depletion of the Wnt4 transcript in adult muscle fibres would have the same consequences that were observed in injured mice. The results showed a clear increase in the number of active stem cells, with a substantial increase in the expression of *MyoD*. *MyoD* overexpression is consistent with the role played by Wnt4 transcript in quiescence, as *MyoD* is known to be involved in the sustaining conditions leading to the reproduction of MSCs, and its repression is known to maintain MSC quiescence (Morré et al., 2017). This shows that Wnt4 from the niche interacts with the stem cells, in a way that clearly discards the plausibility of (H3). Yet it is still not clear the metaphysical role it plays.

To answer the latter question, it is necessary to know how Wnt4 acts mechanistically. Eliazer et al. proved that the Rho-ROCK axis (Rho GTPase + Rho kinase) gets inhibited when the amount of Wnt4 in the niche is drastically reduced. The activation of the Rho-ROCK axis increases intracellular tension and reduces the degree of circularity of cells by repressing the YAP transcript. YAP expression is known to trigger the synthesis of *MyoD* in a way that eventually starts and sustains the process of cell division until completion. If the amount of Wnt4 in the niche increases, however, the Rho-ROCK axis gets activated, the YAP transcript gets repressed, and this eventually arrests the process of cell division and maintains MSCs in a quiescent state. This specific role of Wnt4 and the Rho-ROCK axis suggests that these

elements from the niche cannot be part of the stimulus or the sustaining conditions that lead to the manifestation of stemness, proving (H1) to be false.¹⁸ But a more positive argument is needed to prove that this is so.

Let us start supposing that Wnt4 and the Rho-ROCK axis are part of the stimulus conditions. In this case, it turns out that the stimulus conditions would be overdetermined: on the one hand, the injury; on the other, the decrease in the Wnt4 transcript levels and the cascade effects that follow. Of course, this does not seem a big challenge: as stem cell research is molecularly based, it is expected that the aim of the scientists will be to find the molecular *triggers*. So, it may be argued that the injury triggers some molecular changes that are in the end the ultimate triggers of the activation. Hence, in principle, the thesis that Wnt4 is a stimulus seems plausible. But this thesis seems problematic in a second respect. Stimulus conditions are concrete (although plausibly heterogeneous) actions that affect the object that bears the disposition. For example, *striking* a fragile object, *provoking* an irascible person, *immersing in water* a soluble object, etc. Analogously, thus, Wnt4 must affect the activation of quiescent stem cells *by doing* something. But the result from Eliazzer et al. suggest that Wnt4 acts by *being repressed*, or *eliminated* from the niche. It is hard to see how a negative action may be a trigger of a disposition. In fact, a more plausible assumption is that the trigger is merely being injured, and as such this triggers a cascade of effects on stem cells that includes, among others, its particular relation to the niche as expressed in terms of the (decrease in) Wnt4 transcript density.¹⁹ It follows that Wnt4 is not part of the stimulus conditions.

One may object that even if not a stimulus, it is plausible to conceptualize *the reduction in Wnt4 transcript density* as part of the sustaining conditions involved in *Cproc*. This would make sense, as this reduction triggers the cascade effects starting with the repression of the Rho-ROCK axis and causing the production of YAP, which ultimately leads to the manifestation. As a matter of fact, Eliazzer et al. observed that YAP depletion also prevents MSC activation even when Rho-ROCK signalling is repressed. However, this response must cope with another challenge. If the key is the change in the density of Wnt4 transcript, rather than the transcript itself, it is hard to understand how the sustaining condition may also work in the scenarios of blocked expression or inactive function. Recall that Eliazzer et al. proved that Wnt4-depleted niches also cause quiescent stem cell activation, i.e. *Cproc* also occurs under these circumstances. But a manifestation is not expected to occur if the sustaining condition does not play its role, or it is not present. On the contrary, one would expect *Cproc* to be arrested, or to lead to a different manifestation. But this case shows precisely the opposite: the manifestation occurs both in cases of

¹⁸ This does not mean that other elements from the niche may be part of these conditions. But this would be orthogonal to what I aim to establish.

¹⁹ An objection to this argument would consist in arguing that Wnt4 acts as a trigger by means of being a negative cause (Barros 2013). I do not disagree that scientists may conceptualize Wnt4 depletion as an *explanatory cause*, but I am more inclined to think, with those that oppose assigning an ontological role to negative causes, that negative causes are not *ontological causes* (Beebe 2004). As this paper is about ontology, then, I must reject that Wnt4 plays such a role.

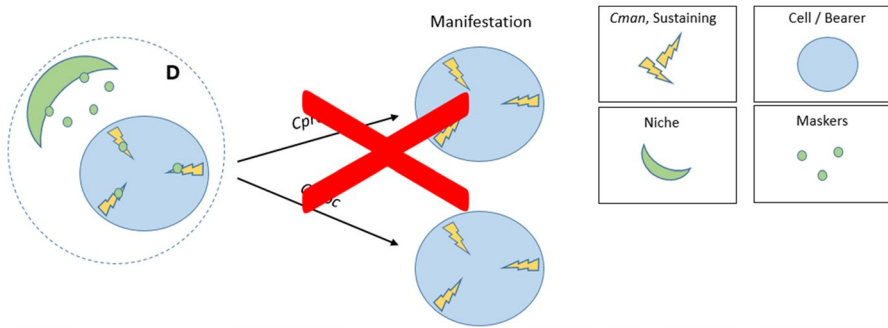


Fig. 6 Schematic representation of stemness as a structurally masked disposition (SMD). The components from the niche contribute towards *Cinst* by inhibiting *Cman*. In this scenario, *Cproc* (cell reproduction) is arrested, stemness does not manifest, and thus it is instantiated

reduction and in cases of depletion. Therefore, Wnt4 is not part of the sustaining conditions.

6 Stemness as an extrinsically structurally masked disposition

Having discarded that Wnt4 and the components of Rho-ROCK axis from the niche are part of the *Cman* of stemness (H1), and having shown that these components interact with the stem cells in the niche (H3), it follows that the niche must establish a relation of dependency with the stem cells. That is, the niche is part of the *Cinst* of stemness. This would automatically make stemness, at least in MSC, an extrinsic disposition, as in §2 I said that a property is extrinsic if its instantiation depends on properties of the environment of the bearer, i.e., on relational properties of the bearer of the property. The niche is clearly the environment where stem cells reside, and the components of the niche establish a relationship with the stem cells residing in it. Therefore, it follows that stemness is, in this case, an extrinsic disposition.

I have arrived to this conclusion by discarding (H1) and (H3), but an independent argument for the same conclusion can also be given. Assume Wnt4 and the components of Rho-ROCK axis from the niche are not part of *Cinst* in MSC. Then, their presence or absence should not affect the instantiation of stemness. Let us build a scenario where there is no Wnt4 or its action is blocked, and the Rho-ROCK axis is impelled in the microenvironment of MSCs. We would observe that every MSC will immediately manifest stemness, as the overexpression of *YAP* and *MyoD* in Eliazer et al.'s experiment suggested. But if this is so, we are trapped in the ontological deadlock: every cell in the niche that instantiates stemness immediately manifests it; stemness manifestation entails stemness destruction, as it consists in cell reproduction; thus, in a scenario where Wnt4 is absent or the Rho-ROCK axis is blocked in the MSC niche, stemness is never instantiated even though the cells are dividing in the way required by the [SC Concept]. But this is contradictory with the hypothesis that some cells in the MSC niche are stem cells. Thus, Wnt4 must be part of *Cinst* of stemness, and thus stemness must be an extrinsic property of the cells.

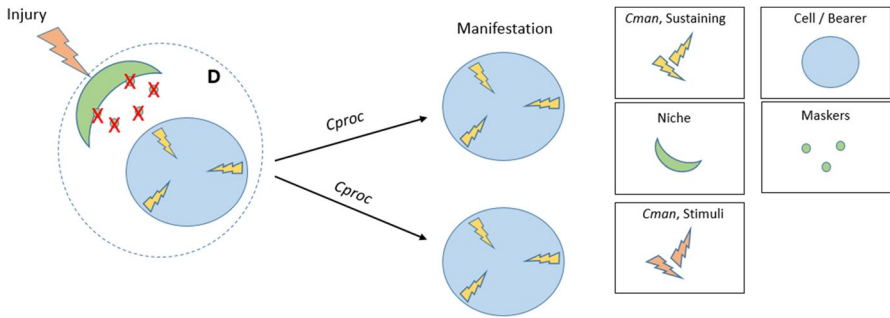


Fig. 7 Schematic representation of stemness manifestation, according to my hypothesis. The injury causally interferes with the masker, so that the cascade effects of the *Cproc* occur causing the manifestation

The question that still remains, though, is how the relationship between the niche components and the MSC in the niche works, so that stemness can be instantiated. At this point, I argue that the components of the niche act as *maskers of stemness*, and thus stemness becomes a SMD, that is, a disposition whose instantiation requires the interaction between a masker and a bearer (Suárez, unpublished manuscript). Figure 6 schematically illustrates the hypothesis.

The role of the components of the niche as maskers stands from the experiments plus the definition of masking I offered in §2. A masker is an event or object that interferes with the *Cman* of a disposition so that, even if the latter obtains, *Cproc* does not occur and thus the disposition fails to manifest. This is so *even while the object still instantiates the disposition*. *Wnt4*, and the components involved in the formation of the Rho-ROCK axis act precisely by interfering with the synthesis of *YAP* and *MyoD*, in such a way that what would be an otherwise normally produced *Cproc* leading to cell reproduction gets arrested. This action is coherent with the definition of masking. But there is a contrast, given the specific character of stemness as a dispositional property. In the case of other dispositional properties, the presence or absence of the masker affects the manifestation of the disposition, but not its instantiation. In other words, in conventional cases of masking, the masker is not ontologically necessary for the bearer to instantiate the disposition, but an external element that a priori does not affect the metaphysics of the disposition. In contrast, my argument at this point leads to the conclusion that the elements from the niche, *acting as maskers*, also create a relationship of ontological dependency with the bearer of the disposition such that, if their absence were total, stemness would never be instantiated. This makes stemness a SMD.

To see why stemness is a SMD, it is necessary to revisit all the premises that have structured my argument so far. I said that a SMD is a disposition whose instantiation requires, *as a condition of possibility*, the interaction between the bearer and a masker (Suárez, unpublished manuscript). Let us examine why this is a requirement affecting the conditions of possibility of the property. I said that the object instantiating the property, the cell in the niche, ceases to exist as soon as *Cproc* starts, for its identity is compromised as it starts becoming two different cells. If the bearer ceases to exist, then the properties it instantiated during its existence also stop instantiating

in this object. Therefore, for stemness to instantiate, it must do so before *Cproc* starts. The paradox, though, is that *Cproc* starts as soon as the cell appears (i.e., as soon as reproduction from the previous cell generation finishes), as the cell bears all the transcript factors required for *Cproc* to happen, including its sustaining conditions—*YAP* and *MyoD*. If every cell in a vertebrate multicellular behaved like this, then nothing can differentiate stem from non-stem cells in the multicellular, as they would have exactly the same ontology. Therefore, stemness would not be possible in these organisms, as the property only exists in its contrast with non-stem cells—see especially below for an evolutionary argument supporting this claim. For stemness to be possible, then there must be a time lapse, distinct from *Cproc*, during which it gets instantiated. This time lapse requires, as a condition of possibility, that an object, process or event interferes with *Cman* so that the manifestation gets blocked, the cell does not get destroyed, and the property can instantiate. By definition, an object, process or event that interferes with *Cman* so that the manifestation of a disposition gets blocked is called a *masker*. Therefore, stemness is a SMD.

An obvious objection would be that the components of the niche do not really act as maskers because my argument has only proven that they interfere with the sustaining conditions, but not with the stimulus conditions. In fact, what happens when the stimulus occurs is that *Wnt4* gets repressed, and cellular division follows, as illustrated by Fig. 7, so the critic would have a serious objection. I already said in §2 that I do not think maskers should be exclusively defined in terms of stimulus, but rather in terms of *Cman* in general, which are more encompassing. But I must grant the critic with the benefit of the doubt. Interestingly, though, the components of the niche can also act as maskers of the stimulus. Recall that, in Eliazar et al.'s study, the stimulus was a BaCl_2 injury. They observed that artificially overexpressing the levels of *Wnt4* after injury blocks tissue regeneration by avoiding quiescent stem cell activation even when the stimulus is present. This shows that *Wnt4* from the niche acts as a masker even if one maintains a restrictive view of maskers by requiring exclusively a direct interaction with the stimulus, rather than with any other *Cman*.

Additionally, someone may be persuaded of the role of the niche components as maskers, but reject that they need to be considered together with the bearer as part of a SMD, even while accepting the ontological deadlock. They may argue the following: it is true that the niche masks the manifestation, but this only proves that stemness is an intrinsic property. If the niche were depleted from its maskers—the critic would continue—the cells, which are intrinsically stem cells, would reproduce, but they would still instantiate the property for a short time lapse—say, the duration of *Cproc*.

This is an interesting objection, and one that allows me to better articulate the reasons supporting my position. The reason why the concept of stemness is introduced and, likely, the reason why stemness evolved in vertebrates on the first place, was to guarantee the regenerative capacities of multicellular organisms (Rinkevich et al., 2021). In these organisms, somatic cell division is constant, evolutionarily expected (Stencel & Suárez, 2021), and frequently leads to problems of malfunctioning ultimately leading to aging. In these phyla, the adult organism needs a fresh pool of cells that can undergo division in any moment that the organism requires it, while simultaneously being protected from the potential damages of persistent

reproduction affecting somatic or non-stem cells. This fresh pool of cells is what we call *stem cells*. Note that if stem cells were constantly reproducing, but still we could argue that they are stem cells for a short time lapse, then there would be no principled reasons to distinguish them from somatic/non-stem cells. But that would be ontologically mistaken, as evolution must have produced stem cells with distinct properties, given that the evidence clearly shows that multicellular organisms have such a fresh pool of cells. Additionally, once the *Cproc* starts, the events that follow for a stem cells are not different from the events that follow in the reproductive process of any somatic/non-stem cell. They only differ from each other due to the result of their division [SC Concept]. Therefore, the starting point of *Cproc* must be the moment where stemness stops instantiating. If this is so, then the reason why stem cells differ from non-stem cells, at least in vertebrates, must be due to the existence of masking. In the case of MSC, masking comes from the niche, as my case study reveals. Where masking lies in other stem cells is, however, outside the scope of my analysis.

In view of these two points, then it seems plausible to conclude that my analysis of stemness provides, in some sense, an argument for the conditions of possibility of stemness. Stemness requires that stem cells are somehow different from somatic/non-stem cells, and they require to be so because their instantiation is somehow different. It is not plausible to say that they differ in their *Cproc*, or to argue that they are differently instantiated even if they behave in the same way. To be fully instantiated, stem cells must keep their capacities so that regeneration is possible. In multicellular organisms, and at least in the case of MSCs, this requires that the property is masked by the niche. Therefore, I conclude, that stemness in MSCs is an extrinsically SMD.

7 Conclusions

The discussion so far has shown that: (1) quiescence is the key state to understand the dispositional character of stemness, due to the difficulties presented by the ontological deadlock; (2) the analysis of quiescence in MSC suggests that stemness is an extrinsic property of stem cells insofar as the cell is the bearer but relational properties between the cell and the niche play a role in the *Cinst* of the property; (3) the extrinsicness derives from the role of the niche as a masker of stemness. Interestingly, the combination of (2) and (3) suggests that stemness is an extrinsically structurally masked disposition (SMD), i.e., a disposition whose instantiation requires, as a condition of possibility, the interaction between a masker and a bearer (Suárez, unpublished manuscript). This observation opens up the possibility of rethinking the role of maskers more generally in understanding the metaphysics of some dispositional properties, particularly in the case of the life sciences. I take this to be an important lesson for the philosophical study of dispositions with important consequences that deserve further scrutiny.

On the other hand, this observation may also have important implications for the study of stemness, and I want to speculate upon them here. The first one concerns the role of quiescence to understand stemness; two further implications concern the thesis that at least some stem cells are extrinsically SMD; finally, a

fourth implication concerns the potential of the dispositional framework to think of stemness more broadly.

Firstly, the paper has shown that quiescence is a key state to understand stemness. If this is correct, then quiescence may turn out to be a fundamental state to gain any experimental control in the selection of candidate stem cells that transcends the methods that are currently available, with potentially important consequences for processes like stem cell transplant. This would happen insofar as quiescence can be tested without destroying the bearer of the property, and it can be tested across environments, allowing the discovery of cells that are pluripotent. If this were feasible for many stem cells, then this would make certain treatments to be much more directed, although of course empirical research is required to understand the real possibilities.

Secondly, if stemness is an extrinsically masked disposition of some cells (like MSC as studied in this paper) but not of other cells (like the pluripotent cells studied by Fagan, or some of the different property-types of stem cells studied by Laplane), then it would seem that this adds to the known complexity of stemness and suggests that a new type of stem cell must be added to our current picture. Note, however, that this new category comes with the promise of a new method for intervening in at least a subtype of stem cells: those stem cells that are extrinsically SMD can be experimentally controlled by intervening on the maskers provided by the niche. This is important because it opens up the possibility for new medical treatments for treating diseases with stemness cells, or treating diseases that are primarily caused by stem cells, such as cancer.

Thirdly, if stemness is an extrinsically SMD of some cells, then this raises important questions about the evolution of stemness. It may happen that the evolution of stemness in these cells has to do with the evolution of the niche, or a specific niche-cell relationship in which the niche somehow blocked the reproduction of the cell. In doing so, the evolution of stemness would have been to a certain extent directed by the niche, and thus its study would require study how the niche acquired the capacity to block cell reproduction in the first place. Note that this contrasts sharply with the study of stemness by studying specific genetic markers of stem cells, as in this later case the evolution of stemness would be assumed to be intrinsic. While the intrinsic alternative may be true for some stem cells, it must be noted, although in passing, that if the extrinsic alternative is correct, and it is correct in the sense I have suggested above *at least* for some cells in the body, then the evolution of stemness is much more connected to the evolution the capacity of the niche to interfere with cell reproduction. In this case, epigenetic factors may play a more prominent role in the evolution of stemness, which opens interesting avenues for the study of the evolution of stem cells.

Finally, the dispositional analysis I offered and the consequences I drew about stemness could be further applied to the analysis of other stem cells in the body, illuminating further ways in which philosophy can nourish science. For instance, in the schema I put forward, I have distinguished between three different types of conditions that determine whether a cell manifests its stemness: *Cinst*, stimulus and sustaining conditions (the later parts of *Cman*). The alternative of intervening on maskers is an alternative for intervening on *Cinst* to control stemness. But note that the

schema also entails that interventions on different aspects of *Cman* must possibly allow a certain experimental control over stemness. It may be interesting to explore how exactly this allows understanding interventions and allowing new interventions that have not yet been fully envisioned. Doing so, however, is outside the scope of this paper and I will leave it for future exploration.

Acknowledgements I thank all members of the BioDispositions project (Marie Kaiser, María Ferreira, Fabian Hundertmark) for helpful comments and discussions on the topic of this paper. Also, I thank Lucie Laplane, Adrian Stencil and Sophie Veigl for having read and discussed different versions of this paper with me. Finally, I thank two reviewers from EJPS for helpful comments on the manuscript that helped to clarify its content. The Narodowe Centrum Nauki (Grant Opus No: 2019/35/B/HS1/01998) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) in the project “Complex Biological Dispositions: A Case Study in the Metaphysics of Biological Practice” (288923097) as part of the research group “Inductive Metaphysics” (FOR 2495) are formally acknowledged for funding. The first draft of this paper was written as part of my postdoc in Bielefeld, and further versions were developed at Jagiellonian University and University of Oviedo.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature.

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