



What is the nature of stem cells? A unified dispositional framework

Javier Suárez^{1,2,3} 

Received: 19 October 2022 / Accepted: 8 September 2023 / Published online: 29 September 2023
© The Author(s) 2023

Abstract

This paper presents an account of the nature of stem cells based on the philosophical concept of disposition. It is argued that stem cells can be conceived as dispositional objects, and adopting this attitude allows overcoming some of the controversies surrounding the nature of stemness (most notably, the state vs. entity debate) because it offers a framework that accommodates the lessons from different theories. Additionally, the account is simultaneously useful for interpreting stem cell experiments and guiding potential interventions. The account shows how different levels, both molecular and emergent network-level, play the primary causal role in explaining some empirical results, and hence they suggest that the explanations can be mechanistic or topological, respectively. The realization that any of these levels may play a more prominent causal role than another allows suggesting interventions at the genetic, molecular and population levels.

Keywords Biological dispositions · Stem cells · Stemness · Philosophy in science · Inductive metaphysics

Introduction

The nature of stem cells is a widely debated topic in contemporary biology (Loeffler and Roeder 2002; Zipori 2004, 2009; Nombela-Arrieta et al. 2011; Martello and Smith 2014; De Rooij 2017) and philosophy of stem cell biology (Fagan 2013; Laplane 2016; Laplane and Solary 2019). Particularly, stem cell biologists want to know what stem cells ultimately *are*, as they work under the impression that having a good characterization of their nature would allow them to carry out better

✉ Javier Suárez
Javier.suarez@uniovi.es

¹ Department of Philosophy, University of Oviedo, Oviedo, Spain

² Institute of the Philosophy of the Natural Sciences, Jagiellonian University, Krakow, Poland

³ Department of Philosophy, Bielefeld University, Bielefeld, Germany

experiments, and use them more widely in other endeavours, especially in treatments of several diseases, for transplants, or in their desire to slow down processes like aging (Mirzaei et al. 2017). So far, the most we know is that standard textbook definitions characterize stem cells as undifferentiated cells that *can* divide asymmetrically, resulting in a self-renewing and a specialized lineages (Lanza and Atala 2014; Slack 2018; cf. Lander 2009). The self-renewing lineage would generate a new stem cell, and the specialized lineages would produce a tissue cell (e.g., epithelial, blood cell, neuron, etc.) Thus, the driving idea for asking a question about the nature of stem cells is that a better knowledge of this question will allow to gain better manipulation capacities over them, following the famous Baconian dictum that *knowledge is power*.¹

So far, despite the general agreement that stem cells are cells that can divide asymmetrically, the debate about the nature of stem cells is not solved at all. In fact, the specialized literature shows a plurality of different conceptions, most of them not necessarily consistent with one another as I will show below (see [Other approaches to the nature of stemness and their limitations](#)). Particularly, the plurality of views about stem cells that is present in the literature makes one wonder whether it is possible to provide a unified stem cell concept. To be satisfactory, such a concept should accommodate all our current knowledge about stem cells and simultaneously serve stem cell biologists as a guide to conduct their research.

While plurality of concepts and definitional vagueness can sometimes be a virtue in fostering research, they may also be problematic in some circumstances (Strunz 2012). In the case of stem cell research, these problems manifest in at least three aspects: one “pedagogical”, and two epistemic. Firstly, as convincingly argued by Fagan (2021: 10), this plurality generates an important problem for beginners who aim to introduce themselves into stem cell research. The difficulty increases given that stem cell research is basically experimentally-driven (Fagan 2013; Suárez 2023), which requires that one familiarizes with several technologies, methodologies, research standards, concepts, and even some (research) group idiosyncrasies, many of which are constantly changing. Sometimes, some stem cell conceptions reflect some of these idiosyncrasies (see [Other Approaches to the Nature of Stemness and Their Limitations](#)). A unified stem cell concept that could be useful to think across all these different conceptions may help novel researchers to orientate themselves more easily than doing so solely on the basis of experimental training.

Secondly, while the existence of a plurality of conceptions of stem cells has been and still is important for the development of stem cell research, it generates a problem regarding which biological features are relevant and need to be investigated in stem cell research. This is because each of the conceptions puts emphasis on different types of characteristics, and in doing so they highlight some specific causes

¹ Across the paper, I will use the notion of “manipulation” and “intervention” to mean any type of experimental procedure (including simulations) that allows altering the manifestation of stemness via altering some aspects of the property. These aspects can be altered at the molecular and network levels). While the notion has some resemblance with Woodward’s (2003) use of intervention in his account of causation, it differs in that network-level interventions cannot be considered causal, even though they are counterfactual (Moreno and Suárez 2020; Deulofeu et al. 2021; Díez & Suárez 2023).

as *the relevant ones* to investigate stemness. The problem is that this automatically precludes the investigation of any other type of causes that may also be important, but that have been highlighted only by a competing conception of the nature of stem cells. It would seem as if adopting a specific conception of stem cells would unconsciously drive researchers to narrow down the conceptual and empirical space of possibilities, holding them back (Lander 2009). While this is positive insofar as it can help in focusing research, it is at the same time problematic, since it may close certain potential avenues of research that may be as rich as the ones opened by the specific conception of stem cells that a research group may be using. This is something that stem cell researchers even consider nowadays as an important task. For instance, in a recent Comment in *Nature*, Sipp et al. (2018) argue that a clear concept of stem cell may help in “clearing up” what they call “the stem cell mess.” By the latter, they refer to the problem that a lot of research still refers to so-called *mesenchymal stem cells* as *stem cells*. They claim that part of the problem stands from the fact that researchers working with mesenchymal stem cells “fail to observe the rigorous definition of stem cell” (Sipp et al. 2018: 456). This, therefore, creates an important tension between different and competing conceptions about the nature of stem cells, which instead of favouring investigating more hypotheses, may end up narrowing them down, with the consequent problems this imposes on scientific development (Chang 2012). Therefore a concept that unifies all practices and allows coordinating them should be preferable as it should foster the practical investigation of more possibilities.

Thirdly, there is an important problem regarding the integration of the results. The existence of different conceptions of stem cells, each pointing to different and even incompatible characteristics makes it hard to integrate the knowledge derived from different stem cell practices. This difficulty is for instance presented by Fagan (2016), who highlights how different stem cell communities clash with one another because they do not share the same explanatory practices. While Fagan’s (2016) point is mostly epistemic, I think similar limitations exists when a community does not share the same conception about the nature of stem cells. For example, if one community suspects that stem cells are stem cells as a result of their genetic activation, the results derived from a research group pointing out the importance of stem cell population structure may be ignored, or simply reinterpreted in terms of genetic activation. But, as Mitchell (2003) has convincingly argued, the sciences of complexity frequently do better when knowledge from different families of models are integrated with one another, as the picture of the phenomenon that they provide is more complete.² I think part of the necessity of a unified framework for stem cells derives precisely from the real dangers of failing to integrate evidence about stem

² There are of course several nuances to this integration, including whether integration is always preferable or even always feasible (Deulofeu & Suárez 2023). Note however that the point here concerns the perils of explicitly ignoring specific pieces of scientific evidence (a component of integration), or interpreting them in ways that fail to properly account for it, which I think is something extremely problematic.

cells whose integration would provide a better picture of what stem cells are, and how they can be experimentally manipulated.

This paper alleviates these tensions by relying on the tools provided by philosophical theorizing. Particularly, I follow the recent way of doing philosophy of biology called “metaphysics in biology,” a branch of metaphysics of biology (Guay and Pradeu 2017) which consists in analysing scientific practices (phenomena or theories) to uncover the metaphysical assumptions and commitments underlying them (Triviño 2022; for some previous applications, see Reydon 2008; Waters 2017; Triviño and Suárez 2020; Suárez and Stencel 2020).³ Drawing on this method, I offer a dispositional view of stemness and stem cells. This view has the advantage that it accommodates the most salient empirical observations guiding different definitions, while not privileging any of them. In doing this, this conception can be used as a general concept to think of stem cell research and stem cell experiments, in a way that allows both partially guiding research, and explaining empirical results. This last consequence matches well with the recent method of philosophy *in science*, consisting in using philosophy to contribute to the development of scientific hypotheses (see Laplane et al. 2019; Pradeu et al. 2022). So, in a sense, my approach combines insights from both methods.

An important outcome of the account is that both potential molecular-level interventions, and network-level (both at the cell or population levels) interventions of the system can be accounted for and accommodated under a single unified framework.⁴ Importantly, my interest is not determining how any of the possibilities I illustrate in the framework apply to empirical cases, which I leave open to empirical applications, but rather to conceptually clarify the metaphysical reasons why some practices in stem cell research provide significant results. So I base my account on the analysis of previous practices in stem cell research. To do so, I first critically discuss previous approaches to the nature of stem cells ([Other approaches to the nature of stemness and their limitations](#)). Second, I introduce my dispositionalist account, and I illustrate its usefulness by relying on two examples ([Stem cells as dispositional objects](#)). Later, I discuss the advantages of the account I have presented, how it solves the main issues derived from the existence of a plurality of conceptions of stem cells, and why it generally illustrates the convenience of conceiving some biological properties as dispositions ([Discussion](#)). Finally, I present my conclusions.

³ For the specific case of stem cell biology, I restrict myself to experimental-practices, for the reasons presented above.

⁴ In what follows, I will use “molecular level” or “network level” to refer to the level at which the causal processes must be controlled to manipulate stemness, and “mechanistic” and “topological” to refer to the type of explanation or manipulation that is preferable at each of these levels. Also, I will assume that the network level is emergent.

Other approaches to the nature of stemness and their limitations

The debate about the nature of stemness became especially agitated due to the so called state vs. entity controversy that flourished among stem cell biologists in the early 2000s. The controversy was mostly focused on whether *being a stem cell* was a property that could be attributed to some stem cells solely in virtue of certain genes that they selectively expressed (entity view) or, rather, it was more adequate to conceive stem cells as a transient state that some cells could enter in certain moments throughout the ontogeny of a multicellular organism via expressing multiple different genes (state view) (Loeffler and Roeder 2002; Zipori 2004, 2009; Leychkis et al. 2009). To put it differently, the question was whether a cell *is* a stem cell (entity) or rather it *becomes* a stem cell (state). If the former hypothesis were true, then one could easily isolate a specific cell population and tell apart stem from non-stem cells. In contrast, if the later were true, then it would be impossible to distinguish between them without also looking at the niche and the ontogeny of the organism, as the niche is taken as part of what determines the identity of stemness.⁵

While it may be thought that the difference is purely a philosophical matter with no empirical consequences, the idea could not be more misguided. These consequences concern especially where stem cell biologists would look for to gain better manipulation capacity over stem cells. For example, if stem cells were entities, then stem cell niches would be of relatively low relevance in determining whether a cell is or is not a stem cell. On the contrary, if stemness were a state that a cell (potentially any cell) can enter depending on the context, then the contrary would be the case (Lander 2009; Lechkis et al. 2009; Laplane 2016). Thus, one view encourages scientists to investigate genetic markers within the cell (see e.g. studies on the molecular pathways involved in stemness activation), whereas the other encourages them to look for molecular cues within the niche (see e.g., studies on the role of the niche for stemness activation). Secondly, if stemness were an entity, then the genetics of the cell becomes the first point to investigate to uncover the source of stem cell capacity, whereas if it were a state, one should always investigate the organismal level, as the organism may induce some non-stem cells to become stem cells (e.g., this seems to be common in some invertebrates, see Rinkevich et al. 2021).

These two positions are presented in plain opposition, as a dichotomous choice between incompatible alternatives that researchers must choose in carrying out their work. The choice of the terminology (state, entity) and the way of presenting the contrasting evidence, I must reckon, are not of help to avoid perceiving these positions as contradictory options. However, the two positions can also be interpreted as illustrating the possibility that, for specific subpopulations or tissues, stem cells may express their stemness differently and, therefore, may be manipulated by applying different procedures. To put it differently, the entity view predicts that, in many

⁵ A reviewer correctly points out that the entity/state debate was hot in the early 2000s but the interest in it declined after Lander (2009). But note that, as the citation from Sipp et al. (2018) that I included in the Introduction shows, stem cell researchers today still care about finding a correct definition of *stemness*. Precisely, the entity/state debate was an initial stage in the development of such definition.

cases, genetic markers and their expression matter and must be known if we aim to have some power to experimentally manipulate stem cells; on the other hand, the state view predicts that focusing exclusively on the genetic markers may block scientific progress, as in some cases the niche has a primary role in determining which cell becomes a stem cell and thus the niche should be our main research focus to create stem cell-based therapies. While it may seem that this debate was settled in the early 2000s, when the search for a set of shared genes that were expressed only by stem cells turned out to be a failure (Li and Akashi 2003; for a review, see Vorotelyak et al. 2020), the issue is not exactly the case, for part of stem cell research continued implicitly relying on one view or the other. Particularly, a strand of stem cell research concentrates primarily on finding the genes accounting for stemness in a specific tissue, organ or body site, while another requires to investigate properties of the stem cell and its niche. Therefore, even if the entity vs. state debate (conceived as a strong dichotomy that explicitly divided stem cell researchers and was an issue of constant debate in the main journals) has not been strongly present in the literature for the last decade or so (but see Sipp et al. 2018, for an exception), the literature partially reflects some implicit assumptions deriving from the ontological assumptions that originally manifested in it.

Partly building on these debates, philosophers of biology have recently substantially contributed to the development of the concept of stemness. There are two main approaches: Fagan's (2013, 2017, 2021) model-theoretic approach, and Laplane's (2016; Laplane and Solary 2019) ontological or four-fold account. Fagan's approach abstracts away from the entity/state debate as a good way to ground a general discussion about stemness. She argues that, since deciding whether a cell is a stem cell cannot be done at once and for certain, it would be better to see the stem cell concept as a platform to think of any potential stem cell experiment. Under these lens, stem cells are not cells with any specific type of property, or with any specific pattern of gene expression. Rather, stem cells are simply those cells derived from an organism of a concrete species that serve as the starting point of a reproductive lineage and a developmental lineage (i.e., a lineage producing specialized cells for their organismal species). Laplane, on the contrary, thinks that an ontological approach is correct, but she convincingly argues that stem cells do not have *only one* nature (i.e., they shouldn't be conceived monistically, as an "either/or" concept), but rather the nature of stem cells depend on the properties they instantiate. Concretely, in Laplane's account, stemness can be a categorical, a dispositional, a relational or a systemic property, and which property one specific stem cell really instantiates will depend on the particular ways in which the cell behaves. The account is illustrated with examples showing how the type of property that a specific population of stem cells instantiates constrains any possible therapeutic interventions. This is definitely an advantageous point for the defender of the four-fold account.

All these views about stem cells have their own weaknesses, though. For example, a defender of the state view may discourage doing research on the genetic markers related to stemness, as she will deem them as irrelevant. Yet, stem cell research may have proven that not all stem cells share exactly the same, or any similar, genetic markers, but it has also proven that, in some cases, knowing the genetic markers is enough to manipulate stem cells. On the other hand, a defender of the entity view

would discourage studying the niche as a prime source of stemness and a primary point for therapeutically manipulating stem cells. However, this view is also at odds with the observation that in some circumstances the niche is actually the key component determining stem cell expression, sometimes leading some to defend that the niche is actually in control on stemness (niche hypothesis; see Lander et al. 2012; Martínez et al. 2022). Therefore, adopting exclusively the state view would entail the loss of potential therapeutic interventions.

The defender of the model-theoretic account seems a priori the best equipped, as the framework is in principle open to account for every possible intervention and thus seems to allow every kind of experiment (Fagan 2013, 2021). However, the account is somehow unconstrained and, hence, it seems not to have many direct empirical implications for the stem cell researchers—with the exception of the emphasis Fagan puts on the possibility that stemness may sometimes result from jointness (see [Comparative analysis of the cases: towards a unified framework of stemness](#)). To put it differently, it may be useful for scientists to know what exactly being the starting point of a stem cell lineage experimentally entails, and the kind of empirical opportunities that this opens up. But the defender of the model-theoretic account does not offer any recipe, because that would always be open to how scientists carry out their experiments. This is a limitation that Fagan (2021: 25) explicitly acknowledges in her more recent work, where she states that “[t]he philosophical model [I] proposed (...) is for philosophers (and other nonexperts), not for stem cell scientists. It connects to the latter’s practices *indirectly*, by further explicating the definitions offered to outsiders in terms of the cell-organism relation and lineage structures generated via stem cells’ essential abilities.” I do not think this is problematic regarding Fagan’s purpose of making stem cell research intelligible for non-experts. However, I think it is problematic if one aims to elucidate the nature of stem cells in a way that can ultimately contribute to stem cell research. This is precisely why I think her approach is limited to answer the question I am focusing on here.

Finally, adopting a pluralist view which conceives stemness as four properties, rather than one, has the advantage that it incorporates the knowledge and takes the lesson from all other approaches, and it doing so it encourages doing research both on the genetic and molecular markers, both from the cells and from their niche (Laplane 2016). Paradoxically, though, the account is problematic because it lacks enough flexibility to accommodate two possibilities.

Firstly, because the account entails that there is no stemness as a unique property, but different types of stemness, it encourages studying exclusively certain markers in relation to the type of property that a stem cell in a specific tissue is. For example, imagine that stemness in muscle cells is a categorical property, in the sense defined by the four-fold account. Then, biologists should investigate genetic markers, and ignore cues from the niche, as these would not be relevant to obtain any possible manipulation on stem cells. However, this is not necessarily the case, as in many cases stemness results from the combination of different signals, and even if genetic markers may play a primary role in stemness expression in cases where stemness is a categorical property, it does not follow that intervening on other aspects does not generate a manipulation capacity on stem cells. Different aspects may interact, in

some circumstances in non-linear ways, and it seems that studying more potential influences seems heuristically wiser than studying less.

Secondly, the account is not flexible enough to accommodate the possibility that a stem cell in a specific tissue changes the type of property it instantiates over time (Copley and Eaves 2013; Hsu et al. 2014). To express the point differently, imagine that the genetic markers of the cell are the primary factor determining stem cell expression during a specific time of the ontogeny of a multicellular organism. At this point, the niche plays no substantial role in stemness expression thus interventions should target the patterns of genetic expression, a prediction correctly made by the four-fold account. However, if after a while the conditions of expression change and the niche acquires a more prominent role in the expression of stemness, then it would seem that the niche should be a primary target for intervention. The four-fold account should say that stemness has shifted from a categorical to a dispositional or relational property. However, this is problematic, for it is hard to see how a cell can shift from instantiating one of these properties to instantiating another. This is so for biological (not for ontological) reasons: stemness is both an evolved feature (i.e., a result of evolution) and a developmental product (i.e., a result of the organism's ontogeny). So both evolution and development will fix whether the stemness of a cell type will depend on the niche or on genetic markers. A change in which of these factors determines the type of property that a stem cell instantiates would require going backwards both in developmental and in evolutionary timescales. But this seems unpalatable, as this type of drastic changes would tend to destroy the organism. Additionally, even if this were possible, it would seem as if during a period of shiftiness, both the genetic markers and the niche would have to co-determine stemness. In these cases, stem cells would be simultaneously a categorical and a dispositional or relational property, according to the four-fold account. I think this is problematic, and it is not the most plausible biological explanation given that it would seem biologically unstable. Nonetheless, a defender of the four-fold account could still argue that this would not be problematic if the account were interpreted pragmatically.⁶ This is correct, but then the account would lose one of its main appeals, which is its normative capacity (i.e., telling stem cell biologists how to investigate stemness), and hence it would be throwing the baby with the bathwater.

Finally, a virtue (but, simultaneously a non-solved issue) of the four-fold account is that it includes the possibility that stemness is a systemic property, i.e., a property that some cells in an organism would acquire simply because of organismal properties. Based on this, the four-fold account suggests that the only possibility for controlling stemness when this is a systemic property would be by intervening on the organism. But it does not specify how to do so.

In the next section, I introduce a dispositional account to stemness that I contend can deal with the problem of the nature of stem cells better than any of the other alternatives I have reviewed so far.

⁶ Thanks to a reviewer for pointing out this possibility.

Stem cells as dispositional objects

The concept of *disposition* is frequently used in the philosophical literature to refer to properties with a functional-causal profile (Mumford 1998; Choi and Fara 2018). That is, a disposition is a property such that it makes an object (called *bearer*) to produce a specific effect (called *manifestation*) usually given a specific cause or set of causes (the *stimulus* or *trigger*)⁷ impinges on it and lasts enough time (Hüttemann and Kaiser 2013). For example, arachnophobia is a disposition that causes some individuals (bearer) to get scared (manifestation) when they perceive a non-dangerous spider (stimulus). And radioactivity is the disposition of some chemical elements (bearer) to decay (manifestation).

Many biological properties are dispositional, too (Nuño de la Rosa 2016; Triviño and Nuño de la Rosa 2016; Hüttemann and Kaiser 2018; Austin and Nuño de la Rosa 2021). For example, plasticity is the property of an organism (bearer) to adapt its phenotype (manifestation) to specific and diverse environments (stimuli) (Nicolglou 2015). Evolvability is the capacity of a biological system (bearer) to evolve (manifestation) (Love 2003; Brigandt et al. 2023). Fitness is the ability of organisms (bearer) to survive and reproduce (manifestation) in their environments (stimuli) (Triviño and Nuño de la Rosa 2016). And foldability is the capacity of the primary sequence of a protein (bearer) to fold into its tertiary structure (manifestation) (Hüttemann and Love 2011).

My purpose here is to use the philosophical knowledge about dispositions to propose a novel conception of stem cells which helps shedding light on some empirical investigations. To do so, I start by introducing some basic theoretical components for thinking about dispositions in general. These components go beyond the three elements introduced above and isolate certain aspects of dispositions that are usually recognised in scientific practices that appeal to dispositions. I refer to these theoretical components as the “schema” of the disposition.⁸

[Bearer of the disposition] Who has the disposition

[Conditions of instantiation—Cinst] How the bearer or its environment need to be for the former to have the disposition. Cinst can be intrinsic or extrinsic

[Manifestation] What the outcome or effect of the disposition is, including both a deterministic and a probabilistic outcome

[Stimulus] What is the cause (single-track) or set of causes (multi-track) that need to impinge on the bearer so that it produces the manifestation

⁷ I say “usually” because there are dispositions that manifest spontaneously.

⁸ This schema has already been used in Suárez (2023), and I follow the same schema here. In addition, I partially clarify some components of the schema relying on Brigandt et al.’s (2023, Box 1), “philosophical vocabulary of a disposition”, which supposes an extremely useful metaphysical toolbox to complete the ontological schema I use here.

[Causal process leading to the manifestation, Cproc]⁹ What are the causal steps that occur after the stimulus and until the manifestation is produced

These components provide the nature of a disposition, i.e., they provide the basic structure of the questions that researchers would ask and investigate when they aim to know how and why a specific object can be said to instantiate a concrete disposition.¹⁰

Additionally, the components in the schema can be conceived as the components that need to be studied and/or experimentally manipulated to test any possible intervention with an object bearing a specific disposition so that the object does not manifest the disposition. Philosophers distinguish two main types of alterations preventing the manifestation of the disposition (Choi and Fara 2018):

a) Finks: causal processes interfering with the Cinst of the disposition, such that they alter the bearer and cause it to have the disposition / remove the disposition from it. For example, someone with arachnophobia may undergo a therapy that allows her to avoid feeling fear when she sees a spider. In this case, the Cinst of arachnophobia have been altered, and the fear is not triggered anymore.

b) Maskers: causal processes interfering with the Cproc of the disposition, such that they impede the manifestation to occur even if the bearer still bears the disposition and the stimulus has occurred. For instance, the same person with arachnophobia may live with someone who deals with the spiders as soon as she is alerted that there is one. In this case, the arachnophobe still perceives the spider (stimuli), but the Cproc leading to panic is deactivated due to a very protective flat mate.

To which I would add another:

c) Stimuli Repressors: causal process interfering with the stimuli and avoiding its occurrence. Note that this requires that these repressors are distinguished from a specific step in Cproc, or a concrete part of Cinst, as well as the fact that the disposition is triggered by a stimulus (i.e., it is not a spontaneously manifesting disposition like e.g., radioactivity). For example, to continue with the case of arachnophobia, a stimuli repressor could consist in eliminating the possibility of encountering spiders (e.g., via a fumigation of the house).

The schema I just presented can be applied to think about stemness and about the nature of stem cells. Generally speaking, the schema would look as follows:

[Bearer of the disposition] Cell in the body of a multicellular organism

⁹ Cproc shouldn't be conflated with the so-called *causal basis* of a disposition, which is a concept I prefer not to use here as it normally includes two conceptually different roles: one pertaining to what I have called the Cinst and the other to what I have called the Cproc (or some components of the Cproc). For a thoughtful discussion of the concept of causal basis, see Ferreira & Hundertmark (forthcoming).

¹⁰ Note that the schema presented here is not primarily normative, but descriptive. That is, it is a schema abstracted away after having investigated the ways in which scientists think about dispositional properties. However, once the schema is formulated and used to shed light on new cases, it may also incidentally lead to the suggestion of new experimental procedures that may shed light on the properties themselves.

[Conditions of instantiation—Cinst]	Genetic markers of the cell involved in cell reproduction; potentially, some environmental components from the niche [Genetic X Niche interactions]; population-level properties at the tissue level
[Manifestation]	Asymmetric division generating a self-renewing lineage and a specialized lineage
[Stimulus]	Cues from the niche or cues from any other part of the organism
[Causal process leading to the manifestation, Cproc]	Molecular pathways sustaining cell reproduction, both from the cell and potentially from the niche (if any)

According to the schema, stem cells would be cells characterized by instantiating a causal functional property (stemness) that, if adequately stimulated, and the causal process correctly maintained over time, leads to an asymmetrical division generating a specialized lineage and a self-renewing one (manifestation). The description of the manifestation is the common way of characterizing stem cells in the literature, in terms of the specific type of lineages they give rise to, as well as their role in the development of the organisms they belong to (Fagan 2017). The reason for the way in which Cinst are Cproc are defined is ontological, particularly when it comes to the role of the genetic markers of the cell involved in cell reproduction vs the molecular pathways sustaining cell reproduction. Namely: genetic markers can be studied before the cell enters the reproductive cycle, whereas the molecular markers sustaining cell reproduction cannot. The paradox of studying markers once the cell has entered the reproductive stage is that the bearer of the property does not exist anymore, since cell reproduction is a process of generating two daughter cells *from the original mother cell*. Therefore, they cannot be part of Cinst as there is no bearer of the property anymore (see Suárez 2023, for an elaborated argument).

Potential ways of intervening with these cells (thus, potential experiments, both theoretical and empirical, and potential treatment interventions) would include: (a) altering the Cinst by finking the stemness of the cell; (b) intervening on the Cproc by masking the cell's stemness; (c) repressing some of the stimuli affecting the cell. While the notions of masking, finking and stimuli repression seem a priori highly abstract, they have important consequences for thinking about stem cell experiments.

Particularly, following the schema of dispositions I offered above, the dispositional nature of stem cells predicts that they can be altered: (a) by intervening on the "Genetic X Niche" interactions or population-level properties (in the case of finking); (b) by intervening directly on the process of cell reproduction which leads to the asymmetric division pattern (in the case of masking); or (c) via interfering with the stimulus (in cases where stemness is not spontaneously manifesting and stimuli repression is feasible). These three possibilities are open to biologists and could be tried with every stem cell or stem cell population so that their stemness can be manipulated to a certain extent. Finking would require: (1) altering some specific genes or blocking out some instances of gene expression by empirically affecting the genetic basis of potential stem cells; (2) altering some higher-level cell-environment interactions, such as altering certain population-level properties of the cell. If either of these, or a combination of both, is feasible, then it is feasible to fink a stem cell so that its behavior (i.e., when it reproduces, when it does not) can be subject to experimental manipulation. Masking, on the other hand, can be attained by altering any of the causal steps during cell reproduction, so that a cell, *even if it is a*

stem cell, does not reproduce and, hence, does not reproduce as a stem cell either. Finally, repressions of the stimulus would require specific interventions that either impede or transform the stimulus into something that does not trigger the disposition anymore.¹¹

In what follows, I evaluate how the dispositional account of stem cells I have introduced would empirically work and how it would be useful to think scientific practice. This will prove both its usefulness and its empirical adequacy. I will specifically focus on two case studies which show the relative independence of the masking vs the fining processes, and how they could be manipulated independently of one another. Additionally, the cases show how intervention can be based on genetic, molecular or population-level features, and how these may directly concern the stem cell, its niche, or the population. Note, however, that the cases have been chosen because they serve as good paradigmatic models to illustrate the dispositional account. But, of course, as it happens with most biological properties, stemness is an extremely complex property that depends on many factors. Therefore, it is expected that most cases will not be as neat as these two because stemness will depend on a combination of factors.

Molecular properties induce stemness: a case of masking

Eliazer et al (2019) provide a good example where stemness can be manipulated by masking the disposition in a way that alters the first causal step in Cproc. In other words, it constitutes a good example of how masking allows gaining manipulation capacity over stem cells.¹²

The following schema illustrates well how muscle stem cells (MSCs) dispositionally behave according to the experiments carried out by Eliazer et al (2019), and also where, and how, one could potentially intervene to manipulate the expression of stemness in MSC. Note that the fact that these possibilities are theoretically open does not entail that they are necessarily empirically open too. Sometimes, it may be easier to manipulate some aspects than others, or some aspects that should be open to empirical manipulation according to the theoretical predictions are not really open to it.

[Bearer of the disposition] MSC in the niche

[Conditions of instantiation—Cinst] Genetic markers of the cell (YAP transcript, *MyoD*)

[Manifestation] Asymmetric division generating a self-renewing lineage and a specialized lineage

¹¹ For the case of stem cells, it is likely to think that the evolution of multicellularity has blocked previous stimuli that triggered the asymmetric division of cells and in doing so it has avoided the possibility of intra-organismic conflict (Rinkevich et al. 2021). Yet, this is not so for every stimulus, and it is worth investigating which are the ones that currently trigger the manifestation of stemness to think of potential interventions.

¹² While this example has been previously analysed in Suárez (2023), the case was used there with a different purpose (showing how the study of stem cells could illuminate our knowledge about dispositions), and thus the example was studied quite differently.

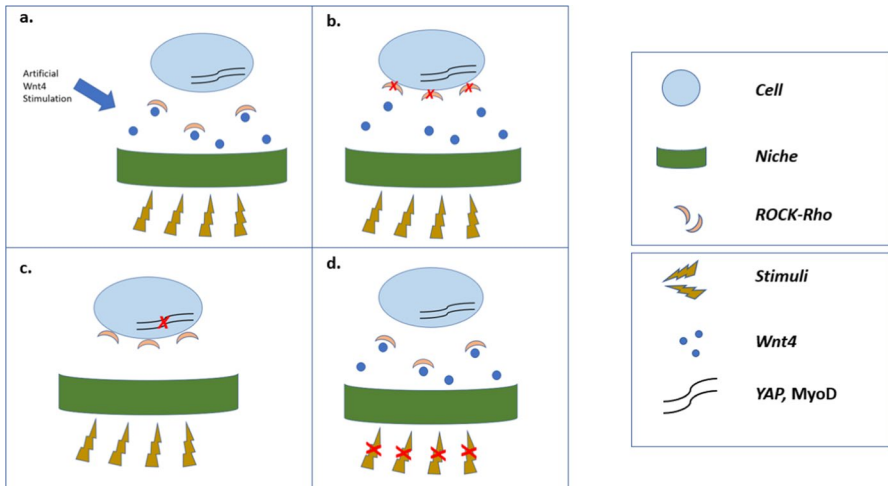


Fig. 1 Range of potential interventions. **a** Artificial stimulation of Wnt4; **b** Deactivation of the ROCK-Rho axis; **c** Repression of YAP or *MyoD*; **d** Repression of the stimulus. Note that the figure is an idealization and a combination of two or more practices is always feasible, as well as the possibility that even if one tried one intervention, backup mechanisms could avoid getting the expected result, in which case stemness would be an emergent phenomenon

[Stimulus] BaCl₂ injury

[Causal process leading to the manifestation, Cproc] Wnt4 repression, ROCK-Rho axis deactivation, YAP expression, *MyoD* expression

Experimentally, Eliazer et al. started looking at MSC activation in mice. The process begins after a BaCl₂ injury. When this occurs, the stem cell niche stops producing Wnt4, whose density in the niche decreases drastically. The descent is followed by a deactivation of the Rho-ROCK niche-cell axis, which is followed by an activation of the YAP transcript and an increased *MyoD* expression within the residing stem cells. This decreases their intracellular tension and the cell's circular shape, starting the division process that will lead to a self-renewal and differentiation cycle.

Based on this, it is now possible to determine the potential ranges of experimental manipulation that are feasible in this case (Fig. 1). In principle, it seems that the potential ranges of manipulation are primarily genetic and/or molecular, both from the cell and from the niche, and include:

- First, directly intervening on the Cinst of stemness in MSC and thus fining stemness. In this case, the intervention could be based on repressing the YAP transcript by silencing its genetic basis, or silencing *MyoD*. Another possibility would consist in creating an alternative causal route between the stimulus and Cinst. For example, modifying the cells genetically so that when the BaCl₂ injury occurs, *YAP* and/or *MyoD* are repressed, contrary to what would happen in normal circumstances.

- Second, intervening on the Cproc of stemness in MSC by masking stemness. In this case, the range of interventions is wider, and includes, in addition to the possibilities included above, the options of avoiding Wnt4 repression, or the deactivation of the ROCK-Rho axis. There are several ways of obtaining this. For instance, Wnt4 or any elements stimulating the ROCK-Rho axis may be artificially inoculated in the niche when the stimulus occurs. Alternatively, a combination of both is possible, and sometimes would be preferred to avoid any backup pathways causing stemness manifestation despite the stimulation of Wnt4 and/or the ROCK-Rho axis.
- Finally, there is a possibility of directly repressing the stimulus, so that the probability that the manifestation of stemness is triggered is very low. Evolution will have more probably done so for many lineages, so that stemness is only activated in very specific circumstances. Yet, it is open to scientific research to investigate other possibilities.

Eliazer et al.'s research constitutes a case of masking because they decided to intervene on Cproc by experimentally adding Wnt4 to the niche to block stem cell reproduction, once the BaCl₂ injury was produced. In this way, they stopped the Cproc and, in doing so, they experimentally manipulated the behavior of stem cells.

The dispositional schema I presented explains what Eliazer et al. did, and why they could manipulate stemness manifestation. But, additionally, it predicts other feasible interventions that they did not try, but would be open to empirical investigation.

Network-level properties induce stemness: a case of finking

Stumpf et al. (2017) is a good case where stemness could potentially be manipulated by finking the property via interfering with the Cinst at the cell and/or population-levels. To put it differently, it is a good example of how finking at the emergent network level may allow stemness manipulation.

The following schema illustrates well how neural stem cells (NSCs) dispositionally behave according to the study by Stumpf et al. (2017), and also where, and how, one could potentially intervene to manipulate the expression of stemness in NSC, as well as where one could not. Note that the fact that these possibilities are theoretically open does not entail that they are necessarily empirically open too. Sometimes, it may be easier to manipulate some aspects than others, or some aspects that should be open to empirical manipulation according to the theoretical predictions are not really open to it.

[Bearer of the disposition] NSC in the tissue

[Conditions of instantiation – Cinst] Tissue level, population-level in R1 and E14 strains

[Manifestation] Asymmetric division generating a self-renewing lineage and a specialized lineage

[Stimulus] Apparently spontaneous

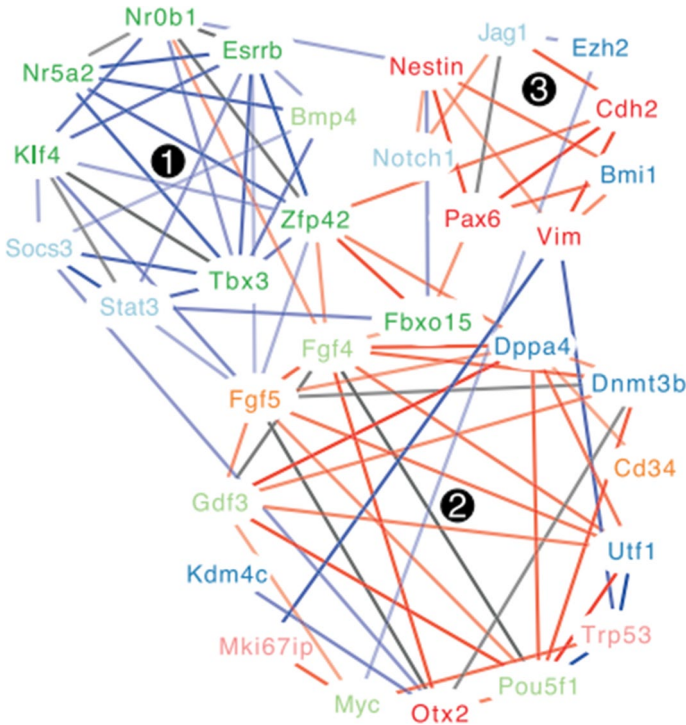


Fig. 2 Main regulatory gene modules showing changes in activity during the process of stem cell differentiation. From Stumpf et al. (2017): Fig. 2E

[Causal process leading to the manifestation, Cproc] Two cell lines with different genetic backgrounds (R1; E14)
 The causal process undergoes 3 stages: initial ESC, primed EPI, final NPC state
 Three gene regulatory gene modules (networks) showed significant changes in their activity over time, and over the three different states, indicating their primary roles in Cproc. Some genes within the modules may play specific roles
 The process takes the form of a non-Markovian stochastic process at the level of the observable microstate dynamics

Experimentally, Stumpf et al. looked at NSC activation in mice. To do so, they studied how two different cell strains (R1 and E14tg2a [E14, for short]) differentiate from the embryonic stem cell state (ESC), through the epiblast-like state (EPI) to the neural progenitor cell state (NPC). They observed that the existence of different genetic or epigenetic states in each of the strains (microstates) does not affect the expression dynamic observed (*from* ESC *to* EPI *to* NPC), which points towards the multiple molecular realizability of these very macrostates. This said, three main regulatory gene modules seem to play a prominent causal role in the process, as their activity substantially changes over time (Fig. 2). They observed that the process follows a non-Markovian dynamic at the level of the macrostates, and it does so regardless of the molecular nature of the microstates,

which they assume may differ across cells. Stumpf et al. take this to suggest that the process of differentiation is non-Markovian stochastic but canalized.

Based on this, it is now possible to determine the potential ranges of experimental manipulation that are feasible in this case, as well as those that seem excluded. Let us start to revise the experimental pathways that seem not to be open:

- First, intervening on the stimulus. For all the information that Stumpf et al. provide, NSC *seem to be* spontaneously manifesting. That is, whether one cell will divide in the way required by the stem cell manifestation description or not, seems not dependent on any specific cause triggering the cell to do so. Therefore, interfering with the stimulus to manipulate stemness expression seems unfeasible for this particular case study and according to the experimental results.
- Second, given the non-Markovian stochasticity shown by the system at the level of the macrostates, it seems unlikely that any intervention on current molecular markers or any markers during Cproc will allow stopping the manifestation of stemness. That is, the system is unmaskable for this particular case and according to the experimental results.

To see why, it is necessary to understand what non-Markovian stochasticity is. A system is said to exhibit Markovian stochasticity whenever its future states depend on its immediate past, but not on the history of the system. Or, to put it differently, its current state is sufficient to know its future state, and knowledge of its past states is irrelevant. For example, the waiting time on a queue at a time t shows Markovian stochasticity, because it does not depend on how much time the customer has been waiting before t , but rather on the waiting time of the person before her plus the time that this very person will need. In contrast, a system exhibits non-Markovian stochasticity when it is said to have “memory”, because its future states do not only depend on its current state, but also on the history of the system. For instance, the transport of ions across the ion channels in cell membranes arguably exhibits non-Markovian stochasticity. Whether an ion trespasses or does not trespass the membrane does not depend on its current state, but rather on the ion concentration within the cell due to its past history of action of the ion channels (Fuliński et al. 1998).

The point concerning unmaskability relates precisely to the non-Markovian nature of the process of cell differentiation. As NSC differentiation exhibits “memory”, then whether a cell in the stem cell niche will manifest stemness or not does not directly depend on its current state, but rather on what the system has done in the past. This will indefectibly lead to the fact that some cells will manifest stemness and others will not, and a change in the current state of the system will at most change *which* cells will manifest stemness, but not the fact that *some* will do. Recall that a masker is a molecular component that is introduced in a system to avoid the manifestation of one dispositional property given the stimulus may occur at some point t leading to a specific state at t' in which the disposition will manifest. A system showing non-Markovian stochasticity, however, lacks by definition this state t , as the whole history of the system is

determining who will manifest the property, and when. Therefore, masking a non-Markovian system is simply empirically unfeasible.

It follows from this that interventions on the molecular states are therefore unfeasible, and any possible intervention in the system may be based on something different. Concretely, given that the system exhibits a specific type of stochasticity that depends on system properties. This opens two possibilities:

- Repressing the stimulus at the population level. While the stimulus cannot be a molecular one for the reasons explained above, the situation at the population-level may be more complex. As a matter of fact, it may be the case that there is a stimulus acting at that level. For instance, a specific population density may represent a critical point that, once reached, starts the asymmetric division process. This is a possibility that Stumpf et al. did not consider but one that the dispositional schema not only allows, but suggests may be feasible.
- Acting on the Cinst of the disposition by directly intervening on the system dynamics. As the system dynamics in Stumpf et al. (2017) is a population-level phenomenon which depends on the cell population, then it is possible to devise a population-level line of intervention which would be attained by directly intervening on the Cinst of stemness in the neural tissue via fining stemness. In other words, it is necessary to alter the population-level properties of the system. These properties would mostly be topological properties, i.e., properties that induce a specific dynamic in the system and thus increase the probability of certain outcomes that would be unexpected did the system lack such topology (Moreno and Suárez 2020).

On this second point, topological properties and how they feature in scientific explanations has been a widely discussed topic in contemporary philosophy of science (Huneman 2010, 2018; Jones 2014; Brigandt et al. 2017; Deulofeu et al. 2021). Shortly, a topological explanation works because the empirical system under study realizes a specific mathematical structure and in doing so it exhibits a specific dynamic behaviour which is the same as the behaviour described by the mathematical structure. Ecosystems (Huneman 2010), the immune system (Jones 2014), or the microbiome (Deulofeu et al. 2021) constitute good examples of systems studied in contemporary biology realizing a topology (i.e., systems that instantiate topological properties) and whose characteristic behaviours are consequently explained topologically. For example, the resilience of some ecosystems is explained by appealing to the way in which the species interact with one another; the vulnerability of the human immunological systems to attacks on the CD4 T-cells is explained by its bowtie structure; and the stability behaviour of the microbiome is explained by appealing to the instantiation of its random network structure with a high-degree of competition between the species.

The way in which topological explanations work immediately suggest some ways of thinking of potential interventions on these systems. In the case of systems realizing a topological structure, interventions are systematically conceived in terms of the network or emergent properties of the system, as these would condition its dynamics and therefore the final outcomes (Wilson 2016; Huneman

2018; Suárez and Triviño 2020; Green 2021). Empirically intervening on these properties requires knowledge of the specific population or system properties that induce the dynamics, as well as how these could be modified to avoid the dynamics or its outcome. To rely on the examples of the ecosystems and the microbiome introduced above, in these systems the dynamics are usually changed by introducing “intruders” in the population, i.e., other species members with the capacity of changing the population structure. Applied to the case of stem cells, this would require introducing new cells or cell combinations in the stem cell population. Treatments here are thus not molecular (i.e., in the sense of affecting gene expression or introducing new molecular components) but rather, they require the introduction of full living cells or even combinations of cells (Tanoue et al. 2019, to see how sometimes a consortium is required, and how it acts differently than single cells). In other words, in these type of cases it is necessary to know how the topology is instantiated in the specific cellular system and how to transform it into a different type of topology where cell manifestation can indeed be manipulated.

Comparative analysis of the cases: towards a unified framework of stemness

The examples I have just relied on to illustrate the account show how a dispositional account of stemness sheds light on what stem cells are and, in doing so, it clarifies experimental results. Particularly, the most salient results of the account are:

- The dispositional account can be used as a unified framework to think of stemness across different families of experiments, without generating a theoretical unsolvable dispute between opposing and theoretically incompatible approaches (like e.g., the state vs entity dispute). Importantly, this has consequences for the problem regarding both the lack of integration in certain areas of stem cell research and the advantages of exploring several models, which I presented as two issues that my account solves (see [Introduction](#)). I will go a bit deeper about this in the [Discussion](#).
- The dispositional account is useful when studying potential interventions at the molecular level, as it allows observing all the possible ranges of interventions where experimental action may be effective. When this occurs, the dispositional account works fairly similarly to any causal-interventionist account *à la* Woodward (2003).
- The dispositional account is useful when it comes to thinking of potential combinations of mechanistic interventions (e.g., in case it is necessary to interfere in more than one variable simultaneously to obtain the desired outcome), as it describes all the potential ranges in an encompassing framework. In these cases, the dispositional account coincides with Fagan’s (2013) joint mechanistic account in requiring that the joint effects of different molecular components are taken into account to explain how stemness works. For example, going back to Eliazer et al.’s experiment, it may be discovered that deactivation of the ROCK-

Rho axis together with the repression of YAP is causally more efficient than just intervening on one of these molecular elements in isolation from the rest.

- The dispositional account is also useful in understanding why mechanistic interventions are sometimes not available. Concretely, there may be some cases where the causal behaviour of stem cells is constrained at the network level, e.g., at the level of the cell population; or simply cases where there are no constraints and the behaviour is simply random. In these cases, while there will be changes at the lower-level, these will result either from the existence of topological constraints or from an unknown cause. Therefore, in these cases, manipulation at the lower-level will not work. While stem cell researchers are conscious that this happens sometimes, and thus they actively investigate the type of constraints that exist at the emergent network level, the dispositional account provides a framework to explain *why* this happens.
- The dispositional account sheds light on which specific experiments would be required whenever mechanistic interventions are not feasible. Concretely, it points out towards the necessity of knowing the dynamics of the system, and how to modify that dynamics, which requires interventions at the higher-level. This point follows from the point made above about why mechanistic interventions may fail, plus the acceptance that higher-level properties do sometimes exert their causal powers downwardly. The dispositional schema justifies why this occurs and, in doing so, it aims to dispel the reluctance that some scientists may have to explore options that go beyond the molecular level.
- The dispositional account shows the necessity of occasionally combining or integrating experiments looking at the molecular and network levels, in cases where both levels may have a causal influence in the expression of stemness. Note that this point is crucial to understand the relevance of the dispositional account, as well as an important aspect of how it could contribute to stem cell science. Concretely, the dispositional account suggests that explanations at these two levels (i.e., mechanistic and topological explanations) must sometimes be combined and integrated. This is because phenomena such as stemness are so complex that their production results from the causal action of different levels, including both the molecular and the emergent network level.

Discussion

The dispositional framework I have just presented has several advantages over the other frameworks that I presented in [Other approaches to the nature of stemness and their limitations](#).

First of all, in contrast with approaches that overemphasise either the role of genetic markers that are expressed by the cell (entity view) or the role of niche components or any extra-genetic component that may induce the cell to become a stem cell (state view), the dispositional view I advocate here considers that both elements may play a role, and none should be overemphasised. Rather, it will be a contextual matter to determine which of the two components plays a more significant role on specific cell types, in specific lineages and during different moments of the

development of the organism. This is positive insofar as it encourages putting the research efforts on the investigation of several different opposing hypotheses, rather than focusing exclusively on some of them (Chang 2012). Importantly, this opens the avenue for certain forms of integration as well, provided one takes a sufficiently nuanced view of what integration means and acknowledges that it may entail the necessity of descriptions at different levels (Mitchell 2003). I will say more about this below.

Secondly, the account I have presented shares Fagan's ideas that it cannot be said at once and for certain whether one cell is a stem cell or not, as well as her idea that stem cells are the starting point of a reproductive lineage and a developmental lineage. Additionally, my account complements and enriches her model-theoretic view by adding that stem cells are a dispositional object. In this sense, the dispositional account contributes not just towards non-experts understanding, but also towards the understanding of stem cell researchers, since the account provides some basic guidelines to interpret stem cell experiments showing how stemness can be experimentally manipulated via several procedures. This is overall positive since it makes the dispositional framework I have presented to fulfil its "pedagogical" purpose, as I defined it in the [Introduction](#). For, sharing part of the virtues of Fagan's model that make it instructive (its simplicity, clarity and elegance), it simultaneously widens the scope of her approach by serving as a useful pedagogical toolbox to stem cell scientists.

Finally, the dispositional account shares Laplane's idea that stem cells must be approached ontologically, as well as her idea that stemness must express differently in different tissues or organs of the same organism. But, in addition, my account complements her view in two senses. Firstly, since the dispositional account does not classify stemness according to a distinct type of property, but constructs stemness as a disposition and explains the different behaviours of stem cells in terms of it, it does not need to cope with the objection that it is hard to biologically understand how a cell can shift from instantiating one of these properties to instantiating another. Secondly, in case that a stem cell instantiates a "systemic property" (according to Laplane's nomenclature), the dispositional account interprets that the Cinst of stemness depend on population-level properties. Therefore, these could be altered by altering the topological landscape of the system. That is, it is necessary to alter the network of interactions between the members of the population and thus alter the expected evolution of the system over time, so that the probability that a cell suddenly starts manifesting stemness is blocked.

These two points connect to the idea I put forward in the [Introduction](#) about the advantages of a unified schema for integration. As it is well-established in the philosophy of science since Mitchell's (2003) work, the kind of complexity that exists in the life sciences usually requires descriptions at different levels, and understanding how levels constrain one another in specific ways, so that biological phenomena occur in the way they do. In other words, as many biological phenomena depend on multiple dependencies across various levels, scientific research normally requires understanding how explanations at different levels may work together in combination. The dispositional account provides a unified framework to understand why many levels can interact with one another

to produce stemness, why they can constrain each other, and how they may work in association. Note, thus, that the kind of integration that my unified account introduces is not monist, but rather pluralist, in the line of integrative pluralism: it accepts that a plurality of levels of explanation is better, but it simultaneously serves as a unified schema to think of how to integrate this plurality. For example, to exploit the examples I introduced above, it may be possible to try to understand whether there are some molecular inducers of the non-Markovian dynamics favouring NSC differentiation. Or, alternatively, it may be possible to understand whether the population structure may partially be affecting MSC behaviour. The unified schema, thus, may serve scientists to integrate topological and mechanistic approaches to stem cells, so that they gain a better understanding of the phenomenon of stemness.

Overall, the account I have presented provides a universally shared guidance to think of stem cells and also to think of empirical interventions on them, both at the molecular and network levels. A key consequence of the account, thus, is that it is feasible to intervene on stem cells in many ways, including alterations at the genetic and molecular levels but also, and more importantly, at the population-level, via changing the topological landscape of the population. Yet, according to the dispositional account, it is not feasible (a priori) to transform a stem cell into a non-stem cell. At most, the Cinst can be modified so that the stem cell does not manifest stemness (or it does so), but the dispositional account entails that it would be a stem cell anyways, as the manifestation or lack of manifestation of a disposition is, *to a great extent*, irrelevant to attribute it to a certain individual. Note that this is enough to justify why it is possible to induce pluripotency: under the dispositional schema I have introduced here, this is possible not because non-stem cells became stem cells, or because cells enter the stemness state. Rather, it is because the Cinst are altered to that they manifest stemness, which was a disposition they were not manifesting before. While one may object that this is problematic, I think other things notwithstanding, this is the best we can go when it comes to stem cell research: we can experimentally manipulate stem cells, know where it is possible to intervene, and understand why, yet we cannot say at once and for certain whether one cell is a stem cell or not.

To finish this section, I would like to briefly reflect on how conceiving stemness as a disposition has helped in articulating a better account of the nature of stem cells than other extant ones. The usefulness of considering several biological properties dispositionally, and the general superiority of a dispositional approach over other types of approaches has already been pointed out by others before me (Nuño de la Rosa 2016; Austin 2017; Austin and Nuño de la Rosa 2021; Brigandt et al. 2023; Villegas and Triviño 2023). In the case of stemness, the superiority is expressed in the ability of conceptually unifying a heterogeneous set of experimental practices, each with its own idiosyncrasies; in the ability of explaining the ontological reasons why different experimental practices emphasise distinct levels and types of explanations; and in the possibility of serving as a general platform that could serve scientists to integrate their results in certain ways that would not be open to them unless a unified schema were available. Therefore, the stem cell example supports the general thesis that conceiving

some biological properties in terms of dispositions, and taking advantage of the multiple concepts that have been developed for thinking of dispositions within philosophy, can foster scientific progress.

Conclusion

I have introduced a dispositional analysis to understand stem cells and interpret stem cell experiments in a unified fashion. The analysis is scientifically useful and promising as it immediately invites the possibility of analysing different levels to manipulate stemness. Concretely, the account allows accounting for experiments showing that stemness can be primarily manipulated at the molecular level in some occasions, while it can only be manipulated at the network level in other occasions. These two levels can in turn be manipulated at the genetic, molecular or population levels. In some occasions, stemness can only be manipulated by controlling both levels simultaneously, and thus stemness needs to be explained in an integrative fashion. Overall, the paper illustrates how studying some biological properties by conceiving them dispositionally or, generally, by using certain metaphysical toolkits, can shed light on many important aspects of the contemporary scientific practice.

Acknowledgment Previous versions of this paper were presented at the 6th COST Maristem Workshop in Lasko (Slovenia), the Institute Gustave Roussy, and the session “Metaphysics of Biology”, in the context of the 2022 Ciclo AIFIBI. I thank all participants for their comments. Additionally, I thank two anonymous reviewers, Pedro Martínez, for very insightful comments on a previous version, and Lucie Laplane, for in-depth discussion of the ideas of this paper, as well as for her encouragement. Finally, I formally acknowledge 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) for financial support.

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

Declarations

Conflict of interest The author declares that he has no conflict of interest.

Human and animal resource Not applicable.

Informed consent Not applicable.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Austin C (2017) Evo-Devo: a science of dispositions. *Eur J Philos Sci* 7(2):373–389
- Austin CJ, Nuño de la Rosa L (2021) Dispositional properties in Evo-Devo. In: Nuño de la Rosa L, Müller GB (eds) *Evolutionary developmental biology*. Springer, Cham
- Brigandt J, Green S, O'Malley MA (2017) Systems biology and mechanistic explanation. In: Glennan S, Illari P (eds) *The Routledge handbook of mechanisms and mechanical philosophy*. Routledge, London
- Brigandt I, Villegas C, Love AC, Nuño de la Rosa L (2023) Evolvability as a disposition: philosophical distinctions, scientific implications. In: Hansen TF, Houle D, Pavličev M, Pélabon C (eds) *Evolvability: a unifying concept in evolutionary biology?* The MIT Press, Cambridge MA, pp 55–72
- Chang H (2012) Is water H₂O? Evidence, realism and pluralism. Springer, Heidelberg
- Choi S, Fara M (2018) Dispositions. In: Zalta E N (ed.): *The stanford encyclopaedia of philosophy* (Fall 2018 edition), URL = <https://plato.stanford.edu/archives/fall2018/entries/dispositions/>. Retrieved 15 Oct 2022
- Copley M, Eaves C (2013) Developmental changes in hematopoietic stem cell properties. *Exp Mol Med* 45:e55
- De Rooij DG (2017) The nature and dynamics of spermatogonial stem cells. *Development* 144(17):3022–3030
- Deulofeu R, Suárez J, Pérez-Cervera A (2021) Explaining the behaviour of random ecological networks: the stability of the microbiome as a case of integrative pluralism. *Synthese* 198:2003–2025
- Deulofeu R, Suárez J (2023) Pluralism and complexity without integration? A critical appraisal of mitchell's integrative pluralism. *Theoria*, <https://doi.org/10.1387/theoria.23871>
- Díez J, Suárez J (2023) How do networks explain? A neo-Hempel approach to network explanations of the ecology of the microbiome. *Eur J Philos Sci* 13(3):44
- Eliazer S, Muncie JM, Christensen J, Sun X, D'Urso RS, Weaver VM, Brack AS (2019) Wnt4 from the niche controls the mechano-properties and quiescent state of muscle stem cells. *Cell Stem Cell* 25:654–665
- Fagan MB (2013) *Philosophy of stem cell biology: knowledge in flesh and blood*. Palgrave-Macmillan, London
- Fagan MB (2021) *Stem cells*. Cambridge University Press, Cambridge
- Fagan M B (2016) Stem cells and systems models: clashing views of explanation. *Synthese* 193:873–907
- Fagan M B (2017) Stem cell lineages: between cell and organism. *Philos Theor Pract Biol* 9(6)
- Ferreira M, Hundertmark F (forthcoming) What are the causal bases of dispositions? *Australasian Journal of Philosophy*
- Fuliński A, Grzywna Z, Mellor I, Siwy Z, Usherwood PNR (1998) Non-Markovian character of ionic current fluctuations in membrane channels. *Phys Rev E* 58:919
- Green S (2017) Philosophy of systems and synthetic biology. *The stanford Encyclopedia of philosophy*. E. N. Zalta (ed.). <https://plato.stanford.edu/entries/systems-synthetic-biology/>. Retrieved 15 Oct 2022
- Guay A, Pradeu T (2020) Right out of the box: how to situate metaphysics of science in relation to other metaphysical approaches. *Synthese* 197(5):1847–1866
- Hsu YC, Li L, Fuchs; E. (2014) Emerging interactions between skin stem cells and their niches. *Nat Med* 20:847–856
- Huneman P (2010) Topological explanations and robustness in biological sciences. *Synthese* 177:213–245
- Huneman P (2018) Realizability and the varieties of explanation. *Stud Hist Philos Sci Part A* 68:37–50
- Hüttemann A, Kaiser MI (2013) Disposition. In: Dubitzky W, Wolkenhauer O, Cho K-H, Yokota H (eds) *Encyclopedia of systems biology*. Springer, New York, pp 594–597
- Hüttemann A, Kaiser MI (2018) Potentiality in biology. In: Engelhard K, Quante M (eds) *Handbook of potentiality*. Springer, Dordrecht, pp 401–427
- Hüttemann A, Love AC (2011) Aspects of reductive explanation in biological science: intrinsicity, fundamentality, and temporality. *Br J Philos Sci* 62:519–549
- Jones N (2014) Bowtie structures, pathway diagrams, and topological explanations. *Erkenntnis* 79(5):1135–1155
- Lander AD (2009) The “stem cell” concept: is it holding us back? *J Biol* 8:70
- Lander AD, Kimble J, Clevers H, Fuchs E, Montarras D, Buckingham M, Calof AL, Trumpp A, Oskarsson T (2012) What does the concept of the stem cell niche really mean today? *BMC Biol* 10:19
- Lanza R, Atala A (2014) (eds.) *Essentials of stem cell biology*. Academic Press.
- Laplaine L (2016) *Cancer stem cells. Philosophy and therapies*. Harvard University Press, Cambridge MA

- Laplaine L, Solary E (2019) Philosophy of biology: towards a classification of stem cells. *Elife* 8:e46563
- Laplaine L, Mantovani P, Adolphs R, Chang H, Mantovani A, McFall-Ngai M, Rovelli C, Sober E, Pradeu T (2019) Opinion: why science needs philosophy. *PNAS* 116(10):3948–3952
- Leychikis Y, Munzer SR, Richardson JL (2009) What is stemness? *Stud History Philos Biol Biomed Sci* 40(4):312–320
- Li L, Akashi K (2003) Unraveling the molecular components and genetic blueprints of stem cells. *Biotechniques* 35:1233–1239
- Loeffler M, Roeder I (2002) Tissue stem cells: definition, plasticity, heterogeneity, self-organization and models—A conceptual approach. *Cells Tissues Organs* 171:8–26
- Love A (2003) Evolvability, dispositions, and intrinsicity. *Philos Sci* 70(5):1015–1027. <https://doi.org/10.1086/377385>
- Martello G, Smith A (2014) The nature of embryonic stem cells. *Annu Rev Cell Dev Biol* 30:647–675
- Martínez P, Ballarin L, Ereskovsky AV et al (2022) Articulating the “stem cell niche” paradigm through the lens of non-model aquatic invertebrates. *BMC Biol* 20:23
- Mirzaei H, Sahebkar A, Shiri L, Moridikia A, Nazari S, Nahand JS et al (2017) Therapeutic application of multipotent stem cells. *J Cell Physiol* 5(10):25990
- Mitchell SD (2003) Biological complexity and integrative pluralism. Cambridge University Press, Cambridge
- Moreno A, Suárez J (2020) Plurality of explanatory strategies in biology: mechanisms and networks. In: Gonzalez WJ (ed) *Methodological prospects for scientific research: from pragmatism to pluralism*. Springer, Cham
- Mumford S (1998) *Dispositions*. Oxford University Press, Oxford
- Nicoglou A (2015) Phenotypic plasticity: from microevolution to macroevolution. In: Heams T, Huneman P, Lecointre G, Silberstein M (eds) *Handbook of evolutionary thinking in the sciences*. Springer, Dordrecht
- Nombela-Arrieta C, Ritz J, Silberstein L (2011) The elusive nature and function of mesenchymal stem cells. *Nat Rev Mol Cell Biol* 12:126–131
- Nuño de la Rosa L (2016) La Vuelta de las Potencias en Biología Evolucionista: hacia una ontología de lo posible. *Ludus Vitalis* 46:1–18
- Pradeu T, Lemoine M, Khelifaoui M, Gingras Y (2022) Philosophy in science: Can philosophers of science permeate through science and produce scientific knowledge?. *Br J Philos Sci*. <https://doi.org/10.1086/715518>.
- Reydon T (2008) Species in three and four dimensions. *Synthese* 164(2):161–184
- Rinkevich B, Ballarin L, Martínez P et al (2021) A pan-metazoan concept for adult stem cells: the wobbling Penrose landscape. *Biol Rev* 97(1):299–325
- Sipp D, Robey PG, Turner L (2018) Clear up this stem-cell mess. *Nature* 561(7724):455–457. <https://doi.org/10.1038/d41586-018-06756-9>
- Slack JMW (2018) *The science of stem cells*. Wiley, USA
- Strunz S (2012) Is conceptual vagueness an asset? Arguments from philosophy of science applied to the concept of resilience. *Ecol Econ* 76:112–118
- Stumpf PS, Smith RCG, Lenz M, Schuppert A, Müller F-J, Bachtie A, Chan TE, Stumpf MPH, Please CP, Howison SD, Arai F, MacArthur BD (2017) Stem cell differentiation as a non-markov stochastic process. *Cell Syst* 5(3):268–282.e7
- Suárez J (2023) Masking, extrinsicness, and the nature of dispositions: the role of niche signals in muscle stem cells. *Euro Jnl Philos Sci* 13:21
- Suárez J, Stencel A (2020) A part-dependent account of biological individuality. Why holobionts are individuals and ecosystems simultaneously. *Biol Rev* 95(5):1308–1324
- Suárez J, Triviño V (2020) What is a hologenomic adaptation? emergent individuality and inter-identity in multispecies systems. *Front Psychol* 11:187
- Tanoue T, Morita S, Plichta DR, Skelly AN, Suda W, Sugiura Y, Narushima S, Vlamakis H, Motoso I, Sugita K, Shiota A, Takeshita K, Yasuma-Mitobe K, Riethmacher D, Kaisho T, Norman JM, Mucida D, Sue-matsu M, Yaguchi T, Honda K (2019) A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* 565(7741):600–605
- Triviño V (2022) Towards a characterization of metaphysics of biology: metaphysics for and metaphysics in biology. *Synthese* 200:428
- Triviño V, Nuño de la Rosa L (2016) A causal dispositional account of fitness. *Hist Philos Life Sci* 38:6
- Villegas C, Triviño V (2023) Typology and organismal dispositions in Evo-Devo: a metaphysical approach. *ArtefactToS* 12(1):79–102

- Villegas C, Love AC, Nuño de la Rosa L, Brigandt I, Wagner GP (2023) Conceptual roles of evolvability across evolutionary biology: between diversity and unification. In: Hansen TF, Houle D, Pavličev M, Pélabon C (eds) *Evolvability: a unifying concept in evolutionary biology?* The MIT Press, Cambridge, MA, pp 35–54
- Vorotelyak E, Vasiliev A, Terskikh V (2020) The problem of stem cell definition. *Cell Tiss Biol* 14:169–177. <https://doi.org/10.1134/S1990519X20030086>
- Waddington CW (1957) *The strategy of the genes; a discussion of some aspects of theoretical biology*. Allen & Unwin, London
- Waters K (2017) No general structure. In: Slater M, Yudell Z (eds) *Metaphysics in the philosophy of science: new essays*. Oxford University Press, Oxford
- Wilson J (2016) *Metaphysical emergence: weak and strong*. In: Bigaj T, Wüthrich C (eds) *Metaphysics in contemporary physics*. Brill Rodopy
- Woodward J (2003) *Making things happen: a theory of causal explanation*. Oxford University Press, Oxford
- Zipori D (2004) The nature of stem cells: state rather than entity. *Nat Rev Genet* 5:873–878
- Zipori D (2009) *Biology of stem cells and the molecular basis of the stem state*. Springer, Dordrecht

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.