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Ratifying frailty

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ABSTRACT

Taking as a point of departure the role that the category of frailty increasingly plays in the classification, sorting and management of ageing populations in contemporary societies, this paper focuses on the crafting and validation of mouse models of frailty. The paper suggests that such models embody therapeutic and techno-economic expectations of ageing research, particularly as these are re-invigorated by current attempts to manipulate or eradicate cell senescence. The paper brings together critical gerontology, social studies of science and more-than-human anthropology to contextualise and analyse ethnographic data collected during fieldwork in a biology of ageing laboratory. The paper proposes that to build a mouse model of frailty, researchers need to learn to 'think like a mouse', provisionally taking the animal's point of view, to then efface that link and reconfigure the scientific chain of reference that enables translation between humans and mouse models of frailty.

Jennifer was introduced to me by Angela as the new PhD working across the Thread Lab where my fieldwork was being conducted, and another more established lab of the Biology of the Ageing Centre. "She'll be working with mice…", Angela added. "Yes, mouse frailty and senescence", Jennifer explained. Having observed the activities of the Thread Lab for a while by then, I had a basic understanding of cell senescence as a state of cell arrest whereby cells lose their capacity to divide and acquire a flattened, irregular shape, which I had myself seen under the microscope. On the other hand, I was also familiar with the technical concept of frailty as a "state in which the ability of older people to cope with […] stressors is compromised" (WHO, 2017: 3), having been involved as a collaborator in a randomised controlled clinical trial of muscle strength training and protein supplementation as a means to delay frailty and its musculoskeletal component - sarcopenia - in older individuals. I was puzzled – and partly beguiled – however, by the notion *'mouse frailty'*. (See Figs. 1–3.)

My reaction to 'mouse frailty' was understandable. It is a relatively novel modelling approach in the field of gerontology (Kane & Howlett, 2018; von Zglinicki et al., 2016), its development being propelled by increased interest in age-retarding, 'health-span' extending interventions in the research, regulatory and commercial worlds in the past decade (Deursen, 2019; Hayden, 2015; Mishra & Howlett, 2021). But its establishment has been a complex process, still riddled with uncertainties and challenges, a process which has captured my attention since I was introduced to Jennifer. This paper focuses on how this process relates to the pragmatics of crafting and validating a new mouse model of frailty.[1] To do this, the paper brings together critical gerontology, social studies of science and more-than-human anthropology to contextualise and analyse ethnographic data related to 'mouse frailty', collected in a cell biology of ageing laboratory.[2]

The paper is motivated by Higgs and Gilleard's (2014) examination of frailty as the defining condition of the Fourth Age, a collectively imagined future last phase of life characterised by ill health and dependency in contemporary societies. The paper suggests that the public articulation of the category of frailty, and the ageing identity transformation that Higgs and Gilleard propose is associated with it, is profoundly shaped by how animal models embody therapeutic and techno-economic expectations of ageing research or 'geroscience'. In this, the paper relies on the sociology of technoscientific expectations' understanding of how technological promises configure contemporaneous networks and organisations, playing a key function in the enrolment of institutional support, the mobilisation of resources and the shaping of socio-technical identities, regardless of whether the specific promise is actually brought to use in practice (e.g. Borup, Brown, Konrad, & Van

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[1] This paper was first presented at the Ageing Otherwise Panel Series, Concordia University, 4 October 2021. I thank the participants in the seminar, and Greg Hollin, Barbara Marshal and Stephen Katz for useful comments on drafts on the paper. Renee Beard's editorial guidance was unvaluable in addressing the reviewers' helpful comments.

[2] The study was approved by the Durham University Department of Sociology Ethics Committee. All names used in the paper are pseudonyms.

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Lente, 2006; Clarke, 2016). To create such anticipatory effects, visions require enactment, crafting normative and material alignment between specific settings, such as animal experiments and socio-technical promises. The paper proposes that to understand how animal models come to translate such promises, it is necessary to focus not only on localised epistemic practices of model construction (Nelson, 2018) but also on how those are interdependent on the making of connections between human and nonhuman life forms (Haraway, 2008).

The paper argues that to build and validate the mouse model of frailty in the laboratory, biologists of ageing have to first learn to 'think like a mouse', temporarily taking the animal's point of view, to then efface this link in standardising the procedures and instruments used to quantify frailty. The title of the paper is evidently a play-on words: to ratify here is intended to mean that, in order to validate a mouse model of frailty, it is required to think like a rat – to become a rat – or rat-ify the standard.[3] In making this argument, Despret's (2009, 2015) critical analysis of animal experimental research is key to describing how, in biology of ageing, researchers build equivalences – temporary zones of transaction - between human frailty and mouse ageing by identifying forms of physical and/or performance decline germane only to the mouse world. I will show how, in the lab, this entails the formulation of the strengths *and* limits of the mouse model of frailty: the careful,

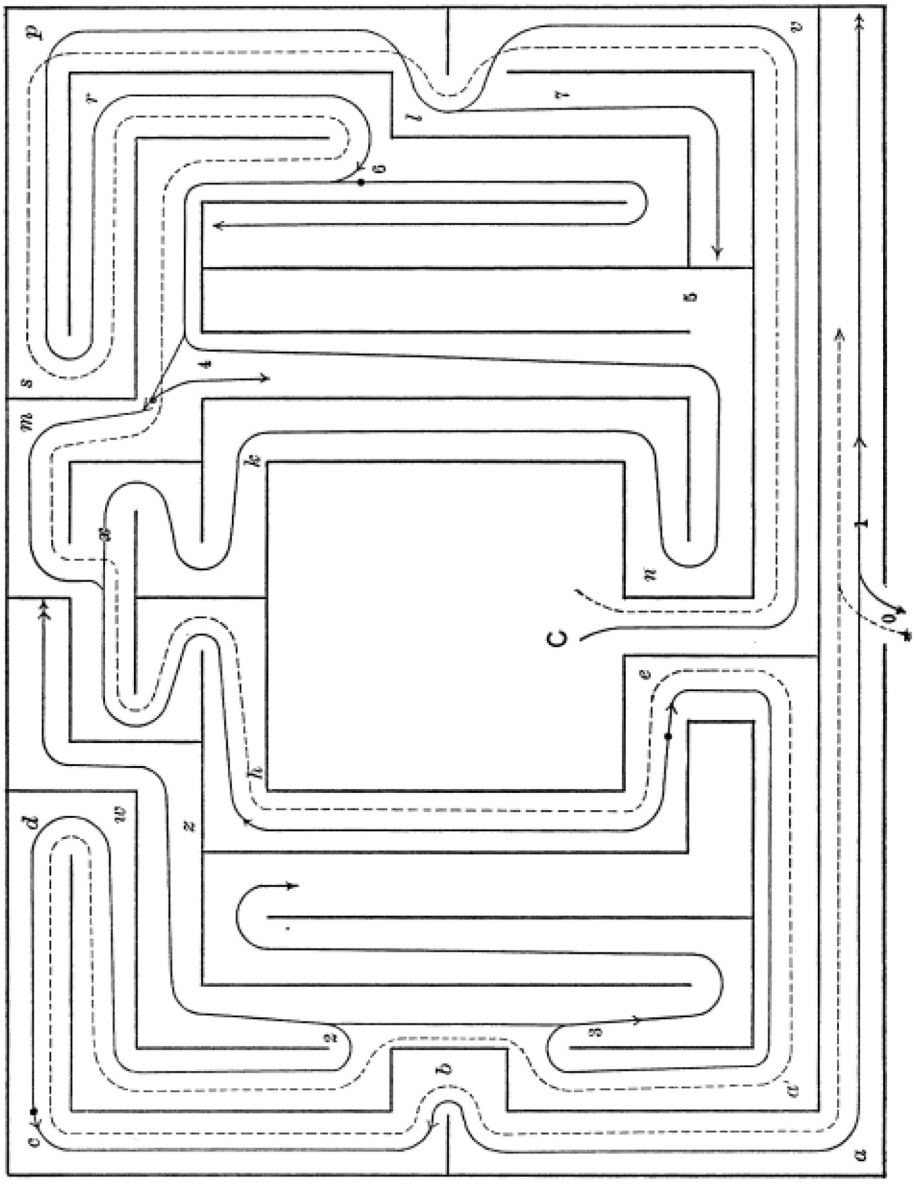

Fig. 1. Ground Plan of Rat Maze (Small, 1901: 207).

[3] To ratify is, according to the OED, to confirm or validate by giving formal consent, approval, or sanction, deriving from the latin ratus (rate), to mean 'established'. For the animal, it is uncertain whether the Latin and Romance words (rattus) are cognate with the Germanic words (ratte), or whether they were borrowed from Germanic, or vice versa; the ultimate origin is uncertain; perhaps imitative of the sound of gnawing.

reflexive delineation of its value for the understanding of ageing more widely.

The paper develops this argument in three key sections. Firstly, I survey the existing literature on animal models in the field of science studies to build a conceptual framework that bridges between an analytical focus on knowledge with a concern with more-than-human relationships. The second main section uses this framework to contextually analyse the emergence and establishment of a focus on animal models of frailty within biology of ageing and how these are linked to translational models of innovation and to therapeutic expectations in 'geroscience'. In the third section, drawing on the framework and the contextual analysis, I examine how these models are pragmatically built and corroborated in the laboratory. Between sections 1 and 2, I provide some methodological background and information to the paper.

Animal models of ageing: between science and care

Understating the central role of animal models in modern and contemporary biology has been one of the concerns of sciences studies in the last 4 decades. Two different but interrelated strands of research are recognizable: one concerned with animal models as epistemic tools and the other exploring the inter-species relationships that are nurtured in the laboratory. Below, I critically review these two domains to then suggest how their combination, underpinned by Despret's work on animal experimentation, provides a solid conceptual basis to understand the making and validation of mouse models of frailty.

In the first type of work, researchers address the question 'How do animals of one species living in a confined, controlled space come to stand for another species – humans – or general biological mechanisms?' Taking as a point of departure the understanding that the operation of representation deployed in animal models requires - indeed, relies on - simplification, attention has been directed to the work of building and maintaining the normative arrangements, epistemic commitments and technological infrastructure that enact model organisms as tools for scientific work. These enable animal models to link between what Ankeny and Leonelli (2020) label representational scope and representational target. In this, models are seen to have interesting epistemological functions, being more akin to cases or exemplars than samples (Ankeny, 2001; Creager, 2001). This is crucial in their ability to support epistemic claims on general biological or disease mechanisms.

One key aspect in establishing this capacity is the historical configuration of particular model organisms. Kohler's (1994) now classic study detailed the institutional and material process of the establishment of a standardised model organism as a pragmatic underpinning of scientific work. Analysis of these processes in different animal models helps in understanding how the dynamics of specific disciplines or fields of research become interlinked with animal models, such that key shifts or 'discoveries' in those fields become exemplified in the animal models that enabled it. This mutual relationship leads Rader to suggest that the standardised model organism should be understood as "the result, rather than the cause, of consensus" in experimental biology (Rader, 2004: 15). Friese and Clarke (2012) have proposed that this standardising work facilitates transposition of modelling approaches across disciplinary and species boundaries, scaling up biomedical 'translational' pathways.

A second dimension relates to the localising and sustaining of animal models in particular laboratories. Lynch (1988), for example, drawing on ethnographic data, examined the deployment of embodied work in rendering the laboratory mouse as an epistemic object, one that can stand for and represent human bodies and diseases. For animal models to maintain their role as knowledge making tools, forms of routinized animal management, such as housing, food and handling (e.g. Davies, 2013; Kirk, 2010), need to be adopted and adapted to local conditions. Drawing on and extending Rheinberger's concept of experimental system, Nelson (2018) has explored the methodological work that supports researchers 'stacking' of epistemic claims about the relationship between representational scopes and targets in and through the model at hand. Again, these demonstrate the complex networks of standards and norms onto which the epistemic value of animal organism is built. Significantly, Nelson suggests that, while the metaphor of the scaffold suggests a temporary nature to these arrangements, scaffolding refers an unremitting aspect of work with animal models, one that can never achieve closure or be stabilised as researchers critique and modify methods, procedures and tests conducted in the lab.

Although animal models have been used in ageing research at least since the 1920s (Comfort, 1964), not much has been written about the role of animal models in ageing research from this first perspective within science studies. Park (2016) documented how McCay's use of the rat as a standard model in his experiments on caloric restriction was key in establishing the relationship between diet and longevity as a central problematic in experimental biology of ageing. Bolman (2018) explored how the stabilisation of beagle dogs as a model of longevity was enabled by and extended the focus on radiation within the Cold War. Huber and Keuck (2013), focusing on the case of transgenic mice for Alzheimer's disease, suggest that modelling human diseases requires a stepped process that explains the proliferation of model organisms in any etiological domain. Moreira (2017) has suggested that modelling modes of reasoning have been instrumental in establishing gerontology's approach to individual variation in function and health.

Another strand of work within science studies has considered more-than-human entanglements, analysing the connections and exchanges between human and nonhuman model life forms (Haraway, 2008; Kirksey & Helmreich, 2010). This framing has enabled interdisciplinary

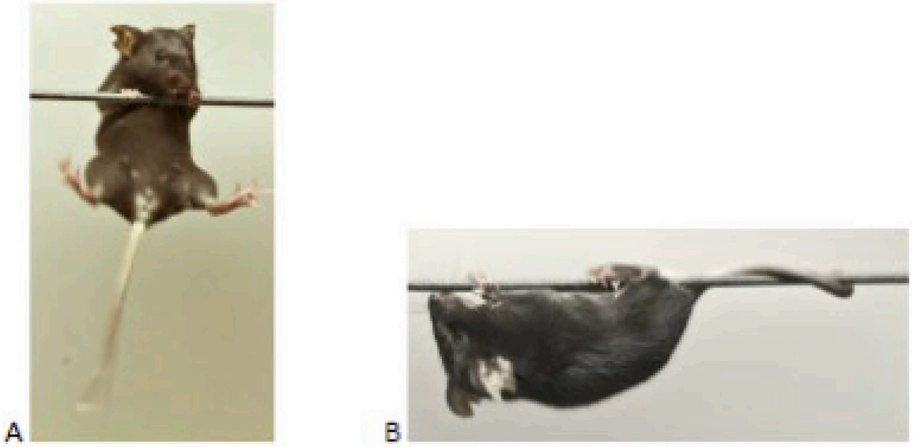

Fig. 2. Correct wire hanging test procedure (Van Putten et al., 2011: 12).

work that traces relations between animals and humans in terms of what Haraway refers to as 'wordlings' - complex processes of becoming together - thus problematising their shifting relationship in specific settings. In this approach, care as a relationship has been a key focus in understanding the assembling and disassembling of those relationships. There are very good reasons for this focus, particularly as it relates to ageing.

Care is an important component of the environmental control that most research based on animal models wants to achieve (Kirk, 2016; Wilkinson et al., 2020). Care can also have an added epistemic dimension, where the production of knowledge is purposely reliant on an organism that has been 'cared for' in experimentally specified ways (Friese, 2013), as is the case with experimental gerontology. In this domain, experimental practices and housing conditions become integral to the understanding of ageing in model organisms (e.g. Bolman, 2019). However, care is also a political, relational practice that cannot be analysed in purely functional or epistemic terms (Friese & Latimer, 2019; Giraud & Hollin, 2016). From this perspective, care affects both experimenter and experimental animals, enabling their becoming together across species (Davies, 2013) and supporting forms of corporeal exchange between scientists and their models (Svendsen & Koch, 2013).

Giraud and Hollin (2016) have argued that, while the concepts of entanglement and interspecies relations might aim to emphasise connectedness rather than separation between humans and non-humans, they might be paradoxically achieving the wrong outcome in terms of a relational ethics of care. Entanglement models might, in this way, be reinforcing only the transposition of bodily qualities and abilities that are aligned with pervasive modes of control over humans and non-humans (also, Hollin, 2022). One possible way to address this paradox is to see animal experimentation as deployed through a two-fold process: a first step, where entanglement dominates, and human and non-human actors exchange qualities and properties, and a second step, where separation of categorical domains is the central concern, and "beings [are] redistributed into different regimes of action" (Despret, 2020: 186). In suggesting this analytical lens, I draw on Despret's reworking of Latour's differentiation between the work of network building and that of purification/valuation.

Latour's original formulation of this dynamic was his distinction between the 'primary mechanism' of composition of heterogeneous, sociotechnical networks/relations through enrolment and the 'secondary mechanisms' of apportionment, where agency/power is discursively attributed to only one or a restricted type of actors in the network and "which might have no relation at all with the first" (Latour, 1987: 119). This distinction came to underpin Latour's anthropological analysis of modernity, where the non-modern 'work of translation', which proliferates hybrid collectives, is contrasted with the modern 'work of purification' that creates and maintains the division between 'nature' and 'culture' (Latour, 1993). More recently, Latour has recognised the limitations of actor-network theory in understanding the productive, generative capacities of purification work. In his proposal for a new 'radical empiricism', it is suggested that secondary mechanisms enable the establishment of normative values – values of veridiction - that pertain to specific types of networks, their deployment resulting in different 'modes of existence' (Latour, 2010, 2013). In this framework, science, along with law, religion or fiction, constitutes a type of practice, it being equally possible to empirically follow its making of 'chains of reference' and its sense-making, valuing activities.

Despret's empirical philosophy of animal behaviour research takes as a point of departure how epistemic claims underpinned by animal models rely on an incongruous, purified, anthropocentric description of the procedures and tests used in the laboratory: how, for example, the water maze comes to stand for a test of general/universal learning and memory processes when its origin can be traced to local, specific conditions of form. Her key argument is that the instauration of the maze as a tool in laboratory research was only possible because researchers "actively integrat[ed] a characteristic of the rat" in its design: its burrowing navigation of the buildings it co-inhabits with humans (Despret, 2015: 12). Indeed, the investigator credited with having invented the maze as a laboratory tool, Willard Small, proposed that his maze design, while drawing on the Hampton Court Maze, was, importantly, "couched in a familiar language" to rodents (Small, 1901: 208). In this, Despret argues, investigators rely on an understanding of what Uexküll (2010) would describe as the rat's *Umwelt* - the creation of a world actively deployed through a species-specific functional circle of perception and action –, a quality that they transpose in designing the 'familiar' environment of the maze. This process is key to the methodological work of epistemically scaffolding the link between the model and the target mechanism or disease (Nelson, 2018: 100–101).

Tracing this chain of reference, it is possible, Despret suggests, to rethink what the rat might make of the maze that is presented to it, making imaginable a "questioning on the subject of the rat" rather than its mere use as instrument or tool – that is to say, as what Latour would label as an intermediary (Despret, 2015: 15). This re-articulation of the chain of reference is conceivable because the methodological traces of this scaffold are partially visible in the everyday practice of animal experimentation and obvious in the making of new procedures and tests, as suggested above. What counts as knower and known, object and subject, human and non-human, etc., is not fully stabilised, thus allowing for negotiations on the boundaries and values that are attached to the entities of the chain of reference and for Depret's and my own

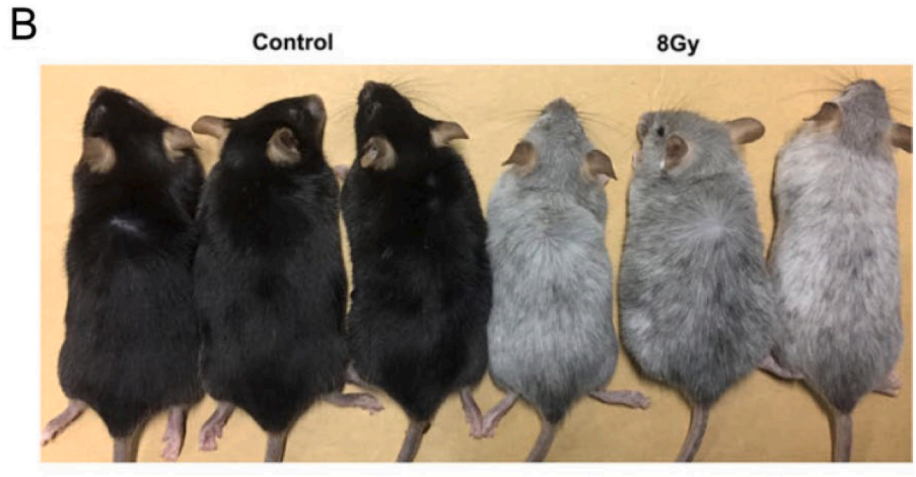

Fig. 3. Total body irradiation mouse model.

conceptual intervention. Such boundary negotiations are generative and performative, and not simply a superficial, post-hoc discursive process. Further, it is a negotiation in which the animal is an active partaker, its role as a 'model', 'subject' or 'knower' being pragmatically at stake.

While analytically this distinction is critical, in practice, in the lab, primary and secondary mechanisms are not neatly distinguished or temporally arranged. As I will demonstrate below, to validate a mouse model of frailty requires both entanglement and valuation. In this dynamic, researchers have to learn to 'think like a mouse', taking the animal's *Unwelt* into account in the construction and deployment of quantifications of frailty. In so doing, they are also required to outline forms of equivalence and difference between animals and humans, to carefully craft the zones of transaction that enable a pragmatic evaluation of the model being built. This results in what is usually described as a *qualification* of the model: the restrictive set of conditions under which it is possible to claim that a finding in the mouse pertains to – or translates to - frailty in humans. Through this process, mouse models of frailty gain methodological robustness but at the cost of becoming more limited in their epistemic claims, allowing and enabling the often heard representational specification about model-based research: "in the mouse!"

Methodological note

To make the argument outlined above, I draw on ethnographic data collected in a laboratory focusing on the role of telomeres and mitochondria in ageing and senescence. The Thread Lab - a fictitious name - has two PIs, normally hosting 2–3 postdocs, about 5 PhDs, and a varying number of MA and undergraduate students throughout the academic year. The lab shares facilities, such as the animal house, tissue culture rooms, freezers and microscopes, with three other labs focused on other aspects of ageing, working in the same research centre and building – the also fictitiously named Biology of the Ageing Centre. The lab collaborates with a variety of other laboratories in the UK, US and Continental Europe, exchanging experimental materials, such as animals and cells, as well as techniques and expertise.

During the 3-year period of fieldwork, I regularly attended the lab's weekly meeting where progress, analysis and experimental results were discussed. I shadowed all of the lab's post-docs and PhDs in their goings about the lab, taking photographs. I also conducted unstructured interviews with most members of the lab, asking questions about biology of ageing and the procedures and techniques they were using.

In ethnography, data collection and analysis are closely interwoven. Analysis might guide further data collection and extension of the 'field' boundaries. For this paper, drawing on the analysis of observations and interviews I conducted in the lab, I extended the data set with documentary material relating to mouse models of frailty and the experimental procedures used to validate them. This came to include a review of relevant literature on mouse models of frailty and of frailty more generally, to contextualise the work done by researchers such as Jennifer in the lab. It is to this literature that I now turn, exploring, in particular, the links between frailty standards, translational models of innovation, and experimental, laboratory animal models of ageing.

Modelling standards of frailty

Frailty has become a central category for the classification and sorting of older people, mainly in the last 2 decades or so. As Pickard (2014) documents, while frailty was used to describe conditions characteristic of 'old age' since the 1940s, it was not until the late 1990s that frailty emerged as a clinical classification. The establishment of this category is clearly linked, in the literature, to the outlining of and the controversy between two different approaches to the condition (also Pickard, 2018). The phenotype approach defines frailty as a syndrome, linking key attributes/criteria to significant clinical outcomes (e.g. falls) within 7 years (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004). It is underpinned by loss of adaptation potential as an underlying cause, and a focus on 'markers', which facilitated transposition across the disciplines aggregated around the US National Institute of Ageing (Walston et al., 2006). The deficit accumulation model identifies a set of incapacities that, in their interplay with older people's 'assets', result in 'risk factors' probabilistically linked to adverse events. These are organised in a Frailty Index (Mitnitski, Mogilner, & Rockwood, 2001), which aims to support an unproblematic identification and recording of deficits, facilitating measurement and calculation at a population level.

The consolidation of both these approaches was achieved in close relationship with the development of specific measurement instruments, which enabled the quantification of prevalence of frailty in older people (e.g. Collard, Boter, Schoevers, & Oude Voshaar, 2012). By becoming transferrable and routinised, such forms of frailty measurement become performative, acquiring their own dynamics, being able to effectively reconfigure norms and institutional arrangements, shaping social life in their wake (Desrosières, 1990). Frailty computings thus bring the condition of vulnerability to bear on social life, enabling the description and organisation of populations. It is in this respect that it is possible to argue that the establishment of frailty as a public health concern (e.g. WHO, 2017) marks its role as a mediator between the 'third' age of healthy and active ageing and the 'fourth' age, linked to senescence and 'geriatric' modes of living (Higgs & Gilleard, 2014). In this, Higgs and Gilleard argue frailty is generative of a sense of abjection towards older people, marking a future unspecified adverse outcome for all concerned.

Research and innovation programmes have been instrumental in the making of the category of frailty and articulating how it shapes the future of the ageing society. Frailty, from this perspective, can be seen as a central component of a techno-economic imaginary that links health and activity to technology in the ageing society. As a set of expectations, this imaginary reinforces material and institutional commitment to 'functional age' and a search for optimal adaptive relations between the ageing organism and the environment (Moreira, 2017: 119–42). This is nowhere better epitomised than in the WHO consensus definition of frailty as, a recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems. (WHO, 2017: viii).

In this, frailty is defined as a state linked to dysregulation and loss of dynamic homeostasis. In this imaginary, technology, as the WHO Consortium Meeting on Frailty makes clear, plays two different roles: as forms of health measurement, such as the Frailty Index, and as forms of re-activation of the ageing body, which can range from bio-cellular therapies to assistive robotics to the design of protein-rich foods (WHO, 2017: 11). Technological practices, in the domain of ageing, offer to monitor and modify health and activity through a set of converging tools and forms of knowledge that align the "molecular and the experiential" (Lappé & Landecker, 2015: 152) through the standard of frailty. The establishment of the category of frailty - and of the field of research on frailty - is thus central to the articulation of a promissory technocientific, social and cultural horizon of transformation, a process that Pickersgill (2019) labelled performative nominalism.

A key part of bringing this vision to bear is enacting it in the lab. Recognising that the proposed alignment between the experiential and the molecular is reliant on "hypothesized" biological mechanisms (WHO, 2017: 10), regulatory and funding agencies as well as researchers have, in the last decade, increasingly advocated for a more intensive focus on the 'biology of frailty'. One of the key strategies to achieve this is the development of animal models of frailty. Choosing the mouse to do this work had three main rationales. As a commonly used species in laboratory ageing research (see above), the physiology of ageing in the mouse is well known, with identifiable visible signs such as the stiffening of the tail and loss of coordination being validated markers (Seldeen, Pang, & Troen, 2015). This is reliant on an established battery to test a variety of outcomes, including stress responses, metabolic outcomes, and complex behavioural and functional assessments. In their

standardised format as lab animals, with reduced genetic variation and relatively short life spans, mice also facilitate epistemic commitment to biomolecular pathways in a process similar to the one described by Rader (2004). Thus, there are now a number of mouse models that target specific cellular mechanisms, such as inflammation (e.g. Nfkb1−/− mice and IL-10 deficient mice). Lastly, the mouse model of frailty "provides a powerful new translational tool for research on ageing [,] a platform for the development of new frailty interventions" (Mishra & Howlett, 2021: 18).

This last aspect is key, as Friese and Clarke (2012) have suggested, because it connects shifts in the frailty research field to the introduction and scaling up of 'translational' approaches in biology of ageing, reinforcing the need for standardised mouse models. The association is bolstered by the therapeutic expectations that hinge on the possibility of extending human 'healthspan' through the deployment of agents such as senolytic drugs (e.g. Campisi et al., 2019; Deursen, 2019). These, according to James Kirkland and colleagues, "are agents that selectively induce apoptosis [cell death] of senescent cells" (Kirkland, Tchkonia, Zhu, Niedernhofer, & Robbins, 2017: 2297). Cell senescence, in turn, is defined as a state of cell arrest – i.e., irreversible loss of division potential in somatic cells - that arises as a response to diverse stimuli such as development, wounds, DNA damage or oncogene activation (e.g. Herranz & Gil, 2018). Senescent cells are believed to accumulate in many tissues with ageing and secrete harmful substances that disrupt nearby healthy tissue, with a variety of deleterious effects, making their elimination an ideal strategy to manage age-associated diseases and risk states such as frailty. Animal models of frailty are thus seen to provide an excellent platform to assess the impact of these new, potential therapies (Khosla, Farr, Tchkonia, & Kirkland, 2020).

The explicit use of the concept of platform in this translational shift is significant because it indicates reflexive engagement with the conventional and delicate basis of knowledge making through animal models (Nelson, 2018). As a discrete structure build for a particular activity, the idea of platform indicates the assembly of types of expertise, technical infrastructure and norms for the specific purpose of smoothing and calibrating the relationship and transit of materials between sites. In the case under analysis, this calibration is unique, as it entails the adaptation of existing methods of quantification of human frailty to - also - already established mouse models of ageing. In an operation that cell biologist of ageing Thomas von Zglinicki et al. (2016) describe as "reverse translation", researchers outline and test equivalences between frailty standards used for humans and markers of health used for the laboratory mouse.

This operation is fraught with uncertainties encased in the form of a methodological debate, a debate which has focused on three interlinked aspects: the reasoning behind the choice of index (cf. Fried vs. Rockwood debate); whether the mouse models on which the quantification is attempted are representationally adequate; and, importantly but usually less articulated, the process of development and validation of the frailty parameters used in the mice themselves. Each of these aspects deserves attention.

In relation to the first issue, the frailty phenotype's main advantage is its flexibility, allowing for modifications of the criteria that are relevant to a particular species. For example, high weight in mice is considered an equivalent to 'unintentional weight loss' as a marker in human frailty phenotype criteria (Baumann, Kwak, & Thompson, 2018). The frailty Index is more detailed and prescriptive in its adaptation but as a result has more inter-scorer reliability (von Zglinicki et al., 2016). Some laboratories have used standard laboratory mouse models, such as the C57BL/6 J, where the effects of dietary interventions are well known. This enables a focus on the development of aspects of the scoring system, expediting external validity tests. Other labs have used genetically manipulated animals, such as the interleukin-10 knock-out model, centring on key mechanistic drivers of the ageing process that underpin frailty. The last dimension of the controversy hinges on how to draw on previously validated procedures developed for other purposes and adapting them to the chosen frailty approach, and to local conditions/resources. An example of this is the use of the wire hanging test – in which "the latency of a mouse to fall off a metal wire upon exhaustion" (Van Putten, Aartsma-Rus, & Louvain-la-Neuve, 2011: 1) is measured - normally used to assess motor neuromuscular impairment and motor coordination in mouse models of CNS disorders as a proxy for a grip strength test used in human frailty assessment (Van Putten et al., 2011).

Describing these solely as the result of deliberate methodological choices is, of course, misleading because, in practice, 'reverse translation' is a complex pragmatic undertaking, one where methodological problems *unfold from and in action*, opening aspects and proliferating questions that could not have been foreseen ahead (e.g. Lynch, 1988). In the Thread Lab, this process of opening up, adapting and adjusting parameters was often described to me using terms relating to the semantic field of 'subjectivity': impressions obtained from observation, judgment, personal familiarisation with conditions, individual learning of procedures, subjective rating of behaviours, etc. While these descriptions emphasised the cognitive aspects of methodological scaffold construction, my fieldwork suggests that the process entailed pragmatically relating these to normative, institutional and material dimensions. In what follows, I will delve into what such description of the process encapsulates.

Reverse translating frailty in the lab

Doing fieldwork in the Thread Lab was a rewarding experience. As a laboratory focusing on senescence and ageing, it was at the intersection of a variety of local and international networks, some of them formalised in collaborations with other labs, with associated circulation of materials, techniques and researchers between sites. The Thread Lab's PIs, post-docs, PhDs and technicians were usually engaged in 8–12 concurrent research projects, within and beyond the research centre where it is located. Jennifer's was one of such projects conducted across the centre's labs, and, strictly speaking, it fell out of the remit I agreed to with the Centre management for my fieldwork. However, perhaps because of its novelty, both for the field of senescence research and for the lab itself, it enabled observations of aspects of animal science-in-the-making that were obscured in other more established domains of the lab's work.

To be exact, some aspects of Jenifer's project became directly related to the core of the Thread Lab's work as the project itself unfolded. Using cell and animal models to understand the role of telomeres, DNA damage and mitochondria in cellular senescence, the Thread Lab was an ideal window to trace and explore the transformation of the contemporary scientific reconfiguration of ageing, as senescent cells are currently thought to accumulate in many tissues in a process linked to multiple age-associated diseases, as explained above. Relatedly, the idea underpinning Jennifer's project was to understand the molecular drivers for the accumulation of cells, which have lost their capacity to divide (senescent cells) in age-associated conditions such as frailty. For this, she and her collaborators were using markers of senescence developed by the Thread Lab itself, linked to a specific mechanistic hypothesis.

Although the lab's main work was on cell models, they were, during the period of my fieldwork, acquiring increasing experience in working with mice models of ageing, particularly mutants. This mostly involved using already validated models of ageing, however. Jennifer's project, on the other hand, entailed working on adapting a relatively novel ageing condition - frailty - to a new mouse model of ageing – that of irradiation-induced senescence. In this, the representation target was the frailty experienced by patients who had been exposed to therapeutic total body irradiation before hematopoietic stem cell transplantation as a treatment for leukaemia, lymphoma and other haematological conditions. This condition was, in itself, taken as a model of frailty more generally. In addition, the mouse model for this type of irradiation had just recently been standardised in other laboratories. Thus, the methodological trials and tribulations of modelling frailty that I referred to at the end of last section were encountered first-hand by Jennifer. This

facilitated my access to the inner workings of experimental practice.

Jennifer was an international PhD, having trained in a collaborating laboratory in continental Europe. Coming from a mixed nationality background, we connected over our common Portuguese ancestry, and she found it easy to relate to me the process of transitioning to a new country, a new lab and a different role. Part of this process was learning to become an animal experimenter, Jennifer having previously mainly worked on cell and tissue models. But this was not straightforward either, as most existing expertise in the lab related to cognitive or musculoskeletal testing in mutant mouse models. Being a new venture in the Thread Lab, for her frailty-focused project, Jennifer had to draw on the developing expertise of a collaborating lab and its networks to acquire a knowledge of the methods and techniques of scoring and quantifying frailty. Formal acquisition, studying existing mouse frailty protocols and more general phenotyping databases,[4] was actively complemented with visits to other labs and animal houses, and countless informal chats with other researchers and lab technicians. Jennifer also had to learn how to work with this specific type of mice, for which there was little experience worldwide. This was an intricate and long practical undertaking to which Angela had shrewdly referred when Jennifer and I were first introduced (see Introduction).

A key part of this complexity concerned the use of the irradiated mouse model. This was underpinned by a prior modelling relationship whereby cancer survivorship was considered a 'model of ageing' because of how irradiation exposure evoked a 'stimulus for senescence', inducing oxidative stress, DNA damage and an inflammation response in organs and tissues. However, total body irradiation has a variety of effects in the respiratory, cardiac and nervous system of mice, some of them linked to senescence, that are still not well understood. This meant that the mice's 'special fragility' had components that were still unclear or unknown. Over the next few months, Jennifer and some of the other researchers in both labs focused on testing and adapting mouse frailty measurement tools to this mouse model.

This adaptation was reliant on learning to think like a laboratory mouse. More specifically, it entailed learning to think both like a standard lab mouse and like the model specifically developed in the Thread Lab. From this point of view, Jennifer's practical question was: what in these mice *Umwelt* counts as frailty? In what ways are these mice frail? The pragmatic complexity of addressing these questions can be understood through a close empirical analysis of two examples of validation work.

One of the seemingly less problematic equivalences to establish between human frailty tests and those used in mice is grip strength, as both humans and mice use forelimbs to grasp objects for locomotion and feeding. In humans, the routine measurement of grip strength uses a low-cost piece of equipment, a dynamometer, a device for measuring mechanical force. In mice, force is substituted by time in versions of the grip strength test, such as the wire hanging test, described above. The wire hanging test, while well validated, requires specialist equipment and takes time to conduct, especially when the grip strength test is to be done as part of the series of tests, as in the mice frailty assessment batteries proposed so far in the literature. Thus, to speed up the process, in mice frailty assessment, instead of a wire, experimenters are instructed to 'Hold the mouse [then] allow it to grip the bars on the cage lid [and] lift animal by the base of the tail to assess grip strength' (Whitehead et al., 2014: Suppl: 3). This should result in a score of grip strength between three values: 'sustained grip (1)', 'reduction in grip strength (0.5)' and 'no grip strength, no resistance (0)'.

While the identifying instances of 0 was relatively straightforward, understanding what 'sustained grip' meant pragmatically for normal mice – so as to also be able to identify the 0.5 cases – was only possible through the establishment of an habitual embodied expertise of mice handling, i.e. of the force to use in lifting the mouse by the base of the tail. To do this, the experimenter has to become 'tuned with' – or learn to be affected by - the physical, haptic affordances of the experimental procedure. This in turn relied on establishing a hermeneutic circle between the mice and the test, in that understanding 'sustained grip' was both dependent upon and generative of the classification of the mouse being tested – as normal, frail, etc. A knowledge of the individual mouse was key in this process because it enabled careful, detailed pairing of grip and mouse 'fitness'. The strength to be used in the tail lifting was derived from this process of embodied learning of the forces in the mice world and coming to distinguish between a 'strong' and 'weak' mouse grip in the model-specific functional circle of perception and action. As the experimenter becomes better at attuning this strength, the procedure loses its 'subjective' character; the variations, the mistakes, and the slight misapplication of strength are smoothed over. In this, it slowly becomes increasingly a standard test, with experimenters being able to conduct and score the assessment swiftly and accurately.

A similar process takes place in the scoring of the condition of mice 'integument' or covering (fur, skin, whiskers, etc.). This includes parameters relating to fur loss, fur colour, skin condition, and quality of grooming. In humans, grey hair and skin elasticity are used in frailty assessment but do not have the same biological meaning as fur, skin and whisker condition in mice because integument maintenance is so central to mouse biology and behaviour. Learning to pragmatically understand - through everyday observation of mouse grooming, for example - how fur is fundamental to the mouse *Umwelt* is thus key to being able to enact mouse frailty. Assessment of fur colour and shade is reliant on a detailed knowledge of individual mice, a familiarity that normally characterises pet relationships. Mice have minor variations on fur shade, and a careful experimenter will come to know how to best spot differences and changes under specific lights in the laboratory. This, in turn, relies on being able to 'gently restrain the animal', a seemingly paradoxical accomplishment that itself stems from a tactile habitual closeness with individual animals.

This pragmatic complexity is further compounded by the fact that, in the mouse, fur or whisker condition is a function of its position in the changing pecking order in the group. Mice are notorious for their in-fighting, particularly between males. Thus, when assessing 'loss of whiskers' or checking skin lesions, Jennifer was confronted with the question of whether these were a sign of frailty or a sign of in-fighting? As the lab members made clear when the results of frailty scores were discussed in one of the usual Wednesday meetings, this was almost an impossible question to answer because frailty itself will impact on the animal's ability to defend itself. As one of them put it, "these conditions are [themselves] related to the ageing phenotype". This made knowing and accounting for conditions of mouse keeping and for an individual mouse's usual position in the group all the more important. Being able to consistently score fur shade and condition required this localised understanding of a mouse life in a laboratory cage, adopting a provisional lab mouse-centric view of body hair.

In both these examples, the validation of the test entailed learning to take the mouse's point of view to then efface that link, as was argued in the first section of the paper. As a consequence, the test results became entangled in local conditions, modifying and qualifying the battery's epistemic power. So, while fur condition assessment was seen as useful for scoring frailty in non-irradiated mice, for irradiated mice, it was seen as a very blunt test because of irradiation's effects on fur colour and texture, even for mice which had been given the senolytic intervention. Validating the battery for the irradiated lab mouse entailed looking in more detail into other parameters, the overall quantification only gaining scientific meaning in light of the enhanced sensitivity of its musculoskeletal measurements, for example. The frailty assessment battery was validated because it was good enough to characterise and quantify the frailty observed on the irradiated mouse model. As a result, the irradiated mouse model became, through the chain of reference just described above, an accepted, workable mouse model of frailty.

Establishing those chains of reference was accomplished by outlining

[4] https://www.mousephenotype.org/

specific equivalences and differences between human and mouse frailty. For this to happen, Jennifer had to generate zones of transaction across assessment batteries by stacking up epistemic claims - the various models being created - onto a provisional platform. In practice, this meant addressing the question 'what in these mice's *Umwelt* counts as frailty?' This had to be done in situ and in the flesh, creating knowledge of 'mouseness' by establishing relationships – through watching, handling, etc. - with individual animals. As local conditions could be transformed into an embodied practice of test deployment, the easier the translation of the epistemic components of the model became.

As I argued, the main consequence of the process of embedding - and embodying - 'mouseness' into the deployment of frailty tests was that it enabled a pragmatic evaluation of the model being built. This was because of the reflexive understanding of the condition under which it was possible to formulate epistemic claims in relation to mouse frailty: how it, for example, depended on being attentive to the role of the tail in the mouse's way of life and being materially attuned to the small differences in how mice's tail wrap around one's finger in the 'tail stiffening test' (Whitehead et al., 2014: Supp: 3). This resulted in a qualification of the model of mouse frailty: the restrictive set of conditions under which it is possible to claim that a finding in mouse pertains to frailty in humans. Through this process, mouse models of frailty gained methodological robustness but at the cost of becoming more limited in their epistemic claims.

One possible objection to the argument presented here is that this qualification of epistemic claims is normally only found in the less important methods section or rarely read methodological appendix of research papers. Jennifer's project demonstrates, however, that validation of the model is key to any substantive scientific work to be conducted on the biological underpinnings of frailty. Her work is supported by the success or otherwise of the 'reverse translation' work she deployed on frailty assessment. In addition, it might be also suggested that these restrictions are meant to be temporary, while methodological work on the specific model in question continues across various laboratories. Once this work is done, the argument might go, the biological mechanisms of frailty will be clarified and established. As Nelson (2018: 85) suggests, however, these temporary scaffolds "often end up becoming permanently provisional structures", becoming "semi-permanent features of the scientific landscape". Thus, mouse frailty is robustly entangled with procedures, such as the tail-stiffening test, and it is, for the moment and for the foreseeable future, difficult to make a knowledge claim on mouse models of frailty - or frailty in general and increasingly ageing more widely - without having such tests as visible, noticeable, and accountable 'obligatory passage points' (Callon, 1986).

Conclusion

In this paper, I have explored how mouse models of frailty are crafted and validated. The justification for the paper's focus is the central place frailty increasingly plays in the classification, sorting and management of ageing populations in contemporary societies. My point of departure was that animal models embody therapeutic, techno-economic and cultural expectations of ageing research, particularly as these are re-invigorated by current attempts to manipulate or eradicate cell senescence. The paper suggested that to understand how animal models come to deploy such economic promises, it is necessary to analyse both epistemic practices of model construction and how those rely on the re-arrangement of human and nonhuman forms of life.

My key argument was that, to build a mouse model of frailty, researchers had to learn to 'think like a mouse', provisionally taking the animal's point of view to then efface that link and reconfigure the chain of reference. In building a mouse model of frailty, researchers scaffold epistemic claims embodied in existing mouse models of ageing against proposed mouse frailty measuring batteries to test the role of specific interventions of mechanisms on senescence and ageing. To do this, it is necessary to understand how particular procedures and tests can be deployed on individual mice; to understand in this situation is not simply a cognitive operation but entails a pragmatic, fully embodied grasp of the mouse's world, its *Umwelt*. It is from this perspective that it is possible to build a - pragmatic - evaluation of the model being built, of its precise chains of translation, i.e. of its strength and limitations.

Thus, the aim of the paper is not to deny the scientific value of mouse models of frailty but to make visible and *understandable* how they are built through a reflexive embedding of their own representational specification, that is to say, of the various, limiting conditions under which it is possible to claim that a finding in the mouse pertains to human frailty and ageing. In this, the paper is aligned with Stengers' (2018) aim to introduce a politics of slowness in the contemporary sciences, a particularly important intervention to attempt in biology of ageing, as it becomes captured by accelerating 'translational research' frameworks and institutions. Such frameworks entail a thinning of 'ambition' and scope of experimental biology of ageing and its opening, generative capacities as it becomes locked into trying the solve the 'problems of [human] ageing'. They also entail a lock-in on a limited range of possible futures for ageing selves as an experiential horizon.

Such lock-in processes prevent biology of ageing from taking seriously the question of mouse or animal ageing for its own sake. In the same way that animal behaviour research configured experimental devices so as to avoid "the questioning on the subject of the rat" (Despret, 2015: pg#), mouse models of frailty serve only as translation instruments for human-centred questions. The paper opens up and analyses the establishment of zones of transaction and equivalences researchers build across humans and mice by coming to understand and care for the mouse *Umwelt*. In this respect, the paper suggests that, while the concept of entanglement might not directly lead to new formulations of new socio-natural worlds, the description of the entanglement that is embedded in the making of models might start a re-negotiation of the roles of the entities of the chain of reference, and perhaps a thorough *ratification* of frailty. It is my wish that this reframing of frailty might re-open the question of ageing itself, not only in the bio-clinical field but more widely in ageing studies, including those taking a social or cultural perspective.

Data availability

Data will be made available on request.

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