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The Role of Biological Plasticity in Model-based Translational Research

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Abstract

Reports of low replicability and translatability of biomedical research have called the value of animal models into question. The problems are real, but abandoning animal research is not the solution. Rather, improving the translatability of model-based research requires attention to relevant differences between humans and models, and to attributes of the models themselves that are essential to both robust science and effective translation. One is biological plasticity, the responsiveness of individual organisms to complex and variable environments. Though under-represented in model systems (for both historical and practical reasons), plasticity is central to human biology. While there are good reasons to minimize environmentally-induced variation in model-based research, doing so may undermine its translatability by eliding the kinds of external influences that are critical to human development, health, and disease. Accounting for plasticity can strengthen both the replicability and the translatability of model-based studies; this paper identifies strategies for doing so at each stage of the research process.

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1. Introduction

In recent years, emerging information about low replicability and translatability of biomedical research in animal models has prompted some to question their utility (Greek and Menache 2013; Pound and Ritskes-Hoitinga 2018). While the problems are real, the answer is not to give up animal studies. Rather, improving the translatability of model-based research requires paying attention to attributes of the models themselves that are essential to both robust science and effective translation (Domínguez-Oliva *et al.* 2023; Garner *et al.* 2017; Pallocca, Rovida, and Leist 2022; Robinson *et al.* 2019; Ferreira *et al.* 2020).

One such attribute is biological plasticity, the responsiveness of individual organisms to complex and variable environments. The effects of plasticity may be adaptive, negative, or neutral (for example, learning and acquired immunity are adaptive; PTSD and anaphylaxis are not). Plasticity is ubiquitous, and recognition of its importance in ecology, evolution, conservation, and medicine is now widespread (Gilbert and Epel 2015; Guidi *et al.* 2021; Levis *et al.* 2018; McCarthy and Birney 2021; Nobile, Di Sipio Morgia, and Vento 2022; Uher 2014; Sultan 2015; West-Eberhard 2003). In particular, environmental influences generate critical variations in development, health, and disease between individuals and across human populations.

In contrast, model systems used for biomedical research are constructed to minimize variation. By deliberate design and as a consequence of their history (which species are chosen, and what happens to them once they enter the research ecosystem; Bolker 1995; Krinke 2000; Logan 2002), models typically show limited phenotypic variation and

Box 1: Plasticity and validity

Study design, including model choice, dictates what form of validity can be claimed for the results. (For discussion and definitions of validity, see Garner *et al.* 2017; van der Staay, Arndt, and Nordquist 2009; Würbel 2017).

Structural validity in a study of plasticity requires that the model and target species share mechanisms for transducing environmental signals into phenotypic changes. The cues and outcomes may differ. For example, while the adrenocortical stress response is conserved across vertebrates, the identity of stressors and external manifestations of stress are shaped by each species' evolution and by individuals' prior experience.

Predictive validity, especially in a biomedical context, does not require that the cue and mechanism match precisely between model and target: a bioassay or screening study can yield useful outcomes (such as predictions about efficacy or toxicity of a drug candidate) even if we do not fully understand how it works. However, the range over which predictions are reliable is difficult to assess without some understanding of mechanism.

Internal validity – replicability and robustness of results – can theoretically be achieved by standardizing or controlling all possible variables. To account for the possibility of plasticity in the study system, it is important to record standardized (and even presumably irrelevant) factors as well as deliberately controlled or manipulated variables. Such background information can also support *post hoc* analysis if experiments stop working or cannot be reproduced in other labs.

External validity corresponds to exportability or translatability, and is often assumed for models where structural validity has been established. Structural validity alone does not guarantee successful translation. To warrant claims of external validity, model-based studies should describe support factors as well as focal mechanisms, noting that support factors for a shared mechanism may differ between species.

relatively little plasticity: they are inherently robust to environmental variation, and embedded in systems of standardized husbandry, genetics, and research practices. For some models, generations of breeding and selection in laboratory environments – the process of "laboratorization" (Robinson 1965) – may have rendered them even less flexible than their wild relatives. These attributes have many benefits: they can increase statistical power, reduce animal numbers and costs, streamline husbandry, and facilitate replication. Such practices are key to stabilizing phenotypes, especially traits that might vary in response to environmental factors.

However, deliberately removing plasticity from model systems has epistemic as well as biological implications: how we use models can weaken their external validity by eliding external influences that are critical to human biology (Voelkl *et al.* 2020b; 2020a; 2020b; Voelkl and Würbel 2016; 2021). While standardized models maintained in constant environments are excellent tools for studying molecular pathways and other internal mechanisms, they are poorly suited for questions where plasticity matters – or might matter. Researchers may fail to recognize the existence or importance of environmental influences simply because their models render such effects invisible. To counter this bias and increase the chance that results from a model system will translate to humans, it is essential to consider plasticity at each stage of the research process.

2. Planning: Is Plasticity a Question or a Challenge?

Choosing a suitable model – the right tool for the job – depends on the research goal: what the question is, and what sort of answer is desired (Bolker 2014; Clarke and Fujimura 1992). Articulating what role the model will play in addressing the question is central to identifying criteria for model choice, as well as assessing the strengths and limitations of whatever model is selected (Bolker 2009).

If the question is about plasticity, then the model needs to match the target with respect to relevant plasticity-related traits. To begin with, it is helpful if the degree of environmental responsiveness is broadly similar between species: using an inflexible model to represent a highly plastic target is not ideal.[a] (If doing so is unavoidable, the implications of this disparity need to be recognized and addressed.) Not everything needs to match: the mechanism that transduces environmental information into a shift in the phenotype or biology of the model need not be identical in model and target, unless that is what the study is about (Box 1). Conversely, if the research centers on transduction mechanisms, it does not matter if the cues or specific outcomes are different provided they operate via the same pathways: structural validity requires similarity of mechanism, not identical inputs and outputs.

[a] This is especially tricky in translational research because humans are much more plastic than most common animal models.

Table 1: What does it mean to "know your species"?

Aspect	***Why it matters***
Phylogenetic and taxonomic position	Informs expectations for exportability, depending on how the model is being used Identifies ancestral vs. specialized traits Documents taxon-wide characteristics (e.g. physiology, life history strategy)
Timing of lineage divergence between model and target species	Provides context for patterns of trait similarity and divergence across clades Describes how long model and target have been evolving independently
Evolutionary history and known or inferred selection pressures in the wild	Helps identify adaptations with implications for model use and/or husbandry practices Suggests behavioral and other preferences that may reflect adaptations to evolutionary niche Guides the search for models with adaptations that make them especially useful (Krogh models)
History of laboratory strains: origins, genetics, breeding, selection in lab environments	Highlights ways laboratory animals may diverge from their recent (wild) ancestors, e.g. genetic bottlenecks and intense selection for tractability under lab conditions Identifies deliberate or incidental selection pressures in research environments that may reduce plasticity in lab strains, leading to an underestimate of its importance in ancestral or "wild type" lineages
Sensory and physiological range	Informs husbandry practices that maximize well-being and reduce stress Enables the design of experimental stimuli and assays that align with subjects' sensory capabilities

How can one choose an appropriate model for studying mechanisms of plasticity, if the research objective is to discover what the mechanisms are, or details of how they operate? One approach is to consider the evolutionary origins of each species' plasticity, and the role and context of the trait with respect to species-specific natural history (Bolker 2019; Levis *et al.* 2018). This is analogous to the strategy recommended by Blanchard and Chalfin of studying functionally and ecologically relevant behaviors in model animals, rather than relying on superficial similarities to humans (Blanchard, Summers, and Blanchard 2013; Chalfin *et al.* 2014). Importantly, similar environmental cues may have disparate impacts in different species (or lab vs. wild populations) as a consequence of their different evolutionary histories – and human evolutionary history, especially in relation to health and disease, is particularly complex (Benton *et al.* 2021; Natterson-Horowitz *et al.* 2023).

One strategy for bolstering the ability of animal models to represent human targets is to assess environmental information in a species-agnostic or at least a translatable way, recognizing that different animals have different needs and different perceptions of the world (Keijer, Li, and Speakman 2019; Makowska and Weary 2019; Yong 2022). For example, "thermoneutral range," "normal social context," "expected microbial exposure," and "low-stress environment" all have species-specific values, ranges, or definitions (Garner *et al.* 2017; Gordon 2017). Performing physiological experiments within the thermoneutral range, or providing adequate nutrition, does not require that temperature or diet be the same for every species: it means that these environmental factors need to be in a species-appropriate range for each of them. This requirement extends to social arrangements. For instance, the presence of other mice improves recovery in a murine cancer model (Hermes *et al.* 2009; Kerr *et al.* 1997), but while pet mice might conceivably enhance recovery in people with cancer, what is relevant to patients is support from other humans (Kroenke *et al.* 2006).

Determining what is species-appropriate requires understanding the species' natural history and evolution [Table 1]. Knowledge of species-specific needs is already built into many husbandry protocols (*e.g.*, provision of adequate nutrition via customized commercial feeds, and physical environments that support the expression of natural behaviors). The natural history and evolution of particular models can have paradoxical implications for how we maintain and use them: for example, the evolution of mice as small ground-dwelling scavengers able to thrive in a microbe-rich environment explains their high tolerance for bacterial toxins (Mestas and Hughes 2004; Perlman 2016; Webb *et al.* 2015). In fact, the per-kilogram dose of endotoxins sufficient to trigger an inflammatory/immune response in mice is far

higher than in humans (Mestas and Hughes 2004; Webb *et al.* 2015). However, laboratory mice raised under standard husbandry practices that strictly limit pathogen exposure have immune systems that never mature to the normal level for an adult mouse (or human) (Beura *et al.* 2016; Reese *et al.* 2016) – though development in the uterus of a wild surrogate yields lab mice with normal adult immune function (Rosshart *et al.* 2019).

If the research question is not centered on plasticity, it is essential to consider whether plasticity might impact the trait or phenomenon anyway, and how to account for that possibility in the study design. Traits or systems that directly mediate an organism's interaction with its environment (via sensory, neurobehavioral, or immune systems) are especially likely to have undergone selection for plasticity (Bolker 2019). But there is no simple, predictive rule. One can look for evidence of plasticity in related species, as well as in more distant taxa with evolutionary histories shaped by similar selection pressures: while not definitive, the occurrence of plasticity in either of those groups can provide clues about its possible role in the prospective model species. Plasticity itself can evolve, certainly at highter taxonomic levels but also potentially between wild and lab-selected lineages (Krinke 2000; Levis *et al.* 2018; West-Eberhard 2003). Here, again, it is critical to know your species [Table 1].

Besides knowing about their species, researchers need to know about the environment in which animals are housed and data collected. Laboratory conditions may generate confounding variation: statistical noise can result from acoustic noise (Lauer *et al.* 2009; Parker *et al.* 2022; Pfaff 1974), or interfere with animals' normal biology in ways that increase stress and/or energy expenditure (Garner *et al.* 2017; Gaskill and Garner 2017; Gordon 2017; Lac, Tavernier, and Moro 2023; Mo, Renoir, and Hannan 2016; Toth 2015). The traditional approach has been to try to standardize everything (Festing 2014; Festing and Altman 2002) – which certainly has advantages, but (besides tending to mask plasticity that might be present) this strategy may miss factors that are not recognized *a priori* as important: the "unknown unknowns" (Mogil 2017).

A dramatic example of an unrecognized but powerful influence was the realization that "standard" commercial rodent feeds contain high and variable levels of phytoestrogens (mainly from soy) that can confound research in areas from cancer to endocrinology (Heindel 2008; Ruhlen 2008). Paradoxically, providing soy-free diets to lab rats induces obesity, likely via perturbation of fetal metabolism; Ruhlen *et al.* suggest that this unexpected result might reflect prior adaptation of lab-bred strains to high phytoestrogen intake from commercial feeds (Ruhlen 2008). Dietary levels of phytoestrogens during pregnancy and early development can have profound impacts; however, researchers purchasing animals from commercial suppliers rarely have access to information about this key environmental variable (Heindel 2008).

Trying to eliminate variation runs the risk of missing some of the sources (such as phytoestrogens in rat chow). Another approach is to deliberately introduce variation in an explicit, systematic way, or attempt to distribute preexisting variation evenly via heterogenization (van der Staay, Arndt, and Nordquist 2010; Richter, Garner, and Würbel 2009; Richter *et al.* 2010; 2011; Würbel 2000). This strategy can potentially account for sources of variation that have yet to be recognized.

In addition to increasing overall variation, plasticity in individual research subjects can lead to results that reflect environmental variation in a systematic way, and can confound or eclipse the effects of the focal experimental variable (Mo, Renoir, and Hannan 2016; Mogil 2017; Toth 2015). Randomizing the placement of subjects or treatment groups within the environment (*e.g.*, locations of plots, tanks, traps, cages on racks) is important, but cannot eliminate biases related to experimental or observational techniques *per se*. For example, experimentally-modified and control animals might differ in their susceptibility to stress from handling or administration of placebo treatments; there can also be significant differences between individuals (Andrews and File 1993; Aydin, Frohmader, and Akil 2015; Hurst and West 2010). Even within individuals, details such as the exact location of injections can have unexpectedly significant effects (Auerbach 1978).

Determining what degree of standardization is appropriate for a given study is context-dependent and difficult (van der Staay, Arndt, and Nordquist 2010). Standardization can reduce the number of animals used and enhance statistical power and the ability to detect small effects. But if the trait being studied is, itself, plastic, over-standardization can reduce external validity (especially translation to humans) and even mask the mechanisms one hopes to understand. The goal should be to "standardize, but not too much" (Bolker 2019; Richter, Garner, and Würbel 2009; Striedter 2022).

3. Performance: Collect Environmental as well as Experimental Data

Along with results of planned experiments, it is essential to document the context in which the study is carried out: environmental factors that might turn out to be relevant, or correlate with unexpected outcomes or variation (Toth 2015). For example, details of husbandry practices or characteristics of research personnel (such as their sex; Sorge *et al.* 2014), while rarely explicitly noted in study designs, can have significant effects on lab rodents and thus on study results (Mogil 2017).

What data are worth collecting? Start by considering what environmental information is known or suspected to matter to the organisms in question. Toth and Neville *et al.* survey the importance of rodent cage environments to the reproducibility of preclinical studies (Neville *et al.* 2023; Toth 2015), and Mogil (2017) reviews external factors that affect the outcomes of pain studies in mice. Notably, both the magnitude and the direction of environmental effects can vary by genetic strain (Crabbe, Wahlsten, and Dudek 1999; Crawley *et al.* 1997; Mogil 2017).

The already long, but likely still incomplete, list of environmental factors that are known to matter suggests that there are a lot of things researchers should be tracking (and describing in published methods), from animal housing and handling to data about the physical environment (Toth 2015; Neville *et al.* 2023; Sundberg and Schofield 2018). Critically, we need to be thinking about this from the perspective of the animals, and collecting data within the species' sensory range, for instance measuring acoustic noise across frequencies audible to rodents (Lauer *et al.* 2009; Parker *et al.* 2022; Turner 2020). Even if mice in a research study are serving as surrogate models for humans, they experience their environment *as mice*: what counts as a normal or a stressful noise level, temperature range, or housing situation for them is not the same as what counts for us (Fischer, Cannon, and Nedergaard 2018; Garner *et al.* 2017; Keijer, Li, and Speakman 2019; Yong 2022; Weber *et al.* 2017)... and what seems normal to a laboratory-bred rodent may differ from its wild ancestors' natural environment, given the divergent selection pressures acting on research populations (Krinke 2000).

As a start, animal facilities should incorporate routine, automatic, continuous monitoring of physical variables such as temperature, humidity, and ambient light and noise. Inexpensive data loggers can be installed in each cage or enclosure, or at least in each room where animals are used (ideally in multiple locations). Time-stamped environmental data from husbandry facilities could be collected as part of routine management, and made available to everyone who has research animals housed there.

Time, itself, can also be an important variable. The developmental stage at which animals are subjected to stressful shipping or procedures can affect their physiological response (Beery 2018). At a smaller scale, the time of day at which data are collected can determine what the data look like: circadian clocks regulate key processes ranging from behavior to cell proliferation to drug response (Andersen 2023; Lévi *et al.* 2024; Sato and Sato 2023).

The biotic environment should be tracked and accounted for as well. Perhaps the most obvious aspect is housing. Not only social vs. individual housing, but social dynamics within shared cages, significantly affect the biology of lab rodents (George, Padilla-Coreano, and Opendak 2023; Arakawa 2018; Beery *et al.* 2020; Kerr *et al.* 1997; Manouze *et al.* 2019; Mo, Renoir, and Hannan 2016; Mogil 2017; Mumtaz *et al.* 2018).

Along with intraspecific interactions, it is critical to consider the influence of other species – particularly microbes (Honda and Littman 2016). Pathogens are routinely monitored in animal facilities, but we should also track at least some of the vast array of commensal and symbiotic species. Microbial communities play crucial roles in the development and function of macroorganisms, shaping host phenotypes at both morphological and behavioral levels, and they can be an unrecognized source of variation in rodent models (Franklin and Ericsson 2017; Gilbert and Epel 2015; Honda and Littman 2016; Kim *et al.* 2017; Shin Yim *et al.* 2017; Witjes, Boleij, and Halffman 2020). Analyzing environmental DNA collected via air filters (as well as routine samples of bedding, surface swabs, etc.) could track the presence, and potentially the abundance, of different microbes at housing or research sites (Albers *et al.* 2023; Ruppert, Kline, and Rahman 2019). The rapid expansion of research on the laboratory animals' microbiomes will shed light on a key aspect of model-based research, in addition to addressing the specific questions targeted in each study (Honda and Littman 2016).

Another aspect of the biotic environment that we may underestimate is the range and impact of odors in housing and testing facilities. Humans are not very good at odor detection, but other animal species are exquisitely sensitive to chemical signals, and rely on them to modulate their behavior and physiology (Yong 2022). Engineering approaches

to odor monitoring focus primarily on chemicals that are detectable by and/or immediately relevant to humans, but in principle the technology could be modified to monitor odors that are detectable by, and may be important to, laboratory animals (Reimringer *et al.* 2022). This would, of course, depend on deciding exactly what should be monitored – which brings us back to unknown unknowns. We could start with a "candidate odor" strategy (analogous to candidate gene approaches), for example monitoring known pheromones, stress hormones, and other molecules with demonstrated impacts on recipients' biology.

Routinely collected environmental information may retrospectively identify a factor that was not intended as a variable, but that turned out to influence results. However, it is unwise to go on a fishing expedition in search of environmental correlates for otherwise unexplained outcomes, in hopes of finding a statistically significant relationship to cite as a cause. Such correlates should be treated as only preliminary or suggestive, if they are not what the study was originally designed to evaluate. For example, if the study did not set out to measure the effects of different bedding materials, but effects seem to have occurred, a subsequent experiment can be carried out to directly assess the effects of bedding under conditions that (otherwise) match those of the original study. Any significant findings from a robust study designed to test the effect of bedding may then shed light on previous work where bedding might have been an uncontrolled but significant variable (*e.g.* Kondo, Kropik, and Wong 2022; Sláma 1966).

4. Interpretation: Accounting for Plasticity as a Possible Cause of Observed Effects

If a study was designed to examine plasticity, interpretation of the results should consider not just individual and internal mechanisms, but also environmental factors that may have contributed to the observed outcome. Beyond the variables whose effect the study is designed to test, it is essential to address other aspects of the environment that may serve as support factors that enable particular outcomes (Cartwright and Hardie 2012). Rather than considering the environment as outside the frame of a study, we need to start thinking about it as part of the frame – or even part of the picture (Bolker 2014).

Considering plasticity can be crucial even for studies that are not designed to assess it, particularly when such studies yield unexpectedly variable or contradictory results (Jaric *et al.* 2022; Voelkl and Würbel 2021). Plasticity is one possible explanation for observed variation. However, caution is required when drawing conclusions about the importance – or irrelevance – of the environment from studies that were not deliberately designed to assess plasticity. While environmentally-driven mechanisms may well help explain observed variation, lack of variation does not necessarily imply lack of plasticity, because standardizing the study environment also standardizes plastic traits. This constitutes an absence of evidence for plasticity, not evidence of its absence. If statistical analysis suggests the existence of batch effects, plasticity in response to unrecognized environmental factors or biases should be considered as a possible cause (Randall *et al.* 2019). Alternative explanations (unrelated to plasticity) could include equipment calibration, variation in reagents, or other factors independent of biology.

Failures to replicate previous work can be due to unrecognized environmental factors. Details of animal husbandry protocols, handling during experiments, and microbial exposure are often omitted from published descriptions of methods because they are assumed to be constant and/or unimportant. That assumption may need to be revisited, and both the original study and the attempted replication scrutinized for potentially significant environmental factors (Jaric *et al.* 2022; Neville *et al.* 2023). (The more thoroughly such factors were monitored and recorded along the way, the easier this will be.) Even in cases where the environment plays no causal role in producing an outcome, it may still provide support factors for conserved mechanisms, thus determining the exportability or translatability of findings to other species (Cartwright and Hardie 2012). Absence of essential support factors can lead to replication failure, even if the mechanism being studied is present.

Environmental standardization is often a deliberate strength, not a weakness, of a particular study, but this approach may limit translatability. Translating results from a tightly controlled model to a highly variable target species is an epistemic challenge; bridging the gap requires understanding the scope and nature of plasticity on both sides. Plasticity need not diminish exportability: what is critical is to identify potential sources of plasticity, and either standardize them, randomize their impacts through systematic variation, or align them appropriately between model and target (Duncan and Keller 2011; Richter 2017). The premise that plasticity is not relevant to a given study needs to be explicit and justified, not just an assumption based on the use of a carefully standardized model species in a tightly controlled environment. Thinking through

ways in which plasticity *might* matter is essential to assessing the extent to which findings from such model systems may be exportable – especially how well they will translate to notoriously flexible and un-standardized humans.

5. Summary and Conclusions

Both the history and the current practice of model-based research focus on standardization and internal processes (Bolker and Brauckmann 2015; Logan 2002). This approach has yielded deep insights into traits and mechanisms that have strong genetic bases and little external connectivity. As described by Ankeny and Leonelli, the standardization, isolation, and artificiality of model species generate a form of "placelessness" that is central to their explanatory power and broad acceptance (Ankeny and Leonelli 2020). From a biological perspective, however, "place" matters a great deal. There is thus a tension between the placelessness researchers attempt to construct (and then implicitly assume) in model-based research, and their ability to draw conclusions about species or phenomena in which the environment plays an important role. Moreover, we find ourselves with a set of dominant models that are generally poorly suited for studying plastic traits (Bolker 2017).

Why does it matter how much plasticity there is in a model species, especially if it does not appear to affect the results of a given study? Many aspects of human health – from immunology (Martin *et al.* 2021), to neuropsychiatric disorders (Uher 2014; Assary *et al.* 2018), to racial disparities in pregnancy outcomes (Leimert and Olson 2020) – depend heavily on environmental factors and gene-by-environment interactions (Benton *et al.* 2021; Duncan and Keller 2011; Guidi *et al.* 2021). Research strategies that seek to understand the underlying mechanisms while ignoring or eliding plasticity are unlikely to succeed. Environmental influences, and plastic biological responses, are central to many of the questions we want to answer in humans: What are the underlying mechanisms of immunological and neuropsychiatric disorders? What causes cancer? What factors influence the onset and progression of chronic disease? What determines whether the presence of genetic risk factors ultimately leads to disease in particular individuals (McCarthy and Birney 2021)?

The solution is not to give up on these questions or on widely-used, powerful models. Rather, recognizing the potential role of environmental factors and integrating that knowledge into the design, performance, and interpretation of experiments can give us the best of both worlds. A "yes-and" approach to biomedical research means studying humans whenever and however we can, and employing animal models in ways that are most likely to yield translatable knowledge. Accounting for plasticity can both improve the translation of model-based research to humans, and expand our understanding of the fundamental biology of all species.

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