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Ethical and legal considerations of digital animal models: pioneering reduction and replacement

Federico Germani ¹,
 Julian W. März ^{1,2,3},
 Alessandro Luciani ⁴,
 Olivier Devuyst ⁴, and
 Nikola Biller-Andorno ^{1,2,3,*}

The development of digital animal models represents a promising avenue for advancing the ethical principles of reduction and replacement in biomedical research. This paper discusses the potential of models built upon artificial intelligence (AI)-generated synthetic datasets simulating the characteristics and behaviors of model organisms, reducing reliance on live animals in research.

In 1959, the Principles of Humane Experimental Technique provided a framework for defining, designing, and implementing the 3R principles of Replacement, Reduction, and Refinement in animal research [1]. These principles have shaped and defined animal research since. With the advent of new technologies with established or putative potential for replacement, the principle of replacement – defined as the substitution, in research, of living animals by insentient material – has become a promising avenue to guarantee animal wellbeing and prevention of harm and suffering. The emergence of replacement technologies in the past two decades, most of which are based on advancing the *in vitro*/cell culture toolbox – including highly differentiated primary cell culture systems, stem

cell technology and three-dimensional tissue engineering such as organoids or organs-on-a-chip – has initiated a shift in focus to animal-free research, in addition to reducing harm to animals, which could potentially dissipate growing public concerns about the suffering of animals in laboratory settings. Despite recent developments in cellular systems and AI models, the use of animals still largely contributes to the advancement of human knowledge and understanding of biology and disease, balanced by limitations due to biological differences between species, inappropriate experimental settings, and the low translatability of much animal research into human findings [2]. These limitations, along with longstanding ethical concerns, have prompted scholars to question whether the continued reliance on animal models reflects scientific necessity or norms often mistaken for gold standards [3].

An exciting prospect is the development of what we call digital animal models. Here we define ‘digital animals’ as animal proxies generated by computational approaches. The development of such digital models will likely become a reality due to advancements in the generation of synthetic data through AI approaches [4], where synthetic data, obtained through computer algorithms, mimic the characteristics and simulate the underlying properties of real data [5]. Synthetic versions of real datasets can find diverse applications in medicine and biology, including drug discovery, clinical trial design, and re-analysis of clinical trial data [4]. In genomics, the emergence of DNA sequencing, RNA sequencing, and proteomics, have paved the way to the more recent development of single-cell DNA sequencing, single-cell RNA sequencing (scRNA-seq), single-cell proteomics, single-cell epigenomics, with sensitive epigenetic profiling of single cells, or single-cell ATAC-sequencing to evaluate chromatin accessibility. The combination of synthetic data technology with these tools, which generate large

volumes of data, have been combined to generate synthetic single-cell DNA sequencing, synthetic single-cell RNA sequencing, and will likely pave the way to the generation of synthetic single-cell proteomic or epigenomic data, too, in the near future. Synthetic transcriptomes have been shown to retain the characteristics or real data, maintaining a similar correlation between differentially expressed genes as for real data [6], although it is still difficult to make inferences from small to larger datasets [7]. By integrating multiple layers of biological information, beginning with data obtained from real animal or cell systems, it could be feasible to create digital versions of these models. These would comprise extensive, combined datasets, accessible for analysis by researchers. This could be achieved through an interface that unifies all layers of data into a single, accessible digital representation of the animal or cell.

Developing digital models of organisms could pave the way towards the development of digital organisms of increasing complexity. As a descriptive example, the nematode *Caenorhabditis elegans* possesses only 302 neurons. Despite the limited number of neuronal cells compared with more complex organisms, behaviors observed in nematodes are rather complex: nematodes can memorize information in the long-term, display associative learning [8], and pass several common criteria of pain sentence (Box 1). Depending on the sex, *C. elegans* is composed of exactly 959 somatic cells in self-fertile females, or exactly 1031 cells in males, plus about 2000 and 1000 germ cells, respectively. From the fertilization of the egg, each division is known and each of the final count of cells can be traced backwards, with the fate of each cell being predictable. Researchers generated a cell atlas at single-cell resolution, based on the single-cell analysis of the transcriptome, analyzing 50 000 cells [9]. This analysis can be further refined by scRNA-

Box 1. Biological basis for ethical concerns of using ‘simple’ animal models in research

Animals possessing the characteristics described for nematodes are regarded by many ethicists as warranting moral consideration. Thus, the use of nematodes in scientific research might itself pose a moral problem, which would be solved by replacement with a digital nematode. Similarly, fruit flies and bumblebees have been found to display potentially emotional attitudes such as fear, pessimism, and optimism. Although ethical concerns with a view to using nematodes as well as fruit flies and other insects still tend to be neglected, these concerns may well be legitimate. Further, research on the emotional experiences and cognitive abilities of fish, particularly zebrafish, has gained attention in recent years. Zebrafish have been found to exhibit behaviors and physiological responses that indicate the presence of fear and emotions. For instance, zebrafish larvae and adults can display avoidance behavior, stress responses, and changes in neurotransmitter levels when exposed to aversive stimuli or stressful situations. These responses suggest a capacity for experiencing fear and potentially other emotional states.

seq analysis of specific tissues and has been used to describe molecular profiles of all neurons [10]. The same analysis can be performed at any stage of *C. elegans* development, potentially obtaining a dynamic, time-dependent scRNA-seq analysis that reconstructs the entire development process. This led to a complete lineage analysis of *C. elegans* embryogenesis with single-cell resolution [11]. Analysis based on *C. elegans* is just an example of what can be achieved with other complex systems, including *Clytia hemisphaerica*, a hydrozoan medusa, or the fruit fly *Drosophila melanogaster*. *C. elegans* has been chosen here as an example as a combination of the exact knowledge of the number of cells in the nematode, combined with the potential to understand the nature of individual cells – in terms of genome, RNA expression, or protein content – could lead to a workable digital model of a worm.

Digital models, such as the digital nematode in our example, could be useful for multiple experimental tasks. Most biological research focuses on how genes and their products contribute to traits linked to diseases or behaviors. Synthetic data and digital animal models could allow researchers to explore these relationships predictively. For example, working on digital animal models could help model and predict how a single gene mutation affects development or behavior, including changes induced at the molecular level.

The journey of developing digital animal models might be in its beginning, but if

the rapid acceleration in AI has taught us anything, it is that we need to anticipate technological advancements and prepare the groundwork for discussion ahead of time. Despite the promises of digital animal models, their use in biomedical research and drug development would raise several ethical and legal issues (Box 2). While data ownership and civil liability are fundamental issues across all data-driven research, digital animal models may pose distinctive challenges due to the layered nature of their construction. Unlike AI applications

operating within one domain (e.g., imaging or genomics), digital animal models might integrate multiple biological levels (genomic, transcriptomic, proteomic, epigenomic, and behavioral) into a unified representation. This mosaic of data types and sources, with varying usage licenses, complicates data provenance and ownership claims. Moreover, the synthetic nature of these data may blur the boundary between derived and original content.

Furthermore, the generation of digital animal models and associated data should adhere to the principles of open science. Making AI-generated data, code, and digital tools publicly available would enable researchers to build upon existing work, fostering collaboration and accelerating the refinement and usability of digital animal models. Finally, the issue of liability for ensuring the integrity, quality, and representativeness of data used to build digital animal models is of fundamental importance: compromised quality in digital

Box 2. Ethical and legal issues related to digital animal models

The development and implementation of digital animal models raise a range of complex ethical and legal questions that must be addressed to ensure their effective and responsible use. Since these models have the potential to inform biomedical research, regulatory testing, and drug development, it is essential to clarify how issues of civil liability, regulatory standards, intellectual property, and accountability and trust should be addressed. Next, we outline key challenges in each of these domains.

Civil liability is one of the most pressing concerns. If a digital animal model produces misleading results – for instance, in a preclinical safety analysis – and a human trial participant is subsequently harmed, it remains unclear who would bear legal responsibility. Would this lie with the producer of the AI-based system, the researcher or institution using the model, or the creator of the primary data on which the model is built? Establishing accountability is critical, as breaches in data integrity, quality, or representativeness could have profound scientific and clinical consequences.

Closely related is the issue of regulatory acceptance. Regulators will need to determine the conditions under which digital animal models may be used in the testing of medicinal products. This includes defining clear validation standards, determining acceptable levels of predictive accuracy for safety and efficacy, and assigning responsibility for any adverse outcomes linked to regulatory reliance on digital animal models. The absence of such standards could impact both innovation and public confidence.

The matter of intellectual property rights introduces another layer of complexity. Beyond questions of ownership of the algorithms and data sets that underpin these models, issues such as licensing terms, rights to use synthetic data in commercial contexts, and restrictions on sharing derivative works must be clarified. Without clear frameworks for managing these rights, the development and collaborative use of digital animal models could be slowed or fragmented.

Beyond legal frameworks, the success of digital animal models will also hinge on user trust and acceptance. Researchers must be confident that these systems are scientifically reliable and that they are adequately protected from potential legal complications. Likewise, the endorsement of research funders and investors will be critical for broader adoption.

animal models can hinder scientific progress and may lead to the generation of false knowledge. Responsibility for data quality standards rests with researchers and private companies that may collaborate on the generation of digital animal models.

Another significant consideration concerns public trust and acceptance. Digital animal models could offer potential advantages that can enhance public support, particularly from animal activists and advocates. They may provide an alternative avenue for scientific advancements, minimizing harm to animals and potentially leading to more humane approaches in biomedical research. In general, however, it remains unclear how patients and the broader public would perceive a shift toward digital animal models in preclinical testing. While some may welcome such approaches as more humane and technologically advanced, others may express concerns about safety, transparency, or the perceived reliability of AI-generated models. While the concept of digital animal models may be too novel for studies on trust in this specific context, research on public trust in AI in healthcare offers useful parallels. These studies often reveal a mix of fascination and optimism as well as concerns about transparency, explainability, and safety (such as in the context of AI-assisted medical diagnosis) [12,13].

It will be crucial to address these concerns and communicate the benefits and limitations of digital animal models to ensure public trust and acceptance. Establishing clear

guidelines, standard operating procedures, and quality control measures could enhance user trust in these models.

Conclusions

The possible development of digital animal models holds significant potential for advancing the ethical principles of reduction and replacement in biomedical research. These models could offer a virtual platform to study biological systems, reducing the reliance on traditional animal experimentation. However, their implementation would raise ethical and legal concerns. Robust frameworks for data use rights, maintaining data quality standards, building user trust, and ensuring public acceptance would be essential steps towards ensuring the benefits of implementing and using digital animal models in research.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process

During the preparation of this work, the author(s) used artificial intelligence large language models to assist with the editorial revision of the manuscript and to enhance language clarity. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Declaration of interests

The authors declare no conflicts of interest.

¹Institute of Biomedical Ethics and History of Medicine, University of Zurich, Zurich, Switzerland

²Digital Society Initiative, University of Zurich, Zurich, Switzerland

³Competence Centre Medicine – Ethics – Law Helveticae

(MERH), University of Zurich, Zurich, Switzerland

⁴Mechanisms of Inherited Kidney Disorders Group, Institute of Physiology, University of Zurich, Zurich, Switzerland

*Correspondence:

biller-andorno@ibme.uzh.ch (N. Biller-Andorno).

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