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Integrating Social Determinants of Health into Ethical Digital Simulations

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In their article, Cho and Martinez-Martin (2023) argue that developers and users of digital simulacra for modelling health and disease should involve a continued focus on *causality* of health states, including epidemiological factors with ethical and social justice implications. The authors contend that this requires model developers to move beyond narrow performance metrics so that performance evaluation standards better reflect patient, clinician, and community values and dynamics. As researchers, clinicians and legal scholars deeply involved in examining the ethical implications of digital health technologies including digital representations of patients via digital phenotyping and other forms of computer perception, we agree with Cho and Martinez-Martin's solutions and wish to highlight some practical challenges, as well as offer recommendations at government, developer and user levels for acknowledging the critical role of social determinants of health (SDoH) in digital simulations.

LACK OF CONSENSUS STANDARDS

A first step to avoid reliance on narrow performance metrics is to identify what outcomes these metrics are/not measuring. To date, there are no consensus standards for evaluating the validity of simulacra. Given that the primary utility of digital simulacra stems from fidelity to human biology, assessing the credibility of simulacra for regulatory evaluation of biomedical products has become a major focus of research in both the US and Europe. The U.S. Food and Drug Administration (FDA) recognized in 2017 (US Food and Drug Administration 2017) that *in silico* testing/trials (IST) using "virtual patients" hold strong potential to lessen risks on human subjects, and later (US Food and Drug Administration 2021) issued Draft Guidance for Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions (US Food and Drug Administration 2021) as a framework for evaluating "non-clinical assessment models" (NAMs) with potential to supplement or eventually replace traditional randomized controlled trials (RCTs). The FDA is also part of the larger Medical Device Innovation Consortium (MDIC), a public–private partnership involving industry, nonprofit organizations, and federal agencies focused on facilitating validation and acceptability of computer modeling and simulation in clinical trials. A significant portion of these initiatives, also underway in Europe (Viceconti, Henney, and Morley-Fletcher 2015), is devoted to identifying standards for verifying and validating computational models and for quantifying and reducing uncertainty (potential sources of stochastic error) (Viceconti et al. 2020). So far, however, we lack reliable and consistently applied methods to ensure "that virtual patients are similar, in a precisely defined way, to real patients (Faris and Shuren 2017).

CAUSAL OPACITY & SOCIAL DETERMINANTS OF HEALTH (SDOH)

As consensus standards evolve, the developer community should consider factors that are often *excluded* from even the best simulacra models, such as those relating to SDoH or environmental health variables that remain enduringly difficult to measure and quantify but greatly impact population health outcomes. As Viceconti et al. (2020) point out, approaches to quantifying metrics of fidelity have largely been formulated

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for physical engineering systems. Simulacra of mechanical systems such as airplanes or ships draw on known causal principles of physics to make reliable predictive models of performance. This causal understanding helps to evaluate model validity, measured by metrics like uncertainty quantification and sensitivity analysis that account for how much error due to unexplained variability in outputs is likely to impact outputs for real-world objects (planes, ships, etc.) with those same specifications.

Such models of causality are far less established in medicine, where human physiology and disease are not purely mechanistic but have complex political, economic and social etiologies. SDoH for example, are notoriously difficult to measure (Marmot 2005) and are therefore more likely to go unrepresented in training data sets and models used to inform digital simulacra. Indeed, the MDIC's "Landscape Report" on computational modeling and simulation in medical device development lacks any mention of SDoH. This is a critical limitation to the development of simulacra for human biological systems. Exacerbating the problem that these potential "root" causes of health and disease may be challenging to incorporate into digital models, Cho and Martinez-Martin argue that developers may lose interest in even trying, as predictive *associations* among more easily observed variables become more robust. We believe developers of simulation models should care deeply about causality, since establishing the "why" behind a model's outputs is critical for extrapolating and adapting them to new contexts and populations, where the parameters of key predictors will have to be modified accordingly. *Understanding causality allows for customization.*

However, we are still far from predictably modeling SDoH over the life course, particularly in ways that could be immortalized in a digital twin. This would require quantifying and digitizing central SDoH indicators (e.g. socioeconomic advantage, mobility, accessibility, social cohesion) and deciding how far up the ladder of causality to go, given the relationship of many SDoH to inequities in power, money and resources within and across nations. Failing to address these challenges limits the relevance and generalizability of simulacra across diverse populations. These complexities are significantly exacerbated in global health settings where simulation technologies could have great impacts but where representative data sets are lacking due to impoverished infrastructures and correspondingly poor population health record-keeping. In such contexts, digital simulacra cannot be evaluated for validity or generalizability because the necessary ground truths are simply undocumented. This limits the most sophisticated validation approaches and leaves real-world 'trial and error' as the only remaining option, with potentially negative consequences on local populations.

DATA (Un)AVAILABILITY

The above concerns will be familiar to those following recent ethical discourse and proposed regulations of artificial intelligence (AI) in healthcare and medicine. Rigorous scholarship (Buolamwini and Gebru, 2018; Obermeyer and Emanuel 2016) and media addressing algorithmic bias have raised public awareness about the need for developers to train computational models on representative data sets. This is especially important for foundational models which form the building blocks for downstream development and innovation. The vision is that, with enough training data, problems of bias, representation and generalizability may be overcome and computer models will be able to accommodate all—or an acceptable threshold—of individual heterogeneity. We now know that more data is not a panacea solution and that data must also be "high quality," defined by both computational and social justice (e.g. fairness) considerations (European Commission 2021). However, as we have previously argued (Blumenthal-Barby et al. 2022), ensuring high quality, representative data sets is not simply a matter of "choice" but shaped by socioeconomic and political forces that are often outside researchers' and developers' control. In most global settings (and the United States and Europe), essential data on SDoH do not exist due to imperfect documentation. In other cases, access to existing relevant datasets is limited by proprietary interests. Some of the richest data needed to train and develop digital twins, including multimodal data from wearables, mobile health applications, and direct to consumer genetic testing data, reside in private datasets controlled by commercial companies (e.g. 23andMe, Ancestry.com, Apple, etc.) and to some extent, by scientific societies who maintain data behind paywalls (even when those data are generated using public funds). A consequence is that developers do not always have easy access to the data they need to build broadly effective simulacra with widely generalizable benefits. This is both an ethical and practical problem that undermines the capacity of digital simulacra to fulfill its promise.

SOME WAYS FORWARD

We recommend three approaches for government, developers and users to responsibly advance simulation modeling: encourage data liquidity, integrate SDoH into simulacra models, and transparently communicate and consider system capacities and limitations.

First, while public funding agencies (e.g. NIH) could offer stopgaps by including data acquisition costs in research budgets, a more sustainable approach would be for governments to explore legislation or other incentives that encourage data liquidity, such as those emerging in the EU through the Data Governance Act (Commission E 2020). This Act aims to discourage data hoarding by incentivizing data sharing and by instituting (e.g. privacy-by-design) frameworks that promote greater transparency in data exchange and more democratized access to diverse data. Similar initiatives are also surfacing among industry and research partnerships (e.g. Owkin) and global data sharing initiatives (e.g. Global Alliance for Genetics in Health), for example using federated machine learning to balance proprietary interests with benefits sharing and enhance our ability to derive insights from larger, more diverse data sets.

Federally supported efforts to establish consensus standards for evaluation (e.g. European Medicines Agency; American Society of Mechanical Engineers) should also dedicate specific resources to ensure that simulation models integrate computational representations of SDoH and other hard-to-measure variables known to shape human biology and health. This is a tall order, given that studies that inform these efforts do not receive adequate funding at the national and international levels. This may be due in part to the likelihood that SDoH research draws attention to societal dynamics and inequities that are deeply entrenched and difficult to rectify. Still, it would not be an exaggeration to argue that responsible development of computer simulation requires political attention to the sources of socioeconomic inequity and more innovative policy approaches to data governance and exchange.

Rather than holding our breaths, the FDA may be called upon in the meantime to revisit and further clarify their viewpoint expressed in 2017, which is that imperfect validation methods and data sets should not be *de facto* showstoppers for medical device approvals informed by computer-based modeling. Specifically, they argued that "for devices for which some uncertainty remains after premarketing studies, postapproval registries may be helpful for providing additional confirmation of device performance." In other words, simulacra should not always be expected to be the *only* source of knowledge, and simulations may be approved with the expectation that real-world deployment will constitute an acceptable form of prospective validation. Clarity is needed around where the FDA, with its risk-based approach to regulation, plans to set approval thresholds of validity (fidelity to human counterparts) and uncertainty, given that these metrics and standards continue to be debated.

As regulatory and scientific standards remain in flux, we as developers and users of simulacra can assume certain norms and responsibilities in the interim. An important consensus takeaway from recent debates around machine trustworthiness is that developers should transparently communicate specific capacities and limitations of their systems (see for example Gerke (2023) "nutrition facts labels" for AI) to help end-users make responsible decisions about how to use a system. Transparency around a tool's intended uses, training data set composition, data processing approaches, validation settings and populations, etc. can prevent over- or under-reliance on models, as can strategic interface designs that encourage critical reflection and nonbias in decision-making (Kostick-Quenet and Gerke 2022).

Users have responsibilities, too. If developers provide users with information about system capacity and limitation, users have a responsibility (as Cho and Martinez-Martin point out) to critically engage with that information to make cognitive and moral decisions and to avoid over- or underreliance behaviors that can negatively impact patients and communities. We also agree with them that we cannot lose interest in causality, because "epistemological complacency," as we might call it, dissuades users from reflecting on the moral significance of our observations. Without this, simulacra easily become merely simulacrum, empty representations untethered from their distant originals.

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Digital Simulacra, Bias, and Self-Reinforcing Exclusion Cycles

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Digital simulacra present an entrancing vision of a research-rich future shorn of the messiness that comes from dealing with real live patients as part of the research enterprise—and in that shearing, Cho and Martinez-Martin convincingly lay out, lurks a host of potential ethical problems (Cho and Martinez-Martin 2023). We retain some scepticism about the epistemic limits of the underlying project; there seem especially high barriers to developing new knowledge about unknown biochemical reactions, given the limits of modelling and biochemical data for the foreseeable future. But assuming for the moment that these limits can be overcome, simulacra promise to enable many research tasks, deepen understanding, and facilitate

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