Federal Register Notice: 89 FR 51554, Federal Register :: Networking and Information Technology Research and Development Request for Information on Digital Twins Research and Development, June 18, 2024.

Request for Information on the National Digital Twins R&D Strategic Plan

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Comments on digital twins

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The “Ecosystem” topic seeks to establish a national digital twin R&D ecosystem that establishes inter-agency collaborations to address foundational research gaps. I believe this is a critical need, as differences in the challenges and use cases across applications drive methodology development in distinct directions that can be valuable for other communities.

In the mathematical biology / medicine setting, digital twins or mathematical models of living systems have long been used as a tool in the scientific discovery of biological mechanisms (testing/refining mechanistic hypotheses using bidirectional feedback between experimental/clinical data and models), as well as in prediction, e.g. of disease progression and treatment strategy optimization. With exciting current developments and tremendous interest in the space of living biologic therapies, e.g. immune cell therapies, protein replacement using living cell populations, base editing, etc, it is especially critical to develop digital twin models of the complex interactions between living these therapeutic agents and their in vivo, dynamic microenvironment. Such models can aid in therapy design and feasibility analysis (e.g. determining gene editing targets, quantifying achievable protein levels), therapy use recommendations (e.g. understanding optimal/minimum sufficient dose and timing), and trial design (e.g. patient selection, trial endpoint design).

To meet these challenges, I believe it will be very important for researchers in different applications to be able to work together to address similar obstacles in development and use of their digital twin models, and to share technologies and best practices. Some of the specific challenges and questions from my perspective of mathematical medicine include:

- **Data limitations and heterogeneity** - specifically, limited longitudinal observations for validating/refining digital twin models, high noise, high variability between samples (patients), highly multimodal data (e.g. ex vivo sample testing + in vivo clinical follow-up, electronic health records, imaging + genomic + phenotypic profiling) often at a single or limited time points. Need for principled data augmentation approaches incorporating domain specific knowledge or invariances.
- **Need for robust, mechanistically justifiable predictions** - need for treatment design and predictions to meet ethical and regulatory considerations, cost considerations, equity considerations, as well as cultural considerations associated with adoption of digital twin recommendations, etc.
- **Development of mechanistic learning approaches** - need for methods for integrating biological mechanism knowledge (possibly encoded via mathematical models) with ML/data driven methods

- **Multiple models at different scales** - in many cases, data informing digital twin models come from a variety of experimental models at different scales (e.g. mouse models, in vitro 2D culture (plates), in vitro 3D culture (spheroids, organoids, organ on chip) and mathematical models or digital twins are developed at each scale. There is a critical need for developing an understanding of mapping digital twin models between experimental platforms and the in vivo setting.

While these are a few challenges currently addressed in the mathematical biology/medicine community, I would be quite interested in learning about challenges addressed by other communities (e.g. climate modeling, agriculture, military planning, etc) - and in leveraging different perspectives to collaboratively develop solutions. Developing the scientific infrastructure and opportunities to form these connections may include the organization/facilitation of working groups, collaborative research and education funding opportunities targeted at the methodological challenges described above, etc.