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True Medical Digital Twins and Multiscale Virtual Tissue Models of Health and Disease: Challenges and Opportunities

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Unlike personalized predictive models, which operate independently of the real world and are sometimes incorrectly labeled as digital twins, Medical Digital Twins require a tightly integrated workflow. This workflow includes sensors to monitor the health state, predictive models (propagators) to forecast changes in that state over time, comparators to assess the agreement between forecast and observation, and actuators to respond to any discrepancies. Depending on the application (e.g., diagnosis, prognosis, or therapy design and delivery), the actuators may notify a human to intervene, adjust the real-world system by administering a treatment, or update the digital twin model itself. At the core of modeling lies the propagator, which forecasts the future state based on the current one. In medical contexts, this involves understanding how molecular states translate into physiological outcomes at the tissue and organ levels. Forecasting these outcomes is complex due to feedback mechanisms across cellular, multicellular, organ, and organismal scales. These feedback interactions make classical data-driven AI/ML approaches less accurate, as they often struggle to account for dynamic, interdependent biological processes. In such cases, mechanistic models—which explicitly incorporate these interactions—are often necessary for reliable forecasting. Virtual Tissue simulations, which use an agent-based, middle-out approach, model cell behaviors and interactions, scaling up and down to different biological levels. These simulations have improved our understanding of development, homeostasis, disease mechanisms, and toxicology, and their integration into clinical applications holds promise for therapy discovery and personalized medical digital twins. However, both Virtual Tissues and Medical Digital Twins face significant technical challenges. One major challenge is the incomplete and noisy nature of real-world clinical data, which can degrade model accuracy and make validation more difficult. Noisy data feeds from sensors or diagnostics may lead to poor agreement between predicted and observed outcomes, requiring advanced data-cleaning and preprocessing techniques. Additionally, parameterization, model updating, and optimal control inference remain technical bottlenecks, especially for complex stochastic spatial models where validation data is patient-specific and not easily reproducible. These challenges are further exacerbated by the time-consuming nature of individualized simulations. Socially, the field lacks a culture of shared model development, reuse, and standardization, which undermines credibility in medical and regulatory settings. To fully realize the potential of Virtual Tissue modeling in medical discovery and personalized therapy, solutions to these technical challenges are required, along with a shift towards community-based model development and validation. There are also promising opportunities, particularly in integrating mechanistic modeling with AI/ML approaches for forecasting, parameter optimization, anomaly detection, and therapy design. I will briefly review key issues in implementing digital twins, the achievements and limitations of Virtual Tissues so far, and potential paths forward for delivering effective Medical Digital Twins. Insights from more mature disciplines like weather forecasting may offer valuable lessons in advancing Medical Digital Twins, despite significant differences between fields.

Presenter: GLAZIER, James A. (Indiana University Bloomington)

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