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Reviews

From Virtual Cell Challenge to Virtual Organs: Navigating the Deep Waters of Medical AI Models

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Haisong Qin[1], Sanqi An[1], Shuaiyi Liang[1], Jiapeng Qu[2], Lixin Liang[2], Ziyi Liu[2], Ziyang Luo[3], Xiaocong Kuang[4*], Xuyong Sun[3*]

Recent advances in single-cell profiling and artificial intelligence have enabled the construction of virtual cells, computational entities that simulate cellular states and responses with unprecedented resolution. Initiatives such as the Virtual Cell World Challenge highlight the potential of large AI models to move beyond annotation toward predictive and generative simulations. Yet, the next frontier lies in scaling from virtual cells to virtual organs, where thousands of cell types interact across spatial, temporal, and biophysical dimensions. This transition exposes major challenges: incomplete cellular atlases, limited integration of spatial and longitudinal data, difficulties in cross-scale modeling, and the lack of robust validation frameworks. Addressing these obstacles requires embedding biological priors into foundation models, developing multi-modal integration strategies, and adopting graph-based and hybrid mechanistic-statistical approaches. The emergence of digital twins--organ- or patient-specific replicas--illustrates how virtual organ models can inform drug discovery, predict toxicity, and guide precision medicine. Ultimately, the trajectory from virtual cells to virtual organs points toward the vision of a virtual human, enabling in silico experimentation at scale. Realizing this goal will demand not only technical breakthroughs but also collaborative validation, ensuring that medical AI navigates these deep waters toward safe and transformative clinical application.

Virtual Cells: From Single-cell Data to Computational Entities

The convergence of artificial intelligence and biomedicine has entered a transformative stage. In the past decade, single-cell profiling technologies have unveiled the molecular heterogeneity of tissues at unprecedented resolution, producing multi-omic atlases that serve as the foundation for computational modeling[1-3]. Coupled with the rapid advances in deep learning and the emergence of large foundation models, these datasets have given rise to the concept of virtual cells[4-6]: computational entities that simulate cellular identity, dynamics, and responses to perturbations.

While the idea of a virtual cell was once aspirational, it is now being materialized through international initiatives such as the **Virtual Cell Challenge**, which has become a crucible for benchmarking algorithms, and stress-testing predictive models[4,7]. These competitions demonstrate that AI can generalize beyond descriptive annotation, toward generative predictions of how cells transition, differentiate, or respond to pharmacological interventions.

The Deep-water Challenge: From Virtual Cells to Virtual Organs

Biology is not organized around isolated cells but around organs and systems, where thousands of cell types interact within spatial and temporal frameworks[8,9]. Moving from virtual cells to virtual organs is therefore the next frontier for medical AI. The complexity arises not simply from the sheer number of cells, but from the emergent properties of tissues: spatial architectures that scaffold function, dynamic signaling that regulates adaptation, and biophysical forces that shape physiology.

From the perspective of single-cell analysis, several limitations become evident. Current atlases remain incomplete and biased, often emphasizing immune or malignant populations while underrepresenting stromal, neuronal, or vascular cells, and unevenly sampling across health and disease[1]. Spatial and temporal dimensions also remain bottlenecks. Although spatial transcriptomics now enables subcellular mapping, and longitudinal profiling captures developmental or pathological progression, integrating these dynamic modalities into coherent organ-level simulations is still far from solved. More fundamentally, cross-scale integration is formidable: molecular interactions must be reconciled with tissue biomechanics, electrophysiological networks, and endocrine feedback loops. Validation adds another layer of complexity; perturbational assays that are routine at single-cell resolution cannot be applied to entire organs, and surrogates such as organoids or animal models only partially capture human physiology.

Navigating Complexity: Strategies for Virtual Organ Construction

Addressing these challenges requires both computational and conceptual innovation. Large AI models, such as transformer architectures and diffusion models, have demonstrated remarkable ability to generalize across domains, but biomedical data are sparser and noisier than the internet-scale corpora that fuel general-purpose AI[10-12]. Thus, biological priors--signaling networks, gene ontologies, and spatial neighborhood c

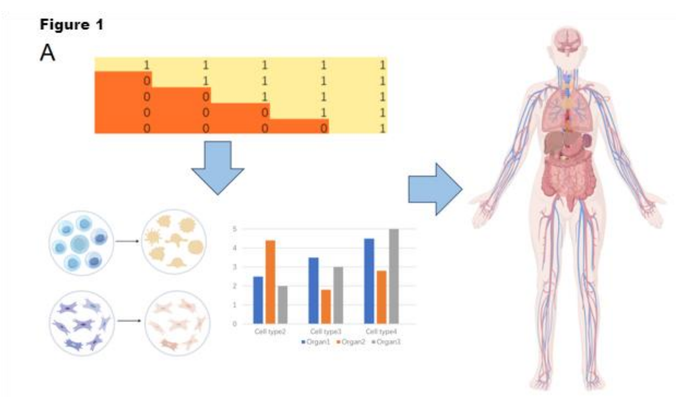
Affiliations:
1. Life Science Institute, Guangxi Medical University, Nanning 530021, Guangxi, China.
2. Runjian Co.,Ltd. 32 Floor, C Building of Huarun Centre, No 136-5 Minzu Avenue, Qingxiu , District, Nanning 530013, Guangxi, China.
3.Institute of Transplant Medicine,The Second Affiliated Hospital of Guangxi Medical University.Guangxi Clinical Research Center for Organ Transplantation.Guangxi Key Laboratory of Organ Donation and Transplantation, Nanning 530007, Guangxi, China.
4.School of Basic Medical Sciences, Guangxi Medical University, Nanning 530021, Guangxi, China.

onstraints--must be embedded into these models to ensure that their predictions are interpretable and physiologically meaningful.

Multi-modal data fusion is another pillar. Single-cell RNA sequencing, ATAC-seq, proteomics, metabolomics, and imaging each capture different layers of biology; integrating them into a shared embedding space allows for richer reconstructions[13]. Graph neural networks and hybrid mechanistic–statistical approaches are particularly promising in linking cellular molecular states with organ-level emergent behaviors, such as cardiac conduction or hepatic metabolism[14].

A particularly powerful translational application is the concept of digital twins[15-17]. While virtual cells serve as the atomic units of biological simulation, digital twins extend these models into organ- or patient-specific replicas. For instance, digital twins of the heart are being developed that integrate electrophysiological models with patient-specific ECG and imaging data, allowing prediction of arrhythmia risk or drug-induced cardiotoxicity. Similarly, digital twins of the liver may be used to simulate drug metabolism and toxicity, integrating cellular transcriptomics with physiologically based pharmacokinetic models. These frameworks embody the transition from research to clinic, offering in silico experimentation before intervention, and thus heralding a new era of precision medicine[18-20].

To ensure reliability and adoption, collaborative validation frameworks are essential. The Virtual Cell Challenge has already demonstrated the catalytic role of community competitions in benchmarking at the cellular scale[21]. A logical extension is the creation of Virtual Organ Challenges, leveraging shared reference datasets, organoid platforms, and organ-on-chip technologies as intermediate validation systems[22,23]. Such initiatives would not only standardize metrics but also accelerate cross-disciplinary innovation between computational scientists, biologists, and clinicians (Figure 1).



Toward a Virtual Human

Looking forward, the trajectory from virtual cells to virtual organs naturally extends toward a virtual human. While still aspirational, the conceptual pipeline is clear: single-cell models provide the foundational elements, organ-scale simulations constitute the functional modules, and integration across modules will eventually yield whole-body simulations. Such a system could transform drug development by enabling large-scale in silico trials, redefine preventive medicine through continuous monitoring and forecasting, and ultimately reshape our understanding of health and disease.

In summary, virtual cells have demonstrated the transformative potential of AI-driven biology, but scaling toward virtual organs exposes the limits of current data, models, and validation paradigms. By embedding biological priors into large models, integrating across modalities and scales, building digital twins for translational application, and fostering collaborative validation, the field may successfully navigate these deep waters. If achieved, the promise of virtual organs will redefine the landscape of biomedical research and clinical practice, bringing us closer to a future where medicine is not only personalized but also computationally pre-visualized.

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