

EDITORIAL

From molecules to models: Advances in
biomedicine and bioinformatics engineering for
precision medicinePier Paolo Piccaluga^{1,2*}, Mohsen Navari^{3,4,5}, and Chen Ming⁶¹Hematology Unit, University of Pristina, Pristina, Kosovo²Biobank of Research, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy³Health Sciences Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran⁴Department of Medical Biotechnology, School of Paramedical Sciences, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran⁵Research Center of Advanced Technologies in Medicine, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran⁶Department of Bioinformatics, College of Life Sciences, Zhejiang University, Hangzhou, Zhejiang, China(This editorial belongs to the *Special Issue: Biomedicine and Bioinformatics Engineering*)

Precision medicine was conceived as a promise: the right treatment, for the right patient, at the right time. For decades, that promise outpaced the tools available to fulfill it. The gap between molecular understanding and clinical application remained wide, bridged only partially by genomics and pharmacogenomics. What has changed is not the ambition; it is the infrastructure.

The past decade has witnessed a fundamental realignment. High-resolution omics technologies now generate data at single-cell and spatial resolution. Computational frameworks simulate biological tissue at the subcellular scale. Engineered delivery systems translate molecular targets into programmable therapeutics. Together, they constitute something more consequential: the dissolution of the boundary between biological discovery and biomedical engineering.

This Special Issue on *Biomedicine and Bioinformatics Engineering* documents that dissolution in practice. The contributions gathered here span virology, immunology, oncology, neuroscience, cardiology, and pharmacology, yet they share a common logic. Each begins with a biological question and moves, through computation or engineering, toward a translational answer. Three methodological axes organize this convergence: bioinformatics-driven discovery, computational modeling and virtual simulation, and engineered biomedical solutions. Understanding how these axes interact—and where they remain disconnected—is the central task of precision medicine today.

The first axis, bioinformatics-driven discovery, provides the foundation for this convergence. Before a therapeutic target can be engineered and before a computational model can be built, a biological signal must be identified, validated, and interpreted. Bioinformatics-driven discovery provides that foundation—and the contributions in this issue demonstrate how substantially its scope has expanded.

The most consequential recent development is the transition from bulk to spatially

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resolved, single-cell transcriptomics. Conventional RNA sequencing averages gene expression across heterogeneous cell populations, obscuring the microenvironmental dynamics that govern disease progression and treatment response. Spatial transcriptomics resolves this limitation by maintaining spatial context while profiling gene expression at single-cell resolution.¹ In this issue, that paradigm is applied to patient-derived synovial tissue from rheumatoid arthritis and systemic lupus erythematosus, integrating spatial single-cell data with machine learning to stratify patients into responders and non-responders before treatment initiation. The identification of spatially defined immune niches—including interferon-gamma-responsive macrophages and exhausted T-cell subsets—as predictors of drug resistance illustrates how bioinformatics can reframe clinical decision-making from empirical to anticipatory.

A complementary illustration comes from network-based transcriptomic analysis applied to bone biology. By interrogating osteoporosis expression microarray data through gene ontology and protein interaction networks, this issue identifies two ubiquitin-specific proteases—*USP17L2* and *USP19*—as statistically significant differentially expressed genes with diagnostic potential confirmed by receiver operating characteristic analysis.

This pipeline does not stop at biomarker identification: antisense oligonucleotide sequences targeting *USP19* are designed and validated computationally, closing the loop from computational discovery to candidate therapeutic design.

Data, however, are interpretable only within a framework. The biological signals identified through bioinformatics acquire predictive and mechanistic depth when embedded in computational models—which is where the second axis begins (Figure 1).

The biological signals identified through bioinformatics acquire predictive and mechanistic depth when embedded in computational models. This leads to the second axis: computational modeling and virtual simulation as active engines of biomedical knowledge.

Bioinformatics-driven discovery produces maps of gene expression, protein interactions, and cell-state distribution. However, a map of biological terrain is not a model of biological behavior. To move from identifying a signal to understanding its dynamics, from cataloging a structure to predicting its function under perturbation, computation is required not merely as an analytical tool but as a generative one. This is the second axis: computational modeling and virtual simulation as active engines of biomedical knowledge.

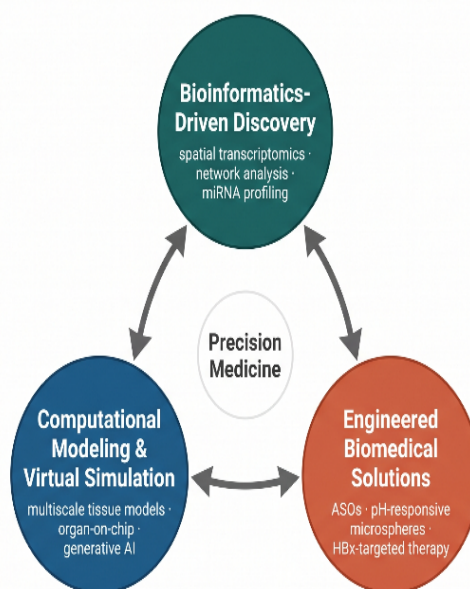


Figure 1. The three methodological pillars of this Special Issue and their convergence toward precision medicine. Each axis—bioinformatics-driven discovery, computational modeling, and engineered biomedical solutions—is represented with the corresponding contributions from the issue mapped accordingly.

Abbreviations: AI: Artificial intelligence; ASOs: Antisense oligonucleotides; HBx: Hepatitis B virus X protein; miRNA: MicroRNA.

The distinction matters. A computational model is not a surrogate for experiments; it is a hypothesis made executable. This is illustrated in this issue by a three-dimensional multiscale deformable cardiac tissue model, constructed across five hierarchical levels from individual cardiomyocytes to sheetlet assemblies, with free-form deformation applied per object to improve simulation accuracy. The goal is not anatomical recreation for its own sake but the generation of virtual imaging data against which real acquisition parameters and imaging biomarkers can be benchmarked—a validation framework that would be prohibitively costly to replicate experimentally.² The model's capacity to simulate both parallel laminar and branching laminar sheetlet structures represents a level of microstructural resolution with direct consequences for diffusion-weighted imaging interpretation.

A parallel logic governs the blood-brain barrier simulation review. The progression from artificial membrane systems to multicellular co-culture to organ-on-chip platforms is not merely a technological chronology - it reflects successive attempts to encode more biological variables into a controllable computational and physical framework. Each model generation extends the parameter space available for interrogation rather than replacing its predecessor.

The third modeling modality discussed here is categorically different: generative artificial intelligence. Latent diffusion models applied to diabetic retinopathy fundus image synthesis do not simulate physiology - they model the statistical distribution of clinical imaging data, learning to generate examples that are visually realistic and diagnostically coherent.³ This distinction defines the power and limits of generative models as biomedical tools: they augment datasets, they do not explain mechanisms.

What unites these three approaches is directionality—computation here is always oriented toward an implementable output. That output is the domain of the third axis.

Computation orients toward an output. That output, in the contributions gathered here, takes a concrete form: a molecule designed to silence a pathological target, a microsphere engineered to release a drug at a defined anatomical site, a therapeutic strategy architected around a viral protein whose disruption would interrupt both replication and oncogenesis. The third axis is where biological understanding and computational modeling become material—where precision medicine acquires a delivery mechanism.

The most molecularly targeted example in this issue concerns chronic hepatitis B. The hepatitis B virus X

protein occupies a position of unusual strategic value: it is simultaneously required for viral replication, implicated in immune evasion, and causally linked to hepatocarcinogenesis. Current antiviral nucleos(t)ide analogues suppress viral replication effectively but leave the covalently closed circular DNA reservoir intact, precluding functional cure. HBx-directed strategies—including RNA interference, antisense oligonucleotides, and proteasome-mediated destabilization—address this reservoir directly, with the potential to reduce both viral antigen load and relapse risk after treatment discontinuation.⁴ The engineering challenge here is not chemical synthesis alone but selectivity: disrupting a multifunctional viral protein without collateral interference in host cell pathways.

A different scale of engineering is represented by the pH-responsive microsphere system designed for intestinal glipizide delivery. The core-shell architecture—polylactic acid encapsulating the drug, coated with glycidyl trimethyl ammonium chloride-modified dextran—exploits the gastrointestinal pH gradient to achieve acid-resistant, mucoadhesive, intestinally targeted release.⁵ The precision here is spatial and pharmacokinetic rather than molecular: the therapeutic window is defined by anatomy, not genotype. Yet the underlying logic is identical—engineering a solution whose behavior is specified in advance by the biological context it must navigate.

Taken together, these contributions are best understood not as applied science but as co-design - dependent on the targets identified through bioinformatics and the parameters established by computational modeling. This interdependence carries consequences for how gaps in current knowledge must be approached.

Interdependence, however, is not the same as integration. The three axes described above remain partially disconnected in practice, and the contributions in this issue make those disconnections as visible as the progress they document.

The most persistent gap is scalar: from discovery to validation. Spatial transcriptomic atlases generated from small patient cohorts, however methodologically rigorous, carry predictive metrics that must be interpreted with proportional caution. Biomarkers identified in small patient cohorts have a poor track record of replicating at the clinical scale. The field requires not more signatures but better-powered validation frameworks, ideally federated across institutions to preserve the cellular resolution that makes spatial transcriptomics clinically valuable.

A second gap is translational: the mouse-to-human distance in both hepatocellular carcinoma microRNA discovery and bone biology models remains

underaddressed. Murine systems generate hypotheses efficiently; they validate them poorly. Computational integration of multi-species transcriptomic data offers a partial bridge, but it is not yet standard practice.

A third gap is interpretive: the metrics used to evaluate generative artificial intelligence models—Fréchet Inception Distance, Inception Score—are image quality proxies with no direct clinical meaning. Establishing biologically grounded evaluation criteria for synthetic medical imaging data is an unresolved methodological priority.

Finally, the absence of shared benchmarks across in vitro blood-brain barrier and cardiac tissue models limits cross-study comparability and slows the translation of computational findings into experimental design. Standardization in this domain is unglamorous work—and essential. These are not failures of ambition. They are the predictable frontier conditions of a field moving faster than its validation infrastructure. Addressing them will require the same methodological convergence that defines the best work in this issue.

Collectively, the contributions assembled in this Special Issue do not resolve the challenges of precision medicine; rather, they advance it along three methodological vectors that are, individually, maturing and, collectively, transformative. Bioinformatics identifies the signal. Computation tests its behavior. Engineering gives it form. What unites them is not subject matter but logic, and the most consequential advances documented here sit precisely at the boundaries where that logic is shared.

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Conflict of interest

The authors declare they have no competing interests.

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