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Molecular & Cell & Biomedicine EDITORIAL

What's next in life sciences: From "dark matter" decoding to system-level design

Dake Zhang,[1] Lin Zhang,[2] Tao Huang,[3] Haibo Zhang,[4] Changshun Ruan,[5] Caihuan Tian,[6] Huaiyu Wang,[5] Yi-Zhou Gao,[7] Bao-Jun Sun,[8] and Ming Luo[9,*]

[1]Key Laboratory of Biomechanics and Mechanobiology, Ministry of Education, School of Engineering Medicine, Beihang University, Beijing 100191, China

[2]Hubei Shizhen Laboratory, School of Basic Medical Sciences, Hubei University of Chinese Medicine, Wuhan 430065, China

[3]CAS Key Laboratory of Computational Biology, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai 200031, China

[4]Qingdao Institute of Bioenergy and Bioprocess Technology, Chinese Academy of Sciences, Qingdao 266101, China

[5]Research Center for Human Tissue and Organ Degeneration, Institute of Biomedicine and Biotechnology, Shenzhen Institute of Advanced Technology, CAS, Shenzhen 518055, China

[6]Institute of Vegetables and Flowers, Chinese Academy of Agricultural Sciences, Beijing 100081, China

[7]Department of Environmental Hygiene, School of Public Health, Harbin Medical University, Harbin 150081, China

[8]Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China

[9]South China Botanical Garden, Chinese Academy of Sciences, Guangzhou 510650, China

*Correspondence: luoming@scbg.ac.cn

Received: January 11, 2026; Accepted: January 15, 2026; Published Online: January 17, 2026; https://doi.org/10.59717/j.xinn-life.2026.100199

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Citation: Zhang D., Zhang L., Huang T., et al. (2026). What's next in life sciences: From "dark matter" decoding to system-level design. *The Innovation Life* **4**:100199.

The past several years have witnessed many data-rich areas of the life sciences have accelerated from description toward prediction and, increasingly, design—driven by high-throughput measurement, artificial intelligence (AI), and programmable perturbations. With breakthroughs in synthetic genomics, AI-driven decoding of protein structures, and whole-brain connectomes at physical resolution, the long-standing blind spots from molecular machines to neural networks have been removed.[1] This editorial highlights the digital turn of structural biology, cross-scale dissection of physiological mechanisms, the regulatory evolution from gene editing toward epigenetic modulation, and the rise of physical biology in regeneration.

Looking ahead, as cellular digital twins (real-cell–aligned) and digital cells (executable *in silico*) integrate with synthetic biology, an engineering era is on the dawn in which biology becomes programmable, computable, and creatable (Figure 1).

THE MOLECULAR "POLYMERASE CHAIN REACTION (PCR) MOMENT": AI PREDICTION AND *IN SITU* DYNAMIC RESOLUTION

In the past five years, structural biology has seen a PCR-like inflection point by removing a key bottleneck: PCR made DNA easy to prepare, while deep-learning structure prediction reduces reliance on difficult crystallization, challenging purification, and high-abundance samples. In particular, AlphaFold2 and RoseTTAFold have made macromolecular structure determination more accessible by providing broadly available structural hypotheses.[1] Beyond accurate monomer prediction, these tools increasingly enable prediction of protein–nucleic acid interactions within complex assemblies. Structural biology is therefore moving from explanatory to predictive, as researchers can now systematically predict atomic-resolution assembly of homologous and heterologous oligomers across species, exposing a large "dark matter" of quaternary structures that is widespread in living systems but previously inaccessible.[2]

At the same time, cryo-electron tomography (cryo-ET) combined with generative AI approaches is extending analysis into the native cellular environment, which paradigm is shifting from static snapshots of purified molecules to dynamic "molecular sociology" inside crowded cells. Continuous conformational heterogeneity of large machines, such as ribosome assembly intermediates and viral capsid packaging states, can now be captured directly *in situ*. This "*in situ* dynamic resolution" provides physical evidence that many biological processes are stochastic yet coordinated.

CELLULAR CONTROL: FROM GENE CUTTING TO EPIGENETIC REPROGRAMMING

Once mechanisms are resolved, the next step is control. Genome intervention now encompasses both irreversible cutting and reversible, software-like regulation.[3] Classical CRISPR–Cas editing is increasingly complemented by epigenetic editors that rewrite chromatin state without double-strand breaks, enabling durable yet potentially reversible silencing or activation of genes, which reframes editing as functional tuning of cellular programs that includes cell fate, metabolism and stress resistance rather than single mutations, and it generalizes naturally across organisms, from mammalian cells to plant developmental regulators and microbial circuits.

TISSUE REPAIR AND DEVELOPMENT: BIOELECTRIC CONTROL, TIME-DEPENDENT MECHANICS, AND NETWORK-LEVEL COORDINATION

Molecular interventions yield tissue-level outcomes when higher-scale assemblies can form, persist, and return after disturbance. Repair and regeneration are influenced by physical boundary conditions, as

Figure 1. Life engineering cycle across scales Silhouettes of representative model systems (human, mouse, Arabidopsis, and yeast) anchor a four-stage workflow. Clockwise: intracellular decoding to map the full repertoire of molecular interactions, from disordered protein "dark matter" to structured complexes and epigenetically marked DNA; tissue regeneration and organoids, where biophysical control—including bioelectric cues and mechanical forces—guides repair and mini-tissue assembly; the digital cell, driven by expanding multi-omics datasets that enable increasingly accurate cellular digitization and simulation; and synthetic biology for planetary adaptation, using modular design and engineered bioreactors to enhance organismal functions and support population-level resilience under Mars-like stressors. A closed loop of arrows links the stages, framed by Earth's curvature and deep space.

electric potentials and fields, mechanical loading and constraint, and the evolving chemistry and rheology of the extracellular milieu.

Injury often produces local voltage discontinuities and electric-field gradients. These gradients bias directed migration, polarity re-establishment, and matrix remodeling in diverse cell types, providing a control channel that is spatially extended and rapidly reconfigurable. Materials that transduce deformation into electrical signals (e.g., piezoelectric systems) can supply analogous cues *in situ*, maintaining electrophysiological-like conditions and biasing stem and cell progenitor programs toward constructive remodeling.

Mechanical signaling is intrinsically multidimensional and dependent upon history. Cells integrate elasticity, viscoelasticity, stress-relaxation kinetics, degradability, and micro-/nano-topography over time rather than sampling a single stiffness value. Force transmission into the nucleus couples to chromatin organization and can stabilize altered regulatory states, yielding mechanical memory and history-dependent outcomes in cell-fate selection, dormancy, and remodeling. As a result, scaffolds are moving from passive supports to 4D instruction: matrices that prescribe trajectories of stiffness, dissipation, and degradation, optionally coordinated with metabolic constraints that set the permissive range of state transitions.

At tissue and organism scales, repair reflects integration among excitable signaling, immune dynamics, and structural mechanics. Long-range coupling can synchronize inflammatory polarization and remodeling programs across distant sites, so altering mechanical and electrical boundary conditions can shift resolution dynamics without changing exogenous biochemical agents. This drives interest in bioelectronic and wireless interfaces that can read and write relevant signals across scales, and in organoid/microphysiological platforms that render tissue physics programmable through defined matrices, transport control, and multicompartment coupling.[4]

Next, the integration of real-time bioelectric monitoring with adaptive biomaterials and organoid platforms will enable closed-loop control of tissue repair—where scaffolds sense local field states and dynamically adjust mechanical and electrical cues to guide regeneration toward desired outcomes.

SYSTEM-LEVEL PHYSICAL PANORAMAS: WIRING-DIAGRAM RECONSTRUCTION AND BODY-EXCITABLE-NETWORK COUPLING

Mesoscale reconstruction is yielding quantitative wiring diagrams of excitable networks. Large-volume nanometer-scale imaging combined with automated segmentation enables dense graphs of neurons and synapses, exposing higher-order structure (hub cores, rich-club organization) and imposing hard constraints on mechanistic models, while dynamics under realistic connectivity are often set by distributed microcircuit interactions rather than uniform global synchrony, supporting more specific strategies for decoding and stimulation.

Connectivity-first physiology links peripheral state variables to identifiable control motifs within these graphs. Distinct subcircuits can implement separable computations such as intake suppression versus protective/aversive responses, while peripheral metabolic signals can entrain oscillatory regimes and plasticity in valuation and action-selection networks via long-range afferent channels. The implication is general: metabolic regulation and behavioral state share coupled dynamical variables realized in specific network subgraphs, making the coupling measurable and, in principle, controllable.

EXTREME ENVIRONMENTS AND PLANETARY PERSPECTIVES: LIFE'S STRESS TESTS

Amid accelerating climate change, life on Earth is undergoing a large-scale stress test that includes heatwaves, megadroughts, acidification, hypoxia, and shifting niches, turning ecosystems into a natural laboratory for probing robustness limits.[5] When coupled to digital twins and synthetic biology, extreme adaptation gains an explicit engineering framework. In cardiology, patient-specific heart digital twins already combine cardiac MRI and electroanatomical mapping to predict arrhythmia risk and guide ablation for scar-dependent ventricular tachycardia. By analogy, "cellular digital twins" can merge structural and single-cell data with environmental variables to simulate responses to heat, salinity, radiation, and low oxygen, generating testable predictions of stress trajectories. High-resolution structural biology, live-cell imaging, and generative AI further move toward 4D reconstructions capturing molecular motion, metabolic flux, and gene regulation under planetary-analog conditions.

Synthetic biology supplies the physical substrate for validation. DNA-enabled synthetic and biomimetic artificial cells can implement minimal, programmable versions of metabolism, growth, division, and compartmentalization. Non-equilibrium self-assembly, programmable gene circuits, and synthetic organelle-like condensates can be combined into stress-response modules, while sequence-defined digital polymers enable chemically robust data storage in hostile environments. Together, digital twins and synthetic constructs close a "design–simulate–build–test" loop: models propose survival strategies (e.g., genome recoding, multicompartment architectures), and synthetic cells/tissues implement and validate them. This constrains scenarios for early life under ancient extremes and supports rational astrobiology and the design of ecosystems or minimal life adapted to Martian, icy-moon, or exoplanet conditions—before generalizing to broader modeling and engineering of life across scales.

OUTLOOK: CONVERGENCE OF DIGITAL AND SYNTHETIC LIFE

By 2030, the field may shift from "understanding" to "creating" living systems, enabled by the digital cell: a cell-level digital twin built from high-fidelity multimodal data. The concept arose from the convergence of single-cell omics, high-resolution imaging, lineage tracing, and mechanistic modeling, making it practical to represent a cell as an integrated, computable system. Built on multidimensional reconstructions, digital cells unify molecular states, spatial organization, and dynamics into simulatable models that can be perturbed in silico and updated as new data arrive—shifting cell biology from descriptive mapping toward predictive design and intervention.

In development, single-cell "digital embryos" chart spatiotemporal gene-expression trajectories and signaling networks governing organogenesis. In neuroscience, collaborative AI platforms generate cross-species 3D atlases of neuronal morphology. As data streams accumulate, digital cells become continuously updatable and optimizable predictive entities.

Insights from these models can be translated back to matter through synthetic biology. Photocuring bioprinting and molecular self-assembly can convert "digital blueprints" into engineered living systems with tailored functions—from biomimetic immune cells with hierarchical nanoscale architectures to synthetic cells powered by designed genomes. Taken together, life science is becoming a crucible where physics, chemistry, mathematics, and engineering fuse, enabling systematic design and repair of living systems from atomic detail to ecosystem scale.

Looking ahead, life sciences are entering an era where molecular-scale insights, physical boundary conditions, and system-level coordination converge into an integrated design framework. The 'PCR moment' in structural prediction, the reversible epigenetic control, the recognition of physical fields as regulatory channels, and the assembly of wiring-diagram physiology together enable a new biology: one that is predictable, computable, and constructible. Digital twins provide the simulation layer, synthetic biology supplies the physical implementation, and their iterative coupling closes the loop from hypothesis to validated living system.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Shenzhen Medical Research Fund (B2502015); the Guangdong Natural Science Funds for Distinguished Young Scholars (2022B1515020026); the Youth Innovation Promotion Association, Chinese Academy of Sciences (Y2021094); and the National Natural Science Foundation of China (NSFC) (32571758). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.