

From gene editing to system design: Reprogramming agriculture for resilience and sustainability

Yilong Yao,¹ Wei Xiao,¹ Shijin Qi,¹ Kui Xu,^{1,*} and Yulong Yin^{1,*}

¹Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China

*Correspondence: xukui@isa.ac.cn (K.X.); yinyulong@isa.ac.cn (Y.L.Y.)

Received: March 30, 2026; Accepted: April 17, 2026; Published Online: April 17, 2026; <https://doi.org/10.59717/j.xinn-life.2026.100216>

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Citation: Yao Y., Xiao W., Qi S., et al. (2026). From gene editing to system design: Reprogramming agriculture for resilience and sustainability. *The Innovation Life* 4:100216.

Climate change, resource constraints, and intensifying ecological pressures are systematically reshaping the operational boundaries of global agriculture. Extreme climate events (such as heatwaves, droughts, and floods) are exhibiting increased frequency and increasingly non-stationary spatiotemporal patterns, causing persistent disruptions across regions and seasons in agricultural production. Meanwhile, climate warming, the migration of agro-ecological zones, and the expansion of global trade networks are

also reshaping the occurrence, transmission, and suitability ranges of pests and diseases. Against the backdrop of increasingly constrained key inputs such as land, water resources, fertilizers, and energy, these factors collectively render agricultural systems more volatile and uncertain, while significantly increasing their sensitivity to systemic risks. In livestock systems, high-density intensive farming, long-distance cross-regional transportation, and the expansion of human-livestock-wildlife interfaces further enhance the

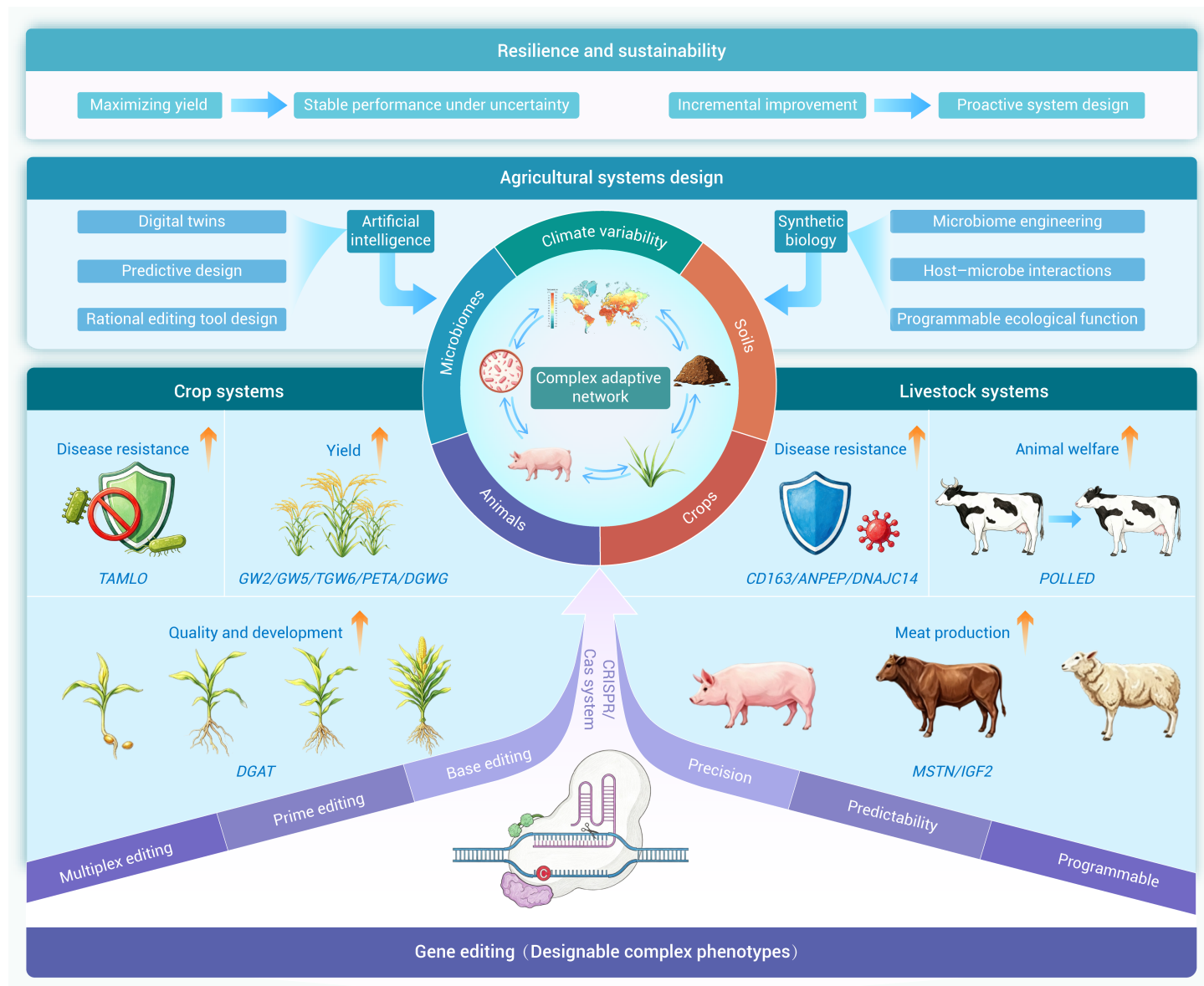


Figure 1. Integrated strategy for resilient, sustainable agriculture Artificial intelligence, synthetic biology, and gene editing provide complementary tools for improving adaptive traits in crops and livestock by enabling targeted interventions in the biological and environmental networks that link organisms, soils, microbiomes, and climatic conditions.

complexity of cross-species and cross-regional transmission of infectious diseases, and generate cascading effects through feed supply systems, cropping systems, and global supply chains. At the same time, long-term direc-

tional selection and the uneven deployment of genetic resources have led to a progressively simplified genetic basis for certain production traits, thereby weakening the overall resilience of agricultural systems to multiple stresses.

Under the combined influence of these multiple pressures, modern agricultural breeding is shifting from a trait-centered framework focused primarily on yield or resistance toward a systems-oriented paradigm centered on system stability and multi-objective coordination, namely, from “maximizing yield under optimal conditions” to “maintaining stable performance under uncertain environments.” This transition is not driven by a single factor, but rather by the continuous accumulation of large-scale genomic and multi-omics data, advances in genetic improvement toolkits, deepening understanding of gene regulation and developmental biology mechanisms, and increasing societal demands for sustainability, nutritional quality, and biosafety.

This transition also highlights the inherent limitations of traditional breeding approaches. Conventional breeding relies on natural variation, recombination, and multi-generational selection, processes that are typically characterized by high stochasticity, long cycles, and limited controllability. Under rapidly changing and highly uncertain environmental conditions, such approaches are increasingly constrained in achieving multi-trait coordinated optimization. Therefore, agricultural breeding is transitioning from empirically driven incremental improvement toward a rational design paradigm based on systems biology. Within this framework, multiple technologies constitute an integrated enabling system, among which gene editing serves as a key technology for precise genetic intervention. Genome engineering technologies represented by the CRISPR/Cas system (including base editing, prime editing, and multiplex editing) have substantially enhanced the programmability of targeting multiple genomic loci, providing a technical foundation for the dissection and targeted engineering of complex traits. In crop systems, the application of gene editing has expanded from single-gene trait improvement to multi-locus coordinated regulation and pathway-level optimization (Figure 1). For example, in rice, simultaneous knockout of the grain weight-related genes *GW2*, *GW5*, and *TGW6* produces pronounced additive phenotypic effects, thereby increasing grain weight.¹ In wheat, CRISPR/Cas9 technology has been used to knock out all six *TaMLO* alleles, resulting in plants with enhanced resistance to powdery mildew.¹ At the metabolic pathway level, the key enzyme *DGAT* in triacylglycerol (TAG) biosynthesis represents a critical node; modulation of its expression or activity can significantly influence seed oil accumulation, illustrating a strategy of trait optimization through the targeted manipulation of key steps within metabolic pathways.² In addition, through whole-genome sequencing combined with CRISPR/Cas9-based approaches, 57 genes consistently retained across high-yield cultivars were identified, and subsequent editing using Cas9 or dCas9 demonstrated that most of these genes make important contributions to rice yield, including *PETA* and *DGWR*.¹ In livestock systems, early gene editing efforts mainly focused on single-gene trait improvement and disease resistance breeding. For instance, knockout of *MSTN* has been demonstrated across multiple livestock species to significantly enhance muscle growth and improve meat production performance; moreover, introduction of the polled (*POLLED*) allele enables the generation of naturally hornless cattle, improving animal welfare and management efficiency.³ In recent years, strategies have expanded toward multi-gene coordination and modular design (Figure 1). For example, simultaneous editing of *IGF2*, *ANPEP*, *CD163*, and *MSTN* using Cas12iMax enables coordinated optimization of growth performance and antiviral resistance within a single genetic background.⁴ *CD163* and *pAPN* double-knockout pigs are resistant to PRRSV and TGEV and exhibit decreased susceptibility to PDCoV while maintaining normal production performance.⁵ These advances collectively indicate that multiplex genome editing and pathway/module-level regulation are becoming key technological routes for complex trait improvement.

Against this background, the significance of gene editing in agricultural transformation lies primarily in its role as a critical translational platform linking systems biology understanding with molecular intervention. Agricultural systems are inherently cross-scale complex adaptive networks encompassing the genome, individual organisms, communities, and ecosystems. Within such systems, optimization at different levels often involves substantial trade-offs; therefore, the central question has shifted from “which genes to edit” to “how to coordinate multi-level networks to achieve overall resilience and stability.” This broader transformation is being driven by advances in artificial intelligence and synthetic biology. By integrating multi-omics data with environmental information, artificial intelligence enables the identification of key regulatory nodes in complex genotype-environment interactions and supports the design of multiplex and network-level intervention strategies.

Meanwhile, protein structure prediction and generative modeling further enhance the engineering capacity of gene editing tools and delivery systems, while synthetic biology extends the scope of designable interventions to host-microbiome-environment systems. Within this framework, key agricultural functions such as nutrient cycling, stress buffering, and disease suppression are reinterpreted as emergent properties arising from multi-level biological interactions, which can be optimized through coordinated genetic and ecological interventions. For instance, engineered rhizosphere microbial communities can enhance drought tolerance and nutrient use efficiency in crops, while modulation of livestock microbiomes can improve feed conversion efficiency, highlighting the convergence of genetic engineering and ecological engineering.

Therefore, the future development of agriculture will not depend on breakthroughs in a single technology, but rather on the synergistic integration of multiple technologies within a unified systems design framework. Artificial intelligence provides predictive and optimization capabilities, synthetic biology expands the range of options for cross-scale functional engineering, and gene editing, as one of several complementary tools, serves as the implementation layer for precise genomic modification. Accordingly, governance frameworks must be adapted to address the complexity introduced by multiplex genome editing, network-level interventions, and engineered ecological systems. Regulatory systems should encompass the entire pipeline of design, validation, deployment, and long-term monitoring, and integrate systems modeling, causal inference, and traceability analysis, while incorporating biocontainment and ecological boundary design strategies. Ultimately, the key to modern agricultural development lies not in the number of edited organisms, but in the depth of integration among multiple technologies within system-level design—that is, how to achieve holistic optimization of agricultural systems under environmental constraints, resource limitations, and biosafety considerations (Figure 1). This transformation marks a shift from trait-oriented incremental improvement toward a paradigm reconstruction centered on systems-level design.

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FUNDING AND ACKNOWLEDGMENTS

This work is supported by the Yuelushan Laboratory Breeding Program (YLS-2025-ZY01005), Hunan Provincial Major Science and Technology Tackling Program: “Development of Gene-Edited Medical Pigs” (2025QK2003). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Yilong Yao: Conceptualization, Investigation, Writing-Original Draft; Wei Xiao: Visualization, Writing-Review & Editing; Shijin Qi: Supervision, Resources; Kui Xu: Supervision, Writing-Review & Editing, Funding Acquisition; Yulong Yin: Conceptualization, Supervision, Resources, Writing-Review & Editing, Funding Acquisition. All authors contributed to this work and approved the final version of the manuscript.

DECLARATION OF INTERESTS

Yulong Yin is an Editorial Board member of The Innovation Life and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.