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ROYAL SOCIETY OF CHEMISTRY

EDITORIAL

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Cite this: *Mol. Syst. Des. Eng.*, 2026, **11**, 242

Molecular bioengineering: computational tools, smart materials, and therapeutic systems

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DOI: 10.1039/d6me90005d

rsc.li/molecular-engineering

Molecular systems bioengineering sits at the intersection of chemistry, biology, physics, and materials science, enabling the rational design of molecules and systems with tailored properties for applications in health, biotechnology, and sustainability. By integrating experimental, computational, and theoretical approaches, the field continues to evolve toward increasingly precise control over molecular interactions, self-assembly, and molecular systems function across scales.

This themed collection in *Molecular Systems Design & Engineering* showcases 15 original research articles and 4 reviews that reflect the breadth and innovation of current efforts in molecular bioengineering. From computational drug design and artificial intelligence to responsive biomaterials, enzymatic systems, and targeted delivery platforms, the articles presented here collectively demonstrate how molecular-level insights and molecular systems control are driving advances in diagnostics, therapeutics, and engineered living systems.

A foundational aspect of molecular bioengineering lies in understanding and navigating chemical space to develop molecules with desired systems properties. In this context, two articles present computational frameworks that advance molecular design and analysis. Vieira *et al.* (http://doi.org/10.1039/d3me00107e) developed a robust *in silico* pipeline for identifying novel PqsD inhibitors targeting quorum systems sensing in *Pseudomonas aeruginosa*, integrating docking, MD simulations, and MM/GBSA calculations across large compound libraries. Their findings highlight the potential of computational systems strategies for discovering anti-virulence agents.

Similarly, Stewart and Buehler (http://doi.org/10.1039/d4me00174e) propose a generative artificial intelligence system based on the X-LoRA-Gemma LLM to explore molecular design *via* multi-agent modeling. By mimicking biological problem-solving, their AI framework efficiently generates molecules with improved dipole moments and polarizabilities, pushing the frontier of data-driven material discovery. Extending this theme, Dicks *et al.* (http://doi.org/10.1039/d3me00189j) introduce a physics-inspired landscape analysis for molecular representations. By quantifying "roughness" in structure–property relationships through frustration metrics, they offer predictive insights into regions of poor ML performance, with applications in out-of-distribution molecular prediction.

Protein and peptide engineering play a central role in tuning molecular systems function for biotechnological applications. Several studies in this issue focus on modulating structure–function relationships and optimizing molecular interactions for delivery or catalysis. Li *et al.* (http://doi.org/10.1039/d3me00196b) engineered an artificial disulfide bond in human cytochrome *c* to modulate its coordination state and peroxidase activity. Their biophysical and spectroscopic characterization demonstrated enhanced reactivity and altered protein–partner interactions, showing how intramolecular covalent modifications can tune metalloprotein function. Bannon *et al.* (http://doi.org/10.1039/d4me00072b) applied reversible multi-site esterification to tailor the hydrophobicity and degradation profiles of the therapeutic peptide αCT11, significantly enhancing cell migration *in vitro* without compromising its bioactivity. Wang *et al.* (http://doi.org/10.1039/d4me00167b) explored how amphiphilic design and micellar assembly morphology were related to cellular internalization of VIP-conjugated peptide amphiphiles. Their systematic study shows that spherical and short cylindrical micelles targeting the VPAC receptor optimize uptake by macrophages.

Complementing these original studies, Hooe, Breger, and Medintz (http://doi.org/10.1039/d4me00017j) reviewed recent advances in nanoparticle-enhanced enzymatic catalysis. Their comprehensive analysis highlights how surface chemistry, enzyme orientation, and interfacial effects contribute to catalytic systems

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activity enhancements up to 125-fold, offering a roadmap for integrating enzymes into bioengineered platforms. Also, Montis *et al.* (http://doi.org/10.1039/d4me00021h) present a mini-review on short antimicrobial peptides (AMPs), summarizing how physicochemical tuning and chemical modifications (*e.g.*, halogenation, D-amino acids) improve bacterial targeting while minimizing cytotoxicity —key strategies in the fight against antimicrobial resistance.

Hydrogels and soft materials continue to be powerful platforms for responsive and programmable systems with potential applications across many technology sectors. This themed collection features papers that illustrate new approaches to their design and application. Bashir *et al.* (http://doi.org/10.1039/d3me00138e) modeled a one-pot antagonistic enzyme system to create transient pH pulses for reversible PVA–borate gelation. Their kinetic model helped map optimal systems compositions to control gel–sol transitions, offering a new route to temporally controlled soft matter properties. Xian *et al.* (http://doi.org/10.1039/d4me00106k) enhanced the glucose-responsiveness of PBA–diol hydrogels by weakening PBA–diol crosslinking rather than increasing glucose affinity. Their design led to greater insulin release and improved responsiveness under physiological glucose levels, suggesting a new direction for glucose-responsive biomaterials and devices.

Kawaguchi *et al.* (http://doi.org/10.1039/d4me00023d) investigated the formation of anisotropic gelatin hydrogels through template-directed self-assembly. Their findings highlight how surface-induced gel system structuring can enhance mechanical and directional swelling properties, offering inspiration for biomimetic materials. Hill *et al.* (http://doi.org/10.1039/d4me00029c) engineered a modular, genetically encoded NGT tag for temperature-responsive protein gels. The fusion proteins self-assembled into shear-thinning and self-healing gels with optical functionality, suitable for drug delivery and biosensing. The review by Nagaraja *et al.* (http://doi.org/10.1039/d4me00001c) complements these efforts by detailing recent innovations in polysaccharide-based bio-inks for 3D bioprinting. They present a case study analysis of how extrusion techniques, and formulation strategies can be used to control and optimize tissue regeneration, providing a valuable guide for how these glycan-based ink systems can be engineered for regenerative medicine applications.

The development of nanostructured systems for targeted therapy and diagnostics remains a major pillar of molecular systems bioengineering. Pornnoppadol *et al.* (http://doi.org/10.1039/d3me00173c) created hybrid melanin-gold nanoparticles functionalized with EGF for near-infrared photothermal therapy. Their ep-Au-MNPs showed superior photothermal efficiency and cancer cell selectivity *in vitro* and *in vivo*, demonstrating therapeutic potential with minimal side effects. Hirose *et al.* (http://doi.org/10.1039/d4me00028e) designed a dual-stimuli-responsive drug delivery system using photothermal liquid metals and thermoresponsive polylysines. This novel composite enabled localized DOX release and concentration under NIR irradiation, effectively enhancing cytotoxicity in cancer cells.

Nakagawa *et al.* (http://doi.org/10.1039/d4me00105b) reported dual-labeled polymeric micelle assemblies designed for real-time singlet oxygen detection in biological systems. Their SOSG@Cy5-PIC/m micelles provided robust $^1O_2$ reporting and deep penetration into 3D tumor spheroids, establishing a promising tool for oxidative stress monitoring. In a related domain, Han *et al.* (http://doi.org/10.1039/d4me00010b) reviewed recent strategies in photothermal therapy for antibacterial wound healing. Their comprehensive analysis of PTAs and advanced dressings underscores the potential of PTT and synergistic PTT/PDT systems to augment antibiotics in treating resistant infections.

Finally, the issue includes a contribution to synthetic biology and metabolic engineering. Couto *et al.* (http://doi.org/10.1039/d3me00199g) used genome-scale system modeling to optimize chondroitin production in *E. coli*. Through *in silico* predictions and experimental validations, they identified gene modifications that significantly improved glycosaminoglycan yields, offering a scalable route to valuable biotherapeutics.

This themed collection highlights how molecular bioengineering continues to redefine the boundaries of what is possible at the interface of biology, chemistry, and engineering. The diverse set of contributions, from foundational theoretical frameworks and machine learning approaches to the development of smart materials and therapeutics, reflects the interdisciplinary spirit and translational potential of the field. The advances presented here not only increase our understanding of complex molecular systems behaviors but pave the way for impactful engineering for applications in medicine, biotechnology, energy, and sustainable materials. We hope this collection will inspire further innovation and cross-disciplinary collaboration in the years ahead.