

Engineering biocomputability in living and material systems

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From subcellular to population levels and beyond, living systems continuously sense and robustly interpret a diverse, ever-changing collection of signaling inputs and produce a near-limitless set of functional outputs. This process, referred to as biocomputation, combines information sensing, transfer and response algorithmically, using modular biological circuitry such as cells, proteins, nucleic acids and small molecules. By hijacking, evolving and repurposing these processes, biologists, chemists and engineers have exploited biocomputational frameworks in a growing number of sectors, including advanced chemical processing, additive manufacturing and tissue engineering. Here we examine the methods by which live cell and engineered biomaterial functions can now be (re) programmed with increased complexity and multiplexability. We categorize approaches based on the type of circuitry used, and highlight the resulting advances in synthetic biology and stimuli-responsive materials. We also explore how these fields have evolved independently but with similar underlying methods and goals, and discuss the exciting opportunities that are emerging from their convergence.

Synthetic biology broadly refers to methods through which native biological function can be augmented—or wholly novel function introduced—within living systems¹. Initial implementations used simple microorganisms such as *Escherichia coli* and *Saccharomyces cerevisiae*. In the 1960s, François Jacob and Jacques Monod performed a seminal study of the *lac* operon in bacteria and its role in gene regulation—an early example of a genetic feedback loop². With the development of gene cloning tools (including polymerase chain reaction, DNA sequencing and computational software) toward the end of the twentieth century, researchers have modularized and dramatically extended these methods to gain precise control over intracellular signaling and coordinate the multistep synthesis of high-value chemicals within bacterial and mammalian cells alike^{2–5}.

Pre-dating these efforts in synthetic biology, the science and engineering of biomaterials extends back more than 2,000 years, to when precious metals constituted the material of choice in dentistry,

and rudimentary glass globes were used to magnify text. Spurred by Staudinger's macromolecular theory, which gained broad acceptance throughout the 1920s and 1930s, the field shifted its near-exclusive focus on metals as medical materials to one that embraced soft matter, newly tunable through the then-nascent science of polymer chemistry⁶. Seminal early work cemented the use of polymeric materials to engineer controlled release⁷, and the importance of the extracellular matrix—alongside cell biology proper—was formalized as a prerequisite for engineering tissue mimics *ex vivo*⁸. In parallel, steady advances made in (bio)chemical reaction schemes led to the development and refinement of programmable biomaterials that could be modulated in time and space⁹. These biomaterials can function as tunable unit operations that can be combined to achieve more complex logic-based responses. Today, the field has reached a point of maturity such that organoids can be engineered reliably *ex vivo*^{10,11}, and organ physiology and pathophysiology can be faithfully recapitulated on microfluidic

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chips¹², bringing nanomedicine and tissue engineering closer to a technological reality.

Although the histories of synthetic biology and biomaterial science are different, modern efforts in each center around the development of modular systems that can exercise biocomputation^{13,14}. Under this shared framework, input signals are sensed, interpreted and responded to in a preprogrammed and multiplexable fashion using ‘circuitry’ composed of biological building blocks such as nucleic acids, proteins or whole cells. In this Review we introduce and critically examine the biocomputational strategies by which living cells and engineered biomaterials can be functionally modulated in a user-defined manner, with the goal of generating scalable high-value products. Categorizing efforts based on their main underlying medium (synthetic, nucleic acid or protein), we highlight previous advances within each field and the promising opportunities that arise at their intersection, which could be facilitated by a shared design framework.

Biocomputability in living systems

Computability and the methods to engineer it within cells have been at the center of biological research for decades. Although the routine use of the word ‘biocomputability’ is a fairly recent phenomenon, the use of ideas from computation in biological systems extends back to the beginnings of synthetic biology. Shortly after the discovery of the *lac* operon and its role in effecting a predictably inducible metabolic switch with well-defined kinetics in a rudimentary Boolean circuit, Monod formalized the connection that the ‘logic of biological regulatory systems abides not by Hegelian laws but, like the workings of computers, by the propositional algebra of George Boole’^{15,16}. The abstraction of biological processes to ‘circuits’ is a useful framework to reduce complexity and increase modularity in the design and engineering of functions in living systems. The most commonly used logical operators are simple YES, OR, AND and Exclusive OR (XOR) gates, but these can be extended to more complex gates such as inverse gates (NOT, NOR, NAND, XNOR) or layered circuits. A visualization of various Boolean logical operations is provided in Fig. 1. Biological circuits can be found on many levels of organization and scale, making them difficult to categorize. To facilitate understanding, we will highlight biocomputation methods in synthetic biology based on the primary circuit material and level of control, either nucleic acid-based (transcriptional or translational) or protein-based (post-translational) within living systems.

Nucleic acid circuitry

As direct effectors of the ‘blueprint’ of life, DNA-based genetic circuits form the foundation of computation in synthetic biology. In the simplest implementations, small molecules are externally introduced to modulate gene expression. Concentrations of DNA-binding proteins and synthetic inducers act as inputs controlling transcriptional output, functioning as an IMPLY gate¹⁷. In the quintessential *lac* operon example, isopropyl β-D-1-thiogalactopyranoside (IPTG)—a synthetic analog of allolactose—removes the *lac* operon repressor, inducing gene expression; titrating its concentration provides precise process control over protein production, with predictable dose–response kinetics¹⁷. Spatiotemporal gene activation has been achieved using photocaged inducers (for example, IPTG, erythromycin¹⁸, arabinose¹⁹ and carbohydrates²⁰) in *E. coli*²¹ and other prokaryotic strains^{22,23}, with analogous studies conducted in eukaryotes with other photoactivatable activators (doxycycline²⁴, cyclofen²⁵ and others^{26,27}). These reports collectively demonstrate light-controlled logic gates and bandpass filters for spatiotemporal control over protein production.

To achieve further logical operations, artificial combinations of transcriptional regulatory genes and their corresponding promoters can be assembled such that the encoded genes activate or repress one another in prespecified manners^{28,29}. For instance, a bistable toggle switch³⁰, composed of two operons with constitutive promoters encoding mutual repressors, enables switching between two states

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Fig. 1 | Overview of logical operator symbols and their associated truth tables.

Standard Boolean logic gates (YES, OR, AND, XOR, NOT, NOR, NAND, XNOR, PASS 0, IMPLY and INHIBIT) are shown alongside their circuit symbols and corresponding truth tables for one or two binary inputs (A, B). Input and output states are denoted as 0 (false/absent) or 1 (true/present), illustrating the full set of operators available for encoding combinatorial logic into responsive material or biological systems.

and functions as a cellular memory unit upon transient induction. Another classic example from the 2000s, the ‘repressilator’ achieved predictable oscillations by arranging three fast-decaying transcriptional repressors and their promoters cyclically, producing periodic oscillations with characteristic frequency and amplitude under appropriate kinetic conditions³¹.

Since the first basic genetic circuits were established, there have been ongoing efforts to expand the suite of usable transcription effectors. Beyond cataloging existing DNA-binding domains (DBDs) and promoter sequences, efforts focused on engineering customizable DNA-binding proteins. These include engineered proteins based on the Cys2His2 zinc-finger domain, transcription-activator-like effectors (TALEs) or nuclease-deficient CRISPR–dCas³². User-defined DNA targets can be specified by manipulating amino acids within DBDs or, in the case of CRISPR–dCas, modifying guide RNA sequences³³. CRISPR inactivation/activation (CRISPRi/CRISPRa) technologies follow a similar strategy for controlling the expression levels of target gene transcription³⁴. Advances in computational protein design are also enabling the design of de novo DNA-binding proteins with user-defined sequence specificity³⁵.

Genetic circuits have also incorporated control by engineering interactions besides those of transcription factors (TFs) with DNA. One approach combines TF control with translational regulation to improve circuit process efficiency and dynamic range. For example, a genetic AND gate was engineered from two promoters, one controlling a gene with internal amber stop codons suppressing translation, and the other an amber-suppressor tRNA *supD*. Only when both promoters were activated under optimal operating conditions was the output fluorescent protein translated³⁶. Regulation can also emerge from engineering interactions among TFs or other effector molecules. For instance, TF chimeras are commonly made from a DBD fused to a transcriptional activator or repressor, as well as a dimerization domain. Chimeras are

designed to have a stronger repressive or activating function than dimers, so inputs that affect chimera dimerization will impact final gene expression. Dimerization domains can be easily swapped (for example, from FK506-binding protein (FKBP) or FKBP12-rapamycin-binding (FRB) dimerization domains to ligand-binding domains for ribose), enabling many-input genetic circuits without requiring multiple TFs to co-regulate a single promoter³⁷. Aside from expanding the input space, TF chimeras can also facilitate more complex circuit architectures and outputs. A recent example describes engineering zinc-finger–TF chimeras with the same dimerization domains that transcriptionally self-activate as homodimers but mutually inhibit one another as heterodimers, achieving as many as seven stable states in one synthetic circuit architecture³⁸.

Finally, extending beyond intermolecular interactions to the alteration of molecular structure during computation can enable uniquely powerful genetic circuits. Specifically, recombinases—DNA-modifying enzymes that site-specifically cleave and rejoin DNA—have been exploited to regulate gene expression by changing the positioning or presence of regulatory elements. The ability of recombinases to act as both transcriptional activators and repressors, as well as to operate on the DNA itself, removes the need for intricate cascading connections in circuits based on TF logic. For instance, Cre and Flp site-specific DNA recombinases have been leveraged to develop 113 circuits, including a six-input–one-output Boolean logic look-up table and a two-input–four-output decoder circuit³⁹ (Fig. 2a). Because DNA rearrangements persist longer than biomolecular binding events, recombinases have been used as permanent switches where a single dose of small molecules or illumination is sufficient to permanently alter the circuit state⁴⁰. Recent work has shown that recombinase-based circuits can store temporal information about inputs—analogue to computer memory—enabling advanced cellular ‘programs’. This has been realized through recombinase-based state machines (RSMs) that encode input order and combinations into DNA ‘registers’, with regulatory elements embedded within these registers conferring sensitivity to input order⁴¹. In another arrangement, strategically placed recombinase recognition sites, promoters and reporters have allowed three successive recombinases to drive the cell through four sequential fluorescent states⁴². Similarly, recombinases have been deployed to regulate multicellular consortia, where population morphologies and cell fates can be controlled by parallel and series gene circuits, enabling population management and control over biosynthesis^{43,44}. Circuits can additionally control cell-surface display or synthetic adhesion molecules to engineer self-organizing cellular architectures with controllable geometries⁴³.

Although the majority of nucleic acid-based biocomputational circuitry incorporates DNA, solely RNA-based methods are also of interest, as their orthogonality with DNA- and protein-based systems further expands potential signal complexity and process flexibility. RNA-based systems, or riboregulators, can provide faster dynamics than transcriptional-level control while still being easier to design than purely protein-based networks. The first riboregulators, pioneered in 2004, inserted a complementary sequence upstream of the ribosome-binding site to form a stem-loop that blocked translation until a small *trans*-acting RNA bound, acting as a YES gate^{45,46}. Since then, a diverse set of riboregulators have been developed, including some that utilize ribozymes⁴⁷ and others that are edited using CRISPR–Cas systems⁴⁸ or adenosine deaminases acting on RNA (ADARs)⁴⁹. Many notable examples use a combination of toehold switches and stem-loop structures to turn translation on or off. For example, ribocomputing circuits have been engineered with the capability for four-input AND, six-input OR and a complex 12-input Boolean-based expression (Fig. 2b). The OR gates were implemented through the concatenation of multiple toehold-switch and stem-loop structures upstream of the sequence of a reporter gene output. AND gates were implemented by dividing the trigger RNA sequence of the toehold switch into separate input

RNAs⁵⁰. Although engineered trigger RNAs remain the dominant input, aptamers—short DNA or RNA strands with specific binding—and small-molecule inputs have been reported^{51,52}.

The design of biocomputational circuits is challenging owing to the large design space, interdependence or crosstalk between components, as well as complex interactions between the circuits and their host-cell context. Thus, computational tools to speed up the rational design and optimization of synthetic circuits are important. Ongoing computational efforts target individual circuit components including promoters⁵³, other *cis*-regulatory elements⁵⁴, bacterial ribosome-binding sites⁵⁵, untranslated regions⁵⁶, RNA aptamers⁵⁷ and toehold-mediated riboregulators⁵⁸. Software tools that integrate full circuit designs into the computational pipeline are rarer but do exist. For example, the Cello suite and its updated version Cello 2.0 (published in 2022) convert abstract circuit designs into explicit DNA sequences that can be tested in the laboratory (Fig. 2c). Cello provides a graphical interface for the full design process, generating sequences from a library of characterized Boolean logic-gate components^{59,60}. However, tools to address other circuit-specific issues, such as mitigating or incorporating interactions of circuit components with external cellular context, are not so well established⁶¹. As the toolbox of nucleic acid circuit components and methods expands, we will continue to see the creation of increasingly intricate programmable networks.

Protein circuitry

Although potentially more challenging to implement than their nucleic acid-based counterparts, protein-based methods for biocomputation have distinct advantages in finely controlling protein presentation and dosage, as required for applications in cell–cell communication⁶² or intracellular phase separation⁶³. Such methods exhibit minimal actuation ‘lag time’ and involve species able to interact directly with cellular pathways without host genomic modifications and with high mass-transfer efficiency. Throughout this section, various protein-based tools for installing biocomputation into protein circuits are highlighted.

Small molecules can be used to stabilize or degrade proteins of interest (POIs)⁶⁴. Shield-1 is a membrane-permeable small molecule that has been shown to reversibly stabilize a POI by binding to its destabilization domain⁶⁵. Upon the addition of Shield-1, POIs can be stabilized with rapid mass-transfer kinetics, where degradation can be induced by the removal of the small molecule. Similarly, mutant dehalogenase (HaloTag2) can be fused to POIs, and the addition of small-molecule HaloTag2 Stabilizer (HALTS1) or hydrophobic tag (HyT36) will control whether the POI is stabilized or degraded^{64,66}. This method enables fine dose-dependent control over intracellular-protein steady-state levels and the exploration of protein functions across different operating conditions. Others have used proteolysis targeting chimeras (PROTACs), a combination of small molecules to target POIs and peptide ligands to bind to E3 ligase, hijacking the ubiquitination pathway to drive protein degradation by the proteasome⁶⁴. PROTACs hold great promise as a family of new therapeutics that can target previously ‘undruggable’ POIs. Recent work has extended these systems to incorporate sensitivity to light⁶⁷, or hypoxia AND cathepsin-L⁶⁸, to further improve process control over PROTAC-mediated degradation.

Alternatively, one of the most promising methods to encode stimuli-responsive circuitry within living cells has been through protease-based signaling networks^{69–71}. Proteases catalyze the irreversible hydrolysis of peptide bonds, reactions that can be repurposed to (in)activate proteins with controlled reaction kinetics, making them promising therapeutic candidates⁷², potential activators for prodrugs⁷³ or valuable reagents in preparative biochemistry⁷⁴. Many proteases, particularly those from potyviral origins, display stringent substrate specificity to typically six-residue peptides⁷⁴. As these recognition sequences are largely absent on native proteins, proteases can be exploited for high-precision biocomputing⁷⁵.

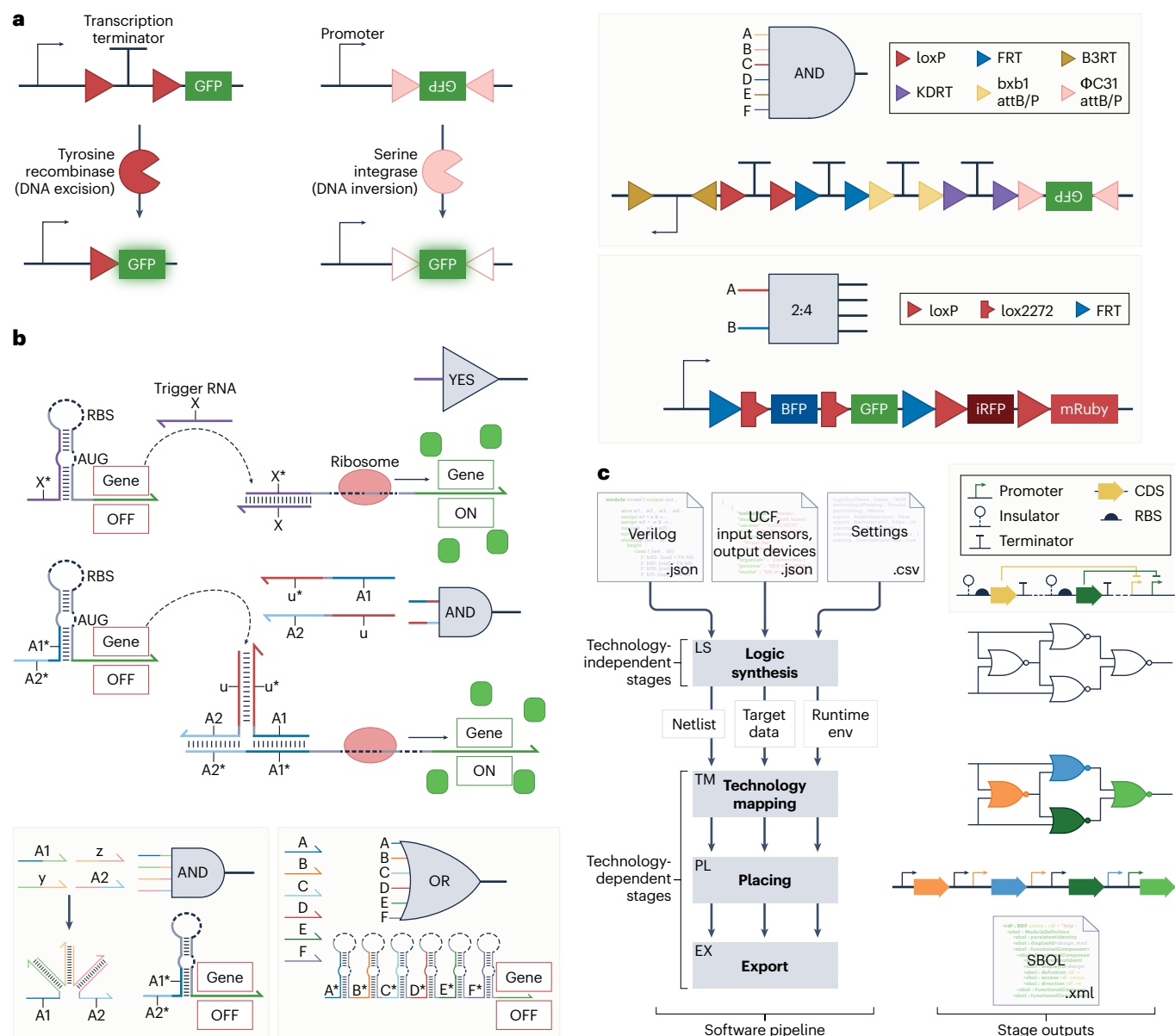


Fig. 2 | Nucleic acid-based circuitry for biocomputation within living systems.

a, DNA recombinases and integrases have been combined to create complex circuits to control gene transcription of reporter fluorescent proteins³⁹. Shown on the right are a six-input one-output AND gate and a two-input four-output decoder. **b**, A riboregulator system utilizes toehold switches to activate or deactivate ribosome-binding sites (RBSs) and control translation⁵⁰. Trigger RNA (X) binds to its complementary sequence (X*), allowing for ribosome binding. Simple or complex circuitry can be created, ranging from AND gates to a four-input AND gate or a six-input OR gate by utilizing matching trigger RNAs

(A1/A2/u/y/z or A to F) to complementary sequences (A1*/A2*/u*/y*/z* or A* to F*). **c**, The Cello 2.0 software pipeline generates user-defined genetic circuitry⁵⁹. Once the desired circuit is described and a library of parts is uploaded as a user-constraint file (UCF), the Boolean logic network is designed (logic synthesis), then biological gates are assigned to each node and optimized (technology mapping); linear DNA sequences are written (placing) and then exported as a Synthetic Biology Open Language (SBOL) file. Here, CDS references the protein-coding sequence. Panels adapted from: **a**, ref. 39, Springer Nature America, Inc.; **b**, ref. 50, Springer Nature Limited; **c**, ref. 59, Springer Nature Limited.

In a landmark study, circuits of hacked orthogonal modular proteases (CHOMP) were developed, utilizing multiple orthogonal proteases (such as TEVp, TVMVp and HCVp) in tandem and as composable elements to build numerous biocomputational functions into mammalian cell lines with predictable steady-state behavior⁷⁶ (Fig. 3a). Here, proteins are expressed in either a protease-activatable manner (if the reporter is fused to a protease-removable degren) or a protease-repressible manner (if one protease is conditionally repressed by another). Through further modifications to the reporter architecture—that is, whether protease cleavage sequences were engineered accessibly in series, in parallel or alternatively shielded until activation—a suite of Boolean logical operators were engineered that sense

and actuate upon two orthogonal protease inputs with tunable conversion efficiency, alongside an analog signal filtering motif. In a separate study, four mutually orthogonal split proteases (TEVp, PPVp, SbMVp and SuMMVp) were shown to re-assemble via orthogonal coiled-coil dimerization with defined binding equilibrium constants⁷⁷. This split-protease-cleavable orthogonal coiled-coil (SPOC)-based circuit enables another powerful route for the engineering of Boolean computability into mammalian cell populations or the engineering of designer signaling cascades with controlled mass-transfer characteristics.

Since the initial reports of CHOMP- and SPOC-based circuits, many studies have extended similar frameworks to achieve novel cellular functions or programs through combined orthogonal protease

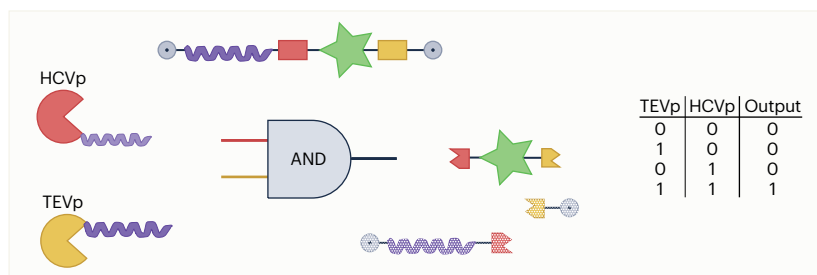
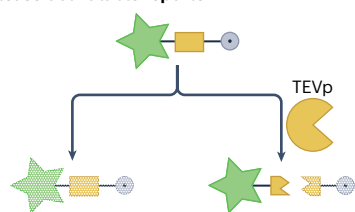
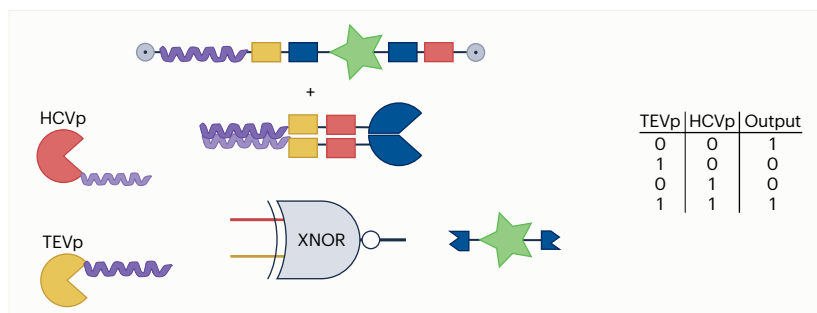
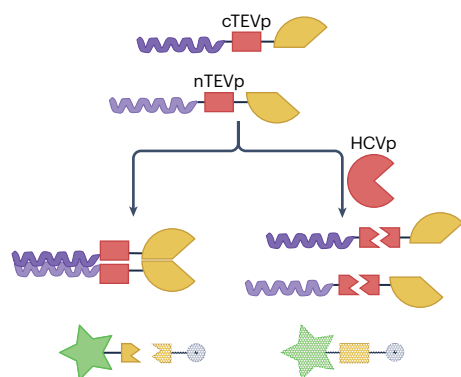
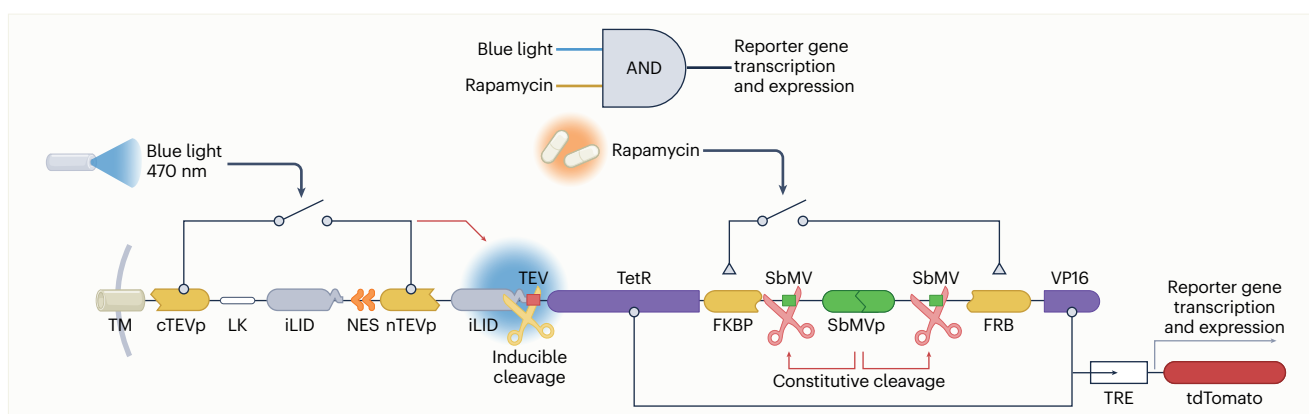
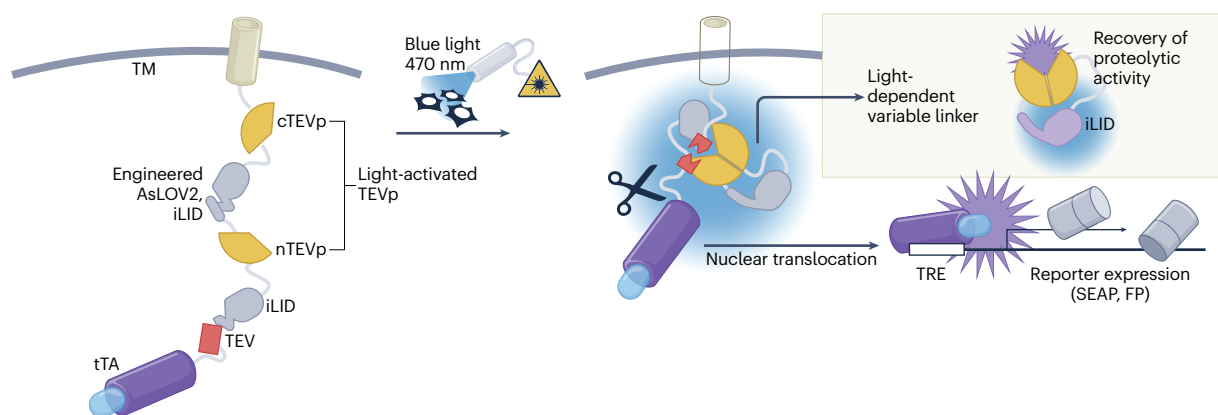
a Protease-activatable reporter**Protease-repressible reporter****b**

Fig. 3 | Protein-based biocomputability within mammalian cells. a, In the CHOMP system, split proteases (including cTEVp and nTEVp) can be activated or repressed to remove attached degron tags and prevent cargo degradation⁷⁶. These systems can then be layered into complex Boolean circuits. **b**, The light-assisted uncaging switch for endoproteolytic release (LAUNCHER) system controls gene transcription via light and small molecules. Split proteases are

reassembled in the presence of inputs, enabling the release of a transactivation domain (tTA) to trigger reporter protein expression. N- and C-terminal protease fragments are labeled (n or c) before protease abbreviation. TM, transmembrane domain; iLID, improved light-inducible dimer; TRE, tetracycline-response element; SEAP, secreted embryonic alkaline phosphatase; LK, linker; FP, fluorescent protein. Panel **b** adapted from ref. 95, Springer Nature America, Inc.

inputs (which may themselves be conditionally activated^{78,79}) and create bespoke logical operations with optimized performance metrics. Among these, the RELEASE (retained endoplasmic cleavable secretion) platform was developed to control protein secretion from the endoplasmic reticulum via two-input OR/AND-type operations or a protease signaling cascade⁸⁰. Additionally, morphogen signaling dynamics and ligand shuttling have been elucidated through extracellular protein circuits operating under diffusion-limited transport conditions⁸¹. De novo protein design has been used to create cooperatively inducible protein heterodimer (CIPHR) proteins with varying binding affinities, which, when layered, yield a suite of logic operations controlling protease or gene transcriptional repressor function with well-characterized transfer functions⁸². Chemical biology tools have also been used to autonomously compile single-peptide chains through thermodynamically favorable reactions into complex topologies within cells, affording Boolean YES/OR/AND-gated control over protein presentation⁸³. To further expand the logical complexity and achieve enhanced catalytic efficiency and substrate selectivity, additional orthogonal proteases are being generated via directed evolution⁸⁴, sequestration screening^{85,86} and AI-driven methods^{87,88}.

Beyond protease-sensitive systems, directly photocleavable proteins (PhoCl) enable spatiotemporal control over biomolecule presentation and localization within living cells^{89–91}. PhoCl has been employed to initiate a phase-separation process and cause light-triggered formation of biomolecular condensates, in a method called SPLIT⁹². This method can be applied to control mechanotransduction through the photocleavage of cell–cell junctions⁹³, and for optical activation of Cre recombinase-based genome editing⁹⁴. The recently introduced light-assisted uncaging switch for endoproteolytic release (LAUNCHER) system extends this further as a single-component photocleavable switch⁹⁵ (Fig. 3b). When combined with a chemically inducible FRB/FKBP dimerization pair, a dual-stimuli AND gate could be created, functioning as a multivariable control system with parallel processing capabilities.

Photoactivatable inteins—split proteins that autocatalytically form a peptide bond and splice themselves out—have previously been reported for the conditional assembly of functional proteins in response to light and/or enzyme inputs^{96,97}. Although light-based protein modulation benefits from high spatiotemporal control, challenges associated with attenuation place practical limits on its use in many contexts. Ultrasound offers an alternative actuator, leveraging mechanical energy transfer and cavitation phenomena to activate reporter genes and bioswitches for ‘sonogenetics’⁹⁸. Most ultrasound-responsive protein systems rely on recombinant protein-based gas vesicles that rupture with ultrasound through pressure-driven phase transitions. Magneto-protein gas vesicles have been used as contrast agents for the non-invasive imaging of tissues and the determination of in vivo tissue mechanics with robust signal and detection sensitivity, owing to their enhanced heat- and mass-transfer coefficients compared with other gas vesicle systems⁹⁹. These efforts offer exciting opportunities for controlling when and where advanced biocomputation occurs within living cells, by incorporating distributed control systems and process intensification strategies.

Biocomputability in materials

‘Smart’ biomaterials—those that exercise biocomputation—can operate as sophisticated chemical processing units with programmable reaction pathways and functionality not previously seen¹⁰⁰. Initially, these biomaterials were largely static, formed from synthetic and/or biologically derived precursors¹⁰¹. With advances in genetic engineering, stimuli-responsive recombinant proteins and nucleic acids have been incorporated, affording a new level of user-programmability with modular unit operations and controllable mass-transfer mechanisms. Transitioning beyond single-input–single-output-type systems, toolkits based on synthetic monomers, nucleic acids or proteins are now increasingly layered into higher-order circuits, expanding both

a biomaterial’s functional complexity with process intensification strategies and its potential in therapeutic delivery, tissue engineering, biosensing and beyond. In the following sections we highlight tools (arranged by their type of circuitry polymer) that have enabled such biocomputability, with a focus on soft-matter-based and nanoparticle-based systems.

Synthetic circuitry

Synthetic chemistry has been the primary driver of engineering advanced computability in biomaterial platforms. Most commonly, stimuli-responsive domains (for example, hydrolytic, photolytic or pH-sensitive) are included directly within material precursors that undergo molecular-level responses (such as scission, multimerization and isomerization) with predictable reaction kinetics and stoichiometry. Simple YES-gated systems respond to a single and specific environmental input. Although examples of YES-gated systems are abundantly reported as ‘smart’ materials, and span applications from bench to bedside (such as in hydrolytically degradable implants), this Boolean logic-type classification is rarely associated with them. Layered multi-materials and interpenetrating networks—in which different network components are individually responsive to a different stimulus—afford an additional level of functional complexity via parallel processing pathways. This has been demonstrated with a double network hydrogel, whose constituent networks respond to different chemical triggers (reactive oxygen species and proteases), each releasing a distinct therapeutic cargo (interleukin-10 or bone morphogenetic protein-2) to drive macrophage polarization and osteoblast differentiation¹⁰².

To develop a generalizable strategy for Boolean-type control over hydrogel properties¹⁴, controlled molecular topology can serve as an effective route toward materials that respond to prespecified input combinations. When such topologically specified species are included as crosslinkers, their complete cleavage yields macroscopic material dissolution¹⁰³ (Fig. 4a). Engineering crosslink structures through precise stoichiometric control and reaction engineering principles recapitulates all 17 operators that arise from YES/AND/OR combinations of three inputs—light, redox state and protease—yielding synthetic logic gates for small-molecule and cell delivery from hydrogels based on user-defined material degradation. Related designs tether cargo to hydrogel networks for Boolean-responsive small-molecule release¹⁰⁴, and these biomolecular tethers act as produgs that use three inputs (reducing agents, proteolytic cleavage and/or photoscission) to sequentially degrade and release small-molecule drugs according to user-defined inputs. Modifying these tethers with N-terminal polyglycine moieties allows sortase to covalently ligate protein therapeutics to the tethers through enzymatic coupling reactions with high selectivity and yield, enabling site-specific modification and delivery of protein therapeutics from synthetic hydrogels based on Boolean computation¹⁰⁵.

Other researchers have used synthetic logic-based polymer crosslinks to assemble nanoparticles that degrade or release drugs through logic-based computation. Computational design has been leveraged to generate an extensive library of stimuli-responsive monomers, enabling plug-and-play platforms for logically responsive nanoparticles with controlled drug release¹⁰⁶ (Fig. 4b). The monomers in the library react to an extensive suite of user and environmental inputs, such as UV light, visible light, hydrogen peroxide (H₂O₂), glutathione, acidic pH (pH 5.0), esterase, phosphatase, formaldehyde, hydrogen sulfide, various metal ions and β -galactosidase, through multiple competing reaction mechanisms with distinct activation energies and reaction orders. Based on intuitive polymer design, these monomers can be compiled to form YES/OR/AND gates, as well as higher-order operations that function as complex reaction networks with feedback control, and enable the release of therapeutics (such as kinase inhibitors, drugs and short interfering RNA) from nanoparticles, based on disease biomarker inputs¹⁰⁶.

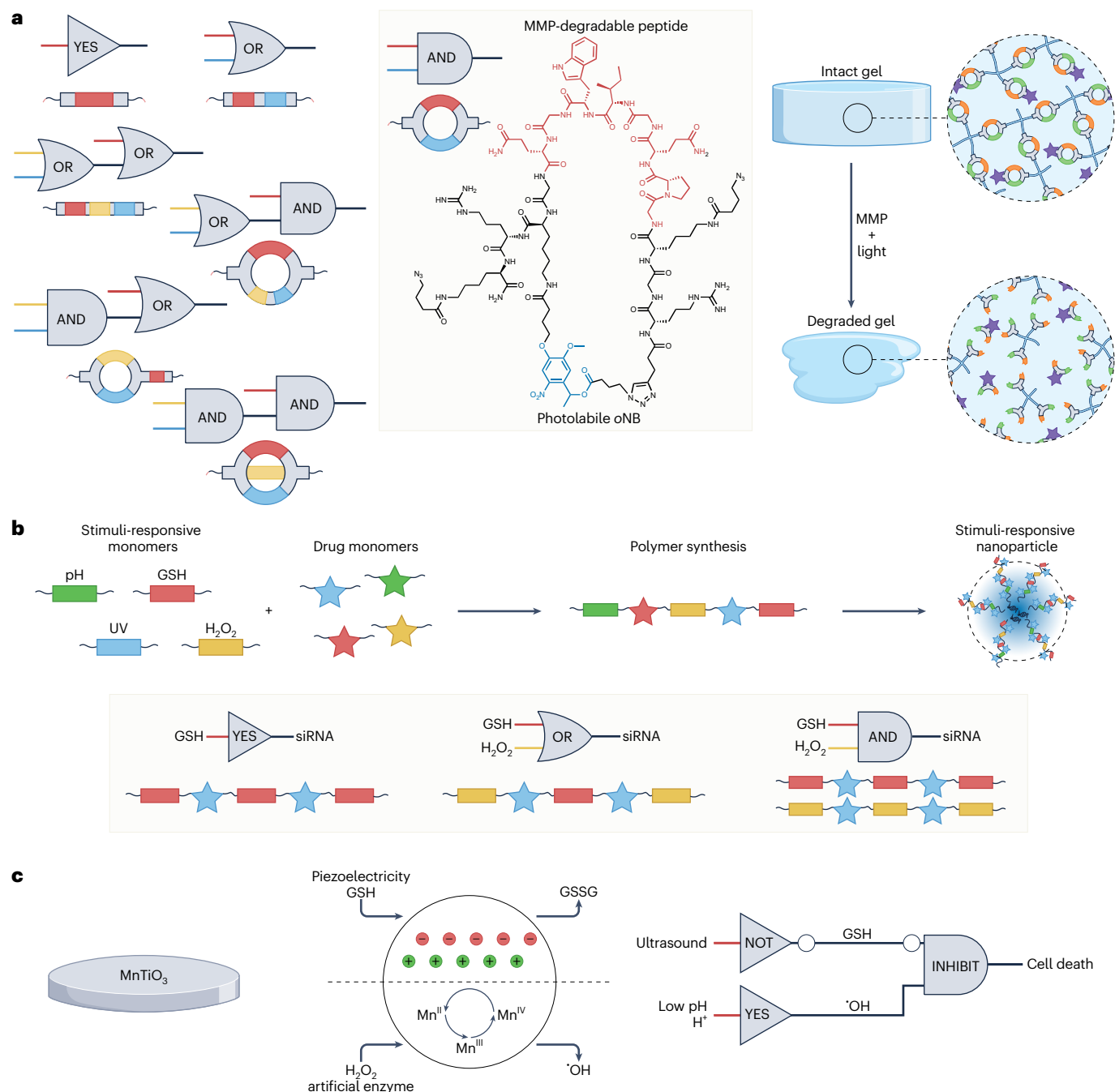


Fig. 4 | Synthetic-based materials for Boolean logic operation. **a**, Material crosslinks utilize light, reduction and/or protease cleavage as logical inputs for bulk hydrogel degradation. A cyclic peptide containing a matrix metalloproteinase (MMP)-cleavable sequence and a photodegradable *ortho*-nitrobenzyl ester (oNB) forms the basis of an AND-gated material crosslinker. **b**, A library of monomers that respond to stimuli including pH, ultraviolet light (UV), glutathione (GSH) and H_2O_2 can be used in polymer assembly to

support the intuitive design and incorporation of Boolean circuits to control nanoparticle drug release¹⁰⁶. **c**, Innate Boolean-responsive nanodisks oxidize GSH to glutathione disulfide (GSSG) in response to ultrasound, while naturally converting H_2O_2 to hydroxide with a manganese catalyst. Nanodisks selectively kill tumor cells in the presence of low pH and ultrasound¹¹⁰. Panel **a** adapted from ref. 103, Springer Nature Limited.

Similarly, other groups have designed AND logic-gated micelles and nanoparticles that utilize stimuli-responsive polymers for the release of cargos in response to cues from a tumor microenvironment (TME)^{107,108}. Micelles were designed to respond to boramino acid and reactive oxygen species, which are commonly found in a TME, thus increasing the tumor-selectivity of the released drug and reducing off-target side effects in healthy tissues¹⁰⁷. Polymeric crosslinked nanoparticles have been designed to incorporate monomers that are reactive to other TME stimuli (for example, extracellular matrix

metalloproteinases, acidity and glutathione) to create YES/AND logic operations for more specific drug release in combination cancer immunotherapy¹⁰⁸. By tuning the composition of monomers before nanoparticle synthesis, tight control over the circuitry can be achieved without stepping up circuit and synthesis complexity.

There are materials that can perform innate logical operation when introduced to various stimuli through intrinsic reaction pathways and transport-limited processes. For example, holmium(III)-doped carbon nanodots (Ho-CDs) were developed as dual-readout logic

devices for fluorescence and magnetic resonance imaging, based on pH-responsive behavior and signal quenching from metal ions¹⁰⁹. The range of logical operations was expanded to YES, NOT, OR, NOR, XOR, PASS 0, INHIBIT and a combination of these gates, with H^+ , Fe^{3+} and Fe^{2+} as chemical inputs providing control over fluorescence and magnetic resonance output signals¹⁰⁹. Another example is $MnTiO_3$ nanodisks, which can act as ‘artificial enzymes’ that respond to environmental pH and ultrasound through mechanochemical activation¹¹⁰ (Fig. 4c). The nanodisks piezocatalytically oxidize glutathione and react with environmental H_2O_2 to produce hydroxide under acidic pH or water at neutral pH. $MnTiO_3$ nanodisks are selectively cytotoxic to tumor cells based on environmental cues, and operate as stimulus-responsive catalytic reactors with conditional activity when both ultrasound AND low pH are present¹¹⁰. In addition, pH-sensitive polymers can form a switchable electrode for the detection of liver injury based on enzymatic biomarkers¹¹¹; both alanine transaminase and lactate dehydrogenase—common enzymes produced by liver injury—must be present to trigger the electrode, resulting in a positive signal¹¹¹. Using materials with innate logical operation enables the incorporation of biocomputation without the need for complex material synthesis.

Nucleic acid circuitry

DNA-based approaches have proven trailblazing in the engineering of new dynamic biomaterials, operating as programmable molecular assembly systems with controlled polymerization kinetics. Advances in understanding the design rules of nucleic acids have upgraded DNA from a genetic blueprint to the basis of a bona fide engineering approach to control synthetic biology and design nucleic acid nanostructures. Early pioneering work recognized that DNA ‘sticky ends’ (that is, single-stranded overhangs) and Holliday junctions could be used to create three-dimensional crystalline materials—some of the first attempts at making biomaterials from DNA that function as structured phase formations with predictable thermodynamic properties¹¹². The use of DNA as an engineering building block developed rapidly from an early theoretical curiosity to the manipulation of DNA into lattices and junction points¹¹³, and was eventually co-opted to assemble a wide variety of geometries, including cubes¹¹⁴ and octahedra¹¹⁵, yielding complex multi-unit DNA origami¹¹⁶. The field has recently evolved to incorporate biocomputation within DNA-based materials, paving the way for robust biosensing, therapeutics and controlled drug delivery.

DNA computation holds great promise for massive parallel information processing and environmental sensing. However, most previously reported systems utilized single DNA strands, which reduces computing capacity and necessitates more sensitive labeling and instrumentation for detection. These challenges have been tackled through advances in enzyme-free amplification, creating new possibilities in the field of material computing through autocatalytic reaction networks and signal amplification cascades. For example, DNA double crossover-like motifs have been used to form macroscopic crystals upon assembly by controlled precipitation and phase separation processes, providing a visual output if computation occurs¹¹⁷. Various logical operations controlling crystal formation have also been introduced by altering the sticky end sequences.

Others have designed DNA nanodevices that utilize triplex-induced allosteric regulation to instill logical operation by controlling conformational changes and cooperative binding equilibria¹¹⁸ (Fig. 5a). Linear DNA Z-switches have been induced into a Z-formation upon the addition of a triplex-forming oligo (TFO), exposing binding sites at the Z corners and enabling the DNA to form combs, wheels or two-dimensional networks. The switching equilibrium constants were used to control the degree of native OFF versus ON states, while the base-pair lengths of the Z-switches and TFOs controlled output geometries. These knobs were then used to logically control the formation of advanced DNA structures based on AND, OR, XOR, NAND, NOR and XNOR logic gates.

Aptamers have become a popular tool owing to their ability to bind to target ligands with high specificity, which is favored for applications in biosensing, ligand capture and binding, and, recently, DNA computation¹¹⁹. For instance, DNA aptamers can be formed into three-input DNA AND logic gates to diagnose colorectal cancer using patient blood-derived extracellular vesicles that operate through multicomponent binding equilibria and signal-amplification networks¹²⁰. When exposed to patient extracellular vesicles, the complex of DNA aptamers with specificity for common membrane-bound biomarkers of colorectal cancer (such as EpCAM, CD63 and protein tyrosine kinase 7 (PTK7)) will undergo enzyme-free entropy-driven amplification and trigger a fluorescence signal that enables diagnosis¹²⁰.

Aptamers can also shape a locking mechanism to control drug release based on logical computation. DNA origami ‘nanorobots’ have been designed with aptamer-based locks that follow AND-gated logic; the aptamers change conformation in the presence of tumor biomarkers, thereby ‘unlocking’ the box and releasing the cargo via controlled desorption and diffusion-limited transport¹²¹ (Fig. 5b). By changing the aptamer locks, cargo can be selectively released, triggered by various types of tumor cell. Aptamers are also used for cellular uptake control and tumor intracellular redox monitoring via cell-derived nanovesicles loaded with gold carbon dots¹²² (Fig. 5c). Aptamers with specificity for PTK7, a membrane biomarker commonly overexpressed by tumor cells, are bound to the nanovesicles and blocked with an I-motif sequence to instill AND-logical operation through pH-sensitive conformational switching and conditional binding. In the presence of low pH AND PTK7, the I-motif releases the aptamer binding sites, allowing uptake of the nanovesicles only by tumor cells, through selective membrane transport.

Synthetic materials can be combined with DNA logic-based systems to create hybrid material architectures that integrate multiple unit operations and transport mechanisms. For instance, photocleavable linkers can be installed on DNA to encode responsiveness to light with controllable bond-scission kinetics, enabling selective delivery of DNA drugs to tissues for spatially controlled release and targeted mass transfer¹²³. Other researchers have also enhanced their DNA logical systems with compatible chemistries. An intelligent DNA nanoreactor (iDNR) exploits AND logic to control nanoparticle deposition into tumors, thereby enabling better imaging and NIR-triggered ablation¹²⁴. The iDNR selectively binds to nucleolin, a tumor membrane protein biomarker. In the presence of H_2O_2 , the peroxidase-like activity of the iDNR oxidizes dopamine into polydopamine, a compound with strong photothermal properties under infrared radiation, enabling tumor ablation.

Focusing on the reaction between zirconium and single-stranded DNA phosphate backbones, a metal–organic framework (MOF) has been designed to function as a logic-based biosensor for disease detection¹²⁵. When the Zr-MOF forms bonds with DNA in the absence of environmental phosphate, the conjugated fluorescence probe is quenched; otherwise, the presence of phosphate blocks the MOF through competitive binding equilibria and displacement reactions, preventing the single-strand DNA binding. Based on inputs, three INHIBIT gates and one YES gate were constructed, enabling the precise detection of both alkaline phosphatase and inorganic pyrophosphatase, which are commonly found in mammalian fluid and tissue¹²⁵. Furthermore, MOFs can form protective shells and delivery vehicles for DNA biocomputation. A zeolitic imidazolate framework-8 (ZIF-8) nanoparticle encapsulated in a HeLa cell membrane has served as a biocompatible, protective shell with controlled mass-transfer properties for a DNA bioreactor that detects HeLa tumors¹²⁶. Within the nanoparticle, a tri-input DNA AND gate, through toehold-mediated strand displacement, identifies the presence of three tumor microRNA biomarkers. If present, bioamplification is triggered using the primer exchange reaction (operating as an autocatalytic amplification system with exponential signal growth), resulting in fluorescence and the

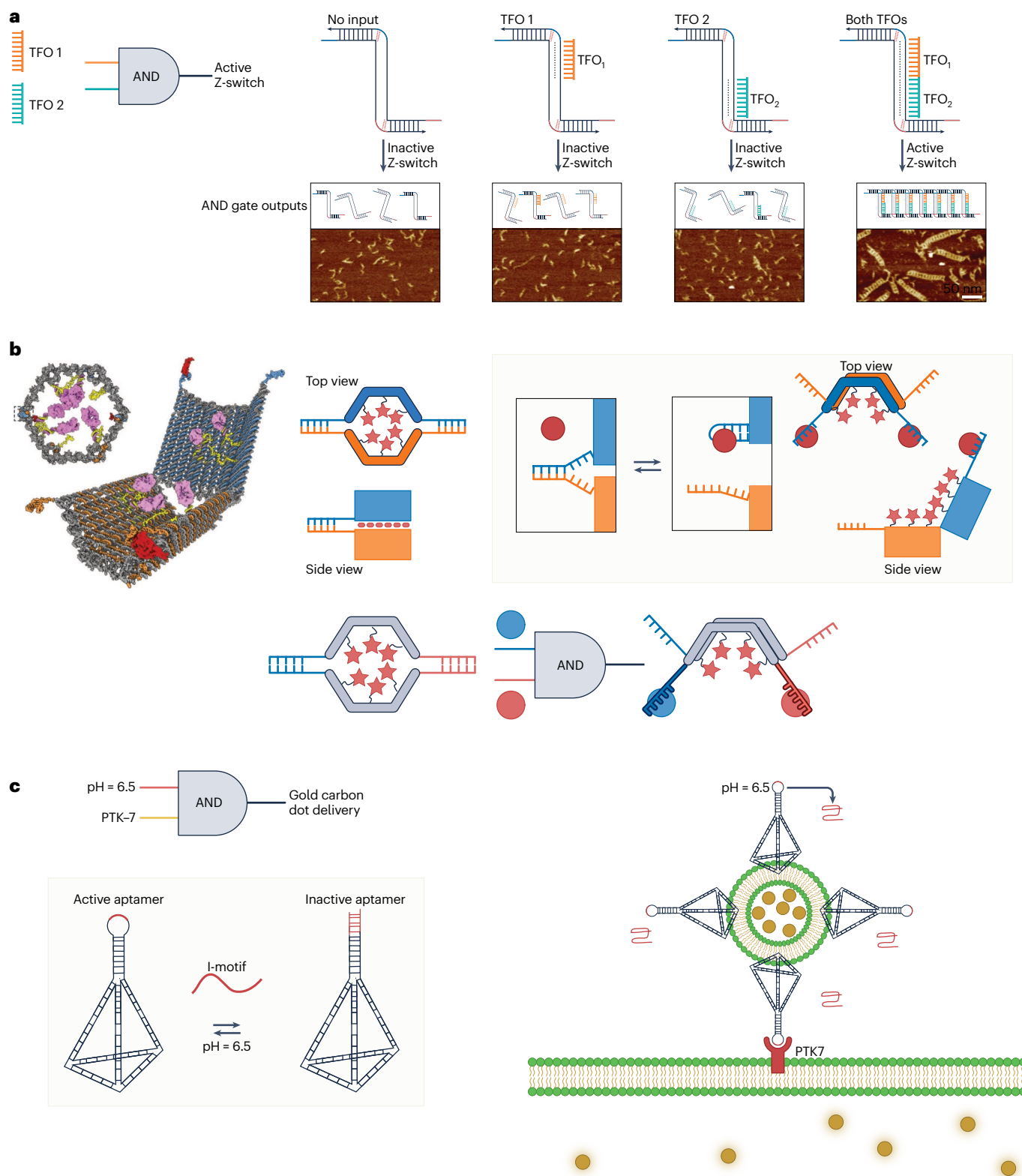


Fig. 5 | Nucleic acid-based materials for logical operation. a, DNA-based Z-switches utilize TFOs to control material conformations, enabling the creation of ladders, combs and networks based on input TFOs¹¹⁸. **b**, DNA 'nanorobots' employ aptamers (red, yellow and blue combs) specific to tumor biomarkers (red and blue circles) that unlock the nanorobot and release their cargo¹²¹.

c, Nanovesicles with aptamers specific for tumor receptor PTK7 utilize a pH-sensitive I-motif to achieve AND-gated controlled delivery of gold carbon dots, leading to tumor death¹²². Panels adapted with permission from: **a**, ref. 118, American Chemical Society; **b**, ref. 121, AAAS; **c**, ref. 122, American Chemical Society.

detection of tumor cells. These nanoparticles were used in mice to efficiently transport cargo to tumor sites, then selectively detect the presence of HeLa tumors in real time. This is one of the first reports

of a bioamplifier incorporated to increase the signal-to-noise ratio, thus achieving picomolar sensitivity and an output that is detectable by imaging¹²⁶.

Protein circuitry

The use of recombinant proteins for biomaterial design is a relatively new field compared with synthetic materials, with many spaces still unexplored. Protein-enabled approaches support increasingly sophisticated methods to control biomaterial properties. Protein engineering has been used to develop crosslinks or polymers with precise molecular design and controlled polymerization mechanisms. Many protein-based tools (such as proteases, light-responsive proteins and inteins) can be used to engineer circuitry that imparts new material properties and expands material function by creating integrated bioprocessing platforms with multiple unit operations and feedback control systems. For example, beyond their applications in synthetic biology, inteins have been deployed to great effect in synthesizing biomaterials and biohybrids with tunable properties. They have been co-opted for the assembly of circularized nanodiscs¹²⁷, protein–quantum dot fusions¹²⁸ and bespoke nanostructures with impressive stability profiles¹²⁹. Beyond protein nanostructures, the *Npu* intein has also been used to scarlessly assemble hydrogel constructs^{130,131}, which could serve as a convenient route for enzyme immobilization in industrial biocatalysis applications.

Another powerful stimulus for material actuation is light, where proteins with photoresponsiveness can be used to alter material properties or trigger interactions¹³². For example, PhoCl can be expressed heterologously as a fusion with different bioactive proteins, and then be used to dictate photo-release from materials with spatiotemporal control¹³³ or to degrade intact gels^{134,135}. Dronpa, derived from coral, has been re-engineered into a photoswitchable dimeric protein, pdDronpa¹³⁶, for which different wavelengths of light drive reversible assembly. By controlling the tether length of cell adhesion motifs from material surfaces, pdDronpa enables light-based control of integrin tension and spatiotemporal control over cell fate¹³⁷. Light–oxygen–voltage-sensing domain 2 (LOV2) has been used in materials to add reversible stiffening–softening behavior and spatiotemporal control over mechanical properties, hence controlling cell fate^{138,139}.

Enzymes such as transpeptidases have proven useful for controlled material functionalization with proteins, enabling the addition of fluorescent or bioactive cargo to materials. For example, sortase has been used to attach photo-responsive cages to proteins and control ligation to hydrogels spatiotemporally through photochemical uncaging and controlled binding kinetics, making advanced material patterning possible with bioactive proteins¹⁴⁰. Sortase has also been used in a conjugation technique to site-specifically ligate proteins to microgels¹⁴¹ or nanoparticles¹⁴², enabling controlled surface functionalization. Sortase can be employed to degrade biomaterial networks that contain its recognition sequence within the polymer backbone¹⁴³, with orthogonal sortases useful for the stepwise softening of interpenetrating networks¹⁴⁴.

Another suite of important protein tools consists of those based on fragment reconstitution¹⁴⁵. A widely adopted example is the SpyTag/SpyCatcher chemistry¹⁴⁶, in which a smaller peptide—the Tag—recognizes a larger protein partner—its cognate Catcher—and forms a covalent isopeptide bond with diffusion-limited kinetics. SpyTag/SpyCatcher has been co-opted to great success in protein cyclization¹⁴⁷, chromatographic purification¹⁴⁸ and antibody engineering¹⁴⁹. Similarly, penicillin-binding protein 3 has been re-engineered into PenTag, a small protein that can form a covalent bond with its target ligand, ampicillin¹⁵⁰. These protein technologies enable the design of biohybrid materials with molecular computing capabilities. For example, PenTag modified with flanking protease-labile sequences serves as a covalent crosslink for ampicillin-modified polymeric hydrogels, enabling YES and OR logic-based release¹⁵⁰.

Another approach to creating biohybrid hydrogels is attaching split proteases to functionalized natural materials and then activating or inhibiting them based on input signal. Thus, the split proteases operate as conditional biocatalysts with signal-dependent activity

(Fig. 6a)¹⁵¹. For example, when a specific antibiotic (for example, novobiocin) and/or ethylenediaminetetraacetic acid (EDTA) are added, the TEVp and TVMvp split proteases are released from the materials with high specificity, restoring function via YES logic. In a third construct, caspase-3 with protease sites flanking its N- and C-termini supplements agarose crosslinking and then enables AND-gated release and, subsequently, deactivation of both split proteases TEVp and TVMvp.

Harnessing recombinant expression and several aforementioned chemical biology tools, autonomously compiling single-chain topologies have been created that follow YES/OR/AND logic in response to proteases and can be hierarchically stacked for complex logical operations⁸³ (Fig. 6b). These topologies contain protein cargos that can be site-specifically tethered to and conditionally released from biomaterials following user-programmable Boolean logic. These materials have enabled multiplexed delivery of three distinct biomacromolecules, five-input-based conditional cargo liberation, and the release of growth factors, enzymes, nanobodies and de novo cytokines¹⁵².

An alternative protein-based strategy for incorporating Boolean logic within materials is enzyme cascading, in which inputs are processed within the material—acting as a bioreactor—into a stimulus that triggers a desired output. For example, supramolecular assembled peptide-based hydrogels with encapsulated enzymes (nitroreductase and glucose oxidase) have been engineered to incorporate logic-based degradation¹⁵³ (Fig. 6c). The peptides were designed to be redox-responsive, enabling programmable gel–sol transitions upon a range of stimuli that trigger enzymatic production of H₂O₂ and subsequent gel degradation. OR and AND responses were achieved in hydrogel–enzyme hybrid materials, enabling release of an antibody drug on demand.

Similarly, a bioreactor hydrogel system has been designed that uses enzymes to create a temporal pH feedback loop, enabled by a tandem YES-then-NAND gate¹⁵⁴. When the ground state (0 = acidic, pH < 7) is neutralized by the addition of a base, the desired output (1 = alkaline, pH > 7) is achieved, leading Fmoc-ethylenediamine hydrochloride to assemble into fibrils and form a hydrogel. Upon the addition of sugar, invertase or β -galactosidase AND glucose oxidase, the pH slowly reduces to the ground state (0). The result is a gel–sol transition, which resets the system; of note, reversibility of computation has only rarely been demonstrated in stimuli-responsive biomaterials. In a related design, a double-spherical porous polymer nanoparticle could be selectively loaded with enzymes or drugs into either sphere, based on surface chemistry and pore size¹⁵⁵. These nanoparticles function as compartmentalized reactors with size-selective separation and controlled loading capacity. Depending on the inputs, the enzymes within convert the input into an acid and release doxorubicin when a low internal pH is achieved, using YES/OR/AND logic.

These examples demonstrate the benefits of installing biocomputing in material systems to create intelligent processing materials with adaptive response capabilities. These systems could revolutionize personalized medicine, biosensing, tissue engineering and more by enabling precision manufacturing and targeted therapeutic delivery. Although there has been extensive progress in the design of proteinaceous tools, the convergence of recombinant polymers with enzyme-mediated pathways in materials represents a transformative frontier. Future work could unlock materials that bridge biology and engineering through hybrid bioprocessing systems that combine the precision of biological systems with the robustness of engineered materials.

The interface of living systems and biomaterials

We now stand at a remarkable nexus of chemical engineering innovation. On the one hand, synthetic biology has enabled the metabolic engineering of valuable chemicals across different industries. Small molecules and nucleic acids can provide tight control over gene transcription and expression, while protein technology enables tailored presentation and release of functional molecules in living systems.

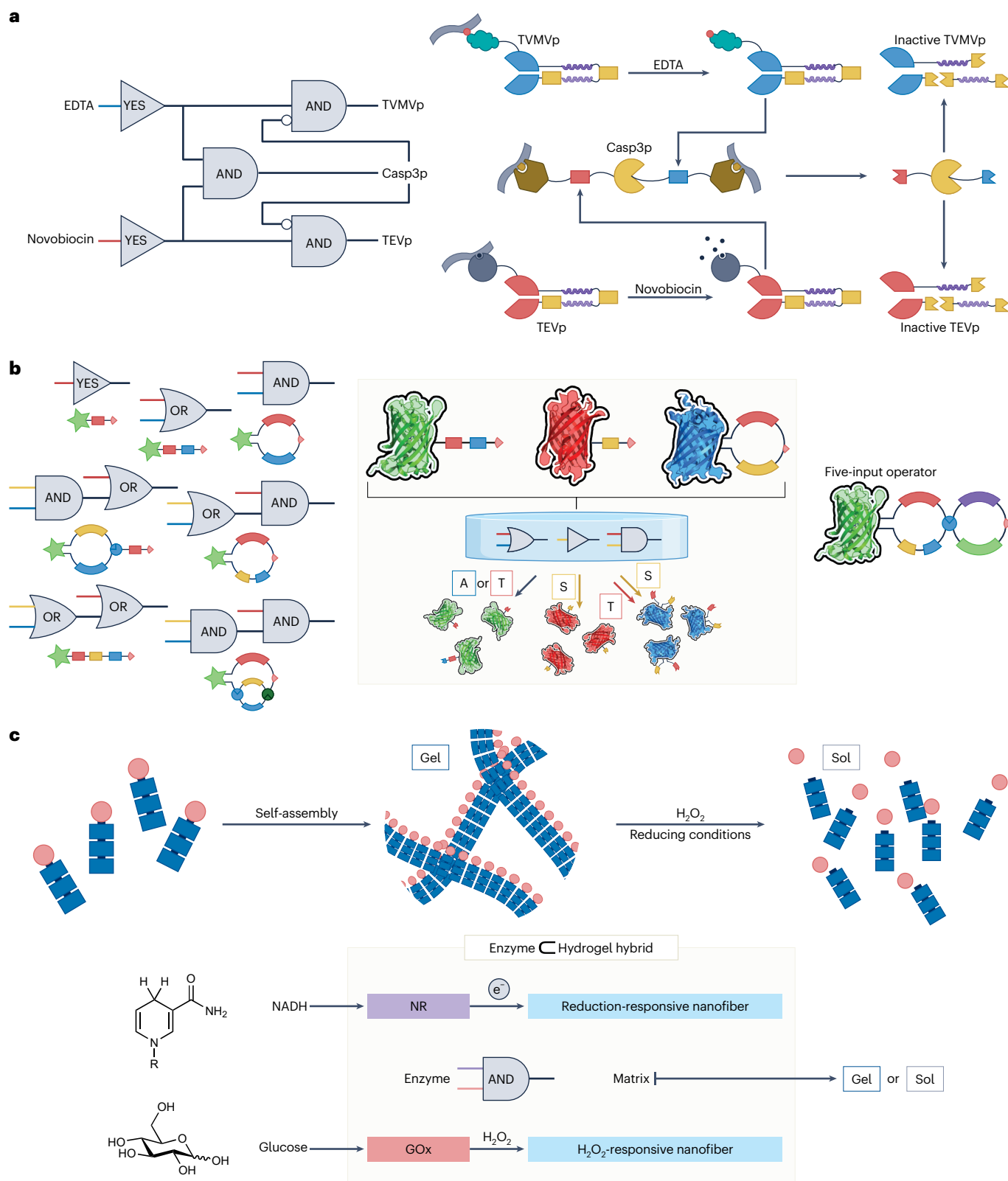


Fig. 6 | Protein-based material approaches to incorporate biocomputation.

a, Design of a binary decoder¹⁵¹ based on split proteases (TVMVp and TEVp). When the inputs are added (the antibiotic novobiocin and ethylenediaminetetraacetic acid, EDTA), active proteases are released from the material, resulting in the freedom of crosslinked Caspase3 protease (Casp3p) and inactivation of both split proteases. **b**, Recombinant protein-based logical operators use the tools of chemical biology to autonomously compile topologies. Logical operators can be used to site-specifically tether and conditionally release proteins in the presence

of proteolytic inputs (denoted A, T and S) from polyethylene-glycol (PEG) hydrogels (such as mGreenLantern, mCherry and mCerulean). Methods have been extended for up to five inputs⁸³. **c**, Tri-peptide monomers self-assemble into fibrils until redox inputs (such as NADH or glucose) cause gel dissolution. When the enzymes nitroreductase (NR) and glucose oxidase (GOx) are encapsulated, small-molecule inputs can be used to control the gel–sol transition¹⁵³. Panels adapted with permission from: **a**, ref. 151 under a Creative Commons license CC BY 4.0; **b**, ref. 83, Springer Nature America, Inc.; **c**, ref. 153, Springer Nature Limited.

On the other hand, to name a few examples, biomaterials can now be programmed to exhibit on-demand degradation and drug release via synthetic crosslinks or protein-based constructs, while aptamers can dictate precise therapeutic targeting. As engineers continue to expand the level of design precision through biocomputation, many nuanced physiological structures become a closer reality *ex vivo*.

We envision a future ripe with innovation provided synergies between living systems and biomaterials can be captured. As with any major chemical engineering undertaking, a convergence of disciplines that bridge concepts from genome sciences, electronic circuits and protein design, among others, will be necessary to drive the field forward. In the following sections, we examine how biocomputation is an enabling framework for innovation, and the future directions for combining living systems with biomaterials to form living materials.

Boolean logic as an enabling framework

As evidenced by the many works we have cited in this Review, formalizing the design of stimuli-responsiveness into Boolean logic frameworks has led to a powerful upgrade in programmable cellular populations and bioactive materials. Boolean circuits enable spatiotemporal control over gene and protein expression, advancing bioprocessing and the exploration of cellular function. The field continues to push toward greater functional complexity while addressing limitations in scalability. Circuits within living systems have achieved multi-input and output biocomputation, reversible switches, information storage and complex feedback loops. Expanding biomaterial response complexity remains a goal of the community. Although Boolean logic has enabled rudimentary material computation, the broader adoption of synthetic biology principles could substantially expand biomaterial capabilities. Multi-pathway biocomputation and feedback mechanisms could enable biomaterials to autonomously release drugs, control degradation, and perform advanced sensing for medical and environmental applications. For example, integrating information-processing and storage capabilities directly into biocompatible materials could enable multiplexed biosensors without an electrochemical interface¹⁵⁶. Generally, it seems that the encoding of Boolean logic circuits into materials is only the beginning of a new era of biomaterials that aspire to match cellular sophistication, achieving true biocomputation with multi-stimuli responsiveness and signal bidirectionality.

The underlying similarity between current design frameworks for synthetic biology and for biomaterials highlights interesting possibilities for each. Historically, living systems and materials have been considered distinct domains. In synthetic biology, even when engineering biomolecular components or whole cells, the structure of biological information is generally retained. This is reflected in how engineered circuits map onto natural transcriptional, translational or post-translational control. The idea of synthetic genomes—entire genomes designed and constructed *de novo*—remains tied to the biological importance of a genetic blueprint¹⁵⁷. Synthetic cells, or artificial constructs engineered to mimic cellular functions, still rely on biological building blocks such as membranes, nucleic acids and proteins¹⁵⁸. However, a unifying Boolean framework opens the door to biomaterials with cellular sophistication and, in turn, living systems that transcend current biological frames of reference.

Creating ‘living’ materials

Living materials are those that integrate living components (such as encapsulated microorganisms) alongside an abiotic yet stimulus-responsive scaffold¹⁵⁹. Autonomous growth, sensing, metabolite release and regeneration are hallmarks of natural tissues that engineered living materials (ELMs) aim to synthetically recreate¹⁶⁰. By incorporating engineered cells that respond to the external environment following user-installed biocomputation, control over material formation and degradation and other new functions can be achieved^{161,162}.

Inspired by natural biofilms, several groups have designed ELMs with a protein-based nanofiber scaffold to encapsulate bacterial cultures. In one approach, a genetic circuit was leveraged to induce His-tagged nanofiber expression, generating inducible proteinaceous domes over individual bacterial colonies that could be functionalized with gold nanoparticles conjugated with a Ni-nitrilotriacetic acid (NTA) group. These flexible, conductive composites were used as electrical pressure sensors¹⁶³. Another more recent example combined protein design with genetic circuit assembly in *Lactococcus lactis* to establish controllable biofilm assembly and decomposition: besides classic TF regulation, deactivated Cas9 was directed to promoters to turn off biofilm assembly, while proteases were linked to inducible circuits to control biofilm breakdown¹⁶⁴. ELMs have also been developed using stable co-cultures of cellulose-producing bacteria and yeast, enabling separated but symbiotic material production and functional modification for applications in biosensing or the degradation of environmental pollutants¹⁶¹.

In some ELMs, the living component only confers new functions to the encapsulating static material. ‘Bactosensors’ are engineered cells containing computing circuits that produce reporter signals upon detection of target analytes such as disease-relevant oligosaccharides¹⁶⁵ and IPTG¹⁶⁶. These engineered cells can be encapsulated in static matrices that allow the inward diffusion of analytes while providing a permissive scaffold for sustained cell viability¹⁶⁷.

Some recent work has also invoked the term ‘living material’ in approaches that utilize cells as both the material and the living system. Synthetic protocells were designed from lysing separate living bacterial populations in coacervate droplets. The encapsulation of living *E. coli* within protocells was also demonstrated, and it was noted that these living bacteria could be used to establish robust genetic circuitry within these protocells^{168,169}. Another example of living cells used as a material is in bioactuators for soft robots. Engineered skeletal muscle tissue can move *in vitro* as a result of applied electric fields and has been widely studied as a controllable actuator in biohybrid machines¹⁷⁰.

As illustrated by these examples, most current ELMs utilize the living component as the information processor, while the material adopts a passive role. Few designs exploit material signals (such as stress, immobilized cargo or recognition tags) to trigger computation in living components. By embedding circuitry into scaffold materials, increasingly powerful and tissue-like ELMs could be created. Cells could modify their underlying ‘circuits’ over time in response to computing materials, in addition to cells rearranging the circuits of materials. With more advanced information processing within the encapsulation material, it might be possible to implement functions that require physical rearrangement—such as long-term memory—outside the cell, while enabling the cell to access this external information through a synthetic intercellular signaling strategy.

On an extreme level, material–cell interactions could act analogously to intercellular interactions in a multicellular circuit. Complex behavior might emerge at the level of the entire living-material composite. An evolving theme among bioengineers is that of collective intelligence¹⁷¹, which refers to the capacity of distinct biological levels (cellular, tissue and whole organism) to solve problems. As biocomputation and the techniques of implementation continue to improve in biomaterials, it may become possible to develop logical operations at the macroscopic level of a living material by layering circuits within both the encapsulated microorganisms and the material matrix: for example, building circuits within the bridging material between two cells that would generate an output (such as releasing small binding proteins) based on the secretion or communication between the cells. If these small binding proteins could then interact with the synthetic receptors on the surface of the cells and regulate their gene expression, a simple feedback circuit with a well-defined and controllable input on a supra-cellular scale could be established. Another exciting thought is the possibility of material–cell composites with circuits that can be

mutually and reversibly rearranged. Although cells naturally remodel materials, the reciprocal effect of materials on cellular activity is often overlooked. With a unifying Boolean logic framework, this reciprocal effect can be better clarified and intentionally engineered.

From a practical standpoint, engineering the interaction between materials and living systems comes with its own set of challenges. A primary challenge is designing matrices that can support the survival of living components, which are often short-lived and sensitive to harsh material processing conditions. As a result, an important obstacle to the real use of ELMs is designing these materials to have a longer life span and still retain their intended function¹⁷². The challenge is exacerbated by the lack of understanding of matrix–cell interactions, especially from an engineering perspective. Controllable systems and quantitative tools need to be designed that can capture these interactions across spatial and temporal scales¹⁷³. Most reports on ELMs have been published in the past five years, so safety and quality control still need to be standardized, particularly for medical applications where biomaterial compatibility standards for living organisms have not yet been rigorously studied. Tackling these issues while designing circuits into both materials and cells is certainly not a trivial task.

Further efforts must be made to better understand the interaction between cells and their surrounding materials. Engineering matrices to support cells with more intentionality through a Boolean framework may help with formalizing such knowledge for engineering purposes. Current work to expand the biocomputing toolbox, with particular emphasis on expanding input types and physical substrates, should remain a priority. Additionally, methods linking external material signals to gene expression or other cellular outputs also warrant further development. Living materials are an exciting frontier of research, as the shift begins from passive biomaterials to those that can autonomously sense, process and respond to their environment, creating opportunities to address the most pressing challenges in therapeutics, manufacturing and sustainability.

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R.G., M.L.R., A.L., S.P.K. and C.A.D. wrote the paper. M.L.R. prepared the figures, with input from all other authors.

Competing interests

The authors declare no competing interests.

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