

Could Living Cells Use Phase Transitions to Process Information?

Arvind Murugan^{1,*} David Zwicker² Charlotta Lorenz³ and Eric R. Dufresne^{3,†}

¹*Department of Physics, University of Chicago, Chicago, Illinois, USA*

²*Max Planck Institute for Dynamics and Self-Organization, Göttingen, Germany*

³*Department of Physics, Department of Materials Science And Engineering, Cornell University, Ithaca, New York, USA*



(Received 8 March 2024; revised 11 September 2025; published 12 May 2026)

To maintain homeostasis, living cells process information with networks of interacting molecules. Traditional models for cellular information processing have focused on networks of chemical reactions between molecules. Here, we describe how networks of physical interactions could contribute to the processing of information inside cells. In particular, we focus on the impact of biomolecular condensation, a structural phase transition found in cells. Biomolecular condensation has recently been implicated in diverse cellular processes. Some of these are essentially computational, including classification and control tasks. We place these findings in the broader context of embodied computation, an emerging framework for describing how the native dynamics of nonlinear physical systems can be leveraged to perform complex computations. The synthesis of these ideas raises questions about expressivity (the range of problems that cellular phase transitions might be able to solve) and learning (how these systems could adapt and evolve to solve different problems). This emerging area of research presents diverse opportunities across molecular biophysics, soft matter, and embodied computation.

DOI: [10.1103/j16b-xnms](https://doi.org/10.1103/j16b-xnms)

Subject Areas: Biological Physics, Complex Systems, Nonlinear Dynamics

I. INTRODUCTION

Living systems are far from thermodynamic equilibrium. They achieve a healthy steady state (i.e., *homeostasis*) across length scales through energy-consuming closed-loop control. Even an individual cell can sense and compute to mount appropriate responses to external stimuli or internal changes of state, shown schematically in Fig. 1(a). Environmental cues could include sources of nutrients or stress [1–3]. Internal signals can originate from many sources, including stochastic expression of genes [4] or the depletion of metabolites [5].

From an information perspective, homeostasis is a *control* problem. In some cases, cells respond to relatively simple “one-dimensional” stimuli such as the concentration of a single species. For example, *E. coli* and neutrophils move themselves up a concentration gradient in a process called chemotaxis [7,8]. More generally, cells process a vast array of physical (e.g., matrix stiffness) and chemical signals (e.g., soluble and matrix-bound growth factors). Processing of

these high-dimensional stimuli can include *classification*, the assignment of a label to a broad range of input values to summarize the relevant pattern in the signal. Classification allows cells to mount distinct responses to complex stimuli, such as advancement in the cell cycle (growing, dividing, or going dormant), switching of mechanical state (free-floating, adhering, or crawling), and differentiation into a specific cell type [9–12]. Indeed, classification has been recognized as an essential step in stem cell differentiation [13,14]. The patterns triggering particular differentiation pathways require discrimination between many ligand combinations [15,16] and temporal patterns [17,18].

Mechanisms for information processing, i.e., methods to draw inferences about the environment, are woven into the molecular fabric of life. At this scale, information processing is often thought to be realized by complex networks of chemical reactions. Such *regulatory pathways* respond on short timescales through the interactions of proteins in the cytoplasm [19], and at longer timescales by coupling to gene expression in the nucleus [20]. While some functional subnetworks can be neatly dissected from the whole [21], this is usually not possible, as a typical node (i.e., molecule) can interact with many partners and contribute to many different functions [22,23].

In this Perspective, we discuss how two emerging topics in physics—biomolecular condensates and embodied computation—could complement each other and provide fresh insights and new tools for information processing by

*Contact author: eric.r.dufresne@cornell.edu

†Contact author: amurugan@uchicago.edu

molecular networks, particularly those inside living cells. After providing some concrete biological motivations, we describe how the basic physics of condensates could automatically achieve certain computational tasks, like classification and control. We then generalize these behaviors using essential ideas of embodied computation and highlight open research questions.

II. COMPUTING BY BIOMOLECULAR CONDENSATES

After briefly describing biomolecular condensates, a recently appreciated class of structures in cells, we describe how the physics of condensation can simply solve classification and control problems, and place these observations into the framework of embodied computation.

A. What are biomolecular condensates?

Biological cells comprise thousands of different molecular components, which are organized into many spatial compartments. While some compartments are enclosed by lipid membranes (like the nucleus), *biomolecular condensates* are domains enriched in specific proteins and nucleic acids that form spontaneously through cohesive interactions of their constituents.

Typical biomolecular condensates include many distinct components. Stress granules, shown in Fig. 1(b), are thought to have hundreds of components [24]. These

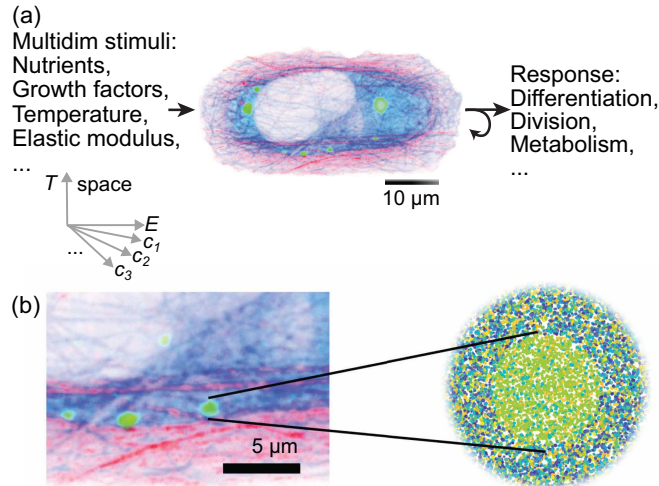


FIG. 1. Living cells compute, potentially using biomolecular condensates. (a) Cells integrate diverse chemical (e.g., concentrations c_1, c_2, c_3) and physical stimuli (e.g., elastic moduli E , temperature T), to determine their biological response. The shown U2OS cell is labeled for actin (pink), tubulin (blue), and the stress granule component G3BP1 (green) [6]. (b) Detail of (a) showing stress granules in green (left), which are fluidlike biomolecular condensates found in the cytoplasm that enrich many specific proteins and nucleic acids (schematic picture on the right).

components are enriched selectively based on physical interactions, which are dictated by specific sequences and chemical modifications (like oligomerization and post-translational modifications) [25,26]. While there has been no systematic census of condensates, merging the results of independent studies suggests that there are at least tens of distinct coexisting condensates [27]. The compositional variation across different types of biomolecular condensates yields compartments with distinct physical and chemical properties. Chemically, they can localize biochemistry through enrichment or depletion of enzymes [28] and diverse small molecules, including ions and metabolites [29,30]. Further, macromolecules could adopt novel conformations in condensates [31–33] that could impact their reactivity. Physically, condensates have diverse rheological properties (i.e., viscosity and elasticity), interfacial tensions, and electrostatic potential [34–38].

Condensation of these biological molecules can be conceptualized as *phase separation*, where a homogeneous mixture sorts itself into at least two different macroscopic domains. For systems near equilibrium, phase separation is understood as a competition of translational entropy favoring a homogeneous mixed state and cohesive interactions favoring segregation into different phases. The equilibrium configuration is described by phase diagrams, which show the preferred state of the system as a function of external parameters (Fig. 2).

When we consider an entire cell on timescales where production and degradation are negligible, the total amount of material in the system is conserved and we work in the canonical ensemble. In that case, large sections of the phase

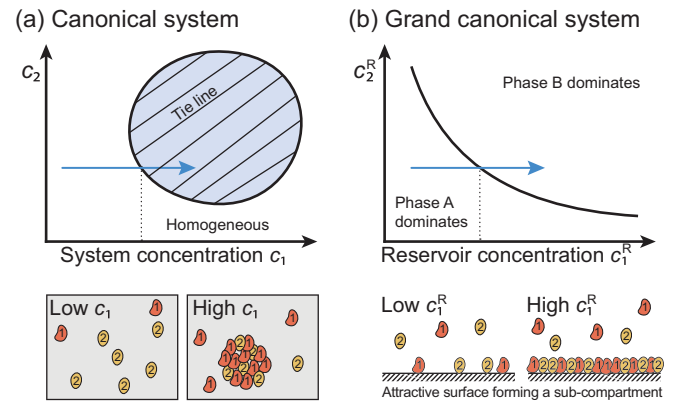


FIG. 2. Phase diagrams of biomolecular condensates. (a) Phase behavior of a closed system (canonical ensemble) as a function of the concentrations c_1 and c_2 of two components. In this example of associative phase separation (light blue area), domains rich in both components form as c_1 is increased to cross the phase boundary (blue arrow). (b) Phase behavior of a subcompartment coupled to a reservoir (grand canonical ensemble) as a function of the reservoir concentrations c_1^R and c_2^R . The composition in the subcompartment undergoes a discontinuous jump when c_1^R is increased to cross the phase boundary (blue arrow).

diagram will correspond to coexistence of multiple phases, which can differ in concentration by orders of magnitude [Fig. 2(a)]. Coexistence typically manifests as droplets enriched in a suite of molecules that are depleted in the surrounded “dilute” phase. For example, stress granules [Fig. 1(b)] are enriched with the protein G3BP1 among many other biomolecules. Stress granules can form spontaneously when the concentration of G3BP1 crosses a threshold [blue arrow in Fig. 2(a)]. Consequently, increasing the concentration of one component (c_1 in Fig. 2) can induce droplets that locally increase the concentrations of many components [lower right-hand panel in Fig. 2(a)].

Many condensates in cells form in small compartments, e.g., on membranes or at specific anchor sites [39,40]. If components are exchanged with the surroundings, the surroundings can be conceptualized as a reservoir maintaining fixed concentrations, which corresponds to the grand canonical ensemble [Fig. 2(b)]. In the associated phase diagram, regions of coexisting phases collapse into phase boundaries—off these boundaries, the system is either in one phase or another. For example, only a few molecules will associate with the compartment (low c_1 and c_2) if the concentration c_1^R in the surrounding bulk is low [lower left-hand panel in Fig. 2(b)]. When c_1^R is increased across the phase boundary [blue arrow in Fig. 2(b)], both concentrations c_1 and c_2 suddenly increase across the entire compartment [Fig. 2(b)]. This occurs when affinity toward the compartment and cohesive interactions of the components combine to overcome the entropic penalty of confinement.

In the following sections, we will describe how multicomponent phase separation could achieve complex computational tasks.

B. Condensation and classification

Classification is a challenging computational task, where a high-dimensional input $\vec{x}$, such as an image, is assigned to a discrete category y known as a “class.” A classic example is the discrimination of cats and dogs from images. A single image corresponds to a point $\vec{x}$ in a high-dimensional space of possible images, shown schematically in Fig. 3(a). Since nearby $\vec{x}$ typically correspond to the same class, the mapping $\vec{x} \mapsto y$ can be visualized by decision boundaries, defined as regions where y changes for small variations in $\vec{x}$.

Artificial neural networks have emerged as a powerful means to classify high-dimensional data [41]. They are represented by a set of synaptic weights w_{ij} that describe interactions between the “neurons” i and j in the network [Fig. 3(b)]. To achieve a particular classification task, the weights w_{ij} are adjusted in a process called “training.” Typically, artificial neural networks are implemented in software on generalized computing platforms.

An analogous picture holds for multicomponent phase separation in the grand canonical ensemble, represented by the schematic phase diagram in Fig. 3(c). A point $\vec{x}$ in a

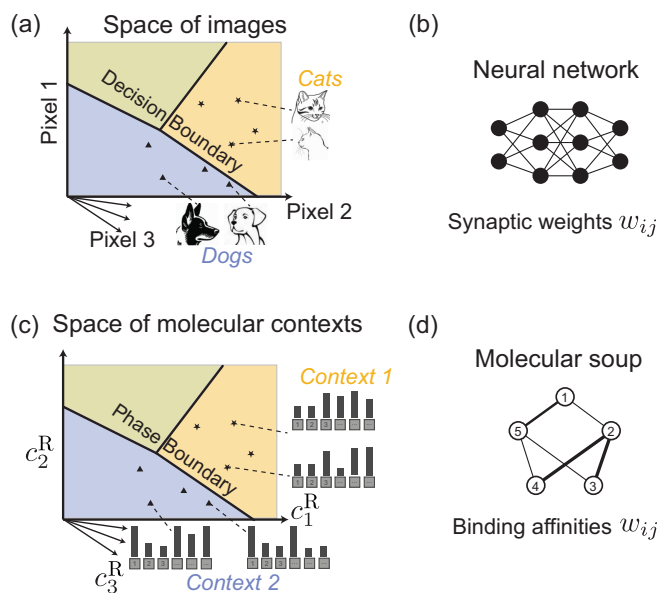


FIG. 3. Phase boundaries in multicomponent systems as decision boundaries. (a) A classification problem is solved by the right set of decision boundaries in the space of inputs (e.g., images). Each point in this diagram represents an image; the color denotes the output of classification (e.g., discrete classes such as “cat” or “dog” or other category). (b) Decision boundaries can be placed in the desired locations by tuning the parameters w_{ij} of a neural network. (c) In analogy, we interpret phase boundaries of multicomponent phase separation as decision boundaries. Each point in this diagram represents a high-dimensional molecular input, i.e., concentrations c_i of several molecular species. Molecular inputs on different sides of a phase boundary trigger the formation of distinct phases (outputs). (d) Phase boundaries can be placed as desired by tuning interaction parameters w_{ij} of molecular mixtures. Numbered nodes represent distinct molecular species; edges represent pairwise interaction parameters w_{ij} .

multidimensional phase diagram represents reservoir concentrations of the relevant “input” species. Crossing a phase boundary corresponds to a discontinuous change in structure and properties of the mixture, i.e., the formation of distinct phase y .

Comparing Figs. 3(a) and 3(c), we reinterpret phase transitions in a multicomponent system as classification of high-dimensional chemical compositions. Intriguingly, mean-field models of multicomponent phase separation [42,43] are analogous to artificial neural networks. They are built upon a network representation of molecular interactions, where a set of parameters w_{ij} describe the physical coupling of different molecular species, shown in Fig. 3(d). Just as w_{ij} adjusts decision boundaries in an artificial neural network, w_{ij} moves phase boundaries in a multicomponent system.

C. Condensation and control

Closed-loop control is an essential element of robust functional systems. In a typical control system, one uses feedback regulation to maintain some aspect of the

system—the controlled variable z —at a set point in the face of fluctuations in a high-dimensional external input $\vec{x}$ [44]. For example, a chemostat can maintain a fixed pH within a reactor, even as nonstationary chemical reactions consume and produce pH -active species. An engineered control system has subsystems for sensing, computation, and actuation. A sensing system transduces the system state into an abstract signal. A computational system processes signals from sensors, calculates the desired response, and communicates it to actuators. In the chemostat example, a pH sensor transduces the pH into a voltage, a microprocessor processes the pH history and communicates with an injector to introduce chemical species that offset the reaction’s effect on the pH .

Phase separation can greatly simplify control into a single physical process, without separate entities to sense, compute, and actuate. In a widely discussed example, phase coexistence can suppress concentration fluctuations [28]. Consider a molecule whose total concentration fluctuates (due to factors like cell division or stochastic gene expression), which serves as an external input or disturbance x . Phase coexistence in the canonical ensemble suppresses these fluctuations by maintaining stable concentrations z within each of the coexisting phases. To absorb changes to the total concentration, the system adjusts the fraction of volume occupied by either phase. This mechanism is well established in simple one- and two-component systems and has been observed in some strongly self-segregating cellular components [45]. However, it remains unclear whether such robust buffering through phase separation extends to condensates containing many components without requiring fine-tuning [46].

D. Examples from living cells

Cells utilize biomolecular condensates to trigger discrete courses of action, e.g., to decide which genes to express. Gene expression requires the assembly of many proteins (RNA polymerase, mediator complex, and others) at a particular location on the chromatin to initiate transcription [47,48]. The assembly is triggered by the presence of regulating molecules (transcription factor, coactivators, and enhancers), which recognize a motif on the chromatin. The formation of such transcriptional condensates is a classification, which converts the high-dimensional regulatory input into a discrete transcriptional outcome.

The immune system provides another example for classification via phase separation: When T cell receptors are exposed to the right combination of input features on an antigen-presenting cell (e.g., antigen affinity, dwell time, costimulatory ligands, and local kinase activity), signaling proteins condense at the immunological synapse [49,50]. This drives full T cell activation, effectively classifying diverse ligand inputs into an all-or-none immune response.

Condensates also naturally help the cell solve control problems since the reorganization of molecules into

condensates allows cells to maintain homeostasis. Compared to other regulatory mechanisms, such as transcription, translation, or protein degradation, condensation is more rapid and metabolically efficient. For example, most prestress mRNAs and many RNA-binding proteins (e.g., translation initiation factors, poly(A)-binding proteins) condense into stress granules [51,52] in response to stress. This sequestration reduces bulk translation, freeing up ribosomes to prioritize newly transcribed messages critical for stress survival, while preserving older transcripts for later reuse [53]. In this way, stress granules rapidly rewire translation without requiring new transcription. A similar sequestration is observed for ribosomal subunits that cannot form a complete ribosome [54]; such sequestration provides a more metabolically efficient mode of regulation than protein degradation.

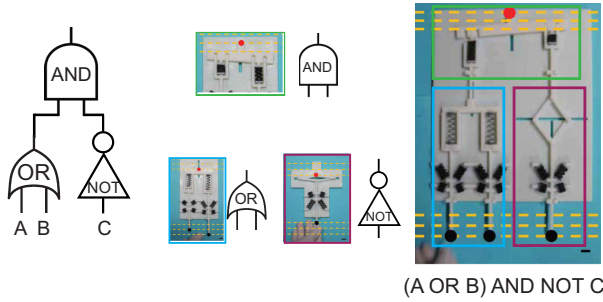
Similarly, condensates allow for quick response time when unfolded proteins accumulate in the endoplasmic reticulum (the unfolded protein response) [55]. These unfolded proteins trigger a condensate composed of an enzyme (IRE1) and its substrate (specific mRNA to be spliced) that alleviates that stress. Here, condensates allow for quick on and off response to stress by forming and dissolving the condensate that colocalizes enzyme and substrate.

E. Embodied computation and condensates

Our discussion has demonstrated the potential for phase separation to achieve classification and control. In this section, we place these observations in a broader context and contrast two approaches to achieving computation in a physical system: (a) classic systems engineering based on “separation of concerns” [56–58] and (b) embodied computation, though related ideas have been explored under analog computing and morphological computing [59–66].

A separation of concerns approach emphasizes abstraction and general solutions that are not tied to or exploit the physics idiosyncratic to a particular system [Fig. 4(a)]. Typical examples in biomolecular computation include systems and synthetic biology networks such as circuits of logic gates implemented with molecules. With this strategy, a control task might be split into subtasks of sensing, computation, and actuating a response; a layer of receptors might sense environmental “input” signals, a well-mixed molecular network (e.g., phosphorylation or dephosphorylation network) might carry out the computation, and finally a downstream physical process (gene expression, self-assembly, condensation) is actuated as the output [57,67–71]. This approach tends to produce modular solutions, with independent subsystems that complete discrete subtasks. This approach enables the familiar process of writing high-level computer code that can be implemented across a range of hardware platforms. It can be applied, for example, to the creation of an artificial neural network for classification.

(a) Separation of concerns-based computation



(b) Embodied computation

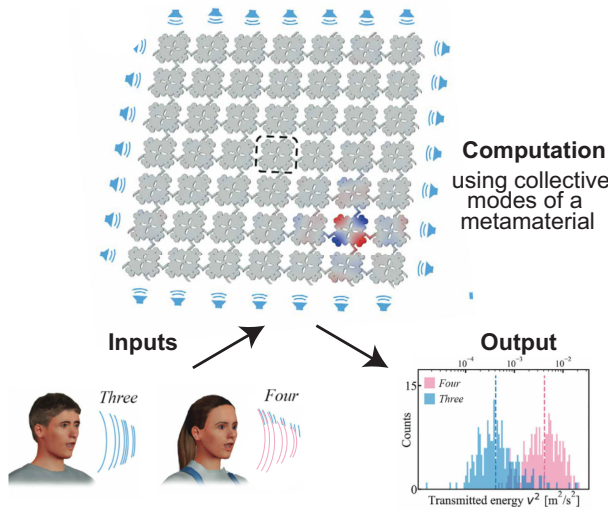


FIG. 4. Contrasting separation of concerns and embodied computation in mechanical systems. (a) A complex logical function is broken down into a network of elementary logic gates. Modular mechanical devices mimic logic gates and are assembled to realize the desired input-output relationship [72]. Adapted from Ref. [72] under a Creative Commons Attribution-Non-Commercial 4.0 International License (CC BY-NC 4.0). (b) An acoustic metamaterial consisting of a lattice of coupled vibrating plates whose resonance frequencies and couplings are optimized to classify audio input, separating the words “three” and “four.” Adapted from Ref. [73] under a Creative Commons Attribution (CC BY) license.

An alternative physics-first approach—embodied computation—does not separate software from hardware [59,60,63]. Instead, it exploits the intrinsic physics of a specific system to solve a problem [Fig. 4(b)]. Embodied computing solutions have been developed for classification problems in the optical [74], electronic [75], mechanical [76], and molecular domains [77–79]. For example, in the mechanical domain, the vibrational modes of a nonperiodic phononic metamaterial can be trained to recognize certain spoken words [73], as shown in Fig. 4(b). In robotics, complex control and computation have been off-loaded to passive mechanical dynamics, e.g., creating passive

dynamic walkers that can stably walk down a ramp without any sensors or electronic control loops [80–82]. In the molecular context, the kinetics of nucleation and growth in DNA self-assembly can classify patterns in the concentration of a many-component mixture [79].

Such physically embodied computation generally affords compelling advantages. This framework tends to produce solutions that are energy efficient, with the input signal often providing the energy needed for the computation [73,75,79]. In addition, solutions tend to be compact, since the collective physics of a set of components can achieve sensing [51], many layers of computation, and response without dedicating separate modules to each role. For example, the embodied computation approach to molecular pattern recognition in Ref. [79] used phase boundaries as decision boundaries (as described in Sec. II and Fig. 3); environmental conditions that were to be classified into two different categories (with different molecular responses) were separated by placing a phase boundary (for crystallization) between those conditions. In this approach, the entire process of sensing, computation, and response is achieved by one physical process, namely, the nucleation and growth of a specific phase in a specific part of the phase diagram.

The main downside of embodied computation is that solutions cannot be devised in the abstract, independent of the physics of the system. This aspect is a limitation for general purpose computing [63], but in the context of biology, parsimony, compactness, lower energy costs, and robustness appear to give embodied computation a decisive advantage.

III. CLASSIFICATION POWER OF CONDENSATES

In this section, we discuss the potential for phase separating systems to classify complex high-dimensional inputs. After describing the classification problem in more detail, we discuss open questions in classification by phase separation.

A. Quantifying computational abilities

Just as physicists have metrics for physical properties (transport coefficients, elastic moduli), computer scientists have developed metrics for quantifying computational abilities of a system. Here, we describe metrics developed to quantify the ability of systems to solve diverse classification problems.

Sharpness. The most elementary property of a decision boundary relevant to information processing is its sharpness, e.g., characterized by the maximum slope of sigmoidal response curves in Fig. 5(a). A shallow slope implies a graded response, which can reduce computational precision by introducing ambiguity near the decision threshold. In contrast, sharp transitions can enable decisive, high-fidelity

outcomes. Idealized phase transitions in the grand canonical ensemble are infinitely sharp. In real molecular systems, sharpness can be limited by finite system size and kinetic effects (described below).

Capacity. We define capacity as the number of potential outputs that a system can produce; it limits the number of distinct categories that high-dimensional inputs can be mapped onto. In a wide family of recurrent neural network models inspired by Hopfield's work [83], capacity quantifies the number of distinct stable attractor states that a system can support. In these systems, capacity is known to scale with the number of neurons and depends on the architecture of the underlying network [84,85]. For phase separation in the grand canonical ensemble, capacity can be quantified by the number of distinct phases in a phase diagram as reservoir concentrations are varied [e.g., like that shown in Fig. 5(b)]. Such a capacity has been quantified for crystalline phases [86], polymer states [87] and, most relevant to this perspective, for liquid phases [43,88]. In the canonical ensemble, multiple phases can coexist. In this case, capacity is greatly expanded, and can be quantified as the number of distinct combinations of coexisting phases.

Expressivity. Expressivity quantifies the range of classification tasks a system can perform or, more broadly, the system's ability to compute outputs from inputs (e.g., approximating arbitrary functions [89]). There are multiple measures of expressivity [90,91], but they all capture the range of input-output relationships that a system can encode. For example, given an input space and an output

space, a more expressive system can solve more complex classification tasks as system parameters w_{ij} are varied; see Fig. 5(c). One quantification of expressivity (Vapnik-Chervonenkis dimension [91]) relies on determining the most complex classification problem a particular family of systems can solve (how many arbitrarily chosen points can it discriminate as belonging to one of two classes); more expressive systems can distinguish sets with more points. Expressivity correlates with the possibility of placing decision boundaries flexibly in the input space as parameters of the underlying system (e.g., neural network weights w_{ij}) are varied. For instance, deeper neural networks have higher expressivity under this metric [90].

For phase separation, expressivity would be summarized by phase boundaries in a phase diagram, as shown in Fig. 5(c). When physical parameters (e.g., binding affinities w_{ij}) are optimized, systems with higher expressivity can place their decision boundaries to accommodate more complex input patterns than less expressive systems, e.g., deploying different responses to stimuli that differ only through subtle higher order correlations; see Fig. 5(c).

B. Physical determinants of computational abilities

Research over the years has shown how neural network architecture impacts computational abilities as quantified by these metrics; e.g., deeper networks are more expressive. However, we do not currently understand how the physics of multicomponent phase separation determines its computational abilities. Here, we highlight some key questions

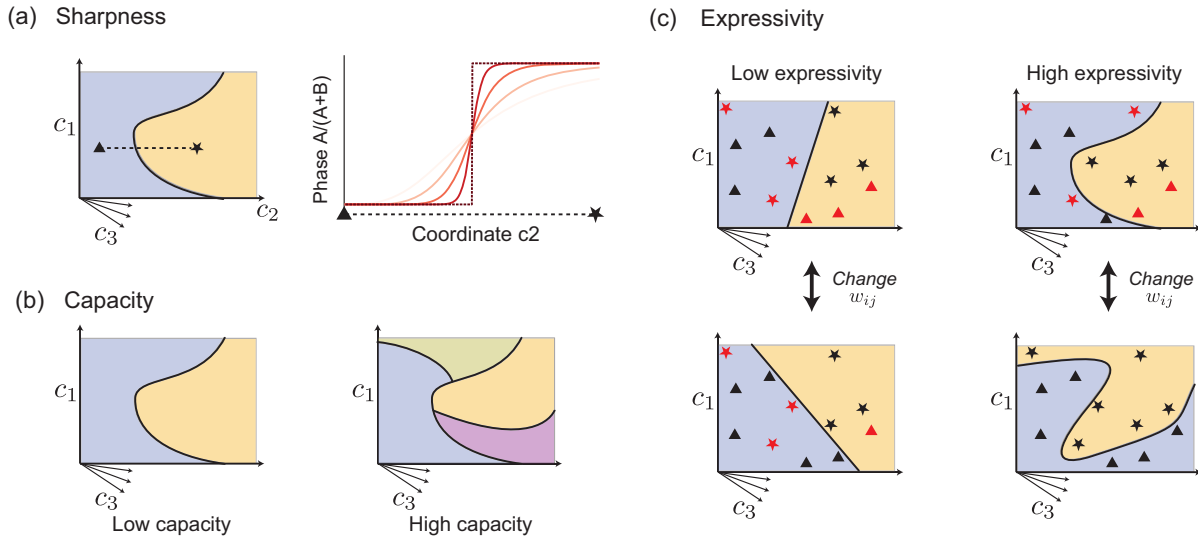


FIG. 5. Quantifying computational capabilities of phase diagrams. In all panels, axes correspond to representative input dimensions (e.g., concentrations of molecular species), and distinct colors denote different phase responses (outputs). (a) Sharpness of phase boundaries can be quantified by the maximal slope of the response as one crosses a phase boundary; low sharpness can limit the decision quality by producing mixed or ambiguous outcomes. (b) Capacity, the number of distinct phases in a phase diagram, limits the number of distinct output categories. (c) Expressivity quantifies the ability to classify diverse datasets by tuning interaction parameters w_{ij} . Stimuli corresponding to triangles and stars are meant to evoke two different phases (blue and yellow, respectively) as responses. Black and red symbols denote stimuli that evoke correct and incorrect responses, respectively.

and preliminary work done toward this question and work that remains to be done.

Hidden components as hidden neurons. Phase separation can involve molecular species that are neither “inputs” nor “outputs.” These “hidden” species can mediate more complex phase behavior by interacting and cocondensing with the input and output molecules [76,79,92,93]. Consider a molecular system with N species, where only M species serve as inputs and outputs. Even if the full $N \times N$ interaction matrix ω_{ij} is fixed, the $M \times M$ apparent interaction matrix for the inputs and outputs depends on the concentrations of the $N - M$ hidden species. Thus, the concentrations of these hidden components can be tuned to expressively manipulate the positions of phase boundaries relative to the concentrations of input species. In this way, hidden molecules would play the role of hidden layers in deep neural networks that do not directly interface with input or output, but increase the expressivity of input-output maps [90,94]. Since hidden molecules interact in a reciprocal manner (i.e., $\omega_{ij} = \omega_{ji}$), they are analogous to hidden neurons that increase expressivity in Boltzmann machines [95] rather than in feedforward networks with nonreciprocal interactions.

Nucleation boundaries for higher expressivity. Phase boundaries, like that shown in Fig. 5, are usually understood to describe first-order equilibrium phase transitions. However, condensation outcomes are rarely determined solely by equilibrium thermodynamics. Instead, they could be dominated by nucleation. For example, certain concentration patterns of input species might preferentially promote the nucleation of one type of droplet over another, even if the latter is thermodynamically more stable. In this case, decision surfaces shown in Fig. 5 are determined by the competitive nucleation of different phases. Despite not being thermodynamic boundaries, such kinetically determined boundaries can nevertheless be sharp, especially when coupled to competition effects [79,92].

Decision surfaces determined by kinetics are known to be more expressive than equilibrium phase boundaries for self-assembly [79,96]. For example, a region of the phase diagram with only one equilibrium phase can nevertheless show multiple kinetic phases. The stabilization of specific kinetic phases could be achieved through surfactantlike species that reduce nucleation barriers. Such computational benefits of nucleation in the context of liquid-liquid phase separation have yet to be systematically explored.

Ripening for temporal information processing. Phase separation involves numerous transient phenomena. The finite timescales of these phenomena can be used for processing temporally coded information in input signals [18]. One recent example exploits the kinetics of Ostwald ripening to deploy DNA damage repair programs in response to specific oscillatory waveforms in the upstream transcription factor p53 [97]. A similar coarsening process

also ensures a well-defined arrangement of droplets that determine where maternal and paternal genetic material is exchanged in germ cells of sexually reproducing organisms [98]. Finally, time delays inherent to nucleation of condensates of transmembrane proteins (LAT) are thought to be exploited for kinetic proofreading in T cell receptor signaling pathway [99–101]. This time delay is used to prevent activation of T cells by low affinity ligands. We do not have a broader sense of the range of temporal information processing enabled by the many kinetic aspects of phase separation.

Competition leads to sharper decisions. Both equilibrium and nonequilibrium mechanisms can enhance decision sharpness in phase-separating systems near phase boundaries. At equilibrium, ensemble choice has a defining role. When the system is coupled to a large reservoir of components (approximating the grand canonical ensemble), sharp transitions in droplet composition and volume can emerge from small changes in reservoir concentrations. In contrast, with fixed total concentrations (the canonical ensemble), equilibrium behavior yields more graded transitions, as droplets form gradually and grow continuously when control parameters (e.g., a component’s concentration) cross a phase boundary. Real systems can lie somewhere in between, depending on the size of the reservoir relative to the condensing subsystem [102].

Sharp decision making is still possible in the canonical ensemble setting if kinetic effects are considered. For example, if multiple phases capable of coexistence share a limiting component, small differences in nucleation rates can be amplified. A phase with slightly faster nucleation can rapidly deplete the shared resource, suppressing droplet formation elsewhere and leading to a winner-take-all outcome. This kinetic competition can produce sharp, effectively irreversible decisions that go beyond what equilibrium thermodynamics predicts.

Such depletion-driven competition has been shown to enhance classification in molecular systems with low intrinsic cooperativity, such as growth factor gradients [15,16,92] and other contexts [103,104]. Similarly, recent work in multicomponent self-assembly demonstrates that shared-component competition can sharpen phase boundaries beyond equilibrium limits [79]. While these effects have yet to be fully explored in the context of phase separation and computation, they suggest that even modest physical asymmetries can be harnessed to produce precise molecular decisions.

Nonequilibrium dynamics for enhanced control. Computation by condensate networks could be further enhanced when biomolecular reactions are actively driven using a source of energy, such as ATP hydrolysis. Such driven reactions feature prominently in known cellular regulatory networks, and their coupling to the cooperative physics of phase separation would extend their capabilities [105]. Driven reactions that affect droplet material can

suppress nucleation and effectively shift phase boundaries [106,107]. Cells could use this mechanism to suppress condensation until energy becomes scarce, which could trigger condensation in times of crisis [108]. Driven reactions can also control when and where droplets form, how large they become [109–111], and divide droplets when they are too large [112]. Such delicate control over morphology affects the physical interactions of droplets and thus also the integrated reaction network.

Chemical reactions coupled to phase separation can enable spatial control of pattern formation, as in nonideal reaction networks [113–116]. Driven reactions can maintain long-ranged compositional gradients, which could power information processing schemes. For example, active *in vitro* condensates have been shown to sense and “swim” toward each other, mediated through the chemical gradients they generate [107]. Similarly, spatial gradients inherent to condensates can be exploited to power proofreading mechanisms that enhance classification accuracy [117], without needing the molecular complexity required by traditional kinetic proofreading schemes [118].

C. Learning by condensates

A natural question raised by the idea of computation through phase transitions is how the relevant interaction parameters arise and how they can change due to experiences. While evolutionary processes can in principle tune biophysical interactions to generate functional phase diagrams, cellular adaptation often occurs on much faster timescales, requiring nongenetic mechanisms.

Recent work on “physical learning” suggests one possibility: Materials can acquire new behaviors by experiencing examples during a “training” period [94,119]. However, this framework has faced a mechanistic challenge: How can physical interaction parameters, the analog of neural network weights, be updated through local rules without genetic change? One solution is post-translational modification of proteins, which can alter their effective interactions by changing charge, conformation, or binding affinities, thereby reprogramming phase behavior [120,121]. The concept of hidden components in multicomponent phase separation, introduced earlier, provides another natural mechanism for training. In such systems, expression levels of hidden species modulate apparent interactions among inputs and outputs, even when the underlying interaction matrix is fixed [79,92,93]. When components are densely and promiscuously connected, modifying expression levels alone can reconfigure phase behavior—enabling distinct computations in different cell types [15,16,92] or subcellular locations, without requiring mutations. If expression levels are themselves influenced by the outcome of phase behavior, the system can, in principle, undergo Hebbian-like updates: For instance, phase separation may induce scaffolding protein expression [43,79,122], altering future interactions and behaviors. Selective degradation that preferentially

removes noncondensed molecules while sparing those sequestered in condensates can also reconfigure phase behavior [93,123]. Other plausible mechanisms for nongenetic learning include proximity-based chemical modifications that depend on colocalization in condensates; for example, transfer of acetylation marks between nearby chromatin regions implements a form of chemical Hebbian learning [124], with related ideas explored in synthetic systems [125,126]. While experimental training rules remain to be investigated, such architectures suggest a plausible route to local, nongenetic learning in molecular systems.

IV. CONCLUSION

This Perspective explores the potential of phase separation to process information in living cells. While phase separation has already been implicated in essential regulatory processes [28,51,127], this Perspective presents a broader view inspired by artificial neural networks. In lieu of the dominant systems biology perspective on signaling and gene regulation, which emphasizes modularity [57], we advocate for a physically embodied computation perspective, which emphasizes compact solutions that seamlessly integrate sensing, computation, and actuation. Phase separation is well suited to embodied computation because it involves many species, with a rich web of interactions. While embodied computing solutions may not be interpretable or portable, they could be favored by natural selection for their effectiveness and efficiency.

This perspective requires much experimental and theoretical investigation to be fully realized. The main experimental challenges revolve around the development of tractable model systems, where input signals can be readily controlled, output signals can be reliably read out, and physical and chemical couplings can be measured and manipulated. We expect that *in vitro* experiments with model systems will be necessary to reveal the essential capabilities and limitations of embodied computation in biomolecular systems [107,128–132]. While the basic physics of equilibrium phase separation has long been understood, viewing multicomponent phase separation as a computation raises new theoretical questions, which we have highlighted and organized. This research program requires understanding how traditionally studied physical effects—kinetics and nucleation, active processes, and spatial patterning—impact computational abilities such as expressivity, memory capacity, and sharpness of decision making. Solutions will integrate concepts from computer science, information theory, and physics, and will push the frontiers of active matter and biological physics.

ACKNOWLEDGMENTS

We thank Frank Jülicher, Peter McMahon, Robert Style, Mason Rouches, Erik Winfree, Cameron Chalk, Krishna

Shrinivas, Carla Fernandez-Rico, Jennifer Schwarz, William Jacobs, Gregory Carlson, and Richard Prum for their feedback on this manuscript. C.L. has received funding from the Deutsche Forschungsgemeinschaft (Project No. 523842861, No. LO 3088/1-1). A.M. acknowledges support from NIGMS of the National Institutes of Health under Award No. R35GM151211, National Science Foundation through the Center for Living Systems (Grant No. 2317138) and No. DMR-2239801. E.R.D. and A.M. acknowledge the NSF-Simons National Institute for Mathematics and Theory in Biology (National Science Foundation Award No. DMS-2235451 and Simons Foundation Award No. MPS-NITMB-00005320).

-
- [1] B. Desvergne, L. Michalik, and W. Wahli, *Transcriptional regulation of metabolism*, *Physiol. Rev.* **86**, 465 (2006).
 - [2] V. W. Wu, N. Thieme, L. B. Huberman, A. Dietschmann, D. J. Kowbel, J. Lee, S. Calhoun, V. R. Singan, A. Lipzen, Y. Xiong *et al.*, *The regulatory and transcriptional landscape associated with carbon utilization in a filamentous fungus*, *Proc. Natl. Acad. Sci. U.S.A.* **117**, 6003 (2020).
 - [3] R. R. Alfieri and P. G. Petronini, *Hyperosmotic stress response: comparison with other cellular stresses*, *Pflügers Arch.-Eur. J. Physiol.* **454**, 173 (2007).
 - [4] J. M. Raser and E. K. O'Shea, *Noise in gene expression: origins, consequences, and control*, *Science* **309**, 2010 (2005).
 - [5] B. R. Parry, I. V. Surovtsev, M. T. Cabeen, C. S. O'Hern, E. R. Dufresne, and C. Jacobs-Wagner, *The bacterial cytoplasm has glass-like properties and is fluidized by metabolic activity*, *Cell* **156**, 183 (2014).
 - [6] T. J. Bödeker, K. A. Rosowski, D. Berchtold, L. Emmanouilidis, Y. Han, F. H. Allain, R. W. Style, L. Pelkmans, and E. R. Dufresne, *Non-specific adhesive forces between filaments and membraneless organelles*, *Nat. Phys.* **18**, 571 (2022).
 - [7] O. D. Weiner, *Regulation of cell polarity during eukaryotic chemotaxis: The chemotactic compass*, *Curr. Opin. Cell Biol.* **14**, 196 (2002).
 - [8] H. H. Mattingly, K. Kamino, B. B. Machta, and T. Emonet, *Escherichia coli chemotaxis is information limited*, *Nat. Phys.* **17**, 1426 (2021).
 - [9] A. Dongre and R. A. Weinberg, *New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer*, *Nat. Rev. Mol. Cell Biol.* **20**, 69 (2019).
 - [10] B. L. Bohnsack and K. K. Hirschi, *Nutrient regulation of cell cycle progression*, *Annu. Rev. Nutr.* **24**, 433 (2004).
 - [11] D. T. Scadden, *The stem-cell niche as an entity of action*, *Nature (London)* **441**, 1075 (2006).
 - [12] A. J. Engler, S. Sen, H. L. Sweeney, and D. E. Discher, *Matrix elasticity directs stem cell lineage specification*, *Cell* **126**, 677 (2006).
 - [13] A. H. Lang, H. Li, J. J. Collins, and P. Mehta, *Epigenetic landscapes explain partially reprogrammed cells and identify key reprogramming genes*, *PLoS Comput. Biol.* **10**, e1003734 (2014).
 - [14] M. Smart and A. Zilman, *Emergent properties of collective gene-expression patterns in multicellular systems*, *Cell Rep. Phys. Sci.* **4**, 101247 (2023).
 - [15] Y. E. Antebi, J. M. Linton, H. Klumpe, B. Bintu, M. Gong, C. Su, R. McCardell, and M. B. Elowitz, *Combinatorial signal perception in the BMP pathway*, *Cell* **170**, 1184 (2017).
 - [16] C. J. Su, A. Murugan, J. M. Linton, A. Yeluri, J. Bois, H. Klumpe, M. A. Langley, Y. E. Antebi, and M. B. Elowitz, *Ligand-receptor promiscuity enables cellular addressing*, *Cell Syst.* **13**, 408 (2022).
 - [17] A. S. Hansen and E. K. O'Shea, *Limits on information transduction through amplitude and frequency regulation of transcription factor activity*, *eLife* **4**, e06559 (2015).
 - [18] J. E. Purvis and G. Lahav, *Encoding and decoding cellular information through signaling dynamics*, *Cell* **152**, 945 (2013).
 - [19] J. A. Papin, T. Hunter, B. O. Palsson, and S. Subramaniam, *Reconstruction of cellular signalling networks and analysis of their properties*, *Nat. Rev. Mol. Cell Biol.* **6**, 99 (2005).
 - [20] T. I. Lee, N. J. Rinaldi, F. Robert, D. T. Odom, Z. Bar-Joseph, G. K. Gerber, N. M. Hannett, C. T. Harbison, C. M. Thompson, I. Simon *et al.*, *Transcriptional regulatory networks in Saccharomyces cerevisiae*, *Science* **298**, 799 (2002).
 - [21] M. M. Babu, N. M. Luscombe, L. Aravind, M. Gerstein, and S. A. Teichmann, *Structure and evolution of transcriptional regulatory networks*, *Curr. Opin. Struct. Biol.* **14**, 283 (2004).
 - [22] J. Huelsken and J. Behrens, *The Wnt signalling pathway*, *J. Cell Sci.* **115**, 3977 (2002).
 - [23] D. E. Clapham, *Calcium signaling*, *Cell* **131**, 1047 (2007).
 - [24] J.-Y. Youn, B. J. Dyakov, J. Zhang, J. D. Knight, R. M. Vernon, J. D. Forman-Kay, and A.-C. Gingras, *Properties of stress granule and P-body proteomes*, *Mol. Cell* **76**, 286 (2019).
 - [25] A. S. Holehouse and B. B. Kragelund, *The molecular basis for cellular function of intrinsically disordered protein regions*, *Nat. Rev. Mol. Cell Biol.* **25**, 187 (2024).
 - [26] J.-M. Choi, A. S. Holehouse, and R. V. Pappu, *Physical principles underlying the complex biology of intracellular phase transitions*, *Annu. Rev. Biophys.* **49**, 107 (2020).
 - [27] N. Rostam, S. Ghosh, C. F. W. Chow, A. Hadarovich, C. Landerer, R. Ghosh, H. Moon, L. Hersemann, D. M. Mitrea, I. A. Klein, A. A. Hyman, and A. Toth-Petroczy, *CD-CODE: Crowdsourcing condensate database and encyclopedia*, *Nat. Methods* **20**, 673 (2023).
 - [28] S. F. Banani, H. O. Lee, A. A. Hyman, and M. K. Rosen, *Biomolecular condensates: Organizers of cellular biochemistry*, *Nat. Rev. Mol. Cell Biol.* **18**, 285 (2017).
 - [29] S. Ambadi Thody, H. D. Clements, H. Baniyadi, A. S. Lyon, M. S. Sigman, and M. K. Rosen, *Small-molecule properties define partitioning into biomolecular condensates*, *Nat. Chem.* **16**, 1794 (2024).
 - [30] A. E. Posey, A. Bremer, N. A. Erkamp, A. Pant, T. P. Knowles, Y. Dai, T. Mittag, and R. V. Pappu, *Biomolecular condensates are characterized by interphase electric potentials*, *J. Am. Chem. Soc.* **146**, 28268 (2024).

- [31] M. Farag, S. R. Cohen, W. M. Borchers, A. Bremer, T. Mittag, and R. V. Pappu, *Condensates formed by prion-like low-complexity domains have small-world network structures and interfaces defined by expanded conformations*, *Nat. Commun.* **13**, 7722 (2022).
- [32] N. Galvanetto, M. T. Ivanović, A. Chowdhury, A. Sottini, M. F. Nüesch, D. Nettels, R. B. Best, and B. Schuler, *Extreme dynamics in a biomolecular condensate*, *Nature (London)* **619**, 876 (2023).
- [33] L. Emmanouilidis, L. Esteban-Hofer, F. F. Damberger, T. de Vries, C. K. X. Nguyen, L. F. Ibáñez, S. Mergenthal, E. Klotzsch, M. Yulikov, G. Jeschke, and F. H.-T. Allain, *NMR and EPR reveal a compaction of the RNA-binding protein FUS upon droplet formation*, *Nat. Chem. Biol.* **17**, 608 (2021).
- [34] C. P. Brangwynne, T. J. Mitchison, and A. A. Hyman, *Active liquid-like behavior of nucleoli determines their size and shape in *Xenopus laevis* oocytes*, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 4334 (2011).
- [35] L. Jawerth, E. Fischer-Friedrich, S. Saha, J. Wang, T. Franzmann, X. Zhang, J. Sachweh, M. Ruer, M. Ijavi, S. Saha, J. Mahamid, A. A. Hyman, and F. Jülicher, *Protein condensates as aging Maxwell fluids*, *Science* **370**, 1317 (2020).
- [36] M. Ijavi, R. W. Style, L. Emmanouilidis, A. Kumar, S. M. Meier, A. L. Torzynski, F. H. Allain, Y. Barral, M. O. Steinmetz, and E. R. Dufresne, *Surface tensiometry of phase separated protein and polymer droplets by the sessile drop method*, *Soft Matter* **17**, 1655 (2021).
- [37] I. Alshareedah, M. M. Moosa, M. Pham, D. A. Potoyan, and P. R. Banerjee, *Programmable viscoelasticity in protein-RNA condensates with disordered sticker-spacer polypeptides*, *Nat. Commun.* **12**, 6620 (2021).
- [38] Y. Dai, Z. Zhou, W. Yu, Y. Ma, K. Kim, N. Rivera, J. Mohammed, E. Lantelme, H. Hsu-Kim, A. Chilkoti, and L. You, *Biomolecular condensates regulate cellular electrochemical equilibria*, *Cell* **187**, 5951 (2024).
- [39] M. Zeng, Y. Shang, Y. Araki, T. Guo, R. L. Haganir, and M. Zhang, *Phase transition in postsynaptic densities underlies formation of synaptic complexes and synaptic plasticity*, *Cell* **166**, 1163 (2016).
- [40] S. A. Shelby, I. Castello-Serrano, K. C. Wisser, I. Levental, and S. L. Veatch, *Membrane phase separation drives responsive assembly of receptor signaling domains*, *Nat. Chem. Biol.* **19**, 750 (2023).
- [41] Y. LeCun, Y. Bengio, and G. Hinton, *Deep learning*, *Nature (London)* **521**, 436 (2015).
- [42] A. Zentner, E. V. Halingstad, C. Chalk, M. P. Brenner, A. Murugan, E. Winfree, and K. Shrinivas, *Information processing driven by multicomponent surface condensates*, *arXiv:2509.08100*.
- [43] R. Braz Teixeira, G. Carugno, I. Neri, and P. Sartori, *Liquid Hopfield model: Retrieval and localization in multi-component liquid mixtures*, *Proc. Natl. Acad. Sci. U.S.A.* **121**, e2320504121 (2024).
- [44] K. J. Åström and R. M. Murray, *Feedback Systems: An Introduction for Scientists and Engineers* (Princeton University Press, Princeton, NJ, 2021).
- [45] A. Klosin, F. Oltsch, T. Harmon, A. Honigmann, F. Jülicher, A. A. Hyman, and C. Zechner, *Phase separation provides a mechanism to reduce noise in cells*, *Science* **367**, 464 (2020).
- [46] D. Deviri and S. A. Safran, *Physical theory of biological noise buffering by multicomponent phase separation*, *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2100099118 (2021).
- [47] B. R. Sabari *et al.*, *Coactivator condensation at super-enhancers links phase separation and gene control*, *Science* **361**, eaar3958 (2018).
- [48] A. Boija, I. A. Klein, B. R. Sabari, A. Dall'Agnese, E. L. Coffey, A. V. Zamudio, C. H. Li, K. Shrinivas, J. C. Manteiga, N. M. Hannett, B. J. Abraham, L. K. Afeyan, Y. E. Guo, J. K. Rimel, C. B. Fant, J. Schuijers, T. I. Lee, D. J. Taatjes, and R. A. Young, *Transcription factors activate genes through the phase-separation capacity of their activation domains*, *Cell* **175**, 1842 (2018).
- [49] X. Su, J. A. Ditlev, E. Hui, W. Xing, S. Banjade, J. Okrut, D. S. King, J. Taunton, M. K. Rosen, and R. D. Vale, *Phase separation of signaling molecules promotes T cell receptor signal transduction*, *Science* **352**, 595 (2016).
- [50] S. F. Shimobayashi, P. Ronceray, D. W. Sanders, M. P. Haataja, and C. P. Brangwynne, *Nucleation landscape of biomolecular condensates*, *Nature (London)* **599**, 503 (2021).
- [51] H. Yoo, C. Triandafillou, and D. A. Drummond, *Cellular sensing by phase separation: Using the process, not just the products*, *J. Biol. Chem.* **294**, 7151 (2019).
- [52] D. S. Protter and R. Parker, *Principles and properties of stress granules*, *Trends Cell Biol.* **26**, 668 (2016).
- [53] H. Glauninger, J. A. Bard, C. J. W. Hickernell, E. M. Airolidi, W. Li, R. H. Singer, S. Paul, J. Fei, T. R. Sosnick, E. W. Wallace, and D. A. Drummond, *Transcriptome-wide mRNA condensation precedes stress granule formation and excludes stress-induced transcripts*, *bioRxiv* (2024).
- [54] A. Ali, R. Garde, O. C. Schaffer, J. A. M. Bard, K. Husain, S. K. Kik, K. A. Davis, S. Luengo-Woods, M. G. Igarashi, D. A. Drummond, A. H. Squires, and D. Pincus, *Adaptive preservation of orphan ribosomal proteins in chaperone-dispersed condensates*, *Nat. Cell Biol.* **25**, 1691 (2023).
- [55] C. Hetz, K. Zhang, and R. J. Kaufman, *Mechanisms, regulation and functions of the unfolded protein response*, *Nat. Rev. Mol. Cell Biol.* **21**, 421 (2020).
- [56] E. W. Dijkstra, *Selected Writings on Computing: A Personal Perspective* (Springer, New York, 1982), pp. 60–66.
- [57] L. H. Hartwell, J. J. Hopfield, S. Leibler, and A. W. Murray, *From molecular to modular cell biology*, *Nature (London)* **402**, C47 (1999).
- [58] D. Endy, *Foundations for engineering biology*, *Nature (London)* **438**, 449 (2005).
- [59] R. A. Brooks, *Intelligence without representation*, *Artif. Intell.* **47**, 139 (1991).
- [60] B. Ulmann, *Analog Computing* (Oldenbourg Wissenschaftsverlag Verlag, Berlin/Boston, 2013).
- [61] V. Braitenberg, *Vehicles: Experiments in Synthetic Psychology* (MIT Press, Cambridge, MA, 1986).
- [62] M. S. Bull, L. A. Kroo, and M. Prakash, *Excitable mechanics embodied in a walking cilium*, *arXiv:2107.02930*.
- [63] J. Laydevant, L. G. Wright, T. Wang, and P. L. McMahon, *The hardware is the software*, *Neuron* **112**, 180 (2023).

- [64] M. Levin, *Technological approach to mind everywhere: An experimentally-grounded framework for understanding diverse bodies and minds*, *Front. Syst. Neurosci.* **16**, 768201 (2022).
- [65] R. Pfeifer and G. Gómez, in *Creating Brain-Like Intelligence*, Lecture Notes in Computer Science (Springer, Berlin, 2009), pp. 66–83.
- [66] H. Hauser, A. J. Ijspeert, R. M. Fuchslin, R. Pfeifer, and W. Maass, *Towards a theoretical foundation for morphological computation with compliant bodies*, *Biol. Cybern.* **105**, 355 (2011).
- [67] D. Bray, *Protein molecules as computational elements in living cells*, *Nature (London)* **376**, 307 (1995).
- [68] S. Erbas-Cakmak, S. Kolemen, A. C. Sedgwick, T. Gunnlaugsson, T. D. James, J. Yoon, and E. U. Akkaya, *Molecular logic gates: The past, present and future*, *Chem. Soc. Rev.* **47**, 2228 (2018).
- [69] N. Nandagopal and M. B. Elowitz, *Synthetic biology: Integrated gene circuits*, *Science* **333**, 1244 (2011).
- [70] L. Qian, E. Winfree, and J. Bruck, *Neural network computation with DNA strand displacement cascades*, *Nature (London)* **475**, 368 (2011).
- [71] N. E. Buchler, U. Gerland, and T. Hwa, *On schemes of combinatorial transcription logic*, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 5136 (2003).
- [72] H. Zhang, J. Wu, D. Fang, and Y. Zhang, *Hierarchical mechanical metamaterials built with scalable tristable elements for ternary logic operation and amplitude modulation*, *Sci. Adv.* **7**, eabf1966 (2021).
- [73] T. Dubček, D. Moreno-Garcia, T. Haag, P. Omidvar, H. R. Thomsen, T. S. Becker, L. Gebraad, C. Bärlöcher, F. Andersson, S. D. Huber *et al.*, *In-sensor passive speech classification with phononic metamaterials*, *Adv. Funct. Mater.* **34**, 2311877 (2024).
- [74] P. L. McMahon, *The physics of optical computing*, *Nat. Rev. Phys.* **5**, 717 (2023).
- [75] L. G. Wright, T. Onodera, M. M. Stein, T. Wang, D. T. Schachter, Z. Hu, and P. L. McMahon, *Deep physical neural networks trained with backpropagation*, *Nature (London)* **601**, 549 (2022).
- [76] M. Stern, C. Arinze, L. Perez, S. E. Palmer, and A. Murugan, *Supervised learning through physical changes in a mechanical system*, *Proc. Natl. Acad. Sci. U.S.A.* **117**, 14843 (2020).
- [77] D. Woods, D. Doty, C. Myhrvold, J. Hui, F. Zhou, P. Yin, and E. Winfree, *Diverse and robust molecular algorithms using reprogrammable DNA self-assembly*, *Nature (London)* **567**, 366 (2019).
- [78] E. Winfree, *Algorithmic self-assembly of DNA*, Ph.D. thesis, California Institute of Technology, Pasadena, CA, 1998.
- [79] C. G. Evans, J. O'Brien, E. Winfree, and A. Murugan, *Pattern recognition in the nucleation kinetics of non-equilibrium self-assembly*, *Nature (London)* **625**, 500 (2024).
- [80] R. Pfeifer, M. Lungarella, and F. Iida, *Self-organization, embodiment, and biologically inspired robotics*, *Science* **318**, 1088 (2007).
- [81] S. Collins, A. Ruina, R. Tedrake, and M. Wisse, *Efficient bipedal robots based on passive-dynamic walkers*, *Science* **307**, 1082 (2005).
- [82] T. Wang, C. Pierce, V. Kojouharov, B. Chong, K. Diaz, H. Lu, and D. I. Goldman, *Mechanical intelligence simplifies control in terrestrial limbless locomotion*, *Sci. Robot.* **8**, eadi2243 (2023).
- [83] J. J. Hopfield, *Neural networks and physical systems with emergent collective computational abilities*, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2554 (1982).
- [84] D. Krotov and J. J. Hopfield, *Large associative memory problem in neurobiology and machine learning*, *arXiv:2008.06996*.
- [85] J. A. Hertz, A. S. Krogh, and R. G. Palmer, *Introduction to the Theory of Neural Computation* (Basic Books, Boca Raton, FL, 1991), Vol. 1.
- [86] A. Murugan, Z. Zeravcic, M. P. Brenner, and S. Leibler, *Multifarious assembly mixtures: Systems allowing retrieval of diverse stored structures*, *Proc. Natl. Acad. Sci. U.S.A.* **112**, 54 (2015).
- [87] Thomas M. A. Fink and R. C. Ball, *How many conformations can a protein remember?*, *Phys. Rev. Lett.* **87**, 198103 (2001).
- [88] W. M. Jacobs, *Self-assembly of biomolecular condensates with shared components*, *Phys. Rev. Lett.* **126**, 258101 (2021).
- [89] K. Hornik, M. Stinchcombe, and H. White, *Multilayer feedforward networks are universal approximators*, *Neural Netw.* **2**, 359 (1989).
- [90] M. Raghu, B. Poole, J. Kleinberg, S. Ganguli, and J. Sohl-Dickstein, *Survey of expressivity in deep neural networks*, *arXiv:1611.08083*.
- [91] M. J. Kearns and U. Vazirani, *An Introduction to Computational Learning Theory* (MIT Press, London, 2019).
- [92] J. Parres-Gold, M. Levine, B. Emert, A. Stuart, and M. B. Elowitz, *bioRxiv*, 2023.10.30.564854 (2023).
- [93] C. Chalk, S. Buse, K. Shrinivas, A. Murugan, and E. Winfree, *Learning and inference in a lattice model of multicomponent condensates*, in *30th International Conference on DNA Computing and Molecular Programming (DNA 30)*, Leibniz International Proceedings in Informatics (LIPIcs) Vol. 314, edited by S. Seki and J. M. Stewart (Schloss Dagstuhl—Leibniz-Zentrum für Informatik, Dagstuhl, Germany, 2024), pp. 5:1–5:24.
- [94] J. Gunawardena, *Learning outside the brain: Integrating cognitive science and systems biology*, *Proc. IEEE* **110**, 590 (2022).
- [95] G. Montufar, *Restricted Boltzmann machines: Introduction and review*, *arXiv:1806.07066*.
- [96] W. Zhong, D. J. Schwab, and A. Murugan, *Associative pattern recognition through macro-molecular self-assembly*, *J. Stat. Phys.* **167**, 806 (2017).
- [97] M. S. Heltberg, A. Lucchetti, F.-S. Hsieh, D. P. Minh Nguyen, S. hong Chen, and M. H. Jensen, *Enhanced DNA repair through droplet formation and p53 oscillations*, *Cell* **185**, 4394 (2022).
- [98] C. Girard, D. Zwicker, and R. Mercier, *The regulation of meiotic crossover distribution: a coarse solution to a century-old mystery?*, *Biochem. Soc. Trans.* **51**, 1179 (2023).
- [99] D. B. McAfee, M. K. O'Dair, J. J. Lin, S. T. Low-Nam, K. B. Wilhelm, S. Kim, S. Morita, and J. T. Groves, *Discrete LAT condensates encode antigen information*

- from single pMHC: TCR binding events, *Nat. Commun.* **13**, 7446 (2022).
- [100] W. Y. C. Huang, S. Alvarez, Y. Kondo, Y. K. Lee, J. K. Chung, H. Y. M. Lam, K. H. Biswas, J. Kuriyan, and J. T. Groves, *A molecular assembly phase transition and kinetic proofreading modulate Ras activation by SOS*, *Science* **363**, 1098 (2019).
- [101] W. L. White, H. K. Yirdaw, A. J. Ben-Sasson, J. T. Groves, D. Baker, and H. Y. Kueh, *Proofreading and single-molecule sensitivity in T cell receptor signaling by condensate nucleation*, *Proc. Natl. Acad. Sci. U.S.A.* **122**, e2422787122 (2025).
- [102] R. Rossetto, G. Wellecke, and D. Zwicker, *Binding and dimerization control phase separation in a compartment*, *Phys. Rev. Res.* **7**, 023145 (2025).
- [103] A. J. Genot, T. Fujii, and Y. Rondelez, *Computing with competition in biochemical networks*, *Phys. Rev. Lett.* **109**, 208102 (2012).
- [104] C. Kieffer, A. J. Genot, Y. Rondelez, and G. Gines, *Molecular computation for molecular classification*, *Adv. Biol.* **7**, e2200203 (2023).
- [105] D. Zwicker, *The intertwined physics of active chemical reactions and phase separation*, *Curr. Opin. Colloid Interface Sci.* **61**, 101606 (2022).
- [106] N. Zithen, J. Kirschbaum, and D. Zwicker, *Nucleation of chemically active droplets*, *Phys. Rev. Lett.* **130**, 248201 (2023).
- [107] E. Jambon-Puillet, A. Testa, C. M. Lorenz, R. W. Style, A. Rebane, and E. R. Dufresne, *Phase-separated droplets swim to their dissolution*, *bioRxiv* (2023).
- [108] J. D. Wurtz and C. F. Lee, *Stress granule formation via ATP depletion-triggered phase separation*, *New J. Phys.* **20**, 045008 (2018).
- [109] D. Zwicker, A. A. Hyman, and F. Jülicher, *Suppression of Ostwald ripening in active emulsions*, *Phys. Rev. E* **92**, 012317 (2015).
- [110] J. Soeding, D. Zwicker, S. Sohrabi-Jahromi, M. Boehning, and J. Kirschbaum, *Mechanisms for active regulation of biomolecular condensates*, *Trends Cell Biol.* **30**, 4 (2020).
- [111] J. Kirschbaum and D. Zwicker, *Controlling biomolecular condensates via chemical reactions*, *J. R. Soc. Interface* **18**, 20210255 (2021).
- [112] D. Zwicker, R. Seyboldt, C. A. Weber, A. A. Hyman, and F. Jülicher, *Growth and division of active droplets provides a model for protocells*, *Nat. Phys.* **13**, 408 (2017).
- [113] D. Carati and R. Lefever, *Chemical freezing of phase separation in immiscible binary mixtures*, *Phys. Rev. E* **56**, 3127 (1997).
- [114] T. Aslyamov, F. Avanzini, E. Fodor, and M. Esposito, *Nonideal reaction-diffusion systems: Multiple routes to instability*, *Phys. Rev. Lett.* **131**, 138301 (2023).
- [115] L. Demarchi, A. Goychuk, I. Maryshev, and E. Frey, *Enzyme-enriched condensates show self-propulsion, positioning, and coexistence*, *Phys. Rev. Lett.* **130**, 128401 (2023).
- [116] L. Menou, C. Luo, and D. Zwicker, *Physical interactions in non-ideal fluids promote Turing patterns*, *J. R. Soc. Interface* **20**, 20230244 (2023).
- [117] V. Galstyan, K. Husain, F. Xiao, A. Murugan, and R. Phillips, *Proofreading through spatial gradients*, *eLife* **9**, e60415 (2020).
- [118] J. J. Hopfield, *Kinetic proofreading: A new mechanism for reducing errors in biosynthetic processes requiring high specificity*, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 4135 (1974).
- [119] M. Stern and A. Murugan, *Learning without neurons in physical systems*, *Annu. Rev. Condens. Matter Phys.* **14**, 417 (2023).
- [120] M. Hofweber and D. Dormann, *Friend or foe—Post-translational modifications as regulators of phase separation and RNP granule dynamics*, *J. Biol. Chem.* **294**, 7137 (2019).
- [121] J. Wang, J.-M. Choi, A. S. Holehouse, H. O. Lee, X. Zhang, M. Jahnel, S. Maharana, R. Lemaitre, A. Pozniakovsky, D. Drechsel, I. Poser, R. V. Pappu, S. Alberti, and A. A. Hyman, *A molecular grammar governing the driving forces for phase separation of prion-like RNA binding proteins*, *Cell* **174**, 688 (2018).
- [122] R. Zhu, J. M. Del Rio-Salgado, J. Garcia-Ojalvo, and M. B. Elowitz, *Synthetic multistability in mammalian cells*, *Science* **375**, eabg9765 (2022).
- [123] K. Trifonova, M. J. Falk, M. Rouches, S. Vaikuntanathan, M. Elowitz, and A. Murugan, *Trainable computation in molecular networks*, *bioRxiv* (2025), 10.64898/2025.12.28.696421.
- [124] J. A. Owen, D. Osmanović, and L. Mirny, *Design principles of 3D epigenetic memory systems*, *Science* **382**, eadg3053 (2023).
- [125] T. E. Schaus, S. Woo, F. Xuan, X. Chen, and P. Yin, *A DNA nanoscope via auto-cycling proximity recording*, *Nat. Commun.* **8**, 696 (2017).
- [126] K. M. Cherry and L. Qian, *Scaling up molecular pattern recognition with DNA-based winner-take-all neural networks*, *Nature (London)* **559**, 370 (2018).
- [127] S. Alberti, A. Gladfelter, and T. Mittag, *Considerations and challenges in studying liquid-liquid phase separation and biomolecular condensates*, *Cell* **176**, 419 (2019).
- [128] V. A. Baulin *et al.*, *Intelligent soft matter: Towards embodied intelligence*, *Soft Matter* **21**, 4129 (2025).
- [129] J. Gong, N. Tsumura, Y. Sato, and M. Takinoue, *Computational DNA droplets recognizing miRNA sequence inputs based on liquid-liquid phase separation*, *Adv. Funct. Mater.* **32**, 2202322 (2022).
- [130] M. Takinoue, *DNA droplets for intelligent and dynamical artificial cells: From the viewpoint of computation and non-equilibrium systems*, *Interface Focus* **13**, 20230021 (2023).
- [131] H. Udono, J. Gong, Y. Sato, and M. Takinoue, *DNA droplets: Intelligent, dynamic fluid*, *Adv. Biol.* **7**, e2200180 (2023).
- [132] G. Fabrini, S. P. Nuccio, J. M. Stewart, S. Li, A. Tang, P. W. K. Rothmund, E. Franco, M. Di Antonio, and L. Di Michele, *bioRxiv* 2023.10.06.561174 (2023).