

Phase Separation Induces Oscillations in Negative Feedback Loops

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Oscillations constitute a defining feature of nonequilibrium processes of life. We analyze a minimal degradation-mediated negative feedback loop, in which the final species in a linear cascade enzymatically degrades the first component. By coupling mean-field ordinary differential equations with a phase-separated component, we reveal novel inhibition scalings that expand the parameter regime supporting oscillations. Extending to arbitrary sublinear exponents and network sizes, we derive general bifurcation criteria and identify universal relations for oscillation onset in a reduced time-delay model. Our results show that phase separation promotes oscillations, uncovering a nonequilibrium mechanism for dynamic regulation in cellular systems.

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Introduction—Oscillatory dynamics is a hallmark of many physical and biological systems, arising from feedback regulation and time delays. In cells, oscillations in protein concentrations span timescales from minutes to days, and are often controlled by relatively simple regulatory networks [1–3]. A prominent example is the p53 signaling network, where DNA damage triggers sustained oscillations in p53 levels with a characteristic period of ≈ 5.5 h, driven by negative feedback from its downstream target Mdm2 [4–6].

While the emergence of oscillations in chemical and genetic systems has been extensively studied, theoretical models typically rely on mean-field approximations via coupled ordinary differential equations (ODEs) [4,7–11]. These models assume homogeneous mixing and mass-action kinetics, where reaction rates scale linearly with reactant concentrations [12]. However, such assumptions may break down in the presence of cellular compartmentalization.

Recent work has shown that liquid-liquid phase separation (LLPS) plays a central role in organizing the intracellular environment, forming biomolecular condensates that sequester specific proteins and nucleic acids [13–16], including in processes such as transcriptional regulation [17–19] and metabolic enzyme organization [20–22].

In this context, proteins undergoing phase separation can suddenly demix, leading to highly heterogeneous spatial distributions that dramatically alter both molecular availability, often limiting it to molecules at the condensate

surface, and interaction kinetics. This may not only affect reaction rate constants but also change the fundamental scaling relationships between reactants, requiring a reevaluation of traditional ODE-based models.

In this Letter, we develop a minimal mathematical framework to investigate how LLPS affects the dynamics of genetic negative feedback loops. By coupling mean-field ODEs with a compartmentalized phase-separated species, we show that LLPS can induce oscillatory behavior via a Hopf bifurcation—even in systems that remain stable in the well-mixed limit. Our results highlight a new mechanism by which spatial heterogeneity can generate or enhance dynamic complexity in biological regulatory networks.

From well-mixed (WM) to phase-separated (PS) environments—We start by considering the following set of coupled ODEs, which describe the time evolution of the concentrations $[\cdot]$ of N species (x_i , $i \in [1, \dots, N]$):

$$\dot{[x_i]} = \begin{cases} a_1 - b_1[x_1][x_N] & i = 1, \\ a_i[x_{i-1}] - b_i[x_i] & i \in [2, \dots, N]. \end{cases} \quad (1)$$

The model describes a linear signaling cascade, where each species x_i activates the next, culminating in the N th species being an enzyme that mediates the degradation of the first species [Fig. 1(a)]. Equation (1) corresponds to an effective low-saturation regime in which this process is well described by a mass-action term.

In order to do a linear stability analysis (LSA) of the system, we compute the fixed points

$$[x_i]^* = \sqrt{\prod_{j=1}^i \frac{a_j}{b_j} \prod_{j=i+1}^N \frac{b_j}{a_j}},$$

and the Jacobian, which takes the form

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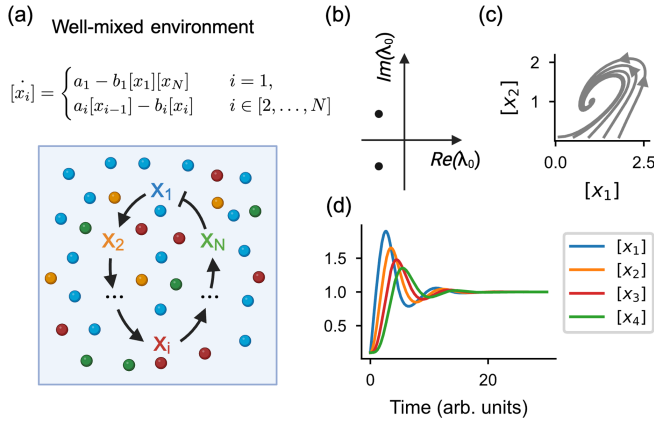


FIG. 1. (a) Negative-feedback-loop equations and schematics for N species in a well-mixed environment. (b) The dominant eigenvalue is complex with negative real part, preventing sustained oscillations. (c) Simulation of Eq. (1) for $N = 4$ and 5 initial conditions shows the fixed point is a stable spiral. (d) Time evolution of the $N = 4$ species shows damped oscillations.

$$\mathcal{J} = \begin{pmatrix} -b_1[x_N]^* & 0 & \cdots & 0 & -b_1[x_1]^* \\ a_2 & -b_2 & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & a_N & -b_N \end{pmatrix}. \quad (2)$$

If we assume for simplicity that $b_i = 1 \forall i$ and $\prod_{j=1}^N a_j = 1$, one can show (see Supplemental Material [23])

that the characteristic equation is $(\lambda + 1)^N + 1 = 0$, thus the dominant root, i.e., the one with the largest real part, is

$$\lambda_0^{\text{WM}} = \cos\left(\frac{\pi}{N}\right) - 1 \pm i \sin\left(\frac{\pi}{N}\right). \quad (3)$$

This system has therefore complex eigenvalues with negative real parts [Fig. 1(b)], which results in damped oscillations around the fixed point, but not sustained ones [Figs. 1(c) and 1(d)]. The result remains valid for any value of the constants a_i , with $b_i = 1 \forall i$ (see Supplemental Material [23]).

We now consider the case in which x_1 strongly phase-separates from the other components [Fig. 2(a)], forming a spherical condensate (of radius R_1), with a constant internal concentration (c_{in}), and a negligible concentration outside ($c_{\text{out}} \approx 0$). If we also assume that the other species are excluded from the condensate, the degradation of x_1 by x_N is no longer governed by the classical Smoluchowski reaction rate, which assumes homogeneous mixing and is given by

$$k_{x_1, x_N}^{\text{WM}} = 4\pi(D_1 + D_N)R_{1,N}[x_1][x_N].$$

Here, D_1 and D_N are the diffusion coefficients of the reactant x_1 and x_N , respectively, and $R_{1,N}$ is the encounter radius, i.e., the distance at which the molecules are considered to have reacted upon contact. In contrast, when x_1 is sequestered within a condensate, and x_N is excluded from it, their interaction is limited to encounters at the condensate interface. Because of this change in geometry, the rate of breakdown of x_1 takes new functional forms

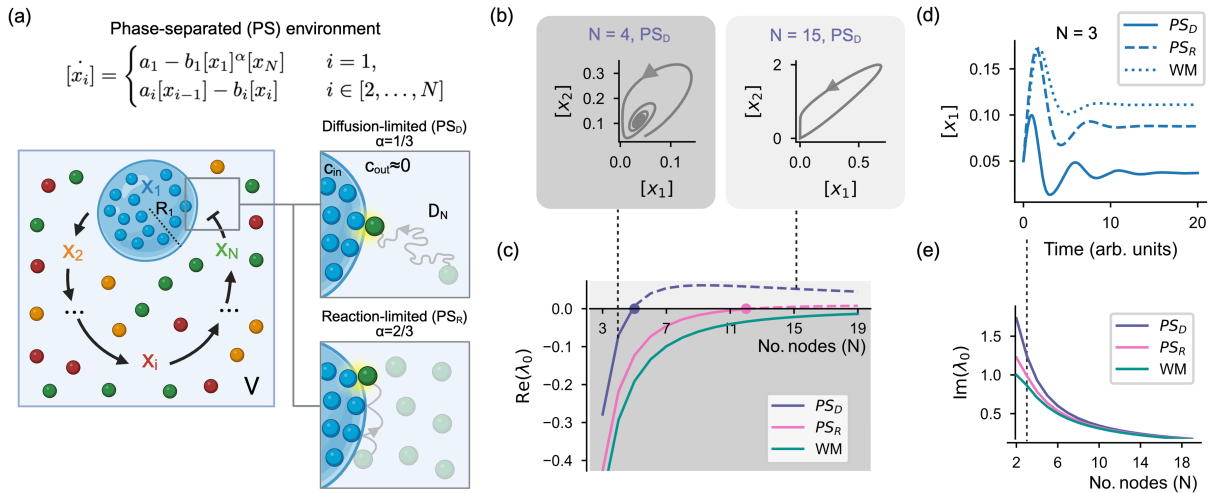


FIG. 2. (a) Negative-feedback-loop equations and schematic drawing for N species in a phase-separated (PS) environment, where inhibition of x_1 by x_N follows a sublinear scaling with exponent α : in the diffusion limited case (PS_D) $\alpha = 1/3$, and in the reaction-limited case (PS_R) $\alpha = 2/3$. (b) Examples of two trajectories for $N = 4$ (stable spiral) and $N = 15$ (limit cycle) in the PS_D case. (c) Real part of the dominant root is always negative in the well-mixed (WM) case and becomes positive for $N > 4$ and $N > 12$ in the PS_D and PS_R case, respectively, leading the system through a Hopf bifurcation. (d) Three trajectories for $[x_1]$ show higher frequency for $\text{PS}_{D,R}$ compared to WM. (e) Imaginary part of the dominant root is higher for $\text{PS}_{D,R}$ compared to WM case, explaining the higher frequency observed in (d).

depending on rates of reaction and diffusion. If decay of x_N is slow and reactions with x_1 at the interface are fast, breakdown is controlled by the diffusive arrival of x_N at the condensate. This transforms the reaction kinetics into a diffusion-limited (PS_D), first-passage problem, with the effective rate given by (see Supplemental Material [23] and also Refs. [24–26] therein)

$$J_{\text{PS}_D} = 4\pi D_N R_1 [x_N] = 4\pi D_N \left(\frac{N_1}{\frac{4}{3}\pi c_{\text{in}}} \right)^{1/3} [x_N], \quad (4)$$

where N_1 is the number of particles of species x_1 in the condensate. On the other hand, if breakdown is reaction-limited (PS_R), the effective rate is

$$J_{\text{PS}_R} = 4\pi D_N k_s R_1^2 [x_N] = 4\pi D_N k_s \left(\frac{N_1}{\frac{4}{3}\pi c_{\text{in}}} \right)^{2/3} [x_N], \quad (5)$$

where k_s is the reaction rate constant at the interface of the condensate. Considering that $[x]$ represents the mean concentration change across the entire system, we must divide the effective rate by the system volume V to get the degradation rate of x_1 . By doing so, and using the relation $N_1/V = [x_1]$, we get the full set of ODEs in the case of phase separation,

$$\dot{[x_i]} = \begin{cases} a_1 - b_1 [x_1]^\alpha [x_N] & i = 1, \\ a_i [x_{i-1}] - b_i [x_i] & i \in [2, \dots, N], \end{cases} \quad (6)$$

where $b_1 = [4\pi D_N V^{-2/3} / (\frac{4}{3}\pi c_{\text{in}})^{1/3}]$ and $\alpha = 1/3$ in the PS_D case, and $b_1 = [4\pi D_N k_s V^{-1/3} / (\frac{4}{3}\pi c_{\text{in}})^{1/3}]$ and $\alpha = 2/3$ in the PS_R case.

Moreover, we can estimate the ratio of the degradation rates of x_1 , in the WM and PS_D case, if we make the simplifying assumptions that $D_1 \approx D_N$, and that the encounter radius is about double the radius ϵ of the particles ($R_{1,N} \approx 2\epsilon$). We additionally consider the case of densely packed particles in the condensates so that $c_{\text{in}} = 1/\nu$, where ν is the molecular volume of the particles, assumed spherical. Under these assumptions we find that

$$\begin{aligned} \frac{\text{degr rate}^{\text{PS}}}{\text{degr rate}^{\text{WM}}} &= \frac{\frac{4\pi D_N}{(\frac{4\pi V^2}{3\nu})^{1/3}} [x_1]^{1/3} [x_N]}{4\pi (D_1 + D_N) R_{1,N} [x_1] [x_N]} \\ &\approx \frac{[x_1]^{-2/3}}{2R_{1,N}} \left(\frac{4\pi V^2}{3\nu} \right)^{-1/3} \approx \frac{1}{4} N_1^{-2/3}. \end{aligned}$$

Overall, this highlights a striking consequence of phase separation: the effective reaction rate in the PS_D case can be significantly smaller than in the WM regime, scaling roughly as $N_1^{-2/3}$. More importantly, the functional dependence of the degradation term on $[x_1]$ is fundamentally altered, from linear ($[x_1]$) in the WM case to sublinear ($[x_1]^{1/3}$ and $[x_1]^{2/3}$) in the PS_{D,R} regimes. This change

reflects the geometric nature of diffusion to a condensate: reactions are now constrained by the condensate surface area rather than by bulk concentrations.

We thus aim to investigate how such scaling shifts, which break a core assumption of classical mass-action kinetics, can impact network dynamics. To do so, we perform again an LSA of the phase-separated model by first computing the fixed points of Eq. (6),

$$\begin{aligned} [x_1]^* &= \left(\prod_{j=1}^N \frac{b_j}{a_j} \right)^{\frac{1}{\alpha+1}} \left(\frac{a_1}{b_1} \right)^{\frac{2}{\alpha+1}}, \\ [x_N]^* &= \left(\prod_{j=1}^N \frac{a_j}{b_j} \right)^{\frac{\alpha}{\alpha+1}} \left(\frac{a_1}{b_1} \right)^{\frac{1-\alpha}{\alpha+1}}, \end{aligned}$$

and the Jacobian,

$$\mathcal{J} = \begin{pmatrix} -b_1 \alpha [x_1]^{*\alpha-1} x_N^* & 0 & \cdots & 0 & -b_1 [x_1]^*{}^\alpha \\ a_2 & -b_2 & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & a_N & -b_N \end{pmatrix}.$$

One can show (see Supplemental Material [23]) that the dominant root for this system in the particular case of $a_1 = (1/\alpha)^{(\alpha+1)/(\alpha-1)}$ and $\prod_{j=1}^N a_j = 1$ is

$$\lambda_0^{\text{PS}} = \alpha^{-\frac{1}{N}} \cos\left(\frac{\pi}{N}\right) - 1 \pm i \alpha^{-\frac{1}{N}} \sin\left(\frac{\pi}{N}\right). \quad (7)$$

This result shows that the formation of condensates in which the negatively regulated component resides moves the system closer to the Hopf bifurcation: indeed, compared to the well-mixed case where $\text{Re}(\lambda_0^{\text{WM}}) < 0$, we observe numerically that $\text{Re}(\lambda_0^{\text{PS}}) > 0$ both in the diffusion- and reaction-limited cases, for $N_c = 4.85$ and $N_c = 12.31$, respectively. This means that for these systems, phase separation of one component induces a Hopf bifurcation at $N \approx 5$ and $N \approx 13$ [Figs. 2(b) and 2(c)]. Moreover, comparing the imaginary part of the eigenvalues in the three cases shows that for the PS case it is always higher, resulting in faster oscillations [Figs. 2(d) and 2(e)]. The result remains valid if phase separation occurs in any other node of the feedback (see Supplemental Material [23]).

Generalization of α exponent—We now generalize the previous system by introducing an arbitrary α exponent in the degradation term, while setting all $a_i, b_i = 1$ for tractability. This results in the following set of N ODEs:

$$\dot{[x_i]} = \begin{cases} 1 - [x_1]^\alpha [x_N] & i = 1, \\ [x_{i-1}] - [x_i] & i \in [2, \dots, N]. \end{cases}$$

This formulation captures a broader class of interaction kinetics, where $\alpha \in]0, 1]$ interpolates between the standard mass-action ($\alpha = 1$) and the diffusion-limited condensate case ($\alpha = 1/3$). This generalized model allows us to explore how the degree of nonlinearity in feedback shapes the emergence of oscillations.

The fixed point for this system is $[x_1]^* = \dots = [x_N]^* = 1$, while the characteristic equation is given by

$$(\alpha + \lambda)(1 + \lambda)^{N-1} + 1 = 0.$$

At the Hopf bifurcation, the eigenvalue crosses the imaginary axis and can therefore be written as a purely imaginary number $\lambda = i\omega$. We then substitute it in the characteristic equation and express the power series in polar form, which yields

$$(\alpha + i\omega)(r^M[\cos(M\theta) + i\sin(M\theta)]) + 1 = 0, \quad (8)$$

where we defined $r^2 = 1 + \omega^2$ and $\tan \theta = \omega$, and we call $N - 1 = M$ for simplicity of notation. Splitting real and imaginary parts, one can show (see Supplemental Material [23]) that

$$N = -\frac{\arctan(\omega/\alpha) + \pi k}{\arctan(\omega)} + 1, \quad (9)$$

$$\frac{\arctan(\omega/\alpha) + \pi k}{\arctan(\omega)} = \frac{\log(\alpha^2 + \omega^2)}{\log(1 + \omega^2)}. \quad (10)$$

We can now solve Eq. (10) numerically to get an expression for $\omega(\alpha)$, which we can insert in Eq. (9) to find $N(\alpha)$, as shown in Fig. 3(a). The curve confirms that the system is always below the Hopf bifurcation in the WM case ($\alpha = 1$), whereas PS ($\alpha = 1/3$ or $\alpha = 2/3$) can drive the system above the bifurcation line.

Time delays—Finally, to further simplify the model analysis, while keeping the essence of the regulatory network, we reduced the full system of N ODEs to a

system of two delayed differential equations, where the time delays effectively capture the cumulative effects of all intermediate steps in the linear signaling cascade (see Supplemental Material [23] and also Ref. [27] therein),

$$\begin{aligned} \dot{x}_1 &= 1 - [x_2](t - \tau)[x_1]^\alpha = f\{[x_1], [x_2](t - \tau)\}, \\ \dot{x}_2 &= [x_1] - [x_2] = g([x_1], [x_2]). \end{aligned}$$

The fixed point for this system is again given by $[x_1]^* = [x_2]^* = 1$. In order to do an LSA of this system, we perform a small perturbation around the fixed point,

$$\begin{cases} [x_1](t) = [x_1]^* + q(t) = 1 + q(t), \\ [x_2](t) = [x_2]^* + p(t) = 1 + p(t). \end{cases}$$

Therefore, up to linear order, the perturbation evolves as

$$\begin{cases} \dot{q}(t) = \frac{df}{dx_1|_*} q(t) + \frac{df}{dx_2|_*} p(t - \tau) = -\alpha q - p(t - \tau), \\ \dot{p}(t) = \frac{dg}{dx_1|_*} q(t) + \frac{dg}{dx_2|_*} p(t) = q(t) - p(t). \end{cases} \quad (11)$$

In order to find the characteristic equation, we insert the ansatz $q(t) = q_0 e^{\lambda t}$, $p(t) = p_0 e^{\lambda t}$ into Eq. (11), which yields, in matrix form (see Supplemental Material [23]),

$$\begin{bmatrix} \lambda + \alpha & e^{-\lambda\tau} \\ 1 & -(\lambda + 1) \end{bmatrix} \begin{bmatrix} q_0 \\ p_0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}. \quad (12)$$

The only nontrivial solution is when the determinant is null, which leads to the characteristic equation for λ ,

$$-(\lambda + \alpha)(\lambda + 1) - e^{-\lambda\tau} = 0. \quad (13)$$

We again consider the condition at the Hopf bifurcation ($\lambda = i\omega$), which we substitute in Eq. (13),

$$-\omega^2 + i(\alpha + 1)\omega + \alpha + \cos(\omega\tau) - i\sin(\omega\tau) = 0. \quad (14)$$

Splitting real and imaginary parts of Eq. (14), and solving for α (see Supplemental Material [23]), yields an expression for $\tau(\alpha)$ [Fig. 3(b)],

$$\begin{aligned} \tau &= \frac{1}{\omega} \arccos(\omega^2 - \alpha) = \frac{\sqrt{2}}{\sqrt{\sqrt{\alpha^4 - 2\alpha^2 + 5} - (\alpha^2 + 1)}} \\ &\times \arccos\left(\frac{\sqrt{\alpha^4 - 2\alpha^2 + 5} - (\alpha^2 + 1)}{2} - \alpha\right). \end{aligned} \quad (15)$$

One can show (see Supplemental Material [23]) that the same calculations can be carried out to determine the Hopf-bifurcation curve of the system for general a_i , b_i parameters, which has the same qualitative behavior as Eq. (15). This confirms that for a negative feedback loop

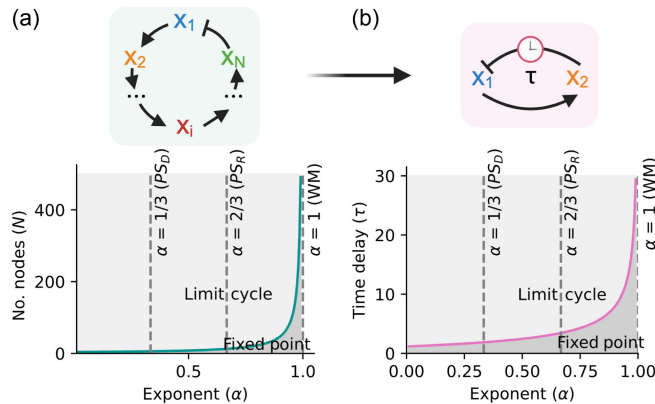


FIG. 3. (a) Numerical plot of the analytical solution for $N(\alpha)$. (b) Analytical solution of $\tau(\alpha)$ given by Eq. (15).

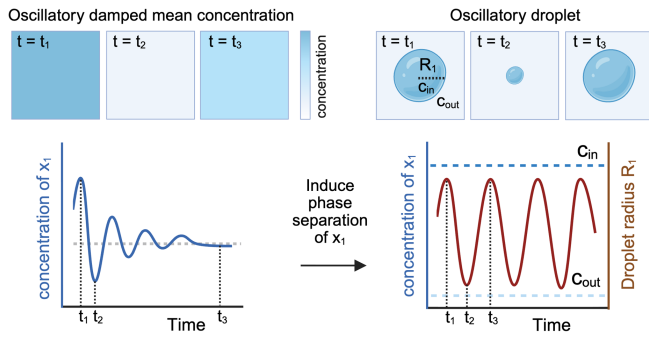


FIG. 4. Testable predictions of the model: in the well-mixed case, the negative feedback loop for species x_1 is stable and exhibits only damped oscillations in its mean concentration (light-to-dark blue gradient indicating low to high concentration). When phase separation is induced, this same system displays sustained oscillations in the droplet radius (R_1), while the internal and external concentrations ($c_{in,out}$) remain constant over time.

with time delay, which is stable in the WM limit, PS induces the emergence of oscillations above a certain critical time delay, both in the diffusion- and reaction-limited cases.

Discussion—Our Letter demonstrates that the physical sequestration of molecular species by phase separation fundamentally reshapes feedback dynamics, creating oscillations in systems that are otherwise in a steady state.

Importantly, it also suggests clear experimentally testable predictions. As schematized in Fig. 4: (i) inducing phase separation of a component in a negative feedback loop that is stable in the well-mixed regime leads to the onset of sustained oscillations of the droplet radius $R(t)$, (ii) the internal and external concentrations ($c_{in,out}$) remain approximately constant, and (iii) the oscillations emerge above a critical network size N_c . These predictions could be tested by constructing a synthetic genetic circuit of N components [11], in which one component exhibits inducible phase separation, for example via optogenetic tools [28,29] or post-translational modifications of the phase-separating proteins [15], that enable external control of condensate formation. Observing the onset of oscillations upon induction of phase separation for $N > N_c$, and their absence in a non-phase-separating control, would provide a direct test of the proposed mechanism.

This route to oscillations is distinct from classical reaction-diffusion instabilities [30,31], as it does not arise from differential transport but rather from the altered scaling of reaction rates imposed by condensate geometry. Related effects have been explored in more detailed spatial descriptions, including Cahn-Hilliard models with reactions (“active emulsions” [24,32]). In that framework, it was shown how phase separation of scaffold molecules affects the reaction rates of clients [33] and recently, how nonequilibrium fueling can drive droplets into excitable regimes, resulting in self-sustained oscillations of droplet

formation and dissolution [34]. Our approach, in contrast, deliberately retains the simplicity and analytical tractability of ODEs, identifying LLPS as a generic source of dynamical instabilities in nonlinear networks. While our model focuses on linear interactions and a single phase-separated component, omitting the richness of multiple condensates and nonlinear biochemistry, and isolating the effect of phase separation on degradation-mediated feedback, it nevertheless points to a general principle. Nonideal physical interactions can provide regulatory circuits with behaviors inaccessible under mean-field kinetics, expanding the landscape of mechanisms by which complex spatiotemporal dynamics emerge in soft matter and biological physics.

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Data availability—The data that support the findings of this article are openly available at [35].

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