

Nonmonotonic dynamics of nuclear-to-cellular volume ratio under osmotic shocks

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How the nuclear size dynamically scales with the cellular size during osmotic shock treatments remains controversial. We develop a dynamic model by incorporating the typical interactions between polydisperse biomolecules and the mechanical elasticity of the cytoplasm and nucleoplasm to investigate this long-standing critical issue. We find the nontrivial phenomenon that the nuclear-to-cellular volume ratio can vary nonmonotonically with time, instead of maintaining a constant as usually known, under the osmotic shocks. Combining simulations and analytical argument, we validly account for this nonmonotonic dynamic behavior, and identify its essential regulatory mechanism to be the collaboration of the excluded volume interactions between the polydisperse biomolecules and the spatial constraint from the nuclear envelope on the macromolecule diffusions. Our results agree well with the published experiments for cellular and nuclear size controls of the protoplasts. Our model offers energetic insight in characterizing biology-associated dynamic processes such as macromolecular crowding, and biophase separation occurring in cytoplasm and nucleoplasm.

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Cells are the fundamental units that make up living organisms. In particular, the emergence of eukaryotes evolving more complex intracellular organizations has made the kingdom of life flourish [1,2]. A long-standing concern for the eukaryotic cell types is how the nucleus size dynamically scales with the cell size during cell response to external stimuli [3–5]. The traditional experience believes that the nuclear-to-cellular volume ratio, i.e., the N/C ratio, always remains a constant for many intracellular organization scenarios [4,5]. Research on this issue, however, is far from completely conclusive. Several avenues such as modifying protein transport, modulating apparent mechanics of the nuclear envelope (NE), and electrostatic interactions at an intracellular biointerface were shown to function experimentally in disrupting the maintenance of the N/C ratio [6–8]. These studies evidence the biological complexity that the controls of the cellular and the nuclear size highly depend on the time evolution of self-organization and diffusive exchange of diverse biomolecules between the organelles inside the cell [3,9–12].

Recent experiments evidenced that the cells with the nucleus inside behaves as an ideal nested osmometer due to their respective soft nature, suggesting that the osmotic pressures created by the osmotically active biomolecules, also termed as (bio)osmolytes, can govern their sizes [4,12]. Whereas, the existing models [4,5], based upon the van't Hoff relationship at the osmotic equilibria state, can hardly quantify the dynamics of the N/C ratio under the osmotic shocks; in particular, the interactions between the intracellular biomolecules with

polydispersity in size [13–17] and the mechanical elasticity of the cell (due to inherent cytoskeletons) [18–20] have been largely ignored.

In this Letter, we develop a new theoretical framework to study the osmotically driven dynamics of the N/C ratio. In our model, the cell and its nucleus are treated as the microgel and the nanogel, as depicted in Fig. 1, respectively. The crosslinked gel network (nonosmotic phase) represents the alike biofunctions of the cytoskeletons to ensure different elasticities for the cytoplasm and the nucleoplasm [2]. Of note, the cell membrane is intrinsically viscoelastic, while such a hallmark has been ignored in our model by considering a simple scenario that the cell takes the small deformation under the moderate external stimuli. It showed previously that there exist prevalently the excluded volume interactions between the polydisperse (bio)osmolytes in the intracellular crowding [21–24]. Herein, we consider the intracellular plasma to be a binary mixture of small and large (bio)osmolytes, regarded as the hard colloids, and employ the depletion theory at thermodynamic equilibria in a free energy density model for their interactions [16,25,26].

We consider a cell with an initial radius R_{C0} , as well as a nucleus with R_{N0} , to take the respective radii $R_C(t)$ and $R_N(t)$ over time. In this problem, we dictate that the small and the large osmolytes are both restricted by the cell membrane (CM), but only water can freely pass through the CM under the osmotic shocks. It is this widely adopted assumption that guarantees the conservation in numbers of the polydisperse osmolytes inside the cell [4,5]. Within the cell, the nuclear envelope, a semipermeable membrane, allows the small osmolytes with a Stokes radius $r_a \leq 3$ nm, e.g., glycerol and nucleotide, to freely pass, while it remains impermeable to the large osmolytes with the radius r_b in the range of 6–40 nm, e.g., proteins, DNA, and mRNA [4,5,15]. We denote the components of water, the gel network, and small and large osmolytes by the subscripts “w,” “g,” “a,” and “b,”

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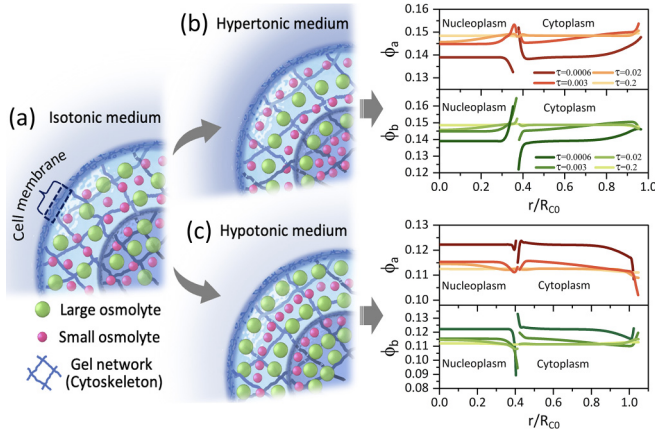


FIG. 1. Schematics of gel-like colloids mimicking the cell (microgel) consisted of the nucleus (nanogel). The cell under (a) isotonic condition, (b) hyperosmotic shifts, and (c) hypoosmotic shifts. The concentration profiles in (b) and (c) manifest the respective segregation configurations of small and large osmolytes over time. Here, $\phi_{a0} = \phi_{b0} = 0.13$, $\phi_{w0} = 0.7$, $r_a = 3$ nm, and $r_b = 20$ nm.

respectively. Their individual volumes are $\sigma_i = 4\pi r_i^3/3$ with r_i being the radii (r_g means gyration radius of a segment in the gel network). The time-dependent volume fractions of these components are $\phi_i(r, t)$, and $\sum_i \phi_i = 1$ in the cell. The kinematic equations of water and the osmolytes are governed by the force balance between the thermodynamic force and the hydrodynamic dissipative force. Since the components are the same in the cytoplasm and the nucleoplasm, these equations can be represented universally in the cell:

$$\zeta_{wa}(V_w - V_a) + \zeta_{wb}(V_w - V_b) + \zeta_{wg}V_w + \nabla\mu_w = 0 \quad (1a)$$

$$f = k_B T \left(\sum_{i=w,a,b} \frac{1}{\sigma_i} \phi_i \ln \phi_i + \sum_{\substack{i=a,b \\ j=a,b}} \frac{1}{\sigma_i \sigma_j} a_{ij} \phi_i \phi_j + G_0 \left(\frac{\phi_g - \phi_{g0}}{\phi_{g0}} \right)^2 \right), \quad (3)$$

where $a_{ij} = (2\pi/3)(r_i + r_j)^3$ is the second-order virial coefficient to represent the excluded volume interactions between the osmolytes, and the third term accounts for the elastic energy due to the small deformation of gel-like cytoskeletons with the initial concentration ϕ_{g0} , where $G_0 = mk_B T / \sigma_g$ is the elastic modulus with m crosslinking degree.

Solving Eq. (1) by substituting Eqs. (2) and (3) and the condition $\sum_{i=w,a,b,g} v_i \phi_i = 0$, we obtain the velocities V_i for water and the osmolytes (see [27] for their expressions). One then arrives at the time evolution equations of ϕ_i with one-dimensional spherical symmetry

$$\dot{\phi}_i = -\frac{1}{r^2} \frac{\partial(r^2 J_i)}{\partial r}, \quad (4)$$

where $J_i = V_i \phi_i$ are the fluxes. Here, the use of velocities V_i instead of the velocities v_i is to implement “soft-cell” approach (SCA) for solving Eq. (4) numerically with the appropriate boundary conditions. The SCA we proposed previously is very portable in addressing moving boundary complexes for

$$\zeta_{aw}(V_a - V_w) + \zeta_{ab}(V_a - V_b) + \zeta_{ag}V_a + \nabla\mu_a = 0, \quad (1b)$$

$$\zeta_{bw}(V_b - V_w) + \zeta_{ba}(V_b - V_a) + \zeta_{bg}V_b + \nabla\mu_b = 0, \quad (1c)$$

where velocities (relative to the gel network) are used as $V_i = v_i - v_g$ ($i = w, a, b$) with v_i being the components velocities relative to the laboratory, and $\mu_i = \sigma_i \partial f / \partial \phi_i$ are the respective chemical potentials with f being the free energy density model. In Eq. (1), assuming the dilute regime, the frictional coefficient of water molecules percolating through the osmolytes are much less than that penetrating through the gel network ζ_{wg} , i.e., ζ_{wa} and ζ_{wb} are ignored. The frictional coefficients of the osmolytes diffusing in water, the plasma, and the gel network are all given by the Einstein relation $\zeta_{ij} = k_B T / D_{ij}$ ($i = a, b, j = w, a, b, g, i \neq j$) with D_{ij} being the self-diffusivities of the osmolytes. The osmolyte diffusivities in water are given by Stokes-Einstein-type $D_{iw} = k_B T / 6\pi \eta r_i$, where η is the water viscosity, and those in the gel network D_{ig} , as well as the ζ_{wg} , are all fully discussed in Sec. I of the Supplemental Material [27]. To determine the diffusivities of the osmolytes in the plasma, D_{ab} and D_{ba} , we follow Phillies’ model [5] which is frequently used to fit the microrheological experiments in vivo [15], which yields

$$D_{ij} = D_{iw} \exp(-\omega \beta_i \phi_j), \quad (2)$$

where $i = a, b, j = b, a$ ($i \neq j$), and the scaling parameters are suggested as $\beta_i = r_i \beta_{40} / 20$ with $\beta_{40} \approx 7.4$ measured for a genetically encoded multimeric (GEM) nanoparticle with a diameter of 40 nm [15]. Note that these diffusivities in Eq. (2) are often measured on the magnitude of 10^{-13} m²/s [5,15], which can be matched by taking factor $\omega = 10$ in our model. The free energy density model $f(\phi_w, \phi_a, \phi_b, \phi_g)$ can be simply given akin to that for the colloidal gel solutions [25,29]:

gel dynamics [26,28]. The boundary conditions used here become concise: (i) At the nucleus center $r = 0$, no fluxes exist, $J_i = 0$; (ii) at the CM $r = R_C$, the fluxes of the osmolytes are zero, $J_a = J_b = 0$, whereas the water flux is related to the cell radius by $J_w = -\dot{R}_C(t)$; (iii) an extra condition is needed for the constraint from the NE upon the large osmolytes by $J_b|_{r=R_N} = 0$; (iv) due to condition (iii), the concentration gradient of the large osmolytes could become very large at the NE, leading to unexpected instability for the continuous diffusion equations of the small osmolytes and water. For simplicity, we assume $\partial \phi_b / \partial r = 0$ only at the NE in their diffusion equations.

In our model, the NE has been assumed to be infinitely thin such that its interfacial energy is negligible [4,5], while the CM thickness varies with the cell size by $h = h_0 (R_C / R_{C0})^{-\alpha}$ with h_0 an initial CM thickness [19]. The cellular size, as validated experimentally [5,19], exclusively relies on the osmotic pressure difference causing the water flux passing through the CM, which can be determined by Darcy’s law

$\dot{R}_C(t) = \kappa \Delta \Pi / \eta h$, where κ is the CM permeability and $\Delta \Pi = \Pi_{\text{cyt}} - \Pi_{\text{sur}}$ is the osmotic pressure difference between the cytoplasm and the surroundings. Strictly, $\Pi_{\text{cyt}}(t)$ determined by the solid phases $\phi_i(t)$ in the cytoplasm is time dependent. If we first crudely assume $\Delta \Pi$ a constant, R_C can be expressed analytically for $\alpha = 1$ as

$$R_C/R_{C0} = \exp(t \Delta \Pi \kappa / \eta h_0 R_{C0}) \quad (5)$$

which typifies an exponential mode of cellular size control, a prevalent mode in experiments [5,15]. For the sake of simplicity, Eq. (5) is preapplied for the boundary condition (ii), while during the SCA calculations, we revisit the time-dependent nature of Π_{cyt} in Eq. (5) by

$$\Pi_{\text{cyt}}(t) = nk_B T \sum_{i=a,b} \frac{\bar{\phi}_i}{\sigma_i} z(\bar{\phi}_i), \quad (6)$$

where the contribution of the cytoskeletons to the pressure is ignored due to its very dilute concentration (e.g., $\phi_{g0} = 0.04$), n is the matching factor, and the solution compressibility factors are given by $z(\bar{\phi}_i) = \frac{1+a_1\bar{\phi}_i+a_2\bar{\phi}_i^2+a_3\bar{\phi}_i^3}{1-\bar{\phi}_i/\phi_p}$, where the coefficients are $a_1 = 4 - 1/\phi_p$, $a_2 = 10 - 4/\phi_p$, and $a_3 = 18 - 10/\phi_p$, and $\phi_p = 0.58$ being the loose packing fraction [29,30]. The osmolyte concentrations used in Eq. (6) are the volumetric average in the cytoplasm $\bar{\phi}_i(t) = 3 \int_{R_N}^{R_C} r^2 \phi_i dr / (R_C^3 - R_N^3)$. A set of coupled diffusion equations in Eq. (4) can be made dimensionless, such as the dimensionless time $\tau = t D_{aw} / R_{C0}^2$ (see Sec. III the Supplemental Material [27]). Herein, the cellular size in Eq. (5) can be rewritten in its dimensionless form by $R_C(\tau)/R_{C0} = \exp(\text{Cont} \Delta \tilde{\Pi} \tau)$ with $\Delta \tilde{\Pi} = \sigma_a \Delta \Pi / k_B T$ and $\text{Cont} = 5 \kappa R_{C0} / h_0 r_a^2$. We dictate some main parameters fixed in this problem: $R_{C0} = 3 \mu\text{m}$, $h_0 = 100 \text{ nm}$, $r_w = 0.2 \text{ nm}$, $r_a = 3 \text{ nm}$, $r_g = 30 \text{ nm}$, $\kappa \approx 7 \times 10^{-19} \text{ m}^2$, and $R_{N0}/R_{C0} = 0.406$. Generally, the nucleus may be softer than the cell [2], and we then subdivide G_0 into $G_0^N \approx 0.11 \text{ kPa}$ in the nucleoplasm and $G_0^C \approx 10 \text{ kPa}$ in the cytoplasm. We set the water initial concentration as $\phi_{w0} = 0.7$, and the initial concentrations of the osmolytes as $\phi_{a0} = \phi_{b0} = 0.13$. This produces, revisiting Eq. (6), an initial isotonic pressure in the cytoplasm $\Pi_{\text{cyt}}^0 \approx 0.923 \text{ MPa}$ for $r_b = 20 \text{ nm}$ ($n = 110$) [15].

We first examine the influences of the osmotic shocks. As Figs. 1(b) and 1(c) show, the hypertonic shock, leading to shrinkage of the cell, raises the osmolyte concentrations, while the hypotonic shock, causing swelling of the cell, lowers them in the cell. We find that the osmotic shocks can cause the formation of concentration patterns of the osmolytes. For example, under the hyperosmotic shocks, in the cytoplasm, the small osmolytes enrich (monotonic increases in ϕ_a) at the domains near the CM and the NE, while the large osmolytes are driven towards the middle domain, and meanwhile, in the nucleoplasm, the large osmolytes enrich (monotonic increases in ϕ_b) towards the NE, while the small osmolytes are repelled away from the NE (a negative gradient of ϕ_a). The strong size asymmetry of the osmolytes enhances the cross interactions [virial coefficients $a_{ab} = a_{ba}$ in Eq. (3)] whose effect on the diffusions of the osmolytes is not symmetric [27], which essentially leads to the formation of specific segregation configurations in the osmolyte concentrations. The exhaustive

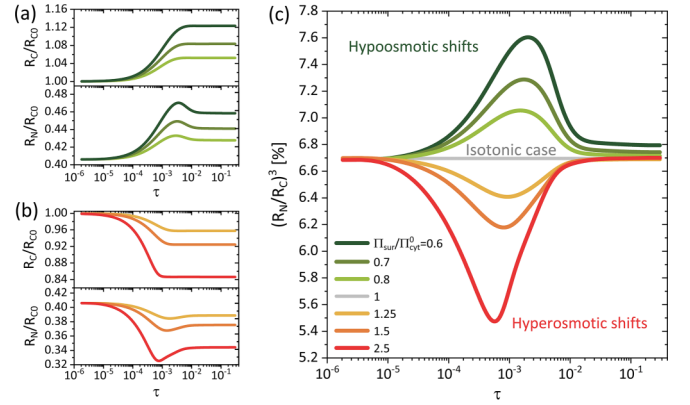


FIG. 2. Dynamics of the cellular size control and the nuclear size control for (a) hypoosmotic shifts and (b) hyperosmotic shifts. (c) Nonmonotonic dynamics of the N/C ratio under variable osmotic shifts. The initial N/C ratio $\varepsilon_0 = 6.69\%$ and $r_b = 20 \text{ nm}$.

analyses, which are also available for our problem, can be cited in the work on the stratification in drying the binary colloidal mixtures [31].

Figure 2 shows the dynamics of cellular size, the nuclear size, and the N/C ratio for different osmotic shocks. Comparing to the R_C , the R_N displays the nonmonotonic variations over time [Figs. 2(a) and 2(b)]. In Fig. 2(c), we further surprisingly find that the N/C ratio varies nonmonotonically over time, instead of maintaining a constant [4,5], during the osmotic treatment. For the hyperosmotic shocks, the profile of the N/C ratio behaves as a shape with initial falling and following rising, while a shape with initial rising and following falling for the hypoosmotic shocks. Particularly, the N/C ratio at the steady state could maintain the same value as the initial one. We speculate that the resulting concentration configurations arising from the coupled diffusions of the polydisperse bio-osmolytes [as characterized by the nonlinear partial differential equations in Eq. (4)] act as a major cause of this nonmonotonic dynamics of the N/C ratio, as well as its maintenance at the steady state. Although formulating an analytical expression finely fitting the numerical profiles of the N/C ratio in Fig. 2(c) has still remained elusive, we shall simply formulate the functional dependence of the N/C ratio (especially at the steady state) on the osmolyte concentrations by employing a signature that the polydisperse osmolytes are intrinsically conserved in numbers within nucleoplasm and cytosol. Let $\varepsilon(t) = R_N^3/R_C^3$ be the N/C ratio. Since the large osmolytes are conserved in numbers within the nucleoplasm and the cytoplasm, respectively, we then have $R_N^3 = R_{C0}^3 \phi_{b0}^{\text{nuc}} / \bar{\phi}_b^{\text{nuc}}$ and $R_C^3 - R_N^3 = (R_{C0}^3 - R_{N0}^3) \phi_{b0}^{\text{cyt}} / \bar{\phi}_b^{\text{cyt}}$, where $\bar{\phi}_b^{\text{nuc}}(t)$ and $\bar{\phi}_b^{\text{cyt}}(t)$ are assumed to be the volumetric average concentrations with spatial independence. The N/C ratio is then written as $\varepsilon(t) = \varepsilon_0 / [\varepsilon_0(1-k) + k]$, where $\varepsilon_0 = R_{N0}/R_{C0}$ is an initial N/C ratio and $k = \phi_{b0}^{\text{cyt}} \bar{\phi}_b^{\text{nuc}} / \phi_{b0}^{\text{nuc}} \bar{\phi}_b^{\text{cyt}}$. Our calculations confirm that the factor k can closely approximate to 1 for a wide range of concentrations considered here [27]. Therefore, the N/C ratio can be estimated by $\varepsilon(t) \cong \varepsilon_0/k$. Numerical calculations repeatedly suggest that for the special initial condition $\phi_{b0}^{\text{nuc}} = \phi_{b0}^{\text{cyt}}$ [used for calculations in Figs. 2(c) and S3 [27]], the

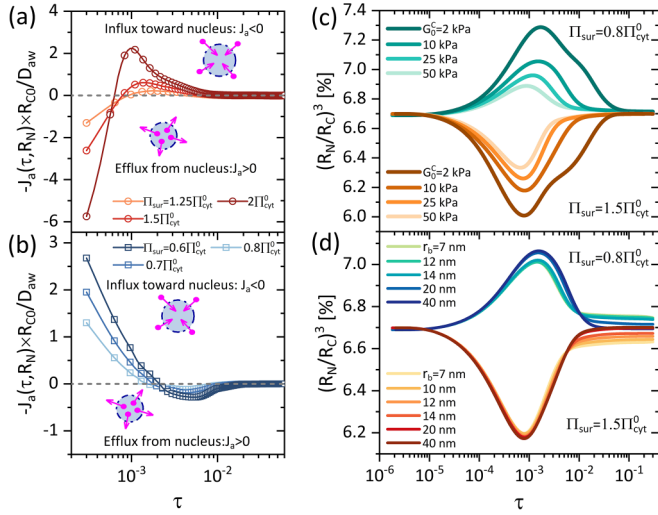


FIG. 3. Volumetric flux of the small osmolytes across the NE $J_a(\tau, R_N)$ varies with time under (a) hyperosmotic shocks and (b) hypoosmotic shocks. The used parameters are the same as in Figs. 1 and 2. The N/C ratio dynamics can be modulated by (c) the cellular elasticity and (d) the radius of large osmolyte for different osmotic shocks.

concentrations $\bar{\phi}_b^{nuc}$ and $\bar{\phi}_b^{cyt}$ are seen to be totally comparable at the steady state [Figs. 1(b), 1(c), and S3 [27]], signifying $k = 1$, which leads to $\varepsilon(t \rightarrow \infty) = \varepsilon_0$. We then argue that if the large osmolytes in the nucleoplasm and the cytoplasm are initially equal in concentrations, their concentrations most likely maintain to be totally comparable as the cell takes the new steady state. This regime ($k = 1$) naturally allows the maintenance of the N/C ratio at the steady state. Of note, though the conservation laws of the osmolytes are physically precise, the present argument, also relying on the numerical output of the osmolyte concentrations, appears qualitatively instead of analytically. Our results show that this N/C ratio maintenance is more robust for the cells exposed to the hyperosmotic shocks (similar to the macromolecular crowding [7,15,16]) than the hypoosmotic shocks [Fig. 2(c)]. In addition, this maintenance is shown to remain unaffected by the osmotic shocks and the cellular elasticity [Fig. 3(c)], though these factors significantly alter the N/C ratio dynamics. For a more general case $\bar{\phi}_{b0}^{nuc} \neq \bar{\phi}_{b0}^{cyt}$, also indicating $\bar{\phi}_b^{nuc} \neq \bar{\phi}_b^{cyt}$ at the steady state, we find the visible deviations of $\varepsilon(t \rightarrow \infty)$ from ε_0 [Fig. S4(a) in Ref. [27]]. We shall suggest here another form to readily evaluate $\varepsilon(t)$ for this general case,

$$\varepsilon(t) \cong \varepsilon_0 \frac{\bar{\phi}_{b0}^{cyt}}{\bar{\phi}_{a0}} \frac{\bar{\phi}_a(t)}{\bar{\phi}_b^{cyt}(t)}, \quad (7)$$

where we have adopted the conservation law of the small osmolytes within the cell $R_C^3 = R_{C0}^3 \bar{\phi}_{a0} / \bar{\phi}_a(t)$. Equation (7) manifests that the N/C ratio, especially at the steady state, can be well estimated by only accessing the average concentrations of the osmolytes in the cytosol instead of the nucleoplasm, which is an avenue experimentally preferred.

To further explore analytically the physical origin of the nonmonotonic dynamics of the N/C ratio, we start from its time derivative $\dot{\varepsilon} = 3\varepsilon(\dot{R}_N/R_N - \dot{R}_C/R_C)$, and naturally $\dot{\varepsilon} < 0$

for a decreasing ε , while $\dot{\varepsilon} > 0$ for an increasing ε . The $\text{sgn}(\dot{\varepsilon})$ (the sign of $\dot{\varepsilon}$) merely depends on the $\text{sgn}(\dot{R}_N/R_N - \dot{R}_C/R_C)$. By revisiting the conservation equations in Eq. (4), if considering the concentrations independent of r , we can rewrite them as $-J_i(t, r) = r\dot{\phi}_i/3$ ($i = a, w$). The cellular size and the nuclear size are related to the fluxes of the small osmolytes and water by $\dot{R}_C = -J_w(t, R_C)$ and $\dot{R}_N = -[J_a(t, R_N) + J_w(t, R_N)]$, respectively. We then obtain $\dot{R}_C/R_C \cong \dot{\phi}_w$ and $\dot{R}_N/R_N \cong \dot{\phi}_a + \dot{\phi}_w$, and therefore arrive at $\dot{R}_N/R_N - \dot{R}_C/R_C \cong \dot{\phi}_a$. This underlines that the rate of change of the N/C ratio is negatively correlated with the flux of the small osmolytes across the NE, i.e., $\dot{\varepsilon}(t) \cong -\varepsilon J_a(t, R_N)/R_N$. Accordingly, it produces

$$\text{sgn}[\dot{\varepsilon}(t)] \Leftrightarrow \text{sgn}[-J_a(t, R_N)]. \quad (8)$$

It is clear that the flux of the small osmolytes across the NE can phenomenally predict the nonmonotonic behaviors of the N/C ratio over time. Clearly, as seen in Fig. 3(a), the hyperosmotic shocks lead to the efflux of the small osmolytes, as well as water, from the nucleus, i.e., $J_a(R_N) > 0$, at the earlier stage, while as the segregations of the osmolytes form near the NE [Fig. 1(b)], in which the concentration of the small osmolytes at the outer side of the NE becomes higher than that at the inner side of the NE, suggesting that the small osmolytes will diffuse backward the nucleus, i.e., an influx towards the nucleus $J_a(R_N) < 0$, at the later stage. This manifests that, by revisiting Eq. (8), $\text{sgn}(\dot{\varepsilon}) < 0$ (the falling part) is followed by $\text{sgn}(\dot{\varepsilon}) > 0$ (the rising part) over time, corresponding to the profile shape of the N/C ratio for the hyperosmotic shocks [Fig. 2(c)]. A similar analysis, as shown in Fig. 3(b), could be applied to understand the inverse profile shape for hypoosmotic shocks [Fig. 2(c)]. With these results, we argue that the excluded volume interactions between the osmolytes of different sizes and the preferential localization of the large osmolytes constrained by the NE mutually determine either the efflux or the influx of the small osmolytes from the nucleus, which essentially dominates the nonmonotonic configurations of the N/C ratio dynamics under the osmotic shocks.

We probe the effects of the cytoplasm elasticity G_0^C (roughly regarded as the cellular elasticity) and the radius of the large osmolyte on the N/C ratio dynamics in Figs. 3(c) and 3(d), respectively. As G_0^C varies, i.e., the cell gets softer or harder, the dynamics of the N/C ratio is significantly affected, while its value at the steady state remains unaffected. Instead, the large osmolyte radius can markedly affect the N/C ratio at the steady state rather than its dynamics. It is indicated that the biological factors, such as the concentration and the size of the osmolytes, which are directly involved in modulating the depletion interactions between the osmolytes, could break the maintenance of the N/C ratio at the steady state.

Lastly, we compare our simulations with the experiments for the cellular and the nuclear size controls obtained from the whole fission yeast cells and the protoplasts [5] in Fig. 4. Comparing to the whole cell, the protoplast is the cell whose elastic wall has been removed. Our model in which the elastic interfacial energy from the cell wall has been ignored for simplicity is nearly identical to the case of protoplasts. In fact, though we simply refer to the exponential mode of R_C in Eq. (5), the employment of the time-dependent osmotic

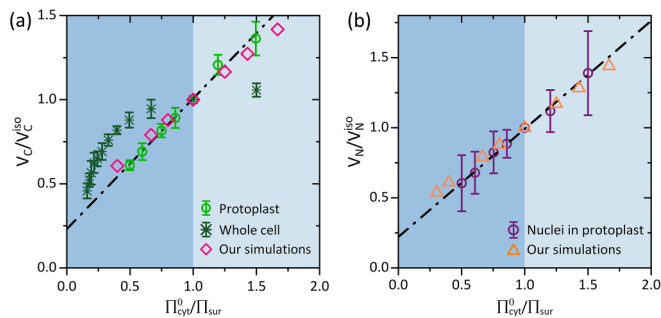


FIG. 4. Comparisons between the experiments (symbols with error bars) and our simulations for (a) the cellular volume V_C/V_C^{iso} and (b) the nuclear volume V_N/V_N^{iso} , where V_C^{iso} and V_N^{iso} are the volumes in the isotonic medium, as the functions of the osmotic shocks. The experiments are taken from Ref. [5], and the dashed lines, i.e., Boyle van't Hoff fitting, depict the behaviors of the ideal osmometers in the absence of membrane tension from the elastic cell wall. The initial N/C ratio $\varepsilon_0 = 8\%$.

pressure $\Pi_{\text{cyt}}(t)$ in Eq. (6) prevents us from formulating the cellular size analytically, but allows us to access it numerically. Apparently, our simulations and the experimental measurements share the same linear dependence of the cellular size, as well as the nuclear size, on the osmotic shocks. This evidences that our model which is capable of quantifying the nontrivial dynamic behaviors of cellular and nuclear volume controls can also remain coherent with the existing data for their volumes at steady state. We also expect our theory

to be further validated by future experiments in terms of nontrivial phenomena including segregation configurations in the osmolyte concentrations and the resulting nonmonotonic dynamics of the N/C ratio.

In conclusion, we have presented a theoretical framework to investigate the dynamics of nuclear-to-cellular volume ratio. We confirm the surprising finding of nonmonotonic dynamics of the N/C ratio, instead of maintaining a constant, under the osmotic shocks, which challenges the traditional knowledge [4,5]. We show that this nontrivial dynamics can be characterized phenomenologically by the specific segregation configurations in the concentrations of the polydisperse osmolytes. We further spotlight that the collaboration of the excluded volume interactions between the osmotically active osmolytes and the preferential localizations of the large osmolytes separated by the NE serves as the dominant physical origin of these observed phenomena. Future work may focus on extending our simple framework by integrating the factors, such as homeostasis regimes [5,15] and biointerfacial features [32,33], to explore the biology-associated dynamic processes, e.g., macromolecular crowding and biophase separations, which hold physiological importance for living organisms.

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- [1] T. Gabaldón, Origin and early evolution of the eukaryotic cell, *Annu. Rev. Microbiol.* **75**, 631 (2021).
- [2] M. E. Allen, J. W. Hindley, D. K. Baxani, O. Ces, and Y. Elani, Hydrogels as functional components in artificial cell systems, *Nat. Rev. Chem.* **6**, 562 (2022).
- [3] Y. Kalukula, A. D. Stephens, J. Lammerding, and S. Gabriele, Mechanics and functional consequences of nuclear deformations, *Nat. Rev. Mol. Cell Biol.* **23**, 583 (2022).
- [4] D. Deviri and S. A. Safran, Balance of osmotic pressures determines the nuclear-to-cytoplasmic volume ratio of the cell, *Proc. Natl. Acad. Sci. USA* **119**, E2118301119 (2022).
- [5] J. Lemièrre, P. Real-Calderon, L. J. Holt, T. G. Fai, and F. Chang, Control of nuclear size by osmotic forces in *Schizosaccharomyces Pombe*, *eLife* **11**, E76075 (2022).
- [6] H. Cantwell and P. Nurse, Unravelling nuclear size control, *Curr. Genet.* **65**, 1281 (2019).
- [7] J. D. Finan, K. J. Chalut, A. Wax, and F. Guilak, Nonlinear osmotic properties of the cell nucleus, *Ann. Biomed. Eng.* **37**, 477 (2009).
- [8] R. Rollin, J.-F. Joanny, and P. Sens, Physical basis of the cell size scaling laws, *eLife* **12**, E82490 (2023).
- [9] A. S. Verkman, Solute and macromolecule diffusion in cellular aqueous compartments, *Trends Biochem. Sci.* **27**, 27 (2002).
- [10] G. Rivas and A. P. Minton, Macromolecular crowding *in vitro*, *in vivo*, and in between, *Trends Biochem. Sci.* **41**, 970 (2016).
- [11] J. Berry, C. P. Brangwynne, and M. Haataja, Physical principles of intracellular organization via active and passive phase transitions, *Rep. Prog. Phys.* **81**, 046601 (2018).
- [12] C. Cadart, L. Venkova, P. Recho, M. C. Lagomarsino, and M. Piel, The physics of cell-size regulation across timescales, *Nat. Phys.* **15**, 993 (2019).
- [13] C. A. Brackley, M. E. Cates, and D. Marenduzzo, Intracellular facilitated diffusion: Searchers, crowders, and blockers, *Phys. Rev. Lett.* **111**, 108101 (2013).
- [14] G. Nettesheim, I. Nabti, C. U. Murade, G. R. Jaffe, S. J. King, and G. T. Shubeita, Macromolecular crowding acts as a physical regulator of intracellular transport, *Nat. Phys.* **16**, 1144 (2020).
- [15] B. Alric, C. Formosa-Dague, E. Dague, L. J. Holt, and M. Delarue, Macromolecular crowding limits growth under pressure, *Nat. Phys.* **18**, 411 (2022).
- [16] A. Pastore and P. A. Temussi, Crowding revisited: Open questions and future perspectives, *Trends Biochem. Sci.* **47**, 1048 (2022).
- [17] T. Skóra, M. Janssen, A. Carlson, and S. Kondrat, Crowding-regulated binding of divalent biomolecules, *Phys. Rev. Lett.* **130**, 258401 (2023).
- [18] D. A. Fletcher and R. D. Mullins, Cell mechanics and the cytoskeleton, *Nature (London)* **463**, 485 (2010).
- [19] H. Li, Y. Zheng, Y. L. Han, S. Q. Cai, and M. Guo, Non-linear elasticity of biological basement membrane revealed by rapid inflation and deflation, *Proc. Natl. Acad. Sci. USA* **118**, E2022422118 (2021).
- [20] S. Grosser, J. Lippoldt, L. Oswald, M. Merkel, D. M. Sussman, F. Renner, P. Gottheil, E. W. Morawetz, T. Fuhs, X. F. Xie, S. Pawlizak, A. W. Fritsch, B. Wolf, L.-C. Horn, S. Briest,

- B. Aktas, M. L. Manning, and J. A. Käs, Cell and nucleus shape as an indicator of tissue fluidity in carcinoma, *Phys. Rev. X* **11**, 011033 (2021).
- [21] D. Gnutt, M. Gao, O. Brylski, M. Heyden, and S. Ebbinghaus, Excluded-volume effects in living cells, *Angew. Chem. Int. Ed.* **54**, 2548 (2015).
- [22] G. Bajpai, D. A. Pavlov, D. Lorber, T. Volk, and S. Safran, Mesoscale phase separation of chromatin in the nucleus, *eLife* **10**, E63976 (2021).
- [23] Y. Zhang, D. S. W. Lee, Y. Meir, C. P. Brangwynne, and N. S. Wingreen, Mechanical frustration of phase separation in the cell nucleus by chromatin, *Phys. Rev. Lett.* **126**, 258102 (2021).
- [24] J. D. Wurtz and C. F. Lee, Chemical-reaction-controlled phase separated drops: Formation, size selection, and coarsening, *Phys. Rev. Lett.* **120**, 078102 (2018).
- [25] J.-P. Hansen and I. R. McDonald, *Theory of Simple Liquids with Applications to Soft Matter*, 4th ed. (Academic Press of Elsevier, Oxford, UK, 2013).
- [26] J. Z. Sui, Osmotic release of drugs via deswelling dynamics of microgels: Modeling of collaborative flow and diffusions, *Phys. Chem. Chem. Phys.* **25**, 410 (2023).
- [27] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/PhysRevResearch.6.L012014> for expressions of the velocities of water, small and large osmolytes, free energy density model, Soft-Cell approach (SCA) with dimensionless procedure, and some supplementary results.
- [28] J. Z. Sui, Self-growing nano-liquid-crystal film from dynamic swollen hydrogel substrates, *Phys. Rev. E* **106**, 054701 (2022).
- [29] J. Z. Sui, Dynamic behaviors of sedimenting colloidal gel materials: hydrodynamic interactions, *Phys. Chem. Chem. Phys.* **22**, 14340 (2020).
- [30] J. Z. Sui, Transport dynamics of charged colloidal particles during directional drying of suspensions in a confined microchannel, *Phys. Rev. E* **99**, 062606 (2019).
- [31] J. J. Zhou, Y. Jiang, and M. Doi, Cross interaction drives stratification in drying film of binary colloidal mixtures, *Phys. Rev. Lett.* **118**, 108002 (2017).
- [32] W. T. Jiang, Z. Y. Wu, Z. Gao, M. M. Wan, M. Zhou, C. Mao, and J. Shen, Artificial cells: Past, present and future, *ACS Nano* **16**, 15705 (2022).
- [33] B. Gouveia, Y. Kim, J. W. Shaevitz, S. Petry, H. A. Stone, and C. P. Brangwynne, Capillary forces generated by biomolecular condensates, *Nature (London)* **609**, 255 (2022).