



Towards modeling molecular cooperativity on the cellular scale

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ABSTRACT

Formulated originally to describe the subtle blend of kinetics and thermodynamics that drives protein folding and ligand binding, the molecular cooperativity concept extrapolates readily to the cellular scale. Here it constitutes a thermally driven mode of cytological organization which can be provisionally explored within the equation of state (EOS) framework of classical statistical mechanics. We give a unified EOS account of the 'proto-cooperative' phenomena of phase separation and gelation in cytoplasm, emphasizing osmoregulatory control mechanism. In an extension to this framework, we show that a significant thermodynamic partitioning of ribosomes could occur spontaneously in conjunction with phase separation. This would be tantamount to a translation–transcription decoupling, with relevance to cellular evolution.

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1. Introduction

Meaningful simulation of an entire biological cell has long been one of the loftier goals of computational Newtonian dynamics. In certain respects it is already achievable on today's laptops; for example in simulations of the constricting effect of crowding on diffusional timescales governing the approach of enzymes to their targets [1]. But 'cooperative' effects occurring on the whole-cell scale, such as the formation of subcellular compartments, arguably present a more considerable challenge, raising the bar somewhat.

As in the case of protein folding, the natural theoretical starting point for understanding this cytological dimension to cooperativity is the equilibrium thermodynamics concept of a phase transition: The early coil–globule phase change description of folding remains a phenomenologically correct first base for tertiary structural prediction [2]. So it is reasonable to suppose that phase behavioral idealization is also a valid initial template for cooperativity acting on larger length scales.

If the degree of idealization is very high, then explicit molecular dynamics becomes overkill. The Newtonian equations of motion can instead be absorbed into an analytically tractable 'equation of state' (EOS) derived via classical statistical mechanics. A successful example is Odijk's treatment of compaction of the bacterial nucleoid [3]. To describe compaction as a whole-cell cooperative phenomenon driven by volume exclusion, Odijk relied on an extremely simple hard sphere EOS to represent the cell's entire protein complement, deriving a theoretical picture remarkably consistent with subsequent experiments [4].

A second motivation for EOS idealization is to link Newtonian dynamics to an energy landscape description [5], since the landscape

view affords probably the best intuitive feel for what sets biological cooperativity apart from ordinary matter: Whereas for ordinary liquids a temperature quench into the low-lying slopes of the landscape ends in the arrested structural randomness of a glass transition, in a cooperative system these slopes are negotiated in a more directed fashion [6].

Thus while in the not-too-distant future it should be possible to model whole cells via simulations accounting fairly comprehensively for the huge array of molecular species and interactions involved, there certainly exists an interim role for the pared-down EOS approach. With these remarks for motivation, our purpose in the following is to apply EOS description to 'proto'-cooperativity interpretations of (i) subcellular compartmentation; and (ii) translation–transcription decoupling.

The point (i) that phase behavior provides a coarse mechanism for subcellular compartmentation is already qualitatively established [7,8], and the first part of our discussion will serve just to put it on an EOS footing, adequately primed for the more novel direction (ii). We technically review the two distinct phase behavioral phenomena implicated in subcellular compartmentation: Liquid–liquid phase separation, which will tend to drive the formation of bubbles with cytosol-like macromolecular concentrations; versus gelation, which we associate with denser compartments with inclusion body consistency [9–13]. To describe gelation, it is natural to use the energy landscape picture, although at this stage we do not attempt to specifically introduce a cooperative element. In Section 4 we address the modulation of phase behavior by compatible osmolytes. This is of interest because by implication compatible osmolytes provide a mechanism for regulatory control of cooperativity.

The last section adapts the EOS framework to accommodate ribosome partitioning under a phase separation. When such partitioning is strong, it constitutes a transition–transcription decoupling,

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our item (ii) above. So here there exists a tentative link to the nuclear compartmentation event which marks the cell–evolutionary transition from prokaryote to eukaryote.

2. Cytoplasmic phase separation

We base everything on an orthodox ‘colloidal’ mode of EOS description which is known to successfully capture the main phase behavioral features exhibited by in vitro protein solutions [14,15]. The term ‘colloidal’ applies loosely to any solvated suspension of microscopic particles, tending to attract one another (Latin inf. *colligere* = clump together), though not strongly with respect to the thermal energy kT . It is worthwhile to stress that as a paradigm for treating protein–protein interaction, this is somewhat removed from structural biology. The specific aspect of biochemical molecular recognition is not at all of the essence in the colloidal view. The focus is instead on the sort of non-specific interactions which occur during random collisions, comprising sphere-like volume exclusion (i.e. crowding [16]), salt-attenuated electrostatics, dispersion forces and the hydrophobic effect.

Sear has pointed out that these pose a promiscuous distraction to specific binding partners, a sort of noisy hubbub over which they must shout to be heard [17]. However, the label ‘non-functional’ adopted on this basis by Zhang et al. [18], in performing an analysis similar to Sear’s, is a misnomer. Notably in this respect, Hlevnjak et al. [19] have recently looked for and found evidence that known groups of co-localized proteins tend to share various coarse-grained physicochemical features in common, substantiating a functional role for non-specific interactions in connection with subcellular compartmentation.

From the EOS modeling perspective, there is a major *ansatz* to be made by noting that the colloidal components we have listed are all nearest-neighbor interactions in the statistical mechanical sense, and so may be feasibly lumped together in a single effective square well, or some similarly short-ranged model potential such as the Baxter or Yukawa [15,20,21]. Quite sophisticated EOS methods exist for such potentials [22], but it is sufficient for our purpose to go with the elementary Van der Waals form

$$\Pi = \rho kT / (1 - \varphi) - 2\pi \varepsilon a d^2 \rho^2. \quad (1)$$

Irrespective of their relative sophistication, all EOSs have this same essential anatomy in common: Thermodynamics on the l.h.s., in this case osmotic pressure Π , is defined analytically with respect to microscopic interactions and structure on the r.h.s. The set of microscopic parameters in this particular instance comprises ρ for protein concentration, d for the protein lengthscale (i.e., an effective diameter), and $\varphi = \pi \rho d^3 / 6$ for the protein-occupied volume fraction. Well depth and range are denoted respectively by ε and a , but it is convenient in practice to absorb these into a dimensionless ‘attraction’ $\alpha = 3(a/d)\varepsilon/kT$, so that $\Pi/\rho kT = 1/(1 - \varphi) - 4\alpha\varphi$. Cellular protein volume fractions lie typically around $\varphi = 20$ –30%, while for a realistic selection of parameter values $d = 6$ nm, $a = 1$ nm, and $\varepsilon = 2kT$ we expect $\alpha \approx 1$.

Phase separation is read off the EOS as the locus of diverging compressibility $\partial\rho/\partial\Pi \rightarrow \infty$, the ‘spinodal’. The phase separating domain of (φ, α) extends off the spinodal’s extremum, the venerable Van der Waals ‘critical point’ $\varphi_c = 1/3$; $\alpha_c = 27/32$. Insofar as this falls within what we expect to be the physiological region of (φ, α) , it verifies that phase behavioral effects are well within striking distance of a real cytoplasm.

3. Cytoplasmic gelation

There exist a number of rival theories of gelation. The landscape one takes precedence in the present context primarily because of the

traditional association of landscapes with biological cooperativity we already remarked on. However, it also has the virtue that it derives easily from first principles [5,21]. Briefly, the high terrain of the landscape represents states in which there are very few attractive bonds between the cell’s protein components, hence the interaction enthalpy per particle is negligible, $e \approx 0$. The low terrain on the other hand corresponds to states in which the proteins are lumped in clusters [23] so that e becomes significant. With decreasing thermal energy kT relative to landscape topology, these low-lying states become increasingly difficult to escape from, until the system finally gels. Mathematically this onset is distilled by the device of an ideal glass, a single nondegenerate state at the very bottom of the landscape, characterized by $e = e_{ig}$ and zero per-particle entropy $s = 0$. When the condition $(\partial f / \partial e)_{e_{ig}} = 0$ is met, where f is the Helmholtz free energy, the ideal glass becomes thermodynamically stable.

The condition is solved by writing $f = e - Ts(e)$ and invoking a quadratic interpolation $s(e)/s^* = 1 - (e/e_{ig})^2$, to yield

$$T_{gel} = e_{ig} / (2s^*), \quad (2)$$

where s^* is similar to the usual Van der Waals translational entropy $s/k = \ln(1 - \varphi) - \ln\varphi + \text{const}$, but subject to the constraint there are no bonds in the system. We can neatly implement this constraint just by renormalizing effective particle diameter from d to $d + a$, where a is the bonding range,

$$s^* / k \approx \ln \frac{1 - \gamma\varphi}{\gamma\varphi} + \text{const}, \quad (3)$$

where $\gamma = 1 + 3a/d$. The constant is fixed by requiring $T_{ig} \rightarrow \infty$ in the random close packing limit $\varphi = 0.64$. Substituting back into Eq. (2) the result for the gelation volume fraction is then

$$\varphi_{gel} = \left[\gamma + (1/0.64 - \gamma) \exp(e_{ig}/2kT) \right]^{-1}. \quad (4)$$

If we write $e_{ig} = -n_{ig}\varepsilon/2$, where $n_{ig} \approx 4$ is a reasonable guess for the average number of nearest-neighbor bonds per protein in the gel phase, then in the (φ, α) projection we have roughly

$$\alpha_{gel} \approx \frac{1}{2} \ln \left(\frac{2}{3\varphi} - 1 \right) + \frac{3}{2}. \quad (5)$$

This result is not just so much pie-in-the-sky! An applied biotechnological arena where it is conceivably of practical use is in predicting the odds on successful recombinant protein expression. A web-based bioinformatic tool devised along such lines can be accessed at <https://sites.google.com/site/dewcheckcell/>.

4. Compatible osmolytes

Should phase behavior slip out of regulatory control, then clearly it can easily end up being highly detrimental to a cell’s wellbeing, as happens in the well documented sickle cell and Alzheimer pathologies. Control is arguably enforced at least in part by evolutionary negative selection, acting on expression levels in particular [24,25]. On the other hand, for the cell to actively maneuver around a phase diagram in the dynamic manner we anticipate for cooperativity effects, there must presumably also exist more immediate physiological mechanisms, to which the cell has recourse ‘in real-time’. The most obvious candidate for this is just the usual means by which a cell safeguards its osmotic wellbeing, regulation of its internal osmolyte concentration.

In addition to ordinary salts, the cell scavenges the environment for small organic molecules such as glycine betaine [26] which are of premium ‘compatible’ osmoregulatory character in that they do not

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