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Generalized Flory Theory for Rotational Symmetry Breaking of Complex Macromolecules

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We report on spontaneous rotational symmetry breaking in a minimal model of complex macromolecules with branches and cycles. The transition takes place as the strength of the self-repulsion is increased. At the transition point, the density distribution transforms from isotropic to anisotropic. We analyze this transition using a variational mean-field theory that combines the Gibbs-Bogolyubov-Feynman inequality with the concept of the *Laplacian matrix*. The density distribution of the broken symmetry state is shown to be determined by the eigenvalues and eigenvectors of this Laplacian matrix. Physically, this reflects the increasing role of the underlying topological structure in determining the density of the macromolecule when repulsive interactions generate internal *tension*. Eventually, the variational free energy landscape develops a complex structure with multiple competing minima.

It is well known that when attractive interactions between the units (“monomers”) of a flexible macromolecule become sufficiently strong, the molecule can undergo a folding transition from a disordered isotropic state to an ordered structure with a specific shape [1]. Less familiar is the fact that when repulsive interactions dominate, macromolecules with more complex topologies also can transform from an isotropic state to one with a distinct shape. Examples are dendrimers [2] and certain biopolymers [3–6]. The shape is determined in this case by the competition between two effects. On the one hand, the combination of thermal fluctuations and short-range repulsive interactions between the monomers favors isotropic swelling, since that maximizes the entropy of the molecule. On the other hand, the connectivity of the macromolecule constrains the swelling. The swelling generates internal *tension* along the bonds, which reduces the dominance of thermal fluctuations and entropy. Swollen polymer gels [7] and polymer brushes in good solvent [8] are familiar examples of polymeric systems where swelling-induced tension suppresses fluctuations and confers a distinct shape. This suppression of thermal fluctuations means that tense macromolecules of this type can be described by mean-field theory [8], as opposed to linear polymers that have no internal tension [7].

Suppose one gradually increases the strength of the repulsions in a macromolecule with a complex topology, is there a well-defined threshold where such a molecule develops a distinct shape? If there is such a threshold then what is the nature of the rotational symmetry-breaking transition and how is the resulting shape related to the underlying topology? Finally, if the number of topological constraints is increased, does a complex macromolecule eventually become over-constrained and “frustrated” with a free energy landscape that has multiple competing minima [9]?

In this paper we propose a theory for the development of shape of topologically complex macromolecules with repulsive interactions. The theory starts from a minimal model that was introduced by Edwards to describe linear polymers and polymer gels [10, 11] in good solvent (i.e., solutions where repulsive interactions dominate). We construct a generalization of Flory mean-field theory and apply this to the Edwards

Hamiltonian. We find that the density distribution of complex branched polymers indeed undergoes a transition where it loses rotational symmetry. The structure of the broken symmetry state is determined by the eigenvalues and eigenvectors of the *Laplacian matrix* of the molecule, a concept borrowed from graph theory. As the strength of the repulsive interactions further increases, a complex energy landscape emerges with multiple competing minima. We find that at least the coarse-grained features of the density distribution of complex macromolecules and the tension profile can be predicted on the basis of the eigenvalues and eigenvectors of the Laplacian matrix.

The Edwards Hamiltonian for a macromolecule is defined by

$$\beta H = \underbrace{\frac{d}{2a^2} \sum'_{m < n} (\mathbf{r}_m - \mathbf{r}_n)^2}_{\beta H_0} + \sum_{m < n} u(\mathbf{r}_m - \mathbf{r}_n) \quad (1)$$

The summations are here over N point-like monomers located at sites \mathbf{r}_m with $m = 1, 2, \dots, N$ that are linked into a connected network by identical Gaussian springs. The prime in summation for H_0 indicates that this double sum is to be restricted to monomers pairs that are linked by springs. The second term in Eq. (1) represents short-range repulsive monomer-monomer interactions with strength $v = \int u(r) d^d r$ and range σ in units of a .

Our approach is based on the Gibbs-Bogolyubov-Feynman (GBF) variational principle [12, Section 1], which states that

$$F \leq F_T + \langle (H - H_T) \rangle_T \quad (2)$$

Here, $\langle \dots \rangle_T$ indicates that a Boltzmann average is to be taken with respect to the trial Hamiltonian H_T . F_T is the free energy associated with H_T . The variational free energy $F_V = F_T + \langle (H - H_T) \rangle_T$ provides an upper bound for the free energy.

Our construction of trial Hamiltonian H_T is motivated by presenting the ideal molecule (i.e., $v = 0$) Hamiltonian H_0 in terms of the eigenvectors and eigenvalues of the $N \times N$ real, square, symmetric Laplacian matrix $L_{n,m}$. The Laplacian matrix is the Laplace operator in matrix form defined on a

graph of the nodes and bonds of the molecule [12, Section 2]. Diagonal entries $L_{n,n}$ are equal to the number of monomers linked to monomer n (“vertex degree”) while off-diagonal entries $L_{n,m}$ are equal to -1 when monomer n and m are linked and 0 if they are not. The rows and columns of $L_{n,m}$ add to zero so the N component vector with all entries equal is an eigenvector with zero eigenvalue. The non-zero eigenvalues λ_j , with $j = 1, 2, \dots, N-1$, are strictly positive for connected graphs. The lowest non-zero eigenvalue, henceforth denoted by λ , is known as the “spectral gap” [13]. The eigenvalues and eigenvectors of the Laplacian matrix reflect only the topology of the graph of the molecule and do not relate to the geometrical space in which the molecule is embedded.

The usefulness of the Laplacian matrix lies in the fact that the expression for H_0 can be diagonalized as $\beta H_0 = \frac{d}{2} \sum_{j=1}^{N-1} \lambda_j |\mathbf{A}^{(j)}|^2$ where the λ_j are the (rank-ordered) eigenvalues of the Laplacian matrix and where the $\mathbf{A}^{(j)} = \sum_{i=1}^{N-1} \mathbf{r}_i \xi_i^{(j)} / a$ are normal mode amplitudes. These are vectors in the d -dimensional embedding space expressed in terms of the orthonormal N -component eigenvectors $\xi_n^{(j)}$ of the Laplacian matrix [14]. The expectation value of the mean square radius of gyration of the molecule without pair interactions ($v = 0$) can be directly expressed in terms of the eigenvalues of the Laplacian as $R_0^2 = \frac{a^2}{N} \sum_{j=1}^{N-1} \frac{1}{\lambda_j}$ [14]; we emphasize that there are only $N-1$ terms in this sum, the $j=0$ term (with $\lambda_0 = 0$) is automatically excluded. The spectrum of eigenvalues of the Laplacian also determines the spectrum of relaxation rates of the ideal ($v = 0$) molecule for the case of Rouse dynamics [15]. For the present purpose, an important aspect of H_0 is that it has d zero modes (associated with translation symmetry). However, the correct number of zero modes of a physical molecule – including translation and rotation symmetry – is $d(d+1)/2 > d$ so the modes of H_0 can not be simply identified with the physical modes of a molecule.

As a first example, let H_T equal H_0 except that the lowest non-zero eigenvalue, the spectral gap λ , is replaced by a variational parameter γ :

$$\beta H_T = \frac{d}{2} \gamma |\mathbf{A}^{(1)}|^2 + \frac{d}{2} \sum_{i=2}^{N-1} \lambda_i |\mathbf{A}^{(i)}|^2 \quad (3)$$

It can be shown (see [12, Section 3]) that this leads to the variational free energy which in the interesting case $\gamma \ll \lambda$ has the form:

$$\beta F_V(\gamma) \simeq \frac{d}{2} \frac{\lambda}{\gamma} + C(N) \frac{v}{a^d} \left(\frac{d}{2\pi} \gamma \right)^{d/2} \quad (4)$$

where $C(N) = \sum_{m < n=1}^N \left(\frac{1}{(\xi_m - \xi_n)^2 + \gamma \sigma^2} \right)^{d/2}$ with ξ_m the eigenvector associated with the spectral gap $\lambda \equiv \lambda_1$, and σ the range of the excluded volume interaction in units of a . It also can be shown, by generalizing methods of [16–21] (see [12, Section 4]), that for structures without symmetry this expression can be rewritten as a variational expression for the radius

of gyration R :

$$\beta F_V(R) \simeq \frac{3}{2} \lambda N \left(\frac{R}{a} \right)^2 + B \frac{N^2}{(4/3)\pi R^3} \quad (5)$$

with B proportional to v . This expression represents an extension of the Flory variational free energy for linear polymers [7] to polymers with complex structures. The first term on the right hand side represents entropic elasticity resisting the swelling while the second term represents osmotic swelling due to monomer-monomer repulsion in second virial form. This form of the Flory free energy for complex structures can be further simplified if there exists a big gap between first and second eigenvalues, in that case $R_0^2 \simeq a^2/N\lambda$, and λ in the entropic elasticity term can be replaced in favor of a more physical R_0^2 . The resulting expression has been extensively compared to experimental and simulation data on branched polymers [22] with good results. However, for very dense structures, such as high generation dendrimers, this version of Flory theory is not satisfactory, and more rigorous form (5) has to be used; for these cases, there is also a different approach suggested in [23].

Next, include in H_T the possibility of non-zero expectation values $\mathbf{A}_0^{(i)}$ for the M mode amplitudes with the lowest M eigenvalues (see [12, Section 3]):

$$\beta H_T = \frac{d}{2} \sum_{i=1}^M \gamma_i \left(|\mathbf{A}^{(i)} - \mathbf{A}_0^{(i)}| \right)^2 + \frac{d}{2} \sum_{i=M+1}^N \lambda_i |\mathbf{A}^{(i)}|^2 \quad (6)$$

The general case $\gamma_i = \lambda_i$ and $M = N$ is interesting. The set of order-parameters \mathbf{A}_0^i then defines a set of N particle vectors $\mathbf{r}_{0m}/a = \sum_{i=1}^{N-1} \mathbf{A}_0^i \xi_m^{(i)}$ (up to an overall translation). Expressing the trial Hamiltonian in real space with this variational ansatz leads to:

$$\beta H_T = \frac{d}{2a^2} \sum'_{m < n} (\mathbf{r}_m - \mathbf{r}_n - \Delta \mathbf{r}_{0m,n})^2 \quad (7)$$

where $\Delta \mathbf{r}_{0m,n} = (\mathbf{r}_{0m} - \mathbf{r}_{0n})$. This is the Hamiltonian of the ideal molecule except that Gaussian bonds $\mathbf{r}_m - \mathbf{r}_n$ linking monomers m and n have been placed under internal tension. The expectation value of the bond separations $\Delta \mathbf{r}_{0m,n}^0$ have a certain direction in space so rotational symmetry is broken. Formally, Eq. (7) is identical to the *Gaussian Network Model* that has been used with good results to obtain the normal modes of folded proteins [24]. Formula (7) is also instructive in terms of the aforementioned issue of zero mode counting. In the presence of non-vanishing bond-stretching vectors $\Delta \mathbf{r}_{0m,n}$, the bonds in macromolecule do form a solid object whose overall $d(d+1)/2$ rotations and translations are all zero modes. This is to be compared with an artificial system under purely harmonic Hamiltonian H_0 where all monomers in the ground state are assembled in one point which, as a point, does not have any rotational modes.

Finally, allow both the eigenvalues and the bond expectation values to be variational parameters. The simplest case is

again $M = 1$ (see [12, Section 3]):

$$\begin{aligned} \beta F_V(\gamma, \mathbf{A}_0) &\simeq \frac{d}{2} \ln \gamma + \frac{d}{2} \lambda \left(|\mathbf{A}_0|^2 + \frac{1}{\gamma} \right) \\ &+ C(N) \frac{v}{a^d} \left(\frac{d}{2\pi} \gamma \right)^{d/2} e^{-\gamma d \mathbf{A}_0^2/2} \end{aligned} \quad (8)$$

The function $F_V(\gamma, \mathbf{A}_0)$ always has a stable minimum at $|\mathbf{A}_0| = 0$ and small γ , corresponding to Flory theory. However, $F_V(\gamma, \mathbf{A}_0)$ also has a second minimum for large γ and a non-zero value of $|\mathbf{A}_0|$. As a function of increasing v/a^d , the absolute minimum shifts discontinuously from the Flory minimum to the new minimum. The density distribution of the new minimum has an elongated shape, as can be shown from concrete realizations (see [12, Section 2]). If the spectral gap eigenvalue is non-degenerate then the symmetry-breaking transition has the character of a simple saddle-node bifurcation. Since the thermal fluctuations of the $M = 1$ mode are strongly suppressed for large γ , we will refer to the appearance of a non-zero expectation value of a mode as the ‘‘condensation’’ of that mode. If the eigenvalue is degenerate, which happens if the structure has symmetry, then other bifurcation types become possible. The transition also can be productively compared to the first-order isotropic-to-nematic phase transition.

The numerical simulations of the symmetry-breaking transition shows that the density distribution becomes more complex with increasing strength of the excluded volume parameter v . It is necessary to allow multiple modes to freeze out to describe this case. The variational free energy $F_V(\{\gamma_i, \mathbf{A}_0^{(i)}\})$ for M coupled vectorial order parameters is a natural extension of Eq. (8) (see [12, Section 3]). However, minimization of $F_V(\{\gamma_i, \mathbf{A}_0^{(i)}\})$ requires numerical methods. Numerical minimization of $F_V(\{\gamma_i, \mathbf{A}_0^{(i)}\})$ for the concrete case of a second-generation dendrimer in $d = 2$ shows that for increasing v/a^d , there is a series of transitions where modes with larger and larger eigenvalues freeze out. Importantly, the interacting system has the correct number of zero modes in $d = 2$ [25]. The numerical minimization of $F_V(\{\gamma_i, \mathbf{A}_0^{(i)}\})$ for a 36-node branched graph with a maximum of $M = 18$ mode expectation values is shown in Fig. 1. For v/a^2 less than about 0.75, the isotropic Flory minimum was the lowest free energy state, as illustrated by the case $v/a^2 = 0.24$. For $v/a^2 = 1.20$ the density profile is anisotropic. The elongation expected from the $M = 1$ analysis is clearly visible but there are also three diffuse maxima, which indicates that more than one mode has condensed. The power spectrum of mode amplitudes in this state is dominated by the lowest few eigenvalues. For $v/a^2 = 2.05$, all of the $M = 18$ modes have condensed with a complex power spectrum of eigenvector amplitudes. The numerical minimization of the variational free energy was, for larger values of v/a^2 , complicated by the fact that the variational free energy had numerous minima with comparable energies. The $v/a^2 = 2.05$ density profile should be viewed only as representative.

For comparison, we also performed a $d = 2$ Monte-Carlo (MC) simulations on the same system (Fig. 2). One of the

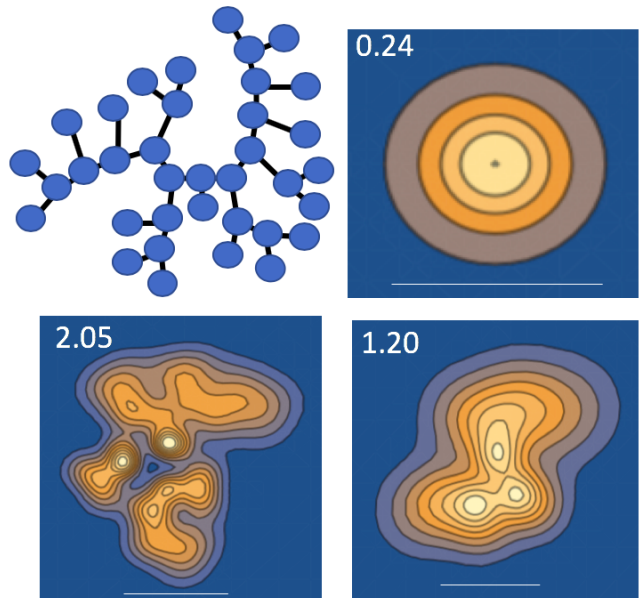


FIG. 1. Two-dimensional density profiles obtained using the GBF variational method for a 36 node branched polymer with a maximum of $M = 18$ non-zero mode expectation values. Top left: Graph of the molecule. Top right: $v/a^2 = 0.24$ in units of $k_B T$. The density profile is isotropic. Bottom right: $v/a^2 = 1.20$. A few low-lying modes have condensed. Bottom left: $v/a^2 = 2.05$. Most modes have condensed. White space bar: $5a$

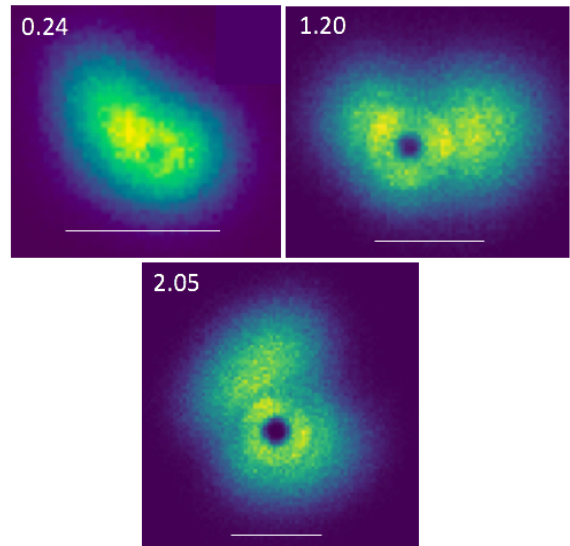


FIG. 2. Density profiles obtained by Monte-Carlo simulation for the same molecule and interaction strengths as Fig. 1. White space bar: $5a$.

nodes was pinned to suppress rigid-body Brownian motion of the center of mass. The Kabsch algorithm [26] was used to compensate for rigid-body rotational Brownian motion. The top left image in Fig. 2, with $v/a^2 = 0.24$, has a radius of gyration comparable to the theoretical prediction and a weak but noticeable rotational asymmetry. For $v/a^2 = 1.20$, the predicted and computed densities have comparable sizes and both have three maxima. The onset of rotational asymmetry thus appears to be less sharp than predicted by the theory while for $v/a^2 = 2.05$ the theoretical density profile is significantly more detailed than the computed profile. The MC simulations were, in this last case, complicated by long relaxation times.

As an alternative route for a quantitative test of the theory, we compared the moduli $|\Delta r_{0i,j}|$ of the bond extensions predicted by the GBF variational principle with those obtained from the MC simulation. We found that the variational method correctly produces the bond extensions of the outer monomers but it somewhat over-estimates the bond extensions of the inner monomers (see [12, Section 5]). The development of significant internal tension provides an *a-posteriori* justification of the use of a self-consistent mean-field theory. We interpret the contrast between the good agreement of the bond tensions as compared with the density profiles as indicating that there are multiple competing free energy minima with have similar patterns of bond tension. Finally, we found that the stretching of the bonds in the center of the molecule approaches 50 percent for $v/a^2 = 2.05$. It may well be that in practice this amount of stretching exceeds the limit of the harmonic Gaussian interaction of the Edwards model. In fact, limited stretchability of bonds may well help rotational symmetry breaking (see also [27]).

A natural area where our theory could be applied is that of biopolymers with non-trivial topology that are dominated by repulsive interactions. An increasing number of functional but disordered proteins has been identified. The interactions between the different parts of these proteins are predominantly repulsive (“good solvent”) yet they have distinct, reproducible shapes [3, 4], as confirmed by Molecular Dynamics simulations [5]. Though proteins have a linear polymer primary structure, they still can adopt a non-trivial topology due to bonding between specific residues (e.g., cysteine residues forming disulfide bridges). Another possible area of

application involves the shape of large, single-stranded RNA molecules. A graph of the secondary structure of an RNA molecule has a branched topology without circuits, The tertiary structure of an RNA molecule is generated by pairing between non-adjacent nucleic acids that were not paired as part of the secondary structure and these tertiary contacts could be included as bonds in the graph of the molecule, which would produce cycles. Cryo-EM studies of large, swollen single-stranded RNA molecules in good solvents reveal that they are disordered but their density profile has a distinct anisotropy [6].

We note that there is a related problem where the method discussed in this paper could be applied namely the computation of the most likely structure of a biopolymer for which it already has been experimentally determined that certain elements of the primary structure are adjacent to each other, for example in the form of a contact map obtained by NMR [28] or by HiC [29]. Though the distance constraints are here *knowledge-based*, instead of physical bonds or links, the Laplacian matrix method still could be used to encode the NMR contact map after which likely density profiles could be computed using the method we outlined here.

We close by briefly mentioning several directions in which our method could be possibly generalized. These include various symmetric structures (such as dendrimers) for which Laplacian has degenerate spectrum (and, accordingly, related eigenvectors ξ_i), other peculiar structures (such as small world networks), and also densely branched structures for which connections between branched points are shorter than persistence length and thus Edwards Hamiltonian (1) needs to be generalized. Although our specific results may not be applied for these cases, we expect that the variational approach should still be valid.

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