Influence of Network Defects on the Conformational Structure of Nanogel Particles: From 'Closed Compact' to 'Open Fractal' Nanogel Particles

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We propose an approach to generate a wide range of randomly branched polymeric structures to gain general insights into how polymer topology encodes configurational structure in solution. Nanogel particles can take forms ranging from relatively symmetric sponge-like compact structures to relatively anisotropic open fractal structures observed in some nanogel clusters and in some self-associating polymers in solutions, such as aggrecan solutions under physiologically relevant conditions. We hypothesize that this broad 'spectrum' of branched polymer structures derives from the degree of regularity of bonding in the network defining these structures. Accordingly, we systematically introduce bonding defects in an initially perfect network having a lattice structure in three and two topological dimensions corresponding to 'sponge' and 'sheet' structures, respectively. The introduction of bonding defects causes these 'closed' and relatively compact nanogel particles to transform near a well-defined bond percolation threshold into 'open' fractal objects with the inherent anisotropy of randomly branched polymers. Moreover, with increasing network decimation, the network structure of these polymers acquires other configurational properties similar to randomly branched polymers. In particular, the mass scaling of the radius of gyration and its eigenvalues, as well as hydrodynamic radius, intrinsic viscosity, and form factor for scattering, all undergo abrupt changes that accompany these topological transitions. Our findings support the idea that randomly branched polymers can be considered to be equivalent to perforated sheets from a 'universality class' standpoint. We utilize our model to gain insight into scattering measurements made on aggrecan solutions.

I. INTRODUCTION

Polymer networks, more commonly known as 'gels,' play an important role in the function of many biological processes¹ and are increasingly become essential components of modern (bio)-manufacturing.^{2–4} These complex networks are composed of linear polymer chain subunits connected to form higher-order structures, such as branched and loop structures, which eventually lead to the formation of a polymer network when the crosslink density is sufficiently large.^{5,6} Our previous understanding of polymer networks is based on perfect threedimensional networks in which the chains are connected into a structure with lattice-like connectivity⁷⁻¹¹ or homogeneous tree-like structures without loops.^{5,6,12–17} The existence of loops in the polymer network is known to influence the material properties, e.g., primary loops are elastically inactive, while higher-order loops may contribute to elasticity differently depending upon their specific topology. However, our inability to quantify aspects of network structure in macrocopic networks has hindered the testing the validity of the affine and phantom network models in real polymer networks, a longstanding problem in polymer science.^{6,18} This general problem of network characterization clearly extends to the nanoscale networks investigated in the present work.

The initial motivation of the current study is to gain insight into the nature of assemblies formed by aggrecan, a bottlebrush-like polymer that associates with hyaluronic acid and a small glycoprotein, link protein, to form multi-molecular polymeric networks.^{19,20} These networks reside, immobilized due to their large size, within an extracellular organized fibrillar collagen network, serving as a tensile element. The biological importance of these networks in cartilage is that they exert a high osmotic swelling pressure resisting external compressing loads.¹ Aggrecan is also present in significant concentrations in the extracellular matrices of other tissues, including the tendon, brain, and muscle. Degradation in the synthesis and structure of the aggrecan polymer network in cartilage results in changes in its functional properties and failure of joint cartilage in osteoarthritis.²¹⁻²⁴ Thus, understanding the topology of this polymer network influences biological function is the key in developing a rational treatment to prevent the destruction of joint cartilage in arthritis and the development of synthetic cartilage transplants.

Previous computational models depict aggrecan as a regular bottlebrush polymer.^{25–28} However, these models do not capture the associative behavior of aggrecan, and this supramolecular organization of the aggrecan into a hierarchical network is not addressed in most previous studies. Indeed, experimental comparison between bottlebrush poly(sodium acrylate) and natural

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aggrecan solutions revealed that the former synthetic polymers exhibit a distinctive scattering peak in their structure factor. However, no such peak is observed in aggrecan solutions.^{29,30} Understanding how to control the topology of the assemblies of aggrecan should have large ramifications in treating socially significant diseases such as arthritis and diverse respiratory and intestinal diseases where bottlebrush molecules are implicated in the disease state, as well as, in developing new materials having functional properties similar to their biological counterparts. More generally, it has been demonstrated that the synthesis protocol plays a key role in the resulting properties of such gels,³¹ suggesting that any insights gained into the physical nature of the aggrecan self-assembled structure in solution should lead to a better understanding of the properties of these materials to their biological function. We also anticipate that a general study of the influence of molecular topology on the conformational and transport properties (radius of gyration and intrinsic viscosity of gel particles) should have benefits to characterizing both synthetic and naturally occurring gel particles that arise in diverse contexts.

Toward this goal, we propose a general approach to efficiently generate and characterize a wide range of randomly branched structures and identify which of these structures resemble the multimolecular assembled structures that aggrecan forms. Our proposed approach is based on the construction of 'perfect' nanogel particles having a lattice structure, as discussed in a previous study.³² Then, we introduce 'defects' in the nanogel particle structure. We explore two kinds of defects. The first type of defect is introduced by randomly cutting the bonds between the repeating units of the nanogel structure while maintaining the integrity of the nanogel particle intact. The second type of defect is introduced by randomly removing repeating units from the nanogel particle. We demonstrate that these two approaches are equivalent and reduce the number of loops in the network, leading to open and fractal-like network structures. The latter type of networks resembles to the selfassembled network structures found in aggrecan solutions under physiologically relevant conditions.

The study of particles with a network internal structure formed by 'randomly' cross-linking individual polymer chains or a small number of polymer chains in dilute polymer solutions. Such network particles have been termed 'single chain nanoparticles' (SCNPs). The melt properties of these nanogel particles can be greatly altered from linear polymer melts of the same polymer species because of the 'softness' of these particles and, no doubt, their altered average shape.^{33–37} Based on the results of our paper, we may expect that introducing a relatively small number of intermolecular crosslinks (physical or chemical) should first convert linear polymer chains into open gel particles having the fractal dimension of swollen randomly branched polymers having moderate grafting density $(d_f = 2)$. Upon increasing the high grafting density even further, the SC- NPs should change then their scaling 'universality' class to the 'sponge,'³⁸ corresponding to effectively a threedimensional (topological rather than spatial dimension) network structure. At any rate, the observed change in the mass scaling of the radius of gyration of SCNPs has been found to be qualitatively consistent with the expectations just stated that cross-linking in effect alters the effective topological dimension of the polymer network and this impacts the universality class of polymer scaling characteristics.³³

Notably, the change of mass scaling is predicted to occur in a good solvent so that this type of change of mass scaling does not necessarily imply a change in solvent quality, as Diesendruck and coworkers have interpreted their observations on the dimensions of SC-NPs as the cross-link density is varied.³⁵ Moreover, new $R_{\rm g}$ mass scaling exponents are predicted 38 to occur at the θ -point of SCNPS, based on the model indicated above, where the second virial coefficient vanishes if this correspondence SCNPs and our gel model holds. We also suggest that SCNPs cross-linked under relatively poor solvent conditions should acquire a 3-dimensional network-like structure ('sponge') at lower cross-link density than polymer chains cross-linked in a good solvent. Reductions in the mass scaling exponents have also been observed with increasing branching in synthetic polymers,³⁹ but there was no theoretical framework in this previous study for interpreting these exponent changes with changes in the branching density.

Our findings are also relevant to thermally reversible and irreversible gels formed under diverse conditions in diverse forms of soft matter. Furthermore, our results on networks having a two-dimensional reference network structure are highly relevant to two-dimensional polymers, such as graphene,⁴⁰ the spectrin network of red blood cells,⁴¹ and polymer membranes.⁴² While such two-dimensional polymers or 'sheet polymers' are often depicted as a two-dimensional network similar geometrically to a tennis net, we note that randomly branched polymers can be thought of as imperfect sheetlike polymers, i.e., having a topological dimensionality of two,^{38,43,44} despite not having an obvious physical resemblance. Our proposed approach can explore the transition from a sheet-like structure to a randomly branched polymeric one. Specifically, we find that sheetlike structures and randomly branched polymers having a moderate grafting density exhibit the same mass scaling exponent of their radius of gyration, suggesting that these polymers belong to the same universality class. However, we find that near the percolation transition, there is a crossover from a more compact sheet-like conformation dominated by loops to one more open and fractal-like nanogel particle. Our model thus can 'interpolate' between these limiting types of nanogel particles. We also provide some preliminary calculations for three-dimensional networks, which we term 'sponges' and the crossover of these networks into more openbranched polymers exhibiting different scaling characteristics from the case of the 2D sheet network case. These networks have much stronger excluded volume interactions, and much larger networks are required for the full characterization of the fractal scaling characteristics of this type of gel particle. However, we are able to gain at least some qualitative characterization of this type of branched polymer having a high grafting density.

The paper is organized as follows. Section II contains details of the simulation methods, the two different approaches to introduce defects in our coarse-grained nanogel particle model. The results are presented in section III, where we investigate the influence of topology on the conformational properties of the nanogel particles in subsections III A and III B, the scattering profiles that these structures exhibit are discussed in subsection III D, and a brief comparison with aggrecan is presented in subsection III E. Finally, we draw our conclusions in Sec. IV.

II. METHODS AND MODELS

We employ a bead-spring model suspended in an implicit solvent. All particles are assigned the same mass m, size σ , and strength of interaction ε ; we set ε and σ as the units of energy and length. The segmental interactions are described by the cut-and-shifted Lennard-Jones (LJ) potential with a cutoff distance $r_c = 2^{1/6} \sigma$, corresponding to an athermal solvent. The segments along a chain are connected with their neighbors via a stiff harmonic spring, $V_{\rm H}(r) = k(r - l_0)^2$, where $l_0 = 0.99 \sigma$ is the equilibrium length of the spring, and $k = 2500 \varepsilon/\sigma^2$ is the spring constant.

We first construct a perfect compact gel, which is composed of stars polymers placed in a square or in a cubic lattice and with two or more of their free ends bonded with the free ends of the neighboring stars, the number of branched points (or star polymers) in each direction is labelled as N_x , N_y , and N_z , see Fig. 1. The repeating structural unit of the polymer network studied here is a branched structure that is identical to a regular star polymer. Other polymeric structures and/or other lattices could be utilized but these are out of the scope of the current study. A regular star polymer has a core particle, which is connected with the free end of f chains (or arms) composed of M segments. Thus, the total number of interaction centers per star polymer is $M_{w,star} = fM + 1$. The molecular mass of a nanogel particle is $M_{\rm w} = (N_x N_y N_z) M_{\rm w, star}$. We use the quantity N_b to characterize the mesh size, since we focus on nanogel particles having $N_b = N_x = N_y = N_z$; we note that for two-dimensional polymeric structures $N_z = 1 \neq N_b$. We note that 'mesh size' is typically referred in the literature to the average size of the compartment created by the polymer chains that form the mesh. For the purposes of our current study, we instead refer to 'mesh size' as the size of the whole mesh. Every star polymer unit at the interior of the nanogel is fully bonded with its neighbors and thus the only dangling



FIG. 1. Schematic of the molecular architecture of the nanogel particle, along with the resulting configurations by introducing defects by two mechanisms: i) cutting bonds between the repeating units of the nanogel particle; ii) removing repeating units from the nanogel particle.

polymer chains are located at the exterior of the nanogel structure. This type of nanogel particles is dominated by both branches and loops. We also note that nanogel particles having f = 4 result in the formation of fewer but larger loops compared to f = 6 nanogel particles.³²

Once a compact nanogel particle is constructed, we utilize one of the two proposed mechanisms for introducing defects into the nanogel particles. In both cases, we start from the construction of 'perfect' nanogel particles as described above. In the first mechanism, we randomly cut a fraction of bonds that connect neighboring star polymers provided that the nanogel integrity is maintained. This mechanism keeps the molecular mass of the nanogel particle fixed. In the second mechanism, we randomly remove a fraction of repeating units from the structure provided that the nanogel integrity is maintained in each attempt of removing a unit or by keeping the largest remaining network. Clearly, this approach reduces the molecular mass of the original structure. Both mechanisms eliminate the existence of loops in the original structure, see Fig. 1. We note that the first mechanism is inspired by the work of Grest et. al,⁴⁵ where the repeating unit was a single bead instead of a star polymer. Our approach provides ways to tune the resulting molecular nanogel structure. We also note that these two mechanisms could be used in conjunction with each other to generate a wider variety of randomly branched structures. This will be part of a future study. The systems were equilibrated at constant temperature $k_{\rm B}T/\varepsilon = 1.0$ conditions, maintained by a Nosé-Hoover thermostat. Typical simulations equilibrate for 5000τ and data is accumulated over a $150\,000 \tau$ interval, where $\tau = \sigma (m/\varepsilon)^{1/2}$ is the MD time unit; the time step used was $\Delta t / \tau = 0.005$.

A. Path-integration package, ZENO

Hydrodynamic radius and intrinsic viscosity calculations are based on the use of path-integration algorithm ZENO, which calculates hydrodynamic, electrical, and shape properties of polymer and particle suspensions, $\frac{46-48}{6}$ and has been used in many real systems.^{49,50} The computational method used by ZENO for calculating $R_{\rm h}$, as well other hydrodynamic properties, involves placing a polymeric structure inside an enclosing sphere and then launching random walks from the surface of the sphere. The fraction of walks that hit the molecule as opposed to walks ending in infinity can be directly related to $R_{\rm h}$. We repeat this process for 10^4 distinct molecular conformations and then construct distributions of $R_{\rm h}$ for each molecular topology and $M_{\rm w}$. We also determine the mean and the standard deviation for these distributions. Through an extension of the process just described,⁴⁷ which considers both where the launched trajectories initiate on the probing sphere and where they end when they hit the polymer, other basic polymer characterization properties can be estimated from ZENO such as the intrinsic conductivity of conducting particles and the intrinsic viscosity due to the mathematical similarities between electrical and hydrodynamical properties.^{47,51}

For the ZENO-related calculations, we consider 1 000 or more distinct molecular conformations. For each molecular configurations, 4 000 and 2 000 random walks were performed for the exterior (e.g., intrinsic viscosity) and interior-type (e.g., $R_{\rm g}$ eigenvalues) calculations. We also note that one realization of the bonding network is considered; below the percolation threshold no significant deviation is found, but above it deviations between different bonding networks having the same number of defects are found. These deviations will be part of a future study.

III. RESULTS AND DISCUSSION

We first obtain the mass scaling behavior of the average radius of gyration (R_g) of two- and three- dimensional nanogel particles in an athermal solvent with a variation of mesh size and different degrees of defects. We also calculate the intrinsic viscosity $([\eta])$. Following this analysis, we calculate the form factor for these structures and identify the conditions at which particlelike features emerge in the scattering profiles. Finally, we utilize our model of open nanogels to gain insight into recent scattering and rheological observations made on aggrecan solutions, a system of great particular interest to our research group because of the relevance to this self-assembly process to arthritis when this assembly process does occur as required to maintain the normal physiological function of joints, a condition that leads to tissue damage.

A. Molecular size

We briefly revisit the scaling of the average molecular size in solution (e.g., radius of gyration, $R_{\rm g}$) with increasing molecular mass $M_{\rm w}$ of basic classes of polymers: Linear and randomly branched polymers. Linear and randomly branched polymers at equilibrium form the most basic classes of polymers, which exhibit universal scaling of their average size in solution with increasing molecular mass $M_{\rm w}$. In particular, $R_{\rm g}$ scales as $M_{\rm w}^{\nu}$ in athermal solvents with $\nu \approx 10/17 \approx 0.588$ and $\nu = 1/2$ for self-avoiding walks and lattice animals in three-dimensions, respectively.52-55 Moreover, near the θ -point in solution at which attractive interactions between the polymer segments compensate the repulsive binary excluded volume interactions, we have $\nu = 1/2$ for linear chains⁵⁶ and $\nu \approx 2/5$ for randomly branched polymers.^{38,57,58} Polymers having different topologies than linear chains and randomly branched polymers raise the question of how their scaling characteristics relate to polymers having a different topological struc-Often, real polymers having different topoloture. gies lie in between these limiting 'universality classes' of polymers⁵⁹ and the properties of polymers are attracted to one fixed point scaling behavior or the other as molecular mass or other molecular parameters are varied through their allowed physical range.

We initiate our discussion by calculating the $R_{\rm g}$ mass scaling of 'perfect' two- (2D) and three-dimensional (3D) nanogel particles, see Fig. 2. A perfect 3D nanogel particle exhibits a scaling exponent of 1/3 indicating that these highly cross-linked networks exhibit the characteristics of a compact particle, as discussed in detail in our previous study.³² On the other hand, 2D nanogel particles exhibit a 'flat' conformation arising from the resistance to in-plane shear deformations leading to an anomalous stiffening of the surface in the presence of thermal fluctuations.^{45,60–64} Fluctuation-induced rigidification, which also occurs in linear polymer chains,⁶⁵ nanogel particles having a 2D network topology exhibit a scaling exponent of 1/2, which is in agreement with previous simulation studies of 'tethered' polymer membranes.

Next, we examine the effect of introducing 'defects' by cutting the bonds between the repeating units. We focus on 2D nanogel particles, though the findings are similar to 3D nanogel particles. As we increase the fraction of bonds being cut over the total number of bonds between the repeating units (f_{cb}) , we find no significant changes in R_g for $f_{cb} \leq 0.4$, see Fig. 3. We see that the defects alter the overall structure of the original nanogel



FIG. 2. Radius of gyration, $R_{\rm g}$, of two- (circles) and three-dimensional (squares) nanogel particles, having degree of branching f = 4 and chain length M = 1, as a function of molecular mass, $M_{\rm w}$. Screenshots of typical equilibrated molecular configurations are also presented. The uncertainty estimates correspond to two standard deviations and the dashed lines are power-laws as guides for the eye.

particle by reducing the number of loops and increasing the number of dangling branched chains. The average size of the network polymers are not changed that much by these topological changes, primarily due to the existence of large loops that tend to preserve it. However, the overall *shape* is much more sensitive to this bond decimation process, as we shall discuss below. As we continue to cut bonds, we reach a critical threshold $(f_{\rm cb} \approx 0.4)$ where the structure swells significantly as the last loops maintaining the integrity of the original structure are cut, see Fig. 3. The location of this critical threshold is approximately the same as in 3D nanogel particles having f = 4. Even further decimation, the networks undergo another transformation to structures that are similar to linear polymer chains as the effective dimensionality becomes reduced further.

We find similar trends by removing repeating units from the nanogel particle. We note that by removing units from the polymer structure and so $M_{\rm w}$ changes. Removing less than 39% of the repeating units, the $R_{\rm g}$ of the decimated sheet exhibits a mass scaling $R_{\rm g} \sim M_{\rm w}^{1/2},$ see Fig. 4. This scaling accords with the previous simulations by Grest⁴⁵ and the predictions of the Wiener sheet model.³⁸ Importantly, there is a critical threshold around 39% at which the nanogel structure transforms from the relatively compact and symmetric form of the perfect gel nanogel particle to a relatively open and asymmetric nanogel particle, whereupon the average size of the nanogel particle, e.g., the radius of gyration, undergoes a rapid increase. In other words, defects around this point in the polymeric structure create dangling chains extending from a tree-like backbone and these dangling chains extend further away from the



FIG. 3. Radius of gyration, $R_{\rm g}$, of (a) 2D nanogel and (b) 3D nanogel particles, as a function of the fraction of bonds cut, $f_{\rm cb}$. The uncertainty estimates correspond to two standard deviations. Typical molecular configurations are also presented. The dotted lines are guides for the eye.

main body of the nanogel particle and lead to a significant increase of $R_{\rm g}$. This topological transition occurs for both networks with the topology of a sheet-like network (two-dimensional polymers) and polymers with initial 3-D network topology, i.e., 'sponges'.³⁸

We can note here that ν of 3D network or 'sponge' is predicted³⁸ based on an approximate Flory-type model to be 7/15 in the swollen limit, 11/30 under θ -conditions where the binary polymer-polymer interaction vanishes and 1/6 in the limit at which all excluded volume interactions are neglected. This corresponds to spatial dimensions larger than 12.³⁸ The universality of these scaling exponents is bit of a question because of the high segmental density in these polymers, which makes many-body interactions of orders relevant, as in the case of linear polymers in two spatial dimensions⁶⁶ and collapsed linear polymer chains.⁶⁷ In particular, the dimensionless many-body excluded volume parameters scale with the crossover exponent $\phi_m = m - (m - 1)d/2d_m$



FIG. 4. Radius of gyration, $R_{\rm g}$, of (a) 2D nanogel particles $(N_{\rm b} = 30, f = 4, \text{ and } M = 1)$ and (b) 3D nanogel particles $(N_{\rm b} = 10, f = 4, \text{ and } M = 1)$ by increasing the fraction of removed units, $f_{\rm ru}$. Typical molecular conformations at initial conditions (top row) and at equilibrium (bottom row) are also presented. The uncertainty estimates correspond to two standard deviations.

where *m* is the order of the excluded volume interaction, *d* is the dimension of the embedding space and d_m is the manifold dimension, e.g. $d_m = 3$ for the 'sponge'.³⁸ Simulations of very large networks of this kind will be required to resolve the true large mass asymptotic scaling limit of R_g and other solution properties with polymer mass. Our results for this class of network polymers are 6

thus tentative.

In the conformational properties of our networks, the critical threshold identified in both approaches can be understood from the percolation theory,^{71–73} which describes the behavior of a network when nodes or links are added. The primary focus of percolation theories and models is on a geometric phase transition, where small disconnected clusters merge into a significantly more extensive connected network, the so-called spanning cluster. The percolation transition is relevant to many different types of applications, such as the spreading of fires, diseases, and traffic, to name a few. 74 Near this percolation transition, the network exhibits fractal-like behavior, and the exponents characterizing this fractal behavior are universal. On the other hand, the location of this transition depends on the local network structure/connectivity. Indeed, if p is the probability a node in the network is filled then for a square lattice the percolation transition occurs at $p_c \approx 0.59$,⁷⁵ meaning that the unoccupied fraction (decimated nodes or 'holes') is $1 - p_c \approx 0.41$. The latter condition is equivalent to the critical threshold found in our models, suggesting that the conformation crossover observed in our model is apparently related with the percolation transition of the network. Specifically, the elimination of few remaining loops in the network near the percolation transition results in significant changes in the conformational properties of the polymeric structure. Future work will focus on the precise conditions at which these topological transitions occur.

B. Molecular shape

We focus on the average molecular shape of these model branched polymers. Linear chain polymers exhibit highly anisotropic conformations,^{76,77} while molecular architectures that contain loops and high degree of branching, such as star,^{70,78–82} rings^{70,78,79,83–85} and bottlebrush⁵⁹ polymers, tend to exhibit more isotropic conformations.

One way to quantify the molecular shape is by the eigenvalues of the radius of gyration tensor S_p . These eigenvalues are denoted below by λ_1 , λ_2 , and λ_3 and are related to R_g^2 as follows:

Tr
$$S_p = \langle R_g^2 \rangle = \langle \lambda_1 \rangle + \langle \lambda_2 \rangle + \langle \lambda_3 \rangle,$$
 (1)

where $\lambda_1 \leq \lambda_2 \leq \lambda_3$ and the brackets $\langle \rangle$ represent time averages. The eigenvalue data are organized by comparing the two larger eigenvalues with respect to the smallest one. A sphere has $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle = \langle \lambda_2 \rangle / \langle \lambda_1 \rangle = 1$ and infinite long thin rod has $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle \to \infty$ and $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ is finite.

By increasing the number of defects, either by cutting bonds or removing repeating units, we find a more complex behavior in the molecular shape of nanogel particles than in $R_{\rm g}$. In particular, we find that a small number of defects (less then 5%) make the 2D nanogel particles more flat, i.e., $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ and $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ increase,



FIG. 5. Ratio of the radius of gyration eigenvalues $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ versus $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$. Reference points from Ref. 68 for random walks (RW), lattice animals (LA), percolation clusters (PC), and Gaussian rings (GR) are also presented. The dot-dashed line correspond to a correlation $\langle \lambda_2 \rangle \sim \sqrt{\langle \lambda_3 \rangle \langle \lambda_1 \rangle}$ for star polymers (see Ref. 69,70). Typical molecular conformations of 2D and 3D nanogel particles having f = 4 arms and M = 1 chain length are also presented.



FIG. 6. Ratio of the radius of gyration eigenvalues $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ (filled symbols) and $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ (open symbols) as a function of the fraction of bonds cut $f_{\rm cb}$ for (circles) 2D nanogel particles having $N_{\rm b} = 30$, f = 4, M = 1 and (squares) 3D nanogel particle having $N_{\rm b} = 10$, f = 4, M = 1.

see Figs. 5 and 6. These defects reduce the stiffness of the sheet polymer, effectively making the sheet to resist shape-changes induced by thermal fluctuations. Nanogel particles with more than 5% of defects result in the creation of tangling chains that make the overall molecular shape more isotropic, i.e., $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ and $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ decrease. We note that $R_{\rm g}$ remains nearly constant in magnitude so that these changes in molecular shape do not influence the molecular size of the nanogel particle. Moreover, these changes in molecular shape seem to follow the empirical relation, $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle \approx$ $1.11 \langle \lambda_2 \rangle / \langle \lambda_1 \rangle + 0.99$. The molecular shape of the sheet becomes more isotropic by increasing defects until the critical threshold is reached, $f_{\rm cb} \approx 0.4$. Interestingly this configurational transition occurs when the molecular shape becomes similar to a randomly branched polymer,⁶⁸ the molecular shape of a regular star polymer resembles a soft ellipsoid having dimensions that follow a geometric mean, $\langle \lambda_2 \rangle \sim \sqrt{\langle \lambda_3 \rangle \langle \lambda_1 \rangle}$.⁵⁹ Above the critical threshold, the molecular shape starts to become highly anisotropic, with $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ increasing while $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ remains flat, and the molecular shape becomes similar to the shape of random walks, see Figs. 5 and 6. Up to this point, both kinds of defects resulted in similar behavior, however, the molecular shape can become more anisotropic by further increasing the number of defects by removing units from the nanogel structure. The anisotropy continues to grow and reaches a maximum $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle \approx 17$ at around 60% to 80% of the units removed. After this point, the remaining structure becomes relatively small and more isotropic, see Fig. 5.

The molecular shape of 3D nanogel particles is different from that of 2D analogs. The original defect-free structure is rather compact, meaning that $\langle \lambda_3 \rangle / \langle \lambda_1 \rangle$ and $\langle \lambda_2 \rangle / \langle \lambda_1 \rangle$ are both small, see Figs. 5 and 6. As we introduce defects in the 3D nanogel particle structure, dangling branched chains start to emerge and become longer, resulting in the overall molecular shape becoming more anisotropic. Interestingly, it follows the geometric mean, $\langle \lambda_2 \rangle \sim \sqrt{\langle \lambda_3 \rangle \langle \lambda_1 \rangle}$ which star polymers exhibit.⁵⁹ Near the bond percolation transition, the molecular shape is relatively similar to that of 2D nanogel particle before it unfolds. Unlike the 2D nanogel particles where the molecular shape starts from being anisotropic shape of defect-free sheet to a more spherically symmetric, in 3D nanogel particles the molecular shape starts from a isotropic shape of defectfree cubuidal shape to a more anisotropic one. This suggests that topology of the initial defect-free nanogel structure play an important role in the final defect dominated nanogel structure, compare typical molecular configurations in Fig. 5 C & F.

An alternative and more experimentally accessible way to quantify the shape of the molecular conformations of the nanogel particles is by utilizing the difference in the variation between of $R_{\rm h}$ and $R_{\rm g}$ when molecular shape is varied. Indeed, the ratio $R_{\rm h}/R_{\rm g}$, the hydrodynamic 'penetration function', 47,68,86,87 is often used as a descriptor to quantify the shape of polymers.^{46,47} For the purposes of the current study, $R_{\rm h}$ is determined with the use of a path-integration algorithm ZENO, which calculates hydrodynamic, electrodynamic, and shape properties of the polymer and particle suspensions, as described in the subsection II A. The values of $R_{\rm h}/R_{\rm g}$ for a uniform sphere is $R_{\rm h}/R_{\rm g} =$ $(5/3)^{1/2} \approx 1.29$, for a random walk is 0.79, and for an infinite long rod is $0.^{68,88}$ Each molecular architecture (linear chain, ring, and star) exhibits a relatively simple trend as $M_{\rm w}$ increased, as discussed in our pre-vious studies.^{59,70} For example, $R_{\rm h}/R_{\rm g}$ of linear chains decreases from the uniform sphere limit (when the linear chain is composed of a single segment) to the more anisotropic conformations characteristic of polymer random coils $R_{\rm h}/R_{\rm g} \approx 0.79$ at larger molecular masses. Highly branched stars exhibit little variation $R_{\rm h}/R_{\rm g}$ with molecular mass and this ratio takes a value close to the value of a uniform sphere $R_{\rm h}/R_{\rm g} \approx 1.29.^{70}$

The trends in $R_{\rm h}/R_{\rm g}$ (Fig. 7) further support the behavior of molecular shape as quantified by the eigenvalues of $R_{\rm g}$. Specifically, when there are no or few defects the nanogel particles exhibit $R_{\rm h}/R_{\rm g}$ values near those for a uniform sphere where $R_{\rm h}/R_{\rm g} \approx 1.29$ and a circular disc where $R_{\rm h}/R_{\rm g} \approx 0.9$ for 3D and 2D nanogel particles, respectively. We also note that $R_{\rm h}/R_{\rm g}$ for cube and square plate equal 1.32 and 0.898^{47} so that sensitivity of $R_{\rm h}/R_{\rm g}$ to the boundary shape is not great when the boundary shape is not highly irregular. Evidently, a small number of defects does not influence $R_{\rm h}/R_{\rm g}$ for 3D nanogel particles. However, we find that $R_{\rm h}/R_{\rm g}$ progressively increases for initially perfect 2D nanogel particles towards a value of this ratio near 1.1, near that estimated for percolation clusters⁶⁸ near the geometrical percolation threshold of these network structures, see Fig. 7. Decimation of the three-dimensional network causes this limit to be approached from the opposite direction. Introducing a still larger concentration of defects causes $R_{\rm h}/R_{\rm g}$ for both networks to a sharp drop to a value corresponding to a more anisotropic value. For 2D nanogel particles, $R_{\rm h}/R_{\rm g}$ drops from a value near percolation clusters to a value corresponding to the shape of star polymers $(R_{\rm h}/R_{\rm g} \approx 0.88)$ from which the network is constructed.^{70,89} For 3D nanogel particles, $R_{\rm h}/R_{\rm g}$ drops from a value near uniform sphere to a value slightly smaller than percolation clusters. Even though the 2D and 3D nanogel particles are composed of the same repeating unit, the resulting structures after decimation of the bonding network can evidently be differ-



FIG. 7. Ratio of the average hydrodynamic radius over the average radius of gyration $R_{\rm h}/R_{\rm g}$ of 2D (circles) and 3D (squares) nanogel particles as a function of the fraction of bonds cut (f_{cb}) or removing units (f_{ru}) without the nanogel structure disintegrating. Circles correspond to 2D nanogel particle having $N_{\rm b} = 30$, f = 4, and M = 1, squares correspond to 3D nanogel particle having $N_{\rm b} = 10, f = 4$, and M = 1, open symbols correspond to introducing defects by cutting bonds, and filled symbols correspond to introducing defects by removing units. From top to bottom, the dotted lines correspond to exact results of $R_{\rm h}/R_{\rm g}$ for uniform spheres, a circular discs, and an estimate of this ratio for random walks, self-avoiding walks, and percolation clusters.⁶⁸ The highlighted region outlines approximately the regime near the percolation transition for these systems. The uncertainty estimates correspond to two standard deviations.

ent, which signifies the importance of the topology of the original structure. The 'penetration function'^{47,68,86,87} $R_{\rm h}/R_{\rm g}$ then contains valuable information about the 'universality class' of network polymers that it is difficult to obtain by simply examining the scaling of polymer size (e.g., $R_{\rm g}$) with polymer mass.

C. Intrinsic viscosity

The size and compactness of nanogel particles also influence hydrodynamic solution properties. The viscosity of a dilute dispersion of particles can be developed in a power series in the particle volume fraction (ϕ) as,

$$\eta(\text{dispersion}) = \eta(\text{dispersing fluid})\{1 + [\eta]\phi + O(\phi^2)\}.$$
(2)

The first coefficient in ϕ is independent of interparticle interaction and is conventionally called the 'intrinsic viscosity', $[\eta]$, and is defined in the limit of the particle concentration in the solution $c \to 0$ as,

$$[\eta] = \lim_{c \to 0} \frac{\eta - \eta_s}{c \eta_s},\tag{3}$$

where η and η_s are the solution and solvent viscosity. The intrinsic viscosity is a useful metric to character-



FIG. 8. Intrinsic viscosity, $[\eta]$, of 2D nanogel particles as a function of the fraction bonds cut, $f_{\rm cb}$ (squares) and as a function of the fraction units removed, $f_{\rm ru}$ (circles). The nanogel particles have a degree of branching f = 4, chain length M = 1 and $N_b = 30$. The highlighted region outlines approximately the regime near the percolation transition for these systems.

ize how the molecular structure influences the hydrodynamic properties of the solution, especially in the dilute regime.^{87,90,91} Solution properties are often described in reduced concentration, e.g., $c[\eta]$. For the purposes of the current study, $[\eta]$ is determined with the use if a path-integration algorithm ZENO, which calculates hydrodynamic, electrical, and shape properties of the polymer and particle suspensions, as described in subsection II A.

The introduction of defects is expected to influence $[\eta]$, in a similar fashion as it influences $R_{\rm g}$. Indeed, a small number of defects, either by cutting bonds or by removing units, does not significantly influence $[\eta]$, as seen in Fig. 8. However, $[\eta]$ sharply increases as the number of defects increases and approaches the percolation transition. As discussed above, the loops keeping the original structure are broken near this point, causing the polymer structure to swell considerably. This swelling significantly alters the segmental distribution of the nanogel particle in a way that would more efficiently change the dynamic properties of the solution. Both mechanisms/approaches of introducing defects exhibit the same trends, however, the approach of removing units provides systems beyond the percolation point, where $[\eta]$ has a significant decrease because $M_{\rm w}$ decreases by the removal of repeating units, Fig. 8. This decrease in $M_{\rm w}$ may also make $[\eta]$ of nanogel particles more sensitive as the percolation threshold is approached, which may explain the deviation in $[\eta]$ between the two methods at $f_{\rm cb} \approx f_{\rm ru} \approx 0.4$.

Now that we have an understanding of the effect of defects on $[\eta]$, we focus on its mass scaling. The molecular mass dependence of the intrinsic viscosity is often represented by the Mark-Houwink equation,



FIG. 9. Intrinsic viscosity, $[\eta]$, of 2D (squares) and 3D (circles) nanogel particles. The open symbols correspond to nanogel particles having no defects, while the filled symbols correspond to nanogel particles near the percolation transition by randomly cutting the bonds between the repeating units of the nanogel particles. The nanogel particles have a degree of branching f = 4 and chain length M = 1. Results for linear chains (cross) and unknotted rings (stars) are also presented. The dashed lines are power-laws as guide for the eye.

 $[\eta] = K M_w^{\alpha},^{52,92,93}$ where K and α are material specific parameters. The exponent α becomes $\alpha \approx 0.71$ and $\alpha \approx 0.5$ for linear polymer chains in good and θ -solvent conditions, respectively. This is supported by experimental⁹⁴ and simulation studies.^{32,95} However, deviation from this is expected for molecular structures that differ from linear polymer chains. For example, $\alpha \approx 2$ for rod-like polymers like Tobacco mosaic virus⁹⁶ and $[\eta] = 5/2$ for rigid spheres at infinite dilution.⁹⁷ Nanogel particles exhibit significantly smaller $[\eta]$ than the corresponding value for linear chains and unknotted rings at the same M_w , providing a measure of their compact nature.

Polymer sheets without any defects exhibit a mass scaling exponent $\alpha \approx 0.35$ for small molecular masses, $M_{\rm w} \lesssim 1\,000$, and for larger molecular masses $\alpha \approx 0.45$, see Fig. 9. The same systems near the percolation transition by cutting bonds exhibit a mass scaling exponent $\alpha \approx 0.45$. However, the values of $[\eta]$ near the percolation transition are higher by a factor of approximately 2.8 compared to the polymer sheets without defects. Both cases exhibit the same scaling exponent is further supports that randomly branched polymers can be thought of as imperfect or perforated sheets. We find that 3D polymer gels without defects exhibit little dependence on molecular mass. This is understandable because compact 3D gels behave similarly to rigid spheres.³² However, introducing defects results in the mass scaling becoming $\alpha \approx 0.44$ similar to 2D cases. Nevertheless, these structures are smaller in size than randomly branched structures near percolation transition generated from 2D nanogel particles and as a result $[\eta]_{2\text{D,perc}} / [\eta]_{3\text{D,perc}} \approx 1.24 \pm 0.1$. We then see that the crossover from a sheet-like structure to randomly branched polymer structure does not influence this ratio significantly since the structure remains within the same universality class. On the other hand, the crossover from a compact 3D gel structure to a structure near its percolation regime results in significant changes and the intrinsic viscosities between them, and this difference diverges as a function of molecular mass, $[\eta]_{3\text{D,perc}} / [\eta]_{3\text{D,compact}} \approx M_{\rm w}^{0.4}$.

D. Form factor of 'Open' versus 'Closed' Nanogel Particles

To probe the structure of nanogel particles, we focus on calculating the spatial correlations between the polymer segments. The form structure factor, P(q), is a suitable property for this purpose and describes the mean correlations in the positions of a collection of point particles distributed in space. P(q) is defined as:

$$P(q) = \frac{1}{N_s} \left\langle \sum_{j=1}^{N_s} \sum_{k=1}^{N_s} \exp\left[-i\mathbf{q} \cdot (\mathbf{r}_j - \mathbf{r}_k)\right] \right\rangle, \quad (4)$$

where $i = \sqrt{-1}$, $q = |\mathbf{q}|$ is the wave number, \mathbf{r}_j is the position of particle j, $\langle \rangle$ denote the time average, and N_s is the total number of polymer segments defined as $N_s = N_x N_y N_z (fM + 1)$.

In the scattering profile of a defect-free polymer sheet, we find two distinct power-law behaviors with our model. In the high q-regime $(q \sigma \gtrsim 0.8)$, we find that P(q) exhibits $P(q) \sim q^{-2.5}$ and in the low q-regime $(q \sigma \lesssim 0.8)$, P(q) is described by a power-law $P(q) \sim q^{-2}$, see Fig. 10. The structure is swollen at large scale and has the exponent of the 2D swollen sheet and at higher q (smaller length scales) there is some screening and the apparent exponent corresponds to the θ exponent for the sheet. The latter behavior in the low q-range is superficially reminiscent of the scattering of ordinary uncharged polymers in solution where the scattering intensity decays smoothly with a powerlaw near -2, corresponding to ideal non-interacting random coils in solution. Evidently, a power-law scaling of P(q) with a power-law around -2 certainly does not imply that the conformations of polymer sheets and randomly branched polymers are anything like 'random coil' polymer. The range of power-law behavior with an exponent of -2 becomes larger for higher $M_{\rm w}$ sheets (not shown here). As mentioned above, a different power-law behavior emerges in the high q-regime, $q\sigma \gtrsim 0.8$ due to the excluded volume interactions between the repeating units. Indeed, the length scale at which this crossover is observed occurs roughly at the length span of two repeating units, which have a length span of $l_s \approx 2(2M+1)$ for $M \lesssim 3$ corresponding to $q \approx 2\pi/l_s \approx 1$ for M = 1. Cutting the bonds between the repeating units in 2D nanogel particles re-



FIG. 10. Form factor of 2D nanogel particles having a degree of branching f = 4, chain length M = 1, and mesh size $N_b = 30$ at different fractions of bonds cut, $f_{\rm cb}$. The dashed lines are power-laws as guides for the eye. Representative molecular configurations for $f_{\rm cb} = 0$ and $f_{\rm cb} = 0.44$ are also presented as indicated by the arrows.



FIG. 11. Form factor of 3D nanogel particles having a degree of branching f = 4, chain length M = 15, and mesh size $N_b = 8$ at different fractions of bonds cut, f_{cb} . Representative molecular configurations for $f_{cb} = 0$ and $f_{cb} = 0.44$ are also presented as indicated by the arrows.

duces the impact of excluded volume interactions and as a result the difference between the power-law behaviors between the low q- and high q-regimes of the original structure becomes smaller. Near the percolation threshold, the structure becomes fractal with the scattering profile been described mainly by a single powerlaw, i.e., q^{-2} . Interestingly, while we find significant changes in the molecular shape of 2D nanogel particles with the introduction of defects (see Figs. 5 and 6), the scattering profiles exhibit less pronounced changes.

We continue with some general comments on scat-



FIG. 12. Form factor of 3D nanogel particles having a degree of branching f = 4, chain length M = 15, and a fraction of bonds cut $f_{\rm cb} \approx 0.44$. Results for different mesh sizes are also presented. The arrows indicate the average $R_{\rm g}$ of the nanogel particles. The dashed lines are power-laws as guides for the eye.

tering characteristics of 3D compact gels, see Ref. 32 At intermediate length scales, for further details. $\pi/(2M) \lesssim q \sigma \lesssim \pi/M$, a power-law regime emerges that is distinct from the power-law behavior of the linear chains for nanogel particles having M fixed and increasing the mesh size. At these length scales, P(q)reflects the conformation of multiple chains forming an empty compartment in the nanogel structure. This feature is absent in P(q) profiles of smaller in size nanogel particles, suggesting a 'critical' threshold for this type of structure to be identified by scattering experiments. The scaling exponent that characterizes this regime decreases towards zero (an exponent of zero corresponds) to a perfect plateau) with increasing the mesh size. P(q) reaches to a plateau at low q corresponding to $P(q \to 0) \to M_w$. However, nanogel particles having a large enough mesh size $N_b \gtrsim 5$ start to exhibit a scattering peak in P(q) at length scales close to $q \sigma \sim R_{\rm g}$, as illustrated in Fig. 11.

The introduction of defects decreases the structural correlations of the compact nanogel particle by breaking up the loops and enhancing the tree-like backbone structure of branched polymer structure where many dangling chain ends are prevalent in the polymer. As a result, the scattering peak and the intermediate power-law observed in 3D compact nanogel particles, as discussed above, starts to disappear progressively, see Fig. 11. Near the percolation threshold, the scattering profiles of a 3D nanogel particle at relatively high q values exhibits a power-law behavior with an exponent of -1.7, which corresponds to the scaling of self-avoiding random walks. At this range of length scales, we are probing the mesh structure of the network, which are similar geometrically to linear self-avoiding polymers in solution. At lower q, $q\sigma \lesssim 2\pi/R_{\rm g}$, where the overall net-



FIG. 13. Small angle neutron scattering (SANS) profile of natural 0.06% m/m aggrecan solution; the data are reproduced from F. Horkay, A. Chremos, J. F. Douglas, R. Jones, J. Lou, Y. Xia, J. Chem. Phys. 155, 074901 (2021) with the permission of the AIP Publishing. The dashed lines are power-laws as a guide for the eye.

work structure is probed, we see an extensive powerlaw regime characterized by an apparent power-law near -2.7. This scaling corresponds to a 'fractal' dimension $d_f = 2.7$, which is the expected value of d_f for branched polymers having a relatively high grafting density or a three-dimensional network corresponding to the θ -value of the Wiener sheet model.³⁸ The range of this powerlaw regime increases by increasing $N_{\rm b}$. However, we find that for $N_{\rm b} \gtrsim 10$, the exponent in this power-law regime changes to -2.5, see Fig. 12. This accords with d_f for randomly branched polymers ('lattice animals') with screened binary excluded volume interactions,^{98,99} i.e., percolation clusters.^{57,100} We then see evidence of appreciable excluded volume screening in these densely branched structures.

E. Scattering profile of aggrecan

Before we conclude our study, we briefly discuss the usefulness of our approach in generating randomly branched structures for the specific study of aggrecan. Indeed, the scattering²⁹ and rheological observations on aggrecan under physiologically relevant conditions of aggrecan concentration, salt, etc., are consistent with the formation of branched polymer network structures in solution.

At high q-regime, where we probe the small-scale structure of the aggrecan, we see a wavevector scaling exponent close to -1, reflecting the 'rod-like' structure of the molecules; see Fig. 13. This effect also arises in linear polymer chains with some bending stiffness, and it can be captured by increasing the intrinsic stiffness in the chains composing our nanogel particles (not shown here). At intermediate q-values, aggrecan scatters with a power-law having a scaling exponent of -2.7. This behavior provides a clue on the topology of the aggrecan assemblies in solution. Our previous work³⁰ discusses the differences in molecular interactions in the synthetic and aggrecan bottlebrush solutions that would naturally lead to their different solution organization, but this is not the topic of the present work. This power-law regime coincides with the emerging power-law behavior found in 3D nanogel particles near the percolation threshold, corresponding to the open sponge structure; compare Figs. 12 and 13. At larger distances (lower q-values), the simple power-law scaling starts to break down, suggesting a limit size of the aggrecan clusters in these measurements. Future work will focus on developing models of the open clusters to incorporate modeling that addresses the structural organization of the aggrecan clusters more faithfully. At this stage, we confirm only that the aggrecan solution scattering data is qualitatively consistent with a hierarchical structure having the form of an open sponge network, as inferred in previous work.³²

IV. CONCLUSIONS

We proposed a novel approach to generate a wide range of randomly branched polymeric structures, and their conformational properties are investigated with molecular dynamics simulations. Our approach is based on constructing 'perfect' compact nanogel particles in two- or three-dimensions and then introducing defects that break the loops of the original structure resulting in a more open and fractal structure. Two distinct types of defects are explored: randomly cutting the bonds between the repeating units composing the nanogel particle, and the other kind of defect is by randomly removing the repeating units from the nanogel particle. We quantify the structure of the generated branched polymers by calculating the radius of gyration and its eigenvalues, as well as, the intrinsic viscosity, with the variation of the number of defects. We also calculate the form factor for a wide range of nanogel particles. We find that two-dimensional polymers (having no defects) and randomly branched polymers (generated from two- or three-dimensional polymers by introducing defects) exhibit similar $R_{\rm g}$ and $[\eta]$ mass scaling behavior and scaling behavior in their scattering profiles. In other words, our findings support the general idea that self-avoiding randomly branched polymers ('lattice animals') can be considered as highly perforated sheets.³⁸ However, different kinds of randomly generated structures are formed, depending on the topology of the structure before introducing defects. In addition to a topological transition between 'closed' and 'open' nanogel particles with an increasing concentration of defects, we also find a reduction in the effective topological dimension with defect density. These topological changes are accompanied by changes in the mass scaling exponents and the 'penetration function', quantifying the change in polymer universality class. Finally, we point out that our calculations should provide valuable insights into single chain nanoparticles and selfassociating polymers such as aggrecan.

In future work, we hope to explore this interpretation of the configurational properties of single chain nanoparticles and the implications of the relationship for the solution properties of these gel-like particles at higher particle concentrations. Measurements^{57,58,101} indicate that branched polymers having moderate cross-link density at their θ -point, or screened binary excluded volume interactions, should have a fractal dimension near 2.5, the fractal dimension of percolation clusters. This exponent value has often been estimated for the θ -exponent for randomly branched polymers.¹⁰² We expect the same scaling relation for $R_{\rm g}$ in θ -solvents to hold for SCNPs (having a relatively low cross-linking density), moderately branched commodity polymers and other gel particles in solution where the cross-links can be physical (associative) and chemical bonds.

This correspondence also provides insight into recent observations indicating that SCNPs form compact structures in the melt state,¹⁰³ similar again to model randomly branched polymers¹⁰⁴ and also to unknotted ring polymers in the melt.⁸⁵ The latter connection is natural given our proposed connection between SCNPs and lattice animals under melt conditions, and the known correspondence between ring melts and lattice animal melts.^{105,106} All the known concentration and mass scaling laws for linear chain solutions and melts are changed for the branched polymers, which belong to separate universality classes of polymers. We note, however, that SCNPs exhibit a change from universality class of linear polymers to branched polymers with increased cross-linking density, which is a different crossover than studied in the present paper by decimating networks to obtain branched polymers and it remains to be seen whether the 'random' nature of the cross-linking in chemically cross-linked networks leads to networks having similar topological networks as found from our decimation process. This type of randomly cross-linked network will have to be studied separately to determine if these polymers really lie in the same universality classes and, if so, under what conditions this is true.

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VI. DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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