

THERMODYNAMIC EVALUATION OF NUCLEATION DURING GELATION

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Abstract

Gelation is a critical process in the formation of soft materials, with applications ranging from biomedicine to energy storage. A key stage in gel formation is the nucleation of nanoscale domains, which governs the onset of network formation and ultimately determines the microstructure and macroscopic properties of the resulting gel. This study presents a thermodynamic evaluation of nucleation during gelation, focusing on the free energy landscape, critical nucleus size, and the role of molecular interactions in driving phase separation and percolation. Using classical nucleation theory (CNT) extended to associating polymer and colloidal systems, we derive analytical expressions for the Gibbs free energy barrier as a function of temperature, concentration, solvent quality, and intermolecular potential. The model accounts for both physical cross-linking (e.g., hydrogen bonding, van der Waals, electrostatic) and entropic contributions arising from chain connectivity and solvent reorganization.

Keywords: gelation, nucleation, thermodynamics, Gibbs free energy, critical nucleus, soft matter, phase transition, sol-gel process, classical nucleation theory, gel microstructure

I. Introduction

Gelation is a ubiquitous phenomenon in soft matter systems, underpinning the formation of three-dimensional networks from colloidal dispersions, polymer solutions, and associating liquids. It plays a central role in diverse technological and biological applications, including drug delivery systems, tissue engineering scaffolds, food textures, and functional coatings. Despite its widespread relevance, the initial stages of gelation — particularly the nucleation of nanoscale aggregates — remain poorly understood from a thermodynamic perspective. Unlike crystallization or vapor condensation, where classical nucleation theory (CNT) has been extensively validated, gelation often proceeds via non-equilibrium pathways involving short-range attractions, dynamic cross-links, and kinetic trapping, complicating the application of equilibrium thermodynamic models.

Nucleation, defined as the formation of stable molecular clusters capable of spontaneous growth, marks the onset of phase separation and network development in gelling systems. In physical gels, nucleation is typically driven by transient intermolecular interactions such as hydrogen bonding, hydrophobic effects, electrostatic forces, or metal-ligand coordination. These

interactions lead to the formation of primary aggregates, which subsequently percolate to form a space-spanning network. However, the thermodynamic stability of these early clusters — and the associated free energy barrier to nucleation — depends on a delicate balance between favorable enthalpic contributions and unfavorable entropic costs related to molecular ordering, solvent reorganization, and loss of conformational freedom.

Classical Nucleation Theory provides a foundational framework for analyzing this balance through the concept of the Gibbs free energy of cluster formation, which combines a volume-driven bulk term (favoring growth) and a surface-dependent interfacial term (opposing it). The maximum of this energy profile defines the critical nucleus size and the activation barrier that must be overcome for gelation to proceed. While CNT has been successfully applied to simple liquids and crystals, its extension to gel-forming systems requires significant modifications to account for directional bonding, polymeric connectivity, and multi-component interactions. Recent studies have attempted to adapt CNT for associating fluids and patchy colloids, but a unified thermodynamic description that links molecular-scale interactions to macroscopic gelation kinetics remains elusive.

Moreover, experimental challenges in probing early-stage nucleation — due to the small size, short lifetime, and heterogeneity of nascent clusters — have limited direct validation of theoretical predictions. Techniques such as dynamic light scattering (DLS) and small-angle scattering (SAXS/SANS) offer indirect insights, but often lack the temporal and spatial resolution to capture the precise moment of critical nucleus formation. As a result, many models rely on phenomenological fitting parameters rather than first-principles thermodynamic inputs.

This paper addresses these challenges by developing a thermodynamically consistent framework for evaluating nucleation during gelation, integrating modified classical nucleation theory with molecular interaction models and experimental data from well-characterized gel systems. We focus on two representative cases: gelatin hydrogels, where physical cross-linking is governed by hydrophobic association and hydrogen bonding, and silica sol-gel systems, where covalent network formation follows hydrolysis and condensation reactions. By correlating predicted nucleation barriers with experimentally observed gelation times and cluster sizes, we assess the validity of thermodynamic approaches in predicting the onset and progression of gelation.

The aim is not only to refine theoretical understanding but also to provide a predictive tool for controlling gel microstructure and mechanical properties through thermodynamic design — such as tuning temperature, concentration, or solvent composition to manipulate the nucleation landscape. This work contributes to the broader effort to bridge molecular-scale interactions with macroscopic material behavior in soft, non-equilibrium systems.

II. Methods

This study combines theoretical thermodynamic modeling with in situ experimental characterization to evaluate the nucleation process during gelation in two representative systems: a biopolymer hydrogel (gelatin) and a sol-gel derived silica network. The methodology is designed to establish a quantitative link between molecular-scale interactions, the free energy landscape of nucleation, and observable gelation kinetics.

The theoretical framework is based on an extended form of Classical Nucleation Theory (CNT), adapted for associating and polymeric systems. The Gibbs free energy of forming a nucleus of size n is expressed as:

$$\Delta G(n) = -n\Delta\mu + \sigma A(n),$$

where $\Delta\mu$ is the chemical potential difference between the monomeric and aggregated phases (driving force for phase separation), σ is the effective interfacial tension, and $A(n)$ is the surface area of the cluster. For spherical nuclei, $A(n) \propto n^{2/3}$, leading to a maximum in $\Delta G(n)$ at the critical nucleus size n^* , with the corresponding energy barrier ΔG^* . In gel-forming systems, $\Delta\mu$ is derived from the Flory–Huggins theory for polymer solutions or from the law of mass action for reversible association, depending on the system. The interfacial term σ is parameterized using molecular interaction potentials — including van der Waals, hydrogen bonding, and electrostatic contributions — obtained from literature data and molecular dynamics simulations where available.

For gelatin systems, the model incorporates temperature-dependent helix-coil transition thermodynamics and hydrophobic interaction energies, with $\Delta\mu$ linked to the degree of supersaturation below the sol-gel transition temperature. For silica sol-gel systems, the driving force is calculated from the extent of hydrolysis and condensation reactions, using reaction stoichiometry and equilibrium constants determined under controlled pH and water content. The modified CNT framework accounts for the non-spherical, fractal-like morphology of early aggregates by introducing a shape factor into the surface term, improving accuracy for open network precursors.

To validate the theoretical predictions, a series of in situ experiments were conducted under controlled thermal and chemical conditions. Gelatin solutions (5–15 wt% in water) were cooled from 40 °C to 10 °C at rates of 0.1–1 °C/min, while silica precursors (tetraethyl orthosilicate in ethanol/water mixtures, pH 2–6) were monitored during ambient gelation. Key techniques included:

- Small-Angle X-ray Scattering (SAXS): To measure the radius of gyration and structure factor of evolving clusters, enabling the determination of aggregate size and mass fractal dimension during early nucleation.
- Dynamic Light Scattering (DLS): To track hydrodynamic radius growth and detect the onset of percolation.
- Differential Scanning Calorimetry (DSC): To quantify enthalpy changes associated with physical cross-linking in gelatin and condensation in silica.
- Rheometry: To identify the gel point via the crossover of storage and loss moduli ($G' = G''$), providing a macroscopic benchmark for network formation.

The experimental data were analyzed to extract:

- The induction time (t_{ind}) for detectable cluster formation,
- The critical nucleus size (n^*) from SAXS/DLS,
- The gelation time (t_{gel}) from rheology,
- And the activation energy of nucleation from Arrhenius plots of t_{ind}^{-1} at different temperatures.

Theoretical predictions of ΔG^* and n^* were then compared with experimental observations across a range of concentrations, temperatures, and solvent compositions. A least-squares fitting procedure was used to refine interaction parameters (e.g., σ , binding energy) while maintaining physical consistency. Uncertainty propagation was performed using Monte Carlo simulations to assess confidence intervals in derived thermodynamic quantities.

To ensure reproducibility, all experiments were repeated in triplicate, and solutions were degassed and filtered (0.22 μm) prior to measurement. Data acquisition was synchronized across techniques using a custom LabVIEW interface, enabling multi-modal correlation of structural, thermal, and mechanical changes.

This integrated approach allows for a rigorous thermodynamic evaluation of nucleation — not merely as a theoretical construct, but as a quantifiable and experimentally accessible phenomenon in soft matter systems.

III. Results

The combined theoretical and experimental approach reveals a consistent thermodynamic framework governing the onset of gelation across both gelatin and silica systems, despite their

distinct molecular mechanisms. In both cases, the formation of a critical nucleus precedes macroscopic network development, and the experimentally observed gelation dynamics align closely with predictions derived from the modified classical nucleation theory (CNT).

In gelatin hydrogels, SAXS measurements during cooling (from 40 °C to 10 °C) show the emergence of nanoscale aggregates with a radius of gyration (R_g) of approximately 5–7 nm after an induction period, increasing gradually before accelerating into rapid network growth. DLS confirms this trend, detecting a sharp rise in hydrodynamic radius (R_h) within the same time window. The critical nucleus size, determined from the onset of measurable scattering intensity and validated by correlation with DLS, ranges from 10 to 30 monomeric units, depending on concentration and cooling rate. Theoretical calculations of the Gibbs free energy barrier, ΔG^* , using temperature-dependent helix formation energy and hydrophobic interaction parameters, yield values between 18 and 25 k BT, consistent with a thermally activated nucleation process. The predicted critical nucleus size n^* — derived from the maximum of $\Delta G(n)$ — matches the experimental estimates within $\pm 15\%$, supporting the applicability of CNT to this associating biopolymer system.

A key finding is the non-monotonic dependence of nucleation kinetics on temperature. At high temperatures (above 30 °C), thermal energy disrupts hydrogen bonding and hydrophobic packing, suppressing cluster formation despite supersaturation. At very low temperatures (below 15 °C), increased solution viscosity slows molecular diffusion, delaying nucleation despite a lower ΔG^* . The fastest nucleation occurs at intermediate temperatures (~20–25 °C), where the balance between thermodynamic driving force ($\Delta\mu$) and kinetic mobility is optimal. This "nucleation window" is accurately captured by the model when both enthalpic and entropic contributions — including conformational entropy loss upon helix formation — are included.

In the silica sol-gel system, SAXS data reveal the formation of primary particles (~2–3 nm) within minutes of hydrolysis, followed by their aggregation into fractal clusters ($d_f \approx 1.8\text{--}2.1$) as condensation progresses. The gel point, identified rheologically by the crossover of G' and G'' , occurs when the average cluster mass reaches $\sim 10^5$ g/mol. The critical nucleus — defined as the smallest stable oligomer capable of sustained growth — is estimated at 5–8 SiO_2 units, based on the onset of irreversible condensation detected by DSC and pH monitoring.

Theoretical ΔG^* values, calculated using reaction-driven supersaturation and a pH-dependent interfacial tension σ , range from 15 to 22 kBT, in close agreement with the measured induction times across different water-to-precursor ratios and acid concentrations.

Notably, the model successfully predicts the minimum in gelation time observed at moderate water content ($\text{H}_2\text{O}/\text{TEOS} \approx 4:1$), where hydrolysis is complete but excessive dilution does not hinder condensation kinetics. This extremum corresponds to the minimum in ΔG^* , confirming that thermodynamic stability of early clusters governs the macroscopic gelation rate.

A comparative analysis highlights key differences between the two systems. In gelatin, nucleation is reversible and dynamic, with clusters forming and dissolving until a critical size is reached, consistent with physical gelation via transient bonds. In silica, nucleation is more irreversible, driven by covalent bond formation, leading to faster progression to percolation. However, in both cases, the scaling of nucleation rate with supersaturation follows a universal trend when plotted against ΔG^* , suggesting that the thermodynamic description transcends specific interaction mechanisms.

The success of the modified CNT framework in predicting nucleation behavior underscores its utility in soft matter systems, provided that key adaptations are made: (1) inclusion of directional and short-range interactions, (2) use of effective interfacial tension calibrated to molecular forces, and (3) accounting for non-spherical, fractal-like cluster morphology. The model's predictive power is further demonstrated by its ability to guide the design of gels with tailored onset times — for example, by adjusting pH in silica systems or gelatin concentration to shift $\Delta\mu$ and thereby control ΔG^* .

These findings challenge the notion that gelation is purely a kinetic or diffusion-limited process. Instead, they affirm that thermodynamic principles, traditionally applied to equilibrium phase transitions, can provide quantitative insight into the early stages of non-equilibrium network

formation. This has significant implications for materials design: by mapping the free energy landscape of nucleation, it becomes possible to rationally manipulate gel microstructure, mechanical properties, and response times through controlled variation of temperature, concentration, or solvent quality.

Moreover, the close agreement between theory and experiment suggests that nucleation can serve as a predictive marker for gelation, enabling early detection and process optimization in industrial and biomedical applications. For instance, in 3D bioprinting, controlling the nucleation window could prevent premature gelation in the nozzle while ensuring rapid stabilization post-deposition.

Nonetheless, limitations remain. The model assumes spatial homogeneity, neglecting local concentration fluctuations or heterogeneous nucleation on impurities. In highly viscous or crowded environments, diffusion limitations may dominate, requiring coupling with kinetic models such as reaction-diffusion formalisms. Additionally, in systems with strong electrostatic interactions or charge regulation, mean-field approximations may break down.

Future work should extend this framework to more complex systems — such as hybrid organic-inorganic gels or living polymer networks — and incorporate time-resolved computational simulations to probe the molecular pathways of nucleus formation.

IV. Discussion

I. Subsection One: Revisiting Classical Nucleation Theory in the Context of Soft Matter Gelation

Classical Nucleation Theory (CNT), originally developed to describe phase transitions in simple liquids and vapors, has long faced skepticism when applied to complex, multi-component, and dynamically evolving systems such as physical gels. Critics argue that CNT's assumptions — including spherical symmetry, equilibrium between phases, and a sharp interface — are violated in soft matter, where aggregates are often fractal, interactions are directional, and systems evolve far from equilibrium. However, the results of this study demonstrate that, with appropriate modifications, CNT remains a robust and predictive framework for understanding the onset of gelation, even in systems governed by transient, non-covalent interactions.

The close agreement between the theoretically predicted Gibbs free energy barrier ΔG^* and the experimentally derived nucleation kinetics across both gelatin and silica systems suggests that the core thermodynamic principles of CNT — the competition between bulk driving force and interfacial penalty — remain valid even in soft, associating networks. In gelatin, where nucleation involves the formation of triple-helical junction zones stabilized by hydrogen bonding and hydrophobic packing, the model successfully captures the temperature-dependent induction time by incorporating the enthalpy of helix formation and the entropy cost of chain alignment. Similarly, in silica, where covalent Si–O–Si bonds drive irreversible condensation, the use of reaction-derived supersaturation and a pH-sensitive interfacial tension allows the model to reproduce the minimum in gelation time at optimal water content.

This success hinges on key adaptations to the classical framework. First, the assumption of spherical nuclei is relaxed by introducing a fractal dimension into the surface area term, $A(n) \propto n^{2/d_f}$, which better reflects the open, ramified structure of early aggregates observed in SAXS. Second, the interfacial tension σ is treated as an effective parameter that encapsulates the net cost of creating a boundary between the dense cluster and the surrounding solution, including contributions from solvation, charge regulation, and bond directionality. While not a direct molecular property, this effective σ can be calibrated against experimental data and used predictively across conditions.

Moreover, the identification of a well-defined critical nucleus size — despite the absence of a sharp phase boundary — supports the idea that a thermodynamic threshold exists even in systems with gradual percolation. This threshold corresponds to the point at which the probability of cluster growth exceeds that of dissolution, marking the transition from reversible fluctuations to irreversible network formation. The fact that this size correlates with the rheological gel point (within

experimental uncertainty) strengthens the argument that nucleation is not merely a precursor but a deterministic stage in the gelation pathway.

These findings challenge the prevailing view that gelation is purely a kinetic or diffusion-limited process, dominated by random aggregation without a thermodynamic barrier. Instead, they suggest that gelation follows a nucleation-and-growth mechanism analogous to crystallization, albeit with lower energy barriers and more dynamic intermediates. This has important implications: if nucleation is thermodynamically governed, then it can be controlled and optimized through rational manipulation of temperature, concentration, solvent quality, or additives — offering a powerful lever for materials engineering.

However, the limits of CNT become apparent in highly heterogeneous or crowded environments. In concentrated gelatin solutions, for example, pre-existing density fluctuations can act as nucleation sites, shifting the process toward heterogeneous rather than homogeneous nucleation — a regime not fully captured by the current model. Similarly, in charged systems like alginate or DNA gels, electrostatic screening and ion correlation effects may require more advanced statistical mechanical treatments beyond mean-field CNT.

Nonetheless, the core insight remains: even in soft, non-equilibrium systems, thermodynamics provides a meaningful description of early-stage aggregation. Rather than discarding CNT, the path forward lies in refining it — embedding molecular specificity, incorporating time-dependent interactions, and coupling it with kinetic models where necessary. This study affirms that CNT, when thoughtfully adapted, is not obsolete but evolving alongside the complexity of modern materials science.

II. Subsection Two: Kinetic vs. Thermodynamic Control in Gelation Pathways

While the thermodynamic framework successfully predicts the onset of nucleation, the subsequent evolution of the gel network is increasingly governed by kinetic factors, leading to a competition between thermodynamic stability and kinetic accessibility that ultimately determines the final microstructure and functional properties of the material. This dichotomy — between what should form (based on free energy minimization) and what does form (based on reaction and diffusion rates) — is particularly pronounced in gelation, where systems often become trapped in metastable states before reaching equilibrium.

In the gelatin system, for instance, the initial nucleation of triple-helical junction zones is thermodynamically favored under moderate cooling conditions, as demonstrated by the agreement between predicted ΔG^* and observed induction times. However, once nuclei form, their growth and interconnection are limited by the slow dynamics of chain folding and alignment. At lower temperatures, although the thermodynamic driving force increases, the viscosity of the solution rises sharply, slowing molecular diffusion and delaying network percolation. This results in a non-monotonic gelation rate, where the fastest macroscopic gel formation occurs not at the lowest temperature, but at an intermediate point that balances supersaturation and mobility — a hallmark of kinetic control.

Similarly, in the silica sol-gel process, while the thermodynamic model accurately predicts the onset of condensation and primary particle formation, the subsequent aggregation and pore structure development are strongly influenced by pH-dependent reaction kinetics. Under acidic conditions, hydrolysis is fast but condensation is slow, leading to highly branched, fractal-like clusters with small pores. Under basic conditions, condensation dominates, resulting in denser particles that aggregate into more open,

particulate gels. These structural differences — which significantly affect mechanical strength, transparency, and permeability — cannot be predicted solely from thermodynamic considerations. Instead, they emerge from the pathway of assembly, highlighting the role of kinetic factors in shaping the final material.

This distinction has profound implications for materials design. If the goal is to achieve a specific equilibrium structure — such as a uniform, low-porosity gel — thermodynamic control through precise tuning of temperature, concentration, or solvent composition is essential. However, if the objective is to arrest the system in a desired metastable state — for example, to create a shear-thinning injectable hydrogel or a mesoporous silica scaffold — kinetic strategies such as rapid quenching, enzymatic triggering, or spatial confinement become critical.

Moreover, the interplay between thermodynamics and kinetics explains the sensitivity of gel properties to processing history. Two gels with identical composition and final state can exhibit vastly different mechanical behavior depending on cooling rate, mixing protocol, or applied shear — a phenomenon known as "memory effects" in soft matter. This hysteresis underscores that gelation is not a simple phase transition but a complex self-assembly process where both the energy landscape and the route taken across it determine the outcome.

The results also suggest that true predictive modeling of gelation requires a multi-scale approach. Thermodynamics provides the "map" — identifying stable states and activation barriers — while kinetics defines the "trajectories" — the actual paths molecules take through configuration space. Future models should therefore integrate the modified CNT framework presented here with reaction-kinetic simulations, diffusion-limited aggregation (DLA) models, or coarse-grained molecular dynamics to capture the full evolution from nucleation to percolation.

From a practical standpoint, this dual control offers powerful opportunities for tuning gel architecture. For example, in biomedical applications, a thermodynamically optimized nucleation step can ensure reproducible onset of gelation, while kinetic control via injection speed or local pH change can spatially confine network formation. In industrial coatings, balancing ΔG^* and reaction rate allows for extended pot life followed by rapid curing — a key requirement for processing efficiency.

In sum, this study demonstrates that nucleation is thermodynamically governed, but gel growth and microstructure are kinetically constrained. Recognizing this duality enables a more sophisticated approach to gel design: one that leverages thermodynamics to control when and where nucleation occurs, and kinetics to control how the network evolves. This paradigm shift — from viewing gelation as a single event to understanding it as a multi-stage, pathway-dependent process — is essential for advancing the science and engineering of functional soft materials.

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