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Effect of Multivalent Interactions on Phase Separation: A Reaction Diffusion Dynamics Study

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Abstract

Phase Separation is referred to as the process in which a solution spontaneously separates into two distinct phases, a dense and a dilute one, and stably coexist. Recent studies exhibit that phase separation is responsible for formation of biomolecular condensates. Altered protein dynamics in the biomolecular condensates are linked to several neurodegenerative diseases. Within the cellular environment, multivalent Intrinsically Disordered Proteins (IDPs) are the main drivers of phase separation. The number of interacting sites on proteins determines their valency which plays a key role in modulating phase separation. In this study, we employ a minimal coarse-grained approach to study phase separation, wherein the proteins are represented by spherical beads with interacting sites on them. The beads are governed by reaction diffusion dynamics. The effects of varying valency, concentration of species, and Lennard-Jones potential well depth on the interaction of beads has been studied. We also demonstrate the effects of specific binding site reactions on the system. Results indicate how minor changes in the simulation parameters lead to modifications in phase change behaviour. This work will help us to understand how these multivalent protein species modulate phase separation within the cellular environment.
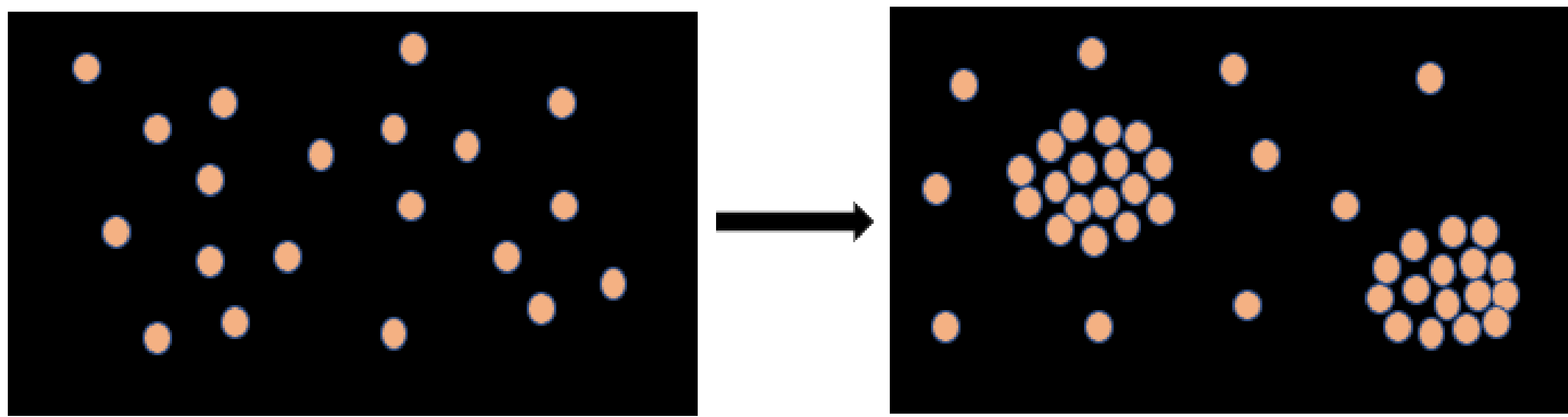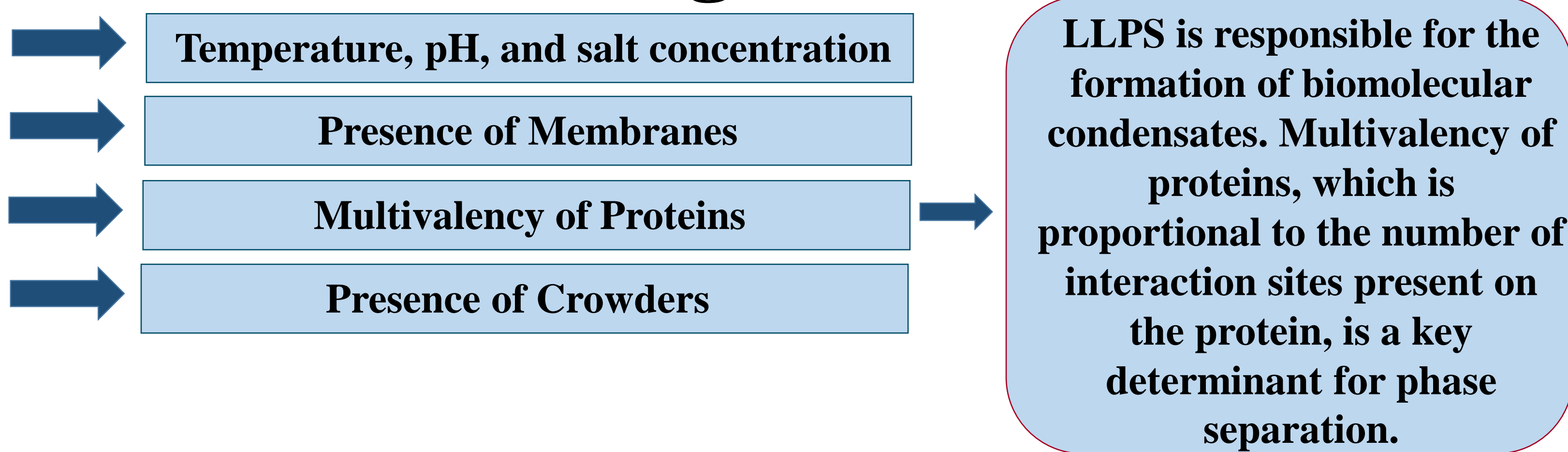
Introduction

Figure 1 – Liquid – Liquid Phase Separation - The process through which a solution of components spontaneously separates into two phases, a dense phase and a dilute phase, which then coexist.

Factors Affecting LLPS in Cells

→ Temperature, pH, and salt concentration

→ Presence of Membranes

→ Multivalency of Proteins

→ Presence of Crowders

LLPS is responsible for the formation of biomolecular condensates. Multivalency of proteins, which is proportional to the number of interaction sites present on the protein, is a key determinant for phase separation.

Coarse Grained Model

Figure 2 – Minimal Coarse Grained Model of particles having different valencies is designed using ReaDDy – Monovalent, Divalent and Trivalent Particles
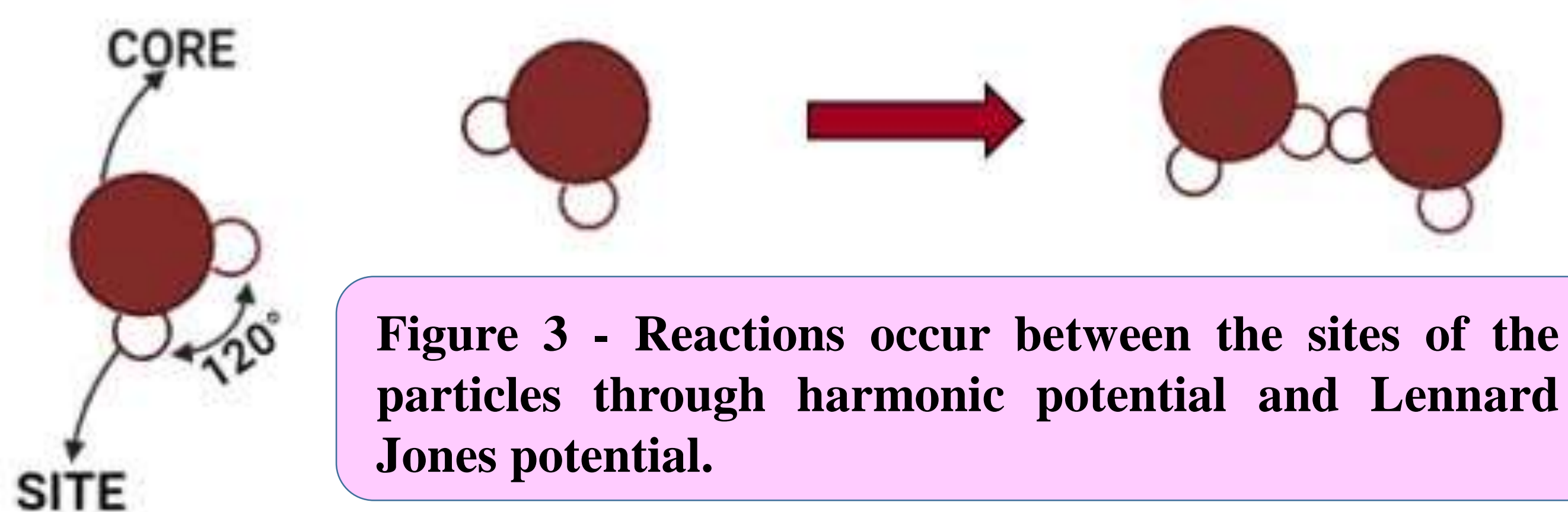

Figure 3 - Reactions occur between the sites of the particles through harmonic potential and Lennard Jones potential.

Simulation Parameters

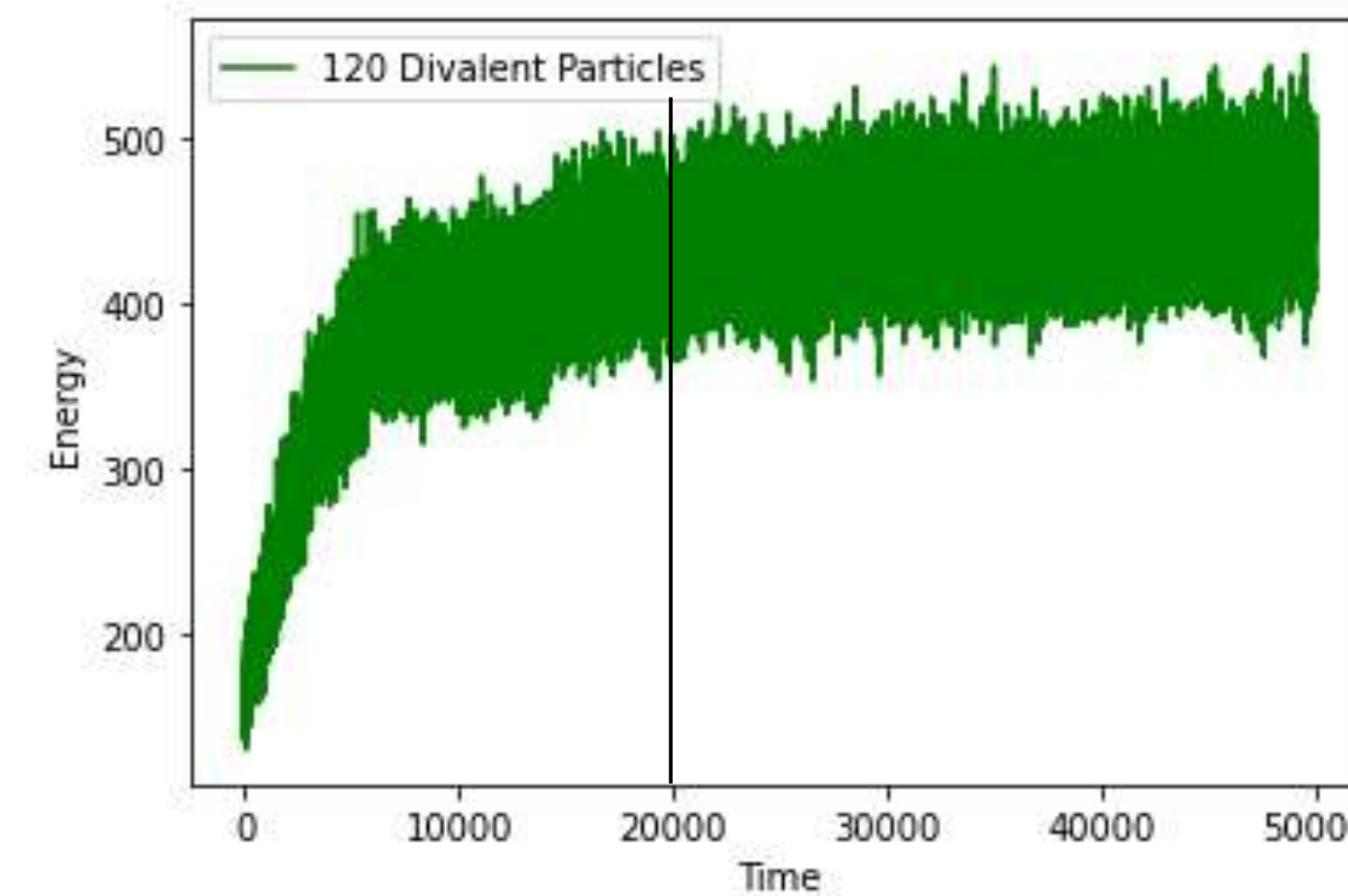| Simulation Parameters	Values
Box Size	40σ
Number of Particles	30, 60, 90, 120
Site –Site LJ interaction strength $\epsilon_{ss}(k_BT)$	1, 1.5, 2, 2.5, 3, 3.5
Core –Core LJ interaction strength $\epsilon_{cc}(k_BT)$	0.5
Valency of Particles	1, 2, 3

Figure 4 – Typical energy plot used for analysis of phase separating behaviour.

Binder Cumulant as shown below, with energy of the system as order parameter has been estimated for all configurations to characterise phase separation.

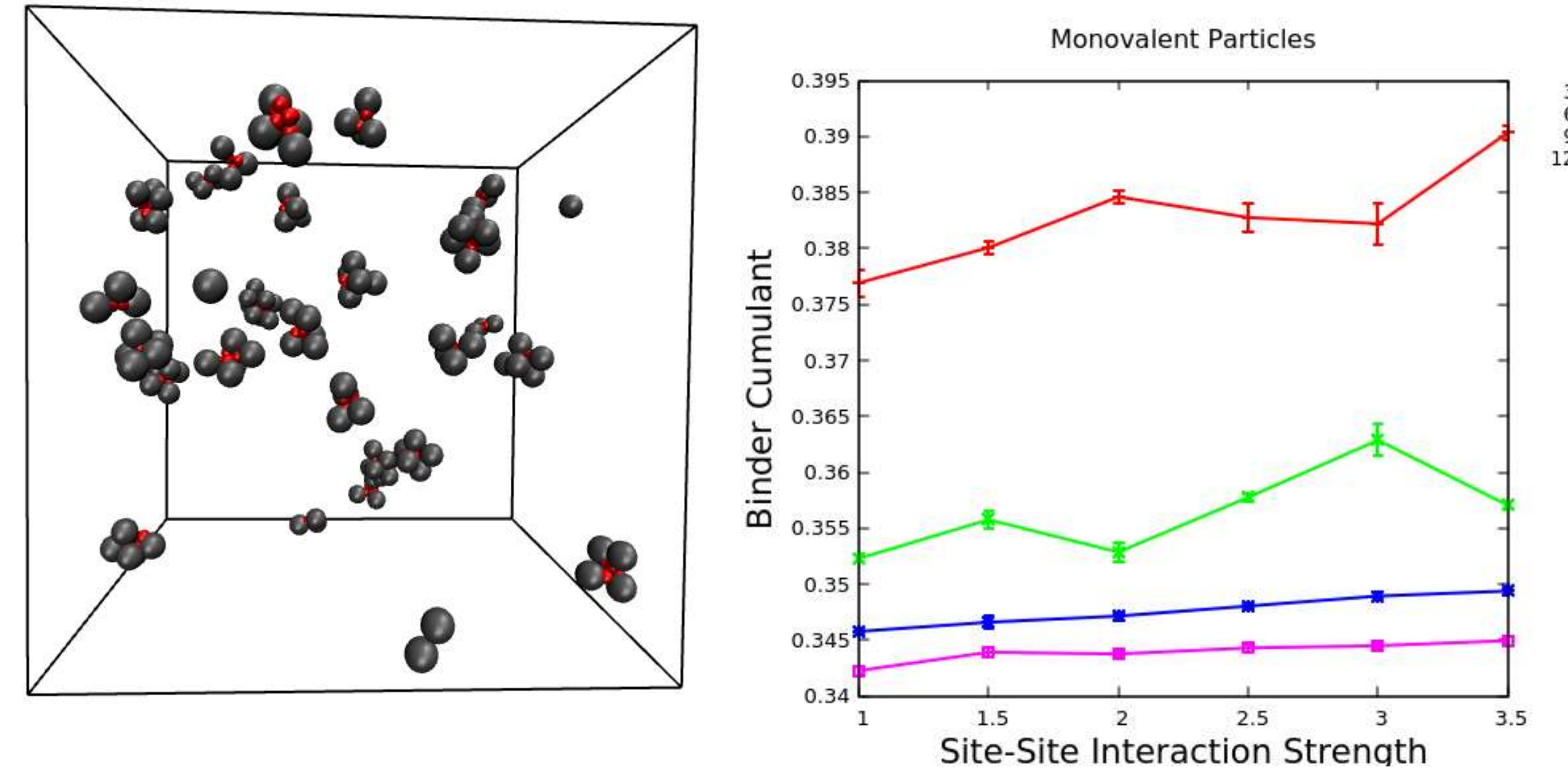$$V = 1 - \frac{<E>^4}{3<E^2>^2}$$

Results

Figure 5 - Monovalent Particles (a) Final configuration at 120 particles and $\epsilon_{ss} = 3.5 k_BT$ - show limited cluster forming properties. (b) Binder Cumulant v/s ϵ_{ss} plot - A peak in cumulant values signifies phase separation. In few cases of, Binder Cumulant values do not corroborate the visual results.
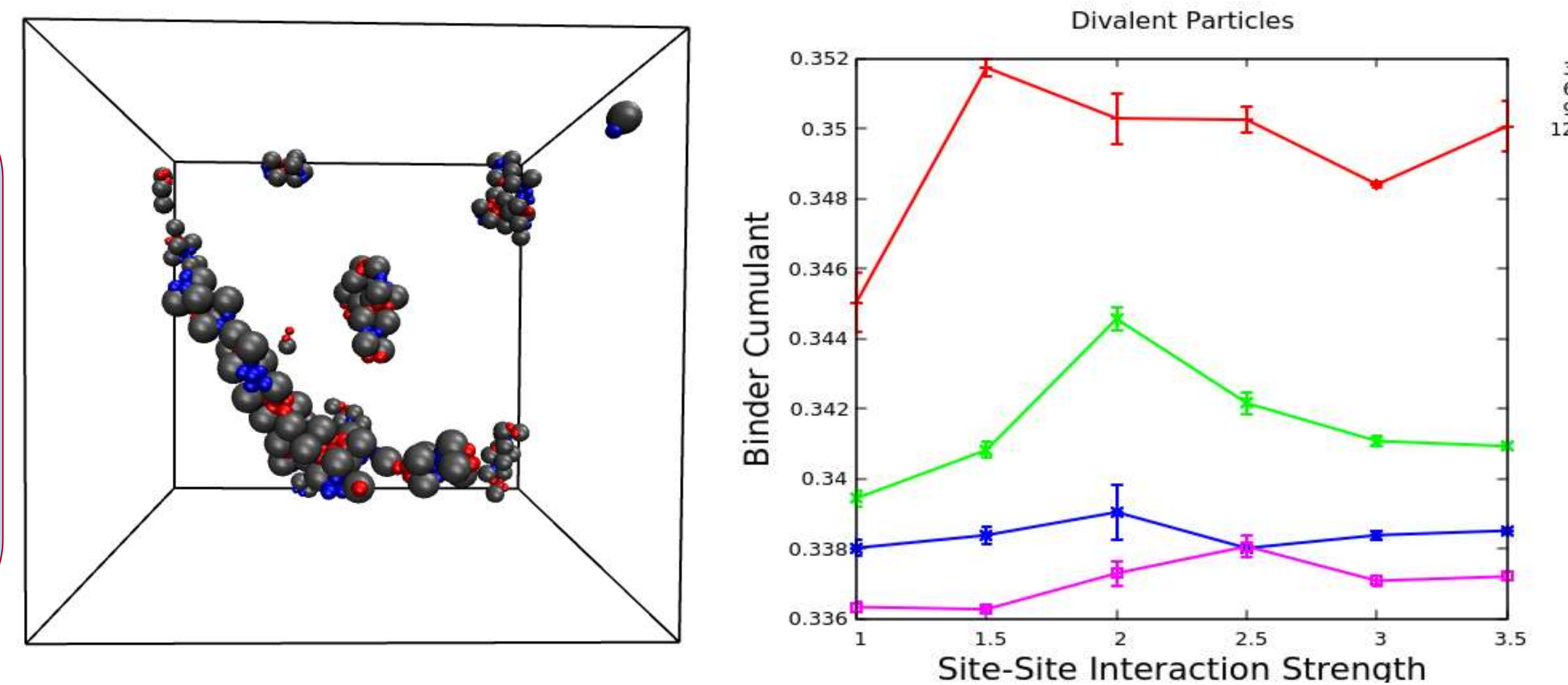

Figure 6 - Divalent Particles (a) Final configuration at 120 particles and $\epsilon_{ss} = 3.5 k_BT$ - show cluster forming abilities at higher concentration. (b) Binder Cumulant v/s ϵ_{ss} plot - Binder Cumulant values corroborate the visual results in this case.

Figure 7 - Trivalent Particles (a) Final configuration at 120 particles and $\epsilon_{ss} = 3.5 k_BT$ - show cluster forming abilities at higher concentration. (b) Binder Cumulant v/s ϵ_{ss} plot -Binder Cumulant values corroborate the visual results in this case.
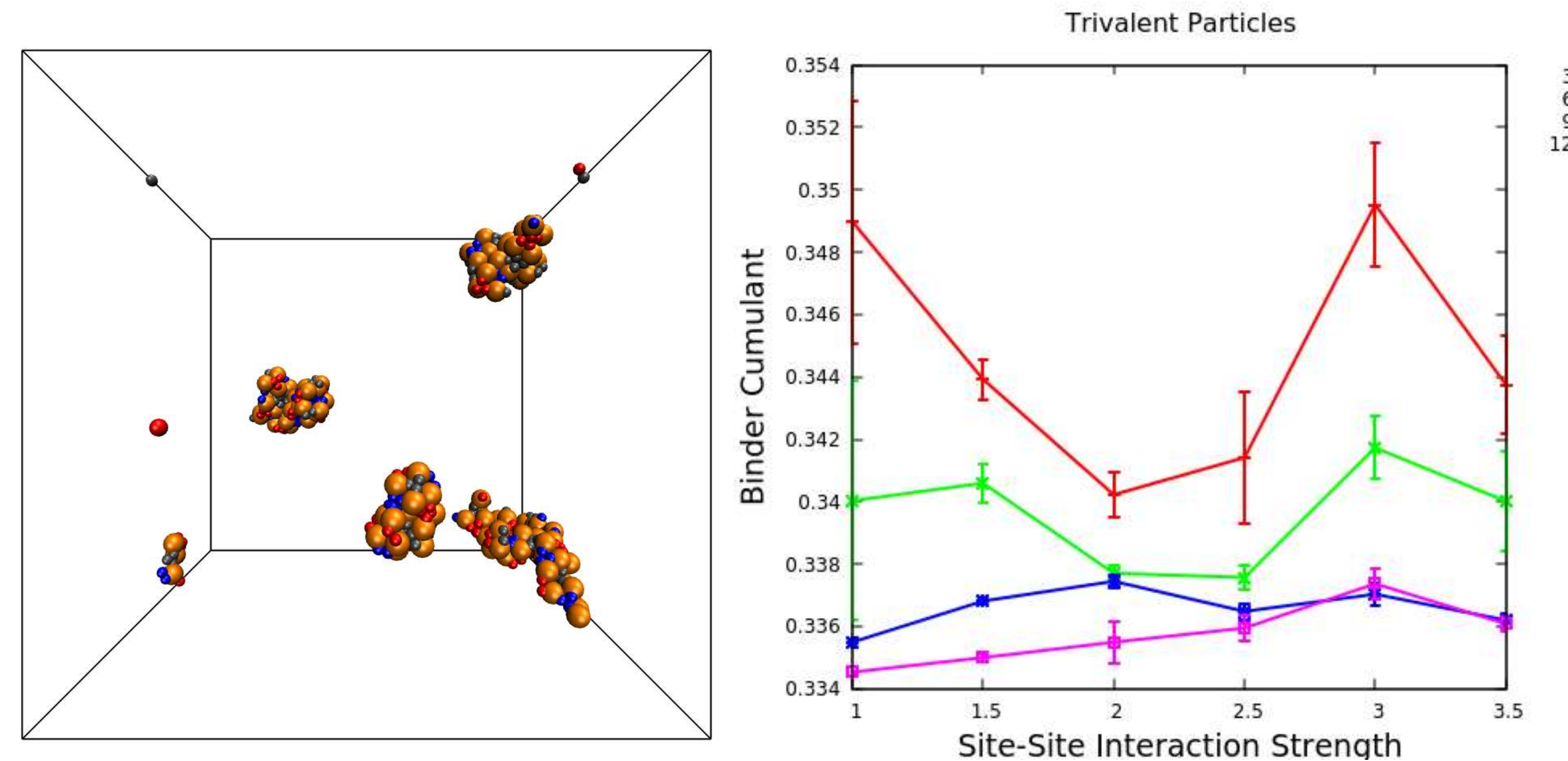
Conclusion

- Increasing the **valency** and the **concentration of particles** aids in the formation of a denser phase. Phase separation is facilitated at these values.

References

[1] Emiko Zumbro and Alfredo Alexander-Katz. "Multivalent polymers can control phase boundary, dynamics, and organization of liquid-liquid phase separation". In: PLOS ONE 16.11 (Nov. 2021), pp. 1–28

[2] Johannes Schoneberg and Frank Noe. "ReaDDy - A Software for Particle-Based Reaction-Diffusion Dynamics in Crowded Cellular Environments". In: PloS one 8 (Sept.2013), e74261.