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Peer Review

Review of: "Separation of Sticker-Spacer Energetics Governs the Coalescence of Metastable Condensates"

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In this work, the authors reported a systematic simulation study on the structure and fusion dynamics of droplets based on the sticker-spacer model. They found two different fusion mechanisms: while two droplets at weak sticker-sticker attraction can coalesce rapidly into a single thermodynamically stable droplet, they may not coalesce when the sticker-sticker attraction is strong, and thus the finite-sized droplet may exist in a thermodynamic metastable state for a long time. They rationalized this kinetically arrested state as being due to the slow exchange rate for the stickers, in contrast to that in homopolymer solutions. The findings provide new understanding of the long-lived droplets found in cells, and the manuscript is well-written. Here are some comments to further improve the quality of the manuscript.

1. In the second paragraph of the Introduction, the authors stated that certain amino acids (polar or aromatic side chains) may serve as stickers. But it is usually regarded that the polar residues are spacers instead of stickers in the literature. Please double-check this.

2. In the model part in Section 1.3, the authors state that once a pair of two stickers is formed, they cannot form another bond. This ensures a one-to-one bonding feature, but how does the potential setting enforce this one-to-one pairing? Could the authors provide further explanation on this point? Moreover, the authors mentioned that when two stickers form a bond, Ens get turned off and are overridden by Es. Does this mean that the formed sticker pairs do not have any non-specific LJ potential? Further, is this requirement necessary, and how will it affect the final conclusion?

3. In the main text, the authors stated that the minimum combination (critical level) that yields a stable cluster is Es = 8kT and Ens = 0.3kT. I think the minimum combination of Es and Ens to form a

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state cluster should be a curve in the plane of Es and Ens. The combination of Es = 8kT and Ens = 0.3kT should be just one point on this curve. This issue should be carefully stated.

4. In Fig S3, 5, the ranges of small Rg and large Rg where the PMF is flat are meaningless and should be removed to avoid confusion.

Declarations

Potential competing interests: No potential competing interests to declare.