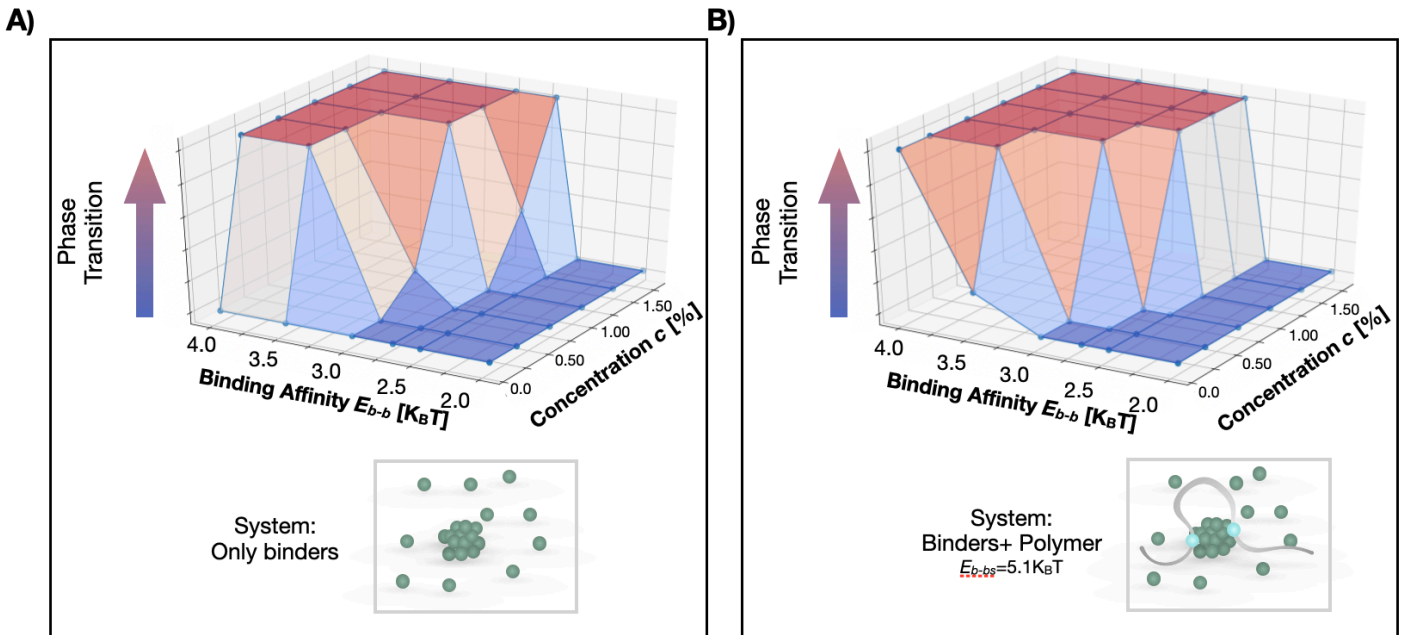


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**Supplemental Information**

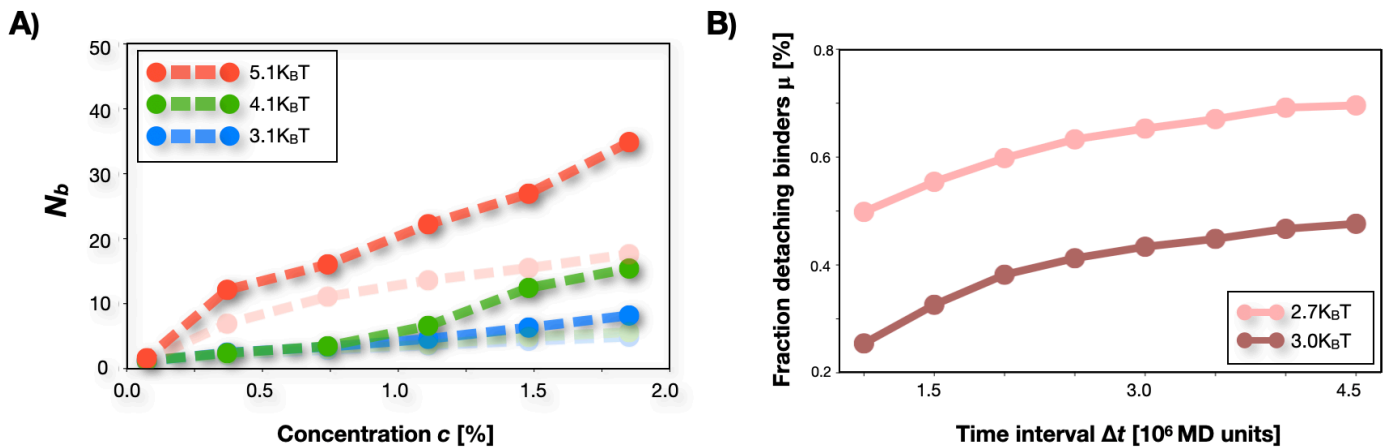
**The Interplay between Phase Separation and Gene-Enhancer Communication: A Theoretical Study**

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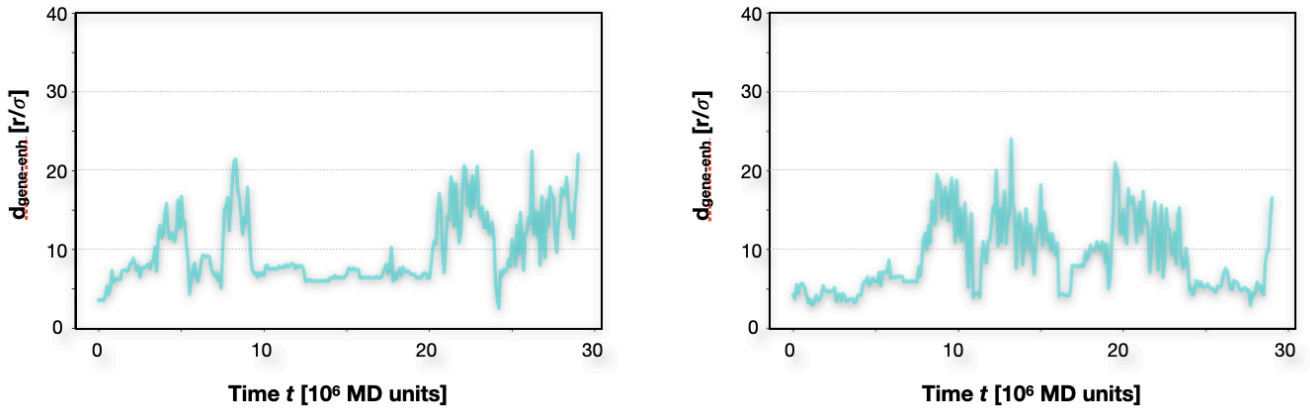
### Supplementary Figure 1: Phase diagram in different conditions

Phase diagram can be influenced by the presence of the polymer. **A)** Phase diagram for the system composed only by the binders. Note that the diagram is very similar to the diagram of Figure 1E, where the system is composed by binders and a weakly interacting polymer. **B)** Phase diagram of the system composed by binders and a strongly interacting polymer, with a high affinity  $E_{b-bs} = 5.1 K_B T$ . Note that such interaction enhances the formation of phase-separated clusters for more combinations of control parameters.



**Supplementary Figure 2: Influence of the binding sites and structural properties of the phase-separated clusters**

**A)** Number of binders  $N_b$  in the largest cluster as a function of the concentration  $c$ , for different values of the affinity  $E_{b-bs}$ . The affinity  $E_{b-b}$  between the binders is in the very weak range (2.5K<sub>B</sub>T and 2.0K<sub>B</sub>T for the opaque and transparent curves respectively), so to not induce phase-separation. Note that the presence of the binding sites induces a local increase in the concentration. **B)** Fraction of binders that detach from the cluster at least one time in a given time interval. For low affinities, the cluster exhibits highly dynamical properties since after enough time, which is comparable with the characteristic time between two contact events of regulatory elements, roughly 70% of the binders experience a detaching event.



**Supplementary Figure 3: Gene-enhancer dynamics regimes are stable across changes of the system parameters**

Two independent examples of simulated gene-enhancer dynamics in the regime colored in cyan in Figure 3A. In this case, the binder diameter is  $0.5\sigma$ . Binding regions are made of 1 and 3 binding sites respectively, separated by an average linear distance of 50 beads. Affinity parameters ( $E_{b-b}$  and  $E_{b-bs}$ ) are the same used in Figure 3C, with a similar concentration per volume unit ( $c \sim 1\%$ ). Note the stability of the contact with sharp increases of the gene-enhancer distance, due to detaching events of the polymer binding sites from the phase-separated cluster. In this respect, the behavior is analogous to the distance dynamics reported in Figure 3C.