We study the dynamics of diffusion-limited irreversible aggregation of monomers, where bonds are mediated by linkers. We combine kinetic Monte Carlo simulations of a lattice model with a mean-field theory to study the dynamics when the diffusion of aggregates is negligible and only monomers diffuse. We find two values of the number of linkers per monomer which maximize the size of the largest aggregate. We explain the existence of the two maxima based on the distribution of linkers per monomer. This observation is well described by a simple mean-field model. We also show that a relevant parameter is the ratio of the diffusion coefficients of monomers and linkers. In particular, when this ratio is close to ten, the two maxima merge at a single maximum.

I. INTRODUCTION

The growth of large structures from the spontaneous aggregation of individual constituents (monomers) is a subject of interest across fields and disciplines [1–18]. From the nucleation and growth of crystallites at the nanoscale, flocculation and self-assembly of colloidal suspensions at the micron scale, to the formation of social networks at the human scale, there are many examples where the dynamics of aggregation has been described by simple mechanisms such as diffusion and reaction/bond formation [19–28].

Most of the previous studies considered monomer-monomer bonds that are either independent or activated by enzymes, where each enzyme may activate more than one bond [29–32]. Recently, however, the interest has shifted towards monomer-monomer bonds mediated by a second species, the linkers [33–39]. Linkers are different from enzymes, for they mediate at most one bond. The idea is to control aggregation through the properties of the linkers (e.g., their size, shape, chemistry, and concentration), keeping the properties of individual monomers intact. But linkers provide many more control parameters to the dynamics. The dependence on each one of them is still elusive.

Here, we investigate the dependence of the aggregation dynamics on the number of linkers per monomer and their relative diffusion coefficients, when the diffusion of aggregates is negligible. We consider the limit of irreversible aggregation, not only for theoretical simplicity but also due to its practical relevance [40, 41]. For many applications, strong irreversible bonds are instrumental to yield resilience to thermal fluctuations and mechanical perturbations [42]. Numerical simulations reveal two optimal numbers of linkers per monomer for which the average size of the aggregates is maximized. We propose a mechanism responsible for this effect and show that the results may be described by a mean-field calculation. We also discuss how the existence and the values of the maxima depend on the diffusion coefficients of the two species.

We introduce the model and simulation details in Sec. II, present the main results in Sec. III, and draw some conclusions in Sec. IV.

II. MODEL

Let us consider a cubic lattice with a diluted mixture of two species: monomers and linkers. Monomers occupy one lattice site and move by a sequence of random hops between nearest neighboring sites. The hopping rate is equal to the translational diffusion coefficient $D_m$. A lattice site cannot be occupied by more than one monomer. The initial concentration of monomers $n_m$ is defined as the fraction of lattice sites occupied by monomers at $t = 0$. Monomers have a number $f$ of patches on their surface with $f$ and the symmetry of their spatial distribution given by the topology of the lattice. For example, on the cubic lattice considered here, $f = 6$ and the patches are oriented along the three directions of the nearest neighbors. A patch is either occupied, when forming a bond to a linker or free, otherwise. Each monomer also rotates with a rotational diffusion coefficient $D_r$ (see Fig. 1b), which we consider to be $D_r = D_m$.

The linkers also occupy one lattice site and hop with a diffusion coefficient $D_l$. A lattice site can be occupied by at most one linker. The concentration of linkers $n_l$ is defined analogously to $n_m$. Linkers form bonds only to patches, turning a free patch into an occupied patch (see Fig. 1b). By forming at most two bonds, linkers mediate bonds between monomers (see Fig. 1c). We define an aggregate as a set of monomers connected by linker-mediated bonds. In this work, we focus on the limit where the diffusion of monomers is much faster than that of aggregates, such that the latter may be neglected. We also consider that all bonds are irreversible, i.e., there is no bond breaking in the timescale of interest.
We consider that the formation of a bond is much faster than all other processes, and thus follow the kinetics by means of kinetic Monte Carlo simulations (kMC), with only three processes: translational and rotational diffusion of monomers and translational diffusion of linkers (see Fig. 1).

III. RESULTS

The model described above has four relevant parameters: the concentrations of monomers and linkers \(n_m\) and \(n_l\), respectively, and their diffusion coefficients \(D_m\) and \(D_l\), respectively. For simplicity, time can be rescaled such that the diffusion coefficient of monomers is unity, reducing the latter two parameters to a single adimensional one, the ratio of diffusion coefficients, defined as,

\[
\Delta = \frac{D_m}{D_l}.
\]

Below, we investigate first the limit of fast linkers, where \(\Delta \to 0\), and then generalize the study to any value of \(\Delta\).

A. Fast linkers (\(\Delta \to 0\))

Let us first consider the limit where linkers are much faster than monomers, i.e., \(\Delta \to 0\). We define the size of an aggregate as the number of monomers in it. In Fig. 2a is the time evolution of the size of the largest aggregate \(S_{\text{max}}\) and the average size of the aggregates \(\langle S \rangle\), obtained numerically for \(\Delta = 10^{-3}\). \(\langle S \rangle\) is defined as

\[
\langle S \rangle = \frac{N}{N_{\text{agg}} + N_{\text{mon}}},
\]

where \(N\) is the total number of monomers, \(N_{\text{agg}}\) is the number of aggregates, and \(N_{\text{mon}}\) is the number of free monomers, i.e., monomers without linker-mediated bonds. Note that for \(\langle S \rangle\) we considered also the monomers. Both parameters increase monotonically in time and saturate asymptotically, for the following reason. As monomers and linkers find each other through diffusion, free patches become occupied. When an occupied patch finds a free one, they form a linker-mediated bond between the corresponding monomers. For irreversible aggregation, the number of free monomers \(N_{\text{mon}}(t)\) is a decreasing function of time. Both the average size of the aggregates \(\langle S \rangle\) and the size of the largest aggregate \(S_{\text{max}}\) increase in time and they saturate when all possible bonds are formed. The asymptotic values of \(S_{\text{max}}\) and \(\langle S \rangle\) depend strongly on the number of linkers per patch \(\phi\),

\[
\phi = \frac{n_l}{n_m},
\]

as shown in Fig. 2b. While for \(\phi = 0.05\) all linkers form bonds to patches in the asymptotic limit, as there are more patches than linkers, for \(\phi = 0.95\) the aggregation ceases long before all linkers form a bond. Note that, for \(\phi > 0.5\), there are more linkers than needed for each patch to form a bond.

Figure 2c shows the dependence of \(\langle S \rangle\) on \(\phi\) for two values of the time. At the earliest time (triangles), \(\langle S \rangle\) is maximal for \(\phi = 0.5\), as one would expect, for it corresponds to an equal amount of free and occupied patches and therefore a maximal number of possible bonds. However, at later times (circles), one finds two maxima instead (for \(\phi_{\text{max}1} = 0.12\) and \(\phi_{\text{max}2} = 0.88\)) and \(\phi = 0.5\) is in fact a local minimum. We performed simulations for different box sizes, namely, \(L_{\text{box}} \in \{16, 25, 32, 64\}\), and observed no significant finite-size effects.

To understand the dependence on \(\phi\), let us focus on the limit where linkers are infinitely faster than monomers.
linker-monomer bonds are formed. If we neglect spatial correlation, this probability is given by the binomial distribution,

\[ d_{\text{Occ}}(O) = \binom{f}{O} \phi^O (1 - \phi)^{f-O} , \tag{4} \]

where \( \phi \) is the probability that a given patch is occupied.

Figure 4 depicts the probability distributions \( d_{\text{Occ}}(O) \) obtained from Eq. (4) and from numerical simulations at the same value of the concentration of monomers considered in Fig. 3 but with \( \Delta = 0 \), showing that for this concentration, spatial correlations are practically negligible.

Figure 5(a) shows the dependency on \( \phi \) of the asymptotic number of free monomers \( N_{\text{mon}} \) in the asymptotic limit. Lines are obtained from Eqs. (2), (5a), (7), and (8). In both a) and b), open circles are obtained from simulating the original model and filled circles are obtained from simulating the point-like model. The dashed (vertical) lines mark the local maxima and minimum corresponding to \( \phi = \{0.12, 0.50, 0.88\} \). Simulations were performed on a cubic lattice of lateral size \( L_{\text{box}} = 25 \) in units of the lattice constant, for a ratio of monomer and linker diffusion coefficients \( \Delta = 10^{-3} \) and a concentration of monomers of \( n_m = 0.01 \). Results are averages over 500 samples.

\[ \langle S \rangle = \sum_{m=0}^{\infty} m N_m P(m|\phi) , \]
boundaries that coincide with the maxima in the asymptotic $<S>$. In the regime of low $\phi$ ($\phi \in [0, 0.12]$), most monomers only have free patches and so the number of bonds equals that of linkers. Since aggregates are immobile, every new linker-mediated bond involves one monomer (at least). Thus, the monotonic decrease of $N_{\text{mon}}$ is well described by a linear dependence on $\phi$. Accordingly, $N_{\text{agg}}$ increases with $\phi$ but, since a free monomer with occupied patches can either form a bond with another free monomer or with a larger aggregate, $N_{\text{agg}}$ is sub-linear in $\phi$. By symmetry, the same is observed in the regime of large values of $\phi$ ($\phi \in [0.88, 1]$), where $N_{\text{mon}}$ increases and $N_{\text{agg}}$ decreases with $\phi$, as the number of monomers with all patches free is $(1 - \phi)^f$.

For the intermediate regime, $\phi \in [0.12, 0.88]$, all monomers form at least one bond, i.e., $N_{\text{mon}} = 0$. Thus, the average size of aggregates $<S>$ depends only on the number of aggregates, i.e., $<S> = N/N_{\text{agg}}$. Since it requires a pair of an occupied and a free patch to form a bond, a monomer with both free and occupied patches may form bonds with any other monomer. Instead, monomers with only occupied (or only free) patches cannot form bonds among each other. Note that, in Fig. 5(a), $N_{\text{agg}}$ is maximized for $\phi = 0.5$, which corresponds to the maximum number of monomers with both occupied and free patches, as given by Eq. (4). Since for $\phi = 0.5$, more than 95% of all monomers can form bonds with each other, there is a tendency to form dimers. For $\phi = 0.12$, almost 50% of the monomers have only free patches. Since those cannot form bonds among each other, they diffuse for a long time (on average) until they find a monomer (or an aggregate) with one or more occupied patches to form a bond with, what favors the growth of larger aggregates. The positions of the maxima ($\phi = (0.12, 0.88)$) correspond to the limiting values for which $N_{\text{mon}} = 0$.

Let us now develop a mean-field approach for the dynamics of the monomers, where we neglect spatial correlations and assume that the diffusion of linkers is infinitely faster than that of monomers. As discussed above, the distribution of occupied patches is given by $d_{\text{Occ}}$. We define $N_{\text{both}}(t)$ as the number of free monomers with both free and occupied patches, and $N_{\text{only}}(t)$ as the number of free monomers with only free or occupied patches. In the mean-field limit, the time evolution of these quantities is given by,

$$
\dot{N}_{\text{agg}} = q_0 N_{\text{both}} N_{\text{only}} + \frac{q_0}{2} N_{\text{both}}^2, \\
\dot{N}_{\text{both}} = -q_0 N_{\text{both}} N_{\text{only}} - q_0 N_{\text{both}}^2 - q_1 N_{\text{both}} N_{\text{agg}}, \\
\dot{N}_{\text{only}} = -q_0 N_{\text{both}} N_{\text{only}} - q_1 N_{\text{only}} N_{\text{agg}},
$$

with initial conditions,

$$
N_{\text{agg}}(0) = 0, \\
N_{\text{both}}(0) = N \sum_{n=1}^{f-1} d_{\text{Occ}}(n), \\
N_{\text{only}}(0) = N [d_{\text{Occ}}(0) + d_{\text{Occ}}(f)].
$$

The first term in Eqs. (5a)–(5c) is related to the aggregation between monomers with both occupied and free patches and monomers with only free or occupied patches. The second term in Eqs. (5a) and (5b) is related to the aggregation between monomers with both occupied and free patches. The third term in Eq. (5b) and the second term in Eq. (5c) are related to the formation of bonds between monomers and aggregates.

The absolute value of $q_0$ sets the timescale. Since we are not interested in the asymptotic behavior, without loss of generality, we consider $q_0 = 1$. We neglected also the aggregation between monomers with only occupied patches and those with only free patches, for when the number of monomers of one type is significant the number of the other is negligible. In Fig. 5, the lines for $N_{\text{agg}}$ and $<S>$ are obtained numerically from Eqs. (2) and (5a), where for $\phi \in [0.12, 0.88]$, we set $N_{\text{mon}} = 0$. The results obtained are in qualitative agreement with the results from the numerical simulations (open circles).

To write down Eqs. (5b) and (5c), we assumed that all monomers form bonds. However, this is not the case for the first and the third regimes. To obtain $<S>$ in those cases, we now consider that aggregates are treelike, such that $N_{\text{agg}} + N_{\text{mon}}$ is always reduced by one when a new bond is formed, i.e., either a dimer is formed or a monomer is added to a pre-existing aggregate. For $\phi < 0.12$ (first regime), all $L$ linkers are mediating a bond. Thus, $N_{\text{agg}} + N_{\text{mon}} = N - L$ and

$$
<S>_{\text{treelike}} = \frac{N}{N - L} = \frac{1}{1 - f\phi}, \quad \phi \leq \frac{1}{f},
$$

which diverges at $\phi = 1/f \approx 0.17$. Note that the first regime stops before that. For $\phi > 0.88$, all patches that are initially free will participate in a bond. In this case, $N_{\text{agg}} + N_{\text{mon}} = N - (Nf - L)$. In the same way, we obtain,

$$
<S>_{\text{treelike}} = \frac{N}{N - (Nf - L)} = \frac{1}{1 - f(1 - \phi)} \frac{f - 1}{f} < \phi.
$$

Figure 5 shows that Eqs. (7) and (8) (lines) reproduce quantitatively the dependence of the average size of the aggregates on $\phi$ for the first and third regimes. The intersections of $<S>_{\text{treelike}}$ with the prediction for the second
regime, in Eq. [5a], coincides with the limits of the different regimes obtained numerically. Thus, in spite of its simplicity, our mean-field approach describes qualitatively the average size of the aggregates for the three different regimes and quantitatively for the first and the third regimes. For the second, the mean-field approach predicts a larger number of aggregates and (consequently) smaller aggregates than observed numerically (open circles in Fig. 5).

To understand the discrepancies observed in the second regime, we discuss now the role of the shape of the aggregates. Studies in irreversible aggregation often report non-compact structures [20, 44]. In general, the shape of the aggregates should also depend on \( \phi \). We now consider a point-like lattice model, where we neglect the shape of the aggregates, i.e., each aggregate occupies a single lattice site. Accordingly, every patch in an aggregate (either free or occupied) is equally likely to form a bond with a monomer/linker. Thus, when a linker and a monomer or an aggregate try to occupy the same lattice site while diffusing, they form a bond with a probability given by,

\[
p_{\text{LM}} = \frac{F}{F + O},
\]

where \( F \) and \( O \) are the number of free and occupied patches of the aggregate, respectively. Also, when a monomer \( i \) hops to a lattice site that is occupied by an aggregate \( j \), they form a bond with a probability,

\[
p_{\text{MM}} = \frac{F_i O_j + F_j O_i}{(F_i + O_i)(F_j + O_j)},
\]

where \( \{F_i, O_i\} \) and \( \{F_j, O_j\} \) are the number of free and occupied patches of \( i \) and \( j \), respectively. The numbers of free and occupied patches of the resulting aggregate \( (F_{\text{final}} \text{ and } O_{\text{final}}, \text{ respectively}) \) are then

\[
F_{\text{final}} = F_1 + F_2 - 1,
\]

\[
O_{\text{final}} = O_1 + O_2 - 1.
\]

Note that we consider that all aggregates are treelike (no loops).

The numerical results for the point-like model are shown also in Fig. 5 (filled circles). There is a remarkable quantitative agreement between the point-like and the mean-field calculation. This suggests that the deviations from the mean-field behavior for the second regime are due to the size of the aggregates.

**B. Dependence on the linker diffusivity**

So far, we have considered \( \Delta \to 0 \) and assumed a separation of timescales between the diffusion of linkers and the one of monomers. However, above a certain value of \( \Delta \), these two mechanisms should compete and therefore the assumption is no longer reasonable. We now discuss the behavior of the average size of the aggregates \( \langle S \rangle \) for different values of \( \Delta \) in a range covering six orders of magnitude \((10^{-3}, 10^{3})\). The first remarkable observation is that the positions of the two maxima \( \phi_{\text{max1}} \) and \( \phi_{\text{max2}} \) and that of the minimum \( \phi_{\text{min}} \) do not vary significantly with \( \Delta \) (not shown). Also, for low values of \( \Delta < 10^{-2} \), \( \langle S \rangle \) is constant and consistent with the mean-field value (see Fig. 6). But, as \( \Delta \) increases, the differences between the optimal and the (local) minimum value of \( \langle S \rangle \) decrease and, for \( \Delta > 10 \), they are indistinguishable.

A monomer-monomer bond is always preceded by the formation of a linker-monomer bond. As discussed in the previous section, for low values of \( \Delta \), the diffusion of linkers is much faster than the one of monomers, thus all possible linker-monomer bonds are formed in a timescale that is much faster than that of the diffusion of monomers. For large values of \( \Delta \), since aggregates are immobile, and monomers are much faster than linkers, it is also more likely that a free linker forms a bond to a free monomer rather than to an immobile aggregate. In the same way, it is more likely that the next monomer-linker bond leads to the formation of a new immobile aggregate than to the growth of a pre-existing one. This competition promotes the growth of the number of aggregates rather than their size. That is why, for all values of \( \phi \) considered in Fig. 6 we observe a monotonic decrease of \( \langle S \rangle \) with \( \Delta \).

In Fig. 6 it is clear that, for \( \phi_{\text{max1}} \), the regime of fast linkers \((\Delta \to 0)\) is valid for a larger range of values of \( \Delta \) than for \( \phi_{\text{max2}} \). In the case of \( \phi_{\text{max1}} \), every linker mediates a monomer-monomer bond (asymptotically). Thus, it is only when the diffusion of monomers is comparable to the diffusion of linkers \((\Delta \approx 1)\) that the formation of linker-monomer bonds competes with the formation
of the next monomer-monomer bond. For \( \phi_{\text{max}}^2 \), this competition becomes relevant at lower values of \( \Delta \) for the following reason. When \( \Delta \ll 1 \) (see previous section), all linkers form linker-monomer bonds promptly and the dynamics of monomer-monomer bonds is controlled by the few monomers with free patches. Thus, the number of pairs of monomers that can form a new aggregate is reduced as \( \phi \) increases, what promotes the growth of immobile aggregates. As \( \Delta \) increases, the formation of linker-monomer bonds competes with the one of monomer-monomer bonds. The larger is the value of \( \Delta \), the more likely it is that, a monomer with occupied patches forms a monomer-monomer bond before all its patches are occupied. This process favors the formation of new aggregates over the growth of pre-existing ones.

IV. CONCLUSION

We studied the dynamics of irreversible aggregation mediated by linkers. In the limit of linkers much faster than monomers, we report a bimodal dependence of the average size of the aggregates on the ratio of the concentrations of linkers and monomers, with two maxima appearing at non-trivial values. This behavior appears at long times, being preceded by a transient regime in which the average size of the aggregates is maximized when the concentration of linkers is half that of the patches. With a mean-field approach we have shown that the two maxima appear when the number of free monomers vanishes asymptotically. This simple approach describes qualitatively and quantitatively the results obtained numerically. The deviations from the mean-field behavior result from effects due to the shape and size of the aggregates that are neglected in the theoretical description.

We investigated also the dependence on the diffusion coefficient of linkers and monomers. We found that the two maxima disappear when the diffusion of linkers is comparable to that of monomers (or even lower). This effect results from the competition between the formation of linker-monomer and monomer-monomer bonds.

For simplicity, we considered only irreversible aggregation and immobile aggregates. However, these two mechanisms are expected to play a role, at least on much longer timescales. Future studies might consider the effects of both. The symmetry of the results is an artefact of the model and in more realistic settings is not expected to occur. However, the mechanisms are general and do not rely on a particular symmetry and thus the effects reported here are expected to be observed in more realistic, including off-lattice, models and in experiments.

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[27] J. M. Tavares, P. I. C. Teixeira, and M. M. Telo da Gama, Phys. Rev. E 81, 010501 (2010).
[28] D. Joshi, D. Bargtei, A. Caciagli, J. Burelbach, Z. Xing, A. S. Nunes, D. E. P. Pinto, N. A. M. Araújo, J. Bruijc, and E. Eiser, Sci. Adv. 2, e1600881 (2016).
[29] A. L. Margolin, J.-Y. Crenne, and A. M. Klibanov, Tetrahedron Letters 28, 1607 (1987).
[30] J. S. Dordick, M. A. Marletta, and A. M. Klibanov, Biotechnol. Bioeng. 30, 31 (1987).
[31] D. R. Patil, J. S. Dordick, and D. G. Rethwisch, Macromolecules 24, 3462 (1991).
[32] K. S. Bisht, L. A. Henderson, R. A. Gross, D. L. Kaplan, and G. Swift, Macromolecules 30, 2705 (1997).
[33] B. Bharti, J. Meissner, S. H. L. Klapp, and G. H. Findenegg, Soft Matter 10, 718 (2014).
[34] J. Chen, S. R. Kline, and Y. Liu, J. Chem. Phys. 142, 084904 (2015).
[35] C. J. Cyron, K. W. Müller, K. M. Schmoller, A. R. Bausch, W. A. Wall, and R. F. Bruinsma, EPL 102, 38003 (2013).
[36] B. A. Lindquist, R. B. Jadrich, D. J. Milliron, and T. M. Truskett, J. Chem. Phys. 145, 074906 (2016).
[37] J. Luo, G. Yuan, C. Zhao, C. C. Han, J. Chen, and Y. Liu, Soft Matter 11, 2494 (2015).
[38] K. W. Müller, R. F. Bruinsma, O. Lieleg, A. R. Bausch, W. A. Wall, and A. J. Levine, Phys. Rev. Lett. 112, 238102 (2014).
[39] J. Peng, A. Kroes-Nijboer, P. Venema, and E. van der Linden, Soft Matter 12, 3514 (2016).
[40] J. Zhang, E. Luijten, and S. Granick, Annu. Rev. Phys. Chem. 66, 581 (2015).
[41] K. Aran, L. A. Sasso, and J. D. Zahn, Lab Chip 10, 548 (2010).
[42] W. C. Yount, D. M. Loveless, and S. L. Craig, Journal of the American Chemical Society 127, 14488 (2005).
[43] S. Chandrasekhar, Rev. Mod. Phys. 15 (1943).
[44] P. Meakin, Phys. Rev. Lett. 51, 1119 (1983).