Dynamic feedback in an aggregation-disaggregation model

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We study an aggregation-disaggregation model which is relevant to biological processes such as the growth of senile plaques in Alzheimer disease. In this model, during the aggregation each deposited particle has a probability of producing a new particle in its vicinity, while during disaggregation the particles are annihilated randomly. The model is held in a dynamic equilibrium by a feedback mechanism which changes the disaggregation probability in proportion to the change in the total number of particles. We also include surface diffusion which influences the morphology of growing aggregates and colonies. A colony includes the descendants of a single particle. We investigate the statistical properties of the model in two dimensions. We find that unlike the colonies, individual aggregates are fractals with a fractal dimension of $D_f = 1.92 \pm 0.06$ in the absence of surface diffusion. We show that the surface diffusion changes the fractal dimension of aggregates: at a small aggregation-disaggregation rate, $D_f$ is independent of the strength of the surface diffusion, $D_f = 1.73 \pm 0.03$. At larger aggregation-disaggregation rates and different strengths of surface diffusion, aggregates with fractal dimensions between $D_f = 1.73$ and $1.92$ form. The steady-state distribution of aggregate sizes is shown to be power law if the aggregation-disaggregation process dominates over the surface diffusion. In the limit of weak aggregation-disaggregation and strong surface diffusion the size distribution is log-normal.

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I. INTRODUCTION

Pattern formation and fractal growth phenomena in physics have attracted much attention in recent years [1,2]. Physical pattern formation phenomena have many interesting analogies in biological systems that are usually too complex to be described in terms of simple equations [3]. Although biological growth involves biochemical reactions, transport and production, the specific processes that underlie biological growth and its rate are unknown. In part this is because the essential processes that give rise to a particular structure of a growing aggregate cannot be examined directly. Rather, lattice models [4,5] are used to mimic the essential features of the observed growth patterns [6]. Accurate modeling of the growth in turn sheds light on the possible biochemical mechanisms that govern the phenomena, and contributes to a deeper understanding of biological morphogenesis and evolution.

In this paper we study a model motivated by the growth of senile plaques in the cortex of the brain of Alzheimer patients [7]. It is well known that Alzheimer disease is associated with senile plaques, macroscopic aggregates of amyloid-$\beta$ (A$\beta$) protein of 40-42 amino acids in length. Our approach to the modeling of plaque formation is based on several experimental observations. Although the precursor peptide A$\beta$ is produced uniformly throughout the cortex of the brain, the aggregated A$\beta$ deposits are anatomically discrete, roughly spherical aggregates of A$\beta$ fibrils. The amount of A$\beta$ deposits is not correlated with the duration or the severity of the disease [8,9]. This observation suggests that after the onset of the disease the process of plaque formation reaches a dynamic equilibrium. Computerized image analysis has shown that the size distribution of A$\beta$ senile plaques can be well fit to a log-normal distribution [10]. Finally, recent quantitative analysis of confocal micrographs of senile plaques in three dimensions has revealed their very specific porous structure [11].

In order to answer the question of what kind of mechanisms produce such porous morphology at equilibrium, we consider general principles of aggregation. Mechanisms which are responsible for the growth should depend on the diffusion constant of A$\beta$ as compared to its aggregation rate. If the diffusion is slower than aggregation, an aggregate with a ramified treelike structure is formed that belongs to a diffusion limited aggregation (DLA) universality class [12]. If the diffusion is faster than aggregation, a compact spherical structure is formed, which belongs to the Eden universality class [12]. These two models are limiting cases of a more general finite-diffusion-length model [13] that also predicts DLA-like nonfractal structures. The DLA and Eden models are essentially mimicking nonequilibrium phenomena, which is in disagreement with dynamic equilibrium. The DLA model can be modified into an equilibrium process by introducing disaggregation [14]. However, the resulting aggregates have a smaller fractal dimension than DLA aggregates, and are thus appropriate to describe branched-polymer configurations but not the observed porous senile plaques. There are also cluster-cluster aggregation (CCA) models [1], based on DLA, that can be modified into equilibrium growth models by introducing sources and sinks [15] (steady-state CCA) or by allowing aggregates to break (reversible CCA) [16]. However, the morphologies of the resulting aggregates are

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highly ramified, exhibiting fractal properties. Moreover, since plaque aggregation in the brain is believed to be a slow process on a time scale of years as opposed to a much faster diffusion, the models of the DLA type are unlikely to be directly relevant to the growth of \(\beta\beta\) plaques.

Our approach to modeling senile plaque formation is based on the birth-death type of aggregation models that are generally used for studying the dynamics of populations, epidemics [17], chemical reactions with creation and annihilation processes [18], and even evolution through mutations [19]. Our model, based on aggregation and disaggregation, is modified in such a way that it accounts for both a dynamic equilibrium and a specific porous structure of the observed senile plaques [11]. The disaggregation process is natural to postulate, since recent experiments suggest that certain biochemical processes that give rise to \(\beta\beta\) aggregation and potentially trigger reversal of \(\beta\beta\) aggregate [20].

The model is introduced in Sec. II. In order to achieve the growth at a dynamic equilibrium, we introduce a feedback mechanism into our model. The disaggregation process is modified at each simulation step such that it accounts for both a dynamic equilibrium and a specific porous structure of the observed senile plaques [11]. The disaggregation process is natural to postulate, since recent experiments suggest that certain agents in the brain interfere with \(\beta\beta\) aggregation and potentially trigger reversal of \(\beta\beta\) aggregate [20].

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The model is based on two processes, aggregation and disaggregation. At each simulation step the rules for aggregation and disaggregation are applied to each particle in the lattice, thus mimicking the time evolution of particles. The whole growth process can thus be viewed as an example of a birth-and-death branching process [22,23]. Although a particle in our terminology means an aggregate composed of many \(\beta\beta\) molecules, it is, on the other hand, much smaller compared to a fully evolved senile plaque. One can think of a particle as a fibril of amyloid \(\beta\) peptides as experimentally observed in vitro [24]. We are not modeling the microscopic biochemical processes that give rise to \(\beta\beta\) fibrils, but we take them as basic to our explanation of the anatomical experimental observations of \(\beta\beta\) deposits. In this sense our model is phenomenological ("coarse grained") and not microscopic.

A. Aggregation-disaggregation process

We study the model on a two-dimensional discrete lattice. Each lattice site is either empty or occupied by a particle. For each particle we first decide with equal probabilities, \(\frac{1}{2}\), which rule, either for aggregation or disaggregation, will be applied.

(i) If a particle is chosen to aggregate at a time step \(t\), it has a certain aggregation probability \(P_{agg}\) to create a new particle in the next time step \(t+1\) at some empty site in its vicinity; otherwise nothing happens. The new particle performs a random walk from the original particle site in the lattice until it encounters the first vacant site, where it is attached. In this way every particle in the lattice has an equal probability to create a new particle; thus the growth is uniform.

(ii) If the disaggregation rule applies, the particle will be annihilated with the disaggregation probability \(P_{dis}\) at the time step \(t+1\).

Since the rules defining the growth model are independent of the local geometry of the growing aggregates, we can relate the number of particles \(N_{t+1}\) at time \(t+1\) with the number of particles \(N_t\) at time \(t\):

\[
N_{t+1} = N_t + \frac{1}{2}(P_{agg} - P_{dis})N_t.
\]

The factor of \(\frac{1}{2}\) comes from the fact that on average half of the particles follow the aggregation rule and the other half the disaggregation rule. We have to emphasize that Eq. (1) applies only on average, it is thus a "mean-field" equation. The solution of the above recursion relation [Eq. (1)] is

\[
N_t = N_0 \left(1 + \frac{P_{agg} - P_{dis}}{2}\right)^t.
\]

For \(P_{agg} > P_{dis}\) the number of particles increases exponentially, while for \(P_{agg} < P_{dis}\) it decreases exponentially. Starting from a given configuration of particles, the system, according to Eq. (1), reaches equilibrium if \(P_{agg} = P_{dis}\). In the parameter space \((P_{agg} versus P_{dis})\), \(P_{agg}^* = P_{dis}\) is the critical line.

We can use a theory of branching processes [22] to calculate what happens to the descendents of one particle after \(t\) time steps at the critical point, \(P_{dis} = P_{agg}\). We define a probability \(P_{N,t}\) such that after \(t\) steps we end up with \(N\) descendents of the initial particle. We create a generating function \(g_t(x)\),

\[
g_t(x) = \sum_{N=0}^{\infty} x^N P_{N,t},
\]

which is by definition normalized such that \(g_t(x = 1) = 1\). By taking into account three possible outcomes for each particle from the time step \(t\) to the time step \(t+1\), we can express \(g_{t+1}(x)\) in terms of \(g_t(x)\) through the recursion relation

\[
g_{t+1}(x) = \frac{P_{dis}}{2} + \left(1 - \frac{P_{agg} + P_{dis}}{2}\right)g_t(x) + \frac{P_{agg}}{2}g_t^2(x).
\]

For \(P_{dis} = P_{agg}\) it is possible to show [22] that the solution is

\[
g_t(x) = 1 - \frac{2}{P_{agg}^t} + \frac{4}{P_{agg}^2} \sum_{N=1}^{\infty} \exp\left[-\frac{2N}{P_{agg}^t}\right] x^N \left(1 \right)_{\frac{1}{2}}.
\]

For \(x = 1\), the term with the sum in the Eq. (4) represents a probability that after \(t\) steps there will be one or more descendents of the original particles. The probability that after
t steps the number of descendents will be zero is equal to $1 - 2(P_{agg}t)$. Thus asymptotically at large $t$ the probability of having zero descendents of one particle goes to 1. Note that the generating function given by Eq. (4) consists of two parts, one corresponding to $N=0$ and the other corresponding to $N \geq 1$. This latter part is analytical, and, as we show in the Appendix, can be derived from the Fokker-Planck equation.

Knowing the probabilities $P_{N,t}$, we can calculate the moments $\langle N \rangle$ and $\langle N^2 \rangle$. As expected, $\langle N \rangle = 1$, meaning that on average we expect that the number of descendents is 1. On the other hand, $\langle N^2 \rangle = P_{agg}t$. This means that the standard deviation of the distribution $P_{N,t}$ at large times grows as $\sqrt{t}$.

If we start with $N_0$ original particles at $P_{dis} = P_{agg}$, the probability of having zero particles after large $t$ is $[1 - 2(P_{agg}t)]^{N_0} = 1 - 2N_0/P_{agg}t$. This probability is thus increasing with time, although the average number of particles remains the same, equal to $N_0$. We therefore showed that for any finite system of initial particles, even at the critical point ($P_{dis} = P_{agg}$), the model as defined above is unstable due to fluctuations and will eventually yield an empty lattice.

**B. Dynamic feedback**

The model defined in Sec. II A is unstable: regardless of the initial state and regardless of the number of particles for aggregation and disaggregation $P_{agg}$ and $P_{dis}$ are chosen, the system either dies or grows until the whole lattice is fully covered by particles. In order to be able to describe a dynamical system with both processes at equilibrium, it is necessary to introduce a feedback mechanism that pushes the system toward equilibrium. The importance of the feedback mechanism has been recognized in other cellular automata models, in particular in self-organized critical models where feedback plays the role of a restoring force that drives the system back to the dynamical critical point [25].

One way to introduce a feedback mechanism is to specify the average number of particles in the steady state $N_f$, and to modify $P_{dis}$ at each step according to

$$P_{dis}(t+1) = P_{dis}(t) + W(N_f - N_f)/V,$$

where $W$ is a feedback parameter and $V$ is the total number of lattice sites, so that $N_f/V$ is the concentration of particles in the steady state.

In order to find the approximate asymptotic behavior of the model with the feedback defined by Eq. (5), we replace the difference $N_{f+1} - N_f$ in Eq. (1) by $dN_f/dt$, and the difference $P_{dis}(t+1) - P_{dis}(t)$ by $dP_{dis}(t)/dt$, and then assume that, as $t \to \infty$, $N_f = N_f + x$ and $P_{dis} = P_{agg} + y$. For small $x$ and $y$, we can linearize Eqs. (1) and (5) and find

$$x = \Delta N \cos \omega t,$$

where $\Delta N$ is an amplitude that depends on the initial conditions and $\omega = \sqrt{WN_f/(2V)}$. As we can see, the feedback defined by Eq. (5) yields an oscillatory behavior of the system which is difficult to justify in biological growth (see Fig. 1).

We therefore adopt another type of feedback, one that changes the disaggregation probability in proportion to the change in the total number of particles,

$$\frac{dN_f}{dt} = aN_f - bN_f^2,$$
with the constants $2a = P_{\text{agg}} - P_{\text{dis}}(0) + wN_0/V$ and $2b = w/V$. The initial value of the disaggregation probability is denoted by $P_{\text{dis}}(0)$ and the initial number of occupied sites by $N_0$. Denoting the asymptotic solution (as $t \to \infty$ and $dN_t/dt = 0$) by $N_\infty = a/b$, the time dependence of $N_t$ is given by

$$N_t = \frac{N_\infty}{1 + [(N_\infty - N_0)/N_0] \exp(-at)}.$$  \hspace*{1cm} (9)

If $N_0 \ll N_\infty$ and $N_t \ll N_\infty$, for a short time the number of particles grows exponentially, as in the absence of feedback. At longer times, the feedback inhibits further growth and the growth process reaches a dynamic equilibrium with the average number of particles $N_\infty$ conserved over time. The simulations shown in Fig. 1 are in good agreement with Eq. (9). As shown in Fig. 1, the approximate solution (thick solid line) approaches the exact asymptotic value and is close to the solution found by simulations (open triangles) at all times.

As for the average number of particles $N_t$ as $t \to \infty$, there is no difference between the model in the absence of the feedback at $P_{\text{dis}} = P_{\text{agg}}$ and the model with the feedback defined by Eq. (7). However, there is an essential difference regarding the fluctuations of the number of particles around its “mean-field” asymptotic value, $N_\infty$, as presented in the Appendix. While without feedback the standard deviation of the number of particles increases with time, in the presence of the feedback defined by Eq. (7) the distribution of the number of particles around the mean value $N_\infty$ can be approximated by a Gaussian distribution with a time-independent width. Moreover, the width can be varied by changing the feedback parameter $w$.

### C. Surface diffusion

For a typical biological tissue there is always “surface tension” which suppresses random spatial fluctuations along the edges of the aggregate [4]. Algorithms for boundary smoothing are well known also in the field of the surface growth as noise-reduction methods [26].

We implement the surface diffusion in the following way: After each step of aggregation and disaggregation (one step in our terminology means that every particle in the lattice is exposed to the rules of the model), each particle has a probability of moving one step in a randomly chosen direction if and only if after the move the particle ends up with more nearest neighbors. In this way particles that are totally surrounded by other particles do not move, whereas the isolated particles tend to “find a better environment,” i.e., an environment with more occupied nearest neighbors. The strength of the surface diffusion $J$ can be varied by the number of times that all the occupied sites in the lattice make such a step.

The influence of the surface diffusion on the morphology of a growing colony of aggregates is presented in Figs. 2(a) (no surface diffusion) and 2(b) (with surface diffusion, $J = 20$).

### III. Statistical Properties of the Model

There is an inherent difference between aggregation and disaggregation processes, even though the two processes are at equilibrium due to the feedback. There is an overall larger probability for larger aggregates to grow in time or, conversely, a smaller probability for isolated particles to survive too far away from a larger aggregate. This causes clustering of aggregates into larger formations which are dynamically stable as simulation time $t \to \infty$ [27]. Thus, no matter what the initial configuration is, either randomly distributed particles or a solid disk of particles, the system always evolves into a dynamical steady state which is one clustered colony, composed of many connected objects, aggregates, as shown in Figs. 2(a) and 2(b).

We want to examine statistical properties of the model, such as the fractal dimension of aggregates and colonies, the rate of colony growth and the size distribution of aggregates within a colony. The theory of branching processes is appropriate to predict a “mean-field” behavior of the aggregation-disaggregation behavior, but it is not able to account for any
presented in an inset of the Fig. 3.

dashed lines in Fig. 3

plotted in Fig. 3

0.50

5

3

5

2

0.90, and

5

50 pixels on a 2D lattice of size 2048

5

(512, 512, P_{agg}=P_{dis}(t=0)=0.10, and w=2]. The dotted lines have slopes of 0.50±0.05. The curves are averaged over ten runs. The inset of the figure shows the scaling of the number of particles \( N \) within a colony with its radius of gyration \( R_g \). (b) The effect of the surface diffusion on the fractal dimension \( D_f \) of aggregates (connected clusters that form a colony) in dependence on the simulation time. The solid line is a linear fit to \( D_f(t) \) in the absence of diffusion \((J=0)\), while the dashed line is a linear fit to \( D_f(t) \) for \( J=1, 10, \) and 100 [the lattice size is 512 \( \times 512, P_{agg}=P_{dis}(t=0)=0.10, \) and \( w=2 \)].

FIG. 3. (a) The effect of surface diffusion on the time dependence of the colony growth: the radius of gyration \( \langle R^2 \rangle^{1/2} \) of a colony. The initial configuration is a solid disk with a radius \( R = 50 \) pixels on a 2D lattice of size 2048 \( \times 2048 \) \( [P_{agg}=P_{dis}(t=0)=0.90, \) and \( w=2]. \) The dotted lines have slopes of 0.50±0.05. The curves are averaged over ten runs. The inset of the figure shows the scaling of the number of particles \( N \) within a colony with its radius of gyration \( R_g \). (b) The effect of the surface diffusion on the fractal dimension \( D_f \) of aggregates (connected clusters that form a colony) in dependence on the simulation time. The solid line is a linear fit to \( D_f(t) \) in the absence of diffusion \((J=0)\), while the dashed line is a linear fit to \( D_f(t) \) for \( J=1, 10, \) and 100 [the lattice size is 512 \( \times 512, P_{agg}=P_{dis}(t=0)=0.10, \) and \( w=2 \)].

geometrical properties of growing aggregates, neither morphology, nor the rate of growth, nor their size distribution.

A. Morphology of colonies and aggregates

Figure 2 shows individual colonies grown in the model: One colony is grown in the absence of the surface diffusion and the other in the presence of the surface diffusion. We can see that the surface diffusion changes the morphology of the colonies and aggregates by smoothing the surfaces of clusters.

The time development of the radius of gyration \( \langle R^2 \rangle^{1/2} \) is plotted in Fig. 3(a) for short times, i.e., before the colony reaches the steady-state size. From the graph [solid and dashed lines in Fig. 3(a)] we can extract the exponent of the growth of the radius \( \langle R^2 \rangle^{1/2} \); \( \langle R^2 \rangle^{1/2} \) grows as \( t^\nu \), where \( \nu = 0.50±0.05 \), corresponding to a normal diffusion rate. The results show that the presence of the surface diffusion has no influence on the exponent \( \nu \). The scaling of the number of particles \( N \) in a colony with the radius of gyration \( R_g \) is presented in an inset of the Fig. 3(a). The scaling is close to

\[ N \sim R_g^2 \], meaning that the whole colony scales as a nonfractal two-dimensional object.

On the other hand, the geometrically connected objects (aggregates) that form a colony have fractal properties. The radius of gyration of an aggregate, \( r_g \), scales with the size of the aggregate \( S \) (\( S \) is equal to the number of particles that form the aggregate) as \( r_g \sim S^{1/d_f} \), where \( D_f \) is a fractal dimension. In the absence of the surface diffusion \((J=0)\), \( D_f = 1.92±0.06 \), independent of the aggregation-disaggregation rate. As shown in Fig. 3(b), at a small aggregation-disaggregation rate \( P_{agg}=(P_{dis})=0.10 \), \( D_f = 1.73±0.02 \) for the model with surface diffusion, independently of the strength of the surface diffusion \( J \). For a large aggregation-disaggregation rate \( P_{agg}=(P_{dis})=0.90 \), \( D_f \) depends on the strength of the surface diffusion \( J \); at \( J = 1 \), we find \( D_f = 1.88±0.05 \), and at \( J = 100 \) our results yield \( D_f = 1.81±0.05 \). Thus by an appropriate choice of the aggregation-disaggregation rate and the strength of the surface diffusion, the aggregates in our model can have any fractal dimension between \( D_f = 1.73 \) and 1.92.

B. Distribution of aggregate sizes

Figures 4(a) and 4(b) show the steady-state size distributions of aggregates for various surface diffusion strengths \( J \) and for two different aggregation-disaggregation probabilities; (a) corresponds to low and (b) to high probabilities. There are two limiting cases. At low aggregation-disaggregation probabilities and high surface diffusion [Fig. 4(a)], the distribution can be well approximated by a log-normal form. At high aggregation-disaggregation probabilities and in the absence of surface diffusion, the size distribution suggests a power-law behavior with the exponent \( \sim 1.79±0.05 \). As one can notice, the effect of the surface diffusion on the power-law behavior of the distribution is not significant in this limiting case. However, at small aggregate sizes the power-law distribution is somewhat flattened out, meaning that there are fewer small aggregates in the system.

In percolation [28] the size distribution of percolating clusters is a power-law distribution, as well as in our limiting case of high aggregation-disaggregation probabilities and no surface diffusion. We define the size distribution exponent \( \tau \),

\[ D(S) \sim S^{-\tau}. \]  

According to the theory [1], there is a relationship between the fractal dimension \( D_f \) and \( \tau \),

\[ \tau = 1 + \frac{d}{D_f}, \]

where \( d \) is the lattice dimension, in our case \( d = 2 \). The prediction for \( \tau \) from the scaling relation given by Eq. (10) is thus \( \tau = 2.04 \) (here we take into account our result for the fractal dimension \( D_f = 1.92 \)). This value is, however, slightly different from the one from our simulation, \( \tau = 1.79 \). This can be due to finite size effects: It is known that the simulations consistently yield a too small value for \( \tau \) (very close to \( \tau = 1.79 \)) unless the lattice size is very large (linear size close to 100,000), in which case the theoretical value for \( \tau = 2.04 \) [28] can be achieved.
different from that of DLA. Quantitative analysis of the distribution of aggregate sizes shows that, depending on parameters of the model, the steady-state size distribution of aggregates changes from a power-law distribution (high aggregation-disaggregation probabilities and no surface diffusion) to a log-normal distribution (the surface diffusion dominates over the aggregation-disaggregation process).

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APPENDIX: PROBABILITY DISTRIBUTION OF THE NUMBER OF PARTICLES

Here we derive the steady-state probability distribution of the number of particles in the presence of the feedback defined by Eq. (7). As opposed to an average ("mean-field") number of particles at a time step $N_i$, we consider a new statistical variable for the number of particles at the time $t$, $\mathcal{N}(t)$, a continuous function of $t$, which is allowed to fluctuate from its mean-field value $N_i$.

We consider the system at the critical point, $P_{agg} = P_{dis}$. Every particle in the system has a probability $P_{agg}/2$ of creating a new particle, the same probability of being annihilated, and the probability $1 - P_{agg}$ of remaining unchanged. Thus for each particle $i$ in the system at every time step there are three possible outcomes that affect the total number of particles $\mathcal{N}(t)$:

$$\Delta N_i = \begin{cases} 1 & \text{with probability } P_{agg}/2 \\ -1 & \text{with probability } P_{agg}/2 \\ 0 & \text{with probability } 1 - P_{agg} \end{cases}$$

(A1)

The square of the width of the distribution of $\Delta N_i$, given by Eq. (A1), $\sigma_i^2$, is then equal to $\sigma^2 = P_{agg}$. For the total number of particles $\mathcal{N}$ the square of the width of the distribution $\sigma^2$ is then $\sigma^2 = P_{agg} \mathcal{N}$ (since $\Delta N = \sum_i \Delta N_i$).

Starting from the mean-field equation given by Eq. (8), we can write a master equation for $\mathcal{N}(t)$,

$$\frac{d\mathcal{N}}{dt} = a\mathcal{N} - b\mathcal{N}^2 + \eta \sigma,$$

(A2)

where $\eta$ is a random variable which is distributed according to Gaussian distributions $P(\eta) = 1/\sqrt{2\pi \exp(\eta^2/2)}$ and $\sigma = \sqrt{P_{agg} \mathcal{N}}$.

The Fokker-Planck equation for the probability distribution of the number of particles, $P(\mathcal{N},t)$, which corresponds to Eq. (A2), is then

$$\frac{\partial P}{\partial t} = \frac{1}{2} \frac{\partial^2}{\partial \mathcal{N}^2} [\sigma^2 P] - \frac{\partial}{\partial \mathcal{N}} \left[ P(a\mathcal{N} - b\mathcal{N}^2) \right].$$

(A3)

We only focus on a steady-state solution ($\partial P/\partial t = 0$) of Eq. (A3) around the mean value $\langle \mathcal{N} \rangle = N_0 = alb$. By defining a new variable $x = \mathcal{N} - N_0 = N - alb$ and by approximating $\sigma^2$ by its mean-field value $\sigma^2 = P_{agg} N_0$, Eq. (A3) transforms into...
\[
\frac{d^2 P}{dx^2} + \gamma x \frac{dP}{dx} + \gamma P = 0,
\]
where \(\gamma = 2b/P_{agg}\). The solution of Eq. (A4) is
\[
P(N) = A \exp \left[ -\frac{(N-N_0)^2}{P_{agg}/b} \right],
\]
where \(A\) can be determined by normalization. Under the approximations made, the distribution given by Eq. (A5) is Gaussian with the standard deviation \(\sigma_p\),

\[
\sigma_p = \sqrt{\frac{P_{agg}V}{w}}.
\]

where we took into account that \(b = w/2V\). This result shows that the stronger the feedback parameter \(w\), the smaller will be the fluctuations of the number of particles \(N\) around the average mean-field value \(N_0\).

On the other hand, in the absence of the feedback, \(a = b = 0\), the Fokker-Planck equation given by Eq. (A3) does not have a stable steady-state solution. However, by solving the time-dependent Fokker-Planck equation, we obtain the result which is consistent with the one given by the generating function in Eq. (4), except for the diverging part corresponding to \(N = 0\) that cannot be covered by such a continuous differential approach.

[6] If detailed interactions among particles forming aggregates, as well as the temperature and chemical potentials of the aggregate and the surrounding liquid, are known, lattice models could be replaced by a standard Monte Carlo simulation approach.
[21] We define an aggregate as an object consisting of particles which are connected to each other by at least one of the eight nearest neighbors in a square lattice. A colony is a group of aggregates which descend from the same original particle or aggregate.