Electronic Supplementary Material (ESI) for Soft Matter.

Supplementary Information for: Mechanism for the stabilization of protein clusters above the solubility curve

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I. SOLUTION OF THE DDFT EQUATIONS

As stated in the main text, we began our calculations by locating the critical cluster for the pure dimer system. We then make this supercritical by increasing its radius using the algorithm $n_2(r) = n_2(\max(0, r - \Delta R))$. Then, there are two methods used to add the monomers. For clusters that subsequently grow, it is sufficient to simply add a uniform background of monomers with the desired density. However, in the reported runs in which we create an over-sized cluster that then shrinks, we used as a rough guess as to the final monomer distribution $n_1(r) = \max\left(0, n_1^{(\infty)} + n_2^{(\infty)} - n_2(r)\right)$ which is to say that their density is chose so as to keep the sum of densities as close as possible to that in the background. This is because when the clusters began over-sized and the monomers were introduced as a uniform background, we found they were not expelled from the cluster, presumably because the cluster is, at the same time, expelling dimers as well. Instead, a small fraction of monomers end up sequestered in the center of the cluster forming its core and surrounded by a thick layer of dimers. In reality, the clusters should begin small and grow so we consider this behavior to be an artifact of beginning with an unrealistic initial condition and therefore used the alternative initial condition to suppress it.

The numerical solution of the DDFT equations was performed by discretizing the radial coordinate as $r_i = (i + 0.5)\delta$ for $i = 0, ..., N-1$. For the results reported in the text, $N = 1000$ points were used with increment $\delta = 0.2$ giving a maximal radius of about 200 units. We followed the Crank-Nicholson semi-implicit scheme for the diffusional term and treated the reaction terms explicitly. The two density fields were taken to be defined at times $t_i = i\tau$ for the monomers and at times $t_i = (i + 0.5)\tau$ for the dimers. This leapfrog scheme meant that when solving the equation for the monomers, the dimers did not have to be treated implicitly and vice versa. For the spatial boundary condition, we assumed the density followed the stationary solution of the diffusion equation, $n(r) = n_\infty + r_{N-1}(n(r_{N-1}) - n_\infty)/r$ which therefore gives the required value of n_N to close the numerical equations. The explicit form of the discretization can be found in Ref. 1.

II. GROWTH OF SUPERCRITICAL DROPLET IN A SINGLE COMPONENT SYSTEM

A test of the conformity of the microscopic model and the capillary theory model is the growth of a super-critical droplet in an oversaturated, single component system. The prediction of the capillary approximation is that

$$\frac{dR}{dt} = -\frac{D n_2^{(\infty)}}{\left(n_2^{(0)} - n_2^{(\infty)}\right)^2 4\pi R^3} \frac{\partial \beta \Delta\Omega(R)}{\partial R} \tag{1}$$

where D is the diffusion constant for a dimer molecule and $\Delta Omega(R)$ is the excess grand canonical free energy for the cluster with radius R and $\beta = 1/k_B T$ with T the temperature and k_B Boltzmann's constant. The general expression for the free energy is that it is a sum of two contributions

$$\Delta\Omega = \frac{4\pi R^3}{3}\left(\omega(n_0) - \omega(n_\infty)\right) + 4\pi R^2 \gamma \tag{2}$$

where $\omega(n)$ is the grand canonical free energy per unit volume of a homogeneous system evaluated at the density n: note that this is simply equation to the pressure $P(n)$ of the homogeneous phase. The densities n_0 and n_∞ are

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the equilibrium densities for the new and old phase respectively. Finally, the last term accounts for surface tension and involves the excess free energy per unit area of a planar interface between the two phases, γ, which can easily be calculated based on the squared-gradient free energy model (see e.g. Ref.2). Combining these gives the explicit evolution equation

$$\frac{dR}{dt} = \frac{1}{2}a\left(R^{-1} - R_c R^{-2}\right),\ \ a = \frac{2Dn_2^{(\infty)}\left(P(n_0) - P(n_\infty)\right)}{\left(n_2^{(0)} - n_2^{(\infty)}\right)^2} \tag{3}$$

where we have introduced the critical radius, $R_c = 2\gamma/\left(\omega(n_0) - \omega(n_\infty)\right)$. In the limit of large radii, the second term becomes negligible and the result used in the main text is obtained giving the asymptotic behavior $R(t)^2 = at$. Keeping all terms, one can integrate to get the implicit solution

$$\begin{aligned} a\left(t - t_0\right) =& (R(t) - R(t_0))(R(t) + R(t_0) + 2R_c) \\ &+ R_c^2 \ln\left(\tfrac{R(t) - R_c}{R(t_0) - R_c}\right) \end{aligned} \tag{4}$$

For the conditions used here, $k_B T = 0.8\epsilon$, we find that the squared-gradient coefficient is $\beta g = 8.08$ and the surface tension is $\beta\gamma = 1.286$ and $a = 0.017$. Before proceeding to discuss the correspondence between the capillary and microscopic models, one other issue that must be addressed is the definition of the radius to use in the capillary model. For the critical cluster, the natural quantity is the equimolar radius defined as that radius for which the capillary model cluster has the same excess density as the actual cluster, i.e.

$$\frac{4\pi}{3}R^3 n_0 = 4\pi \int (n(r) - n_\infty) r^2 dr \tag{5}$$

which is well-defined as the density field decays quickly to the background density outside the cluster. However, for the growing super-critical cluster, there is both a depletion zone outside the cluster (i.e. a region of density below the background) and a density field that is assumed in CNT to have the form of the stationary density field for diffusion with a fixed density at the boundary of the cluster, i.e. $n(r) \sim n_\infty + (n(r_0) - n_\infty) r_0/r$ for some value of r_0 and the integral of this quantity diverges. Both of these effects are illustrated in Fig. 1. Of course, in reality, the density field can only change relative to the background at a finite rate so that the excess mass is always finite but it would take prohibitively large simulations to follow this. As a consequence, we have to use some other - heuristic - measure of the radius. The one reported here is the value of r for which the density is half the average of the density at the origin and at the outer edge of the simulation cell. For this reason, convergence of the numerical results to the capillary theory can be expected to be much slower than is normally found to be the case for the properties of the critical cluster.

Figure 2 shows the squared-radius as a function of time. After an initial transient, it assumes the expected linear form. The slope determined from a fit excluding the transient gives a value of $dR^2/dt = 0.016$ which compares well with the asymptotic capillary theory result of 0.017. To compare the more detailed prediction of Eq.(5), which includes the effect of surface tension, the numerical results were analyzed as follows. The numerical results of solving the DDFT equations give a series of times and radii, (t_i, R_i). For each value of i, we take $t_0 = t_i$ and use all the points from $i + 1$ onward to estimate the value of a, the asymptotic slope, by least squares. The rationale is that as t_0 increases, the effect of the initial transient diminishes. This then gives a sequence of values a_i as shown in Fig. 3. A simple fit gives an asymptotic value of $a = 0.1697$ which is in excellent agreement with the asymptotic prediction of the capillary model.

Finally, Fig. 4 shows the structure of the stable cluster confirming the fact that most of the monomers are expelled from the cluster.

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[1] J. F. Lutsko, J. Chem. Phys. **137**, 154903 (2012).
[2] J. F. Lutsko, Adv. Chem. Phys. **144** (2010).

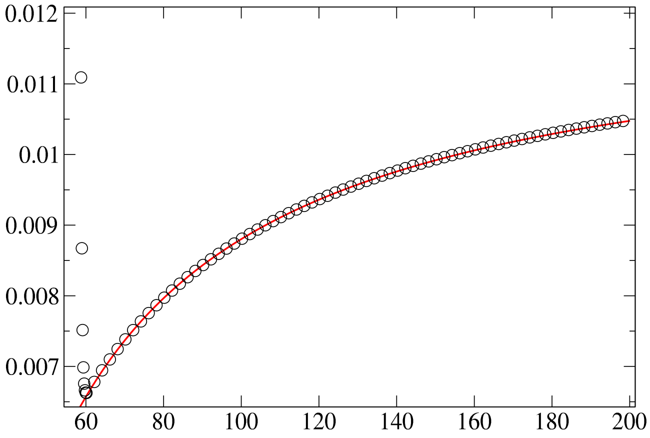

FIG. 1. Blowup of the structure of the growing super-critical cluster showing the depletion zone outside the cluster (circles) and the analytic form $n(r) = n_\infty + (n(r = 200) - n_\infty) * 200/r$ (line). Note that for $r > 60$ only every tenth point of the numerical data (circles) is shown. The agreement between the numerical results and the analytic form shows that the depletion zone has the structure of a stationary diffusion profile.

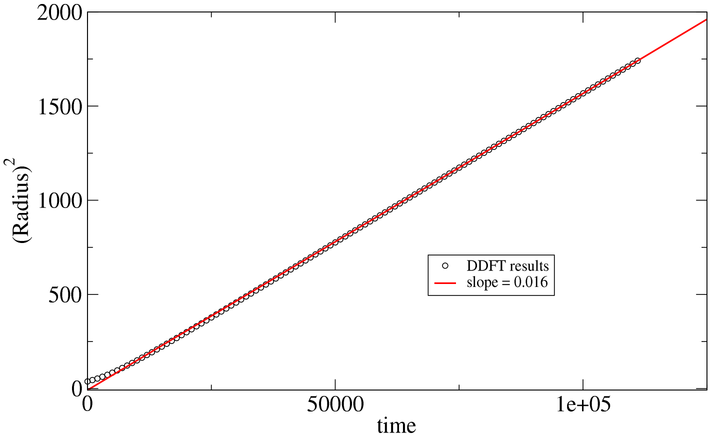

FIG. 2. The square of the equimolar radius of a super-critical cluster in the pure dimer solution as a function of time (both shown in dimensionless units) and a linear fit excluding the initial transient.

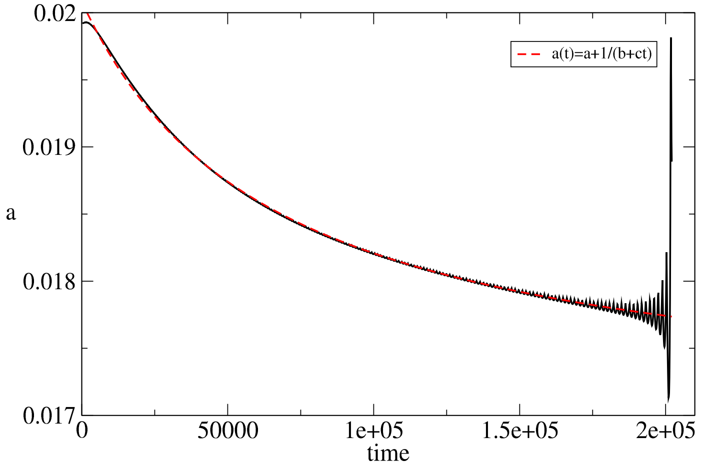

FIG. 3. Value of the coefficient a determined as a function of the initial time, t_0. The noise in the determination of the coefficient increases with increasing time as only the data points for times larger than t_0 are used in the estimation. Also shown is a fit to the analytic form $a(t_0) = a + 1/(b + ct)$ with the constants a, b, c determined by least-squares. The fit gives the asymptotic value $\lim_{t_0 \to \infty} a(t_0) = a = 0.01697$ in good agreement with the simple estimate of the main text, $a = 0.0171$.

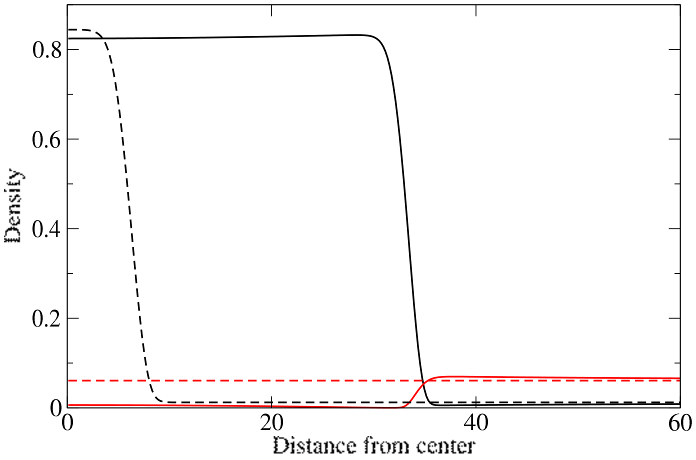

FIG. 4. Structure of the stable cluster for $k_1^* = 7.5 \times 10^{-5}$. The density (concentration) of the monomer species (solid red line) and the dimer species (solid black line) is shown as functions of distance from the center of the cluster. The initial condition is also shown using dashed-lines.