A Kinetic theory for swarming with birth and death events

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1 Intro

Let us consider a particle system where the number of constituents may vary, due to birth or death events. For the case of N particles, we denote by $f_N(\{\vec{x}_i\}, \{\vec{v}_i\}, t)$ the probability density of finding each of these particles at position x_i, velocity v_i and within a volume $d\vec{x}_i, d\vec{v}_i$ in phase space. Since the number of particles may change, N is also a variable. Conservation of probability requires that particles is all N-ensembles must satisfy

$$f_0(t) + \int_{N=1}^{\infty} \int f_N(\{\vec{x}_i\}, \{\vec{v}_i\}, t) d\Omega_N = 1 \tag{1}$$

where $\Omega_N = d\mathbf{x}_1 \dots d\mathbf{x}_N d\mathbf{v}_1 d\mathbf{v}_N$. Each of the f_N functions obeys its related Liouville equation

$$\frac{\partial f^{(N)}}{\partial t} + \sum_{i=1}^{N} \left[\div_{\mathbf{x_i}} (\dot{\mathbf{x}}_i f^{(N)}) + \div_{\mathbf{v}_i} (\dot{\mathbf{v}}_i f^{(N)}) \right] = 0. \tag{2}$$

In the prion model we have a pool of folded monomers that are unable to aggregate but that can transition into a pool of unfolded ones that instead can form clusters. The transition is reversible but rates are not symmetric so that transitioning into the unfolded state is a much rarer event than returning to the folded state. However, it is in the misfolded state that homogeneous nucleation can occur. We thus denote by n_1^* the number of folded proteins and by n_1 the number of misfolded ones. Similarly we denote by $n_{k>1}$ the number of clusters made of misfolded proteins. We denote by $P(n_1^*, n_1, n_2, n_3, \dots, n_N)$ the probability distribution of having a state in the $\{n\} = n_1^*, n_1, n_2, n_3 \dots n_N$ configuration where N is the maximum cluster size. We can thus write the following Master Equation:

$$
\begin{aligned}
\frac{dP(\{n\})}{dt} = & -\gamma^* n_1^* P(\{n\}) + \gamma^*(n_1^*+1)P(n_1^*+1, n_1-1, n_2, n_3 \dots) - \\
& \gamma n_1 P(\{n\}) + \gamma(n_1+1)P(n_1^*-1, n_1+1, n_2, n_3 \dots) - \\
& \left[\frac{pn_1(n_1-1)}{2} + p\sum_{i=1}^{N-1} n_1 n_i + q\sum_{i=2}^{N} n_i\right] P(\{n\}) + \\
& \frac{p(n_1+2)(n_1+1)}{2} P((n_1^*, n_1+2, n_2-1, n_3, \dots) + \\
& q(n_2+1)P(n_1^*, n_1-2, n_2+1, n_3, \dots) + \\
& p\sum_{i=2}^{N-1}(n_1+1)(n_i+1)P(n_1^*, n_1+1, \dots, n_i+1, n_{i+1}-1, \dots) + \\
& q\sum_{i=3}^{N}(n_i+1)P(n_1^*, n_1-1, \dots, n_{i-1}-1, n_i+1, \dots).
\end{aligned} \tag{3}
$$

1.1 Within Becker-Doering

The same model can be considered through a BD framework. The relevant equations are

$$
\begin{aligned}
\dot{c}_1^*(t) &= -\gamma^* c_1^* + \gamma c_1 \\
\dot{c}_1(t) &= \gamma^* c_1^* - \gamma c_1 - pc_1^2 - pc_1 \sum_{j=2}^{N-1} c_j + 2qc_2 + q\sum_{j=3}^{N} c_j \\
\dot{c}_2(t) &= -pc_1c_2 + \frac{p}{2}c_1^2 - qc_2 + qc_3 \\
\dot{c}_k(t) &= -pc_1c_k + pc_1c_{k-1} - qc_k + qc_{k+1} \\
\dot{c}_N(t) &= pc_1c_{N-1} - qc_N
\end{aligned} \tag{4}
$$

where the initial conditions are $c_1^*(t=0) = M$ and $c_k(t=0) = 0$, for all k. The dynamics are such that $p \ll q$ and that $\gamma^* \ll \gamma$: transitioning into the misfolded state occurs over slower timescales than transitioning back into the folded state and similarly attachment of the misfolded clusters is slower than detachment. The goal of this work is to find, for example cluster configurations and the mean first time of reaching a cluster of size N.

2 The first passage time

In this section we consider the simplified case of homogeneous nucleation when $\gamma^* \to \infty$ and $\gamma = 0$, so that we can assume that at time $t = 0$ all the mass is in the misfolded state so that $n_1^* = 0$ and $n_k = M\delta_{k,1}$ and there is no coupling to the folded reservior. To illustrate the method we will use to calculate the first passage times we consider the very simple, yet illustrative case of $M = 7$, $N = 3$ where the entire dynamics is represented by

$$\begin{array}{ccccc}
(7,0,0) & & & & \\
\downarrow\uparrow & & & & \\
(5,1,0) & & & & \\
\downarrow\uparrow & \searrow\nwarrow & & & \\
(3,2,0) & & (4,0,1) & & \\
\downarrow\uparrow & \searrow\nwarrow & \downarrow\uparrow & & \\
(1,3,0) & & (2,1,1) & & \\
 & & \downarrow\uparrow & \searrow\nwarrow & \\
 & & (0,2,1) & & (1,0,2)
\end{array} \tag{5}$$

and where we have omitted the n^* configuration. If we are interested in the first passage time to completion of an N-mer, a maximal cluster, we can consider the survival probability $S(n_1, n_2, n_3, t)$ which is the probability of having survived up to time t, given an initial configuration $\{n_1, n_2, n_3\}$ out of the completed state. In this case we have the constraint $S(n_1, n-2, n_3 > 0, t) = 0$.

The equations for the survival probability $S(n_1, n_2, n_3, t)$ can be written in terms of the backward Kolmogorov equations which in this case are

$$\frac{dS(7,0,0)}{dt} = \frac{7 \cdot 6}{2}[S(5,1,0) - S(7,0,0)], \tag{6}$$

$$\frac{dS(5,1,0)}{dt} = q[S(7,0,0) - S(5,1,0)] + \frac{5 \cdot 4}{2}[S(3,2,0) - S(5,1,0)] + 5[S(4,0,1) - S(5,1,0)], \tag{7}$$

$$\frac{dS(3,2,0)}{dt} = 2q[S(5,1,0) - S(3,2,0)] + \frac{3 \cdot 2}{2}[S(1,3,0) - S(3,2,0)] + 3 \cdot 2[S(2,1,1) - S(3,2,0)], \tag{8}$$

$$\frac{dS(1,3,0)}{dt} = 3q[S(3,2,0) - S(1,3,0)] + 3[S(0,2,1) - S(1,3,0)], \tag{9}$$

where we have assumed that time is now renormalized so that $p = 1$ and q is unitless. These equations can be numerically solved as a set of coupled ODEs. Note that some terms are zero, for example

$S(2,1,1,t) = S(0,2,1,t) = S(4,0,1,t) = 0$ due to our quest for the first passage time to *any* cluster of size $N = 3$. The solution to the above ODEs will lead to the full survival distributions. If we are only interested in the mean first passage time T, starting from configuration $\{n_1, n_2.n_3\}$ we can recall that

$$T(n_1, n_2, n_3) \;=\; -\int_0^\infty t\frac{dS(n_1,n_2,n_3)}{dt}dt = \int_0^\infty S(n_1,n_2,n_3)dt = \tilde{S}(n_1,n_2,n_3,s=0) \tag{10}$$

where the first equality is obtained via integration by parts and where $\tilde{S}(n_1, n_2, n_3, s)$ is the Laplace transform of $S(n_1, n_2, n_3, t)$. If we now denote by $\mathcal{S}(s)$ the vector of all Laplace transform survival states such that

$$\mathcal{S}(s) = (\tilde{S}(7,0,0,s), \tilde{S}(5,1,0,s), \tilde{S}(3,2,0,s), \tilde{S}(1,3,0,s))^\top \tag{11}$$

and take the Laplace transform of Eqs. 6-9 we find

$$s\mathcal{S}(s) - (1,1,1,1)^\top = \mathbf{M}\,\mathcal{S}(s) \tag{12}$$

where $(1,1,1,1)^\top$ are the initial condtions of survival probabilities being unity if $n_3 \neq 0$ in all states in $\mathcal{S}$ and where $\mathbf{M}$ is the matrix associated to Eqs. 6-9 so that

$$\mathbf{M} = \begin{pmatrix} -21 & 21 & 0 & 0 \\ q & -(15+q) & 10 & 0 \\ 0 & 2q & -(9+2q) & 0 \\ 0 & 0 & 3q & -(3+3q) \end{pmatrix} \tag{13}$$

Finally, since we are interested in the case of $s = 0$ we can also write

$$\mathcal{S}(s) = -\mathbf{M}^{-1} \cdot (1,1,1,1)^\top \tag{14}$$

which can be solve by inverting $\mathbf{M}$ to find

$$T(7,0,0) \;=\; \frac{1}{21} + \frac{1}{15} + \frac{q}{315} \tag{15}$$

$$T(5,1,0) \;=\; \frac{1}{15} + \frac{q}{315} \tag{16}$$

$$T(3,2,0) \;=\; \frac{1}{2(3+q)} + \frac{q}{15(3+q)} + \frac{q^2}{315} \tag{17}$$

$$T(1,3,0) \;=\; \frac{1}{3(1+q)} + \frac{q}{2(1+q)(3+q)} + \frac{q^2}{15(1+q)(3+q)} + \frac{q^3}{315(1+q)(3+q)} \tag{18}$$