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Nucleated polymerization with secondary pathways II. Determination of self-consistent solutions to growth processes described by non-linear master equations

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Abstract

Nucleated polymerisation processes are involved in many growth phenomena in nature, including the formation of cytoskeletal filaments and the assembly of sickle hemoglobin and amyloid fibrils. Closed form rate equations have, however, been challenging to derive for these growth phenomena in cases where secondary nucleation processes are active, a difficulty exemplified by the highly non-linear nature of the equation systems that describe monomer dependent secondary nucleation pathways. We explore here the use of fixed point analysis to provide self-consistent solutions to such growth problems. We present iterative solutions and discuss their convergence behaviour. We establish a range of closed form results for linear growth processes, including the scaling behaviours of the maximum growth rate and of the reaction end-point. We further show that a self-consistent approach applied to the master equation of filamentous growth allows the determination of the evolution of the shape of the length distribution including the mean, the standard deviation and the mode. Our results demonstrate the power of fixed-point approaches in finding closed form self-consistent solutions to growth problems characterised by highly non-linear master equations.

I Introduction

There has been recently considerable renewed interest in the development of theoretical models that describe the general problem of growth of filamentous protein structures[1–7]. The theoretical analysis of such polymerising protein systems was initiated in the 1960s in the context of a range of functional biological assembly phenomena[8–13], including the growth of actin and tubulin filaments. Furthermore, much experimental and theoretical attention has focused on aberrant biological assembly, starting with sickle hemoglobin assembly[14–16], and more recently the processes leading to the formation of amyloid fibrils often observed in association with neurodegenerative and other diseases[17–24]. In the overall kinetics of growth, secondary nucleation processes, including filament fragmentation, have emerged as dominant factors for amyloid formation[1, 3, 25–27] and prion assembly[1, 28, 29]. Such secondary events lead to a description of the growth problem through kinetic equations that are commonly highly non-linear.

In order to address the difficulty in obtaining analytical results for the full time course of the reaction, we proposed[30, 31] a self-consistent analysis scheme and showed that this approach yields closed form solutions to the growth problem. The focus of the present paper

is to extend this approach to highly non-linear master equations by exploring the nature of the higher order solutions that emerge from the repeated application of the fixed-point iteration to the moment equations (Sections II–VII) and also by exploring self-consistent solutions to the full length distribution (Section VIII). We show that closed form solutions of high accuracy can be generated using this general and powerful approach. In particular, we derive analytical results, valid for the full duration of the reaction, which describe in closed form the time evolution of lower principal moments of filament systems which grow through primary nucleation, filament elongation and either monomer independent or monomer dependent secondary nucleation. These higher order iterations also allow access to important corrections to the scaling laws that emerge from the analysis of lower order solutions, as well as to information on the shape of the length distribution.

The differential equations that describe monomer-dependent secondary pathways involve very strong non-linearities in addition to those originating from the primary nucleation. These types of equations are not readily amenable to perturbative treatments as all of the non-linear terms contribute significantly to the overall reaction as shown in Fig. 2. The main result of this paper is an approach to treat such highly non-linear growth problems, and we provide an iterative scheme to obtain a closed form expression of high accuracy for the integrated rate laws (c.f. Appendix), the result of which is illustrated in Fig. 2.

II Second Order Self-Consistent Solutions

In the first part of this paper, we focus on higher order iterative solutions for the case where the secondary pathway is filament fragmentation, and is hence monomer independent. This type of secondary pathway does not introduce non-linear terms into the master equation, and therefore the only source of non-linearity is the elongation process [terms proportional to $M(t)P(t)$] and the primary nucleation [terms proportional to a polynomial of degree n_c in $M(t)$][31]. The evolution of the principal moments, the polymer number concentration $P(t)$ and the polymer mass concentration $M(t)$, has been shown to obey the differential equations[5, 9, 29, 34]:

$$\frac{dP(t)}{dt} = k_- [M(t) - (2n_c - 1)P(t)] + k_n m(t)^{n_c} \quad (1)$$

$$\frac{dM(t)}{dt} = 2[m(t)k_+ - k_{\text{off}} - k_- n_c(n_c - 1)/2]P(t) + n_c k_n m(t)^{n_c} \quad (2)$$

where $m(t) = m_{\text{tot}} - M(t)$ is the free monomer concentration and k_+ , k_{off} , k_- and k_n are the rate constants for elongation, depolymerisation, fragmentation and primary nucleation, respectively. In order to recover the detailed scaling exhibited by solutions to the problem of filament growth under conditions where filament fragmentation enhances the number of free filament ends, we require self-consistent solutions that go beyond those previously obtained as the first order corrections restoring mass conservation[30, 31] to the linearized solutions[5, 16, 32, 33] which do not include mass conservation. We base our discussion on

a fixed-point analysis. The kinetic problem is reformulated as a fixed-point equation[31]. Subsequent applications of the fixed-point operator yield increasingly accurate iterative self-consistent solutions. The first improvement beyond the low order result [30, 31] is obtained by establishing the second order self-consistent solution to the filament growth problem.

The self-consistent result obtained after one iteration has been shown to emerge as the simple closed form expression[31] for the polymer mass concentration:

$$M_1(t) = M(\infty)[1 - \exp(-C_+ e^{\kappa t} + C_- e^{-\kappa t} + D)] \quad (3)$$

where the filament multiplication rate is defined as:

$$\kappa = \sqrt{2[m(0)k_+ - k_{\text{off}}]k_-} \quad (4)$$

for initial monomer concentration $m(0)$. The final polymer mass concentration $M(\infty)$ is given approximately by[31, 35]:

$$M(\infty) = \frac{2k_+ m_{\text{tot}} - 2k_{\text{off}} - n_c(n_c - 1)k_-}{2k_+} \quad (5)$$

The constants are functions of the initial conditions and of the rate constants k_n , k_+ , k_{off} and k_- :

$$C_{\pm} = \frac{k_+ P(0)}{\kappa} \pm \frac{M(0)k_+}{2[m(0)k_+ - k_{\text{off}}]} \pm \frac{\lambda_0^2}{2\kappa^2} \quad (6)$$

$$D = \frac{\lambda_0^2}{\kappa^2} - \frac{M(0)}{M(\infty)} + \frac{k_+ M(0)}{m(0)k_+ - k_{\text{off}}} \quad (7)$$

where $\lambda_0 = \sqrt{2k_+ k_n m(0)^{n_c}}$ is the effective rate constant derived by Oosawa[8, 9, 31] for nucleated polymerization without secondary pathways. The aim of the present section of this paper is to generalise the equation (3) to higher order approximations and recover the corresponding corrections to the scaling behaviour in the system kinetics. The two components of the fixed-point operator $\mathcal{A}$, appropriate for this system, are derived by formal integration of Eqs. (1) and (2) to yield [30, 31]:

$$M(t) = M(\infty) \left(1 - e^{-\frac{M(0)}{M(\infty)} - 2k_+ \int_0^t P(\tau) d\tau} \right) \quad (8)$$

$$P(t) = k_- e^{-(2n_c-1)k_- t} \left(P(0) + \int_0^t e^{(2n_c-1)k_- \tau} M(\tau) d\tau \right) \quad (9)$$

The convergence of the fixed-point scheme is most effective when the operator acts on a solution which is close to the final fixed point. In our first order solutions, this condition is better satisfied for early times, and therefore the accuracy of the first order self-consistent solution is less good for times corresponding to the reaction end point. The accuracy of the expression for $M(t)$ in Eq. (3) may be improved with higher order corrections from further fixed point iterations. This improvement corresponds to substituting the first order expression $P_1(t)$ into the integral operator for $M(t)$ in Eq. 8 to find a more accurate solution in this self-consistent scheme.

By substituting Eq. (3) into Eq. (9), the first order result for $P_1(t)$ has been shown to obey[31]:

$$P_1(t) = k_- e^{-(2n_c-1)k_- t} \left\{ P(0) + \int_0^t e^{(2n_c-1)k_- \tau} M(\infty) [1 - \exp(-C_+ e^{\kappa\tau} + C_- e^{-\kappa\tau} + D)] d\tau \right\} \quad (10)$$

For sufficiently large breakage rates ($C_+ C_- \ll 1$) and at early times ($t \ll \kappa^{-1}$), the exponential term may be approximated as:

$$\exp(-C_+ e^{\kappa\tau} + C_- e^{-\kappa\tau} + D) \approx \exp(-C_+ e^{\kappa\tau}) + \exp(C_- e^{-\kappa\tau}) - 1 \quad (11)$$

On rearrangement and expansion for early times $t \ll \kappa^{-1} \ll k_-^{-1}$ Eq. (10) yields:

$$P_1^e(t) = k_- M(\infty) e^{-(2n_c-1)k_- t} \left\{ \frac{P(0)}{k_- M(\infty)} - \int_0^t [\exp(-C_+ e^{\kappa\tau}) + \exp(C_- e^{-\kappa\tau}) + 2t] + \mathcal{O}(k_- t) d\tau \right\} \quad (12)$$

This integral has a closed form expression valid for early times:

$$P_1^e(t) = e^{-(2n_c-1)k_- t} \left(P(0) + \frac{k_- M(\infty)}{\kappa} \left[E_1(C_+ e^{\kappa t}) - E_1(C_+) - E_1(-C_- e^{-\kappa t}) + E_1(-C_-) + 2\kappa t \right] \right) \quad (13)$$

This result is accurate for significantly longer times than the linearized solution[31, 32] used to generate $M_1(t)$, and would, therefore, be expected to produce an improved expression for $M(t)$ when operated on by Eq. (8). Indeed the correction for the first moment can now be obtained from Eq. (13) and Eq. (8) as $M_2(t)$. In this case, we obtain:

$$\frac{M_2 t}{M(\infty)} = 1 - \exp \left(-2k_+ \int_0^t \mathcal{O}(k_- t)^2 + \frac{k_- M(\infty)}{\kappa} [E_1(C_+ e^{\kappa t}) - E_1(C_+) + \kappa t] - \frac{k_- M(\infty)}{\kappa} [E_1(-C_- e^{-\kappa t}) - E_1(-C_-) - \kappa t] dt - \frac{M(\infty)}{M(\infty)} \right) \quad (14)$$

In order to carry out the integration in Eq. (14), the integrand is rewritten as:

$$I = I_y + I_z \\ = \frac{k_- M(\infty)}{\kappa} [\log(y) + E_1(C_+ y) - E_1(C_+)] - \frac{k_- M(\infty)}{\kappa} [\log(z) + E_1(-C_- z) - E_1(-C_-)] \quad (15)$$

with $y = e^{\kappa t}$ and $z = e^{-\kappa t}$. The terms I_y and I_z may be integrated using an identical approach; we carry out the integration for I_y . Expansions around $y = 1$ ($t = 0$) yield:

$$\log(y) = \sum_{p=1}^{\infty} (-1)^{p+1} \frac{(y-1)^p}{p} \quad (16)$$

$$E_1(C_+ y) - E_1(C_+) = \sum_{p=1}^{\infty} (-1)^p \frac{C_+^p E_{1-p}(C_+) (y-1)^p}{p!} \quad (17)$$

and expanding the exponential integral about $C_+ = 0$ gives:

$$E_{1-p}(C_+) = C_+^{-p} (p-1)! + \sum_{q=1}^{\infty} (-1)^q \frac{C_+^{q-1}}{(q-1)!(q-1+p)} \quad (18)$$

Due to the convergence of the series, I_y may be obtained exactly:

$$I_y = \frac{k_- M(\infty)}{\kappa} \sum_{p=1}^{\infty} \sum_{q=1}^{\infty} (-1)^{p+q} \frac{C_+^{p+q-1} (y-1)^p}{p!(q-1)!(q-1+p)} \quad (19)$$

Transforming the rest of the integral into to be a function of the variable y , and writing $(y-1)^p$ as a binomial sum, the integration can be carried out exactly term by term. For small depolymerization rates[31, 36], $k_{\text{off}} \ll k_+ m_{\text{tot}}$, this operation results in:

$$\int_0^t I_y dt \approx -\frac{1}{2k_+} \sum_{p=1}^{\infty} \sum_{q=1}^{\infty} (-1)^{p+q+1} C_+^{p+q-1} \frac{(-1)^p \kappa t + \sum_{r=0}^{p-1} (-1)^r \frac{p!}{r!(p-r)!(p-r)} (e^{(p-r)\kappa t} - 1)}{p!(q-1)!(q-1+p)} \quad (20)$$

The major contribution to the summation over r in Eq. (20) originates in the leading order exponentials where $r = 0$ and, similarly, for $C_+ \ll 1$ the leading order terms in the summation over q are given from $q = 1$, resulting in:

$$\int_0^t I_y dt = \frac{1}{2k_+} \sum_{p=1}^{\infty} (-C_+)^p \frac{e^{p\kappa t}}{p^2 p!} \quad (21)$$

The result for I_z may be found through the replacement $C_+ \rightarrow -C_-$, with the minus sign before the integral cancelling with that from the change of variable $dt \rightarrow dz$ in the integration. This yields a compact result for $M_2(t)$:

$$\frac{M_2(t)}{M(\infty)} = 1 - \exp \left(\sum_{p=1}^{\infty} (-C_+)^p \frac{e^{p\kappa t}}{p^2 p!} + C_-^p \frac{e^{-p\kappa t}}{p^2 p!} \right) \quad (22)$$

We now use this solution obtained in the early time limit $t \ll \kappa$ and sufficiently large k_- ($C_- C_+ \ll 1$) to construct the full time-course solution. To this effect, we first note that the full second order solution must match in the early time limit the first order iteration result, which is itself exact in this limit [31]. Furthermore, we also know the limit that should be obtained in the absence of fragmentation and depolymerisation (Oosawa limit [9, 31]). Using these two conditions to complete the missing terms in Eq. (22) by comparison with the two special cases, the full result for the second order iteration is obtained as:

$$\frac{M_2(t)}{M(\infty)} = 1 - \exp \left(\sum_{p=1}^{\infty} \left[\frac{(-C_+)^p}{p^2 p!} \left(e^{p\kappa t} - \sum_{q=0}^{2p-2} \frac{(p\kappa t)^q}{q!} \right) + \frac{C_-^p}{p^2 p!} \left(e^{-p\kappa t} - \sum_{q=0}^{2p-2} \frac{(-p\kappa t)^q}{q!} \right) \right] - \frac{M(0)}{M(\infty)} \right) \quad (23)$$

This equation has an analogous form to the first order solution discussed in [30, 31], but we note the presence of additional terms in the exponential. As in Part I [31], a linear term $n_c k_n m_{\text{tot}}^{n_c-1} t$ has been neglected since the breakage rate is small such that most bonds in the system do not break over the reaction time.

Fig. 3 shows the first and second order iterations, given by Eqs. (3) and (23). From this figure, it is evident that the second order iteration offers a significant improvement in accuracy over the first order result in matching the exact solution - which it does almost exactly - and in particular offers significant improvement over the first order result towards the end of the growth phase.

In considering after how many terms the summation in Eq. (23) can be terminated while still offering a good approximation for $M(t)$, first note that the summation is absolutely convergent for any given t , with the absolute ratio between the $(p+1)$ th and p th terms for long times:

$$\frac{u_{p+1}}{u_p} = \frac{p^2}{(p+1)^3} C_+ e^{\kappa t} \quad (24)$$

Using the parameters of Fig. 3, for $t = 14$ hours the ratio of the $p = 3$ to $p = 2$ terms is ~ 0.01 . This same ratio is ~ 18 at $t = 60$ hours. Generally, the series converges in a small number of terms for times such that $C_+ e^{\kappa t} \ll 1$, but for longer times than this, a very large number of terms is needed. Due to the alternating nature of the series, if the sum is terminated after an odd number of terms then in the limit $t \rightarrow \infty$ it will yield a large negative number; whereas for termination after an even number of terms the result gives a large positive number in this limit. Since the summation is within an exponential function in Eq. (23), for the case of termination after an odd number of terms the exponential term tends to zero and $M(t) \rightarrow M(\infty)$ in the long time limit, as required. Conversely, if the sum is terminated after an even number of terms then in the limit $t \rightarrow \infty$, $M(t) \rightarrow -\infty$. As such, to achieve a good approximation of $M(t)$, enough terms must be included before terminating the summation such that the ratio between the last included and first omitted term, given by Eq. (24), is small for times before which $M(t) \sim M(\infty)$, and the summation must also be terminated after an odd number of terms.

Using the parameters of Fig. 3, these conditions are fully satisfied terminating the summation after 25 terms. The result including just 3 terms, offering the first improvement over the first order iteration $M_1(t)$ [31], is given explicitly by:

$$\begin{aligned} \frac{M_2(t)}{M(\infty)} = & 1 - \exp(-(e^{\kappa t} - 1)C_+ + (e^{-\kappa t} - 1)C_-) \\ & + (e^{2\kappa t} - 1 - 2\kappa t - 2\kappa^2 t^2) \frac{C_+^2}{8} \\ & + (e^{-2\kappa t} - 1 + 2\kappa t - 2\kappa^2 t^2) \frac{C_-^2}{8} \\ & - \left(e^{3\kappa t} - 1 - 3\kappa t - \frac{9\kappa^2 t^2}{2} - \frac{9\kappa^3 t^3}{2} - \frac{27\kappa^4 t^4}{8} \right) \frac{C_+^3}{54} \\ & + \left(e^{-3\kappa t} - 1 + 3\kappa t - \frac{9\kappa^2 t^2}{2} + \frac{9\kappa^3 t^3}{2} - \frac{27\kappa^4 t^4}{8} \right) \frac{C_-^3}{54} - \frac{M(0)}{M(\infty)} \end{aligned} \quad (25)$$

We note that compared with the first order result

$M_1(t) = M(\infty)[1 - \exp(-C_+ e^{\kappa t} + C_- e^{-\kappa t} + D)]$ there are new terms $\sim e^{2\kappa t}$, $e^{3\kappa t}$ and associated polynomials in κt in the exponent.

III Analysis of Limiting Cases

The equation Eq. (23) is a general result valid for all initial conditions. For many special cases, however, the growth kinetics are described by expressions which are considerably simpler, and can be obtained from (23) in the appropriate limit. We discuss three examples of practical importance below.

A Long time limit

The result for long time limits, for $t \gg \kappa^{-1}$, is given from Eq. (23):

$$\frac{M_2(t)}{M(\infty)} = 1 - \exp \left(\sum_{p=1}^{\infty} (-C_+)^p \frac{e^{p\kappa t}}{p^2 p!} \right) \quad (26)$$

as the decaying exponentials $e^{-p\kappa t}$ and polynomial terms in κt can be neglected in front of the growing exponential terms $e^{p\kappa t}$.

B Absence of seed material

When $M(0) = P(0) = 0$, Eq. (23) reduces to:

$$\frac{M_2(t)}{M(\infty)} = 1 - \exp \left(\sum_{p=1}^{\infty} \left[\frac{(-C_+)^p}{p^2 p!} \left(4 \sinh^2 \left(\frac{p\kappa t}{2} \right) - 2 \sum_{q=1}^{p-1} \frac{(p\kappa t)^{2q}}{(2q)!} \right) \right] \right) \quad (27)$$

$$C_+ = \frac{\lambda^2}{\kappa^2} \quad (28)$$

for $\lambda = \sqrt{2k_+k_-m_{\text{tot}}}$ since $C_+ = -C_-$ and $m(0) = m_{\text{tot}}$, and the resulting symmetry in the expression Eq. (23) allows the regrouping of the exponential terms using the double angle formula.

The time evolution of the polymer mass in this case depends only upon two combination of the kinetics parameters, κ and λ ; for comparison, in the case derived by Oosawa[8, 9] for nucleated polymerization without secondary pathways, the rate law depended primarily only upon λ in the absence of seed material.

C Infrangible filaments

For a system of infrangible filaments, $k_- = 0$, undergoing irreversible growth, $k_{\text{off}} = 0$, the limit of Eq. (27) is given as:

$$\frac{M_2(t)}{m_{\text{tot}}} = 1 - \exp \left(\sum_{p=1}^{\infty} \frac{(-C_+)^p}{p^2 p!} \frac{(k_n k_+ m_{\text{tot}}^{n_c})^p}{(2p)!} (pt)^{2p} \right) \quad (29)$$

where the first few terms are given by:

$$\frac{M_2(t)}{m_{\text{tot}}} = 1 - \exp \left(-t^2 k_+ k_n m_{\text{tot}}^{n_c} + \frac{1}{6} t^4 k_+^2 k_n^2 m_{\text{tot}}^{2n_c} - \frac{3}{80} t^6 k_+^3 k_n^3 m_{\text{tot}}^{3n_c} + \mathcal{O}(t^8) \right) \quad (30)$$

In particular, higher powers of t are now present in comparison with the first order result[31]. It is interesting to note that the exact Oosawa result for irreversible growth of infrangible filaments[9] in the absence of seeds and depolymerisation,

$$M(t) = m_{\text{tot}} \left(1 - \text{sech}^{2/n_c} \left[\sqrt{n_c k_n k_+ m_{\text{tot}}^{n_c}} \right] \right), \text{ admits the series expansion:}$$

$$\frac{M(t)}{m_{\text{tot}}} = 1 - \exp \left(-t^2 k_+ k_n m_{\text{tot}}^{n_c} + \frac{1}{6} t^4 k_+^2 k_n^2 m_{\text{tot}}^{2n_c} - \frac{2}{45} t^6 k_+^3 k_n^3 m_{\text{tot}}^{3n_c} + \mathcal{O}(t^8) \right) \quad (31)$$

It can be seen that whilst the first order result is correct to $\mathcal{O}(t^2)$ [31], the second order iteration now reproduces the correct limit to $\mathcal{O}(t^4)$. The limits given by the first and second order analytical results are compared with the exact result in Fig. 4, where the second order result is seen to provide a significant improvement.

IV Lag Time Scaling

The availability of a highly accurate analytical solution to the growth kinetics over the full time course of the polymerisation reaction provides us with the opportunity to analyse the corrections to the scaling behaviour in the lag time that has emerged from lower order solutions[30–32]. In this section, we show that the numerical values of the coefficients in the scaling laws from the first order solutions are significantly improved when considering the corrections obtained from the second order results. We recall that in the case of the first iteration, the following results hold, where we label the time at which the maximum growth rate occurs t_{max} :

$$t_{\text{max}} = \frac{\log(1/C_+)}{\kappa}; \quad r_{\text{max}} = \frac{M(\infty) \kappa}{e} \quad (32)$$

The lag time is found to scale as:

$$M(t_{\text{max}}) / (t_{\text{max}} - \tau_{\text{lag}}) = r_{\text{max}} \Rightarrow \tau_{\text{lag}} = t_{\text{max}} - \frac{M(t_{\text{max}})}{r_{\text{max}}} \quad (33)$$

$$\tau_{\text{lag}} = [\log(1/C_+) - e + 1] \kappa^{-1} \approx [\log(1/C_+) - 1.718] \kappa^{-1} \quad (34)$$

The exact numerical result for this scaling from the master equation has been shown to be [37]:

$$\tau_{\text{lag}} = [\log(1/C_+) - 1.825] \kappa^{-1} \quad (35)$$

We now derive the equivalent result for the scaling of the lag time predicted by the second order analytical iteration, Eq. (23); as shown below, the result from the first order result is only semi-quantitatively correct, whereas the scaling laws obtained from the analysis of the second order result are highly accurate when compared with the numerical results.

In order to obtain the expressions for t_{max} , r_{max} and $M(t_{\text{max}})$ we first perform a substitution to introduce the dimensionless quantity $y = C_+ e^{\kappa t}$ in Eq. (26) and obtain:

$$M_2(y) = M(\infty) \left[1 - \exp \left(\sum_{p=1}^{\infty} (-1)^p \frac{y^p}{p^2 p!} \right) \right] \quad (36)$$

The value of y that occurs when $t = t_{\text{max}}$ is y_{max} :

$$y_{\text{max}} = C_+ e^{\kappa t_{\text{max}}} \quad (37)$$

whereby the explicit dependencies on C_+ and κ have been subsumed into the change of variable. Explicitly, t_{max} is given by:

$$t_{\text{max}} = \frac{\log \left(\frac{y_{\text{max}}}{C_+} \right)}{\kappa} = \frac{\log \left(\frac{1}{C_+} \right) + \log(y_{\text{max}})}{\kappa} \quad (38)$$

Remarkably, this form maintains the inverse correlation between the multiplication rate κ and the lag time, but introduces a correction to the proportionality constant. Note that $y_{\text{max}} = 1$ recovers the first iteration result.

The determination of y_{max} requires the evaluation of the inflection point of $M_2(t)$ Eq. (36) Under the substitution $dy/dt = \kappa y$:

$$\frac{d^2 M_2}{dt^2} = \kappa^2 y \left(y \frac{d^2 M_2}{dy^2} + \frac{dM_2}{dy} \right) \quad (39)$$

Hence the inflection point is found as:

$$\left(\frac{d^2 M_2}{dy^2} + \frac{1}{y} \frac{dM_2}{dy} \right)_{y=y_{max}} = 0 \quad (40)$$

After substituting for the derivatives, Eq. 40 becomes a polynomial equation for y_{max} :

$$0 = \left(\sum_{q=1}^{\infty} \frac{(-1)^q y_{max}^{q-1}}{q q!} \right)^2 + \sum_{q=1}^{\infty} \frac{(-1)^q y_{max}^{q-2}}{q!} \quad (41)$$

This equation must be solved numerically and results in:

$$y_{max} = 0.99616 \quad (42)$$

This value determines the maximum growth rate, $r_{max} = (dM/dt)_{t=t_{max}} = \kappa y (dM/dy)_{y=y_{max}}$ as:

$$r_{max} = 0.3267 M(\infty) \kappa \quad (43)$$

which may be compared with the first order and exact numerical results to show a significant improvement over the first order:

$$r_{max} = \begin{cases} 0.3679 M(\infty) \kappa & \text{First iteration} \\ 0.3267 M(\infty) \kappa & \text{Second iteration} \\ 0.3182 M(\infty) \kappa & \text{Exact numerical} \end{cases} \quad (44)$$

Substituting y_{max} into Eq. 33 yields the lag time scaling:

$$\tau_{lag} = [\log(1/C_+) + s] \kappa^{-1} \quad (45)$$

where the constant s is defined by:

$$s = \log(y_{max}) + \frac{1 - \exp\left(\sum_{p=1}^{\infty} \frac{(-1)^p y_{max}^p}{p^2 p!}\right)}{\left(\sum_{p=1}^{\infty} \frac{(-1)^p y_{max}^p}{p p!}\right) \exp\left(\sum_{p=1}^{\infty} \frac{(-1)^p y_{max}^p}{p^2 p!}\right)} = -1.8053 \quad (46)$$

Therefore:

$$\tau_{\text{lag}} = [\log(1/C_+) - 1.805] \kappa^{-1} \quad (47)$$

As a consistency check we can verify that setting the upper limits of the summations to unity and setting $y_{\text{max}} = 1$ recovers $s = -e + 1 \approx -1.718$, which is the first iteration result[31], as expected. Summarising the three results:

$$\tau_{\text{lag}} = \begin{cases} [\log(1/C_+) - 1.718] \kappa^{-1} & \text{First iteration} \\ [\log(1/C_+) - 1.805] \kappa^{-1} & \text{Second iteration} \\ [\log(1/C_+) - 1.825] \kappa^{-1} & \text{Exact numerical} \end{cases} \quad (48)$$

The second order result is a substantial improvement over the first with the numerical constant now correct to within 1% of the exact result.

V Higher Order Iterations

In this section, we discuss briefly the convergence behaviour of the fixed-point scheme beyond the second order solutions for the case of fragmenting filaments. In the fixed-point analysis presented so far, the fixed-point operator neglects terms $\mathcal{O}(k_n)$. This is an accurate approximation for the first two self-consistent solutions in the case of fragmenting filaments which we have presented, since the influence of the primary nucleation comes mainly from its effect on the linear solutions used as the starting point of the fixed point scheme. Whilst the rate of creation of filaments from fragmentation increases as the reaction proceeds, the rate of creation of filaments from primary nucleation slows as monomer is depleted. Hence primary nucleation is most important for earlier times, and its relative importance compared to secondary nucleation decreases monotonically.

Repeated iteration, however, using our fixed point scheme, would result in higher order solutions that ultimately converge towards the solution of the master equation neglecting $\mathcal{O}(k_n)$; in other words, further iterations will converge towards the solution of our model with k_n set equal to zero, as if there were no primary nucleation.

A strategy to correct for this convergence behavior in higher order iterations is to develop, or *seed*, the system using the linearized early time solutions $M_e(t)$ and $P_e(t)$ derived in Part I[31], which include $\mathcal{O}(k_n)$, for as long as the early time solution is a good approximation to the exact solution. If the time for which the early solution remains a good approximation is denoted t_e for times greater than t_e the fixed point iteration scheme is then used to find $M(t)$, but now using $M_e(t_e)$, $P_e(t_e)$ from the early time solutions as the initial conditions. The final solution, which converges to the solution including $\mathcal{O}(k_n)$, is then given by the early time limit result continued piecewise to the higher order fixed point iteration at t_e .

This completes our discussion of the polymerisation when the secondary pathway is concentration independent and given by filament fragmentation.

VI Monomer Dependent Secondary Nucleation

In the second part of this paper, we focus on polymerisation processes where the secondary pathway is concentration dependent[4, 32]. The analysis of this type of growth process was pioneered by Eaton and Ferrone[16, 32] in their analysis of sickle hemoglobin gelation. Linear solutions can be obtained much in the same way as for fragmentation, but this type of process introduces more non-linear terms into the master equations which become relevant when mass conservation is enforced. Consequently, such processes are more challenging to treat than the fragmentation case, and we anticipate less rapid convergence of the fixed point scheme. In addition, since the secondary nucleation term is now also affected by monomer depletion, the relative importance of primary and secondary nucleation may vary in a more complicated way than in the fragmentation case where the relative importance of primary to secondary nucleation decreases monotonically as the reaction proceeds. In the case of monomer-dependent secondary nucleation, the inclusion of primary nucleation only in the early time limit is expected to be insufficient in describing accurately the full time course of the reaction.

For the case of monomer dependent secondary nucleation, the equations for the moments become[4, 16, 32]:

$$\frac{dP(t)}{dt} = k_2 M(t) m(t)^{n_2} + k_n m(t)^{n_c} \quad (49)$$

$$\frac{dM(t)}{dt} = 2(m(t)k_+ - k_{\text{off}})P(t) + n_c k_n m(t)^{n_c} + n_2 k_2 M(t) m(t)^{n_2} \quad (50)$$

The first order result for the kinetics of this process was shown to be[30, 31]:

$$M_1(t) \approx M(\infty) \left[1 - \exp(-C_+ e^{\kappa t} + C_- e^{-\kappa t} + D) \right] \quad (51)$$

for the polymer mass concentration M_1 with $\kappa = \sqrt{2m(0)^{n_2}[m(0)k_+ - k_{\text{off}}]k_2}$ and

$$C_{\pm} \approx \frac{k_+ P(0)}{\kappa} \pm \frac{k_+ M(0)}{2[m(0)k_+ - k_{\text{off}}]} \pm \frac{\lambda_0^2}{2\kappa^2}, \quad D = \frac{\lambda_0^2}{\kappa^2} - M(0)/M(\infty) + \frac{k_+ M(0)}{m(0)k_+ - k_{\text{off}}}. \quad \text{The}$$

long-time limit is given by $M(\infty) = M(\infty) \approx m_{\text{tot}} - k_{\text{off}}/k_+$.

Whilst this first order result is a significant improvement over the linear results previously known, it becomes increasingly inaccurate as n_2 is increased as shown in Fig. 2. The strategy for finding a more accurate solution is first to perform a second order iteration, following the fragmentation case, neglecting $\mathcal{O}(k_n)$. This result will be accurate for early and intermediate times, but would be expected to be inaccurate for later times, in particular for high values of n_2 and intermediate values of k_n . As a general strategy, the accuracy of the solution at later times can be improved by using the solution itself to provide a new linearization as an input

for a subsequent fixed-point scheme that will be accurate at later times. An additional advantage of this two part approach is the possibility of including explicitly the primary nucleation terms in the fixed point operator for later times. Our two solutions, each requiring only a small number of terms to remain convergent over a smaller time range, can then be continued piecewise together at an appropriate time given in closed form; in this paper we will chose the point of inflection of $P(t)$ for this purpose.

A Solution prior to the inflection point

In analogy with the fragmentation case, the second order solution in our original fixed point scheme can be obtained from:

$$M(t)=M(\infty) \left[1 - \exp \left(-\frac{M(0)}{M(\infty)} - 2k_+ \int_0^t P(\tau) d\tau \right) \right] \quad (52)$$

Following the fragmentation case, we first derive a result for $P_1(t)$ for early times. To obtain the first iteration result for $P(t)$, we substitute Eq. (51) into Eq. (49). Neglecting terms $\mathcal{O}(k_n)$, the equation to be solved for $P_1(t)$ becomes:

$$\frac{dP_1^e(t)}{dt} = k_2 M_1(t) m_1(t)^{n_2} \quad (53)$$

We substitute $M_1(t) = m_{\text{tot}} - m_1(t)$ using conservation of mass. This reduces the moment equation to:

$$\frac{dP_1^e(t)}{dt} = k_2 m_{\text{tot}} m_1(t)^{n_2} - k_2 m_1(t)^{n_2+1} \quad (54)$$

where the monomer concentration $m(t)$ can be approximated for small depolymerisation rates by making use of Eq. (51):

$$m_1(t) \approx m(0) \exp \left(-C_+ e^{\kappa t} + C_- e^{-\kappa t} + D \right) \quad (55)$$

Performing an equivalent approximation to that of Eq. (11) results in the expression:

$$\frac{dP_1^e(t)}{dt} \approx k_2 m(0)^{n_2+1} \left[\exp \left(-n_2 C_+ e^{\kappa t} \right) - \exp \left(n_2 C_- e^{-\kappa t} \right) - \exp \left(-(n_2+1) C_+ e^{\kappa t} \right) + \exp \left((n_2+1) C_- e^{-\kappa t} \right) \right] \quad (56)$$

Integrating both sides with respect to time yields the self-consistent solution for the polymer number concentration:

$$P_1^e(t) = P(0) + \frac{k_2 m(0)^{n_2+1}}{\kappa} \left[\begin{aligned} &E_1((n_2+1)C_+ e^{\kappa t}) - E_1((n_2+1)C_+) \\ &- E_1(-(n_2+1)C_- e^{-\kappa t}) + E_1(-(n_2+1)C_-) \\ &- E_1(n_2 C_+ e^{\kappa t}) + E_1(n_2 C_+) \\ &+ E_1(-n_2 C_- e^{-\kappa t}) - E_1(-n_2 C_-) \end{aligned} \right] \quad (57)$$

which is analogous to Eq. (13) from our treatment of fragmenting filaments.

We substitute $y = e^{\kappa t}$, $z = e^{-\kappa t}$ so that the integrand from Eq. (52) can be written as:

$$I = \frac{k_2 m(0)^{n_2+1}}{\kappa} \left[\begin{aligned} &E_1(n_2 C_+) - E_1(n_2 C_+ y) \\ &- E_1(-n_2 C_-) + E_1(-n_2 C_- z) \\ &- E_1((n_2+1)C_+) + E_1((n_2+1)C_+ y) \\ &+ E_1(-(n_2+1)C_-) - E_1(-(n_2+1)C_- z) \end{aligned} \right] \quad (58)$$

This expression is the difference between two integrands of the same form as in the fragmentation case, Eq. (15), for which we already know the solutions. Thus, splitting the integral in two, the solution is given by the difference between these two known results Eq. (21). Making the same asymptotic analysis as in the fragmentation case Eq. (23) to acquire the full result gives immediately the closed form expression:

$$\begin{aligned} &\frac{M_2^{\text{series}}(t)}{M(\infty)} \\ &= 1 - \exp \left(\sum_{p=1}^{\infty} \left[\frac{(-C_+)^p ((1+n_2)^p - n_2^p)}{p^2 p!} \left(e^{p\kappa t} - \sum_{q=0}^{2p} \frac{(p\kappa t)^q}{q!} \right) \right. \right. \\ &\quad \left. \left. + \frac{C_-^p ((1+n_2)^p - n_2^p)}{p^2 p!} \left(e^{-p\kappa t} - \sum_{q=0}^{2p} \frac{(-p\kappa t)^q}{q!} \right) \right. \right. \\ &\quad \left. \left. + \frac{(-C_+)^p}{p^2 p!} \left(\frac{((2p-1)\kappa t)^{2p-1}}{(2p-1)!} + \frac{(2p\kappa t)^{2p}}{(2p)!} \right) \right. \right. \\ &\quad \left. \left. + \frac{(C_-)^p}{p^2 p!} \left(\frac{(-(2p-1)\kappa t)^{2p-1}}{(2p-1)!} + \frac{(-2p\kappa t)^{2p}}{(2p)!} \right) \right] - \frac{M(0)}{M(\infty)} \right) \quad (59) \end{aligned}$$

This equation, which is accurate for early times, has an analogous form to the result obtained for the fragmentation case, Eq. (23), except for the presence of the multiplying factor $(1+n_2)^p - n_2^p$ in each term, and also additional polynomial terms. Furthermore, as expected, Eq. (59) reduces to Eq. (23) for $n_2 = 0$ [31].

The convergence discussion from the fragmenting growth section applies to this result as well, except that here the additional multiplicative factor, which increases exponentially with the index of summation, will reduce the convergence rate of the series. Specifically, the rate of convergence in Eq. (59), for the same timescale, is approximately a factor of $(1+n_2)$ slower than that observed for the analogous series in the fragmentation case, Eq. (24), for large p . Crucially, however, whilst the first order iteration result predicts a similar timescale for the completion of the reaction both for the fragmentation and monomer-dependent

secondary nucleation cases, the more accurate second order iteration result shows that the kinetic profile in the latter case is extended in time, with the end point being severely underestimated by the first iteration. A consequence of this observation is that the truncation of the summation must be valid in the monomer dependent secondary nucleation case over a much longer timescale than analogous curves in the fragmentation case. This implies that, although only $(1 + n_2)$ times more terms are required to give convergence over the same timescale, many more terms are required to provide a valid truncation over the extended timescale present in the monomer-dependent case.

The convergence behaviour is demonstrated in Fig. 5, where the first two analytical iterations and the corresponding numerical results (including $\mathcal{O}(k_n)$), are shown. For comparison we also consider the analogous fragmentation induced growth process obtained by identifying $k_- = k_2 m(0)^{n_2}$ and resulting in a secondary process which for $t = 0$ has the same effect as that of the monomer-dependent case. In this analogous fragmentation case, 25 terms in the summation are sufficient to prevent any significant errors from being introduced in to the summation; this success is due to the fact that the divergence in the series occurs after the reaction end point when $M(t) \approx m_{\text{tot}}$ and is therefore inconsequential to the description of the growth phenomenon. In agreement with the convergence discussion above, it is observed in Fig. 5 that with $n_2 + 1 = 3$ times as many terms, i.e. 75, the summation is valid to the same time in the monomer dependent secondary nucleation case as in the fragmentation case, as shown by the fact that the step indicating the divergence in the series Eq. (59) occurs precisely at the end-point of the first order result. Due to the nature of the monomer-dependent secondary processes, the overall growth profile is extended in time in comparison to fragmentation driven polymerisation reactions; this behavior originates from the fact that the rate of monomer-dependent secondary nucleation decreases monotonically as the reaction proceeds, whereas the fragmentation rate remains constant in time. The black dotted in Fig. 5 shows the exact solution in the fragmentation case; it is clear that the first order iteration is significantly better for this class of growth phenomena.

The change in the shape of the curve relative to the fragmentation case can also be seen in the scaling of the lag time. Although this has the same form as the fragmentation case, the constant term in the scaling law is changed, reflecting the change in the shape of the trace. The scaling law from the second iteration result can be found using the same approach as in the fragmentation case, and the results for different vales of n_2 are shown below. We note that $n_2 = 0$ recovers the scaling characteristic of the growth of fragmenting filaments.

$$\tau_{\text{lag}} = \begin{cases} [\log(1/C_+) - 1.718] \kappa^{-1} & \text{First iteration, all } n_2 \\ [\log(1/C_+) - 1.805] \kappa^{-1} & \text{Second iteration, } n_2=0 \\ [\log(1/C_+) - 2.202] \kappa^{-1} & \text{Second iteration, } n_2=1 \\ [\log(1/C_+) - 2.225] \kappa^{-1} & \text{Second iteration, } n_2=2 \\ [\log(1/C_+) - 2.684] \kappa^{-1} & \text{Second iteration, } n_2=5 \\ [\log(1/C_+) - 3.167] \kappa^{-1} & \text{Second iteration, } n_2=10 \end{cases} \quad (60)$$

As n_2 is increased, the first iteration result becomes increasingly poor. In particular, the end time is increasingly underestimated for increasing n_2 , and so more and more terms are needed in the summation for the second order iteration using Eq. (59).

We note that the integrand from Eq. 58 may also be integrated by re-writing:

$$I = \frac{k_2 m(0)^{n_2+1}}{\kappa} (g_+(n_2+1) - g_+(n_2) - g_-(n_2+1) + g_-(n_2) + E_1(n_2 C_+) - E_1((n_2+1)C_+) - E_1(-n_2 C_-) + E_1(-(n_2+1)C_-)) \quad (61)$$

with the functions $g_+(x) = E_1(x C_+ e^{\kappa t})$ and $g_-(x) = E_1(-x C_- e^{-\kappa t})$. Since the integrand contains the same functions $g_{\pm}$ evaluated with different arguments, the integrand can be rewritten exactly as:

$$I = \frac{k_2 m(0)^{n_2+1}}{\kappa} \left(\sum_{i=1}^{\infty} \frac{1}{i!} \frac{d^i g_+(x)}{dx^i} \Big|_{x=n_2} - \sum_{i=1}^{\infty} \frac{1}{i!} \frac{d^i g_-(x)}{dx^i} \Big|_{x=n_2} + E_1(n_2 C_+) - E_1((n_2+1)C_+) - E_1(-n_2 C_-) + E_1(-(n_2+1)C_-) \right) \quad (62)$$

This expression can be evaluated and integrated analytically term by term. For $n_2 = 2$, an expansion to the fifth derivative is sufficient to give an excellent approximation to the exact result, with the result becoming more accurate as n_2 increases. For $n_2 = 1$, however, the expansion in Eq. (62) is poorly convergent.

B Solution post-inflection point

The result Eq. (59) is accurate for all initial conditions and early and intermediate times and gives in closed form the time evolution of a filamentous system that grows through monomer dependent secondary nucleation and filament elongation. In order to extend the applicability of the solution to later times, we will use Eq. (59) to provide the appropriate initial conditions at the characteristic inflection point in the sigmoidal growth curve to initiate a new fixed point iteration providing a more accurate description past the inflection point. Crucially, this approach will also enable us to include exactly the primary nucleation terms into the fixed-point operator, which is vital as the relative balance of primary and secondary nucleation varies as the reaction proceeds.

We consider as the initial input to the late-time fixed point scheme the straight line $P_0^{t_{\max P}}(t)$ that matches $P(t)$ and its gradient at its point of inflection in the reaction profile; the time corresponding to the inflection point is denoted $t_{\max P}$. This choice for the separation between the early and late time solutions is made since at the point of inflection the second derivative of $P(t)$ is zero and therefore a linear approximation is valid here up to the third derivative. The concentration of free monomer $m^* = m(t_{\max P})$ at the time corresponding to

the point of inflection is given through differentiation of Eq. (49) and enforcing the condition $d^2P/dt^2 = 0$ to yield:

$$0 = k_2 n_2 m_*^{n_2-1} m_{\text{tot}} - k_2 (n_2 + 1) m_*^{n_2} + n_c k_n m_*^{n_c-1} \quad (63)$$

First note that in the case $k_n = 0$ has the simple solution:

$$m_* = \frac{n_2}{n_2 + 1} m_{\text{tot}} \quad (64)$$

and to lowest order the nucleation terms can be included through the use of a Newton-Raphson correction to yield:

$$m_* = \frac{n_2}{1 + n_2} m_{\text{tot}} - \frac{k_n \eta^{n_c-1} n_c}{k_n n_c (n_c - 1) \eta^{n_c-2} - k_2 n_2 \eta^{n_2-2} m_{\text{tot}}} \quad (65)$$

where $\eta = m_{\text{tot}} n_2 / (1 + n_2)$. From the first order iteration result, Eq. (51), the time to reach m_* is approximately given by:

$$t_{\text{maxP}} = \begin{cases} \kappa^{-1} \log \left(\frac{-b + \sqrt{b^2 + 4C_+ C_-}}{2C_+} \right) & P''(0)/m'(0) < 0 \\ 0 & P''(0)/m'(0) > 0 \end{cases} \quad (66)$$

for $b = \log(m_*/m(0)) - D$ with m_* from Eq. (65). The condition on the second derivative accounts explicitly for cases where no point of inflection exists, where:

$$P''(0)/m'(0) = k_2 n_2 m(0)^{n_2-1} m_{\text{tot}} - k_2 (n_2 + 1) m(0)^{n_2} + n_c k_n m(0)^{n_c-1} \quad (67)$$

Hence, our new initial linearization of $M(t)$ is given as:

$$M_0^{\text{tmaxP}}(t) = \alpha + \beta (t - t_{\text{maxP}}) \quad (68)$$

To ensure that our solution is also valid for cases without a point of inflection ($t_{\text{maxP}} = 0$), the definitions of α and β are given by:

$$\alpha = \begin{cases} M_2(t_{\text{maxP}}) & t_{\text{maxP}} > 0 \\ M(0) & t_{\text{maxP}} = 0 \end{cases} \quad (69)$$

$$\beta = \begin{cases} M_2'(t_{\max P}) & t_{\max P} > 0 \\ 2(m(0)k_+ - k_{\text{off}})P(0) + n_c k_n m(0)^{n_c} + n_2 k_2 M(0)m(0)^{n_2} & t_{\max P} = 0 \end{cases} \quad (70)$$

where $M(0)$, $m(0)$ and $P(0)$ are initial conditions and $M_2(t)$ is given by Eq. (59); as we only require the pre-inflection point solution Eq. (59) to be valid until $t_{\max P}$ typically only terms in the sum until $p = 3$ are required for adequate convergence.

The corresponding initial solution for $P(t)$ may be found from the differential equations Eqs. (49):

$$P_0^{t_{\max P}}(t) = \gamma + \delta(t - t_{\max P}) \quad (71)$$

where:

$$\gamma = \begin{cases} \frac{M_2'(t_{\max P}) - n_c k_n m_2(t_{\max P})^{n_c} - n_2 k_2 M_2(t_{\max P})m_2(t_{\max P})^{n_2}}{2(m_2(t_{\max P})k_+ - k_{\text{off}})} & t_{\max P} > 0 \\ P(0) & t_{\max P} = 0 \end{cases} \quad (72)$$

$$\delta = \begin{cases} k_2 M_2(t_{\max P})m_2(t_{\max P})^{n_2} + k_n m_2(t_{\max P})^{n_c} & t_{\max P} > 0 \\ k_n m(0)^{n_c} + k_2 M(0)m(0)^{n_2} & t_{\max P} = 0 \end{cases} \quad (73)$$

and $m_2(t) = m_{\text{tot}} - M_2(t)$. Inserting Eq. (71) into Eq. (50), the first self-consistent solution for M is found by direct integration neglecting $\mathcal{O}(k_n)$. With the condition $M(t_{\max P}) = \alpha$ we obtain:

$$\begin{aligned} & \frac{M_1^{t_{\max P}}(t)}{M(\infty)} \\ &= 1 - \frac{(M(\infty) - \alpha)}{M(\infty)} \exp(-2k_+ [\gamma(t - t_{\max P}) \\ & - \delta t_{\max P}(t - t_{\max P}) + (1/2)\delta(t^2 - t_{\max P}^2)]) \end{aligned} \quad (74)$$

The first post-inflection point self-consistent solution for the moment $P(t)$ is found similarly by inserting $M_1^{t_{\max P}}$ into Eq. (49); crucially, we include here exactly the term $\mathcal{O}(k_n)$. Together with the condition $P(t_{\max P}) = \gamma$ this yields:

$$P_1^{t_{\max P}}(t) = \gamma + k_2 m_{\text{tot}} h(n_2, t) - k_2 h(n_2 + 1, t) + k_n h(n_c, t) \quad (75)$$

where

$$h(x, t) = \frac{e^{\frac{\gamma}{\delta} k_+ \gamma x} \sqrt{\pi} (\operatorname{erf}(x, t) - \operatorname{erf}(x, t_{\max P})) (M(\infty) - \alpha)^x}{2 \sqrt{k_+ \delta x}} \quad (76)$$

and

$$\operatorname{erf}(z, t) = \operatorname{Erf} \left(\frac{\gamma}{\delta} \sqrt{k_+ \delta z} + (t - t_{\max P}) \sqrt{k_+ \delta z} \right) \quad (77)$$

for the error function $\operatorname{Erf}(z) = \frac{2}{\sqrt{\pi}} \int_0^z e^{-t^2} dt$. If an expression only in terms of elementary functions is desired, the error function can be approximated as

$\operatorname{Erf}(z) \approx \sqrt{1 - \exp(-z^2 (4/\pi + 0.147z^2) / (1 + 0.147z^2))}$ [38]. A further iteration can be performed from Eq. (50) upto $\mathcal{O}(k_n)$ by direct integration, yielding the final result for the post-inflection point solution $M_2^{t_{\max P}}$:

$$\frac{M_2^{t_{\max P}}(t)}{M(\infty)} = 1 - \frac{(M(\infty) - \alpha)}{M(\infty)} \exp \left[-2k_+ \gamma (t - t_{\max}) - \kappa_0^2 v(n_2, t) + \kappa_0^2 v(n_2 + 1, t) - \lambda_0^2 v(n_c, t) \right] \quad (78)$$

where

$$v(x, t) = \left(\frac{\gamma}{\delta} + (t - t_{\max P}) \right) \frac{h(x, t)}{m(0)^x} + \frac{\left(e^{-k_+ \delta x (t - t_{\max P})^2 - 2k_+ \gamma x (t - t_{\max P})} - 1 \right) (M(\infty) - \alpha)^x}{2k_+ \delta x m(0)^x} \quad (79)$$

for $\kappa_0 = \kappa|_{k_{\text{off}}=0} = \sqrt{2m(0)^{n_2+1} k_+ k_-}$. Apart from the influence of the boundary conditions defined by α and β , these new results for M , Eqs. (74) and (78), depend on the rate constants only through the combinations $k_+ \gamma$, $k_+ \delta$ and their ratio γ/δ . For cases with a lag phase, these combinations are given approximately as:

$$k_+ \gamma \approx \frac{k_+ M_2'(t_{\max P})}{2(k_+ m_2(t_{\max P}) - k_{\text{off}})} \quad (80)$$

$$k_+ \delta = \frac{M_2(t_{\max P}) m_2(t_{\max P})^{n_2}}{2m(0)^{n_2+1}} \kappa_0^2 + \frac{m_2(t_{\max P})^{n_c}}{2m(0)^{n_c}} \lambda_0^2 \quad (81)$$

We note that due to the explicit inclusion of primary nucleation terms, we recover the combination λ_0 which is the single parameter that defines growth of filaments in the absence of secondary nucleation [9, 31]. These terms governed by λ_0 in Eq. (78) become important for kinetic parameters that result in primary nucleation being more significant than secondary nucleation for creating seeds for times after $t_{\max P}$. In many cases, particularly for $n_c > n_2$, these terms are not significant.

The result Eq. (78) can be continued piecewise at $t_{\max P}$ with the result for M_2^{series} from Eq. (59) to give a final result which is continuous by construction. The result is illustrated in Fig. 6 and written out fully up to third order terms in the pre-inflection point solution in the Appendix.

Although these closed form solutions contain more terms than in the case where the secondary pathway is fragmentation, Eq. (23), it is interesting to note that the dependencies on the kinetic parameters are analogous. In particular, in the case of irreversible growth, $k_{\text{off}} = 0$, Eq. (78) continued piecewise with Eq. (59) depends only upon the three kinetic parameters κ , λ_0 and k_+ . Additionally, in the absence of seed material, $M(0) = P(0) = 0$, the closed-form result depends only upon the two combinations of kinetic parameters κ and λ , similarly to Eq. (27).

VII End Point Scaling

The polymerization reaction comes to completion when the free monomer has been partially depleted, and an equilibrium is established between the aggregated and soluble phases. The time at which this equilibrium is reached depends on the initial concentration of monomer at the beginning of the reaction. We show here that this dependence is essentially a power-law of a form analogous to that governing the lag-time, but with a different proportionality constant. We consider here the case where the overall reaction is driven by secondary nucleation processes, and the primary nucleation terms described by λ can be neglected.

For times $t \gg \kappa^{-1}$, Eqs. (23) and (59) show that (for any given n_2) the fractional polymer mass concentration is approximately a function only of the combination $C_+ e^{\kappa t}$. As such, the time needed to reach each given fractional polymer mass concentration in this time limit must correspond to a constant value of $C_+ e^{\kappa t}$. In particular, if the end point of the reaction is defined as τ_{end} such that $M(t_{\text{end}})/M(\infty) = s$, for some constant $s \rightarrow 1$, then it must be the case that $C_+ e^{\kappa \tau_{\text{end}}}$ is constant. Explicitly, for any given n_2 there is a constant c such that:

$$C_+ e^{\kappa \tau_{\text{end}}} = c \quad (82)$$

If τ_{end} is determined from any one curve (choosing some s to define the end point) and used to determine c , it is then possible to rearrange the above result and predict the end time τ_{end} for any other set of parameters via the allometric law:

$$\tau_{\text{end}} = [\log(1/C_+) + \log(c)] \kappa^{-1} \quad (83)$$

For $s = 0.999$, approximate scaling results for some specific cases are found to be:

$$\tau_{\text{end}} = \begin{cases} [\log(1/C_+) + 3.0] \kappa^{-1} & n_2=0 \text{ (fragmentation)} \\ [\log(1/C_+) + 6.9] \kappa^{-1} & n_2=1 \\ [\log(1/C_+) + 11] \kappa^{-1} & n_2=2 \\ [\log(1/C_+) + 25] \kappa^{-1} & n_2=5 \\ [\log(1/C_+) + 47] \kappa^{-1} & n_2=10 \end{cases} \quad (84)$$

which are similar in form to the lag time scaling Eq. (60). This scaling is also of practical interest as it allows the prediction of the relevant timescale of a reaction at the design stage of experiments. In particular, the scaling law reveals approximately $\tau_{\text{end}} \sim m(0)^{-\frac{n_2+1}{2}}$, which is useful in predicting the relevant timescales of reactions at different total monomer concentrations.

VIII Self-Consistent Solution for the Length Distribution

We have derived earlier[31] the time evolution of the mean and standard deviation of the length distribution of fragmenting filaments in the case of a constant monomer concentration[31]. In the case of the standard deviation, these results were obtained under the assumption that the distribution is not heavily skewed. The availability of expressions for both the mean and standard deviation makes it possible to evaluate the time evolution of the full filament length distribution within a self-consistent framework and determine the skewness and higher central moments of the length distribution. To this effect, we demonstrate the wider applicability and power of our self-consistent approach by finding the first correction to the symmetric Gaussian approximation to the length distribution using a self-consistent scheme. We use this result to determine the correction, relative to the mean, to the time evolution of the mode of the distribution, which is not available simply through knowledge of the first three moments of the distribution.

Formally integrating the master equation, the solution for the full length distribution can be written as:

$$\frac{\partial f(t, j)}{\partial t} = 2m_{\text{tot}} k_+ f(t, j-1) - 2m_{\text{tot}} k_+ f(t, j) - k_- (j-1) f(t, j) + 2k_- \sum_{i=j+1}^{\infty} f(t, i) + k_n m_{\text{tot}}^{n_c} \delta_{j, n_c} \quad (85)$$

Formally integrating, the solution can be written as:

$$\begin{aligned}
 f(t, j) = & 2m_{\text{tot}}k_+ e^{-2m_{\text{tot}}k_+t} \int_0^t e^{2m_{\text{tot}}k_+\tau} f(\tau, j-1) d\tau \\
 & - k_- e^{-2m_{\text{tot}}k_+t} \int_0^t e^{2m_{\text{tot}}k_+\tau} \left[(j-1) f(t, j) - 2 \sum_{i=j+1}^{\infty} f(t, i) \right] d\tau \\
 & + k_n m_{\text{tot}}^{n_c} \delta_{j, n_c} e^{-2m_{\text{tot}}k_+t} \int_0^t e^{2m_{\text{tot}}k_+\tau} d\tau
 \end{aligned} \quad (86)$$

We note that it is possible to solve this equation exactly for any $f(j, t)$ recursively beginning with $f(t, n_c)$ and integrating $j - n_c$ times. However, given the considerable coupling of equations in this system through the summation term relating to filament breakage, this approach becomes impractical beyond small j . Instead, it is possible to remove the coupling originating in the fragmentation related terms using a self-consistent approach.

Consider initially the master equation without filament fragmentation, $k_- = 0$. In this case each equation is only coupled to its nearest neighbours and the solution $f_{k_- = 0}(j, t)$, found by repeated integration, is given as:

$$\frac{f_{k_- = 0}(j, t)}{P(t)} = \frac{k_n m_{\text{tot}}^{n_c - 1}}{2k_+} \left(1 - e^{-2m_{\text{tot}}k_+t} \right) - \frac{k_n m_{\text{tot}}^{n_c - 1}}{2k_+} e^{-2m_{\text{tot}}k_+t} \sum_{i=1}^{j-n_c} \frac{(2m_{\text{tot}}k_+t)^i}{i!} \quad (87)$$

In this case the master equation is a discretization of an advection equation and so the solution describes a travelling wave in j moving to encompass larger filament sizes at velocity $2k_+m_{\text{tot}}$.

We now account in a self-consistent manner for the terms in the master equation describing fragmentation by introducing for the filament length distribution in these terms the Gaussian approximation with mean $L(t)$ and standard deviation $L(t)/\sqrt{3}$:

$$f_0(j, t) = \sqrt{\frac{3}{2\pi}} \frac{e^{-\frac{3(j-L(t))^2}{2L(t)^2}}}{L(t)} \frac{P(t)}{E_{\infty}} \quad (88)$$

where E_{∞} is a normalization constant for the distribution between $j = n_c$ and $j = \infty$,

$E_{\infty} \approx 1/2 \left(1 + \text{Erf} \left(\sqrt{3/2} \right) \right) \approx 0.96$, where the approximation is valid since $L(t) \gg n_c$.

Note that the distribution $f_0(j, t)$, due to the cut-off at n_c , has a mean length, $L_0(t)$, different to the exact value, $L(t)$:

$$L_0(t) = \int_{n_c}^{\infty} s f_0(s, t) ds = L(t) + \frac{1}{3} L(t)^2 f_0(n_c, t) \quad (89)$$

We now consider the breakage related terms in Eq. (86). Introducing the initial Gaussian approximation and replacing the summation term in Eq. (86) with a continuum approximation leaves:

$$-k_- e^{-2m_{\text{tot}}k_+t} \int_0^t e^{2m_{\text{tot}}k_+\tau} \left[(j-1) f_0(t, j) - 2P(t) + 2 \int_{i=n_c}^j f_0(t, i) di \right] d\tau \quad (90)$$

In addition, we must account for the coupling of these breakage related terms to nearest neighbours through the first term in Eq. (86), which introduces a summation over j . This allows us to write within this self-consistent framework the full length distribution as a function of time:

$$f_1(j, t) = f_{k_-=0} - k_- e^{-2m_{\text{tot}}k_+t} \int_{n_c}^j \int_0^t e^{2m_{\text{tot}}k_+\tau} \left[(s-1) f_0(t, j) - 2P(t) + 2 \int_{i=n_c}^s f_0(t, i) di \right] d\tau ds \quad (91)$$

Performing the integration with respect to time using the general expansion for large α , $e^{-\alpha t} \int_0^t e^{\alpha \tau} y(\tau) d\tau = y(t)/\alpha + \mathcal{O}(y'(t)/\alpha^2)$, allows us to evaluate these integrals to first-order approximation to give a new expression for the filament length distribution:

$$f_1(j, t) = f_{k_-=0} + \frac{k_-}{2m_{\text{tot}}k_+} (2P(t)(j - n_c) - 2F_1(j, t) - F_2(j, t)) \quad (92)$$

where the functions $E(j, t)$, $F_1(j, t)$ and $F_2(j, t)$ are given in terms of error functions:

$$E(j, t) = \int_{n_c}^j f_0(s, t) ds = \frac{P(t)}{2E_\infty} \left[-\text{Erf} \left(\frac{\sqrt{\frac{3}{2}}(L(t) - j)}{L(t)} \right) + \text{Erf} \left(\sqrt{\frac{3}{2}} \right) \right] \quad (93)$$

$$F_1(j, t) = \int_{n_c}^j E(s, t) ds = \int_{n_c}^j \int_{n_c}^s f_0(r, t) dr ds = [j - L(t)] E(j, t) + \frac{1}{3} L(t)^2 [f_0(j, t) - f_0(n_c, t)] \quad (94)$$

$$F_2(j, t) = \int_{n_c}^j (s-1) f_0(s, t) ds = [L(t) - 1] E(j, t) - \frac{1}{3} L(t)^2 [f_0(j, t) - f_0(n_c, t)] \quad (95)$$

For large j , the errors $\mathcal{O}(\alpha^{-2})$ accumulate due to the integral over j in Eq. (91), resulting in excellent accuracy for small and intermediate j but an incorrect limit for $j \rightarrow \infty$. This limit, however, can be evaluated exactly, yielding $L_0(t) - 2n_c + 1$. Removing the associated terms yields:

$$f_1(j, t) = f_{k_- = 0} + \frac{k_-}{2m_{\text{tot}}k_+} \left[2[1 - E(j, t)][j - n_c] - \frac{1}{3}L(t)^2 [f_0(j, t) - [1 - E(j, t)]f_0(n_c, t)] \right] \quad (96)$$

The result $f_1(j, t)$, Eq. (96), is expected to be highly accurate for small filament sizes, since the coupled integration over j is most accurate in this regime. Due to the contribution from the solution of the advection equation, Eq. (87), we would expect the result to be accurate up to lengths $2L(t)$, or equivalently $\sqrt{3} \approx 1.7$ standard deviations above the mean, thus being accurate for all but the tail of the distribution. The improvement over the initial Gaussian solution obtained using the information from the first three principal moments is shown in Fig. 7.

The mode of the distribution can be obtained from the condition:

$$0 = f_0(j_{\text{mode}}, t)(2 - L_0(t) - j) + 2 - 2E(j_{\text{mode}}, t) \quad (97)$$

Expanding the Gaussian $f_0(j, t)$ to lowest order about the mean results in:

$$0 = \frac{\sqrt{\frac{3}{2\pi}}}{L(t)E_\infty} [2 - L_0(t) - j_{\text{mode}}] + 2 - 2 \left(\frac{1}{2E_\infty} \text{Erf} \left(\sqrt{\frac{3}{2}} \frac{L(t) - n_c}{L(t)} \right) + \frac{\sqrt{\frac{3}{2\pi}}}{L(t)E_\infty} [j_{\text{mode}} - L(t)] \right) + \mathcal{O}(j_{\text{mode}}^2) \quad (98)$$

Using $L(t) \gg n_c$ and Eq. (89) yields the simple result:

$$j_{\text{mode}} = \frac{1}{3} \left(1 + \sqrt{\frac{2\pi}{3}} - \frac{1}{3} \sqrt{\frac{3}{2\pi}} \frac{e^{-\frac{3}{2}}}{E_\infty} \right) L(t) \approx 0.8L(t) \quad (99)$$

As expected, the mode of the distribution is below the mean, and we recover the interesting result that the ratio of the mode to the mean, and hence also to the standard deviation, is approximately a constant in time for this system; the mode evolves with the same functional form as the mean and variance. The improvement in the value of the mode of the filament distribution in the distribution $f_1(j, t)$ compared with the original Gaussian $f_0(j, t)$ is shown in Fig. 8.

IX Conclusion

We have used the power of iterative fixed point schemes to provide self-consistent solutions to growth processes described by highly non-linear master equations. We have shown that corrections to the scaling behaviour emerging from first order results can be well captured by second order self-consistent solutions, which yield coefficients for the characteristic scaling laws which are very close to ones obtained from numerical evaluation. More generally, these results illustrate the value of fixed-point analysis strategies in order to provide self-consistent solutions to complex growth problems beyond perturbative treatments.

Appendix

The second-order self-consistent solution to the non-linear equation system describing filamentous growth:

$$\frac{dP(t)}{dt} = k_2 M(t) m(t)^{n_2} + k_n m(t)^{n_c} \quad (100)$$

$$\frac{dM(t)}{dt} = 2(m(t)k_+ - k_{\text{off}})P(t) + n_c k_n m(t)^{n_c} + n_2 k_2 M(t) m(t)^{n_2} \quad (101)$$

with $m(t) = m_{\text{tot}} - M(t)$ derived in this paper is written out in full in terms of only elementary functions as:

$$\frac{M(t)}{M(\infty)} = \begin{cases} 1 - \exp \left[\kappa^2 t^2 + \frac{4\kappa^4 t^4}{3} + \frac{81\kappa^6 t^6}{40} + \left(e^{-\kappa t} - 1 + \kappa t - \frac{\kappa^2 t^2}{2} \right) C_- - \left(e^{\kappa t} - 1 - \kappa t - \frac{\kappa^2 t^2}{2} \right) C_+ \right. \\ \quad \left. + \frac{1}{8} \left(e^{-2t\kappa} - 1 + 2t\kappa - 2t^2\kappa^2 + \frac{4t^3\kappa^3}{3} - \frac{2t^4\kappa^4}{3} \right) C_-^2 - \left((1+n_2)^2 - n_2^2 \right) \right. \\ \quad \left. + \frac{1}{8} \left(e^{2t\kappa} - 1 - 2t\kappa - 2t^2\kappa^2 - \frac{4t^3\kappa^3}{3} - \frac{2t^4\kappa^4}{3} \right) C_+^2 - \left((1+n_2)^2 - n_2^2 \right) \right] & t \leq t_{\text{maxP}} \\ \quad + \frac{1}{54} \left(e^{-3t\kappa} - 1 + 3t\kappa - \frac{9t^2\kappa^2}{2} + \frac{9t^3\kappa^3}{2} - \frac{27t^4\kappa^4}{8} + \frac{81t^5\kappa^5}{40} - \frac{81t^6\kappa^6}{80} \right) C_-^3 - \left((1+n_2)^3 - n_2^3 \right) \\ \quad - \frac{1}{54} \left(e^{3t\kappa} - 1 - 3t\kappa - \frac{9t^2\kappa^2}{2} - \frac{9t^3\kappa^3}{2} - \frac{27t^4\kappa^4}{8} - \frac{81t^5\kappa^5}{40} - \frac{81t^6\kappa^6}{80} \right) C_+^3 - \left((1+n_2)^3 - n_2^3 \right) - \frac{M(0)}{M(\infty)} & \\ 1 - \frac{(M(\infty)-\alpha)}{M(\infty)} \exp \left[-2k_+ \gamma (t - t_{\text{max}}) - \kappa_0^2 v(n_2, t) + \kappa_0^2 v(n_2+1, t) - \lambda_0^2 v(n_c, t) \right] & t > t_{\text{maxP}} \end{cases} \quad (102)$$

where the dependencies on the rate constants and initial conditions are defined through:

$$\kappa = \sqrt{2(k_+ m(0) - k_{\text{off}}) m(0)^{n_2} k_2} \quad \kappa_0 = \sqrt{2m(0)^{n_2+1} k_+ k_2} \quad \lambda_0 = \sqrt{2m(0)^{n_c} k_+ k_n} \quad (103)$$

$$C_{\pm} = \frac{k_+ P(0)}{\kappa} \pm \frac{k_+ M(0)}{2[m(0)k_+ - k_{\text{off}}]} \pm \frac{\lambda_0^2}{2\kappa^2} \quad t_{\text{maxP}} = \begin{cases} \kappa^{-1} \log \left(\frac{-b + \sqrt{b^2 + 4C_+ C_-}}{2C_+} \right) & P''(0)/m'(0) < 0 \\ 0 & P''(0)/m'(0) > 0 \end{cases}$$

(104)

$$M(\infty) = m_{\text{tot}} - k_{\text{off}}/k_+ \quad \alpha = M(t_{\text{maxP}}) \quad b = \log \left(\frac{m_*}{m(0)} \right) - \frac{\lambda_0^2}{\kappa^2} + \frac{M(0)}{M(\infty)} - \frac{k_+ M(0)}{k_+ m(0) - k_{\text{off}}}$$

(105)

$$m_* = \frac{n_2}{1+n_2} m_{\text{tot}} - \frac{k_n \left(\frac{m_{\text{tot}} n_2}{1+n_2} \right)^{n_c-1} n_c}{k_n n_c (n_c - 1) \left(\frac{m_{\text{tot}} n_2}{1+n_2} \right)^{n_c-2} - k_2 m_{\text{tot}} n_2 \left(\frac{m_{\text{tot}} n_2}{1+n_2} \right)^{n_2-2}} \quad (106)$$

$$h(x, t) = \frac{e^{\frac{\gamma}{\delta} k_+ \gamma x} \sqrt{\pi} (\text{erf}(x, t) - \text{erf}(x, t_{\text{maxP}})) (M(\infty) - \alpha)^x}{2 \sqrt{k_+ \delta x}} \quad (107)$$

$$\text{erf}(z, t) = \text{Erf} \left(\frac{\gamma}{\delta} \sqrt{k_+ \delta z} + (t - t_{\text{maxP}}) \sqrt{k_+ \delta z} \right) \approx \sqrt{1 - \exp \left(- \left(\frac{\gamma}{\delta} \sqrt{k_+ \delta z} + (t - t_{\text{maxP}}) \sqrt{k_+ \delta z} \right)^2 \frac{4/\pi + 0.147 \left(\frac{\gamma}{\delta} \sqrt{k_+ \delta z} + (t - t_{\text{maxP}}) \sqrt{k_+ \delta z} \right)}{1 + 0.147 \left(\frac{\gamma}{\delta} \sqrt{k_+ \delta z} + (t - t_{\text{maxP}}) \sqrt{k_+ \delta z} \right)} \right)}$$

(108)

$$v(x, t) = \left(\frac{\gamma}{\delta} + (t - t_{\text{maxP}}) \right) \frac{h(x, t)}{m(0)^x} + \frac{\left(e^{-k_+ \delta x (t - t_{\text{maxP}})^2 - 2k_+ \gamma x (t - t_{\text{maxP}})} - 1 \right)}{2k_+ \delta x} \frac{(M(\infty) - \alpha)^x}{m(0)^x}$$

(109)

$$k_+\gamma \approx \frac{k_+M_2'(t_{\max P})}{2(k_+m_2(t_{\max P})-k_{\text{off}})} \quad k_+\delta = \frac{M_2(t_{\max P})m_2(t_{\max P})^{n_2}}{2m(0)^{n_2+1}}\kappa_0^2 + \frac{m_2(t_{\max P})^{n_c}}{2m(0)^{n_c}}\lambda_0^2 \quad (110)$$

The accuracy of this solution even for high exponents n_2, n_c is demonstrated in Fig. 2.

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Fig. 1.

Highly non-linear processes in protein polymerisation. The primary nucleation rate depends on the monomer concentration $m(t)$ with a power of the critical nucleus size n_c , and secondary nucleation processes depend on both the polymer concentration $M(t)$ and the monomer concentration to a power n_2 ; values of n_2 up to $n_2 = 30$ have been reported[14, 16]. The special case of filament fragmentation[1] is monomer independent $n_2 = 0$.

Fig. 2.

Illustration of the nature of the solutions to highly non-linear growth problems derived using the fixed point scheme (insert). An analytical solution to filament growth through primary nucleation, monomer dependent secondary nucleation, filament elongation and depolymerization [Eqs. (49), (50)] is shown in red and the complete closed form self-consistent solution is provided in the Appendix. The black line is the exact numerical result. For comparison, the green dashed line is the numerical result neglecting primary nucleation, the purple dashed line is the numerical result neglecting secondary nucleation. The blue dotted line is the first order result[31] and the orange dot-dashed line is the linearized solution[5, 16, 32, 33]. The parameters are: $n_c = 35$, $n_2 = 20$, $k_+ = 5 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{off}} = k_+ m_{\text{tot}}/30$, $k_2 m_{\text{tot}}^{n_2} = 2 \cdot 10^{-8} \text{ s}^{-1}$, $k_n m_{\text{tot}}^{n_c-1} = 5 \cdot 10^{-10} \text{ s}^{-1}$, $m_{\text{tot}} = 5 \cdot 10^{-5} M$, $M(0) = 5 \cdot 10^{-11} M$, $R(0) = M(0)/5000$.

Fig. 3.

Convergence of the first two fixed point analytical iterations towards the exact solution. The blue dotted line is the first order result, the red dashed line is the second order result and the solid black line is the exact result. The orange dot-dashed line is the early time limit linearized solution. The parameters are: $k_+ = 5 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{off}} = k_+ m_{\text{tot}}/100$, $k_- = 2 \cdot 10^{-8} \text{ s}^{-1}$, $k_p = 5 \cdot 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, $m_{\text{tot}} = 1 \cdot 10^{-6} \text{ M}$, $n_c = 2$, $M(0) = 1 \cdot 10^{-8} \text{ M}$, $P(0) = M(0)/5000$. The summation in the second order iteration is truncated after 25 terms.

Fig. 4.

Convergence of the first two fixed-point analytical iterations towards the exact solution in the absence of breakage. The blue dotted line is the first order result, the red dashed line is the second order result and the solid black line is the numerical result. The parameters are: $k_+ = 5 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{off}} = k_- = 0 \text{ s}^{-1}$, $k_n = 5 \cdot 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, $m_{\text{tot}} = 5 \cdot 10^{-6} \text{ M}$, $n_c = 2$, $M(0) = P(0) = 0$.

Fig. 5.

Convergence of the p th fixed point iteration, $M_n(t)$, using the early time linearization. M_1 (blue dashed, Eq. (3)), M_2^{series} (red dashed, Eq. (59) with 75 terms), exact solution including $\mathcal{O}(k_n)$ (black). The lighter solid lines show the corresponding numerical results. The black dotted line is the exact result for the analogous fragmentation case for comparison. The orange dot-dashed line is the early time linearization. The parameters are $M(0) = P(0) = 0M$, $k_+ = 5 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{off}} = 0$, $k_2 m(0)^{n_2} = 2 \cdot 10^{-8} \text{ s}^{-1}$, $k_n = 2 \cdot 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, $m_{\text{tot}} = 5 \cdot 10^{-6} M$, $n_c = 2$, $n_2 = 2$.

Fig. 6.

The solution found using a second linearization about the point of inflection, $t_{\max P}$ (indicated by the vertical black dotted line), is continued piecewise to M_2^{series} . The cyan dot-dashed line is the new initial approximation, Eq. (68). For $t < t_{\max P}$, the red dashed line is M_2^{series} (Eq. (59) with 25 terms). For $t > t_{\max P}$, the blue dashed line is the first order iteration given by the new expansion, $M_1^{t_{\max P}}$ (Eq. (74)), and the red dashed line is the corresponding second order iteration, $M_2^{t_{\max P}}$ (Eq. (78)). The orange dot-dashed line is the early time linearization. The parameters are $M(0) = 5 \cdot 10^{-8} M$, $P(0) = M(0)/5000$, $k_+ = 2 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{off}} = k_+ m_{\text{tot}}/20$, $k_2 m_{\text{tot}}^{n_2} = 5 \cdot 10^{-8} \text{ s}^{-1}$, $k_n = 1 \cdot 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, $m_{\text{tot}} = 5 \cdot 10^{-6} M$, $n_c = 2$, $n_2 = 1$.

Fig. 7.

The solution derived for the time evolution of the full filament length distribution in our self-consistent scheme, Eq. (96), is shown in red (dashed). The numerical result is shown in black, and the initial Gaussian approximation, Eq. (88), is shown in blue (dotted).

Fig. 8.

The correction to the mode in relation to the mean, Eq. (99), exhibited by our solution to the full length distribution, Eq. (96), is shown in red (dashed). The numerical result is shown in black, and the result from the initial Gaussian approximation is shown in blue (dotted).

Table I

Comparison of the first and second order self-consistent solutions for irreversible filament growth with fragmentation with exact results calculated numerically

	First order analytical	Second order analytical	Exact numerical[37]
Polymer mass $\frac{M(t)}{M(\infty)} =$	$1 - \exp\left(-C_+ e^{-\kappa t} + C_- e^{-\kappa t} + \frac{\lambda_0^2}{\kappa}\right)$	$1 - \exp\left(\sum_{p=1}^{\infty} \left[\frac{(-C_+)^p}{2^p p!} e^{p\kappa t} - \sum_{q=0}^{2p-1} \frac{(p\kappa t)^q}{q!}\right] + \frac{C_-^p}{2^p p!} \left(e^{-p\kappa t} - \sum_{q=0}^{2p-1} \frac{(-p\kappa t)^q}{q!}\right) - \frac{M(0)}{M(\infty)}\right)$	
	$\kappa = \sqrt{2m(0)k_+k_-} \lambda_0 = \sqrt{2m(0)} k_+ k_n = \frac{k_+ P(0)}{\kappa} \pm \frac{M(0)}{2m(0)} \pm \frac{\lambda_0^2}{2\kappa^2}$		
Lag time $\tau_{\text{lag}} =$	$[\log(1/C_+) - 1.718] \kappa^{-1}$	$[\log(1/C_+) - 1.805] \kappa^{-1}$	$[\log(1/C_+) - 1.825] \kappa^{-1}$
Maximal growth rate $r_{\text{max}}/M(\infty)=$	0.3679κ	0.3267κ	0.3182κ
No breakage limit $\frac{M(t)}{m_{\text{tot}}} \approx$ (no seeding $M(0) = 0$)	$1 - \exp\left(-t^2 k_+ k_n m_{\text{tot}}^c\right)$	$1 - \exp\left(-t^2 k_+ k_n m_{\text{tot}}^c + \frac{1}{6} t^4 k_+^2 k_n^2 m_{\text{tot}}^{2n_c} + \mathcal{O}(t^6)\right)$	$1 - \exp\left(-t^2 k_+ k_n m_{\text{tot}}^c + \frac{1}{6} t^4 k_+^2 k_n^2 m_{\text{tot}}^{2n_c} + \mathcal{O}(t^6)\right)$