Applied Mathematics Letters 40 (2015) 97–101

Contents lists available at ScienceDirect

Applied Mathematics Letters

journal homepage: www.elsevier.com/locate/aml

A study in nucleated polymerization models of protein aggregation

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ARTICLE INFO

Article history:
Received 11 September 2014
Accepted 12 September 2014
Available online 16 October 2014

Keywords:
Difference equation
Generating function
Prions
Protein aggregates
Nucleated polymerization

ABSTRACT

The nucleated polymerization model is a mathematical framework that has been applied to aggregation and fragmentation processes in both the discrete and continuous settings. In particular, this model has been the canonical framework for analyzing the dynamics of protein aggregates arising in prion and amyloid diseases such as Alzheimer's and Parkinson's disease.

We present an explicit steady-state solution to the aggregate size distribution governed by the discrete nucleated polymerization equations. Steady-state solutions have been previously obtained under the assumption of continuous aggregate sizes; however, the discrete solution allows for direct computation and parameter inference, as well as facilitates estimates on the accuracy of the continuous approximation.

1. Introduction

Prion proteins are the cause underlying a host of fatal, mammalian diseases—including bovine spongiform encephalopathy (mad cow disease), fatal familial insomnia, and Creutzfeldt–Jakob disease [1–3]. These diseases arise when a misfolded (prion) form of a protein appears and forms aggregates. Aggregates of the misfolded form act as templates to convert the normally folded protein to its misfolded state. Fragmentation of prion aggregates amplifies the number of templates facilitating the spread of the disease [4,5]. Beyond prions, linear protein aggregates (amyloids) are associated with over 20 neurodegenerative diseases such as Alzheimer's and Parkinson's disease [6].

Since the formation of an initial stable nucleus of misfolded proteins is viewed as the time-limiting step in spontaneous or genetic prion diseases, most mathematical models have focused on the time-evolution of the aggregate size distribution [7,8]. The nucleated polymerization model [9] has been extensively analyzed and results on the existence, uniqueness, and stability of solutions are known [10–12]; with a continuous relaxation on aggregate size, the asymptotic density is also known [12,13]. While the continuous-size approximation is valid for large average aggregate sizes [14], this condition need not apply to all prion systems [15].

Aggregates of protein monomers are discrete in nature and much can still be said regarding the original, discrete formulation. We provide an explicit, closed-form solution for the steady-state distribution of discrete aggregate sizes. By doing so, we consider the asymptotic aggregate dynamics without resorting to continuous approximations. The closed form solution allows for explicit computation of statistics that may be useful for parameter inference. Finally, we compare our discrete steady-state solution to the continuous approximation.

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http://dx.doi.org/10.1016/j.aml.2014.09.007

2. Mathematical analysis of prion aggregation and fragmentation

2.1. Discrete nucleated polymerization model

The dynamics of prion aggregates are typically modeled by the nucleated polymerization model first introduced by Masel et al. [9]. In this model, normal protein is converted to the prion form through contact with existing aggregates. Existing aggregates may also fragment into two smaller aggregates. The equations for the nucleated polymerization model may be written as follows:

$$\frac{ds}{dt} = \alpha - \mu s(t) - 2\beta s(t)\sum_{i=n_0}^{\infty} u_i(t) + \gamma n_0(n_0-1)\sum_{i=n_0}^{\infty} u_i(t) \tag{1}$$

$$\frac{du_i}{dt} = -2\beta s[u_i(t) - u_{i-1}(t)] - \mu u_i(t) - \gamma(i-1)u_i(t) + 2\gamma\sum_{j=i+1}^{\infty} u_j(t). \tag{2}$$

Above, $s(t)$ denotes the concentration of the healthy (non-prion) protein monomers, $u_i(t)$ the concentration of prion aggregates of size i, n_0 the minimum stable aggregate size (we write $u_i(t) \equiv 0$ for $i < n_0$), α the rate of translation of monomers, μ the dilution or degradation rate, and β the rate of conversion of monomers by prion aggregates. The parameter γ describes the rate of aggregate fragmentation. In our formulation, we follow the conventional assumption that prion aggregates are linear polymers and thus fragmentation may occur between any two prion monomers [9–12]. That is, if γ is the rate of fragmentation between any two prion monomers, then the rate of fragmentation of an aggregate of size $i \geq n_0$ is $\gamma(i-1)$. (Note that alternative models for aggregate conversion and fragmentation have also been considered [14,16].)

The standard approach for analyzing the discrete nucleated polymerization model is to define auxiliary variables for the zeroth and first moments of the aggregate sizes [1,9]. Let $\eta = \sum_{i=n_0}^{\infty} u_i$ and $z = \sum_{i=n_0}^{\infty} iu_i$. Then, the system will close over the moments of the density:

$$\frac{ds}{dt} = \alpha - \mu s(t) - 2\beta s(t)\eta(t) + \gamma n_0(n_0-1)\eta(t) \tag{3}$$

$$\frac{d\eta}{dt} = -\left[\mu + \gamma(2n_0-1)\right]\eta(t) + \gamma z(t) \tag{4}$$

$$\frac{dz}{dt} = 2\beta s(t)\eta(t) - \mu z(t) - \gamma n_0(n_0-1)\eta(t). \tag{5}$$

This 3-dimensional system has two steady-state solutions, one corresponding to a disease-free state where all prion aggregates are eliminated and one corresponding to persistence of the prion disease [11], i.e. an endemic equilibrium. Furthermore, Prüss et al. [11] observed that the system can be transformed to a standard epidemiological model and found the basic reproductive number, $\mathcal{R}_0$, that determines the stability of the disease. However, these results say little about the density profile of aggregate sizes. Since this system has solutions that exist for all time, we treat $s(t)$, $\eta(t)$, and $z(t)$ as known functions and rewrite (2) as follows:

$$\frac{du_i}{dt} = -2\beta s(t)[u_i(t) - u_{i-1}(t)] - \mu u_i(t) - \gamma(i+1)u_i(t) + 2\gamma\left[\eta(t) - \sum_{j=n_0}^{i-1} u_j(t)\right]. \tag{6}$$

Henceforth we consider only the system at equilibrium, i.e. when $\frac{du_i}{dt} = 0$ for each i and $\frac{ds}{dt} = 0$. We write $s(t)$, $\eta(t)$, $z(t)$, $u_i(t) \to s, \eta, z, u_i$ as $t \to \infty$, where $s = \alpha/\mu$, $\eta = z = 0$ in the case of the disease-free state or

$$\frac{2\beta s}{\gamma} = \left(n_0 + \frac{\mu}{\gamma}\right)\left(n_0 + \frac{\mu}{\gamma} - 1\right), \qquad \frac{z}{\eta} = 2n_0 - 1 + \frac{\mu}{\gamma}, \qquad s + z = \frac{\alpha}{\mu}, \tag{7}$$

in the case of the endemic state.

2.2. Asymptotic distribution of aggregate sizes

Let $\zeta = n_0 + \frac{\mu}{\gamma}$ and define $v_i = (u_{n_0-1+i})/\eta$ and $v_0 = 0$, $w_0 = 1$. Though we divided by η, we treat this formally—our result will still be valid in the disease-free case when $\eta = 0$. As observed by Masel et al. [9], the density will satisfy the following recurrence relation:

$$v_i = \frac{\left(\zeta^2 - \zeta\right)v_{i-1} + 2w_{i-1}}{\zeta^2 + i}, \tag{8}$$

$$w_i = w_{i-1} - v_i. \tag{9}$$