A Discrete Time Branching Process Model of Yeast Prion Curing Curves

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Abstract

Prion proteins are implicated in a variety of neurodegenerative diseases in mammals and heritable phenotypes in fungi. The infectious agent of these disorders is thought to be small aggregates of prion protein, which are transmitted between cells. Recent work in yeast supports this hypothesis by demonstrating only aggregates below a critical size are efficiently transmitted. The number of transmissible aggregates in a typical cell is a key determinant of the strain infectivity. Previous models developed to estimate this quantity in yeast assumed the pool of transmissible aggregates remains constant throughout an experiment, and will underestimate the true number.

We develop a discrete time branching process model of yeast prions taking into account the dynamic nature of the aggregate pool. Prion aggregates increase in size according to a Poisson process and only aggregates below a threshold size are transmitted during cell division. We derive an expression for the number of cells with aggregates in a population and discuss practical considerations in analyzing experiments.
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AMS 2000 Mathematics Subject Classification Codes: 60G99, 60K99, 62P10, 92D25.

1 Introduction

Transmission of an observable trait, or phenotype, typically involves changes to DNA, the genetic code. However, there are heritable phenotypes that are passed on by a special class of proteins called prions. In mammals, the prion protein PrP has been implicated in a variety of neurodegenerative disorders such as "mad-cow disease" (Bovine Spongiform Encephalopathy or BSE) and Creutzfeldt-Jakob Disease (Griffith 1967, Prusiner 1982, Collinge 1999). In the yeast *S. cerevisiae* prion proteins, such as Sup35 and Ure2, create heritable phenotypes but unlike their mammalian counterparts these prions do not impact the viability of the organism (Tuite & Cox 2009, Fowler & Kelly 2009, Sindi & Serio 2009). Thus, yeast provides an ideal model system for studying the processes influencing prion proteins.

According to the prion hypothesis, new phenotypes arise when misfolded versions of a protein appear and are joined together in aggregates. These misfolded (prion) proteins self-replicate their conformation by converting normal proteins and being passed to other cells. There are four biochemical processes essential to maintaining the prion phenotype (Figure 1): (1) **synthesis** of new normal protein; (2) **conversion** of normal protein to the misfolded state by existing aggregates; (3) creation of new prion aggregates through **fragmentation** of existing aggregates into smaller complexes and (4) **transmission** of prions to daughter cells.

Although all steps are essential to the persistence of the prion phenotype, many open questions remain. Inducing loss, by perturbing one of the steps in the prion cycle, has

often been used to study aspects of the prion process. For example, loss of the prion state has been used to investigate the number of prion aggregates in a typical yeast cell.

For the yeast prion protein Sup35, the addition of guanidine hydrochloride (GdnHCl) has been shown to halt the fragmentation process (Byrne et al. 2007). Since no new prion aggregates are created, the existing aggregates are gradually diluted through cell division and the population is eventually **cured** of the prion state because the fraction of cells with prion aggregates decreases to 0.

Morgan et al. (2003) developed a novel way to estimate the number of **propagons**, transmissable prion aggregates by studying cultures grown with the addition of GdnHCl. Authors estimated the number of initial propagons, n_0, in a typical cell by analyzing the rate of loss of the prion state in a population of cells grown in the presence of GdnHCl from a founder with prion aggregates. In Morgan et al. (2003), cell division is modeled as a binary fission process; that is, during cell division prion aggregates are equally likely to end up in either resulting cell.

Cole et al. (2004) developed an improvement to Morgan et al. (2003) by incorporating two biologically relevant asymmetries in yeast cell division. First, a newly born daughter takes longer to divide the first time than in subsequent divisions. Second, the volume difference between mature (mother) and newly born (daughter) cells suggests that daughter cells will inherit fewer than 50% of the propagons. In Cole et al. (2004) and later Byrne et al. (2009), parameters related to cell growth were fixed and the number of propagons, n_0, and proportion transmitted to daughter cells, π, were estimated from the experimental results.

Both Cole et al. (2004) and Morgan et al. (2003) assume all prion aggregates are all equally transmissable. However, recent studies (Sindi & Serio 2009, Derdowski et al. 2010, Calvez et al. 2009, Ghaemmaghami et al. 2007), suggest that only a subset of the aggregate population is capable of transmission. A combination of experimental work and mathematical simulations indicate that for the yeast prion Sup35, only aggregates below a threshold size about 20 monomers, can be efficiently transmitted during cell division (Derdowski et al. 2010). This suggests that rather than being a static entity, the set of transmissable aggregates (propagons) changes over time and at any instance is simply a sub-population of aggregates below the transmission threshold.

Since the addition of GdnHCl halts only the fragmentation process, aggregates will continue to grow by converting soluble protein (Ness et al. 2002, Satpute-Krishnan et al. 2007). Thus, over time some aggregates will become too large to transmit and remain in the mother cell. Without size-dependent transmission of prion aggregates, prior models (Byrne et al. 2009, Cole et al. 2004) will underestimate the number of transmissible aggregates in the founding cell.

In this manuscript, we develop a branching process to model loss of the prion state in a growing culture of yeast cells without aggregate fragmentation, continued growth of aggregates and size limited aggregate transmission. Our model represents the first theoretical formulation of the prion curing process under these biological assumptions,

although the recent work of Palmer et al. (2010) studies simulations of the curing process under similar conditions. We consider a discrete model of cell division, and thus implicitly equal division times for mother and daughter cells. We derive an expression for the fraction of cells containing prion aggregates in a growing colony. We use simulations to demonstrate that models assuming equal transmissibility of aggregates will underestimate the number of propagons and provide discuss practical considerations for estimating parameters.

2 Branching Process Model

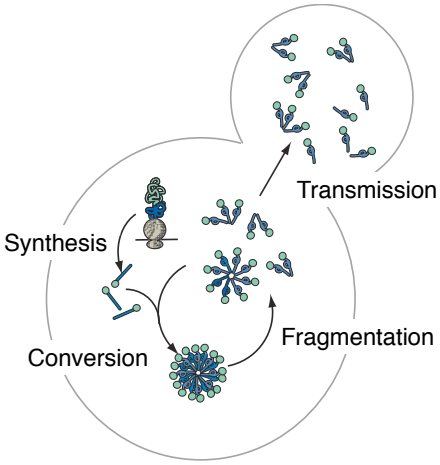


Figure 1: **Yeast Prion Cycle.** There are four steps essential for the persistence of the prion state: synthesis, conversion, fragmentation and transmission from mother to daughter cell.

A curing experiment begins with a single cell with some initial number of prion aggregates each with an associated size. In the discrete time model, the population grows through non-overlapping generations during which each individual cell divides, thus doubling the population at each iterate. Although this model neglects asynchronous effects due to individual lifetime variation, the model is still a useful approximation, especially if the variability in individual lifetimes is low. Our model will also be used to point out the effect on estimation of the initial prion number when prion conversion is taken into account.

A given cell can be either a mother, M, if it has previously reproduced, or a daughter, D, if it has not yet reproduced. After each reproduction event, we consider the two resulting cells to be newborn, even though one of them is, in reality, the mother. Thus, a mother gives birth to a mother and a daughter, and a daughter gives birth to a mother and a

daughter as well. The importance of distinguishing between mothers and daughters comes from prion conversion.

We model conversion by having each prion aggregate independently growing in size, one unit at a time, according to a Poisson process with rate β (see Figure 1). We take the generation time to be unity, thus, β is the expected number of conversion events per cell per generation. Once a prion has grown to a critical size, it can no longer be transmitted to the daughter and is retained in the mother cell during division. That is, when cells divide aggregates smaller than the transmission threshold T are transmitted to newly created daughter cells according to a binomial distribution with success probability p. Aggregates with size greater than or equal to T will remain in the mother cell from that point onward.

In any given generation there will be cells with and without prion aggregates. Our goal is to get an expression for the expected proportion of cells with prions which is the type of data that can be assessed in curing experiments. In our derivations we do not consider cell death. Since a typical yeast cell survives for roughly 25 generations (Sinclair et al. 1998), and the time scale for a typical curing experiment is typically less than 30 hours, ≈ 20 generations, loss of the prion state due to cell death is negligible (Cole et al. 2004, Morgan et al. 2003).

2.1 Uniform Initial Aggregate Size

Let Z_n be the number of cells with prions in generation n, starting from an ancestor with N_i prions that are i units from reaching the critical size, at which point transmission to a daughter cell is no longer possible. The expected proportion of cells with prions in generation n conditioned on N_i is then

$$P_n^{(N_i)} = \frac{E[Z_n|N_i]}{2^n}$$

and the unconditional expected proportion is

$$P_n = \frac{E[Z_n]}{2^n} \tag{2.1}$$

First we find an expression for the conditional expectation $E[Z_n|N_i]$. Each cell in the nth generation can be described by a sequence of mothers and daughters and that once a prion reaches critical size, it cannot be transmitted to the daughter but must stay in the mother. Thus, we divide the set of the 2^n possible sequences of mothers and daughters into subsets S_{nld} of sequences where the last daughter is in position l and there is a total of d daughters. For example, the sequence DDMMM is in S_{522}, the sequences DMDMM and MDDMM are both in S_{532}, and so on. Let n_{ld} be the number of sequences in S_{nld}; then $n_{ld} = \binom{l-1}{d-1}$ for $l = 0, ..., n$ and $d = 0, ..., l$ [where $\binom{-1}{-1} = 1$ and $\binom{l-1}{-1} = 0$ for $l \geq 1$]. Note that the number n_{ld} does not depend on n since after the final daughter, there are no further choices. Also note that for fixed n, the n_{ld} sum to 2^n as they should.

Let A_n be the event that a cell has prions in the nth generation and let $P_{ld}^{(r)}$ denote the probability measure for a sequence in S_{nld} given that the initial number of prions is r. We have

$$E[Z_n|N_i] = \sum_{l=0}^{n}\sum_{d=0}^{l}\binom{l-1}{d-1}P_{ld}^{(N_i)}(A_n) \tag{2.2}$$

Since different prions are transmitted independently of each other, we get

$$P_{ld}^{(N_i)}(A_n) = 1 - \left(1 - P_{ld}^{(1)}(A_n)\right)^{N_i} \tag{2.3}$$

where $1 - P_{ld}^{(1)}(A_n)$ is the probability that a given prion in the ancestor does not appear in the nth generation, in the given sequence. If N_i has probability generating function (pgf) φ, given by

$$\varphi(s) = E\left[s^{N_i}\right]$$

we get the unconditional probability

$$\begin{aligned} P_{ld}(A_n) &= E\left[P_{ld}^{(N_i)}(A_n)\right] \\ &= 1 - E\left[\left(1 - P_{ld}^{(1)}(A_n)\right)^{N_i}\right] \\ &= 1 - \varphi\left(1 - P_{ld}^{(1)}(A_n)\right) \end{aligned}$$

so that

$$E[Z_n] = \sum_{l=0}^{n}\sum_{d=0}^{l}\binom{l-1}{d-1}\left(1 - \varphi\left(1 - P_{ld}^{(1)}(A_n)\right)\right).$$

To obtain an expression for $P_{ld}^{(1)}(A_n)$, we condition on the critical generation G, that is, the generation in which the prion reaches its critical size and is no longer transmissible to daughters. What is important here is that l is the position for the final daughter so from $l+1$ on, the sequence consists of only mother cells. Thus, if $G < l$, the prion cannot be present in the sequence since it cannot be passed on to the final daughter cell, hence, the probability is positive only for $G \geq l$. Specifically, if $G = j$ where $l \leq j < n$, the prion must successfully reach generation j by chance after which it stays in the mother cell. Let p be the probability that the prion is passed on to the daughter so that $1 - p$ is the probability it stays in the mother. We then get

$$P_{ld}^{(1)}(A_n|G=j) = p^d(1-p)^{j-d}$$

for $l = 0, ..., n$ and $d = 0, ..., l$ which gives

$$P_{ld}^{(1)}(A_n) = \sum_{j=l}^{n-1} p^d(1-p)^{j-d} P_i(G=j) + p^d(1-p)^{n-d} P_i(G \geq n). \tag{2.4}$$

Before the first generation, $n = 0$ which implies $l = d = 0$ and gives $P_{00}^{(1)}(A_0) = 1$ as expected. The notation P_i indicates the the distribution of G depends on i, the remaining number of conversion events until the critical size is reached. The expression (2.1) for the expected fraction of cells with prions in generation n is

Proposition 2.1.

$$P_n = 2^{-n}\left[\sum_{l=0}^{n}\sum_{d=0}^{l}\binom{l-1}{d-1}\left(1-\varphi\left(1-P_{ld}^{(1)}(A_n)\right)\right)\right]$$

where φ is the pgf of the initial number of prions, N_i, and the $P_{ld}^{(1)}(A_n)$ are given by (2.4).

To compute the probabilities $P_i(G = j)$ that appear in (2.4), note that prion conversion is a Poisson process with rate β so that times between successive conversion events are independent random variables having the exponential distribution with rate β (mean $1/\beta$). Denoting their common distribution function by H we thus have

$$P_i(G=j) = H^{*i}(j+1) - H^{*i}(j)$$

where $*$ denotes convolution; thus, H^{*i} is the distribution function for the gamma distribution with parameters i and β. For $j = 0$ we get

$$P_i(G=0) = H^{*i}(1)$$

the probability that there are at least i conversion events before the ancestor divides.

In the special case when $N_i \sim \text{Poi}(n_i)$, a Poisson distribution with mean n_i, we have $\varphi(s) = \exp(n_i(s-1))$ which gives

$$E[Z_n] = \sum_{l=0}^{n}\sum_{d=0}^{l}\binom{l-1}{d-1}\left(1-\exp\left(-n_i P_{ld}^{(1)}(A_n)\right)\right) \tag{2.5}$$

2.2 Many Initial Aggregate Sizes

We next consider a generalization where there are m different initial aggregate sizes. That is, the initial cell contains N_i prions that are i units away from the critical size for $i = 1, 2, ..., m$. In a slight generalization from the previous section, let $P_{ld}^{(N_1,...,N_m)}$ be the probability measure for a sequence in S_{ld} given these initial conditions, and let $P_{ld}^{(1,i)}$ be the probability measure for a sequence in S_{ld} for one initial prion i units away from the critical size. The analog of (2.3) is

$$P_{ld}^{(N_1,...,N_m)}(A_n) = 1 - \prod_{i=1}^{m} \left(1 - P_{ld}^{(1,i)}(A_n)\right)^{N_i}$$

which gives the unconditional probability

$$P_{ld}(A_n) = 1 - \varphi\left(1 - P_{ld}^{(1,1)}(A_n), 1 - P_{ld}^{(1,2)}(A_n), ..., 1 - P_{ld}^{(1,m)}(A_n)\right)$$

where φ now denotes the joint pgf of the random vector $(N_1, N_2, ..., N_m)$. With this adjustment, the expression for P_n given in Proposition 2.1 remains the same. If the N_i are independent, the pgf factors into the product of the individual pgfs. In particular, if the N_i are independent with $N_i \sim \text{Poi}(n_i)$, we get

$$P_{ld}(A_n) = 1 - \exp\left(-\sum_{i=1}^{m} n_i P_{ld}^{(1,i)}(A_n)\right) \tag{2.6}$$

The $P_{ld}^{(1,i)}$ are computed as in (2.4), substituting $P_{ld}^{(1,i)}$ for $P_{ld}^{(1)}$, noting the dependence on i of the distribution of G.

3 Simulations

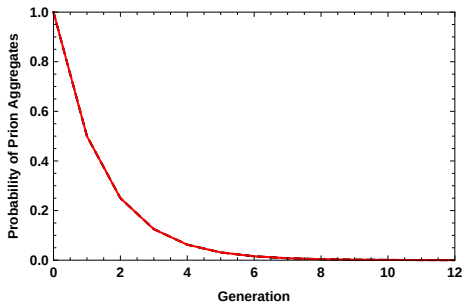
We demonstrate the accuracy of the results developed in the previous section by comparing to simulations of the prion curing process. In addition, we show that models of prion curing neglecting continued conversion and size limited transmission will underestimate the number of prion aggregates in the initial cell. Finally, we give some insight into practical limitations in estimating model parameters from the data directly.

3.1 Uniform Initial Aggregate Size

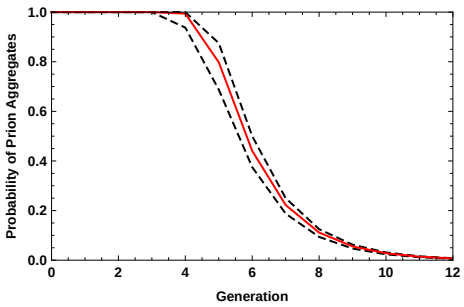
In the following simulations, we assume that all aggregates in the founder cell at time 0 have the same size. In Figure 3.1 we compare our theoretical result to simulations of prion curing for three different regimes of β: fast, medium and slow prion growth. In each simulation, the population begins with a single cell with a Poisson distributed number of initial aggregates, with mean $n_0 = 200$ and $i = 20$. We plot our theoretical curing curve

along with 5th and 95th percentiles from 50 independent simulated curing experiments. Over all rates of prion growth, our theoretical curves agree with the simulations.

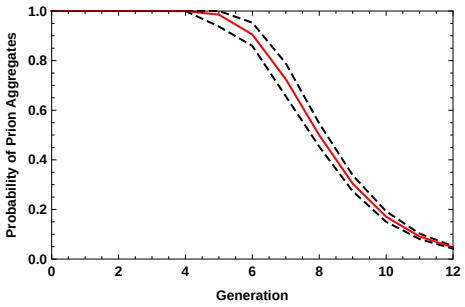
Depending on the rate of aggregate growth, loss of the prions in the population is caused by distinct mechanisms. When prion growth is much faster than cell division, with high probability all prions reach maximum size before the initial cell divides. Thus, the rate of curing is simply the rate of exponential population growth, see Figure 2(a). When prion growth is much slower than cell division, aggregates remain transmissible for a longer amount of time. Thus, the rate of loss of the prion state in Figure 2(c) is slower than that of Figures 2(a) and 2(b). For intermediate rates of growth, loss of the prion state becomes a combination of dilution of aggregates due to exponential population growth and eventually the transmission deficiency from larger aggregates.



(a) Fast Prion Growth



(b) Medium Prion Growth



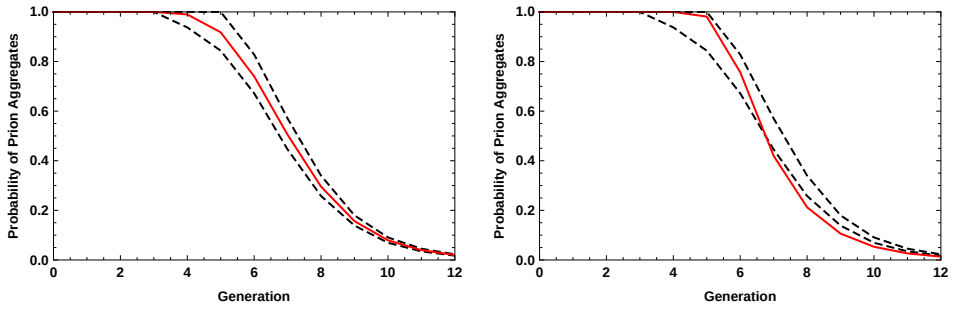
(c) Slow Prion Growth

Figure 2: We demonstrate agreement of our theoretical results for hundreds of initial prions and three regimes of prion growth: fast, medium and slow. In all cases we show our theoretical distribution (red) and the 5th and 95th percentiles from 50 independent simulations. For fast prion growth 2(a) loss of the prion state is dominated by exponential population growth, for slow growth 2(c) loss of the prion state is dominated by dilution of aggregates during cell division. Finally in medium growth 2(b) prions become too large to transmit during the experiment and loss is impacted by both effects.

3.2 Many Initial Aggregate Sizes

Next we consider the loss of the prion state in populations founded by a cell with aggregates of multiple initial sizes. When the variance of initial aggregate sizes is large, the rate of loss is not well described by a model with only a single aggregate size. In Figure 3.2 we show 5th and 95th percentiles from 50 simulations where the founding cell has an average of 100 aggregates 10 conversions away from T and 100 aggregates 40 conversions from T.

As shown in Figure 3(a), our theoretical curve, Equation (2.6), closely matches the simulations. In contrast, considering only the average initial aggregate size, Equation (2.5), results in deviations from the simulations (see Figure 3(b)). By considering only the average we underestimate early loss, because aggregates becoming intransmissible faster than predicted by the average size, and overestimate later loss, because aggregates remain transmissible longer than predicted by the average size.



(a) Multiple Aggregate Sizes (b) Single Aggregate Size

Figure 3: We demonstrate accuracy of our derivation for loss of the prion state when the founding cell has aggregates with two different initial sizes, ($i_1 = 10$, $i_2 = 40$), $\beta = 0.21$ and $n_0 = 200$. Our model with multiple initial aggregate sizes (a) describes the data more accurately than the using the average initial aggregate size in our initial formulation (b).

3.3 Neglecting Conversion and Size-Limited Transmission Underestimates the Number of Prion Aggregates

Earlier work modeling curing curves assumed prions to be transmissible at all times (Cole et al. 2004, Morgan et al. 2003). These models assume that the appearance of loss during a curing experiment comes from dilution of aggregates by cell division, rather than retention of larger aggregates in the mother. When the rate of aggregate growth is much slower than the rate of cell division, loss is not effected by conversion and, as such, estimating the number of prion aggregates using these models should closely match the true number. However, when aggregates become too large to transmit before the population grows large enough to fully dilute the aggregates, such models will underestimate the number of initial aggregates.

When aggregates of all sizes are transmissible the probability of an aggregate in a cell at generation n is purely a function of the binomial probability of transmission. Thus, Equation (2.4) greatly simplifies since we need not distinguish between different sequences in S_{nld}:

$$P_{ld}^{(1)}(A_n) = p^d(1-p)^{(n-d)} \tag{3.1}$$

Applying Proposition 2.1 and simplifying yields the following expected fraction of cells with prions in generation n:

$$P_n = 2^{-n} \sum_{d=0}^{n} \binom{n}{d} \left(1 - \exp\left(-n_0 p^d (1-p)^{n-d}\right)\right). \tag{3.2}$$

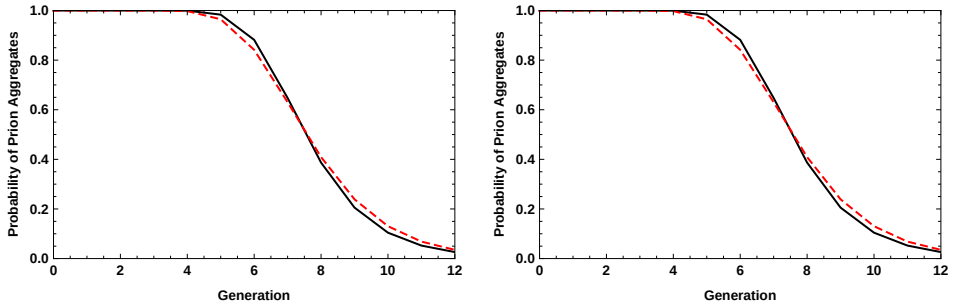
In Figure 4 we plot theoretical curing curves from our model (black) along with estimated curing curves assuming aggregates of all sizes are transmissible (red). Theoretical curing curves shown in Figure 4(a) and 4(b) have $\beta = 0.37$ and $i = 20$. To estimate parameters for the model neglecting conversion, we fixed $p = 0.40$, as this parameter is known in the literature Cole et al. (2004), Morgan et al. (2003), Palmer et al. (2010) and select n_0 to minimizing the least-squared error between curing curves. Although the model without conversion produces very similar curing curves, with least squared error ≤ 0.09, it underestimates the number of aggregates by 25% when $n_0 = 200$ ($\hat{n_0} = 147.89$) and 40% when $n_0 = 400$ ($\hat{n_0} = 235.06$).

The increased deviation with increasing n_0 comes from the fact that as the number of aggregates increase, the minimum observed critical generation decreases. Thus, the more aggregates present, the more likely that some aggregate will have had at least i conversions by generation n. The deviation between the true n_0 and the estimate for n_0 obtained using Equation (3.2) will also increase with increasing conversion β and decreasing i as both factors will decrease the number of generations an aggregate will remain transmissible.

3.4 Parameter Estimation

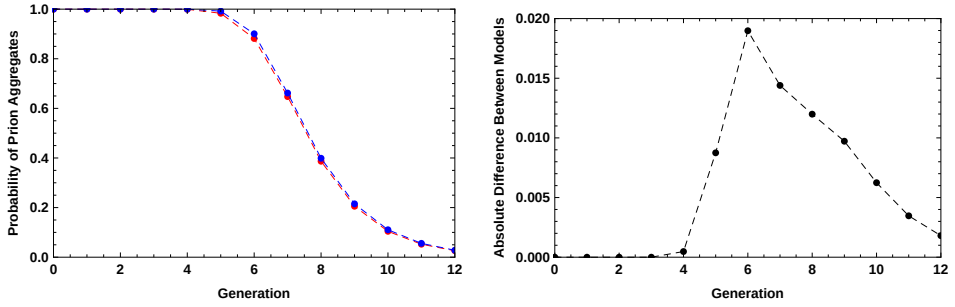
Although our model predicts more prion aggregates than models without conversion, consideration should be taken when estimating parameters from data. Since aggregates larger than the threshold size cannot be transmitted, many aggregates growing rather quickly can look like fewer aggregates growing more slowly. In Figure 5, two theoretical curves have strikingly different numbers of initial aggregates, $n_0 = 200$ and $n_0 = 372$, yet the underlying curing curves are extremely similar.

The similarity of curing curves for distinct parameter combinations means that prior knowledge may be important when estimating parameters from data. In Figures 6(a)-6(f) we show the deviation, according to the log-least-squares error, from three simulated curing curves generated with $n_0 = 200, i = 20, \beta = 0.37$, over a range of parameters, $10^{-6} \leq \beta \leq 0.74$, $0 \leq n_0 \leq 400$ and $5 \leq i \leq 30$. For a fixed choice of i, a wide range of choices for n_0 and β will produce similar least-squared deviation from the theoretical



(a) $n_0 = 200, \hat{n_0} = 147.90$ (b) $n_0 = 400, \hat{n_0} = 235.06$

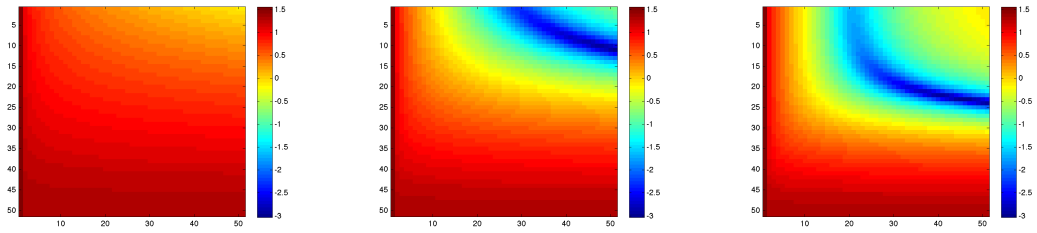
Figure 4: Models of prion curing curves without conversion and size-limited transmission will underestimate the initial number of aggregates. In (a) and (b) we plot our theoretical curves (black) and estimated curing curves (red) assuming no size limit on transmission. Although this model produced very similar curing curves, the number of aggregates is underestimated by 25% (a) and 40% (b).



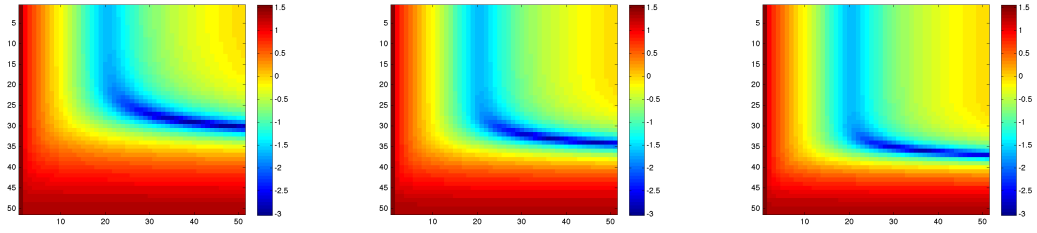
(a) Curing Curve Comparison (b) Absolute Difference

Figure 5: To demonstrate the similarity in curing curves for different parameters, we compare (a) two theoretical curing curves and (b) their absolute differences. In (a) we show curing curves for different parameter values, (red) $\beta = 0.37$,$n_0 = 200$, and $i = 20$ with (blue) $\beta = 1$, $n_0 = 372$ and $i = 6$. As shown in (b), the two curing curves are extremely similar, with least squares difference of ≈ 0.01.

curve. These figures illustrate the dependency between n_0 and β with respect to the trade-off between many aggregates growing slowly and fewer aggregates growing quickly.



(a) $i = 5$ (b) $i = 10$ (c) $i = 15$



(d) $i = 20$ (e) $i = 25$ (f) $i = 30$

Figure 6: We plot the log-least-squares error between a three curing curves simulated with $n_0 = 200, \beta = 0.36$ and $i = 20$ and theoretical curves for choices for β (x-axis, $10^{-6} \leq \beta \leq 0.74$), n_0 (y-axis; $0 \leq n_0 \leq 400$) and i, denoting the initial prion size. The true parameters used to simulate the process lie in the center of Figure 6(d). As discussed in the text, there is a trade-off between many aggregates growing slowly and fewer growing faster and multiple parameter combinations yield highly similar curing curves.

4 Conclusion

We derived expressions for theoretical curing curves based on the assumption of discrete-time division and that aggregates larger than a certain size become intransmissible. In addition to including the biological complexities of continued aggregate growth by conversion and size-limited transmission, our work provides several novel contributions.

First, our work provides an explicit formulation to estimate the number of transmissible aggregates in the founding cell. By neglecting conversion and transmission deficiencies, previous models will underestimate this number. Second, our model provides the first mathematical approach to estimate the rate of conversion from curing experiments. Previously, most estimates of the rate of conversion were based on the analysis of *in vitro* experiments (Tanaka et al. 2006, Palmer et al. 2010).

Since different parameter combinations can yield strikingly similar curing curves, it may be difficult to estimate the true parameters from real data using the discrete model presented without prior knowledge about the initial size or rate of aggregate conversion. However, we anticipate that a continuous model of cell division will alleviate some of these issues as well as provide a more realistic depiction of the biological processes.

Finally, in our derivations we do not consider cell death because in most curing experiments, there is total loss of the prion aggregates before the first expected cell death (Byrne et al. 2009, Cole et al. 2004). Although, our models could be modified to consider cell death, in previous work on modeling aging in yeast, contributions from including cell death were negligible (Olofsson & Daileda 2011, Olofsson & Bertuch 2010).

Acknowledgements

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