Branching process models of prion dynamics

Peter Olofsson, Suzanne Sindi, Jason Davis

Trinity University and UC Merced

Mathematics Applied Mathematics

April 7, 2015

PRIONS

Infectious agents composed of misfolded proteins.

PRIONS

Infectious agents composed of misfolded proteins.

Mad cow disease, Creutzfeldt–Jakob disease.

PRIONS

Infectious agents composed of misfolded proteins.

Mad cow disease, Creutzfeldt–Jakob disease.

Studied in yeast (do no harm).

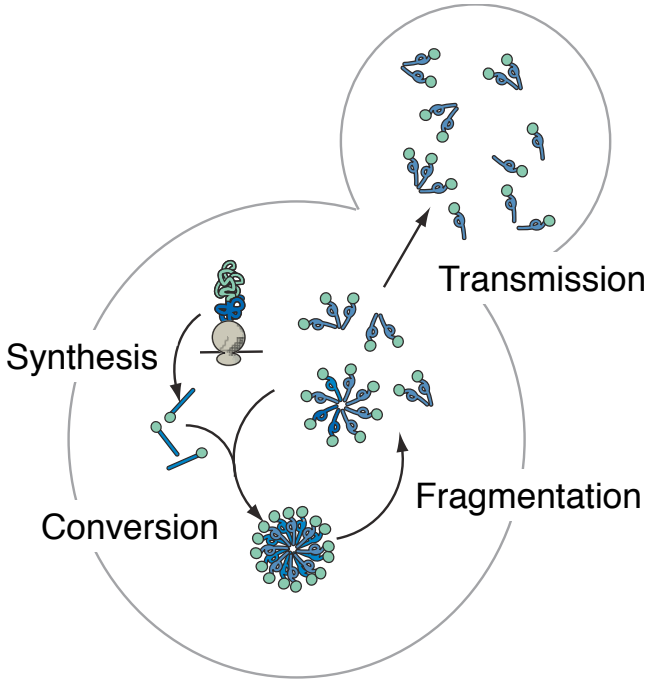
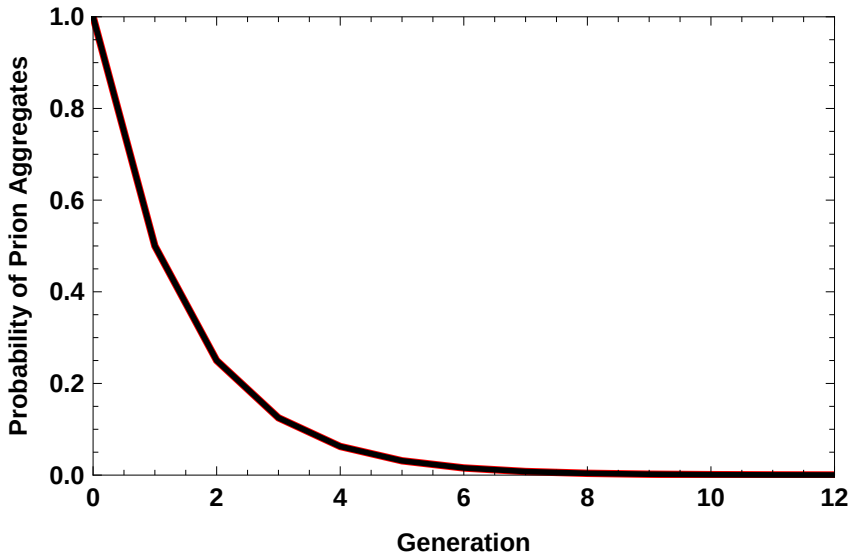
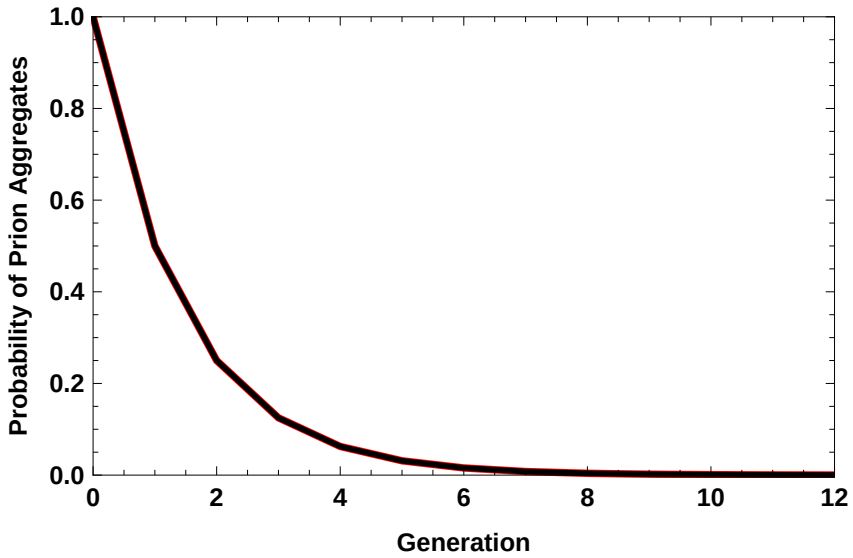


Figure : **Yeast Prion Cycle.** There are four steps essential for the persistence of the prion state: synthesis, conversion, fragmentation and transmission from mother to daughter cell.

CURING CURVE: The fraction of cells that have prions as a function of time. Starts at 100%, declines toward 0%. Many prions initially means slower decline.



CURING CURVE: The fraction of cells that have prions as a function of time. Starts at 100%, declines toward 0%. Many prions initially means slower decline.



Note: Without fragmentation, the number of prions stays constant.

One goal: estimate number of prions in initial cell from curing curve.

One goal: estimate number of prions in initial cell from curing curve.

SOME PREVIOUS WORK:

L.J. Byrne, D.J. Cole, B.S. Cox, M.S. Ridout, B.J.T. Morgan, and M.F. Tuite. The number and transmission of [PSI+] prion seeds (propagons) in the yeast Saccharomyces cerevisiae. *PLoS One*, 4(3):4670, 2009.

DJ Cole, BJT Morgan, MS Ridout, LJ Byrne, and MF Tuite. Estimating the number of prions in yeast cells. *Mathematical Medicine and Biology*, 21(4):369, 2004.

One goal: estimate number of prions in initial cell from curing curve.

SOME PREVIOUS WORK:

L.J. Byrne, D.J. Cole, B.S. Cox, M.S. Ridout, B.J.T. Morgan, and M.F. Tuite. The number and transmission of [PSI+] prion seeds (propagons) in the yeast Saccharomyces cerevisiae. *PLoS One*, 4(3):4670, 2009.

DJ Cole, BJT Morgan, MS Ridout, LJ Byrne, and MF Tuite. Estimating the number of prions in yeast cells. *Mathematical Medicine and Biology*, 21(4):369, 2004.

No conversion (prions do not grow). Tends to underestimate initial number of prions since larger prions are more difficult to pass on to daughter.

DISCRETE MODEL:

Binary splitting, no death. After splitting: one mother, one daughter. A given prion is transmitted to the daughter cell with probability $p < 0.5$ (literature suggests $p \approx 0.4$).

DISCRETE MODEL:

Binary splitting, no death. After splitting: one mother, one daughter. A given prion is transmitted to the daughter cell with probability $p < 0.5$ (literature suggests $p \approx 0.4$).

$Z_n =$ number of cells with prions in nth generation.

DISCRETE MODEL:

Binary splitting, no death. After splitting: one mother, one daughter. A given prion is transmitted to the daughter cell with probability $p < 0.5$ (literature suggests $p \approx 0.4$).

$Z_n =$ number of cells with prions in nth generation.

Fraction of cells with prions: $P_n = \dfrac{E[Z_n]}{2^n}$

Cell in nth generation has ancestry of the type

$$MMDDM....MMDM$$

of d daughters and m mothers.

Cell in nth generation has ancestry of the type

$$MMDDM....MMDM$$

of d daughters and m mothers.

Without prion growth: Initial prion present with probability $p^d(1-p)^m$.

Cell in nth generation has ancestry of the type

$$MMDDM....MMDM$$

of d daughters and m mothers.

Without prion growth: Initial prion present with probability $p^d(1-p)^m$.

With prion growth: easier to be in $MDMMM$ than in $MMMMD$.

Cell in nth generation has ancestry of the type

$$MMDDM....MMDM$$

of d daughters and m mothers.

Without prion growth: Initial prion present with probability $p^d(1-p)^m$.

With prion growth: easier to be in $MDMMM$ than in $MMMMD$.

Prions grow one unit at a time according to a Poisson process with rate β (continuous time).

Assume a critical size after which prions can no longer be transmitted to the daughter cell.

Assume a critical size after which prions can no longer be transmitted to the daughter cell.

Consider sequences in generation n where the final daughter is in position k and there is a total of l daughters. There are $\binom{k-1}{l-1}$ such sequences.

Assume a critical size after which prions can no longer be transmitted to the daughter cell.

Consider sequences in generation n where the final daughter is in position k and there is a total of l daughters. There are $\binom{k-1}{l-1}$ such sequences.

Example: $n = 5, k = 3, l = 2 : DMDMM, MDDMM$

Assume a critical size after which prions can no longer be transmitted to the daughter cell.

Consider sequences in generation n where the final daughter is in position k and there is a total of l daughters. There are $\binom{k-1}{l-1}$ such sequences.

Example: $n = 5, k = 3, l = 2 : DMDMM, MDDMM$

Initial prion is i units (conversion events) from critical size. Probability p_{nkl} it is present in such a sequence? Depends on critical generation G when initial prion gets too big. Before G, random allocation ($p = 0.4$). From G on, prion stays in mother.

Assume a critical size after which prions can no longer be transmitted to the daughter cell.

Consider sequences in generation n where the final daughter is in position k and there is a total of l daughters. There are $\binom{k-1}{l-1}$ such sequences.

Example: $n = 5, k = 3, l = 2 : DMDMM, MDDMM$

Initial prion is i units (conversion events) from critical size. Probability p_{nkl} it is present in such a sequence? Depends on critical generation G when initial prion gets too big. Before G, random allocation ($p = 0.4$). From G on, prion stays in mother.

If $G < k$, $p_{nkl} = 0$ and if $G = j \geq k$, $p_{nkl} = p^l(1-p)^{j-l}$.

Hence

$$p_{nkl} = \sum_{j=k}^{n-1} p^l (1-p)^{j-l} P(G = j) + p^l (1-p)^{n-l} P(G \geq n)$$

What is $P(G = j)$?

Hence

$$p_{nkl} = \sum_{j=k}^{n-1} p^l (1-p)^{j-l} P(G = j) + p^l (1-p)^{n-l} P(G \geq n)$$

What is $P(G = j)$?

Critical generation is $j \Leftrightarrow i$ conversion events (Poisson points) have occurred by time $j+1$ but not by time j

Hence

$$p_{nkl} = \sum_{j=k}^{n-1} p^l (1-p)^{j-l} P(G = j) + p^l (1-p)^{n-l} P(G \geq n)$$

What is $P(G = j)$?

Critical generation is $j \Leftrightarrow i$ conversion events (Poisson points) have occurred by time $j+1$ but not by time j

Let H be the distribution function of the $\exp(\beta)$ distribution:

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

where H^{*i} is the distribution function for the gamma distribution with parameters i and β.

Now assume N_i initial prions of size i. Conditional probability at least one is in given sequence:

$$P_{nkl}^{N_i} = 1 - (1 - p_{nkl})^{N_i}$$

Now assume N_i initial prions of size i. Conditional probability at least one is in given sequence:

$$P_{nkl}^{N_i} = 1 - (1 - p_{nkl})^{N_i}$$

Unconditionally:

$$P_{nkl} = 1 - \varphi(1 - p_{nkl})$$

where φ is the pgf of N_i:

$$\varphi(s) = E[s^{N_i}] = \sum_k s^k P(N_i = k)$$

All taken together: expected fraction of cells with prions is

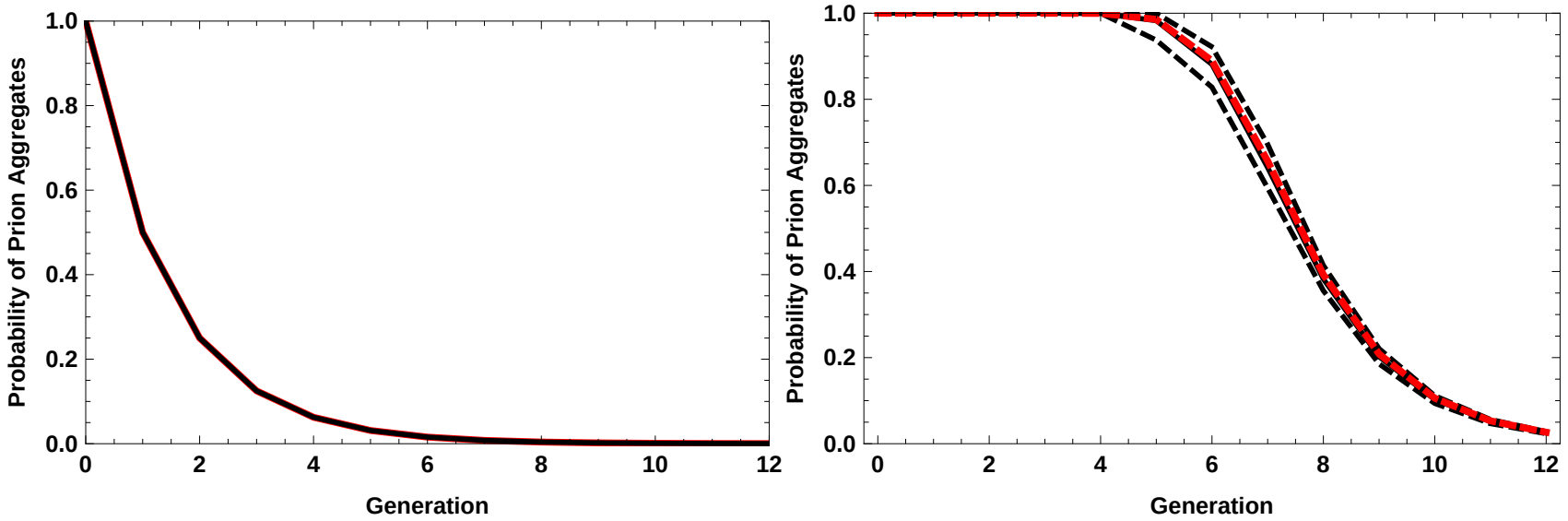
$$P_n = 2^{-n} \left[\sum_{k=0}^{n} \sum_{l=0}^{k} \binom{k-1}{l-1} (1 - \varphi(1 - p_{nkl})) \right]$$

All taken together: expected fraction of cells with prions is

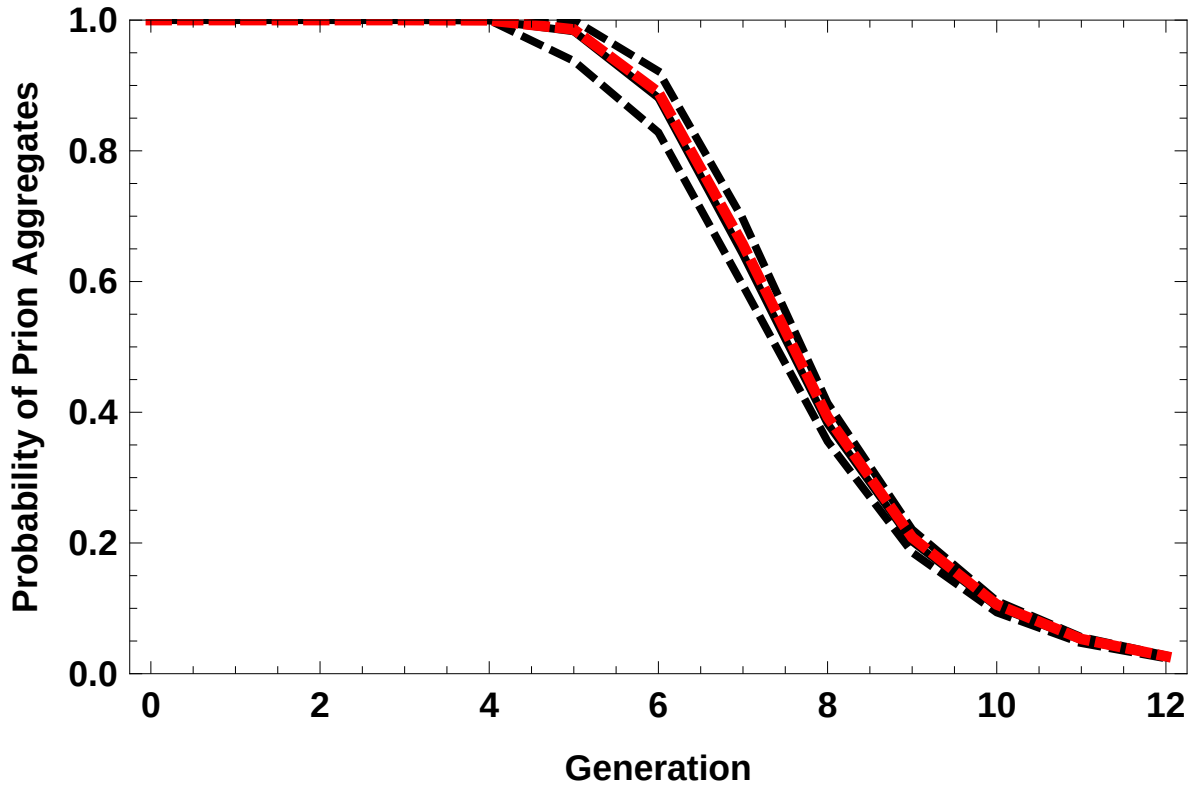
$$P_n = 2^{-n} \left[\sum_{k=0}^{n} \sum_{l=0}^{k} \binom{k-1}{l-1} (1 - \varphi(1 - p_{nkl})) \right]$$

Obvious extension to many different i and N_i: multivariate pgf's.

Simulations, 5th and 95th percentiles (black), model with estimated parameters (red), large β (fast growth) and small β (slow growth).



Initial number of prions $n_0 = 209$, our estimate $\widehat{n_0} = 191.8$, disregarding prion growth $\widehat{n_0} = 150.6$.



CONTINUOUS MODEL (Crump-Mode-Jagers process)

Newborn cell needs time to grow and mature, produces first daughter cell at time D, then produces daughter cells at times $D + M_1, D + M_1 + M_2, ...$

CONTINUOUS MODEL (Crump-Mode-Jagers process)

Newborn cell needs time to grow and mature, produces first daughter cell at time D, then produces daughter cells at times $D + M_1, D + M_1 + M_2, ...$

Reproduction process

$$\xi(dt) = \delta_D(dt) + \sum_{k=1}^{N} \delta_{D+M_1+\cdots M_k}(dt)$$

where $N =$ total number of daughter cells (can practically assume $N = \infty$) [Green (1981)].

$$P_t \approx \frac{E[Z_t]}{E[Y_t]} = \frac{\text{expected number of cells with prions at time } t}{\text{expected number of cells at time } t}$$

$$P_t \approx \frac{E[Z_t]}{E[Y_t]} = \frac{\text{expected number of cells with prions at time } t}{\text{expected number of cells at time } t}$$

Expressions similar to but much more complicated than discrete case.

$$P_t \approx \frac{E[Z_t]}{E[Y_t]} = \frac{\text{expected number of cells with prions at time } t}{\text{expected number of cells at time } t}$$

Expressions similar to but much more complicated than discrete case.

$$E[Y_t] = 1 - F_A(t)$$

$$+ \sum_{n=1}^{\infty} \sum_{d=0}^{n} \left[\binom{n-1}{d-1} \left(F_A * F_{n-1,d-1}(t) - F_A * F_{n,d}(t) \right) \right.$$

$$\left. + \binom{n-1}{d} \left(F_A * F_{n-1,d}(t) - F_A * F_{n,d}(t) \right) \right].$$

Current work: Include fragmentation (prion division).
Numbers of prions inside cells change before division.

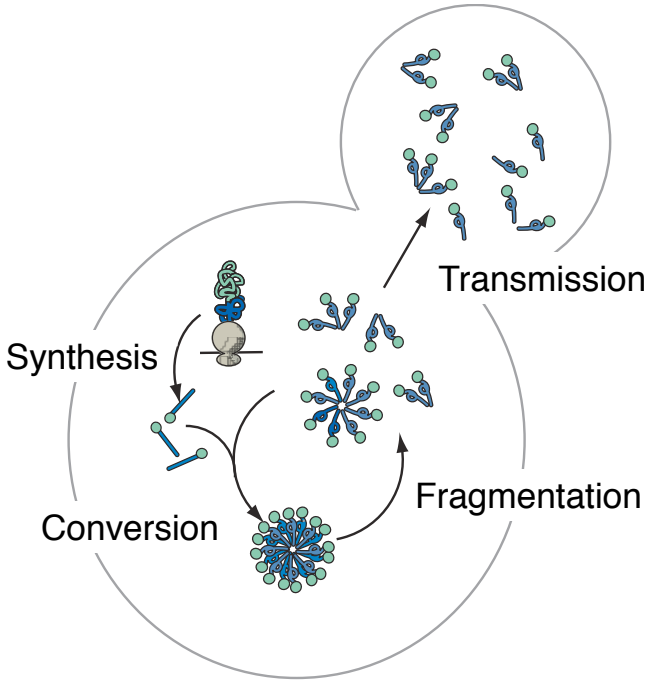


Figure : **Yeast Prion Cycle.** There are four steps essential for the persistence of the prion state: synthesis, conversion, fragmentation and transmission from mother to daughter cell.

Let

$X =$ number of free protein
$Y =$ number of prions
$Z =$ number of binding sites (where prions may break)

Let

$X =$ number of free protein
$Y =$ number of prions
$Z =$ number of binding sites (where prions may break)

$\alpha =$ synthesis rate
$\beta =$ conversion (growth) rate per prion
$\gamma =$ fragmentation rate per binding site

Let

$X =$ number of free protein
$Y =$ number of prions
$Z =$ number of binding sites (where prions may break)

$\alpha =$ synthesis rate
$\beta =$ conversion (growth) rate per prion
$\gamma =$ fragmentation rate per binding site

$$(X, Y, Z) \to \begin{cases} (X+1, Y, Z) & \text{at rate } \alpha \\ (X-1, Y, Z+1) & \text{at rate } \beta XY \\ (X, Y+1, Z-1) & \text{at rate } \gamma Z \end{cases}$$

Continuous time Markov chain, probability generating function of $(X(t), Y(t), Z(t))$:

$$\varphi(q, r, s, t) = \sum_{i,j,k} q^i r^j s^k P(X(t) = i, Y(t) = j, Z(t) = k)$$

Continuous time Markov chain, probability generating function of $(X(t), Y(t), Z(t))$:

$$\varphi(q, r, s, t) = \sum_{i,j,k} q^i r^j s^k P(X(t) = i, Y(t) = j, Z(t) = k)$$

satisfies the PDE

$$\frac{d}{dt}\varphi = \alpha(q-1)\varphi + \gamma(r-s)\frac{d}{ds}\varphi + \beta r(s-q)\frac{\partial^2}{\partial q \partial r}\varphi$$

Continuous time Markov chain, probability generating function of $(X(t), Y(t), Z(t))$:

$$\varphi(q,r,s,t) = \sum_{i,j,k} q^i r^j s^k P(X(t) = i, Y(t) = j, Z(t) = k)$$

satisfies the PDE

$$\frac{d}{dt}\varphi = \alpha(q-1)\varphi + \gamma(r-s)\frac{d}{ds}\varphi + \beta r(s-q)\frac{\partial^2}{\partial q \partial r}\varphi$$

Next: Incorporate prion loss due to reconversion to free protein.

Publications:

Sindi and O, A discrete time branching process model of yeast prion curing curves, *Mathematical Population Studies*, 2013, **20(1)**, 1–13

O and Sindi, A continuous time branching process model of yeast prion curing curves, *Journal of Applied Probability*, 2014, **51(2)**, 453–465

Grant support:

NIH grant 1 F32 GM089049-01 (Sindi)

NIH grant 1 R15 GM093957-01 (O)