

# Notes on the prion model

## Introduction

Written by Jeremy Gunawardena (jeremy@hms.harvard.edu) for MCB 195, “A systems approach to biology”, on 10 February 2005, with thanks to Shai Shen-Orr and Becky Ward for their helpful editorial suggestions.

This note should be read in conjunction with what we discussed in Lectures 1 and 2, the slides for which are available on the website. It goes through the details of how to derive the “full model” of prion growth in terms of the state variables  $x$  and  $y_i$  and then shows how to convert this to the “simple model”, which uses only the state variables  $x$ ,  $y$  and  $z$ . Recall that these variables are defined as follows

$$\begin{aligned}x &= \text{amount of monomer} \\y_i &= \text{amount of polymer of length } i \\y &= \text{total amount of polymer } y = \sum y_i \\z &= \text{total mass of polymer in monomer units } z = \sum iy_i\end{aligned}$$

and that this model of polymerisation has a nucleus of size  $n$  but no nucleation process, so  $y_i = 0$  for  $1 \leq i \leq n - 1$ . See the last section for more background.

## Monomer production and degradation

We assume that monomer is produced at a constant rate  $\lambda$  (zero-order rate constant, with units of (mols)(time)<sup>-1</sup>) and degraded at a rate that is proportional to the amount of monomer present, with  $d$  being the constant of proportionality (first order rate constant, with units of (time)<sup>-1</sup>). If  $x$  is the amount of monomer present, in units of (mols), then the rate at which  $x$  is produced,  $dx/dt$ , is given by the difference between production and degradation

$$\frac{dx}{dt} = \lambda - dx . \tag{1}$$

This equation is simple but it is instructive to remember how to solve it. If we make the substitution  $y = x - \lambda/d$ , then

$$\frac{dy}{dt} = \frac{dx}{dt} = \lambda - d(y + \lambda/d) = -dy .$$

It follows that  $y(t) = \exp(-dt)y(0)$ , where  $y(0)$  is the initial condition, or starting value, of  $y$ . Transforming back to  $x$ , we see that

$$x(t) = \exp(-dt)(x(0) - \lambda/d) + \lambda/d . \tag{2}$$

If we start this with more monomer than  $\lambda/d$ , so that  $x(0) > \lambda/d$ , then  $x(t)$  decreases rapidly towards  $\lambda/d$ . If we start it with less monomer than  $\lambda/d$ , so that  $x(0) < \lambda/d$  then  $x(t)$  increases rapidly to  $\lambda/d$ . Either way, the tendency of the system is always to move towards the point at which production and degradation are exactly in balance, which is achieved when  $x = \lambda/d$ . If we start the system at this point, so that  $x(0) = \lambda/d$ , then we see from (2) that the system stays there forever,  $x(t) = \lambda/d$ . The point  $\lambda/d$  is an example of a steady state, at which  $dx/dt = 0$ .

## Polymer clearance and growth

Now lets add polymer into the mix. We assume that polymer is cleared at a rate  $a$  (first order rate constant) and grows by adding monomer at either end at a rate  $\beta$  (second order rate constant, with units of (mols)<sup>-1</sup>(time)<sup>-1</sup>). Let  $y_i$  denote the amount of polymer of length  $i$ , in units of (mols). The

effect of polymer on the equation for monomer, (1), is that it introduces a new term corresponding to removal of monomer by incorporation onto growing polymer. Polymer of length  $i$  incorporates monomer at a rate  $\beta xy_i$ . This takes place for polymers of all lengths at or above the nucleus size,  $n$ . Hence, the overall contribution to the equation for  $dx/dt$  is

$$\frac{dx}{dt} = \lambda - dx - \sum_{i=n}^{\infty} \beta xy_i .$$

As for polymer of length  $i$ , that grows by addition of monomer to polymer of length  $i - 1$ , while it disappears by incorporation into polymer of length  $i + 1$ . It is also cleared at rate  $a$ . Hence, the equation for  $dy_i/dt$  has 3 contributions

$$\frac{dy_i}{dt} = \beta xy_{i-1} - \beta xy_i - ay_i \quad \text{for } i \geq n .$$

This was the point we got to at the end of the first lecture. You should convince yourself that although each individual polymer grows, the number of polymers does not change. To allow for explosive growth in the number of polymers we have to introduce breakage.

### Polymer breakage

A polymer of length  $i$  can break after its  $j$ -th monomer component, where  $j$  runs from 1 to  $i - 1$ . This produces two smaller polymers, a left-hand one of length  $j$  and a right hand one of length  $i - j$ . The rate for this breakage is given by a first order rate constant  $b$ , which we assume for simplicity, following [1], to be independent of both  $i$  and  $j$ . If either of the smaller pieces is smaller than the nucleus size, it immediately disintegrates into its constituent monomers. Note that a small piece of size  $j$ , where  $j < n$ , produces  $j$  monomers.

This affects the growth of polymer of length  $i$  in two ways. First, it diminishes polymer by breaking at any of  $i - 1$  positions. Each such breakage happens at rate  $by_i$ . The total contribution is therefore  $(i - 1)by_i$ . Second, it increases polymer of length  $i$  by breaking polymers of greater length. If  $j > i$  then there are two ways for a polymer of length  $j$  to break off a piece of length  $i$ , once from the left and once from the right. Each happens at rate  $by_j$ . The total rate for both ways of breaking is  $2by_j$  and this happens for all  $j > i$ . Hence, the rate of growth of  $y_i$  acquires two additional terms

$$\frac{dy_i}{dt} = \beta xy_{i-1} - \beta xy_i - ay_i - (i - 1)by_i + \sum_{j=i+1}^{\infty} 2by_j \quad \text{for } i \geq n .$$

As for monomer, it is affected only by the breaking off of pieces of length smaller than the nucleus size. For a polymer of length  $i$ , this can happen on the left at  $n - 1$  positions. Let  $j$  denote the position, so that  $1 \leq j \leq n - 1$ . This breakage takes place at a rate  $by_i$  but it produces  $j$  monomer units, so its contribution to the growth of  $x$  is  $jby_i$ . Breakage on the right is exactly symmetric, so the contribution from both forms of breaking is  $2jby_i$ . This takes place for each  $i \geq n$  and for each  $1 \leq j \leq n - 1$ . Hence,  $dx/dt$  is given by

$$\frac{dx}{dt} = \lambda - dx - \sum_{i=n}^{\infty} \beta xy_i + \sum_{i=n}^{\infty} \sum_{j=1}^{n-1} 2jby_i .$$

## The full model

Putting everything together, we have the following set of equations for the growth of  $x$  and  $y_i$

$$\begin{aligned}\frac{dx}{dt} &= \lambda - dx - \sum_{i=n}^{\infty} \beta xy_i + \sum_{i=n}^{\infty} \sum_{j=1}^{n-1} 2bjy_i \\ \frac{dy_i}{dt} &= \beta xy_{i-1} - \beta xy_i - ay_i - (i-1)by_i + \sum_{j=i+1}^{\infty} 2by_j \quad \text{for } i \geq n \\ y_i &= 0 \quad \text{for } 1 \leq i \leq n.\end{aligned}\tag{3}$$

## Simplifying the full model

Let  $y = \sum_{i=n}^{\infty} y_i$  denote the total amount of polymer and  $z = \sum_{i=n}^{\infty} iy_i$  denote the total mass of polymer in monomer units. Let us first simplify the equation for  $dx/dt$ . Since  $\beta$  and  $x$  do not depend on  $i$ ,

$$\sum_{i=n}^{\infty} \beta xy_i = \beta x \left( \sum_{i=n}^{\infty} y_i \right) = \beta xy.$$

Similarly, since  $2by_i$  does not depend on  $j$ ,

$$\sum_{i=n}^{\infty} \sum_{j=1}^{n-1} 2bjy_i = \sum_{i=n}^{\infty} 2by_i \left( \sum_{j=1}^{n-1} j \right).$$

The sum of the first  $n-1$  integers is easily evaluated as  $n(n-1)/2$  (Gauss, who gave us the Gaussian distribution and many other wonderful things, is supposed to have worked this out for himself at the age of 4!). Hence, this term simplifies to  $byn(n-1)$ . The equation for  $dx/dt$  now looks like

$$\frac{dx}{dt} = \lambda - dx - \beta xy + bn(n-1)y.$$

Now consider  $dy/dt$ . Since differentiation is a linear operation,

$$\frac{dy}{dt} = \sum_{i=n}^{\infty} \frac{dy_i}{dt}.$$

It follows that we have to take the equations for  $dy_i/dt$  and add them to each other. Consider only the first two terms in the equation for  $dy_i/dt$  taken from (3) above. Adding these up for each  $i$  from  $n$  onwards

$$\begin{array}{c} 0 - \beta xy_n \\ \beta xy_n - \beta xy_{n+1} \\ \beta xy_{n+1} - \beta xy_{n+2} \\ \vdots \end{array}$$

evidently results in everything cancelling out (note that the 0 on the first row comes about because  $y_i = 0$  for  $i$  smaller than the nucleus size  $n$ ).

The next term in the equation for  $dy_i/dt$  gives  $-ay$  in the equation for  $dy/dt$  and the term after that gives  $-b(z-y)$ .

Now consider the last term in the equation for  $dy_i/dt$  and let us write it out in full, omitting the constant factor  $2b$  for the moment

$$\begin{array}{ccccccc} y_{n+1} & + & y_{n+2} & + & y_{n+3} & + & \cdots \\ \vdots & & + & y_{n+2} & + & y_{n+3} & + \cdots \\ \vdots & & & \vdots & + & y_{n+3} & + \cdots \end{array}$$

It is very important to note that the first term on the row for  $dy_i/dt$  is  $y_{i+1}$  and not  $y_i$ . You should refer back to the derivation of (3) to see why this is so. If we add the above array vertically first and then horizontally (using the same trick that young Gauss discovered for working out the sum of an arithmetic progression), we get

$$y_{n+1} + 2y_{n+2} + 3y_{n+3} + \cdots = \sum_{i=n+1}^{\infty} (i-n)y_i . \quad (4)$$

However, we know that

$$\sum_{i=n+1}^{\infty} y_i = y - y_n \quad \text{and} \quad \sum_{i=n+1}^{\infty} iy_i = z - ny_n \quad (5)$$

Hence, (4) can be simplified so that the contribution to  $dy/dt$  is (remembering to put back the  $2b$  we left out above)

$$2b(z - ny_n - n(y - y_n)) = 2b(z - ny) .$$

Note the little bit of magic that causes  $ny_n$  to disappear. It would have been a nuisance if it hadn't! The total contribution of all the pieces to  $dy/dt$  is

$$-ay - b(z - y) + 2b(z - ny) = -ay + b(z + y) - 2nby ,$$

so that

$$\frac{dy}{dt} = -ay + b(z + y) - 2nby .$$

Finally, consider  $dz/dt$ . Again because differentiation is a linear operation,

$$\frac{dz}{dt} = \sum_{i=n}^{\infty} i \frac{dy_i}{dt} .$$

As before, first consider the contribution to  $dz/dt$  made by the first two terms in the equation for  $dy_i/dt$ ,

$$\begin{array}{c} 0 - n\beta xy_n \\ (n+1)\beta xy_n - (n+1)\beta xy_{n+1} \\ (n+2)\beta xy_{n+1} - (n+2)\beta xy_{n+2} \\ \vdots \end{array}$$

When these rows are added together, it is easy to check that the only terms that remain are

$$\beta xy_n + \beta xy_{n+1} + \beta xy_{n+2} + \cdots = \beta xy .$$

The next term in  $dy_i/dt$  contributes  $-az$  to  $dz/dt$ . The term after that is potentially a problem as it contributes

$$-b \sum_{i=n}^{\infty} i^2 y_i + bz . \quad (6)$$

We had better get rid of these  $i^2 y_i$  terms or we will need to introduce yet another variable like  $z$  in an infinite regress. This piece of magic comes from the last term in the equation for  $dy_i/dt$ . Writing it out in full, without the  $2b$ , we get

$$\begin{array}{ccccccc} ny_{n+1} & + & ny_{n+2} & + & ny_{n+3} & \cdots & \\ \vdots & & (n+1)y_{n+2} & + & (n+1)y_{n+3} & \cdots & \\ \vdots & & \vdots & & (n+2)y_{n+3} & \cdots & \end{array}$$

Note that the rows start with  $y_{i+1}$  but are multiplied by  $i$ . It is easy to make a mistake about this, with disastrous results! Adding this array up vertically first and then horizontally, we get

$$ny_{n+1} + (n+n+1)y_{n+2} + (n+n+1+n+2)y_{n+3} + \cdots . \quad (7)$$

If we look at the term with  $y_i$ , where  $i \geq n+1$ , the factor multiplying  $y_i$  is the sum of all the integers from  $n$  to  $i-1$ . Since the sum of all the integers from 1 to  $i-1$  is  $i(i-1)/2$  and the sum of all the integers from 1 to  $n-1$  is  $n(n-1)/2$ , we can rewrite (7) as

$$\sum_{i=n+1}^{\infty} (i(i-1)/2 - n(n-1)/2)y_i = \frac{1}{2} \left( \sum_{i=n+1}^{\infty} i^2 y_i - (z - ny_n) - n(n-1)(y - y_n) \right),$$

where we have used (5) as we did above while calculating  $dy/dt$ . This is almost what we need to cancel out the  $i^2 y_i$  sum that appeared in (6) but the  $i$  index runs from  $n+1$ , not  $n$ . Forgetting about the  $1/2$  for the moment, we can rewrite what we have as

$$\sum_{i=n}^{\infty} i^2 y_i - n^2 y_n - (z - ny_n) - n(n-1)(y - y_n).$$

Rearranging the terms in this, we get

$$\sum_{i=n}^{\infty} i^2 y_i - z - n(n-1)y - (n^2 - n - n(n-1))y_n.$$

Once again, the term with  $y_n$  magically disappears and we are left with

$$\sum_{i=n}^{\infty} i^2 y_i - z - n(n-1)y.$$

If we put back the  $1/2$  and the  $2b$  and combine this with (6) we see that the terms with  $i^2 y_i$  cancel. Combining this with all the other terms we worked out above we finally get

$$\beta xy - az + bz - bz - bn(n-1)y = \beta xy - az - bn(n-1)y.$$

## The simple model

Putting together all the pieces, we arrive at the following simplified model, in terms of the quantities  $x$ ,  $y$  and  $z$

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy + bn(n-1)y \\ \frac{dy}{dt} &= -ay + b(z+y) - 2nby \\ \frac{dz}{dt} &= \beta xy - az - bn(n-1)y. \end{aligned}$$

which is what we used in the lectures. It is quite remarkable that so many things cancel out and allow us to make this simplification. Of course, we have helped to make it so by assuming that parameters like  $b$  do not depend on polymer length. Nevertheless, even having made that assumption, lots of “magic” has to happen. That is usually a sign that something systematic is going on “behind the scenes”, as is the case in real magic, but I have no idea what that something could be.

## Discussion

This simplified model was first written down by Masel, Jansen and Nowak in [1]. The discussion in the Appendix asserts that it can be derived from the full model (3) by “summation”. Indeed it can but, as you see, it takes a little work. Surprisingly, MJN did not analyse the simple model as we did in class but instead made a linear approximation to it under the assumption that the amount of monomer was approximately constant. This is true for the values of rate constants that we have been using, where the monomer rates are much faster than the polymer rates. You may have noticed this *quasi-steady state* when playing with MATLAB.

This same polymerisation model was discussed again by Pöschel, Brilliantov and Frömmel in [2]. Unfortunately, they made a serious error in formulating the detailed model and made things even worse by suggesting that MJN had made the mistake. MJN pointed out the error in a letter (Biophysical Journal, 87:728, 2004) with which PBF had to agree (Biophysical Journal, 87:729, 2004). You should read the letters before reading PBF, which has some nice observations in it despite the error (particularly about the distribution of polymer lengths, which is something we did not look at in class). Surprisingly, once again, they fail to point out the transcritical bifurcation from polymer collapse to polymer growth and seem to confuse it with a concentration threshold. In many ways, the bifurcation is the most interesting feature of the model.

## References

- [1] J. Masel, V. Jansen, and M. Nowak. Quantifying the kinetic parameters of prion replication. *Biophysical Chemistry*, 77:139–52, 1999.
- [2] T. Pöschel, N. V. Brilliantov, and C. Frömmel. Kinetics of prion growth. *Biophysical Journal*, 85:3460–74, 2003.