Theoretical Studies of an Autocatalytic Prion Model

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The Gillespie Algorithm is used to simulate a prion model so that the kinetics of the prions may be observed. The model is purely autocatalytic, that is, there is no fusion or fission of the infectious units. There is only conversion of PrP^C into prions through a mechanism comprised of attaching PrP^C to a PrP^{Sc} *p*-mer, domain swapping, and splitting. It is well known that any model of an infectious disease must show exponential growth, which we show is the case with the presented model. We indeed find exponential growth in this model. Some conclusions based on a thorough sensitivity analysis of the parameters used in the model are also given. A brief introduction to proteins and their structure, prions, and the Gillespie Algorithm are provided as well.

1 Background

1.1 Proteins

Proteins are the workhorses of any living organism. They are involved in every process inside cells. Proteins are composed of amino acids attached to each other by peptide bonds. There may be as few as 20 amino acids in a protein, or there may be thousands. There are 20 different amino acids, which are composed of carbon, hydrogen, oxygen, nitrogen, and sulfur. The bonded amino acids in a protein form a linear sequence. This is called the primary structure of the protein, and is determined by the genetic code carried in the DNA of the organism. Through hydrogen bonding, certain short sequences can lead to structures such as α- and β- helices. These structures are called secondary structures. The entire protein taken as a whole is called the tertiary structure. The tertiary structure of a protein largely affects what task or tasks it is to accomplish. Finally, the quaternary structure of a protein is the arrangement of multiple protein molecules into one large unit. These structures may be called dimers, trimers, etc., where the prefix relates the number of proteins in the complex.

1.2 Prions

Prions are proteinaceous infectious particles. They are implicated in diseases such as Bovine Spongiform Encephalopathy (BSE, also known as Mad Cow Disease) in cattle, Scrapies (in sheep), and a human disease, Creutzfeldt-Jakob Disease (CJD). These diseases are invariably terminal. In the case of CJD, once symptoms have appeared the disease will prove fatal in less than a year. These prions are created when a certain harmless protein becomes misfolded, that is, when it's tertiary structure changes into an infectious conformation.

1.3 PrP^C and PrP^{Sc}

The protein that prions are made from is found on cell membranes throughout the body. It is called PrP^C, or cellular PrP. The function it serves is unknown at this point. PrP^{Sc} is a conformational variant of PrP^C, and is the protein that causes disease. The presence of PrP^{Sc} among PrP^C leads to catalysis of the PrP^C into PrP^{Sc}. The exact mechanism of this catalysis is not known, but is hypothesized in the model described later in this paper.

2 Technique

It is well known that unchecked replication of an infectious disease leads to exponential growth of the population of the infectious particles. We suppose that an oligomeric autocatalytic model may be able to satisfy this exponential growth condition. The model supposes that the C-terminus of one of the proteins in an infectious unit, when exhibiting a more β-helical conformation, is able act as a template for the N-terminus of a PrPC, which is known to carry the disease-causing content. Through domain-swapping [2], it is believed that stable oligomeric conformations may be achieved.

2.1 Model

This model has $p + 5$ chemical species interacting through seven reaction pathways, where p is the number of proteins in the quaternary structure of a single infectious unit. The different species and reactions are laid out in Figure 1.

The symbols located to the left of each reaction are the parameters corresponding to the speed of each reaction. The reactions may require some further explanation:

(gkp) corresponds to the reaction in which the C-terminals of the misfolded PrP^C in an infectious unit (aggregate of misfolded PrP^C of size p) are changed from a more α-helical structure to a β-helical form.

(gkm) corresponds to the opposite of the reaction in (gkp). It is a reaction in which the C-terminals of the misfolded PrP^C are converted from a β-helical to α-helical shape.

(gq) is the reaction in which a PrP^C with a hardened N-terminal β-helix, which a sort of intermediate form, is converted back into a regular PrP^C.

(gr) in this reaction, a PrP^C joins on to a developing aggregate and becomes and PrP*. The aggregates begin with a $p\beta^{Sc}$ and can have up to as many as p PrP* attached to them.

(gd) it is hypothesized that when the (gr) reaction occurs enough that a $p^*p\beta^{Sc}$ is formed that the p PrP^Cs may domain swap, that is, exchange some of their material with one another. They become entangled and new bonds form.

(gs) corresponds to a reaction in which a $l^*p\beta^{Sc}$ has its $p\beta^{Sc}$ be converted into a $p\alpha^{Sc}$. This causes the l PrP*s to fall off.

(gst) in this final reaction, an aggregate of two $p\beta^{Sc}$s have their C-terminals converted into α-helical structures. This causes the two p-mers to separate.

PrP^C	– the cellular PrP^C protein
$p\alpha^{Sc}$	– p-mer of PrP^C with a hardened N-terminal β-helix and an α-helical C-terminus
$p\beta^{Sc}$	– p-mer of PrP^C with a hardened N-terminal β-helix and a β-helical C-terminus
PrP*	– PrP^C with a hardened N-terminal β-helix
l*$p\beta^{Sc}$	– $1 \le l \le p$ PrP* bound to $p\beta^{Sc}$
$p\beta^{Sc}$,$p\beta^{Sc}$	– a p*$p\beta^{Sc}$ that has domain-swapped

(gkp)	$p\alpha^{Sc} \rightarrow p\beta^{Sc}$
(gkm)	$p\beta^{Sc} \rightarrow p\alpha^{Sc}$
(gq)	$PrP^* \rightarrow PrP^C$
(gr)	$PrP^C + (l\text{-}1)^*p\beta^{Sc} \rightarrow l^*p\beta^{Sc}$
(gd)	$p^*p\beta^{Sc} \rightarrow p\beta^{Sc},p\beta^{Sc}$
(gs)	$l^*p\beta^{Sc} \rightarrow l\ PrP^* + p\alpha^{Sc}$
(gst)	$p\beta^{Sc},p\beta^{Sc} \rightarrow 2\ p\alpha^{Sc}$

Figure 1: The $p + 5$ species and seven reactions used in the model

$$akp = gkp * pop(p\alpha^{Sc})$$

$$akm = gkm * pop(p\beta^{Sc})$$

$$aq = gq * pop(PrP^*)$$

$$ar = gr * pop(PrP^C) * pop(p\beta^{Sc}) * \sum_{l=1}^{p-1} (p - l) * pop(l^*p\beta^{Sc})$$

$$ad = gd * pop(p^*p\beta^{Sc})$$

$$as = gs * pop(l^*p\beta^{Sc})$$

$$ast = gst * pop(p\beta^{Sc},p\beta^{Sc})$$

Fig 2: The propensities of the seven reactions for the Gillespie Algorithm.

2.2 Gillespie Algorithm

The Gillespie Algorithm is a simple stochastic simulation algorithm. It works by having a random number select which reaction is to occur and another random number to select how much time that reaction will require. One surely will note that not every reaction should have an equal likelihood of being chosen. This is taken into account by assigning a propensity to each reaction. This propensity is calculated as the product of the parameter corresponding to the reaction and the number of distinct reactions possible for that reaction. Thus, for example, if there is a reaction that turns As and Bs into Cs ($A + B \rightarrow C$) with a parameter of K, the propensity of the reaction would be the product of K, the population (count) of As, and the population of Bs. The propensities of each reaction are shown in Figure 2. A complete run-through of the Gillespie Algorithm is shown in Figure 3.

3 Results and Discussion

As shown in Figure 4, we found robust exponential growth with every set of parameters attempted. It seems that there is no question of whether or not exponential growth occurs in our model, in fact, we can't get rid of it! As can be seen in Figure 4, changing the parameters of the simulation simply modulates the slope of the exponential growth or changes the y-intercept by a slight amount.

4 Future Work

We are currently working on developing a semi-analytic treatment to solve the model. These solutions provide us with the ability to compare our stochastic results with experimental data quantitatively rather than just qualitatively. Such comparisons would allow us to determine the quality of our model and may suggest future alterations for improvements.

Figure 3: The Gillespie Algorithm

1. Input the initial populations for all species and the parameters for the reactions. Also set the final time.
2. Set $t = 0$.
3. Given the parameters and populations, calculate the propensity for each reaction to occur. Let *a0* be the sum of the propensities.
4. Generate two random numbers, *r1* and *r2* in the range (0,1).
   Set $\tau = (1 / a0) * \ln (1 / r1)$.
   Use the product *a0 * r2* to determine which reaction is to take place.
5. Update the populations to reflect that the reaction chosen in step 4. has occurred.
6. Put $t = t + \tau$. If t exceeds the final time, stop the process; otherwise, return to step 3.

5 Acknowledgments

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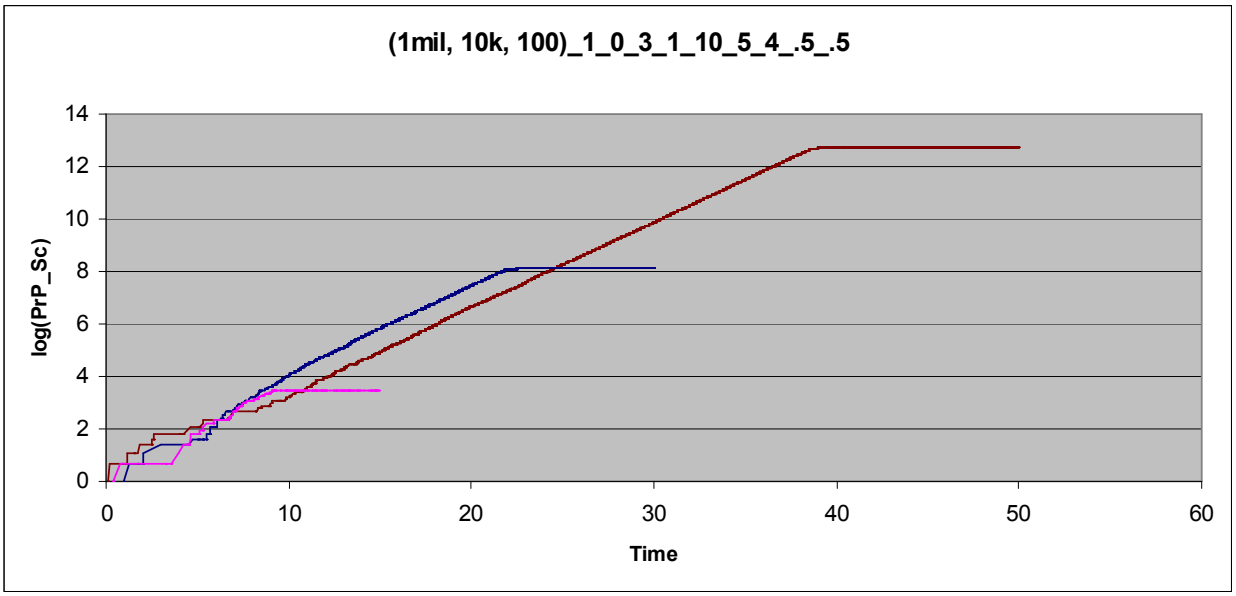

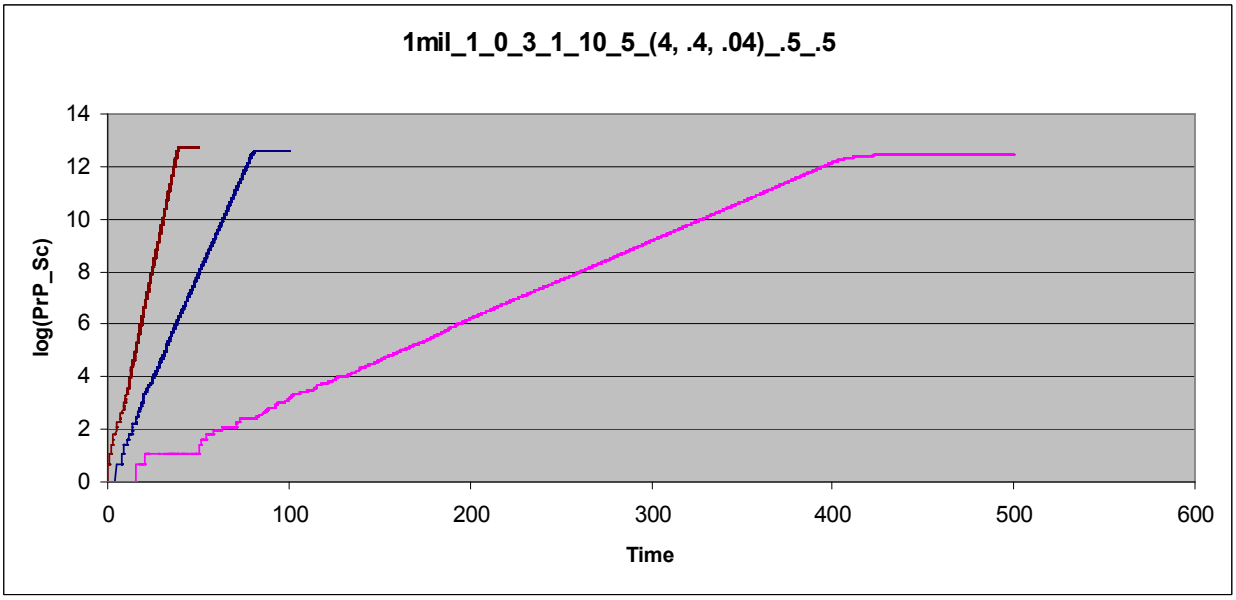

Figure 4: The first plot shows that exponential growth is achieved as the initial count of PrPC is varied from one million to ten thousand to one hundred (brown, blue, then pink, respectively). The second plot shows how the slope changes as the parameter corresponding to the domain-swapping reaction (gd) is changed from four to one fourth to four one-hundredths (brown, blue, then pink, respectively).

References

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[2] D. Gillespie. Exact Stochastic Simulation of Coupled Chemical Reactions. The Journal of Physical Chemistry. 1977. 2340-2361.