The so-called prion diseases comprise a group of fatal transmissible spongiform encephalopathies (TSE) like the well known bovine spongiform encephalopathy (BSE) and sheep scrapie. In humans, these progressive neurodegenerative diseases include Kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). Common pathology includes spongiform degeneration and characteristic formation of plaques in the brain tissue. Variant CJD correlated with a (BSE)-like prion strain, have been identified and are believed to be linked to the consumption of contaminated food.\[2, 3, 4, 5\].

Transmissible spongiform encephalopathies like the bovine spongiform encephalopathy (BSE) and the Creutzfeldt-Jakob disease (CJD) in humans are neurodegenerative diseases for which prions are the attributed pathogenic agents. A widely accepted theory assumes that prion replication is due to a direct interaction between the pathologic (PrP$^{\text{Sc}}$) form and the host encoded (PrP$^{\text{C}}$) conformation, in a kind of an autocatalytic process. Here we show that the overall features of the incubation time of prion diseases are readily obtained if the prion reaction is described by a simple mean-field model. An analytical expression for the incubation time distribution then follows by associating the rate constant to a stochastic variable log normally distributed. The incubation time distribution is then also shown to be log normal and fits the observed BSE data very well. The basic ideas of the theoretical model are then incorporated in a cellular automata model. The computer simulation results yield the correct BSE incubation time distribution at low densities of the host encoded protein.

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The protein-only hypothesis states that the infectious agent is a protein, named prion, which is devoid of nucleic acid and capable of replicating itself in the absence of these traditional genetic material. Two conformations of this protein are important for characterizing the disease, namely, the normally folded host-encoded cellular protein called PrP$^{\text{C}}$ and an abnormal pathogenic conformation named PrP$^{\text{Sc}}$. The latter form is hydrophobic, has a tendency to form aggregates and may be found in different strains. The pathogenic form PrP$^{\text{Sc}}$ is more stable than the endogenous cellular form, and is known to be resistant to enzymatic digestion, radiation and high temperatures. One of the most accepted models for prion replication assumes that this form acts as a template for converting the host prion into its own conformation in a kind of an autocatalytic reaction. Understanding the dynamics of the PrP$^{\text{C}}$ → PrP$^{\text{Sc}}$ transformation is crucial if one is attempting to explain and predict the main stages of the disease. The reaction is complex, perhaps involving other participants possibly acting as chaperone, to help mediate protein folding. The number of parameters involved for thoroughly describing the reaction process is thus expected to be very large. It is therefore important to be able to recognize which ones are mandatory, i.e., responsible for the major aspects of the dynamics.

Here we present a simple, analytically solvable, mean-field model for describing the prion reaction problem, which focuses on realistically reproducing the incubation time of the disease. For notational convenience it is useful to introduce the following definitions: $A$ stands for the host protein (PrP$^{\text{C}}$) and $B$ stands for the pathogenic form (PrP$^{\text{Sc}}$) with $a = [A]$ and $b = [B]$ denoting volume concentrations. We then write the autocatalytic conversion reaction simply as

$$A + B \xrightarrow{K} 2B$$

(1)

where $K$ is the reaction rate. For simplicity we shall assume that the total concentration $a + b = \rho$ is kept fixed at all times. This means that there is no metabolic decomposition of $B$ and any metabolic decomposition of $A$ is immediately compensated by the host genetic system. It also implies that the host takes no action for producing new, normal protein, as the reaction takes place. In order to stick to the simplest possible case we are also assuming that the reaction is unidirectional and favors the most stable form PrP$^{\text{Sc}}$. No other strains are supposed to be present and both forms are assumed to be uniformly distributed. The kinetic evolution is then given by $db/dt = Kab = K(\rho - b)b$ which is the simplest possible nonlinear equation describing an autocatalytic reaction. This equation can be easily integrated up to the time $T$ giving

$$T = \frac{1}{K(a_0 + b_0)} \ln \left[ \frac{a_0}{b_0} \left( \frac{b(T)}{a_0 + b_0 - b(T)} \right) \right]$$

(2)

with $b_0$ being the infection dose given at time $t = 0$ and $a_0$ the initial concentration of $A$. According to this expression $b(t)$ is slowly varying for small $t$, followed by
a period of rapid increase in a short time interval, then reaching a plateau for long enough times when the reaction stops \[10 \pm 3\].

We now define the incubation time \((T_I)\) as the time it takes for the number of pathogenic prions to reach a given value \(b_1\), i.e., \(b(T_I) = b_1\). (It makes no difference to our calculations whether \(b_1\) represents a number of prions or an aggregate with size \(b_1\).) A useful approximation can be obtained by assuming, reasonably, that \(b_0/a_0 < 1\). This gives

\[
T_I \approx \frac{1}{K a_0} \ln \left[ \frac{b_I}{b_0} \left( \frac{1}{1 + b_I/a_0} \right) \right]. \tag{3}
\]

This log-dependence of the incubation time on the initial dose was quantitatively observed by Prusiner \[16\] from inoculation of a form of scrapie in hamsters (Fig. 1). Prusiner’s results also indicate that the survival time is practically independent of the dose. Eqn. (3) is consistent with this finding (see also \[13\]). If we define the time of death as the time it takes for the number of \(B\)’s to reach the value \(b_D\), i.e., \(b(T_D) = b_D\), we find that \(T_D - T_I\) does not depend on \(b_0\). Moreover, eqn. (3) can be easily adapted to fit Prusiner’s data. In order to mimic the end-point titration method used in the experiment, we first define all concentrations relative to the largest experimental concentration which we shall call \(b_0\). We then write \(b_0/b_0 = 10^{n - 10} \) \((n = \text{dose})\) and allow \(n\) to vary from \(n = 0\) (smallest concentration) to \(n = 10\) (largest concentration). We can now apply regression to the data (using only the integral values for \(n\)) to obtain the best fit. Notice, however, that the experimental curves are composed of two branches, both exhibiting a sudden increase in the inclination for \(n \lesssim 2\) (see Fig. 1). This behavior seems to be indicative of a threshold, possibly leading to a smaller rate constant at high dilutions. One can simulate a \(dose\) dependent activation mechanism linked to the rate constant \(K\) by making the following “ansatz”: we make \(K \rightarrow K_{\text{eff}}\) with \(K_{\text{eff}} = K[1 - a_1/(a_2 + \exp(n))]\). With these implementations, eqn. (2) reads \(T_I = C - [\ln 10/(K a_0)]n\), \(C\) being a constant (independent of \(b_0\)). The phenomenological constants, estimated with a non-linear least-squares fitting to this equation, with \(K\) replaced by \(K_{\text{eff}}\), are \(a_1 = 0.23(4)\) \((0.61(2))\) and \(a_2 = -0.51(6)\) \((2.1(2))\) for the incubation (death) curve. The result of the full fitting is shown in the inset of Fig. 1. Notice that \(K_{\text{eff}}\) rapidly approaches \(K\) for \(n > 2\).

However, we decided to avoid dealing with the controversial features associated with the region \(n \lesssim 2\) (containing only two points) and stick to the (larger) less inclined part of the experimental curve. Therefore any parameter obtained from the \(y\)-intercepts in Fig. 1 will not be taken into account. The regression coefficient gives \(1/(K a_0) = 3.12(3)\) days for the incubation part of the curve and \(1/(K a_0) = 3.02(6)\) days for the death part of the curve. This (partial) fitting is represented by the continuous line in the main part of Fig. 1. We can easily check the reasonableness of these figures. Notice that we could have started with the Michaelis-Menten equation, namely, \(db/dt = K_T[a/b/(K_M + a)]\) with \(K_T\) and \(K_M\) being the turnover number and the Michaelis constant respectively \[13\]. Direct integration of this equation yields

\[
K_T \times T = \frac{1}{a_0 + b_0} \left[ K_M \ln \left( \frac{a_0}{a_0 + b_0 - b(T)} \right) \right] + (K_M + a_0 + b_0) \ln \left( \frac{b(T)}{b_0} \right), \tag{4}
\]

which is consistent with eqn. (2) for \(K_M >> a_0 >> b_0\) and \(K \approx K_T/K_M\). We can therefore estimate the prion \(K_T/K_M\) ratio for the scrapie strain used by Prusiner \[16\] in hamsters. If we assume \(a_0 \sim \text{nanomole liter}^{-1}\) \[12\] \[13\] we find \(K_T/K_M \sim 10^3\) \(\text{M}^{-1}\) \(\text{s}^{-1}\). This value is within the range expected for enzymes, in which case \(K_M\) lies between \(10^{-7}\) \(\text{M}\) to \(10^{-1}\) \(\text{M}\) and \(K_T\) falls in the range from \(10^{-1}\) \(\text{s}^{-1}\) and \(10^7\) \(\text{s}^{-1}\).

Having discussed the behavior of the incubation time on \(b_0\), we now turn our attention to the dependence of \(T_I\) on \(a_0\). The role played by the host prion initial concentration is useful for describing reactions, such as \[12\], in numerical simulation approaches. The explicit power law dependence of \(T_I\) on \(a_0\) can be seen by expanding eqn. (2) in terms of \(b_I/a_0\). This gives

\[
T_I \sim \frac{1}{K a_0} \left[ \ln \frac{b_I}{b_0} + \frac{b_I}{a_0} + O \left( \frac{b_I}{a_0}^2 \right) \right], \tag{5}
\]

and therefore \(T_I \sim A_1/a_0 + A_2/a_0^2\). This kind of behavior, having the form of a sum of monomer and dimer terms, has already been suggested in the literature \[17\]. However, the determination of the explicit dependence of the coefficients \(A_1\) and \(A_2\) on \(b_I\) and \(b_0\), as shown here, was only possible because of the simplicity of the model.

The initial concentration of the endogenous PrP protein is determinant for the dynamics of the prion reaction since it represents the reaction fuel. The higher the initial concentration \(a_0\), the lower the time for the PrP\(^{Sc}\) concentration to reach the value \(b_I\). These results have been obtained through careful computer simulations by Cox et al. \[17\]. They also showed that the incubation time distributions for different \(a_0\) collapse to a single form if the time scale is properly normalized to unity. Will our simple, minimally parametrized model represented by the basic reaction \[11\], be able to reproduce such results? In order to address this question, we ran computer simulations based on a cellular automata (CA) with rules following a close resemblance to our model.

According to the CA rules, an \(N \times N\) \((N = 200)\) square lattice is randomly populated with a number \((N_{A0})\) of the host \(A = \text{PrP}^C\) protein and a number \((N_{I0} = 6)\) of the \(B = \text{PrP}^{Sc}\) misfolded protein. \(N_{A0}\) is given as a small
FIG. 1: Dependence of the incubation time ($T_I$) on the infection (initial) dose ($= n$ with $b_0/b_0 = 10^{n-10}$). The experimental data were obtained from Prusiner’s work [18] and dashed lines are just meant to lead the eye. In the main figure we apply regression to the data ($n > 2$) to obtain the best fit with eqn. 3. The most diluted part ($n \lesssim 2$) was left out due to the abrupt change in behavior in this region, leaving only two points ($n = 1, 2$) for the fitting. Therefore only the inclinations ($= 1/(K_{\alpha_0})$) are kept. The inset shows a non-linear least-squares full fitting (all $n$) to eqn. 3 with the ansatz $K \rightarrow K_{\text{eff}} = K[1 - a_1/(a_2 + \exp(n))]$.

FIG. 2: Incubation time distributions with the time scale normalized by the mean incubation time, i.e., $t_I = T_I/T_I$. The full circles represent the observed incubation time distribution for BSE-infected cattle in UK [17]. Fig. 2(a) shows the results from computer simulations on an $N \times N$ ($N = 200$) square lattice, with a number of PrP$^\text{Sc}$ seeds $N_{B0} = 6$ (see text). The values of $N_{A0}$ shown represent the initial PrP$^\text{C}$ concentration and only few curves for $N_{A0}$ were drawn to avoid figure cluttering. Notice the tendency for better agreement with the observed results as $N_{A0}$ gets smaller. Fig. 2(b) shows the same experimental data as in (a), along with the proposed analytical distribution $G(t_I)$, obtained from our model assuming a log normal distribution for the rate constant. When the time units are scaled by the mean time we are left with a single parameter, namely $\sigma$, whose best fitted value is given by $\sigma = 0.255 \pm 6$.

percentage of the total number of sites available and to each of the $B$ sites is assigned a “mass” ($m$), initially set to unity. The $A$’s and $B$’s are allowed to diffuse randomly to their nearest neighbor sites and a reaction occurs when a $B$ is approached by an $A$ at a distance $d \leq \sqrt{m}$. In this case the normal Prion disappears and the misfolded Prion has its mass increased by one. The reaction is unidirectional, favoring $B$, with the $A$’s slowly disappearing from the system, keeping $A + B = constant$. One site-by-site sweep through the lattice is made for diffusion followed by another one for reaction. The time unit is then increased by one (arbitrary units). The reaction stops when one of the masses reaches the value $m = 40$, the corresponding computer time thus characterizing the incubation time. The above values for the parameters (not the CA rules) were adjusted from the numerical simulations of Cox et al. [17] in a hexagonal lattice. The mass is here to mimic clusterization without assigning any geometric form to the cluster. Besides simplifying the computer code and speeding up the simulations, this helps reducing the influence of local topology on the final results.

Fig. 2(a) shows the simulation results for the incubation time distributions for several values of $N_{A0}$, with the time scale normalized by the mean time. Notice that as the PrP$^C$ concentration is decreased, the corresponding distribution converge asymptotically to the experimental results (BSE-infected cattle in UK [17, 18, 19]) represented by the full circles. Increasing $N_{A0}$ makes the
system more homogeneous which diminishes fluctuations and narrows the distribution. The biological concentrations (believed to be nanomolar) correspond to an areal concentration around $N_{A0}^{bio} = 0.001\%$ [17]. With the CA rules above, such small concentrations would require very large computing time, if feasible at all. The best agreement is obtained for $N_{A0} = 0.6\%$ which is far as we could go with these simulations.

Our next issue is to search for an analytical form for the incubation time distribution. Knowledge of such a function is not only important to check the reliability of the model but also to provide a distribution that can be used in statistical studies [20]. We need to adapt the deterministic model to accommodate a stochastic variable following a known distribution and associate it with eqn (5). Since the protein-folding process actually involves many steps [13], possibly chaperone-assisted [21], the end result of the prionic reaction can adequately be viewed as a series of multiplicative processes. It is therefore reasonable to assume that the distribution of the reaction rate $K$ in a population is $log$ normal [22]. Since $K \propto 1/T_I$ it is easy to show that $T_I$ also follows a $log$ normal distribution with the same deviation. The scaled distribution $G(t_I)$, with $t_I = T_I/T_1$, is then readily obtained. One finds

$$G(t_I) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{1}{2} \left( \frac{\ln t_I + (5/2)\sigma^2}{\sigma} \right)^2}$$  \hspace{1cm} (6)$$

which does not depend neither on the initial variables nor on $b_I$. We are therefore left with a single fitting parameter, namely $\sigma$, the standard deviation of $\ln K$. Applying non-linear least squares fitting to Eqn. (6) we get $\sigma = 0.255(\pm 6)$. The final result is shown in Fig. 2(b). In this Figure the observed data are the same used in reference [17] for BSE-infected cattle in the United Kingdom born in 1987 [18][19].

In conclusion, a simple mean field model, based on an autocatalytic mechanism, is shown to contain the basic ingredients necessary to describe the essential features associated with the incubation time of the complex prion conversion reactions. Assuming that the rate constant is a random variable, following a $log$ normal distribution, we were able to provide a closed form for the incubation time distribution of BSE-infected cattle. The surprisingly simple analytical expression derived for the incubation time distribution contains only one parameter, namely the variance of the logarithm of the rate constant. The simplicity of the model is characterized by the almost naive differential equation upon which it is based, by simple computer simulations, and by the minimal set of parameters used to describe the autocatalytic process.

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