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Modeling and analysis of prion dynamics in the presence of a chaperone

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Abstract

Prions are infectious agents and are polymers called PrP^{Sc}—Prion protein scrapies, of a normal protein, a monomer called PrP^{c}—Prion protein cellular. These $PrP^{Sc}s$ cause TSEs—transmissible spongiform encephalopathies such as bovine spongiform encephalopathy (BSE) in cattle, scrapies in sheep, Kuru and Creutzfeld–Jacob diseases in humans. Cellular molecular chaperones, which are ubiquitous, stress-induced proteins, and newly found chemical and pharmacological chaperones have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several neurodegenerative disorders and many other protein-misfolding diseases. In this work, we propose a model for the replication of prions by nucleated polymerization in the presence of a chaperone. According to this model, the biological processes of coagulation, splitting and the inhibitory effects of the chaperone can be described by a coupled system consisting of ordinary differential equations and a partial differential equation. The model is converted into a system of ordinary differential equations and the equilibrium points are computed and their stability is studied. We give a numerical simulation of the model and we find that a disease free state can be achieved in the presence of a chaperone. The duration of the disease free state is found to increase with the amount of chaperone and this amount of chaperone can be computed from the model.

Keywords: Prions; Chaperones; Nucleated polymerization

1. Introduction

Prions are pathogens responsible for a variety of animal and human neurodegenerative diseases, such as bovine spongiform encephalopathy (BSE), scrapie of sheep, Creutzfeldt–Jacob and Gerstmann–Straussler–Scheinker diseases of humans. Bewilderingly, all these diseases can be sporadic, genetic and infectious, thus making the identification of the disease mechanism a challenging task. For many years, the prion diseases were thought to be caused by slow-acting viruses. These diseases were often referred to as slow virus diseases, transmissible spongiform encephalopathies, or unconventional viral diseases. Considerable effort was expended searching for the scrapie virus; yet none was found either with respect to the discovery of a virus-like particle or a genome composed of RNA or DNA [1].

The unusual properties of the infectious agent became the focus of attention beginning in the 1960s, and in the early 1980s Stanley Prusiner, building upon earlier suggestions proposed the prion hypothesis [2]. This stated that the infectious agent in human and animal spongiform encephalopathies was composed exclusively of a single kind of protein molecule designated PrP^{Sc} without any encoding nucleic acid. Based on foregoing findings, the term prion was introduced to distinguish the proteinaceous infectious particles that cause scrapie from both viroids and viruses. Perhaps, the best current working definition of a prion is a proteinaceous infectious particle that lacks nucleic acid [3].

This protein can appear in two forms that differ only in their conformation. One form is the mainly α-helical form, called cellular prion protein (or PrP^{c}). This is the native form of the protein which naturally appears in many tissues, however with a notable abundance in the brain,

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where it is mainly located at synaptic areas. It is commonly believed that the agent causing prion diseases is composed of the second form, called scrapie prion protein (or PrP^{Sc}). It differs from PrP^{c} only by its secondary structure which is dominated by beta-sheet. The structural differences cause differences in physical and chemical properties, for instance a high resistance of PrP^{Sc} to proteases and a tendency of PrP^{Sc} to aggregate and form polymers and even large amyloid plaques. Furthermore, interaction of the two forms leads to a conversion of PrP^{c} into PrP^{Sc}. In this way, PrP^{Sc} multiplies and acts as an infective agent [4].

Prions proliferate by a process called nucleated polymerization. The infective agent, PrP^{Sc} is not a single protein, but a polymer or short oligomer. The PrP^{Sc} increases its length by attaching units of PrP^{c} in a string like fashion. Then, the PrP^{c} which is attached to the PrP^{Sc} is converted to the infectious form. Once the PrP^{Sc} is long enough to wrap into a helical shape called the nucleus, it forms stabilising bonds and thus becomes stable. $PrP^{Sc}s$ can consist of thousands of monomer units. PrP^{Sc} polymers may split into two smaller infectious polymers which can lengthen further. If the split PrP^{Sc} falls below a critical length, it degrades immediately into normal PrP^{c} monomers. Thus, the instability of short polymers is a barrier to the formation of PrP^{Sc} polymers. Since, the formation of the nuclei is believed to be a very slow process, this model accounts for the long incubation periods of the TSEs [5].

In this paper, we model the replication of prions by nucleated polymerization under the effects of a chaperone. Chaperones are known to inhibit PrP^{Sc} production and they can be molecular chaperones, chemical chaperones or pharmacological chaperones. Molecular chaperones are proteins that facilitate the folding of polypeptides during their biosynthesis and transport into organelles and that help prevent protein aggregation during conditions of cellular stress [6]. These cellular chaperones along with some chemical and pharmacological chaperones have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several neurodegenerative disorders and many other protein-misfolding diseases like the prion diseases. The role of molecular, chemical and pharmacological chaperones in suppressing the production of $PrP^{Sc}s$ have resulted in them being potential therapeutic agents against different types of degenerative diseases, including neurodegenerative disorders like the TSEs [7].

This paper is organised as follows: In Section 2, the model which is a coupled system consisting of ordinary differential equations and a partial differential equation is described. In Section 3, the model is converted into a system of ordinary differential equations and the equilibrium points are computed. In Section 4, the stability of the steady states are studied. In Section 5, the numerical simulations for the model is presented and the conclusions are given in Section 6.

2. The model

In this section, we describe the model of prion proliferation under the inhibitory effects of a chaperone. The assumption is that the prions replicate by nucleated polymerization [8]. Let $V(t)$ denote the population of PrP^{c} monomers at time t, $u(x,t)$ be the population of PrP^{Sc} polymers of length x at time t and $C(t)$ denotes the amount of chaperone in the system at time t. Let λ denote the constant rate of production of PrP^{c} in the system and γ be the constant rate of degradation of the PrP^{c} due to metabolic processes. τ is the conversion rate of monomers PrP^{c} to polymers PrP^{Sc} and they are converted at a rate proportional to the population of the total number of polymers $\int_{x_0}^{\infty} u(x,t)\mathrm{d}x$. $\beta(x)$ is the binary splitting rate of the PrP^{Sc} polymers of length x and $\kappa(x,y)$ is the probability density function that a polymer of length y splits into one of length x and another of length $y-x$. x_0 is the critical length of the polymer below which the polymer degrades into normal PrP^{c} monomers. Thus, the rate of change of the monomer population is given by

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = \lambda - \gamma V(t) - \tau V(t)\int_{x_0}^{\infty} u(x,t)\mathrm{d}x + 2\int_{0}^{x_0} x \times \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(y,t)\mathrm{d}y\,\mathrm{d}x$$

where the last term on the right hand side represents the monomers gained when a PrP^{Sc} polymer splits with at least one polymer shorter than the minimum length x_0. We assume that such a polymer piece degrades immediately into PrP^{c} monomers.

The 2 in the expression accounts for the fact that a polymer of length x greater than x_0 splits into two PrP^{Sc} polymers.

The polymer lengths have been shown to range over thousands of monomer units[12]. In [12], polymer lengths x were assumed to be integer values, but we assume continuous values for mathematical tractability. $\mu(x)$ is the constant rate of degradation of the $PrP^{Sc}s$ due to metabolism. δ_2 denotes the rate at which the PrP^{Sc} population gets reduced due to the presence of the chaperone. $-\tau V(t)\frac{\partial u(x,t)}{\partial x}$ accounts for the loss of polymers of length x due to lengthening. $2\int_{x}^{\infty}\beta(y)\kappa(x,y)u(y,t)\mathrm{d}y$ denotes the number of $PrP^{Sc}s$ which are added to the population when longer polymers split into polymers of length x.

Therefore, the rate of change of $PrP^{Sc}s$ is given by

$$\frac{\partial u(x,t)}{\partial t} = -\tau V(t)\frac{\partial u(x,t)}{\partial x} - (\mu(x)+\beta(x)+\delta_2 C(t))u(x,t) + 2\int_{x}^{\infty}\beta(y)\kappa(x,y)u(y,t)\mathrm{d}y$$

δ_0 denotes the rate at which the chaperone is degraded from the system due to metabolic processes and δ_1 is the rate at which the chaperone is getting increased in the system.

Therefore, the rate of change of chaperone in the system is given by

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t) \int_{x_0}^{\infty} u(x,t)dx$$

Now, in the above model we make the following assumptions:

Let $\mu(x) = \mu, \beta(x) = \beta x$,

For every $y > x_0, \kappa(x,y) = 1/y$ for $x \in (0,y)$ and 0 otherwise.

Substituting the above in our model, the model transforms into the following:

$$\frac{dV(t)}{dt} = \lambda - \gamma V(t) - \tau V(t) \int_{x_0}^{\infty} u(x,t)dx + \beta x_0^2 \int_{x_0}^{\infty} u(x,t)dx \quad (1)$$

$$\frac{\partial u(x,t)}{\partial t} = -\tau V(t) \frac{\partial u(x,t)}{\partial x} - (\mu + \beta x + \delta_2 C(t))u(x,t) + 2\beta \int_x^{\infty} u(y,t)dy \quad (2)$$

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t) \int_{x_0}^{\infty} u(x,t)dx \quad (3)$$

$$V(0) = V_0 \quad (4)$$

$$C(0) = C_0 \quad (5)$$

$$u(x,0) = u_0(x), \quad x_0 < x < \infty \quad (6)$$

$$u(x_0,t) = 0, \quad t \geqslant 0 \quad (7)$$

where the constants $\lambda, \gamma, \tau, \beta, \delta_0, \delta_1$ and δ_2 are all positive.

3. The steady states of the system

In this section, we convert the model into a system of ordinary differential equations and compute the steady states of the system [9].

Introduce the functions $U(t) = \int_{x_0}^{\infty} u(x,t)dx$ which denotes the total number of $Pr P^{5c}$ polymers and $P(t) = \int_{x_0}^{\infty} xu(x,t)dx$ which is the total number of monomers in the polymers. Now, substituting these functions in Eqs. (1) and (3), we get

$$\dot{V}(t) = \lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t) \quad (8)$$

$$\dot{C}(t) = -\delta_0 C(t) + \delta_1 C(t)U(t) \quad (9)$$

Now integrating Eq. (2) for $u(x,t)$ between x_0 and ∞, we get

$$\begin{aligned}\frac{dU(t)}{dt} &= -\tau V(t)[u(x,t)]_{x_0}^{\infty} - \mu U(t) - \beta P(t) - \delta_2 C(t)U(t) + 2\beta \int_{x_0}^{\infty} \int_x^{\infty} u(y,t)dy = -\mu U(t) - \beta P(t) \\ &\quad - \delta_2 C(t)U(t) + 2\beta \int_{x_0}^{\infty} (y - x_0)u(y,t)dy \\ &= -\mu U(t) - \beta P(t) - \delta_2 C(t)U(t) + 2\beta P(t) - 2\beta x_0 U(t)\end{aligned}$$

Thus simplifying further, we get

$$\dot{U}(t) = -\mu U(t) - \delta_2 C(t)U(t) - 2\beta x_0 U(t) + \beta P(t) \quad (10)$$

Now multiplying Eq. (2) with x and integrating for $u(x,t)$ between x_0 and ∞, we get

$$\begin{aligned}\frac{dP(t)}{dt} &= -\tau V(t)\left[[xu(x,t)]_{x_0}^{\infty} - \int_{x_0}^{\infty} u(y,t)dy\right] - \mu P(t) - \beta \int_{x_0}^{\infty} x^2 u(x,t)dx - \delta_2 C(t)P(t) \\ &\quad + 2\beta \int_{x_0}^{\infty} x \int_x^{\infty} u(y,t)dy\,dx \\ &= \tau V(t)U(t) - \mu P(t) - \beta \int_{x_0}^{\infty} x^2 u(x,t)dx - \delta_2 C(t)P(t) \\ &\quad + \beta \int_{x_0}^{\infty} (y^2 - x_0^2)u(y,t)dy\end{aligned}$$

Thus, we get

$$\dot{P}(t) = \tau V(t)U(t) - \mu P(t) - \delta_2 C(t)P(t) - \beta x_0^2 U(t) \quad (11)$$

Combining Eqs. (8)–(11), we get the transformed system of ODES for our model given by

$$\dot{V}(t) = \lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t)$$

$$\dot{U}(t) = -\mu U(t) - \delta_2 C(t)U(t) - 2\beta x_0 U(t) + \beta P(t)$$

$$\dot{P}(t) = \tau V(t)U(t) - \mu P(t) - \delta_2 C(t)P(t) - \beta x_0^2 U(t)$$

$$\dot{C}(t) = -\delta_0 C(t) + \delta_1 C(t)U(t)$$

$$V(0) = V_0 \geqslant 0$$

$$C(0) = C_0 \geqslant 0$$

$$U(0) = U_0 \geqslant 0$$

$$P(0) = P_0 \geqslant x_0 U_0$$

For the system of ODES, we now compute the steady state solutions.

Set $\dot{V}(t) = 0 = \dot{U}(t) = \dot{P}(t) = \dot{C}(t)$

Now, solving $\dot{C}(t) = 0$,

we get

$$-\delta_0 C + \delta_1 CU = 0$$

$$\Rightarrow (-\delta_0 + \delta_1 U)C = 0$$

$$\Rightarrow \text{either } C = 0 \text{ or } (-\delta_0 + \delta_1 U) = 0.$$

Case 1: When $C = 0$, the system $\dot{V}(t) = 0 = \dot{U}(t) = \dot{P}(t)$ reduces to the following:

$$\lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t) = 0$$

$$-\mu U(t) - 2\beta x_0 U(t) + \beta P(t) = 0$$

$$\tau V(t)U(t) - \mu P(t) - \beta x_0^2 U(t) = 0$$

Now solving the above, we get the disease free equilibrium point as $E_1 = (\lambda/\gamma, 0, 0, 0) = (\tilde{V}, \tilde{U}, \tilde{P}, \tilde{C})$.

The disease state equilibrium point is given by $E_2 = (\acute{V}, \acute{U}, \acute{P}, \acute{C})$ where

$$\acute{V} = \frac{(\beta x_0 + \mu)^2}{\beta\tau}$$
$$\acute{U} = \frac{\beta\lambda\tau - \gamma(\beta x_0 + \mu)^2}{\mu\tau(2\beta x_0 + \mu)}$$
$$\acute{P} = \frac{\beta\lambda\tau - \gamma(\beta x_0 + \mu)^2}{\beta\mu\tau}$$
$$\acute{C} = 0$$

where $\sqrt{\frac{\beta\lambda\tau}{\gamma}} > \beta x_0 + \mu$.

Case: 2 When $-\delta_0 + \delta_1 U = 0$, we get the equilibrium to be $E_3 = (V^*, U^*, P^*, C^*)$ where

$$V^* = \frac{\lambda + \beta x_0^2 U^*}{\gamma + \tau U^*}$$
$$U^* = \frac{\delta_0}{\delta_1}$$
$$P^* = \frac{\tau V^* U^* - \beta x_0^2 U^*}{\mu + \delta_2 C^*} \quad \text{where } \tau V^* > \beta x_0^2$$
$$C^* = \frac{\sqrt{\beta\tau V^*} - (\mu + \beta x_0)}{\delta_2} \quad \text{where } \sqrt{\beta\tau V^*} > (\mu + \beta x_0).$$

4. Stability of the equilibrium points

In this section, we give some results on the stability of the equilibrium points.

Theorem 1. *The disease free equilibrium* $E_1 = (\lambda/\gamma, 0, 0, 0) = (\tilde{V}, \tilde{U}, \tilde{P}, \tilde{C})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{\beta\lambda\tau}{\gamma}} < (\mu + \beta x_0)$.

Proof. We compute the jacobian matrix of the system about the equilibrium point E_1. The jacobian matrix is given by

$$\begin{pmatrix} -\gamma & -\lambda\tau/\gamma + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - 2\beta x_0 & \beta & 0 \\ 0 & \lambda\tau/\gamma - \beta x_0^2 & -\mu & 0 \\ 0 & 0 & 0 & -\delta_0 \end{pmatrix}$$

The eigenvalues of the above matrix are

$$-\delta_0, \quad -\gamma, \quad -\sqrt{\frac{\beta\lambda\tau}{\gamma}} - (\mu + \beta x_0), \quad \sqrt{\frac{\beta\lambda\tau}{\gamma}} - (\mu + \beta x_0)$$

Now, the equilibrium E_1 is locally asymptotically stable iff all the eigenvalues of the jacobian matrix have negative real parts. But, all the eigenvalues will have negative real parts iff the condition $\sqrt{\frac{\beta\lambda\tau}{\gamma}} < (\mu + \beta x_0)$ is satisfied. This proves the theorem. □

Theorem 2. *The disease state equilibrium* $E_2 = (\acute{V}, \acute{U}, \acute{P}, \acute{C})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{\beta\lambda\tau}{\gamma}} > (\mu + \beta x_0)$ *and* $\acute{U} < \frac{\delta_0}{\delta_1}$.

Proof. The jacobian matrix is given by

$$\begin{pmatrix} -\gamma - \tau\acute{U} & -\tau\acute{V} + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - 2\beta x_0 & \beta & -\delta_2\acute{U} \\ \tau\acute{U} & \tau\acute{V} - \beta x_0^2 & -\mu & -\delta_2\acute{P} \\ 0 & 0 & 0 & -\delta_0 + \delta_1\acute{U} \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$(-\delta_0 + \delta_1\acute{U} - A)(A^3 + a_1A^2 + a_2A + a_3) = 0$$

where the coefficients

$$a_1 = \frac{-x_0^2\beta^2(\gamma - 4\mu) + 6\beta x_0\mu^2 + 2\mu^3 + \beta\lambda\tau}{\mu(2x_0\beta + \mu)}$$
$$a_2 = \frac{-2\beta(\mu + \beta x_0)(\beta x_0^2\gamma - \lambda\tau)}{\mu(2x_0\beta + \mu)}$$
$$a_3 = -\gamma(\mu + \beta x_0)^2 + \beta\lambda\tau$$

One eigenvalue is $A = -\delta_0 + \delta_1\acute{U}$ and this eigenvalue will have negative real part when $\acute{U} < \frac{\delta_0}{\delta_1}$.

To conclude about the other eigenvalues, we apply the Routh–Hurwitz criterion to the polynomial [10,11]

$$A^3 + a_1A^2 + a_2A + a_3$$

Therefore, the other eigenvalues of the matrix will have negative real parts if and only if

$$a_1, a_2, a_3 > 0 \text{ and } a_1a_2 - a_3 > 0$$

This condition is satisfied when

$$\sqrt{\frac{\beta\lambda\tau}{\gamma}} > (\mu + \beta x_0)$$

Hence, the proof. □

Theorem 3. *Let*

$$a_1 = \gamma + \tau U^* + 2\mu + 2\delta_2 C^* + 2\beta x_0$$
$$B = \delta_1\delta_2 C^{*2} + 2\mu\gamma + 2\gamma\delta_2 C^* + 2\beta x_0\gamma + 2\mu\tau U^* + 2\delta_2 C^*\tau U^* + 2\beta x_0\tau U^* + \mu^2 + 2\mu\delta_2 C^* + \delta_2^2 C^{*2} + 2\mu\beta x_0 + 2\beta\delta_2 x_0 C^*$$
$$Q = \beta\tau V^* - \beta^2 x_0^2$$
$$D = \gamma\delta_1\delta_2 C^{*2} + \tau\delta_1\delta_2 U^* C^{*2} + \delta_1\delta_2\beta C^* P^* + \mu\delta_1\delta_2 C^{*2} + \delta_1\delta_2^2 C^{*3} + \mu^2\gamma + 2\mu\gamma\delta_2 C^* + \gamma\delta_2^2 C^{*2} + 2\mu\gamma\beta x_0 + 2\beta\gamma\delta_2 x_0 C^* + \tau U^*\mu^2 + 2\tau\mu\delta_2 U^* C^* + \delta_2^2 C^{*2}\tau U^* + 2\mu\beta x_0\tau U^* + 2\beta x_0\delta_2 C^*\tau U^*$$
$$E = \delta_1\delta_2\beta\gamma C^* P^* + \gamma\mu\delta_1\delta_2 C^{*2} + \gamma\delta_1\delta_2^2 C^{*3} + \tau\delta_1\delta_2\beta U^* C^* P^* + \tau\mu\delta_1\delta_2 U^* C^{*2} + \tau\delta_1\delta_2^2 C^{*3} U^*$$

Then, the equilibrium $E_3 = (V^*, U^*, P^*, C^*)$ *is locally asymptotically stable if and only if*

$$\sqrt{\beta\tau V^*} > (\mu + \beta x_0) \tag{12}$$

$$\tau V^* > \beta x_0^2 \tag{13}$$

$$B > Q \tag{14}$$

$$D > Q(\gamma + \tau U^*) \tag{15}$$

$$E > Q(\tau U^*) \text{ and} \tag{16}$$

$$a_1 BD + a_1 Q^2(\gamma + \tau U^*) + a_1^2 \tau U^* Q + 2QD(\gamma + \tau U^*) > a_1 QD + a_1 BQ(\gamma + \tau U^*) + D^2 + Q^2(\gamma + \tau U^*)^2 + a_1^2 E. \tag{17}$$

Proof. The jacobian matrix about the equilibrium point E_3 is given by

$$\begin{pmatrix} -\gamma - \tau U^* & -\tau V^* + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - \delta_2 C^* - 2\beta x_0 & \beta & -\delta_2 C^* \\ \tau U^* & \tau V^* - \beta x_0^2 & -\mu - \delta_2 C^* & -\delta_2 P^* \\ 0 & \delta_1 C^* & 0 & 0 \end{pmatrix}$$

The characteristic equation of the jacobian matrix is

$$A^4 + a_1 A^3 + a_2 A^2 + a_3 A + a_4 = 0$$

where

$$\begin{aligned} a_1 &= \gamma + \tau U^* + 2\mu + 2\delta_2 C^* + 2\beta x_0 \\ a_2 &= \delta_1\delta_2 C^{*2} + 2\mu\gamma + 2\gamma\delta_2 C^* + 2\beta x_0\gamma + 2\mu\tau U^* \\ &\quad + 2\delta_2 C^*\tau U^* + 2\beta x_0 \tau U^* + \mu^2 + 2\mu\delta_2 C^* + \delta_2^2 C^{*2} + 2\mu\beta x_0 \\ &\quad + 2\beta\delta_2 x_0 C^* - (\beta\tau V^* - \beta^2 x_0^2) \stackrel{\text{def}}{=} B - Q \\ a_3 &= \gamma\delta_1\delta_2 C^{*2} + \tau\delta_1\delta_2 U^* C^{*2} + \delta_1\delta_2\beta C^* P^* + \mu\delta_1\delta_2 C^{*2} + \delta_1\delta_2^2 C^{*3} + \mu^2\gamma \\ &\quad + 2\mu\gamma\delta_2 C^* + \gamma\delta_2^2 C^{*2} + 2\mu\gamma\beta x_0 + 2\beta\gamma\delta_2 x_0 C^* + \tau U^*\mu^2 + 2\tau\mu\delta_2 U^* C^* \\ &\quad + \delta_2^2 C^{*2}\tau U^* + 2\mu\beta x_0\tau U^* + 2\beta x_0\delta_2 C^*\tau U^* - (\gamma + \tau U^*)(\beta\tau V^* - \beta^2 x_0^2) \\ &\stackrel{\text{def}}{=} D - Q(\gamma + \tau U^*) \\ a_4 &= \delta_1\delta_2\beta\gamma C^* P^* + \gamma\mu\delta_1\delta_2 C^{*2} + \gamma\delta_1\delta_2^2 C^{*3} + \tau\delta_1\delta_2\beta U^* C^* P^* \\ &\quad + \tau\mu\delta_1\delta_2 U^* C^{*2} + \tau\delta_1\delta_2^2 C^{*3} U^* - \tau U^*(\beta\tau V^* - \beta^2 x_0^2) \\ &\stackrel{\text{def}}{=} E - Q(\tau U^*) \end{aligned}$$

Since, the equilibrium point is required to be positive, Eqs. (12) and (13) follow from that. Now, we apply the Routh–Hurwitz condition to the characteristic polynomial of the jacobian matrix about E_3. By Routh–Hurwitz criterion, the eigenvalues of the matrix will have negative real parts if and only if

$$a_1, a_2, a_3, a_4 > 0 \text{ and}$$

$$a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$$

Now, since all the constants are positive in the model,this $\Rightarrow a_1 > 0$.

Now, Eq. (14) $\Rightarrow a_2 > 0$,
Eq. (15) $\Rightarrow a_3 > 0$,
Eq. (16) $\Rightarrow a_4 > 0$,
Eq. (17) $\Rightarrow a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$.

Therefore, the Routh–Hurwitz condition is satisfied and hence all the eigenvalues of the Jacobian matrix have negative real parts. The negativity of all the eigenvalues implies that the equilibrium point E_3 is locally asymptotically stable. Hence, the proof. □

5. Numerical illustration

Our model can be used for simulations based on experimental data for prion proliferation. The model has nine parameters: $\lambda, \tau, \gamma, \beta, \mu, x_0, \delta_0, \delta_1$ and δ_2.

The minimum stable polymer x_0 is estimated as 6–30 in [12]. The model parameters are as follows. The parameter values were taken from [12]. $\lambda = 4400$ day^{-1}, $\tau = 0.3$ (Scrapie-Associated Fibrils (SAF)/sq. unit)$^{-1}$ day^{-1}, $\gamma = 5$ day^{-1}, $\beta = 0.0001$ (SAF/sq.)$^{-1}$ day^{-1}, $\mu = 0.04$ day^{-1}, $x_0 = 6$, $\delta_0 = 0.1$day^{-1}, $\delta_1 = 0.0004$day^{-1} and $\delta_2 = 0.002$day^{-1}. MATLAB software has been used to simulate our model. Fig. 1 shows the variation of U, V and P with time. All the graphs show the population reaching the steady state U^*, V^*, and P^*, respectively. The simulations assume an initial PrP^c population $V_0 = 880$ along with $U_0 = 5$, $P_0 = 1000$ and $C_0 = 1000$. A biologically more useful result is obtained when we study the population of polymers along with chaperone concentration. The change in $U(t)$ and $C(t)$ for different values of chaperone dose with time is plotted in Fig. 2. From the figure we see that the infection is curbed in the presence of chaperone in the system. We found that, with increasing levels of chaperone, the disease was under control for longer periods of time.

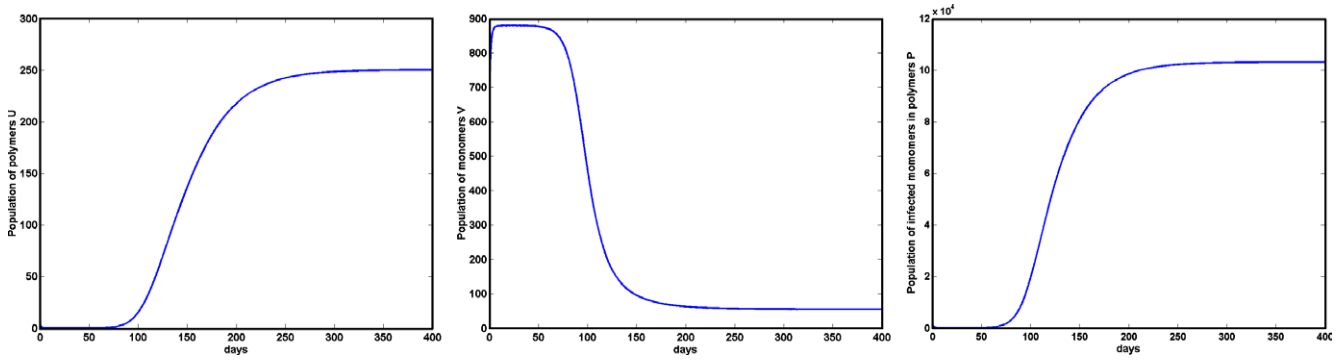

Fig. 1. Profile of population of polymers U, population of monomers V and population of infected monomers in polymers P vs. time.

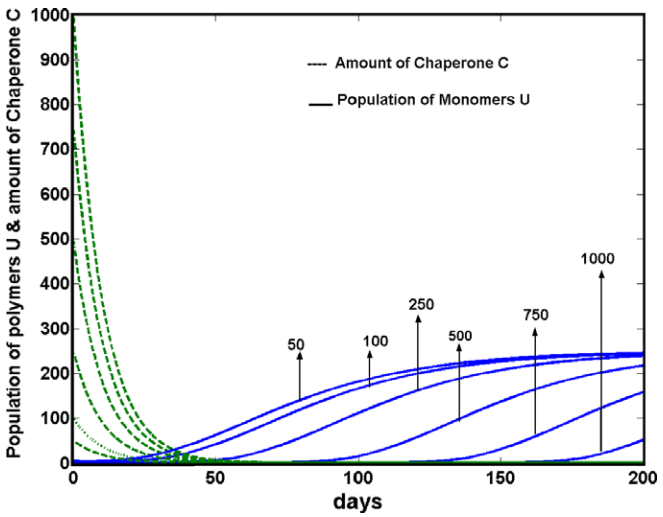

Fig. 2. Dose–response curve of population of polymers U for varying amounts of Chaperone C (50, 100, 250, 500, 750 and 1000 units of chaperone).

The disease free state was achieved for a period of 180 days when a dose of 1000 units of chaperone was administered.

6. Conclusions

In this work, we have proposed a model of prion proliferation with the effects of a chaperone. Our model provides an extension to the model of Webb et al. [8]. We have studied the stability of the equilibrium points of the model and have proved that the steady state solutions of the model are locally asymptotically stable. From the analysis of the model and the results proved in Section 4, we conclude the following: Let $T = \frac{\lambda\beta\tau}{\gamma(\mu+\beta x_0)^2}$ denote the number of secondary infections produced on average by one infectious prion.

If $T < 1$, then the disease dies out and the disease free equilibrium E_1 is locally asymptotically stable. If $T > 1$, then the disease persists and the disease state equilibrium E_2 is locally asymptotically stable. The above two conclusions are drawn by analysing the equilibrium points, when the amount of chaperone is zero.

From the numerical illustration in Section 5, we find that a disease free state can be achieved in the presence of a chaperone. The duration of the disease free state is found to increase with the amount of chaperone and this amount of chaperone can be computed from the model.

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