

## ANALYSIS OF A MODEL FOR THE DYNAMICS OF PRIONS

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**ABSTRACT.** A mathematical model for the dynamics of prion proliferation is analyzed. The model involves a system of three ordinary differential equations for the normal prion forms, the abnormal prion forms, and polymers comprised of the abnormal forms. The model is a special case of a more general model, which is also applicable to other models of infectious diseases. A theorem of threshold type is derived for this general model. It is proved that below and at the threshold, there is a unique steady state, the disease-free equilibrium, which is globally asymptotically stable. Above the threshold, the disease-free equilibrium is unstable, and there is another steady state, the disease equilibrium, which is globally asymptotically stable.

**1. Introduction.** In this paper we analyze a system of ordinary differential equations, which is applicable to a model of prion proliferation dynamics. The model is a special case of a more general model, which is also applicable to SEIS epidemic models and models of in-host viral infection dynamics. The prion model has been introduced in [11], based on the works of Masel, Jansen and Nowak [25], Nowak, Krakauer, Klug and May [27] and others. For a comprehensive explanation of the prion model and relevant biochemical literature we refer to [11], Eigen [13], and Prusiner [31]. Prions are proteins that are believed to be responsible for certain diseases such as *bovine spongiform encephalopathy* and *Creutzfeldt-Jacob disease*. There are two basic forms of prions of interest here, the *Prion Protein*

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*Cellular PrP<sup>C</sup>* and the *Prion Protein Scrapie PrP<sup>Sc</sup>*. The single molecule proteins *PrP<sup>C</sup>*, also called *monomers* in the sequel, are protease resistant proteins produced normally in the body. It is hypothesized that *PrP<sup>C</sup>* provide a protective function against cell apoptosis (Roucou, Gains and Lablanc [32]). On the other hand, the infectious prions *PrP<sup>Sc</sup>* convert *PrP<sup>C</sup>* to the *PrP<sup>Sc</sup>* form, which attach and lengthen in long string-like fibrils. Above a critical length  $x_0 > 0$  the fibrils are stable, and can contain thousands of infectious *PrP<sup>Sc</sup>*. These fibrils have the ability to split into two pieces, which can elongate, and split again. There are six processes which govern the dynamics of prions in the model:

- elongation of fibrils at rate  $\tau$ ;
- splitting of fibrils of length  $y > 0$  into lengths  $0 < x < y$  and  $y - x$  with probability  $\kappa(x, y)$  at rate  $\beta(y)$ ;
- degradation of *PrP<sup>C</sup>* monomers at rate  $\gamma$ ;
- degradation of fibrils of length  $x$  at rate  $\mu(x)$ .
- production of normal *PrP<sup>C</sup>* monomers at rate  $\lambda$ ;
- decomposition of fibrils of length  $\leq x_0$  resulting from splitting into *PrP<sup>C</sup>* monomers, where  $x_0 \geq 1$  is the minimum viable fibril length.

Denoting the number of *PrP<sup>C</sup>* monomers at time  $t$  by  $V(t)$  and the density of polymers of length  $x$  at time  $t$  by  $u(t, x)$ , we obtain the following model equations:

$$\begin{aligned} \frac{d}{dt}V(t) &= \lambda - \gamma V(t) - \tau V(t) \int_{x_0}^{\infty} u(t, x) dx \\ &\quad + 2 \int_0^{x_0} x \int_{x_0}^{\infty} \beta(y) \kappa(x, y) u(t, y) dy dx, \\ \frac{\partial}{\partial t}u(t, x) + \tau V(t) \frac{\partial}{\partial x}u(t, x) + (\mu(x) + \beta(x))u(t, x) &= 2 \int_x^{\infty} \beta(y) \kappa(x, y) u(t, y) dy, \\ V(0) \geq 0, \quad u(t, x_0) = 0, \quad u(0, x) = u_0(x), \quad x \geq x_0, \end{aligned} \tag{1}$$

where  $t \geq 0$  and  $1 \leq x_0 \leq x < \infty$ . The factor 2 in (1) arises from the symmetry of a fibril splitting into 2 pieces, one of length  $x$  and its complement of length  $y - x$ .

Observe that the splitting kernel  $\kappa(y, x)$  should satisfy the following properties:

$$\kappa(y, x) \geq 0, \quad \kappa(y, x) = \kappa(x - y, x), \quad \int_0^x \kappa(y, x) dy = 1,$$

for all  $x \geq x_0$ ,  $y \geq 0$ , and  $\kappa(y, x) = 0$  if  $y > x$  or  $x \leq x_0$ . We assume that splitting is equi-distributed, the rate of splitting is proportional to length, and the degradation rate of polymers is constant. Therefore, we make the further assumptions

$$\kappa(y, x) = 1/x \text{ if } x > x_0 \text{ and } 0 < y < x, \quad \kappa(y, x) = 0 \text{ elsewhere,}$$

$\beta(x) = \beta x$  is linear, and  $\mu(x) \equiv \mu$  is constant. Under these assumptions the model contains only the 6 parameters  $\lambda, \tau, \gamma, \mu, \beta$ , and  $x_0$ , and can be reduced to a system of 3 ordinary differential equations. In fact, introducing the new functions

$$U(t) = \int_{x_0}^{\infty} u(t, y) dy \quad \text{and} \quad P(t) = \int_{x_0}^{\infty} y u(t, y) dy,$$

representing the total number of polymers, and the total number of monomers in polymers at time  $t$ , respectively, and integrating the equation for  $u(t, x)$  over

$[x_0, \infty)$ , assuming  $u(t, x_0) = 0$ , and  $\lim_{x \rightarrow \infty} u(x, t) = 0$ , we obtain

$$\begin{aligned} \frac{d}{dt}U(t) &= -\tau V(t)u(t, x)|_{x_0}^\infty - \mu U(t) - \beta P(t) + 2\beta \int_{x_0}^\infty \int_x^\infty u(t, y)dydx \\ &= -\mu U(t) - \beta P(t) + 2\beta \int_{x_0}^\infty u(t, y)(y - x_0)dy \\ &= -\mu U(t) - \beta P(t) + 2\beta P(t) - 2\beta x_0 U(t). \end{aligned}$$

Multiplying the equation for  $u(t, x)$  by  $x$ , assuming  $\lim_{x \rightarrow \infty} xu(x, t) = 0$ , and integrating yields

$$\begin{aligned} \frac{d}{dt}P(t) &= -\tau V(t)(xu(t, x)|_{x_0}^\infty - \int_{x_0}^\infty u(t, y)dy) \\ &\quad - \mu P(t) - \beta \int_{x_0}^\infty u(t, x)x^2dx + 2\beta \int_{x_0}^\infty x \int_x^\infty u(t, y)dydx \\ &= \tau V(t)U(t) - \mu P(t) - \beta \int_{x_0}^\infty u(t, x)x^2dx + \beta \int_{x_0}^\infty u(t, y)(y^2 - x_0^2)dy \\ &= \tau V(t)U(t) - \mu P(t) - \beta x_0^2 U(t). \end{aligned}$$

We thus obtain the following system of three ordinary differential equations:

$$\begin{aligned} \dot{U} &= \beta P - \mu U - 2\beta x_0 U, \\ \dot{V} &= \lambda - \gamma V - \tau UV + \beta x_0^2 U, \\ \dot{P} &= \tau UV - \mu P - \beta x_0^2 U \end{aligned} \tag{2}$$

with initial conditions

$$U(0) = U_0 \geq 0, \quad V(0) = V_0 \geq 0, \quad P(0) = P_0 \geq x_0 U_0.$$

Once the solutions of (2) are known, one has only to solve the linear partial integro-differential equation in (1) to obtain the density with respect to fibril length  $u(t, x)$ . The full pde-system (1), which contains also the dynamics of the fibril density  $u(t, x)$ , is analyzed in [12] and Simonett and Wallker [35]. Our goal is to analyze the global behavior of the solutions of (2) in the cone  $U \geq 0, V \geq 0, P \geq x_0 U$ . We prove the following result concerning the qualitative behavior of the system (2):

**THEOREM 1.1.** *Suppose  $x_0, \beta, \gamma, \lambda, \mu, \tau > 0$ . The system (2) induces a global semi-flow on the set  $K = \{(U, V, P) \in \mathbb{R}^3 : U, V, P - x_0 U \geq 0\}$ . There is precisely one disease-free equilibrium  $(0, \lambda/\gamma, 0)$  which is globally asymptotically stable if and only if  $\mu + x_0\beta \geq \sqrt{\lambda\beta\tau/\gamma}$ . On the other hand, if  $\mu + x_0\beta < \sqrt{\lambda\beta\tau/\gamma}$ , then there is a unique disease equilibrium*

$$\left( \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\mu\tau(\mu + 2\beta x_0)}, \frac{(\mu + \beta x_0)^2}{\beta\tau}, \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\beta\mu\tau} \right),$$

*which is globally asymptotically stable in  $K \setminus [\{0\} \times \mathbb{R}_+ \times \{0\}]$ .*

This result shows that the solutions of (2) exhibit the typical behavior of epidemic models. Let  $R_0 = \lambda\beta\tau/\gamma(\mu + \beta x_0)^2$ , which is the number of secondary infections produced on average by one infectious prion. If  $R_0 \leq 1$ , then the disease dies out and the disease-free equilibrium is globally asymptotically stable. If  $R_0 > 1$ , a unique nontrivial steady state, the disease equilibrium, bifurcates from the trivial one and subsumes the global asymptotic stability. Thus, for  $R_0 > 1$ , the disease persists and exhibits strong stability properties. In Fig. 1 below we illustrate the

global attractivity of the disease steady state in a simulation of prion proliferation dynamics corresponding to data from Rubentstein *et al.* [34].

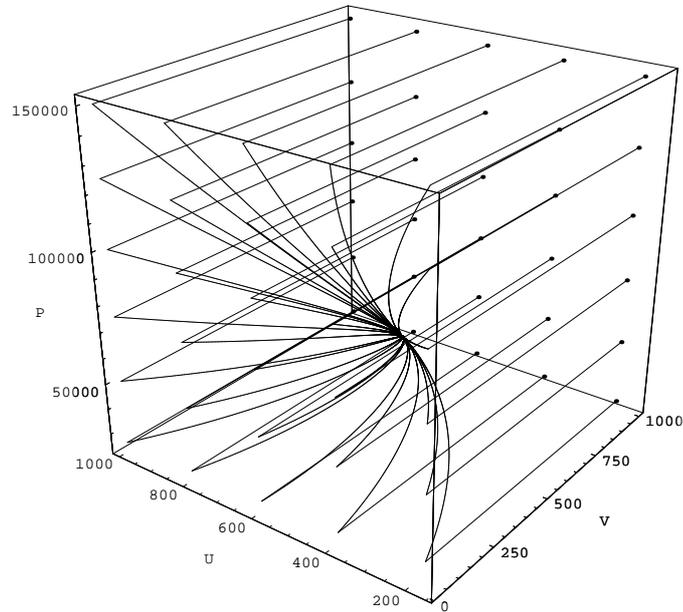


FIGURE 1. Phase portrait for the system (2). The solutions  $(U(t), V(t), P(t))$  corresponding to different initial values converge to the globally attracting disease steady state. The parameters of the simulations are derived from [25] and [34]:  $\lambda = 4400 \text{ day}^{-1}$ ,  $\tau = .3 \text{ SAF/sq}^{-1} \text{ day}^{-1}$ ,  $\beta = .0001 \text{ SAF/sq}^{-1} \text{ day}^{-1}$ ,  $\mu = .04 \text{ day}^{-1}$ ,  $\gamma = 5.0 \text{ day}^{-1}$ ,  $x_0 = 6$ , where  $\text{SAF/sq}$  denotes scrapie associated fibrils per square unit of measurement.

**2. A General Three Compartment Model of Infection Dynamics.** As general references for the theoretical results employed below we refer to the monographs of Amann [1] or Chicone [5]. We first transform the model of prion proliferation (2) to the following more general system:

$$\begin{aligned} \dot{x} &= z - \xi x, \\ \dot{y} &= \sigma - \rho y - xy + \delta x, \\ \dot{z} &= xy - z, \end{aligned} \tag{3}$$

with initial conditions  $x(0) = x_0 \geq 0$ ,  $y(0) = y_0 \geq 0$ ,  $z(0) = z_0 \geq 0$ . We prove the following theorem for (3):

**THEOREM 2.1.** *Suppose  $\xi > 0$ ,  $\sigma > 0$ ,  $\rho > 0$  and  $\delta \in [0, \xi)$ . The system (3) induces a global semiflow on the set  $\mathbb{R}_+^3$ . There exists precisely one (disease-free) equilibrium  $(0, \sigma/\rho, 0)$ , which is globally asymptotically stable, if and only if  $\sigma \leq \xi\rho$ . On the other hand, if  $\sigma > \xi\rho$  there is one additional (disease) equilibrium  $(\frac{\sigma - \xi\rho}{\xi - \delta}, \xi, \xi \frac{\sigma - \xi\rho}{\xi - \delta})$ , which is globally asymptotically stable in  $\mathbb{R}_+^3 \setminus [\{0\} \times \mathbb{R}_+ \times \{0\}]$ .*

Theorem 1.1 is proved by Theorem 2.1, with (2) converted to (3) as follows: First, to work in the standard positive cone  $\mathbb{R}_+^3$ , we replace the variable  $P$  by  $W = P - x_0U$  (the feasible values of  $P$  and  $U$  satisfy  $P \geq x_0U$ , since the minimum value for  $P$  is  $x_0U$ ). This gives the system

$$\begin{aligned} x_0\dot{U} &= \beta x_0W - (\mu + \beta x_0)x_0U, \\ \dot{V} &= \lambda - \gamma V - \frac{\tau}{x_0}x_0UV + \beta x_0x_0U, \\ \dot{W} &= \frac{\tau}{x_0}x_0UV - (\mu + \beta x_0)W, \end{aligned}$$

with initial values  $U(0) = U_0 \geq 0, V(0) = V_0 \geq 0$  and  $W(0) = W_0 = P_0 - x_0U_0 \geq 0$ . Next, perform a scaling of the variables by setting

$$x_0U(t) = ax(\alpha t), \quad V(t) = by(\alpha t), \quad W(t) = cz(\alpha t).$$

With  $\alpha = \mu + \beta x_0, a = (\mu + \beta x_0)x_0/\tau, b = c = (\mu + \beta x_0)^2/\beta\tau$  we obtain the system (3) with  $\xi = 1, \sigma = \lambda\beta\tau/(\mu + \beta x_0)^3 > 0, \rho = \gamma/(\mu + \beta x_0) > 0, \delta = (\beta x_0/(\mu + \beta x_0))^2 \in (0, 1)$ .

The model (3) also admits an interpretation for SEIS epidemics. Consider the populations of susceptibles  $S(t)$  (individuals capable of acquiring the disease), exposed  $E(t)$  (infected individuals who are not yet contagious), and infectious  $I(t)$  (infected individuals who are capable of transmitting the disease to susceptibles). We assume a constant influx of susceptibles  $\lambda > 0$  and natural death rate  $\gamma > 0$  of susceptibles. Susceptibles enter the exposed class at a rate proportional to the product of the susceptible and infectious populations with rate constant  $\tau$ . Exposed individuals enter the infectious class with rate  $\alpha$  or are otherwise removed with rate  $\mu$ . Infectious individuals return to the susceptible class with rate  $\beta$  or are otherwise removed with rate  $\nu$ . Thus, infectious individuals either die, recover with permanent immunity, or recover with no immunity. The equations of the model are

$$\begin{aligned} \dot{S} &= \lambda - \gamma S - \tau IS + \beta I, \\ \dot{E} &= \tau IS - (\alpha + \mu)E, \\ \dot{I} &= \alpha E - (\beta + \nu)I, \end{aligned} \tag{4}$$

**THEOREM 2.2.** *Suppose  $\lambda, \gamma, \tau, \beta, \alpha, \mu, \nu > 0$ . The system (4) induces a global semi-flow in  $R_+^3$ . Let  $R_0 = \frac{\alpha\lambda\tau}{\gamma(\alpha+\mu)(\beta+\nu)}$ . There is precisely one disease-free equilibrium  $\bar{S} = \lambda/\gamma, \bar{E} = 0, \bar{I} = 0$ , which is globally asymptotically stable if and only if  $R_0 \leq 1$ . On the other hand, if  $R_0 > 1$ , then there is a unique disease equilibrium*

$$\bar{S} = \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\mu\tau(\mu + 2\beta x_0)}, \bar{E} = \frac{(\mu + \beta x_0)^2}{\beta\tau}, \bar{I} = \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\beta\mu\tau},$$

*which is globally asymptotically stable in  $R_+^3 \setminus [\mathbb{R}_+ \times \{0\} \times \{0\}]$ .*

The conversion of (4) to (3) is accomplished as follows: Set  $x(t) = \frac{\tau}{\alpha+\mu}I(\frac{t}{\alpha+\mu}), y(t) = \frac{\alpha\tau}{(\alpha+\mu)^2}S(\frac{t}{\alpha+\mu}), z(t) = \frac{\alpha\tau}{(\alpha+\mu)^2}E(\frac{t}{\alpha+\mu}), \xi = \frac{\beta+\nu}{\alpha+\mu}, \sigma = \frac{\alpha\tau\lambda}{(\alpha+\mu)^3}, \rho = \frac{\gamma}{\alpha+\mu}, \delta = \frac{\alpha\beta}{(\alpha+\mu)^2}$ . Note that  $\delta < \xi$ . For the SEIS model (4)  $R_0 = \frac{\alpha\lambda\tau}{\gamma(\alpha+\mu)(\beta+\nu)} = \frac{\sigma}{\xi\rho}$  is the number of secondary infections produced by a single infectious individual.

SEIS models have been studied extensively, and many results are known ([3], [4], [6], [7], [8], [10], [14], [15], [16], [17], [19], [20], [21], [22], [23], [24], [26], [33], [36], [37]). In [22] the global stability of the disease equilibrium was established for a

SEIRS model with constant total population size, which reduces to a SEIS model similar to (4) as the parameter for transition from  $I$  to  $R$  tends to infinity. In [7] the global stability of the disease equilibrium was established for a model similar to (4), but with more restrictive loss rates.

The model (4) can also be interpreted in terms of viral-host cell interactions (Bonhoeffer, May, Shaw, and Nowak [2] and May and Nowak [28]). Consider the populations of virus  $V(t)$ , uninfected host cells  $T(t)$ , and infected host cells  $T^*(t)$  in an infected host at time  $t$ . Virus is produced at a rate proportional to the population of infected cells with rate constant  $\alpha$  and loss rate  $\nu$ . There is a constant source  $\lambda$  and normal loss rate  $\gamma$  of uninfected cells, an additional loss of uninfected cells (and gain of infected cells) proportional to the product of infected cells and virus with rate constant  $\tau$ , and virus-stimulated production of uninfected cells at a rate  $\beta$ . Infected cells have loss rate  $\mu$ . The equations of this model are

$$\begin{aligned}\dot{V} &= \alpha T^* - \nu V, \\ \dot{T} &= \lambda - \gamma T - \tau VT + \beta V, \\ \dot{T}^* &= \tau VT - \mu T^*,\end{aligned}\tag{5}$$

**THEOREM 2.3.** *Suppose  $\alpha, \nu, \lambda, \gamma, \tau, \mu > 0$ ,  $\beta \geq 0$  and  $\alpha\beta < \mu\nu$ . The system (5) induces a global semiflow in  $\mathbb{R}_+^3$ . Let  $R_0 = \frac{\alpha\lambda\tau}{\gamma\mu\nu}$ . There is precisely one disease-free equilibrium  $\bar{V} = 0, \bar{T} = \lambda/\gamma, \bar{T}^* = 0$ , which is globally asymptotically stable if and only if  $R_0 \leq 1$ . On the other hand, if  $R_0 > 1$ , then there is a unique disease equilibrium*

$$\bar{V} = \frac{\alpha\lambda\tau - \gamma\mu\nu}{\tau(\mu\nu - \alpha\beta)}, \bar{T} = \frac{\mu\nu}{\alpha\tau}, \bar{T}^* = \frac{\nu(\alpha\lambda\tau - \gamma\mu\nu)}{\tau\alpha(\mu\nu - \alpha\beta)}.$$

*which is globally asymptotically stable in  $\mathbb{R}_+^3 \setminus [\{0\} \times \mathbb{R}_+ \times \{0\}]$ .*

The conversion of (5) to (3) is accomplished as follows: Set  $x(t) = \frac{\tau}{\mu}V(\frac{t}{\mu})$ ,  $y(t) = \frac{\alpha\tau}{\mu^2}T(\frac{t}{\mu})$ ,  $z(t) = \frac{\alpha\tau}{\mu^2}T^*(\frac{t}{\mu})$ ,  $\xi = \frac{\nu}{\mu}$ ,  $\sigma = \frac{\alpha\tau\lambda}{\mu^3}$ ,  $\rho = \frac{\gamma}{\mu}$ ,  $\delta = \frac{\alpha\beta}{\mu^2}$ . The condition  $\delta < \xi$  requires  $\alpha\beta < \mu\nu$ . For the virus-host cell dynamics model (5)  $R_0 = \frac{\alpha\lambda\tau}{\gamma\mu\nu} = \frac{\sigma}{\xi\rho}$  is the number of secondary host cell infections from a single infected host cell. In the case that  $\beta = 0$  the global asymptotics of system (5) have been analyzed by Korobeinikov [17], [18], by transforming (5) to an equivalent SEIR model with constant host population size. The system (5) (with  $\beta = 0$ ) has been used extensively in modeling the within-host dynamics of HIV infection (Perelson, Neumann, Markowitz, Leonard, and Ho [29], Perelson and Nelson [30], Gilchrist, Coombs, and Perelson [9]).

### 3. Proof of the Theorems.

**3.1. Global Well-Posedness.** Since the right hand sides of (3) are polynomial, this system generates a local flow on  $\mathbb{R}^3$ . Recall that an ode-system  $\dot{u} = f(u)$  on  $\mathbb{R}^n$  is called quasipositive if the condition

$$u \geq 0, u_k = 0 \Rightarrow f_k(u) \geq 0$$

is valid for all  $k = 1, \dots, n$ . System (3) obviously is quasipositive, hence solutions with nonnegative initial data  $(x_0, y_0, z_0) \in \mathbb{R}_+^3$  stay in the standard cone  $\mathbb{R}_+^3$  for all

positive times. From the three equations we get with  $\varphi = \frac{\xi+\delta}{2\xi}x + y + z$

$$\dot{\varphi} = \sigma - \rho y - \frac{\xi - \delta}{2}x - \frac{\xi - \delta}{2\xi}z \leq \sigma - \varepsilon\varphi,$$

where  $\varepsilon = \min\{\rho, \frac{\xi-\delta}{2}, \frac{\xi-\delta}{2\xi}\}$ . Hence we obtain the bound

$$0 \leq \varphi(t) \leq \frac{\sigma}{\varepsilon} + \varphi(0)e^{-\varepsilon t},$$

whenever  $(x_0, y_0, z_0) \in \mathbb{R}_+^3$  and  $t \geq 0$ . This implies boundedness of the solutions, hence global existence for all positive times, which shows that system (3) induces a global semiflow on the standard cone  $\mathbb{R}_+^3$ .

**3.2. Steady States.** Observe that the set  $\{(x, y, z) \in \mathbb{R}_+^3 : x = z = 0\}$  is an invariant subset of (3). Thus, the system trivializes to the single equation

$$\dot{y} = \sigma - \rho y, \quad y(0) = y_0,$$

which admits the single steady state  $\bar{y} = \sigma/\rho$ . Further,  $\bar{y}$  is globally asymptotically stable in the set  $\{(x, y, z) \in \mathbb{R}_+^3 : x = z = 0\}$ . Hence the system (3) has the steady state  $(0, \sigma/\rho, 0)$  which we call the trivial or *disease free equilibrium*.

An simple computation shows that the system admits another steady, namely,  $(x^*, y^*, z^*)$ , where  $x^* = (\sigma - \xi\rho)/(\xi - \delta)$ ,  $y^* = \xi$ , and  $z^* = \xi x^*$ . We call this steady state the nontrivial or *disease equilibrium*. Note that this steady state is only biologically relevant if it lies in  $\mathbb{R}_+^3$  which means that the condition  $\sigma \geq \xi\rho$  must hold. At the critical value  $\sigma = \xi\rho$  this steady state bifurcates from the trivial one via a simple transcritical bifurcation.

To examine the local exponential asymptotic stability properties of these equilibria we compute their linearizations. At the trivial equilibrium we obtain the linearization

$$A = \begin{bmatrix} -\xi & 0 & 1 \\ \delta - \sigma/\rho & -\rho & 0 \\ \sigma/\rho & 0 & -1 \end{bmatrix}.$$

The eigenvalues of this matrix are

$$z_{1,2} = \frac{-1 - \xi \pm \sqrt{(1 - \xi)^2 + 4\sigma/\rho}}{2}, \quad z_3 = -\rho$$

It is easily seen that all three eigenvalues are negative, if  $\sigma < \xi\rho$ . By the principle of linearized stability we thus see that the trivial equilibrium is locally exponentially asymptotically stable if  $\bar{y} = \sigma/\rho < \xi$ , which is precisely the case when the disease equilibrium has no biological relevance.

For the linearization at the disease equilibrium we get

$$A = \begin{bmatrix} -\xi & 0 & 1 \\ \delta - \xi & -\rho - x^* & 0 \\ \xi & x^* & -1 \end{bmatrix},$$

where  $x^* = (\sigma - \xi\rho)/(\xi - \delta) > 0$ . The characteristic polynomial of this matrix is given by

$$p(z) = \det(zI - A) = z^3 + a_1z^2 + a_2z + a_3,$$

$$a_1 = 1 + \xi + \frac{\sigma - \delta\rho}{\xi - \delta}, \quad a_2 = \frac{(1 + \xi)(\sigma - \delta\rho)}{\xi - \delta}, \quad a_3 = \sigma - \xi\rho.$$

Since  $a_1 a_2 > (1 + \xi)(\sigma - \delta\rho) > a_3$ , the Ruth-Hurwitz criterion implies that all roots of  $p$  have negative real parts, which shows that the disease equilibrium is locally exponentially asymptotically stable if it is biologically meaningful, i.e. if  $\sigma > \xi\rho$ .

**3.3. Global Asymptotic Stability of the Trivial Equilibrium.** Suppose  $\sigma \leq \xi\rho$ . By means of a *Ljapunov* function we show that in this case the trivial equilibrium is globally asymptotically stable in  $\mathbb{R}_+^3$ . For this purpose we set

$$\Phi(x, y, z) = \frac{1}{2}(y - \bar{y})^2 + (2\xi - \delta - \bar{y})(x + z). \quad (6)$$

Then for  $\sigma = \rho\bar{y}$ ,

$$\begin{aligned} \dot{\Phi} &= -\rho(y - \bar{y})^2 + x(\delta - y)(y - \bar{y}) + x(2\xi - \delta - \bar{y})(y - \xi) \\ &= -\rho(y - \bar{y})^2 - x[(y - \xi)^2 + (\xi - \frac{\sigma}{\rho})(2\xi - \delta - \xi)] \leq 0, \end{aligned}$$

Thus  $\Phi$  is a Ljapunov function for (3) in  $\mathbb{R}_+^3$  if  $\sigma \leq \xi\rho$ . Further, in this case we have  $\dot{\Phi} = 0$  only if  $y = \bar{y} = \sigma/\rho$  and  $x = 0$ . Now the only invariant subset of the set  $y = \bar{y}$  is the disease free steady state, hence it is globally asymptotically stable in  $\mathbb{R}_+^3$ .

**3.4. Global Asymptotic Stability of the Disease Equilibrium.** Consider now the disease case  $\sigma > \xi\rho$ . It is convenient to translate the equation to the disease equilibrium. We set  $u = x - x^*$ ,  $v = y - y^*$ ,  $w = z - z^*$ , where  $(x^*, y^*, z^*) = (\frac{\sigma - \xi\rho}{\xi - \delta}, \xi, \xi \frac{\sigma - \xi\rho}{\xi - \delta})$ , and obtain the following new system:

$$\begin{aligned} \dot{u} &= w - \xi u, \\ \dot{v} &= -(\rho + x)v - (\xi - \delta)u, \\ \dot{w} &= xv + \xi u - w. \end{aligned} \quad (7)$$

We compute the derivatives of the following functions which are well-known in the theory of epidemics. For  $x > 0, y > 0, z > 0$ ,

$$\begin{aligned} \frac{d}{dt}(u - x^* \log(x/x^*)) &= \frac{\dot{x}}{x}(x - x^*) \\ &= (z - \xi x)(x - x^*)/x = z - \xi x - \frac{z}{x}x^* + \xi x^*, \end{aligned} \quad (8)$$

$$\begin{aligned} \frac{d}{dt}(v - y^* \log(y/y^*)) &= \frac{\dot{y}}{y}(y - y^*) \\ &= -\frac{\rho}{y}v^2 + \delta \frac{uv}{y} - xy + \xi x - \frac{\xi^2 x^*}{y} + \xi x^*, \end{aligned} \quad (9)$$

$$\begin{aligned} \frac{d}{dt}(w - z^* \log(z/z^*)) &= \frac{\dot{z}}{z}(z - z^*) \\ &= xy - z - \frac{xy}{z}z^* + z^*. \end{aligned}$$

Summing these equations, we obtain the Ljapunov function

$$\psi_0(x, y, z) = (u - x^* \log(x/x^*)) + (v - y^* \log(y/y^*)) + (w - z^* \log(z/z^*)),$$

$$\dot{\psi}_0(x, y, z) = -\frac{\rho}{y}v^2 + \delta \frac{uv}{y} - x^* \left[ \frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi \right].$$

Observe that  $\psi_0(x, y, z)$  approaches infinity at the boundary of the positive octant of  $\mathbb{R}^3$ . To remove the second term in  $\dot{\psi}_0(x, y, z)$ , which does not have a negative sign, we consider the modified Ljapunov function

$$\psi = \psi_0 + \frac{\delta}{\xi - \delta}(v - \xi \log y).$$

Note that  $\psi(x, y, z)$  approaches infinity at the boundary of the positive octant of  $\mathbb{R}^3$  and is bounded below. For this function we obtain

$$\begin{aligned} \dot{\psi} &= -\frac{\rho}{y}v^2 + \frac{\delta uv}{y} - x^*\left(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi\right) - \frac{\delta}{\xi - \delta}(v(\rho + x) + u(\xi - \delta))\frac{v}{y} \\ &= -\frac{v^2}{y}\left(\rho + \frac{\delta(\rho + x)}{\xi - \delta}\right) - x^*\left(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi\right) \\ &= -\frac{\delta x + \xi\rho}{(\xi - \delta)y}v^2 - x^*\left(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi\right). \end{aligned}$$

Now the first term is obviously nonpositive. Concerning the second term note that  $x^* > 0$  in the disease case. Set  $a = z/x > 0$ ,  $b = \xi^2/y > 0$ , and consider  $\varphi(a, b) = a + b + \frac{\xi^3}{ab} - 3\xi$  on  $(0, \infty)^2$ . Clearly this function is strictly positive for  $a + b \geq 3\xi$  and for  $ab \leq \xi^2/3$ , but  $\varphi(\xi, \xi) = 0$ . Therefore it has an absolute minimum in  $(0, \infty)^2$ . Computing the derivatives of  $\varphi$  one finds that  $(a, b) = (\xi, \xi)$  is the unique absolute minimum. Therefore we see that for all values of  $\sigma > \xi\rho$  and  $\delta \in [0, \xi)$  the function  $\psi$  is a Ljapunov function for system (3), and  $\dot{\psi} = 0$  if and only if  $y = \xi$  and  $z = \xi x$  hold. Looking at the equation for  $v$  we obtain in case  $y = \xi$ , i.e.  $v = 0$

$$\dot{v} = -(\xi - \delta)u \neq 0$$

unless  $u = 0$ , i.e.  $x = x^*$ . Thus the only invariant set contained in the set  $\dot{\psi} = 0$  is the disease equilibrium  $(x^*, y^*, z^*) = (x^*, \xi, \xi x^*)$ , hence La Salle's theorem ([1] implies convergence of the solutions to this equilibrium, for all initial values not in the set  $\{0\} \times \mathbb{R}_+ \times \{0\}$ . This shows that the disease equilibrium is globally asymptotically stable in  $\mathbb{R}_+^3 \setminus [\{0\} \times \mathbb{R}_+ \times \{0\}]$ . If the initial data is in  $\{0\} \times \mathbb{R}_+ \times \{0\}$ , then the solution obviously converges to the disease free equilibrium.

Thus, Theorem 2.1, and hence Theorems 1.1, 2.2, and 2.3 are proved. The results of Theorem 2.2 are applicable to the models (2), (4), and (5), since each can be converted to model (3). Thus, for each of these models of infectious disease, there is a threshold value  $R_0$ , dependent on the specific model parameters, such that if  $R_0 \leq 1$ , then all solutions converge to the unique disease-free equilibrium, and if  $R_0 > 1$ , then all solutions converge to the unique disease-endemic equilibrium.

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