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# Neuron scale modeling of prion production with the Unfolded Protein Response* 

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#### Abstract

We develop a mathematical model that describes concentration dynamics of $\operatorname{PrP}^{C}$ and $\operatorname{PrP}^{S c}$ prion proteins at the neuron scale and includes the effect of the Unfolded Protein Response (UPR). We first introduce a single neuron model taking the UPR mechanism into account. We investigate it and propose a stability study among which a bifurcation analysis with respect to three of its parameters. Then, we generalize it to two neurons showing $\operatorname{PrP}^{S c}$ proteins interaction. Stability results are given when neurons exhibit identical parameters but interact differently (strong, weak or no interaction).


Keywords: Prion, Unfolded Protein Response, Delay Differential Equation, Hopf bifurcation, prion Modeling, Neurodegenerative Model
AMS: 34K18, 34K20, 37G99, 37N25, 92B05, 92C20

## 1 Introduction

Prions are proteins capable of existing in multiple shapes (or conformations). The normal form, denoted $\operatorname{PrP}^{c}$ (for Prion Protein Cellular), is a cell surface protein mainly expressed by neurons [32]. However, $\mathrm{PrP}^{c}$ can change its conformation to become a misfolded $\operatorname{PrP}^{S c}$ (for Prion Proteins Scrapie) pathological element for mammals. They are responsible for the so called prion-diseases, also known as Transmissible Spongiform Encephalopathies, among which one can include the Creutzfeldt-Jakob disease in humans or the Bovine Spongiform Encephalopathy in cattle [29,32]. In prion diseases, an initial seed of $\operatorname{PrP}^{S c}$, either inherited, infectious (acquired) or sporadic (spontaneous) [28], converts

[^0]$\operatorname{PrP}^{C}$ and produces de novo $\operatorname{PrP}^{S c}$ that aggregate extra-cellularly and spread the process. In fact, $\operatorname{PrP}^{S c}$ become templating interfaces, inducing the misfolding of $\mathrm{PrP}^{c}$. This mechanism is known as propagated protein misfolding [44]. It is thought to be at stake in the pathogenesis of prion-diseases but also of a larger group of neuro-degenerative disorders commonly labeled as Protein Misfolding Disorders (PMDs) including Parkinson's or Alzheimer's diseases [18, 16].

Actually PMDs share a common hallmark: some specific proteins ${ }^{1}$ misfold, aggregate, replicate and propagate in a prion-like mechanism [18, 40, 41]. In this paradigm, pathogenic proteins, generally assembled in oligomers or aggregates, act as corruptive templates that trigger the misfolding of otherwise normally folded proteins [28, 41, 44].

The Unfolded Protein Response (UPR) is another biological phenomenon that seems to be involved in PMDs [18, 20, 21, 16, 39]. UPR is a cellular mechanism that aims to recover protein homeostasis in a reaction to Endoplasmic Reticulum (ER) stress [39, 20]. The link between misfolded proteins involved in PMDs, ER stress and UPR is still not clear : underlying mechanisms and consequences are the subject of current research (for review see e.g. [18, 39, 20, 21]). Nonetheless, studies seem to agree on the fact that accumulation ${ }^{2}$ of abnormally folded proteins triggers ER stress that subsequently activate the UPR [27, 39, 20, 38, 33].

In the context of prion-diseases, knowledge becomes clearer as some studies performed on mice highlight links between $\operatorname{PrP}^{S c}$ aggregates, ER stress and UPR mechanism [19, 45, 27, 26, 43, 38, 33]. For instance, some works seem to indicate that UPR downregulates $\mathrm{PrP}^{S c}$ through secreted chaperones acting over the extracellular proteostasis $[15,16]$. Other studies, investigating the role of UPR upon neurodegeneration in prion diseases, indicate that a high concentration of $\operatorname{PrP}^{S c}$ triggers ER stress. This activates the UPR and results in a transient global shutdown of protein synthesis [27, 26, 43, 38, 33]. The latter studies, which will constitute the basis of our biological assumptions, lead us to suggest that UPR indirectly downregulates $\mathrm{Pr}^{S c}$ : by preventing global protein translation, UPR activation shuts down the production of $\mathrm{PrP}^{c}$ which ultimately hampers the production of $\mathrm{PrP}^{S c}$.

It appears that, as the influence and effects of UPR on prion diseases are still unclear, mathematical models may provide valuable insights. Actually, they have already been used to investigate different issues in prion diseases and PMDs (for reviews see [36, 10]). They focus on some aspects of the disease such as the propagated misfolding mechanism and the aggregate size distribution $[24,31,17,13,30,9,8,11]$, the spatio-temporal progression of misfolded proteins (see e.g $[1,6,7,48,4,3]$ in Alzheimer's disease or [42, 25] in prion-diseases) or the strain diversity of prions [23]. However, to the best of our knowledge, there is no existing model describing $\mathrm{PrP}^{S c}$ production in the framework of neuronal UPR.

The few existing mathematical approaches of UPR lie in the framework of gene regulatory networks and focus neither on neurons nor on prion proteins. They deal with the concentration dynamics of unfolded and/or misfolded proteins through different biological pathways of UPR [34, 12, 49, 47, 46]. Closer to our work here, Trusina et al. [47, 46] developed a model describing regula-

[^1]tion of unfolded proteins inside the cell when submitted to a manageable ${ }^{3}$ ER stress. They incorporated the main UPR-pathways acting over unfolded proteins concentrations among which we find translation attenuation, a mechanism analogous to the translation shutdown we wish to take into account. In order to proceed to mathematical analysis and qualitative investigations, we only focus, in our study, on the latter mechanism and integrate it into a simple model of prion production.

Here, we propose a mathematical modeling that describes $\operatorname{PrP}^{c}$ and $\operatorname{PrP}{ }^{S c}$ concentrations at the neuron scale and incorporates the role of UPR through an induced shutdown of global protein synthesis. Based on recent studies [27, 26, 43, 38, 33], we model the effect UPR with a negative feedback mechanism reflecting a global translation attenuation. To do so, we suppose that a high concentration of misfolded $\mathrm{PrP}^{S c}$ around neurons triggers ER stress and UPR activation. This shuts down global protein translation thus reducing cellular $\operatorname{PrP}^{c}$ synthesis and as well as $\mathrm{PrP}^{S c}$ production. For simplicity, we neglect the influence of UPR-induced secreted chaperones over aggregation and templating (whose effect is likely to be less important compared to global translation shutdown) and thus do not take into account the $\operatorname{PrP}^{S c}$ downregulation through secreted chaperones.

Our mathematical approach is based on previous studies dedicated to delay differential equations and bifurcation analysis [22, 5, 2, 14]. In 2 we introduce our new model. We give some of its properties and study the asymptotic stability of its steady states. In 3, we extend our system to two neurons whose associated scrapie prion concentrations can interact. We finally discuss and conclude this work in 4.

## 2 Model of prion production at the neuron scale

Before studying a complete model with several billions of neurons, let start by investigating the process in the environment of a single cell. This section is then dedicated to the UPR acting on one neuron only.

### 2.1 The model

Our model, illustrated in 1, consists in describing the concentration dynamics of $\operatorname{PrP}^{c}$ and $\mathrm{PrP}^{S c}$ proteins produced by a single neuron. We note $x$ and $y$ the concentrations of $\operatorname{PrP}^{c}$ and $\operatorname{PrP}^{S c}$ respectively. They are ruled, for $t>0$, by the following system,

$$
\begin{aligned}
& \frac{\mathrm{d} x}{\mathrm{~d} t}(t)=K A(t)-\mu x(t)-d x(t) y(t) \\
& \frac{\mathrm{d} y}{\mathrm{~d} t}(t)=d x(t) y(t)-\alpha y(t)
\end{aligned}
$$

where $K>0$ represents the $\operatorname{PrP}^{c}$ production rate of the neuron and $d>0$ characterizes the strength of the interaction between $\operatorname{PrP}^{c}$ and $\operatorname{PrP}{ }^{S c}$. The term $d x(t) y(t)$ stands for the concentration of newly produced $\operatorname{PrP}^{S c}$. Parameter $\mu>0$ describes the metabolic loss rate of $\operatorname{PrP}^{c}$ and $\alpha>0$ the rate at which

[^2]

Figure 1: Neuron scale prion production model with Unfolded Protein Response (UPR) mechanism. A first compartment, structured by the biological processing time $a \in[0, T]$, describes the evolution of the neuron activity denoted by $u$. After a fixed time $T, u(t, T)$ mediates the $\operatorname{PrP}^{c}$ production rate $K$. Concentration of $\operatorname{PrP}^{c}$ proteins $x(t)$ decreases metabolically at a rate $\mu . \operatorname{PrP}^{c}$ proteins are also converted into $\operatorname{PrP}^{S c}$ at a rate $d . \operatorname{PrP}^{S c}$ proteins are mainly lost through diffusion represented by the rate $\alpha$. The feedback loop, standing for the UPR, is represented by a dashed line and depends on the $\operatorname{PrP}{ }^{S c}$ concentration $y(t)$ through a Hill function $\beta_{n}(\cdot)$. This is a negative feedback loop regulating the input of the neuron biological activity variable $u$.
$\operatorname{PrP}^{S c}$ proteins are lost metabolically or through diffusion. Finally, $A(t)$ models the protein synthesis activity of the neuron at time $t$ and is given by

$$
A(t)=u(t, T)
$$

where $T>0$ is the biological processes duration. It represents the time taken by all biological processes linked with UPR to induce the global translation shutdown. We assume that $u(t, a)$ describes the biological activity of the neuron at time $t$ and after a biological processing time $a \in[0, T]$. It is ruled by the following equation:

$$
\begin{equation*}
\frac{\partial u}{\partial t}(t, a)+\frac{\partial u}{\partial a}(t, a)=0, t>0,0<a<T \tag{1}
\end{equation*}
$$

Since $\operatorname{PrP}^{S c}$ around the neuron downregulate $\operatorname{PrP}^{c}$ production. We model this negative feedback through a decreasing Hill function. The influence of $\mathrm{PrP}^{S c}$ concentration over the neuron activity is then given by the input boundary condition of $u$ as :

$$
u(t, 0)=\frac{1}{1+\left(y(t) / y_{c}\right)^{n}}:=\beta_{n}(y(t)), \text { for all } t \geq 0
$$

where $n>0$ is the UPR sensitivity to an overload of $\operatorname{PrP}{ }^{S c}$. Parameter $y_{c}>0$ is the threshold density of $\mathrm{PrP}^{S c}$ over which the neuron (and its surrounding astrocytes) turn off global translation and thus $\operatorname{PrP}^{c}$ production.

In this framework, we use the method of characteristics to obtain the system of equations ruling our model :

$$
\begin{align*}
& \frac{\mathrm{d} x}{\mathrm{~d} t}=K \beta_{n}(y(t-T))-\mu x(t)-d x(t) y(t) \\
& \frac{\mathrm{d} y}{\mathrm{~d} t}=d x(t) y(t)-\alpha y(t) \tag{2}
\end{align*}
$$

System 2 may be interpreted as follows: a high concentration of $\mathrm{PrP}^{S c}$ proteins results, a biological time $T$ later, in a decrease of $\operatorname{PrP}^{c}(\operatorname{term} K \beta(y(t-T)))$ that consequently reduces the $\mathrm{PrP}^{S c}$ production (term $\left.d x(t) y(t)\right)$. The amount of $\operatorname{PrP}^{S c}$ surrounding the neuron decreases and misfolded protein homeostasis around the neuron is restored. Note that in this paradigm, we omit the notion of neuronal death and assume that the UPR is able to cope with the overload of $\operatorname{PrP}^{S c}$ proteins.

The initial condition $u(0, \cdot)$ of the biological activity variable has been chosen in order to guarantee the well-posedness of system 2 (provided that initial conditions $\left(x_{0}, y_{0}(\cdot)\right)$ are defined on $\left.\mathbb{R} \times C([-T, 0], \mathbb{R})\right)$. More precisely, we chose $u(0, a)=\beta_{n}\left(y_{0}(-a)\right)$ for all $a \in[0, T]$.

### 2.2 Model properties, steady states and characteristic equation

We state and prove some properties ensuring the well-posedness of our model as well as a result about existence of steady states.

For every non negative initial conditions $\left(x_{0}, y_{0}(\cdot)\right) \in \mathbb{R} \times C([-T, 0], \mathbb{R})$, system 2 admits a unique non negative solution $(x, y) \in C\left([0,+\infty), \mathbb{R}^{2}\right)$ such that
$x(t) \leq \max \left\{x(0), \frac{K}{\mu}\right\}$ and $x(t)+y(t) \leq \max \left\{x(0)+y(0), \frac{K}{\min (\mu, \alpha)}\right\}$, for all $t \geq 0$.
Moreover, either there exists $\bar{t} \geq 0$ such that $x(\bar{t}) \leq K / \mu$ and then $x(t) \leq K / \mu$ for all $t \geq \bar{t}$, or $\lim _{t \rightarrow+\infty} x(t)=K / \mu$. Existence, uniqueness and positiveness of solutions can be proved by standard methods (e.g. see the theorems 3.1 and 3.4 of [37]), the rest of the proof consisting in a simple application of [2] (Proof of Proposition 3.1.) and the fact that $x(t)$ satisfies the differential inequality $x^{\prime}(t) \leq K-\mu x(t)$.

Positive invariance and attractivity of $[0, K / \mu] \times \mathbb{R}_{+}$results from equation 3.

Now, we focus on steady-states $\left(x^{*}, y^{*}\right)$ of system 2 characterized by the following Proposition. The system 2 always admits a trivial equilibrium $(K / \mu, 0)$. There exists a unique endemic steady state $(\alpha / d, \bar{y})$ with $\bar{y}$ satisfying 5 if and only if

$$
\begin{equation*}
R_{0}:=\frac{K d}{\mu \alpha}>1 \tag{4}
\end{equation*}
$$

If condition 4 holds, $\bar{y}$ is a continuously differentiable function of each model parameters. In particular, $\bar{y}$ is decreasing with respect to $\mu>0$ and $\alpha>0$ and increasing with respect to $y_{c}$ and verifies

$$
0<\bar{y}<\frac{\mu}{d}\left(R_{0}-1\right), \text { with } \lim _{\alpha \rightarrow d K / \mu} \bar{y}=0 \text { and } \lim _{\alpha \rightarrow 0} \bar{y}=+\infty
$$

Furthermore, if $\alpha=0$ then any solution $(x, y)$ has the limit $\lim _{t \rightarrow+\infty}(x(t), y(t))=$ $(0,+\infty)$. A steady state $\left(x^{*}, y^{*}\right)$ of system 2 satisfies :

$$
\begin{aligned}
K \beta_{n}\left(y^{*}\right) & =\mu x^{*}+d x^{*} y^{*} \\
\left(d x^{*}-\alpha\right) y^{*} & =0
\end{aligned}
$$

We easily see that a trivial steady-state $\left(x^{*}, y^{*}\right)=(K / \mu, 0)$ always exists. An endemic steady state $\left(x^{*}, y^{*}\right)=(\bar{x}, \bar{y})$ with $\bar{x}, \bar{y}>0$ would verify $\bar{x}=\alpha / d$ and

$$
\begin{equation*}
F(\bar{y}):=\frac{d K}{\mu \alpha} \beta_{n}(\bar{y})=1+\frac{d}{\mu} \bar{y} . \tag{5}
\end{equation*}
$$

Noticing that $F$ is decreasing, $F(0)=d K / \mu \alpha=R_{0}$ and that $\lim _{y \rightarrow+\infty} F(y)=$ 0 , we obtain that the endemic steady state $(\bar{x}, \bar{y})$ exists if and only if condition 4 holds. Moreover, if $R_{0}>1$, we have

$$
\frac{\mathrm{d} \bar{y}}{\mathrm{~d} \mu}=\frac{1}{\frac{K}{\alpha} \beta_{n}^{\prime}(\bar{y})-1}, \quad \frac{\mathrm{~d} \bar{y}}{\mathrm{~d} \alpha}=\frac{\frac{K}{\alpha^{2}} \beta_{n}(\bar{y})}{\frac{K}{\alpha} \beta_{n}^{\prime}(\bar{y})-1}
$$

and

$$
\frac{\mathrm{d} \bar{y}}{\mathrm{~d} y_{c}}=\frac{n K}{y_{c} \alpha}\left(\frac{\bar{y}}{y_{c}}\right)^{n} \beta_{n}(\bar{y})^{2}\left(1+\frac{n K}{y_{c} \alpha}\left(\frac{\bar{y}}{y_{c}}\right)^{n-1} \beta_{n}(\bar{y})^{2}\right)^{-1}
$$

with

$$
\beta_{n}^{\prime}(y)=-\frac{n}{y_{c}}\left(\frac{y}{y_{c}}\right)^{n-1} \beta_{n}(y)^{2}, \text { for all } y \in \mathbb{R}^{+}
$$

From these formulas and the implicit function theorem, we establish that $\bar{y}$ is a continuously differentiable function of each model parameters. Especially, it is decreasing with respect to $\mu>0, \alpha>0$ and increasing function of $y_{c}$.
Finally, assume that $\alpha=0$. The system 2 implies that $y^{\prime}(t)=d x(t) y(t) \geq 0$ from which we know that $y$ is non-decreasing. By contradiction, assume that $y$ is bounded and admits a positive limit. Then $\lim _{t \rightarrow+\infty} y^{\prime}(t)=0$. So it implies that $\lim _{t \rightarrow+\infty} x(t)=0$. As $t \mapsto x^{\prime}(t)$ is uniformly continuous on $\left(t_{0},+\infty\right), t_{0}>0$ large enough, we obtain that $\lim _{t \rightarrow+\infty} x^{\prime}(t)=0$. Taking the limit as $t$ goes to infinity in the first equation of 2 leads to a contradiction. We thus obtained that $\lim _{t \rightarrow+\infty} y(t)=+\infty$. Now, we associate this result, the continuity and boundedness of $x$ as well as the first equation of 2 to claim that there exists $\tilde{t} \geq 0$ such that $x$ is non-increasing on $[\tilde{t},+\infty)$. We conclude that $x$ goes to 0 as $t$ goes to infinity. The result is thus proven when $\alpha=0$.

### 2.3 Asymptotic stability of steady states

We linearise system 2 about any steady state $\left(x^{*}, y^{*}\right)$ and obtain

$$
\begin{aligned}
& \frac{\mathrm{d} u}{\mathrm{~d} t}=-\left(\mu+d y^{*}\right) u(t)-d x^{*} v(t)+K \beta_{n}^{\prime}\left(y^{*}\right) v(t-T) \\
& \frac{\mathrm{d} v}{\mathrm{~d} t}=d y^{*} u(t)-\left(\alpha-d x^{*}\right) v(t)
\end{aligned}
$$

from which we deduce, the associated characteristic equation

$$
\left|\begin{array}{cc}
\lambda+\mu+d y^{*} & d x^{*}-K \beta_{n}^{\prime}\left(y^{*}\right) e^{-\lambda T}  \tag{6}\\
-d y^{*} & \lambda+\alpha-d x^{*}
\end{array}\right|=0
$$

In the next section, we focus on the roots of this equation to determine the local asymptotic stability of the steady state $\left(x^{*}, y^{*}\right)$ under consideration.

### 2.3.1 Disease free equilibrium

Let us start with the disease free equilibrium. The endemic one follows in the next subsection. The trivial-steady state (disease free equilibrium) is locally asymptotically stable if and only if $R_{0} \leq 1$. It is then destabilized through a transcritical bifurcation when $R_{0}=1$ (i.e. $d K=\mu \alpha$ ) and unstable otherwise. For the trivial steady-state, the characteristic equation 6 reads

$$
(\lambda+\mu)\left(\lambda+\alpha-\frac{d K}{\mu}\right)=0, \quad \lambda \in \mathbb{C}
$$

Thus, we have two eigenvalues $-\mu<0$ and $\frac{d K}{\mu}-\alpha=\alpha\left(R_{0}-1\right)$, from which we can easily conclude local asymptotic stability when $R_{0}<1$ and instability when $R_{0}>1$. Now consider the case $R_{0}=1$. If we suppose that for all $t \geq 0$ $x(t) \geq K / \mu$, then from system 2 we have $x^{\prime}(t) \leq 0$ and $y^{\prime}(t) \geq 0$, for all $t \geq 0$. Since $y$ is bounded and its only possible limit is 0 , we get a contradiction. We conclude from Lemma 2.2 the existence of $\bar{t} \geq 0$ such that $x(t)<K / \mu$ for all $t \geq \bar{t}$. The second equation of system 2 implies that $y^{\prime}(t) \leq(d K / \mu-\alpha) y(t)=0$. We deduce that $y$ is non-increasing with $\lim _{t \rightarrow+\infty} y(t)=0$ and then the function $z: t \mapsto K \beta_{n}(y(t-T)) /(\mu+d y(t))$ is non-decreasing whose limit when $t \rightarrow+\infty$ is given by $K / \mu$. Using the first equation of 2 and the fact that $z$ is non-decreasing, we observe that the function $x$ can only change monotonicity when it intersects the curve of $z$ coming from its left and by being non-increasing before this intersection and non-decreasing after. We conclude that there exists $\tilde{t} \geq \bar{t}$ such that for all $t \geq \tilde{t}, x(t) \leq z(t)$. Otherwise, $x(t)>z(t)$ for all $t \geq \bar{t}$. This means that the function $x$ is non-increasing on $[\bar{t},+\infty)$, which is absurd. Then, we have $x$ non-decreasing on $[\tilde{t},+\infty)$. We deduce that $\lim _{t \rightarrow+\infty} x(t)=K / \mu$. We proved that if $R_{0}=1$, the trivial steady state is globally asymptotically stable. The biological interpretation of Proposition 2.3.1 is that if the production term $d K$ is smaller than the product of degradation term of the two prion species $\mu \alpha$, as one would expect, the trivial steady state is locally asymptotically stable otherwise it is unstable.

If $R_{0} \leq 1$ then the trivial steady state $\left(\frac{K}{\mu}, 0\right)$ is globally asymptotically stable. The global asymptotic stability in the case $R_{0}=1$ has already been proved above. For the case $R_{0}<1$, we adapt the method used in [2] (Theorem 5.1).

Define the set $G$ as

$$
G=\left[0, \frac{K}{\mu}\right] \times \mathbb{R}_{+}
$$

For $(x, y) \in G$, we define the Lyapunov candidate $V$ such that

$$
V(x, y)=\frac{1}{2} y^{2}
$$

Note that $V$ does not depend on $x$.
Let us denote $\dot{V}: G \rightarrow \mathbb{R}_{+}$, the Lie derivative of $V$ along solutions of system 2. It follows that for all $(x, y) \in G$ :

$$
\dot{V}(x, y)=y \cdot \frac{\mathrm{~d} y}{\mathrm{~d} t}=d x y^{2}-\alpha y^{2}=\left(\frac{d}{\alpha} x-1\right) \alpha y^{2}
$$

But given that $(x, y) \in G$, we have $x \leq K / \mu$ and consequently

$$
\dot{V} \leq\left(\frac{d K}{\mu \alpha}-1\right) \alpha y^{2}(t)=\left(R_{0}-1\right) \alpha y^{2}(t)
$$

hence $\dot{V}(x, y) \leq 0$, if $R_{0}<1$. Moreover, let us define the set $S=\{(x, y) \in G \mid \dot{V}(x, y)=0\}$. Let $(x, y) \in S$, then we have

$$
(d x-\alpha) y^{2}=0
$$

but $0 \leq x \leq K / \mu$ and given that $R_{0}<1$ we also know that $K / \mu<\alpha / d$. Consequently it is necessary that $y(\cdot)=0$. Hence $S=[0, K / \mu] \times\{0\}$. From the LaSalle's invariance theorem, we conclude that the set $S$ is attractive in $G$.

Furthermore, for every solution $t \mapsto(x(t), y(t))$ of 2 lying in $S$, it follows that $x$ is governed by $\frac{\mathrm{d} x}{\mathrm{~d} t}(t)=K-\mu x(t)$, for all $t \geq 0$. Hence

$$
x(t)=x(0) \mathrm{e}^{-\mu t}+\frac{K}{\mu}\left(1-\mathrm{e}^{-\mu t}\right), \text { for all } t \geq 0
$$

All in all, we obtain that every solution $t \mapsto(x(t), y(t))$ of 2 lying in $S$, is such that :

$$
(x(t), y(t)) \underset{t \rightarrow+\infty}{\longrightarrow}\left(\frac{K}{\mu}, 0\right)
$$

We conclude that every solution $(x, y)$ of 2 reaching $G$ (i.e. $x(t) \leq K / \mu$ ) for $t$ large enough (such solution remains in $G$ from 2.2) converges to ( $K / \mu, 0$ ). Now, let $(x, y)$ be a solution of 2 such that $x(t)>K / \mu$ for all $t \geq 0$. Then from 2.2 we know that $x$ converges to $K / \mu$ as $t$ goes to infinity. Thus, we need to check that $y$ goes to 0 at infinity in order to conclude about the global stability. In this situation, $x$ is a strictly decreasing and continuous function such that $x(t) \underset{t \rightarrow+\infty}{\longrightarrow} K / \mu$. Hence, $\lim _{t \rightarrow \infty} x^{\prime}(t)=0$ and taking the limit as $t \rightarrow+\infty$ in the first equation of system 2 we obtain :

$$
1+\frac{d}{\mu} \lim _{t \rightarrow \infty} y(t)=\lim _{t \rightarrow \infty} \beta_{n}(y(t-T))
$$

from which we obtain that $y(t)$ goes to 0 as $t \rightarrow+\infty$.
In conclusion, all solutions of system 2 tends to $(K / \mu, 0)$ if $R_{0} \leq 1$ and we obtained the global stability of $(K / \mu, 0)$.

### 2.3.2 Endemic steady state

The characteristic equation of system 2 linearised about its endemic steady state $(\bar{x}, \bar{y})=(\alpha / d, \bar{y})$, reads

$$
\begin{equation*}
\lambda^{2}+a \lambda+b+c \mathrm{e}^{-T \lambda}=0, \lambda \in \mathbb{C} \tag{7}
\end{equation*}
$$

with

$$
\begin{aligned}
a & =\frac{d K}{\alpha} \beta_{n}(\bar{y})=\mu+d \bar{y} \\
b & =\alpha\left(\frac{d K}{\alpha} \beta_{n}(\bar{y})-\mu\right)=\alpha(a-\mu), \\
c & =-K \beta_{n}^{\prime}(\bar{y})\left(\frac{d K}{\alpha} \beta_{n}(\bar{y})-\mu\right)=-K \beta_{n}^{\prime}(\bar{y})(a-\mu) .
\end{aligned}
$$

The parameters $a, b$ and $c$ do not depend on the delay $T$. The characteristic equation 7 has been studied in details [22,5,14]. In this paper, we use their methods and results to establish a stability result about the endemic steady state and to perform a bifurcation analysis with respect to three parameters.

First, we notice that 0 is not a root of the characteristic equation 7 , given that $a>0, b>0$ and $c>0$. Then we state the following proposition about absolute stability that is stability independent of the delay [37] of the endemic steady steady state. If

$$
\begin{equation*}
b>c \text { and } a^{2}-2 b>-2 \sqrt{b^{2}-c^{2}} \tag{8}
\end{equation*}
$$

then the endemic steady state $(\alpha / d, \bar{y})$ is locally asymptotically stable for all $T \geq 0$, that is $\operatorname{Re}(\lambda)<0$ for every root $\lambda \in \mathbb{C}$ of equation 7 and all $T \geq 0$.

We apply directly Proposition 4.9 of [37] and Chapter 3.3 of [22].
Now, we state and prove a lemma about the local asymptotic stability of the co-existence equilibrium that legitimates the subsequent bifurcation analysis.

If

$$
T=0 \text { or } y_{c} \rightarrow+\infty,
$$

then the co-existence steady state $(\alpha / d, \bar{y})$ is locally asymptotically stable.
The local asymptotic stability when $T=0$ simply results from the fact that $a, b, c>0$.

Then, consider $\bar{y}, a, b$ and $c$ as functions of $y_{c}>0$. We remind that we necessarily have $R_{0}=d K / \alpha \mu>1$ for the existence of the co-existence steady state. Given that $\bar{y}$ is bounded, we have $\lim _{y_{c} \rightarrow+\infty} \frac{\bar{y}}{y_{c}}=0$ from which follows that $\lim _{y_{c} \rightarrow+\infty} \beta_{n}(\bar{y})=1$ and $\lim _{y_{c} \rightarrow+\infty} a=\mu R_{0}>0, \lim _{y_{c} \rightarrow+\infty} b=\alpha \mu\left(R_{0}-1\right)>0$, $\lim _{y_{c} \rightarrow+\infty} c=0$. So, when $y_{c} \rightarrow+\infty$, the characteristic equation would thus read

$$
\lambda^{2}+\mu R_{0} \lambda+\alpha \mu\left(R_{0}-1\right)=0, \lambda \in \mathbb{C}
$$

If this equation admits some roots, given that $R_{0}>1$, they would always have negative real parts. All in all, the proposition is proven.

Given that $\alpha \mapsto(\bar{x}, \bar{y})$ is continuous and tends to $(0,+\infty)$ as $\alpha \rightarrow 0$, and $\lim _{t \rightarrow+\infty}(x(t), y(t))=(0,+\infty)$ for $\alpha=0$, we claim that the steady state $(\bar{x}, \bar{y})$ is locally asymptotically stable for $\alpha>0$ small enough. This was also confirmed by the numerical simulations.

Let $\psi \in \mathcal{P}$ be a varying parameter, the other parameters are assumed to be fixed. The set $\mathcal{P}$ gathers all possible values for the chosen parameter $\psi$.

If $\psi$ is varied continuously, the only way for roots of 7 with positive real parts to appear is through the imaginary axis. We easily verify that roots with positive real parts cannot appear in the right half complex plane. Starting from parameters verifying 2.3 .2 , we vary $\psi$ and see if a Hopf bifurcation occurs using the methods in $[5,14]$. Given that $\lambda=0$ is not a root of 7 , we look for purely imaginary solutions $\lambda=i \omega(\psi)$, with $\omega(\psi)>0$. We assume, implicitely, that $\omega$ is a continuously differentiable function of $\psi$. This property has to be verified a posteriori. Hence $\omega:=\omega(\psi)$ verifies

$$
\begin{align*}
\cos (T \omega) & =\frac{\omega^{2}-2 b}{c}  \tag{9}\\
\sin (T \omega) & =\frac{a \omega}{c}
\end{align*}
$$

Summing the square of the right-hand sides, we obtain

$$
\begin{equation*}
\omega^{4}-\left(2 b-a^{2}\right) \omega^{2}+b^{2}-c^{2}=0 \tag{10}
\end{equation*}
$$

which also reads $Q\left(\omega^{2}\right)=0$, with the polynomial $Q$ defined by

$$
\begin{equation*}
Q(X)=X^{2}-S X+P \tag{11}
\end{equation*}
$$

with

$$
S=-\left(a^{2}-2 b\right)=2 b-a^{2} \text { and } P=b^{2}-c^{2},
$$

the sum and the product of its roots. The discriminant of $Q$ is

$$
\Delta=\left(a^{2}-2 b\right)^{2}-4\left(b^{2}-c^{2}\right)=a^{4}-4 b a^{2}+4 c^{2}
$$

Let us define the sets

$$
I_{1}=\left\{\psi \mid b(\psi)<c(\psi) \text { or }\left[2 b(\psi)>a(\psi)^{2} \text { and } b(\psi)=c(\psi)\right]\right\},
$$

and

$$
I_{2}=\left\{\psi \mid b(\psi)>c(\psi) \text { and } a(\psi)^{2}-2 b(\psi) \leq-2 \sqrt{b(\psi)^{2}-c(\psi)^{2}}\right\}
$$

and remind that $\Delta(\psi)=a(\psi)^{4}-4 b(\psi) a(\psi)^{2}+4 c(\psi)^{2}>0$ for $\psi \in I_{1} \cup I_{2}$. We emphasize that $I_{1}$ and $I_{2}$ may possibly consist in multiple sub-intervals of different lengths. The previous study of the polynomial $Q$ enables us to state the following proposition (adapted from Lemma 1 of [14] and part 3.3 of [22]). (i) If $\psi \in I_{1}$, i.e.

$$
\begin{equation*}
b(\psi)<c(\psi) \text { or }\left[2 b(\psi)>a(\psi)^{2} \text { and } b(\psi)=c(\psi)\right] \tag{12}
\end{equation*}
$$

then equation 10 has a single positive real root $\omega_{+}(\psi)$ such that

$$
\begin{equation*}
\omega_{+}(\psi)^{2}=\frac{1}{2}\left[2 b(\psi)-a(\psi)^{2}+\sqrt{\Delta(\psi)}\right] . \tag{13}
\end{equation*}
$$

(ii) If $\psi \in I_{2}$, i.e.

$$
\begin{equation*}
b(\psi)>c(\psi) \text { and } a(\psi)^{2}-2 b(\psi) \leq-2 \sqrt{b(\psi)^{2}-c(\psi)^{2}} \tag{14}
\end{equation*}
$$

then equation 10 has, on top of $\omega_{+}(\psi)$, a second positive real root $\omega_{-}(\psi)$ such that

$$
\begin{equation*}
\omega_{-}(\psi)^{2}=\frac{1}{2}\left[2 b(\psi)-a(\psi)^{2}-\sqrt{\Delta(\psi)}\right] . \tag{15}
\end{equation*}
$$

(iii) Otherwise, if $\psi \notin I_{1}$ and $\psi \notin I_{2}$, then there are no positive real roots of 10 . Hence it follows that, if $I_{1}=\emptyset$ and $I_{2}=\emptyset$ then there are no positive real roots of 10 , and no Hopf bifurcation can occur. Thanks to the latter proposition, we know that the set

$$
I=I_{1} \cup I_{2},
$$

actually gathers the values of $\psi$ for which equation 10 has, at least one positive real root and for which Hopf bifurcation might occur.

It is thus valuable to find sufficient conditions (in terms of model parameters) under which the set $I$ exists. This will enable us to clarify the conditions under
which stability switches are likely to happen. Hence, we first make a remark that renders aforementioned conditions over $a, b$ and $c$ clearer. Then we look for conditions in terms of model parameters under which 12 or 14 hold. Condition $b<c$ is equivalent to

$$
\begin{equation*}
\frac{K d^{2}}{\alpha}<(\mu+d \bar{y})^{2} \frac{n}{y_{c}}\left(\frac{\bar{y}}{y_{c}}\right)^{n-1} \tag{16}
\end{equation*}
$$

If parameters verify

$$
\begin{equation*}
\mu+d y_{c}<\frac{K d}{2 \alpha}<2 n \mu \tag{17}
\end{equation*}
$$

then $I_{1} \neq \emptyset$ and $I_{2}=\emptyset$. From simple arguments, the first condition $d K / 2 \alpha<$ $2 n \mu$ implies that

$$
0<\left(\frac{\mu}{d}\right)^{2}+\left(\frac{2 \mu}{d}-\frac{K}{n \alpha}\right) y_{c}+y_{c}^{2}
$$

from which it follows that

$$
\frac{K d^{2}}{\alpha}<\left(\mu+d y_{c}\right)^{2} \frac{n}{y_{c}}
$$

Moreover, the second condition $\mu+d y_{c}<d K / 2 \alpha$ added to simple considerations about equation 5 ensures that $\bar{y}>y_{c}$. All in all, if condition 17 holds, we have

$$
\frac{K d^{2}}{\alpha}<\left(\mu+d y_{c}\right)^{2} \frac{n}{y_{c}}<(\mu+d \bar{y})^{2} \frac{n}{y_{c}}\left(\frac{\bar{y}}{y_{c}}\right)^{n-1}
$$

From 2.3.2, we thus know that $b<c$ and we have $I_{1} \neq \emptyset$ and $I_{2}=\emptyset$. Reformulations of condition 17 lead to the following corollary.
(i) Let the varying parameter be $\alpha=\psi$. If parameters (different from $\alpha$ ) verify

$$
\mu+d y_{c}<2 n \mu
$$

then $I \neq \emptyset$ and

$$
\left[\frac{K d}{4 n \mu} ; \frac{K d}{2\left(\mu+d y_{c}\right)}\right] \subset I_{1} \subset I
$$

(ii) If $y_{c}=\psi$, and parameters (different from $y_{c}$ ) verify

$$
\mu<\frac{K d}{2 \alpha}<2 n \mu
$$

then $I \neq \emptyset$ and

$$
\left[0 ; \frac{K}{2 \alpha}-\frac{\mu}{d}\right] \subset I_{1} \subset I
$$

(iii) If $T=\psi$, and parameters verify condition 17 then $I=\mathbb{R}_{+}^{*}$ with $I_{2}=\emptyset$ and $I_{1}=I$.

Simple but long computations lead to these results. We only underline that (iii) is easily obtained by noticing that $a, b$ and $c$ are independent from $T$. In fact, variations of $\psi=T$ do not modify the values of $\bar{y}, a, b$ and $c$.
2.3.2 does not give precise information on the changes in stability but still provides with sufficient conditions ensuring the existence of an interval $I$ in which these stability switches could occur. In fact, 2.3.2 should not be considered in the context of the previously established stability of the endemic steady state when $\alpha \rightarrow 0$ or $y_{c} \rightarrow+\infty$. They should rather be considered as preliminary results for the existence of an interval on which a Hopf bifurcation with respect to the three parameters is possible. In the following, we assume that $I \neq \emptyset$ and vary $\psi$ first starting from a value (possibly outside the interval $I$ ) where the endemic steady state is locally asymptotically stable and then through $I$ where stability switches could occur.

We continue our bifurcation analysis and introduce, for all $\psi \in I$, the variable $\Theta_{ \pm}(\psi) \in[0,2 \pi]$ such that:

$$
\begin{align*}
\cos \left(\Theta_{ \pm}(\psi)\right) & =\frac{\omega_{ \pm}(\psi)^{2}-b}{c}  \tag{18}\\
\sin \left(\Theta_{ \pm}(\psi)\right) & =\frac{a \omega_{ \pm}(\psi)}{c}
\end{align*}
$$

where the signs have to be adapted according to where $\omega_{+}$or $\omega_{-}$are defined. Given that $\omega_{ \pm} \geq 0$, we always have $\sin \left(\Theta_{ \pm}(\psi)\right) \geq 0$. Consequently, $\Theta_{ \pm}(\psi) \in$ $[0, \pi]$ for all $\psi \in I$. Hence, we obtain for all $\psi \in I$ :

$$
\begin{equation*}
\Theta_{+}(\psi)=\arccos \left(\frac{\omega_{+}(\psi)^{2}-b}{c}\right) \tag{19}
\end{equation*}
$$

and, for $\psi \in I_{2}$ :

$$
\begin{equation*}
\Theta_{-}(\psi)=\arccos \left(\frac{\omega_{-}(\psi)^{2}-b}{c}\right) . \tag{20}
\end{equation*}
$$

Then, we define the functions $z_{ \pm}$such that for all $\psi \in I$ and $k \in \mathbb{N}$

$$
z_{ \pm}(\psi, k)=T-\frac{\Theta_{ \pm}(\psi)+2 k \pi}{\omega_{ \pm}(\psi)}
$$

where the sign has to be adapted accordingly. One could have thought to follow the work of [5] and use arctan functions to define $\Theta_{+}$and $\Theta_{-}$. However, the signs involved in system 18 led us to use the arccos function instead. We get the following Theorem, adapted from Theorem 2.1 and 3.1 of [5]. Assume that the parameters (different from $\psi$ ) are fixed such that $I \neq \emptyset$. The characteristic equation 7 admits a pair of simple conjugate purely imaginary roots $\pm \mathrm{i} \omega_{+}\left(\psi_{+}^{*}\right)$ in $\psi_{+}^{*} \in I$, with

$$
\begin{equation*}
\omega_{+}\left(\psi^{*}\right)=\sqrt{\frac{1}{2}\left[2 b\left(\psi_{+}^{*}\right)-a\left(\psi_{+}^{*}\right)^{2}+\sqrt{\Delta\left(\psi_{+}^{*}\right)}\right]} \tag{21}
\end{equation*}
$$

if and only if there exists $k \in \mathbb{N}$ such that $z_{+}\left(\psi_{+}^{*}, k\right)=0$ with

$$
\begin{equation*}
z_{+}(\psi, k)=T-\frac{1}{\omega_{+}(\psi)}\left[\arccos \left(\frac{\omega_{+}(\psi)^{2}-b}{c}\right)+2 k \pi\right] \text { for all }(\psi, k) \in I \times \mathbb{N} \tag{22}
\end{equation*}
$$

Moreover, if $I_{2} \neq \emptyset$ then the characteristic equation 7 admits a second pair of simple conjugate purely imaginary roots $\pm \mathrm{i} \omega_{-}\left(\psi_{-}^{*}\right)$ in $\psi_{-}^{*} \in I_{2}$, with

$$
\begin{equation*}
\omega_{-}\left(\psi_{-}^{*}\right)=\sqrt{\frac{1}{2}\left[2 b\left(\psi_{-}^{*}\right)-a\left(\psi_{-}^{*}\right)^{2}-\sqrt{\Delta\left(\psi_{-}^{*}\right)}\right]} \tag{23}
\end{equation*}
$$

if and only if there exists $k \in \mathbb{N}$ such that $z_{-}\left(\psi_{-}^{*}, k\right)=0$ with

$$
\begin{equation*}
z_{-}(\psi, k)=T-\frac{1}{\omega_{-}(\psi)}\left[\arccos \left(\frac{\omega_{-}(\psi)^{2}-b}{c}\right)+2 k \pi\right] \text { for all }(\psi, k) \in I_{2} \times \mathbb{N} . \tag{24}
\end{equation*}
$$

Furthermore, when a boundary value $\psi^{*} \in I$ exists and is reached due to a variation of $\psi$, its associated pair of simple conjugate purely imaginary roots cross the imaginary axis - possibly inducing a stability switch - from left to right if $\delta\left(\psi^{*}\right)>0$ and from right to left if $\delta\left(\psi^{*}\right)<0$ where

$$
\delta\left(\psi^{*}\right)=\operatorname{sign}\left\{\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}\left(\psi^{*}\right)\right\} .
$$

For given parameter values under which $I \neq \emptyset$, a stability switch is possible only if there exists $k \in \mathbb{N}$ such that $z_{+}(\cdot, k)$ or $z_{-}(\cdot, k)$ vanish at least one time. When the parameter $\psi$ varies from a value $\psi_{0}$ such that $(\alpha / d, \bar{y})$ is stable, a Hopf bifurcation must occur at the first boundary value $\psi_{h}^{*}$ such that
$\psi_{h}^{*}=\min \left\{\psi^{*} \mid\right.$ there exists $k \in \mathbb{N}$ such that $z_{+}\left(\psi^{*}, k\right)=0$ or $\left.z_{-}\left(\psi^{*}, k\right)=0\right\}$,
if the transversality condition $\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}\left(\psi_{h}^{*}\right) \neq 0$ holds. Explicit form of $\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}$ is obtained by differentiating the characteristic equation 7 following the branch of roots $\lambda(\psi)$ defined such that $\lambda\left(\psi^{*}\right)=\mathrm{i} \omega^{*}$ with $\omega^{*}=\omega_{+}\left(\psi^{*}\right)$ or $\omega^{*}=\omega_{-}\left(\psi^{*}\right)$ depending on the situation under consideration. After some computations, when $\psi^{*}=T^{*}$, one gets:

$$
\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} T}\left(T^{*}\right)=\frac{\left(a^{2}-2 b\right) \omega^{* 2}+2 \omega^{* 4}}{\left(-T^{*} \omega^{* 2}+a+b\right)^{2}+\left(2+a T^{*}\right)^{2} \omega^{* 2}} .
$$

Inserting the expression of $\omega_{ \pm}\left(T^{*}\right)$ into this expression always gives $\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} T}\left(T^{*}\right)>$ 0 when $\omega^{*}=\omega_{+}\left(T^{*}\right)$ and $\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} T}\left(T^{*}\right)<0$ when $\omega^{*}=\omega_{-}\left(T^{*}\right)$ (as noticed in [22]). It ensures us that if a purely imaginary root $\lambda\left(T^{*}\right)\left(=i \omega_{+}\left(T^{*}\right)\right.$ or $\left.i \omega_{-}\left(T^{*}\right)\right)$ exists, it is necessarily simple.

If $\psi^{*} \neq T^{*}\left(e . g . \psi^{*}=\alpha^{*}\right.$ or $\left.\psi^{*}=y_{c}{ }^{*}\right)$, we have :

$$
\begin{aligned}
\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}\left(\psi^{*}\right)= & \frac{\left(-\frac{\omega^{* 2}}{c} \frac{\mathrm{~d} c}{\mathrm{~d} \psi}\left(\psi^{*}\right)+\frac{b}{c} \frac{\mathrm{~d} c}{\mathrm{~d} \psi}\left(\psi^{*}\right)-\frac{\mathrm{d} b}{\mathrm{~d} \psi}\left(\psi^{*}\right)\right)\left(-T \omega^{* 2}+a+T b\right)}{\left(-T \omega^{* 2}+a+T b\right)^{2}+(2+T a)^{2} \omega^{* 2}} \\
& +\frac{\omega^{* 2}(2+T a)\left(\frac{a}{c} \frac{\mathrm{~d} c}{\mathrm{~d} \psi}\left(\psi^{*}\right)-\frac{\mathrm{d} a}{\mathrm{~d} \psi}\left(\psi^{*}\right)\right)}{\left(-T \omega^{* 2}+a+T b\right)^{2}+(2+T a)^{2} \omega^{* 2}} .
\end{aligned}
$$

When $\psi=T$, we use 2.3.2 and the previous remarks to obtain a more precise and concise result. Assume that model parameters different from $T$ are fixed and such that $I \neq \emptyset$. If $T$ is increased starting from 0 , then the system undergoes a Hopf bifurcation at $T=T_{h}^{*}$ with

$$
\begin{equation*}
T_{h}^{*}=\frac{1}{\omega_{+}} \arccos \left(\frac{\omega_{+}^{2}-b}{c}\right), \tag{25}
\end{equation*}
$$

where $\omega_{+}=\sqrt{\frac{1}{2}\left[2 b-a^{2}+\sqrt{a^{4}-4 b a^{2}+4 c^{2}}\right]}$. First, due to 2.3.2, we know that the co-existence steady state is locally asymptotically stable when $T=0$.

Then, if $I \neq \emptyset$ then $I=\mathbb{R}^{+}$(since $a, b$ and $c$ are independent from $T$ ). If they are defined, both $z_{+}(\cdot, k)$ and $z_{-}(\cdot, k)$ cross the horizontal axis (as increasing functions of $T$ ) and thus stability switches must occur at these crossings labeled $T^{*}$. Moreover, a Hopf bifurcation could happen at the smallest value $T_{h}^{*}$ of these delays. This smallest delay correspond either (as $z_{+}$and $z_{-}$are decreasing functions of $k \in \mathbb{N}$ ) to a zero of $z_{+}(\cdot, 0)$ or $z_{-}(\cdot, 0)$, if defined. If $I_{2}=\emptyset$ then only $z_{+}(\cdot, 0)$ is well defined, thus $T_{h}^{*}$ is the zero of this function and we consequently obtain the expression 25 . If $I_{2} \neq \emptyset$, then $z_{+}(\cdot, 0)$ and $z_{-}(\cdot, 0)$ are defined, thus $T_{h}^{*}$ corresponds to the smallest zero of these two functions which is the zero of $z_{+}(\cdot, 0)$, as $\omega_{+}>\omega_{-}$and $\omega \mapsto \frac{1}{\omega} \arccos \left(\frac{\omega^{2}-b}{c}\right)$ is decreasing on its interval of definition. All in all, regardless the situation, the first, i.e. the smallest, delay at which a stability switch occurs $T_{h}^{*}$ corresponds to the zero of $T \mapsto z_{+}(T, 0)$ and is given by equation 25 . Finally, we conclude that a Hopf bifurcation occurs at $T=T_{h}^{*}$ since the transversality condition $\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} T}\left(T_{h}^{*}\right) \neq 0$ is always verified.

In 2a, 2c and 2 d we present stability diagrams obtained when $\psi=T, \alpha$ or $y_{c}$. These diagrams give us insights in the dynamics of the system in the parameter space. Boundaries (indicated by continuous or dashed lines) separate the parameter space into regions of different dynamics.
Notice that 2a and 2c are similar as they both display stability boundaries in the ( $T, \alpha$ ) plane.
In 2b we illustrate - through an arbitrary example of two model trajectories - the Hopf bifurcation that occurs as $\psi=T$ increased from 0 : increasing the parameter $T$ from a value where the endemic steady state is stable destabilizes it through a Hopf bifurcation when $T$ reaches the first boundary value $T^{*}$ ( $\simeq 4.13$ days in our example).
2 d presents stability boundaries in the $\left(T, y_{c}\right)$ when $\psi=y_{c}$ is the varying parameter. In such situation, when $T$ is set to a fixed value, decreasing the parameter $y_{c}$ from infinity triggers a Hopf bifurcation when $y_{c}$ reaches the first boundary value $y_{c}{ }^{*}$.
From a biological point of view, the Hopf bifurcation study is important in the following sense. Our goal is to understand the start and stop mechanism of UPR which may possibly lead the neuron to show an oscillatory stress state. In other words, a neuron may leave and enter stress conditions periodically depending on its environment. If such a phenomenon occurs, this oscillatory behavior may propagate eventually to the other neurons, and some synchronicity could appear from this group. This last point will be the subject of a future work. We prove here that not only such an oscillatory behavior is possible, but we are also able to determine which parameters need to change to get it. From the study above, we manage to prove for instance that increasing the protein formation process duration $T$ (which could happen for weak of damaged cells), may lead to oscillations in protein productions. We show that other parameters are involved such as the loss of diffusion term $\alpha$ or the threshold density $y_{c}$ of $\operatorname{PrP}^{S c}$ implying it stress condition.

We used the function dde23 [35] from MATLAB® for numerical simulations. We underline that asymptotic solutions turned out to be independent from initial conditions and densities. We thus arbitrarily decided to compute each trajectories showed in 2 b with an initial condition corresponding to $50 \%$ of the associated steady state specified by parameter values.


Figure 2: (a), (c), (d): Stability diagrams in the $(\alpha, T)$ plane with $T=\psi$ $((\mathbf{a}))$ or $\alpha=\psi((\mathbf{c}))$ as the varying parameter and in the $\left(y_{c}, T\right)$ plane with $\psi=y_{c}$ as the varying parameter $((\mathbf{d}))$. Boundary parameters $\left(\psi^{*}=T^{*}\right.$ in (a), $\psi^{*}=\alpha^{*}$ in (c) and $\psi^{*}=y_{c}{ }^{*}$ in (d)) are specified by continuous $\left(\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}\left(\psi^{*}\right)>0\right)$ or dashed $\left(\frac{\mathrm{d}(\operatorname{Re} \lambda)}{\mathrm{d} \psi}\left(\psi^{*}\right)<0\right)$ lines. For clarity, we only plotted the two first boundaries $(k=0$ and $k=1)$ in the ( $T, \alpha$ ) plane, the three first boundaries $(k=1,2,3)$ in the $\left(T, y_{c}\right)$ plane and indicated in green the area where the endemic equilibrium is stable. The situation in (d) being complex, we decide not to highlight the stability area of the endemic equilibrium for clarity. The values of the parameters used to obtain these plots are specified in 1 , we underline that parameter values ensure that we always have $R_{0}>1$ in each figure. (b): Illustration through an arbitrary example of two trajectories before ( $T_{1}$ in red) and after ( $T_{2}$ in blue) the Hopf bifurcation. For all the figures, we chose the range for $\psi$ (i.e. $T, \alpha$ or $y_{c}$ ) so that stability switches could appear with $I \neq \emptyset$ (i.e. $b(\psi)<c(\psi)$ when a stability switch occurs).

Table 1: Values of parameters used in 2. Orders of magnitude are consistent with the values used in $[17,23]$.

| Parameters | Values | Units |
| :--- | :--- | :--- |
| $T$ | variable | days |
| $\mu$ | 5 | days $^{-1}$ |
| $\alpha$ | variable (2a, and 2c $)$ or $0.04(2 \mathrm{~b}$ and | days $^{-1}$ |
|  | $2 \mathrm{~d})$ |  |
| $K$ | 1500 | (Fibrils per volume unit).days |
| $y_{c}$ | $130(2 \mathrm{a}, 2 \mathrm{~b}$ and 2c) or variable (2d) | Fibrils per volume unit |
| $d$ | 0.1 | ${\text { (Fibrils per volume unit })^{-1} . \text { days }^{-1}}^{n}$ |
| $n$ | $10(2 \mathrm{a}, 2 \mathrm{~b}$ and 2c) or $250(2 \mathrm{~d})$ | - |

## 3 Model of prion production with 2 neurons

In this section we generalize the previous modeling and describe prion production and dynamic at the scale of two neurons. We first describe the model, then proceed to the stability analysis of the steady states.

### 3.1 The model



Figure 3: Two neurons' prion production model. This model generalizes the one presented in 1. Interactions between prion species are introduced through the coupling constant $\kappa \in[0,1]$ in the $\operatorname{PrP}^{S c}$ production terms of the neurons: $d x_{1} \kappa \alpha_{2} x_{2}$ and $d x_{2} \kappa \alpha_{1} x_{1}$.

The model illustrated in 3 describes the dynamics of $\operatorname{PrP}^{C}$ protein concen-
trations associated to neuron 1 and neuron $2-x_{1}$ and $x_{2}$ - as well as the $\operatorname{PrP}^{S c}$ concentrations in the close vicinity of neuron 1 and neuron $2-y_{1}$ and $y_{2}$. This model is governed, for $t \geq 0$, by the following system:

$$
\begin{align*}
\frac{\mathrm{d} x_{1}}{\mathrm{~d} t} & =K_{1} \beta_{n}\left(y_{1}\left(t-T_{1}\right)\right)-\mu_{1} x_{1}(t)-d x_{1}(t)\left(y_{1}(t)+\kappa \alpha_{2} y_{2}(t)\right) \\
\frac{\mathrm{d} x_{2}}{\mathrm{~d} t} & =K_{2} \beta_{n}\left(y_{2}\left(t-T_{2}\right)\right)-\mu_{2} x_{2}(t)-d x_{2}(t)\left(y_{2}(t)+\kappa \alpha_{1} y_{1}(t)\right)  \tag{26}\\
\frac{\mathrm{d} y_{1}}{\mathrm{~d} t} & =d x_{1}(t)\left(y_{1}(t)+\kappa \alpha_{2} y_{2}(t)\right)-\alpha_{1} y_{1}(t) \\
\frac{\mathrm{d} y_{2}}{\mathrm{~d} t} & =d x_{2}(t)\left(y_{2}(t)+\kappa \alpha_{1} y_{1}(t)\right)-\alpha_{2} y_{2}(t)
\end{align*}
$$

The parameters $K_{1}, K_{2}, \mu_{1}, \mu_{2}, \alpha_{1}, \alpha_{2}, T_{1}, T_{2}, d, y_{c}, n$ and variables $u_{1}, u_{2}$ have the same meanings as in 2 . Variables $u_{1}$ and $u_{2}$ - associated to biological processes duration $T_{1}$ and $T_{2}$ - are both ruled by an equation identical to 1. Parameters characterizing the UPR mechanism - threshold concentration $y_{c}$ and sensivity $n$ - are assumed to be identical for the two neurons. The UPR feedback function $\beta_{n}$ is thus also identical for the two neurons.
We underline that neuron's proteins concentrations - $\left(x_{1}, y_{1}\right)$ for neuron 1 and $\left(x_{2}, y_{2}\right)$ for neuron 2 - are ruled by a system similar to 2 except that the interactions between $\mathrm{PrP}^{S c}$ concentrations of the two neurons are now taken into account. Actually, we consider that diffusion enables the $\mathrm{PrP}^{S c}$ proteins of one neuron to migrate near the other neuron and become templates for the generation of new $\operatorname{PrP}^{S c}$ proteins. We decide to include these interactions in the $\operatorname{PrP}^{S c}$ production terms: $d x_{1} \kappa \alpha_{2} y_{2}$ (resp. $d x_{2} \kappa \alpha_{1} y_{1}$ ) models the production of $\mathrm{PrP}^{S c}$ proteins by neuron 1 (resp. 2) generated from the interaction between $\mathrm{PrP}^{S c}$ proteins associated to neuron 2 (resp. 1) and $\mathrm{PrP}^{c}$ proteins of neuron 1 (resp. 2). Moreover we wish to grasp two properties: (i) isotropic and spatial properties of diffusion and (ii) possibly different interactions between $\operatorname{PrP}^{c}$ and $\mathrm{PrP}^{S c}$ originating from different neurons compared to the situation where $\operatorname{PrP}^{c}$ and $\operatorname{PrP}^{S c}$ come from the same neuron. Hence, we assume that the quantity of $\mathrm{PrP}^{S c}$ that interacts - from one neuron to the other - decays with a factor $0<\kappa \leq 1$. The parameter $\kappa$ thus stands for a coupling constant between neurons that gathers both migration efficiency (induced by diffusion) and the ability for proteins originating from different neurons to interact.

The well-posedness of system 26 (existence, unicity and positivity of solutions) can be easily verified thanks to well-known theorems [37] (a result similar to 2.2 holds).

### 3.2 Steady states

Let $\left(x_{1}^{*}, x_{2}^{*}, y_{1}^{*}, y_{2}^{*}\right) \in \mathbb{R}_{+}^{4}$ be a steady state of 26 , it verifies

$$
\begin{align*}
& 0=K_{1} \beta_{n}\left(y_{1}^{*}\right)-\mu_{1} x_{1}^{*}-d x_{1}^{*}\left(y_{1}^{*}+\kappa \alpha_{2} y_{2}^{*}\right),  \tag{27}\\
& 0=K_{2} \beta_{n}\left(y_{2}^{*}\right)-\mu_{2} x_{2}^{*}-d x_{2}^{*}\left(y_{2}^{*}+\kappa \alpha_{1} y_{1}^{*}\right),  \tag{28}\\
& 0=d x_{1}^{*}\left(y_{1}^{*}+\kappa \alpha_{2} y_{2}^{*}\right)-\alpha_{1} y_{1}^{*},  \tag{29}\\
& 0=d x_{2}^{*}\left(y_{2}^{*}+\kappa \alpha_{1} y_{1}^{*}\right)-\alpha_{2} y_{2}^{*} . \tag{30}
\end{align*}
$$

Then, summing 27 with 29 and 28 with 30 we obtain

$$
K_{1} \beta_{n}\left(y_{1}^{*}\right)-\mu_{1} x_{1}^{*}-\alpha_{1} y_{1}^{*}=0 \text { and } K_{2} \beta_{n}\left(y_{2}^{*}\right)-\mu_{2} x_{2}^{*}-\alpha_{2} y_{2}^{*}=0
$$

which also reads, for $i, j \in\{1,2\}$ and $i \neq j$ :

$$
\begin{equation*}
x_{i}^{*}=G_{i}\left(y_{i}^{*}\right), \tag{31}
\end{equation*}
$$

with

$$
\begin{equation*}
G_{i}(y)=\frac{1}{\mu_{i}}\left(K_{i} \beta_{n}(y)-\alpha_{i} y\right), \text { for all } y \geq 0 \tag{32}
\end{equation*}
$$

The function $G_{i}$ is decreasing on $\mathbb{R}_{+}$and non negative on $\left[0, \hat{y}_{i}\right]$ with

$$
G_{i}(0)=\frac{K_{i}}{\mu_{1}} \text { and } G_{i}\left(\hat{y_{i}}\right)=0
$$

Now, inserting expression 31 into 29 and 30 leads to

$$
\begin{align*}
& y_{1}^{*}=y_{2}^{*} H_{2}\left(y_{2}^{*}\right),  \tag{33}\\
& y_{2}^{*}=y_{1}^{*} H_{1}\left(y_{1}^{*}\right), \tag{34}
\end{align*}
$$

where the function $H_{i}$ for $i, j \in\{1,2\}, i \neq j$ is defined as :

$$
H_{i}(y)=\frac{1}{\kappa \alpha_{j}}\left(\frac{\alpha_{i}}{d G_{i}(y)}-1\right), \text { for all } y \in\left[0, \hat{y}_{i}\right)
$$

Inserting expression 33 and 34 into each other leads to

$$
\begin{align*}
& y_{1}^{*} H_{1}\left(y_{1}^{*}\right) H_{2}\left(y_{1}^{*} H_{1}\left(y_{1}^{*}\right)\right)=y_{1}^{*}  \tag{35}\\
& y_{2}^{*} H_{2}\left(y_{2}^{*}\right) H_{1}\left(y_{2}^{*} H_{2}\left(y_{2}^{*}\right)\right)=y_{2}^{*} \tag{36}
\end{align*}
$$

Before going further, we underline that the function $H_{i}$ (for $i, j \in\{1,2\}$, $i \neq j)$ is increasing on $\left[0, \hat{y_{i}}\right)$ and such that

$$
\begin{equation*}
H_{i}(0):=\frac{1}{\kappa \alpha_{j}}\left(R_{0 i}^{-1}-1\right) \text { and } \lim _{y \rightarrow \hat{y}_{i}} H_{i}(y)=+\infty \tag{37}
\end{equation*}
$$

where we define for further simplicity

$$
R_{01}:=\frac{d K_{1}}{\mu_{1} \alpha_{1}} \text { and } R_{02}:=\frac{d K_{2}}{\mu_{2} \alpha_{2}}
$$

We want to study existence and uniqueness of a possible co-existence steady state of $26,\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right) \in \mathbb{R}_{+}^{* 4}$, different from the trivial steady state $\left(K_{1} / \mu_{1}, K_{2} / \mu_{2}, 0,0\right)$ (which always exists). We know that ( $\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}$ ) verifies 36. It follows that $\bar{y}_{2}>0$ is solution of

$$
\begin{equation*}
H\left(\bar{y}_{2}\right)=1 \tag{38}
\end{equation*}
$$

where the function $H$ is defined as

$$
H(y)=H_{2}(y) H_{1}\left(y H_{2}(y)\right)
$$

for all $y \in\left(0, \hat{y}_{2}\right)$ in the domain of $H$. Depending on parameter values, $\bar{y}_{2}$ - solution of 38 - must lie in a given interval to ensure well-posedness of the
co-existence equilibria ( $\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}$ ). The three following Lemmas tackle this issue and unveil conditions about existence and uniqueness of the co-existence steady state $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right)$. If $R_{01}>1$ and $R_{02}>1$ then there exists a unique co-existence equilibrium $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right) \in \mathbb{R}_{+}^{* 4}$ verifying 31-33-34. By definition of $H_{1}$ of $H_{2}$, as $H_{1}(0), H_{2}(0)<0$, there exist unique $\breve{y}_{1}, \breve{y}_{2}>0$ such that $H_{1}\left(\breve{y}_{1}\right)=0$ and $H_{2}\left(\breve{y}_{2}\right)=0$. Moreover, as $\bar{y}_{2}>0$ and $\bar{y}_{1}>0$, we know from equations 33 and 34 that we are looking for an equilibria $\bar{y}_{2}$, solution of 38 in $\left(\breve{y}_{2}, \hat{y}_{2}\right)$. In addition, we notice that $y \mapsto y H_{2}(y)$ is positive and increasing on ( $\left.\breve{y}_{2}, \hat{y}_{2}\right)$ and such that

$$
\breve{y}_{2} H_{2}\left(\breve{y}_{2}\right)=0 \text { and } \lim _{y \rightarrow \hat{y}_{2}} y H_{2}(y)=+\infty .
$$

Hence, there exist unique $\tilde{\tilde{y}}<\tilde{y} \in\left(\breve{y}_{2}, \hat{y}_{2}\right)$ such that

$$
\tilde{\tilde{y}} H_{2}(\tilde{\tilde{y}})=\breve{y}_{1} \text { and } \tilde{y} H_{2}(\tilde{y})=\hat{y}_{1} .
$$

Consequently, $H_{1}\left(y H_{2}(y)\right)<0$ and thus $H(y)<0$ for all $y \in\left(\breve{y}_{2}, \tilde{y}\right)$. And, by product and composition of positive increasing functions, $H$ is positive, increasing on $[\tilde{y}, \tilde{y})$ and such that $H(\tilde{\tilde{y}})=0$ and $\lim _{y \rightarrow \tilde{y}} H(y)=+\infty$. All in all, if $R_{01}>1$ and $R_{02}>1$ then there exists a unique solution $\bar{y}_{2} \in(\tilde{\tilde{y}}, \tilde{y})$ of equation 38 and 3.2 is proven. Then, we focus on the situation in which only one neuron has its $R_{0}$ greater than one.

If $R_{0 i}>1$ and $R_{0 j}<1$ with $i, j \in\{1,2\}$ and $i \neq j$, then there exists a unique co-existence equilibrium $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right) \in \mathbb{R}_{+}^{* 4}$ verifying 31-33-34. For simplicity and without loss of generality, we assume that $i=2$ and $j=1$. By definition of $H_{2}$, we know that $H_{2}(0)<0$ and from the increasing property of $H_{2}$, we obtain that there exists a unique $\breve{y}_{2} \in\left(0, \hat{y_{2}}\right)$ such that $H_{2}\left(\breve{y}_{2}\right)=0$. Moreover from equations 33 and 34 , since $\overline{y_{1}}>0$, it is necessary that $\overline{y_{2}} \in$ ( $\breve{y}_{2}, \hat{y_{2}}$ ). From equations 35 and 36 , we are consequently looking for a solution $\overline{y_{2}} \in\left(\breve{y}_{2}, \hat{y_{2}}\right)$ of 38. By the increasing properties of $H_{1}$ and $H_{2}$ and by the positiveness of $H_{1}$ on its domain, we know that $H$ is positive and increasing on $\left(\breve{y}_{2}, \hat{y_{2}}\right)$ and such that

$$
H\left(\breve{y}_{2}\right)=0 \text { and } \lim _{y \rightarrow y_{2}} H(y)=+\infty
$$

All in all, if $R_{02}>1$ and $R_{01}<1$, then there exists a unique solution $\overline{y_{2}} \in\left(\breve{y}_{2}, \hat{y_{2}}\right)$ to equation 38 and 3.2 is proven.

Assume that

$$
\begin{equation*}
R_{01}<1 \text { and } R_{02}<1 \tag{39}
\end{equation*}
$$

There exists another unique co-existence equilibrium $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right) \in \mathbb{R}_{+}^{* 4}$ verifying 31-33-34 if and only if

$$
\begin{equation*}
\kappa^{2}>\frac{1}{R_{01} R_{02} \alpha_{1} \alpha_{2}}\left[1-R_{01}\right]\left[1-R_{02}\right] . \tag{40}
\end{equation*}
$$

First we know from the definition of $H_{2}$ that there exists a unique $\tilde{y} \leq \hat{y_{2}}$ such that

$$
\tilde{y} H_{2}(\tilde{y})=\hat{y_{1}} .
$$

Then conditions $R_{01}<1$ and $R_{02}<1$ implies the positiveness of $H_{1}, H_{2}$ and $y \mapsto H_{1}\left(y H_{2}(y)\right)$ on $(0, \tilde{y})$. By operations, $H$ is thus well defined and increasing on its domain $(0, \tilde{y})$ and such that

$$
\lim _{y \rightarrow \tilde{y}} H(y)=+\infty \text { and } H(0)=\frac{1}{\kappa^{2} \alpha_{1} \alpha_{2}}\left[R_{01}^{-1}-1\right]\left[R_{02}^{-1}-1\right] .
$$

All things considered, when condition 39 holds, the co-existence equilibrium $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right)$ with $\bar{y}_{2}>0$ verifiying equation 38 exists and is unique if and only if condition 40 holds (i.e $H(0)<1$ ). This concludes the proof.

We summarize the results in the following Theorem. The system 26 always admits a trivial equilibrium $\left(\frac{K_{1}}{\mu_{1}}, \frac{K_{2}}{\mu_{2}}, 0,0\right)$. Moreover, there exists another unique co-existence equilibrium $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right) \in \mathbb{R}_{+}^{* 4}$ verifying equations 31-3334 if and only if
(i)

$$
\begin{equation*}
R_{01}<1, R_{02}<1 \text { and } \kappa^{2}>\frac{1}{R_{01} R_{02} \alpha_{1} \alpha_{2}}\left[1-R_{01}\right]\left[1-R_{02}\right] \tag{41}
\end{equation*}
$$

or
(ii) there exists $i \in\{1,2\}$ such that $R_{0 i}>1$.

If we denote by

$$
\begin{equation*}
R_{00}=\kappa^{2} \alpha_{1} \alpha_{2} \frac{R_{01} R_{02}}{\left[1-R_{01}\right]\left[1-R_{02}\right]} \tag{42}
\end{equation*}
$$

we can see that the existence of the co-existence equilibrium is equivalent to $R_{01}<1, R_{02}<1$ and $R_{00}>1$, or there exists $i \in\{1,2\}$ such that $R_{0 i}>1$. The main information here is that even if $R_{01}$ and $R_{02}$ of each neuron is less than 1 , a large coupling constant $\kappa$ between the two neurons allows $R_{00}$ of the coupling to be greater than 1.

Finally, we state and prove a result concerning the continuous differentiability of the co-existence steady state with respect to the coupling parameter $\kappa$. Assume that there exists $i \in\{1,2\}$ such that $R_{0 i}>1$. The co-existence steady state $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right)$ is a continuously differentiable function of $\kappa$ on an open set $U \subset \mathbb{R}^{+}$with $0 \in U$, if and only if

$$
K_{i} \beta_{n}^{\prime}\left(\bar{y}_{i}\right)-\alpha_{i}>0 \text { for } i \in\{1,2\} \text { such that } R_{0 i}>1
$$

The system composed of steady-state equations 27-28-29-30 could also be written $F\left(\kappa,\left(x_{1}^{*}, x_{2}^{*}, y_{1}^{*}, y_{2}^{*}\right)\right)=0$ where $F: \mathbb{R}_{+} \times \mathbb{R}_{+}^{4} \rightarrow \mathbb{R}$. Let $J_{F}\left(\kappa,\left(x_{1}^{*}, x_{2}^{*}, y_{1}^{*}, y_{2}^{*}\right)\right)$ be the jacobian determinant of $F$ with respect to its second variable in $\mathbb{R}_{+}^{4}$. In this framework, simple computations lead to :

$$
\begin{align*}
& J_{F}\left(\kappa,\left(x_{1}^{*}, x_{2}^{*}, y_{1}^{*}, y_{2}^{*}\right)\right)= \\
& \left|\begin{array}{cccc}
-\left(\mu_{1}+d y_{1}^{*}+d \kappa \alpha_{2} y_{2}^{*}\right) & 0 & K_{1} \beta_{n}^{\prime}\left(y_{1}^{*}\right)-d x_{1}^{*} & -d x_{1}^{*} \kappa \alpha_{2} \\
0 & -\left(\mu_{2}+d y_{2}^{*}+d \kappa \alpha_{1} y_{1}^{*}\right) & -d x_{2}^{*} \kappa \alpha_{1} & K_{2} \beta_{n}^{\prime}\left(y_{2}^{*}\right)-d x_{2}^{*} \\
d\left(y_{1}^{*}+\kappa \alpha_{2} y_{2}^{*}\right) & 0 & d x_{1}^{*}-\alpha_{1} & d x_{1}^{*} \kappa \alpha_{2} \\
0 & d\left(y_{2}^{*}+\kappa \alpha_{1} y_{1}^{*}\right) & d x_{2}^{*} \kappa \alpha_{1} & d x_{2}^{*}-\alpha_{2}
\end{array}\right| . \tag{43}
\end{align*}
$$

For clarity, we note ( $\overline{x_{1}}, \overline{x_{2 \kappa}}, \overline{y_{1 \kappa}}, \overline{y_{2}}$ ) the co-existence steady state of system 26 for $\kappa \in[0,1]$.

We want to apply the implicit function theorem at $\kappa=0$ and thus need to evaluate $J_{F}$ in the co-existence steady state obtained for the decorrelated situation $(\kappa=0)$. However, in the decorrelated situation, since $\kappa=0$, we notice that $\left(\overline{x_{1 \kappa=0}}, \overline{y_{1}}{ }_{\kappa=0}\right)$ and $\left(\overline{x_{2}}{ }_{\kappa=0}, \overline{y_{2}}{ }_{\kappa=0}\right)$ are steady states of neuron 1 and 2 independently. Consequently, depending on the values of $R_{01}$ and $R_{02}$ with respect to 1 , two different situations must be distinguished.

First, if $R_{01}>1$ and $R_{02}>1$ then condition 4 is satisfied for each neuron. We thus know that $\overline{x_{1 \kappa=0}}=\alpha_{1} / d$ and $\overline{x_{2 \kappa=0}}=\alpha_{2} / d$ and that $\overline{y_{1}=0}$ and $\overline{y_{2}}{ }_{\kappa=0}$ verify equations similar to equation 5 . These expressions and a Laplace expansion of 43 leads to
$J_{F}\left(0,\left(\overline{x_{1}}{ }_{\kappa=0}, \overline{x_{2}}{ }_{\kappa=0}, \overline{y_{1}}{ }_{\kappa=0}, \overline{y_{2}}{ }_{\kappa=0}\right)\right)=d^{2} \overline{y_{1}}{ }_{\kappa=0} \overline{y_{2}}{ }_{\kappa=0}\left[K_{1} \beta_{n}^{\prime}\left(\overline{y_{1}}{ }_{\kappa=0}\right)-\alpha_{1}\right]\left[K_{2} \beta_{n}^{\prime}\left(\overline{y_{2}}{ }_{\kappa=0}\right)-\alpha_{2}\right]$.
This expression and the implicit function theorem enable us to conclude for the situation in which $R_{01}>1$ and $R_{02}>1$.

Then, let $i, j \in\{1,2\}, i \neq j$ and assume that $R_{0 i}>1$ and $R_{0 j}<1$. Without loss of generality and for clarity, we assume that $R_{01}>1$ and $R_{02}<1$. In this situation, we thus have $\overline{x_{\kappa}}{ }_{\kappa=0}=K_{2} / \mu_{2}, \overline{y_{2}}{ }_{\kappa=0}=0, \overline{x_{1}=0}=\alpha_{1} / d$ and $\overline{y_{1}=0}{ }_{1}$ verifies equation 5 (with parameters adapted to neuron 1). Hence, from these expressions and with a Laplace expansion of 43 we obtain
$J_{F}\left(0,\left(\overline{x_{1 \kappa=0}}, \overline{x_{2 \kappa=0}}, \overline{y_{1}}{ }_{\kappa=0}, \overline{y_{2}}{ }_{\kappa=0}\right)\right)=d \mu_{2} \alpha_{2}\left(R_{02}-1\right) \overline{y_{1}}{ }_{\kappa=0}\left[K_{1} \beta_{n}^{\prime}\left(\overline{y_{1}}{ }_{\kappa=0}\right)-\alpha_{1}\right]$.
Using the latter expression and the implicit function theorem, if $R_{01}>1$ and $R_{02}<1$, we conclude that ( $\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}$ ) is continuous and differentiable with respect to $\kappa$ in an open set $U \subset \mathbb{R}_{+}^{* 4}$ containing $\kappa=0$ if and only if $K_{1} \beta_{n}^{\prime}\left(\overline{y_{1}}{ }_{\kappa=0}\right)-\alpha_{1} \neq 0$.

Proof of 3.2 is thus completed.
When $\kappa=0$, each neuron is expected to evolve independently from the other and to have its own prion dynamics. 3.2 thus guarantees the coherence with our previous modelling of a single neuron and ensures the well-posedness of our model.

When neurons are identical (i.e. symmetrical situation), more precise theoretical results become simpler. 3.2 leads to the following corollary.

If neurons are identical with $K:=K_{1}=K_{2}, \mu:=\mu_{1}=\mu_{2}$ and $\alpha:=\alpha_{1}=$ $\alpha_{2}$, then system 26 admits a unique co-existence steady state $\left(\bar{x}_{1}, \bar{x}_{2}, \bar{y}_{1}, \bar{y}_{2}\right)$ if and only if

$$
\begin{equation*}
\kappa>\frac{1-R_{0}}{\alpha R_{0}} \text { with } R_{0}:=R_{01}=R_{02}=\frac{d K}{\mu \alpha} \tag{44}
\end{equation*}
$$

If 44 holds, we have

$$
\bar{x}:=\bar{x}_{1}=\bar{x}_{2}=\frac{\alpha}{d(1+\kappa \alpha)}
$$

and $\bar{y}:=\bar{y}_{1}=\bar{y}_{2} \in(0, \hat{y})$ solution of

$$
\begin{equation*}
R_{0} \beta_{n}(\bar{y})=\frac{d}{\mu} \bar{y}+\frac{1}{1+\kappa \alpha}, \bar{y} \in(0, \hat{y}) \tag{45}
\end{equation*}
$$

If neurons are identical, the condition $\kappa>\left(1-R_{0}\right) / \alpha R_{0}$ is in fact equivalent to $R_{00}:=\left[\kappa \alpha R_{0} /\left(1-R_{0}\right)\right]^{2}>1$. By symmetry we have $x_{1}^{*}=x_{2}^{*}:=x^{*}$ and
$y_{1}^{*}=y_{2}^{*}:=y^{*}$. Hence, inserting the latter equality in equations 33 and 34 leads to

$$
y^{*}=y^{*} h\left(y^{*}\right),
$$

where $h:=H_{1}=H_{2}$ in the symmetrical situation under consideration here. As $x^{*}>0$ and $y^{*}>0$, it is necessary that $y^{*}<K / \alpha$. Hence, existence and uniqueness of a co-existence steady state $y^{*} \in[0, \hat{y})$ relies on the solution of

$$
1=h(y)=\frac{1}{\kappa \alpha}\left(\frac{\alpha \mu}{d\left(K \beta_{n}(y)-\alpha y\right)}-1\right), y \in[0, \hat{y}),
$$

which corresponds to equation 45 . Function $h$ being increasing on $[0, \hat{y})$ and such that $\lim _{y \rightarrow \hat{y}} h(y)=+\infty$, we consequently obtain existence and uniqueness of the co-existence steady state $\left(x^{*}, x^{*}, y^{*}, y^{*}\right)$ if and only if $h(0)<1$. This condition is also equivalent to 44 . Finally, a trivial solving of equation 31 leads to an explicit expression of $x^{*}$.

### 3.3 Linearised system, characteristic equation and asymptotic stability

System 26 linearised with the perturbations $u_{1}, u_{2}, u_{3}$ and $u_{4}$ about any steady state $\left(x_{1}^{*}, x_{2}^{*}, y_{1}^{*}, y_{2}^{*}\right)$, reads
$\frac{\mathrm{d} u_{1}}{\mathrm{~d} t}=K_{1} \beta_{n}^{\prime}\left(y_{1}^{*}\right) u_{3}\left(t-T_{1}\right)-\left(\mu_{1}+d y_{1}^{*}+d \kappa \alpha_{2} y_{2}^{*}\right) u_{1}(t)-d x_{1}^{*} u_{3}(t)-d \kappa \alpha_{2} x_{1}^{*} u_{4}(t)$,
$\frac{\mathrm{d} u_{2}}{\mathrm{~d} t}=K_{2} \beta_{n}^{\prime}\left(y_{2}^{*}\right) u_{4}\left(t-T_{2}\right)-\left(\mu_{2}+d y_{2}^{*}+d \kappa \alpha_{1} y_{1}^{*}\right) u_{2}(t)-d \kappa \alpha_{1} x_{2}^{*} u_{3}(t)-d x_{2}^{*} u_{4}(t)$,
$\frac{\mathrm{d} u_{3}}{\mathrm{~d} t}=\left(d y_{1}^{*}+d \kappa \alpha_{2} y_{2}^{*}\right) u_{1}(t)+\left(d x_{1}^{*}-\alpha_{1}\right) u_{3}(t)+d \kappa \alpha_{2} x_{1}^{*} u_{4}(t)$,
$\frac{\mathrm{d} u_{4}}{\mathrm{~d} t}=\left(d y_{2}^{*}+d \kappa \alpha_{1} y_{1}^{*}\right) u_{2}(t)+d \kappa \alpha_{1} x_{2}^{*} u_{3}(t)+\left(d x_{2}^{*}-\alpha_{2}\right) u_{4}(t)$,
from which we deduce, the associated characteristic equation for $\lambda \in \mathbb{C}$ :
$\left|\begin{array}{cccc}W_{1}(\lambda) & 0 & d x_{1}^{*}-K_{1} \beta_{n}^{\prime}\left(y_{1}^{*}\right) \mathrm{e}^{-\lambda T_{1}} & d \kappa \alpha_{2} x_{1}^{*} \\ 0 & W_{2}(\lambda) & d \kappa \alpha_{1} x_{2}^{*} & d x_{2}^{*}-K_{2} \beta_{n}^{\prime}\left(y_{2}^{*}\right) \mathrm{e}^{-\lambda T_{2}} \\ -\left(d y_{1}^{*}+d \kappa \alpha_{2} y_{2}^{*}\right) & 0 & \lambda+\alpha_{1}-d x_{1}^{*} & -d \kappa \alpha_{2} x_{1}^{*} \\ 0 & -\left(d y_{2}^{*}+d \kappa \alpha_{1} y_{1}^{*}\right) & -d \kappa \alpha_{1} x_{2}^{*} & \lambda+\alpha_{2}-d x_{2}^{*}\end{array}\right|=0$.
where we defined, for $i, j \in\{1,2\}, i \neq j$ :

$$
W_{i}(\lambda)=\lambda+\mu_{i}+d y_{i}^{*}+d \kappa \alpha_{j} y_{j}^{*}
$$

The trivial steady state is the only steady state and locally asymptotically stable if and only if

$$
\begin{equation*}
R_{01}<1, R_{02}<1, \text { and } 0 \leq \kappa^{2}<\frac{1}{R_{01} R_{02} \alpha_{1} \alpha_{2}}\left[1-R_{01}\right]\left[1-R_{02}\right] \tag{47}
\end{equation*}
$$

Otherwise, the trivial steady is unstable. Using the notation 42, we can see that the condition 47 is equivalent to $R_{0 i}<1$, for all $i \in\{0,1,2\}$. For the trivial steady-state, the characteristic equation 46 reads
$\left(\lambda+\mu_{1}\right)\left(\lambda+\mu_{2}\right)\left[\left(\lambda+\alpha_{1}-\frac{d K_{1}}{\mu_{1}}\right)\left(\lambda+\alpha_{2}-\frac{d K_{2}}{\mu_{2}}\right)-\frac{d^{2} \kappa^{2} K_{1} K_{2} \alpha_{1}}{\mu_{1} \mu_{2}}\right]=0, \quad \lambda \in \mathbb{C}$.

Thus, we have at least two eigenvalues $-\mu_{1}<0$ and $-\mu_{2}<0$. Others possible eigenvalues verify

$$
\begin{aligned}
& \lambda^{2}+\left(\alpha_{1}+\alpha_{2}-d\left(\frac{K_{1}}{\mu_{1}}+\frac{K_{2}}{\mu_{2}}\right)\right) \lambda \\
& \quad+\left(\alpha_{1}-\frac{d K_{1}}{\mu_{1}}\right)\left(\alpha_{2}-\frac{d K_{2}}{\mu_{2}}\right)-\frac{d^{2} \kappa^{2} K_{1} K_{2} \alpha_{1} \alpha_{2}}{\mu_{1} \mu_{2}}=0, \quad \lambda \in \mathbb{C} .
\end{aligned}
$$

From the Routh-Hurwtiz criterion, it follows that this equation has roots with negative real parts if and only if
$\alpha_{1}\left(1-R_{01}\right)+\alpha_{2}\left(1-R_{02}\right)>0$ and $\left(\alpha_{1}-\frac{d K_{1}}{\mu_{1}}\right)\left(\alpha_{2}-\frac{d K_{2}}{\mu_{2}}\right)-\frac{d^{2} \kappa^{2} K_{1} K_{2} \alpha_{1} \alpha_{2}}{\mu_{1} \mu_{2}}>0$,
which is also equivalent to

$$
\alpha_{1}\left(1-R_{01}\right)+\alpha_{2}\left(1-R_{02}\right)>0 \text { and } \frac{1}{R_{01} R_{02} \alpha_{1} \alpha_{2}}\left[1-R_{01}\right]\left[1-R_{02}\right]>\kappa^{2}
$$

As $\kappa^{2} \geq 0$, the latter conditions is finally equivalent to condition 47 .
Interchanging lines and columns and using $2 \times 2$ block matrices, the characteristic equation 46 reads

$$
\left|\begin{array}{cc}
A_{1}(\lambda) & B_{1}  \tag{48}\\
B_{2} & A_{2}(\lambda)
\end{array}\right|=0, \lambda \in \mathbb{C},
$$

with, for $i, j \in\{1,2\}, i \neq j$ :
$A_{i}(\lambda)=\left(\begin{array}{cc}W_{i}(\lambda) & d x_{i}^{*}-K_{i} \beta_{n}^{\prime}\left(y_{i}^{*}\right) \mathrm{e}^{-\lambda T_{i}} \\ -d y_{i}^{*}-d \kappa \alpha_{j} y_{j}^{*} & \lambda+\alpha_{i}-d x_{i}^{*}\end{array}\right)$ and $B_{i}=d \kappa \alpha_{j} x_{i}^{*}\left(\begin{array}{cc}0 & 1 \\ 0 & -1\end{array}\right)$.
In order to obtain theoretical result, we decide to consider the symmetrical situation in which neurons are identical with $T:=T_{1}=T_{2}$. In such situation, for any steady state $\left(x^{*}, x^{*}, y^{*}, y^{*}\right)$, the characteristic equation 48 reads:

$$
\left|\begin{array}{cc}
A(\lambda) & B \\
B & A(\lambda)
\end{array}\right|=0, \lambda \in \mathbb{C},
$$

where

$$
A(\lambda):=A_{1}(\lambda)=A_{2}(\lambda) \text { and } B:=B_{1}=B_{2}
$$

Hence, in the symmetrical situation, the characteristic equation for the coexistence steady state $(\bar{x}, \bar{x}, \bar{y}, \bar{y}) \in \mathbb{R}_{+}^{* 4}$ is a product of two second order polynomials :

$$
\begin{equation*}
\operatorname{det}(A(\lambda)+B) \operatorname{det}(A(\lambda)-B)=0, \lambda \in \mathbb{C} \text {, } \tag{49}
\end{equation*}
$$

where, after simple computations using results of 3.2 , we have

$$
\begin{align*}
\operatorname{det}(A(\lambda)+B)=\lambda^{2} & +\left[\mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \lambda-\alpha \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \\
& +K \beta_{n}^{\prime}(\bar{y}) \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \mathrm{e}^{-\lambda T}, \tag{50}
\end{align*}
$$

and

$$
\begin{align*}
\operatorname{det}(A(\lambda)-B)=\lambda^{2} & +\left[\mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})+\frac{2 \kappa \alpha^{2}}{1+\kappa \alpha}\right] \lambda \\
& +2 \frac{\kappa \alpha^{2}}{1+\kappa \alpha} \mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})-\frac{\alpha(1-\kappa \alpha)}{1+\kappa \alpha} \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \\
& +K \beta_{n}^{\prime}(\bar{y}) \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \mathrm{e}^{-\lambda T} \tag{51}
\end{align*}
$$

Now, we state and prove some results about the local asymptotic stability of the co-existence steady state in the situation of identical neurons (i.e. symmetrical situation).

If
(i) neurons are identical with $K:=K_{1}=K_{2}, \alpha:=\alpha_{1}=\alpha_{2}$ and $\mu:=\mu_{1}=$ $\mu_{2}$,
(ii) $\kappa>\frac{1-R_{0}}{\alpha R_{0}}$ (condition equivalent to $R_{00}>1$ ),
(iii) $T_{1}=T_{2}=0$,
then the co-existence steady state $(\bar{x}, \bar{x}, \bar{y}, \bar{y}) \in \mathbb{R}_{+}^{* 4}$ is locally asymptotically stable. If $T_{1}=T_{2}=0$, then the two terms 50 and 51 of the characteristic equation 49 read (computations are not shown for clarity) for $\lambda \in \mathbb{C}$ :
$\operatorname{det}(A(\lambda)+B)=\lambda^{2}+\left[\mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right] \lambda-\left(\alpha-K \beta_{n}^{\prime}(\bar{y})\right) \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right]$, and

$$
\begin{aligned}
\operatorname{det}(A(\lambda)-B)=\lambda^{2} & +\left[\mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})+2 \frac{\kappa \alpha^{2}}{1+\kappa \alpha}\right] \lambda \\
& +\frac{\kappa \alpha^{2}}{1+\kappa \alpha}\left[\mu R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})+\mu\right] \\
& -\left(\frac{\alpha}{1+\kappa \alpha}-K \beta_{n}^{\prime}(\bar{y})\right) \mu\left[1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})\right]
\end{aligned}
$$

From the results obtained in 3.2, from the positiveness of $\bar{y}$ and from the decreasing shape of $\beta_{n}$, we verify that $1-R_{0}(1+\kappa \alpha) \beta_{n}(\bar{y})<0$ and thus obtain that each factors of the two latter polynomials are positive. Hence, we conclude using the Routh-Hurwitz criterion applied to the two latter polynomials.

From 3.3, we use a continuity argument to obtain the following corollary. If conditions (i) and (ii) of 3.3 hold and $T:=T_{1}=T_{2}$, then there exists a unique $T^{*} \in(0,+\infty)$ such that the co-existence steady state $(\bar{x}, \bar{x}, \bar{y}, \bar{y}) \in \mathbb{R}_{+}^{* 4}$ is locally asymptotically stable for all $T<T^{*}$ and unstable for $T \geq T^{*}$ at the neighborhood of $T^{*}$.

If $T$ is increased from 0 to $+\infty$ with fixed values of other model parameters, the system of two identical neurons can undergo a stability switch through a Hopf bifurcation when $T$ reaches $T^{*}$.
Similarly to what has been done for a single neuron, we used the method detailed in [14] to determine theoretical conditions and expressions of the boundary delays at which stability switches could occur. For different values of $\kappa \in[0,1]$,
we thus numerically obtained the corresponding values of $T^{*}$ at which a Hopf bifurcation could occur.
In 4 , we present stability diagrams ( 4 a and 4 c ) and illustrate the stability switch that could occur when $R_{0}>1$ and $R_{0}<1$ through two different plots (4b and 4 d ). These figures highlight the influence of the coupling between the two neurons over the stability of the co-existence steady state. The more important is the coupling, the smaller is the boundary value of $T$ at which a stability switch occurs. As observed in stability diagrams, neuron coupling ( $\kappa>0$ ) actually promotes instability by lowering the value of the biological processes duration $T^{*}$ at which a stability switch occurs compared to the situation without coupling ( $\kappa=0$, single neuron).

Because of the lack of referenced biological values we chose model parameters values according to relevant order magnitudes following previous modelling works [17, 23]. Yet, the threshold concentration $y_{c}$ was chosen arbitrarily. The value of the sensitivity coefficient $n$ significantly influences the time complexity of simulations. Thus, we chose the value $n=10$ as a compromise between a reasonable computational time complexity and reasonable sharpness of the UPR feedback function $\beta_{n}$. Finally, the value of $R_{0}$ (either greater or lower than 1) was set by adjusting the value of $\alpha$.

Table 2: Values of parameters used in 4. Orders of magnitude are consistent with the values used in $[17,23]$.

| Parameters | Values | Units |
| :--- | :--- | :--- |
| $T$ | variable (4a and 4 c$)$ or $0.15(4 \mathrm{~d})$ | days |
| $\mu_{1}=\mu_{2}=\mu$ | 20 | days $^{-1}$ |
| $K_{1}=K_{2}=K$ | 1500 | $($ Fibrils per volume unit) $)$ days $^{-1}$ |
| $\alpha_{1}=\alpha_{2}=\alpha$ | $2.0833(4 \mathrm{a}$ and 4 b$)$ or $4.6875(4 \mathrm{c}$ and | days $^{-1}$ |
|  | $4 \mathrm{~d})$ |  |
| $\kappa$ | variable $(4 \mathrm{a}, 4 \mathrm{c}$ and 4 d$)$ or $0.2(4 \mathrm{~b})$ | - |
| $y_{c}$ | 130 | Fibrils per volume unit |
| $d$ | 0.05 | ${\text { (Fibrils per volume unit })^{-1} . d^{2}}^{n}$ |
| 10 | - |  |

## 4 Discussion and conclusion

The formalism we used to depict prion dynamics with two neurons can be easily generalized to describe prion dynamics in a system of $N$ neurons. Doing so, we obtain a model similar to the one developed by Stumpf and Krakauer [42], except our approach incorporates the UPR feedback and do not assume preferential diffusion along axons.
In this paradigm, each neuron $i \in \llbracket 1, N \rrbracket$ is modeled with its associated $\operatorname{PrP}^{c}$


Figure 4: (a), (c) : Stability diagrams in the $(\kappa, T)$ plane when neurons are strictly identical with $R_{0}>1$ (a) or $R_{0}<1$ (c). Full lines locate $T^{*}$ : the first crossing of the imaginary axis by the characteristic roots associated to the co-existence steady state. It corresponds to the first value of $T$ (when increased from 0) that induces a stability switch through a Hopf bifurcation. Colored areas indicate stability regions for the trivial (blue) or co-existence (red) steady states. In (a), that is $R_{0}>1$, we also highlight by a dashed line the value of $T^{*}$ obtained for the model of a single neuron (presented in 2). We verify the coherence between the two models as $\kappa \rightarrow 0$ and observe the effect of neuron coupling: the boundary value $T^{*}$ decreases with $\kappa$. Neuron coupling thus promote instability. In (c), that is $R_{0}<1$, if $\kappa$ is small enough, the disease free equilibrium is the only steady state but also asymptotically stable. However, when coupling parameter $\kappa$ is large enough, the disease steady state eventually appears and becomes also stable. This means that even with $R_{0}<1$, the coupling allows the disease to play a major role. (b): Example trajectories when $R_{0}>1$ illustrating the Hopf bifurcation that occurs when $T$ crosses the boundary. Trajectories are colored according to their parameter values and correspond to the colored crosses of 4a. (d) Evolution of normalized $\operatorname{PrP}{ }^{S c}$ steady state values $y^{*} / y_{c}$ with respect to the coupling constant $\kappa$ when $R_{0}<1$. For a given value of $\kappa$, then there is one or two steady states which can be stable (full line) or unstable (dashed line). When there are 2 unstable steady states, the solution is periodic and we indicate its maximum and minimum with red and blue lines, respectively. Values of other model parameters (specified in 2) are set to relevant orders of magnitudes.
and $\operatorname{PrP}^{S c}$ concentrations $x_{i}$ and $y_{i}$ ruled by

$$
\begin{aligned}
\frac{\mathrm{d} x_{i}}{\mathrm{~d} t} & =K_{i} \beta_{n}\left(y_{i}\left(t-T_{1}\right)\right)-\mu_{i} x_{i}(t)-d x_{i}\left(y_{i}(t)+\sum_{j \neq i} \kappa_{i, j} \alpha_{j \rightarrow i} y_{j}(t)\right) \\
\frac{\mathrm{d} y_{i}}{\mathrm{~d} t} & =d x_{i}(t)\left(y_{i}(t)+\sum_{j \neq i} \kappa_{i, j} \alpha_{j \rightarrow i} y_{j}(t)\right)-\left(\sum_{j \neq i} \alpha_{i \rightarrow j}\right) y_{2}(t)
\end{aligned}
$$

Parameters $d, K_{i}$ and $\mu_{i}$ have the same meaning as before concerning neuron $i \in \llbracket 1, N \rrbracket$. The parameter $\alpha_{i \rightarrow j}$ transcribes the diffusive property of $\operatorname{PrP}^{S c}$ to the neuron $j \neq i$. We still assume that interactions between $\operatorname{PrP}^{S c}$ from neuron $i$ to $\operatorname{PrP}^{C}$ of an other neuron $j \neq i$ is modeled with a coupling factor $0 \leq \kappa_{i, j}<1$. We remind that these coupling constants should be viewed as damping coefficients characterizing both diffusion properties and difference of origin between prion species.

In conclusion, we developed a modeling approach of prion production at the scale of one (2) or two (3) neurons. Our approach incorporates the effect of the Unfolded Protein Response through a negative feedback describing the global translation shutdown induced by an overload of $\operatorname{PrP}{ }^{S c}$ around a neuron.

We investigated existence, uniqueness and (local) stability of steady states associated to each of the two models presented in this paper. In these models, a bifurcation analysis with respect to the variation of three parameter (for the single neuron's prion model) or a continuity argument (for the two neuron's model) led to condition for autonomous oscillations of $\mathrm{PrP}^{S c}$ to appear. Stability diagrams and numerical simulations gave us insight in the stability of steady states as well as in the dynamics of solutions. In the case of two neurons, we established - both theoretically and numerically - an interesting result. Interactions between $\operatorname{PrP}^{S c}$ and $\operatorname{PrP}^{c}$ originating from different neurons enable - if the coupling constant $\kappa$ is greater than a minimum value - existence and uniqueness of a co-existence steady state (and possibly $\operatorname{PrP}^{S c}$ oscillations to appear) even when the $R_{0}$ associated to each single neuron ${ }^{4}$ is lower than one. Theoretical results and numerical simulations concerning the case of 2 identical neurons indicate that the value of $\kappa$ dictates prion dynamics at the scale of two neurons and show that the co-existence steady state could be destabilized inducing $\mathrm{PrP}^{S c}$ oscillations - when the biological processes duration $T$ excesses a boundary value $T^{*}$.

Even if, our models aim at describing $\mathrm{PrP}^{c}$ and $\mathrm{PrP}^{S c}$ concentrations around neurons, future research may extend and/or modify our modeling approach to describe concentrations of different misfolded proteins involved in other Protein Misfolding Disorders, such as $\mathrm{A} \beta$ proteins in the context of Alzheimer's Disease.

Moreover, by considering the effect of a global translation shutdown at the neuron scale (through protein synthesis activity and biological activity variables), our model paves the way for future investigations into the effect of neuron synchronization in prion diseases. Actually, this work constitutes the building block of a future wider modeling approach in which neurons could interact through $\mathrm{PrP}^{S c}$ diffusion and possibly oscillates (depending on their environment and biological parameters) and then potentially see their protein synthesis activities become synchronized thus triggering detrimental outcomes.

[^3]To this aim, we will have to take several important physiological features of the neuronal network into account. Indeed, since prion proteins are anchored to the cell membrane, the $\mathrm{PrP}^{S c}$ formation follows the synaptic entanglement and thus do not propagate equally in all directions. Thus, some of the neurons not located in the neighborhood of a stressed one, could be impacted by its behavior and propagate the UPR mechanism in an unexpected heterogeneous way. Furthermore, similarly to a group of persons tied together and trying to figure out how to progress in a jungle, diffusion coefficient of $\operatorname{PrP}{ }^{S c}$ proteins depends mainly on the on its size (called the polymer length). The longer the protein is, the less it diffuses. And thus, secondary nucleation could appear far from the source of the onset of the pathology in a group of neurons if polymers of small sizes are produced in a sufficient quantity. Then, the synchronicity could be described either through a local connection in standard but technical way, or through an unexpected non local heterogeneous way. This has to be clearly observed in vivo through image analysis, and described with new mathematical models and technical approaches. This is the object of our future but promising work.

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[^0]:    *Submitted to the editors /09/21.

[^1]:    ${ }^{1}$ characteristic of the disease : amyloid-beta and tau in Alzheimer's disease, $\alpha$-synuclein in Parkinson's disease and prion proteins in Prion-related diseases
    ${ }^{2}$ intra or extra cellularly depending on the disease

[^2]:    ${ }^{3}$ i.e. that does not induce the apoptosis of the cell

[^3]:    ${ }^{4}$ characterizing existence and uniqueness of the endemic steady state

