



**University of Dundee**

## **Hopf bifurcation in a gene regulatory network model**

Chaplain, Mark ; Ptashnyk, Mariya; Sturrock, Marc

*Published in:*  
Mathematical Models and Methods in Applied Sciences

*DOI:*  
[10.1142/S021820251550030X](https://doi.org/10.1142/S021820251550030X)

*Publication date:*  
2015

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Chaplain, M., Ptashnyk, M., & Sturrock, M. (2015). Hopf bifurcation in a gene regulatory network model: Molecular movement causes oscillations. *Mathematical Models and Methods in Applied Sciences*, 25(6), 1179-1215. DOI: 10.1142/S021820251550030X

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## Hopf bifurcation in a gene regulatory network model: Molecular movement causes oscillations

Mark Chaplain\* and Mariya Ptashnyk†

*Division of Mathematics, University of Dundee,  
Dundee DD1 4HN, Scotland  
\*chaplain@maths.dundee.ac.uk  
†mptashnyk@maths.dundee.ac.uk*

Marc Sturrock

*Mathematical Biosciences Institute,  
Ohio State University, 377 Jennings Hall,  
1735 Neil Avenue, Columbus, OH, USA  
sturrock.3@mbi.osu.edu*

Received 17 February 2014

Revised 6 October 2014

Accepted 16 November 2014

Published 8 January 2015

Communicated by O. Diekmann

Gene regulatory networks, i.e. DNA segments in a cell which interact with each other indirectly through their RNA and protein products, lie at the heart of many important intracellular signal transduction processes. In this paper, we analyze a mathematical model of a canonical gene regulatory network consisting of a single negative feedback loop between a protein and its mRNA (e.g. the Hes1 transcription factor system). The model consists of two partial differential equations describing the spatio-temporal interactions between the protein and its mRNA in a one-dimensional domain. Such intracellular negative feedback systems are known to exhibit oscillatory behavior and this is the case for our model, shown initially via computational simulations. In order to investigate this behavior more deeply, we undertake a linearized stability analysis of the steady states of the model. Our results show that the diffusion coefficient of the protein/mRNA acts as a bifurcation parameter and gives rise to a Hopf bifurcation. This shows that the spatial movement of the mRNA and protein molecules alone is sufficient to cause the oscillations. Our result has implications for transcription factors such as p53, NF- $\kappa$ B and heat shock proteins which are involved in regulating important cellular processes such as inflammation, meiosis, apoptosis and the heat shock response, and are linked to diseases such as arthritis and cancer.

This is an Open Access article published by World Scientific Publishing Company. It is distributed under the terms of the Creative Commons Attribution 3.0 (CC-BY) License. Further distribution of this work is permitted, provided the original work is properly cited.

*Keywords:* Gene regulatory network; transcription factor; negative feedback loop; oscillations; Hopf bifurcation; center manifold and normal form; weakly nonlinear analysis.

AMS Subject Classification: 22E46, 34K18, 37G05, 35Bxx, 53C35, 57S20, 92C40, 92C42

## 1. Introduction

A gene regulatory network (GRN) can be defined as a collection of DNA segments in a cell which interact with each other indirectly through their RNA and protein products. GRNs lie at the heart of intracellular signal transduction and indirectly control many important cellular functions. A key component of GRNs is a class of proteins called transcription factors. In response to various biological signals, transcription factors change the transcription rate of genes, allowing cells to produce the proteins they need at the appropriate times and in the appropriate quantities. It is now well established that GRNs contain a small set of recurring regulation patterns, commonly referred to as network motifs,<sup>50</sup> which can be thought of as recurring circuits of interactions from which complex GRNs are built. A GRN is said to contain a negative feedback loop if a gene product inhibits its own production either directly or indirectly. Negative feedback loops are commonly found in diverse biological processes including inflammation, meiosis, apoptosis and the heat shock response,<sup>1,12,41</sup> and are known to exhibit oscillations in mRNA and protein levels.<sup>15,38,54</sup>

Mathematical modeling of GRNs goes back to the work of Goodwin,<sup>19</sup> where an initial system of two ordinary differential equations (ODEs) was used to model a self-repressing gene. In the final part of the paper a system of three ODEs was shown to produce limit cycle behavior. This work was continued by Griffith<sup>21</sup> who demonstrated that the introduction of the third species was necessary for the oscillatory dynamics. An analysis of theoretical chemical systems whereby two chemicals produced at distinct spatial locations (heterogeneous catalysis) diffused and reacted together was carried out by Glass and co-workers.<sup>17,61</sup> Their results showed that the number and stability of the steady states of the system changed depending on the distance between the two catalytic sites. The authors concluded that “*These examples indicate that geometrical considerations must be explicitly considered when analyzing the dynamics of highly structured (e.g. biological) systems.*”<sup>61</sup> Mahaffy and co-workers<sup>6,44,45</sup> developed this work further by considering an explicitly spatial model and also time delays accounting for the processes of transcription (production of mRNA) and translation (production of proteins). Tiana *et al.*<sup>67</sup> proposed that introducing delays to ODE models of negative feedback loops could produce sustained oscillatory dynamics and Jensen *et al.*<sup>32</sup> found that the invocation of an unknown third species (as Griffith had done<sup>21</sup>) could be avoided by the introduction of delay terms to a model of the Hes1 GRN (the justification being to account for the processes of transcription and translation). The Hes1 system is a simple example of a GRN which possesses a single negative feedback loop and benefits from having been the subject of numerous biological experiments.<sup>27,33,37–39</sup> A delay differential

equation (DDE) model of the Hes1 GRN has also been studied by Monk and co-workers.<sup>51,52</sup> More recently, a spatio-temporal model of the Hes1 GRN considering diffusion of the protein and mRNA was developed by Sturrock *et al.*<sup>65</sup> and then later extended to account for transport across the nuclear membrane and directed transport via microtubules.<sup>66</sup>

A key feature of all mathematical models of the Hes1 GRN (and other negative feedback systems) is the existence of oscillatory solutions characterized by a Hopf bifurcation. In the Hopf, or Poincaré–Andronov–Hopf bifurcation (first described by Hopf<sup>28</sup>), a steady state changes stability as two complex conjugate eigenvalues of the linearization cross the imaginary axis and a family of periodic orbits bifurcates from the steady state. Many studies are devoted to the existence and stability of Hopf bifurcations in ordinary and partial differential equations.<sup>7,25,35,36,40,46</sup> The question of the existence of global Hopf bifurcation for nonlinear parabolic equations has also been considered.<sup>13,14,31</sup> There are many results concerning the stability of constant (i.e. spatially homogeneous) steady states and the existence of periodic solutions bifurcating from such constant steady states. There are some results on the stability of spike-solutions and the existence of Hopf bifurcations in the shadow Gierer–Meinhardt model,<sup>10,55,69,70</sup> as well as on the stability of spiky solutions in a reaction–diffusion system with four morphogens<sup>72</sup> and of cluster solutions for large reaction–diffusion systems.<sup>71</sup> In the analysis of the stability and Hopf bifurcations in systems with spike-solutions as stationary solutions, the properties of the corresponding nonlocal eigenvalue problem were used. Perturbation theory has been applied to analyze the stability of non-constant steady-states for a system of nonlinear reaction–diffusion equations coupled with ordinary differential equations.<sup>18</sup> In considering the relation between the spectrum of a linearized operator for singularly perturbed predator–prey-type equations with diffusion and the limit operator as the perturbation parameter tends to zero, Dancer<sup>9</sup> analyzed the stability of strictly positive stationary solutions and the existence of Hopf bifurcations.

In this paper, we analyze a mathematical model of the Hes1 transcription factor — a canonical GRN consisting of a single negative feedback loop between the Hes1 protein and its mRNA. The format of this paper is as follows. In Sec. 2, we present our mathematical model derived from that first formulated by Sturrock *et al.*<sup>65</sup> First, we demonstrate the existence of oscillatory solutions numerically, indicating the existence of Hopf bifurcations. Next, applying linearized stability analysis, we study the stability of a (spatially inhomogeneous) steady state of the model and prove the existence of a Hopf bifurcation. The main difficulty of the analysis is that the steady state of the model is not constant. In a similar manner to Dancer<sup>9</sup> we show the existence of a Hopf bifurcation by considering a limit problem associated with the original model. The method of collective compactness<sup>2,9</sup> is applied to relate the spectrum of the limit operator to the spectrum of the original operator. To show the stability of periodic solutions and to determine the type of Hopf bifurcation, we use a weakly nonlinear analysis, see, for example, Matkowski,<sup>47</sup> and normal form theory, see, for example, Hassard, Haragus.<sup>24,25</sup> The techniques

of weakly nonlinear analysis<sup>8,11,42,58</sup> and normal form theory,<sup>24,25</sup> are widely used to study the nonlinear behavior of solutions near bifurcation points.

## 2. The Mathematical Model of the Hes1 Gene Regulatory Network

The basic model of a self-repressing gene<sup>52</sup> describing the temporal dynamics of hes1 mRNA concentration,  $m(t)$ , and Hes1 protein concentration,  $p(t)$ , takes the general form:

$$\frac{\partial m}{\partial t} = \alpha_m f(p) - \mu_m m, \quad (2.1)$$

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p, \quad (2.2)$$

for positive constants  $\alpha_m, \alpha_p, \mu_m, \mu_p$  and some function  $f(p)$  modeling the suppression of mRNA production by the protein. It can be shown using Bendixson's Negative Criterion (cf. Verhulst,<sup>68</sup> Theorem 4.1) that, irrespective of the function  $f(p)$  (e.g. a Hill function), there are no periodic solutions of the above system. In order to account for the experimentally observed oscillations in both mRNA and protein concentration levels,<sup>27</sup> a discrete delay has often been introduced into such models being justified as taking into account the time taken to produce mRNA (transcription) and produce protein (translation).<sup>52</sup> Applying a discrete delay  $\tau$  to (2.1), (2.2), a delay differential equation model is obtained of the form:

$$\frac{\partial m}{\partial t} = \alpha_m f(p - \tau) - \mu_m m, \quad (2.3)$$

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p. \quad (2.4)$$

Such a system is observed to exhibit oscillations for a suitable value of the delay parameter  $\tau$  representing the sum of the transcriptional and translational time delays. This delay differential equation approach has also been used to model other feedback systems involving transcription factors such as p53<sup>4,16,67</sup> and NF- $\kappa$ B.<sup>54</sup> Other papers have used a distributed delay to model this effect,<sup>20</sup> which in fact is equivalent to the original three ODE model of a self-repressing gene proposed by Goodwin<sup>19</sup> and Griffith.<sup>21</sup>

Here, we study an explicitly spatial model of the Hes1 GRN originally formulated by Sturrock *et al.*<sup>65,66</sup> and investigate the role that spatial movement of the molecules may play in causing the oscillations in concentration levels. The model consists of a system of coupled nonlinear partial differential equations describing the temporal and spatial dynamics of the concentration of hes1 mRNA,  $m(x, t)$ , and Hes1 protein,  $p(x, t)$ , and accounts for the processes of transcription (mRNA production) and translation (protein production). Transcription is assumed to occur in a small region of the domain representing the gene site. Both mRNA and protein

also diffuse and undergo linear decay. The non-dimensionalized model is given as:

$$\begin{aligned} \frac{\partial m}{\partial t} &= D \frac{\partial^2 m}{\partial x^2} + \alpha_m f(p) \delta_{x_M}^\varepsilon(x) - \mu_m m && \text{in } (0, T) \times (0, 1), \\ \frac{\partial p}{\partial t} &= D \frac{\partial^2 p}{\partial x^2} + \alpha_p g(x) m - \mu_p p && \text{in } (0, T) \times (0, 1), \\ \frac{\partial m(t, 0)}{\partial x} &= \frac{\partial m(t, 1)}{\partial x} = 0, \quad \frac{\partial p(t, 0)}{\partial x} = \frac{\partial p(t, 1)}{\partial x} = 0 && \text{in } (0, T), \\ m(0, x) &= m_0(x), \quad p(0, x) = p_0(x) && \text{in } (0, 1), \end{aligned} \quad (2.5)$$

where  $D$ ,  $\alpha_m$ ,  $\alpha_p$ ,  $\mu_m$  and  $\mu_p$  are positive constants (the diffusion coefficient, transcription rate, translation rate and decay rates of *hes1* mRNA and Hes1 protein respectively). Full details of the non-dimensionalization can be found in the papers of Sturrock *et al.*<sup>65,66</sup> Here  $l$  denotes the position of the nuclear membrane and therefore the domain is partitioned into two distinct regions,  $(0, l)$  the cell nucleus and  $(l, 1)$  the cell cytoplasm, for some  $l \in (0, 1)$ . The point  $x_M \in (0, l)$  is the position of the center of the gene site and by  $\delta_{x_M}^\varepsilon$  we denote the Dirac approximation of the  $\delta$ -distribution located at  $x_M$ , with  $\varepsilon > 0$  a small parameter and  $\delta_{x_M}^\varepsilon$  has compact support.

The nonlinear reaction term  $f: \mathbb{R} \rightarrow \mathbb{R}$  is a Hill function  $f(p) = 1/(1 + p^h)$ , with  $h \geq 2$ , modeling the suppression of mRNA production by the protein (negative feedback). More precisely, as noted by Monk,<sup>52</sup> the Hill coefficient  $h$  measures the degree of cooperativity of nuclear import and binding of Hes1 protein to the promoter region of the *hes1* gene. Since there are three Hes1 binding sites, with cooperative interactions between the sites likely, and Hes1 acts as a dimer, it has been estimated<sup>52</sup> that the value of  $h$  should lie between 2 and 10 i.e.  $2 \leq h \leq 10$ . The function  $g$  is a step function given by

$$g(x) = \begin{cases} 0, & \text{if } x < l, \\ 1, & \text{if } x \geq l, \end{cases}$$

since the process of translation only occurs in the cytoplasm. A schematic diagram of the domain is given in Fig. 1.

First we demonstrate existence and uniqueness of solutions to (2.5).

**Theorem 2.1.** *For  $\varepsilon > 0$  and non-negative initial data  $m_0, p_0 \in H^2(0, 1)$ , there exists a unique non-negative global solution  $m, p \in C([0, \infty); H^2(0, 1))$ ,  $\partial_t m, \partial_t p \in$*



Fig. 1. (Color online) Schematic diagram of the one-dimensional spatial domain for the system (2.5), showing the spatial location of the gene site  $x_M$  and the nuclear membrane  $l$ . The cell nucleus is shown in blue, while the cell cytoplasm is shown in green.

$L^2((0, T) \times (0, 1))$ , and  $m, p \in C^{(\gamma+1)/2, \gamma+1}([0, T] \times [0, 1])$ , for some  $\gamma > 0$  and any  $T > 0$ , of the problem (2.5) satisfying

$$\|m\|_{L^\infty(0, T; H^1(0, 1))} + \|p\|_{L^\infty(0, T; H^1(0, 1))} \leq C, \tag{2.6}$$

$$\|\partial_t m\|_{L^2((0, T) \times (0, 1))} + \|\partial_t p\|_{L^2(0, T; H^1(0, 1))} + \|\partial_x^2 p\|_{L^2((0, T) \times (0, 1))} \leq C,$$

for any  $T \in (0, \infty)$  with the constant  $C$  independent of  $\varepsilon$ .

**Proof.** Since  $f(p)$  is Lipschitz continuous for  $p \geq -\theta$ , with some  $0 < \theta < 1$ , we have that for non-negative initial data  $m_0, p_0$  the existence and uniqueness of a solution of the problem (2.5) in  $(0, T_0) \times (0, 1)$ , for some  $T_0 > 0$ , follows directly from the existence and the regularity theory for systems of parabolic equations, see e.g. Henry,<sup>26</sup> Lieberman.<sup>43</sup> Using the definition of the Dirac sequence, for  $F_m(m, p) = \alpha_m f(p) \delta_{x_M}^\varepsilon(x) - \mu_m m$  and  $F_p(m, p) = \alpha_p g(x) m - \mu_p p$ , we have

$$F_m|_{m=0} \geq 0 \quad \text{for } p \geq 0, \qquad F_p|_{p=0} \geq 0 \quad \text{for } m \geq 0,$$

$$F_m|_{m=\alpha_m/(\mu_m \varepsilon)} \leq 0 \quad \text{for } p \geq 0, \quad F_p|_{p=\alpha_p \alpha_p/(\mu_m \mu_p \varepsilon)} \leq 0 \quad \text{for } m \leq \alpha_m/(\mu_m \varepsilon).$$

Thus applying the theorem of invariant regions, e.g. Theorem 14.7 in Smøller,<sup>63</sup> with  $G_1(m, p) = -m$ ,  $G_2(m, p) = -p$ ,  $G_3(m, p) = m - \alpha_m/(\mu_m \varepsilon)$ , and  $G_4(m, p) = p - \alpha_p \alpha_p/(\mu_m \mu_p \varepsilon)$ , we conclude that  $0 \leq m(t, x) \leq \alpha_m/(\mu_m \varepsilon)$  and  $0 \leq p(t, x) \leq \alpha_p \alpha_p/(\mu_m \mu_p \varepsilon)$  for all  $(t, x) \in (0, T_0) \times (0, 1)$ , whereas the bounds for  $m$  and  $p$  are uniform in  $T_0$ . This ensures global existence and uniqueness of a bounded solution of (2.5) for fixed  $\varepsilon$ .

Using the property of the Dirac sequence, i.e.  $\|\delta_{x_M}^\varepsilon\|_{L^1(0, 1)} = 1$ , continuous embedding of  $H^1(0, 1)$  in  $C([0, 1])$ , and considering  $m$  and  $p$  as test functions for (2.5) we obtain

$$\partial_t \|m(t)\|_{L^2(0, 1)}^2 + \|\partial_x m(t)\|_{L^2(0, 1)}^2 + \|m(t)\|_{L^2(0, 1)}^2 \leq C \|f(p)\|_{L^\infty((0, T) \times (0, 1))}^2,$$

$$\partial_t \|p(t)\|_{L^2(0, 1)}^2 + \|\partial_x p(t)\|_{L^2(0, 1)}^2 + \|p(t)\|_{L^2(0, 1)}^2 \leq C \|m(t)\|_{L^2(0, 1)}^2.$$

Integrating over time and using the uniform boundedness of  $f(p)$  for non-negative  $p$  ensure the estimates in  $L^\infty(0, T; L^2(0, 1))$  and  $L^2(0, T; H^1(0, 1))$ .

Testing the first equation in (2.5) with  $\partial_t m$  and the second equation with  $\partial_t p$  and  $\partial_x^2 p$ , as well as differentiating the second equation with respect to  $t$  and testing with  $\partial_t p$ , and integrating over  $(0, \tau)$  for  $\tau \in (0, T)$  and any  $T > 0$  imply

$$\begin{aligned} &\|\partial_t m\|_{L^2((0, \tau) \times (0, 1))}^2 + \|\partial_x m(\tau)\|_{L^2(0, 1)}^2 + \|m(\tau)\|_{L^2(0, 1)}^2 \leq \delta \|m(\tau)\|_{L^\infty(0, 1)}^2 \\ &\quad + C[\|m(0)\|_{H^1(0, 1)}^2 + \|m\|_{L^2(0, \tau; L^\infty(0, 1))}^2 + \|\partial_t p\|_{L^2(0, \tau; L^\infty(0, 1))}^2 + C_\delta], \\ &\|\partial_t p\|_{L^2((0, \tau) \times (0, 1))}^2 + \|\partial_x p(\tau)\|_{L^2(0, 1)}^2 \leq C[\|m\|_{L^2((0, \tau) \times (0, 1))}^2 + \|p(0)\|_{H^1(0, 1)}^2], \\ &\|\partial_x p(\tau)\|_{L^2(0, 1)}^2 + \|\partial_x^2 p\|_{L^2((0, \tau) \times (0, 1))}^2 \leq C[\|m\|_{L^2((0, \tau) \times (0, 1))}^2 + \|p(0)\|_{H^1(0, 1)}^2], \\ &\|\partial_t p(\tau)\|_{L^2(0, 1)}^2 + \|\partial_x \partial_t p\|_{L^2((0, \tau) \times (0, 1))}^2 \leq \delta \|\partial_t m\|_{L^2((0, \tau) \times (0, 1))}^2 \\ &\quad + C_\delta[\|\partial_t p\|_{L^2((0, \tau) \times (0, 1))}^2 + \|\partial_t p(0)\|_{L^2(0, 1)}^2]. \end{aligned}$$

This together with the continuous embedding of  $H^1(0, 1)$  in  $C([0, 1])$ , the estimate  $\|\partial_t p(0)\|_{L^2(0,1)} \leq C\|p(0)\|_{H^2(0,1)}$ , regularity of initial data and estimates in  $L^\infty(0, T; L^2(0, 1))$  and  $L^2(0, T; H^1(0, 1))$  shown above ensures estimates (2.6).  $\square$

**Remark 2.1.** The *a priori* estimates (2.6) imply the uniform in  $\varepsilon$  boundedness of solutions of (2.5) for every  $T > 0$ .

For the subsequent analysis of (2.5) we consider the following parameter values in the model equations: the basal transcription rate of *hes1* mRNA is given by  $\alpha_m = 1$  and the translation rate of Hes1 protein is  $\alpha_p = 2$ ; the Hill coefficient in the function  $f$  is taken to be  $h = 5$ , as in the original model of Monk<sup>52</sup> (however, we note that the same analysis can be conducted for  $h \geq 3$  and oscillations are still obtained); based on the original experiments of Hirata *et al.*<sup>27</sup> the degradation

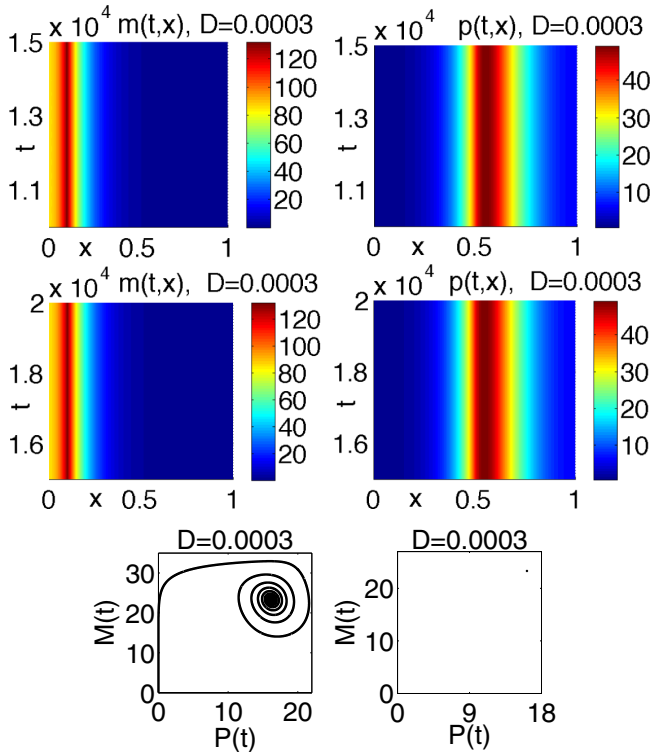


Fig. 2. First two rows: Plots showing the spatio-temporal evolution of mRNA level,  $m(t, x)$ , and protein level,  $p(t, x)$ , from numerical simulations of system (2.5) with zero initial conditions, with  $\varepsilon = 10^{-3}$ ,  $D = 0.0003$ , and  $t \in [10^4, 2 \cdot 10^4]$ . The plots show that the solutions tend to a steady state. Bottom row: The corresponding phase-plots, where  $M(t) = \int_0^1 m(t, x) dx$  and  $P(t) = \int_0^1 p(t, x) dx$ . The figure on the left is for  $t \in [0, 2 \times 10^4]$ , and the figure on the right is for  $t \in [10^4, 2 \times 10^4]$ . These show the trajectory converging to a fixed point, equivalent to the steady state.



rates of *hes1* mRNA and Hes1 protein  $\mu_m = \mu_p = 0.03$  (full details of the parameter values can be found in and references therein, Refs. 3, 27, 30, 52, 64–66). It is assumed that the region of the cytoplasm where the protein is produced is given by  $(1/2, 1)$ , i.e.  $l = 1/2$ , and the position of the center of the gene site is at  $x_M = 0.1$ . The (non-dimensional) diffusion coefficient is a variable parameter in the model and we consider biologically relevant values<sup>48,49,60</sup> in the range  $10^{-4} \leq D \leq 10^{-2}$ . The critical values for the Hopf bifurcation are found in this range. We note that further computational investigations were carried out using values of  $D$  without this biologically relevant range i.e.  $D \in [d_1, d_2]$ , where  $d_1 = 10^{-7}$  and  $d_2 = 0.1$ , which numerically indicated the stability of the steady states for the bifurcation parameter  $D$  above  $10^{-2}$  and below  $10^{-4}$ .

Numerical simulations of the model (2.5) (using the forward Euler scheme in time and a centered difference scheme in space, as well as the Dirac sequence in

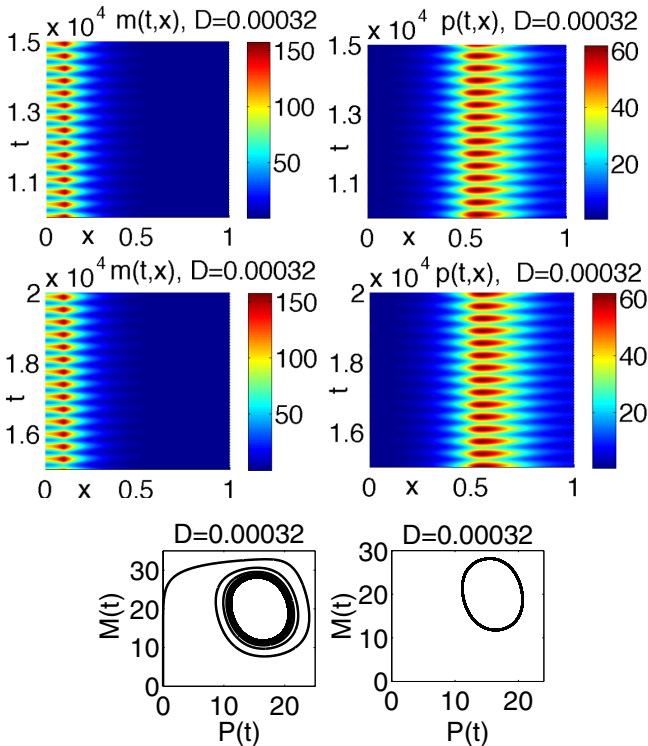


Fig. 3. First two rows: Plots showing the spatio-temporal evolution of mRNA level,  $m(t, x)$ , and protein level,  $p(t, x)$ , from numerical simulations of system (2.5) with zero initial conditions, with  $\varepsilon = 10^{-3}$ ,  $D = 0.00032$  and  $t \in [10^4, 2 \times 10^4]$ . The plots show oscillatory solutions. Bottom row: The corresponding phase-plots, where  $M(t) = \int_0^1 m(t, x) dx$  and  $P(t) = \int_0^1 p(t, x) dx$ . The figure on the left is for  $t \in [0, 2 \times 10^4]$ , and the figure on the right is for  $t \in [10^4, 2 \times 10^4]$ . These show the trajectory converging to a limit-cycle.

the form  $\delta_{x_M}^\varepsilon(x) = \frac{1}{2\varepsilon}(1 + \cos(\pi(x - x_M)/\varepsilon))$  for  $|x - x_M| < \varepsilon$  and  $\delta_{x_M}^\varepsilon(x) = 0$  for  $|x - x_M| \geq \varepsilon$ ) reveal that a stationary solution, stable for small values of the diffusion coefficient  $D$ , becomes unstable for  $D \geq D_{1,\varepsilon}^c$ , with  $D_{1,\varepsilon}^c \approx 3.117 \times 10^{-4}$ , and again stable for  $D > D_{2,\varepsilon}^c$ , where  $D_{2,\varepsilon}^c \approx 7.885 \times 10^{-3}$ . For diffusion coefficients between the two critical values, i.e.  $D \in [D_{1,\varepsilon}^c, D_{2,\varepsilon}^c]$ , numerical simulations show the existence of stable periodic solutions of the model (2.5). These scenarios are shown in Figs. 2–5. We note that the same analysis can be carried out with a Hill coefficient  $h \geq 3$ . For example, in the case  $h = 3$  we obtain the critical values  $D_{1,\varepsilon}^c \approx 0.0004$  and  $D_{2,\varepsilon}^c \approx 0.00139$ .

In the following sections, we shall analyze the existence and stability of a family of periodic solutions bifurcating from the stationary solution. We shall show that at both critical values of the diffusion coefficient a supercritical Hopf bifurcation occurs.

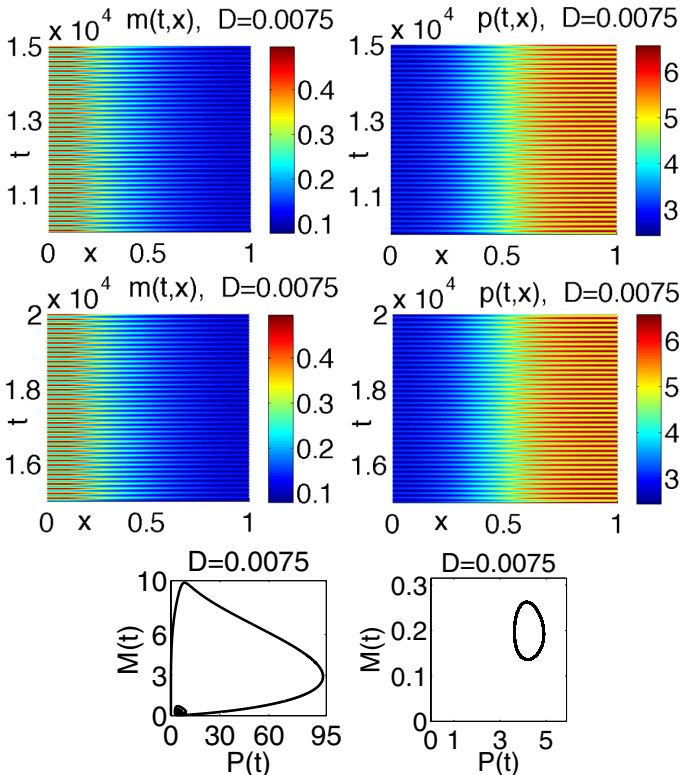


Fig. 4. First two rows: Plots showing the spatio-temporal evolution of mRNA level,  $m(t, x)$ , and protein level,  $p(t, x)$ , from numerical simulations of system (2.5) with zero initial conditions, with  $\varepsilon = 10^{-3}$ ,  $D = 0.0075$  and  $t \in [10^4, 2 \times 10^4]$ . The plots show oscillatory solutions. Bottom row: The corresponding phase-plots, where  $M(t) = \int_0^1 m(t, x) dx$  and  $P(t) = \int_0^1 p(t, x) dx$ . The figure on the left is for  $t \in [0, 2 \times 10^4]$ , and the figure on the right is for  $t \in [10^4, 2 \times 10^4]$ . These show the trajectory converging to a limit-cycle.

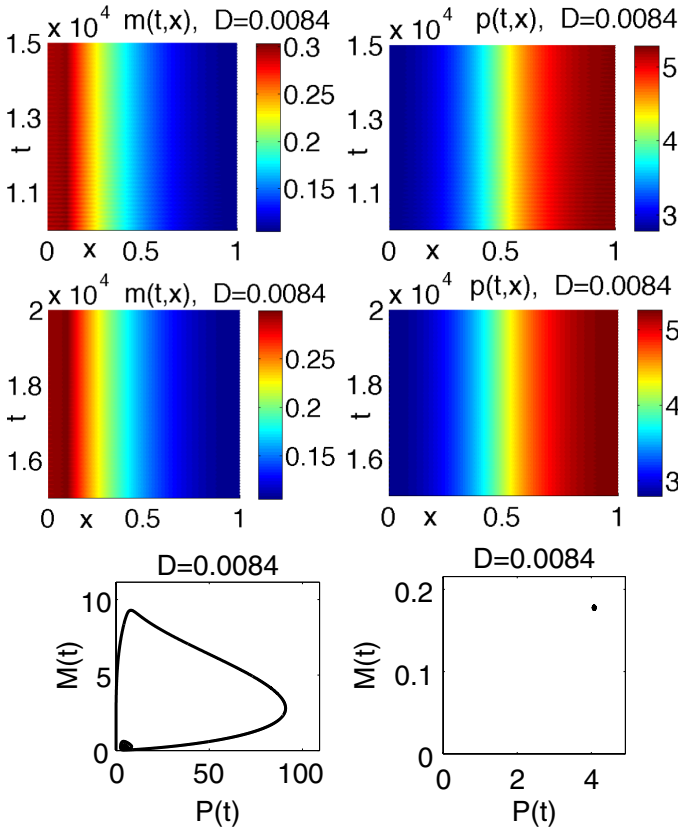


Fig. 5. First two rows: Plots showing the spatio-temporal evolution of mRNA level,  $m(t, x)$ , and protein level,  $p(t, x)$ , from numerical simulations of system (2.5) with zero initial conditions, with  $\varepsilon = 10^{-3}$ ,  $D = 0.0084$  and  $t \in [10^4, 2 \times 10^4]$ . The plots show that the solutions tend to a steady state. Bottom row: The corresponding phase-plots, where  $M(t) = \int_0^1 m(t, x)dx$  and  $P(t) = \int_0^1 p(t, x)dx$ . The figure on the left is for  $t \in [0, 2 \times 10^4]$ , and the figure on the right is for  $t \in [10^4, 2 \times 10^4]$ . These show the trajectory converging to a fixed point, equivalent to the steady state.

### 3. Steady State Solutions

First, we examine the stationary solutions  $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T$  of the system (2.5), satisfying the following one-dimensional boundary-value problem:

$$\begin{aligned}
 D \frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m f(p_\varepsilon^*) \delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^* &= 0 \quad \text{in } (0, 1), \\
 D \frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p g(x) m_\varepsilon^* - \mu_p p_\varepsilon^* &= 0 \quad \text{in } (0, 1), \\
 \frac{dm_\varepsilon^*(0)}{dx} = \frac{dm_\varepsilon^*(1)}{dx} = 0, \quad \frac{dp_\varepsilon^*(0)}{dx} = \frac{dp_\varepsilon^*(1)}{dx} &= 0.
 \end{aligned}
 \tag{3.1}$$

The operators  $\tilde{\mathcal{A}}_{0,j} = (D \frac{d^2}{dx^2} - \mu_j)$ , for  $j = m, p$ , defined on the interval  $[0, 1]$  and subject to the Neumann boundary conditions,

$$\mathcal{D}(\tilde{\mathcal{A}}_{0,j}) = \{v \in H^2(0, 1) : v'(0) = 0, v'(1) = 0\}$$

are invertible and solutions of the problem (3.1) can be defined as

$$\begin{aligned} m_\varepsilon^*(x, D) &= \alpha_m \int_0^1 G_{\mu_m}(x, y) f(p_\varepsilon^*(y, D)) \delta_{x_M}^\varepsilon(y) dy, \\ p_\varepsilon^*(x, D) &= \alpha_m \alpha_p \int_0^1 g(z) G_{\mu_p}(x, z) \int_0^1 G_{\mu_m}(z, y) f(p_\varepsilon^*(y, D)) \delta_{x_M}^\varepsilon(y) dy dz, \end{aligned} \quad (3.2)$$

where

$$G_{\mu_j}(y, x) = \begin{cases} \frac{1}{(\mu_j D)^{1/2} \sinh(\theta_j)} \cosh(\theta_j y) \cosh(\theta_j(1-x)) & \text{for } 0 < y < x < 1, \\ \frac{1}{(\mu_j D)^{1/2} \sinh(\theta_j)} \cosh(\theta_j(1-y)) \cosh(\theta_j x) & \text{for } 0 < x < y < 1, \end{cases}$$

with  $\theta_j = (\mu_j/D)^{1/2}$ , for  $j = m, p$ , the Green's function satisfying the boundary-value problem

$$DG_{yy} - \mu_j G = -\delta_x \quad \text{in } (0, 1), \quad G_y(0, x) = G_y(1, x) = 0.$$

**Lemma 3.1.** *For  $\varepsilon$  small there exists a unique positive stationary solution of the model (2.5) satisfying the estimates*

$$\|m_\varepsilon^*\|_{H^1(0,1)} + \|m_\varepsilon^*\|_{C([0,1])} + \|p_\varepsilon^*\|_{H^2(0,1)} \leq C, \quad (3.3)$$

with a constant  $C$  independent of  $\varepsilon$ .

**Proof.** Due to the boundedness of  $f$  for non-negative  $p_\varepsilon^*$ , the continuous embedding of  $H^1(0, 1)$  into  $C([0, 1])$  and the properties of the Dirac sequence, we obtain for non-negative solutions of (3.1) the *a priori* estimates (3.3).

We rewrite the second equation in (3.2) as the fixed point problem

$$p_\varepsilon^*(x, D) = K(p_\varepsilon^*(x, D)), \quad (3.4)$$

with  $K(p) = \alpha_m \alpha_p (-\tilde{\mathcal{A}}_{0,p})^{-1} (g(-\tilde{\mathcal{A}}_{0,m})^{-1} (\delta_{x_M}^\varepsilon f(p)))$ , where  $K : C([0, 1]) \rightarrow C([0, 1])$  is compact, since  $(-\tilde{\mathcal{A}}_{0,j})^{-1}$ ,  $j = m, p$ , are compact. Consider a closed convex bounded subset  $\mathcal{Q} = \{p \in C([0, 1]) : 0 \leq p(x) \leq C + 1 \text{ for } x \in [0, 1]\}$  of  $C([0, 1])$ , where the constant  $C$  is as in estimates (3.3). The estimates (3.3) and the fact that  $K(p) > 0$  for  $p \geq 0$  imply  $p - K(p) \neq 0$  for  $p \in \partial\mathcal{Q}$ . Thus Leray–Schauder degree theory, e.g. Chap. 12.B in Ref. 63, guarantees the existence of a positive solution of (3.1). The linearized equations for (3.1) at the steady state  $(m_\varepsilon^*, p_\varepsilon^*)^T$

can be written as

$$\mathcal{A}u = 0, \tag{3.5}$$

where  $u = (u_1, u_2)^T$  and  $\mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$  with the operator  $\mathcal{A}_0$  given as

$$\mathcal{A}_0 = \begin{pmatrix} D \frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D \frac{d^2}{dx^2} - \mu_p \end{pmatrix}, \tag{3.6}$$

on the interval  $[0, 1]$ , subject to the Neumann boundary conditions,

$$\mathcal{D}(\mathcal{A}_0) = \{v \in H^2(0, 1) \times H^2(0, 1) : v'(0) = 0, v'(1) = 0\},$$

and the bounded operator

$$\mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p_\varepsilon^*(x, D)) \delta_{x_M}^\varepsilon(x) \\ \alpha_p g(x) & 0 \end{pmatrix}. \tag{3.7}$$

If for a solution  $u = (u_1, u_2)^T$  of (3.5) we have  $u_2(x) = 0$  in  $(x_M - \varepsilon, x_M + \varepsilon)$ , then  $u \equiv (0, 0)^T$  and  $\mathcal{A}$  is invertible. Suppose there exists a non-trivial solution of (3.5) with  $u_2(x) \neq 0$  in  $(x_M - \varepsilon, x_M + \varepsilon)$ . Using the continuity of  $u_2$ , we can assume  $u_2(x) > 0$  in  $(x_M - \varepsilon, x_M + \varepsilon)$  for small  $\varepsilon$ . Then, the properties of  $f$  along with the positivity of  $(-\tilde{\mathcal{A}}_{0,j})$ ,  $j = m, p$ , and of the steady state  $(m_\varepsilon^*, p_\varepsilon^*)^T$  ensure

$$u_2(x) - \alpha_m \alpha_p (-\tilde{\mathcal{A}}_{0,p})^{-1} (g(-\tilde{\mathcal{A}}_{0,m})^{-1} (f'(p_\varepsilon^*) \delta_{x_M}^\varepsilon u_2))(x) > 0,$$

for  $x \in (x_M - \varepsilon, x_M + \varepsilon)$ . This last inequality implies a contradiction, since  $u_2$  was a solution of (3.5). Therefore,  $\mathcal{A}$  is invertible for every  $D \in [d_1, d_2]$ . Thus for every fixed small  $\varepsilon > 0$  we have a family in  $D \in [d_1, d_2]$  of isolated positive stationary solutions  $(m_\varepsilon^*(x, D), p_\varepsilon^*(x, D))^T \in H^2(0, 1) \times H^2(0, 1)$  of (2.5).

The *a priori* estimates (3.3) imply the weak convergences  $m_\varepsilon^* \rightharpoonup m_0^*$  in  $H^1(0, 1)$  and  $p_\varepsilon^* \rightharpoonup p_0^*$  in  $H^2(0, 1)$   $\varepsilon \rightarrow 0$ . Using the compact embedding of  $H^1(0, 1)$  in  $C([0, 1])$  and of  $H^2(0, 1)$  in  $C^1([0, 1])$ , we have also strong convergence in  $C([0, 1])$  and in  $C^1([0, 1])$ , respectively, and  $m_0^*$  and  $p_0^*$  are defined by

$$\begin{aligned} m_0^*(x, D) &= \alpha_m G_{\mu_m}(x, x_M) f(p_0^*(x_M, D)), \\ p_0^*(x, D) &= \alpha_m \alpha_p f(p_0^*(x_M, D)) \int_0^1 g(y) G_{\mu_p}(x, y) G_{\mu_m}(y, x_M) dy, \end{aligned} \tag{3.8}$$

i.e. a solution of the model (3.1) with the delta distribution  $\delta_{x_M}$  instead of the Dirac sequence  $\delta_{x_M}^\varepsilon$ . Since  $x_M < l$  and  $g(y) = 0$  for  $0 \leq y < l$ , we have

$$G_{\mu_m}(y, x_M) = \frac{1}{(\mu_m D)^{1/2} \sinh(\theta_m)} \cosh(\theta_m(1 - y)) \cosh(\theta_m x_M), \quad x_M < y < 1,$$

where  $\theta_m = (\mu_m/D)^{1/2}$  and, using  $g(y) = 1$  for  $l \leq y \leq 1$ , we obtain

$$p_0^*(x, D) = \frac{\alpha_m \alpha_p f(p_0^*(x_M, D)) \cosh(\theta_m x_M)}{2\sqrt{\mu_m \mu_p} D \sinh(\theta_m) \sinh(\theta_p)} \\ \times \left[ \cosh(\theta_p(1-x)) \left( \frac{\sinh((\theta_p + \theta_m)y - \theta_m)}{\theta_p + \theta_m} \Big|_l^x + \frac{\sinh((\theta_p - \theta_m)y + \theta_m)}{\theta_p - \theta_m} \Big|_l^x \right)_{x>l} \right. \\ \left. - \cosh(\theta_p x) \left( \frac{\sinh((\theta_p + \theta_m)(1-y))}{\theta_p + \theta_m} + \frac{\sinh((\theta_p - \theta_m)(1-y))}{\theta_p - \theta_m} \right) \Big|_{\max\{x,l\}}^1 \right],$$

and for  $\theta_m = \theta_p = \theta$  (i.e.  $\mu_m = \mu_p = \mu$ ),

$$p_0^*(x, D) = \frac{\alpha_m \alpha_p f(p_0^*(x_M, D))}{2\mu D \sinh^2(\theta)} \cosh(\theta x_M) \\ \times \left[ \cosh(\theta(1-x)) \left( \cosh(\theta)y \Big|_l^x - \frac{1}{2\theta} \sinh(\theta(1-2y)) \Big|_l^x \right)_{x>l} \right. \\ \left. + \cosh(\theta x) \left( y \Big|_{\max\{x,l\}}^1 - \frac{1}{2\theta} \sinh(2\theta(1-y)) \Big|_{\max\{x,l\}}^1 \right) \right].$$

Using the Bolzano theorem or computing the roots of a polynomial by applying Maple or Matlab we obtain that the nonlinear equation with respect to  $p_0^*(x_M, D)$ ,

$$p_0^*(x_M, D) = f(p_0^*(x_M, D)) \frac{\alpha_p \alpha_m}{2} \frac{\cosh(\theta_m x_M) \cosh(\theta_p x_M)}{\sqrt{\mu_m \mu_p} D \sinh(\theta_m) \sinh(\theta_p)} \\ \times \left[ \frac{\sinh((\theta_p + \theta_m)(1-l))}{\theta_p + \theta_m} + \frac{\sinh((\theta_p - \theta_m)(1-l))}{\theta_p - \theta_m} \right], \quad (3.9)$$

for  $\theta_m \neq \theta_p$ , and for  $\theta_m = \theta_p (= \theta)$

$$p_0^*(x_M, D) = f(p_0^*(x_M, D)) \frac{\alpha_p \alpha_m}{4} \frac{\cosh^2(\theta x_M)}{\mu D \theta \sinh^2(\theta)} [2\theta(1-l) + \sinh(2\theta(1-l))] \quad (3.10)$$

has only one positive solution for all values of  $D \in [d_1, d_2]$ .

Thus, since  $m_0^*(x, D)$  and  $p_0^*(x, D)$  are uniquely defined by  $p_0^*(x_M, D)$ , for every  $D \in [d_1, d_2]$  we have a unique positive solution of (3.1) with  $\varepsilon = 0$ . Then the strong convergence of  $m_\varepsilon^* \rightarrow m_0^*$ ,  $p_\varepsilon^* \rightarrow p_0^*$  as  $\varepsilon \rightarrow 0$  in  $C([0, 1])$  and the fact that non-negative steady states  $(m_\varepsilon^*, p_\varepsilon^*)^T$  are isolated imply the uniqueness of the positive steady state of (2.5) for small  $\varepsilon > 0$ .  $\square$

To better understand the structure of the stationary solutions of (2.5) we can consider their structure under extreme values of the diffusion coefficient  $D$ . For very small diffusion coefficients  $D \ll 1$ , in the zero-order approximation we obtain

$$0 = \alpha_m f(p_\varepsilon^*) \delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^*, \quad 0 = \alpha_p g(x) m_\varepsilon^* - \mu_p p_\varepsilon^* \quad \text{in } (0, 1).$$

Since  $g(x) = 0$  for  $x \in [0, l)$ , the second equation yields that  $p_\varepsilon^*(x, D) = 0$  in  $[0, l)$  and thus  $m_\varepsilon^*(x, D) = \frac{\alpha_m}{\mu_m} \delta_{x_M}^\varepsilon(x)$  in  $[0, 1]$ . Using the fact that  $x_M \in (0, l)$  we obtain for sufficiently small  $\varepsilon > 0$  that  $m_\varepsilon^*(x, D) = 0$  for  $x \in [l, 1]$  and thus  $p_\varepsilon^*(x, D) = 0$  in  $[0, 1]$ . Therefore for very small  $D$  we have localization of mRNA concentration around  $x_M$ , whereas the concentration of protein is approximately zero everywhere in  $[0, 1]$ .

For large diffusion coefficients, i.e.  $D \gg 1$  and therefore  $1/D \ll 1$ , we have

$$\begin{aligned} 0 &= \frac{d^2 m_\varepsilon^*}{dx^2} + \frac{1}{D} (\alpha_m f(p_\varepsilon^*) \delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^*) && \text{in } (0, 1), \\ 0 &= \frac{d^2 p_\varepsilon^*}{dx^2} + \frac{1}{D} (\alpha_p g(x) m_\varepsilon^* - \mu_p p_\varepsilon^*) && \text{in } (0, 1), \\ \frac{dm_\varepsilon^*}{dx}(0) &= \frac{dm_\varepsilon^*}{dx}(1) = 0, && \frac{dp_\varepsilon^*}{dx}(0) = \frac{dp_\varepsilon^*}{dx}(1) = 0. \end{aligned}$$

Thus  $m_\varepsilon^*(x, D) \approx \text{constant}$  and  $p_\varepsilon^*(x, D) \approx \text{constant}$ .

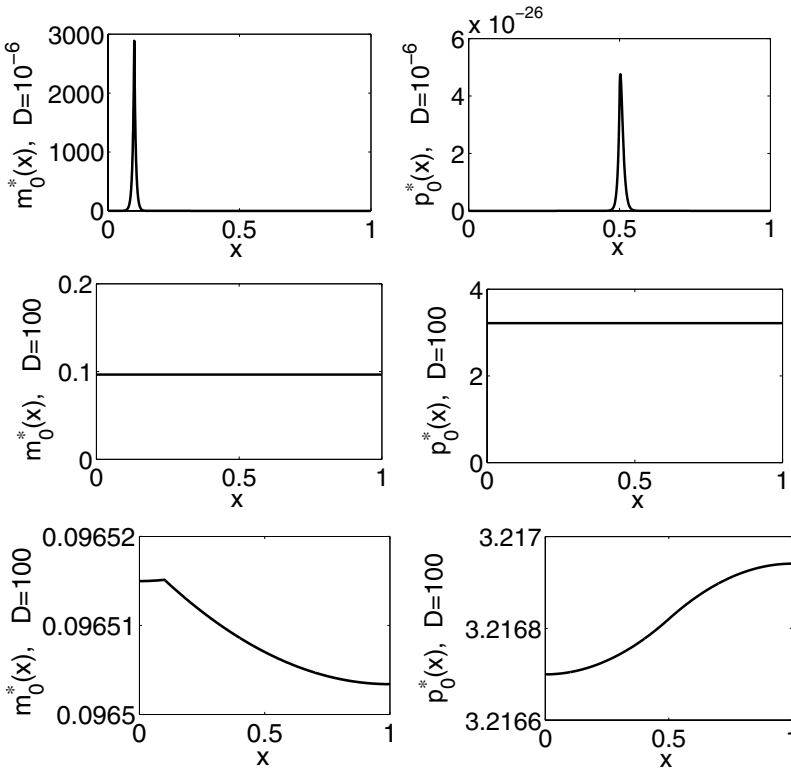


Fig. 6. Plots showing representative stationary solutions of the system (3.8), i.e. mRNA (left plot) and protein (right plot) steady-state concentrations, for  $D = 10^{-6}$  (top row) and  $D = 100$  (middle row, bottom row). The bottom row shows the stationary solution for  $D = 100$  at higher resolution. All other parameter values as given in Sec. 2.

Representative stationary solutions, calculated numerically from (3.8), in the cases  $D = 10^{-6} \ll 1$  and  $D = 100 \gg 1$  can be seen in Fig. 6, confirming the preceding analysis.

#### 4. Linearized Stability Analysis

To study the linearized stability of the positive steady-state solution of the nonlinear model (2.5) we apply Theorems 5.1.1 and 5.1.3 in Ref. 26. We write the system (2.5) in the Hilbert space  $X = L^2(0, 1) \otimes L^2(0, 1)$  as

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \quad (4.1)$$

where  $u = (m, p)^T$ , the operator  $\mathcal{A}_0$  is defined in (3.6) and  $\tilde{f}(u) = (\alpha_m f(p) \delta_{x_M}^\varepsilon(x), \alpha_p g(x) m)^T$ . The operator  $-\mathcal{A}_0$  is sectorial with  $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$ , where  $\mu = \min\{\mu_m, \mu_p\}$ , and we can introduce interpolation spaces  $X^s = ((-\mathcal{A}_0)^s)$ , each of which is a Hilbert subspace of  $H^{2s}(0, 1) \times H^{2s}(0, 1)$ . The function  $\tilde{f} : \mathbb{R}_+^2 \rightarrow \mathbb{R}_+^2$  is smooth and admits the representation

$$\tilde{f}(y + z) = \tilde{f}(y) + B(y)z + r(y, z),$$

where the remainder satisfies the estimate

$$\|r(y, z)\|_{\mathbb{R}^2} \leq C_\varepsilon(y) \|z\|_{\mathbb{R}^2}^2,$$

in a neighborhood of any point  $y \in \mathbb{R}_+^2$ , and

$$B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2) \delta_{x_M}^\varepsilon \\ \alpha_p g(x) & 0 \end{pmatrix}.$$

For a non-negative steady state  $u_\varepsilon^*(x, D) = (m_\varepsilon^*(x, D), p_\varepsilon^*(x, D))^T$ , with  $u_\varepsilon^* \in H^1(0, 1) \times H^2(0, 1)$ , we obtain that  $B(u_\varepsilon^*)$  is a bounded linear operator from  $X^s$  to  $X$  for each  $s \in (0, 1)$ . The estimate for the remainder implies

$$\|r(u_\varepsilon^*, z)\|_X \leq C_\varepsilon \|z\|_X^2 \leq C_\varepsilon \|z\|_{X^s}^2 = o(\|z\|_{X^s}) \rightarrow 0 \quad \text{as } \|z\|_{X^s} \rightarrow 0,$$

for every fixed  $\varepsilon > 0$ . Notice that for  $s \in [5/6, 1)$ , due to the properties of the Dirac sequence and the embedding of  $H^1(0, 1)$  into  $C([0, 1])$  and of  $H^{5/3}(0, 1)$  into  $C^1([0, 1])$ , we have the estimates for  $B$  and  $r$  independent of  $\varepsilon$ , i.e.

$$\|B(u_\varepsilon^*)z\|_X \leq C \|z\|_{X^s}, \quad \|r(u_\varepsilon^*, z)\|_X \leq C \|z\|_{X^s}^2,$$

with a constant  $C$  independent of  $\varepsilon$ .

Thus, all assumptions of Theorems 5.1.1 and 5.1.3 in Ref. 26 are satisfied and to analyze the linearized stability of the stationary solution of the system (2.5) we shall study the eigenvalue problem:

$$\begin{aligned} \lambda \bar{m}^\varepsilon &= D \bar{m}_{xx}^\varepsilon + \alpha_m f'(p_\varepsilon^*(x, D)) \delta_{x_M}^\varepsilon(x) \bar{p}^\varepsilon - \mu_m \bar{m}^\varepsilon && \text{in } (0, 1), \\ \lambda \bar{p}^\varepsilon &= D \bar{p}_{xx}^\varepsilon + \alpha_p g(x) \bar{m}^\varepsilon - \mu_p \bar{p}^\varepsilon && \text{in } (0, 1), \\ \bar{m}_x^\varepsilon(0) &= \bar{m}_x^\varepsilon(1) = 0, \quad \bar{p}_x^\varepsilon(0) = \bar{p}_x^\varepsilon(1) = 0, \end{aligned} \quad (4.2)$$



or in operator form

$$\mathcal{A}w^\varepsilon = \lambda w^\varepsilon, \tag{4.3}$$

where  $w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T$  and  $\mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$ , with  $\mathcal{A}_1$  defined in (3.7).

We can consider  $\mathcal{A}$  as the perturbation of the self-adjoint operator  $\mathcal{A}_0$  with compact resolvent by the bounded operator  $\mathcal{A}_1$ . Thus the spectrum of  $\mathcal{A}$  consists only of eigenvalues. Also the notion of relative boundedness<sup>34</sup> can be applied to  $\mathcal{A}_0$  and  $\mathcal{A}_1$ . Let  $T$  and  $S$  be operators with the same domain space  $\mathcal{H}$  such that  $\mathcal{D}(T) \subset \mathcal{D}(S)$  and

$$\|Su\| \leq a\|u\| + b\|Tu\|, \quad u \in \mathcal{D}(T),$$

where  $a, b$  are non-negative constants. We say that  $S$  is relatively bounded with respect to  $T$ , or simply  $T$ -bounded. Assume that  $T$  is closed and there exists a bounded operator  $T^{-1}$ , and  $S$  is  $T$ -bounded with constants  $a, b$  satisfying the inequality

$$a\|T^{-1}\| + b < 1.$$

Then,  $T + S$  is a closed and bounded invertible operator by Theorem 1.16 of Ref. 34.

With  $|f'(p_\varepsilon^*(x, D))| \leq 10\alpha_m$  for  $D \geq 1$  and  $|f'(p_\varepsilon^*(x, D))| \leq 10\alpha_m D$  for  $D < 1$ , where  $2 \leq h \leq 10$ , and  $|g(x)| \leq 1$  for all  $x \in (0, 1)$  we have the estimate for  $u \in \mathcal{D}(\mathcal{A}_0)$ :

$$\begin{aligned} \|\mathcal{A}_1 u\|_X &\leq \alpha_p \sup_{x \in (0,1)} |g(x)| \|m\|_{L^2(0,1)} + \alpha_m \sup_{x \in (0,1)} |f'(p_\varepsilon^*(x, D))| \|p\|_{H^{5/3}(0,1)} \\ &\leq \alpha_p \|u\|_X + 10\alpha_m \min\{D, 1\} \|u\|_{H^{5/3}(0,1)} \leq \kappa \|u\|_X + 1/4 \|(\mathcal{A}_0 - \lambda_0 I)u\|_X, \end{aligned} \tag{4.4}$$

for  $\mathcal{R}e(\lambda_0) \geq -\mu$ , with  $\mu = \min\{\mu_m, \mu_p\}$ , and constant  $\kappa$  independent of  $\varepsilon$  and  $D$ . Thus, we obtain that  $\mathcal{A}_1$  is relatively bounded with respect to  $\mathcal{A}_0 - \lambda_0 I$  with  $a = \kappa$  and  $b = 1/4$ . Since  $\mathcal{A}_0$  is self-adjoint, we have

$$\|(\mathcal{A}_0 - \lambda_0 I)^{-1}\| = \frac{1}{\text{dist}(\lambda_0, \sigma(\mathcal{A}_0))},$$

and conclude that  $\mathcal{A} - \lambda_0 I = \mathcal{A}_0 + \mathcal{A}_1 - \lambda_0 I$  is bounded and invertible for all  $\lambda_0$  such that  $\mathcal{R}e(\lambda_0) > -\mu$  and  $|\lambda_0| \geq 2\kappa$ . Therefore we have uniform boundedness of eigenvalues  $\lambda$  of the operator  $\mathcal{A}$  with  $\mathcal{R}e(\lambda) \geq 0$ .

For  $\lambda \in \mathbb{C}$  such that  $\mathcal{R}e(\lambda) > -\mu$  or  $\mathcal{I}m(\lambda) \neq 0$  we can solve the first equation in the eigenvalue problem (4.2) for  $\bar{m}^\varepsilon$ :

$$\bar{m}^\varepsilon(x) = \alpha_m (\lambda I - \tilde{\mathcal{A}}_{0,m})^{-1} (f'(p_\varepsilon^*(x, D)) \bar{p}^\varepsilon(x) \delta_{x_M}^\varepsilon(x)),$$

and obtain

$$\lambda \bar{p}^\varepsilon = D \frac{d^2 \bar{p}^\varepsilon}{dx^2} - \mu_p \bar{p}^\varepsilon + \alpha_p \alpha_m g(x) (\lambda I - \tilde{\mathcal{A}}_{0,m})^{-1} (f'(p_\varepsilon^*) \bar{p}^\varepsilon \delta_{x_M}^\varepsilon) \quad \text{in } (0, 1), \tag{4.5}$$

$$\bar{p}_x^\varepsilon(0) = \bar{p}_x^\varepsilon(1) = 0.$$

To determine the values of the parameter  $D$  for which the stationary solution becomes unstable, i.e. the spectrum of  $\mathcal{A}$  crosses the imaginary axis, we shall consider  $\lambda \in \sigma(\mathcal{A})$  such that  $\mathcal{R}e(\lambda) > -\mu$ , with  $\mu = \min\{\mu_m, \mu_p\}$ . Thus  $\lambda \notin \sigma(\tilde{\mathcal{A}}_{0,m})$  and eigenvalue problems (4.2) and (4.5) are equivalent.

To analyze the eigenvalue problem (4.5) further we consider the limit problem obtained from (4.5) as  $\varepsilon \rightarrow 0$ :

$$\begin{aligned} \lambda \bar{p} &= D \frac{d^2 \bar{p}}{dx^2} - \mu_p \bar{p} + \alpha_p \alpha_m g(x) G_{\lambda + \mu_m}(x, x_M) f'(p_0^*(x_M, D)) \bar{p}(x_M) \quad \text{in } (0, 1), \\ \frac{d\bar{p}}{dx}(0) &= \frac{d\bar{p}}{dx}(1) = 0. \end{aligned} \tag{4.6}$$

As in Ref. 9 we show that for small  $\varepsilon$  the stationary solution of (2.5) is stable if the limit eigenvalue problem (4.6) has no eigenvalues with  $\mathcal{R}e(\lambda) \geq 0$ .

**Lemma 4.1.** *If there exist eigenvalues of (4.2) with non-negative real part then such also exist for the limit eigenvalue problem (4.6).*

**Proof.** Assume it is not true. Due to the upper bound for the spectrum of the operator  $\mathcal{A}$ , shown above, we have that a subsequence  $\lambda_{\varepsilon_j}$  of eigenvalues of (4.5), with  $\mathcal{R}e(\lambda_{\varepsilon_j}) \geq 0$  and  $\varepsilon_j \rightarrow 0$  as  $j \rightarrow \infty$ , converges to  $\tilde{\lambda}$  as  $j \rightarrow \infty$  and  $\mathcal{R}e(\tilde{\lambda}) \geq 0$ .

For  $\varepsilon > 0$ , since  $p_\varepsilon^* \in H^2(0, 1)$ ,  $p_\varepsilon^*(x, D) \geq 0$  for  $x \in [0, 1]$  and  $D \in [d_1, d_2]$ , and  $f(p)$  is smooth and bounded for non-negative  $p$ , the regularity theory implies that  $(\bar{m}^\varepsilon, \bar{p}^\varepsilon) \in H^2(0, 1)^2$  and we can normalize the solutions so that  $\|\bar{m}^\varepsilon\|_{L^2(0,1)} + \|\bar{p}^\varepsilon\|_{L^2(0,1)} = 1$ . Considering in Eq. (4.2) such  $\lambda$  that  $|\lambda| \leq 2\kappa$ , using the normalization and continuous embedding of  $H^1(0, 1)$  in  $C([0, 1])$ , we obtain the estimates

$$\|\bar{p}^\varepsilon\|_{H^1(0,1)} \leq C_1, \quad \|\bar{p}^\varepsilon\|_{H^2(0,1)} \leq C_2, \quad \|\bar{m}^\varepsilon\|_{H^1(0,1)} \leq C_3(1 + \|\bar{p}^\varepsilon\|_{H^1(0,1)}),$$

where  $C_1, C_2$  and  $C_3$  are independent of  $\varepsilon$ . Using the compact embedding of  $H^1(0, 1)$  into  $C([0, 1])$  and of  $H^2(0, 1)$  into  $C^1([0, 1])$ , we conclude the convergences (up to a subsequence):

$$\begin{aligned} \bar{m}^\varepsilon &\rightharpoonup \bar{m} \quad \text{weakly in } H^1(0, 1) \quad \text{and strongly in } C([0, 1]), \\ \bar{p}^\varepsilon &\rightharpoonup \bar{p} \quad \text{weakly in } H^2(0, 1) \quad \text{and strongly in } C^1([0, 1]). \end{aligned}$$

Additionally for  $\lambda$  with  $\mathcal{R}e(\lambda) \geq 0$ , taking  $\mathcal{R}e(\bar{m}^\varepsilon) - i\mathcal{I}m(\bar{m}^\varepsilon)$  as a test function in the first equation in (4.2), using the regularity and boundedness of the stationary solution and considering the real part of the equation we obtain

$$D \left\| \frac{d\bar{m}^\varepsilon}{dx} \right\|_{L^2(0,1)}^2 + [\mathcal{R}e(\lambda) + \mu_m] \|\bar{m}^\varepsilon\|_{L^2(0,1)}^2 \leq \alpha_m \|\bar{m}^\varepsilon\|_{L^\infty(0,1)} \|\bar{p}^\varepsilon\|_{L^\infty(0,1)}. \tag{4.7}$$

The continuous embedding of  $H^1(0, 1)$  into  $C([0, 1])$  implies

$$\|\bar{m}^\varepsilon\|_{L^\infty(0,1)} \leq C \|\bar{p}^\varepsilon\|_{L^\infty(0,1)}. \tag{4.8}$$

Considering the strong convergence of  $\bar{p}^{\varepsilon_j}$  and  $p_{\varepsilon_j}^*$  in  $C([0, 1])$  and taking the limit as  $j \rightarrow \infty$  in (4.5) we obtain that  $(\tilde{\lambda}, \tilde{p})$  satisfies the eigenvalue problem (4.6). Since  $\lambda$  with  $\mathcal{R}e(\lambda) \geq 0$  does not belong to  $\sigma(\tilde{\mathcal{A}}_{0,p})$  we obtain from (4.5) that  $|\bar{p}^\varepsilon(x)| > 0$  in  $(x_M - \varepsilon, x_M + \varepsilon)$ . Then, due to the strong convergence of  $\bar{p}^{\varepsilon_j}$  in  $C^1([0, 1])$  we have that  $\tilde{p}(x_M) \neq 0$ . Otherwise, since for  $\tilde{\lambda}$  with  $\mathcal{R}e(\tilde{\lambda}) \geq 0$  yields  $\tilde{\lambda} \notin \sigma(\tilde{\mathcal{A}}_{0,p})$ , we would obtain  $\tilde{p}(x) = 0$  for all  $x \in [0, 1]$ . The last result together with the estimate (4.8) and convergence of  $\bar{m}^\varepsilon$  and  $\bar{p}^\varepsilon$  contradicts the normalization property  $\|\bar{m}\|_{L^2(0,1)} + \|\bar{p}\|_{L^2(0,1)} = 1$ . Thus  $\tilde{p}(x) \neq 0$  in  $(0, 1)$  and the problem (4.6) has non-trivial solution for  $\tilde{\lambda}$  with  $\mathcal{R}e(\tilde{\lambda}) \geq 0$ . Therefore, if there are eigenvalues of (4.5) with non-negative real part (equivalently eigenvalues with non-negative real part of (4.2)) then such also exist for (4.6).  $\square$

We define

$$\tilde{\mathcal{A}} = \begin{pmatrix} D \frac{d^2}{dx^2} - \mu_m & \alpha_m f'(p_0^*(x, D)) \delta_{x_M}(x) \\ \alpha_p g(x) & D \frac{d^2}{dx^2} - \mu_p \end{pmatrix}. \tag{4.9}$$

In a manner similar to Theorem 3 in Ref. 9, we show for the eigenvalue problem (4.2) the following result:

**Theorem 4.1.** (Cf. Ref. 9) *For small  $\varepsilon > 0$  we have that if  $\tilde{\lambda}$  is an eigenvalue of (4.6) with  $\mathcal{R}e(\tilde{\lambda}) > -\mu$ , where  $\mu = \min\{\mu_m, \mu_p\}$ , then there is an eigenvalue  $\lambda_\varepsilon$  of (4.2) with  $\lambda_\varepsilon$  near  $\tilde{\lambda}$  and  $\lambda_\varepsilon \rightarrow \tilde{\lambda}$  as  $\varepsilon \rightarrow \infty$ .*

**Proof.** The proof follows the same steps as in Theorem 3 and Lemma 4 of Ref. 9. In a manner similar to Refs. 2 and 9, the collective compactness of a set of operators is used to show the result of the theorem. Note that for  $\lambda$  with  $\mathcal{I}m(\lambda) \neq 0$  or for real  $\lambda$  with  $\lambda > -\mu$  the operator  $\tilde{\mathcal{A}}_{0,m} - \lambda = D \frac{d^2}{dx^2} - \mu_m - \lambda$  with zero Neumann boundary conditions is invertible. Thus, we have that  $\lambda$  is an eigenvalue of problem (4.2) if it is an eigenvalue of (4.5). We denote

$$W_\varepsilon(\lambda)h = \alpha_p \alpha_m g(x) \int_0^1 G_{\lambda+\mu_m}(x, y) f'(p_\varepsilon^*) \delta_{x_M}^\varepsilon(y) h(y) dy - \lambda h$$

for  $h \in E = C([0, 1])$ ,

and shall prove that for  $\lambda \in T = \{\lambda \in \mathbb{C}, \mathcal{R}e(\lambda) \geq -\mu + \vartheta, |\lambda| \leq \Theta\}$ , for some  $\Theta \geq 2\kappa, 0 < \vartheta < \mu/2$ , and  $\varepsilon > 0$  small,  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda)$  is a collectively compact set of operators on  $E$  and converges pointwise to  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)$  as  $\varepsilon \rightarrow 0$ , i.e.

$$(-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda_\varepsilon)h \rightarrow (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)h,$$

as  $\varepsilon \rightarrow 0$ , for every  $h \in E$ , if  $\lambda_\varepsilon \rightarrow \lambda$  as  $\varepsilon \rightarrow 0$ . Here

$$W_0(\lambda)h = \alpha_p \alpha_m g(x) G_{\lambda+\mu_m}(x, x_M) f'(p_0^*(x_M)) h(x_M) - \lambda h.$$

From the definition of  $W_\varepsilon(\lambda)$  and the properties of the function  $f$  and the Dirac sequence, as well as positivity of the stationary solution  $p_\varepsilon^*$ , follows the boundedness of  $W_\varepsilon$  on  $E$ , i.e.

$$\|W_\varepsilon(\lambda)h\|_E \leq C\|h\|_E \quad \text{for all } \lambda \in T,$$

with a constant  $C$  independent of  $\varepsilon$ . Then the compactness of  $(-\tilde{\mathcal{A}}_{0,p})^{-1}$  implies the collective compactness of  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda)$  for  $\lambda \in T$ . For  $h \in E$  and  $\lambda_\varepsilon \rightarrow \lambda$  as  $\varepsilon \rightarrow 0$ , using strong convergence of  $p_\varepsilon^*$  in  $C([0, 1])$ , we have that  $W_\varepsilon(\lambda_\varepsilon)h \rightarrow W_0(\lambda)h$  weakly in  $L^2(0, 1)$ . By the regularity of  $\tilde{\mathcal{A}}_{0,p}$  we have that  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda_\varepsilon)h \rightarrow (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)h$  weakly in  $H^2(0, 1)$  and thus, by the compact embedding of  $H^2(0, 1)$  into  $C([0, 1])$ , it follows that  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda_\varepsilon)h \rightarrow (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)h$  strongly in  $E$ . Notice that  $W_\varepsilon(\lambda)$  and  $W_0(\lambda)$ , for  $\mathcal{R}e(\tilde{\lambda}) > -\mu$  or  $\mathcal{I}m(\tilde{\lambda}) \neq 0$ , depend analytically on  $\lambda$ , i.e. as products and compositions of analytic functions in  $\lambda$ .

Since  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)$  is compact, we have that  $I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)$  is a Fredholm operator with index zero, see e.g. Ref. 5. Using the theory of Fredholm operators, for  $\tilde{\lambda}$  such that  $I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda})$  is not invertible, there exist closed subspaces  $M$  and  $Y$  of  $E$  such that  $E = \mathcal{N} \oplus M$  and  $E = \mathcal{R} \oplus Y$ , where  $\mathcal{N} = \mathcal{N}(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda}))$  and  $\mathcal{R} = \mathcal{R}(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda}))$ , for which  $\dim(Y) = \dim(\mathcal{N})$ . Let  $Q : E \rightarrow \mathcal{R}$  be the projection onto  $\mathcal{R}$  parallel to  $Y$ .

Now we shall prove that  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda)) : M \rightarrow \mathcal{R}$  is invertible if  $\lambda$  is near  $\tilde{\lambda}$  and  $\varepsilon$  is small. Since  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda)) = Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda)) - Q((-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda) - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\lambda))$ , this is a compact perturbation of a Fredholm operator of index zero and hence is a Fredholm operator of index zero, see e.g. Ref. 5. Then invertibility will follow if we show that  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda))$  has no kernel on  $M$  for small  $\varepsilon$  and  $\lambda$  near  $\tilde{\lambda}$ . We shall prove this by contradiction. Suppose that for a sequence  $(\varepsilon_j, \lambda_{\varepsilon_j})$  such that  $\lambda_{\varepsilon_j} \rightarrow \tilde{\lambda}$  and  $\varepsilon_j \rightarrow 0$  as  $j \rightarrow \infty$ , there exists  $z_{\varepsilon_j} \in M$  with  $\|z_{\varepsilon_j}\| = 1$  and

$$Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j}))z_{\varepsilon_j} = 0. \quad (4.10)$$

Due to the collective compactness property,  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j}) - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda})$  is compact and thus a subsequence of  $[(\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j}) - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda})]z_{\varepsilon_j}$  converges strongly in  $E$ . The latter together with the equality (4.10) ensures that  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda}))z_{\varepsilon_j}$  converges in  $E$ . By invertibility of  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda}))|_M$  we have that  $z_{\varepsilon_j} \rightarrow z$  in  $E$  as  $j \rightarrow \infty$  and, since  $M$  is closed,  $z \in M$  with  $\|z\| = 1$ . We can rewrite  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})z_{\varepsilon_j} = (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})z + (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})(z_{\varepsilon_j} - z)$ . Using the convergence of  $z_{\varepsilon_j}$ , and the uniform boundedness and collective compactness of  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})$  we obtain that  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})z_{\varepsilon_j} \rightarrow (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda})z$  in  $E$  as  $j \rightarrow \infty$ . Thus we can pass to the limit in (4.10) and obtain that  $z \in \mathcal{N}$ . This implies the contradiction since  $z \in M$  and  $\|z\| = 1$ . Therefore  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda))|_M$  is invertible for  $\lambda$  close to  $\tilde{\lambda}$  and small  $\varepsilon$ .

The convergence of  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j}))z_{\varepsilon_j}$  as well as invertibility of  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))|_M$  and of  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda}))|_M$  ensure that there exist  $\rho > 0$ ,  $j_0 > 0$  and  $\delta > 0$ , independent of  $\varepsilon$  and  $\lambda$ , such that

$$\inf\{\|Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))z\|, z \in M, \|z\| = 1, j \geq j_0, |\lambda - \tilde{\lambda}| \leq \delta\} \geq \rho.$$

Thus we have uniform boundedness of operators  $(Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda)))^{-1}$  mapping from  $\mathcal{R}$  to  $M$  by  $\rho^{-1}$  for  $\lambda$  close to  $\tilde{\lambda}$  and  $j \geq j_0$ . The collective compactness property of  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}$  and uniform boundedness of  $(Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda)))^{-1}$  imply also that for  $h \in \mathcal{R}$  we have  $(Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda_{\varepsilon_j})))^{-1}h \rightarrow (Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_0(\tilde{\lambda})))^{-1}h$  as  $j \rightarrow \infty$ ,  $\varepsilon_j \rightarrow 0$  and  $\lambda_{\varepsilon_j} \rightarrow \tilde{\lambda}$ , see Theorem I.6 in Ref. 2.

Now for  $\bar{p}^\varepsilon = k + q \in E$  with  $k \in \mathcal{N}$  and  $q \in M$  we rewrite the eigenvalue equation in (4.5) as  $(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))(k + q) = 0$  and applying projection operator to obtain  $Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))q = -Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))k$ . The invertibility of  $(Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda)))$  on  $M$  implies

$$q = -[Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))]^{-1}(Q(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda))k) = S_{\varepsilon_j}(\lambda)k.$$

By arguments from above  $S_{\varepsilon_j}(\lambda)$  are uniformly bounded with respect to  $\varepsilon_j$  and  $\lambda$  for all  $\lambda$  close to  $\tilde{\lambda}$  and  $j \geq j_0$ . Additionally, for each  $k \in \mathcal{N}$  we have  $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k \rightarrow S_0(\tilde{\lambda})k$  if  $\lambda_{\varepsilon_j} \rightarrow \tilde{\lambda}$  and  $\varepsilon_j \rightarrow 0$  as  $j \rightarrow \infty$ .

Thus the eigenvalue problem (4.5) is reduced to

$$Z_{\varepsilon_j}(\lambda)k = 0 \quad \text{for } k \in \mathcal{N}, \quad \text{where } Z_\varepsilon(\lambda) = (I - Q)(I - (-\tilde{\mathcal{A}}_{0,p})^{-1}W_\varepsilon(\lambda)(I + S_\varepsilon(\lambda))).$$

Due to collective compactness of  $(-\tilde{\mathcal{A}}_{0,p})^{-1}W_{\varepsilon_j}(\lambda)$  and convergence of  $S_{\varepsilon_j}(\lambda_{\varepsilon_j})$  we have that  $Z_{\varepsilon_j}(\lambda_{\varepsilon_j})k \rightarrow Z_0(\lambda)k$  if  $\lambda_{\varepsilon_j} \rightarrow \lambda$  and  $\varepsilon_j \rightarrow 0$  as  $j \rightarrow \infty$  for each fixed  $k \in \mathcal{N}$ . Since  $\mathcal{N}$  is finite-dimensional it follows that

$$\|Z_{\varepsilon_j}(\lambda_{\varepsilon_j}) - Z_0(\lambda)\| \rightarrow 0 \quad \text{as } j \rightarrow \infty.$$

Now the equation for eigenvalues is given by  $\det Z_{\varepsilon_j}(\lambda) = 0$ . The analyticity of  $W_0(\lambda)$  implies that  $Z_0(\lambda)$  is analytic in  $\lambda$ . Since  $\tilde{\mathcal{A}}$  has compact resolvent as relative bounded perturbation of the operator  $\mathcal{A}_0$  with compact resolvent, we have that spectrum of  $\tilde{\mathcal{A}}$  is discrete and consists of eigenvalues, see e.g. Ref. 34. This implies that  $Z_0(\lambda)$  is invertible for some  $\lambda \in T$  and, thus  $\det Z_0(\lambda)$  does not vanish identically on  $T$  and its zeros are isolated, i.e.  $\tilde{\lambda}$  is an isolated zero of the analytic function  $\det Z_0(\lambda)$ . Therefore the topological degree<sup>56</sup> of  $\det Z_0(\lambda)$  is positive in the neighborhood of  $\tilde{\lambda}$ . Using the uniform convergence  $\det Z_{\varepsilon_j}(\lambda_{\varepsilon_j}) \rightarrow \det Z_0(\lambda)$  as  $j \rightarrow \infty$  and homotopy invariance of the topological degree, this implies that the degree of  $\det Z_{\varepsilon_j}(\lambda_{\varepsilon_j})$  is equal to the degree of  $\det Z_0(\lambda)$  and is positive in the neighborhood of  $\tilde{\lambda}$  and small  $\varepsilon_j$ . Thus for small  $\varepsilon$  it follows that  $\det Z_\varepsilon(\lambda_\varepsilon)$  has a solution near  $\tilde{\lambda}$  and hence  $\mathcal{A}$  has an eigenvalue near  $\tilde{\lambda}$ .

Since  $W_\varepsilon(\lambda)$  and  $W_0(\lambda)$  are analytic in  $\lambda$ , the sum of multiplicities of the eigenvalues of  $\mathcal{A}$  near  $\tilde{\lambda}$  is equal to the multiplicity of the eigenvalue  $\tilde{\lambda}$  of (4.6).<sup>9</sup>  $\square$

## 5. Hopf Bifurcation Analysis

In this section, we shall prove the existence of a Hopf bifurcation for the model (2.5) by showing that all conditions of the Hopf bifurcation theorem are satisfied, see e.g. Refs. 7, 31 and 36. For ease of calculation and presentation, here we consider the special case  $\mu_m = \mu_p = \mu$  and  $\mu > 0$ . However, the approach can be modified for the general case  $\mu_m \neq \mu_p$ , with  $\mu_m, \mu_p > 0$ , and the results hold also for this case.

**Theorem 5.1.** *For  $\varepsilon > 0$  small there exist two critical values of the parameter  $D$ , i.e.  $D_{1,\varepsilon}^c$  and  $D_{2,\varepsilon}^c$ , for which a Hopf bifurcation occurs in the model (2.5).*

**Proof.** For  $\varepsilon > 0$  small using Lemma 4.1 and Theorem 4.1 or Theorem 3 in Ref. 9 we obtain that for an eigenvalue  $\tilde{\lambda}$  of (4.6) with  $\mathcal{R}e(\tilde{\lambda}) > -\mu$  or  $\mathcal{I}m(\tilde{\lambda}) \neq 0$  there is an eigenvalue of (4.2) near  $\tilde{\lambda}$ . Also, if (4.2) has an eigenvalue  $\lambda$  with  $\mathcal{R}e(\lambda) > 0$ , then also (4.6) has an eigenvalue with positive real part.

Therefore, if for some  $D \in [d_1, d_2]$  the problem (4.6) does not have eigenvalues with non-negative real parts, then so also for the eigenvalues of (4.2). And, if for some  $D \in [d_1, d_2]$  problem (4.6) has an eigenvalue  $\tilde{\lambda}$  with  $\mathcal{R}e(\tilde{\lambda}) > 0$  then for small  $\varepsilon > 0$  we have in a neighborhood of  $\tilde{\lambda}$  eigenvalues of (4.2) with positive real part.

First we analyze the eigenvalue problem (4.6) (with  $\mu_m = \mu_p = \mu > 0$ ) for small and large values of the bifurcation parameter  $D$ . We rewrite (4.6) as

$$\begin{aligned} \frac{\lambda}{D}\bar{p} &= \frac{d^2\bar{p}}{dx^2} - \frac{\mu}{D}\bar{p} \\ &+ \frac{\alpha_p\alpha_m}{D}g(x)G_{\lambda+\mu}(x, x_M) \times f'(p_0^*(x_M, D))\bar{p}(x_M) \quad \text{in } (0, 1), \end{aligned} \quad (5.1)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0.$$

For  $\hat{\mathcal{A}}_0 = \frac{d^2}{dx^2} - \frac{\mu}{D}I$ , we have that

$$\|(\hat{\mathcal{A}}_0 - \lambda_0)^{-1}\| \leq \frac{1}{\text{dist}(\lambda_0, \sigma(\hat{\mathcal{A}}_0))} = \frac{2D}{\mu} \quad \text{for all } \lambda_0 \text{ with } \mathcal{R}e(\lambda_0) \geq -\frac{\mu}{2D}.$$

Since  $2x_M < 1$  for small  $D$  we have the estimate

$$p_0^*(x_M, D)(1 + (p_0^*(x_M, D))^h) = \frac{\alpha_p\alpha_m}{4} \frac{\cosh^2(\theta x_M)}{\mu D \theta \sinh^2(\theta)} [\theta + \sinh(\theta)] \leq e^{-\delta_1 D^{-\frac{1}{2}}},$$

with some constant  $\delta_1$ . Using the fact that  $g(x) = 0$  for  $x \in (0, l)$  and  $x_M < l$  we obtain

$$\begin{aligned} \|\hat{\mathcal{A}}_1\bar{p}\|_{L^2(0,1)} &= \left\| \frac{\alpha_p\alpha_m}{D}g(x)G_{\lambda+\mu}(x, x_M)f'(p_0^*(x_M, D))\bar{p}(x_M) \right\|_{L^2(0,1)} \\ &\leq C_1 \frac{(p_0^*(x_M, D))^{h-1}}{D} \|\bar{p}\|_{H^1(0,1)} \leq \frac{C_2 e^{-\delta_2 D^{-\frac{1}{2}}}}{D} \|\bar{p}\|_{H^1(0,1)} \\ &\leq \frac{\mu}{4D} \|\bar{p}\|_{L^2(0,1)} + \frac{1}{4} \|(\hat{\mathcal{A}}_0 - \lambda_0)\bar{p}\|_{L^2(0,1)}, \end{aligned}$$

for sufficiently small  $D$ ,  $\mathcal{R}e(\lambda_0) \geq -\frac{\mu}{2D}$  and  $h > 1$ . Hence, the operator  $\hat{\mathcal{A}}_1$  is  $(\hat{\mathcal{A}}_0 - \lambda_0)$ -bounded with  $a = \frac{\mu}{4D}$  and  $b = \frac{1}{4}$ . Therefore,  $\hat{\mathcal{A}}_0 + \hat{\mathcal{A}}_1 - \lambda_0$  is invertible for all  $\lambda_0$  with  $\mathcal{R}e(\lambda_0) \geq -\frac{\mu}{2D}$ . Hence, for  $D$  sufficiently small  $\mathcal{A}_0 + \mathcal{A}_1 - \lambda I$  is invertible for all  $\lambda$  with  $\mathcal{R}e(\lambda) \geq -\frac{\mu}{2}$ .

For large  $D$  we have the estimate

$$\begin{aligned} \|\hat{\mathcal{A}}_1 \bar{p}\|_{L^2(0,1)} &= \left\| \frac{\alpha_p \alpha_m}{D} g(x) G_{\lambda+\mu}(x, x_M) f'(p_0^*(x_M, D)) \bar{p}(x_M) \right\|_{L^2(0,1)} \\ &\leq \frac{1}{D} \|\bar{p}\|_{H^1(0,1)} \leq \frac{2}{D\mu} \left\| \frac{d^2 \bar{p}}{dx^2} \right\|_{L^2(0,1)} + \frac{\mu}{4D} \|\bar{p}\|_{L^2(0,1)}. \end{aligned}$$

Then for sufficient large  $D$  we have that  $\frac{2}{D\mu} \leq \frac{1}{4}$  and

$$\|\hat{\mathcal{A}}_1 \bar{p}\|_{L^2(0,1)} \leq a \|\bar{p}\|_{L^2(0,1)} + b \|(\hat{\mathcal{A}}_0 - \lambda_0) \bar{p}\|_{L^2(0,1)} \quad \text{with } a = \frac{\mu}{4D} \quad \text{and } b = \frac{1}{4},$$

where  $\mathcal{R}e(\lambda_0) \geq -\frac{\mu}{2D}$ . Therefore, we have  $a \|(\hat{\mathcal{A}}_0 - \lambda_0)^{-1}\| + b = \frac{\mu}{4D} \frac{2D}{\mu} + \frac{1}{4} < 1$  and for sufficiently large  $D$  the real part of the eigenvalues of  $\mathcal{A}_1 + \mathcal{A}_0$  is bounded from above by  $-\frac{\mu}{2}$ .

This analysis together with Lemma 4.1 and Theorem 4.1 or Theorem 3 in Ref. 9 ensures that for large and small values of the bifurcation parameter  $D$  all eigenvalues  $\lambda$  of (4.2) have negative real part, i.e.  $\mathcal{R}e(\lambda) \leq -\frac{\mu}{4}$ , and the non-negative steady state solution of (2.5) is stable. We note that a similar analysis can be carried out in the case  $\mu_m \neq \mu_p$ , with  $\mu = \min\{\mu_m, \mu_p\}$ .

Next we show that there exists a value of  $D$  for which the operator  $\mathcal{A}$  has an eigenvalue with positive real part. Then the continuous dependence of eigenvalues on the bifurcation parameter  $D$  along with the fact that  $0 \notin \sigma(\mathcal{A})$  implies that there exist two critical values of  $D$  for which the operator  $\mathcal{A}$  has purely imaginary eigenvalues.

Using the fact  $\lambda \notin \sigma(\tilde{\mathcal{A}}_0)$  and applying  $(\lambda I - \tilde{\mathcal{A}}_0)^{-1}$  in (4.6), where  $\tilde{\mathcal{A}}_0 = \tilde{\mathcal{A}}_{0,m} = \tilde{\mathcal{A}}_{0,p}$  for  $\mu_m = \mu_p = \mu$ , yields

$$\bar{p}(x) = \alpha_p \alpha_m f'(p_0^*(x_M, D)) \bar{p}(x_M) \int_0^1 g(y) G_{\lambda+\mu}(x, y) G_{\lambda+\mu}(y, x_M) dy. \quad (5.2)$$

Considering  $x_M < l$ , as well as  $g(x) = 0$  for  $x < l$  and  $g(x) = 1$  for  $l \leq x \leq 1$  implies

$$\begin{aligned} \bar{p}(x) &= \frac{\alpha_m \alpha_p f'(p_0^*(x_M, D))}{(\mu + \lambda) D \sinh^2(\theta_\lambda)} \bar{p}(x_M) \cosh(\theta_\lambda x_M) \\ &\times \left[ \cosh(\theta_\lambda(1-x)) \left( \frac{1}{2} \cosh(\theta_\lambda) y \Big|_l^x - \frac{1}{4\theta_\lambda} \sinh(\theta_\lambda(1-2y)) \Big|_l^x \right) \right]_{x>l} \\ &+ \cosh(\theta_\lambda x) \left( \frac{1}{2} y \Big|_{\max\{x,l\}}^1 - \frac{1}{4\theta_\lambda} \sinh(2\theta_\lambda(1-y)) \Big|_{\max\{x,l\}}^1 \right), \quad (5.3) \end{aligned}$$

where  $\theta_\lambda = ((\mu + \lambda)/D)^{1/2}$ . Then for  $x = x_M < l$ , where  $l = 1/2$ , we have

$$\bar{p}(x_M) = \frac{\alpha_p \alpha_m}{4} \bar{p}(x_M) f'(p_0^*(x_M, D)) \frac{\cosh^2(\theta_\lambda x_M)}{D(\mu + \lambda) \sinh^2(\theta_\lambda)} \left[ 1 + \frac{1}{\theta_\lambda} \sinh(\theta_\lambda) \right]. \quad (5.4)$$

If  $\bar{p}(x_M) = 0$  and  $\lambda \notin \sigma(\tilde{\mathcal{A}}_0)$  we have  $\bar{p}(x) = 0$  for all  $x \in (0, 1)$ . Therefore, in the context of the analysis of the instability of stationary solutions of the model (2.5), i.e. for  $\lambda \in \sigma(\mathcal{A})$  such that  $\mathcal{R}e(\lambda) \geq 0$ , we can assume that  $\bar{p}(x_M) \neq 0$ . Now dividing both sides of Eq. (5.4) by  $\bar{p}(x_M)$  we obtain a nonlinear equation for eigenvalues  $\lambda$  in terms of the stationary solution and parameters in the model

$$\begin{aligned} R(\lambda) &= \frac{\alpha_p \alpha_m}{4} f'(p_0^*(x_M, D)) \cosh^2(\theta_\lambda x_M) [\theta_\lambda + \sinh(\theta_\lambda)] - \theta_\lambda D(\mu + \lambda) \sinh^2(\theta_\lambda) \\ &= 0, \end{aligned} \quad (5.5)$$

where the value of the stationary solution  $p_0^*(x_M, D)$  is defined by (3.10). We note that a similar analysis can be carried out for the case  $\mu_m \neq \mu_p$  which produces a similar but more unwieldy formula to (5.5).

To show that the limit problem (4.6) has an eigenvalue with positive real part for some  $D$ , we show that for some  $D$  there exists a solution of Eq. (5.5) with  $\mathcal{R}e(\lambda) > 0$ . We consider  $\tilde{R}(\tilde{\lambda}) : B_r(0) \rightarrow \mathbb{C}$ , where  $B_r(0) = \{z \in \mathbb{C} : |z| \leq r\}$ ,  $\lambda = r + ib + \tilde{\lambda}$  and  $\tilde{R}(\tilde{\lambda}) = R(r + ib + \tilde{\lambda})$ , and apply the Brouwer degree theory to  $\tilde{R}$ . We show that the winding number<sup>59</sup> of  $\Phi(t) = \tilde{R}(re^{it}) = R(r + ib + re^{it})$  for  $t \in [0, 2\pi]$  is nonzero. Considering  $D \in [5 \cdot 10^{-4}, 5 \cdot 10^{-3}]$ , a large value of the radius  $r$ , e.g.  $r = 60$ , and varying  $b \in [0, 0.75]$ , we obtain  $\Phi(t) \neq 0$  for  $t \in [0, 2\pi]$  and the winding number

$$W(\Phi) = \frac{1}{2\pi i} \int_0^{2\pi} \frac{\Phi'(t)}{\Phi(t)} dt = 2.$$

Thus, since the eigenvalue problem (4.6) has real coefficients and the function  $\tilde{R}(\tilde{\lambda})$  is complex analytic, for any  $b \in [0, 0.75]$  there exist exactly two eigenvalues<sup>73</sup>  $\tilde{\lambda}_0, \overline{\tilde{\lambda}_0} \in \{z \in \mathbb{C} : |z| < r\}$  such that  $\tilde{R}(\tilde{\lambda}_0) = 0$  and  $\tilde{R}(\overline{\tilde{\lambda}_0}) = 0$ . Hence there exist  $\lambda_0$  and  $\overline{\lambda_0}$  with  $\mathcal{R}e(\lambda_0) > 0$  satisfying  $R(\lambda_0) = 0$  and  $R(\overline{\lambda_0}) = 0$ .

Now we show that all criteria for the existence of a local Hopf bifurcation<sup>7,31,36</sup> are satisfied by the system (2.5) for small  $\varepsilon > 0$ . Since for  $p \geq -\theta$ , with  $0 < \theta < 1$ ,  $f$  is a smooth function with respect to  $p$ , we can write (2.5) as

$$\partial_t \tilde{u} = \mathcal{A} \tilde{u} + F(\tilde{u}, D),$$

where  $\tilde{u} = (\tilde{m}, \tilde{p})^T$  with  $\tilde{m} = m - m_\varepsilon^*$ ,  $\tilde{p} = p - p_\varepsilon^*$ , and  $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p_\varepsilon^*) - f(p_\varepsilon^*) - f'(p_\varepsilon^*)\tilde{p})\delta_{x_M}^\varepsilon(x), 0)^T$ .

We have that  $\mathcal{A} = \mathcal{A}(D)$  is linear in  $D$ . Since  $p_\varepsilon^* = p_\varepsilon^*(D)$  is smooth function for  $D > 0$ , we have  $F \in C^2(U \times (\underline{D}, \overline{D}))$ , for  $U \subset \mathbb{R} \times (-1, \infty)$ , such that



$u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*) \in U$ , and some  $0 < \underline{D} < d_1$  and  $\overline{D} > d_2$ . Additionally we have  $F(0, D) = 0$ ,  $\partial_{\bar{m}}F(0, D) = 0$ , and  $\partial_{\bar{p}}F(0, D) = 0$  for  $D \in (\underline{D}, \overline{D})$ .

The properties of the operator  $\mathcal{A}_0$  and the assumption on the function  $f$  ensure that  $-\mathcal{A}$ , as a bounded perturbation of a self-adjoint sectorial operator, is the infinitesimal generator of a strongly continuous analytic semigroup  $T(t)$  on  $L^2(0, 1)$ ,<sup>34,57</sup> and  $(\lambda I - \mathcal{A})^{-1}$  is compact for  $\lambda$  in the resolvent set of  $\mathcal{A}$  for all values of  $D \in (\underline{D}, \overline{D})$ .

From the analysis above and applying Theorem 4.1 or Theorem 3 in Ref. 9, we conclude that there exist two critical values  $D_1^c$  and  $D_2^c$  of the bifurcation parameter  $D$  such that for small  $\varepsilon$ , all eigenvalues  $\lambda_\varepsilon$  of (4.2) have  $\mathcal{R}e(\lambda_\varepsilon) < 0$  for  $D < D_1^c$  and  $D > D_2^c$  and there exist eigenvalues with  $\mathcal{R}e(\lambda_\varepsilon) > 0$  for  $D_1^c < D < D_2^c$ . As shown in the proof of Lemma 3.1 we have  $0 \notin \sigma(\mathcal{A})$ . This together with continuous dependence of eigenvalues on the parameter  $D$  implies that for small  $\varepsilon > 0$  there are two critical values of  $D$ , i.e.  $D_{1,\varepsilon}^c$  and  $D_{2,\varepsilon}^c$ , close to  $D_1^c$  and  $D_2^c$ , for which we have a pair of purely imaginary eigenvalues  $\lambda_{j,\varepsilon}^c(D_{j,\varepsilon}^c)$  and  $\overline{\lambda_{j,\varepsilon}^c(D_{j,\varepsilon}^c)}$  for the original operator  $\mathcal{A}$ , i.e. solutions of the eigenvalue problem (4.2). We have also that there no eigenvalues of (4.2) with positive real part for  $D \leq D_{1,\varepsilon}^c$  and  $D \geq D_{2,\varepsilon}^c$ .

The fact that  $\lambda_{j,\varepsilon}(D)$  are isolated (as zeros of an analytic function with respect to  $D$  and  $\lambda$ , see proof of Theorem 4.1) implies that the eigenvalues  $\lambda_{j,\varepsilon}^c(D)$  and  $\overline{\lambda_{j,\varepsilon}^c(D)}$  of the problem (4.2) cross the imaginary axis with nonzero speed as the bifurcation parameter  $D$  increases from  $D < D_{j,\varepsilon}^c$  to  $D > D_{j,\varepsilon}^c$ , where  $j = 1, 2$ .

Then the theorem by Ref. 31, ensures the existence in the neighborhood of  $(m_\varepsilon^*, p_\varepsilon^*, D_{j,\varepsilon}^c)$  of a one-parameter family of periodic solutions of the system (2.5), bifurcating from the stationary solution starting from  $(m_\varepsilon^*, p_\varepsilon^*, D_{j,\varepsilon}^c, T_j^0)$ , where  $T_j^0 = 2\pi/\mathcal{I}m(\lambda_{j,\varepsilon}^c)$  with  $j = 1, 2$ , and the period is a continuous function of  $D$ .

To determine the approximate values of  $D_{1,\varepsilon}^c$  and  $D_{2,\varepsilon}^c$  we solve the algebraic equation (5.5) numerically (with parameters as given in Sec. 2). The estimates (4.4) for  $\mathcal{A}$  yield the upper bound for eigenvalues of  $\mathcal{A}$ , i.e.  $|\lambda| \leq 2\kappa$  for  $\mathcal{R}e(\lambda) \geq -\mu$ . Considering the structure of the stationary solution we estimate  $2\kappa \leq 35$  for  $D \in [d_1, d_2]$ . Since the operator  $\mathcal{A}$  is real, we can consider only eigenvalues with positive complex part and the corresponding complex conjugate values will also be eigenvalues. Using Matlab and applying Newton’s method with initial guesses in  $[-5, 35] \times [0, 35]$  with step 0.001 we solved Eq. (5.5) numerically and found two critical values of the bifurcation parameter  $D_1^c \approx 3.117109 \times 10^{-4}$  and  $D_2^c \approx 7.884712 \times 10^{-3}$ , for which we have a pair of purely imaginary eigenvalues  $\lambda_1^c \approx 17.6411537 \times 10^{-3}i$  and  $\overline{\lambda_1^c}$  and  $\lambda_2^c \approx 51.2345925 \times 10^{-3}i$  and  $\overline{\lambda_2^c}$  satisfying (5.5). We showed numerically that for both critical values of the bifurcation parameter all other eigenvalues of (4.6) have negative real part. From numerical simulations of Eq. (5.5), we obtain also that there are no eigenvalues  $\tilde{\lambda}$  of (4.6) with  $\mathcal{R}e(\tilde{\lambda}) \geq 0$  for  $D < D_1^c$  and for  $D > D_2^c$ , and there exist eigenvalues with positive real part for  $D_1^c < D < D_2^c$ . We also obtained numerically that for  $D$  such that  $D_1^c < D < D_2^c$  and close to the critical values, there is only one pair of complex conjugate eigenvalues with positive real part satisfying (5.5).

We verify the simplicity of the purely imaginary eigenvalues by computing the derivative of  $R(\lambda)$  in (5.5) with respect to  $\lambda$ , evaluated at  $\lambda_1^c$  and  $\lambda_2^c$ :

$$R'(\lambda) = \frac{\alpha_m \alpha_p f'(p^*(x_M, D))}{8(\mu + \lambda)^{\frac{1}{2}} D^{\frac{1}{2}}} [\sinh(2\theta_\lambda x_M) x_M (\theta_\lambda + \sinh(\theta_\lambda)) \\ + \cosh^2(\theta_\lambda x_M) (1 + \cosh(\theta_\lambda))] - \frac{1}{2} [3D\theta_\lambda \sinh^2(\theta_\lambda) + (\mu + \lambda) \sinh(2\theta_\lambda)].$$

Simple algebraic calculations using Matlab (or Maple) give  $R'(\lambda_1^c) \approx -3.347 \times 10^6 + 9.901 \times 10^5 i$ ,  $R'(\lambda_2^c) \approx 1.848 + 0.647i$  and thus the simplicity of  $\lambda_j^c$ ,  $\bar{\lambda}_j^c$ , with  $j = 1, 2$ .

To prove the transversality condition we determine the derivative of the eigenvalues with respect to the parameter  $D$ . Differentiation of (5.5) implies:

$$\frac{d\lambda}{dD}(D, \lambda) = \left( f''(p_0^*(x_M, D)) \frac{\partial p_0^*(x_M, D)}{\partial D} \cosh(\theta_\lambda x_M) \left[ 1 + \frac{\sinh(\theta_\lambda)}{\theta_\lambda} \right] + \frac{f'(p_0^*)}{D} \right. \\ \times \left[ \cosh(\theta_\lambda x_M) \left[ \frac{\theta_\lambda \cosh(\theta_\lambda)}{\sinh(\theta_\lambda)} + \frac{\cosh(\theta_\lambda)}{2} - 1 - \frac{D^{\frac{1}{2}} \sinh(\theta_\lambda)}{2(\mu + \lambda)^{\frac{1}{2}}} \right] \right. \\ \left. \left. - x_M \sinh(\theta_\lambda x_M) (\theta_\lambda + \sinh(\theta_\lambda)) \right] \right) \left( f'(p_0^*) \left[ \frac{\cosh(\theta_\lambda x_M)}{2(\mu + \lambda)} \right] \right. \\ \times \left[ \frac{(\mu + \lambda)^{\frac{1}{2}} \cosh(\theta_\lambda)}{D^{\frac{1}{2}} \sinh(\theta_\lambda)} + \cosh(\theta_\lambda) + \frac{3 \sinh(\theta_\lambda)}{\theta_\lambda} + 2 \right] \\ \left. \left. - x_M \frac{\sinh(\theta_\lambda x_M)}{\mu + \lambda} \left[ \frac{(\mu + \lambda)^{\frac{1}{2}}}{D^{\frac{1}{2}}} + \sinh(\theta_\lambda) \right] \right] \right)^{-1},$$

where  $\theta_\lambda = (\frac{\mu + \lambda}{D})^{\frac{1}{2}}$ . The derivative of the stationary solution with respect to the bifurcation parameter  $D$  evaluated at  $x_M$  is as follows:

$$\frac{\partial p_0^*(x_M, D)}{\partial D} = \frac{\alpha_p \alpha_m \cosh(\theta x_M) \sinh^{-2}(\theta)}{4\mu D^{\frac{3}{2}} [1 + (h+1)(p_0^*(x_M, D))^h]} \\ \times \left( \cosh(\theta x_M) \left[ \frac{\mu^{\frac{1}{2}} \cosh(\theta)}{D \sinh(\theta)} - \frac{1}{D^{\frac{1}{2}}} - \frac{\sinh(\theta)}{2\mu^{\frac{1}{2}}} + \frac{\cosh(\theta)}{2D^{\frac{1}{2}}} \right] \right. \\ \left. - x_M \sinh(\theta x_M) \left[ \frac{\mu^{\frac{1}{2}}}{D} + \frac{\sinh(\theta)}{D^{\frac{1}{2}}} \right] \right),$$

where  $\theta = (\frac{\mu}{D})^{\frac{1}{2}}$ . We evaluate the derivative  $\frac{d\lambda}{dD}$  at the two critical parameter values  $D_1^c$  and  $D_2^c$  and the corresponding purely imaginary eigenvalues  $\lambda_1^c$  and  $\lambda_2^c$ . The values obtained are:

$$\frac{d\lambda}{dD}(D_1^c, \lambda_1^c) \approx 70.613 + 47.159i \quad \text{and} \quad \frac{d\lambda}{dD}(D_2^c, \lambda_2^c) \approx -0.681 + 1.696i.$$

Thus  $\text{Re}(\frac{d\lambda}{dD}|_{D_j^c, \lambda_j^c}) \neq 0$  and the eigenvalues  $(\lambda_j^c(D), \bar{\lambda}_j^c(D))$  cross the imaginary axes with nonzero speed, where  $j = 1, 2$ .

The simplicity of eigenvalues  $\lambda_j^c$  of (4.6), the fact that (4.6) has only one pair of complex conjugates eigenvalues with positive real part for  $D_1^c < D < D_2^c$ , close to the critical values, continuous dependence of eigenvalues  $\lambda$  and  $\lambda_\varepsilon$  on  $D$  and  $\varepsilon$  together with Theorem 4.1 or Theorem 3 in Ref. 9 ensure the simplicity of  $\lambda_{j,\varepsilon}^c$  and  $\overline{\lambda_{j,\varepsilon}^c}$  as well as  $\pm n\lambda_{j,\varepsilon}^c \notin \sigma(\mathcal{A})$  for  $n = 2, 3, 4, \dots$ , where  $j = 1, 2$ .

Finally, we note that combining the previous analytical and numerical results yields that all conditions of the Hopf bifurcation theorem, see e.g. Refs. 7 and 36, are satisfied (i.e. simplicity of the purely imaginary eigenvalues and  $\pm n\lambda_{j,\varepsilon}^c \notin \sigma(\mathcal{A})$  in addition to the assumptions in the Ize theorem<sup>31</sup>). □

### 6. Stability of the Hopf Bifurcation

In this section, we analyze the stability of periodic orbits bifurcating from the stationary solution at the two critical values of the bifurcation parameter,  $D_{1,\varepsilon}^c$  and  $D_{2,\varepsilon}^c$ . The stability of the Hopf bifurcation we show by applying two methods, i.e. techniques from weakly nonlinear analysis and the central manifold theory. The method of nonlinear analysis distinguishes between fast and slow time scales in the dynamics of solutions near the steady state. The fast time scale corresponds to the interval of time where the linearized stability analysis is valid, whereas at the slow time scale the effects of the nonlinear terms become important.

**Theorem 6.1.** *At both critical values of the bifurcation parameter,  $D_{1,\varepsilon}^c$  and  $D_{2,\varepsilon}^c$ , a supercritical Hopf bifurcation occurs in the system (2.5) and the family of periodic orbits bifurcating from the stationary solution at each Hopf bifurcation point is stable.*

**Proof.** We consider a perturbation analysis in the neighborhood of the critical parameter value  $D = D_{j,\varepsilon}^c + \delta^2\nu + \dots$ , where  $\nu = \pm 1$ , and the corresponding small perturbation of the critical eigenvalues  $\lambda_{j,\varepsilon}(D) = \lambda_{j,\varepsilon}^c + \frac{\partial \lambda_{j,\varepsilon}}{\partial D} \delta^2\nu + \dots$ , where  $\delta > 0$  is a small parameter and  $j = 1, 2$ . As solutions of (2.5) near the bifurcation points are of the form  $e^{\lambda_{j,\varepsilon} t} \xi(x) + \text{c.c.} + u_\varepsilon^*(x, D) \approx e^{\lambda_{j,\varepsilon}^c t + \frac{\partial \lambda_{j,\varepsilon}}{\partial D} \nu \delta^2 t} \xi(x) + \text{c.c.} + u_\varepsilon^*(x, D_{j,\varepsilon}^c + \delta^2\nu + \dots)$ , where  $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T$  is the stationary solution,  $\xi$  is the corresponding eigenvector and c.c. stands for the complex conjugate terms, we obtain that near the bifurcation points solutions depend on two time scales — the fast time scale  $t$  and the slow time scale  $T = \delta^2 t$ . For small  $\delta > 0$  we shall regard  $t$  and  $T$  as being independent. Thus, we consider the solution of the nonlinear system (2.5) near the steady state in the form:

$$\begin{aligned} m(t, T, x) &= m_\varepsilon^*(x, D) + \delta m_1(t, T, x) + \delta^2 m_2(t, T, x) + \delta^3 m_3(t, T, x) + O(\delta^4), \\ p(t, T, x) &= p_\varepsilon^*(x, D) + \delta p_1(t, T, x) + \delta^2 p_2(t, T, x) + \delta^3 p_3(t, T, x) + O(\delta^4), \end{aligned} \tag{6.1}$$

and  $D = D_{j,\varepsilon}^c + \delta^2\nu$ , where  $\nu = \pm 1$  and  $j = 1, 2$ . We shall use the ansatz (6.1) in Eqs. (2.5) and compare the terms of the same order in  $\delta$ . Using the regularity of  $f(p)$  with respect to  $p$  and of the stationary solution  $u_\varepsilon^*$  with respect to  $D$ , we apply Taylor series expansion to  $f$  and  $u_\varepsilon^*$  about  $u_\varepsilon^*(x, D_{j,\varepsilon}^c)$  and  $D_{j,\varepsilon}^c$ , with  $j = 1, 2$ . For  $\delta$  we have:

$$\begin{cases} \partial_t m_1 = D_{j,\varepsilon}^c \partial_x^2 m_1 - \mu_m m_1 + \alpha_m f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon(x) p_1, \\ \partial_t p_1 = D_{j,\varepsilon}^c \partial_x^2 p_1 - \mu_p p_1 + \alpha_p g(x) m_1, \\ \partial_x m_1(t, 0) = \partial_x m_1(t, 1) = 0, \quad \partial_x p_1(t, 0) = \partial_x p_1(t, 1) = 0. \end{cases} \quad (6.2)$$

The linearity of the equations as well as the fact that the dynamics near the bifurcation point is defined by the largest eigenvalues  $\pm \lambda_{j,\varepsilon}^c$ , imply that we can consider  $m_1$  and  $p_1$  in the form:

$$\begin{aligned} m_1(t, T, x) &= A(T) e^{\lambda_{j,\varepsilon}^c t} \xi_1(x) + \bar{A}(T) e^{\bar{\lambda}_{j,\varepsilon}^c t} \bar{\xi}_1(x), \\ p_1(t, T, x) &= A(T) e^{\lambda_{j,\varepsilon}^c t} \xi_2(x) + \bar{A}(T) e^{\bar{\lambda}_{j,\varepsilon}^c t} \bar{\xi}_2(x), \end{aligned}$$

where  $A(T) \in \mathbb{C}$ ,  $\xi = (\xi_1, \xi_2)$  is a solution of the eigenvalue problem (4.2) for  $\lambda_{j,\varepsilon}^c = i\omega_j^c$ , with  $j = 1, 2$ , and  $\bar{\xi}$  is the complex conjugate of  $\xi$  (we shall omit the dependence on  $\varepsilon$  to simplify the presentation). For  $\delta^2$ , we obtain equations for  $m_2$  and  $p_2$ :

$$\begin{cases} \partial_t m_2 = D_{j,\varepsilon}^c \partial_x^2 m_2 - \mu_m m_2 + \alpha_m \left[ f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) p_2 + f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \frac{p_1^2}{2} \right] \delta_{x_M}^\varepsilon, \\ \partial_t p_2 = D_{j,\varepsilon}^c \partial_x^2 p_2 - \mu_p p_2 + \alpha_p g(x) m_2, \\ \partial_x m_2(t, 0) = \partial_x m_2(t, 1) = 0, \quad \partial_x p_2(t, 0) = \partial_x p_2(t, 1) = 0. \end{cases} \quad (6.3)$$

Then, due to the quadratic term in (6.3) comprising  $p_1$ , the functions  $m_2$  and  $p_2$  are of the form:

$$\begin{aligned} m_2(t, T, x) &= A(T)^2 e^{2i\omega_j^c t} w_1(x) + \text{c.c.} + |A(T)|^2 \tilde{w}_1(x), \\ p_2(t, T, x) &= A(T)^2 e^{2i\omega_j^c t} w_2(x) + \text{c.c.} + |A(T)|^2 \tilde{w}_2(x). \end{aligned} \quad (6.4)$$

Using (6.4) in Eqs. (6.3), we obtain for the terms with  $e^{2i\omega_j^c t}$ :

$$\begin{cases} 2i\omega_j^c w_1 = D_{j,\varepsilon}^c \frac{d^2 w_1}{dx^2} - \mu_m w_1 + \alpha_m \left[ f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) w_2 + f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \frac{\xi_2^2}{2} \right] \delta_{x_M}^\varepsilon, \\ 2i\omega_j^c w_2 = D_{j,\varepsilon}^c \frac{d^2 w_2}{dx^2} - \mu_p w_2 + \alpha_p g(x) w_1, \\ \frac{dw_1}{dx}(0) = \frac{dw_1}{dx}(1) = 0, \quad \frac{dw_2}{dx}(0) = \frac{dw_2}{dx}(1) = 0, \end{cases} \quad (6.5)$$

as well as the corresponding complex conjugate problem for the terms with  $e^{-2i\omega_j^c t}$ , where  $j = 1, 2$ . Considering the terms for  $e^0$ , we obtain that  $\tilde{w} = (\tilde{w}_1, \tilde{w}_2)$  solves

$$\begin{cases} 0 = D_{j,\varepsilon}^c \frac{d^2 \tilde{w}_1}{dx^2} - \mu_m \tilde{w}_1 + \alpha_m f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon \tilde{w}_2 + \alpha_m f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon |\xi_2|^2, \\ 0 = D_{j,\varepsilon}^c \frac{d^2 \tilde{w}_2}{dx^2} - \mu_p \tilde{w}_2 + \alpha_p g(x) \tilde{w}_1, \\ \frac{d\tilde{w}_1}{dx}(0) = \frac{d\tilde{w}_1}{dx}(1) = 0, \quad \frac{d\tilde{w}_2}{dx}(0) = \frac{d\tilde{w}_2}{dx}(1) = 0. \end{cases} \tag{6.6}$$

Considering the terms of order  $\delta^3$ , we obtain the following equations for  $m_3$  and  $p_3$ :

$$\begin{cases} \partial_t m_3 + \partial_T m_1 = D_{j,\varepsilon}^c \partial_x^2 m_3 - \mu_m m_3 + \alpha_m f'(p_\varepsilon^*(D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon p_3 \\ \quad + \nu [\partial_x^2 m_1 + \alpha_m f''(p_\varepsilon^*(D_{j,\varepsilon}^c)) \partial_D p_\varepsilon^*(D_{j,\varepsilon}^c) \delta_{x_M}^\varepsilon p_1] \\ \quad + \alpha_m f''(p_\varepsilon^*(D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon p_1 p_2 + \frac{1}{6} f'''(p_\varepsilon^*(D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon p_1^3, \\ \partial_t p_3 + \partial_T p_1 = D_{j,\varepsilon}^c \partial_x^2 p_3 - \mu_p p_3 + \alpha_p g(x) m_3 + \nu \partial_x^2 p_1, \\ \partial_x m_3(t, 0) = \partial_x m_3(t, 1) = 0, \quad \partial_x p_3(t, 0) = \partial_x p_3(t, 1) = 0. \end{cases}$$

Thus, we obtain that  $m_3(t, T, x)$  and  $p_3(t, T, x)$  have the form

$$\begin{aligned} m_3(t, T, x) &= A(T)^3 e^{3i\omega_j^c t} q_1(x) + A(T)^2 e^{2i\omega_j^c t} s_1(x) + A(T) e^{i\omega_j^c t} \tilde{\xi}_1(x) \\ &\quad + A(T) |A(T)|^2 e^{i\omega_j^c t} r_1(x) + \text{c.c.} + |A(T)|^2 \tilde{u}_1(x), \\ p_3(t, T, x) &= A(T)^3 e^{3i\omega_j^c t} q_2(x) + A(T)^2 e^{2i\omega_j^c t} s_2(x) + A(T) e^{i\omega_j^c t} \tilde{\xi}_2(x) \\ &\quad + A(T) |A(T)|^2 e^{i\omega_j^c t} r_2(x) + \text{c.c.} + |A(T)|^2 \tilde{u}_2(x). \end{aligned}$$

Combining the terms in front of  $e^{i\omega_j^c t}$ , we obtain equations:

$$\begin{cases} i\omega_j^c [A(T) \tilde{\xi}_1 + A(T) |A(T)|^2 r_1] = \left( D_{j,\varepsilon}^c \frac{d^2}{dx^2} - \mu_m \right) [A(T) \tilde{\xi}_1 + A(T) |A(T)|^2 r_1] \\ \quad + \alpha_m f'(p_\varepsilon^*) \delta_{x_M}^\varepsilon [A(T) \tilde{\xi}_2 + A(T) |A(T)|^2 r_2] \\ \quad - \partial_T A(T) \xi_1 + A(T) \nu \left[ \frac{d^2 \xi_1}{dx^2} + \alpha_m f''(p_\varepsilon^*) \delta_{x_M}^\varepsilon \partial_D p_\varepsilon^* \xi_2 \right] \\ \quad + A(T) |A(T)|^2 \alpha_m \delta_{x_M}^\varepsilon \left[ f''(p_\varepsilon^*) (w_2 \bar{\xi}_2 + \tilde{w}_2 \xi_2) + \frac{1}{2} f'''(p_\varepsilon^*) \xi_2^2 \bar{\xi}_2 \right], \\ i\omega_j^c [A(T) \tilde{\xi}_2 + A(T) |A(T)|^2 r_2] = \left( D_{j,\varepsilon}^c \frac{d^2}{dx^2} - \mu_p \right) [A(T) \tilde{\xi}_2 + A(T) |A(T)|^2 r_2] \\ \quad - \partial_T A(T) \xi_2 + A(T) \nu \frac{d^2 \xi_2}{dx^2} + \alpha_p g(x) [A(T) \tilde{\xi}_1 + A(T) |A(T)|^2 r_1]. \end{cases} \tag{6.7}$$

Similar equations are obtained for  $e^{-i\omega_j^c t}$  with corresponding complex conjugate terms. Since  $i\omega_j^c$  is an eigenvalue of  $\mathcal{A}$ , by the Fredholm alternative, the system

(6.7) together with zero-flux boundary conditions has a solution if and only if

$$\begin{aligned} & \partial_T A(T) (\langle \xi_1, \xi_1^* \rangle + \langle \xi_2, \xi_2^* \rangle) \\ & - \nu A(T) \left[ \left\langle \frac{d^2 \xi_1}{dx^2}, \xi_1^* \right\rangle + \alpha_m \langle f''(p_\varepsilon^*) \partial_D p_\varepsilon^* \delta_{x_M}^\varepsilon \xi_2, \xi_1^* \rangle + \left\langle \frac{d^2 \xi_2}{dx^2}, \xi_2^* \right\rangle \right] \\ & - A(T) |A(T)|^2 \alpha_m [\langle f''(p_\varepsilon^*) \delta_{x_M}^\varepsilon (w_2 \bar{\xi}_2 + \tilde{w}_2 \xi_2), \xi_1^* \rangle \\ & \quad + \frac{1}{2} \langle f'''(p_\varepsilon^*) \delta_{x_M}^\varepsilon \xi_2 |\xi_2|^2, \xi_1^* \rangle] = 0, \end{aligned}$$

where  $\xi^*$  is the eigenvector for  $\lambda = -i\omega_j^c$  of the formal adjoint operator  $\mathcal{A}^*$ :

$$\begin{cases} -i\omega_j^c \xi_1^* = D_{j,\varepsilon}^c \frac{d^2}{dx^2} \xi_1^* - \mu_m \xi_1^* + \alpha_p g(x) \xi_2^*, \\ -i\omega_j^c \xi_2^* = D_{j,\varepsilon}^c \frac{d^2}{dx^2} \xi_2^* - \mu_p \xi_2^* + \alpha_m f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon \xi_1^*, \\ \frac{d}{dx} \xi_1^*(0) = \frac{d}{dx} \xi_1^*(1) = 0, \quad \frac{d}{dx} \xi_2^*(0) = \frac{d}{dx} \xi_2^*(1) = 0. \end{cases} \quad (6.8)$$

By choosing  $\xi^*$  in such a way that  $\langle \xi, \xi^* \rangle = \langle \xi_1, \xi_1^* \rangle + \langle \xi_2, \xi_2^* \rangle = 1$ , we obtain the amplitude equation

$$\frac{d}{dT} A(T) = a_{j,\varepsilon} \nu A(T) + b_{j,\varepsilon} A(T) |A(T)|^2,$$

where

$$\begin{aligned} a_{j,\varepsilon} &= \left\langle \frac{d^2}{dx^2} \xi_1, \xi_1^* \right\rangle + \alpha_m \langle f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \partial_D p_\varepsilon^*(x, D_{j,\varepsilon}^c) \delta_{x_M}^\varepsilon \xi_2, \xi_1^* \rangle + \left\langle \frac{d^2}{dx^2} \xi_2, \xi_2^* \right\rangle, \\ b_{j,\varepsilon} &= \alpha_m \langle f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon (w_2 \bar{\xi}_2 + \tilde{w}_2 \xi_2), \xi_1^* \rangle + \frac{1}{2} \langle f'''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon \xi_2 |\xi_2|^2, \xi_1^* \rangle. \end{aligned}$$

We can calculate the values of  $b_{j,\varepsilon}$  for  $\varepsilon = 0$  which then, using the continuity with respect to  $\varepsilon$  and convergence of  $b_{j,\varepsilon}$  to  $b_{j,0}$  as  $\varepsilon \rightarrow 0$ , ensured by the strong convergence in  $C([0, 1])$  of  $p_\varepsilon^*$ ,  $w_2 = w_2^\varepsilon$ ,  $\tilde{w}_2 = \tilde{w}_2^\varepsilon$ ,  $\xi_2 = \xi_2^\varepsilon$  and  $\xi_1^* = \xi_1^{*\varepsilon}$  as  $\varepsilon \rightarrow 0$ , will provide the information on the type of the Hopf bifurcation and the stability of periodic orbits for the original model (2.5) with small  $\varepsilon > 0$ . Since eigenfunctions are defined *modulo* a constant, we can choose  $\xi_2^0(x_M) = 1$  and obtain

$$b_{j,0} = \alpha_m \left[ f''(p^*(x_M, D_j^c)) (w_2^0(x_M) + \tilde{w}_2^0(x_M)) + \frac{1}{2} f'''(p^*(x_M, D_j^c)) \right] \overline{\xi_1^{*,0}}(x_M),$$

where  $j = 1, 2$ ,  $\xi^{*,0} = (\xi_1^{*,0}, \xi_2^{*,0})$  is a solution of the formal adjoint eigenvalue problem with  $\varepsilon = 0$ , and  $w^0 = (w_1^0, w_2^0)$  and  $\tilde{w}^0 = (\tilde{w}_1^0, \tilde{w}_2^0)$  are solutions of (6.5) and (6.6) for  $\varepsilon = 0$ , respectively. Since  $2\lambda_j^c \notin \sigma(\tilde{\mathcal{A}})$ , for  $j = 1, 2$ , and  $0 \notin \sigma(\tilde{\mathcal{A}})$ , with  $\tilde{\mathcal{A}}$  defined in (4.9), there exist unique solutions of the problems (6.5) and (6.6) for  $\varepsilon = 0$ .

For the subsequent computations arising from the previous analysis, and for ease of calculation and presentation (cf. Sec. 5), we consider the case  $\mu_m = \mu_p = \mu$  and  $\mu > 0$ . However, the results hold also for the case  $\mu_m \neq \mu_p$ , with  $\mu_m, \mu_p > 0$ .

Using  $2\lambda_j^c \notin \sigma(\tilde{\mathcal{A}}_0)$  and  $\xi_2^0(x_M) = 1$  we can compute

$$w_2^0(x_M) = \frac{\alpha_p \alpha_m}{2} f''(p_0^*(x_M, D_j^c)) \mathcal{G}_1(x_M) \times (1 - \alpha_p \alpha_m f'(p_0^*(x_M, D_j^c)) \mathcal{G}_1(x_M))^{-1},$$

where

$$\mathcal{G}_1(x_M) = \frac{\cosh^2(\theta_{2\lambda_j^c} x_M)}{4(\mu + 2\lambda_j^c) D_j^c \sinh^2(\theta_{2\lambda_j^c})} \left[ 1 + \frac{1}{\theta_{2\lambda_j^c}} \sinh(\theta_{2\lambda_j^c}) \right], \quad \theta_{2\lambda_j^c} = \left( \frac{\mu + 2\lambda_j^c}{D_j^c} \right)^{\frac{1}{2}}.$$

For  $\tilde{w}_2^0(x)$ , since  $0 \notin \sigma(\mathcal{A}_0)$  and using  $\xi_2^0(x_M) = 1$ , we have

$$\tilde{w}_2^0(x_M) = \alpha_p \alpha_m f''(p^*(x_M, D_j^c)) \mathcal{G}_2(x_M) [1 - \alpha_p \alpha_m f'(p^*(x_M, D_j^c)) \mathcal{G}_2(x_M)]^{-1},$$

where

$$\mathcal{G}_2(x_M) = \frac{\cosh^2(\theta x_M)}{4\mu D_j^c \sinh^2(\theta)} \left[ 1 + \frac{1}{\theta} \sinh(\theta) \right] \quad \text{with } \theta = \left( \frac{\mu}{D_j^c} \right)^{\frac{1}{2}}.$$

Using the fact that  $\xi_2^0(x_M) = 1$  we can compute

$$\begin{aligned} \xi_1^0(x) &= \frac{\alpha_m f'(p^*(x_M, D_j^c))}{((\mu + \lambda_j^c) D_j^c)^{\frac{1}{2}} \sinh(\theta_{\lambda_j^c})} [\cosh(\theta_{\lambda_j^c} x) \cosh(\theta_{\lambda_j^c} (1 - x_M))_{0 < x < x_M} \\ &\quad + \cosh(\theta_{\lambda_j^c} (1 - x)) \cosh(\theta_{\lambda_j^c} x_M)_{x_M < x < 1}]. \end{aligned}$$

To define the solution of (6.8) with  $\varepsilon = 0$  we note that  $-\lambda_j^c \notin \sigma(\mathcal{A}_0)$  and obtain

$$\begin{aligned} \xi_2^{*,0}(x) &= \alpha_m G_{-\lambda_j^c + \mu}(x, x_M) f'(p_0^*(x_M, D_j^c)) \xi_1^{*,0}(x_M) = \frac{\alpha_m f'(p_0^*(x_M, D_j^c)) \xi_1^{*,0}(x_M)}{((\mu - \lambda_j^c) D_j^c)^{1/2} \sinh(\theta_{-\lambda_j^c})} \\ &\quad \times [\cosh(\theta_{-\lambda_j^c} x) \cosh(\theta_{-\lambda_j^c} (1 - x_M))_{x < x_M} \\ &\quad + \cosh(\theta_{-\lambda_j^c} (1 - x)) \cosh(\theta_{-\lambda_j^c} x_M)_{x_M < x}]. \end{aligned}$$

With  $l = \frac{1}{2}$  we have that  $\xi_1^{*,0}$  has the form

$$\begin{aligned} \xi_1^{*,0}(x) &= \frac{\alpha_p \alpha_m f'(p_0^*(x_M, D_j^c)) \cosh(\theta_{-\lambda_j^c} x_M)}{2 (\mu - \lambda_j^c) D_j^c \sinh^2(\theta_{-\lambda_j^c})} \xi_1^{*,0}(x_M) \\ &\quad \times \left[ \cosh(\theta_{-\lambda_j^c} (1 - x)) \left( \cosh(\theta_{-\lambda_j^c}) \left[ x - \frac{1}{2} \right]_+ - \frac{\sinh(\theta_{-\lambda_j^c} (1 - 2x))_{x \geq \frac{1}{2}}}{2\theta_{-\lambda_j^c}} \right) \right. \\ &\quad \left. + \cosh(\theta_{-\lambda_j^c} x) \left( \left[ 1 - \max \left\{ x, \frac{1}{2} \right\} \right] + \frac{\sinh(2\theta_{-\lambda_j^c} [1 - \max \{ x, \frac{1}{2} \}])}{2\theta_{-\lambda_j^c}} \right) \right], \end{aligned}$$

where  $\theta_{-\lambda_j^c} = \left( \frac{\mu - \lambda_j^c}{D_j^c} \right)^{\frac{1}{2}}$ . We define  $\xi_1^{*,0}(x_M)$  in such a way that

$$\langle \xi^0, \xi^{*,0} \rangle = \int_0^1 (\xi_1^0(x) \overline{\xi_1^{*,0}(x)} + \xi_2^0(x) \overline{\xi_2^{*,0}(x)}) dx = 1,$$

and, considering that  $x_M < \frac{1}{2}$ , we obtain

$$\begin{aligned} \overline{\xi_1^{*,0}}(x_M) &= \left[ \frac{\alpha_m^2 \alpha_p [f'(p_0^*)]^2 \cosh(\theta_{\lambda_j^c} x_M)}{((\mu + \lambda_j^c) D_j^c)^{3/2} \sinh^3(\theta_{\lambda_j^c})} \right]^{-1} \left[ \left( \frac{1}{2} + \frac{\sinh(\theta_{\lambda_j^c})}{2\theta_{\lambda_j^c}} \right) \right. \\ &\quad \times \left[ \cosh(\theta_{\lambda_j^c} x_M) \int_{x_M}^{\frac{1}{2}} \cosh(\theta_{\lambda_j^c} (1-x)) \cosh(\theta_{\lambda_j^c} x) dx \right. \\ &\quad \left. \left. + \cosh(\theta_{\lambda_j^c} (1-x_M)) \int_0^{x_M} \cosh^2(\theta_{\lambda_j^c} x) dx \right] + \cosh(\theta_{\lambda_j^c} x_M) \right. \\ &\quad \times \int_{\frac{1}{2}}^1 \cosh(\theta_{\lambda_j^c} (1-x)) \left[ \cosh(\theta_{\lambda_j^c} x) \left( 1-x + \frac{\sinh(2\theta_{\lambda_j^c} (1-x))}{2\theta_{\lambda_j^c}} \right) \right. \\ &\quad \left. \left. + \cosh(\theta_{\lambda_j^c} (1-x)) \left( \cosh(\theta_{\lambda_j^c}) \left( x - \frac{1}{2} \right) - \frac{\sinh(\theta_{\lambda_j^c} (1-2x))}{2\theta_{\lambda_j^c}} \right) \right] dx \right]^{-1}, \end{aligned}$$

where  $\theta_{\lambda_j^c} = \left( \frac{\mu + \lambda_j^c}{D_j^c} \right)^{\frac{1}{2}}$  and  $j = 1, 2$ .

Carrying out all calculations in Matlab, for the critical value of the bifurcation parameter  $D_1^c \approx 3.117 \times 10^{-4}$  (and all other parameters as given in Sec. 2) we obtain  $b_{1,0} \approx -0.0418 - 0.0155i$ . Thus since  $\text{Re}(b_{1,0}) < 0$  we have by continuity and strong convergence that the Hopf bifurcation at  $D_{1,\varepsilon}^c$  is supercritical and we have a stable family of periodic solutions bifurcating from the steady state into the region  $D > D_{1,\varepsilon}^c$  where the stationary solution is unstable, i.e.  $\nu = 1$ . For the second critical value  $D_2^c \approx 7.885 \times 10^{-3}$ , the calculated value is  $b_{2,0} \approx -0.0079 - 0.0206i$  and, since  $\text{Re}(b_{2,0}) < 0$ , the Hopf bifurcation at  $D_{2,\varepsilon}^c$  is also supercritical and stable periodic orbits bifurcate into the region  $D < D_{2,\varepsilon}^c$  where the stationary solution is unstable, i.e.  $\nu = -1$ .  $\square$

The amplitude equation can also be derived using central manifold theory and the corresponding normal form for the system of partial differential equations, see Ref. 24. To apply the known results we shall shift the values of critical parameters and stationary solutions to zero, i.e.  $\tilde{D} = D - D_{j,\varepsilon}^c$  and  $\tilde{m}(t, x) = m(t, x) - m_\varepsilon^*(x, D)$ ,  $\tilde{p}(t, x) = p(t, x) - p_\varepsilon^*(x, D)$ , where  $m_\varepsilon^*(x, D)$  and  $p_\varepsilon^*(x, D)$  are the stationary solutions of (2.5). Then (2.5) can be written as:

$$\partial_t u = \mathcal{A}_{D_{j,\varepsilon}^c} u + \tilde{F}(u, \tilde{D}), \quad (6.9)$$

where  $u(t, x) = (\tilde{m}(t, x), \tilde{p}(t, x))^T$  with

$$\mathcal{A}_{D_{j,\varepsilon}^c} = \begin{pmatrix} D_{j,\varepsilon}^c \frac{\partial^2}{\partial x^2} - \mu_m & \alpha_m f'(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon(x) \\ \alpha_p g(x) & D_{j,\varepsilon}^c \frac{\partial^2}{\partial x^2} - \mu_p \end{pmatrix},$$



and

$$\tilde{F}(u, \tilde{D}) = \left( \begin{array}{c} \alpha_m [f(\tilde{p} + p_\varepsilon^*(\tilde{D})) - f(p_\varepsilon^*(\tilde{D})) - f'(p_\varepsilon^*(D_{j,\varepsilon}^c))\tilde{p}]\delta_{x_M}^\varepsilon + \tilde{D}\partial_x^2 \tilde{m} \\ \tilde{D}\partial_x^2 \tilde{p} \end{array} \right),$$

where  $p_\varepsilon^*(\tilde{D}) = p_\varepsilon^*(D_{j,\varepsilon}^c + \tilde{D})$ . By Theorem 3.3 in Ref. 24, using the results of Theorem 5.1 and the regularity of  $f$  and of the stationary solution  $u_\varepsilon^*(x, D) = (m_\varepsilon^*(x, D), p_\varepsilon^*(x, D))^T$ , we conclude that the system (6.9) possesses a two-dimensional center manifold for sufficiently small  $\tilde{D}$ . Equations in (6.9) reduced to the central manifold can be transformed by the polynomial change of variables in the normal form<sup>24,25</sup>:

$$\frac{dA}{dt} = \lambda_{j,\varepsilon}^c A + a_{j,\varepsilon} \tilde{D}A + b_{j,\varepsilon} A|A|^2 + O(|A|(|\tilde{D}| + |A|^2)^2), \tag{6.10}$$

for  $j = 1, 2$ . The solutions of (6.9) on the center manifold are then of the form

$$u = A\xi + \overline{A\xi} + \Phi(A, \bar{A}, \tilde{D}), \quad A \in \mathbb{C}, \tag{6.11}$$

where  $\xi = (\xi_1, \xi_2)$  is an eigenvector for the eigenvalue  $\lambda_{j,\varepsilon}^c$  and for  $\Phi$  a polynomial ansatz can be made:

$$\Phi(A, \bar{A}, \tilde{D}) = \sum_{r,s,q} \Phi_{rsq} A^r \bar{A}^s \tilde{D}^q,$$

with  $\Phi_{100} = 0$ ,  $\Phi_{010} = 0$  and  $\Phi_{rsq} = \overline{\Phi_{srq}}$ . Substituting the form (6.11) for  $u$  into Eq. (6.9), we obtain

$$(\xi + \partial_A \Phi) \frac{dA}{dt} + (\bar{\xi} + \partial_{\bar{A}} \Phi) \frac{d\bar{A}}{dt} = \mathcal{A}_{D_{j,\varepsilon}^c} (A\xi + \overline{A\xi} + \Phi) + \tilde{F}(A\xi + \overline{A\xi} + \Phi, \tilde{D}).$$

Considering orders of  $\tilde{D}A$ ,  $A^2$ ,  $A\bar{A}$ ,  $A^2\bar{A}$ , implies the equations:

$$\begin{aligned} -\mathcal{A}_{D_{j,\varepsilon}^c} \Phi_{001} &= \partial_{\tilde{D}} \tilde{F}(0, 0), \\ a_{j,\varepsilon} \xi + (\lambda_{j,\varepsilon}^c - \mathcal{A}_{D_{j,\varepsilon}^c}) \Phi_{101} &= \partial_u \partial_{\tilde{D}} \tilde{F}(0, 0) \xi + \partial_u^2 \tilde{F}(0, 0) (\xi, \Phi_{001}), \\ (2\lambda_{j,\varepsilon}^c - \mathcal{A}_{D_{j,\varepsilon}^c}) \Phi_{200} &= \frac{1}{2} \partial_u^2 \tilde{F}(0, 0) (\xi, \xi), \\ -\mathcal{A}_{D_{j,\varepsilon}^c} \Phi_{110} &= \partial_u^2 \tilde{F}(0, 0) (\xi, \bar{\xi}), \\ b_{j,\varepsilon} \xi + (\lambda_{j,\varepsilon}^c - \mathcal{A}_{D_{j,\varepsilon}^c}) \Phi_{210} &= \partial_u^2 \tilde{F}(0, 0) (\bar{\xi}, \Phi_{200}) + \partial_u^2 \tilde{F}(0, 0) (\xi, \Phi_{110}) \\ &\quad + \frac{1}{2} \partial_u^3 \tilde{F}(0, 0) (\xi, \xi, \bar{\xi}). \end{aligned}$$

We have  $\partial_{\tilde{D}} \tilde{F}(0, 0) = (0, 0)^T$  together with

$$\partial_u \partial_{\tilde{D}} \tilde{F}(0, 0) \xi = \left( \begin{array}{c} \frac{d^2 \xi_1}{dx^2} + \alpha_m f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \partial_{\tilde{D}} p_\varepsilon^*(x, D_{j,\varepsilon}^c) \delta_{x_M}^\varepsilon(x) \xi_2 \\ \frac{d^2 \xi_2}{dx^2} \end{array} \right),$$

and multilinear forms  $\partial_u^2 \tilde{F}(0, 0)$  and  $\partial_u^3 \tilde{F}(0, 0)$  are defined as

$$\partial_u^2 \tilde{F}(0, 0)(\xi, \xi) = \begin{pmatrix} \alpha_m f''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon(x) \xi_2^2 \\ 0 \end{pmatrix},$$

and

$$\partial_u^3 \tilde{F}(0, 0)(\xi, \xi, \bar{\xi}) = \begin{pmatrix} \alpha_m f'''(p_\varepsilon^*(x, D_{j,\varepsilon}^c)) \delta_{x_M}^\varepsilon(x) \xi_2^2 \bar{\xi}_2 \\ 0 \end{pmatrix}.$$

Since  $\partial_D \tilde{F}(0, 0) = (0, 0)^T$  and  $0 \notin \sigma(\mathcal{A}_{D_{j,\varepsilon}^c})$ , we obtain that  $\Phi_{001} = 0$ . Applying the Fredholm alternative for the solvability of equations for  $\Phi_{101}$  and  $\Phi_{210}$ , we obtain the same expressions for coefficients  $a_{j,\varepsilon}$  and  $b_{j,\varepsilon}$  as from the weakly nonlinear analysis.

The relation between the normal form and the amplitude equation obtained from the nonlinear analysis can be understood by introducing in the normal form (6.10) the assumption, used in the nonlinear analysis, that the solution near the bifurcation points depends on the fast time scale  $t$  and the slow time scale  $T$ , i.e.  $A = A(t, T)$ . Taking into account  $\tilde{m}(t, x) = m(t, x) - m_\varepsilon^*(x) \approx \delta$ ,  $\tilde{p}(t, x) = p(t, x) - p_\varepsilon^*(x) \approx \delta$ ,  $\tilde{D} \approx \delta^2 \nu$  and  $T = \frac{t}{\delta^2}$ , implies

$$\delta \frac{\partial A}{\partial t} + \delta^3 \frac{\partial A}{\partial T} = \lambda_{j,\varepsilon}^c \delta A + a_{j,\varepsilon} \delta^3 \nu A + \delta^3 b_{j,\varepsilon} A |A|^2 + \delta^5 O(|A|(|\nu| + |A|^2)^2).$$

Then for the terms of orders  $\delta$  and  $\delta^3$ , we obtain the equations derived using weakly-nonlinear analysis, i.e.

$$\frac{\partial A}{\partial t} = \lambda_{j,\varepsilon}^c A \quad \text{and} \quad \frac{\partial A}{\partial T} = a_{j,\varepsilon} \nu A + b_{j,\varepsilon} A |A|^2.$$

## 7. Discussion and Conclusions

Transcription factors play a vital role in controlling the levels of proteins and mRNAs within cells, and are involved in many key processes such as cell-cycle regulation and apoptosis. Such systems are often referred to as gene regulatory networks (GRNs). Those transcription factors which down-regulate (repress/suppress) the rate of gene transcription do so via negative feedback loops, and such intracellular negative feedback systems are known to exhibit oscillations in protein and mRNA levels.

In this paper, we have analyzed a mathematical model of the most basic gene regulatory network consisting of a single negative feedback loop between a protein and its mRNA — the Hes1 system. Our model consisted of a system of two coupled nonlinear partial differential equations describing the spatio-temporal dynamics of the concentration of hes1 mRNA,  $m(x, t)$ , and Hes1 protein,  $p(x, t)$ , describing the processes of transcription (mRNA production) and translation (protein production). Numerical simulations demonstrated the existence of oscillatory solutions as observed experimentally,<sup>27</sup> with the indication that the periodic orbits arose from

supercritical Hopf bifurcations at two critical values of the bifurcation parameter  $D_1^c$  and  $D_2^c$ . These results were then proved rigorously, demonstrating that the diffusion coefficient of the protein/mRNA acts as a bifurcation parameter and showing that the spatial movement of the molecules alone is sufficient to cause the oscillations.

Our result is in line with recent experimental findings<sup>23,29</sup> where the longest delay in several transcription factor systems was due to mRNA export from the nucleus rather than delays associated with the process of gene splicing. These results are also in line with other data which suggest that transcripts have a restricted rate of diffusion according to their mRNP (messenger ribonucleoprotein) composition.<sup>22,53,62</sup> It is not unreasonable to assume that further delays in the export process could also occur due to docking of transcripts with the pores of the nuclear membrane, and transcript translocation across the nuclear pores into the cytoplasm. These experimental observations and the main result of this paper (molecular diffusion causes oscillations) confirm the importance of modeling transcription factor systems where negative feedback loops are involved, using explicitly spatial models.

### Acknowledgments

M.A.J.C. and M.S. gratefully acknowledge the support of the ERC Advanced Investigator Grant 227619, “M5CGS — From Mutations to Metastases: Multiscale Mathematical Modelling of Cancer Growth and Spread”. M.S. would also like to thank the support from the Mathematical Biosciences Institute at the Ohio State University and NSF Grant DMS0931642.

### References

1. B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, *Molecular Biology of the Cell*, 5th edn. (Garland Science, 2008).
2. N. Anselone, *Collectively Compact Operators Approximation: Theory and Applications to Integral Equations* (Prentice-Hall, 1971).
3. A. Audibert, D. Weil and F. Daultry, *In vitro* kinetics of mRNA splicing and transport in mammalian cells, *Molec. Cell Biol.* **22** (2002) 6706–6718.
4. R. L. Bar-Or, R. Maya, L. A. Segel, U. Alon, A. J. Levine and M. Oren, Generation of oscillations by the p53-Mdm2 feedback loop: A theoretical and experimental study, *Proc. Natl. Acad. Sci. USA* **97** (2000) 11250–11255.
5. H. Brezis, *Functional Analysis, Sobolev Spaces and Partial Differential Equations* (Springer, 2011).
6. S. Busenberg and J. M. Mahaffy, Interaction of spatial diffusion and delays in models of genetic control by repression, *J. Math. Biol.* **22** (1985) 313–333.
7. M. Crandall and P. Rabinowitz, The Hopf bifurcation theorem in infinite dimensions, *Arch. Rational Mech. Anal.* **67** (1977) 53–72.
8. G. Cruywagen, J. Murray and P. Maini, Biological pattern formation on two-dimensional spatial domains: A nonlinear bifurcation analysis, *SIAM J. Appl. Math.* **57** (1997) 1485–1509.
9. E. N. Dancer, On uniqueness and stability for solutions of singularly perturbed predator–prey type equations with diffusion, *J. Differ. Equations* **102** (1993) 1–32.

10. E. N. Dancer, On stability and Hopf bifurcations for chemotaxis systems, *Methods Appl. Anal.* **8** (2001) 245–256.
11. R. Eftimie, G. de Vries and M. Lewis, Weakly nonlinear analysis of a hyperbolic model for animal group formation, *J. Math. Biol.* **59** (2009) 37–74.
12. C. P. Fall, E. S. Marland, J. M. Wagner and J. J. Tyson, *Computational Cell Biology*, 5th edn. (Springer, 2002).
13. B. Fiedler, An index for global Hopf bifurcation in parabolic systems, *J. Reine Angew. Math.* **1985** (1985) 1–36.
14. B. Fiedler, Global Hopf bifurcation of two-parameter flows, *Arch. Rational Mech. Anal.* **94** (1986) 59–81.
15. N. Geva-Zatorsky, E. Dekel, E. Batchelor, G. Lahav and U. Alon, Fourier analysis and systems identification of the p53 feedback loop, *Proc. Natl. Acad. Sci. USA* **107** (2010) 13550–13555.
16. N. Geva-Zatorsky, N. Rosenfeld, S. Itzkovitz, R. Milo, A. Sigal, E. Dekel, T. Yarnitzky, Y. Liron, P. Polak, G. Lahav and U. Alon, Oscillations and variability in the p53 system, *Molec. Syst. Biol.* **2** (2006) E1–E13.
17. L. Glass and S. A. Kauffman, Cooperative components, spatial localization and oscillatory cellular dynamics, *J. Theor. Biol.* **34** (1970) 219–237.
18. Y. Golovaty, A. Marciniak-Czochra and M. Ptashnyk, Stability of non-constant stationary solutions in a reaction–diffusion equation coupled to the system of ordinary differential equations, *Commun. Pure Appl. Anal.* **11** (2012) 229–241.
19. B. C. Goodwin, Oscillatory behaviour in enzymatic control processes, *Adv. Enzyme Regul.* **3** (1965) 425–428.
20. K. E. Gordon, I. M. M. V. Leeuwen, S. Laín and M. A. J. Chaplain, Spatio-temporal modelling of the p53-Mdm2 oscillatory system, *Math. Model. Nat. Phenom.* **4** (2009) 97–116.
21. J. S. Griffith, Mathematics of cellular control processes. I. Negative feedback to one gene, *J. Theor. Biol.* **20** (1968) 202–208.
22. D. Grünwald and R. H. Singer, *In vivo* imaging of labelled endogenous  $\beta$ -actin mRNA during nucleocytoplasmic transport, *Nature* **467** (2010) 604–607.
23. A. Hanisch, M. V. Holder, S. Choorapoikayil, M. Gajewski, E. M. Özbudak and J. Lewis, The elongation rate of RNA polymerase ii in zebrafish and its significance in the somite segmentation clock, *Development* **140** (2013) 444–453.
24. M. Haragus and G. Iooss, *Local Bifurcations, Center Manifolds and Normal Forms in Infinite-Dimensional Dynamical Systems* (Springer, 2011).
25. B. Hassard, N. Kazarinoff and Y.-H. Wan, *Theory and Applications of Hopf Bifurcation* (Cambridge Univ. Press, 1981).
26. D. Henry, *Geometric Theory of Semilinear Parabolic Equations* (Springer-Verlag, 1981).
27. H. Hirata, S. Yoshiura, T. Ohtsuka, Y. Bessho, T. Harada, K. Yoshikawa and R. Kageyama, Oscillatory expression of the bHLH factor Hes1 regulated by a negative feedback loop, *Science* **298** (2002) 840–843.
28. E. Hopf, Abzweigung einer periodischen lösung von einer stationären lösung eines differentialsystems, *Ber. d. Sächs. Akad. d. Wiss. (Math.-Phys. Kl). Leipzig* **94** (1942) 1–22.
29. N. P. Hoyle and D. Ish-Horowicz, Transcript processing and export kinetics are rate-limiting steps in expressing vertebrate segmentation clock genes, *Proc. Natl. Acad. Sci. USA* **110** (2013) E4316–E4324.
30. V. Iyer and K. Struhl, Absolute mRNA levels and transcriptional initiation rates in *saccharomyces cerevisiae*, *Proc. Natl. Acad. Sci. USA* **93** (1996) 5208–5212.

31. J. Ize, The global Hopf bifurcation for nonlinear parabolic equations, *Comm. Partial Differential Equations* **4** (1979) 1299–1387.
32. M. H. Jensen, J. Sneppen and G. Tiana, Sustained oscillations and time delays in gene expression of protein Hes1, *FEBS Lett.* **541** (2003) 176–177.
33. R. Kageyama, T. Ohtsuka and T. Kobayashi, The Hes1 gene family: Repressors and oscillators that orchestrate embryogenesis, *Development* **134** (2007) 1243–1251.
34. T. Kato, *Perturbation Theory for Linear Operators* (Springer-Verlag, 1966).
35. H. Kielhöfer, Hopf bifurcation from a differentiable viewpoint, *J. Differential Equations* **97** (1992) 189–232.
36. H. Kielhöfer, *Bifurcation Theory. An Introduction with Applications to Partial Differential Equations* (Springer-Verlag, 2012).
37. T. Kobayashi and R. Kageyama, Hes1 regulates embryonic stem cell differentiation by suppressing notch signaling, *Genes Cells* **15** (2010) 689–698.
38. T. Kobayashi and R. Kageyama, Hes1 oscillations contribute to heterogeneous differentiation responses in embryonic stem cells, *Genes* **2** (2011) 219–228.
39. T. Kobayashi, H. Mizuno, I. Imayoshi, C. Furusawa, K. Shirahige and R. Kageyama, The cyclic gene Hes1 contributes to diverse differentiation responses of embryonic stem cells, *Genes Dev.* **23** (2009) 1870–1875.
40. Y. Kuznetsov, *Elements of Applied Bifurcation Theory* (Springer, 1998).
41. G. Lahav, N. Rosenfeld, A. Sigal, N. Geva-Zatorsky, A. J. Levine, M. B. Elowitz and U. Alon, Dynamics of the p53-Mdm2 feedback loop in individual cells, *Nature Genet.* **36** (2004) 147–150.
42. M. Lewis and J. Murray, Analysis of dynamic and stationary pattern formation in the cell cortex, *J. Math. Biol.* **31** (1992) 25–71.
43. G. Lieberman, *Second-Order Parabolic Differential Equations* (World Scientific, 2005).
44. J. M. Mahaffy, Genetic control models with diffusion and delays, *Math. Biosci.* **90** (1988) 519–533.
45. J. M. Mahaffy and C. V. Pao, Models of genetic control by repression with time delays and spatial effects, *J. Math. Biol.* **20** (1984) 39–57.
46. J. Marsden and M. McCracken, *The Hopf Bifurcation and Its Applications* (Springer, 1976).
47. B. Matkowsky, Nonlinear dynamic stability, *SIAM J. Appl. Math.* **18** (1970) 872–883.
48. T. Matsuda, A. Miyawaki and T. Nagai, Direct measurement of protein dynamics inside cells using a rationally designed photoconvertible protein, *Nature Meth.* **5** (2008) 339–345.
49. V. Mendez, S. Fedotov and W. Horsthemke, *Reaction-Transport Systems* (Springer, 2010).
50. R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii and U. Alon, Network motifs: Simple building blocks of complex networks, *Science* **298** (2002) 824–827.
51. H. Momiji and N. A. M. Monk, Dissecting the dynamics of the Hes1 genetic oscillator, *J. Theor. Biol.* **254** (2008) 784–798.
52. N. A. M. Monk, Oscillatory expression of Hes1, p53, and NF- $\kappa$ B driven by transcriptional time delays, *Curr. Biol.* **13** (2003) 1409–1413.
53. A. Mor, S. Suliman, R. Ben-Yishay, S. Yunger, Y. Brody and Y. Shav-Tal, Dynamics of single mRNP nucleocytoplasmic transport and export through the nuclear pore in living cells, *Nat. Cell Biol.* **12** (2010) 543–552.
54. D. E. Nelson, A. E. C. Ihekweaba, M. Elliott, J. R. Johnson, C. A. Gibney, B. E. Foreman, G. Nelson, V. See, C. A. Horton, D. G. Spiller, S. W. Edwards, H. P. McDowell, J. F. Unitt, E. Sullivan, R. Grimley, N. Benson, D. Broomhead, D. B. Kell

- and M. R. H. White, Oscillations in NF- $\kappa$ B signaling control the dynamics of gene expression, *Science* **306** (2004) 704–708.
55. W.-M. Ni, I. Takagi and E. Yanagika, Stability of least energy pattern of the shadow system for an activator-inhibitor model, *Japan. J. Indust. Appl. Math* **18** (2001) 259–272.
  56. L. Nirenberg, *Topics in Nonlinear Functional Analysis*, Courant Institute of Mathematical Sciences (Amer. Math. Soc., 2011).
  57. A. Pazy, *Semigroups of Linear Operators and Applications to Partial Differential Equations* (Springer-Verlag, 1983).
  58. S. Rodrigues and J. D. Luca, Weakly nonlinear analysis of short-wave elliptical instability, *Phys. Fluid* **21** (2009) 014108–1–014108–10.
  59. F. Sauvigny, *Partial Differential Equations 1: Foundations and Integral Representations* (Springer, 2006).
  60. O. Seksek, J. Biwersi and A. S. Verkman, Translational diffusion of macromolecule-sized solutes in cytoplasm and nucleus, *J. Cell. Biol.* **138** (1997) 131–142.
  61. R. M. Shymko and L. Glass, Spatial switching in chemical reactions with heterogeneous catalysis, *J. Chem. Phys.* **60** (1974) 835–841.
  62. J. P. Siebrasse, T. Kaminski and U. Kubitscheck, Nuclear export of single native mRNA molecules observed by light sheet fluorescence microscopy, *Proc. Natl. Acad. Sci. USA* **109** (2012) 9426–9431.
  63. J. Smøller, *Shock Waves and Reaction–Diffusion Equations* (Springer-Verlag, 1994).
  64. M. Sturrock, A. Hellander, A. Matzavinos and M. A. J. Chaplain, Spatial stochastic modelling of the Hes1 gene regulatory network: Intrinsic noise can explain heterogeneity in embryonic stem cell differentiation, *J. R. Soc. Interface* **10** (2013) 20120988.
  65. M. Sturrock, A. J. Terry, D. P. Xirodimas, A. M. Thompson and M. A. J. Chaplain, Spatio-temporal modelling of the Hes1 and p53-Mdm2 intracellular signalling pathways, *J. Theor. Biol.* **273** (2011) 15–31.
  66. M. Sturrock, A. J. Terry, D. P. Xirodimas, A. M. Thompson and M. A. J. Chaplain, Influence of the nuclear membrane, active transport and cell shape on the Hes1 and p53–Mdm2 pathways: Insights from spatio-temporal modelling, *Bull. Math. Biol.* **74** (2012) 1531–1579.
  67. G. Tiana, M. H. Jensen and K. Sneppen, Time delay as a key to apoptosis induction in the p53 network, *Eur. Phys. J. B* **29** (2002) 135–140.
  68. F. Verhulst, *Nonlinear Differential Equations and Dynamical Systems* (Springer, 1990).
  69. M. Ward and J. Wei, Hopf bifurcation and oscillatory instabilities of spikes solutions for the one-dimensional Gierer–Meinhardt model, *J. Nonlinear Sci.* **13** (2003) 209–264.
  70. M. Ward and J. Wei, Hopf bifurcation of spike solutions for the shadow Gierer–Meinhardt model, *Euro. J. Appl. Math.* **14** (2003) 677–711.
  71. J. Wei and M. Winter, Critical threshold and stability of cluster solutions for large reaction–diffusion systems in  $\mathbb{R}^1$ , *SIAM J. Math. Anal.* **33** (2002) 1058–1089.
  72. J. Wei and M. Winter, Stability of spiky solutions in a reaction–diffusion system with four morphogens on the real line, *SIAM J. Math. Anal.* **42** (2010) 2818–2841.
  73. A. D. Wunsch, *Complex Variables with Applications* (Addison-Wesley, 1994).