ISSN 0315-3681 Volume 122 (2), 2025

Integrability and periodic orbits in the generalized quasispecies model

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Abstract

This paper studies a parametric family of systems of differential equations, which is obtained from the quasispecies model assuming arbitrary parameters without biological constraints. We study equilibria, invariant manifolds and the integrability of the family. It is well known that, by restricting the parameters to the biological domain, the quasispecies model is integrable, and here, we show that it is also the case for general parameters. Moreover, we consider a 4-dimensional realization of the model under the influence of a periodic perturbation. After restricting the system to an invariant manifold and relying on the first-order averaging technique, we demonstrate the existence of unstable periodic orbits in a neighborhood of the equilibrium located at the origin. It shows that periodic orbits emanate from the Zero-Hopf bifurcation that the mentioned equilibrium undergoes when the small parameter equals zero.

Keywords: Invariant manifold, Zero-Hopf bifurcation, First-order averaging, Quasispecies

1 Introduction

We study the quasispecies model presented in [1], a system of differential equations employed in evolutionary dynamics associated with viruses or cancer. Our analysis does not impose biological constraints on the parameters and variables. That is to say, we consider this model at its maximum generality, which will be dubbed as the *generalized quasispecies model*.

Mathematically, the quasispecies model is a system of ordinary nonlinear differential equations whose variables account for the frequencies of the master sequence and its mutants. It is based on an exponential-population approximation of each population plus the fitness term. Our analysis consider the integrability, equilibria and invariant manifolds. We will focus on the dynamics near the equilibrium associated with the master population dominance. Then, we study the effect of a medical treatment modeled as a small periodic perturbation.

The main results of this work are the determination of periodic orbits under the influence of a periodic perturbation and the extension of the integrability and the explicit integration of the generalized model. The perturbation that we consider is based on the one introduced in [7], where the authors presented a modification in the quasispecies model and proved that this new model has periodic orbits near the equilibria corresponding with the dominance of the master sequence. Moreover, when we restrict to the biological constraints, the mentioned perturbation simulates the effect of a periodic medical treatment.

It is well known that the classical quasispecies model is integrable through a convenient change of variables [2,5,6]. This process relies heavily upon biological constraints over the parameters and variables. Here, we extend the integrability to the generalized quasispecies model. Hence, we have an integrable model (for arbitrary parameters), which will be affected by a small, periodic perturbation.

The effect of a similar periodic perturbation was previously analyzed in [7] for the modified quasispecies. In the present work, we employ averaging theory to show that the generalized quasispecies model also has the mechanism leading to Zero-Hopf-type periodic orbits. However, the periodic orbits we find are out of the biological domain of the parameters. From this model's applied point of view, it remains to investigate whether this type of periodic orbit can be found in the presence of biological constraints.

This article is organized as follows: section 2 recall the definition of the quasispecies model and introduce some basic features. Then, in section 3, we provide the integration process of the generalized quasispecies model with no assumption of biological constraints. Once we have stated the integrability and the basic features of the model, we introduce a periodic perturbation in section 4, and we determine the existence and stability of a periodic orbit in section 5 of a 4-dimensional realization of the generalized model. Finally, in section 6, we carry out some numerical experiments illustrating our previous findings.

2. Statement of the problem and basic features

The quasispecies model was first presented in [1] and is given by the following system of differential equations

$$\dot{x}_i = \sum_{j=0}^{n} f_j \, Q_{ji} x_j - \Phi(\mathbf{x}) x_i, \qquad \Phi(\mathbf{x}) = \sum_{j=0}^{n} f_j \, x_j. \tag{1}$$

This system considers a population with $n+1$ compartments and models the competition between a master sequence and its mutants. It was used to analyze single-stranded RNA evolutionary dynamics and may be employed to study the evolution of cancer and virus populations. The vector of variables is given by $\mathbf{x} = (x_0, x_1, \ldots, x_n)$; they represent the proportion of each subpopulation in the total population, f_j is the growth rate of the j-th population, and Q_{ij} is the probability of having a mutation from the i-th to j-th populations.

In the biological context, the parameters of the above system (1) are endowed with several constraints, as well as the variables x_i, which are restricted to be in the real interval $[0,1]$. However, we will study this system from a mathematical point of view at its maximum generality, and we will not impose any restrictions not in the parameters or the variables. Hence, when no restriction is imposed, we refer to system (1) as the *generalized quasispecies model.*

Next, we give some general features of the equilibria and invariant manifolds associated with (1).

Proposition 1. *The origin is always an equilibrium of system* (1). *Additionally, let us consider the following restrictions for a fixed index* $i = k$

(i) $Q_{kj} = 0, j \neq k, \quad Q_{kk} \neq 0.$

(ii) $f_k = 0$

Then, (i) implies that the point $\mathcal{E}_k = (e_0,...,e_n) \in \mathbb{R}^{n+1}$ defined by $e_k = Q_{kk}$ and $e_j = 0$ for $j \neq k$, is an equilibrium. If (ii) is satisfied, the k-axis is full of equilibria.

Proof. The proof is obtained by simply substitution in system (1).

□

Proposition 2. *If the parameters satisfy the following restrictions*

$$\sum_{i=0}^{n} Q_{ji} = Q, \quad j = 0,...,n.$$

Then, the hyperplane $\Delta_Q := \{x \in \mathbb{R}^{n+1}; x_0 + ... + x_n = Q\}$ is an invariant manifold of the system of differential equations given in (1).

Proof. This claim is obtained by adding up the system (1) and taking into account the relation imposed to the parameters. Then, we obtain

$$\Phi(\mathbf{x})\left(\sum_{i=0}^{n} x_i - Q\right).$$

□

In the previous proposition, when $Q = 1$ and $Q_{ji} \geq 0$, we are in the biological domain of the parameters. The model is biologically meaningful when $x_i \in [0,1]$ for all $i = 0,...,n$. Proposition 2 only shows that the sum of all variables constantly equals one. However, it remains to show that, for $Q = 1$ and $Q_{ji} \geq 0$, the variables are restricted to $x_i \in [0,1]$, which is the content of the following result.

Proposition 3. *Let us assume that the parameters satisfy the constraints $\sum_{i=0}^{n} Q_{ji} = Q = 1$ and $f_i, Q_{ji} \geq 0$, for $i,j = 0,...,n$. Then, the following polytope is invariant*

$$\mathcal{P} = \{\mathbf{x} \in \mathrm{R}^{n+1};\ x_i = 1 \wedge 0 \leq x_i \leq 1,\ i = 0, \ldots, n\} \subset \Delta_1. \quad (2)$$

Proof. Let us consider a solution $\mathrm{x}(t)$ with initial condition (t_0, x_0) in $\mathcal{P}$, and assume that $\mathrm{x}(t)$ leaves $\mathcal{P}$ at a certain time $t^* > t_0$. Then, there exists $\epsilon > 0$ such that $\mathrm{x}(t) \in \mathcal{P}$ if $t \in (t^* - \epsilon, t^*]$ and $\mathrm{x}(t) \notin \mathcal{P}$ if $t \in (t^*, t^* + \epsilon)$, which implies that there is a component of the solution $x_i(t)$ satisfying

$$x_i(t) \in [0,1],\ t \in (t^* - \epsilon, t^*] \quad \wedge \quad x_i(t) \notin [0,1],\ t \in (t^*, t^* + \epsilon).$$

Thus, we have that $x_i(t^*) = 0$ or $x_i(t^*) = 1$. In the first case, and considering the differential equation for x_i given in (1), we have that $\dot{x}_i(t^*) > 0$. Proceeding in the same manner for the second case $x_i(t^*) = 1$, we obtain that $\dot{x}_i(t^*) < 0$. Both possibilities are incompatible with our previous claim $x_i(t) \notin [0,1],\ t \in (t^*, t^* + \epsilon)$. Therefore, the solution $\mathrm{x}(t)$ does not leave $\mathcal{P}$.

□

3. On the integrability of the generalized quasispecies model

It is well known [2, 5, 6] that, under the assumption of $\sum_{i=0}^{n} x_i = 1$, the classical quasispecies model can be reduced to a linear one with constant coefficients, which standard methods can quickly solve. Moreover, the solutions of the original system are recovered thanks to the assumptions $\sum_{i=0}^{n} Q_{ij} = 1$ and $\sum_{i=0}^{n} x_i = 1$. However, we seek the integrability of the generalized quasispecies model with no assumptions. This objective can be achieved by modifying the process of the classical model in the following way.

We rewrite equations (1) as follows

$$\dot{x}_i = \mathcal{A}\mathbf{x} - \Phi(\mathbf{x})x_i, \tag{3}$$

where the entries of the matrix $\mathcal{A}$ depends on the parameters f_i and Q_{ij}, $\mathbf{x}^T = (x_0, \ldots, x_n)$ and $\Phi(\mathbf{x}) = \sum_{j=0}^{n} f_j x_j$. Now, we introduce the notation $\mathbf{u}^T = (1, \ldots, 1)$, and $D_s = diag(s_0, \ldots, s_n)$ for any vector $s \in \mathbb{R}^{n+1}$. Then, we introduce the new variables $\mathbf{y} = (y_1, \ldots, y_{n+1})$, as it is done in the classical model given by

$$\mathbf{y} = \exp(f(t))\mathbf{x}, \quad f(t) := \int_0^t \Phi\ (\mathbf{x}(\boldsymbol{\tau}))d\tau,$$

which leads us to a linear constant coefficients system for $\mathbf{y}$

$$\dot{\mathbf{y}} = \mathcal{A}\mathbf{y}, \quad \mathbf{y}(0) = \mathbf{x}(0)$$

The recovery of the original variables $\mathbf{x}$ departs from the classical approach. Precisely, we consider the vector of parameters $F = (f_0, \dots, f_n)$ and the following relations

$$\begin{aligned} \mathbf{u}^T D_F \mathbf{y} &= \mathbf{u}^T D_F \exp(f(t))\mathbf{x} \\ &= \exp(f(t))\, \Phi(\mathbf{x}) \\ &= \exp(f(t))\, f'(t). \end{aligned} \tag{4}$$

Hence, defining

$$h(t) := \mathbf{u}^T D_F \mathbf{y}, \quad H(t) := \int_0^t h(\tau)\, d\tau,$$

and integrating in both sides of (4), we arrive at

$$\exp(f(t)) = H(t) + 1,$$

which gives the expression of $f(t)$ as $f(t) = \ln(H(t) + 1)$.. Therefore, we finally obtain

$$\begin{aligned} \mathbf{x}(t) &= \exp(-f(t))\mathbf{y}(t) \\ &= \frac{1}{1 + \int_0^t \mathbf{u}^T D_F \mathbf{y}(\tau)\, d\tau} \mathbf{y}(t). \end{aligned}$$

4. Analysis of the effect of a periodic perturbation

In this section, we consider a periodic perturbation inspired by the one given in [7] for the modified quasispecies model, where the authors proved the existence of periodic orbits of the zero-Hopf type. Our objective in this work is to show that the exact mechanism is present in the classical quasispecies model.

Now, we include the effects of a periodic treatment as a periodic perturbation. In the same way, it was introduced in [7] for the modified quasispecies model. Hence, we obtain the following system

$$\dot{x}_i = \sum_{j=0}^{n} f_j\, Q_{ji} x_j - \Phi(\mathbf{x}) x_i + \epsilon\, \mathcal{P}_i(\mathrm{x}, t), \tag{5}$$

where $0 < \epsilon \ll 1$ and the perturbation vector $\mathcal{P}(\mathrm{x},t) = (\mathcal{P}_0(\mathrm{x},t), \dots, \mathcal{P}_n(\mathrm{x},t))$, is given as

$$\mathcal{P}_i(\mathrm{x},t) = \delta(\mathrm{x}) \chi_i(\mathrm{x})\, (1 + \alpha\cos(\omega t) + \beta\sin(\omega t)), \tag{6}$$

where ω is the frequency, α,β are constants, $\delta(\mathrm{x}) = \sum_{i=1}^{n} x_i$ determines the dose of the treatment, and $\chi_i(\mathrm{x})$ weighs the influence of the treatment on each subpopulation. Furthermore, we assume the treatment regularly eliminates all coexisting subpopulations in the tumor tissue. This process serves to reduce the number of cells in all populations. However, this reduction does not imply a reduction in the proportion x_j of each subpopulation in all cases. We also consider that medical treatment places a more significant burden on larger subpopulations. Following [7], we consider $\chi_i(\mathrm{x}) = (1-(n+1)x_i)$. This choice for χ_i implies that x_j decreases when greater than the average $1/(n+1)$. In the following proposition, we prove that the biologically significant region of phase space is contained in the invariant hyperplane $x_0 + \dots + x_n = 1$.

Proposition 4. *Let us assume that* $\sum_{i=0}^{n} Q_{ji} = Q$, *for* $j = 0,\dots,n$. *Then, the hyperplane* $\Delta_Q := \{x \in \mathbb{R}^{n+1}; x_0 + \dots + x_n = Q\}$ *is an invariant manifold of the system of differential equations given in* (5).

Proof. This claim is obtained by adding up the system (5) and taking into account that $\sum_{i=0}^{n} Q_{ji} = Q$ for $j = 0,\dots,n$, we obtain

$$\left(\sum_{i=0}^{n} x_i - Q\right)(\Phi(\mathbf{x}) - \delta(\mathbf{x})\,(n+1)\,(1 + \alpha\cos(\omega t) + \beta\sin(\omega t))).$$

□

In the following section, we restrict to the invariant manifold Δ_1, hence we can reduce the number of variables.

5. 4-Dimensional realization of the general model. Dynamics around the equilibrium $\mathcal{E}_1$

This section considers a particular realization of the quasispecies model with four compartments. Our analysis will show that the zero-Hopf mechanism is present in this model. However, the values of the parameters lie outside of the biological domain.

Next, we consider a 4-dimensional quasispecies model; see figure 1. It considers a master population and three mutants with several levels of genetic instability. Moreover, we consider the evolution of this model under the influence of a periodic perturbation, which can be regarded as a medical treatment for the case of the parameters in the biological domain.

In particular, we are considering the following restriction among the parameters

$$Q_{01} = 1 - \delta_1,\ Q_{10} = Q_{02} = Q_{20} = \delta_1,\ Q_{13} = \delta_2,\ Q_{22} = \delta_3,$$
$$Q_{33} = 1,$$
$$Q_{21} = 1 - \delta_1 - \delta_3,\ Q_{12} = 1 - \delta_1 - \delta_2,$$
$$Q_{00} = Q_{03} = Q_{11} = Q_{23} = Q_{30} = Q_{13} = Q_{31} = Q_{32} = 0,$$
$$f_0 = r,\ f_1 = f_2 = \rho\, r,\ f_3 = -2\,\rho\, r,$$

where $\rho > 0$, $r = (120\,\delta_2 - 19)/(2(115\,\delta_2 - 76))$ and $\delta_3 = 2\,\delta_1/r$. Moreover, the periodic perturbation is given as

$$\mathcal{P}_i = (1-4x_i)\,(x_1 + x_2 + x_3)\,(1 + \alpha\cos(\omega t) + \beta\sin(\omega t)),$$

where $\omega = 1$, $\alpha = -1$, $\beta = 0$.

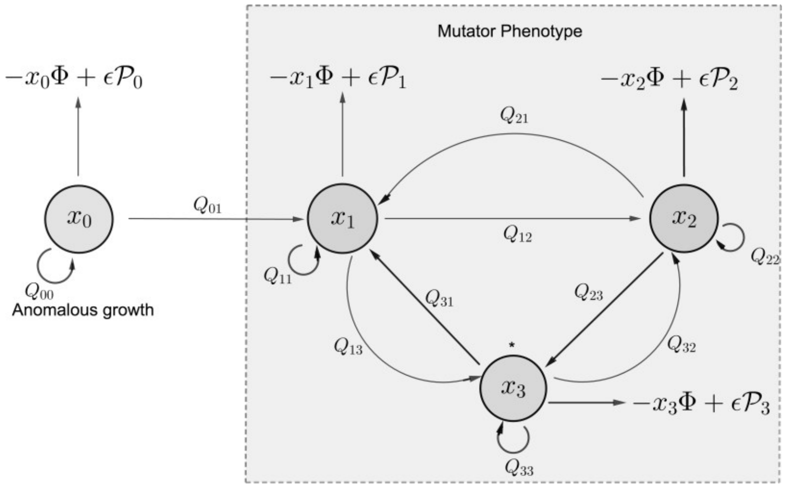

Fig. 1 We illustrate the interaction of the four populations x_0, x_1, x_2, x_3, considering x_0 a genetically stable population. The population corresponding to x_3 collects too many mutations and is not viable, resulting in a negative growth coefficient. This is indicated here by an asterisk.

Considering the previous parameters in equations (5), and using the fact that the hyperplane $x_0 + x_1 + x_2 + x_3 = 1,$ is an invariant manifold, we obtain the following reduced system

$$
\begin{aligned}
\frac{dx_1}{dt} &= \delta_1 \rho x_2 - \delta_1 \rho r x_3 - x_1(\rho(-r x_3 + x_1 + x_2) + 1 - (x_1 + x_2 + x_3)) + \epsilon \mathcal{P}_1, \\
\frac{dx_2}{dt} &= \rho x_3(\delta_1 (r+2) - r) - (\delta_1 - 1)\rho x_1 - x_2(\rho(-r x_3 + x_1 + x_2) \\
&\quad + 1 - (x_1 + x_2 + x_3)) + \epsilon \mathcal{P}_2, \\
\frac{dx_3}{dt} &= \delta_1 \rho x_1 - \rho x_2(\delta_1 + \delta_2 - 1) - 2\delta_1 \rho x_3 - x_3(\rho(-r x_3 + x_1 + x_2) \\
&\quad + 1 - (x_1 + x_2 + x_3)) + \epsilon \mathcal{P}_3.
\end{aligned}
\tag{7}
$$

In the following section, we will pay special attention to the dynamics in a neighborhood of the origin, which is an equilibrium of the reduced system with a remarkable biological interpretation.

5.1 Analysis of dynamics in a neighborhood of the origin

The origin is an equilibrium for the above system (7) of differential equations, corresponding with $\mathcal{E}_1$. This section will study the dynamics in a neighborhood of the origin for the case where the linear analysis does not decide the behavior. In [7], a similar analysis is carried out for the case of the modified quasispecies model, which concludes that the origin undergoes a Zero-Hopf bifurcation with associated parameter ϵ. We will show that this phenomenon is also observed in the classical quasispecies model. However, in the classical quasispecies model, the Zero-Hopf bifurcation occurs for values of the parameters out of the biological domain. Still, we prove that the classical model shares the mechanism leading to the Zero-Hopf orbits type.

Next, we will set conditions for the equilibrium $E_0 = (0,0,0)$ to be of the Zero-Hopf type. We will consider $\epsilon = 0$ and analyze the eigenvalues associated with the linear part of system (7). After that, we will normalize the linear part by means of a linear change of variables leading to the canonical Jordan form.

Let J be the matrix associated with the linearization of system (7) with $\epsilon = 0$, which is given by

$$
J = \begin{pmatrix} -1 & 10\,\delta_1 & -10\,\delta_1 r \\ -10(-1 + \delta_1) & -1 & 10(\delta_1(2+r) - r) \\ 10\,\delta_1 & -10(\delta_1 + \delta_2 - 1) & -1 - 20\,\delta_1 \end{pmatrix}.
$$

The characteristic polynomial associated is

$$P(\lambda) = -(m_0 + m_1\lambda + m_2\lambda^2 + \lambda^3),$$

where

$$\begin{aligned} m_0 &= \frac{(3+20\,\delta_1)}{115\,\delta_2-76}\,(5\,\delta_2(200\,\delta_2(3\,\delta_1-2)-2530\,\delta_1+471)+342(20\,\delta_1-1)),\\ m_1 &= \frac{1}{115\,\delta_2-76}\big(1000\,\delta_2^2(29\,\delta_1-6)+5\,\delta_2\big(9300\,\delta_1^2-11610\,\delta_1+1459\big)\\ &\quad -38\big(650\,\delta_1^2-570\,\delta_1+31\big)\big),\\ m_2 &= 3+20\,\delta_1. \end{aligned}$$

In what follows, we will discuss the case of one zero eigenvalue. Thus, we impose $\delta_1 = -3/20$, so that the equilibrium has the following characteristic polynomial and eigenvalues

$$P(\lambda) = -\left(\lambda^3 - \frac{\omega_1}{4\,\omega_2}\,\lambda\right),$$

where $\omega_1 = 41400\,\delta_2^2 - 68195\,\delta_2 + 19931$, $\omega_2 = 115\,\delta_2 - 76$. This polynomial has roots

$$\lambda_1 = 0, \quad \lambda_2 = -\kappa\, i, \quad \lambda_3 = \kappa\, i,$$

where $\kappa = \frac{1}{2}\sqrt{-\omega_1/\omega_2}$. Notice that the quotient ω_1/ω_2 is greater or equal than zero in the interval $\delta_2 \in [0.3798, 0.6608]$, and strictly negative otherwise. Therefore, since δ_2 is a probability, we are in the scenario of the Zero-Hopf bifurcation for $\delta_2 \in [0, 0.3798) \cup (0.6608, 1]$. Note also that $\delta_1 = -3/20$ has no biological meaning.

5.2 Existence and stability of Periodic Orbits

The following theorem is our main result, and employs the following notation

$$\begin{aligned} J_1 &= 2\,\omega_2\,\kappa_0,\\ J_2 &= 190\,\delta_2^2\,\omega_1^2\kappa_0,\\ J_3 &= \big(\sqrt{3}\big(\omega_2\big)^2\,\delta_2^2\kappa_0(\omega_1)^2(20\,\delta_2(25\,\delta_2(\,\delta_2(5\,\delta_2(460\,\delta_2(16365630\,\delta_2-96682247)\\ &\quad +106612450449)-660229287386)+442846089285)-3790212697827)\\ &\quad +10340819679099))^{1/2}+3\,\delta_2\,\omega_2\kappa_0(10\,\delta_2(3055\,\delta_2-5638)+20957)\big). \end{aligned}$$

Now, we introduce the following notation for the reduced system $x=(x_1,x_2,x_3)$, and establish the main result regarding the existence of periodic orbits.

Theorem 5. *(Existence and stability of periodic orbits) For each small* ϵ *and* $\delta_2 \in [0,0.3798) \cup (0.6608,1]$*, the system of equations* (7) *has a periodic orbit* $x(t,\epsilon)$ *with the following initial condition*

$$x(0,\epsilon) \;=\; \frac{\epsilon}{J_1}\big((10\,\omega_2\,\kappa r^*(11-8\,\delta_2)+3\kappa_0 v^*(60\,\delta_2-19)),(2\,\omega_2\,\kappa r^*(460\,\delta_2-523)+19\,\kappa_0\,v^*),v^*\big)+O(\epsilon^2), \quad (8)$$

with

$$r^* = \frac{(5\,\delta_2-6)(41\,\delta_2-19)}{19\,\delta_2\Omega},$$

$$v^* = \frac{1}{J_2}\big(2482433010000000\,\delta_2^8-15661057828250000\,\delta_2^7+41152370476425000\,\delta_2^6-58121953732978750\,\delta_2^5+47413658707644500\,\delta_2^4-22229977534124025\,\delta_2^3+5526801380303815\,\delta_2^2-561691887664908\,\delta_2+J_3\big). \quad (9)$$

Moreover, this periodic orbit bifurcates from the Zero-Hopf equilibrium $E_0=(0,0,0)$ *when* $\epsilon=0$*, and is unstable.*

Proof. We start by considering a change of variables to get system (7) in a convenient form. For this purpose, we use the eigenvectors associated to λ_i to carry out the following linear change of variables $(x_1,x_2,x_3)\to(u,v,w)$, expressing the linear part of (7) in the origin in the real canonical Jordan form

$$\begin{pmatrix}u\\v\\w\end{pmatrix}=\begin{pmatrix}\dfrac{57-180\,\delta_2}{-2\omega_2} & \dfrac{1300\,\delta_2-1459}{2\kappa_0} & \dfrac{5(11-8\,\delta_2)\,\kappa}{\kappa_0}\\ \dfrac{19}{2\,\omega_2} & \dfrac{1840\,\delta_2-2311}{2\kappa_0} & \dfrac{(460\,\delta_2-523)\,\kappa}{\kappa_0}\\ 1 & 1 & 0\end{pmatrix}\begin{pmatrix}x_1\\x_2\\x_3\end{pmatrix},$$

where $\kappa_0=\big(4600\delta_2^2-10580\delta_2+6097\big)$. We also include here the expression of the inverse transformation

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} \frac{\omega_2\,(460\,\delta_2-523)}{\omega_1} & \frac{5\,\omega_2(8\,\delta_2-11)}{\omega_1} & \frac{-73\,\omega_2}{\omega_1} \\ -\frac{\omega_2\,(460\,\delta_2-523)}{\omega_1} & -\frac{5\,\omega_2(8\,\delta_2-11)}{\omega_1} & \frac{73\,\omega_2}{\omega_1}+1 \\ \frac{3}{2\,\kappa} & \frac{(20\,\delta_2-23)}{2\,\kappa} & \frac{-2}{\kappa} \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix}.$$

Applying this transformation to (7), and with the aid of A_i, and B_i, $i = 1,2,3$ given in Appendix A we are led to the following system

$$\dot{u} = A_1 + \epsilon B_1, \quad \dot{v} = A_2 + \epsilon B_2, \quad \dot{w} = A_3 + \epsilon B_3. \tag{10}$$

The final form of the system is obtained after the rescaling of variables $(u,v,w) = (\epsilon U, \epsilon V, \epsilon W)$, and time reparameterization $dt = (1/\epsilon)ds$, as follows

$$\begin{aligned} U' = {} & \frac{1}{n_1}\epsilon\Big(-\big(57500\,\delta_2^2-112865\,\delta_2+49476\big)\cos(\theta)\,\big(5\big(188600\,\delta_2^3-521180\,\delta_2^2 \\ & +450997\,\delta_2-115843\big)U+2\big(\big(264500\,\delta_2^3-692875\,\delta_2^2+584570\,\delta_2-160056\big)V \\ & +6W\,\omega_2\,\kappa(35\,\delta_2-39)\big)\big)-\omega_1\,U\big(95\,\delta_2\kappa_0 U+\big(-3289000\,\delta_2^3+9976250\,\delta_2^2 \\ & -9193390\,\delta_2+2331927\big)V+108W\,\omega_2\,\kappa(35\,\delta_2-39)\big)+\big(57500\,\delta_2^2-112865\,\delta_2 \\ & +49476\big)\,\big(5\big(188600\,\delta_2^3-521180\,\delta_2^2+450997\,\delta_2-115843\big)U+2\big(\big(264500\,\delta_2^3 \\ & -692875\,\delta_2^2+584570\,\delta_2-160056\big)V+6\,W\,\omega_2\,\kappa(35\,\delta_2-39)\big)\big)\Big)+O(\epsilon^2), \end{aligned} \tag{11}$$

$$\begin{aligned} V' = {} & \Omega W+\frac{1}{n_1}\epsilon\Big(5\big(3220\,\delta_2^2-8934\,\delta_2+5909\big)\cos(\theta)\,\big(5\big(188600\,\delta_2^3-521180\,\delta_2^2 \\ & +450997\,\delta_2-115843\big)U+2\big(\big(264500\,\delta_2^3-692875\,\delta_2^2+584570\,\delta_2-160056\big)V \\ & +6(35\,\delta_2-39)W\,\omega_2\,\kappa\big)\big)+\big(41400\,\delta_2^2-68195\,\delta_2+19931\big)V(-95\,\delta_2\kappa_0 U \\ & +\big(3289000\,\delta_2^3-9976250\,\delta_2^2+9193390\,\delta_2-2331927\big)V \\ & +108\,W\,\omega_2\,\kappa(39-35\,\delta_2))-5\big(3220\,\delta_2^2-8934\,\delta_2+5909\big)\,\big(5\big(188600\,\delta_2^3 \\ & -521180\,\delta_2^2+450997\,\delta_2-115843\big)U+2\big(\big(264500\,\delta_2^3-692875\,\delta_2^2+584570\,\delta_2 \\ & -160056)V+6\,W\,\omega_2\,\kappa(35\,\delta_2-39)\big)\big)\Big)+O(\epsilon^2), \end{aligned} \tag{12}$$

$$W' = -\Omega V + \frac{1}{n_2}\epsilon\big(-4(575\,\delta_2^2-1070\,\delta_2+456)\cos(\theta)\,(5(188600\,\delta_2^3-521180\,\delta_2^2 +450997\,\delta_2-115843)U+2((264500\,\delta_2^3-692875\,\delta_2^2+584570\,\delta_2-160056)V +6\,W\,\omega_2\,\kappa(35\,\delta_2-39)))+4(575\,\delta_2^2-1070\,\delta_2+456)\,(5(188600\,\delta_2^3 -521180\,\delta_2^2+450997\,\delta_2-115843)U+2((264500\,\delta_2^3-692875\,\delta_2^2+584570\,\delta_2 -160056)V+6\,W\,\omega_2\,\kappa(35\,\delta_2-39)))+W(-5750\,\delta_2^3(152U\,\omega_2\,\kappa-1144V\,\omega_2\,\kappa +5355747\,W)+1150\,\delta_2^2(1748\,U\,\omega_2\,\kappa-17350V\,\omega_2\,\kappa+32408694W) -5\,\delta_2(231686\,U\,\omega_2\,\kappa-3677356\,V\,\omega_2\,\kappa+3720999330\,W)-4663854(V\,\omega_2\,\kappa -1368W)+8998290000\,\delta_2^4W))+O(\epsilon^2), \tag{13}$$

where

$$n_1=\omega_1\omega_2\,\kappa_0,\quad n_2=2\omega_2^2\,\kappa\,\kappa_0,\quad \Omega=-\kappa.$$

Notice that the derivative of the variables with respect to the new independent variable is denoted now by a prime instead a dot.

Employing a first order Taylor expansion of the vector field given by equations (11), (12) and (13), and considering the cylindrical coordinates $U=\upsilon, V=r\sin\theta, W=r\cos\theta$ with $r>0$, we obtain

$$\begin{aligned}\frac{dr}{ds} &= \epsilon F_1(r,\theta,\upsilon)+O(\epsilon^2),\\ \frac{d\theta}{ds} &= \Omega+\epsilon F_2(r,\theta,\upsilon)+O(\epsilon^2),\\ \frac{d\upsilon}{ds} &= \epsilon F_3(r,\theta,\upsilon)+O(\epsilon^2),\end{aligned} \tag{14}$$

where F_1,F_2 and F_3 are given in Appendix A. The above equations guarantee that, for $\epsilon>0$ small enough $d\theta/ds\neq 0$, and hence θ may be used as the new independent variable yielding the reduced system

$$\frac{dr}{d\theta}=\epsilon\frac{1}{\Omega}F_1(r,\theta,\upsilon)+O(\epsilon^2),\quad \frac{d\upsilon}{d\theta}=\epsilon\frac{1}{\Omega}F_3(r,\theta,\upsilon)+O(\epsilon^2). \tag{15}$$

Note that this system is in the standard form of the average theory. Thus, we consider the averaged system associated with (15)

$$\frac{dr}{d\theta}=\epsilon\frac{1}{\Omega}\tilde{F}_1(r,\upsilon),\quad \frac{d\upsilon}{d\theta}=\epsilon\frac{1}{\Omega}\tilde{F}_3(r,\upsilon), \tag{16}$$

where

$$\tilde{F}_1(r,v) = \frac{1}{2\pi}\int_0^{2\pi} F_1\,(r,\theta,v), \quad \tilde{F}_2(r,v) = \frac{1}{2\pi}\int_0^{2\pi} F_3\,(r,\theta,v).$$

Precisely,

$$\begin{aligned}\tilde{F}_1(r,v) \;&=\; \Big(\big(1247750\,\delta_2^3 - 2183325\,\delta_2^2 + 779950\,\delta_2 + 77976\big)r^* - 5v(19\,\delta_2\omega_1 r^* \\ &\qquad -4\,\omega_2\,\kappa\big(205\,\delta_2^2 - 341\,\delta_2 + 114\big)\big)\Big),\\ \tilde{F}_2(r,v) \;&=\; 5\kappa_0 v\big(2357500\,\delta_2^3 - 19\,\omega_1\,\delta_2\,v - 5719965\,\delta_2^2 \\ &\qquad +4172951\,\delta_2 - 940044\big) - 32\omega_2^2\kappa(-39 + 35\delta_2)\,(-651 + 500\delta_2)r^*.\end{aligned}$$

After some algebraic manipulations, we check that the non-degenerate equilibrium points of system (16) are given by

$$\begin{aligned} r^* &= \frac{(5\,\delta_2 - 6)\,(41\,\delta_2 - 19)}{19\,\delta_2\,\Omega},\\ v^* &= \frac{1}{J_2}\big(2482433010000000\,\delta_2^8 - 15661057828250000\,\delta_2^7 + 41152370476425000\,\delta_2^6 \\ &\quad -58121953732978750\,\delta_2^5 + 47413658707644500\,\delta_2^4 - 22229977534124025\,\delta_2^3 \\ &\quad +5526801380303815\,\delta_2^2 - 561691887664908\,\delta_2 + J_3\big). \end{aligned} \tag{17}$$

Therefore, applying Theorem (6), we have that system (16) is endowed with a periodic orbit if the non-degeneracy condition is fulfilled. That is to say, if the following determinant does not vanish

$$\det\left(\frac{\partial(\tilde{F}_1,\tilde{F}_2)}{\partial(r,v)}\,|_{(r,v)=(r^*,v*)}\right) \neq 0. \tag{18}$$

A straightforward computation shows that the non-degeneracy condition is satisfied for $\delta_2 \in [0,0.3798) \cup (0.6608,1]$, where the above determinant (18) is negative. Therefore, by virtue of Theorem (6), we may conclude the existence of an unstable periodic orbit with of the non-averaged system with initial condition

$$(r(0,\epsilon),v(0,\epsilon)) = (r^*,v^*) + O(\epsilon).$$

This initial condition is reconstructed to the original frame by employing the inverse of the above transformations, which leads to the initial condition for the original system as

$$x(0,\epsilon) \quad = \quad \frac{\epsilon}{J_1}((10\,\omega_2\,\kappa r^*(11-8\,\delta_2) + 3\kappa_0 \upsilon^*(60\,\delta_2-19)), \\ (2\,\omega_2\,\kappa r^*(460\,\delta_2-523) + 19\,\kappa_0\,\upsilon^*),\upsilon^*) + O(\epsilon^2). \tag{19}$$

□

6. Numerical simulations

In this section, we will show the numerical simulations of the solution of the system (7), where we will illustrate the existence of a periodic orbit for specific values of the parameters. Our experiments have been carried out using the software *Wolfram Mathematica*, version 10.0.0.0 Mac OS X x86 (64-bit). This software is running on the platform Intel Core i5, 1.8 GHz (MacBook Air (13-inch, 2017)).

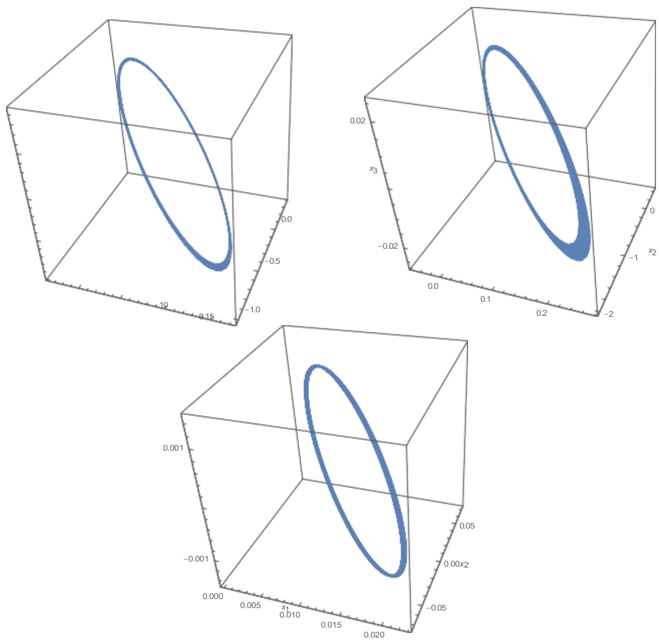

Fig. 2 Periodic orbits: in these simulations we consider the positive parameter ρ = 10. On the other hand, the level of genetic instability increases as δ_2 approaches zero. This simulation corresponds to high levels of genetic instability. From left to right $\delta_2 = 0.9$, $\delta_2 = 0.3$ and $\delta_2 = 0.7$, with $\epsilon = 0.01$, $\delta_1 = -3/20$, respectively.

The reduction in the number of variables, given by the relation $x_0 + x_1 + x_2 + x_3 = 1$, allows visualizing the periodic orbit corresponding to $X(t) = (x_1(t), x_2(t), x_3(t))$ in Figure (2). The averaging theory does not provide the exact initial condition of the periodic orbit but close coordinates. Moreover, in our case, the periodic orbit is unstable. Thus, we observe in Figure (2) how the numerical simulations depart from the actual periodic orbit when we compute the orbit for many periods

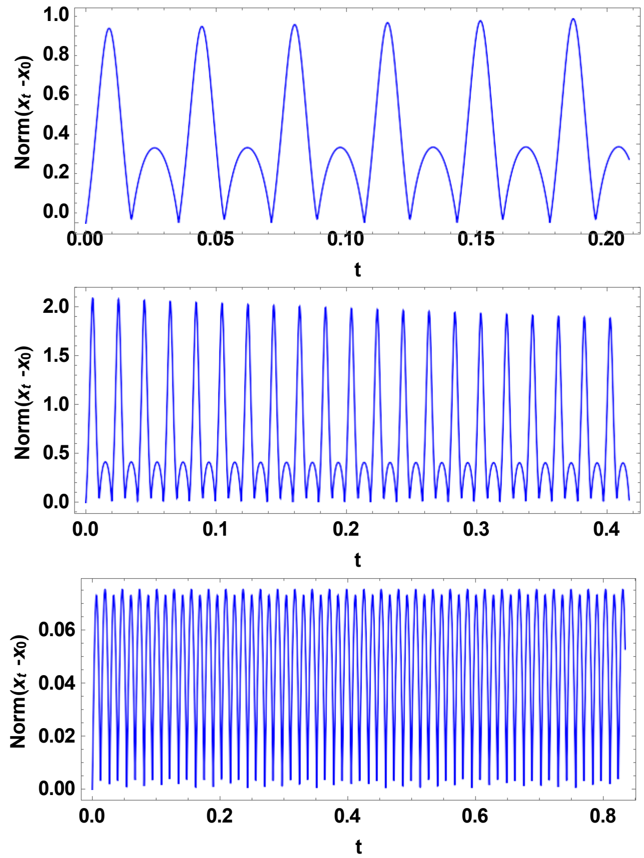

Fig. 3 Periodicity assessment: evolution of $\|X(t) - X_0\|$. We have $\delta_2 = 0.9$, $\delta_2 = 0.3$ and $\delta_2 = 0.7$, with $\epsilon = 0.01$, $\delta_1 = -3/20$, respectively.

To assess the periodicity of the orbit with the initial condition given by (8) we compute the solution $X(t)$ though $X_0 = x(0,\epsilon)$ given in (8). Then we plot in Figure (3) the evolution of $\| X(t) - X_0 \|$, and we observe the periodic passage of $X(t)$ close to its initial condition $X_0 = x(0,\epsilon)$.

Acknowledgments

Support from the research projects GI2310532, FE23202126, RE2482302 and Proyect Implementación año 5 del plan plurianual UBB, etapa 1 Convenio Marco UBB 2055 is acknowledged. The author J.L.Z. was supported by ANID-FONDECYT Iniciación 11250703.

Funding

Support from the research projects GI2310532, FE23202126, RE2482302 and Proyect Implementación año 5 del plan plurianual UBB, etapa 1 Convenio Marco UBB 2055 is acknowledged. The author J.L.Z. was supported by ANID-FONDECYT Iniciación 11250703.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

A Coefficients on the normalized and polar-cylindrical systems

A.1 Coefficients of equation (10)

$$
\begin{aligned}
A_1 = \frac{1}{(\omega_2\,\omega_1)\kappa_0}\big(&-18091800000\,\delta_2^5 u^2 + 136164600000\,\delta_2^5 u\,v + 71412355000\,\delta_2^4 u^2 \\
&-637310105000\,\delta_2^4 u\,v - 101232142500\,\delta_2^3 u^2 + 1126489773750\,\delta_2^3 u\,v \\
&-156492000\,\delta_2^3 u\,w\,\omega_2\,\kappa + 59532215025\,\delta_2^2 u^2 - 922321647600\,\delta_2^2 u\,v \\
&+432153900\,\delta_2^2 u\,w\,\omega_2\,\kappa - 11544334165\,\delta_2 u^2 + 342259217855\,\delta_2 u\,v \\
&-362576520\,\delta_2 u\,w\,\omega_2\,\kappa - 46477637037\,u\,v + 83949372\,u\,w\,\omega_2\,\kappa),
\end{aligned}
$$

$$B_1 = \frac{1}{(\omega_2\omega_1)\kappa_0}\Big(-156160800000\ \delta_2^5 u^2 - 87602400000\ \delta_2^5 u\, v + 54222500000\ \delta_2^5 u + 30417500000\ \delta_2^5 v + 688768580000\ \delta_2^4 u^2 + 373780820000\ \delta_2^4 u\, v - 256270945000\ \delta_2^4 u - 139386210000\ \delta_2^4 v - 1159442650000\ \delta_2^3 u^2 - 613788465000\ \delta_2^3 u\, v - 69552000\ \delta_2^3 u\, w\, \omega_2\, \kappa + 470432409000\ \delta_2^3 u + 17250\ \delta_2^3(14481219\, v + 1400 w\, \omega_2\, \kappa) + 918785583900\ \delta_2^2 u^2 + 482406089400\ \delta_2^2 u\, v + 192068400\ \delta_2^2 u\, w\, \omega_2\, \kappa - 416743252925\ \delta_2^2 u - 50\ \delta_2^2(4378455862\, v + 1486266 w\, \omega_2\, \kappa) + \big(2300\ \delta_2^2(72u - 25) - 5\ \delta_2(54556u - 22573) + 76(1049u - 651)\big)\cos(\theta)\ \big(5\big(188600\ \delta_2^3 - 521180\ \delta_2^2 + 450997\ \delta_2 - 115843\big)u + 2\big(\big(264500\ \delta_2^3 - 692875\ \delta_2^2 + 584570\ \delta_2 - 160056\big)v + 6(35\ \delta_2 - 39)\, w\, \omega_2\, \kappa\big)\big) - 337774691840\ \delta_2 u^2 - 180528668720\ \delta_2 u\, v - 161145120\ \delta_2 u\, w\, \omega_2\, \kappa + 176940738835\ \delta_2\, u + 30\ \delta_2(3132460384\ v + 2453358\ w\, \omega_2\, \kappa) + 46177336660\, u^2 + 25520609088\, u\, v + 37310832\, u\, w\, \omega_2\, \kappa - 28657241340\, u - 11577384(1368\ v + 2\ w\, \omega_2\, \kappa)\Big),$$

$$A_2 = \frac{1}{2(\omega_2\omega_1)\kappa_0}\Big(-36183600000\ \delta_2^5 uv + 272329200000\ \delta_2^5 v^2 + 142824710000\ \delta_2^4 u\, v - 1274620210000\ \delta_2^4 v^2 - 380880000\ \delta_2^4 w\, \omega_2\, \kappa - 202464285000\ \delta_2^3 u\, v + 2252979547500\ \delta_2^3 v^2 - 312984000\ \delta_2^3 v\, w\, \omega_2\, \kappa + 1503418000\ \delta_2^3 w\, \omega_2\, \kappa + 119064430050\ \delta_2^2 u\, v - 1844643295200\ \delta_2^2 v^2 + 864307800\ \delta_2^2 v\, w\, \omega_2\, \kappa - 2131203000\ \delta_2^2 w\, \omega_2\, \kappa - 23088668330\ \delta_2 u\, v + 684518435710\ \delta_2 v^2 - 725153040\ \delta_2 v\, w\, \omega_2\, \kappa + 1253309790\ \delta_2 w\, \omega_2\, \kappa - 92955274074\, v^2 + 167898744\, v\, w\, \omega_2\, \kappa - 243038614\, w\, \omega_2\, \kappa\Big),$$

$$B_2 = \frac{1}{2(\omega_2\omega_1)\kappa_0}\Big(-312321600000\ \delta_2^5 u\, v - 30364600000\ \delta_2^5 u - 175204800000\ \delta_2^5 v^2 - 17033800000\ \delta_2^5 v + 1377537160000\ \delta_2^4 uv + 168157600000\ \delta_2^4 u + 747561640000\ \delta_2^4 v^2 + 91882010000\ \delta_2^4 v - 2318885300000\ \delta_2^3 u\, v - 361143493000\ \delta_2^3 u - 1227576930000\ \delta_2^3 v^2 - 139104000\ \delta_2^3 v\, w\, \omega_2\, \kappa - 192707823000\ \delta_2^3 v - 13524000\ \delta_2^3 w\, \omega_2\, \kappa + 1837571167800\ \delta_2^2 u\, v + 374093713900\ \delta_2^2 u + 964812178800\ \delta_2^2 v^2 + 384136800\ \delta_2^2 v\, w\, \omega_2\, \kappa + 196642541500\ \delta_2^2 v + 52592400\ \delta_2^2 w\, \omega_2\, \kappa + 2\big(2300\ \delta_2^2(72v + 7) - 10\ \delta_2(27278v + 4467) + 79724v + 29545\big)\cos(\theta)\ \big(5\big(188600\ \delta_2^3 - 521180\ \delta_2^2 + 450997\ \delta_2 - 115843\big)u + 2\big(\big(264500\ \delta_2^3 - 692875\ \delta_2^2 + 584570\ \delta_2 - 160056\big)v + 6(35\ \delta_2 - 39)w\, \omega_2\, \kappa\big)\big) - 675549383680\ \delta_2 u\, v - 184994131750\ \delta_2 u - 361057337440\ \delta_2 v^2 - 322290240\ \delta_2 v\, w\, \omega_2\, \kappa - 97683288680\ \delta_2 v - 66628920\ \delta_2\, w\, \omega_2\, \kappa + 187720(491981\ u + 100764)v + 34225814350\ u + 51041218176\ v^2 + 74621664\, v\, w\, \omega_2\, \kappa + 27654120\ w\, \omega_2\, \kappa\Big),$$

$$A_3 = \frac{1}{2(\omega_2(2\omega_2\kappa))\kappa_0}\Big(-21900600000\,\delta_2^5 v + 100919975000\,\delta_2^4 v - 874000\,\delta_2^3 u\,w(2\omega_2\kappa) + 6578000\,\delta_2^3 v\,w(2\omega_2\kappa) - 179674056500\,\delta_2^3 v + 2010200\,\delta_2^2 u\,w(2\omega_2\kappa) - 19952500\,\delta_2^2 v\,w(2\omega_2\kappa) + 153051026925\,\delta_2^2 v + 108\big(166635000\,\delta_2^4 - 570287875\,\delta_2^3 + 690185150\,\delta_2^2 - 344536975\,\delta_2 + 59075484\big)w^2 - 1158430\,\delta_2 u\,w(2\omega_2\kappa) + 18386780\,\delta_2 v\,w(2\omega_2\kappa) - 61600492325\,\delta_2 v + 518206\,v\,(17822 - 9w(2\omega_2\kappa))\Big),$$

$$B_3 = \frac{1}{2(\omega_2(2\omega_2\kappa))\kappa_0}\Big(2433400000\,\delta_2^5 v - 10902690000\,\delta_2^4 v - 7544000\,\delta_2^3 u w(2\omega_2\kappa) - 184000\,\delta_2^3\,v(46\,w\,\omega_2\,\kappa - 104184) + 966000\,\delta_2^3\,w(2\omega_2\kappa) + 20847200\,\delta_2^2 u\,w(2\omega_2\kappa) + 400\,\delta_2^2 v(55430\,w\,\omega_2\,\kappa - 41338924) - 5748000\,\delta_2^2\,w\,\omega_2\,\kappa - 8\cos(\theta)\,\big(2(\omega_2)\,\big(\big(2300\,\delta_2^2 - 4505\,\delta_2 + 2106\big)\,v\big(575\,\delta_2^2 - 1070\,\delta_2 - w(2\omega_2\kappa) + 456\big) + 3(35\,\delta_2 - 39)\,w\big(\big(41400\,\delta_2^2 - 68195\,\delta_2 + 19931\big)\,w + (5\,\delta_2 - 6)\,(2\omega_2\kappa)\big)\big) + 5\big(188600\,\delta_2^3 - 521180\,\delta_2^2 + 450997\,\delta_2 - 115843\big)\,u\big(575\,\delta_2^2 - 1070\,\delta_2 - w(2\omega_2\kappa) + 456\big)\big) + 48\big(166635000\,\delta_2^4 - 570287875\,\delta_2^3 + 690185150\,\delta_2^2 - 344536975\,\delta_2 + 59075484\big)w^2 + 40\big(108445000\,\delta_2^5 - 501480500\,\delta_2^4 + 902987475\,\delta_2^3 - 786834595\,\delta_2^2 + 329606642\,\delta_2 - 52824408\big)u - 18039880\,\delta_2 u\,w(2\omega_2\kappa) - 160\,\delta_2 v(58457w(2\omega_2\kappa) - 43782384) + 2769120\,\delta_2 w(2\omega_2\kappa) + 1976(2345u - 432)\,w(2\omega_2\kappa) + 2560896\,v(w(2\omega_2\kappa) - 456)\Big),$$

A.2 Coefficients of equation (14)

$$F_1(r,\theta,v) = \frac{1}{(\omega_1\omega_2)\kappa_0}\sin(\theta)\,\Big(-5\big(3220\,\delta_2^2 - 8934\,\delta_2 + 5909\big)\,\big(2\big(264500\,\delta_2^3 - 692875\,\delta_2^2 + 584570\,\delta_2 - 160056\big)r\sin(\theta) + 5\big(188600\,\delta_2^3 - 521180\,\delta_2^2 + 450997\,\delta_2 - 115843\big)v + 6(35\,\delta_2 - 39)r(2\omega_2\kappa)\cos(\theta)\big) + 5\big(3220\,\delta_2^2 - 8934\,\delta_2 + 5909\big)\cos(\theta)\,\big(2\big(264500\,\delta_2^3 - 692875\,\delta_2^2 + 584570\,\delta_2 - 160056\big)r\sin(\theta) + 5\big(188600\,\delta_2^3 - 521180\,\delta_2^2 + 450997\,\delta_2 - 115843\big)v + 6(35\,\delta_2 - 39)r(2\omega_2\kappa)\cos(\theta)\big) + \big(41400\,\delta_2^2 - 68195\,\delta_2 + 19931\big)r\sin(\theta)\,\big(-95\,\delta_2\kappa_0 v + \big(3289000\,\delta_2^3 - 9976250\,\delta_2^2 + 9193390\,\delta_2 - 2331927\big)r\sin(\theta) - 54(35\,\delta_2 - 39)r(2\omega_2\kappa)\cos(\theta)\big)\Big) + \frac{1}{(\omega_1\omega_2)\kappa_0}\cos(\theta)\,\Big(6\big(4025\,\delta_2^2 - 7145\,\delta_2 + 2964\big)r\cos^2(\theta)\,\big(9(\omega_1)r - 4(5\,\delta_2 - 6)(2\omega_2\kappa)\big) + \cos(\theta)\,\big(5\big(4600\,\delta_2^2 - 10580\,\delta_2 + 6097\big)v\big(-4\big(23575\,\delta_2^3 - 54795\,\delta_2^2 + 39026\,\delta_2 - 8664\big) - 19\,\delta_2 r(2\omega_2\kappa)\big) + 24\big(20125\,\delta_2^3 - 59875\,\delta_2^2 + 57690\,\delta_2 - 17784\big)r(2\omega_2\kappa) + r\sin(\theta)\,\big(\big(3289000\,\delta_2^3 - 9976250\,\delta_2^2 + 9193390\,\delta_2 - 2331927\big)r(2\omega_2\kappa) + 8\big(681418125\,\delta_2^4 - 1198116000\,\delta_2^3 + 1033473100\,\delta_2^2 - 437823840\,\delta_2 + 72985536\big)\big)\big) + 4\big(2\big(11500\,\delta_2^3 - 36325\,\delta_2^2 + 37560\,\delta_2 - 12636\big)(76 - 115\,\delta_2)^2 r\sin(\theta) + 5\big(\big(108445000\,\delta_2^5 - 501480500\,\delta_2^4 + 902987475\,\delta_2^3 - 786834595\,\delta_2^2 + 329606642\,\delta_2 - 52824408\big)v - 30417500\,\delta_2^5 r\sin(2\theta)\big)\big)\Big),$$

$$F_2(r,\theta,\upsilon) = \frac{1}{r}\cos(\theta)\Big(\frac{-5}{(\omega_1\omega_2)\kappa_0}\big(3220\,\delta_2^2-8934\,\delta_2+5909\big)\big(2\big(264500\,\delta_2^3 -692875\,\delta_2^2+584570\,\delta_2-160056\big)r\sin(\theta)+5\big(188600\,\delta_2^3 -521180\,\delta_2^2+450997\,\delta_2-115843\big)\upsilon+6(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta)\big) +5\big(3220\,\delta_2^2-8934\,\delta_2+5909\big)\cos(\theta)\big(2\big(264500\,\delta_2^3-692875\,\delta_2^2 +584570\,\delta_2-160056)r\sin(\theta)+5\big(188600\,\delta_2^3-521180\,\delta_2^2+450997\,\delta_2 -115843)\upsilon+6(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta))+\big(41400\,\delta_2^2-68195\,\delta_2 +19931)r\sin(\theta)\big(-95\,\delta_2\kappa_0\upsilon+\big(3289000\,\delta_2^3-9976250\,\delta_2^2+9193390\,\delta_2 -2331927)r\sin(\theta)-54(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta)) -\frac{1}{(\omega_1\omega_2)\kappa_0}\tan(\theta)\big(6\big(4025\,\delta_2^2-7145\,\delta_2+2964\big)r\cos^2(\theta)(9(\omega_1)r -4(5\,\delta_2-6)(2\,\omega_2\,\kappa))+\cos(\theta)\big(5\kappa_0\upsilon\big(-4\big(23575\,\delta_2^3-54795\,\delta_2^2+39026\,\delta_2 -8664)-19\,\delta_2 r(2\,\omega_2\,\kappa))+24\big(20125\,\delta_2^3-59875\,\delta_2^2+57690\,\delta_2 -17784)r(2\,\omega_2\,\kappa)+r\sin(\theta)\big(\big(3289000\,\delta_2^3-9976250\,\delta_2^2+9193390\,\delta_2 -2331927)r(2\,\omega_2\,\kappa)+8\big(681418125\,\delta_2^4-1198116000\,\delta_2^3+1033473100\,\delta_2^2 -437823840\,\delta_2+72985536)))+4\big(2\big(11500\,\delta_2^3-36325\,\delta_2^2+37560\,\delta_2 -12636)(76-115\,\delta_2)^2 r\sin(\theta)+5\big(\big(108445000\,\delta_2^5-501480500\,\delta_2^4 +902987475\,\delta_2^3-786834595\,\delta_2^2+329606642\,\delta_2-52824408\big)\upsilon -30417500\,\delta_2^5 r\sin(2\theta)\big)\big)\big)\Big),$$

$$F_3(r,\theta,\upsilon) = \frac{1}{(\omega_1\omega_2)\kappa_0}\big(\big(57500\,\delta_2^2-112865\,\delta_2+49476\big)\big(2\big(264500\,\delta_2^3 -692875\,\delta_2^2+584570\,\delta_2-160056\big)r\sin(\theta)+5\big(188600\,\delta_2^3 -521180\,\delta_2^2+450997\,\delta_2-115843\big)\upsilon+6(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta)\big) -\big(57500\,\delta_2^2-112865\,\delta_2+49476\big)\cos(\theta)\big(2\big(264500\,\delta_2^3-692875\,\delta_2^2 +584570\,\delta_2-160056)r\sin(\theta)+5\big(188600\,\delta_2^3-521180\,\delta_2^2+450997\,\delta_2 -115843)\upsilon+6(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta))+\big(-41400\,\delta_2^2+68195\,\delta_2 -19931)\upsilon\big(95\,\delta_2\kappa_0\upsilon-\big(3289000\,\delta_2^3-9976250\,\delta_2^2+9193390\,\delta_2 -2331927)r\sin(\theta)+54(35\,\delta_2-39)r(2\,\omega_2\,\kappa)\cos(\theta))).$$

B. First Order Averaging Theory

This section recalls the main result of the first-order averaging theory, see [3,4]. Let us consider the differential system

$$\dot{x} = \epsilon F(t,x) + \epsilon^2 R(t,x,\epsilon), \tag{20}$$

with $x \in \tilde{\Omega} \subset \mathbb{R}^n$, $\tilde{\Omega}$ a bounded domain, and $t \geq 0$. Moreover we assume that $F(t,x)$ and $R(t,x,\epsilon)$ are T-periodic in t. The averaged system associated to the system (20) is defined by

$$\dot{y} = \epsilon \tilde{F}(y), \tag{21}$$

where $\tilde{F}(y) = \frac{1}{T}\int_0^T F(t,y)dt$. The next theorem says under what conditions the singular points of the averaged system (21) provide T-periodic orbits for the system (15).

Theorem 6. *Let us consider system* (20) *and assume that the vector functions* F*,* R*,* $D_x F$*,* $D_x^2 F$ *and* $D_x R$ *are continuous and bounded by a constant independent* $\epsilon \in [0,\infty) \times \tilde{\Omega}$*, with* $\tilde{\Omega} \subset \mathbb{R}^2$*. Moreover, we suppose that* F *and* R *are* T *-periodic in* t*, with* T *independent of* ϵ*.*

1. *If* $p \in \tilde{\Omega}$ *is a singular point of the averaged system* (21) *such that* $det\left(D_x \tilde{F}(p)\right) \neq 0$*. Then, for* $|\epsilon| > 0$ *sufficiently small, there exists a* T*-periodic solution* $x(t,\epsilon)$ *of system* (20) *such that* $x(0,\epsilon) \to p$ *as* $\epsilon \to 0$*.*

2. *If the singular point* $y = p$ *of the averaged system (21) has all its eigenvalues with negative real part then, for* $|\epsilon| > 0$ *sufficiently small, the corresponding periodic solution* $x(t,\epsilon)$ *of system (20) is asymptotically stable and, if one of the eigenvalues has positive real part* $x(t,\epsilon)$*, it is unstable.*

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