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Hopf Bifurcation of A Mathematical Model of Blood Partial Pressures in Human Cardiovascular-Respiratory System

Jean Marie Ntaganda
College of Science and Technology
School of Pure and Applied Sciences
Department of Applied Mathematics
University of Rwanda, Huye, Rwanda
jmnta@yahoo.fr
j.m.ntaganga@ur.ac.rw

Roger Muremyi
College of Science and Technology
School of Pure and Applied Sciences
Department of Applied Mathematics
University of Rwanda
Huye, Rwanda
muremyiroger@yahoo.fr

Abstract: *In this paper, we are interested in looking for Hopf bifurcation solutions for mathematical model of arterial and venous pressures during physical activity. The mathematical model is governed by a system of delay differential equations. The algorithm for determining the critical delays that are convenable for Hopf bifurcation is used. The illustrative example for a 30 years old woman is taken.*

Keywords: *Systemic arterial pressure, Systemic venous pressure, cardiovascular/respiratory system, delay, numerical simulation, Hopf bifurcation.*

1. INTRODUCTION

The human cardiovascular system is a transport system of the oxygen, carbon dioxide [1] and nutrients are carried by the blood from the various muscles and organs. The respiratory system is also a transport system of gases between the environment and the tissues [2, 3]. It acts to exchange oxygen which is very important as it is needed by various tissues in terms of metabolism with carbon dioxide produced by metabolic activities. Mathematical models have many applications in the control of the human body include epidemiology, immunology, physiology, cell mobility, the control of the cardiovascular and respiratory system. A very important discussion for human health is the control of the cardiovascular and respiratory system. The knowledge of this control mechanism is very helpful for improving diagnostics and treatment of diseases of this system. In terms of control function in cardiovascular system; the autonomic nervous system controls and regulates all activities. The heart rate is controlled by both systems (sympathetic and parasympathetic nervous systems) [4, 5]. If the sympathetic nervous system excites a particular organ, often parasympathetic nervous system inhibits it [6].

Since the 1950's, the human cardio-respiratory system has been modeled using dynamical mathematical models. The compartmental theory has been used for developing the most of those mathematical models [4, 7, 8, 9, 10]. By setting a set of parameters to link the cycles of heart and respiration mechanism, the models of cardiovascular system and respiratory can be simply integrated. Mathematically, this control consists of solving optimal control problems. The equation of motion is the commonly accepted mathematical model of the respiratory system which provides the basis for the most clinically applied methods of respiratory mechanics analysis. S. Ganzert derives the equations for model identification in respiratory mechanics under conditions of mechanical ventilation [11]. This was the first application of an equation discovery technique to measured respiratory data from intensive care medicine. In 2007, S. Sepehris developed physical based model of human respiration, he modeled the slow deep breathing by tunnel diode oscillator [12]. The numerical simulation results and theoretical analysis on dynamics of cardiovascular- respiratory system and the abnormal cases were compared with the empirical reports to verify the validity of the proposed dynamic models [8]. It was noticed that the heart-lung interaction is inherently unstable, especially if certain heart-lung disease or injuries are present. For realistic contribution, the proposed models can be employed for controller synthesis for medical equipments. They can be used also for determining the variation of trajectories of some determinant parameters of cardiovascular -respiratory system. The behavior of these parameters is provided by a qualitative study. In 2007, a bicompartmental mathematical model for determining blood pressures response to cardiovascular and respiratory system has been designed [10]. Taking two delays we can deal with determining the Hopf bifurcation points of this model during physical activity where we consider three cases: Walking, Jogging, and Running fast.

This paper is organised as follows. In section 2, we set mathematical model equations as well as equilibrium points. The section 3 deals with the asymptotic states and algorithm for determining the bifurcation points. In section 4 we present test results for a 30 years old woman during physical activity. The concluding remarks are presented in section 5.

2. Setting Mathematical Model Equations

One of an important phenomena to human health is the control of the cardiovascular and respiratory system. The question that often arises is of determining heart rate and alveolar ventilation for controlling systemic arterial pressures to prevent cardiac accidents [12]. For a healthy subject, it is well known that heart rate and alveolar ventilation depend on he or she is trained or untrained. The models generally consist of solving control optimal problems of nonlinear differential equations with cumbersome terms, leading to unstable solutions. An interesting global model has been proposed but it possesses unstable equilibrium states [4]. This model requires that we must, first, search stable equilibrium states and, secondly, compute the solution on an interval *0, T* with small value of *T* for the initial state which is very closed to the equilibrium state. Such model doesn't permit to understand a long-term cardiovascular-respiratory system in the case of aerobic physical activities. In this section we would like to present a mathematical model for determining blood partial pressures with respect to heart rate and alveolar ventilation. The diagram of a three compartment is shown in the figure 1 where we consider the systemic arterial compartment *ASC* the systemic venous compartment *VSC*

Based on the diagram presented in the figure 1 and physiology properties of the human cardiovascular and respiratory system the mathematical model equations are [10]:

$$\begin{cases} \dfrac{dP_{as}(t)}{dt} = -P_{as}(t) + P_{vs}^{\gamma}(t)\, f(H,\dot{V}_A) \\ \dfrac{dP_{vs}(t)}{dt} = -P_{vs}(t) + P_{as}^{\delta}(t)\, g(H,\dot{V}_A) \end{cases} , \qquad (1)$$

where the functions f and g have been identified as follows [10].

Walking case:

$$f\; H,V_A \;= \exp(2.6812\,\dot{V}_A^{-0.0479} + 3.4921\,H^{-0.0943}) ,$$

$$g(H,\dot{V}_A) = \dot{V}_A \exp(H^{-30.7207} - 0.0981)$$

Jogging case:

$$f\; H,V_A \;= \exp(0.9990\,H^{0.1179} + 1.1522\,H^{0.2280}) ,$$

$$g(H,\dot{V}_A) = \dot{V}_A \exp(H^{-0.2105} - 0.0981)$$

Running fast:

$$f(H,\dot{V}_A) \quad \exp \quad (0.5472\,\dot{V}_A^{-0.3820} + 0.7518\,H^{0.2846}) ,$$

$$g(H,\dot{V}_A) = \dot{V}_A \exp \quad (H^{-0.0985} - 1.7440) .$$

The constants of the model equations (1) are given as 0.0112, 0.1724 [10].

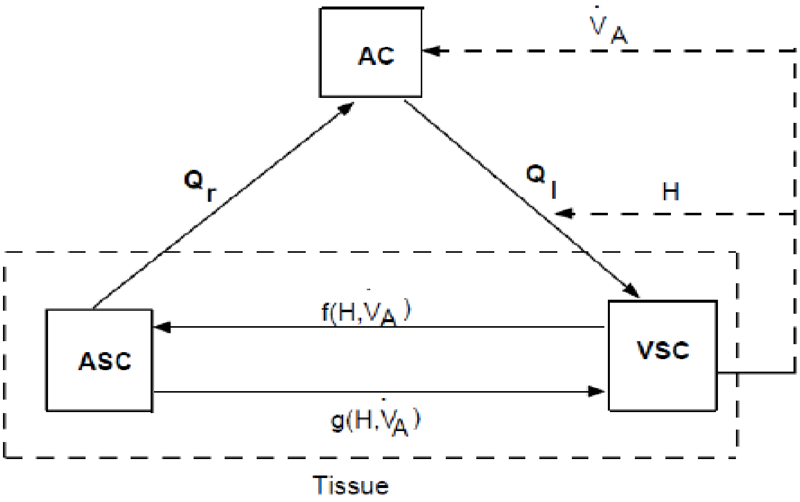

Figure 1. *A three compartment diagram of human cardiovascular system*

It has been shown that the role of the human respiratory is to exchange the unwanted gas by products of metabolism CO_2 for O_2 which is necessary for metabolism. The transfer of these gases is then distributed to the different parts of the body through the capillaries and the alveoli. The figure 1 is composed with three compartments which are systemic and pulmonary, they are arranged in series and two pumps (left and right ventricle). The right heart pumps blood into the pulmonary arteries, which form a tree that distributes the blood to the lungs. The smallest branches of this tree are the pulmonary capillaries, where carbon dioxide leaves and oxygen enters the blood. Leaving the pulmonary capillaries, the oxygenated blood is collected by the pulmonary veins, through which it flows back to the left heart.

Proposition [10].

Assume that f and g are positive functions and differentiable with respect to their argument, then for given positive constants P_{vs}^0 and P_{as}^0 , there exist control functions H , V_A such that the system () admits a unique positive solution P_{as}, P_{vs} $C_{1\ 0,T}{}^{2}$ that satisfies $P_{as}(0) = P_{as}^0$ and P_{vs} 0 $P_{vs.}^{0}$ Moreover this solution is asymptotically stable.

The effectiveness of the control of heart rate and alveolar ventilation is influenced by the transport delays because blood gases must be transported a physical distance from the lungs to the sensory sites where these gases are measured. These delays arise also in the contexts such as the baroreflex loop [13]. The interaction between heart rate, blood pressure, cardiac output, and blood vessel resistance is quite complex and gives the limited knowledge available of this interactions. The model equations (1) present the cardiovascular respiratory control mechanism via an optimal control derived from control theory. This control is stabilizing and is reasonable approach based on mathematical considerations as well as being further motivated by the observations that many physiologists cite optimization as a potential influence in the evolution of biological system [14]. In this work we adapt model equations (1) to include the effects of two transport delays as follows

$$\begin{cases} \dfrac{dP_{as}(t)}{dt} = -P_{as}(t) + P_{vs}^{\gamma}(t-\tau_{vs})f(H,\dot{V}_A) \\ \dfrac{dP_{vs}(t)}{dt} = -P_{vs}(t) + P_{as}^{\delta}(t-\tau_{as})g(H,\dot{V}_A) \end{cases}, \tag{2}$$

where vs, as are respectively systemic arterial and systemic venous delays and [illegible] and [illegible] are positive constants.

We are interested in determination of the equilibrium points and its stability.

Let us take

$x(t) = P_{as}(t),\ y(t) = P_{vs}(t),$

$u_1(t) = f(H, \dot{V}_A),\ u_2(t) = g(H, \dot{V}_A),$

then the model (2) becomes

$$\begin{cases} \dfrac{dx(t)}{dt} = -x(t) + y^{\gamma}(t - \tau_{vs})u_1(t) \\ \dfrac{dy(t)}{dt} = -y(t) + x^{\delta}(t - \tau_{as})u_2(t) \end{cases}. \tag{3}$$

Let $(x^*, y^*)^T$ be an equilibrium point of variable state $(x,y)^T$ and $(u_1,u_2)^T$ be the equilibrium of corresponding control parameters u_1,u_2^T . At the equilibrium point we have

$x(t) = x(t-\tau_{as}) = x^*$, $y(t)$- $y(t-\tau_{vs})$=y^* , $u_1(t) = u^*_1$ and $u_2(t) = u^*_2$

and the system (3) becomes

$$\begin{cases} -x^* + (y^*)^{\gamma} u_1^* = 0 \\ -y^* + (x^*)^{\delta} u_2^* = 0. \end{cases} \tag{4}$$

which can be written as follows

$$\begin{cases} (y^*)^{\gamma} u_1^* = x^* \\ (x^*)^{\delta} u_2^* = y^*. \end{cases} \tag{5}$$

Solving system (5) we get

$$x^* = (u_1^*)^{\frac{1}{1-\gamma\delta}} \times (u_2^*)^{\frac{\gamma}{1-\gamma\delta}} \text{ and } y^* = (u_1^*)^{\frac{\delta}{1-\gamma\delta}} \times (u_2^*)^{\frac{1}{1-\gamma\delta}}.$$

3. Asymptotic States

Assuming

$y_{\tau_{vs}}(t) = y(t - \tau_{vs})$ and $x_{\tau_{as}}(t) = y(t - \tau_{as})$

the system (3) is written as follows

$$\begin{cases} \dfrac{dx(t)}{dt} = f_1(x, y_{\tau_{vs}}, u_1) = -x(t) + y^{\gamma}_{\tau_{vs}}(t)u_1(t) \\ \dfrac{dy(t)}{dt} = f_2(y, x_{\tau_{as}}, u_2) = -y(t) + x^{\delta}_{\tau_{as}}(t)u_2(t) \end{cases}.$$

Using the first order Taylor series around the equilibrium point, we get

$$\begin{cases} \dfrac{dx(t)}{dt} = \dfrac{\partial f_1(x^*, y^*, u_1^*)}{\partial x}(x - x^*) + \dfrac{\partial f_2(x^*, y^*, u_1^*)}{\partial y_{\tau_{vs}}}(y_{\tau_{vs}} - y^*) \\ \qquad + \dfrac{\partial f_3(x^*, y^*, u_1^*)}{\partial u_1}(u_1 - u_1^*) + \ldots \\ \dfrac{dy(t)}{dt} = \dfrac{\partial f_1(x^*, y^*, u_2^*)}{\partial y}(y - y^*) + \dfrac{\partial f_2(x^*, y^*, u_2^*)}{\partial x_{\tau_{as}}}(x_{\tau_{as}} - x^*) \\ \qquad + \dfrac{\partial f_3(x^*, y^*, u_2^*)}{\partial u_2}(u_2 - u_2^*) + \ldots \end{cases}$$

After calculations, the linearized system becomes

$$\begin{cases} \dfrac{dx(t)}{dt} = -(x-x^*) + \gamma(y^*)^{\gamma-1}u_1^*(y_{\tau_{vs}} - y^*) + (y^*)^{\gamma}(u_1 - u_1^*) \\ \dfrac{dy(t)}{dt} = -(y-y^*) + \delta(x^*)^{\delta-1}u_1^*(x_{\tau_{as}} - x^*) + (x^*)^{\delta}(u_2 - u_2^*) \end{cases},$$

which can be written in matrix form as follows

$$\begin{cases} \dfrac{dX(t)}{dt} = A_1X(t) + A_2X(t-\tau_{as}) + A_3X(t-\tau_{vs}) + DU(t) \\ X(t) = X_0, \ -\tau \le t \le 0, \end{cases} \tag{6}$$

where we set

$$X(t) = \begin{pmatrix} x-x^* \\ y-y^* \end{pmatrix}, \ A_1 = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \ U = \begin{pmatrix} u_1 - u_1^* \\ u_2 - u_2^* \end{pmatrix},$$

$$A_2 = \begin{pmatrix} 0 & 0 \\ \delta(x^*)^{\delta-1}u_2^* & 0 \end{pmatrix}, \ A_3 = \begin{pmatrix} 0 & \gamma(y^*)^{\gamma-1}u_1^* \\ 0 & 0 \end{pmatrix}.$$

The solution of the system (6) can be written as

$$\begin{cases} X(t) = H(t)e^{\lambda t} \\ X(0) = H(0). \end{cases} \tag{7}$$

Calculating the derivative from (7) we obtain

$$\frac{dX(t)}{dt} = \frac{dH(t)}{dt}e^{\lambda t} + \lambda H(t)e^{\lambda t}. \tag{8}$$

Taking into account (7) and (8) the system (6) becomes

$$\frac{dH(t)}{dt}e^{\lambda t} + \lambda H(t)e^{\lambda t} = A_1H(t)e^{\lambda t} + A_2H(t)e^{\lambda(t-\tau_{as})} + A_3H(t)e^{\lambda(t-\tau_{vs})} + DU(t),$$

that is $\dfrac{dH(t)}{dt}e^{\lambda t} = (A_1 + A_2e^{-\lambda\tau_{as}} + A_3e^{-\lambda\tau_{vs}} - \lambda I)H(t)e^{\lambda t} + DU.$

We can now find λ such that $(A_1 + A_2e^{-\lambda\tau_{as}} + A_3e^{-\lambda\tau_{vs}} - \lambda I) = 0,$ thus due to this condition $H(t)$ is the solution:

$$\begin{cases} \dfrac{dH(t)}{dt}e^{\lambda t} = DU(t) \\ H(0) = X_0, \end{cases}$$

where $H(t) = D\int_0^t U(s)e^{-\lambda s}ds + X_0.$

Consequently from (7) we have $X(t) = e^{\lambda t}[D\int_0^t U(s)e^{-\lambda s}ds + X_0].$

We know that the stability of this solution depend on the property of the parameter λ. Therefore, to find the stability of the solution of equation (6) is to study the stability of the homogeneous equation of the form

$$\frac{dX(t)}{dt} = A_1X(t) + A_2X(t-\tau_{as}) + A_3X(t-\tau_{vs}) \tag{9}$$

that is $\frac{dX(t)}{dt}=0.$

From the equation (9) we deduce the characteristic equation of the form:

$$\left|A_1+A_2e^{-\lambda\tau_{as}}+A_3e^{-\lambda\tau_{vs}}-\lambda I\right|=0.$$

which is written as

$$\begin{vmatrix} -1-\lambda & \gamma(y^*)^{\gamma-1}(u_1^*)e^{-\lambda\tau_{vs}} \\ \delta(x^*)^{\delta-1}(u_2^*)e^{-\lambda\tau_{as}} & -1-\lambda \end{vmatrix}=0,$$

After the calculations we get

$$(-1-\lambda)^2-\delta(x^*)^{\delta-1}(u_2^*)e^{-\lambda\tau_{as}}\gamma(y^*)^{\gamma-1}(u_1^*)e^{-\lambda\tau_{vs}}=0,$$

that is

$$\lambda^2+2\lambda+1-\delta(x^*)^{\delta-1}\gamma(y^*)^{\gamma-1}(u_2^*)e^{-\lambda\tau_{as}}(u_1^*)e^{-\lambda\tau_{vs}}=0.$$

Since

$$(y^*)^{\gamma}=\frac{x^*}{u_1^*}\text{ and }(x^*)^{\delta}=\frac{y^*}{u_2^*}\text{ (see(5))}$$

we get

$$\lambda^2+2\lambda+1-\delta\frac{y^*}{u_2^*}\frac{1}{x^*}\gamma\frac{x^*}{u_1^*}\frac{1}{y^*}u_2^*e^{-\lambda\tau_{as}}u_1^*e^{-\lambda\tau_{vs}}=0. \qquad (11)$$

Finally we obtain the characteristic polynomial of the form

$$P(\lambda)\equiv\lambda^2+2\lambda+1-\gamma\delta e^{-\lambda(\tau_{as}+\tau_{vs})}=0. \qquad (12)$$

Let us set $\lambda=i\omega$, the determination of Hopf bifurcation points for the equation (12) results in solving the system

$$\begin{cases} K(\omega,\tau_g,\tau_i)=0 \\ L(\omega,\tau_g,\tau_i)=0 \end{cases}$$

where

$$K(\omega,\tau_g,\tau_i)=\operatorname{Re}(P(i\omega)) \;\; and \;\; L(\omega,\tau_g,\tau_i)=\operatorname{Im}(P(i\omega)) \qquad (13)$$

are respectively real and imaginary part of $P(i\omega)$ [15]. The purpose of calculation is to try and find out bifurcation points using the α -dense curves in $\mathbb{R}^2$. The general algorithm for computing the bifurcation points of the system that being have the general form as (9) constitutes the main outcomes presented in [15]. We adopt the algorithm to our situation as follows.

1. Set $\alpha>0$ and define h_α as α -dense curve in $\mathbb{R}^2$
2. Write the functions K and L as defined in (13)
3. Define $K_\alpha(\omega,\phi)=K(\omega,h_\alpha(\phi))$ and $L_\alpha(\omega,\phi)=L(\omega,h_\alpha(\phi))$ where ϕ is angle to be determined

4. Find ($\omega_\alpha^*, \phi_\alpha^*$) solution of $K_\alpha(\omega,\phi)=0$ and $L_\alpha(\omega,\phi)=0$
5. Set $\tau_\alpha^* = h_\alpha(\phi_\alpha^*)$ as bifurcation point.

We apply this algorithm in order to get the critical delays of the system (9). From the results presented in [15] the curve defined by

$$x_1 = \alpha\theta_k \cos\theta_k, \quad x_2 = \alpha\theta_k \sin\theta_k, \; k = 0,1,2,....$$

is $\pi\alpha$ -dense in R^2 where α is a constant to be correctly chosen. The critical delays for Hopf bifurcations are given by $\tau_g^* = \alpha\theta^* \cos\theta^*$, $\tau_i^* = \alpha\theta^* \sin\theta^*$, where θ^* is obtained at step 4 of above algorithm.

4. TEST RESULTS

Our numerical simulations aim to determine the Hopf bifurcation points for a two delays model in the case of physical activities. For this purpose we consider an observed data of walking, jogging, running fast cases for the values presented in the table 1. Taking $\alpha = 3.5$ to have a curve that covers the space R^2 of the delay parameters and setting initial value $\theta_0 =$ 1.3 and considering three physical activities, the delay parameters are given in the table 2, 3 and 4 respectively.

Table 1. *The mean value for the heart rate, the alveolar ventilation, venous and arterial systemic pressure for the rest and three cases of physical activities.*

Exercise intensity	**Rest**	**Walking**	**Jogging**	**Running Fast**
Ventilation (L/min)	6	8.5	15	25
Heart rate (Beats /min)	70	85	140	180
Arterial Pas(mmHg)	140	110	135	170
Venous Pvs(mmHg)	3.566	3.46	3.28	3.23

Table 2. *Delay parameters from the resolution of algorithm in the walking case***.**

Delay parameters	Stability	Hopf bifurcation	Instability
τas	0.6689	0.8989	1.5899
τvs	0.6889	0.9999	1.8901

Table 3. *Delay parameters from the resolution of algorithm in the jogging case***.**

Delay parameters	Stability	Hopf bifurcation	Instability
τas	0.6989	0.8660	0.8989
τvs	0.6999	0.8999	0.9999

Table 4. *Delay parameters from the resolution of algorithm in the running fast case***.**

Delay parameters	Stability	Hopf bifurcation	Instability
τas	0.6698	0.8799	0.8898
τvs	0.6994	0.8669	0.9654

Implementing the algorithm presented in the section 2 we have the results illustrated in the figures 2, 2 and 4.

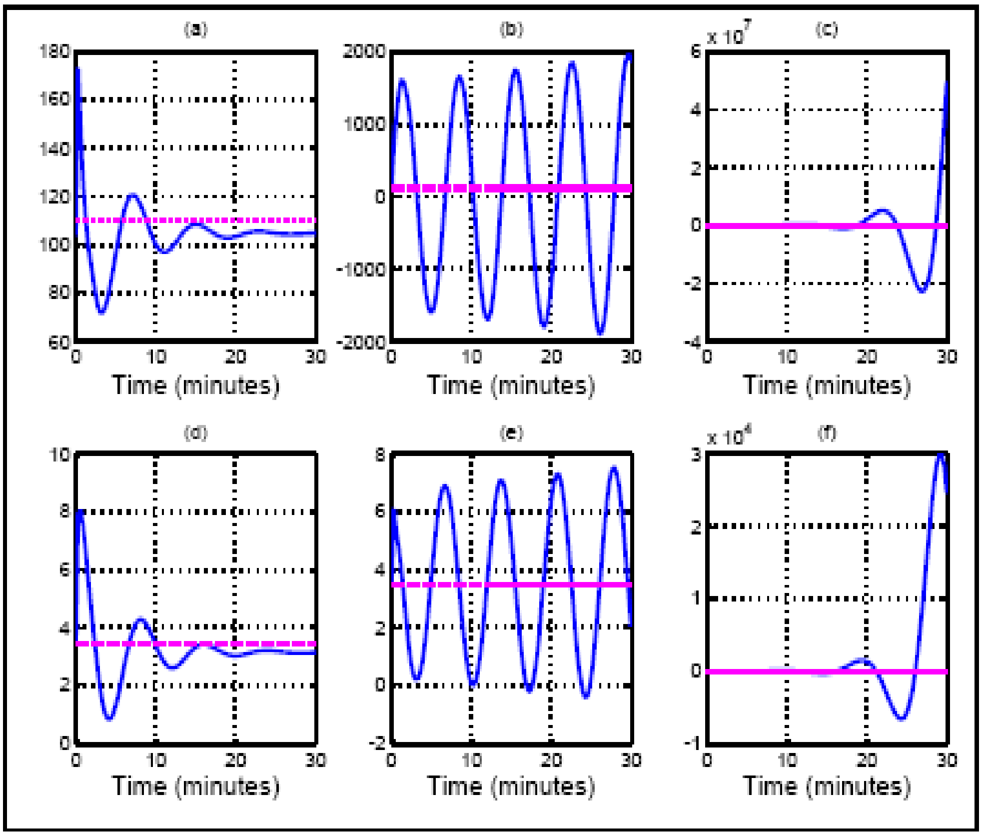

Figure 2: *Variation trajectory of systemic arterial and systemic venous pressures ((a), (b), (c), and (d), (e), (f)) compared to their respective equilibrium (dashed line) for a 30 years old woman during walking physical activity. The simulations are related to delay parameters from table 2. The transition phases are illustrated from left to right (phase asymptotically stable towards unstable phase) and the curve in the middle correspond to Hopf bifurcation parameters.*

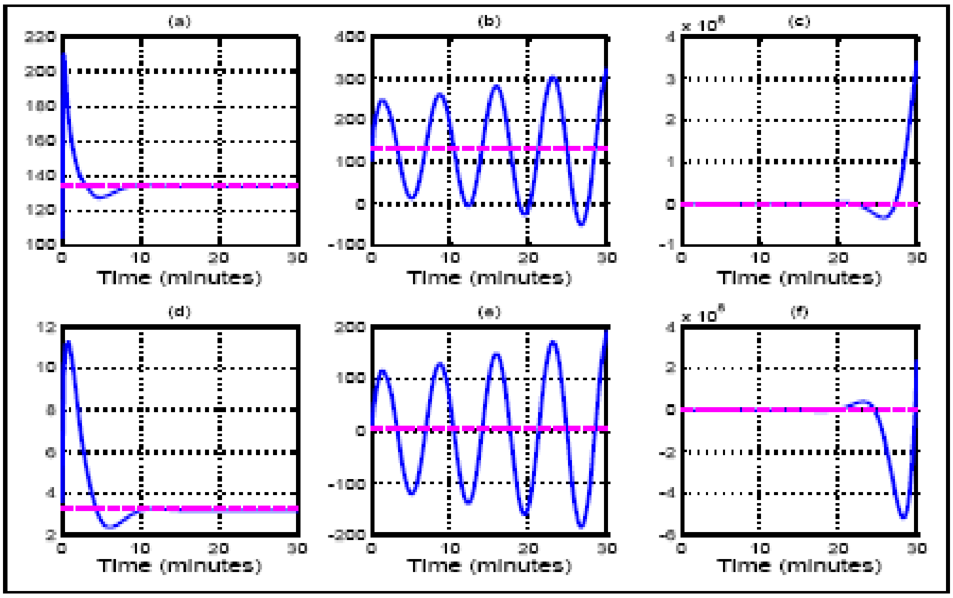

Figure 3: *Variation trajectory of systemic arterial and systemic venous pressures ((a), (b), (c), and (d), (e), (f)) compared to their respective equilibrium (dashed line) for a 30 years old woman during jogging physical activity. The simulations are related to delay parameters from table 3. The transition phases are illustrated from left to right (phase asymptotically stable towards unstable phase) and the curve in the middle correspond to Hopf bifurcation parameters.*

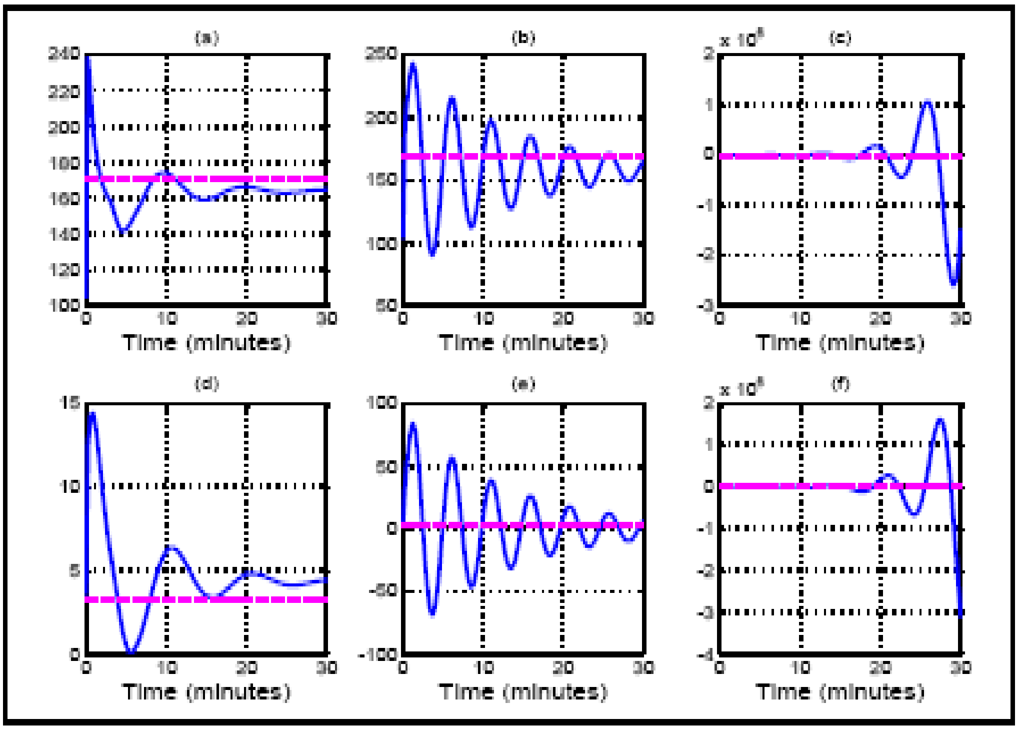

Figure 4: *Variation trajectory of systemic arterial and systemic venous pressures ((a), (b), (c), and (d), (e), (f)) compared to their respective equilibrium (dashed line) for a 30 years old woman during running fast physical activity. The simulations are related to delay parameters from table 4. The transition phases are illustrated from left to right (phase asymptotically stable towards unstable phase) and the curve in the middle correspond to Hopf bifurcation parameters.*

The phase portraits of transition phases for determinant parameters (Systemic arterial and Systemic venous pressures) are plotted in the figures 5, 6 and 7.

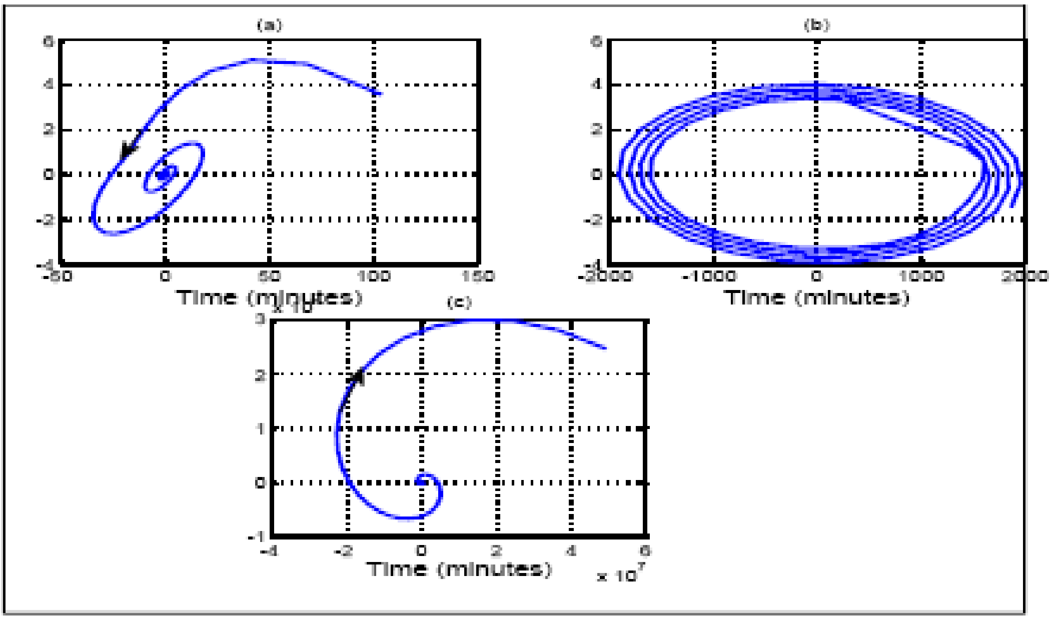

Figure 5: *The phase portrait (systemic arterial pressure versus systemic venous pressure according to variation of transition phases plotted in the figure 2 for a 30 years old woman during walking physical activity. The curves are illustrated from (a) to (c) (phase asymptotically stable towards unstable phase) and the curve in (b) corresponds to Hopf bifurcation.*

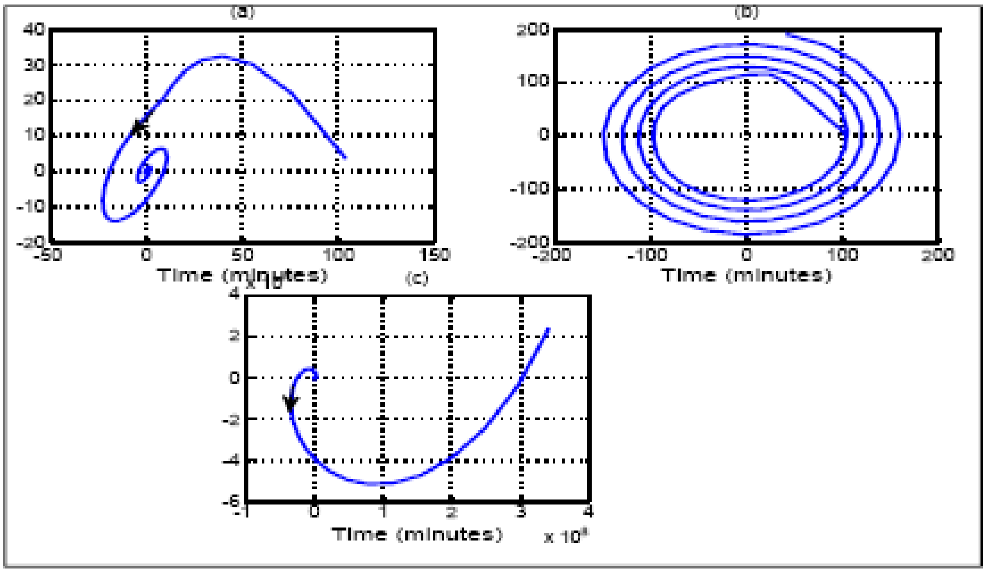

Figure 6: *The phase portrait (systemic arterial pressure versus systemic venous pressure according to variation of transition phases plotted in the figure 3 for a 30 years old woman during jogging physical activity. The curves are illustrated from (a) to (c) (phase asymptotically stable towards unstable phase) and the curve in (b) corresponds to Hopf bifurcation.*

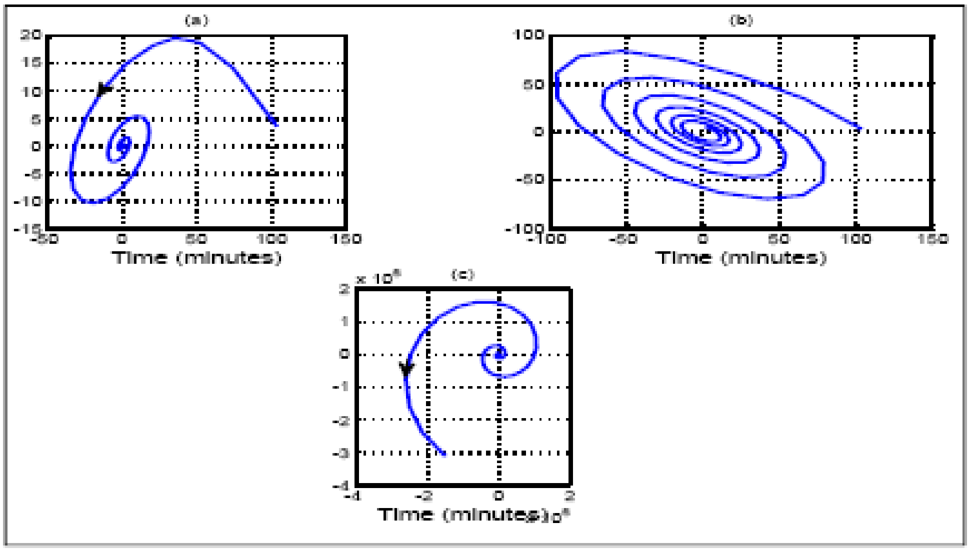

Figure 7: *The phase portrait (systemic arterial pressure versus systemic venous pressure according to variation of transition phases plotted in the figure 4 for a 30 years old woman during running fast physical activity. The curves are illustrated from (a) to (c) (phase asymptotically stable towards unstable phase) and the curve in (b) corresponds to Hopf bifurcation.*

In the walking case as first case of physical activity, the numerical simulation of transition phase of the arterial and venous systemic pressure use the delay parameters given in the table 2. This transition phase is illustrated in the (figure 2(b) and (e)) while phase portrait for those two physiological parameters for systemic arterial and systemic venous pressures are shown in the figure 5. We find that during walking, a small perturbation of Hopf bifurcation's delay parameters allows the subject to pass from stable state (figures 2(a) and (d)) by passing through an intermediate transition to unstable state (figures 2(c) and (f)). In this situation of instability, it appears that the state of subject causes to grow worse from the greatest value to the state closed to the equilibrium. In the case of stability, the state of the subject remains stationary around the equilibrium but a small perturbation causes oscillations which correspond to Hopf bifurcations (figure 2(b) and (e)). A small perturbation of Hopf bifurcation's delay parameters can be used to suffer a sudden downfall to an unstable state. The stability and instability behaviors of transition phase of the systemic arterial and systemic venous pressure are also shown by the phase portrait where we have a stable spiral figure 5(a) and unstable spiral figure 5(c). The results of numerical simulation by taking delay parameters given in the table 3 and 4 respectively show the variation of transition phase of arterial and venous systemic pressures in jogging case (figures 3 and 6) and running fast case (figure 4 and 7). The small perturbation of Hopf bifurcation's delay parameters can be used to suffer a sudden downfall to an unstable state. From these figures we find similarities in the behavior of walking case (figure 2 and figure 5).

5. Concluding Remarks

In this work we have investigated Hopf bifurcation for a bicompartmental mathematical model that describes the responses of arterial and venous pressures of cardiovascular-respiratory system due to its controls (heart rate and alveolar ventilation). An algorithm is used to find delay parameters of stability, instablility and Hopf bifurcation for a 30 years old woman during three different physical activities which are walking, jogging and running. The results show that Hopf bifurcations are the intermediate oscillation solutions from stability to instability regions.

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AUTHORS' BIOGRAPHY

Dr. Ntaganda Jean Marie, PhD holder in Numerical Analysis from Cheikh Anta Diop University of Dakar, Senegal (2004-2006) and Ouagadougou University, Burkina Faso (2004-2007). He is Senior Lecturer at National University of Rwanda, Faculty of Science, Department of Applied Mathematics where he is module leader of computation modules including Numerical Analysis and Programming. Since 2005 he is active researcher in Biomathematics where at least 25 publications have been published in international peer-reviewed journals.

Mr. Muremyi Roger, MSc in Applied Mathematics from University of Rwanda former NUR (National University of Rwanda) and specialization in statistical modeling and actuarial Sciences. Lecturer of Mathematics for economists, Data Analysis, inferential Statistics, econometrics in Economics at I.C.K (Catholic Institute of Kabgayi) in Rwanda.