Cusp bifurcation on cervical cancer mathematical model

T S N Asih1,*, Widodo2, L Aryati2 and F A Kusumo2

1Department of Mathematics, Universitas Negeri Semarang
2Department of Mathematics, Universitas Gadjah Mada

*Corresponding author: inung.mat@mail.unnes.ac.id

Abstract. There are some conditions for the existences of the equilibrium points on cervical cancer mathematical model and their local stability. In this paper we make continuation on some parameter to find a bifurcation phenomena. Bifurcation is the appearance of a topologically non-equivalent phase portrait under variation of parameters. While we make continuation on parameter maximum invasion rate together with continuation on infection rate, we find a Cusp Bifurcation. Cusp bifurcation is a condition where two-bifurcation curve are met. First we do the continuation by AUTO to detect the bifurcation. Further we do some analysis and simulation by Matlab and then make some interpretation for these phenomena.

1. Introduction
Cancer is one of the main causes of death, specially in the developing countries [1]. Cervical cancer is still the fourth most frequently cancer among women [2]. Various studies have been conducted to reduce the incidence and cancer mortality rates, both medical and non-medical studies. In mathematics several cancer models have been published. Some cervical cancer modeling are given by [3] and [4]. In the model on [3] cells in cervical tissue are divided into sub-populations based on the natural history of cervical cancer, namely susceptible cells, infected cells, pre-cancerous cells and cancer cells. Also added is the population of Human Pappilomavirus (HPV) that infects susceptible cells. Then the interaction between sub-populations and viruses is modeled in a dynamic system. Whereas in [4] cervical cancer modeling is viewed from the individual population, which are the male population and female population, and also the interaction between both population. Metastasis behavior of cervical cancer has been given on [5], and global stability of disease-free equilibrium has been given on [6].

The parameter values in the model [3] are not easy to obtain from data, because they are molecular data. On the other hand a study of bifurcation has been carried out. Bifurcation is the phenomena appearance of a topologically non-equivalent phase portrait under variation of parameters [7]. Manifold of the equilibria can be change by continuation of one or some parameters [8]. The discussion about bifurcation is interesting because it will provide a parameter representation that plays an important role in the solution of the model. In [4] a backward bifurcation caused by imperfect vaccination. In this paper we will evaluate bifurcation phenomena on the model given by [3] and see the interpretation. First simulation will be done using Auto then phase portrait will be seen using Matlab.

2. Mathematical Model
Recall a non-dimensional model of HPV infection on cervical cancer from [3]:

\[\text{Model equations} \]
\[
d\frac{dS}{dt} = rS(1 - (S + I)) - \alpha SV
\]
\[
d\frac{dI}{dt} = \alpha SV - aI - \delta I
\]
\[
d\frac{dV}{dt} = nI - cV
\]
\[
d\frac{dP}{dt} = \delta pI + bP - \theta \frac{P^2}{1 + P^2}
\]
\[
d\frac{dC}{dt} = \theta \frac{P^2}{1 + P^2} - kC
\]

where \( S \) is a density of normal cells, \( I \) is a density of infected cells, \( V \) is a density of free virus, \( P \) is a density of pre-cancer cells and \( C \) is a density of cancer cells. The analysis of those system giving a basic reproduction number \( R_0 = \frac{\alpha n}{c(a + \delta)} \).

In this paper we will focus on parameter \( \alpha \), which is infection rate and \( \theta \), which is the maximum invasion rate. The parameters values that given on [4] will be set as basic line parameters. Then we make continuation by AUTO to find bifurcation. AUTO that originally developed by Eusebius Doedel is a software to detect bifurcation problems by make continuation [9].

3. Cusp Bifurcation

Let we do continuation on one parameter and we get a bifurcation curve \( \Gamma \). Then we track this bifurcation curve by varied two parameters simultaneously. There some possibility to get a new bifurcation phenomena. One of them is cusp bifurcation condition [7]. Cusp bifurcation is a condition where two-bifurcation curve are met. Characteristic of cusp bifurcation is coalition of two tangent bifurcation [10].

In this case we do a backward continuation on \( \alpha \) and \( \theta \), then we detect a cusp bifurcation at \( \alpha \approx 9.099997264 \times 10^{-5} \) and \( \theta \approx 1.999999665 \). Cusp point is on point 11 of Figure 1. If we set \( \alpha = 9.2 \times 10^{-5} \) and \( \theta = 2.01 \) we got one negative equilibrium point and two positive equilibrium points. But when we set \( \alpha = 9.2 \times 10^{-5} \) and \( \theta = 1.9 \) the equilibrium changes become one negative equilibrium and one complex conjugate equilibrium. It means that the two positive equilibrium are coalescence and gone.

We also check the phase portrait around cusp point, given on Figure 2.

![Figure 1. Cusp bifurcation by AUTO at point 11.](image-url)
4. Concluding Remark

From the result above we see that parameters $\alpha$ which is infection rate and $\theta$ which is maximum invasion rate, are become a bifurcation parameters. A small changes on values of both parameters making a different behavior of the solution. The infection rate, according to reference [2] that most of cervical cancer cases are result of persistent infection of Human Papillomaviruses. So, it make sense that the infection rate is giving a significant influence in progression of cervical cancer. Some treatment has been done to control the infection rate, such as vaccination.

On the other side, invasion rate also an important factor in the development of cervical cancer. Invasion is a process from pre-cancer become invasive cancer. Some medical investigation also done to control the invasion rate. In [11] after treatment with o-phenanthroline, the rate of invasion was significantly decreased. So the advance investigation in infection rate and maximum invasion rate can be a prospective research in future.

References
[1] Torre L A, Bray F, Siegel R L, Ferlay J, Lortet-Tieulent J and Jemal A 2015 CA Cancer J. Clin. 65 87
[2] Small W, Bacon M, Bajaj A, Chuang L T, Fisher B J, Harkenrider M M, Jhingran A, Kitchener H C, Mileskin L R, Viswanathan A N and Gaffney D K 2017 Cancer 123 2404
[3] Noor Asih T S, Lenhart S, Wise S M, Aryati L, Adi-Kusumo F, Hardianti M S and Forde J 2016 Bull. Math. Biol. 78 4
[4] Omame A, Umana R A, Okuonghae D and Inyama S C 2018 Int. J. Biomath. 11 1850092
[5] Noor Asih T S, Aryati L, Adi-Kusumo F and Hardianti M S 2015 Far East J. Math. Sci. 96 981
[6] Aryati L, Noor Asih T S, Adi-Kusumo F and Hardianti M S 2018 Far East J. Math. Sci. 103 1535
[7] Kuznetsov Y A 1998 Element of Applied Bifurcation Theory, Second Edition Springer New York
[8] Liebscher S 2015 Bifurcation without Parameters Springer New York
[9] Doedel E 1981 Congr. Numer. 30 265
[10] Dizdarevic D, Dast D, Haag D, Main J, Cartarius H and Wunner G 2015 Phys. Rev. A. 91 033636
[11] Kato Y, Yamashita S and Ishikawa M 2002 Onc. Rep. 9 565