Journal of **N**onlinear **A**nalysis and **O**ptimization
Vol. 14, No. 2, No.01 (2023).
ISSN : **1906-9685**

NETWORK TOPOLOGIES DECODING CERVICAL CANCER

P.G.Monisha Assistant professor, Department of Mathematics, Marudhar Kesari Jain College for Women, Vaniyambadi Email: pgmonisha1@gmail.com

Abstract:

We introduce and investigate of Cervical Cancer is one of the leading causes of death among women worldwide. Its gradually increasing in the younger population, exactly in the developing countries. The study also be original that, the disease state has faster signal processing as the underlying network was very close to its corresponding random control.

Key words: Cancer networks, adjacency matrix, configuration model, high degree protein.

Introduction:

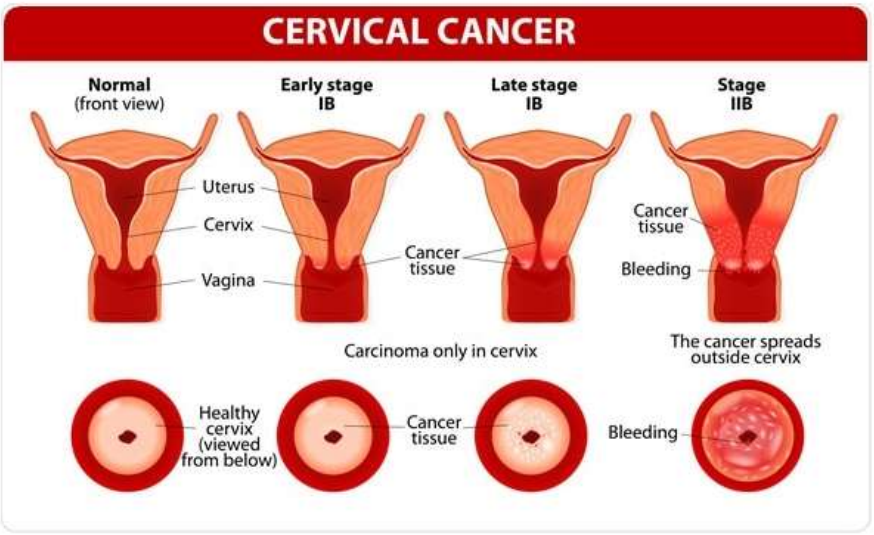
Approximately 528,000 new cases of cervical cancer were diagnosed and 266,000 deaths estimated worldwide in 2012.The incidence is found to be increasing gradually, mainly in the younger population of women. Though, the infection of human papilloma virus (HPV) has an important role in the occurrence of the disease, the percentage of women developing this cancer by infection of HPV alone is about 40%.

Biological processes are considered as complex networks of interactions among numerous components of the cell rather than independent interactions involving only a few molecules. **Earlier studies based on human disease network reveals that various types of cancers are interlinked to each other through number of pathways**, which are altered indifferent diseases.

Overview of cervical cancer:

Cervical cancer is a type of cancer that occurs in the cells of the cervix — the lower part of the uterus that connects to the vagina .Various strains of the human papillomavirus (HPV), a sexually transmitted infection, play a role in causing most cervical cancer.

When exposed to HPV, the body's immune system typically prevents the virus from doing harm. In a small percentage of people, however, the virus survives for years, contributing to the process that causes some cervical cells to become cancer cells.



Structural properties of cancer networks:

Total number of proteins and their interacting partners obtained for normal uterine cervix cell had 4481nodes and21801 connections, followed by 2636 nodes and 20040 links for cervical cancer data sets. From these data sets, we obtained various connected components referred as networks. Different properties of the normal and disease networks are summarized in **Table1**.

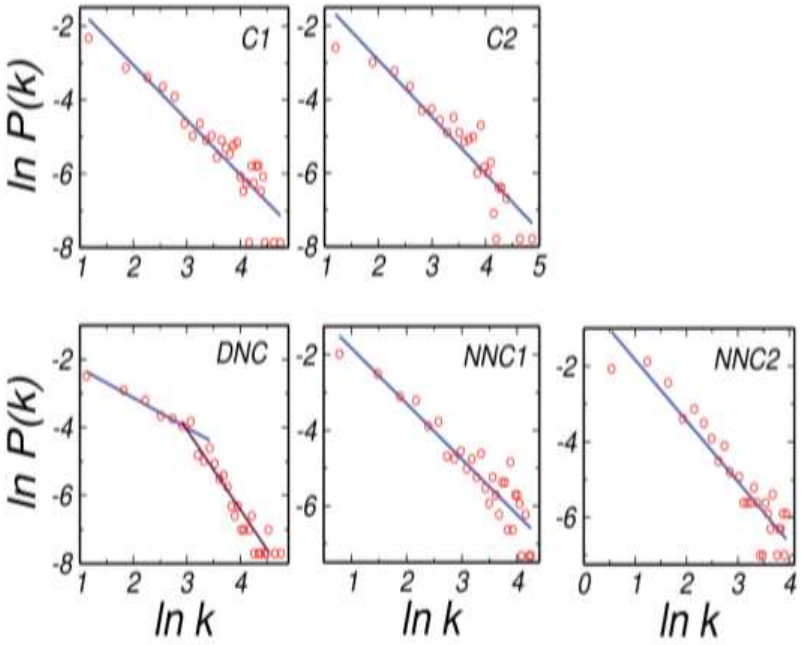
The first column in **Table1** indicated that the total number of proteins in the disease dataset is less than that of the normal data. A probable reason behind this could be more availability of the normal data in compare is onto the disease one.

Table1. Network properties of all the real networks.

Network	N_{ori}	N	Nc	(K)	D	CC	Ncc=1	Ncc=0
C1	1804	912	9132	20	7	0.31	32	163
C2	1804	724	5707	15	10	0.29	32	136
DNC	831	719	4711	13	8	0.31	37	141
NNC1	2677	694	3724	10	10	0.36	61	229
NNC2	2677	640	2263	**7**	12	0.27	49	275

The first column (Nori) represented the total number of proteins (nodes) in the normal not common (NNC1 and NNC2) networks, common (C1 and C2) and disease not common (DNC) networks, collected using various databases (described in result and discussion section), number of proteins in the largest connected cluster (N) and connections (Nc), the average degree (k), diameter (D), average clustering coefficient (CC), the number of nodes having CC = 1 (Ncc =1) and CC = 0 (Ncc =0) for all the networks.

The degree distribution P(k),of all the networks for both the normal and disease dataset followed power law.



Degree Distribution

Degree distribution for C1, C2, DNC, NNC1 and NNC2 datasets following the power law behaviour .Interesting observation is recognised for the DNC network having double power law.

This behavior is not found in other networks such as C1, C2, NNC1and NNC2and hence made the disease network different. Also, for cervical disease networks, the exponent lied below two for all the networks, which may be due to the finite size effect.

Comparison with random control networks:

We compared all the normal and disease networks with the corresponding configuration model which is a random replica of the networks considered here. The configuration model preserves the exact degree sequence of a network. By producing random networks for a given degree sequence of an array of size m $= \frac{1}{2}\sum_{i=1}^{N} k_i$, which have random connections among different elements. We generated ten such realizations for a given degree sequence, various properties of such networks are enlisted in **Table2**.

On comparing all the networks with the corresponding configuration models, we found that the properties of corresponding random controls, which were generated using the same degree sequence as of the real networks, deviated significantly from those of the real networks. This further indicated that communication in DNC network was faster in comparison to the other (NNC1 and NNC2) networks.

Table 2.

Network properties of the corresponding configuration model.

Network	(K)	D	CC	Ncc=1	Ncc=0
C1	20	6	0.11	10	219
C2	16	6	0.09	6	211
DNC	13	6	0.08	5	234
NNC1	11	6	0.08	11	313
NNC2	**7**	7	0.05	5	376

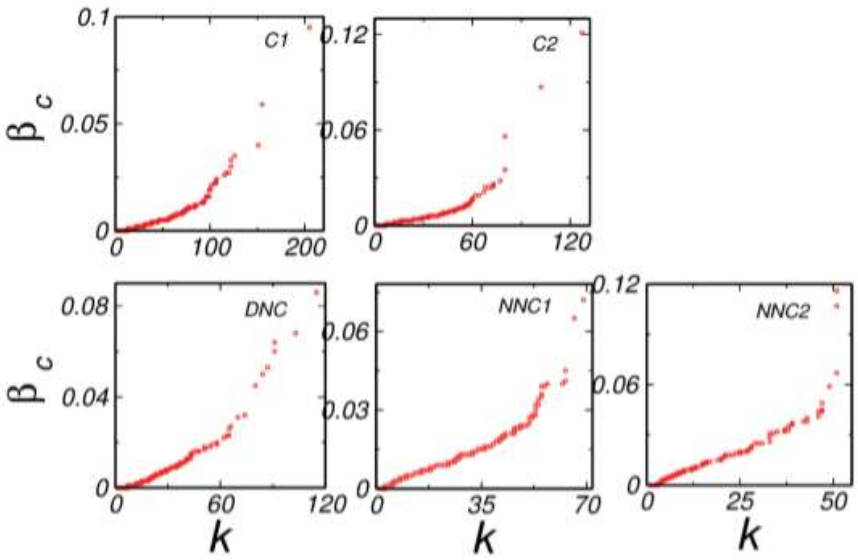


Figure (1) : Degree betweenness centrality correlation. (All the real models common (C1andC2), disease not common (DNC) and normal not common (NNC1 andNNC2) network have positive correlation.)

To one, which reflected that they are a part of complete sub-graphs (cliques). We found that, the k-βc for all the common networks depicted an overall positive correlation as expected (Fig (1)) because the high degree nodes end to have more betweenness centrality. This result was similar to their corresponding configuration model (Fig (2)). For all the real networks, the highest value of βc was very high when compared to the corresponding configuration model (Figs (1)) and (Fig (2)).

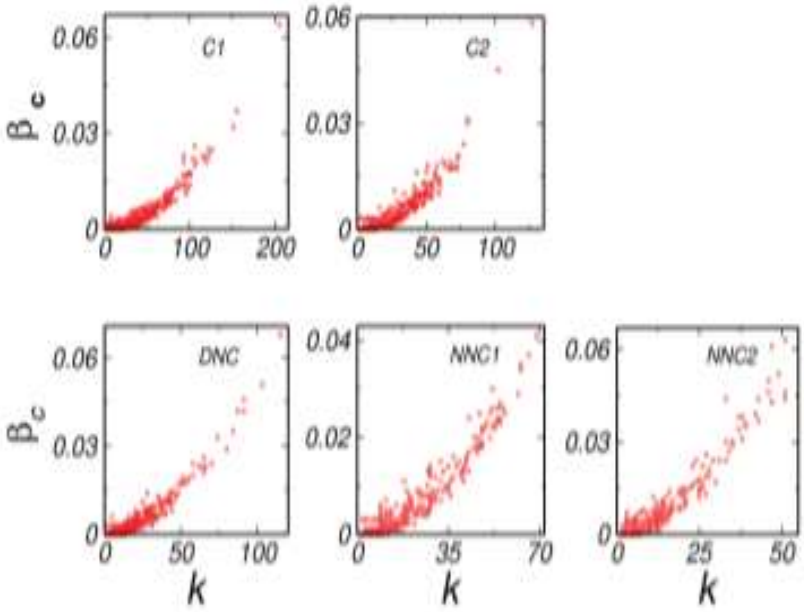


Figure (2): Degree – Betweenness centrality configuration correlation. **(**All the configuration models common (C1andC2), disease not common (DNC) and normal not common (NNC1andNNC2) network shows low betweenness centrality compared to the real model**.)**

According to their degree, and any deviation from it may be arising due to the special position that node possessed due to its functional importance in the network. A lower value of βc indicated no such preference of a high degree no depresent in DNC. In order to get the difference between the normal and disease states, we diverted our focus to aproperty which gave us a detailed information about the local behavior of nodes in the network. The NNC1and NNC2consisted of a part of interactions yielding an overall negative k−CC correlation, with major part of interactions being random reflected in absence of any k−CC correlations.

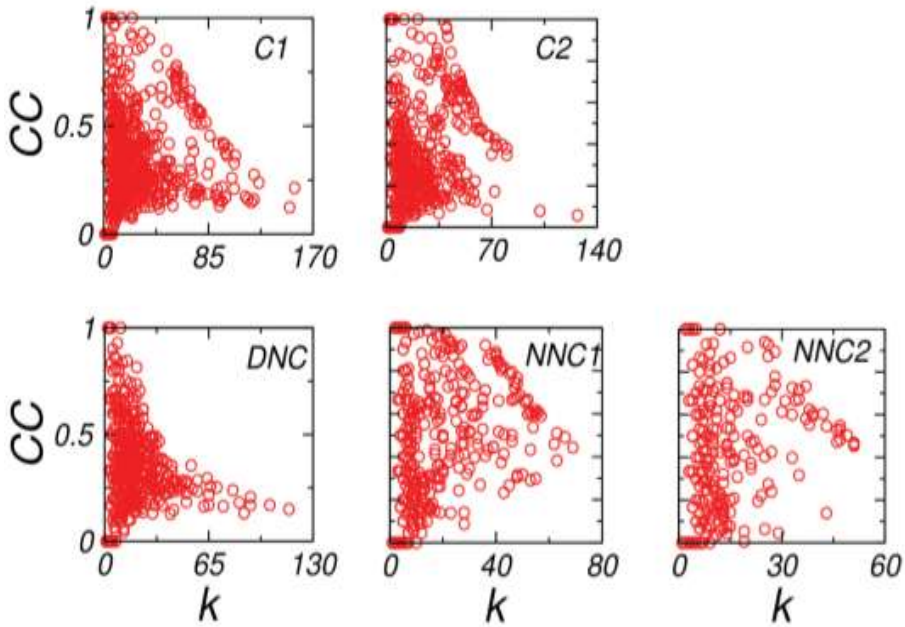


Figure (3) : Degree – clustering coefficient correlation.

(The figure showed k−CC correlation of the common (C1andC2), disease not common (DNC) and normal not common (NNC1andNNC2) networks, while the common and DNC networks reflected less random correlation, normal not common exhibited more towards random correlation.)

We further investigated the functional importance of the nodes which were in the high degree regime to understand the biological significance of these nodes in the occurrence of the cervical cancer**.**

Functional properties of high degree proteins:

We determined the degrees of the nodes in all the normal and disease networks and reviewed the functional properties of all the highest degree proteins available from the literature as these nodes are also known to be structurally very important. The proteins(nodes) having the distinctly high degree in disease states were VEGFA, DIF, IL6, PCNA,ESR1, CCND1, TGFB1. All these proteins were known to have distinct roles in cancer development.

Furthermore, VEGFA-induced activation of mTorsignaling cascades also promoted cancer cell growth through cyclinD1 and CDK4activation. The invasiveness occurred through MMP2andMMP3, while inhibition of VEGFA decreased the tumor growth VEGF-mediated signaling which occurred in tumor cells, contributed to the key aspects of tumorigenesis including the function of cancer stem cells and tumor initiation. Correspondingly clinical

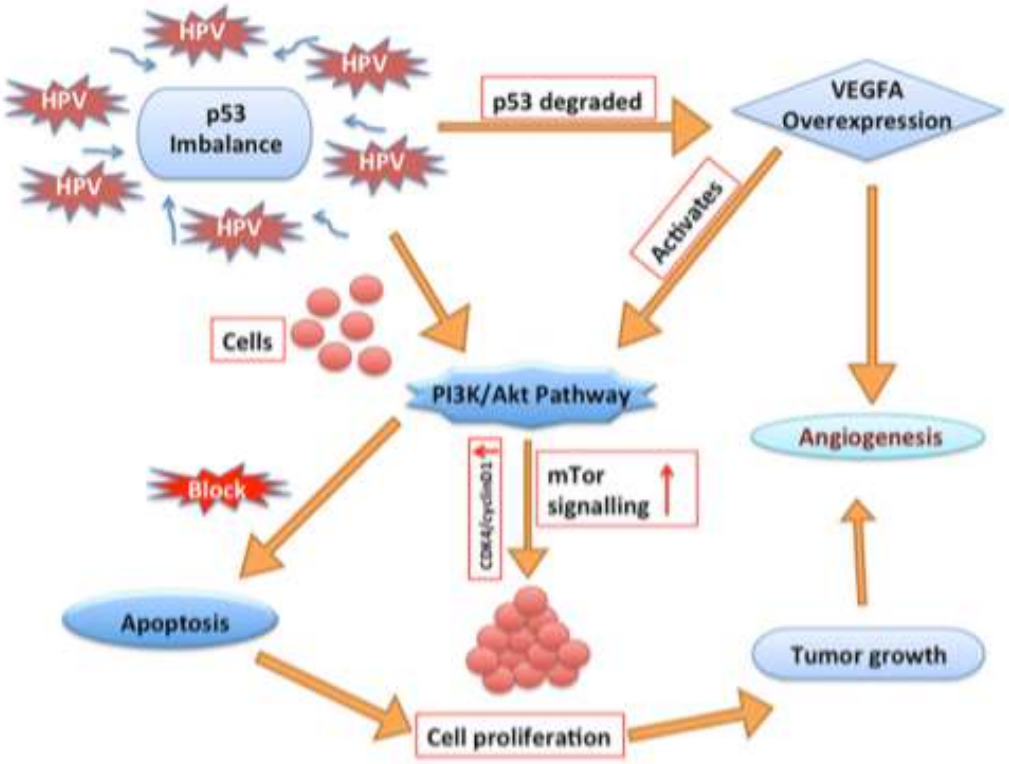


Figure (4) : VGEP regulation by P53.

(The Figure depicted how HPV induced p53 imbalance and regulated the expression of VEGF and PI3K/Akt pathway which in turn leads survival of cells and angiogenesis in cervical cancer.)

Studies have verified that VEGF-C expression is closely related to invasion phenotype and affects the patient's survival in cervical carcinomas. The next protein in the high degree regime was IL6, whose variation in host immune response by single nucleotide polymorphisms may contribute in cervical cancer risk.

This indicated an option to deprive the activated IL-6/STAT3 network against inflammation including fibroblast senescence intumor microenvironment **Fig (5)** which may be considered as a complement to increase the efficacy of the targeted therapy against HPV 16/18 in cervical cancer.

Up-regulation of PCNA was closely associated with HR-HPV and progressive CIN. However, the fact that PCNA is also expressed in normal squamous epithelium precludes the use of this marker as a potential screening tool for this cancer.

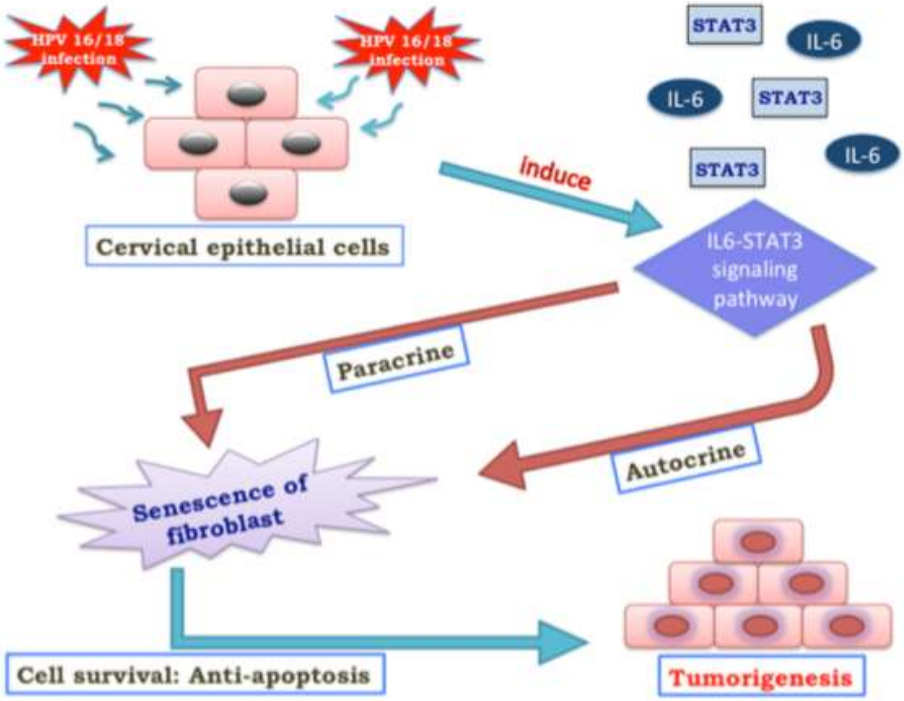


Figure (5) : IL 6 regulation. (The Figure depicted how IL-6up-regulated the STAT3 protein by both autocrine and paracrine signaling.)

Increased cell proliferation and was associated with higher tumor grading of cervical cancer patients. The next protein TGFB1 functioned to stimulate apoptosis and inhibit the growth factor. This also increased migration and invasiveness and resulted in metastases. Metastases contributed to the development of different types of cancer.

Proteins (nodes) having the highest degree in normal states wereCDC6, CCNA2, CENP-F, MKI67IP. Among these, CDC6 played critical roles in DNA replication and carcinogenesis, but biological significance of the CDC6on cervical carcinogenesis is still unknown. The next protein CCNA2 (also known asCyclinA2)was significantly over-expressed in various cancer types, which indicated its potential roles in cancer transformation and progression.

Functional properties of protein shaving CC=1

Next, we explored the nodes forming complete sub-graphs.
i.e. proteins having CC =1 in all the networks as they were known to be important for a network. It turned out that for the common networks, there where 64proteins found which had CC=1(Table 1).

Similarly, for DNC there were 37proteins (Table1).Most of the nodes having CC=1 lied towards a very low degree regime. Initially, we considered only the distinctly high degree proteins from the list with CC=1. From this analysis we found that the proteins having high degree and CC=1in common and disease states were GSG2, CIT and SRPR, PRR11, HNRNPA0respectively.

Data collection and network construction:

The network is a set of nodes linked by the edges corresponding to a relations defined between them. In a PPI network, proteins are the nodes and physical and chemical interaction between pair of nodes depicting the links between them. In an attempt to obtain all the proteins of the normal and cervical cancer we got data from various sources.

To keep the authenticity of data, we considered only those proteins into account which are reviewed and/or cited.We also focussed on most widely studied cervical cancer cell lines whose protein expression data is known in order to add more information.

Adjacency matrix and structural measures:

A number of statistical measures have been proposed to understand specific features of the network. In order to perform such analysis for cervical cancer, we defined the interaction matrix or the adjacency matrix of the network as follows

$$A_{ij} = \{1, if\ i \sim j$$
$$0, otherwise$$

The most basic structural parameter of a network is the degree of anode (di),which is defined as the number of neighbours a node has ($d_i = \sum_{j=1}^{n} A_{ij}$). The degree distribution P(k) reveals the fraction of vertices's having degree k and is known to be a finger print of the underlying network.

Configuration model:

We compared the real networks constructed as equ.1 for the disease and normal states with the corresponding configuration model. To construct a configuration model with degree sequence (d1,d2...dN),

Where, $d_1 \geq d_2 \geq \cdots \geq d_N$ was taken to the degree sequence of the corresponding real networks. We created a collection of N nodes such that first node had degree d1, second node had degree d2, and soon. With equal and uniform probability, two nodes were picked up at random from the collection and they were connected. This process was repeated till no node was left unpicked.

Conclusion:

In this study, we analyzed the PPI networks of cervix cells of the uterine tissue for normal and disease states and investigated their structural properties. This comprehensive study enabled us to identify differences between the **normal and disease** conditions. As discussed earlier, CC of anode corresponds to the connectivity between the neighbours of that node, we further analyzed the degree-CC (k-CC) correlations.

BIBLOGRAPHY

Cohen SJ, Alpaugh RK, Palazzo I et al. Fibroblast activation protein and its relationship to clinical outcome in pancreatic adenocarcinoma. Pancreas 2008;37: 154–158.

Conklin MW, Keely PJ. Why the stroma matters in breast cancer: insights into breast cancer patient outcomes through the examination of stromal biomarkers. Cell Adh Migr 2012;6:249–260.

JalanS, Bandyopadhyay JN.Randomness of random networks : A random matrix analysis. EPL. 2009;87(4):48010.doi:10.1209/0295-5075/87/48010

Newman ME, Strogatz SH, Watts DJ. Random graphs with arbitrary degree distributions and their applications.

PRE.2001;64(2):026118.doi:10.1103/PhysRevE.64.026118PMID:11497662

Nucleic Acids Res 2011;39(1):561–568.doi:10.1093/nar/gkq973 Szklarczyk D, Franceschini A, Kuhn M, Simonovic M ,Roth A, Minguez P.The STRING data base in 2011:functionalinteraction networks of proteins, globally integrated and scored.

Albert R,Jeong H,Barabási AL. Error and attack to lerance of complex networks.

Nature.2000; 406(6794):378–382.doi:10.1038/35019019PMID:10935628