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PREDICTION OF BREAST CANCER GENE USING ELECTRICAL NETWORK MODEL

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ABSTACT: Genomic alterations cause cancer. Therefore, analysis of cancer genome sequence is very important for cancer genomics as it gives insights into the disease. Here, an electrical network modeling concept is realized based on amino acid structure and sequence to predict the cancer gene behavior associated with breast cell. The gene network phase and magnitude are investigated for prediction of breast cancer gene. Network phase provides better outcome with respect to magnitude response and achieves 90% accuracy with 97% sensitivity and 0.7 MCC. The proposed model achieves 60 % better accuracy in comparison with the existing nucleotide based methods. Therefore, the results suggest that the proposed modeling concept can be used as effective tool for accurate prediction of cancerous and healthy genes.
Keywords: Genomics, Breast cancer, Network modeling, Prediction, Hydrophilic

1. INTRODUCTION

Cancer is major genetic disease which causes half of the million deaths in the world [Vogelstein and Kinzler 2004], and breast cancer is one of the most common cancers especially in the female that takes first and second place according to the estimated new cases and deaths respectively [Siegel et. al 2015]. For this reason, early prediction of breast cancer gene is very important for female. Various methods like ultrasound [Stachs et. al 2013], mammography [Moschidis et. al 2014] and biopsy [Veronesi et. al 2010] are used to predict the breast cancer, and among these methods biopsy is best method. But it is very time consuming, requires complicated procedures and most of all invasive. To overcome this restriction of biopsy, network modeling concept is proposed. Over the past few years, network modeling of biological systems is gaining popularity in genomics research to investigate the roles and functions of genetic molecules. For example, an impedance model is developed to study the structural and electrical properties of protein [Alfinito et. al 2008]. A PSpice model of DNA (Deoxyribo nucleic acid) molecule is realized to study the electrical conductivity of DNA [Hodzic and Newcomb 2007]. Passive analog electrical circuits are implemented to model protein structure [Sampath 2006]. Marshall (2010) introduced a passive RC circuit to model DNA/RNA. However, these methods are very complex regarding circuitry and computational load as they are based on nucleotide level. But amino acid based methods are more reliable and simple in predicting genetic abnormalities [McClellan 2012].

Amino acids are the essential 'building blocks' of proteins [Vaidyanathan 2004]. Restriction of certain amino acid production may stop the progression of cancer and help to kill cancer cells [http://www.apjohncancerinstitute.org]. Recently, many studies based on amino acid statistics are suggested to predict the cancer gene behavior [Das and Mitra 2011; Barman et. al 2011; Roy et. al 2014]. But accurately predicting cancer genes is still a significant challenge. To overcome the challenge, in this paper a network modeling concept is made to develop amino acid equivalent model for the prediction of cancer associated genes. The main goals of this paper are:

≡ Realize electrical circuit model for individual amino acid based on their atomic structure using passive electrical components resistor, inductor and capacitor.

≡ Model electrical network system for genes associated with breast cells by cascading individual amino acid circuit model.

≡ Investigate the network responses to predict cancer and healthy genes and analyze performance using measurement parameters i.e. measurement parameters i.e. accuracy, sensitivity, specificity etc.

2. MATERIALS AND METHODS

2.1. Circuit modeling of amino acid structure

In the present work, network model based strategy is applied on amino acid for prediction of cancer genes. The basic structure of amino acid contains a central alpha-carbon to which the backbone structure (carboxyl group and amino group) and the variable side chain (r) are attached (Figure 1A). The chemical compositions of side chain give unique characteristics to individual amino acid [Voet et. al 2002].

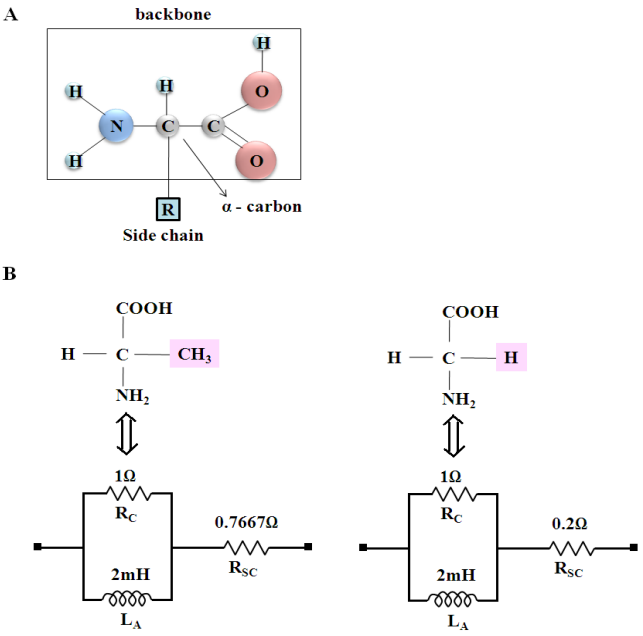

Figure 1. Amino acid structure.
(A) Chemical entity of amino acid consists of backbone and side chain group. The backbone is composed of amino and carboxyl group. (B) Equivalent electrical circuit for amino acid structure. The equivalent model for amino acid Alanine is shown to the left and Glycine to the right. The side chain is highlighted in pink. R_C represents the carboxyl group, L_A is for amino group and R_{SC} represents side chain group.

In the present network model, the carboxyl group (COOH) of backbone structure is represented by resistor R (1Ω) as it is constant for all amino acids and the amino group (NH_2) is represented by L (2mH). The value of L is 2mH for all amino acid except Proline as the NH_2 group consists of 2 hydrogen atoms. The amino acid Proline has distinctive cyclic structure as side chain group is bent and attaches itself with nitrogen in place of one of the hydrogen atoms of amino group. Therefore, Proline is represented by inductor L of 1mH as amino group (NH) has 1 hydrogen atom. The electrical components, representing the COOH and NH_2 groups are connected in parallel; for proline, the connection is series as it is of heterocyclic structure. The alpha carbon is taken as node.

Since the amino acid property varies with the side chain therefore instead of considering the side chain as a group, individual atom is taken here for designing the circuit models using the passive components R, L and C. The numbers of components are based on the atomic numbers of side chain atoms (Table 1). The carbon atom ($_6$C) is modeled by 6 resistor R (each of 1Ω) connected in parallel, nitrogen ($_7$N) by 7 inductor L (each of 1mH) connected in parallel, sulphur ($_{16}$S) by 16 inductor L (each of 1mH) connected in parallel, oxygen ($_8$O) by 8 capacitor C (each of 1μF) connected in series and hydrogen ($_1$H) by 1 resistor R (0.2Ω). The side chain consists of large number of hydrogen atoms compared to other atoms. In order to reduce the circuit complexity, lower value of resistor is chosen for hydrogen atom for modeling. The corresponding electrical circuit models of amino acids Alanine and Glycine are different to each other due to the side chain property a shown in Figure 1B.

The equivalent impedance Z_{eq} of individual amino acid is computed using Eq. (1), and for amino acid Proline Eq. (2) is used.

$$Z_{eq} = \frac{Z_C . Z_A}{Z_C + Z_A} + Z_{SC} \quad (1)$$

$$Z_{eq} = Z_C + Z_A + Z_{SC} \quad (2)$$

where Z_C, Z_A and Z_{SC} are carboxyl group impedance, amino group impedance and side chain group impedance respectively.

Table 1. Analogy between biological and electrical entity of amino acid side chain

Side Chain Atom	Circuit Element	Number of Circuit Element depends on Atomic Number
Carbon ($_6$C)	Resistor (1Ω)	6
Hydrogen ($_1$H)	Resistor (0.2Ω)	1
Nitrogen ($_7$N)	Inductor (1mH)	7
Sulphur ($_{16}$S)	Inductor (1mH)	16
Oxygen ($_8$O)	Capacitor (1mF)	8

2.2. Network modeling of amino acid chain

The individual amino acid circuit models are cascaded together in series to form corresponding gene electrical network (Figure 2A). The gene network is transformed into an equivalent electrical network according to [Temes and LaPatra 1977], where the impedances are replaced by equivalent impedance Z_{th}. This network is stimulated by AC sinusoidal voltage source of angular frequency ω, and the output voltage is measured across a load Z_L i.e. R_L of 1Ω (R_L is used to make the network closed) using Eq. (3).

$$V^{n}_{eq} = V^{n-1}_{eq} \frac{Z_L}{Z_L + \left(\frac{Z^{n}_{C} . Z^{n}_{A}}{Z^{n}_{C} + Z^{n}_{A}} + Z^{n}_{SC} + Z^{n-1}_{eq} \right)} \quad (3)$$

The n numbers of amino acid models are lumped into an equivalent model (Figure 2B), where the circuit arms Z^n_C, Z^n_A and Z^n_{SC} represents the circuit model of the nth amino acid in gene string, and the previous n-1 amino acids are combined into impedance Z^{n-1}_{eq}. The generalized model of a single amino acid chain is obtained by setting n to 1 in the circuit of Figure 2B and V^n_{eq} is the input voltage V_{in}. The entire equivalent model is replaced by Thevenin equivalent (Figure 2C).

The performance of the network model is determined using Bode phase and magnitude of frequency-dependent transfer function G(s) (Eq. (4)).

$$G(s) = \frac{V_{out}(s)}{V_{in}(s)} = \frac{R_L}{R_L + Z^{n}_{eq}(s)} \quad (4)$$

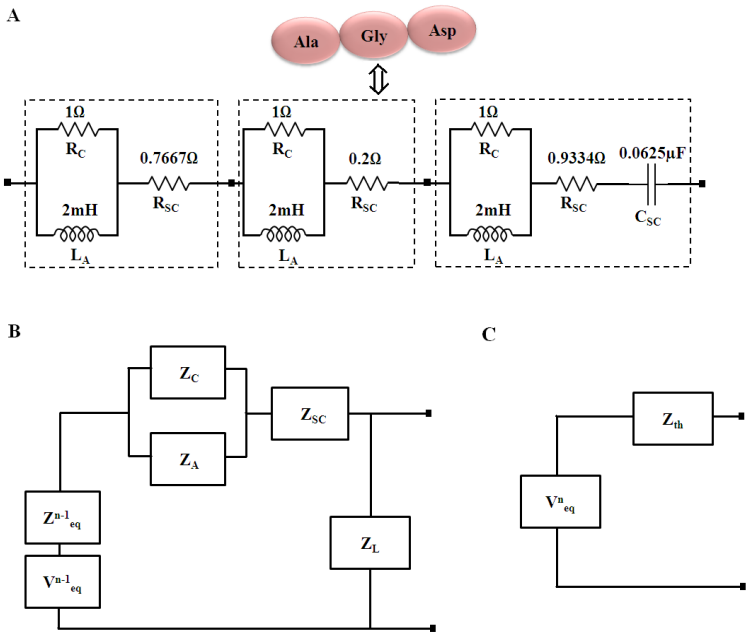

Figure 2. Homo sapiens gene made up with amino acid chain. (A) Amino acid chain is converted into electrical network using modeling concept. Individual amino acid models are cascaded together to form gene network. (B) The generalized equivalent model for amino acid chain of length n. Previous n-1 length amino acid chain is lumped into impedance Z^{n-1}_{eq}. (C) Thevenin equivalent of generalized model.

2.3. Performance evaluation parameters

The performance of the gene transfer function model is evaluated using performance evaluation parameters such as sensitivity (Eq. (5)), specificity (Eq. (6)), accuracy (Eq. (7)), positive predictive value (Eq. (8)), negative predictive value (Eq. (9)), miss rate (Eq. (10)), wrong rate (Eq. (11)) and MCC [Matthews 1975] (Eq. (12)).

$$\text{Sensitivity} = \frac{TP}{TP + FN}; \quad \text{Specificity} = \frac{TN}{TN + FP} \quad (5) \sim (6)$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \times 100 \quad (7)$$

$$PPV = \frac{TP}{TP + FP}; \quad NPV = \frac{TN}{TN + FN} \quad (8) \sim (9)$$

$$M_R = \frac{FN}{FN + TP}; \quad W_R = \frac{FP}{FP + TP} \quad (10) \sim (11)$$

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}} \quad (12)$$

where TP, TN, FP and FN are True Positive, True Negative, False Positive and False Negative respectively.

The robustness of the gene model is judged by calculating the AUC (Area Under Curve) values in the ROC plots [Fawcett 2006; Bewick et. al 2004].

3. RESULTS AND DISCUSSIONS

A total of 40 gene samples associated with cancerous and healthy breast cells are retrieved from NCBI (National centre for biotechnology information) [http://www.ncbi.nlm.nih], and CGAP database (Cancer genome anatomy project) [http://cgap.nci.nih.gov]. Among these 40 genes 31 samples are of cancerous genes and 9 samples are of healthy genes (Table 2). The selection of the sample cancer gene databases is mostly based on literature survey. The cancerous and healthy gene samples which are long chain of amino acid are also searched in GeneCards website [http://www.genecards.org].

Table 2. List of Homo sapiens breast cell associated genes

Gene type	GenBank accession no.	Gene description
Cancer	BC072418.1	breast cancer 1, early onset
	AY436640.1	breast cancer 2, early onset
	AF336980.1	sideroflexin 4
	AF349467.1	SMG8 nonsense mediated mRNA decay factor
	AF012108.1	Amplified in Breast Cancer
	NM_001257386.1	ATP-binding cassette, sub-family G
	NM_007300.3	breast cancer 1, early onset, transcript variant 2
	NM_014567.3	breast cancer anti-estrogen resistance 1
	NM_053056.2	cyclin D1
	BC115037.1	breast cancer 1, mRNA
	NM_001013253.1	lymphocyte-specific protein 1
	NM_001039492.2	four and a half LIM domains 2
	NM_001174087.1	nuclear receptor coactivator 3
	NM_000059.3	breast cancer 2, early onset, mRNA
	NM_001258379.1	solute carrier family 4, sodium bicarbonate cotransporter, member 7
	U43746.1	breast cancer susceptibility mRNA
	NM_001005291.2	sterol regulatory element binding transcription factor 1
	AF098951.2	breast cancer resistance protein
	AY273801.1	breast cancer 1, early onset, complete cds
	NM_000576.2	interleukin 1, beta
	NM_000930.3	plasminogen activator, tissue
	NM_001853.3	collagen, type IX, alpha 3
	NM_003722.4	tumor protein p63
	NM_004056.4	carbonic anhydrase VIII
	NM_007294.3	breast cancer 1, early onset, transcript variant 1
	NM_007298.3	breast cancer 1, early onset, transcript variant 4
	NM_016567.3	BRCA2 and CDKN1A interacting protein
	NM_001144999.2	integrin, alpha V
	AB031549.1	SAM pointed domain containing ETS transcription factor
	AF041259.1	breast cancer putative transcription factor
	AF002672.1	breast cancer suppressor candidate 1
Healthy	NM_130786.3	alpha-1-B glycoprotein
	NM_138340.4	abhydrolase domain containing 3
	NM_024666.4	alpha- and gamma-adaptin binding protein
	NM_015429.3	ABI family, member 3 (NESH) binding protein
	NM_015423.2	aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase
	NM_001605.2	alanyl-tRNA synthetase
	NM_001135704.1	acyl-CoA binding domain containing 4
	NM_032360.3	acyl-CoA binding domain containing 6
	NM_022735.3	acyl-CoA binding domain containing 3

The system phase and magnitude responses are analyzed using Bode analyzer to study the characteristics of cancerous and healthy genes. The network model is realized on MATLAB (R2009btype) environment. The main focus of the study is to identify the genes associated with cancerous and noncancerous activity, and find correlations between biological features of genes and electrical features of gene system.

3.1. Phase analysis of gene system

Initially a total of 40 cancerous and healthy genes are collected from NCBI database to apply modeling concept and analyze their corresponding model phase using Bode analyzer. Hence, a remarkable difference is obtained in the system phase for the genes associated with cancerous and healthy breast tissue (Figure 3A). The phase responses are significantly different in the frequency range [1-100] Hz as most of the phases are negative for cancer gene system and positive for healthy gene (Table 3).

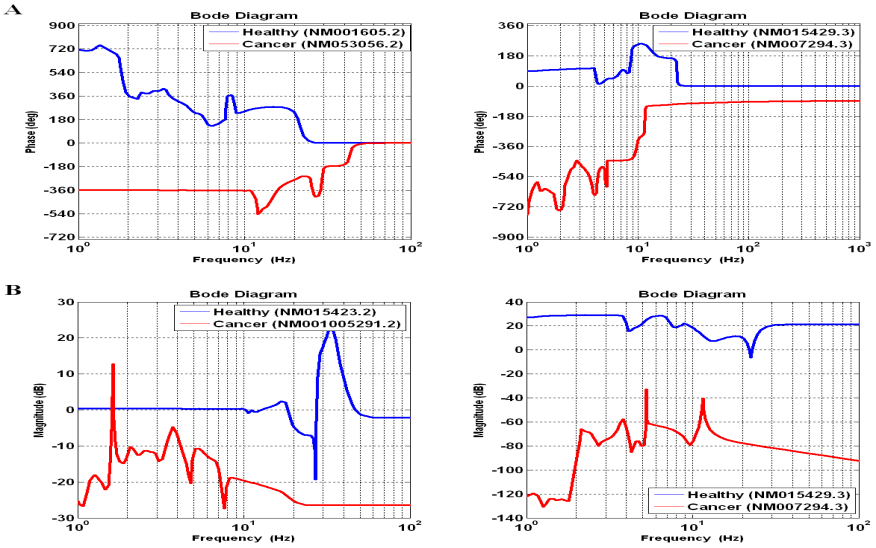

Figure 3. Phase and magnitude response curves for cancer and healthy genes associated with breast tissue. (A) The simulated responses show negative phase for breast cancer genes and positive phase for healthy breast gene within the frequency range [1-100] Hz. (B) The magnitude responses show positive curves for healthy genes and negative curves for cancer genes at same frequency range.

Table 3. Phase values for Homo Sapiens breast associated genes

Gene type	Genbank accession no.	Frequency			
		1 Hz	5 Hz	20 Hz	100 Hz
Cancer	U43746.1	53.1	-273	-249	-266
	NM_001174087.1	199	-5.81	-23.9	-5.34
	NM_001039492.2	-718	-689	-448	-89.8
	NM_001005291.2	354	-223	-32.9	-2.96
	NM_053056.2	-364	-363	-278	-0.059
	NM_016567.3	362	351	47.8	-0.119
	NM_007300.3	-0.00133	-505	-175	-179
	NM_007298.3	-0.00172	17.2	-130	-89.3
	NM_007294.3	-727	-521	-110	-94.2
	NM_000930.3	359	343	49.5	-0.021
	NM_000059.3	-503	-273	-249	-266
	AY436640.1	-500	-273	-249	-266
	AY273801.1	-765	-520	-110	-94.2
	AF041259.1	-0.00115	-175	-201	-89.4
	AF012108.1	-0.00148	-589	-89.2	-90
	AF002672.1	712	735	183	-0.037
	AB031549.1	-360	-362	-192	-0.049
	NM_001257386.1	84.8	-278	-40.1	-0.029
	BC115037.1	-101	-168	-1.33	-0.017
Healthy	NM_001135704.1	2.90E+03	2.12E+03	762	165
	NM_032360.3	350	346	395	0.0805
	NM_024666.4	0.605	-2.63	-103	0.0523
	NM_022735.3	367	275	-86.5	0.18
	NM_015429.3	88.8	32.5	165	0.638
	NM_001605.2	714	234	233	0.00853

Most of the cancer genes exhibit negative phase values, which is analogous to the cancer gene feature i.e. cancer genes are enriched with hydrophilic (charged) amino acids [Stranzl et. al 2012] as hydrophilic amino acids have negative hydropathy index value [Kyte and Doolittle 1982]. Whereas, most of the healthy genes exhibit positive phase values at different frequencies.

3.2. Magnitude analysis of gene system

The magnitude of the gene system is also investigated using Bode analyzer to study the behavior of cancer and healthy genes. In magnitude curve, a significant difference is achieved for the genes associated with breast cancer and healthy tissue. Most of the healthy genes show positive magnitude values and cancer genes show negative magnitude values (Figure 3B; Table 4).

Table 4. Magnitude values for Homo Sapiens breast associated genes

Gene type	Genbank accession no.	Frequency			
		1 Hz	5 Hz	20 Hz	100 Hz
Cancer	U43746.1	-41.9	-70.1	-96.8	-139
	NM_001174087.1	-19.1	-7.15	-31.1	-31.6
	NM_001039492.2	-51	-50.5	-58.5	-56.2
	NM_001005291.2	-25.4	-12.6	-25.2	-26.5
	NM_053056.2	2.31	2.31	-1.42	-0.452
	NM_016567.3	0.278	1.42	-1.53	-2.15
	NM_007300.3	-135	-67.5	-77.9	-106
	NM_007298.3	-79.6	-74.2	-62.3	-76.2
	NM_007294.3	-121	-80	-77.6	-92.5
	NM_000930.3	-10.2	-11.8	3.1	-12
	NM_000059.3	-70.9	-70.1	-96.8	-139
	AY436640.1	-70.9	-70.1	-96.8	-139
	AY273801.1	-121	-80	-77.6	-92.5
	AF041259.1	-53.5	-22.7	-9.75	-34.8
	AF012108.1	-64.9	-15.8	-30.5	-44.3
	AF002672.1	-5.94	-3.5	-17.3	-8.21
	AB031549.1	-0.285	-0.337	-2.16	-2.79
	NM_001257386.1	-11.8	-13	-34.8	-16.1
	BC115037.1	-25.7	-43	-28.4	-28.6
Healthy	NM_001135704.1	849	1.33E+03	2.31E+03	1.96E+03
	NM_032360.3	4.62	0.81	-2.59	0.922
	NM_024666.4	0.889	0.855	-2.4	-1.94
	NM_022735.3	-13.1	8.01	-0.291	-11.8
	NM_015429.3	27.2	22.1	10	21.2
	NM_001605.2	-20.3	-24.3	-19.2	-22.1

3.3. Performance of gene system

Two types of measurements are performed on the given databases to judge the prediction performance of gene system. In first measurement, phase and magnitude of the system are analyzed for each breast gene database, and performance metrics of the proposed technique are measured. The phase and magnitude values are significantly based on the hydrophilic and hydrophobic property of genes. In second measurement, existing technique is employed to classify the databases and compared with proposed technique.

In phase analysis, the negative phase values are considered as TP i.e. True Positive and the positive phases are considered as TN i.e. True Negative. For magnitude analysis, the negative and positive magnitude values are considered as TP and TN respectively.

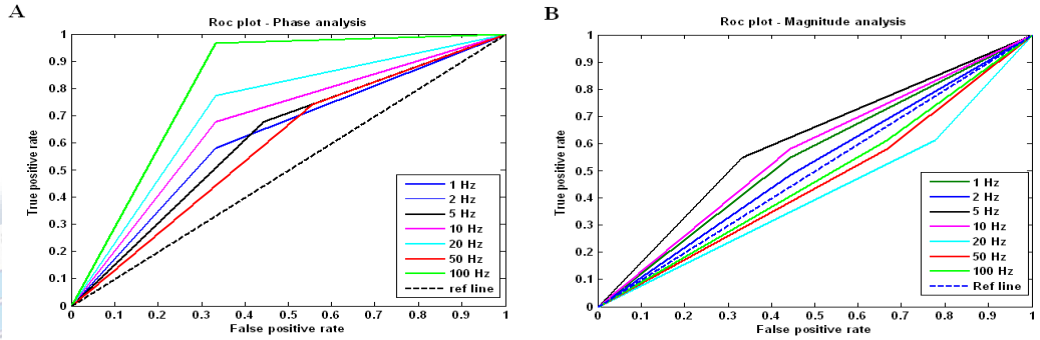

Figure 4. ROC graph showing prediction performances of gene system models for different frequencies. (A) Phase analysis ROC plot. The curve at 100 Hz frequency is showing best prediction performance. (B) Magnitude analysis ROC plot. The curve at 5 Hz frequency is showing best prediction performance.

ROC curve is a fundamental tool for disease diagnosis [Swets and Pickett 1982]. In the present work, ROC plot (Figure 4) and the area under the ROC curve are considered to discriminate between two types of genes i.e. diseased and non-diseased gene. The gene system performance evaluation parameters at different frequencies are evaluated for phase and magnitude analysis (Table 5). The ROC plot (Figure 4A) reveals that maximum numbers of breast genes are correctly identified as cancerous or healthy genes at frequency 100 Hz which is the optimum frequency for all genes. In magnitude ROC plot (Figure 4B), the optimum frequencies for identifying maximum numbers of cancer and healthy genes are 5 Hz and 10 Hz. Therefore, the system phase is more informative than magnitude because it provides highest 97% sensitivity, 67% specificity, 90% accuracy, 0.7 MCC and 0.82 AUC at 100 Hz frequency (Table 5, Figure 5).

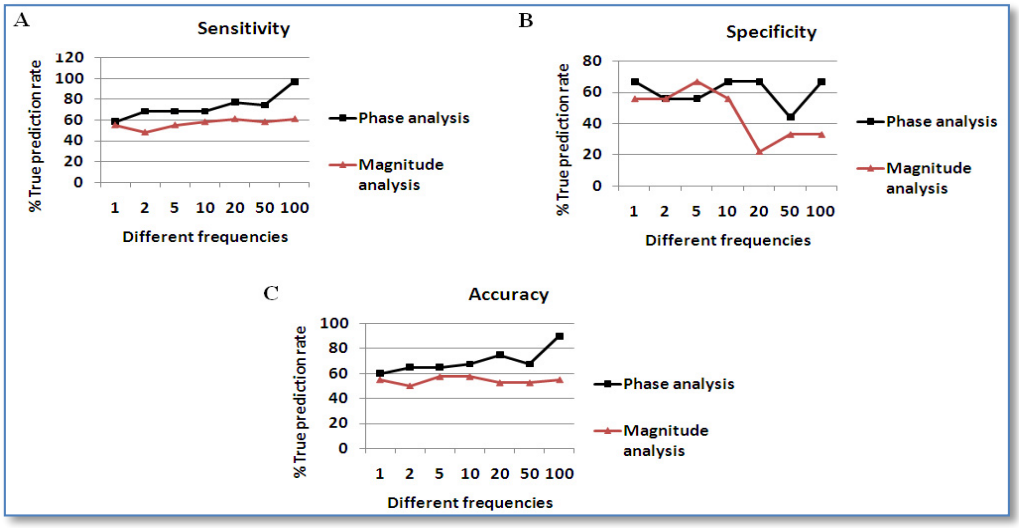

Figure 5. Performance evaluation parameters at different frequencies for gene prediction.

Table 5. Prediction performance using system phase and magnitude at different frequencies

Type of analysis	Frequency in Hz	Sensitivity	Specificity	% Accuracy	PPV	NPV	MR	WR	MCC
Phase	1	0.58	0.67	60	0.86	0.32	0.42	0.33	0.21
	2	0.68	0.56	65	0.84	0.33	0.32	0.44	0.2
	5	0.68	0.56	65	0.84	0.33	0.32	0.44	0.2
	10	0.68	0.67	67.5	0.88	0.38	0.32	0.33	0.29
	20	0.77	0.67	75	0.89	0.46	0.23	0.33	0.39
	50	0.74	0.44	67.5	0.82	0.33	0.26	0.56	0.17
	100	0.97	0.67	90	0.91	0.86	0.03	0.33	0.7
Magnitude	1	0.55	0.56	55	0.81	0.26	0.45	0.44	0.09
	2	0.48	0.56	50	0.79	0.24	0.52	0.44	0.03
	5	0.55	0.67	57.5	0.85	0.3	0.45	0.33	0.18
	10	0.58	0.56	57.5	0.82	0.28	0.42	0.44	0.11
	20	0.61	0.22	52.5	0.73	0.14	0.39	0.78	-0.14
	50	0.58	0.33	52.5	0.75	0.19	0.42	0.67	-0.07
	100	0.61	0.33	55	0.76	0.2	0.39	0.67	-0.05

*Bold value indicates highest performance with balanced sensitivity and specificity.

3.4. Comparison with existing technique

A comparison is drawn between the performance of proposed technique and existing nucleotide based technique (Table 6). The existing technique [Marshall 2010] is executed on the same breast associated gene sample databases and provides inferior performance compared to proposed technique. The proposed technique is 60% better in comparison with the previous technique with the best accuracy of 90%. Considering computational time (CPU time), the proposed technique requires 69.7% lesser time (3.3 times faster) than the previous technique.

Therefore based on the results, the proposed technique is very potential to be used in cancer gene classification and provides a robust performance for accurate identification of healthy and cancerous breast gene sample databases compared to existing technique.

Table 6. Comparison of proposed technique performance with existing technique for cancer gene prediction

Method	Sensitivity	Specificity	% Accuracy	Computational time (CPU time) in sec
Previous method [Marshall 2010]	0.13	0.89	30	6.13
Proposed method	0.97	0.67	90	1.86

4. CONCLUSIONS

Amino acid structure and sequence-based network modeling concept is reported in this paper. The simulated responses reveal a high correlation between biological and electrical systems. Two types of analysis i.e. phase and magnitude analysis, are investigated to predict cancer and healthy breast genes. The system shows better correspondence in cancer gene behavior using phase analysis. The gene system model achieves MCC value of 0.7 and accuracy values of 90%, with 97% sensitivity and 67% specificity respectively for identification of diseased genes. Therefore, the structure based gene network model is a potential tool for cancer disease prediction. In future, the equivalent electrical network modeling concept can be extended to accurate genome-based diagnosis for different kind of genetic diseases also.

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