E Coli environment and stages of cancer - An analysis to develop alternative treatment methodologies for cancer

T Ramanujam, TK Basak

Abstract - Malignancy in cancer - especially metastasis – is directly related to angiogenesis, oxidative stress (oxidant/antioxidant ratio) and Growth factors (GFs) generated in the internal environment and is a direct result of expression of rogue mutant genes generated at gene level as a result of phosphorylation and dephosphorylation processes. Even as kinases like Protein Kinase C (PKC) inhibit GFs through phosphorylation, oxidative phosphorylation in the environment of metabolite E Coli can also inhibit GFs. An analysis (in VHDL) of E Coli environment itself leads to identification of mutant genes causing malignancy. Both these processes (PKC and oxidative phosphorylation in E Coli environment) maintain an alkaline environment conducive to better (lower) oxidant/antioxidant ratio leading to apoptosis and inhibition of GFs. Through simulation of E Coli environment, we can identify stages of cancer caused by mutant genes and the genes themselves. Hence simulation of E Coli environment and its analysis can open a window to evolution of alternative strategies for treatment of cancer. Simulation and analysis can be done using MATLAB and VHDL with MODELSIM.

Index Terms: Metastasis, oxidative phophorylation, dehydrogenases, mutant genes, oxidant/antioxidant ratio, Growth factors, PKC.

---

1. Introduction

1. 1 Oxidative stress (represented byhigher values of oxidant/antioxidant ratio) directly leads to angiogenesis which up regulates Growth Factors. Growth factors are normally down regulated by apoptosis. Protein Kinase C (PKC) and the pH environment of Extracellular fluid (ECF) – acidic or basic - have an important role to play in both these processes of angiogenesis and apoptosis in cancer. PKC, along with E Coli bacteria, through interaction of selenometabolite is able to maintain the alkaline (basic) environment and oxidant/antioxidant ratio conducive to apoptosis in cancer.

1.2. Oxidant/antioxidant ratio in Extra Cellular Fluid (ECF) environment can be simulated using the Electrostrictive energy (ESE) of Cancer cells [7] which is mathematically derived from experimental results of Capacitance Relaxation (CR) phenomenon in cancer cells [6], [1]. It has also been established [3] that E Coli can survive in a wide range of pH (both acidic and alkaline). Fig 3 shows such survivability in terms of pH vs Oxidant/anti-oxidant ratio. It can be seen that in acidic environment (pH < 4.5) where normal human cells turn malignant [4], E Coli encounters lesser oxidant/anti-oxidant ratio conducive to its survival. It can also be seen that situation is similar in alkaline environment (pH > 6.5) .

T Ramanujam BE, M Tech is a Research Scholar at Dr MGR Educational & Research Institute University, Chennai 95, India. He is the corresponding author . Mail : rj1944@gmail.com

Dr TK Basak is the supervisor for T Ramanujam. He is HoD EEE at NIT Agartala India 799055. Mail tkb20042001@yahoo.co.in

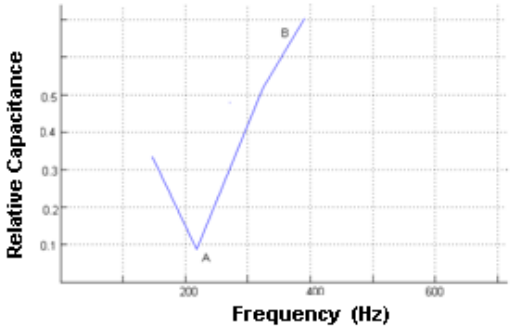

Fig 1

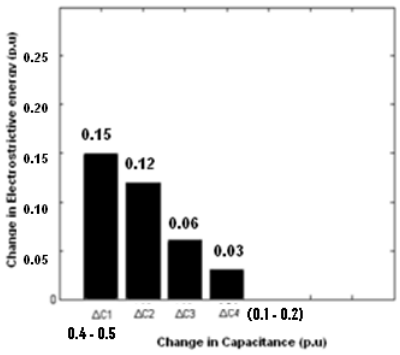

Fig 2

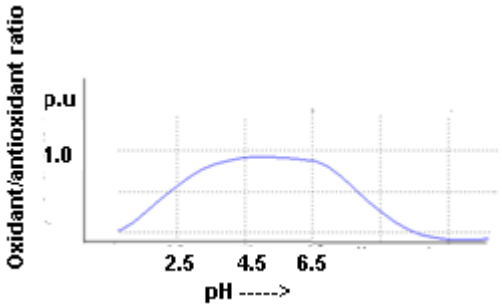

Fig 3

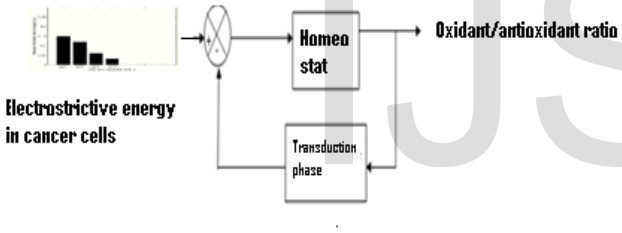

Fig 4

Angiogenesis in E Coli environment with protein kinase C (PKC)

2. Experimental set up and simulation [5]

2.1. A generalized model for metastasis/apoptosis is shown in Fig 4. The input to this model is the ESE of cancer cells (Fig 2) derived from experimentally verified CR phenomenon in cancer cells (Fig 1). Before simulation using ANN, an experimental set up was established to collect 1. pH of ECF 2. Metastasis level 3. Ox/anti-Ox ratio, 4. CR value and 5. Ratio of estrogen receptors from 1000 cancer patients. The output of the simulation is the final stage (of metastasis) of the patient in terms of misclassification %.

2.2. ANN was used as a classifier in MATLAB. Following parameters were used in the simulation.

Training samples and validation samples = 260 each

Error obtained was 18 and hence misclassification was (18/260) * 100 = 6.9%

No. of neurons in hidden layer = 5 ; 2000 iterations carried out till tolerance value of 0.01 was reached. Momentum was taken as 1.2 and learning rate as 0.8 with an initial sum error assumed as 0.

2.3 Fig 5 shows the misclassification tables for training and validation samples. Average misclassification in validation data is about 11.5%. Fig 6 (a) and 6 (b) give snap shots of the simulation - 6(a) shows no. of neurons in hidden layer vs misclassification %. ; 6(b) shows sum error vs iterations

		Actual		Misclassified		
Training	**Data**					
Category	Count	Weight	count	weight	% Misclass	Cost
1	8	8	8	8	100	1.00
2	52	52	2	2	3.846	0.038
3	43	43	0	0	0	0
4	27	27	6	6	22.222	0.222
Total	130	130	16	16	12.308	0.123
Validation	**Data**					
1	8	8	8	8	100	1.00
2	52	52	4	4	7.692	0.077
3	43	43	0	0	0	0
4	27	27	3	3	11.111	0.111
Total	130	130	15	15	11.538	0.115

Fig 5 Misclassification Tables for Trg and validation data.

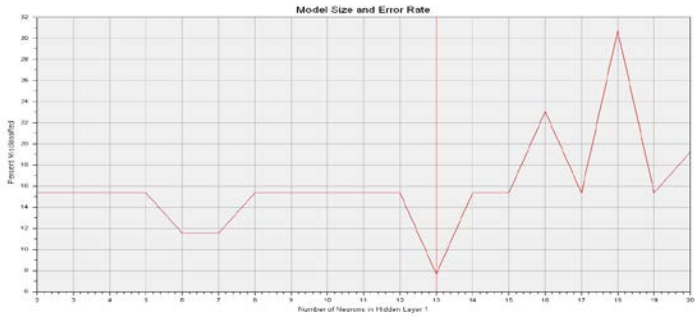

Fig 6(a) Model Size vs misclassification graph

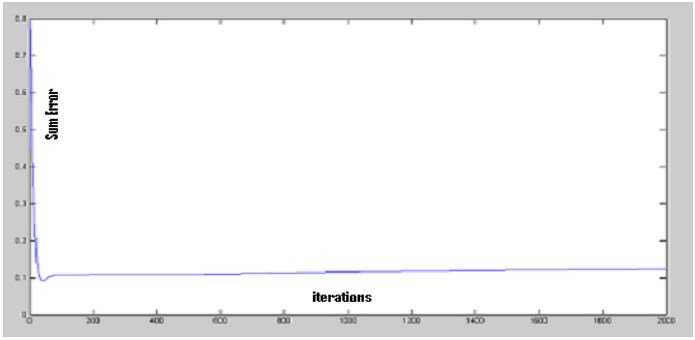

Fig 6(b) iterations Vs sum error

3. Analysis of E Coli environment with Oxidative phosphorylation of Ugd to identify mutant genes

3.1. An analysis of E Coli environment using VHDL with oxidative phosphorylation of E Coli (specifically protein Ugd of E Coli) that is linked to protein tyrosine phosphorylation of UDP glucose dehydrogenase can lead to gene sequence alteration and identification of mutant genes causing malignancy. Tyrosines are amino acids used by cells to synthesize proteins. Protein tyrosine (PT) phosphorylation is mediated by PTKs and PTPs (PT Kinases and phosphates). PTKs and PTPs regulate cellular processes like transduction and oncogenesis [4].

3.2. By-kinases (Bacterial enzymes) have been recently identified to participate in cellular processes and two such by-kinases, Wzc and Etk, can be used to investigate transcription of genes mediated through phosphorylation. Protein Ugd of E Coli, a UDP-glucose dehydroenase, is phosphorylated by Wzc and Etk [4] . Bacterial PTKs autophsphorylate protein Ugd while other PTKs in the same pH range dephosphorylate Ugd. It may be noted that dephosphorylation at gene level leads to generation of mutant genes and malignancy. This is the reason why E Coli survive in acidic environments of pH while normal human cells don't. The ability of E Coli to survive acidic environment is greatly enhanced by addition of SCFA such as acetate, proprionate and butyrate at neutral or near neutral pH (pH value of 7). Gene arrays can be used to characterize changes in gene expression induced by acetate treatment of E Coli during the process of dehydrogenases. Such expression profiling is a powerful tool to analyze gene expression at genomic level such as Ugd gene. In this paper, VHDL analysis with MODELSIM has been used as a tool for expression profiling.

4. Model and Simulation

4.1. The model to be simulated is the same one shown in Fig 4. The model also incorporates features of oxidative phosphorylation of Ugd in E Coli. The transduction phase incorporates PKC corresponding to its isoform Δ and θ (PKCΔ and PKCθ) that suppress metastasis of cancer cell. PKCΔ and PKCθ are pro-apoptic while PKC α, β and ε are anti apoptic in their action in E Coli environment [4]. The homeostat in the model (fwd path) represents the oxidant/antioxidant homestat and the output is used as input to growth factor inhibiting PKC(ox/anti Ox ratio). The model was simulated using Simulink of MATLAB 7.0 and E Coli environment was analyzed using VHDL. Graphical output of the MATLAB (Simulink) simulation is fed as input to the HDL coder shown in Fig 7. From the output of VHDL coder in Fig 7, it is possible to monitor the gene sequencing in the simulated oxidative phosphorylation of Ugd gene, an Ugd dehydrogenase for poly clonal antibody reponse in cancer treatment. Figures 8(a) and 8(b) show the output obtained in VHDL after applying different sets of input from Simulink simulation. Fig 8(c) shows the average values analyzed by the whole model (ox/anti ox ratio vs pH)

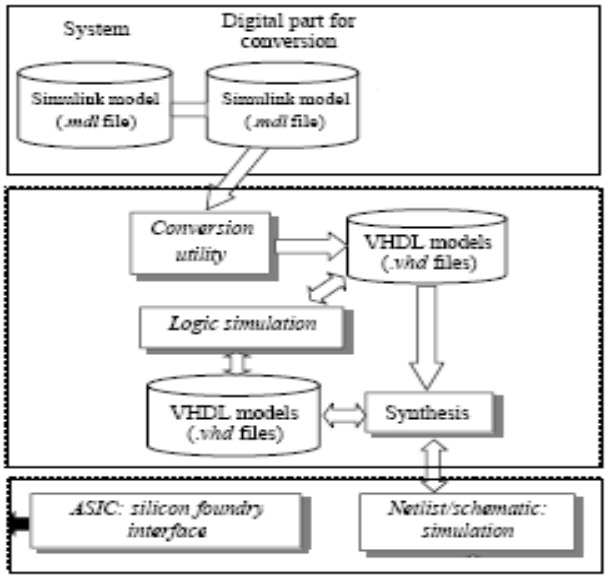

Fig 7 HDL Coder

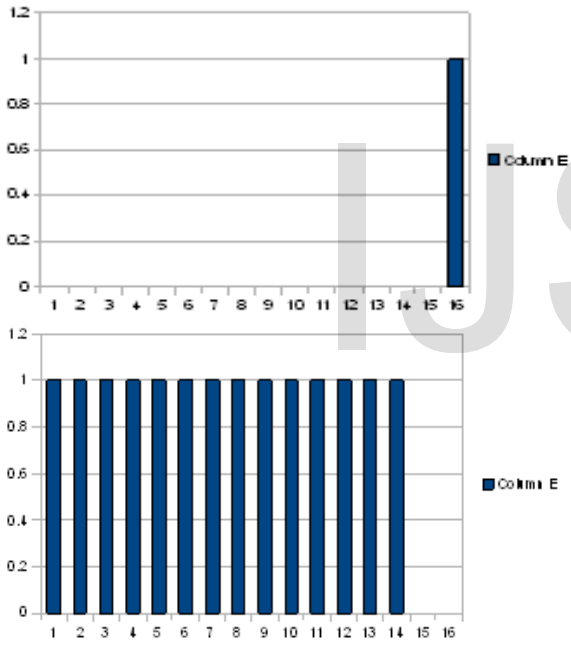

Fig 8 (a) Bar graph representation for input 1111 1111 1111 1101

Fig 8 (b) Bar graph representation for input 0000 0000 0000 1111

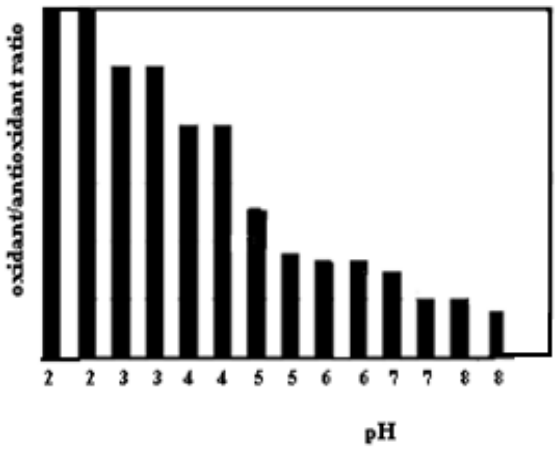

Fig 8(c) VHDL implementation of oxidant/antioxidant ratio Vs pH

5. Discussion and Conclusions.

5.1. In the first part of this paper, the model in Fig 4 is simulated using MATLAB with input as incremental changes in ES energy in cancer cells and output representing oxidant/antioxidant ratio. The homeostat in forward path and transduction phase in feedback path are linked with lipid peroxidation of E Coli archaeabacteria mediated by antiporters in the E Coli environment. The simulation output is mined separately using decision based data mining algorithm. The same data (as mined) is used in ANN with back propagation algorithm. The classifier is used for prediction of the status of the cancer subject in different stages of metastasis corresponding to respective pH range of intracellular fluid simulated in E Coli environment with PKC. Stages of cancer predicted so may be useful in treatment of cancer.

5.2. In the second part of the paper, oxidative phosphorylation of Ugd gene in E Coli environment is simulated. It can be seen that during the process of dehydrogenases , the energy coupled with the anti porters would facilitate growth of Etk knockout mutant gene in specific pH range(s). It can be seen from Fig 8(c) that with decrease in phosphorylation (concomitant with decreased oxidant/antioxidant ratio), there is a decrease in polymixin(a drug used in cancer treatment) resistance to knockout gene Etk. Following the process of each phase of dehydrogenases, there is a specific alteration of gene sequence in exponential order (slope changes od the top of the bar chart in Fig 8(c)) up to a limited value of pH. From this mRNA transcription of gene sequence, it is possible to

make out a correlation with polymixin antibody in treatment of cancer, VHDL output shown in Fig 8(c) represents alteration of mapped gene sequence. Alterations correspond to pH values of 5, 7 and 8. Operon of Etk can thus be effectively mapped in E Coli chromosome in this specific pH order . Such mapping will be useful in the study of antibody response in cancer.

References

[1]. Basak, TK, Shaw. P, Cyril Raj. V, Ravi T **2009-1,** 'Modeling of capacitance relaxation phenomena in a malignant membrane', *Modelling in Medicine and Biology VIII, WIT Transactions on Biomedicine and Health* Edited by CA Brebbia , Vol 13 WIT Press pp 247-256

[2]. Basak, TK, Ramanujam T, Kavitha JC, Poonam Goyal, Deepali Garg, Arpita Gupta, Suman Halder **2009-2**, 'pH Homeostasis linked with Capacitance relaxation phenomenon and Electrostrictive energy in cancer cells' , *Sensors & Transducers Journal,* Vol 109, Iss 10 pp 147-153

[3]. Basak, TK, Ramanujam T, Suman Halder, Poonam Goyal, PM Kulshreshta, Arpita Gupta, S Jeyabalan, V Cyril Raj, Sudheer Patil, Narendra Mustarel **2010**, 'A Model linked to E Coli related to Electrostrictive energy in cancer cells' , *Sensors & Transducers,* Vol 113 Issue 2 pp 158-166

[4]. Basak, TK, Jian Ni. Guangyue Shi, Deepali Garg, Madhubala Bhatt, T Ramanujam, Sudheer Patil, Narendra Mustare, S Jeyabalan **2011,** 'Analysis of oxidative phosphorylation of E Coli in VHDL focused on gene sequence alteration', *Journal of Medicine and Medical Science,* Vol 2(3) pp 758-762

[5]. Guangyue Shi, TK Basak, T Ramanujam, Madhubala Bhatt, Deepali Garg, Richa garg, Sudheer Pati, Narendra Mustare, S Jeyabalan **2011** 'Analysis of E Coli environment related to stages of Cancer' , *Journal of Medicine and Medical Sciences* Vol 2(1) pp 601-608

[6]. Shaw, P. & Basak, TK. & Ghosh, NC. **2006** 'Capacitance Relaxation phenomenon in cartilaginous membrane', *Every Man's Science*, Vol XL No 6.

[7]. Tapas Kumar Basak, , T Ramanujam, Suman Halder, Poonam Goyal, Prachi Mohan Kulshreshta, Shweta Pandey, Himanshu Tripathi **2008**, 'Electrostrictive effect in cancer cells reflected in Capacitance Relaxation phenomenon ' *Sensors & Transducers, Vol 99 Issue 12 Dec 2008* 90-101