CHAPTER 1

INTRODUCTION

1.1 Prologue

1.1.1 Cancer is a major disease affecting a large number of people and has defied the development of an effective methodology of treatment so far. Metastasis that results in the spread of cancer to various parts of the body introduces a new dimension of different types of cancer (lung cancer, breast cancer, ovarian cancer, prostate cancer, melanoma etc) needing different treatments.

1.1.2 Urinary Tract Infection (UTI) is similarly a serious health problem affecting a large number of people. Women are more prone to UTI. In many respects, UTI becomes a recurrent disease and in the process, may become resistant to drugs. A disease developing resistance to drugs may eventually lead to a critical stage of malignancy.

1.1.3 Regulatory Function Homeostasis is an important regulatory function of the human body. The human body is some sort of a social order of about 100 trillion cells organized into different functional structures some of which are called organs. Each functional structure contributes its share to the maintenance of homeostatic conditions (a pseudo-static equilibrium) in the extracellular fluid (fluid surrounding cells) which is called the internal environment of the human body. As long as normal conditions are maintained in this internal environment, the cells continue to live and function while contributing their share to the maintenance of homeostasis.
1.2 Homeostasis

The regulatory function mentioned in section 1.1.3 is carried out by homeostat(s) and the process is called homeostasis. The human body has a number of homeostats involved in regulating the internal environment to maintain a pseudo-static condition of equilibrium. These homeostats are interconnected along with their transduction paths (to be explained in chapter 3). The homeostats and transduction paths communicate with the help of neurotransmitters and receptors, composed of proteins, enzymes and hormones. It will be seen in chapter 3 that the whole process of homeostasis involves a homeostat that regulates the environment in the forward path and a feedback mechanism that influences the regulation mechanism (mentioned above) in the forward path. Each homeostat has a controlling organ and gets inputs from sensory organs or other systems in the body like respiratory system. Output ensures the pseudo-static conditions explained earlier. Important homeostats in the body include pH homeostat, Erythropoietin (EPO) homeostat, Calcium/Phosphate homeostat, temperature homeostat etc. These homeostats are referred to as conventional homeostats and operate at cell level in the internal environment of the body.

If the process of homeostasis takes place at the gene level (in the nucleotides of cells), then the process is referred to as gene homeostasis. Both Cancer and UTI, in critical stages, involve expression of mutant genes against antibodies where the relevant gene homeostats undergo repeated transduction phases linked to processes of dephosphorylation and phosphorylation. Phosphorylation is a dissipative process of adding additional phosphate groups (for example ATP) to modify a protein. This process is carried out by a protein kinase. Dephosphorylation, a conservative process, involves the reverse – removal of a phosphate group from a protein. These processes take place at the gene level and hence gene homeostasis is also a process to reckon with. Thus, in the quest to study the two diseases in detail, it should be understood that both conventional and gene homeostasis are closely involved. Without gene homeostasis, no meaningful analysis of signals can be carried out in respect of cancer and UTI. While conventional homeostats have been modelled earlier using control system concepts, an objective of this thesis is to develop a model for gene homeostat.
In order to analyze related signals, the modelled homeostats have to be simulated with realistic inputs.

1.3 Modelling, Simulation and Analysis of Signals

Modelling of physiological homeostats and simulation and analysis of various signals in the associated pathways can be useful tools in the study of some major diseases and may even aid development of new methodologies to treat these diseases as concluded by Basak et al (2011-1, p 132), Basak et al (2011-2, p. 761), Basak et al (2012) and Guangeue (2011, p.606). Cancer and UTI, especially involve the processes of phosphorylation and dephosphorylation and hence modelling of conventional as well as gene homoestats becomes the starting point in this thesis. It will be seen in chapter 3 that the process of homeostasis is very similar to control systems in Engineering and many tools are available to simulate and study control system models. Modelling conventional homeostats based on control system concepts was done, perhaps for the first time, by Dr TK Basak in his seminal paper Basak (2005). This thesis has improved upon modelling conventional homeostats and attempted to develop a model for gene homeostasis, perhaps for the first time. Modelling and simulation (of both conventional and gene homeostasis) can be carried out by SIMULINK module in MATLAB.

Modelling and simulation involve generation of appropriate control system blocks, their transfer functions and preparation of suitable inputs in addition to a host of other things like delays, slider gains, attenuators etc. Examples of such modeling and simulation by the research scholar are discussed in section3.4. After this simulation, the output of the simulated homeostats can be further analyzed using computational techniques like ANN/ Data mining and statistical tools like regression analysis. Selection of an appropriate tool is an important decision that requires a thorough understanding of the physiology involved, homeostatic processes at cell and gene levels and factor in the requirements of medical profession for an end product. For example, if a subject has disorders involving parenchymal lesions, his or her internal status is likely to indicate exhaustion as in the response of a conservative system. It may or may not be possible to establish the internal state of the subject from output response alone. This aspect has to be kept in mind when developing
models as we are dealing with dynamic systems that depend on and work with genes, hormones, proteins and neurotransmitters. It is not possible to model and simulate such systems with ANN or SVM alone. Depending on the situation, we may have to use all available techniques including MATLAB simulation, control system models, statistical regression etc. Modelling and simulation of physiological systems can use a number of techniques like ANN, SVM, Control system concepts etc. Further analysis requires clustering and classification techniques of which there is plenty of choice in terms of available software. The concepts of biofeedback, modified homeostat and biosensors also become relevant in this context. All these concepts and tools are incorporated/used in this thesis.

1.4 Inputs to the models

1.4.1 For the results to be meaningful and acceptable, the simulations carried out use experimental data as well as mathematically derived data from experimental data as inputs to the homeostats. It will also be established in the thesis that pH homeostasis at cell level and gene level plays a central role in cancer and metastasis. Similarly, pH of urine and pH homeostasis plays a central role in treatment of UTI. The experimental data used as input in the thesis is the result of capacitance relaxation (CR) in cancer cells, experimentally verified and patented by Shaw et al (2006- US patent 5691178 (1977)) , cited by Basak et al (2009-3) and clinically documented data about pH of urine. Electrostrictive (ES) energy in cancer cells, an important entity mathematically derived from capacitance relaxation results using Nyquist Criterion as done by Basak et al (including the Research Scholar) (Basak 2008-4,) is the other data used as input.

1.5 Malignancy, mutant genes and E Coli environment

Malignancy in cancer is directly related to angiogenesis, oxidative stress, and growth factors secreted in the internal environment. A recurrent disease like UTI may turn malignant if it develops resistance to antibodies/drugs. Both the diseases result from the expression of rogue mutant genes as a result of phosphorylation and dephosphorylation at gene level and resulting growth factors. Oxidative stress is the main factor promoting growth factors. There are kinases (kinases carry out phosphorylation) that can inhibit growth factors (like Protein
Kinase C or PKC). There are also metabolites (like E Coli) which can inhibit growth factors through their pH environments. This aspect has been analyzed in chapters 5, 6 and 7.

By correlating pH homeostasis with Capacitance Relaxation and electrostrictive energy in malignant cells, we can establish the pH gradient between intra and extracellular fluids and evolve models for different types of cancer with specificity in pH ranges. Through simulation of E Coli environment, we can then identify stages of cancer caused by mutant genes. This process aids development of alternative strategies for treatment of cancer by identifying appropriate anti oxidants. The process of simulating E Coli environment in human environment can also help in unifying cancer and UTI (Chapters 7 and 8). This has been attempted in this thesis. It is also possible to establish that effective alternative methodologies of treating these major diseases require identification of mutant genes that develop resistance to antibodies/drugs. Such identification requires knowledge of homeostasis (especially pH homeostasis) at gene level. After this, three options are available for development of alternative treatment methodologies:

- Identification of appropriate antioxidant(s) to counter initiation of growth of mutant genes by oxidative phosphorylation.
- If the above approach is not successful, identification of antibodies with improved resistance to mutant genes through administration of appropriate antioxidants
- Identification of drugs that promote growth of mutant genes in an environment of higher pH that will have reduced resistance to antibodies for a longer period

These aspects have also been discussed in chapters 6 and 7.

1.6 Unified concepts and development of Models

Cancer and recurrent UTI have defied an effective methodology of treatment so far. Since recurrent UTI has the potential to turn malignant if it becomes resistant to antibodies/drug, there is a need to unify these diseases for an integrated treatment. This unification has also been attempted in this thesis in chapter 8.
With the help of the models and simulation using appropriate inputs, a generalized model for different types of cancer in specific cellular pH ranges has also been developed in the thesis (chapter 6). In respect of UTI, the effect of inhalation of a phenolic derivative based biosensor (or antioxidant) – Chloropromazine - on UTI has been documented using urine pH simulation analysis and validated by regression analysis (chapter 7).

1.7 Findings and conclusions

Discussions and conclusions summarize the analyses and findings followed by scope for further research which is always a possibility in such areas (chapter 9).