CHAPTER 4

PHENOMENA OF CAPACITANCE RELAXATION (CR) AND ELECTROSTRICTIVE ENERGY (EsE) IN CANCER

4.1 Capacitance Relaxation

4.1.1 Cells in Human Body. Cells in the human body are surrounded by extra cellular fluid (known as the internal environment) and have intracellular fluid which is involved in various chemical reaction and protein formation activities in addition to housing genes. These two fluids are separated by a cell membrane which comprises a bi-layer of highly mobile lipid molecules. This arrangement leads to situation where the membrane acts electrically as a dielectric. A dielectric can behave as an insulator, semiconductor or a composite leaky dielectric depending on various conditions. In normal cells, the membranes behave like an insulator (for example a dielectric polymer) restricting free movement of charged ions and electrons across the membranes except through specialized portions spanning protein ion channels and semiconductors as explained by Gilozzi (1986) and Guyton (2006). In such cases, the capacitance C is given by the equation \( C = \frac{k \varepsilon A}{d} \) where \( k \) is the dielectric constant of the material between the plates (for air, \( k = 1 \)); \( \varepsilon \) is the permittivity of the same dielectric material (\( \varepsilon_0 \) for vacuum); \( A \) is the area of each plate (m\(^2\)) and \( d \) is the separation between plates (m)

However, studies by Mmohammed Awayda (1999) have established that the dielectric constant \( k \) changes with the applied electric field for many dielectric materials and hence the capacitance for such devices is no longer a function of device geometry alone. These dielectric changes under an applied electric field are known as dielectric dispersions. If the electric field is sinusoidal, the dielectric constant (or more aptly, the dielectric permittivity) is a function of the frequency of the electric field. Change of dielectric constant as a function
of frequency of applied electric field is governed by dielectric relaxation processes such as Debye relaxation as stated by Daniel (1967), Sheppard (1970) and M Awayda(1999). The potential across cell membranes in normal cells (called trans-membrane action potential) is usually -100 mV. Cell surfaces generally have a surface charge density which can be negative (mostly and hence the negative sign for membrane potential) or positive depending on cell type. The surface charge density induces a counter ionic cloud around the cells in the surrounding medium. When exposed to an electric field, the counter ions are displaced tangentially around the cell surface giving rise to an induced dipole moment. The insulating nature of cell membrane and the counter ionic orientation of polarization result in a capacitive behaviour of living cells as brought out by Giloazzi (1986) and Basak (2007, p 657).

The state of living tissues/cells can be discerned from two characteristic features - dissipation (absorption of applied energy as it passes through the medium) and dispersion (frequency dependent dissipation of energy as it passes through the medium). Dielectric dispersion is observed from sub-audio to GHz range in frequency. The medium is the cell or tissues (or more aptly, the intracellular fluid). The frequency dependent dispersion is usually characterized by three regions α, β and γ. Since the γ dispersion is in the GHz region, Debye dispersion is normally discussed in terms of alpha and beta regions only. α dispersion which occurs below several K Hz is unique to living organisms (and hence to human cells). While dissipation and dispersion are due to presence of water and other substances, water is the main culprit in α dispersion region for human cells as identified by Basak et al (2007, p.657).

4.1.2 Debye Model. Fig 4.1, cited by Basak et al (2007) shows the Debye dispersion in water (solid red line) and in biological tissue (dashed) with the three regions (α, β and γ) marked therein in terms of variation of dielectric (relative) permittivity against frequency of the applied field. At audio frequencies we have α dispersion which is dominated by counter ion polarization effects. For cells of living organisms, the relative dielectric constant is high in α dispersion region and follows that of pure water in the other regions as can be seen in Fig 4.1. However, in the case of cancer cells, membrane degeneration leads to permeability changes resulting in potassium, magnesium and calcium (all non-water soluble) migrating out of the cell and the water soluble sodium moving in along with water and accumulating
inside the cell. In addition, the membrane area increases significantly due to accumulation of water in the cell. These two phenomena (migration of chemicals and increase in membrane area which is the more important contributory cause) bring about the capacitance relaxation phenomenon – sudden jump in capacitance value around 200 Hz in cancer cells. This accumulation of additional fluid manifests especially after angiogenesis starts and blood begins to flow through the cancer cells. This is CR phenomenon, essentially a diagnostic tool.

![Graph showing Debye dispersion of water and biological tissues](image)

*The Debye dispersion of water (solid) and the dispersion of biological tissue (dashed). Above about 100 MHz, the Debye relaxation of water dominates the dielectric constant of the tissue.*

**Fig 4.1 Debye dispersion of water and biological tissues**

4.1.3 Experimental set up for Capacitance relaxation measurement. The capacitance relaxation phenomenon in normal as well as malignant cells has been experimentally verified and documented by Shaw (2006) and Basak et al (2009-3) for subjects (both male and Female) below and above the age of 50, with and without malignancies. A total of 6 samples from 6 subjects, collected from diagnostic labs, were used and the experiment was conducted in Jadavpur University, Calcutta, India in 2006. The experiment (see Fig 4.2) comprised a glass jar containing pure solvent (acetone) and an extract prepared by dissolving distilled water cleaned lipoproteins from cells of sample subjects in 15 mL of acetone alternately at room temperature of 25° C (i.e 1 mg of cell with lipoproteins dissolved in 15 mL of acetone). Two electrodes (made of Ag/AgCl), dipped in the solution (solvent and extract alternately for each sample) and 1.5 cm apart measured capacitances C1 (capcitance of pure
solvent) and C2 (capacitance of solvent extract with dissolved lipoproteins from cell samples) using HP 428A Precision LCR meter after applying a constant potential of 100 mV (similar to trans-membrane potential in human cells but at varying frequencies - 100 Hz to 1 KHz) across the electrodes. The relative capacitance is given by \( C_{\text{rel}} = K \frac{C_1}{C_2} \) where K is a constant which depends on lipoprotein extract and C1 and C2 are measured capacitances of solvent and lipoprotein extract respectively.

![Diagram of experimental setup]

**Fig 4.2  Experimental set up to measure relative capacitance**

**(CR experiment)**

**4.1.4 Results of CR experiment.** The variation of relative capacitance as measured above for healthy subjects (below and above 50 yrs of age) is shown in Fig 4.3. It can be seen that in the alpha dispersion range, the variation is almost linear (as in a first order system). The variation of relative capacitance with frequency of applied voltage in respect of subjects with malignancy is shown in Fig 4.4 (below 50 yrs) and Fig 4.5 (above 50 yrs). The membrane of the subject comprises lipoproteins, main constituents of which are the phospholipids. The phospholipids play an important role in membrane structure. In the case of malignant cells, the hydrophobic linkage of the polar heads of the lipid bi-layer undergoes spatial orientation concomitant with polarization in presence of electrical stimuli in lipoprotein solvent. As a result, specific capacitance across the lipid bi-layer undergoes changes. This is due to orientation dependant polarization of the lipid constituent of the membrane. The data obtained from the different experimental setups are indicative of the spatial complexities of the lipid bi-layer which may be expressed through relaxation phenomenon associated with the orientation of the polar heads of the constituent lipids which were extracted from human bodies. It can be said that in the case of malignant cells, the lipid profile is asymmetric with
hydrophilic polarization of lipid heads, especially in audio frequency range of alpha dispersion region. However, normal cells (in contrast to malignant cells) exhibit hydrophobicity in higher dispersion regions.

It can be seen from the results of this experiment that the frequency response characteristic of the lipid bi-layer is significant in respect of detecting normal cell and malignant cell present in human bodies. The frequency range was kept from 100 Hz to 1.0 KHz above which the results were not satisfactory for monitoring the relaxation jump. The relaxation phenomenon described above is linked intimately with the proliferation of cells in human bodies under normal and abnormal growth. The experiments were designed in such a way that the investigation for detecting normal cell and malignant cell in human bodies is independent of electrode system and the nature of the solvent. For normal cell, there is no relaxation jump but in malignant cell, there is positive relaxation jump after around 200 Hz as can be seen from Figs 4.4 and 4.5.

Fig 4.3 Capacitance Relaxation – Normal cells below 50 (top) and above 50 (bottom)
Fig 4.4 Capacitance Relaxation – Malignant cells (below 50 Yrs)

Fig 4.5 Capacitance Relaxation – Malignant cells (above 50 Yrs)

The Capacitance Relaxation experiment described above has opened the window for a new technique of Electronic Impedance Scanning (EIS) which can be used as a diagnostic tool to detect presence of malignant cells. Further simulations carried out based on Capacitance relaxation experiment by Basak et al (2007) and Basak et al (2009-3, p. 248) indicate that EIS with corresponding alpha dispersion is useful as an adjunctive imaging modality in differentiation of lymphadenopathy that is equivocal on ultrasound. From Capacitance
Relaxation associated with alpha dispersion, it is possible to determine the signalling pathway in tumour growth and angiogenesis. Vascular Endothelial Growth factor (VEGF) is dependent on alpha dispersion as found by Dinel (2005) and cited by Basak et al (2009-3). VEGF is one of the key regulators of tumour growth and metastatic dissemination. It is well established that molecular basis of tumour angiogenesis is a key interest area in cancer research. Ageing factors play an important role in the regulation of normal cell growth and differentiation. It has been proved now that abnormal production of autocrine and paracrine growth factors and their receptors are the main causes for carcinogenesis. Experimental results have established that there is a direct relation between alpha (α) dispersion and alpha (α) receptor proliferation in angiogenesis as verified by Dinel (2005) and Basak et al (2007).

4.2 Electrostriction

4.2.1 The phenomenon. Electrostriction, as identified by Daniel (1967) and Blatt (1982) and cited by Basak et al (2008-4, p.91 and 2012) is a property of all dielectric materials and is caused by the presence of randomly-aligned electrical domains within the material. It is generally defined as the deformation of a dielectric body as the result of an applied electric field. When an electric field is applied to the dielectric, the opposite sides of the domains become differently charged and attract each other, reducing material thickness in the direction of the applied field (and increasing thickness in the orthogonal directions due to Poisson's ratio). More formally, the electrostriction coefficient is a fourth rank tensor, relating to second order strain and first order polarization tensors as per Blatt (1982). First order compression related to polarization is reversible while the second order strain due to electrostriction is irreversible. Since the process of second order strain is irreversible (reversal of electric field does not reverse direction of deformity), elastic energy is stored in the dielectric as long as the applied field is present. This energy is the electrostrictive energy as identified by Basak et al (2008-4, p.92).

Since the biological membranes (in normal cells) are not rigid lamellae, they deform under the stress of trans-membrane action potential (around 100 mv) as stated by Charman (1996). The compression, to a first approximation, is proportional to the membrane potential and is first order in nature. Cancer cells have different lipid and sterol content than normal cells and
have altered membrane composition and membrane permeability. This results in the movement of potassium, magnesium and calcium out of the cell and the accumulation (through ingestion) of sodium and water into the cell. With the result of these mineral movements, membrane composition changes leading to energy abnormalities, decline in the normal membrane potential and rise in membrane capacitance as found by Cone (1970). The outermost negative zone is separated from the positive cell membrane surface by a distance of about 20 micrometers. This outermost calyx zone of steady negativity makes each cell act as a negatively charged body. The second order strain due to trans-membrane potential, however, is present in both normal and cancer cells.

Therefore cancer cells exhibit both lower electrical membrane potentials and lower electrical impedance than normal cells. The excessive amount of negative charge on the exterior surface of the cell is responsible for carcinogenic change and genetic change resulting from development of cellular electrical abnormalities. Also, the depolarization (fall in membrane potential) of the cancer cell membrane due to the accumulation of excess negative surface charges may precede and create the reduction in intracellular potassium and the rise in the intracellular sodium ions as identified by Basak et al (2008-4, p. 91). This causes the second order strain which is irreversible.

Two of the most outstanding electrical features of cancer cells are, therefore: (1) they constantly maintain their membrane potential at a low value as per Blad (1996) and Charman (1996) and (2) their intracellular concentration of sodium is of high magnitude as found by Cone (1970). This sustained elevation of intracellular sodium may act as a mitotic trigger causing cells to go into cell division (mitosis). In the resting phase normal cells maintain a high membrane potential of around minus 80 mV to minus 100 mV (-80 to -100 mV), but when cells begin cell division and DNA synthesis, the membrane potential falls to around –15 mV as verified in Basak et al (2008-4, p. 91). During this process of DNA synthesis, the composite dielectric property of the cell membrane has different values of permittivity and conductivity leading to a large variation of electrostatic energy. The electrical conductivity and permittivity of cancerous cells have been found to be greater than those of normal cells. The cancerous cells demonstrate greater permittivity, and moreover, cover a larger surface area. As a result, there is large increase in capacitance,
concomitant with Capacitance Relaxation phenomenon. The electrostrictive energy of malignant cells can be computed from the capacitance relaxation curve which is shown in Fig 4.6.

![Graph](image)

**Fig 4.6 Capacitance relaxation – Malignant cells (input Data)**

### 4.2.2 Mathematical derivation of ES energy from CR results.

In order to calculate the electrostrictive energy in cancer cells, the following approach was employed by the research scholar- Basak et al (2008-4, pp 92-97):

(a) Cancer cells demonstrate higher conductivity and permittivity compared to normal cells and they cover a larger surface area. This property is reflected in the jump in capacitance established by the Capacitance relaxation phenomenon (A to B in Fig 4.6).

(b) Accordingly, the cancer cells can be modelled as second order systems having a transfer function of the type $1/(s^2 + s + 1)$ (The electrostriction coefficient is a fourth rank tensor related to second order strain) as against normal cells which have transfer function of the type $1/(1+s)$ vide Basak et al (2008-4, p. 100).

(c) With incremental changes in capacitance (when it starts to relax - Region A to B in Fig 4.6) as input to this second order system model, the output is focused to trace out the locus from which it is possible to obtain electrostatic surfaces containing negative charges. This is done for different increments of capacitance change in the forward (A to B) and for same decrements in reverse (B to A) paths in Fig 4.6. Nyquist criterion in MATLAB has been used to trace out the loci from A to B and
then, B to A

(d) The difference in electrostatic surface areas of forward and reverse paths for a given increment in capacitance value gives the variation in electrostrictive energy ($\Delta\varepsilon S$) for that increment.

(e) This exercise can be carried out for different capacitance increments starting from A and going towards B and then in the reverse path of B to A in Fig 4.6 for capacitance relaxation curves of both normal and malignant cells.

**An example derivation.** One example of such calculation is shown for cancer cells exhibiting properties of a second order system of the type $1/(s^2 + s + 1)$ in Figs 4.7a, 4.7b and 4.7c. The example is for $\Delta C1$ (capacitance change from 0.4 to 0.5 p.u in Fig 4.6 which is the CR output for the second order malignant cells). The electrostatic surfaces obtained for to forward (A towards B in Fig 4.6) and reverse path (B towards A in Fig 4.6) for this $\Delta C1$ are given in Figs. 4.7a and 4.7b. The difference in electrostatic surface areas of Figs 4.7a and 4.7b (as shown in Fig 4.7c) gives the change in electrostrictive energy ($\Delta\varepsilon S$) which is 0.15 p.u in this case. Similar values of $\Delta\varepsilon S$ for $\Delta C2 (0.3 - 0.4)$, $\Delta C3 (0.2 - 0.3)$ and $\Delta C4 (0.1 - 0.2)$ are shown in Fig 4.8 for increments (0.12, 0.06, and 0.03 p.u respectively) and tabulated in Table 4.1.

**Fig 4.7 (a)** Electrostatic Surface area for $\Delta C1$ in forward path
Fig 4.7 (b) Electrostatic Surface area for ΔC1 in reverse path

Fig 4.7 (c) Difference in area (dark shade) representing ΔεS

(0.15 p.u)

The variation of electrostrictive energy as a function of incremental changes in capacitance of malignant cells, calculated as above, is shown in Fig 4.8 for a second order system (malignant cells). For incremental changes in capacitance of the cells (from Fig 4.6), the electrostrictive energy in the cell decreases progressively (exponentially) in the case of cancer cells as the capacitance jumps due to relaxation as can be seen in Fig 4.8. It can be seen that, before A, capacitance change is more (first order) while in the region A to B, the capacitance value jumps but changes slowly (non linear system), thus establishing correlation between ES energy and capacitance relaxation.
4.2.3 Changes in ES Energy. The changes in electrostrictive energy ($\Delta \varepsilon S$) for incremental changes in capacitance $\Delta C$ in Fig 4.8 for cancer cells follow a second order system model as per Basak et al (2008-4, p. 100). Thus, the electrostrictive effect of cancer cells in conjunction with Capacitance Relaxation phenomenon is related to the membrane acting as a composite leaky dielectric material represented by a second order transfer function in simulation. In the model, the electrostrictive energy decreases with differential changes in capacitance of the cell membrane. While normal cell membranes behave like a first order system represented by higher electrostrictive energy and a slow process of cell division and DNA synthesis (close to region A), the electrostrictive energy for the same incremental changes in capacitance of cancer cells is lower (close to region B) compared to normal cells and the simulated model for cancer cell membranes behaves like a second order system. The simulation above using Nyquist criterion can be carried out for a first order system (of type $1/s+1$) representing normal cells. In this case, for $\Delta C1$ of 0.4 to 0.5, the value of $\Delta \varepsilon S = 0.4$ while the corresponding value of $\Delta \varepsilon S$ is 0.15 in a second order system as seen from Table 4.1. Thus, this simulation establishes the fact that the electrostrictive energy is less for cancerous cells compared to that of normal cells for similar incremental changes in capacitance and that the ES energy progressively decreases with differential changes in capacitance of malignant cells. It can be noted that during process of cell division and DNA synthesis in respect of a composite dielectric is relatively slow and hence is assumed to be of
first order. But for the same incremental change in capacitance, change is ES energy is much higher (0.4) in a first order system than in a second order system (0.15).

**Table 4.1 Variation of Electrostrictive Energy with capacitance in cancer cells**

<table>
<thead>
<tr>
<th>ΔC</th>
<th>Incremental relative capacitance changes In reverse path B to A, Fig 4.6</th>
<th>ΔεS Change in εS energy Fig 4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔC1</td>
<td>0.4 to 0.5</td>
<td>0.15 (0.4 for first order system – normal cells)</td>
</tr>
<tr>
<td>ΔC2</td>
<td>0.3 to 0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>ΔC3</td>
<td>0.2 to 0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>ΔC4</td>
<td>0.1 to 0.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**4.2.4 Summary.** The following, thus, summarizes the effect of Capacitance relaxation and electrostriction phenomena in respect of normal and malignant cells:

(a) In normal cells, the membrane capacitance is low, the membrane is a good dielectric, membrane potential is high, electrostrictive energy stored is high and the whole cellular homeostasis system behaves like a first order system.

(b) In the case of malignant cells, due to presence of more water and enlarged area, the membrane becomes a composite leaky dielectric with lower membrane potentials, higher capacitance and lower electrostrictive energy. In essence, the cellular homestasis system in this case behaves like an ordered system.
(c) The electrostrictive energy for first order (normal cells) and second order (malignant cells) systems can be derived from Capacitance relaxation curve for normal and malignant cells using Nyquist creriterion as detailed in section 4.2.5.

4.3 Progression of presence of mutant genes

It was seen in sec 3.5 that the diseases of cancer and UTI (at later stages) are influenced by presence of mutant genes and their expression thereafter. When antibody response is present, mutant genes are suppressed. However, when the antibody response decreases, the presence of mutant genes increases exponentially. It is interesting to note that this increase is similar to the increase in capacitance of cells when they become malignant as can be seen in capacitance relaxation phenomenon curve.