RF-Field Interactions with Biological Systems: Electrical Properties and Biophysical Mechanisms

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Abstract—Electrical properties of tissues, macromolecular solutions, and cell membranes are summarized at frequencies from the extra low frequency (ELF) to microwave range. Previously presented dielectric data are supplemented by new results and a more detailed discussion of the physical mechanisms for the observed temperature coefficients of the dielectric properties. The dielectric data are discussed in terms of the interaction mechanisms which give rise to observed relaxational effects. Possible mechanisms for nonthermal weak interactions between radio-frequency (RF) energy and tissues are discussed and evaluated.

I. INTRODUCTION

In this survey, electrical properties of tissues will be reviewed covering the total frequency spectrum up to microwave frequencies. More recent data, some previously unpublished, will be presented. These new data will help to remove some inconsistencies which have been pointed out [1]. We will also add to the few data presently available at radio frequencies (RF's), discuss temperature dependencies in greater detail than before, and extend some tissue dielectric data to higher microwave frequencies. Biophysical mechanisms responsible for the observed tissue electrical properties will be related to membrane properties, to the state of extra and intracellular water, and to biopolymer properties.

One of the oldest reviews of such data is provided by Rajewsky's monograph [2]. More modern data and interaction mechanisms have been discussed in detail by Schwab [3], and with essentially the same data, by Schwan [4], and by Johnson and Guy [5]. A recommended independent extensive survey is by Geddes [6]. Recommended basic texts on the interaction of alternating electrical fields with matter are those of Froehlich [7], Debye [8], Boettcher [9], Smyth [10], and Hill, Vaughan, Price, and Davies [11]. Other reviews of the electrical properties of biological molecules and tissues are by Grant, Sheppard and South [12], Schanne and P. Ceretti [13], and Cole [14]. These last two books survey the vast field of impedance measurements on cells and cell suspensions at audio and radio frequencies used to study the electrical properties of cell membranes. A recent review of microwave interactions with biological tissues has been presented by Stuchly [15], which contains many additional references.

II. FUNDAMENTALS

The electrical properties to be surveyed include the conductivity \( \sigma \), resistivity \( \rho = 1/\sigma \), and the dielectric permittivity relative to free space \( \varepsilon \). The conductivity is defined as the conductance \( G \) of a unit volume of matter. The dielectric permittivity is the capacitance \( C \) of a unit volume of matter, divided by the permittivity of free space \( \varepsilon_0 = 8.85 \times 10^{-14} \text{ F/cm} \). The admittivity \( Y = \sigma + j\omega \varepsilon_0 \) may be defined as the admittance \( Y = G + j\omega C \) per unit volume, while the impedance \( Z \) is the impedance of a unit volume and the inverse of the admittivity, i.e., \( Z = 1/Y \); \( \omega \) is the frequency in rad/s.

One frequently introduces the complex permittivity \( \varepsilon^* \) as an extension of the permittivity by setting \( \varepsilon^* = \varepsilon' - j\varepsilon'' \) with \( \varepsilon' = \varepsilon \) and \( \omega\varepsilon'' \varepsilon_0 = \sigma \). Magnetic properties shall not be considered since the magnetic permeability of biological matter is not for all practical purposes equal to that of free space, and magnetic losses are negligible. The one exception—magnetotactic bacteria—will not be discussed here [16].

For most material the permittivity and conductivity properties are frequency dependent or dispersive, and, consequently,
time-dependent characteristics prevail in response to a current or voltage step. Consider the simplest possible response, that of an exponential of the form $1 - \exp(-t/\tau)$ for the dielectric displacement, i.e., the charge acquired by a unit volume of matter exposed to a unit step potential. Then it can be shown that [8]

$$e^* = e_\infty + \frac{e_0 - e_\infty}{1 + j\omega \tau}$$  \hspace{1cm} (1)

with the subscripts 0 and $\infty$ indicating the limits of $e^*$ at very low and high frequencies, respectively, and $\omega$ the angular frequency. In like fashion

$$y = y_\infty + \frac{y_0 - y_\infty}{1 + j\omega \tau}$$  \hspace{1cm} (2)

if the time response of the conductivity is characterized by an exponential.

If the response in the time domain is more complex it may be often written simply as a sum of exponentials, and the corresponding responses in the frequency domain are of the form

$$e = e_\infty + \sum \frac{\Delta e_\gamma}{1 + j\omega \tau_\gamma}$$

$$y = y_\infty + \sum \frac{\Delta y_\gamma}{1 + j\omega \tau_\gamma}$$

These equations are special cases of the Kronig–Kramer relationships [9]. It is apparent from them that the response of any system may be modeled as a sum of relaxation processes, with each process being a noninstantaneous exponential relaxation from one state to another. The Kronig-Kramer relationships show that the frequency response of the conductivity entirely determines that of the permittivity and vice versa for linear systems. This is particularly apparent if we write the equations for the case of only one relaxation time

$$e = e_\infty + \frac{e_0 - e_\infty}{1 + j(\omega \tau)^2}$$  \hspace{1cm} (3)

$$\sigma = \sigma_0 + (\sigma_0 - \sigma_\infty) \frac{(\omega \tau)^2}{1 + (j(\omega \tau))^2}$$  \hspace{1cm} (4)

where $e_\infty$ and $\sigma_0$ represent contributions not due to the relaxation process. From [1] or the Kronig-Kramer relationship it follows

$$\sigma_1 - \sigma_2 = (e_2 - e_1)e_r/\tau$$  \hspace{1cm} (5)

so the conductance and capacitance changes between any two frequencies $f_1$ and $f_2$ are interrelated through the time constant.

It is well known that not all responses to an activating step stimulus are exponential. For example, diffusion proceeds intrinsically in a different manner. However, molecular orientational responses and Maxwell–Wagner interface charging processes are known to be exponential. Thus the dielectric properties which result from these mechanisms so prevalent in biological media can be described in terms of relaxation processes as indicated above.

Frequently there is a broad distribution of relaxation times clustered about a single mean value. In this case the behavior can be well approximated by the Cole–Cole function [17]

$$e^* = e_\infty + \frac{e_0 - e_\infty}{1 + (j\omega \tau)^{1-\alpha}}$$  \hspace{1cm} (6)

which leads to a circular representation in the complex permittivity plane, with the center of the circle depressed below the real axis and with $e^* = e$ and $\omega$ as the abscissa and ordinate.

### III. Low-Frequency Data

Data summarized by Schwan and Kay [20] are presented in Table I. The data were obtained on living dogs and care was taken to correct for electrode polarization effects and fluid accumulation near the electrode tip. These data are extended to lower frequencies using excised muscle data from another study [21]. For excised tissue, techniques which are not possible for in situ measurements, to correct for electrode polarization, permitted data collection down to 20 Hz. Table I shows a comparison of these data with data by Schwan and Kay. The specific resistance of the excised samples is lower, no doubt, because excess saline was used to bathe the samples for good contact with the heavily platinum black covered electrodes. The dielectric permittivity data, less affected by this excess saline, connect fairly well with the data given by Schwan and Kay [20]. There are differences in temperature between these two sets of measurements, and hence a shift in the frequency of the dielectric dispersion is to be expected.

Many tissues have anisotropic properties at low frequencies and RF's due to the preferential orientation of the tissue fibers. The measurements by Schwan and Kay were performed with a tip electrode with an approximately hemispherical field, thereby averaging effectively over various orientations. The lower frequency data by Schwan were obtained with the field perpendicular to the muscle fiber orientation. The extent of possible anisotropy remains largely unknown. Application of the Fricke mixture equation (22) to the case of elongated ellipsoidal nonconducting tissue cells in a conducting medium

$$\sigma = \frac{x(1 - p)}{x + p}$$  \hspace{1cm} (7)

where $p$ is the volume fraction of the cells, $\sigma$ and $\sigma_e$ are the conductivities of the cell suspension and medium, and $x$ is 1 and $\infty$, respectively, for long cells perpendicular and parallel...
to the field, would suggest that the ratio of the transverse to longitudinal resistivities should be no larger than a factor of 2. Sapegno [23] reported a ratio of two. Burger and van Dongen [24] and Rush [25] noted substantially larger differences ranging from factors of 3 to over 10. Virtually no work has been done on the permittivities of tissues as a function of the sample orientation to the field.

IV. Properties of RF's

Resistivity data from a variety of tissues are summarized in Table II. We also measured the dielectric permittivity of the tissues, which was not measured by Rajewsky and his group [2], and determined the temperature coefficients for both the conductivity and the dielectric constant [26]. Stoy and Schwan [26] achieved much better reproducibility, thereby reducing the larger range of uncertainty in Rajewsky's data. Some of our data are presented in Fig. 3. The muscle data are fairly typical for most other tissues of high water content, but the brain data are different. While the data connect fairly well with those of Rajewsky et al., they differ somewhat with those given by Osswald [2] to be presented later.

Table II: Specific Resistances of Various Tissues at RF's

<table>
<thead>
<tr>
<th>Tissue</th>
<th>0.1 ohm-cm</th>
<th>0.3 ohm-cm</th>
<th>1 ohm-cm</th>
<th>3 ohm-cm</th>
<th>10 ohm-cm</th>
<th>30 ohm-cm</th>
<th>100 ohm-cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>145-260</td>
<td>140-250</td>
<td>130-215</td>
<td>115-170</td>
<td>105-158</td>
<td>100-155</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>165-200</td>
<td>161-193</td>
<td>150-180</td>
<td>135-165</td>
<td>114-148</td>
<td>105-141</td>
<td>100-140</td>
</tr>
<tr>
<td>(deflated)</td>
<td>440-830</td>
<td>430-780</td>
<td>420-700</td>
<td>390-605</td>
<td>300-460</td>
<td>230-360</td>
<td>200-300</td>
</tr>
<tr>
<td>Brain</td>
<td>172-240</td>
<td>170-230</td>
<td>165-200</td>
<td>160-185</td>
<td>150-170</td>
<td>140-160</td>
<td>130-155</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>172-240</td>
<td>170-230</td>
<td>165-200</td>
<td>150-170</td>
<td>140-160</td>
<td>130-155</td>
<td></td>
</tr>
</tbody>
</table>

Measured immediately after excision. Typically 5 to 10 samples. Upper and lower limits are given. Temperature 23°C. (Data taken by Rajewsky et al. [2] from human autopsy material.)

Table III: Specific Resistances of Various Tissues at Low Frequencies

<table>
<thead>
<tr>
<th>Tissue</th>
<th>0.1 MHz</th>
<th>0.3 MHz</th>
<th>1 MHz</th>
<th>3 MHz</th>
<th>10 MHz</th>
<th>30 MHz</th>
<th>100 MHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>145-260</td>
<td>140-250</td>
<td>130-215</td>
<td>115-170</td>
<td>105-158</td>
<td>100-155</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>165-200</td>
<td>161-193</td>
<td>150-180</td>
<td>135-165</td>
<td>114-148</td>
<td>105-141</td>
<td>100-140</td>
</tr>
<tr>
<td>(deflated)</td>
<td>440-830</td>
<td>430-780</td>
<td>420-700</td>
<td>390-605</td>
<td>300-460</td>
<td>230-360</td>
<td>200-300</td>
</tr>
<tr>
<td>Brain</td>
<td>172-240</td>
<td>170-230</td>
<td>165-200</td>
<td>160-185</td>
<td>150-170</td>
<td>140-160</td>
<td>130-155</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>172-240</td>
<td>170-230</td>
<td>165-200</td>
<td>150-170</td>
<td>140-160</td>
<td>130-155</td>
<td></td>
</tr>
</tbody>
</table>

To be most noticeable at low frequencies. Loss of moisture might account for recorded changes with time after excision in the dielectric properties of fat at millimeter wavelengths [28].

VI. Properties at Microwave Frequencies

The data of Schwan and Li [29] and those of Herrick et al. [30] are presented in Table III. They show good agreement, and agree as well with data by Osswald [31] and Herrick [30] presented in the same table. Unfortunately, Herrick's data have never been published stating the details of the procedure and only were made available as a private communication to one of the authors (H.P.S.). More recently Foster, Schepps, and Schwan [32]–[33] and Lin [34] have repeated some of these measurements with high precision and extended them to higher frequencies. Table IV presents these results for brain and muscle. The need for accurate brain tissue data is particularly important for studies involving microwave energy deposition in head models.

Few data are available above 18 GHz. Edrich and Hardee measured the dielectric properties of muscle and fat using a waveguide technique at 40-54 and 85-90 GHz [28]. The probable errors in these data are greater than for the tabulated data at lower frequencies, and they are consequently not included in this Table. Gandhi et al., on the other hand, have searched with great precision for possible changes in the dielectric properties of cell suspensions between 26.5 and 90 GHz, in order to uncover any changes attributable to resonant effects [35]. However, they did not measure $\varepsilon^\prime$ and $\varepsilon^\prime\prime$ directly. As we show below, the dielectric properties of tissue should, at these high frequencies, be given by the Debye equations for pure water with proper allowance for the fraction of tissue which is occupied by low permittivity protein.

Frequency Dependence

The muscle data (which are fairly typical of soft tissues of high water constant) demonstrate the existence of at least three major relaxation mechanisms labeled $\alpha$, $\beta$, and $\gamma$ (Fig. 1). Corresponding center frequencies where $\varepsilon = \varepsilon^\prime + \varepsilon^\prime\prime$ for each dispersion are near 80 Hz, 50 kHz, and 25 GHz at body temperature. The $\beta$ dispersion in particular shows a broad distribution of relaxation times attributable in part to a variation in distances between intracellular and cell plasma membranes, and can be described by the Cole–Cole function.

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TABLE III
DIELECTRIC CONSTANT AND CONDUCTIVITY IN mmho/cm OF VARIOUS BODY TISSUES AT 37°C

<table>
<thead>
<tr>
<th>Frequency (Mc)</th>
<th>25</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>400</th>
<th>700</th>
<th>1000</th>
<th>3000</th>
<th>8500</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Dielectric constant ε</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>103-115</td>
<td>85-97</td>
<td>71-76</td>
<td>56</td>
<td>52-54</td>
<td>52-53</td>
<td>49-52</td>
<td>45-48</td>
<td>40-42</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>136-138</td>
<td>88-93</td>
<td>76-79</td>
<td>50-56</td>
<td>44-51</td>
<td>42-51</td>
<td>46-47</td>
<td>42-43</td>
<td>34-38</td>
</tr>
<tr>
<td>Liver</td>
<td>&gt;200</td>
<td>135-140</td>
<td>100-101</td>
<td>119-132</td>
<td>87-92</td>
<td>53-55</td>
<td>50-53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>&gt;200</td>
<td>88-93</td>
<td>76-79</td>
<td>50-56</td>
<td>44-51</td>
<td>42-51</td>
<td>46-47</td>
<td>42-43</td>
<td>34-38</td>
</tr>
<tr>
<td>Kidney</td>
<td>&gt;200</td>
<td>135-140</td>
<td>100-101</td>
<td>88-93</td>
<td>76-79</td>
<td>50-56</td>
<td>44-51</td>
<td>42-51</td>
<td>34-38</td>
</tr>
<tr>
<td>Lung</td>
<td>&gt;200</td>
<td>88-93</td>
<td>76-79</td>
<td>50-56</td>
<td>44-51</td>
<td>42-51</td>
<td>46-47</td>
<td>42-43</td>
<td>34-38</td>
</tr>
<tr>
<td>Brain</td>
<td>&gt;200</td>
<td>135-140</td>
<td>100-101</td>
<td>88-93</td>
<td>76-79</td>
<td>50-56</td>
<td>44-51</td>
<td>42-51</td>
<td>34-38</td>
</tr>
<tr>
<td>Fat</td>
<td>11-13</td>
<td>8.6-7.7</td>
<td>4-7</td>
<td>5.3-7.5</td>
<td>3.9-7.2</td>
<td>3.5-4.5</td>
<td></td>
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<tr>
<td>Bone</td>
<td>11-13</td>
<td>8.6-7.7</td>
<td>4-7</td>
<td>5.3-7.5</td>
<td>3.9-7.2</td>
<td>3.5-4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(b) Conductivity κ in mmho/cm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>6.80-8.85</td>
<td>9.52-10.5</td>
<td>11.1-11.8</td>
<td>12.7-13.7</td>
<td>12.7-13.3</td>
<td>21.7-23.3</td>
<td>83.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart muscle</td>
<td>6.80-8.85</td>
<td>9.52-10.5</td>
<td>11.1-11.8</td>
<td>12.7-13.7</td>
<td>12.7-13.3</td>
<td>21.7-23.3</td>
<td>83.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>0.4-0.59</td>
<td>0.29-0.95</td>
<td>0.36-1.11</td>
<td>0.83-1.49</td>
<td>1.11-2.27</td>
<td>2.7-4.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>0.2-0.36</td>
<td>0.43-1.16-2.25</td>
<td>1.67-4.76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Values at 25, 50, and 100 MHz from Osswald (1937); at 200, 400, and 700 MHz from Schwan and Li (1953); at 1000, 3000, and 8500 MHz from Herrick et al. (1950). The values from 200 to 700 MHz have been obtained at 27°C and are adjusted to 37°C with the help of temperature coefficients discussed above. (From [4].)

TABLE IV
DIELECTRIC PROPERTIES OF TISSUE—RECENT RESULTS

<table>
<thead>
<tr>
<th>Tissue (water content, weight percent)</th>
<th>37°C Frequency, GHz</th>
<th>0.7</th>
<th>1</th>
<th>3</th>
<th>8.5</th>
<th>10</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dielectric Constant ε</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog skeletal muscle (0.75)</td>
<td>56</td>
<td>54</td>
<td>50</td>
<td>42</td>
<td>40</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Dog spleen (0.75)</td>
<td>54</td>
<td>52</td>
<td>47</td>
<td>40</td>
<td>38</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Dog brain—white matter (0.72)</td>
<td>38</td>
<td>37</td>
<td>34</td>
<td>29</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog brain—grey matter (0.82)</td>
<td>48</td>
<td>45</td>
<td>43</td>
<td>38</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specific Resistance ρ, ohm-cm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>71</td>
<td>67</td>
<td>31</td>
<td>10</td>
<td>8.6</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>105</td>
<td>83</td>
<td>36</td>
<td>11</td>
<td>9.1</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Brain—white matter</td>
<td>143</td>
<td>133</td>
<td>77</td>
<td>19</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain—grey matter</td>
<td>105</td>
<td>91</td>
<td>48</td>
<td>13</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More recent data by Foster et al. ([32] and unpublished). The variability in the permittivity and conductivity was about 2 percent in ε and ρ at all frequencies. At 3 GHz, Lin [34] quote ε = 35 ± 5 and ρ = 50 ± 25 for unspecified brain tissue at a temperature of 37°C.

As demonstrated in Fig. 2. At microwave frequencies between 1 and 20 GHz, the tissue conductivity increases quadratically with frequency, because of the dipolar reorientation of tissue water, while the permittivity more slowly decreases.

VIII. TEMPERATURE COEFFICIENTS

Temperature coefficients are obtainable from the data presented by Osswald [31], Stoy and Schwan [26] (Fig. 3), Schwan and Li [29], and Foster et al. [32]-[33]. As indicated above, the dielectric constant may be represented by

$$
\varepsilon = \varepsilon_\infty + \sum_{\gamma=1}^{3} \frac{\Delta \varepsilon_\gamma}{1 + (i \omega \gamma)^\alpha}.
$$

If the three dispersion ranges are well separated, i.e., if \( \tau_1 >> \tau_2 >> \tau_3 \), then the analysis proceeds fairly readily. For each
Fig. 2. Impedance plane plot of the impedance $Z = R + jX$ of muscle tissue. The main circle with suppressed center reflects the $\beta$-dispersion effect, while the small circle attached to the big one at low frequencies is caused by the $\alpha$ dispersion.

displacement the temperature coefficient reflects those of $\varepsilon_0$, $\varepsilon_\infty$ and $\tau = 1/2\pi f_c$. The critical frequency $f_c$ increases with temperature at a rate of about 2 percent/°C for all dispersions (1.91 percent average for the temperature range for 16°C to 36°C for electrolytes). This value is suggested by the following argument.

1) $\alpha$ Dispersion: The $\alpha$ dispersion may be due to a frequency-dependent access impedance of the folded inner membrane system of the cell or tubular system [36]. This access is ionic and hence its temperature coefficient is equal to that of the conductivity of the electrolyte, i.e., about 2 percent/°C. If, on the other hand, the $\alpha$ dispersion arises from mobile counterions associated with fixed charges on cell membranes, then from theory proposed by Schwarz [37], the characteristic frequency is proportional to the mobility of these counterions, giving temperature coefficients similar to that of the conductivity of electrolytes.

2) $\beta$ Dispersion: This dispersion range is caused by Maxwell-Wagner polarization effects in which the cellular membranes are charged through the electrolytes. Hence the membrane charging time constant varies inversely with the conductivity of the electrolyte, i.e., 2 percent/°C.

3) $\gamma$ Dispersion: Here the relaxation frequency $\gamma$ is close if not identical to that of free water and, hence, its temperature dependence is equal to that of water. This happens again to be close to 2 percent/°C.

In the discussion above, we have ignored possible changes in the impedance of cell membranes. This is justified by the small change in the membrane capacitance with temperature (e.g., 0.3 percent/°C for erythrocytes [38]). At audio frequencies and above, the membrane conductance, which has a larger temperature coefficient, is always negligible compared to its reactance. The values $\varepsilon_0$, $\varepsilon_\infty$ and $\varepsilon_0 - \varepsilon_\infty$ change comparatively little with temperature since the difference $\varepsilon_0 - \varepsilon_\infty$ is proportional to the membrane capacitance (12) or close to the static permittivity of water which has a small negative temperature coefficient comparable to that of the membrane capacitance.

Thus, for each of the three dispersion regions, the dielectric constant exhibits a small negative temperature coefficient at low and high frequencies, and a positive coefficient in between which results from the strongly shifting dispersion.

Temperature coefficients are more difficult to predict if there is a distribution of relaxation times. But an upper estimate of the temperature coefficient near the relaxation frequency may be provided by assuming one time constant.

Consequently, near the characteristic frequency, $\varepsilon_0 = \sigma / \varepsilon$, and with $\varepsilon_0$ and $\varepsilon_\infty$ fairly independent of temperature. In all cases we note also that $\varepsilon_0$ is much larger than $\varepsilon_\infty$. We conclude, therefore, that the temperature coefficient varies with increasing frequency.

Fig. 3. Dielectric properties of muscle and brain tissue as function of frequency through the RF range.
through the dispersion range from about -0.3 through a maximum of +2 and back to -0.3 percent°C.

Similar considerations apply to the conductivity; however, some important differences exist. For one relaxation process,

\[ \sigma = \sigma_0 + (\sigma_\infty - \sigma_0) \frac{(ffc)^2}{1 + (ffc)^2} \]  

the infinite frequency value is

\[ \sigma_\infty = \sigma_0 + (\epsilon_0 - \epsilon_\infty) f_c/18 \times 10^{11} \text{ mho/cm}. \]  

Since \( \sigma_\infty \gg \sigma_0 \), this \( \sigma_\infty \) is proportional to \( f_c \) which has a temperature coefficient of about 2 percent/°C. If the frequency \( f \) is close to \( f_c \), the numerator of the ratio \( (ffc)^2/(1 + (ffc)^2) \) decreases with increasing temperature twice as quickly as the denominator, so that the ratio itself changes with a temperature coefficient of about -1 percent/°C. Thus conductivity temperature coefficients of about 2 percent/°C at frequencies well above and below \( f_c \) change to only 1 percent/°C in the dispersion range. For overlapping dispersions and distributions of time constants these differences should become somewhat smaller as may be judged from an appropriate discussion of (6). For \( \alpha \) values near 0.5 one can derive a temperature coefficient of about 1 percent/°C for \( \epsilon \) and 1 to 2 percent/°C for \( \sigma \) for the upper part of the RF dispersion range and in excellent agreement with the values derived from the brain tissue data in Fig. 3. The above discussed values are also in agreement with the values quoted for the lower microwave frequency range in [3, table 9].

IX. Interaction Mechanisms

An insight into how electrical fields might affect biological matter is gained from a discussion of the dielectric properties of the various tissue components.

A. Water

The dielectric properties of pure water have been well established from dc up to microwave frequencies, approaching the infrared [39]. For all practical purposes they are characterized by a single relaxation process centered near 20 GHz at room temperature. Static and infinite frequency permittivity values are, at room temperature, close to 78 and 5, respectively. Hence the microwave conductivity increase predicted by (5) or (11) is close to 0.8 mho/cm above 20 GHz, much larger than typical low-frequency conductivities of biological fluids which are about 0.01 mho/cm. The dielectric properties of water are independent of field strength up to fields of the order 100 kV/cm.

Three dielectric parameters are characteristic of the electrical and viscous properties of water: a) the static dielectric permittivity \( \epsilon_0 \) observed at \( f \ll f_c = 20 \text{ GHz} \), b) the relaxation frequency \( f_c \), and c) the conductance of ions in water. A detailed study of the internal conductivity of erythrocytes revealed the intracellular ionic mobility to be identical with that of ions in dilute electrolyte solutions if appropriate allowance is made for internal friction with suspended macromolecules [40]. Tissue conductivities near 100 or 200 MHz, sufficiently high that cell membranes do not affect tissue electrical properties, are comparable to the conductivity of blood and to somewhat similar protein suspensions in electrolytes of physiological strength. Hence, it appears that the mobility of ions in the tissue fluids is not noticeably different from their mobility in water.

Characteristic frequencies may be found from dielectric permittivity data or, even better, from conductivity data. The earlier data by Herrick et al. [30] suggest that there is no apparent difference between the relaxation frequency of tissue water and that of the pure liquid [41]. However, these data only extend to 8.5 GHz, one-third the relaxation frequency of pure water at 37°C (25 GHz) so small discrepancies might not have been uncovered. We have recently completed measurements on muscle at 37°C and 1°C (where the pure water relaxation frequency is 9 GHz), up to 17 GHz. The dielectric properties of the tissue above 1 GHz show a Debye relaxation at the expected frequency of 9 GHz [33] (Fig. 4).

The dielectric properties of electrolytes are almost identical to those of water with the addition of a \( q_0 \) term in (14) due to the ionic conductance of the dissolved ion species. The static dielectric permittivity of electrolytes of usual physiological strength (0.15 N) is about two units lower than that of pure water [42], a negligible change.

B. Protein Solutions

The dielectric properties of proteins and nucleic acids have been extensively reviewed [43], [44]. Protein solutions exhibit three major dispersion ranges. One occurs at RF's and is believed to arise from molecular rotation in the applied electric field. Typical characteristic frequencies range from about 1 to 10 MHz, depending on the protein size. Dipole moments are of the order of 200-500 Debye and low-frequency increments of dielectric permittivity vary between 1 and 10 units/g protein/100 ml of solution. The high-frequency dielectric permittivity of this dispersion is lower than that of water because of the low dielectric permittivity of the protein leading to a high-frequency decrement of the order of 1 unit/g protein/100 ml. This RF dispersion is quite noticeable in pure protein solutions, but in tissues and cell suspensions it only contributes slightly to the large \( \beta \) dispersion found in these materials.

At microwave frequencies the dielectric properties of tissues are dominated by the water relaxation centered near 20 GHz. The magnitude of this water dispersion in tissues is typically diminished by some 20 dielectric units due to the proteins which displace a corresponding volume of water.

Between these two readily noticeable dispersions is a small one, termed the \( \delta \) dispersion by Grant. It was first noted for hemoglobin [45] and then carefully examined for hemoglobin [46] and albumin [47]. This dispersion is characterized by a
counterion redistribution caused by the applied field is difficult to experimentally distinguish from the rotational response to an electric field in proteins. The field strengths required to saturate submolecular vibrational transitions are higher and for nonlinear RF responses due to counter ion movement and chemical relaxation the levels are unknown, but probably also high. In all these processes reversible polarizations occur in competition with large thermal energies and irreversible changes are not expected at field strength levels of the order of a few volts per centimeter.

C. Membranes

Membranes are responsible for the dielectric properties of tissues and cell suspensions at RF's, as demonstrated by studies involving cell suspensions. Yeast, blood, bacteria, pleuropneumonialike organisms, vesicles, and cellular organelles have been extensively investigated by many investigators including Fricke [56], Cole [14], and Schwan [3]. This work has led to a detailed understanding of the role of cell membranes in the polarization processes of biological media in the RF range, which was facilitated by the relatively simple geometrical shapes which cells in suspensions possess. The principal mechanism for dielectric polarization at RF's and below is the accumulation of charges at membranes from extra and intracellular fluids. For spherical particles the following expressions were derived [3]

\[ \varepsilon_0 - \varepsilon_\infty = \frac{9}{4\pi r^2} \frac{pRC_m}{(1 + RG_m(\rho_i + \frac{1}{2}\rho_a))^2} \rightarrow \frac{9}{4\pi} pRC_m \]

\[ \sigma_0 = \sigma_a \left[ \frac{1 - 1.5p}{1 + RG_m(\rho_i + \frac{1}{2}\rho_a)} \right] \rightarrow \sigma_a(1-1.5p) \]  

\[ \sigma_\infty = \sigma_a \left[ \frac{1 + 3p}{\sigma_i - \sigma_a} \right] \frac{\sigma_i}{\sigma_i + 2\sigma_a} \]

for the limit values of the simple dispersion which characterizes the frequency dependence. The time constant is

\[ \tau = \frac{RC_m}{\sigma_0 \sigma_i + RG_m} \rightarrow RC_m(\rho_i + 0.5\rho_a) \]

In these equations \( C_m \) and \( G_m \) are capacitance and conductance per cm² of the cell membrane, \( R \) is the cell radius, \( p \) the cellular volume fraction, \( \sigma_i = 1/\rho_i \), and \( \sigma_a = 1/\rho_a \) are the conductivities of the cell interior and suspending medium. The equations apply for small volume fractions \( p \) and assume that the radius of the cell is very large compared with the membrane thickness. More elaborate closed form expressions have been developed for cases when these assumptions are no longer valid [57], [58], and an exact representation of the suspension dielectric properties as a sum of two dispersions is available [59]. If, as is usually the case, the membrane conductance is sufficiently low, equations (12)-(15) reduce to the simple forms to the right of the arrows.

A physical insight into (17)-(20) is gained by considering the equivalent circuit shown in Fig. 5, which displays the same frequency response defined in (12)-(15). The membrane

\[ ^1 \text{poly-\gamma-} \text{benzyl-L-glutamate.} \]
capacitance per unit length $C_m$ appears in series with the access impedances $\rho_1$ and $\rho_a/2$, while the term $\sigma_a(1-1.5\,\rho)$ provides for the conductance of the shunting extracellular fluid. Hence the time constant $\tau$ which determines the frequency where the impedance $1/\omega C_m R$ and $(\sigma_i + \sigma_a/2)$ are equal is given by (15). Using typical values of $\sigma_i$, $\sigma_a$~0.01 mho/cm, $C_m = 1$ F/cm$^2$, $R = 10$ $\mu$m and $p = 0.5$, with (12)–(15), we see that the dispersion must occur at RF's and its magnitude $\varepsilon_0 - \varepsilon_m$ is exceptionally high.

From experimental dispersion curves and, hence, values of the four quantities $\varepsilon_0$, $\varepsilon_m$, $(\varepsilon_0 - \varepsilon_m)$, and $\tau$, the three quantities $C_m$, $\sigma_i$, and $\sigma_a$ can be determined with an additional equation available to check for internal consistency. Values for extracellular and intracellular resistivities thus obtained agree well with independent measurements. Dispersions disappear as expected after destroying the cell membranes, and their characteristic frequencies are readily shifted to higher or lower frequencies by experimentally changing intracellular or extracellular ionic strengths. This gives confidence in the model, whose validity is now generally accepted.

This work led to the important conclusion that the capacitance of all biological membranes, including cellular membranes and those of subcellular organelles such as mitochondria, is of the order of 1 $\mu$F/cm$^2$. This value is apparently independent of frequency in the total RF range; at low audio frequencies, capacitance values increase with decreasing frequencies due to additional relaxation mechanisms in or near the membranes [3], [60]. These mechanisms will not be discussed here and have been summarized elsewhere [3], [60].

From the membrane capacitance, we can estimate values for the transmembrane potentials induced by microwave fields. At frequencies well above the characteristic frequency (a few MHz), the membrane capacitance impedance becomes very small by comparison with the cell access impedance $(\rho_1 + \rho_a/2)$ and the membrane behaves electrically like a short circuit. Since intracellular and extracellular conductivities are comparable, the average current density through the tissue is comparable to that in the membrane. For an in situ field of 1 V/cm (induced by an external microwave field flux of about 10 mW/cm$^2$) the current density $i$ through the membrane is about 10 mA/cm$^2$ since typical resistivities of tissues are of the order of 100 $\Omega$-cm at microwave frequencies. Thus the evoked membrane potential $\Delta V = i/\omega C_m$ is about 0.5 $\mu$V at 3 GHz and diminishes with increasing frequency. This value is 1000 times lower than potentials recognized as being biologically significant. Action potentials can be triggered by potentials of about 10 $\mu$V across the membrane, but (dc) transmembrane potentials somewhat below 1 mV have been recognized as being important [61].

Frey [62] has disputed the applicability of the model discussed above. He also quoted Terzuola and Bullock [63] who had observed that rather low potentials in tissue can be significant. But there is overwhelming evidence to support the classical biophysical model discussed above, and it is not contradicted by the findings of Terzuola and Bullock. These authors carried out their work at low frequencies, where responses to small in situ fields are possible as we shall discuss now.

If $f << f_c$, the total potential difference applied across the cell is developed across the membrane capacitance. In this limit, the induced membrane potential $\Delta V$ across a spherical cell is $\Delta V = 1.5 E$, where $E$ represents the applied external field. Thus the cell samples the external field strength over its dimensions and delivers this integrated voltage to the membranes, which is a few mV at these low frequencies for cells larger than 10 $\mu$m and external fields of about 1 V/cm. These transmembrane potentials can be biologically significant. Since at low frequencies the resistivity of tissue is 500 to 1000 $\Omega$-cm, the corresponding current densities are about 1 mA/cm$^2$. This current density happens to approximate that which, if applied to the total human body, produces resistive heating equal to the basal metabolic rate.

The ability to integrate an external field over large cellular dimensions in order to achieve significant transmembrane potentials is found in certain electrosensitive fish such as rays and sharks [64]. These animals have long tubular structures, the Ampullae of Lorenzini, which extend over distances of more than 10 cm. These tubular structures are filled with highly conducting seawater and the total potential difference between their ends is applied to the receptor epithelium located at their inner end. Detection capability is furthermore restricted from dc to a few hertz by the geometry of these structures. Thus spatial integration is combined with an extremely low-pass filter response in order to overcome thermal noise which is typically about 1 $\mu$V across the membrane. Obviously, such high-field sensitivities in electric fish do not imply any special sensitivity of mammalian nervous tissues to low-intensity microwave radiation.

X. POSSIBILITY OF WEAK NONTHERMAL INTERACTIONS

The considerations presented above do not suggest any weak nonthermal mechanism by which biological systems could react to low-intensity microwave fields. It requires fields of the order of a few kV/cm to orient long biopolymers, and probably still higher fields to excite internal vibrations or produce submolecular orientation. External fields acting on biopolymers must further overcome strong local fields, which are 1.5 kV/cm at a distance of 100 $\AA$ from a monovalent ion and 1.8 kV/cm at the same distance from a hemoglobin molecule. Microwave frequencies are well above those corresponding to significant rotational diffusion times, excluding orientational effects. Transmembrane potentials induced by typical non-
thermal microwave fields are vanishingly small relative to potentials required for stimulation and compare with membrane noise. Field induced force effects are unlikely to be significant on a single molecular or cellular level, since the threshold field strengths necessary to overcome thermal disturbances are too high [65].

However, some principles emerge regarding possible mechanisms of weak microwave interaction, if such a concept exists. Field force effects become more probable as the volume of the exposed particle increases [65]. Transmembrane potentials become larger for a given in situ field strength as the cell size is increased. Finally, molecules can become significantly re-oriented by the field if $\mu E > kT$, (where $\mu$ is the dipole moment, $E$ the field strength, $k$ is the Boltzmann constant, and $T$ is the absolute temperature). Thus larger physical dimensions or larger permanent or induced dipole moments are more likely to respond to weak fields. But these very factors tend to limit responses to low frequencies for these interaction mechanisms.

The large dimensions necessary for biological responses to weak microwave fields might be achieved by a cooperative reaction of a number of cells or macromolecules to the microwave stimulus, which increases the effective size of the structure and correspondingly reduces the threshold that is required for an effect. Adey suggested that such cooperativity might be induced in the counter ions loosely bound near membrane surfaces which contain a loose framework of charged polysaccharides [66].

Froehlich has suggested [67], [68] that giant dipole moments may be formed during enzyme substrate reactions and that the corresponding dielectric absorption processes might be highly resonant and nonlinear and likely to channel energy into lower frequency modes of vibration. He also considered the membrane as a likely site of resonant electromagnetic (EM) interactions, and derived an estimate of the resonant frequencies from the velocity of sound and the membrane thickness to be of the order of 100 GHz. Acceleration and deceleration of variety of biological responses which suggest effects, and derived an estimate of the resonant frequency as the cell size and correspondingly reduces the threshold that is required for an effect. Adey suggested that such cooperativity might be induced in the counter ions loosely bound near membrane surfaces which contain a loose framework of charged polysaccharides [66].

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REFERENCES


