We have also provided representative numerical results to emphasize the characteristics of the magnetic wave interactions. Although the present theory is rigorously valid only for a film of infinite length in the propagation direction, if the end effects are negligible, the coupled-mode equations can be used to deduce the insertion loss of a filter of finite length by imposing a phenomenological boundary condition on the wave amplitude.

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The Effects of Nonlinear Membrane Capacity on the Interaction of Microwave and Radio Frequencies with Biological Materials

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***Abstract*—A model for the capacitance of biological membranes as a function of voltage is used to predict signal mixing and difference-frequency generation in membranes.**

Production of low-frequency signals by the biomembrane from modulated *RF* is predicted, and implications for macroscopic modification of membrane function are discussed.

I. Introduction

RECENT realization of the significance of nonthermal interactions of radio and microwave frequency fields with biological materials generates a need for theoretical models to account for effects presently being observed [1]–[18]. Furthermore, the biological membrane is a likely locus for some of these effects [1], [4]–[6], [12]–[14], [16]–[18]. A model, based on the nonlinear conductance properties of the membrane, has been proposed to describe possible mixing phenomena and rectification [3].

In this paper, we examine voltage-variable membrane capacitance as another possible mechanism for generating difference frequencies. An approach taken is to treat the biological membrane as a "device" similar, in many respects, to a p-n junction diode as used in parametric amplifiers and harmonic generators. The characterization for the high-frequency response of the nonlinear capacitance is derived from low-frequency measurements on artificial membranes.

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II. Nonlinear Capacitance

The variation of capacitance with voltage allows for signal mixing (production of harmonic and sum/difference frequency components) in response to applied ac signals. Several investigators have observed a nonlinear capacitance in artificial bilayer-lipid membranes (BLM) [19]–[24]. In this study, we make the following assumptions.

1) Biological membranes also possess a nonlinear capacitance of the form observed in BLM's at low frequencies.

2) The nonlinearities hold at high frequency, i.e., charge displacements in membranes occur with sufficient speed so as to make measured low-frequency variations applicable. To our knowledge, no measurements have been made of membrane capacity at high frequencies and at voltage levels which would reveal the nonlinearities. The frequency characteristics of the membrane capacitance depend on the time required to redistribute charges in the vicinity of the membrane. Thus measurements of this characteristic as a function of frequency will help separate out ionic and electronic components of the membrane capacitance and reveal a good deal about the membrane structure and the charge flow through it. Similar measurements on p-n junctions are extremely important in characterizing both the junction and the materials [27] and [28].

The numerical values for the BLM capacitance are usually approximated by [19]–[24]

$$C_m = C_0 + \beta V^2$$

where

- C_m the membrane capacity (μF/cm^2);
- C_0 static capacity (μF/cm^2);
- V the magnitude of applied voltage; and
- β a constant (with voltage) dependent on membrane, geometry, and temperature.

It is difficult to assign precise terms of a polynomial expansion to a nonlinear experimental curve. Thus we take the voltage dependence to be of a more general form:

$$C_m = C_0 + \alpha V + \beta V^2 + \cdots . \tag{1}$$

If we eliminate third-order and higher terms and define the charge q with

$$q = CV$$

the membrane current density is given by

$$J_m = \frac{d(CV)}{dt} = C_0 \frac{dV}{dt} + 2\alpha V \frac{dV}{dt} + 3\beta V^2 \frac{dV}{dt}. \tag{2}$$

Assume an externally applied signal

$$V_{\text{app}} = V_1 \cos(\omega_1 t) + V_2 \cos(\omega_2 t + \phi_2)$$

and a transmembrane potential V_0. The transmembrane potential is set by the natural concentration imbalance across the membrane and is usually of the order of 50 mV. Then

$$V_m = V_0 + V_1 \cos(\omega_1 t) + V_2 \cos(\omega_2 t + \phi_2). \tag{3}$$

In the general case, for nonlinearities with inputs at frequencies f_1 and f_2, the resultant frequencies f_0 are given by

$$f_0 = \pm m f_1 \pm n f_2$$

where m and n are integers.

If we assume that outputs most likely to be of interest are those close to the natural biological signaling frequencies (less than 1 kHz), then the difference term is of greatest significance.

The solution of (2) with $V = V_m$ as in (3) yields a difference term of the form

$$J_{\omega_0} = -\left[\alpha + 3\beta V_0\right] V_1 V_2 \omega_0 \sin(\omega_0 t - \phi_2) \tag{4}$$

where

$$\omega_0 \equiv \omega_1 - \omega_2.$$

Thus, if a modulated ac signal is applied, the membrane may produce a low-frequency output.

III. Estimate and Implications of Response Magnitude

We know of no measured values which have been made on cell membranes or tissue at the frequencies of interest in the radio and microwave region. However, measurements of capacitance variation have been made on artificial membranes by White [23] at low frequencies (less than 300 Hz) and he obtained, at 20°C, values of $C_0 \approx 0.6$ μF/cm^2 and $\beta \approx 1.2 \times 10^{-6}$ μF/cm^2(mV)^2. If we assume high peak fields of approximately 2 kV/cm^2 at 3 GHz, which might be appropriate in the vicinity of a radar antenna, $|J_{\omega_0}| \approx 5 \times 10^{-10}$ A/cm^2, at a difference frequency $\omega_0 = 10$ Hz. This data is obtained using the plane wave model of [3] and the data from [11]. If the cell area is approximately equal to 10^{-6} cm^2, this translates to an ion current of ≈ 1000 ions/s. This is a small signal even for the relatively high pulsed fields that are assumed. Work on cell chemotaxis, however, shows an ability of cells to detect signals of this magnitude [29]. It is not clear whether this mechanism will prove important in microwave safety.

IV. Appendix
Solution for Membrane Current Density

$$J_m(V_m)=J_{m1}+J_{m2}$$
$$=\left[C_0\frac{dV_m}{dt}+2\alpha V_m\frac{dV_m}{dt}\right]+\left[3\beta V_m^2\frac{dV_m}{dt}\right].$$
$$V_m=V_0+V_1\cos(\omega_1 t)+V_2\cos(\omega_2 t+\phi_2).$$

This leads to

$$J_{m1}(V_m)=-\{\omega_1V_1\sin(\omega_1 t)[C_0+2\alpha V_0]$$
$$+\omega_2V_2\sin(\omega_2t+\phi_2)[C_0+2\alpha V_0]$$
$$+\alpha[\omega_1V_1^2\sin 2(\omega_1t)+\omega_2V_2^2\sin 2(\omega_2t+\phi_2)$$
$$+V_1V_2\sin[(\omega_1+\omega_2)t+\phi_2][\omega_1+\omega_2]$$
$$+V_1V_2\sin[(\omega_1-\omega_2)t-\phi_2][\omega_1-\omega_2]\}$$

and

$$J_{m2}(V_m)=-3\beta\left\{\omega_1V_1\sin(\omega_1t)\left[V_0^2+\frac{V_1^2}{4}+\frac{V_2^2}{2}\right]\right.$$
$$+\omega_2V_2\sin(\omega_2t+\phi_2)\left[V_0^2+\frac{V_1^2}{2}+\frac{V_2^2}{4}\right]$$
$$+\omega_1V_0V_1^2\sin 2(\omega_1t)+\omega_2V_0V_2^2\sin 2(\omega_2t+\phi_2)$$
$$+\frac{\omega_1V_1^3}{4}\sin 3(\omega_1t)+\frac{\omega_2V_2^3}{4}\sin 3(\omega_2t+\phi_2)$$
$$+V_1V_2^2\sin[(\omega_1+2\omega_2)t+\phi_2]\left[\frac{\omega_1}{4}+\frac{\omega_2}{2}\right]$$
$$+V_1V_2^2\sin[(\omega_1-2\omega_2)t-\phi_2]\left[\frac{\omega_1}{4}-\frac{\omega_2}{2}\right]$$
$$+V_1^2V_2\sin[(\omega_2+2\omega_1)t+\phi_2]\left[\frac{\omega_2}{4}+\frac{\omega_1}{2}\right]$$
$$+V_1^2V_2\sin[(\omega_2-2\omega_1)t+\phi_2]\left[\frac{\omega_2}{4}-\frac{\omega_1}{2}\right]$$
$$+V_0V_1V_2\sin[(\omega_1+\omega_2)t+\phi_2][\omega_1+\omega_2]$$
$$\left.+V_0V_1V_2\sin[(\omega_1-\omega_2)t-\phi_2][\omega_1-\omega_2]\right\}.$$

Thus

$$J_{m(\omega_1-\omega_2)}=J_{m1(\omega_1-\omega_2)}+J_{m2(\omega_1-\omega_2)}$$
$$=-\{\alpha V_1V_2\sin[(\omega_1-\omega_2)t-\phi_2][\omega_1-\omega_2]\}$$
$$+-\{3\beta V_0V_1V_2\sin[(\omega_1-\omega_2)t-\phi_2][\omega_1-\omega_2]\}.$$

Therefore

$$J_{m\omega 0}=-[\alpha+3\beta V_0]V_1V_2\omega_0\sin(\omega_0t-\phi_2),\qquad \omega_0\equiv\omega_1-\omega_2.$$

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