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# Understanding conditions for which biological effects of nonionizing electromagnetic fields can be expected

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**Abstract**

Scientific interest in the interaction of nonionizing electromagnetic fields with biological systems is longstanding, but often still controversial. Theories, models and computer simulations have usually emphasized physical interactions with subsystems (e.g. cell membranes) of a biological system. By extending this first necessary physical step to a second step of explicitly and quantitatively considering chemical changes, increased understanding appears possible. In the case of "strong fields", the role of field-altered chemistry is important to electrochemotherapy [Biochem. Pharmacol. 42, Suppl. (1991) 567] and creation of transdermal microconduits [Bioelectrochem. Bioenerg. 49 (1999) 11; J. Controlled Release 61 (1999) 185; J. Invest. Dermatol. 116 (2001) 40] For "weak fields" (a topic with much more controversy) consideration of chemical change shows that organized multicellular systems can be understood to respond to extremely small electric [Chaos 8 (1998) 576] or magnetic fields [Nature 405 (2000) 707]. In contrast, isolated individual cells interacting via voltage-gated channels [Proc. Natl. Acad. Sci. 92 (1995) 3740; Biophys. J. 75 (1998) 2251; Bioelectromagnetics 20 (1999) 102], or processes without "temperature compensation" [Biophys. J. 76 (1999) 3026], appear implausible. Satisfactory understanding is likely only if experimental and theoretical work is reconciled, which should therefore be emphasized. The interaction of electromagnetic fields with biological systems is of interest because of fundamental scientific curiosity, potential medical benefits and possible human health hazards. © 2002 Published by Elsevier Science B.V.

*Keywords:* Nonionizing; Electromagnetic fields; Chemical changes; Strong fields; Weak fields

## 1. Introduction

Prediction of both physical and chemical changes is central to understanding weak field interactions from DC to microwave frequencies [2,3,4] [5,7,11–16] and for understanding heating, electroporation and other responses for strong fields used in vitro [17,18] and in vivo [19–21] (Fig. 1).

Quantitative understanding of chemical change is mostly lacking, but is directly relevant to electrical drug delivery, and indirectly relevant to electromagnetic field sensory systems and exposure of humans to electromagnetic fields. Experimental determination of the amount of chemical change, particularly for individual cells within a system, is important to making comparisons with theoretical predictions [23]. Such measurements have been reported only occasionally, even for electroporation [1,24–30]. Individual cell electroporation under controlled conditions that measure both electrical quantities and molecular uptake will be particularly valuable [17,18].

## 2. Methods

Attention is directed to quantitative understanding of chemical change due to both a field exposure and competing

$$\mathbf{PHYS} \longrightarrow \mathbf{CHEM} \longrightarrow \mathbf{BIOL}$$

Fig. 1. Emphasis of the fact that an electromagnetic field is a physical and not a chemical agent. In the chemical change approach, a field can create a biological effect only through the sequence of the physical field ("PHYS") altering one or more chemical processes ("CHEM") within the context of a biological system ("BIOL"). This basic sequence has not been emphasized in most prior analysis, where mainly physical considerations have been used. In the "chemical change approach", theoretical models representing classes of biophysical mechanism are used to generate quantitative estimates of the alteration of chemistry within a biological system by a field exposure [5–10,22].

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influences. The basic, simple idea is that the field-induced change should stand out against changes due to other sources. This leads to consideration of a signal-to-noise ratio criterion,

$$(S/N)_{\mathrm{CHEM}} \approx \frac{S}{[N^2 + V^2 + C^2 + I^2 + B^2]^{1/2}}, \quad (1)$$

based on chemical changes (Fig. 2), rather than the purely physical quantities that have usually been considered [15]. Eq. (1) holds for the case that competing chemical changes (Table 1) can be approximated as independent and random around their mean values.

Nonionizing fields are considered, even for electroporation (maximum transmembrane voltage of $\sim 1$ V) involving an energy per elementary charge of $\sim 1$ eV ($1.6 \times 10^{-19}$ J$\gg$kT), which is too small to ionize most molecules. Alteration of the rate of an ongoing, metabolically driven chemical reaction or transport process by a field can, however, alter biochemistry, and thereby create a potentially causal chemical change.

## 3. Results and discussion

Significant progress has been made with respect to chemical change analysis. For example, two types of sensory systems have been shown to be consistent with theoretical models. Elasmobranch fish, such as the shark, are known to respond to seawater environmental electric fields of the order $E_e \approx 5 \times 10^{-7}$ V m$^{-1}$ within about 1 s [14]. This can be accounted for by a theoretical model based on a slight alteration of ion transport across the membrane of the $\sim 10^4$ detector cells in each ampulla of Lorenzini [5]. In the case of weak magnetic fields, there are many examples of observations of animal behavior that involves detection of small differences (in magnitude or direction) of essentially constant magnetic fields [32,33]. Some theoretical models have postulated involvement of radical-pair reactions [34,35]. An explicit chemistry-based signal-to-noise ratio model supports this possibility, and shows that a minimum size should be involved [6]. Multicellular structures are therefore probably essential for biological detection of weak fields, because a coordinated sharing of chemical change improves a chemistry-based signal-to-noise ratio. Both the elasmobranch fish model [5] and the magnetic field model [6] involve many cells, and therefore satisfy this condition. Without a strong coupling between electromagnetic fields and biochemical processes, this makes responses by individual cells implausible.

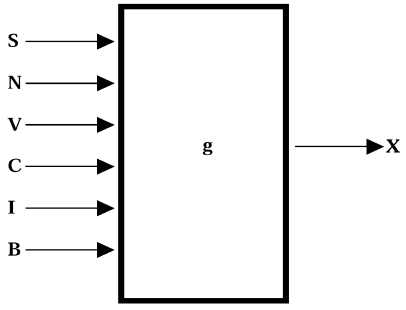


Fig. 2. Illustration of a field-induced chemical change and competing chemical changes for one step in a biochemical pathway, with biochemical amplification (gain = $g$) that results in a measured quantity, $x$. This is analogous to an electronic amplifier in which the signal ($S$) and competing effects are all referenced to an input. See Table 1 for definitions of competing changes $N$, $V$, $C$, $I$ and $B$. This representation allows one to consider the magnitude and variability in experimentally measured effects, and to make comparisons with what is expected from theoretical estimates of chemical change.

Table 1
Chemical change due to a field exposure and to competing influences

| Symbol | Chemical change | Source |
|---|---|---|
| $S$ | $\bar{n}_S$ | Field-induced chemical change signal |
| $N$ | $\sqrt{\bar{n}} \approx \sqrt{\bar{n}_0}$ | Molecular shot noise (fundamental) [5–9,22] |
| $V$ | $\bar{n}_V$ | Chemical change due to temperature variations [10] |
| $C$ | $\bar{n}_C$ | Chemical change due to concentration variations |
| $I$ | $\bar{n}_M$ | Chemical change due to mechanical interference |
| $B$ | $\bar{n}_B$ | Chemical change due to background fields |

How can a field-induced chemical change (the "signal", $S$) be understood to stand out against changes that are due to competing sources of change? The above origins of chemical change are distinguished to assist in analyzing experiments and understanding conditions for which a biological effect could be expected. In some cases, one or two sources may predominate, so that not all sources need be considered. Fundamental "chemical noise" (molecular shot noise) is always present, but may not be the largest source of competition. Theoretical models for biological sensing of weak electric fields [5] and small magnetic field differences [6], as well as electroporative uptake of small amounts of the anticancer drug bleomycin, have been shown to satisfy a chemical change-based signal-to-noise ratio using fundamental chemical noise, $N$ [31].

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