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Review

Bioelectromagnetics in Morphogenesis

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Understanding the factors that allow biological systems to reliably self-assemble consistent, highly complex, four dimensional patterns on many scales is crucial for the biomedicine of cancer, regeneration, and birth defects. The role of chemical signaling factors in controlling embryonic morphogenesis has been a central focus in modern developmental biology. While the role of tensile forces is also beginning to be appreciated, another major aspect of physics remains largely neglected by molecular embryology: electromagnetic fields and radiations. The continued progress of molecular approaches to understanding biological form and function in the post genome era now requires the merging of genetics with functional understanding of biophysics and physiology in vivo. The literature contains much data hinting at an important role for bioelectromagnetic phenomena as a mediator of morphogenetic information in many contexts relevant to embryonic development. This review attempts to highlight briefly some of the most promising (and often underappreciated) findings that are of high relevance for understanding the biophysical factors mediating morphogenetic signals in biological systems. These data originate from contexts including embryonic development, neoplasm, and regeneration. Bioelectromagnetics 24:295–315, 2003. © 2003 Wiley-Liss, Inc.

Key words: electromagnetic fields; embryology; development; regeneration; cancer; ultraweak photons; self-assembly

INTRODUCTION

One of the most interesting aspects of biology is morphogenesis: the ability of living systems to self-organize simultaneously on many scales to produce the exquisitely complex pattern which underlies function. Molecular genetics and biochemistry have focussed on unraveling the role of biochemical messengers in this process, and are beginning to understand the role of tensile forces and adhesion. However, one major aspect of biophysics remains largely neglected by modern embryology: electromagnetic fields and radiations. The continued progress of molecular approaches to understanding biological form and function in the post-genome era requires the functional understanding of biophysics and physiology.

The literature contains much data hinting at an important role for bioelectromagnetic phenomena as a mediator of morphogenetic information in many contexts relevant to embryonic development. However, many of these papers were published in journals not indexed in Medline or other biomedically focussed databases and were published prior to when it was feasible to place full content or even abstracts online. Thus, much of this work remains unknown to researchers in the field. This review attempts to highlight some of the most promising (and often little appreciated) findings that are of high relevance for understanding the biophysical factors mediating morphogenetic signals in biological systems. Papers were selected based on quality, importance of result, or in some cases uniqueness individual reports which have not been followed up but may indicate extremely promising and novel findings.

For reasons of brevity, well known and popular aspects of bioelectromagnetics will not be addressed. These include ionic conduction in neurons, detection of physiological electric and magnetic fields via ECG and SQUID, light, ionizing radiation, and the mountain of literature on controversial epidemiological claims of human disorders caused by exposure to fields of technological origin (extremely low frequency (ELF) and microwave). The fundamental biophysics of

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electromagnetic fields is likewise too vast a subject to cover here.

Instead, this survey presents a terse compilation of important but often little known ''classical'' and modern studies relevant to the idea that electromagnetic fields are carriers of morphogenetic information. The reports listed under the different headings often vary greatly with respect to the depth in which the phenomenon is characterized and thus, with respect to the degree to which the putative role of EM fields is proven. The individual cases discussed below most often concern static (DC) electric fields, but sometimes involve magnetic fields, electromagentic radiation, or ultraweak photon emission. While being examples of ''electromagnetism,'' each type of phenomenon clearly involves a different set of physical properties and may involve completely different biological mechanisms. The type of bioelectromagnetic event is thus specified in each case.

Many properties of biological systems, such as polarity, long range spatial order, and positional information are present in the physics of electromagnetic fields. There is suggestive evidence that endogenous DC electric fields, magnetic fields, and ultra-weak photon emission are part of the medium by which information flows in biological systems. To begin to set the context for these studies, it is helpful to consider more generally the range of applications of bioelectromagnetics in biology and medicine [O'Connor et al., 1990; Basset, 1993; Ho et al., 1994; Pilla and Markov, 1994].

In order to give a flavor of the ubuiqitous presence of EM fields in biology, Table 1 presents some examples of bioelectromagnetics in a variety of areas. It is seen that EM phenomena manifest at many levels of organization and are involved in a wide range of bioprocesses (Table 2). Organisms from bacteria to mammals are all sensitive to EM fields [Gould, 1984]. A

TABLE 1. Applied Fields Affect a Plethora of Biological Processes and Systems

Type of phenomenon	Specifics	Reference
EM field effects on biochemical processes	ELF fields affect enzyme reactions	Moses and Martin, 1993; Holian et al., 1996
Sensitivity to EM fields in animals and plants	Mud snail detects electric fields	Webb et al., 1961
	Termites detect weak AC magnetic fields	Becker, 1976
	Humans detect magnetic fields	Baker, 1984; Bell et al., 1991
	Magnetotropism in plants	Audus, 1960; Barnothy, 1964
	Mollusk neuron detects GMF	Lohmann et al., 1991
Effects of applied fields on neurophysiology	ELF AC magnetic fields cause calcium efflux in brain tissue	Blackman, 1984; Blackman et al., 1988
	Weak AC magnetic fields alter analgesia	Kavaliers and Ossenkopp, 1986a,b
	DC magnetic field alters EEG	Kholodov, 1966
EM fields and higher-level neurobiology and behavior	Animals avoid certain types of fields	Sheppard and Eisenbud, 1977; Kermarrec, 1981; Rai, 1986
	Applied fields alter behavior	Persinger, 1974a; Horn, 1981
	Applied fields affect learning rates in mammals	Levine et al., 1995; Lai et al., 1998
	Depth of hypnosis correlates with electric measurements on skin	Ravitz, 1959; Friedman et al., 1962; Ravitz, 1962
Applied fields affect several systems in human body	Reproductive effects	Krueger et al., 1975; Brewer, 1979
	Skeletal system; applied fields used clinically to improve bone growth	Bruce et al., 1987; McCleary et al., 1991; Nagai and Ota, 1994
	Circadian cycle changes	McBride and Comer, 1975; Brown and Scow,1978; Scaiano, 1995
	Immune system effects	Smialowicz, 1987, review
Applied fields affect cell behavior and parameters	Cell motility and galvanotaxis	McCaig and Zhao, 1997, review
	Applied fields can cause differentiation and even dedifferentiation!	Harrington and Becker, 1973; Chiabrera et al., 1979, Chiabrera et al., 1980; Grattarola et al., 1985; Robinson, 1985
	Changes in growth rate	Patel et al., 1985; Ross, 1990
	Transcription and translation rates are all altered by field exposure	Liboff et al., 1982; Goodman et al., 1985; Goodman and Henderson, 1988; Greene et al., 1991; Lai and Singh, 1997
ELF fields and ionizing radiation	Exposure to ELF fields mitigates effects of ionizing radiation	Barnothy, 1963a; Amer and Tobias, 1965; Zecca et al., 1984

TABLE 2. Importance of the Earth's Fields for Biosystems

Type of phenomenon	Specifics	Reference
GMF & GEF state correlated with biological parameters	Correlation with heart attacks	Brown et al., 1979; Malin and Srivastava, 1979
	Lunar cycle correlates with response to magnetic field in animals	Brown et al., 1955b; Brown and Webb, 1961; Brown and Barnwell, 1961b
	Correlation with psychiatric hospital admissions	Friedman et al., 1963
Effects caused by shielding from GMF	Anomalous root growth	Shultz et al., 1967
	Altered circadian rhythms	Wever, 1968; Borodin and Letiagin, 1990
	Teratological effects on embryonic development	Shibib et al., 1987; Asashima et al., 1991
	Altered termite building behavior	Becker, 1976

review of EM sensors in living systems is presented in Tenforde [1989]. Human beings probably detect the Earth's geomagnetic field (GMF) via the pineal gland, which may transduce weak magnetic fields into neuronal activity [Semm et al., 1980; Olcese et al., 1988; Olcese, 1990].

The Earth's GMF and geoelectric field (GEF) carry information and may be a fundamental part of large scale information flow in the biosphere [Cole and Graf, 1974] (Table 2). Indeed, shielding from the Earth's fields results in a wide range of patterning defects and physiological alterations in plants and animals [Conley, 1970; Brown and Chow, 1973]. Geological changes in GMF have been linked to extinctions [Harrison and Funnel, 1964; Watkins and Goodell, 1967; Hays, 1971], as well as aspects of the large scale evolutionary course of a number of species [Simpson, 1966; Kopper and Papamarinopoulos, 1978; Ivanhoe, 1979, 1982].

Bioinformation transfer through the electromagnetic spectrum figures prominently in ecology and animal communication [Presman, 1970; Becker, 1976]. At the level of the organism, the idea that the morphology (embryonic geometry) of organisms is mediated, in part, by the action of endogenous electromagnetic fields, has been proposed by a number of workers. Two of the most prolific were Lund [1947] and Burr [Burr et al., 1937; Burr and Hovland, 1937a; Burr et al., 1938c]. Both labs conducted studies on a wide range of both plant and anmal organisms; they showed correlations of changes in natural electric fields with development and regeneration, and demonstrated for the first time that externally applied electric fields can affect morphogenesis of various organisms.

During embryogenesis, a developing organism must achieve, within fairly tight parameters, a very particular morphology of external form and internal organization, from organelles all the way to the whole organism. The process of regeneration illustrates the maintenance and restoration of that morphology in light of environmental injury. Finally, to complement reductive studies on oncogenes and the molecular basis of cellular transformation, cancer can be viewed as a disease of geometry. Tumor tissue results from growth, which is not patterned appropriately, because it is unable to perceive or execute morphogenetic cues. The studies of the roles of EM fields in these process which are cited below generally fall into three classes of evidence: (1) characterization of existing electric or magnetic field within organisms and showing that their parameters correlate with biological patterning events, (2) demonstrating the effects of exogenous (applied) fields of correct physiological parameters on organisms, organs, tissues, or cells, which suggest that these systems are responsive to electromagnetic signals (this is analogous to a ''gain of function'' experiment in molecular embryology), and (3) examination of the consequences of abrogation of a specific subset of the endogenous EM fields in a particular context (the ''loss of function'' experiment). Together, these three lines of investigation can demonstrate a functional, causal relationship and thus show that EM fields are an integral part of information flow in some morphogenetic process.

PATTERNING FIELDS IN REGENERATION

Regeneration is a special case of morphogenesis, since it involves the recreation of an existing structure, in the context of mature surrounding tissue. In replacing a lost body part, embryonic developmental mechanisms may be recruited to restore pattern. Some animals normally exhibit a striking degree of regeneration, ranging from tails or limbs in the case of some amphibians [Tsonis, 1983; Brockes, 1998] to regenerating a complete animal from a small piece of tissue in the case of planarian flatworms [Bröndsted, 1969; Agata and Watanabe, 1999]. It is important to note that even animals which are not normally known for their regenerative ability can regenerate in special cases. For example, human children will regenerate severed fingertips if the stump is not pulled over with skin after a

clean amputation [Illingworth, 1974; Illingworth and Barker, 1980; Borgens, 1982a]. The difference between regenerating and nonregenerating systems has been suggested to depend upon the bioelectrical properties of the tissue (see below).

The regenerating limb system in amphibians has an electrical component, including electrically mediated dedifferentiation and axial control [Becker and Murray, 1967; Becker, 1972a; Becker, 1984; Borgens et al., 1979d]. This model is supported by the observations that (1) strong endogenous EM fields exist in regenerating limbs, (2) there are differences between regenerating and nonregenerating animals' field characteristics, most often consisting of variations in resistance and efflux currents, (3) disruption of endogenous fields by shunting inhibits regeneration, and (4) application of exogenous fields is able to alter regeneration and even induce it in normally nonregenerating species. These data are summarized in Table 3.

One good example of bioelectrical control of regeneration was described in the context of whole body regeneration in the segmented earthworm [Moment, 1946, 1949; Kurtz and Schrank, 1955]. Wherever the worm is cut, new segments are added until there are about 90 segments. The number of segments appears to be controlled by electrical potential. Each segment has a voltage, and segments are added until the overall voltage totals the correct endogenous value for a full length worm.

One of the most fruitful contexts in which to study electric phenomena in regeneration is that of the vertebrate limb. When a limb is amputated, an injury current appears, which is thought to induce dedifferentiation into or activation of blastema cells. It further serves to pattern the limb forming from these cells by attracting neuronal growth and providing spatial information for cells migrating into the new limb. An exciting series of experiments has shown that electrical fields can induce regeneration in normally nonregenerating species [Smith, 1974]. For example, minute, steady electrical fields imposed within forelimb stumps of adult frogs initiated limb regeneration [Smith, 1979]. Becker and Sparado [1972; Becker, 1972a] report partial limb regeneration in mammals using an applied electric field.

Shunt experiments, disturbing the natural fields, provide a way to test the causal importance of the natural currents in regeneration. Short circuiting the endogenous fields by means of ionic depletion of the medium, skin flaps, or with conducting wires, results in a cessation of regeneration [Borgens et al., 1979c,d; Borgens, 1982]. This is evidence that the currents are of prime importance in regeneration. It has been suggested that frogs do not regenerate limbs because they possess a very loose skin which overlays large subdermal lymph spaces; urodeles (regenerating salamanders) do not. These lymph spaces may serve as shunts (low resistance paths) which short circuit the current, thus interfering with the currents' normal role in regeneration [Borgens et al., 1979b]. Understanding the endogenous basis of bioelectrical controls of regeneration has great potential as a medical tool to augment regeneration [Borgens, 1999; Borgens et al., 1999; Moriarty and Borgens, 2001].

PATTERNING FIELDS IN EMBRYONIC DEVELOPMENT

Developing embryos are the paradigmatic case of unfolding and elaboration of complex, consistent, four-dimensional pattern and form. Embryonic morphology is epigenetically derived, the results of independent units following local, small scale rules, but some contexts suggest nonlocal (or field) properties. Electrical activity due to ion channel function has been extensively studied in the function and structure of the

TABLE 3. Bioelectric Fields and Regeneration

Type of phenomenon	Specifics	Reference
Natural fields associated with regenerating systems	Field peaks correlate with points of highest regenerative ability	Mathews, 1903
	Characteristic fields accompany regeneration events	Rehm, 1938; McGinnis and Vanable, 1985
	Animals which regenerate produce fields upon amputation; animals which don't regenerate do not	Borgens et al., 1979b; Harrington et al., 1981
Augmenting regeneration by exogenous applied fields	Spinal cord neuronal regeneration	Borgens et al., 1986, 1987b, 1990, 1999; Moriarty and Borgens, 2001
	Limb regeneration	Becker, 1972b; Becker and Sparado, 1972; Smith, 1974, 1979; Harrington et al., 1974
Inhibiting regeneration by disrupting endogenous fields	Limb regeneration is inhibited by shunts	Borgens et al., 1979c,d; Borgens, 1982b; Jenkins et al., 1996

nervous system. However, there exists a large but often little recognized literature that supports a regulative role for endogenous ion flows and standing (DC) potential differences in many aspects of embryonic morphogenesis unrelated to the function of neurons [Lund, 1947; Jaffe and Nuccitelli, 1977]. The discovery of strong endogenous DC electric fields within living systems have been augmented by functional experiments suggesting that these fields have a causal role in physiology and development [Jaffe, 1981]. Table 4 summarizes data showing that endogenous EM fields exist in a wide variety of developing systems and correlate with and predict spatio-temporal events in embryonic development.

Developing systems generally drive steady ion currents and produce substantial fields within themselves; examples include currents that enter the prospective and continuing growth point of several tip growing plant cells, voltage across the cytoplasmic bridge between an insect oocyte and its nurse cell, current traversing a recently fertilized egg from animal to vegetal pole, and early potentials across embryonic

TABLE 4. Bioelectromagnetic Fields and Embryonic Development

Class	Specifics	Reference
Endogenous fields exist in developing organisms	Fields between egg-ovary systems drive materials into oocyte	Hagiwara and Jaffe, 1979; Jaffe and Woodruff, 1979; Barish, 1983; Nuccitelli, 1983; Bohrmann et al., 1984; Kunkel, 1986, 1991; Bowdan and Kunkel, 1990; Kindle et al., 1990; Diehl-Jones and Huebner, 1993; Anderson et al., 1994; Kunkel and Faszewski, 1995
	Eggs drive currents around themselves	Chambers and de Armendi, 1979; Robinson, 1979; Bohrmann et al., 1986a; Bowdan and Kunkel, 1990; Kindle et al., 1990; Coombs et al., 1992; Anderson et al., 1994; Kunkel and Smith, 1994; Kunkel and Faszewski, 1995; Faszewski and Kunkel, 2001
	Mouse and chick embryos drive fields around themselves	Burr and Hovland, 1937b; Kucera and de Ribaupierre, 1989; Hotary and Robinson, 1990; Keefe et al., 1995
	Neural tube of amphibians generates large fields	Nuccitelli, 1984; Hotary and Robinson, 1991
	Plants drive a variety of fields which correlate with sites of growth and also predict growth rates and dimensions of final shape	Burr, 1942, 1950; Burr and Sinnot, 1944; Burr and Nelson, 1946; Rosene and Lund, 1953; Stump et al., 1980; Miller and Gow, 1989; Wang et al., 1989; Rathore et al., 1991; Messerli and Robinson, 1997, 1998; Feijo et al., 1999; Messerli et al., 1999, 2000; Feijo et al., 2001
Fields correlate with morphogenetic events	Field nodes predict appearance of the head in eggs	Burr, 1941a, 1947a
	Fields in amphibians predict many morphogenetic events	Burr and Hovland, 1937a; Burr and Bullock, 1941; Brick et al., 1974
	Electrical characteristics predict polarity of axial structures such as the nervous system or the major embryonic axes	Becker, 1960, 1974; Nuccitelli and Wiley, 1985; Levin and Mercola, 1998, 1999; Levin et al., 2002
	Ion fluxes correlate with cytokinesis and meiosis	Wibrand et al., 1992; Honore and Lazdunski, 1993; King et al., 1996
	Fields precede and predict appearance of limbs in several species	Robinson, 1983; Borgens et al., 1983, 1987a; Borgens, 1984
	Suppression of fields can cause standstill of growth and differentiation	Weisennseel and Kicherer, 1981b
Applied fields alter morphology of embryos	Magnetic fields can affect embryogenesis of many species	Kim, 1976; Delgado et al., 1981, 1982; Ubeda et al., 1985; Juutilainen et al., 1986; Koch et al., 1993; Levin and Ernst,1997
	Electric fields can modify polarity and break symmetry of many developing embryos	Lund, 1921, 1923; Thomas, 1939; Stern, 1982b
	Electric fields of physiological parameters cause specific changes in morphology	Hotary and Robinson, 1994; Metcalf and Borgens, 1994; Borgens and Shi, 1995
	Shunting fields in chick embryos results in morphogenesis defects	Hotary and Robinson, 1992

epithelia. These currents can be anywhere from 1 to 1000 μA/cm [Jaffe, 1982]; and it is now known that in several types of embryos, ion channels and pumps are expressed at very early stages, long prior to the formation of neurons [Rutenberg et al., 2002]. The presence of a chick embryo at 24 h of development can be determined noninvasively by detection of changes in conductivity and dielectric constant of the very large egg [Romanoff, 1941]. Several excellent reviews can be found in Robinson and McCaig [1980], Jaffe [1982], Nuccitelli et al. [1986], Stern [1986], McCaig [1988], Borgens et al. [1989], McCaig and Rajnicek [1991], Robinson and Messerli [1996], McCaig and Zhao [1997], and McCaig et al. [2002]. Most importantly, it is seen that altering the normal EM field pattern in developing embryos often has a direct and specific effect on embryonic morphology [see also Nuccitelli, 1986, 1988].

One example of a very early role of endogenous ion flux is in the establishment of consistent embryonic left-right asymmetry. As early as 1956, it was reported that a DC electric current imposed across the chick blastoderm was able to induce a high number of cardiac reversals [Sedar, 1956]. Using modern techniques which combined genetics, molecular biology, and electrophysiology, a number of studies have recently demonstrated that endogenous differences in ion flux create voltage gradients across the embryonic midline, which combined with embryo-wide current paths through gap junctions, serve to direct the sidedness of asymmetric gene expression and the *situs* of the visceral organs [Levin and Mercola, 1998, 1999; Levin et al., 2002; Albrieux and Villaz, 2000; Pennekamp et al., 2002]. These mechanisms endogenously occur as early as the two cell stage in *Xenopus* and ascidian embryos and the primitive streak stages in the chick.

Other contexts for electrical control of morphogenesis occur in later development. For example, a number of functional studies suggest a role for endogenous ion currents in limb development in several vertebrate species; this process is likely to be directly related to the currents' roles in limb regeneration [Robinson, 1983; Borgens, 1984; Altizer et al., 2001]. Voltage gradients associated with the neural tube during neurulation appear to be required for cranial development [Shi and Borgens, 1994]. Inhibition of the transneural tube potential [Hotary and Robinson, 1991] produces a remarkable disaggregation of internal morphology (otic primordia, brain, notochord) coupled with fairly normal external form in amphibian embryos [Borgens and Shi, 1995]. Currents arising in the posterior intestinal portal are necessary for tail development [Hotary and Robinson, 1992] in avians. Lastly, K^+ currents appear to be required for the function of the hatching gland in *Xenopus* [Cheng et al., 2002].

Important advances in merging electrophysiology data with molecular biology have been made in a couple of cases, such as the role of Ca^{2+} flux in amphibian neural induction [Moreau et al., 1994; Drean et al., 1995; Leclerc et al., 1997, 1999, 2000; Palma et al., 2001]. Transient calcium gradients are generated by L-type Ca^{2+} channels during blastula and gastrula stages, prior to the morphological differentiation of the nervous system. These fluxes are downstream of the neural inducer *noggin*, and over- and underexpression analysis strongly suggests that the activity of the L-type channels specifies dorsoventral identity of embryonic mesoderm.

Because the Na^+/K^+-ATPase is instrumental in generating the voltage gradients used by neurons, it has been studied more than others during development of a number of organisms, including gastrulating sea urchins [Marsh et al., 2000] and pregastrulation mammalian embryos, where it is thought to be involved in transtrophectodermal fluid transport [Watson and Kidder, 1988; Watson et al., 1990; Jones et al., 1997; Betts et al., 1998]. Similarly, it is likely that the activity of the Na^+/K^+-ATPase is involved in gastrulation and neuronal differentiation in amphibians [Burgener-Kairuz et al., 1994; Uochi et al., 1997; Messenger and Warner, 2000]. In ascidians, analysis of developmental calcium currents [Simoncini et al., 1988] has led to the identification of a novel role for early expression of channel and pump mRNAs. The ascidian blastomeres contain a maternal transcript of a truncated voltage dependent Ca^{++} channel that is able to reduce the activity of the full length form, suggesting that mRNA expression may be used by embryos as an endogenous dominant negative to regulate the function of gene products [Okagaki et al., 2001]. Ca^{++} fluxes also appear to control morphogenesis in hydra, one of the simplest multicellular organisms with a clear large scale polarity [Zeretzke et al., 2002].

A number of important questions remain, concerning the embryonic patterning mechanisms that rely on electromagnetic fields, as well as the molecular mechanisms at the cellular level, by which cells transmit and sense electromagnetic signals. Voltage sensitive ion channels can respond to electric gradients, but their output is ion flux that once again needs to be transduced to other second messenger systems [Olivotto et al., 1996]. One such mechanism concerns the ability of electromagnetic fields to interact with DNA [Chiabrera et al., 1985; Noda et al., 1987; Matzke and Matzke, 1996]. By direct influence on chromatin structure or electrostatic interactions with the nuclear membrane, endogenous bioelectromagnetic phenom-

ena may alter gene expression and thus modify any aspect of cell behavior.

One large scale mechanism commonly proposed for how endogenous currents participate in patterning events is the providing of spatial guidance cues for cells [Poo and Robinson, 1977; Robinson and McCaig, 1980; Hinkle et al., 1981; McCaig, 1986a,b, 1987, 1988, 1989a,b, 1990a,b; McCaig and Dover, 1991, 1993; McCaig and Rajnicek, 1991; McCaig and Stewart, 1992; Rajnicek et al., 1992, 1994, 1998; Davenport and McCaig, 1993; Erskine and McCaig, 1995a,b; Erskine et al., 1995; Stewart et al., 1995; Britland and McCaig, 1996; McCaig and Erskine, 1996; Stewart et al., 1996; Zhao et al., 1996a, 1997, 1999; McCaig and Zhao, 1997; Gruler and Nuccitelli, 2000; McCaig et al., 2000, 2002; Wang et al., 2000; Djamgoz et al., 2001]. It has been suggested that three dimensional systems of voltage gradients during amphibian neurulation may be the coordinates for cell migration and morphogenesis [Hotary and Robinson, 1994; Shi and Borgens, 1995]. In particular, neural crest cells are galvanotactic and are a good candidate for the target of endogenous electrical cues [Nuccitelli and Erickson, 1983; Gruler and Nuccitelli, 1991]. A related observation that electric fields are involved in wound healing [Stump and Robinson, 1986; Rajnicek et al., 1988], may help explain the impressive regulatory ability of embryos under experimental manipulation.

Modern work has begun to merge cell biology with physiology to understand the mechanisms of galvanotaxis in multicellular systems [reviewed in McCaig and Zhao, 1997; McCaig et al., 2002]. Recent studies have characterized the additive effects of pharmacological agents, e.g., adenyl cyclase activators such as forskolin, etc., electric field in control of orientation and migration rate of *Xenopus* neurons [McCaig, 1990b; McCaig and Dover, 1993], and role of inositol phosphate second messenger system, calcium entry, and microfilament polymerization in controlling the perpendicular elongation of embryonic muscle cells exposed to a small electric field [McCaig and Dover, 1991, 1993; Erskine et al., 1995; Erskine and McCaig, 1995a; Stewart et al., 1995]. The roles of growth factor receptors and substrates on which cells move are now known to be integral parts of the process of galvanotaxis in the growth cone [McCaig and Stewart, 1992; Erskine and McCaig, 1995b; Rajnicek et al., 1998a; Zhao et al., 1999; McCaig et al., 2000] and are suggesting clinical approaches to nerve regeneration based on combinations of chemical growth factors, haptic conditions, and electric fields. Neurites are able to detect and integrate at least two morphogenetic guidance cues simultaneously [Britland and McCaig, 1996]. These data can now begin to be incorporated into a predictive biophysical model [e.g., Gruler and Nuccitelli, 2000].

In contrast to these complex cell types, the mechanisms of galvanotropism are also being used to throw light on novel properties of the bacterial cell wall [Rajnicek et al., 1994]. Indeed, galvanotaxis was observed in unicellular organisms more than 100 years ago [Verworn, 1889]. Unlike in other cell types [Poo and Robinson, 1977; Orida and Poo, 1978; Poo et al., 1978; McLaughlin and Poo, 1981; Patel and Poo, 1982; Lin-Liu et al., 1984], lateral electrophoresis of membrane proteins is unlikely to explain the galvanotactic response of amoebae, where modifications of ionic conditions in the local vicinity of ion channels are proposed to play a major role [Erskine et al., 1995; Korohoda et al., 2000].

A few studies [Bohrmann et al., 1986a,b; Bohrmann and Gutzeit, 1987; Sun and Wyman, 1987; Sun and Wyman, 1993] failed to confirm the large body of work showing that endogenous electrophoresis is utilized to load the oocyte with materials from the nurse cell sin insect ovarioles (see Table 4). It is possible that *Drosophila* oocytes may be too small for proper analysis via vibrating probe. In contrast, larger polytrophic oocytes have been much more amenable to functional testing of this model [Deloof, 1983; Deloof and Geysen, 1983; Verachtert and Deloof, 1988, 1989; Verachtert et al., 1989; Deloof et al., 1990]. These models are discussed in detail and compared to other models of pattern formation in insect oocytes in Kunkel [1991].

In functional experiments, EM fields have been shown mainly to disturb morphogenesis; at this point, this is to be expected since our knowledge of endogenous field characteristics is inadequate to produce coherent morphological changes. Cameron et al. [1993] provides a brief review of applied EM effects on embryonic development. One of the best examples is illustrated by planarians, where a simple head-tail dipole field was discovered. This field persisted in cut regenerating segments. Induced reversal of the field produced reversed anterior-posterior polarity in fragments, suggesting that the simple field can transmit morphogenetic information [Marsh, 1957, 1969]. Planarian pieces with their original anterior end oriented toward the cathode developed normally, but pieces oriented toward the anode showed head development in the tail end, developed two heads, or underwent reversal of original polarity, depending on current density [Marsh and Beams, 1957]. This phenomenon is at once an example of currents' involvement in both development and regeneration, since many planarian species normally reproduce by fissioning in half.

PATTERNING FIELDS IN CANCER

Cancer is highly relevant to patterning mechanisms because it is, in part, an error of geometry. Tumor cells grow, migrate, and function without regard for the orderly structure within which they occur. This is seen most acutely in teratomas, embryonic tumors which display extensive differentiation of a number of tissues, including bone, muscle, and hair, combined with a complete absence of orderly organization of the whole. Much modern work has addressed the genetic basis of cellular transformation, but these reductive studies are complemented by higher order models which consider the tumor tissue in its biological context. Based on considerations of ultraweak photon emission (see below), it has been suggested that cancer is the result of reversion of morphogenetic control to the scale of 10^{-5} m, the dimension of an autonomous cell [Jezowska-Trzebiatowska et al., 1986, p. 35]. This results in growth which lacks the normal spatial and temporal pattern. Thus, interactions between cancer and tumors and EM fields are interesting because they may throw light on normal processes of morphogenesis, as well as suggest approaches for detecting or preventing neoplastic transformation or for controlling the growth of existing tumors (Table 5).

Aspects of patterning that distinguish tumor cells from normal tissue include the fine control of proliferation and morphogenesis, which are precisely orchestrated during embryonic development. It is now beginning to be appreciated that ion flux and standing membrane voltage play a prominent role in carcinogenesis. Ion channel function controls the proliferation rate of a number of cells that often form tumors [Cone, 1974a, 1980; Knutson et al., 1997; Kamleiter et al., 1998; Wang et al., 1998; Dalle-Lucca et al., 2000; MacFarlane and Sontheimer, 2000; Wohlrab and Hein, 2000; Wohlrab et al., 2000], while membrane voltage has been shown to control cell fate during differentiation [Jones and Ribera, 1994; Arcangeli et al., 1996]. Tumor cells differ from untransformed cells in terms of the type of ion channels and pumps they express and in the resulting membrane potential of the cells [Martinez-Zaguilan and Gillies, 1992; Martinez-Zaguilan et al., 1993; Bianchi et al., 1998]. In human breast cancer cells, K^+ current controls progression through the cell cycle [Klimatcheva and Wonderlin, 1999]; activation of an ATP-sensitive potassium channel is required for breast cancer cells to undergo the G_1/G_0-S transition [Strobl et al., 1995]. Finally, certain channelopathies result in syndromes associated with cancer such as the lung cancer seen in Lambert-Eaton syndrome [Takamori, 1999].

Another recent study showed that ability to respond to galvanotactic cues correlates with metastatic propensity in cell culture, and this process is likely to be mediated by voltage-gated Na^+ channel activity [Djamgoz et al., 2001]. H^+ pumps called V-ATPases determine the membrane voltage potential and pH in many cell types; because these factors are crucial in controlling protein trafficking, proliferation, and differentiation of cells in development, the V-ATPase is

TABLE 5. Bioelectromagnetic Fields and Cancer

Type of phenomenon	Specifics	Reference
EM characteristics of cancerous cells and tissues differ from those of normal tissue	Appearance of tumors alters electric field of host organism	Burr et al., 1938a, 1940a; Burr, 1941b, 1952; Langman and Burr, 1949
	Differences in DC electric fields of tissue itself	Burr and Lane, 1935; Burr, 1952; Marino et al., 1994b
	Differences in ultraweak photon emission	Pyatenko and Tarusov, 1964; Scholz et al., 1988; Grasso et al., 1992; van Wijk and van Aken, 1992
	Difference in magnetic field susceptibility	Senftle and Thorpe, 1961; Kim, 1976
	Cancer cells are electrically isolated, whereas normal cells are in electrical communication via gap junctions	Loewenstein and Kanno, 1966; Jamakosmanovic and Loewenstein, 1969; Hotz-Wagenblatt and Shalloway, 1993; Yamasaki et al., 1995; Omori et al., 2001
Application of EM fields can affect tumor growth and progression	Applied fields can selectively cause death of tumor tissue	Humphrey and Seal, 1959; Kim, 1976; Sheppard and Eisenbud, 1977; Schauble et al., 1977
	Applied fields can increase growth of tumor tissue	Phillips, 1987; Mevissen et al., 1993
EM fields can cause interconversion between normal tissue and cancerous tissue	Magnetic fields can cause neoplastic behavior in chick cells	Jacobson, 1988; Parola et al., 1988
	Magnetic fields affect oncogene expression	Ryaby et al., 1986; Hiraoka et al., 1992
	Electric fields can cause differentiation and de-differentiation, which is key to cancer progression	Becker and Murray, 1967b; Cone and Tongier, 1971; Harrington and Becker, 1973; Chiabrera et al., 1979

emerging as a key factor in the regulation of embryonic morphogenesis and physiology [Ives and Rector, 1984; Martinez-Zaguilan and Gillies, 1992; Martinez-Zaguilan et al., 1993; Jones and Ribera, 1994; Sater et al., 1994; Arcangeli et al., 1996; Shrode et al., 1997; Bianchi et al., 1998; Uzman et al., 1998].

Gap junctions are an important aspect of bioelectrical controls of tumor growth because they provide direct cytoplasmic contact between neighboring cells and thus enable isopotential syncitia of cells. Gap junctional communication (GJC) allows electric events occurring in one cell to be immediately transferred to its neighbors, bypassing second messenger pathways or receptor/ligand interactions; gap junctions are known to be crucial components in the signal exchange which underlies embryonic patterning and many physiological events [Lo, 1996; Levin, 2001]. Gap junction genes are recognized tumor suppressors [Mesnil et al., 1995; Yamasaki et al., 1995, 1999; Omori et al., 2001]. These data form a powerful complement of molecular genetic studies to older work showing that membrane voltage potential is a key factor in determining cell division rates [Cone, 1969, 1970, 1971, 1974b, 1980]. Effects on gap junctional communication also provide an appealing model for explaining tumor growth induced by exposure to weak magnetic fields. ELF exposure generally does not transmit nearly enough energy to cause mutagenesis of DNA, but has been shown to affect gap junction states and thus potentially to control proliferation and differentiation [Schimmelpfeng et al., 1995; Ubeda et al., 1995; Li et al., 1999; Griffin et al., 2000a,b; Hu et al., 2001; Yamaguchi et al., 2002].

MITOGENETIC RADIATION

Living cells and tissues emit a wide range of ultraweak photons in the ultraviolet and infrared ranges, as well as ELF and high frequency EM waves; these fields are correlated with developmental events (see Table 6), and several studies indicate that signals can be passed between living systems in the absence of chemical communication. Traditional experiments involved optically coupled, but chemically isolated, cultures of bacteria or yeast. Gurwitsch was one of the first to study mitogenetic radiation [Gurwitsch, 1988], which is related to many facets of cell cycle control and cellular metabolism. Mei [in Ho et al., 1994, p. 269] reviews the history of biophoton research [also see Tsong, 1989; Popp et al., 1992].

The emphasis in this work is on coherence among the photon field emitted by cells, the ability of such a field to carry information over biologically relevant distances, and the possible causal roles of this radiation in the maintenance of the biosystem. Popp and Nagl [1983a,b, 1988] present a detailed model of differentiation based on DNA's interaction with biophotons: the existence of a feedback loop between the conformation of DNA and the biophoton field of a cell. They suggest that the competition of DNA molecules for photons results in changes of statistical properties of the cell photon field and that this participation depends on a conformation of base pairs. Chwirot [1986, 1988] presents data which supports this model of the proposed role of mitogenetic radiation in vivo as the carrier of intercellular information.

MECHANISMS

While it is impossible to do full justice here to the many possible models for bioelectromagnetic mechanisms, a few directions [see Wood, 1993; Engstrom and Fitzsimmons, 1999] should be noted since they are valuable starting points for interpreting known effects and formulating future studies. At the level of the

TABLE 6. Mitogenetic Radiation and EM Wave Emission From Living Systems

Type of phenomenon	Specifics	Reference
Cells emit ultraweak photons (ultraviolet range), which carry information	Cells and organisms emit a wide range of ultraweak photons	Colli et al., 1955; Popp, 1979; van Wijk and Schamhart, 1988
	Radiation correlates with cell cycle stage	Quickenden and Hee, 1974; Quickenden and Hee, 1976; Chwirot and Popp, 1991, 1995; Grasso et al., 1991
	Radiation correlates with cell division rates and morphogenetic events	Perelygin and Tarusov, 1966; Chwirot, 1986; Chwirot and Dygdala, 1986, 1991; Bajpai et al., 1991
	Radiation can induce changes in chemically-isolated systems	Galle et al., 1991, Galle, 1992; Schauf et al., 1992
Cells emit specific ELF EM waves	Waves correlate with growth events	Pohl and Hawk, 1966; Pohl, 1981, 1984
Cells emit millimeter EM waves	Models based on long-range coherence via these fields have been proposed	Pohl, 1980; Cooper, 1981; Fröhlich and Kremer, 1983; Fröhlich, 1988
Cells also communicate in the infra-read (IR) range	Cells emit IR pulses	Albrecht-Buehler, 1992b
	Cells detect IR (probably through centrioles)	Albrecht-Buehler, 1979, 1981, 1990, 1992a, 1994
	Cells use IR signals for migration cues	Albrecht-Buehler, 1991

biophysics of electromagnetic field interactions with molecular systems, electric fields exert forces on ions, while magnetic fields exert forces on magnetic particles and on moving ions.

Barnes [1992] presents an overview of mechanisms, along with possible theories as to how fields whose energies are very weak relative to ambient thermal energy can be detected by biosystems. In general, EM fields can affect biochemical reactions and the behavior of charged molecules near membranes. Both mechanisms can be readily visualized as having direct effects on cell behavior. Magnetic fields can exert influence in one of several ways: generate electric fields in conductors; exert force on moving charge carriers; exert torque on permanent magnetic dipoles and nonspherical para- or diamagnetic particles; exert force on permanent magnetic dipoles or para and diamagnetic particles, though only in inhomogeneous fields; change rate of diffusion across membranes; distort bond angles, which affects protein binding and macromolecule synthesis; and change rates of quantum proton tunneling between nucleotide bases in DNA [Barnothy, 1969]. Ultraweak photons have been suggested to affect subtle structure of molecules such as DNA, and infrared radiation can plausibly be detected by centrioles. The sensing of extracellular electric fields by voltage sensitive ion channels in membranes is well established.

CONCLUSION

Development of the vibrating (self-referencing) probe allowed the mapping of extracellular ion fluxes in real time in living organisms [Jaffe, 1981]. Prior to these advances, Burr et al. formulated the field concept in terms of standing voltage potential differences [Burr and Northrop, 1937, 1939] and explicitly proposed that a complex pattern of DC electric fields present within living organisms is a key factor in morphogenesis and contains part of the information needed to produce a three dimensional organism. ''The fundamental basis of this theory is that the pattern of organization of any biological system is established by a complex electro-dynamical field which is in part determined by its atomic physico-chemical components and which in part determines the behavior and orientation of those components. This field is electrical in the physical sense'' [Northrop and Burr, 1937; Burr, 1944].

While the evidence for the importance of bioelectromagnetic fields in various disparate aspects of morphogenesis is strong, much future research into this area will be necessary before it becomes clear to what extent such a global view of biological EM information is valid. At this stage, it is important to concentrate on mapping the fields as individual currents or contour maps of potential differences and investigating externally applied field effects on cells and tissues, as necessary components to the elucidation of the mechanistic roles of electrical events in specific patterning events. Eventually, it may be possible to formulate models of development which take advantage of real field properties of bioelectromagnetic phenomena, in addition to purely local interactions mediated by ion fluxes [see for example, Cohen and Morrill, 1969a,b]. A number of embryonic contexts could benefit from such directions, including for example, the context of regenerating limbs [French et al., 1966], which clearly displays field properties without a known material basis. Larter and Ortoleva [1981] present a detailed mathematical model of natural electric fields functioning as patterning mechanisms in early development; this excellent paper also discusses information storage, symmetry conservation and breaking, and nonlinear stochastic mechanisms as they apply to an electrically controlled self-organizing system.

It is necessary to determine to what extent it is profitable to understand EM field interactions with organisms as information, rather than mechanical influence. A related issue is the possible interaction between the level of complexity of a given biosystem and the degree of involvement of bioelectromagnetic phenomena. This is hinted at, for example, by the observation that to achieve the same effects, greater magnetic fields must be used on individual cells and tissues than on the whole organism [Barnothy, 1964]. In its simplest form, this suggests an amplification effect which manifests itself as a systems property and appears with increasing organizational complexity [Adey, 1980]. ''It has been found that entire organisms are most sensitive to EMFs, isolated organs and cells less, and solutions of macromolecules are even less sensitive . . . . The appearance of enhanced sensitivity to EMFs only in fairly complexly organized biological systems can be regarded as one of the manifestations of the specific nature of life—its organization'' [Presman, 1970]. Other hints for an informational role for endogenous EM fields, rather than separate mechanical influences, come from studies such as those summarized in Table 7.

''Informational interactions play a significant (if not the main) role in these processes. Such interactions entail the transmission, coding, and storage of information.The biological effects due to these interactions do not depend on the amount of energy introduced into the system, but on the amount of information introduced into it. The information-carrying signal merely causes the redistribution of the energy in the system itself, and regulates the processes occurring in it.

TABLE 7. Bioelectromagnetic Fields as Information

Type of phenomenon	Specifics	Reference
Amplification of small signals	Trigger effects, filtering and amplification in light of ambient thermal noise in the cell	Fröhlich, 1977; Colacicco and Pilla, 1984; Litovitz et al., 1992, 1994; Mullins et al., 1992
Only very specific field parameters are effective in some systems	Specific pulse waveforms needed; nonlinear effects—bigger signals do not produce bigger effects (windows in power or frequency)	Wilson et al., 1974; Christel et al., 1979; Christel and Pilla, 1981; Klueber, 1981; Aarholt et al., 1982; Rein and Pilla, 1985; Juutilainen and Saali, 1986; Thomas et al., 1986
AC electric field effects	AC fields produce no net transfer of chemical messengers	Rehm, 1939; Marsh and Beams, 1957; Sheppard and Eisenbud, 1977
Effects persist after EM field has gone	Systems have a memory for field exposure	Rosene, 1937; Kholodov, 1973
Fields used for communication between organisms	Numerous examples, not including visible light signals and electric fish.	Presman, 1970; Becker, 1979; König, 1979; Tsong and Gross [in Ho et al., 1994, p. 131]

If the sensitivity of the receiving system is high, little energy is required for the information transfer. The information can be built up by the repetition of weak signals'' [Presman, 1970, p. 5–6].

Much progress can be made in the near future by using modern cell biology techniques and screening of genetically tractable organisms such as zebrafish, which would also be amenable to rapid fluorescent analysis of ion and voltage events, to identify novel processes dependent on electrogenic genes. Genetic manipulation using wild type and dominant negative constructs for ion channel and pump proteins, specific pharmacological ion pump blockers [Levin et al., 2002], pH- and voltage-sensitive fluorescent dye technology [Loew, 1992], self-referencing, ion selective extracellular probes [Smith et al., 1999], and high resolution SQUID probes [Thomas et al., 1993] are just some of the approaches which will be used to characterize, in molecular detail, the contribution of EM signals to individual morphogenetic contexts.

Such work can then be augmented by theoretical and modeling approaches seeking to understand informational aspects of endogenous electric and magnetic fields and possible applicability of true field properties to patterning events. In particular, it is crucial to identify downstream targets, which sense pH and voltage gradients and transduce them to gene expression and other cellular events. The information and insights gained will be crucial in elucidating the nature and origin of high level morphogenetic control in growth and development of biosystems, and will have enormous implications for human medicine as well as basic understanding of biology.

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