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A THEORETICAL APPROACH TO PERTURBATION OF BIOLOGICAL SYSTEMS BY ELECTRICAL CURRENTS

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ABSTRACT

In view of the current controversy whether external electrical currents are beneficial or detrimental to biological systems, a hypothesis is proposed attempting to reconcile the opposite viewpoints. Using the concept of minimum entropy production for systems far from thermodynamic equilibrium, it can be shown that a healthy (normal) biological system residing in its homeostatic (i.e., stable-steady) state is not affected by currents of physiologically acceptable magnitudes. If the system resides in stressed (unstable-steady) state, small perturbations may produce large changes in the state of the system. The changes caused by external electrical currents might be beneficial as well as detrimental, according to the proposed hypothesis. However, at the present state of knowledge, beneficial effects are supported by a solid body of experiments at the laboratory and clinical levels, whereas detrimental effects are hitherto suggested only by epidemiological studies.

INTRODUCTION

At the beginnings of bioelectricity—more than 200 years ago—high hopes were put on the beneficial effects of electrical currents for the well-being of mankind (1). Already at the time of the Galvani-Volta controversy, it was suggested that electrical currents might bring dead people to life, since leg movements could be elicited in a

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dead frog after application of electrical currents to the appropriate nerve (2). At the end of the nineteenth century, electrotherapy was a quite respectable therapeutic modality and "every good American physician" applied some electrical treatments to his patients (3). In this century the popularity of electrotherapy has oscillated between miracle cures and quackery. With the fast progress of the pharmaceutical industry, electrical treatment lost its appeal and became confined to departments of physical medicine and rehabilitation. In the seventies, the first suspicions regarding possible detrimental effects of electromagnetic fields were raised with growing awareness of pollution by different environmental agents (4).

Since then it has seemed that scientists conducting epidemiological investigations in an attempt to prove health risk effects of electromagnetic fields have not been aware of another set of researchers who have studied various applications of electrical currents in medicine and rehabilitation. Both directions of research are consuming substantial amounts of funding and investigation resources with apparently diametrically opposite goals: in the biomedical engineering community, most investigations attempt to prove the beneficial effects of electrical currents for biological systems, whereas the research of the environmental protection and power engineering community aims to detect possible harmful effects of exposure to electromagnetic fields. In view of this controversial situation, we attempt to propose a unifying outlook at this disturbing problem, which has doubtless huge medical and socioeconomic implications.

In the next sections we shall present short reviews of beneficial and possible harmful effects of electrical currents and finally propose a general model, with intention to reconcile data on opposite effects of electrical currents. In short, the aim of this paper is to discuss possible answers to the question: Are electrical currents applied to humans a panacea, placebo, or poison?

BENEFICIAL EFFECTS

The number of useful applications of electrical currents or electromagnetic fields in humans and other biological systems is enormous. In the following survey we shall comment on some of the best-known examples, i.e., functional electrical stimulation, bone healing, nerve regeneration, wound healing, cancer treatment, and pain relief.

Functional electrical stimulation excites malfunctioning nerve or muscle systems and provides them with proper signals, thus restoring function. The best-known examples are the cardiac pacemaker, cochlear implants for improved hearing, functional electrical stimulation for extremities to restore function of paralyzed extremities, and pacing of the phrenic nerve to enable breathing (5,6). These systems are worn by the patients for years, and we are not aware of any reports regarding adverse effects that might be ascribed to functional electrical stimulation. This modality has also been applied for therapeutic purposes to alleviate neuromuscular disorders such as spasticity (7) and cerebral palsy (8).

Quite different techniques are used in applying electrical currents to nonhealing fractures and other bone diseases (9,10). They all seem to accelerate the healing process to various degrees, but it is important to note the comment by McLeod *et al.* (11), who observed that "no reports have surfaced indicating any measurable growth of 'normal' cells near the site of the nonunion, even though these normal cells are exposed for the same time and to the same fields as the bone." There are also some encouraging reports regarding accelerated regeneration of crushed peripheral nerves in animals, but no reliable clinical data are available as yet (12,13).

Various currents and fields have been successfully applied to chronic wounds (decubitus ulcers, wounds due to vascular diseases) either directly to the site of the wound or to the spinal cord or acupuncture points (14). Since healing requires the formation of new cells and tissue, it is important to note that their production always stops when the wound is healed.

While extensive clinical data in cancer treatment are still lacking, there is enough experimental evidence to justify the statement that electrical currents might reduce or even cure tumors (15,16). Compared with wound healing, almost the same currents produced cell growth and proliferation in wounds whereas tumor cells stopped proliferating and eventually died (17). Even if the current also traversed neighboring, nontumor cells, only tumor cells were affected (18).

After the "gate theory" was proposed, and when it was found that electrical stimulation might trigger the production of endogenous endorphins, electrical pain suppression became widespread (19). This technique is generally known by the term transcutaneous electrical nerve stimulation (TENS). Electrodes are applied over the painful area or to some acupuncture points or to the spinal cord (20,21). Reports about success rates are mixed, but there is no doubt that electrical pain suppression is the most popular application of electrical currents in humans.

All these studies are well documented and offer ample evidence that electrical currents may be used as an efficient treatment modality with no known side effects when applied within physiological limits.

HARMFUL EFFECTS

The literature on harmful effects of electromagnetic fields is much less precise and less well documented than reports regarding the beneficial effects (22). In 1987, the IEEE Engineering in Medicine and Biology Society devoted a whole issue of its journal to problems of electromagnetic radiation (23). The Department of Energy as well as the Environmental Protection Agency are sponsoring numerous workshops and conferences, and rather detailed safety standards are appearing, which should contribute to better protection of the population. Several international organizations are concerned with safety from electromagnetic pollution, notably the International Radiation Protection Association (IRPA) and its International Non-Ionising Radiation Committee (INIRC) (24). Recently the Commission of the European Communities issued its report for basic restrictions for protection against exposure to electromagnetic nonionizing radiation (25). Very detailed limits for fields, current densities, and power are proposed, but there is no physiological experimental evidence that such restrictions are justified.

Since most of the positive results regarding risky exposure to electromagnetic fields is epidemiological, we shall cite only Jauchem and Merritt (26), who published an overview of the recent literature quoting 118 references. After analyzing the evidence, they state:

> Possible links to incidence of cancer and abnormal fetal development have been suggested by some investigators. In general, the results have been inconsistent. There are many deficiencies in the studies, and many questions have been raised about the validity of some of the conclusions proposed. There is currently no definitive evidence of an association between exposure to electromagnetic fields and the alleged risks. Due to problems and limitations inherent in future studies (misconceptions about exposure levels, uncertainty about field variability, criticism of surrogate measures, uncontrolled carcinogens), this question is unlikely ever to be answered with certainty. Unfortunately, many highly publicised accounts of speculative and unsubstantiated claims have caused undue concern among the general public.

At the moment there are still no adequate results obtained on animal models.

Thus, there is solid evidence that electrical (and/or electromagnetic) fields and currents can be beneficial; there might be cases when there is no effect, and the evidence for harmful effects is rather scanty and still unreliable. However, we have to accept the possibility that weak electromagnetic fields might be detrimental to human health (27,28). Therefore, it is essential to explore this problem carefully, with equal attention all three possibilities.

With these facts in mind we shall propose a phenomenological model that might contribute to an improved understanding of the intricate actions of electrical currents on biological systems.

GENERAL MODEL

Due to Darwinian evolution, biological systems, including humans, are quite stable in the sense that small external perturbations do not affect their essential functions. A normal biological system is an open system in a steady, homeostatic state, thermodynamically far from equilibrium. Such a system can compensate for various environmental perturbations and override them with its feedback control mechanisms. External electrical fields may be considered as such a perturbation. The ability of a cell or a larger system to compensate for such electrical perturbations was called by Findl "electrical homeostasis" (29).

The same ideas have been recently proposed also by McLeod *et al.* (30). They suggest that "the fact that a biological system is alive and functioning implies that it contains sufficient 'feedback' or 'protection' mechanisms to prevent most weak exogenous environmental signals (such as electric fields) from causing significant changes in biological behaviour."

These observations are quite in accordance with our general experience that moderate electrical currents have essentially no effect on a normal biological system that is in a state of electrical homeostasis.

However, the situation may change dramatically if the system is not in its homeostatic state. Findl notes: "A prime factor that is slowly being recognised is that low level fields are most effective in modifying cellular activity when the target cells are under some genetic or chemical stress" (29). Also, other investigators have observed that "extremely low frequency electromagnetic field interactions with biological systems occur or are maximised only when the biosystem is in a state of nonequilibrium" (31). We may thus hypothesize that application of electric fields to a "stressed" system may have a much stronger effect on it than on a system in homeostasis. In principle, the effect could be beneficial, pulling the system back to homeostasis, or harmful, pushing it to another pathological state (e.g., patients with multiple allergy reactions or autonomic dysreflexia may have extreme sensitivity to electric fields) (32).

For easier visualization of the situation it would be convenient to develop a simple model that would have some physicochemical relevance to a self-organized biological system.

Several concepts have been advanced to analyze biological self-organization. Despite differences in verbal description, the mathematical foundation lies in two or more coupled nonlinear differential equations or partial differential equations. Typical examples are the Brusselator of Prigogine, Eigen's models for competition and evolution, and Haken's principles of synergetics (33,34).

In general, all the mathematical analyses become quite complex and are difficult to visualize. An approach that enables a simplified two- or three-dimensional visualization is the so-called energy or potential profile. The state of the system is represented by a massless particle that moves as a function of a state variable along the energy landscape. Examples of such visualization are the laser and symmetry braking (34). Energy landscapes are also used in visualizing local minima of computational energy in neural networks (35).

All these approaches use the concept of potential or energy hills and wells in mostly mathematical terms without a physical background. Such a physical background, however, is given by nonequilibrium thermodynamics, which offers a theoretical basis for the existence of life (36). We believe, therefore, that such an approach is the most appropriate for our hypothesis and will continue the discussion in terms of thermodynamics.

Despite criticism regarding the usefulness of nonlinear thermodynamics far from thermodynamic equilibrium, it seems the only tool that might give our model some physical meaning. Being fully aware of the "slippery notion of entropy, reasonably well defined for thermodynamic purposes in terms of heat and temperature, but devilishly hard to pin down as a measure of order" (37), we still decided to use the concept of entropy production for our model.

In agreement with our former deliberations, we assume a normal healthy biological system as an open thermodynamic system in a steady state far from equilibrium. Such a system is continuously exposed to generalized forces X_i, such as gradients in electrical potentials, temperature gradients, chemical affinity, and concentration gradients. These forces produce generalized fluxes J_i, i.e., electrical currents, heat flow, reaction rates, and mass flow.

It can be shown that a system's total entropy production is:

$$P = \frac{dS}{dt} \int (\Sigma X_i J_i)\, dV \tag{1}$$

where

$$\sigma = \Sigma X_i J_i \tag{2}$$

is the local entropy production and S is the total entropy of the system.

Prigogine (38) proved that a system close to thermodynamic equilibrium, when Onsager's principle is still valid, has a minimal entropy production. After any small perturbation from this state the system will return to its steady state (Fig. 1).

A living system cannot be approximated by a system close to equilibrium since organisms typically have a high rate of exchange in matter and energy and are generally considered as being in steady state far from equilibrium. These steady states, characterized by minimum entropy production, are stable in general (36).

Prigogine and co-workers explored also systems remote from equilibrium (40). They found three types of situations. First, the assumption of a local minimum of entropy production may prove to be invalid, since Onsager's relations are not realized. Second, a local minimum of entropy production (steady state) is preserved, but the system's properties change continuously with deviations from steady state. In this case, the theorem on minimum production of entropy in a steady state remains valid. Third, new types of organization of matter in space and time emerge. Since we are dealing with inherently dissipative systems, new structures and properties are determined by essential instabilities of thermodynamic states.

Let us now illustrate, in an extremely simplified way, a living system in a two-dimensional plane (Fig. 2). A normal, healthy biological system resides at its steady state with its state variable x_k at x_k^0 and a local minimum of entropy production σ_0. After small perturbations Δx_k the system returns to its reference state of self-organization. With increasing perturbations, ultimately a critical value x_k^c is reached. The system is at the state from which, after a minimal perturbation, it might be pushed either back to normal x_k^0 or to a new state with $\sigma = 0$, which is equivalent to death. The "strength" of self-organization may be illustrated with the slope of the σ-func-

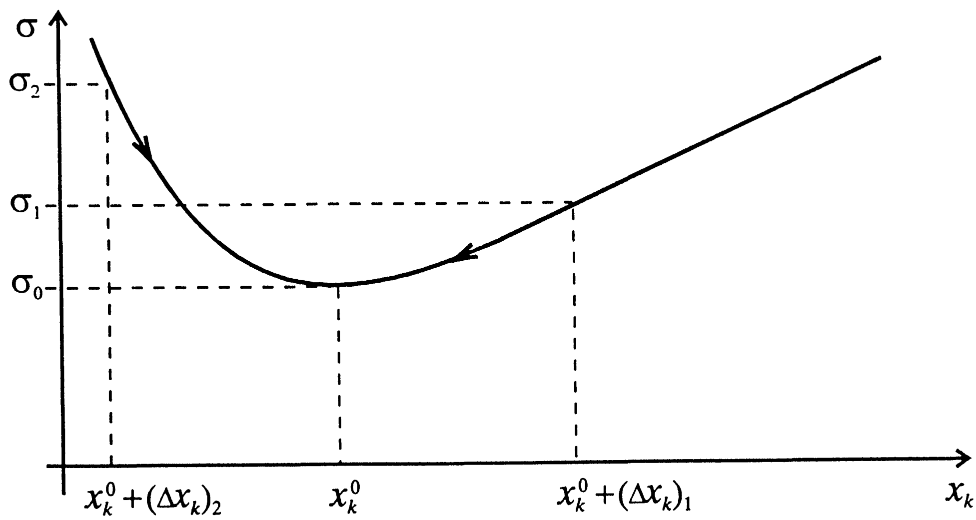

FIGURE 1. When Onsager's principle is still valid, a system close to thermodynamic equilibrium resides in a steady state x_k^0, which is characterized by minimal entropy production σ_0. After any small perturbation this system will return to its former, i.e., reference, state x_k^0. (Redrawn from Ref. 39.)

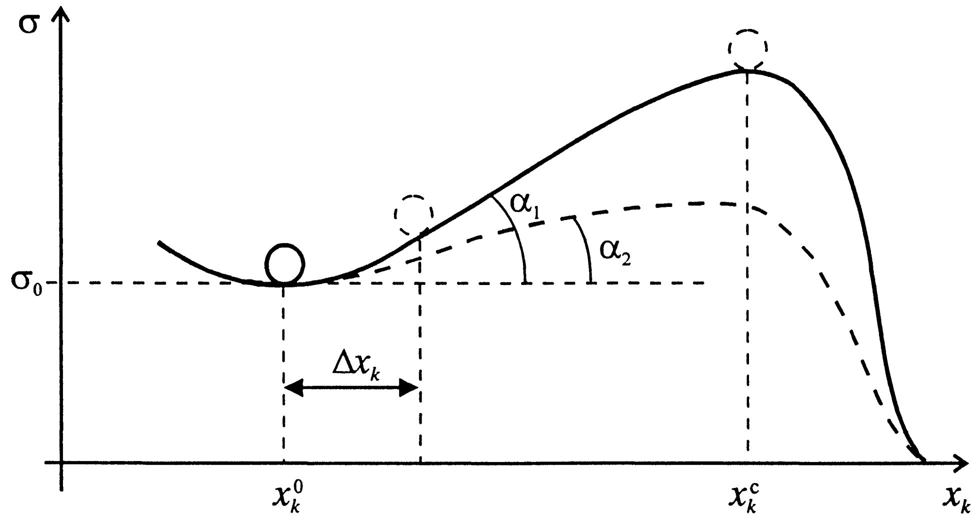

FIGURE 2. A living system is illustrated in two-dimensional plane in its steady state x_k^0. For small perturbations Δx_k the system returns to its reference state. However, increasing perturbations would drive the system ultimately toward the critical state x_k^c, i.e., the last point of return. From the unstable state x_k^c a minimal external perturbation pushes the system toward its reference state or toward death ($\sigma = 0$). The strength of the system's self-organization is associated with angle α, i.e., the slope of the $\sigma(x_k)$ curve; more robust systems have α_1.

tion. A "robust" system would thus be represented by a large α_1, while a "weak" or "sensitive" system would display small values of α, such as $\alpha_2 < \alpha_1$. Smaller perturbations are required to reach x_k^c in a sensitive system compared to a robust one. We suggest, therefore, that the magnitude of the perturbation that transfers the system to x_k^c could be a measure of the self-organizing (homeostatic) strength of the system.

A biological system does not possess only two steady states: x_k^0 and death. A chronic disease might be a steady state, but with higher entropy production. In fact, throughout life we experience many steady states, and we usually attempt to return the system to the reference state by taking drugs, undergoing surgery or psychotherapy, or applying physical medicine. Let us continue by concentrating on one of the best-known methods of physical medicine—electrotherapy.

We are rather ignorant regarding the detailed mechanisms of action of the various electrotherapeutic approaches. Let us therefore assume that electrical currents act on the living system as a general external perturbation. If the system is in its stable steady state of minimum entropy production, external electrical perturbations will not affect it permanently, since the system will return to its former (i.e., reference) state. This is in agreement with experiences with various electrotherapeutical modalities—usually they do not affect a normal, healthy system (11,18,29). It should be mentioned, however, that excessive perturbations can always cause damage and ultimately death. In the case of electrotherapy, the extreme perturbation would lead to death through electrocution.

Assume now a system being at another steady, but now pathological, state x_k^p (Fig. 3) with entropy production $\sigma_p > \sigma_o$. If an electrical perturbation of adequate magnitude is applied to such a system, the system may change its steady state from x_k^p to x_k^0—the normal healthy state, in order to reside at lower entropy production. This is the most general, and obviously the most nonspecific, explanation of all electrotherapeutic treatments. We have already mentioned that large perturbations can lead to damage and death. What about small perturbations? How small can they be in order still to be effective? In accordance with our model, we conjecture that the effective stimulus can be in principle arbitrarily small. Its effectiveness depends on the shape of the $\sigma(x_k)$ curve. If the system is in a very weak—unstable—pathological state, an extremely small perturbation may bring the system back to its reference normal state. This might explain why some patients experience therapeutic effects from stimulators that produce quite small field strengths. Thus, it follows from this model that a search for optimal stimulation parameters is going to be quite difficult, since we may safely assume that the shapes of the $\sigma(x_k)$ curves vary individually, and each patient might require his or her own optimum. However, it seems quite plausible that the shapes of the curves for a given illness might be rather similar for a large part of a given patient population. Only in this sense it is useful to seek optimal parameters for a specific illness.

Finally, let us discuss the possible harmful effects of electromagnetic fields. The steady states far from equilibrium are not necessarily stable, which means that in a given state, if the system is perturbed, it will not just adapt to the new constraints by slightly changing all its thermodynamic parameters. On the contrary, the fluctuations open new possibilities for energy dissipation states, which in turn may drive the system into other steady states at least some of which must show stability (33). We

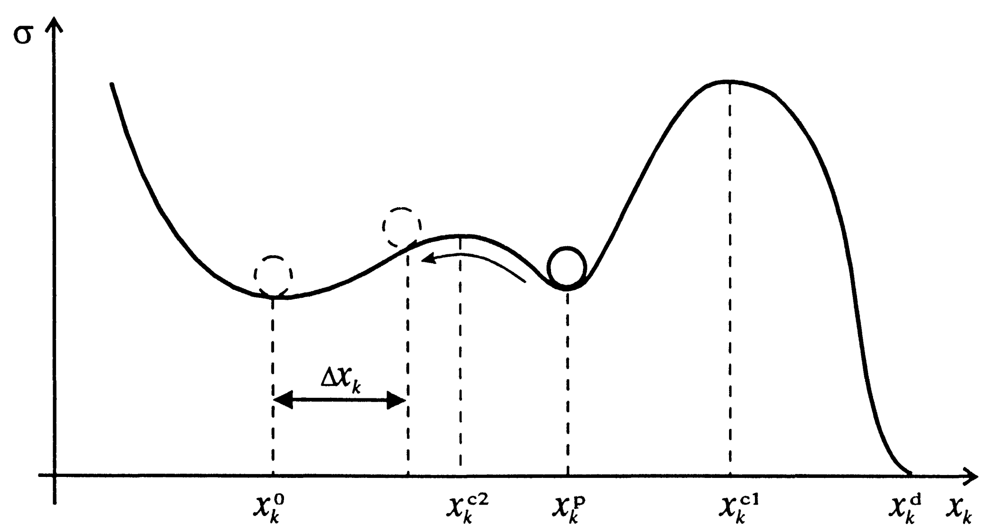

FIGURE 3. A chronic disease might be represented by steady state x_k^p indicating that the external perturbation of adequate magnitude may drive the system into its reference state x_k^0 (healthy state) with lower entropy production.

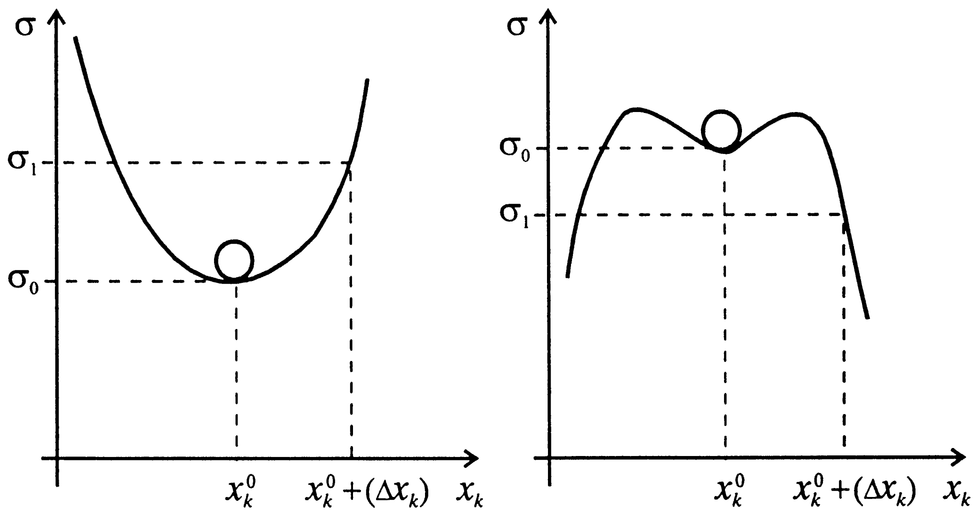

FIGURE 4. Steady states far from equilibrium are generally stable (left). However, some of them may be unstable (right). The former represents the globally stable homeostatic state of biological systems in which most of the population resides. These systems are not affected by external perturbations Δx_k of physiological magnitudes since once perturbation is removed, the system returns to its reference state x_k^0. The steady state of the system represented on the right is in locally stable homeostatic state. From this state x_k^0 the system is irreversibly driven by the perturbation Δx_k of the same magnitude to another steady state that may be pathological. (Redrawn and adapted from Ref. 41.)

would therefore like to introduce the terms "globally stable homeostatic state" for stable steady states and "locally stable homeostatic state" for unstable steady states, as illustrated in Figure 4. It should be noted that healthy subjects may exist in either or both steady states, the former being more common. However, a part of the population—presumably a smaller one—may reside in the locally stable homeostatic state, being therefore more susceptible to external forces, in our case to electric fields. Several epidemiological studies suggest that electromagnetic fields from power lines, antennas, and other electrical equipment might affect the health of people exposed to these fields. Such persons may be originally in an unstable steady state. Any small perturbation might take them to another steady state that might be pathological (32).

DISCUSSION

The proposed simple model posits the following conclusions:

A normal living system, being in stable steady state, does not change its state when exposed to electrical perturbations of reasonable magnitudes.

The same perturbations may move a system from a pathological state to normal, i.e., from the changed to its reference state.

Very sensitive normal living systems in unstable steady states may be affected by weak perturbations and shifted to pathological states.

However, several problems that are not incorporated in the model remain open for further investigation. One of them is the time factor. Does long-term exposure to electrical perturbations have different effects on the system than short applications? Are we to expect a cumulative effect? Thinking of pacemakers, one would tend toward a negative answer. On the other hand, long-term applications of electrical energy may not only act as minor perturbations on a given shape for $\sigma(x_k)$, but may actually affect the overall shape itself. Namely, assume that electricity affects the immune system. The strength of this system is definitely one of the self-organizing factors, and changes in the immune system would be reflected in changes of the $\sigma(x_k)$.

Obviously this model offers no specific solutions or mechanisms. But this is true for any model based on thermodynamics. The strength and weakness of thermodynamics is just this generality. Thermodynamics cannot explain life or the origin of structure, but it can give proof that life is in principle possible. In this sense, we have attempted to show that electrical perturbations of biological systems can be useful, without effect, or harmful. The hypothesis thus attempts to reconcile the divergent claims of researchers regarding the effects of electricity on living systems. The basic mechanisms are obviously numerous, and it will take several years of hard confrontation with many problematic biochemical details before we understand what electricity does to living systems, how to apply optimal treatment regimens to patients, and how to avoid possible environmental risks.

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REFERENCES

1. Geddes, L. A.: The beginnings of electromedicine, IEEE Eng. Med. Biol. Mag. *3*, 8–22, 1984.
2. Geddes, C. A. and Hoff, H. E.: The discovery of bioelectricity and current electricity, IEEE Spectrum, 38–46, 1971.
3. McNeal, D. R.: 2000 years of electrical stimulation, in Functional Electrical Stimulation, F. T. Hambrecht and J. B. Reswick, eds., Marcel Dekker, New York, 3–35, 1977.
4. Wertheimer, N. and Leeper, E.: Electrical wiring configurations and childhood cancer, Am. J. Epidemiol. *109*, 273–284, 1979.
5. Kralj, A. R. and Bajd, T.: Functional Electrical Stimulation: Standing and Walking After Spinal Cord Injury, CRC, Boca Raton, FL, 1989.

6. Hambrecht, F. T. and Reswick, J. B.: Functional Electrical Stimulation, Marcel Dekker, New York, 1977.
7. Stefanovska, A., Reberšek, S., Bajd, T., and Vodovnik, L.: Effects of electrical stimulation on spasticity, CRC Crit. Rev. Phys. Rehabil. Med. *3*(1), 59–99, 1991.
8. Gračanin, F.: Functional electrical stimulation in control of motor output and movements, in Contemporary Clinical Neurophysiology, W. A. Cobb and H. van Duijn, eds., Electroenceph. Clin. Neurophysiol. (Suppl. 34), 357–368, 1978.
9. Bassett, C. A. L.: Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFS), CRC Crit. Rev. Biomed. Eng. *17*, 451–529, 1989.
10. Cané, V., Botti, P., Farneti, D., and Soana, S.: Electromagnetic stimulation of bone repair: a histomorphometric study, J. Orthop. Res. *9*, 908–917, 1991.
11. McLeod, B. R., Liboff, A. R., Smith, S. D., and Mohr, T. A.: Selecting a system to evaluate a model describing ELF/biological system interactions, Trans. BRAGS *11*, 3, 1991.
12. Ribarič, S., Stefanovska, A., Brzin, M., Kogovšek, M., and Krošelj, P.: Functional, biochemical and morphological changes during peripheral nerve regeneration, Mol. Chem. Neuropathol. *15*, 143–157, 1991.
13. Sisken, B.: Nerve and limb regeneration, IEEE Eng. Med. Biol. Mag. *2*, 32–39, 1983.
14. Vodovnik, L. and Karba, R.: Treatment of chronic wounds by means of electric and electromagnetic fields. Part 1. Literature review, Med. Biol. Eng. Comput. *30*, 257–266, 1992.
15. Watson, B. W.: The treatment of tumors with direct electric current, Med. Sci. Res. *19*, 103–105, 1991.
16. Miklavčič, D., Serša, G., Vodovnik, L., Bobanovič, F., Novakovič, S., Golouh, R., and Reberšek, S.: Local treatment of murine tumors by electrical direct current, Electro- and Magnetobiol. *11*, 109–125, 1992.
17. Vodovnik, L., Miklavčič, D., and Serša, G.: Modified cell proliferation due to electrical currents, Med. Biol. Eng. Comput. *30*, CE21–CE28, 1992.
18. Miklavčič, D., Serša, G., Bobanovič, F., Novakovič, S., and Reberšek, S.: Tumor growth retardation due to exogenous electrical current and/or field, Trans. BRAGS *11*, 50, 1991.
19. Melzack, R. P. and Wall, P. D.: Pain mechanisms: a new theory, Science *150*, 971–979, 1965.
20. Shealy, C. N., Mortimer, J. T., and Hagfors, N. R.: Dorsal column electroanalgesia, J. Neurosurg. *32*, 560–564, 1970.
21. Malizia, E., Andreucci, G., Paolucci, D., Crescenzi, F., Fabrri, A., and Fraioli, F.: Electroacupuncture and peripheral β-endorphin and ACTH levels, Lancet, *2*, 535–536, 1979.
22. Current status of research on power-frequency electric and magnetic fields and cancer, Electra *111*, 10–11, 1991.
23. Effects of EM radiation, IEEE Eng. Med. Biol. *6*, 15–57, 1987.
24. Interim guidelines on limits of exposure to 50/60 Hz electric and magnetic fields, Health Phys. *58*, 113–122, 1990.
25. Allen, S. G., Bernhardt, J. H., Driscoll, C. M. H., Grandolfo, M., Marintti, G. F., Matthes McKinlay, A. F., Steinmetz, M., Vecchia, P., and Willack, M.:

Proposals for basic restrictions for protection against occupational exposure to electromagnetic non-ionizing radiations: recommendations of an international working group set up under the auspices of the Commission of the European Communities. Phys. Med. *7*, 77-89, 1991.

26. Jauchem, J. R. and Merritt, J. H.: The epidemiology of exposure to electromagnetic fields: an overview of the recent literature, J. Clin. Epidemiol. *44*, 895-906, 1991.
27. Tynes, T., Andersen, A., and Langmark, F.: Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields, Am. J. Epidemiol. *136*, 81-88, 1992.
28. Stuchly, M. A., McLean, J. R. N., Burnett, R., Goddard, M., Lecuyer, D. W., and Mitchel, R. E. J.: Modification of tumor promotion in the mouse skin by exposure to an alternating magnetic field, Cancer Lett. *65*, 1-7, 1992.
29. Findl, E.: Membrane transduction of low energy level fields and the Ca^{++} hypothesis, in Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems, M. Blank and E. Findl, eds., Plenum Press, New York, 15-38, 1987.
30. McLeod, B. R., Smith, S. D., and Liboff, A. R.: Timing and biosystem changes: two important parameters in modeling ELF interactions with living systems, Trans. BRAGS *11*, 1, 1991.
31. McLeod, B. R., Liboff, A. R., and Smith, S. D.: The state of cell equilibrium: one key to cell/ELF interaction, in Electromagnetics in Biology and Medicine, C. T. Brighton and S. R. Polack, eds., San Francisco Press, San Francisco, 101-103, 1991.
32. Rea, W. J., Pan, Y., Fenyves, E. J., Sujisawa, I., Samadi, N., and Ross, G. H.: Electromagnetic field sensitivity, J. Bioelectricity *10*, 241-256, 1991.
33. Babloyantz, A.: Molecules, Dynamics and Life: An Introduction to Self-Organization of Matter, Wiley, New York, 1986.
34. Haken, H.: Synergetics—an approach to self-organization, in Self-Organizing Systems: The Emergence of Order, F. E. Yates, ed., Plenum Press, New York, 417-434, 1987.
35. Hopfield, J. J.: Neurons with graded response have collective computational properties like those of two-state neurons, Proc. Natl. Acad. Sci. USA *81*, 3088-3092, 1984.
36. von Bertalanffy, L.: The theory of open systems in physics and biology, Science *111*, 23-29, 1950.
37. Gleick, J.: Chaos, Penguin Press, New York, 308, 1987.
38. Prigogine, I.: Etude thermodynamique des phenomenes irreversibles, Durrod, paris, 1947.
39. Nicolis, G. and Prigogine, I.: Self-Organization in Nonequilibrium Systems, Wiley, New York, 1977.
40. Volkenstein, M. V.: General Biophysics, Vol. 1, Academic Press, New York, 1983.
41. Berlinski, D.: On System Analysis, MIT Press, Cambridge, MA, 101, 1976.