



Review Article

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# Why the Biomedical Research Paradigm Must Change if we are to Win the “War on Cancer”

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## Abstract

**Objectives:** The purpose of this article is to begin a dialogue concerning the consequences for research design and data interpretation of outdated assumptions underpinning current biomedical research.

**Methods:** Integrated analysis and review of the ways in which the exclusion of physics (quantum theory) and biophysics data (endogenous bioelectric signaling) in biomedicine have biased research design and data interpretation. Concrete consequences for clinical oncology research are used as illustrations.

**Results:** Accumulating data demonstrate that biomedicine is about 100 years out of date with respect to its understanding of physics. This has led to detrimental consequences for clinical oncology.

**Conclusions:** Evidence based medicine is only as good as the completeness and veracity of the data that support it. Widespread emphasis on particulate aspects of wave/particle duality to the exclusion of wave characteristics in biomedical research designs have seriously biased the data we collect and the interpretation of their clinical implications. It is time to integrate biophysics into mainstream oncology research.

**Keywords:** Biophysics, Cancer, Biomedicine

## Introduction

“There is no such thing as philosophy free science; only science whose philosophical baggage is taken on board without examination.” [1]

As a biomedical scientist and not a philosopher, my objective is to try to explain the data I observe. The motivation for this article is that the current scientific paradigm is proving more and more inadequate to the task. The biomedical/clinical research enterprise proceeds based on axiomatic assumptions concerning the nature of reality that are not openly discussed and unfortunately, not well supported by the data. The demonstrably inaccurate nature of some of these assumptions constitutes philosophical baggage that is hindering scientific progress in areas as diverse as research on cancer and consciousness. The purpose of this article is to begin a dialogue concerning these unrecognized biases so that they cease to be obstructive.

## Genetic Reductionism and Wave/Particle Duality

The first issue is a failure of the biomedical community to incorporate modern physics into its working hypotheses. The underlying assumption of current biomedical research is nowhere clearly stated but assumes that particulate matter is the ultimate source of all life, consciousness and chronic disease conditions. Much of this is based on a limited understanding of DNA, which is considered to be the source of life. Genes code for amino acids, which make up proteins, which are involved in all cellular processes in the body. One of the most prominent characteristics of genes is that they are passive. They contain a code that must first be read and initiated before it can be implemented. Like recipes in a cookbook, genes cannot read themselves and they cannot bake the chocolate cake. They resemble a computer program that is initiated and interpreted by the user. Gene expression occurs only



when a multitude of other factors in the cell have read, activated, transcribed and translated the code. Furthermore, many genes have multiple functions contributing to the robustness and adaptability that are necessary for maintaining health and were necessary for evolution to occur. The body must be robust enough not to collapse at the slightest challenge (e.g., bacterial infection) and adaptable enough to change with changing environmental conditions. The focus of epigenetics is to study mechanisms influencing variations in gene function. The function that a gene fulfills in any given context is partially determined by the microenvironment of the cell, which consists not only of other (regulatory) genes but also of a chemical 'soup' that results from many systemic inputs related to factors such as dietary nutrients, age, hormones, medications, environmental chemicals, co-morbidities, psychosocial stress, etc. These interactions between genes and their surrounding microenvironment are nonlinear and have been demonstrated to play an important role in carcinogenesis.

Environmental influences were also important in evolution. The nonlinear Cambrian explosion that resulted in a plethora of multi-celled organisms where previously only single celled organisms had existed was partially dependent upon a change in earth's atmospheric conditions that allowed the survival of aerobic organisms, where previously only anaerobic organisms could exist. The mitochondrial DNA present in human cells, which is different from the nuclear DNA, suggests what biologists have known for a long time, namely that horizontal transfer (e.g., through symbiosis) was a part of evolution and that DNA transmission is not limited to vertical transference from parent to offspring. It is now known that horizontal gene transfer is a not uncommon method of gene diversification in multiple microbial species [2]. As we shall see below, the theory of DNA as the sole cause of morphogenesis is incomplete. Particles such as genes and proteins are only one aspect of physiological development. The other and equally important aspect requires an understanding of quantum theory.

Quantum mechanics has taught us something essential about the nature of reality, namely that at a subatomic level, waves and particles are indivisible. Depending on when and how they are measured, an observation may register as a particle or a wave. This wave/particle duality is not a result of measurement error but is inherent in the fundamental essence of being at a quantum level. This fact is of central importance to our research questions and the way we design experiments. Determining genotype involves separating the two strands of the double helix to access and measure the sequence of base pairs. These sequencing methods and their offshoots are continually improving in speed and efficiency and have provided a great deal of very useful information concerning genetic risks and artificial synthesis of DNA.

However, this methodology highlights only one aspect of DNA, namely its particulate aspects. In so doing, it obscures another fundamental characteristic, which is that DNA also functions as an electrical conductor [3-6]. DNA is a highly charged molecule [7] but in order to see the 'wave' characteristics, i.e., the electrical conductance, the double helix must be left intact. We cannot see base pair sequence and conductance in the same experiment. They are mutually exclusive. The charge conduction pathway consists of wave functions that extend perpendicular to the base planes, overlapping with neighboring planes to form a  $\pi$  orbital system [8]. These wave/particle aspects of DNA illustrate another important aspect of quantum theory, namely that the observer is never separate from the observed phenomenon. In this case, the observer influences the results by the way s/he designs the experiment. The biomedical research community seems completely unaware that the way they set up their experiments determines which aspects of DNA they see--wave or particle. Most scientists are unaware that DNA even has any characteristics other than those of particulate matter. However, what we choose to measure and what we choose to leave out of our experiments determine the results [9].

DNA codes for amino acids that are the building blocks of proteins but the DNA in every cell is the same. Proteins are like the bricks that are used to build bodily organs and tissues but there is no actual evidence that DNA codes for the 'architectural plan'. Arms and legs have the same types of muscles and blood cells, but they differ from each other in form. This is where biophysics data have become increasingly important in understanding function. Accumulating experimental evidence from regenerative and developmental biology implicates an important role for endogenous bioelectric networks in non-genetic patterning information during development [10,11]. Specifically, this work has demonstrated the involvement of endogenous spatio-temporal patterns of resting potentials in somatic cells as having an instructive role in embryogenesis, craniofacial patterning, eye induction and head-tail polarity in amphibians [10-12].

Unfortunately, this data has not been incorporated into mainstream theoretical research in biomedicine. DNA is considered to be the source of life. However, it is present in ancient human remains of people who have been dead for thousands of years. The DNA is there but life is not. This suggests that its primary function may be programming the building blocks of proteins rather than giving life to the organism. In recent years, experiments have successfully reprogrammed bacteria using synthetic DNA, creating a different bacterial phenotype [13]. However, in order for the experiment to work, the synthetic DNA must be inserted into receptive cytoplasm, i.e. a cell that is living cell despite the fact that the DNA has already been removed [14]. The implications of this have not been discussed in mainstream biomedical research.

## **Integrating Biophysics into Biomedical Research: Endogenous Cellular Voltage Potentials and Networks**

The belief in particulate matter as the underlying cause of all physical and mental phenomena has led to the persistent disregard by mainstream biomedicine of data that demonstrate wave aspects of health and disease. This has become a particularly important issue with regard to cancer etiology and progression. Endogenous bioelectric signal processing exists in all somatic cells (not just neurons) [15]. It complements and interacts with biochemical regulatory pathways in physiological functioning. Accumulating data reveal that these bioelectric signaling mechanisms stem from multiple sources: the membrane surrounding the cell [16], the mitochondrial membrane [16] and microtubules within the cell [17].

In general, the cell membrane voltage potential of somatic cells arises from multiple types of embedded ion channels that serve as 'gates' that regulate exchanges between the cell and its surrounding environment. These ion channels function by creating and modulating a voltage gradient across the lipid membrane and interact with voltage potentials from other cells to form spatially distributed networks. These networks are of particular importance because they are systemic and impose constraints (inhibitory feedback loops) on what happens at the molecular level, forcing the system into a specific differentiated state [18]. Biophysical networks are also extremely important in cancer because what happens in malignancy is a transition from a differentiated to an undifferentiated state. Because the networks function systemically, they cannot be understood by confining investigations to molecular level genes and proteins, [18] which is currently the focus of oncology research. A review of these concepts [18] summarizes implications from physics and engineering that are applicable to biology and more specifically cancer. They note that what is needed is a shift away from investigating causes acting at a single site that instigate changes in a linear pathway, to examining the behavior of entire systems. This should accompany a shift from studying molecular events to studying discrete pattern states involving biophysical networks. Clinically this implies a shift from pharmacologic agents that briefly control a single target to treatments that put constraints on many parts of the organism and can be sustained over time.

### **Tumorigenesis**

The implications of this research, though highly relevant for the etiology and progression of cancer, are basically being met with ignorance by the oncology community. The origin of a tumor's ability to respond to drugs by bypassing targeted mechanisms is strongly based on the fact that tumors are not just aggregates of mutated cells but are "complex living entities of different cell types that work together to acquire nutrients, survive, and evade efforts ... trying to kill them." [19]. The surface potential of healthy cells is

more negative on the inside than the outside. However, this changes during the transition to tumor cells, when ion channels malfunction, causing depolarization in the cell membrane and a change in cell shape, structure, and function [20]. Cell shape, which is mainly influenced by biophysical constraints, is a critical determinant of cellular function, influencing proliferation, metabolism, and stem cell commitment [21]. Research from the Department of Regenerative Medicine at Tufts has demonstrated in salamanders that "any form of depolarization causes metastatic conversion, even without oncogenes, DNA damage, or cancer-causing chemicals" [19]," and likewise can be reversed without toxic chemotherapy by modulating resting potential appropriately in vivo [22]. In essence, depolarizing the cell membrane was sufficient to cause metastatic conversion without any genetic mutation, i.e., without particulate matter. Further research has demonstrated that network voltage potentials can instigate changes in chemical signaling pathways that are involved in the initiation of metastatic behavior [6]. Yet currently available therapeutic interventions target almost exclusively molecular biochemical mechanisms.

A well-known hallmark of cancer cells is disturbed energy metabolism in the mitochondria. Cancer cells proliferate quickly, requiring an increased amount of energy [23]. In the process, their energy production transitions from aerobic metabolism to being more anaerobic, i.e., metabolizing a large percentage of glucose directly to lactic acid even in the presence of oxygen [24]. In conjunction with this, the mitochondrial membrane surface potential changes to a predominantly negative charge. Although we know relatively little about how the bioelectric signals from the cell membrane, mitochondrial membrane and microtubules interact with each other [8], mitochondria have been found to 'co-localize' with microtubules, providing tracks for mitochondrial movement [25].

Most biological scientists are unaware that somatic cells even have a membrane voltage potential, let alone that it plays an important role in physiological functioning. The 'cultural' tradition of designing experiments to investigate matter ('particles' such as genes and proteins) results in experiments that are not set up to measure waves [8], and thus preclude the ability to observe bioelectric or quantum wave phenomena. This focus on molecular targets leaves a large gap in the data available for interpretation of mechanisms. Materialist hypotheses of causality thus become self-perpetuating. Biased study designs lead to inaccurate conclusions that lead to more biased study designs. Evidence based medicine is only as good as the data that support it. If an important number of data points (evidence) are missing, the interpretation of the evidence will be biased.

### **Implications of Biophysics for Systems Level Patterning**

The current focus of anti-cancer therapeutics is molecular

targets. However, as discussed above, tumors are complex dynamic organisms that are capable of responding to drugs by circumventing them with new survival strategies. However, the number of anti-cancer defense systems in the body (e.g., DNA repair, immune, autophagy, apoptosis) that must malfunction in early stages in order for mutations to survive, means that mutations are only one aspect of cancer etiology. Host susceptibility is another. It has been estimated that the number of single-stranded breaks in DNA may be as high as 104-105 *per cell per day* [26,27], meaning that if these mutations were not repaired on a regular basis, most of us would have cancer. From this perspective, single molecular targets do not make a lot of sense as clinical endpoints. The nature of biophysical and biochemical networks controlling physiological states means that knocking out a single receptor or gene will have multiple unanticipated effects but are unlikely to achieve a systems level pattern change that could reverse the process of malignancy.

### The Fallacy of Materialism

Those of us who do research, consider ourselves to be objective scientists in well-defined scientific disciplines. We design our studies based on state-of-the-art evidence in our respective fields. However, there is a pervasive underlying assumption across disciplines that remains unexamined, and in this author's view, scientifically unsupported by the data. It is the assumption that because medical conditions occur in the physical body, their causality must be traceable to some form of particulate matter (such as genes or proteins) in the body.

There are two fallacies underlying these assumptions: 1) ignorance of the nature of reality reflected by modern physics (wave/particle duality), and 2) a misunderstanding of the valid rules of inference, i.e., logic. The logical fallacy is the belief that correlation=causality. This is best illustrated by pictures on a television screen. Most of us do not assume that the images and programs we see on television originate in its physical components. We know that the pictures and programs cannot be found inside the television set but stem from radio signals that have been transmitted from another location and transduced by the television into visual images. If we change one of the internal components so that it picks up different frequencies, the new picture is still a reflection of an outside frequency and does not emanate from the physical characteristics of the newly inserted part [9]. This would be analogous to saying that because the wheels of a car turn every time it goes uphill the wheels are causing the car to go uphill. Obviously, without a motor, the wheels would carry the car downhill. Correlation is not causality.

This paper addresses how faulty but unacknowledged assumptions have led to biased research designs and erroneous conclusions in oncology. Basing conclusions on only a subset of the data biases hypotheses and experimental designs. A scientist

who believes that wheels are causal, might design an experiment to test the hypothesis by having one group of cars (the experimental group) drive uphill and a control group of cars remain parked in a parking lot. When the control group is compared to the experimental group, the statistical difference in wheel movement is highly significant. The wheels turn on every car that goes uphill but on no cars that stay parked in the parking lot. This is then interpreted as confirming the hypothesis that wheels cause cars to go uphill. The misinterpretation results from a flawed experimental design. If the experiment had been planned to compare cars driving uphill with those driving downhill, the outcome would have been completely different. Preconceived notions (hypotheses) about causality determine the design of the experiment, the variables that are included, and the conditions under which it is measured. Hypotheses based on faulty assumptions lead to the omission of important data, in the case of cancer, biophysical signaling.

### Implications of Quantum Theory

Both relativity theory and quantum mechanics have demonstrated that it is not scientifically accurate to attempt to separate the observer from the observed event because the observer and the measurement influence the outcome of the experiment [28]. Einstein's work on relativity demonstrated that space cannot be separated from time and that together they form an indivisible whole. The speed of a train is not independent from but relative to the observer. Wave/particle duality in quantum theory has demonstrated that at a quantum level, waves and particles are indivisible, i.e., two aspects of the same thing. Position and velocity cannot be determined until the collapse of the wave function. The quantum state itself, i.e., before measurement, is indivisible. Despite these fundamentals of physics, the biomedical community still believes in a firm separation between observer and observed phenomena. As the previous examples show, the observer influences the measurement by how they design the experiment and which variables they decide to include. If the DNA helix is split for sequencing, base pairs (particles) can be observed but not the wave form. If the double helix is left intact to measure electrical conductance, the wave aspects can be observed but base pair sequence cannot. The current emphasis in biomedical research on measuring particles to the exclusion of waves is not congruent with modern physics and is greatly biasing some of the evidence on which we base clinical decisions. It puts the biomedical sciences out of step with modern physics by about 100 years. Biomedicine has not understood that the molecular targets have fundamentally different properties than macro level systems and therefore tend to ignore the emergent properties that epigenetically influence what happens at a molecular level.

### Conclusion

Accumulating data on the importance of biophysics in understanding biomedical science illustrates that the current



doctrine of materialist reductionism is out of date. What it has *de facto* accomplished through its domination of the life sciences, is to declare certain types of data (e.g., bioelectric phenomena in biological systems and macro-level approaches to understanding disease causality) as unscientific. There exist certain widely held beliefs in the life sciences that are not based on objective data. These consist of the belief that all life, consciousness and physiological conditions are attributable to particulate matter; and its companion belief, reductionism, which has led to a biomedical focus on trying to reduce complex conditions and illnesses that display emergent properties to single causality, e.g., “the gene for...” An elephant cannot be understood by only examining its toenails or its tusks or its tail. The ‘whole’ (essence) of the elephant is complex and more than the sum of its parts. It is high time we demand the same rigor from our underlying scientific assumptions that we purport to demand from experimental procedures. At the very minimum, this requires the inclusion of biophysics as an integral part of research in every area of the biomedical sciences.

The problem is not that scientists have biases. Bias is an inherent characteristic of the human condition. The problem is rather that scientists are unaware of their biases and therefore continue to perpetuate them. When the majority of scientists have the same bias, the risk is high that scientific progress will be severely impeded. Cancer is the most blatant example in modern medicine, referred to by one reviewer by the statement: “oncology has one of the poorest records for investigational drugs in clinical development [29].” I’d like to end with a fitting quote by Bertrand Russell: “The fact that an opinion has been widely held is no evidence whatever that it is not utterly absurd...” [30].

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### Conflict of Interest

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