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Workshop Summary

Applying Principles from Complex Systems to Studying the Efficacy of CAM Therapies

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Abstract

In October 2007, a National Center for Complementary and Alternative Medicine (NCCAM)–sponsored workshop, entitled "Applying Principles from Complex Systems to Studying the Efficacy of CAM Therapies," was held at Georgetown University in Washington, DC. Over a 2-day period, the workshop engaged a small group of experts from the fields of complementary and alternative medicine (CAM) research and complexity science to discuss and examine ways in which complexity science can be applied to CAM research. After didactic presentations and small-group discussions, a number of salient themes and ideas emerged. This paper article describes the workshop program and summarizes these emergent ideas, which are divided into five broad categories: (1) introduction to complexity; (2) challenges to CAM research; (3) applications of complexity science to CAM; (4) CAM as a model of complexity applied to medicine; and (5) future directions. This discusses possible benefits and challenges associated with applying complexity science to CAM research. By providing an introductory framework for this collaboration and exchange, it is hoped that this article may stimulate further inquiry into this largely unexplored area of research.

Introduction

Rationale and goal of the workshop

The American public routinely uses complementary and alternative medicine (CAM) systems that involve complex combinations of natural products and/or combinations of CAM therapies for health maintenance, disease prevention, and treatments. For example, patients being seen in integrative medicine clinics for gastrointestinal (GI) problems may be given a regimen including Chinese herbs and acupuncture, both of which usually are individualized to the patient based on symptom presentation. The use of complex systems in traditional and conventional systems of medicine historically has been based on clinical experience as opposed to systematic evaluation. The need for research methodology to evaluate such systems approaches, combinations of different treatments, and individualized therapies is not unique to CAM. Similar issues are raised in selecting cancer treatments using chemotherapy and radiation, in psychotherapy research using medication and interpersonal therapy, and in HIV/AIDS for which patients are given combination therapies while being treated for opportunistic infections. Typically, individual therapies that are known to work are combined together, thus, creating a complex, multimodal intervention. In CAM, the complex intervention is frequently the starting point of investigation. What is common to these combination or multimodal approaches is the concept of positive interactions or synergy among the components. However, it is not clear whether the multimodal approach provides distinct advantages in practice over single-modality therapy and, more importantly, whether the whole is, in fact, greater than the parts, or if they work at all.

To address these difficult issues, a workshop entitled, "Applying Principles from Complex Systems to Studying the

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Efficacy of CAM Therapies" was held October 8–10, 2007 at Georgetown University in Washington, DC. The overall goal of the workshop was to engage a small group of experts from diverse disciplines to explore the approaches and tools used to study both complexity and CAM and to determine whether core principles would emerge from the discussions that could guide the investigation of efficacy and mechanisms of action among complex multimodal and/or individualized interventions.

Description of the program

The workshop program was organized into seven sessions. The first four were composed of short, didactic presentations designed to enhance a rich discussion. As outlined in Table 1, the first session served to introduce the concepts with overview presentations by Ary Goldberger, MD ("Introduction to Complexity Science and Complex Systems"), and Jacob Shoham, MD, PhD ("Complex Systems and CAM—Why and How Are They Related?"). Session 2 focused on the tools used to study complex systems and how these tools could be applied to CAM. Session 3 followed with the issue of research designs and the practical approaches to studying complex systems. The final session of the first day dealt with the specific challenges inherent in studying CAM, ranging from the context of clinical practice and the patient–practitioner interaction to an analysis of the impact of multimodal and individualized interventions. The second day of the workshop began with a keynote address by Ken Resnicow, PhD, entitled "Embracing Chaos and Complexity: A

Table 1. Workshop Program for Applying Principles from Complex Systems to Studying the Efficacy of CAM Therapies[a]

Session	*Topics*	*Presenter*
Session 1	**Introduction of the Concepts**	
	Purpose and Goals of the Workshop	Aviad Haramati, PhD, Georgetown University School of Medicine Chair, Workshop Steering Committee
	Introduction to Complexity Science and Complex Systems	Ary Goldberger, MD Harvard Medical School
	Complex Systems and CAM—Why and How They Are Related	Jacob Shoham, MD Bar-Ilan University, Israel
Session 2	**Approaches to Studying Complex Systems: The Tools**	
	Symbolic Dynamics: Alternative Ways to Classify Information	Chung-Kang Peng, PhD, Harvard Medical School
	How to Measure Complexity: Applications to CAM Research	Madalena Damasio Costa, PhD, Harvard Medical School
	Models, Simulations and Experiments in Complex Systems: Control of Breathing	David Paydarfar, MD, University of Massachusetts
	Dynamic System Attractors as a Metaphor for CAM Research	Mikel Aickin, PhD, University of Arizona
Session 3	**Practical Approaches to Studying Complex Systems: Research Design**	
	Balance and Design Using Propensity Scores for Public Health Research	Tom Love, PhD, Case Western Reserve University
	Qualitative Research in Building and Refining CAM Interventions: Lessons from the Development of a Guided Imagery Program for Obese Teens	Marc Weigensberg MD University of Southern California
	Experimental Designs for Building and Refining CAM Interventions	Bibhas Chakraborty, PhD(Candidate), University of Michigan
Session 4	**Practical Considerations and Challenges to Studying Complexity of CAM Interventions**	
	The Context of CAM Practice	Ted Kaptchuk, OMD, LAc, Harvard Medical School
	The Impact of Patient–Practitioner Interactions on Outcomes	John Tilburt, MD, Center for Bioethics, National Institutes of Health
	The Impact of Multimodal, Individualized Interventions	Iris Bell, MD, PhD University of Arizona
Session 5	**Keynote Presentation**	
	Embracing Chaos and Complexity: A Quantum Change for Public Health	Ken Resnicow, PhD, University of Michigan
Session 6	**Using Case Studies to Design Clinical Research**	
	Case 1: Acupuncture and Chinese Herbs for Osteoarthritis	All Participants
	Case 2: Attitudes, Nutritional and Lifestyle Interventions for Breast Cancer	
	Case 3: Novel Approaches to treating Type 2 Diabetes	
	Case 4: Integrated Treatments for Fibromyalgia	
	Case 5: Using CAM to Improve Health and Wellbeing	
Session 7	**Summary and Recommendations**	All Participants

[a]This workshop was held October 8–10, 2007 at Georgetown University, Washington, DC.

Quantum Change for Public Health." Dr. Resnicow presented his ideas about how complexity science might explain behavioral change. The entire group of approximately 40 participants then separated into 5 groups to deliberate on case studies that had been prepared by the steering committee. The rest of the day was spent on group discussions of the case studies and subsequent reports from each of the groups. At the end of the day, a small subgroup was selected to synthesize the lessons learned and to prepare a summary of the deliberations that would be presented to the workshop participants the next morning. This article represents a synthesis of that summary, which we hope will inform readers of this journal and provide the impetus to stimulate further research in these areas.

What is Complexity?

Complexity theory provides a theoretical framework for evaluating and analyzing complex systems. These systems are "complex," because they exhibit global properties not made obvious from the properties of the individual components, and they are "systems," because they are composed of interconnected parts. Historically, complexity theory borrows concepts and tools from a range of disciplines, including chaos theory (physics), control theory (engineering), cybernetics (mathematics), and General Systems Theory (biology). More broadly, these disciplines share a common theme of nonlinearity—a concept maintaining that the size of an output is not proportional to the size of an input. Because of this shared theme, these disciplines may be categorized within a broader field of nonlinear dynamics.

Complex systems are commonly dynamic and contain interacting components whereby feedback and feedforward loops can be formed. The need to characterize the observed properties stemming from these dynamic interactions has led complexity theory to develop concepts that are unique and distinct from traditional reductionist sciences. These concepts include, and are not limited to: emergence—the concept that patterns or properties arise or emerge from the interactions of multiple simple parts; fractal characteristics—the presence of recursive and "self-similar" patterns over multiple spatial or temporal scales; and sensitivity to initial conditions—the idea that small perturbation can have large, unpredictable effects. Most of the models proposed for complex systems are nonlinear, which means that the system response to a sum of inputs is not simply the sum of their separate responses.

This conceptual departure from reductionism results in a heuristic approach that is also noticeably different from traditional methods. Problems are evaluated at the global systems level, and numerous factors are assessed at many time points and/or spatial conditions. The goal is to identify "patterns" that reflect global behavior rather than to identify a singular, distinguishing marker or variable. In addition, because complex systems are frequently sensitive to initial conditions, and thus are often unpredictable, the analyses and their resulting solutions are frequently stochastic—in other words, more probabilistic than deterministic. To accomplish these analytical tasks, sophisticated computational and mathematical tools are commonly used and incorporate a mix of linear algebra, differential calculus, statistics, information theory, and/or computational science.

As a scientific discipline, complexity science is young and continually evolving. Its applications to biology and medicine have a particularly short history and did not become broadly relevant until the postgenomic era. The completion of the human genome project, the development of high throughput tools, and improvements in computer software/hardware were confluent factors that led to the rise of complexity sciences in biology and to the important recognition that reductionist approaches were inadequate for addressing biological complexity. Molecular biology, biochemistry, and biophysics were highly proficient in characterizing individual molecules but did not have the means to describe and capture systemwide behavior effectively. The increased importance of complexity science is reflected by the growth of systems-biology divisions in academic institutions and pharmaceutical industries across the world. The National Institutes of Health (NIH) Roadmap is another testament to the increased importance placed on complexity science and interdisciplinary research.[1]

Applying complexity-based analytical methods to medicine has a number of theoretical advantages over the applications of traditional reductionist methods. First, complexity-based analytical methods offer the means to analyze "holistically" multivariate and/or time-varying data. The methods help identify distinguishing patterns that exist within a disease condition or between individuals who share a common diagnosis. Second, these methods can be used to extract hidden information from clinical data. One of many examples used throughout the meeting was the use of nonlinear dynamic analyses to show that heart rate over time is predictive for cardiac mortality and arrhythmias despite the fact that the means or variances of heart rate may not differ significantly across individuals.[2–4] Third, complexity-based tools may present a revolutionary bridge between qualitative and quantitative measures. Terms such as *adaptability*, *robustness*, or *health* were previously considered qualitative terms and thus were quantitatively intractable. Yet, complexity science has identified analytical methods that can help assess these features.[5] Given that "quality" is a global, emergent property not readily traced to a single variable, complexity science appears to be ideally suited to evaluate and provide an explanation for it.[6] Finally, complexity science offers a conceptual framework that reflects reality better. In the real world, small inputs can have large effects, processes are dynamic, interactive effects can span across many temporal and spatial scales, and transformations from one state to another can happen gradually or precipitously.

While used relatively sparingly in medicine, complexity-based analytical methods have become increasingly important tools for examining the relationships among genes, proteins, RNA, and other molecules involved with the immune response.[7] Use of these techniques is expected to increase as the analytical toolbox for systems-based approaches expand, and awareness of these techniques grows. For studies focused on complexity, the tools that have been used can be categorized into static and dynamic methods. Static analytical methods evaluate many variables at once, assess their interactions, and/or identify patterns that may emerge from them. Examples of these methods include clustering methods[8] (agglomerative, hierarchical, disjoint, k-means clustering, Bayesian mixture models, and latent class analysis), factor analyses,[9] structural equation modeling,[10] and neural networks,[11] among others. Dynamic analytical methods evaluate a single or few variable(s) over numerous timepoints (i.e., time series) and assess for patterns across many temporal scales. Examples include correlation dimensions (a measure of dimensionality of fractal objects or time series),[12] detrended fluctuation analysis (ameasure of statistical self-affinity of a signal),[13] and multiscale entropy (assessment of sample entropy over multiple time scales).[14] This categorization of methods is a simplification, as analytical tools can combine both the temporal and multivariate aspects of a process and can also incorporate spatial dimensions as well.

Challenges to CAM Research

Research on CAM faces challenges similar to those inherent in conventional clinical trials, such as participant self-selection bias and parsing the effect of the patient–provider relationship, although these challenges may be exacerbated when studying CAM. Additional research challenges include the heterogeneity of CAM systems, the use of diverse diagnostic schemes that may not overlap with those of conventional medicine, the use of individualized multimodal treatments, and the simultaneous emphasis on patient-centered, global and preventive outcomes.

While many individuals in the United States may self-medicate with dietary supplements, other patients seek care from learned practitioners of traditional systems of medicine including Ayurveda from India, *Kampo* from Japan, Traditional Chinese Medicine (TCM), Native American medicine in all its variations, and more recently developed systems such as homeopathy, naturopathic medicine, and chiropractic. Most types of CAM are relatively unregulated in the United States, with only five (acupuncture, chiropractic, homeopathy, massage, and naturopathy) licensed in three or more states. Even with the regulation provided by licensure, the substantial heterogeneity found within these traditions contributes to the difficulty of translating CAM practice into CAM research.

A primary research challenge is rooted in the tendency of CAM practices to individualize for the patient, not the disease. As a result, treatment may vary for individual patients presenting with the same conventional diagnosis. For example, an acupuncturist who sees 2 patients with migraine headache may tailor their treatments quite differently, after making decisions on the selection of acupuncture points, the depth of needle insertion, and the frequency and scheduling of treatment. These choices are made on a patient-by-patient basis, informed by each patient's specific strengths, weaknesses, and needs. A research investigator must make similar decisions in designing a randomized controlled trial (RCT) for acupuncture. Unless these choices are made in an evidence-based fashion, the acupuncture trial may be considered compromised by some methodologists. The investigator must decide, for example, whether a standardized acupuncture protocol or individually prescribed acupuncture, or a combination thereof, will be delivered in an RCT. Implicitly, this choice entails either compromising traditional acupuncture practice or straining the validity of the medical model RCT originally designed to test the effect of a single intervention on an outcome or many independent interactions.

The translation of a type of CAM as practiced clinically into research has often meant streamlining a complex healing system into a simplified intervention. As a result, most research has investigated only one modality at a time within the wider rubric of a traditional system of medicine. For instance, there are hundreds of studies examining the efficacy of acupuncture alone for treating asthma, pain, hypertension, or nausea. Yet, in real practice, acupuncture would be just one of an arsenal of interventions used by a licensed acupuncturist, including botanical potions, cupping, dietary changes, exercise therapy (e.g., *t'ai chi* or *qigong*), moxibustion, and Chinese massage. The same can be said of assessing yoga, or a single botanical, or meditation alone, given that all are merely single components of larger, complex systems of medicine. The research challenge of whether to study a single component or a combination of many modalities echoes the methodological issue of choosing individualized versus standardized CAM treatment for an RCT. The investigator is faced with either designing a trial with a single modality that does not reflect true clinical practice accurately or, alternatively, undertaking a multifaceted intervention trial that complicates interpretation from a conventional perspective.

Recognizing the difficulties involved with conducting multifaceted intervention trials, observational studies may provide an alternative approach to generating data on CAM. Observational studies could provide information on the numbers and types of patients who use CAM therapies, and elucidate issues regarding treatment delivery, dosage, relevant side-effects, and patient outcomes. Such studies may inform the design of further intervention studies by providing an estimate of treatment effect-size. Observational studies also may be helpful for summarizing the use of CAM nosologies that differ from conventional diagnosis of illness.

To date, little research has examined CAM interventions using the nosologies or diagnostic schemes associated with particular CAM systems. In general, CAM diagnostic schemes are complex, individualized, and prone to intra- and interpractitioner variability. However, it might prove beneficial to investigate CAM therapies using them, especially when the conventional medical diagnosis is unspecific and prone to subjective interpretation. In the case of fibromyalgia (FM), temporomandibular disorder, or irritable bowel syndrome (IBS), for example, the addition of a CAM diagnostic scheme to inform clinical-trial inclusion criteria might allow more specific classification of the disease or condition and increase the homogeneity of the patient population included in the study.

Assessing the role of the placebo or meaning effect in CAM therapies, and controlling for it, has been another challenge for researchers. CAM treatments typically involve extended and intensive interactions between patients and practitioners, which greatly increase the possibility of nonspecific effects. At the same time, the patient–provider relationship itself is considered a key element of many CAM therapies. As a result, finding appropriate placebos or shams for treatments such as TCM and homeopathy—with their extensive provider–patient diagnostic interviews—or chiropractic, massage therapy, acupuncture, or complex herbal mixtures, remains a challenge. Double-blinding of the interventions may not be possible because an experienced practitioner will know which treatment is sham and which is true. The practitioner, in turn, may consciously or unconsciously convey this information to the patient, undermining the trial design. Variations in practice also affect the choice of a placebo or sham. For instance, superficial insertion of acupuncture needles at valid acupuncture points has been used as a sham control in many acupuncture trials. Yet, the Japanese school of acupuncture advocates such superficial needling as an effective treatment. More innovative placebo and sham controls are required for future CAM RCTs.

Selecting appropriate outcome measures in CAM research may be challenging, and is influenced by the holistic view of health often imbued in traditional medicine systems. CAM providers emphasize the treatment of the whole patient by addressing the totality of the person's physical, mental, and spiritual attributes, rather than focusing on a specific pathogenic process. What is intrinsic to the whole-person approach is a focus on therapies that are designed to stimulate a patient's recuperative powers, correct an imbalance among individual organs or physiologic systems, or even enhance a patient's ability to relate well to other individuals, society, or the environment. As such, a coordinated set of interventions are often chosen for their interactive synergistic roles in treating what is conceived of as one central or global disturbance within the patient. Because of this focus on the total person, CAM providers often measure treatment success in terms of holistic outcomes rather than focusing on curing a given disease or disorder. In this view, global improvement is more important than specific results, and it is possible for a patient to be healed without the disease being cured, although the intent is always to do both.

The unique characteristics of CAM systems described here affect the types of questions that might be asked in future research. For instance, instead of asking whether a specific herb is efficacious for joint pain, it might be more appropriate to ask for whom, and in what environmental context, a given treatment package is effective. When answering this question, outcome measures that capture overall benefit to the patient need to be considered.

Applying Complexity to CAM

Many of the aforementioned challenges facing CAM researchers stem from a paradigmatic mismatch between the fundamental principles espoused by CAM theory and many of the analytical tools and methods generally applied in clinical research. The conventional RCT tends to reduce the evaluated system into individual parts and thus risks missing the active elements of a CAM healing encounter premised on inherently complex treatment and diagnostic processes.

To the extent that difficulties in conducting CAM research have their origins in this paradigmatic incongruity, then a science based on holistic complexity should theoretically be a better alternative. Because the theory matches practice, complexity-based tools should be able to be used to evaluate CAM ecologically and thus elucidate its diagnostic approaches and therapeutic effects without significant adulteration. At present, however, this claim remains theoretical and untested.

How can complexity science be applied practically to CAM research? The answer is constrained by the availability of complexity tools that are clinically applicable, feasible, and validated. Presently, few tools fit these criteria, and few data are collected that would be appropriate for the existing tools. However, established analytical methods can be useful as transitional steps toward complexity-grounded applications. One major methodological category that may serve this role is multivariate analyses. Techniques, such as factor analyses and cluster analyses, are distinct from simple linear-regression models in that these analyses use composites of multiple relevant variables instead of single variables to identify any hidden unapparent groupings.

Factor analysis groups variables into factors. Factor analysis describes variability of the observed measures in terms of smaller number of underlying latent variables or "factors." For instance, factor analyses applied to psychologic variables may categorize depression, anxiety, and anger into a single "negative emotions" factor and joy, optimism, and relaxation into another "positive emotions" factor. While factor analysis groups variables into factors, cluster analysis groups individuals into subsets of individuals with similar profiles of variables. In cancer research, cluster analyses have identified subgroups of individuals with non-Hodgkin's lymphoma—with each group sharing distinct genetic profiles or disease subtypes.[15] Interestingly, the subgroups were associated with varied prognoses and responsiveness to chemotherapy, implying that, not only do different categories exist for a specific condition, but the categorizations are clinically meaningful.[16]

In the Georgetown workshop, applications of clustering techniques were described within the context of English literature. Words within a novel were assigned numeric values and subsequently clustered into a phylogenetic tree—which is an illustrative way to demonstrate relationships among specific entities. This application of multivariate methods to literature, termed "symbolic dynamics," was able to distinguish whether a book was written by William Shakespeare or by John Fletcher.

Multivariate analyses can be applied to CAM research in a number of ways. These analyses can be applied to conventionally based diagnoses, CAM-based diagnoses, and treatment interventions. For example, can we identify multiple subtypes of knee osteoarthritis (OA)? Do these subtypes correlate with CAM diagnoses such as *Bi* syndromes of Wind-Dampness? Conversely, are *Bi*-syndromes of Wind-Dampness explainable by a constellation of conventionally based variables, such as immune cytokines, biomechanical parameters, or psychologic factors? Are there clusters of acupuncture points used in the clinical treatment of knee OA? These questions also can be extended to clinical response: Do these subtypes for knee OA respond differently to a certain acupuncture treatment? Is there a particular cluster of acupuncture points that are associated with significant reductions in pain or disability? Does a person's pattern or subtype categorization change with treatment over time? The answers to these questions may provide critical insights into how CAM therapies operate and how individuals respond to particular CAM therapies. Conceivably, other more-sophisticated analytical tools, such as structural equation modeling and neural networks, may yield additional discerning answers. These multivariate models typically are classified as static analytical methods.

Dynamic analytical methods are another class of complexity-based tools that can be potentially applied to CAM research. Dynamic methods use temporally varying variable(s) and incorporate techniques, such as detrended fluctuation analysis, multiscale entropy, and correlation dimensions. These techniques are typically applied to heart rate variability (HRV), although any time-varying measure could theoretically be analyzed. According to existing studies, increased complexity in heart rate across many time scales—as determined by these techniques—is associated with reduced arrhythmic events and death.[2–4]

At the Georgetown workshop, Madelena Damasio Costa, PhD, discussed the application of multiscale entropy analyses to heart rate data derived from the CAST [Cardiac Arrhythmia Suppression Trial].* Heart rate data obtained from Holter monitors were partitioned at varying levels of time intervals, and the sample entropy (a measure of orderliness) was calculated for each time interval and then averaged. The averaged entropy can be graphed against each time scale (i.e., the length of the time intervals). Good health is believed to show fractal properties whereas the amount of complexity or orderliness is insensitive to the time scale. Indeed, for the CAST cohort, individuals who maintained constant levels of entropy in heart rate across a large range of temporal scales were associated with improved survival compared to subjects who did not.

Because heart rate is dynamically balanced through many elements, including the autonomic nervous system, respiration, hormones, and other physiologic systems, the heart theoretically should be responsive to, and exhibit increased complexity across, multiple time scales in concert with fluctuations in these elements. The temporal changes of a variable therefore may contain hidden information that is useful for describing the overall system. This capacity to capture the global state of a system or an individual suggests these complexity-based measures may act as surrogates for concepts that were traditionally difficult to measure but considered important for CAM research (e.g., "health" and "adaptability"). Does a homeopathy prescription or massage treatment affect complexity measures of HRV? Does an imbalanced *dosha* or *Yin* Deficiency correlate with reduced complexity in respiration?

Another example of temporal analysis of complex systems data applied to medical research was provided in the conference by David Paydarfar, MD. He looked at the physiologic patterns of infants experiencing breathing apnea that may be associated with sudden infant death syndrome (SIDS). Given that respiratory rhythmicity originates in the brainstem and involves nerves descending to the diaphragm, Paydarfar wanted to explore what is involved in the transition between breathing and apnea. In chaos theory, a pendulum put into motion will start a pattern, but added information or "noise" can change that pattern. Paydarfar observed that swallowing was the additional noise that could affect the respiratory pattern. If the esophageal action occurred at just the wrong time, it could stop the "pendulum" of breathing and create apnea. He and his colleagues are measuring channels of information in a neonatal intensive care unit (NICU) to study these signals, and their patterns and interactions, and have developed a low-level vibratory stimulation mattress that can transform the irregular apneic rhythm to eupnea. When breathing rate slows, the mattress stimulates the infant to resume breathing by adding "noise" (low-level vibratory stimulation) to the system (i.e., a pacemaker at the system level).[17]

Complexity-based analytical methods are broadly applicable and theoretically can be applied across multiple outcome measures and CAM interventions. Other tools also may become applicable as complexity-science is increasingly developed and applied to biologic sciences. In the end, these analytical methods may not validate specific CAM therapies or diagnostic approaches. However, complexity science may, if anything, provide support for the fundamental principles promoted by CAM therapies—namely, that treatments should be individualized, that optimal treatments can change with time, and that many modalities can be synergistic. These conclusions, in of themselves, can have transformative effects on the way modern medicine is practiced although fundamental barriers (e.g., structural pressures on doctors to spend reduced amounts of time with patients) may impede such changes.

CAM as a Model for Applying Complexity to Medicine

Although the CAM community may instinctively identify complexity science as a means to understand CAM better, CAM therapies themselves can be thought of as exemplars for how complexity theory can be applied to clinical medicine. Historically, conventional medicine has evolved and developed under a reductionist Cartesian framework. Complex problems such as chronic diseases were typically divided into smaller, simpler, and thus tractable, units. This approach has affected the way practitioners diagnose, treat, and prevent illnesses. Importantly, it has also shaped the practitioner's worldview and heuristic approach to medicine. To incorporate a distinct philosophical framework such as complexity theory to medicine may therefore challenge pervasive entrenched beliefs and perspectives. How can treatments be individualized when it means that some individuals with poorly controlled diabetes will be treated with something other than hypoglycemics? How can rigorous science be performed without the randomized control trial (RCT)?

In this regard, CAM is uniquely poised to provide the needed perspective and experience. Many CAM therapies are rooted in a worldview most consistent with complexity and systems theory. The human body is viewed holistically and considered dynamic and complex; the mind, body, and spirit are inextricably linked; and the interactions among the organs and individuals are as important as the components themselves. This worldview has led to the evolution of numerous sophisticated concepts and diagnostic/therapeutic tools, many of which are powerful models for complexity-applied medicine. They include, but are not limited, to individualized treatments, diagnosis by patterns (e.g., whole-systems medicine, homeopathy), elaboration of networks and localized hubs (e.g., acupuncture points on meridians, connective tissue network), synergy (e.g., herbs), health defined as a state of balance, treatment combinations across different factors (e.g., chemical, behavioral, energetic, spiritual), the importance of the practitioner–patient interaction in healing, fractal patterns within the body (e.g., reflexology, auricular acupuncture), and the use of minimal interventions to affect the larger system (e.g., acupuncture and homeopathy).

Moreover, the significance placed on dynamic interactions and whole systems has led CAM therapies to appreciate

*Costa M, unpublished data.

physiologic processes that are frequently overlooked. These processes include interactions between the mind and body; electromagnetic field effects on human physiology, connective tissue, and musculoskeletal networks; the influence of nutrition and environment on gene expression; and the importance of social networks on health, among others. As conventional medicine progressively adopts a systems-based perspective, these processes may be increasingly recognized as important and, in some cases, critical for establishing good health. If this occurs, the lessons learned through CAM research and practice can provide a rich foundation for further investigation and understanding.

Finally, in research, CAM may provide valuable insights to scientists interested in incorporating complexity science to medical research. CAM researchers frequently struggle with issues related to working across differing paradigms or perspectives. Researchers wrestle with applying systems-based therapies to reductionistically defined diagnoses, with using qualitative outcomes in quantitative statistical analyses, and with using individualized approaches despite the need for identifying generalizable interventions. The need to straddle these separate worlds is leading researchers to develop translational tools capable of working with one perspective while remaining true to another. Manualized protocols and techniques for validating qualitative outcomes are two examples. The challenges encountered with CAM research will similarly confront complexity scientists as integrating information across reductionist and systems-based disciplines becomes increasingly important.

Because CAM and complexity-science share similar orientations and challenges, the insights and lessons learned from one will be likely to benefit the other. Ultimately, the clinical setting is where theory meets reality, and, in this respect, CAM is well-positioned to provide the human-level perspectives for a complexity-applied medicine. Thus far, the medical community has focused predominantly on applying complexity principles to the molecular and cellular level. Because of this, the opportunity to inform applications of complexity science to more macroscopic levels (i.e., human and community) remain relatively open. CAM has the potential to play this important role in cooperation with clinical and translational researchers.

Future Directions

As a system of practice that values dynamic interactions and systems-based thinking, CAM is poised to provide the conceptual models and techniques that embody practical applications of complexity-science to medicine. Conversely, complexity science can yield important analytical insights into the diagnostic and therapeutic approaches of CAM. The level at which CAM and complexity science interact will depend on the actions taken by the CAM community within the next 5–10 years.

For meaningful interactions to occur between complexity-science and CAM, a number of barriers must be overcome. First is the lack of familiarity. Because CAM practitioners and researchers lack knowledge of complexity-science, they are unable to conceive of ways in which complexity analytical tools can be incorporated clinically. In the Georgetown conference, this was one of the most commonly cited barriers. Conversely, systems biologists and complexity scientists are unaware of the principles underlying CAM therapies and, thus, are unable to recognize the practical lessons obtainable from them. Second, the infrastructure necessary to accommodate a consequential exchange between CAM and complexity science does not yet exist. While this Georgetown conference and the North American Research Conference for Complementary and Integrative Medicine (held in Minneapolis in May 2009) are initial steps, forums, websites, courses, and organizations do not yet exist to catalyze widespread intellectual exchanges between the two communities. Third, the analysis is only as good as the data allow. A number of CAM concepts—such as *qi*, CranioSacral pulses, patient–practitioner rapport, or homeopathic potentiation—are not sufficiently standardized or measurable in a way that would allow meaningful incorporation into complexity-based methods. Clearly, elucidating the underlying physiologic processes, if any, would greatly help establish objective, measurable markers. Finally, complexity science itself has not fully matured. Available analytical tools, computational programs, and theory are limited, and those in present use generally are associated with various constraints. For instance, nonlinear dynamic analyses require a certain amount of time points obtained above a particular frequency. Similarly, static complexity tools require more data points and variables than may be captured in current research designs.

To address these barriers, three broad efforts are proposed: (1) education; (2) networking; and (3) research. For education, CAM researchers and practitioners may begin to learn basic concepts attached to nonlinear dynamics and complexity theory. This may occur in conference settings or in CAM and conventional medicine institutions where complexity-based methods or concepts may be incorporated into the curricula. A website may be created to distribute complexity theory tutorials, to list useful references, and to link to other useful sites.

For networking, increasing dialogue between CAM researchers and complexity scientists/mathematicians, between clinicians and system biologists, and across CAM researchers interested in complexity science can significantly advance research inquiries into the applications of complexity to CAM and vice versa. Interdisciplinary conferences between CAM researchers/practitioners and complexity scientists may provide the nidus for this intellectual exchange.

Finally, for research, CAM journals may consider publishing case series or clinical examples to highlight the systems-oriented approaches in CAM therapies, the parallels between complexity theory and CAM perspectives, and the manner in which this may inform future complexity-based projects. Furthermore, efforts to elaborate the contextual complexities of healing should continue by incorporating qualitative or mixed-methods study designs and including biopsychosocial and cultural measures, often through collaborations with psychologists, medical anthropologists, and social scientists, among others. There is also no reason why existing complexity tools (e.g., complexity measures in HRV or cluster analyses) cannot be immediately applied to CAM studies. Ongoing and future clinical trials should also consider adding various static variables or temporal measures to permit complexity-based analyses once the tools become available. Such information can also be placed in an open-access websites, much like Physionet.org, to permit others to explore and experiment with complexity-based methods.

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