Models for the Study of Whole Systems

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This article summarizes a network and complex systems science model for research on whole systems of complementary and alternative medicine (CAM) such as homeopathy and traditional Chinese medicine. The holistic concepts of networks and nonlinear dynamical complex systems are well matched to the global and interactive perspectives of whole systems of CAM, whereas the reductionistic science model is well matched to the isolated local organ, cell, and molecular mechanistic perspectives of pharmaceutically based biomedicine. Whole systems of CAM are not drugs with specific actions. The diagnostic and therapeutic approaches of whole systems of CAM produce effects that involve global and patterned shifts across multiple subsystems of the person as a whole. For homeopathy, several characteristics of complex systems, including the probabilistic nature of attractor patterns, variable sensitivity of complex systems to initial conditions, and emergent behaviors in the evolution of a system in its full environmental context over time, could help account for the mixed basic science and controlled clinical trial research findings, in contrast with the consistently positive outcomes of observational studies in the literature. Application of theories and methods from complex systems and network science can open a new era of advances in understanding factors that lead to good versus poor individual global outcome patterns and to rational triage of patients to one type of care over another. The growing reliance on complex systems thinking and systems biology for cancer research affords a unique opportunity to bridge between the CAM and conventional medical worlds with some common language and conceptual models.

Keywords: whole systems research; complementary and alternative medicine; complex systems; global and local patterns; chaos theory; network science; homeopathy; systems biology

Overview: Reductionism Versus Holism in Theory, Practice, and Research

The purpose of this article is to provide an introduction to models of complex systems/network theory-driven clinical research in cancer, involving whole systems of complementary and alternative medicine (CAM) such as homeopathy, traditional Chinese medicine (TCM), Ayurveda, and naturopathy. Distinguishing features of whole systems of CAM include their historically well-established approaches to care across a spectrum of acute and chronic diseases and complete diagnostic and therapeutic systems derived from comprehensive worldviews of nature that are holistic and vitalistic. The major theme of the present article is that nonlinear dynamical complex systems and network theory provide a coherent conceptual basis and scientific approach that matches the holistic aspect of whole systems of CAM. Consequently, complex systems theory facilitates an understanding of and ability to move beyond the perplexing difficulties in reproducibility of randomized controlled trials (RCTs) on homeopathy and other whole systems of CAM.

The global and multidimensional worldviews of whole systems of CAM differ from the implicitly reductionistic and materialistic worldview of much of mainstream medicine as currently practiced, in which diagnosis and treatment focus on (a) local body parts in isolation from one another and (b) the molecular mechanisms of local symptom expression (Table 1). As discussed elsewhere in detail, attempts to perform reductionistic research, applying the mainstream pharmaceutical model for RCTs (testing the question of specific efficacy) to whole systems of CAM (where overall effectiveness is the most appropriate question), often produce conflicting and controversial results. The mismatch between the simplified direct causal model inherent in reductionism that underlies RCTs and the indirect multifactorial causal models inherent in holistic complex systems and networks helps account for the discrepancies (Table 2).

Networks and Whole Systems Research Models

Network research is a growing area within complex systems science relevant to the whole systems of CAM view of the whole person as an emergent organism.
arising from interrelationships and interactions among the parts. In turn, the person is part of and in ongoing interaction with the larger environmental context in which he or she exists. Network science focuses on the patterns and strengths of interrelationships and interactions between the component parts of a system that has self-organized into a whole. Thus, the behaviors of a given system or network receive greater emphasis in complexity research than do the static structures of the parts themselves. Precisely because of the indivisibility of a network (complex system) into its component parts, the focus of study differs from the focus of study from a reductionistic perspective.

By analogy, researchers cannot understand the organization of or interactions within the Internet by studying how a silicon chip is manufactured. Rather, they study the Internet as a whole network. In a systems model, networks occur at every level of scale from ecological to social and economic to biological and biochemical. At the person level, the acupuncture meridian and acupoint system from CAM is one example of a network. However, this may not be unique to whole systems of CAM. In the conventional medical arena, network scientists have uncovered and begun to map networks of biochemical interactions within single cells and genetic regulation across the genome.

Network models for research highlight patterns of outcomes, with emphasis on interrelationships between the parts of the whole. For homeopathic
research, network science is far more likely than reductionism to match the multidimensional patterns of outcomes described by clinicians. In homeopathy, for example, healing from chronic disease is not a random process. Rather, it is reported to follow a hierarchically self-organized pattern of gradual change over time in accord with Hering’s Law of Cure. Hering’s Law states that healing shifts from above downward (head to toes), from inside out (more important to less important organs), and in reverse order of time of original appearance of a condition or symptom. The homeopathic clinical construct of suppression assumes but does not articulate a network perspective. That is, homeopaths believe that treatment focused on preventing expression of local disease in a body part, whether a conventional drug or an alternative medicine treatment, only forces the organismic-level disturbances out of one body part and into another, without true cure.

Thus, for a whole system of CAM such as homeopathy, if the therapy itself addresses the whole system of the person, then systems-relevant questions include these: Does the intervention affect network function? If so, how does it differ in pattern of effects from other interventions (perturbations) of the overall system? These queries differ from reductionistic questions such as this: Does the intervention have a specific active ingredient with a biological mechanism beyond that of placebo?

Clearer directions for research can emerge from these considerations. For example, can clinical network scientists document evidence for Hering’s Law of Cure over the person as a whole during homeopathic treatment? Do conventional drug and placebo responses follow Hering’s Law or not? The patterning of changes over the person could provide a theory-driven outcome for controlled research on whole systems of CAM, instead of isolated measurements at single points in time. The nature of the relevant questions depends on the worldview and theory underlying the research.

**Nonlinear Dynamical Characteristics of Complex Systems**

A complex system is a set of multiple component parts self-organized into an interactive, indivisible whole. Within complexity, in addition to network interactions, investigators evaluate the nonlinear dynamics of a system and focus on patterns of change or movement of a system over time, for example, attractors. Dynamics introduce time and patterns as major factors in understanding the behavior of a system. An attractor is a recurrent overall pattern within multidimensional phase space toward which the trajectory of a given system will evolve, without necessarily passing through exactly the same place twice (Figure 1).
Leading complexity researchers hypothesize that complex living systems function at the edge of chaos, where the system can exhibit marked sensitivity to initial conditions (the “butterfly effect”). Small perturbations in the system can lead to large changes if they occur at critical points in the dynamics of the system (nonlinearity). Furthermore, small differences in the state of a given system at the start of a study can lead to progressively more divergent outcomes as a complex system evolves within its environment over time (Figure 2).

Thus, the very nature of complex systems is such that replicability or reproducibility of patterns is likely, but precise repetition of any specific outcome at an isolated point in time or space is unlikely. It is extremely difficult to do reproducible reductionistic research on a whole system. A whole system is nonreductionistic (cannot meaningfully study the parts in isolation from their interactions with one another and with their environment) and nonlinear (with outcomes that could manifest as either increases or decreases in a given variable at a given point in time, depending on multiple factors) by nature.

In complexity, the whole is greater than the sum of the parts in that the behaviors of the whole are emergent, that is, not predicted by understanding the behaviors of the parts. With emergence, the system’s behaviors and outcomes evolve over time through interactions between the parts and between the overall system and its total environment, such that the system is never in exactly the same place from one moment to the next. In general, concepts such as self-organization, emergence, self-similarity (fractality) at different levels of scale (from global to local), nonlinearity (output disproportionate to input), and dynamics (processes of change) are characteristics of complex systems that underlie the empirical and computer simulation methods of complex systems science.

As a result, because of (a) the imprecision of attractor patterns to predict reliably a specific measured outcome, (b) sensitivity of a system’s dynamical evolution to small differences in initial conditions, and (c) emergent behaviors over time, any intervention that targets and acts at the level of the whole system will not produce predictably repeatable isolated specific effects at an isolated local level. The outcomes in complex systems are probabilistic, not certain. Sometimes, at a current moment of observation, the system (or one of its parts) may be close in trajectory to the point it was in the previous moment of observation; sometimes, it will be elsewhere. In short, whole systems of CAM do not act—or even claim to act—with local specificity like pharmaceutical drugs. Predictably, studies focused on testing the specific but not the global effects of whole systems of CAM reflect theory-mismatched designs.

Thus, the “results,” especially in terms of static isolated endpoints typical of conventional medical research, sampled at an arbitrary time point in an RCT such as 12 weeks after the start of treatment and at an arbitrary part of the system (one organ or type of cell), could easily happen to be anywhere along the
trajectory, from very close by to polar opposite points in phase space from study to study, even within the same patient. The point is to zoom out by enough levels of scale to be able to assess the big picture, that is, the global or holistic, pattern rather than zoom in too close onto one transient point along a moving target. Therefore, if a therapy such as a pharmaceutical drug or even a particular CAM modality (eg, an herb) is intended to target a specific local body part or mechanism, then it is a reasonable match to employ reductionistic study designs and methods to evaluate the results. However, if a therapy such as a whole system of CAM (homeopathy, TCM [acupuncture], Ayurveda, or naturopathy) is used clinically to target the person level of scale as a whole system (Figure 3), it is a far more rational match to use holistic study designs including (but not limited to) complex systems models and methods (Table 2).

In addition, the statistical procedure of averaging together data from groups of subjects increases the risk of cancelling the ability to observe changes that are occurring within each subject, but are out of phase with each other in time. The analogy here is the ability of two sine waves moving out of phase with one another to cancel each other, resulting in no net measured change from baseline (destructive interference; Figure 4; see also ref no. 25).

### Computer Simulation Approaches in Complex Systems Research

A leading methodology that systems researchers have used to approach the challenges of poor reproducibility in complex systems is computer simulation models, with agent-based or nonlinear differential equation-based approaches. In agent-based research, often used
in the social sciences, investigators systematically modify the rules by which the local parts (agents) interact with one another. They then observe and document global outcome scenarios as the whole system evolves over time.\(^{26,27}\) At the level of scale of the person, agent-based research might be a useful match for studies of acupuncture, to model differential global outcomes based on varying the pattern of acupuncture points chosen and people in the patient’s social environment (both the points and the people—acupuncturist, family, friends, other health care providers, etc., are potentially agents, albeit at different levels of scale), relative degrees of stimulation or sedation for the points and types of interactional patterns with the people (rules), and the presumptive meridian pathways for interactions between them across the person as a whole (network).

In addition to agent-based research, Figures 1a (low-functioning team dynamics) and 1b (high-functioning team dynamics) give an example of nonlinear differential equation-based modeling of human interactions in the context of business teams, based on models from the field of fluid dynamics\(^ {28,29}\) (see further description in the section below on translating phenotypes within whole systems of CAM). Low-functioning teams appear stuck in adverse dynamical attractor patterns of repetitive, restrictive trajectories called limit cycles and point attractors (Figure 1a). However, several complexity and chaos science researchers have noticed a generalizability and even "archetypal" quality across many different disciplines for what are termed the Lorenz equations\(^ {28,30}\) (see Figure 1b—leading dynamically to a butterfly-appearing attractor pattern, named after the meteorologist who developed them to model changes in weather). Lorenz equations appear to characterize systems with healthier dynamics, including flexibility in the face of environmental challenges, creativity, capacity to innovate, positivity, and balanced interactions between self and others.\(^ {28,31}\) Small changes in initial conditions within the Lorenz equations can lead to variations of the essential pattern but, nonetheless, a recognizable "essence."\(^ {29,32}\)

The relevance of the Lorenz equations\(^ {33}\) at different levels of scale, that is, both human interactions (living systems) and fluid dynamics, may be especially relevant for improving understanding of the interaction between the person and homeopathy. In homeopathy, at the person level, clinicians strive to perceive the essence or global pattern of the person, as expressed overall and, concomitantly, in his or her body parts. For treatment, the homeopath then chooses the single remedy with an essence most closely matched (similar) to the patient’s own core pattern. At the remedy level of scale (a remedy derives from an animal, mineral, or plant environmental source), preparation of homeopathic remedies involves serial dilution and succussion of liquids. Succussion is vigorous shaking, with induced turbulence of water solvent in which the original source material has been dissolved, leading to measurable and evolving changes in the physical chemistry properties of the solvent molecule network.\(^ {34,36}\) Notably, water is also a hub molecule in the network of bodily biochemistry\(^ {37}\) and therefore a potential mediator of the dynamical interactions between patient and remedy as a system.\(^ {38}\) As in any whole system of CAM, of course, the practitioner and the rest of the person’s social network also are part of the complex systems context for the treatment. Milgrom has developed the notion of a complex system in homeopathy to encompass the patient, the practitioner (a component of the social environment), and the remedy (a component of the natural environment).\(^ {29,40}\)

More than 25 years ago, Vithoulkas\(^ {41}\) defined health in homeopathy in terms of behaviors that researchers today might view as consistent with a Lorenz attractor pattern, \(^ {28,29,31}\) that is, freedom from physical and emotional pain, freedom from selfishness, increased adaptability, and creativity. Synthesizing contemporary systems science approaches such as Lorenz models with homeopathic theories of health could enable researchers to model and test for the evolution of healing during successful homeopathic care. Ultimately, improved predictions of which individuals will and will not benefit globally (though not necessarily in specific local outcomes) from homeopathic treatment under particular contextual conditions could result.

**Systems Biology in Medicine and Cancer Research: A Bridge to Complexity Models for Whole Systems of CAM**

The concepts of complex systems are familiar in cancer research.\(^ {42,45}\) Mainstream researchers already use complex systems approaches to improve delivery of cancer care and refine prognostic predictions for individual patients, as well as to understand the basic biology of the disease. Systems biology is the integrative interdisciplinary academic field that studies the relationships and interactions between gene and protein networks in a living organism toward understanding the behavior of the organism itself as a whole. Systems biology researchers rely on both multivariate empirical investigations and mathematical computer simulation modeling studies to advance their field. Genes and proteins interact in complex ways, and it is not useful to attempt reductionistic study of a single gene in isolation from its context, for the study of how, when, and why a patient expresses the phenotype of a particular cancer or other disease.\(^ {46,47}\) Systems-oriented researchers seek therapies that are highly individualized and capable of addressing the multifactorial processes, including polygenic influences.
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that result in disease development and progression such as specific cancers.\textsuperscript{47-49}

At the same time, complex systems concepts are beginning to lead to empirical studies revealing genome-wide gene regulatory networks that control the dynamical patterns of cell differentiation. That is, systems research is beginning to show evidence for integrated controllers of the body’s complex networks with thousands of “separate” parts.\textsuperscript{11} Other network researchers have shown interactive influences as well between global and local levels of organization.\textsuperscript{9} Self-similarity over different levels of scale, that is, fractality, is a feature of complex systems.

Notably, homeopathy researchers such as Hyland and Lewith\textsuperscript{26} have previously postulated that the ability of a single homeopathic constitutional remedy to modulate global and multiple outcomes derives from its therapeutic influence on function of the controller hubs for the person as a whole. If so, then the “mechanism” by which homeopathic remedies act would hold particular relevance to systems biology research and could provide empirical probes for studying genome-wide gene regulatory networks. Some homeopaths report significant clinical remissions and cures of the primary cancer disease process,\textsuperscript{51} in addition to palliation of adjunctive symptoms from the disease and conventional cancer treatments such as radiotherapy and chemotherapy.\textsuperscript{52-54}

Mainstream researchers at the cutting edge of conventional medicine have explicitly recognized that cancer biology is complex and multifactorial. Systems biologists are grappling with the reality that different people can exhibit the same phenotype but arrive at the same “destination” via multiple different, multifactorial pathways. In turn, when trying to use drugs as the interventional tool in cancer, systems biologists know that people differ in their ability to benefit from and metabolize any given agent. The goal of modern genomics/proteomics research is individualized treatment. To determine the most effective and best tolerated drug for a specific patient, they first need to know the many variants of the phenotype and the multiple different pathways to the same apparent end-result.

Individual persons differ in their phenotypic expression of the essential pattern at any given time because of small differences in initial conditions and interactions between the person and a multitude of endogenous and exogenous factors. Disease represents a convergence of the person as a system into an unhealthy attractor pattern\textsuperscript{23,28,55} (see Figure 1a). The homeopathic and TCM interventions then serve as small course corrections at critical points in the trajectories of the person as a network-system, shifting the system back into an optimal dynamical expression of the person’s essential and unique nature, that is, a healthy variant of the self (see Figure 1b).

In complex systems research, Dabby\textsuperscript{32} with musical composers and Losada\textsuperscript{28,29} with business teams have successfully shown precedents for defining the dynamical global essence of a given system and demonstrating divergent trajectories (outcomes) based on varying initial starting conditions and/or interactional patterns. Frederickson and Losada\textsuperscript{31} have further outlined a dynamical systems model for healthy individual human flourishing, which might apply to the system-wide, biopsychosocial-spiritual transformation that a subset of patients treated with homeopathy and acupuncture report. In a conceptual sense, when coordinated modulation of global network processes is the goal, whole systems of CAM may be better suited than pharmaceutical drugs to serve as potential therapies in complex systemic diseases.

**Evidence in Homeopathy and Acupuncture Consistent With the Nonlinear Dynamical Complex Systems Model**

The findings from a large British study of homeopathically prepared dust mite, prescribed isopathically in asthmatics (all patients received the same remedy in 30 c potencies) provide evidence for the large-scale effects of homeopathically prepared remedies on nonlinear dynamics. That is, as seen in Figure 5 for the 3 main outcome measures, lung function, global asthma ratings, and mood ratings, the verum group fluctuated in an oscillatory pattern over time, ending up in the same place as the placebo group at the end of the 16-week study. However, the placebo group showed a flatter set of curves, without the same kind of oscillatory change during the study. The data lead to seemingly paradoxical conclusions, from a reductionistic perspective, that homeopathically prepared dust mite is therapeutically not different from placebo, but that the homeopathically prepared dust mite is not a placebo (ie, it is biologically active, not inert). From a complex systems perspective, however, the verum remedy was actively altering the trajectory of the system as a whole. The data showed that the
verum had destabilized the disease dynamics of the subjects in the active treatment group from their usual attractor patterns, whereas placebo had not.

What occurs over time with homeopathy in the pattern of large-scale outcomes if the verum treatment is therapeutically helpful? Bell et al have such an example with an objective electrophysiological biomarker assessed at initial remedy exposure and after 3 months and 6 months of individualized classical homeopathic treatment in patients with fibromyalgia. As published previously, only patients who subsequently had both an exceptionally good global health change and local tender point pain lessening to treatment had shown an initial difference from placebo in prefrontal electroencephalographic cordance patterns for the alpha frequency (8-12 Hz), averaged over 16 acute sniff test exposures/sessions to their remedy under double-blind conditions.\(^{56}\) Cordance is an algorithmically derived measure of the ratio between relative and absolute alpha power.

However, the direction of the cordance finding changed over the course of time. Unpublished follow-up analyses revealed a shifting of cordance findings over the 6-month study, consistent with the evolution of divergent nonlinear electrophysiological changes in the therapeutically responsive patients as nonlinear dynamical complex systems. That is, Figure 6 shows that the exceptional responders diverged for cordance difference scores (mean treatment solution minus mean remedy-free solvent control sniff effects) from verum clinical nonresponders and placebo patients at all 3 time points. However, the direction of the difference scores in the verum responders transitioned over the 6 months of the study, from strongly negative to strongly positive.

Again, the data are suggestive of a biphasic pattern in which true verum differed from placebo effects over time. As in many other homeopathic studies, the direction of the initial finding did not replicate 3 or 6 months later. However, verum acting therapeutically

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**Figure 5** Oscillatory response of outcome measures in asthmatics (mean of individual patient means during morning [am] assessments) to therapeutically ineffective, homeopathically prepared dust mite remedy.\(^{50,122}\) PEF = Peak Expiratory Flow; VAS = Visual Analogue Scale Score. Reprinted with Permission from BMJ Publishing Group, Ltd.\(^{122}\)

**Figure 6** Divergence and shifts in quantitative electroencephalographic cordance magnitude and direction over time in treatment for excellent verum responders versus all others in study (on verum or placebo without excellent clinical response). Subjects were designated as excellent, intermediate, or poor responders as follows: excellent = top 1/3 of the sample (n = 62) for both changes in global health and reduction in tender point pain on examination; intermediate = top 1/3 for either global health OR pain, but not both; poor = bottom 2/3 of the sample for both global health and pain.\(^{123}\)
altered the overall dynamics of the response pattern over time at the level of the central nervous system in a way that therapeutically ineffective remedy and placebo did not. This study demonstrates an important methodological consideration based on systems biology and complex systems empirical research.\textsuperscript{51} That is, it is necessary to identify the real-world phenotype of interest (exceptionally good clinical responders to verum remedy, as defined by both global and local improvements in this case), and then look for multifactorial mediators and the evolution of emergent patterns of change over time that contribute to the eventual phenotypic expression.

The animal and other research literature on homeopathy contains additional evidence in support of a nonlinear complex systems interpretation. For example, as a crude example of sensitivity to initial conditions, Bertani et al\textsuperscript{57} used the same mixture of homeopathically prepared minerals at the same potency in a rodent model of carrageenan-induced paw edema. In the latter study, they varied only the time of administration of the remedy in 3 different groups of rats: 60 minutes before, during, or 30 minutes after the induction of the injury. The direction of the results depended on the timing of administration of the remedy. In fact, the results ended up completely opposite in the before-injury (increased approximately 15\% over controls) and after-injury (decreased approximately 14\% over controls) groups. The simultaneous injury/remedy timing led to only a small increase in edema over control (approximately 4\%). The implications of the findings are that the responses to homeopathic remedies are nonlinear. The direction of responses to homeopathic remedies is dependent upon the state of the host as a system at the time of intervention and time point of observation.

As the interventions of homeopathy, TCM, and Ayurveda target the person level of organization, complex systems theory predicts that outcomes will not be consistently reproducible between studies with the same designs and similar procedures (procedures can never be absolutely identical because of variations in multiple interactive factors, including participants, their social contacts [family, friends, business associates], research personnel, time of year, environmental fluctuations, ambient laboratory conditions). Clinically, homeopaths themselves often report that the same remedy at the same potency in the same individual patient at 2 different points in time has vastly different effects (eg, ranging from none to major improvements to minor improvements or even worsening).

In summary, nonlinear dynamical complex system theory predicts the situation documented throughout the homeopathic research and clinical literature as well as in acupuncture. In view of the fact that effectiveness studies capture the more holistic, real-world contextual conditions of treatment far better than RCTs, observational trials, especially well-designed observational trials,\textsuperscript{58,59} would merit greater weight than RCTs as evidence of presence or absence of therapeutic benefit for a given whole system of CAM. Observational data overwhelmingly demonstrate favorable outcomes for homeopathic treatment\textsuperscript{60-63} in contrast with the much more mixed results for RCTs and controlled basic science studies that focus on parts of the whole system. Cohort- or case-controlled observational studies that document both global and local outcomes and include assessments of dynamics are most likely to provide optimal tests of homeopathy.

Furthermore, acupuncture researchers using mixed qualitative and quantitative methods have demonstrated the phenomenon of emergence. That is, patients report both global and multidimensional changes over the course of treatment.\textsuperscript{64-69} They can even forget to mention the original chief complaint because of their enthusiastic description of multiple other changes that they had not originally anticipated. Attempts at individualization of symptoms for prospective designs have been unable to capture emergence during treatment. For example, Paterson’s group in the United Kingdom developed and validated a patient-centered outcome scale, the MYMOP.\textsuperscript{70} This scale asks patients to name and rate their respective leading symptoms in their own words. Although the MYMOP is sensitive to change in the original chief complaint compared with baseline, open-ended interviews with patients revealed that the MYMOP completely missed a wide range of additional global and local changes, that is, emergents, that the patients experienced in the course of the acupuncture treatment. Efforts to modify the MYMOP to capture emergent changes are under way.\textsuperscript{65,67,71}

Skeptics will undoubtedly assert that the above argument is only an excuse for the failures of replication in homeopathic or acupuncture clinical RCT and basic science research. Perhaps it is. On the other hand, within Jonas’s evidence house construct,\textsuperscript{72,73} the complex systems argument opens the door to a more inclusive perspective in which both holistic and reductionistic models can belong. That is, for a given therapy, depending on its clinical target in terms of level of scale (person or part), theory-driven testable hypotheses and research using the best-matched methods for the intervention are appropriate and feasible.

With complex systems models, it is possible to examine outcomes with far greater face and construct validity than otherwise possible from a reductionistic or even patient-centered/humanistic point of view. In other words, measuring endpoint change in a
bio-marker, a chief complaint rating, or even quality-of-life score in isolation cannot capture the holistic (global well-being, energy, organism-wide multiple symptom pattern) and dynamical patterns of nonlinear changes that the interaction of a complex system of CAM, the complex system of a person as a living organism, and the environmental context (the person’s biological, chemical, physical, and social world) would be expected to generate in the course of treatment.

Rather, evaluating patterns of systemwide changes over time series of repeated measure data (within both multiple variables by themselves, at various levels of scale, and across the interrelationships between multiple variables within the person overall), assessing emergent changes not present at baseline, and studying multiple mediating factors contributing to markedly good versus poor outcomes in individual patients in large observational studies have much greater potential than reductionistic designs to advance whole systems CAM research. Naturalistic studies based on well-established qualitative methods also have the capacity to provide fuller pictures of patient outcomes over time than do RCTs and related reductionistic approaches.74

**Theory-Driven Study Design Strategies in a Complex Systems Model**

Finally, another strategy within the nonlinear dynamical complex systems model is to work out the multiple parameters of a given experimental protocol as a system, in advance of performing the actual controlled study. Some experimental systems will generate more repeatable results than others. For instance, Frei et al published a series of studies on children with attention deficit disorder treated with individualized homeopathic remedies in LM (1 part per 1,000) potencies. First, they did open-label treatment to determine the length of time needed for most of the children to show improvement on homeopathy, if it occurred.75 They also defined “improvement” as at least a 50% reduction in behavioral disturbance ratings by the parents. As is typical in clinical cases, the point in time at which this reduction occurred varied from patient to patient. Furthermore, they refined the clinical diagnostic procedures for determining the correct prescription.76 for example, from 21% to 54% for the first remedy chosen and from 68% to 84% for the fifth remedy chosen. Methodologically, this fundamental research is long overdue in the clinical field of homeopathy,77 as homeopaths often miss the correct remedy initially, thereby rendering an unknown subset of the verum remedies in the “active” group therapeutically inactive within a typical short-term double-blind RCT.

Notably, the study design assessed the amount of time from the start of treatment to threshold improvement, rather than averaging improvement scores at a fixed time point. This tactic permitted the investigators to capture the individualized time course of change (thereby avoiding the problems with patients being out of phase with one another in their change patterns and cancelling the ability to document any net change—see above). The investigators also tested for the possibility of a washout period that might enable a crossover design for the LM potencies.

For their actual double-blind RCT, the Frei group chose to enroll only patients who had already shown not only good clinical responsivity to the remedy in LM potencies but also a susceptibility to relapse with a 3-week washout period off remedy. Their eventual modified RCT study showed that homeopathy was superior to placebo.78 A separate study by another research group who launched immediately into a conventionally designed double-blind pilot RCT without pretesting the parameters of their experimental protocol or the treatment responsivity of their subjects failed to show a difference between verum individualized treatment and placebo.79 Given the clinical realities that homeopaths often do not find the “right” or most appropriate remedy for the case in their first choice and that the time course of responses varies individually, any RCT study that has not pretested the study subjects’ actual capacity for responsivity to the remedy and documented the individualized time course of follow-up runs the risk of Type II error. The methodological strategy used by Frei avoided potential confounds that homeopathic researchers otherwise have encountered.80 In addition to disease-related static endpoints, measurement of nonlinear dynamical patterns of behavior and physiology, such as documented in previous human behavior studies,28,31,81 would also lower the risk of Type II error. These ideas are not the only possible approach but point the way toward a hybrid methodology in which valid RCT designs may be possible for whole systems of CAM, but only when the systems issues have been accommodated (and vice versa).

To approach the issue of predefining the experimental system from a nonlinear dynamical perspective, the systems model predicts that an experimental protocol (itself a system) whose dynamics are more stable (less chaotic) will generate results that are more reproducible than will a less stable experimental system. It is possible to characterize and quantify the dynamics of some systems in terms of their sensitivity to small differences in initial conditions, using a parameter known as the largest Lyapunov exponent. A testable hypothesis is that an experimental system whose dynamics are less sensitive to initial conditions...
(eg, with a more negative Lyapunov exponent) should generate more repeatable results from trial to trial or study to study than a different experimental system whose dynamics are more sensitive to initial conditions (eg, with a more positive Lyapunov exponent).

Skeptics might argue that the need to define the experimental system with so much pretesting precludes the ability to answer the broad public health question that a typical RCT answers—as to whether or not homeopathy is a desirable treatment for a particular conventional medical diagnosis in general. In this criticism, the skeptics would be correct. Awareness of these issues, however, could lead to asking the clinically relevant, patient-centered question of individualization—that is, how can researchers identify and triage people for whom a given system of care will probably be very helpful so that these individuals receive the intervention sooner rather than later or not at all? Conversely, how can people for whom the intervention will probably not be helpful be triaged elsewhere with less loss of time and money, as well as lower risk?

**Summary and Implications**

The methodological implications of the complex systems perspective are that well-designed observational trials, which permit assessment of the patient in his or her full, real-world environmental context, are the type of clinical research that better matches the holistic worldview of complex systems theory than do RCTs. In the conventional health field, it has been behavioral rather than biomedical scientists who have already recognized the need for multilevel or multiscale analysis of outcomes. Inclusion of patient-provider relationship measures, quality-of-life measures, individualized symptom variables, or even global outcomes, when used in isolation from the overall systemic patterns of outcomes in time and space, is part of patient-centered research. However, patient-centered selection of variables does not by itself move whole systems of CAM research studies into a complex systems and network theory–driven model.

Appropriate outcome measures will be those capturing both global changes and patterns of multiple local changes across the person in terms of diseased and healthy network interactions and system dynamics. Plotting changes in attractor patterns in phase space using sets of nonlinear differential equations, computing descriptive measures of shifts in systemic complexity, and adapting other types of pattern analysis from systems biology will provide a starting place for assessing quantitative outcomes within a complexity science research model.

It will also be important to compare the ability of nonlinear methods with conventional multivariate statistical techniques such as latent variable/path analysis modeling and cluster analysis to describe the processes and outcomes of whole systems of CAM. Moreover, as several leading CAM researchers have commented, qualitative methods also provide essential tools with which to characterize the scope and nuances of changes at the whole person level of organization.

What whole systems of CAM add to the discussion conceptually is a focus on a higher order level of scale just above that of biological systems, that is, the person as an indivisible network-system, in the context of his or her biopsychosocial environment. The clinical interventions of CAM offer practical, currently available tools for modulating the presumptive integrated controllers of the body’s complex networks, long before conventional medicine will have the personalized drugs that it now seeks to develop through systems biology research. As such, the synthesis of whole systems of CAM and systems biology technologies may be a bridge leading to truly integrative medical research.

A skeptic of CAM could argue that invoking complexity theory is merely providing a sophisticated “excuse” for why CAM therapies sometimes do not perform as well as drugs or better than placebo in randomized placebo-controlled double-blind efficacy trials with targeted endpoints. On the contrary, the scientific evidence is that living organisms are complex nonlinear dynamical systems by nature. Consequently, it is logical to predict that conventional drugs, which are developed to perform well in reductionistic causal systems, might not perform as well as whole systems of CAM in effectiveness trials.

Effectiveness designs involve the real-world complexity of indirect causality and interactions between multiple interventions, multiple providers, the patient and his or her biopsychosocial environment, especially in terms of the full patterns of multidimensional outcomes and nonlinear dynamical processes that occur in a person as a whole system over time. The clinical literature is already providing initial evidence in support of the latter perspective. Data indicate greater safety (“side effects” are part of the complete picture of outcomes from a complex systems perspective) as well as sometimes shorter acute illnesses and lower costs for certain CAM therapies, including homeopathy, compared with conventional drugs in noncancer conditions.

Finally, it is beyond the scope of this article to discuss the macro-entanglement model for CAM clinical research, which has received extensive coverage elsewhere. Nonetheless, it is important to acknowledge that entanglement is an emergent phenomenon.
in the behavior of closed systems in quantum mechanics. However, it is possible, but not essential, to invoke macro-entanglement concepts to apply the complex systems thinking outlined in the present article. Thus, although entanglement may be a valid and at least indirectly testable hypothesis to explain the findings and methodological limitations of some RCT designs, the current argument can stand on its own as a direction for new research programs more compatible than typical RCT designs with the theory and clinical practice of whole systems of CAM.

Conclusions

Despite the political pressures to evaluate CAM through mainstream reductionistic medical science, complex systems/network theories offer a more relevant epistemological framework for scientifically based research on whole systems of CAM than do mainstream reductionistic medical models (Table 2). At the same time, complex systems and network science are a potential meeting place for CAM and conventional medicine researchers to find common ground. Cancer research is the mainstream field where the 2 worlds converge conceptually. Challenging and ground-breaking advances in understanding the nature of disease and developing expanded tools for health care in chronic illness such as cancer could result. In the least, complex systems and network science offers the possibility of evaluating whole systems of CAM where they claim to have their strong suit, that is, improving the person’s function as a whole by optimizing the ability of the parts to play their healthiest roles possible in relationship to one another. Depending on the nature of the question that needs to be answered, one or the other or both models for research (complexity or reductionism) may be appropriate.

In conclusion, Bell et al previously proposed that homeopathy is the therapeutics for the dynamics of the person as a whole complex system. Hyland et al further suggested that homeopathy changes phenotypic expression by modulating the controller hubs of the body as a network. The complexity/network model, taken together with the body of empirical literature on whole systems of CAM, especially homeopathy and acupuncture, points the way to a potential productive resolution of the current impasse between CAM and conventional researchers on how to move forward toward the “truth” about the nature of the basic and preclinical effects and the clinical effectiveness of whole systems of CAM.

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References


