2012

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Iris R. Bell
University of Arizona

Mary Koithan
University of Arizona

David Pincus
Chapman University, pincus@chapman.edu

Recommended Citation

Bell, Iris R., Mary Koithan, and David Pincus. (2012). "Methodological implications of nonlinear dynamical systems models for whole systems of complementary and alternative medicine." *Forschende Komplementarmedizin 19*(1), 15-21. doi: 10.1159/000335183

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Comments
This is a pre-copy-editing, author-produced PDF of an article accepted for publication in *Forschende Komplementärmedizin / Research in Complementary Medicine*, volume 19, supplement 1, in 2012 following peer review. The definitive publisher-authenticated version is available online at DOI:10.1159/000335183.

For submission to: *Forschende Komplementarmedizin*
(updated 06/15/11)

Running Head: Methodological Implications of NDS for CAM

Keywords: complementary and alternative medicine, complex adaptive systems, world hypotheses, nonlinear dynamical systems, attractor, time-series analysis, well-being, healing

Methodological Implications of Nonlinear Dynamical Systems Models for Whole Systems of Complementary and Alternative Medicine

Iris R. Bell, MD PhD,[1-6] Mary Koithan, RN PhD,[1,2] and David Pincus, PhD[7]

For reprints and all correspondence: Dr. Iris Bell, Dept. of Family and Community Medicine, The University of Arizona College of Medicine, 1450 N. Cherry Ave., Tucson, AZ 85719-5052, USA. Tel. 520-626-4188; FAX 520-626-2030; Email: ibell@email.arizona.edu.

From: The Department of Family and Community Medicine,[1,2] Psychiatry,[3] Psychology,[4] Medicine (Integrative Medicine),[5] and Public Health,[6] and the College of Nursing,[2] The University of Arizona, Tucson, AZ; and the Crean School of Health and Life Sciences, Chapman University, Orange, CA.

Funding: This work was supported in part by grant funding from the Lotte and John Hecht Foundation; the Samueli Institute; and the National Center for Complementary and Alternative Medicine/National Institutes of Health grants R13 AT005189-01, K24 AT 000057, T32 AT01287.

Conflict of Interest: Financial Disclosure -- Dr. Bell is a consultant to Standard Homeopathic/Hyland's Inc., Los Angeles, CA.

Acknowledgments: The authors thank Stephen J. Guastello, PhD, for his helpful comments on earlier versions of this manuscript.

Abstract

This paper focuses on the world view hypotheses and research design approaches from nonlinear dynamical complex systems (NDS) science that can inform future studies of whole systems of complementary and alternative medicine (WS-CAM), e.g., Ayurveda, traditional Chinese medicine, and homeopathy. The world view hypotheses that underlie NDS and WS-CAM (contextual, organismic, interactive-integrative (Pepper, 1942) overlap with each other, but differ fundamentally from those of biomedicine (formistic, mechanistic). Differing views on the nature of causality itself lead to different types of study designs. Biomedical efficacy studies assume a simple direct mechanistic cause-effect relationship between a specific intervention and a specific bodily outcome, an assumption less relevant to WS-CAM outcomes. WS-CAM practitioners do not necessarily treat a symptom directly. Rather, they intervene to modulate an intrinsic central imbalance of the person as a system and to create a more favorable environmental context for the emergence of health, e.g., with dietary changes compatible with the constitutional type. The rebalancing of the system thereby fosters the emergence of indirect, diffuse, complex effects throughout the person and the person's interactions with his/her environment. NDS theory-driven study designs thus have the potential for greater external and model validity than biomedically-driven efficacy studies (e.g., clinical trials) for evaluating the indirect effects of WS-CAM practices. Potential applications of NDS analytic techniques to WS-CAM include characterizing different constitutional types and documenting the evolution and dynamics of whole person healing and well-being over time. Furthermore, NDS provides models and methods for examining interactions across organizational scales, from genomic/proteomic/metabolomic networks to individuals and social groups.

Introduction

Our previous paper (see in this issue) proposes that nonlinear dynamical systems (NDS) and offers a holistic conceptual approach for developing theory-driven research programs on whole systems of complementary and alternative medicine (WS-CAM, e.g, traditional Chinese medicine, classical homeopathy, Ayurveda). NDS models offer not only theory, but also methods for improving the external validity and model validity (1) of WS-CAM study designs. A major problem for WS-CAM research to date has been the focus on designing randomized controlled trials for efficacy with increasingly better internal validity while ignoring or compromising the external and model validity of many studies (2). Thus, CAM practitioners repeatedly object to negative efficacy studies, citing their lack of relevance to the holistic practice theory of the WS-CAM and to real-world practice by properly trained and experienced providers. Not uncommonly, even when efficacy study results are negative or mixed, observational studies tell a different story, typically more favorable to the WS-CAM. Why?

For external and model validity, WS-CAM practitioners would need to (a) use indivisible, interdependent packages of care rather than elements of a package; (b) ensure that practitioners involved in studies are well-trained and highly experienced; and (c) evaluate complex, emergent patient-wide outcomes in each case, rather than the isolated, subsystem-specific effects of conventional drugs. The major features of WS-CAM, coordinated indivisible packages of care and emergent patient-wide outcomes, are fundamentally incompatible with the assumptions of conventional biomedical research methods.

These methods including: random clinical trials (RCT's), dismantling studies, and traditional regression models, each are predicated upon the assumptions of the general linear model (GLM). As such, they are well suited to phenomena that meet a set of linear and reductionist assumptions: (1) Cause-effect relationships are proportional; (2) Causes are independent with additive effects; and (3) error variance is independently and identically distributed (IID). Nonlinear research models, by contrast, allow phenomena to have multiple and complex causes, with error components containing varying degrees of determinism – such as momentum effects and systemic memory (3). Causal processes in biopsychosocial dynamics appear to be irreducible and non-modular (i.e., the whole is greater than the sum of the parts), with the emergence and spread of health and illness typically over-determined - caused by more than sufficient causal processes involving a pull toward global coherence (4).

In addition to faulty assumptions regarding cause and effect, the GLM is a poor fit for modeling most WS-CAM phenomena because the "error" variance in patient responses to WS-CAM interventions should not be IID. Indeed, a key factor in the roughly 2:1 advantage of nonlinear models over their linear alternatives in studies where such comparisons are made (5) lies in the ability of nonlinear models to account for situations where increases or decreases in variance over time are deterministic rather than random. Increasing flexibility in some health related outcome is a simple example of such situations. Indeed, changes in the levels and types of noise produced by a physiological, psychological, or social system is a key point of interest, rather than a statistical nuisance to be minimized to allow for a better canvas upon which to view simple differences in patient means (6). Some social scientists, recognizing that real world clinical practice is complex and adaptive over time, are grappling to find better designs (7-9), but these insights are rare in biomedical or WS-CAM research.

In WS-CAM, unlike conventional drug treatment and research, the outcomes themselves are not singular, simple, specific, separate from one another, or easily predefined. Rather, WS-CAM outcomes are emergent, multiple, complex, interactive with one another and with the environment, interdependent, and hard to predict (10). Thus, the mainstream methodology of dividing the patient into a list of subsystems with a priori identifiable endpoints, even if seemingly lengthy and "comprehensive," lacks validity for appropriately evaluating the complex and fluid outcomes of WS-CAM interventions in individual patients.

These methodological issues stem from even more fundamental differences in the world views that underlie biomedical versus WS-CAM practice theories. Pepper (11) originally described four levels of world view hypotheses that range from simple to complex (Table 1). Biomedicine bases its assumptions and its questions for research on the simplest levels of world views, i.e., formistic, which views all structures and functions as existing as separate categories (e.g. your lab test value is either normal or abnormal; you either have XYZ disease or not), and mechanistic, which assumes that all effects have identifiable causes that precede them (e.g., a specific bacterium has "caused" symptoms of infection).

In contrast, WS-CAM utilize at least two higher level world views, i.e., contextual and organismic, both of which are map better onto the complexity of chronic diseases and the nature of living systems. Chronic diseases are inherently multi-factorial (e.g, genes and early life stressors, as well as current nutritional status, food and drug intolerances, environmental pollutant exposures, biological age, social environment, daily hassles and uplifts, coping skill style, and more all contribute to the person's emergent condition), but none alone is sufficient as a sole explanation. Contextual world views assume that natural phenomena always depend on the broader context in which they exist. Each patient is embedded within and interactive with his/her environment. Furthermore, balance among contextual constraints allow behavior to reorganize flexibly to produce different patterns (12). For example, flexible constraint between the heart and its nesting context (i.e., degree of exertion required) allows a healthy heart to adapt in a fluid manner to changing conditions, while a diseased heart under equivalent conditions might arrest (13).

Beyond the contextual world view is Pepper's organismic world view. The essence of the organismic world view is that the whole is more than the sum of the parts; it is not possible to predict the emergent properties of the whole by dissecting it into its parts and studying those separately, which is equivalent to the assumptions of complexity theory and emergence within NDS (14). Not surprisingly, among patients with chronic pain, those who endorse a formistic world view are significantly less likely to report CAM utilization (15).

The world views of WS-CAM start at contextual and organismic levels and thus map better onto the assumptions of NDS methods than biomedicine and the general linear model. Questions that NDS study designs on WS-CAM can best address involve (a Including patient-provider interactions within a biopsychosocial framework (cf. Pincus, 2011, this issue); (b) observing shifts to global emergent patterns of patient behaviorover the course of WS-CAM treatment (successful or unsuccessful); (c) understanding the processes of stuckness (disease) and unstuckness using indices of flexibility and rigidity from NDS (10, 16-17).

Exemplars from NDS Research in Behavioral Sciences Relevant to WS-CAM

Dynamics involve continuing change. NDS methods allow scientists to study the processes of change in a complex system. However, it is misleading to assume that the "change" is simply movement from one static stable state (sick) to another (well). Even a person stuck in the rut of disease is a dynamical system in continuous motion. However, the pattern of the recurring motion, i.e., the dynamical attractor pattern, from which the diseased state emerges, is very constrained and differs from that of a healthy state, whose pattern is more flexible (13, 19-21)

Examples from NDS research illustrate these points. For instance, Mandell and Selz (22-24) computed the dynamical properties of the different behavioral styles with which persons with borderline personality disorder versus obsessive-compulsive disorder performed the same computerized drawing task in the laboratory. The task performance patterns of the more impulsive and affectively unstable borderlines translated in NDS analysis into greater global entropy and smaller local entropies. In contrast, the obsessive-compulsives exhibited smaller values of global entropy and larger local entropy. The dynamics of the task performance were a microcosmic manifestation of each person's macroscopic behavioral pattern as a living system, i.e., a motif (25), in the larger world around them. Measuring one key parameter within a complex system to characterize the holistic qualities of the broader system is a common strategy in NDS, which has been replicated successfully in various contexts (12). For WS-CAM, an NDS-theory driven study could test the hypothesis that behavioral dynamics produced from analogue tasks such (e.g., drawing, finger tapping, articulation in speech, and problem-solving) can differentiate people with variations of specific constitutional types, e.g., in TCM (root disturbance), homeopathy (constitutional remedy), or Ayurveda (dominant dosha).

NDS methods can also differentiate unique dynamics of sick versus healthy persons, as well as old versus young individuals. For example, Goldberger et al (26-31) have done multiple studies showing loss of complexity in the cardiac variability of heart disease patients versus normals and of older versus younger persons across different time scales. Different types of cardiac conditions are associated with different dynamical patterns. Woyshville et al (32) showed that Alzheimer's disease patients have less neurophysiological complexity in terms of lower fractal dimension of their electroencephalographic patterns compared with normal controls. Affective disorder patients also exhibit less mood complexity, i.e., more constrained behaviors, in the dynamics of their daily mood ratings with lower fractal dimension 33). Depressed or even bipolar patients are stuck in a more rigid dynamic of mood changes day to day, less flexible, adaptable or resilient to events, than are affectively normal persons.

Many individuals use WS-CAM to optimize health and well-being, not just to treat sickness and disease. The goal is achieve well-being beyond the absence of disease, as in the World Health Organization's definition of health (34). Can NDS methods assist in differentiating varying degrees of well-being, from languishing to "normal" to flourishing? Losada et al (35-37) studied three different small groups as complex systems, i.e., business teams with previously documented real-world differences in their performance outcomes, i.e., high (healthy), intermediate or mixed (average), low (unhealthy) as measured by productivity, customer satisfaction, profitability, and co-worker evaluations. Here the question was the degree of functionality, cf. well-being, of each team as a social system with interdependent relationships and interactions. The researchers asked the teams to work together as they usually would to generate a business plan for the upcoming year. Independent trained judges observed and coded the behaviors of the team members, moment-to-moment for mutual influences on one another, such as positivity versus negativity, inquiry, and advocacy for their own or others' ideas. The investigators used a set of differential equations to model the features of the time series and compared the goodness of fit between the mathematical model and the empirical data on the dynamics of these behavioral patterns and processes of each group.

The different business teams showed striking differences in their dynamics. The high performing team showed flexible and adaptive complex behaviors toward one another, with a preponderance of positivity over negativity (cf. the butterfly-like complexor pattern seen in Figure 1a (35-37). The poor performing group, languishers, exhibited much more restricted, rigid, and negative range of interpersonal behavioral dynamics, more like limit cycle attractors (Figure 1b). The intermediate performing group showed dynamics between the high and low performing teams.

In the Losada research, the mathematical models for conditions under which systems manifested well-being revealed that ratios of positive to negative (P/N) system behaviors of at least 2.9:1 were the cut-off for bifurcation of the system dynamics to occur. For a P/N ratio between 2.9 and 11.6, people and groups as complex living systems exhibited the healthier, optimally complex dynamics of human flourishing in the short-term and greater objectively-measured success in the long-term. On the other hand, positivity-negativity ratios below 2.9 correlated with more dysfunctional, rigid dynamics and poorer outcomes. This ratio is common in various human flourishing context, for example in marital interactions where a 5:1 of positive to negative interaction has provided a useful cutoff in predicting stable from unstable marriages (cite Gottman). in marital interactions

We posit that the dynamics of human flourishing are key to studying the positive dimensions of intra-individual clinical outcomes, including positive life-altering transformative changes, reported in a subset of patients treated with various WS-CAM (38-41). Because of the NDS-based hypothesis that the patient will express his/her dynamics across the many and varied contexts of their daily lives, it would be possible to adapt a variety of NDS study designs for WS-CAM research. A Mandell and Selz type of design (22) could look at the flexibility of dynamics at the individual level of scale. A Losada-type design and methods (35, 37) could examine the health of the person's dynamics, i.e., flexibility, positivity versus negativity, and resilience, in interaction with their usual social group such as a spouse/significant other, family, or work group.

Hollenstein and colleagues (cf. Howerter et al., 2011, this issue) have shown the feasibility of documenting the dynamics of behavioral improvement with successful treatment intervention in individuals and in family systems (20, 42-44). What is relevant for WS-CAM research is that regardless of the nature of the intervention (it could be a package of coordinated TCM therapies, rather than family therapy), the same types of NDS methods could apply to study changes in the dynamics of the person over the course of WS-CAM treatment. The data points are the moment to moment change in the state of the system's dynamics under some sort of environmental challenge or stressor. Investigators can sample the system dynamics at baseline and multiple times over the course of treatment.

Anecdotal case reports as well as interviews from systematic qualitative studies on WS-CAM suggest the conclusion that the patient initially consults the practitioner for help with a specific chief complaint, but later realizes that a number of things in addition to the chief complaint changed during the treatment (38, 45-48). These types of changes might include adopting everyday healthier behaviors, improving in sense of well-being, spiritual connectedness and sense of purpose, gaining perspective on and taking action to change positive and negative relationship patterns, and experiencing major improvements in other physical or emotional symptoms (10). Such outcomes strongly suggest that treatment effects are manifestations of a complex system in action involving cascades of indirect over time rather than simple direct effects.

The underlying hypothesis for NDS-driven research on WS-CAM is that the intervention packages constitute a positive "force" interacting with the person as a complex adaptive system. The multidimensional changes reflect the various indirect effects in space (i.e., other parts of the body or other behaviors, including the individual's interpersonal behaviors) and time (the evolution and persistence of improvements after the treatment ends). It is also possible to use a defined negative stressor, such as a public speaking task, treadmill exercise, or interaction with another person (familiar or unfamiliar) as the “force” to perturb the broader system(s), to evaluate the flexibility, adaptability, and resilience before, during, and after WS-CAM treatment. Methods from NDS research provide some innovative ways to capture evidence of and to characterize such changes (49), typically through the use of time-series analyses to characterize temporal complexity, recurrence, and structure. Time series data collection tools for NDS research in WS-CAM can include continuous computerized task performance recordings (22); videotaped behaviors during interpersonal interactions (20) with WS-CAM providers, family members, business associates, or strangers; ambulatory, home, and laboratory physiological monitoring (50-54) of actigraphic motor activity levels, heart rate variability, blood pressure, photoplethysmography, electrodermal responses, and/or respiration patterns; frequent daily ratings of overall wellbeing (54) or mood (33); and activation patterns of gene arrays (55). Technology already allows ambulatory field studies of interpersonal conversations (56-59) and of physiological functioning (54) while the individual pursues his/her real world everyday life. In the end, the important outcomes for patients (and providers) with regard to WS-CAM outcomes are not only improved laboratory tests, better quality of life ratings on questionnaires, and less health care utilization/costs, but also real-world quality of life in the person’s everyday dynamics of living. The methods and the data collection tools currently available for NDS/complexity theory-driven research have laid a foundation for undertaking these types of studies on WS-CAM.

Conclusions

NDS science is not limited to studies at the level of scale of the patient as a living organism. Rather, NDS can examine a complex system at any level of scale, from gene and biochemical networks (see Abu-Asab and Amri, 2011; this issue) to cells to physiological systems, to individual persons, to social systems. NDS methods, while no panacea for all of the methodological limitations in current WS-CAM research, offer two significant advantages. That is, NDS study designs allow the intervention to stay intact and the patient (or whatever complex system at a given level of scale is under study) to exhibit emergent, dynamic outcomes as a whole, indivisible complex adaptive system in environmental context. The capacity to capture real-world dynamics and to accommodate the indirect causality inherent in WS-CAM theories and practices is a step forward toward WS-CAM studies with greater external and model validity.

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