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Testing the Nanoparticle-Allostatic Cross Adaptation-Sensitization Model for Homeopathic Remedy Effects

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Abstract

Key concepts of the Nanoparticle-Allostatic Cross-Adaptation-Sensitization (NPCAS) Model for the action of homeopathic remedies in living systems include source nanoparticles as low level environmental stressors, heterotypic hormesis, cross-adaptation, allostasis (stress response network), time-dependent sensitization with endogenous amplification and bidirectional change, and self-organizing complex adaptive systems.

The model accommodates the requirement for measurable physical agents in the remedy (source nanoparticles and/or source adsorbed to silica nanoparticles). Hormetic adaptive responses in the organism, triggered by nanoparticles; bipolar, metaplastic change, dependent on the history of the organism. Clinical matching of the patient's symptom picture, including modalities, to the symptom pattern that the source material can cause (cross-adaptation and cross-sensitization). Evidence for nanoparticle-related quantum macro-entanglement in homeopathic pathogenetic trials.

This paper examines research implications of the model, discussing the following hypotheses: Variability in nanoparticle size, morphology, and aggregation affects remedy properties and reproducibility of findings. Homeopathic remedies modulate adaptive allostatic responses, with multiple dynamic short- and long-term effects. Simillimum remedy nanoparticles, as novel mild stressors corresponding to the organism's dysfunction initiate time-dependent cross-sensitization, reversing the direction of dysfunctional reactivity to environmental stressors.

The NPCAS model suggests a way forward for systematic research on homeopathy. The central proposition is that homeopathic treatment is a form of nanomedicine acting by modulation of

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Supplementary References

Supplementary references numbered 100–278 associated with this article can be found in the online version.

endogenous adaptation and metaplastic amplification processes in the organism to enhance long-term systemic resilience and health.

Keywords

nanoparticle; homeopathy; allostasis; time-dependent sensitization; metaplasticity; crosssensitization; research design; complex adaptive systems; physiological stress response

Introduction

Bell and Koithan¹ have proposed the Nanoparticle-Allostatic Cross-Adaptation (hormesis)-Sensitization (NPCAS) Model for the action of homeopathic remedies in living systems. (See table 1 for definitions of some of the concepts referred to in this paper). The model makes three assumptions, derived from extensive literature research:

- A. Human beings are complex adaptive systems.²
- B. The allostatic stress response network of interconnected nervous, endocrine, immune, and metabolic pathways is the major hub within the organism that interfaces with the environment to maintain homeostasis
- C. Progressive allostatic overload of the adaptive capacity of the organism by higher intensity stressors leads over time to the emergence of disease in a unique complex, nonlinear, dynamical pattern of maladaptive function, determined by genetic and epigenetic factors.^{3–6}

The current disease state of the system reflects previous metaplastic priming^{7–9} by cumulative effects of higher intensity stressors, with persistent changes in allostatic function.³ Low dose homeopathic remedy nanoparticles act on the disease-primed system⁷ as novel physiological stressors reflecting its dysfunction. The result is to elicit amplified, cross-adapted oscillatory changes in the opposite direction^{10–12} to those caused by the disease. When the remedy is the simillimum for the individual patient, the process ultimately leads to healing across the person as a complex adaptive network, with greater systemic resilience to future stressors.

The NPCAS model is based on four main considerations:^{1,13}

1. Homeopathic remedies are considered as source nanoparticles,^{14–20} and/or remedy source-modified silica nanoparticles,^{15,19,20} not bulk form material drugs. Nanoparticles have altered physical, chemical, biological, optical, electrical, magnetic, and quantum properties that can differ substantially from the bulk forms of the same substance.^{21–24} Nanoparticles are by nature highly reactive and serve as enhanced drug and herb delivery vehicles which can reduce the amount of agent needed to achieve a given effect;^{21,22,25–27}
2. Remedy nanoparticles initiate a complex adaptive response in the allostatic network,^{3,4,28} with cascading effects that emerge across the entire self-organizing organism over time.²
3. The mediating processes for the remedy effects are physiological, not pharmacological. These processes include well-documented physiological phenomena involving bidirectional adaptive metaplasticity (plasticity modified by the history of prior activity)^{9,10} and plasticity.^{9,29–36} Mediating processes include, hormesis (low dose beneficial stimulation rather than inhibition of adaptive function),^{37–39} cross-adaptation (one stressor can initiate adaptive changes that

improve or worsen resilience to an entirely different type of stressor),^{40–46} and time-dependent sensitization (TDS)^{10,47–49} (progressive endogenous response amplification over time, including cross-sensitized oscillation in direction of responses at physiological limits);

4. The homeopathic simillimum medicine consists of nanoparticles²⁷ which act as *low level* stressors ultimately enhancing resilience to higher intensity homeostatic disruptors as a complex adaptive system at whole organism and local levels of organization.⁵⁰ The highly reactive characteristics of nanoparticles^{21,22} shift the already low hormetic dose-response curve even lower in terms of the dose needed to mobilize adaptive changes.^{27,51}

The endogenous adaptations include multiple, interacting shifts in central nervous system function,^{9,52,53} autonomic balance,⁵⁴ heat shock protein activation,^{55–57} cortisol release,^{58–65} inflammatory cytokine expression,^{66,67} and/or immune system mobilization.^{68–70} A homeopath might describe the patient as “never having been well since” an adverse life event.⁷¹ The resulting maladaptive allostatic pattern of dysfunction, not the receptors which merely mediate end-organ symptoms, is what the remedy nanoparticles address and reverse.

As a result, the system responds differently to subsequent low intensity, heterotypic stressors which reflect the dysfunction: the remedy nanoparticles. The process of homeopathic prescribing⁷¹ takes advantage of cross-adaptation between different types of stressors (post-conditioning heterotypic hormesis).^{41,72} In contrast, isopathic prescribing⁷³ involves low dose reversal of direction in manifestations of high dose toxicity from the same agent or stressor¹² (post-conditioning isotypic hormesis).^{55,57} Low dose homeopathic nanoparticles stimulate specific compensatory responses within the organism, reversing the direction of adaptations. In the central nervous system, for example, metaplastic synaptic changes, which can occur at subthreshold dose levels,⁷⁴ prime the system to reverse plastic changes that the neuronal synapses will later make in response to the next encounter with the same or a cross-adapted stimulus or stressor.⁷⁴

Although priming and cross-adaptive responses to low dose homeopathically-prepared remedies⁷⁵ and/or environmental nanoparticles^{76,77} also occur in isolated cell systems, the brain is a central controller hub, the coordinator of allostatic network regulation for the intact organism.⁷⁸ Mediators of inflammatory, endocrine, immune, and metabolic responses interact bidirectionally with the central nervous system and with one another to mount an overall homeostatic regulatory response to environmental stressors.^{3,48,49} Then, as homeostatic changes develop in the allostatic stress response network components,⁷⁹ the indirect effects within the larger system trigger an evolving series of changes in other interconnected systems and the whole organism.⁸⁰ Improved health and greater resilience are the outcomes.² The NPCAS model provides a testable theory for how homeopathic remedies act and leads to hypothesis-driven research. The results will support or refute the basic tenets, and/or suggest appropriate modifications of the model to accommodate the scientific data as it accumulates.

Figure 1 summarizes the allostatic model of disease and NPCAS model for homeopathic remedy actions. Notably, the homeopathic remedy mobilizes multiple components of the allostatic stress response network; it likely has little to no effect on conventional pharmacological receptors. Individual differences in coping styles and biological adaptation patterns contribute to the emergent dysfunctional symptom picture in disease and the capacity to improve under treatment with the simillimum remedy.

The purpose of the current paper is to explore the implications of the NPCAS model for a research program⁸¹ of basic and translational science on homeopathic practice theory and, ultimately, improve homeopathic clinical care. Rather than outline a long list of possible studies, we will focus on key methodological and design issues that the NPCAS model raises for future homeopathic research.¹³

Homeopathic remedies are source nanoparticles, not bulk material drugs

Hypothesis: Variability in nanoparticle size, morphology, and aggregation will affect remedy properties, effects and reproducibility of findings.

Background Findings on Nanoparticles

One of the challenges in both homeopathic practice and research has been difficulty in reproducing previous results.^{82,83} Skeptics argue that homeopathy is a placebo with no true biological effects. The NPCAS model suggests alternative hypotheses. Current data suggest that remedy effects are present on average and replicable across different laboratories – but not in every experiment or every laboratory.⁸⁴ How would variations in the remedy nanoparticles contribute to the reproducibility issue?

The nature of nanoparticles provides valuable clues to the answer.⁸⁵ Existing basic science data show that the ways in which homeopathic remedies are prepared (trituration, succussions, glass containers, dilution in ethanol-water fluids, manual transfers from one dilution step to the next) can lead to different nanoparticle sizes and shapes,^{14,19} and thus to different properties.^{21,86,87} These homeopathic procedures are crude manual methods for “top-down” mechanical attrition or grinding and microfluidization techniques used now in modern nanotechnology manufacturing processes.^{88,89} By their nature, top-down manufacturing methods are prone to generating variability in sizes, shapes and structural defects in the resultant nanoparticles.⁸⁵

For instance, Chikramane et al.¹⁴ found that the nanoparticles of the same metal remedy at the same potency manufactured by two different homeopathic manufacturers showed significant variation. Within batch variation was much less. Both manufacturers reportedly make their remedies by classical manual methods involving trituration and 10 succussions per dilution step. Nanotechnology studies have shown that plant mother tinctures can biosynthesize nanoparticles from silica,^{90,91} silver²⁰ or gold²⁵ chemical precursors. Different amounts of trituration (mechanical grinding) can generate different lactose nanostructures, themselves with variations in surface adsorptive capacity for remedy source materials.^{92–94} Data show that the resultant nanoparticles vary in sizes and biological effects as a function of the plant sources with which they were originally manufactured.^{20,95} Notably, Upadhyay and Nayak also observed variable sizes and shapes of nanostructures and silicon in three different homeopathic plant remedy potencies from 1C to 15C.¹⁹

In another study, Bhattacharyya et al.⁹⁶ reported that succussion in glass versus polypropylene vials, as well as three different methods of succussion (hand, vortexing, or sonication) produced measurably different fluorescence emission spectra findings on the same remedy (Gelsemium). Even when a homeopathic manufacturer uses glass vials, variations in the nanoparticles of silica, boron, and other materials released from the walls of containers from different glassware manufacturers during succussion would contribute more variability in experimental results.^{15,16,19,94,97,98} Different amounts of remedy source plants,²⁰ animal proteins,^{26,93,99} nosode DNA, and other metal nanoparticles can adsorb to the surfaces²² of the silica or polypropylene nanoparticles from containers, causing differences in remedy characteristics as a function of the source material and type of container, as well as dilution and succussion procedures.^{25,100–102} Nanosilica can also self-

assemble specific larger, “bottom up” nanostructures in solution over time, using DNA, proteins, cells or other crystals as templates,^{103,104} thereby adding even more variability to the final remedy. As in nanoparticle technology,^{98,105,106} the mere recency of preparation could alter particle dispersion, sizes, shapes, and surface adsorption capacity as well. These factors could each contribute to the variability in homeopathic remedy effects in both basic science and clinical studies.⁸²

Elia et al.¹⁰⁷ observed an aging effect in homeopathic remedies simply stored in small volume containers at room temperature. Older solutions of a given remedy release more heat in calorimetry than do younger solutions of the same material when exposed to changes in pH. The changes in physicochemical properties could occur via modifications in self-assembly and aggregation of remedy source and silica nanoparticles^{85,103,108} originally created in the succussion process and left to interact in small volume colloidal solutions. Smaller particles will form larger particles in solution over time in solution, i.e., Ostwald ripening.¹⁰⁸ Different size and shape nanoparticles have different physical chemistry and biological properties from each other and from their respective bulk forms.^{20–22,86}

Elia et al.’s findings included not only heat release, but also increases in electrical conductivity with pH changes compared to untreated solvent controls. The conductivity observations are another physical chemistry finding consistent with the presence of nanoparticles in remedy solutions.^{15,19,94,96} Nanosilica, for example, exhibits increased electrical conductivity with increases in temperature.¹⁰⁹ Dilute aqueous solutions appear to foster solute aggregation, including with nanoparticles.¹¹⁰ Together these data suggest that requiring more specificity in research reporting details of remedy preparation and storage could contribute to reducing inter-experimental variability in homeopathic studies.

In addition to the multiple factors affecting the nanostructure nature of remedies, the recipient cells or organisms will bring their own nonlinear dynamics into play interacting with any given remedy.^{111,112} That is, successive potencies of the same remedy produce nonlinear effects,¹¹³ i.e., in opposite directions or with markedly different magnitude (see Figure 2a for *Argentum Nitricum* effects on plant development¹¹⁴). The 25D (25X) potency produced effects smaller than those of the 24D and 26D potencies of the same remedy. By comparison, successively larger platinum nanoparticle cluster sizes produce nonlinear oscillation in the magnitude of their catalytic effects²¹ (Figure 2b). Similarly, Figure 3 shows a markedly nonlinear, sinusoidal dose-response curve for homeopathically-prepared formaldehyde on bacterial cell metabolism carried through successive serial dilutions and succussions from a 1C to the 20C potency.¹¹³ Even with improved standardization of glassware, ethanol concentration, and succussion procedures in remedy manufacturing, specific nanoparticles inherently acquire unique nonlinear properties. Different sizes and morphologies of the “same” material at nanoscale could lead to very different effects.^{20,21}

Nanoparticles of silica, gold, silver, carbon, polystyrene, and other substances can self-assemble into various larger nanostructures and adsorb proteins, DNA, drugs, and herbs onto their surfaces.^{22,99,103} Their properties, including biological effects, would then differ from those of the “same” material at the bulk form macro level,⁸⁶ if only in terms of improved bioavailability and enhanced effects at a lower dose.^{20,21,25,26,115,116} The extent of the effects themselves can vary simply as a function of particle size.⁸⁶ Such considerations could have major implications for clinical selection of remedy potencies and dosing frequencies.^{117,118} The potential interaction of nonlinear sinusoidal hormetic dose-response relationships¹¹³ with specific potencies (which would reflect specific differences in NP sizes, shapes, and properties) would be factors in the nature and direction of treatment effects (Figure 3).

If homeopathic remedies are complex colloidal solutions of nanoparticles of silica with remedy source material adsorbed,²⁶ in addition to nanoparticles of the remedy source material itself, the number and force of succussions (or vortexing/sonication time) could change the nature and properties of the resultant product.^{105,119} Compared with some other nanoparticle materials, nanosilica has a well-documented ability to mobilize the immune/inflammatory and stress response networks of the body.^{120,121} However, even those findings depend on the size and concentration of the silica NPs and the type of cells that they encounter.^{122–124} Such data highlight the potential value of evaluating remedies as nanostructures, guided by the large and growing research literature on the manufacturing parameters and testing protocols for biological effects of NPs at systemic and local cellular levels.^{125,126}

The original homeopathic literature varies in the number of manual succussions used, from one to 150 succussions after each dilution. Higher potencies by definition will have undergone more succussions, and higher remedy potencies can exert longer duration effects.¹²⁷ For comparison, simply increasing amounts of sonication of a carbon nanofluid generates smaller nanocluster sizes, but highly nonlinear variations in the physico-chemical properties of the colloidal solution.¹⁰⁵ A moderate duration of 40 minutes produced the maximal effects compared with either no time or maximal duration (1355 minutes) of sonication. However, in homeopathic remedy manufacturing, it is not just the number and force of succussions that might modify the characteristics of the resultant nanoparticles; the type of container (glass, polypropylene, other material), proportion of ethanol solvent, and the method of succussion (manual, mechanical arm, vortexing, sonication etc) and volume could all cause variation in the resultant nanoparticle sizes, shapes, quantities, and properties.⁹⁶

In general, remedies are manufactured at room temperature, but differences in ambient temperature, e.g., variable amounts of air conditioning or heating, could also subtly affect the resultant nanoparticle sizes and morphologies.¹¹⁹ Figure 4 illustrates how differences in the type of solvent used and sonication power can lead to variations in the resultant nanostructures at a given temperature. Different concentrations of ethanol, for instance, can alter the amount of surface area on the nanoparticles available to adsorb other materials in solution.^{119,128}

Any model for homeopathic remedy actions must account for as much as possible of the empirical data. Walach, Milgrom and others have reported puzzling clinical research evidence of suggesting quantum macro entanglement in homeopathic pathogenetic trials and double-blind placebo-controlled treatment trials.^{129–134} Although beyond the scope of this paper, the evidence for macroscopic entanglement between two spatially-separated quantum dots (colloidal semiconductor nanocrystals) of nanoparticles on a chip¹³⁵ is an intriguing example from the nanotechnology literature that may be relevant to macro-entanglement in homeopathy. Certain semiconductor (many of which are silica based) or metal nanoparticle crystallites can possess “pseudo-atom” quantum properties (quantum dots), in part because of their extremely large surface to volume ratio and the delocalized positioning of the source material electrons close to the surface of each particle.^{21,22} Thus, while demonstration of actual macro-entanglement properties of homeopathic remedy nanoparticles per se awaits direct empirical testing, the discovery of nanoparticles in remedies^{14,19} places homeopathy in a scientifically plausible and testable framework that could relate biological adaptive processes to their unique chemical properties as low level stressors,^{27,51} as well as quantum macro entanglement-like phenomena.^{129,136,137}

Research Implications for Remedy Nanoparticles

Taken together, nanoparticle research data suggest the need for systematic studies in homeopathy on the parameters of remedy manufacturing.⁹⁶ Nanotechnology assessment methods such as transmission electron microscopy, atomic force microscopy¹³⁸ and other NP characterization techniques such as dynamic light scattering or nanoparticle tracking analysis¹³⁹ permit detection and characterization of aggregates or even single nanoparticles. Factors requiring systematic re-examination as potentially critical variables in optimizing remedy nanoparticle preparation and product reliability¹⁴ would include:

- Materials in the container (specific type of glass or polymer)^{15,96,98}
- Size of container¹⁰⁷
- Method of dilution (Hahnemannian vs. Korsakovian)
- Method of succussion⁹⁶
- Number and force of triturations (mechanical grinding) and succussions (microfluidization)⁸⁸
- Concentration of ethanol in diluent^{119,128}
- Other physico-chemical parameters (pH, temperature)^{103,119}

The importance of nanoparticles (either of the source material or derived from the glassware etc) makes their size, shape, and properties potential criteria for developing additional quality assessment standards for homeopathic pharmacopoeias in the future.⁹⁶ For example, it might be useful to establish minimum/maximum quantities of source nanoparticles or tolerance specifications of particle morphology in finished products.¹⁴ Improving reporting standards¹⁴⁰ on methods of homeopathic remedy preparation might reduce and/or help account for some of the interexperimental variability observed in the field to date.⁸²

Moreover, directly comparing biological effects of specific homeopathically-prepared remedies with their more standardized commercial nanoparticle counterparts, e.g., silica, gold, silver, copper, platinum, or calcium phosphate, may also reveal valuable new insights into possible clinical strengths and limitations of both homeopathy and modern nanomedicines. Studies could explore features and effects of higher and lower concentrations of specific commercial nanoparticles, tested with and without additional dilutions and/or succussions versus homeopathic remedy and solvent controls.^{25,141} The research might help control for and limit variability in remedy nanoparticles by determining the relative contributions of remedy variability versus other factors, e.g., the state of the recipient organism,¹⁴² in reproducibility of effects in basic science and clinical studies. Studying of nanoparticles will facilitate additional research to determine the way(s) in which remedy nanoparticles alert the organism to the foreignness or threat that they pose.^{27,51} Available data indicate that the nanoparticles could convey such organism-specific information with chemical, electromagnetic, magnetic, structural, and/or even optical or quantum effects.^{21,102,135,143–146}

Remedy nanoparticles elicit a complex adaptive response in the allostatic network

Hypothesis: Homeopathic remedies modulate patterns of allostatic responses in the biological components of the stress response network (in vitro and in vivo), with measurable, multiple dynamical short- and long-term effects, based upon systemic priming by higher intensity stressors that have previously affected the organism.

In the NPCAS model, it is the stimulus quality of the salient remedy nanoparticles that disrupts the disease-related, dysfunctional allostatic setpoint and initiates the re-organizing effects on living systems. Silica nanoparticles generated during remedy manufacturing in glass would serve not only as remedy delivery vehicles, but also as non-specific biological amplifiers of the cellular stress response.^{13,26,120,121,147} A well matched homeopathic medicine mobilizes changes in the adaptive plasticity of the biological stress response system (allostasis).^{1,13} Individual symptoms recede as the conditions for their expression from interactions of the network of stress response mediators are eliminated by the hormetic compensatory responses.^{27,51} To initiate the healing process, the organism has to recognize a novel stimulus from the entry of low doses of the salient remedy nanoparticles into the system.¹ The correct remedy would need to cross-adapt with the cumulative maladaptations that the organism has accumulated in its failed attempts to restore homeostasis after disruptions from previous stressors. The reversal of direction from disease towards health stems from the ability of low doses of nanoparticles to initiate hormesis, i.e., compensatory adaptive changes prepare the organism to better resist the pre-established or future adverse effects of the same or cross-adapted stressors.

The well-documented, albeit complex, process of metaplasticity⁹ offers a neurophysiological basis for learning and memory, including the bidirectionality of future responsivity to a stressor. In addition to short-term adaptive plasticity changes, a stimulus also initiates metaplasticity. Metaplastic changes prime synapses to alter their subsequent plasticity. Metaplastic changes persist long after the original stimulus has ended.¹⁴⁸ After the priming event, the arrival of the next stimulus (including low doses of simillimum remedy nanoparticles) activate the same synapses or neighboring synapses and causes *opposite effects* to the original stimulus. High intensity and low intensity stressors may produce subsequent biobehavioral effects in opposite directions, depending on the intensity of original prestressor.¹² Adaptive plasticity is not limited to the brain; in a living system, other cells also exhibit the capacity to change function and reverse the direction of shifts in setpoint as a result of prior activity.^{72,75} Metaplastic bidirectionality reflects the organism's innate homeostatic tendency to maintain function within a range around a setpoint. Thus, change in one direction prepares the system to reverse direction upon the next encounter with a stressor or cross-adapted stressor. For recovery from chronic disease with homeopathy, the net effect is to cancel the disease-related dynamics in the system, as the setpoint around which the function operates shifts back toward the normal range.

This perspective offers insight into homeopathic practice and a rationale for the clinical materia medica and repertories used to determine appropriate remedies. Given the emphasis in the NPCAS model on the allostatic stress response network as the locus of action, the diversity of symptoms described for each remedy begins to make sense. The goal in homeopathic prescribing is to identify the single remedy that is cross-adapted to the cumulative pattern of disease-related maladaptations. Homoeopaths attempt to find a pattern match between documented effects of a homeopathic medicine and the individual patient's unique clinical picture. Biological, infectious, chemical, dietary, physical and psychological aggravating and ameliorating factors could converge in the allostatic stress response network to create an unique symptom pattern.^{1,40,42,149} The better the pattern match to the maladaptive state at highest level of organizational scale in the organism (generalities, recurring functional themes, or network motifs found in both global and local symptoms⁸⁰), the more likely it is that the remedy nanoparticles in low dose could evoke compensatory changes to reverse direction of the existing maladaptive state, improve well-being, and strengthen systemic resilience.¹⁵⁰ If the cross-adapted pattern match for the remedy nanoparticles is at a lower level of organizational scale in the organism, e.g. Local physical dysfunction in one organ, more limited changes and more modest clinical improvements would result.^{151,152}

Research Implications of Allostatic Stress Response Network Involvement

A starting point for translational studies would be evaluating patterns of nonlinear effects of individualized homeopathic remedy treatment on mediators of the stress response network.^{28,75,78,153–155} This interconnected, interactive set of subsystems includes immune, inflammatory and anti-inflammatory cytokines, endocrine, central, autonomic, and peripheral nervous systems, oxidative stress and metabolism, which collectively contribute to a wide range of clinical conditions. This suggests that homeopathic treatment could thus be particularly effective not only for stress-related problems – broadly defined, but also for many different conditions involving imbalances or disturbances in regulatory subsystems of the organism that stress – biological, infectious, chemical, physical, and/or psychological -- initiates or exacerbates.^{154,156–160}

For instance, in an animal model of autism, a condition that homeopathic treatment has been claimed to help,¹⁶¹ elevated pro-inflammatory interleukin IL-6 changes neuronal dendritic spine patterns and leads to autistic-like behavioral, cognitive and learning impairments.¹⁵⁹ Study designs would include testing the ability of the correct remedy to reverse changes in CNS structure and function, and cytokine IL-6 (and the other interconnected subnetwork of cytokines with which it interacts). Changes in nonlinear dynamics of the EEG in autism may also be a useful functional biomarker in the brain as a complex adaptive network.¹⁶²

The NPCAS model suggests that measuring intermediary biomarkers such as changes in inflammatory cytokines¹⁶³ or heat shock protein patterns^{55,57} would be more sensitive option apart from self-report or other clinical outcomes to assess homeopathic remedy effects in shorter-term, small sample studies. Asthma is one such candidate condition for study. The homeopathic clinical literature includes many reports of successful treatment of asthma,^{164,165} but the randomized clinical trial findings are limited and less favorable.^{166,167} Asthma is one of many medical conditions associated with adverse childhood experiences and/or stressors.^{156,168,169} Research has shown that unfavorable psychosocial circumstances early in life lead to persistent pro-inflammatory epigenetic and cytokine patterns.¹⁷⁰ Treatment with low doses of cytokines can modulate underlying immune system imbalances and resolve allergic asthma bronchial hyperresponsivity in animals.¹⁷¹ Thus, the testable hypothesis is that the correctly-chosen homeopathic remedy in an identifiable subset of children or adults with asthma will elicit an anti-inflammatory response involving detectable reversal of pre-treatment epigenetic, immune, and cytokine activation patterns.

As in systems biology,¹⁷² the major focus for homeopathy research would then become multivariate mediating processes¹⁷³ and patterns^{174–179} of change in the biological stress response network, rather than the isolated specific endpoints typical of many pharmacologically-driven clinical trial designs.¹⁸⁰ In the NPCAS model, changes in the clinical endpoints occur distal in time and space to the original locus of action of the simillimum remedy.^{111,112} Therefore the methodological approaches of quantitative holistic systems biology,^{172,174,175,181} with the ability to analyze complex gene activation arrays, protein complexes, and/or metabolic profiles for multivariate functional modifications^{57,182} are more likely to be relevant in testing the NPCAS model. As with nanoparticles,^{24,26,183,184} some studies already offer evidence that homeopathic remedies can modulate epigenetic and biological signaling expression patterns.^{117,182,185,186} Salient biological signaling events that start at the local cellular level can initiate a cascade of system-wide effects.¹²⁵

The overarching hypothesis is that nanoparticles of the matching remedy act in low doses as dynamical biological triggers to modulate multiple interactive functions in the allostatic stress response network of the individual. Especially in patients with chronic diseases, intermediate patterns of change in components of the allostatic network are the predicted

measurable outcome,⁷⁵ before function of a specific local organ and associated symptoms would improve. For acute diseases, the time frame of adaptive changes is much faster.

The mediating processes for homeopathic effects are physiological, not pharmacological

Hypothesis: Active remedies will initiate and/or elicit time-dependent sensitization-based (progressive amplification) reversal of environmental stressor reactivity.

Corollary hypothesis: The effects of the simillimum remedy nanoparticles on the organism are crossadapted and cross-sensitized to the previously-established maladaptive processes that allow the emergence of disease from prior high level stressors.

Time-Dependent Endogenous Response Amplification: Physiological Phenomena

The NPCAS model states that salient homeopathic remedy nanoparticles serve as a novel and foreign low dose stressor for the organism, initiating compensatory adaptive changes.^{1,13} The organism-dependent amplification of effects derives from time-dependent sensitization of the adaptations to the administration of intermittently administered, sometimes repeated, remedy doses. In order for the nonlinear healing response to the simillimum remedy to develop and evolve, the body amplifies the response with the passage of time. In 1994, Davidson originally suggested the possibility that sensitization plays a role in homeopathic remedy actions.¹⁸⁷ If so, then the correct remedy, like any other type of low intensity stressor to which the organism is sensitised, should set the biology of time-dependent sensitization into motion. When the sick organism receives the simillimum, the cumulative past high level stressors in the allostatic overload have already initiated TDS (Figure 1). In that circumstance, the correct remedy acts as a low level stressor eliciting a cross-sensitized, cross-adapted response in the opposite direction to the original direction that led to dysfunction and disease. In general, it should be possible to use the same types of biomarkers, for instance EEG spectral power changes^{188–191} or cardiovascular reactivity,^{192,193} or cytokine patterns (interleukins 1 and 2, tumor necrosis factor)⁴⁷ that other types of stressors can sensitize in tests of remedy sensitization and oscillatory responses.

We have already found supportive evidence for TDS responses in human subjects given one or more doses of an individually matched homeopathic remedy. In the first study, fibromyalgia patients underwent a series of 3 separate laboratory sessions (baseline, 3 months, 6 months) in which they repeatedly sniffed either their constitutional remedy diluted in LM (Q) potencies or a water solvent placebo control. Between laboratory sessions, half of the subjects were randomized under double-blind conditions to take their constitutional remedy daily in oral LM potency and half to take a placebo. The verum group improved significantly more in clinical outcome measures,¹⁹⁴ and also showed a progressive increase in EEG alpha magnitude over time – i.e., time-dependent sensitization. In contrast, the placebo group showed a progressive decrease in EEG alpha activity.¹⁸⁹ From the first encounter with the remedy, the best responders to verum also exhibited a unique pattern of prefrontal EEG changes in an algorithm-based measure called cordance (derived from the ratio of relative and absolute EEG power at each electrode site) during remedy sniffs.¹⁹⁵ The best responder cordance patterns differed from those of placebo patients and other verum patients at each time point. EEG alpha cordance correlates with changes in brain blood flow and/or metabolism.¹⁹⁶ In turn, prefrontal brain areas regulate executive cognitive ability, including decision-making and changing behavior as new information becomes available. This relates to the flexibility and resilience seen in higher functioning individuals.^{111,112,197,198} Better responders to any type of intervention program across

various different conditions have better executive function.^{199–204} The prefrontal cordance difference of the best responders remained significantly different from the other groups' at 3 and 6 months. However, the magnitude and direction of the cordance effect progressively changed from very negative to moderately negative to very positive over time (Figure 5). That is, the best responders differed from others, but the polarity of the response difference gradually reversed from the beginning to end of treatment. This study provides physiological data consistent with the NPCAS model for remedy actions.

A second study from our laboratory also demonstrated complex nonlinear patterns of short-term EEG responses within sessions and over sessions to matched remedy by olfactory administration in healthy young adults.²⁰⁵ The subgroup with higher levels of the individual different trait of chemical intolerance (CI) or sensitivity, the reportedly “universal provers” of homeopathic pathogenetic trials,²⁰⁶ diverged in their patterns from those of the subgroup lower in trait CI.²⁰⁷ Of note, females are more sensitizable than males in both human and animal TDS research.¹⁸⁸ Previous studies have demonstrated that high CI individuals have sensitized EEG responses to repeated low level exposure challenges to a variety of common chemical odors,¹⁹⁰ sucrose,²⁰⁸ milk,¹⁹³ and stress.²⁰⁹ Randolph described these individuals as highly susceptible to specific adaptations to environmental agents and prone to food addictions.^{149,210} TDS is a leading model for the development of cravings in addictions,²¹¹ chronic pain,²¹² multiple chemical sensitivity,²¹³ and posttraumatic stress disorders.⁴⁹ A large proportion of fibromyalgia patients also score high in measures of both CI and carbohydrate craving.²⁰⁸ Specific food cravings and aversions, as well as ameliorating and aggravating foods, are taken account of in clinical remedy selection.

TDS is a form of neural learning and memory. Based on the animal literature on TDS and metaplasticity, when the system reaches its physiological limits but then encounters a relevant cross-sensitized stressor, the direction of the elicited responses may reverse or oscillate with repeated intermittent dosing.¹⁰ For instance, if the cumulative allostatic load has previously induced a specific pattern of maladaptive changes in the stress response network, then nanoparticles of the relevant remedy, as a low intensity stressor, could evoke a salutary reversal in the direction away from maladaptive functioning. In TDS, lower and higher intensity stressors prime the system with metaplastic effects that can lead to changes in opposite directions.¹² The system has a cellular memory for its response to past encounters with an environmental stimulus.⁹ As a result, the organism will try to keep functioning within physiological bounds by making compensatory adjustments in a different direction the next time that the same or a cross-sensitized stimulus activates the same neurons.

The ability of a low dose of homeopathic remedy nanoparticles to produce beneficial effects is highly dependent on the cross-adaptational pattern match between the remedy and the pre-established disease state. With TDS, the magnitude of the response to an intermittent, pulsed remedy challenge should grow spontaneously over time, between repeat doses. The emergence of the healing process derives only indirectly from the properties of the treatment. The self-organization of the cells¹⁵⁵ and organism as a complex adaptive system dictate the process and pathways of the healing.²

Research Implications of Metaplasticity, Cross-Adaptation, and Time-Dependent Sensitization

Because of the importance of evolution and emergence of recovery over time following administration of a dose of the simillimum, prospective study designs are essential. Such studies must also employ assessment methods that capture the process of change,¹⁷³ not merely static endpoints. Research on the processes and patterns of change after a dose of remedy will ultimately help improve clinical selection of dosing regimes. Study designs

should include repeated challenge tests. Many studies have demonstrated that resting states and/or single challenges are often inadequate to detect pre-existing sensitization or change over time. In animal research on TDS, sensitized and nonsensitized animals exhibit similar baseline and resting physiological and behavioral findings, but diverge significantly with the passage of time between repeated intermittent (pulsed) challenges with the initiating agent or stressor or a cross-sensitized agent or stressor.^{58,214} The effects of TDS include priming subsequent elicited changes in glucocorticoid hormone responsivity, amplified behavioral responses to drugs, chemical, sucrose, and/or stress, progressive increases in cardiovascular reactivity, and increases in EEG alpha power on subsequent re-challenge.^{11,60,191–193,213,215–217}

A testable hypothesis is that administering the next dose is only appropriate if the organism has manifestations of disease and the remedy-related adaptive compensatory response to the previous remedy dose, if any, has plateaued or relapsed.¹⁴² LM or Q may be more suitable for such experiments, they are typically administered daily in liquid form, with intermediate dilutions and succussions in regular but small increments of potency. Hahnemann introduced LM potency dosing late in his career, as a method to accelerate recovery from chronic diseases.²¹⁸ Two positive randomized, placebo-controlled clinical trials of homeopathy (one in fibromyalgia¹⁹⁴ and one in attention-deficit hyperactivity disorder²¹⁹) used LM potencies. From a TDS perspective, the daily LM dilution and succussion steps would introduce incremental novelty of the remedy nanoparticles for each successive dose to challenge the organism's adaptive processes. Hahnemann indicated that LM treatment had to continue until some dose eventually elicited a new clinical worsening rather than progressive improvement.²¹⁸ This reversal would be the point at which beneficial adaptive changes in TDS reach the organism's physiological limits and, therefore, reverse direction.^{10,47} At such a point, continued dosing would reverse direction of the systemic changes reverting towards maladaptation and disease relapse.¹⁰

Measuring allostatic network biomarkers,^{75,220} e.g., inflammatory and anti-inflammatory cytokine activation patterns,²²¹ would permit testing the above hypothesis after each remedy dose. If symptoms worsen again in a patient taking LM potencies, it should be possible to demonstrate that the organism has again shifted the direction of its adaptive responses to the remedy nanoparticles -- e.g. From the beneficial anti-inflammatory back toward adverse inflammatory physiological patterns. In terms of NPCAS model, the organism has reached allostatic overload from excessive repetition of challenges. The most responsive conditions in the NPCAS model for homeopathic remedy actions will involve prior sensitization of components of the stress response system, including the central nervous system.²²² For example, fibromyalgia²²³ is a functional chronic pain syndrome whose primary mechanisms include central and peripheral nervous system sensitization.^{208,224,225} Diverse environmental factors contribute to triggering fibromyalgia, including road traffic accidents, psychological stress, chemical exposures, and childhood abuse.^{226–229} Two double-blind randomized clinical trials (RCT) have shown significant efficacy of individualized homeopathic remedies over placebo.^{194,230} The hypothesis would be that properly-timed remedy nanoparticles will reverse the central sensitization in response to painful stimuli that characterizes fibromyalgia. Empirically, not only tender point pain evoked by standardized physical examination,¹⁹⁴ but also other types of experimentally-elicited pain should decrease under successful homeopathic remedy nanoparticle treatment in FM patients.²³¹

The net clinical outcome of the simillimum remedy interaction is improvement in global health and systemic resilience to future stressors, in addition to resolution of local symptoms

Hypothesis: The simillimum remedy administered to a sick person will produce persistent improvement in systemic resilience, including global well-being and resolution of local symptoms.^{195,232}

*Corollary hypothesis: A remedy corresponding to elements of the disease maladaptations and state of the organism will change a subset of the total symptoms without improving global well-being or strengthening systemic resilience.*¹⁵¹

Corollary hypothesis: A remedy with no correspondence to the specific maladaptations and state of the organism will initiate little or no change, but minor adverse metaplastic changes without improvements in symptoms or systemic resilience.

*Corollary hypothesis: A remedy or remedy potency that is repeated too often will cause or worsen symptoms and lower systemic resilience.*¹⁴²

Resilience as a Manifestation of Emergent Health in the Complex Adaptive System

Vaiserman has proposed that hormetic adaptations to low intensity stressors earlier in life could mobilize systemic epigenetic reorganization of the organism and long-term resilience to subsequent higher intensity stressors.^{233,234} For other experimental tests of this notion, experts in complex adaptive systems emphasize the importance of perturbing the system and measuring the direct and indirect effects of the perturbation across the organism.^{155,235} For instance, Fredrickson and Losada found more flexible and resilient behaviors in higher-functioning than in lower-functioning social systems given an interactive group task to perform under pressure.¹⁹⁷ Thus, an essential consideration for proper tests of the NPCAS model is that researchers should test the resilience of the system under stress, not at rest. Prospective studies would need to examine the stress reactivity and recovery of the same patients at pre-treatment and post-treatment. Again, stress is any biological, infectious, physical, chemical, electromagnetic, or psychosocial factor that disrupts homeostasis.

Krug et al,¹⁷⁷ among others, have emphasized that physiological challenge tests, i.e., experimental stressors, elicit interindividual variation in otherwise phenotypically similar human subjects. In metabolic studies, challenge tests can reveal metabolic types not apparent in resting measurements by showing different metabolite profiles or patterns of change. In the specific adaptation literature, Randolph pointed out the clinical necessity of using food and environmental chemical challenge testing to determine each of the multiple specific offending agents that could trigger the same set of food addiction cravings and/or adverse sensitivity symptoms in a given patient.^{149,210}

A requisite step in homeopathic treatment is to identify the correct, best-matched remedy or simillimum, for the patient's total clinical picture. The clinical picture includes not only patterns of specific symptoms, but also the modalities and generalities of global adaptive behaviors that ameliorate or worsen symptoms. Thus, in complex systems terminology, the simillimum is a microcosmic encapsulation of personalized coping behaviors within the cumulative experienced environment, or fitness landscape²³⁶ (Figure 6). The organism as a complex adaptive system is continually trying to survive as well as possible within his/her world.²³⁷ Successful treatment stimulates compensatory cross-adaptations that optimize ability to function as well as possible within the individual's fitness landscape, manifested as resilience to future stress.

Research Implications of Systemic Resilience as a Primary Clinical Outcome

Resilience as a concept revolves around the ability of a system to adapt to change. In complex adaptive systems terms, Pincus has defined resilience as “the meta-flexibility of the system; the ability to respond to a perturbation by either becoming rigid and robust, or flexible and fluid without becoming stuck or falling apart respectively.”² If the hypothesized locus of remedy action is the stress response system and the process involved is adaptation, it will be essential to go beyond assessments of resting states and evaluate the system’s response to a novel stressor before and after treatment. A limited but accessible outcome measure for research would be validated questionnaires on psychosocial resilience, such as the Connor-Davidson Resilience Scale.^{238,239} However, resilience is not limited to the psychosocial realm. In view of the need to examine not just subjectively perceived changes, but also the dynamics of objective physiological resilience over time, standardized physical (e.g., high or low temperature or altitude environments), physiological (e.g., treadmill test), metabolic (e.g., glucose tolerance test), and psychological (e.g., Treier Social Stress Test of simulated job interview)²⁴⁰ stress tests are preferable.

At a practical level, studying remedy nanoparticle effects on short term changes in resilience may be initially more feasible than planning long term outcome studies. For instance, stress response measures before and after 3–6 months of treatment would include reactivity to and recovery from acute stressors, using patterns of not only mood, but also EEG, neurochemical, autonomic, stress hormone (glucocorticoids, DHEA), cytokine, and metabolic (including heat shock protein) changes.^{55,57} At the cellular level,^{55,57} it may be possible to characterize patterns of heat shock protein responses to in vitro stressors and develop adjunctive laboratory blood tests that will assist in individualized selection of the correct remedy for a patient’s current state. During treatment, biomarker measures would be followed at each assessment point from resting baseline to peak change, with examination of time to recovery to baseline or failure to regain normal baseline after a specified period of time.²⁴¹ Applying nonlinear time series analytic techniques²⁴² and cusp catastrophe or network modeling to physiological patterns of change are sensitive approaches to evaluating systemic resilience under stress.²

Other methods such as state space grids evaluate the quantitative and qualitative dynamics of behavioral reactivity (organism level of organizational scale) during social interactions in a specified interpersonal task.²⁴³ State space grid study designs can assess the degree of behavioral and physiological flexibility and resilience versus rigidity under social stress. The social task stressor in these studies elicits the typically less structured, real-world behaviors with which patients interact with family members, friends, or strangers.^{173,244,245}

As noted above, another primary target of the allostatic stress response network for study might be the inflammasome protein complexes,⁷⁶ inflammatory and anti-inflammatory cytokines, and their regulatory role in the organism.²⁴⁶ These endogenous mediators play major roles in modulating inflammation, responses to immune challenges, and central nervous system function. Cytokine dysregulation and inflammation contribute to poorer mental and physical health, and impair quality of life and well being in many disorders.^{159,247–249} Adaptive changes in allostasis initiated by low dose nanoparticles during homeopathic treatment could help restore more normal balance between pro- and anti-inflammatory cytokines, as suggested by previous studies.^{66–69,163,182,185,250–252} The result would be improvements of both psychological and physical well being across a wide range of conditions, as is claimed in hundreds of anecdotal case reports from homeopaths and supported by a number of observational trials.^{253,254}

Other practical design considerations are important. Allopathic drugs can interfere with the subtle physiological regulation, adaptation, and modulation of components of the stress

response network, e.g., glucocorticoids and/or tumor necrosis factor (TNF- α) inhibitors in rheumatoid arthritis. Patients taking such drugs might be treated less successfully with even properly-chosen homeopathic remedies. Indeed, RCT studies of classical homeopathy in rheumatoid arthritis show more mixed results,^{255,256} especially with more recent studies done after the introduction of TNF- α inhibitor disease-modifying drugs.²⁵⁵ TNF- α plays a significant role in stress-related central sensitization.^{257,258} Animal studies suggest that the ability to activate glucocorticoid reactivity plays a role in initiation of TDS and subsequent reactivity to stressors.^{58,64} Pharmacologic agents which interfere with endogenous regulatory pathways for glucocorticoids or cytokine TNF- α in the allostatic network might impede or distort the ability to regulate endogenous adaptive mechanisms. On the other hand, antioxidants, some herbal agents and acupuncture may also modify components of the allostatic network by blocking inflammation, generation of reactive oxygen species and/or the biology of neural sensitization.^{259–263} Hormetic effects from low doses of antioxidant substances may be cytoprotective.²⁶⁴ Both nanoparticles^{23,24,265,266} and homeopathic remedies^{267–269} by themselves modulate generation of reactive oxygen species and oxidative stress responses. Consequently, one clinically-relevant NPCAS-theory-driven line of integrative medicine research would include systematic investigation of specific exogenous agents that may impair or facilitate hormesis and the capacity to recover from disease in response to homeopathic treatment.²⁷⁰

Summary and Discussion

A homeopathic remedy is a small stimulus that initiates a large response in the organism.^{271–274} Homeopathic effects are inherently nonlinear in nature. The dose level of the remedy nanoparticle stimulus as an environmental stressor is low, in the hormetic dose range,^{27,275} and not capable of directly causing large pharmacological effects. However, nanoparticles are highly reactive, possessing different mechanical, biological, physical, chemical, electrical, magnetic, optical, and quantum properties than their respective bulk forms.^{21,22,135} The simillimum homeopathic remedy must be capable of triggering the same types and patterns of adaptations that the organism has already demonstrated the capacity to make to other types of higher intensity stressors. Clinical indicators of the allostatic adaptations include Generalities and Modalities that modulate symptom expression, including but not limited to, amelioration or aggravation from extremes of heat or cold, altitude or sea level, specific foods, times of day, social environments, and specific behavioral states.

Cells and organism detect and react to the remedy nanoparticles as a salient, novel, and foreign threat to survival, i.e., a relevant environmental stressor,^{276,277} thereby mobilizing previously disease-primed adaptive responses. At that point, the organism produces a response amplification to the low dose of nanoparticles via endogenous changes in a variety of biological mechanisms involved in adaptive plasticity, cross-sensitization, and cross-adaptation.^{9,30,33,35} These changes were previously primed by larger magnitude biological and psychosocial stressors that originally led to maladaptive processes and disease. The NPCAS model postulates that the initial locus of action is the allostatic stress response network, which includes the central and autonomic nervous systems, endocrine, immune, inflammatory and anti-inflammatory mediators, and metabolic regulators. The components of the allostatic network which first encounter and react to the remedy nanoparticles initiate complex regulatory signaling²⁷⁷ and homeostatic adaptive changes throughout the rest of the network.²⁷⁶ With the true simillimum, epigenetic changes may occur.¹⁸⁶

Consequently, the isolated single specific endpoints that pharmacological research designs employ to assess conventional drug actions are not well-suited to capture the nonlinear dynamical effects of homeopathic remedies on living systems.^{111,112} Good homeopathic

treatment outcomes include global and local improvements.^{195,278} Because of the multicomponent dynamical complexity involved in allostatic network adaptations, research on the model must include multivariate profiles of systems biology and time-dependent, iterative complex systems science methods on nonlinear dynamics.¹¹¹ The prior history of the organism with stressors will shape the nonlinear patterns of allostatic change observed in response to a remedy. The evolution of changes in the whole organism over time, e.g., the development of more robust immune responses and commonly-observed emergence of acute infections early in homeopathic treatment²⁷⁸ must be accounted for in the proper assessment of homeopathic treatment effects.

Conclusions

The NPCAS model and the research program derived from it offer a path out of the circular and unproductive debate over whether or not a homeopathic remedy, which is clearly not an allopathic drug, has allopathic drug-like properties. We hypothesise that homeopathic medicines consist of nanoparticles which are low level environmental stressors physiologically cross-adapted in varying degrees to the allostatic overload to which the individual has previously developed maladaptive responses. The large and growing literature on nanoparticles, hormesis, the allostatic stress response network, metaplasticity, and bidirectional time-dependent sensitization can inform progress in homeopathic research and the nature of systemic healing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Nanoparticle-Allostasis-Cross-Adaptation-Sensitization Model for Homeopathic Remedy Effects

Allostatic overload includes cumulative disruptive effects on homeostasis of higher intensity stressors such as adverse childhood experiences, traumas, infections, biological, psychosocial, chemical, physical, and nutritional stressors. A stressor is any type of stimulus that can disrupt homeostasis. The simillimum homeopathic remedy enhances health and systemic resilience to future stressors by eliciting a salutary reversal in direction of the organism's maladaptive processes.

a. Homeopathic Silver Nitrate Effects on Plant**Growth by Successive Remedy Potencies¹¹⁴ ^** **b. Nanoparticulate Platinum Effects on N₂O****catalytic decomposition by Cluster Size²¹ #** **Figure 2.****a,b.** Oscillatory Nonlinear Dose-Response Effects of a Successive Series of Homeopathic Remedy Potencies and of Nanoparticle Cluster Sizes

^ Homeopathic D potencies are the same as X potencies in terms of dilution factor. Based on ultrasonication data on nanoparticles⁸⁶, the additional succussions inherent in the homeopathic manufacturing process could lead to progressively smaller cluster size with unique properties in a D25 and then D26, compared with a D24 potency. Reprinted with permission from reference 114.

Solid squares represent cationic patterns; open circles represent anionic patterns for absolute rate constants in the catalytic reaction of N₂O with Platinum in nanoparticle clusters of different size. Reprinted with permission from reference 21.

Figure 3.

Demethylation of veratric acid by *Rhodococcus erythropolis* cells. Metabolic tests were performed after a 6-hour incubation with successive formaldehyde (FA) dilutions in water or in 75% ethanol, together with control values for water and 75% ethanol. Each dilution factor is in a ratio of 1/100, with 1 = 1C and 20 = 20C on the x-axis. Succussions ('dynamically shaken') were reported, but number and type of succussion method were not specified. Reprinted with permission from reference 113.

Figure 4. Variability in Silver Bromide (AgBr) Nanostructure Sizes as a Function of Preparation Parameters. Particle images are scanning electron micrographs. Reprinted with permission from reference 119.

Figure 5. Shifts in the Magnitude and Direction of Prefrontal EEG Cordance Responses to Individualized Homeopathic Treatment in Excellent Clinical Responders with Fibromyalgia from Initial Treatment Day to 3 and 6 Month Follow-up. Excellent responders were defined by both large gains in global health and reductions in local tender point pain during double-blind examiner pressure-based challenge testing. Reprinted with permission from reference 198.

Figure 6.

Diagrammatic representation of a rugged fitness landscape. It offers an analogy for the experienced environment that the homeopathic remedy simillimum needs to encapsulate in order to stimulate the evolution of salutary cross-adaptations, optimal healing resilience, and well-being (fitness) in the individual patient over time.

Note: This diagram actually represents evolution of genetic codes in a rugged fitness landscape (a cartoon illustration). $r1$, $r2$: random codes with the same block structure as the standard code. $o1$, $o2$: codes obtained from $r1$, $r2$ after optimization. $R1$, $R2$: random codes with fitness values greater than the fitness of the standard code. $O1$, $O2$: codes obtained from $R1$, $R2$ after optimization. Figure used with Creative Commons License from an open access source (<http://www.biology-direct.com/content/2/1/24>).²³⁶

Table 1**Glossary of Key Terms in the NPCAS Model**

Term	Definition
Nanoparticle	A small particle with one or more dimensions measuring 100 nanometers or less. ^{1,13,24} Nanoparticles (NPs) have different properties from their bulk forms in terms of mechanical, optical, electrical, magnetic, chemical, biological, and quantum behaviors. NPs adsorb proteins, DNA, and other substances onto their surfaces; cross membranes easily; act as highly reactive and catalytic agents that lower the amount of drug or herb needed to produce a given effect. ^{25,115}
Stress	Any environmental or endogenous change that serves to perturb physiological or cellular homeostasis in an organism, i.e., the stable internal state of functioning necessary for maintenance of life. ^{3,4}
Hormesis	A biphasic dose response relationship involving low dose stimulation (beneficial compensatory changes) and high dose inhibition (toxicity); an adaptive response of cells and organisms to a moderate intermittent stress. ^{27,38–39,51,55–57}
Adaptation	Evolutionary process affecting structure, behavior, and/or physiology in which an organism changes to survive and thrive over time within a given environment. A form of biological learning or plasticity. ^{42–45}
Cross-adaptation	Physiological phenomenon in which exposure to a given adverse environment leads to an increase in tolerance not only for the original environment, but also to changes in tolerance to other adverse factors that the adapted organism had never previously encountered. ^{41,43,45}
Allostasis	Physiological adaptive process of achieving or restoring homeostasis through physiological and/or behavioral change involving positive and/or negative feedback. ^{3,4}
Allostatic overload	Adverse physiological consequences of long-term exposure to repeated or chronic stress, leading to disease; involves nonlinear interactions of central and autonomic nervous systems, neuroendocrine, immune, and metabolic networks of the organism. ^{3,4}
Time dependent sensitization	Progressive amplification of the response of an organism from the repeated intermittent exposure to the same or a cross-sensitizing stressor or agent (drug, chemical, biological factor); at physiological limits, TDS can oscillate in biphasic directions. ^{10–12,47}
Metaplasticity	Adaptive plasticity of synaptic plasticity in which the past history of the synaptic activity determines its current plasticity, including the direction and magnitude of the response to a subsequent stimulus. ^{8,9} Important in learning and memory processes in brain areas involved in regulating cognitive, emotional, and somatosensory functioning. ^{8,9,32–36}
Complex adaptive system	A complex self-organizing collection of components that interact with one another and adapt to changes in the environment, i.e., learn, to optimize fitness for survival. The systemic behavior is an emergent evolving property not seen in any single component by itself, and the organism operates far from equilibrium conditions. A healthy CAS is resilient and can recover from effects of environmental stress or change. ² A cell and an organism are both examples of complex adaptive systems. In an animal or plant, a cell is also a component of the organism, an interactive part of a lower level of organizational scale within a larger organism.
Nonlinear dynamical system	A complex system whose output is not proportionate to its input; a complex system that changes nonlinearly over time in ways that make outcomes difficult to predict; the initial conditions or starting state influence the subsequent pattern of change. ²
Scale free network	A complex network of interconnected, interdependent components such as an organism or cell, whose organization follows a scale free power law distribution; an ultra small world network. ^{2,155}