

Homeopathy as Systemic Adaptational Nanomedicine: The Nanoparticle-Cross-Adaptation-Sensitization Model

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Abstract: This paper presents an overview of the nanoparticle-cross-adaptation-sensitization (NPCAS) model for homeopathic remedy actions in living systems. The model builds upon an extensive interdisciplinary scientific literature outside conventional biomedicine. The way in which homeopathic remedies are made, involving trituration with or without succussion, is a type of top-down mechanical manufacturing process for nanoparticles (NPs, measuring <100 nanometers in diameter) of source material. Chikramane et al (2010) documented the presence of source nanoparticles in commercial homeopathic remedies. NPs acquire unique biological, chemical, electromagnetic, and quantum properties as a function of their high ratio of surface area to volume. Their ability to cross cell membranes and adsorb other materials onto their highly reactive surfaces makes them excellent herb, nutraceutical, drug, and vaccine delivery vehicles with enhanced bio-availability. Nanoforms of materials lower the dose needed even for conventional medical applications. For homeopathic dosing, very low doses of NPs can mobilize hormetic adaptational mechanisms in complex living systems by serving as novel, foreign stressors to stimulate beneficial compensatory responses in the organism as a whole. The organism's adaptive responses grow and evolve over time via nonlinear metaplastic and plastic sensitization mechanisms in bodily cells across the endogenous, self-organized network of the dynamical living system. The primary pathways involve adaptive reactions rather than direct pharmacological actions. Taken together, the evidence-based NPCAS model offers a testable, scientifically-grounded foundation for advancing homeopathic clinical care and research.

Keywords: homeopathic medicine, nanoparticles, hormesis, allostatic stress response network, self-organization, nonlinear dynamical systems, cross adaptation, sensitization

Introduction

This paper presents an emerging synthesis of scientific research on the nature of homeopathic remedies and their mode of action in living systems. In the years following Hahnemann's original observations and publications developing the field, most of the focus of homeopaths has been on expanding and refining clinical theory and practice. Meanwhile, modern scientific research on homeopathy has largely gotten lost in a defensive effort to show that remedies "work" as if they were conventional drugs with specific mechanisms of action at the local level.

As a result, allopathic standards for biomedical clinical research design and assessment of specific mechanisms have driven the agenda for homeopathic medical research.^{1,2} The problem with this direction has been that the underlying assumptions – i.e., that homeopathic remedies are conventional drugs with specific local biological mechanisms – are false. Rather, the present model proposes that homeopathic medicines are nanoparticles (NPs) carrying source material, whose ability to stimulate healing involves mobilizing adaptational amplification mechanisms that lead to changes in global and local function of the individual as a whole complex, self-organized living network. The scientific foundation for this model appears across vast sets of research literatures in materials science,

physiology, neurosciences, and complex systems. Multiple homeopathic investigators have also contributed major aspects in both conceptual and experimental work.³⁻²¹

Homeopathic Remedies as Nanoparticles

What are homeopathic remedies? Contemporary scientific research is finally beginning to catch up with what Hahnemann began documenting 200 years ago. Aphorism 269 of the 6th edition of the *Organon* (completed in 1842) states: *"For its own special purpose, the homeopathic medical art develops to a formerly unheard of degree the internal, spirit-like medicinal powers of crude substances. It does so by means of a procedure which belongs exclusively to it (and which was untried before my time) whereby these substances become altogether more than ever – indeed, immeasurably – penetratingly effective and helpful, even those substances which, in their crude state do not manifest the least medicinal power in the human body... This remarkable alteration in the properties of natural bodies is achieved through mechanical action on their smallest particles by trituration [in milk sugar] and succussion [in distilled water-ethanol solution] while these particles are*

separated from one another by means of an intervening, indifferent substance that is either dry or liquid... ”²²

Without the modern scientific terminology, Hahnemann was describing how to make nanoparticles. Nanoparticles are small particles of a given source material with at least one dimension measuring less than 100 nanometers in diameter.²³ Recently, in 2010, using transmission electron microscopy, electron diffraction and inductively-coupled plasma-atomic emission spectroscopy, Chikramane et al²⁴ demonstrated that liquid forms of six different commercial homeopathic metal remedies from two different manufacturers indeed contain nanoparticles of their bulk form source materials. The homeopathic NPs were present, albeit in small quantities, at 6C potencies, up to 30C and 200C.

Even trituration without succussion may be sufficient to generate biologically active homeopathic remedies. Ives et al²⁵ have shown that *Arsenicum Album* triturated but not succussed to make potencies up to 200C can still improve the viability of a human T-cell line stressed by material doses of arsenic trioxide *in vitro*. For comparison with traditional homeopathic manufacturing processes, here is a passage from a 2002 nanotechnology book chapter entitled, “Nanoparticles from Mechanical Attrition:”²⁶ “... nanoparticles from mechanical attrition are produced by a ‘top-down’ process. Such nanoparticles are formed in a mechanical device, generically referred to as a ‘mill,’ in which energy is imparted to a [coarse]-grained material to effect a reduction in particle size...” The authors go on to discuss the point that mechanical top-down manufacturing methods generate NPs of more irregular size and inconsistent shape compared with other types of modern manufacturing approaches.

This inherent variability of NPs made with a top-down method may contribute to the perplexing observations in homeopathic research of inter-experimental variability, even in basic science studies.^{24,27} Size and morphology of nanoparticles significantly affect their properties.^{23,28} Seemingly minor differences in cluster size and shape of NPs, for instance, can change the magnitude and direction of changes in thermal conductivity or catalytic activity of a given nanomaterial, in nonlinear ways.^{23,26,28} Thus, in the nanotechnology field, it is necessary to know not only the name of the source material, but also the size and morphology properties of its nanoparticles in order to better predict how it will act in a system.²³ Different types and amounts of trituration and succussion methods could lead to significantly different homeopathic treatment agents at a presumably “same” potency, as one research group has demonstrated.²⁹ For homeopathic clinicians, variability in remedy NPs between manufacturers and even batches within the same manufacturer²⁴ could help account for differences in patient responses to a given remedy at a specific potency from one administration to the next.

Nanoparticle Properties: Implications for Bioavailability

What are the implications for treatment with homeopathic remedies as nanoparticles? The large surface area to volume ratio of a nanoparticle confers several unique size-related properties. That is, NPs are more atom-like. They acquire different mechanical, chemical, optical, thermal,²⁸ electrical,³⁰ magnetic,^{23,31} biological, and quantum³² properties compared with the bulk forms of the “same” source material.²³ For example, NPs readily adsorb other nanoparticles and materials such as herbs,³³⁻³⁵ drugs, DNA, and proteins onto their surfaces.³⁶ Modern nanotechnology uses herbs to make ecologically less toxic forms of NPs, e.g., *Phytolacca decandra* tincture to generate silver nanoparticles from silver nitrate.³⁷ Nanotechnology experts are beginning to use plants rather than toxic chemicals to generate “green” nanomedicines because of the tendency of the resultant nanomaterials to adsorb any materials used in their manufacturing process onto their surface.³⁷⁻³⁹ Adsorbing a benign botanical agent is far preferable to a toxic chemical for NPs made for use in allopathic medical applications.⁴⁰

Furthermore, NPs can cross biological membranes without difficulty and translocate around the body in blood and lymph.³⁶ Cell membranes and even the blood-brain barrier allow NPs easy access across the gut or into brain and other bodily cells.⁴¹ As a result, conventional researchers are now working to develop targeted nanomedicine approaches for treating intracellular infectious diseases such as tuberculosis, hepatitis, and HIV/AIDs.⁴¹ These are conditions that homeopaths have been treating with remedies for many years.⁴²⁻⁴⁴ Researchers have developed NPs as targeted drug delivery vehicles that provide better bioavailability and reduce the drug (e.g., glyburide, carbamazepine), herb (e.g., *Gelsemium sempervirens*, *Hypericum perforatum*), nutraceutical (e.g., curmucin, resveratrol), or vaccine doses needed to produce clinically-relevant effects.^{45,46,34,35,47-49} sometimes by several orders of magnitude.^{50,51} Silica, which is found in pharmaceutical and homeopathic aqueous solutions prepared in glass containers,^{29,52,53} is also a common material used to make NPs as drug delivery vehicles.⁵⁴⁻⁵⁹ In general, some doses of source NPs used in allopathically-oriented studies of nanomedicines overlap those found in low potencies of homeopathic remedies, e.g., nanovaccines⁵⁰ vs nosode⁶⁰⁻⁶² remedies.

Nanoparticles as Biological Stressors and Hormetic Agents

At this point in the model, an obvious objection is that even if there are nanoparticles of source still present in remedies, how could they act in a therapeutic manner? The quantities of NPs are still very low in homeopathically-prepared medicines.²⁴ The answer may lie in the enhanced catalytic properties of nanoparticles.^{50,63} Amounts on the order of 1 nanomolar concentration of certain environmental nanoparticles can cause biologically significant

effects.⁶³ Used homeopathically (low doses, administered in a discrete, pulsed manner), NPs would trigger adaptive reactions across the cellular stress response networks^{3,4,64} and overall organism, rather than exerting direct pharmacological actions at local organs.

In this model, the organism detects and perceives the low dose remedy nanoparticles as a foreign environmental threat to survival, i.e. a novel stressor^{65,66} (Figure 1). In 1992, Antelman et al first discovered that two drugs with opposing specific pharmacological effects (haloperidol and amphetamine) could nevertheless both act as similarly foreign stressors for the organism, in terms of their effects on plasma corticosterone in animals.⁶⁶ “Stress” in physiology is the result of responses to perturbations in the internal milieu of the organism from changes in the environment – biological, metabolic, infectious, chemical, physical, or psychological in nature. The organism reacts to such perturbations by attempting to restore homeostatic function. This can mean upregulation of certain pathways and downregulation of others – or vice versa if the system was already primed by a previous exposure.^{67,68}

Specificity of the NPs would derive from the salience of the source material as a perceived threat to the global organism, rather than their brute force direct local effects on specific drug receptors.^{65,66} That is, the simillimum remedy is the nanoparticle source best matched to the unique pre-established, cumulative (mal)adaptive patterns of the organism as a whole. The nanobubbles that previous investigators have suggested to occur during succussion in homeopathic liquid potencies^{24,69,70} may also provide increased biological accessibility of the nanoparticles they surround to get into cells.^{51,71} The correct remedy is a low intensity global stressor for the person as a complex adaptive system. In accord with the biology of adaptive plasticity and metaplasticity,^{67,72} the direction of change depends on the low dose and on the state of the organism at the time of remedy administration.

Many, though not all, nanoparticles are toxic at relatively higher doses.^{73,74} Some are toxic at extremely low doses of nanoparticles.⁶³ Natural and man-made NPs are implicated in the etiology of a large number of chronic illnesses, including neurodegenerative disorders, emphysema, lung cancer, arteriosclerosis, cardiac disease, Crohn’s disease, autoimmune conditions, and Kaposi’s sarcoma.³⁶ Environmental pollutants such as diesel exhaust can contain toxic levels of hydrocarbon nanoparticles.^{75,76} Other nanoparticles, infectious agents, and even silica crystals at relatively higher doses can also trigger the biological cascade of inflammation and cytokine mobilization by activating the intracellular inflammasome proteins of macrophages and monocytes.⁷⁷⁻⁷⁹

In turn, inflammasome proteins release the pro-inflammatory cytokine interleukin 1 beta,^{80,81} which can modulate brain chemistry and behavior. Inflammasome proteins are considered intracellular danger sensors,^{64,82-84} though they are only one component of a complex, interactive stress

response biological network in the body that interfaces with the environment.⁸⁵⁻⁹¹ Heat shock proteins are also a key set of endogenous intracellular proteins that homeopathic remedies have been demonstrated to activate.³⁻⁶ Heat shock proteins mobilize as part of the adaptive response to biological stressors such as environmental heat, toxins, oxidative stress, hypoxia, nutritional deficiencies, or radiation and modulate immune and inflammatory mediators.⁸⁹ Taken together, these findings suggest that as nanoparticles, homeopathic remedies taken in higher, allopathic doses could cause adverse biological effects. In short, the body should recognize NPs, homeopathic remedy or not, as a potentially toxic biological danger, a threat to survival.^{64,76} Adaptive biological events ensue.

Unlike allopaths, however, homeopaths administer remedies in very low doses at widely-spaced intervals of time, i.e., pulsed dosing regimens. The amounts of nanoparticles that Chikramane et al found in remedies were on the order of pictograms to perhaps fractions of a microgram.²⁴ Even the silica quantities that Ives et al⁵³ found in liquid homeopathic potencies were only in the micromolar range. Both research groups concluded that their findings could not produce clinically meaningful effects *by conventional pharmacological mechanisms*. Nevertheless, nanoparticles are highly reactive and can exert meaningful effects as biological stressors for cellular and organism defense networks^{86,92,93} at very low doses.^{50,51,63}

How? Nanoparticles can also cause hormesis.⁹⁴ Hormesis is a physiological adaptational phenomenon of the recipient organism, in which low doses of a substance stimulate, whereas higher doses inhibit, biological functions.^{3-5,94-106} Hormetic dose-response curves are biphasic and nonlinear in nature.⁹⁵ Hormesis occurs with many different drugs, toxins, radiation, and even stress itself. Hormesis can also develop upon administration of a low dose either before (preconditioned) or after (postconditioned) exposure to a higher, i.e., toxic dose of an agent.

Hormesis involves adaptive or compensatory changes that the organism initiates to protect itself from the future damaging effects of a given agent or other, cross-adapted agents at higher doses.^{94,107,108} The stimulatory or beneficial doses for hormesis tend to occur in the dose range below the toxicological no-observed-adverse-effect-level (NOAEL)(Figure 2).^{95,96} With their enhanced bioavailability^{35,41,45,50} and catalytic/reactive activity,^{23,36} nanoparticles would potentially shift the cut-off point for NOAEL on dose-response curve even further to the left along the x-axis, lower than the already low dose range (below toxic levels) where scientists usually observe beneficial hormetic effects for bulk form materials or ordinary environmental stressors.^{95,105,106}

Cross-Adaptation in Hormesis: Heterologous or Heterotypic Factors

Cross-adaptation^{93,109-114} as well as cross-sensitization (endogenous response amplification)^{65,110} can also occur.

That is, hormetic doses of one agent can reverse the direction of adverse effects of a different, unrelated agent (heterologous or heterotypic hormesis).¹¹⁰ The environmental factors that cross-adapt or cross-sensitize can be completely different in nature from a pharmacological or local receptor mechanism perspective. Hypoxia can cross-adapt with low temperature stress, for instance.^{112,115} That is, once an organism has adapted to hypoxic stress, its ability to subsequently tolerate an extreme temperature stress also improves. The adaptive mechanisms for different environmental stressors apparently overlap within the organism, even though the specific, e.g., pharmacological, effects of the original and subsequent stressor are mechanistically different at the local tissues.^{6,66} Even in the empirical literature in pharmacology, stress can cross-sensitize with amphetamine;¹¹⁶ sucrose can cross-sensitize with amphetamine;¹¹⁷ formaldehyde can cross-sensitize with cocaine.¹¹⁸ In homeopathy, van Wijk and Wiegant have repeatedly demonstrated experimental evidence for the similia principle. That is, homeopathically-prepared remedies in low dose can cause hormetic and even cross-sensitized responses within another branch of the biological stress response of cells, i.e., heat shock proteins.^{3-6,92,93}

Thus, the evidence indicates that homeopathic remedies are nanoparticles of source substances, given in very low doses at spaced time intervals. The empirically-demonstrated adaptational phenomenon of hormesis, especially heterologous or heterotypic postconditioning hormesis, provides a precedent for homeopathic NPs triggering a reversal in direction for the whole system, from disease toward healthier dynamics of function.¹¹⁹ Higher intensity stressors of various types, from adverse childhood experience to infections to traumas to injuries to psychological stressors, may have originally accumulated and overwhelmed the adaptive capacity of the organism in the past to cause disease. The latter phenomena are part of McEwen et al's allostatic overload model of chronic disease in modern stress physiology terms.⁸⁵⁻⁸⁷

In the current model, the salience of the simillimum remedy to the cumulative, net picture of maladaptive responses can initiate the reversal in direction of the changes across the organism. The low dose simillimum nanoparticles are cross-adapted to the unique maladaptive biobehavioral repertoire that the previous allostatic overload⁸⁵ of high intensity stressors of all classes induced in the individual's life. There are not enough nanoparticles of the remedy in a typical homeopathic low dose to force the body to make changes in the direct pharmacological way that a conventional bulk form drug dose can cause at specific local receptors. Rather, the complex regulatory adaptive pathways are where the low dose remedy nanoparticles act, by serving as an organism-specific stressor. The next missing piece in the model is response amplification of the adaptive responses as part of the organism's plasticity and bidirectional metaplasticity response capabilities,^{65,67} together with the network nature of a complex living sys-

tem.¹¹⁹⁻¹²¹

Endogenous Amplification via Time-Dependent Sensitization

The likely mechanisms of response amplification lie not in the remedy's direct pharmacological actions at end organ receptors, but rather, in the ability of the body to detect and react to nanoparticles as a biological threat to survival.⁶⁵ In that situation, the body mobilizes its own endogenous response amplification and self-organizing capabilities as a complex adaptive system or network. Doses even lower than those needed to produce adaptive plasticity changes in the central nervous system, can nonetheless induce metaplastic changes that shape the direction and nature of the next plastic response of neurons and synapses to a salient stimulus.⁶⁷ As a result, the small stimulus that a homeopathic simillimum remedy stressor represents induces cascading, amplified, emergent modifications of multiple interactive functions across the organism that grow endogenously over time. Epigenetic and multiple, inter-regulatory physiological and biochemical events participate.

In time-dependent sensitization (TDS), the well-documented process is a progressive amplification over time of a response in the organism. TDS is mobilized by repeated, intermittent exposures to the sensitizing or cross-sensitizing stressor(s).⁶⁵ The dose of any given stressor can be low and remain low, but the organism begins to mount a larger and larger response as time passes. A classic example of TDS is limbic kindling in the brain. In kindling, a low level electrical stimulus that initially produces only a minor local change in neuronal function and no overt changes in behavior on first application will lead to the emergence of full-blown tonic-clonic seizures after enough intermittent, pulsed repetitions of the same low level stimulus. Sensitized changes in the central nervous system are long-lasting without further intervention. Yet, discrete, pulsed interventions -- timed differently -- can also cause the dysfunctional dynamics of an acute seizure or a cardiac arrhythmia to revert promptly to normal.¹²²⁻¹²⁴

Drugs (e.g., stimulants, benzodiazepines, antidepressants, nicotine, ethanol, morphine), stressors (psychological, physical), environmental chemicals (e.g., solvents,¹²⁵ diesel fuel,¹²⁶ formaldehyde,¹¹⁸ pesticides,¹²⁷ fungicides), endotoxins,¹²⁸ and cytokines^{65,129} can all initiate and/or elicit sensitized reactions.^{65,129} Sensitized responses can occur at biochemical, cellular and organism behavioral levels of network organizational scale, including persistent changes in glucocorticoid stress responses.¹³⁰⁻¹³² Heightened glucocorticoid activity, in turn, can then prime neuro-inflammatory responses in the larger system.^{133,134} TDS is a leading animal model for diverse conditions such as post-traumatic stress disorder, seizures, drug and food addiction and cravings, multiple chemical sensitivity fibromyalgia and other types of chronic pain.¹³⁵⁻¹³⁸ Modulators of TDS include gender, genetic and epigenetic factors.^{139,140} The brain regions involved in modulating TDS, e.g., limbic and

mesolimbic pathways and prefrontal cortex, are also central nervous system hubs within the larger stress response network.^{85,87,141}

Patterns of the Hierarchical Healing Response: The Self-Organizing Nature of the Person as a Complex Adaptive Network

The bidirectional regulatory involvement of the CNS with endocrine and immune mediators, i.e., other components of the biological stress response, raises another point. In constitutional homeopathic treatment, many successfully-treated patients exhibit spatial shifts and qualitative changes in the nature of their main symptoms over time. The center of gravity for disease manifestations in the organism shifts.¹⁴² Symptoms change as to which area(s) of the body manifests the strongest or primary symptomatology.¹⁴² In the ideal case, the healing responses roughly follow Hering's hierarchical Law of Cure – i.e., from above downward, inside out, and in reverse order of time of the original appearance of symptoms.¹⁴³

Homeopathic treatment induces an organism-wide pattern of multidimensional changes that conventional drugs do not produce.¹⁴⁴ The hierarchical nature of the healing response further supports the likelihood that endogenous organism-based adaptational processes are the underlying mechanisms for remedy effects.^{21,145-147} An exogenous agent, all on its own, could not “choose” to induce such emergent spatial and categorical changes, in location and nature of symptom manifestations across different areas of the body over time. Changes that emerge, such as gradually stopping expression of a mood disorder and starting expression of more asthma or an acute infection, or even moving a skin eruption from the upper part of a leg down toward the foot and out toward the toes, are not within the pharmacological therapeutic potential of a conventional bulk form drug. However, homeopathic remedies, by focusing most of their effects on the self-regulating adaptational networks of the patient, can initiate such extensive, albeit indirect, healing responses.

Living systems such as human beings or animals are complex self-organized, self-regulating networks whose healthy “ideal” dynamics fall in an optimal functional range between excessive order and excessive flexibility.¹¹⁹ No single outcome variable can capture the effects of interventions such as homeopathic remedies that might modulate components of the stress response in the body.^{87,148,149} Repeatedly assessing multiple allostatic load biomarkers of elements of the stress response system at the same, multiple time points over the course of treatment¹⁴⁸ is a more appropriate strategy for determining whether or not a homeopathic remedy is acting optimally to promote the healing process. *In vitro* studies, for instance, previously found that commercial combination remedies can exert antiviral effects and stimulate complex cytokine activation patterns.¹⁵⁰⁻¹⁵³ In the intact individual, the brain and the rest

of the organism would also be involved in organizing, coordinating, and self-regulating the patterns of effects as a complex interdependent and interactive system.^{88,120,154,155}

The group means generated by statistical analyses in biomedical research also obscure individual differences in clinical pictures and processes.^{156,157} A more sophisticated holistic multivariate methodological approach would borrow from mainstream systems biology to assess complex heterogeneous patterns of genomic, epigenomic,¹⁵⁸ transcriptomic, metabolomic, and proteomic functions^{6,156,157,159} of disease manifestations and healing. These more integrative and holistic interdisciplinary methods would be able to move past the limitations of reductionistic biomedical science research approaches to provide a more nuanced, individualized, and complete picture of disease and remedy responses in individuals.

Summary and Conclusions

In summary, homeopathic remedies are low doses of source nanoparticles formed during trituration and/or succussion.^{24,26} Silica from the walls of remedy containers can also form nanoparticles during succussion. NPs adsorb other nanoparticles and materials onto their highly reactive surfaces and carry them across membranes into cells.^{160,161} Nanoparticles are highly catalytic forms of source material with properties that their bulk forms do not possess, including the ability to markedly lower the plant, drug, or antigen dose needed to evoke a biological response.^{35,36,41} Other NP properties include biological, chemical, thermal, optical, electrical,³⁰ magnetic, and quantum³² effects that the bulk forms of the “same” material lack.²³ Remedy nanoparticles are likely experienced by the organism as a novel, low dose but salient biological threat or danger to survival. Compensatory reactions result in a healing response that develops and evolves over time, if the individual is sick at the moment of remedy administration. Nanoparticles can cause hormesis at very low doses.⁹⁴ Hormesis is an organism-based adaptive response that is nonlinear and bidirectional. The specific pattern of effects that a remedy source could cause would trigger organism-specific cross-adaptations¹⁴⁷ that previous higher intensity stressors in the individual's life have already primed and sensitized.^{4,93} Because of the previous priming by the disease-related stressors,⁶⁸ the low dose remedy nanoparticles elicit a cross-adapted reversal in the direction of the pre-existing adverse functional changes. The intermittent, pulsed dosing regimen for remedies allows the organism's adaptive responses to unfold over time throughout the interconnected self-organized complex living network of the person.^{15,17,19-21,145} The adaptive immune system, metaplasticity and plasticity in the central nervous system, and endocrine factors probably all play an interactive role in mediating remedy responses.

Overall, the Nanoparticle-Cross-Adaptation-Sensitization model offers a scientifically rational basis for developing focused programs of research on how homeopathic

Homeopathic Concept	Related Scientific Terminology	Implications
Remedy preparation via source titration and/or dilution and succussion (by manual pounding, wetting, or sonication) to generate homeopathic medicines. ^{22,24,28}	Top-down mechanical milling and wet milling, with or without sonication to generate source nanoparticles. ^{24,28} Adsorption of source material to nanoparticle surfaces as herb and drug delivery vehicles. ²⁸⁻³⁰	Remedies are nanoparticles of mineral, plant, or animal source material and/or source material adsorbed to lactose, ²⁸ silica or polymer nanoparticles from walls of preparation container. ²⁸
Law of Similars ²²	Cross-adaptation, ^{4,8,28} specific adaptation ¹⁴⁷ Self-similar dynamics across levels of organizational scale – Global and local network motifs (large-scale attributes and local interaction patterns – themes) ¹²⁴	Similimum remedy is cross-adapted and cross-sensitized to the cumulative adaptational changes that the whole organism has in its biological and behavioral repertoire as a result of allostatic overload from past higher intensity stressors.
Minimum Dose ²³	Hormesis ^{24,28,29} Nanoparticles can cause hormesis ²⁴	Low doses below the no-observed-adverse-event-level (NOAEL) initiate beneficial compensatory responses in the organism that counteract the adverse effects of higher doses of the same or cross-adapted agents or stressors
Medicine Action ²²	Specific direct drug action (pharmacological)	Allopathic drugs act primarily on specific local receptors, thereby hiding any compensatory local reactions on the part of the organism until the drug presence is removed (rebound).
Organism Counter-action ²²	Adaptive plasticity and metaplasticity ⁶⁸ Time-dependent sensitization ⁶⁸ Allostatic stress response: biological network ⁶⁸	Homeopathic medicines given in pulsed doses rely primarily on evoking systemic global adaptive reactions that evolve and grow in magnitude over time without needing additional stimuli until the organism's ability to continue changing reaches a plateau or relapses. Overly frequent dose repetitions will interrupt and even reverse the favorable direction of organism-based change: from beneficial to adverse (and back again) ⁶⁸
Disease ²² Stickness ²⁴	Allostatic Overload ²³ Disease-related dynamical networks ^{104,131,133} Stickness in a limited dynamical range ²⁴²	Disease results from the inability of a system to make adaptations to the impingements of higher intensity environmental stressors (all categories) and still maintain biological set points within the normal range
Law of Cure (Healing) ²⁴²	Self-organization in complex systems ^{122,242} Hierarchical modular network of cells and organisms ^{24-28,144,244}	Healing occurs in a hierarchical, self-organized process over the organism as a whole network, shifting functional setpoints back toward the normal range over the organism as a whole network
Health as freedom ²⁴²	Biopsychosocial resilience and nonlinear dynamics ¹¹⁰	Well being emerges from resilience, "the meta-flexibility of the system to respond to perturbation by either becoming rigid and robust or flexible and fluid without becoming stuck or falling apart" ¹¹⁰

Table 1. Overlap and Implications of Concepts from Homeopathic Medicine and Mainstream Scientific Research Terminology

remedies affect living systems. Table 1 summarizes relevant homeopathic concepts, overlapping mainstream scientific concepts, and implications within the overall model. As noted above, the model derives from synthesizing the research of multiple homeopathic investigators with a large body of scientific evidence from various disciplines outside of the narrow scope of the drug-oriented randomized clinical trial methods of biomedicine.

For homeopathic clinicians, this integrative model has potential to reveal new insights into the best ways to use remedies in treating patients. Understanding the nonlinear relationships between NP sizes and shapes and their effects²³ could help clinical selection of the most appropriate potency for a given patient. It might also save time and improve patient retention in treatment if new multivariate assessment strategies of allostatic load biomarkers provided more certainty early in treatment whether or not a given remedy is going to have longer-term clinical benefits.¹⁶² Other lines of research on hormesis^{107,108} suggest the hypothesis that homeopathic remedies could beneficially modify epigenetic expression and perhaps, as low dose hormetic stressors for the organism, extend telomere length and lifespan.^{107,108}

The model could also help explain the divergence between the generally positive clinical and observational trial literature versus the more mixed placebo-controlled clinical trial literature on homeopathy.^{1,2} If the initiating events in homeopathic remedy nanoparticle responses involve activating the stress response system and/or macro entanglement-like effects, then both verum and placebo might serve as initial stressors for the system. If patients experience either the verum or the placebo initially as stressors, the short-term phenotypic effects might appear to be similar clinically. However, the underlying biological mechanisms are probably different, based on basic science findings of van Wijk and Wiegant.^{4,6,93}

Findings from prior studies suggest that differential biological mechanisms in the central nervous system underlie verum versus placebo responses in allopathic medicine,¹⁶³ homeopathy,^{162,164-166} and acupuncture,^{167,168} e.g., prefrontal EEG cordance changes^{162,163} or biphasic dynamical response patterns.^{8,164,165} Our laboratory has previously demonstrated time-dependent sensitization of EEG alpha magnitude¹⁶⁹ to repeated intermittent individualized homeopathic remedy sniffs in verum-treated fibromyalgia patients, with a pattern that diverged significantly from that of placebo recipients over 3 to 6 months of treatment.¹⁶⁹ However, individuals receiving (a) overly frequent olfactory exposures to the same remedy in different potencies once a week^{164,170} or (b) the day of, versus the day after, an initial single oral remedy dose at 30C¹⁶⁵ show a more biphasic, oscillatory nonlinear EEG response pattern.

Nanoparticle forms of source materials that homeopaths routinely use as remedies are already under study in conventional nanomedicine.^{29,34,35,37,39,55,171-180} Relevant remedies would include *Silica*, *Calcarea Carbonica*, *Cal-*

carea Phosphoricum, *Magnesium Phosphoricum*, *Aurum metallicum*, *Argentum metallicum*, the *Ferrum* series, the *Carbon-based* remedies, *Adamas*, *Gelsemium*, and *Hypericum*. Even without objective clinical outcome biomarker patterns, additional studies on the nanoparticle nature of remedies themselves could improve the standardization and reliability of remedy products for clinical care. The fact that the size and even morphology¹⁸¹ of nanoparticles markedly change their properties²⁸ could underlie the reported differences in effects, duration of action and other properties of sequential potencies^{182,183} or high versus low potency forms of the same remedy.¹⁸⁴ More speculatively, the documented quantum properties of nanoparticles, including macro entanglement phenomena,³² may also contribute to the quantum entanglement-like findings that several homeopathic remedy provings researchers have reported in double-blind studies, with placebo-treated participants exhibiting verum-specific symptoms.¹⁸⁵⁻¹⁸⁷

Finally, the existing research evidence provides a rigorous case for the plausibility, mechanisms, and potential benefits of homeopathic treatment. The data put prior basic science and clinical data^{69,70,188-1911,2,192,193} into perspective, including understanding and possibly reducing variability of results from study to study or patient to patient.²⁷ Rather than taking a defensive stance in presenting homeopathy to skeptical medical colleagues, homeopaths can begin to explain their field in contemporary scientific terminology.

In conclusion, this model leads to a series of testable hypotheses that we have further outlined in other papers.^{164,165,194-196} Researchers can utilize currently available methodologies and technologies to perform key experiments. In the tradition of Hahnemann, the findings from the resultant studies can also guide empirically-informed changes in clinical practice. Homeopathy is an evidence-based form of systemic adaptational nanomedicine. It is time to move ahead with research initiatives appropriate to the nature of this uniquely holistic system of complementary and alternative medicine.

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Conflict of Interest

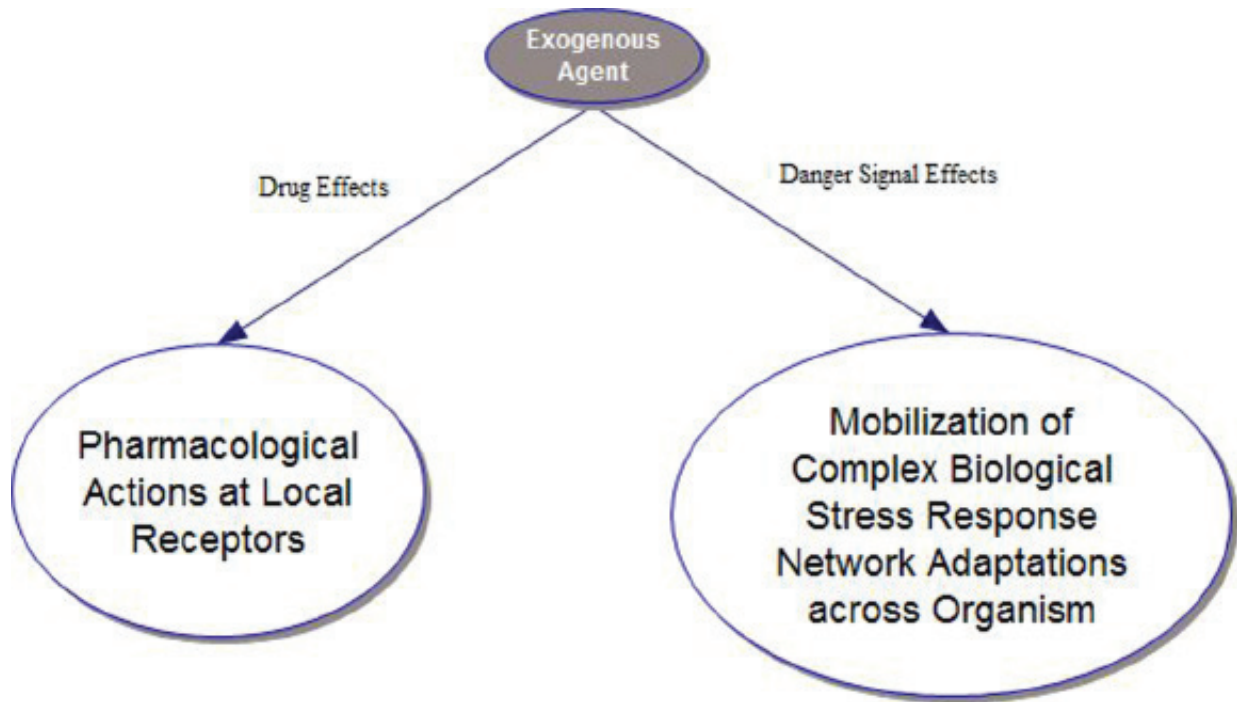
Drs. Bell serves as a consultant to Standard Homeopathic Co./Hyland's Inc., a homeopathic manufacturer whose products were not used in the cited studies. Standard Homeopathic Co./Hyland's Inc. did not provide any funding for the current paper.

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Figure 1. Dual Pathways that Environmental Agents Can Mobilize: (a) Pharmacological Direct Local Receptor Effects; (b) Stress Response Adaptation Network Indirect Reactions



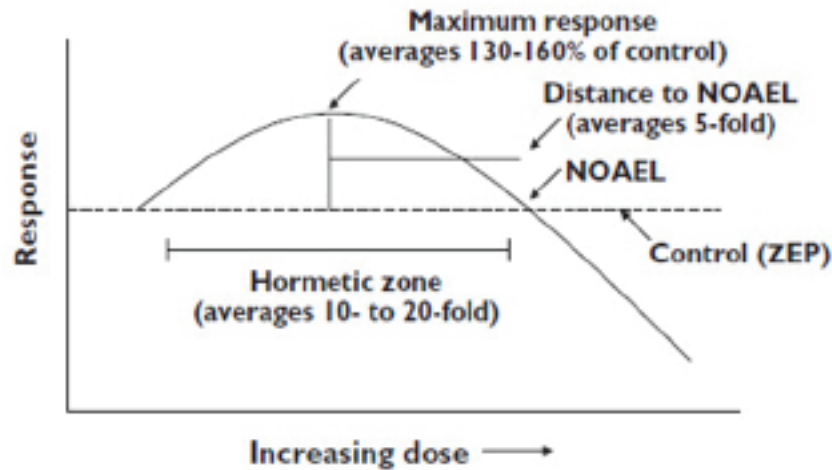
Allopathic drugs in bulk form higher doses or allopathic nanomedicines in moderate doses rely on direct local receptor-specific pharmacological effects for their effectiveness. Their effects on the stress response network overwhelm adaptive defenses with continued higher effective dose, direct receptor actions. Drug withdrawal can lead to symptom rebound because of the drug-specific adaptations that the continuous high doses have induced but masked.

The agent is directly salient for treatment of the specific local symptom manifestations, but not the organism as a whole.

Homeopathic medicines as low dose nanoparticles, in the current model, serve as an organism-specific highly-reactive danger signal or stressor to mobilize compensatory, endogenously amplified responses across the stress response network and rest of the organism. Their direct drug-like effects are minimal as the low doses given in pulsed dosing regimens, spaced over time, allow the organism to complete its indirect set of adaptive changes before the arrival of the next dose.

The agent is salient for treatment of the organism's maladaptive dynamical repertoire as a whole, and only indirectly to any specific local symptom manifestations. Functional setpoints for multiple interactive elements of the biological stress response network (CNS, endocrine, immune, inflammatory, metabolic) would be readjusted over time as a result of the self-organizing, interconnected nature of the organism.

Figure 2. Nonlinear Dose-Response Curve, NOAEL (No-Observed-Adverse-Effect-Level), and Quantitative Features of Hormesis⁹⁵



ZEP = Zero equivalent point, where capacity for repair or recovery equals amount of damage that an agent can cause.

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