

ORIGINAL PAPER

Enhancement of adaptive biological effects by nanotechnology preparation methods in homeopathic medicines



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Multiple studies have demonstrated that traditional homeopathic manufacturing reagents and processes can generate remedy source and silica nanoparticles (NPs). Homeopathically-made NPs would initiate adaptive changes in an organism as a complex adaptive system (CAS) or network. Adaptive changes would emerge from several different endogenous amplification processes that respond to exogenous danger or threat signals that manufactured nanomaterials convey, including (1) stochastic resonance (SR) in sensory neural systems and (2) time-dependent sensitization (TDS)/oscillation. SR is nonlinear coherent amplification of a weak signal by the superposition of a larger magnitude white noise containing within it the same frequencies of the weak signal. TDS is progressive response magnitude amplification and oscillatory reversal in response direction to a given low dose at physiological limits with the passage of time.

Hormesis is an overarching adaptive phenomenon that reflects the observed nonlinear adaptive dose–response relationship. Remedies would act as enhanced micro- and nano-scale forms of their source material via direct local ligand-receptor interactions at very low potencies and/or by triggering systemic adaptive network dynamical effects via their NP-based electromagnetic, optical, and quantum mechanical properties at higher potencies. Manufacturing parameters including dilution modify sizes, shapes, and surface charges of nanoparticles, thereby causing differences in physico-chemical properties and biological effects. Based on surface area, size, shape, and charge, nanoparticles adsorb a complex pattern of serum proteins, forming a protein corona on contact that constitutes a unique biological identity. The protein corona may capture individualized dysfunctional biological mediator information of the organism onto the surfaces of the salient, i.e., resonant, remedy nanostructures.

SR would amplify this weak signal from the salient remedy NPs with protein corona adsorbed, leading to sensitized nonlinear dynamical modulation of gene expression and associated changes in biological signaling pathways. When the system reaches its physiological limits during a homeopathic aggravation or the natural disease state, the amplified remedy signal triggers a nonlinear reversal in dynamical direction back towards health. *Homeopathy* (2015) 104, 123–138.

Keywords: Nanoparticles; Homeopathy; Top down; Bottom up; Nanotechnology; Complex adaptive system; Nonlinear dynamics; Stochastic resonance; Time dependent sensitization; Hormesis

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Introduction and Overview

The purpose of this paper is to discuss how traditional homeopathic manufacturing reagents and processes could generate the ability of a given potency to initiate nonlinear adaptive changes in an organism as a complex adaptive system (CAS) or network. As previously proposed,^{1–4} the homeopathic medicine (HM) would be a heterogeneous mixture of nano-sized particles (NPs, small particles that measure 1–100 nanometers along at least one dimension) of the source material, with or without the nonspecific presence of nanosilica released during succussions of solutions in borosilicate glassware.⁵ Other materials in solution also readily adsorb to, dope or seed silica NPs, thereby creating unique surface ‘defects’ and modifying their properties.^{6–12}

The smallest nanoparticles, termed quantum dots, range in size from 1 to 10 nanometers or so and exhibit quantum mechanical properties as a function of the very small size trapping of a large proportion of the atoms and their associated electrons, close to the particle surface.^{13–17} Nanoparticles in general are more bioavailable and biologically-active forms of their source material.^{18,19} Quantum dots and other very small nanomaterials can readily cross cell membranes.^{13,20,21} Their small size facilitates olfactory, oral, or dermal administration by allowing passive entry into cells and translocation via blood and lymph, including crossing the blood–brain barrier in experimental cancer treatments.²²

At least six different laboratories have now found some type of nanoparticle or nanostructure in homeopathically-prepared materials.^{1,23–27} Multiple laboratories have also identified silicates from glassware in succussed solutions.^{5,23,26,28–30} Two of those laboratories have shown biological interactions of proteins in solution with these agitation-released silica materials *in vitro*.^{5,28} Nanoparticle characterization methods included transmission electron microscopy, scanning electron microscopy, and dynamic light scattering.

Nanomedicine researchers have shown marked reductions of dose size and/or repetitions of nanoscale forms versus conventional bulk (larger) forms of a given agent by orders of magnitude, ranging from 10 to 1000 times lower for direct pharmacological effects.^{31–34} Lowering dose requirements for therapeutic effects also means that some NPs are toxic at significantly lower doses than ordinary bulk forms of the same material^{35–37} and that the cut-off level for no-observed-adverse-effects (NOAEL), i.e., where hormesis usually occurs, nonlinear low-dose responses would also be correspondingly reduced.^{4,38–41} Despite their low concentrations in HMs, e.g., in the parts per million and parts per billion range, perhaps even lower,^{1,5,42} the enhanced highly reactive large surface areas of NPs still leave them chemically^{43,44} and/or biologically^{36,45} highly active.

With NPs, however, effects are never just a matter of material composition or dose alone. Different sugars used during manufacturing can lead to different sizes of the manufactured NPs.⁴¹ Lactose but not other sugar coatings,

enhances uptake of silver NPs into cancer cells.⁴⁷ Nanosilica coating on other NPs can stabilize them.⁴⁸ Particle size, shape, and surface charge,^{13,49–51} as well as the set of serum proteins that attach or adsorb onto the nanoparticle surfaces in the body to form a unique protein corona,^{46,52} play a major role as well.^{53–56} The protein corona confers a unique biological identity apart from the physical chemical identity onto nanoparticles that get into living systems (Figure 1).

Cartwright reported in a recent conference paper on HMs that the silanol groups (silicon with an alcohol –OH hydroxyl group)⁵⁷ on the walls of the glassware in which succussions occur may play a key role in carrying the homeopathic information into higher potencies.⁵⁸ Variations in hydroxyl density on NP surfaces affect how a major serum protein like fibrinogen attaches to silica nanoparticles (NPs) as part of the protein corona at physiological concentrations.⁵⁹ Ions in solutions also affect the final NP product.⁶⁰ Thus, even subtly different manufacturing procedures would lead to variations in the chemistry and protein corona biology of specific remedy nanostructures. In turn, the interaction of the remedy NPs with the specific biology of the individual recipient would lead to the individualized physiological responses that characteristically unfold during homeopathic treatment.

Understanding HMs as various types of nanostructures with unique surface properties enables a meaningful synthesis for a larger understanding of the biology of homeopathic effects. For instance, the patterns of proteins attached to the surfaces of NPs like silica nanoparticles can determine the nature of biological effects on monocytes and macrophages in serum.^{61,62} Previous studies on homeopathically-prepared combination remedies like Canova (various potencies of Aconite, Arsenicum, Bryonia, Lachesis, and Thuja in 1% ethanol) or individual remedies like Belladonna or Echinacea demonstrated that HMs can mobilize macrophages,^{63–66} which in turn can activate lymphocytes to exert anti-cancer effects.⁶⁷

Nanoparticles of materials such as silica (silicon dioxide) and titanium dioxide also activate intracellular defenses involving the inflammasome set of proteins.⁶⁸ When the inflammasome cascade is activated, cytokines are released. Studies on other combination homeopathically-prepared remedies have shown that HMs can also induce cytokine release.⁶⁹ Cytokines are part of the endogenous neuro-immune-inflammatory network that carries biological signals from cell to cell, as well as from local tissues to brain.^{70,71}

It is important to step back from the conventional assumptions of mainstream medicine that require therapeutic agents to always act as structural ligands that fit into specific local receptors. Biology is increasingly understood as a nanoscale process with electromagnetic^{72,73} and quantum mechanical aspects⁷⁴ in a self-organized living CAS or network. By definition, a CAS is ever-responsive to environmental change.^{75,76}

Exogenous nanoparticles and nanostructures speak to the biology of the organism as a whole CAS with nonlinear dynamics. One aspect of the adaptive network communication

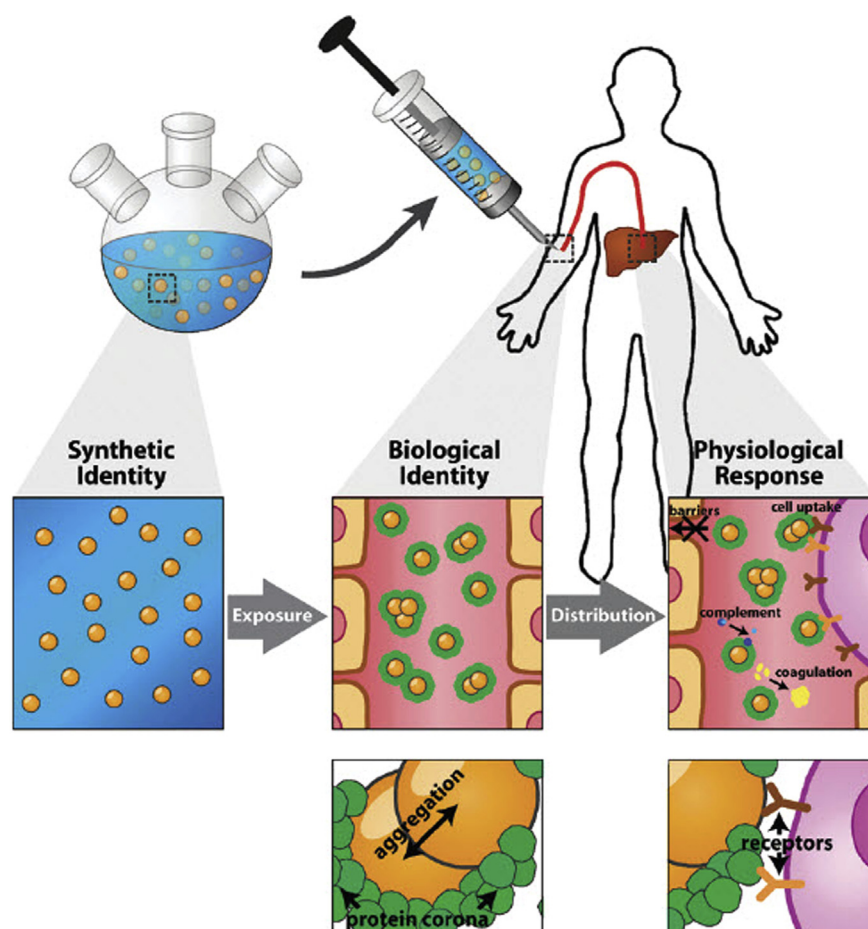


Figure 1 Relationship between synthetic identity, biological identity, and physiological response. Synthetic identity is the size, shape, and surface chemistry of a nanomaterial post-synthesis. Biological identity is the size and aggregation state of the nanomaterial in a physiological environment, along with the structure and composition of the protein corona. Physiological response is the subsequent interaction of nanomaterials with biomolecules, biological barriers, and cells in the body. Reprinted with permission.⁴⁶

carried by biological mediator signals relies on ligand-receptor features, but other major aspects can stem from the electromagnetic, optical, and quantum mechanical properties of small nanoparticles. Every reagent, contaminant, and procedure involved in manufacturing nanomaterials can modify their surface chemistry and thus, their biological effects.⁷⁷

Homeopathic manufacturing as nanotechnology: top-down and bottom-up methods

Modern nanotechnology has developed two classes of methods by which to make nanoparticles of a given source material (Figure 2).

- (1) **Top-down methods** mechanically mill or grind larger sized insoluble materials including insoluble drugs into increasingly smaller particles, using dry or wet media.^{1,23,42,79–83} Some of these mechanical methods rely on ball mills⁸⁴; others use multi-directional glass tubing to cause materials in colloidal solutions under pressure to move back and forth and collide with one another,

thereby shearing off smaller particles from larger sized materials.⁸⁵ Nanotechnologists have reported that ball milling generates NPs from rice husk ash.⁸¹ Ball milling of eggshells, combined with ultrasound, makes calcium carbonate nanoparticles (cf., *Calcareo Carbonica*)

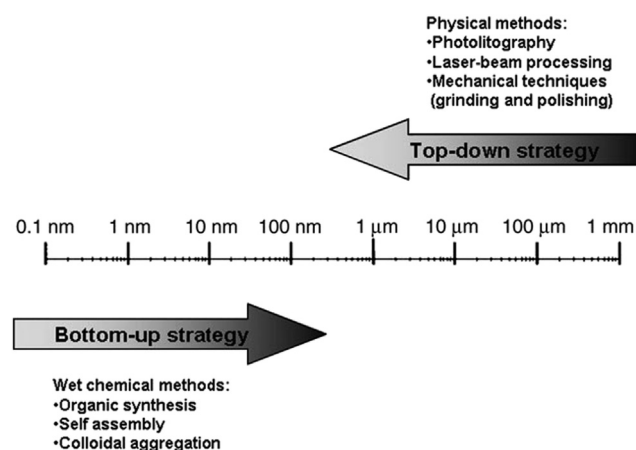


Figure 2 Top Down and Bottom Up Manufacturing Strategies for Nanoparticles. Reprinted with permission.⁷⁸

of different sizes and shapes with different surface areas in various solvents.⁷⁹

These nanotechnology processes are respectively analogous to homeopathic manual trituration in dry lactose or succussions in liquid solutions.^{79,81,86} One nanotechnology group found that combining milling with ultrasound agitation of the solutions was most effective for creating and dispersing the resultant NPs compared with either method by itself.⁸⁷ Clearly the traditional methods of homeopathic manufacturing with triturating and succussing are not identical to the procedures of modern nanotechnology, but the mechanical processes of prolonged grinding and agitation in solution overlap.

It is an open empirical question as to whether or not traditionally-made HM NPs are the same, better, or worse in their clinical effectiveness and safety compared with modern manufactured NPs. Clearly homeopathic manufacturing is 'green' in that the reagents are natural materials rather than synthetic chemicals that can leave trace toxic adsorbants on the NP surfaces.⁸⁸

A common method for less toxic nanotechnology manufacturing of nanoparticles is to apply ultrasound or sonication as the means of agitating a given solution.⁸⁶ A variant of this mechanical method with soluble source materials such as sodium chloride (cf., *Natrum muriaticum*) or potassium iodide (cf., *Kalium iodatum*) involves intense agitation of a solute-solvent solution with ultrasound to concomitantly generate source nanoparticles and embed them into the walls of the glassware container.⁸⁹ The sodium chloride or potassium iodide NPs then diffuse off the glassware walls over time.

The latter observations may be particularly relevant to Korsakovian manufacturing methods, in which the same container is used and reused to make higher potency HMs. Small amounts of remedy source NPs could also dope or seed some of the nanosilica⁶ in solution to create a unique silica-amplified signal containing remedy-specific information.^{90–94} Increasing the number of succussions can reportedly reduce particle size of homeopathic plant extracts to less than 14 nanometers on dynamic light scattering.²⁷

(2) **Bottom-up methods** take advantage of the self-organizing, self-assembly properties of certain nanomaterials such as nano-silica.^{95–101} In molecular imprinting, researchers use templates such as viruses,¹⁰² DNA,¹⁰³ plant-based constituents such as diosgenin from wild yam,⁹⁹ or toxic chemicals such as bisphenol^{104,105} anchored onto larger silica surfaces. They then add silica precursors in solution. The silica self assembles and builds up highly-specific nanostructures around the template source materials.

The investigators then remove the original template source material and use the molecularly-imprinted silica nanostructures as highly sensitive and specific sensors or extractors to detect or remove the template material from subsequent test samples, even at extremely low concentrations in the parts per trillion range.^{106,107} Perhaps relevant

to the nano-domain model for HMs,¹⁰⁸ nanotechnologists have also synthesized drug-specific nano-domains inside silica microspheres, e.g., ibuprofen.¹⁰⁹ Other types of drug nanoencapsulation can occur by bottom up self assembly as well.¹¹⁰

Biological synthesis of nanoparticles from precursors in solution with plant or fungus extracts or other biological sources involves naturally containing enzymes that biochemically reduce the precursor reagents, e.g., silver nitrate, into silver nanoparticles.¹¹¹ Biosynthesis methods are categorized as a subtype of bottom-up NP manufacturing methods.

The extensive evidence from multiple independent laboratories that succussions release silicates into solution raises a testable follow-up question. That is, do the silicates released from the glassware self assemble into new structures and/or are biosynthesized into biologically active nanosilica components in higher potency HMs? The nanotechnology evidence suggests that non-specific nanosilica structures,^{28,112} remedy-doped nanosilicon/silica,¹¹³ and/or remedy source template-specific imprinted nanosilica^{99,102} are possible.

Dilution in nanoscience: possible relevance to homeopathic manufacturing

What role might the serial dilution process play from a nanotechnology perspective? The nanotoxicology^{114,115} and nanochemistry^{43,44,116} research literature shows clear-cut dilution-related phenomena. Unlike bulk form materials in dilution, diluted colloidal solutions of nanoparticles do not necessarily exhibit the same properties as more concentrated solutions of the same source material.¹¹⁵ For instance, nanotoxicologists sometimes find that certain more diluted nanomaterials at low, environmentally relevant concentrations can be more toxic to living systems than are more concentrated quantities.¹¹⁴

Even in the nanochemistry laboratory context, palladium NPs used as chemical catalysts are more effective in greater dilutions than in more concentrated solutions.^{43,44,116} The dilute palladium NPs in trace amounts measured at parts per million or even parts per billion are more able to regenerate themselves as intact active catalysts and continue to catalyze chemical reactions for longer periods of time compared with more concentrated solutions. The ability of low concentrations of some NPs to regenerate themselves as catalysts or persist inside cells at very low concentrations may be a therapeutic advantage in nanomedicine as well. That is, nanomedicines typically persist and act for longer periods of time once inside cells, permitting widely-spaced doses in time, compared with bulk conventional forms of drugs.³³

One explanation for the dilution-related phenomena of nanomaterials is that physically separating the highly reactive nanoparticle surfaces from one another leaves the smaller NPs' surface reactivity intact.¹¹⁴ The separation by

Table 1 Manufacturing variables that can affect sizes, shapes, and surface charges of manufactured Nanomaterials^{55,56,60,114,115,118,119}

Type, force and duration of milling or grinding
Type, force and duration of agitation in solution
Presence of lactose or other sugars
Presence of inorganic reagents even in trace amounts
Presence of organic materials, particularly proteins
Temperature
Pressure
pH of solutions
Ions in solutions
Silicate-shedding Glassware
Dilution
Time factors – Brownian motion, particle agglomeration and aging in colloidal solutions

dilution reduces NP collisions from random Brownian motion in a given volume that would otherwise lead to agglomeration into larger, less reactive particles with less surface area and fewer atoms trapped near the surface. In agglomeration, not only surface reactivity and surface charge can change, but surface area of larger particles to adsorb other materials is much lower than of smaller particles.¹¹⁷

Agglomeration can also modify the shape of the resultant particles, which again can change their physical, chemical, and biological properties. Larger or bulk forms of materials have invariant properties in different quantities; nanoscale forms of materials do not. Table 1 lists the variables that nanotechnology research has found can modify the sizes, shapes, and surface charges of manufactured nanomaterials.

Biosynthesizing metal NPs with plant extracts such as garlic can sometimes modify and stabilize surface properties, thus reducing particle agglomeration.¹¹¹ Drying manufactured NPs for storage is also a practical way by which nanotechnologists reduce agglomeration risks and stabilize nanomedicine properties for eventual reconstitution.^{120,121} Methods include spray freeze-drying or drying onto

lactose surfaces.^{122,123} Nanosilica and other nanostructures can survive drying.^{48,124,125}

Nanoparticles and homeopathic remedy actions

As Hahnemann originally observed,¹²⁶ any given agent or stressor will exert both direct actions and elicit indirect (counter-action) adaptive reactions. At lower NP concentrations after serial dilution removal of bulk forms, it is the indirect, adaptive response of the organism that would assume greater importance than direct effects for homeopathic treatment. Both local and non-local phenomena may underlie the indirect adaptive effects.

Very low homeopathic potencies may simply offer micro-sizing and some nano-sizing enhancement as better drug delivery vehicles⁸² for direct ligand-receptor effects of herbs, minerals, and animal materials.^{32,127,128} However, higher potency homeopathics, which would contain low concentrations of small remedy source and silica NPs without residual bulk forms to interfere, probably act mainly to elicit indirect adaptive responses rather than direct pharmacological (local ligand-receptor) effects in the body (Figure 3).

Silica is a non-specific amplifier of antigen and other NP effects in the body. NPs, for example, can activate the intracellular inflammasome proteins that lead to cytokine activation, as well as mobilize dendritic cells in the immune system to cause inflammatory reactions. Cytokines then signal the brain of changes in the inflammatory steady state of the rest of the body. Additional elements of the biological stress response network are then mobilized. Silica NPs also induce the release of exosomes, nanosized vesicles from cells that serve as cell to cell communicators.^{129,130} NPs enhance the anti-cancer cell effects of a snake venom against various types of malignancies.^{131,132}

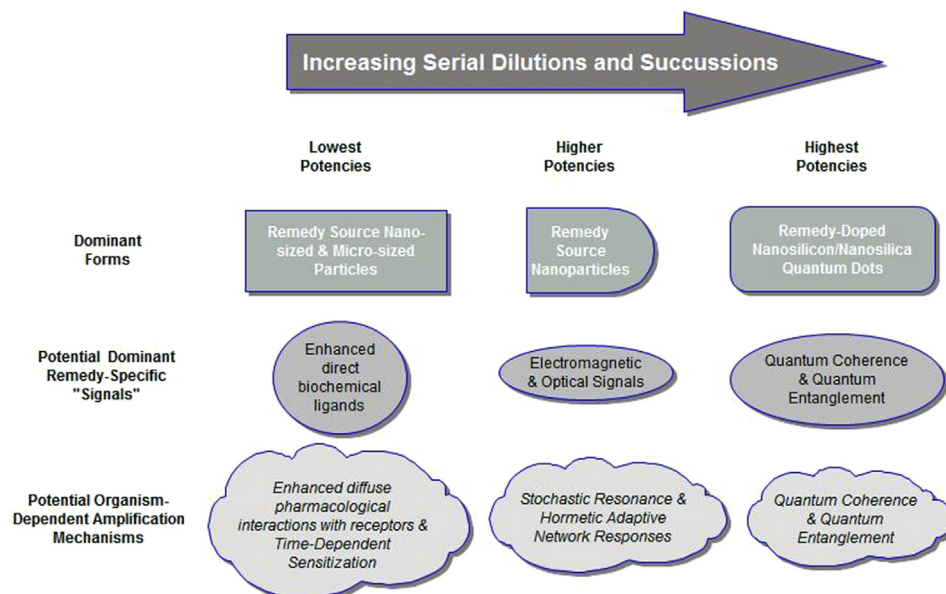


Figure 3 Homeopathically-prepared materials May exert biological effects via multiple adaptive Amplification processes in the body.

Thus, whenever silica NPs are in solution with remedy source NPs or carried in dry form with remedy NPs on sugar pellets, the prediction would be that the amount of remedy source NPs needed to elicit vigorous biological adaptive responses will be even lower than it already would be from the presence of the remedy-specific reactive nanomaterials alone.^{133,134} Nanosilica is an immune adjuvant.^{134,135}

Are silica NPs a necessary part of homeopathic remedies? No.¹³⁶ Very low potency remedies may only be lactose triturated and never put into glassware. Trituration per se will grind the starting bulk materials into micro-sized and nano-sized particles with increased bioavailability and biological activity. Moreover, for plastic containers, polystyrene and polypropylene can also generate nanoparticles with some of their own adsorptive and immune system effects.^{34,137–140} Nanoparticles can adsorb onto stainless steel container surfaces as well.^{141,142} However, if a manufacturer uses traditional methods to make their higher potency remedies, borosilicate glassware — and hence, silica — will likely be involved during succussion steps.⁵

In contrast with conventional bulk form materials, smaller nanoscale structures, including nano-silica, acquire unusual electromagnetic, magnetic, optical, electronic, and quantum mechanical properties.¹⁴³ The ability of NPs to evoke adaptive changes in an organism would stem from their capacity to communicate organism-salient, i.e., ‘resonant,’ information in the biological realm at the nanoscale with not only their structural particle-based local ligand-receptor features, but also across the biological networks of the body their wave frequency-based electromagnetic, magnetic, optical, and nonlocal quantum information properties.¹⁴⁴ One well-known opto-electronic property of metal nanoparticles is localized surface plasmon resonance (LSPR). In LSPR, light excites collective electron charge oscillations that propagate along the interface of the particle surface and surrounding medium. Particle shape and materials adsorbed onto the NP surfaces will change these oscillations and the associated resonant frequency.^{145,146}

When nanomaterials interact with biological systems, complex effects emerge. An overarching hypothesis in the present update of the nanoparticle-cross-adaptation-sensitization (NPCAS) model^{3,4,147} is that the properly-chosen HM is a low dose nanomaterial that signals biological danger to the survival of the recipient as a CAS. Subsequent biological signaling and amplification processes in the body carry out the adaptive response amplification across the larger network of the living system.¹⁴⁷

Environment—organism interface: homeopathic nanomaterials as exogenous danger signals for stochastic resonance (SR) amplification in a CAS

A large body of evidence indicates that human beings, animals, or plants are all complex living systems with inter-

related, interactive, interconnected parts that self-organize into an emergent complex whole.⁷⁶ Researchers in complementary, integrative, and alternative medicine increasingly recognize that the conceptual and methodological features of contemporary complex systems science map better than reductionistic, mechanistic models onto the practice theories of CAM systems such as classical homeopathy.^{148–151}

Complexity science focuses on the interconnectedness and network nature of a living system as a whole and on changes in the nonlinear dynamics of which such systems are capable in adapting to environmental change.^{149,152–157} Independent homeopathic research groups have demonstrated objective evidence of the ability of homeopathically-prepared medicines to modulate the nonlinear dynamics of the recipients and/or self-organized fractal patterns of systems in the relatively short term. For example, Hyland and Lewith¹⁵⁸ showed oscillatory patterns of change over 15 weeks’ treatment with verum dust mite 30C but not placebo in adult asthmatics. Bell et al. found acute changes in multiscale entropy of sleep EEG, a measure of system complexity, after single doses of *Nux vomica* 30C or *Coffea cruda* 30C, with rebounds in direction of sleep EEG complexity on the subsequent night.¹⁵⁹ Baumgartner et al. produced unique in vitro complex self organized structural patterns of biocrystallization with homeopathic remedies that differed from controls.¹⁶⁰ Baumgartner has pointed out that HM effects are larger with increasing complexity of the recipient system, from isolated remedies to organism levels of scale.¹⁶¹

The unique electromagnetic, optical, and quantum mechanical properties of nanomaterials in HMs outlined above translate into the potential to trigger and modulate biological changes amplified across a CAS or network. Recent data suggest that nanomaterials, like pathogens (viruses, bacteria) or endogenous tissue damage with mediator release, can serve as homeostatic danger signals^{70,162} and biological defense pathway modulators. That is, NPs in HMs literally could communicate with living systems via signals from their specific electromagnetic and optical wavelengths or frequencies. Empirical data in homeopathy indicate that HM potencies emit detectable electromagnetic¹⁶³ and photon-based^{164–167} signals.

How would the intact body even detect such weak environmental signals or threats? Many skeptics of homeopathy dismiss the plausibility of the field because of the seemingly obvious fact that the remedy signal must be small and weak at such low concentrations, if present at all. However, homeopaths only predict a robust clinical response if the specific chosen remedy is salient to the individual’s whole picture, i.e., a good pattern match, to the organism’s expressed symptom pattern. The individualized symptom pattern is a proxy or the emergent phenotypic expression for the underlying biological disturbances taking place dynamically throughout the organism. That is, the disease would generate a specific emergent pattern of complex biological noise.

Because of the self-similarity across levels of organization scale in CASs,^{168–170} symptom patterns may thus

serve as reflections of the underlying maladaptive biology that the properly-chosen HM can modulate back towards wellness. Nature has well-developed nonlinear amplification mechanisms for recognition of and communication about meaningful or salient environmental signals.^{171,172}

In a complex network, local and global levels of organizational scale interact and modify one another.¹⁷³

One widely-recognized way in which cells as living systems amplify information and communicate with one another over long distances within an organism is termed SR. SR¹⁷⁴ is the nonlinear coherent amplification of a weak signal by the superposition of a larger magnitude white noise containing within it some of the same frequencies of the weak signal.¹⁷⁵ The best studied evidence of SR in biology is in sensory neural systems.^{176–178}

Extensive research shows that animals and human beings engage with the environment via sensory neural (olfaction, taste, touch, vision, hearing) and/or immune system surveillance. In the face of the much larger exogenous and endogenous noise in the system, biological systems take advantage of the fluctuating exogenous and endogenous noise to amplify small but salient signals with SR. In turn, the organism can respond with nonlinear dynamical shifts that lead to large magnitude biological and behavioral adaptive responses.

SR occurs in both natural and artificial systems, but only in nonlinear complex systems,^{179,180} e.g., the human body. SR would be most relevant to the transduction of the remedy information from higher potencies (containing lower concentrations of specific NPs) into endogenous self-amplified biological signaling events embedded in the larger biological noise of disease that result in healing.

Animals can detect predators by SR of small but specific environmental perturbations that signal survival danger to the prey via low levels of specific sensory information.^{176,181–184} Research also reveals that SR occurs in quantum systems.^{177,185–189} Thus, even if the remedy NPs were conveying information via quantum tunneling¹⁹⁰ or quantum entanglement,^{191,192} SR could be involved.¹⁸² SR, first proposed as a mechanism for homeopathy by Torres in 1996,¹⁷⁴ is one plausible, testable model for remedy signal detection, recognition, and nonlinear sensory neuron amplification that would occur at the environment–organism interface.

The clinical pattern matching that homeopaths seek between remedy properties and symptom pictures of the individual patient would have its biological parallels in the electromagnetic, opto-electronic, and/or quantum mechanical signal or frequencies generated by the nanomaterials that constitute the correctly chosen HM. SR would be the mechanism that enables detection of the otherwise small – but salient – signal of a remedy that could be electromagnetic^{193–195} and/or photon-based^{164,165,196} in nature. SR pertains to nanoscale quantum mechanical systems as well.^{182,197}

For a danger signal, salience rather than magnitude of the signal as an environmental or homeostatic threat to survival is foremost. In the body, the salience derives from the pattern match between the specific frequency of the small

signal and the endogenous capacity to detect, recognize, and amplify the information. The pre-existing state of the system, i.e., disease or aging, would create the biological noise¹⁹⁸ that can amplify the homeopathic information via SR. As a result, even a small danger signal (e.g., predator odorant in the parts per trillion concentration¹⁹⁹ or other subtle perturbations affecting not only olfaction, but also taste, vision, audition, and tactile senses^{181,200}) once detected, can initiate a complex cascade of endogenous events and amplification that lead to large magnitude biological and behavioral adaptive responses.

Endogenous response amplification: time-dependent sensitization (TDS) to perceived danger signals

How the intact living system utilizes the SR-amplified information from salient nanomaterials in HM makes a significant difference in how the nonlinear adaptive response unfolds across the organism. Any organism or CAS is embedded within its larger environment. Changes in the environment evoke multiple coordinated adaptations in the CAS to optimize resilience as much as possible.¹⁵² The potential interplay between nanostructures in HMs, the recipient CAS, and the individual's larger environment leads to a pattern of nonlinear dynamical changes in the organism that can produce an emergent healing response.

Studies suggest that a salient small signal can initiate a sudden switch in biological or psychological states from one condition to its opposite,¹⁵² e.g., a bifurcation in nonlinear dynamics. For example, model systems have shown the potential for a small salient SR signal to cause changes between bistable states in gene expression patterns.¹⁷⁵ That is, if a gene is 'on,' the response to the SR-amplified weak signal turns it off, or vice versa.^{201,202}

Multiple laboratories have now reported precisely such extensive biological responses to homeopathically-prepared remedies, i.e., complex patterns of changes in gene expression.^{203–206} Data show that it is not necessary to administer a toxic dose of NPs to produce oxidative stress, cell injury or to set homeostatic danger signaling in motion.^{40,207–210}

When an agent triggers adaptive changes in gene expression, evidence of those effects appears in the downstream modulation of the biological signaling mediators controlled by the affected genes. In the case of HMs, data from multiple laboratories already indicate that HMs mobilize and modulate the biological stress response pathways.²⁰³ These pathways participate in immune, inflammatory, metabolic, hormonal, and nervous system regulation.²¹¹ In homeopathic research, Khuda-Bukhs²¹² postulated that homeopathically-prepared medicines act via mobilization of biological signaling pathways.

As predicted, his research group and other investigators^{63,203–206,213,214} have now shown that remedies up to at least 30C can modulate gene expression in various animal and cell types, effecting complex regulatory changes in multiple variables at once and activate

cascades of complex biological signaling events. Furthermore, other studies have documented the ability of homeopathically-prepared medicines to modulate heat shock protein patterns, cytokine release, macrophages and lymphocytes activation in the immune system. These biological mediators are part of the larger cellular stress response defense network.^{71,211,215}

The next type of endogenous adaptive bidirectional amplification that intermittent and repeated danger signals can initiate is TDS. *TDS/oscillation*^{216–222} is the progressive non-linear amplification of response magnitude by the passage of time between the initiating agent or stressor and the same or a cross-sensitized eliciting agent or stressor. One exposure to a given agent or stressor can initiate TDS, but repeated intermittent exposure schedules are more common.

Agents and stressors from entirely different categories can cross-sensitize; structural chemical similarity is not necessary. The ‘dose’ of the sensitizing agent can remain low, but the size of the response grows with the passage of time. Cytokines can initiate or mediate TDS,²²² but immune system involvement is not necessary for this type of adaptive phenomenon to occur.^{223,224} Central nervous system sensitization is implicated in development of chronic pain, for instance.^{225,226}

TDS is an organism-dependent phenomenon. Variations in sensitizability stem from individual difference factors such as female gender, genetics (parental substance abuse histories), and high sucrose preferences.²²⁷ The past history of the recipient organism and the endogenous capacity for sensitizing affect the emergence of TDS adaptations.

Excessive intermittent repetition of an initiating or cross-sensitized eliciting agent can reverse the direction of response. This directional reversal occurs at physiological limits.²²¹ Consequently, a testable hypothesis is that a homeopathic aggravation would occur when the CAS to close to but not at its physiological limits. Then, once the system does reach its limits, the direction of the TDS amplified response oscillates, i.e., reverses in direction. For homeopathy, the ability of one or many high intensity agent(s) or stressor(s) (life events, adverse environmental exposures) to initiate adaptive/maladaptive changes, but a low intensity dose of a different agent or stressor (simillimum remedy nanostructures) to elicit the amplified reaction is a core aspect of the overall model.

In two different placebo-controlled randomized and blinded studies, our laboratory has demonstrated TDS and oscillation of objective electroencephalographic (EEG) responses to individually-salient HMs.^{228–230} We also observed individual differences in the recipient host affected the stability versus instability in the direction of the EEG responses.²³¹

Notably, empirical evidence on odorant recognition in olfaction indicate that these agents may utilize shape-related ligand-receptor mechanisms or vibrational characteristics of the odorant molecules. The vibration-related recognition model involves electron quantum tunnelling for odorant discrimination.²³² Since aerosolized small nanoparticles are capable of deposition in the nose and transport by olfactory nerves into the brain,²¹ the EEG ef-

fects that we observed might reflect not only ligand-receptor interactions, but also the quantum properties of the smaller NPs (10 nanometers or smaller in size) in the higher potency HMs on the olfactory sensory system.

Hormesis: emergent outcome of adaptive amplification events in the organism

Research has also shown that nanoparticles exhibit hormetic nonlinear dose–response relationships in which low and high doses of a given NP can produce effects in opposite directions.^{233,234} Hormesis,^{235–237} is a non-linear dose–response relationship in which low doses elicit responses opposite in direction to those that high doses cause. Hormesis would be most relevant to bidirectional effects as a function of low versus high dose per se.

Hormesis describes a wide range of low versus high dose phenomena, with increasing research on specific potential biological mechanisms.²³⁸ SR and hormesis are conceptually compatible and potentially complementary to one another as conceptual models. SR amplification of low-dose NP signal properties at the interface of the body with its external environment could initiate the adaptive events of hormesis.

Allostasis is the tendency of a living system to adapt and maintain steady state through changes in the internal and external environment. Multiple investigators have found that past and ongoing experiences with unrelenting environmental stressors may shift physiological setpoints away from a healthy into a diseased state. Allostatic load refers to the cumulative effects of this type of chronic wear and tear on the body systems from inability to restore true health.

The shift translates in biology into the epigenetics of disease. The system adapts to the repeated or continuous impact of chronic stressors and environmental agents by generating symptoms and chronic diseases.^{71,215,239} In the present model, the correctly-chosen HM induces a beneficial switch in dynamics that shift the maladapted setpoints and epigenetic expression back toward health (see Figure 4).

Summary and conclusions

Researchers in each type of nonlinear adaptive phenomenon, SR, TDS/oscillation, and hormesis, have independently postulated that the body perceives the environmental agent or stressor as a threat or danger to survival.^{200,224,233,240,241} The biological and behavioral responses would reflect the adaptive efforts of the organism to throw off or avoid current threats or prepare for future threats from the same or a cross-adapted agent or stressor. Nature uses these phenomena in living systems to optimize chances of survival in the face of environmental change and challenge.

For the nanoparticles in HMs to initiate adaptive change in the organism, the source material’s properties must be

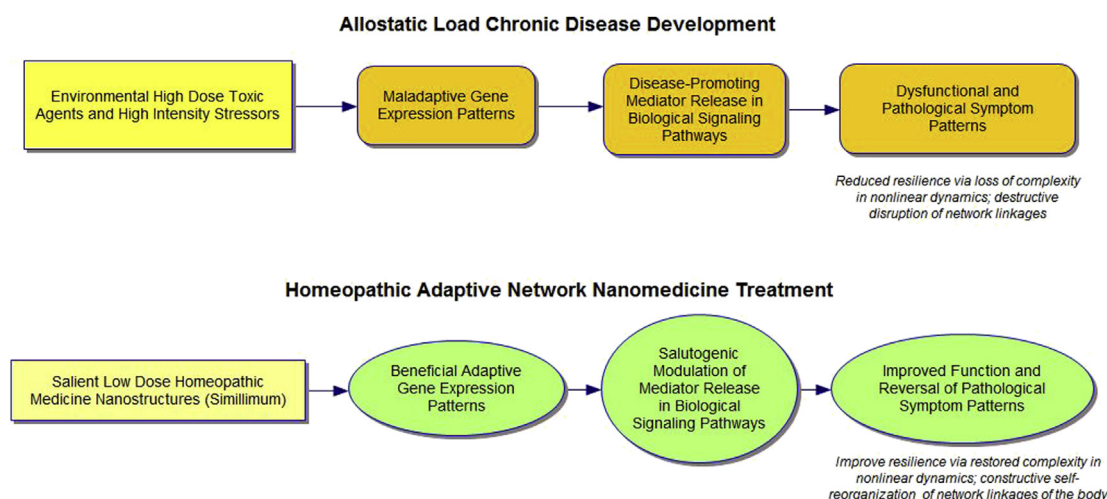


Figure 4 Schematic of Biological Event Flow Model for Salient Homeopathic NP Actions. The salient remedy serves as an environmental danger signal to modulate adaptive changes across the organism as a complex adaptive system or network. Initial remedy detection from nonlinear signal amplification occurs as a result of stochastic resonance *at sensory interfaces and other cellular defense subsystems* between the individual and the environment. The reversal in directionality from disease toward health stems from hormesis-related adaptive processes and the growth of the response over time via time-dependent sensitization processes.

salient as a danger signal for the unique biological history and adaptive capacity of that individual recipient. Nano-scale forms of materials are more bioavailable and more potent at a lower dose. Different sizes and shapes of nanoparticles with different surface charges will exert different effects via a variety of mechanisms. These mechanisms would include conventional ligand-receptor interactions as well as electromagnetic, optical, and quantum mechanical properties.

The multiple variables that affect NP manufacturing processes will ultimately affect the nature and quality of the specific signal information that a given dose of HM can communicate to the body. Serum protein patterns, disease-related biological mediators and the nonlinear dynamical state of the organism at the time of administration, would all contribute to the emergent effects of the remedy dose on the individual. Subtle differences in NP size, shape and surface properties will alter biological effects.

The crudeness of the 200-year-old homeopathic manufacturing methods for grinding, milling, and agitating HM sources produces many irregular sizes, shapes, surface roughness with defects, and surface nanopatterning of nanoparticles.^{242–244} This structural crudeness at the nanoscale may turn out to be a clinical advantage for HMs over modern, spherical homogeneous NPs as exogenous danger signals to initiate biological adaptation.

Increased roughness and irregularity of nanoparticle surfaces confers greater surface area and increases the likelihood that the body will recognize homeopathic NPs as foreign danger signals or novel biological threats from the environment.^{242,245} Nanoscience studies show that such particle irregularities, surface roughness and defects generate greater surface area and biological signal properties for the cell danger detection pathways than do the more uniform particles made with modern sophisticated nanotechnology methods.²⁴⁶ For example, nanoparticles mimicking the rough surface topography of

viruses (which are inherently nano-sized)²⁰ are taken up better than by cells than are NPs with more regular surfaces.²⁴⁵ Arrays of non-identical NPs are also capable of reliable SR amplification in model systems.^{179,180}

On the other hand, these irregularities during homeopathic manufacturing may continue to make it difficult for researchers to reliably reproduce effects in experimental settings.^{161,247} Evaluating details of manufacturing parameters in the laboratory setting may improve the likelihood of replications. However, difficulty in reproducibility is also a hallmark of nanomaterials in general.^{56,248–250} It may be the case that the mechanisms underlying the difficulty in reproducibility may be similar for HMs and NPs.

In conclusion, living systems are capable of detecting, reacting and adapting to seemingly small nanoscale threats that herald the possibility of a subsequent larger onslaught from the same agent or stressor. The interaction of nanostructures in HM with the organism as a nonlinear dynamical adaptive system provides a plausible and integrative scientific foundation for how the small signals of homeopathy can initiate the large magnitude healing processes that clinicians report.

Competing interests

Dr. Bell is a consultant to Standard Homeopathic/Hylands Inc, a U.S.-based manufacturer of homeopathic medicines. This company did not provide any financial support for the paper or its publication costs, and none of the homeopathic studies cited here utilized their products.

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