

# Nonlinear Response Amplification Mechanisms for Low Doses of Natural Product Nanomedicines: Dynamical Interactions with the Recipient Complex Adaptive System

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## Abstract

The purpose of the present paper is (a) to outline the self-organized, complex adaptive network nature of the organism as recipient of nanomedicines; (b) to propose several nonlinear endogenous amplification processes by which pulsed low doses of traditional, homeopathically-manufactured natural product nanomedicines may stimulate a return toward healthier function; and (c) to discuss their potential relevance to novel, but safer than conventional dosing strategies for contemporary nanomedicines. Homeopathy is an over 200-year-old system of complementary and alternative medicine (CAM) that uses low doses of natural plant-, mineral-, and animal-sourced nanomedicines. Homeopathic manufacturing is “green”, with mechanical grinding in lactose and agitation in ethanol-water as primary reagents. Agitation within glass containers at room temperature may also contribute nanosilica and nanosilicon as drug delivery vehicles and biological amplifiers. The medicine selection is matched to the recipient organism’s systemic patterns of dysfunction and pulsed in the timing of the discrete doses. Endogenous amplification processes within the recipient organism may involve hormesis, time-dependent sensitization, and/or stochastic resonance. Effects are adaptive and systemically diffuse, i.e., causally indirect, rather than pharmacological and local, i.e., direct. All of these nonlinear response processes require interaction of the nanoparticle (NP) dose with the organism as a complex adaptive system. The pulsed NP dose serves as a low intensity salient danger signal for the organism to make network-wide adaptive changes that can lead to healing. The historically safe therapeutic approach of homeopathic nanomedicine dosing avoids risks of high, continuous doses and cumulative toxicity that contemporary nanomedicine researchers are now trying to solve while using NPs as if they were conventional bulk drugs. Integrating the insights, technical procedures, and clinical dosing approaches from modern and homeopathic nanomedicine could lead to major advances in the field for more effective and safer translational applications.

**Keywords:** Nanomedicine; Homeopathy; Nanoparticles; Hormesis; Stochastic resonance; Nonlinear dynamical systems; Complex adaptive systems

## Introduction

The purpose of the present paper is (a) to outline the self-organized, complex adaptive network nature of the organism as recipient of nanomedicines; (b) to propose several nonlinear amplification processes by which pulsed low doses of traditional, homeopathically-manufactured natural product nanomedicines may stimulate a return toward healthier function; and (c) to discuss their potential relevance to novel, but safer than conventional, dosing strategies for contemporary nanomedicines. Homeopathy is an over 200-year-old system of complementary and alternative medicine (CAM) that uses low doses of natural plant, mineral, and animal sourced nanomedicines. The medicine selection is matched to the recipient organism’s systemic patterns of dysfunction, prepared in a “green” manner and pulsed in timing of the discrete doses [1,2]. Effects are adaptive and systemically diffuse, i.e., indirect causality, rather than pharmacological and local, i.e., direct causality.

Convergent basic science studies reveal the presence of mechanically-generated source material [3-5] and silica/silicon nanoparticles (NPs) in homeopathically-prepared medicines [4,6-9]. Nanobubbles made during the manufacturing process may also contribute to the final product [8,10,11], which retains physico-chemical properties of the original source material [12]. The evidence further suggests the presence of a polydisperse population of the source

NPs in homeopathic medicines [3]. NP concentrations are low, but measurable [3]. Like modern manufactured NPs [13], homeopathically-manufactured medicines in solution also can exhibit aging effects [9,14]. These nanomedicines are delivered either in ethanolic liquids or sprayed and dried onto lactose or lactose/sucrose pellets for oral administration.

Homeopathic manufacturing materials and methods are inherently “green” [15,16]. Previous papers have addressed the striking similarities between modern top-down mechanical attrition procedures for making nanoparticles (NPs) [17] and historical homeopathic medicine manufacturing methods and materials [15,18-21]. These similarities include mechanically grinding source materials in lactose for hours and repeatedly agitating ethanol-water solutions containing the source

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materials within glass containers at room temperature. Lactose may serve as a reducing, capping, and coating agent to modify and deliver homeopathically-made NPs [11,22-26].

Multiple laboratories have demonstrated release of nanosilica and silicon from the inside walls of glassware from agitation of liquid solutions [6-9,27-29]. Mechanical agitation also disperses larger structures into small nanoparticles [30-32]. Ethanol concentrations modify the size and shape of any resultant nanosilica [33]. Nanosilica and nanosilicon, when present from agitating the liquid medicines in glassware, would add (a) biological amplification and adjuvant effects [34,35] and (b) the possibility of serving as drug delivery vehicles [36,37] for homeopathically-manufactured natural source nanomedicines. Plants can coat the surface of such nanostructures [38] and minerals can serve as dopants to modify nanosilica/silicon properties [39]. Thus, surface-modified nanosilica/silicon could convey unique amplified plant- or mineral-derived information into cells, just as plant-synthesized gold nanoparticles can do [40].

The manufacturing methods encompass not only top-down mechanical methods, but potentially also bottom-up plant extract-based biosynthesis [40] and self-assembly of silica and silicon nanoparticles [41-44]. The serial "dilution" process of homeopathic manufacturing apparently removes bulk form materials from the agitated solutions, but ends up transferring the source nanoparticles from one preparation step to the next [11]. The final product is then delivered for oral administration either in ethanolic solutions or sprayed and dried onto lactose or lactose-sucrose pellets.

The specific ways in which homeopaths make and use their natural product nanomedicines are often overlooked in discussions of this field. It is essential to take a closer look at this aspect of homeopathic clinical theory and practice. The resultant insights may open new directions for how to use modern nanomedicines more safely and for greater effect.

### Dosing Nanoparticles for Safety: Low Pulsed Doses

An emerging concern and challenge for the field of modern nanomedicine is clinical safety [45]. NPs are typically biologically super-potent forms of their source material [46]. Therapeutic dose ranges are lower than for bulk forms of the same medicines or herbs [47-50]. In addition, nano-forms can also lower the dose at which toxicity can occur, thereby necessitating use of even lower doses for therapy. In some organisms, NP concentrations are as low as 1 nanomolar can still exert toxic effects [45,51,52]. Accumulation of toxic levels *in vivo* is a significant concern. Nanoscale agents acquire properties that are dependent not only upon material composition and dose, but also nanoparticle sizes, shapes, and surface chemistries [22,23,40,53-56].

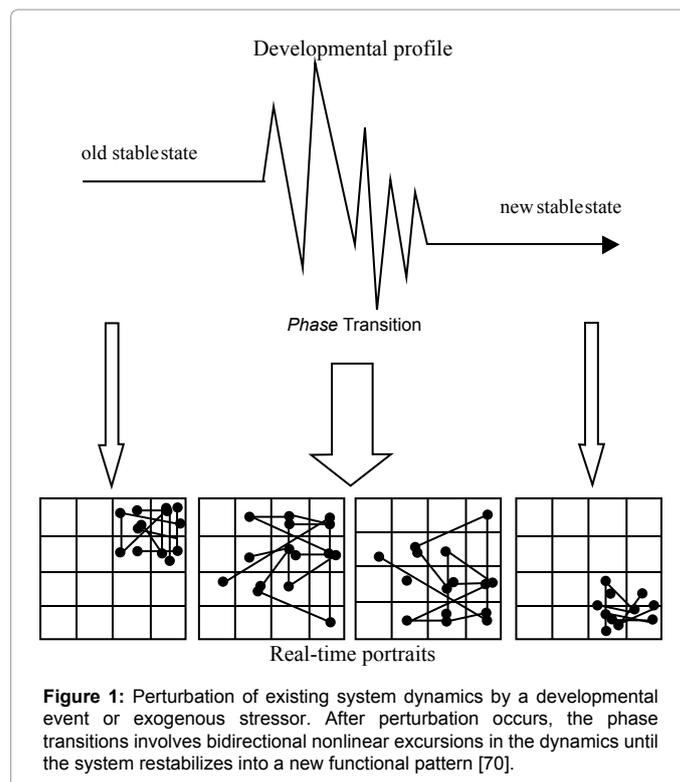
Yet, properly-prescribed homeopathic nanomedicines have a strong 200-year safety record in real-world use [1,57,58]. Homeopathic practice theory offers specific, practical strategies for choosing and dosing nanomedicines to avoid the risks of toxic NP effects. The core concept is to use the NPs not as pharmacological ligands for specific local cell receptors responsible for specific symptoms, but rather as low dose, pulsed discrete danger signals to mobilize the biological adaptation networks of the whole organism [21]. The treatment goal is to stimulate endogenous plasticity via self-amplifying functional networked changes across the organism as a whole, rather than to suppress expression of specific symptoms [59,60]. If they occur, the majority of "side effects" in homeopathy are early transient worsening of pre-existing symptoms, prior to evolution of improvements [1,61].

Low dose stimulation of biological adaptation networks provides

an explanatory mechanism for why sublingual, olfactory or even topical administration can produce far-reaching changes in biological networks [62-64]. Homeopathic medicines have traditionally been administered sublingually. These routes of administration are very accessible for NPs [46,65]. NP stimulation of multi-system networks exerted by ultra low NP doses administered orally would be predicted to have widespread and rapid effects on multi-system hierarchies of the nested and interactive systems that make up the living organism [60].

The homeopathically-inspired dosing strategies require a shift in mindset away from using nanomedicines in the same ways that conventional medicine uses bulk form drugs. The homeopathic approach takes advantage of the (a) organism-wide network integration of any living system as a complex adaptive system (CAS) with nonlinear dynamics; and (b) endogenous self-amplifying processes in which a complex adaptive system can engage to respond to the signal qualities of salient low level external threats. These processes include hormesis, time-dependent sensitization, and stochastic resonance. As noted above, the therapeutic goal is to induce adaptive and diffuse changes via cascades of events over the stress response pathways rather than just symptom-inhibitory local effects at specific receptors. Consistent with the inherent nature of cause-effect in complex systems [66,67], the quality of the organism's response to a dose is indirect rather than direct and nonlinear rather than linear in causality.

The salience derives from the quality of the signal to herald a potential danger or threat to survival for the individual organism. Such a stimulus, stressor or signal delivered to an already-diseased organism perturbs or disrupts ongoing disease dynamics and functional network organization of the system [68,69]. The disruption leads to transient wider fluctuations of bidirectional change for a period of time prior to re-stabilization [70-72] (Figure 1). Shaping the overall direction of the dynamics of change toward lasting health is the process and goal of treatment.



Homeopathic dosing stops once improvement begins. The homeopathic clinical decision to give a subsequent dose occurs when the patient's overall symptom picture of dysfunctions is clear-cut and rises above day-to-day background fluctuations. The multiple changes that follow a single dose can evolve across the organism over a period of minutes to hours (acute conditions) to months to years (chronic conditions) in homeopathy. The evolution of changes across the organism would reflect the complex interconnected nature of the person as a biological network [21,59,60].

One previous clinical trial documented oscillatory, sinusoidal response curves for several different outcomes over time to a verum homeopathically-prepared medicine compared with placebo [73]. When clinical improvement does occur, it can be reversed by overly frequent repetition of the homeopathic nanomedicine doses. Timing of repetitions can be more important than quantity of a given low dose in homeopathic treatment. Dosing a healthy organism pushes the system in the direction of disease (Table 1) [74]. Homeopathic medicine practices can provide insights into how best to dose and time NP therapies.

### Recipient Organisms as Self-Organized Complex Adaptive Networks

In living systems, amplification processes go far beyond the enhanced bioavailability and biological potency of the nanomaterials themselves. The history and state of the recipient organism at the time it encounters NPs has an impact on the effects. Individual differences among organisms lead to divergent outcomes upon interaction with NPs [51]. Living systems such as human beings, animals, and plants are Complex Adaptive Systems (CAS) [62-64,75]. A CAS is a system or indivisible collection of multiple interconnected, interdependent, interactive parts embedded within a larger environment. A defining feature of CAS is their dynamic nature and capacity to adapt and evolve with changes in the environment [71]. Resilience in the face of environmental change is the hallmark of a successful CAS. They also possess other important characteristics.

First, biological processes take place at the nanoscale. Therefore, NPs intended for therapeutic applications often have unique capabilities for targeting specific cells, crossing membranes to enter cells more effectively than bulk form materials, and exerting effects for longer periods of time per dose. NP-based vaccines also provide indications of markedly enhanced adjuvant capacity for immune activation, thereby reducing the antigen doses required to evoke a vigorous response in the overall organism [48,76]. NPs from silica can mobilize inflammasome proteins inside a cell [35,77,78]. In turn, inflammasome mobilization leads to cytokine activation. Some NPs can also induce exosome release from cells [79,80]. Recent studies indicate that exosomes serve as cell-to-cell signaling mediators [79,81-84].

Amplification of effects can readily occur in mobilizing cascades

of events in the immune system, which would in turn send signaling mediators such as cytokines to the brain and other stress response pathways of the body. The brain per se is particularly capable of monitoring ongoing biological "noise" and sensory information for weak but relevant signals from internal and external stimuli and generating a large response when indicated. Thus, there are several interacting biological pathways in the neuro-immune network alone that can ultimately initiate robust biological adaptations much larger in magnitude than the original stimulus [85,86]. Immune and nervous system amplification is only one interconnected biological stress response pathway by which NPs could trigger changes in an organism as a whole.

Second, living systems are self-organized, complex adaptive systems (CAS) or networks with nonlinear dynamics and emergent properties that are not predicted by understanding the properties of their component parts [60,87,88]. NPs can both readily translocate around the organism and set cascades of biological signaling into motion, e.g., via activating exosome release [80,89], inflammasome proteins and cytokines [65,77], and epigenetic modulation [90,91]. As a result, nano-drugs and natural products can elicit changes in cells and distant parts of an organism not obvious from a bulk medicine focus on only local inhibitory effects for specific symptoms [69]. These concepts imply the importance of the salience of an NP as a potential danger signal, or therapeutic stimulus, for the organism as a whole, especially at low doses [21,92].

Complexity in the nonlinear dynamics and functional organization of an intact cell or organism involves multiple interdependent and interactive functional relationships that can lead to indirect effects throughout the larger system [68,69,93,94]. The magnitude of those effects is nonlinear, i.e., it can be disproportionately larger than the magnitude of the original stimulus [62-64]. As in any complex system, such effects occur distant in time and space from the original interface with NPs [95]. Within homeopathic practice theory, recovery of health proceeds down the body, from internal organs out toward the skin, and in reverse order of original appearance in time of the symptoms [60]. Such 200-year-old medical observations may help translate nanomedicine more efficiently into clinical practice.

### Endogenous Amplification Phenomena in Complex Adaptive Systems

If a nanomedicine is correctly chosen and dosed to stimulate amplified responses and cross-adaptation, the resultant changes in the organism can even evolve into a recovery from a pre-existing disease over time. Such a process is a key principle in homeopathic practice theory [1]. Endogenous amplification in a complex adaptive system is inherently nonlinear [60]. That is, (a) the size of the response is disproportionate to the size of the input; (b) the direction of responses can be bidirectional or even oscillatory in nature [71]; (c) the location of the changes can be distant from the original site of the stimulus

Timing of Homeopathic Medicine Dose Relative to Experimentally-Induced Injury	Impact after 1 hour on Injury-Related Edema Compared with Saline Control Treatment
60 minutes before injury induction	+14.6%*
Simultaneously with injury induction	+3.57%
30 minutes after injury induction	-13.63%**

\*  $p < 0.05$

\*\*  $p < 0.01$

Note: Experimental acute injury = carrageenan-induced paw edema. Verum medicine and saline control treatments were also given by injection

**Table 1:** Timing of intervention interacts with host state: bidirectional effects of a combination mineral homeopathic medicine dose relative to time of treatment versus time of experimental injury in an animal model of paw edema (N=307 rats). Data from first hour post-dose, after Figure 1, Bertani et al. [74].

administration [66,95,96]. The discrete nanomedicine dose constitutes the pulsed input signal. The result is resistance or cross-resistance (adaptation or cross-adaptation) to same or similar biological stressor or injury, whether they already have occurred or might occur at higher intensities in the future [97-101].

The purpose of homeopathic treatment is not to force a specific change in a single target tissue with continuous dosing, in the manner of a conventional bulk form drug. Instead, the intent is to stimulate a cascade of multiple systemic adaptations around the network, all set into motion by the original salient stimulus of a discrete low dose of specific NPs [21]. The signal properties of the dose indicate a potential danger or threat that the treatment agent would pose for the whole organism at higher dose. The organism then takes its cue and makes functional biological changes across its networks to resist such current or future dangers [18,21,68]. That is, the organism adapts itself to perceived exogenous changes in order to maximize its fitness for survival in its "new" environmental context or landscape [102].

High doses of a toxic or dangerous agent, including many nanoparticles, can damage the organism or even cause death [45,97]. However, the direction of change from adaptation to a low dose that the organism can survive instead enhances resistance against the adverse effects of the same agent [97,98,103-105]. Furthermore, such beneficial changes can modify responses to not only the same, but also a cross-adapted agent or stressor. If the higher intensity past stressors have already done damage by causing maladaptive dynamical changes [106], i.e., disease, then the low dose treatment agent cross-adapted to the effects of those stressors could initiate a reversal of direction in the system dynamics [21].

For treatment of disease with this dosing strategy, the nanomedicine must be cross-adapted, cross-sensitized, and/or cross-resistant in its effects to pre-existing biological "noise" in the system. That is, the emergent noise derives from the disease itself, i.e., systemic maladaptations or dysfunctions caused by past higher intensity stressors and disease-related factors [99-101] (Figure 2).

This conceptualization is somewhat similar to the basis for using vaccines in preventive health care. For example, cowpox vaccines given to a person in advance of contracting the more deadly, cross-adapted smallpox virus were able to prevent the latter infection. In nanomedicine, some investigators are studying tumor-derived exosomes (nanoscale vesicles) vaccines to treat existing cancers [107]. Notably, some homeopaths in India already use breast cancer tissue-derived, homeopathically-prepared nanomedicines in some of their cancer treatment regimens [20,108-110]. For conditions that rely on immune function, this strategy may be particularly useful.

Moreover, complex adaptive systems can interact with environmental factors to amplify responses disproportionately to low intensity stimuli, drugs, or other stimuli with salience for the organism. Global and local motifs of recurring interaction patterns within and across a CAS can affect one another [95]. The timing of even a small stimulus can lead to major shifts and even disruption of the ongoing nonlinear dynamics of the whole system. For instance, under a certain set of conditions, with a stimulus that is properly timed and placed in the system, bifurcations of dynamics or cusp catastrophe events can suddenly manifest (Figure 3).

Notably, with homeopathic nanomedicines, timing of dose can alter the direction of the host response. For example, Table 1 shows the results of an animal study in which timing the administration of the homeopathic medicine relative to the time of an experimentally-

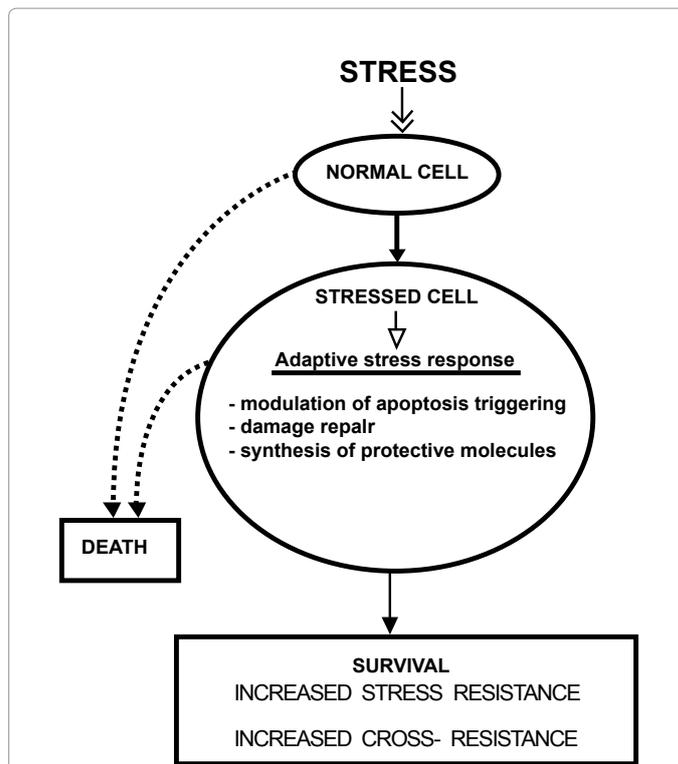


Figure 2: Model for induction of therapeutic adaptive changes from an environmental stressor [97].

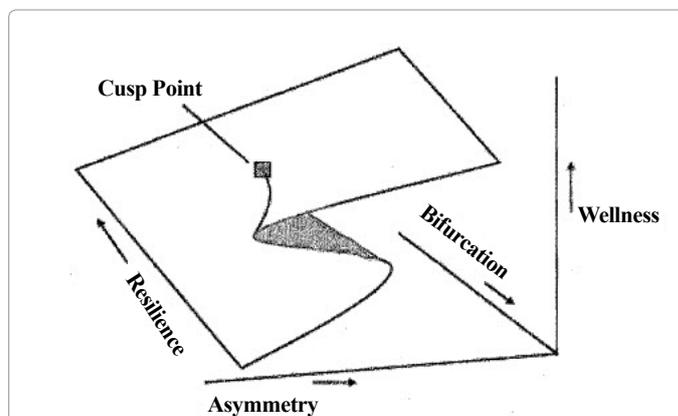


Figure 3: Nonlinear dynamics in a complex adaptive system (CAS): cusp catastrophe model for resilience and wellness in a CAS (cell or organism) [71]. Abrupt shifts from one state to another can occur with system conditions triggered at certain critical dynamical points.

induced acute injury changes the direction of the effects of treatment compared with saline control treatment [74]. Giving the medicine before the injury increases the subsequent edema response from the experimental injury. It is only after the injury has occurred that the medicine leads to reduction in severity of the edema. Although seemingly abstract, such nonlinear dynamical changes can lead to lasting functional reorganization of the system dynamics [68]. For desirable therapeutic benefits, the disruption of disease dynamics could also give the system an opportunity to self-re-organize back into a healthier mode of functioning [70,71,88,111-113] (Figures 1 and 3).

From the perspective of an organism as a CAS, disease and aging lead to a loss of complexity in the system dynamics [114-117]. As a result, the organism is less flexible and resilient against adverse endogenous or exogenous factors. One measure of complexity known as multiscale entropy (MSE) analyzes time series physiological data across different time scales to determine recurring patterns. For example, Costa et al. [114] showed quantitative individual differences in heart rate variability complexity with MSE as a function of age and health status [114,118]. Younger healthy persons show greater complexity compared with older healthy persons. However, like older people, unhealthy individuals of any age, i.e., people with congestive heart failure, also exhibit less heart rate variability complexity. In this case, reduced complexity in heart rate variability leaves the individual more susceptible to aberrant beats and resultant life-threatening arrhythmias.

Restoring optimal complexity to system dynamics underlies the therapeutic goal [59,60,88,104]. Systemic resilience to future stressors emerges with a meta-flexibility to adapt more effectively to environmental stressors/agents that impinge on the system. The beneficial therapeutic outcome results from the interaction of the treatment with the organism [71].

### Organism-Dependent Response Amplification Phenomena

Homeopathic researchers have highlighted three endogenous amplification phenomena as ways in which a relevant exogenous stimulus such as a one-time or infrequently-pulsed dose of a salient NP could affect the whole organism. These phenomena are: hormesis [99,119], time-dependent sensitization [21], and stochastic resonance [120]. All three forms of endogenous amplification share an essential feature. That is, the treatment agent must possess salience as a subtoxic or nontoxic, but biologically meaningful, danger signal to the organism.

The low level foreign stimulus signifies a relevant environmental stressor or future potential biological threat to survival. In short, all three mechanisms depend on the nonlinear interaction of the low dose (or signal) with the living organism as a complex adaptive

system (CAS) [60]. Table 2 summarizes the features of the proposed mechanisms. Initial studies suggest that doses of certain nanoparticles can alter the nonlinear dynamics of a complex biological system in clinically meaningful ways, e.g., to offset expression of autoimmune patterns [121].

Hormesis (Figure 4) is a nonlinear dose-response relationship. In hormesis, low doses of an agent or a different, cross-adapted agent can initiate beneficial adaptive responses that can either reverse existing toxicity or protect the organism against future higher (toxic) dose exposures [122]. More than 8,000 scientific papers have now demonstrated hormetic effects as a manifestation of biological plasticity [103]. Low doses of nanoparticles can cause hormesis [105,123]. Other studies have demonstrated that low doses of homeopathically-prepared metals, including cadmium and arsenic, can produce beneficial hormetic reversal of effects of higher, toxic doses of the same or cross-sensitized agent on heat shock protein activation patterns [124]. Heat shock proteins are among the biological modulators of the stress response networks involved in adaptation to various environmental stressors [94,125].

In the homeopathic NP dose range, the low dose hormetic effects can take on the sinusoidal oscillatory dose-response patterns reported in various preclinical and clinical studies [5,73,126]. To avoid toxicity but still elicit the adaptive response of hormesis with nanoforms of some agents such as poisonous plants, that are otherwise toxic at higher doses, extremely low doses, i.e., picogram/milliliter to low nanogram levels, may be necessary [21].

Available estimates of concentrations of source NPs in homeopathic metal remedies range from a low of 0-10 picograms/milliliter to 2-4 nanograms/milliliter [3]. If (a) nanoscale forms of a drug can lower pharmacological dose requirements up to 1000 times compared with conventional bulk forms of the same drug to cause direct, local receptor effects [50] and (b) some nanoparticles can be toxic at 1 nanomolar concentrations [51,52], then the corresponding hormetic dose ranges to elicit adaptive effects in the opposite direction for each given agent would have to fall below an already very low dose [21].

Nonlinear Amplification Phenomenon	Nanomedicine Dose Characteristic	Signal Role of Nanomedicine Dose
Hormesis	Low dose as mild stressor Depends on interaction with organism more than on specific pharmacological nature of stressor/agent Able to initiate adaptive response	Low dose evokes response in opposite direction to that for high dose. Cross-adaptation between chemically-unrelated stressors/agents observed. Nanoparticles can evoke hormesis.
Time-Dependent Sensitization (TDS)	Low dose as danger signal Pulsed dose administration (repeated intermittent timing) Salient threat or stressor for the system	Passage of time between discrete doses leads to progressive growth of host response to next dose. Overly frequent doses will cause sequential oscillatory reversals in direction of response from dose to dose. Cross-sensitization between chemically-unrelated stressors/agents observed. Homeopathic medicines can initiate and elicit TDS.
Stochastic Resonance (SR)	Low dose as signal Concomitant background noise present (systemic biology of the organism-wide emergent disease process) Salient signal for the system	Host response amplification in response to the weak signal value of the low dose by the background noise in the system. SR in animal sensory systems for detecting approach of a dangerous predator observed. SR between two quantum dot (small NPs) and with carbon nanotubes or metal NPs observed.

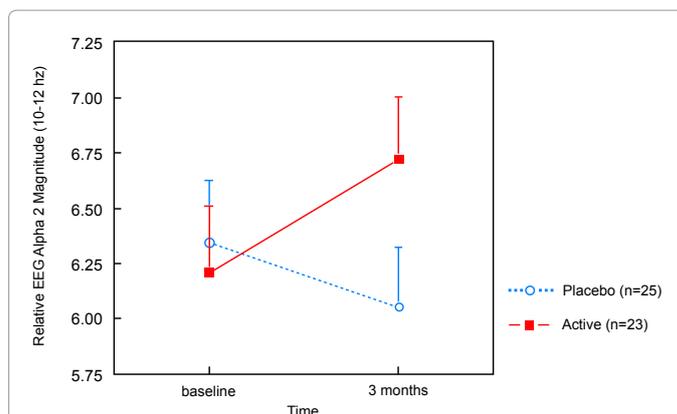
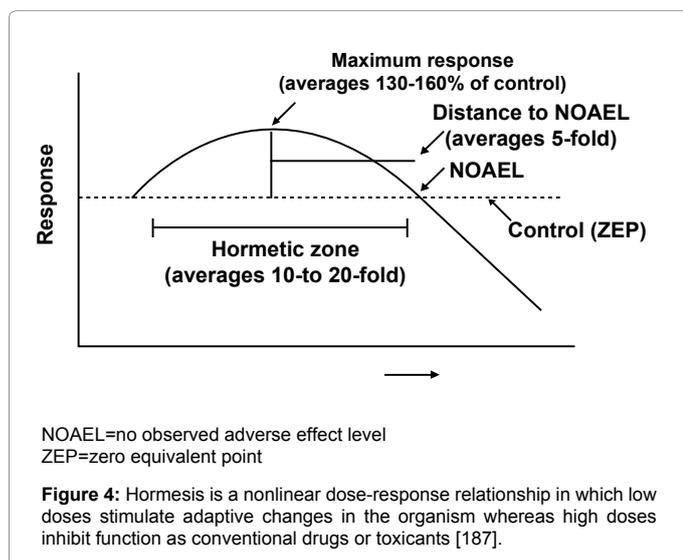
**Table 2:** Proposed low dose effects: mediating processes for therapeutic effects from pulsed low doses of nanomedicines in a complex adaptive system. Amplification phenomena depend on nonlinear interactions with the dynamics of the organism as a complex adaptive system.

Time-dependent sensitization (TDS) is another organism-dependent response amplification process. TDS involves the progressive amplification of the system's response to a given low dose of an agent or stressor with the mere passage of time between the initial and subsequent re-exposures to the same or a cross-sensitized agent or stressor. The dose remains low, and the initial exposure does not elicit much, if any, overt response. However, each subsequent repeat exposure to the same or a cross-sensitized stressor or agent elicits an increasingly larger response. Immune system involvement is not necessary for TDS to occur; the process is especially common in certain central nervous system pathways. Neuronal and endocrine stress response pathways may be more important than immune function in TDS [127-131].

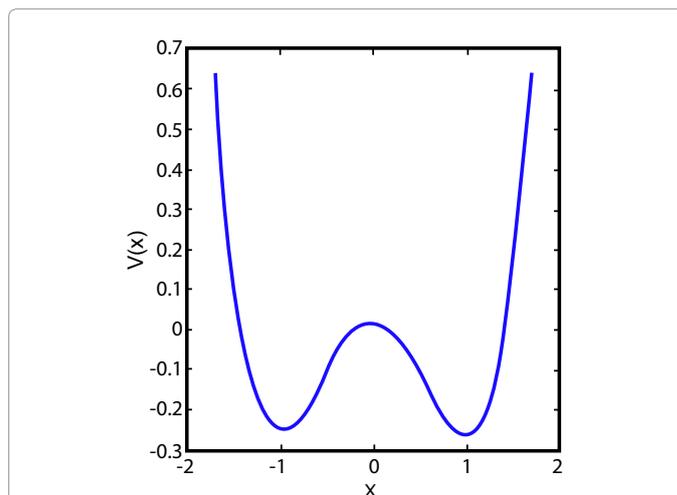
This type of sensitization and cross-sensitization is a well-documented phenomenon between agents and stressors of very different classes, especially affecting the central nervous system [131]. Thus, to initiate TDS, the stressful or foreign nature of a drug for the individual is more important than the specific pharmacological properties of the agent [131]. Overly frequent repetition of a sensitizing agent can also cause a within-subject oscillatory reversal in direction of the response [132]. Two different placebo-controlled, double-blind studies using electroencephalographic alpha effects have shown that homeopathically-prepared medicines initiate and elicit time-dependent sensitization (response amplification) in human subjects [133,134] (Figure 5).

Stochastic resonance (SR) is amplification of a small periodic signal by concomitant presentation within a larger random noise background pre-existing within the complex system [135]. Stochastic resonance is a common phenomenon in biological systems, especially neural networks and sensory systems. One example of SR in animals is the capacity for sensory detection of weak environmental signals heralding arrival of a predator threat [136,137]. Figures 6 and 7 illustrate the mechanism and nature of stochastic resonance. The graphs show a sinusoidal response dependent upon the different noise levels [136] and a peak value at a specific noise level [135]. Such sinusoidal dose-response phenomena are similar to the sinusoidal dose-response curves noted for homeopathically-prepared medicines in a bacterial cell metabolism model [126].

In statistical physics, Joshi has also shown that weak coupling in a



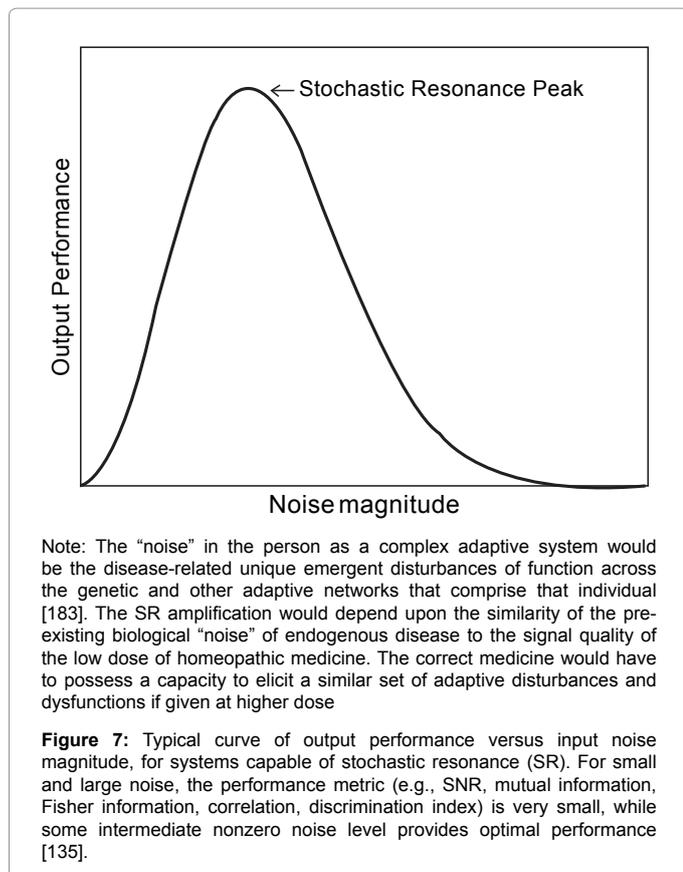
**Figure 5:** Time-dependent sensitization of electroencephalographic (EEG) alpha-2 band (10-12 hertz) magnitude during olfactory sniffs of individualized homeopathic medicine (liquid form) by people with fibromyalgia [133]. Controlled for baseline mood, medications, and placebo sniffing in both groups. Verum (Active) dose was "lower" by conventional pharmacological criteria at the 3-month test than at baseline test, i.e., "higher" in homeopathic potency. However, EEG response had nonetheless grown in size over 3 months of once-daily oral treatments between the pre-treatment olfactory-administered laboratory test sessions.



Note: The system response depends upon the noise level. Stochastic resonance occurs in biological systems, including sensory systems detecting weak signals of danger from predators and neural networks

**Figure 6:** The mechanism of stochastic resonance. The double well potential  $V(x)$  represents a physical system with two stable states. In absence of noise, a particle, which at one time is within one of the two wells, relaxes towards the intrawell minimum and then stops. When stochastic perturbation is added to this system the particle can hop between the two wells with a rate predicted by reaction-rate theory. If a weak periodic forcing is present the overall potential minimum changes periodically from one side to the other. Stochastic resonance happens when the typical escape time from the lower barrier and the periodic forcing are synchronized [136].

double quantum dot system can exhibit stochastic resonance [138]. A substantial proportion of NPs in at least some homeopathic medicines fall into the quantum dot size range of 1-10 nanometers in diameter [3]. Carbon nanotube transistors can also exhibit SR [139]. Biological systems are typically associated with  $1/f$  spectrum noise [140]. Introducing  $1/f$  noise into silicon-based nanomechanical resonators in nanoelectronics can lead to SR-based signal amplification [141].



Thus, for SR to occur, the pulsed dosing regimens of homeopathic nanomedicines spaced in time would present each low nanostructured dose as a discrete, small danger signal input. The small signal of the medicine as input would occur against the background of the pre-existing endogenous biological noise from the unique maladaptive dysfunctional patterns associated with emergent disease in the individual organism [120,142,143]. The medicine signal "needs" the presence of the disease noise for amplification of effects.

The organism would detect the threat value of the isolated dose and respond nonlinearly with adaptive changes. If the salience addresses the organism-wide disease process, then the response would be more pronounced, perhaps coordinated by the central nervous system [144]. For example, one double-blind randomized controlled trial compared changes in the prefrontal Electroencephalographic (EEG) cordance response to the first dose of an individually-matched homeopathic medicine in subsequently exceptionally good clinical responders versus all other study participants [144]. The EEG cordance verum responders to the first dose showed not only initial EEG differences, but also significantly better clinical improvements that diverged from those of verum non-responders and placebo patients. The prefrontal region of the brain is involved in planning, coordinating executive decision-making capacity, and regulating emotional and sentient experiences. Prefrontal cortex also regulates the hypothalamic-pituitary-adrenal axis of the stress response pathways [145].

If the salience is less relevant to the organism's biology as an integrated dynamical system, the endogenous protective response may be more local and limited in scope. Non-salient NPs at low pulsed doses would have minimal transient effects either in terms of overall

toxicity or therapeutic effects at the level of organizational scale of the organism. Response mechanisms may not engage the central nervous system or other parts of the stress response network as fully.

To date, the limited attempts to use SR for clinical problems include adding vibrational noise to the feet to enhance signal detection in failing sensory systems, e.g., for balance problems in the elderly [146]. In contrast, homeopathic dosing may instead take advantage of the established biological disease "noise" and the stress response pathways first responders by instead adding a weak but highly salient signal into the noise.

The reader is referred to other papers on these low dose, organism-dependent response amplification phenomena for more in-depth explanations [21,99,119,120]. Given the quantum dot size of some homeopathically-prepared metal NPs [3], it is not also possible to rule out quantum mechanical phenomena in some of the homeopathically-induced low dose responses [147-149]. Quantum dots per se possess inherent unpredictability in their properties [150-152] as another potential explanation for the variability and anomalies of homeopathic medicine effects. Even so [136,153], the evidence suggests that these three adaptive biological amplification mechanisms are scientifically indicated as a starting point for systematic empirical studies into how homeopathically-manufactured nanomedicines could initiate healing responses.

It is possible that certain dose ranges of NPs evoke one or more of these processes, but not others. In homeopathic treatment of chronic diseases, for instance, the scope of possible medicine selections is in the thousands. A key homeopathic practice principle is the need to select a medicine whose toxic properties are a very similar match to the unique pattern of individualized symptoms that the patient already experiences as a whole. Without the comprehensive match to the organism's adaptive susceptibilities, an "active" medicine at low dose has little or no effect.

With a good match, the medicine mobilizes a nonlinear cascade of changes leading to recovery across the entire organism. In parallel, it may require a more salient match between the signal quality of the small medicine dose and the endogenous emergent "noise" of the disease dysfunctions occurring within the system to evoke stochastic resonance. At higher potency medicines, SR could account for the hormesis-like phenomena observed and explain in part why the dose-response curve is sinusoidal in nature [126].

On the other hand, simple nanoparticle-based biological amplification of beneficial herbal or mineral salt effects may be more relevant than SR at very low potencies (trituated and/or minimally diluted and succussed nanoparticles). In this scenario, repeated doses might lead to time-dependent sensitization. Acute illnesses can respond well to very low potencies of homeopathically-prepared medicines [154]. In homeopathy, "low potencies" translate into minimally diluted and succussed (agitated) medicines, probably containing both bulk and nanoforms of source material.

In fact, many homeopathic clinicians report the ability to treat a large proportion of the population for acute infectious illnesses with only a few different medicines. The direction of the response depends upon the state of the organism at the time of the dose. If an injury is already established, the response direction is toward recovery. However, if the injury occurs after the exposure to the homeopathic nanomedicine, the response may be amplified in an adverse direction [74].

## Experimental Questions

The above points raise many questions. For instance, under what experimental and clinical conditions do hormesis, stochastic resonance, and/or time-dependent sensitization come into play during adaptive responses to homeopathically-prepared nanomedicines and other NPs? Can quantum mechanical phenomena such as quantum confinement, quantum coherence, and/or quantum entanglement be experimentally demonstrated with some very small sized homeopathically-prepared medicine NPs and their interactions with living organisms? Under what circumstances might some homeopathic nanomedicines prevent disease [155], or is their primary role in treatment of pre-existing disease?

Is the polydisperse nature of homeopathic nanomedicines as crudely -made top down naturally-sourced NPs a clinical advantage or disadvantage? For public health purposes, providing multiple NP sizes in a given dose may facilitate effects across more individuals. Some evidence suggests that including different sizes of the same source material NPs in antennas or multi-component nano-ensembles leads to better self-similar amplification of effects [138,142,143,156-160], including stochastic resonance [139,142,161]. For higher potencies made traditionally in glass-contained liquids, the release and presence of nanosilica and/or nanosilicon in solution from successions in glassware could contribute a drug-delivery vehicle and a biological [34,37,162], microelectronic and photonic amplifier [163,164].

Some homeopathically-manufactured nanostructures from bacteria emit characteristic electromagnetic signals that can be detected and recorded [165]. Agitation of the solutions during manufacturing is necessary to generate such phenomena. Nanosilicon may also acquire quantum mechanical properties at small quantum dot sizes [42,164,166,167], a feature that may help account for certain other observations in the homeopathic drug development research literature [147,148,168]. Doping of the nanosilicon and nanosilica by the medicine source material and other trace contaminants in solution during early preparation steps [9] may add more memory and amplification mechanisms [164,169,170].

Other components of the manufacturing process could change the therapeutic potential and safety of homeopathic nanomedicines. Thus, what are the roles of lactose and ethanol in modifying the natural source nanoparticle surfaces and properties? Ethanol can affect nanosilica particle sizes and shapes [33]. Evidence on homeopathically-prepared materials and on modern nanoparticles suggests that lactose on the NP surface can change the physico-chemical properties [11] and/or ability to enter cancer cells [23]. Surface charge can also affect cancer cell response to NP treatments [171].

For treatment of conditions such as specific cancers, some homeopaths use a diagnosis-driven protocol approach for selecting homeopathically-manufactured medicine [108,109,172]. The diagnosis-based selection of medicines facilitates providing care from a public health perspective to a large number of patients. Bulk herb extracts of *Ruta graveolens*, for instance, exert anti-cancer effects [173,174]; and an oral nanoscale formulation of one of its main constituents, rutin, has good bioavailability [175].

The nanoparticle form of calcium phosphate has antiproliferative and pro-apoptotic effects on glioma [176] and osteosarcoma [54] cells. Similarly, their homeopathically-manufactured counterparts, e.g., *Ruta graveolens* 6C and *Calcarea Phosphorica* 3X [172], are part of a leading combination anti-cancer protocol for gliomas [108,172]. Homeopathic

*Calcarea Phosphorica* 3X combined with the plant-derived homeopathic medicine *Symphytum* 200C and another homeopathic medicine is used for osteosarcomas in India [20,108,109,172]. In low potency vs controls, homeopathic *Symphytum* 6C can also enhance bone formation around experimental titanium implants in rats [177].

Furthermore, silica NPs also biologically amplify the anti-neoplastic effects of a traditional snake venom medicine against breast and prostate cancer as well as multiple myeloma [162,178,179]. Extensive nanoscience evidence demonstrates not only biological amplification effects of nanosilica, but also bottom up self-assembly of silica-based nanostructures using biological materials as templates [180]. Could homeopathic plant or other source material-modified silica nanostructures retain structural and functional information for reproduction into higher potencies, similar to plant-synthesized silver and gold NPs [40] or nanosilica doped or coated with other materials [181]? Silicatein enzymes from sponges and other plant materials can provide unique structure-guiding proteins [182]. Stochastic resonance [138,161] involving plant-modified nanosilicon quantum dots is a potential amplification mechanism from interaction with a living system for which the specific homeopathically-prepared medicine is a salient but mild danger signal [138,183].

As noted earlier, the more widely-used classical homeopathic prescribing method is patient-, not diagnosis-centered. In classical homeopathy, the patient's complete pattern of biological, psychological, emotional, and social symptoms and behaviors in all subsystems is weighted and integrated to choose a single homeopathic medicine for the person as a whole. Such a medicine then reportedly initiates a healing response across the entire individual as an indivisible organism [1,184]. In most clinical situations, given time and resources, homeopaths prefer the patient-centered approach to selecting their medicines. Nonetheless, with the ability to understand better the nature of homeopathically-manufactured natural nanomedicines and their interactions with living systems, the relative advantages and disadvantages of diagnosis-based versus patient-centered selection of natural nanomedicines also becomes a relevant empirical question.

## Conclusions

Homeopathic medicines have enjoyed widespread use in treatment of acute and chronic conditions, including infections [15,64,154] and cancers [20,109,172]. During over more than two centuries of real-world use, millions of people in many different countries have reported excellent safety, tolerability, and clinical benefits from these natural product-based nanomedicines [58,154]. Pulsed low doses can minimize risks from *in vivo* accumulation of NPs. Thus, relying on the interaction of NPs with the recipient organism as a complex adaptive system, rather than using NPs as if they were super-potent conventional bulk drugs, could lead to enhanced effects and safety benefits.

In clinical practice, homeopaths emphasize (a) selection of the therapeutic agent for its salience to the pre-existing emergent pattern of dysfunctions (symptoms) across the entire organism, rather than for blockade of local receptors in one symptomatic organ of the body; and (b) a pulsed discrete dosing approach that pauses or stops treatment once transient worsening or initial improvement has begun. Treatment resumes with repeat dosing only if improvement stops short of full recovery. As a result, homeopathic nanomedicines are different from conventional bulk drugs and natural products because of their nature, clinical indications, low dose levels, and pulsed or intermittent dosing schedules.

On the one hand, homeopathic practice theory, combined with complex systems science, could inform new treatment strategies for dosing nanomedicines more safely [58]. Relying on the organism as self-organized nonlinear amplifier, rather than the nanoparticles alone to carry the change, could lead to novel treatment approaches. Hormesis, time-dependent sensitization, and stochastic resonance offer a starting place for research on endogenous amplification mechanisms for pulsed low doses of nanomedicines to initiate clinically significant emergent effects.

On the other hand, the historical methods for homeopathic medicine manufacturing might benefit from updating, based on advances in modern nanotechnology [21]. Making more consistent homeopathic nanomedicines with well-characterized particle properties could result in more reliable effects in both research and clinical contexts [185,186]. Integrating the insights, technical manufacturing expertise, and particle characterization procedures of modern nanotechnology with the green manufacturing approach, clinical medicine selection, and pulsed low dosing approaches of homeopathic nanomedicine could lead to major advances in the field [187]. The outcome for contemporary nanomedicine can be more effective and safer translational applications to improve patient care.

#### Competing interests

Dr. Bell is a consultant to Standard Homeopathic/HylandsInc, a U.S.-based manufacturer of homeopathic medicines. The company did not provide any financial support for the studies cited or for publication costs for the present paper.

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