The Complexity of the Homeopathic Healing Response Part 2: The Role of the Homeopathic Simillimum as a Complex System in Initiating Recovery from Disease

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Abstract

Background Evidence indicates that homeopathic medicines are complex self-organizing nano-scale systems that generate unique low-intensity electromagnetic signals and/or quantum coherence domains. In Part 1, we reviewed relevant concepts from complex adaptive systems science on living systems for the nature of homeopathic healing.

Aim In Part 2, we discuss the complex-system nature of homeopathic medicines. The aim is to relate the evidence on the nature and properties of homeopathic medicines to the complex systems model for homeopathic healing.

Methods and Results The work is a narrative review, with complexity model development for the nature of homeopathic medicines. Studies suggest that homeopathic manufacturing generates nano-structures of source material, silica and silicon quantum dots if succussed in glassware or including botanical source materials; or carbon quantum dots if succussed in plastic or including any organic source materials, as well as solute-induced water nano-structures carrying medicine-specific information. On contact with physiological fluids (e.g., blood plasma), there is evidence that nano-structures additionally adsorb individualized patterns of the recipient's own proteins on to their surfaces to create a unique protein corona coat (shell). Thus, the simillimum may generate a personalized biological identity upon administration. Consequently, a medicine can serve as an individually salient, self-similar information carrier, whose protein corona constituent pattern reflects the individual's current internal state of health/disease. Homeopathic medicine complexity emerges from interactions of the component parts from source, silica from glassware or carbon from plastic containers, solvents (lactose, water, ethanol), adsorbed biomolecule layers from plant or animal sources, and adsorbed biomolecules of the recipient. Low doses of these complex medicines can act as biological signaling agents to initiate hormesis via a network-wide pattern of adaptive responses by the recipient complex adaptive system, rather than as conventional pharmaceutical drugs. Biological mediators of adaptive responses include inter-connected network elements of the cell danger/damage defense system: for example, gene expression, reactive oxygen species, heat shock proteins, cytokines, macrophages, T-cells, and associated brain–immune system mediator pathways.

Conclusions Every homeopathic medicine is a complex nano-scale system involving multiple inter-connected, interacting components, and emergent properties.

Keywords
- homeopathy
- complex systems
- nanostructure
- protein corona
- biological identity

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Simillimum individualization derives from formation of a unique personalized protein corona shell adsorbed to the reactive surface of the homeopathic nano-structures on contact with the recipient's body fluids. Low doses of such complex nano-structures initiate the adaptive processes of hormesis to mobilize endogenous healing of a disease state. The capacity for self-organization and self-similarity in complex systems is the key to future research on the nature of homeopathic medicines and systemic healing during individualized homeopathic treatment.

Introduction

This two-part paper focuses on the integrative model for the complex, self-organizing nature of both (a) recipient living systems[1–4] and (b) homeopathic medicines[5–10] as the basis for homeopathic healing. In Part 1, we covered the basics of complex systems science to frame understanding of health and disease. Living systems are inherently complex adaptive systems (CAS). In Part 2, we synthesize and integrate thinking from a growing body of research on the nature of homeopathic medicines with evidence from modern nano-science to accommodate the data in the field. These concepts are empirically testable with appropriate study designs.

Homeopathic medicines are not conventional drugs. Conventional drugs act via biochemical, mechanistically targeted, specific *direct local effects*. In contrast, in this complexity model, the correct homeopathic medicine serves as a low-dose stimulus or individualized signal for inducing patterns of functional adaptive changes globally and locally in the body. The homeopathic signal captures and conveys a low or weak "dose" of the salient complex disease frequency information to the body, thereby setting in motion personalized hormetic (biphasic, non-linear) adaptive multi-system responses to reverse the disease.[11]

In this proposed model, the homeopathic potency signal derives from the manufacturing process. The form of the "signal" may include multi-component core-shell nano-structures from (a) source, (b) doped silicon dots from glass or (c) carbon dots from polymer plastic containers or organic manufacturing materials (lactose, ethanol, plant or animal medicine source materials) during succussions, (d) solute- and electromagnetically induced self-organized water nano-structures, and (e) surface-adsorbed biomolecules of the recipient patient upon administration. For mineral or mineral salt homeopathic medicine sources, the source materials may serve as dopants that tune the properties of whatever nano-structures form.[12–15]

In the present model, electromagnetic and/or optical (photon-based) information, including quantum mechanical, arises from the manufacturing procedures.[16] There is nano-science evidence that the body would recognize the personal salience of the homeopathic potency signal to its current disease state because of the personalized protein corona shell from the recipient individual's own biomolecules that would immediately adsorb to form a coating around the surfaces of the medicine-related nano-structures on contact with the individual's biological fluids.[17,18] It is well established that the constituent proteins from the blood plasma that form the protein corona on contact with a nano-structure reflect the current disease and/or physiological state of the individual patient.[17] The nano-biointerface becomes the ultimate area for treatment personalization.

Homeopathic Medicines as Complex Systems

Given the complexity model for how healing occurs (see Part 1 of this paper), what is a homeopathic medicine that can initiate such dramatic changes in the body? Converging evidence indicates that a homeopathic medicine is itself a complex nano-scale system.[19] Homeopathic medicine complexity emerges from the interaction of the component parts from source, glass (silica) or plastic (carbon) containers, solvents (lactose, ethanol, water as additional surface modifiers, and as carbon sources in the case of lactose and/or ethanol as well as organic source materials) and, ultimately, the surface-adsorbed human biomolecules of the recipient at the moment of treatment dosing. At least two separate lines of research support this postulate.

First, the homeopathic potency is capable of self-organizing and inducing formation of self-similar nano-structures in surrounding water.[5,8,20–27] Second, multiple studies of plants have shown that homeopathic potencies induce formation of self-organized, unique poly-crystalline structures in the exudates of treated plant seedlings versus controls.[6,7,28,29] In other words, homeopathically prepared medicines may induce formation of self-similar crystalline nano-structures in water and/or in biological fluids within a living system. These medicines may induce *patterns* of self-similar crystalline information in their surrounding environment.[30]

Traditional homeopathic manufacturing processes generate nano-scale structures that may or may not include measurable amounts of source material (with measurement limited to the practical detection limits of the instrumentation),[31–37] lactose if triturated (milled) with an insoluble source material, and, if succussed in classical glassware stoppered with natural corks, silica[38] and/or cork (Quercus) or other source plant bioactive coatings.[39,40] In nanotechnology, silica coatings[41,42] and silicon quantum dots[43] are well-known to contribute not only electronic but also biological amplification effects.[44–52] Doping and/or coating core nano-

structures with other materials alter and tune the resultant nano-structure properties.[53–58]

Nanoparticles are smaller than 100 nano-meters (nm) in diameter; the smallest sized nanoparticles are called quantum dots, with a size less than 10 nm in diameter. Nanoparticles in general possess extremely large reactive surface areas to which other nanoparticles and materials can adsorb, as a function of their nano-scale size. Because of their extremely small sizes, quantum dots also acquire unique electromagnetic, optical, and quantum mechanical properties.[59]

As an aspect of manufacturing-generated nano-structures, one study in mainstream nanotechnology indicates that ultrasound agitation of a salt solution (sodium chloride, potassium iodide) creates nanoparticles of the source material and concomitantly embeds them *onto glass or polymer slide surfaces* in contact with the liquid. The resultant nanoparticles can then leach back into the solution over time.[60] This type of phenomenon parallels what succussions might cause in any mineral salt solution. The findings further suggest the need to compare both composition and structure of nano-structures generated during *Hahnemannian* (different containers for every dilution–succussion step) versus *Korsakovian* (the same container re-used for dilution–succussion steps at higher potencies) manufacturing methods.

Furthermore, if succussed in plastic polymer containers, it is likely that the manufacturing container, along with any lactose, ethanol or other organic materials of plant or animal origin also in solution, might also contribute photo-luminescent carbon quantum nano-dots (<10 nm in diameter) and other carbon-derived nano-structures.[12,61–65] Carbon dots are now a major nano-component of sensitive sensors and signal amplifiers for extremely low quantities of specific physiological metabolites and biomolecules, mineral ions, herbs, vitamins, drugs, volatile organic compounds, and other agents.[66–69] As a proof of principle, it is even possible to process food waste water sources *per se* to synthesize photo-luminescent carbon nano-dots from their organic source material.[70,71]

Thus, homeopathic medicines containing carbon dots might literally serve as very crude sensor-carriers for the medicine source material and its constituent information at profoundly low femtomolar[72] or picogram concentrations.[73,74] One research group has termed certain carbon dots as "optic noses" for detecting and amplifying the signal of small quantities of their target agent.[68] Not surprisingly, carbon as an element is detectable in plant-derived homeopathically prepared medicines.[19,34]

Recent work by Cartwright suggests that the homeopathic medicine's signal may depend on its dipole moment properties. Dipole emissions are a capability also documented for certain carbon nano-materials such as carbon nano-dots.[65] As is true for other types of nano-materials, it is possible to tune carbon nano-dot properties by doping, modifying particle surfaces with different functional groups and adsorbents and/or changing pH.[75] In parallel, Elia's laboratory previously demonstrated that pH changes induce measurable heat release and alterations in electrical conductance of homeopathically prepared medicine solutions.[8]

Furthermore, multiple research groups have reported evidence that homeopathic manufacturing induces persistent formation of electromagnetic signal-induced, self-organized crystalline *water nano-structures*, termed "dissipative structures" by Elia et al,[8,76,77] "nano-associates" by Konovalov et al,[20,21] or "nano-pearls" (poly-crystals formed of many microscopic crystallites) by Meessen.[5] Crystalline structures at the nano-scale (or larger) spontaneously self-organize from an interaction of their constituent parts with each other and with their environment.

A crucial characteristic of nano-structures is that their large surfaces are highly reactive and interactive with their immediate environment.[78] Materials in that environment, including but not limited to other nano-structures and various molecules (e.g., organic materials from lactose, plant or animal proteins and nucleic acids, dyes and/or minerals/ions in colloidal solutions with nano-structures), will attach (adsorb) to the outer surfaces of nano-scale structures to form new layers, coatings, or shells around the nano-structure.[78–80]

Multiple factors, especially surface structure and surface energetics, as well as pH of the surrounding solution,[81] modulate the emergent properties of the resultant nano-structure coating. During the agitation such as sonication, vortexing, or manual succussions of a colloidal nano-structure solution, some of those elemental constituents, for example, nitrogen or phosphorus, as well as ethanol, may also dope the particles.[58,80,82] The implosion of succussion-induced nano-bubbles that form around or near nanoparticles would also add heat energy and pressure effects in generating homeopathic medicine nano-structures.[31,83–86] These coatings and dopants can significantly alter the physical, chemical, and biological properties of any given nano-structure.[53]

Some recent research indicates that the composition of nanoparticles found in homeopathic medicines may not always contain detectable amounts of the source material because of the detection limits of the available technology.[19] As always, lower limits for detection ability of the measurement instruments can be a methodological factor in these types of findings.

However, apart from debate over what the *composition* of the nanoparticles might be,[19] there is nonetheless ample convergent evidence for the presence of poly-disperse (heterogeneous sizes) nano-structures and other materials in homeopathically prepared medicines.[32,40] Evidence shows that homeopathically prepared medicines, even in higher potencies diluted past Avogadro's number for bulk forms of source materials, nonetheless retain the thermoluminescence signature signal of the original source material.[87,88]

Sizes of homeopathic medicine nano-structures studied range from the size of quantum dots (<10 nanometers) to isolated nanoparticles (<100 nm diameter) to larger aggregates measuring hundreds of nm in size.[32,34–37,39,89,90] Data on variations in sizes and zeta potentials (surface electrical charge properties at the interface with surrounding liquids) and calorimetric pH effects on potentized medicines further indicate

differences from controls, consistent with possible differences in nano-structure coatings.[8,19,38,39,76,77,90,91]

It is also important to note for any homeopathic medicine that the cumulative effect of a greater number of triturations (mechanical milling in dry lactose) or of succussions (vigorous agitation in liquid solvent) to make higher potencies affect the final, albeit heterogeneous, nanoparticle sizes.[92] Such procedures likely parallel the progressive *reductions in nanoparticle sizes* that occur with longer periods of mechanical milling, vortexing or ultrasonication in conventional top-down nano-technology manufacturing.[93,94] As a result, smaller sized nanoparticles occur in relatively greater quantities at higher versus lower potencies.[92] There is also the potential for a low dose (i.e., smaller quantity or concentration) by smaller size (e.g., homeopathic potency nano-structures) interaction in producing various biological effects.[18,95]

Notably, finding evidence for a given type of agent, structure, process, or signal does not preclude the concomitant existence or possible role of another one in homeopathic information capture and delivery to the organism. In physics, electrons in atoms are electromagnetic phenomena. When an electron absorbs a photon, the electron jumps to a higher energy level. During quantum confinement of atoms and their electrons near the surface of the smallest sized nano-structures, photons (light particles, optical signals) are emitted when electrons move from a higher to a lower energy state.

Past findings of electromagnetic,[8,25,26] optical,[87,88,96,97] or other signals[98–100] emitted from homeopathic medicines do not preclude the initial generation of different types and sizes of nanoparticles during manufacturing,[19,31–37,39,89,90,101,102] including the presumptive electromagnetic signal-induced nano-structures[8,76,77] and/or quantum dot sizes already observed in potentized medicines.[32,35–37] Gayen et al recently demonstrated that adding homeopathic *Cuprum arsenicosum* 200C potency into an electroactive polymer film used in the electronic industry markedly enhanced the conductivity and dielectric constant of the film.[103] Again, homeopathic medicines appear to acquire photo-electronic properties during traditional manufacturing procedures.

Nano-structures formed in the course of serial dilutions and succussions during manufacturing, even if they represent interaction of information-containing quantum coherence domains with water,[19,27,104–106] would themselves be able to generate weak (low intensity) electromagnetic and optical signals.[25,26,63,103,107]

Homeopathic medicine nanoparticles that are as small as quantum dots (<10 nm in diameter)[32,35–37] comprise small numbers of atoms with their electron clouds trapped close to the particle surface. As a result, electron movement in quantum dot-sized nanoparticles can lead to quantum confinement, quantum entanglement, and quantum coherence phenomena, as claimed by other researchers for higher homeopathic potencies.[77,96,104,108–116]

Indeed, some investigators have proposed that the medicine information emerges from persistent supra-molecular aggregates of water, reflective of quantum coherence domains at the nano-scale.[10,27,105,106,117] The signal information derives from the original homeopathic manufacturing process of serial dilutions followed at each dilution step by multiple succussions (intense agitation or shaking of the liquid carrier, i.e., the non-linear dynamics of fluid turbulence).[27,98–100,106] Of relevance, there is a separate body of evidence for the field of quantum biology,[118–123] including observations that biological information transfer occurs at the nano-scale level of the organism.[10,23,26,108,120,121,123–131]

Thus, there are multiple types of materials and sizes of nano-structures documented in homeopathic medicines at a wide range of potencies. Skeptics have long questioned how any homeopathic medicine could exert different effects from any other homeopathic medicine if it were composed of "just" silica nanoparticles or some other material common in homeopathic manufacturing. Variations in particle sizes, cores and surfaces, as a function of the methods and materials used during manufacturing, may provide much of the answer. Complex interactions between the surfaces of the medicine nano-structures and the recipient patient's own biological fluids—for example, plasma or serum proteins—may provide the rest of the answer.[18]

The Role of the Nano-Biointerface in Homeopathic Potency Effects

Moreover, during treatment, homeopathic medicine-specific information may derive from *both* (a) the complex electromagnetic and/or quantum properties of the medicine itself, and (b) the emergent biological disease state of the individual recipient. In the present model, it is not possible to discover the scientific basis of homeopathic individualization by studying only the medicine, in isolation from its interaction with the individual patient who needs it. The nano-biointerface plays an essential role.

That is, critics of a nano-medicine model for homeopathic medicines overlook the enormous area and reactive nature of the surfaces of nano-structures.[78] Other materials in solution with the nano-materials adsorb to the surface of most nano-structures. Most nano-technology research shows that presence or absence of ethanol in solution will affect the properties of the resultant nano-structures and their surfaces.[58,132,133] Smaller versus larger particle size affects the nature of the protein corona layer adsorbed onto a given particle.[18] Thus, although it is possible to make seemingly "cleaner" or "simpler" potentized medicines for research study as nano-structures, the precise materials and methods during their preparation for clinical or research use will influence their ultimate properties in vitro and in vivo.

More important for homeopathic treatment, on contact with an individual's body fluids (e.g., plasma, serum, and saliva), homeopathic nano-structures, like any nano-structures, would adsorb onto their surfaces various patterns of not only other materials in solution during manufacturing, but also a complex specific pattern of endogenous proteins from the recipient organism.[134] Sick organisms exhibit unique disease- and patient-specific patterns of proteins in body fluids (►**Fig. 1**).[135,136]

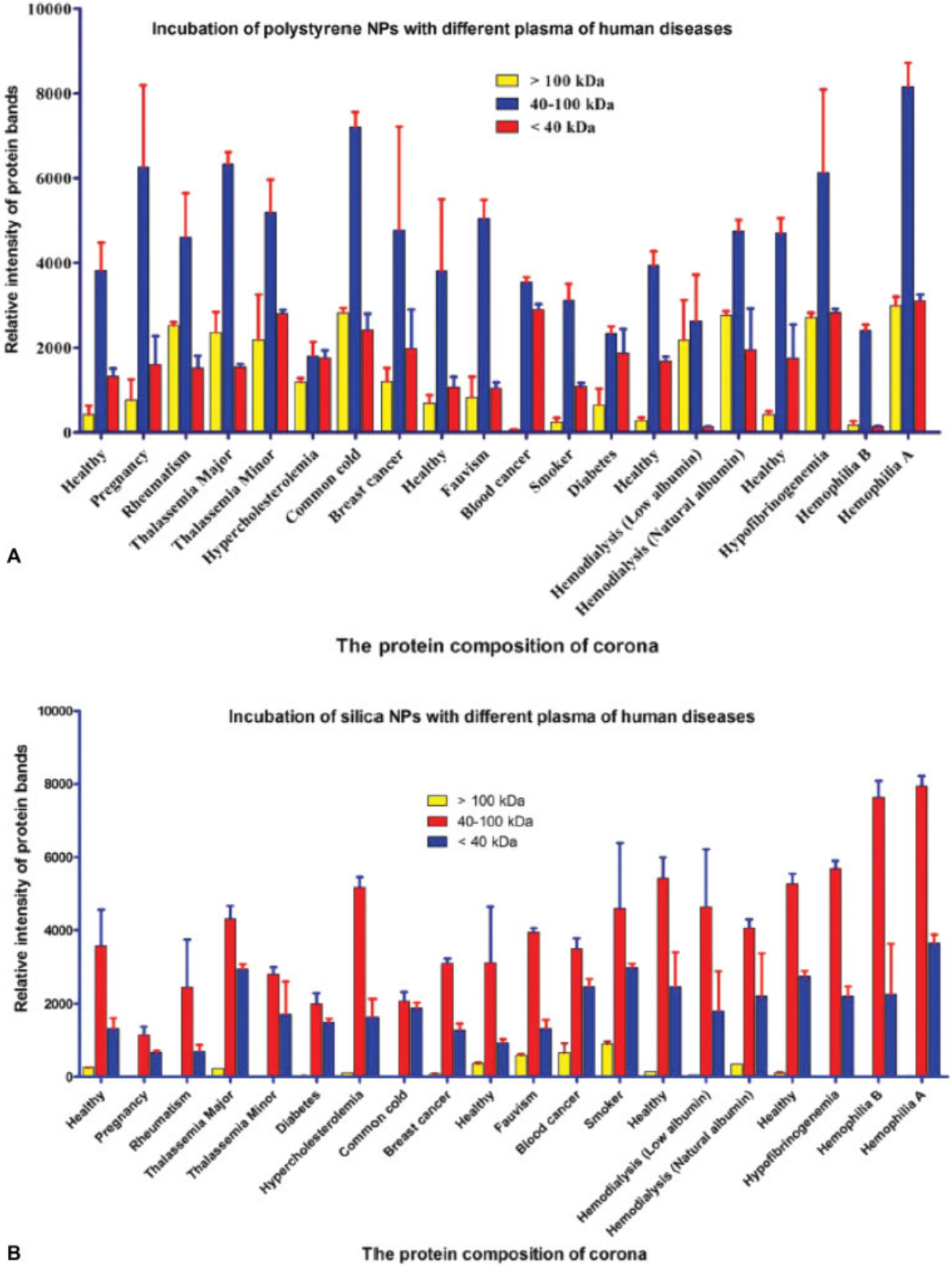

Fig. 1 Histogram of the [protein corona] alterations in band intensities during incubation of (**A**) polystyrene and (**B**) silica nanoparticles with human plasma (50%) from different patients/persons *in different clinical states* (healthy, pregnant, rheumatism, thalassemia major, thalassemia minor, hypercholesterolemia, common cold, breast cancer, fauvism, blood cancer, smoking, diabetes, hemodialysis (low albumin), hemodialysis (natural albumin), hyperfibrinogenemia, hemophilia B, and hemophilia A). [Data represent findings for individual patients/persons, not group averages.] Graph created from data extracted from original publication[135] with permission from Royal Society of Chemistry. Note: kDA refers to kilodaltons, where a Dalton (Da) equals 1/12th the mass of a carbon atom. An average amino acid has a molecular weight of 110 to 135 Daltons. Most proteins have masses on the order of thousands of Daltons (kilodaltons, kD).

Protein adsorption from the recipient's blood onto homeopathic nano-structures creates a protein corona layer (coating, shell) that would thereby generate *a unique biological identity* from that person's biological state.[137–142] Notably, different allopathic diseases and clinical states (e.g., pregnancy) in conventional medicine can generate different *protein corona* patterns from human blood plasma on nano-structures, including both silica and polystyrene nanoparticles (►**Fig. 1**).[135,136,141,143]

Disease-related metabolomics play a role in how blood plasma proteins interact with exogenous nanoparticles.[136] Smaller nanoparticle sizes, which occur at greater concentrations in higher versus lower potencies,[36,92] are known to modulate the formation, composition, and properties of the protein corona that becomes the nanoparticle coat.[17,18,134] In vivo, higher versus lower homeopathic potencies exert longer durations of action.[144]

Consequently, homeopathic nano-structures in any potency would instantly acquire a unique, *individualized identity from the patient's current biological state* upon administration. As a result, the simillimum would serve as a low-dose, personalized nano-encapsulation of the patient's current clinical state to signal the need for adaptive biological responses to the emergent disease process.

In this model, smaller nano-structures, including quantum dot sizes, especially in higher homeopathic potencies created by the cumulative effects of large numbers of succussions, would show not only smaller particle sizes,[92] but also particle size-related variations in protein coronas formed on contact with the recipient's biological fluids (e.g., blood serum or plasma).[134]

In turn, the smaller nano-structures in higher potencies with their particle size-dependent unique protein coronas might initiate different biological effects than would larger nano-structures with their adsorbed protein coronas at lower homeopathic potencies (►**Fig. 2**). Consistent with this hypothesis, a recent plant-model study revealed that a greater number of succussions improves the effectiveness of a given medicine potency (45x) in fostering more robust plant seedling germination resilience to a toxic stressor.[28]

Hormesis is a well-documented adaptive biological phenomenon in CAS involving low-dose stimulation versus high-dose inhibition or toxicity of function.[145] If the homeopathic medicine dose is quantitatively low, that is, in the hormetic range,[146] the present model predicts that the nano-medicine information with its personalized biological identity from the protein corona would stimulate non-linear systemic changes in the opposite direction to the emergent current disease pattern for that specific patient.

The scope and specificity of the response derive from the initial conditions (i.e., dynamical biological state of the disease) of the recipient complex adaptive system. The outcome would be multiple changes in the direction of healing. For instance, acute and chronic inflammation underlie the dysfunction and pathologies across a broad spectrum of disease processes.[147] However, homeopathic medicines typically mobilize multiple reversals in the biological/symptom manifestations of whatever disease or health conditions that a given individual may be experiencing. Thus, in homeopathic treatment, the quantitatively low doses of the simillimum medicine should exhibit evidence of some anti-inflammatory effects across different diseases as part of the systemic change.

In mechanistic hormesis research, Calabrese et al have documented that *quantitatively low doses* of many different agents/stressors—including but not limited to nano-sized particles[145]—initiate hormesis in part by polarizing macrophage activation patterns toward *anti-inflammatory effects*.[148] In contrast, high or toxic doses of such agents/stressors induce macrophage pro-inflammatory effects.[148] A question that follows is whether or not homeopathic simillimum treatment modulates epigenetic expression of inflammatory biomarkers, including but not limited to favoring macrophage anti-inflammatory activation patterns.

Thus, homeopathic treatment involves treating the individual patient literally with a quantitatively low dose of his or her own current holistic biological disease state information at the nano-scale level (the homeopathic simillimum in vivo as a personalized hormetic stimulus). This first step initiates an endogenous cascade of adaptive biological signaling and hormetic systemic adaptations. The literature to date already shows that homeopathic medicines do modulate macrophage activation patterns.[149,150]

As a result, an area worthy of future study is the nature of the protein coronas for people with different homeopathic constitutional types or acute health conditions at baseline and over the course of treatment. This type of emergent biological identity from protein coronas potentially distinguishes homeopathic treatments using potentization-induced nano-structures from the non-individualized chemical identity of conventional drugs or even non-homeopathic nano-structures from outside the body.

In homeopathy, one investigator recently proposed using an individual's own homeopathically prepared DNA (which is inherently nano-scale), in their unique current epigenetic state of gene expression isopathically to treat miasmatic diseases.[151] Separately, mainstream nano-medicine researchers are already beginning to consider the therapeutic potential of different personalized protein corona coatings on quantitatively higher dose nano-structures.[135,136,143]

For most clinical scenarios, however, the simillimum for the patient's current state would still be the single correctly chosen homeopathic medicine whose information resonates with and literally adsorbs onto its surface the most relevant pattern of endogenous proteins reflecting the patient's current state: that is, the biological information pattern of the recipient individual in the protein corona.[152] The clinically claimed need in homeopathy for even more precise symptom pattern matching to choose the correct homeopathic medicine at higher versus lower potencies may derive in part from differences in potency-related nanoparticle sizes and consequently the resultant protein corona patterns that form.[18]

To a limited extent, particle sizes and zeta potential values, which assess electrical potential around nanoparticles, provide some indication of nano-structure stability

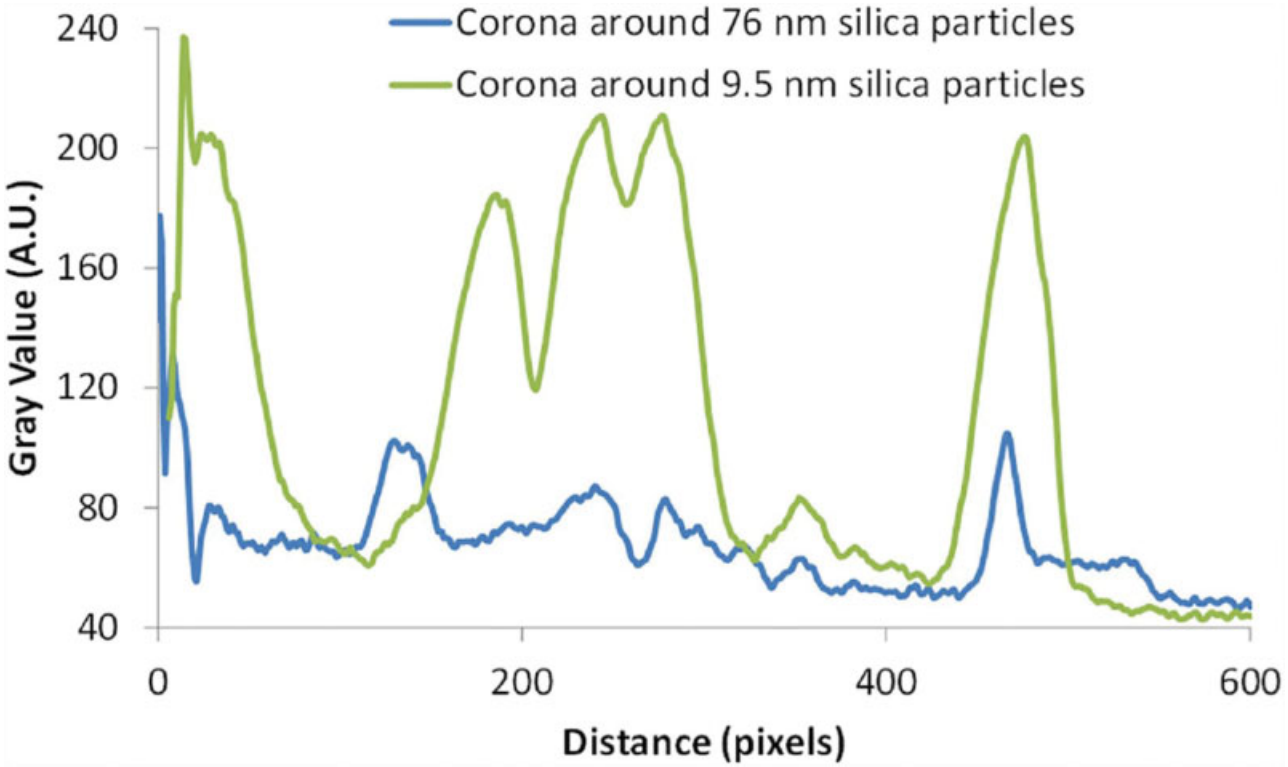

Fig. 2 Comparing the intensity of different [protein] bands for two plasma coronas from silica nanoparticles. Plasma corona from 9.5-nm silica particles in green and from 76-nm silica particles in blue. The x-axis has been adjusted for the 10-nm silica sample since the data come from different gels. [Lundqvist et al[18]: used with Creative Commons License, with attribution.] Note: Smaller versus larger particle sizes with their respective associated variants of protein corona patterns imply potential for different biological and clinical responses to higher versus lower homeopathic simillimum potencies.

and surface differences between verum homeopathic medicine and solvent controls.[39,90] However, zeta potentials are not a useful measure for evaluating or differentiating the composition and properties of the protein corona. Applying newer nano-technology for examining the protein corona at the nano-biointerface, such as fluorescence correlation spectroscopy, may be necessary in studying homeopathic healing.[17,135,136,143]

Once the simillimum homeopathic signal interfaces and acquires its personalized biological identity from the recipient's own body, the endogenous biological signaling networks of the body can take over (see also Part 1 of this paper). Cell biology naturally involves molecular mediators of the cell danger response system as well as structures and cascades of signaling processes at the nano-sized level of scale[153–157] (e.g., DNA double helix is 2 nm in diameter; cell membranes are approximately 10 nm thick—https://www.news-medical.net/life-sciences/Nanoscience-Advances-in-Biology.aspx).

Nano-scale signaling for systemic change mobilizes intercellular messengers,[158] including cell membrane-derived intraluminal nano-vesicles (exosomes, ranging from 30 to 100 nm in size),[156] as well as damage/danger-associated molecular patterns (DAMPs) and associated immune cells and mediators.[158–160]

Consider for example the homeopathic medicine (nosode) *Carcinosin*,[161,162] prepared from breast cancer tissue. *Carcinosin* potencies can induce breast cancer cell death.[161,163] Most likely, *Carcinosin* in potency contains low quantities of cancer cell exosomes and/or genetic material information expressing the biology of cancer after undergoing the agitation of succussions.

In mainstream nano-medicine, researchers are now testing breast cancer exosomes—that is, nano-sized extracellular vesicles formed from breast cancer cells—in vaccines to prevent and/or treat breast cancer.[157,164] Homeopaths have been using *Carcinosin* for patients with a much broader clinical picture, in addition to breast cancer per se, for a much longer period of time. Apart from malignancy, other, non-cancerous, cells normally use exosomes for intercellular communication via the plasma.[156,165]

Environmental stressors and danger signals (from the internal and/or external environment) can arrive in the form of chemical bulk-form agents, nano-structured agents,[158] electromagnetic and/or optical (photon) information,[166,167] altitude, other physical factors such as cold or hot temperatures,[168] or endogenous damage-related cell to cell messengers (e.g., hormones, cytokines, exosomes [nano-sized vesicles carrying DNA, RNA, and proteins from their original biological cell], cell signaling pathways).[169] However, it is the quantitatively low dose of the self-similar homeopathic medicine in potency that can best trigger hormesis and personalized biological healing, rather than suppress symptoms of the disease in a sick individual.[170]

Summary and Discussion

The fundamental description of homeopathic healing readily translates into the modern scientific terms from the field of

complex systems or complexity. The working hypothesis here is that the correct homeopathic medicine triggers the body as a complex adaptive system (an open system far from thermodynamic equilibrium) to self-re-organize system-wide toward better health.[146,170,171] The biology of the body itself occurs at the nano-scale level of organization[172] using adaptive non-linear dynamical change as an essential feature in restoring and maintaining health.[171,173,174] Healing is an emergent biological process.

Homeopathic medicines exhibit features of complex systems, especially self-similarity and self-organization, as shown in previously published studies of both water and plant exudates. The emergent properties of homeopathic medicines include the capacity for generating unique electromagnetic and optical emissions.

Self-organization is also a key characteristic of recipient living systems (that is, CAS). Whatever the nature of homeopathic medicines,[175] the net clinical result is improved bio-psychosocial resilience of the biological organism as a whole.[145,171,176] The healing process engages the capacity for biological self-organization inherent in CAS to reverse disease processes.[4,177] Moreover, the healing process is non-linear, in that the weak signal of the correct simillimum medicine initiates a disproportionately large response in the body.

The signal from the correct homeopathic medicine reflects resonance between the emergent information carried by the potency as a complex system[22,178] and the emergent electromagnetic and biochemical properties of the recipient organism as a complex adaptive system reflected in adsorbed protein patterns from the individual's blood plasma or serum[17] (►**Fig. 1**).[22–24,178–180] In addition to surface electrical charge and smoothness or roughness, the size, shape, and hydrophobicity of the nano-structures affect the quantity and affinities of blood proteins that adsorb onto the nano-structure surfaces to make the personalized protein corona coats.[181]

The current model then suggests that quantitatively low doses of the various nano-structure–protein complexes generate the individually salient and low-intensity signal that serves as the hormetic stimulus (personalized hormetin). During homeopathic treatment of human beings or animals, the body takes over the process in two ways:

(i) adsorbing unique patterns of biomolecules (e.g., proteins) that reflect the current emergent disease state of the organism on to the homeopathic medicine nano-structure surfaces to create the protein corona coat and thus generate a personalized biological identity for the patient's body. The result would *enhance specific treatment salience* for the individual's current state;

(ii) modulating the biology of symptoms and healing via functional changes in neural, immune, and inflammatory pathway networks and mediators[149,160,182–185]: for example, interactive components of the cell danger/damage molecular pattern response system.[158,170] A feature of the biological response is modulation of complex gene expression patterns by specific medicines.[150,186–188]

These adaptations are all in the service of optimizing the individual's fitness to survive in a biologically perceived environment that includes the potential disease damage or disease-encapsulated "danger" of the homeopathic medicine, as signaled by detection of the low-dose homeopathic information (that is, an individualized integrated form of the current disease state of the person).

The implication is that using the homeopathic simillimum medicine as a personalized hormetin will modulate the interrelationships and interactions of *endogenous biological signaling networks* to initiate disease recovery, a hypothesis supported by studies of certain homeopathic medicines in animal or cellular models for cancer.[189–193]

If the system is already diseased in some way, it is at or close to its physiological limits (cf. time-dependent sensitization and oscillation).[194,195] The body will potentially exhibit transient aggravation up to its physiological limits and then reverse its direction of change back from disease toward a healthier degree of complexity, following the arrival of a quantitatively low-dose, hormetic salient stimulus to do so.[196,197]

As a quantitatively low-dose warning signal to adapt,[11,190] the homeopathic medicine does not require a conventional pharmaceutical-level dose or quantity, be it some type of nano-structure,[19–21,31,32,34–37,39,83,84,90,107,185] an electromagnetic and/or optical signal that emanates from such structures,[8,25,26,76,87,97,198] and/or some other physical-chemistry phenomenon.[98–100]

This present complexity-based model requires the nano-biointerface between the individual patient's current biological condition and the simillimum nano-medicine properties. The clinical state-dependent individual protein corona forms a unique biological identity for the medicine nano-structures to fulfil their simillimum role, on contact with the patient's own blood plasma, serum, and/or saliva.

Hormesis evolves as an adaptive pattern of endogenous responses to the homeopathic information/signal. It follows from the model that effective homeopathic treatment requires not only (1) quantitatively low doses of unique nano-structures salient to the current state of the recipient patient; but also (2) an interaction at the nano-biointerface between the medicine nano-structure surfaces and the patient's own blood plasma or serum proteins to form the personalized protein corona as the hormetic signal; and (3) subsequent adaptive evolution of better health via interactive self-reorganization of the organism's non-linear dynamical networks and sub-systems across multiple levels of scale (see Part 1).

Finally, research questions for testing this model include:

- Does the homeopathic simillimum medicine, but not a clinically incorrect medicine or a placebo, emit unique homeopathic signal information that attracts a highly representative, patient state-specific pattern of plasma protein adsorption on to the nano-structure surfaces?
- Does the complex medicine system, on interface with the body as a complex adaptive system, thereby create a low quantitative dose, personalized hormetic signal

encapsulating the individual's current disease state (protein corona adsorption pattern) to initiate the adaptive changes of healing?
- Do higher versus lower homeopathic potencies of the same medicine exhibit different physico-chemical and/or biological properties at the nano-scale level of organization: for example, different nano-structure sizes and shapes, surface charges, protein corona adsorption patterns, durations of action?
- To what extent do the biological mechanisms of endogenous signal amplification processes, such as stochastic resonance, hormesis, and time-dependent sensitization (see Part 1), play a role in the nature, direction, and magnitude of clinical responses to homeopathic simillimum treatment?
- Do the biological networks involved in simillimum responses include reactive oxygen species, DAMPs, including but not limited to heat shock proteins, exosomes, and specific components of the immune system such as macrophages as part of the endogenous signaling process?

This complexity model for homeopathic medicine also requires adopting nano-materials research technologies and methods that can objectively document existence of—and manufacturing materials and methods-related variations in—the complexity of homeopathic medicine-derived signals, protein corona formation, and biological effects.

Conclusions

In conclusion, the evidence suggests that every homeopathic medicine is a complex nano-scale system involving multiple inter-connected, interacting components (core-shell nano-structures of source, silica/silicon or carbon, modified by lactose and/or ethanol–water solvent), and emergent electromagnetic, opto-electronic, quantum, and biological properties.

Homeopathic nano-structure sizes may vary as a function of trituration and subsequent succussions, surface electrical and adsorptive properties, shells formed from lactose, silica, and/or other materials in solution (e.g., made from plant source extracts, or from cork extract if containers are stoppered with natural cork), and animal source materials. The smallest nano-structures, for example, source, silicon, or carbon quantum dots, may or may not be detectable in a given study because of limitations in methodological approaches or in technological instrumentation tools (e.g., lower limits for assays of trace amounts of elements with specialized mass spectroscopy or lower limits for very small particle size detection [e.g., quantum dots] with nanoparticle tracking analysis instruments).

In this adaptive network nano-medicine model,[146,170] specific biological individualization would derive from the formation of a unique personalized protein corona layer that instantly adsorbs on to the reactive surface of the homeopathic simillimum nano-structures on contact with a patient's own blood plasma, serum, or saliva. The protein components of the patient's biological fluids reflect the current biological state of the patient as reflected in the self-similar symptom pattern exhibited across the self-organized complex adaptive system of the body. Furthermore, the smaller nanoparticle sizes found at higher homeopathic potencies[92] may play a role in variations in the protein corona patterns formed on contact with biological fluids and their subsequent physiological effects[18]: for example, longer duration of action.[144]

These quantitatively low doses of such complex nano-structures in homeopathic potencies initiate the endogenous adaptive processes of hormesis and related phenomena to mobilize reversal of disease manifestations (see Part 1). The capacity for self-organization, structural and functional self-similarity, and emergence in complex systems, is the key to designing future research on not only the nature of homeopathic medicines, but also emergent systemic healing during individualized homeopathic treatment. The previously proposed term of "adaptive network nanomedicine"[146,170] for the present model encompasses the existing data and suggests a research path forward.

Highlights
- Evidence suggests that each homeopathic medicine is a complex multi-component, core-shell and/or doped nano-structured system ranging in sizes from 1 to 100 nm in diameter and exhibiting properties of self-organization, self-similarity, and emergence.
- The nano-scale components of homeopathic medicine's core and shell include source materials, silica and silicon quantum dots (if manufactured in glassware and/or containing plant-source materials), carbon nano-structures including carbon quantum dots (if manufactured in plastic containers and/or containing any organic materials from source, lactose, or ethanol), and water nano-structures.
- The homeopathic simillimum nano-structures emit unique electromagnetic and opto-electronic signals as well as exhibit quantum mechanical properties.
- On contact with a specific patient's plasma or serum, the current model proposes that the homeopathic nano-structures adsorb clinical state-specific patterns of proteins and other biomolecules on to their surfaces, thereby creating a personalized protein corona coat and biological identity reflective of the patient's current biological state (e.g., health versus specific disease or clinical state).
- Homeopathic simillimum as an individualized treatment would derive, at the nano-biointerface from the interaction of the emergent signal, properties of the correctly matched medicine and the individual patient's own unique biological state (protein corona state-specific pattern) at quantitatively low – that is, hormetic – doses. Smaller nanoparticle sizes in higher versus lower potencies may also affect the specific protein corona patterns and thus biological effects.
- Hormetic doses of the individual's encapsulated illness biology on the simillimum's nano-structure surface protein corona coat/layer would serve as adaptive triggers for homeopathic healing from disease.

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Conflict of Interest
Dr. Bell is a consultant to Standard Homeopathic/Hyland's Inc., a US-based manufacturer of homeopathic medicines. The company did not provide financial support for this manuscript.

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