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ORIGINAL PAPER

A quantum-like model of homeopathy clinical trials: importance of *in situ* randomization and unblinding

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Background: **The randomized controlled trial (RCT) is the 'gold standard' of modern clinical pharmacology. However, for many practitioners of homeopathy, blind RCTs are an inadequate research tool for testing complex therapies such as homeopathy.**
Methods: **Classical probabilities used in biological sciences and in medicine are only a special case of the generalized theory of probability used in quantum physics. I describe homeopathy trials using a quantum-like statistical model, a model inspired by quantum physics and taking into consideration superposition of states, non-commuting observables, probability interferences, contextuality, etc.**
Results: **The negative effect of blinding on success of homeopathy trials and the 'smearing effect' ('specific' effects of homeopathy medicine occurring in the placebo group) are described by quantum-like probabilities without supplementary *ad hoc* hypotheses. The difference of positive outcome rates between placebo and homeopathy groups frequently vanish in centralized blind trials. The model proposed here suggests a way to circumvent such problems in masked homeopathy trials by incorporating *in situ* randomization/unblinding.**
Conclusion: **In this quantum-like model of homeopathy clinical trials, success in open-label setting and failure with centralized blind RCTs emerge logically from the formalism. This model suggests that significant differences between placebo and homeopathy in blind RCTs would be found more frequently if *in situ* randomization/unblinding was used.** *Homeopathy* (2013) **102**, 106–113.

Keywords: Quantum probabilities; Entanglement; Contextuality; Non-local interactions

"*Inexplicable observations are not always signs of the supernatural*"

John Maddox[1]

Introduction

Homeopathic remedies are considered by many scientists and physicians as implausible and ineffective. At best they consider that homeopathy works, but only because of the consultation.[2,3] For many detractors of homeopathy, the final word has been spoken with the study of Shang *et al*.[4–6] The authors of this study reported a comparison of randomized placebo-controlled trials of homeopathy and allopathy; they concluded that – despite comparable quality of homeopathy and allopathy trials – the clinical effects of homeopathic medicines were not different from placebo effects. In contrast with allopathy, blinding of trials of homeopathic drugs strongly decreased the probability of success compared to open-label setting.

Although this study was heavily criticized,[7–9] its conclusions were not completely unexpected since the main reason for rejection of homeopathy is the difficulty for homeopathic remedies to pass successfully the test of blind randomized controlled trials (RCTs), which is the 'gold standard' of modern clinical pharmacology. Some supporters of homeopathy argue that blind RCTs are an inadequate research tool for testing complex therapies

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such as homeopathy.[10,11] In the present article, I propose a possible way to increase the chance of demonstrating a difference between homeopathy and control in blind RCTs.

Homeopathy and non-local theories

Homeopaths are convinced that homeopathy is effective, but there is a debate among them about the way in which it works.[12] For many homeopaths, there is 'something' in the homeopathic medicine, which explains the patient's response. In other words, there is a specific factor or cause located in the water or in the granules that acts locally as does a pharmacological compound. The 'local' explanation – frequently referred as 'Memory of Water' since Benveniste's experiments – is supported by some laboratory investigations.[13–17] In these experiments, the states of biological systems were significantly different in the presence of highly diluted pharmacological compounds or corresponding controls. Shaking between each dilution appeared to be necessary for 'memory' while some physico-chemical treatments such as heating were reported to erase it. However modification of water structure or local information storage in high dilutions remains to be convincingly demonstrated by physical methods.[17]

Besides the 'classical' hypothesis of local causality, other authors have more recently proposed that the cause of homeopathy effectiveness is not specifically located in water samples or remedy. Instead they used concepts derived from quantum physics, such as non-locality and entanglement.[18–21] Entanglement is a central concept of quantum theory: two quantum systems isolated from environment become entangled after interaction and as a consequence they share a single quantum state. This means that when a measurement occurs, the respective outcomes of the two quantum systems are correlated. Entanglement is also expected in systems that need both local and global descriptions; if these descriptions are complementary, then theoretical models predict non-local correlations between the elements of the system.[22,23]

The authors who apply quantum concepts to homeopathy differ in what is entangled among practitioner, patient and medicine.[12] Moreover, quantum physics describes particles and atoms and quantum phenomena are supposed to vanish in macroscopic world due to the decoherence mechanism, which is related to the numerous interactions of any macroscopic object with its environment. To overcome this obstacle, Walach proposed applying a 'generalized' version of quantum theory to homeopathy, which makes the theory applicable in more general contexts than the original quantum physics.[22,24]

In the present article, I present a simple model for global description of homeopathy trials. This model describes the cognitive states of practitioner and patient using notions from quantum physics such as superposition and non-commuting observables. Operations are non-commutative if changing the order of operations does not change the result. For instance washing and drying clothes are not commutative, the order in which the operations are carried out makes a big difference to the outcome. Putting on socks is commutative, the order in which they are put on makes no difference to the outcome.

This modeling is in the spirit of an emerging discipline named 'quantum cognition' at the frontiers of artificial intelligence, psychology and social sciences. Indeed, in some research areas, which have in common the description of cognition mechanisms and information processing in the brain, quantum probabilities have been proposed to address problems that were unresolved in a classical frame.[25] A quantum-like formalism has thus been applied to human memory, information retrieval, decision making, opinion forming, personality psychology, etc.[26–30] This new approach does not rest on the hypothesis that there is something quantum mechanical about the physical brain. The quantum formalism is simply used as a source of alternative new tools such as contextuality or entanglement. In these studies, the mental states of agents were characterized by state vectors in Hilbert space and, in several experimental models, quantum probabilities had better predictive power than classical probabilities. Some 'paradoxical' statistical data, particularly in psychology and cognitive sciences, can be modeled by this method.[26,27,31–33]

In order to make the notions of quantum physics more easily understandable, I will draw a formal comparison between homeopathy trials and single-particle interference in quantum physics. In both cases, contextuality has been shown to play a chief role.

From single-particle interference to trials of homeopathy

Single-particle quantum interference illustrates the superposition principle and some characteristics of quantum probabilities. The classical two-slit interferometer of Young is usually used for such a description, but the Mach–Zehnder device has the advantage of including only two detectors (D1 and D2) as depicted in Figure 1.[34] Light is emitted from a monochromatic light source: 50% of light is transmitted by beam splitter (BS1) in path T and 50% is reflected in path R. In BS2, the two beams are combined and 50% of light is transmitted by beam splitter in detector D1 and 50% in detector D2. If light is considered as a wave, it can be calculated that waves from the two paths are constructive when they arrive in D1 and destructive in D2. Therefore, clicks after light detection are heard only in D1. This is indeed what experiment shows and it is an argument for the wave-like nature of light.

On the contrary, if we consider light as a collection of small balls (photons), they should randomly go into path T or R (with a probability of 0.5 for each path) and then in BS2 they go into D1 or D2 randomly (again with a probability of 0.5 for D1 or D2). As a consequence D1 should click in 50% of cases and D2 in 50% of cases. However, even if photons are emitted one by one (by decreasing light intensity), the interference pattern persists (100% of clicks in D1). This is a quite counterintuitive result. Even more

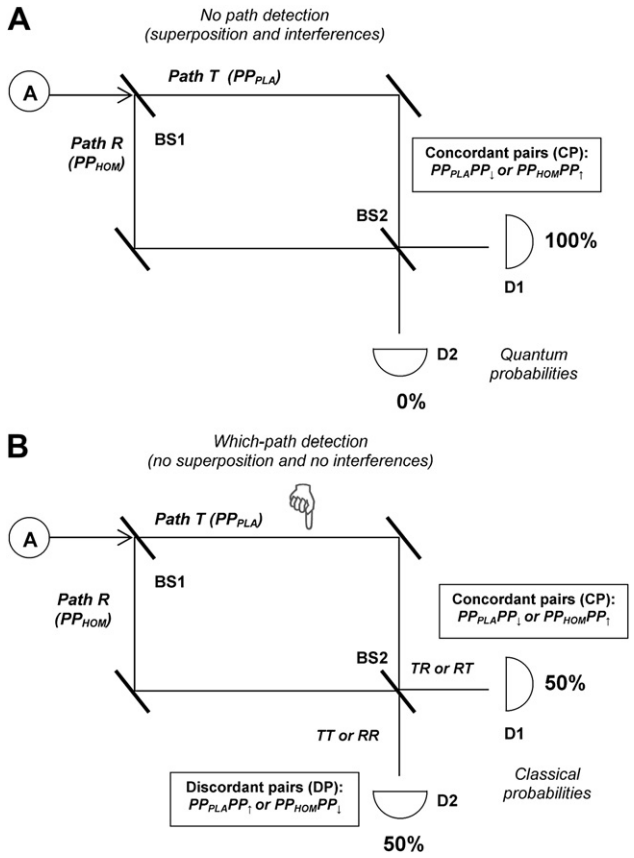

Figure 1 Interpretation of the outcomes of homeopathy trials as a consequence of quantum-like interferences (for an experiment with optimal interference term). A. In an open-label trial or with *in situ* randomization and unblinding, the cognitive state of patient/practitioner (described by the state vector $|\mathrm{PP}\rangle$) is able to interfere with itself (as a single-particle interferes with itself) and the rate of correlated pairs is high. B. In a centralized blind RCT, the cognitive state of PP cannot interfere with itself (there is no superposition) and the rate of correlated pairs is not better than random; 'specific' effects from homeopathy group are described in placebo group ('smearing effect').

astonishingly, this unexpected (non-classical) behavior disappears if the initial path (T or R) is detected by any means: then either D1 or D2 clicks, each in 50% of cases (classical probabilities apply) (Figure 1; lower drawing).

I draw an analogy between the one-particle interference experiment and homeopathic trials, which appear to have comparable mathematical structures. Indeed, according to the context of the clinical trial (both observables − labels and pair concordance − measured by patient/practitioner *vs.* 'external' measure of labels), either only concordant pairs (CP) (equivalent to detection in D1) or both CP/discordant pairs (DP) (i.e., equivalent to random detection by D1 and D2) are obtained (Figure 1 and Table 1). This suggested that a quantum (or more precisely quantum-like) model could be built to describe homeopathy trials, including the 'paradoxical' failure of homeopathy blind RCT.

Quantum probability

In classical probability theory, probabilities add; if P1 and P2 are the probabilities for two events E1 and E2

Table 1 Parallelism between single-photon interference experiment with interferometer and randomized placebo-controlled homeopathy trials

	Interferometer experiment	*Randomized placebo-controlled homeopathy trials**
First path λ_1^2	Path T Prob(path T)	PP_{PLA} Prob(PP_{PLA})
Second path λ_2^2	Path R Prob(path R)	PP_{HOM} Prob(PP_{HOM})
Superposition (quantum probabilities)	Path T and path R	PP_{PLA} and PP_{HOM}
Outcome 1	100% Detector D1	100% 'CP'
Outcome 2	0% Detector D2	0% 'DP'
No superposition (classical probabilities)	Path T or path R	PP_{PLA} or PP_{HOM}
Outcome 1	50% Detector D1	50% 'CP'†
Outcome 2	50% Detector D2	50% 'DP'‡

PP, cognitive state of the couple practitioner−patient; PLA, placebo label; HOM, homeopathy label; ↓, negative outcome; ↑, positive outcome; T, transmission; R, reflection; CP, concordant pairs; DP, discordant pairs.
* For an experiment with optimal correlations between labels and outcome (and with $\lambda_1^2 = \lambda_2^2$).
† PP_{PLA} with $PP_{\downarrow}$ or PP_{HOM} with $PP_{\uparrow}$.
‡ PP_{PLA} with $PP_{\uparrow}$ or PP_{HOM} with $PP_{\downarrow}$.

(for example head or tail in a coin toss), the probability for either event to occur is Prob(E1 or E2) = P1 + P2. With quantum probabilities, there is a key difference. First, we must write P1 = a^2 and P2 = b^2; the letters a and b are two (complex) numbers, named probability amplitudes and their squares allow calculation of the corresponding probabilities. The second key point is that for quantum probabilities, probability amplitudes, not probabilities add:

$$\begin{aligned}\mathrm{Prob}\big(\mathrm{E1\ or\ E2}\big) &= (a+b)^2 \\ &= \mathrm{P1} + \mathrm{P2} + \text{interference term.}\end{aligned}$$

The interference term is thus added to or subtracted to the classical probabilities to give quantum probabilities.

The objective of my study was to describe the possible outcomes of the cognitive states of patient/practitioner in different contexts. Mathematically, a state is represented by a vector in a Hilbert space. Using the quantum formalism, the cognitive state A of an agent (observer, experimenter, practitioner or patient) is represented by a state vector $|\psi_A\rangle$, which summarizes all the information on the quantum system. The linear combination of any states is itself a possible state (superposition principle). Thus, if $|A_1\rangle$ and $|A_2\rangle$ are two possible states of the system, then $|\psi_A\rangle = \lambda_1|A_1\rangle + \lambda_2|A_1\rangle$ is also a possible state of A (with λ_1 and λ_2 real or complex numbers). Therefore, a quantum system exists in all its particular and theoretically possible states. When the system is 'measured', only one state among the possible states is observed. In the quantum formalism, the probability to observe$|A_1\rangle$ is the square of the probability amplitude λ_1 associated with this state.

An example of superposition that is directly observable is the interference pattern observed in the two-slit experiment. Interferences are the hallmark of superposed states

and are the heart of quantum physics. In a single-photon interference experiment, if one can (even in principle) distinguish the path each photon has taken, then interferences vanish and classical probabilities apply. In Figure 1, the initial path (R or T) cannot be distinguished in upper drawing, and interferences occur; in lower drawing, paths are distinguished by measurement and consequently classical probabilities apply (without interference term).

The notion of 'non-commuting observables' is a key concept of quantum probabilities. Technically speaking, physical observables are mathematical 'operators' and for each operator there is a spectrum of possible results, which are named the 'eigenvectors' of the operator (they constitute an orthogonal basis in the vector space). When an operator is applied to a random state vector, the vector is split into different components, which are the eigenvectors of the operator. If the original state vector to be observed is an eigenvector of the operator, then it is not affected (this means that the value of the parameter to be measured was already fixed before measurement). Two observables are said to commute with each other when they share eigenvectors (the shared eigenvectors are not affected by the measure of the other observable). As a consequence, the outcomes will not differ according to the order of the measurements.

When two observables are non-commuting, the set of eigenvectors of one observable (orthogonal basis) can be expressed as a linear combination of the set of eigenvectors of the other observable; as a consequence, there are two different bases for the same vector space and the outcomes will be different according to the order of the measurements.

Put more simply, different results according to experimental devices (e.g., presence or absence of interference pattern in Young's experiment) are the consequence of non-commuting observables. The different experimental outcomes are said to be complementary, since both aspects (wave and photon) are necessary to describe the system in terms of classical physics. Another consequence is the establishment of non-local correlations between the different parts of the system, which are thus entangled.

Quantum-like formalism applied to trials of homeopathy

Definitions

The purpose of a randomized controlled clinical trial is to assess whether a therapy is associated more frequently with a positive outcome than a placebo or a reference treatment. No change or a worse outcome is referred as negative outcome. For example, in a randomized placebo-controlled homeopathy trial, one calculates whether the homeopathy therapy (labelled HOM) is more frequently associated with positive outcome denoted '↑' than placebo (PLA). A negative outcome is denoted '↓'.

The aim of this formal description is to calculate the probabilities of the possible cognitive states of the patient/practitioner before and after the trial. We define the cognitive states of practitioner and patient by using a single state vector: $|\psi_{Pr}\rangle|\psi_{Pa}\rangle = |\psi_{PrPa}\rangle = |PP\rangle$ with eigenvectors (i.e., state vectors of possible outcomes) written with indexes corresponding to cognitive state. For example, $|PP_{\uparrow}\rangle$ summarizes the cognitive states of the couple patient/practitioner that are associated with positive outcome.

We define 'CP' as the association of the label PLA with outcome '↓' or the association of label HOM with outcome '↑' (i.e., CP are $PP_{PLA}PP_{\downarrow}$ and $PP_{HOM}PP_{\uparrow}$); DP are defined as the association of PLA label with outcome '↑' or the association of HOM label with outcome '↓' (i.e., DP are $PP_{PLA}PP_{\uparrow}$ and $PP_{HOM}PP_{\downarrow}$).

Using this notation, $Prob_{class}(PP_{CP})$ is defined as the *classical probability* for the cognitive states of patient/practitioner associated with CP; $Prob_{quant}(PP_{CP})$ is the *quantum probability* of the cognitive states of patient/practitioner associated with CP. $Prob_{class}(PP_{DP})$ and $Prob_{quant}(PP_{DP})$ are the respective classical and quantum probabilities for DP.

It is important to note that we adopt the point of view of an observer who describes the system formed by the cognitive states of patient/practitioner, using concepts of quantum mechanics. The observer knows the initial state of the system and does not perform any measurement on this system during its evolution (from randomization to assessment of the CP).

First case: patient/practitioner measure both observables

In this situation, we consider that patient/practitioner 'measure' both labels and pair concordance (Figure 1A). The state vector of the cognitive state of patient/practitioner is described in terms of the eigenvectors of the first observable (PP indexed with labels PLA or HOM). From the point of view of the observer defined above, for each treatment chosen for a given patient by a given physician:

$$|\psi_{PrPa}\rangle = \lambda_1|PP_{PLA}\rangle + \lambda_2|PP_{HOM}\rangle, \quad (1)$$

${\lambda_1}^2$ and ${\lambda_2}^2$ are the probabilities associated with label PLA or label HOM after randomization, respectively.

The eigenvectors of the first observable (labels) are developed on the eigenvectors of the second observable (concordance of pairs). It is postulated that PP indexed with 'labels' and PP indexed with 'concordance of pairs' are non-commuting observables:

$$|PP_{PLA}\rangle = \mu_{11}|PP_{CP}\rangle + \mu_{12}|PP_{DP}\rangle, \quad (2)$$

$$|PP_{HOM}\rangle = \mu_{21}|PP_{CP}\rangle + \mu_{22}|PP_{DP}\rangle. \quad (3)$$

Therefore, $|\psi_{PrPa}\rangle$ can be expressed as a superposed state of $|PP_{CP}\rangle$ and $|PP_{DP}\rangle$:

$$|\psi_{PrPa}\rangle = (\lambda_1\mu_{11} + \lambda_2\mu_{21})|PP_{CP}\rangle + (\lambda_1\mu_{12} + \lambda_2\mu_{22})|PP_{DP}\rangle.$$

The probability of PP_{CP} is the square of the probability amplitude associated with its state:

$$\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}}) = |\lambda_1\mu_{11} + \lambda_2\mu_{21}|^2.$$

Similarly, $\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{DP}})$ is calculated:

$$\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{DP}}) = |\lambda_1\mu_{12} + \lambda_2\mu_{22}|^2.$$

Since ${\mu_{11}}^2 + {\mu_{12}}^2 = 1$, ${\mu_{21}}^2 + {\mu_{22}}^2 = 1$ and $\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}}) + \mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{DP}}) = 1$, we can easily calculate that $\mu_{11}\mu_{21} = -\mu_{22}\mu_{12}$, ${\mu_{11}}^2 = {\mu_{22}}^2$ and ${\mu_{12}}^2 = {\mu_{21}}^2$. This means that the matrix for change of basis is a rotation matrix (rotation sense has been chosen for proper association of labels with pair concordance):

$$\begin{pmatrix} \mu_{11} & \mu_{12} \\ \mu_{21} & \mu_{22} \end{pmatrix} = \begin{pmatrix} \mu_{11} & -\mu_{21} \\ \mu_{21} & \mu_{11} \end{pmatrix} = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}.$$

Therefore, we can replace the probability amplitudes in the equations calculated above:

$$|\mathrm{PP}_{\mathrm{PLA}}\rangle = \cos\theta|\mathrm{PP}_{\mathrm{CP}}\rangle - \sin\theta|\mathrm{PP}_{\mathrm{DP}}\rangle, \quad (4)$$

$$|\mathrm{PP}_{\mathrm{HOM}}\rangle = \sin\theta|\mathrm{PP}_{\mathrm{CP}}\rangle + \cos\theta|\mathrm{PP}_{\mathrm{DP}}\rangle, \quad (5)$$

$$|\psi_{\mathrm{PrPa}}\rangle = (\lambda_1\cos\theta + \lambda_2\sin\theta)|\mathrm{PP}_{\mathrm{CP}}\rangle + (\lambda_2\cos\theta - \lambda_1\sin\theta)|\mathrm{PP}_{\mathrm{DP}}\rangle,$$

$$\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}}) = |\lambda_1\cos\theta + \lambda_2\sin\theta|^2,$$

$$\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{DP}}) = |\lambda_2\cos\theta - \lambda_1\sin\theta|^2.$$

Second case: one observable is measured by 'outside' supervisor (centralized blind RCT)

In a centralized blind RCT, the context changes; labels are now measured/observed by a statistician or by the main investigator who supervises the trial (Figure 1B). This experimental situation is formally equivalent to a which-path measurement in single-particle interference experiment. Indeed, the information on the path must be taken into account; therefore, conditional classical probabilities, which include path data, must be used for calculation of the probability for the cognitive states of patient/practitioner to be associated with CP:

$$\mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\mathrm{CP}}) = \mathrm{Prob}(\mathrm{PP}_{\mathrm{PLA}}) \times \mathrm{Prob}(\mathrm{PP}_{\mathrm{CP}}|\mathrm{PP}_{\mathrm{PLA}}) + \mathrm{Prob}(\mathrm{PP}_{\mathrm{HOM}}) \times \mathrm{Prob}(\mathrm{PP}_{\mathrm{CP}}|\mathrm{PP}_{\mathrm{HOM}}).$$

With $\mathrm{Prob}(\mathrm{PP}_{\mathrm{CP}}|\mathrm{PP}_{\mathrm{PLA}}) = \cos^2\theta$ and $\mathrm{Prob}(\mathrm{PP}_{\mathrm{CP}}|\mathrm{PP}_{\mathrm{HOM}}) = \sin^2\theta$ (see Eqs. (4) and (5)), we calculate:

$$\mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\mathrm{CP}}) = \lambda_1^2\cos^2\theta + \lambda_2^2\sin^2\theta.$$

And similarly:

$$\mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\mathrm{DP}}) = \lambda_2^2\cos^2\theta + \lambda_1^2\sin^2\theta.$$

We conclude that $\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}}) \neq \mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\mathrm{CP}})$ in the general case. In the squaring of the sum, we have obtained an additional term $2\lambda_1\lambda_2\cos\theta\sin\theta$, which is typical of quantum probability interferences:

$$\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}}) - \mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\mathrm{CP}}) = 2\lambda_1\lambda_2\sin\theta\cos\theta.$$

Therefore, we dispose now of a simple description of clinical trials for homeopathy (Table 2). Assuming non-commuting observables and superposition of cognitive states, this model describes 1) the establishment of correlations when patient/practitioner measure both observables and 2) correlations not better than random in trials with labels blinded by external supervisor. The higher probability of CP in the first experimental situation compared to the second one is due to the interference term.

This formal description supports Walach's suggestion that if homeopathy effects are based on some form of entanglement, then these effects cannot be treated causally.[35] As a consequence, he predicted that placebo-controlled trials and experiments that force the non-local effect into a causal framework are not adequate.

Table 2 Summary of the quantum-like model describing open-label *vs.* double-blind placebo-controlled randomized trials of homeopathy

	Non-commuting observables ($\theta \neq 0$)		*Commuting observables ($\theta = 0$)*
	With interference term (superposition)	*Without interference term (no superposition)*	
Positive outcomes	Yes*	Yes†	No‡
Concordance of labels and outcomes§	High‖	Low	NA
Probability of CP: $\mathrm{Prob}(\mathrm{PP}_{\mathrm{CP}})$	$\lvert\lambda_1\cos\theta + \lambda_2\sin\theta\rvert^2$	${\lambda_1}^2\cos^2\theta + {\lambda_2}^2\sin^2\theta$	${\lambda_1}^2$
Probability of DP: $\mathrm{Prob}(\mathrm{PP}_{\mathrm{DP}})$	$\lvert\lambda_2\cos\theta - \lambda_1\sin\theta\rvert^2$	${\lambda_2}^2\cos^2\theta + {\lambda_1}^2\sin^2\theta$	${\lambda_2}^2$
Corresponding experimental situations	Open-label trial or *in situ* randomization and unblinding	Centralized blind RCT	Only negative outcomes

NA: not applicable; RCT: randomized clinical trial.
* $\mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\uparrow}) = {\lambda_1}^2 \times \mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{DP}}) + {\lambda_2}^2 \times \mathrm{Prob}_{\mathrm{quant}}(\mathrm{PP}_{\mathrm{CP}})$.
† $\mathrm{Prob}_{\mathrm{class}}(\mathrm{PP}_{\uparrow}) = {\lambda_1}^2 \times \mathrm{Prob}(\mathrm{PP}_{\uparrow}|\mathrm{PP}_{\mathrm{PLA}}) + {\lambda_2}^2 \times \mathrm{Prob}(\mathrm{PP}_{\uparrow}|\mathrm{PP}_{\mathrm{HOM}}) = {\lambda_1}^2\sin^2\theta + {\lambda_2}^2\sin^2\theta = \sin^2\theta$.
‡ Observables commute with $\cos\theta = 1$ and $\sin\theta = 0$; then $\mathrm{Prob}(\mathrm{PP}_{\uparrow}) = 0$ and $\mathrm{Prob}(\mathrm{PP}_{\downarrow}) = 1$ (only negative outcome is observed by practitioner and patient; there is no positive outcome).
§ CP: $\mathrm{PP}_{\mathrm{PLA}}$ associated with $\mathrm{PP}_{\downarrow}$ or $\mathrm{PP}_{\mathrm{HOM}}$ associated with $\mathrm{PP}_{\uparrow}$.
‖ For $\sin\theta = \lambda_2$ (and consequently $\cos\theta = \lambda_1$), the quantum interference term is maximal with $\mathrm{Prob}_{\mathrm{quant}}(A_{\mathrm{CP}}) = 1$ and $\mathrm{Prob}_{\mathrm{quant}}(A_{\mathrm{DP}}) = 0$.

What does θ stand for?

In the proposed model, θ is the only parameter to be adjusted. This parameter allows the passage from classical to quantum probabilities. When $\theta = 0$, the observables commute:

$$|\mathrm{PP_{PLA}}\rangle = 1 \times |\mathrm{PP_{CP}}\rangle - 0 \times |\mathrm{PP_{DP}}\rangle = |\mathrm{PP_{CP}}\rangle,$$

$$|\mathrm{PP_{HOM}}\rangle = 0 \times |\mathrm{PP_{CP}}\rangle + 1 \times |\mathrm{PP_{DP}}\rangle = |\mathrm{PP_{DP}}\rangle.$$

In this case, the two observables share their eigenvectors: $|\mathrm{PP_{PLA}}\rangle = |\mathrm{PP_{CP}}\rangle$ and $|\mathrm{PP_{HOM}}\rangle = |\mathrm{PP_{DP}}\rangle$. Thus, if $\theta = 0$, PLA label is always associated with CP and HOM label is always associated with DP; no positive outcome is observed. This indicates that $\theta \neq 0$ (non-commuting observables) is necessary not only for high rate of CP, but also for high rate of positive outcome. Note also that positive outcome should be present in the experimental background: before the trial, the probability of positive outcome to be spontaneously observed is low but not equal to zero and thanks to entanglement, the rate of positive outcomes increases.

The only postulates of the model are 1) non-commuting observables ($\theta \neq 0$) and 2) superposition of the states of PP. We simply enlarge the description of clinical trials from classical probabilities to quantum probabilities; indeed, classical probabilities are only a special case of quantum probabilities (with $\theta = 0$).

I did not hypothesise what θ stands for; this parameter connects together expected effects (symbolized by labels) and observed success/failure (concordance of pairs) without making hypotheses on the underlying mechanisms. Thus, θ could summarize cognitive and mental phenomena as different as empathy, physician's experience, expectation of patient and/or practitioner related to beliefs about treatment effectiveness and other cultural beliefs, Pavlovian conditioning, implicit learning, unconscious mechanisms and unknown mechanisms.

This model does not rule out an entanglement of homeopathic medicine with patient and/or practitioner as proposed by some authors, but it does not support either assumption.[18,19,21,24] The homeopathic medicine appears in the equations of the formalism through its label, i.e., its meaning or, in other words, the expected effect. The only hypothesis that appears to be excluded is a strict causal/local explanation, such as an ordinary pharmacological effect. In this case, label blinding by external supervisor would be without consequence on the result of the RCT.

Smearing in controlled trials of homeopathy

Non-local correlations cannot be used to transmit information; it has been pointed out that one consequence of non-local theories was that – if the effects are treated causally – "*they go away, change channel or do something crazy*".[35] Indeed, with entangled quantum objects, the same randomness is observed at two distant locations, but cannot be controlled and used to send useful information.

Pilot studies of blind homeopathic pathogenetic trials (HPTs, provings) suggest that such 'channel change' does indeed occur. In these HPTs, symptoms typical of one remedy were found in another study group.[36,37] One of the reasons for the difficulties in obtaining significant differences between placebo and homeopathy remedy in blind trials could be related to 'smearing' between placebo and homeopathy groups since the difference between groups is then erased.[6]

'Channel change' between treatment groups emerges from the formalism without additional hypotheses. For example, we can calculate the probability of positive outcome. For simplicity, we suppose that the probabilities for a given patient to be randomized in homeopathy group or in placebo group are equal ($\lambda_1{}^2 = \lambda_2{}^2 = 0.5$) and that the concordance of pairs is optimal ($\cos\theta = \lambda_1$ and $\sin\theta = \lambda_2$). In open-label setting, we calculate that as expected $\mathrm{Prob_{quant}(PP_{CP})} = |\lambda_1 \cos\theta + \lambda_2 \sin\theta|^2 = 1$: all patients who receive homeopathy have positive outcome and all patients who receive placebo have a negative outcome. In blind setting, we calculate:

$$\mathrm{Prob_{class}(PP_{CP})} = \lambda_1^2 \cos^2\theta + \lambda_2^2 \sin^2\theta = 0.5,$$

$$\mathrm{Prob_{class}(PP_{DP})} = \lambda_2^2 \cos^2\theta + \lambda_1^2 \sin^2\theta = 0.5.$$

In other words, the proportion of patients in homeopathy group associated with positive outcome is decreased to 0.5 in blind setting and *half of patients in placebo group are associated with positive outcome*. The 'smearing' of positive outcomes from 'active' group to placebo group is thus a direct consequence of the proposed formalism.

'Channel changes' have also been described during Benveniste's experiments. They were particularly obvious when Benveniste's team used the Langendorff system in experimental protocols that were similar to blind RCTs; these experiments and their 'anomalies' have been extensively described elsewhere.[38–42] Because Benveniste searched for a local explanation to explain his results on high dilutions and 'digital biology', the 'channel changes' were considered as failures due to molecular contamination, electromagnetic interferences, 'jumps' of activity from sample to sample, errors of manipulation, etc. Benveniste's later work, based on 'digital biology' concepts and using an automated analyzer could not be replicated by an independent team despite promising initial results.[43] Therefore, although the successive experimental systems of Benveniste's team benefited from important methodological improvements, the weirdness persisted and has been an obstacle to convincing other scientists of the validity of the results.

The experiments with high dilutions in the basophil system also exhibited comparable spreading of activity between samples in large-scale blind experiments. Both Benveniste's team[15,44] and Sainte-Laudy and Belon (see

Figure 2 in Ref. 45) have reported numerous experiments with regular 'waves' of basophil degranulation (or inhibition of degranulation). In large-scale blind experiments from the same authors, the mean difference between highly diluted control and 'active' samples strongly decreased and the usual regular patterns of degranulation according to dilution titer vanished.[13,15] Despite the small mean difference between control and 'active' samples, statistical significance was nevertheless achieved thanks to the high statistical power of the experiments. The detrimental consequences of blinding in these *in vitro* experiments also suggest nonlocal correlations.[40,46]

Is an 'Aspect experiment' possible?

The 'successes' or 'failures' of homeopathy trials appear to be dependent on experimental context: as for a quantum object, we can decide to observe either 'waves' (open-label trial) or 'particles' (centralized blind trials). In the single-particle interference experiment, there is no 'failure' when particles are observed and there is no 'success' when waves are observed. Waves and particles are two complementary aspects of the same quantum object. Due to these complementary aspects, if homeopathy trials follow quantum logic, we are then faced with the impossibility of getting significant correlations if we want to 'prove' the efficacy of homeopathy by blind RCTs, the current 'gold standard' for evaluating treatments.

A recent double-blind study in patients with rheumatoid arthritis concluded that homeopathic consultations, but not homeopathic remedies, were associated with clinical improvement.[2] As pointed out by Milgrom, although these results did not prove entanglement during homeopathy therapy, they nevertheless reveal the efficacy of the homeopathic consultation.[3] This comment is valuable because it means that homeopathic consultation could be a starting point to study which parameters influence clinical outcome.

Our quantum-like model suggests that the correlations between positive outcomes and homeopathy treatment observed in open-label conditions vanish in conditions comparable to blind RCT. The crucial point is the measurement/observation of the two observables: labels of treatments and clinical outcomes. If both observables are assessed by patient/practitioner, then non-local correlations of cognitive states are possible (with the hypothesis of noncommuting observables).

This suggests a method to overcome the 'glass ceiling' of blind RCTs in homeopathy. In this method, each practitioner would receive two sets of treatment units (homeopathy medicine and placebo) under code names. After a random choice of treatment by the physician, the patient would receive the chosen treatment (A or B). After assessment of clinical outcome, the result of each individual trial would be recorded in an electronic device with no possibility of erasing or modifying it. Then, the treatment name (stored in the memory of the device) − placebo or verum − administered to patient would be unblinded to the patient/practitioner. By this method, the two observables (treatment label and concordance of pairs) would be 'measured' locally. Therefore, all operations from randomization to unblinding would be performed *in situ* in doctor's office in a defined order without need of centralized supervision.

In an editorial in Homeopathy, Fisher noted that the hypotheses for nonlocal effects in homeopathy were not proven and added: "*A decisive 'Aspect' experiment has not even been proposed, much less conducted*".[12] Indeed, the experiment performed by Aspect *et al.* in 1982 was a convincing proof that the microscopic world was nonlocal as predicted by quantum physics.[47] Comparing *in situ* randomization/unblinding *vs.* centralized supervision of clinical trials could be the equivalent of the Aspect's experiment for quantum theories of homeopathy. Thus, positive results in homeopathy blind RCT using the *in situ* methodology would be not only a means to circumvent the gold standard, but also a very strong argument in favor of nonlocal theories for homeopathy. Nor can we exclude the possibility that non-local effects also occur in allopathy trials and add to the causal/local pharmacological effect; comparing *in situ* and centralized randomization/unblinding in the same trial would give evidence of such effects.

Conclusion

Success in open-label setting and failure with centralized blind RCTs emerge logically from the formalism in this quantum-like model of homeopathy clinical trials. This model suggests that the probability of observing significant differences between placebo and homeopathy therapy in blind RCTs would be increased by using *in situ* randomization/unblinding.

Conflict of interest

The author has no conflict of interest.

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