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ORIGINAL PAPER

‘Unconventional’ experiments in biology and medicine with optimized design based on quantum-like correlations

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In previous articles, a description of ‘unconventional’ experiments (e.g. *in vitro* or clinical studies based on high dilutions, ‘memory of water’ or homeopathy) using quantum-like probability was proposed. Because the mathematical formulations of quantum logic are frequently an obstacle for physicians and biologists, a modified modeling that rests on classical probability is described in the present article. This modeling is inspired from a relational interpretation of quantum physics that applies not only to microscopic objects, but also to macroscopic structures, including experimental devices and observers. In this framework, any outcome of an experiment is not an absolute property of the observed system as usually considered but is expressed relatively to an observer. A team of interacting observers is thus described from an external view point based on two principles: the outcomes of experiments are expressed relatively to each observer and the observers agree on outcomes when they interact with each other. If probability fluctuations are also taken into account, correlations between ‘expected’ and observed outcomes emerge. Moreover, quantum-like correlations are predicted in experiments with local blind design but not with centralized blind design. No assumption on ‘memory’ or other physical modification of water is necessary in the present description although such hypotheses cannot be formally discarded.

In conclusion, a simple modeling of ‘unconventional’ experiments based on classical probability is now available and its predictions can be tested. The underlying concepts are sufficiently intuitive to be spread into the homeopathy community and beyond. It is hoped that this modeling will encourage new studies with optimized designs for *in vitro* experiments and clinical trials. *Homeopathy* (2017) **106**, 55–66.

Keywords: Randomized clinical trials; Memory of water; Quantum-like probabilities

Introduction

In 2017, despite several decades of clinical trials and *in vitro* studies, the scientific community remains highly sceptic about homeopathy and high dilutions.[1,2] In particular, many scientists remain unconvinced by randomized controlled blind trials and meta-analyses with homeopathy medicines.[3,4] The recent systematic review of randomized clinical trials and meta-analysis of Mathie *et al.* concluded that, despite the small number of trials with reliable evidence, homeopathy might have small effect.[5] Hahn *et al.* performed a review of meta-analyses in homeopathy and reported that clinical trials of homeopathic remedies were most often superior to placebo.[6] They noted also that different meta-analyses could have opposite conclusions even though they were based on practically the same data. As pointed out by Hahn *et al.*, the heterogeneity of the trials and their various quality levels encourage interpretation and personal bias (for or against homeopathy) during the selection process of the data to be pooled.

The absence of rationale for diluting active compounds beyond Avogadro’s limit is also a frequent argument to

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disprove homeopathy.[7] Explanations for the persistence of a biological or therapeutic efficacy in the absence of the active molecules have been developed, which can be classified in two categories: local and non-local hypotheses. Historically, local hypotheses have been prevailing and continue to be explored. To put it in simple terms, local hypotheses propose that the efficacy of homeopathy is related to physical agents that are present in medicines or test samples. Because the initial molecules have been eliminated in the highly diluted samples, it has been proposed that the 'memory' of the starting molecule is nevertheless kept in water despite the apparent unstructured character of the liquid element. This hypothesis has been popularized under the well-known expression 'memory of water' after 'Benveniste's affair'.[8]

In favor of the role of water, one can cite the initial studies of Demangeat who reported physical changes in high dilutions using nuclear magnetic resonance; more recently these changes have been related to the formation of nanostructures and nanobubbles during the diluting process.[9] Other recent results suggested that the supramolecular chemistry of solvatochromic dyes was modified by a homeopathic medicine and could allow to detect high dilutions.[10] The role of supposed modifications of water whatsoever for carrying specific biological activity remain however to be established. Benveniste suggested that diluted molecules emitted an electromagnetic 'signature' that could be captured by a copper coil and transmitted to samples of 'naïve' water that acquired the biological properties of the initial molecules as a magnetic tape does.[11,12]

The physicists Del Giudice and Preparata proposed that long-range 'quantum-coherent domains' could be a support for 'memory of water', but how these domains might create a specific 'memory' remained undefined.[13] Moreover, a difficulty arises for applying hypotheses related to the physical properties of water to homeopathy since the most frequent mode of administration of homeopathic medicines is granules made of sugar. What becomes the role of water in these dry conditions is a question that is not addressed by the local theories of 'memory of water'. Finally, all mechanisms that have been proposed as a support for the biological activity of high dilutions lack key experimental data on specificity to be convincing. Indeed, until now, no correlation has been demonstrated between *specific* modifications of the physical properties of water and the corresponding *specific* biological changes.

For the sake of completeness on local theories, one should add that some authors have suggested that low amounts of the active substance were, in fact, present in highly diluted samples. Thus, Temgire *et al.* recently proposed that silicates from glass walls participated in the formation of silica-coated nanostructures that transported the initial ingredient throughout the dilution process.[14] If true, this explanation would be however incomplete because it cannot apply to high dilutions performed in plastic tubes as it is usual in biology laboratories. Ironically, similar arguments emphasizing 'contamination' from tube to tube or imperfect dilution process have been repeatedly put forward to dismiss the reality of the effects of high dilutions.[8] In all cases, it remains to demonstrate that such tiny traces of the initial active ingredient are sufficient to trigger a biological change.

Non-local or quantum-like descriptions of homeopathy trials

The idea that the blind randomized clinical trial (RCT) is an inadequate tool for assessing homeopathy is widely shared in homeopathy community.[15,16] Meanwhile all homeopathy practitioners agree that the medicines they use do not act as mere placebos. Local theories are unable to explain this discrepancy and hypotheses have been built on some ideas from quantum physics. Thus, Walach proposed a non-local interpretation of homeopathy in order to escape the classical relationship between homeopathic remedies and symptoms.[17] Atmanspacher *et al.* described a generalized quantum physics (formerly weak quantum physics) in order to define more precisely the usage of notions such as complementarity and entanglement in domains outside physics.[18] Entanglement is the property that allows correlations between quantum objects after they have interacted even if astronomical distances separate them. These ideas have been developed more specifically for homeopathy mainly by Walach and Milgrom in series of articles and also by other authors.[19–24]

Although most of these authors refer to entanglement to explain the action of homeopathy, their versions differ, particularly on what is entangled (patient, practitioner and/or homeopathic medication). In 2013, I proposed a modeling of homeopathy clinical trials using quantum-like probabilities where the negative effects of blinding in homeopathy trials were taken into account.[25] This modeling was an adaptation of a previous model aimed to describe Benveniste's *in vitro* experiments.[26]

Most physicians and biologists are admittedly unenthusiastic to read articles with mathematical reasoning. The quantum formalism conveys counterintuitive notions that are described with unfamiliar mathematical tools (Hilbert's space, state vectors, non commutative observables, etc). In the present article, I propose a more finalized version of the previous modeling that has the supplementary advantage to rest on classical probability (a quantum-like logic is nevertheless at work).

Brief review of Benveniste's experiments

Because the present modeling of 'unconventional' experiments in biology and medicine is the result of reflections on Benveniste's experiments, I will briefly summarize the story of the 'memory of water', which is well known by most readers of *Homeopathy*.[27–32] I will not describe the experimental details and results with high dilutions and 'digital biology' that can be found elsewhere.[8,33] I prefer to emphasize the stumbling block that prevented Benveniste to achieve the intended

purpose of his work, namely, to demonstrate the role of water as a support for biological activity.

For 20 years, approximately from 1984 to 2004, Benveniste's team accumulated data from different biological systems (mainly basophil degranulation, isolated rodent heart and plasma coagulation) that were apparently in favor of biological effects related to highly diluted compounds and digital biology. However, one could wonder, if these results were so obvious, why Benveniste did not succeed to convince his peers and why these experiments were not easily reproduced by other teams?

Indeed, although these results were consistent in open-label and even in in-house blind experiments, the apparent relationship between samples and biological changes vanished for unknown reasons during experiments that were designed as *proof of concept*. In this latter case, a supervisor coded the samples and kept the code secret until the end of the measurements; he did not participate in the measurements and was not informed before the end of testing. When sample testing had been completed, he received the list of results under code and he could then establish the rate of success by comparing the two lists. Because the results of experiments with an external supervisor were always not better than chance, Benveniste could not cross this hurdle. I described recently the details and the analysis of a series of experiments including both in-house and 'external' blinding.[34]

Of interest, this stumbling block occurred with different biological systems, different active molecules, different experimenters and different devices to 'imprint' water (high dilutions, 'transmission' experiments, digital biology experiments). The fact that a simple modification of the blind design could have such consequences in these different experimental models over an extended period of time is in my opinion the scientific fact of this story.[35] Therefore, understanding the nature of this obstacle could also cast some light on other 'unconventional' experiments. In 2001, a team of experts mandated by the Defense Advanced Research Projects Agency (DARPA) examined a robot analyzer designed by Benveniste's team. This machine automatically performed digital biology experiments based on plasma coagulation, a quite simple biological model.[8] The experts reported that they observed results in favor of digital biology, but they concluded on the absence of reproducible effects because they were unable to replicate these experiments independently of Benveniste's team. In the article reporting their observations, they suggested that unknown experimenter factors could be an explanation for this discrepancy.[36]

Failures of proof-of-concept experiments with external supervision were not interpreted by Benveniste as a 'falsification' – in the sense of K. Popper – of the possibility of a 'memory of water'. Mismatches of outcomes were considered as the consequence of uncontrolled factors such as electromagnetic waves in the environment, pollution of water, contaminations, human errors, unknown interferences with experimenter, etc. The possibility that the initial hypothesis – water as a support of biological activity – was erroneous was not really considered. One can understand this attitude to hang on to the 'memory of water' interpretation. Indeed, a biological 'signal' (i.e. a change of a biological parameter) repeatedly emerged from background noise, although not always at the good place, and there was no explanation for its presence in the current state of knowledge.[37] However, I think that a global view on all results – including unexpected findings – is necessary. Indeed, the fact that in-house blind samples – prepared in the same conditions as samples with external supervision and submitted to the same supposed 'disturbances' – behaved as 'expected' was inconsistent.[34]

One must underscore that such a difference according to blind design was not specific to Benveniste's experiments. Simply, mismatches were more obvious with protocols designed to minimize experimental loopholes and with the desire of Benveniste to convince other scientists with flawless results. As an example, a trial performed independently of Benveniste, namely the multicenter trial of Belon *et al.* with highly diluted histamine on basophil degranulation, exhibited also issues about blinding. Overall, the results obtained with four laboratories in centralized conditions were statistically significant, a result that was in favor of an effect of high dilutions.[38] Nevertheless, a detailed analysis indicates that the results were different according to the laboratories, sometimes at the opposite, and that one team did not achieve a significant difference between controls and 'active' samples. Moreover, the regular pseudo-sinusoidal inhibitory dose-responses that were previously reported with highly diluted histamine were no longer observed.[39] It was as if blinding scrambled the outcomes, a phenomenon that should not be observed if only local mechanisms were prevailing.

Definition of an elementary unconventional experiment

In experimental biology and medicine, the purpose of most experiments is to explore a possible relationship between a supposed cause and a biological (or clinical) effect. For the description of 'unconventional' experiments (e.g. homeopathy clinical trial, 'memory of water' experiments), we make no assumptions on physical differences among the experimental 'causes' (e.g. high dilutions, homeopathic granules). In other words, we assume that all samples that are evaluated in an experiment are physically comparable and interchangeable. Test samples *differ only by the label* that is attributed in accordance with a defined protocol, generally after a procedure (such as serial dilutions or 'impregnation of activity' by various means). After such a process, two categories of samples (or medications) are defined: those with 'inactive' (or placebo) label and those with 'active' (or 'verum') label. Note that 'inactive' *versus* 'active' naming does not prejudge the outcomes of the experiment; it simply reflects the results 'expected' by the experimenter or the physician.

For simplicity, we will use only the vocabulary related to biology experiments; of course the logic is exactly the same for clinical trials. A 'successful' experiment is thus defined as the association of the 'inactive' label (*IN*) with

the resting state (i.e. a change not different from background noise noted '↓') of the biological system or the association of the 'active' label (*AC*) with a biological change (i.e. a change above background noise noted '↑'). 'Failure' is defined as *AC* associated with '↓' or *IN* associated with '↑' (Figure 1). Because all samples are considered physically identical, experiments with a series of samples are *repetitions* of assessments of the state of the experimental model associated with either the label *AC* or the label *IN*. The aim of the experiments is to establish whether the state '↑' is more frequently associated with the label *AC* than with the label *IN*.

Description of experimental outcomes with the relational interpretation

Some of the concepts of quantum physics (superposition of states, entanglement, etc) are beyond understanding through our daily concepts. To give a view of quantum physics more compatible with our classical view of the world, different interpretations have been proposed (Copenhagen's interpretation, Everett's relative states, etc). Despite their differences, all these interpretations are compatible with the mathematics of quantum physics.

Rovelli's relational interpretation is one of these interpretations.[40,41] This interpretation has the advantage to apply not only to microscopic systems such as particles, but also to macroscopic systems such as measurement devices or human observers. In Rovelli's interpretation, a physical system can be said to possess a certain property only relative to another system (called an 'observer'). It means that this property is not absolute, but that it belongs in common to the object and to the observer. In other words, any observation of a physical event must be expressed relatively to an observer. An unavoidable consequence that is at the heart of the relational interpretation is that different observers can give different reports of the same outcome (there is no meta-observer of the reality). Nevertheless, all observers agree when they interact (an interaction is equivalent to a measurement).

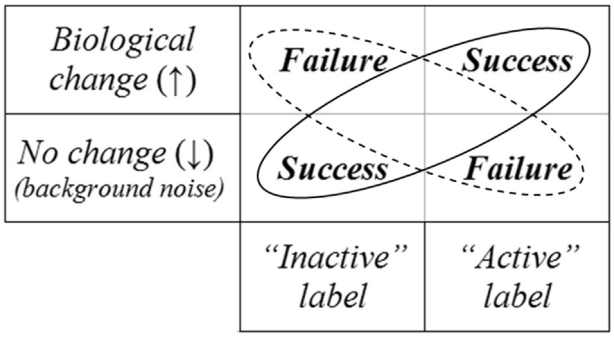


Figure 1 The different possible associations of labels and states of the experimental system in the modeling. The two labels are 'inactive' and 'active' and there are two possible states for the experimental system: (1) 'resting' state or background ('↓') i.e. no change of the biological parameter and (2) 'activated' state or biological change above background ('↑'). Success is defined as the association of 'inactive' label with no change or 'active' label with biological change.

Consider, for example, the situation depicted in Figure 2. In this picture, an observer O is measuring a quantum system S (i.e. any microscopic or macroscopic system) that can have two outcomes after measurement: '1' or '2'. For O, this system is in a *defined 'state'* after measurement (either '1' or '2'). The external observer P has a full knowledge of the initial conditions, but he *does not interact* with S and O during their evolution. For P, the system O−S is in an *undefined 'state'* after O has measured S: O_1 having observed '1' *or* O_2 having observed '2'. More exactly, P knows *that* O is in a defined state, but he does not know *what* state.

The two different accounts of O (defined outcome) and P (undefined outcome) are both correct. Only after interaction the 'state' of O becomes defined for P. It must be underscored that the interaction of P with O *does not force* P to observe what O observed before interaction (there is no 'hidden variable'). This does not make sense in the context of the relational interpretation to speculate about what each observer has *really* observed. Indeed, we can suppose an observer Q who does not interact with S, O or P; for this observer, the system P−O−S is in an undefined 'state' even after interaction of P with O−S. The properties of objects are relational and this interpretation deals only with the consistency of reports of different observers, not with elusive absolute properties of objects (there is no absolute 'state' of an object). In other words, for a non-participating observer, a form (but not a content) can be assigned to the information available for concrete observers.

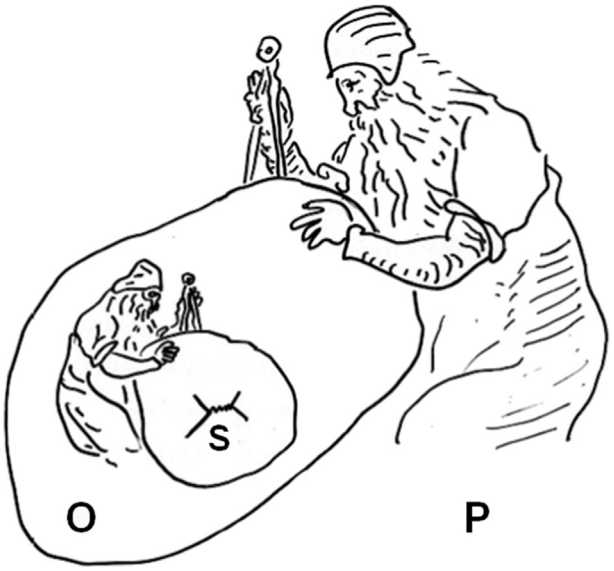


Figure 2 Internal and external observers in the relational interpretation. The internal observer O measures the system S and the external participant P assesses the evolution of the system formed by S and O. The external observer P has full knowledge of the initial conditions, but *he does not interact* with S and O. According to the relational interpretation, two observers can make different accounts of an outcome; both accounts are nevertheless correct and when observers interact they agree on their observations (interaction is also a measurement). In the modeling, P describes a team of interacting observers (named O and O′) committed in the study of a relationship between labels and a biological system S. The evolution of O, O′ and S is described from the point of view of P (*GNU Free Documentation License*).

Application of the relational interpretation to unconventional experiments

Description of the experimental system and observers

For the present modeling, we describe an experiment from the point of view of P as defined above and in Figure 1. We consider that P describes the *evolution of a team of observers* who are committed in an 'unconventional' experiment and who interact with each other. We postulate that P has full information on the states of the team of observers and the system S at the beginning of the experiment and *does not interact* with them.

For simplicity, we suppose that this team is composed of only two observers named O and O′ who observe the experimental system S. 'Observation' means expectation (which requires an *a priori* framework on what is measured) and then feedback (recording of the outcome). We suppose an experiment where, for a given configuration of the experimental device, the probability to observe 'success' as defined above is p (the probability of 'failure' is equal to q with $p + q = 1$). Thus, before they interact, the probability of success is p for O and is also p for O'.

According to the relational interpretation, each outcome must be expressed relatively to a given observer. In other words, a system has one 'state' relative to a given observer and it has another 'state' relative to a second observer. Therefore, from the point of view of P, for two observers O and O′ who have not yet interacted, the outcomes associated relatively to O and O′ are *independent*. To take into account this independence, we have to remember that the probability of two independent events A and B have well-known mathematical properties:

$$\text{Prob}\,(A \cap B) = \text{Prob}\,(A) \times \text{Prob}\,(B) \qquad (1)$$

Calculation of the probability of 'success' for a 'team of interacting observers'

Starting from Eq. (1), we continue to describe the experimental situation from the point of view of P *after the two observers interact*. As depicted in Figure 3, the joint probability of 'success' is $p \times p$ (outcomes associated relatively to O and O′ are independent) divided by the sum of the probabilities of all events ('failure' and 'success') *allowed by the intersubjective agreement* that requires that all observers agree on the outcome:[a]

$$\text{Prob}\,(success) = \frac{p^2}{p^2 + q^2} \qquad (2)$$

Eq. (2) can be written with only p as a variable by dividing both the numerator and the denominator by p^2 and by taking into account that $p + q = 1$:

$$\text{Prob}\,(success) = \frac{1}{1 + \left(\frac{1}{p} - 1\right)^2} \qquad (3)$$

We can generalize Eq. (3) to N observers:[b]

$$\text{Prob}\,(success) = \frac{1}{1 + \left(\frac{1}{p} - 1\right)^N} \qquad (4)$$

The importance of Eqs. (3) and (4) will appear in the next section when *probability fluctuations* will be taken into consideration.

Consequences of probability fluctuations

In the laboratory, obtaining the outcome of an experiment, particularly with biological models, is not immediate; it takes time during which small random fluctuations occur. Indeed, fluctuations affect all macroscopic objects. At each elementary time, a tiny random bias is inevitably introduced. Therefore, from the point of view of P, Prob (*success*) must be updated after each fluctuation.

We can calculate with Eq. (5) that Prob (*success*) is equal to 1/2 in the absence of observers (i.e. with $N = 0$). Therefore, we write out that the initial value of Prob (*success*) at time t_0 before the first fluctuation is equal to $p_0 = 1/2$ for any experiment.

An elementary random fluctuation of Prob (*success*) that occurs during an elementary interval of time is noted ε (with ε positive or negative real random number such as $|\varepsilon| << 1$).[c] The probability of success is obtained by completing Eq. (5). After a first fluctuation ε_1, a new probability is calculated which is based on $p_0 = 1/2$. One can thus generalize the formula for any evaluation $n + 1$ based on previous evaluation n and fluctuation $n + 1$.[d] The formula of the mathematical sequence for calculating successive evaluations of Prob (*success*) taking into account fluctuations is:

$$\text{Prob}_{n+1}\,(success) = p_{n+1} = \frac{1}{1 + \left(\frac{1}{p_n + \varepsilon_{n+1}} - 1\right)^N} \text{ with } p_0 = 1/2 \qquad (5)$$

The computer calculations of the sequence from $n = 0$ to $n = 100$ random elementary fluctuations with small ε values (about 10^{-15}) and with two observers ($N = 2$) show that the

[a] The concomitant consideration of these two principles (independence of the outcomes relative to O and O′ and intersubjective agreement) implies that the 'shared reality' of O and O′ does not pre-exist to their interaction from the point of view of P. This is a characteristic of quantum measurements. In the language of quantum mechanics, the 'state' of O would be said 'superposed' before interaction (idem for O′); O and O′ would be said 'entangled' after interaction.

[b] Note that for a number of observers $N > 2$, they interact anyway by pairs; this equation will be useful for $N = 0$.

[c] This means that the probability to observe '↑' is not null, even if this probability is very low.

[d] We assume here that probability after fluctuation $n + 1$ is dependent on probability after fluctuation n; this will be justified in the section "*Which experimental systems are appropriate for 'unconventional' experiments?*"

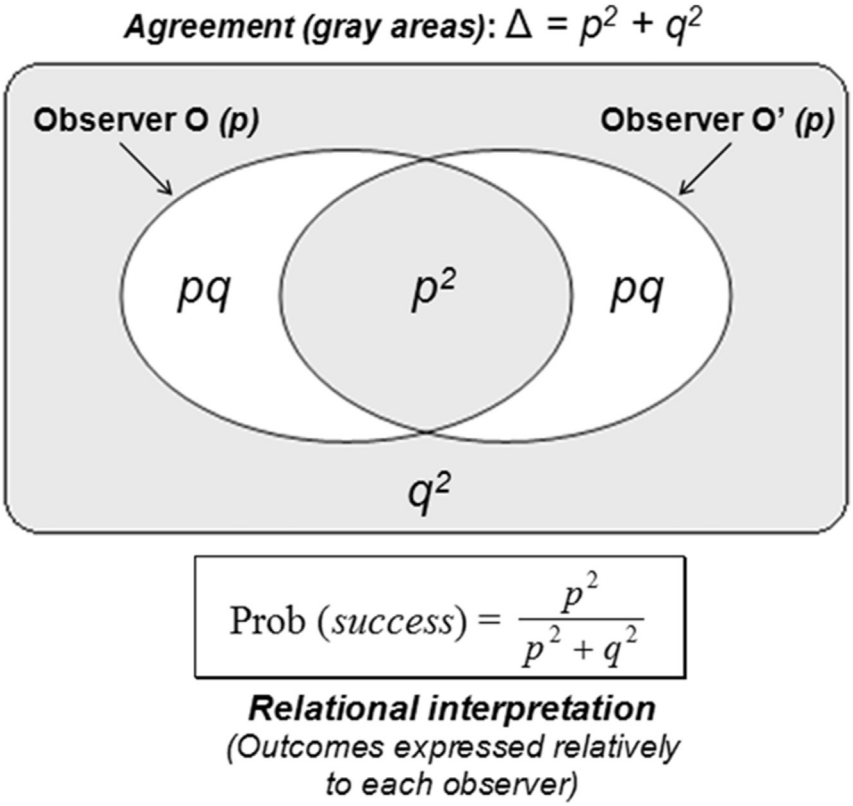


Figure 3 Schematic description of a team of observers (O and O′) of 'unconventional' experiments according to the relational interpretation. We suppose a probability equal to p for the event 'success' and equal to q for the event 'failure' (with $p + q = 1$). The situation is described from the point of view of P (see Figure 2). The outcome of an experiment is indexed relatively to O and O′, but these observers nevertheless agree on the outcome after they interact. The white areas correspond to unauthorized situations where the outcomes are not consistent among observers after they interact (e.g. 'success' for the experimenter and 'failure' for another observer). The white areas are consequently excluded for the calculation of joint probability. The probability that both agents observe 'success' is thus calculated by the ratio of the central gray area ('success' for both observers) divided by the probability of outcomes (either 'success' or 'failure') consistent for both observers (all gray areas).

initial situation ($p_0 = 1/2$) is, in fact, *metastable* (Figure 4). Indeed, after several dozens of fluctuations, there is *in all cases* (i.e. whatever the series of ε terms) a dramatic transition and one of two mutually exclusive stable positions is achieved:

$$\begin{gathered}\text{Prob}\,(success) = 1/2\ \text{(metastable position)} \\ \downarrow \\ \text{Prob}\,(success) = 1\ or\ 0\ \text{(two possible stable positions)}\end{gathered} \tag{6}$$

Note that fluctuations are required for the transition of probability toward 0 or 1: indeed, with $\varepsilon = 0$, Prob (*success*) remains equal to 1/2. Moreover, expressing the outcomes relatively to each observer O and O′ before the interaction is also necessary to allow this transition.

In stable position #1, the observed results are similar to the 'expected' results, whereas, in stable position #2, there is a *systematic* inverse relationship to what is expected (Figures 1 and 4).

Therefore, an important consequence of the modeling is the *emergence of a relationship* between labels and biological outcomes. Moreover, in both stable positions, the probability to observe '↑' increases from ∼0 to 1/2. Nevertheless, there is no reason in the formalism itself to choose between stable position #1 (systematic 'success') and stable position #2 (systematic 'failure') that are randomly obtained. We can go further nevertheless if we note that biological systems are prepared in an *asymmetrical* state. Indeed, the resting state (background noise) is always implicitly associated with the 'inactive' label. Therefore, only the stable position #1 is a possible state for the observers and the 'expected' results in this case fit the observed results. The only possible evolution of Prob (*success*) is thus:

$$\begin{gathered}\text{Prob}\,(success) = 1/2\ \text{(metastable position)} \\ \downarrow \\ \text{Prob}\,(success) = 1\ \text{(stable positions)}\end{gathered} \tag{7}$$

Consequences of blind experiments in the modeling

Blind experiments with local assessment of 'success'

In the case of local (in-house) blind experiments, the automatic device or the observer who keeps secret the code of the samples until the end of the experiment are also elements of the experiment and the rates of 'success' are locally assessed. Therefore, these experiments can be

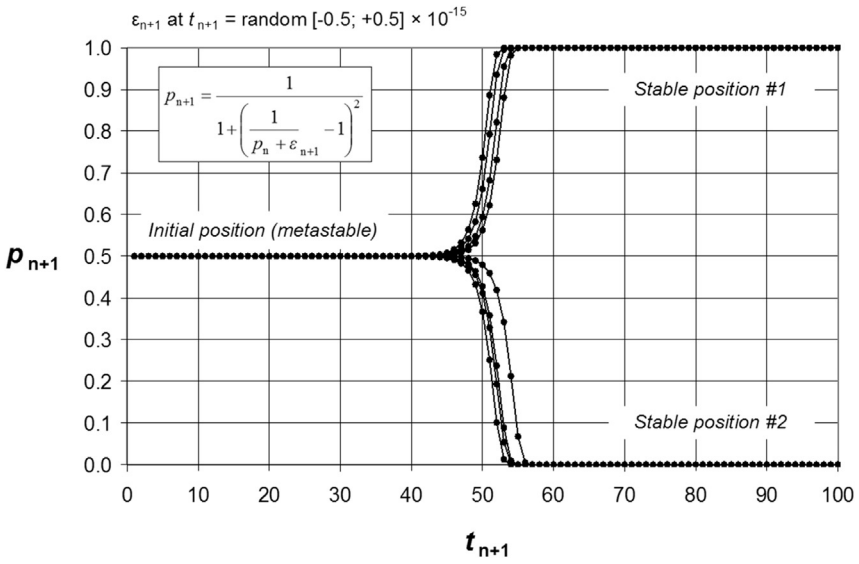


Figure 4 Estimation of the probability for 'success' taking into account probability fluctuations. This figure describes the evolution of the probability of 'success' for a team composed of two members who interact (the experimenter and one observer for example). In this figure, the probability defined in Figure 2 is computed by taking into account tiny random fluctuations. The equation in the cartouche defines a mathematical sequence that allows estimating this probability of 'success' at defined times after successive fluctuations. Each successive term p_{n+1} of the mathematical sequence is calculated by using p_n and the random probability fluctuation ε_{n+1}. The starting value of Prob (*success*) at time t_0 is $p_0 = 1/2$. The values of ε_{n+1} at each calculation step (corresponding to the successive times t_{n+1}) are randomly obtained in the interval -0.5 to $+0.5 \times 10^{-15}$. One observes in this computer simulation that the probability of 'success' is metastable and, after a few dozens of calculation steps, one of the two stable positions is achieved: either Prob ('*success*') = 1 or Prob ('*success*') = 0. Fluctuations ε_{n+1} with higher values lead to a transition that occurs after a lower number of calculation steps. The figure depicts the results obtained after eight computer simulations.

described with the same modeling as open-label experiments and Prob (*success*) = 1.

Blind experiments with the assessment of 'success' by an external supervisor

In Benveniste's experiments, blind experiments with an external supervisor were performed as described above. In clinical trials, a centralized design is also the rule for blinding in accordance with modern methodological standards. The distant/external supervisor who holds the code of the samples does not interact with the experimenters before all measurements are done.[e] When he receives the outcomes for all samples, the external supervisor separately assesses the rate of 'success' for labels *IN* and *AC* thus allowing calculations of Prob (*success*|*IN*) and Prob (*success*|*AC*) where Prob ($x|y$) is the conditional probability of x given y.

Note that the 'inactive' and 'active' labels are 'expected' to be present in the series; therefore there is a transition from the metastable position toward one of the two stable positions, but at random for the two labels; as a consequence, Prob (*success*|*IN*) = Prob (*success*|*AC*) = 1/2. Prob (*success*) is calculated according to the law of total probability:

$$\text{Prob}\,(success) = \text{Prob}\,(IN) \times \text{Prob}\,(success|IN) + \text{Prob}\,(AC) \times \text{Prob}\,(\,success|\text{AC}) \quad (8)$$

$$= 1/2 \times 1/2 + 1/2 \times 1/2 = 1/2 \quad (9)$$

This result means that a biological change is observed but at random places. Consequently, statistical tests do not evidence a significant difference of the effects associated with *IN* and *AC* labels. We see with Eq. (9) that the random 'spreading' of outcomes between *IN* and *AC* samples (or 'jumps of activity') can be simply described according to logic and does not require calling upon external physical disturbances to explain failures with an external supervisor.

Which experimental systems are appropriate for unconventional experiments?

It could be argued that this modeling could apply to any experimental situation such as bets on coin flipping. The use of Eq. (5) rests, however, on some conditions that must be clarified.

The transition of Prob (*success*) from 1/2 to 1 (calculated with Eq. (5) and described in Figure 4) supposes that the experimental system S is based on a phenomenon that possesses an internal structure submitted to small random fluctuations (e.g. thermal fluctuations). Moreover, Eq. (5)

[e] The remote supervisor should not be confused with the uninvolved observer P who describes the experiment. Indeed, P has no interaction with the system and the team members and, from his point of view, labels and corresponding outcomes remain undefined.

assumes that each p_{n+1} value is strongly dependent on p_n value; in other words, the probabilities p_{n+1} are correlated with the probabilities p_n. This characteristic is known as *temporal autocorrelation*. According to these considerations, different types of experimental systems can be described:

- Experimental systems based on a phenomenon not submitted to internal fluctuations such as radioactive decay (Schrödinger's cat) or systems with sufficient mechanical inertia to be not influenced ('rigid' systems; e.g. coin flipping, dice rolling). In Eq. (5), ε is equal to zero and there is no transition.
- Experimental systems submitted to internal fluctuations, but with successive states that are not autocorrelated due to strong restoring forces ('elastic' systems). An example of such system is a beam splitter that randomly transmits or reflects photons. In Eq. (5), p_n is replaced with 1/2 and there is no transition (only fluctuations of about 1/2 are observed).
- Experimental systems with internal fluctuations but with successive states that are not autocorrelated due to large random fluctuations. Examples of such systems are devices based on electronic noise. For these systems, there is no correlation between p_n and p_{n+1} and no transition towards 0 or 1.
- Experimental systems based on a random phenomenon with successive autocorrelated states. Examples of such systems are structures submitted to Brownian motion or biological systems. Indeed, temporal autocorrelation is characteristic of phenomena with *slow random fluctuations*.

Only the last type of experimental systems appears to be suitable for evidencing quantum-like correlations between 'labels' and experimental outcomes. The appropriateness of biological models for the appearance of quantum-like correlations could explain why the question of 'unconventional' experiments arose in medical and biological experimental contexts.

Role of the observers and their commitment in the experiments

In this section we will deepen the role of the observers in the outcomes of the experiments. We have seen that expressing the outcomes relatively to each observer O and O′ was a prerequisite for a transition of the relationship between labels and biological outcomes from 1/2 towards 0 or 1. The joint probability of two independent events A and B is equal to the product of the separate probabilities of the events as reported in Eq. (1). We now generalize this equation for two events whatever their degree of independence:

$$\text{Prob}\,(A \cap B) = \text{Prob}\,(A) \times \text{Prob}\,(B) + d \quad (\text{with } 0 \leq d \leq 1) \tag{10}$$

If $d = 0$, the two events are independent; the degree of independence decreases when d increases (i.e. the correlation between the two events increases). For our modeling, the estimation of the joint probability for 'success' as described in Eq. (2) can be easily modified (see Figure 5 and legend for details):

$$\text{Prob}\,(\textit{success}) = \frac{p^2 + d}{p^2 + q^2 + 2d} \quad (\text{with } 0 \leq d \leq 1/4) \tag{11}$$

Therefore, a transition of Prob (*success*) is progressively allowed when the parameter d changes from $d = pq = 1/4$ (outcomes expressed relatively to the observed system; classical interpretation) to $d = 0$ (outcomes expressed relatively to each observer; relational interpretation).

As seen in Figure 4, the calculation of Prob (*success*) requires at each step a definition of the expected relationship between labels and biological outcomes. Moreover, labels are arbitrarily defined and the expected relationship is an abstract idea (remember that no physical difference between samples is postulated in the modeling). The transition of the probability supposes observation (defined as expectation followed by feedback). From the point of view of P, no transition of Prob (*success*) towards the stable position is possible *in the absence of observation* by the team's observers ($N = 0$ in Eq. (5)). The conclusion is the same if the observers are physically present in the laboratory, but with attention not focused on this specific relationship (they expect nothing about the system and do not receive feedback). Therefore, the parameter d can be considered as an evaluation of the persistence of commitment to observe the relationship between labels and biological outcomes. When $d = 0$, the observers are fully committed and for $d = pq$, there is no commitment at all to observe the relationship. For intermediate values, the persistence of commitment is more or less high.

Therefore, the modeling suggests a possible explanation for the issues of reproducibility of 'unconventional' experiments by other teams, as it was the case, for example, with Benveniste's experiments. Indeed, experimenters' qualities, such as attentiveness, commitment and persistence, appear to be needed for the emergence of quantum-like correlations.

By the way, this modeling suggests a possible link between psychological and physical parameters. Note that this link does not allow a causal relationship between mental states and physical states. We will see in the next section that only quantum-like correlations are allowed.

Emergence of a quantum-like relationship from classical probability

In this section, we will see that, although we did not formally use quantum mathematical tools in the modeling, quantum-like logic was nevertheless at work unbeknown to us. We start the demonstration by squaring Prob (IN) + Prob (AC) = 1:

$$[\text{Prob}\,(IN) + \text{Prob}\,(AC)]^2 = [\text{Prob}\,(IN)]^2 + [\text{Prob}\,(AC)]^2 + 2 \times \text{Prob}\,(IN) \times \text{Prob}\,(AC) = 1 \tag{12}$$

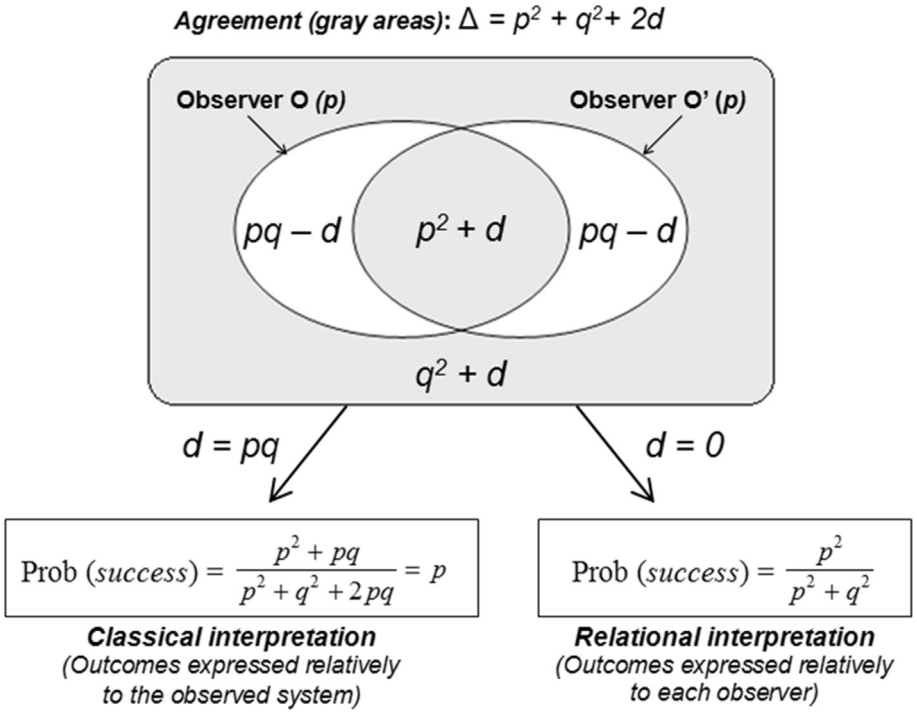


Figure 5 General case for the calculation of the probability for 'success'. This figure is a generalization of Figure 2 with variations the parameter *d*. The values of the two areas with unauthorized configurations ('success' for one observer and 'failure' for the other one) are easily calculated: $p - (p^2 + d) = p \times (1 - p) - d = pq - d$. When $d = 0$, quantum-like probabilities emerge; when $d = pq$, the joint probability of 'success' is equal to p as in classical probability.

Let Prob $(IN) = a^2$ (or $a \cdot a$) and Prob $(AC) = b^2$ (or $b \cdot b$); this situation corresponds to the stable position #1 (note that for position #2, b^2 must be taken equal to $-b \times -b$):

$$[a \cdot a + b \cdot b]^2 = (a \cdot a)^2 + (b \cdot b)^2 + 2 \times (a \cdot b)^2 = 1 \quad (13)$$

$$[a \cdot a + b \cdot b]^2 + [b \cdot a - a \cdot b]^2 = (a \cdot a)^2 + (b \cdot b)^2 + (b \cdot a)^2 + (a \cdot b)^2 = 1 \quad (14)$$

$$1 \quad + \quad 0 \quad = \quad 1/2 \quad + \quad 1/2 \quad = \quad 1 \quad (15)$$

With the help of Figure 6, we easily recognize in the left arm of Eq. (14) the sum of Prob (*success*) plus Prob (*failure*) without an external supervisor and in the right arm the sum of Prob (*success*) plus Prob (*failure*) with an external supervisor. We also identify a and b as probability amplitudes (their squaring gives the corresponding probabilities).

In Figure 6, the probability of 'success' in the absence of external supervisor is calculated by doing the sum of the probability amplitudes of the two paths that lead to 'success' and then by squaring it. With an external supervisor, the probability of 'success' is obtained by squaring the probability amplitude of each path that leads to 'success' and then by making the sum of the probabilities of the two paths. This logic is thus reminiscent of single-photon interferences such as in Young's double-slit experiment.

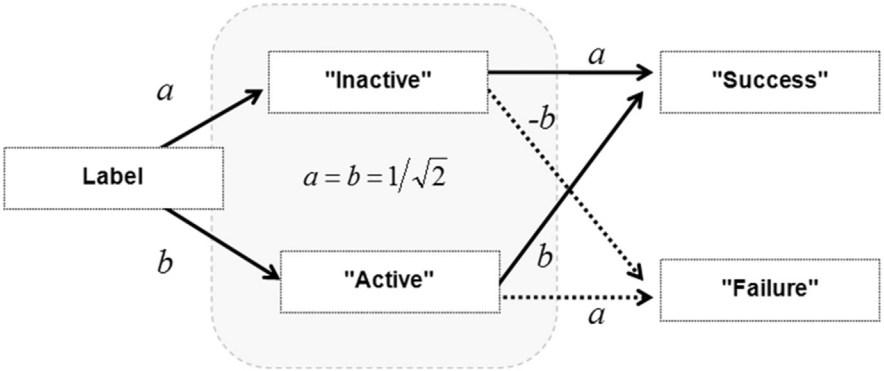
Concordance of the different points of view

The modeling has been built from the point of view of P. From the point of view of O, if he observes 'success' or 'failure', then he is sure that O′ will tell him that he observes the same event. Therefore the 'joint' probability of O and O′ is p as stated by classical probability, a result that is different from the point of view of P according to the relational interpretation (Eq. (2)). The points of view of P and O–O′ are concordant when:

$$p = \frac{p^2}{p^2 + q^2} \quad \text{and} \quad q = \frac{q^2}{p^2 + q^2} \quad (16)$$

We can easily calculate that these two equations are equivalent to $(2p - 1)(p - 1) = 0$ and $(2q - 1)(q - 1) = 0$, respectively. Therefore, there are only three possible values for p, namely 1/2, 1 or 0, which are the probabilities of initial position, stable position #1 and stable position #2, respectively. Only P who is *not involved* in the experiment is able to describe the quantum-like 'interferences' (cross-terms with probability amplitudes b and $-b$ in Figure 6).

The discrepancy between the points of view of O and P is in line with the demonstration of Breuer, which showed that a complete self-measurement is impossible. Thus, a measurement apparatus (or an observer) cannot distinguish all the states of a system in which he is contained,



Without external supervisor (square of the sum of the probability amplitudes of the paths) :

$$\text{Prob}(success) = (a \times a + b \times b)^2 = 1$$

$$\text{Prob}(failure) = (b \times a - a \times b)^2 = 0$$

With external supervisor (sum of the squares of the probability amplitudes of the paths) :

$$\text{Prob}(success) = (a \times a)^2 + (b \times b)^2 = 1/2$$

$$\text{Prob}(failure) = (b \times a)^2 + (a \times b)^2 = 1/2$$

Figure 6 Probability of 'success' without or with an external supervisor. The probabilities of 'success' are different without or with an external supervisor. Indeed, quantum-like probability is calculated as the *square of the sum* of the probability amplitudes of the different possible 'paths'. With an external supervisor, classical probabilities apply and they are calculated as the *sum of squares* of the probability amplitudes of the 'paths'.

irrespective of whether this system is classical or quantum mechanical.[42,43] All correlations between an apparatus (O) and the observed system (S) are only measurable by a second external apparatus (P) that observes both the system (S) and the first apparatus (O).

Experimental arguments in favor of the present modeling

Initially designed after a reflection on Benveniste's experiments, the present modeling describes all their characteristics: emergence of a 'signal' (biological change), concordance between labels and biological outcomes and erratic 'jumps' of the biological 'signal' in blind experiments with an external distant supervisor. The random 'jumps' or spreading of the 'biological activities' among samples is thus described without *ad hoc* explanations such as cross-contaminations or electromagnetic perturbations. Although the hypothesis of 'memory of water' or any other local explanation cannot be formally discarded, no hypothesis on the physical differences between test samples was introduced (only labels of samples are different).

In a letter published in 2008, I draw the attention on the importance of blind design in Benveniste's experiments.[35] In an article in 2013, I made a parallel between homeopathy clinical trials and single-photon interference in a Mach–Zehnder apparatus, a device whose principle is similar to Young's two-slit experiment.[25] On the basis of this modeling resting on quantum-like logic, I predicted that higher successes should be achieved in blind homeopathy clinical trials with local blind design.[25] Indeed, as we have seen, a local or in-house blind design is equivalent to an open-label design according to the modeling. In contrast, the spreading of outcomes between placebo and verum was predicted for centralized blind design. In other words, no statistical difference between treatment groups could be evidenced in this latter situation.

An editorial of *Homeopathy* encouraged scientists to test the hypothesis of an improvement of the difference of outcomes between treatment groups with local blind design.[44] Thieves *et al.* have taken up the challenge and they recently reported results comparing local and. centralized blind designs for a homeopathic compound.[45] Before designing a clinical trial, these authors studied the effect of homeopathic sulfur on wheat germination. The initial hypothesis was confirmed: there was a statistical difference for local *versus* centralized blind designs ($p = 0.003$ for the interaction test). These results are therefore a strong argument in favor of the quantum-like logic of 'unconventional' experiments.[f] Indeed, hypotheses such as 'memory of water', modifications of water structure or contaminations with active compounds cannot explain this difference between the two blind designs. Moreover, beyond 'unconventional' experiments, these results are also unexplainable and counterintuitive in a classical framework. From a historical point of view, it is also pleasing to note that these experiments reproduced in a different model the stumbling block that prevented Benveniste to convince his peers as explained at the beginning of the article.

[f] Note that Rovelli's interpretation preserves the principle of locality; therefore, quantum correlations cannot be considered in this framework as 'non local'.

Which design for clinical trials?

For scientists or physicians seeking to reproduce the study of Thieves *et al.* either in *in vitro* studies or in clinical trials, it is important to underscore that experiments comparing central and local blind designs are very demanding because they require performing a double trial. These 'meta-experiments' should be performed only if the purpose is to test the quantum-like nature of a relationship. If the main objective is to improve the difference of outcomes between placebo and homeopathy medicine in blind randomized trials, then a local blind design is sufficient and only slight adjustments of a classical blind RCT are required.

We can hope that both the present simplified theoretical description and the positive results of Thieves *et al.* will encourage other authors to design new experiments to confirm these promising results. Moreover, it is not excluded that such quantum-like phenomena could add to the classical local causal relationship in 'conventional' clinical trials.

Conclusion

A simple modeling of 'unconventional' experiments based on classical probability is now available and its predictions can be tested. The underlying concepts are sufficiently intuitive to be spread into the homeopathy community and beyond. It is hoped that this modeling will encourage new studies with optimized designs for *in vitro* experiments and clinical trials.

Conflict of interest statement

No conflict of interest.

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